Catalysis Based on Ruthenium Pincer Complexes

By

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Bhubaneswar, Odisha – 752050

A thesis submitted to the

Board of Studies in Chemical Sciences

In partial fulfillment of requirements

for the Degree of

DOCTOR OF PHILOSOPHY

of

HOMI BHABHA NATIONAL INSTITUTE

August, 2020

Homi Bhabha National Institute[1]

Recommendations of the Viva Voce Committee

As members of the Viva Voce Committee, we certify that we have read the dissertation prepared by Mr. Thiyagarajan S entitled "Catalysis Based on Ruthenium Pincer Complexes" and recommend that it may be accepted as fulfilling the thesis requirement for the award of Degree of Doctor of Philosophy.

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(Dr. C. Gunanathan)

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S. Thiyagarajan

Thiyagarajan S

DECLARATION

I, hereby declare that the investigation presented in the thesis has been carried out by me. The work is original and has not been submitted earlier as a whole or in part for a degree / diploma at this or any other Institution / University.

S. Thiyagarajan

Thiyagarajan S

List of Publications arising from the thesis

Journal

1) "Facile Ruthenium(II)-Catalyzed α-Alkylation of Arylmethyl Nitriles Using Alcohols Enabled by Metal–Ligand Cooperation", **Thiyagarajan, S**.; Gunanathan, C., *ACS Catal.,* **2017**, *7*, 5483-5490.

2) "Ruthenium-Catalyzed α-Olefination of Nitriles Using Secondary Alcohols", **Thiyagarajan, S**.; Gunanathan, C., *ACS Catal.,* **2018**, *8*, 2473-2478.

3) "Catalytic Cross-Coupling of Secondary Alcohols", **Thiyagarajan, S**.; Gunanathan, C., *J. Am. Chem. Soc.,* **2019**, *141*, 3822-3827.

4) "Ruthenium-Catalyzed Direct Cross-Coupling of Secondary Alcohols to β-Disubstituted Ketones", **Thiyagarajan, S**.; Gunanathan, C., *Synlett*, **2019**, *30*, 2027-2034 *(Invited Synpacts article).*

5) "Ruthenium-Catalyzed Selective Hydrogenation of Epoxides to Secondary Alcohols", **Thiyagarajan, S**.; Gunanathan, C., *Org. Lett.,* **2019**, *21*, 9774-9778.

6) "Direct Catalytic Symmetrical, Unsymmetrical N,N-Dialkylation and Cyclization of Acylhydrazides Using Alcohols", **Thiyagarajan, S**.; Gunanathan, C., *Org. Lett.,* **2020**, *22*, 6617-6622.

Publications not included in the thesis

1) "Ruthenium(II)-Catalyzed Direct Synthesis of Ketazines Using Secondary Alcohols", Kishore, J.; **Thiyagarajan, S.;** Gunanathan, C., *Chem. Commun.,* **2019**, *55*, 4542-4545.

2) "KO^{t}Bu-Catalyzed Michael Addition Reactions Under Mild and Solvent-Free Conditions", **Thiyagarajan, S.;** Krishnakumar, V.; Gunanathan, C., *Chem. Asian. J.*, **2020**, *15*, 518- 523. *(Invited Article)*

3) "Ruthenium Catalyzed α-Alkylation of Ketones Using Secondary Alcohols to β-Disubstituted Ketones", **Thiyagarajan, S.;**[†] Vijaya Sankar, R.;[†] Gunanathan, C., *Org. Lett.*, **2020**, *22*, 7879-7884. ([†]equal contribution)

Conferences:

1) Thiyagarajan, S.; Gunanathan, C. *Ruthenium(II)-Catalyzed α-Alkylation and α - Olefination of Nitriles Using Alcohols.* "**XIV J-NOST Conference for Research Scholars**", Nov 28 -Dec 1, 2018, CSIR-IICT, Hyderabad, Telangana, India. **(Oral Presentation)**

2) Thiyagarajan, S.; Gunanathan, C. *Ruthenium-Catalyzed α-Alkylation and α-Olefination of Nitriles Using Alcohols.* "**ACS on Campus**", Jul 23, 2018. NISER, Bhubaneswar, India. **(Poster Presentation)**

3) Thiyagarajan, S.; Gunanathan, C. *Facile Ruthenium(II)-Catalyzed α-Alkylation of Arylmethyl Nitriles Using Alcohols Enabled by Metal-Ligand Cooperation.* "**Inter IISER & NISER Chemistry Meet (IINCM-2017)**", Dec 22-24, 2017. NISER, Bhubaneswar, India. Awarded 'Best Poster' of the symposium. **(Poster Presentation)**

S. Thyagarajan

Thiyagarajan S

Dedicated to....

To my parents

&

Dr. C. Gunanathan

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…Thiyagarajan S

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List of Schemes

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List of Abbreviations Used

Å	Angstrom
Anal.	Analytically
Anhyd	Anhydrous
aq	Aqueous
bp	Boiling Point
br	Broad
°C	Degree Celcius
Calcd	Calculated
cm	Centimeter
Conc	Concentrated
conv	Conversion
d	Doublet, Days

Chapter 7

Conclusions

The activation of unreactive chemical bonds by transition metal complexes is an area of utmost importance. In this context, catalytic activation of C–H, N–H and O–H bonds via greener pathway is a challenging task. The classical methodology for the construction of C–C and C–X (X = H, O, N, S, halides, etc.) bonds involves enolate substitution reactions using organometallic reagents or organohalides. However, there are several disadvantages associated with these traditional synthetic methods, including handling of reactive and air-sensitive organometallic reagents and the production of copious salt-based waste during the course of the reactions. Thus, the development of green and sustainable chemical transformations using transition metal catalysis emerged as topic of interest chemical research and strongly desired. In the last two decades, pincer complexes-based catalysts have made tremendous impact in several fundamental chemical transformations and helped achieving greener procedures with high atom efficiency. Pincer ligands having planar framework with presence of bulky substituents on donor atoms covers much coordination sphere around the metal center, which offer control over vacant coordination sites and enhance stability of the resulting pincer complexes. Thus, pincer complexes possess unique balance of stability versus reactivity. As a result, "pincer complexes" once considered, as a favorite adventure for probing reaction mechanism by organometallic chemists became preferred catalysts for various challenging transformations in organic synthesis.

Chapter 1 covered the synthesis, reactivity and previous reports on catalysis by Ru-MACHO (**1**). The unusual reactivity in pincer complexes named, as "Metal-ligand

cooperation" has become an important concept in catalysis for various bond activation reactions in green catalytic pathway. Borrowing hydrogen methodology and acceptorless dehydrogenation concepts allow construction of both C–C and C–N bonds from alcohols and provide an efficient, atom-economical access to an assortment of useful products. On the basis of these two concepts, new C–C, C=C and C–N bond formation reactions were developed using catalyst **1**, which are presented in Chapters 2-6. Further, based on stoichiometric studies, characterization of transient intermediates and labeling experiments the plausible reaction mechanisms for the developed catalytic methods are presented.

Chapter 2 consists of a facile α-alkylation of arylmethyl nitriles with primary alcohols using ruthenium pincer catalyst **1**. An assortment of arylmethyl nitriles can be effectively alkylated using unactivated aliphatic primary alcohols, including challenging ethylation and methylation were also achieved. This green catalytic transformation follows the principle of the borrowing hydrogen methodology and produced water as the only byproduct. Notably, secondary alcohols didn't undergo alkylation reactions. When deuterium-labeled alcohol was used, the expected deuterium transposition occurred, provided both α-alkylation and α-deuteration of arylmethyl nitriles. Further, consumption of nitrile was monitored by GC, which indicated the involvement of first order kinetics. Experimental evidences are suggested the possible mechanistic pathway. The ruthenium catalyst **1** reacts with base and generates an unsaturated reactive intermediate, which reacts with both nitriles and alcohols. Further, oxidation of alcohols to aldehydes and also formed a [2+2] cycloadduct with nitriles that tautomerizes to its enamine intermediate, which further undergo conjugate addition leading to condensation reactions. Subsequent hydrogenation of the intermediate vinyl nitriles (resulted from condensation reactions) provided the selective α-alkylated products.

Overall, an efficient α-alkylation of nitriles using primary alcohols can be attributed to the amine-amide metal-ligand cooperation that is operative in the pincer catalyst **1**, which enables all the catalytic intermediates to remain in +2 oxidation state throughout the catalytic cycle.

In chapter 3, direct coupling of secondary alcohols with nitriles, which delivered β-disubstituted vinyl nitriles, was achieved. Arylmethyl nitriles, heteroarylmethyl nitriles and also aliphatic nitriles were directly coupled with cyclic, acyclic as well as symmetrical and unsymmetrical secondary alcohols, which resulted β-disubstituted vinyl nitriles in good to excellent yields. Notably, liberated H_2 and water are the only byproducts. The acceptorless dehydrogenation of nitriles and alcohols proceeds via amine-amide metal-ligand cooperation that occurs in the activated complex **1**. This new C=C bond formation proceeds through activation of the O–H bond of secondary alcohols via an unsaturated 16-electron intermediate ruthenium pincer complex **1**. Further condensation of in situ formed ketones reaction with nitriles provides expected vinyl nitrile products.

In chapter 4, an unprecedented direct cross coupling of two different secondary alcohols to β-disubstituted ketones was demonstrated. A variety of cyclic, acyclic, symmetrical and unsymmetrical secondary alcohols were selectively coupled with aromatic benzylic secondary alcohols to resulted ketone products. A single catalyst oxidizes both secondary alcohols to provide selectively β-disubstituted ketones. Number of bond activation and bond formation reactions occurs in selective sequence via amine-amide metal-ligand cooperation operative in catalyst **1**. Kinetic and deuterium-labeling experiments suggested that the aliphatic secondary alcohols oxidize faster than benzylic secondary alcohols, which selectively assimilating to provide the cross-coupled ketone products. Interestingly, this new C–C bond forming methodology produces H_2 and H_2O

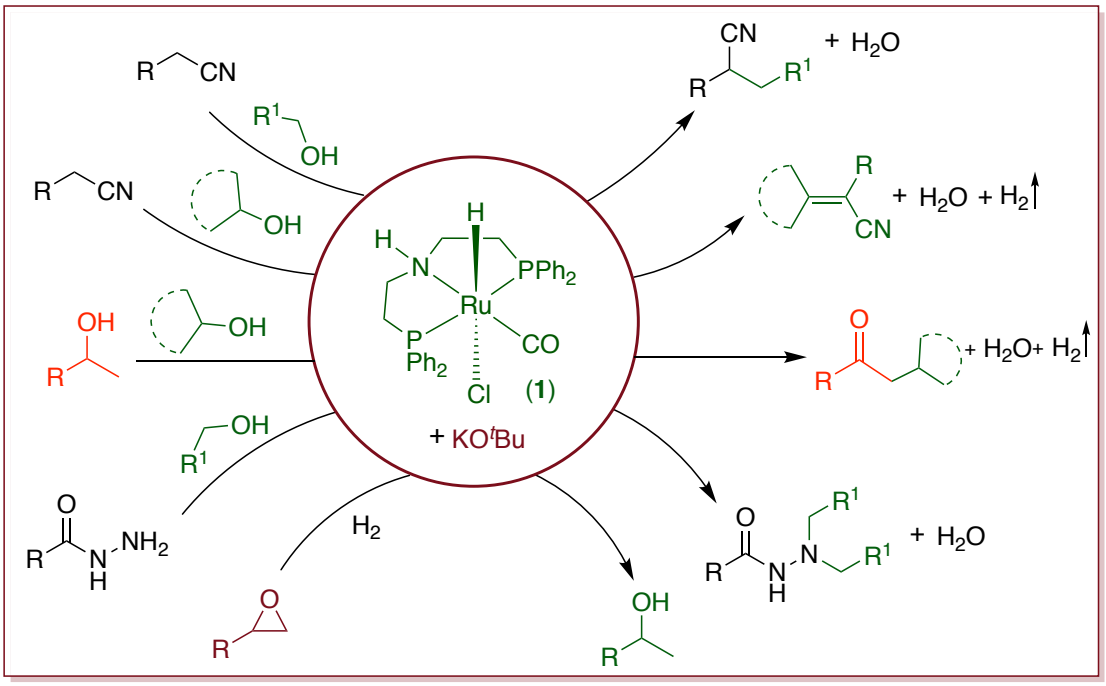
as the only byproducts, which make this protocol greener, atom economical and environmentally benign.

In chapter 5, an unprecedented direct N,N-dialkylation of acylhydrazides using alcohols was reported. This catalytic protocol employs catalyst **1** and provides one-pot synthesis of both symmetrical and unsymmetrical N,N-disubstituted acylhydrazides. Challenging diethylation and dimethylation reactions are performed using ethanol and methanol, respectively as alkylating reagents. Assortment of primary and secondary alcohols can be used with remarkable selectivity and the products were obtained in excellent yields. Interestingly, the use of diols resulted in intermolecular cyclization of acyhydrazides and such products are privileged structures in biologically active compounds. Further, one-pot synthesis of N,N-dialkylated acylhydrazides directly from ester via tandem reaction process also demonstrated. Preliminary mechanistic and deuterium labeling studies indicate that the reaction follows O–H bond activation of alcohols and hydrazone intermediates. Water is the only byproduct, which makes this catalytic protocol sustainable and environmentally benign.

In chapter 6, highly selective Markovnikov hydrogenation of terminal epoxides to secondary alcohols was reported. Diverse aromatic and aliphatic terminal epoxides underwent facile hydrogenation to secondary alcohols with exclusive selectivity and excellent yields. Interestingly, diepoxides also hydrogenated to diols in excellent yields. Notably, internal epoxides did not undergo hydrogenation reactions. Metal-ligand cooperation mediated dihydrogen activation to ruthenium trans-dihydride formation and its preferential reaction with oxygen and less substituted terminal carbon of the epoxide is suggested to be the origin of observed selectivity.

Overall, efficient atom economical and environmentally benign methods are discovered for the range of important products using Ru-MACHO pincer complex (**1**). It is evident

that metal–ligand cooperation stems from aliphatic amine backbone of pincer complex **1**, namely amine-amide metal-ligand cooperation is a powerful approach for bond activation and catalyst design. I believe that future research on amine-amide metal–ligand cooperation would enhance our understanding on fundamental bond activation processes, and also provide new opportunities for the design of sustainable catalytic reactions aimed at solving valuable synthetic problems.



SUMMARY

The thesis provides a detailed study on the catalytic application of Ru-Macho pincer catalyst. Metal-ligand cooperation operative in these catalytic systems and other catalytic applications reported in the literature are introduced in the first chapter. The second chapter describes the Ru-Macho catalyzed α-alkylation of arylmethyl nitriles using various primary alcohols. This green catalytic alkylation reactions in which alcohols are used as alkylating reagents are facilitated the metal-ligand cooperation. Water is the only byproduct in the reaction. On the basis of kinetic and mechanistic studies the possible mechanistic pathway is proposed.

A unique, ruthenium(II) pincer-catalyzed direct olefination nitrile compounds using secondary alcohols are presented in the chapter 3. An extensive substrate scope with arylmethyl nitriles, heteroaryl-methyl nitriles, and aliphatic nitriles as well as cyclic, acyclic, symmetrical, and unsymmetrical secondary alcohols are explored in the reaction, which provided diverse α-vinyl nitriles.

We describe the discovery of a new catalytic reaction, namely, the cross-coupling of secondary alcohols. Cyclic, acyclic, symmetrical, and unsymmetrical secondary alcohols are selectively coupled with aromatic benzylic secondary alcohols to provide β-disubstituted ketones products. The product-induced diastereoselectivity was observed. Kinetic and deuterium labeling experiments suggested that the aliphatic secondary alcohols undergo oxidation reaction faster than benzylic secondary alcohols, selectively assimilating to provide the cross-coupled products. Both olefination of nitrile and cross coupling of secondary alcohols produced H_2 and H_2O as the only byproducts, which make these catalytic protocols greener, atom economical and environmentally benign.

The direct N,N-dialkylation and cyclization of acylhydrazides using alcohols are developed in Chapter 5. This is new catalytic protocol, which provided one-pot synthesis of both symmetrical and unsymmetrical N,N-disubstituted acylhydrazides using variety of primary and secondary alcohols. Products were obtained in with remarkable selectivity and excellent yields. Notably, use of diols resulted in intermolecular cyclization of acylhydrazides. Involvements of hydrazone intermediate in these transformations are established through mechanistic studies.

In chapter 6, ruthenium(II)-catalyzed highly selective Markovnikov hydrogenation of terminal epoxides to secondary alcohols is presented. Benzylic, glycidyl, and aliphatic epoxides as well as diepoxides were subjected hydrogenation to provide secondary alcohols with exclusive selectivity to secondary alcohols. Metal−ligand cooperation-mediated ruthenium trans-dihydride formation and its selective reaction involving oxygen and the less substituted terminal carbon of the epoxide is proposed for the origin of the observed selectivity.

CHAPTER 1

Introduction-Ru-MACHO Pincer Complexes and Their Reactivity

In general, the rate of chemical reactions can be accelerated by increasing the temperature, which requires high energy and therefore, it is very expensive. Moreover, high temperatures may also induce competing side reactions that will diminish yield of the desired products. Alternatively, chemical reactions can be accelerated using a catalyst. A catalyst participates in catalytic cycle by lowering the activation energy of the chemical process and the catalytically active species is regenerated upon completion of each catalytic cycle.[1] In the modern industrial world catalysis is a core area of contemporary science posing major fundamental and conceptual challenges. Catalysis plays an important role in the manufacturing of synthetic fibers and plastics, in petroleum refineries, production of different chemicals and synthesis of medicines and pharmaceuticals. Also, catalysis helps in the suppression of atmospheric pollution through environmental friendly technologies, and in the pursuit of new ways to generate energy.[2] Moreover, catalysis is essential for the sustainable development and is a key technology in achieving sustainability goals in chemical synthesis. Thus, catalysis is considered as pillar of green chemistry in the conservation of our environment.

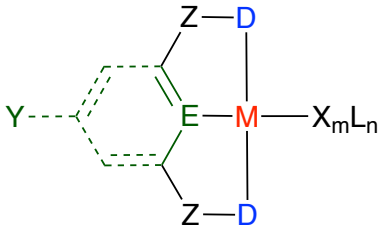
Conventional synthesis involving stoichiometric reactions produce enormous chemical wastes, which are harmful to environment. On contrary, catalytic reactions are developed in environmental friendly green chemistry pathway and generate only minimal or no waste. Transition metal catalyzed activation of unreactive small molecules has become one of the ubiquitous processes in synthetic organic chemistry, such as medicinal chemistry, agrochemical and natural product synthesis. Generally, ligands are employed to stabilize the transition metals via coordination, thus enhancing stability of the resulting complexes even at elevated temperature. In recent times ligands

are designed to participate actively in the catalytic cycle by stabilizing metal center and their unusual oxidation states, referred as non-innocent ligands.

Pincer complexes are the types of coordination complexes of pincer ligands that are tridentate ligands, which enforces meridional geometry upon complexation with metal precursors.[3] In rare cases tridenate ligands attain to facial geometry and those complexes are not considered as pincer complexes.[4] The planar framework of backbone and presence of bulky substituents on donor atoms of pincer ligands cover much coordination sites, which enhance stability of the resulting complexes and enforce selectivity in catalytic reactions. Reactivities of the pincer complexes can be fine tuned by varying the steric and electronic properties of the pincer ligands. Thus, pincer-based complexes possess an exceptional stability versus reactivity. Compared to traditional metal complexes, pincer complexes often present high stability, efficiency, selectivity and functional group tolerance. Considerable progress has been made in the chemistry of pincer complexes after pioneering reports from Shaw and coworkers in the 1970's.[5] Since then pincer complexes and their chemistry underwent exciting developments. Notably, in recent years highly efficient pincer-based catalysts are revealed for activation of unreactive bonds and small molecules.[6] Diverse types of ruthenium pincer complexes were utilized in a range of catalytic transformations.

Pincer complexes consist of a central aryl ring (phenyl, pyridinyl, pyrazinyl, acridinyl, etc.), which is 1,3-disubstituted with two chelating side arms containing donor groups (Figure 1.1).[7] These octahedral complexes attained in meridional geometry in which all three binding sites situated in the same plane and with the remaining three ligands in a plane perpendicular to it, thus offer strong coordination to the resulting pincer complexes. In recent years, also aliphatic backbone containing pincer complexes have been developed.

Figure 1.1. General Structure of Transition Metal Based Pincer Complexes

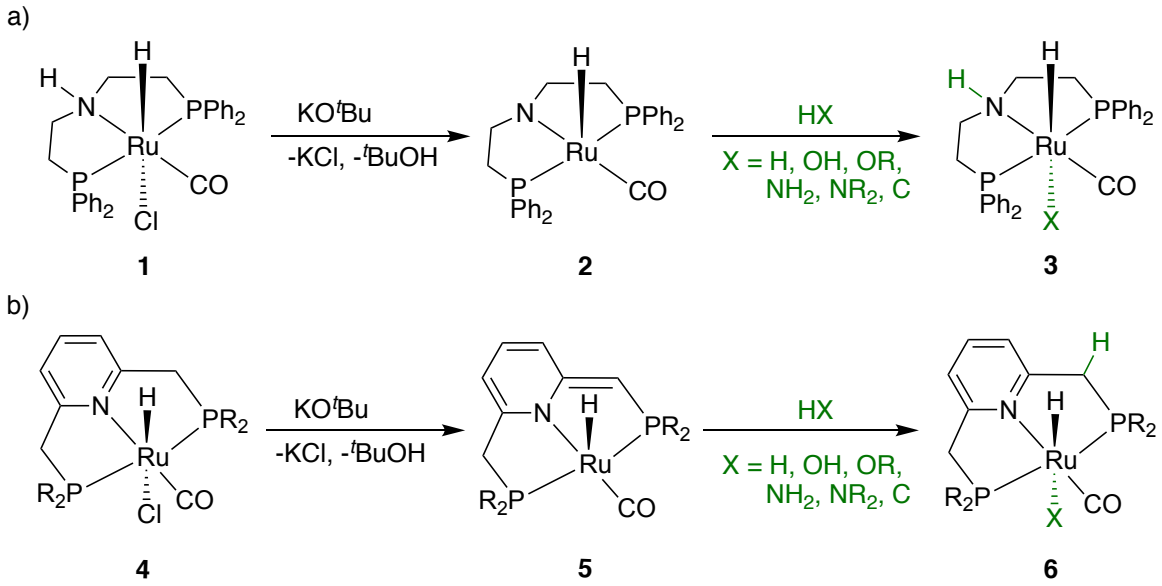


D = PR_2, NR_2, SR, OR, NHC
Z = CR_2, NR, O
E = N, NH, C, B, S, Si, P
M = Ru, Rh, Ir, Pd, Pt, Fe, Mn etc.
X = CO, Halogen, H, H_2, etc.
Y = CO_2-,SO_3-, electron donating, electron withdrawing groups

Bond activation in enzymatic reactions are known to occur involving participation by ligands, which act in cooperation with metal and without change of metal oxidation states.[8] Such cooperative effect is widely found in nature; for example, an enzyme galactose containing Cu(II)-complex can oxidize chemoselectively primary alcohols to aldehydes by a mechanism in which the tyrosinyl radical ion coordinated to Cu(II) center participates in the reaction.[9] Similarly, hemoglobin (Hb) is also capable of exhibiting such cooperative effect, which stimulates in change of spin state for the coordinated iron center and enhances the affinity of Hb towards oxygen.[10] Such metal-ligand cooperation is also observed in transition metal catalyzed reactions and also called as "bifunctional catalysis". Noyori type catalysts contain the transition metal coordinated amine ligand, which acts as a proton (H^+) donor or acceptor and facilitates transformations taking place at the metal center.[11] For example, in the ruthenium catalyzed hydrogenation reactions, in which the activation of H_2 molecule involves both the metal center and amine ligand and concerted transfer of acidic and hydridic hydrogens to an unsaturated substrates to provide hydrogenated products.[12] In recent times, bifunctional catalysis was shown to play an important role in the development of various hydrogenation reactions including asymmetric hydrogenation.

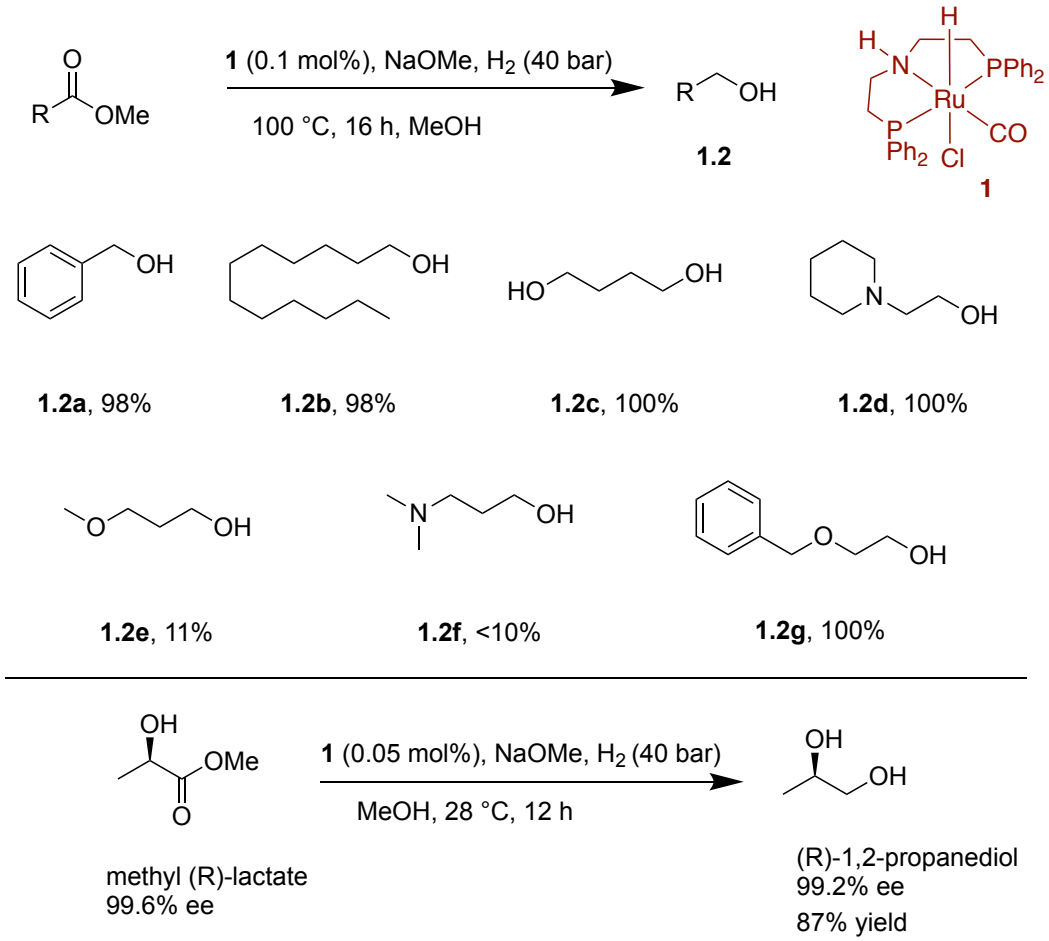
In 2005, Milstein and coworkers observed an unusual reactivity in pincer complexes mainly emanated from metal-ligand cooperation.[3,12] When reacted with base, the ruthenium aliphatic backbone PNP pincer complex **1** undergoes a facile dehydrohalogenation of coordinated amine functionality to generate a reactive and unsaturated intermediate complex **2** in which the backbone amine ligand is transformed to amide ligand. Further, the unsaturated intermediate **2**, which is capable of activating unreactive bonds (like H_2, H_2O, ROH, NH_3, H–NR_2, C–H, etc.) to provide coordinatively saturated complex **3** with regeneration of amine coordination (Scheme 1.1a). Green and sustainable chemical transformations are developed based on amine-amide metal-ligand cooperation operative in complex **1**. Similarly, upon reaction with base, the ruthenium pyridine backbone pincer complex **4** undergoes facile deprotonation at the acidic α-CH_2 protons leading to the formation of dearomatized unsaturated reactive intermediate **5** in which the pyridine motif of the ligand is dearomatized. Further, the dearomatized reactive intermediate **5** can activate unreactive chemical bonds of small molecules and can regenerate aromatized saturated ruthenium complex **6** (Scheme 1.1b). Such a unique metal-ligand cooperation involving ligand aromatization-dearomatization process enabled facile activation of various inert chemical bonds and environmentally benign catalysis.

Scheme 1.1. Different Modes of MLC (a) MLC Based on Amine-Amide (b) MLC Based on Aromatization-Dearomatization



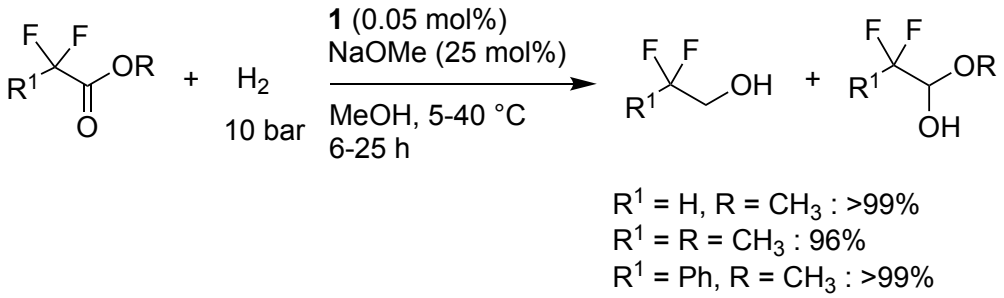
Using Ru-MACHO catalyst **1**, Kuriyama group demonstrated the hydrogenation of esters to alcohols as depicted in Scheme 1.2.[13] Catalyst **1** showed good catalytic activity and a variety of esters have been hydrogenated under mild reaction conditions. Notably, methanol was found to be the most suitable solvent for hydrogenation using the catalyst **1**. Assortments of esters were reduced to corresponding alcohols with good conversion and selectivity in the presence of a base, NaOMe. Substrates containing oxygen and nitrogen functionalities at α-position of the esters didn't impact reactivity. Hydrogenation of methyl (R)-lactate to optically pure (R)-1,2-propanediol was also demonstrated.

Scheme 1.2. Catalytic Hydrogenation of Esters Catalyzed by **1**



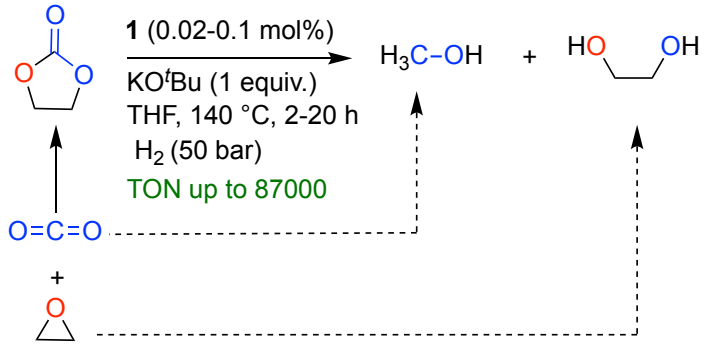
Later, Ikariya and coworkers have reported a practical and selective hydrogenation of α-fluorinated esters to alcohols using catalyst **1** under mild conditions.[14] The α-fluorinated alcohols and fluoral hemiacetal intermediates were also obtained in good to excellent yields. Both aliphatic and aromatic difluro esters were reduced to corresponding alcohols in almost quantitative yields (Scheme 1.3). Aliphatic monofluoro esters were hydrogenated smoothly in good yields but less selectivity was observed.

Scheme 1.3. Practical Hydrogenation of α-Fluorinated Esters Catalyzed by **1**



Using Ru-pincer catalyst **1,** facile catalytic hydrogenation of cyclic carbonates to diols and methanol has been reported.[15] Importantly, from ethylene carbonate facile production of ethylene glycol and methanol was developed, which are important bulk chemicals. Apart from the clean production of diol, efficient chemical utilization of CO_2 was demonstrated, which represents a distinct advantage in terms of sustainability over the omega process, which release back CO_2. Moreover, this catalytic system has also been applied for the utilization of waste poly(propylene carbonate) as a resource to afford 1,2-propylene diol and methanol via hydrogenative depolymerization processes.

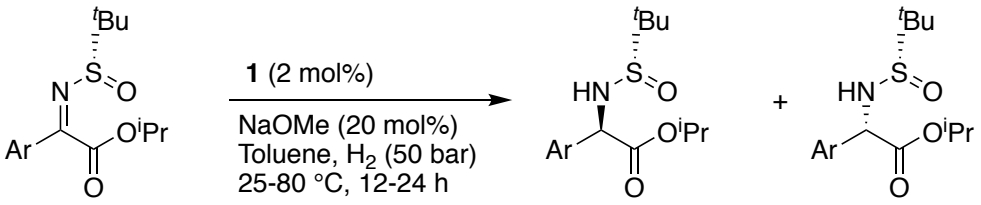
Scheme 1.4. Catalytic Hydrogenation of Cyclic Carbonates



Wei and coworkers have reported highly efficient hydrogenation of N-*tert*-butylsulfinyl

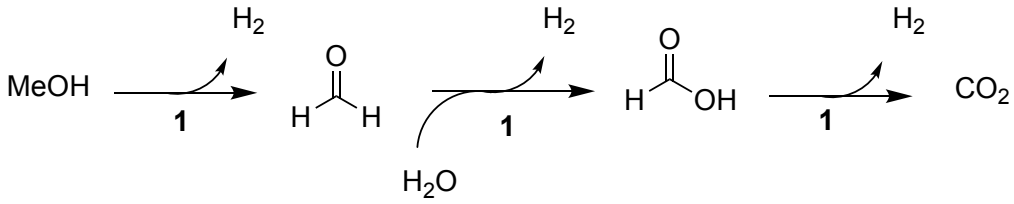
ketimines for the synthesis of aryl glycine derivatives with high yields and diastereoselectivities (Scheme 1.5).[16] In addition, substituted ketimino esters were smoothly hydrogenated with high diastereoselectivities and good to excellent isolated yields. This hydrogenation protocol also applied to synthesis of chiral amino alcohols for practical applications.

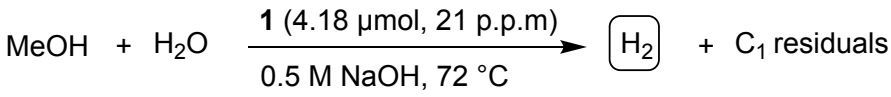
Scheme 1.5. Diastereoselective Hydrogenation of *N-tert* Butylsulfinyl Ketimines



Hydrogen is a potential source of energy and practical hydrogen generation from renewable resources like methanol is attractive. The implementation of sustainable hydrogen production and further hydrogen conversion to energy is called "hydrogen economy". The physical properties of hydrogen gas make the transport and handling of hydrogen gas very difficult. In 2013, Beller and coworkers have developed an efficient low temperature aqueous phase methanol dehydrogenation catalyzed by ruthenium catalyst **1** (Scheme 1.6).[17] Interestingly, compared to previously reported heterogeneous systems low contaminant CO and CH_4 gases were observed. Using complex **1** turnover frequency up to 4700 h^{-1} and turnover number >350,000 were achieved. Advantageously, methanol acts as the hydrogen carrier, which would make the delivery of hydrogen gas in mobile services.

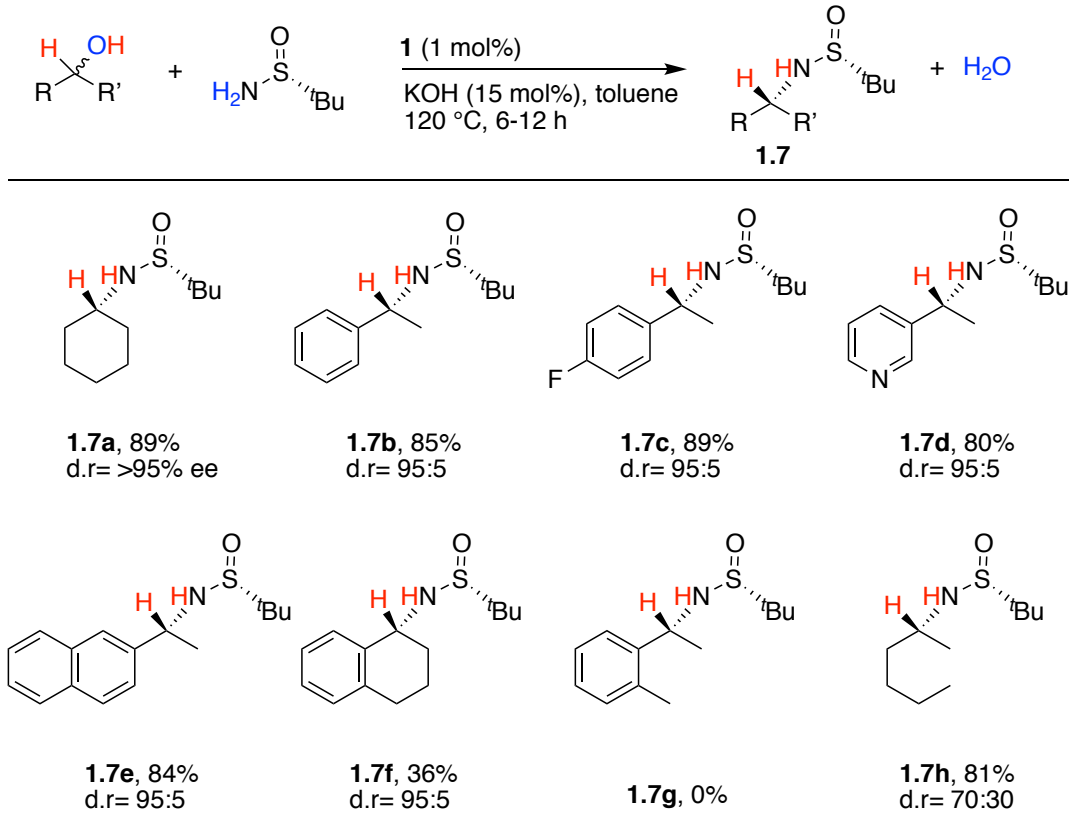
Scheme 1.6. Ru-Catalyzed Aqueous-Phase Methanol Dehydrogenation





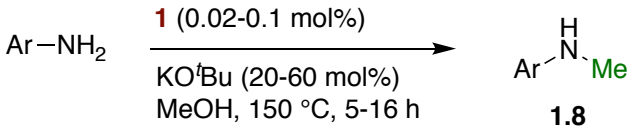
In 2014, Guan and coworkers have reported the formation of α-chiral *tert*-butanesulfinylamines from racemic secondary alcohols and Ellman's chiral tert-butanesulfinamide via borrowing hydrogen methodology.[18] Remarkably, the α-chiral butanesulfinylamine products were isolated in good to excellent yields and most examples displayed >95:5 diastereomeric ratio (d.r) (Scheme 1.7). An assortment of racemic secondary alcohols reacts with Ellman's sulfinamide and resulted chiral amine products in one step. Importantly, this protocol enables access to methyl substituted chiral amines, which are challenging to obtain with methyl organometallic reagents. Notably, this pincer catalyst **1** is sensitive to steric hindrance; thus, ortho-substituted alcohol shows no reactivity under these conditions (Scheme 1.7).

Scheme 1.7. Ru-Catalyzed Diastereoselective Amination Using Racemic Alcohols to Enantiopure Amines

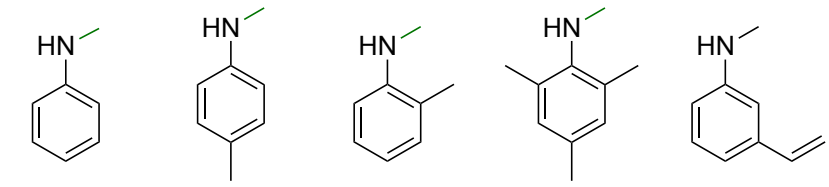


N-Methylated aromatic amines are important compounds in pharmaceuticals, agrochemicals, dyes and fine chemical industries. Ogata and coworkers have developed the selective mono-methylation of aromatic amines using methanol with Ru-MACHO catalyst **1.**[19] A range of substituted aromatic amines was transformed to the corresponding mono-methylated secondary amines in excellent yields (Scheme 1.8). Remarkably, the catalyst loading could be lowered to 0.02 mol % by increasing the base concentration that makes this catalytic protocol is environmentally benign, easily handled and CO tolerant catalyst.

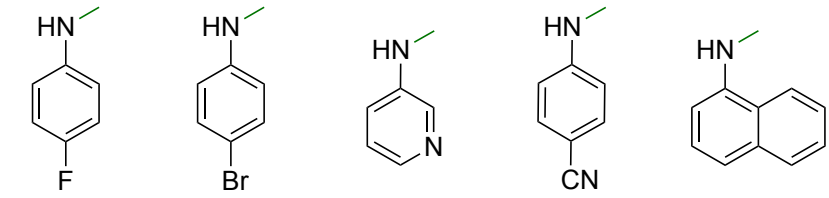
Scheme 1.8. *N*-Monomethylation of Aromatic Amines with Methanol



1.8



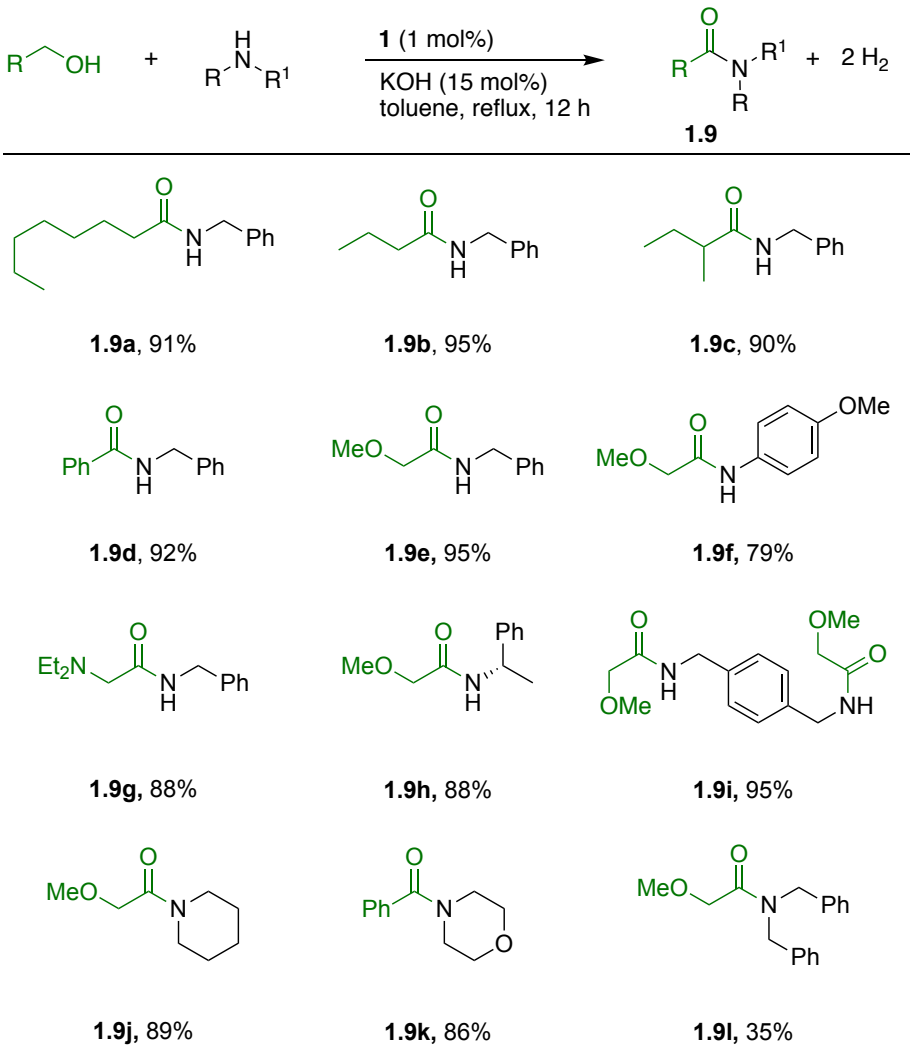
1.8a, 93% **1.8b,** 100% **1.8c,** 91% **1.8d,** 13% **1.8e,** 87%



1.8f, 97% **1.8g,** 87% **1.8h,** 94% **1.8i,** 84% **1.8j,** 65%

Amide molecules are prevalent in natural products, proteins and widely used in synthetic organic chemistry. In this direction, Guan and coworkers have developed Ru-MACHO (**1**) catalyzed formation of amides directly from alcohols and amines via an acceptorless dehydrogenation pathway (Scheme 1.9).[20] Good reactivity was observed with secondary amines for the synthesis of tertiary amides and also optically active amine was utilized to provide optically pure amide product (**1.9h**) without racemization. Reaction of diamines with diols provided diamides in high yields, suggesting the applicability of making of polyamides using this catalyst **1**.

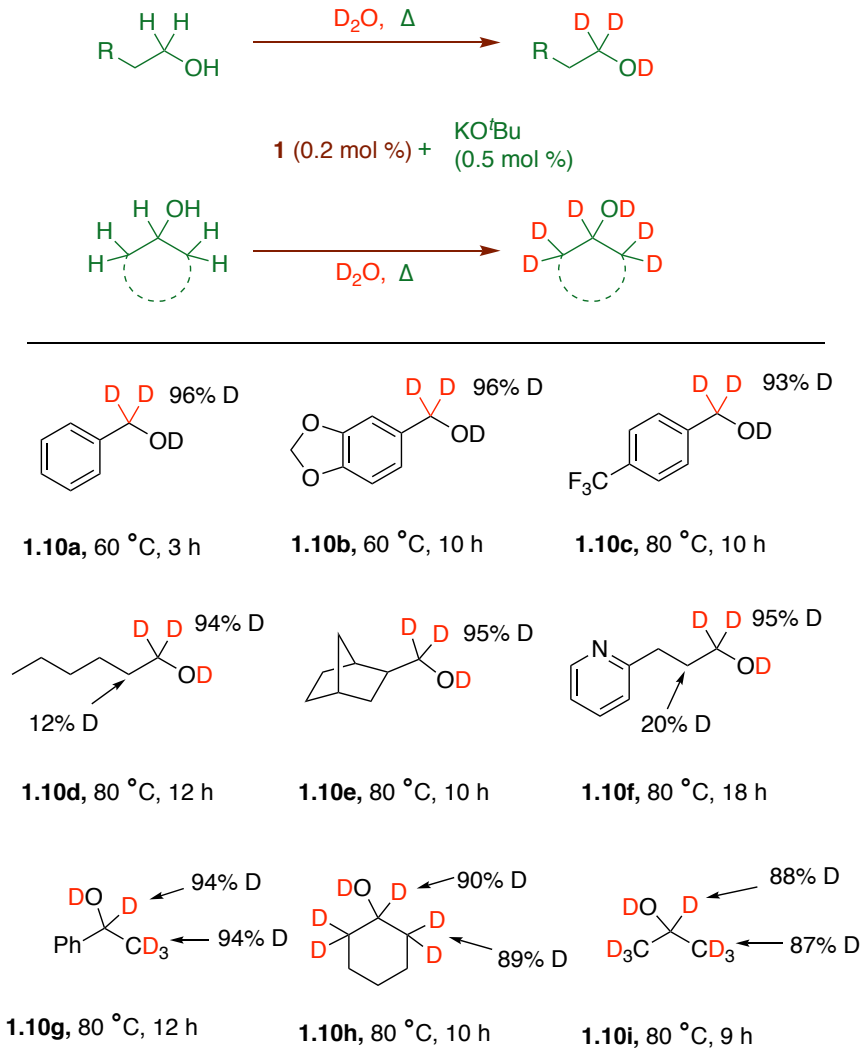
Scheme 1.9. Ru-Catalyzed Construction of Amides via Acceptorless Dehydrogenation



Synthesis of efficient deuterium labeling compounds is an important transformation in current organic chemistry as deuterated pharmaceuticals and bioactive organic molecules have emerged, as valuable targets.[21] Deuterium oxide is a cheapest source of deuterium and green deuterium labeling reagent. Gunanathan and coworkers have demonstrated ruthenium catalyzed highly selective α-deuteration of primary alcohols and α,β-deuteration of secondary alcohols using D_2O as a deuterium source (Scheme 1.10).[22] Notably, with the use of low catalyst load with catalytic amount of base (KO^tBu) and heating at lower temperature provided excellent deuteration of alcohols,

which makes this protocol is practically attractive and environmentally benign. The reaction proceeded via O–D activation of deuterium oxide and alcohols by the Ru-MACHO catalyst (**1**), which subsequently dehydrogenated to corresponding carbonyl compounds through amine-amide metal-ligand cooperation. While the hydrogenation of carbonyl motif provided selective α-deuteration, the β-deuteration perhaps occurred via keto-enol tautomerization.

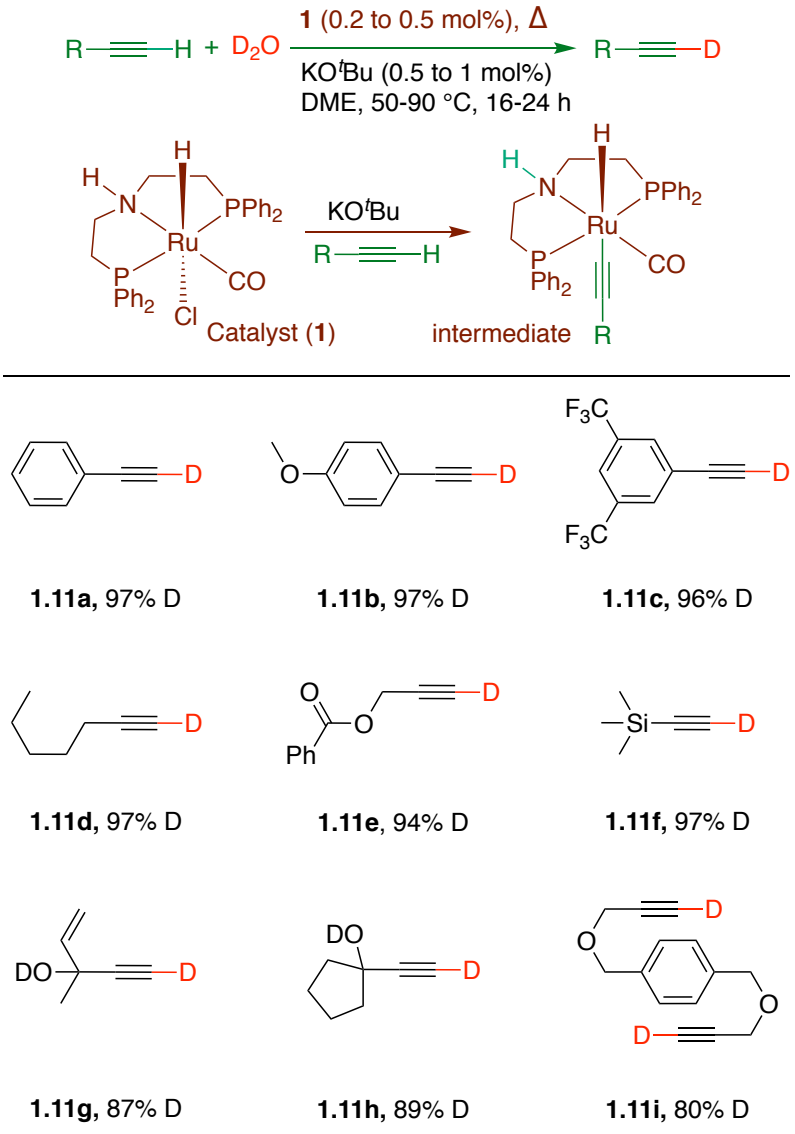
Scheme 1.10. Ru-Catalyzed Selective α-and α,β-Deuteration of Alcohols Using D_2O



Deuterated terminal alkynes are used as highly reliable probe in mechanistic investigations. Recently, using ruthenium pincer catalyst **1**, an efficient catalytic method

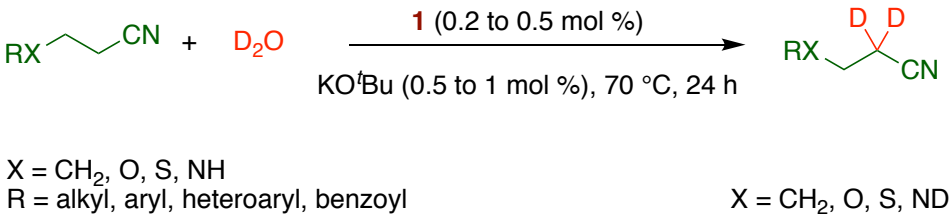
for the synthesis of mono-deuterated terminal alkynes using deuterium oxide has been reported.[23] Interestingly, terminal alkynes were chemoselectively deuterated in presence of other sensitive functional groups (Scheme 1.11). Amine-amide metal-ligand cooperation is operative in catalyst **1**, the reaction proceeded via Ru-acetylide intermediates and H/D exchange of backbone amine donor on catalyst **1** with deuterium oxide leads to selective deuteration of terminal alkynes. Notably, this catalytic protocol needs low catalyst load, catalytic amount of base and devoid of any deleterious side reactions.

Scheme 1.11. Selective Synthesis of Mono-Deuterated Terminal Alkynes



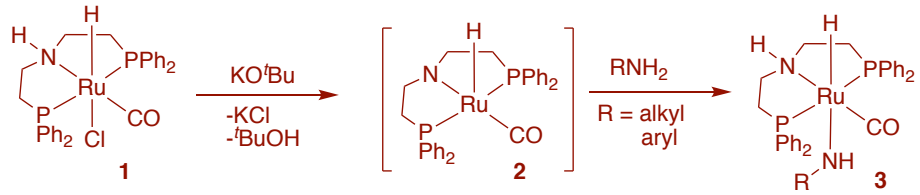
Recently, an efficient and highly selective α-deuteration of aliphatic nitriles using D_2O catalyzed by Ru-MACHO (**1**) has been reported.[24] Using low catalyst load of **1** under mild reaction conditions an efficient α-deuteration of aliphatic nitriles in presence of other reactive functional groups was successfully achieved. Amine-amide metal-ligand cooperation operative in catalyst **1** facilitate the selective [2+2] cycloadduct formation of nitriles followed by imine-enamine tautomerization and H/D exchange between enamine intermediate and D_2O, leading to the selective α-deuterated nitriles was proposed as possible reaction mechanism. Notably, this method can be applied for the large-scale synthesis of acetonitrile-D_3 and other useful deuterated nitrile compounds.

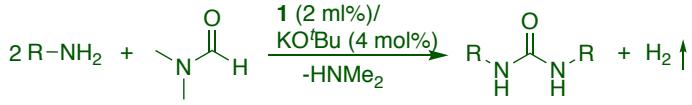
Scheme 1.12. Ru-catalyzed selective α-deuteration of aliphatic nitriles using D_2O



Gunanathan and coworkers have reported activation of N–H bond of amines by ruthenium pincer complex **1**.[25] Catalytic activation of formyl C–H of DMF was observed in situ, which resulted in situ formation of CO to synthesis urea derivatives with liberation of hydrogen. This method avoids the direct use of fatal CO gas. Both symmetrical and unsymmetrical urea derivatives were synthesized in good to excellent yields (Scheme 1.13). The catalytic carbonylation of amines occurred at low temperature and the *N*-formamide intermediates were isolated. Further, consecutive addition of amines to in situ formed formamide intermediates for the synthesis of unsymmetrical urea derivatives was successfully achieved.

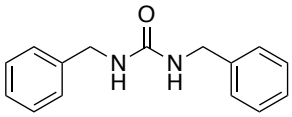
Scheme 1.13. Ru-Catalyzed Urea Synthesis by N−H Activation of Amines



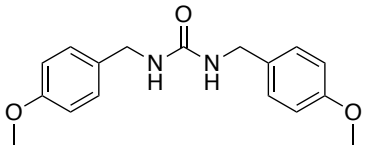


R = aryl, benzyl, alkyl

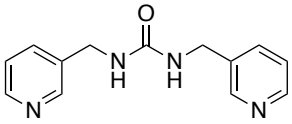
1.13



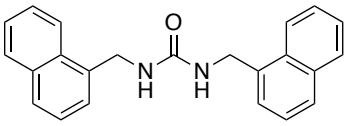
1.13a, 91%



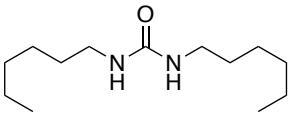
1.13b, 91%



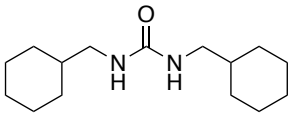
1.13c, 77%



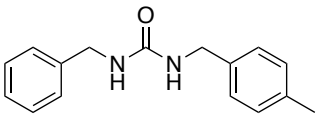
1.13d, 91%



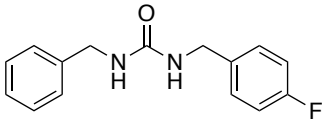
1.13e, 90%



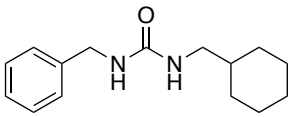
1.13f, 99%



1.13g, 79%



1.13h, 71%



1.13i, 76%

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(24) "The Ruthenium-Catalyzed Selective Synthesis of mono-Deuterated Terminal Alkynes", Chatterjee, B.; Gunanathan, C., *Chem. Commun.,* **2016**, *52*, 4509-4512.

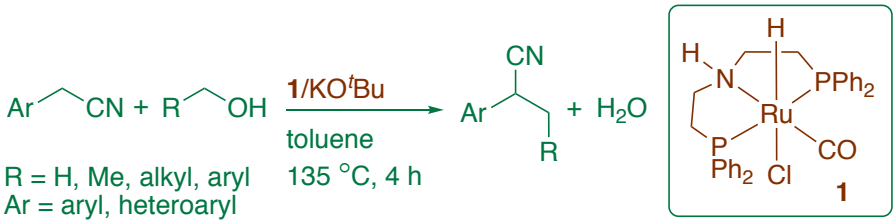
(25) "Ruthenium-Catalyzed Selective α-Deuteration of Aliphatic Nitriles Using D_2O", Krishnakumar, V.; Gunanathan, C., *Chem. Commun.,* **2018**, *54*, 8705-8708.

(26) “Ruthenium-Catalyzed Urea Synthesis by N–H Activation of Amines”, Krishnakumar, V.; Chatterjee, B.; Gunanathan, C., *Inorg. Chem.,* **2017**, *56*, 7278-7284.

CHAPTER 2

Facile Ruthenium(II)-Catalyzed α-Alkylation of Arylmethyl Nitriles Using Alcohols Enabled by Metal-Ligand Cooperation

2.1 ABSTRACT



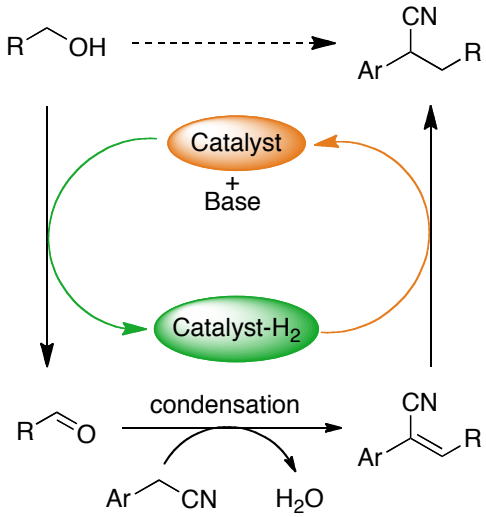
A ruthenium(II)-catalyzed facile α-alkylation of arylmethyl nitriles using alcohols is reported. Ruthenium pincer catalyst serves as an efficient catalyst for this atom-economical transformation that undergoes alkylation via borrowing hydrogen pathways, producing water as the only by-product. Arylmethyl nitriles containing different substituents can be effectively alkylated using diverse primary alcohols. Notably, using ethanol and methanol as alkylating reagents, challenging ethylation and methylation of arylmethyl nitriles were performed. Secondary alcohols do not undergo alkylation reaction. Thus, phenylacetonitrile was chemoselectively alkylated using primary alcohols in the presence of secondary alcohols. Diols provided mixture of products. When deuterium labeled alcohol was used, expected deuterium transposition occurred, providing both α-alkylation and α-deuteration of arylmethyl nitriles. Consumption of nitrile was monitored by GC, which indicated the involvement of first order kinetics. Plausible mechanistic pathways are suggested on the basis of experimental evidences. The ruthenium catalyst reacts with base and generates an unsaturated intermediate, which further reacts with both nitriles and alcohols. While nitrile is transformed to enamine via [2+2] cycloaddition, alcohol is oxidized to aldehyde. The metal bound enamine-adduct reacts with aldehyde via conjugate addition

resulting in ene-imine adduct, which perhaps undergo direct hydrogenation by the Ru-dihydride intermediate, produced from alcohol oxidation. However, in situ monitoring of the reaction mixture confirmed the presence of unsaturated vinyl nitrile in the reaction mixture in minor amounts (10%), indicating the possible dissociation of ene-imine adduct during the catalysis, which may further be hydrogenated to provide the α-alkylated nitriles. Overall, the efficient α-alkylation of nitriles using alcohols can be attributed to the amine-amide metal-ligand cooperation that is operative in ruthenium pincer catalyst, which enables all the catalytic intermediates to remain in +2 oxidation state throughout the catalytic cycle.

2.2 INTRODUCTION

Alkylation reactions that can result in formation of C–C bonds are an important transformation in organic synthesis. Conventional alkylation reactions involve toxic alkyl halides and use of stoichiometrically excess amount of base, which also produce salt waste. Advancement in homogeneous catalysis and catalyst design led to the development of an alternative protocol for alkylation reactions in which alcohols are used as alkylating partners.[1] These transformations are highly atom-economical and environmentally benign as they release water as the only by-product. They are often referred as "borrowing hydrogen" and also as "hydrogen autotransfer" methods as the catalytically liberated hydrogen from the oxidation of alcohols is later reinstalled in the unsaturated intermediates that form via condensation reactions resulting in redox neutral-alkylation reactions (Scheme 2.1).[1,2]

Scheme 2.1 Selective Catalytic α-Alkylation of Arylmethyl Nitriles Enabled by Borrowing Hydrogen Concept



From this perspective, catalytic alkylation of nitriles using alcohols gains prominent significance as nitriles serve as important compounds from which a number of carboxylic derivatives can be easily derived and widely used in fine chemical industry and also in synthesis of biologically active compounds.[3] Grigg and coworkers reported the pioneering ruthenium mediated α-alkylation of acetonitriles in 1981.[4] Later, iridium[5,6,7] and rhodium[8,9] based catalytic protocols were developed for this transformation. Despite the well-known catalytic activity of ruthenium in borrowing hydrogen strategies,[1] its application in α-alkylation of nitriles is poorly documented. Kaneda and coworkers developed hydrotalcite supported ruthenium heterogeneous catalysts, which required prolonged heating at high temperature (180 °C, 20-30 h) in addition to the use of alkylating alcohols as solvents (2 mL alcohols for 1 mmol of nitriles).[10] Ruthenium(II) half-sandwich complexes developed for this transformation exhibited poor catalytic activity; provided partial hydrogenation, resulting in presence of unsaturated vinyl nitrile predominantly in mixture of products.[11] Fukuyama and Ryu

group also reported the ruthenium catalyzed alkylation of acetonitrile using primary alcohols.[12] Recently, the groups of Esteruelas and Yus reported an osmium(II) half-sandwich complex catalyzed alkylation of benzyl nitriles by benzyl alcohols, which required removal of in situ formed water using Dean-Stark method.[13] Invariably, in all these homogeneous catalytic reactions sub-stoichiometric to stoichiometrically excess amount of various bases (20 to 110%) were also used.

The general problem in this method is the water, which is formed in situ, that can effectively hydrolyze the unstable intermediates to regenerate aldehydes. In addition, the homogeneous catalyst should be compatible with water. The chemoselectivity of the overall reaction also depends on the efficient hydrogenation of vinyl nitriles. Due to these challenges, in general, α-alkylated nitriles are still being synthesized using alkyl halides with stoichiometrically excess amount of base.[14] Thus, an efficient catalyst for the α-alkylation of arylmethyl nitriles is highly desirable. N–H activation of amines and formyl C–H activation of DMF by ruthenium(II) pincer complex **1** (Ru-MACHO) was established recently, which are utilized in the catalytic synthesis of urea derivatives using DMF as a CO surrogate.[15] We have also disclosed the highly efficient and selective deuteration of terminal alkynes,[16] α- and α,β-deuteration of primary and secondary alcohols,[17] upon using deuterium oxide, catalyzed by complex **1**. In these studies, we have established the sp-C–H activation of terminal alkynes and O–H activation of alcohols and water by complex **1** upon deprotonation by a base. As the work in our laboratory confirmed that complex **1** is very much compatible with water, I have envisaged employing complex **1** for the catalytic alkylation of nitriles using alcohols. Herein, I describe ruthenium pincer complex [(PNP^{Ph})RuHCl(CO)] **1** (PNP =

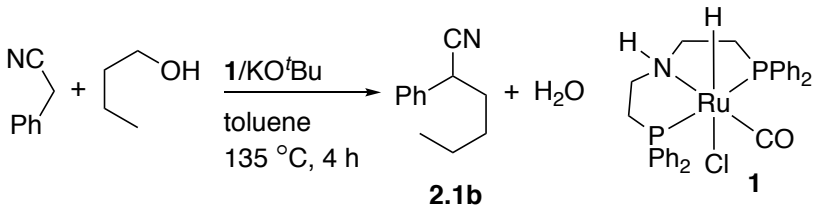
bis(2-(diphenylphosphino)ethyl)amine)[18] catalyzed highly efficient α-alkylation of arylmethyl nitriles using alcohols.

2.3 RESULTS AND DISCUSSIONS

In continuation of our efforts in the development of atom-economical catalytic transformations using the ruthenium pincer complex-catalyzed environmentally benign processes, I have envisaged to develop a facile catalytic method for the alkylation of arylmethyl nitriles using alcohols as alkylating partner. At the outset of our work, phenylacetonitrile and 1-butanol were selected as benchmark substrates to find the optimal reaction conditions for the ruthenium pincer complex **1** catalyzed alkylation reactions and the results are summarized in Table 2.1. Thus, reaction of 1 mol% of ruthenium pincer catalyst **1**, base (2 mol%), phenylacetonitrile (1 mmol) and 1-butanol (5 mmol) in toluene solvent at 135 °C (entry 1, Table 2.1) was performed. The desired product of 2-phenylhexanenitrile was isolated in 98% yield. Similar outcome was obtained when only two equivalents of alcohol (2 mmol) were used in the reaction (entry 2, Table 2.1). Upon reducing the reaction temperature to 110 °C, both the conversion and yield of this alkylation reaction were decreased (80% and 78%, respectively, entry 3, Table 2.1). Further, decreasing the equivalents of 1-butanol also resulted in diminished conversion and yield of the product (entries 4-5). When the catalyst load was lowered to 0.5 mol% with two equivalents of 1-butanol, alkylation of phenylacetonitrile provided the quantitative conversion and 98% yield of the product after 4 h (entry 6). From the above condition (entry 6), further lowering of the catalyst loads (0.3 mol% and 0.1 mol%) resulted in decreased yields (entries 7-8, Table 2.1). Finally, when control experiments were carried out without catalyst **1** in the presence of base (entry 9, Table 2.1) and in the absence of both catalyst and base (entry 10, Table

2.1), no product was found, implying that a catalyst is essential for alkylation of nitriles using alcohols.

Table 2.1 Optimization of Reaction Conditions for the α-Alkylation of Arylmethyl Nitriles[a]

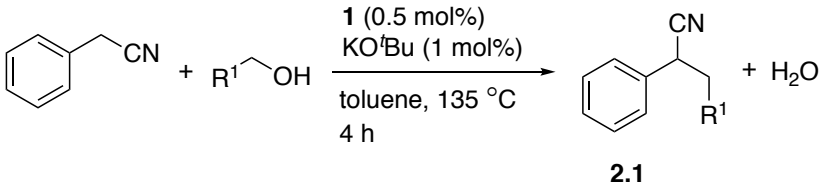


entry	**1** (mol%)	base (mol%)	alcohol (equiv.)	conv. (%)[b]	yield (%)[c]
1	1	2	5	>99	98
2	1	2	2	>99	98
3[d]	1	2	2	80	78
4	1	2	1.2	80	72
5	1	2	1.5	83	78
6	0.5	1	2	>99	98
7[e]	0.3	0.6	2	>99	90
8[e]	0.1	0.2	2	88	76
9[f]	-	1	2	-	-
10[f]	-	-	2	-	-

Reaction conditions: [a]Phenylacetonitrile (1 mmol), butanol (2 mmol), catalyst, base and toluene (1.5 mL) were heated at 135 °C for 4 h under the nitrogen flow. [b]Conversion of nitriles; determined by GC using mesitylene as an internal standard. [c]Isolated yields after column chromatography. [d]Heated at 110 °C. [e]Minor amount of alkene formation was also observed. [f]Reaction performed up to 24 h.

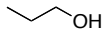
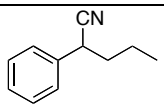
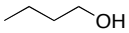
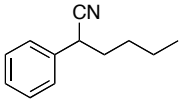
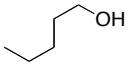
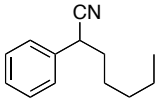
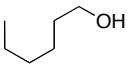
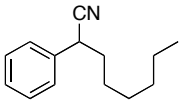
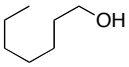
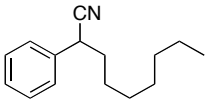
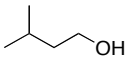
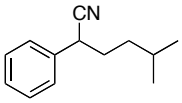
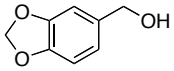
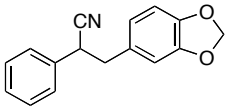
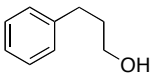
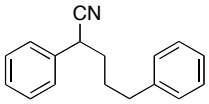
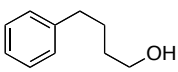
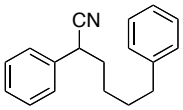
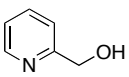
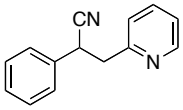
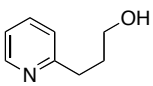
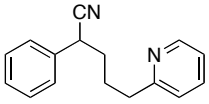
With the optimized condition in hand, I have examined the reaction of an assortment of alcohols using phenylacetonitrile (Table 2.2). In general, quantitative conversions occurred with low loading of catalyst **1** (0.5 mol%) leading to the efficient oxidation of alcohols and subsequent C–C bond formation. Use of low boiling alcohol, 1-propanol (bp-97 °C) provided the 2-phenylpentanenitrile (**2.1a**) in 91% yield (95% conversion, entry 1, Table 2.2). Further, a series of non-activated alcohols such as 1-butanol, 1-pentanol, 1-hexanol, 1-heptanol and 3-methyl-1-butanol were reacted with 2-phenylacetonitrile. These alcohols resulted in quantitative conversions and provided the corresponding 2-phenylalkylnitriles (**2.1b-2.1f**) in good isolated yields of 95-98% (entries 2-6, Table 2.2). Next I have investigated the reaction of electron rich piperonyl alcohol, which also provided the quantitative conversion and 95% yield of the alkylated product **2.1g** (entry 7, Table 2.2). Linear alcohols appended with aryl and heteroaryl ring systems in general provided excellent yields (**2.1h-2.1k**) with quantitative conversions (entries 8-11, Table 2.2); however, 2-pyridine methanol provided only 66% conversion and the alkylation product **2.1j** was obtained in 61% yield (entry 10, Table 2.2). This low conversion and yield with 2-pyridine methanol may be due to its chelation properties, which perhaps diminish the catalyst reactivity.

Table 2.2 Ruthenium-Catalyzed α-Alkylation of Phenylacetonitrile with Primary Alcohols[a]



2.1

entry	alcohol	product	conv. (%)[b]	yield (%)[c]

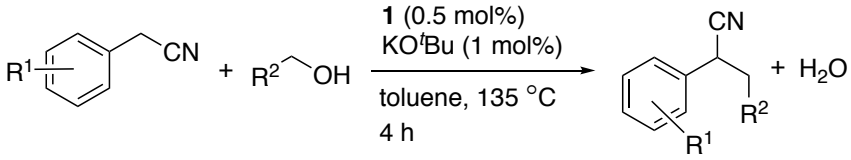
1			**2.1a**	95	91
2			**2.1b**	>99	98
3			**2.1c**	>99	98
4			**2.1d**	>99	98
5			**2.1e**	>99	95
6			**2.1f**	98	96
7			**2.1g**	>99	95
8			**2.1h**	>99	98
9			**2.1i**	>99	97
10			**2.1j**	66	61
11			**2.1k**	>99	98

Reaction conditions: [a]Phenylacetonitrile (1 mmol), alcohol (2 mmol), toluene (1.5 mL) and catalyst **1** (0.5 mol%), KO^{t}Bu (1 mol%) were heated at 135 °C under the flow of nitrogen atmosphere for 4 h. [b]Conversion of nitrile; determined by GC using mesitylene as an internal standard. [c]Isolated yield after column chromatography.

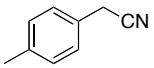
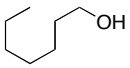
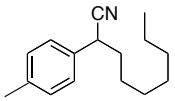
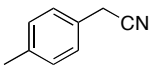
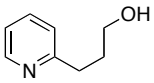
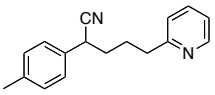
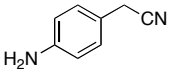
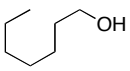
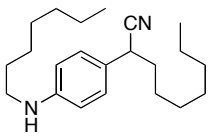
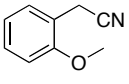
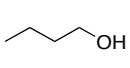
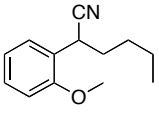
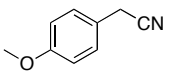
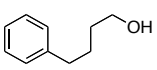
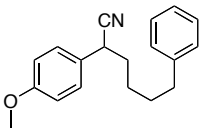
Then, I have explored the scope of different arylmethyl nitriles in the catalytic α-alkylation reactions using different alcohols (Table 2.3). Substrates bearing various electron-donating substituents on the aryl ring of nitriles were well tolerated to afford the α-alkylated nitriles in excellent yields. When 4-methylphenyl acetonitrile reacted with 1-heptanol and 3-(pyridine-2-yl)propanol in the presence of catalyst **1** (0.5 mol%), quantitative conversion of nitrile was observed and the corresponding α-alkylated products (**2.2a, 2.2b**) were obtained in excellent yield and selectivity (entries 1,2, Table 2.3). Interestingly, with use of only two equivalents of 1-hexanol, 2-(4-aminophenyl)acetonitrile exhibited both α-alkylation and *N*-alkylation to provide the dialkylated product in 97% yield with complete selectivity (entry 3, Table 2.3), indicating the facile catalytic *N*-alkylation under this condition. Mono, di and trimethoxy substituents containing benzylnitriles were reacted with various alcohols (entries 4-12, Table 2.3). Apart from the reaction of 3-methyl butanol with piperonyl nitrile (92% conversion, 90% yield, entry 9, Table 2.3), quantitative conversion of nitriles was observed with all the substrates and the corresponding α-alkylated benzylnitriles (**2.2d-2.2l**) were isolated in 96-98% yields. Notably, the electron withdrawing groups on benzene ring of arylmethyl nitriles slightly diminish the reactivity. Thus, when 2-(4-bromophenyl)acetonitrile and 2-(2,4-dichlorophenyl)acetonitrile were reacted with 1-butanol and 1-hexanol, 92% and 85% conversion of nitriles were observed and the corresponding α-alkylated products **2.2m**

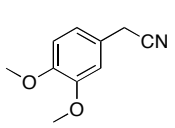
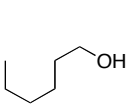
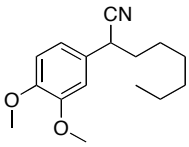
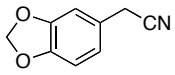
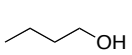
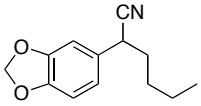
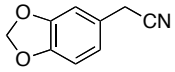
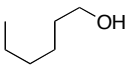
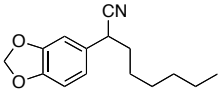
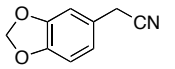
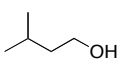
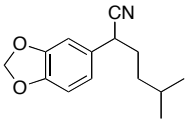
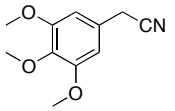
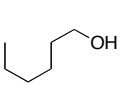
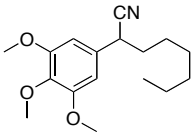
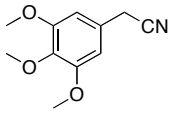
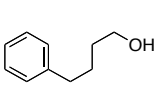
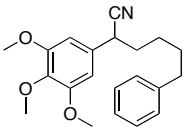
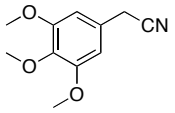
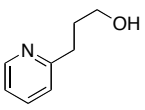
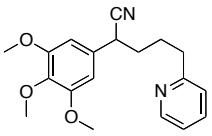
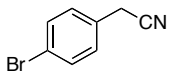
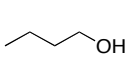
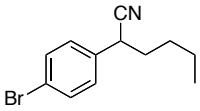
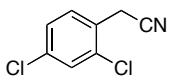
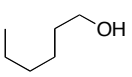
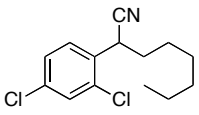
and **2.2n** were isolated in 90% and 82% yields, respectively (entries 13,14, Table 2.3). Unlike the reaction of 2-pyridine methanol (entry 10, Table 2.2), 2-pyridine acetonitrile was quantitatively converted to provide the α-alkylated product **2.2o** in 96% yield (entry 15, Table 2.3).

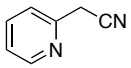
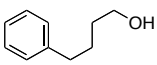
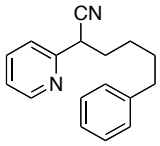
Table 2.3 Ruthenium-Catalyzed α-Alkylation of Arylmethyl Nitriles with Primary Alcohols[a]



2.2

entry	nitrile	alcohol	product		conv (%)[b]	yield (%)[c]
1				**2.2a**	>99	93
2				**2.2b**	>99	97
3				**2.2c**	>99	97
4				**2.2d**	>99	96
5				**2.2e**	>99	96

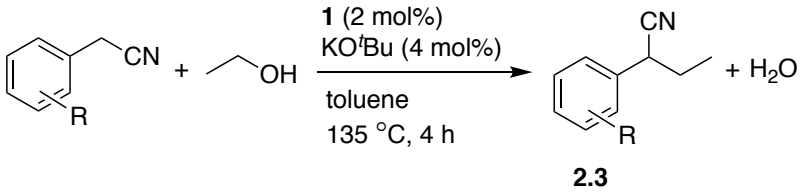
6				**2.2f**	>99	97
7				**2.2g**	>99	96
8				**2.2h**	>99	96
9				**2.2i**	92	90
10				**2.2j**	>99	97
11				**2.2k**	>99	98
12				**2.2l**	>99	96
13				**2.2 m**	92	90
14				**2.2n**	85	82

15				**2.2o**	>99	96

Reaction conditions: [a]Nitrile (1 mmol), alcohol (2 mmol), toluene (1.5 mL), catalyst **1** (0.5 mol%) and KO^{t}Bu (1 mol%) were heated at 135 °C under the flow of nitrogen atmosphere for 4 h. [b]Conversion of nitriles; determined by GC using mesitylene as an internal standard. [c]Isolated yield of products after column chromatography.

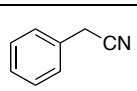
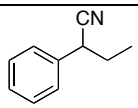
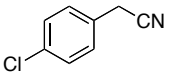
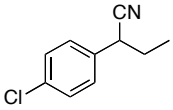
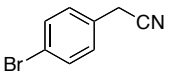
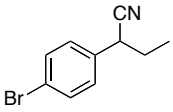
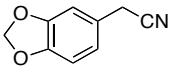
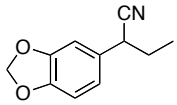
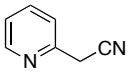
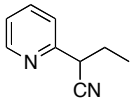
To extend the scope of alcohols employed in the ruthenium catalyzed α-alkylation of nitriles, ethanol and methanol were investigated as potential primary alcohols. First, on the basis of optimized condition, I have performed reaction of α-alkylation of different nitriles using two equivalents of ethanol, which provided the products in poor yields. Then I have used five equivalents of ethanol, which provided efficient α-ethylation of all arylacetonitriles (entries 1-5, Table 2.4) and the corresponding ethylated products (**2.3a-2.3e**) were isolated in good yields.

Table 2.4 Ruthenium-Catalyzed α-Ethylation of Arylmethyl Nitriles Using Ethanol[a]



2.3

entry	nitrile	product	conv. (%)[b]	yield (%)[c]

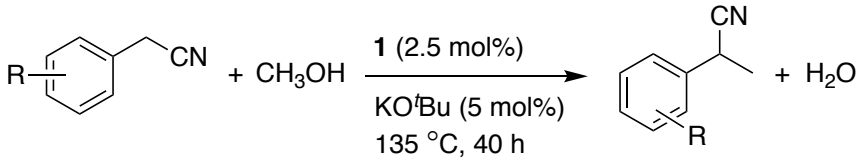
1			**2.3a**	88	83
2			**2.3b**	74	66
3			**2.3c**	87	78
4			**2.3d**	79	66
5			**2.3e**	>99	82

Reaction conditions: [a]Nitrile (1 mmol), ethanol (5 mmol), toluene (1.5 mL), catalyst **1** (2 mol%) and KO^{t}Bu (4 mol%) were heated at 135 °C under the flow of nitrogen atmosphere for 4 h. [b]Conversion of nitriles; determined by GC using mesitylene as an internal standard. [c]Isolated yield of products after column chromatography.

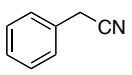
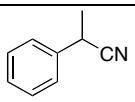
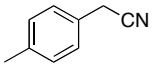
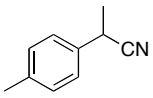
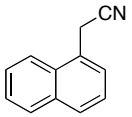
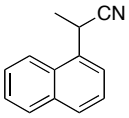
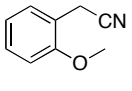
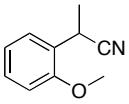
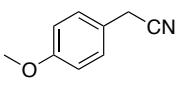
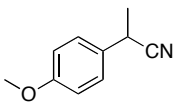
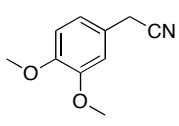
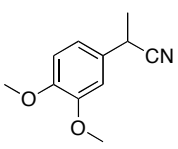
Next, I have investigated the challenging methylation of nitrile compounds using methanol and ruthenium catalyst **1**. Due to the lower boiling point and difficulty associated with the oxidation of methanol, methylation reaction using methanol is rarely documented.[19] In general, methylation is an important transformation in chemical synthesis, which is invariably achieved by using methyl iodide or toxic dimethyl sulfate reagents.[14] Reaction of various arylmethyl nitriles with methanol (2 mL) and catalyst **1** (2.5 mol%) under the closed condition for a prolonged time (40 h), resulted in good conversion and provided the corresponding methylated products in moderate to good

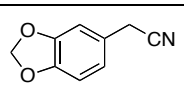
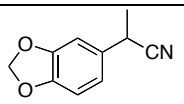
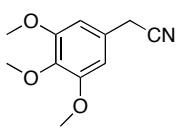
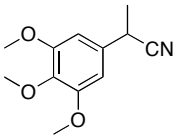
yields of 40-83% (Table 2.5). Unlike the α-alkylation of long chain alcohols, selectivity for both α-ethylation and α-methylation of nitriles decreased to some extent, perhaps due to longer reaction time resulting in other side reactions.

Table 2.5 Ruthenium-Catalyzed α-Methylation of Arylmethyl Nitriles Using Methanol[a]



2.4

entry	nitrile	product		conv. (%)[b]	yield (%)[c]
1			**2.4a**	94	83
2			**2.4b**	58	48
3			**2.4c**	67	44
4			**2.4d**	55	44
5			**2.4e**	58	40
6			**2.4f**	56	42

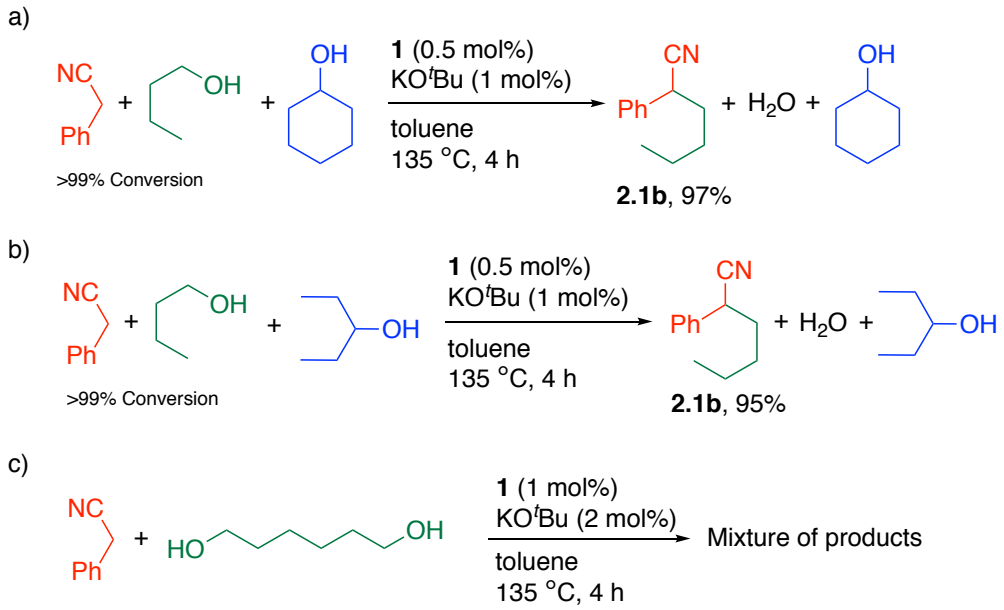
7			**2.4g**	72	61
8			**2.4h**	95	82

Reaction conditions: [a]Nitrile (1 mmol), methanol (2 mL), catalyst **1** (2.5 mol%) and KO^{t}Bu (5 mol%) were heated for 40 h at 135 °C in a sealed pressure tube. [b]Conversion of nitrile; determined by GC using toluene as an internal standard. [c]Isolated yield of products after column chromatography.

Such α-alkylation of arylmethyl nitriles occurs only with primary alcohols. When secondary alcohols such as 1-phenylethanol and cyclohexanol were employed as alkylating partners under the optimized condition, no alkylation products were observed. Thus, chemoselective alkylation by primary alcohols in the presence of secondary alcohols was explored. Phenylacetonitrile (1 equivalent) was reacted with 1-butanol and cyclohexanol (each 2 equivalents) in the presence of catalyst **1** (0.5 mol%) and KO^{t}Bu (1 mol%) in which quantitative conversion of nitrile was observed to provide the exclusive formation of 2-phenylhexanenitrile (**2.1b**) (97% isolated yield, Scheme 2.2a). Cyclohexanol remained unreacted and recovered quantitatively from column chromatographic purification of the reaction mixture. Similar experiments using 3-pentanol also provided almost identical results (Scheme 2.2b). When diols such as 1,3-propanediol and 1,6-hexanediol were subjected to the alkylation of phenylacetonitrile, a mixture of products was formed (Scheme 2.2c). Diols having both primary and secondary alcohols functionalities were also employed in the catalytic α-

alkylation of phenylacetonitrile. While no reaction was observed with 1,2-propanediol, 1,3-butanediol provided a mixture of products.

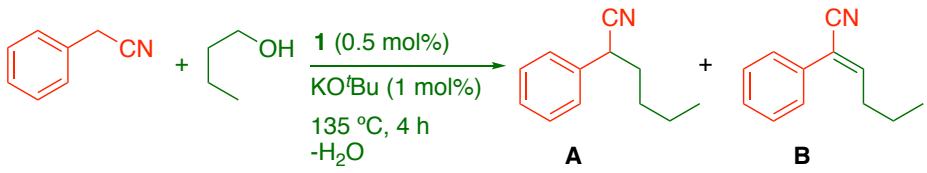
Scheme 2.2 Ruthenium-Catalyzed Chemoselective α-Alkylation of Phenylacetonitrile



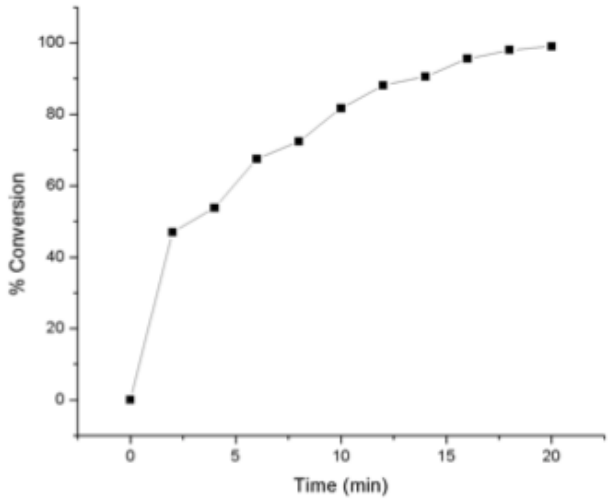
Mechanistic Investigations: To understand the reaction mechanism of the selective α-alkylation of arylmethyl nitriles using alcohols catalyzed by complex **1**, I have carried out in situ monitoring of the reactions progress and labeling studies. GC monitoring of the reactions progress for phenylacetonitrile with 1-butanol catalyzed by **1** (0.5 mol%), confirmed the complete conversion of nitrile substrate in 20 min. Reaction followed first order kinetics with respect to consumption of nitriles (Figure 2.1a). The formation of α-alkylated product and an unsaturated intermediate were also observed in GC and ^{1}H NMR of the reaction mixture. ^{1}H NMR analysis of the reaction mixture showed a triplet signal at δ = 6.75 ppm (J = 7.8 Hz) indicating formation of olefin intermediate, whereas the alkylated product displayed the characteristic doublet of doublets at δ = 3.69 ppm ($^3J_1$ = 6.48 Hz, $^3J_2$ = 1.8 Hz, Figure 2.4). The progress of the catalytic α-

alkylation reaction was rapid; almost 90% of the product formation was observed in just 20 min on GC (Figure 2.1b), while 10% unsaturated intermediate was present in solution. Further completion of the α-alkylation reaction occurred at a slow rate over a 4 h period.

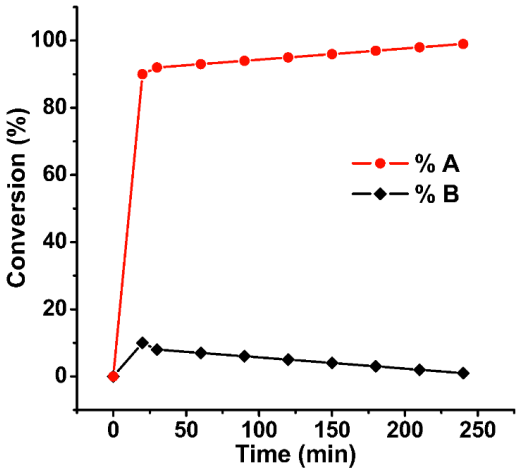
Figure 2.1 GC Monitoring of the Reaction Progress: α-Alkylation of Phenylacetonitrile Catalyzed by **1** using 1-Butanol.



a)



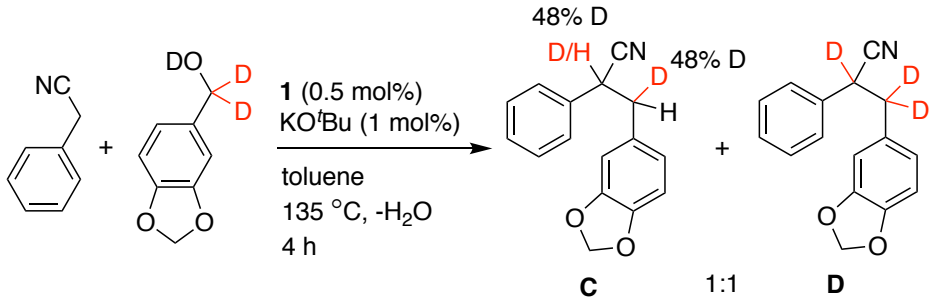
b)



a) Conversion of 2-phenylacetonitrile. b) Formation of α-alkylation product **A** and unsaturated intermediate **B** in the reaction mixture.

The deuterium labeling experiment confirmed the expected deuterium incorporation at the α-position of alkylation product. Upon reaction of phenylacetonitrile with piperonyl alcohol-D_3 catalyzed by **1** under standard optimized conditions, α-alkylated isotopomers **C** and **D** were obtained in 1:1 ratio, indicating that the dideuterium liberated upon catalytic oxidation of piperonyl alcohol- D_3 was predominantly reinstalled in the unsaturated intermediate, which resulted from the aldol condensation reaction. The incorporation of protons in the labeling experiment indicate the H/D exchange between the pincer backbone ND/H_2O and Ru-D/H_2O (Scheme 2.3).[17]

Scheme 2.3 Ruthenium-Catalyzed Selective α-Alkylation of Phenylacetonitrile Using a Labeled Alcohol

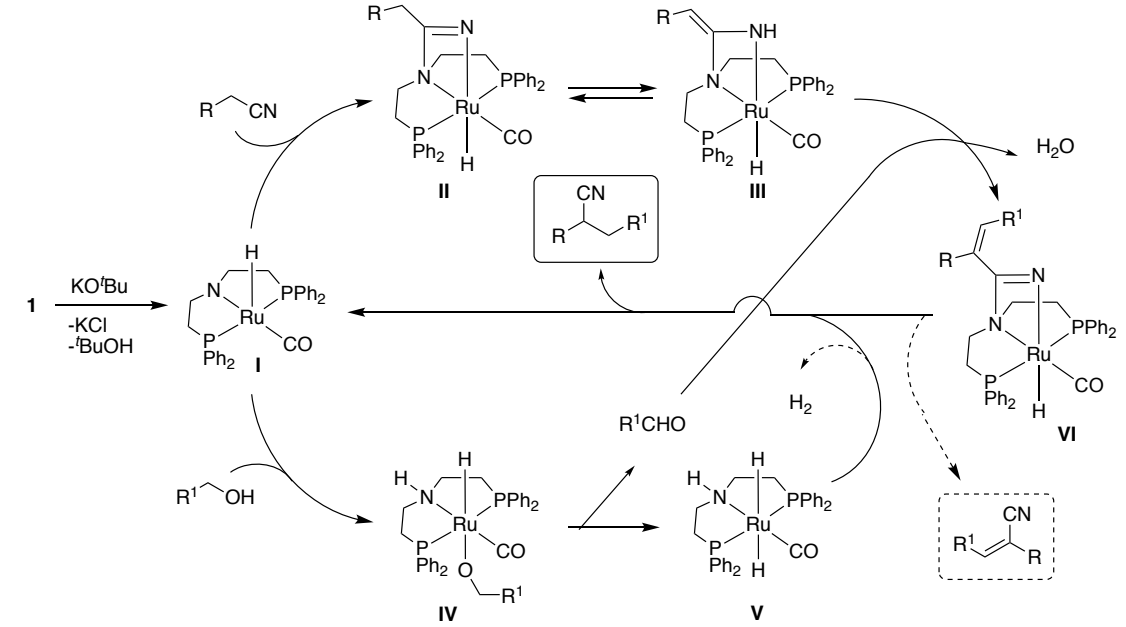


On the basis of these observations and the experimental studies involving catalyst **1** in our earlier work[17] on selective deuteration reactions, I propose the reaction mechanism for the selective α-alkylation of arylmethyl nitriles as depicted in Scheme 2.4. The catalyst **1** displayed robust amine-amide metal ligand cooperation, which made this green transformation possible. Catalyst **1** underwent dechlorination and deprotonation upon reaction with base to provide the 16 electron-unsaturated intermediate **I**. Intermediate **I** react with both alcohol and nitrile reactants. Reaction of **I** with nitrile leads to the formation of 1,2-cycloadduct **II** involving ruthenium center and deprotonated amide-backbone. Such four membered metallocycle intermediate containing ruthenium has its precedence in alkene metathesis process by Grubb's catalyst.[20,21] The imine intermediate **II** tautomerize to become enamine form **III**, which are in equilibrium (Scheme 2.4a). The unsaturated intermediate **I** also reacts with alcohol to provide alkoxy ligated complex **IV**, which resulted from the O–H activation of alcohols.[17] Further, β-hydride elimination of ruthenium ligated alkoxy ligand on intermediate **IV** provides the corresponding aldehydes and Ru-dihydride complex **V**. Conjugate addition of ruthenium enamine adduct **III** over the in situ formed aldehyde generates the intermediate **VI**. The detailed mechanism of this conjugate addition and

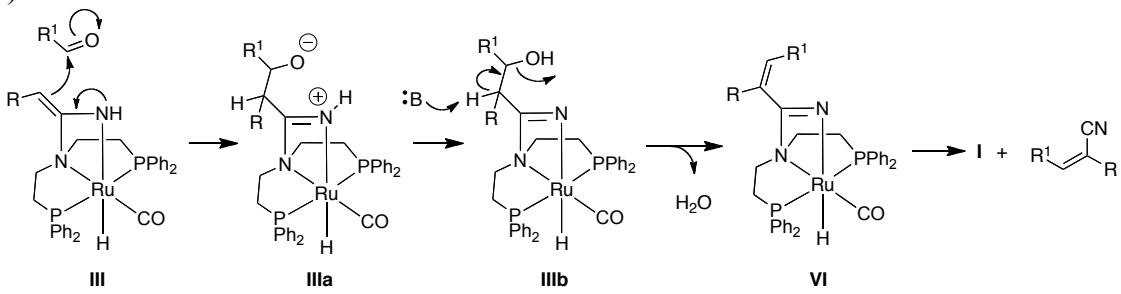
subsequent water elimination, perhaps assisted by base is delineated in Scheme 2.4b. Intermediate **VI**, resulting from the condensation of enamine and aldehydes reacts directly with ruthenium-dihydride **V**, to deliver the selective α-alkylated products with regeneration of catalytically active unsaturated intermediate **I**. Rapid formation of the α-alkylated product as shown in Figure 2.1b suggests that this pathway is predominantly operative. However, formation of the minor amount of vinyl nitrile intermediate (as observed in Figure 2.1b, ^{1}H NMR and GC) observed during the progress of the reaction, indicates the possible dissociation of the vinyl nitrile, which can undergo insertion into Ru−H upon reaction with Ru-dihydride intermediate **V** to generate the intermediate **VII** as delineated in Scheme 2.4c. Further elimination of Ru-alkyl ligand and ligand backbone N−H proton, can provide the α-alkylated arylmethyl nitrile product and regenerate the intermediate **I.**

Scheme 2.4 Proposed Reaction Mechanism: (a) Selective α-alkylation of Arylmethyl Nitriles Catalyzed by Ruthenium Pincer Complex 1 (b) Coupling of In Situ Generated Enamine and Aldehyde Intermediates by Conjugate Addition (C) Catalytic Hydrogenation of Olefin Intermediates

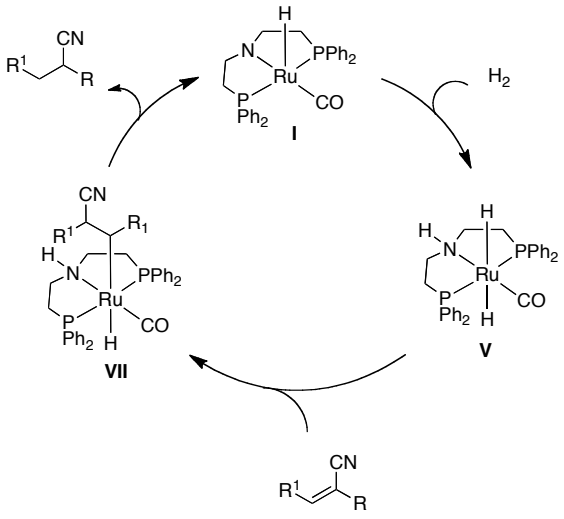
a)



b)



c)



2.4 CONCLUSIONS

In summary, I have demonstrated ruthenium-catalyzed facile α-alkylation of arylmethyl nitriles using alcohols as alkylating reagents and ruthenium pincer complex **1** in which the amine-amide metal-ligand cooperation is operative, which facilitated the overall transformation. Notably, using minimal catalyst load (0.5 mol%) and base (1 mol%), various arylmethyl nitriles can be efficiently and selectively α-alkylated with assortment of linear alcohols in excellent yields. Interestingly, this efficient alkylation is also extended to ethylation as well as challenging methylation reactions using ethanol and methanol, respectively. Chemoselective alkylation by primary alcohols was also demonstrated in the presence of secondary alcohols in an intermolecular fashion. This green catalytic transformation follows the principle of borrowing hydrogen strategy. The ruthenium pincer catalyst **1**, successfully oxidized the primary alcohols to aldehydes and also formed a [2+2] cycloadduct with nitriles, which tautomerizes to its enamine form to undergo conjugate-addition leading to condensation reactions. Subsequent hydrogenation of the intermediate vinyl nitrile (predominantly bound to ruthenium and minor amount in free form) provides the selective α-alkylated products.

2.5 EXPERIMENTAL SECTION

General Experimental: All stoichiometric reactions were performed in nitrogen atmosphere MBRAUN glove box. All catalytic reactions were performed under nitrogen atmosphere using standard Schlenk techniques. Chemicals were purchased from Acros, Sigma-Aldrich, Alfa-aesar, Himedia Chemicals and used without further purification. Catalyst **1** was purchased from Sigma-Aldrich. Dry solvents were prepared according to standard procedures. ^{1}H, ^{13}C spectra were recorded at Bruker AV-400 (^{1}H: 400 MHz, ^{13}C: 100.6 MHz). ^{1}H and ^{13}C $\{^{1}H\}$ NMR chemical shifts were reported in ppm downfield from tetramethyl silane. Multiplicity is abbreviated as: s, singlet; d,

doublet; dd, doublet of doublets; dt, doublet of triplets; t, triplet; q, quartet; dq, doublet of quartets; td, triplet of doublets; m, multiplet; br, broad. Assignment of spectra was done based on one-dimensional (DEPT-135) NMR techniques. Mass spectra were recorded on Bruker micrOTOF-Q II Spectrometer.

General Procedure for α-Alkylation of Phenylacetonitrile Using Alcohols:

To a 15 mL Schlenk tube equipped with a stirrer bar was added catalyst **1** (0.005 mmol), KO^{t}Bu (0.01 mmol), phenylacetonitrile (1 mmol), alcohol (2 mmol) and toluene (1.5 mL) sequentially in the nitrogen atmosphere. The flask was fitted to a condenser and the solution refluxed (oil bath temperature 135 °C) with stirring under the flow of argon for 4 h. The completion of the reaction was monitored using GC. After completion, the solvent was evaporated and crude reaction mixture was purified by column chromatography over silica-gel (100-200 mesh) using ethyl acetate/hexane mixture as an eluent. The conversion of phenylacetonitrile was calculated using GC and yields were determined for pure products after column chromatography.

General Procedure for α-Alkylation of Arylmethyl Nitriles Using Alcohols:

To a 15 mL Schlenk tube equipped with a stirrer bar was added catalyst **1** (0.005 mmol), KO^{t}Bu (0.01 mmol), phenylacetonitrile (1 mmol), alcohol (2 mmol) and toluene (1.5 mL) sequentially in the nitrogen atmosphere and the flask was fitted to a condenser. The reaction mixture was refluxed (oil bath temperature 135 °C) with stirring under the flow of argon for 4 h. The completion of the reaction was monitored using GC. After completion, the solvent was evaporated and the crude reaction mixture was purified by column chromatography over silica-gel (100-200 mesh) using ethyl acetate/hexane mixture as an eluent. The conversion of the nitrile was calculated using GC and yield of the product was determined after column chromatography.

General Procedure for α-Ethylation of Arylmethyl Nitriles Using Ethanol:

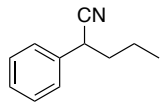
To a 15 mL Schlenk tube equipped with a stirrer bar was added catalyst **1** (0.02 mmol), KO^{t}Bu (0.04 mmol), nitrile (1 mmol), ethanol (5 mmol) and toluene (1.5 mL) sequentially in the nitrogen atmosphere and the flask was fitted to a condenser. The reaction mixture was refluxed (oil bath temperature 135 °C) with stirring under the flow of argon for 4 h. The completion of the reaction was monitored using GC. Upon completion of the reaction, solvent was evaporated and the resulted crude was purified by column chromatography over silica-gel (100-200 mesh) using ethyl acetate/hexane mixture as an eluent. Conversion of the nitrile was calculated using GC and yield of the product was determined by column chromatography.

General Procedure for α-Methylation of Arylmethyl Nitriles Using Methanol:

To a 35 mL sealed tube equipped with a stirrer bar was added catalyst **1** (0.025 mmol), KO^{t}Bu (0.05 mmol), nitrile (1 mmol), methanol (2 mL) sequentially in the nitrogen atmosphere. The solution was refluxed (oil bath temperature 135 °C) with stirring for 40 h under closed condition. After cooling, the solvent was evaporated and the resulted crude was purified by column chromatography over silica-gel (100-200 mesh) using ethyl acetate/hexane mixture as an eluent. The conversion of the nitrile was calculated using GC and the yield was determined after purification from column chromatography.

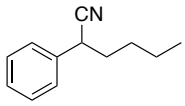
Spectral Data of the α-Alkylated Nitriles:

2-Phenylpentanenitrile (2.1a):[22] Colorless liquid. Yield (91%). IR (DCM): 3032, 2959, 2875, 2240, 1455, 1111, 1074, 1031, 756, 699 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.22-7.30 (m, 5H, ArC*H*), 3.69 (dd, J_1 = 6.4 Hz, J_2 = 2 Hz, 1H, C*H*), 1.71-1.85 (m, 2H, CH_2), 1.37-1.46 (m, 2H, CH_2), 0.87 (t, J = 6.8 Hz, 3H, CH_3). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 136.09 (quat-*C*), 129.06 (Ar*C*H), 127.99 (Ar*C*H),



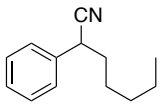
127.26 (Ar*C*H), 120.95 (*C*N), 37.90 (*C*H), 37.16 (CH_2), 20.32 (CH_2), 13.43 (CH_3). MS (ESI) m/z calcd for $C_{11}H_{13}N$ $(M+H)^+$: 160.11, found: 160.11.

2-Phenylhexanenitrile (2.1b):[23] Colorless liquid. Yield (98%). IR (DCM): 3032, 2959,



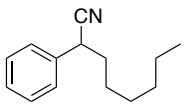
2933, 2863, 2241, 1494, 1455, 755, 698 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.18-7.26 (m, 5H, ArC*H*), 3.64 (dd, J_1 = 6.4 Hz, J_2= 2 Hz, 1H, C*H*), 1.71-1.80 (m, 2H, CH_2), 1.18-1.39 (m, 4H, CH_2), 0.78 (t, J = 6.8 Hz, 3H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 136.05 (quat-*C*), 128.91 (Ar*C*H), 127.84 (Ar*C*H), 127.12 (Ar*C*H), 120.84 (*C*N), 37.20 (*C*H), 35.49 (CH_2), 28.99 (CH_2), 21.97 (CH_2), 13.65 (CH_3). MS (ESI) m/z calcd for $C_{12}H_{15}N$ $(M+H)^+$: 174.12, found: 174.12.

2-Phenylheptanenitrile (2.1c):[23] Colorless liquid. Yield (98%). IR (DCM): 3032,



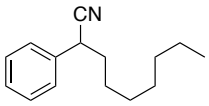
2928, 2862, 2241, 1599, 1494, 1457, 1029, 753, 697 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.19-7.27 (m, 5H, ArC*H*), 3.65 (dd, J_1 = 6.4 Hz, J_2 = 2.4 Hz, 1H, C*H*), 1.69-1.83 (m, 2H, CH_2), 1.31-1.41 (m, 2H, CH_2), 1.17-1.21 (m, 4H, CH_2), 0.78 (t, J = 6.8 Hz, 3H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 136.07 (quat-*C*), 128.95 (Ar*C*H), 127.87 (Ar*C*H), 127.15 (Ar*C*H), 120.88 (*C*N), 37.28 (*C*H), 35.80 (CH_2), 31.02 (CH_2), 26.62 (CH_2), (CH_2), 22.28 (CH_2), 13.86 (CH_3). MS (ESI) m/z calcd for $C_{13}H_{17}N$ $(M+H)^+$: 188.14, found: 188.14.

2-Phenyloctanenitrile (2.1d): Colorless liquid. Yield (98%). IR (DCM): 3063, 3033,

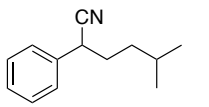


2931, 2861, 2241, 1455, 1379, 1248, 1113, 1076, 1031, 757, 699 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.20-7.28 (m, 5H, ArC*H*), 3.66 (dd, J_1 = 6.4 Hz, J_2 = 2.4 Hz, 1H, C*H*), 1.74-1.83 (m, 2H, CH_2), 1.32-1.43 (m, 2H, CH_2), 1.18-1.24 (m, 6H, CH_2), 0.78 (t, J = 6.8 Hz, 3H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 136.13 (quat-*C*), 129.01 (Ar*C*H), 127.93 (Ar*C*H), 127.21 (Ar*C*H), 120.92 (*C*N), 37.36 (*C*H), 35.90 (CH_2), 31.46 (CH_2), 28.60 (CH_2), 26.97 (CH_2), 22.50 (CH_2), 13.99 (CH_3). HRMS (ESI) m/z calcd for $C_{14}H_{19}N$ $(M+H)^+$: 202.1590, found: 202.1571.

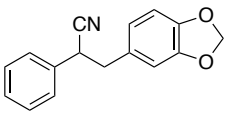
2-Phenylnonanenitrile (2.1e): Colorless liquid. Yield (95%). IR (DCM): 3032, 2929, 2859, 2241, 1455, 1249, 1113, 1076, 1031, 938, 756, 698 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.21-7.27 (m, 5H, ArC*H*), 3.67 (dd, J_1 = 6.4 Hz, J_2 = 2.4 Hz, 1H, C*H*), 1.72-1.84 (m, 2H, CH_2), 1.33-1.43 (m, 2H, CH_2), 1.17-1.21 (m, 8H, CH_2), 0.79 (t, J_H = 6.8 Hz, 3H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 136.15 (quat-*C*), 129.03 (Ar*C*H), 127.96 (Ar*C*H), 127.24 (Ar*C*H), 120.95 (*C*N), 37.40 (*C*H), 35.93 (*C*H_2), 31.71 (*C*H_2), 28.98 (*C*H_2), 28.93 (*C*H_2), 27.05 (*C*H_2), 22.60 (*C*H_2), 14.06 (*C*H_3). HRMS (ESI) m/z calcd for $C_{15}H_{21}N$ $(M+Na)^+$: 238.1566, found: 238.1569.



5-Methyl-2-phenylhexanenitrile (2.1f):[24] Colorless liquid. Yield (96%). IR (DCM): 2955, 2924, 2867, 2241, 1495, 1459, 1368, 1266, 739, 699 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.21-7.31 (m, 5H, ArC*H*), 3.66 (dd, J_1 = 6.4 Hz, J_2 = 2.4 Hz, 1H, C*H*), 1.76-1.85 (m, 2H, CH_2), 1.45-1.55 (m, 1H, C*H*), 1.22-1.34 (m, 2H, CH_2), 0.81 (dd, J_1 = 4 Hz, J_2 = 2.4 Hz, 6H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 136.19 (quat-*C*), 129.12 (Ar*C*H), 128.06 (Ar*C*H), 127.30 (Ar*C*H), 121.03 (*C*N), 37.71 (*C*H_2), 36.12 (*C*H), 34.0 (*C*H_2), 27.71 (*C*H), 22.54 (*C*H_3), 22.32. (*C*H_3). MS (ESI) m/z calcd for $C_{13}H_{17}N$ $(M+H)^+$: 188.14, found: 188.14.



3-(Benzo[*d*][1,3]dioxol-5-yl)-2-phenylpropanenitrile (2.1g): Colorless liquid. Yield (95%). IR (DCM): 2922, 2857, 2241, 1686, 1495, 1446, 1251, 1038, 930, 699 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.25-7.31 (m, 3H, ArC*H*), 7.19 (d, *J* = 6.8 Hz, 2H, ArC*H*), 6.65 (d, *J* = 8 Hz, 1H, ArC*H*), 6.50-6.54 (m, 2H, ArC*H*), 5.87 (s, 2H, CH_2), 3.88 (dd, J_1 = 6.4 Hz, J_2 =2.4 Hz, 1H, C*H*), 2.95-3.06 (m, 2H, CH_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 147.89 (quat-*C*), 147.02 (quat-*C*), 135.27 (quat-*C*), 130.07 (quat-*C*), 129.18 (Ar*C*H), 128.37 (Ar*C*H), 127.61 (Ar*C*H), 122.63 (Ar*C*H), 120.47 (*C*N), 109.62 (Ar*C*H), 108.50 (Ar*C*H), 101.20 (*C*H_2), 42.10 (*C*H_2), 40.19 (*C*H). HRMS (ESI) m/z calcd for $C_{16}H_{13}NO_2$ $(M+H)^+$: 252.1019, found 252.1035.



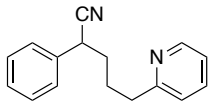
2,5-Diphenylpentanenitrile (2.1h):[24] Colorless liquid. Yield (98%). IR (DCM): 3028, 2933, 2860, 2241, 1600, 1494, 1452, 1266, 737, 695 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.17-7.29 (m, 7H, ArC*H*), 7.04-7.12 (m, 3H, ArC*H*), 3.67 (dd, J_1 = 6.4 Hz, J_2 = 2.4 Hz, 1H, C*H*), 2.56 (t, *J*= 8 Hz, 2H, CH_2), 1.66-1.88 (m, 4H, CH_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 141.16 (quat-*C*), 135.79 (quat-*C*), 129.04 (Ar*C*H), 128.44 (Ar*C*H), 128.34 (Ar*C*H), 128.01 (Ar*C*H), 127.21 (Ar*C*H), 126.05 (Ar*C*H), 120.77 (*C*N), 37.18 (*C*H_2), 35.17 (*C*H_2), 35.05 (*C*H), 28.53 (*C*H_2). MS (ESI) m/z calcd for $C_{17}H_{17}N$ $(M+Na)^+$: 258.12, found: 258.12.

2,6-Diphenylhexanenitrile (2.1i): Colorless liquid. Yield (97%). IR (DCM): 3032, 2930, 2860, 2241, 1494, 1455, 1265, 911, 739, 699 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.18-7.32 (m, 7H, ArC*H*), 7.06-7.12 (m, 3H, ArC*H*), 3.68 (dd, J_1 = 6.4 Hz, J_2= 2.4 Hz, 1H, C*H*), 2.53 (t, *J*= 8 Hz, 2H, CH_2), 1.79-1.90 (m, 2H, CH_2), 1.42-1.61 (m, 4H, CH_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 142.06 (quat-*C*), 136.01 (quat-*C*), 129.12 (Ar*C*H), 128.42 (Ar*C*H), 128.40 (Ar*C*H), 128.07 (Ar*C*H), 127.28 (Ar*C*H), 125.91 (Ar*C*H), 120.90 (*C*N), 37.38 (*C*H_2), 35.82 (*C*H_2), 35.63 (*C*H_2), 30.86 (*C*H), 26.74 (*C*H_2). HRMS (ESI) m/z calcd for $C_{18}H_{19}N$ $(M+Na)^+$: 272.1410, found: 272.1413

2-Phenyl-3-(pyridin-2-yl)propanenitrile (2.1j): Colorless liquid. Yield (61%). IR (DCM): 3058, 2925, 2854, 2241, 1591, 1475, 1439, 1264, 735, 701 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.52 (d, *J* = 4.8 Hz, 1H, ArC*H*), 7.54 (td, J_1 = 5.6 Hz, J_2 = 2 Hz, 1H, ArC*H*), 7.23-7.29 (m, 5H, ArC*H*), 7.13 (dd, J_1= 6.8 Hz, J_2 = 4.8 Hz, 1H, ArC*H*), 7.05 (d, *J*= 8 Hz, 1H, ArC*H*), 4.41 (dd, J_1= 6.4 Hz, J_2 = 8.4 Hz, 1H, C*H*), 3.18-3.31 (m, 2H, CH_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 156.71 (quat-*C*), 150.20 (Ar*C*H), 137.34 (Ar*C*H), 136.01 (quat-*C*), 129.64 (Ar*C*H), 128.73 (Ar*C*H), 127.96

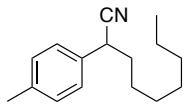
(Ar*C*H), 124.50 (Ar*C*H), 122.94 (Ar*C*H), 121.12 (*C*N), 44.71 (*C*H), 37.86 (*C*H_2). HRMS (ESI) m/z calcd for $C_{14}H_{12}N_2$ $(M+H)^+$: 209.1073, found: 209.1058.

2-Phenyl-5-(pyridin-2-yl)pentanenitrile (2.1k): Colorless liquid. Yield (98%). IR



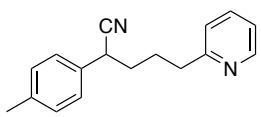
(DCM): 3058, 2928, 2861, 2241, 1591, 1437, 1305, 1150, 994, 754, 698 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.44 (d, J = 4.8 Hz, 1H, ArC*H*), 7.53 (td, J_1 = 6 Hz, J_2 = 2 Hz, 1H, ArC*H*), 7.21-7.31 (m, 5H, ArC*H*), 7.04 (dd, J_1 = 8 Hz, J_2 = 4 Hz, 2H, ArC*H*), 3.75 (dd, J_1 = 6.4 Hz, J_2 = 2.4 Hz, 1H, C*H*), 2.77 (t, J = 7.2 Hz, 2H, CH_2), 1.80-1.94 (m, 4H, CH_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 160.94 (quat-*C*), 149.37 (Ar*C*H), 136.57 (Ar*C*H), 135.84 (quat-*C*), 129.14 (Ar*C*H), 128.12 (Ar*C*H), 127.31 (Ar*C*H), 122.83 (Ar*C*H), 121.37 (Ar*C*H), 120.84 (*C*N), 37.39 (*C*H), 37.28 (*C*H_2), 35.34 (*C*H_2), 27.11 (*C*H_2). HRMS (ESI) m/z calcd for $C_{16}H_{16}N_2$ $(M+H)^+$: 237.1386, found: 237.1393.

2-(*p*-Tolyl)nonanenitrile (2.2a): Colorless liquid. Yield (93%). IR (DCM): 2925, 2857,



2241, 1514, 1460, 1277, 1119, 813, 724 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.12 (dd, J_1 = 8.4 Hz, J_2 = 5.2 Hz, 4H, ArC*H*), 3.66 (dd, J_1 = 6.4 Hz, J_2 = 2 Hz, 1H, C*H*), 2.28 (s, 1H, CH_3), 1.72-1.85 (m, 2H, CH_2), 1.34-1.43 (m, 2H, CH_2), 1.18-1.23 (m, 8H, CH_2) 0.80 (t, J = 7.2 Hz, 3H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 137.88 (quat-*C*), 133.21 (quat-*C*), 129.80 (Ar*C*H), 127.23 (Ar*C*H), 121.26 (*C*N), 37.15 (*C*H_2), 36.06 (*C*H), 31.82 (*C*H_2), 29.09 (*C*H_2), 29.06 (*C*H_2), 27.16 (*C*H_2), 22.71 (*C*H_2), 21.17 (*C*H_2), 14.17 (*C*H_3). HRMS (ESI) m/z calcd for $C_{16}H_{23}N$ $(M+H)^+$: 230.1903, found: 230.1911.

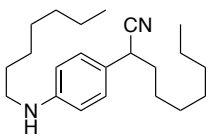
5-(Pyridin-2-yl)-2-(p-tolyl)pentanenitrile (2.2b): Colorless liquid. Yield (97%). IR



(DCM): 3058, 2927, 2861, 2241, 1590, 1513, 1435, 1264, 813, 732 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.43 (d, J = 4.8 Hz, 1H, ArC*H*), 7.51 (td, J_1= 6 Hz, J_2 = 1.6 Hz, 1H, ArC*H*), 7.02-7.13 (m, 6H, ArC*H*), 3.71 (dd, J_1 = 6

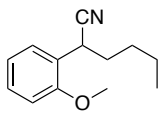
Hz, J_2 = 4 Hz, 1H, C*H*), 2.75 (t, J = 7.2 Hz, 2H, CH_2), 2.26 (s, 3H, CH_3), 1.80-1.92 (m, 4H, CH_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 161.00 (quat-*C*), 149.36 (Ar*C*H), 137.94 (quat-*C*), 136.61 (Ar*C*H), 132.84 (Ar*C*H), 129.81 (Ar*C*H), 127.21 (Ar*C*H), 122.87 (Ar*C*H), 121.39 (Ar*C*H), 121.04 (*C*N), 37.44 (*C*H), 36.91 (*C*H_2), 35.40 (*C*H_2), 27.13 (*C*H_2), 21.13 (*C*H_3). HRMS (ESI) m/z calcd for $C_{17}H_{18}N_2$ $(M+H)^+$: 251.1543, found: 251.1532.

2-(4-(Heptylamino)phenyl)nonanenitrile (2.2c): Colorless liquid. Yield (97%). IR



(DCM): 2926, 2857, 2241, 1615, 1523, 1463, 1326, 1264, 731, 699 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.10 (d, J = 8.4 Hz, 2H, ArC*H*), 6.58 (d, J = 8.8 Hz, 2H, ArC*H*), 3.64 (dd, J_1 = 6.4 Hz, J_2 = 2 Hz, 1H, C*H*), 3.10 (t, J = 7.2 Hz, 2H, CH_2), 1.78-1.89 (m, 2H, CH_2), 1.58-1.65 (m, 2H, CH_2), 1.26-1.43 (m, 19H, CH_2 & N*H*), 0.88 (dd, J_1 = 7.2 Hz, J_2 = 6 Hz, 6H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 148.15 (quat-*C*), 128.25 (Ar*C*H), 124.36 (quat-*C*), 121.74 (*C*N), 113.09 (Ar*C*H), 44.17 (*C*H_2), 36.67 (*C*H_2), 36.11 (*C*H), 31.92 (*C*H_2), 31.84 (*C*H_2), 29.58 (*C*H_2), 29.22 (*C*H_2), 29.12 (*C*H_2), 29.08 (*C*H_2), 27.22 (*C*H_2), 27.14 (*C*H_2), 22.73 (*C*H_2), 22.72 (*C*H_2), 14.20 (*C*H_3), 14.17 (*C*H_3). HRMS (ESI) m/z calcd for $C_{22}H_{36}N_2$ $(M+H)^+$: 329.2951, found: 329.2950.

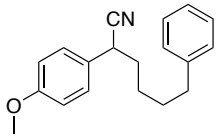
2-(2-Methoxyphenyl)hexanenitrile (2.2d): Colorless liquid. Yield (96%). IR (DCM):



2959, 2864, 2241, 1601, 1469, 1250, 1029, 753, 704 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.30 (dd, J_1 = 6 Hz, J_2 = 1.2 Hz, 1H, ArC*H*), 7.19 (td, J_1 = 6.4 Hz, J_2 =1.6 Hz, 1H, ArC*H*), 6.88 (td, J_1 = 7.2 Hz, J_2 = 0.4 Hz, 1H, ArC*H*), 6.79 (d, J = 8 Hz, 1H, ArC*H*), 4.08 (dd, J_1 = 6.8 Hz, J_2 = 1.2 Hz, 1H, C*H*), 3.74 (s, 1H, OCH_3), 1.72-1.78 (m, 2H, CH_2), 1.23-1.41 (m, 4H, CH_2), 0.82 (t, J = 7.2 Hz, 3H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 156.08 (quat-*C*), 129.22 (Ar*C*H), 128.24 (Ar*C*H), 124.49 (quat-*C*), 121.37 (Ar*C*H), 120.89 (*C*N), 110.79 (Ar*C*H), 55.47 (*C*H_3), 33.47 (*C*H_2), 31.33 (*C*H_2),

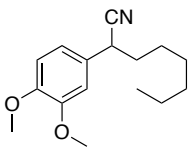
29.30 (*C*H), 22.07 (*C*H_2), 13.78 (*C*H_3). HRMS (ESI) m/z calcd for $C_{13}H_{17}NO$ $(M+H)^+$: 204.1383, found: 204.1371.

2-(4-Methoxyphenyl)-6-phenylhexanenitrile (2.2e): Colorless liquid. Yield (96%). IR



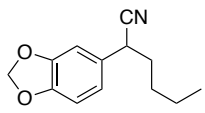
(DCM): 3026, 2930, 2857, 2241, 1609, 1510, 1249, 1179, 1032, 830, 745 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.05-7.20 (m, 7H, ArC*H*), 6.80 (d, *J* = 8.4 Hz, 2H, ArC*H*), 3.71 (s, 3H, OCH_3), 3.60 (dd, J_1 = 6.4 Hz, J_2 = 2 Hz, 1H, C*H*), 2.51 (t, *J* = 7.6 Hz, 2H, CH_2), 1.72-1.87 (m, 2H, CH_2), 1.53-1.60 (m, 2H, CH_2), 1.36-1.48 (m, 2H, CH_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 159.37 (quat-*C*), 142.12 (quat-*C*), 128.43 (Ar*C*H), 128 (Ar*C*H), 125.92 (Ar*C*H), 121.22 (*C*N), 114.49 (Ar*C*H), 55.41 (O*C*H_3), 36.58 (*C*H_2), 35.88 (*C*H_2), 35.67 (*C*H_2), 30.89 (*C*H), 26.71 (*C*H_2). HRMS (ESI) m/z calcd for $C_{19}H_{21}NO$ $(M+Na)^+$: 302.1515, found: 302.1511.

2-(3,4-Dimethoxyphenyl)octanenitrile (2.2f): Colorless liquid. Yield (97%). IR



(DCM): 3055, 2929, 2855, 2241, 1516, 1422, 1264, 1150, 1030, 895, 730 cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.75-7.78 (m, 3H, ArC*H*), 3.83 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 3.64 (dd, J_1 = 6.4 Hz, J_2 = 2 Hz, 1H, C*H*), 1.73-1.86 (m, 2H, CH_2), 1.35-1.45 (m, 2H, CH_2), 1.18-1.27 (m, 6H, CH_2), 0.81 (t, *J* = 6.4 Hz, 3H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 149.45 (quat-*C*), 148.86 (quat-*C*), 128.61 (quat-*C*), 121.28 (Ar*C*H), 119.66 (*C*N), 111.50 (Ar*C*H), 110.34 (Ar*C*H), 56.10 (O*C*H_3), 56.07 (O*C*H_3), 37.11 (*C*H_2), 36.05 (*C*H), 31.61 (*C*H_2), 28.73 (*C*H_2), 27.11 (*C*H_2), 22.62 (*C*H_2), 14.11 (*C*H_3). HRMS (ESI) m/z calcd for $C_{16}H_{23}NO_2$ $(M+Na)^+$: 284.1621, found: 284.1618.

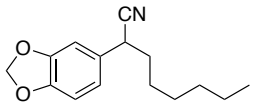
2-(Benzo[*d*][1,3]dioxol-5-yl)hexanenitrile (2.2g): Colorless liquid. Yield (96%). IR



(DCM): 2957, 2933, 2874, 2241, 1483, 1248, 1040, 932, 811, 737 cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.70 (s, 1H, ArC*H*), 6.67 (s, 2H, ArC*H*), 5.85 (s, 2H, CH_2), 3.58 (dd, J_1 = 6.8 Hz, J_2 = 1.6 Hz, 1H, C*H*), 1.67-1.79 (m, 2H, CH_2),

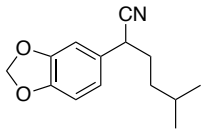
1.19-1.39 (m, 4H, CH_2), 0.80 (t, J = 7.2 Hz, 3H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 148.12 (quat-*C*), 147.26 (quat-*C*), 129.67 (quat-*C*), 120.95 (Ar*C*H), 120.55 (*C*N), 108.41 (Ar*C*H), 107.52 (Ar*C*H), 101.30 (*C*H_2), 36.84 (*C*H_2), 35.52 (*C*H), 28.93 (*C*H_2), 21.97 (*C*H_2), 13.67 (*C*H_3). HRMS (ESI) m/z calcd for $C_{13}H_{15}NO_2$ $(M+Na)^+$: 240.0995, found: 240.0987.

2-(Benzo[*d*][1,3]dioxol-5-yl)octanenitrile (2.2h): Colorless liquid. Yield (96%). IR



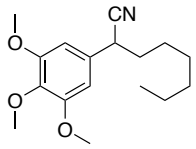
(DCM): 2953, 2927, 2858, 2240, 1487, 1443, 1245, 1037, 931, 808, 725 cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.71 (s, 1H, ArC*H*), 6.69 (s, 2H, ArC*H*), 5.87 (s, 2H, CH_2), 3.59 (dd, J_1 = 6.4 Hz, J_2 = 2 Hz, 1H, C*H*), 1.69-1.81 (m, 2H, CH_2), 1.32-1.39 (m, 2H, CH_2), 1.19-1.27 (m, 6H, CH_2), 0.79 (t, J = 7.2 Hz, 3H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 148.21 (quat-*C*), 147.36 (quat-*C*), 129.76 (quat-*C*), 121.04 (Ar*C*H), 120.66 (*C*N), 108.54 (Ar*C*H), 107.63 (Ar*C*H), 101.39 (*C*H_2), 37.02 (*C*H_2), 35.94 (*C*H), 31.49 (*C*H_2), 28.61 (*C*H_2), 26.92 (*C*H_2), 22.52 (*C*H_2), 14.01 (*C*H_3). HRMS (ESI) m/z calcd for $C_{15}H_{19}NO_2$ $(M+Na)^+$: 268.1308, found: 268.1294.

2-(Benzo[*d*][1,3]dioxol-5-yl)-5-methylhexanenitrile (2.2i): Colorless liquid. Yield



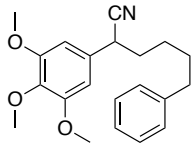
(90%). IR (DCM): 2957, 2929, 2906, 2872, 2240, 1487, 1445, 1368, 1249, 1040, 932, 810 cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.71 (s, 1H, ArC*H*), 6.68 (s, 2H, ArC*H*), 5.86 (s, 2H, CH_2), 3.56 (dd, J_1 = 6.4 Hz, J_2 = 2 Hz, 1H, C*H*), 1.71-1.81 (m, 2H, CH_2), 1.43-1.53 (m, 1H, C*H*), 1.17-1.29 (m, 2H, CH_2), 0.79 (dd, J_1 = 6.4 Hz, J_2 = 1.6 Hz, 6H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 148.18 (quat-*C*), 147.33 (quat-*C*), 129.73 (quat-*C*), 120.99 (*C*N), 120.61 (Ar*C*H), 108.49 (Ar*C*H), 107.57 (Ar*C*H), 101.35 (*C*H_2), 37.18 (*C*H_2), 35.91 (*C*H), 33.89 (*C*H_2), 27.59 (*C*H), 22.41 (*C*H_3), 22.22 (*C*H_3). HRMS (ESI) m/z calcd for $C_{14}H_{17}NO_2$ $(M+Na)^+$: 254.1151, found: 254.1170.

2-(3,4,5-Trimethoxyphenyl)octanenitrile (2.2j):[25] Colorless liquid. Yield (97%). IR (DCM): 2930, 2859, 2241, 1591, 1458, 1334, 1238, 1124, 1006, 828, 732 cm^{-1}. ^1H



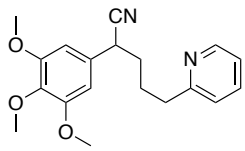
NMR ($CDCl_3$): δ 6.50 (s, 2H, ArC*H*), 3.85 (s, 6H, OCH_3), 3.82 (s, 3H, OCH_3), 3.68 (dd, J_1 = 6.4 Hz, J_2 = 2 Hz, 1H, C*H*), 1.78-1.94 (m, 2H, CH_2), 1.41-1.53 (m, 2H, CH_2), 1.27-1.35 (m, 6H, CH_2), 0.87 (t, J = 6.8 Hz, 3H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 153.63 (quat-*C*), 137.69 (quat-*C*), 131.76 (quat-*C*), 120.97 (*C*N), 104.37 (Ar*C*H), 60.89 (O*C*H3), 56.26 (O*C*H3), 37.72 (*C*H_2), 35.97 (*C*H), 31.53 (*C*H_2), 28.66 (*C*H_2), 27.13 (*C*H_2), 22.55 (*C*H_2), 14.04 (*C*H_3). MS (ESI) m/z calcd for $C_{17}H_{25}NO_3$ $(M+H)^+$: 292.19, found: 292.19.

6-Phenyl-2-(3,4,5-trimethoxyphenyl)hexanenitrile (2.2k): Colorless liquid. Yield



(98%). IR (DCM): 3025, 2932, 2859, 2241, 1593, 1456, 1333, 1239, 1126, 742, 697 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.19-7.23 (m, 2H, ArC*H*), 7.07-7.13 (m, 3H, ArC*H*), 6.43 (s, 2H, ArC*H*), 3.80 (s, 6H, OCH_3), 3.77 (s, 3H, OCH_3), 3.61 (dd, J_1 = 6.4 Hz, J_2 = 2.4 Hz, 1H, C*H*), 2.56 (t, J = 7.2 Hz, 2H, CH_2), 1.77-1.90 (m, 2H, CH_2), 1.56-1.64 (m, 2H, CH_2), 1.41-1.55 (m, 2H, CH_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 153.56 (quat-*C*), 141.92 (quat-*C*), 137.62 (quat-*C*), 131.53 (quat-*C*), 128.31 (Ar*C*H), 125.82 (Ar*C*H), 120.81 (*C*N), 104.28 (Ar*C*H), 60.80 (O*C*H_3), 56.17 (O*C*H_3), 37.54 (*C*H_2), 35.75 (*C*H_2), 35.55 (*C*H), 30.75 (*C*H_2), 26.72 (*C*H_2). HRMS (ESI) m/z calcd for $C_{21}H_{25}NO_3$ $(M+H)^+$: 340.1907, found: 340.1904.

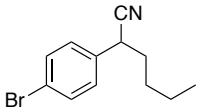
6-(Pyridin-2-yl)-2-(3,4,5-trimethoxyphenyl)pentanenitrile (2.2l): Colorless liquid.



Yield (96%). IR (DCM): 3055, 2936, 2843, 2241, 1591, 1460, 1239, 1125, 1004, 731 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.43 (d, J = 4.4 Hz, 1H, ArC*H*), 7.50-7.55 (m, 1H, ArC*H*), 7.05 (dd, J_1 = 5.6 Hz, J_2 = 2 Hz, 2H, ArC*H*), 6.43 (s, 2H, ArC*H*), 3.78 (s, 6H, OCH_3), 3.75 (s, 3H, OCH_3), 3.69 (dd, J_1 = 5.6 Hz, J_2 = 4.4 Hz, 1H, C*H*), 2.77 (t, J = 6.8 Hz, 2H, CH_2), 1.82-1.94 (m, 4H, CH_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 160.89 (quat-*C*), 153.65 (quat-*C*), 149.29 (Ar*C*H), 137.74 (Ar*C*H), 136.62 (quat-*C*), 131.39 (quat-*C*), 122.87 (Ar*C*H), 121.40 (Ar*C*H), 120.80 (*C*N), 104.39

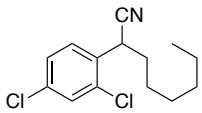
(ArCH), 60.89 (OCH$_3$), 56.26 (OCH$_3$), 37.45 (CH$_2$), 37.30 (CH$_2$), 35.30 (CH), 27.11 (CH$_2$). HRMS (ESI) m/z calcd for $C_{19}H_{22}N_2O_3$ $(M+H)^+$: 327.1703, found: 327.1706.

2-(4-Bromophenyl)hexanenitrile (2.2m): Colorless liquid. Yield (90%). IR (DCM):



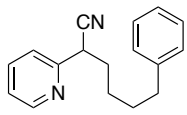
2958, 2930, 2862, 2242, 1625, 1472, 1265, 1073, 824, 739 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.41 (d, J = 8.4 Hz, 2H, ArCH), 7.12 (d, J = 8.4 Hz, 2H, ArCH), 3.66 (dd, J_1 = 6.4 Hz, J_2 = 2 Hz, 1H, CH), 1.75-1.81 (m, 2H, CH$_2$), 1.25-1.38 (m, 4H, CH$_2$), 0.81 (t, J = 7.2 Hz, 3H, CH$_3$). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 135.14 (quat-C), 132.21 (ArCH), 128.99 (ArCH), 122.03 (quat-C), 120.45 (CN), 36.89 (CH$_2$), 35.46 (CH), 29.03 (CH$_2$), 22.08 (CH$_2$), 13.79 (CH$_3$). HRMS (ESI) m/z calcd for $C_{12}H_{14}N$ $(M+H)^+$: 252.0382, found: 252.0388.

2-(2,4-Dichlorophenyl)octanenitrile (2.2n): Colorless liquid. Yield (82%): IR (DCM):



2949, 2930, 2860, 2241, 1470, 1249, 1103, 1040, 935, 868, 818 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.41 (d, J = 8.4 Hz, 1H, ArCH), 7.33 (d, J = 2 Hz, 1H, ArCH), 7.22 (dd, J_1 = 6 Hz, J_2 = 2.4 Hz, 1H, ArCH), 4.14 (dd, J_1 = 6.4 Hz, J_2 = 1.6 Hz, 1H, CH), 1.73-1.79 (m, 2H, CH$_2$), 1.38-1.50 (m, 2H, CH$_2$), 1.17-1.27 (m, 6H, CH$_2$), 0.80 (t, J = 6.8 Hz, 3H, CH$_3$). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 134.74 (quat-C), 133.38 (quat-C), 132.67 (quat-C), 129.87 (ArCH), 129.79 (ArCH), 128 (ArCH), 120.01 (CN), 34.35 (CH$_2$), 34.17 (CH$_2$), 31.52 (CH$_2$), 28.55 (CH), 27.06 (CH$_2$), 22.57 (CH$_2$), 14.07 (CH$_3$). HRMS (ESI) m/z calcd for $C_{14}H_{18}Cl_2N$ $(M+H)^+$: 270.0810, found: 270.0837.

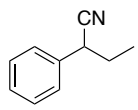
6-Phenyl-2-(pyridin-2-yl)hexanenitrile (2.2o): Colorless liquid. Yield (96%). IR



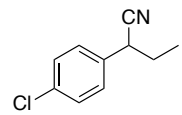
(DCM): 3026, 2932, 2860, 2242, 1635, 1589, 1372, 1241, 1046, 746, 698 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 8.48 (d, J = 4.8 Hz, 1H, ArCH), 7.59 (dd, J_1 = 6 Hz, J_2 = 1.6 Hz, 1H, ArCH), 7.29 (d, J = 8 Hz, 1H, ArCH), 7.11-7.18 (m, 3H, ArCH), 7.03-7.08 (m, 3H, ArCH), 3.85 (t, J = 7.2 Hz, 1H, CH), 2.50 (t, J = 7.2 Hz, 2H, CH$_2$), 1.94 (dd, J_1 = 8, J_2 = 7.6 Hz, 2H, CH$_2$), 1.40-1-61 (m, 6H, CH$_2$). ^{13}C{^{1}H} NMR

($CDCl_3$): δ 155.26 (quat-*C*), 149.88 (Ar*C*H), 141.98 (quat-*C*), 137.27 (Ar*C*H), 128.32 (Ar*C*H), 125.80 (Ar*C*H), 122.91 (Ar*C*H), 121.67 (Ar*C*H), 120.13 (*C*N), 39.73 (*C*H_2), 35.49 (*C*H_2), 33.95 (*C*H_2), 30.75 (*C*H), 26.62 (*C*H_2). HRMS (ESI) m/z calcd for $C_{17}H_{18}N_2$ $(M+H)^+$: 251.1543, found: 251.1551.

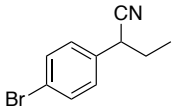
2-Phenylbutanenitrile (2.3a):[24] Colorless liquid. Yield (83%). IR (DCM): 3030, 2971, 2936, 2879, 2241, 1463, 1090, 1031, 912, 760, 699 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.24-7.32 (m, 5H, ArC*H*), 3.66 (t, *J* = 7.2 Hz, 1H, C*H*), 1.83-1.90 (m, 2H, CH_2), 1.00 (t, *J* = 7.2 Hz, 3H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 135.87 (quat-*C*), 129.14 (Ar*C*H), 128.13 (Ar*C*H), 127.41 (Ar*C*H), 120.87 (*C*N), 39.04 (*C*H), 29.33 (*C*H_2), 11.60 (*C*H_3). MS (ESI) m/z calcd for $C_{10}H_{11}N$ $(M+H)^+$: 146.08, found: 146.08.



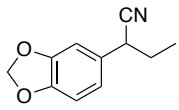
2-(4-Chlorophenyl)butanenitrile (2.3b):[26] Colorless liquid. Yield (78%). IR (DCM): 2972, 2933, 2877, 2241, 1491, 1264, 1092, 1015, 824, 731 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.18-7.31 (m, 4H, ArC*H*), 3.64 (t, *J* = 6.8 Hz, 1H, C*H*), 1.82-1.89 (m, 2H, CH_2), 0.99 (t, *J* = 7.2 Hz, 3H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 134.34 (quat-*C*), 134.16 (quat-*C*), 129.35 (Ar*C*H), 128.78 (Ar*C*H), 120.41 (*C*N), 38.46 (*C*H), 29.25 (*C*H_2), 11.49 (*C*H_3). MS (ESI) m/z calcd for $C_{10}H_{10}ClN$ $(M+H)^+$: 180.05, found: 180.05.



2-(4-Bromophenyl)butanenitrile (2.3c): Colorless liquid. Yield (66%). IR (DCM): 3054, 2972, 2936, 2241, 1489, 1265, 1074, 1012, 737 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.43 (d, *J* = 8.4 Hz, 2H, ArC*H*), 7.13 (d, *J* = 8.4 Hz, 2H, ArC*H*), 3.63 (t, *J* = 6.8 Hz, 1H, C*H*), 1.79-1.90 (m, 2H, CH_2), 0.99 (t, *J* = 7.2 Hz, 3H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 134.85 (quat-*C*), 132.29 (Ar*C*H), 129.10 (Ar*C*H), 122.17 (quat-*C*), 120.32 (*C*N), 38.50 (*C*H), 29.17 (*C*H_2), 11.47 (*C*H_3). HRMS (ESI) m/z calcd for $C_{10}H_{10}BrN$ $(M+H)^+$: 224.0069, found: 224.0077.

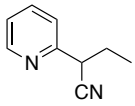


2-(Benzo[*d*][1,3]dioxol-5-yl)butanenitrile (2.3d): Colorless liquid. Yield (66%). IR



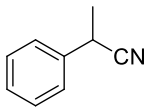
(DCM): 3055, 2972, 2932, 2241, 1490, 1445, 1265, 1040, 932, 811, 740 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 6.70-6.73 (m, 3H, ArC*H*), 5.90 (s, 2H, CH_2), 3.57 (t, *J* = 6.8 Hz, 1H, C*H*), 1.79-1.87 (m, 2H, CH_2), 0.98 (t, *J* = 7.6 Hz, 3H, CH_3). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 148.30 (quat-*C*), 147.49 (quat-*C*), 129.50 (quat-*C*), 120.93 (*C*N), 120.84 (Ar*C*H), 108.64 (Ar*C*H), 107.78 (Ar*C*H), 101.48 (O*C*H_2), 38.67 (*C*H), 29.36 (*C*H_2), 11.53 (*C*H_3). HRMS (ESI) m/z calcd for $C_{11}H_{11}NO_2$ $(M+H)^+$: 190.0863, found: 190.0887.

2-(Pyridin-2-yl)butanenitrile (2.3e):[27] Colorless liquid. Yield (82%). IR (DCM): 2971,



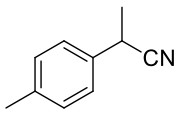
2929, 2877, 2241, 1586, 1467, 1436, 1266, 995, 748 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 8.51 (d, *J* = 4.4 Hz, 1H, ArC*H*), 7.66 (td, J_1 = 6 Hz, J_2 = 1.6 Hz, 1H, ArC*H*), 7.36 (d, *J* = 8 Hz, 1H, ArC*H*), 7.17-7.21 (m, 1H, ArC*H*), 3.87 (t, J_1 = 6 Hz, J_2 = 2 Hz, 1H, C*H*), 1.93-2.06 (m, 2H, CH_2), 1.02 (t, *J* = 7.6 Hz, 3H, CH_3). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 155.26 (quat-*C*), 149.97 (Ar*C*H), 137.33 (Ar*C*H), 122.99 (Ar*C*H), 121.83 (Ar*C*H), 120.12 (*C*N), 41.36 (*C*H), 27.68 (*C*H_2), 11.49 (*C*H_3). MS (ESI) m/z calcd for $C_9H_{10}N_2$ $(M+H)^+$: 147.09, found: 147.09.

2-Phenylpropanenitrile (2.4a):[23] Colorless liquid. Yield (83%). IR (DCM): 3030,



2983, 2934, 2241, 1493, 1450, 1077, 754, 694 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.25-7.32 (m, 5H, ArC*H*), 3.82 (q, *J* = 7.6 Hz, 1H, C*H*), 1.57 (d, *J* = 7.2 Hz, 3H, CH_3). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 137.16 (quat-*C*), 129.22 (Ar*C*H), 128.12 (Ar*C*H), 126.78 (Ar*C*H), 121.68 (*C*N), 31.31 (*C*H), 21.53 (*C*H_3). MS (ESI) m/z calcd for C_9H_9N $(M+H)^+$: 132.08, found: 132.08.

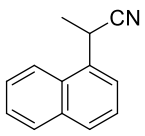
2-(*p*-Tolyl)propanenitrile (2.4b):[28] Colorless liquid. Yield (48%). IR (DCM): 2984,



2937, 2925, 2241, 1513, 1453, 1378, 1084, 814, 731 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.16 (d, *J* = 8.4 Hz, 2H, ArC*H*), 7.11 (d, *J* = 8 Hz, 2H,

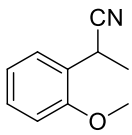
ArC*H*), 3.78 (q, *J* = 7.2 Hz, 1H, C*H*), 2.27 (s, 3H, CH_3), 1.54 (d, *J* = 7.2 Hz, 3H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 137.97 (quat-*C*), 134.22 (quat-*C*), 129.89 (Ar*C*H), 126.69 (Ar*C*H), 121.89 (*C*N), 30.99 (*C*H), 21.61 (*C*H_3), 21.15 (*C*H_3). MS (ESI) m/z calcd for $C_{10}H_{11}N$ $(M+H)^+$: 146.09, found: 146.09.

2-(Naphthalen-1-yl)propanenitrile (2.4c):[23] Colorless liquid. Yield (44%): IR (DCM):



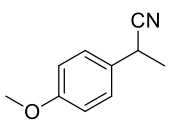
3030, 2983, 2934, 2241, 1493, 1450, 1077, 754, 694 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.85 (t, *J* = 8.4 Hz, 2H, ArC*H*), 7.77 (d, *J* = 8.4 Hz, 1H, ArC*H*), 7.63 (d, *J* = 7.2 Hz, 1H, ArC*H*), 7.41-7.54 (m, 3H, ArC*H*), 4.55 (q, *J* = 7.6 Hz, 1H, C*H*), 1.72 (d, *J* = 7.2 Hz, 3H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 134.12 (quat-*C*), 132.78 (quat-*C*), 129.91 (quat-*C*), 129.43 (Ar*C*H), 129.06 (Ar*C*H), 127.04 (Ar*C*H), 126.24 (Ar*C*H), 125.68 (Ar*C*H), 124.81 (Ar*C*H), 122.19 (Ar*C*H), 121.92 (*C*N), 28.36 (*C*H), 20.68 (*C*H_3). MS (ESI) m/z calcd for $C_{13}H_{11}N$ $(M+Na)^+$: 204.07, found: 204.07.

2-(2-Methoxyphenyl)propanenitrile (2.4d):[28] Colorless liquid. Yield (44%). IR



(DCM): 2941, 2840, 2242, 1596, 1493, 1459, 1248, 1026, 734 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.33 (dd, J_1 = 6 Hz, J_2 = 1.6 Hz, 1H, ArC*H*), 7.22 (td, J_1 = 6.8 Hz, J_2 = 1.6 Hz, 1H, ArC*H*), 6.90 (td, J_1 = 6.8 Hz, J_2 = 0.8 Hz, 1H, ArC*H*), 6.81 (dd, *J* = 7.6 Hz, J_2 = 0.8 Hz, 1H, ArC*H*), 4.16 (q, *J* = 7.2 Hz, 1H, C*H*), 3.37 (s, 3H, OCH_3), 1.49 (d, *J* = 7.2 Hz, 3H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 156.11 (quat-*C*), 129.40 (Ar*C*H), 127.64 (Ar*C*H), 125.45 (Ar*C*H), 122.07 (*C*N), 121.05 (quat-*C*), 110.85 (Ar*C*H), 55.54 (O*C*H_3), 25.68 (*C*H), 19.58 (*C*H_3). MS (ESI) m/z calcd for $C_{10}H_{11}NO$ $(M+Na)^+$: 184.07, found: 184.07.

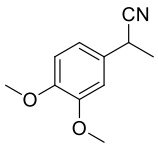
2-(4-Methoxyphenyl)propanenitrile (2.4e):[28] Colorless liquid. Yield (40%). IR



(DCM): 2936, 2841, 2241, 1611, 1511, 1458, 1247, 1031, 830, 732 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.19 (dd, J_1 = 4.4 Hz, J_2 = 2 Hz, 2H, ArC*H*), 6.83 (dd, J_1 = 4.8 Hz, J_2 = 2 Hz, 2H, ArC*H*), 3.77 (q, *J* = 7.2 Hz, 1H, C*H*), 3.73 (s, 3H,

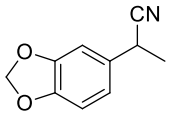
OC*H*$_3$), 1.54 (d, *J* = 7.2 Hz, 3H, C*H*$_3$). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 159.41 (quat-*C*), 129.20 (quat-*C*), 127.95 (Ar*C*H), 121.98 (*C*N), 114.59 (Ar*C*H), 55.46 (O*C*H$_3$), 30.56 (*C*H), 21.62 (*C*H$_3$). MS (ESI) m/z calcd for $C_{10}H_{11}NO$ $(M+H)^+$: 162.09, found: 162.09.

2-(3,4-Dimethoxyphenyl)propanenitrile (2.4f):[28] Colorless liquid. Yield (42%). IR



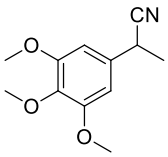
(DCM): 2937, 2838, 2241, 1596, 1513, 1457, 1235, 1146, 1024, 810 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 6.77-6.83 (m, 3H, ArC*H*), 3.83 (s, 3H, OC*H*$_3$), 3.80 (s, 3H, OC*H*$_3$), 3.77 (q, *J* = 7.2 Hz, 1H, C*H*), 1.56 (d, *J* = 7.2 Hz, 3H, C*H*$_3$). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 149.49 (quat-*C*), 148.89 (quat-*C*), 129.59 (quat-*C*), 121.89 (*C*N), 119.01 (Ar*C*H), 111.57 (Ar*C*H), 109.91 (Ar*C*H), 56.06 (O*C*H$_3$), 30.92 (*C*H), 21.59 (*C*H$_3$). MS (ESI) m/z calcd for $C_{11}H_{13}NO_2$ $(M+H)^+$: 192.10, found: 192.10.

2-(Benzo[*d*][1,3]dioxol-5-yl)propanenitrile (2.4g):[28] Colorless liquid. Yield (61%). IR



(DCM): 2987, 2904, 2242, 1490, 1442, 1239, 1035, 926, 810, 733 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 6.74 (s, 1H, ArC*H*), 6.71 (dd, J_1 = 6 Hz, J_2 = 1.6 Hz, 2H, ArC*H*), 5.89 (s, 2H, C*H*$_2$), 3.73 (q, *J* = 7.6 Hz, 1H, C*H*), 1.52 (d, *J* = 7.6 Hz, 3H, C*H*$_3$). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 148.34 (quat-*C*), 147.48 (quat-*C*), 130.86 (quat-*C*), 121.72 (*C*N), 120.15 (Ar*C*H), 108.71 (Ar*C*H), 107.30 (Ar*C*H), 101.48 (O*C*H$_2$), 31.01 (*C*H), 21.63 (*C*H$_3$). MS (ESI) m/z calcd for $C_{10}H_9NO_2$ $(M+Na)^+$: 198.05, found: 198.05.

2-(3,4,5-Trimethoxyphenyl)propanenitrile (2.4h):[25] Colorless liquid. Yield (42%). IR



(DCM): 2939, 2837, 2241, 1590, 1457, 1330, 1120, 1003, 827 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 6.48 (s, 2H, ArC*H*), 3.80 (s, 6H, OC*H*$_3$), 3.76 (s, 3H, OC*H*$_3$), 3.76 (q, *J* = 7.2 Hz, 1H, C*H*), 1.56 (d, *J* = 7.2 Hz, 3H, C*H*$_3$). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 153.65 (quat-*C*), 137.67 (quat-*C*), 132.70 (quat-*C*), 121.59 (*C*N), 103.84 (Ar*C*H), 60.82 (O*C*H$_3$), 56.20 (O*C*H$_3$), 31.44 (*C*H), 21.48 (*C*H$_3$). MS (ESI) m/z calcd for $C_{12}H_{15}NO_3$ $(M+H)^+$: 244.09, found: 244.09.

General Procedure for the Chemoselective α-Alkylation of Phenylacetonitrile:

To a 15 mL Schlenk tube equipped with a stirrer bar was added catalyst **1** (0.005 mmol), KO^{t}Bu (0.01 mmol), phenylacetonitrile (1 mmol), primary alcohol (2 mmol), secondary alcohol (2 mmol) and toluene (1.5 mL) sequentially in the nitrogen atmosphere. The flask was fitted to a condenser and the solution refluxed (oil bath temperature 135 °C) with stirring under the flow of argon for 4 h. The completion of the reaction was monitored using GC. After completion, the solvent was evaporated and crude reaction mixture was purified by column chromatography over silica-gel (100-200 mesh) using ethyl acetate/ hexane mixture as an eluent. The conversion of phenylacetonitrile was calculated using GC and yields were determined for pure products after column chromatography.

Figure 2.2 GC Spectrum for reaction mixture of Scheme **2.2a**:

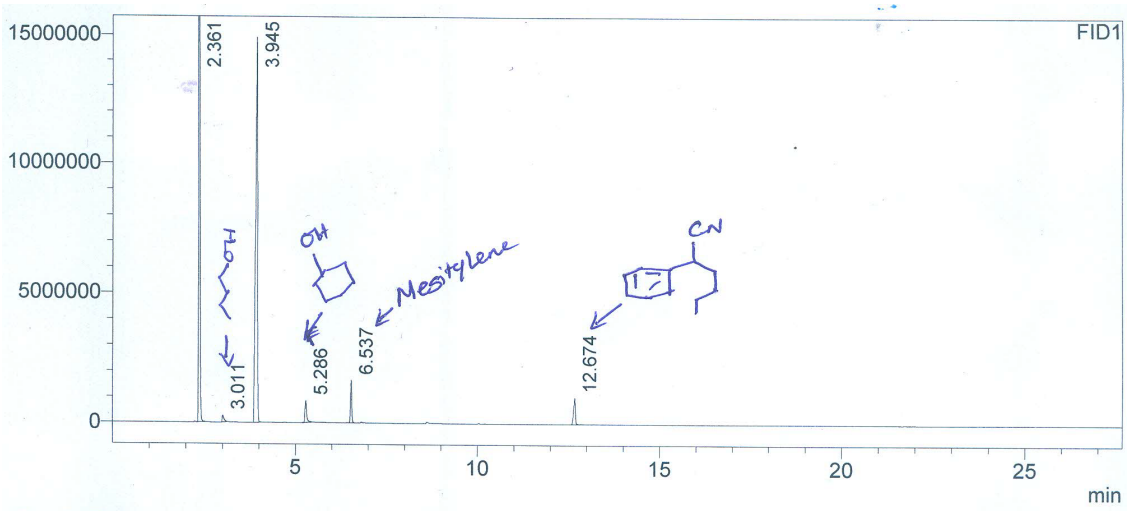
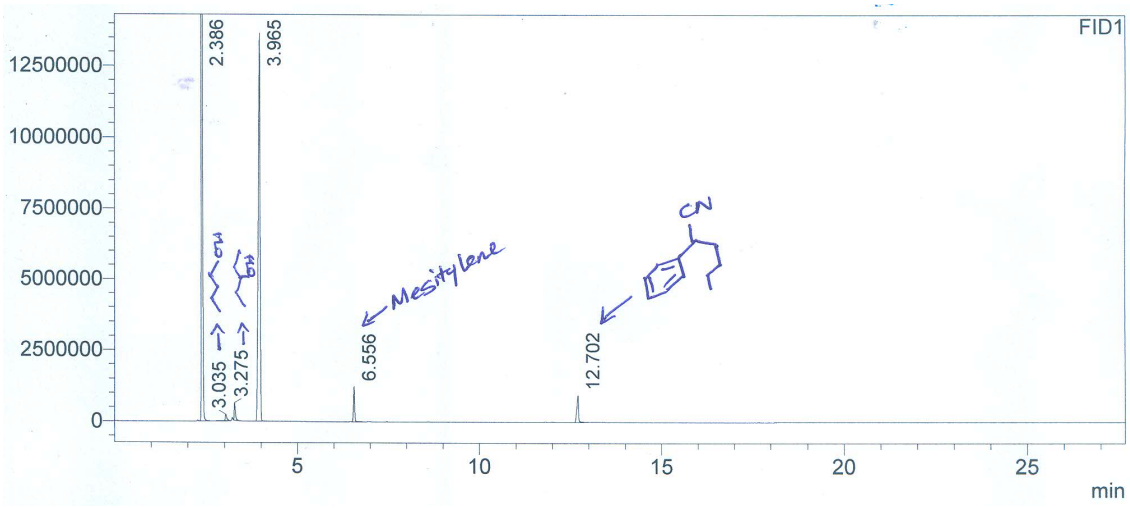


Figure 2.3 GC Spectrum for reaction mixture of Scheme **2.2b**:



The Observation of α-Alkylated Product and an Unsaturated Intermediate in Reaction Mixture:

To a 15 mL Schlenk tube equipped with a stirrer bar was added catalyst **1** (0.005 mmol), KO^{t}Bu (0.01 mmol), nitrile (1 mmol), and butanol (5 mmol) sequentially in the nitrogen atmosphere and the flask was fitted to a condenser. The solution was refluxed (oil path temperature 135 °C) with stirring under the flow of argon. After 20 minutes the reaction progress was monitored by GC and ^{1}H NMR. In situ I have observed both α-alkylated product (**A**) and an unsaturated intermediate (**B**).

Scheme 2.5 The Formation of α-Alkylated Product and an Unsaturated Intermediate in Reaction Mixture

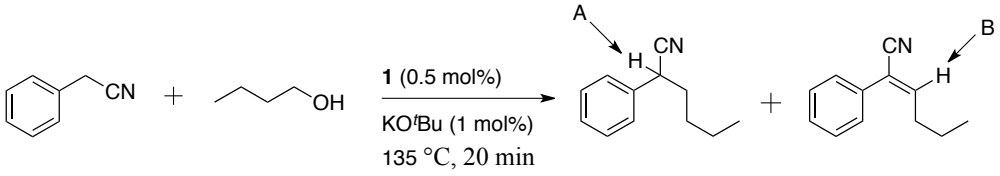
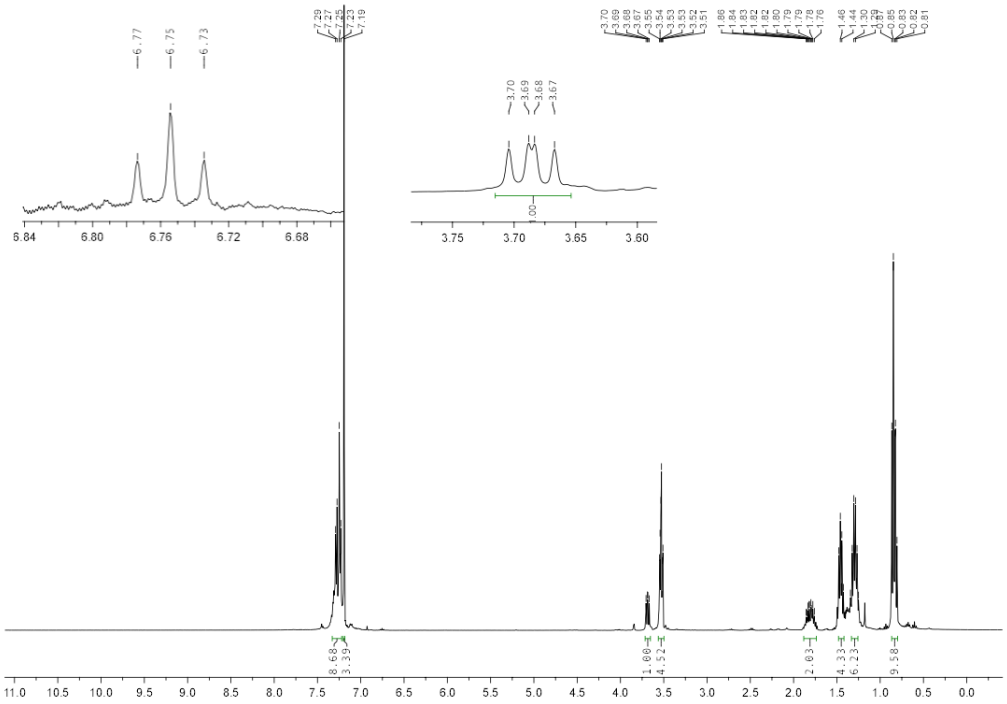


Figure 2.4 ^{1}H NMR Spectrum of Scheme **2.5**:



Procedure for α-Alkylation of Phenylacetonitrile Using Deuterated Primary Alcohol:

To a 15 mL Schlenk tube equipped with a stirrer bar was added catalyst **1** (0.005 mmol), KO^{t}Bu (0.01 mmol), phenylacetonitrile (1 mmol), deuterated alcohol (2 mmol) and toluene (1.5 mL) sequentially in the nitrogen atmosphere and the flask was fitted to a condenser. The solution was refluxed (oil bath temperature 135 °C) with stirring under the flow of argon for 4 h. The completion of the reaction was monitored using GC. After completion, the solvent was evaporated and resulted crude was purified by column chromatography over silica-gel (100-200 mesh) using ethyl acetate/hexane mixture as an eluent. The conversion of the nitrile was calculated from GC analysis of the reaction mixture and yields were determined for pure product after the column chromatography.

Figure 2.5 ^{1}H NMR spectrum of Scheme **2.3**:

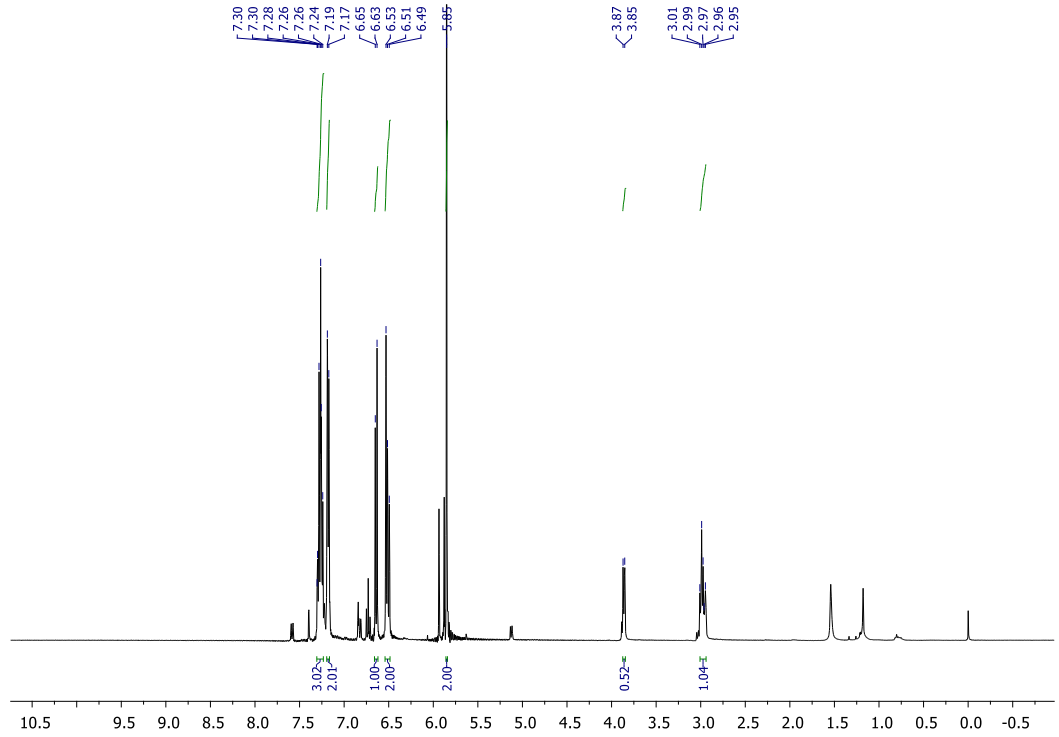
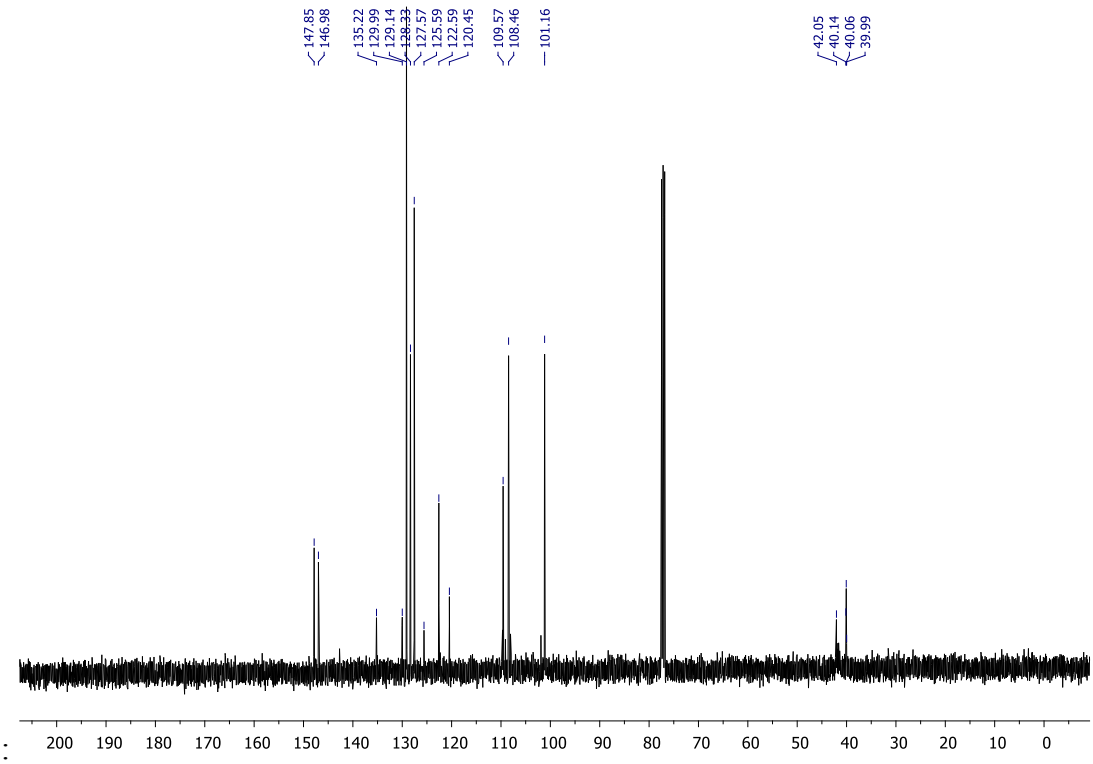


Figure 2.6 ^{13}C NMR Spectrum Scheme **2.3**:



2.6 NOTES AND REFERENCES

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^{1}H and ^{13}C NMR Spectra of the α-Alkylated Nitriles:

Figure 2.7 ^{1}H NMR spectrum of 2-phenylhexanenitrile:

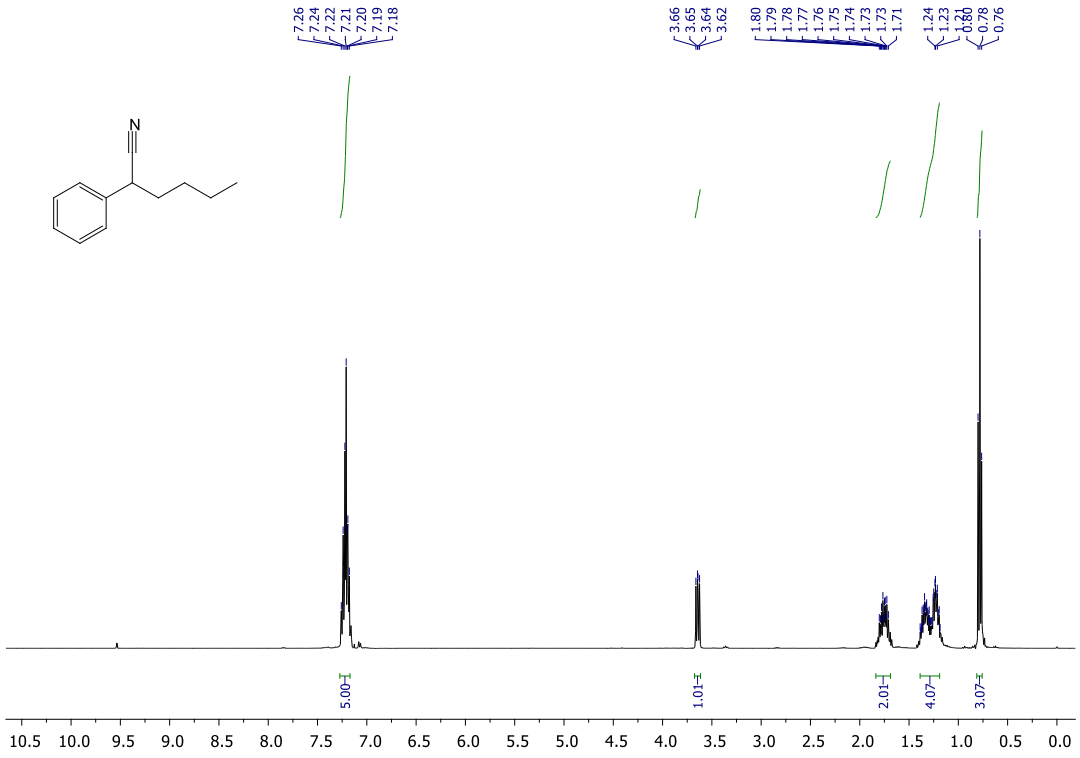


Figure 2.8 ^{13}C NMR spectrum of 2-phenylhexanenitrile:

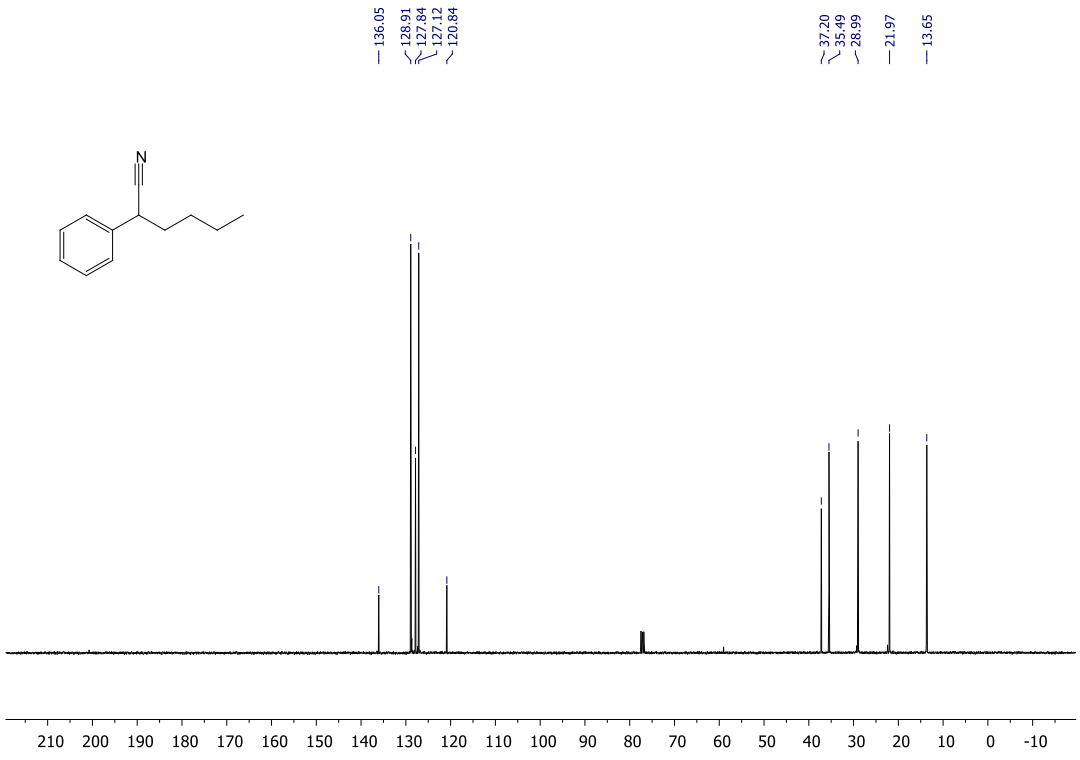


Figure 2.9 ^{1}H NMR spectrum of 6-phenyl-2-(pyridin-2-yl)hexanenitrile:

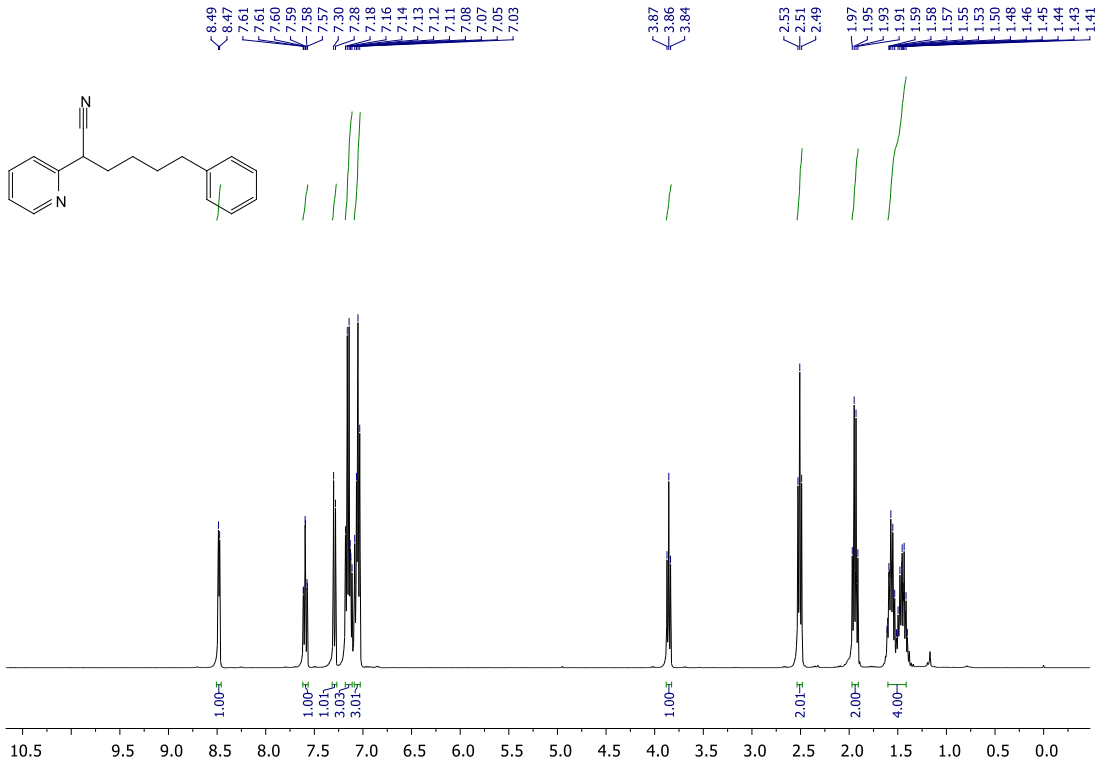


Figure 2.10 ^{13}C NMR spectrum of 6-phenyl-2-(pyridin-2-yl)hexanenitrile:

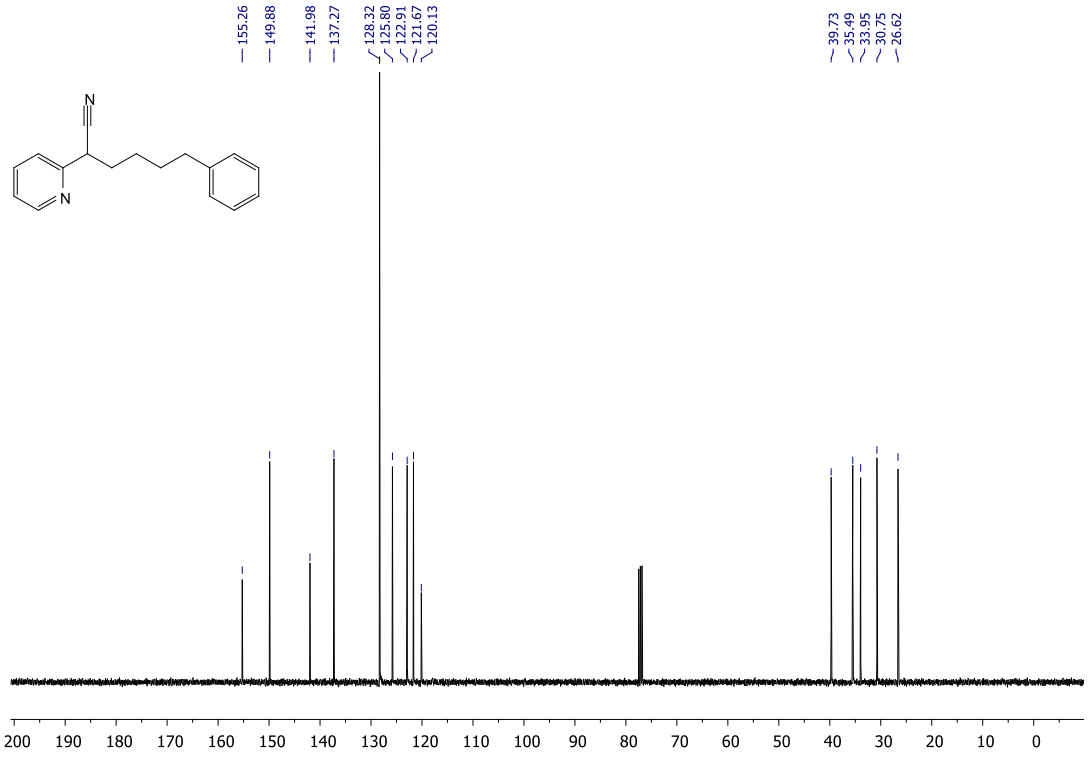


Figure 2.11 ^{1}H NMR spectrum of 2-(4-bromophenyl)butanenitrile:

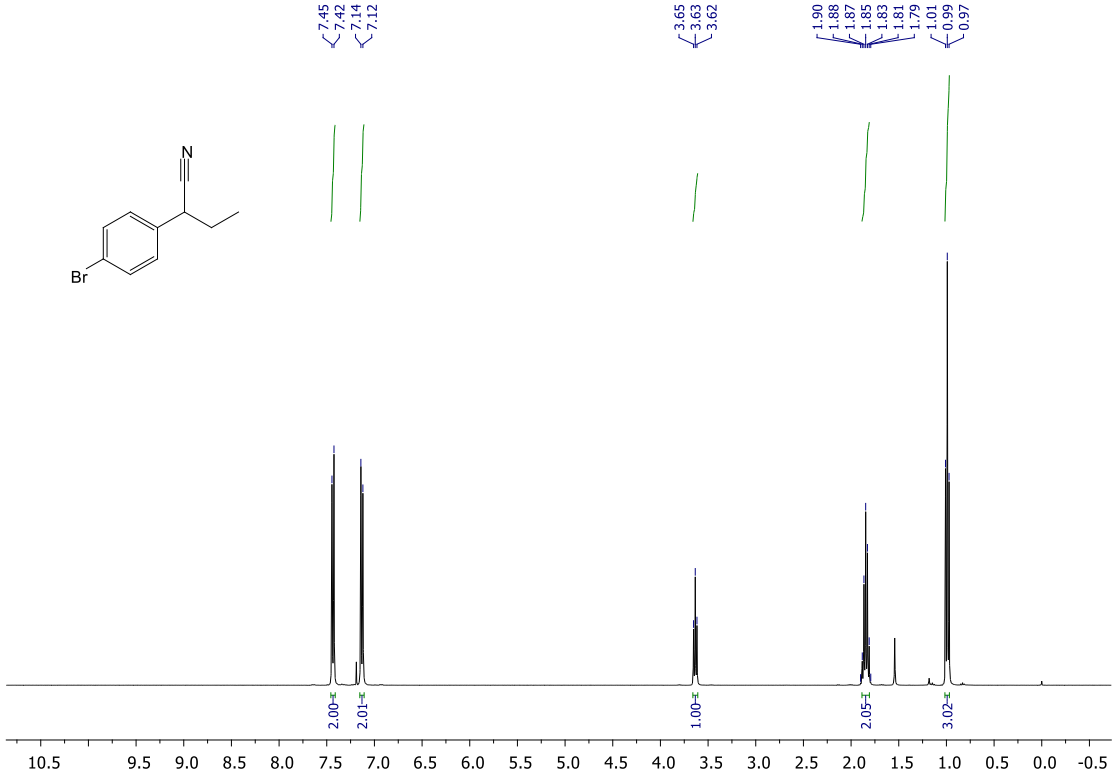
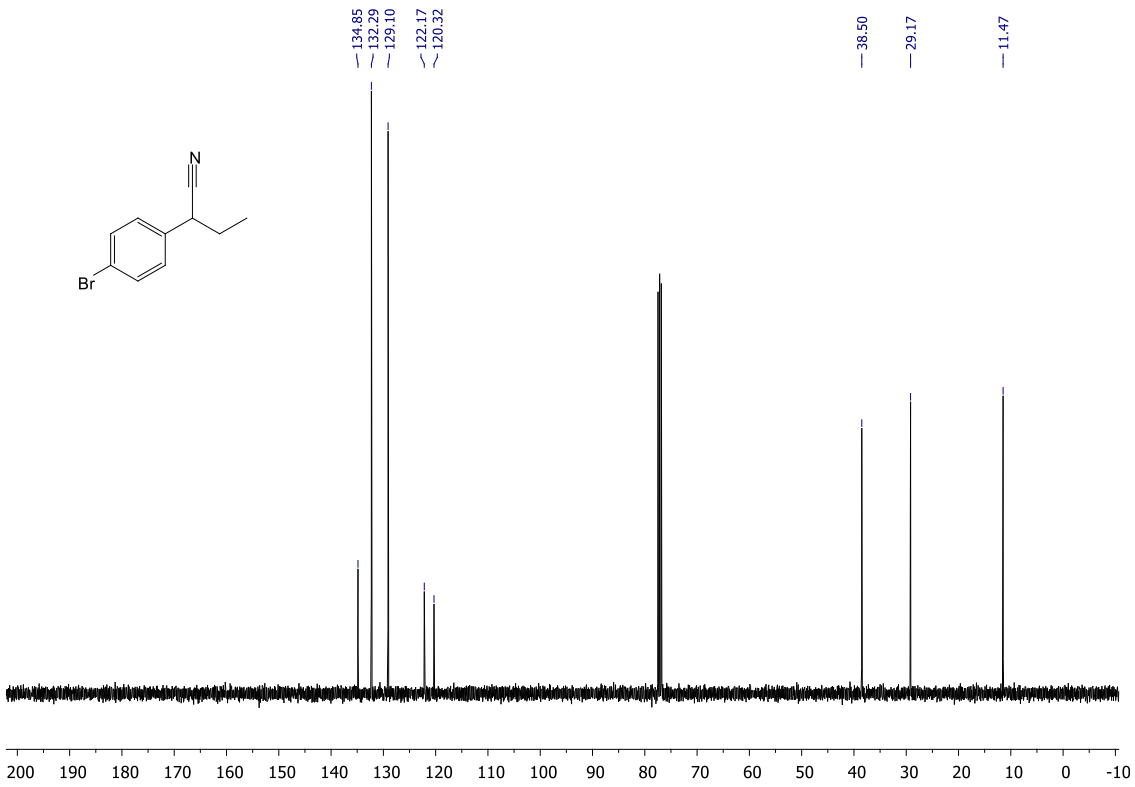


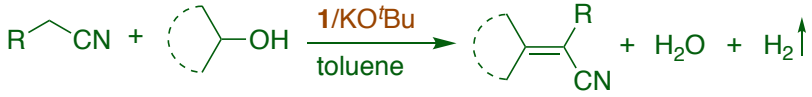
Figure 2.12 ^{13}C NMR spectrum of 2-(4-bromophenyl)butanenitrile:



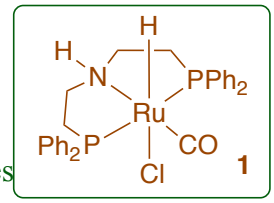
CHAPTER 3

Ruthenium Catalyzed α-Olefination of Nitriles Using Secondary Alcohols

3.1 ABSTRACT



- low catalyst load
- low cost of alcohols
- only byproducts: H_2 and H_2O
- new route to trisubstituted acrylonitriles



Ruthenium(II) pincer catalyzed α-olefination of nitriles is reported. This simple protocol provides an unprecedented transformation for the catalytic synthesis of β-disubstituted vinylnitriles using secondary alcohols. This catalytic method has extensive substrates scope, as arylmethyl nitriles, heteroarylmethyl nitriles and aliphatic nitriles as well as cyclic, acyclic, symmetrical and unsymmetrical secondary alcohols are all can be employed in the reaction to provide diverse α-vinylnitriles. C=C bond formation proceeds through activation of O–H bond of secondary alcohols via an unsaturated 16-electron intermediate ruthenium pincer complex and further condensation of in situ formed ketones with nitriles. Remarkably, H_2 and H_2O are the only byproducts of this atom economical and environmentally benign method.

3.2. INTRODUCTION

Construction of C=C bond is central to chemical synthesis. While there are several methods available to introduce an unsaturation intramolecularly in a substrate, methods

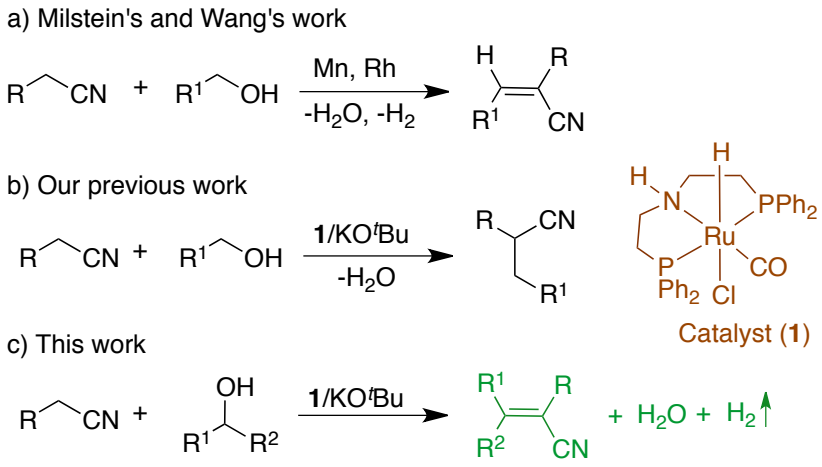
for the intermolecular olefin synthesis remain scarce. Working strategically towards this goal, Wittig reaction with its variants,[1] Peterson olefination,[2] and carbonyl coupling reactions[3] are employed by the conventional methods. However, these transformations in general, require extensive pre-functionalization of reactants and involve stoichiometric amount of toxic reagents. Catalytic methods for the intermolecular olefin synthesis are limited to ruthenium catalyzed alkene metathesis[4] and rhodium catalyzed diazo coupling.[5]

Vinyl nitriles are important intermediates in organic synthesis and prevalent among natural products and pharmaceuticals.[6] They serve as key building blocks and intermediates in number of chemical transformations. Notably, vinyl nitriles have found applications in optoelectronic materials and synthesis of light-emitting diodes.[7] Conventional synthesis of vinyl nitriles require stoichiometric amount of bases, which mediate the reaction of carbonyl compounds and nitriles (Knoevenagel condensation).[8] However, base promoted condensation reactions involve side reactions such as aldol reaction, Cannizzaro reaction and self-condensation of nitriles are limited to the substrates that are not sensitive to the basic conditions.[8b,9] Thus, attractive alternative methods are devised for the condensation of carbonyl compounds and nitriles to provide the vinyl nitriles. However, such methods often require the use of toxic reagents, elongated synthetic processes leading to the copious waste generation and poor yields.[10,11]

Acceptorless dehydrogenation of alcohols[12] and concomitant condensation of the resulting carbonyl compounds with nucleophilic molecules afforded atom economical and sustainable chemical transformations.[13,14] In this direction, employing the borrowing hydrogen concept, attractive methods for the construction of C–C and C–N

bonds were developed.[13-15] Recently, I have reported the ruthenium-catalyzed α-alkylation of arylmethyl nitriles using primary alcohols as alkylating reagents (Scheme 3.1b).[16] Water is the only by-product in this green and efficient alkylation reaction, which was enabled by metal-ligand cooperation operative in Ru-pincer complex **1** and the reactions proceeded via borrowing hydrogen pathway. In continuation of this work, I have explored the coupling of secondary alcohols and nitriles, which delivered the β-disubstituted vinylnitriles (Scheme 3.1c). Remarkably, liberated H_2 and water are the only byproducts from this green catalytic method. To our knowledge, secondary alcohols were never utilized in the transition metal catalyzed acceptorless dehydrogenative coupling with nitriles to provide vinylnitriles. However, when this manuscript was under preparation Milstein and Wang reported the manganese and rhodium catalyzed α-olefination of nitriles respectively, by employing primary alcohols (Scheme 3.1a).[17]

Scheme 3.1 Catalytic α-Olefination of Nitriles Using Alcohols

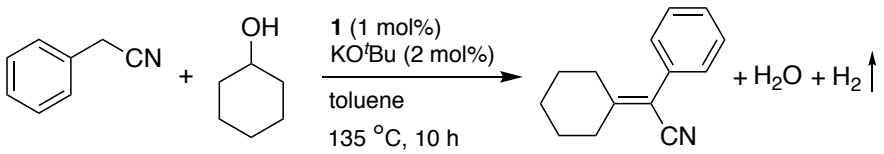


3.3 RESULTS AND DISCUSSIONS

At the outset, phenylacetonitrile, slight excess of cyclohexanol and ruthenium pincer catalyst **1** (1 mol%, Ru-MACHO) were reacted in toluene. Although, complete

conversion of nitrile was observed in 16 h, the desired olefin product **3.1a** was isolated in only moderate yields (entries 1, 2, Table 3.1). Analysis of the reaction mixture using ^{1}H NMR indicated the possible formation of aldol condensation products resulting from the in situ formed cyclohexanone intermediate. However, in contrary to the primary alcohol, no alkylation product was observed.[16] Thus, the catalytic olefination was performed using two equivalents of cyclohexanol, which resulted in quantitative conversion of nitrile in 10 h and the olefin product was isolated in 84% yield (entry 3, Table 3.1). Further, lowering the catalyst load from 1 mol% to 0.5 mol% and temperature from 135 °C to 120 °C turned out to be detrimental to the reaction progress as incomplete conversions were observed even after 24 h (entries 4, 5, Table 3.1). Control experiments using only base and without catalyst and base proved that the olefination requires catalyst (entries 6, 7, Table 3.1).

Table 3.1 Optimization of the Reaction Conditions for the α-Olefination of Nitriles Catalyzed by 1[a]



3.1a

entry	alcohol (equiv.)	time (h)	conv. (%)[b]	yield (%)[c]
1	1.05	16	>99	70
2	1.2	16	>99	78
3	2	10	>99	84
4[d]	2	24	57	40
5[e]	2	24	78	60
6[f]	2	24	-	-

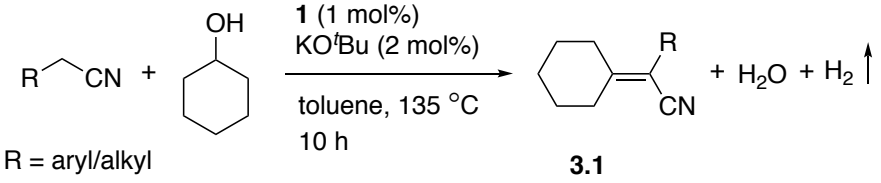
7[g]	2	24	-	-

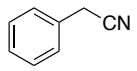
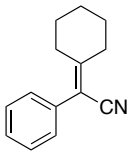
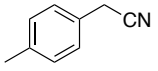
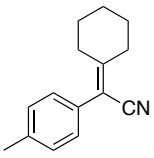
[a]Reaction conditions: phenylacetonitrile (1 mmol), cyclohexanol (2 mmol), catalyst **1**, base and toluene (1.5 mL) were heated at 135 °C under argon flow. [b]Conversion of nitrile was determined by GC using benzene as an internal standard. [c]Isolated yields after column chromatography. [d]0.5 mol% catalyst and 1 mol% base was used. [e]Heated at 120°C. [f]Only 2 mol% of base was used. [g]Reaction performed without catalyst and base.

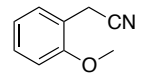
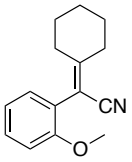
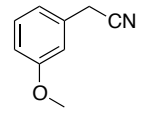
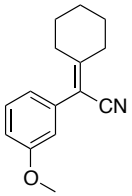
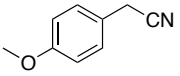
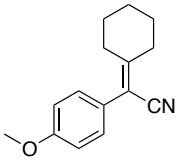
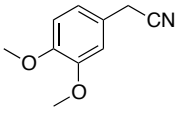
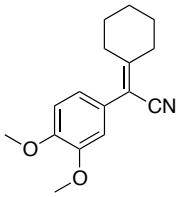
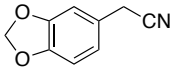
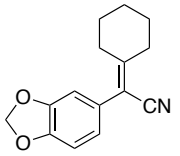
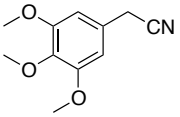
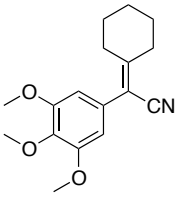
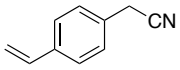
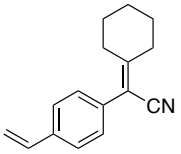
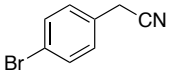
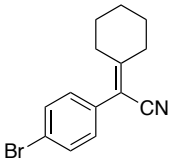
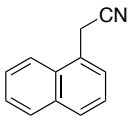
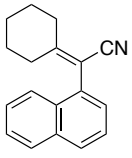
Having established the optimum reaction conditions, scope of the different nitriles on the catalytic olefination reaction was examined using cyclohexanol (Table 3.2). Reaction of cyclohexanol with 4-methyl phenylacetonitrile afforded the corresponding olefin product **3.1b** in 78% yield**.** When 2-methoxy phenylacetonitrile was subjected to the reaction under standard condition, diminished conversion (77%) and yield (**3.1c**, 72%) of the product were obtained indicating that the catalytic olefination is sensitive to steric hindrance in the proximity. However, *m*- and *p*-methoxy phenylacetonitrile provided 94% and quantitative conversions, respectively and the corresponding products **3.1d** and **3.1e** were isolated in very good yields**.** Similarly, reactions with di-, tri-methoxy substituted arylmethyl nitriles afforded the desired olefin products **3.1f**, **3.1g** and **3.1h** in good to excellent yields. Notably, 4-vinyl substituted arylmethyl nitriles provided complete conversion under standard experimental conditions and the corresponding product **3.1i** was obtained in 72% yield. Presence of electron-withdrawing substituent on the aryl ring was also tolerated. Upon reaction of 4-bromo phenylacetonitrile with cyclohexanol provided the α-olefinated product **3.1j** in 70% yield; however, complete conversion of nitrile required 24 h. When I have examined 1-naphthyl acetonitrile under standard experimental conditions, only 34% olefin product

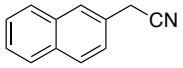
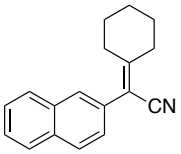
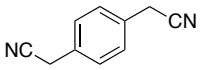
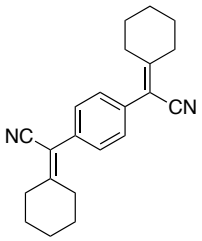
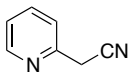
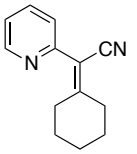
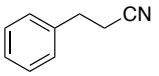
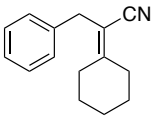
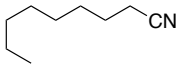
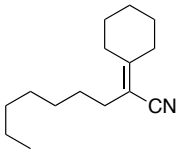
was isolated. Thus, the catalyst load was increased to 2 mol%, which provided the product **3.1k** in 80% yield. The similar reactivity was also observed with 2-naphthyl acetonitrile (entry 12, Table 3.2). Further, a dinitrile such as 1, 4-phenylenediacetonitrile was tested for the olefination reaction using cyclohexanol, which provided divinylnitrile **3.1m** in 48% yield. Despite the 99% conversion of dinitrile, the observed low yield of the product may be due to deleterious side reactions. Notably, heteroarylmethyl nitriles are also well tolerated in the olefination reaction. When, (pyridine-2-yl)acetonitrile was used the α-olefinated product **3.1n** was isolated in 62% yield. Remarkably, aliphatic nitriles were amenable to catalytic synthesis of vinylnitriles upon reaction with secondary alcohols. Reaction of 3-phenylpropionitrile and nonanenitrile were evaluated, which resulted the corresponding vinylnitrile products **3.1o** and **3.1p** in 62% and 48% yields, respectively.

Table 3.2. Ruthenium-Catalyzed α-Olefination of Nitriles Using Cyclohexanol[a]



entry	nitrile	product		conv. (%)[b]	yield (%)[c]
1			**3.1a**	>99	84
2			**3.1b**	85	78

3			**3.1c**	77	72
4			**3.1d**	94	80
5			**3.1e**	>99	85
6			**3.1f**	70	65
7			**3.1g**	92	87
8			**3.1h**	92	83
9			**3.1i**	>99	72
10[d,e]			**3.1j**	>99	70
11[d]			**3.1k**	90	80

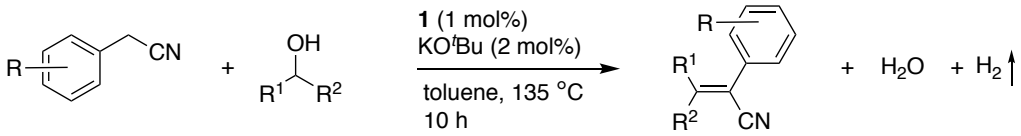
12[d]			**3.1l**	>99	81
13			**3.1m**	99	48
14[f]			**3.1n**	70	62
15[f]			**3.1o**	80	62
16[f]			**3.1p**	68	48

[a]Reaction conditions: Nitrile (1 mmol), cyclohexanol (2 mmol), toluene (1.5 ml), catalyst **1** (1 mol%) and KO^{t}Bu (2 mol%) were heated at 135 °C under argon flow. [b]Conversion of nitriles determined by GC using benzene as an internal standard. [c]Isolated yields after column chromatography. [d]2 mol% catalyst and 4 mol% base was used. [e]Reaction time 24 h. [f]Reaction performed with 0.25 mmol of nitrile and 0.5 mmol of cyclohexanol using 3 mol% catalyst **1** and 6 mol% base.

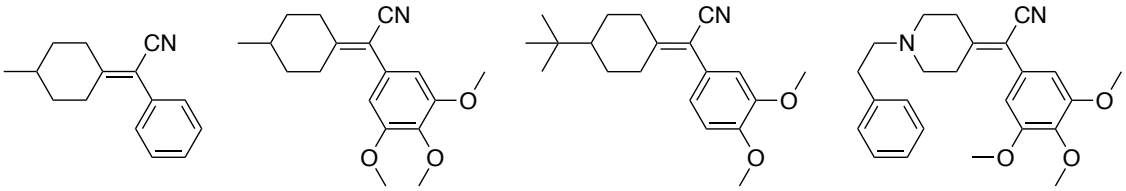
Further the scope of the secondary alcohols on the catalytic olefination using different nitriles was investigated. In general, variety of cyclic secondary alcohols can be employed under the reaction conditions to deliver α-olefinated products in good to excellent yields (Scheme 3.2). When 4-methyl cyclohexanol was reacted with

phenylacetonitrile and 2-(3,4,5-trimethoxyphenyl) acetonitrile, the corresponding olefin products were obtained in 75% and 93%, respectively (**3.2a**, **3.2b**, Scheme 3.2). Similarly, 4-*tert*-butyl cyclohexanol also exhibited very good reactivity. Remarkably, the nitrogen containing cyclic secondary alcohol, 1-phenethylpiperidin-4-ol underwent olefination with 2-(3,4-dimethoxyphenyl) acetonitrile to provide the product in 60% isolated yield (**3.2d**). Cycloheptanol reacted with phenylacetonitrile and 2-(4-methoxyphenyl)acetonitrile to provide the corresponding products in 86% and 70% isolated yields (**3.2e**, **3.2f**). A bulky cyclic alcohol such as cyclooctanol provided the corresponding olefin product **3.2g** in 46% yield with 2 mol% catalyst loads; further, increasing catalyst load to 5 mol% enhanced the yield of **3.2g** to 66%. Sterically demanding substrate, 2-adamantanol delivered the α-olefinated product **3.2h** in 69% yield. Ultimately aliphatic secondary alcohol such as 3-pentanol and 4-heptanol were subjected to catalytic olefin synthesis, which provided the corresponding vinylnitriles **3.2i** and **3.2j** in 58% and 48% isolated yields, respectively. Finally, unactivated unsymmetrical secondary alcohols such as 2-butanol, 2-hexanol and 2-heptanol were investigated with different arylmethylnitriles using catalyst **1** (5 mol%, 24 h), which provided the vinylnitrile products **3.2k-3.2m** as E/Z mixture in moderate yields. Overall, this protocol can allow the rapid access to highly branched β-disubstituted vinylnitriles from very simple and readily available starting materials with liberated dihydrogen and water as the only byproducts.

Scheme 3.2 Ruthenium-Catalyzed α-Olefination of Nitriles Using Secondary Alcohols[a]



3.2

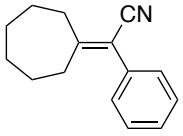


3.2a, 75% (>99%)

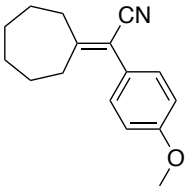
3.2b, 93% (>99%)

3.2c, 80% (88%)

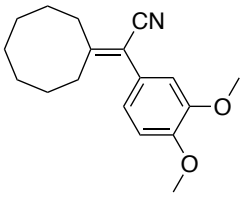
3.2d, 60% (89%)



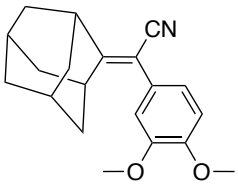
3.2e, 86% (>99%)



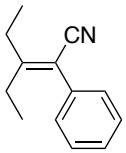
3.2f, 70% (78%)



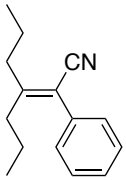
3.2g, 66% (85%)[c]



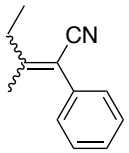
3.2h, 69% (90%)[b]



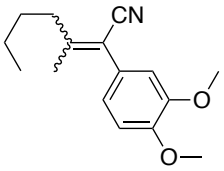
3.2i, 58% (99%)[b,d]



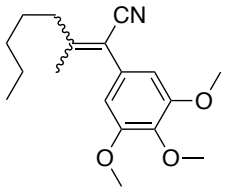
3.2j, 48% (65%)[c,d]



3.2k, 58% (99%)[c,d,e]



3.2l, 20% (40%)[c,d,e]

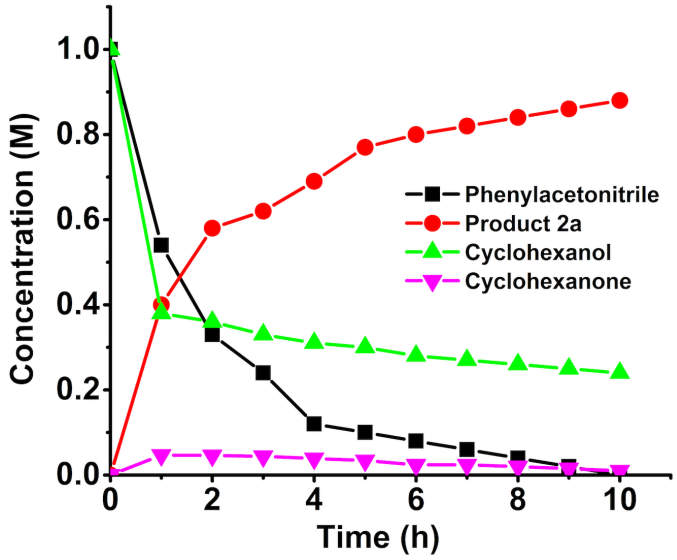


3.2m, 20% (40%)[c,d,e]

[a]Reaction conditions: nitrile (1 mmol), alcohol (2 mmol), toluene (1.5 ml), catalyst (1 mol%) and KO^{t}Bu (2 mol%) were heated at 135°C under argon flow. Reported yields correspond to isolated pure compounds. Conversion of nitriles is given within parenthesis and determined by GC analysis using benzene as an internal standard. [b]2 mol% catalyst **1** and 4 mol% base was used. [c]Reaction performed with 0.25 mmol of nitrile and 0.5 mmol of secondary alcohol using 5 mol% catalyst **1** and 10 mol% base. [d]Reaction time 24 h. [e]Isolated as E/Z mixture.

Mechanistic Investigations: GC monitoring on progress of the catalytic α-olefination reaction of phenylacetonitrile using cyclohexanol catalyzed by **1** indicated that the reaction follows first order kinetics with respect to phenylacetonitrile (Figure 3.1). Over the time, decreasing concentration of phenylacetonitrile (black line) can be corroborated with increasing concentration of product **3.1a** (red line). While nearly 1.5 equivalent of cyclohexanol (green line) was consumed in the reaction, the intermediate cyclohexanone (magenta line) was only short lived as it undergoes rapid condensation reaction with phenylacetonitrile.

Figure 3.1 Monitoring of the reaction progress by GC.

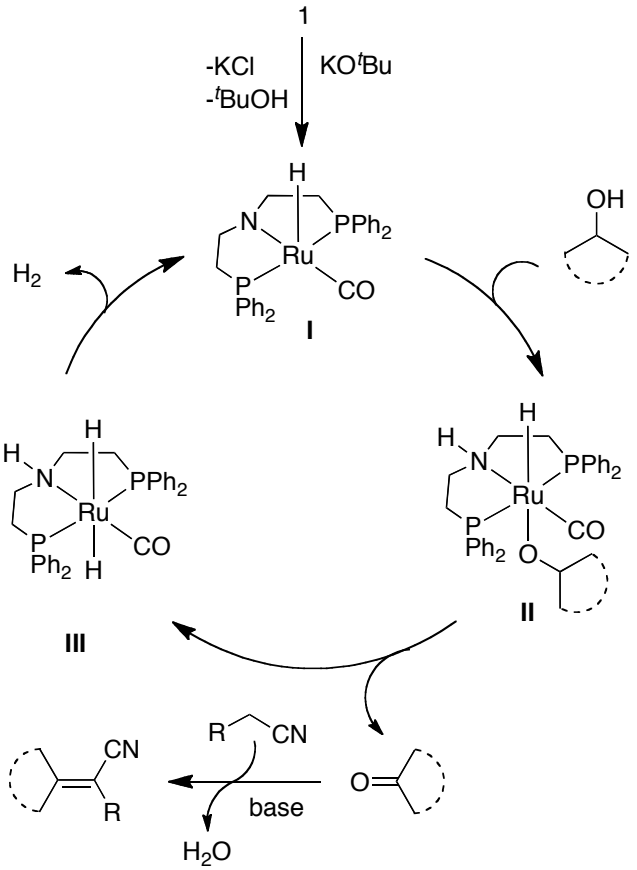


Concentration of phenylacetonitrile (black line), cyclohexanol (green line), product **3.1a** (red line) and the intermediate cyclohexanone (magenta line) in the catalytic α-olefination nitriles.

Plausible mechanism for α-olefination of nitriles using secondary alcohols catalyzed by **1** is depicted in Scheme 3.3. Our previous work with catalyst **1** established facile O–H,

N–H and spC–H bond activation reactions.[16,18] Catalyst **1** reacts with base to generate a coordinatively unsaturated reactive intermediate **I** (under similar condition the formation of **I** from catalyst **1** in the reaction mixture is previously established by us),[18a] which further reacts with secondary alcohols to provide an alkoxy ligand coordinated intermediate **II** (such alkoxy complex coordinated with benzyloxy ligand was characterized in situ by us)[18c] upon O–H activation of secondary alcohol.[18c] The amide donor present in unsaturated intermediate **I** accept the proton upon activation of O–H bond and becomes the amine donor in **II**. In concert with metal center, the ligand motif participates in the bond formation and bond breaking and hence displaying the metal-ligand cooperation. At this point, a dehydrogenation reaction takes place by a *β*-hydride elimination reaction (perhaps proceed via decoordination of one of donor atoms), which releases the ketone and generates a ruthenium dihydride complex **III**. However, although such mechanism is often invoked to explain the apparent *β*-hydride elimination reaction (which require coordinative unsaturation) in transition metal alkoxo ligated pincer complexes[14e-f,19] the involvement of other mechanistic pathway cannot be ruled out.[20] Further, complex **III** liberates dihydrogen to regenerate the catalytically active intermediate **I**. Finally, the Knoevenagel condensation between in situ formed ketones and nitriles provides *β*-disubstituted vinylnitriles by elimination of water molecule.

Scheme 3.3 Proposed Mechanism for the Ruthenium-Catalyzed α-Olefination of Nitriles Using Secondary Alcohols



3.4 CONCLUSIONS

In conclusion, I have presented an unprecedented transition metal catalyzed α-olefination of nitriles using secondary alcohols, which resulted in β-disubstituted vinylnitriles. Notably, arylmethyl nitriles, heteroarylmethyl nitriles and aliphatic nitriles were amenable to this catalytic transformation. Similarly, cyclic and acyclic as well as symmetrical and unsymmetrical secondary alcohols were also employed in this reaction, which resulted in assortment of α-vinylnitrile products. The acceptorless dehydrogenative coupling of nitriles and alcohols proceed via amine-amide metal-ligand cooperation operative in activated complex of **1**. Remarkably, dihydrogen and

water are the only byproducts in this catalytic olefination reaction, which make this method highly attractive for the synthesis of different kinds of fine and bulk chemicals.

3.5 EXPERIMENTAL SECTION

General Experimental: All catalytic reactions were performed under nitrogen atmosphere using standard Schlenk techniques. All stoichiometric reactions were performed in nitrogen atmosphere MBRAUN glove box. Chemicals were purchased from Acros, Sigma-Aldrich, Alfa-aesar, Himedia Chemicals and used without further purification. Dry solvents were prepared according to standard procedures. ^{1}H, ^{13}C spectra were recorded at Bruker AV-700 (^{1}H: 700 MHz, ^{13}C: 175 MHz) and Bruker AV-400 (^{1}H: 400 MHz, ^{13}C: 100.6 MHz). ^{1}H and ^{13}C $\{^{1}H\}$ NMR chemical shifts are referenced in ppm with respect to tetramethyl silane. NMR spectroscopy abbreviations: s, Singlet; d, doublet; dd, doublet of doublets; dt, doublet of triplets; t, triplet; q, quartet; dq, doublet of quartets; td, triplet of doublets; m, multiplet; br, broad. Assignment of spectra was done based on one-dimensional (DEPT-135) NMR techniques. IR spectra were recorded in Perkin-Elmer FT-IR spectrophotometer. Mass spectra were recorded on Bruker micrOTOF-Q II Spectrometer. E/Z isomers are assigned from cited references.[21]

General Procedure for α-Olefination of Nitriles Using Cyclohexanol:

In a glove box, 25 mL Schlenk flask was charged with a stirring bar, catalyst **1** (0.01 mmol), base (0.02 mmol), nitriles (1 mmol), cyclohexanol (2 mmol) and toluene (1.5 mL) under nitrogen atmosphere. The flask was taken out of the glove box, equipped with a condenser and the solution was refluxed (oil bath temperature 135 °C) with stirring under a flow of argon for 10 h. After cooling to room temperature, 1 mmol of internal standard (benzene) was added into the reaction mixture. After cooling to room

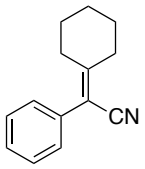
temperature, 1 mmol of internal standard (benzene) was added and the reaction mixture was subjected GC analysis. The solvent was evaporated and crude reaction mixture was purified by column chromatography over silica-gel (100-200 mesh) using ethyl acetate / hexane mixture as an eluent. The conversion of nitriles was calculated using GC analysis and yields were determined for pure products after column chromatography.

Procedure for α-Olefination of Heteroarylmethyl Nitriles Using Cyclohexanol:

In a glove box, 25 mL Schlenk flask was charged with a stirring bar, catalyst **1** (0.01 mmol), base (0.02 mmol), cyclohexanol (2 mmol) and toluene (1 mL) under nitrogen atmosphere. Heteroaryl nitrile (1 mmol) was taken in a 10 mL round bottom flask with toluene (1 mL) solvent and closed with a septum. The both flasks were taken out of the glove box. Schlenk flask was equipped with a condenser and solution was refluxed (oil bath temperature 135 °C) with stirring under a flow of argon. The nitrile solution from the round bottom flask was slowly added to the Schlenk flask over the time of 3 h under the flow of argon. The reaction mixture was further allowed to reflux for 7 h. After cooling to room temperature, 1 mmol of internal standard (benzene) was added into the reaction mixture. After cooling to room temperature, 1 mmol of internal standard (benzene) was added and the reaction mixture was subjected GC analysis. The solvent was evaporated and crude reaction mixture was purified by column chromatography over silica-gel (100-200 mesh) using ethyl acetate / hexane mixture as an eluent. The conversion of nitriles was calculated using GC analysis and yields were determined for pure products after column chromatography.

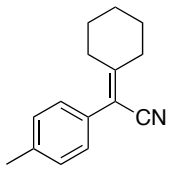
Spectral Data of the α-Olefinated Nitrile Products:

2-Cyclohexylidene-2-phenylacetonitrile (3.1a): Colorless liquid. Yield (84%). IR



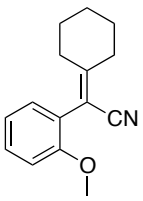
(DCM): 3057, 3026, 2935, 2858, 2209, 1618, 1491, 1445, 1266, 981, 762, 734, 702 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.18-7.31 (m, 5H, ArC*H*), 2.60 (t, *J* = 6.4 Hz, 2H, CH_2), 2.23 (t, *J* = 6.4 Hz, 2H, CH_2), 1.69 (quint, *J* = 6 Hz, 2H, CH_2), 1.48-1.58 (m, 4H, CH_2). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 161.97 (olefinic-*C*), 133.93 (quat-*C*), 129.30 (Ar*C*H), 128.70 (Ar*C*H), 128.24 (Ar*C*H), 118.75 (*C*N), 107.78 (olefinic-*C*), 35.41 (*C*H_2), 31.34 (*C*H_2), 28.17 (*C*H_2), 27.98 (*C*H_2), 25.95 (*C*H_2). HRMS (ESI) m/z calcd for $C_{14}H_{15}N$ $(M+H)^+$: 198.1277, found: 198.1289.

2-Cyclohexylidene-2-(*p*-tolyl)acetonitrile (3.1b): Colorless liquid. Yield (78%). IR



(DCM): 3053, 2938, 2859, 2208, 1609, 1445, 1265, 1115, 983, 896, 733 cm^{-1}. ^1H NMR (700 MHz, $CDCl_3$): δ 7.18 (dd, J_1 = 7.7 Hz, J_2 = 6.3 Hz, 4H, ArC*H*), 2.68 (t, *J* = 6.3 Hz, 2H, CH_2), 2.36 (s, 3H, CH_3), 2.32 (t, *J* = 6.3 Hz, 2H, CH_2), 1.77 (quint, *J* = 6.3 Hz, 2H, CH_2), 1.64 (quint, *J* = 6.3 Hz, 2H, CH_2), 1.58 (quint, *J* = 6.3 Hz, 2H, CH_2). $^{13}C\{^1H\}$ NMR (175 MHz, $CDCl_3$): δ 161.54 (olefinic-*C*), 138.21 (quat-*C*), 131.08 (quat-*C*), 129.43 (Ar*C*H), 129.24 (Ar*C*H), 118.97 (*C*N), 107.76 (olefinic-*C*), 35.47 (*C*H_2), 31.40 (*C*H_2), 28.23 (*C*H_2), 28.04 (*C*H_2), 26.06 (*C*H_2), 21.34 (*C*H_3). HRMS (ESI) m/z calcd for $C_{15}H_{17}N$ $(M+H)^+$: 212.1434, found: 212.1442.

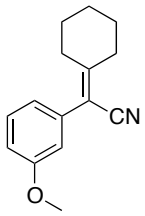
2-Cyclohexylidene-2-(2-methoxyphenyl)acetonitrile (3.1c): Colorless liquid. Yield



(72%). IR (DCM): 3055, 2938, 2858, 2841, 2209, 1627, 1495, 1465, 1250, 1116, 1028, 734, 705 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.32 (dt, J_1 = 7.6 Hz, J_2 = 1.6 Hz, 1H, ArC*H*), 7.11 (dd, J_1 = 5.6 Hz, J_2 = 2 Hz, 1H, ArC*H*), 6.91-6.97 (m, 2H, ArC*H*), 3.84 (s, 3H, OCH_3), 2.68 (t, *J* = 6 Hz, 2H, CH_2), 2.13 (t, *J* = 6

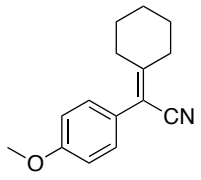
Hz, 2H, CH_2), 1.77 (quint, J = 6.8 Hz, 2H, CH_2), 1.56-1.65 (m, 4H, CH_2). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 162.77 (olefinic-*C*), 157.19 (quat-*C*), 131.29 (Ar*C*H), 130.12 (Ar*C*H), 122.64 (Ar*C*H), 120.63 (quat-*C*), 118.50 (*C*N), 111.34 (Ar*C*H), 103.75 (olefinic-*C*), 55.71 (O*C*H_3), 34.89 (*C*H_2), 31.74 (*C*H_2), 28.16 (*C*H_2), 27.81 (*C*H_2), 26.08 (*C*H_2). HRMS (ESI) m/z calcd for $C_{15}H_{17}NO$ $(M+Na)^+$: 250.1202, found: 250.1203.

2-Cyclohexylidene-2-(3-methoxyphenyl)acetonitrile (3.1d): Colorless liquid. Yield



(80%). IR (DCM): 3052, 2943, 2857, 2210, 1599, 1453, 1268, 1049, 994, 875, 782, 735, 706 cm^{-1}. ^1H NMR (700 MHz, $CDCl_3$): δ 7.29 (t, J = 7.7 Hz, 1H, ArC*H*), 6.84-6.88 (m, 2H, ArC*H*), 6.81 (s, 1H, ArC*H*), 3.81 (s, 3H, OCH_3), 2.67 (t, J = 6.3 Hz, 2H, CH_2), 2.32 (t, J = 5.6 Hz, 2H, CH_2), 1.78 (quint, J = 6.3 Hz, 2H, CH_2), 1.64 (quint, J = 5.6 Hz, 2H, CH_2), 1.59 (quint, J = 6.3 Hz, 2H, CH_2). $^{13}C\{^1H\}$ NMR (175 MHz, $CDCl_3$): δ 162.25 (olefinic-*C*), 159.79 (quat-*C*), 135.22 (quat-*C*), 129.79 (Ar*C*H), 121.74 (Ar*C*H), 118.71 (*C*N), 114.92 (Ar*C*H), 113.90 (Ar*C*H), 107.67 (olefinic-*C*), 55.44 (O*C*H_3), 35.46 (*C*H_2), 31.53 (*C*H_2), 28.24 (*C*H_2), 28.07 (*C*H_2), 26.02 (*C*H_2). HRMS (ESI) m/z calcd for $C_{15}H_{17}NO$ $(M+H)^+$: 228.1383, found: 228.1381.

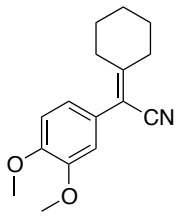
2-Cyclohexylidene-2-(4-methoxyphenyl)acetonitrile (3.1e): Colorless liquid. Yield



(85%). IR (DCM): 3058, 2937, 2858, 2840, 2209, 1624, 1492, 1465, 1251, 1117, 1028, 736, 703 cm^{-1}. ^1H NMR (700 MHz, $CDCl_3$): δ 7.19 (dd, J_1 = 9.1 Hz, J_2 = 2.1 Hz, 2H, ArC*H*), 6.89 (dd, J_1 = 9.1 Hz, J_2 = 2.8 Hz, 2H, ArC*H*), 3.80 (s, 3H, OCH_3), 2.65 (t, J = 6.3 Hz, 2H, CH_2), 2.30 (t, J = 6.3 Hz, 2H, CH_2), 1.75 (quint, J = 5.6 Hz, 2H, CH_2), 1.63 (quint, J = 3.5 Hz, 2H, CH_2), 1.57 (quint, J = 7.7 Hz, 2H, CH_2). $^{13}C\{^1H\}$ NMR (175 MHz, $CDCl_3$): δ 161.09 (olefinic-*C*), 159.44 (quat-*C*), 130.52 (Ar*C*H), 126.19 (quat-*C*), 118.95 (*C*N), 114.07 (Ar*C*H), 107.30

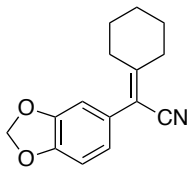
(olefinic-*C*), 55.36 (O*C*H$_3$), 35.35 (*C*H$_2$), 31.26 (*C*H$_2$), 28.14 (*C*H$_2$), 27.94 (*C*H$_2$), 25.97 (*C*H$_2$). HRMS (ESI) m/z calcd for $C_{15}H_{17}NO$ $(M+Na)^+$: 250.1202, found: 250.1206.

2-Cyclohexylidene-2-(3,4-dimethoxyphenyl)acetonitrile (3.1f): Colorless liquid.



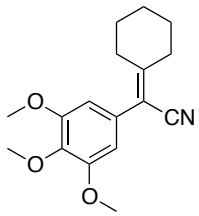
Yield (87%). IR (DCM): 3057, 2936, 2858, 2208, 1605, 1513, 1450, 1251, 1027, 815, 733, 703 cm^{-1}. ^{1}H NMR (700 MHz, $CDCl_3$): δ 6.82 (d, *J* = 8.4 Hz, 1H, ArC*H*), 6.77 (d, *J* = 9.8 Hz, 1H, ArC*H*), 6.75 (s, 1H, ArC*H*), 3.84 (s, 6H, OC*H*$_3$), 2.62 (t, *J* = 5.6 Hz, 2H, C*H*$_2$), 2.29 (t, *J* = 6.3 Hz, 2H, C*H*$_2$), 1.73 (quint, *J* = 6.3 Hz, 2H, C*H*$_2$), 1.60 (quint, *J* = 5.6 Hz, 2H, C*H*$_2$), 1.54 (quint, *J* = 6.3 Hz, 2H, C*H*$_2$). ^{13}C{^{1}H} NMR (175 MHz, $CDCl_3$): δ 161.32 (olefinic-*C*), 148.91 (quat-*C*), 148.88 (quat-*C*), 126.33 (quat-*C*), 121.88 (Ar*C*H), 118.77 (*C*N), 112.18 (Ar*C*H), 111.04 (Ar*C*H), 107.35 (olefinic-*C*), 55.92 (O*C*H$_3$), 55.88 (O*C*H$_3$), 35.24 (*C*H$_2$), 31.31 (*C*H$_2$), 28.05 (*C*H$_2$), 27.88 (*C*H$_2$), 25.87 (*C*H$_2$). HRMS (ESI) m/z calcd for $C_{16}H_{19}NO_2$ $(M+Na)^+$: 280.1308, found: 280.1328.

2-(Benzo[*d*][1,3]dioxol-5-yl)-2-cyclohexylideneacetonitrile (3.1g): Colorless liquid.



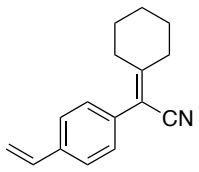
Yield (65%). IR (DCM): 3055, 2986, 2938, 2859, 2209, 1636, 1488, 1265, 1240, 1040, 734, 705 cm^{-1}. ^{1}H NMR (700 MHz, $CDCl_3$): δ 6.80 (d, *J* = 8.4 Hz, 1H, ArC*H*), 6.73-6.74 (m, 2H, ArC*H*), 5.98 (s, 2H, OC*H*$_2$), 2.65 (t, *J* = 5.6 Hz, 2H, C*H*$_2$), 2.30 (t, *J* = 5.6 Hz, 2H, C*H*$_2$), 1.76 (quint, *J* = 8.4 Hz, 2H, C*H*$_2$), 1.63 (quint, *J* = 6.3 Hz, 2H, C*H*$_2$), 1.57 (quint, *J* = 5.6 Hz, 2H, C*H*$_2$). ^{13}C{^{1}H} NMR (175 MHz, $CDCl_3$): δ 161.77 (olefinic-*C*), 147.93 (quat-*C*), 147.64 (quat-*C*), 127.62 (quat-*C*), 123.18 (Ar*C*H), 118.82 (*C*N), 109.75 (Ar*C*H), 108.58 (Ar*C*H), 107.38 (olefinic-*C*), 101.48 (O*C*H$_2$), 35.40 (*C*H$_2$), 31.45 (*C*H$_2$), 28.21 (*C*H$_2$), 28.03 (*C*H$_2$), 26.03 (*C*H$_2$). HRMS (ESI) m/z calcd for $C_{15}H_{15}NO_2$ $(M+Na)^+$: 264.0995, found: 264.0994.

2-Cyclohexylidene-2-(3,4,5-trimethoxyphenyl)acetonitrile (3.1h): Colorless liquid.



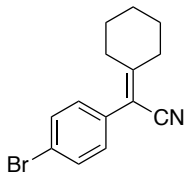
Yield (83%). IR (DCM): 3056, 2940, 2859, 2209, 1635, 1413, 1265, 1129, 1003, 737, 705 cm^{-1}. ^{1}H NMR (700 MHz, $CDCl_3$): δ 6.45 (s, 2H, ArC*H*), 3.84 (s, 9H, OCH_3), 2.65 (t, *J* = 5.6 Hz, 2H, CH_2), 2.32 (t, *J* = 6.3 Hz, 2H, CH_2), 1.76 (quint, *J* = 7.7 Hz, 2H, CH_2), 1.63 (quint, *J* = 6.3 Hz, 2H, CH_2), 1.58 (quint, *J* = 7 Hz, 2H, CH_2). $^{13}C\{^{1}H\}$ NMR (175 MHz, $CDCl_3$): δ 162.10 (olefinic-*C*), 153.36 (quat-*C*), 138.06 (quat-*C*), 129.36 (quat-*C*), 118.65 (*C*N), 107.69 (olefinic-*C*), 106.53 (Ar*C*H), 60.98 (O*C*H_3), 56.29 (O*C*H_3), 35.35 (*C*H_2), 31.61 (*C*H_2), 28.18 (*C*H_2), 28.05 (*C*H_2), 25.96 (*C*H_2). HRMS (ESI) m/z calcd for $C_{17}H_{21}NO_3$ $(M+H)^+$: 288.1594, found: 288.1572.

2-Cyclohexylidene-2-(4-vinylphenyl)acetonitrile (3.1i): Colorless liquid. Yield



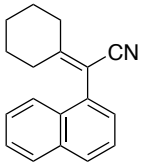
(77%). IR (DCM): 3056, 2940, 2859, 2209, 1638, 1418, 1265, 1129, 1003, 737, 705 cm^{-1}. ^{1}H NMR (700 MHz, $CDCl_3$): δ 7.35 (d, *J* = 8.4 Hz, 2H, ArC*H*), 7.18 (t, *J* = 7 Hz, 2H, ArC*H*), 6.64 (dd, J_1 = 10.5 Hz, J_2 = 7 Hz, 1H, olefinic-C*H*), 5.70 (d, *J* = 17.5 Hz, 1H, olefinic-CH_2), 5.22 (d, *J* = 10.5 Hz, 1H, olefinic-CH_2), 2.61 (t, *J* = 6.3 Hz, 2H, CH_2), 2.26 (t, *J* = 6.3 Hz, 2H, CH_2), 1.71 (quint, *J* = 5.6 Hz, 2H, CH_2), 1.58 (quint, *J* = 5.6 Hz, 2H, CH_2), 1.52 (quint, *J* = 6.3 Hz, 2H, CH_2). $^{13}C\{^{1}H\}$ NMR (175 MHz, $CDCl_3$): δ 162.12 (olefinic-*C*), 137.61 (quat-*C*), 136.22 (olefinic-*C*), 133.35 (quat-*C*), 129.59 (Ar*C*H), 126.53 (Ar*C*H), 118.75 (*C*N), 114.92 (olefinic-*C*), 107.62 (olefinic-*C*), 31.48 (*C*H_2), 31.06 (*C*H_2), 28.25 (*C*H_2), 28.06 (*C*H_2), 26.03 (*C*H_2). HRMS (ESI) m/z calcd for $C_{16}H_{17}N$ $(M+H)^+$: 223.1362, found: 223.1370.

2-(4-Bromophenyl)-2-cyclohexylideneacetonitrile (3.1j): Colorless liquid. Yield (70%). IR (DCM): 3053, 2933, 2857, 2211, 1688, 1448, 1264, 1073, 896, 830, 745 cm^{-1}. ^{1}H NMR (700 MHz, $CDCl_3$): δ 7.51 (d, *J* = 8.4 Hz, 2H, ArC*H*), 7.15 (d, *J* = 9.1 Hz,



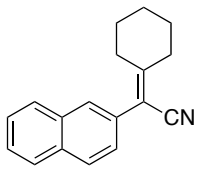
2H, ArC*H*), 2.67 (t, *J* = 6.3 Hz, 2H, CH_2), 2.29 (t, *J* = 5.6 Hz, 2H, CH_2), 1.78 (quint, *J* = 5.6 Hz, 2H, CH_2), 1.65 (quint, *J* = 5.6 Hz, 2H, CH_2), 1.59 (quint, *J* = 5.6 Hz, 2H, CH_2). $^{13}C\{^1H\}$ NMR (175 MHz, $CDCl_3$): δ 162.88 (olefinic-*C*), 132.90 (quat-*C*), 132.02 (Ar*C*H), 131.04 (Ar*C*H), 122.57 (quat-*C*), 118.36 (*C*N), 106.86 (olefinic-*C*), 35.56 (*C*H_2), 31.47 (*C*H_2), 28.22 (*C*H_2), 28.04 (*C*H_2), 25.96 (*C*H_2). HRMS (ESI) m/z calcd for $C_{14}H_{14}NBr$ $(M+H)^+$: 276.0382, found: 276.0370.

2-Cyclohexylidene-2-(naphthalen-1-yl)acetonitrile (3.1k): Colorless liquid. Yield



(80%). IR (DCM): 3054, 2939, 2860, 2207, 1438, 1265, 1117, 909, 775, 737 cm^{-1}. ^1H NMR (700 MHz, $CDCl_3$): δ 7.87-7.90 (m, 3H, ArC*H*), 7.52-7.56 (m, 2H, ArC*H*), 7.48 (t, *J* = 7 Hz, 1H, ArC*H*), 7.36 (dd, J_1 = 7 Hz, J_2 = 1.4 Hz, 1H, ArC*H*), 2.79-2.86 (m, 2H, CH_2), 1.99-2.05 (m, 2H, CH_2), 1.84-1.90 (m, 2H, CH_2), 1.64 (quint, *J* = 5.6 Hz, 2H, CH_2), 1.50 (quint, *J* = 5.6 Hz, 2H, CH_2). $^{13}C\{^1H\}$ NMR (175 MHz, $CDCl_3$): δ 164.38 (olefinic-*C*), 133.79 (quat-*C*), 131.45 (quat-*C*), 131.08 (quat-*C*), 129.15 (Ar*C*H), 128.62 (Ar*C*H), 127.79 (Ar*C*H), 126.83 (Ar*C*H), 126.34 (Ar*C*H), 125.44 (Ar*C*H), 124.71 (Ar*C*H), 118.38 (*C*N), 105.16 (olefinic-*C*), 34.83 (*C*H_2), 31.72 (*C*H_2), 28.29 (*C*H_2), 27.86 (*C*H_2), 25.86 (*C*H_2). HRMS (ESI) m/z calcd for $C_{18}H_{17}N$ $(M+H)^+$: 248.1434, found: 248.1430.

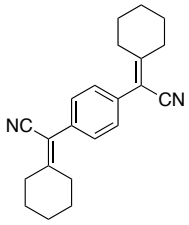
2-Cyclohexylidene-2-(naphthalen-2-yl)acetonitrile (3.1l): Colorless liquid. Yield



(81%). IR (DCM): 3052, 2934, 2858, 2209, 1590, 1443, 1267, 1185, 946, 895, 859, 736 cm^{-1}. ^1H NMR (700 MHz, $CDCl_3$): δ 7.83-7.87 (m, 3H, ArC*H*), 7.76 (s, 1H, ArC*H*), 7.51 (dd, J_1 = 3.5 Hz, J_2 = 2.8 Hz, 2H, ArC*H*), 7.38 (d, *J* = 9.1 Hz, 1H, ArC*H*), 2.74 (t, *J* = 5.6 Hz, 2H, CH_2), 2.38 (t, *J* = 6.3 Hz, 2H, CH_2), 1.82 (quint, *J* = 6.3 Hz, 2H, CH_2), 1.67 (quint, *J* = 5.6 Hz, 2H, CH_2), 1.60-1.63 (m, 2H, CH_2). $^{13}C\{^1H\}$ NMR (175 MHz, $CDCl_3$): δ 162.43 (olefinic-*C*),

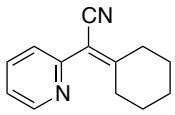
133.23 (quat-*C*), 132.90 (quat-*C*), 131.37 (quat-*C*), 128.74 (Ar*C*H), 128.50 (Ar*C*H), 128.17 (Ar*C*H), 127.83 (Ar*C*H), 126.88 (Ar*C*H), 126.78 (Ar*C*H), 126.70 (Ar*C*H), 118.87 (*C*N), 107.88 (olefinic-*C*), 35.56 (*C*H_2), 31.57 (*C*H_2), 28.28 (*C*H_2), 28.08 (*C*H_2), 26.04 (*C*H_2). HRMS (ESI) m/z calcd for $C_{18}H_{17}N$ $(M+Na)^+$: 270.1253, found: 270.1277.

2,2'-(1,4-Phenylene)bis(2-cyclohexylideneacetonitrile) (3.1m): White solid. Yield



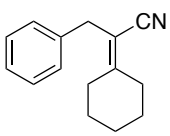
(48%). IR (DCM): 3055, 2984, 2928, 2206, 1611, 1427, 1264, 983, 897, 749 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.24 (s, 4H, ArC*H*), 2.62 (t, *J* = 6 Hz, 4H, C*H*$_2$), 2.26 (t, *J* = 6.4 Hz, 4H, C*H*$_2$), 1.72 (quint, *J* = 5.6 Hz, 4H, C*H*$_2$), 1.51-1.62 (m, 8H, C*H*$_2$). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 162.81 (olefinic-*C*), 133.93 (quat-*C*), 129.70 (Ar*C*H), 118.57 (*C*N), 107.22 (olefinic-*C*), 35.57 (*C*H_2), 31.50 (*C*H_2), 28.24 (*C*H_2), 28.07 (*C*H_2), 25.97 (*C*H_2). HRMS (ESI) m/z calcd for $C_{22}H_{24}N_2$ $(M+H)^+$: 317.2012, found: 317.2000.

2-Cyclohexylidene-2-(pyridin-2-yl)acetonitrile (3.1n): Pale yellow liquid. Yield



(62%). IR (DCM): 3056, 2985, 2860, 2214, 1618 1431, 1264, 991, 897, 743 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.57 (d, *J* = 2.8 Hz, 1H, ArC*H*), 7.66 (td, J_1 = 4.4 Hz, J_2 = 0.8 Hz, 1H, ArC*H*), 7.32 (d, *J* = 4.4 Hz, 1H, ArC*H*), 7.17 (ddd, J_1 = 2.8 Hz, J_2 = 1.6 Hz, J_3 = 0.8 Hz, 1H, ArC*H*), 2.66 (t, *J* = 3.6 Hz, 2H, C*H*$_2$), 2.47 (t, *J* = 3.6 Hz, 2H, C*H*$_2$), 1.74 (quint, *J* = 3.2 Hz, 2H, C*H*$_2$), 1.56-1.60 (m, 4H, C*H*$_2$). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 165.50 (olefinic-*C*), 152.81 (quat-*C*), 149.74 (Ar*C*H), 136.84 (Ar*C*H), 124.42 (Ar*C*H), 122.84 (Ar*C*H), 118.34 (*C*N), 108.27 (olefinic-*C*), 35.96 (*C*H_2), 31.48 (*C*H_2), 28.24 (*C*H_2), 27.96 (*C*H_2), 25.95 (*C*H_2). HRMS (ESI) m/z calcd for $C_{13}H_{14}N_2$ $(M+H)^+$: 199.1230, found: 199.1236.

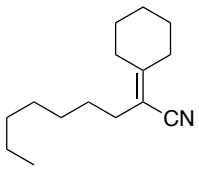
2-Cyclohexylidene-3-phenylpropanenitrile (3.1o): Colorless liquid. Yield (62%). IR



(DCM): 3055, 2929, 2857, 2209, 1449, 1262, 1026, 902, 728 cm^{-1}. ^1H

NMR (400 MHz, $CDCl_3$): δ 7.25 (t, *J* = 7.2 Hz, 2H, ArC*H*), 7.13-7.19 (m, 3H, ArC*H*), 3.50 (s, 2H, CH_2), 2.49 (t, *J* = 6 Hz, 2H, CH_2), 2.31 (t, *J* = 6 Hz, 2H, CH_2), 1.51-1.61 (m, 6H, CH_2). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 160.24 (olefinic-*C*), 137.98 (quat-*C*), 128.85 (Ar*C*H), 128.36 (Ar*C*H), 126.91 (Ar*C*H), 119.39 (*C*N), 105.21 (olefinic-*C*), 35.41 (*C*H_2), 35.31 (*C*H_2), 30.70 (*C*H_2), 28.10 (*C*H_2), 27.76 (*C*H_2), 26.09 (*C*H_2). HRMS (ESI) m/z calcd for $C_{15}H_{17}N$ $(M+H)^+$: 234.1253, found: 234.1232.

2-Cyclohexylidenenonanenitrile (3.1p): Colorless liquid. Yield (48%). IR (DCM): 3054, 2929, 2858, 2207, 1630, 1453, 1264, 910, 738 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 2.43 (t, *J* = 5.2 Hz, 2H, CH_2), 2.18 (t, *J* = 5.6 Hz, 2H, CH_2), 2.13 (t, *J* = 7.2 Hz, 2H, CH_2), 1.52-1.59 (m, 6H, CH_2), 1.43 (quint, *J* = 7.6 Hz, 2H, CH_2), 1.12-1.27 (m, 8H, CH_2), 0.81 (t, *J* = 6.4 Hz, 3H, CH_3). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 158.90 (olefinic-*C*), 119.53 (*C*N), 106.33 (olefinic-*C*), 35.33 (*C*H_2), 31.84 (*C*H_2), 30.35 (*C*H_2), 29.27 (*C*H_2), 29.11 (*C*H_2), 28.93 (*C*H_2), 28.79 (*C*H_2), 28.12 (*C*H_2), 27.79 (*C*H_2), 26.17 (*C*H_2), 22.71 (*C*H_2), 14.16 (*C*H_3). HRMS (ESI) m/z calcd for $C_{15}H_{25}N$ $(M+H)^+$: 220.2060, found: 220.2042.

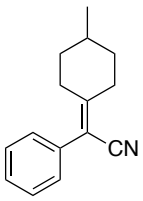


General Procedure for α-Olefination of Nitriles Using Secondary Alcohols:

In a glove box, 25 mL Schlenk flask was charged with a stirring bar, catalyst **1** (0.01 mmol), base (0.02 mmol), nitriles (1 mmol), secondary alcohols (2 mmol) and toluene (1.5 mL) under nitrogen atmosphere. The flask was taken out of the glove box, equipped with a condenser and the solution was refluxed (oil bath temperature 135 °C) with stirring under a flow of argon for 10-24 h. After cooling to room temperature, 1 mmol of internal standard (benzene) was added and the reaction mixture was subjected GC analysis. The solvent was evaporated and crude reaction mixture was purified by column chromatography over silica-gel (100-200 mesh) using ethyl acetate / hexane

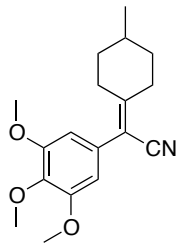
mixture as an eluent. The conversion of nitriles was calculated using GC analysis and yields were determined for pure products after column chromatography.

2-(4-Methylcyclohexylidene)-2-phenylacetonitrile (3.2a): Colorless liquid. Yield



(75%). IR (DCM): 3058, 3026, 2952, 2925, 2209, 1618, 1492, 1444, 1267, 951, 763, 737, 700 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.18-7.31 (m, 5H, ArC*H*), 2.97-3.03 (m, 1H, CH_2), 2.57-2.63 (m, 1H, CH_2), 2.21-2.28 (m, 1H, CH_2), 1.86-1.94 (m, 2H, CH_2), 1.68-1.73 (m, 1H, C*H*), 1.56-1.64 (m, 1H, CH_2), 1.14-1.21 (m, 1H, CH_2), 0.90-1.01 (m, 1H, CH_2), 0.85 (d, J = 6.4 Hz, 3H, CH_3). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 161.63 (olefinic-*C*), 133.97 (quat-*C*), 129.29 (Ar*C*H), 128.68 (Ar*C*H), 128.24 (Ar*C*H), 118.76 (*C*N), 107.90 (olefinic-*C*), 36.01 (*C*H), 35.85 (*C*H_2), 34.75 (*C*H_2), 32.04 (*C*H_2), 30.64 (*C*H_2), 21.44 (*C*H_3). HRMS (ESI) m/z calcd for $C_{15}H_{17}N$ $(M+H)^+$: 212.1434, found: 212.1415.

2-(4-Methylcyclohexylidene)-2-(3,4,5-trimethoxyphenyl)acetonitrile (3.2b):

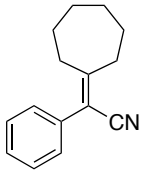


Colorless liquid. Yield (93%). IR (DCM): 3051, 2927, 2850, 2210, 1584, 1449, 1346, 1239, 1128, 1006, 914, 841, 734 cm^{-1}. ^1H NMR (700 MHz, $CDCl_3$): δ 6.46 (s, 2H, ArC*H*), 3.84 (s, 9H, OCH_3), 3.04 (dd, J_1 =14 Hz, J_2 =1.4 Hz, 1H, CH_2), 2.70 (dd, J_1 =14 Hz, J_2 =2.1 Hz, 1H, CH_2), 2.30 (dt, J_1 =13.3 Hz, J_2 =4.9 Hz, 1H, CH_2), 1.97-2.01 (m, 2H, C*H* & CH_2), 1.67-1.71 (m, 2H, CH_2) 1.24 (dq, J_1 =13.3 Hz, J_2 =3.5 Hz, 1H, CH_2), 1.02 (dq, J_1 =11.9 Hz, J_2 =4.2 Hz, 1H, CH_2), 0.93 (d, J =7 Hz, 3H, CH_3). $^{13}C\{^1H\}$ NMR (175 MHz, $CDCl_3$): δ 161.78 (olefinic-*C*), 153.37 (quat-*C*), 138.09 (quat-*C*), 129.42 (quat-*C*), 118.69 (*C*N), 107.83 (olefinic-*C*), 106.55 (Ar*C*H), 61.01 (O*C*H_3), 56.31 (O*C*H_3), 36.04 (*C*H_2), 35.94 (*C*H_2), 34.72 (*C*H), 32.12 (*C*H_2), 30.94 (*C*H_2), 21.48 (*C*H_3). HRMS (ESI) m/z calcd for $C_{18}H_{23}NO_3$ $(M+Na)^+$: 324.1570, found: 324.1588.

2-(4-(*tert*-Butyl)cyclohexylidene)-2-(3,4-dimethoxyphenyl)acetonitrile (3.2c): White solid. Yield (80%). IR (DCM): 3055, 2987, 2863, 2209, 1605, 1422, 1262, 1027, 896, 739, 703 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 6.84 (s, 1H, ArC*H*), 6.81 (d, *J* =1.6 Hz, 1H, ArC*H*), 6.78 (d, J_1 =1.6 Hz, 1H, ArC*H*), 3.88 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 3.12 (dd, J_1 =14 Hz, J_2 =2.4 Hz, 1H, CH_2), 2.79 (dd, J_1 =14 Hz, J_2 =2.4 Hz, 1H, CH_2), 2.24 (dt, J_1 =13.2 Hz, J_2 =4.8 Hz, 1H, CH_2), 2.02-2.06 (m, 1H, C*H*), 1.86-1.96 (m, 2H, CH_2) 1.22-1.32 (m, 2H, CH_2), 1.01-1.09 (m, 1H, CH_2), 0.86 (s, 9H, CH_3). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 161.33 (olefinic-*C*), 149.01 (quat-*C*), 148.97 (quat-*C*), 126.46 (quat-*C*), 122.05 (Ar*C*H), 118.93 (*C*N), 112.30 (Ar*C*H), 111.08 (Ar*C*H), 107.24 (olefinic-*C*), 56.06 (O*C*H_3), 56.01 (O*C*H_3), 47.66 (*C*H), 35.24 (*C*H_2), 32.53 (quat-*C*), 31.29 (*C*H_2), 28.84 (*C*H_2), 28.70 (*C*H_2), 27.61 (*C*H_3). HRMS (ESI) m/z calcd for $C_{20}H_{27}NO_2$ $(M+Na)^+$: 336.1934, found: 336.1929.

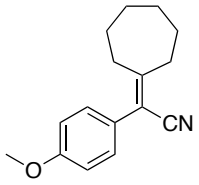
2-(1-Phenethylpiperidin-4-ylidene)-2-(3,4,5-trimethoxyphenyl)acetonitrile (3.2d): Colorless liquid. Yield (60%). IR (DCM): 3041, 2987, 2867, 2212, 1682, 1431, 1265, 1002, 896, 841, 747, 703 cm^{-1}. ^1H NMR (700 MHz, $CDCl_3$): δ 7.29 (t, *J* = 7.7 Hz, 2H, ArC*H*), 7.20-7.22 (m, 3H, ArC*H*), 6.48 (s, 2H, ArC*H*), 3.86 (s, 9H, OCH_3), 2.80-2.84 (m, 4H, CH_2), 2.72 (t, *J* = 5.6 Hz, 2H, CH_2), 2.65 (t, *J* = 8.4 Hz, 2H, CH_2), 2.51-2.54 (m, 4H, CH_2). $^{13}C\{^1H\}$ NMR (175 MHz, $CDCl_3$): δ 158.09 (olefinic-*C*), 153.49 (quat-*C*), 140.19 (quat-*C*), 138.34 (quat-*C*), 128.81 (Ar*C*H), 128.79 (Ar*C*H), 128.58 (Ar*C*H), 126.30 (Ar*C*H), 118.32 (*C*N), 109.04 (Ar*C*H), 106.64 (olefinic-*C*), 61.06 (O*C*H_3), 59.84 (*C*H_2), 56.40 (O*C*H_3), 54.17 (*C*H_2), 54.02 (*C*H_2), 34.52 (*C*H_2), 33.94 (*C*H_2), 31.23 (*C*H_2). HRMS (ESI) m/z calcd for $C_{24}H_{28}N_2O_3$ $(M+H)^+$: 393.2173, found: 393.2194.

2-Cycloheptylidene-2-phenylacetonitrile (3.2e): Colorless liquid. Yield (86%). IR



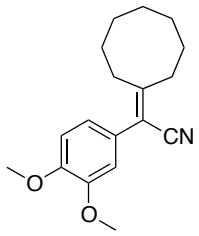
(DCM): 3048, 2984, 2927, 2855, 2208, 1605, 1421, 1264, 1048, 896, 749, 703 cm^{-1}. ^{1}H NMR (700 MHz, $CDCl_3$): δ 7.38 (t, *J* = 7.7 Hz, 2H, ArC*H*), 7.33 (t, *J* = 7 Hz, 1H, ArC*H*), 7.28 (d, *J* = 7.7 Hz, 2H, ArC*H*), 2.80 (t, *J* = 6.3 Hz, 2H, CH_2), 2.42 (t, *J* = 6.3 Hz, 2H, CH_2), 1.80 (quint, *J* = 6.3 Hz, 2H, CH_2), 1.62 (quint, *J* = 5.6 Hz, 4H, CH_2), 1.53 (quint, *J* = 5.6 Hz, 2H, CH_2). $^{13}C\{^{1}H\}$ NMR (175 MHz, $CDCl_3$): δ 164.64 (olefinic-*C*), 134.47 (quat-*C*), 129.22 (Ar*C*H), 128.76 (Ar*C*H), 128.27 (Ar*C*H), 118.94 (*C*N), 110.57 (olefinic-*C*), 36.25 (*C*H_2), 32.96 (*C*H_2), 29.74 (*C*H_2), 28.87 (*C*H_2), 27.37 (*C*H_2), 27.06 (*C*H_2). HRMS (ESI) m/z calcd for $C_{15}H_{17}N$ $(M+H)^+$: 212.1434, found: 212.1430.

2-Cycloheptylidene-2-(4-methoxyphenyl)acetonitrile (3.2f): Colorless liquid. Yield



(70%). IR (DCM): 3052, 2985, 2856, 2207, 1607, 1422, 1264, 1035, 896, 748, 703 cm^{-1}. ^{1}H NMR (700 MHz, $CDCl_3$): δ 7.20 (d, *J* = 9.1 Hz, 2H, ArC*H*), 6.90 (d, *J* = 9.1 Hz, 2H, ArC*H*), 3.82 (s, 3H, OCH_3), 2.78 (t, *J* = 5.6 Hz, 2H, CH_2), 2.42 (t, *J* = 6.3 Hz, 2H, CH_2), 1.79 (quint, *J* = 5.6 Hz, 2H, CH_2), 1.62 (quint, *J* = 6.3 Hz, 4H, CH_2), 1.52 (quint, *J* = 6.3 Hz, 2H, CH_2). $^{13}C\{^{1}H\}$ NMR (175 MHz, $CDCl_3$): δ 163.82 (olefinic-*C*), 159.46 (quat-*C*), 130.46 (quat-*C*), 126.79 (Ar*C*H), 119.16 (*C*N), 114.13 (Ar*C*H), 110.15 (olefinic-*C*), 55.45 (O*C*H_3), 36.19 (*C*H_2), 32.96 (*C*H_2), 29.77 (*C*H_2), 28.90 (*C*H_2), 27.43 (*C*H_2), 27.11 (*C*H_2). HRMS (ESI) m/z calcd for $C_{16}H_{19}NO$ $(M+H)^+$: 242.1539, found: 242.1533.

2-Cyclooctylidene-2-(3,4-dimethoxyphenyl)acetonitrile (3.2g): Colorless liquid.



Yield (66%). IR (DCM): 3051, 2932, 2861, 2206, 1600, 1421, 1263, 1027, 895, 742, 704 cm^{-1}. ^{1}H NMR (700 MHz, $CDCl_3$): δ 6.80 (s, 1H, ArC*H*), 6.77 (d, *J* =3.5 Hz, 1H, ArC*H*), 6.71 (d, *J* =3.5 Hz, 1H, ArC*H*), 3.83 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 2.62 (t, *J* =11.2 Hz,

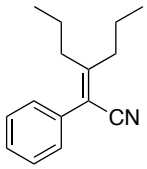
2H, CH_2), 2.31 (t, J =10.5 Hz, 2H, CH_2), 1.84-1.91 (m, 2H, CH_2), 1.59-1.64 (m, 2H, CH_2), 1.50-1.55 (m, 2H, CH_2) 1.38-1.42 (m, 4H, CH_2). $^{13}C\{^1H\}$ NMR (175 MHz, $CDCl_3$): δ 165.83 (olefinic-*C*), 149.16 (quat-*C*), 149.04 (quat-*C*), 127.16 (quat-*C*), 121.83 (Ar*C*H), 119.18 (*C*N), 112.22 (Ar*C*H), 111.34 (Ar*C*H), 109.71 (olefinic-*C*), 56.12 (O*C*H_3), 56.06 (O*C*H_3), 34.41 (*C*H), 32.94 (*C*H_2), 28.53 (*C*H_2), 27.81 (*C*H_2), 25.98 (*C*H_2), 25.71 (*C*H_2), 23.97 (*C*H_2). HRMS (ESI) m/z calcd for $C_{18}H_{23}NO_2$ $(M+H)^+$: 286.1802, found: 286.1787.

(2-Adamantan-2-ylidene)-2-(3,4-dimethoxyphenyl)acetonitrile (3.2h): Colorless liquid. Yield (69%). IR (DCM): 3054, 2987, 2926, 2206, 1590, 1430, 1261, 1026, 896, 763, 749 cm^{-1}. ^1H NMR (700 MHz, $CDCl_3$): δ 6.85 (s, 1H, ArC*H*), 6.82 (d, J = 2.1 Hz, 1H, ArC*H*), 6.80 (d, J = 2.1 Hz, 1H, ArC*H*), 3.89 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 2.06-2.09 (m, 2H, C*H*), 2.01-2.03 (m, 3H, C*H* & CH_2), 1.95-1.97 (m, 2H, CH_2), 1.89-1.92 (m, 4H, CH_2), 1.85-1.87 (m, 1H, C*H*), 1.76-1.80 (m, 2H, CH_2). $^{13}C\{^1H\}$ NMR (175 MHz, $CDCl_3$): δ 169.69 (olefinic-*C*), 149.12 (quat-*C*), 149.03 (quat-*C*), 126.36 (quat-*C*), 121.74 (Ar*C*H), 118.88 (*C*N), 112.22 (Ar*C*H), 111.24 (Ar*C*H), 103.13 (olefinic-*C*), 56.09 (O*C*H_3), 56.07 (O*C*H_3), 39.62 (*C*H_2), 39.38 (*C*H_2), 38.77 (*C*H_2), 36.60 (*C*H), 34.36 (*C*H), 27.76 (*C*H). HRMS (ESI) m/z calcd for $C_{20}H_{23}NO_2$ $(M+H)^+$: 310.1802, found: 310.1799.

3-Ethyl-2-phenylpent-2-enenitrile (3.2i): Colorless liquid. Yield (58%). IR (DCM): 3055, 2977, 2879, 2210, 1449, 1266, 1076, 896, 737, 704 cm^{-1}. ^1H NMR (700 MHz, $CDCl_3$): δ 7.19-7.32 (m, 5H, ArC*H*), 2.53 (q, J = 7.7 Hz, 2H, CH_2), 2.16 (q, J = 7.7 Hz, 2H, CH_2), 1.14 (t, J = 7.7 Hz, 3H, CH_3), 0.96 (t, J = 7.7 Hz, 3H, CH_3). $^{13}C\{^1H\}$ NMR (175 MHz, $CDCl_3$): δ 165.66 (olefinic-*C*), 134.33 (quat-*C*), 129.09 (Ar*C*H), 128.83 (Ar*C*H), 128.39 (Ar*C*H), 118.84 (*C*N), 110.35

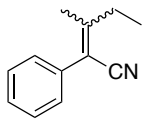
(olefinic-*C*), 28.35 (*C*H_2), 24.77 (*C*H_2), 12.99 (*C*H_3), 12.67 (*C*H_3). HRMS (ESI) m/z calcd for $C_{13}H_{15}N$ $(M+H)^+$: 186.1277, found: 186.1270.

2-Phenyl-3-propylhex-2-enenitrile (3.2j): Colorless liquid. Yield (48%). IR (DCM):



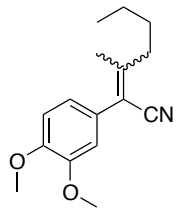
3055, 2918, 2849, 2210, 1613, 1422, 1265, 1075, 896, 747, 704 cm^{-1}. ^1H NMR (700 MHz, $CDCl_3$): δ 7.31 (t, *J* = 7.7 Hz, 2H, ArC*H*), 7.26 (t, *J* = 7 Hz, 1H, ArC*H*), 7.19 (d, *J* = 5.6 Hz, 2H, ArC*H*), 2.48 (t, *J* = 7.7 Hz, 2H, C*H*$_2$), 2.09 (t, *J* = 8.4 Hz, 2H, C*H*$_2$), 1.54-1.59 (m, 2H, C*H*$_2$), 1.34-1.40 (m, 2H, C*H*$_2$), 0.97 (t, *J* = 7 Hz, 3H, C*H*$_3$), 0.75 (t, *J* = 7 Hz, 3H, C*H*$_3$). $^{13}C\{^1H\}$ NMR (175 MHz, $CDCl_3$): δ 162.91 (olefinic-*C*), 134.48 (quat-*C*), 129.23 (Ar*C*H), 128.82 (Ar*C*H), 128.36 (Ar*C*H), 119.05 (*C*N), 111.47 (olefinic-*C*), 37.35 (*C*H_2), 33.79 (*C*H_2), 21.79 (*C*H_2), 21.42 (*C*H_2), 14.14 (*C*H_3), 14.07 (*C*H_3). HRMS (ESI) m/z calcd for $C_{15}H_{19}N$ $(M+H)^+$: 214.1590, found: 214.1585.

3-Methyl-2-phenylpent-2-enenitrile (3.2k): Pale yellow liquid. Yield (58%). Isomer



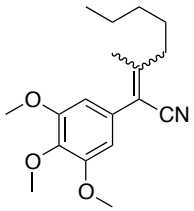
ratio = 62:38 (*Z*/*E*) (according to ^1H NMR) IR (DCM): 3021, 2931, 2879, 2209, 1613, 1472, 1072, 856, 747 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.19-7.33 (m, 10H, ArC*H*) (both isomers), 2.52 (q, *J* = 7.6 Hz, 2H, C*H*$_2$)-major, 2.14 (q, *J* = 7.6 Hz, 2H, C*H*$_2$)-minor, 2.16 (s, 3H, C*H*$_3$C=)-minor, 1.83 (s, 3H, C*H*$_3$C=)-major, 1.14 (t, *J* = 7.6 Hz, 3H, C*H*$_3$CH$_2$)-major, 0.99 (t, *J* = 7.6 Hz, 3H, C*H*$_3$CH$_2$)-minor, 0.75 (t, *J* = 7 Hz, 3H, C*H*$_3$). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 160.15, 159.92 (olefinic-*C*), 134.25, 134.15 (quat-*C*), 129.17, 128.97 (Ar*C*H), 128.75, 128.65 (Ar*C*H), 128.32, 128.25 (Ar*C*H), 118.95, 118.66 (*C*N), 110.78, 110.25 (olefinic-*C*), 31.85, 27.54 (CH$_3$*C*H$_2$), 21.81, 19.08 (*C*H$_3$C=), 12.60, 12.46 (*C*H$_3$CH$_2$). HRMS (ESI) m/z calcd for $C_{12}H_{13}N$ $(M+H)^+$: 172.1121, found: 172.1128.

2-(3,4-Dimethoxyphenyl)-3-methylhept-2-enenitrile (3.2l): Colorless liquid. Yield (20%). Isomer ratio = 58:42 (*Z*/*E*) (according to ^1H NMR) IR (DCM): 3059, 2931,



2865, 2209, 1597, 1422, 1260, 1027, 913, 734 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 6.70-6.81 (m, 6H, ArC*H*) (both isomers), 3.83 (s, 6H, OCH_3)-major, 3.82 and 3.81 (s, 6H, OCH_3)-minor, 2.50 (t, *J* = 7.6 Hz, 2H, CH_2)-major, 2.14 (t, *J* = 7.6 Hz, 2H, CH_2)-minor, 2.14 (s, 3H, CH_3C=)-minor, 1.83 (s, 3H, CH_3C=)-major, 1.45-1.55 (m, 4H, CH_2) (both isomers), 1.34-1.40 (m, 4H, CH_2) (both isomers), 1.16-1.21 (m, 4H, CH_2) (both isomers), 0.91 (t, *J* = 7.6 Hz, 3H, CH_3)-major, 0.77 (t, *J* = 7.6 Hz, 3H, CH_3)-minor. $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 158.51, 158.30 (olefinic-*C*), 149.06, 149.02, 148.98 (quat-*C*), 126.94, 126.79 (quat-*C*), 122.04, 121.78 (Ar*C*H), 119.17, 119.03 (*C*N), 112.19, 112.11 (Ar*C*H), 111.17, 111.09 (olefinic-*C*), 56.10, 56.04 (O*C*H_3), 38.48, 34.28 (*C*H_3C=), 30.30, 30.15 (*C*H_2), 22.70, 22.62 (*C*H_2), 22.27, 19.72 (*C*H_2), 14.06, 13.93 (*C*H_3). HRMS (ESI) m/z calcd for $C_{16}H_{21}NO_2$ $(M+H)^+$: 260.1645, found: 260.1643.

3-Methyl-2-(3,4,5-trimethoxyphenyl)oct-2-enenitrile (3.2m): Colorless liquid. Yield



(20%). Isomer ratio = 66:34 (*Z*/*E*) (according to ^1H NMR). IR (DCM): 3009, 2927, 2858, 2207, 1590, 1495, 1126, 916, 847 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 6.41 (s, 2H, ArC*H*)-major, 6.39 (s, 2H, ArC*H*)-minor, 3.79 (s, 9H, OCH_3)-major, 3.78 (s, 9H, OCH_3)-minor, 2.49 (t, *J* = 7.6 Hz, 2H, CH_2C=)-major, 2.14 (t, *J* = 7.6 Hz, 2H, CH_2C=)-minor, 2.14 (s, 3H, CH_3C=)-minor, 1.84 (s, 3H, CH_3C=)-major, 1.53 (quint, *J* = 7.2 Hz, 2H, CH_2)-major, 1.40 (quint, *J* = 7.2 Hz, 2H, CH_2)-minor, 1.31-1.33 (m, 4H, CH_2)-major, 1.15-1.20 (m, 4H, CH_2)-minor, 0.87 (t, *J* = 5.6 Hz, 3H, CH_3)-major, 0.78 (t, *J* = 5.6 Hz, 3H, CH_3)-minor. $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 159.07, 159.00 (olefinic-*C*), 153.35, 153.31 (quat-*C*), 138.00 (quat-*C*), 129.79, 129.65 (quat-*C*), 118.91, 118.76 (*C*N), 110.99, 110.74 (olefinic-*C*), 106.45, 106.22 (Ar*C*H), 61.00, 56.30, 56.22 (O*C*H_3), 38.63, 34.59 (*C*H_2), 31.72, 31.59 (*C*H_2C=), 27.81, 27.73 (*C*H_2), 22.56, 22.46 (*C*H_2),

22.21, 19.78 (*C*H_3C=), 14.06, 13.98 (*C*H_3). HRMS (ESI) m/z calcd for $C_{18}H_{25}NO_3$ $(M+H)^+$: 304.1907, found: 304.1915.

3.6 NOTES AND REFERENCES

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^{1}H and ^{13}C NMR Spectra of α-Olefinated Nitriles:

Figure 3.2 ^{1}H NMR spectrum of 2-cyclohexylidene-2-phenylacetonitrile (**3.1a**):

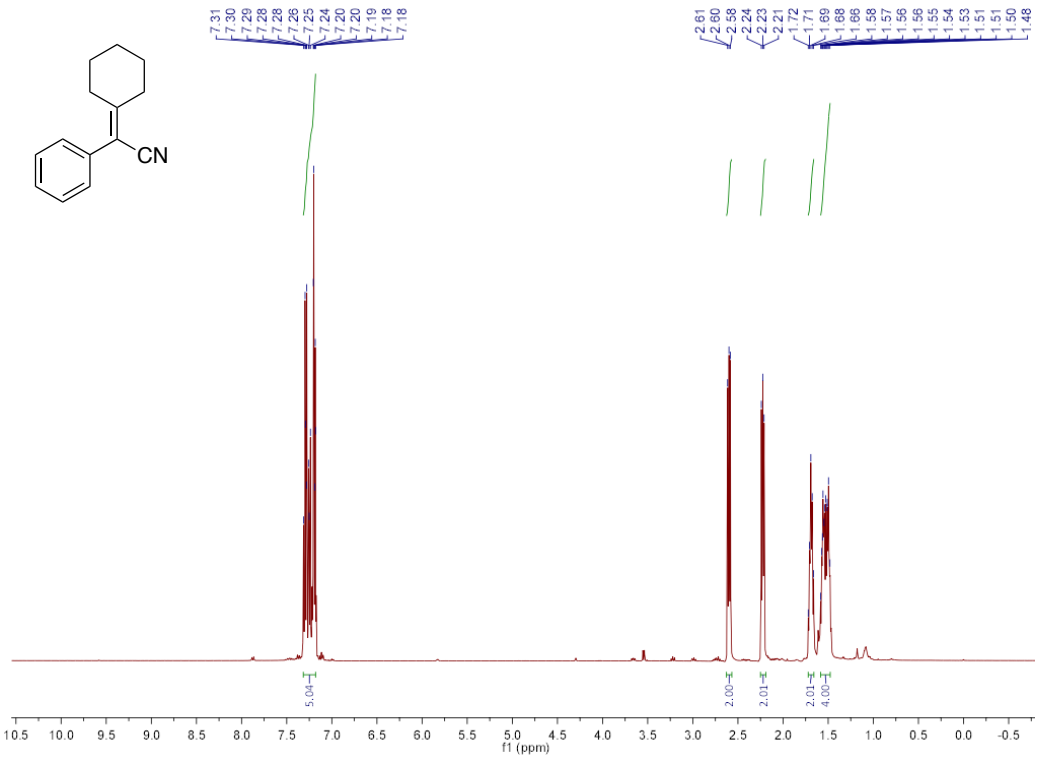


Figure 3.3 ^{13}C NMR spectrum of 2-cyclohexylidene-2-phenylacetonitrile (**3.1a**):

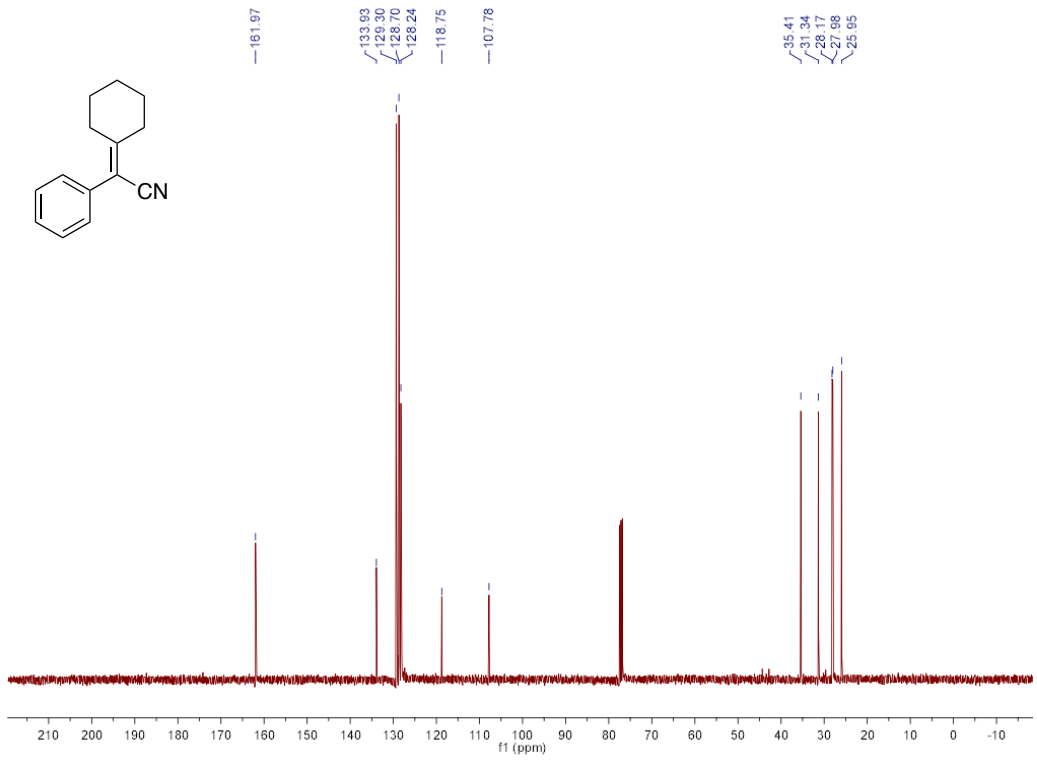


Figure 3.4 ^{1}H NMR spectrum of 2-cycloheptylidene-2-(4-methoxyphenyl)acetonitrile (**3.2f**):

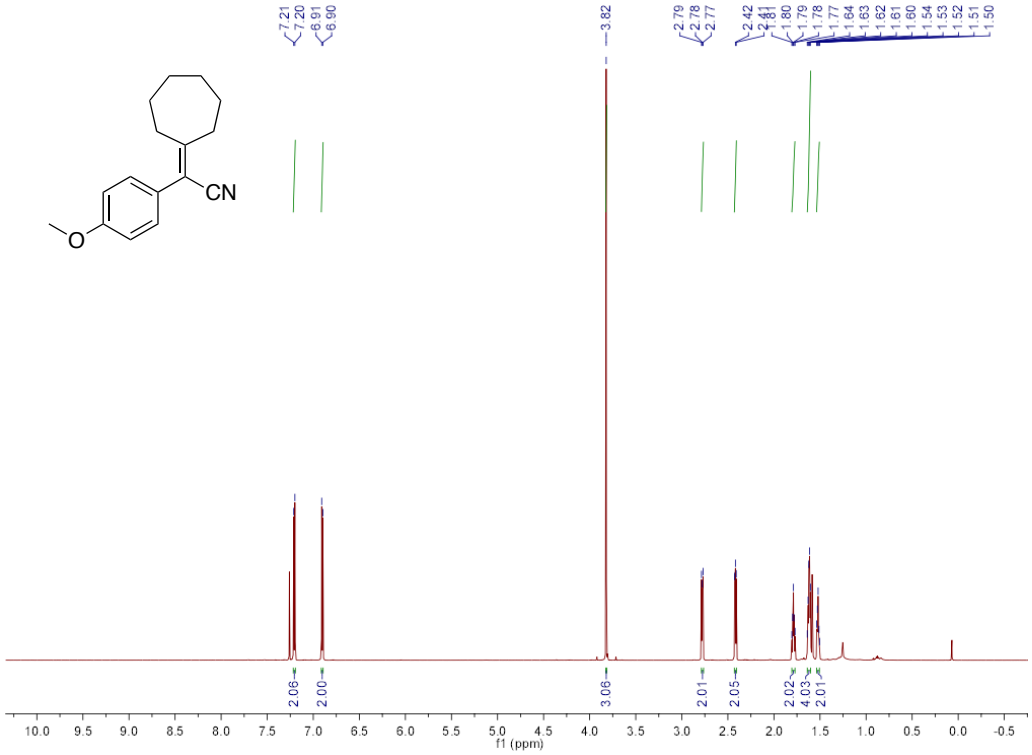


Figure 3.5 ^{13}C NMR spectrum of 2-cycloheptylidene-2-(4-methoxyphenyl)acetonitrile (**3.2f**):

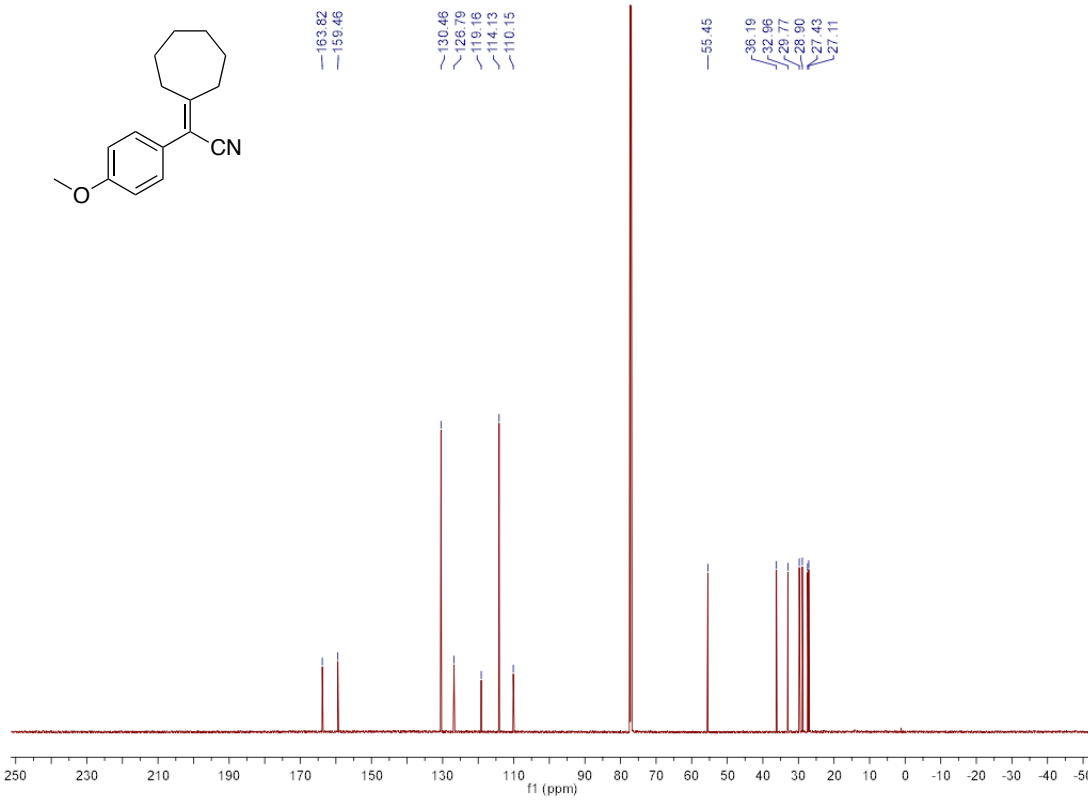


Figure 3.6 ^{1}H NMR spectrum of 3-methyl-2-phenylpent-2-enenitrile (**3.2k**):

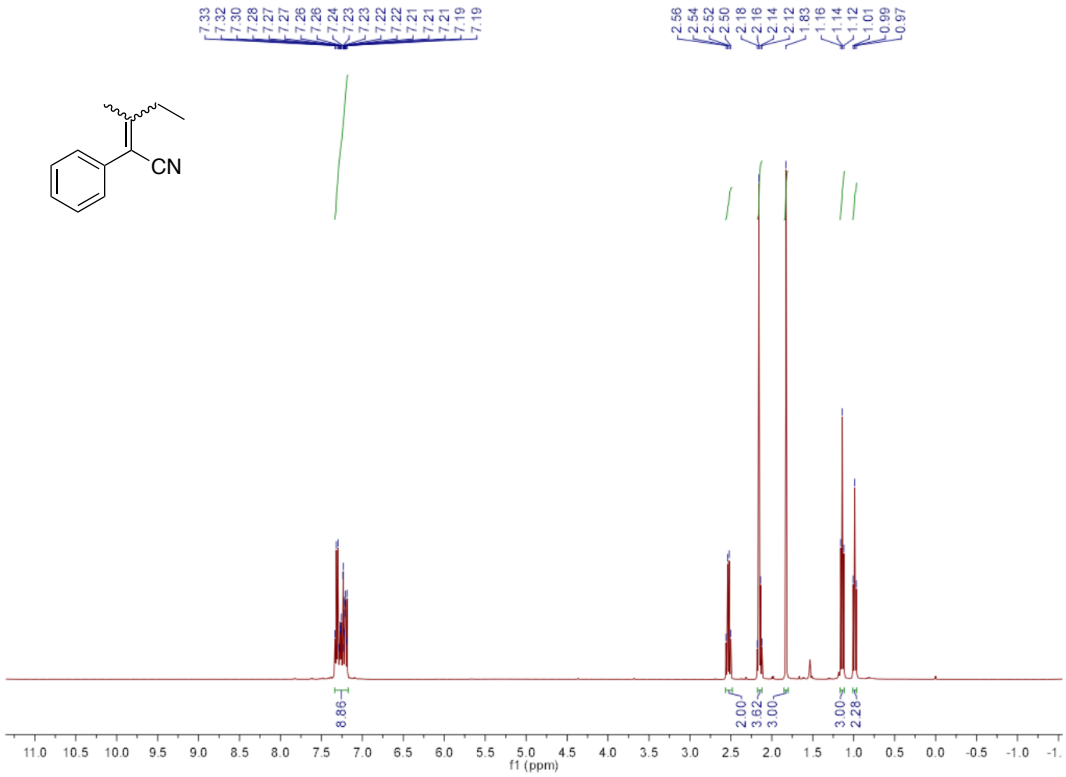
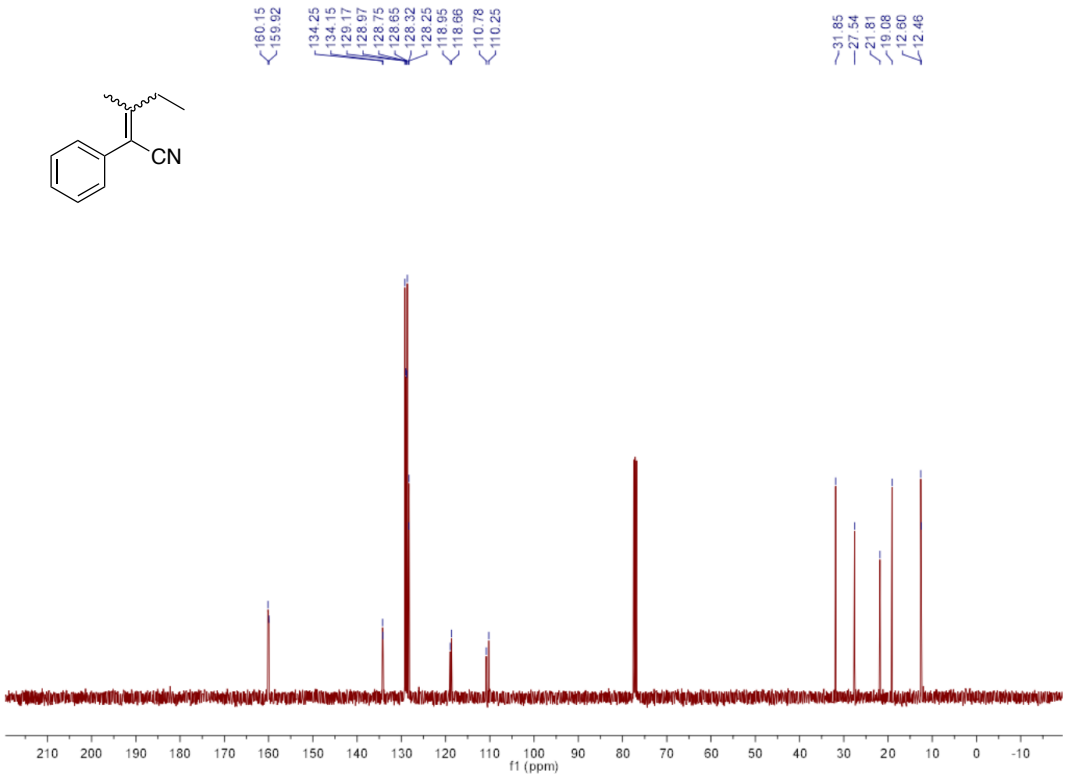


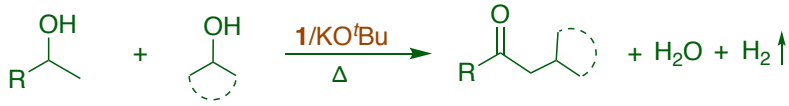
Figure 3.7 ^{13}C NMR spectrum of 3-methyl-2-phenylpent-2-enenitrile (**3.2k**):



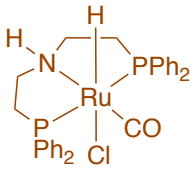
CHAPTER 4

Catalytic Cross-Coupling of Secondary Alcohols

4.1 ABSTRACT



- broad substrate scope
- low cost of alcohols
- no stoichiometric base
- H_2 and H_2O: only byproducts
- new method to β-disubstituted ketones



Catalyst **1**

Herein, an unprecedented ruthenium(II) catalyzed direct cross-coupling of two different secondary alcohols to β-disubstituted ketones is reported. Cyclic, acylic, symmetrical, and unsymmetrical secondary alcohols are selectively coupled with aromatic benzylic secondary alcohols to provide ketone products. A single catalyst oxidizes both secondary alcohols to provide selectively β-disubstituted ketones to broaden the scope of this catalytic protocol. Number of bond activation and bond formation reactions occurs in selective sequence via amine-amide metal-ligand cooperation operative in Ru-MACHO catalyst. The product-induced diastereoselectivity was also observed. Kinetic and deuterium labeling experiments suggested that the aliphatic secondary alcohols undergo oxidation reaction faster than benzylic secondary alcohols, selectively assimilating to provide the cross-coupled products. Reactions are sensitive to steric hindrance. This new C–C bond forming methodology requires low catalyst load and catalytic amount of base. Notably, the reaction produces H_2 and H_2O as the only by-products making the protocol greener, atom economical and environmentally benign.

4.2 INTRODUCTION

Alcohols and ketones are prevalent in nature and are highly promising industrial feedstock chemicals. Ketones are versatile building blocks for the construction of natural products, polymers, biological and pharmaceutical compounds and extensively used as industrial solvents.[1] Traditional synthesis of α- and β-substituted ketones involves reaction of carbonyl compounds under cryogenic conditions with strong bases (^{n}BuLi, LDA, etc) followed by addition of toxic alkyl halides (Scheme 4.1a). This enolate alkylation approach suffers from serious drawbacks, which include (i) generation of stoichiometric metal halides as chemical waste (ii) over alkylation to di- or trisubstituted ketones, and (iii) homolytic coupling of carbonyl compounds curtailing the atom economy of the reactions.[2] In addition, organic halides and carbonyl compounds are expensive and they are not readily available substrates, which can be replaced by most abundant, cheap and environmentally benign alcohols for alkylation reactions. Moreover, alcohols can be obtained from renewable resources such as lignocellulosic biomass.[3] The recent development in transition metal catalysis aims to develop sustainable, one-step, and atom economical efficient methodologies for the preparation of valuable synthetic building blocks by using easily available starting materials. In this regard, "borrowing hydrogen" methodology has become one of the most attractive transformation for C–C and C–N bond formation in organic synthesis.[4,5] Synthesis of α-substituted ketones from ketones and alcohols is well established.[5] Direct cross-coupling of alcohols with hydrogen evolution via acceptorless dehydrogenation is one of the most atom economical and environmentally benign methods for constructing new C–C bonds (Scheme 4.1b).[6] Catalytic self-coupling[7,8] and cross-coupling[9] of primary alcohols to esters and higher alcohols are reported. Cross-coupling of secondary alcohols with primary alcohols has been widely explored.[10,11]

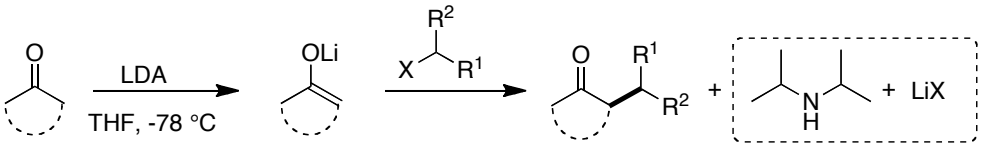
There are two reports on self-coupling of secondary alcohols.[12] However, the catalytic cross-coupling of two different secondary alcohols remains unknown.

The major challenge in cross-coupling of secondary alcohols is to overcome the unwanted self-coupling from aldol reactions, which generates undesired by-products and hence, diminishes the atom economy of the overall transformation (Scheme 4.1c). More importantly, synthesis of β-disubstituted ketones directly from two different secondary alcohols can usually be accomplished via four-step transformations (oxidation, aldol condensation, hydrogenation, and oxidation). Recently, Donohoe and co-workers reported the synthesis of β-disubstituted ketones via borrowing hydrogen methodology.[13] However, the reaction requires stoichiometrically excess amount of base and the substrate scope is limited to bulky ketones (e.g., Ph*$COCH_3$, Ph* = pentamethyl phenyl). Thus, it is desirable to develop a new strategy for the synthesis of β-disubstituted ketones directly from two different secondary alcohols (Scheme 4.1d).

Recently, selective α-alkylation and α-olefination of nitrile compounds by alcohols were reported from our laboratory using a commercially available Ru-MACHO catalyst (**1**).[14] On the basis of these reports, I have further envisaged the cross-coupling of secondary alcohols. Herein, I describe the synthesis of β-disubstituted ketones directly from two different secondary alcohols. This catalytic method does not require stoichiometric oxidants; it only requires a catalyst and catalytic amount of base. Water and liberated H_2 are the only byproducts of this reaction.

Scheme 4.1 Traditional and Selectivity Challenges in Synthesis of β-Disubstituted Ketones and Cross-Coupling of Secondary Alcohols

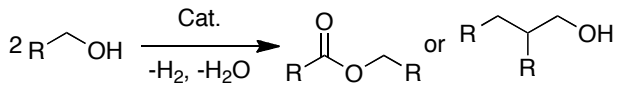
a) Traditional approach: synthesis of β-disubstituted ketones



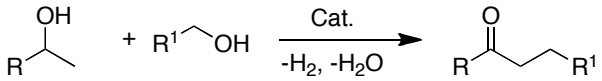
Hazardous waste

Drawbacks: (i) use of stoichiometric strong metallic base
(ii) stoichiometric metal halide as the waste
(iii) not environmentally benign and not atom economical reaction

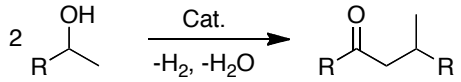
b) Catalytic coupling of alcohols



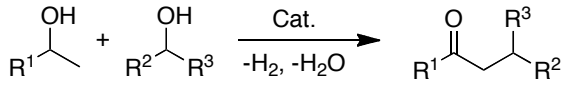
self-coupling of primary alcohols: well known



cross-coupling of primary and secondary alcohols: very much explored



self-coupling of secondary alcohols: reported



cross-coupling of secondary alcohols: unknown

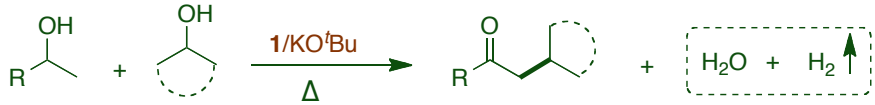
c) Selectivity challenges: direct cross-coupling of secondary alcohols

self-coupled product olefinated product alcohol product

desired product
highly challenging

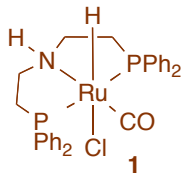
competing side products

d) Our approach: direct cross-coupling of secondary alcohols



green byproducts

Advantages:
(i) alcohols: cheap industrial feedstock
(ii) no stoichiometric base required
(iii) only byproducts: H_2 and H_2O
(iv) direct synthesis of β-disubstituted ketones from two different secondary alcohols

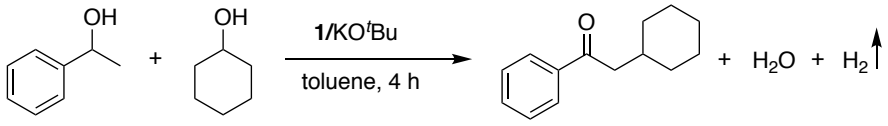


1

4.3 RESULTS AND DISCUSSIONS

Reaction of 1-phenylethanol (0.5 mmol) with cyclohexanol (0.5 mmol), catalyst **1** (1 mol%), and base (2 mol%) in toluene solution was heated to 135 °C for an initial investigation. Further, the reaction mixture was analyzed by ^{1}H NMR spectroscopy and gas chromatography (GC), which confirmed the complete conversion of 1-phenylethanol and high reactivity for cross-coupling reaction along with unreacted acetophenone (in situ generated intermediate) and trace amount of self-coupled aldol product were detected (entry 1, Table 4.1). Notably, over-alkylation products and *β*-alkylated secondary alcohols were not observed (Scheme 4.1c). However, upon increasing base load to 5 mol% and lowering temperature to 125 °C, resulted in a better outcome and the cross-coupled product was isolated in 85% and 86% yields (entries 2, 3, Table 4.1). Use of 10 mol% of base, diminished the product formation presumably due to aldol side reactions (entry 4, Table 4.1). Further, upon increasing the amount of cyclohexanol no significant improvement in yield was observed (entry 5, Table 4.1). On decreasing catalyst load, use of lower temperature and replacing KO^{t}Bu with NaO^{t}Bu provided considerably lower yields (entries 6-8, Table 4.1). Other bases and changing solvent were not effective on the reaction (entries 9-11, Table 4.1). In control experiments performed by employing only base, and without catalyst and base, no cross-coupling product was observed, indicating that catalyst and base are essential for the success of the reaction (entries 14,15, Table 4.1). When the reaction was performed using [RuHCl(CO)(PPh_3)$_3$] no cross-coupled product was observed, which indicates the necessity of pincer catalyst for this transformation.

Table 4.1 Optimization for Cross-Coupling of Secondary Alcohols Catalyzed by 1[a]



4.1a

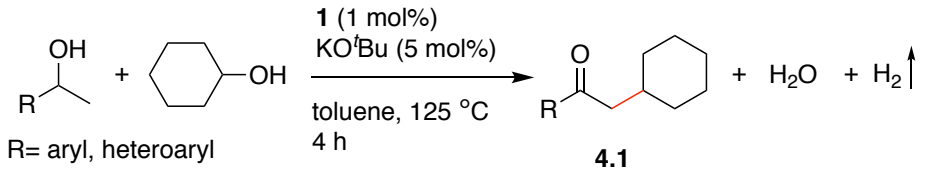
entry	cat. (mol%)	base (mol%)	temp. (°C)	conv. (%)[b]	yield (%)[c]
1	1	2	135	>99	69 (74)
2	1	5	135	>99	85 (90)
3	**1**	**5**	**125**	**>99**	**86 (91)**
4	1	10	125	>99	70 (76)
5[d]	1	5	125	>99	87 (94)
6	1	5	115	94	63 (69)
7	0.5	5	125	>99	70 (72)
8[e]	1	5	125	>99	79 (83)
9[f]	1	5	125	75	60 (66)
10[g]	1	5	125	5	-
11[h]	1	5	125	85	65 (67)
12[i]	1	5	125	77	42 (48)
13[j]	1	-	125	90	-
14[k]	-	5	125	5	-
15[k]	-	-	125	-	-
16[l]	1	5	125	30	-

[a]Reaction conditions: 1-Phenylethanol (0.5 mmol), cyclohexanol (0.5 mmol), toluene (1.5 ml), catalyst **1** (1 mol%) and KO^{t}Bu (5 mol%) were heated at 125 °C under argon flow. [b]Conversion of 1-phenylethanol was determined by GC analysis using benzene as an internal standard. [c]Yields were calculated for isolated products after column chromatography; yields calculated from GC analysis of the reaction mixtures are given within parenthesis. [d]2 equiv. of cyclohexanol was used. [e]5 mol% of NaO^{t}Bu was used.

[f]5 mol% KOH was used. [g]5 mol% Cs_2CO_3 was used. [h]1,4-Dioxane was used as solvent. [i]Reaction mixture prepared in fume hood using standard Schlenk techniques (without using glove box). [j]Reaction performed using activated precatalyst and without use base. [k]Reaction performed for 24 h. [l]Reaction was performed using [$RuHCl(CO)(PPh_3)_3$] catalyst (1 mol%) and KO^{t}Bu (5 mol%).

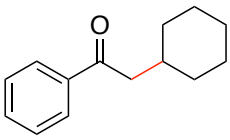
Having optimal reaction conditions in hand, the scope of the various secondary alcohols on cross-coupling was investigated (Scheme 4.2). In general, methyl, methoxy and benzyloxy substituted 1-phenylethanols reacted well with cyclohexanol and provided the corresponding cross-coupled products **4.1b-4.1i** in good to high yields. The electron withdrawing group present in aromatic ring of secondary alcohol slightly diminished the reactivity as observed in 1-(4-chlorophenyl)ethan-1-ol to **4.1j**. Notably, heteroaryl and bicyclic aromatic secondary alcohols were tolerated well and the cross-coupling products **4.1k-4.1o** were obtained in good yields (Scheme 4.2).

Scheme 4.2 Ruthenium-Catalyzed Selective Cross-Coupling of Secondary Alcohols Using Cyclohexanol[a]

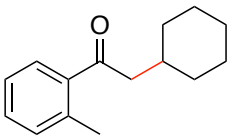


R= aryl, heteroaryl

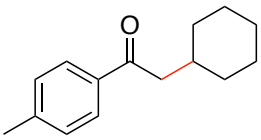
4.1



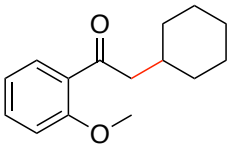
4.1a, 86% (>99%)



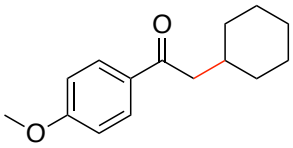
4.1b, 90% (>99%)



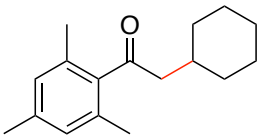
4.1c, 85% (>99%)



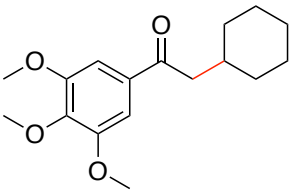
4.1d, 67% (75%)



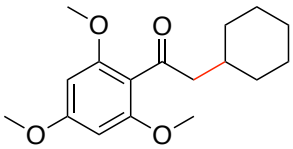
4.1e, 87% (>99%)



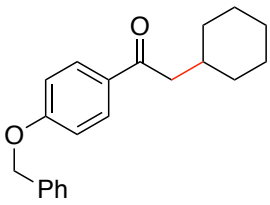
4.1f, 60% (83%)



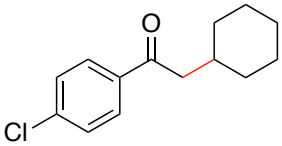
4.1g, 63% (>99%)



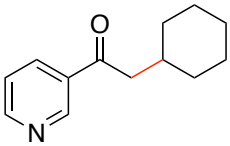
4.1h, 78% (>99%)[b]



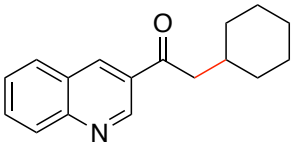
4.1i, 78% (91%)



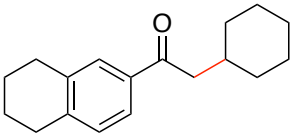
4.1j, 48% (60%)[c]



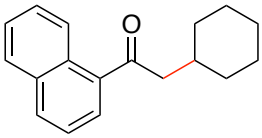
4.1k, 72% (99%)



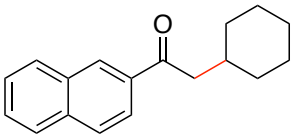
4.1l, 82% (>99%)



4.1m, 87% (>99%)



4.1n, 83% (>99%)[b]



4.1o, 86% (97%)[b]

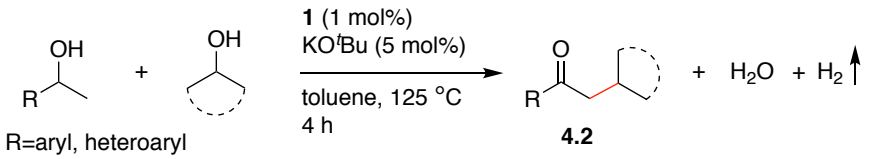
[a]Reaction conditions: 1-arylethanol (0.5 mmol), cyclohexanol (0.5 mmol), toluene (1.5 ml), catalyst **1** (1 mol%) and KO^{t}Bu (5 mol%) were heated at 125 °C under argon flow

for 4 h. Conversion of 1-arylethanols were determined by GC analysis using benzene as an internal standard is given within parentheses. Reported yields correspond to isolated pure compounds. [b]Reaction was performed using 2 mol% catalyst **1** and 10 mol% base. [c]4 mol% of catalyst **1** and 20 mol% of base was used.

Encouraged by these results, a range of secondary alcohols was further explored for catalytic cross-coupling reaction. Both cyclic and acyclic secondary alcohols were directly coupled with benzylic secondary alcohols, which afforded cross-coupled ketone products in good to excellent yields (Scheme 4.3). Substitution on cyclohexyl ring provided products as a mixture of diastereoisomers and the diastereomeric ratios were obtained from ^{1}H NMR of crude reaction mixture. 4-Methylcyclohexanol was selectively coupled with various 1-arylethanol derivatives to provide the products **4.2a-4.2c** (d.r, 80:20, 81:19, 78:22, respectively) in very good yields as a mixture of diastereoisomers. Representatively, the single-crystal X-ray structure for major isomer of product **4.2b** is solved, which revealed the 1,4-cis conformation on cyclohexyl ring. Accordingly, similar 1,4-cis conformation is assigned for all major isomers of products **4.2a-4.2g.** Good yields with similar diastereoselectivities were also obtained for 4-propyl, 4-*tert*-butyl, and 4-phenyl-substituted cyclohexanol derivatives (**4.2d-4.2g**). Gratifyingly, 1-cycloheptanol and 2-norborneol were reacted with 1-phenylethanol derivatives and the corresponding products **4.2h**-**4.2k** were isolated in very good yields (Scheme 4.3). 4-Hydroxycyclohexanone ethyleneacetal with 1-(4-methylphenyl)ethanol provided product **4.2l** in moderate yield. A sterically hindered substrate, 1,1-diphenylmethanol delivered cross-coupled product **4.2m** in 68% yield. Finally, the highly challenging unactivated acyclic aliphatic secondary alcohols were subjected to catalysis with increased catalyst load of **1** (4 mol%) and base (20 mol%). A variety of

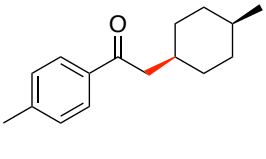
secondary alcohols such as 2-propanol, 2-butanol, 2-pentanol, 3-pentanol and 4-heptanol were well tolerated and selectively converted into *β*-disubstituted ketones (**4.2n-4.2t**).

Scheme 4.3 Ruthenium-Catalyzed Selective Cross-Coupling of Secondary Alcohols[a]

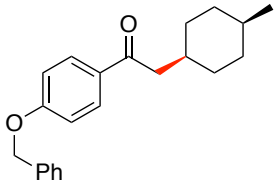


R=aryl, heteroaryl

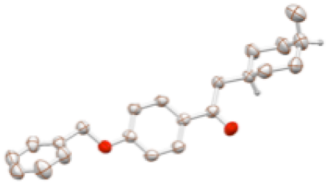
4.2



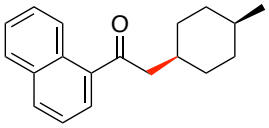
4.2a, 87% (>99%)
d.r = 80:20



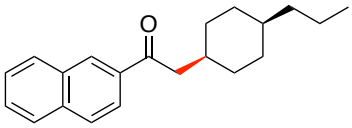
4.2b, 68% (78%)
d.r = 81:19



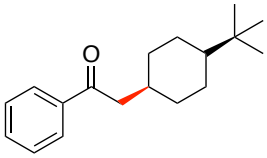
4.2b



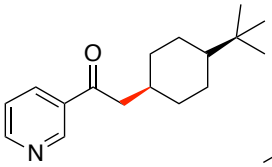
4.2c, 90% (95%)
d.r = 78:22



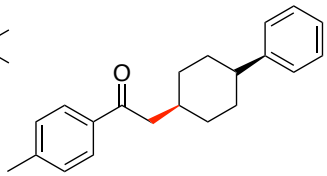
4.2d, 72% (92%)[b]
d.r = 87:13



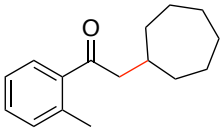
4.2e, 78% (87%)
d.r = 86:14



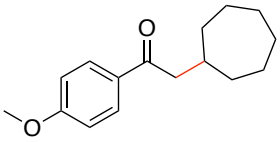
4.2f, 90% (99%)
d.r = 90:10



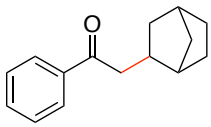
4.2g, 82% (>99%)
d.r = 80:20



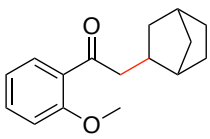
4.2h, 80% (>99%)[c]



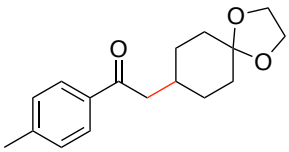
4.2i, 68% (98%)[c]



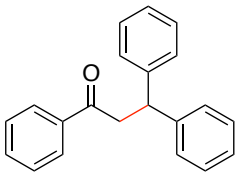
4.2j, 75% (98%)



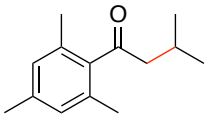
4.2k, 75% (91%)[b]



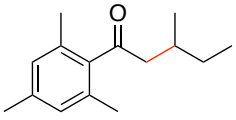
4.2l, 48% (97%)[b]



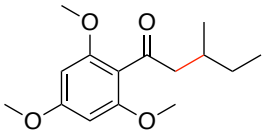
4.2m, 68% (>99%)[d]



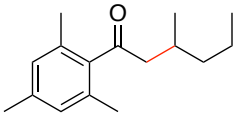
4.2n, 82% (95%)[e]



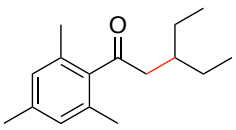
4.2o, 90% (>99%)[f]



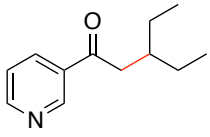
4.2p, 30% (40%)[f]



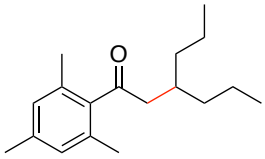
4.2q, 65% (72%)[f]



4.2r, 97% (>99%)[f]



4.2s, 60% (>99%)[f]



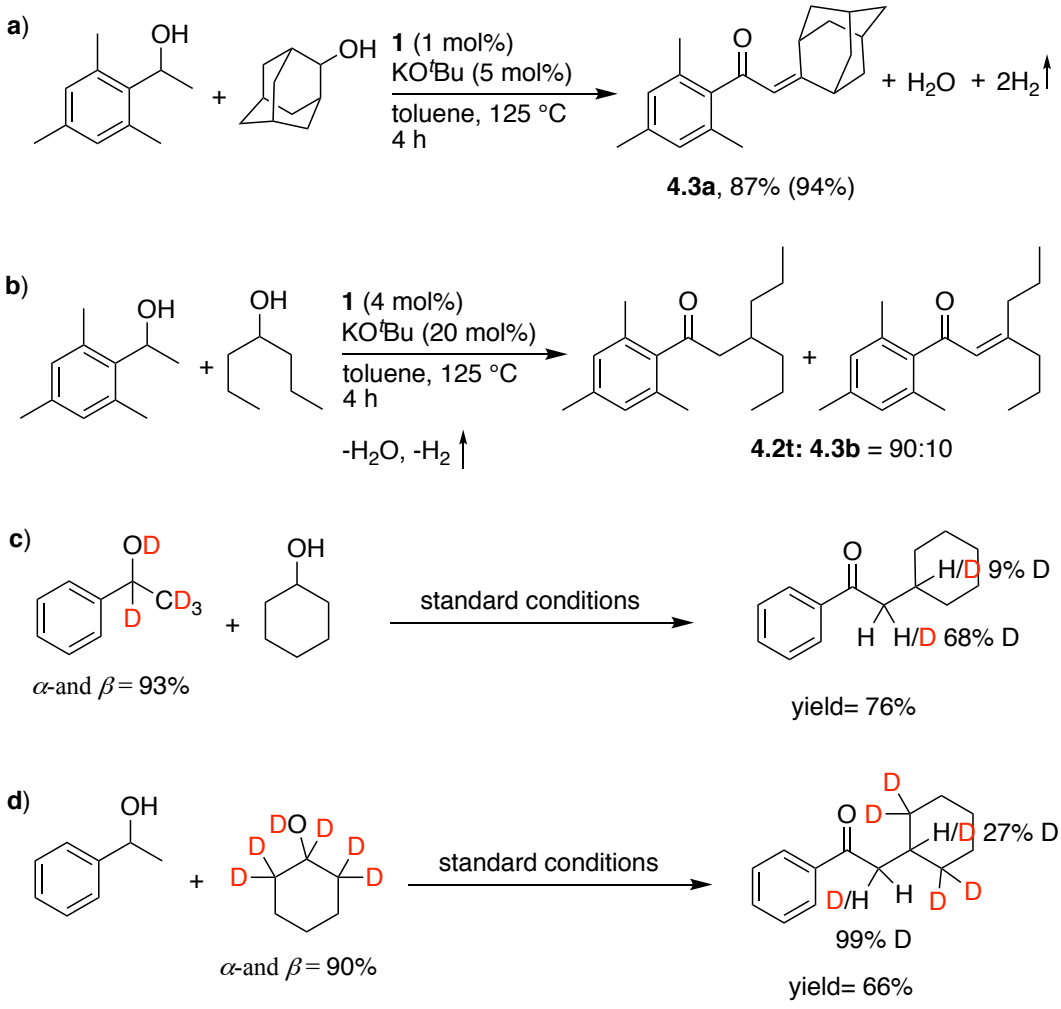
4.2t, 83% (>99%)[f]

[a]Reaction conditions: A mixture of two secondary alcohols (each 0.5 mmol scale at 1:1 ratio), toluene (1.5 ml), catalyst **1** (1 mol%) and KO^{t}Bu (5 mol%) were heated at 125 °C under the argon flow. Diastereomeric ratios (d.r) were determined by ^{1}H NMR analysis of crude reaction mixture; major isomer shown. Conversion of secondary alcohols was determined by GC analysis using benzene as an internal standard and given within parentheses. Reported yields correspond to isolated pure compounds. [b]2 mol% catalyst **1** and 10 mol% base was used. [c]3 mol% catalyst **1** and 15 mol% base and 3 equivalents of cycloheptanol were used. [d]5 mol% of catalyst and 10 mol% base was used. [e]4 mol% catalyst **1** and 20 mol% base and 10 equivalents of isopropanol were used. [f]Reaction was performed using 5 equivalent of aliphatic secondary alcohol, 4 mol% catalyst **1** and 20 mol% base.

Further, experiments aimed at deciphering the mechanistic insights were performed. When 1-mesitylethanol was reacted with sterically hindered 2-adamantanol, selective formation of olefin product **4.3a** was observed (Scheme 4.4a). GC analysis of this reaction mixture clearly indicated the absence of alkylated product. However, the reaction of 1-mesitylethanol with 4-heptanol under optimized conditions provided alkylated product **4.2t** and olefin product **4.3b** in 90:10 ratio (Scheme 4.4b). These results indicate the borrowing hydrogen pathway is interrupted due to sterically encumbered ruthenium on catalyst **1** and the reaction proceeds via α,β-unsaturated ketone intermediates. In addition to that, deuterium-labeling experiments were conducted and the results imply that the liberated dideutrium/dihydrogen from cyclohexanol are predominantly reinstalled to unsaturated intermediate rather than dideutrium/dihydrogen liberated from 1-phenylethanol (Scheme 4.4c-d). These observations clearly indicate that the catalytic cross-coupling of secondary alcohols

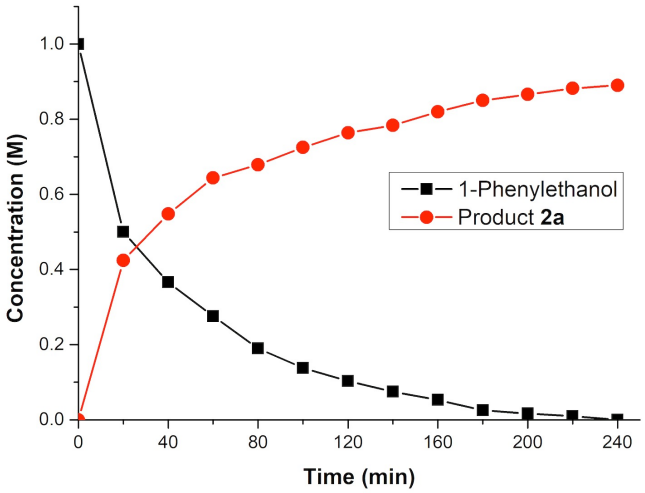
reactions are sensitive to steric hindrance. Thus, in addition to the faster dehydrogenation of aliphatic secondary alcohols by catalyst **1**, the higher reactivity of aliphatic cyclic ketones intermediates presumably due to the conformation strain and the steric compatibility also facilitates the formation of cross-coupling products by precluding the self-coupling reactions.

Scheme 4.4 Mechanistic Studies for the Cross-Coupling of Secondary Alcohols



GC monitoring of reaction progress shows the reaction follows first order kinetics with respect to 1-phenylethanol consumption (Figure 4.1). The decreasing concentration of 1-phenylethanol (black line) and increasing concentration product **4.1a** (red line) with respect to time in the catalytic cross-coupling of secondary alcohols.

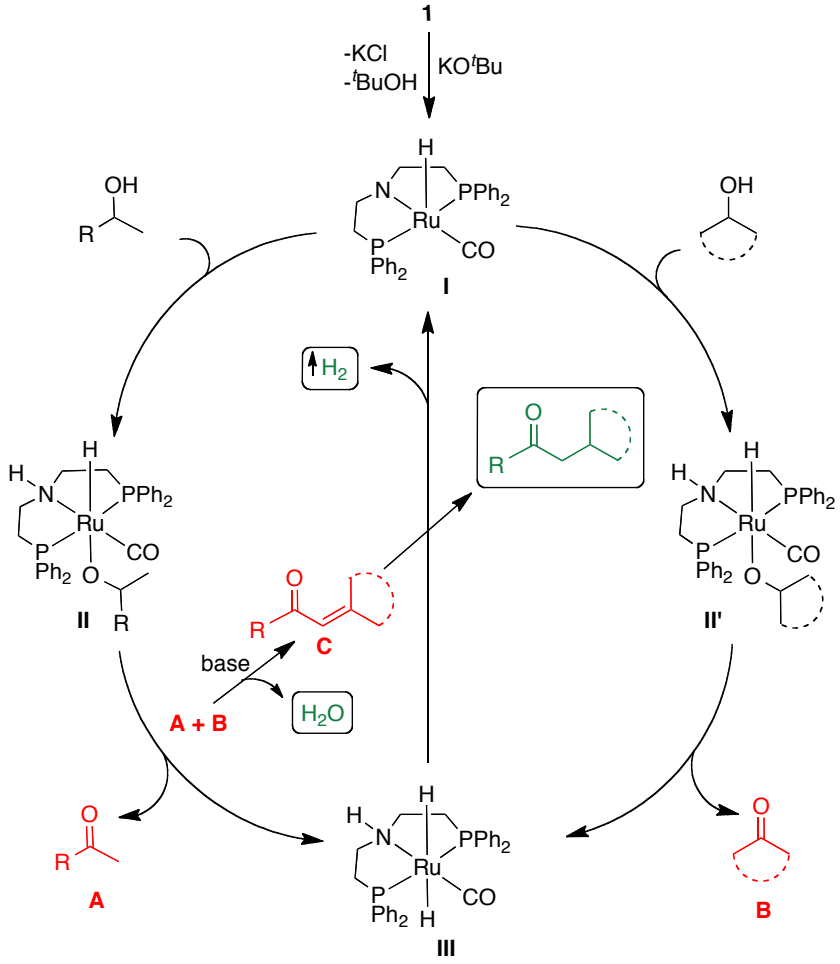
Figure 4.1 Kinetic Profile for the Cross-Coupling of Secondary Alcohols



On the basis of these experimental evidences, catalytic cycle for cross-coupling of secondary alcohols catalyzed by **1** is proposed in Scheme 4.5. Facile O–H, O–D, N–H, and spC–H bond activation reactions by catalyst **1** have been established in our previous reports.[14,15] Catalyst **1** reacts with base to generate an unsaturated reactive intermediate **I**, which has been previously observed in mass spectrometry analysis.[15b,16] The resulted reactive intermediate **I** further reacts with both secondary alcohols to provide an alkoxo coordinated ruthenium intermediates **II** and **II'** as already established.[15d] β-Hydride elimination reaction from alkoxoide ligands may result in formation of ketone intermediates **A** and **B** and both dehydrogenation reactions converge to provide the same ruthenium dihydride complex **III**. However, involvement of other mechanistic pathways cannot be ruled out.[17] A base mediated cross-aldol condensation reaction between in situ formed ketones **A** and **B** produces α,β-unsaturated carbonyl compound **C**, which undergoes selective hydrogenation by complex **III** to provide desired β-disubstituted ketones. The amine-amide metal ligand cooperation operative in these

catalytic intermediates allow the regeneration of active intermediate **I** upon hydrogenation as well as liberation of a H_2 molecule by ruthenium dihydride **III**.

Scheme 4.5 Proposed Mechanism for Cross-Coupling of Secondary Alcohols



4.4 CONCLUSIONS

In summary, I have developed an efficient catalytic cross-coupling of secondary alcohols to provide β-branched ketones. This methodology provides broad substrate scope. Various aromatic, heteroaromatic, cyclic, linear, symmetrical, and unsymmetrical secondary alcohols were well tolerated. The reaction proceeded by O–H bond activation of secondary alcohols by catalyst via amine-amide metal-ligand cooperation to provide

corresponding carbonyl intermediates, which condensed and underwent catalytic hydrogenation to eventually deliver the products. Overall two equivalents of molecular H_2 are obtained from oxidation of two different secondary alcohols. While one equivalent is used for the hydrogenation of the α,β-unsaturated carbonyl compound to provide the desired β-branched ketones, the other equivalent is liberated as H_2. Remarkably, H_2O and H_2 are the only by-products. Use of readily available and challenging starting materials, broad scope, high selectivity and absence of any deleterious side reactions in this C–C bond formation will be beneficial and contribute to the development of new "green" and "sustainable" catalytic processes in future.

4.5 EXPERIMENTAL SECTION

General Experimental: All catalytic reactions were performed under inert atmosphere using standard Schlenk techniques. All stoichiometric reactions were performed in nitrogen atmosphere MBRAUN glove box. Ru-MACHO **[Carbonylchlorohydrido{bis[2-(diphenylphosphinomethyl) ethyl]amino}ethyl]amino}ruthenium(II)]** was purchased from Sigma-Aldrich and stored inside glove box. Chemicals were purchased from Acros, Sigma-Aldrich, Alfa-aesar, Himedia Chemicals and used without further purification. Dry solvents were prepared according to standard procedures. Infrared (IR) spectra were recorded in Perkin-Elmer FT-IR and Thermo-Nicolet FT-IR spectrophotometers. High-resolution mass spectra (HRMS) were obtained on Bruker micrOTOF-Q II Spectrometer and are reported as m/z (relative intensity). Accurate masses are reported for the molecular ion $[M+Na]^+$, $[M+H]^+$, $[M]^+$. Nuclear magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded at Bruker AV-700 (^{1}H at 700 MHz, ^{13}C at 175 MHz) and Bruker AV-400 (^{1}H at 400 MHz, ^{13}C at 100.6 MHz). ^{1}H NMR chemical shifts are referenced in parts per million (ppm) with respect to tetramethyl silane (TMS) (δ 0.00 ppm) and ^{13}C $\{^1$H$\}$

NMR chemical shifts are referenced in parts per million (ppm) with respect to $CDCl_3$ (δ 77.160 ppm). Coupling constants are reported in Hertz (Hz). ^1H NMR spectroscopy abbreviations: s, Singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; dt, doublet of triplets; dq, doublet of quartets; td, triplet of doublets; qd, quartets of doublets; ddd, doublets of doublets of doublets; m, multiplet; br, broad. Assignment of spectra was done based on one-dimensional (DEPT-135) NMR techniques.

GC Method: Gas chromatography data were obtained using a gas chromatograph equipped with a SH-Rtx-1 capillary column (30 m × 250 μm). The instrument was set to an injection volume of 1 μL, an inlet split ratio of 10:1, and inlet and detector temperatures of 300 and 330 °C, respectively. The temperature program used for all of the analyses is as follows: 50 °C, 1 min; 12 °C/min to 320 °C, 7 min. Response factor for all of the necessary compounds with respect to standard benzene was calculated from the average of three independent GC runs.

General Optimization Procedure for Cross-Coupling of Secondary Alcohols:

A Schlenk flask (25 mL) was equipped with a stir bar, catalyst **1** (0.01 mmol), base (0.05 mmol), 1-phenylethanol (0.5 mmol), cyclohexanol (0.5 mmol) and toluene (1.5 mL) under nitrogen atmosphere in a glove box. The flask was taken out of the glove box, equipped with a condenser and the solution was heated at 125 °C (oil bath temperature, internal temperature of the reaction mixture is found to be 115 °C) with stirring under a flow of argon for 4 h. The completion of the reaction was monitored using GC analysis. After cooling to room temperature, 0.5 mmol of internal standard (benzene) was added into the reaction mixture and the conversion of 1-phenylethanol was calculated using GC analysis. Further, the solvent was evaporated and crude reaction mixture was purified by column chromatography over silica-gel (100-200

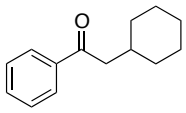
mesh) using ethyl acetate/petroleum ether mixture as an eluent. Yields were calculated from crude reaction mixture using GC analysis and also for isolated pure products.

General Procedure for Cross-Coupling of Secondary Alcohols Using Cyclohexanol:

A Schlenk flask (25 mL) was equipped with a stirr bar, catalyst **1** (0.01 mmol), base (0.05 mmol), secondary alcohol (0.5 mmol), cyclohexanol (0.5 mmol) and toluene (1.5 mL) under nitrogen atmosphere in a glove box. The flask was taken out of the glove box, equipped with a condenser and the solution was heated at 125 °C (oil bath temperature) with stirring under the flow of argon for 4 h. The completion of the reaction was monitored using GC analysis. After cooling to room temperature, 0.5 mmol of internal standard (benzene) was added into the reaction mixture and the conversion of 1-arylethanols was calculated using GC analysis. Further, the solvent was evaporated and crude reaction mixture was purified by column chromatography over silica-gel (100-200 mesh) using ethyl acetate/petroleum ether mixture as an eluent. Yields were calculated for isolated pure products.

Spectral Data of the Cross-Coupled Products:

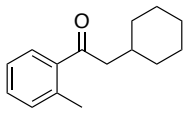
2-Cyclopentyl-1-phenylethanone (4.1a):[18] Colorless liquid. Yield: 86%. IR (DCM):



3052, 2987, 2853, 1672, 1447, 1267, 1047, 895, 747 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.86 (dd, J_1 =8.4 Hz, J_2 =1.2 Hz, 2H, ArC*H*), 7.46 (tt, J_1 =7.6 Hz, J_2 =1.2 Hz, 1H, ArC*H*), 7.37 (td, J_1 =7.2 Hz, J_2 =1.2 Hz, 2H, ArC*H*), 2.73 (d, J = 6.8 Hz, 2H, COCH_2), 1.85-1.94 (m, 1H, C*H*), 1.56-1.70 (m, 5H, CH_2), 1.19 (qt, J_1 =12.8 Hz, J_2 =2.8 Hz, 2H, CH_2), 1.02-1.10 (m, 1H, CH_2), 0.92 (qd, J_1 =12.8 Hz, J_2 =2.4 Hz, 2H, CH_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100.6 MHz): δ 200.36 (*C*=O), 137.60 (quat-*C*), 132.93 (Ar*C*H), 128.63 (Ar*C*H), 128.24 (Ar*C*H), 46.32 (CO*C*H_2),

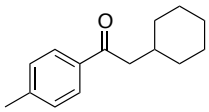
34.65 (*C*H), 33.55 (*C*H_2), 26.37 (*C*H_2), 26.26 (*C*H_2). HRMS (ESI) m/z calcd for $C_{14}H_{18}O$ $(M+H)^+$: 203.1430, found: 203.1429.

2-Cyclohexyl-1-(*o*-tolyl)ethan-1-one (4.1b): Colorless liquid. Yield: 90%. IR (DCM):



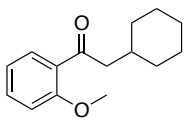
3062, 3020, 2922, 2850, 1682, 1600, 1448, 1293, 1221, 1190, 956, 755 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.50 (d, *J* = 7.7 Hz, 1H, ArC*H*), 7.25-7.29 (m, 1H, ArC*H*), 7.16 (t, *J* = 8.1 Hz, 2H, ArC*H*), 2.67 (d, *J* = 6.8 Hz, 2H, COCH_2), 2.40 (s, 3H, CH_3), 1.84-1.90 (m, 1H, C*H*), 1.56-1.69 (m, 5H, CH_2), 1.21 (ddd, J_1 = 15.5 Hz, J_2 = 11.3 Hz, J_3 = 3.2 Hz, 2H, CH_2), 1.02-1.12 (m, 1H, CH_2), 0.91 (qt, J_1 =12.8 Hz, J_2 =2.4 Hz, 2H, CH_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100.6 MHz): δ 204.88 (*C*=O), 138.90 (quat-*C*), 137.82 (quat-*C*), 131.97 (Ar*C*H), 131.05 (Ar*C*H), 128.41 (Ar*C*H), 125.69 (Ar*C*H), 49.53 (CO*C*H_2), 34.58 (*C*H), 33.49 (*C*H_2), 26.38 (*C*H_2), 26.26 (*C*H_2), 21.23 (*C*H_3). HRMS (ESI) m/z calcd for $C_{15}H_{20}O$ $(M+H)^+$: 217.1587, found: 217.1586.

2-Cyclohexyl-1-(*p*-tolyl)ethanone (4.1c):[18] Colorless liquid. Yield: 85%. IR (DCM):



3051, 2923, 2851, 1675, 1605, 1447, 1264, 1005, 908, 736 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.77 (d, *J* =8 Hz, 2H, ArC*H*), 7.17 (d, *J* =8 Hz, 2H, ArC*H*), 2.71 (d, *J* = 6.8 Hz, 2H, COCH_2), 2.33 (s, 3H, CH_3), 1.86-1.91 (m, 1H, C*H*), 1.56-1.69 (m, 5H, CH_2), 1.15-1.26 (m, 2H, CH_2), 1.02-1.11 (m, 1H, CH_2), 0.95 (qd, J_1 =12.4 Hz, J_2 =2.4 Hz, 2H, CH_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100.6 MHz): δ 200.15 (*C*=O), 143.70 (quat-*C*), 135.12 (quat-*C*), 129.32 (Ar*C*H), 128.41 (Ar*C*H), 46.25 (CO*C*H_2), 34.81 (*C*H), 33.57 (*C*H_2), 26.39 (*C*H_2), 26.28 (*C*H_2), 21.73 (*C*H_3). HRMS (ESI) m/z calcd for $C_{15}H_{20}O$ $(M+H)^+$: 217.1587, found: 217.1579.

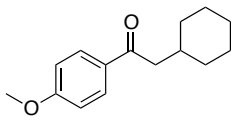
2-Cyclohexyl-1-(2-methoxyphenyl)ethan-1-one (4.1d):[19] Colorless liquid. Yield:



67%. IR (DCM): 3053, 2986, 2926, 2852, 1669, 1597, 1265, 895, 738 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.53 (dd, J_1 =7.7 Hz, J_2 =1.6 Hz, 1H, ArC*H*), 7.33-7.38 (m, 1H, ArC*H*), 6.86-6.93 (m, 2H, ArC*H*), 3.81 (s, 3H, OCH_3),

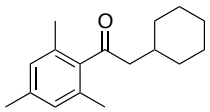
2.76 (d, J = 6.8 Hz, 2H, COCH_2), 1.81-1.85 (m, 1H, CH), 1.54-1.66 (m, 5H, CH_2), 1.14-1.23 (m, 2H, CH_2), 1.01-1.12 (m, 1H, CH_2), 0.86-0.95 (m, 2H, CH_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100.6 MHz): δ 203.29 (C=O), 158.26 (quat-C), 133.07 (ArCH), 130.10 (ArCH), 129.42 (quat-C), 120.73 (ArCH), 111.58 (ArCH), 55.58 (OCH$_3$), 51.50 (COCH$_2$), 34.46 (CH), 33.49 (CH$_2$), 26.44 (CH$_2$), 26.32 (CH$_2$). HRMS (ESI) m/z calcd for $C_{15}H_{20}O_2$ $(M+H)^+$: 233.1536, found: 233.1533.

2-Cyclohexyl-1-(4-methoxyphenyl)ethanone (4.1e):[18] Colorless liquid. Yield: 87%. IR



(DCM): 3052, 2985, 2851, 1667, 1427, 1264, 895, 704 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.85 (d, J =8.8 Hz, 2H, ArCH), 6.84 (d, J =8.8 Hz, 2H, ArCH), 3.78 (s, 3H, OCH_3), 2.68 (d, J = 6.8 Hz, 2H, COCH_2), 1.84-1.92 (m, 1H, CH), 1.55-1.69 (m, 5H, CH_2), 1.06-1.25 (m, 3H, CH_2), 0.92 (qd, J_1 =12.4 Hz, J_2 =1.6 Hz, 2H, CH_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100.6 MHz): δ 199.01 (C=O), 163.41 (quat-C), 130.73 (quat-C), 130.52 (ArCH), 113.75 (ArCH), 55.53 (OCH$_3$), 46.01 (COCH$_2$), 34.93 (CH), 33.59 (CH$_2$), 26.38 (CH$_2$), 26.28 (CH$_2$). HRMS (ESI) m/z calcd for $C_{15}H_{20}O_2$ $(M+H)^+$: 233.1536, found: 233.1538.

2-Cyclohexyl-1-mesitylethanone (4.1f): Colorless liquid. Yield: 60%. IR (DCM):



3052, 2924, 2852, 1696, 1609, 1447, 1265, 1034, 908, 736 cm^{-1}. ^1H NMR ($CDCl_3$, 700 MHz): δ 6.74 (s, 2H, ArCH), 2.51 (d, J = 6.4 Hz, 2H, COCH_2), 2.19 (s, 3H, CH_3), 2.11 (s, 6H, CH_3), 1.92-2.00 (m, 1H, CH), 1.74 (d, J = 12 Hz, 2H, CH_2), 1.58-1.64 (m, 3H, CH_2), 1.18-1.34 (m, 3H, CH_2), 0.90 (qd, J_1 =12 Hz, J_2 =2.8 Hz, 2H, CH_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 175 MHz): δ 210.21 (C=O), 140.02 (quat-C), 138.24 (quat-C), 132.55 (quat-C), 128.61 (ArCH), 52.60 (COCH$_2$), 33.48 (CH$_2$), 32.80 (CH), 26.42 (CH$_2$), 26.26 (CH$_2$), 21.13 (CH$_3$), 19.18 (2×CH$_3$). HRMS (ESI) m/z calcd for $C_{17}H_{24}O$ $(M+Na)^+$: 267.1719, found: 267.1708.

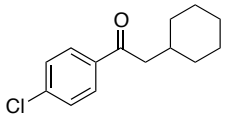
2-Cyclohexyl-1-(3,4,5-trimethoxyphenyl)ethan-1-one (4.1g): Colorless solid. Yield: 63%. IR (DCM): 3054, 2985, 2925, 2852, 1676, 1584, 1463, 1412, 1265, 1129, 738, 704 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.14 (s, 2H, ArC*H*), 3.85 (s, 6H, OCH_3), 3.84 (s, 3H, OCH_3), 2.71 (d, *J* = 6.8 Hz, 2H, COCH_2), 1.85-1.95 (m, 1H, C*H*), 1.57-1.70 (m, 5H, CH_2), 1.18-1.27 (m, 2H, CH_2), 1.04-1.15 (m, 1H, CH_2), 0.90-0.99 (m, 2H, CH_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100.6 MHz): δ 199.16 (*C*=O), 153.11 (quat-*C*), 142.48 (quat-*C*), 132.92 (quat-*C*), 105.72 (Ar*C*H), 61.03 (O*C*H_3), 56.39 (2×O*C*H_3), 46.00 (CO*C*H_2), 34.85 (*C*H), 33.59 (*C*H_2), 26.35 (*C*H_2), 26.27 (*C*H_2). HRMS (ESI) m/z calcd for $C_{17}H_{24}O_4$ $(M+H)^+$: 293.1747, found: 293.1755.

2-Cyclohexyl-1-(2,4,6-trimethoxyphenyl)ethan-1-one (4.1h): Colorless solid. Yield: 78%. IR (DCM): 3001, 2922, 2849, 1695, 1606, 1456, 1413, 1336, 1226, 1132, 913, 732 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 6.02 (s, 2H, ArC*H*), 3.74 (s, 3H, OCH_3), 3.69 (s, 6H, OCH_3), 2.54 (d, *J* = 6.8 Hz, 2H, COCH_2), 1.80-1.87 (m, 1H, C*H*), 1.69 (d, *J* = 12.8 Hz, 2H, CH_2), 1.54-1.61 (m, 3H, CH_2), 1.15-1.25 (m, 2H, CH_2), 1.01-1.12 (m, 1H, CH_2), 0.82-0.92 (m, 2H, CH_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100.6 MHz): δ 204.55 (*C*=O), 162.13 (quat-*C*), 158.15 (quat-*C*), 114.18 (quat-*C*), 90.69 (Ar*C*H), 55.85 (2×O*C*H_3), 55.49 (O*C*H_3), 52.83 (CO*C*H_2), 33.99 (*C*H), 33.35 (*C*H_2), 26.47 (*C*H_2), 26.28 (*C*H_2). HRMS (ESI) m/z calcd for $C_{17}H_{24}O_4$ $(M+H)^+$: 293.1747, found: 293.1734.

1-(4-(Benzyloxy)phenyl)-2-cyclohexylethan-1-one (4.1i): Colorless solid. Yield: 78%. IR (DCM): 3056, 2983, 2929, 2853, 1733, 1669, 1599, 1241, 1046, 747 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.84-7.87 (m, 2H, ArC*H*), 7.26-7.36 (m, 5H, ArC*H*), 6.91-6.94 (m, 2H, ArC*H*), 5.05 (s, 2H, OCH_2), 2.68 (d, *J* = 6.8 Hz, 2H, COCH_2), 1.85-1.89 (m, 1H, C*H*), 1.51-1.68 (m, 5H, CH_2), 1.06-1.22

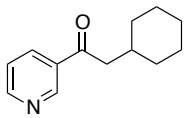
(m, 3H, CH_2), 0.92 (dd, J_1 =23.8 Hz, J_2 =11.9 Hz, 2H, CH_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100.6 MHz): δ 199.04 (*C*=O), 162.59 (quat-*C*), 136.37 (quat-*C*), 130.95 (quat-*C*), 130.57 (Ar*C*H), 128.82 (Ar*C*H), 128.36 (Ar*C*H), 127.60 (Ar*C*H), 114.64 (Ar*C*H), 70.25 (O*C*H_2), 46.06 (CO*C*H_2), 34.94 (*C*H), 33.62 (*C*H_2), 26.41 (*C*H_2), 26.31 (*C*H_2). HRMS (ESI) m/z calcd for $C_{21}H_{24}O_2$ $(M+H)^+$: 309.1849, found: 309.1845.

1-(4-Chlorophenyl)-2-cyclohexylethanone (4.1j):[18] Colorless liquid. Yield: 48%. IR



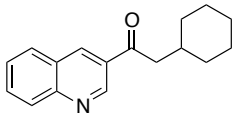
(DCM): 3052, 2987, 2859, 1680, 1430, 1264, 1062, 897, 740, 707 cm^{-1}. ^1H NMR ($CDCl_3$, 700 MHz): δ 7.81 (d, *J* = 13.3 Hz, 2H, ArC*H*), 7.35 (d, *J* = 13.3 Hz, 2H, ArC*H*), 2.71 (d, *J* = 11.9 Hz, 2H, COCH_2), 1.81-1.94 (m, 1H, C*H*), 1.53-1.69 (m, 5H, CH_2), 1.07-1.26 (m, 3H, CH_2), 0.93 (q, *J* =21 Hz, 2H, CH_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 175 MHz): δ 199.16 (*C*=O), 139.42 (quat-*C*), 135.90 (quat-*C*), 129.71 (Ar*C*H), 128.98 (Ar*C*H), 46.32 (CO*C*H_2), 34.69 (*C*H), 33.55 (*C*H_2), 26.35 (*C*H_2), 26.26 (*C*H_2). HRMS (ESI) m/z calcd for $C_{14}H_{17}ClO$ $(M+H)^+$: 237.1041, found: 237.1053.

2-Cyclohexyl-1-(pyridin-3-yl)ethanone (4.1k): Colorless liquid. Yield: 72%. IR



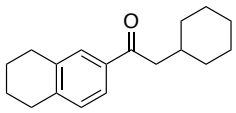
(DCM): 3051, 2984, 2851, 1686, 1445, 1265, 895, 704 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 9.08 (dd, J_1 =2.4 Hz, J_2 =0.8 Hz, 1H, ArC*H*), 8.69 (dd, J_1 =4.8 Hz, J_2 =2 Hz, 1H, ArC*H*), 8.14 (dt, J_1 =8 Hz, J_2 =2 Hz, 1H, ArC*H*), 7.34 (ddd, J_1 =5.2 Hz, J_2 =2.8 Hz, J_3 =0.8 Hz, 1H, ArC*H*), 2.77 (d, *J* = 6.8 Hz, 2H, COCH_2), 1.86-1.97 (m, 1H, C*H*), 1.57-1.72 (m, 5H, CH_2), 1.18-1.27 (m, 2H, CH_2), 1.07-1.15 (m, 1H, CH_2), 0.96 (qd, J_1 =11.6 Hz, J_2 =2.4 Hz, 2H, CH_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100.6 MHz): δ 199.10 (*C*=O), 153.44 (Ar*C*H), 149.87 (Ar*C*H), 135.52 (Ar*C*H), 132.76 (quat-*C*), 123.73 (Ar*C*H), 46.63 (CO*C*H_2), 34.53 (*C*H), 33.52 (*C*H_2), 26.31 (*C*H_2), 26.23 (*C*H_2). HRMS (ESI) m/z calcd for $C_{13}H_{17}NO$ $(M+H)^+$: 204.1383, found: 204.1359.

2-Cyclohexyl-1-(quinolin-3-yl)ethanone (4.1l): Colorless solid. Yield: 82%. IR



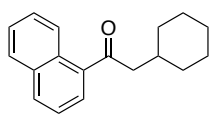
(DCM): 3053, 2926, 2853, 1684, 1618, 1420, 1265, 1027, 738 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 9.36 (s, 1H, ArC*H*), 8.64 (s, 1H, ArC*H*), 8.10 (d, *J* =8.4 Hz, 1H, ArC*H*), 7.89 (d, *J* =8 Hz, 1H, ArC*H*), 7.77 (t, *J* =8.4 Hz, 1H, ArC*H*), 7.56 (t, *J* =7.2 Hz, 1H, ArC*H*), 2.88 (d, *J* = 6.8 Hz, 2H, COCH_2), 1.90-2.02 (m, 1H, C*H*), 1.59-1.75 (m, 5H, CH_2), 1.09-1.28 (m, 3H, CH_2), 1.00 (q, *J* =12 Hz, 2H, CH_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100.6 MHz): δ 199.15 (*C*=O), 149.85 (quat-*C*), 149.41 (Ar*C*H), 137.15 (Ar*C*H), 132.01 (Ar*C*H), 129.71 (quat-*C*), 129.56 (Ar*C*H), 129.49 (Ar*C*H), 127.63 (Ar*C*H), 127.04 (quat-*C*), 46.68 (CO*C*H_2), 34.67 (*C*H), 33.55 (*C*H_2), 26.31 (*C*H_2), 26.24 (*C*H_2). HRMS (ESI) m/z calcd for $C_{17}H_{19}NO$ $(M+H)^+$: 254.1539, found: 254.1542.

2-Cyclohexyl-1-(5,6,7,8-tetrahydronaphthalen-2-yl)ethan-1-one (4.1m): Colorless



liquid. Yield: 87%. IR (DCM): 3051, 2923, 2852, 1676, 1603, 1448, 1281, 1264, 738, 703 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.58 (d, *J* =3.8 Hz, 2H, ArC*H*), 7.05 (d, *J* =8.4 Hz, 1H, ArC*H*), 2.69-2.74 (m, 6H, CH_2 & COCH_2), 1.83-1.93 (m, 1H, C*H*), 1.73 (dt, J_1 =6.4 Hz, J_2 =3.4 Hz, 4H, CH_2), 1.55-1.68 (m, 5H, CH_2), 1.15-1.25 (m, 2H, CH_2), 1.02-1.13 (m, 1H, CH_2), 0.92 (qd, J_1 =12.3 Hz, J_2 =2.3 Hz, 2H, CH_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100.6 MHz): δ 200.47 (*C*=O), 143.02 (quat-*C*), 137.49 (quat-*C*), 135.11 (quat-*C*), 129.37 (Ar*C*H), 129.15 (Ar*C*H), 125.41 (Ar*C*H), 46.22 (CO*C*H_2), 34.83 (*C*H), 33.56 (*C*H_2), 29.72 (*C*H_2), 29.52 (*C*H_2), 26.40 (*C*H_2), 26.28 (*C*H_2), 23.10 (*C*H_2), 22.96 (*C*H_2). HRMS (ESI) m/z calcd for $C_{18}H_{24}O$ $(M+H)^+$: 257.1899, found: 257.1908.

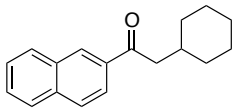
2-Cyclohexyl-1-(naphthalen-1-yl)ethan-1-one (4.1n): Colorless liquid. Yield: 83%.



IR (DCM): 3051, 2924, 2851, 1683, 1507, 1448, 1285, 1264, 1085, 738, 703 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 8.46 (d, *J* =8.6 Hz, 1H,

ArC*H*), 7.88 (d, *J* =8.2 Hz, 1H, ArC*H*), 7.78 (d, *J* =7.9 Hz, 1H, ArC*H*), 7.73 (dd, J_1 =7.1 Hz, J_2 =0.6 Hz, 1H, ArC*H*), 7.38-7.51 (m, 3H, ArC*H*), 2.83 (d, *J* = 6.9 Hz, 2H, COCH_2), 1.91-1.99 (m, 1H, C*H*), 1.72 (d, *J* = 11.6 Hz, 2H, CH_2), 1.55-1.64 (m, 3H, CH_2), 1.16-1.26 (m, 2H, CH_2), 1.05-1.12 (m, 1H, CH_2), 0.96 (qd, J_1 =12.4 Hz, J_2 =2.8 Hz, 2H, CH_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100.6 MHz): δ 205.04 (*C*=O), 136.97 (quat-*C*), 134.11 (quat-*C*), 132.38 (Ar*C*H), 130.22 (quat-*C*), 128.53 (Ar*C*H), 127.89 (Ar*C*H), 127.38 (Ar*C*H), 126.50 (Ar*C*H), 125.88 (Ar*C*H), 124.47 (Ar*C*H), 50.13 (CO*C*H_2), 35.02 (*C*H), 33.52 (*C*H_2), 26.36 (*C*H_2), 26.26 (*C*H_2). HRMS (ESI) m/z calcd for $C_{18}H_{20}O$ $(M+H)^+$: 253.1587, found: 253.1586.

2-Cyclohexyl-1-(naphthalen-2-yl)ethanone (4.1o):[20] Colorless solid. Yield: 86%. IR



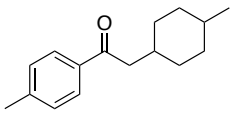
(DCM): 3062, 2925, 2853, 1676, 1627, 1468, 1265, 1003, 739 cm^{-1}. ^1H NMR ($CDCl_3$, 700 MHz): δ 8.37 (s, 1H, ArC*H*), 7.94 (dd, J_1 =9.1 Hz, J_2 =1.4 Hz, 1H, ArC*H*), 7.88 (d, *J* =8.4 Hz, 1H, ArC*H*), 7.79 (dd, J_1 =8.4 Hz, J_2 =2.8 Hz, 2H, ArC*H*), 7.50 (td, J_1 =8.4 Hz, J_2 =0.7 Hz, 1H, ArC*H*), 7.46 (td, J_1 =8.4 Hz, J_2 =0.7 Hz, 1H, ArC*H*), 2.86 (d, *J* = 6.3 Hz, 2H, COCH_2), 1.94-1.98 (m, 1H, C*H*), 1.72 (d, *J* = 12.6 Hz, 2H, CH_2), 1.57-1.63 (m, 3H, CH_2), 1.21 (qt, J_1 =12.6 Hz, J_2 =3.5 Hz, 2H, CH_2), 1.09 (qt, J_1 =12.6 Hz, J_2 =3.5 Hz, 1H, CH_2), 0.98 (qd, J_1 =11.9 Hz, J_2 =3.5 Hz, 2H, CH_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 175 MHz): δ 200.43 (*C*=O), 135.62 (quat-*C*), 134.96 (quat-*C*), 132.67 (quat-*C*), 129.84 (Ar*C*H), 129.68 (Ar*C*H), 128.49 (Ar*C*H), 128.45 (Ar*C*H), 127.87 (Ar*C*H), 126.81 (Ar*C*H), 124.15 (Ar*C*H), 46.40 (CO*C*H_2), 34.88 (*C*H), 33.62 (*C*H_2), 26.40 (*C*H_2), 26.30 (*C*H_2). HRMS (ESI) m/z calcd for $C_{18}H_{20}O$ $(M+H)^+$: 253.1587, found: 253.1591.

General Procedure for Cross-Coupling of Secondary Alcohols:

A Schlenk flask (25 mL) was equipped with a stir bar, catalyst **1** (0.01-0.05 mmol), base (0.05-0.20 mmol), benzylic secondary alcohol (0.5 mmol), aliphatic secondary alcohol

(0.5-2.5 mmol) and toluene (1.5 mL) under nitrogen atmosphere in a glove box. The flask was taken out of the glove box, equipped with a condenser and the solution was refluxed (oil bath temperature 125 °C) with stirring under the flow of argon for 4 h. The completion of the reaction was monitored using GC analysis. After cooling to room temperature, 0.5 mmol of internal standard (benzene) was added into the reaction mixture and the conversion of 1-arylethanols was calculated using GC analysis. Further, the solvent was evaporated and crude reaction mixture was purified by column chromatography over silica-gel (100-200 mesh) using ethyl acetate / petroleum ether mixture as an eluent. Yields were calculated for isolated pure products. The product-induced diastereoselectivity was also observed and the diastereomeric ratios (d.r) were determined by ^{1}H NMR analysis of crude reaction mixture. The cross-coupling products were obtained as a mixture of diastereoisomers and the diastereoisomeric signals in ^{1}H and ^{13}C NMR were assigned according to previous report.[13]

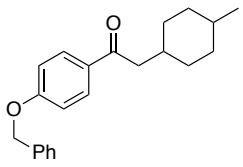
2-(4-Methylcyclohexyl)-1-(*p*-tolyl)ethan-1-one (4.2a): Colorless liquid. Yield: 87%.



^{1}H NMR analysis of the crude reaction mixture showed a d.r. of 80:20, as determined by comparison of the following signals: δ 2.81 (d, *J* =7.0 Hz, 2H, COC*H*$_2$)-major, 2.71 (d, *J* =6.7 Hz, 2H, COC*H*$_2$)-minor. IR (DCM): 3053, 2921, 2851, 1679, 1606, 1264, 1015, 738 cm^{-1}. ^{1}H NMR ($CDCl_3$, 700 MHz): δ 7.78 (d, *J* =8 Hz, 2H, ArC*H*), 7.17 (d, *J* =7.9 Hz, 2H, ArC*H*), 2.81 (d, *J* = 7.0 Hz, 2H, COC*H*$_2$)-major, 2.71 (d, *J* = 6.7 Hz, 2H, COC*H*$_2$)-minor, 2.33 (s, 3H, ArC*H*$_3$), 2.03-2.17 (m, 1H, C*H*), 1.56-1.70 (m, 2H, C*H*$_2$), 1.42-1.45 (m, 3H, C*H*&C*H*$_2$), 1.30-1.37 (m, 2H, C*H*$_2$), 1.17-1.26 (m, 2H, C*H*$_2$), 0.85 (d, *J* =6.8 Hz, 3H, C*H*$_3$)-major, 0.79 (d, *J* =6.5 Hz, 3H, C*H*$_3$)-minor. ^{13}C{^{1}H} NMR ($CDCl_3$, 175 MHz): (Mixture of diastereoisomers) δ 200.30 (*C*=O), 143.69 (quat-*C*), 135.14 (quat-*C*), 129.34 (Ar*C*H), 128.40 (Ar*C*H), 46.18 (CO*C*H$_2$), 43.28 (CO*C*H$_2$), 35.15 (*C*H), 34.64 (*C*H), 33.52 (*C*H), 32.63 (*C*H), 32.17

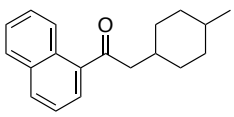
(*C*H_2), 30.88 (*C*H_2), 30.02 (*C*H_2), 29.01 (*C*H_2), 27.03 (Ar*C*H_3), 22.73 (*C*H_3), 21.72 (Ar*C*H_3), 20.33 (*C*H_3). HRMS (ESI) m/z calcd for $C_{16}H_{22}O$ $(M+H)^+$: 231.1749, found: 231.1752.

1-(4-(Benzyloxy)phenyl)-2-(4-methylcyclohexyl)ethan-1-one (4.2b): Colorless solid.



Yield: 68%. ^{1}H NMR analysis of the crude reaction mixture showed a d.r. of 81:19, as determined by comparison of the following signals: δ 2.79 (d, *J* =7.0 Hz, 2H, COC*H*$_2$)-major, 2.68 (d, *J* =6.8 Hz, 2H, COC*H*$_2$)-minor. IR (DCM): 2964, 2944, 2890, 1705, 1614, 1462, 853, 742 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.87 (d, *J* =8.8 Hz, 2H, ArC*H*), 7.25-7.37 (m, 5H, ArC*H*), 6.93 (d, *J* =8.8 Hz, 2H, ArC*H*), 5.05 (s, 2H, OC*H*$_2$), 2.79 (d, *J* =7.0 Hz, 2H, COC*H*$_2$)-major, 2.68 (d, *J* =6.8 Hz, 2H, COC*H*$_2$)-minor, 2.10-2.12 (m, 1H, C*H*), 1.42-1.48 (m, 4H, C*H*$_2$), 1.30-1.37 (m, 2H, C*H*$_2$), 1.16-1.23 (m, 3H, C*H*&C*H*$_2$), 0.85 (d, *J* =6.8 Hz, 3H, C*H*$_3$)-major, 0.79 (d, *J* =6.5 Hz, 3H, C*H*$_3$)-minor. ^{13}C{^{1}H} NMR ($CDCl_3$, 100.6 MHz): (Mixture of diastereoisomers) δ 199.23 (*C*=O), 162.57 (quat-*C*), 136.35 (quat-*C*), 130.88 (quat-*C*), 130.56 (Ar*C*H), 128.83 (Ar*C*H), 128.36 (Ar*C*H), 127.61 (Ar*C*H), 114.64 (Ar*C*H), 70.24 (O*C*H$_2$), 45.99 (CO*C*H$_2$), 43.09 (CO*C*H$_2$), 35.15 (*C*H), 34.74 (*C*H), 33.55 (*C*H), 32.64 (*C*H), 32.28 (*C*H$_2$), 30.89 (*C*H$_2$), 30.02 (*C*H$_2$), 29.02 (*C*H$_2$), 22.76 (*C*H$_3$), 20.36 (*C*H$_3$). HRMS (ESI) m/z calcd for $C_{22}H_{26}O_2$ $(M+H)^+$: 323.2006, found: 323.2002.

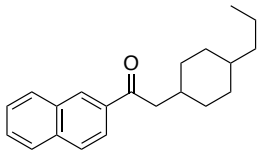
2-(4-Methylcyclohexyl)-1-(naphthalen-1-yl)ethan-1-one (4.2c): Colorless liquid.



Yield: 90%. ^{1}H NMR analysis of the crude reaction mixture showed a d.r. of 78:22, as determined by comparison of the following signals: δ 2.92 (d, *J* =7.1 Hz, 2H, COC*H*$_2$)-major, 2.82 (d, *J* =6.9 Hz, 2H, COC*H*$_2$)-minor. IR (DCM): 3052, 2985, 2851, 1684, 1435, 1264, 895, 729, 703 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.44 (d, *J* =8.3 Hz, 1H, ArC*H*), 7.86 (d, *J* =8.2 Hz, 1H, ArC*H*),

7.71-7.78 (m, 2H, ArC*H*), 7.37-7.50 (m, 3H, ArC*H*), 2.92 (d, *J* =7.1 Hz, 2H, COCH_2)-major, 2.82 (d, *J* =6.9 Hz, 2H, COCH_2)-minor, 2.14-2.20 (m, 1H, C*H*), 1.39-1.53 (m, 7H, C*H*&CH_2), 1.13-1.25 (m, 2H, CH_2), 0.83 (d, *J* =6.8 Hz, 3H, CH_3)-major, 0.77 (d, *J* =6.5 Hz, 3H, CH_3)-minor. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100.6 MHz): (Mixture of diastereoisomers) δ 205.12 (*C*=O), 137.06 (quat-*C*), 134.13 (quat-*C*), 132.31 (Ar*C*H), 130.27 (quat-*C*), 128.52 (Ar*C*H), 127.86 (Ar*C*H), 127.22 (Ar*C*H), 126.50 (Ar*C*H), 125.88 (Ar*C*H), 124.48 (Ar*C*H), 50.07 (CO*C*H_2), 47.17 (CO*C*H_2), 35.14 (*C*H), 34.84 (*C*H), 33.48 (*C*H), 32.61 (*C*H), 32.38 (*C*H_2), 30.86 (*C*H_2), 30.05 (*C*H_2), 29.05 (*C*H_2), 22.71 (*C*H_3), 20.35 (*C*H_3). HRMS (ESI) m/z calcd for $C_{19}H_{22}O$ $(M+H)^+$: 267.1743, found: 267.1724.

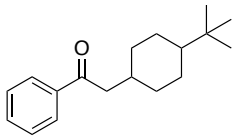
1-(Naphthalen-2-yl)-2-(4-propylcyclohexyl)ethan-1-one (4.2d): Colorless liquid.



Yield: 72%. ^1H NMR analysis of the crude reaction mixture showed a d.r. of 87:13, as determined by comparison of the following signals: δ 2.97 (d, *J* =7.0 Hz, 2H, COCH_2)-major, 2.88 (d, *J* =6.8 Hz, 2H, COCH_2)-minor. IR (DCM): 3059, 2922, 2848, 1673, 1628, 1289, 1121, 737 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 8.39 (s, 1H, ArC*H*), 7.96 (dd, J_1 =8.6 Hz, J_2 =1.4 Hz, 1H, ArC*H*), 7.90 (d, *J* =7.9 Hz, 1H,ArC*H*), 7.81 (t, *J* =8 Hz, 2H, ArC*H*), 7.46-7.54 (m, 2H, ArC*H*), 2.97 (d, *J* =7.0 Hz, 2H, COCH_2)-major, 2.88 (d, *J* =6.8 Hz, 2H, COCH_2)-minor, 2.19-2.21 (m, 1H, C*H*), 1.44-1.52 (m, 4H, CH_2), 1.35-1.41 (m, 3H, C*H*&CH_2), 1.18-1.33 (m, 6H, CH_2), 0.78-0.84 (m, 3H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100.6 MHz): (Mixture of diastereoisomers) δ 200.63 (*C*=O), 135.65 (quat-*C*), 134.97 (quat-*C*), 132.72 (quat-*C*), 129.82 (Ar*C*H), 129.71 (Ar*C*H), 128.53 (Ar*C*H), 128.47 (Ar*C*H), 127.90 (Ar*C*H), 126.84 (Ar*C*H), 124.20 (Ar*C*H), 46.42 (CO*C*H_2), 43.59 (CO*C*H_2), 39.79 (*C*H), 37.32 (*C*H), 36.68 (*C*H), 35.15 (*C*H), 34.90

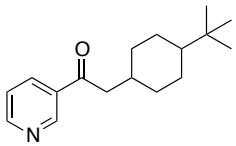
(*C*H_2), 33.60 (*C*H_2), 33.15 (*C*H_2), 32.56 (*C*H_2), 29.22 (*C*H_2), 29.04 (*C*H_2), 20.55 (*C*H_2), 14.52 (*C*H_3). HRMS (ESI) m/z calcd for $C_{21}H_{26}O$ $(M+H)^+$: 295.2056, found: 295.2045.

2-(4-(*tert*-Butyl)cyclohexyl)-1-phenylethanone (4.2e): Colorless liquid. Yield: 78%.



^{1}H NMR analysis of the crude mixture showed a d.r. of 86:14, as determined by comparison of the following signals: δ 2.91 (d, *J* =7.2 Hz, 2H, COC*H*$_2$)-major, 2.73 (d, *J* =6.5 Hz, 2H, COC*H*$_2$)-minor. IR (DCM): 3052, 2984, 2863, 1674, 1419, 1262, 895, 749 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.87-7.90 (m, 2H, ArC*H*), 7.45-7.49 (m, 1H, ArC*H*), 7.36-7.40 (m, 2H, ArC*H*), 2.91 (d, *J* =7.2 Hz, 2H, COC*H*$_2$)-major, 2.73 (d, *J* =6.5 Hz, 2H, COC*H*$_2$)-minor, 2.35-2.38 (m, 1H, C*H*), 1.58-1.61 (m, 2H, C*H*$_2$), 1.42-1.51 (m, 4H, C*H*$_2$), 1.05-1.15 (m, 2H, C*H*$_2$), 0.88-0.94 (m, 1H, C*H*), 0.78 (s, 9H, 3×C*H*$_3$)-major, 0.75 (s, 9H, 3×C*H*$_3$)-minor. ^{13}C{^{1}H} NMR ($CDCl_3$, 100.6 MHz): (Mixture of diastereoisomers) δ 200.70 (*C*=O), 137.51 (quat-*C*), 132.93 (Ar*C*H), 128.66 (Ar*C*H), 128.23 (Ar*C*H), 48.43 (CO*C*H$_2$), 47.99 (CO*C*H$_2$), 46.27 (*C*H), 40.49 (*C*H), 34.84 (quat-*C*), 33.98 (quat-*C*), 32.67 (*C*H), 32.50 (*C*H), 30.86 (*C*H$_2$), 29.26 (*C*H$_2$), 27.66 (*C*H$_2$), 27.61 (*C*H$_3$), 27.24 (*C*H$_3$), 22.02 (*C*H$_2$). HRMS (ESI) m/z calcd for $C_{18}H_{26}O$ $(M+H)^+$: 259.2056, found: 259.2074.

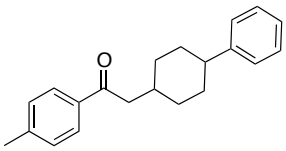
2-(4-(*tert*-Butyl)cyclohexyl)-1-(pyridin-3-yl)ethanone (4.2f): Colorless liquid. Yield: 90%.



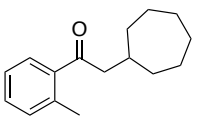
^{1}H NMR analysis of the crude mixture showed a d.r. of 90:10, as determined by comparison of the following signals: δ 2.94 (d, *J* =7.1 Hz, 2H, COC*H*$_2$)-major, 2.76 (d, *J* =6.4 Hz, 2H, COC*H*$_2$)-minor. IR (DCM): 3052, 2942, 2865, 1684, 1419, 1264, 1003, 895, 737 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.11 (s, 1H, ArC*H*), 8.70 (d, *J* =4.2 Hz, 1H, ArC*H*), 8.16 (d, *J* =7.7 Hz, 1H, ArC*H*), 7.34-7.37 (m, 1H, ArC*H*), 2.94 (d, *J* =7.1 Hz, 2H, COC*H*$_2$)-major, 2.76 (d, *J* =6.4 Hz, 2H, COC*H*$_2$)-minor, 2.31-2.44 (m, 1H, C*H*), 1.69-1.78 (m, 1H, C*H*), 1.45-1.62 (m, 6H, C*H*$_2$), 1.04-1.14 (m, 2H, C*H*$_2$), 0.90-0.99 (m, 2H, C*H*$_2$), 0.79 (s, 9H,

3×CH_3)-major, 0.77 (s, 9H, 3×CH_3)-minor. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100.6 MHz): (Mixture of diastereoisomers) δ 199.44 (*C*=O), 153.43 (Ar*C*H), 149.84 (Ar*C*H), 135.57 (Ar*C*H), 132.63 (quat-*C*), 123.77 (Ar*C*H), 48.39 (CO*C*H_2), 47.32 (CO*C*H_2), 46.56 (*C*H), 40.86 (*C*H), 36.24 (*C*H_2), 34.69 (quat-*C*), 33.93 (*C*H), 32.69 (quat-*C*), 30.80 (*C*H_2), 29.15 (*C*H), 27.78 (*C*H_3), 27.61 (*C*H_3), 25.74 (*C*H_2), 22.00 (*C*H_2). HRMS (ESI) m/z calcd for $C_{17}H_{25}NO$ $(M+H)^+$: 260.2009, found: 260.1996.

2-(4-Phenylcyclohexyl)-1-(*p*-tolyl)ethanone (4.2g): Colorless liquid. Yield: 82%. ^1H NMR analysis of the crude mixture showed a d.r. of 80:20, as determined by comparison of the following signals: δ 2.95 (d, *J* =7.1 Hz, 2H, COCH_2)-major, 2.78 (d, *J* =6.7 Hz, 2H, COCH_2)-minor. IR (DCM): 3052, 2984, 2855, 1680, 1436, 1264, 1045, 895, 753 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.80 (d, *J* = 8.2 Hz, 2H, ArC*H*), 7.16-7.22 (m, 5H, ArC*H*), 7.09-7.12 (m, 2H, ArC*H*), 2.95 (d, *J* =7.1 Hz, 2H, COCH_2)-major, 2.78 (d, *J* =6.7 Hz, 2H, COCH_2)-minor, 2.49-2.57 (m, 1H, CH_2), 2.37-2.44 (m, 1H, C*H*), 2.33 (s, 3H, CH_3), 1.80-1.86 (m, 1H, C*H*), 1.66-1.71 (m, 4H, CH_2), 1.59-1.64 (m, 3H, CH_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100.6 MHz): (Mixture of diastereoisomers) δ 200.06 (*C*=O), 147.18 (quat-*C*), 143.78 (quat-*C*), 135.12 (quat-*C*), 129.40 (Ar*C*H), 128.44 (Ar*C*H), 128.40 (Ar*C*H), 127.05 (Ar*C*H), 125.96 (Ar*C*H), 46.06 (*C*H), 44.37 (*C*H), 43.18 (CO*C*H_2), 41.26 (CO*C*H_2), 34.45 (*C*H), 34.16 (*C*H_2), 33.78 (*C*H_2), 30.35 (*C*H_2), 29.96 (*C*H_2), 29.83 (*C*H), 29.14 (*C*H_2), 21.73 (*C*H_3). HRMS (ESI) m/z calcd for $C_{21}H_{24}O$ $(M+H)^+$: 293.1900, found: 293.1906.

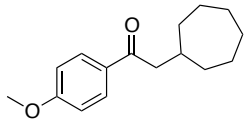


2-Cycloheptyl-1-(*o*-tolyl)ethan-1-one (4.2h): Colorless liquid. Yield: 80%. IR (DCM): 3053, 2926, 2853, 1683, 1458, 1265, 895, 739 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.50 (d, *J* = 7.7 Hz, 1H, ArC*H*), 7.27 (t, *J* = 7.5 Hz, 1H, ArC*H*), 7.17 (t, *J* = 7.7 Hz, 2H, ArC*H*), 2.72 (d, *J* = 7.0 Hz, 2H, COCH_2), 2.40 (s, 3H,



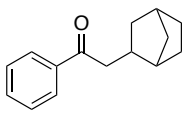
CH_3), 2.05-2.13 (m, 1H, C*H*), 1.62-1.67 (m, 2H, CH_2), 1.51-1.60 (m, 4H, CH_2), 1.36-1.42 (m, 4H, CH_2), 1.14-1.22 (m, 2H, CH_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100.6 MHz): δ 205.10 (*C*=O), 138.92 (quat-*C*), 137.78 (quat-*C*), 131.96 (Ar*C*H), 131.03 (Ar*C*H), 128.35 (Ar*C*H), 125.69 (Ar*C*H), 50.14 (CO*C*H_2), 36.06 (*C*H), 34.92 (*C*H_2), 28.43 (*C*H_2), 26.41 (*C*H_2), 21.22 (*C*H_3). HRMS (ESI) m/z calcd for $C_{16}H_{22}O$ $(M+H)^+$: 231.1743, found: 231.1742.

2-Cycloheptyl-1-(4-methoxyphenyl)ethanone (4.2i): Colorless liquid. Yield: 68%. IR



(DCM): 3051, 2983, 2964, 1675, 1455, 1257, 1028, 895, 733 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.86 (d, *J* = 8.8 Hz, 2H, ArC*H*), 6.85 (d, *J* = 8.8 Hz, 2H, ArC*H*), 3.79 (s, 3H, OCH_3), 2.74 (d, *J* = 6.9 Hz, 2H, COCH_2), 2.10-2.17 (m, 1H, C*H*), 1.65-1.69 (m, 2H, CH_2), 1.52-1.61 (m, 4H, CH_2), 1.37-1.46 (m, 4H, CH_2), 1.15-1.23 (m, 2H, CH_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100.6 MHz): δ 199.19 (*C*=O), 163.42 (quat-*C*), 130.76 (quat-*C*), 130.53 (Ar*C*H), 113.78 (Ar*C*H), 55.57 (O*C*H_3), 46.60 (CO*C*H_2), 36.41 (*C*H), 35.02 (*C*H_2), 28.46 (*C*H_2), 26.42 (*C*H_2). HRMS (ESI) m/z calcd for $C_{16}H_{22}O_2$ $(M+H)^+$: 247.1693, found: 247.1696.

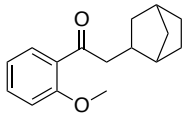
2-(Bicyclo[2.2.1]heptan-2-yl)-1-phenylethan-1-one (4.2j): Colorless liquid. Yield:



75%. IR (DCM): 3026, 2950, 2869, 1684, 1597, 1265, 1001, 737 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.87-7.89 (m, 2H, ArC*H*), 7.47 (t, *J* =7.3 Hz, 1H, ArC*H*), 7.38 (t, *J* =7.5 Hz, 2H, ArC*H*), 2.92 (ddd, J_1 = 24.6 Hz, J_2 = 16.4 Hz, J_3 = 7.3 Hz, 2H, COCH_2), 2.31-2.33 (m, 1H, C*H*), 2.13 (d, *J* =13.1 Hz, 2H, CH_2), 1.79-1.87 (m, 1H, C*H*), 1.41-1.50 (m, 2H, CH_2), 1.29-1.33 (m, 2H, CH_2), 1.22 (dd, J_1 =9.4 Hz, J_2 =1.8 Hz, 1H, C*H*), 1.06 (ddd, J_1 = 11.4 Hz, J_2 = 6.7 Hz, J_3 = 2.4 Hz, 1H, CH_2), 0.62 (ddd, J_1 = 12.3 Hz, J_2 = 5.2 Hz, J_3 = 2.3 Hz, 1H, CH_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100.6 MHz): δ 200.63 (*C*=O), 137.41 (quat-*C*), 132.93 (Ar*C*H), 128.66 (Ar*C*H), 128.17 (Ar*C*H), 42.03 (CO*C*H_2), 40.43 (*C*H), 39.94 (*C*H), 37.24 (*C*H_2), 37.14

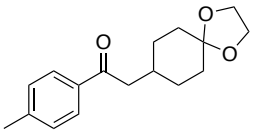
(CH_2), 35.96 (CH), 30.22 (CH_2), 23.03 (CH_2). HRMS (ESI) m/z calcd for $C_{15}H_{18}O$ $(M+H)^+$: 215.1436, found: 215.1440.

2-(Bicyclo[2.2.1]heptan-2-yl)-1-(2-methoxyphenyl)ethan-1-one (4.2k): Colorless



liquid. Yield: 75%. IR (DCM): 3052, 2948, 2867, 1672, 1597, 1485, 1464, 1294, 1244, 1026, 738 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.53 (dd, J_1 = 7.6 Hz, J_2 = 1.6 Hz, 1H, ArC*H*), 7.34-7.38 (m, 1H, ArC*H*), 6.87-6.93 (m, 2H, ArC*H*), 3.82 (s, 3H, OCH_3), 2.93 (qd, J_1 = 16.5 Hz, J_2 = 7.4 Hz, 2H, $COCH_2$), 2.24-2.27 (m, 1H, C*H*), 2.09 (d, J =3.8 Hz, 2H, CH_2), 1.73-1.79 (m, 1H, C*H*), 1.38-1.46 (m, 2H, CH_2), 1.24-1.29 (m, 2H, CH_2), 1.18-1.20 (m, 1H, C*H*), 1.00-1.09 (m, 1H, CH_2), 0.59 (ddd, J_1 = 12.2 Hz, J_2 = 5.2 Hz, J_3 = 2.3 Hz, 1H, CH_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100.6 MHz): δ 203.64 (*C*=O), 158.24 (quat-*C*), 133.03 (Ar*C*H), 130.05 (Ar*C*H), 129.28 (quat-*C*), 120.74 (Ar*C*H), 111.56 (Ar*C*H), 55.61 (OCH_3), 47.23 ($COCH_2$), 40.48 (*C*H), 39.90 (*C*H), 37.24 (CH_2), 36.97 (CH_2), 35.95 (*C*H), 30.18 (CH_2), 23.05 (CH_2). HRMS (ESI) m/z calcd for $C_{16}H_{20}O_2$ $(M+H)^+$: 245.1536, found: 245.1533.

2-(1,4-Dioxaspiro[4.5]decan-8-yl)-1-(*p*-tolyl)ethan-1-one (4.2l): Colorless liquid.



Yield: 48%. IR (DCM): 3052, 2894, 2863, 1676, 1419, 1262, 1006, 894, 748, 703 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.78 (d, J =8.1 Hz, 2H, ArC*H*), 7.18 (d, J =8.2 Hz, 2H, ArC*H*), 3.86 (s, 4H, OCH_2), 2.78 (d, J =6.8 Hz, 2H, $COCH_2$), 2.34 (s, 3H, CH_3), 1.93-1.99 (m, 1H, CH_2), 1.65-1.73 (m, 4H, CH_2), 1.48-1.59 (m, 2H, CH_2), 1.22-1.33 (m, 2H, CH_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100.6 MHz): δ 199.68 (*C*=O), 143.88 (quat-*C*), 135.03 (quat-*C*), 129.39 (Ar*C*H), 128.38 (Ar*C*H), 108.86 (quat-*C*), 64.35 (OCH_2), 44.85 ($COCH_2$), 34.54 (CH_2), 33.15 (*C*H), 30.46 (CH_2), 21.74 (CH_3). HRMS (ESI) m/z calcd for $C_{17}H_{22}O_3$ $(M+Na)^+$: 297.1461, found: 297.1450.

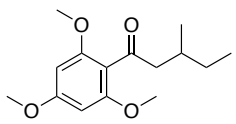
1,3,3-Triphenylpropan-1-one (4.2m):[21] Colorless solid. Yield: 68%. IR (DCM): 3058, 3028, 2926, 1687, 1597, 1494, 1449, 1363, 1264, 1205, 983, 737 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.84 (dd, J_1 = 7.8 Hz, J_2 = 0.5 Hz, 2H, ArC*H*), 7.44 (t, *J* =7.4 Hz, 1H, ArC*H*), 7.33 (t, *J* =7.6 Hz, 2H, ArC*H*), 7.18 (d, *J* =4.4 Hz, 8H, ArC*H*), 7.08 (dd, J_1 = 8.5 Hz, J_2 = 4.3 Hz, 2H, ArC*H*), 4.74 (t, *J* =7.3 Hz, 1H, *C*H), 3.65 (d, *J* =7.3 Hz, 2H, COCH_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100.6 MHz): δ 198.11 (*C*=O), 144.26 (quat-*C*), 137.18 (quat-*C*), 133.19 (Ar*C*H), 128.71 (Ar*C*H), 128.67 (Ar*C*H), 128.16 (Ar*C*H), 127.96 (Ar*C*H), 126.49 (Ar*C*H), 46.05 (*C*H), 44.84 (CO*C*H_2). HRMS (ESI) m/z calcd for $C_{21}H_{18}O$ $(M+Na)^+$: 309.1250, found: 309.1226.

1-Mesityl-3-methylbutan-1-one (4.2n):[22] Colorless liquid. Yield: 82%. IR (DCM): 2958, 2926, 2871, 1696, 1610, 1467, 1265, 737 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 6.74 (s, 2H, ArC*H*), 2.52 (d, *J* =6.6 Hz, 2H, COCH_2), 2.19-2.29 (m, 1H, C*H*), 2.19 (s, 3H, ArCH_3), 2.12 (s, 6H, ArCH_3), 0.93 (d, *J* =6.7 Hz, 6H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100.6 MHz): δ 210.24 (*C*=O), 139.98 (quat-*C*), 138.27 (quat-*C*), 132.60 (quat-*C*), 128.64 (Ar*C*H), 53.84 (CO*C*H_2), 23.72 (*C*H), 22.86 (*C*H_3), 21.13 (Ar*C*H_3), 19.20 (Ar*C*H_3). HRMS (ESI) m/z calcd for $C_{14}H_{20}O$ $(M+H)^+$: 205.1592, found: 205.1602.

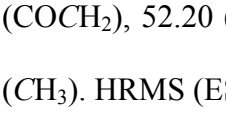
1-Mesityl-3-methylpentan-1-one (4.2o): Colorless liquid. Yield: 90%. IR (DCM): 2961, 2922, 2875, 1695, 1610, 1265, 1036, 738 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 6.75 (s, 2H, ArC*H*), 2.62 (dd, J_1 =18.3 Hz, J_2 =5.2 Hz, 1H, COCH_2), 2.46 (dd, J_1 =18.3 Hz, J_2 =7.9 Hz, 1H, COCH_2), 2.19 (s, 3H, ArCH_3), 2.12 (s, 6H, ArCH_3), 1.96-2.05 (m, 1H, C*H*), 1.32-1.42 (m, 1H, CH_2), 1.11-1.22 (m, 1H, CH_2), 0.93 (d, *J* =6.7 Hz, 3H, CH_3), 0.84 (t, *J* =7.4 Hz, 3H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100.6 MHz): δ 210.43 (*C*=O), 140.05 (quat-*C*), 138.27 (quat-*C*), 132.60

(quat-*C*), 128.65 (Ar*C*H), 51.99 (CO*C*H_2), 29.89 (*C*H), 29.61 (*C*H_2), 21.14 (Ar*C*H_3), 19.66 (*C*H_3), 19.22 (Ar*C*H_3), 11.47 (*C*H_3). HRMS (ESI) m/z calcd for $C_{15}H_{22}O$ $(M+H)^+$: 219.1749, found: 219.1751.

3-Methyl-1-(2,4,6-trimethoxyphenyl)pentan-1-one (4.2p): Colorless liquid. Yield: 30%. IR (DCM): 2961, 2922, 2875, 1695, 1610, 1265, 1036, 738 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 6.02 (s, 2H, ArC*H*), 3.74 (s, 3H, OCH_3), 3.70 (s, 6H, OCH_3), 2.67 (dd, J_1 =16.3 Hz, J_2 =5.6 Hz, 1H, COCH_2), 2.46 (dd, J_1 =16.3 Hz, J_2 =8.1 Hz, 1H, COCH_2), 1.87-1.94 (m, 1H, C*H*), 1.14-1.31 (m, 2H, CH_2), 0.78-0.86 (m, 6H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100.6 MHz): δ 204.79 (*C*=O), 162.19 (quat-*C*), 158.23 (quat-*C*), 114.15 (quat-*C*), 90.74 (Ar*C*H), 55.87 (O*C*H_3), 55.51 (CO*C*H_2), 52.20 (O*C*H_3), 31.71 (O*C*H_3), 31.04 (*C*H), 29.63 (*C*H_2), 19.56 (*C*H_3), 11.42 (*C*H_3). HRMS (ESI) m/z calcd for $C_{15}H_{22}O_4$ $(M+Na)^+$: 289.1410, found: 289.1392.



1-Mesityl-3-methylhexan-1-one (4.2q): Colorless liquid. Yield: 65%. IR (DCM): 2963, 2926, 2875, 1694, 1610, 1264, 1037, 738, 703 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 6.74 (s, 2H, ArC*H*), 2.61 (dd, J_1 =18.3 Hz, J_2 =5.1 Hz, 1H, COCH_2), 2.45 (dd, J_1 =18.3 Hz, J_2 =7.9 Hz, 1H, COCH_2), 2.19 (s, 3H, ArCH_3), 2.12 (s, 6H, ArCH_3), 2.03-2.09 (m, 1H, C*H*), 1.21-1.32 (m, 3H, CH_2), 1.08-1.15 (m, 1H, CH_2), 0.92 (d, J =6.6 Hz, 3H, CH_3), 0.83 (t, J =7.0 Hz, 3H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100.6 MHz): δ 210.36 (*C*=O), 140.04 (quat-*C*), 138.24 (quat-*C*), 132.59 (quat-*C*), 128.64 (Ar*C*H), 52.36 (CO*C*H_2), 39.28 (*C*H_2), 28.07 (*C*H), 21.13 (Ar*C*H_3), 20.20 (*C*H_3), 20.10 (*C*H_2), 19.21 (Ar*C*H_3), 14.32 (*C*H_3). HRMS (ESI) m/z calcd for $C_{16}H_{24}O$ $(M+H)^+$: 233.1900, found: 233.1872.



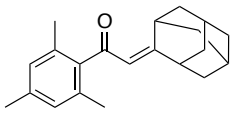
3-Ethyl-1-mesitylpentan-1-one (4.2r): Colorless liquid. Yield: 97%. IR (DCM): 2962, 2921, 2875, 1700, 1611, 1458, 1400, 1378, 1003, 850 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 6.75 (s, 2H, ArC*H*), 2.56 (d, J =6.3 Hz, 2H,

COCH_2), 2.20 (s, 3H, ArCH_3), 2.12 (s, 6H, ArCH_3), 1.88-1.92 (m, 1H, CH), 1.27-1.39 (m, 4H, CH_2), 0.81 (t, J =7.4 Hz, 6H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100.6 MHz): δ 210.59 (*C*=O), 140.15 (quat-*C*), 138.24 (quat-*C*), 132.58 (quat-*C*), 128.66 (Ar*C*H), 49.02 (CO*C*H_2), 35.56 (*C*H), 25.75 (*C*H_2), 21.15 (Ar*C*H_3), 19.24 (Ar*C*H_3), 10.97 (*C*H_3). HRMS (ESI) m/z calcd for $C_{16}H_{24}O$ $(M+H)^+$: 233.1905, found: 233.1909.

3-Ethyl-1-(pyridin-3-yl)pentan-1-one (4.2s): Colorless liquid. Yield: 60%. IR (DCM): 2963, 2932, 2875, 1733, 1457, 1265, 1045, 739 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 9.10 (s, 1H, ArCH), 8.70 (d, J =4.5 Hz, 1H, ArCH), 8.16 (dd, J_1 =8.0 Hz, J_2 = 1.7 Hz, 1H, ArCH), 7.35 (dd, J_1 =7.9 Hz, J_2 = 4.8 Hz, 1H, ArCH), 2.82 (d, J =6.7 Hz, 2H, COCH_2), 1.89-1.96 (m, 1H, CH), 1.27-1.35 (m, 4H, CH_2), 0.83 (t, J =7.4 Hz, 6H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100.6 MHz): δ 199.65 (*C*=O), 153.37 (Ar*C*H), 149.76 (Ar*C*H), 135.61 (Ar*C*H), 132.78 (quat-*C*), 123.81 (Ar*C*H), 43.11 (CO*C*H_2), 37.23 (*C*H), 26.11 (*C*H_2), 11.06 (*C*H_3). HRMS (ESI) m/z calcd for $C_{12}H_{17}NO$ $(M+H)^+$: 192.1383, found: 192.1381.

1-Mesityl-3-propylhexan-1-one (4.2t): Colorless liquid. Yield: 83%. IR (DCM): 2956, 2927, 2871, 1699, 1610, 1457, 1400, 1378, 1222, 1034, 983, 850 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 6.74 (s, 2H, ArCH), 2.56 (d, J =6.3 Hz, 2H, COCH_2), 2.19 (s, 3H, ArCH_3), 2.11 (s, 6H, ArCH_3), 1.95-2.07 (m, 1H, CH), 1.12-1.29 (m, 8H, CH_2), 0.82 (t, J =5.9 Hz, 6H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100.6 MHz): δ 210.54 (*C*=O), 140.05 (quat-*C*), 138.19 (quat-*C*), 132.54 (quat-*C*), 128.62 (Ar*C*H), 49.75 (CO*C*H_2), 36.13 (*C*H_2), 32.35 (*C*H), 21.11 (Ar*C*H_3), 19.84 (*C*H_2), 19.21 (Ar*C*H_3), 14.47 (*C*H_3). HRMS (ESI) m/z calcd for $C_{18}H_{28}O$ $(M+H)^+$: 261.2212, found: 261.2211.

2-(Adamantan-2-ylidene)-1-mesitylethan-1-one (4.2a): Colorless solid. Yield: 87%. IR (DCM): 3049, 2982, 2851, 1662, 1435, 1264, 1047, 895, 737 cm^{-1}. ^1H NMR ($CDCl_3$,



400 MHz): δ 6.74 (s, 2H, ArC*H*), 6.04 (s, 1H, olefinic-C*H*), 3.46-3.57 (m, 1H, C*H*), 2.30-2.37 (m, 1H, C*H*), 2.19 (s, 3H, ArCH_3), 2.14 (s, 6H, ArCH_3), 1.69-1.93 (m, 12H, C*H*&CH_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100.6 MHz): δ 200.75 (*C*=O), 171.32 (olefinic-*C*), 140.76 (quat-*C*), 137.97 (quat-*C*), 133.14 (quat-*C*), 128.53 (Ar*C*H), 120.12 (olefinic-*C*), 41.95 (*C*H), 40.45 (*C*H), 39.51 (*C*H_2), 36.90 (*C*H), 33.38 (*C*H_2), 28.00 (*C*H_2), 21.18 (Ar*C*H_3), 19.37 (Ar*C*H_3). HRMS (ESI) m/z calcd for $C_{21}H_{26}O$ $(M+H)^+$: 295.2056, found: 295.2061.

Procedure for Kinetic Experiments for Cross-Coupling of Secondary Alcohols

A Schlenk flask (25 mL) was equipped with a stir bar, catalyst **1** (0.01 mmol), base (0.05 mmol), 1-phenylethanol (0.5 mmol), cyclohexanol (0.5 mmol), mesitylene (0.5 mmol, internal standard) and toluene (1.5 mL) under nitrogen atmosphere in a glove box. The flask was taken out of the glove box and equipped with a condenser and the solution was heated at 125 °C (oil bath temperature) with stirring under a flow of argon. The reaction mixture was monitored by gas chromatography (GC) at every 20 minutes for 4 hours period. The consumption of 1-phenylethanol was corroborated with increasing concentration of cross-coupling product **4.1a**, which indicated that the reaction follows first-order kinetics with respect to 1-phenylethanol consumption (Figure 4.1).

The Observation of *β*-Disubstituted Ketone and Olefin Intermediate in Reaction Mixture:

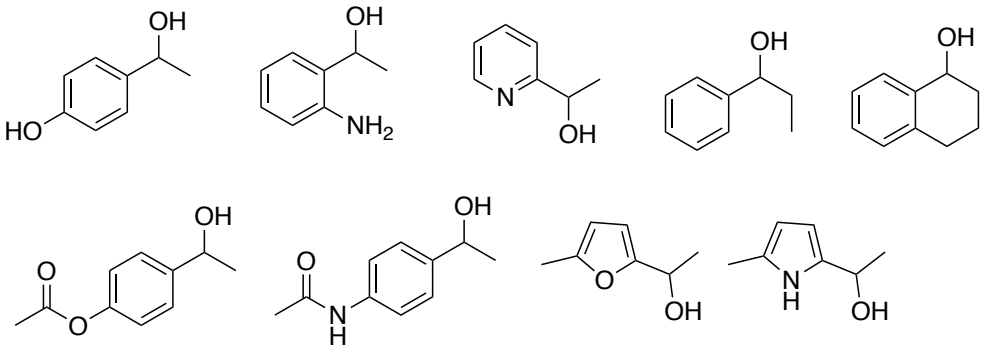
A Schlenk flask (25 mL) was equipped with a stir bar, catalyst **1** (0.04 mmol), base (0.20 mmol), 1-mesitylethanol (0.5 mmol), 4-heptanol (2.5 mmol) and toluene (1.5 mL) under nitrogen atmosphere in a glove box. The flask was taken out of the glove box, equipped with a condenser and the solution was heated at 125 °C (oil bath temperature) with stirring under a flow of argon for 4 h. After 4 hours the reaction mixture was

cooled down to room temperature, the solvent was evaporated and crude reaction mixture was subjected ^{1}H, ^{13}C NMR and GC analyses, which revealed the presence of major amount of alkylated product **4.2t** and minor amount of olefin product **4.3b** (4.2t: 4.3b = 90:10) (see Scheme 4.4b). ^{1}H NMR data for reaction mixture: 1-mesityl-3-propylhexan-1-one: (**4.2t**, 90%) δ 6.74 (s, 2H, ArC*H*), 2.56 (d, *J* =6.3 Hz, 2H, COCH_2), 2.19 (s, 3H, ArCH_3), 2.11 (s, 6H, ArCH_3), 1.95-2.07 (m, 1H, C*H*), 1.12-1.29 (m, 8H, CH_2), 0.82 (t, *J* =5.9 Hz, 6H, CH_3). 1-mesityl-3-propylhex-2-en-1-one: (**4.3b**, 10%) (Only distinguishable peaks) 6.09 (s, 1H, olefinic-C*H*), 2.46-2.50 (m, 4H, CH_2), 1.42 (dt, J_1 =14.6 Hz, J_2 =7.4 Hz, 4H, CH_2), 1.03 (t, *J* =7.5 Hz, 6H, CH_3). ^{13}C NMR data: (5b), 164.65 (olefinic-*C*), 125.34 (olefinic-*C*) (Figure 4.12).

Procedure for Deuterium Labeling Experiments for Cross-Coupling of Secondary Alcohols:

A Schlenk flask (25 mL) was equipped with a stir bar, catalyst **1** (0.01 mmol), base (0.05 mmol), secondary alcohols (0.5 mmol), deuterated secondary alcohols (0.5 mmol) and toluene (1.5 mL) under nitrogen atmosphere in a glove box. The flask was taken out of the glove box and equipped with a condenser and the solution was heated at 125 °C (oil bath temperature) with stirring under a flow of argon for 4 h. The completion of the reaction was monitored using GC analysis. After cooling to room temperature, 0.5 mmol of internal standard (benzene) was added into the reaction mixture and the conversion of secondary alcohols was calculated using GC analysis. Further, the solvent was evaporated and crude reaction mixture was purified by column chromatography over silica-gel (100-200 mesh) using ethyl acetate/petroleum ether mixture as an eluent. Yields were calculated for isolated pure products (Scheme 4.4c and 4.4d).

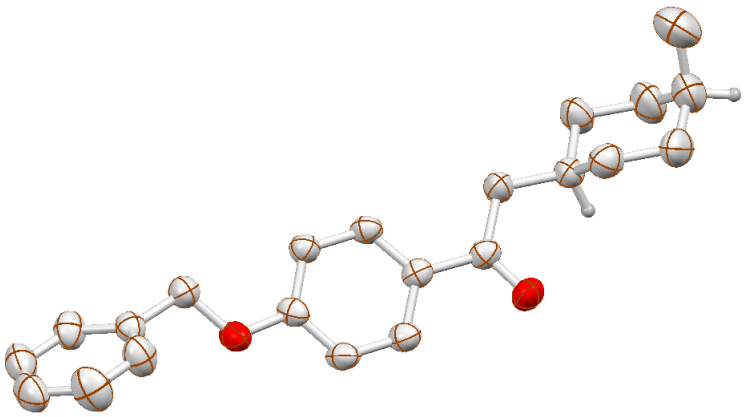
Figure 4.2 List of Unsuccessful Substrates in Cross-Coupling of Secondary Alcohols



X-Ray Analysis of the Cross-Coupling Product 4.2b: Crystals suited for single crystal x-ray diffraction measurements were mounted on a glass fiber. Geometry and intensity data were collected with a Bruker SMART D8 goniometer equipped with an APEXCCD detector and with an Incoatecmicrosource (Mo-Kα radiation, λ = 0.71073 Å, multilayer optics). Temperature was controlled using an Oxford Cryostream 700 instrument. Intensities were integrated with SAINT+[23] and corrected for absorption with SADABS.[24] The structure was solved by direct methods and refined on F^2 with SHELXL-97[25] using Olex-2[26] software.

Crystal Data of Cross-Coupling Product 4.2b: $C_{22}H_{26}O_2$, clear white, M = 322.19 gm/mol, monoclinic with space group P 1 21/c 1, a = 18.4511 (8) Å, b = 7.8907 (2) Å, c = 13.3139 (4) Å, α = 90°, β = 108.175°(4), γ = 90°, V = 1841.69 (12) Å^3, Z = 1, F(000) = 696, μ-(CuK$_\alpha$) = 0.138 mm^{-1}, 2θ$_{max}$ = 151.3320, ρ$_{calcd}$ = 1.163 g/cm^3, T = 294.8 (3) K, 12839 Reflections collected, 2741 unique, R_1 = 0.1433, WR_2 = 0.3537 (all data). Residual electron density max/min = 0.529/-0.663e.Å^{-3}. The structure has been deposited at the CCDC data center and can be retrieved using the deposit number CCDC 1896614.

Figure 4.3: Ortep Structure of 1-(4-(benzyloxy)phenyl)-2-((1*s*,4*s*)-4-methylcyclohexyl)ethan-1-one **4.2b.** Ellipsoids are Drawn with 50% Probability



4.6 NOTES AND REFERENCES

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^{1}H and ^{13}C NMR Spectra of β-Disubstituted Ketones:

Figure 4.4 ^{1}H NMR spectrum of 2-cyclohexyl-1-phenylethanone (**4.1a**):

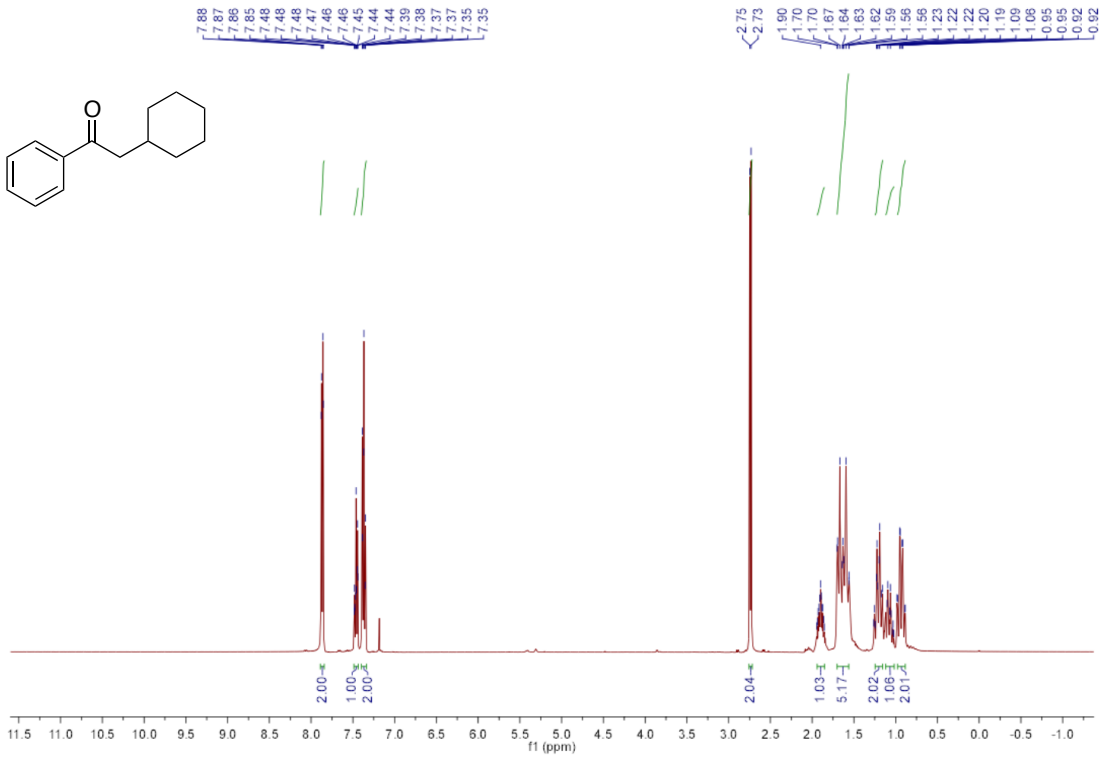


Figure 4.5 ^{13}C NMR spectrum of 2-cyclohexyl-1-phenylethanone (**4.1a**):

Figure 4.6 [1]H NMR spectrum of 2-(4-methylcyclohexyl)-1-(naphthalen-1-yl)ethan-1-one (**4.2c**):

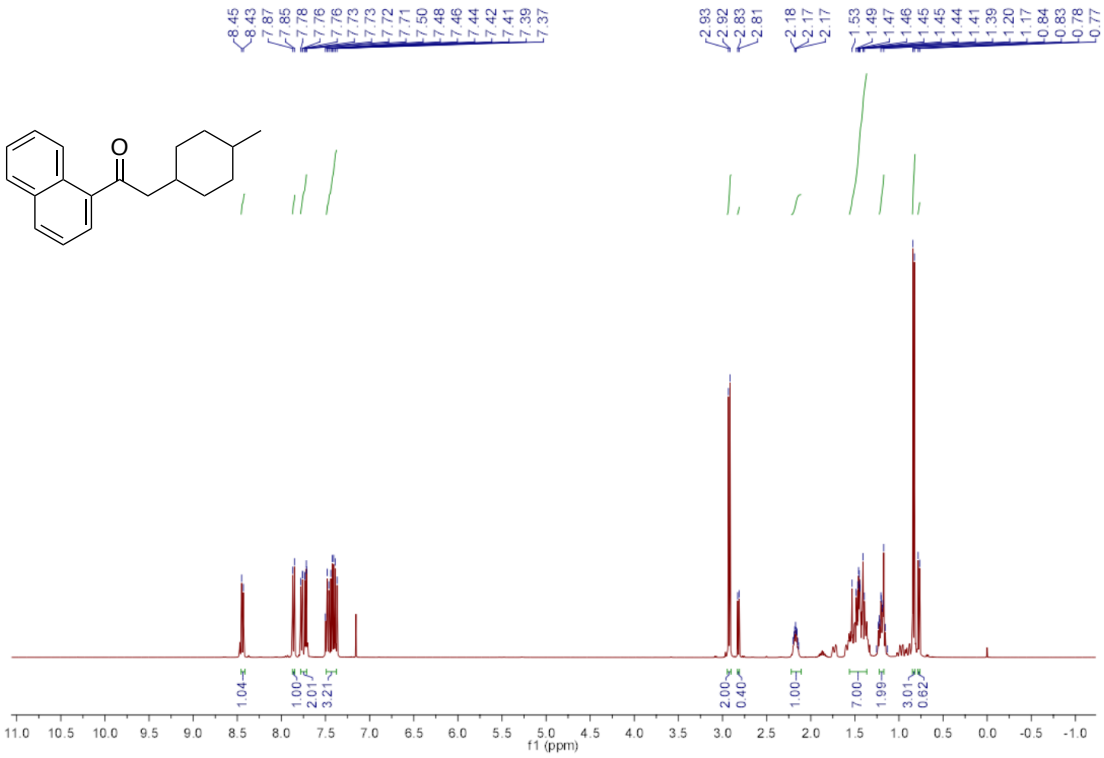


Figure 4.7 [13]C NMR spectrum of 2-(4-methylcyclohexyl)-1-(naphthalen-1-yl)ethan-1-one (**4.2c**):

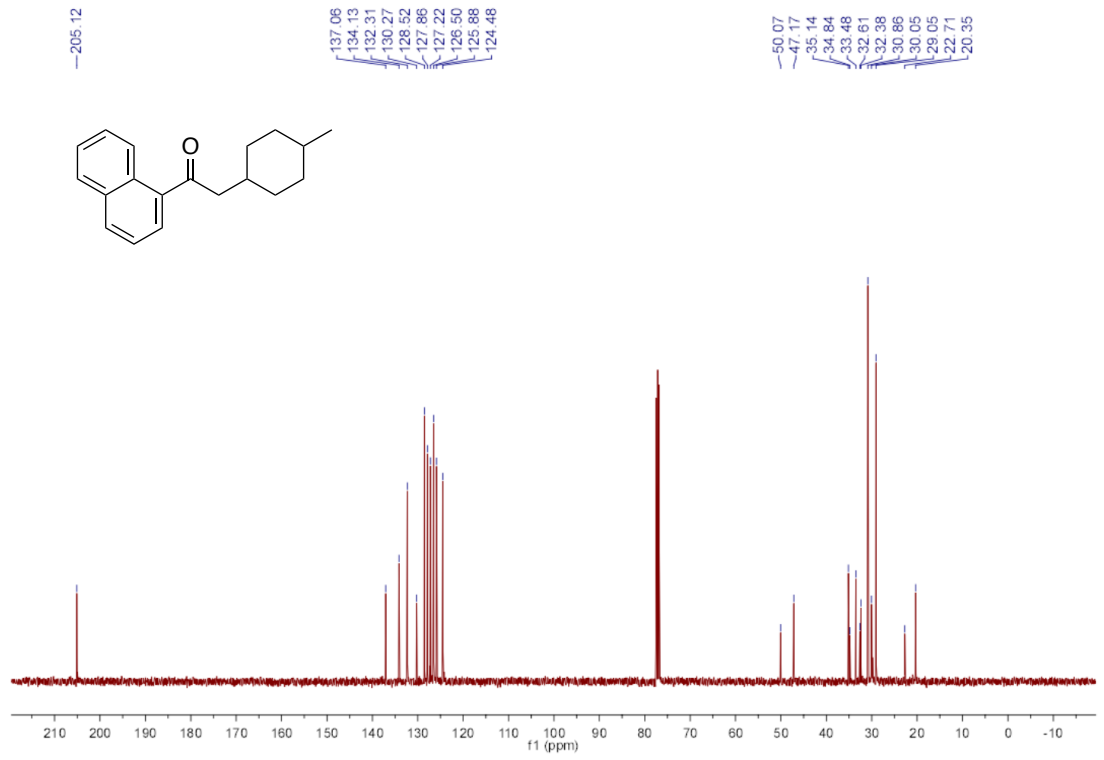


Figure 4.8 ^{1}H NMR spectrum of 3-ethyl-1-mesitylpentan-1-one (**4.2r**):

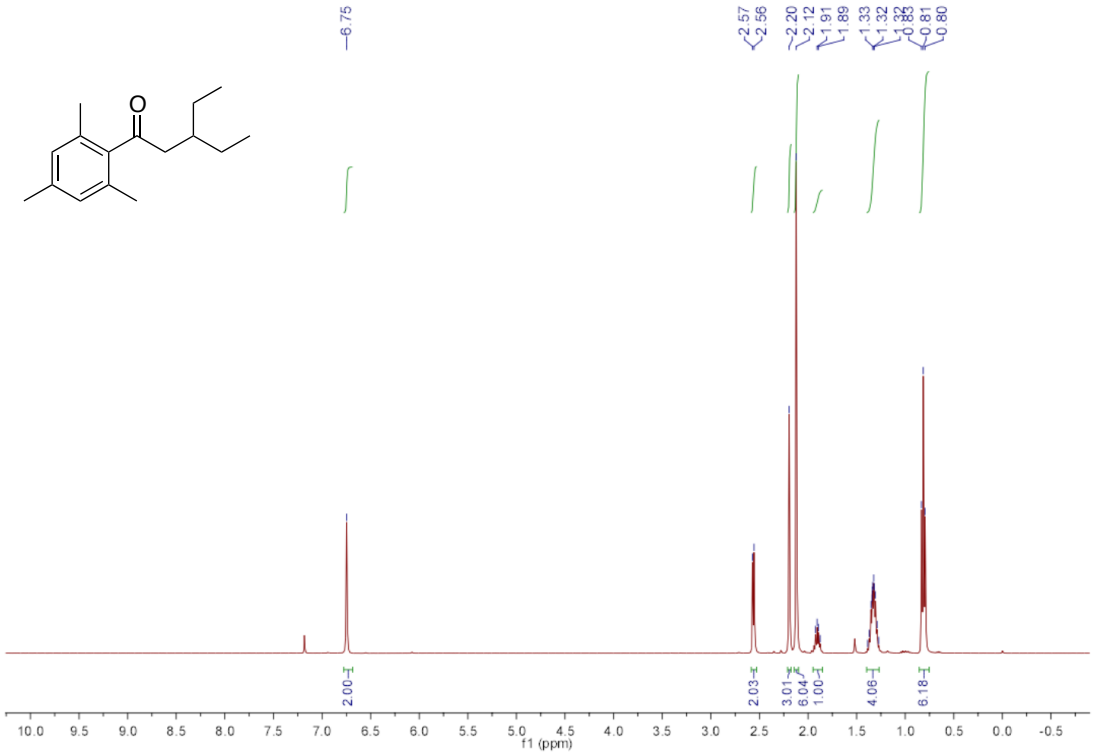


Figure 4.9 ^{13}C NMR spectrum of 3-ethyl-1-mesitylpentan-1-one (**4.2r**):

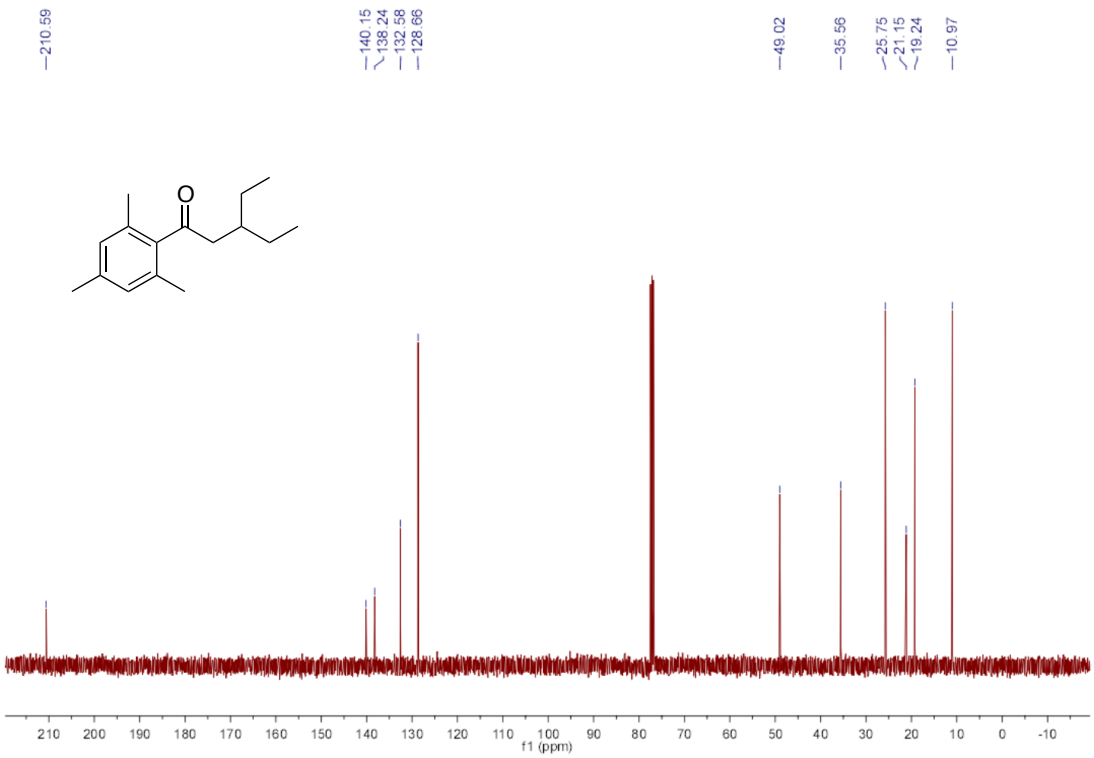


Figure 4.10 ^{1}H NMR spectrum of 2-(adamantan-2-ylidene)-1-mesitylethan-1-one (**4.3a**):

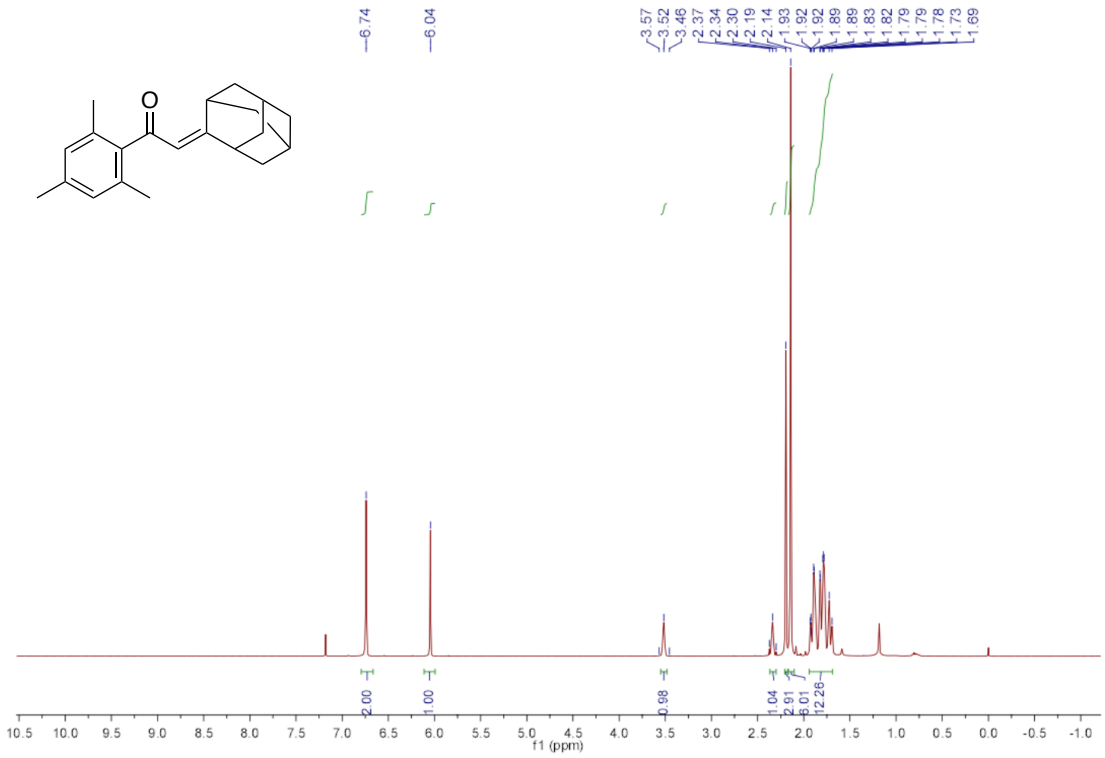


Figure 4.11 ^{13}C NMR spectrum of 2-(adamantan-2-ylidene)-1-mesitylethan-1-one (**4.3a**):

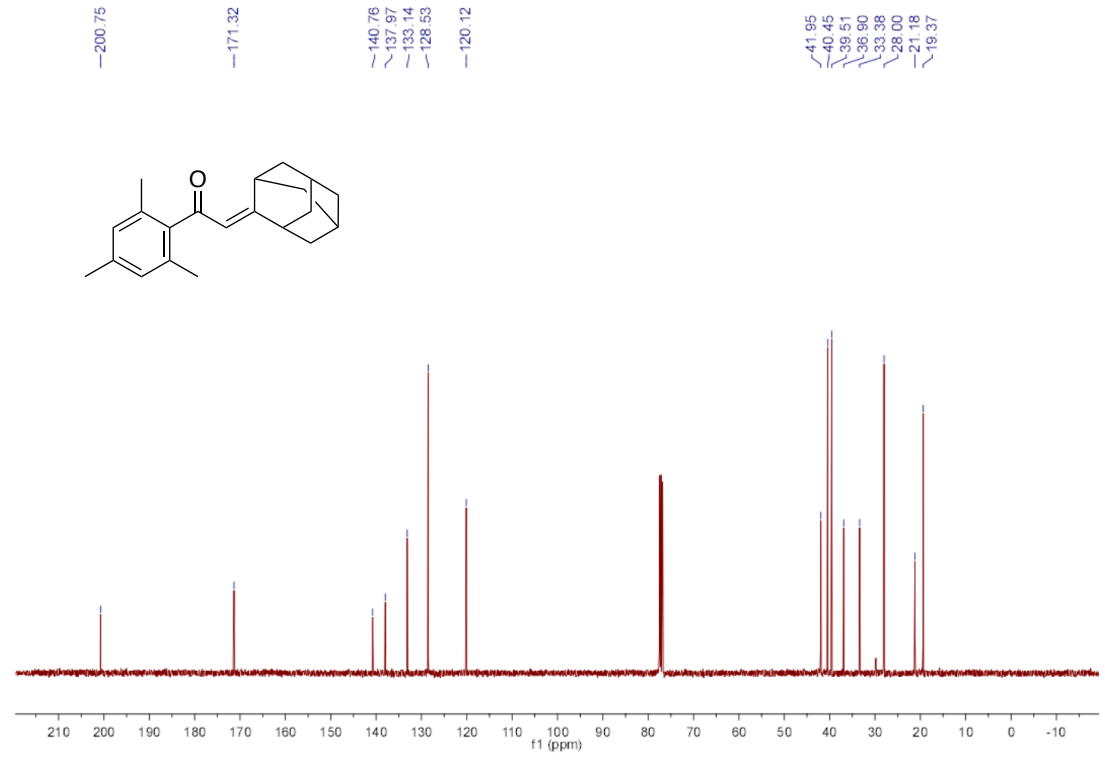


Figure 4.12 ^{1}H NMR Spectrum of β-Disubstituted Ketone and Olefin Intermediate in Reaction Mixture:

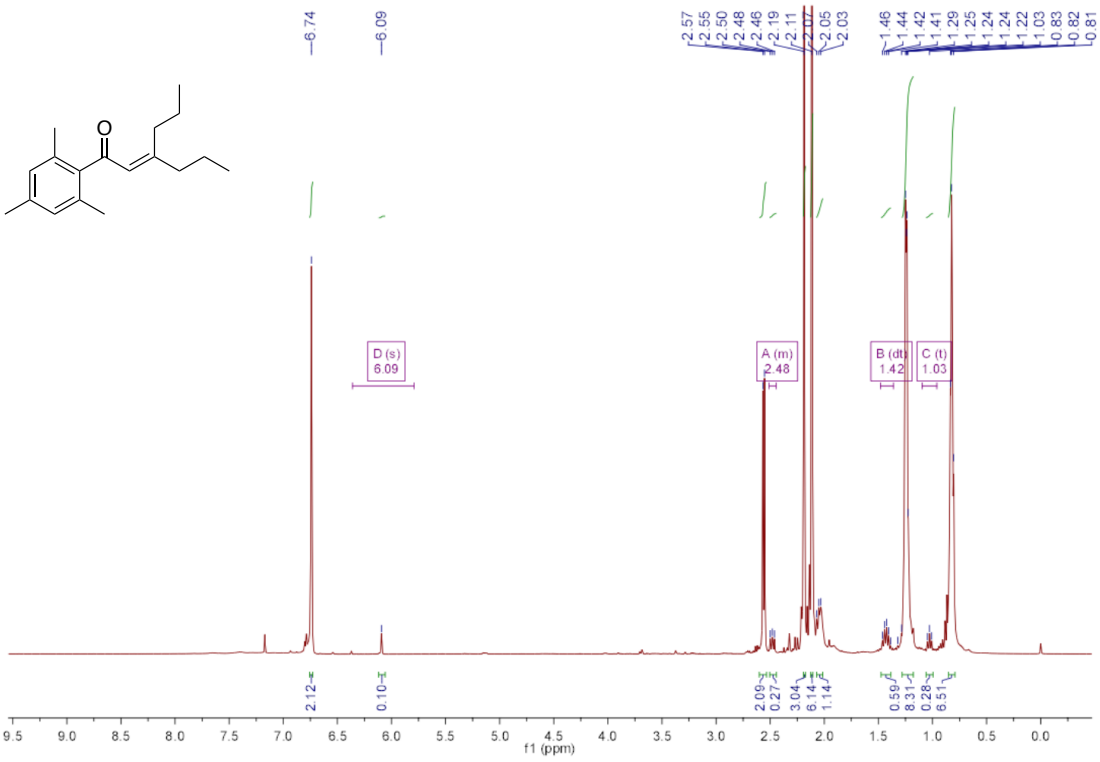


Figure 4.13 ^{1}H NMR Spectrum of Isolated Product in Scheme **4.4c**:

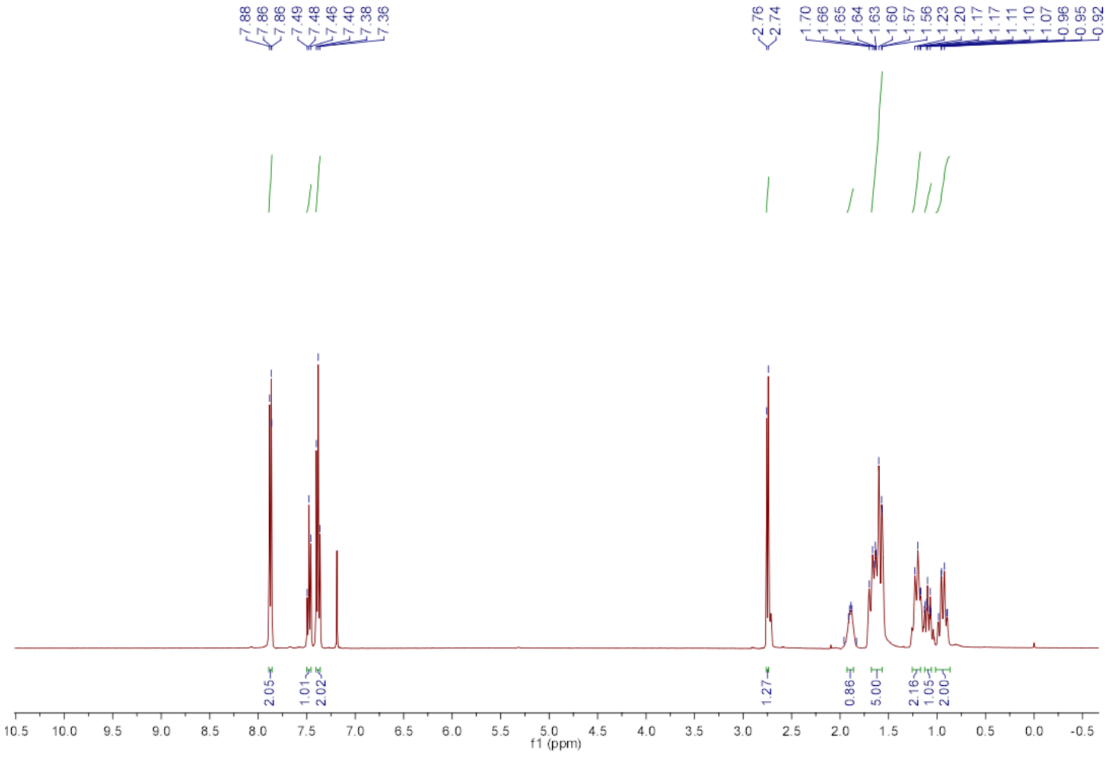


Figure 4.14 HRMS Spectrum of the Isolated Product in Scheme **4.4c**:

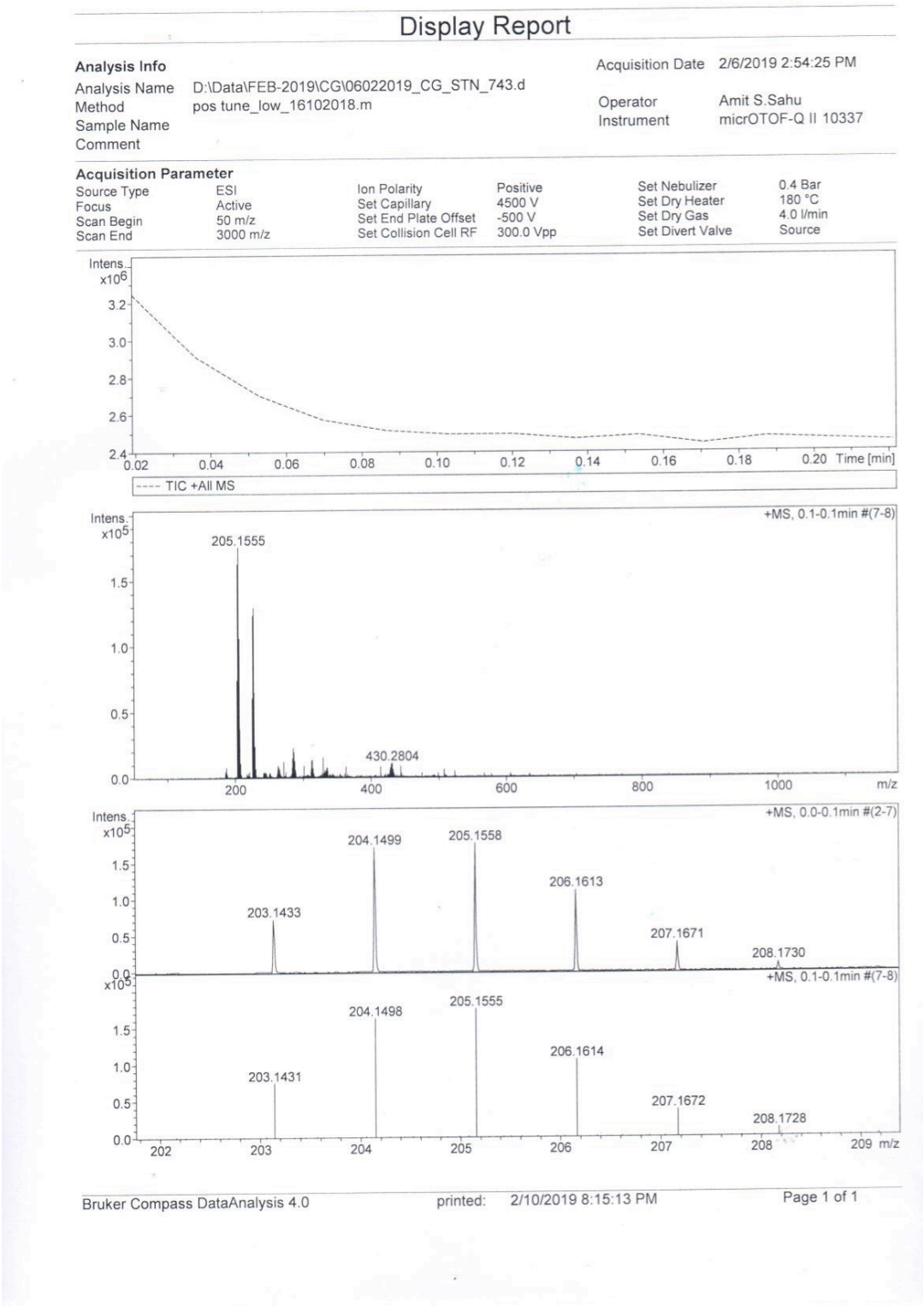


Figure 4.15 ^{1}H NMR Spectrum of the Isolated Product in Scheme **4.4d**:

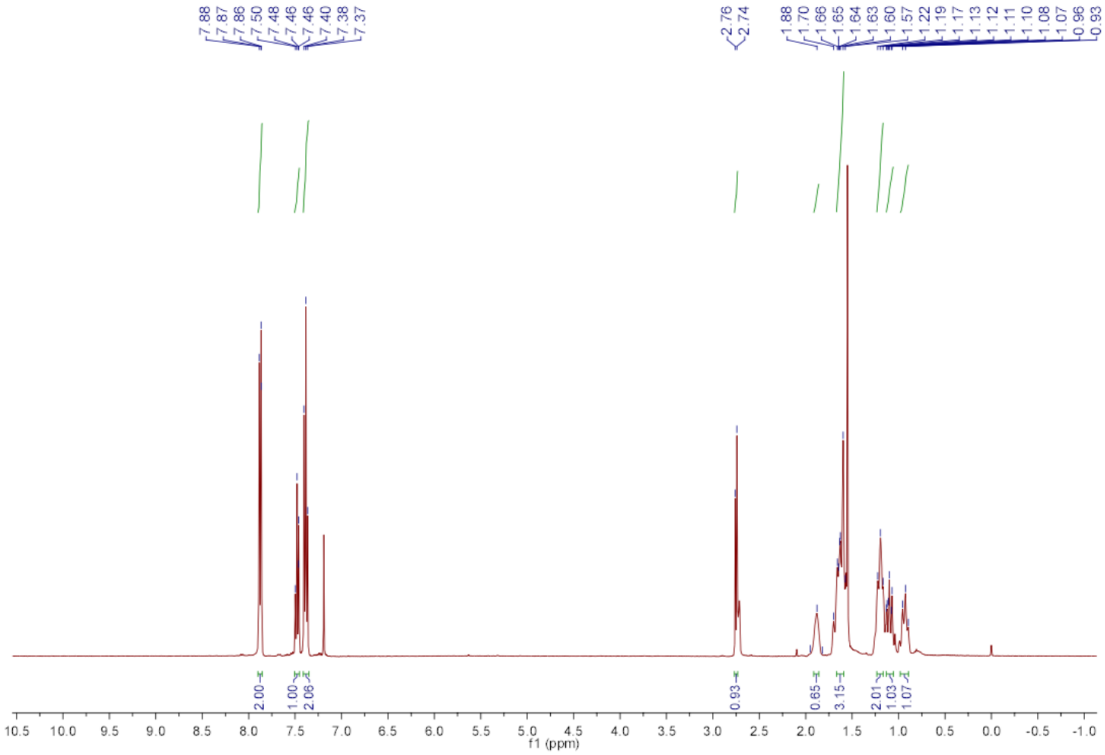
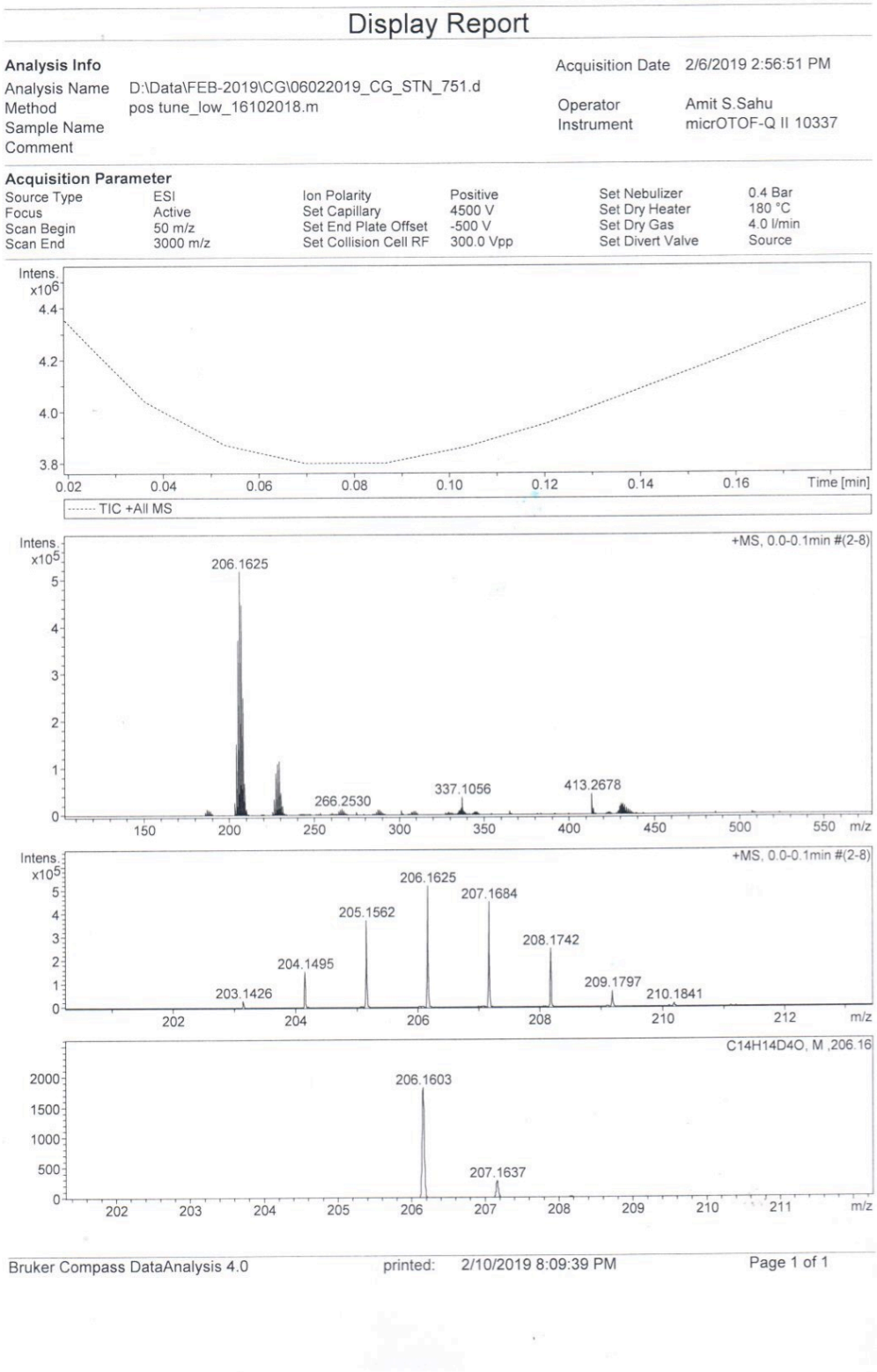


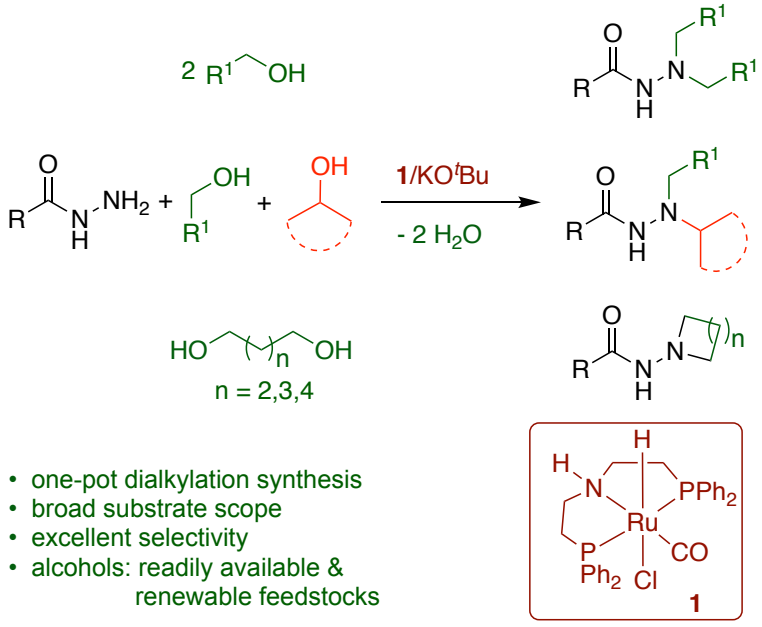
Figure 4.16 HRMS Spectrum of the Isolated Product in Scheme **4.4d:**



CHAPTER 5

Direct Catalytic Symmetrical, Unsymmetrical N,N-Dialkylation and Cyclization of Acylhydrazides Using Alcohols

5.1 ABSTRACT



Rapid and efficient construction of C–N bonds with minimal functional group inter conversion is a desirable process and can lead to ideal synthesis in organic chemistry. I have developed, unprecedented direct N,N-dialkylation of acylhydrazides using alcohols. This catalytic protocol employs a ruthenium pincer catalyst (Ru-MACHO) and provides one-pot synthesis of both symmetrical and unsymmetrical N,N-disubstituted acylhydrazides. Challenging diethylation and dimethylation reactions are performed using ethanol and methanol, respectively as alkylating reagents. Assortment of primary and secondary alcohols can be used with remarkable selectivity and the products were obtained in excellent yields. Interestingly, the use of diols resulted in intermolecular cyclization of acylhydrazides and such products are privileged structures in biologically active compounds. Preliminary mechanistic and deuterium labelling studies indicate

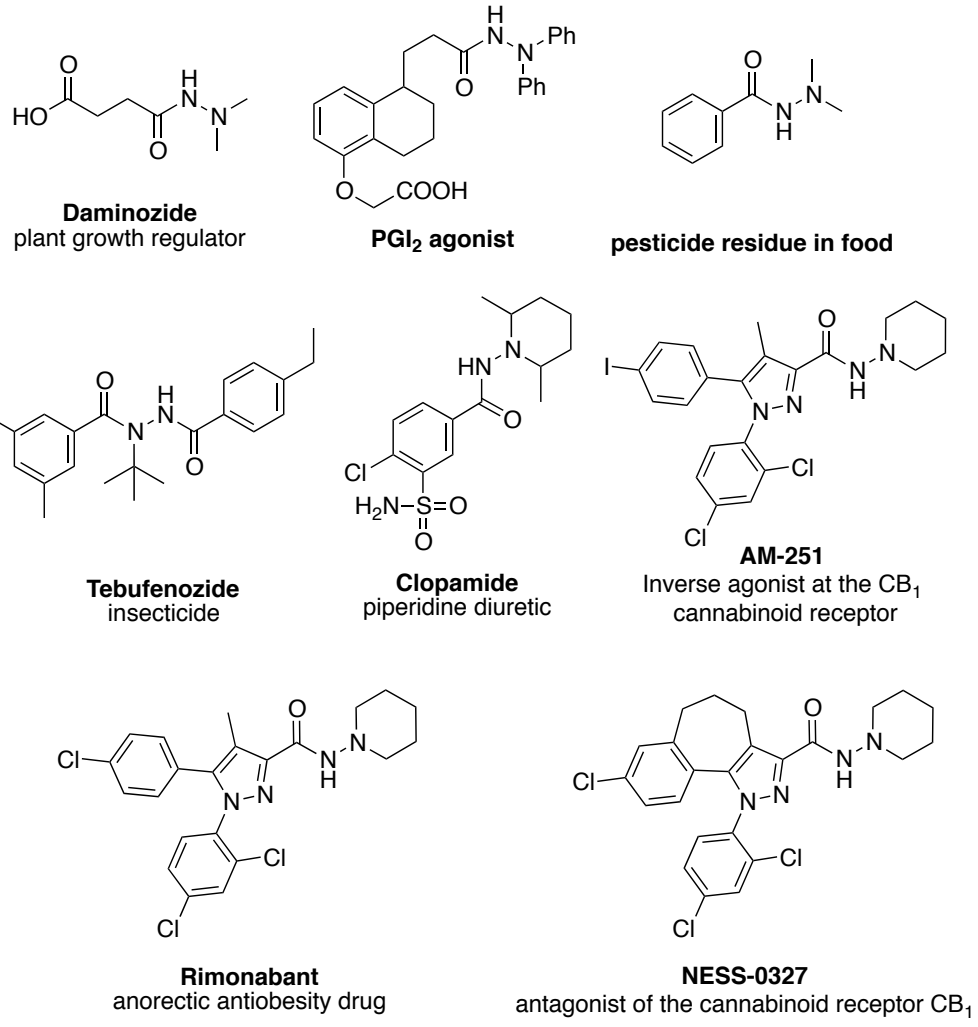
that the reaction follows O–H bond activation of alcohols and hydrazone intermediates. Water is the only byproduct, which makes this catalytic protocol sustainable and environmentally benign.

5.2 INTRODUCTION

N-Acyl hydrazides are valuable reactive intermediates with widespread applications in synthesis of pharmaceuticals, polymer materials, and in agricultural chemistry and chemical industries.[1,2] Acylhydrazides analogues possess biological activities like PGI_2 agonists[3] papilloma virus inhibitors,[4] D_1 dopamine receptor antagonists,[5] tuberculostatic,[6] antibacterial,[7] anticonvulsant,[8] antifungal activities[9] and they are widely used as precursors for the synthesis of heterocyclic compounds.[2] In particular, the cyclic acylhydrazide products are highly important in biological applications and drugs synthesis (Figure 5.1).[10] Substituted acylhydrazides are conventionally synthesized from the reaction of acyl halides with substituted hydrazines or reaction of acylhydrazides with stoichiometric strong bases, followed by addition of toxic alkyl halides (Scheme 5.1).[10] Recently, reductive alkylation of hydrazine derivatives using a-picoline-borane (used in stoichiometric amount) to provide alkylated hydrazides has been reported.[11] Copper catalyzed synthesis of N-acyl-N,N- disubstituted hydrazines using aryl halides via coupling reaction also reported.[12,13] These methods suffer from harsh reaction conditions, use of toxic acyl chlorides and alkyl or aryl halides, poor yields and produce stoichiometric amount of toxic byproducts, which curtail the atom economy of the reactions. Alcohols are sustainable chemical feedstock for alkylation reactions due to their ready availability, biorenewability, cheap and environmentally benign nature.[14] Despite these advances, synthesis of N,N-disubstituted acylhydrazides using alcohols remains unknown. Thus, direct catalytic N,N-dialkylation of N-

acylhydrazides using alcohols is highly desirable and offers the potential routes to synthesis of pharmaceutically important hydrazide derivatives (Figure 5.1).

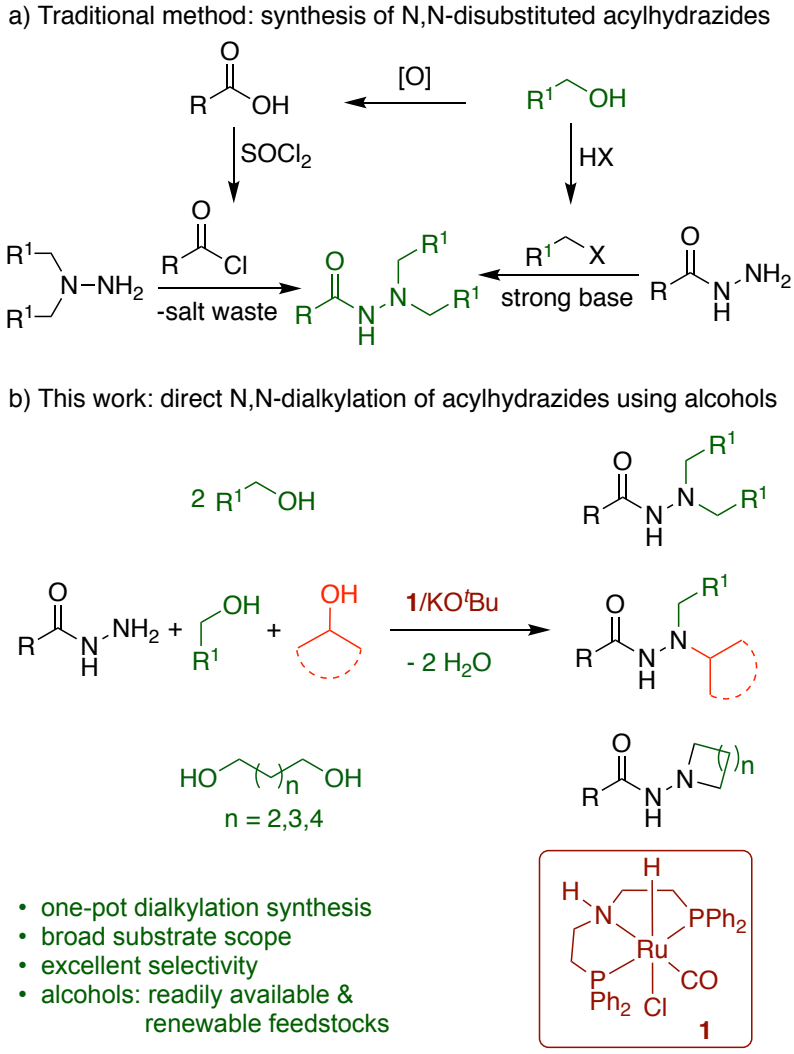
Figure 5.1 Biologically Active N,N-Disubstituted Acylhydrazides



Borrowing hydrogen methodology and acceptorless dehydrogenative coupling reactions are remarkable recent progress for the construction of new C–C, C–N and C–O bonds, producing molecular hydrogen and water as the only byproducts.[15,16] Sustainable production of amines directly from alcohols is well developed following these two interesting concepts.[15,16] However, currently known methods largely limited to mono-alkylation of amines.[17] One-pot dialkylation of amines is less developed and also suffers from poor selectivity due to the competing side reactions.[15,16] On the other hand,

selective N-alkylation of acylhydrazides is poorly studied. Recently, Zhou group reported the selective mono-*N*-alkylation of acylhydrazides using racemic alcohols to enantiomeric amine products.[18] Due to the lack of selectivity and limitation of methods for dialkylation reaction and biological importance of the N,N-disubstituted acylhydrazide products, developing a green and sustainable process is important and urgently required.

Scheme 5.1 Conventional Methods and Selective N,N-Dialkylation of Acylhydrazides Using Alcohols



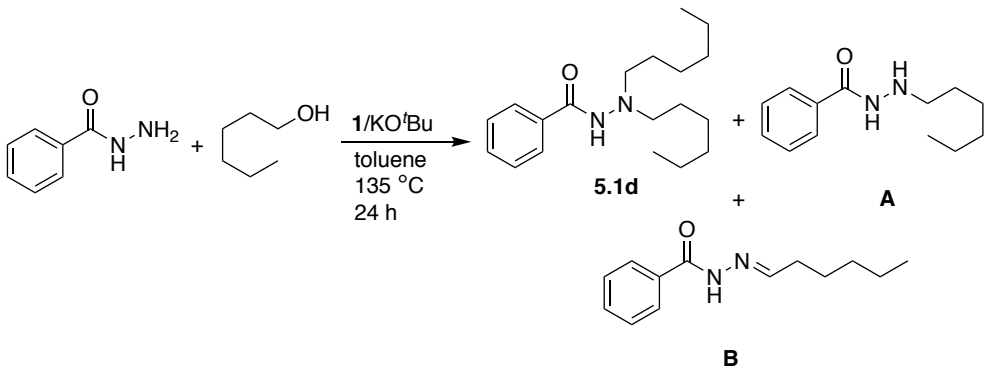
I have recently reported the ruthenium catalyzed regioselective hydrogenation of epoxides,[19] cross-coupling of secondary alcohols,[20] ketazines synthesis directly from secondary alcohols,[21] selective α-alkylation and α-olefination of nitriles using alcohols.[22] Followed by these recent reports, herein I describe the Ru-MACHO (**1**) catalyzed N,N-dialkylation and cyclization of acylhydrazides using alcohols as alkylating agents. As far as I know, there is no report on the catalytic N,N-dialkylation and intermolecular cyclization of acylhydrazides using alcohols in the literature.

5.3 RESULTS AND DISCUSSIONS

Reaction of benzohydrazide (0.5 mmol), 1-hexanol in toluene with ruthenium pincer catalyst **1** (Ru-MACHO) and KO^{t}Bu at 135 °C was selected as a model reaction to optimize the dialkylation of N,N-acylhydrazides. Interestingly, challenging formation of N,N-dialkylated benzohydrazide (**5.1d**) was observed predominantly and the corresponding hydrazone (**B**) compound also observed in minor amount (entry 1, Table 5.1). Notably, no mono-alkylated product (**A**) was observed under this condition. Increasing 1-hexanol to 2.2 equivalents resulted in slight enhancement of dialkylation product; however, mono-alkylation and hydrozaone formation were observed (entry 2, Table 5.1). Decreasing the base load to 5 mol% provided 78% of the dialkylation (entries 3,4, Table 5.1). Upon, increasing catalyst load to 2 mol% with base load at 5 mol% the complete dialkylation occurred and the product *N,N*-di(1-hexyl)-benzohydrazide was isolated in 98% yield (entry 4, Table 5.1). Further, varying temperature and base resulted in diminished yield (entries 5-7, Table 5.1). No dialkylation was observed on changing the solvent from toluene to polar solvent such as *tert*-amyl alcohol (entry 8, Table 5.1). Notably, no product formation was observed in the absence of catalyst as well as in the absence of catalyst and base (entries 9,10, Table 5.1). When the reaction was performed using [RuHCl(CO)(PPh_3)$_3$] only 10% of

dialkylated product **5.1d** was observed, which indicates the necessity of pincer catalyst in this dialkyaltion reactions (Table 5.1, entry 11).

Table 5.1 Optimization of Reaction Conditions[a]



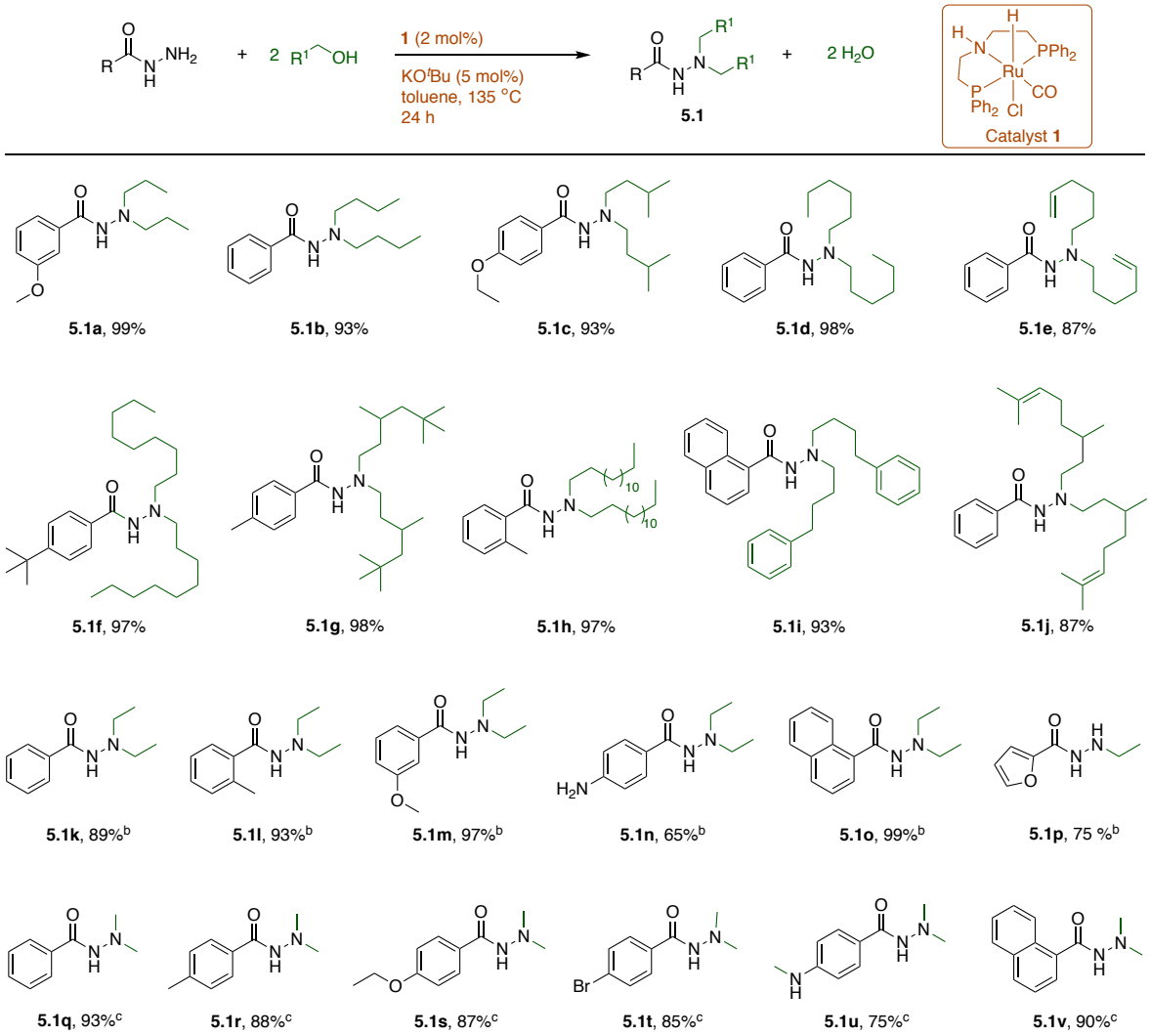
entry	cat. (mol%)	base (mol%)	alcohol (equiv)	yield (%)[b]		
				5.1d	A	B
1	1	100	2	60	-	30
2	1	100	2.2	68	5	20
3	1	5	2.2	78	10	4
4	**2**	**5**	**2.2**	**98**	**-**	**-**
5[c]	2	5	2.2	80	2	6
6	2	2	2.2	63	18	-
7[d]	2	5	2.2	93	2	-
8[e]	2	5	2.2	-	10	5
9[f]	-	5	2.2	-	-	5
10[g]	-	-	2.2	-	-	-
11[h]	1	5	2.2	10	-	-

[a]Reaction conditions: catalyst **1**, KO^{t}Bu, benzohydrazide (0.5 mmol, 1 equiv), 1-hexanol and toluene (2 mL) were heated at 135 °C in a Schlenk flask for 24 h. [b]Isolated yield after column chromatography. [c]Reaction was performed at 125 ^{o}C. [d]5 mol% of NaO^{t}Bu was used as a base. [e]The reaction was performed using *tert*-amyl alcohol as a solvent. [f]Only 5 mol% of KO^{t}Bu was used. [g]Reaction was performed without catalyst **1**

and base. [h]Reaction was performed using [RuHCl(CO)(PPh_3)$_3$] (1 mol%) and KO^{t}Bu (5 mol%).

Having optimized reaction condition in hand, the scope of the different acyhydrazides using alcohols was examined (Scheme 5.2). Reaction of unactivated aliphatic alcohols such as 1-propanol, 1-butanol, 3-methyl-1-butanol and 1-hexanol with acylhydrazides provided the corresponding N,N-dialkylated products **5.1a-5.1d** in excellent yields (Scheme 5.2). The reactions of 5-hexen-1-ol and a monoterpenoid citronellol with benzohydrazide resulted the corresponding N,N-dialkylated products **5.1e** and **5.1j** in very good yields without affecting both terminal and internal alkene functionalities. Long-chain linear, branched and aryl group embedded aliphatic primary alcohols with acylhydrazides resulted the products **5.1f-5.1i** (Scheme 5.2). Further, challenging diethylation and dimethylation reactions were performed using ethanol and methanol as alkylating agents. Acylhydrazides bearing different substituents on the aryl ring were subjected in catalytic diethylation reaction, which provided the products in excellent yields (**5.1k-5.1p**, Scheme 5.2). Interestingly, 4-amino benzohydrazide underwent chemoselective acylhydrazide N,N-diethylation without affecting the aniline amine group (**5.1n**, Scheme 5.2). Furylhydrazide was amenable to the reaction, however, unexpectedly only monoethylation occurred to provide **5.1p**, perhaps due to the involvement of intramolecular hydrogen bonding. Increased catalyst load (**1**, 5 mol%) and base KO^{t}Bu (50 mol%) with a prolonged reaction time (48 h) was employed to effect the dimethylation using methonol. Notably, N,N-dimethylbenzohydrazide **5.1q** was obtained in 93% yield (and this compound is found to be a pesticide residue in food).[2b] Other functionalized benzohydrazides with methanol provided products in good to excellent yields (**5.1r-5.1v**, Scheme 5.2).

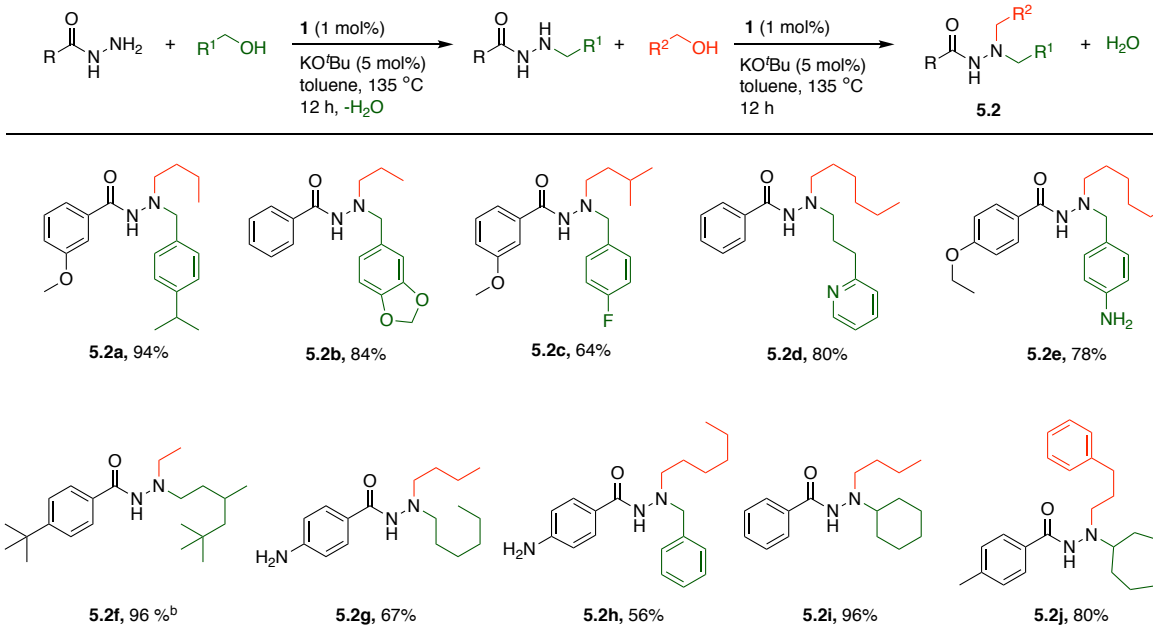
Scheme 5.2 Ruthenium-Catalyzed Symmetrical N,N-Dialkylation of Acylhydrazides Using Alcohols[a]



[a]Reaction conditions: acylhydrazide (0.5 mmol, 1 equiv), primary alcohol (1.1 mmol, 2.2 equiv), toluene (2 mL), catalyst **1** (2 mol%) and KO^{t}Bu (5 mol%) were heated at 135 °C under argon flow for 24 h. Reported yields correspond to isolated pure compounds. [b]10 equiv of ethanol was used. [c]2 mL of methanol and 5 mol% of catalyst **1** and 50 mol% KO^{t}Bu were used and the reaction performed for 48 h.

Another feature of the reaction is the potential to achieve unsymmetrical N,N-dialkylation of acylhydrazides using two different alcohols with remarkable selectivity. An assortment of acylhydrazides was reacted with one equivalent of functionalized benzyl and heteroarene embedded primary alcohols to provide mono-alkylation. Subsequently, a different primary alcohol was introduced in the reaction to provide an unsymmetrical N,N-dialkylation products with excellent selectivity and yields (**5.2a-5.2e**, Scheme 5.3). Impressively, the amine group in 4-aminobenzyl alcohol didn't undergo alkylation reaction under this condition and the chemoselective second alkylation occurred on monoalkylated hydrazide-amine functionality to deliver the product **5.2e** in 78% yield. Further, challenging aliphatic alcohols, including ethanol was used and the product **5.2f** isolated in excellent yield (96%). Surprisingly, 4-amino benzohydrazide underwent selective terminal unsymmetrical N,N-dialkylation without affecting of aniline amine group (**5.2g** and **5.2h**). Such chemoselective *N*-alkylation reaction is unknown in the literature. Interestingly, the secondary alcohols like cyclohexanol and cycloheptanol also underwent selective mono-alkylation; followed by reaction with primary alcohols resulted in unsymmetrical N,N-dialkylated products **5.2i** and **5.2j** in very good yields (Scheme 5.3).

Scheme 5.3 Ruthenium-Catalyzed Unsymmetrical N,N-Dialkylation of Acylhydrazides Using Alcohols[a]

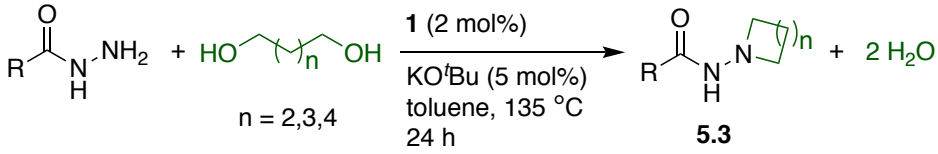


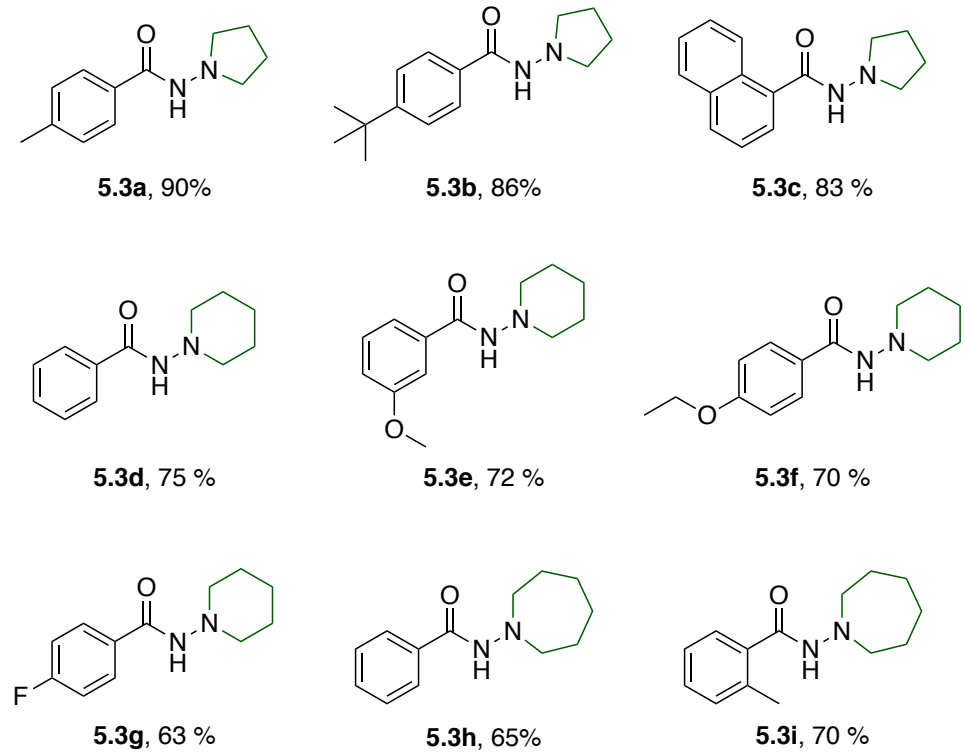
[a]Reaction conditions: acylhydrazide (0.5 mmol, 1 equiv), alcohol (0.55 mmol, 1.1 equiv), toluene (1.5 mL), catalyst **1** (1 mol%) and KO^{t}Bu (5 mol%) heated at 135 °C under argon flow for 12 h. After 12 h, different alcohol (0.55 mmol, 1.1 equiv), toluene (1.5 mL), catalyst **1** (1 mol%) and KO^{t}Bu (5 mol%) were added into the reaction mixture and heating continued for another 12 h. Reported yields correspond to isolated pure compounds. [b]10 equivalent of ethanol was used.

Next, a challenging intermolecular cyclization was tested using acylhydrazides and diols. Surprisingly, reaction of 4-methyl benzohydrazide, 4-*tert*-butyl benzohydrazide and 1-naphthohydrazide with 1,4-butandiol provided cyclized five membered ring hydrazide products **5.3a, 5.3b** and **5.3c** in 90%, 86% and 83% yields, respectively (Scheme 5.4). Reaction of 1, 5-pentanediol with different benzohydrazide derivatives delivered six-membered cyclized products in good yields (**5.3d-5.3g**). Upon employing

1,6-hexanediol, seven-membered cyclization occurred and the corresponding products **5.3h** and **5.3i** are isolated in 65 % and 70 % yields, respectively (Scheme 5.4).

Scheme 5.4 Selective Intermolecular Cyclization of Acylhydrazides Using Diols[a]



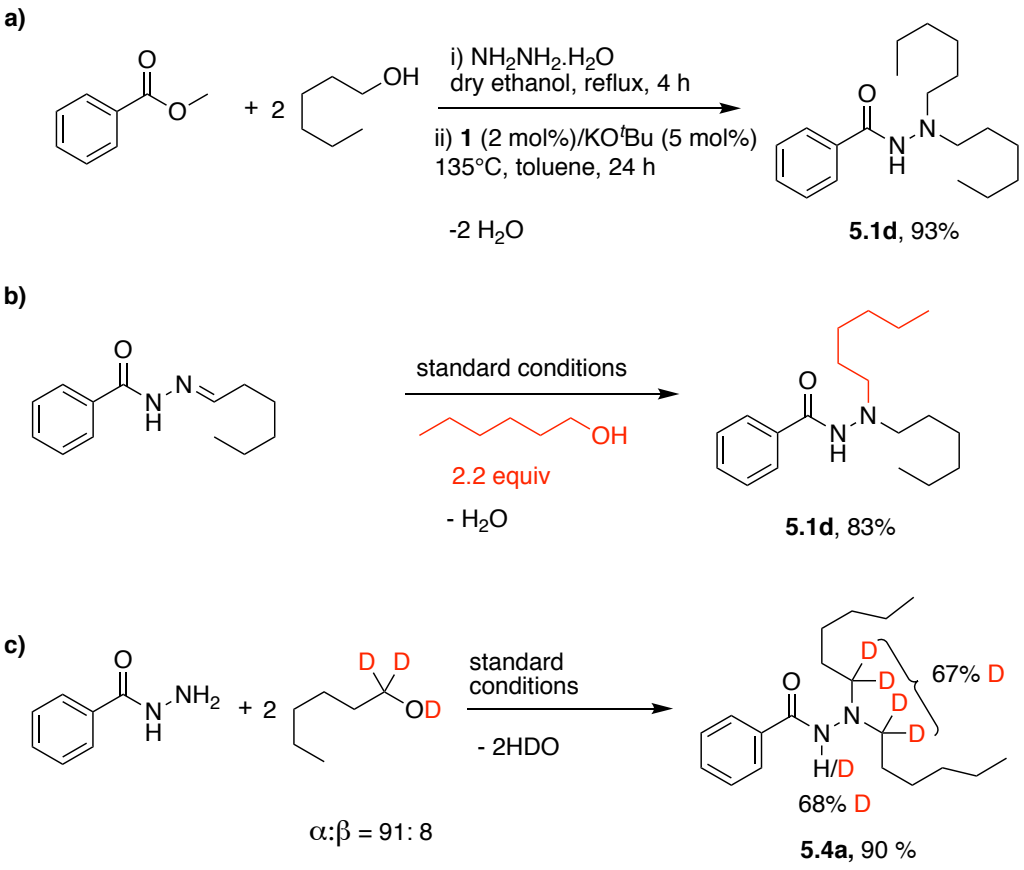


[a]Reaction conditions: acylhydrazide (0.5 mmol, 1 equiv), diol (1 mmol, 2 equiv), toluene (2 mL), catalyst **1** (2 mol%) and KO^{t}Bu (5 mol%) were heated at 135 °C under argon flow for 24 h. Reported yields correspond to isolated pure compounds.

Further, experiments that can decipher the mechanistic insight of N,N-dialkylation of acylhydrazides using alcohols were designed and demonstrated (Scheme 5.5). A one pot-reaction was performed using methyl benzoate and hydrazine hydrate for 4 hours to provide benzohydrazide, and further catalytic dialkylation was carried out under standard reaction conditions using 1-hexanol (2.2 equiv). The expected N,N-

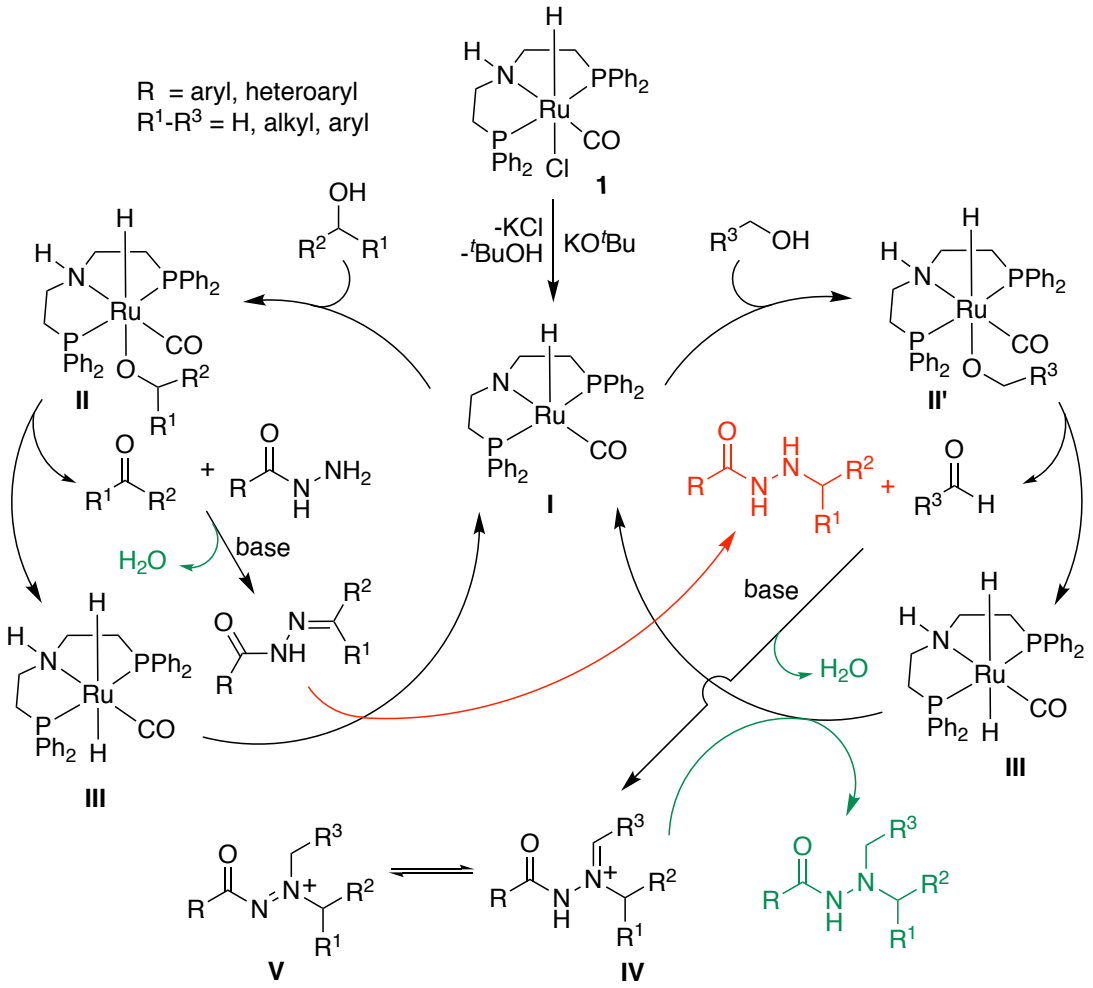
dialkylation product **5.1d** was isolated in 93% yield (Scheme 5.5a). When the hydrazone intermediate **B** (see Table 5.1) was reacted with 1-hexanol (2.2 equiv) under standard reaction conditions, the corresponding N,N-dialkylation product **5.1d** was isolated in 83% yield (Scheme 5.5b). This experiment clearly indicates that the reaction proceeds via hydrazone intermediate. The deuterium labelling experiment confirmed the expected deuterium incorporation at the α-methylene positions of the alkylation product. Reaction of benzohydrazide with 1-hexanol-D_3 under standard reaction conditions resulted the product **5.4a** in 90% yield with 67% deuterium incorporation at α-carbon of the dialkylation product indicating the involvement of borrowing hydrogen pathway.

Scheme 5.5 Mechanistic Studies for the Selective N,N-Dialkylation of Acylhydrazides Using Alcohols



Based on the previous reports[19-23] and preliminary mechanistic studies, a plausible mechanism is proposed for the N,N-dialkylation of acylhydrazides using alcohols (Scheme 5.6). Catalyst **1** reacts with base leading to dehydrohalogenation and formation of active unsaturated intermediate **I** (which is previously observed in mass spectrometry analysis).[23b,24] Intermediate **I** reacts with alcohol by O–H bond activation resulting in an alkoxo-coordinated ruthenium intermediate **II** or **II′** as already established.[23d] Perhaps, *β*-hydride elimination reaction from alkoxide ligands may result in formation of carbonyl intermediate and provide the ruthenium complex **III**. A base catalyzed condensation reaction between in situ formed carbonyl intermediate (aldehyde or ketone) with *N*-acylhydrazide generates a hydrazone intermediate (see Table 5.1 and Scheme 5.5b). In situ formed hydrazone undergoes hydrogenation by ruthenium dihydride intermediate **III** to provide mono-alkylated acylhydrazide and regenerates the catalytically active intermediate **I**. Further, the second condensation of mono-alkylated acylhydrazide with in situ formed aldehyde intermediate occurs to provide iminium intermediate **IV** (which can also be in equilibrium with intermediate **V** under basic condition). Hydrogenation of iminium intermediate **IV** by ruthenium dihydride **III** results in expected N,N-dialkylated acylhydrazide product and regenerates the catalytically active intermediate **I**. Notably, this highly selective catalysis and +2 oxidation state of in all catalytic intermediates are facilitated by amine-amide metal-ligand cooperation.

Scheme 5.6 Proposed Mechanism for the Direct N,N-Dialkylation of Acylhydrazides Using Alcohols



5.4 CONCLUSIONS

In conclusion, I have successfully demonstrated an unprecedented ruthenium(II) catalyzed efficient and direct coupling of acylhydrazides and alcohols to N,N-dialkylacylhydrazides. The reactions require only catalytic amount of base. Both symmetrical and unsymmetrical N,N-dialkylation of acylhydrazides using alcohols is achieved in a one-pot synthesis. Expediently, various functionalities such as olefins, halides, amines, and heteroaromatic groups were tolerated in this catalytic protocol. Remarkably, chemoselective N,N-dialkylation of acylhydrazides over the amine

functionality is also developed. Synthetically challenging diethylation and dimethylation were attained using ethanol and methanol, respectively as alkylating agents. Interestingly, using diols the formation of five, six, and seven-membered heterocyclic acylhydrazides were obtained, which are analogous to various drugs and biologically active molecules. This catalytic method also performed on direct N,N-dialkylation from corresponding ester under one-pot tandem reaction conditions. Mechanistic studies indicated that the reaction undergoes via hydrazone intermediate and follows borrowing hydrogen pathway. This N,N-dialkylation strategy can inspire the development of new C–N bond formation reactions and sustainable transformations.

5.5 EXPERIMENTAL SECTION

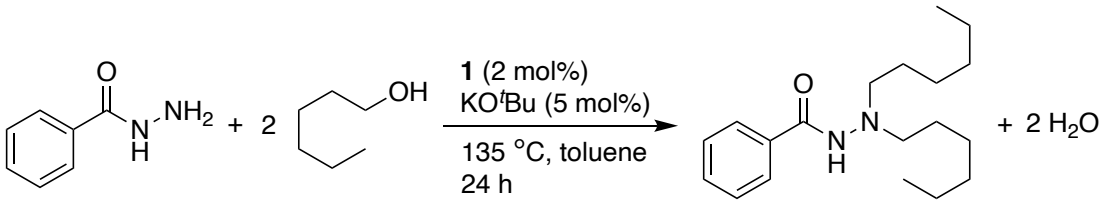
General Experimental: Unless otherwise noted, all catalytic reactions were performed under inert atmosphere using standard Schlenk techniques. All stoichiometric reactions were performed in nitrogen atmosphere MBRAUN glove box. Ru-MACHO **[Carbonylchlorohydrido{bis[2-(diphenylphosphinomethyl)ethyl]amino}ethyl]amino}ruthenium(II)]** and KO^{t}Bu were purchased from Sigma-Aldrich and stored inside glove box. Acylhydrazides were prepared from previous reported procedure.[25] Chemicals were purchased from Sigma-Aldrich, Acros, Alfa-aesar, Himedia and TCI Chemicals and used without further purification. Dry solvents were prepared according to standard procedures. Infrared (IR) spectra were recorded in Thermo-Nicolet FT-IR spectrophotometers. High-resolution mass spectra (HRMS) were obtained on Bruker micrOTOF-Q II Spectrometer and are reported as m/z (relative intensity). Accurate masses are reported for the molecular ion $[M+Na]^+$, $[M+H]^+$, $[M]^+$. Nuclear magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded at Bruker AV-400 (^{1}H at 400 MHz, ^{13}C at 100.6 MHz). ^{1}H NMR

chemical shifts are referenced in parts per million (ppm) with respect to tetramethyl silane (TMS) (δ 0.00 ppm) and ^{13}C {^{1}H} NMR chemical shifts are referenced in parts per million (ppm) with respect to $CDCl_3$ (δ 77.160 ppm). Coupling constants are reported in Hertz (Hz). ^{1}H NMR spectroscopy abbreviations: s, Singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; dt, doublet of triplets; dq, doublet of quartets; td, triplet of doublets; qd, quartets of doublets; ddd, doublets of doublets of doublets; m, multiplet; br, broad. Assignment of spectra was done based on one-dimensional (DEPT-135) NMR techniques.

General Procedure for Optimization of N,N-Dialkylation of Acylhydrazides Using Alcohols:

An oven-dried Schlenk flask (25 mL) was equipped with a stir bar, catalyst **1** (0.01-0.02 mmol), base (1-0.02 mmol), benzohydrazide (0.5 mmol, 1 equiv), 1-hexanol (1.1 mmol, 2.2 equiv) and dry toluene (2 mL) under nitrogen atmosphere in a glove box. The flask was taken out of the glove box, equipped with a condenser and the solution was heated at 135 °C (oil bath temperature) with stirring under a flow of argon for 24 h. The completion of the reaction was monitored using TLC analysis. After 24 hours the reaction was stopped and cooled to room temperature and the solvent was evaporated. Further, the crude reaction mixture was purified by column chromatography over silica-gel (100-200 mesh) using ethyl acetate/hexane mixture as an eluent (deactivated silica gel by Et_3N). Yields were calculated for isolated pure products.

1 mmol Scale Reaction of Symmetrical N,N-Dialkylation of Benzohydrazide Using 1-Hexanol:



5.1d, 97% yield

Procedure:

An oven-dried Schlenk flask (25 mL) was equipped with a stir bar, catalyst 1 (0.02 mmol), base (0.05 mmol), benzohydrazide (1 mmol, 1 equiv), 1-hexanol (2.2 mmol, 2.2 equiv) and dry toluene (2 mL) under nitrogen atmosphere in a glove box. The flask was taken out of the glove box, equipped with a condenser and the solution was heated at 135 °C (oil bath temperature) with stirring under a flow of argon for 24 h. The completion of the reaction was monitored using TLC analysis. After 24 hours the reaction was stopped and cooled to room temperature and the solvent was evaporated. Further, the crude reaction mixture was purified by column chromatography over silica-gel (100-200 mesh) using ethyl acetate / hexane mixture as an eluent (deactivated silica gel by Et_3N). The reaction provided the product **5.1d** in 97% (295 mg) yield.

General Procedure for Symmetrical N,N-Dialkylation of Acylhydrazides Using Alcohols:

An oven-dried Schlenk flask (25 mL) was equipped with a stir bar, catalyst **1** (0.02 mmol), KO^{t}Bu (0.05 mmol), acylhydrazide (0.5 mmol, 1 equiv), alcohol (1.1 mmol, 2.2 equiv) and dry toluene (2 mL) under nitrogen atmosphere in a glove box. The flask was taken out of the glove box, equipped with a condenser and the solution was heated at 135 °C (oil bath temperature) with stirring under a flow of argon for 24 h. The completion of the reaction was monitored using TLC analysis. After 24 hours the

reaction was stopped and cooled to room temperature. Further, the solvent was evaporated and crude reaction mixture was purified by column chromatography over silica-gel (100-200 mesh) using ethyl acetate/hexane mixture as an eluent (deactivated silica gel by Et_3N). Yields were calculated for isolated pure products.

General Procedure for N,N-Diethylation of Acylhydrazides Using Ethanol:

An oven-dried Schlenk flask (25 mL) was equipped with a stir bar, catalyst **1** (0.02 mmol), KO^{t}Bu (0.05 mmol), acylhydrazide (0.5 mmol, 1 equiv), ethanol (5 mmol, 10 equivalent) and dry toluene (1.5 mL) under nitrogen atmosphere in a glove box. The flask was taken out of the glove box, equipped with a condenser and the solution was heated at 135 °C (oil bath temperature) with stirring under a flow of argon for 24 h. The completion of the reaction was monitored using TLC analyses. After 24 hours the reaction was stopped and cooled to room temperature. Further, the solvent was evaporated and crude reaction mixture was purified by column chromatography over silica-gel (100-200 mesh) using ethyl acetate/hexane mixture as an eluent (deactivated silica gel by Et_3N). Yields were calculated for isolated pure products.

General Procedure for N,N-Dimethylation of Acylhydrazides Using Methanol:

An oven-dried pressure tube (35 mL) was equipped with a stir bar, catalyst **1** (0.05 mmol), KO^{t}Bu (0.5 mmol), acylhydrazide (0.5 mmol, 1 equivalent) and dry methanol (2 mL) under nitrogen atmosphere in a glove box. The pressure tube was taken out of the glove box and the solution was heated at 150 °C (oil bath temperature) with stirring for 48 h. After 48 hours the reaction was stopped and cooled to room temperature. Further, pressure was released and the solvent was evaporated and crude reaction mixture was purified by column chromatography over silica-gel (100-200 mesh) using ethyl acetate/ hexane mixture as an eluent (deactivated silica gel by Et_3N). Yields were calculated for isolated pure products.

General Procedure for Unsymmetrical N,N-Dialkylation of Acylhydrazides Using Alcohols:

An oven-dried Schlenk flask (25 mL) was equipped with a stir bar, catalyst **1** (0.01 mmol), KO^{t}Bu (0.05 mmol), acylhydrazide (0.5 mmol, 1 equivalent), alcohol (0.55 mmol, 1.1 equivalent) and dry toluene (1.5 mL) under nitrogen atmosphere in a glove box. The flask was taken out of the glove box, equipped with a condenser and the solution was heated at 135 °C (oil bath temperature) with stirring under a flow of argon for 12 h. After 12 hours, catalyst **1** (0.01 mmol), base (0.05 mmol), alcohol (0.55 mmol, 1.1 equivalent) and toluene (1 mL) were taken in a separate vial from glove box and the solution was added inside the reaction mixture under argon atmosphere. Further, the reaction continued for another 12 hours and the completion of the reaction was monitored using TLC analysis. After the completion the reaction was stopped and cooled to room temperature. Then, the solvent was evaporated and crude reaction mixture was purified by column chromatography over silica-gel (100-200 mesh) using ethyl acetate / hexane mixture as an eluent (deactivated silica gel by Et_3N). Yields were calculated for isolated pure products.

General Procedure for the Intermolecular Cyclization of Acylhydrazides Using Alcohols:

An oven-dried Schlenk flask (25 mL) was equipped with a stir bar, catalyst **1** (0.02 mmol), KO^{t}Bu (0.05 mmol), acylhydrazide (0.5 mmol, 1 equivalent), alcohol (1 mmol, 2 equivalent) and dry toluene (2 mL) under nitrogen atmosphere in a glove box. The flask was taken out of the glove box, equipped with a condenser and the solution was heated at 135 °C (oil bath temperature) with stirring under a flow of argon for 24 h. The completion of the reaction was monitored using TLC analysis. After 24 hours the reaction was stopped and cooling to room temperature. Further, the solvent was

evaporated and crude reaction mixture was purified by column chromatography over silica-gel (100-200 mesh) using ethyl acetate / hexane mixture as an eluent (deactivated silica gel by Et_3N). Yields were calculated for isolated pure products.

Procedure for One-Pot Synthesis of N,N-Dialkylated Acylhydrazide From Methyl Benzoate:

An oven-dried Schlenk flask (25 mL) was equipped with a stir bar, methyl benzoate (0.5 mmol), hydrazine hydrate (5 mmol) and ethanol solvent (2 mL) refluxed for 4 hours. Further, the solvent was evaporated and the flask was taken inside glove box. Catalyst **1** (0.02 mmol), KO^{t}Bu (0.05 mmol), acylhydrazide (0.5 mmol, 1 equivalent), 1-hexanol (1.1 mmol, 2.2 equivalent) and dry toluene (2 mL) were added to the same flask under nitrogen atmosphere in a glove box. The flask was taken out of the glove box, equipped with a condenser and the solution was heated at 135 °C (oil bath temperature) with stirring under a flow of argon for 24 h. The completion of the reaction was monitored using TLC analysis. After 24 hours the reaction was stopped and cooling to room temperature. Further, the solvent was evaporated and crude reaction mixture was purified by column chromatography over silica-gel (100-200 mesh) using ethyl acetate / hexane mixture as an eluent (deactivated silica gel by Et_3N). Product **5.1d** was isolated in 93% yield.

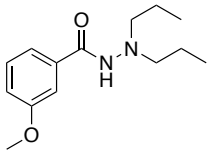
Procedure for the Deuterium Labeling Experiment:

An oven-dried Schlenk flask (25 mL) was equipped with a stir bar, catalyst **1** (0.02 mmol), KO^{t}Bu (0.05 mmol), benzohydrazide (0.5 mmol, 1 equivalent), 1-hexanol-D_3 (1.1 mmol, 2.2 equivalent) and dry toluene (2 mL) under nitrogen atmosphere in a glove box. The flask was taken out of the glove box, equipped with a condenser and the solution was heated at 135 °C (oil bath temperature) with stirring under a flow of argon for 24 h. The completion of the reaction was monitored using TLC analysis. After 24

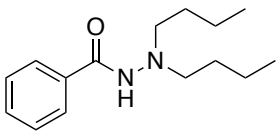
hours the reaction was stopped and cooled to room temperature. Further, the solvent was evaporated and crude reaction mixture was purified by column chromatography over silica-gel (100-200 mesh) using ethyl acetate / hexane mixture as an eluent (deactivated silica gel by Et_3N). Product **5.4a** is isolated 90% yield.

Spectral Data of N,N-Dialkylated of Acylhydrazides:

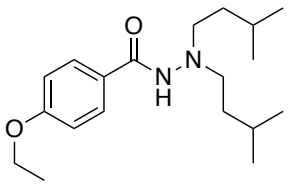
3-Methoxy-*N*',*N*'-dipropylbenzohydrazide (5.1a): Purified by silica gel column chromatography using ethyl acetate/hexane (10:90) mixture as an eluent. White solid. Yield: 124 mg, 99%. IR (DCM): 3263, 3052, 2962, 2874, 2836, 1654, 1582, 1484, 1265, 1041, 895, 739 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.26-7.13 (m, 3H, ArC*H*), 6.96-6.90 (m, 1H, ArC*H*), 6.86 (s, N*H*), 3.74 (s, 3H, OCH_3), 2.70 (t, J = 8 Hz, 4H, CH_2), 1.55-1.45 (m, 4H, CH_2), 0.84 (t, J = 7.4 Hz, 6H, CH_3). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 166.6, 159.7, 135.3, 129.5, 118.6, 117.6, 112.4, 60.1, 55.4, 20.3, 11.6. HRMS (ESI) m/z calcd for $C_{14}H_{22}N_2O_2$ $(M+H)^+$: 251.1754, found: 251.1775.



***N*',*N*'-Dibutylbenzohydrazide (5.1b):** Purified by silica gel column chromatography using ethyl acetate/hexane (10:90) mixture as an eluent. White solid. Yield: 115 mg, 93%. IR (DCM): 3243, 2958, 2864, 1651, 1468, 1275, 748 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.68-7.63 (m, 2H, ArC*H*), 7.48-7.39 (m, 1H, ArC*H*), 7.38-7.30 (m, 2H, ArC*H*), 6.63 (s, 1H, N*H*), 2.76 (t, J = 7.6 Hz, 4H, CH_2), 1.48 (ddd, J_1 = 15.2 Hz, J_2 = 8.7 Hz, J_3 = 6.4 Hz, 4H, CH_2), 1.30 (dt, J_1 = 15.1 Hz, J_2 = 7.4 Hz, 4H, CH_2), 0.83 (t, J = 7.4 Hz, 6H, CH_3). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 166.7, 134.2, 131.5, 128.6, 127.0, 58.2, 29.2, 20.5, 14.0. HRMS (ESI) m/z calcd for $C_{15}H_{24}N_2O$ $(M+H)^+$: 249.1961, found: 249.1971.

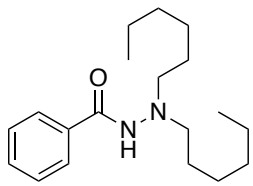


4-Ethoxy-*N*',*N*'-diisopentylbenzohydrazide (5.1c): Purified by silica gel column chromatography using ethyl acetate/hexane (10:90) mixture as an eluent. White solid.

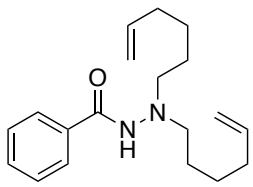


Yield: 149 mg, 93%. IR (DCM): 3237, 3047, 2955, 2869, 1643, 1607, 1467, 1252, 1045, 765 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63 (d, *J* = 8.7 Hz, 2H, ArC*H*), 6.83 (d, *J* = 7.8 Hz, 2H, ArC*H*), 6.52 (s, 1H, N*H*), 3.99 (tt, J_1 = 6.9 Hz, J_2 = 3.5 Hz, 2H, OCH_2), 2.76 (t, *J* = 8 Hz, 4H, CH_2), 1.55 (dt, J_1 = 13.2 Hz, J_1 = 6.6 Hz, 2H, C*H*), 1.37 (ddd, J_1 = 14.0 Hz, J_2 = 11.8 Hz, J_3 = 7.0 Hz, 7H, CH_2 & CH_3), 0.81 (d, *J* = 6.6 Hz, 12H, CH_3). $^{13}C\{^{1}H\}$ NMR (100.6 MHz, $CDCl_3$): δ 166.3, 161.6, 128.8, 126.0, 114.3, 63.7, 57.0, 35.8, 26.4, 22.8, 14.7. HRMS (ESI) m/z calcd for $C_{19}H_{32}N_2O_2$ $(M+H)^+$: 321.2537, found: 321.2533.

***N*',*N*'-Dihexylbenzohydrazide (5.1d):** Purified by silica gel column chromatography using ethyl acetate/hexane (10:90) mixture as an eluent. White solid. Yield: 149 mg, 98% (for 0.5 mmol scale) and 295 mg, 97% (for 1 mmol scale). IR (DCM): 3430, 3053, 2956, 2930, 1672, 1457, 1265, 895, 741 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (d, *J* = 7.3 Hz, 2H, ArC*H*), 7.43 (t, *J* = 7.3 Hz, 1H, ArC*H*), 7.35 (t, *J* = 7.4 Hz, 2H, ArC*H*), 6.57 (s, 1H, N*H*), 2.75 (t, *J* = 7.6 Hz, 4H, CH_2), 1.59-1.38 (m, 4H, CH_2), 1.27-1.19 (dd, J_1 = 26.5 Hz, J_1 = 8.0 Hz, 12H, CH_2), 0.79 (t, *J* = 6.7 Hz, 6H, CH_3). $^{13}C\{^{1}H\}$ NMR (100.6 MHz, $CDCl_3$): δ 166.7, 134.2, 131.6, 128.7, 127.0, 58.5, 31.8, 27.1, 27.0, 22.7, 14.1. HRMS (ESI) m/z calcd for $C_{19}H_{32}N_2O$ $(M+H)^+$: 305.2587, found: 305.2569.

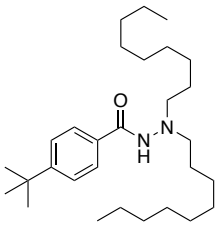


***N*',*N*'-Di(hex-5-en-1-yl)benzohydrazide (5.1e):** Purified by silica gel column chromatography using ethyl acetate/hexane (10:90) mixture as an eluent. White solid. Yield: 130 mg, 87%. IR (DCM): 3427, 3270, 3053, 2933, 2857, 1663, 1487, 1265, 1072, 914, 739 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66-7.62 (m, 2H, ArC*H*), 7.40 (dd, J_1 = 10.6 Hz, J_2 = 4.1 Hz, 1H, ArC*H*), 7.31 (t, *J* = 7.4 Hz, 2H, ArC*H*), 6.94 (s, 1H, N*H*), 5.69 (ddt, J_1 = 16.9

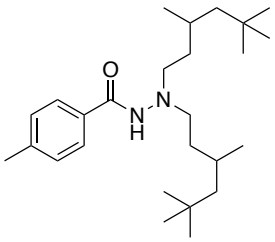


Hz, J_2 = 10.2 Hz, J_3 = 6.7 Hz, 2H, olefinic-C*H*), 4.86 (ddd, J_1= 13.7 Hz, J_2= 11.0 Hz, J_3= 1.2 Hz, 4H, olefinic-C*H*), 2.76 (t, *J* = 7.2 Hz, 4H, CH_2), 1.97 (dt, J_1 = 13.9 Hz, J_2 = 7.1 Hz, 4H, CH_2), 1.55-1.44 (m, 4H, CH_2), 1.35 (dt, J_1 = 14.9 Hz, J_2 = 7.4 Hz, 4H, CH_2). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 166.7, 138.6, 134.0, 131.4, 128.5, 127.0, 114.5, 57.9, 33.5, 26.5, 26.4. HRMS (ESI) m/z calcd for $C_{19}H_{28}N_2O$ $(M+H)^+$: 301.2274, found: 301.2290.

4-(*tert*-Butyl)-*N*',*N*'-dinonylbenzohydrazide (5.1f): Purified by silica gel column chromatography using ethyl acetate/hexane (10:90) mixture as an eluent. White solid. Yield: 215 mg, 97%. IR (DCM): 3429, 3269, 3051, 2926, 2854, 1654, 1466, 1264, 1053, 895, 742 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.61 (d, *J* = 8.3 Hz, 2H, ArC*H*), 7.35 (d, *J* = 8.2 Hz, 2H, ArC*H*), 6.66 (s, 1H, N*H*), 2.74 (t, *J* = 7.6 Hz, 4H, CH_2), 1.47 (dd, J_1 = 14.3 Hz, J_2 = 7.3 Hz, 4H, CH_2), 1.25 (s, 9H, 3×CH_3), 1.20-1.17 (m, 24H, CH_2), 0.79 (t, *J* = 6.7 Hz, 6H, CH_3). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 166.6, 155.0, 131.2, 126.9, 125.5, 58.5, 34.9, 31.9, 31.2, 29.6, 29.3, 27.3, 27.1, 22.7, 14.1. HRMS (ESI) m/z calcd for $C_{29}H_{52}N_2O$ $(M+H)^+$: 445.4152, found: 445.4135.



4-Methyl-*N*',*N*'-bis(3,5,5-trimethylhexyl)benzohydrazide (5.1g): Purified by silica gel column chromatography using ethyl acetate/hexane (10:90) mixture as an eluent. White solid. Yield: 197 mg, 98%. IR (DCM): 3246, 3043, 2954, 2866, 1644, 1466, 1264, 834, 741 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.55 (d, *J* = 7.8 Hz, 2H, ArC*H*), 7.14 (d, *J* = 7.8 Hz, 2H, ArC*H*), 6.55 (s, 1H, N*H*), 2.75 (t, *J* = 12.8 Hz, 4H, CH_2), 2.31 (s, 3H, CH_3), 1.50 (dd, J_1 = 18.1 Hz, J_1 = 8.1 Hz, 4H, CH_2), 1.40-1.27 (m, 2H, C*H*), 1.13 (dd, J_1 = 13.8 Hz, J_2 = 2.4 Hz, 2H, CH_2), 0.97 (dd, J_1 = 14.0 Hz, J_2 = 6.0 Hz, 2H, CH_2), 0.84 (t, *J* = 5.8 Hz, 6H, CH_3), 0.79 (s, 18H, 3×CH_3). $^{13}C\{^1H\}$ NMR



(100.6 MHz, $CDCl_3$): δ 166.6, 141.9, 131.3, 129.3, 127.0, 56.7, 51.4, 36.4, 31.1, 30.0, 27.6, 22.8, 21.5. HRMS (ESI) m/z calcd for $C_{26}H_{46}N_2O$ $(M+H)^+$: 403.3683, found: 403.3692.

2-Methyl-*N*',*N*'-ditetradecylbenzohydrazide (5.1h): Purified by silica gel column chromatography using ethyl acetate/hexane (10:90) mixture as an eluent. White solid. Yield: 263 mg, 97%. IR (DCM): 3417, 3206, 3053, 2919, 2849, 1651, 1447, 1265, 895, 748 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.22 (q, J = 7.0 Hz, 2H, ArC*H*), 7.12 (dd, J_1 = 16.4 Hz, J_2 = 8.3 Hz, 2H, ArC*H*), 6.14 (s, 1H, N*H*), 2.72 (t, J = 7.6 Hz, 4H, CH_2), 2.37 (s, 3H, CH_3), 1.59-1.48 (m, 4H, CH_2), 1.35-1.07 (m, 44H, CH_2), 0.81 (t, J = 6.7 Hz, 6H, CH_3). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 168.9, 136.4, 135.6, 131.0, 130.0, 126.7, 125.7, 58.6, 32.0, 29.8, 29.8, 29.7, 29.7, 29.7, 29.4, 27.3, 27.1, 22.8, 19.7, 14.2. HRMS (ESI) m/z calcd for $C_{36}H_{66}N_2O$ $(M+H)^+$: 543.5248, found: 543.5254.

***N*',*N*'-bis(4-Phenylbutyl)-1-naphthohydrazide (5.1i):** Purified by silica gel column chromatography using ethyl acetate/hexane (10:90) mixture as an eluent. White solid. Yield: 209 mg, 93%. IR (DCM): 3413, 3317, 3053, 2937, 2859, 1676, 1452, 1265, 895, 738 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.15-8.07 (m, 1H, ArC*H*), 7.82-7.71 (m, 2H, ArC*H*), 7.45-7.39 (m, 2H, ArC*H*), 7.31-7.19 (m, 2H, ArC*H*), 7.15 (t, J = 7.4 Hz, 4H, ArC*H*), 7.06 (dd, J_1 = 12.8 Hz, J_2 = 7.0 Hz, 6H, ArC*H*), 6.35 (s, 1H, N*H*), 2.74 (t, J = 6.7 Hz, 4H, CH_2), 2.55 (t, J = 7.1 Hz, 4H, CH_2), 1.70-1.50 (m, 8H, CH_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100.6 MHz): δ 168.5, 142.3, 133.6, 133.3, 130.6, 130.3, 128.5, 128.3, 128.3, 128.2, 127.2, 126.5, 125.7, 125.3, 124.8, 124.6, 58.1, 35.8, 28.9, 26.7. HRMS (ESI) m/z calcd for $C_{31}H_{34}N_2O$ $(M+H)^+$: 451.2744, found: 451.2758.

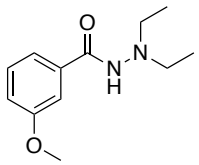
***N*',*N*'-Bis(3,7-dimethyloct-6-en-1-yl)benzohydrazide (5.1j):** Purified by silica gel column chromatography using ethyl acetate/hexane (10:90) mixture as an eluent. Colorless liquid. Yield: 179 mg, 87%. IR (DCM): 3422, 3238, 3056, 2958, 2925, 2856, 1650, 1461, 1267, 740 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.65 (d, *J* = 7.4 Hz, 2H, ArC*H*), 7.42 (t, *J* = 7.3 Hz, 1H, ArC*H*), 7.34 (t, *J* = 7.5 Hz, 2H, ArC*H*), 6.57 (s, 1H, N*H*), 4.99 (t, *J* = 7.0 Hz, 2H, olefinic-C*H*), 2.78 (tt, J_1 = 16.2 Hz, J_2 = 8.1 Hz, 4H, CH_2), 1.99-1.77 (m, 4H, CH_2), 1.59 (s, 6H, CH_3), 1.49 (s, 6H, CH_3), 1.30 (dddd, J_1 = 15.2 Hz, J_2 = 12.0 Hz, J_3 = 11.1 Hz, J_4 = 6.1 Hz, 8H, CH_2 &C*H*), 1.16-1.02 (m, 2H, CH_2), 0.82 (d, *J* = 6.5 Hz, 6H, CH_3). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 166.7, 134.2, 131.5, 131.2, 128.7, 127.0, 124.8, 56.6, 37.2, 34.0, 30.8, 25.7, 25.5, 19.7, 17.7. HRMS (ESI) m/z calcd for $C_{27}H_{44}N_2O$ $(M+H)^+$: 413.3526, found: 413.3529.

***N*',*N*'-Diethylbenzohydrazide (5.1k):** Purified by silica gel column chromatography using ethyl acetate/hexane (30:70) mixture as an eluent. White solid. Yield: 85 mg, 89%. IR (DCM): 3245, 2957, 2865, 1656, 1466, 1265, 741 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.68 (d, *J* = 7.3 Hz, 2H, ArC*H*), 7.43 (t, *J* = 7.3 Hz, 1H, ArC*H*), 7.35 (t, *J* = 7.4 Hz, 2H, ArC*H*), 6.69 (s, 1H, N*H*), 2.83 (q, *J* = 7.1 Hz, 4H, CH_2), 1.09 (t, *J* = 7.1 Hz, 6H, CH_3). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 167.1, 134.0, 131.6, 128.7, 127.0, 52.2, 12.0. HRMS (ESI) m/z calcd for $C_{11}H_{16}N_2O$ $(M+H)^+$: 193.1335, found: 193.1329.

***N*',*N*'-Diethyl-2-methylbenzohydrazide (5.1l):** Purified by silica gel column chromatography using ethyl acetate/hexane (30:70) mixture as an eluent. White solid. Yield: 96 mg, 93%. IR (DCM): 3243, 2958, 2867, 1657, 1465, 1265, 742 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.23 (t, *J* = 7.2 Hz, 2H, ArC*H*), 7.12 (dd, J_1 = 16.9 Hz, J_2 = 8.2 Hz, 2H, ArC*H*), 6.11 (s,

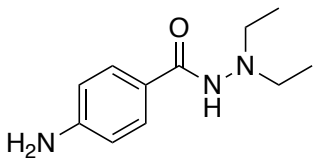
1H, N*H*), 2.77 (q, *J* = 7.0 Hz, 4H, CH_2), 2.37 (s, 3H, CH_3), 1.12 (t, *J* = 7.1 Hz, 6H, CH_3). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 169.2, 136.2, 135.5, 130.9, 129.9, 126.6, 125.6, 52.3, 19.6, 12.1. HRMS (ESI) m/z calcd for $C_{12}H_{18}N_2O$ $(M+H)^+$: 207.1492, found: 207.1491.

***N*',*N*'-Diethyl-3-methoxybenzohydrazide (5.1m):** Purified by silica gel column



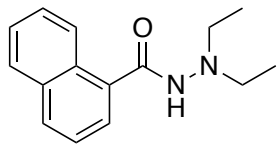
chromatography using ethyl acetate/hexane (30:70) mixture as an eluent. White solid. Yield: 108 mg, 97%. IR (DCM): 3266, 3053, 2967, 2878, 1647, 1583, 1487, 1265, 1043, 895, 740 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.31-7.16 (m, 3H, ArC*H*), 6.96 (dd, J_1 = 7.9 Hz, J_2 = 1.3 Hz, 1H, ArC*H*), 6.60 (s, 1H, N*H*), 3.77 (s, 3H, OCH_3), 2.81 (q, *J* = 7.1 Hz, 4H, CH_2), 1.09 (t, *J* = 7.1 Hz, 6H, CH_3). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 166.9, 159.9, 135.4, 129.6, 118.7, 117.8, 112.5, 55.5, 52.3, 12.0. HRMS (ESI) m/z calcd for $C_{12}H_{18}N_2O_2$ $(M+H)^+$: 223.1441, found: 223.1448.

4-Amino-*N*',*N*'-diethylbenzohydrazide (5.1n): Purified by silica gel column



chromatography using ethyl acetate/hexane (70:30) mixture as an eluent. Pale yellow solid. Yield: 65 mg, 63%. IR (DCM): 3466, 3265, 3052, 2950, 2874, 1647, 1487, 1265, 1041, 896, 739 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.54 (d, *J* = 8.5 Hz, 2H, ArC*H*), 6.59 (t, 3H, ArC*H* & N*H*), 3.93 (s, 2H, NH_2), 2.85 (dd, J_1 = 14.2 Hz, J_2 = 7.1 Hz, 4H, CH_2), 1.09 (t, *J* = 7.1 Hz, 6H, CH_3). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 166.9, 149.9, 128.7, 122.9, 114.2, 52.0, 11.9. HRMS (ESI) m/z calcd for $C_{11}H_{17}N_3O$ $(M+H)^+$: 208.1444, found: 208.1459.

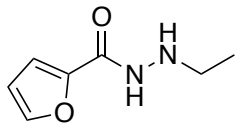
***N*',*N*'-Diethyl-1-naphthohydrazide (5.1o):** Purified by silica gel column



chromatography using ethyl acetate/hexane (30:70) mixture as an eluent. White solid. Yield: 120 mg, 99%. IR (DCM): 3266,

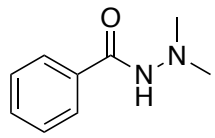
3054, 2963, 2874, 2835, 1653, 1484, 1265, 895, 739 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.19 (d, *J* = 8.2 Hz, 1H, ArC*H*), 7.86-7.74 (m, 2H, ArC*H*), 7.50-7.42 (m, 3H, ArC*H*), 7.35 (t, *J* = 7.6 Hz, 1H, ArC*H*), 6.33 (s, 1H, N*H*), 2.83 (q, *J* = 7.0 Hz, 4H, CH_2), 1.18 (t, *J* = 7.1 Hz, 6H, CH_3). $^{13}C\{^{1}H\}$ NMR (100.6 MHz, $CDCl_3$): δ 168.8, 133.7, 133.4, 130.8, 130.4, 128.3, 127.4, 126.6, 125.4, 124.8, 124.6, 52.5, 12.2. HRMS (ESI) m/z calcd for $C_{15}H_{18}N_2O$ $(M+H)^+$: 243.1492, found: 243.1477.

***N'*-Ethylfuran-2-carbohydrazide (5.1p):** Purified by silica gel column



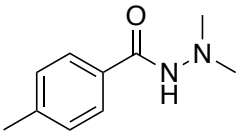
chromatography using ethyl acetate/hexane (40:60) mixture as an eluent. White solid. Yield: 58 mg, 75%. IR (DCM): 3263, 3052, 2987, 2854, 1672, 1447, 1267, 1047, 895, 747 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 (d, *J* = 0.8 Hz, 1H, ArC*H*), 7.07 (d, *J* = 3.4 Hz, 1H, ArC*H*), 6.43 (dd, J_1 = 3.5 Hz, J_2 = 1.7 Hz, 1H, ArC*H*), 5.27 (s, 1H, N*H*), 2.91 (q, *J* = 7.1 Hz, 2H, CH_2), 1.07 (t, *J* = 7.2 Hz, 3H, CH_3). $^{13}C\{^{1}H\}$ NMR (100.6 MHz, $CDCl_3$): δ 158.2, 146.9, 144.2, 114.8, 112.1, 46.7, 13.0. HRMS (ESI) m/z calcd for $C_7H_{10}N_2O_2$ $(M+H)^+$: 155.0815, found: 155.0811.

***N'*,*N'*-Dimethylbenzohydrazide (5.1q):** Purified by silica gel column chromatography



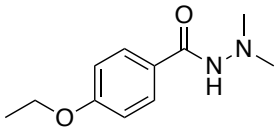
using ethyl acetate/hexane (50:50) mixture as an eluent. White solid. Yield: 76 mg, 93%. IR (DCM): 3263, 3052, 2962, 2850, 1657, 1580, 1484, 1267, 1041, 895, 739 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (d, *J* = 7.4 Hz, 2H, ArC*H*), 7.41 (d, *J* = 7.1 Hz, 1H, ArC*H*), 7.33 (dd, J_1 = 11.4 Hz, J_2 = 4.2 Hz, 2H, ArC*H*), 6.97 (s, 1H, N*H*), 2.63 (s, 6H, CH_3). $^{13}C\{^{1}H\}$ NMR (100.6 MHz, $CDCl_3$): δ 165.8, 133.8, 131.6, 128.6, 127.1, 47.7. HRMS (ESI) m/z calcd for $C_9H_{12}N_2O$ $(M+H)^+$: 165.1022, found: 165.1022.

***N'*,*N'*,4-Trimethylbenzohydrazide (5.1r):** Purified by silica gel column chromatography using ethyl acetate/hexane (75:25) mixture as an eluent. White solid. Yield: 76.5 mg, 86%. IR (DCM): 3263, 3052, 2962, 2874, 2836, 1654, 1265, 1041, 895,



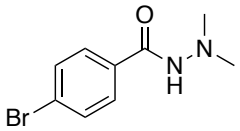
739 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.58 (d, *J* = 7.1 Hz, 2H, ArC*H*), 7.16 (t, *J* = 13.4 Hz, 3H, ArC*H* & N*H*), 2.66 (s, 6H, CH_3), 2.32 (s, 3H, CH_3). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 165.8, 142.2, 130.7, 129.3, 127.1, 47.7, 21.5. HRMS (ESI) m/z calcd for $C_{10}H_{14}N_2O$ $(M+H)^+$: 179.1178, found: 179.1184.

4-Ethoxy-*N*',*N*'-dimethylbenzohydrazide (5.1s): Purified by silica gel column



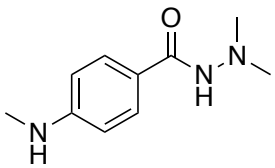
chromatography using ethyl acetate/hexane (50:50) mixture as an eluent. White solid. Yield: 90 mg, 87%. IR (DCM): 3264, 3052, 2987, 2850, 1660, 1447, 1260, 895, 742 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.63 (d, *J* = 8.1 Hz, 2H, ArC*H*), 6.87-6.76 (m, 3H, ArC*H* & N*H*), 3.99 (q, *J* = 7.0 Hz, 2H, CH_2), 2.63 (s, 6H, CH_3), 1.35 (t, *J* = 7.0 Hz, 3H, CH_3). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 165.4, 161.7, 128.9, 125.8, 114.3, 63.7, 47.8, 14.7. HRMS (ESI) m/z calcd for $C_{11}H_{16}N_2O_2$ $(M+H)^+$: 209.1286, found: 209.1290.

4-Bromo-*N*',*N*'-dimethylbenzohydrazide (5.1t): Purified by silica gel column



chromatography using ethyl acetate/hexane (70:30) mixture as an eluent. White solid. Yield: 103 mg, 85%. IR (DCM): 3265, 3052, 2966, 2878, 1657, 1480, 1267, 1045, 895, 739 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.55 (d, *J* = 8.5 Hz, 2H, ArC*H*), 7.48 (d, *J* = 8.4 Hz, 2H, ArC*H*), 7.06 (s, 1H, N*H*), 2.64 (s, 6H, CH_3). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 164.9, 132.5, 131.9, 128.8, 127.1, 126.4, 47.6. HRMS (ESI) m/z calcd for $C_9H_{11}BrN_2O$ $(M+H)^+$: 243.0127, found: 243.0142

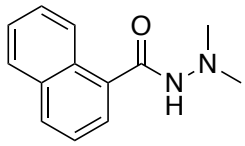
***N*',*N*'-Dimethyl-4-(methylamino)benzohydrazide (5.1u):** Purified by silica gel



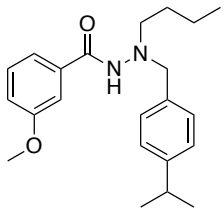
column chromatography using ethyl acetate solvent (100%) as an eluent. White solid. Yield: 72 mg, 75%. IR (DCM): 3440, 3260, 3050, 2988, 2853, 1661, 1447, 1265, 1047, 895, 743 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 (d, *J* = 7.2 Hz, 2H, ArC*H*), 6.74 (s, 1H, amide-N*H*), 6.52-6.43 (m, 2H, ArC*H*), 3.37 (s, 1H, amine-N*H*), 2.78 (s, 3H, CH_3), 2.61 (s, 6H, CH_3). ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$): δ 165.8, 152.1, 128.8, 121.4, 111.4, 47.9, 30.3. HRMS (ESI) m/z calcd for $C_{10}H_{15}N_3O$ $(M+H)^+$: 194.1287, found: 194.1290.

***N*',*N*'-Dimethyl-1-naphthohydrazide (5.1v):** Purified by silica gel column chromatography using ethyl acetate/hexane (75:25) mixture as an eluent.White solid. Yield: 96 mg, 90%. IR (DCM): 3250, 3059, 2980, 2857, 1650, 1447, 1266, 1047, 897, 742 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.27-8.17 (m, 1H, ArC*H*), 7.91-7.79 (m, 2H, ArC*H*), 7.58-7.44 (m, 3H, ArC*H*), 7.44-7.34 (m, 1H, ArC*H*), 6.84 (s, 1H, N*H*), 2.76-2.72 (m, 6H, CH_3). ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$): δ 167.4, 133.7, 132.8, 130.9, 130.4, 128.4, 127.3, 126.6, 125.2, 124.7, 47.7. HRMS (ESI) m/z calcd for $C_{13}H_{14}N_2O$ $(M+H)^+$: 215.1178, found: 215.1189.

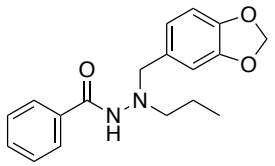


***N*'-Butyl-*N*'-(4-isopropylbenzyl)-3-methoxybenzohydrazide (5.2a):** Purified by silica gel column chromatography using ethyl acetate/hexane (10:90) mixture as an eluent. White solid. Yield: 166 mg, 94%. IR (DCM): 3250, 3056, 2987, 2857, 1640, 1447, 1267, 1048, 897, 741 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.19 (t, *J* = 5.0 Hz, 2H, ArC*H*), 7.16 (d, *J* = 7.9 Hz, 1H, ArC*H*), 7.13-7.06 (m, 3H, ArC*H*), 7.01-6.96 (m, 1H, ArC*H*), 6.91 (ddd, J_1 = 8.3 Hz, J_2 = 2.6 Hz, J_3 = 0.9 Hz, 1H, ArC*H*), 6.76 (s, 1H, N*H*), 4.05 (s, 2H, CH_2), 3.72 (s, 3H, OCH_3), 2.83 (ddd, J_1 = 20.7 Hz, J_2 = 14.3 Hz, J_3 = 7.1 Hz, 3H, CH_2&C*H*), 1.48 (ddd, J_1 = 14.9 Hz, J_2 = 8.5 Hz, J_3 = 6.3 Hz, 2H, CH_2), 1.40-1.24 (m, 2H, CH_2), 1.15 (d, *J* = 6.9 Hz, 6H, CH_3), 0.82 (t, *J* = 7.3 Hz, 3H, CH_3). ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$): δ 166.7, 159.8, 148.3, 135.6, 133.6, 129.6, 129.6, 126.5, 118.7, 117.8,



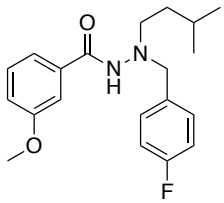
112.3, 60.7, 56.1, 55.4, 33.8, 29.6, 24.0, 20.4, 14.1. HRMS (ESI) m/z calcd for $C_{22}H_{30}N_2O_2$ $(M+H)^+$: 355.2380, found: 355.2403.

***N*'-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-*N*'-propylbenzohydrazide (5.2b):** Purified by



silica gel column chromatography using ethyl acetate/hexane (10:90) mixture as an eluent. White solid. Yield: 131 mg, 84%. IR (DCM): 3251, 3057, 2980, 2856, 1647, 1440, 1268, 1047, 897, 747 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.56-7.51 (m, 2H, ArC*H*), 7.40 (t, *J* = 7.4 Hz, 1H, ArC*H*), 7.31 (t, *J* = 7.5 Hz, 2H, ArC*H*), 6.83 (s, 1H, ArC*H*), 6.76 (s, 1H, N*H*), 6.70 (dd, J_1 = 19.2 Hz, J_2 = 8.4 Hz, 2H, ArC*H*), 5.87 (s, 2H, OCH_2), 4.01 (s, 2H, CH_2), 2.90-2.77 (m, 2H, CH_2), 1.53 (dt, J_1 = 14.8 Hz, J_2 = 7.4 Hz, 2H, CH_2), 0.87 (t, *J* = 7.4 Hz, 3H, CH_3). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 166.9, 147.8, 147.1, 134.0, 131.6, 130.3, 128.7, 126.9, 122.8, 109.9, 108.1, 101.0, 60.7, 57.9, 20.8, 11.7. HRMS (ESI) m/z calcd for $C_{18}H_{20}N_2O_3$ $(M+H)^+$: 313.1547, found: 313.1570.

***N*'-(4-Fluorobenzyl)-*N*'-isopentyl-3-methoxybenzohydrazide (5.2c):** Purified by



silica gel column chromatography using ethyl acetate/hexane (10:90) mixture as an eluent. White solid. Yield: 110 mg, 64%. IR (DCM): 3255, 3059, 2960, 2888, 1657, 1440, 1264, 1049, 890, 745 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.26 (dd, J_1 = 8.3 Hz, J_2 = 5.6 Hz, 2H, ArC*H*), 7.20-7.14 (m, 1H, ArC*H*), 7.08 (s, 1H, ArC*H*), 6.97 (d, *J* = 7.6 Hz, 1H, ArC*H*), 6.94-6.89 (m, 3H, ArC*H*), 6.80 (s, 1H, N*H*), 4.04 (s, 2H, CH_2), 3.72 (s, 3H, OCH_3), 3.04-2.79 (m, 2H, CH_2), 1.59 (td, J_1 = 13.4 Hz, J_2 = 6.7 Hz, 1H, C*H*), 1.39 (dd, J_1 = 14.9 Hz, J_2 = 7.0 Hz, 2H, CH_2), 0.80 (d, *J* = 6.6 Hz, 6H, CH_3). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 166.8, 163.5, 161.1, 159.8, 135.4, 132.6, 131.0, 131.0, 129.7, 128.8, 128.7, 118.6, 117.8, 115.3, 115.1, 112.3, 60.3, 55.4, 54.7, 36.3, 26.1, 22.7. HRMS (ESI) m/z calcd for $C_{20}H_{25}FN_2O_2$ $(M+H)^+$: 345.1973, found: 345. 1991.

***N*'-Hexyl-*N*'-(3-(pyridin-2-yl)propyl)benzohydrazide (5.2d):** Purified by silica gel column chromatography using ethyl acetate/hexane (40:60) mixture as an eluent. Pale yellow solid. Yield: 136 mg, 80%. IR (DCM): 3257, 3050, 2969, 2887, 1658, 1447, 1260, 1045, 890, 747 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.40 (d, J = 4.8 Hz, 1H, ArC*H*), 7.70-7.64 (m, 2H, ArC*H*), 7.49 (td, J_1 = 7.7 Hz, J_2 = 1.7 Hz, 1H, ArC*H*), 7.41 (t, J = 7.4 Hz, 1H, ArC*H*), 7.33 (t, J = 7.4 Hz, 2H, ArC*H*), 7.11 (d, J = 7.8 Hz, 1H, ArC*H*), 7.01 (dd, J_1 = 6.9 Hz, J_2 = 5.4 Hz, 1H, ArC*H*), 6.91 (s, 1H, N*H*), 2.87-2.74 (m, 6H, CH_2), 1.98-1.86 (m, 2H, CH_2), 1.53-1.39 (m, 2H, CH_2), 1.30-1.14 (m, 6H, CH_2), 0.78 (t, J = 6.8 Hz, 3H, CH_3). $^{13}C\{^{1}H\}$ NMR (100.6 MHz, $CDCl_3$): δ 166.8, 161.8, 149.0, 136.5, 134.1, 131.5, 128.6, 127.1, 123.2, 121.1, 58.3, 57.3, 35.7, 31.8, 27.1, 27.1, 26.9, 22.6, 14.1. HRMS (ESI) m/z calcd for $C_{21}H_{29}N_3O$ $(M+H)^+$: 340.2383, found: 340.2400.

***N*'-(4-Aminobenzyl)-4-ethoxy-*N*'-heptylbenzohydrazide (5.2e):** Purified by silica gel column chromatography using ethyl acetate/hexane (40:60) mixture as an eluent. Pale yellow solid. Yield: 149 mg, 78%. IR (DCM): 3422, 3255, 3056, 2955, 2886, 1647,1480, 1268, 1040, 890, 748 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 (d, J = 8.4 Hz, 2H, ArC*H*), 7.03 (d, J = 7.9 Hz, 2H, ArC*H*), 6.77 (d, J = 8.5 Hz, 2H, ArC*H*), 6.64 (s, 1H, N*H*), 6.55 (d, J = 7.9 Hz, 2H, ArC*H*), 4.02-3.90 (m, 4H, CH_2), 3.66 (s, 2H, NH_2), 2.86-2.72 (m, 2H, CH_2), 1.47 (dd, J_1 = 13.9 Hz, J_2 = 7.1 Hz, 2H, CH_2), 1.32 (dd, J_1 = 15.3 Hz, J_2 = 8.4 Hz, 3H, CH_3), 1.30-1.07 (m, 10H, CH_2), 0.78 (t, J = 6.2 Hz, 3H, CH_3). $^{13}C\{^{1}H\}$ NMR (100.6 MHz, $CDCl_3$): δ 166.1, 161.6, 145.9, 131.0, 128.7, 126.1, 125.6, 115.0, 114.2, 63.6, 60.6, 56.2, 31.8, 29.2, 27.5, 27.2, 22.6, 14.7, 14.1. HRMS (ESI) m/z calcd for $C_{23}H_{33}N_3O_2$ $(M+H)^+$: 384.2646, found: 384.2797.

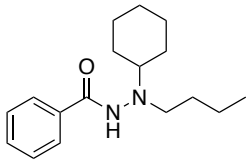
4-(*tert*-Butyl)-*N*'-ethyl-*N*'-(3,5,5-trimethylhexyl)benzohydrazide (5.2f): Purified by silica gel column chromatography using ethyl acetate/hexane (10:90) mixture as an eluent. White solid. Yield: 166 mg, 96%. IR (DCM): 3255, 3052, 2986, 2852, 1647, 1447, 1265, 1047, 897, 740 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.61 (d, J = 8.3 Hz, 2H, ArC*H*), 7.37 (d, J = 8.3 Hz, 2H, ArC*H*), 6.51 (s, 1H, N*H*), 2.90-2.64 (m, 4H, CH_2), 1.57-1.42 (m, 2H, CH_2), 1.41-1.30 (m, 1H, C*H*), 1.25 (s, 9H, 3×CH_3), 1.14 (dd, J_1 = 13.8 Hz, J_2 = 3.2 Hz, 1H, CH_2), 1.07 (t, J = 7.1 Hz, 3H, CH_3), 0.98 (dd, J_1 = 14.0 Hz, J_2 = 6.1 Hz, 1H, CH_2), 0.85 (d, J = 6.4 Hz, 3H, CH_3), 0.80 (s, 9H, 3×CH_3). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 166.8, 155.1, 131.2, 126.9, 125.6, 56.5, 52.6, 51.4, 36.4, 35.0, 31.2, 31.1, 30.0, 27.6, 22.8, 12.1. HRMS (ESI) m/z calcd for $C_{22}H_{38}N_2O$ $(M+H)^+$: 347.3057, found: 347.3076.

4-Amino-*N*'-butyl-*N*'-hexylbenzohydrazide (5.2g): Purified by silica gel column chromatography using ethyl acetate/hexane (40:60) mixture as an eluent. White solid. Yield: 98 mg, 67%. IR (DCM): 3476. 3256, 3056, 2960, 2887, 1647, 1442, 1265, 1040, 890, 742 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.50 (d, J = 8.3 Hz, 2H, ArC*H*), 6.57 (d, J = 8.4 Hz, 3H, ArC*H* & N*H*), 3.92 (s, 2H, NH_2), 2.79-2.68 (m, 4H, CH_2), 1.45 (dd, J_1 = 13.2 Hz, J_2 = 6.5 Hz, 4H, CH_2), 1.32-1.13 (m, 8H, CH_2), 0.86-0.74 (m, 6H, CH_3). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 166.5, 149.8, 128.7, 123.3, 114.2, 58.7, 58.3, 31.8, 29.2, 27.0, 22.6, 20.5, 14.1. HRMS (ESI) m/z calcd for $C_{17}H_{29}N_3O$ $(M+H)^+$: 292.2383, found: 292.2390.

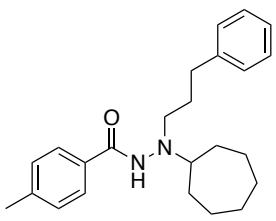
4-Amino-*N*'-benzyl-*N*'-hexylbenzohydrazide (3h): Purified by silica gel column chromatography using ethyl acetate/hexane (40:60) mixture as an eluent. White solid. Yield: 91 mg, 56%. IR (DCM): 3422, 3052, 2986, 2856, 1650, 1448, 1265, 1047, 895, 743

cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.36 (d, J = 8.3 Hz, 2H, ArC*H*), 7.23 (dq, J_1 = 13.5 Hz, J_2 = 7.4 Hz, 5H, ArC*H*), 6.70 (s, 1H, N*H*), 6.51 (d, J = 8.5 Hz, 2H, ArC*H*), 4.08 (s, 2H, CH_2), 3.90 (s, 2H, NH_2), 2.93-2.81 (m, 2H, CH_2), 1.48 (dt, J_1 = 14.7 Hz, J_2 = 7.3 Hz, 2H, CH_2), 1.32-1.14 (m, 6H, CH_2), 0.78 (t, J = 6.7 Hz, 3H, CH_3). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 166.6, 149.8, 136.5, 129.7, 128.6, 128.4, 127.5, 123.3, 114.2, 61.1, 56.4, 31.8, 27.5, 26.9, 22.7, 14.1. HRMS (ESI) m/z calcd for $C_{20}H_{27}N_3O$ $(M+H)^+$: 326.2227, found: 326.2236.

***N*'-Butyl-*N*'-cyclohexylbenzohydrazide (5.2i):** Purified by silica gel column chromatography using ethyl acetate/hexane (10:90) mixture as an eluent. White solid. Yield: 131 mg, 96%. IR (DCM): 3256, 3052, 2967, 2886, 1649, 1447, 1265, 1046, 880, 747 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.68 (d, J = 6.5 Hz, 2H, ArC*H*), 7.42 (d, J = 6.5 Hz, 1H, ArC*H*), 7.36 (t, J = 6.7 Hz, 2H), 6.60 (s, 1H, N*H*), 2.74 (d, J = 30.1 Hz, 3H, CH_2 & C*H*), 1.92 (s, 2H, CH_2), 1.73 (s, 2H, CH_2), 1.44-1.61 (m, 3H, CH_2), 1.24 (dt, J_1 = 48.8 Hz, J_2 = 14.8 Hz, 7H, CH_2), 0.83 (t, J = 6.7 Hz, 3H, CH_3). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 167.1, 134.2, 131.5, 128.7, 127.1, 64.4, 54.3, 29.3, 29.0, 26.0, 25.3, 20.5, 14.1. HRMS (ESI) m/z calcd for $C_{17}H_{26}N_2O$ $(M+H)^+$: 275.2118, found: 275.2099.

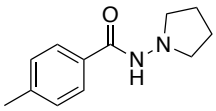


***N*'-Cycloheptyl-4-methyl-*N*'-(3-phenylpropyl)benzohydrazide (5.2j):** Purified by silica gel column chromatography using ethyl acetate/hexane (10:90) mixture as an eluent. White solid. Yield: 146 mg, 80%. IR (DCM): 3255, 3056, 2967, 2880, 1647, 1449, 1266, 1046, 890, 744 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.54 (d, J = 8.0 Hz, 2H, ArC*H*), 7.20-7.05 (m, 7H, ArC*H*), 6.47 (s, 1H, N*H*), 3.00-2.79 (m, 1H, C*H*), 2.70 (t, J = 7.2 Hz, 2H, CH_2), 2.63 (t, J = 7.6 Hz, 2H, CH_2), 2.32 (s, 3H, CH_3), 1.91 (dd, J_1 = 13.0 Hz, J_2 = 4.1 Hz, 2H, CH_2), 1.81 (dd, J_1 = 14.8 Hz, J_2 = 7.5 Hz, 2H, CH_2),



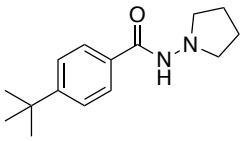
1.67-1.54 (m, 2H, CH_2), 1.41 (ddd, J_1 = 26.0 Hz, J_2 = 12.2 Hz, J_3 = 6.0 Hz, 8H, CH_2). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 167.0, 142.2, 142.0, 131.4, 129.3, 128.6, 128.4, 127.1, 125.8, 66.4, 54.6, 33.5, 29.8, 29.2, 28.1, 25.2, 21.5. HRMS (ESI) m/z calcd for $C_{24}H_{32}N_2O$ $(M+H)^+$: 365.2587, found: 365.2630.

4-Methyl-*N*-(pyrrolidin-1-yl)benzamide (5.3a): Purified by silica gel column



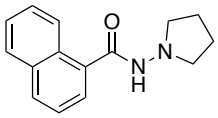
chromatography using ethyl acetate/hexane (40:60) mixture as an eluent. White solid. Yield: 92 mg, 90%. IR (DCM): 3250, 3059, 2960, 2886, 1650, 1447, 1267, 1058, 898, 742 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.57 (d, J = 7.7 Hz, 2H, ArCH), 7.14 (d, J = 7.9 Hz, 2H, ArCH), 3.14-2.83 (m, 4H, CH_2), 2.31 (s, 3H, CH_3), 1.96-1.77 (m, 4H, CH_2). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 166.3, 142.1, 131.0, 129.3, 127.1, 55.7, 22.4, 21.5. HRMS (ESI) m/z calcd for $C_{12}H_{16}N_2O$ $(M+H)^+$: 205.1335, found: 205.1330.

4-(*tert*-Butyl)-*N*-(pyrrolidin-1-yl)benzamide (5.3b): Purified by silica gel column



chromatography using ethyl acetate/hexane (40:60) mixture as an eluent. White solid. Yield: 106 mg, 86%. IR (DCM): 3267, 3010, 2966, 2889, 1657, 1447, 1270, 1046, 890, 739 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.61 (d, J = 8.0 Hz, 2H, ArCH), 7.35 (d, J = 8.1 Hz, 2H, ArCH), 3.11-2.76 (m, 4H, CH_2), 1.97-1.70 (m, 4H, CH_2), 1.25 (s, 9H, 3×CH_3) $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 166.2, 155.2, 130.9, 127.0,125.6, 55.6, 35.0, 31.2, 22.4. (ESI) m/z calcd for $C_{15}H_{22}N_2O$ $(M+H)^+$: 247.1805, found: 247.1817.

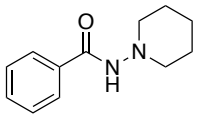
***N*-(Pyrrolidin-1-yl)-1-naphthamide (5.3c):** Purified by silica gel column



chromatography using ethyl acetate/hexane (40:60) mixture as an eluent. White solid. Yield: 100 mg, 83%. IR (DCM): 3250, 3077, 2960, 2889, 1650, 1448, 1260, 1049, 890, 742 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.15 (d, J = 7.6 Hz, 1H, ArCH), 7.75 (dt, J_1 = 19.0 Hz, J_1 = 9.4 Hz, 2H, ArCH), 7.47-7.37

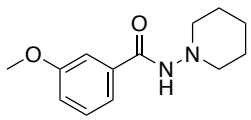
(m, 3H, ArC*H*), 7.29 (t, *J* = 7.6 Hz, 1H, ArC*H*), 6.88 (s, 1H, N*H*), 3.04-2.80 (m, 4H, CH_2), 1.94-1.62 (m, 4H, CH_2). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 167.9, 133.6, 133.0, 130.6, 130.3, 128.3, 127.1, 126.4, 125.3, 125.1, 124.6, 55.5, 22.2. (ESI) m/z calcd for $C_{15}H_{16}N_2O$ $(M+H)^+$: 241.1335, found: 241.1325.

***N*-(Piperidin-1-yl)benzamide (5.3d):** Purified by silica gel column chromatography



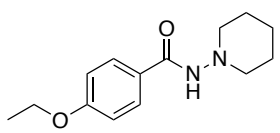
using ethyl acetate/hexane (40:60) mixture as an eluent. White solid. Yield: 77 mg, 75%. IR (DCM): 3300, 3109, 2956, 2887, 1651, 1447, 1265, 1049, 890, 747 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.66 (d, *J* = 7.1 Hz, 2H, ArC*H*), 7.47-7.38 (m, 1H, ArC*H*), 7.34 (t, *J* = 7.3 Hz, 2H, ArC*H*), 6.86 (s, 1H, N*H*), 2.88-2.63 (m, 4H, CH_2), 1.78-1.52 (m, 4H, CH_2), 1.44-1.24 (m, 2H, CH_2). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 165.4, 134.1, 131.6, 128.6, 127.1, 57.2, 25.4, 23.3. (ESI) m/z calcd for $C_{12}H_{16}N_2O$ $(M+H)^+$: 205.1335, found: 205.1336.

3-Methoxy-*N*-(piperidin-1-yl)benzamide (5.3e): Purified by silica gel column



chromatography using ethyl acetate/hexane (40:60) mixture as an eluent. White solid. Yield: 84 mg, 72%. IR (DCM): 3250, 3053, 2956, 2878, 1649, 1449, 1262, 1047, 898, 745 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.29-7.13 (m, 4H, ArC*H* & N*H*), 6.95 (dd, J_1 = 8.2 Hz, J_2 = 2.4 Hz, 1H, ArC*H*), 3.77 (s, 3H, OCH_3), 2.91-2.75 (m, 4H, CH_2), 1.69 (dt, J_1 = 11.1 Hz, J_2 = 5.6 Hz, 4H, CH_2), 1.38 (dd, J_1 = 14.9 Hz, J_2 = 9.9 Hz, 2H, CH_2). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 165.3, 159.9, 135.5, 129.6, 118.9, 117.7, 112.6, 57.2, 55.5, 25.4, 23.3. (ESI) m/z calcd for $C_{13}H_{18}N_2O_2$ $(M+H)^+$: 235.1441, found: 235.1464.

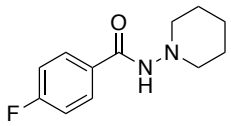
4-Ethoxy-*N*-(piperidin-1-yl)benzamide (5.3f): Purified by silica gel column



chromatography using ethyl acetate/hexane (40:60) mixture as an eluent. White solid. Yield: 87 mg, 70%. IR (DCM): 3266, 3156, 2960, 1652, 1447, 1269, 1040, 890, 751 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.63

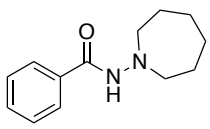
(d, *J* = 8.2 Hz, 2H, ArC*H*), 6.81 (d, *J* = 8.6 Hz, 2H, ArC*H*), 3.99 (q, *J* = 7.0 Hz, 2H, CH_2), 2.95-2.54 (m, 4H, CH_2), 1.85-1.51 (m, 4H, CH_2), 1.35 (t, *J* = 7.0 Hz, 5H, CH_3 & CH_2). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 165.0, 161.7, 128.9, 126.0, 114.3, 63.7, 57.3, 25.4, 23.3, 14.8. (ESI) m/z calcd for $C_{14}H_{20}N_2O_2$ $(M+H)^+$: 249.1597, found: 249.1603.

4-Fluoro-*N*-(piperidin-1-yl)benzamide (5.3g): Purified by silica gel column



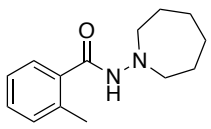
chromatography using ethyl acetate/hexane (45:55) mixture as an eluent. White solid. Yield: 70 mg, 63%. IR (DCM): 3253, 3052, 2956, 2881, 1649, 1447, 1269, 1047, 890, 742 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.85 (s, 1H, N*H*), 7.72-7.66 (m, 2H, ArC*H*), 7.02 (t, *J* = 8.4 Hz, 2H, ArC*H*), 2.93-2.67 (m, 4H, CH_2), 1.81-1.62 (m, 4H, CH_2), 1.44-1.28 (m, 2H, CH_2). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 166.1, 164.5, 163.6, 130.0, 129.6, 129.5, 115.8, 115.6, 57.3, 25.3, 23.2. (ESI) m/z calcd for $C_{12}H_{15}FN_2O$ $(M+H)^+$: 223.1241, found: 223.1235.

***N*-(Azepan-1-yl)benzamide (5.3h):** Purified by silica gel column chromatography



using ethyl acetate/hexane (40:60) mixture as an eluent. White solid. Yield: 71 mg, 65%. IR (DCM): 3266, 3046, 2950, 2856, 1640, 1402, 1276, 1049, 892, 745 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.66 (d, *J* = 7.3 Hz, 2H, ArC*H*), 7.41 (t, *J* = 6.9 Hz, 1H, ArC*H*), 7.33 (t, *J* = 7.4 Hz, 2H, ArC*H*), 3.11-3.08 (m, 4H, CH_2), 1.76-1.67 (m, 4H, CH_2), 1.57-1.52 (m, 4H, CH_2). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 165.7, 134.1, 131.5, 128.6, 127.0, 58.2, 27.1, 26.2. (ESI) m/z calcd for $C_{13}H_{18}N_2O$ $(M+H)^+$: 219.1492, found: 219.1510.

***N*-(Azepan-1-yl)-2-methylbenzamide (5.3i):** Purified by silica gel column



chromatography using ethyl acetate/hexane (40:60) mixture as an eluent. White solid. Yield: 80 mg, 70%. IR (DCM): 3266, 3076, 2966, 2887, 1640, 1449, 1267, 890, 743 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.22 (dd,

J_1 = 13.4 Hz, J_2 = 6.4 Hz, 2H, ArC*H*), 7.12 (dd, J_1 = 13.6 Hz, J_1 = 6.5 Hz, 2H, ArC*H*), 6.81 (s, 1H, N*H*), 3.14-3.05 (m, 4H, CH_2), 2.36 (s, 3H, CH_3), 1.76-1.60 (m, 4H, CH_2), 1.60-1.54 (m, 4H, CH_2). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 167.8, 136.3, 135.3, 130.9, 130.0, 126.9, 125.7, 58.4, 27.0, 26.1, 19.6. (ESI) m/z calcd for $C_{14}H_{20}N_2O$ $(M+H)^+$: 233.1648, found: 233.1640.

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^{1}H and ^{13}C NMR Spectra of *N,N*-Dialkylated Products:

Figure 5.2 ^{1}H NMR spectrum of *N*',*N*'-Dibutylbenzohydrazide (**5.1b**):

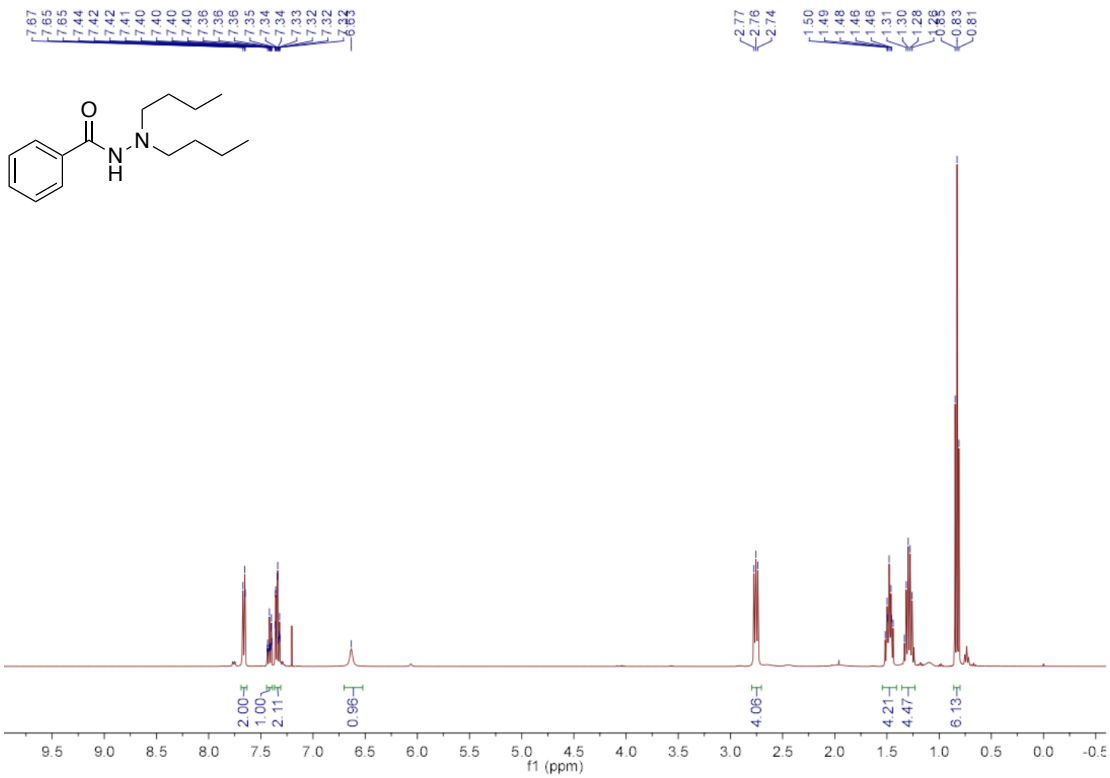


Figure 5.3 ^{13}C NMR spectrum of *N*',*N*'-Dibutylbenzohydrazide (**5.1b**):

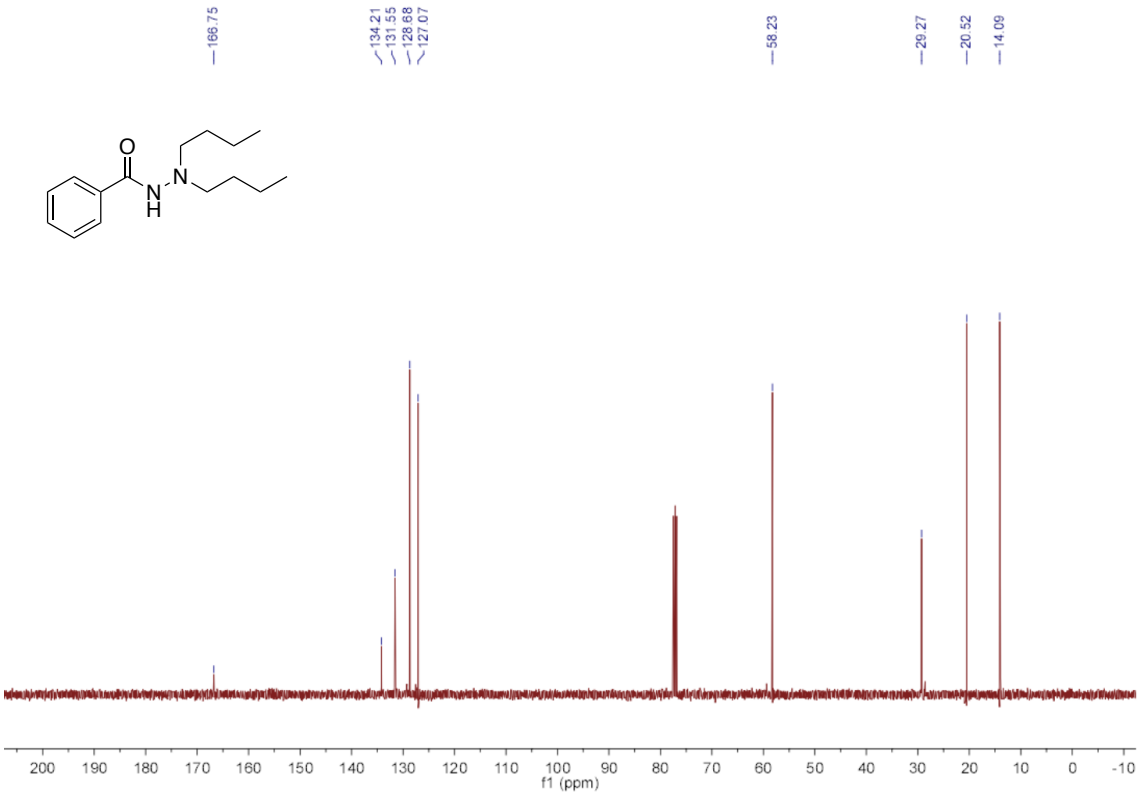


Figure 5.4 ^{1}H NMR spectrum of 4-(*tert*-butyl)-*N*'-ethyl-*N*'-(3,5,5-trimethylhexyl)benzohydrazide (**5.2f**):

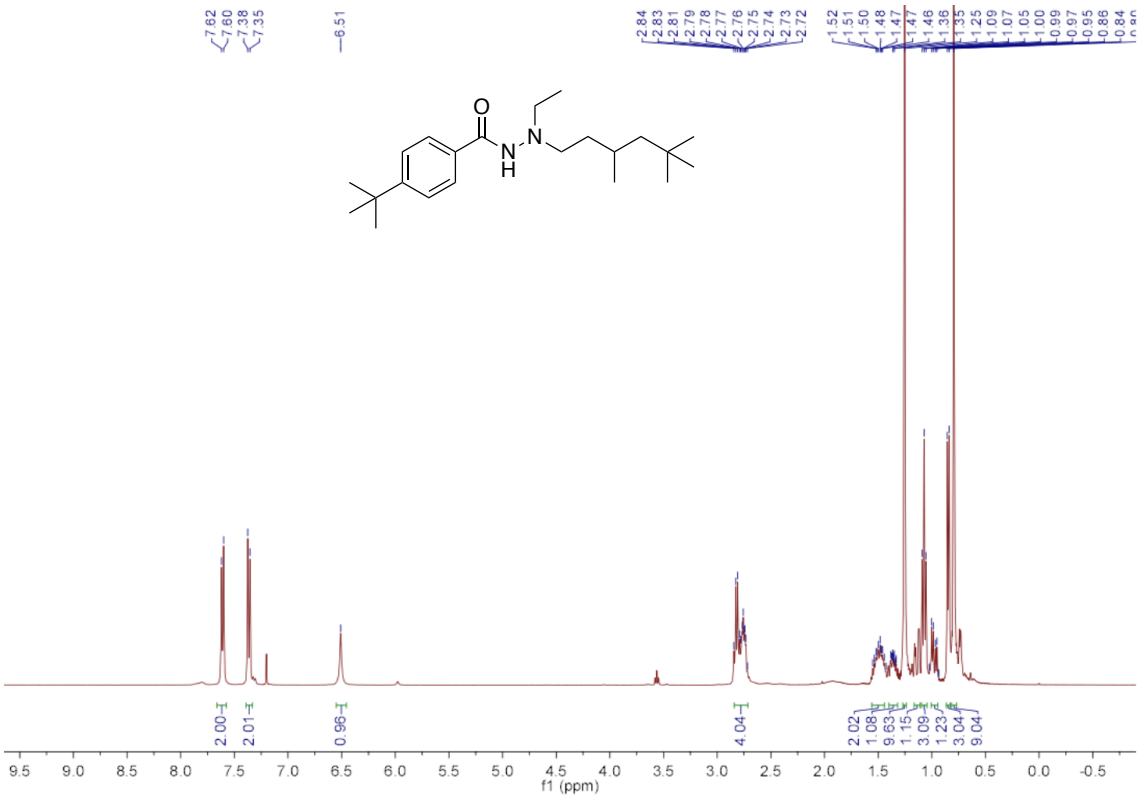


Figure 5.5 ^{13}C NMR spectrum of 4-(*tert*-butyl)-*N*'-ethyl-*N*'-(3,5,5-trimethylhexyl)benzohydrazide (**5.2f**):

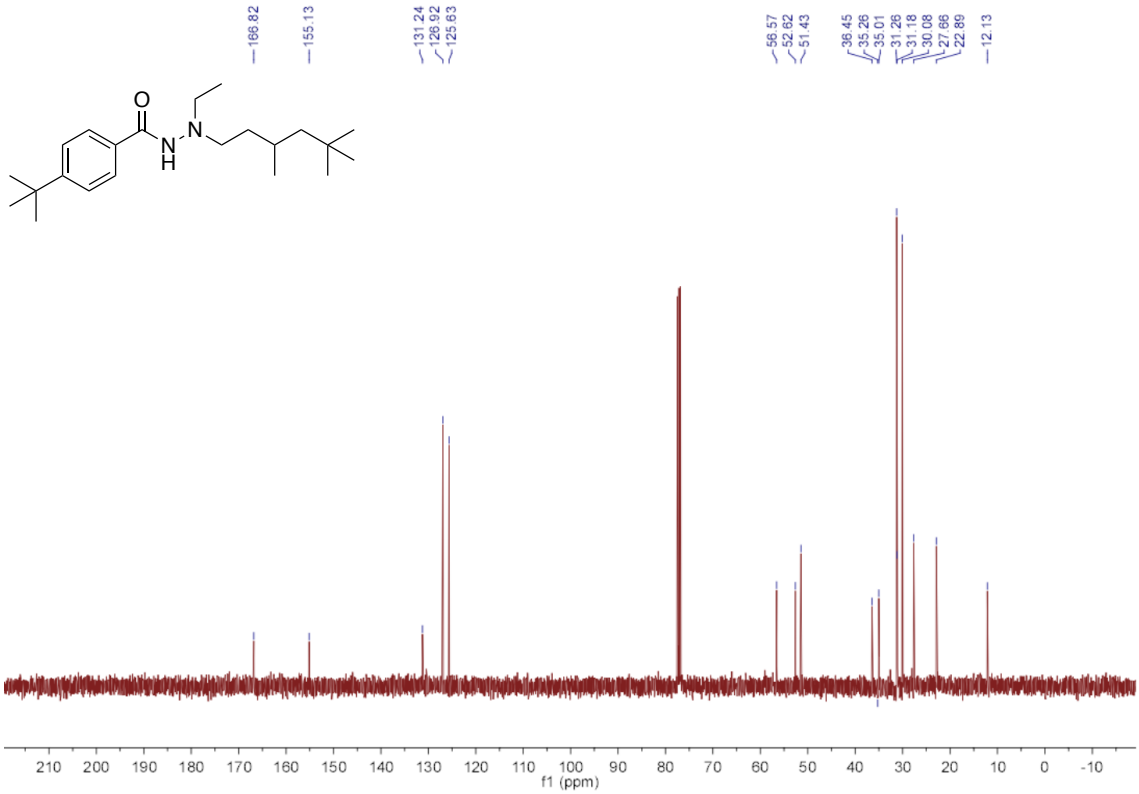


Figure 5.6 ^{1}H NMR spectrum of 4-methyl-*N*-(pyrrolidin-1-yl)benzamide (**5.3a**):

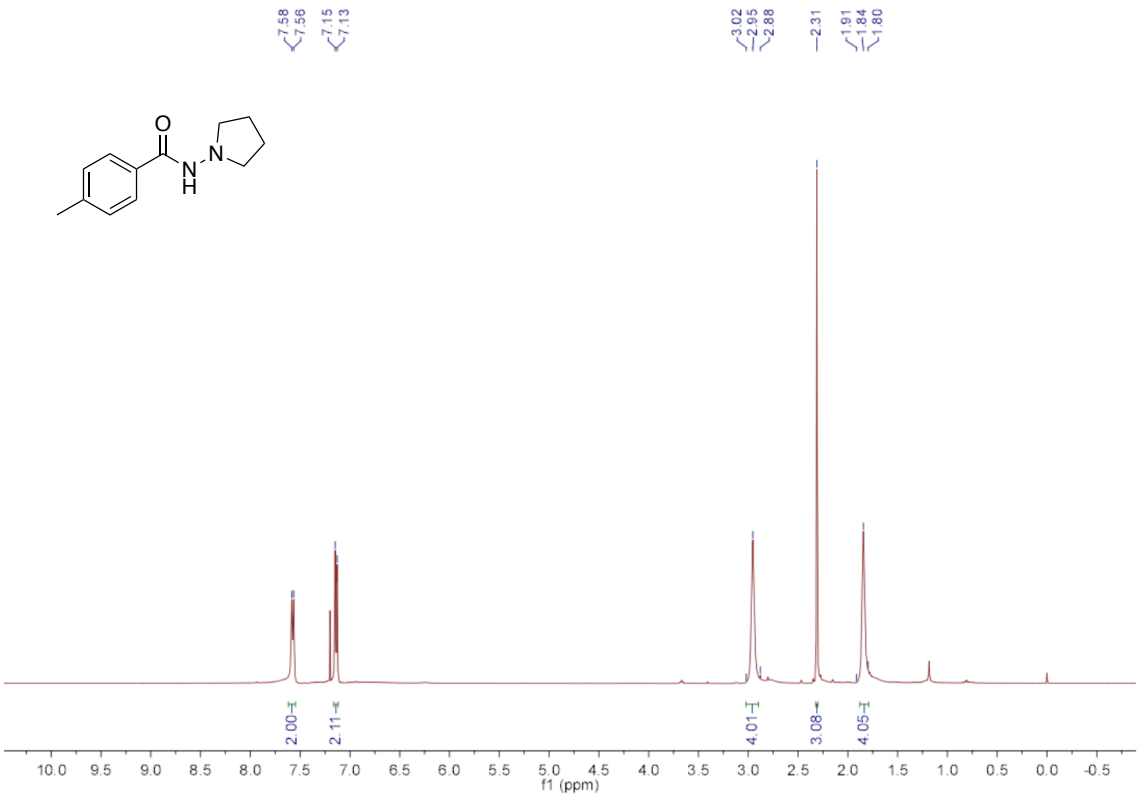


Figure 5.7 ^{13}C NMR spectrum of 4-methyl-*N*-(pyrrolidin-1-yl)benzamide (**5.3a**):

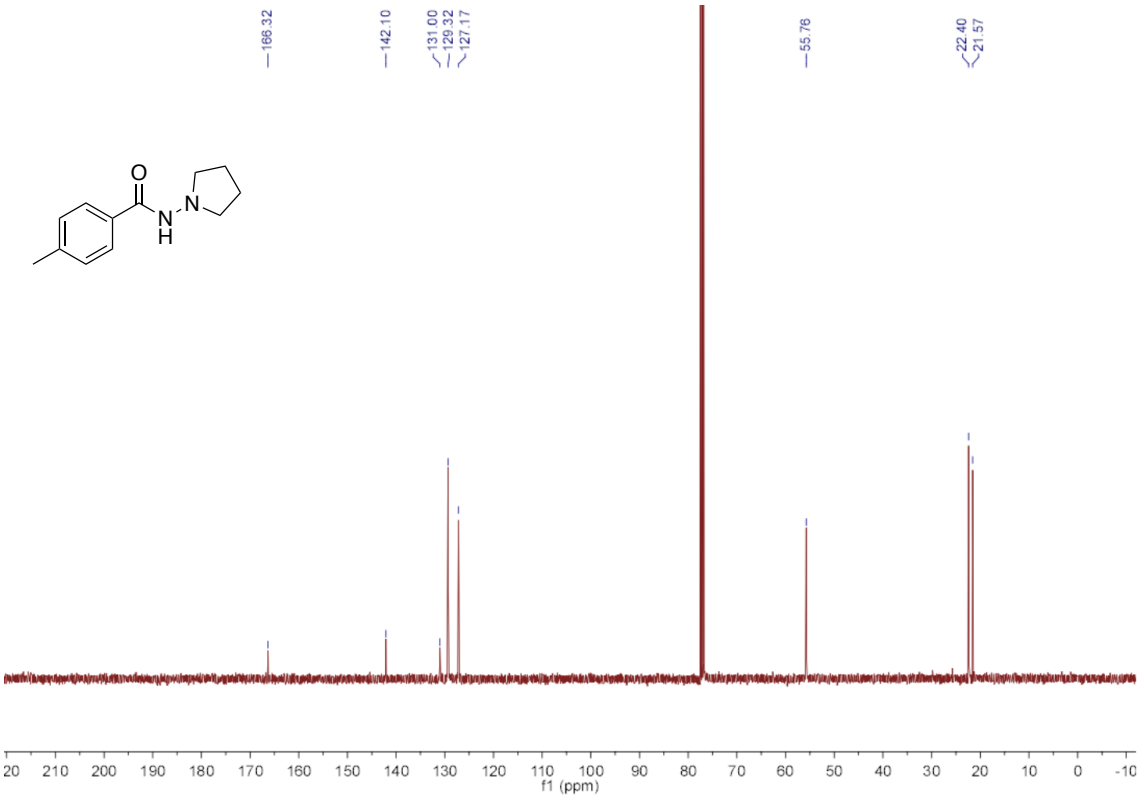


Figure 5.8 ^{1}H NMR spectrum of the product **5.4a**:

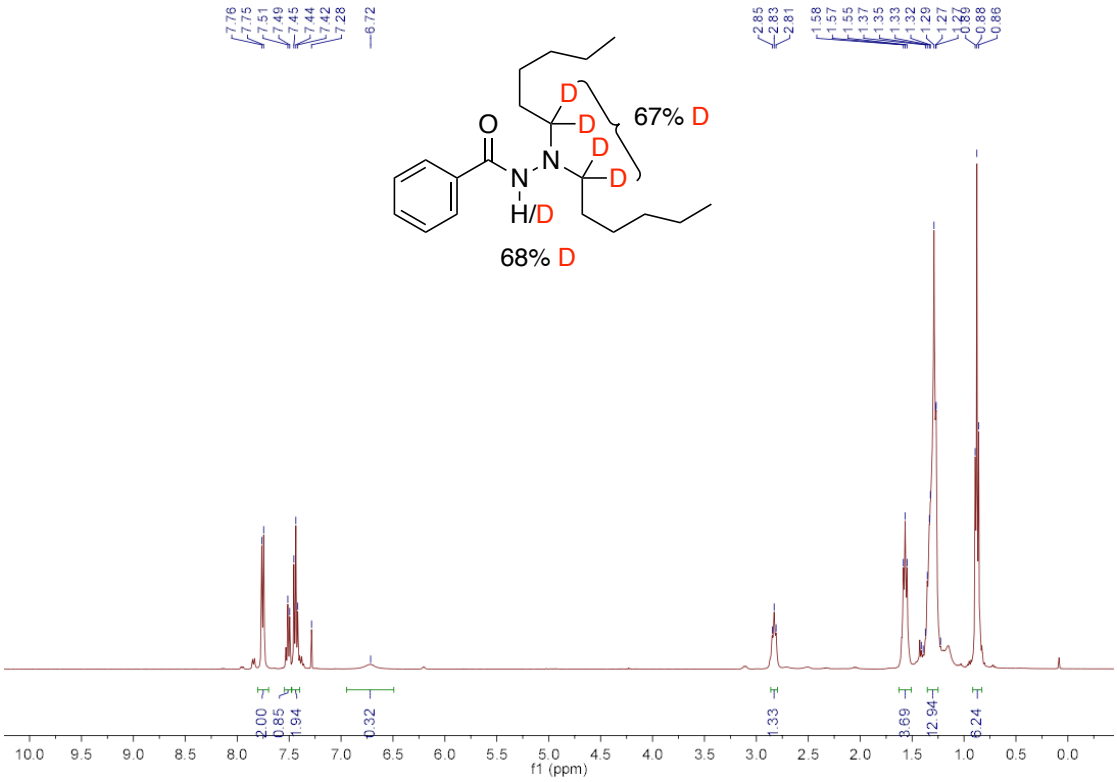
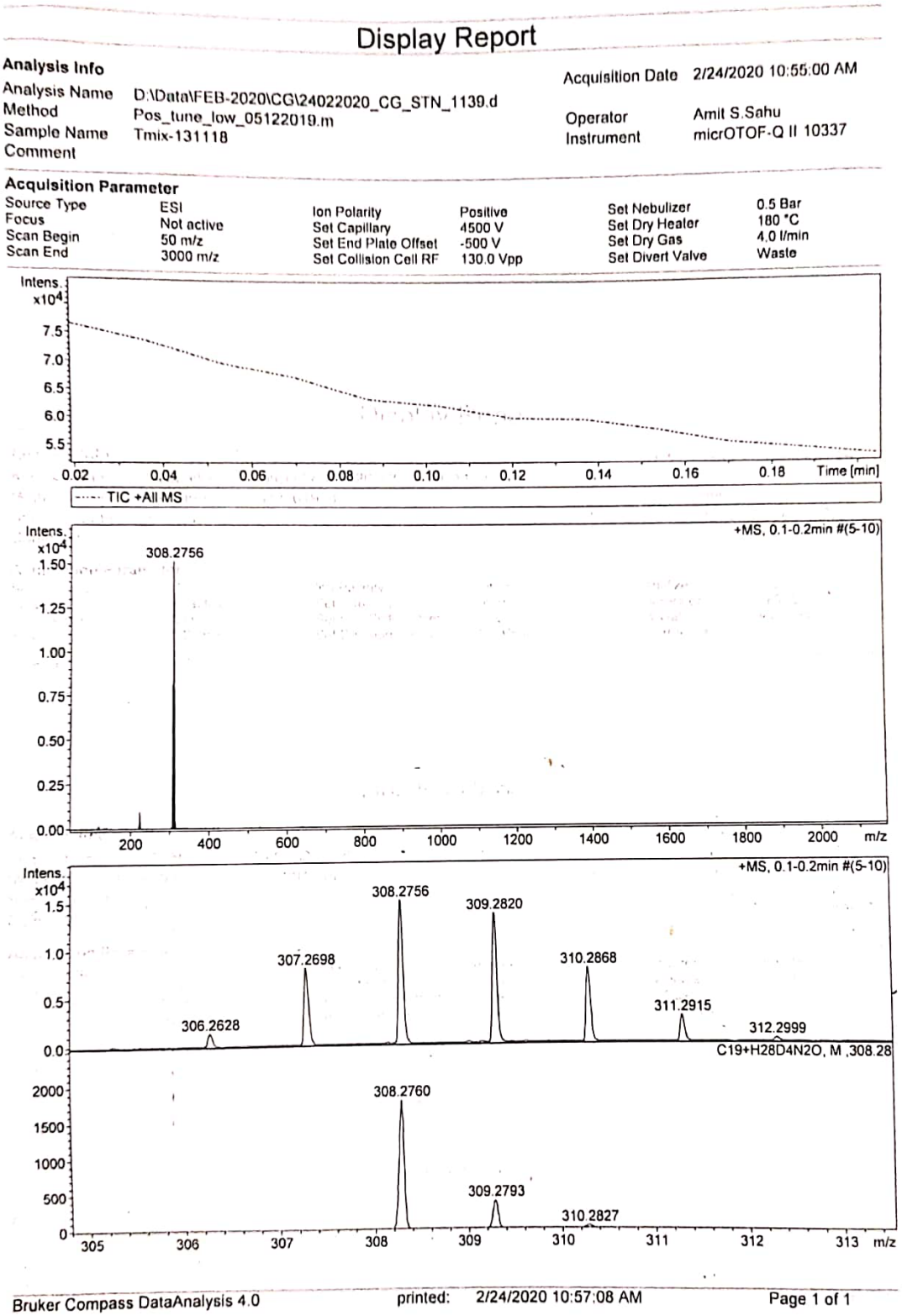


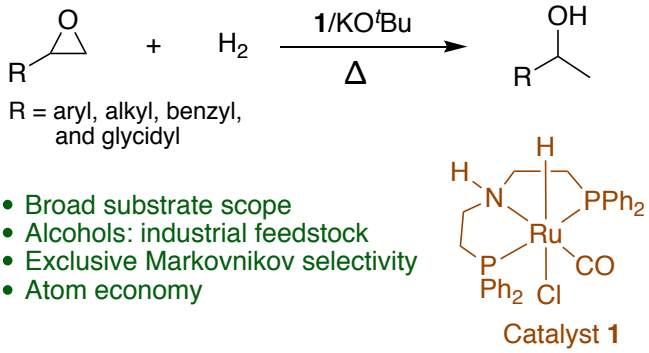
Figure 5.9 HRMS spectrum of the product **5.4a**:



CHAPTER 6

Ruthenium-Catalyzed Selective Hydrogenation of Epoxides to Secondary Alcohols

6.1 ABSTRACT



A ruthenium(II) catalyzed highly selective Markovnikov hydrogenation of terminal epoxides to secondary alcohols is reported. Diverse substitutions on aryl ring of styrene oxides are tolerated. Benzylic, glycidyl, aliphatic and diepoxides also underwent facile hydrogenation to provide secondary alcohols with exclusive selectivity. Metal-ligand cooperation mediated ruthenium trans-dihydride formation and its reaction involving oxygen and less substituted terminal carbon of epoxide is envisaged for the origin of observed selectivity.

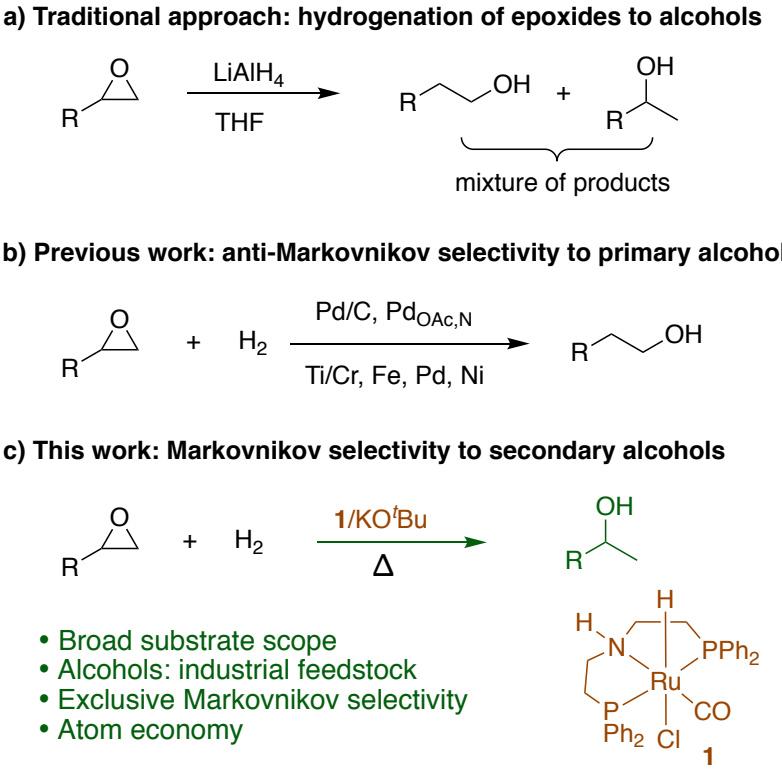
6.2 INTRODUCTION

Regioselective ring opening of epoxides to provide selectively one of the two isomeric products is an important transformation in medicinal chemistry and highly promising industrial process for the synthesis of alcohols.[1] Conventional methods for the epoxide hydrogenation reactions are mainly based on the use of stoichiometric amounts of strong reducing reagents such as $LiAlH_4$, which provide mixture of both primary and secondary alcohols (Scheme 6.1a).[2] The classical methods often failed to provide

satisfactory results and suffer from (i) requirement and safety issues on use of cryogenic condition (ii) difficulties associated with more reactive lithium base leading to mixture of alcohol products (iii) generation of copious reactive waste to the environment. Moreover, presence of sensitive functionalities limits the substrate scope. However, preparation of secondary alcohols directly from alkenes via acid catalyzed hydration reactions[3] and two-step Wacker oxidation of alkenes to ketones followed by reduction is also extensively studied in the literature.[4,5] Modern transition metal catalysis is an attractive and alternative method for the selective ring opening of epoxides.

During last two decades, heterogeneous and homogeneous catalyst systems have been developed for selective hydrogenation of epoxides to provide alcohols. Palladium heterogeneous catalyst (Pd/C) was extensively studied for the hydrogenolysis of epoxides to alcohols.[6] However, controlling regioselectivity of ring opening, and substrate scope have been less documented in heterogeneous catalysis. Thus, homogenous catalyzed reactions were developed for the selective ring opening of epoxides exploring the specific reactivity of transition metal complexes.[7,8] Hydroelementation (hydroboration and hydrosilylation) reactions are an alternative protocol for the selective ring opening of epoxides, which delivered the protected alcohols.[9,10]

Scheme 6.1 Traditional and Catalytic Approaches in Hydrogenation of Epoxides

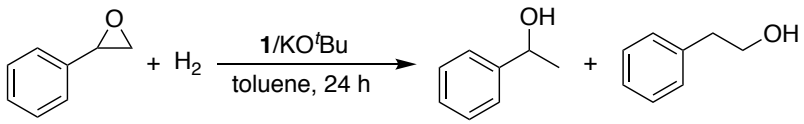


Very recently, the groups of Gansäuer, Norton and Beller have reported the anti-Markovnikov selective hydrogenation epoxides to primary alcohols.[11] Despite these enticing developments to attain anti-Markovnikov selective reactions, studies toward Markovnikov selective products remain limited in the literature.[6,7] Ikariya and coworkers have reported the pioneering ruthenium catalyzed Markovnikov hydrogenation of terminal epoxides.[8] However, the reported methods explored a narrow substrate scope and predominantly pertain to styrene oxides. Thus, developing a new protocol for the selective Markovnikov ring opening of epoxides is highly desirable. Recently, I have reported pincer Ru-MACHO (**1**) catalyzed cross-coupling of secondary alcohols,[12] synthesis of ketazines,[13] and α-olefination[14] and α-alkylation [15] of nitriles using alcohols. Herein, I present the highly selective Markovnikov hydrogenation of epoxides to secondary alcohols catalyzed by **1**.

6.3 RESULTS AND DISCUSSIONS

At the outset, styrene oxide (0.5 mmol), catalyst **1** (1 mol%), and base (2 mol%) in toluene solution was heated at 75 °C under hydrogen pressure (10 bar). Upon completion, GC and ^{1}H NMR analyses of the reaction mixture indicated 40% conversion of styrene oxide and formation of both isomers of alcohols 80:20 (branched: linear, entry 1, Table 6.1). This result implies predominant formation of secondary alcohol in our catalytic conditions. Increasing hydrogen pressure to 30 bar resulted in higher conversion and yield (78% and 76%, respectively) and provided increased selectivity for secondary alcohol (92:8, entry 2, Table 6.1). Upon increasing hydrogen pressure to 50 bar under similar catalytic conditions resulted in quantitative conversion of styrene oxide and alcohols were isolated in 99% yield with very good selectivity for secondary alcohol (94:6, entry 3, Table 6.1). Further, varying temperature and reducing catalyst load were found to be less effective on catalysis (entries 4-6, Table 6.1). No product formation was observed by employing only base, and without catalyst and base (entries 7,8, Table 6.1). These results clearly indicated that catalyst **1** and base are playing a crucial role in promoting selective ring opening of epoxides.

Table 6.1 Optimization for Regioselective Hydrogenation of Styrene Oxide Catalyzed by 1[a]



6.1a **6.1b**

entry	H_2 (bar)	temp (°C)	conv (%)[b]	yield (%)[c]	ratio 6.1a:6.1b[d]
1	10	75	40	38	80:20
2	30	75	78	76	92:8

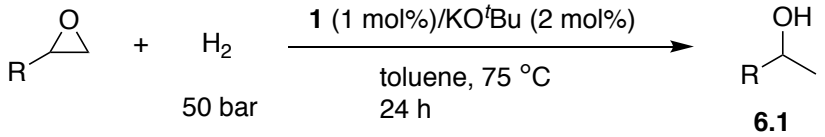
3	50	75	>99	99	94:6
4	50	100	>99	98	90:10
5	50	50	30	28	>99:<1
6[e]	50	75	60	54	>99:<1
7[f]	50	75	-	-	-
8[g]	50	75	-	-	-
9[h]	50	75	>99	97	94:6

[a]Reaction conditions: styrene oxide (0.5 mmol), catalyst **1** (1 mol%) and KO^{t}Bu (2 mol%) and toluene (1.5 mL), heated at indicated temperature under H_2 pressure. [b]Conversion of styrene oxide was determined by GC analysis using benzene as an internal standard. [c]Yields were calculated for isolated mixture of products 6.1a and 6.1b after column chromatography. [d]Alcohols ratio was determined from ^{1}H NMR analysis of the reaction mixture. [e]0.5 mol% catalyst **1** was used. [f]Only 5 mol% of KO^{t}Bu was used. [g]Reaction was performed without catalyst and base. [h]Reaction was performed in 1 mmol scale.

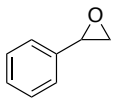
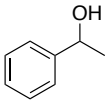
As the optimal reaction condition was attained, the substrate scope of epoxides was investigated (Table 6.2). Remarkably, except four substrates (see below) all other terminal epoxides subjected to catalysis exhibited complete regioselectivity for Markovnikov hydrogenation and delivered only secondary alcohols. Presence of electron donating and halogen substitutions on the aromatic ring of epoxide was very well tolerated. 4-Methylstyrene oxide afforded 90% conversion with 72% yield of **6.1c** while 10% of corresponding primary alcohol was also isolated (entry 2, Table 6.2). 4-*tert*-Butylstyrene oxide provided only 28% conversion, however, with exclusive regioselectivity for secondary alcohol under the optimized condition. With increased

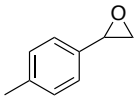
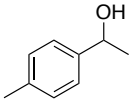
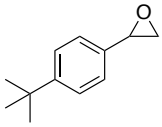
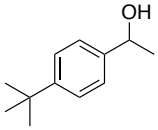
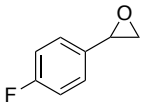
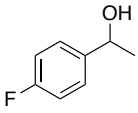
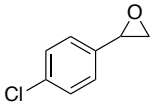
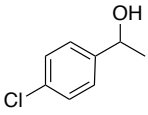
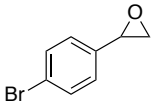
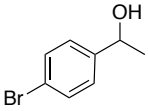
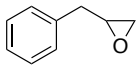
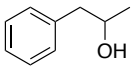
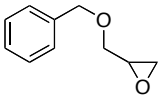
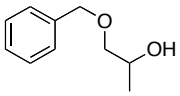
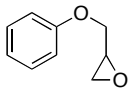
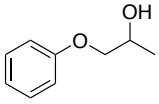
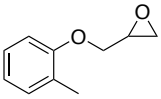
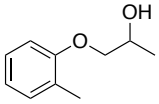
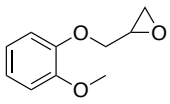
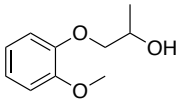
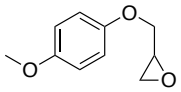
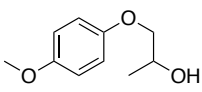
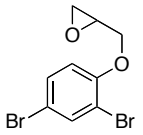
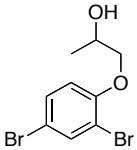
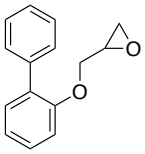
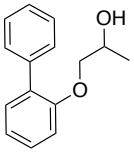
catalyst load and temperature (3 mol% and 100 °C), 75% conversion was observed in which 42% and 26% of secondary and primary alcohols were isolated, respectively (entry 3, Table 6.2). Gratifyingly, electron-withdrawing group containing styrene oxides provided excellent selectivity with moderate to excellent yields (entries 4-6, Table 6.2). 2-Benzyloxirane provided high yield and exclusive selectivity for secondary alcohol (entry 7, Table 6.2). Notably, the palladium catalyzed hydrogenation of 2-benzyloxirane under heterogeneous conditions provided mixture of both primary and secondary alcohols.[6b] Further, a variety of aromatic and aliphatic glycidyl terminal epoxides were tested, which resulted in very good yields of secondary alcohols with exclusive selectivity (entries 8-14, Table 6.2). Unactivated aliphatic epoxides were subjected with increased catalyst load (5 mol%) and base (10 mol%) in which most of the substrates provided quantitative conversion and the products were isolated in good to excellent yields (entries 15-19, Table 6.2). However, under similar condition when 1,1-disubstituted epoxide 2-methyl-2-phenyloxirane was subjected to hydrogenation, the formation of mixture of both isomeric alcohols was observed in the reaction mixture (branched: linear, 50:49, entry 20, Table 6.2).

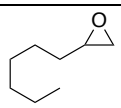
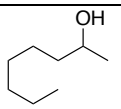
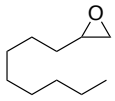
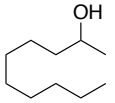
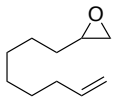
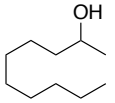
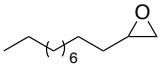
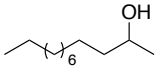
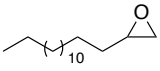
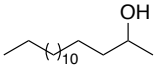
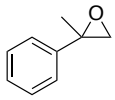
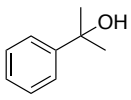
Table 6.2 Scope of Regioselective Hydrogenation of Terminal Epoxides Catalyzed by 1[a]



6.1

entry	epoxide	product		conv (%)[b]	yield (%)[c]
1[d]			**6.1a**	>99	99

2[e]			**6.1c**	90	72
3[f,g]			**6.1d**	75	42
4[g]			**6.1e**	>99	96
5[g]			**6.1f**	41	40
6[g]			**6.1g**	41	37
7[g]			**6.1h**	>99	95
8			**6.1i**	>99	98
9			**6.1j**	>99	98
10			**6.1k**	>99	97
11			**6.1l**	73	67
12			**6.1m**	>99	97
13			**6.1n**	67	65
14			**6.1o**	>99	98

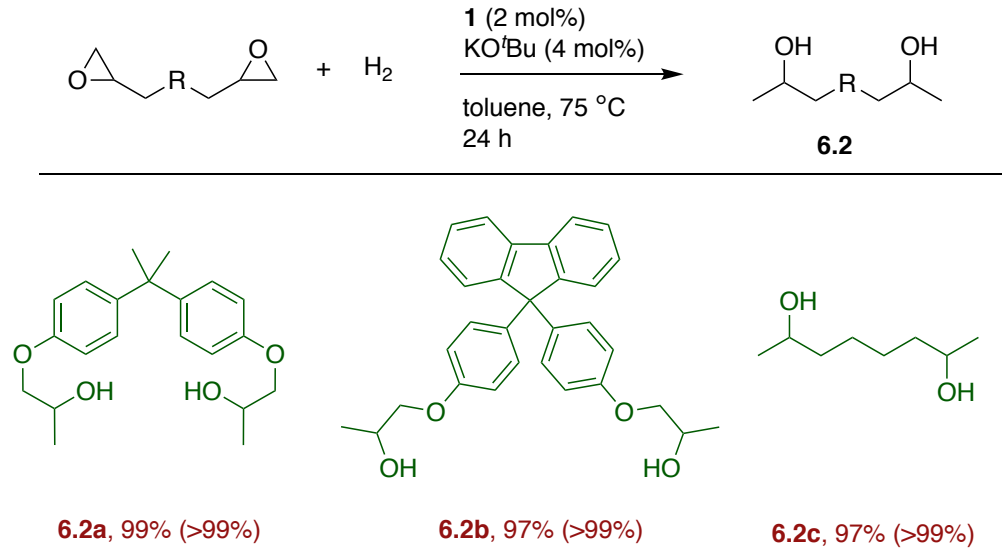
15[h]			**6.1p**	>99	98
16[h]			**6.1q**	>99	99
17[h]			**6.1q**	>99	99
18[h]			**6.1r**	>99	98
19[h]			**6.1s**	67	62
20[h,i]			**6.1t**	>99	46

[a]Reaction conditions: epoxide (0.5 mmol), catalyst **1** (1 mol%) and KO^{t}Bu (2 mol%) and toluene (1.5 mL) were heated at 75 °C under 50 bar H_2 pressure for 24 h. [b]Conversion of epoxides determined by GC analysis using benzene as an internal standard. [c]Reported yields correspond to isolated pure compounds. [d]Isolated as a mixture of 6.1a and 6.1b (94:6). [e]10% of primary alcohol is isolated. [f]26% of primary alcohol isolated. [g]Reaction was performed using 3 mol% of catalyst and 6 mol% of base at 100 °C. [h]Reaction was performed using 5 mol% of catalyst **1** and 10 mol% of base at 100 °C. [i]42% of primary alcohol was isolated.

To further expand the scope of the protocol, I turned our attention to diepoxides. Interestingly, aromatic and aliphatic diepoxides provided quantitative conversion and yield with complete formation of the corresponding secondary diols (Scheme 6.2). The products are isolated as mesomers due to presence of C_2 symmetry. In contrast to

previous reports the exclusive regioselectivity to secondary alcohols make this process a new green alternative for the synthesis of diols.[6]

Scheme 6.2 Scope of Regioselective Hydrogenation of Terminal Diepoxides Catalyzed by 1[a]

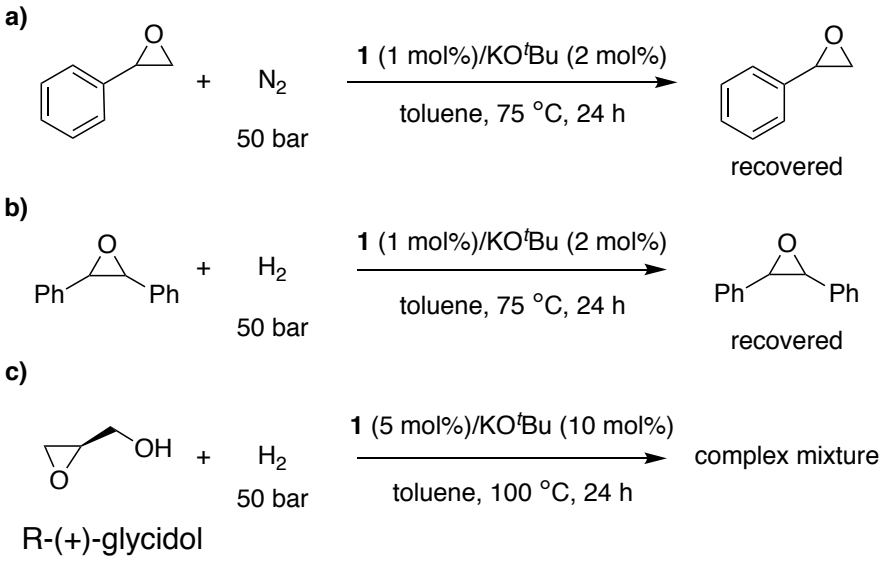


[a]Reaction conditions: diepoxide (0.5 mmol), catalyst **1** (2 mol%) and KO^{t}Bu (4 mol%) and toluene (1.5 mL) were heated at 75 °C under 50 bar H_2 pressure for 24 h. Conversion of diepoxides determined by GC analysis using benzene as an internal standard is given within parentheses. Reported yields correspond to isolated pure compound. [b]Reaction was performed using 10 mol% of catalyst and 20 mol% of base at 100 °C.

Towards understanding the reaction mechanism, reaction with N_2 gas (50 bar) was performed (devoid of hydrogen) in which no epoxide ring opening was occurred (Scheme 6.3a). The absence of isomerization of epoxide to ketone confirms the reaction do not proceed via Meinwald rearrangement.[16] This result indicates the importance of H_2 gas in the initial formation of ruthenium dihydride intermediate **II** and its role in the selective epoxide ring opening reactions. Notably, internal epoxides did not undergo

ring opening under the optimized reaction conditions (Scheme 6.3b). An enantiopure chiral epoxide R-(+)-glycidol was subjected in our catalysis, which provided a complex mixture (Scheme 6.3c).

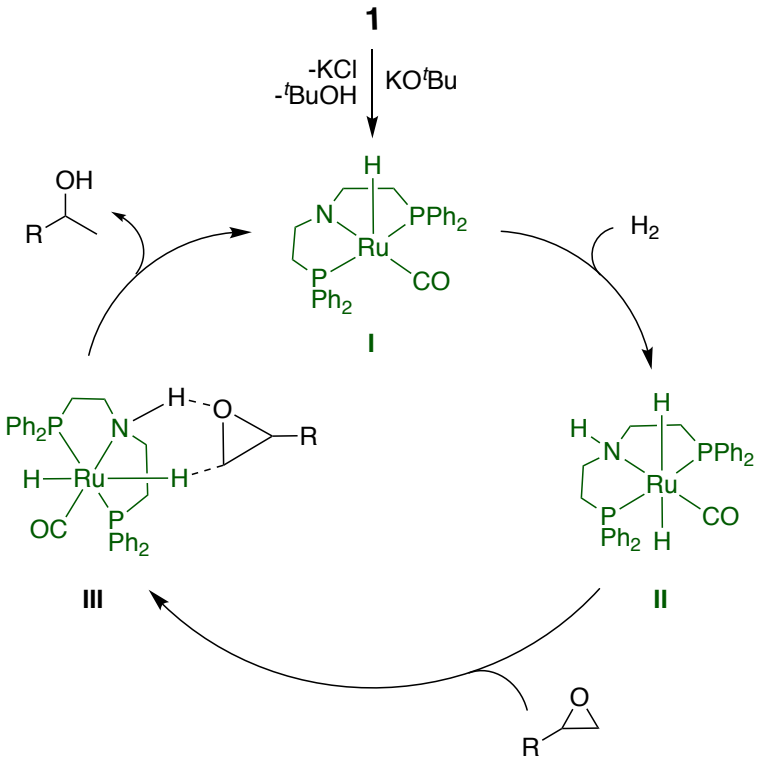
Scheme 6.3 Mechanistic Studies for the Hydrogenation of Terminal Epoxides Catalyzed by 1



On the basis of these experimental observations and our previous reports[12-15,17] involving catalyst **1**, a catalytic cycle for regioselective ring opening of epoxides to secondary alcohols is proposed (Scheme 6.4). The catalyst **1** in the presence of base is converted into reactive unsaturated intermediate **I**.[17b,18] Heterolytic activation of H_2 by **I** involving amine-amide metal-ligand cooperation leads to the formation of saturated ruthenium dihydride intermediate **II**.[19] Perhaps the formation of intermediate **III** upon reaction of **II** with epoxide preferably involves less substituted carbon and oxygen centers of terminal epoxide. Hydrogen pressure is also plays important role in the conversion of epoxide as well as product selectivity. At 10 bar hydrogen pressure, only 40% conversion of epoxide occurred, in which the considerable amount of anti-Markovnikov primary alcohol was formed in 20% (Table 6.1, entry 1) indicating the

involvement of other mechanistic pathways at low pressure. Whereas use of 50 bar hydrogen pressure provided the complete conversion and very high selectivity for the Markovnikov secondary alcohols (Table 6.1, entries 3,9 and Table 6.2) indicating that the high hydrogen pressure is essential for the effective formation of ruthenium dihydride intermediate **II** and its further selective reaction with epoxide. Notably, internal epoxide failed to undergo ring opening when subjected to catalysis (Scheme 6.2b). Thus, preferential approach of metal hydride to less substituted terminal carbon of epoxide, precluding the internal tertiary carbon and interaction of acidic amine proton to epoxide oxygen leads to the selective formation of intermediate **III**. On **III**, metal-hydride and amine proton are concomitantly transferred to epoxide through a six-membered cyclic transition state, resulting in the selective formation of secondary alcohol and regeneration of active intermediate **I** to complete a catalytic cycle.

Scheme 6.4 Plausible Mechanism for the Selective Hydrogenation of Epoxides Catalyzed by 1



6.4 CONCLUSIONS

In conclusion, a ruthenium catalyzed highly Markovnikov selective hydrogenation of epoxides is demonstrated. The catalyst exhibits superior reactivity to control regioselectivity with a wide substrate scope. Diverse aromatic, benzylic, glycidyl, aliphatic terminal epoxides and also diepoxides were well tolerated to provide secondary alcohol products in good to excellent yields. Interestingly, this transformation contrasts the recently reported catalytic anti-Markovnikov selective hydrogenation of epoxides and compliments the efficient and selective synthesis of secondary alcohols from epoxides.[11] Metal-ligand cooperation mediated dihydrogen activation to ruthenium trans-dihydride formation and its preferential reaction with oxygen and less substituted terminal carbon of epoxide is suggested to be the origin of observed Markovnikov selectivity. Concomitant transfer of amine proton and metal-hydride to epoxide through a six-membered cyclic transition state is proposed to provide the selective formation of secondary alcohols. Synthetic utilities of such mechanistic pathway are currently under investigation.

6.5 EXPERIMENTAL SECTION

General Experimental: All catalytic reactions were performed in H_2 atmosphere using Buchi tinyclave steel vessel with a Teflon sleeve (25 mL) high-pressure reactors. All stoichiometric reactions were performed in nitrogen atmosphere MBRAUN glove box. Ru-MACHO **[Carbonylchlorohydrido{bis[2-(diphenylphosphinomethyl)ethyl]amino}ethyl]amino} ruthenium(II)]** and KO^{t}Bu were purchased from Sigma-Aldrich and stored inside glove box. Epoxides were purchased from Acros, Sigma-Aldrich, Alfa-aesar, TCI chemicals and used without further purification. Epoxides required for the secondary alcohol products **6.1c**, **6.1d** and **6.1t** were prepared by epoxidation of corresponding alkenes using *m*-CPBA.[11b] Dry

solvents were prepared according to standard procedures. Infrared (IR) spectra were recorded in Perkin-Elmer FT-IR and Thermo-Nicolet FT-IR spectrophotometers. Mass spectra (ESI-MS) were obtained on Bruker micrOTOF-Q II Spectrometer and are reported as m/z (relative intensity). Nuclear magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded at Bruker AV-400 and JEOL-400 (^{1}H at 400 MHz, ^{13}C at 100.6 MHz). ^{1}H NMR chemical shifts are referenced in parts per million (ppm) with respect to tetramethyl silane (TMS) (δ 0.00 ppm) and ^{13}C {^{1}H} NMR chemical shifts are referenced in parts per million (ppm) with respect to $CDCl_3$ (δ 77.160 ppm). Coupling constants are reported in Hertz (Hz). ^{1}H NMR spectroscopy abbreviations: s, Singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; dt, doublet of triplets; dq, doublet of quartets; td, triplet of doublets; qd, quartets of doublets; ddd, doublets of doublets of doublets; m, multiplet; br, broad. Assignment of spectra was done based on one-dimensional (DEPT-135) NMR techniques.

GC Method: Gas chromatography data were obtained using a gas chromatograph equipped with a SH-Rtx-1 capillary column (30 m × 250 μm). The instrument was set to an injection volume of 1 μL, an inlet split ratio of 10:1, and inlet and detector temperatures of 300 and 330 °C, respectively. The temperature program used for all of the analyses is as follows: 50 °C, 1 min; 12 °C/min to 320 °C, 7 min. Response factor for all of the necessary compounds with respect to standard benzene was calculated from the average of three independent GC runs.

General Optimization Procedure for Regioselective Hydrogenation of Styrene Oxide:

A Buchi tinyclave steel high-pressure reactor containing a Teflon sleeve (25 mL) was equipped with a stirring bar, catalyst **1** (0.01-0.005 mmol), base (0.02-0.01 mmol), styrene oxide (0.5 mmol) and toluene (1.5 mL) under nitrogen atmosphere inside the

glove box. The pressure reactor was taken out of the glove box, charged with H_2 and heated at indicated temperature (using preheated oil bath) with stirring for 24 h. After cooling to room temperature, the H_2 pressure was released. Benzene internal standard (0.5 mmol) was added into the reaction mixture. The conversion of styrene oxide was calculated using GC analysis. Further, the solvent was evaporated and crude reaction mixture was purified by column chromatography over silica-gel (100-200 mesh) using ethyl acetate/hexane mixture as an eluent. Yields were calculated for isolated pure products of **6.1a** and **6.1b**.

Procedure for 1 mmol Scale Reaction of Regioselective Hydrogenation of Styrene Oxide:

A Buchi tinyclave steel high-pressure reactor containing a Teflon sleeve (25 mL) was equipped with a stirring bar, catalyst **1** (0.01 mmol), base (0.02 mmol), styrene oxide (1 mmol) and toluene (1.5 mL) under nitrogen atmosphere inside the glove box. The pressure reactor was taken out of the glove box, charged with H_2 (50 bar) and heated at indicated temperature (using preheated oil bath) with stirring for 24 h. After cooling to room temperature, the H_2 pressure was released. Benzene internal standard (1 mmol) was added into the reaction mixture. The conversion of styrene oxide was calculated using GC analysis. Further, the solvent was evaporated and crude reaction mixture was purified by column chromatography over silica-gel (100-200 mesh) using ethyl acetate/hexane mixture as an eluent. The reaction provided a complete conversion of styrene oxide and 97 % yield isolated as the mixtures **6.1a** and **6.1b** (94:6 selectivity).

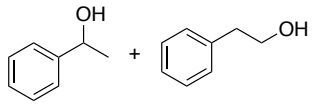
General Procedure for Regioselective Hydrogenation of Epoxides:

A Buchi tinyclave steel high-pressure reactor containing a Teflon sleeve (25 mL) was equipped with a stirring bar, catalyst **1** (0.01 mmol), base (0.02 mmol), epoxide (0.5 mmol) and toluene (1.5 mL) under nitrogen atmosphere inside the glove box. The

pressure reactor was taken out of the glove box, charged with H_2 gas (50 bar) and heated at 75 °C (using preheated oil bath) with stirring for 24 h. After cooling to room temperature, the H_2 pressure was released. Benzene internal standard (0.5 mmol) was added into the reaction mixture. The conversion of epoxides was calculated using GC analysis. Further, the solvent was evaporated and crude reaction mixture was purified by column chromatography over silica-gel (100-200 mesh) using ethyl acetate/hexane mixture as an eluent. Yields were calculated for isolated pure products.

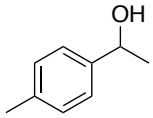
Spectral Data of the Secondary Alcohol Products:

1-Phenylethan-1-ol (6.1a):[20] Purified by silica gel column chromatography using ethyl acetate/hexane (20:80) mixture as an eluent. Colorless liquid. Isolated as a mixture of isomers **6.1a** and **6.1b**, ca. 96:4 ratio. Yield: 60 mg, 99% (for 0.5 mmol scale) and 118 mg, 97% (for 1 mmol scale). IR (DCM): 3413, 3054, 2976, 1452, 1265, 896, 745 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.14-7.26 (m, 5H, ArC*H*), 4.74 (q, *J* = 6.4 Hz, 1H, C*H*-isomer-A), 3.69 (t, *J* = 6.6 Hz, 2H, CH_2-isomer-B), 2.72 (t, *J* = 6.7 Hz, 2H, CH_2- isomer-B), 2.39 (s, 1H, O*H*), 1.36 (d, *J* = 6.5 Hz, 3H, CH_3-isomer-A). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 145.87, 128.47, 127.41, 125.42, 70.29, 63.56, 39.15, 25.15. MS (ESI) m/z calcd for $C_8H_{10}O$ $(M+H)^+$: 123.08, found: 123.08.



6.1a 6.1b

1-(*p*-Tolyl)ethan-1-ol (6.1c):[20] Purified by silica gel column chromatography using ethyl acetate/hexane (20:80) mixture as an eluent. Colorless liquid. Yield: 49 mg, 72%. IR (DCM): 3506, 3026, 2921, 1495, 1217, 911, 729 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.14 (d, *J* = 7.9 Hz, 2H, ArC*H*), 7.04 (d, *J* = 7.8 Hz, 2H, ArC*H*), 4.71 (q, *J* = 6.2 Hz, 1H, C*H*), 2.24 (s, 4H, Ar-CH_3 & O*H*), 1.35 (d, *J* = 6.4 Hz, 3H, CH_3). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 142.98, 137.08, 129.17, 125.44, 70.18, 25.11, 21.13. MS (ESI) m/z calcd for $C_9H_{12}O$ $(M+H)^+$: 137.09, found: 137.09.

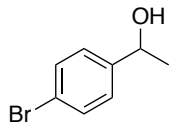


1-(4-(*tert*-Butyl)phenyl)ethan-1-ol (6.1d):[20] Purified by silica gel column chromatography using ethyl acetate/hexane (20:80) mixture as an eluent. Colorless liquid. Yield: 37.4 mg, 42%. IR (DCM): 3419, 3053, 2965, 1265, 1086, 741 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.28-7.33 (m, 2H, ArC*H*), 7.21-7.26 (m, 2H, ArC*H*), 4.80 (q, *J* = 6.5 Hz, 1H, C*H*), 1.83 (s, 1H, O*H*), 1.42 (d, *J* = 6.5 Hz, 3H, CH_3), 1.25 (s, 9H, 3×CH_3). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 150.59, 142.89, 125.54, 125.30, 70.32, 34.63, 31.48, 25.03. MS (ESI) m/z calcd for $C_{12}H_{18}O$ $(M+H)^+$: 179.14, found: 179.14.

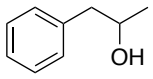
1-(4-Fluorophenyl)ethan-1-ol (6.1e):[20] Purified by silica gel column chromatography using ethyl acetate/hexane (20:80) mixture as an eluent. Colorless liquid. Yield: 67 mg, 96%. IR (DCM): 3425, 3052, 2963, 2905, 1259, 1089, 801, 746 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.22 (dd, J_1 = 7.8 Hz, J_2 = 5.8 Hz, 2H, ArC*H*), 6.92 (t, *J* = 8.6 Hz, 2H, ArC*H*), 4.76 (q, *J* = 6.4 Hz, 1H, C*H*), 2.21 (s, 1H, O*H*), 1.36 (d, *J* = 6.4 Hz, 3H, CH_3). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 163.41, 160.98, 141.64 (d, *J* = 3.1 Hz), 127.15 (d, *J* = 8.0 Hz), 115.31 (d, *J* = 21.3 Hz), 69.80, 25.33. MS (ESI) m/z calcd for C_8H_9FO $(M+H)^+$: 141.07, found: 141.07.

1-(4-Chlorophenyl)ethan-1-ol (6.1f):[20] Purified by silica gel column chromatography using ethyl acetate/hexane (20:80) mixture as an eluent. Colorless liquid. Yield: 31 mg, 40%. IR (DCM): 3446, 3053, 2985, 1492, 1265, 742, 735 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.18 (q, *J* = 8.3 Hz, 4H, ArC*H*), 4.72 (q, *J* = 6.4 Hz, 1H, C*H*), 2.39 (s, 1H, O*H*), 1.34 (d, *J* = 6.4 Hz, 3H, CH_3). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 144.33, 133.06, 128.63, 126.88, 69.70, 25.27. MS (ESI) m/z calcd for C_8H_9ClO $(M+H)^+$: 157.04, found: 157.04.

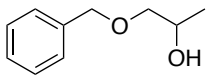
1-(4-Bromophenyl)ethan-1-ol (6.1g):[20] Purified by silica gel column chromatography using ethyl acetate/hexane (20:80) mixture as an eluent. Colorless liquid. Yield: 37 mg,

37%. IR (DCM): 3413, 3053, 2968, 2932, 1435, 1376, 1265, 746 cm^{-1}. 

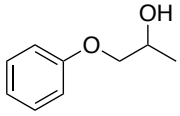
^1H NMR (400 MHz, $CDCl_3$): δ 7.34 (d, J = 8.0 Hz, 2H, ArC*H*), 7.10 (d, J = 8.1 Hz, 2H, ArC*H*), 4.70 (dd, J_1 = 11.0 Hz, J_2 = 4.7 Hz, 1H, C*H*), 2.48 (s, 1H, O*H*), 1.32 (d, J = 6.4 Hz, 3H, CH_3). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 144.78, 131.51, 127.19, 121.09, 69.65, 25.18. MS (ESI) m/z calcd for C_8H_9BrO $(M+H)^+$: 200.99, found: 200.99.

1-Phenylpropan-2-ol (6.1h):[6c] Purified by silica gel column chromatography using ethyl acetate/hexane (20:80) mixture as an eluent. Colorless liquid. Yield: 64.6 mg, 95%. IR (DCM): 3372, 3061, 2967, 2928, 1452, 1120, 741 cm^{-1}. 

^1H NMR (400 MHz, $CDCl_3$): δ 7.19-7.23 (m, 2H, ArC*H*), 7.10-7.15 (m, 3H, ArC*H*), 3.90 (ddd, J_1 = 7.7 Hz, J_2 = 6.2 Hz, J_3 = 5.1 Hz, 1H, C*H*), 2.63 (qd, J_1 = 13.4 Hz, J_2 = 6.4 Hz, 2H, CH_2), 1.81 (s, 1H, O*H*), 1.13 (d, J = 6.2 Hz, 3H, CH_3). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 138.65, 129.48, 128.58, 126.50, 68.91, 45.82, 22.80. MS (ESI) m/z calcd for $C_9H_{12}O$ $(M+H)^+$: 137.09, found: 137.09.

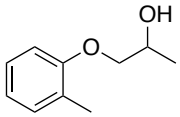
1-(Benzyloxy)propan-2-ol (6.1i):[10a] Purified by silica gel column chromatography using ethyl acetate/hexane (20:80) mixture as an eluent. Colorless liquid. Yield: 81 mg, 98%. IR (DCM): 3446, 3053, 2973, 2863, 1453, 1265, 1096, 743 cm^{-1}. 

^1H NMR (400 MHz, $CDCl_3$): δ 7.18-7.28 (m, 5H, ArC*H*), 4.45 (s, 2H, CH_2), 3.87-3.91 (s, 1H, C*H*), 3.35 (dd, J_1 = 9.4 Hz, J_2 = 3.2 Hz, 1H, CH_2), 3.19 (dd, J_1 = 9.4 Hz, J_2 = 8.0 Hz, 1H, CH_2), 2.69 (s, 1H, O*H*), 1.04 (d, J = 6.4 Hz, 3H, CH_3). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 138.01, 128.47, 127.78, 75.85, 73.28, 66.45, 18.73. MS (ESI) m/z calcd for $C_{10}H_{14}O_2$ $(M+H)^+$: 167.10, found: 167.10.

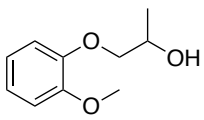
1-Phenoxypropan-2-ol (6.1j):[6c] Purified by silica gel column chromatography using ethyl acetate/hexane (20:80) mixture as an eluent. Colorless liquid. Yield: 74.5 mg, 98%. IR (DCM): 3392, 3054, 2937, 2856, 1447, 1265, 

895, 747 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.19 (t, *J* = 7.8 Hz, 2H, ArC*H*), 6.87 (t, *J* = 7.3 Hz, 1H, ArC*H*), 6.81 (d, *J* = 8.2 Hz, 2H, ArC*H*), 4.05-4.13 (m, 1H, C*H*), 3.82 (dd, J_1 = 9.2 Hz, J_2 = 3.0 Hz, 1H, CH_2), 3.68-3.72 (m, 1H, CH_2), 2.55 (s, 1H, O*H*), 1.18 (d, *J* = 6.4 Hz, 3H, CH_3). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 158.64, 129.58, 121.16, 114.64, 73.29, 66.30, 18.87. MS (ESI) m/z calcd for $C_9H_{12}O_2$ $(M+H)^+$: 153.09, found: 153.09.

1-(*o*-Tolyloxy)propan-2-ol (6.1k):[21] Purified by silica gel column chromatography using ethyl acetate/hexane (20:80) mixture as an eluent. Colorless liquid. Yield: 80.6 mg, 97%. IR (DCM): 3421, 3052, 2975, 2928, 1495, 1265, 1051, 741 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.02-7.10 (m, 2H, ArC*H*), 6.79 (td, J_1 = 7.4 Hz, J_2 = 1.0 Hz, 1H, ArC*H*), 6.68-6.75 (m, 1H, ArC*H*), 4.04-4.23 (m, 1H, C*H*), 3.83 (dd, J_1 = 9.2 Hz, J_2 = 3.5 Hz, 1H, CH_2), 3.71 (dd, J_1 = 9.2 Hz, J_2 = 7.4 Hz, 1H, CH_2), 2.46 (s, 1H, O*H*), 2.15 (s, 3H, CH_3), 1.21 (d, *J* = 6.4 Hz, 3H, CH_3). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 156.65, 130.85, 126.94, 126.77, 120.87, 111.27, 73.31, 66.49, 18.96, 16.33. MS (ESI) m/z calcd for $C_{10}H_{14}O_2$ $(M+H)^+$: 167.10, found: 167.10.



1-(2-Methoxyphenoxy)propan-2-ol (6.1l):[22] Purified by silica gel column chromatography using ethyl acetate/hexane (20:80) mixture as an eluent. Colorless liquid. Yield: 61 mg, 67%. IR (DCM): 3485, 2971, 2931, 2837, 1732, 1504, 1027, 742 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 6.80-6.91 (m, 4H, ArC*H*), 4.08-4.13 (m, 1H, C*H*), 3.92 (dd, J_1 = 9.7 Hz, J_2 = 3.0 Hz, 1H, CH_2), 3.77 (s, 3H, OCH_3), 3.72 (dd, J_1 = 9.6 Hz, J_2 = 8.4 Hz, 1H, CH_2), 2.95 (s, 1H, O*H*), 1.16 (d, *J* = 6.4 Hz, 3H, CH_3). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 150.00, 148.27, 122.20, 121.15, 115.38, 112.04, 75.93, 66.05, 55.90, 18.50. MS (ESI) m/z calcd for $C_{10}H_{14}O_3$ $(M+H)^+$: 183.10, found: 183.10.



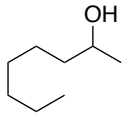
1-(4-Methoxyphenoxy)propan-2-ol (6.1m):[23] Purified by silica gel column chromatography using ethyl acetate/hexane (20:80) mixture as an eluent. Colorless liquid. Yield: 88 mg, 97%. IR (DCM): 3586, 3053, 2934, 2835, 1508, 1265, 1041, 741 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 6.74-6.79 (m, 4H, ArC*H*), 4.07-4.12 (m, 1H, C*H*), 3.82 (dd, J_1 = 9.2 Hz, J_2 = 2.9 Hz, 1H, CH_2), 3.65-3.69 (m, 4H, OCH_3 & CH_2), 2.37 (s, 1H, O*H*), 1.19 (d, J = 6.4 Hz, 3H, CH_3). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 154.24, 152.87, 115.72, 114.82, 74.23, 66.45, 55.85, 18.83. MS (ESI) m/z calcd for $C_{10}H_{14}O_3$ $(M+H)^+$: 183.10, found: 183.10.

1-(2,4-Dibromophenoxy)propan-2-ol (6.1n):[24] Purified by silica gel column chromatography using ethyl acetate/hexane (20:80) mixture as an eluent. Colorless liquid. Yield: 101 mg, 65%. IR (DCM): 3521, 3054, 2983, 2853, 1734, 1244, 1047, 911, 735 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.60 (d, J = 2.4 Hz, 1H, ArC*H*), 7.29 (dd, J_1 = 8.7 Hz, J_2 = 2.4 Hz, 1H, ArC*H*), 6.70 (d, J = 8.7 Hz, 1H, ArC*H*), 4.16 (dqd, J_1 = 13.0 Hz, J_2 = 6.5 Hz, J_3 = 3.2 Hz, 1H, C*H*), 3.92 (dd, J_1 = 9.1 Hz, J_2 = 3.2 Hz, 1H, CH_2), 3.74 (dd, J_1 = 9.0 Hz, J_2 = 7.5 Hz, 1H, CH_2), 2.10 (s, 1H, O*H*), 1.23 (d, J = 6.4 Hz, 3H, CH_3). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 154.26, 135.52, 131.34, 114.83, 113.61, 113.32, 74.86, 66.09, 18.64. MS (ESI) m/z calcd for $C_9H_{10}Br_2O_2$ $(M+H)^+$: 308.91, found: 308.91

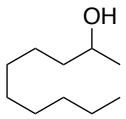
1-([1,1'-Biphenyl]-2-yloxy)propan-2-ol (6.1o):[25] Purified by silica gel column chromatography using ethyl acetate/hexane (20:80) mixture as an eluent. Colorless liquid. Yield: 112 mg, 98%. IR (DCM): 3582, 3053, 2983, 1583, 1434, 1265, 744 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.37-7.40 (m, 2H, ArC*H*), 7.24-7.29 (m, 2H, ArC*H*), 7.14-7.21 (m, 3H, ArC*H*), 6.89-6.94 (m, 1H, ArC*H*), 6.82 (d, J = 8.2 Hz, 1H, ArC*H*), 3.84-3.90 (m, 1H, C*H*), 3.78 (dd, J_1 = 9.2 Hz, J_2 = 3.5 Hz, 1H, CH_2), 3.58-3.63 (m, 1H, CH_2), 2.24 (s, 1H, O*H*), 1.02 (dd, J_1 =

6.4 Hz, J_2 = 2.0 Hz, 3H, CH_3). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 155.44, 138.45, 131.37, 130.89, 129.47, 128.73, 128.09, 127.05, 121.58, 113.31, 74.20, 66.12, 18.72. MS (ESI) m/z calcd for $C_{15}H_{16}O_2$ $(M+H)^+$: 229.12, found: 229.12.

Octan-2-ol (6.1p):[26] Purified by silica gel column chromatography using ethyl acetate/hexane (20:80) mixture as an eluent. Colorless liquid. Yield: 64 mg, 98%. IR (DCM): 3430, 3052, 2987, 1460, 1267, 747 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.68-3.76 (m, 1H, C*H*), 1.85 (s, 1H, O*H*), 1.32-1.41 (m, 2H, CH_2), 1.22-1.30 (m, 8H, CH_2), 1.11 (dd, J_1 = 6.2 Hz, J_2 = 0.6 Hz, 3H, CH_3), 0.81 (t, J = 6.7 Hz, 3H, CH_3). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 68.31, 39.51, 31.96, 29.44, 25.86, 23.60, 22.73, 14.20. MS (ESI) m/z calcd for $C_8H_{18}O$ $(M+H)^+$: 131.14, found: 131.14.



Decan-2-ol (6.1q):[26] Purified by silica gel column chromatography using ethyl acetate/hexane (20:80) mixture as an eluent. Colorless liquid. Yield: 78 mg, 99%. IR (DCM): 3432, 3052, 2928, 2855, 1466, 1264, 909, 731 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.67-3.72 (m, 1H, C*H*), 1.79 (s, 1H, O*H*), 1.31-1.38 (m, 2H, CH_2), 1.20-1.26 (m, 12H, CH_2), 1.10 (d, J = 6.1 Hz, 3H, CH_3), 0.81 (t, J = 6.7 Hz, 3H, CH_3). ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$): δ 68.15, 39.45, 31.97, 29.76, 29.68, 29.37, 25.88, 23.50, 22.75, 14.16. MS (ESI) m/z calcd for $C_{10}H_{22}O$ $(M+H)^+$: 159.17, found: 159.17.



Dodecan-2-ol (6.1r):[26] Purified by silica gel column chromatography using ethyl acetate/hexane (20:80) mixture as an eluent. Colorless liquid. Yield: 91 mg, 98%. IR (DCM): 3446, 3053, 2927, 2854, 1436, 1263, 895, 720 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.69-3.76 (m, 1H, C*H*), 1.96 (s, 1H, O*H*), 1.22-1.46 (m, 17H, CH_2), 1.13 (dd, J_1 = 6.2 Hz, J_2 = 0.9 Hz, 3H, CH_3), 0.84 (t, J = 6.8 Hz, 3H, CH_3). ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$): δ 68.10, 39.44, 31.99, 29.76, 29.71,

29.42, 25.87, 23.47, 22.75, 14.15. MS (ESI) m/z calcd for $C_{12}H_{26}O$ $(M+H)^+$: 187.20, found: 187.20.

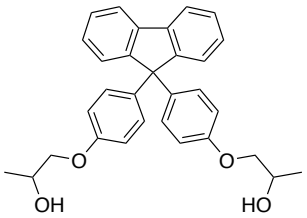
Hexadecan-2-ol (6.1s):[27] Purified by silica gel column chromatography using ethyl acetate/hexane (20:80) mixture as an eluent. Colorless liquid. Yield: 75 mg, 62%. IR (DCM): 3447, 3053, 2927, 2854, 1421, 1265, 895, 738 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.66-3.77 (m, 1H, C*H*), 1.49 (s, 1H, O*H*), 1.30-1.42 (m, 2H, CH_2), 1.19-1.26 (m, 23H, CH_2), 1.11 (d, J = 6.2 Hz, 3H, CH_3), 0.81 (t, J = 6.9 Hz, 3H, CH_3). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 68.32, 39.52, 32.06, 29.80, 29.50, 25.92, 23.59, 22.83, 14.24. MS (ESI) m/z calcd for $C_{16}H_{34}O$ $(M+H)^+$: 243.27, found: 243.27.

2-Phenylpropan-2-ol (6.1t):[28] Purified by silica gel column chromatography using ethyl acetate/hexane (20:80) mixture as an eluent. Colorless liquid. Yield: 31.2 mg, 46%. IR (DCM): 3447, 3058, 3003, 1450, 1267, 895, 747, 703 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.37 -7.39 (m, 2H, ArC*H*), 7.23 (t, J = 7.6 Hz, 2H, ArC*H*), 7.13 (t, J = 7.3 Hz, 1H, ArC*H*), 2.05 (s, 1H, O*H*), 1.47 (s, 6H, CH_3). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 149.22, 128.26, 126.72, 124.48, 72.56, 31.77. MS (ESI) m/z calcd for $C_9H_{12}O$ $(M+H)^+$: 136.08, found: 136.08.

1,1'-((Propane-2,2-diylbis(4,1-phenylene))bis(oxy))bis(propan-2-ol) (6.2a):[29] Purified by silica gel column chromatography using ethyl acetate/hexane (20:80) mixture as an eluent. Colorless liquid. Yield: 170.5 mg, 99%. IR (DCM): 3438, 3052, 2971, 2932, 1607, 1510, 1249, 1306, 744 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.03-7.07 (m, 4H, ArC*H*), 6.70-6.75 (m, 4H, ArC*H*), 4.06-4.10 (m, 2H, C*H*), 3.82 (dd, J_1 = 9.3 Hz, J_2 = 3.3 Hz, 2H, CH_2), 3.69 (dd, J_1 = 9.3 Hz, J_2 = 7.7 Hz, 2H, CH_2), 2.48 (s, 2H, O*H*), 1.55 (s, 6H, CH_3), 1.18 (d, J = 6.4 Hz, 6H, CH_3). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 156.50,

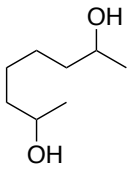
143.66, 127.88, 114.05, 73.37, 66.36, 41.82, 31.13, 18.87. MS (ESI) m/z calcd for $C_{21}H_{28}O_4$ $(M+H)^+$: 345.20, found: 345.20.

1,1'-(((9*H*-Fluorene-9,9-diyl)bis(4,1-phenylene))bis(oxy))bis(propan-2-ol) (6.2b):[30]



Purified by silica gel column chromatography using ethyl acetate/hexane (20:80) mixture as an eluent. Colorless white solid. Yield: 226 mg, 97%. IR (DCM): 3433, 3053, 2977, 2929, 1507, 1265, 1038, 739 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.66 (d, *J* = 7.4 Hz, 2H, ArC*H*), 7.26 (dd, J_1 =14.6 Hz, J_2 =7.5 Hz, 4H, ArC*H*), 7.17 (t, *J* = 7.3 Hz, 2H, ArC*H*), 7.03 (d, *J* = 8.6 Hz, 4H, ArC*H*), 6.67 (d, *J* = 8.6 Hz, 4H, ArC*H*), 3.95-4.23 (m, 2H, C*H*), 3.78 (dd, J_1= 9.2 Hz, J_2 = 2.9 Hz, 2H, CH_2), 3.64 (t, *J* = 8.5 Hz, 2H, CH_2), 2.29 (s, 2H, O*H*), 1.16 (d, *J* = 6.3 Hz, 6H, CH_3). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 157.42, 151.79, 140.06, 138.70, 129.34, 127.83, 127.50, 126.09, 120.28, 114.31, 73.34, 66.36, 64.27, 18.85. MS (ESI) m/z calcd for $C_{31}H_{30}O_4$ $(M+H)^+$: 467.22, found: 467.22.

Octane-2,7-diol (6.2c):[6c] Purified by silica gel column chromatography using ethyl



acetate/hexane (20:80) mixture as an eluent. Colorless liquid. Yield: 71 mg, 97%. IR (DCM): 3470, 3052, 2987, 1572, 1267, 895, 747 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.67-3.70 (m, 2H, C*H*), 2.72 (s, 2H, O*H*), 1.23-1.41 (m, 8H, CH_2), 1.09 (dd, J_1 = 6.2 Hz, J_2 = 1.1 Hz, 6H, CH_3). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 67.73, 67.64, 39.16, 25.75, 25.66, 23.41. MS (ESI) m/z calcd for $C_8H_{18}O_2$ $(M+H)^+$: 147.14, found: 147.14

6.6 NOTES AND REFERENCES

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^{1}H and ^{13}C NMR Spectra of the Secondary Alcohol Products:

Figure 6.1 ^{1}H NMR spectrum of 1-phenylethan-1-ol (**6.1a**):

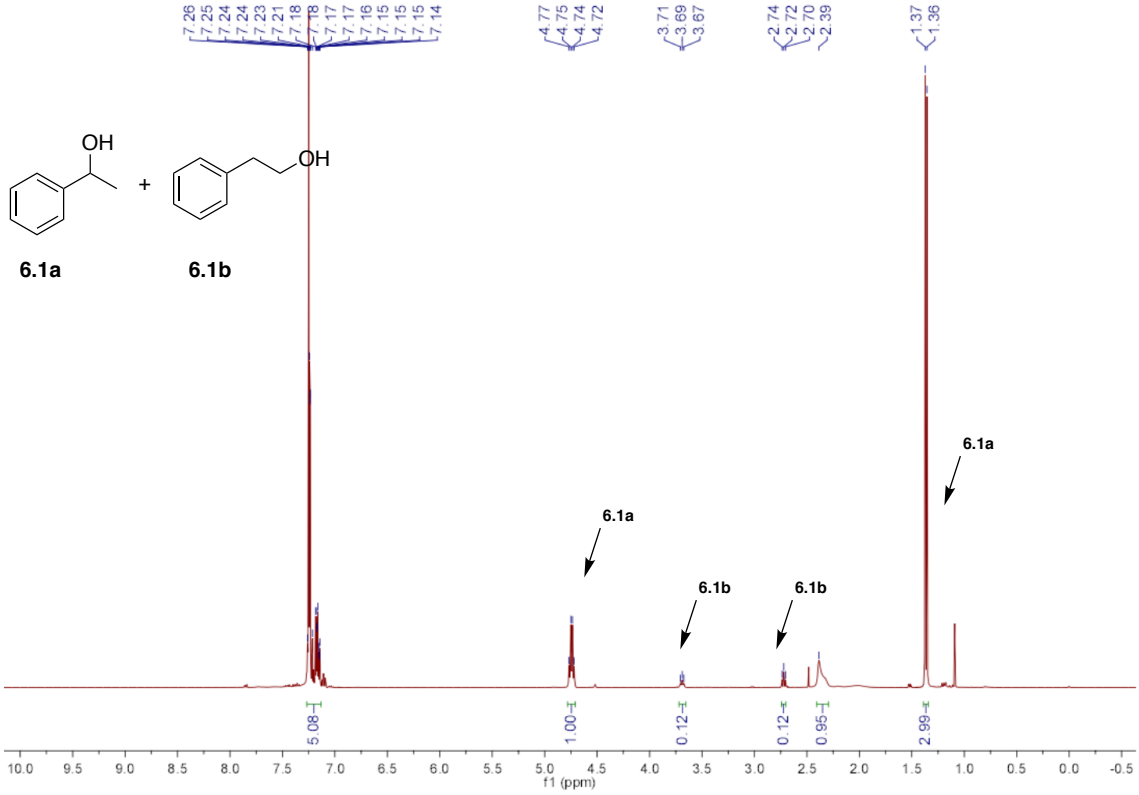


Figure 6.2 ^{13}C NMR spectrum of 1-phenylethan-1-ol (**6.1a**):

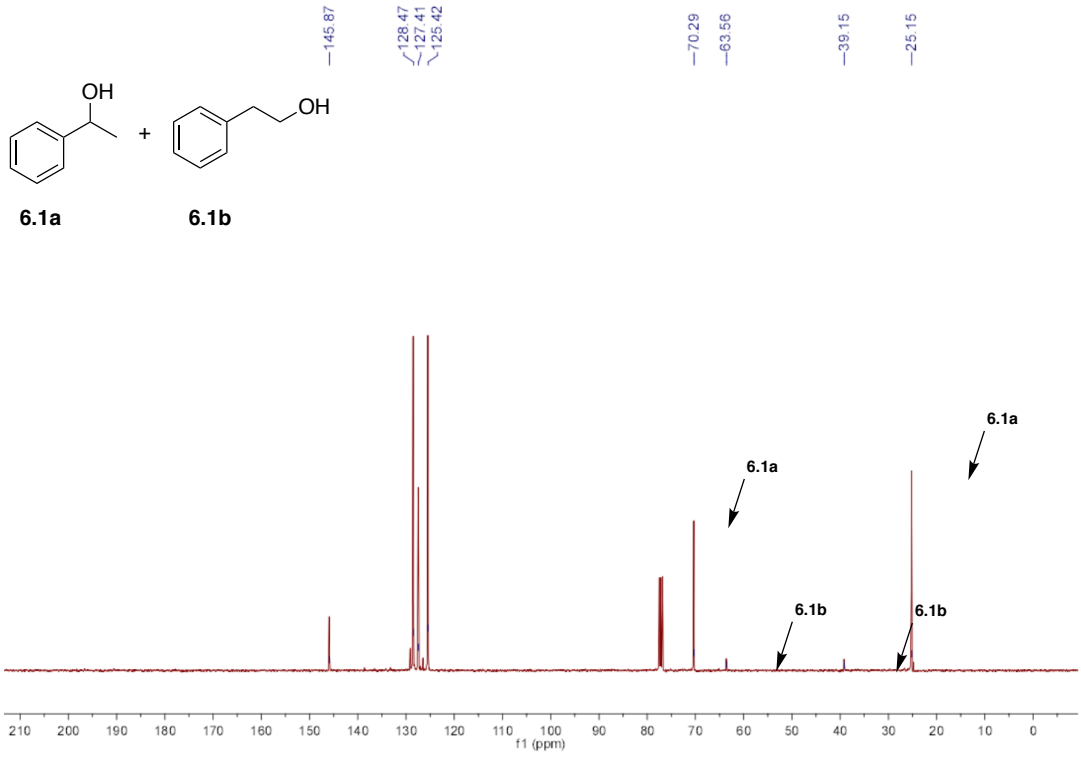


Figure 6.3 ^{1}H NMR spectrum of 1-(2-methoxyphenoxy)propan-2-ol (**6.1l**):

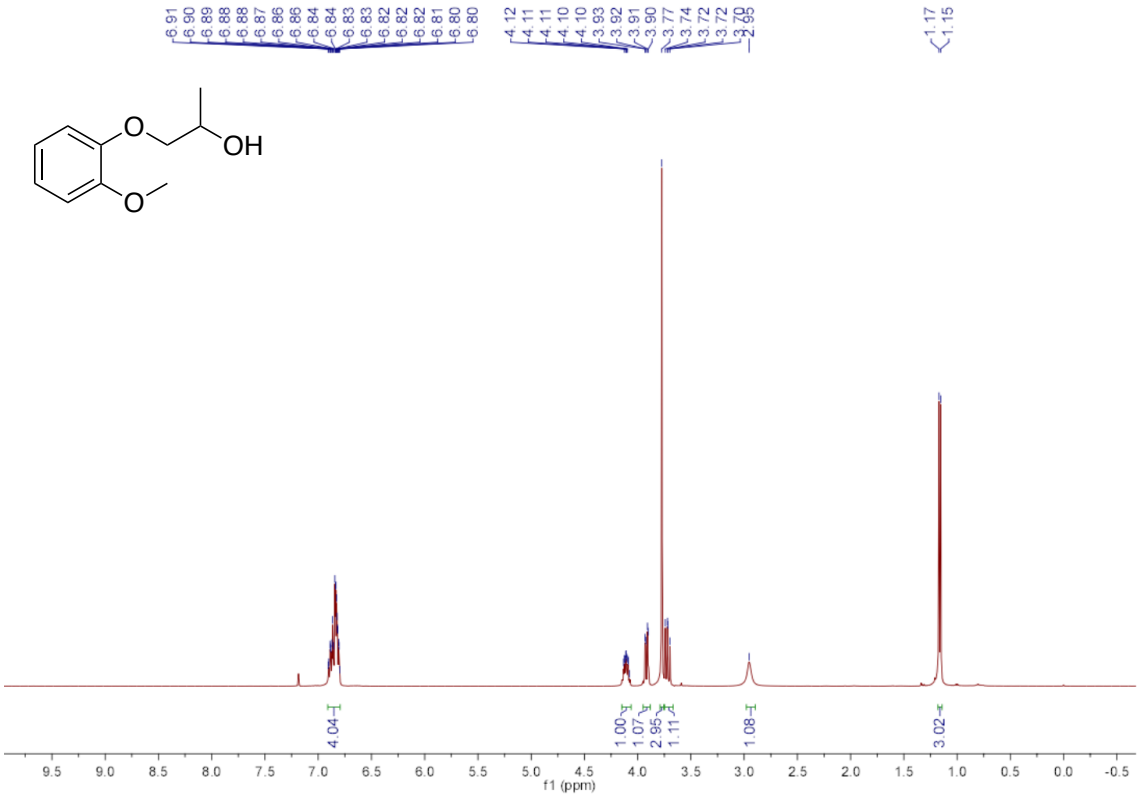


Figure 6.4 ^{13}C NMR spectrum of 1-(2-methoxyphenoxy)propan-2-ol (**6.1l**):

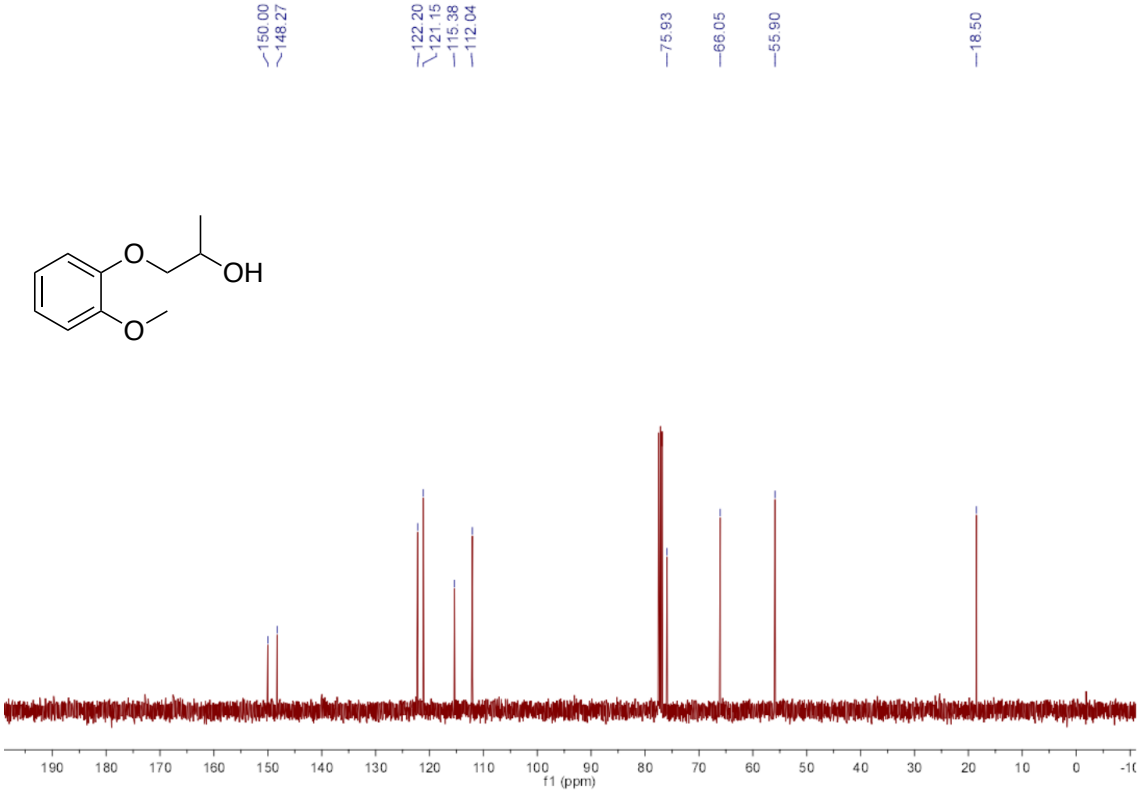


Figure 6.5 ^{1}H NMR spectrum of 1,1'-((propane-2,2-diylbis(4,1-phenylene))bis(oxy))bis(propan-2-ol) (**6.2a**):

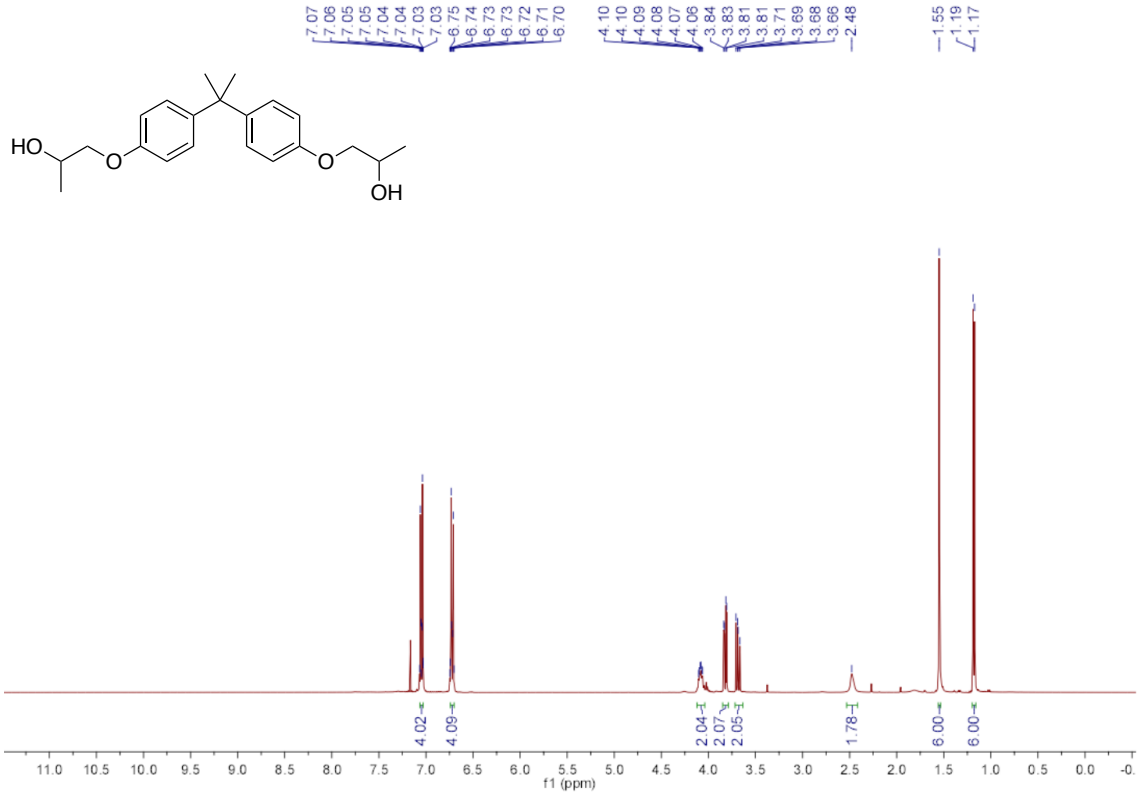
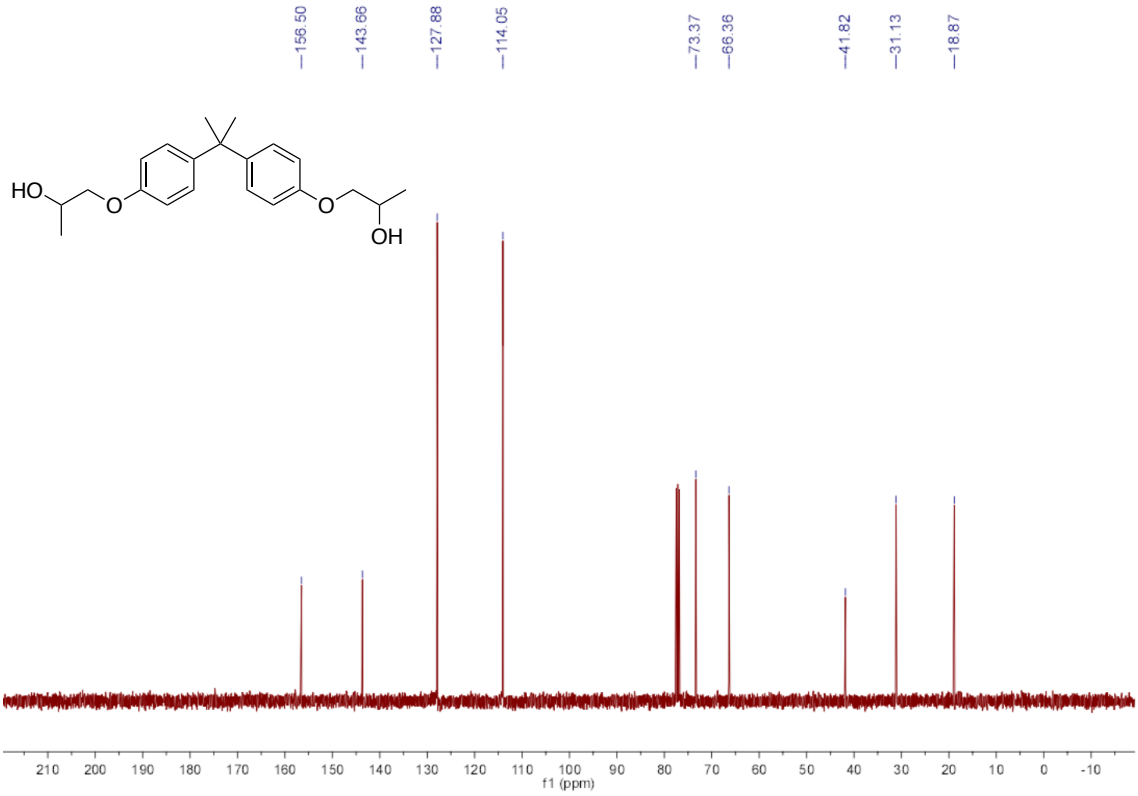


Figure 6.6 ^{13}C NMR spectrum of 1,1'-((propane-2,2-diylbis(4,1-phenylene))bis(oxy))bis(propan-2-ol) (**6.2a**):



Chapter 7

Conclusions

The activation of unreactive chemical bonds by transition metal complexes is an area of utmost importance. In this context, catalytic activation of C–H, N–H and O–H bonds via greener pathway is a challenging task. The classical methodology for the construction of C–C and C–X (X = H, O, N, S, halides, etc.) bonds involves enolate substitution reactions using organometallic reagents or organohalides. However, there are several disadvantages associated with these traditional synthetic methods, including handling of reactive and air-sensitive organometallic reagents and the production of copious salt-based waste during the course of the reactions. Thus, the development of green and sustainable chemical transformations using transition metal catalysis emerged as topic of interest chemical research and strongly desired. In the last two decades, pincer complexes-based catalysts have made tremendous impact in several fundamental chemical transformations and helped achieving greener procedures with high atom efficiency. Pincer ligands having planar framework with presence of bulky substituents on donor atoms covers much coordination sphere around the metal center, which offer control over vacant coordination sites and enhance stability of the resulting pincer complexes. Thus, pincer complexes possess unique balance of stability versus reactivity. As a result, "pincer complexes" once considered, as a favorite adventure for probing reaction mechanism by organometallic chemists became preferred catalysts for various challenging transformations in organic synthesis.

Chapter 1 covered the synthesis, reactivity and previous reports on catalysis by Ru-MACHO (**1**). The unusual reactivity in pincer complexes named, as "Metal-ligand

cooperation" has become an important concept in catalysis for various bond activation reactions in green catalytic pathway. Borrowing hydrogen methodology and acceptorless dehydrogenation concepts allow construction of both C–C and C–N bonds from alcohols and provide an efficient, atom-economical access to an assortment of useful products. On the basis of these two concepts, new C–C, C=C and C–N bond formation reactions were developed using catalyst **1**, which are presented in Chapters 2-6. Further, based on stoichiometric studies, characterization of transient intermediates and labeling experiments the plausible reaction mechanisms for the developed catalytic methods are presented.

Chapter 2 consists of a facile α-alkylation of arylmethyl nitriles with primary alcohols using ruthenium pincer catalyst **1**. An assortment of arylmethyl nitriles can be effectively alkylated using unactivated aliphatic primary alcohols, including challenging ethylation and methylation were also achieved. This green catalytic transformation follows the principle of the borrowing hydrogen methodology and produced water as the only byproduct. Notably, secondary alcohols didn't undergo alkylation reactions. When deuterium-labeled alcohol was used, the expected deuterium transposition occurred, provided both α-alkylation and α-deuteration of arylmethyl nitriles. Further, consumption of nitrile was monitored by GC, which indicated the involvement of first order kinetics. Experimental evidences are suggested the possible mechanistic pathway. The ruthenium catalyst **1** reacts with base and generates an unsaturated reactive intermediate, which reacts with both nitriles and alcohols. Further, oxidation of alcohols to aldehydes and also formed a [2+2] cycloadduct with nitriles that tautomerizes to its enamine intermediate, which further undergo conjugate addition leading to condensation reactions. Subsequent hydrogenation of the intermediate vinyl nitriles (resulted from condensation reactions) provided the selective α-alkylated products.

Overall, an efficient α-alkylation of nitriles using primary alcohols can be attributed to the amine-amide metal-ligand cooperation that is operative in the pincer catalyst **1**, which enables all the catalytic intermediates to remain in +2 oxidation state throughout the catalytic cycle.

In chapter 3, direct coupling of secondary alcohols with nitriles, which delivered β-disubstituted vinyl nitriles, was achieved. Arylmethyl nitriles, heteroarylmethyl nitriles and also aliphatic nitriles were directly coupled with cyclic, acyclic as well as symmetrical and unsymmetrical secondary alcohols, which resulted β-disubstituted vinyl nitriles in good to excellent yields. Notably, liberated H_2 and water are the only byproducts. The acceptorless dehydrogenation of nitriles and alcohols proceeds via amine-amide metal-ligand cooperation that occurs in the activated complex **1**. This new C=C bond formation proceeds through activation of the O–H bond of secondary alcohols via an unsaturated 16-electron intermediate ruthenium pincer complex **1**. Further condensation of in situ formed ketones reaction with nitriles provides expected vinyl nitrile products.

In chapter 4, an unprecedented direct cross coupling of two different secondary alcohols to β-disubstituted ketones was demonstrated. A variety of cyclic, acyclic, symmetrical and unsymmetrical secondary alcohols were selectively coupled with aromatic benzylic secondary alcohols to resulted ketone products. A single catalyst oxidizes both secondary alcohols to provide selectively β-disubstituted ketones. Number of bond activation and bond formation reactions occurs in selective sequence via amine-amide metal-ligand cooperation operative in catalyst **1**. Kinetic and deuterium-labeling experiments suggested that the aliphatic secondary alcohols oxidize faster than benzylic secondary alcohols, which selectively assimilating to provide the cross-coupled ketone products. Interestingly, this new C–C bond forming methodology produces H_2 and H_2O

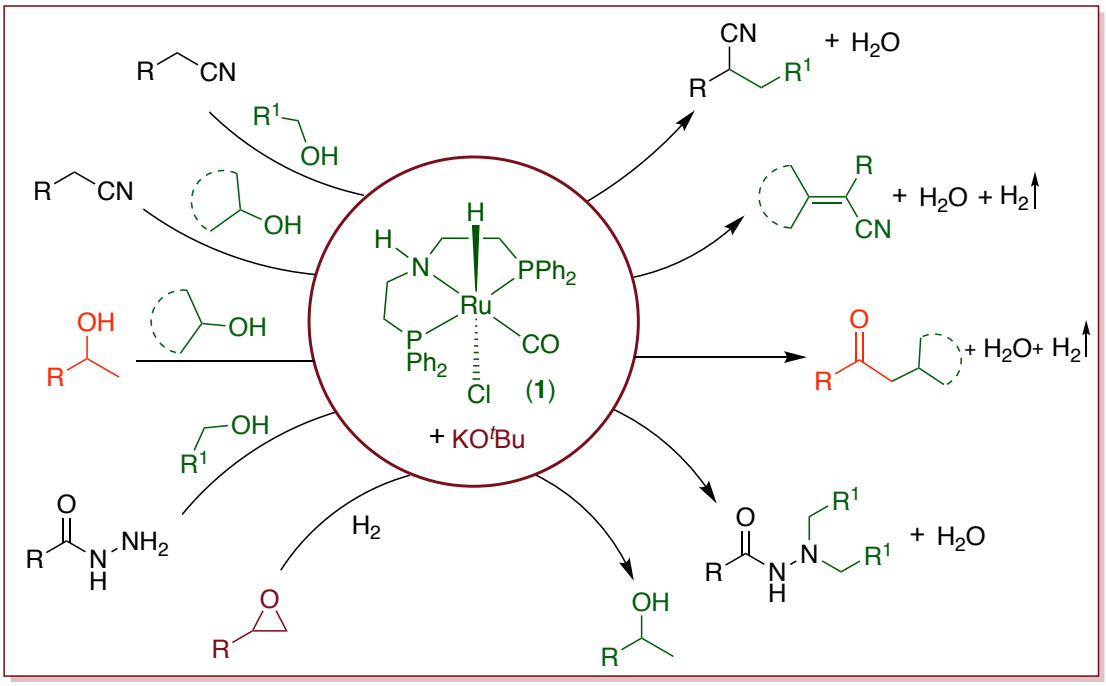
as the only byproducts, which make this protocol greener, atom economical and environmentally benign.

In chapter 5, an unprecedented direct N,N-dialkylation of acylhydrazides using alcohols was reported. This catalytic protocol employs catalyst **1** and provides one-pot synthesis of both symmetrical and unsymmetrical N,N-disubstituted acylhydrazides. Challenging diethylation and dimethylation reactions are performed using ethanol and methanol, respectively as alkylating reagents. Assortment of primary and secondary alcohols can be used with remarkable selectivity and the products were obtained in excellent yields. Interestingly, the use of diols resulted in intermolecular cyclization of acyhydrazides and such products are privileged structures in biologically active compounds. Further, one-pot synthesis of N,N-dialkylated acylhydrazides directly from ester via tandem reaction process also demonstrated. Preliminary mechanistic and deuterium labeling studies indicate that the reaction follows O–H bond activation of alcohols and hydrazone intermediates. Water is the only byproduct, which makes this catalytic protocol sustainable and environmentally benign.

In chapter 6, highly selective Markovnikov hydrogenation of terminal epoxides to secondary alcohols was reported. Diverse aromatic and aliphatic terminal epoxides underwent facile hydrogenation to secondary alcohols with exclusive selectivity and excellent yields. Interestingly, diepoxides also hydrogenated to diols in excellent yields. Notably, internal epoxides did not undergo hydrogenation reactions. Metal-ligand cooperation mediated dihydrogen activation to ruthenium trans-dihydride formation and its preferential reaction with oxygen and less substituted terminal carbon of the epoxide is suggested to be the origin of observed selectivity.

Overall, efficient atom economical and environmentally benign methods are discovered for the range of important products using Ru-MACHO pincer complex (**1**). It is evident

that metal–ligand cooperation stems from aliphatic amine backbone of pincer complex **1**, namely amine-amide metal-ligand cooperation is a powerful approach for bond activation and catalyst design. I believe that future research on amine-amide metal–ligand cooperation would enhance our understanding on fundamental bond activation processes, and also provide new opportunities for the design of sustainable catalytic reactions aimed at solving valuable synthetic problems.



Catalysis Based on Ruthenium Pincer Complexes

By

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Recommendations of the Viva Voce Committee

As members of the Viva Voce Committee, we certify that we have read the dissertation prepared by Mr. Thiyagarajan S entitled "Catalysis Based on Ruthenium Pincer Complexes" and recommend that it may be accepted as fulfilling the thesis requirement for the award of Degree of Doctor of Philosophy.

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S. Thiyagarajan

Thiyagarajan S

DECLARATION

I, hereby declare that the investigation presented in the thesis has been carried out by me. The work is original and has not been submitted earlier as a whole or in part for a degree / diploma at this or any other Institution / University.

S. Thiyagarajan

Thiyagarajan S

List of Publications arising from the thesis

Journal

1) "Facile Ruthenium(II)-Catalyzed α-Alkylation of Arylmethyl Nitriles Using Alcohols Enabled by Metal–Ligand Cooperation", **Thiyagarajan, S**.; Gunanathan, C., *ACS Catal.,* **2017**, *7*, 5483-5490.

2) "Ruthenium-Catalyzed α-Olefination of Nitriles Using Secondary Alcohols", **Thiyagarajan, S**.; Gunanathan, C., *ACS Catal.,* **2018**, *8*, 2473-2478.

3) "Catalytic Cross-Coupling of Secondary Alcohols", **Thiyagarajan, S**.; Gunanathan, C., *J. Am. Chem. Soc.,* **2019**, *141*, 3822-3827.

4) "Ruthenium-Catalyzed Direct Cross-Coupling of Secondary Alcohols to β-Disubstituted Ketones", **Thiyagarajan, S**.; Gunanathan, C., *Synlett*, **2019**, *30*, 2027-2034 *(Invited Synpacts article).*

5) "Ruthenium-Catalyzed Selective Hydrogenation of Epoxides to Secondary Alcohols", **Thiyagarajan, S**.; Gunanathan, C., *Org. Lett.,* **2019**, *21*, 9774-9778.

6) "Direct Catalytic Symmetrical, Unsymmetrical N,N-Dialkylation and Cyclization of Acylhydrazides Using Alcohols", **Thiyagarajan, S**.; Gunanathan, C., *Org. Lett.,* **2020**, *22*, 6617-6622.

Publications not included in the thesis

1) "Ruthenium(II)-Catalyzed Direct Synthesis of Ketazines Using Secondary Alcohols", Kishore, J.; **Thiyagarajan, S.;** Gunanathan, C., *Chem. Commun.,* **2019**, *55*, 4542-4545.

2) "KO^{t}Bu-Catalyzed Michael Addition Reactions Under Mild and Solvent-Free Conditions", **Thiyagarajan, S.;** Krishnakumar, V.; Gunanathan, C., *Chem. Asian. J.*, **2020**, *15*, 518- 523. *(Invited Article)*

3) "Ruthenium Catalyzed α-Alkylation of Ketones Using Secondary Alcohols to β-Disubstituted Ketones", **Thiyagarajan, S.;**† Vijaya Sankar, R.;† Gunanathan, C., *Org. Lett.*, **2020**, *22*, 7879-7884. (†equal contribution)

Conferences:

1) Thiyagarajan, S.; Gunanathan, C. *Ruthenium(II)-Catalyzed α-Alkylation and α -Olefination of Nitriles Using Alcohols.* "**XIV J-NOST Conference for Research Scholars**", Nov 28 -Dec 1, 2018, CSIR-IICT, Hyderabad, Telangana, India. **(Oral Presentation)**

2) Thiyagarajan, S.; Gunanathan, C. *Ruthenium-Catalyzed α-Alkylation and α-Olefination of Nitriles Using Alcohols.* "**ACS on Campus**", Jul 23, 2018. NISER, Bhubaneswar, India. **(Poster Presentation)**

3) Thiyagarajan, S.; Gunanathan, C. *Facile Ruthenium(II)-Catalyzed α-Alkylation of Arylmethyl Nitriles Using Alcohols Enabled by Metal-Ligand Cooperation.* "**Inter IISER & NISER Chemistry Meet (IINCM-2017)**", Dec 22-24, 2017. NISER, Bhubaneswar, India. Awarded 'Best Poster' of the symposium. **(Poster Presentation)**

S. Thyagarajan

Thiyagarajan S

Dedicated to....

To my parents

&

Dr. C. Gunanathan

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…Thiyagarajan S

SUMMARY

The thesis provides a detailed study on the catalytic application of Ru-Macho pincer catalyst. Metal-ligand cooperation operative in these catalytic systems and other catalytic applications reported in the literature are introduced in the first chapter. The second chapter describes the Ru-Macho catalyzed α-alkylation of arylmethyl nitriles using various primary alcohols. This green catalytic alkylation reactions in which alcohols are used as alkylating reagents are facilitated the metal-ligand cooperation. Water is the only byproduct in the reaction. On the basis of kinetic and mechanistic studies the possible mechanistic pathway is proposed.

A unique, ruthenium(II) pincer-catalyzed direct olefination nitrile compounds using secondary alcohols are presented in the chapter 3. An extensive substrate scope with arylmethyl nitriles, heteroaryl-methyl nitriles, and aliphatic nitriles as well as cyclic, acyclic, symmetrical, and unsymmetrical secondary alcohols are explored in the reaction, which provided diverse α-vinyl nitriles.

We describe the discovery of a new catalytic reaction, namely, the cross-coupling of secondary alcohols. Cyclic, acyclic, symmetrical, and unsymmetrical secondary alcohols are selectively coupled with aromatic benzylic secondary alcohols to provide β-disubstituted ketones products. The product-induced diastereoselectivity was observed. Kinetic and deuterium labeling experiments suggested that the aliphatic secondary alcohols undergo oxidation reaction faster than benzylic secondary alcohols, selectively assimilating to provide the cross-coupled products. Both olefination of nitrile and cross coupling of secondary alcohols produced H_2 and H_2O as the only byproducts, which make these catalytic protocols greener, atom economical and environmentally benign.

The direct N,N-dialkylation and cyclization of acylhydrazides using alcohols are developed in Chapter 5. This is new catalytic protocol, which provided one-pot synthesis of both symmetrical and unsymmetrical N,N-disubstituted acylhydrazides using variety of primary and secondary alcohols. Products were obtained in with remarkable selectivity and excellent yields. Notably, use of diols resulted in intermolecular cyclization of acylhydrazides. Involvements of hydrazone intermediate in these transformations are established through mechanistic studies.

In chapter 6, ruthenium(II)-catalyzed highly selective Markovnikov hydrogenation of terminal epoxides to secondary alcohols is presented. Benzylic, glycidyl, and aliphatic epoxides as well as diepoxides were subjected hydrogenation to provide secondary alcohols with exclusive selectivity to secondary alcohols. Metal−ligand cooperation-mediated ruthenium trans-dihydride formation and its selective reaction involving oxygen and the less substituted terminal carbon of the epoxide is proposed for the origin of the observed selectivity.

List of Schemes

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List of Abbreviations Used

Å	Angstrom
Anal.	Analytically
Anhyd	Anhydrous
aq	Aqueous
bp	Boiling Point
br	Broad
°C	Degree Celcius
Calcd	Calculated
cm	Centimeter
Conc	Concentrated
conv	Conversion
d	Doublet, Days

DCM	Dichloromethane
dd	Doublet of a Doublet
DMF	N,N-Dimethyl Formamide
eq	Equation
equiv	Equivalent
Et	Ethyl
g	Grams
h	Hours
HRMS	High-resolution Mass Spectrometry
IR	Infrared
K	Kelvin
kcal	Kilo calories
lit	Liter
m	Multiplet
M	Molar
MeCN	Acetonitrile
mp	Melting point
Me	Methyl
MHz	Mega Hertz
Min	Minutes
mL	Milliliter
mM	Millimolar
mmol	Millimole
mol	Mole
MS	Mass Spectra
N	Normal

NMR	Nuclear Magnetic Resonance
ppm	Parts per Million
rt	Room Temperature
s	Singlet, Seconds
TLC	Thin Layer Chromatography
TOF	Turn Over Frequency
TON	Turn Over Number
XRD	X-Ray Diffraction
NaOMe	Sodium methoxide
RCM	Ring Closing Metathesis

Table of Contents

CHAPTER 1

Introduction-Ru-MACHO Pincer Complexes and Their Reactivity

In general, the rate of chemical reactions can be accelerated by increasing the temperature, which requires high energy and therefore, it is very expensive. Moreover, high temperatures may also induce competing side reactions that will diminish yield of the desired products. Alternatively, chemical reactions can be accelerated using a catalyst. A catalyst participates in catalytic cycle by lowering the activation energy of the chemical process and the catalytically active species is regenerated upon completion of each catalytic cycle.[1] In the modern industrial world catalysis is a core area of contemporary science posing major fundamental and conceptual challenges. Catalysis plays an important role in the manufacturing of synthetic fibers and plastics, in petroleum refineries, production of different chemicals and synthesis of medicines and pharmaceuticals. Also, catalysis helps in the suppression of atmospheric pollution through environmental friendly technologies, and in the pursuit of new ways to generate energy.[2] Moreover, catalysis is essential for the sustainable development and is a key technology in achieving sustainability goals in chemical synthesis. Thus, catalysis is considered as pillar of green chemistry in the conservation of our environment.

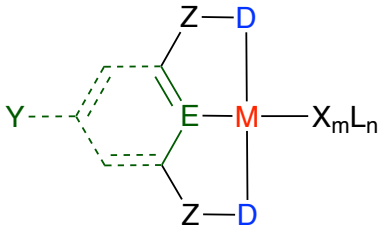
Conventional synthesis involving stoichiometric reactions produce enormous chemical wastes, which are harmful to environment. On contrary, catalytic reactions are developed in environmental friendly green chemistry pathway and generate only minimal or no waste. Transition metal catalyzed activation of unreactive small molecules has become one of the ubiquitous processes in synthetic organic chemistry, such as medicinal chemistry, agrochemical and natural product synthesis. Generally, ligands are employed to stabilize the transition metals via coordination, thus enhancing stability of the resulting complexes even at elevated temperature. In recent times ligands

are designed to participate actively in the catalytic cycle by stabilizing metal center and their unusual oxidation states, referred as non-innocent ligands.

Pincer complexes are the types of coordination complexes of pincer ligands that are tridentate ligands, which enforces meridional geometry upon complexation with metal precursors.[3] In rare cases tridenate ligands attain to facial geometry and those complexes are not considered as pincer complexes.[4] The planar framework of backbone and presence of bulky substituents on donor atoms of pincer ligands cover much coordination sites, which enhance stability of the resulting complexes and enforce selectivity in catalytic reactions. Reactivities of the pincer complexes can be fine tuned by varying the steric and electronic properties of the pincer ligands. Thus, pincer-based complexes possess an exceptional stability versus reactivity. Compared to traditional metal complexes, pincer complexes often present high stability, efficiency, selectivity and functional group tolerance. Considerable progress has been made in the chemistry of pincer complexes after pioneering reports from Shaw and coworkers in the 1970's.[5] Since then pincer complexes and their chemistry underwent exciting developments. Notably, in recent years highly efficient pincer-based catalysts are revealed for activation of unreactive bonds and small molecules.[6] Diverse types of ruthenium pincer complexes were utilized in a range of catalytic transformations.

Pincer complexes consist of a central aryl ring (phenyl, pyridinyl, pyrazinyl, acridinyl, etc.), which is 1,3-disubstituted with two chelating side arms containing donor groups (Figure 1.1).[7] These octahedral complexes attained in meridional geometry in which all three binding sites situated in the same plane and with the remaining three ligands in a plane perpendicular to it, thus offer strong coordination to the resulting pincer complexes. In recent years, also aliphatic backbone containing pincer complexes have been developed.

Figure 1.1. General Structure of Transition Metal Based Pincer Complexes

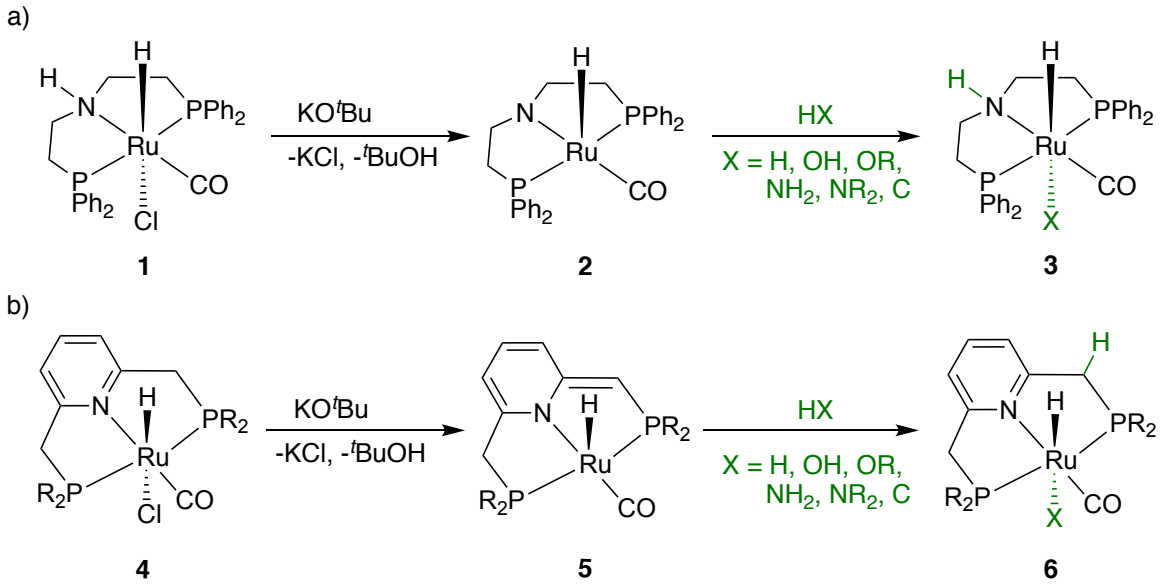


D = PR_2, NR_2, SR, OR, NHC
Z = CR_2, NR, O
E = N, NH, C, B, S, Si, P
M = Ru, Rh, Ir, Pd, Pt, Fe, Mn etc.
X = CO, Halogen, H, H_2, etc.
Y = CO_2-,SO_3-, electron donating, electron withdrawing groups

Bond activation in enzymatic reactions are known to occur involving participation by ligands, which act in cooperation with metal and without change of metal oxidation states.[8] Such cooperative effect is widely found in nature; for example, an enzyme galactose containing Cu(II)-complex can oxidize chemoselectively primary alcohols to aldehydes by a mechanism in which the tyrosinyl radical ion coordinated to Cu(II) center participates in the reaction.[9] Similarly, hemoglobin (Hb) is also capable of exhibiting such cooperative effect, which stimulates in change of spin state for the coordinated iron center and enhances the affinity of Hb towards oxygen.[10] Such metal-ligand cooperation is also observed in transition metal catalyzed reactions and also called as "bifunctional catalysis". Noyori type catalysts contain the transition metal coordinated amine ligand, which acts as a proton (H^+) donor or acceptor and facilitates transformations taking place at the metal center.[11] For example, in the ruthenium catalyzed hydrogenation reactions, in which the activation of H_2 molecule involves both the metal center and amine ligand and concerted transfer of acidic and hydridic hydrogens to an unsaturated substrates to provide hydrogenated products.[12] In recent times, bifunctional catalysis was shown to play an important role in the development of various hydrogenation reactions including asymmetric hydrogenation.

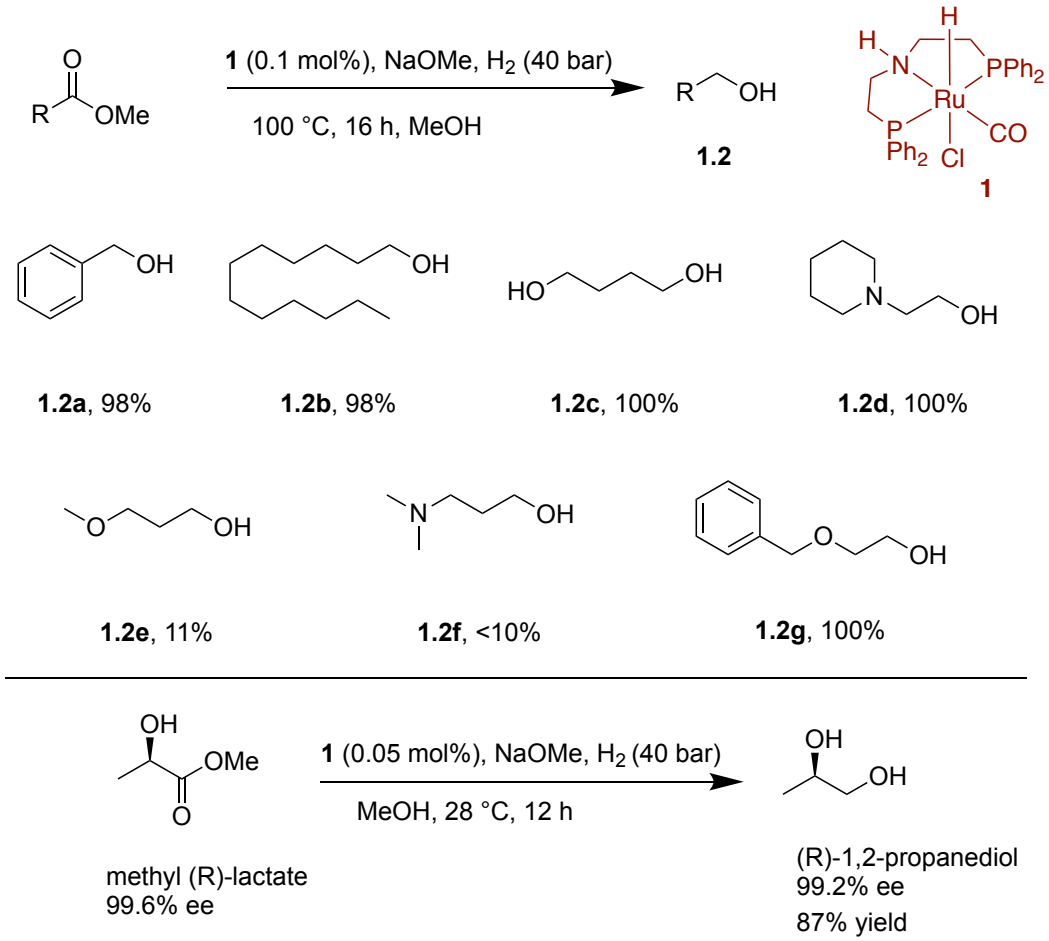
In 2005, Milstein and coworkers observed an unusual reactivity in pincer complexes mainly emanated from metal-ligand cooperation.[3,12] When reacted with base, the ruthenium aliphatic backbone PNP pincer complex **1** undergoes a facile dehydrohalogenation of coordinated amine functionality to generate a reactive and unsaturated intermediate complex **2** in which the backbone amine ligand is transformed to amide ligand. Further, the unsaturated intermediate **2**, which is capable of activating unreactive bonds (like H_2, H_2O, ROH, NH_3, H–NR_2, C–H, etc.) to provide coordinatively saturated complex **3** with regeneration of amine coordination (Scheme 1.1a). Green and sustainable chemical transformations are developed based on amine-amide metal-ligand cooperation operative in complex **1**. Similarly, upon reaction with base, the ruthenium pyridine backbone pincer complex **4** undergoes facile deprotonation at the acidic α-CH_2 protons leading to the formation of dearomatized unsaturated reactive intermediate **5** in which the pyridine motif of the ligand is dearomatized. Further, the dearomatized reactive intermediate **5** can activate unreactive chemical bonds of small molecules and can regenerate aromatized saturated ruthenium complex **6** (Scheme 1.1b). Such a unique metal-ligand cooperation involving ligand aromatization-dearomatization process enabled facile activation of various inert chemical bonds and environmentally benign catalysis.

Scheme 1.1. Different Modes of MLC (a) MLC Based on Amine-Amide (b) MLC Based on Aromatization-Dearomatization



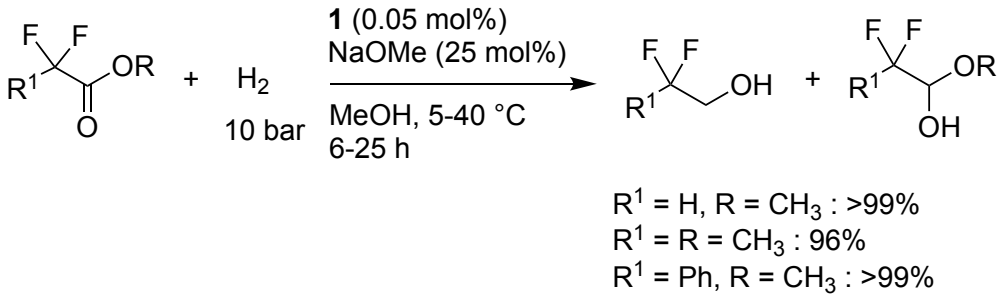
Using Ru-MACHO catalyst **1**, Kuriyama group demonstrated the hydrogenation of esters to alcohols as depicted in Scheme 1.2.[13] Catalyst **1** showed good catalytic activity and a variety of esters have been hydrogenated under mild reaction conditions. Notably, methanol was found to be the most suitable solvent for hydrogenation using the catalyst **1**. Assortments of esters were reduced to corresponding alcohols with good conversion and selectivity in the presence of a base, NaOMe. Substrates containing oxygen and nitrogen functionalities at α-position of the esters didn't impact reactivity. Hydrogenation of methyl (R)-lactate to optically pure (R)-1,2-propanediol was also demonstrated.

Scheme 1.2. Catalytic Hydrogenation of Esters Catalyzed by **1**



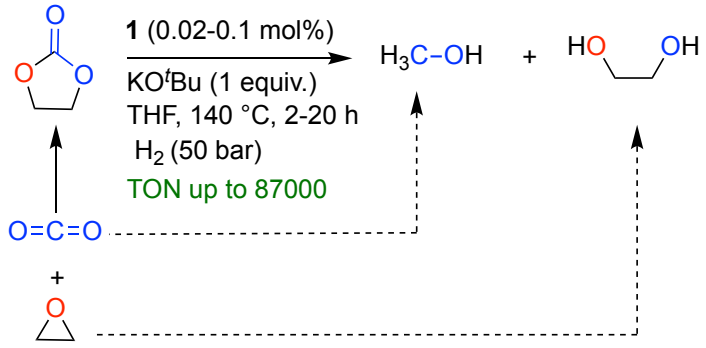
Later, Ikariya and coworkers have reported a practical and selective hydrogenation of α-fluorinated esters to alcohols using catalyst **1** under mild conditions.[14] The α-fluorinated alcohols and fluoral hemiacetal intermediates were also obtained in good to excellent yields. Both aliphatic and aromatic difluro esters were reduced to corresponding alcohols in almost quantitative yields (Scheme 1.3). Aliphatic monofluoro esters were hydrogenated smoothly in good yields but less selectivity was observed.

Scheme 1.3. Practical Hydrogenation of α-Fluorinated Esters Catalyzed by **1**



Using Ru-pincer catalyst **1,** facile catalytic hydrogenation of cyclic carbonates to diols and methanol has been reported.[15] Importantly, from ethylene carbonate facile production of ethylene glycol and methanol was developed, which are important bulk chemicals. Apart from the clean production of diol, efficient chemical utilization of CO_2 was demonstrated, which represents a distinct advantage in terms of sustainability over the omega process, which release back CO_2. Moreover, this catalytic system has also been applied for the utilization of waste poly(propylene carbonate) as a resource to afford 1,2-propylene diol and methanol via hydrogenative depolymerization processes.

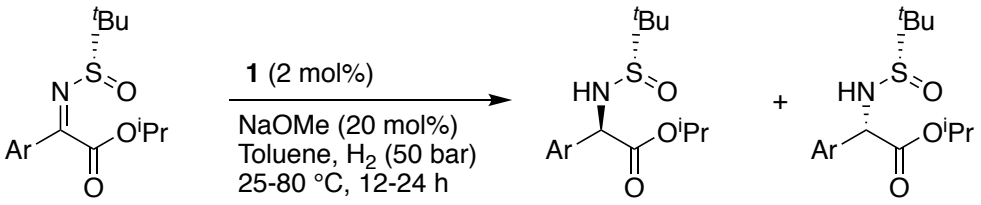
Scheme 1.4. Catalytic Hydrogenation of Cyclic Carbonates



Wei and coworkers have reported highly efficient hydrogenation of N-*tert*-butylsulfinyl

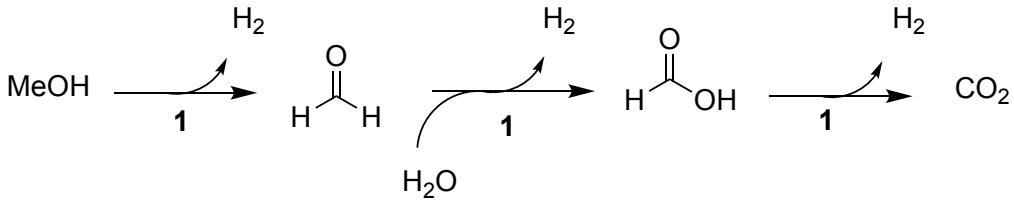
ketimines for the synthesis of aryl glycine derivatives with high yields and diastereoselectivities (Scheme 1.5).[16] In addition, substituted ketimino esters were smoothly hydrogenated with high diastereoselectivities and good to excellent isolated yields. This hydrogenation protocol also applied to synthesis of chiral amino alcohols for practical applications.

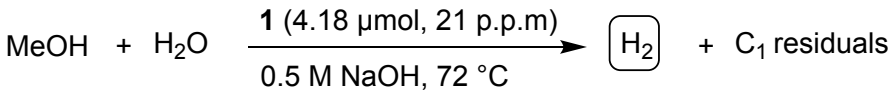
Scheme 1.5. Diastereoselective Hydrogenation of *N-tert* Butylsulfinyl Ketimines



Hydrogen is a potential source of energy and practical hydrogen generation from renewable resources like methanol is attractive. The implementation of sustainable hydrogen production and further hydrogen conversion to energy is called "hydrogen economy". The physical properties of hydrogen gas make the transport and handling of hydrogen gas very difficult. In 2013, Beller and coworkers have developed an efficient low temperature aqueous phase methanol dehydrogenation catalyzed by ruthenium catalyst **1** (Scheme 1.6).[17] Interestingly, compared to previously reported heterogeneous systems low contaminant CO and CH_4 gases were observed. Using complex **1** turnover frequency up to 4700 h^{-1} and turnover number >350,000 were achieved. Advantageously, methanol acts as the hydrogen carrier, which would make the delivery of hydrogen gas in mobile services.

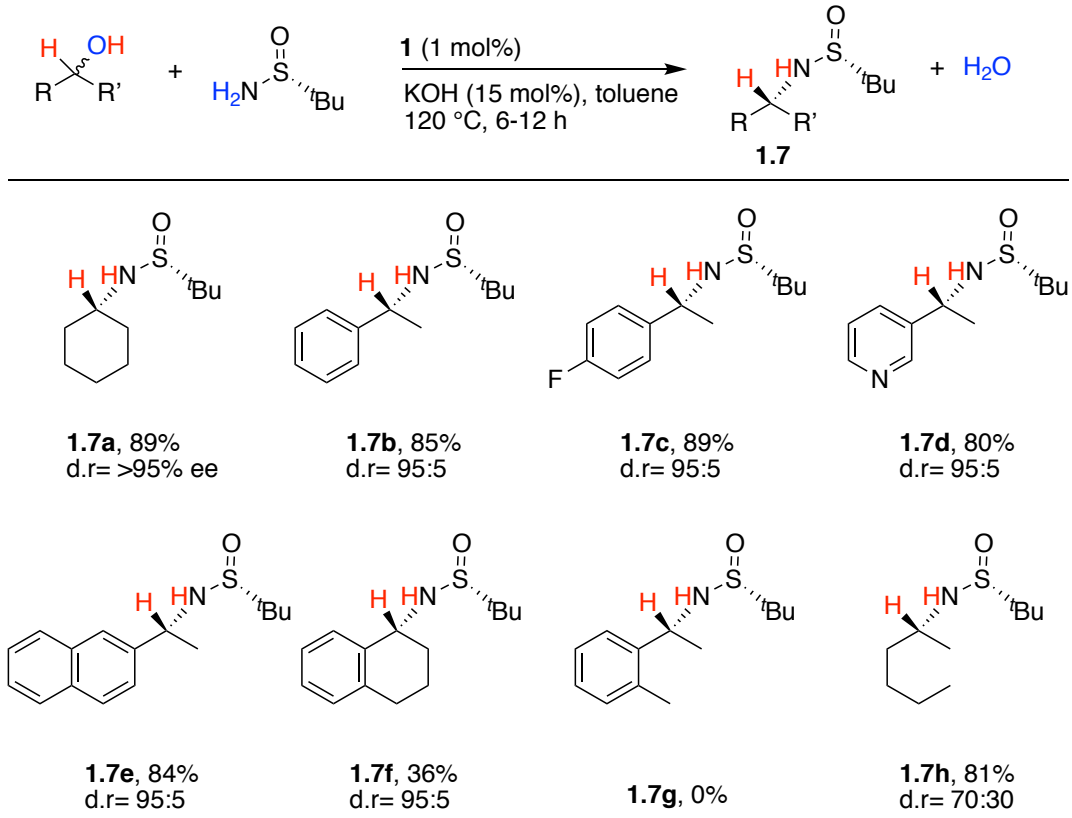
Scheme 1.6. Ru-Catalyzed Aqueous-Phase Methanol Dehydrogenation





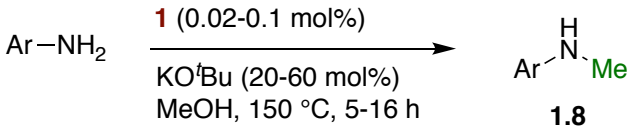
In 2014, Guan and coworkers have reported the formation of α-chiral *tert*-butanesulfinylamines from racemic secondary alcohols and Ellman's chiral tert-butanesulfinamide via borrowing hydrogen methodology.[18] Remarkably, the α-chiral butanesulfinylamine products were isolated in good to excellent yields and most examples displayed >95:5 diastereomeric ratio (d.r) (Scheme 1.7). An assortment of racemic secondary alcohols reacts with Ellman's sulfinamide and resulted chiral amine products in one step. Importantly, this protocol enables access to methyl substituted chiral amines, which are challenging to obtain with methyl organometallic reagents. Notably, this pincer catalyst **1** is sensitive to steric hindrance; thus, ortho-substituted alcohol shows no reactivity under these conditions (Scheme 1.7).

Scheme 1.7. Ru-Catalyzed Diastereoselective Amination Using Racemic Alcohols to Enantiopure Amines

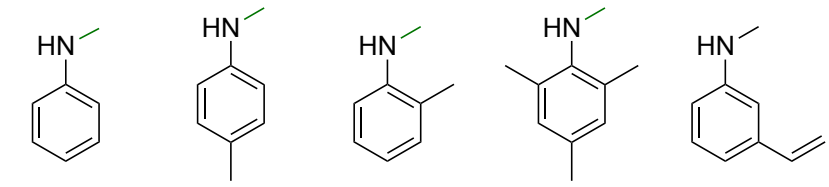


N-Methylated aromatic amines are important compounds in pharmaceuticals, agrochemicals, dyes and fine chemical industries. Ogata and coworkers have developed the selective mono-methylation of aromatic amines using methanol with Ru-MACHO catalyst **1.**[19] A range of substituted aromatic amines was transformed to the corresponding mono-methylated secondary amines in excellent yields (Scheme 1.8). Remarkably, the catalyst loading could be lowered to 0.02 mol % by increasing the base concentration that makes this catalytic protocol is environmentally benign, easily handled and CO tolerant catalyst.

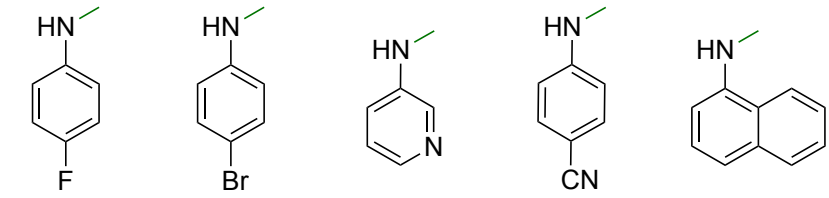
Scheme 1.8. *N*-Monomethylation of Aromatic Amines with Methanol



1.8



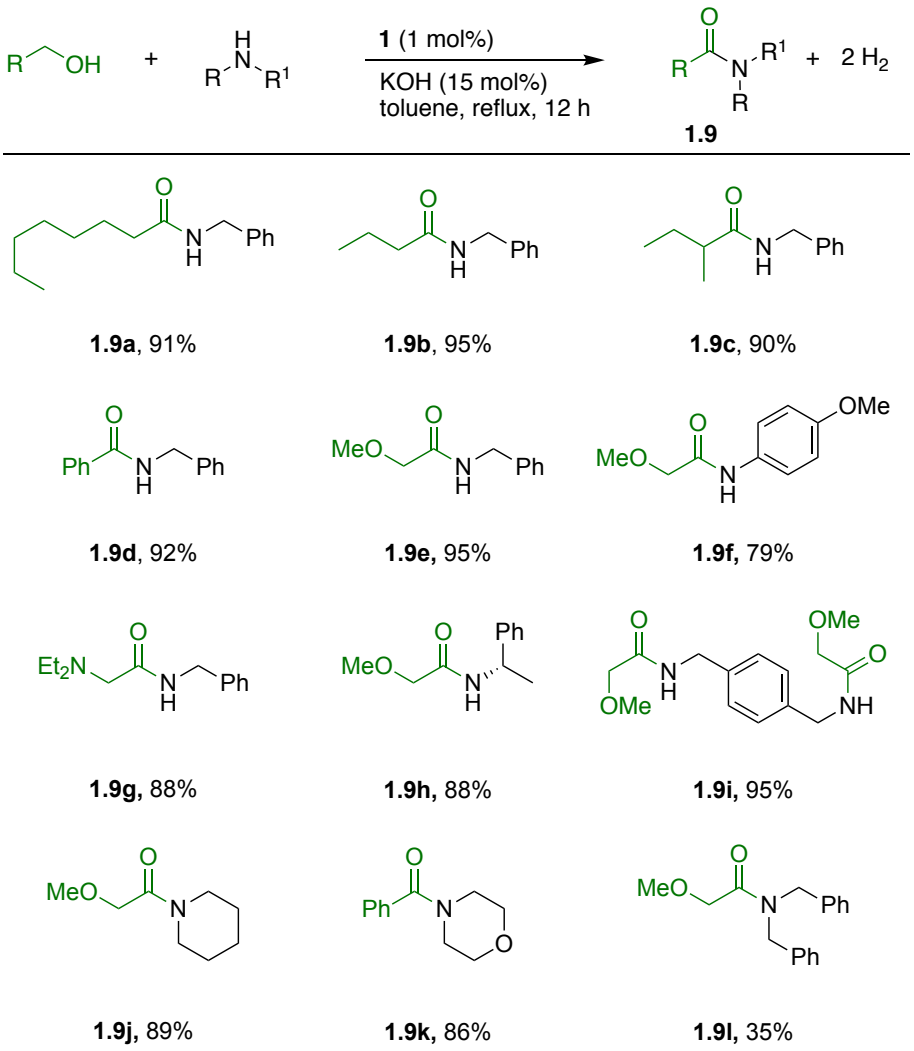
1.8a, 93% **1.8b,** 100% **1.8c,** 91% **1.8d,** 13% **1.8e,** 87%



1.8f, 97% **1.8g,** 87% **1.8h,** 94% **1.8i,** 84% **1.8j,** 65%

Amide molecules are prevalent in natural products, proteins and widely used in synthetic organic chemistry. In this direction, Guan and coworkers have developed Ru-MACHO (**1**) catalyzed formation of amides directly from alcohols and amines via an acceptorless dehydrogenation pathway (Scheme 1.9).[20] Good reactivity was observed with secondary amines for the synthesis of tertiary amides and also optically active amine was utilized to provide optically pure amide product (**1.9h**) without racemization. Reaction of diamines with diols provided diamides in high yields, suggesting the applicability of making of polyamides using this catalyst **1**.

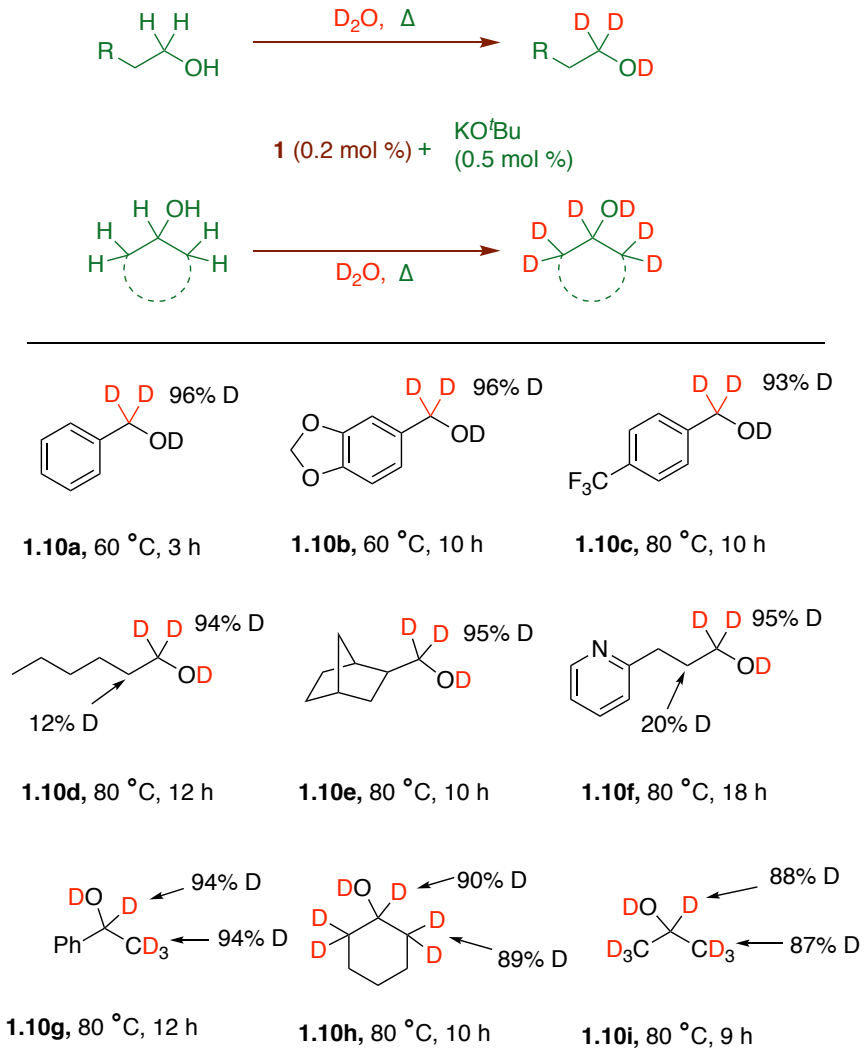
Scheme 1.9. Ru-Catalyzed Construction of Amides via Acceptorless Dehydrogenation



Synthesis of efficient deuterium labeling compounds is an important transformation in current organic chemistry as deuterated pharmaceuticals and bioactive organic molecules have emerged, as valuable targets.[21] Deuterium oxide is a cheapest source of deuterium and green deuterium labeling reagent. Gunanathan and coworkers have demonstrated ruthenium catalyzed highly selective α-deuteration of primary alcohols and α,β-deuteration of secondary alcohols using D_2O as a deuterium source (Scheme 1.10).[22] Notably, with the use of low catalyst load with catalytic amount of base (KO^tBu) and heating at lower temperature provided excellent deuteration of alcohols,

which makes this protocol is practically attractive and environmentally benign. The reaction proceeded via O–D activation of deuterium oxide and alcohols by the Ru-MACHO catalyst (**1**), which subsequently dehydrogenated to corresponding carbonyl compounds through amine-amide metal-ligand cooperation. While the hydrogenation of carbonyl motif provided selective α-deuteration, the β-deuteration perhaps occurred via keto-enol tautomerization.

Scheme 1.10. Ru-Catalyzed Selective α-and α,β-Deuteration of Alcohols Using D_2O



1.10a, 60 °C, 3 h **1.10b,** 60 °C, 10 h **1.10c,** 80 °C, 10 h

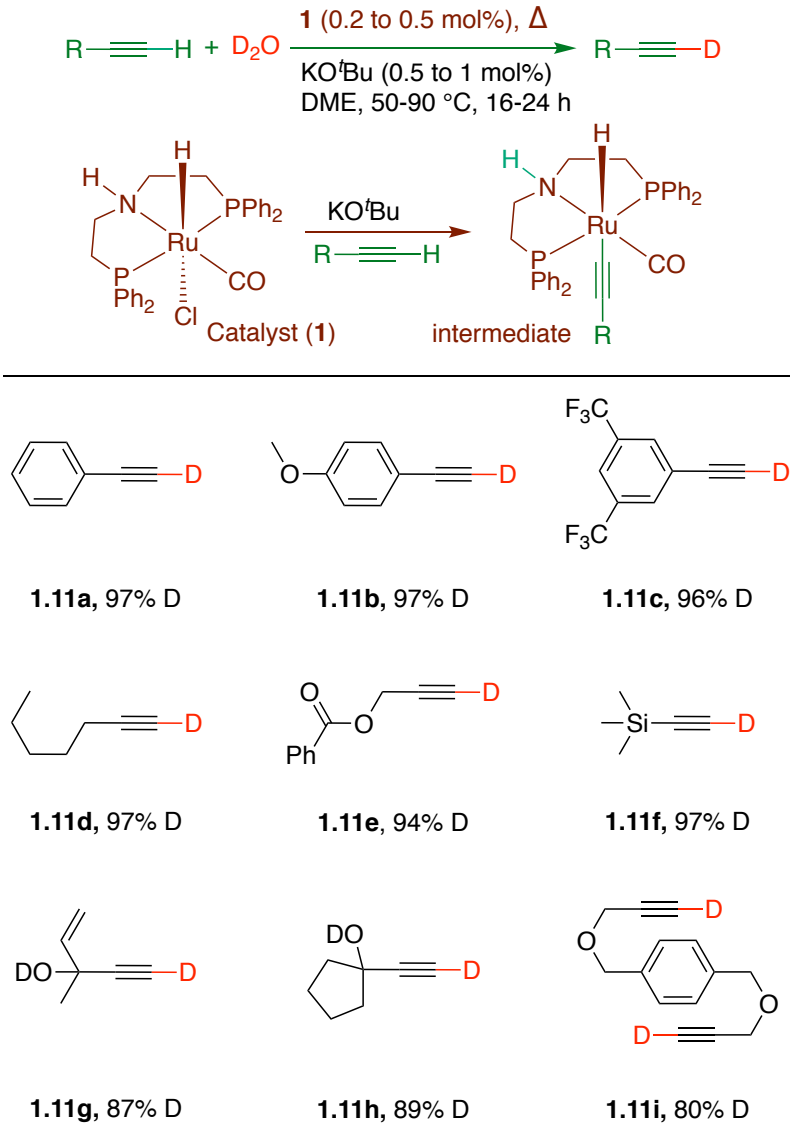
1.10d, 80 °C, 12 h **1.10e,** 80 °C, 10 h **1.10f,** 80 °C, 18 h

1.10g, 80 °C, 12 h **1.10h,** 80 °C, 10 h **1.10i,** 80 °C, 9 h

Deuterated terminal alkynes are used as highly reliable probe in mechanistic investigations. Recently, using ruthenium pincer catalyst **1**, an efficient catalytic method

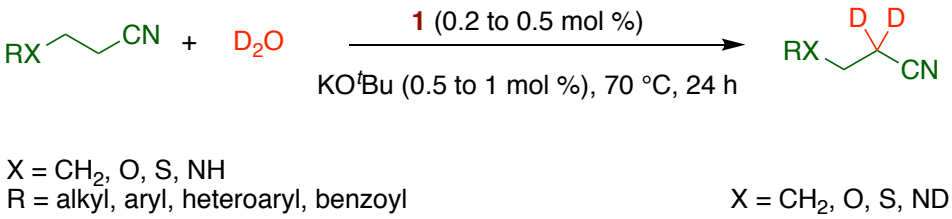
for the synthesis of mono-deuterated terminal alkynes using deuterium oxide has been reported.[23] Interestingly, terminal alkynes were chemoselectively deuterated in presence of other sensitive functional groups (Scheme 1.11). Amine-amide metal-ligand cooperation is operative in catalyst **1**, the reaction proceeded via Ru-acetylide intermediates and H/D exchange of backbone amine donor on catalyst **1** with deuterium oxide leads to selective deuteration of terminal alkynes. Notably, this catalytic protocol needs low catalyst load, catalytic amount of base and devoid of any deleterious side reactions.

Scheme 1.11. Selective Synthesis of Mono-Deuterated Terminal Alkynes



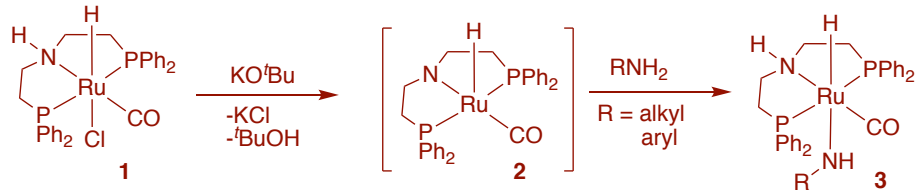
Recently, an efficient and highly selective α-deuteration of aliphatic nitriles using D_2O catalyzed by Ru-MACHO (**1**) has been reported.[24] Using low catalyst load of **1** under mild reaction conditions an efficient α-deuteration of aliphatic nitriles in presence of other reactive functional groups was successfully achieved. Amine-amide metal-ligand cooperation operative in catalyst **1** facilitate the selective [2+2] cycloadduct formation of nitriles followed by imine-enamine tautomerization and H/D exchange between enamine intermediate and D_2O, leading to the selective α-deuterated nitriles was proposed as possible reaction mechanism. Notably, this method can be applied for the large-scale synthesis of acetonitrile-D_3 and other useful deuterated nitrile compounds.

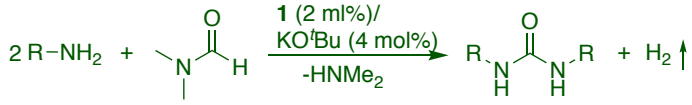
Scheme 1.12. Ru-catalyzed selective α-deuteration of aliphatic nitriles using D_2O



Gunanathan and coworkers have reported activation of N–H bond of amines by ruthenium pincer complex **1**.[25] Catalytic activation of formyl C–H of DMF was observed in situ, which resulted in situ formation of CO to synthesis urea derivatives with liberation of hydrogen. This method avoids the direct use of fatal CO gas. Both symmetrical and unsymmetrical urea derivatives were synthesized in good to excellent yields (Scheme 1.13). The catalytic carbonylation of amines occurred at low temperature and the *N*-formamide intermediates were isolated. Further, consecutive addition of amines to in situ formed formamide intermediates for the synthesis of unsymmetrical urea derivatives was successfully achieved.

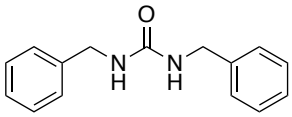
Scheme 1.13. Ru-Catalyzed Urea Synthesis by N−H Activation of Amines



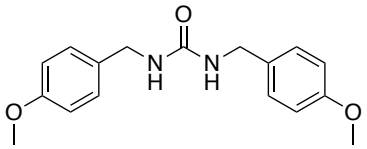


R = aryl, benzyl, alkyl

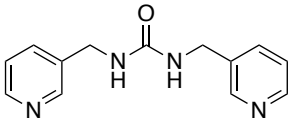
1.13



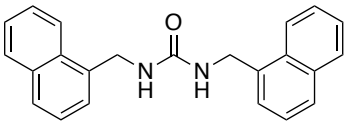
1.13a, 91%



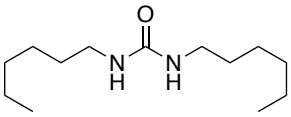
1.13b, 91%



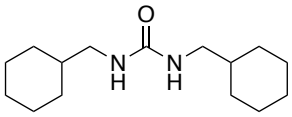
1.13c, 77%



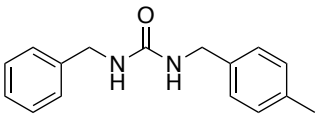
1.13d, 91%



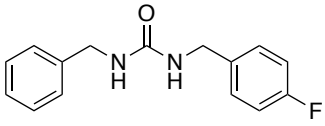
1.13e, 90%



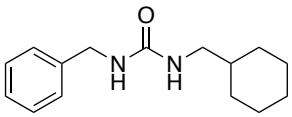
1.13f, 99%



1.13g, 79%



1.13h, 71%



1.13i, 76%

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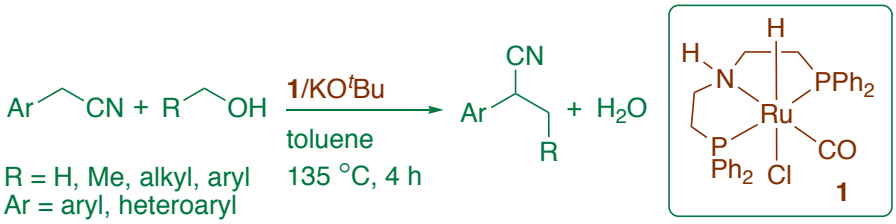
CHAPTER 2

Facile Ruthenium(II)-Catalyzed α-Alkylation of Arylmethyl Nitriles Using Alcohols Enabled by Metal-Ligand Cooperation

2.1 ABSTRACT



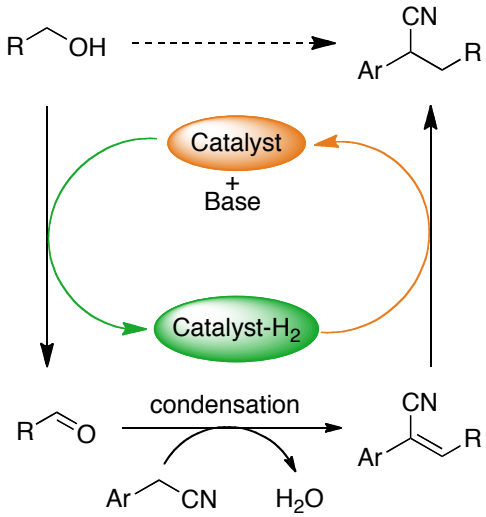
A ruthenium(II)-catalyzed facile α-alkylation of arylmethyl nitriles using alcohols is reported. Ruthenium pincer catalyst serves as an efficient catalyst for this atom-economical transformation that undergoes alkylation via borrowing hydrogen pathways, producing water as the only by-product. Arylmethyl nitriles containing different substituents can be effectively alkylated using diverse primary alcohols. Notably, using ethanol and methanol as alkylating reagents, challenging ethylation and methylation of arylmethyl nitriles were performed. Secondary alcohols do not undergo alkylation reaction. Thus, phenylacetonitrile was chemoselectively alkylated using primary alcohols in the presence of secondary alcohols. Diols provided mixture of products. When deuterium labeled alcohol was used, expected deuterium transposition occurred, providing both α-alkylation and α-deuteration of arylmethyl nitriles. Consumption of nitrile was monitored by GC, which indicated the involvement of first order kinetics. Plausible mechanistic pathways are suggested on the basis of experimental evidences. The ruthenium catalyst reacts with base and generates an unsaturated intermediate, which further reacts with both nitriles and alcohols. While nitrile is transformed to enamine via [2+2] cycloaddition, alcohol is oxidized to aldehyde. The metal bound enamine-adduct reacts with aldehyde via conjugate addition

resulting in ene-imine adduct, which perhaps undergo direct hydrogenation by the Ru-dihydride intermediate, produced from alcohol oxidation. However, in situ monitoring of the reaction mixture confirmed the presence of unsaturated vinyl nitrile in the reaction mixture in minor amounts (10%), indicating the possible dissociation of ene-imine adduct during the catalysis, which may further be hydrogenated to provide the α-alkylated nitriles. Overall, the efficient α-alkylation of nitriles using alcohols can be attributed to the amine-amide metal-ligand cooperation that is operative in ruthenium pincer catalyst, which enables all the catalytic intermediates to remain in +2 oxidation state throughout the catalytic cycle.

2.2 INTRODUCTION

Alkylation reactions that can result in formation of C–C bonds are an important transformation in organic synthesis. Conventional alkylation reactions involve toxic alkyl halides and use of stoichiometrically excess amount of base, which also produce salt waste. Advancement in homogeneous catalysis and catalyst design led to the development of an alternative protocol for alkylation reactions in which alcohols are used as alkylating partners.[1] These transformations are highly atom-economical and environmentally benign as they release water as the only by-product. They are often referred as "borrowing hydrogen" and also as "hydrogen autotransfer" methods as the catalytically liberated hydrogen from the oxidation of alcohols is later reinstalled in the unsaturated intermediates that form via condensation reactions resulting in redox neutral-alkylation reactions (Scheme 2.1).[1,2]

Scheme 2.1 Selective Catalytic α-Alkylation of Arylmethyl Nitriles Enabled by Borrowing Hydrogen Concept



From this perspective, catalytic alkylation of nitriles using alcohols gains prominent significance as nitriles serve as important compounds from which a number of carboxylic derivatives can be easily derived and widely used in fine chemical industry and also in synthesis of biologically active compounds.[3] Grigg and coworkers reported the pioneering ruthenium mediated α-alkylation of acetonitriles in 1981.[4] Later, iridium[5,6,7] and rhodium[8,9] based catalytic protocols were developed for this transformation. Despite the well-known catalytic activity of ruthenium in borrowing hydrogen strategies,[1] its application in α-alkylation of nitriles is poorly documented. Kaneda and coworkers developed hydrotalcite supported ruthenium heterogeneous catalysts, which required prolonged heating at high temperature (180 °C, 20-30 h) in addition to the use of alkylating alcohols as solvents (2 mL alcohols for 1 mmol of nitriles).[10] Ruthenium(II) half-sandwich complexes developed for this transformation exhibited poor catalytic activity; provided partial hydrogenation, resulting in presence of unsaturated vinyl nitrile predominantly in mixture of products.[11] Fukuyama and Ryu

group also reported the ruthenium catalyzed alkylation of acetonitrile using primary alcohols.[12] Recently, the groups of Esteruelas and Yus reported an osmium(II) half-sandwich complex catalyzed alkylation of benzyl nitriles by benzyl alcohols, which required removal of in situ formed water using Dean-Stark method.[13] Invariably, in all these homogeneous catalytic reactions sub-stoichiometric to stoichiometrically excess amount of various bases (20 to 110%) were also used.

The general problem in this method is the water, which is formed in situ, that can effectively hydrolyze the unstable intermediates to regenerate aldehydes. In addition, the homogeneous catalyst should be compatible with water. The chemoselectivity of the overall reaction also depends on the efficient hydrogenation of vinyl nitriles. Due to these challenges, in general, α-alkylated nitriles are still being synthesized using alkyl halides with stoichiometrically excess amount of base.[14] Thus, an efficient catalyst for the α-alkylation of arylmethyl nitriles is highly desirable. N–H activation of amines and formyl C–H activation of DMF by ruthenium(II) pincer complex **1** (Ru-MACHO) was established recently, which are utilized in the catalytic synthesis of urea derivatives using DMF as a CO surrogate.[15] We have also disclosed the highly efficient and selective deuteration of terminal alkynes,[16] α- and α,β-deuteration of primary and secondary alcohols,[17] upon using deuterium oxide, catalyzed by complex **1**. In these studies, we have established the sp-C–H activation of terminal alkynes and O–H activation of alcohols and water by complex **1** upon deprotonation by a base. As the work in our laboratory confirmed that complex **1** is very much compatible with water, I have envisaged employing complex **1** for the catalytic alkylation of nitriles using alcohols. Herein, I describe ruthenium pincer complex [(PNP^{Ph})RuHCl(CO)] **1** (PNP =

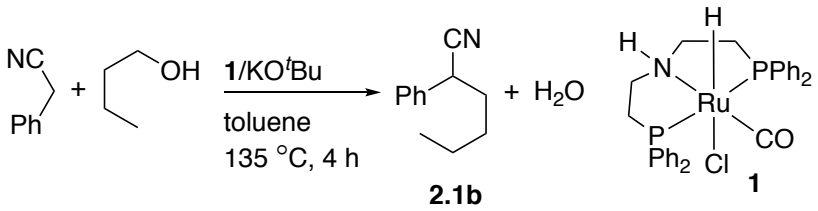
bis(2-(diphenylphosphino)ethyl)amine)[18] catalyzed highly efficient α-alkylation of arylmethyl nitriles using alcohols.

2.3 RESULTS AND DISCUSSIONS

In continuation of our efforts in the development of atom-economical catalytic transformations using the ruthenium pincer complex-catalyzed environmentally benign processes, I have envisaged to develop a facile catalytic method for the alkylation of arylmethyl nitriles using alcohols as alkylating partner. At the outset of our work, phenylacetonitrile and 1-butanol were selected as benchmark substrates to find the optimal reaction conditions for the ruthenium pincer complex **1** catalyzed alkylation reactions and the results are summarized in Table 2.1. Thus, reaction of 1 mol% of ruthenium pincer catalyst **1**, base (2 mol%), phenylacetonitrile (1 mmol) and 1-butanol (5 mmol) in toluene solvent at 135 °C (entry 1, Table 2.1) was performed. The desired product of 2-phenylhexanenitrile was isolated in 98% yield. Similar outcome was obtained when only two equivalents of alcohol (2 mmol) were used in the reaction (entry 2, Table 2.1). Upon reducing the reaction temperature to 110 °C, both the conversion and yield of this alkylation reaction were decreased (80% and 78%, respectively, entry 3, Table 2.1). Further, decreasing the equivalents of 1-butanol also resulted in diminished conversion and yield of the product (entries 4-5). When the catalyst load was lowered to 0.5 mol% with two equivalents of 1-butanol, alkylation of phenylacetonitrile provided the quantitative conversion and 98% yield of the product after 4 h (entry 6). From the above condition (entry 6), further lowering of the catalyst loads (0.3 mol% and 0.1 mol%) resulted in decreased yields (entries 7-8, Table 2.1). Finally, when control experiments were carried out without catalyst **1** in the presence of base (entry 9, Table 2.1) and in the absence of both catalyst and base (entry 10, Table

2.1), no product was found, implying that a catalyst is essential for alkylation of nitriles using alcohols.

Table 2.1 Optimization of Reaction Conditions for the α-Alkylation of Arylmethyl Nitriles[a]

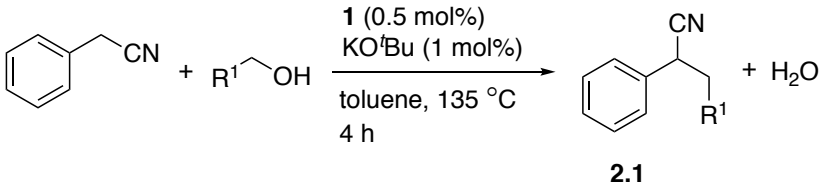


entry	**1** (mol%)	base (mol%)	alcohol (equiv.)	conv. (%)[b]	yield (%)[c]
1	1	2	5	>99	98
2	1	2	2	>99	98
3[d]	1	2	2	80	78
4	1	2	1.2	80	72
5	1	2	1.5	83	78
6	0.5	1	2	>99	98
7[e]	0.3	0.6	2	>99	90
8[e]	0.1	0.2	2	88	76
9[f]	-	1	2	-	-
10[f]	-	-	2	-	-

Reaction conditions: [a]Phenylacetonitrile (1 mmol), butanol (2 mmol), catalyst, base and toluene (1.5 mL) were heated at 135 °C for 4 h under the nitrogen flow. [b]Conversion of nitriles; determined by GC using mesitylene as an internal standard. [c]Isolated yields after column chromatography. [d]Heated at 110 °C. [e]Minor amount of alkene formation was also observed. [f]Reaction performed up to 24 h.

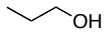
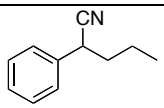
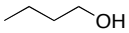
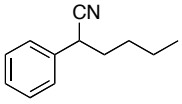
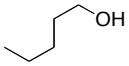
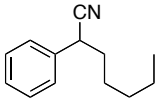
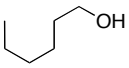
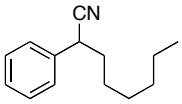
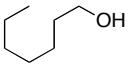
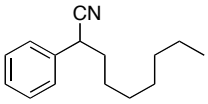
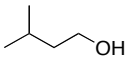
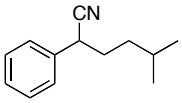
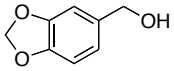
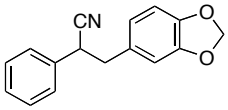
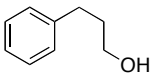
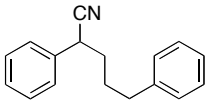
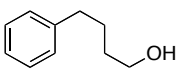
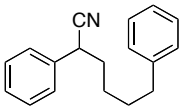
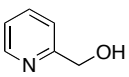
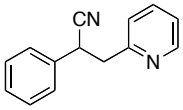
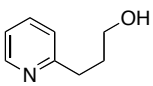
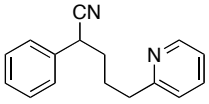
With the optimized condition in hand, I have examined the reaction of an assortment of alcohols using phenylacetonitrile (Table 2.2). In general, quantitative conversions occurred with low loading of catalyst **1** (0.5 mol%) leading to the efficient oxidation of alcohols and subsequent C–C bond formation. Use of low boiling alcohol, 1-propanol (bp-97 °C) provided the 2-phenylpentanenitrile (**2.1a**) in 91% yield (95% conversion, entry 1, Table 2.2). Further, a series of non-activated alcohols such as 1-butanol, 1-pentanol, 1-hexanol, 1-heptanol and 3-methyl-1-butanol were reacted with 2-phenylacetonitrile. These alcohols resulted in quantitative conversions and provided the corresponding 2-phenylalkylnitriles (**2.1b-2.1f**) in good isolated yields of 95-98% (entries 2-6, Table 2.2). Next I have investigated the reaction of electron rich piperonyl alcohol, which also provided the quantitative conversion and 95% yield of the alkylated product **2.1g** (entry 7, Table 2.2). Linear alcohols appended with aryl and heteroaryl ring systems in general provided excellent yields (**2.1h-2.1k**) with quantitative conversions (entries 8-11, Table 2.2); however, 2-pyridine methanol provided only 66% conversion and the alkylation product **2.1j** was obtained in 61% yield (entry 10, Table 2.2). This low conversion and yield with 2-pyridine methanol may be due to its chelation properties, which perhaps diminish the catalyst reactivity.

Table 2.2 Ruthenium-Catalyzed α-Alkylation of Phenylacetonitrile with Primary Alcohols[a]



2.1

entry	alcohol	product	conv. (%)[b]	yield (%)[c]

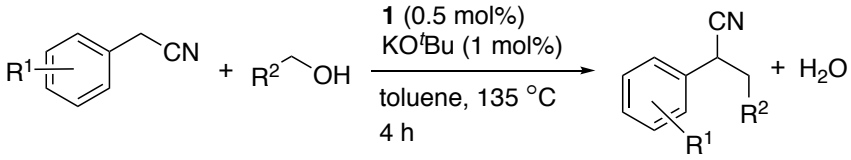
1			**2.1a**	95	91
2			**2.1b**	>99	98
3			**2.1c**	>99	98
4			**2.1d**	>99	98
5			**2.1e**	>99	95
6			**2.1f**	98	96
7			**2.1g**	>99	95
8			**2.1h**	>99	98
9			**2.1i**	>99	97
10			**2.1j**	66	61
11			**2.1k**	>99	98

Reaction conditions: [a]Phenylacetonitrile (1 mmol), alcohol (2 mmol), toluene (1.5 mL) and catalyst **1** (0.5 mol%), KO^{t}Bu (1 mol%) were heated at 135 °C under the flow of nitrogen atmosphere for 4 h. [b]Conversion of nitrile; determined by GC using mesitylene as an internal standard. [c]Isolated yield after column chromatography.

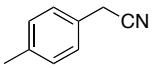
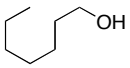
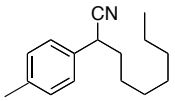
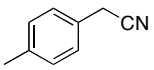
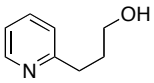
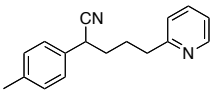
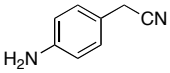
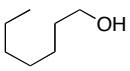
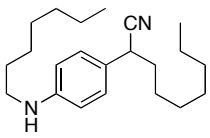
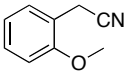
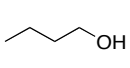
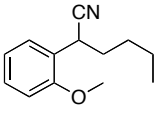
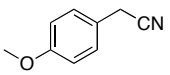
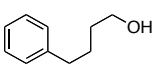
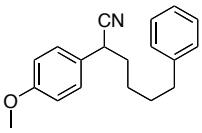
Then, I have explored the scope of different arylmethyl nitriles in the catalytic α-alkylation reactions using different alcohols (Table 2.3). Substrates bearing various electron-donating substituents on the aryl ring of nitriles were well tolerated to afford the α-alkylated nitriles in excellent yields. When 4-methylphenyl acetonitrile reacted with 1-heptanol and 3-(pyridine-2-yl)propanol in the presence of catalyst **1** (0.5 mol%), quantitative conversion of nitrile was observed and the corresponding α-alkylated products (**2.2a, 2.2b**) were obtained in excellent yield and selectivity (entries 1,2, Table 2.3). Interestingly, with use of only two equivalents of 1-hexanol, 2-(4-aminophenyl)acetonitrile exhibited both α-alkylation and *N*-alkylation to provide the dialkylated product in 97% yield with complete selectivity (entry 3, Table 2.3), indicating the facile catalytic *N*-alkylation under this condition. Mono, di and trimethoxy substituents containing benzylnitriles were reacted with various alcohols (entries 4-12, Table 2.3). Apart from the reaction of 3-methyl butanol with piperonyl nitrile (92% conversion, 90% yield, entry 9, Table 2.3), quantitative conversion of nitriles was observed with all the substrates and the corresponding α-alkylated benzylnitriles (**2.2d-2.2l**) were isolated in 96-98% yields. Notably, the electron withdrawing groups on benzene ring of arylmethyl nitriles slightly diminish the reactivity. Thus, when 2-(4-bromophenyl)acetonitrile and 2-(2,4-dichlorophenyl)acetonitrile were reacted with 1-butanol and 1-hexanol, 92% and 85% conversion of nitriles were observed and the corresponding α-alkylated products **2.2m**

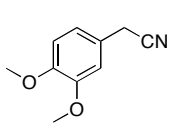
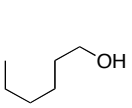
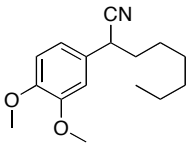
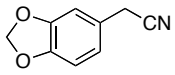
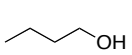
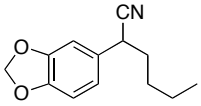
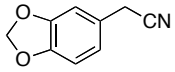
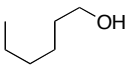
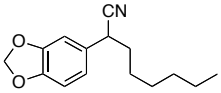
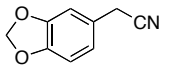
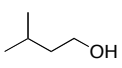
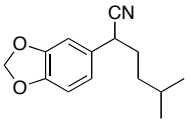
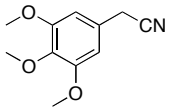
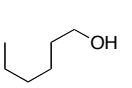
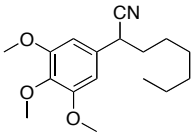
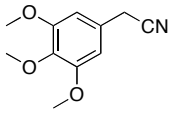
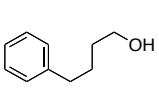
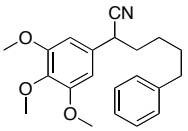
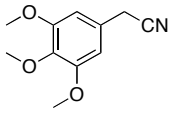
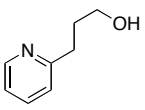
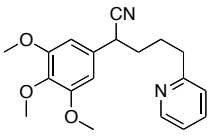
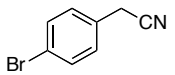
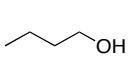
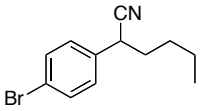
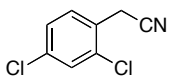
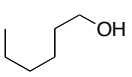
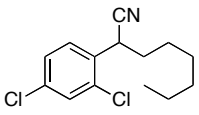
and **2.2n** were isolated in 90% and 82% yields, respectively (entries 13,14, Table 2.3). Unlike the reaction of 2-pyridine methanol (entry 10, Table 2.2), 2-pyridine acetonitrile was quantitatively converted to provide the α-alkylated product **2.2o** in 96% yield (entry 15, Table 2.3).

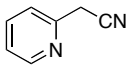
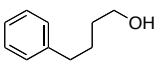
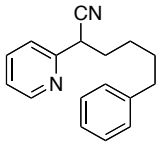
Table 2.3 Ruthenium-Catalyzed α-Alkylation of Arylmethyl Nitriles with Primary Alcohols[a]



2.2

entry	nitrile	alcohol	product		conv (%)[b]	yield (%)[c]
1				**2.2a**	>99	93
2				**2.2b**	>99	97
3				**2.2c**	>99	97
4				**2.2d**	>99	96
5				**2.2e**	>99	96

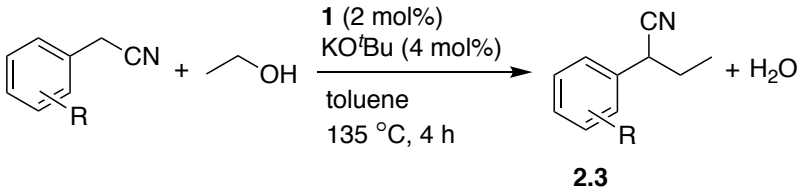
6				**2.2f**	>99	97
7				**2.2g**	>99	96
8				**2.2h**	>99	96
9				**2.2i**	92	90
10				**2.2j**	>99	97
11				**2.2k**	>99	98
12				**2.2l**	>99	96
13				**2.2 m**	92	90
14				**2.2n**	85	82

15				**2.2o**	>99	96

Reaction conditions: [a]Nitrile (1 mmol), alcohol (2 mmol), toluene (1.5 mL), catalyst **1** (0.5 mol%) and KO^{t}Bu (1 mol%) were heated at 135 °C under the flow of nitrogen atmosphere for 4 h. [b]Conversion of nitriles; determined by GC using mesitylene as an internal standard. [c]Isolated yield of products after column chromatography.

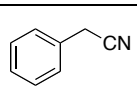
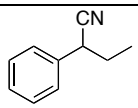
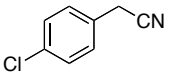
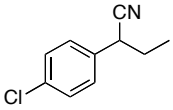
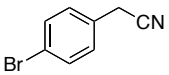
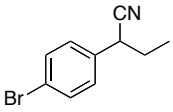
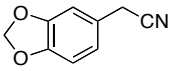
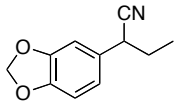
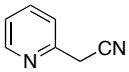
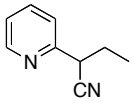
To extend the scope of alcohols employed in the ruthenium catalyzed α-alkylation of nitriles, ethanol and methanol were investigated as potential primary alcohols. First, on the basis of optimized condition, I have performed reaction of α-alkylation of different nitriles using two equivalents of ethanol, which provided the products in poor yields. Then I have used five equivalents of ethanol, which provided efficient α-ethylation of all arylacetonitriles (entries 1-5, Table 2.4) and the corresponding ethylated products (**2.3a-2.3e**) were isolated in good yields.

Table 2.4 Ruthenium-Catalyzed α-Ethylation of Arylmethyl Nitriles Using Ethanol[a]



2.3

entry	nitrile	product	conv. (%)[b]	yield (%)[c]

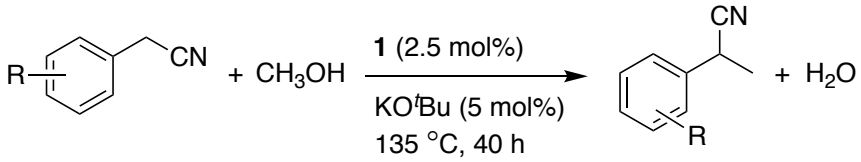
1			**2.3a**	88	83
2			**2.3b**	74	66
3			**2.3c**	87	78
4			**2.3d**	79	66
5			**2.3e**	>99	82

Reaction conditions: [a]Nitrile (1 mmol), ethanol (5 mmol), toluene (1.5 mL), catalyst **1** (2 mol%) and KO^{t}Bu (4 mol%) were heated at 135 °C under the flow of nitrogen atmosphere for 4 h. [b]Conversion of nitriles; determined by GC using mesitylene as an internal standard. [c]Isolated yield of products after column chromatography.

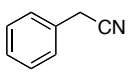
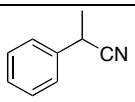
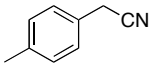
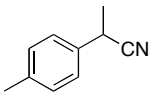
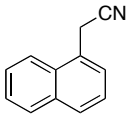
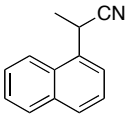
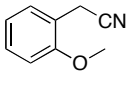
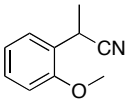
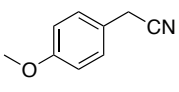
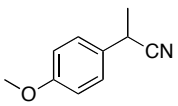
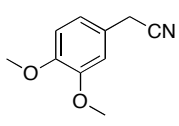
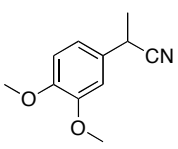
Next, I have investigated the challenging methylation of nitrile compounds using methanol and ruthenium catalyst **1**. Due to the lower boiling point and difficulty associated with the oxidation of methanol, methylation reaction using methanol is rarely documented.[19] In general, methylation is an important transformation in chemical synthesis, which is invariably achieved by using methyl iodide or toxic dimethyl sulfate reagents.[14] Reaction of various arylmethyl nitriles with methanol (2 mL) and catalyst **1** (2.5 mol%) under the closed condition for a prolonged time (40 h), resulted in good conversion and provided the corresponding methylated products in moderate to good

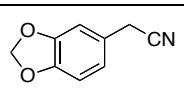
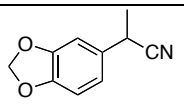
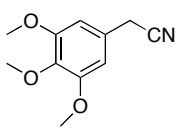
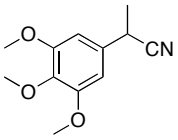
yields of 40-83% (Table 2.5). Unlike the α-alkylation of long chain alcohols, selectivity for both α-ethylation and α-methylation of nitriles decreased to some extent, perhaps due to longer reaction time resulting in other side reactions.

Table 2.5 Ruthenium-Catalyzed α-Methylation of Arylmethyl Nitriles Using Methanol[a]



2.4

entry	nitrile	product		conv. (%)[b]	yield (%)[c]
1			**2.4a**	94	83
2			**2.4b**	58	48
3			**2.4c**	67	44
4			**2.4d**	55	44
5			**2.4e**	58	40
6			**2.4f**	56	42

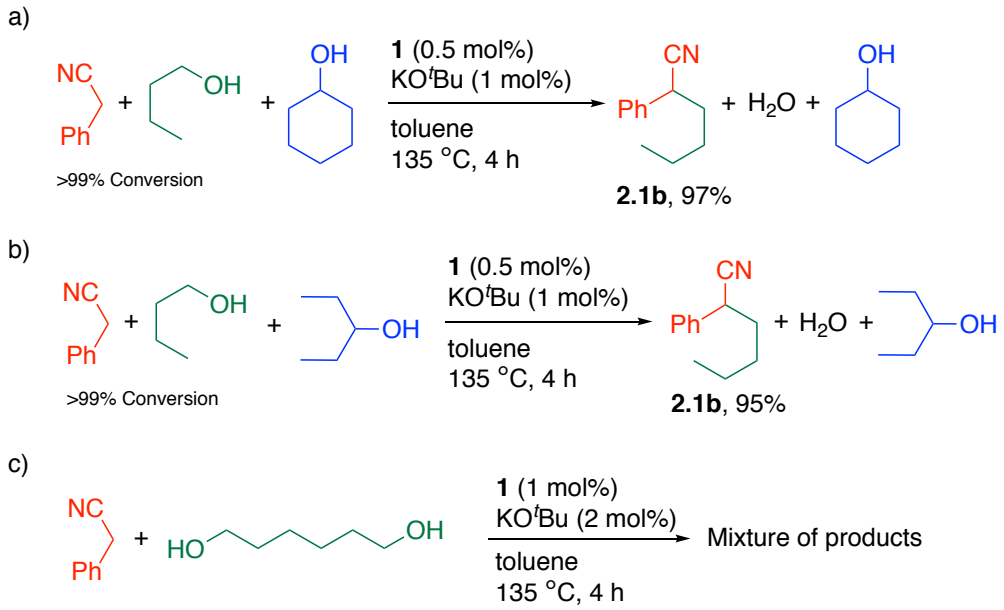
7			**2.4g**	72	61
8			**2.4h**	95	82

Reaction conditions: [a]Nitrile (1 mmol), methanol (2 mL), catalyst **1** (2.5 mol%) and KO^{t}Bu (5 mol%) were heated for 40 h at 135 °C in a sealed pressure tube. [b]Conversion of nitrile; determined by GC using toluene as an internal standard. [c]Isolated yield of products after column chromatography.

Such α-alkylation of arylmethyl nitriles occurs only with primary alcohols. When secondary alcohols such as 1-phenylethanol and cyclohexanol were employed as alkylating partners under the optimized condition, no alkylation products were observed. Thus, chemoselective alkylation by primary alcohols in the presence of secondary alcohols was explored. Phenylacetonitrile (1 equivalent) was reacted with 1-butanol and cyclohexanol (each 2 equivalents) in the presence of catalyst **1** (0.5 mol%) and KO^{t}Bu (1 mol%) in which quantitative conversion of nitrile was observed to provide the exclusive formation of 2-phenylhexanenitrile (**2.1b**) (97% isolated yield, Scheme 2.2a). Cyclohexanol remained unreacted and recovered quantitatively from column chromatographic purification of the reaction mixture. Similar experiments using 3-pentanol also provided almost identical results (Scheme 2.2b). When diols such as 1,3-propanediol and 1,6-hexanediol were subjected to the alkylation of phenylacetonitrile, a mixture of products was formed (Scheme 2.2c). Diols having both primary and secondary alcohols functionalities were also employed in the catalytic α-

alkylation of phenylacetonitrile. While no reaction was observed with 1,2-propanediol, 1,3-butanediol provided a mixture of products.

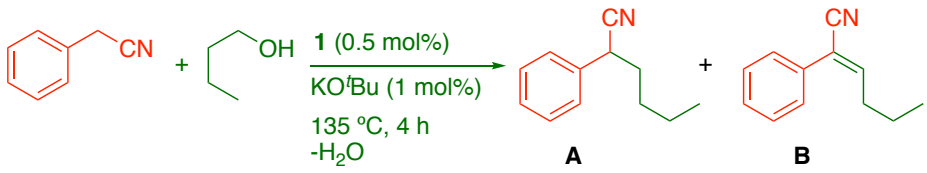
Scheme 2.2 Ruthenium-Catalyzed Chemoselective α-Alkylation of Phenylacetonitrile



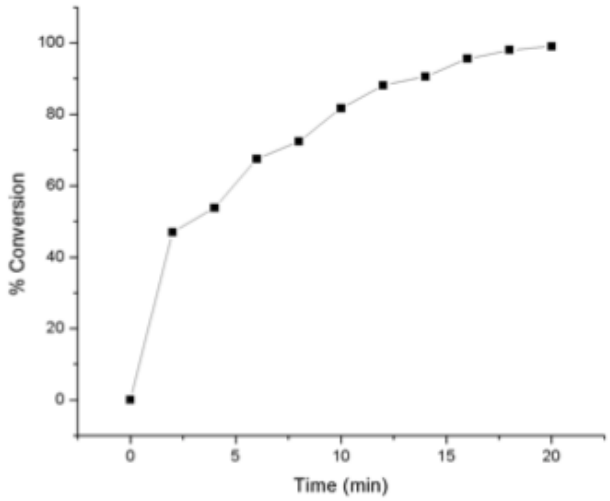
Mechanistic Investigations: To understand the reaction mechanism of the selective α-alkylation of arylmethyl nitriles using alcohols catalyzed by complex **1**, I have carried out in situ monitoring of the reactions progress and labeling studies. GC monitoring of the reactions progress for phenylacetonitrile with 1-butanol catalyzed by **1** (0.5 mol%), confirmed the complete conversion of nitrile substrate in 20 min. Reaction followed first order kinetics with respect to consumption of nitriles (Figure 2.1a). The formation of α-alkylated product and an unsaturated intermediate were also observed in GC and ^{1}H NMR of the reaction mixture. ^{1}H NMR analysis of the reaction mixture showed a triplet signal at δ = 6.75 ppm (J = 7.8 Hz) indicating formation of olefin intermediate, whereas the alkylated product displayed the characteristic doublet of doublets at δ = 3.69 ppm ($^3J_1$ = 6.48 Hz, $^3J_2$ = 1.8 Hz, Figure 2.4). The progress of the catalytic α-

alkylation reaction was rapid; almost 90% of the product formation was observed in just 20 min on GC (Figure 2.1b), while 10% unsaturated intermediate was present in solution. Further completion of the α-alkylation reaction occurred at a slow rate over a 4 h period.

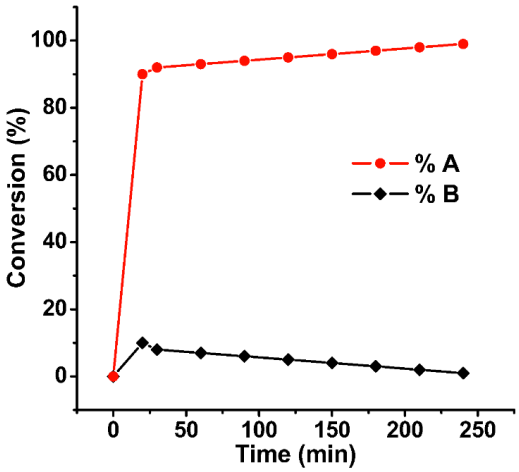
Figure 2.1 GC Monitoring of the Reaction Progress: α-Alkylation of Phenylacetonitrile Catalyzed by **1** using 1-Butanol.



a)



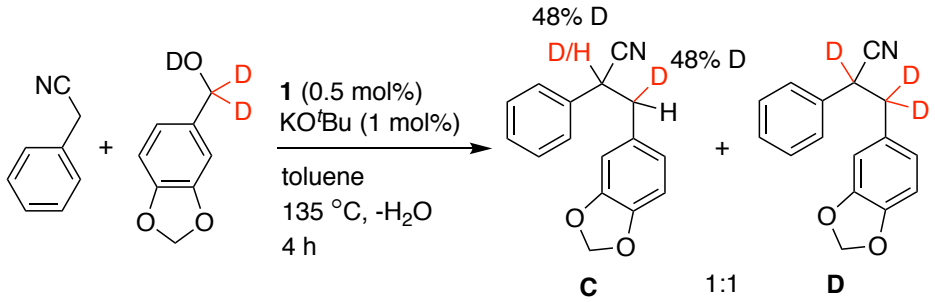
b)



a) Conversion of 2-phenylacetonitrile. b) Formation of α-alkylation product **A** and unsaturated intermediate **B** in the reaction mixture.

The deuterium labeling experiment confirmed the expected deuterium incorporation at the α-position of alkylation product. Upon reaction of phenylacetonitrile with piperonyl alcohol-D_3 catalyzed by **1** under standard optimized conditions, α-alkylated isotopomers **C** and **D** were obtained in 1:1 ratio, indicating that the dideuterium liberated upon catalytic oxidation of piperonyl alcohol- D_3 was predominantly reinstalled in the unsaturated intermediate, which resulted from the aldol condensation reaction. The incorporation of protons in the labeling experiment indicate the H/D exchange between the pincer backbone ND/H_2O and Ru-D/H_2O (Scheme 2.3).[17]

Scheme 2.3 Ruthenium-Catalyzed Selective α-Alkylation of Phenylacetonitrile Using a Labeled Alcohol

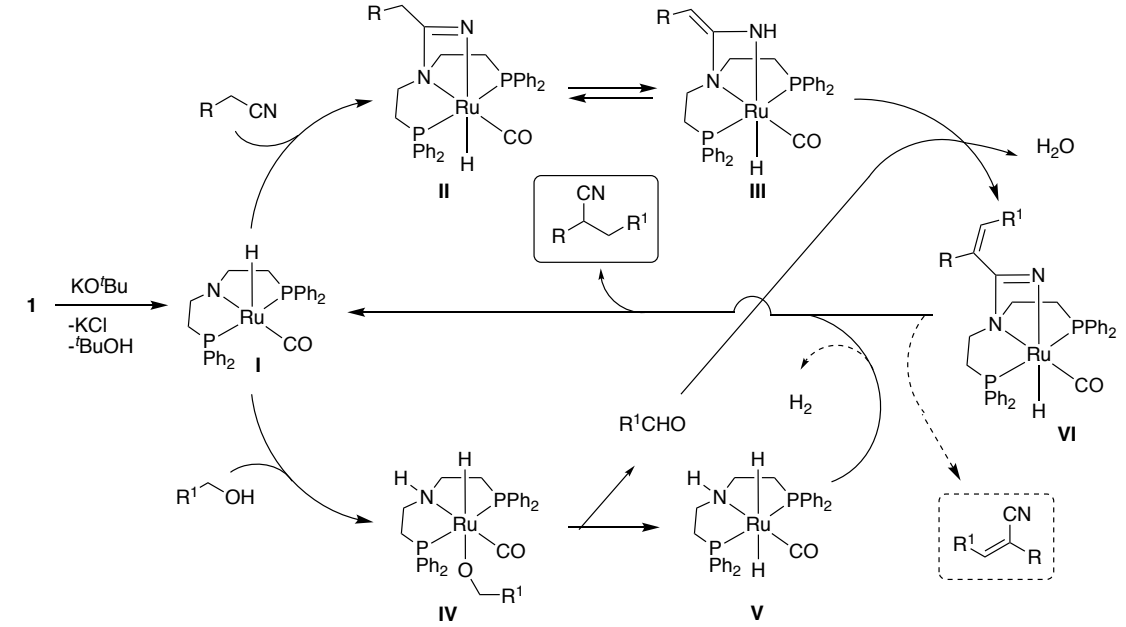


On the basis of these observations and the experimental studies involving catalyst **1** in our earlier work[17] on selective deuteration reactions, I propose the reaction mechanism for the selective α-alkylation of arylmethyl nitriles as depicted in Scheme 2.4. The catalyst **1** displayed robust amine-amide metal ligand cooperation, which made this green transformation possible. Catalyst **1** underwent dechlorination and deprotonation upon reaction with base to provide the 16 electron-unsaturated intermediate **I**. Intermediate **I** react with both alcohol and nitrile reactants. Reaction of **I** with nitrile leads to the formation of 1,2-cycloadduct **II** involving ruthenium center and deprotonated amide-backbone. Such four membered metallocycle intermediate containing ruthenium has its precedence in alkene metathesis process by Grubb's catalyst.[20,21] The imine intermediate **II** tautomerize to become enamine form **III**, which are in equilibrium (Scheme 2.4a). The unsaturated intermediate **I** also reacts with alcohol to provide alkoxy ligated complex **IV**, which resulted from the O–H activation of alcohols.[17] Further, β-hydride elimination of ruthenium ligated alkoxy ligand on intermediate **IV** provides the corresponding aldehydes and Ru-dihydride complex **V**. Conjugate addition of ruthenium enamine adduct **III** over the in situ formed aldehyde generates the intermediate **VI**. The detailed mechanism of this conjugate addition and

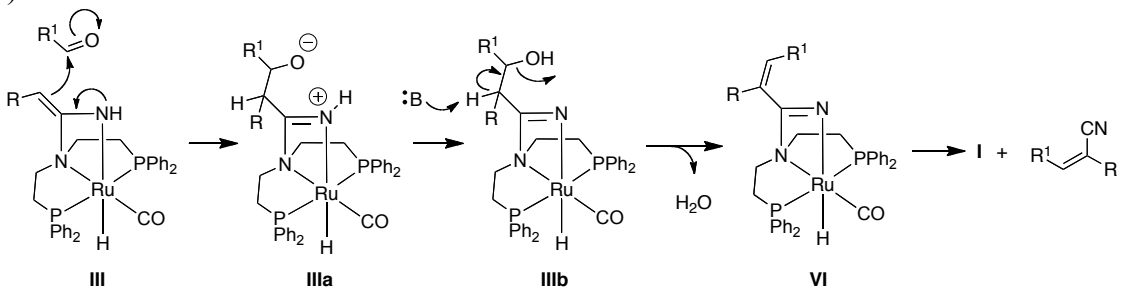
subsequent water elimination, perhaps assisted by base is delineated in Scheme 2.4b. Intermediate **VI**, resulting from the condensation of enamine and aldehydes reacts directly with ruthenium-dihydride **V**, to deliver the selective α-alkylated products with regeneration of catalytically active unsaturated intermediate **I**. Rapid formation of the α-alkylated product as shown in Figure 2.1b suggests that this pathway is predominantly operative. However, formation of the minor amount of vinyl nitrile intermediate (as observed in Figure 2.1b, ^{1}H NMR and GC) observed during the progress of the reaction, indicates the possible dissociation of the vinyl nitrile, which can undergo insertion into Ru−H upon reaction with Ru-dihydride intermediate **V** to generate the intermediate **VII** as delineated in Scheme 2.4c. Further elimination of Ru-alkyl ligand and ligand backbone N−H proton, can provide the α-alkylated arylmethyl nitrile product and regenerate the intermediate **I.**

Scheme 2.4 Proposed Reaction Mechanism: (a) Selective α-alkylation of Arylmethyl Nitriles Catalyzed by Ruthenium Pincer Complex 1 (b) Coupling of In Situ Generated Enamine and Aldehyde Intermediates by Conjugate Addition (C) Catalytic Hydrogenation of Olefin Intermediates

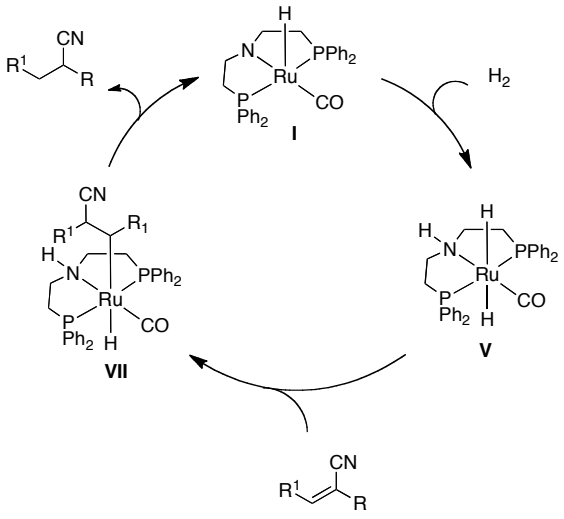
a)



b)



c)



2.4 CONCLUSIONS

In summary, I have demonstrated ruthenium-catalyzed facile α-alkylation of arylmethyl nitriles using alcohols as alkylating reagents and ruthenium pincer complex **1** in which the amine-amide metal-ligand cooperation is operative, which facilitated the overall transformation. Notably, using minimal catalyst load (0.5 mol%) and base (1 mol%), various arylmethyl nitriles can be efficiently and selectively α-alkylated with assortment of linear alcohols in excellent yields. Interestingly, this efficient alkylation is also extended to ethylation as well as challenging methylation reactions using ethanol and methanol, respectively. Chemoselective alkylation by primary alcohols was also demonstrated in the presence of secondary alcohols in an intermolecular fashion. This green catalytic transformation follows the principle of borrowing hydrogen strategy. The ruthenium pincer catalyst **1**, successfully oxidized the primary alcohols to aldehydes and also formed a [2+2] cycloadduct with nitriles, which tautomerizes to its enamine form to undergo conjugate-addition leading to condensation reactions. Subsequent hydrogenation of the intermediate vinyl nitrile (predominantly bound to ruthenium and minor amount in free form) provides the selective α-alkylated products.

2.5 EXPERIMENTAL SECTION

General Experimental: All stoichiometric reactions were performed in nitrogen atmosphere MBRAUN glove box. All catalytic reactions were performed under nitrogen atmosphere using standard Schlenk techniques. Chemicals were purchased from Acros, Sigma-Aldrich, Alfa-aesar, Himedia Chemicals and used without further purification. Catalyst **1** was purchased from Sigma-Aldrich. Dry solvents were prepared according to standard procedures. ^{1}H, ^{13}C spectra were recorded at Bruker AV-400 (^{1}H: 400 MHz, ^{13}C: 100.6 MHz). ^{1}H and ^{13}C $\{^{1}H\}$ NMR chemical shifts were reported in ppm downfield from tetramethyl silane. Multiplicity is abbreviated as: s, singlet; d,

doublet; dd, doublet of doublets; dt, doublet of triplets; t, triplet; q, quartet; dq, doublet of quartets; td, triplet of doublets; m, multiplet; br, broad. Assignment of spectra was done based on one-dimensional (DEPT-135) NMR techniques. Mass spectra were recorded on Bruker micrOTOF-Q II Spectrometer.

General Procedure for α-Alkylation of Phenylacetonitrile Using Alcohols:

To a 15 mL Schlenk tube equipped with a stirrer bar was added catalyst **1** (0.005 mmol), KO^{t}Bu (0.01 mmol), phenylacetonitrile (1 mmol), alcohol (2 mmol) and toluene (1.5 mL) sequentially in the nitrogen atmosphere. The flask was fitted to a condenser and the solution refluxed (oil bath temperature 135 °C) with stirring under the flow of argon for 4 h. The completion of the reaction was monitored using GC. After completion, the solvent was evaporated and crude reaction mixture was purified by column chromatography over silica-gel (100-200 mesh) using ethyl acetate/hexane mixture as an eluent. The conversion of phenylacetonitrile was calculated using GC and yields were determined for pure products after column chromatography.

General Procedure for α-Alkylation of Arylmethyl Nitriles Using Alcohols:

To a 15 mL Schlenk tube equipped with a stirrer bar was added catalyst **1** (0.005 mmol), KO^{t}Bu (0.01 mmol), phenylacetonitrile (1 mmol), alcohol (2 mmol) and toluene (1.5 mL) sequentially in the nitrogen atmosphere and the flask was fitted to a condenser. The reaction mixture was refluxed (oil bath temperature 135 °C) with stirring under the flow of argon for 4 h. The completion of the reaction was monitored using GC. After completion, the solvent was evaporated and the crude reaction mixture was purified by column chromatography over silica-gel (100-200 mesh) using ethyl acetate/hexane mixture as an eluent. The conversion of the nitrile was calculated using GC and yield of the product was determined after column chromatography.

General Procedure for α-Ethylation of Arylmethyl Nitriles Using Ethanol:

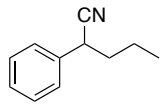
To a 15 mL Schlenk tube equipped with a stirrer bar was added catalyst **1** (0.02 mmol), KO^{t}Bu (0.04 mmol), nitrile (1 mmol), ethanol (5 mmol) and toluene (1.5 mL) sequentially in the nitrogen atmosphere and the flask was fitted to a condenser. The reaction mixture was refluxed (oil bath temperature 135 °C) with stirring under the flow of argon for 4 h. The completion of the reaction was monitored using GC. Upon completion of the reaction, solvent was evaporated and the resulted crude was purified by column chromatography over silica-gel (100-200 mesh) using ethyl acetate/hexane mixture as an eluent. Conversion of the nitrile was calculated using GC and yield of the product was determined by column chromatography.

General Procedure for α-Methylation of Arylmethyl Nitriles Using Methanol:

To a 35 mL sealed tube equipped with a stirrer bar was added catalyst **1** (0.025 mmol), KO^{t}Bu (0.05 mmol), nitrile (1 mmol), methanol (2 mL) sequentially in the nitrogen atmosphere. The solution was refluxed (oil bath temperature 135 °C) with stirring for 40 h under closed condition. After cooling, the solvent was evaporated and the resulted crude was purified by column chromatography over silica-gel (100-200 mesh) using ethyl acetate/hexane mixture as an eluent. The conversion of the nitrile was calculated using GC and the yield was determined after purification from column chromatography.

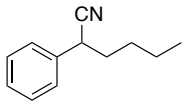
Spectral Data of the α-Alkylated Nitriles:

2-Phenylpentanenitrile (2.1a):[22] Colorless liquid. Yield (91%). IR (DCM): 3032, 2959, 2875, 2240, 1455, 1111, 1074, 1031, 756, 699 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.22-7.30 (m, 5H, ArC*H*), 3.69 (dd, J_1 = 6.4 Hz, J_2 = 2 Hz, 1H, C*H*), 1.71-1.85 (m, 2H, CH_2), 1.37-1.46 (m, 2H, CH_2), 0.87 (t, J = 6.8 Hz, 3H, CH_3). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 136.09 (quat-*C*), 129.06 (Ar*C*H), 127.99 (Ar*C*H),



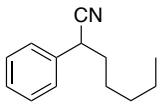
127.26 (Ar*C*H), 120.95 (*C*N), 37.90 (*C*H), 37.16 (CH_2), 20.32 (CH_2), 13.43 (CH_3). MS (ESI) m/z calcd for $C_{11}H_{13}N$ $(M+H)^+$: 160.11, found: 160.11.

2-Phenylhexanenitrile (2.1b):[23] Colorless liquid. Yield (98%). IR (DCM): 3032, 2959,



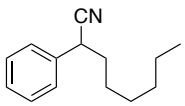
2933, 2863, 2241, 1494, 1455, 755, 698 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.18-7.26 (m, 5H, ArC*H*), 3.64 (dd, J_1 = 6.4 Hz, J_2= 2 Hz, 1H, C*H*), 1.71-1.80 (m, 2H, CH_2), 1.18-1.39 (m, 4H, CH_2), 0.78 (t, J = 6.8 Hz, 3H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 136.05 (quat-*C*), 128.91 (Ar*C*H), 127.84 (Ar*C*H), 127.12 (Ar*C*H), 120.84 (*C*N), 37.20 (*C*H), 35.49 (CH_2), 28.99 (CH_2), 21.97 (CH_2), 13.65 (CH_3). MS (ESI) m/z calcd for $C_{12}H_{15}N$ $(M+H)^+$: 174.12, found: 174.12.

2-Phenylheptanenitrile (2.1c):[23] Colorless liquid. Yield (98%). IR (DCM): 3032,



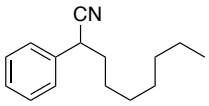
2928, 2862, 2241, 1599, 1494, 1457, 1029, 753, 697 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.19-7.27 (m, 5H, ArC*H*), 3.65 (dd, J_1 = 6.4 Hz, J_2 = 2.4 Hz, 1H, C*H*), 1.69-1.83 (m, 2H, CH_2), 1.31-1.41 (m, 2H, CH_2), 1.17-1.21 (m, 4H, CH_2), 0.78 (t, J = 6.8 Hz, 3H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 136.07 (quat-*C*), 128.95 (Ar*C*H), 127.87 (Ar*C*H), 127.15 (Ar*C*H), 120.88 (*C*N), 37.28 (*C*H), 35.80 (CH_2), 31.02 (CH_2), 26.62 (CH_2), (CH_2), 22.28 (CH_2), 13.86 (CH_3). MS (ESI) m/z calcd for $C_{13}H_{17}N$ $(M+H)^+$: 188.14, found: 188.14.

2-Phenyloctanenitrile (2.1d): Colorless liquid. Yield (98%). IR (DCM): 3063, 3033,

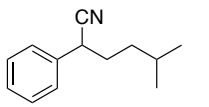


2931, 2861, 2241, 1455, 1379, 1248, 1113, 1076, 1031, 757, 699 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.20-7.28 (m, 5H, ArC*H*), 3.66 (dd, J_1 = 6.4 Hz, J_2 = 2.4 Hz, 1H, C*H*), 1.74-1.83 (m, 2H, CH_2), 1.32-1.43 (m, 2H, CH_2), 1.18-1.24 (m, 6H, CH_2), 0.78 (t, J = 6.8 Hz, 3H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 136.13 (quat-*C*), 129.01 (Ar*C*H), 127.93 (Ar*C*H), 127.21 (Ar*C*H), 120.92 (*C*N), 37.36 (*C*H), 35.90 (CH_2), 31.46 (CH_2), 28.60 (CH_2), 26.97 (CH_2), 22.50 (CH_2), 13.99 (CH_3). HRMS (ESI) m/z calcd for $C_{14}H_{19}N$ $(M+H)^+$: 202.1590, found: 202.1571.

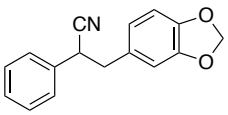
2-Phenylnonanenitrile (2.1e): Colorless liquid. Yield (95%). IR (DCM): 3032, 2929, 2859, 2241, 1455, 1249, 1113, 1076, 1031, 938, 756, 698 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.21-7.27 (m, 5H, ArC*H*), 3.67 (dd, J_1 = 6.4 Hz, J_2 = 2.4 Hz, 1H, C*H*), 1.72-1.84 (m, 2H, CH_2), 1.33-1.43 (m, 2H, CH_2), 1.17-1.21 (m, 8H, CH_2), 0.79 (t, J_H = 6.8 Hz, 3H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 136.15 (quat-*C*), 129.03 (Ar*C*H), 127.96 (Ar*C*H), 127.24 (Ar*C*H), 120.95 (*C*N), 37.40 (*C*H), 35.93 (*C*H_2), 31.71 (*C*H_2), 28.98 (*C*H_2), 28.93 (*C*H_2), 27.05 (*C*H_2), 22.60 (*C*H_2), 14.06 (*C*H_3). HRMS (ESI) m/z calcd for $C_{15}H_{21}N$ $(M+Na)^+$: 238.1566, found: 238.1569.



5-Methyl-2-phenylhexanenitrile (2.1f):[24] Colorless liquid. Yield (96%). IR (DCM): 2955, 2924, 2867, 2241, 1495, 1459, 1368, 1266, 739, 699 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.21-7.31 (m, 5H, ArC*H*), 3.66 (dd, J_1 = 6.4 Hz, J_2 = 2.4 Hz, 1H, C*H*), 1.76-1.85 (m, 2H, CH_2), 1.45-1.55 (m, 1H, C*H*), 1.22-1.34 (m, 2H, CH_2), 0.81 (dd, J_1 = 4 Hz, J_2 = 2.4 Hz, 6H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 136.19 (quat-*C*), 129.12 (Ar*C*H), 128.06 (Ar*C*H), 127.30 (Ar*C*H), 121.03 (*C*N), 37.71 (*C*H_2), 36.12 (*C*H), 34.0 (*C*H_2), 27.71 (*C*H), 22.54 (*C*H_3), 22.32. (*C*H_3). MS (ESI) m/z calcd for $C_{13}H_{17}N$ $(M+H)^+$: 188.14, found: 188.14.



3-(Benzo[*d*][1,3]dioxol-5-yl)-2-phenylpropanenitrile (2.1g): Colorless liquid. Yield (95%). IR (DCM): 2922, 2857, 2241, 1686, 1495, 1446, 1251, 1038, 930, 699 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.25-7.31 (m, 3H, ArC*H*), 7.19 (d, *J* = 6.8 Hz, 2H, ArC*H*), 6.65 (d, *J* = 8 Hz, 1H, ArC*H*), 6.50-6.54 (m, 2H, ArC*H*), 5.87 (s, 2H, CH_2), 3.88 (dd, J_1 = 6.4 Hz, J_2 =2.4 Hz, 1H, C*H*), 2.95-3.06 (m, 2H, CH_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 147.89 (quat-*C*), 147.02 (quat-*C*), 135.27 (quat-*C*), 130.07 (quat-*C*), 129.18 (Ar*C*H), 128.37 (Ar*C*H), 127.61 (Ar*C*H), 122.63 (Ar*C*H), 120.47 (*C*N), 109.62 (Ar*C*H), 108.50 (Ar*C*H), 101.20 (*C*H_2), 42.10 (*C*H_2), 40.19 (*C*H). HRMS (ESI) m/z calcd for $C_{16}H_{13}NO_2$ $(M+H)^+$: 252.1019, found 252.1035.



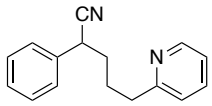
2,5-Diphenylpentanenitrile (2.1h):[24] Colorless liquid. Yield (98%). IR (DCM): 3028, 2933, 2860, 2241, 1600, 1494, 1452, 1266, 737, 695 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.17-7.29 (m, 7H, ArC*H*), 7.04-7.12 (m, 3H, ArC*H*), 3.67 (dd, J_1 = 6.4 Hz, J_2 = 2.4 Hz, 1H, C*H*), 2.56 (t, *J*= 8 Hz, 2H, CH_2), 1.66-1.88 (m, 4H, CH_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 141.16 (quat-*C*), 135.79 (quat-*C*), 129.04 (Ar*C*H), 128.44 (Ar*C*H), 128.34 (Ar*C*H), 128.01 (Ar*C*H), 127.21 (Ar*C*H), 126.05 (Ar*C*H), 120.77 (*C*N), 37.18 (*C*H_2), 35.17 (*C*H_2), 35.05 (*C*H), 28.53 (*C*H_2). MS (ESI) m/z calcd for $C_{17}H_{17}N$ $(M+Na)^+$: 258.12, found: 258.12.

2,6-Diphenylhexanenitrile (2.1i): Colorless liquid. Yield (97%). IR (DCM): 3032, 2930, 2860, 2241, 1494, 1455, 1265, 911, 739, 699 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.18-7.32 (m, 7H, ArC*H*), 7.06-7.12 (m, 3H, ArC*H*), 3.68 (dd, J_1 = 6.4 Hz, J_2= 2.4 Hz, 1H, C*H*), 2.53 (t, *J*= 8 Hz, 2H, CH_2), 1.79-1.90 (m, 2H, CH_2), 1.42-1.61 (m, 4H, CH_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 142.06 (quat-*C*), 136.01 (quat-*C*), 129.12 (Ar*C*H), 128.42 (Ar*C*H), 128.40 (Ar*C*H), 128.07 (Ar*C*H), 127.28 (Ar*C*H), 125.91 (Ar*C*H), 120.90 (*C*N), 37.38 (*C*H_2), 35.82 (*C*H_2), 35.63 (*C*H_2), 30.86 (*C*H), 26.74 (*C*H_2). HRMS (ESI) m/z calcd for $C_{18}H_{19}N$ $(M+Na)^+$: 272.1410, found: 272.1413

2-Phenyl-3-(pyridin-2-yl)propanenitrile (2.1j): Colorless liquid. Yield (61%). IR (DCM): 3058, 2925, 2854, 2241, 1591, 1475, 1439, 1264, 735, 701 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.52 (d, *J* = 4.8 Hz, 1H, ArC*H*), 7.54 (td, J_1 = 5.6 Hz, J_2 = 2 Hz, 1H, ArC*H*), 7.23-7.29 (m, 5H, ArC*H*), 7.13 (dd, J_1= 6.8 Hz, J_2 = 4.8 Hz, 1H, ArC*H*), 7.05 (d, *J*= 8 Hz, 1H, ArC*H*), 4.41 (dd, J_1= 6.4 Hz, J_2 = 8.4 Hz, 1H, C*H*), 3.18-3.31 (m, 2H, CH_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 156.71 (quat-*C*), 150.20 (Ar*C*H), 137.34 (Ar*C*H), 136.01 (quat-*C*), 129.64 (Ar*C*H), 128.73 (Ar*C*H), 127.96

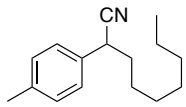
(Ar*C*H), 124.50 (Ar*C*H), 122.94 (Ar*C*H), 121.12 (*C*N), 44.71 (*C*H), 37.86 (*C*H_2). HRMS (ESI) m/z calcd for $C_{14}H_{12}N_2$ $(M+H)^+$: 209.1073, found: 209.1058.

2-Phenyl-5-(pyridin-2-yl)pentanenitrile (2.1k): Colorless liquid. Yield (98%). IR



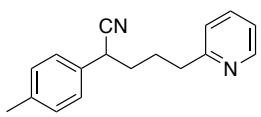
(DCM): 3058, 2928, 2861, 2241, 1591, 1437, 1305, 1150, 994, 754, 698 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.44 (d, J = 4.8 Hz, 1H, ArC*H*), 7.53 (td, J_1 = 6 Hz, J_2 = 2 Hz, 1H, ArC*H*), 7.21-7.31 (m, 5H, ArC*H*), 7.04 (dd, J_1 = 8 Hz, J_2 = 4 Hz, 2H, ArC*H*), 3.75 (dd, J_1 = 6.4 Hz, J_2 = 2.4 Hz, 1H, C*H*), 2.77 (t, J = 7.2 Hz, 2H, CH_2), 1.80-1.94 (m, 4H, CH_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 160.94 (quat-*C*), 149.37 (Ar*C*H), 136.57 (Ar*C*H), 135.84 (quat-*C*), 129.14 (Ar*C*H), 128.12 (Ar*C*H), 127.31 (Ar*C*H), 122.83 (Ar*C*H), 121.37 (Ar*C*H), 120.84 (*C*N), 37.39 (*C*H), 37.28 (*C*H_2), 35.34 (*C*H_2), 27.11 (*C*H_2). HRMS (ESI) m/z calcd for $C_{16}H_{16}N_2$ $(M+H)^+$: 237.1386, found: 237.1393.

2-(*p*-Tolyl)nonanenitrile (2.2a): Colorless liquid. Yield (93%). IR (DCM): 2925, 2857,



2241, 1514, 1460, 1277, 1119, 813, 724 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.12 (dd, J_1 = 8.4 Hz, J_2 = 5.2 Hz, 4H, ArC*H*), 3.66 (dd, J_1 = 6.4 Hz, J_2 = 2 Hz, 1H, C*H*), 2.28 (s, 1H, CH_3), 1.72-1.85 (m, 2H, CH_2), 1.34-1.43 (m, 2H, CH_2), 1.18-1.23 (m, 8H, CH_2) 0.80 (t, J = 7.2 Hz, 3H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 137.88 (quat-*C*), 133.21 (quat-*C*), 129.80 (Ar*C*H), 127.23 (Ar*C*H), 121.26 (*C*N), 37.15 (*C*H_2), 36.06 (*C*H), 31.82 (*C*H_2), 29.09 (*C*H_2), 29.06 (*C*H_2), 27.16 (*C*H_2), 22.71 (*C*H_2), 21.17 (*C*H_2), 14.17 (*C*H_3). HRMS (ESI) m/z calcd for $C_{16}H_{23}N$ $(M+H)^+$: 230.1903, found: 230.1911.

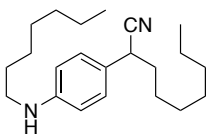
5-(Pyridin-2-yl)-2-(p-tolyl)pentanenitrile (2.2b): Colorless liquid. Yield (97%). IR



(DCM): 3058, 2927, 2861, 2241, 1590, 1513, 1435, 1264, 813, 732 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.43 (d, J = 4.8 Hz, 1H, ArC*H*), 7.51 (td, J_1= 6 Hz, J_2 = 1.6 Hz, 1H, ArC*H*), 7.02-7.13 (m, 6H, ArC*H*), 3.71 (dd, J_1 = 6

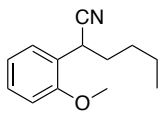
Hz, J_2 = 4 Hz, 1H, C*H*), 2.75 (t, J = 7.2 Hz, 2H, CH_2), 2.26 (s, 3H, CH_3), 1.80-1.92 (m, 4H, CH_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 161.00 (quat-*C*), 149.36 (Ar*C*H), 137.94 (quat-*C*), 136.61 (Ar*C*H), 132.84 (Ar*C*H), 129.81 (Ar*C*H), 127.21 (Ar*C*H), 122.87 (Ar*C*H), 121.39 (Ar*C*H), 121.04 (*C*N), 37.44 (*C*H), 36.91 (*C*H_2), 35.40 (*C*H_2), 27.13 (*C*H_2), 21.13 (*C*H_3). HRMS (ESI) m/z calcd for $C_{17}H_{18}N_2$ $(M+H)^+$: 251.1543, found: 251.1532.

2-(4-(Heptylamino)phenyl)nonanenitrile (2.2c): Colorless liquid. Yield (97%). IR



(DCM): 2926, 2857, 2241, 1615, 1523, 1463, 1326, 1264, 731, 699 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.10 (d, J = 8.4 Hz, 2H, ArC*H*), 6.58 (d, J = 8.8 Hz, 2H, ArC*H*), 3.64 (dd, J_1 = 6.4 Hz, J_2 = 2 Hz, 1H, C*H*), 3.10 (t, J = 7.2 Hz, 2H, CH_2), 1.78-1.89 (m, 2H, CH_2), 1.58-1.65 (m, 2H, CH_2), 1.26-1.43 (m, 19H, CH_2 & N*H*), 0.88 (dd, J_1 = 7.2 Hz, J_2 = 6 Hz, 6H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 148.15 (quat-*C*), 128.25 (Ar*C*H), 124.36 (quat-*C*), 121.74 (*C*N), 113.09 (Ar*C*H), 44.17 (*C*H_2), 36.67 (*C*H_2), 36.11 (*C*H), 31.92 (*C*H_2), 31.84 (*C*H_2), 29.58 (*C*H_2), 29.22 (*C*H_2), 29.12 (*C*H_2), 29.08 (*C*H_2), 27.22 (*C*H_2), 27.14 (*C*H_2), 22.73 (*C*H_2), 22.72 (*C*H_2), 14.20 (*C*H_3), 14.17 (*C*H_3). HRMS (ESI) m/z calcd for $C_{22}H_{36}N_2$ $(M+H)^+$: 329.2951, found: 329.2950.

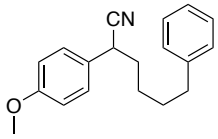
2-(2-Methoxyphenyl)hexanenitrile (2.2d): Colorless liquid. Yield (96%). IR (DCM):



2959, 2864, 2241, 1601, 1469, 1250, 1029, 753, 704 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.30 (dd, J_1 = 6 Hz, J_2 = 1.2 Hz, 1H, ArC*H*), 7.19 (td, J_1 = 6.4 Hz, J_2 =1.6 Hz, 1H, ArC*H*), 6.88 (td, J_1 = 7.2 Hz, J_2 = 0.4 Hz, 1H, ArC*H*), 6.79 (d, J = 8 Hz, 1H, ArC*H*), 4.08 (dd, J_1 = 6.8 Hz, J_2 = 1.2 Hz, 1H, C*H*), 3.74 (s, 1H, OCH_3), 1.72-1.78 (m, 2H, CH_2), 1.23-1.41 (m, 4H, CH_2), 0.82 (t, J = 7.2 Hz, 3H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 156.08 (quat-*C*), 129.22 (Ar*C*H), 128.24 (Ar*C*H), 124.49 (quat-*C*), 121.37 (Ar*C*H), 120.89 (*C*N), 110.79 (Ar*C*H), 55.47 (*C*H_3), 33.47 (*C*H_2), 31.33 (*C*H_2),

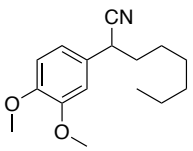
29.30 (*C*H), 22.07 (*C*H_2), 13.78 (*C*H_3). HRMS (ESI) m/z calcd for $C_{13}H_{17}NO$ $(M+H)^+$: 204.1383, found: 204.1371.

2-(4-Methoxyphenyl)-6-phenylhexanenitrile (2.2e): Colorless liquid. Yield (96%). IR



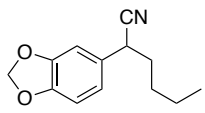
(DCM): 3026, 2930, 2857, 2241, 1609, 1510, 1249, 1179, 1032, 830, 745 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.05-7.20 (m, 7H, ArC*H*), 6.80 (d, *J* = 8.4 Hz, 2H, ArC*H*), 3.71 (s, 3H, OCH_3), 3.60 (dd, J_1 = 6.4 Hz, J_2 = 2 Hz, 1H, C*H*), 2.51 (t, *J* = 7.6 Hz, 2H, CH_2), 1.72-1.87 (m, 2H, CH_2), 1.53-1.60 (m, 2H, CH_2), 1.36-1.48 (m, 2H, CH_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 159.37 (quat-*C*), 142.12 (quat-*C*), 128.43 (Ar*C*H), 128 (Ar*C*H), 125.92 (Ar*C*H), 121.22 (*C*N), 114.49 (Ar*C*H), 55.41 (O*C*H_3), 36.58 (*C*H_2), 35.88 (*C*H_2), 35.67 (*C*H_2), 30.89 (*C*H), 26.71 (*C*H_2). HRMS (ESI) m/z calcd for $C_{19}H_{21}NO$ $(M+Na)^+$: 302.1515, found: 302.1511.

2-(3,4-Dimethoxyphenyl)octanenitrile (2.2f): Colorless liquid. Yield (97%). IR



(DCM): 3055, 2929, 2855, 2241, 1516, 1422, 1264, 1150, 1030, 895, 730 cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.75-7.78 (m, 3H, ArC*H*), 3.83 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 3.64 (dd, J_1 = 6.4 Hz, J_2 = 2 Hz, 1H, C*H*), 1.73-1.86 (m, 2H, CH_2), 1.35-1.45 (m, 2H, CH_2), 1.18-1.27 (m, 6H, CH_2), 0.81 (t, *J* = 6.4 Hz, 3H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 149.45 (quat-*C*), 148.86 (quat-*C*), 128.61 (quat-*C*), 121.28 (Ar*C*H), 119.66 (*C*N), 111.50 (Ar*C*H), 110.34 (Ar*C*H), 56.10 (O*C*H_3), 56.07 (O*C*H_3), 37.11 (*C*H_2), 36.05 (*C*H), 31.61 (*C*H_2), 28.73 (*C*H_2), 27.11 (*C*H_2), 22.62 (*C*H_2), 14.11 (*C*H_3). HRMS (ESI) m/z calcd for $C_{16}H_{23}NO_2$ $(M+Na)^+$: 284.1621, found: 284.1618.

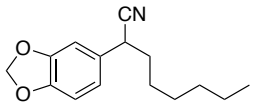
2-(Benzo[*d*][1,3]dioxol-5-yl)hexanenitrile (2.2g): Colorless liquid. Yield (96%). IR



(DCM): 2957, 2933, 2874, 2241, 1483, 1248, 1040, 932, 811, 737 cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.70 (s, 1H, ArC*H*), 6.67 (s, 2H, ArC*H*), 5.85 (s, 2H, CH_2), 3.58 (dd, J_1 = 6.8 Hz, J_2 = 1.6 Hz, 1H, C*H*), 1.67-1.79 (m, 2H, CH_2),

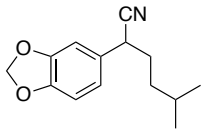
1.19-1.39 (m, 4H, CH_2), 0.80 (t, J = 7.2 Hz, 3H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 148.12 (quat-*C*), 147.26 (quat-*C*), 129.67 (quat-*C*), 120.95 (Ar*C*H), 120.55 (*C*N), 108.41 (Ar*C*H), 107.52 (Ar*C*H), 101.30 (*C*H_2), 36.84 (*C*H_2), 35.52 (*C*H), 28.93 (*C*H_2), 21.97 (*C*H_2), 13.67 (*C*H_3). HRMS (ESI) m/z calcd for $C_{13}H_{15}NO_2$ $(M+Na)^+$: 240.0995, found: 240.0987.

2-(Benzo[*d*][1,3]dioxol-5-yl)octanenitrile (2.2h): Colorless liquid. Yield (96%). IR



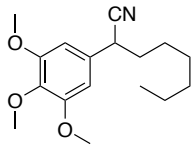
(DCM): 2953, 2927, 2858, 2240, 1487, 1443, 1245, 1037, 931, 808, 725 cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.71 (s, 1H, ArC*H*), 6.69 (s, 2H, ArC*H*), 5.87 (s, 2H, CH_2), 3.59 (dd, J_1 = 6.4 Hz, J_2 = 2 Hz, 1H, C*H*), 1.69-1.81 (m, 2H, CH_2), 1.32-1.39 (m, 2H, CH_2), 1.19-1.27 (m, 6H, CH_2), 0.79 (t, J = 7.2 Hz, 3H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 148.21 (quat-*C*), 147.36 (quat-*C*), 129.76 (quat-*C*), 121.04 (Ar*C*H), 120.66 (*C*N), 108.54 (Ar*C*H), 107.63 (Ar*C*H), 101.39 (*C*H_2), 37.02 (*C*H_2), 35.94 (*C*H), 31.49 (*C*H_2), 28.61 (*C*H_2), 26.92 (*C*H_2), 22.52 (*C*H_2), 14.01 (*C*H_3). HRMS (ESI) m/z calcd for $C_{15}H_{19}NO_2$ $(M+Na)^+$: 268.1308, found: 268.1294.

2-(Benzo[*d*][1,3]dioxol-5-yl)-5-methylhexanenitrile (2.2i): Colorless liquid. Yield



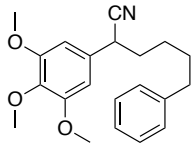
(90%). IR (DCM): 2957, 2929, 2906, 2872, 2240, 1487, 1445, 1368, 1249, 1040, 932, 810 cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.71 (s, 1H, ArC*H*), 6.68 (s, 2H, ArC*H*), 5.86 (s, 2H, CH_2), 3.56 (dd, J_1 = 6.4 Hz, J_2 = 2 Hz, 1H, C*H*), 1.71-1.81 (m, 2H, CH_2), 1.43-1.53 (m, 1H, C*H*), 1.17-1.29 (m, 2H, CH_2), 0.79 (dd, J_1 = 6.4 Hz, J_2 = 1.6 Hz, 6H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 148.18 (quat-*C*), 147.33 (quat-*C*), 129.73 (quat-*C*), 120.99 (*C*N), 120.61 (Ar*C*H), 108.49 (Ar*C*H), 107.57 (Ar*C*H), 101.35 (*C*H_2), 37.18 (*C*H_2), 35.91 (*C*H), 33.89 (*C*H_2), 27.59 (*C*H), 22.41 (*C*H_3), 22.22 (*C*H_3). HRMS (ESI) m/z calcd for $C_{14}H_{17}NO_2$ $(M+Na)^+$: 254.1151, found: 254.1170.

2-(3,4,5-Trimethoxyphenyl)octanenitrile (2.2j):[25] Colorless liquid. Yield (97%). IR (DCM): 2930, 2859, 2241, 1591, 1458, 1334, 1238, 1124, 1006, 828, 732 cm^{-1}. ^1H



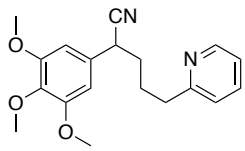
NMR ($CDCl_3$): δ 6.50 (s, 2H, ArC*H*), 3.85 (s, 6H, OCH_3), 3.82 (s, 3H, OCH_3), 3.68 (dd, J_1 = 6.4 Hz, J_2 = 2 Hz, 1H, C*H*), 1.78-1.94 (m, 2H, CH_2), 1.41-1.53 (m, 2H, CH_2), 1.27-1.35 (m, 6H, CH_2), 0.87 (t, J = 6.8 Hz, 3H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 153.63 (quat-*C*), 137.69 (quat-*C*), 131.76 (quat-*C*), 120.97 (*C*N), 104.37 (Ar*C*H), 60.89 (O*C*H3), 56.26 (O*C*H3), 37.72 (*C*H_2), 35.97 (*C*H), 31.53 (*C*H_2), 28.66 (*C*H_2), 27.13 (*C*H_2), 22.55 (*C*H_2), 14.04 (*C*H_3). MS (ESI) m/z calcd for $C_{17}H_{25}NO_3$ $(M+H)^+$: 292.19, found: 292.19.

6-Phenyl-2-(3,4,5-trimethoxyphenyl)hexanenitrile (2.2k): Colorless liquid. Yield



(98%). IR (DCM): 3025, 2932, 2859, 2241, 1593, 1456, 1333, 1239, 1126, 742, 697 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.19-7.23 (m, 2H, ArC*H*), 7.07-7.13 (m, 3H, ArC*H*), 6.43 (s, 2H, ArC*H*), 3.80 (s, 6H, OCH_3), 3.77 (s, 3H, OCH_3), 3.61 (dd, J_1 = 6.4 Hz, J_2 = 2.4 Hz, 1H, C*H*), 2.56 (t, J = 7.2 Hz, 2H, CH_2), 1.77-1.90 (m, 2H, CH_2), 1.56-1.64 (m, 2H, CH_2), 1.41-1.55 (m, 2H, CH_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 153.56 (quat-*C*), 141.92 (quat-*C*), 137.62 (quat-*C*), 131.53 (quat-*C*), 128.31 (Ar*C*H), 125.82 (Ar*C*H), 120.81 (*C*N), 104.28 (Ar*C*H), 60.80 (O*C*H_3), 56.17 (O*C*H_3), 37.54 (*C*H_2), 35.75 (*C*H_2), 35.55 (*C*H), 30.75 (*C*H_2), 26.72 (*C*H_2). HRMS (ESI) m/z calcd for $C_{21}H_{25}NO_3$ $(M+H)^+$: 340.1907, found: 340.1904.

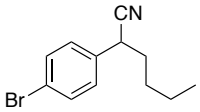
6-(Pyridin-2-yl)-2-(3,4,5-trimethoxyphenyl)pentanenitrile (2.2l): Colorless liquid.



Yield (96%). IR (DCM): 3055, 2936, 2843, 2241, 1591, 1460, 1239, 1125, 1004, 731 cm^{-1}. ^1H NMR ($CDCl_3$): δ 8.43 (d, J = 4.4 Hz, 1H, ArC*H*), 7.50-7.55 (m, 1H, ArC*H*), 7.05 (dd, J_1 = 5.6 Hz, J_2 = 2 Hz, 2H, ArC*H*), 6.43 (s, 2H, ArC*H*), 3.78 (s, 6H, OCH_3), 3.75 (s, 3H, OCH_3), 3.69 (dd, J_1 = 5.6 Hz, J_2 = 4.4 Hz, 1H, C*H*), 2.77 (t, J = 6.8 Hz, 2H, CH_2), 1.82-1.94 (m, 4H, CH_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 160.89 (quat-*C*), 153.65 (quat-*C*), 149.29 (Ar*C*H), 137.74 (Ar*C*H), 136.62 (quat-*C*), 131.39 (quat-*C*), 122.87 (Ar*C*H), 121.40 (Ar*C*H), 120.80 (*C*N), 104.39

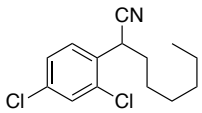
(ArCH), 60.89 (OCH$_3$), 56.26 (OCH$_3$), 37.45 (CH$_2$), 37.30 (CH$_2$), 35.30 (CH), 27.11 (CH$_2$). HRMS (ESI) m/z calcd for $C_{19}H_{22}N_2O_3$ $(M+H)^+$: 327.1703, found: 327.1706.

2-(4-Bromophenyl)hexanenitrile (2.2m): Colorless liquid. Yield (90%). IR (DCM):



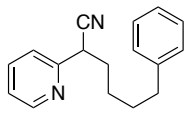
2958, 2930, 2862, 2242, 1625, 1472, 1265, 1073, 824, 739 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.41 (d, J = 8.4 Hz, 2H, ArCH), 7.12 (d, J = 8.4 Hz, 2H, ArCH), 3.66 (dd, J_1 = 6.4 Hz, J_2 = 2 Hz, 1H, CH), 1.75-1.81 (m, 2H, CH$_2$), 1.25-1.38 (m, 4H, CH$_2$), 0.81 (t, J = 7.2 Hz, 3H, CH$_3$). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 135.14 (quat-C), 132.21 (ArCH), 128.99 (ArCH), 122.03 (quat-C), 120.45 (CN), 36.89 (CH$_2$), 35.46 (CH), 29.03 (CH$_2$), 22.08 (CH$_2$), 13.79 (CH$_3$). HRMS (ESI) m/z calcd for $C_{12}H_{14}N$ $(M+H)^+$: 252.0382, found: 252.0388.

2-(2,4-Dichlorophenyl)octanenitrile (2.2n): Colorless liquid. Yield (82%): IR (DCM):



2949, 2930, 2860, 2241, 1470, 1249, 1103, 1040, 935, 868, 818 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.41 (d, J = 8.4 Hz, 1H, ArCH), 7.33 (d, J = 2 Hz, 1H, ArCH), 7.22 (dd, J_1 = 6 Hz, J_2 = 2.4 Hz, 1H, ArCH), 4.14 (dd, J_1 = 6.4 Hz, J_2 = 1.6 Hz, 1H, CH), 1.73-1.79 (m, 2H, CH$_2$), 1.38-1.50 (m, 2H, CH$_2$), 1.17-1.27 (m, 6H, CH$_2$), 0.80 (t, J = 6.8 Hz, 3H, CH$_3$). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 134.74 (quat-C), 133.38 (quat-C), 132.67 (quat-C), 129.87 (ArCH), 129.79 (ArCH), 128 (ArCH), 120.01 (CN), 34.35 (CH$_2$), 34.17 (CH$_2$), 31.52 (CH$_2$), 28.55 (CH), 27.06 (CH$_2$), 22.57 (CH$_2$), 14.07 (CH$_3$). HRMS (ESI) m/z calcd for $C_{14}H_{18}Cl_2N$ $(M+H)^+$: 270.0810, found: 270.0837.

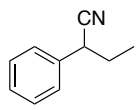
6-Phenyl-2-(pyridin-2-yl)hexanenitrile (2.2o): Colorless liquid. Yield (96%). IR



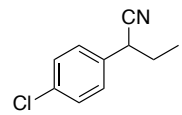
(DCM): 3026, 2932, 2860, 2242, 1635, 1589, 1372, 1241, 1046, 746, 698 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 8.48 (d, J = 4.8 Hz, 1H, ArCH), 7.59 (dd, J_1 = 6 Hz, J_2 = 1.6 Hz, 1H, ArCH), 7.29 (d, J = 8 Hz, 1H, ArCH), 7.11-7.18 (m, 3H, ArCH), 7.03-7.08 (m, 3H, ArCH), 3.85 (t, J = 7.2 Hz, 1H, CH), 2.50 (t, J = 7.2 Hz, 2H, CH$_2$), 1.94 (dd, J_1 = 8, J_2 = 7.6 Hz, 2H, CH$_2$), 1.40-1-61 (m, 6H, CH$_2$). ^{13}C{^{1}H} NMR

($CDCl_3$): δ 155.26 (quat-*C*), 149.88 (Ar*C*H), 141.98 (quat-*C*), 137.27 (Ar*C*H), 128.32 (Ar*C*H), 125.80 (Ar*C*H), 122.91 (Ar*C*H), 121.67 (Ar*C*H), 120.13 (*C*N), 39.73 (*C*H_2), 35.49 (*C*H_2), 33.95 (*C*H_2), 30.75 (*C*H), 26.62 (*C*H_2). HRMS (ESI) m/z calcd for $C_{17}H_{18}N_2$ $(M+H)^+$: 251.1543, found: 251.1551.

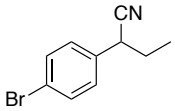
2-Phenylbutanenitrile (2.3a):[24] Colorless liquid. Yield (83%). IR (DCM): 3030, 2971, 2936, 2879, 2241, 1463, 1090, 1031, 912, 760, 699 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.24-7.32 (m, 5H, ArC*H*), 3.66 (t, *J* = 7.2 Hz, 1H, C*H*), 1.83-1.90 (m, 2H, CH_2), 1.00 (t, *J* = 7.2 Hz, 3H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 135.87 (quat-*C*), 129.14 (Ar*C*H), 128.13 (Ar*C*H), 127.41 (Ar*C*H), 120.87 (*C*N), 39.04 (*C*H), 29.33 (*C*H_2), 11.60 (*C*H_3). MS (ESI) m/z calcd for $C_{10}H_{11}N$ $(M+H)^+$: 146.08, found: 146.08.



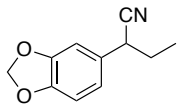
2-(4-Chlorophenyl)butanenitrile (2.3b):[26] Colorless liquid. Yield (78%). IR (DCM): 2972, 2933, 2877, 2241, 1491, 1264, 1092, 1015, 824, 731 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.18-7.31 (m, 4H, ArC*H*), 3.64 (t, *J* = 6.8 Hz, 1H, C*H*), 1.82-1.89 (m, 2H, CH_2), 0.99 (t, *J* = 7.2 Hz, 3H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 134.34 (quat-*C*), 134.16 (quat-*C*), 129.35 (Ar*C*H), 128.78 (Ar*C*H), 120.41 (*C*N), 38.46 (*C*H), 29.25 (*C*H_2), 11.49 (*C*H_3). MS (ESI) m/z calcd for $C_{10}H_{10}ClN$ $(M+H)^+$: 180.05, found: 180.05.



2-(4-Bromophenyl)butanenitrile (2.3c): Colorless liquid. Yield (66%). IR (DCM): 3054, 2972, 2936, 2241, 1489, 1265, 1074, 1012, 737 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.43 (d, *J* = 8.4 Hz, 2H, ArC*H*), 7.13 (d, *J* = 8.4 Hz, 2H, ArC*H*), 3.63 (t, *J* = 6.8 Hz, 1H, C*H*), 1.79-1.90 (m, 2H, CH_2), 0.99 (t, *J* = 7.2 Hz, 3H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 134.85 (quat-*C*), 132.29 (Ar*C*H), 129.10 (Ar*C*H), 122.17 (quat-*C*), 120.32 (*C*N), 38.50 (*C*H), 29.17 (*C*H_2), 11.47 (*C*H_3). HRMS (ESI) m/z calcd for $C_{10}H_{10}BrN$ $(M+H)^+$: 224.0069, found: 224.0077.

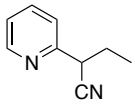


2-(Benzo[*d*][1,3]dioxol-5-yl)butanenitrile (2.3d): Colorless liquid. Yield (66%). IR



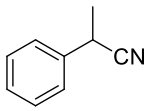
(DCM): 3055, 2972, 2932, 2241, 1490, 1445, 1265, 1040, 932, 811, 740 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 6.70-6.73 (m, 3H, ArC*H*), 5.90 (s, 2H, CH_2), 3.57 (t, *J* = 6.8 Hz, 1H, C*H*), 1.79-1.87 (m, 2H, CH_2), 0.98 (t, *J* = 7.6 Hz, 3H, CH_3). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 148.30 (quat-*C*), 147.49 (quat-*C*), 129.50 (quat-*C*), 120.93 (*C*N), 120.84 (Ar*C*H), 108.64 (Ar*C*H), 107.78 (Ar*C*H), 101.48 (O*C*H_2), 38.67 (*C*H), 29.36 (*C*H_2), 11.53 (*C*H_3). HRMS (ESI) m/z calcd for $C_{11}H_{11}NO_2$ $(M+H)^+$: 190.0863, found: 190.0887.

2-(Pyridin-2-yl)butanenitrile (2.3e):[27] Colorless liquid. Yield (82%). IR (DCM): 2971,



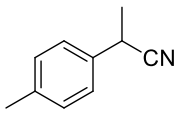
2929, 2877, 2241, 1586, 1467, 1436, 1266, 995, 748 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 8.51 (d, *J* = 4.4 Hz, 1H, ArC*H*), 7.66 (td, J_1 = 6 Hz, J_2 = 1.6 Hz, 1H, ArC*H*), 7.36 (d, *J* = 8 Hz, 1H, ArC*H*), 7.17-7.21 (m, 1H, ArC*H*), 3.87 (t, J_1 = 6 Hz, J_2 = 2 Hz, 1H, C*H*), 1.93-2.06 (m, 2H, CH_2), 1.02 (t, *J* = 7.6 Hz, 3H, CH_3). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 155.26 (quat-*C*), 149.97 (Ar*C*H), 137.33 (Ar*C*H), 122.99 (Ar*C*H), 121.83 (Ar*C*H), 120.12 (*C*N), 41.36 (*C*H), 27.68 (*C*H_2), 11.49 (*C*H_3). MS (ESI) m/z calcd for $C_9H_{10}N_2$ $(M+H)^+$: 147.09, found: 147.09.

2-Phenylpropanenitrile (2.4a):[23] Colorless liquid. Yield (83%). IR (DCM): 3030,



2983, 2934, 2241, 1493, 1450, 1077, 754, 694 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.25-7.32 (m, 5H, ArC*H*), 3.82 (q, *J* = 7.6 Hz, 1H, C*H*), 1.57 (d, *J* = 7.2 Hz, 3H, CH_3). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$): δ 137.16 (quat-*C*), 129.22 (Ar*C*H), 128.12 (Ar*C*H), 126.78 (Ar*C*H), 121.68 (*C*N), 31.31 (*C*H), 21.53 (*C*H_3). MS (ESI) m/z calcd for C_9H_9N $(M+H)^+$: 132.08, found: 132.08.

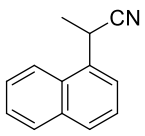
2-(*p*-Tolyl)propanenitrile (2.4b):[28] Colorless liquid. Yield (48%). IR (DCM): 2984,



2937, 2925, 2241, 1513, 1453, 1378, 1084, 814, 731 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.16 (d, *J* = 8.4 Hz, 2H, ArC*H*), 7.11 (d, *J* = 8 Hz, 2H,

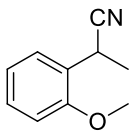
ArC*H*), 3.78 (q, *J* = 7.2 Hz, 1H, C*H*), 2.27 (s, 3H, CH_3), 1.54 (d, *J* = 7.2 Hz, 3H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 137.97 (quat-*C*), 134.22 (quat-*C*), 129.89 (Ar*C*H), 126.69 (Ar*C*H), 121.89 (*C*N), 30.99 (*C*H), 21.61 (*C*H_3), 21.15 (*C*H_3). MS (ESI) m/z calcd for $C_{10}H_{11}N$ $(M+H)^+$: 146.09, found: 146.09.

2-(Naphthalen-1-yl)propanenitrile (2.4c):[23] Colorless liquid. Yield (44%): IR (DCM):



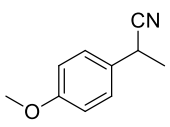
3030, 2983, 2934, 2241, 1493, 1450, 1077, 754, 694 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.85 (t, *J* = 8.4 Hz, 2H, ArC*H*), 7.77 (d, *J* = 8.4 Hz, 1H, ArC*H*), 7.63 (d, *J* = 7.2 Hz, 1H, ArC*H*), 7.41-7.54 (m, 3H, ArC*H*), 4.55 (q, *J* = 7.6 Hz, 1H, C*H*), 1.72 (d, *J* = 7.2 Hz, 3H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 134.12 (quat-*C*), 132.78 (quat-*C*), 129.91 (quat-*C*), 129.43 (Ar*C*H), 129.06 (Ar*C*H), 127.04 (Ar*C*H), 126.24 (Ar*C*H), 125.68 (Ar*C*H), 124.81 (Ar*C*H), 122.19 (Ar*C*H), 121.92 (*C*N), 28.36 (*C*H), 20.68 (*C*H_3). MS (ESI) m/z calcd for $C_{13}H_{11}N$ $(M+Na)^+$: 204.07, found: 204.07.

2-(2-Methoxyphenyl)propanenitrile (2.4d):[28] Colorless liquid. Yield (44%). IR



(DCM): 2941, 2840, 2242, 1596, 1493, 1459, 1248, 1026, 734 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.33 (dd, J_1 = 6 Hz, J_2 = 1.6 Hz, 1H, ArC*H*), 7.22 (td, J_1 = 6.8 Hz, J_2 = 1.6 Hz, 1H, ArC*H*), 6.90 (td, J_1 = 6.8 Hz, J_2 = 0.8 Hz, 1H, ArC*H*), 6.81 (dd, *J* = 7.6 Hz, J_2 = 0.8 Hz, 1H, ArC*H*), 4.16 (q, *J* = 7.2 Hz, 1H, C*H*), 3.37 (s, 3H, OCH_3), 1.49 (d, *J* = 7.2 Hz, 3H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 156.11 (quat-*C*), 129.40 (Ar*C*H), 127.64 (Ar*C*H), 125.45 (Ar*C*H), 122.07 (*C*N), 121.05 (quat-*C*), 110.85 (Ar*C*H), 55.54 (O*C*H_3), 25.68 (*C*H), 19.58 (*C*H_3). MS (ESI) m/z calcd for $C_{10}H_{11}NO$ $(M+Na)^+$: 184.07, found: 184.07.

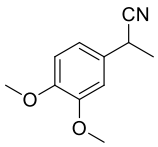
2-(4-Methoxyphenyl)propanenitrile (2.4e):[28] Colorless liquid. Yield (40%). IR



(DCM): 2936, 2841, 2241, 1611, 1511, 1458, 1247, 1031, 830, 732 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.19 (dd, J_1 = 4.4 Hz, J_2 = 2 Hz, 2H, ArC*H*), 6.83 (dd, J_1 = 4.8 Hz, J_2 = 2 Hz, 2H, ArC*H*), 3.77 (q, *J* = 7.2 Hz, 1H, C*H*), 3.73 (s, 3H,

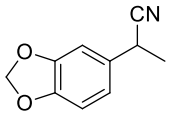
OC*H*$_3$), 1.54 (d, *J* = 7.2 Hz, 3H, C*H*$_3$). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 159.41 (quat-*C*), 129.20 (quat-*C*), 127.95 (Ar*C*H), 121.98 (*C*N), 114.59 (Ar*C*H), 55.46 (O*C*H$_3$), 30.56 (*C*H), 21.62 (*C*H$_3$). MS (ESI) m/z calcd for $C_{10}H_{11}NO$ $(M+H)^+$: 162.09, found: 162.09.

2-(3,4-Dimethoxyphenyl)propanenitrile (2.4f):[28] Colorless liquid. Yield (42%). IR



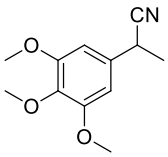
(DCM): 2937, 2838, 2241, 1596, 1513, 1457, 1235, 1146, 1024, 810 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 6.77-6.83 (m, 3H, ArC*H*), 3.83 (s, 3H, OC*H*$_3$), 3.80 (s, 3H, OC*H*$_3$), 3.77 (q, *J* = 7.2 Hz, 1H, C*H*), 1.56 (d, *J* = 7.2 Hz, 3H, C*H*$_3$). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 149.49 (quat-*C*), 148.89 (quat-*C*), 129.59 (quat-*C*), 121.89 (*C*N), 119.01 (Ar*C*H), 111.57 (Ar*C*H), 109.91 (Ar*C*H), 56.06 (O*C*H$_3$), 30.92 (*C*H), 21.59 (*C*H$_3$). MS (ESI) m/z calcd for $C_{11}H_{13}NO_2$ $(M+H)^+$: 192.10, found: 192.10.

2-(Benzo[*d*][1,3]dioxol-5-yl)propanenitrile (2.4g):[28] Colorless liquid. Yield (61%). IR



(DCM): 2987, 2904, 2242, 1490, 1442, 1239, 1035, 926, 810, 733 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 6.74 (s, 1H, ArC*H*), 6.71 (dd, J_1 = 6 Hz, J_2 = 1.6 Hz, 2H, ArC*H*), 5.89 (s, 2H, C*H*$_2$), 3.73 (q, *J* = 7.6 Hz, 1H, C*H*), 1.52 (d, *J* = 7.6 Hz, 3H, C*H*$_3$). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 148.34 (quat-*C*), 147.48 (quat-*C*), 130.86 (quat-*C*), 121.72 (*C*N), 120.15 (Ar*C*H), 108.71 (Ar*C*H), 107.30 (Ar*C*H), 101.48 (O*C*H$_2$), 31.01 (*C*H), 21.63 (*C*H$_3$). MS (ESI) m/z calcd for $C_{10}H_9NO_2$ $(M+Na)^+$: 198.05, found: 198.05.

2-(3,4,5-Trimethoxyphenyl)propanenitrile (2.4h):[25] Colorless liquid. Yield (42%). IR



(DCM): 2939, 2837, 2241, 1590, 1457, 1330, 1120, 1003, 827 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 6.48 (s, 2H, ArC*H*), 3.80 (s, 6H, OC*H*$_3$), 3.76 (s, 3H, OC*H*$_3$), 3.76 (q, *J* = 7.2 Hz, 1H, C*H*), 1.56 (d, *J* = 7.2 Hz, 3H, C*H*$_3$). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 153.65 (quat-*C*), 137.67 (quat-*C*), 132.70 (quat-*C*), 121.59 (*C*N), 103.84 (Ar*C*H), 60.82 (O*C*H$_3$), 56.20 (O*C*H$_3$), 31.44 (*C*H), 21.48 (*C*H$_3$). MS (ESI) m/z calcd for $C_{12}H_{15}NO_3$ $(M+H)^+$: 244.09, found: 244.09.

General Procedure for the Chemoselective α-Alkylation of Phenylacetonitrile:

To a 15 mL Schlenk tube equipped with a stirrer bar was added catalyst **1** (0.005 mmol), KO^{t}Bu (0.01 mmol), phenylacetonitrile (1 mmol), primary alcohol (2 mmol), secondary alcohol (2 mmol) and toluene (1.5 mL) sequentially in the nitrogen atmosphere. The flask was fitted to a condenser and the solution refluxed (oil bath temperature 135 °C) with stirring under the flow of argon for 4 h. The completion of the reaction was monitored using GC. After completion, the solvent was evaporated and crude reaction mixture was purified by column chromatography over silica-gel (100-200 mesh) using ethyl acetate/ hexane mixture as an eluent. The conversion of phenylacetonitrile was calculated using GC and yields were determined for pure products after column chromatography.

Figure 2.2 GC Spectrum for reaction mixture of Scheme **2.2a**:

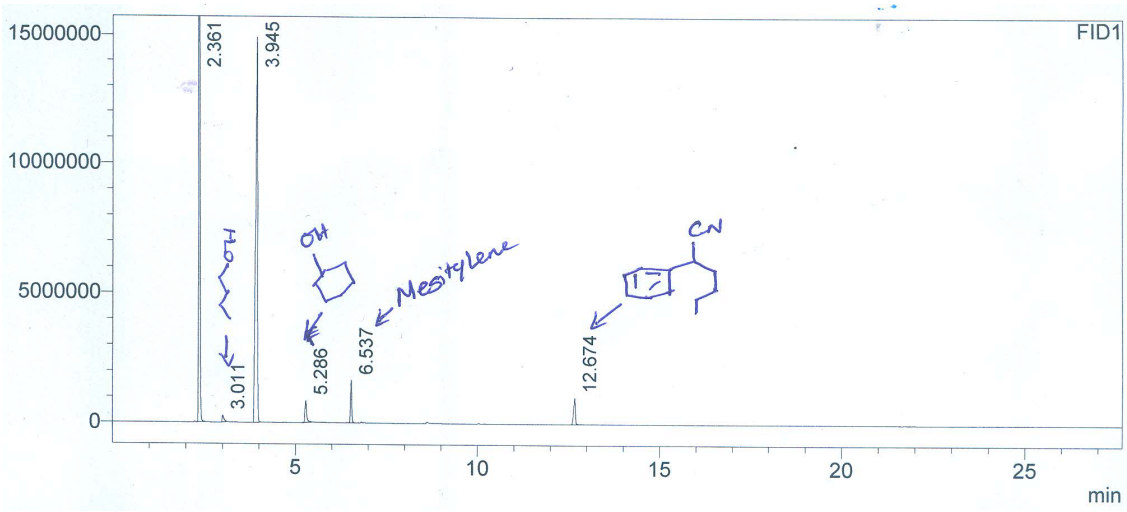
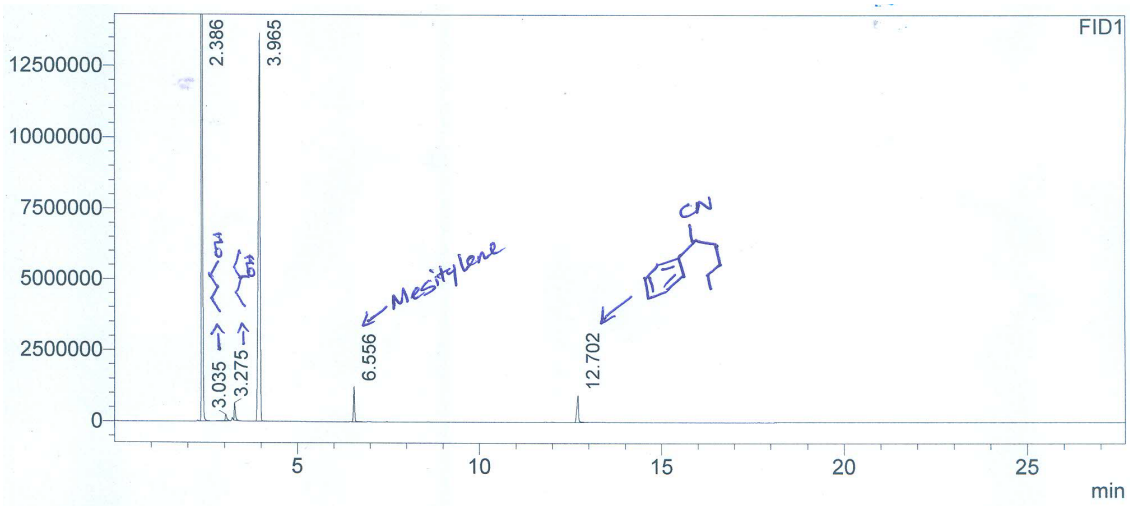


Figure 2.3 GC Spectrum for reaction mixture of Scheme **2.2b**:



The Observation of α-Alkylated Product and an Unsaturated Intermediate in Reaction Mixture:

To a 15 mL Schlenk tube equipped with a stirrer bar was added catalyst **1** (0.005 mmol), KO^{t}Bu (0.01 mmol), nitrile (1 mmol), and butanol (5 mmol) sequentially in the nitrogen atmosphere and the flask was fitted to a condenser. The solution was refluxed (oil path temperature 135 °C) with stirring under the flow of argon. After 20 minutes the reaction progress was monitored by GC and ^{1}H NMR. In situ I have observed both α-alkylated product (**A**) and an unsaturated intermediate (**B**).

Scheme 2.5 The Formation of α-Alkylated Product and an Unsaturated Intermediate in Reaction Mixture

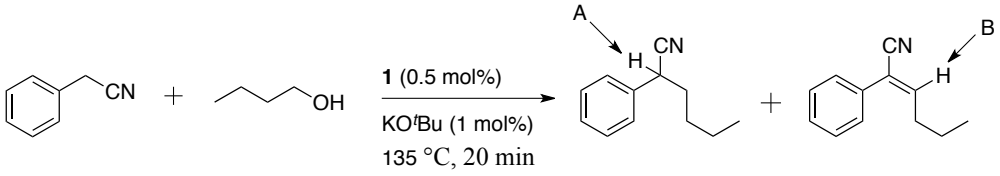
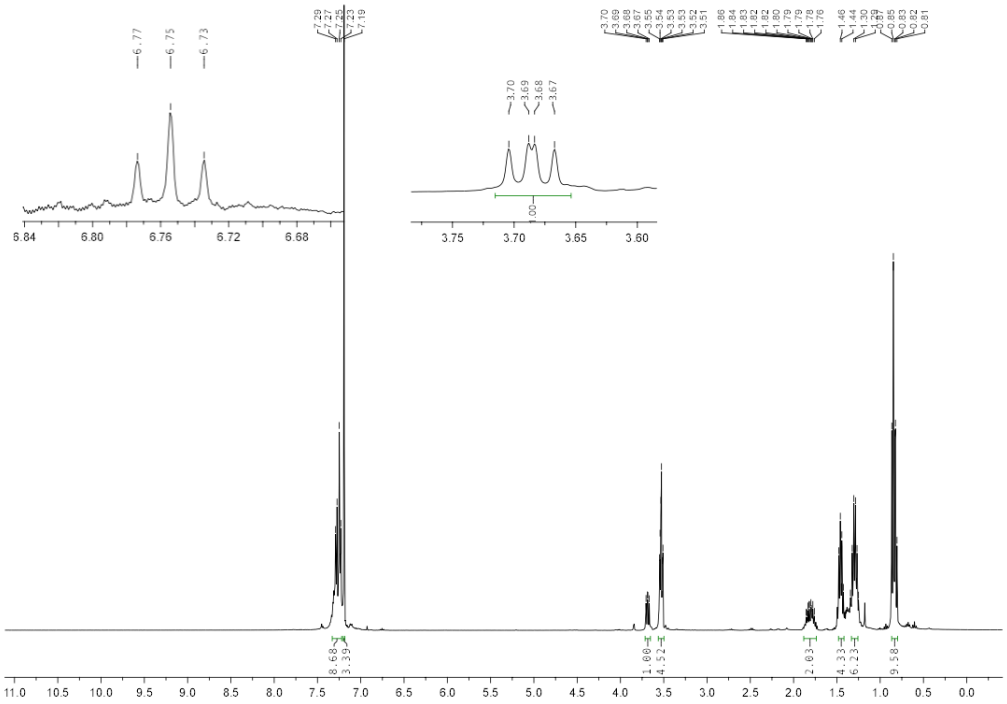


Figure 2.4 ^{1}H NMR Spectrum of Scheme **2.5**:



Procedure for α-Alkylation of Phenylacetonitrile Using Deuterated Primary Alcohol:

To a 15 mL Schlenk tube equipped with a stirrer bar was added catalyst **1** (0.005 mmol), KO^{t}Bu (0.01 mmol), phenylacetonitrile (1 mmol), deuterated alcohol (2 mmol) and toluene (1.5 mL) sequentially in the nitrogen atmosphere and the flask was fitted to a condenser. The solution was refluxed (oil bath temperature 135 °C) with stirring under the flow of argon for 4 h. The completion of the reaction was monitored using GC. After completion, the solvent was evaporated and resulted crude was purified by column chromatography over silica-gel (100-200 mesh) using ethyl acetate/hexane mixture as an eluent. The conversion of the nitrile was calculated from GC analysis of the reaction mixture and yields were determined for pure product after the column chromatography.

Figure 2.5 ^{1}H NMR spectrum of Scheme **2.3**:

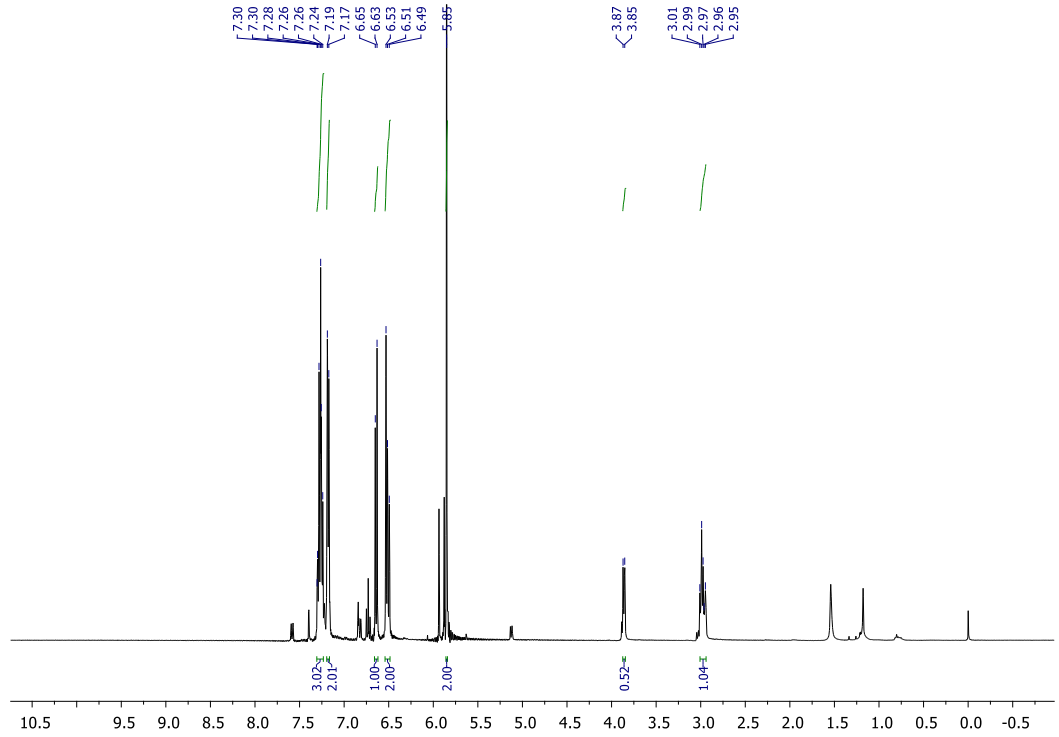
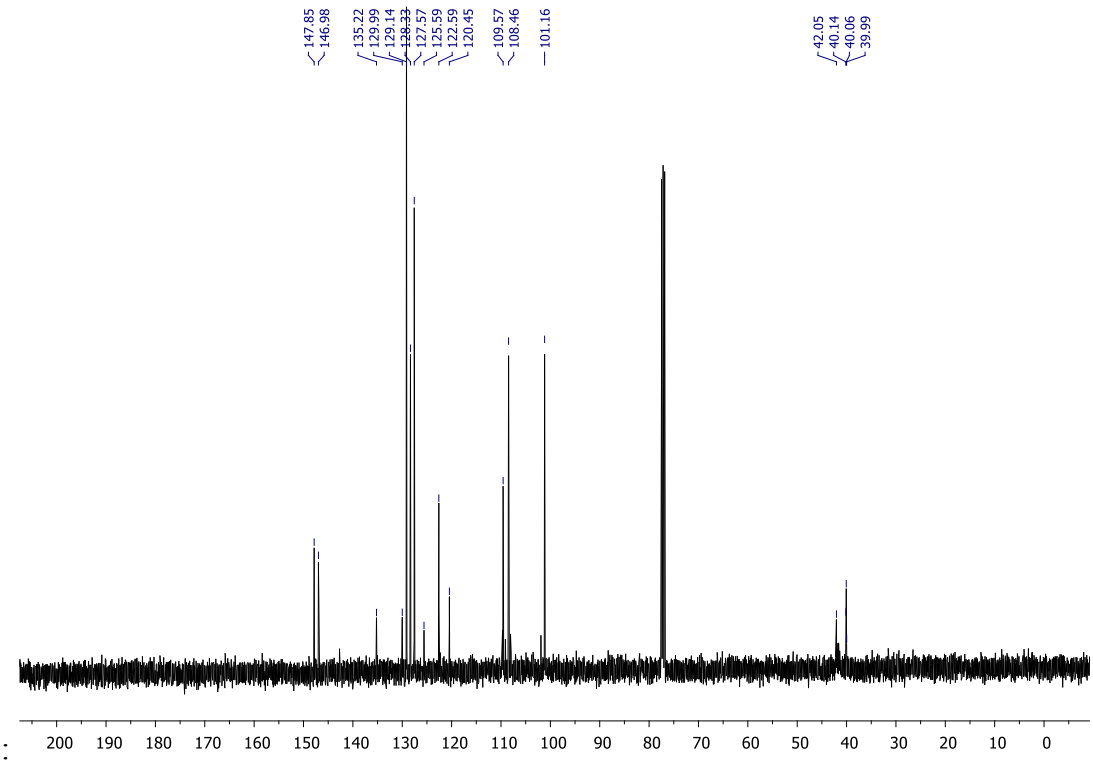


Figure 2.6 ^{13}C NMR Spectrum Scheme **2.3**:



2.6 NOTES AND REFERENCES

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^{1}H and ^{13}C NMR Spectra of the α-Alkylated Nitriles:

Figure 2.7 ^{1}H NMR spectrum of 2-phenylhexanenitrile:

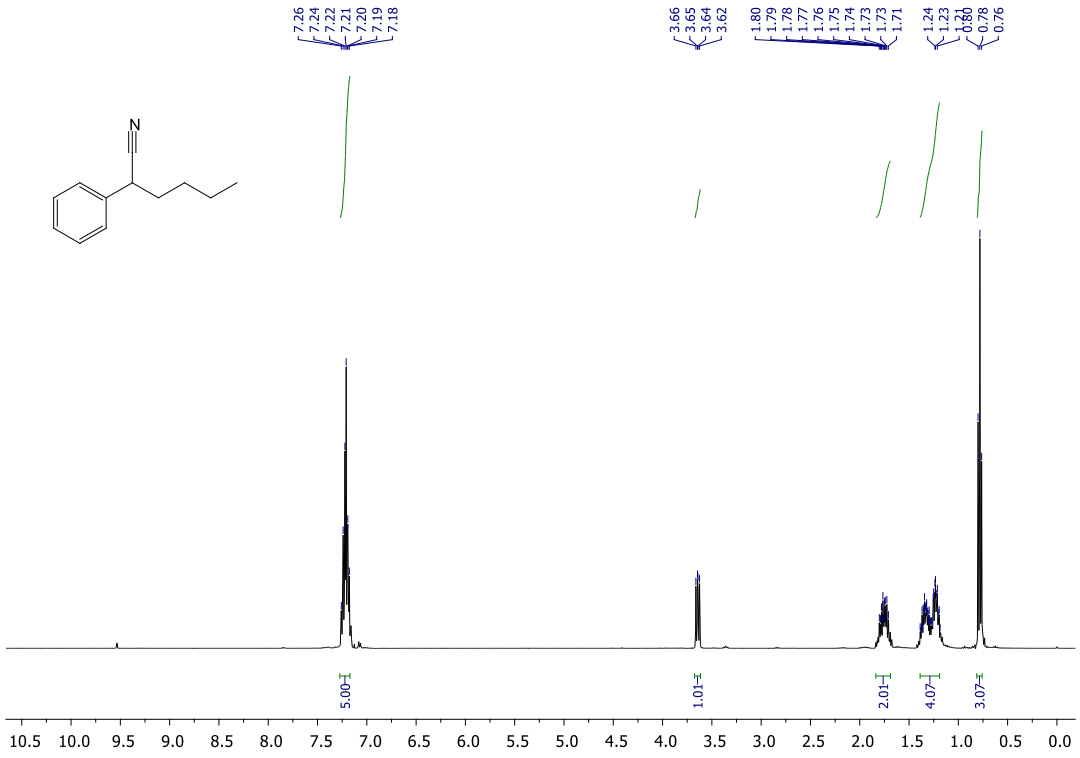


Figure 2.8 ^{13}C NMR spectrum of 2-phenylhexanenitrile:

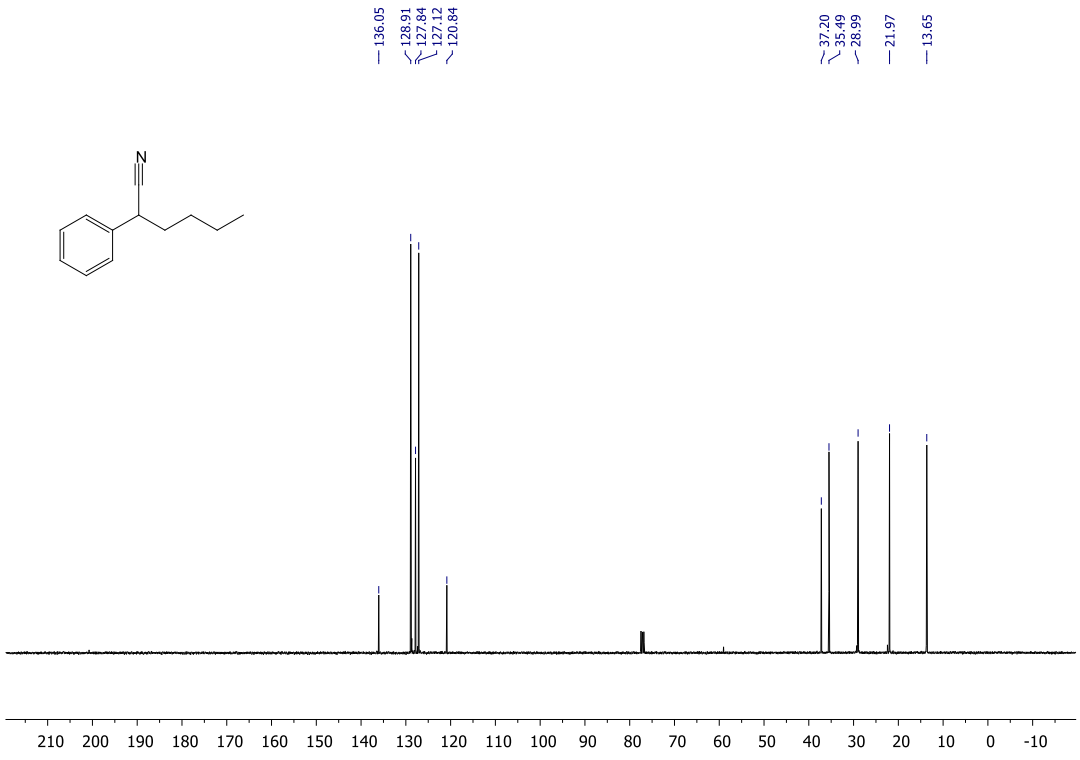


Figure 2.9 ^{1}H NMR spectrum of 6-phenyl-2-(pyridin-2-yl)hexanenitrile:

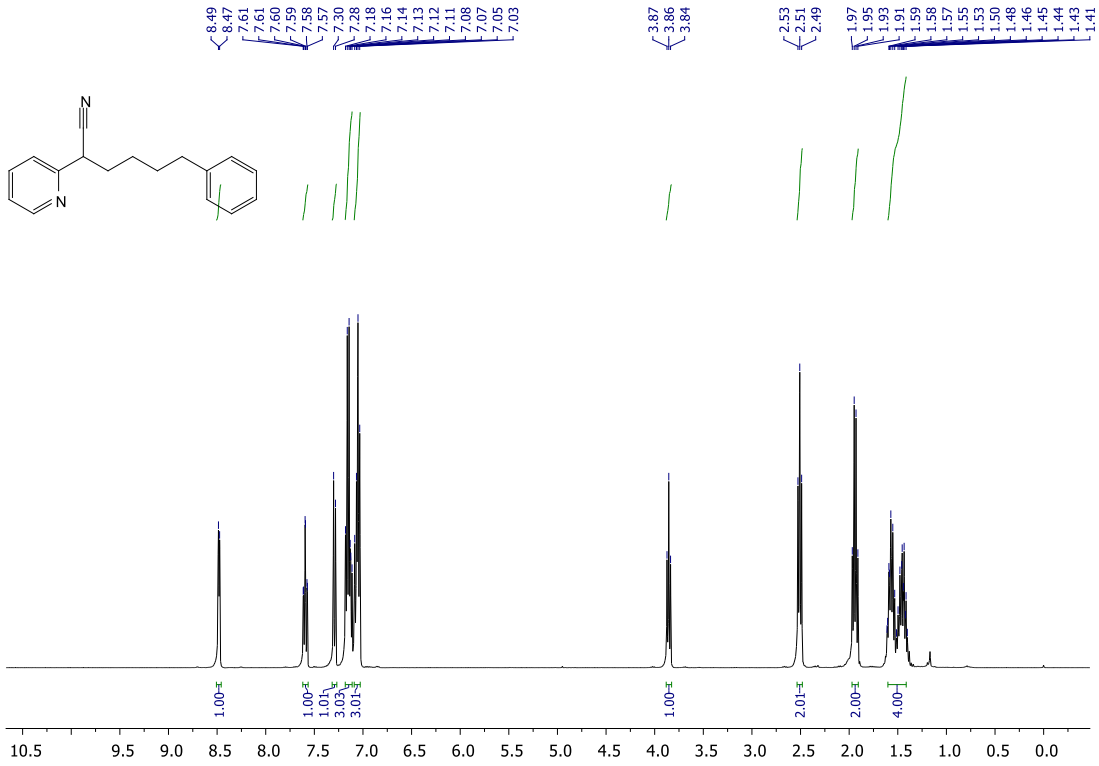


Figure 2.10 ^{13}C NMR spectrum of 6-phenyl-2-(pyridin-2-yl)hexanenitrile:

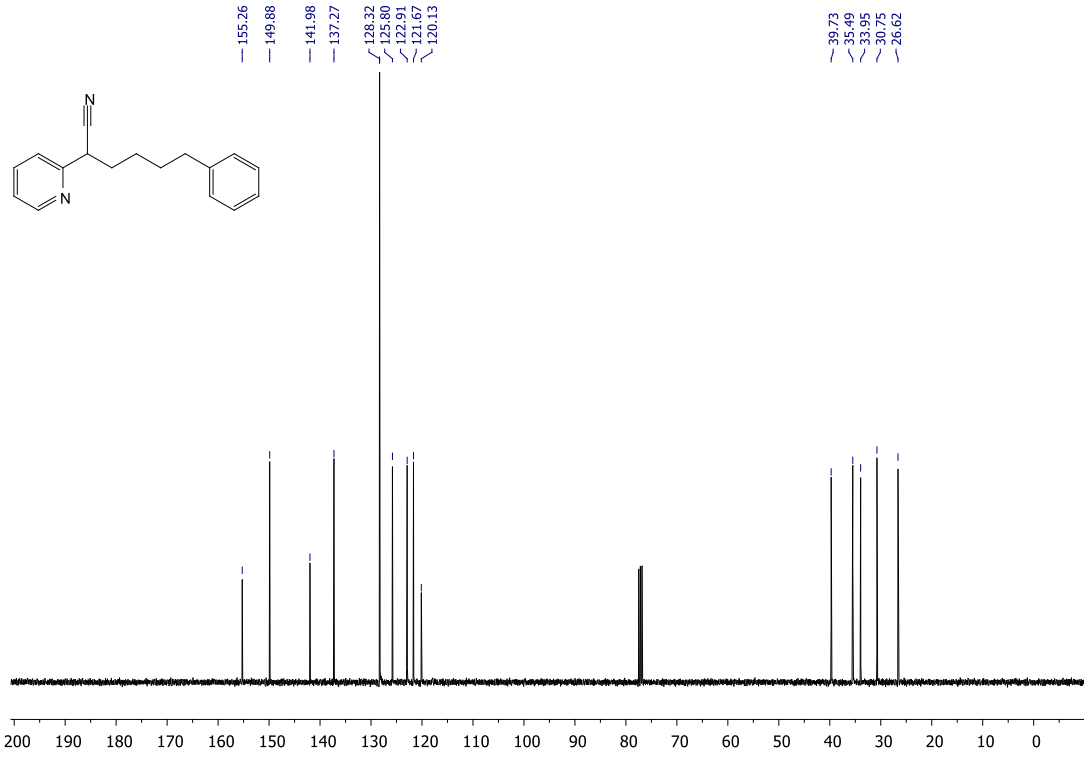


Figure 2.11 ^{1}H NMR spectrum of 2-(4-bromophenyl)butanenitrile:

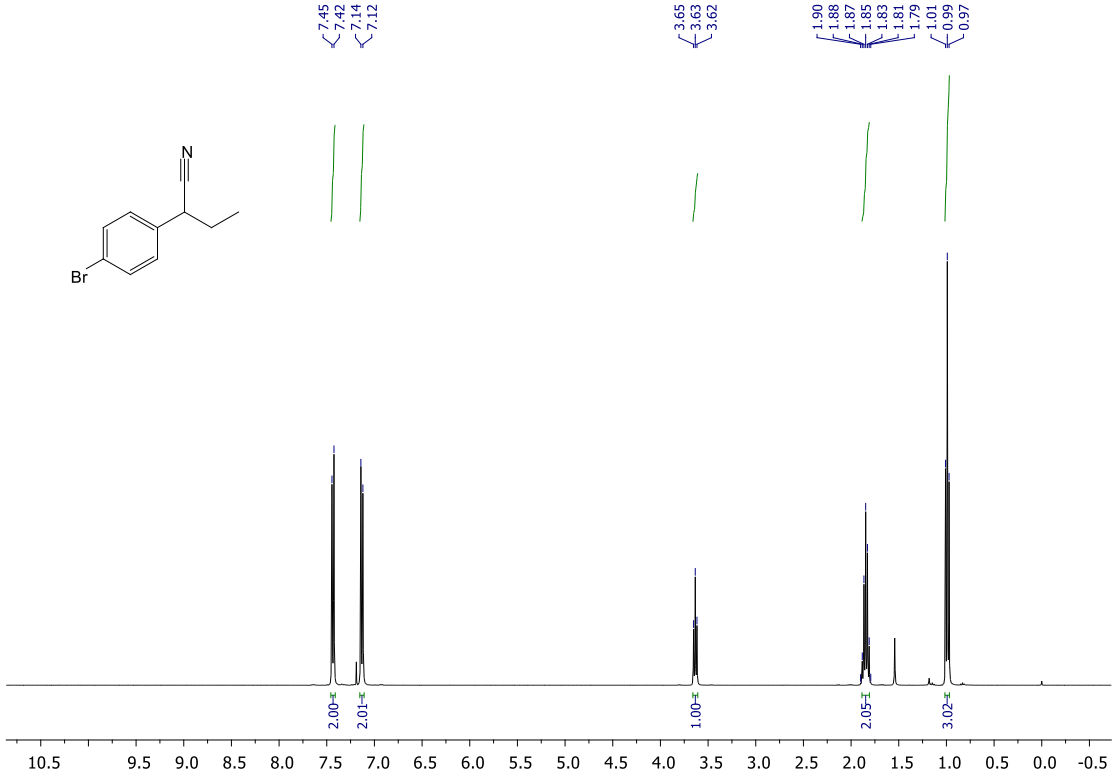
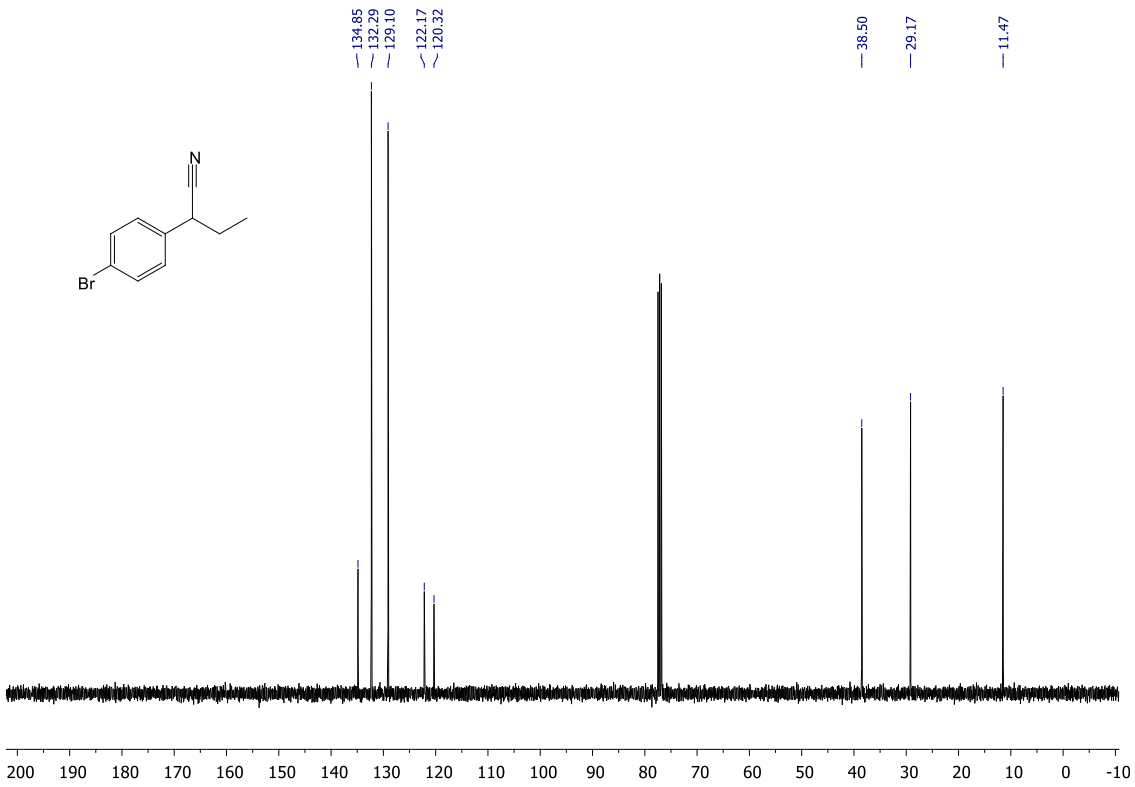


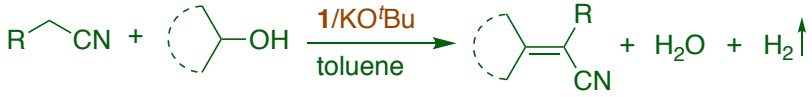
Figure 2.12 ^{13}C NMR spectrum of 2-(4-bromophenyl)butanenitrile:



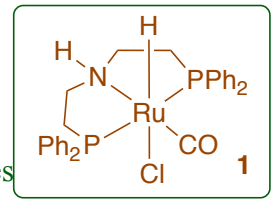
CHAPTER 3

Ruthenium Catalyzed α-Olefination of Nitriles Using Secondary Alcohols

3.1 ABSTRACT



- low catalyst load
- low cost of alcohols
- only byproducts: H_2 and H_2O
- new route to trisubstituted acrylonitriles



Ruthenium(II) pincer catalyzed α-olefination of nitriles is reported. This simple protocol provides an unprecedented transformation for the catalytic synthesis of β-disubstituted vinylnitriles using secondary alcohols. This catalytic method has extensive substrates scope, as arylmethyl nitriles, heteroarylmethyl nitriles and aliphatic nitriles as well as cyclic, acyclic, symmetrical and unsymmetrical secondary alcohols are all can be employed in the reaction to provide diverse α-vinylnitriles. C=C bond formation proceeds through activation of O–H bond of secondary alcohols via an unsaturated 16-electron intermediate ruthenium pincer complex and further condensation of in situ formed ketones with nitriles. Remarkably, H_2 and H_2O are the only byproducts of this atom economical and environmentally benign method.

3.2. INTRODUCTION

Construction of C=C bond is central to chemical synthesis. While there are several methods available to introduce an unsaturation intramolecularly in a substrate, methods

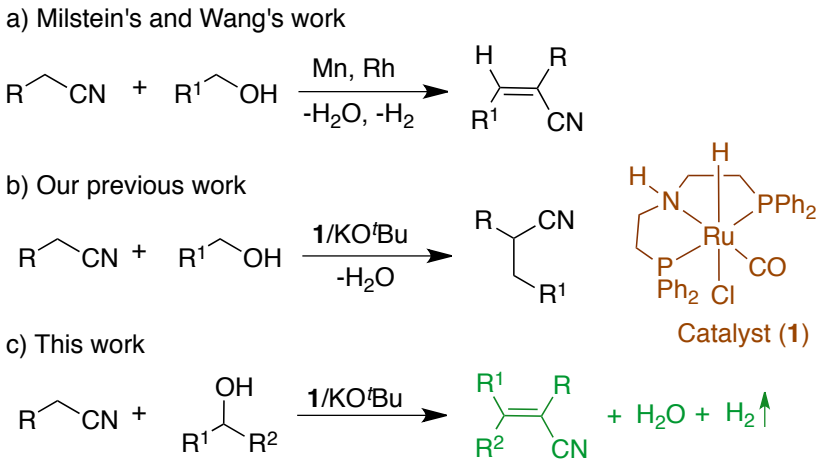
for the intermolecular olefin synthesis remain scarce. Working strategically towards this goal, Wittig reaction with its variants,[1] Peterson olefination,[2] and carbonyl coupling reactions[3] are employed by the conventional methods. However, these transformations in general, require extensive pre-functionalization of reactants and involve stoichiometric amount of toxic reagents. Catalytic methods for the intermolecular olefin synthesis are limited to ruthenium catalyzed alkene metathesis[4] and rhodium catalyzed diazo coupling.[5]

Vinyl nitriles are important intermediates in organic synthesis and prevalent among natural products and pharmaceuticals.[6] They serve as key building blocks and intermediates in number of chemical transformations. Notably, vinyl nitriles have found applications in optoelectronic materials and synthesis of light-emitting diodes.[7] Conventional synthesis of vinyl nitriles require stoichiometric amount of bases, which mediate the reaction of carbonyl compounds and nitriles (Knoevenagel condensation).[8] However, base promoted condensation reactions involve side reactions such as aldol reaction, Cannizzaro reaction and self-condensation of nitriles are limited to the substrates that are not sensitive to the basic conditions.[8b,9] Thus, attractive alternative methods are devised for the condensation of carbonyl compounds and nitriles to provide the vinyl nitriles. However, such methods often require the use of toxic reagents, elongated synthetic processes leading to the copious waste generation and poor yields.[10,11]

Acceptorless dehydrogenation of alcohols[12] and concomitant condensation of the resulting carbonyl compounds with nucleophilic molecules afforded atom economical and sustainable chemical transformations.[13,14] In this direction, employing the borrowing hydrogen concept, attractive methods for the construction of C–C and C–N

bonds were developed.[13-15] Recently, I have reported the ruthenium-catalyzed α-alkylation of arylmethyl nitriles using primary alcohols as alkylating reagents (Scheme 3.1b).[16] Water is the only by-product in this green and efficient alkylation reaction, which was enabled by metal-ligand cooperation operative in Ru-pincer complex **1** and the reactions proceeded via borrowing hydrogen pathway. In continuation of this work, I have explored the coupling of secondary alcohols and nitriles, which delivered the β-disubstituted vinylnitriles (Scheme 3.1c). Remarkably, liberated H_2 and water are the only byproducts from this green catalytic method. To our knowledge, secondary alcohols were never utilized in the transition metal catalyzed acceptorless dehydrogenative coupling with nitriles to provide vinylnitriles. However, when this manuscript was under preparation Milstein and Wang reported the manganese and rhodium catalyzed α-olefination of nitriles respectively, by employing primary alcohols (Scheme 3.1a).[17]

Scheme 3.1 Catalytic α-Olefination of Nitriles Using Alcohols

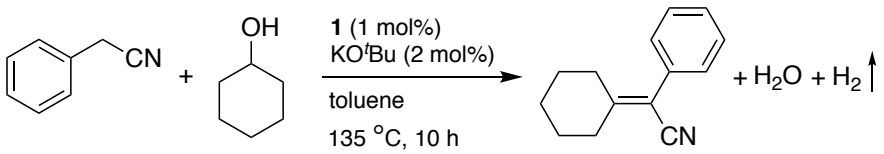


3.3 RESULTS AND DISCUSSIONS

At the outset, phenylacetonitrile, slight excess of cyclohexanol and ruthenium pincer catalyst **1** (1 mol%, Ru-MACHO) were reacted in toluene. Although, complete

conversion of nitrile was observed in 16 h, the desired olefin product **3.1a** was isolated in only moderate yields (entries 1, 2, Table 3.1). Analysis of the reaction mixture using ^{1}H NMR indicated the possible formation of aldol condensation products resulting from the in situ formed cyclohexanone intermediate. However, in contrary to the primary alcohol, no alkylation product was observed.[16] Thus, the catalytic olefination was performed using two equivalents of cyclohexanol, which resulted in quantitative conversion of nitrile in 10 h and the olefin product was isolated in 84% yield (entry 3, Table 3.1). Further, lowering the catalyst load from 1 mol% to 0.5 mol% and temperature from 135 °C to 120 °C turned out to be detrimental to the reaction progress as incomplete conversions were observed even after 24 h (entries 4, 5, Table 3.1). Control experiments using only base and without catalyst and base proved that the olefination requires catalyst (entries 6, 7, Table 3.1).

Table 3.1 Optimization of the Reaction Conditions for the α-Olefination of Nitriles Catalyzed by 1[a]



3.1a

entry	alcohol (equiv.)	time (h)	conv. (%)[b]	yield (%)[c]
1	1.05	16	>99	70
2	1.2	16	>99	78
3	2	10	>99	84
4[d]	2	24	57	40
5[e]	2	24	78	60
6[f]	2	24	-	-

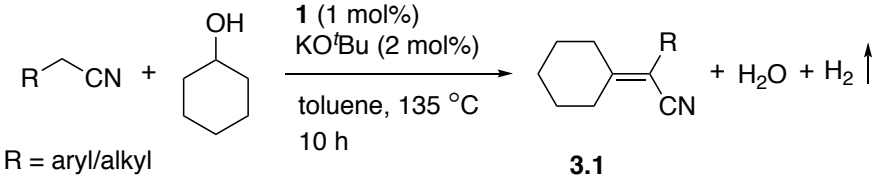
7[g]	2	24	-	-

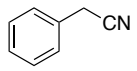
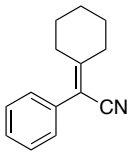
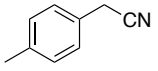
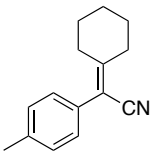
[a]Reaction conditions: phenylacetonitrile (1 mmol), cyclohexanol (2 mmol), catalyst **1**, base and toluene (1.5 mL) were heated at 135 °C under argon flow. [b]Conversion of nitrile was determined by GC using benzene as an internal standard. [c]Isolated yields after column chromatography. [d]0.5 mol% catalyst and 1 mol% base was used. [e]Heated at 120°C. [f]Only 2 mol% of base was used. [g]Reaction performed without catalyst and base.

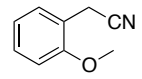
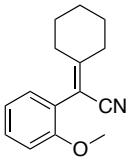
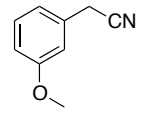
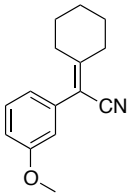
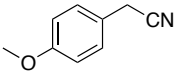
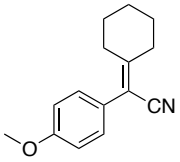
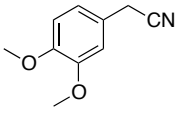
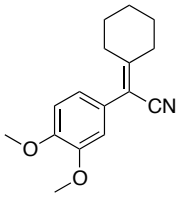
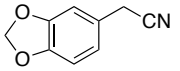
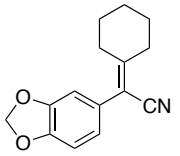
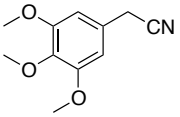
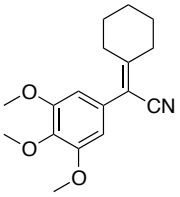
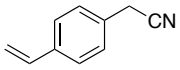
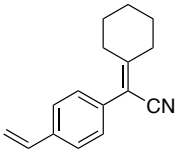
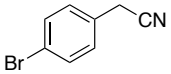
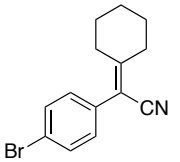
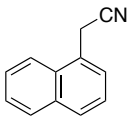
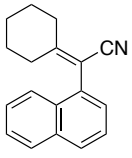
Having established the optimum reaction conditions, scope of the different nitriles on the catalytic olefination reaction was examined using cyclohexanol (Table 3.2). Reaction of cyclohexanol with 4-methyl phenylacetonitrile afforded the corresponding olefin product **3.1b** in 78% yield**.** When 2-methoxy phenylacetonitrile was subjected to the reaction under standard condition, diminished conversion (77%) and yield (**3.1c**, 72%) of the product were obtained indicating that the catalytic olefination is sensitive to steric hindrance in the proximity. However, *m*- and *p*-methoxy phenylacetonitrile provided 94% and quantitative conversions, respectively and the corresponding products **3.1d** and **3.1e** were isolated in very good yields**.** Similarly, reactions with di-, tri-methoxy substituted arylmethyl nitriles afforded the desired olefin products **3.1f**, **3.1g** and **3.1h** in good to excellent yields. Notably, 4-vinyl substituted arylmethyl nitriles provided complete conversion under standard experimental conditions and the corresponding product **3.1i** was obtained in 72% yield. Presence of electron-withdrawing substituent on the aryl ring was also tolerated. Upon reaction of 4-bromo phenylacetonitrile with cyclohexanol provided the α-olefinated product **3.1j** in 70% yield; however, complete conversion of nitrile required 24 h. When I have examined 1-naphthyl acetonitrile under standard experimental conditions, only 34% olefin product

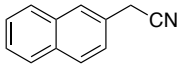
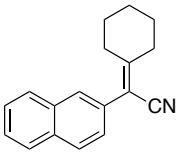
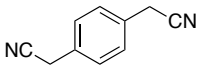
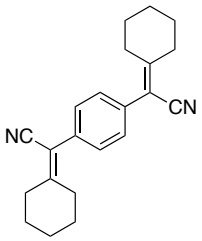
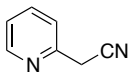
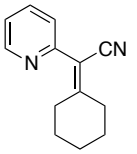
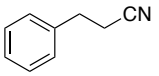
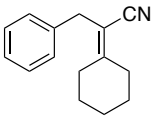
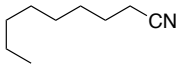
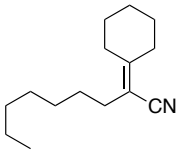
was isolated. Thus, the catalyst load was increased to 2 mol%, which provided the product **3.1k** in 80% yield. The similar reactivity was also observed with 2-naphthyl acetonitrile (entry 12, Table 3.2). Further, a dinitrile such as 1, 4-phenylenediacetonitrile was tested for the olefination reaction using cyclohexanol, which provided divinylnitrile **3.1m** in 48% yield. Despite the 99% conversion of dinitrile, the observed low yield of the product may be due to deleterious side reactions. Notably, heteroarylmethyl nitriles are also well tolerated in the olefination reaction. When, (pyridine-2-yl)acetonitrile was used the α-olefinated product **3.1n** was isolated in 62% yield. Remarkably, aliphatic nitriles were amenable to catalytic synthesis of vinylnitriles upon reaction with secondary alcohols. Reaction of 3-phenylpropionitrile and nonanenitrile were evaluated, which resulted the corresponding vinylnitrile products **3.1o** and **3.1p** in 62% and 48% yields, respectively.

Table 3.2. Ruthenium-Catalyzed α-Olefination of Nitriles Using Cyclohexanol[a]



entry	nitrile	product		conv. (%)[b]	yield (%)[c]
1			**3.1a**	>99	84
2			**3.1b**	85	78

3			**3.1c**	77	72
4			**3.1d**	94	80
5			**3.1e**	>99	85
6			**3.1f**	70	65
7			**3.1g**	92	87
8			**3.1h**	92	83
9			**3.1i**	>99	72
10[d,e]			**3.1j**	>99	70
11[d]			**3.1k**	90	80

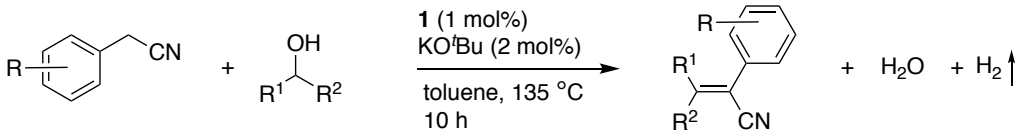
12[d]			**3.1l**	>99	81
13			**3.1m**	99	48
14[f]			**3.1n**	70	62
15[f]			**3.1o**	80	62
16[f]			**3.1p**	68	48

[a]Reaction conditions: Nitrile (1 mmol), cyclohexanol (2 mmol), toluene (1.5 ml), catalyst **1** (1 mol%) and KO^{t}Bu (2 mol%) were heated at 135 °C under argon flow. [b]Conversion of nitriles determined by GC using benzene as an internal standard. [c]Isolated yields after column chromatography. [d]2 mol% catalyst and 4 mol% base was used. [e]Reaction time 24 h. [f]Reaction performed with 0.25 mmol of nitrile and 0.5 mmol of cyclohexanol using 3 mol% catalyst **1** and 6 mol% base.

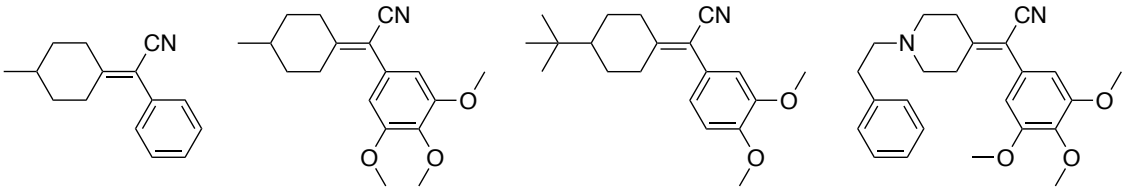
Further the scope of the secondary alcohols on the catalytic olefination using different nitriles was investigated. In general, variety of cyclic secondary alcohols can be employed under the reaction conditions to deliver α-olefinated products in good to excellent yields (Scheme 3.2). When 4-methyl cyclohexanol was reacted with

phenylacetonitrile and 2-(3,4,5-trimethoxyphenyl) acetonitrile, the corresponding olefin products were obtained in 75% and 93%, respectively (**3.2a**, **3.2b**, Scheme 3.2). Similarly, 4-*tert*-butyl cyclohexanol also exhibited very good reactivity. Remarkably, the nitrogen containing cyclic secondary alcohol, 1-phenethylpiperidin-4-ol underwent olefination with 2-(3,4-dimethoxyphenyl) acetonitrile to provide the product in 60% isolated yield (**3.2d**). Cycloheptanol reacted with phenylacetonitrile and 2-(4-methoxyphenyl)acetonitrile to provide the corresponding products in 86% and 70% isolated yields (**3.2e**, **3.2f**). A bulky cyclic alcohol such as cyclooctanol provided the corresponding olefin product **3.2g** in 46% yield with 2 mol% catalyst loads; further, increasing catalyst load to 5 mol% enhanced the yield of **3.2g** to 66%. Sterically demanding substrate, 2-adamantanol delivered the α-olefinated product **3.2h** in 69% yield. Ultimately aliphatic secondary alcohol such as 3-pentanol and 4-heptanol were subjected to catalytic olefin synthesis, which provided the corresponding vinylnitriles **3.2i** and **3.2j** in 58% and 48% isolated yields, respectively. Finally, unactivated unsymmetrical secondary alcohols such as 2-butanol, 2-hexanol and 2-heptanol were investigated with different arylmethylnitriles using catalyst **1** (5 mol%, 24 h), which provided the vinylnitrile products **3.2k-3.2m** as E/Z mixture in moderate yields. Overall, this protocol can allow the rapid access to highly branched β-disubstituted vinylnitriles from very simple and readily available starting materials with liberated dihydrogen and water as the only byproducts.

Scheme 3.2 Ruthenium-Catalyzed α-Olefination of Nitriles Using Secondary Alcohols[a]



3.2

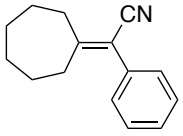


3.2a, 75% (>99%)

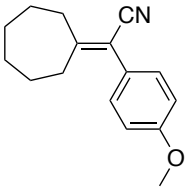
3.2b, 93% (>99%)

3.2c, 80% (88%)

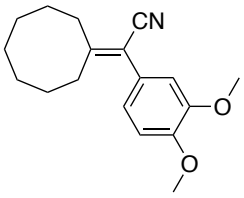
3.2d, 60% (89%)



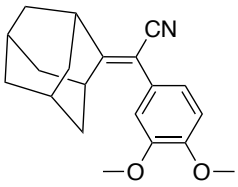
3.2e, 86% (>99%)



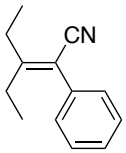
3.2f, 70% (78%)



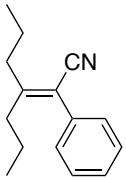
3.2g, 66% (85%)[c]



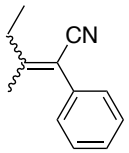
3.2h, 69% (90%)[b]



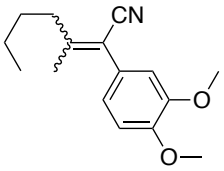
3.2i, 58% (99%)[b,d]



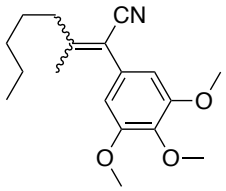
3.2j, 48% (65%)[c,d]



3.2k, 58% (99%)[c,d,e]



3.2l, 20% (40%)[c,d,e]

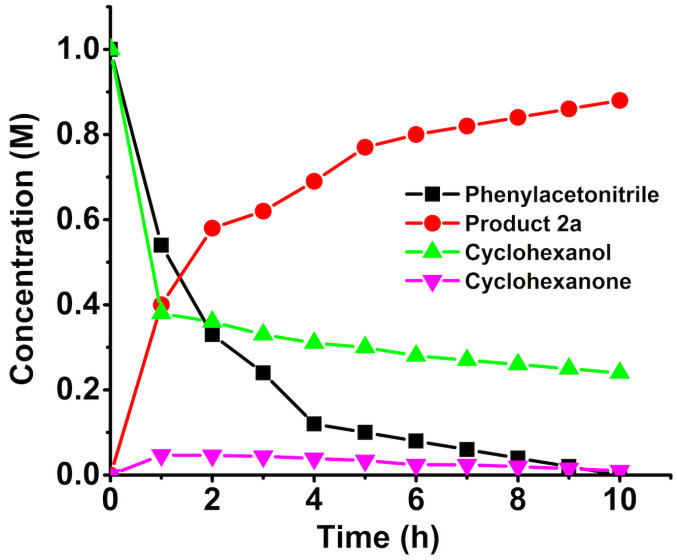


3.2m, 20% (40%)[c,d,e]

[a]Reaction conditions: nitrile (1 mmol), alcohol (2 mmol), toluene (1.5 ml), catalyst (1 mol%) and KO^{t}Bu (2 mol%) were heated at 135°C under argon flow. Reported yields correspond to isolated pure compounds. Conversion of nitriles is given within parenthesis and determined by GC analysis using benzene as an internal standard. [b]2 mol% catalyst **1** and 4 mol% base was used. [c]Reaction performed with 0.25 mmol of nitrile and 0.5 mmol of secondary alcohol using 5 mol% catalyst **1** and 10 mol% base. [d]Reaction time 24 h. [e]Isolated as E/Z mixture.

Mechanistic Investigations: GC monitoring on progress of the catalytic α-olefination reaction of phenylacetonitrile using cyclohexanol catalyzed by **1** indicated that the reaction follows first order kinetics with respect to phenylacetonitrile (Figure 3.1). Over the time, decreasing concentration of phenylacetonitrile (black line) can be corroborated with increasing concentration of product **3.1a** (red line). While nearly 1.5 equivalent of cyclohexanol (green line) was consumed in the reaction, the intermediate cyclohexanone (magenta line) was only short lived as it undergoes rapid condensation reaction with phenylacetonitrile.

Figure 3.1 Monitoring of the reaction progress by GC.

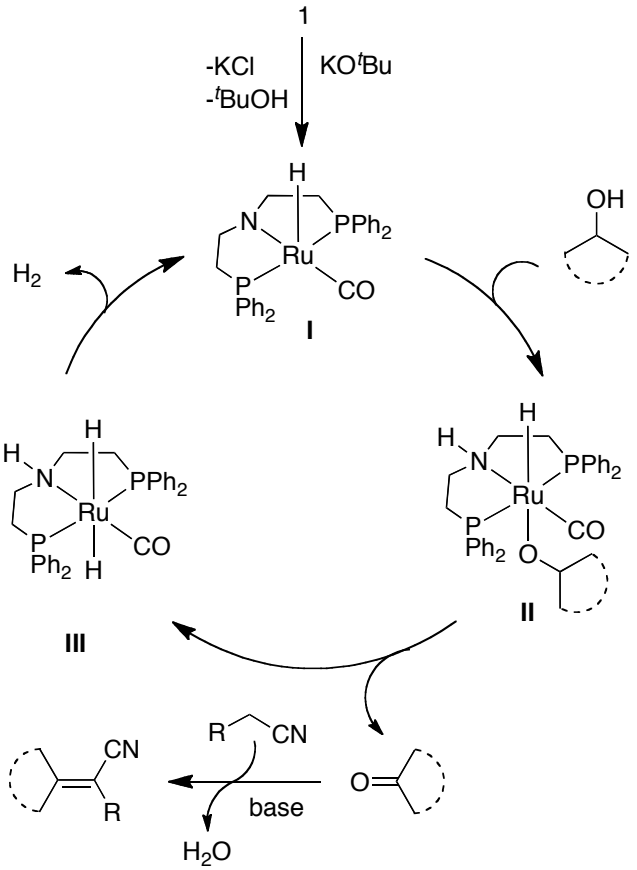


Concentration of phenylacetonitrile (black line), cyclohexanol (green line), product **3.1a** (red line) and the intermediate cyclohexanone (magenta line) in the catalytic α-olefination nitriles.

Plausible mechanism for α-olefination of nitriles using secondary alcohols catalyzed by **1** is depicted in Scheme 3.3. Our previous work with catalyst **1** established facile O–H,

N–H and spC–H bond activation reactions.[16,18] Catalyst **1** reacts with base to generate a coordinatively unsaturated reactive intermediate **I** (under similar condition the formation of **I** from catalyst **1** in the reaction mixture is previously established by us),[18a] which further reacts with secondary alcohols to provide an alkoxy ligand coordinated intermediate **II** (such alkoxy complex coordinated with benzyloxy ligand was characterized in situ by us)[18c] upon O–H activation of secondary alcohol.[18c] The amide donor present in unsaturated intermediate **I** accept the proton upon activation of O–H bond and becomes the amine donor in **II**. In concert with metal center, the ligand motif participates in the bond formation and bond breaking and hence displaying the metal-ligand cooperation. At this point, a dehydrogenation reaction takes place by a β-hydride elimination reaction (perhaps proceed via decoordination of one of donor atoms), which releases the ketone and generates a ruthenium dihydride complex **III**. However, although such mechanism is often invoked to explain the apparent β-hydride elimination reaction (which require coordinative unsaturation) in transition metal alkoxo ligated pincer complexes[14e-f,19] the involvement of other mechanistic pathway cannot be ruled out.[20] Further, complex **III** liberates dihydrogen to regenerate the catalytically active intermediate **I**. Finally, the Knoevenagel condensation between in situ formed ketones and nitriles provides β-disubstituted vinylnitriles by elimination of water molecule.

Scheme 3.3 Proposed Mechanism for the Ruthenium-Catalyzed α-Olefination of Nitriles Using Secondary Alcohols



3.4 CONCLUSIONS

In conclusion, I have presented an unprecedented transition metal catalyzed α-olefination of nitriles using secondary alcohols, which resulted in β-disubstituted vinylnitriles. Notably, arylmethyl nitriles, heteroarylmethyl nitriles and aliphatic nitriles were amenable to this catalytic transformation. Similarly, cyclic and acyclic as well as symmetrical and unsymmetrical secondary alcohols were also employed in this reaction, which resulted in assortment of α-vinylnitrile products. The acceptorless dehydrogenative coupling of nitriles and alcohols proceed via amine-amide metal-ligand cooperation operative in activated complex of **1**. Remarkably, dihydrogen and

water are the only byproducts in this catalytic olefination reaction, which make this method highly attractive for the synthesis of different kinds of fine and bulk chemicals.

3.5 EXPERIMENTAL SECTION

General Experimental: All catalytic reactions were performed under nitrogen atmosphere using standard Schlenk techniques. All stoichiometric reactions were performed in nitrogen atmosphere MBRAUN glove box. Chemicals were purchased from Acros, Sigma-Aldrich, Alfa-aesar, Himedia Chemicals and used without further purification. Dry solvents were prepared according to standard procedures. ^{1}H, ^{13}C spectra were recorded at Bruker AV-700 (^{1}H: 700 MHz, ^{13}C: 175 MHz) and Bruker AV-400 (^{1}H: 400 MHz, ^{13}C: 100.6 MHz). ^{1}H and ^{13}C $\{^{1}H\}$ NMR chemical shifts are referenced in ppm with respect to tetramethyl silane. NMR spectroscopy abbreviations: s, Singlet; d, doublet; dd, doublet of doublets; dt, doublet of triplets; t, triplet; q, quartet; dq, doublet of quartets; td, triplet of doublets; m, multiplet; br, broad. Assignment of spectra was done based on one-dimensional (DEPT-135) NMR techniques. IR spectra were recorded in Perkin-Elmer FT-IR spectrophotometer. Mass spectra were recorded on Bruker micrOTOF-Q II Spectrometer. E/Z isomers are assigned from cited references.[21]

General Procedure for α-Olefination of Nitriles Using Cyclohexanol:

In a glove box, 25 mL Schlenk flask was charged with a stirring bar, catalyst **1** (0.01 mmol), base (0.02 mmol), nitriles (1 mmol), cyclohexanol (2 mmol) and toluene (1.5 mL) under nitrogen atmosphere. The flask was taken out of the glove box, equipped with a condenser and the solution was refluxed (oil bath temperature 135 °C) with stirring under a flow of argon for 10 h. After cooling to room temperature, 1 mmol of internal standard (benzene) was added into the reaction mixture. After cooling to room

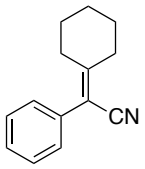
temperature, 1 mmol of internal standard (benzene) was added and the reaction mixture was subjected GC analysis. The solvent was evaporated and crude reaction mixture was purified by column chromatography over silica-gel (100-200 mesh) using ethyl acetate / hexane mixture as an eluent. The conversion of nitriles was calculated using GC analysis and yields were determined for pure products after column chromatography.

Procedure for α-Olefination of Heteroarylmethyl Nitriles Using Cyclohexanol:

In a glove box, 25 mL Schlenk flask was charged with a stirring bar, catalyst **1** (0.01 mmol), base (0.02 mmol), cyclohexanol (2 mmol) and toluene (1 mL) under nitrogen atmosphere. Heteroaryl nitrile (1 mmol) was taken in a 10 mL round bottom flask with toluene (1 mL) solvent and closed with a septum. The both flasks were taken out of the glove box. Schlenk flask was equipped with a condenser and solution was refluxed (oil bath temperature 135 °C) with stirring under a flow of argon. The nitrile solution from the round bottom flask was slowly added to the Schlenk flask over the time of 3 h under the flow of argon. The reaction mixture was further allowed to reflux for 7 h. After cooling to room temperature, 1 mmol of internal standard (benzene) was added into the reaction mixture. After cooling to room temperature, 1 mmol of internal standard (benzene) was added and the reaction mixture was subjected GC analysis. The solvent was evaporated and crude reaction mixture was purified by column chromatography over silica-gel (100-200 mesh) using ethyl acetate / hexane mixture as an eluent. The conversion of nitriles was calculated using GC analysis and yields were determined for pure products after column chromatography.

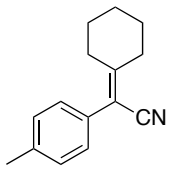
Spectral Data of the α-Olefinated Nitrile Products:

2-Cyclohexylidene-2-phenylacetonitrile (3.1a): Colorless liquid. Yield (84%). IR



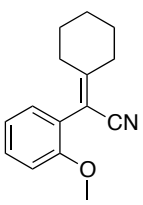
(DCM): 3057, 3026, 2935, 2858, 2209, 1618, 1491, 1445, 1266, 981, 762, 734, 702 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.18-7.31 (m, 5H, ArC*H*), 2.60 (t, *J* = 6.4 Hz, 2H, CH_2), 2.23 (t, *J* = 6.4 Hz, 2H, CH_2), 1.69 (quint, *J* = 6 Hz, 2H, CH_2), 1.48-1.58 (m, 4H, CH_2). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 161.97 (olefinic-*C*), 133.93 (quat-*C*), 129.30 (Ar*C*H), 128.70 (Ar*C*H), 128.24 (Ar*C*H), 118.75 (*C*N), 107.78 (olefinic-*C*), 35.41 (*C*H_2), 31.34 (*C*H_2), 28.17 (*C*H_2), 27.98 (*C*H_2), 25.95 (*C*H_2). HRMS (ESI) m/z calcd for $C_{14}H_{15}N$ $(M+H)^+$: 198.1277, found: 198.1289.

2-Cyclohexylidene-2-(*p*-tolyl)acetonitrile (3.1b): Colorless liquid. Yield (78%). IR



(DCM): 3053, 2938, 2859, 2208, 1609, 1445, 1265, 1115, 983, 896, 733 cm^{-1}. ^1H NMR (700 MHz, $CDCl_3$): δ 7.18 (dd, J_1 = 7.7 Hz, J_2 = 6.3 Hz, 4H, ArC*H*), 2.68 (t, *J* = 6.3 Hz, 2H, CH_2), 2.36 (s, 3H, CH_3), 2.32 (t, *J* = 6.3 Hz, 2H, CH_2), 1.77 (quint, *J* = 6.3 Hz, 2H, CH_2), 1.64 (quint, *J* = 6.3 Hz, 2H, CH_2), 1.58 (quint, *J* = 6.3 Hz, 2H, CH_2). $^{13}C\{^1H\}$ NMR (175 MHz, $CDCl_3$): δ 161.54 (olefinic-*C*), 138.21 (quat-*C*), 131.08 (quat-*C*), 129.43 (Ar*C*H), 129.24 (Ar*C*H), 118.97 (*C*N), 107.76 (olefinic-*C*), 35.47 (*C*H_2), 31.40 (*C*H_2), 28.23 (*C*H_2), 28.04 (*C*H_2), 26.06 (*C*H_2), 21.34 (*C*H_3). HRMS (ESI) m/z calcd for $C_{15}H_{17}N$ $(M+H)^+$: 212.1434, found: 212.1442.

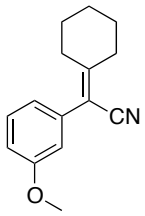
2-Cyclohexylidene-2-(2-methoxyphenyl)acetonitrile (3.1c): Colorless liquid. Yield



(72%). IR (DCM): 3055, 2938, 2858, 2841, 2209, 1627, 1495, 1465, 1250, 1116, 1028, 734, 705 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.32 (dt, J_1 = 7.6 Hz, J_2 = 1.6 Hz, 1H, ArC*H*), 7.11 (dd, J_1 = 5.6 Hz, J_2 = 2 Hz, 1H, ArC*H*), 6.91-6.97 (m, 2H, ArC*H*), 3.84 (s, 3H, OCH_3), 2.68 (t, *J* = 6 Hz, 2H, CH_2), 2.13 (t, *J* = 6

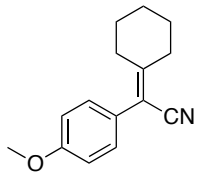
Hz, 2H, CH_2), 1.77 (quint, J = 6.8 Hz, 2H, CH_2), 1.56-1.65 (m, 4H, CH_2). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 162.77 (olefinic-*C*), 157.19 (quat-*C*), 131.29 (Ar*C*H), 130.12 (Ar*C*H), 122.64 (Ar*C*H), 120.63 (quat-*C*), 118.50 (*C*N), 111.34 (Ar*C*H), 103.75 (olefinic-*C*), 55.71 (O*C*H_3), 34.89 (*C*H_2), 31.74 (*C*H_2), 28.16 (*C*H_2), 27.81 (*C*H_2), 26.08 (*C*H_2). HRMS (ESI) m/z calcd for $C_{15}H_{17}NO$ $(M+Na)^+$: 250.1202, found: 250.1203.

2-Cyclohexylidene-2-(3-methoxyphenyl)acetonitrile (3.1d): Colorless liquid. Yield



(80%). IR (DCM): 3052, 2943, 2857, 2210, 1599, 1453, 1268, 1049, 994, 875, 782, 735, 706 cm^{-1}. ^1H NMR (700 MHz, $CDCl_3$): δ 7.29 (t, J = 7.7 Hz, 1H, ArC*H*), 6.84-6.88 (m, 2H, ArC*H*), 6.81 (s, 1H, ArC*H*), 3.81 (s, 3H, OCH_3), 2.67 (t, J = 6.3 Hz, 2H, CH_2), 2.32 (t, J = 5.6 Hz, 2H, CH_2), 1.78 (quint, J = 6.3 Hz, 2H, CH_2), 1.64 (quint, J = 5.6 Hz, 2H, CH_2), 1.59 (quint, J = 6.3 Hz, 2H, CH_2). $^{13}C\{^1H\}$ NMR (175 MHz, $CDCl_3$): δ 162.25 (olefinic-*C*), 159.79 (quat-*C*), 135.22 (quat-*C*), 129.79 (Ar*C*H), 121.74 (Ar*C*H), 118.71 (*C*N), 114.92 (Ar*C*H), 113.90 (Ar*C*H), 107.67 (olefinic-*C*), 55.44 (O*C*H_3), 35.46 (*C*H_2), 31.53 (*C*H_2), 28.24 (*C*H_2), 28.07 (*C*H_2), 26.02 (*C*H_2). HRMS (ESI) m/z calcd for $C_{15}H_{17}NO$ $(M+H)^+$: 228.1383, found: 228.1381.

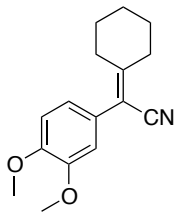
2-Cyclohexylidene-2-(4-methoxyphenyl)acetonitrile (3.1e): Colorless liquid. Yield



(85%). IR (DCM): 3058, 2937, 2858, 2840, 2209, 1624, 1492, 1465, 1251, 1117, 1028, 736, 703 cm^{-1}. ^1H NMR (700 MHz, $CDCl_3$): δ 7.19 (dd, J_1 = 9.1 Hz, J_2 = 2.1 Hz, 2H, ArC*H*), 6.89 (dd, J_1 = 9.1 Hz, J_2 = 2.8 Hz, 2H, ArC*H*), 3.80 (s, 3H, OCH_3), 2.65 (t, J = 6.3 Hz, 2H, CH_2), 2.30 (t, J = 6.3 Hz, 2H, CH_2), 1.75 (quint, J = 5.6 Hz, 2H, CH_2), 1.63 (quint, J = 3.5 Hz, 2H, CH_2), 1.57 (quint, J = 7.7 Hz, 2H, CH_2). $^{13}C\{^1H\}$ NMR (175 MHz, $CDCl_3$): δ 161.09 (olefinic-*C*), 159.44 (quat-*C*), 130.52 (Ar*C*H), 126.19 (quat-*C*), 118.95 (*C*N), 114.07 (Ar*C*H), 107.30

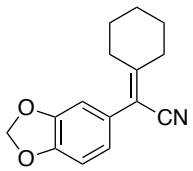
(olefinic-*C*), 55.36 (O*C*H$_3$), 35.35 (*C*H$_2$), 31.26 (*C*H$_2$), 28.14 (*C*H$_2$), 27.94 (*C*H$_2$), 25.97 (*C*H$_2$). HRMS (ESI) m/z calcd for $C_{15}H_{17}NO$ $(M+Na)^+$: 250.1202, found: 250.1206.

2-Cyclohexylidene-2-(3,4-dimethoxyphenyl)acetonitrile (3.1f): Colorless liquid.



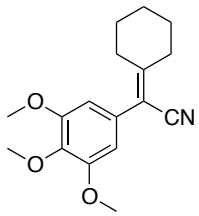
Yield (87%). IR (DCM): 3057, 2936, 2858, 2208, 1605, 1513, 1450, 1251, 1027, 815, 733, 703 cm^{-1}. ^{1}H NMR (700 MHz, $CDCl_3$): δ 6.82 (d, *J* = 8.4 Hz, 1H, ArC*H*), 6.77 (d, *J* = 9.8 Hz, 1H, ArC*H*), 6.75 (s, 1H, ArC*H*), 3.84 (s, 6H, OC*H*$_3$), 2.62 (t, *J* = 5.6 Hz, 2H, C*H*$_2$), 2.29 (t, *J* = 6.3 Hz, 2H, C*H*$_2$), 1.73 (quint, *J* = 6.3 Hz, 2H, C*H*$_2$), 1.60 (quint, *J* = 5.6 Hz, 2H, C*H*$_2$), 1.54 (quint, *J* = 6.3 Hz, 2H, C*H*$_2$). ^{13}C{^{1}H} NMR (175 MHz, $CDCl_3$): δ 161.32 (olefinic-*C*), 148.91 (quat-*C*), 148.88 (quat-*C*), 126.33 (quat-*C*), 121.88 (Ar*C*H), 118.77 (*C*N), 112.18 (Ar*C*H), 111.04 (Ar*C*H), 107.35 (olefinic-*C*), 55.92 (O*C*H$_3$), 55.88 (O*C*H$_3$), 35.24 (*C*H$_2$), 31.31 (*C*H$_2$), 28.05 (*C*H$_2$), 27.88 (*C*H$_2$), 25.87 (*C*H$_2$). HRMS (ESI) m/z calcd for $C_{16}H_{19}NO_2$ $(M+Na)^+$: 280.1308, found: 280.1328.

2-(Benzo[*d*][1,3]dioxol-5-yl)-2-cyclohexylideneacetonitrile (3.1g): Colorless liquid.



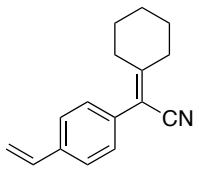
Yield (65%). IR (DCM): 3055, 2986, 2938, 2859, 2209, 1636, 1488, 1265, 1240, 1040, 734, 705 cm^{-1}. ^{1}H NMR (700 MHz, $CDCl_3$): δ 6.80 (d, *J* = 8.4 Hz, 1H, ArC*H*), 6.73-6.74 (m, 2H, ArC*H*), 5.98 (s, 2H, OC*H*$_2$), 2.65 (t, *J* = 5.6 Hz, 2H, C*H*$_2$), 2.30 (t, *J* = 5.6 Hz, 2H, C*H*$_2$), 1.76 (quint, *J* = 8.4 Hz, 2H, C*H*$_2$), 1.63 (quint, *J* = 6.3 Hz, 2H, C*H*$_2$), 1.57 (quint, *J* = 5.6 Hz, 2H, C*H*$_2$). ^{13}C{^{1}H} NMR (175 MHz, $CDCl_3$): δ 161.77 (olefinic-*C*), 147.93 (quat-*C*), 147.64 (quat-*C*), 127.62 (quat-*C*), 123.18 (Ar*C*H), 118.82 (*C*N), 109.75 (Ar*C*H), 108.58 (Ar*C*H), 107.38 (olefinic-*C*), 101.48 (O*C*H$_2$), 35.40 (*C*H$_2$), 31.45 (*C*H$_2$), 28.21 (*C*H$_2$), 28.03 (*C*H$_2$), 26.03 (*C*H$_2$). HRMS (ESI) m/z calcd for $C_{15}H_{15}NO_2$ $(M+Na)^+$: 264.0995, found: 264.0994.

2-Cyclohexylidene-2-(3,4,5-trimethoxyphenyl)acetonitrile (3.1h): Colorless liquid.



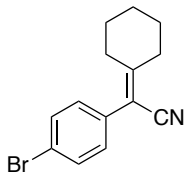
Yield (83%). IR (DCM): 3056, 2940, 2859, 2209, 1635, 1413, 1265, 1129, 1003, 737, 705 cm^{-1}. ^{1}H NMR (700 MHz, $CDCl_3$): δ 6.45 (s, 2H, ArC*H*), 3.84 (s, 9H, OCH_3), 2.65 (t, *J* = 5.6 Hz, 2H, CH_2), 2.32 (t, *J* = 6.3 Hz, 2H, CH_2), 1.76 (quint, *J* = 7.7 Hz, 2H, CH_2), 1.63 (quint, *J* = 6.3 Hz, 2H, CH_2), 1.58 (quint, *J* = 7 Hz, 2H, CH_2). $^{13}C\{^{1}H\}$ NMR (175 MHz, $CDCl_3$): δ 162.10 (olefinic-*C*), 153.36 (quat-*C*), 138.06 (quat-*C*), 129.36 (quat-*C*), 118.65 (*C*N), 107.69 (olefinic-*C*), 106.53 (Ar*C*H), 60.98 (O*C*H_3), 56.29 (O*C*H_3), 35.35 (*C*H_2), 31.61 (*C*H_2), 28.18 (*C*H_2), 28.05 (*C*H_2), 25.96 (*C*H_2). HRMS (ESI) m/z calcd for $C_{17}H_{21}NO_3$ $(M+H)^+$: 288.1594, found: 288.1572.

2-Cyclohexylidene-2-(4-vinylphenyl)acetonitrile (3.1i): Colorless liquid. Yield



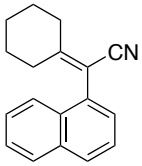
(77%). IR (DCM): 3056, 2940, 2859, 2209, 1638, 1418, 1265, 1129, 1003, 737, 705 cm^{-1}. ^{1}H NMR (700 MHz, $CDCl_3$): δ 7.35 (d, *J* = 8.4 Hz, 2H, ArC*H*), 7.18 (t, *J* = 7 Hz, 2H, ArC*H*), 6.64 (dd, J_1 = 10.5 Hz, J_2 = 7 Hz, 1H, olefinic-C*H*), 5.70 (d, *J* = 17.5 Hz, 1H, olefinic-CH_2), 5.22 (d, *J* = 10.5 Hz, 1H, olefinic-CH_2), 2.61 (t, *J* = 6.3 Hz, 2H, CH_2), 2.26 (t, *J* = 6.3 Hz, 2H, CH_2), 1.71 (quint, *J* = 5.6 Hz, 2H, CH_2), 1.58 (quint, *J* = 5.6 Hz, 2H, CH_2), 1.52 (quint, *J* = 6.3 Hz, 2H, CH_2). $^{13}C\{^{1}H\}$ NMR (175 MHz, $CDCl_3$): δ 162.12 (olefinic-*C*), 137.61 (quat-*C*), 136.22 (olefinic-*C*), 133.35 (quat-*C*), 129.59 (Ar*C*H), 126.53 (Ar*C*H), 118.75 (*C*N), 114.92 (olefinic-*C*), 107.62 (olefinic-*C*), 31.48 (*C*H_2), 31.06 (*C*H_2), 28.25 (*C*H_2), 28.06 (*C*H_2), 26.03 (*C*H_2). HRMS (ESI) m/z calcd for $C_{16}H_{17}N$ $(M+H)^+$: 223.1362, found: 223.1370.

2-(4-Bromophenyl)-2-cyclohexylideneacetonitrile (3.1j): Colorless liquid. Yield (70%). IR (DCM): 3053, 2933, 2857, 2211, 1688, 1448, 1264, 1073, 896, 830, 745 cm^{-1}. ^{1}H NMR (700 MHz, $CDCl_3$): δ 7.51 (d, *J* = 8.4 Hz, 2H, ArC*H*), 7.15 (d, *J* = 9.1 Hz,



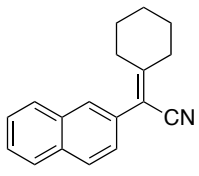
2H, ArC*H*), 2.67 (t, *J* = 6.3 Hz, 2H, CH_2), 2.29 (t, *J* = 5.6 Hz, 2H, CH_2), 1.78 (quint, *J* = 5.6 Hz, 2H, CH_2), 1.65 (quint, *J* = 5.6 Hz, 2H, CH_2), 1.59 (quint, *J* = 5.6 Hz, 2H, CH_2). $^{13}C\{^1H\}$ NMR (175 MHz, $CDCl_3$): δ 162.88 (olefinic-*C*), 132.90 (quat-*C*), 132.02 (Ar*C*H), 131.04 (Ar*C*H), 122.57 (quat-*C*), 118.36 (*C*N), 106.86 (olefinic-*C*), 35.56 (*C*H_2), 31.47 (*C*H_2), 28.22 (*C*H_2), 28.04 (*C*H_2), 25.96 (*C*H_2). HRMS (ESI) m/z calcd for $C_{14}H_{14}NBr$ $(M+H)^+$: 276.0382, found: 276.0370.

2-Cyclohexylidene-2-(naphthalen-1-yl)acetonitrile (3.1k): Colorless liquid. Yield



(80%). IR (DCM): 3054, 2939, 2860, 2207, 1438, 1265, 1117, 909, 775, 737 cm^{-1}. ^1H NMR (700 MHz, $CDCl_3$): δ 7.87-7.90 (m, 3H, ArC*H*), 7.52-7.56 (m, 2H, ArC*H*), 7.48 (t, *J* = 7 Hz, 1H, ArC*H*), 7.36 (dd, J_1 = 7 Hz, J_2 = 1.4 Hz, 1H, ArC*H*), 2.79-2.86 (m, 2H, CH_2), 1.99-2.05 (m, 2H, CH_2), 1.84-1.90 (m, 2H, CH_2), 1.64 (quint, *J* = 5.6 Hz, 2H, CH_2), 1.50 (quint, *J* = 5.6 Hz, 2H, CH_2). $^{13}C\{^1H\}$ NMR (175 MHz, $CDCl_3$): δ 164.38 (olefinic-*C*), 133.79 (quat-*C*), 131.45 (quat-*C*), 131.08 (quat-*C*), 129.15 (Ar*C*H), 128.62 (Ar*C*H), 127.79 (Ar*C*H), 126.83 (Ar*C*H), 126.34 (Ar*C*H), 125.44 (Ar*C*H), 124.71 (Ar*C*H), 118.38 (*C*N), 105.16 (olefinic-*C*), 34.83 (*C*H_2), 31.72 (*C*H_2), 28.29 (*C*H_2), 27.86 (*C*H_2), 25.86 (*C*H_2). HRMS (ESI) m/z calcd for $C_{18}H_{17}N$ $(M+H)^+$: 248.1434, found: 248.1430.

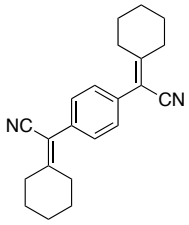
2-Cyclohexylidene-2-(naphthalen-2-yl)acetonitrile (3.1l): Colorless liquid. Yield



(81%). IR (DCM): 3052, 2934, 2858, 2209, 1590, 1443, 1267, 1185, 946, 895, 859, 736 cm^{-1}. ^1H NMR (700 MHz, $CDCl_3$): δ 7.83-7.87 (m, 3H, ArC*H*), 7.76 (s, 1H, ArC*H*), 7.51 (dd, J_1 = 3.5 Hz, J_2 = 2.8 Hz, 2H, ArC*H*), 7.38 (d, *J* = 9.1 Hz, 1H, ArC*H*), 2.74 (t, *J* = 5.6 Hz, 2H, CH_2), 2.38 (t, *J* = 6.3 Hz, 2H, CH_2), 1.82 (quint, *J* = 6.3 Hz, 2H, CH_2), 1.67 (quint, *J* = 5.6 Hz, 2H, CH_2), 1.60-1.63 (m, 2H, CH_2). $^{13}C\{^1H\}$ NMR (175 MHz, $CDCl_3$): δ 162.43 (olefinic-*C*),

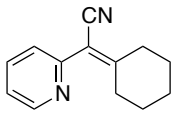
133.23 (quat-*C*), 132.90 (quat-*C*), 131.37 (quat-*C*), 128.74 (Ar*C*H), 128.50 (Ar*C*H), 128.17 (Ar*C*H), 127.83 (Ar*C*H), 126.88 (Ar*C*H), 126.78 (Ar*C*H), 126.70 (Ar*C*H), 118.87 (*C*N), 107.88 (olefinic-*C*), 35.56 (*C*H_2), 31.57 (*C*H_2), 28.28 (*C*H_2), 28.08 (*C*H_2), 26.04 (*C*H_2). HRMS (ESI) m/z calcd for $C_{18}H_{17}N$ $(M+Na)^+$: 270.1253, found: 270.1277.

2,2'-(1,4-Phenylene)bis(2-cyclohexylideneacetonitrile) (3.1m): White solid. Yield



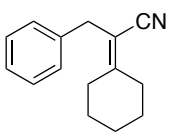
(48%). IR (DCM): 3055, 2984, 2928, 2206, 1611, 1427, 1264, 983, 897, 749 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.24 (s, 4H, ArC*H*), 2.62 (t, *J* = 6 Hz, 4H, C*H*$_2$), 2.26 (t, *J* = 6.4 Hz, 4H, C*H*$_2$), 1.72 (quint, *J* = 5.6 Hz, 4H, C*H*$_2$), 1.51-1.62 (m, 8H, C*H*$_2$). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 162.81 (olefinic-*C*), 133.93 (quat-*C*), 129.70 (Ar*C*H), 118.57 (*C*N), 107.22 (olefinic-*C*), 35.57 (*C*H_2), 31.50 (*C*H_2), 28.24 (*C*H_2), 28.07 (*C*H_2), 25.97 (*C*H_2). HRMS (ESI) m/z calcd for $C_{22}H_{24}N_2$ $(M+H)^+$: 317.2012, found: 317.2000.

2-Cyclohexylidene-2-(pyridin-2-yl)acetonitrile (3.1n): Pale yellow liquid. Yield



(62%). IR (DCM): 3056, 2985, 2860, 2214, 1618 1431, 1264, 991, 897, 743 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.57 (d, *J* = 2.8 Hz, 1H, ArC*H*), 7.66 (td, J_1 = 4.4 Hz, J_2 = 0.8 Hz, 1H, ArC*H*), 7.32 (d, *J* = 4.4 Hz, 1H, ArC*H*), 7.17 (ddd, J_1 = 2.8 Hz, J_2 = 1.6 Hz, J_3 = 0.8 Hz, 1H, ArC*H*), 2.66 (t, *J* = 3.6 Hz, 2H, C*H*$_2$), 2.47 (t, *J* = 3.6 Hz, 2H, C*H*$_2$), 1.74 (quint, *J* = 3.2 Hz, 2H, C*H*$_2$), 1.56-1.60 (m, 4H, C*H*$_2$). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 165.50 (olefinic-*C*), 152.81 (quat-*C*), 149.74 (Ar*C*H), 136.84 (Ar*C*H), 124.42 (Ar*C*H), 122.84 (Ar*C*H), 118.34 (*C*N), 108.27 (olefinic-*C*), 35.96 (*C*H_2), 31.48 (*C*H_2), 28.24 (*C*H_2), 27.96 (*C*H_2), 25.95 (*C*H_2). HRMS (ESI) m/z calcd for $C_{13}H_{14}N_2$ $(M+H)^+$: 199.1230, found: 199.1236.

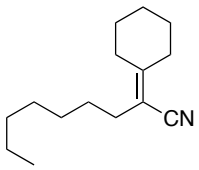
2-Cyclohexylidene-3-phenylpropanenitrile (3.1o): Colorless liquid. Yield (62%). IR



(DCM): 3055, 2929, 2857, 2209, 1449, 1262, 1026, 902, 728 cm^{-1}. ^1H

NMR (400 MHz, $CDCl_3$): δ 7.25 (t, *J* = 7.2 Hz, 2H, ArC*H*), 7.13-7.19 (m, 3H, ArC*H*), 3.50 (s, 2H, CH_2), 2.49 (t, *J* = 6 Hz, 2H, CH_2), 2.31 (t, *J* = 6 Hz, 2H, CH_2), 1.51-1.61 (m, 6H, CH_2). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 160.24 (olefinic-*C*), 137.98 (quat-*C*), 128.85 (Ar*C*H), 128.36 (Ar*C*H), 126.91 (Ar*C*H), 119.39 (*C*N), 105.21 (olefinic-*C*), 35.41 (*C*H_2), 35.31 (*C*H_2), 30.70 (*C*H_2), 28.10 (*C*H_2), 27.76 (*C*H_2), 26.09 (*C*H_2). HRMS (ESI) m/z calcd for $C_{15}H_{17}N$ $(M+H)^+$: 234.1253, found: 234.1232.

2-Cyclohexylidenenonanenitrile (3.1p): Colorless liquid. Yield (48%). IR (DCM): 3054, 2929, 2858, 2207, 1630, 1453, 1264, 910, 738 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 2.43 (t, *J* = 5.2 Hz, 2H, CH_2), 2.18 (t, *J* = 5.6 Hz, 2H, CH_2), 2.13 (t, *J* = 7.2 Hz, 2H, CH_2), 1.52-1.59 (m, 6H, CH_2), 1.43 (quint, *J* = 7.6 Hz, 2H, CH_2), 1.12-1.27 (m, 8H, CH_2), 0.81 (t, *J* = 6.4 Hz, 3H, CH_3). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 158.90 (olefinic-*C*), 119.53 (*C*N), 106.33 (olefinic-*C*), 35.33 (*C*H_2), 31.84 (*C*H_2), 30.35 (*C*H_2), 29.27 (*C*H_2), 29.11 (*C*H_2), 28.93 (*C*H_2), 28.79 (*C*H_2), 28.12 (*C*H_2), 27.79 (*C*H_2), 26.17 (*C*H_2), 22.71 (*C*H_2), 14.16 (*C*H_3). HRMS (ESI) m/z calcd for $C_{15}H_{25}N$ $(M+H)^+$: 220.2060, found: 220.2042.

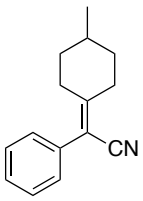


General Procedure for α-Olefination of Nitriles Using Secondary Alcohols:

In a glove box, 25 mL Schlenk flask was charged with a stirring bar, catalyst **1** (0.01 mmol), base (0.02 mmol), nitriles (1 mmol), secondary alcohols (2 mmol) and toluene (1.5 mL) under nitrogen atmosphere. The flask was taken out of the glove box, equipped with a condenser and the solution was refluxed (oil bath temperature 135 °C) with stirring under a flow of argon for 10-24 h. After cooling to room temperature, 1 mmol of internal standard (benzene) was added and the reaction mixture was subjected GC analysis. The solvent was evaporated and crude reaction mixture was purified by column chromatography over silica-gel (100-200 mesh) using ethyl acetate / hexane

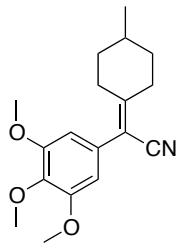
mixture as an eluent. The conversion of nitriles was calculated using GC analysis and yields were determined for pure products after column chromatography.

2-(4-Methylcyclohexylidene)-2-phenylacetonitrile (3.2a): Colorless liquid. Yield



(75%). IR (DCM): 3058, 3026, 2952, 2925, 2209, 1618, 1492, 1444, 1267, 951, 763, 737, 700 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.18-7.31 (m, 5H, ArC*H*), 2.97-3.03 (m, 1H, CH_2), 2.57-2.63 (m, 1H, CH_2), 2.21-2.28 (m, 1H, CH_2), 1.86-1.94 (m, 2H, CH_2), 1.68-1.73 (m, 1H, C*H*), 1.56-1.64 (m, 1H, CH_2), 1.14-1.21 (m, 1H, CH_2), 0.90-1.01 (m, 1H, CH_2), 0.85 (d, J = 6.4 Hz, 3H, CH_3). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 161.63 (olefinic-*C*), 133.97 (quat-*C*), 129.29 (Ar*C*H), 128.68 (Ar*C*H), 128.24 (Ar*C*H), 118.76 (*C*N), 107.90 (olefinic-*C*), 36.01 (*C*H), 35.85 (*C*H_2), 34.75 (*C*H_2), 32.04 (*C*H_2), 30.64 (*C*H_2), 21.44 (*C*H_3). HRMS (ESI) m/z calcd for $C_{15}H_{17}N$ $(M+H)^+$: 212.1434, found: 212.1415.

2-(4-Methylcyclohexylidene)-2-(3,4,5-trimethoxyphenyl)acetonitrile (3.2b):

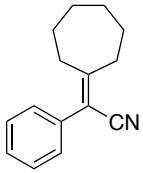


Colorless liquid. Yield (93%). IR (DCM): 3051, 2927, 2850, 2210, 1584, 1449, 1346, 1239, 1128, 1006, 914, 841, 734 cm^{-1}. ^1H NMR (700 MHz, $CDCl_3$): δ 6.46 (s, 2H, ArC*H*), 3.84 (s, 9H, OCH_3), 3.04 (dd, J_1 =14 Hz, J_2 =1.4 Hz, 1H, CH_2), 2.70 (dd, J_1 =14 Hz, J_2 =2.1 Hz, 1H, CH_2), 2.30 (dt, J_1 =13.3 Hz, J_2 =4.9 Hz, 1H, CH_2), 1.97-2.01 (m, 2H, C*H* & CH_2), 1.67-1.71 (m, 2H, CH_2) 1.24 (dq, J_1 =13.3 Hz, J_2 =3.5 Hz, 1H, CH_2), 1.02 (dq, J_1 =11.9 Hz, J_2 =4.2 Hz, 1H, CH_2), 0.93 (d, J =7 Hz, 3H, CH_3). $^{13}C\{^1H\}$ NMR (175 MHz, $CDCl_3$): δ 161.78 (olefinic-*C*), 153.37 (quat-*C*), 138.09 (quat-*C*), 129.42 (quat-*C*), 118.69 (*C*N), 107.83 (olefinic-*C*), 106.55 (Ar*C*H), 61.01 (O*C*H_3), 56.31 (O*C*H_3), 36.04 (*C*H_2), 35.94 (*C*H_2), 34.72 (*C*H), 32.12 (*C*H_2), 30.94 (*C*H_2), 21.48 (*C*H_3). HRMS (ESI) m/z calcd for $C_{18}H_{23}NO_3$ $(M+Na)^+$: 324.1570, found: 324.1588.

2-(4-(*tert*-Butyl)cyclohexylidene)-2-(3,4-dimethoxyphenyl)acetonitrile (3.2c): White solid. Yield (80%). IR (DCM): 3055, 2987, 2863, 2209, 1605, 1422, 1262, 1027, 896, 739, 703 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 6.84 (s, 1H, ArC*H*), 6.81 (d, *J* =1.6 Hz, 1H, ArC*H*), 6.78 (d, J_1 =1.6 Hz, 1H, ArC*H*), 3.88 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 3.12 (dd, J_1 =14 Hz, J_2 =2.4 Hz, 1H, CH_2), 2.79 (dd, J_1 =14 Hz, J_2 =2.4 Hz, 1H, CH_2), 2.24 (dt, J_1 =13.2 Hz, J_2 =4.8 Hz, 1H, CH_2), 2.02-2.06 (m, 1H, C*H*), 1.86-1.96 (m, 2H, CH_2) 1.22-1.32 (m, 2H, CH_2), 1.01-1.09 (m, 1H, CH_2), 0.86 (s, 9H, CH_3). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 161.33 (olefinic-*C*), 149.01 (quat-*C*), 148.97 (quat-*C*), 126.46 (quat-*C*), 122.05 (Ar*C*H), 118.93 (*C*N), 112.30 (Ar*C*H), 111.08 (Ar*C*H), 107.24 (olefinic-*C*), 56.06 (O*C*H_3), 56.01 (O*C*H_3), 47.66 (*C*H), 35.24 (*C*H_2), 32.53 (quat-*C*), 31.29 (*C*H_2), 28.84 (*C*H_2), 28.70 (*C*H_2), 27.61 (*C*H_3). HRMS (ESI) m/z calcd for $C_{20}H_{27}NO_2$ $(M+Na)^+$: 336.1934, found: 336.1929.

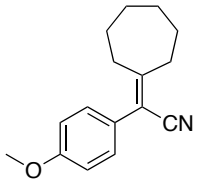
2-(1-Phenethylpiperidin-4-ylidene)-2-(3,4,5-trimethoxyphenyl)acetonitrile (3.2d): Colorless liquid. Yield (60%). IR (DCM): 3041, 2987, 2867, 2212, 1682, 1431, 1265, 1002, 896, 841, 747, 703 cm^{-1}. ^1H NMR (700 MHz, $CDCl_3$): δ 7.29 (t, *J* = 7.7 Hz, 2H, ArC*H*), 7.20-7.22 (m, 3H, ArC*H*), 6.48 (s, 2H, ArC*H*), 3.86 (s, 9H, OCH_3), 2.80-2.84 (m, 4H, CH_2), 2.72 (t, *J* = 5.6 Hz, 2H, CH_2), 2.65 (t, *J* = 8.4 Hz, 2H, CH_2), 2.51-2.54 (m, 4H, CH_2). $^{13}C\{^1H\}$ NMR (175 MHz, $CDCl_3$): δ 158.09 (olefinic-*C*), 153.49 (quat-*C*), 140.19 (quat-*C*), 138.34 (quat-*C*), 128.81 (Ar*C*H), 128.79 (Ar*C*H), 128.58 (Ar*C*H), 126.30 (Ar*C*H), 118.32 (*C*N), 109.04 (Ar*C*H), 106.64 (olefinic-*C*), 61.06 (O*C*H_3), 59.84 (*C*H_2), 56.40 (O*C*H_3), 54.17 (*C*H_2), 54.02 (*C*H_2), 34.52 (*C*H_2), 33.94 (*C*H_2), 31.23 (*C*H_2). HRMS (ESI) m/z calcd for $C_{24}H_{28}N_2O_3$ $(M+H)^+$: 393.2173, found: 393.2194.

2-Cycloheptylidene-2-phenylacetonitrile (3.2e): Colorless liquid. Yield (86%). IR



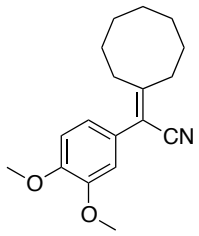
(DCM): 3048, 2984, 2927, 2855, 2208, 1605, 1421, 1264, 1048, 896, 749, 703 cm^{-1}. ^{1}H NMR (700 MHz, $CDCl_3$): δ 7.38 (t, *J* = 7.7 Hz, 2H, ArC*H*), 7.33 (t, *J* = 7 Hz, 1H, ArC*H*), 7.28 (d, *J* = 7.7 Hz, 2H, ArC*H*), 2.80 (t, *J* = 6.3 Hz, 2H, CH_2), 2.42 (t, *J* = 6.3 Hz, 2H, CH_2), 1.80 (quint, *J* = 6.3 Hz, 2H, CH_2), 1.62 (quint, *J* = 5.6 Hz, 4H, CH_2), 1.53 (quint, *J* = 5.6 Hz, 2H, CH_2). $^{13}C\{^{1}H\}$ NMR (175 MHz, $CDCl_3$): δ 164.64 (olefinic-*C*), 134.47 (quat-*C*), 129.22 (Ar*C*H), 128.76 (Ar*C*H), 128.27 (Ar*C*H), 118.94 (*C*N), 110.57 (olefinic-*C*), 36.25 (*C*H_2), 32.96 (*C*H_2), 29.74 (*C*H_2), 28.87 (*C*H_2), 27.37 (*C*H_2), 27.06 (*C*H_2). HRMS (ESI) m/z calcd for $C_{15}H_{17}N$ $(M+H)^+$: 212.1434, found: 212.1430.

2-Cycloheptylidene-2-(4-methoxyphenyl)acetonitrile (3.2f): Colorless liquid. Yield



(70%). IR (DCM): 3052, 2985, 2856, 2207, 1607, 1422, 1264, 1035, 896, 748, 703 cm^{-1}. ^{1}H NMR (700 MHz, $CDCl_3$): δ 7.20 (d, *J* = 9.1 Hz, 2H, ArC*H*), 6.90 (d, *J* = 9.1 Hz, 2H, ArC*H*), 3.82 (s, 3H, OCH_3), 2.78 (t, *J* = 5.6 Hz, 2H, CH_2), 2.42 (t, *J* = 6.3 Hz, 2H, CH_2), 1.79 (quint, *J* = 5.6 Hz, 2H, CH_2), 1.62 (quint, *J* = 6.3 Hz, 4H, CH_2), 1.52 (quint, *J* = 6.3 Hz, 2H, CH_2). $^{13}C\{^{1}H\}$ NMR (175 MHz, $CDCl_3$): δ 163.82 (olefinic-*C*), 159.46 (quat-*C*), 130.46 (quat-*C*), 126.79 (Ar*C*H), 119.16 (*C*N), 114.13 (Ar*C*H), 110.15 (olefinic-*C*), 55.45 (O*C*H_3), 36.19 (*C*H_2), 32.96 (*C*H_2), 29.77 (*C*H_2), 28.90 (*C*H_2), 27.43 (*C*H_2), 27.11 (*C*H_2). HRMS (ESI) m/z calcd for $C_{16}H_{19}NO$ $(M+H)^+$: 242.1539, found: 242.1533.

2-Cyclooctylidene-2-(3,4-dimethoxyphenyl)acetonitrile (3.2g): Colorless liquid.



Yield (66%). IR (DCM): 3051, 2932, 2861, 2206, 1600, 1421, 1263, 1027, 895, 742, 704 cm^{-1}. ^{1}H NMR (700 MHz, $CDCl_3$): δ 6.80 (s, 1H, ArC*H*), 6.77 (d, *J* =3.5 Hz, 1H, ArC*H*), 6.71 (d, *J* =3.5 Hz, 1H, ArC*H*), 3.83 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 2.62 (t, *J* =11.2 Hz,

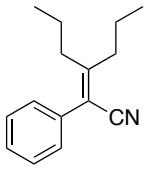
2H, CH_2), 2.31 (t, J =10.5 Hz, 2H, CH_2), 1.84-1.91 (m, 2H, CH_2), 1.59-1.64 (m, 2H, CH_2), 1.50-1.55 (m, 2H, CH_2) 1.38-1.42 (m, 4H, CH_2). $^{13}C\{^1H\}$ NMR (175 MHz, $CDCl_3$): δ 165.83 (olefinic-*C*), 149.16 (quat-*C*), 149.04 (quat-*C*), 127.16 (quat-*C*), 121.83 (Ar*C*H), 119.18 (*C*N), 112.22 (Ar*C*H), 111.34 (Ar*C*H), 109.71 (olefinic-*C*), 56.12 (O*C*H_3), 56.06 (O*C*H_3), 34.41 (*C*H), 32.94 (*C*H_2), 28.53 (*C*H_2), 27.81 (*C*H_2), 25.98 (*C*H_2), 25.71 (*C*H_2), 23.97 (*C*H_2). HRMS (ESI) m/z calcd for $C_{18}H_{23}NO_2$ $(M+H)^+$: 286.1802, found: 286.1787.

(2-Adamantan-2-ylidene)-2-(3,4-dimethoxyphenyl)acetonitrile (3.2h): Colorless liquid. Yield (69%). IR (DCM): 3054, 2987, 2926, 2206, 1590, 1430, 1261, 1026, 896, 763, 749 cm^{-1}. ^1H NMR (700 MHz, $CDCl_3$): δ 6.85 (s, 1H, ArC*H*), 6.82 (d, J = 2.1 Hz, 1H, ArC*H*), 6.80 (d, J = 2.1 Hz, 1H, ArC*H*), 3.89 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 2.06-2.09 (m, 2H, C*H*), 2.01-2.03 (m, 3H, C*H* & CH_2), 1.95-1.97 (m, 2H, CH_2), 1.89-1.92 (m, 4H, CH_2), 1.85-1.87 (m, 1H, C*H*), 1.76-1.80 (m, 2H, CH_2). $^{13}C\{^1H\}$ NMR (175 MHz, $CDCl_3$): δ 169.69 (olefinic-*C*), 149.12 (quat-*C*), 149.03 (quat-*C*), 126.36 (quat-*C*), 121.74 (Ar*C*H), 118.88 (*C*N), 112.22 (Ar*C*H), 111.24 (Ar*C*H), 103.13 (olefinic-*C*), 56.09 (O*C*H_3), 56.07 (O*C*H_3), 39.62 (*C*H_2), 39.38 (*C*H_2), 38.77 (*C*H_2), 36.60 (*C*H), 34.36 (*C*H), 27.76 (*C*H). HRMS (ESI) m/z calcd for $C_{20}H_{23}NO_2$ $(M+H)^+$: 310.1802, found: 310.1799.

3-Ethyl-2-phenylpent-2-enenitrile (3.2i): Colorless liquid. Yield (58%). IR (DCM): 3055, 2977, 2879, 2210, 1449, 1266, 1076, 896, 737, 704 cm^{-1}. ^1H NMR (700 MHz, $CDCl_3$): δ 7.19-7.32 (m, 5H, ArC*H*), 2.53 (q, J = 7.7 Hz, 2H, CH_2), 2.16 (q, J = 7.7 Hz, 2H, CH_2), 1.14 (t, J = 7.7 Hz, 3H, CH_3), 0.96 (t, J = 7.7 Hz, 3H, CH_3). $^{13}C\{^1H\}$ NMR (175 MHz, $CDCl_3$): δ 165.66 (olefinic-*C*), 134.33 (quat-*C*), 129.09 (Ar*C*H), 128.83 (Ar*C*H), 128.39 (Ar*C*H), 118.84 (*C*N), 110.35

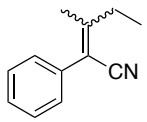
(olefinic-*C*), 28.35 (*C*H_2), 24.77 (*C*H_2), 12.99 (*C*H_3), 12.67 (*C*H_3). HRMS (ESI) m/z calcd for $C_{13}H_{15}N$ $(M+H)^+$: 186.1277, found: 186.1270.

2-Phenyl-3-propylhex-2-enenitrile (3.2j): Colorless liquid. Yield (48%). IR (DCM):



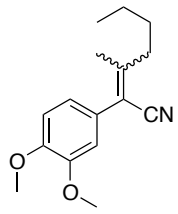
3055, 2918, 2849, 2210, 1613, 1422, 1265, 1075, 896, 747, 704 cm^{-1}. ^1H NMR (700 MHz, $CDCl_3$): δ 7.31 (t, *J* = 7.7 Hz, 2H, ArC*H*), 7.26 (t, *J* = 7 Hz, 1H, ArC*H*), 7.19 (d, *J* = 5.6 Hz, 2H, ArC*H*), 2.48 (t, *J* = 7.7 Hz, 2H, C*H*$_2$), 2.09 (t, *J* = 8.4 Hz, 2H, C*H*$_2$), 1.54-1.59 (m, 2H, C*H*$_2$), 1.34-1.40 (m, 2H, C*H*$_2$), 0.97 (t, *J* = 7 Hz, 3H, C*H*$_3$), 0.75 (t, *J* = 7 Hz, 3H, C*H*$_3$). $^{13}C\{^1H\}$ NMR (175 MHz, $CDCl_3$): δ 162.91 (olefinic-*C*), 134.48 (quat-*C*), 129.23 (Ar*C*H), 128.82 (Ar*C*H), 128.36 (Ar*C*H), 119.05 (*C*N), 111.47 (olefinic-*C*), 37.35 (*C*H_2), 33.79 (*C*H_2), 21.79 (*C*H_2), 21.42 (*C*H_2), 14.14 (*C*H_3), 14.07 (*C*H_3). HRMS (ESI) m/z calcd for $C_{15}H_{19}N$ $(M+H)^+$: 214.1590, found: 214.1585.

3-Methyl-2-phenylpent-2-enenitrile (3.2k): Pale yellow liquid. Yield (58%). Isomer



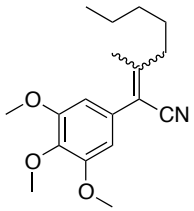
ratio = 62:38 (*Z*/*E*) (according to ^1H NMR) IR (DCM): 3021, 2931, 2879, 2209, 1613, 1472, 1072, 856, 747 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.19-7.33 (m, 10H, ArC*H*) (both isomers), 2.52 (q, *J* = 7.6 Hz, 2H, C*H*$_2$)-major, 2.14 (q, *J* = 7.6 Hz, 2H, C*H*$_2$)-minor, 2.16 (s, 3H, C*H*$_3$C=)-minor, 1.83 (s, 3H, C*H*$_3$C=)-major, 1.14 (t, *J* = 7.6 Hz, 3H, C*H*$_3$CH$_2$)-major, 0.99 (t, *J* = 7.6 Hz, 3H, C*H*$_3$CH$_2$)-minor, 0.75 (t, *J* = 7 Hz, 3H, C*H*$_3$). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 160.15, 159.92 (olefinic-*C*), 134.25, 134.15 (quat-*C*), 129.17, 128.97 (Ar*C*H), 128.75, 128.65 (Ar*C*H), 128.32, 128.25 (Ar*C*H), 118.95, 118.66 (*C*N), 110.78, 110.25 (olefinic-*C*), 31.85, 27.54 (CH$_3$*C*H$_2$), 21.81, 19.08 (*C*H$_3$C=), 12.60, 12.46 (*C*H$_3$CH$_2$). HRMS (ESI) m/z calcd for $C_{12}H_{13}N$ $(M+H)^+$: 172.1121, found: 172.1128.

2-(3,4-Dimethoxyphenyl)-3-methylhept-2-enenitrile (3.2l): Colorless liquid. Yield (20%). Isomer ratio = 58:42 (*Z*/*E*) (according to ^1H NMR) IR (DCM): 3059, 2931,



2865, 2209, 1597, 1422, 1260, 1027, 913, 734 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 6.70-6.81 (m, 6H, ArC*H*) (both isomers), 3.83 (s, 6H, OCH_3)-major, 3.82 and 3.81 (s, 6H, OCH_3)-minor, 2.50 (t, *J* = 7.6 Hz, 2H, CH_2)-major, 2.14 (t, *J* = 7.6 Hz, 2H, CH_2)-minor, 2.14 (s, 3H, CH_3C=)-minor, 1.83 (s, 3H, CH_3C=)-major, 1.45-1.55 (m, 4H, CH_2) (both isomers), 1.34-1.40 (m, 4H, CH_2) (both isomers), 1.16-1.21 (m, 4H, CH_2) (both isomers), 0.91 (t, *J* = 7.6 Hz, 3H, CH_3)-major, 0.77 (t, *J* = 7.6 Hz, 3H, CH_3)-minor. $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 158.51, 158.30 (olefinic-*C*), 149.06, 149.02, 148.98 (quat-*C*), 126.94, 126.79 (quat-*C*), 122.04, 121.78 (Ar*C*H), 119.17, 119.03 (*C*N), 112.19, 112.11 (Ar*C*H), 111.17, 111.09 (olefinic-*C*), 56.10, 56.04 (O*C*H_3), 38.48, 34.28 (*C*H_3C=), 30.30, 30.15 (*C*H_2), 22.70, 22.62 (*C*H_2), 22.27, 19.72 (*C*H_2), 14.06, 13.93 (*C*H_3). HRMS (ESI) m/z calcd for $C_{16}H_{21}NO_2$ $(M+H)^+$: 260.1645, found: 260.1643.

3-Methyl-2-(3,4,5-trimethoxyphenyl)oct-2-enenitrile (3.2m): Colorless liquid. Yield



(20%). Isomer ratio = 66:34 (*Z*/*E*) (according to ^1H NMR). IR (DCM): 3009, 2927, 2858, 2207, 1590, 1495, 1126, 916, 847 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 6.41 (s, 2H, ArC*H*)-major, 6.39 (s, 2H, ArC*H*)-minor, 3.79 (s, 9H, OCH_3)-major, 3.78 (s, 9H, OCH_3)-minor, 2.49 (t, *J* = 7.6 Hz, 2H, CH_2C=)-major, 2.14 (t, *J* = 7.6 Hz, 2H, CH_2C=)-minor, 2.14 (s, 3H, CH_3C=)-minor, 1.84 (s, 3H, CH_3C=)-major, 1.53 (quint, *J* = 7.2 Hz, 2H, CH_2)-major, 1.40 (quint, *J* = 7.2 Hz, 2H, CH_2)-minor, 1.31-1.33 (m, 4H, CH_2)-major, 1.15-1.20 (m, 4H, CH_2)-minor, 0.87 (t, *J* = 5.6 Hz, 3H, CH_3)-major, 0.78 (t, *J* = 5.6 Hz, 3H, CH_3)-minor. $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 159.07, 159.00 (olefinic-*C*), 153.35, 153.31 (quat-*C*), 138.00 (quat-*C*), 129.79, 129.65 (quat-*C*), 118.91, 118.76 (*C*N), 110.99, 110.74 (olefinic-*C*), 106.45, 106.22 (Ar*C*H), 61.00, 56.30, 56.22 (O*C*H_3), 38.63, 34.59 (*C*H_2), 31.72, 31.59 (*C*H_2C=), 27.81, 27.73 (*C*H_2), 22.56, 22.46 (*C*H_2),

22.21, 19.78 (*C*H_3C=), 14.06, 13.98 (*C*H_3). HRMS (ESI) m/z calcd for $C_{18}H_{25}NO_3$ $(M+H)^+$: 304.1907, found: 304.1915.

3.6 NOTES AND REFERENCES

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^{1}H and ^{13}C NMR Spectra of α-Olefinated Nitriles:

Figure 3.2 ^{1}H NMR spectrum of 2-cyclohexylidene-2-phenylacetonitrile (**3.1a**):

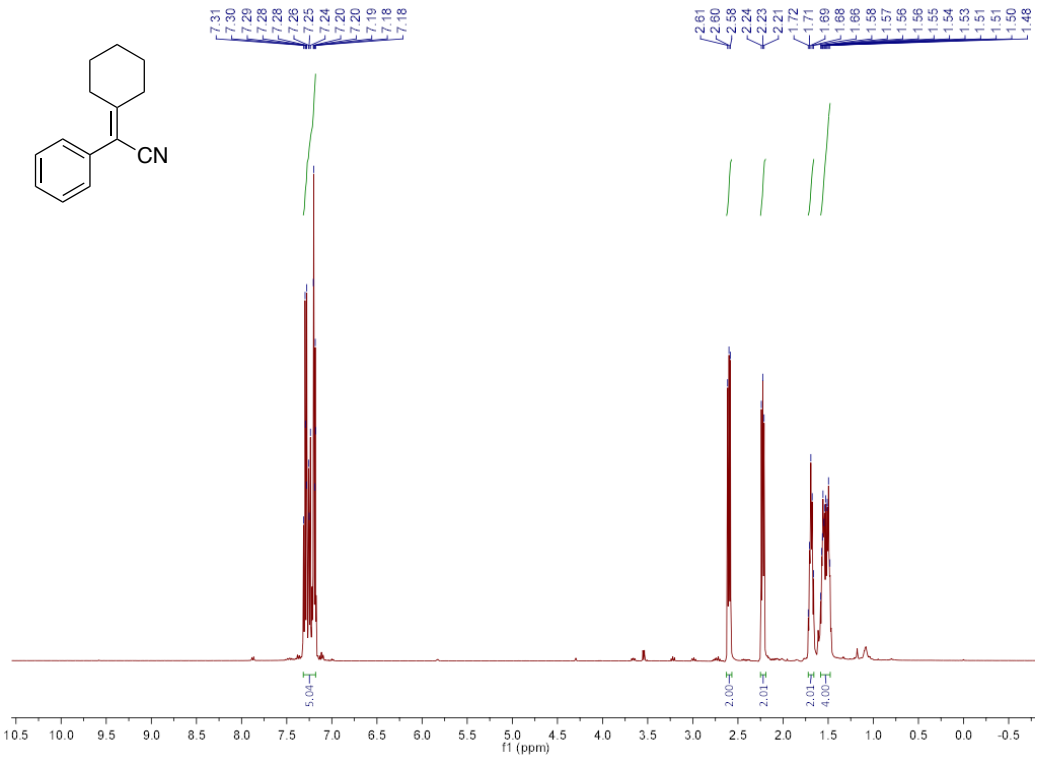


Figure 3.3 ^{13}C NMR spectrum of 2-cyclohexylidene-2-phenylacetonitrile (**3.1a**):

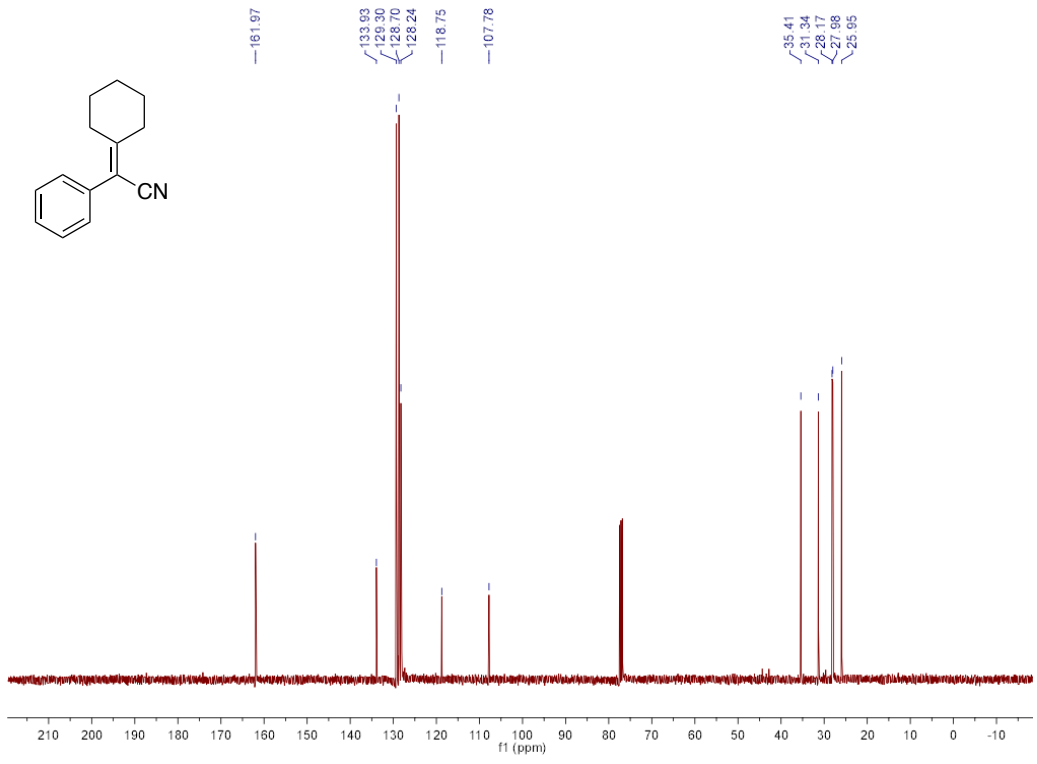


Figure 3.4 ^{1}H NMR spectrum of 2-cycloheptylidene-2-(4-methoxyphenyl)acetonitrile (**3.2f**):

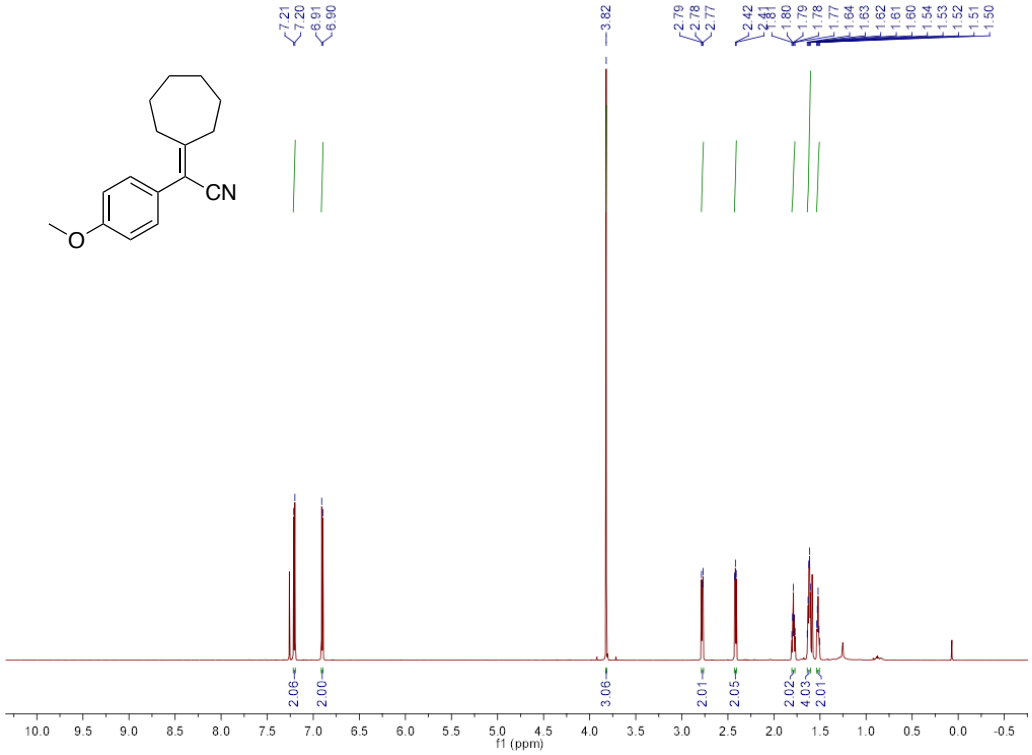


Figure 3.5 ^{13}C NMR spectrum of 2-cycloheptylidene-2-(4-methoxyphenyl)acetonitrile (**3.2f**):

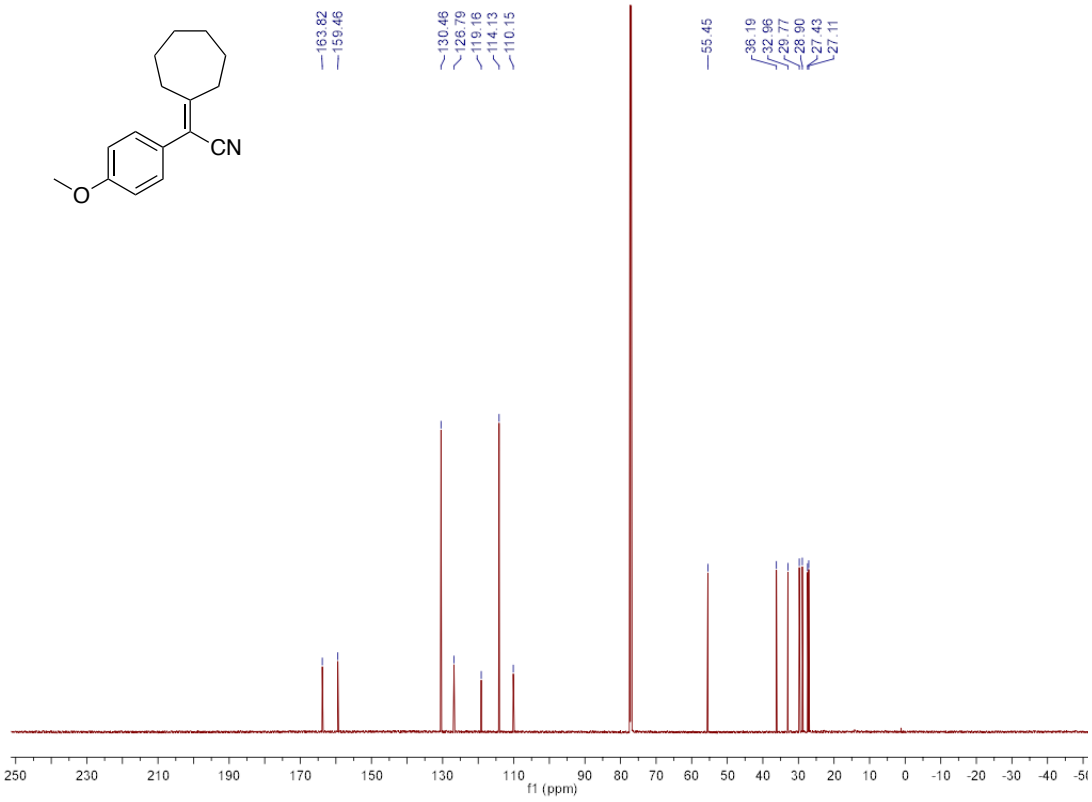


Figure 3.6 ^{1}H NMR spectrum of 3-methyl-2-phenylpent-2-enenitrile (**3.2k**):

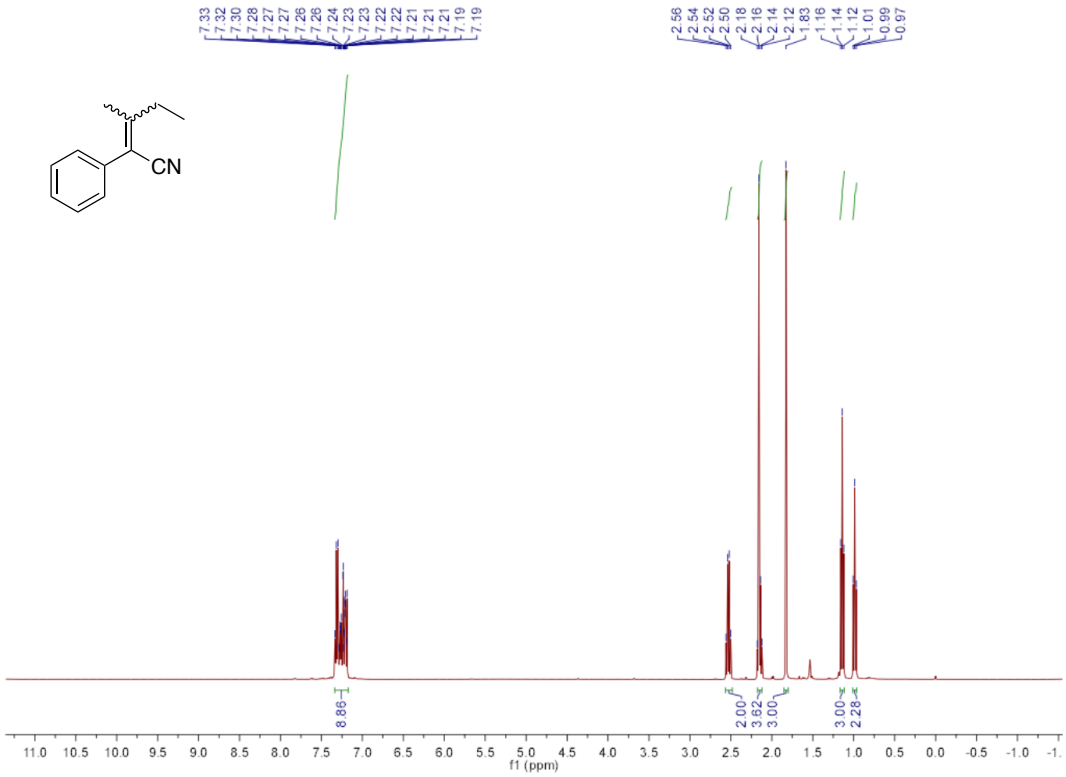
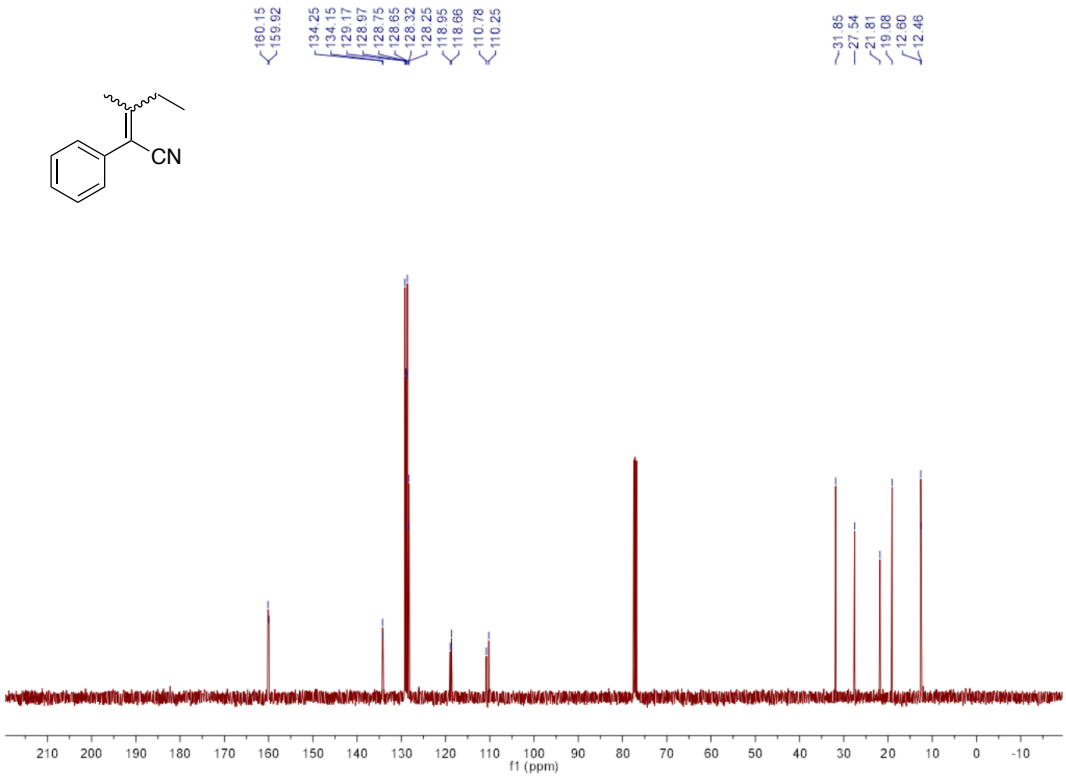


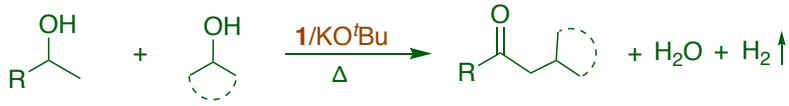
Figure 3.7 ^{13}C NMR spectrum of 3-methyl-2-phenylpent-2-enenitrile (**3.2k**):



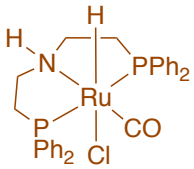
CHAPTER 4

Catalytic Cross-Coupling of Secondary Alcohols

4.1 ABSTRACT



- broad substrate scope
- low cost of alcohols
- no stoichiometric base
- H_2 and H_2O: only byproducts
- new method to β-disubstituted ketones



Catalyst **1**

Herein, an unprecedented ruthenium(II) catalyzed direct cross-coupling of two different secondary alcohols to β-disubstituted ketones is reported. Cyclic, acylic, symmetrical, and unsymmetrical secondary alcohols are selectively coupled with aromatic benzylic secondary alcohols to provide ketone products. A single catalyst oxidizes both secondary alcohols to provide selectively β-disubstituted ketones to broaden the scope of this catalytic protocol. Number of bond activation and bond formation reactions occurs in selective sequence via amine-amide metal-ligand cooperation operative in Ru-MACHO catalyst. The product-induced diastereoselectivity was also observed. Kinetic and deuterium labeling experiments suggested that the aliphatic secondary alcohols undergo oxidation reaction faster than benzylic secondary alcohols, selectively assimilating to provide the cross-coupled products. Reactions are sensitive to steric hindrance. This new C–C bond forming methodology requires low catalyst load and catalytic amount of base. Notably, the reaction produces H_2 and H_2O as the only by-products making the protocol greener, atom economical and environmentally benign.

4.2 INTRODUCTION

Alcohols and ketones are prevalent in nature and are highly promising industrial feedstock chemicals. Ketones are versatile building blocks for the construction of natural products, polymers, biological and pharmaceutical compounds and extensively used as industrial solvents.[1] Traditional synthesis of α- and β-substituted ketones involves reaction of carbonyl compounds under cryogenic conditions with strong bases (^{n}BuLi, LDA, etc) followed by addition of toxic alkyl halides (Scheme 4.1a). This enolate alkylation approach suffers from serious drawbacks, which include (i) generation of stoichiometric metal halides as chemical waste (ii) over alkylation to di- or trisubstituted ketones, and (iii) homolytic coupling of carbonyl compounds curtailing the atom economy of the reactions.[2] In addition, organic halides and carbonyl compounds are expensive and they are not readily available substrates, which can be replaced by most abundant, cheap and environmentally benign alcohols for alkylation reactions. Moreover, alcohols can be obtained from renewable resources such as lignocellulosic biomass.[3] The recent development in transition metal catalysis aims to develop sustainable, one-step, and atom economical efficient methodologies for the preparation of valuable synthetic building blocks by using easily available starting materials. In this regard, "borrowing hydrogen" methodology has become one of the most attractive transformation for C–C and C–N bond formation in organic synthesis.[4,5] Synthesis of α-substituted ketones from ketones and alcohols is well established.[5] Direct cross-coupling of alcohols with hydrogen evolution via acceptorless dehydrogenation is one of the most atom economical and environmentally benign methods for constructing new C–C bonds (Scheme 4.1b).[6] Catalytic self-coupling[7,8] and cross-coupling[9] of primary alcohols to esters and higher alcohols are reported. Cross-coupling of secondary alcohols with primary alcohols has been widely explored.[10,11]

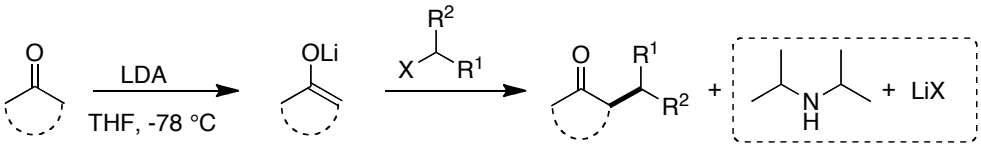
There are two reports on self-coupling of secondary alcohols.[12] However, the catalytic cross-coupling of two different secondary alcohols remains unknown.

The major challenge in cross-coupling of secondary alcohols is to overcome the unwanted self-coupling from aldol reactions, which generates undesired by-products and hence, diminishes the atom economy of the overall transformation (Scheme 4.1c). More importantly, synthesis of β-disubstituted ketones directly from two different secondary alcohols can usually be accomplished via four-step transformations (oxidation, aldol condensation, hydrogenation, and oxidation). Recently, Donohoe and co-workers reported the synthesis of β-disubstituted ketones via borrowing hydrogen methodology.[13] However, the reaction requires stoichiometrically excess amount of base and the substrate scope is limited to bulky ketones (e.g., Ph*$COCH_3$, Ph* = pentamethyl phenyl). Thus, it is desirable to develop a new strategy for the synthesis of β-disubstituted ketones directly from two different secondary alcohols (Scheme 4.1d).

Recently, selective α-alkylation and α-olefination of nitrile compounds by alcohols were reported from our laboratory using a commercially available Ru-MACHO catalyst (**1**).[14] On the basis of these reports, I have further envisaged the cross-coupling of secondary alcohols. Herein, I describe the synthesis of β-disubstituted ketones directly from two different secondary alcohols. This catalytic method does not require stoichiometric oxidants; it only requires a catalyst and catalytic amount of base. Water and liberated H_2 are the only byproducts of this reaction.

Scheme 4.1 Traditional and Selectivity Challenges in Synthesis of β-Disubstituted Ketones and Cross-Coupling of Secondary Alcohols

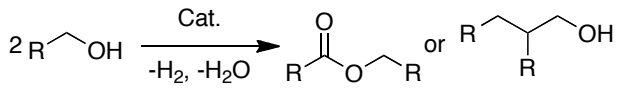
a) Traditional approach: synthesis of β-disubstituted ketones



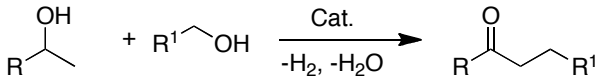
Hazardous waste

Drawbacks: (i) use of stoichiometric strong metallic base
(ii) stoichiometric metal halide as the waste
(iii) not environmentally benign and not atom economical reaction

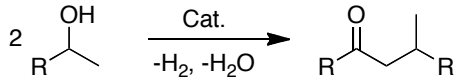
b) Catalytic coupling of alcohols



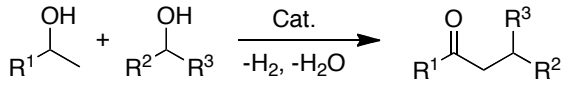
self-coupling of primary alcohols: well known



cross-coupling of primary and secondary alcohols: very much explored



self-coupling of secondary alcohols: reported



cross-coupling of secondary alcohols: unknown

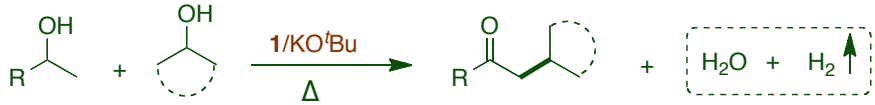
c) Selectivity challenges: direct cross-coupling of secondary alcohols

self-coupled product olefinated product alcohol product

desired product
highly challenging

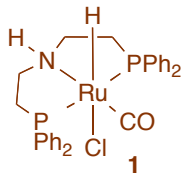
competing side products

d) Our approach: direct cross-coupling of secondary alcohols



green byproducts

Advantages:
(i) alcohols: cheap industrial feedstock
(ii) no stoichiometric base required
(iii) only byproducts: H_2 and H_2O
(iv) direct synthesis of β-disubstituted ketones from two different secondary alcohols

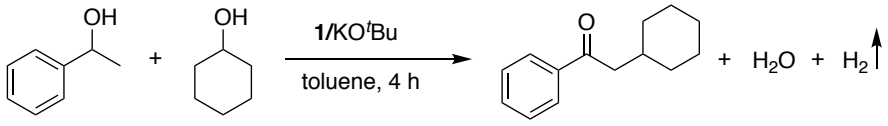


1

4.3 RESULTS AND DISCUSSIONS

Reaction of 1-phenylethanol (0.5 mmol) with cyclohexanol (0.5 mmol), catalyst **1** (1 mol%), and base (2 mol%) in toluene solution was heated to 135 °C for an initial investigation. Further, the reaction mixture was analyzed by ^{1}H NMR spectroscopy and gas chromatography (GC), which confirmed the complete conversion of 1-phenylethanol and high reactivity for cross-coupling reaction along with unreacted acetophenone (in situ generated intermediate) and trace amount of self-coupled aldol product were detected (entry 1, Table 4.1). Notably, over-alkylation products and *β*-alkylated secondary alcohols were not observed (Scheme 4.1c). However, upon increasing base load to 5 mol% and lowering temperature to 125 °C, resulted in a better outcome and the cross-coupled product was isolated in 85% and 86% yields (entries 2, 3, Table 4.1). Use of 10 mol% of base, diminished the product formation presumably due to aldol side reactions (entry 4, Table 4.1). Further, upon increasing the amount of cyclohexanol no significant improvement in yield was observed (entry 5, Table 4.1). On decreasing catalyst load, use of lower temperature and replacing KO^{t}Bu with NaO^{t}Bu provided considerably lower yields (entries 6-8, Table 4.1). Other bases and changing solvent were not effective on the reaction (entries 9-11, Table 4.1). In control experiments performed by employing only base, and without catalyst and base, no cross-coupling product was observed, indicating that catalyst and base are essential for the success of the reaction (entries 14,15, Table 4.1). When the reaction was performed using [RuHCl(CO)(PPh_3)$_3$] no cross-coupled product was observed, which indicates the necessity of pincer catalyst for this transformation.

Table 4.1 Optimization for Cross-Coupling of Secondary Alcohols Catalyzed by 1[a]



4.1a

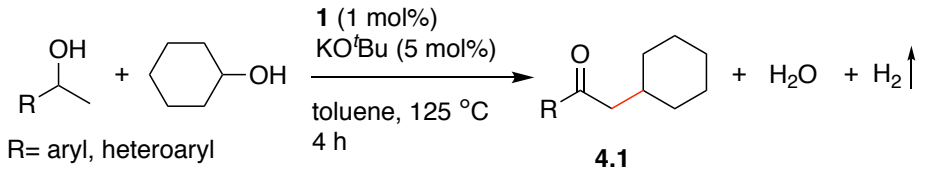
entry	cat. (mol%)	base (mol%)	temp. (°C)	conv. (%)[b]	yield (%)[c]
1	1	2	135	>99	69 (74)
2	1	5	135	>99	85 (90)
3	**1**	**5**	**125**	**>99**	**86 (91)**
4	1	10	125	>99	70 (76)
5[d]	1	5	125	>99	87 (94)
6	1	5	115	94	63 (69)
7	0.5	5	125	>99	70 (72)
8[e]	1	5	125	>99	79 (83)
9[f]	1	5	125	75	60 (66)
10[g]	1	5	125	5	-
11[h]	1	5	125	85	65 (67)
12[i]	1	5	125	77	42 (48)
13[j]	1	-	125	90	-
14[k]	-	5	125	5	-
15[k]	-	-	125	-	-
16[l]	1	5	125	30	-

[a]Reaction conditions: 1-Phenylethanol (0.5 mmol), cyclohexanol (0.5 mmol), toluene (1.5 ml), catalyst **1** (1 mol%) and KO^{t}Bu (5 mol%) were heated at 125 °C under argon flow. [b]Conversion of 1-phenylethanol was determined by GC analysis using benzene as an internal standard. [c]Yields were calculated for isolated products after column chromatography; yields calculated from GC analysis of the reaction mixtures are given within parenthesis. [d]2 equiv. of cyclohexanol was used. [e]5 mol% of NaO^{t}Bu was used.

[f]5 mol% KOH was used. [g]5 mol% Cs_2CO_3 was used. [h]1,4-Dioxane was used as solvent. [i]Reaction mixture prepared in fume hood using standard Schlenk techniques (without using glove box). [j]Reaction performed using activated precatalyst and without use base. [k]Reaction performed for 24 h. [l]Reaction was performed using [$RuHCl(CO)(PPh_3)_3$] catalyst (1 mol%) and KO^{t}Bu (5 mol%).

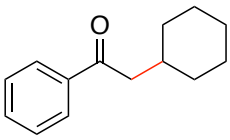
Having optimal reaction conditions in hand, the scope of the various secondary alcohols on cross-coupling was investigated (Scheme 4.2). In general, methyl, methoxy and benzyloxy substituted 1-phenylethanols reacted well with cyclohexanol and provided the corresponding cross-coupled products **4.1b-4.1i** in good to high yields. The electron withdrawing group present in aromatic ring of secondary alcohol slightly diminished the reactivity as observed in 1-(4-chlorophenyl)ethan-1-ol to **4.1j**. Notably, heteroaryl and bicyclic aromatic secondary alcohols were tolerated well and the cross-coupling products **4.1k-4.1o** were obtained in good yields (Scheme 4.2).

Scheme 4.2 Ruthenium-Catalyzed Selective Cross-Coupling of Secondary Alcohols Using Cyclohexanol[a]

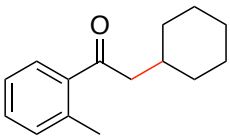


R= aryl, heteroaryl

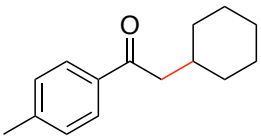
4.1



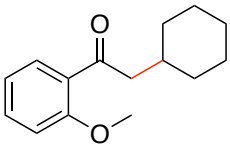
4.1a, 86% (>99%)



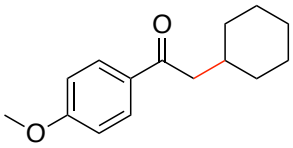
4.1b, 90% (>99%)



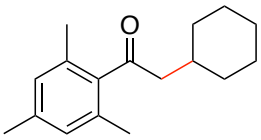
4.1c, 85% (>99%)



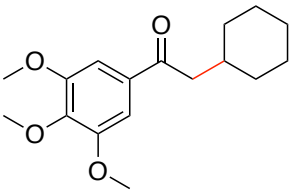
4.1d, 67% (75%)



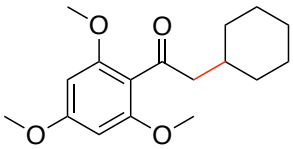
4.1e, 87% (>99%)



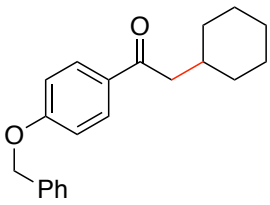
4.1f, 60% (83%)



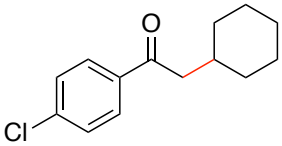
4.1g, 63% (>99%)



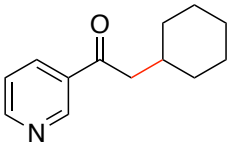
4.1h, 78% (>99%)[b]



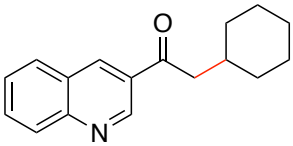
4.1i, 78% (91%)



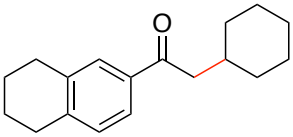
4.1j, 48% (60%)[c]



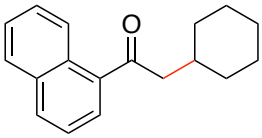
4.1k, 72% (99%)



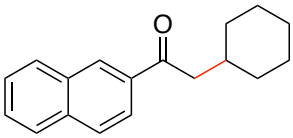
4.1l, 82% (>99%)



4.1m, 87% (>99%)



4.1n, 83% (>99%)[b]



4.1o, 86% (97%)[b]

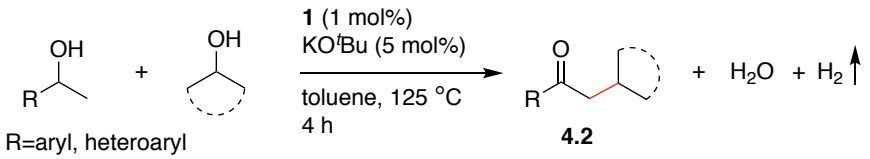
[a]Reaction conditions: 1-arylethanol (0.5 mmol), cyclohexanol (0.5 mmol), toluene (1.5 ml), catalyst **1** (1 mol%) and KO^{t}Bu (5 mol%) were heated at 125 °C under argon flow

for 4 h. Conversion of 1-arylethanols were determined by GC analysis using benzene as an internal standard is given within parentheses. Reported yields correspond to isolated pure compounds. [b]Reaction was performed using 2 mol% catalyst **1** and 10 mol% base. [c]4 mol% of catalyst **1** and 20 mol% of base was used.

Encouraged by these results, a range of secondary alcohols was further explored for catalytic cross-coupling reaction. Both cyclic and acyclic secondary alcohols were directly coupled with benzylic secondary alcohols, which afforded cross-coupled ketone products in good to excellent yields (Scheme 4.3). Substitution on cyclohexyl ring provided products as a mixture of diastereoisomers and the diastereomeric ratios were obtained from ^{1}H NMR of crude reaction mixture. 4-Methylcyclohexanol was selectively coupled with various 1-arylethanol derivatives to provide the products **4.2a-4.2c** (d.r, 80:20, 81:19, 78:22, respectively) in very good yields as a mixture of diastereoisomers. Representatively, the single-crystal X-ray structure for major isomer of product **4.2b** is solved, which revealed the 1,4-cis conformation on cyclohexyl ring. Accordingly, similar 1,4-cis conformation is assigned for all major isomers of products **4.2a-4.2g.** Good yields with similar diastereoselectivities were also obtained for 4-propyl, 4-*tert*-butyl, and 4-phenyl-substituted cyclohexanol derivatives (**4.2d-4.2g**). Gratifyingly, 1-cycloheptanol and 2-norborneol were reacted with 1-phenylethanol derivatives and the corresponding products **4.2h**-**4.2k** were isolated in very good yields (Scheme 4.3). 4-Hydroxycyclohexanone ethyleneacetal with 1-(4-methylphenyl)ethanol provided product **4.2l** in moderate yield. A sterically hindered substrate, 1,1-diphenylmethanol delivered cross-coupled product **4.2m** in 68% yield. Finally, the highly challenging unactivated acyclic aliphatic secondary alcohols were subjected to catalysis with increased catalyst load of **1** (4 mol%) and base (20 mol%). A variety of

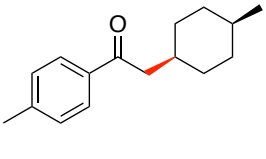
secondary alcohols such as 2-propanol, 2-butanol, 2-pentanol, 3-pentanol and 4-heptanol were well tolerated and selectively converted into *β*-disubstituted ketones (**4.2n-4.2t**).

Scheme 4.3 Ruthenium-Catalyzed Selective Cross-Coupling of Secondary Alcohols[a]

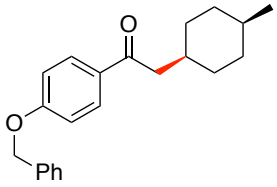


R=aryl, heteroaryl

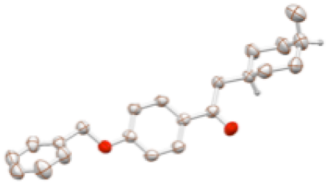
4.2



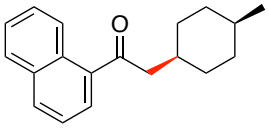
4.2a, 87% (>99%)
d.r = 80:20



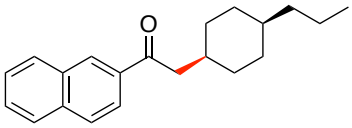
4.2b, 68% (78%)
d.r = 81:19



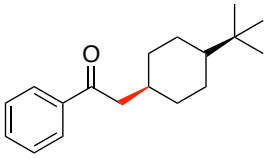
4.2b



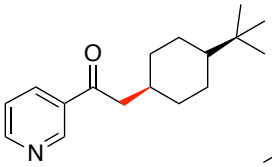
4.2c, 90% (95%)
d.r = 78:22



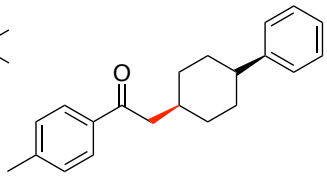
4.2d, 72% (92%)[b]
d.r = 87:13



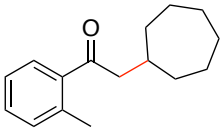
4.2e, 78% (87%)
d.r = 86:14



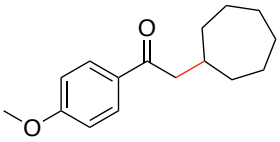
4.2f, 90% (99%)
d.r = 90:10



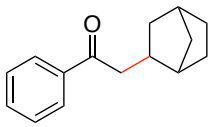
4.2g, 82% (>99%)
d.r = 80:20



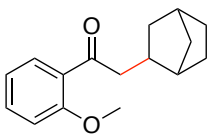
4.2h, 80% (>99%)[c]



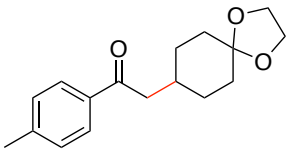
4.2i, 68% (98%)[c]



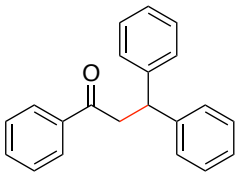
4.2j, 75% (98%)



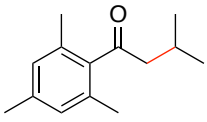
4.2k, 75% (91%)[b]



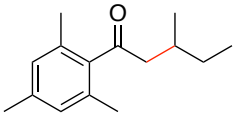
4.2l, 48% (97%)[b]



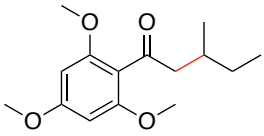
4.2m, 68% (>99%)[d]



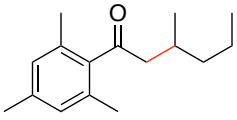
4.2n, 82% (95%)[e]



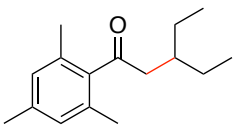
4.2o, 90% (>99%)[f]



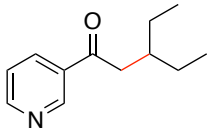
4.2p, 30% (40%)[f]



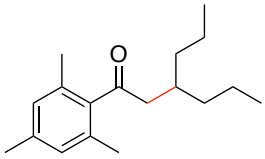
4.2q, 65% (72%)[f]



4.2r, 97% (>99%)[f]



4.2s, 60% (>99%)[f]



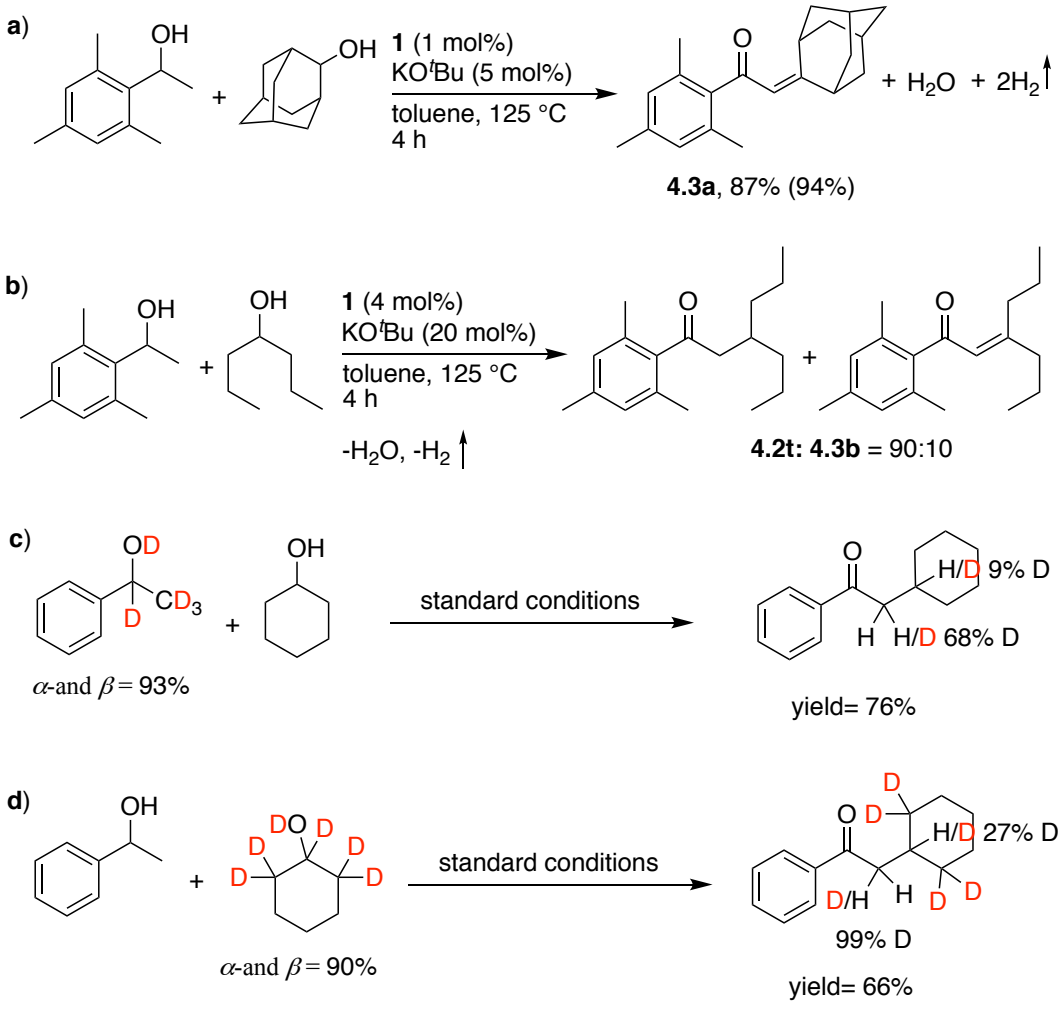
4.2t, 83% (>99%)[f]

[a]Reaction conditions: A mixture of two secondary alcohols (each 0.5 mmol scale at 1:1 ratio), toluene (1.5 ml), catalyst **1** (1 mol%) and KO^{t}Bu (5 mol%) were heated at 125 °C under the argon flow. Diastereomeric ratios (d.r) were determined by ^{1}H NMR analysis of crude reaction mixture; major isomer shown. Conversion of secondary alcohols was determined by GC analysis using benzene as an internal standard and given within parentheses. Reported yields correspond to isolated pure compounds. [b]2 mol% catalyst **1** and 10 mol% base was used. [c]3 mol% catalyst **1** and 15 mol% base and 3 equivalents of cycloheptanol were used. [d]5 mol% of catalyst and 10 mol% base was used. [e]4 mol% catalyst **1** and 20 mol% base and 10 equivalents of isopropanol were used. [f]Reaction was performed using 5 equivalent of aliphatic secondary alcohol, 4 mol% catalyst **1** and 20 mol% base.

Further, experiments aimed at deciphering the mechanistic insights were performed. When 1-mesitylethanol was reacted with sterically hindered 2-adamantanol, selective formation of olefin product **4.3a** was observed (Scheme 4.4a). GC analysis of this reaction mixture clearly indicated the absence of alkylated product. However, the reaction of 1-mesitylethanol with 4-heptanol under optimized conditions provided alkylated product **4.2t** and olefin product **4.3b** in 90:10 ratio (Scheme 4.4b). These results indicate the borrowing hydrogen pathway is interrupted due to sterically encumbered ruthenium on catalyst **1** and the reaction proceeds via α,β-unsaturated ketone intermediates. In addition to that, deuterium-labeling experiments were conducted and the results imply that the liberated dideutrium/dihydrogen from cyclohexanol are predominantly reinstalled to unsaturated intermediate rather than dideutrium/dihydrogen liberated from 1-phenylethanol (Scheme 4.4c-d). These observations clearly indicate that the catalytic cross-coupling of secondary alcohols

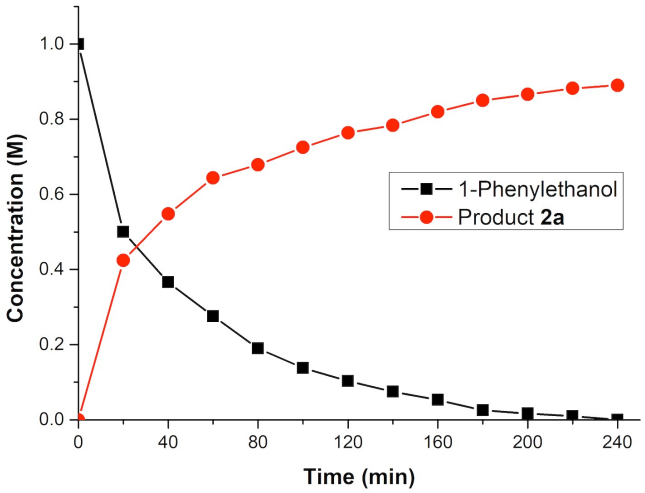
reactions are sensitive to steric hindrance. Thus, in addition to the faster dehydrogenation of aliphatic secondary alcohols by catalyst **1**, the higher reactivity of aliphatic cyclic ketones intermediates presumably due to the conformation strain and the steric compatibility also facilitates the formation of cross-coupling products by precluding the self-coupling reactions.

Scheme 4.4 Mechanistic Studies for the Cross-Coupling of Secondary Alcohols



GC monitoring of reaction progress shows the reaction follows first order kinetics with respect to 1-phenylethanol consumption (Figure 4.1). The decreasing concentration of 1-phenylethanol (black line) and increasing concentration product **4.1a** (red line) with respect to time in the catalytic cross-coupling of secondary alcohols.

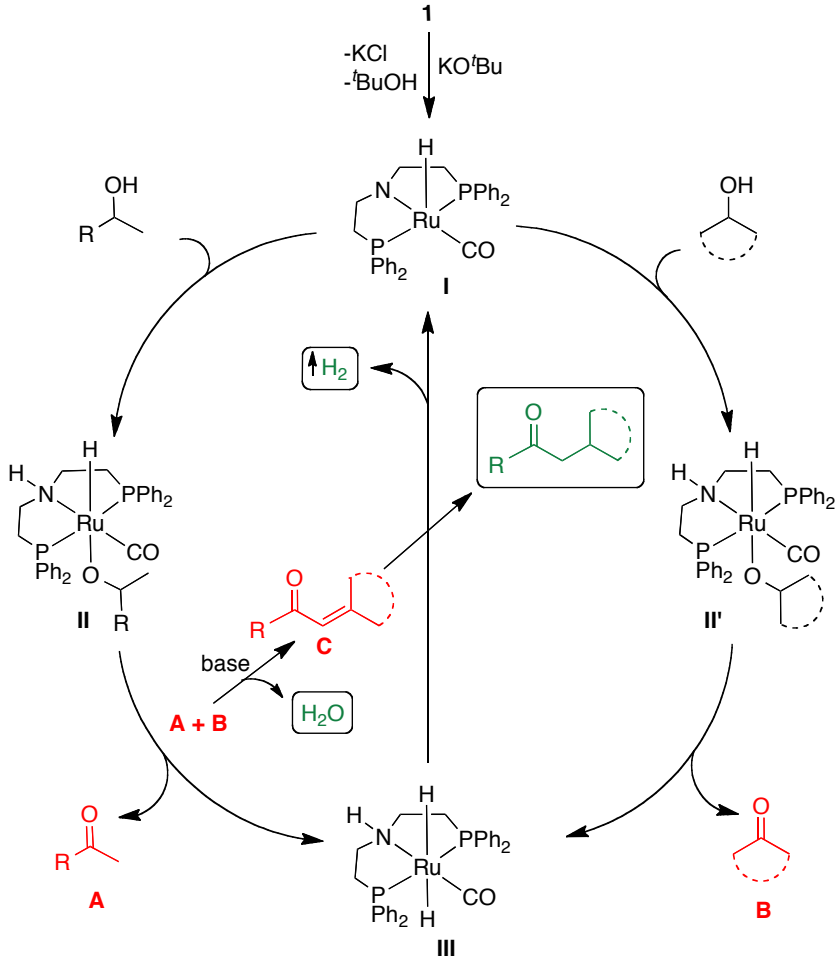
Figure 4.1 Kinetic Profile for the Cross-Coupling of Secondary Alcohols



On the basis of these experimental evidences, catalytic cycle for cross-coupling of secondary alcohols catalyzed by **1** is proposed in Scheme 4.5. Facile O–H, O–D, N–H, and spC–H bond activation reactions by catalyst **1** have been established in our previous reports.[14,15] Catalyst **1** reacts with base to generate an unsaturated reactive intermediate **I**, which has been previously observed in mass spectrometry analysis.[15b,16] The resulted reactive intermediate **I** further reacts with both secondary alcohols to provide an alkoxo coordinated ruthenium intermediates **II** and **II'** as already established.[15d] β-Hydride elimination reaction from alkoxoide ligands may result in formation of ketone intermediates **A** and **B** and both dehydrogenation reactions converge to provide the same ruthenium dihydride complex **III**. However, involvement of other mechanistic pathways cannot be ruled out.[17] A base mediated cross-aldol condensation reaction between in situ formed ketones **A** and **B** produces α,β-unsaturated carbonyl compound **C**, which undergoes selective hydrogenation by complex **III** to provide desired β-disubstituted ketones. The amine-amide metal ligand cooperation operative in these

catalytic intermediates allow the regeneration of active intermediate **I** upon hydrogenation as well as liberation of a H_2 molecule by ruthenium dihydride **III**.

Scheme 4.5 Proposed Mechanism for Cross-Coupling of Secondary Alcohols



4.4 CONCLUSIONS

In summary, I have developed an efficient catalytic cross-coupling of secondary alcohols to provide β-branched ketones. This methodology provides broad substrate scope. Various aromatic, heteroaromatic, cyclic, linear, symmetrical, and unsymmetrical secondary alcohols were well tolerated. The reaction proceeded by O–H bond activation of secondary alcohols by catalyst via amine-amide metal-ligand cooperation to provide

corresponding carbonyl intermediates, which condensed and underwent catalytic hydrogenation to eventually deliver the products. Overall two equivalents of molecular H_2 are obtained from oxidation of two different secondary alcohols. While one equivalent is used for the hydrogenation of the α,β-unsaturated carbonyl compound to provide the desired β-branched ketones, the other equivalent is liberated as H_2. Remarkably, H_2O and H_2 are the only by-products. Use of readily available and challenging starting materials, broad scope, high selectivity and absence of any deleterious side reactions in this C–C bond formation will be beneficial and contribute to the development of new "green" and "sustainable" catalytic processes in future.

4.5 EXPERIMENTAL SECTION

General Experimental: All catalytic reactions were performed under inert atmosphere using standard Schlenk techniques. All stoichiometric reactions were performed in nitrogen atmosphere MBRAUN glove box. Ru-MACHO **[Carbonylchlorohydrido{bis[2-(diphenylphosphinomethyl) ethyl]amino}ethyl]amino}ruthenium(II)]** was purchased from Sigma-Aldrich and stored inside glove box. Chemicals were purchased from Acros, Sigma-Aldrich, Alfa-aesar, Himedia Chemicals and used without further purification. Dry solvents were prepared according to standard procedures. Infrared (IR) spectra were recorded in Perkin-Elmer FT-IR and Thermo-Nicolet FT-IR spectrophotometers. High-resolution mass spectra (HRMS) were obtained on Bruker micrOTOF-Q II Spectrometer and are reported as m/z (relative intensity). Accurate masses are reported for the molecular ion $[M+Na]^+$, $[M+H]^+$, $[M]^+$. Nuclear magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded at Bruker AV-700 (^{1}H at 700 MHz, ^{13}C at 175 MHz) and Bruker AV-400 (^{1}H at 400 MHz, ^{13}C at 100.6 MHz). ^{1}H NMR chemical shifts are referenced in parts per million (ppm) with respect to tetramethyl silane (TMS) (δ 0.00 ppm) and ^{13}C $\{^1$H$\}$

NMR chemical shifts are referenced in parts per million (ppm) with respect to $CDCl_3$ (δ 77.160 ppm). Coupling constants are reported in Hertz (Hz). ^1H NMR spectroscopy abbreviations: s, Singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; dt, doublet of triplets; dq, doublet of quartets; td, triplet of doublets; qd, quartets of doublets; ddd, doublets of doublets of doublets; m, multiplet; br, broad. Assignment of spectra was done based on one-dimensional (DEPT-135) NMR techniques.

GC Method: Gas chromatography data were obtained using a gas chromatograph equipped with a SH-Rtx-1 capillary column (30 m × 250 μm). The instrument was set to an injection volume of 1 μL, an inlet split ratio of 10:1, and inlet and detector temperatures of 300 and 330 °C, respectively. The temperature program used for all of the analyses is as follows: 50 °C, 1 min; 12 °C/min to 320 °C, 7 min. Response factor for all of the necessary compounds with respect to standard benzene was calculated from the average of three independent GC runs.

General Optimization Procedure for Cross-Coupling of Secondary Alcohols:

A Schlenk flask (25 mL) was equipped with a stir bar, catalyst **1** (0.01 mmol), base (0.05 mmol), 1-phenylethanol (0.5 mmol), cyclohexanol (0.5 mmol) and toluene (1.5 mL) under nitrogen atmosphere in a glove box. The flask was taken out of the glove box, equipped with a condenser and the solution was heated at 125 °C (oil bath temperature, internal temperature of the reaction mixture is found to be 115 °C) with stirring under a flow of argon for 4 h. The completion of the reaction was monitored using GC analysis. After cooling to room temperature, 0.5 mmol of internal standard (benzene) was added into the reaction mixture and the conversion of 1-phenylethanol was calculated using GC analysis. Further, the solvent was evaporated and crude reaction mixture was purified by column chromatography over silica-gel (100-200

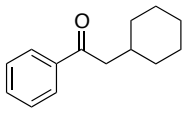
mesh) using ethyl acetate/petroleum ether mixture as an eluent. Yields were calculated from crude reaction mixture using GC analysis and also for isolated pure products.

General Procedure for Cross-Coupling of Secondary Alcohols Using Cyclohexanol:

A Schlenk flask (25 mL) was equipped with a stirr bar, catalyst **1** (0.01 mmol), base (0.05 mmol), secondary alcohol (0.5 mmol), cyclohexanol (0.5 mmol) and toluene (1.5 mL) under nitrogen atmosphere in a glove box. The flask was taken out of the glove box, equipped with a condenser and the solution was heated at 125 °C (oil bath temperature) with stirring under the flow of argon for 4 h. The completion of the reaction was monitored using GC analysis. After cooling to room temperature, 0.5 mmol of internal standard (benzene) was added into the reaction mixture and the conversion of 1-arylethanols was calculated using GC analysis. Further, the solvent was evaporated and crude reaction mixture was purified by column chromatography over silica-gel (100-200 mesh) using ethyl acetate/petroleum ether mixture as an eluent. Yields were calculated for isolated pure products.

Spectral Data of the Cross-Coupled Products:

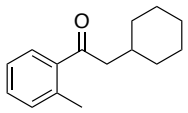
2-Cyclopentyl-1-phenylethanone (4.1a):[18] Colorless liquid. Yield: 86%. IR (DCM):



3052, 2987, 2853, 1672, 1447, 1267, 1047, 895, 747 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.86 (dd, J_1 =8.4 Hz, J_2 =1.2 Hz, 2H, ArC*H*), 7.46 (tt, J_1 =7.6 Hz, J_2 =1.2 Hz, 1H, ArC*H*), 7.37 (td, J_1 =7.2 Hz, J_2 =1.2 Hz, 2H, ArC*H*), 2.73 (d, J = 6.8 Hz, 2H, COCH_2), 1.85-1.94 (m, 1H, C*H*), 1.56-1.70 (m, 5H, CH_2), 1.19 (qt, J_1 =12.8 Hz, J_2 =2.8 Hz, 2H, CH_2), 1.02-1.10 (m, 1H, CH_2), 0.92 (qd, J_1 =12.8 Hz, J_2 =2.4 Hz, 2H, CH_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100.6 MHz): δ 200.36 (*C*=O), 137.60 (quat-*C*), 132.93 (Ar*C*H), 128.63 (Ar*C*H), 128.24 (Ar*C*H), 46.32 (CO*C*H_2),

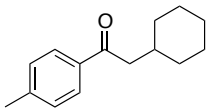
34.65 (*C*H), 33.55 (*C*H_2), 26.37 (*C*H_2), 26.26 (*C*H_2). HRMS (ESI) m/z calcd for $C_{14}H_{18}O$ $(M+H)^+$: 203.1430, found: 203.1429.

2-Cyclohexyl-1-(*o*-tolyl)ethan-1-one (4.1b): Colorless liquid. Yield: 90%. IR (DCM):



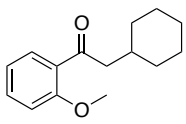
3062, 3020, 2922, 2850, 1682, 1600, 1448, 1293, 1221, 1190, 956, 755 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.50 (d, *J* = 7.7 Hz, 1H, ArC*H*), 7.25-7.29 (m, 1H, ArC*H*), 7.16 (t, *J* = 8.1 Hz, 2H, ArC*H*), 2.67 (d, *J* = 6.8 Hz, 2H, COCH_2), 2.40 (s, 3H, CH_3), 1.84-1.90 (m, 1H, C*H*), 1.56-1.69 (m, 5H, CH_2), 1.21 (ddd, J_1 = 15.5 Hz, J_2 = 11.3 Hz, J_3 = 3.2 Hz, 2H, CH_2), 1.02-1.12 (m, 1H, CH_2), 0.91 (qt, J_1 =12.8 Hz, J_2 =2.4 Hz, 2H, CH_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100.6 MHz): δ 204.88 (*C*=O), 138.90 (quat-*C*), 137.82 (quat-*C*), 131.97 (Ar*C*H), 131.05 (Ar*C*H), 128.41 (Ar*C*H), 125.69 (Ar*C*H), 49.53 (CO*C*H_2), 34.58 (*C*H), 33.49 (*C*H_2), 26.38 (*C*H_2), 26.26 (*C*H_2), 21.23 (*C*H_3). HRMS (ESI) m/z calcd for $C_{15}H_{20}O$ $(M+H)^+$: 217.1587, found: 217.1586.

2-Cyclohexyl-1-(*p*-tolyl)ethanone (4.1c):[18] Colorless liquid. Yield: 85%. IR (DCM):



3051, 2923, 2851, 1675, 1605, 1447, 1264, 1005, 908, 736 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.77 (d, *J* =8 Hz, 2H, ArC*H*), 7.17 (d, *J* =8 Hz, 2H, ArC*H*), 2.71 (d, *J* = 6.8 Hz, 2H, COCH_2), 2.33 (s, 3H, CH_3), 1.86-1.91 (m, 1H, C*H*), 1.56-1.69 (m, 5H, CH_2), 1.15-1.26 (m, 2H, CH_2), 1.02-1.11 (m, 1H, CH_2), 0.95 (qd, J_1 =12.4 Hz, J_2 =2.4 Hz, 2H, CH_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100.6 MHz): δ 200.15 (*C*=O), 143.70 (quat-*C*), 135.12 (quat-*C*), 129.32 (Ar*C*H), 128.41 (Ar*C*H), 46.25 (CO*C*H_2), 34.81 (*C*H), 33.57 (*C*H_2), 26.39 (*C*H_2), 26.28 (*C*H_2), 21.73 (*C*H_3). HRMS (ESI) m/z calcd for $C_{15}H_{20}O$ $(M+H)^+$: 217.1587, found: 217.1579.

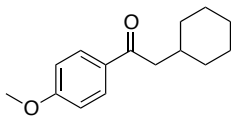
2-Cyclohexyl-1-(2-methoxyphenyl)ethan-1-one (4.1d):[19] Colorless liquid. Yield:



67%. IR (DCM): 3053, 2986, 2926, 2852, 1669, 1597, 1265, 895, 738 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.53 (dd, J_1 =7.7 Hz, J_2 =1.6 Hz, 1H, ArC*H*), 7.33-7.38 (m, 1H, ArC*H*), 6.86-6.93 (m, 2H, ArC*H*), 3.81 (s, 3H, OCH_3),

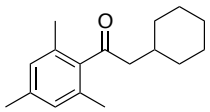
2.76 (d, J = 6.8 Hz, 2H, COCH_2), 1.81-1.85 (m, 1H, CH), 1.54-1.66 (m, 5H, CH_2), 1.14-1.23 (m, 2H, CH_2), 1.01-1.12 (m, 1H, CH_2), 0.86-0.95 (m, 2H, CH_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100.6 MHz): δ 203.29 (C=O), 158.26 (quat-C), 133.07 (ArCH), 130.10 (ArCH), 129.42 (quat-C), 120.73 (ArCH), 111.58 (ArCH), 55.58 (OCH$_3$), 51.50 (COCH$_2$), 34.46 (CH), 33.49 (CH$_2$), 26.44 (CH$_2$), 26.32 (CH$_2$). HRMS (ESI) m/z calcd for $C_{15}H_{20}O_2$ $(M+H)^+$: 233.1536, found: 233.1533.

2-Cyclohexyl-1-(4-methoxyphenyl)ethanone (4.1e):[18] Colorless liquid. Yield: 87%. IR



(DCM): 3052, 2985, 2851, 1667, 1427, 1264, 895, 704 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.85 (d, J =8.8 Hz, 2H, ArCH), 6.84 (d, J =8.8 Hz, 2H, ArCH), 3.78 (s, 3H, OCH_3), 2.68 (d, J = 6.8 Hz, 2H, COCH_2), 1.84-1.92 (m, 1H, CH), 1.55-1.69 (m, 5H, CH_2), 1.06-1.25 (m, 3H, CH_2), 0.92 (qd, J_1 =12.4 Hz, J_2 =1.6 Hz, 2H, CH_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100.6 MHz): δ 199.01 (C=O), 163.41 (quat-C), 130.73 (quat-C), 130.52 (ArCH), 113.75 (ArCH), 55.53 (OCH$_3$), 46.01 (COCH$_2$), 34.93 (CH), 33.59 (CH$_2$), 26.38 (CH$_2$), 26.28 (CH$_2$). HRMS (ESI) m/z calcd for $C_{15}H_{20}O_2$ $(M+H)^+$: 233.1536, found: 233.1538.

2-Cyclohexyl-1-mesitylethanone (4.1f): Colorless liquid. Yield: 60%. IR (DCM):



3052, 2924, 2852, 1696, 1609, 1447, 1265, 1034, 908, 736 cm^{-1}. ^1H NMR ($CDCl_3$, 700 MHz): δ 6.74 (s, 2H, ArCH), 2.51 (d, J = 6.4 Hz, 2H, COCH_2), 2.19 (s, 3H, CH_3), 2.11 (s, 6H, CH_3), 1.92-2.00 (m, 1H, CH), 1.74 (d, J = 12 Hz, 2H, CH_2), 1.58-1.64 (m, 3H, CH_2), 1.18-1.34 (m, 3H, CH_2), 0.90 (qd, J_1 =12 Hz, J_2 =2.8 Hz, 2H, CH_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 175 MHz): δ 210.21 (C=O), 140.02 (quat-C), 138.24 (quat-C), 132.55 (quat-C), 128.61 (ArCH), 52.60 (COCH$_2$), 33.48 (CH$_2$), 32.80 (CH), 26.42 (CH$_2$), 26.26 (CH$_2$), 21.13 (CH$_3$), 19.18 (2×CH$_3$). HRMS (ESI) m/z calcd for $C_{17}H_{24}O$ $(M+Na)^+$: 267.1719, found: 267.1708.

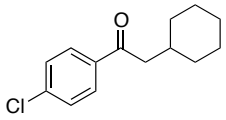
2-Cyclohexyl-1-(3,4,5-trimethoxyphenyl)ethan-1-one (4.1g): Colorless solid. Yield: 63%. IR (DCM): 3054, 2985, 2925, 2852, 1676, 1584, 1463, 1412, 1265, 1129, 738, 704 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.14 (s, 2H, ArC*H*), 3.85 (s, 6H, OCH_3), 3.84 (s, 3H, OCH_3), 2.71 (d, *J* = 6.8 Hz, 2H, COCH_2), 1.85-1.95 (m, 1H, C*H*), 1.57-1.70 (m, 5H, CH_2), 1.18-1.27 (m, 2H, CH_2), 1.04-1.15 (m, 1H, CH_2), 0.90-0.99 (m, 2H, CH_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100.6 MHz): δ 199.16 (*C*=O), 153.11 (quat-*C*), 142.48 (quat-*C*), 132.92 (quat-*C*), 105.72 (Ar*C*H), 61.03 (O*C*H_3), 56.39 (2×O*C*H_3), 46.00 (CO*C*H_2), 34.85 (*C*H), 33.59 (*C*H_2), 26.35 (*C*H_2), 26.27 (*C*H_2). HRMS (ESI) m/z calcd for $C_{17}H_{24}O_4$ $(M+H)^+$: 293.1747, found: 293.1755.

2-Cyclohexyl-1-(2,4,6-trimethoxyphenyl)ethan-1-one (4.1h): Colorless solid. Yield: 78%. IR (DCM): 3001, 2922, 2849, 1695, 1606, 1456, 1413, 1336, 1226, 1132, 913, 732 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 6.02 (s, 2H, ArC*H*), 3.74 (s, 3H, OCH_3), 3.69 (s, 6H, OCH_3), 2.54 (d, *J* = 6.8 Hz, 2H, COCH_2), 1.80-1.87 (m, 1H, C*H*), 1.69 (d, *J* = 12.8 Hz, 2H, CH_2), 1.54-1.61 (m, 3H, CH_2), 1.15-1.25 (m, 2H, CH_2), 1.01-1.12 (m, 1H, CH_2), 0.82-0.92 (m, 2H, CH_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100.6 MHz): δ 204.55 (*C*=O), 162.13 (quat-*C*), 158.15 (quat-*C*), 114.18 (quat-*C*), 90.69 (Ar*C*H), 55.85 (2×O*C*H_3), 55.49 (O*C*H_3), 52.83 (CO*C*H_2), 33.99 (*C*H), 33.35 (*C*H_2), 26.47 (*C*H_2), 26.28 (*C*H_2). HRMS (ESI) m/z calcd for $C_{17}H_{24}O_4$ $(M+H)^+$: 293.1747, found: 293.1734.

1-(4-(Benzyloxy)phenyl)-2-cyclohexylethan-1-one (4.1i): Colorless solid. Yield: 78%. IR (DCM): 3056, 2983, 2929, 2853, 1733, 1669, 1599, 1241, 1046, 747 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.84-7.87 (m, 2H, ArC*H*), 7.26-7.36 (m, 5H, ArC*H*), 6.91-6.94 (m, 2H, ArC*H*), 5.05 (s, 2H, OCH_2), 2.68 (d, *J* = 6.8 Hz, 2H, COCH_2), 1.85-1.89 (m, 1H, C*H*), 1.51-1.68 (m, 5H, CH_2), 1.06-1.22

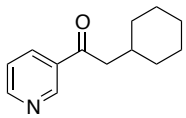
(m, 3H, CH_2), 0.92 (dd, J_1 =23.8 Hz, J_2 =11.9 Hz, 2H, CH_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100.6 MHz): δ 199.04 (*C*=O), 162.59 (quat-*C*), 136.37 (quat-*C*), 130.95 (quat-*C*), 130.57 (Ar*C*H), 128.82 (Ar*C*H), 128.36 (Ar*C*H), 127.60 (Ar*C*H), 114.64 (Ar*C*H), 70.25 (O*C*H_2), 46.06 (CO*C*H_2), 34.94 (*C*H), 33.62 (*C*H_2), 26.41 (*C*H_2), 26.31 (*C*H_2). HRMS (ESI) m/z calcd for $C_{21}H_{24}O_2$ $(M+H)^+$: 309.1849, found: 309.1845.

1-(4-Chlorophenyl)-2-cyclohexylethanone (4.1j):[18] Colorless liquid. Yield: 48%. IR



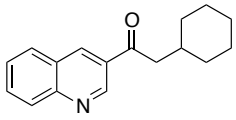
(DCM): 3052, 2987, 2859, 1680, 1430, 1264, 1062, 897, 740, 707 cm^{-1}. ^1H NMR ($CDCl_3$, 700 MHz): δ 7.81 (d, *J* = 13.3 Hz, 2H, ArC*H*), 7.35 (d, *J* = 13.3 Hz, 2H, ArC*H*), 2.71 (d, *J* = 11.9 Hz, 2H, COCH_2), 1.81-1.94 (m, 1H, C*H*), 1.53-1.69 (m, 5H, CH_2), 1.07-1.26 (m, 3H, CH_2), 0.93 (q, *J* =21 Hz, 2H, CH_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 175 MHz): δ 199.16 (*C*=O), 139.42 (quat-*C*), 135.90 (quat-*C*), 129.71 (Ar*C*H), 128.98 (Ar*C*H), 46.32 (CO*C*H_2), 34.69 (*C*H), 33.55 (*C*H_2), 26.35 (*C*H_2), 26.26 (*C*H_2). HRMS (ESI) m/z calcd for $C_{14}H_{17}ClO$ $(M+H)^+$: 237.1041, found: 237.1053.

2-Cyclohexyl-1-(pyridin-3-yl)ethanone (4.1k): Colorless liquid. Yield: 72%. IR



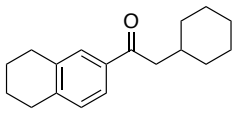
(DCM): 3051, 2984, 2851, 1686, 1445, 1265, 895, 704 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 9.08 (dd, J_1 =2.4 Hz, J_2 =0.8 Hz, 1H, ArC*H*), 8.69 (dd, J_1 =4.8 Hz, J_2 =2 Hz, 1H, ArC*H*), 8.14 (dt, J_1 =8 Hz, J_2 =2 Hz, 1H, ArC*H*), 7.34 (ddd, J_1 =5.2 Hz, J_2 =2.8 Hz, J_3 =0.8 Hz, 1H, ArC*H*), 2.77 (d, *J* = 6.8 Hz, 2H, COCH_2), 1.86-1.97 (m, 1H, C*H*), 1.57-1.72 (m, 5H, CH_2), 1.18-1.27 (m, 2H, CH_2), 1.07-1.15 (m, 1H, CH_2), 0.96 (qd, J_1 =11.6 Hz, J_2 =2.4 Hz, 2H, CH_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100.6 MHz): δ 199.10 (*C*=O), 153.44 (Ar*C*H), 149.87 (Ar*C*H), 135.52 (Ar*C*H), 132.76 (quat-*C*), 123.73 (Ar*C*H), 46.63 (CO*C*H_2), 34.53 (*C*H), 33.52 (*C*H_2), 26.31 (*C*H_2), 26.23 (*C*H_2). HRMS (ESI) m/z calcd for $C_{13}H_{17}NO$ $(M+H)^+$: 204.1383, found: 204.1359.

2-Cyclohexyl-1-(quinolin-3-yl)ethanone (4.1l): Colorless solid. Yield: 82%. IR



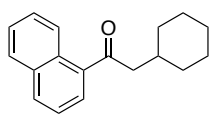
(DCM): 3053, 2926, 2853, 1684, 1618, 1420, 1265, 1027, 738 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 9.36 (s, 1H, ArC*H*), 8.64 (s, 1H, ArC*H*), 8.10 (d, *J* =8.4 Hz, 1H, ArC*H*), 7.89 (d, *J* =8 Hz, 1H, ArC*H*), 7.77 (t, *J* =8.4 Hz, 1H, ArC*H*), 7.56 (t, *J* =7.2 Hz, 1H, ArC*H*), 2.88 (d, *J* = 6.8 Hz, 2H, COCH_2), 1.90-2.02 (m, 1H, C*H*), 1.59-1.75 (m, 5H, CH_2), 1.09-1.28 (m, 3H, CH_2), 1.00 (q, *J* =12 Hz, 2H, CH_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100.6 MHz): δ 199.15 (*C*=O), 149.85 (quat-*C*), 149.41 (Ar*C*H), 137.15 (Ar*C*H), 132.01 (Ar*C*H), 129.71 (quat-*C*), 129.56 (Ar*C*H), 129.49 (Ar*C*H), 127.63 (Ar*C*H), 127.04 (quat-*C*), 46.68 (CO*C*H_2), 34.67 (*C*H), 33.55 (*C*H_2), 26.31 (*C*H_2), 26.24 (*C*H_2). HRMS (ESI) m/z calcd for $C_{17}H_{19}NO$ $(M+H)^+$: 254.1539, found: 254.1542.

2-Cyclohexyl-1-(5,6,7,8-tetrahydronaphthalen-2-yl)ethan-1-one (4.1m): Colorless



liquid. Yield: 87%. IR (DCM): 3051, 2923, 2852, 1676, 1603, 1448, 1281, 1264, 738, 703 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.58 (d, *J* =3.8 Hz, 2H, ArC*H*), 7.05 (d, *J* =8.4 Hz, 1H, ArC*H*), 2.69-2.74 (m, 6H, CH_2 & COCH_2), 1.83-1.93 (m, 1H, C*H*), 1.73 (dt, J_1 =6.4 Hz, J_2 =3.4 Hz, 4H, CH_2), 1.55-1.68 (m, 5H, CH_2), 1.15-1.25 (m, 2H, CH_2), 1.02-1.13 (m, 1H, CH_2), 0.92 (qd, J_1 =12.3 Hz, J_2 =2.3 Hz, 2H, CH_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100.6 MHz): δ 200.47 (*C*=O), 143.02 (quat-*C*), 137.49 (quat-*C*), 135.11 (quat-*C*), 129.37 (Ar*C*H), 129.15 (Ar*C*H), 125.41 (Ar*C*H), 46.22 (CO*C*H_2), 34.83 (*C*H), 33.56 (*C*H_2), 29.72 (*C*H_2), 29.52 (*C*H_2), 26.40 (*C*H_2), 26.28 (*C*H_2), 23.10 (*C*H_2), 22.96 (*C*H_2). HRMS (ESI) m/z calcd for $C_{18}H_{24}O$ $(M+H)^+$: 257.1899, found: 257.1908.

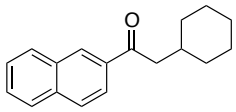
2-Cyclohexyl-1-(naphthalen-1-yl)ethan-1-one (4.1n): Colorless liquid. Yield: 83%.



IR (DCM): 3051, 2924, 2851, 1683, 1507, 1448, 1285, 1264, 1085, 738, 703 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 8.46 (d, *J* =8.6 Hz, 1H,

ArC*H*), 7.88 (d, *J* =8.2 Hz, 1H, ArC*H*), 7.78 (d, *J* =7.9 Hz, 1H, ArC*H*), 7.73 (dd, J_1 =7.1 Hz, J_2 =0.6 Hz, 1H, ArC*H*), 7.38-7.51 (m, 3H, ArC*H*), 2.83 (d, *J* = 6.9 Hz, 2H, COCH_2), 1.91-1.99 (m, 1H, C*H*), 1.72 (d, *J* = 11.6 Hz, 2H, CH_2), 1.55-1.64 (m, 3H, CH_2), 1.16-1.26 (m, 2H, CH_2), 1.05-1.12 (m, 1H, CH_2), 0.96 (qd, J_1 =12.4 Hz, J_2 =2.8 Hz, 2H, CH_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100.6 MHz): δ 205.04 (*C*=O), 136.97 (quat-*C*), 134.11 (quat-*C*), 132.38 (Ar*C*H), 130.22 (quat-*C*), 128.53 (Ar*C*H), 127.89 (Ar*C*H), 127.38 (Ar*C*H), 126.50 (Ar*C*H), 125.88 (Ar*C*H), 124.47 (Ar*C*H), 50.13 (CO*C*H_2), 35.02 (*C*H), 33.52 (*C*H_2), 26.36 (*C*H_2), 26.26 (*C*H_2). HRMS (ESI) m/z calcd for $C_{18}H_{20}O$ $(M+H)^+$: 253.1587, found: 253.1586.

2-Cyclohexyl-1-(naphthalen-2-yl)ethanone (4.1o):[20] Colorless solid. Yield: 86%. IR



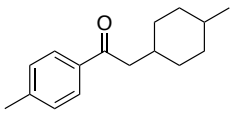
(DCM): 3062, 2925, 2853, 1676, 1627, 1468, 1265, 1003, 739 cm^{-1}. ^1H NMR ($CDCl_3$, 700 MHz): δ 8.37 (s, 1H, ArC*H*), 7.94 (dd, J_1 =9.1 Hz, J_2 =1.4 Hz, 1H, ArC*H*), 7.88 (d, *J* =8.4 Hz, 1H, ArC*H*), 7.79 (dd, J_1 =8.4 Hz, J_2 =2.8 Hz, 2H, ArC*H*), 7.50 (td, J_1 =8.4 Hz, J_2 =0.7 Hz, 1H, ArC*H*), 7.46 (td, J_1 =8.4 Hz, J_2 =0.7 Hz, 1H, ArC*H*), 2.86 (d, *J* = 6.3 Hz, 2H, COCH_2), 1.94-1.98 (m, 1H, C*H*), 1.72 (d, *J* = 12.6 Hz, 2H, CH_2), 1.57-1.63 (m, 3H, CH_2), 1.21 (qt, J_1 =12.6 Hz, J_2 =3.5 Hz, 2H, CH_2), 1.09 (qt, J_1 =12.6 Hz, J_2 =3.5 Hz, 1H, CH_2), 0.98 (qd, J_1 =11.9 Hz, J_2 =3.5 Hz, 2H, CH_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 175 MHz): δ 200.43 (*C*=O), 135.62 (quat-*C*), 134.96 (quat-*C*), 132.67 (quat-*C*), 129.84 (Ar*C*H), 129.68 (Ar*C*H), 128.49 (Ar*C*H), 128.45 (Ar*C*H), 127.87 (Ar*C*H), 126.81 (Ar*C*H), 124.15 (Ar*C*H), 46.40 (CO*C*H_2), 34.88 (*C*H), 33.62 (*C*H_2), 26.40 (*C*H_2), 26.30 (*C*H_2). HRMS (ESI) m/z calcd for $C_{18}H_{20}O$ $(M+H)^+$: 253.1587, found: 253.1591.

General Procedure for Cross-Coupling of Secondary Alcohols:

A Schlenk flask (25 mL) was equipped with a stir bar, catalyst **1** (0.01-0.05 mmol), base (0.05-0.20 mmol), benzylic secondary alcohol (0.5 mmol), aliphatic secondary alcohol

(0.5-2.5 mmol) and toluene (1.5 mL) under nitrogen atmosphere in a glove box. The flask was taken out of the glove box, equipped with a condenser and the solution was refluxed (oil bath temperature 125 °C) with stirring under the flow of argon for 4 h. The completion of the reaction was monitored using GC analysis. After cooling to room temperature, 0.5 mmol of internal standard (benzene) was added into the reaction mixture and the conversion of 1-arylethanols was calculated using GC analysis. Further, the solvent was evaporated and crude reaction mixture was purified by column chromatography over silica-gel (100-200 mesh) using ethyl acetate / petroleum ether mixture as an eluent. Yields were calculated for isolated pure products. The product-induced diastereoselectivity was also observed and the diastereomeric ratios (d.r) were determined by ^{1}H NMR analysis of crude reaction mixture. The cross-coupling products were obtained as a mixture of diastereoisomers and the diastereoisomeric signals in ^{1}H and ^{13}C NMR were assigned according to previous report.[13]

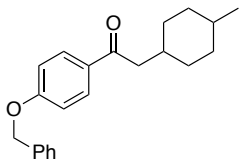
2-(4-Methylcyclohexyl)-1-(*p*-tolyl)ethan-1-one (4.2a): Colorless liquid. Yield: 87%.



^{1}H NMR analysis of the crude reaction mixture showed a d.r. of 80:20, as determined by comparison of the following signals: δ 2.81 (d, *J* =7.0 Hz, 2H, COC*H*$_2$)-major, 2.71 (d, *J* =6.7 Hz, 2H, COC*H*$_2$)-minor. IR (DCM): 3053, 2921, 2851, 1679, 1606, 1264, 1015, 738 cm^{-1}. ^{1}H NMR ($CDCl_3$, 700 MHz): δ 7.78 (d, *J* =8 Hz, 2H, ArC*H*), 7.17 (d, *J* =7.9 Hz, 2H, ArC*H*), 2.81 (d, *J* = 7.0 Hz, 2H, COC*H*$_2$)-major, 2.71 (d, *J* = 6.7 Hz, 2H, COC*H*$_2$)-minor, 2.33 (s, 3H, ArC*H*$_3$), 2.03-2.17 (m, 1H, C*H*), 1.56-1.70 (m, 2H, C*H*$_2$), 1.42-1.45 (m, 3H, C*H*&C*H*$_2$), 1.30-1.37 (m, 2H, C*H*$_2$), 1.17-1.26 (m, 2H, C*H*$_2$), 0.85 (d, *J* =6.8 Hz, 3H, C*H*$_3$)-major, 0.79 (d, *J* =6.5 Hz, 3H, C*H*$_3$)-minor. ^{13}C{^{1}H} NMR ($CDCl_3$, 175 MHz): (Mixture of diastereoisomers) δ 200.30 (*C*=O), 143.69 (quat-*C*), 135.14 (quat-*C*), 129.34 (Ar*C*H), 128.40 (Ar*C*H), 46.18 (CO*C*H$_2$), 43.28 (CO*C*H$_2$), 35.15 (*C*H), 34.64 (*C*H), 33.52 (*C*H), 32.63 (*C*H), 32.17

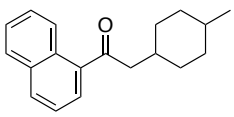
(*C*H_2), 30.88 (*C*H_2), 30.02 (*C*H_2), 29.01 (*C*H_2), 27.03 (Ar*C*H_3), 22.73 (*C*H_3), 21.72 (Ar*C*H_3), 20.33 (*C*H_3). HRMS (ESI) m/z calcd for $C_{16}H_{22}O$ $(M+H)^+$: 231.1749, found: 231.1752.

1-(4-(Benzyloxy)phenyl)-2-(4-methylcyclohexyl)ethan-1-one (4.2b): Colorless solid.



Yield: 68%. ^{1}H NMR analysis of the crude reaction mixture showed a d.r. of 81:19, as determined by comparison of the following signals: δ 2.79 (d, *J* =7.0 Hz, 2H, COC*H*$_2$)-major, 2.68 (d, *J* =6.8 Hz, 2H, COC*H*$_2$)-minor. IR (DCM): 2964, 2944, 2890, 1705, 1614, 1462, 853, 742 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.87 (d, *J* =8.8 Hz, 2H, ArC*H*), 7.25-7.37 (m, 5H, ArC*H*), 6.93 (d, *J* =8.8 Hz, 2H, ArC*H*), 5.05 (s, 2H, OC*H*$_2$), 2.79 (d, *J* =7.0 Hz, 2H, COC*H*$_2$)-major, 2.68 (d, *J* =6.8 Hz, 2H, COC*H*$_2$)-minor, 2.10-2.12 (m, 1H, C*H*), 1.42-1.48 (m, 4H, C*H*$_2$), 1.30-1.37 (m, 2H, C*H*$_2$), 1.16-1.23 (m, 3H, C*H*&C*H*$_2$), 0.85 (d, *J* =6.8 Hz, 3H, C*H*$_3$)-major, 0.79 (d, *J* =6.5 Hz, 3H, C*H*$_3$)-minor. ^{13}C{^{1}H} NMR ($CDCl_3$, 100.6 MHz): (Mixture of diastereoisomers) δ 199.23 (*C*=O), 162.57 (quat-*C*), 136.35 (quat-*C*), 130.88 (quat-*C*), 130.56 (Ar*C*H), 128.83 (Ar*C*H), 128.36 (Ar*C*H), 127.61 (Ar*C*H), 114.64 (Ar*C*H), 70.24 (O*C*H$_2$), 45.99 (CO*C*H$_2$), 43.09 (CO*C*H$_2$), 35.15 (*C*H), 34.74 (*C*H), 33.55 (*C*H), 32.64 (*C*H), 32.28 (*C*H$_2$), 30.89 (*C*H$_2$), 30.02 (*C*H$_2$), 29.02 (*C*H$_2$), 22.76 (*C*H$_3$), 20.36 (*C*H$_3$). HRMS (ESI) m/z calcd for $C_{22}H_{26}O_2$ $(M+H)^+$: 323.2006, found: 323.2002.

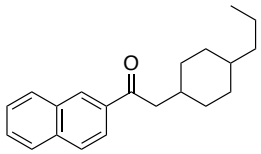
2-(4-Methylcyclohexyl)-1-(naphthalen-1-yl)ethan-1-one (4.2c): Colorless liquid.



Yield: 90%. ^{1}H NMR analysis of the crude reaction mixture showed a d.r. of 78:22, as determined by comparison of the following signals: δ 2.92 (d, *J* =7.1 Hz, 2H, COC*H*$_2$)-major, 2.82 (d, *J* =6.9 Hz, 2H, COC*H*$_2$)-minor. IR (DCM): 3052, 2985, 2851, 1684, 1435, 1264, 895, 729, 703 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.44 (d, *J* =8.3 Hz, 1H, ArC*H*), 7.86 (d, *J* =8.2 Hz, 1H, ArC*H*),

7.71-7.78 (m, 2H, ArC*H*), 7.37-7.50 (m, 3H, ArC*H*), 2.92 (d, *J* =7.1 Hz, 2H, COCH_2)-major, 2.82 (d, *J* =6.9 Hz, 2H, COCH_2)-minor, 2.14-2.20 (m, 1H, C*H*), 1.39-1.53 (m, 7H, C*H*&CH_2), 1.13-1.25 (m, 2H, CH_2), 0.83 (d, *J* =6.8 Hz, 3H, CH_3)-major, 0.77 (d, *J* =6.5 Hz, 3H, CH_3)-minor. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100.6 MHz): (Mixture of diastereoisomers) δ 205.12 (*C*=O), 137.06 (quat-*C*), 134.13 (quat-*C*), 132.31 (Ar*C*H), 130.27 (quat-*C*), 128.52 (Ar*C*H), 127.86 (Ar*C*H), 127.22 (Ar*C*H), 126.50 (Ar*C*H), 125.88 (Ar*C*H), 124.48 (Ar*C*H), 50.07 (CO*C*H_2), 47.17 (CO*C*H_2), 35.14 (*C*H), 34.84 (*C*H), 33.48 (*C*H), 32.61 (*C*H), 32.38 (*C*H_2), 30.86 (*C*H_2), 30.05 (*C*H_2), 29.05 (*C*H_2), 22.71 (*C*H_3), 20.35 (*C*H_3). HRMS (ESI) m/z calcd for $C_{19}H_{22}O$ $(M+H)^+$: 267.1743, found: 267.1724.

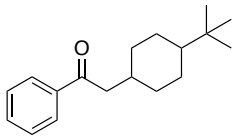
1-(Naphthalen-2-yl)-2-(4-propylcyclohexyl)ethan-1-one (4.2d): Colorless liquid.



Yield: 72%. ^1H NMR analysis of the crude reaction mixture showed a d.r. of 87:13, as determined by comparison of the following signals: δ 2.97 (d, *J* =7.0 Hz, 2H, COCH_2)-major, 2.88 (d, *J* =6.8 Hz, 2H, COCH_2)-minor. IR (DCM): 3059, 2922, 2848, 1673, 1628, 1289, 1121, 737 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 8.39 (s, 1H, ArC*H*), 7.96 (dd, J_1 =8.6 Hz, J_2 =1.4 Hz, 1H, ArC*H*), 7.90 (d, *J* =7.9 Hz, 1H,ArC*H*), 7.81 (t, *J* =8 Hz, 2H, ArC*H*), 7.46-7.54 (m, 2H, ArC*H*), 2.97 (d, *J* =7.0 Hz, 2H, COCH_2)-major, 2.88 (d, *J* =6.8 Hz, 2H, COCH_2)-minor, 2.19-2.21 (m, 1H, C*H*), 1.44-1.52 (m, 4H, CH_2), 1.35-1.41 (m, 3H, C*H*&CH_2), 1.18-1.33 (m, 6H, CH_2), 0.78-0.84 (m, 3H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100.6 MHz): (Mixture of diastereoisomers) δ 200.63 (*C*=O), 135.65 (quat-*C*), 134.97 (quat-*C*), 132.72 (quat-*C*), 129.82 (Ar*C*H), 129.71 (Ar*C*H), 128.53 (Ar*C*H), 128.47 (Ar*C*H), 127.90 (Ar*C*H), 126.84 (Ar*C*H), 124.20 (Ar*C*H), 46.42 (CO*C*H_2), 43.59 (CO*C*H_2), 39.79 (*C*H), 37.32 (*C*H), 36.68 (*C*H), 35.15 (*C*H), 34.90

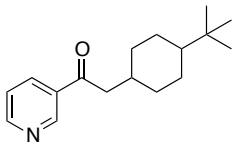
(*C*H_2), 33.60 (*C*H_2), 33.15 (*C*H_2), 32.56 (*C*H_2), 29.22 (*C*H_2), 29.04 (*C*H_2), 20.55 (*C*H_2), 14.52 (*C*H_3). HRMS (ESI) m/z calcd for $C_{21}H_{26}O$ $(M+H)^+$: 295.2056, found: 295.2045.

2-(4-(*tert*-Butyl)cyclohexyl)-1-phenylethanone (4.2e): Colorless liquid. Yield: 78%.



^{1}H NMR analysis of the crude mixture showed a d.r. of 86:14, as determined by comparison of the following signals: δ 2.91 (d, *J* =7.2 Hz, 2H, COC*H*$_2$)-major, 2.73 (d, *J* =6.5 Hz, 2H, COC*H*$_2$)-minor. IR (DCM): 3052, 2984, 2863, 1674, 1419, 1262, 895, 749 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.87-7.90 (m, 2H, ArC*H*), 7.45-7.49 (m, 1H, ArC*H*), 7.36-7.40 (m, 2H, ArC*H*), 2.91 (d, *J* =7.2 Hz, 2H, COC*H*$_2$)-major, 2.73 (d, *J* =6.5 Hz, 2H, COC*H*$_2$)-minor, 2.35-2.38 (m, 1H, C*H*), 1.58-1.61 (m, 2H, C*H*$_2$), 1.42-1.51 (m, 4H, C*H*$_2$), 1.05-1.15 (m, 2H, C*H*$_2$), 0.88-0.94 (m, 1H, C*H*), 0.78 (s, 9H, 3×C*H*$_3$)-major, 0.75 (s, 9H, 3×C*H*$_3$)-minor. ^{13}C{^{1}H} NMR ($CDCl_3$, 100.6 MHz): (Mixture of diastereoisomers) δ 200.70 (*C*=O), 137.51 (quat-*C*), 132.93 (Ar*C*H), 128.66 (Ar*C*H), 128.23 (Ar*C*H), 48.43 (CO*C*H$_2$), 47.99 (CO*C*H$_2$), 46.27 (*C*H), 40.49 (*C*H), 34.84 (quat-*C*), 33.98 (quat-*C*), 32.67 (*C*H), 32.50 (*C*H), 30.86 (*C*H$_2$), 29.26 (*C*H$_2$), 27.66 (*C*H$_2$), 27.61 (*C*H$_3$), 27.24 (*C*H$_3$), 22.02 (*C*H$_2$). HRMS (ESI) m/z calcd for $C_{18}H_{26}O$ $(M+H)^+$: 259.2056, found: 259.2074.

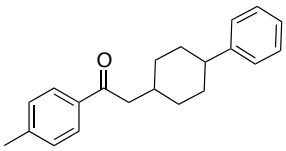
2-(4-(*tert*-Butyl)cyclohexyl)-1-(pyridin-3-yl)ethanone (4.2f): Colorless liquid. Yield: 90%.



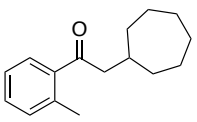
^{1}H NMR analysis of the crude mixture showed a d.r. of 90:10, as determined by comparison of the following signals: δ 2.94 (d, *J* =7.1 Hz, 2H, COC*H*$_2$)-major, 2.76 (d, *J* =6.4 Hz, 2H, COC*H*$_2$)-minor. IR (DCM): 3052, 2942, 2865, 1684, 1419, 1264, 1003, 895, 737 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.11 (s, 1H, ArC*H*), 8.70 (d, *J* =4.2 Hz, 1H, ArC*H*), 8.16 (d, *J* =7.7 Hz, 1H, ArC*H*), 7.34-7.37 (m, 1H, ArC*H*), 2.94 (d, *J* =7.1 Hz, 2H, COC*H*$_2$)-major, 2.76 (d, *J* =6.4 Hz, 2H, COC*H*$_2$)-minor, 2.31-2.44 (m, 1H, C*H*), 1.69-1.78 (m, 1H, C*H*), 1.45-1.62 (m, 6H, C*H*$_2$), 1.04-1.14 (m, 2H, C*H*$_2$), 0.90-0.99 (m, 2H, C*H*$_2$), 0.79 (s, 9H,

3×CH_3)-major, 0.77 (s, 9H, 3×CH_3)-minor. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100.6 MHz): (Mixture of diastereoisomers) δ 199.44 (*C*=O), 153.43 (Ar*C*H), 149.84 (Ar*C*H), 135.57 (Ar*C*H), 132.63 (quat-*C*), 123.77 (Ar*C*H), 48.39 (CO*C*H_2), 47.32 (CO*C*H_2), 46.56 (*C*H), 40.86 (*C*H), 36.24 (*C*H_2), 34.69 (quat-*C*), 33.93 (*C*H), 32.69 (quat-*C*), 30.80 (*C*H_2), 29.15 (*C*H), 27.78 (*C*H_3), 27.61 (*C*H_3), 25.74 (*C*H_2), 22.00 (*C*H_2). HRMS (ESI) m/z calcd for $C_{17}H_{25}NO$ $(M+H)^+$: 260.2009, found: 260.1996.

2-(4-Phenylcyclohexyl)-1-(*p*-tolyl)ethanone (4.2g): Colorless liquid. Yield: 82%. ^1H NMR analysis of the crude mixture showed a d.r. of 80:20, as determined by comparison of the following signals: δ 2.95 (d, *J* =7.1 Hz, 2H, COCH_2)-major, 2.78 (d, *J* =6.7 Hz, 2H, COCH_2)-minor. IR (DCM): 3052, 2984, 2855, 1680, 1436, 1264, 1045, 895, 753 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.80 (d, *J* = 8.2 Hz, 2H, ArC*H*), 7.16-7.22 (m, 5H, ArC*H*), 7.09-7.12 (m, 2H, ArC*H*), 2.95 (d, *J* =7.1 Hz, 2H, COCH_2)-major, 2.78 (d, *J* =6.7 Hz, 2H, COCH_2)-minor, 2.49-2.57 (m, 1H, CH_2), 2.37-2.44 (m, 1H, C*H*), 2.33 (s, 3H, CH_3), 1.80-1.86 (m, 1H, C*H*), 1.66-1.71 (m, 4H, CH_2), 1.59-1.64 (m, 3H, CH_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100.6 MHz): (Mixture of diastereoisomers) δ 200.06 (*C*=O), 147.18 (quat-*C*), 143.78 (quat-*C*), 135.12 (quat-*C*), 129.40 (Ar*C*H), 128.44 (Ar*C*H), 128.40 (Ar*C*H), 127.05 (Ar*C*H), 125.96 (Ar*C*H), 46.06 (*C*H), 44.37 (*C*H), 43.18 (CO*C*H_2), 41.26 (CO*C*H_2), 34.45 (*C*H), 34.16 (*C*H_2), 33.78 (*C*H_2), 30.35 (*C*H_2), 29.96 (*C*H_2), 29.83 (*C*H), 29.14 (*C*H_2), 21.73 (*C*H_3). HRMS (ESI) m/z calcd for $C_{21}H_{24}O$ $(M+H)^+$: 293.1900, found: 293.1906.

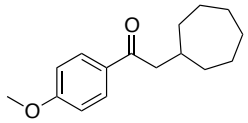


2-Cycloheptyl-1-(*o*-tolyl)ethan-1-one (4.2h): Colorless liquid. Yield: 80%. IR (DCM): 3053, 2926, 2853, 1683, 1458, 1265, 895, 739 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.50 (d, *J* = 7.7 Hz, 1H, ArC*H*), 7.27 (t, *J* = 7.5 Hz, 1H, ArC*H*), 7.17 (t, *J* = 7.7 Hz, 2H, ArC*H*), 2.72 (d, *J* = 7.0 Hz, 2H, COCH_2), 2.40 (s, 3H,



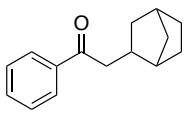
CH_3), 2.05-2.13 (m, 1H, C*H*), 1.62-1.67 (m, 2H, CH_2), 1.51-1.60 (m, 4H, CH_2), 1.36-1.42 (m, 4H, CH_2), 1.14-1.22 (m, 2H, CH_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100.6 MHz): δ 205.10 (*C*=O), 138.92 (quat-*C*), 137.78 (quat-*C*), 131.96 (Ar*C*H), 131.03 (Ar*C*H), 128.35 (Ar*C*H), 125.69 (Ar*C*H), 50.14 (CO*C*H_2), 36.06 (*C*H), 34.92 (*C*H_2), 28.43 (*C*H_2), 26.41 (*C*H_2), 21.22 (*C*H_3). HRMS (ESI) m/z calcd for $C_{16}H_{22}O$ $(M+H)^+$: 231.1743, found: 231.1742.

2-Cycloheptyl-1-(4-methoxyphenyl)ethanone (4.2i): Colorless liquid. Yield: 68%. IR



(DCM): 3051, 2983, 2964, 1675, 1455, 1257, 1028, 895, 733 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.86 (d, *J* = 8.8 Hz, 2H, ArC*H*), 6.85 (d, *J* = 8.8 Hz, 2H, ArC*H*), 3.79 (s, 3H, OCH_3), 2.74 (d, *J* = 6.9 Hz, 2H, COCH_2), 2.10-2.17 (m, 1H, C*H*), 1.65-1.69 (m, 2H, CH_2), 1.52-1.61 (m, 4H, CH_2), 1.37-1.46 (m, 4H, CH_2), 1.15-1.23 (m, 2H, CH_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100.6 MHz): δ 199.19 (*C*=O), 163.42 (quat-*C*), 130.76 (quat-*C*), 130.53 (Ar*C*H), 113.78 (Ar*C*H), 55.57 (O*C*H_3), 46.60 (CO*C*H_2), 36.41 (*C*H), 35.02 (*C*H_2), 28.46 (*C*H_2), 26.42 (*C*H_2). HRMS (ESI) m/z calcd for $C_{16}H_{22}O_2$ $(M+H)^+$: 247.1693, found: 247.1696.

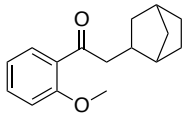
2-(Bicyclo[2.2.1]heptan-2-yl)-1-phenylethan-1-one (4.2j): Colorless liquid. Yield:



75%. IR (DCM): 3026, 2950, 2869, 1684, 1597, 1265, 1001, 737 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.87-7.89 (m, 2H, ArC*H*), 7.47 (t, *J* =7.3 Hz, 1H, ArC*H*), 7.38 (t, *J* =7.5 Hz, 2H, ArC*H*), 2.92 (ddd, J_1 = 24.6 Hz, J_2 = 16.4 Hz, J_3 = 7.3 Hz, 2H, COCH_2), 2.31-2.33 (m, 1H, C*H*), 2.13 (d, *J* =13.1 Hz, 2H, CH_2), 1.79-1.87 (m, 1H, C*H*), 1.41-1.50 (m, 2H, CH_2), 1.29-1.33 (m, 2H, CH_2), 1.22 (dd, J_1 =9.4 Hz, J_2 =1.8 Hz, 1H, C*H*), 1.06 (ddd, J_1 = 11.4 Hz, J_2 = 6.7 Hz, J_3 = 2.4 Hz, 1H, CH_2), 0.62 (ddd, J_1 = 12.3 Hz, J_2 = 5.2 Hz, J_3 = 2.3 Hz, 1H, CH_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100.6 MHz): δ 200.63 (*C*=O), 137.41 (quat-*C*), 132.93 (Ar*C*H), 128.66 (Ar*C*H), 128.17 (Ar*C*H), 42.03 (CO*C*H_2), 40.43 (*C*H), 39.94 (*C*H), 37.24 (*C*H_2), 37.14

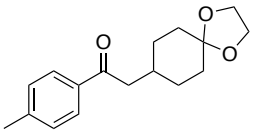
(CH_2), 35.96 (CH), 30.22 (CH_2), 23.03 (CH_2). HRMS (ESI) m/z calcd for $C_{15}H_{18}O$ $(M+H)^+$: 215.1436, found: 215.1440.

2-(Bicyclo[2.2.1]heptan-2-yl)-1-(2-methoxyphenyl)ethan-1-one (4.2k): Colorless



liquid. Yield: 75%. IR (DCM): 3052, 2948, 2867, 1672, 1597, 1485, 1464, 1294, 1244, 1026, 738 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.53 (dd, J_1 = 7.6 Hz, J_2 = 1.6 Hz, 1H, ArC*H*), 7.34-7.38 (m, 1H, ArC*H*), 6.87-6.93 (m, 2H, ArC*H*), 3.82 (s, 3H, OCH_3), 2.93 (qd, J_1 = 16.5 Hz, J_2 = 7.4 Hz, 2H, $COCH_2$), 2.24-2.27 (m, 1H, C*H*), 2.09 (d, J =3.8 Hz, 2H, CH_2), 1.73-1.79 (m, 1H, C*H*), 1.38-1.46 (m, 2H, CH_2), 1.24-1.29 (m, 2H, CH_2), 1.18-1.20 (m, 1H, C*H*), 1.00-1.09 (m, 1H, CH_2), 0.59 (ddd, J_1 = 12.2 Hz, J_2 = 5.2 Hz, J_3 = 2.3 Hz, 1H, CH_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100.6 MHz): δ 203.64 (*C*=O), 158.24 (quat-*C*), 133.03 (Ar*C*H), 130.05 (Ar*C*H), 129.28 (quat-*C*), 120.74 (Ar*C*H), 111.56 (Ar*C*H), 55.61 (OCH_3), 47.23 ($COCH_2$), 40.48 (*C*H), 39.90 (*C*H), 37.24 (CH_2), 36.97 (CH_2), 35.95 (*C*H), 30.18 (CH_2), 23.05 (CH_2). HRMS (ESI) m/z calcd for $C_{16}H_{20}O_2$ $(M+H)^+$: 245.1536, found: 245.1533.

2-(1,4-Dioxaspiro[4.5]decan-8-yl)-1-(*p*-tolyl)ethan-1-one (4.2l): Colorless liquid.



Yield: 48%. IR (DCM): 3052, 2894, 2863, 1676, 1419, 1262, 1006, 894, 748, 703 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.78 (d, J =8.1 Hz, 2H, ArC*H*), 7.18 (d, J =8.2 Hz, 2H, ArC*H*), 3.86 (s, 4H, OCH_2), 2.78 (d, J =6.8 Hz, 2H, $COCH_2$), 2.34 (s, 3H, CH_3), 1.93-1.99 (m, 1H, CH_2), 1.65-1.73 (m, 4H, CH_2), 1.48-1.59 (m, 2H, CH_2), 1.22-1.33 (m, 2H, CH_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100.6 MHz): δ 199.68 (*C*=O), 143.88 (quat-*C*), 135.03 (quat-*C*), 129.39 (Ar*C*H), 128.38 (Ar*C*H), 108.86 (quat-*C*), 64.35 (OCH_2), 44.85 ($COCH_2$), 34.54 (CH_2), 33.15 (*C*H), 30.46 (CH_2), 21.74 (CH_3). HRMS (ESI) m/z calcd for $C_{17}H_{22}O_3$ $(M+Na)^+$: 297.1461, found: 297.1450.

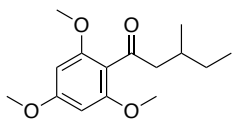
1,3,3-Triphenylpropan-1-one (4.2m):[21] Colorless solid. Yield: 68%. IR (DCM): 3058, 3028, 2926, 1687, 1597, 1494, 1449, 1363, 1264, 1205, 983, 737 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.84 (dd, J_1 = 7.8 Hz, J_2 = 0.5 Hz, 2H, ArC*H*), 7.44 (t, *J* =7.4 Hz, 1H, ArC*H*), 7.33 (t, *J* =7.6 Hz, 2H, ArC*H*), 7.18 (d, *J* =4.4 Hz, 8H, ArC*H*), 7.08 (dd, J_1 = 8.5 Hz, J_2 = 4.3 Hz, 2H, ArC*H*), 4.74 (t, *J* =7.3 Hz, 1H, *C*H), 3.65 (d, *J* =7.3 Hz, 2H, COCH_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100.6 MHz): δ 198.11 (*C*=O), 144.26 (quat-*C*), 137.18 (quat-*C*), 133.19 (Ar*C*H), 128.71 (Ar*C*H), 128.67 (Ar*C*H), 128.16 (Ar*C*H), 127.96 (Ar*C*H), 126.49 (Ar*C*H), 46.05 (*C*H), 44.84 (CO*C*H_2). HRMS (ESI) m/z calcd for $C_{21}H_{18}O$ $(M+Na)^+$: 309.1250, found: 309.1226.

1-Mesityl-3-methylbutan-1-one (4.2n):[22] Colorless liquid. Yield: 82%. IR (DCM): 2958, 2926, 2871, 1696, 1610, 1467, 1265, 737 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 6.74 (s, 2H, ArC*H*), 2.52 (d, *J* =6.6 Hz, 2H, COCH_2), 2.19-2.29 (m, 1H, C*H*), 2.19 (s, 3H, ArCH_3), 2.12 (s, 6H, ArCH_3), 0.93 (d, *J* =6.7 Hz, 6H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100.6 MHz): δ 210.24 (*C*=O), 139.98 (quat-*C*), 138.27 (quat-*C*), 132.60 (quat-*C*), 128.64 (Ar*C*H), 53.84 (CO*C*H_2), 23.72 (*C*H), 22.86 (*C*H_3), 21.13 (Ar*C*H_3), 19.20 (Ar*C*H_3). HRMS (ESI) m/z calcd for $C_{14}H_{20}O$ $(M+H)^+$: 205.1592, found: 205.1602.

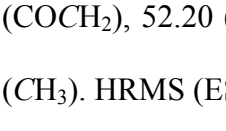
1-Mesityl-3-methylpentan-1-one (4.2o): Colorless liquid. Yield: 90%. IR (DCM): 2961, 2922, 2875, 1695, 1610, 1265, 1036, 738 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 6.75 (s, 2H, ArC*H*), 2.62 (dd, J_1 =18.3 Hz, J_2 =5.2 Hz, 1H, COCH_2), 2.46 (dd, J_1 =18.3 Hz, J_2 =7.9 Hz, 1H, COCH_2), 2.19 (s, 3H, ArCH_3), 2.12 (s, 6H, ArCH_3), 1.96-2.05 (m, 1H, C*H*), 1.32-1.42 (m, 1H, CH_2), 1.11-1.22 (m, 1H, CH_2), 0.93 (d, *J* =6.7 Hz, 3H, CH_3), 0.84 (t, *J* =7.4 Hz, 3H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100.6 MHz): δ 210.43 (*C*=O), 140.05 (quat-*C*), 138.27 (quat-*C*), 132.60

(quat-*C*), 128.65 (Ar*C*H), 51.99 (CO*C*H_2), 29.89 (*C*H), 29.61 (*C*H_2), 21.14 (Ar*C*H_3), 19.66 (*C*H_3), 19.22 (Ar*C*H_3), 11.47 (*C*H_3). HRMS (ESI) m/z calcd for $C_{15}H_{22}O$ $(M+H)^+$: 219.1749, found: 219.1751.

3-Methyl-1-(2,4,6-trimethoxyphenyl)pentan-1-one (4.2p): Colorless liquid. Yield: 30%. IR (DCM): 2961, 2922, 2875, 1695, 1610, 1265, 1036, 738 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 6.02 (s, 2H, ArC*H*), 3.74 (s, 3H, OCH_3), 3.70 (s, 6H, OCH_3), 2.67 (dd, J_1 =16.3 Hz, J_2 =5.6 Hz, 1H, COCH_2), 2.46 (dd, J_1 =16.3 Hz, J_2 =8.1 Hz, 1H, COCH_2), 1.87-1.94 (m, 1H, C*H*), 1.14-1.31 (m, 2H, CH_2), 0.78-0.86 (m, 6H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100.6 MHz): δ 204.79 (*C*=O), 162.19 (quat-*C*), 158.23 (quat-*C*), 114.15 (quat-*C*), 90.74 (Ar*C*H), 55.87 (O*C*H_3), 55.51 (CO*C*H_2), 52.20 (O*C*H_3), 31.71 (O*C*H_3), 31.04 (*C*H), 29.63 (*C*H_2), 19.56 (*C*H_3), 11.42 (*C*H_3). HRMS (ESI) m/z calcd for $C_{15}H_{22}O_4$ $(M+Na)^+$: 289.1410, found: 289.1392.



1-Mesityl-3-methylhexan-1-one (4.2q): Colorless liquid. Yield: 65%. IR (DCM): 2963, 2926, 2875, 1694, 1610, 1264, 1037, 738, 703 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 6.74 (s, 2H, ArC*H*), 2.61 (dd, J_1 =18.3 Hz, J_2 =5.1 Hz, 1H, COCH_2), 2.45 (dd, J_1 =18.3 Hz, J_2 =7.9 Hz, 1H, COCH_2), 2.19 (s, 3H, ArCH_3), 2.12 (s, 6H, ArCH_3), 2.03-2.09 (m, 1H, C*H*), 1.21-1.32 (m, 3H, CH_2), 1.08-1.15 (m, 1H, CH_2), 0.92 (d, J =6.6 Hz, 3H, CH_3), 0.83 (t, J =7.0 Hz, 3H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100.6 MHz): δ 210.36 (*C*=O), 140.04 (quat-*C*), 138.24 (quat-*C*), 132.59 (quat-*C*), 128.64 (Ar*C*H), 52.36 (CO*C*H_2), 39.28 (*C*H_2), 28.07 (*C*H), 21.13 (Ar*C*H_3), 20.20 (*C*H_3), 20.10 (*C*H_2), 19.21 (Ar*C*H_3), 14.32 (*C*H_3). HRMS (ESI) m/z calcd for $C_{16}H_{24}O$ $(M+H)^+$: 233.1900, found: 233.1872.



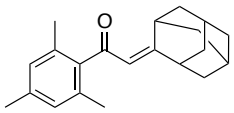
3-Ethyl-1-mesitylpentan-1-one (4.2r): Colorless liquid. Yield: 97%. IR (DCM): 2962, 2921, 2875, 1700, 1611, 1458, 1400, 1378, 1003, 850 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 6.75 (s, 2H, ArC*H*), 2.56 (d, J =6.3 Hz, 2H,

COCH_2), 2.20 (s, 3H, ArCH_3), 2.12 (s, 6H, ArCH_3), 1.88-1.92 (m, 1H, CH), 1.27-1.39 (m, 4H, CH_2), 0.81 (t, J =7.4 Hz, 6H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100.6 MHz): δ 210.59 (*C*=O), 140.15 (quat-*C*), 138.24 (quat-*C*), 132.58 (quat-*C*), 128.66 (Ar*C*H), 49.02 (CO*C*H_2), 35.56 (*C*H), 25.75 (*C*H_2), 21.15 (Ar*C*H_3), 19.24 (Ar*C*H_3), 10.97 (*C*H_3). HRMS (ESI) m/z calcd for $C_{16}H_{24}O$ $(M+H)^+$: 233.1905, found: 233.1909.

3-Ethyl-1-(pyridin-3-yl)pentan-1-one (4.2s): Colorless liquid. Yield: 60%. IR (DCM): 2963, 2932, 2875, 1733, 1457, 1265, 1045, 739 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 9.10 (s, 1H, ArCH), 8.70 (d, J =4.5 Hz, 1H, ArCH), 8.16 (dd, J_1 =8.0 Hz, J_2 = 1.7 Hz, 1H, ArCH), 7.35 (dd, J_1 =7.9 Hz, J_2 = 4.8 Hz, 1H, ArCH), 2.82 (d, J =6.7 Hz, 2H, COCH_2), 1.89-1.96 (m, 1H, CH), 1.27-1.35 (m, 4H, CH_2), 0.83 (t, J =7.4 Hz, 6H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100.6 MHz): δ 199.65 (*C*=O), 153.37 (Ar*C*H), 149.76 (Ar*C*H), 135.61 (Ar*C*H), 132.78 (quat-*C*), 123.81 (Ar*C*H), 43.11 (CO*C*H_2), 37.23 (*C*H), 26.11 (*C*H_2), 11.06 (*C*H_3). HRMS (ESI) m/z calcd for $C_{12}H_{17}NO$ $(M+H)^+$: 192.1383, found: 192.1381.

1-Mesityl-3-propylhexan-1-one (4.2t): Colorless liquid. Yield: 83%. IR (DCM): 2956, 2927, 2871, 1699, 1610, 1457, 1400, 1378, 1222, 1034, 983, 850 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 6.74 (s, 2H, ArCH), 2.56 (d, J =6.3 Hz, 2H, COCH_2), 2.19 (s, 3H, ArCH_3), 2.11 (s, 6H, ArCH_3), 1.95-2.07 (m, 1H, CH), 1.12-1.29 (m, 8H, CH_2), 0.82 (t, J =5.9 Hz, 6H, CH_3). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100.6 MHz): δ 210.54 (*C*=O), 140.05 (quat-*C*), 138.19 (quat-*C*), 132.54 (quat-*C*), 128.62 (Ar*C*H), 49.75 (CO*C*H_2), 36.13 (*C*H_2), 32.35 (*C*H), 21.11 (Ar*C*H_3), 19.84 (*C*H_2), 19.21 (Ar*C*H_3), 14.47 (*C*H_3). HRMS (ESI) m/z calcd for $C_{18}H_{28}O$ $(M+H)^+$: 261.2212, found: 261.2211.

2-(Adamantan-2-ylidene)-1-mesitylethan-1-one (4.2a): Colorless solid. Yield: 87%. IR (DCM): 3049, 2982, 2851, 1662, 1435, 1264, 1047, 895, 737 cm^{-1}. ^1H NMR ($CDCl_3$,



400 MHz): δ 6.74 (s, 2H, ArC*H*), 6.04 (s, 1H, olefinic-C*H*), 3.46-3.57 (m, 1H, C*H*), 2.30-2.37 (m, 1H, C*H*), 2.19 (s, 3H, ArCH_3), 2.14 (s, 6H, ArCH_3), 1.69-1.93 (m, 12H, C*H*&CH_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100.6 MHz): δ 200.75 (*C*=O), 171.32 (olefinic-*C*), 140.76 (quat-*C*), 137.97 (quat-*C*), 133.14 (quat-*C*), 128.53 (Ar*C*H), 120.12 (olefinic-*C*), 41.95 (*C*H), 40.45 (*C*H), 39.51 (*C*H_2), 36.90 (*C*H), 33.38 (*C*H_2), 28.00 (*C*H_2), 21.18 (Ar*C*H_3), 19.37 (Ar*C*H_3). HRMS (ESI) m/z calcd for $C_{21}H_{26}O$ $(M+H)^+$: 295.2056, found: 295.2061.

Procedure for Kinetic Experiments for Cross-Coupling of Secondary Alcohols

A Schlenk flask (25 mL) was equipped with a stir bar, catalyst **1** (0.01 mmol), base (0.05 mmol), 1-phenylethanol (0.5 mmol), cyclohexanol (0.5 mmol), mesitylene (0.5 mmol, internal standard) and toluene (1.5 mL) under nitrogen atmosphere in a glove box. The flask was taken out of the glove box and equipped with a condenser and the solution was heated at 125 °C (oil bath temperature) with stirring under a flow of argon. The reaction mixture was monitored by gas chromatography (GC) at every 20 minutes for 4 hours period. The consumption of 1-phenylethanol was corroborated with increasing concentration of cross-coupling product **4.1a**, which indicated that the reaction follows first-order kinetics with respect to 1-phenylethanol consumption (Figure 4.1).

The Observation of *β*-Disubstituted Ketone and Olefin Intermediate in Reaction Mixture:

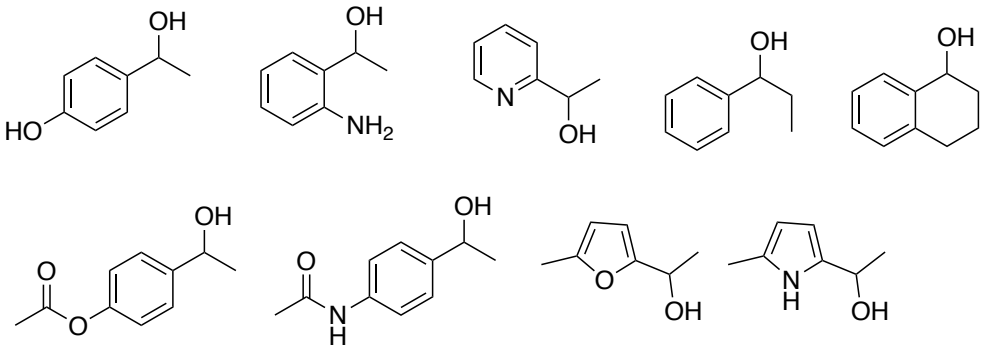
A Schlenk flask (25 mL) was equipped with a stir bar, catalyst **1** (0.04 mmol), base (0.20 mmol), 1-mesitylethanol (0.5 mmol), 4-heptanol (2.5 mmol) and toluene (1.5 mL) under nitrogen atmosphere in a glove box. The flask was taken out of the glove box, equipped with a condenser and the solution was heated at 125 °C (oil bath temperature) with stirring under a flow of argon for 4 h. After 4 hours the reaction mixture was

cooled down to room temperature, the solvent was evaporated and crude reaction mixture was subjected ^{1}H, ^{13}C NMR and GC analyses, which revealed the presence of major amount of alkylated product **4.2t** and minor amount of olefin product **4.3b** (4.2t: 4.3b = 90:10) (see Scheme 4.4b). ^{1}H NMR data for reaction mixture: 1-mesityl-3-propylhexan-1-one: (**4.2t**, 90%) δ 6.74 (s, 2H, ArC*H*), 2.56 (d, *J* =6.3 Hz, 2H, COCH_2), 2.19 (s, 3H, ArCH_3), 2.11 (s, 6H, ArCH_3), 1.95-2.07 (m, 1H, C*H*), 1.12-1.29 (m, 8H, CH_2), 0.82 (t, *J* =5.9 Hz, 6H, CH_3). 1-mesityl-3-propylhex-2-en-1-one: (**4.3b**, 10%) (Only distinguishable peaks) 6.09 (s, 1H, olefinic-C*H*), 2.46-2.50 (m, 4H, CH_2), 1.42 (dt, J_1 =14.6 Hz, J_2 =7.4 Hz, 4H, CH_2), 1.03 (t, *J* =7.5 Hz, 6H, CH_3). ^{13}C NMR data: (5b), 164.65 (olefinic-*C*), 125.34 (olefinic-*C*) (Figure 4.12).

Procedure for Deuterium Labeling Experiments for Cross-Coupling of Secondary Alcohols:

A Schlenk flask (25 mL) was equipped with a stir bar, catalyst **1** (0.01 mmol), base (0.05 mmol), secondary alcohols (0.5 mmol), deuterated secondary alcohols (0.5 mmol) and toluene (1.5 mL) under nitrogen atmosphere in a glove box. The flask was taken out of the glove box and equipped with a condenser and the solution was heated at 125 °C (oil bath temperature) with stirring under a flow of argon for 4 h. The completion of the reaction was monitored using GC analysis. After cooling to room temperature, 0.5 mmol of internal standard (benzene) was added into the reaction mixture and the conversion of secondary alcohols was calculated using GC analysis. Further, the solvent was evaporated and crude reaction mixture was purified by column chromatography over silica-gel (100-200 mesh) using ethyl acetate/petroleum ether mixture as an eluent. Yields were calculated for isolated pure products (Scheme 4.4c and 4.4d).

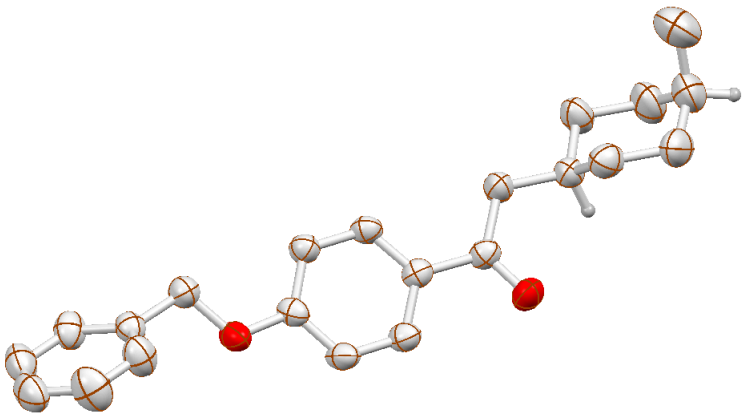
Figure 4.2 List of Unsuccessful Substrates in Cross-Coupling of Secondary Alcohols



X-Ray Analysis of the Cross-Coupling Product 4.2b: Crystals suited for single crystal x-ray diffraction measurements were mounted on a glass fiber. Geometry and intensity data were collected with a Bruker SMART D8 goniometer equipped with an APEXCCD detector and with an Incoatecmicrosource (Mo-Kα radiation, λ = 0.71073 Å, multilayer optics). Temperature was controlled using an Oxford Cryostream 700 instrument. Intensities were integrated with SAINT+[23] and corrected for absorption with SADABS.[24] The structure was solved by direct methods and refined on F^2 with SHELXL-97[25] using Olex-2[26] software.

Crystal Data of Cross-Coupling Product 4.2b: $C_{22}H_{26}O_2$, clear white, M = 322.19 gm/mol, monoclinic with space group P 1 21/c 1, a = 18.4511 (8) Å, b = 7.8907 (2) Å, c = 13.3139 (4) Å, α = 90°, β = 108.175°(4), γ = 90°, V = 1841.69 (12) Å^3, Z = 1, F(000) = 696, μ-(CuK$_\alpha$) = 0.138 mm^{-1}, 2θ$_{max}$ = 151.3320, ρ$_{calcd}$ = 1.163 g/cm^3, T = 294.8 (3) K, 12839 Reflections collected, 2741 unique, R_1 = 0.1433, WR_2 = 0.3537 (all data). Residual electron density max/min = 0.529/-0.663e.Å^{-3}. The structure has been deposited at the CCDC data center and can be retrieved using the deposit number CCDC 1896614.

Figure 4.3: Ortep Structure of 1-(4-(benzyloxy)phenyl)-2-((1*s*,4*s*)-4-methylcyclohexyl)ethan-1-one **4.2b.** Ellipsoids are Drawn with 50% Probability



4.6 NOTES AND REFERENCES

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^{1}H and ^{13}C NMR Spectra of β-Disubstituted Ketones:

Figure 4.4 ^{1}H NMR spectrum of 2-cyclohexyl-1-phenylethanone (**4.1a**):

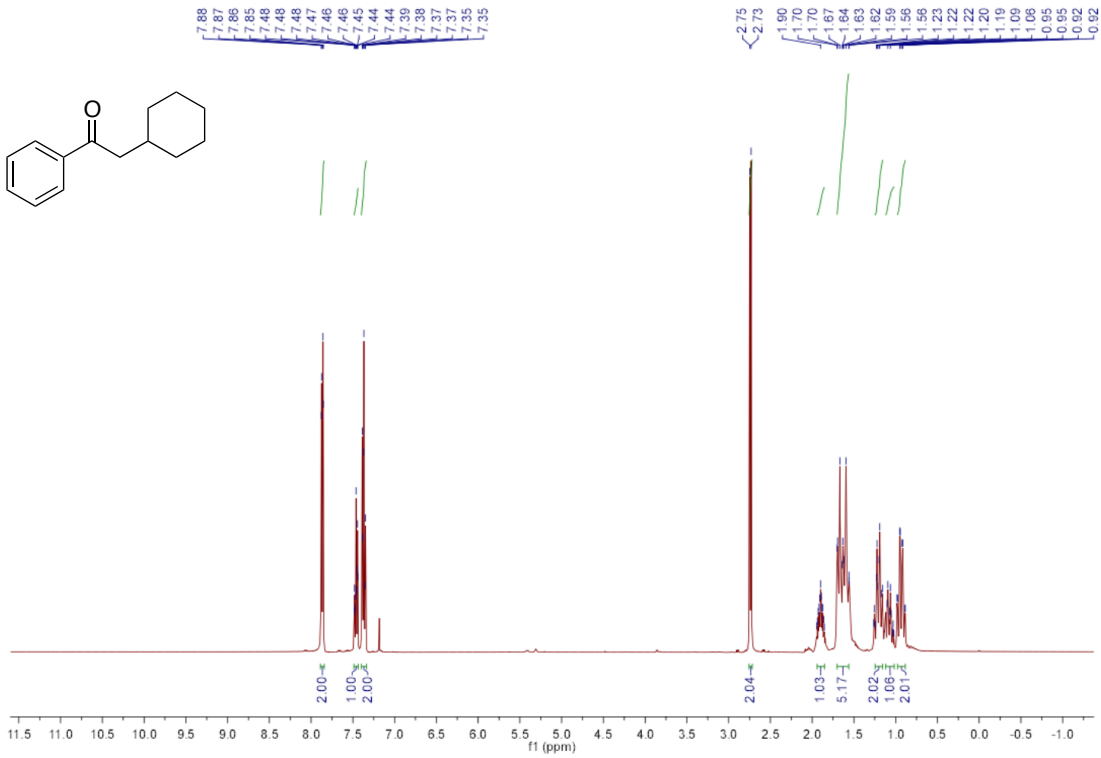


Figure 4.5 ^{13}C NMR spectrum of 2-cyclohexyl-1-phenylethanone (**4.1a**):

Figure 4.6 [1]H NMR spectrum of 2-(4-methylcyclohexyl)-1-(naphthalen-1-yl)ethan-1-one (**4.2c**):

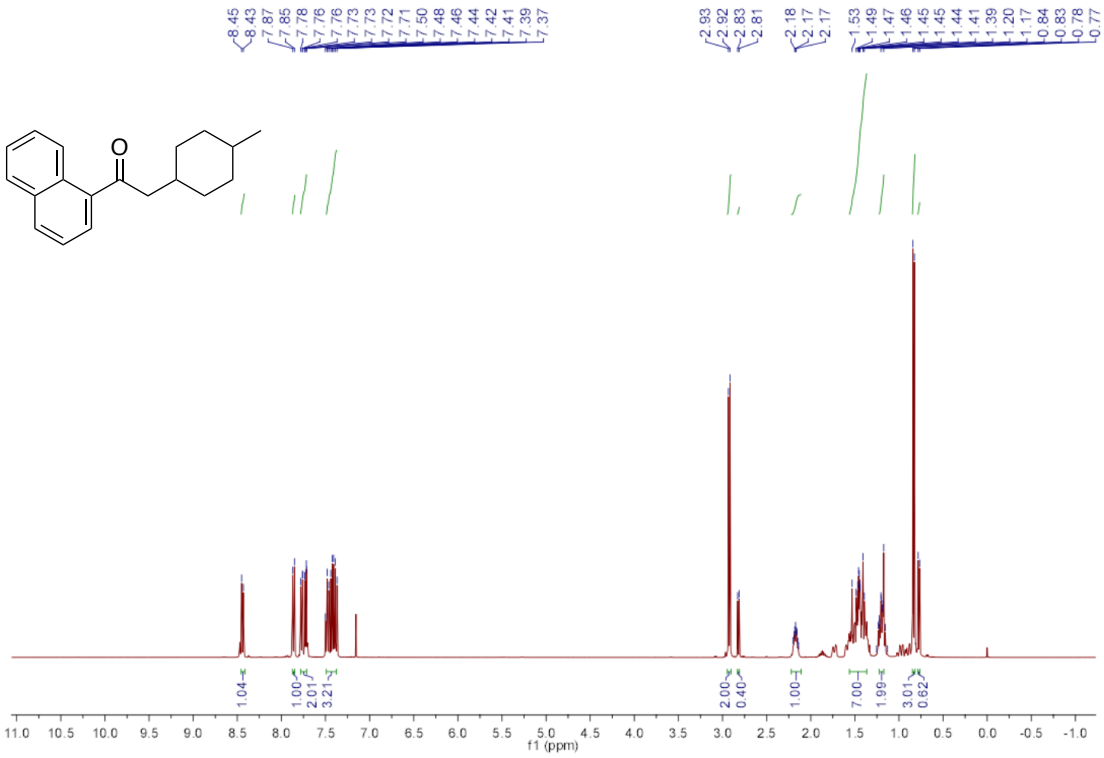


Figure 4.7 [13]C NMR spectrum of 2-(4-methylcyclohexyl)-1-(naphthalen-1-yl)ethan-1-one (**4.2c**):

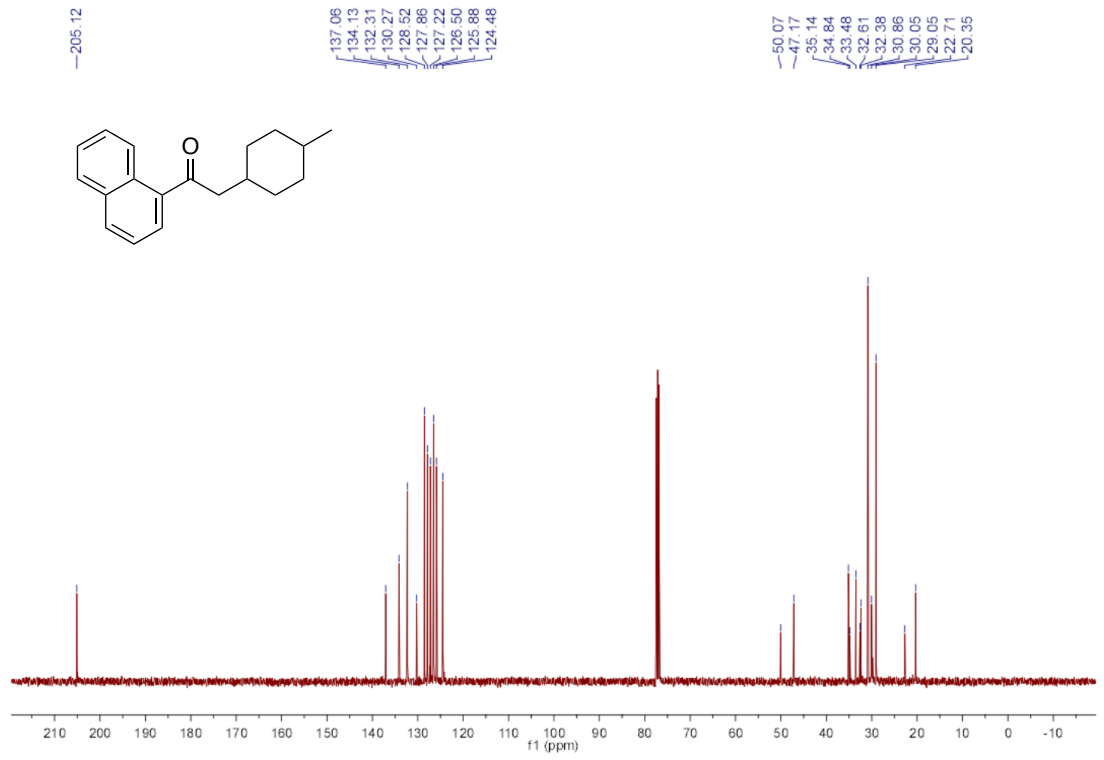


Figure 4.8 ^{1}H NMR spectrum of 3-ethyl-1-mesitylpentan-1-one (**4.2r**):

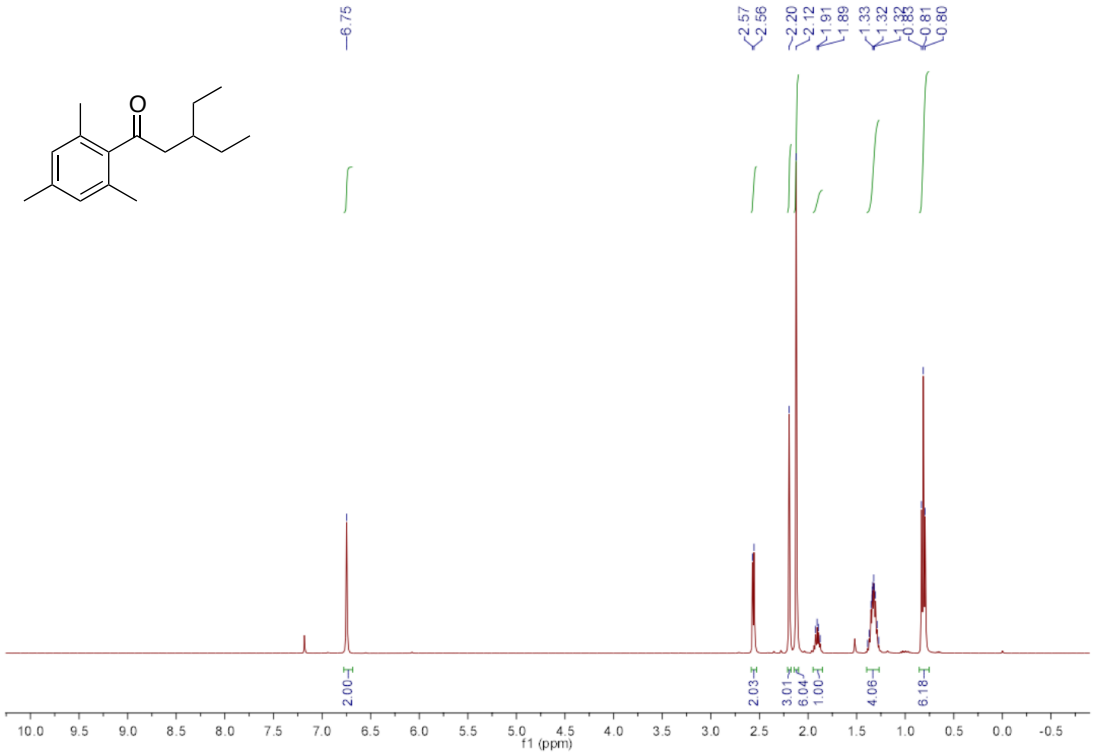


Figure 4.9 ^{13}C NMR spectrum of 3-ethyl-1-mesitylpentan-1-one (**4.2r**):

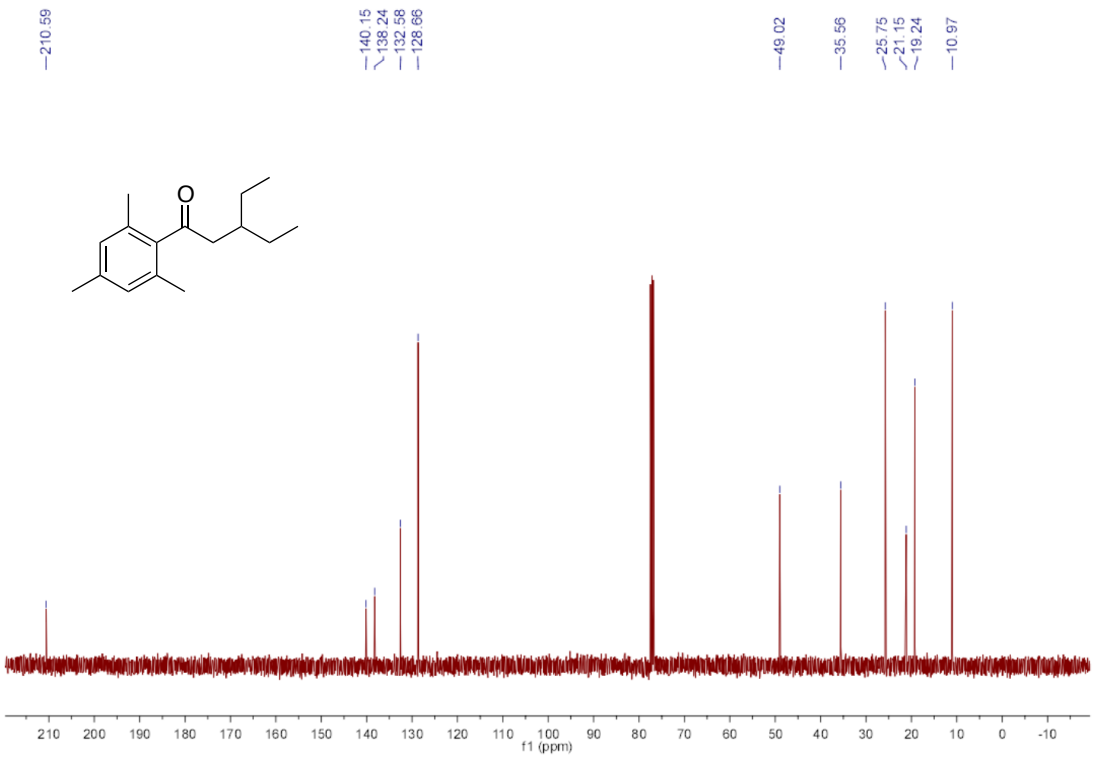


Figure 4.10 ^{1}H NMR spectrum of 2-(adamantan-2-ylidene)-1-mesitylethan-1-one (**4.3a**):

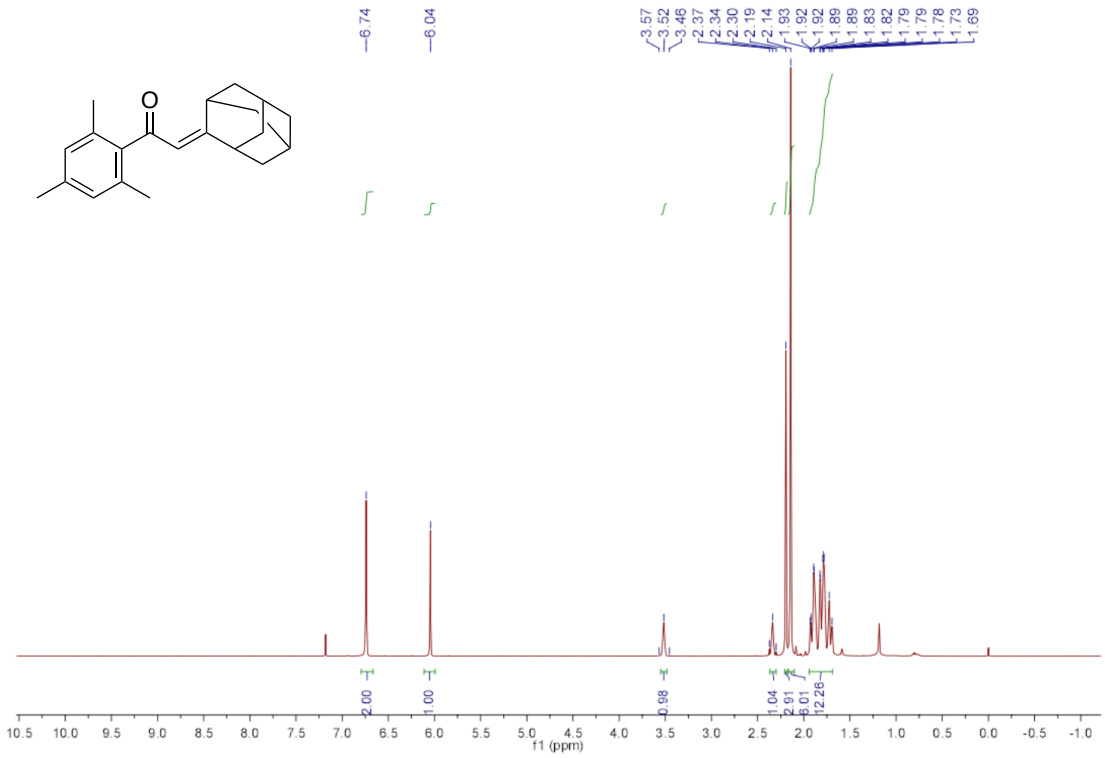


Figure 4.11 ^{13}C NMR spectrum of 2-(adamantan-2-ylidene)-1-mesitylethan-1-one (**4.3a**):

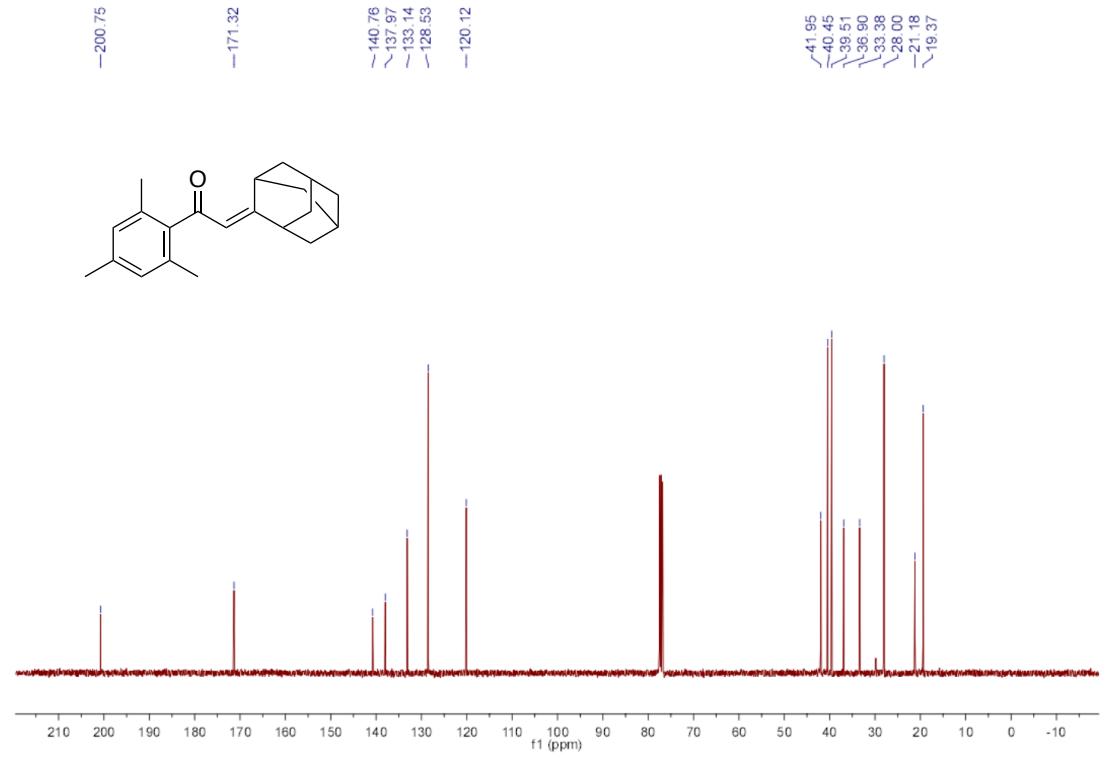


Figure 4.12 ^{1}H NMR Spectrum of β-Disubstituted Ketone and Olefin Intermediate in Reaction Mixture:

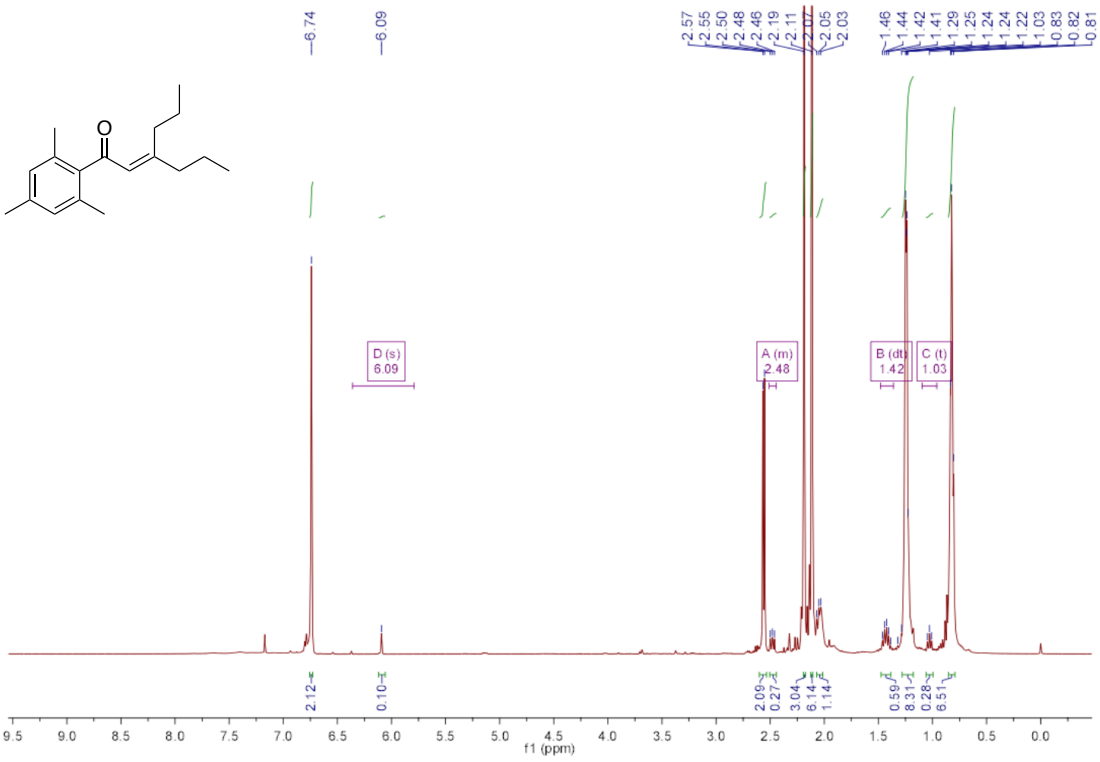


Figure 4.13 ^{1}H NMR Spectrum of Isolated Product in Scheme **4.4c**:

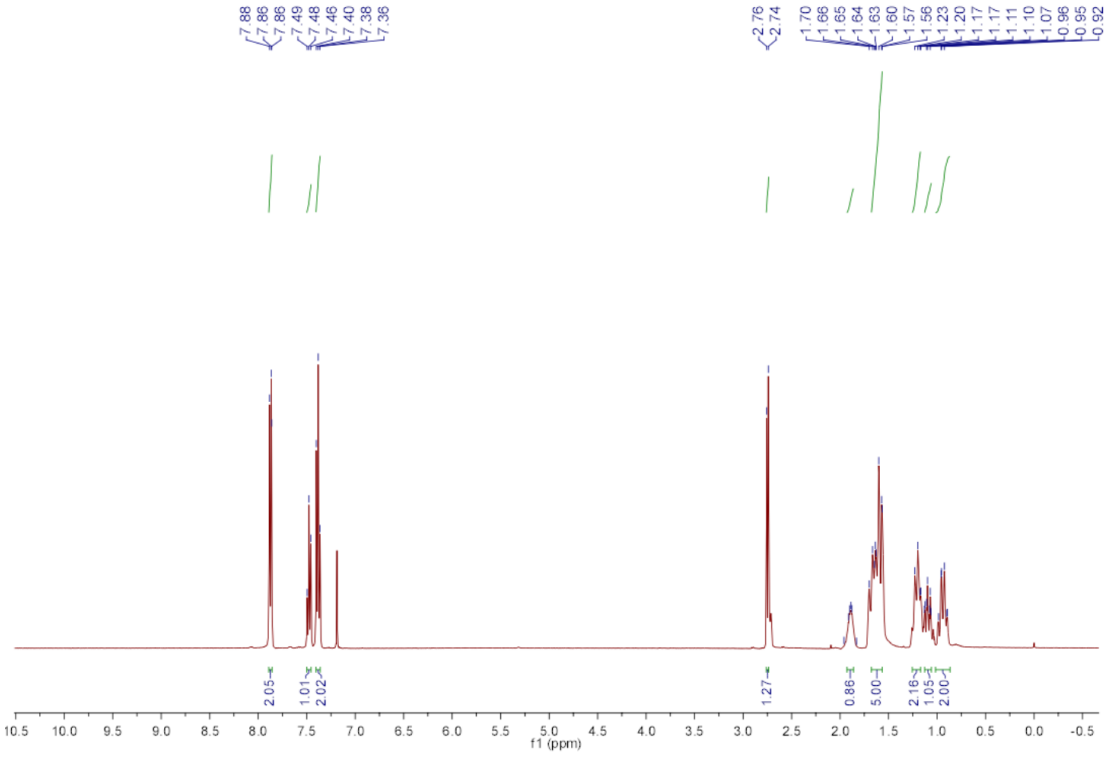


Figure 4.14 HRMS Spectrum of the Isolated Product in Scheme **4.4c**:

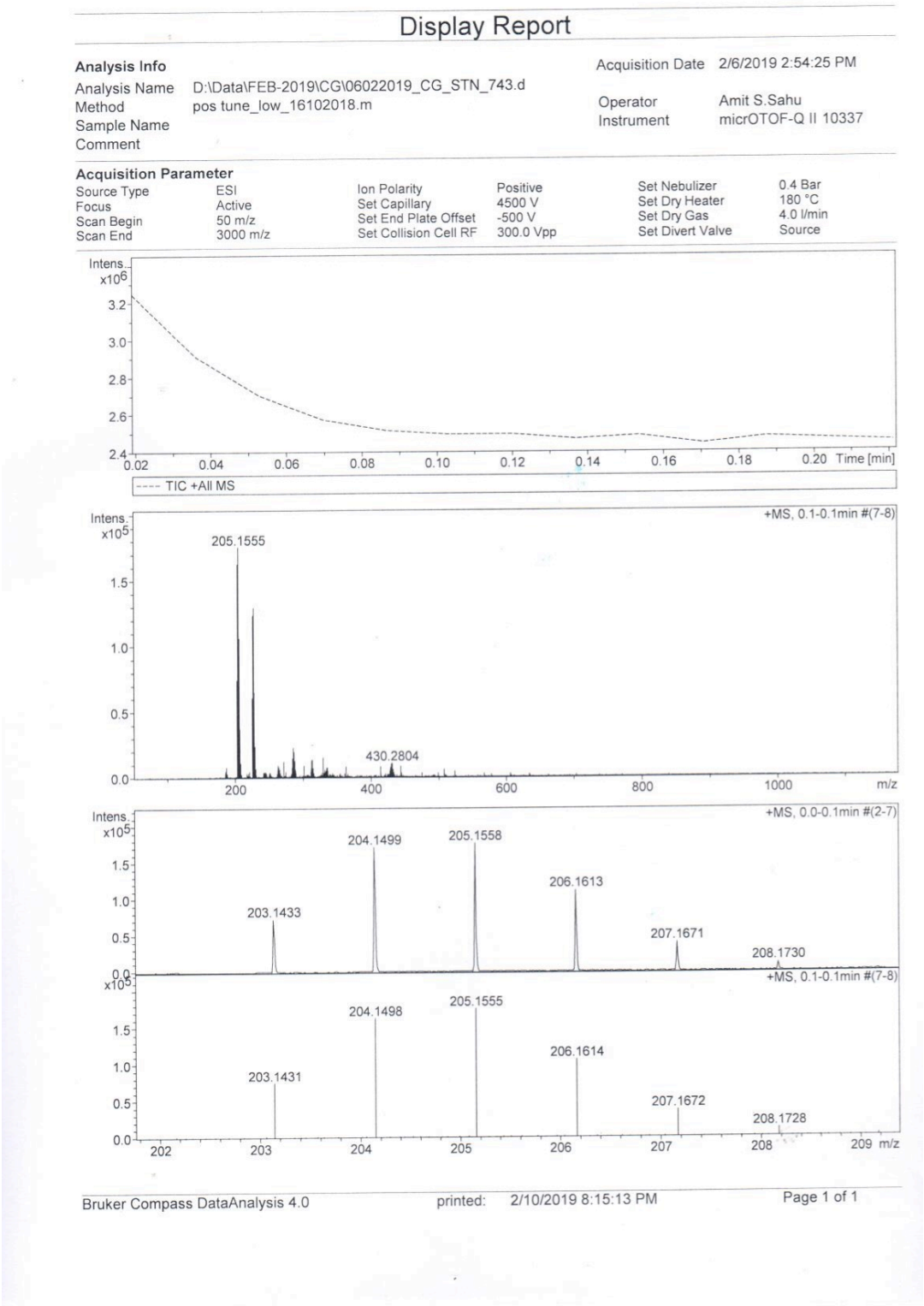


Figure 4.15 ^{1}H NMR Spectrum of the Isolated Product in Scheme **4.4d**:

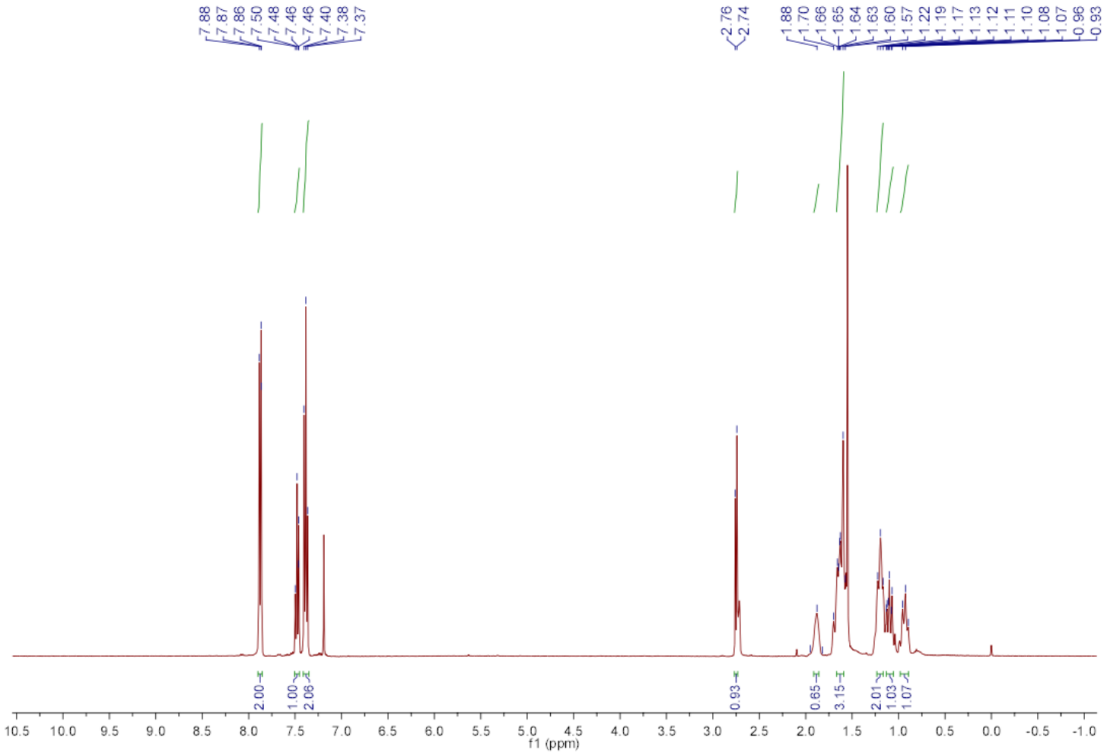
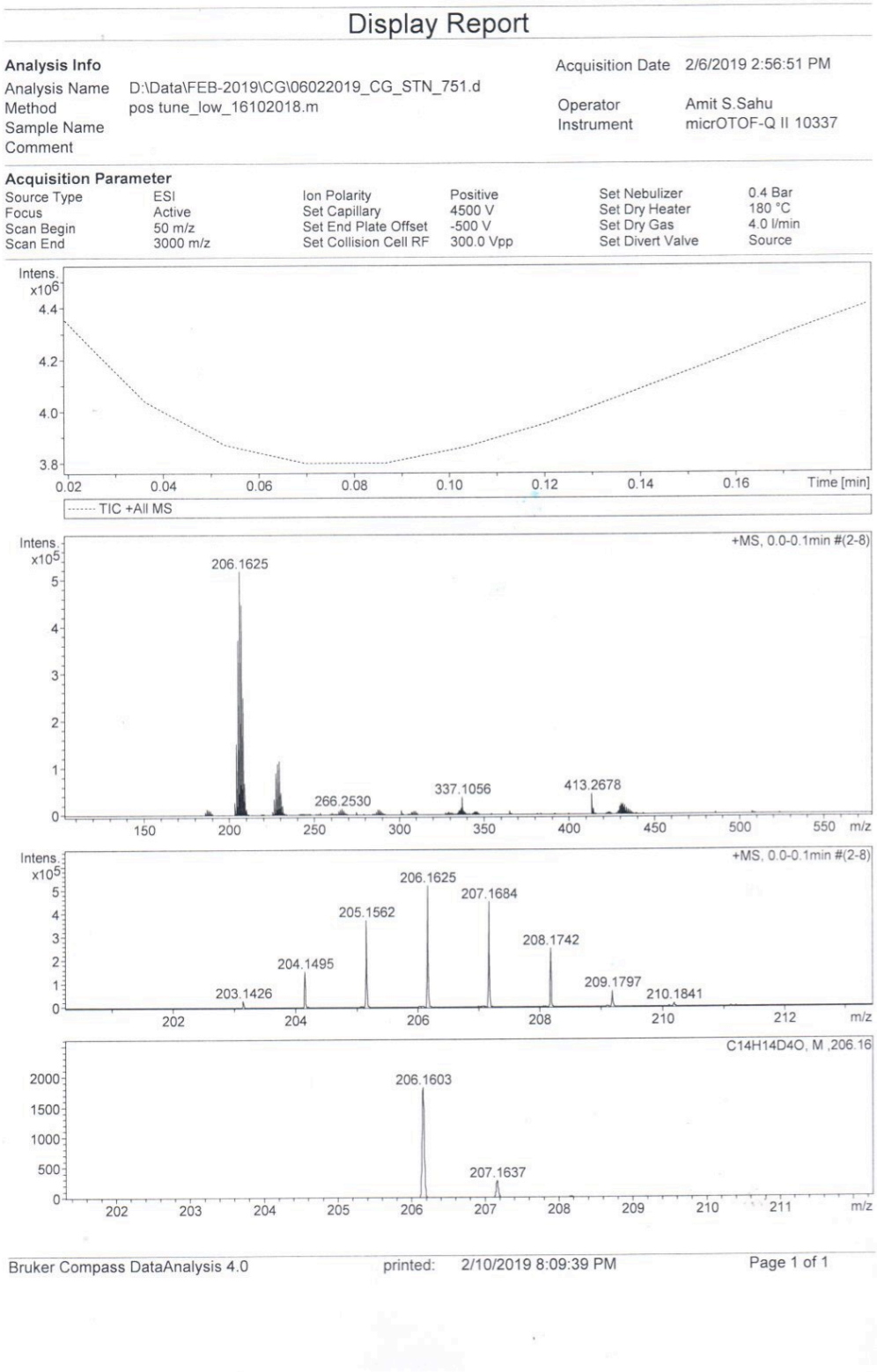


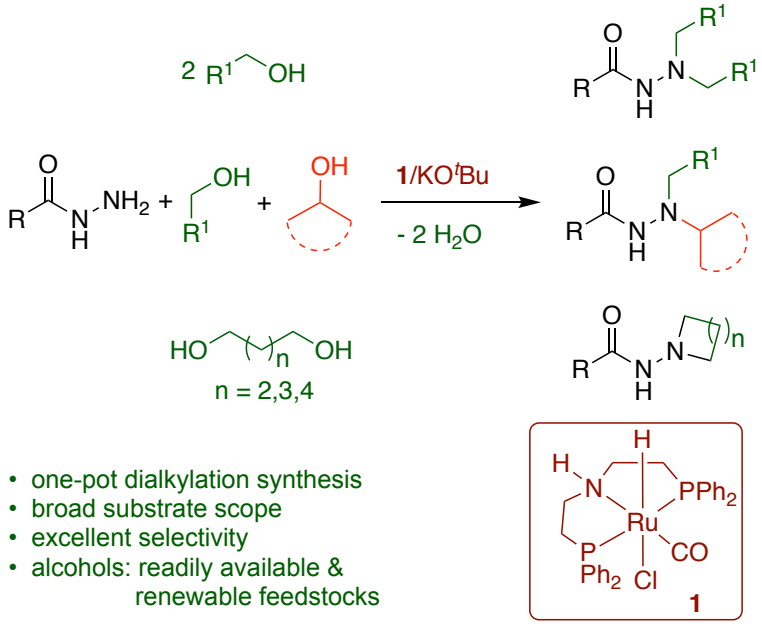
Figure 4.16 HRMS Spectrum of the Isolated Product in Scheme **4.4d:**



CHAPTER 5

Direct Catalytic Symmetrical, Unsymmetrical N,N-Dialkylation and Cyclization of Acylhydrazides Using Alcohols

5.1 ABSTRACT



Rapid and efficient construction of C–N bonds with minimal functional group inter conversion is a desirable process and can lead to ideal synthesis in organic chemistry. I have developed, unprecedented direct N,N-dialkylation of acylhydrazides using alcohols. This catalytic protocol employs a ruthenium pincer catalyst (Ru-MACHO) and provides one-pot synthesis of both symmetrical and unsymmetrical N,N-disubstituted acylhydrazides. Challenging diethylation and dimethylation reactions are performed using ethanol and methanol, respectively as alkylating reagents. Assortment of primary and secondary alcohols can be used with remarkable selectivity and the products were obtained in excellent yields. Interestingly, the use of diols resulted in intermolecular cyclization of acylhydrazides and such products are privileged structures in biologically active compounds. Preliminary mechanistic and deuterium labelling studies indicate

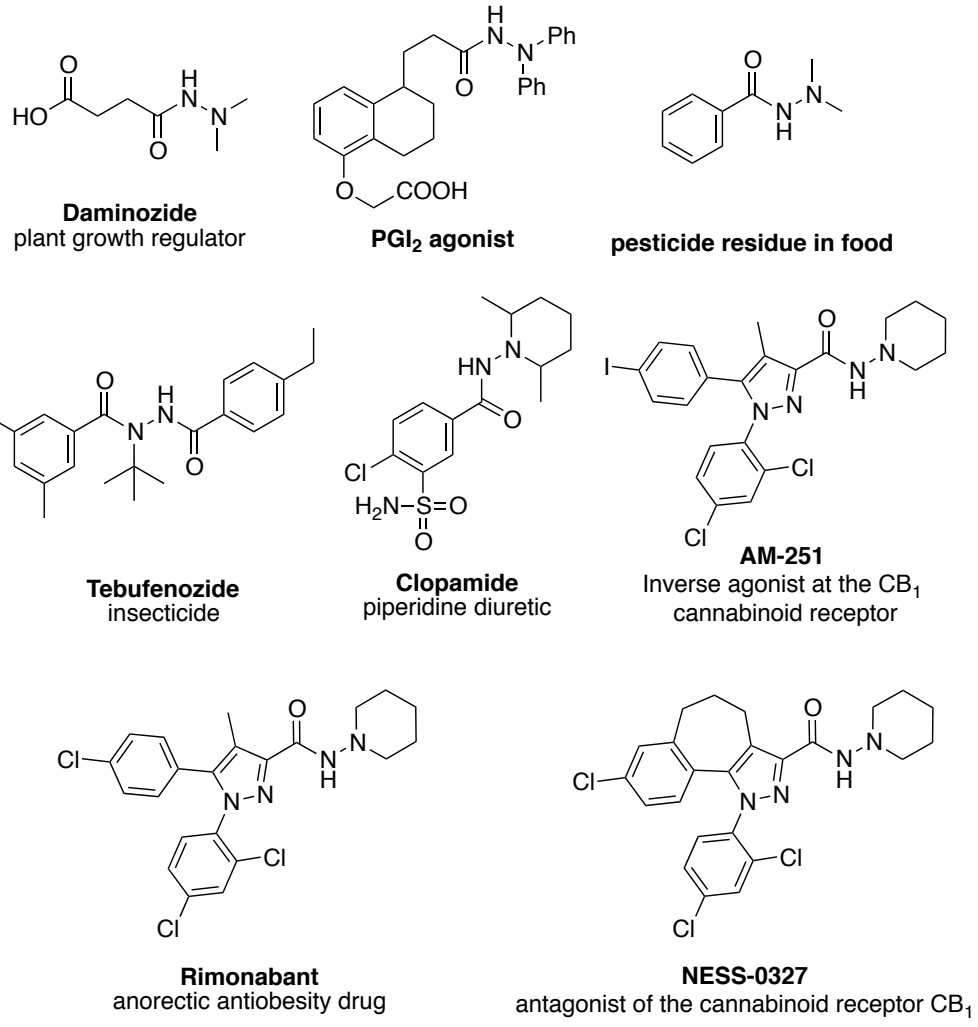
that the reaction follows O–H bond activation of alcohols and hydrazone intermediates. Water is the only byproduct, which makes this catalytic protocol sustainable and environmentally benign.

5.2 INTRODUCTION

N-Acyl hydrazides are valuable reactive intermediates with widespread applications in synthesis of pharmaceuticals, polymer materials, and in agricultural chemistry and chemical industries.[1,2] Acylhydrazides analogues possess biological activities like PGI_2 agonists[3] papilloma virus inhibitors,[4] D_1 dopamine receptor antagonists,[5] tuberculostatic,[6] antibacterial,[7] anticonvulsant,[8] antifungal activities[9] and they are widely used as precursors for the synthesis of heterocyclic compounds.[2] In particular, the cyclic acylhydrazide products are highly important in biological applications and drugs synthesis (Figure 5.1).[10] Substituted acylhydrazides are conventionally synthesized from the reaction of acyl halides with substituted hydrazines or reaction of acylhydrazides with stoichiometric strong bases, followed by addition of toxic alkyl halides (Scheme 5.1).[10] Recently, reductive alkylation of hydrazine derivatives using a-picoline-borane (used in stoichiometric amount) to provide alkylated hydrazides has been reported.[11] Copper catalyzed synthesis of N-acyl-N,N- disubstituted hydrazines using aryl halides via coupling reaction also reported.[12,13] These methods suffer from harsh reaction conditions, use of toxic acyl chlorides and alkyl or aryl halides, poor yields and produce stoichiometric amount of toxic byproducts, which curtail the atom economy of the reactions. Alcohols are sustainable chemical feedstock for alkylation reactions due to their ready availability, biorenewability, cheap and environmentally benign nature.[14] Despite these advances, synthesis of N,N-disubstituted acylhydrazides using alcohols remains unknown. Thus, direct catalytic N,N-dialkylation of N-

acylhydrazides using alcohols is highly desirable and offers the potential routes to synthesis of pharmaceutically important hydrazide derivatives (Figure 5.1).

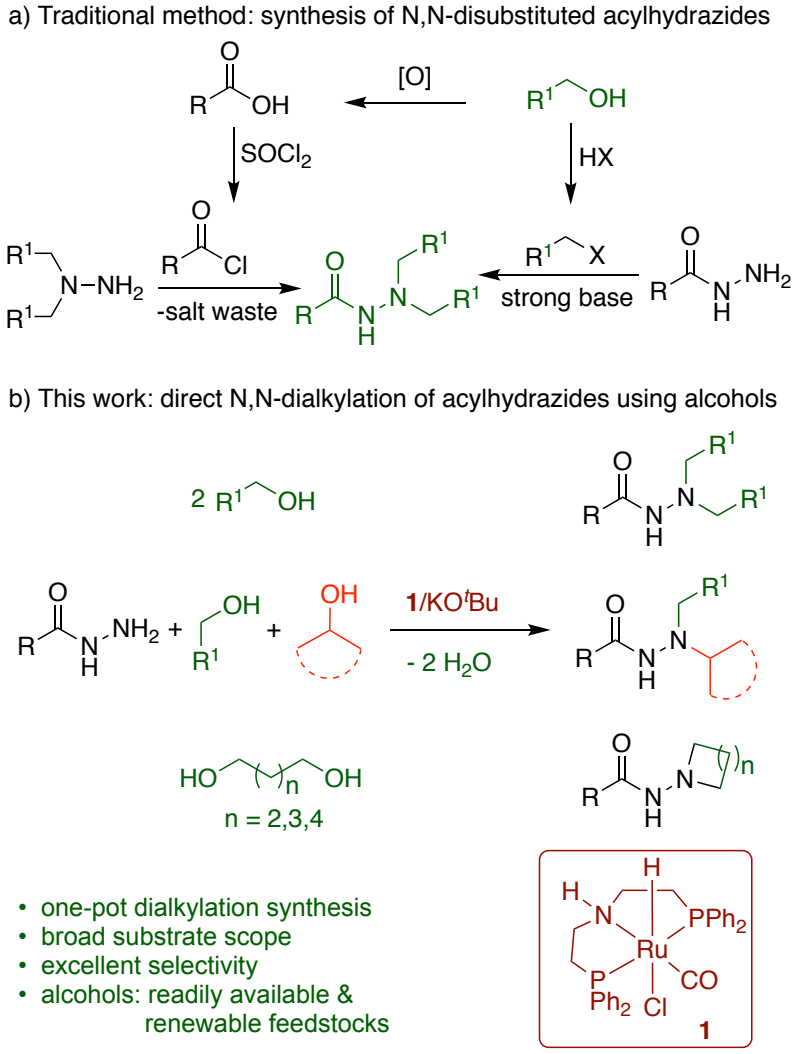
Figure 5.1 Biologically Active N,N-Disubstituted Acylhydrazides



Borrowing hydrogen methodology and acceptorless dehydrogenative coupling reactions are remarkable recent progress for the construction of new C–C, C–N and C–O bonds, producing molecular hydrogen and water as the only byproducts.[15,16] Sustainable production of amines directly from alcohols is well developed following these two interesting concepts.[15,16] However, currently known methods largely limited to mono-alkylation of amines.[17] One-pot dialkylation of amines is less developed and also suffers from poor selectivity due to the competing side reactions.[15,16] On the other hand,

selective N-alkylation of acylhydrazides is poorly studied. Recently, Zhou group reported the selective mono-*N*-alkylation of acylhydrazides using racemic alcohols to enantiomeric amine products.[18] Due to the lack of selectivity and limitation of methods for dialkylation reaction and biological importance of the N,N-disubstituted acylhydrazide products, developing a green and sustainable process is important and urgently required.

Scheme 5.1 Conventional Methods and Selective N,N-Dialkylation of Acylhydrazides Using Alcohols



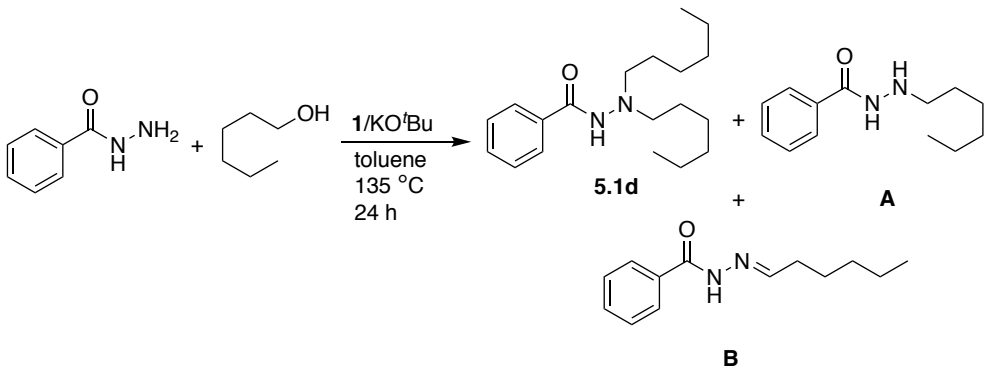
I have recently reported the ruthenium catalyzed regioselective hydrogenation of epoxides,[19] cross-coupling of secondary alcohols,[20] ketazines synthesis directly from secondary alcohols,[21] selective α-alkylation and α-olefination of nitriles using alcohols.[22] Followed by these recent reports, herein I describe the Ru-MACHO (**1**) catalyzed N,N-dialkylation and cyclization of acylhydrazides using alcohols as alkylating agents. As far as I know, there is no report on the catalytic N,N-dialkylation and intermolecular cyclization of acylhydrazides using alcohols in the literature.

5.3 RESULTS AND DISCUSSIONS

Reaction of benzohydrazide (0.5 mmol), 1-hexanol in toluene with ruthenium pincer catalyst **1** (Ru-MACHO) and KO^{t}Bu at 135 °C was selected as a model reaction to optimize the dialkylation of N,N-acylhydrazides. Interestingly, challenging formation of N,N-dialkylated benzohydrazide (**5.1d**) was observed predominantly and the corresponding hydrazone (**B**) compound also observed in minor amount (entry 1, Table 5.1). Notably, no mono-alkylated product (**A**) was observed under this condition. Increasing 1-hexanol to 2.2 equivalents resulted in slight enhancement of dialkylation product; however, mono-alkylation and hydrozaone formation were observed (entry 2, Table 5.1). Decreasing the base load to 5 mol% provided 78% of the dialkylation (entries 3,4, Table 5.1). Upon, increasing catalyst load to 2 mol% with base load at 5 mol% the complete dialkylation occurred and the product *N,N*-di(1-hexyl)-benzohydrazide was isolated in 98% yield (entry 4, Table 5.1). Further, varying temperature and base resulted in diminished yield (entries 5-7, Table 5.1). No dialkylation was observed on changing the solvent from toluene to polar solvent such as *tert*-amyl alcohol (entry 8, Table 5.1). Notably, no product formation was observed in the absence of catalyst as well as in the absence of catalyst and base (entries 9,10, Table 5.1). When the reaction was performed using [RuHCl(CO)(PPh_3)$_3$] only 10% of

dialkylated product **5.1d** was observed, which indicates the necessity of pincer catalyst in this dialkyaltion reactions (Table 5.1, entry 11).

Table 5.1 Optimization of Reaction Conditions[a]



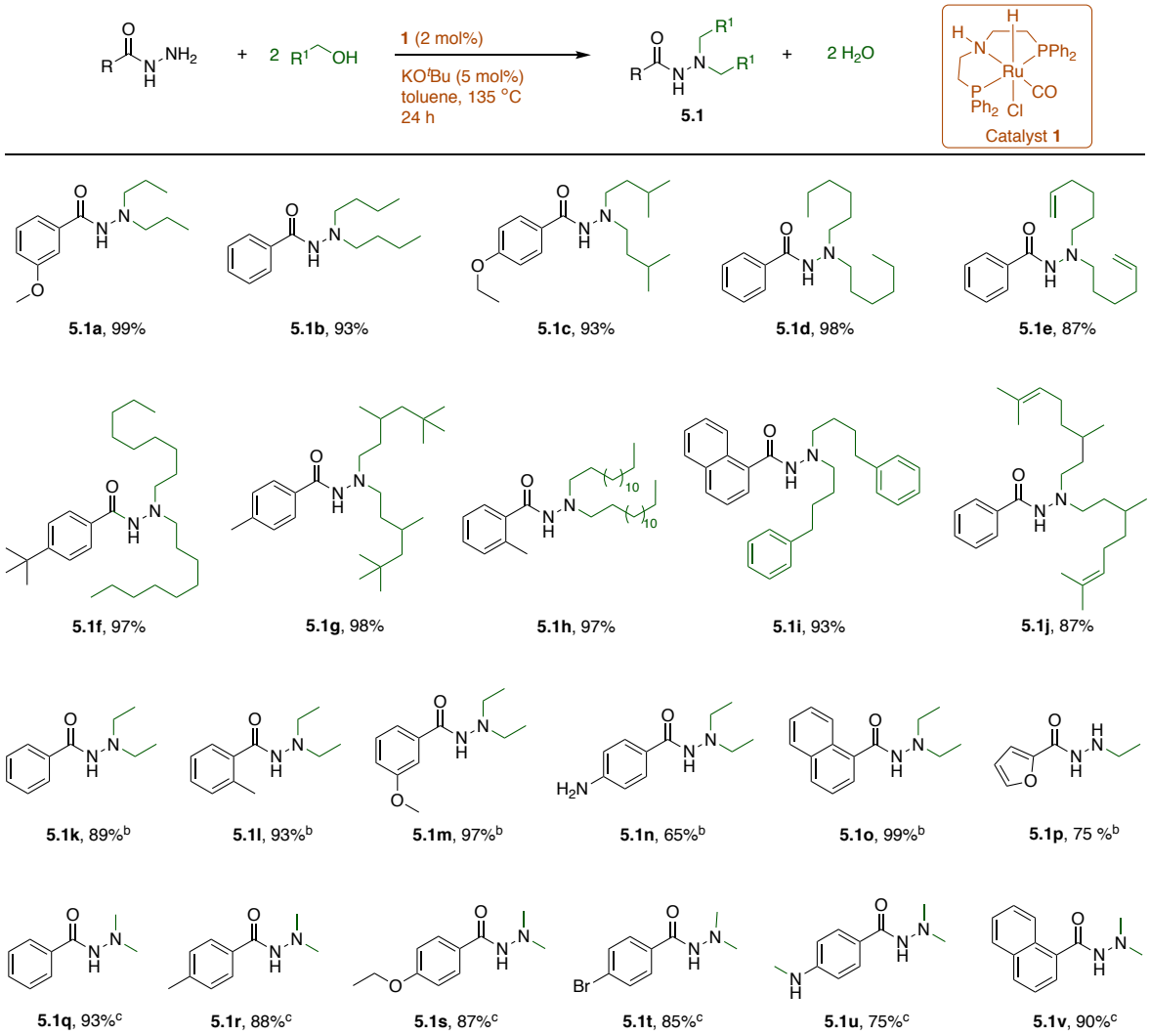
entry	cat. (mol%)	base (mol%)	alcohol (equiv)	yield (%)[b]		
				5.1d	A	B
1	1	100	2	60	-	30
2	1	100	2.2	68	5	20
3	1	5	2.2	78	10	4
4	**2**	**5**	**2.2**	**98**	**-**	**-**
5[c]	2	5	2.2	80	2	6
6	2	2	2.2	63	18	-
7[d]	2	5	2.2	93	2	-
8[e]	2	5	2.2	-	10	5
9[f]	-	5	2.2	-	-	5
10[g]	-	-	2.2	-	-	-
11[h]	1	5	2.2	10	-	-

[a]Reaction conditions: catalyst **1**, KO^{t}Bu, benzohydrazide (0.5 mmol, 1 equiv), 1-hexanol and toluene (2 mL) were heated at 135 °C in a Schlenk flask for 24 h. [b]Isolated yield after column chromatography. [c]Reaction was performed at 125 ^{o}C. [d]5 mol% of NaO^{t}Bu was used as a base. [e]The reaction was performed using *tert*-amyl alcohol as a solvent. [f]Only 5 mol% of KO^{t}Bu was used. [g]Reaction was performed without catalyst **1**

and base. [h]Reaction was performed using [RuHCl(CO)(PPh_3)$_3$] (1 mol%) and KO^{t}Bu (5 mol%).

Having optimized reaction condition in hand, the scope of the different acyhydrazides using alcohols was examined (Scheme 5.2). Reaction of unactivated aliphatic alcohols such as 1-propanol, 1-butanol, 3-methyl-1-butanol and 1-hexanol with acylhydrazides provided the corresponding N,N-dialkylated products **5.1a-5.1d** in excellent yields (Scheme 5.2). The reactions of 5-hexen-1-ol and a monoterpenoid citronellol with benzohydrazide resulted the corresponding N,N-dialkylated products **5.1e** and **5.1j** in very good yields without affecting both terminal and internal alkene functionalities. Long-chain linear, branched and aryl group embedded aliphatic primary alcohols with acylhydrazides resulted the products **5.1f-5.1i** (Scheme 5.2). Further, challenging diethylation and dimethylation reactions were performed using ethanol and methanol as alkylating agents. Acylhydrazides bearing different substituents on the aryl ring were subjected in catalytic diethylation reaction, which provided the products in excellent yields (**5.1k-5.1p**, Scheme 5.2). Interestingly, 4-amino benzohydrazide underwent chemoselective acylhydrazide N,N-diethylation without affecting the aniline amine group (**5.1n**, Scheme 5.2). Furylhydrazide was amenable to the reaction, however, unexpectedly only monoethylation occurred to provide **5.1p**, perhaps due to the involvement of intramolecular hydrogen bonding. Increased catalyst load (**1**, 5 mol%) and base KO^{t}Bu (50 mol%) with a prolonged reaction time (48 h) was employed to effect the dimethylation using methonol. Notably, N,N-dimethylbenzohydrazide **5.1q** was obtained in 93% yield (and this compound is found to be a pesticide residue in food).[2b] Other functionalized benzohydrazides with methanol provided products in good to excellent yields (**5.1r-5.1v**, Scheme 5.2).

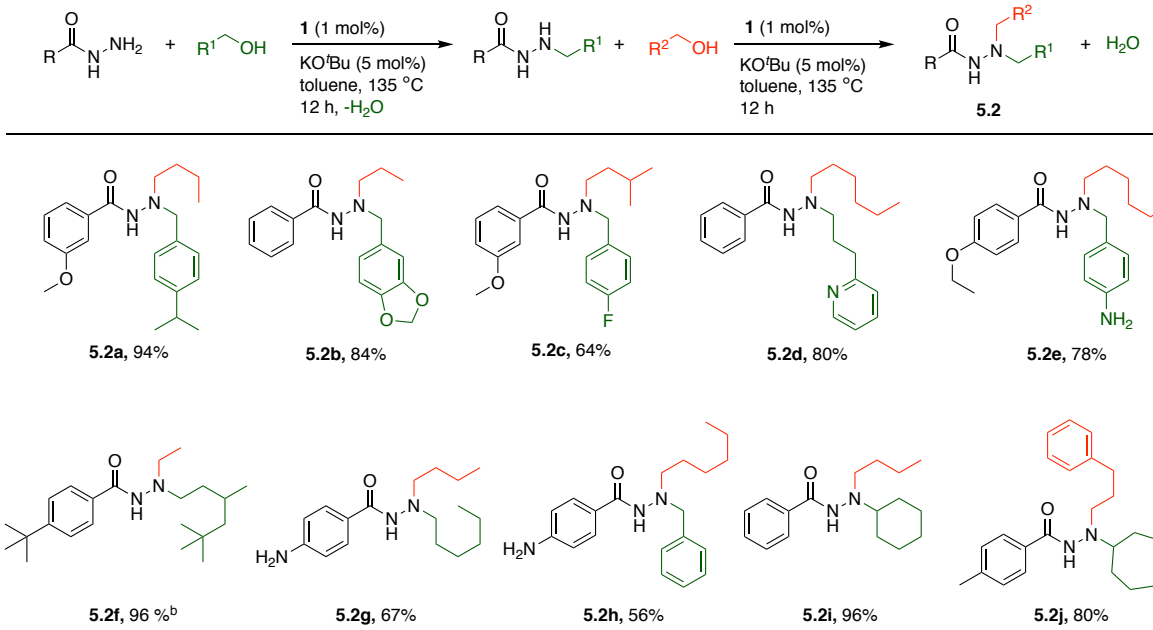
Scheme 5.2 Ruthenium-Catalyzed Symmetrical N,N-Dialkylation of Acylhydrazides Using Alcohols[a]



[a]Reaction conditions: acylhydrazide (0.5 mmol, 1 equiv), primary alcohol (1.1 mmol, 2.2 equiv), toluene (2 mL), catalyst **1** (2 mol%) and KO^{t}Bu (5 mol%) were heated at 135 °C under argon flow for 24 h. Reported yields correspond to isolated pure compounds. [b]10 equiv of ethanol was used. [c]2 mL of methanol and 5 mol% of catalyst **1** and 50 mol% KO^{t}Bu were used and the reaction performed for 48 h.

Another feature of the reaction is the potential to achieve unsymmetrical N,N-dialkylation of acylhydrazides using two different alcohols with remarkable selectivity. An assortment of acylhydrazides was reacted with one equivalent of functionalized benzyl and heteroarene embedded primary alcohols to provide mono-alkylation. Subsequently, a different primary alcohol was introduced in the reaction to provide an unsymmetrical N,N-dialkylation products with excellent selectivity and yields (**5.2a-5.2e**, Scheme 5.3). Impressively, the amine group in 4-aminobenzyl alcohol didn't undergo alkylation reaction under this condition and the chemoselective second alkylation occurred on monoalkylated hydrazide-amine functionality to deliver the product **5.2e** in 78% yield. Further, challenging aliphatic alcohols, including ethanol was used and the product **5.2f** isolated in excellent yield (96%). Surprisingly, 4-amino benzohydrazide underwent selective terminal unsymmetrical N,N-dialkylation without affecting of aniline amine group (**5.2g** and **5.2h**). Such chemoselective *N*-alkylation reaction is unknown in the literature. Interestingly, the secondary alcohols like cyclohexanol and cycloheptanol also underwent selective mono-alkylation; followed by reaction with primary alcohols resulted in unsymmetrical N,N-dialkylated products **5.2i** and **5.2j** in very good yields (Scheme 5.3).

Scheme 5.3 Ruthenium-Catalyzed Unsymmetrical N,N-Dialkylation of Acylhydrazides Using Alcohols[a]

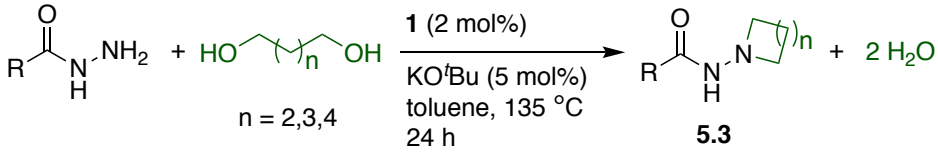


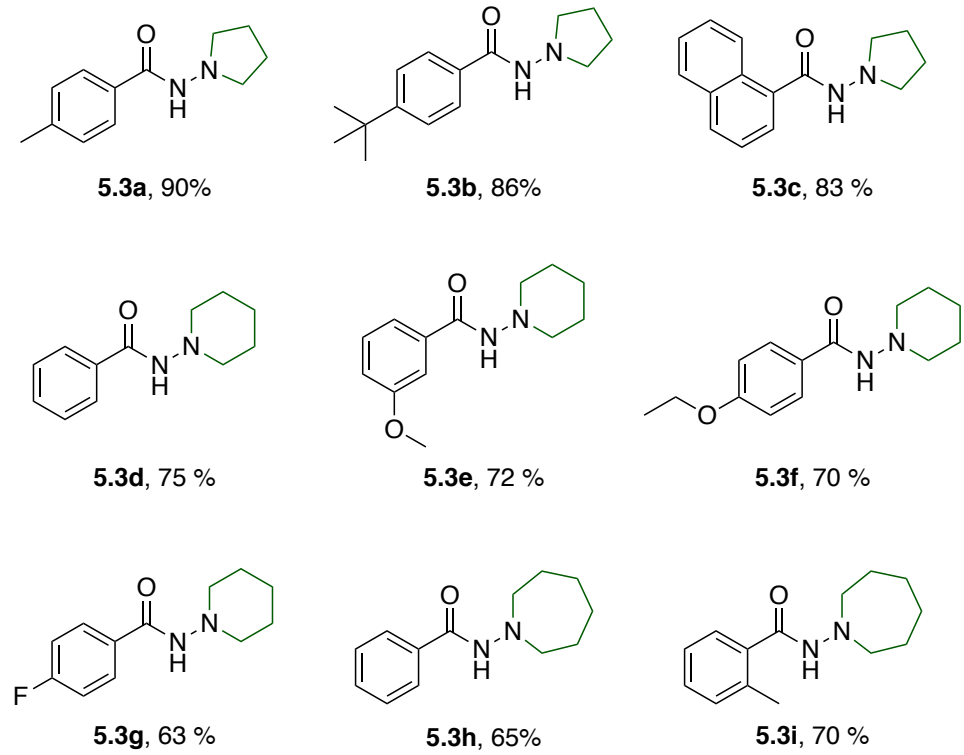
[a]Reaction conditions: acylhydrazide (0.5 mmol, 1 equiv), alcohol (0.55 mmol, 1.1 equiv), toluene (1.5 mL), catalyst **1** (1 mol%) and KO^{t}Bu (5 mol%) heated at 135 °C under argon flow for 12 h. After 12 h, different alcohol (0.55 mmol, 1.1 equiv), toluene (1.5 mL), catalyst **1** (1 mol%) and KO^{t}Bu (5 mol%) were added into the reaction mixture and heating continued for another 12 h. Reported yields correspond to isolated pure compounds. [b]10 equivalent of ethanol was used.

Next, a challenging intermolecular cyclization was tested using acylhydrazides and diols. Surprisingly, reaction of 4-methyl benzohydrazide, 4-*tert*-butyl benzohydrazide and 1-naphthohydrazide with 1,4-butandiol provided cyclized five membered ring hydrazide products **5.3a, 5.3b** and **5.3c** in 90%, 86% and 83% yields, respectively (Scheme 5.4). Reaction of 1, 5-pentanediol with different benzohydrazide derivatives delivered six-membered cyclized products in good yields (**5.3d-5.3g**). Upon employing

1,6-hexanediol, seven-membered cyclization occurred and the corresponding products **5.3h** and **5.3i** are isolated in 65 % and 70 % yields, respectively (Scheme 5.4).

Scheme 5.4 Selective Intermolecular Cyclization of Acylhydrazides Using Diols[a]



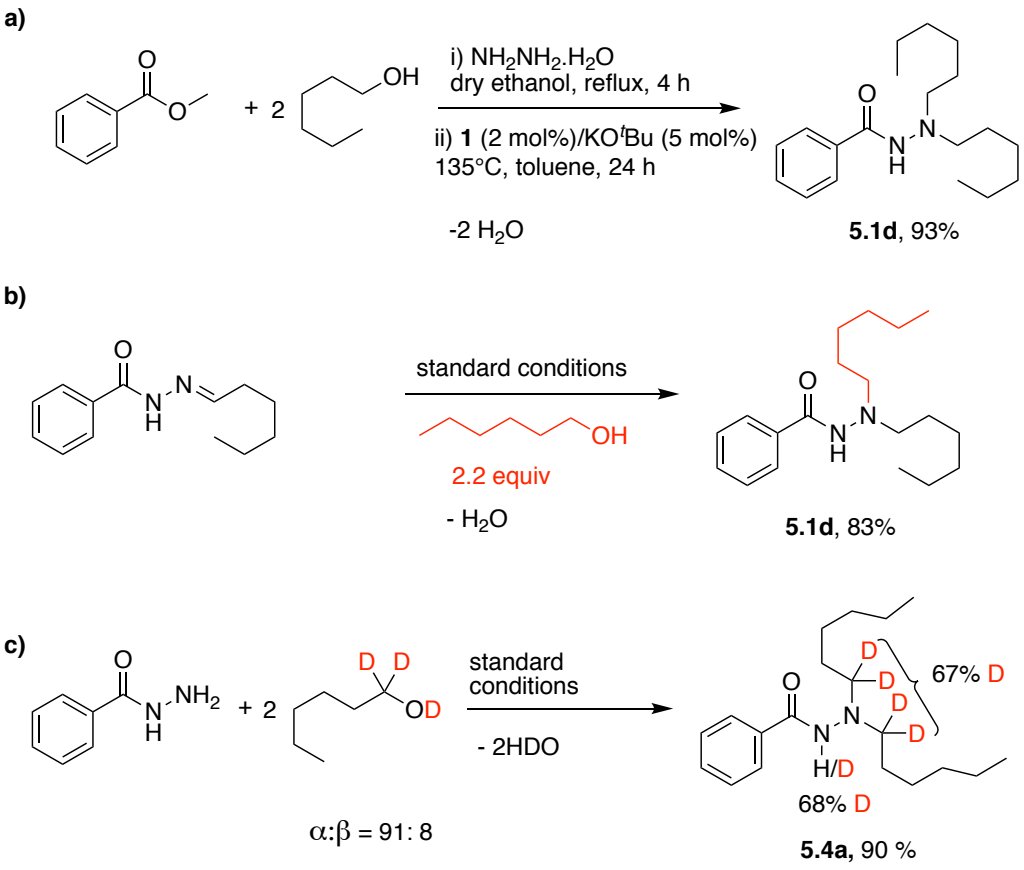


[a]Reaction conditions: acylhydrazide (0.5 mmol, 1 equiv), diol (1 mmol, 2 equiv), toluene (2 mL), catalyst **1** (2 mol%) and KO^{t}Bu (5 mol%) were heated at 135 °C under argon flow for 24 h. Reported yields correspond to isolated pure compounds.

Further, experiments that can decipher the mechanistic insight of N,N-dialkylation of acylhydrazides using alcohols were designed and demonstrated (Scheme 5.5). A one pot-reaction was performed using methyl benzoate and hydrazine hydrate for 4 hours to provide benzohydrazide, and further catalytic dialkylation was carried out under standard reaction conditions using 1-hexanol (2.2 equiv). The expected N,N-

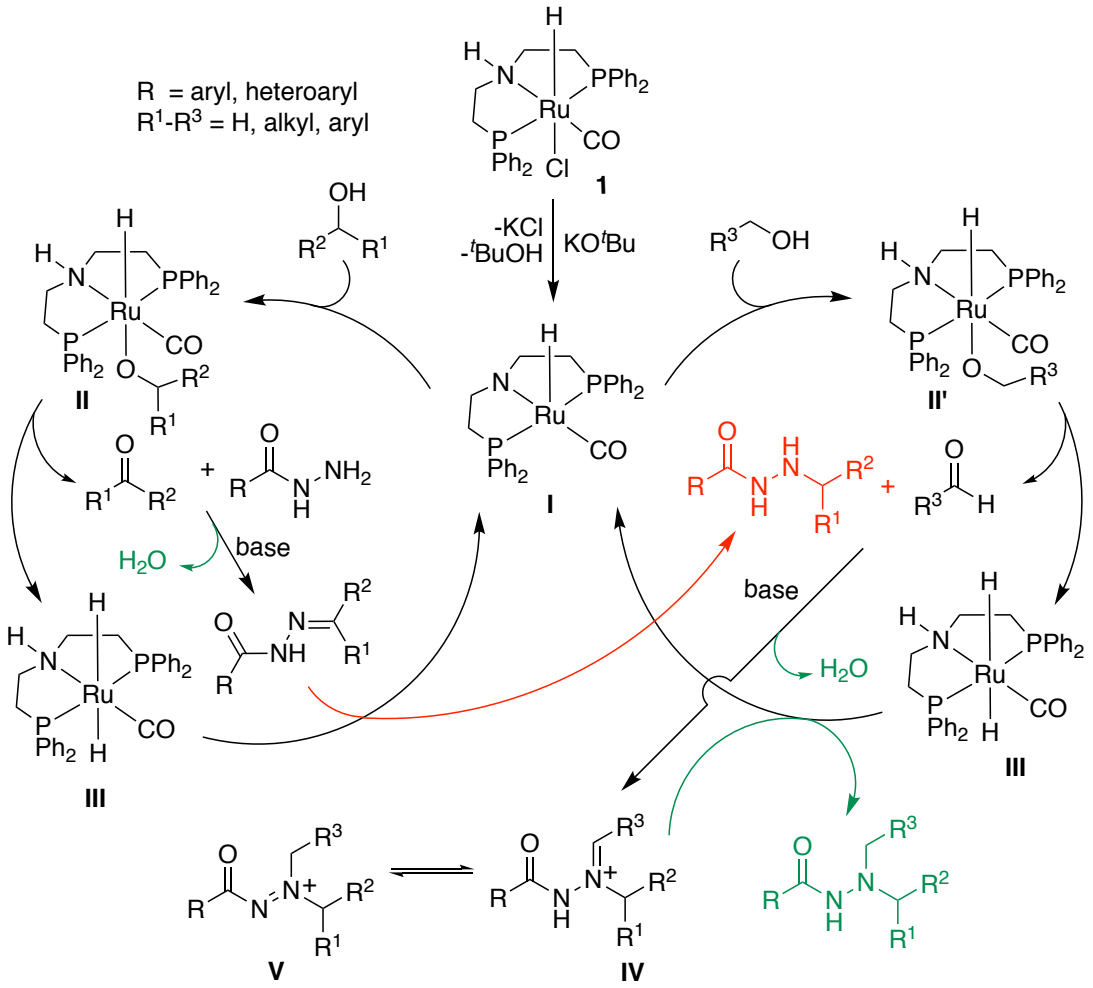
dialkylation product **5.1d** was isolated in 93% yield (Scheme 5.5a). When the hydrazone intermediate **B** (see Table 5.1) was reacted with 1-hexanol (2.2 equiv) under standard reaction conditions, the corresponding N,N-dialkylation product **5.1d** was isolated in 83% yield (Scheme 5.5b). This experiment clearly indicates that the reaction proceeds via hydrazone intermediate. The deuterium labelling experiment confirmed the expected deuterium incorporation at the α-methylene positions of the alkylation product. Reaction of benzohydrazide with 1-hexanol-D_3 under standard reaction conditions resulted the product **5.4a** in 90% yield with 67% deuterium incorporation at α-carbon of the dialkylation product indicating the involvement of borrowing hydrogen pathway.

Scheme 5.5 Mechanistic Studies for the Selective N,N-Dialkylation of Acylhydrazides Using Alcohols



Based on the previous reports[19-23] and preliminary mechanistic studies, a plausible mechanism is proposed for the N,N-dialkylation of acylhydrazides using alcohols (Scheme 5.6). Catalyst **1** reacts with base leading to dehydrohalogenation and formation of active unsaturated intermediate **I** (which is previously observed in mass spectrometry analysis).[23b,24] Intermediate **I** reacts with alcohol by O–H bond activation resulting in an alkoxo-coordinated ruthenium intermediate **II** or **II′** as already established.[23d] Perhaps, *β*-hydride elimination reaction from alkoxide ligands may result in formation of carbonyl intermediate and provide the ruthenium complex **III**. A base catalyzed condensation reaction between in situ formed carbonyl intermediate (aldehyde or ketone) with *N*-acylhydrazide generates a hydrazone intermediate (see Table 5.1 and Scheme 5.5b). In situ formed hydrazone undergoes hydrogenation by ruthenium dihydride intermediate **III** to provide mono-alkylated acylhydrazide and regenerates the catalytically active intermediate **I**. Further, the second condensation of mono-alkylated acylhydrazide with in situ formed aldehyde intermediate occurs to provide iminium intermediate **IV** (which can also be in equilibrium with intermediate **V** under basic condition). Hydrogenation of iminium intermediate **IV** by ruthenium dihydride **III** results in expected N,N-dialkylated acylhydrazide product and regenerates the catalytically active intermediate **I**. Notably, this highly selective catalysis and +2 oxidation state of in all catalytic intermediates are facilitated by amine-amide metal-ligand cooperation.

Scheme 5.6 Proposed Mechanism for the Direct N,N-Dialkylation of Acylhydrazides Using Alcohols



5.4 CONCLUSIONS

In conclusion, I have successfully demonstrated an unprecedented ruthenium(II) catalyzed efficient and direct coupling of acylhydrazides and alcohols to N,N-dialkylacylhydrazides. The reactions require only catalytic amount of base. Both symmetrical and unsymmetrical N,N-dialkylation of acylhydrazides using alcohols is achieved in a one-pot synthesis. Expediently, various functionalities such as olefins, halides, amines, and heteroaromatic groups were tolerated in this catalytic protocol. Remarkably, chemoselective N,N-dialkylation of acylhydrazides over the amine

functionality is also developed. Synthetically challenging diethylation and dimethylation were attained using ethanol and methanol, respectively as alkylating agents. Interestingly, using diols the formation of five, six, and seven-membered heterocyclic acylhydrazides were obtained, which are analogous to various drugs and biologically active molecules. This catalytic method also performed on direct N,N-dialkylation from corresponding ester under one-pot tandem reaction conditions. Mechanistic studies indicated that the reaction undergoes via hydrazone intermediate and follows borrowing hydrogen pathway. This N,N-dialkylation strategy can inspire the development of new C–N bond formation reactions and sustainable transformations.

5.5 EXPERIMENTAL SECTION

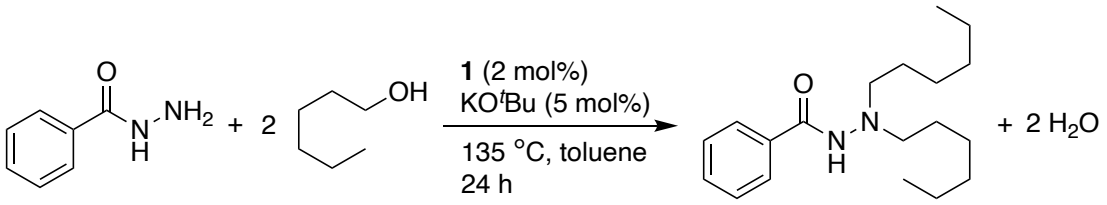
General Experimental: Unless otherwise noted, all catalytic reactions were performed under inert atmosphere using standard Schlenk techniques. All stoichiometric reactions were performed in nitrogen atmosphere MBRAUN glove box. Ru-MACHO **[Carbonylchlorohydrido{bis[2-(diphenylphosphinomethyl)ethyl]amino}ethyl]amino}ruthenium(II)]** and KO^{t}Bu were purchased from Sigma-Aldrich and stored inside glove box. Acylhydrazides were prepared from previous reported procedure.[25] Chemicals were purchased from Sigma-Aldrich, Acros, Alfa-aesar, Himedia and TCI Chemicals and used without further purification. Dry solvents were prepared according to standard procedures. Infrared (IR) spectra were recorded in Thermo-Nicolet FT-IR spectrophotometers. High-resolution mass spectra (HRMS) were obtained on Bruker micrOTOF-Q II Spectrometer and are reported as m/z (relative intensity). Accurate masses are reported for the molecular ion $[M+Na]^+$, $[M+H]^+$, $[M]^+$. Nuclear magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded at Bruker AV-400 (^{1}H at 400 MHz, ^{13}C at 100.6 MHz). ^{1}H NMR

chemical shifts are referenced in parts per million (ppm) with respect to tetramethyl silane (TMS) (δ 0.00 ppm) and ^{13}C {^{1}H} NMR chemical shifts are referenced in parts per million (ppm) with respect to $CDCl_3$ (δ 77.160 ppm). Coupling constants are reported in Hertz (Hz). ^{1}H NMR spectroscopy abbreviations: s, Singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; dt, doublet of triplets; dq, doublet of quartets; td, triplet of doublets; qd, quartets of doublets; ddd, doublets of doublets of doublets; m, multiplet; br, broad. Assignment of spectra was done based on one-dimensional (DEPT-135) NMR techniques.

General Procedure for Optimization of N,N-Dialkylation of Acylhydrazides Using Alcohols:

An oven-dried Schlenk flask (25 mL) was equipped with a stir bar, catalyst **1** (0.01-0.02 mmol), base (1-0.02 mmol), benzohydrazide (0.5 mmol, 1 equiv), 1-hexanol (1.1 mmol, 2.2 equiv) and dry toluene (2 mL) under nitrogen atmosphere in a glove box. The flask was taken out of the glove box, equipped with a condenser and the solution was heated at 135 °C (oil bath temperature) with stirring under a flow of argon for 24 h. The completion of the reaction was monitored using TLC analysis. After 24 hours the reaction was stopped and cooled to room temperature and the solvent was evaporated. Further, the crude reaction mixture was purified by column chromatography over silica-gel (100-200 mesh) using ethyl acetate/hexane mixture as an eluent (deactivated silica gel by Et_3N). Yields were calculated for isolated pure products.

1 mmol Scale Reaction of Symmetrical N,N-Dialkylation of Benzohydrazide Using 1-Hexanol:



5.1d, 97% yield

Procedure:

An oven-dried Schlenk flask (25 mL) was equipped with a stir bar, catalyst 1 (0.02 mmol), base (0.05 mmol), benzohydrazide (1 mmol, 1 equiv), 1-hexanol (2.2 mmol, 2.2 equiv) and dry toluene (2 mL) under nitrogen atmosphere in a glove box. The flask was taken out of the glove box, equipped with a condenser and the solution was heated at 135 °C (oil bath temperature) with stirring under a flow of argon for 24 h. The completion of the reaction was monitored using TLC analysis. After 24 hours the reaction was stopped and cooled to room temperature and the solvent was evaporated. Further, the crude reaction mixture was purified by column chromatography over silica-gel (100-200 mesh) using ethyl acetate / hexane mixture as an eluent (deactivated silica gel by Et_3N). The reaction provided the product **5.1d** in 97% (295 mg) yield.

General Procedure for Symmetrical N,N-Dialkylation of Acylhydrazides Using Alcohols:

An oven-dried Schlenk flask (25 mL) was equipped with a stir bar, catalyst **1** (0.02 mmol), KO^{t}Bu (0.05 mmol), acylhydrazide (0.5 mmol, 1 equiv), alcohol (1.1 mmol, 2.2 equiv) and dry toluene (2 mL) under nitrogen atmosphere in a glove box. The flask was taken out of the glove box, equipped with a condenser and the solution was heated at 135 °C (oil bath temperature) with stirring under a flow of argon for 24 h. The completion of the reaction was monitored using TLC analysis. After 24 hours the

reaction was stopped and cooled to room temperature. Further, the solvent was evaporated and crude reaction mixture was purified by column chromatography over silica-gel (100-200 mesh) using ethyl acetate/hexane mixture as an eluent (deactivated silica gel by Et_3N). Yields were calculated for isolated pure products.

General Procedure for N,N-Diethylation of Acylhydrazides Using Ethanol:

An oven-dried Schlenk flask (25 mL) was equipped with a stir bar, catalyst **1** (0.02 mmol), KO^{t}Bu (0.05 mmol), acylhydrazide (0.5 mmol, 1 equiv), ethanol (5 mmol, 10 equivalent) and dry toluene (1.5 mL) under nitrogen atmosphere in a glove box. The flask was taken out of the glove box, equipped with a condenser and the solution was heated at 135 °C (oil bath temperature) with stirring under a flow of argon for 24 h. The completion of the reaction was monitored using TLC analyses. After 24 hours the reaction was stopped and cooled to room temperature. Further, the solvent was evaporated and crude reaction mixture was purified by column chromatography over silica-gel (100-200 mesh) using ethyl acetate/hexane mixture as an eluent (deactivated silica gel by Et_3N). Yields were calculated for isolated pure products.

General Procedure for N,N-Dimethylation of Acylhydrazides Using Methanol:

An oven-dried pressure tube (35 mL) was equipped with a stir bar, catalyst **1** (0.05 mmol), KO^{t}Bu (0.5 mmol), acylhydrazide (0.5 mmol, 1 equivalent) and dry methanol (2 mL) under nitrogen atmosphere in a glove box. The pressure tube was taken out of the glove box and the solution was heated at 150 °C (oil bath temperature) with stirring for 48 h. After 48 hours the reaction was stopped and cooled to room temperature. Further, pressure was released and the solvent was evaporated and crude reaction mixture was purified by column chromatography over silica-gel (100-200 mesh) using ethyl acetate/ hexane mixture as an eluent (deactivated silica gel by Et_3N). Yields were calculated for isolated pure products.

General Procedure for Unsymmetrical N,N-Dialkylation of Acylhydrazides Using Alcohols:

An oven-dried Schlenk flask (25 mL) was equipped with a stir bar, catalyst **1** (0.01 mmol), KO^{t}Bu (0.05 mmol), acylhydrazide (0.5 mmol, 1 equivalent), alcohol (0.55 mmol, 1.1 equivalent) and dry toluene (1.5 mL) under nitrogen atmosphere in a glove box. The flask was taken out of the glove box, equipped with a condenser and the solution was heated at 135 °C (oil bath temperature) with stirring under a flow of argon for 12 h. After 12 hours, catalyst **1** (0.01 mmol), base (0.05 mmol), alcohol (0.55 mmol, 1.1 equivalent) and toluene (1 mL) were taken in a separate vial from glove box and the solution was added inside the reaction mixture under argon atmosphere. Further, the reaction continued for another 12 hours and the completion of the reaction was monitored using TLC analysis. After the completion the reaction was stopped and cooled to room temperature. Then, the solvent was evaporated and crude reaction mixture was purified by column chromatography over silica-gel (100-200 mesh) using ethyl acetate / hexane mixture as an eluent (deactivated silica gel by Et_3N). Yields were calculated for isolated pure products.

General Procedure for the Intermolecular Cyclization of Acylhydrazides Using Alcohols:

An oven-dried Schlenk flask (25 mL) was equipped with a stir bar, catalyst **1** (0.02 mmol), KO^{t}Bu (0.05 mmol), acylhydrazide (0.5 mmol, 1 equivalent), alcohol (1 mmol, 2 equivalent) and dry toluene (2 mL) under nitrogen atmosphere in a glove box. The flask was taken out of the glove box, equipped with a condenser and the solution was heated at 135 °C (oil bath temperature) with stirring under a flow of argon for 24 h. The completion of the reaction was monitored using TLC analysis. After 24 hours the reaction was stopped and cooling to room temperature. Further, the solvent was

evaporated and crude reaction mixture was purified by column chromatography over silica-gel (100-200 mesh) using ethyl acetate / hexane mixture as an eluent (deactivated silica gel by Et_3N). Yields were calculated for isolated pure products.

Procedure for One-Pot Synthesis of N,N-Dialkylated Acylhydrazide From Methyl Benzoate:

An oven-dried Schlenk flask (25 mL) was equipped with a stir bar, methyl benzoate (0.5 mmol), hydrazine hydrate (5 mmol) and ethanol solvent (2 mL) refluxed for 4 hours. Further, the solvent was evaporated and the flask was taken inside glove box. Catalyst **1** (0.02 mmol), KO^{t}Bu (0.05 mmol), acylhydrazide (0.5 mmol, 1 equivalent), 1-hexanol (1.1 mmol, 2.2 equivalent) and dry toluene (2 mL) were added to the same flask under nitrogen atmosphere in a glove box. The flask was taken out of the glove box, equipped with a condenser and the solution was heated at 135 °C (oil bath temperature) with stirring under a flow of argon for 24 h. The completion of the reaction was monitored using TLC analysis. After 24 hours the reaction was stopped and cooling to room temperature. Further, the solvent was evaporated and crude reaction mixture was purified by column chromatography over silica-gel (100-200 mesh) using ethyl acetate / hexane mixture as an eluent (deactivated silica gel by Et_3N). Product **5.1d** was isolated in 93% yield.

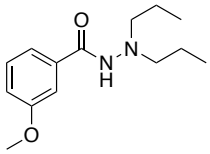
Procedure for the Deuterium Labeling Experiment:

An oven-dried Schlenk flask (25 mL) was equipped with a stir bar, catalyst **1** (0.02 mmol), KO^{t}Bu (0.05 mmol), benzohydrazide (0.5 mmol, 1 equivalent), 1-hexanol-D_3 (1.1 mmol, 2.2 equivalent) and dry toluene (2 mL) under nitrogen atmosphere in a glove box. The flask was taken out of the glove box, equipped with a condenser and the solution was heated at 135 °C (oil bath temperature) with stirring under a flow of argon for 24 h. The completion of the reaction was monitored using TLC analysis. After 24

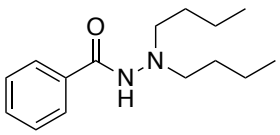
hours the reaction was stopped and cooled to room temperature. Further, the solvent was evaporated and crude reaction mixture was purified by column chromatography over silica-gel (100-200 mesh) using ethyl acetate / hexane mixture as an eluent (deactivated silica gel by Et_3N). Product **5.4a** is isolated 90% yield.

Spectral Data of N,N-Dialkylated of Acylhydrazides:

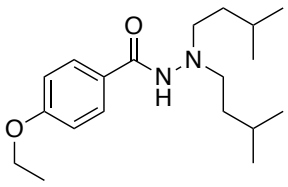
3-Methoxy-*N*',*N*'-dipropylbenzohydrazide (5.1a): Purified by silica gel column chromatography using ethyl acetate/hexane (10:90) mixture as an eluent. White solid. Yield: 124 mg, 99%. IR (DCM): 3263, 3052, 2962, 2874, 2836, 1654, 1582, 1484, 1265, 1041, 895, 739 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.26-7.13 (m, 3H, ArC*H*), 6.96-6.90 (m, 1H, ArC*H*), 6.86 (s, N*H*), 3.74 (s, 3H, OCH_3), 2.70 (t, J = 8 Hz, 4H, CH_2), 1.55-1.45 (m, 4H, CH_2), 0.84 (t, J = 7.4 Hz, 6H, CH_3). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 166.6, 159.7, 135.3, 129.5, 118.6, 117.6, 112.4, 60.1, 55.4, 20.3, 11.6. HRMS (ESI) m/z calcd for $C_{14}H_{22}N_2O_2$ $(M+H)^+$: 251.1754, found: 251.1775.



***N*',*N*'-Dibutylbenzohydrazide (5.1b):** Purified by silica gel column chromatography using ethyl acetate/hexane (10:90) mixture as an eluent. White solid. Yield: 115 mg, 93%. IR (DCM): 3243, 2958, 2864, 1651, 1468, 1275, 748 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.68-7.63 (m, 2H, ArC*H*), 7.48-7.39 (m, 1H, ArC*H*), 7.38-7.30 (m, 2H, ArC*H*), 6.63 (s, 1H, N*H*), 2.76 (t, J = 7.6 Hz, 4H, CH_2), 1.48 (ddd, J_1 = 15.2 Hz, J_2 = 8.7 Hz, J_3 = 6.4 Hz, 4H, CH_2), 1.30 (dt, J_1 = 15.1 Hz, J_2 = 7.4 Hz, 4H, CH_2), 0.83 (t, J = 7.4 Hz, 6H, CH_3). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 166.7, 134.2, 131.5, 128.6, 127.0, 58.2, 29.2, 20.5, 14.0. HRMS (ESI) m/z calcd for $C_{15}H_{24}N_2O$ $(M+H)^+$: 249.1961, found: 249.1971.

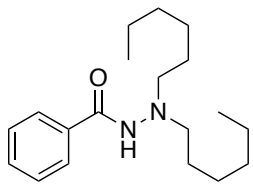


4-Ethoxy-*N*',*N*'-diisopentylbenzohydrazide (5.1c): Purified by silica gel column chromatography using ethyl acetate/hexane (10:90) mixture as an eluent. White solid.

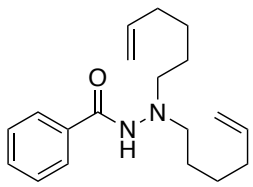


Yield: 149 mg, 93%. IR (DCM): 3237, 3047, 2955, 2869, 1643, 1607, 1467, 1252, 1045, 765 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63 (d, *J* = 8.7 Hz, 2H, ArC*H*), 6.83 (d, *J* = 7.8 Hz, 2H, ArC*H*), 6.52 (s, 1H, N*H*), 3.99 (tt, J_1 = 6.9 Hz, J_2 = 3.5 Hz, 2H, OCH_2), 2.76 (t, *J* = 8 Hz, 4H, CH_2), 1.55 (dt, J_1 = 13.2 Hz, J_1 = 6.6 Hz, 2H, C*H*), 1.37 (ddd, J_1 = 14.0 Hz, J_2 = 11.8 Hz, J_3 = 7.0 Hz, 7H, CH_2 & CH_3), 0.81 (d, *J* = 6.6 Hz, 12H, CH_3). $^{13}C\{^{1}H\}$ NMR (100.6 MHz, $CDCl_3$): δ 166.3, 161.6, 128.8, 126.0, 114.3, 63.7, 57.0, 35.8, 26.4, 22.8, 14.7. HRMS (ESI) m/z calcd for $C_{19}H_{32}N_2O_2$ $(M+H)^+$: 321.2537, found: 321.2533.

***N*',*N*'-Dihexylbenzohydrazide (5.1d):** Purified by silica gel column chromatography using ethyl acetate/hexane (10:90) mixture as an eluent. White solid. Yield: 149 mg, 98% (for 0.5 mmol scale) and 295 mg, 97% (for 1 mmol scale). IR (DCM): 3430, 3053, 2956, 2930, 1672, 1457, 1265, 895, 741 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (d, *J* = 7.3 Hz, 2H, ArC*H*), 7.43 (t, *J* = 7.3 Hz, 1H, ArC*H*), 7.35 (t, *J* = 7.4 Hz, 2H, ArC*H*), 6.57 (s, 1H, N*H*), 2.75 (t, *J* = 7.6 Hz, 4H, CH_2), 1.59-1.38 (m, 4H, CH_2), 1.27-1.19 (dd, J_1 = 26.5 Hz, J_1 = 8.0 Hz, 12H, CH_2), 0.79 (t, *J* = 6.7 Hz, 6H, CH_3). $^{13}C\{^{1}H\}$ NMR (100.6 MHz, $CDCl_3$): δ 166.7, 134.2, 131.6, 128.7, 127.0, 58.5, 31.8, 27.1, 27.0, 22.7, 14.1. HRMS (ESI) m/z calcd for $C_{19}H_{32}N_2O$ $(M+H)^+$: 305.2587, found: 305.2569.

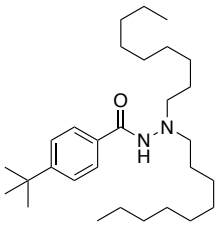


***N*',*N*'-Di(hex-5-en-1-yl)benzohydrazide (5.1e):** Purified by silica gel column chromatography using ethyl acetate/hexane (10:90) mixture as an eluent. White solid. Yield: 130 mg, 87%. IR (DCM): 3427, 3270, 3053, 2933, 2857, 1663, 1487, 1265, 1072, 914, 739 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66-7.62 (m, 2H, ArC*H*), 7.40 (dd, J_1 = 10.6 Hz, J_2 = 4.1 Hz, 1H, ArC*H*), 7.31 (t, *J* = 7.4 Hz, 2H, ArC*H*), 6.94 (s, 1H, N*H*), 5.69 (ddt, J_1 = 16.9

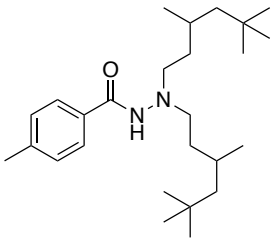


Hz, J_2 = 10.2 Hz, J_3 = 6.7 Hz, 2H, olefinic-C*H*), 4.86 (ddd, J_1= 13.7 Hz, J_2= 11.0 Hz, J_3= 1.2 Hz, 4H, olefinic-C*H*), 2.76 (t, *J* = 7.2 Hz, 4H, CH_2), 1.97 (dt, J_1 = 13.9 Hz, J_2 = 7.1 Hz, 4H, CH_2), 1.55-1.44 (m, 4H, CH_2), 1.35 (dt, J_1 = 14.9 Hz, J_2 = 7.4 Hz, 4H, CH_2). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 166.7, 138.6, 134.0, 131.4, 128.5, 127.0, 114.5, 57.9, 33.5, 26.5, 26.4. HRMS (ESI) m/z calcd for $C_{19}H_{28}N_2O$ $(M+H)^+$: 301.2274, found: 301.2290.

4-(*tert*-Butyl)-*N*',*N*'-dinonylbenzohydrazide (5.1f): Purified by silica gel column chromatography using ethyl acetate/hexane (10:90) mixture as an eluent. White solid. Yield: 215 mg, 97%. IR (DCM): 3429, 3269, 3051, 2926, 2854, 1654, 1466, 1264, 1053, 895, 742 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.61 (d, *J* = 8.3 Hz, 2H, ArC*H*), 7.35 (d, *J* = 8.2 Hz, 2H, ArC*H*), 6.66 (s, 1H, N*H*), 2.74 (t, *J* = 7.6 Hz, 4H, CH_2), 1.47 (dd, J_1 = 14.3 Hz, J_2 = 7.3 Hz, 4H, CH_2), 1.25 (s, 9H, 3×CH_3), 1.20-1.17 (m, 24H, CH_2), 0.79 (t, *J* = 6.7 Hz, 6H, CH_3). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 166.6, 155.0, 131.2, 126.9, 125.5, 58.5, 34.9, 31.9, 31.2, 29.6, 29.3, 27.3, 27.1, 22.7, 14.1. HRMS (ESI) m/z calcd for $C_{29}H_{52}N_2O$ $(M+H)^+$: 445.4152, found: 445.4135.



4-Methyl-*N*',*N*'-bis(3,5,5-trimethylhexyl)benzohydrazide (5.1g): Purified by silica gel column chromatography using ethyl acetate/hexane (10:90) mixture as an eluent. White solid. Yield: 197 mg, 98%. IR (DCM): 3246, 3043, 2954, 2866, 1644, 1466, 1264, 834, 741 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.55 (d, *J* = 7.8 Hz, 2H, ArC*H*), 7.14 (d, *J* = 7.8 Hz, 2H, ArC*H*), 6.55 (s, 1H, N*H*), 2.75 (t, *J* = 12.8 Hz, 4H, CH_2), 2.31 (s, 3H, CH_3), 1.50 (dd, J_1 = 18.1 Hz, J_1 = 8.1 Hz, 4H, CH_2), 1.40-1.27 (m, 2H, C*H*), 1.13 (dd, J_1 = 13.8 Hz, J_2 = 2.4 Hz, 2H, CH_2), 0.97 (dd, J_1 = 14.0 Hz, J_2 = 6.0 Hz, 2H, CH_2), 0.84 (t, *J* = 5.8 Hz, 6H, CH_3), 0.79 (s, 18H, 3×CH_3). $^{13}C\{^1H\}$ NMR



(100.6 MHz, $CDCl_3$): δ 166.6, 141.9, 131.3, 129.3, 127.0, 56.7, 51.4, 36.4, 31.1, 30.0, 27.6, 22.8, 21.5. HRMS (ESI) m/z calcd for $C_{26}H_{46}N_2O$ $(M+H)^+$: 403.3683, found: 403.3692.

2-Methyl-*N*',*N*'-ditetradecylbenzohydrazide (5.1h): Purified by silica gel column chromatography using ethyl acetate/hexane (10:90) mixture as an eluent. White solid. Yield: 263 mg, 97%. IR (DCM): 3417, 3206, 3053, 2919, 2849, 1651, 1447, 1265, 895, 748 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.22 (q, J = 7.0 Hz, 2H, ArC*H*), 7.12 (dd, J_1 = 16.4 Hz, J_2 = 8.3 Hz, 2H, ArC*H*), 6.14 (s, 1H, N*H*), 2.72 (t, J = 7.6 Hz, 4H, CH_2), 2.37 (s, 3H, CH_3), 1.59-1.48 (m, 4H, CH_2), 1.35-1.07 (m, 44H, CH_2), 0.81 (t, J = 6.7 Hz, 6H, CH_3). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 168.9, 136.4, 135.6, 131.0, 130.0, 126.7, 125.7, 58.6, 32.0, 29.8, 29.8, 29.7, 29.7, 29.7, 29.4, 27.3, 27.1, 22.8, 19.7, 14.2. HRMS (ESI) m/z calcd for $C_{36}H_{66}N_2O$ $(M+H)^+$: 543.5248, found: 543.5254.

***N*',*N*'-bis(4-Phenylbutyl)-1-naphthohydrazide (5.1i):** Purified by silica gel column chromatography using ethyl acetate/hexane (10:90) mixture as an eluent. White solid. Yield: 209 mg, 93%. IR (DCM): 3413, 3317, 3053, 2937, 2859, 1676, 1452, 1265, 895, 738 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.15-8.07 (m, 1H, ArC*H*), 7.82-7.71 (m, 2H, ArC*H*), 7.45-7.39 (m, 2H, ArC*H*), 7.31-7.19 (m, 2H, ArC*H*), 7.15 (t, J = 7.4 Hz, 4H, ArC*H*), 7.06 (dd, J_1 = 12.8 Hz, J_2 = 7.0 Hz, 6H, ArC*H*), 6.35 (s, 1H, N*H*), 2.74 (t, J = 6.7 Hz, 4H, CH_2), 2.55 (t, J = 7.1 Hz, 4H, CH_2), 1.70-1.50 (m, 8H, CH_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100.6 MHz): δ 168.5, 142.3, 133.6, 133.3, 130.6, 130.3, 128.5, 128.3, 128.3, 128.2, 127.2, 126.5, 125.7, 125.3, 124.8, 124.6, 58.1, 35.8, 28.9, 26.7. HRMS (ESI) m/z calcd for $C_{31}H_{34}N_2O$ $(M+H)^+$: 451.2744, found: 451.2758.

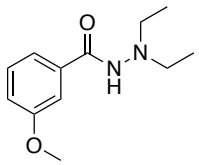
***N*',*N*'-Bis(3,7-dimethyloct-6-en-1-yl)benzohydrazide (5.1j):** Purified by silica gel column chromatography using ethyl acetate/hexane (10:90) mixture as an eluent. Colorless liquid. Yield: 179 mg, 87%. IR (DCM): 3422, 3238, 3056, 2958, 2925, 2856, 1650, 1461, 1267, 740 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.65 (d, *J* = 7.4 Hz, 2H, ArC*H*), 7.42 (t, *J* = 7.3 Hz, 1H, ArC*H*), 7.34 (t, *J* = 7.5 Hz, 2H, ArC*H*), 6.57 (s, 1H, N*H*), 4.99 (t, *J* = 7.0 Hz, 2H, olefinic-C*H*), 2.78 (tt, J_1 = 16.2 Hz, J_2 = 8.1 Hz, 4H, CH_2), 1.99-1.77 (m, 4H, CH_2), 1.59 (s, 6H, CH_3), 1.49 (s, 6H, CH_3), 1.30 (dddd, J_1 = 15.2 Hz, J_2 = 12.0 Hz, J_3 = 11.1 Hz, J_4 = 6.1 Hz, 8H, CH_2 &C*H*), 1.16-1.02 (m, 2H, CH_2), 0.82 (d, *J* = 6.5 Hz, 6H, CH_3). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 166.7, 134.2, 131.5, 131.2, 128.7, 127.0, 124.8, 56.6, 37.2, 34.0, 30.8, 25.7, 25.5, 19.7, 17.7. HRMS (ESI) m/z calcd for $C_{27}H_{44}N_2O$ $(M+H)^+$: 413.3526, found: 413.3529.

***N*',*N*'-Diethylbenzohydrazide (5.1k):** Purified by silica gel column chromatography using ethyl acetate/hexane (30:70) mixture as an eluent. White solid. Yield: 85 mg, 89%. IR (DCM): 3245, 2957, 2865, 1656, 1466, 1265, 741 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.68 (d, *J* = 7.3 Hz, 2H, ArC*H*), 7.43 (t, *J* = 7.3 Hz, 1H, ArC*H*), 7.35 (t, *J* = 7.4 Hz, 2H, ArC*H*), 6.69 (s, 1H, N*H*), 2.83 (q, *J* = 7.1 Hz, 4H, CH_2), 1.09 (t, *J* = 7.1 Hz, 6H, CH_3). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 167.1, 134.0, 131.6, 128.7, 127.0, 52.2, 12.0. HRMS (ESI) m/z calcd for $C_{11}H_{16}N_2O$ $(M+H)^+$: 193.1335, found: 193.1329.

***N*',*N*'-Diethyl-2-methylbenzohydrazide (5.1l):** Purified by silica gel column chromatography using ethyl acetate/hexane (30:70) mixture as an eluent. White solid. Yield: 96 mg, 93%. IR (DCM): 3243, 2958, 2867, 1657, 1465, 1265, 742 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.23 (t, *J* = 7.2 Hz, 2H, ArC*H*), 7.12 (dd, J_1 = 16.9 Hz, J_2 = 8.2 Hz, 2H, ArC*H*), 6.11 (s,

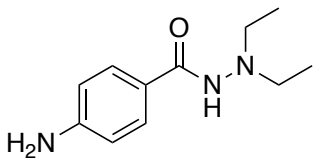
1H, N*H*), 2.77 (q, *J* = 7.0 Hz, 4H, CH_2), 2.37 (s, 3H, CH_3), 1.12 (t, *J* = 7.1 Hz, 6H, CH_3). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 169.2, 136.2, 135.5, 130.9, 129.9, 126.6, 125.6, 52.3, 19.6, 12.1. HRMS (ESI) m/z calcd for $C_{12}H_{18}N_2O$ $(M+H)^+$: 207.1492, found: 207.1491.

***N*',*N*'-Diethyl-3-methoxybenzohydrazide (5.1m):** Purified by silica gel column



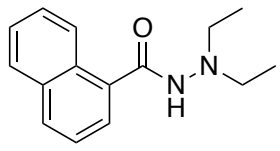
chromatography using ethyl acetate/hexane (30:70) mixture as an eluent. White solid. Yield: 108 mg, 97%. IR (DCM): 3266, 3053, 2967, 2878, 1647, 1583, 1487, 1265, 1043, 895, 740 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.31-7.16 (m, 3H, ArC*H*), 6.96 (dd, J_1 = 7.9 Hz, J_2 = 1.3 Hz, 1H, ArC*H*), 6.60 (s, 1H, N*H*), 3.77 (s, 3H, OCH_3), 2.81 (q, *J* = 7.1 Hz, 4H, CH_2), 1.09 (t, *J* = 7.1 Hz, 6H, CH_3). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 166.9, 159.9, 135.4, 129.6, 118.7, 117.8, 112.5, 55.5, 52.3, 12.0. HRMS (ESI) m/z calcd for $C_{12}H_{18}N_2O_2$ $(M+H)^+$: 223.1441, found: 223.1448.

4-Amino-*N*',*N*'-diethylbenzohydrazide (5.1n): Purified by silica gel column



chromatography using ethyl acetate/hexane (70:30) mixture as an eluent. Pale yellow solid. Yield: 65 mg, 63%. IR (DCM): 3466, 3265, 3052, 2950, 2874, 1647, 1487, 1265, 1041, 896, 739 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.54 (d, *J* = 8.5 Hz, 2H, ArC*H*), 6.59 (t, 3H, ArC*H* & N*H*), 3.93 (s, 2H, NH_2), 2.85 (dd, J_1 = 14.2 Hz, J_2 = 7.1 Hz, 4H, CH_2), 1.09 (t, *J* = 7.1 Hz, 6H, CH_3). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 166.9, 149.9, 128.7, 122.9, 114.2, 52.0, 11.9. HRMS (ESI) m/z calcd for $C_{11}H_{17}N_3O$ $(M+H)^+$: 208.1444, found: 208.1459.

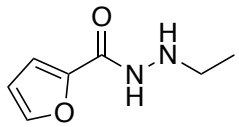
***N*',*N*'-Diethyl-1-naphthohydrazide (5.1o):** Purified by silica gel column



chromatography using ethyl acetate/hexane (30:70) mixture as an eluent. White solid. Yield: 120 mg, 99%. IR (DCM): 3266,

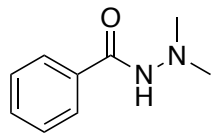
3054, 2963, 2874, 2835, 1653, 1484, 1265, 895, 739 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.19 (d, *J* = 8.2 Hz, 1H, ArC*H*), 7.86-7.74 (m, 2H, ArC*H*), 7.50-7.42 (m, 3H, ArC*H*), 7.35 (t, *J* = 7.6 Hz, 1H, ArC*H*), 6.33 (s, 1H, N*H*), 2.83 (q, *J* = 7.0 Hz, 4H, CH_2), 1.18 (t, *J* = 7.1 Hz, 6H, CH_3). $^{13}C\{^{1}H\}$ NMR (100.6 MHz, $CDCl_3$): δ 168.8, 133.7, 133.4, 130.8, 130.4, 128.3, 127.4, 126.6, 125.4, 124.8, 124.6, 52.5, 12.2. HRMS (ESI) m/z calcd for $C_{15}H_{18}N_2O$ $(M+H)^+$: 243.1492, found: 243.1477.

***N'*-Ethylfuran-2-carbohydrazide (5.1p):** Purified by silica gel column



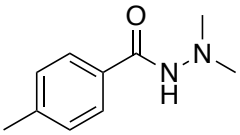
chromatography using ethyl acetate/hexane (40:60) mixture as an eluent. White solid. Yield: 58 mg, 75%. IR (DCM): 3263, 3052, 2987, 2854, 1672, 1447, 1267, 1047, 895, 747 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 (d, *J* = 0.8 Hz, 1H, ArC*H*), 7.07 (d, *J* = 3.4 Hz, 1H, ArC*H*), 6.43 (dd, J_1 = 3.5 Hz, J_2 = 1.7 Hz, 1H, ArC*H*), 5.27 (s, 1H, N*H*), 2.91 (q, *J* = 7.1 Hz, 2H, CH_2), 1.07 (t, *J* = 7.2 Hz, 3H, CH_3). $^{13}C\{^{1}H\}$ NMR (100.6 MHz, $CDCl_3$): δ 158.2, 146.9, 144.2, 114.8, 112.1, 46.7, 13.0. HRMS (ESI) m/z calcd for $C_7H_{10}N_2O_2$ $(M+H)^+$: 155.0815, found: 155.0811.

***N'*,*N'*-Dimethylbenzohydrazide (5.1q):** Purified by silica gel column chromatography



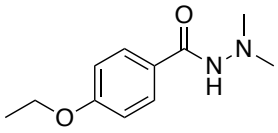
using ethyl acetate/hexane (50:50) mixture as an eluent. White solid. Yield: 76 mg, 93%. IR (DCM): 3263, 3052, 2962, 2850, 1657, 1580, 1484, 1267, 1041, 895, 739 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (d, *J* = 7.4 Hz, 2H, ArC*H*), 7.41 (d, *J* = 7.1 Hz, 1H, ArC*H*), 7.33 (dd, J_1 = 11.4 Hz, J_2 = 4.2 Hz, 2H, ArC*H*), 6.97 (s, 1H, N*H*), 2.63 (s, 6H, CH_3). $^{13}C\{^{1}H\}$ NMR (100.6 MHz, $CDCl_3$): δ 165.8, 133.8, 131.6, 128.6, 127.1, 47.7. HRMS (ESI) m/z calcd for $C_9H_{12}N_2O$ $(M+H)^+$: 165.1022, found: 165.1022.

***N'*,*N'*,4-Trimethylbenzohydrazide (5.1r):** Purified by silica gel column chromatography using ethyl acetate/hexane (75:25) mixture as an eluent. White solid. Yield: 76.5 mg, 86%. IR (DCM): 3263, 3052, 2962, 2874, 2836, 1654, 1265, 1041, 895,



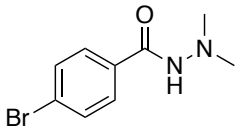
739 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.58 (d, *J* = 7.1 Hz, 2H, ArC*H*), 7.16 (t, *J* = 13.4 Hz, 3H, ArC*H* & N*H*), 2.66 (s, 6H, CH_3), 2.32 (s, 3H, CH_3). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 165.8, 142.2, 130.7, 129.3, 127.1, 47.7, 21.5. HRMS (ESI) m/z calcd for $C_{10}H_{14}N_2O$ $(M+H)^+$: 179.1178, found: 179.1184.

4-Ethoxy-*N*',*N*'-dimethylbenzohydrazide (5.1s): Purified by silica gel column



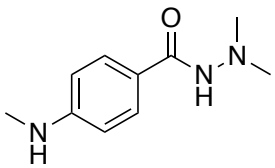
chromatography using ethyl acetate/hexane (50:50) mixture as an eluent. White solid. Yield: 90 mg, 87%. IR (DCM): 3264, 3052, 2987, 2850, 1660, 1447, 1260, 895, 742 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.63 (d, *J* = 8.1 Hz, 2H, ArC*H*), 6.87-6.76 (m, 3H, ArC*H* & N*H*), 3.99 (q, *J* = 7.0 Hz, 2H, CH_2), 2.63 (s, 6H, CH_3), 1.35 (t, *J* = 7.0 Hz, 3H, CH_3). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 165.4, 161.7, 128.9, 125.8, 114.3, 63.7, 47.8, 14.7. HRMS (ESI) m/z calcd for $C_{11}H_{16}N_2O_2$ $(M+H)^+$: 209.1286, found: 209.1290.

4-Bromo-*N*',*N*'-dimethylbenzohydrazide (5.1t): Purified by silica gel column



chromatography using ethyl acetate/hexane (70:30) mixture as an eluent. White solid. Yield: 103 mg, 85%. IR (DCM): 3265, 3052, 2966, 2878, 1657, 1480, 1267, 1045, 895, 739 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.55 (d, *J* = 8.5 Hz, 2H, ArC*H*), 7.48 (d, *J* = 8.4 Hz, 2H, ArC*H*), 7.06 (s, 1H, N*H*), 2.64 (s, 6H, CH_3). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 164.9, 132.5, 131.9, 128.8, 127.1, 126.4, 47.6. HRMS (ESI) m/z calcd for $C_9H_{11}BrN_2O$ $(M+H)^+$: 243.0127, found: 243.0142

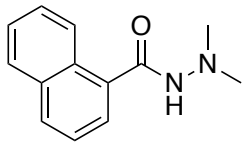
***N*',*N*'-Dimethyl-4-(methylamino)benzohydrazide (5.1u):** Purified by silica gel



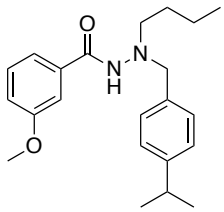
column chromatography using ethyl acetate solvent (100%) as an eluent. White solid. Yield: 72 mg, 75%. IR (DCM): 3440, 3260, 3050, 2988, 2853, 1661, 1447, 1265, 1047, 895, 743 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 (d, *J* = 7.2 Hz, 2H, ArC*H*), 6.74 (s, 1H, amide-N*H*), 6.52-6.43 (m, 2H, ArC*H*), 3.37 (s, 1H, amine-N*H*), 2.78 (s, 3H, CH_3), 2.61 (s, 6H, CH_3). ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$): δ 165.8, 152.1, 128.8, 121.4, 111.4, 47.9, 30.3. HRMS (ESI) m/z calcd for $C_{10}H_{15}N_3O$ $(M+H)^+$: 194.1287, found: 194.1290.

***N*',*N*'-Dimethyl-1-naphthohydrazide (5.1v):** Purified by silica gel column chromatography using ethyl acetate/hexane (75:25) mixture as an eluent.White solid. Yield: 96 mg, 90%. IR (DCM): 3250, 3059, 2980, 2857, 1650, 1447, 1266, 1047, 897, 742 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.27-8.17 (m, 1H, ArC*H*), 7.91-7.79 (m, 2H, ArC*H*), 7.58-7.44 (m, 3H, ArC*H*), 7.44-7.34 (m, 1H, ArC*H*), 6.84 (s, 1H, N*H*), 2.76-2.72 (m, 6H, CH_3). ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$): δ 167.4, 133.7, 132.8, 130.9, 130.4, 128.4, 127.3, 126.6, 125.2, 124.7, 47.7. HRMS (ESI) m/z calcd for $C_{13}H_{14}N_2O$ $(M+H)^+$: 215.1178, found: 215.1189.

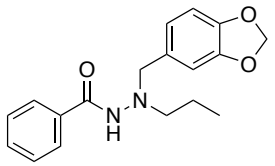


***N*'-Butyl-*N*'-(4-isopropylbenzyl)-3-methoxybenzohydrazide (5.2a):** Purified by silica gel column chromatography using ethyl acetate/hexane (10:90) mixture as an eluent. White solid. Yield: 166 mg, 94%. IR (DCM): 3250, 3056, 2987, 2857, 1640, 1447, 1267, 1048, 897, 741 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.19 (t, *J* = 5.0 Hz, 2H, ArC*H*), 7.16 (d, *J* = 7.9 Hz, 1H, ArC*H*), 7.13-7.06 (m, 3H, ArC*H*), 7.01-6.96 (m, 1H, ArC*H*), 6.91 (ddd, J_1 = 8.3 Hz, J_2 = 2.6 Hz, J_3 = 0.9 Hz, 1H, ArC*H*), 6.76 (s, 1H, N*H*), 4.05 (s, 2H, CH_2), 3.72 (s, 3H, OCH_3), 2.83 (ddd, J_1 = 20.7 Hz, J_2 = 14.3 Hz, J_3 = 7.1 Hz, 3H, CH_2&C*H*), 1.48 (ddd, J_1 = 14.9 Hz, J_2 = 8.5 Hz, J_3 = 6.3 Hz, 2H, CH_2), 1.40-1.24 (m, 2H, CH_2), 1.15 (d, *J* = 6.9 Hz, 6H, CH_3), 0.82 (t, *J* = 7.3 Hz, 3H, CH_3). ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$): δ 166.7, 159.8, 148.3, 135.6, 133.6, 129.6, 129.6, 126.5, 118.7, 117.8,



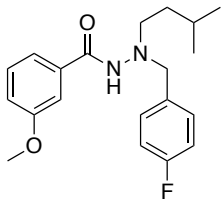
112.3, 60.7, 56.1, 55.4, 33.8, 29.6, 24.0, 20.4, 14.1. HRMS (ESI) m/z calcd for $C_{22}H_{30}N_2O_2$ $(M+H)^+$: 355.2380, found: 355.2403.

***N*'-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-*N*'-propylbenzohydrazide (5.2b):** Purified by



silica gel column chromatography using ethyl acetate/hexane (10:90) mixture as an eluent. White solid. Yield: 131 mg, 84%. IR (DCM): 3251, 3057, 2980, 2856, 1647, 1440, 1268, 1047, 897, 747 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.56-7.51 (m, 2H, ArC*H*), 7.40 (t, *J* = 7.4 Hz, 1H, ArC*H*), 7.31 (t, *J* = 7.5 Hz, 2H, ArC*H*), 6.83 (s, 1H, ArC*H*), 6.76 (s, 1H, N*H*), 6.70 (dd, J_1 = 19.2 Hz, J_2 = 8.4 Hz, 2H, ArC*H*), 5.87 (s, 2H, OCH_2), 4.01 (s, 2H, CH_2), 2.90-2.77 (m, 2H, CH_2), 1.53 (dt, J_1 = 14.8 Hz, J_2 = 7.4 Hz, 2H, CH_2), 0.87 (t, *J* = 7.4 Hz, 3H, CH_3). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 166.9, 147.8, 147.1, 134.0, 131.6, 130.3, 128.7, 126.9, 122.8, 109.9, 108.1, 101.0, 60.7, 57.9, 20.8, 11.7. HRMS (ESI) m/z calcd for $C_{18}H_{20}N_2O_3$ $(M+H)^+$: 313.1547, found: 313.1570.

***N*'-(4-Fluorobenzyl)-*N*'-isopentyl-3-methoxybenzohydrazide (5.2c):** Purified by



silica gel column chromatography using ethyl acetate/hexane (10:90) mixture as an eluent. White solid. Yield: 110 mg, 64%. IR (DCM): 3255, 3059, 2960, 2888, 1657, 1440, 1264, 1049, 890, 745 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.26 (dd, J_1 = 8.3 Hz, J_2 = 5.6 Hz, 2H, ArC*H*), 7.20-7.14 (m, 1H, ArC*H*), 7.08 (s, 1H, ArC*H*), 6.97 (d, *J* = 7.6 Hz, 1H, ArC*H*), 6.94-6.89 (m, 3H, ArC*H*), 6.80 (s, 1H, N*H*), 4.04 (s, 2H, CH_2), 3.72 (s, 3H, OCH_3), 3.04-2.79 (m, 2H, CH_2), 1.59 (td, J_1 = 13.4 Hz, J_2 = 6.7 Hz, 1H, C*H*), 1.39 (dd, J_1 = 14.9 Hz, J_2 = 7.0 Hz, 2H, CH_2), 0.80 (d, *J* = 6.6 Hz, 6H, CH_3). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 166.8, 163.5, 161.1, 159.8, 135.4, 132.6, 131.0, 131.0, 129.7, 128.8, 128.7, 118.6, 117.8, 115.3, 115.1, 112.3, 60.3, 55.4, 54.7, 36.3, 26.1, 22.7. HRMS (ESI) m/z calcd for $C_{20}H_{25}FN_2O_2$ $(M+H)^+$: 345.1973, found: 345. 1991.

***N*'-Hexyl-*N*'-(3-(pyridin-2-yl)propyl)benzohydrazide (5.2d):** Purified by silica gel column chromatography using ethyl acetate/hexane (40:60) mixture as an eluent. Pale yellow solid. Yield: 136 mg, 80%. IR (DCM): 3257, 3050, 2969, 2887, 1658, 1447, 1260, 1045, 890, 747 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.40 (d, J = 4.8 Hz, 1H, ArC*H*), 7.70-7.64 (m, 2H, ArC*H*), 7.49 (td, J_1 = 7.7 Hz, J_2 = 1.7 Hz, 1H, ArC*H*), 7.41 (t, J = 7.4 Hz, 1H, ArC*H*), 7.33 (t, J = 7.4 Hz, 2H, ArC*H*), 7.11 (d, J = 7.8 Hz, 1H, ArC*H*), 7.01 (dd, J_1 = 6.9 Hz, J_2 = 5.4 Hz, 1H, ArC*H*), 6.91 (s, 1H, N*H*), 2.87-2.74 (m, 6H, CH_2), 1.98-1.86 (m, 2H, CH_2), 1.53-1.39 (m, 2H, CH_2), 1.30-1.14 (m, 6H, CH_2), 0.78 (t, J = 6.8 Hz, 3H, CH_3). $^{13}C\{^{1}H\}$ NMR (100.6 MHz, $CDCl_3$): δ 166.8, 161.8, 149.0, 136.5, 134.1, 131.5, 128.6, 127.1, 123.2, 121.1, 58.3, 57.3, 35.7, 31.8, 27.1, 27.1, 26.9, 22.6, 14.1. HRMS (ESI) m/z calcd for $C_{21}H_{29}N_3O$ $(M+H)^+$: 340.2383, found: 340.2400.

***N*'-(4-Aminobenzyl)-4-ethoxy-*N*'-heptylbenzohydrazide (5.2e):** Purified by silica gel column chromatography using ethyl acetate/hexane (40:60) mixture as an eluent. Pale yellow solid. Yield: 149 mg, 78%. IR (DCM): 3422, 3255, 3056, 2955, 2886, 1647,1480, 1268, 1040, 890, 748 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 (d, J = 8.4 Hz, 2H, ArC*H*), 7.03 (d, J = 7.9 Hz, 2H, ArC*H*), 6.77 (d, J = 8.5 Hz, 2H, ArC*H*), 6.64 (s, 1H, N*H*), 6.55 (d, J = 7.9 Hz, 2H, ArC*H*), 4.02-3.90 (m, 4H, CH_2), 3.66 (s, 2H, NH_2), 2.86-2.72 (m, 2H, CH_2), 1.47 (dd, J_1 = 13.9 Hz, J_2 = 7.1 Hz, 2H, CH_2), 1.32 (dd, J_1 = 15.3 Hz, J_2 = 8.4 Hz, 3H, CH_3), 1.30-1.07 (m, 10H, CH_2), 0.78 (t, J = 6.2 Hz, 3H, CH_3). $^{13}C\{^{1}H\}$ NMR (100.6 MHz, $CDCl_3$): δ 166.1, 161.6, 145.9, 131.0, 128.7, 126.1, 125.6, 115.0, 114.2, 63.6, 60.6, 56.2, 31.8, 29.2, 27.5, 27.2, 22.6, 14.7, 14.1. HRMS (ESI) m/z calcd for $C_{23}H_{33}N_3O_2$ $(M+H)^+$: 384.2646, found: 384.2797.

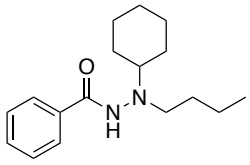
4-(*tert*-Butyl)-*N*'-ethyl-*N*'-(3,5,5-trimethylhexyl)benzohydrazide (5.2f): Purified by silica gel column chromatography using ethyl acetate/hexane (10:90) mixture as an eluent. White solid. Yield: 166 mg, 96%. IR (DCM): 3255, 3052, 2986, 2852, 1647, 1447, 1265, 1047, 897, 740 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.61 (d, J = 8.3 Hz, 2H, ArC*H*), 7.37 (d, J = 8.3 Hz, 2H, ArC*H*), 6.51 (s, 1H, N*H*), 2.90-2.64 (m, 4H, CH_2), 1.57-1.42 (m, 2H, CH_2), 1.41-1.30 (m, 1H, C*H*), 1.25 (s, 9H, 3×CH_3), 1.14 (dd, J_1 = 13.8 Hz, J_2 = 3.2 Hz, 1H, CH_2), 1.07 (t, J = 7.1 Hz, 3H, CH_3), 0.98 (dd, J_1 = 14.0 Hz, J_2 = 6.1 Hz, 1H, CH_2), 0.85 (d, J = 6.4 Hz, 3H, CH_3), 0.80 (s, 9H, 3×CH_3). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 166.8, 155.1, 131.2, 126.9, 125.6, 56.5, 52.6, 51.4, 36.4, 35.0, 31.2, 31.1, 30.0, 27.6, 22.8, 12.1. HRMS (ESI) m/z calcd for $C_{22}H_{38}N_2O$ $(M+H)^+$: 347.3057, found: 347.3076.

4-Amino-*N*'-butyl-*N*'-hexylbenzohydrazide (5.2g): Purified by silica gel column chromatography using ethyl acetate/hexane (40:60) mixture as an eluent. White solid. Yield: 98 mg, 67%. IR (DCM): 3476. 3256, 3056, 2960, 2887, 1647, 1442, 1265, 1040, 890, 742 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.50 (d, J = 8.3 Hz, 2H, ArC*H*), 6.57 (d, J = 8.4 Hz, 3H, ArC*H* & N*H*), 3.92 (s, 2H, NH_2), 2.79-2.68 (m, 4H, CH_2), 1.45 (dd, J_1 = 13.2 Hz, J_2 = 6.5 Hz, 4H, CH_2), 1.32-1.13 (m, 8H, CH_2), 0.86-0.74 (m, 6H, CH_3). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 166.5, 149.8, 128.7, 123.3, 114.2, 58.7, 58.3, 31.8, 29.2, 27.0, 22.6, 20.5, 14.1. HRMS (ESI) m/z calcd for $C_{17}H_{29}N_3O$ $(M+H)^+$: 292.2383, found: 292.2390.

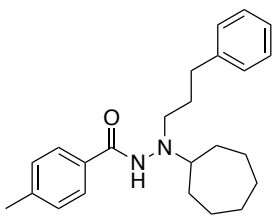
4-Amino-*N*'-benzyl-*N*'-hexylbenzohydrazide (3h): Purified by silica gel column chromatography using ethyl acetate/hexane (40:60) mixture as an eluent. White solid. Yield: 91 mg, 56%. IR (DCM): 3422, 3052, 2986, 2856, 1650, 1448, 1265, 1047, 895, 743

cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.36 (d, J = 8.3 Hz, 2H, ArC*H*), 7.23 (dq, J_1 = 13.5 Hz, J_2 = 7.4 Hz, 5H, ArC*H*), 6.70 (s, 1H, N*H*), 6.51 (d, J = 8.5 Hz, 2H, ArC*H*), 4.08 (s, 2H, CH_2), 3.90 (s, 2H, NH_2), 2.93-2.81 (m, 2H, CH_2), 1.48 (dt, J_1 = 14.7 Hz, J_2 = 7.3 Hz, 2H, CH_2), 1.32-1.14 (m, 6H, CH_2), 0.78 (t, J = 6.7 Hz, 3H, CH_3). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 166.6, 149.8, 136.5, 129.7, 128.6, 128.4, 127.5, 123.3, 114.2, 61.1, 56.4, 31.8, 27.5, 26.9, 22.7, 14.1. HRMS (ESI) m/z calcd for $C_{20}H_{27}N_3O$ $(M+H)^+$: 326.2227, found: 326.2236.

***N*'-Butyl-*N*'-cyclohexylbenzohydrazide (5.2i):** Purified by silica gel column chromatography using ethyl acetate/hexane (10:90) mixture as an eluent. White solid. Yield: 131 mg, 96%. IR (DCM): 3256, 3052, 2967, 2886, 1649, 1447, 1265, 1046, 880, 747 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.68 (d, J = 6.5 Hz, 2H, ArC*H*), 7.42 (d, J = 6.5 Hz, 1H, ArC*H*), 7.36 (t, J = 6.7 Hz, 2H), 6.60 (s, 1H, N*H*), 2.74 (d, J = 30.1 Hz, 3H, CH_2 & C*H*), 1.92 (s, 2H, CH_2), 1.73 (s, 2H, CH_2), 1.44-1.61 (m, 3H, CH_2), 1.24 (dt, J_1 = 48.8 Hz, J_2 = 14.8 Hz, 7H, CH_2), 0.83 (t, J = 6.7 Hz, 3H, CH_3). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 167.1, 134.2, 131.5, 128.7, 127.1, 64.4, 54.3, 29.3, 29.0, 26.0, 25.3, 20.5, 14.1. HRMS (ESI) m/z calcd for $C_{17}H_{26}N_2O$ $(M+H)^+$: 275.2118, found: 275.2099.

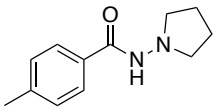


***N*'-Cycloheptyl-4-methyl-*N*'-(3-phenylpropyl)benzohydrazide (5.2j):** Purified by silica gel column chromatography using ethyl acetate/hexane (10:90) mixture as an eluent. White solid. Yield: 146 mg, 80%. IR (DCM): 3255, 3056, 2967, 2880, 1647, 1449, 1266, 1046, 890, 744 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.54 (d, J = 8.0 Hz, 2H, ArC*H*), 7.20-7.05 (m, 7H, ArC*H*), 6.47 (s, 1H, N*H*), 3.00-2.79 (m, 1H, C*H*), 2.70 (t, J = 7.2 Hz, 2H, CH_2), 2.63 (t, J = 7.6 Hz, 2H, CH_2), 2.32 (s, 3H, CH_3), 1.91 (dd, J_1 = 13.0 Hz, J_2 = 4.1 Hz, 2H, CH_2), 1.81 (dd, J_1 = 14.8 Hz, J_2 = 7.5 Hz, 2H, CH_2),



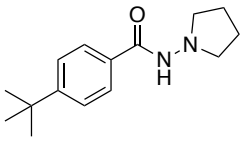
1.67-1.54 (m, 2H, CH_2), 1.41 (ddd, J_1 = 26.0 Hz, J_2 = 12.2 Hz, J_3 = 6.0 Hz, 8H, CH_2). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 167.0, 142.2, 142.0, 131.4, 129.3, 128.6, 128.4, 127.1, 125.8, 66.4, 54.6, 33.5, 29.8, 29.2, 28.1, 25.2, 21.5. HRMS (ESI) m/z calcd for $C_{24}H_{32}N_2O$ $(M+H)^+$: 365.2587, found: 365.2630.

4-Methyl-*N*-(pyrrolidin-1-yl)benzamide (5.3a): Purified by silica gel column



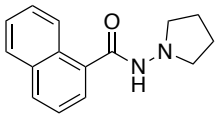
chromatography using ethyl acetate/hexane (40:60) mixture as an eluent. White solid. Yield: 92 mg, 90%. IR (DCM): 3250, 3059, 2960, 2886, 1650, 1447, 1267, 1058, 898, 742 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.57 (d, J = 7.7 Hz, 2H, ArCH), 7.14 (d, J = 7.9 Hz, 2H, ArCH), 3.14-2.83 (m, 4H, CH_2), 2.31 (s, 3H, CH_3), 1.96-1.77 (m, 4H, CH_2). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 166.3, 142.1, 131.0, 129.3, 127.1, 55.7, 22.4, 21.5. HRMS (ESI) m/z calcd for $C_{12}H_{16}N_2O$ $(M+H)^+$: 205.1335, found: 205.1330.

4-(*tert*-Butyl)-*N*-(pyrrolidin-1-yl)benzamide (5.3b): Purified by silica gel column



chromatography using ethyl acetate/hexane (40:60) mixture as an eluent. White solid. Yield: 106 mg, 86%. IR (DCM): 3267, 3010, 2966, 2889, 1657, 1447, 1270, 1046, 890, 739 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.61 (d, J = 8.0 Hz, 2H, ArCH), 7.35 (d, J = 8.1 Hz, 2H, ArCH), 3.11-2.76 (m, 4H, CH_2), 1.97-1.70 (m, 4H, CH_2), 1.25 (s, 9H, 3×CH_3) $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 166.2, 155.2, 130.9, 127.0,125.6, 55.6, 35.0, 31.2, 22.4. (ESI) m/z calcd for $C_{15}H_{22}N_2O$ $(M+H)^+$: 247.1805, found: 247.1817.

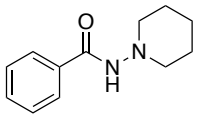
***N*-(Pyrrolidin-1-yl)-1-naphthamide (5.3c):** Purified by silica gel column



chromatography using ethyl acetate/hexane (40:60) mixture as an eluent. White solid. Yield: 100 mg, 83%. IR (DCM): 3250, 3077, 2960, 2889, 1650, 1448, 1260, 1049, 890, 742 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.15 (d, J = 7.6 Hz, 1H, ArCH), 7.75 (dt, J_1 = 19.0 Hz, J_1 = 9.4 Hz, 2H, ArCH), 7.47-7.37

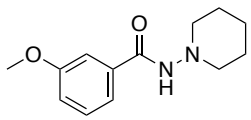
(m, 3H, ArC*H*), 7.29 (t, *J* = 7.6 Hz, 1H, ArC*H*), 6.88 (s, 1H, N*H*), 3.04-2.80 (m, 4H, CH_2), 1.94-1.62 (m, 4H, CH_2). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 167.9, 133.6, 133.0, 130.6, 130.3, 128.3, 127.1, 126.4, 125.3, 125.1, 124.6, 55.5, 22.2. (ESI) m/z calcd for $C_{15}H_{16}N_2O$ $(M+H)^+$: 241.1335, found: 241.1325.

***N*-(Piperidin-1-yl)benzamide (5.3d):** Purified by silica gel column chromatography



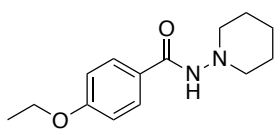
using ethyl acetate/hexane (40:60) mixture as an eluent. White solid. Yield: 77 mg, 75%. IR (DCM): 3300, 3109, 2956, 2887, 1651, 1447, 1265, 1049, 890, 747 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.66 (d, *J* = 7.1 Hz, 2H, ArC*H*), 7.47-7.38 (m, 1H, ArC*H*), 7.34 (t, *J* = 7.3 Hz, 2H, ArC*H*), 6.86 (s, 1H, N*H*), 2.88-2.63 (m, 4H, CH_2), 1.78-1.52 (m, 4H, CH_2), 1.44-1.24 (m, 2H, CH_2). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 165.4, 134.1, 131.6, 128.6, 127.1, 57.2, 25.4, 23.3. (ESI) m/z calcd for $C_{12}H_{16}N_2O$ $(M+H)^+$: 205.1335, found: 205.1336.

3-Methoxy-*N*-(piperidin-1-yl)benzamide (5.3e): Purified by silica gel column



chromatography using ethyl acetate/hexane (40:60) mixture as an eluent. White solid. Yield: 84 mg, 72%. IR (DCM): 3250, 3053, 2956, 2878, 1649, 1449, 1262, 1047, 898, 745 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.29-7.13 (m, 4H, ArC*H* & N*H*), 6.95 (dd, J_1 = 8.2 Hz, J_2 = 2.4 Hz, 1H, ArC*H*), 3.77 (s, 3H, OCH_3), 2.91-2.75 (m, 4H, CH_2), 1.69 (dt, J_1 = 11.1 Hz, J_2 = 5.6 Hz, 4H, CH_2), 1.38 (dd, J_1 = 14.9 Hz, J_2 = 9.9 Hz, 2H, CH_2). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 165.3, 159.9, 135.5, 129.6, 118.9, 117.7, 112.6, 57.2, 55.5, 25.4, 23.3. (ESI) m/z calcd for $C_{13}H_{18}N_2O_2$ $(M+H)^+$: 235.1441, found: 235.1464.

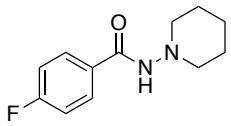
4-Ethoxy-*N*-(piperidin-1-yl)benzamide (5.3f): Purified by silica gel column



chromatography using ethyl acetate/hexane (40:60) mixture as an eluent. White solid. Yield: 87 mg, 70%. IR (DCM): 3266, 3156, 2960, 1652, 1447, 1269, 1040, 890, 751 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.63

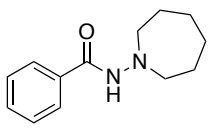
(d, *J* = 8.2 Hz, 2H, ArC*H*), 6.81 (d, *J* = 8.6 Hz, 2H, ArC*H*), 3.99 (q, *J* = 7.0 Hz, 2H, CH_2), 2.95-2.54 (m, 4H, CH_2), 1.85-1.51 (m, 4H, CH_2), 1.35 (t, *J* = 7.0 Hz, 5H, CH_3 & CH_2). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 165.0, 161.7, 128.9, 126.0, 114.3, 63.7, 57.3, 25.4, 23.3, 14.8. (ESI) m/z calcd for $C_{14}H_{20}N_2O_2$ $(M+H)^+$: 249.1597, found: 249.1603.

4-Fluoro-*N*-(piperidin-1-yl)benzamide (5.3g): Purified by silica gel column



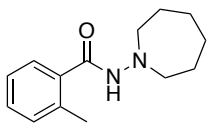
chromatography using ethyl acetate/hexane (45:55) mixture as an eluent. White solid. Yield: 70 mg, 63%. IR (DCM): 3253, 3052, 2956, 2881, 1649, 1447, 1269, 1047, 890, 742 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.85 (s, 1H, N*H*), 7.72-7.66 (m, 2H, ArC*H*), 7.02 (t, *J* = 8.4 Hz, 2H, ArC*H*), 2.93-2.67 (m, 4H, CH_2), 1.81-1.62 (m, 4H, CH_2), 1.44-1.28 (m, 2H, CH_2). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 166.1, 164.5, 163.6, 130.0, 129.6, 129.5, 115.8, 115.6, 57.3, 25.3, 23.2. (ESI) m/z calcd for $C_{12}H_{15}FN_2O$ $(M+H)^+$: 223.1241, found: 223.1235.

***N*-(Azepan-1-yl)benzamide (5.3h):** Purified by silica gel column chromatography



using ethyl acetate/hexane (40:60) mixture as an eluent. White solid. Yield: 71 mg, 65%. IR (DCM): 3266, 3046, 2950, 2856, 1640, 1402, 1276, 1049, 892, 745 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.66 (d, *J* = 7.3 Hz, 2H, ArC*H*), 7.41 (t, *J* = 6.9 Hz, 1H, ArC*H*), 7.33 (t, *J* = 7.4 Hz, 2H, ArC*H*), 3.11-3.08 (m, 4H, CH_2), 1.76-1.67 (m, 4H, CH_2), 1.57-1.52 (m, 4H, CH_2). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 165.7, 134.1, 131.5, 128.6, 127.0, 58.2, 27.1, 26.2. (ESI) m/z calcd for $C_{13}H_{18}N_2O$ $(M+H)^+$: 219.1492, found: 219.1510.

***N*-(Azepan-1-yl)-2-methylbenzamide (5.3i):** Purified by silica gel column



chromatography using ethyl acetate/hexane (40:60) mixture as an eluent. White solid. Yield: 80 mg, 70%. IR (DCM): 3266, 3076, 2966, 2887, 1640, 1449, 1267, 890, 743 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.22 (dd,

J_1 = 13.4 Hz, J_2 = 6.4 Hz, 2H, ArC*H*), 7.12 (dd, J_1 = 13.6 Hz, J_1 = 6.5 Hz, 2H, ArC*H*), 6.81 (s, 1H, N*H*), 3.14-3.05 (m, 4H, CH_2), 2.36 (s, 3H, CH_3), 1.76-1.60 (m, 4H, CH_2), 1.60-1.54 (m, 4H, CH_2). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 167.8, 136.3, 135.3, 130.9, 130.0, 126.9, 125.7, 58.4, 27.0, 26.1, 19.6. (ESI) m/z calcd for $C_{14}H_{20}N_2O$ $(M+H)^+$: 233.1648, found: 233.1640.

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^{1}H and ^{13}C NMR Spectra of *N,N*-Dialkylated Products:

Figure 5.2 ^{1}H NMR spectrum of *N*',*N*'-Dibutylbenzohydrazide (**5.1b**):

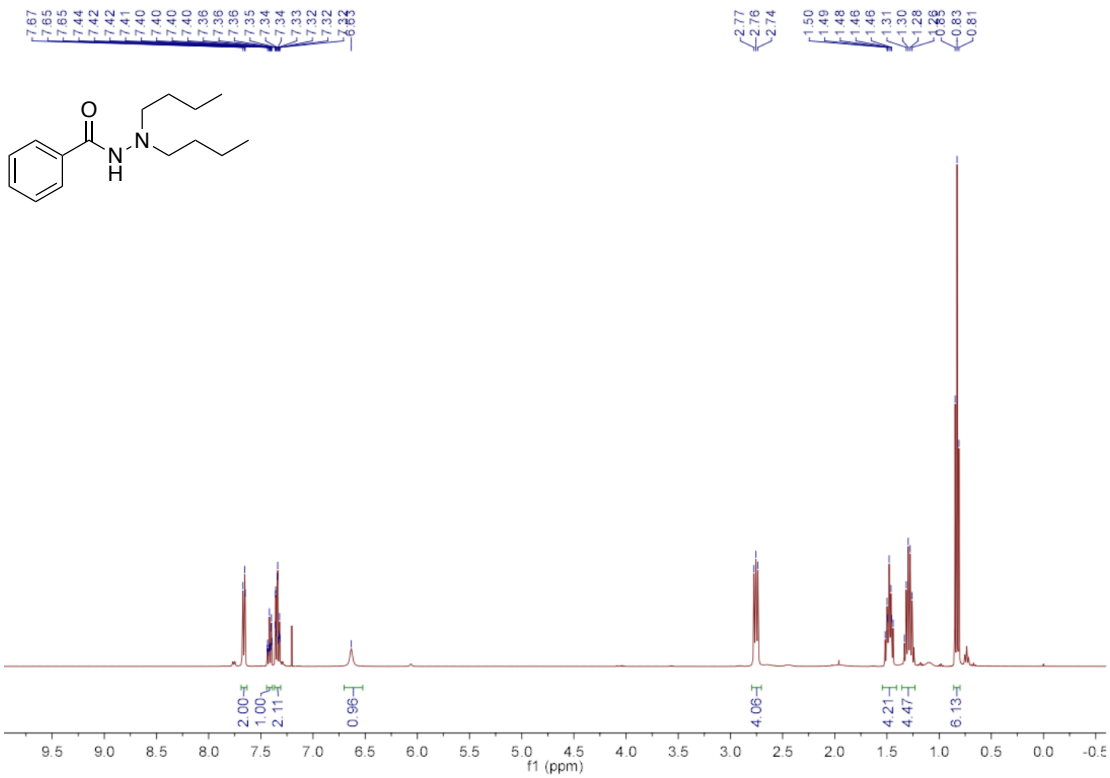


Figure 5.3 ^{13}C NMR spectrum of *N*',*N*'-Dibutylbenzohydrazide (**5.1b**):

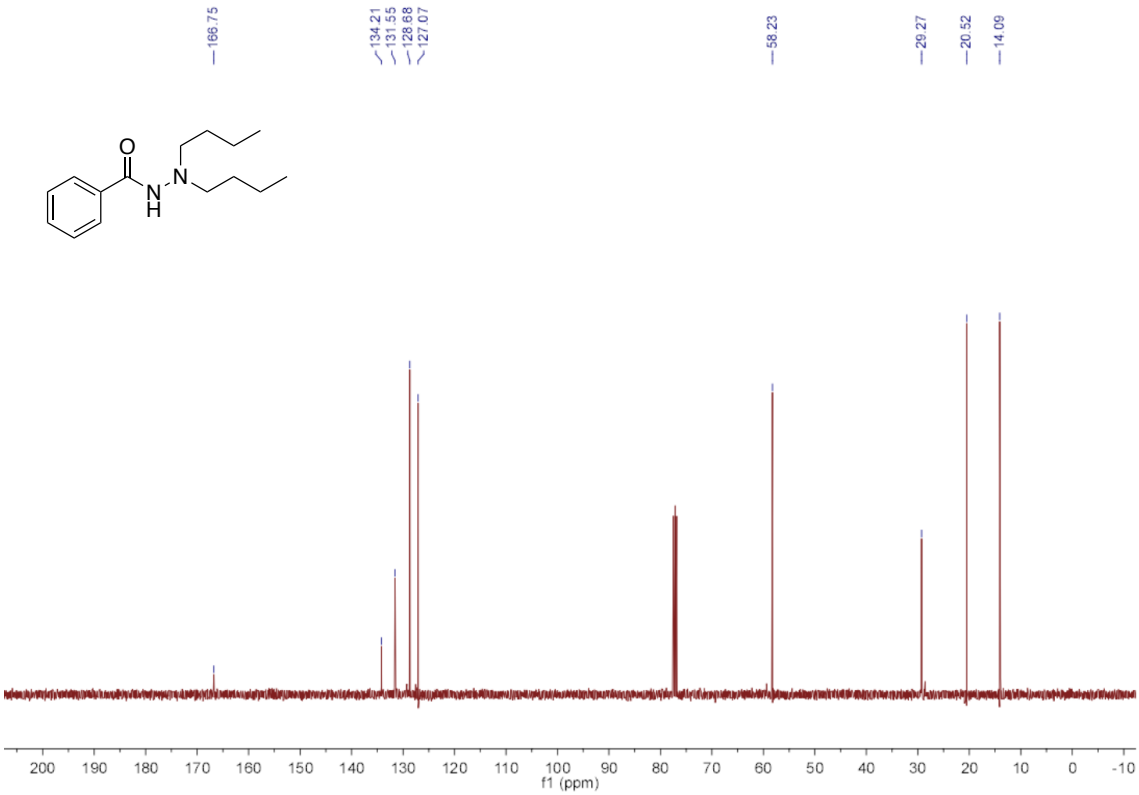


Figure 5.4 ^{1}H NMR spectrum of 4-(*tert*-butyl)-*N*'-ethyl-*N*'-(3,5,5-trimethylhexyl)benzohydrazide (**5.2f**):

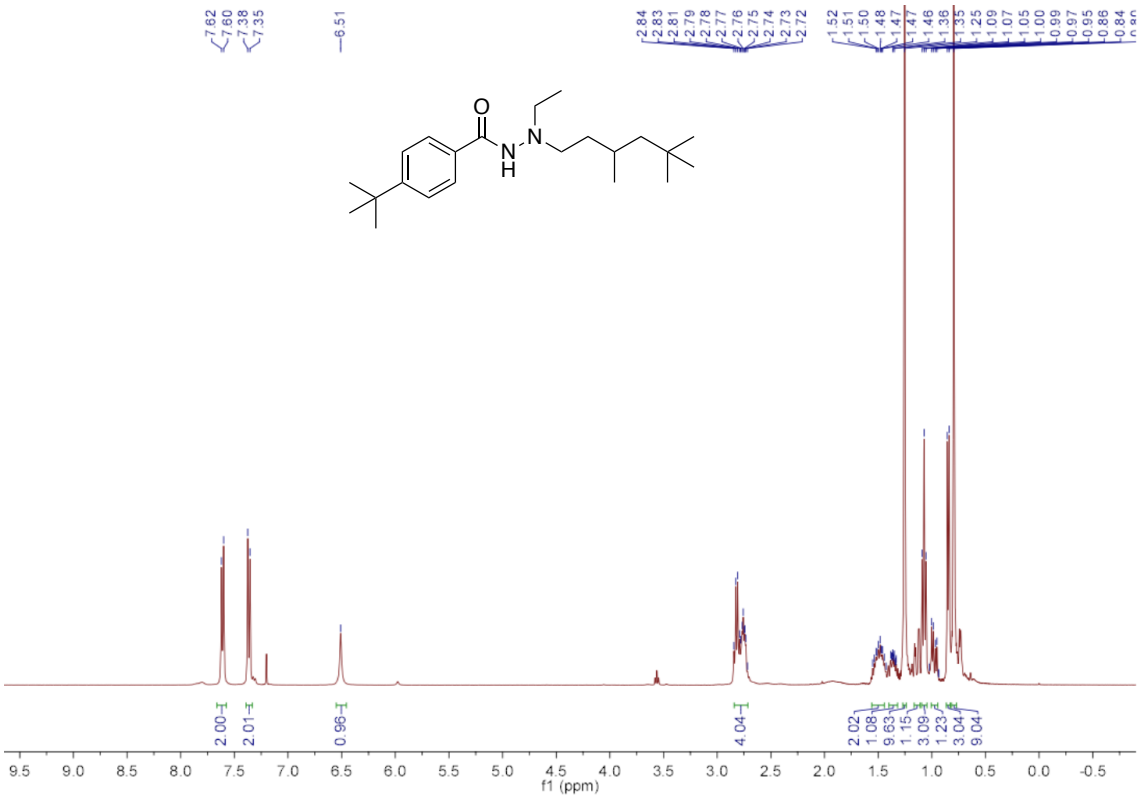


Figure 5.5 ^{13}C NMR spectrum of 4-(*tert*-butyl)-*N*'-ethyl-*N*'-(3,5,5-trimethylhexyl)benzohydrazide (**5.2f**):

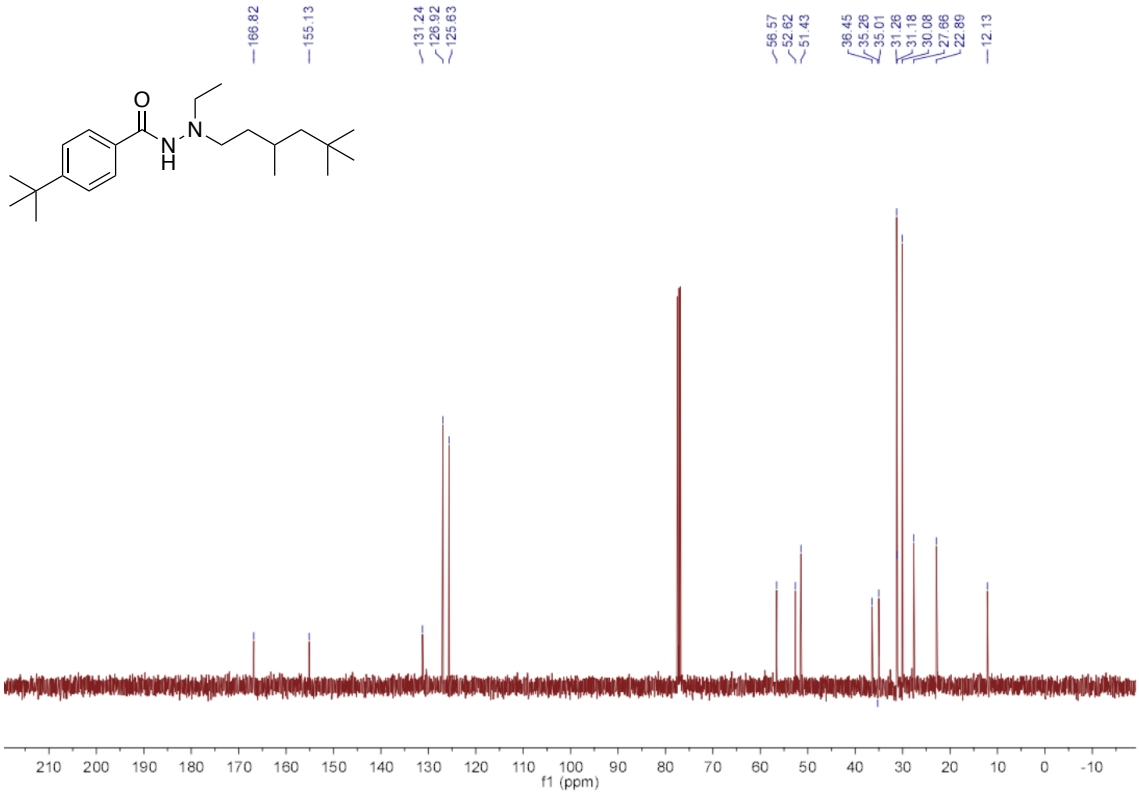


Figure 5.6 ^{1}H NMR spectrum of 4-methyl-*N*-(pyrrolidin-1-yl)benzamide (**5.3a**):

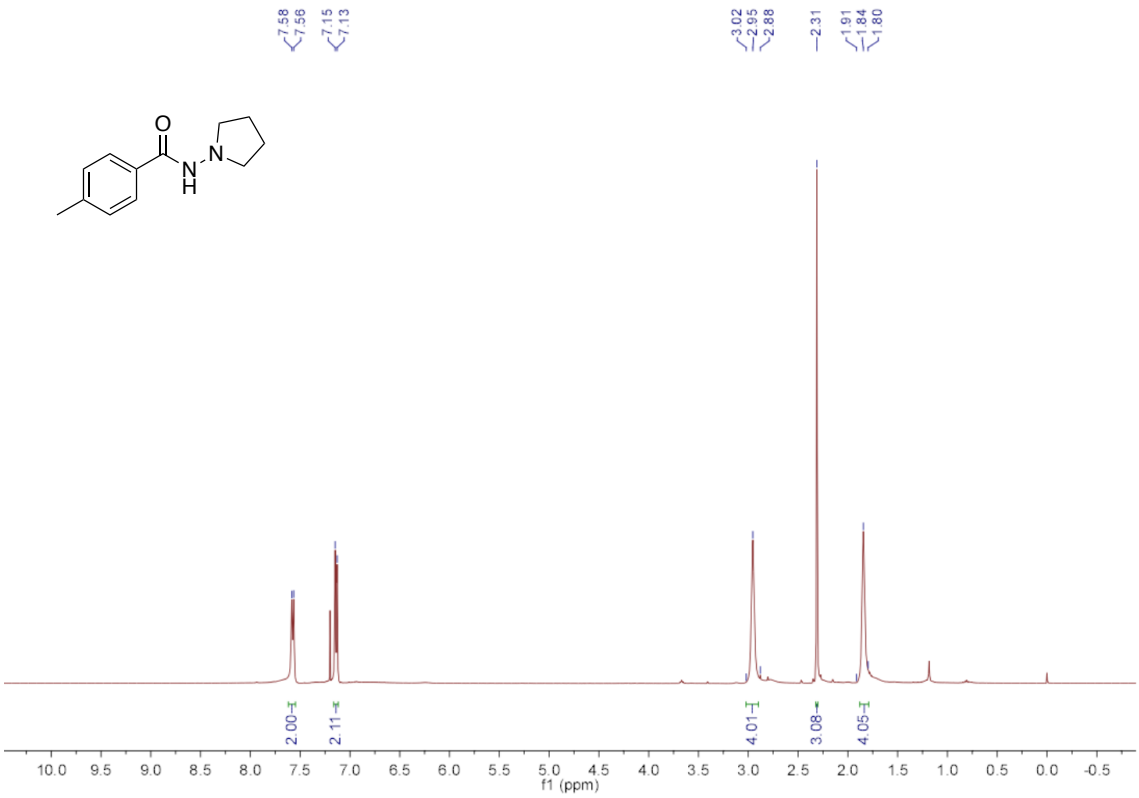


Figure 5.7 ^{13}C NMR spectrum of 4-methyl-*N*-(pyrrolidin-1-yl)benzamide (**5.3a**):

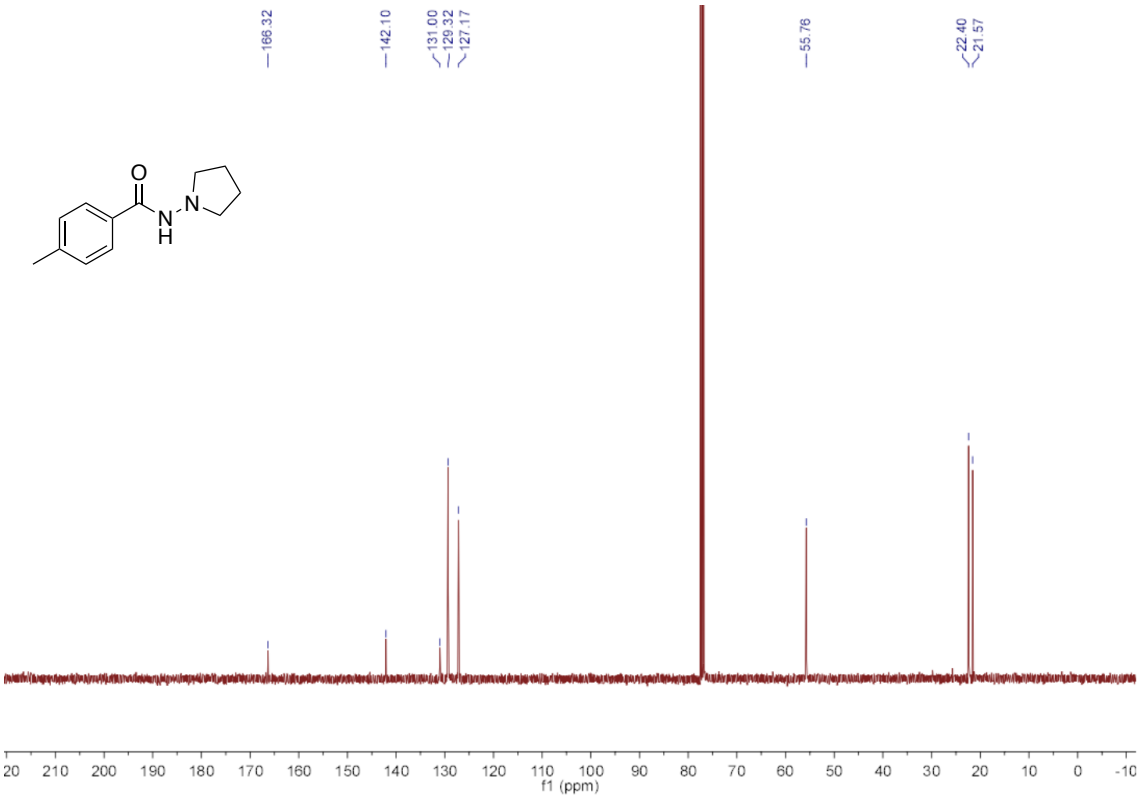


Figure 5.8 ^{1}H NMR spectrum of the product **5.4a**:

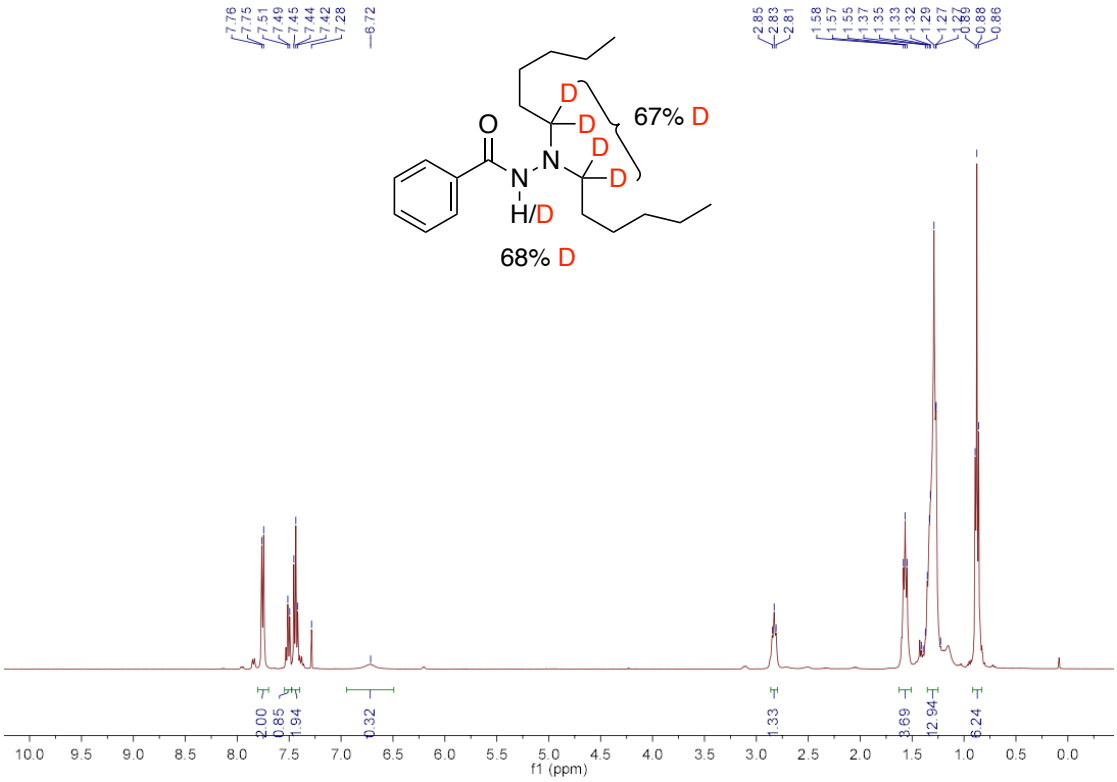
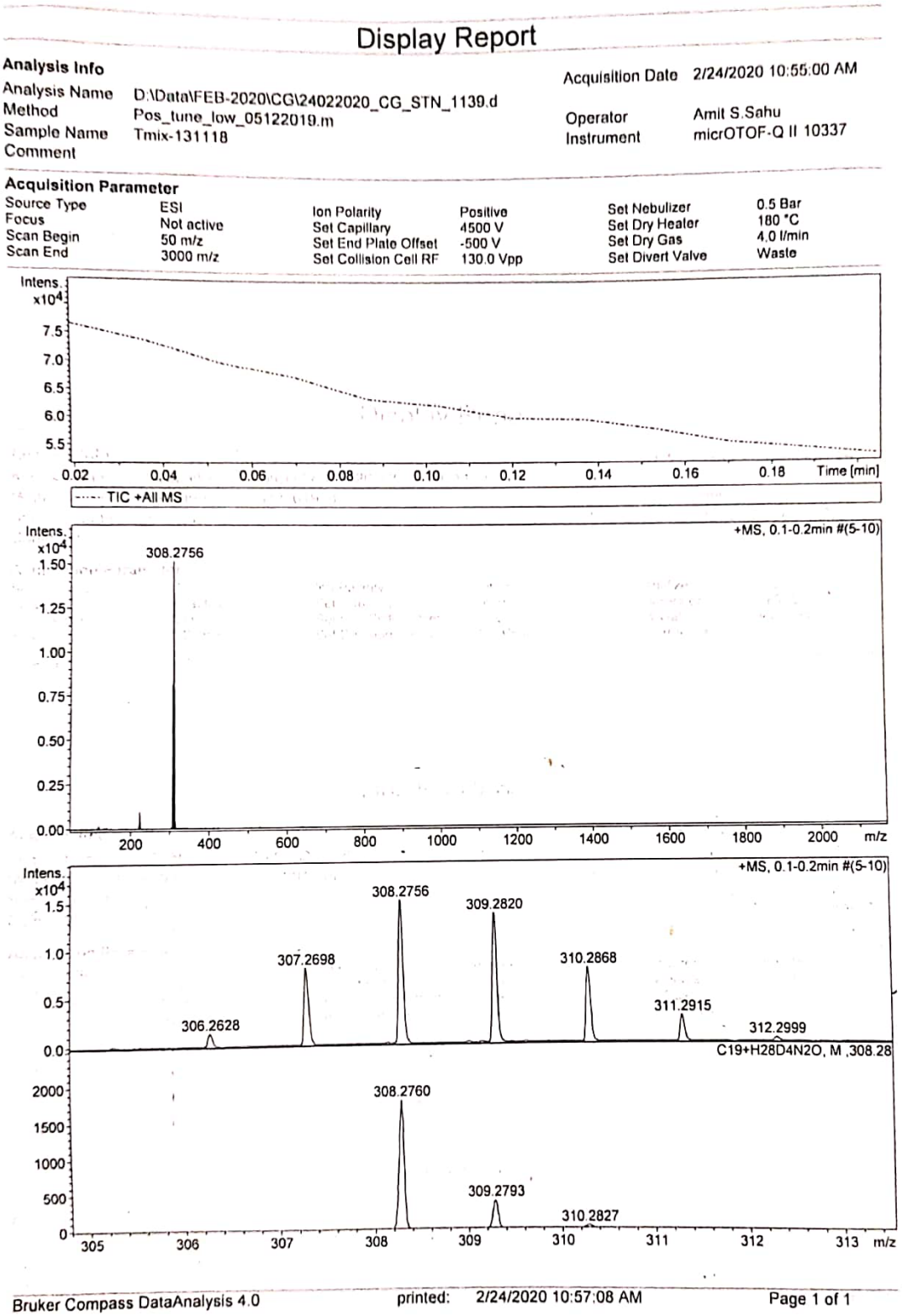


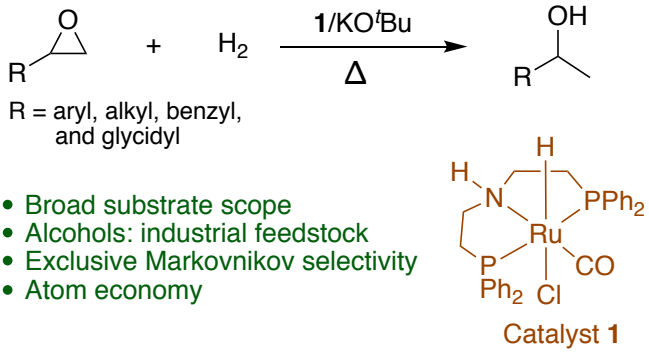
Figure 5.9 HRMS spectrum of the product **5.4a**:



CHAPTER 6

Ruthenium-Catalyzed Selective Hydrogenation of Epoxides to Secondary Alcohols

6.1 ABSTRACT



A ruthenium(II) catalyzed highly selective Markovnikov hydrogenation of terminal epoxides to secondary alcohols is reported. Diverse substitutions on aryl ring of styrene oxides are tolerated. Benzylic, glycidyl, aliphatic and diepoxides also underwent facile hydrogenation to provide secondary alcohols with exclusive selectivity. Metal-ligand cooperation mediated ruthenium trans-dihydride formation and its reaction involving oxygen and less substituted terminal carbon of epoxide is envisaged for the origin of observed selectivity.

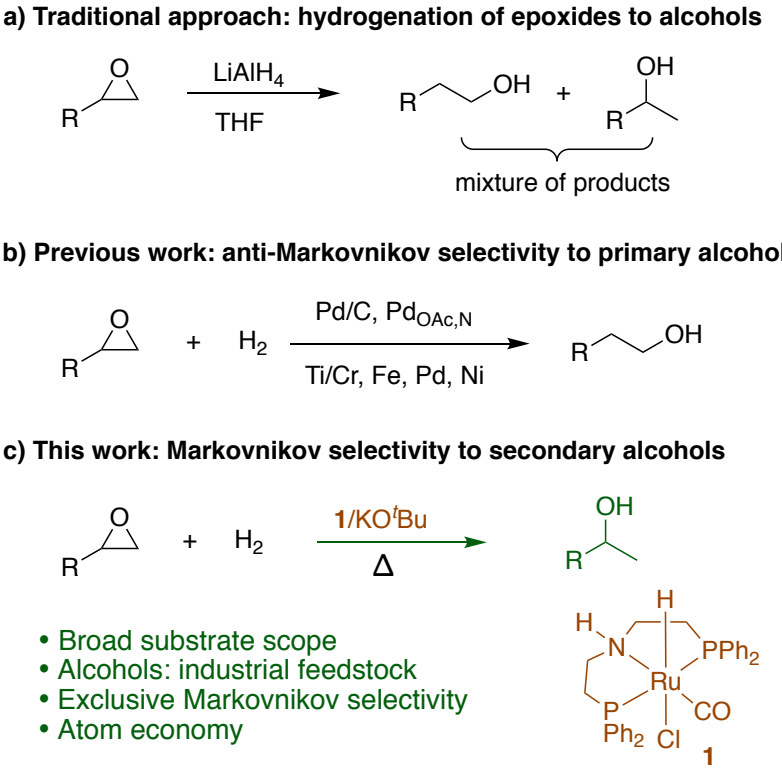
6.2 INTRODUCTION

Regioselective ring opening of epoxides to provide selectively one of the two isomeric products is an important transformation in medicinal chemistry and highly promising industrial process for the synthesis of alcohols.[1] Conventional methods for the epoxide hydrogenation reactions are mainly based on the use of stoichiometric amounts of strong reducing reagents such as $LiAlH_4$, which provide mixture of both primary and secondary alcohols (Scheme 6.1a).[2] The classical methods often failed to provide

satisfactory results and suffer from (i) requirement and safety issues on use of cryogenic condition (ii) difficulties associated with more reactive lithium base leading to mixture of alcohol products (iii) generation of copious reactive waste to the environment. Moreover, presence of sensitive functionalities limits the substrate scope. However, preparation of secondary alcohols directly from alkenes via acid catalyzed hydration reactions[3] and two-step Wacker oxidation of alkenes to ketones followed by reduction is also extensively studied in the literature.[4,5] Modern transition metal catalysis is an attractive and alternative method for the selective ring opening of epoxides.

During last two decades, heterogeneous and homogeneous catalyst systems have been developed for selective hydrogenation of epoxides to provide alcohols. Palladium heterogeneous catalyst (Pd/C) was extensively studied for the hydrogenolysis of epoxides to alcohols.[6] However, controlling regioselectivity of ring opening, and substrate scope have been less documented in heterogeneous catalysis. Thus, homogenous catalyzed reactions were developed for the selective ring opening of epoxides exploring the specific reactivity of transition metal complexes.[7,8] Hydroelementation (hydroboration and hydrosilylation) reactions are an alternative protocol for the selective ring opening of epoxides, which delivered the protected alcohols.[9,10]

Scheme 6.1 Traditional and Catalytic Approaches in Hydrogenation of Epoxides

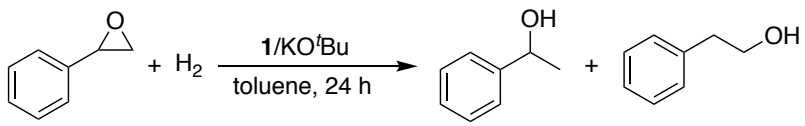


Very recently, the groups of Gansäuer, Norton and Beller have reported the anti-Markovnikov selective hydrogenation epoxides to primary alcohols.[11] Despite these enticing developments to attain anti-Markovnikov selective reactions, studies toward Markovnikov selective products remain limited in the literature.[6,7] Ikariya and coworkers have reported the pioneering ruthenium catalyzed Markovnikov hydrogenation of terminal epoxides.[8] However, the reported methods explored a narrow substrate scope and predominantly pertain to styrene oxides. Thus, developing a new protocol for the selective Markovnikov ring opening of epoxides is highly desirable. Recently, I have reported pincer Ru-MACHO (**1**) catalyzed cross-coupling of secondary alcohols,[12] synthesis of ketazines,[13] and α-olefination[14] and α-alkylation [15] of nitriles using alcohols. Herein, I present the highly selective Markovnikov hydrogenation of epoxides to secondary alcohols catalyzed by **1**.

6.3 RESULTS AND DISCUSSIONS

At the outset, styrene oxide (0.5 mmol), catalyst **1** (1 mol%), and base (2 mol%) in toluene solution was heated at 75 °C under hydrogen pressure (10 bar). Upon completion, GC and ^{1}H NMR analyses of the reaction mixture indicated 40% conversion of styrene oxide and formation of both isomers of alcohols 80:20 (branched: linear, entry 1, Table 6.1). This result implies predominant formation of secondary alcohol in our catalytic conditions. Increasing hydrogen pressure to 30 bar resulted in higher conversion and yield (78% and 76%, respectively) and provided increased selectivity for secondary alcohol (92:8, entry 2, Table 6.1). Upon increasing hydrogen pressure to 50 bar under similar catalytic conditions resulted in quantitative conversion of styrene oxide and alcohols were isolated in 99% yield with very good selectivity for secondary alcohol (94:6, entry 3, Table 6.1). Further, varying temperature and reducing catalyst load were found to be less effective on catalysis (entries 4-6, Table 6.1). No product formation was observed by employing only base, and without catalyst and base (entries 7,8, Table 6.1). These results clearly indicated that catalyst **1** and base are playing a crucial role in promoting selective ring opening of epoxides.

Table 6.1 Optimization for Regioselective Hydrogenation of Styrene Oxide Catalyzed by 1[a]



6.1a **6.1b**

entry	H_2 (bar)	temp (°C)	conv (%)[b]	yield (%)[c]	ratio 6.1a:6.1b[d]
1	10	75	40	38	80:20
2	30	75	78	76	92:8

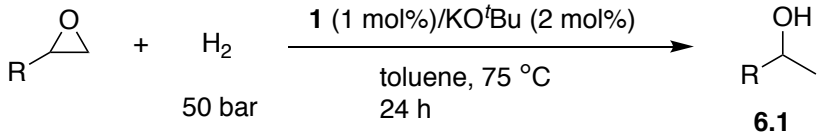
3	50	75	>99	99	94:6
4	50	100	>99	98	90:10
5	50	50	30	28	>99:<1
6[e]	50	75	60	54	>99:<1
7[f]	50	75	-	-	-
8[g]	50	75	-	-	-
9[h]	50	75	>99	97	94:6

[a]Reaction conditions: styrene oxide (0.5 mmol), catalyst **1** (1 mol%) and KO^{t}Bu (2 mol%) and toluene (1.5 mL), heated at indicated temperature under H_2 pressure. [b]Conversion of styrene oxide was determined by GC analysis using benzene as an internal standard. [c]Yields were calculated for isolated mixture of products 6.1a and 6.1b after column chromatography. [d]Alcohols ratio was determined from ^{1}H NMR analysis of the reaction mixture. [e]0.5 mol% catalyst **1** was used. [f]Only 5 mol% of KO^{t}Bu was used. [g]Reaction was performed without catalyst and base. [h]Reaction was performed in 1 mmol scale.

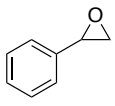
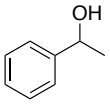
As the optimal reaction condition was attained, the substrate scope of epoxides was investigated (Table 6.2). Remarkably, except four substrates (see below) all other terminal epoxides subjected to catalysis exhibited complete regioselectivity for Markovnikov hydrogenation and delivered only secondary alcohols. Presence of electron donating and halogen substitutions on the aromatic ring of epoxide was very well tolerated. 4-Methylstyrene oxide afforded 90% conversion with 72% yield of **6.1c** while 10% of corresponding primary alcohol was also isolated (entry 2, Table 6.2). 4-*tert*-Butylstyrene oxide provided only 28% conversion, however, with exclusive regioselectivity for secondary alcohol under the optimized condition. With increased

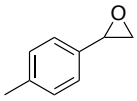
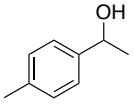
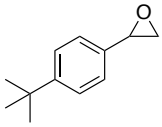
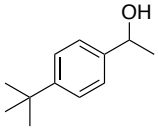
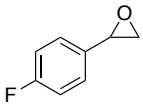
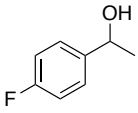
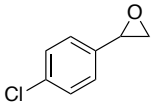
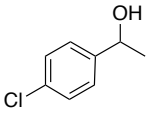
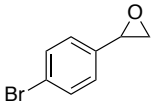
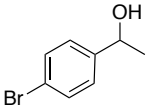
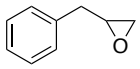
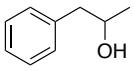
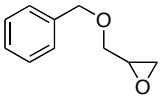
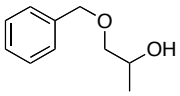
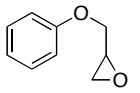
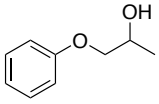
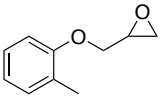
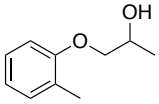
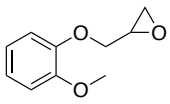
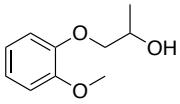
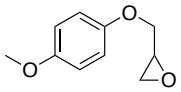
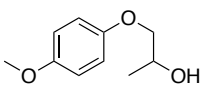
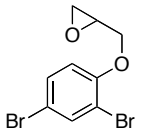
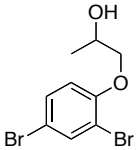
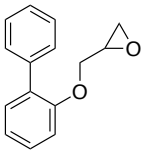
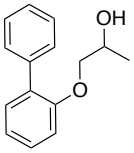
catalyst load and temperature (3 mol% and 100 °C), 75% conversion was observed in which 42% and 26% of secondary and primary alcohols were isolated, respectively (entry 3, Table 6.2). Gratifyingly, electron-withdrawing group containing styrene oxides provided excellent selectivity with moderate to excellent yields (entries 4-6, Table 6.2). 2-Benzyloxirane provided high yield and exclusive selectivity for secondary alcohol (entry 7, Table 6.2). Notably, the palladium catalyzed hydrogenation of 2-benzyloxirane under heterogeneous conditions provided mixture of both primary and secondary alcohols.[6b] Further, a variety of aromatic and aliphatic glycidyl terminal epoxides were tested, which resulted in very good yields of secondary alcohols with exclusive selectivity (entries 8-14, Table 6.2). Unactivated aliphatic epoxides were subjected with increased catalyst load (5 mol%) and base (10 mol%) in which most of the substrates provided quantitative conversion and the products were isolated in good to excellent yields (entries 15-19, Table 6.2). However, under similar condition when 1,1-disubstituted epoxide 2-methyl-2-phenyloxirane was subjected to hydrogenation, the formation of mixture of both isomeric alcohols was observed in the reaction mixture (branched: linear, 50:49, entry 20, Table 6.2).

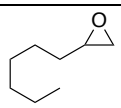
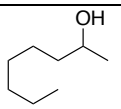
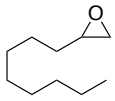
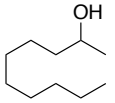
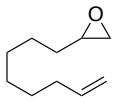
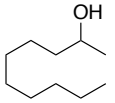
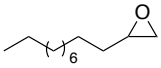
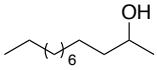
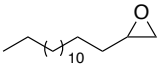
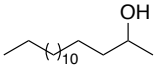
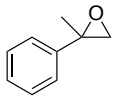
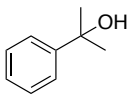
Table 6.2 Scope of Regioselective Hydrogenation of Terminal Epoxides Catalyzed by 1[a]



6.1

entry	epoxide	product		conv (%)[b]	yield (%)[c]
1[d]			**6.1a**	>99	99

2[e]			**6.1c**	90	72
3[f,g]			**6.1d**	75	42
4[g]			**6.1e**	>99	96
5[g]			**6.1f**	41	40
6[g]			**6.1g**	41	37
7[g]			**6.1h**	>99	95
8			**6.1i**	>99	98
9			**6.1j**	>99	98
10			**6.1k**	>99	97
11			**6.1l**	73	67
12			**6.1m**	>99	97
13			**6.1n**	67	65
14			**6.1o**	>99	98

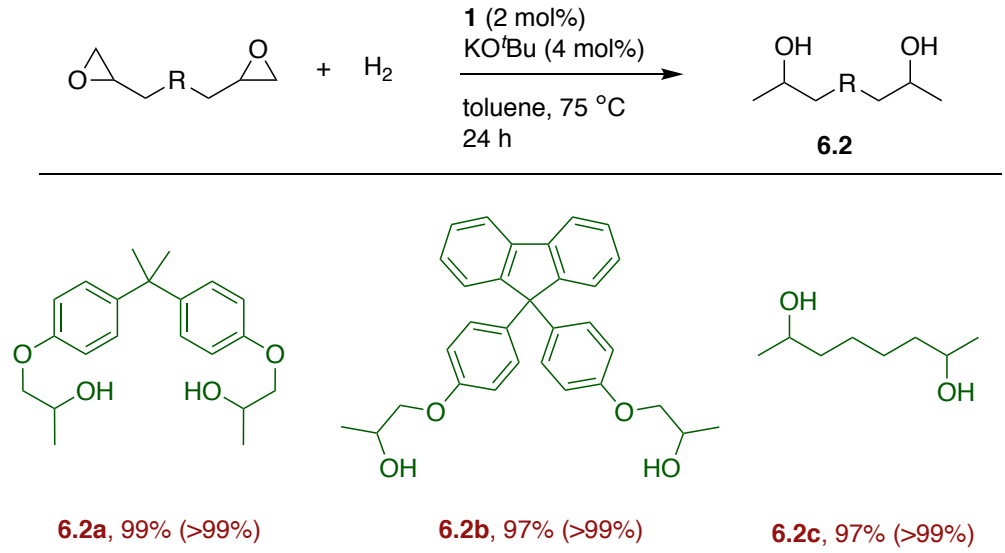
15[h]			**6.1p**	>99	98
16[h]			**6.1q**	>99	99
17[h]			**6.1q**	>99	99
18[h]			**6.1r**	>99	98
19[h]			**6.1s**	67	62
20[h,i]			**6.1t**	>99	46

[a]Reaction conditions: epoxide (0.5 mmol), catalyst **1** (1 mol%) and KO^{t}Bu (2 mol%) and toluene (1.5 mL) were heated at 75 °C under 50 bar H_2 pressure for 24 h. [b]Conversion of epoxides determined by GC analysis using benzene as an internal standard. [c]Reported yields correspond to isolated pure compounds. [d]Isolated as a mixture of 6.1a and 6.1b (94:6). [e]10% of primary alcohol is isolated. [f]26% of primary alcohol isolated. [g]Reaction was performed using 3 mol% of catalyst and 6 mol% of base at 100 °C. [h]Reaction was performed using 5 mol% of catalyst **1** and 10 mol% of base at 100 °C. [i]42% of primary alcohol was isolated.

To further expand the scope of the protocol, I turned our attention to diepoxides. Interestingly, aromatic and aliphatic diepoxides provided quantitative conversion and yield with complete formation of the corresponding secondary diols (Scheme 6.2). The products are isolated as mesomers due to presence of C_2 symmetry. In contrast to

previous reports the exclusive regioselectivity to secondary alcohols make this process a new green alternative for the synthesis of diols.[6]

Scheme 6.2 Scope of Regioselective Hydrogenation of Terminal Diepoxides Catalyzed by 1[a]

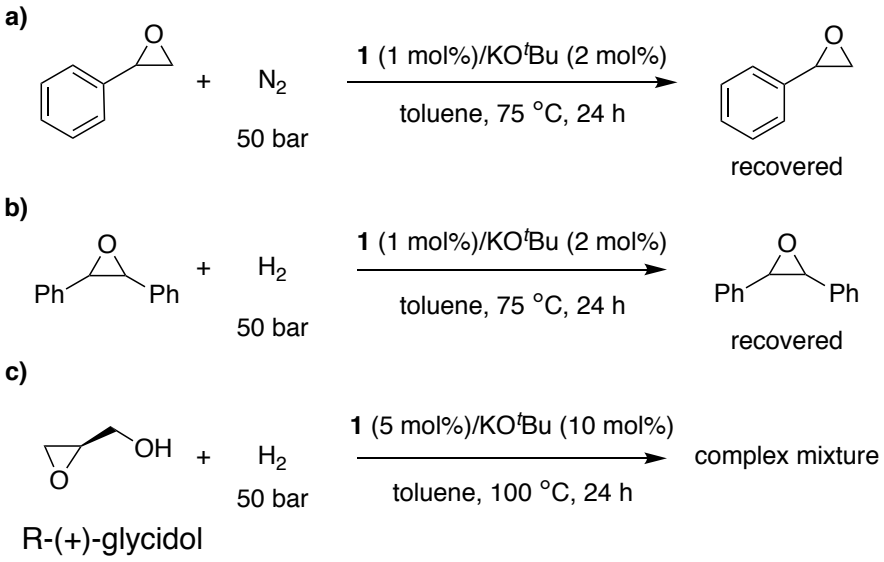


[a]Reaction conditions: diepoxide (0.5 mmol), catalyst **1** (2 mol%) and KO^{t}Bu (4 mol%) and toluene (1.5 mL) were heated at 75 °C under 50 bar H_2 pressure for 24 h. Conversion of diepoxides determined by GC analysis using benzene as an internal standard is given within parentheses. Reported yields correspond to isolated pure compound. [b]Reaction was performed using 10 mol% of catalyst and 20 mol% of base at 100 °C.

Towards understanding the reaction mechanism, reaction with N_2 gas (50 bar) was performed (devoid of hydrogen) in which no epoxide ring opening was occurred (Scheme 6.3a). The absence of isomerization of epoxide to ketone confirms the reaction do not proceed via Meinwald rearrangement.[16] This result indicates the importance of H_2 gas in the initial formation of ruthenium dihydride intermediate **II** and its role in the selective epoxide ring opening reactions. Notably, internal epoxides did not undergo

ring opening under the optimized reaction conditions (Scheme 6.3b). An enantiopure chiral epoxide R-(+)-glycidol was subjected in our catalysis, which provided a complex mixture (Scheme 6.3c).

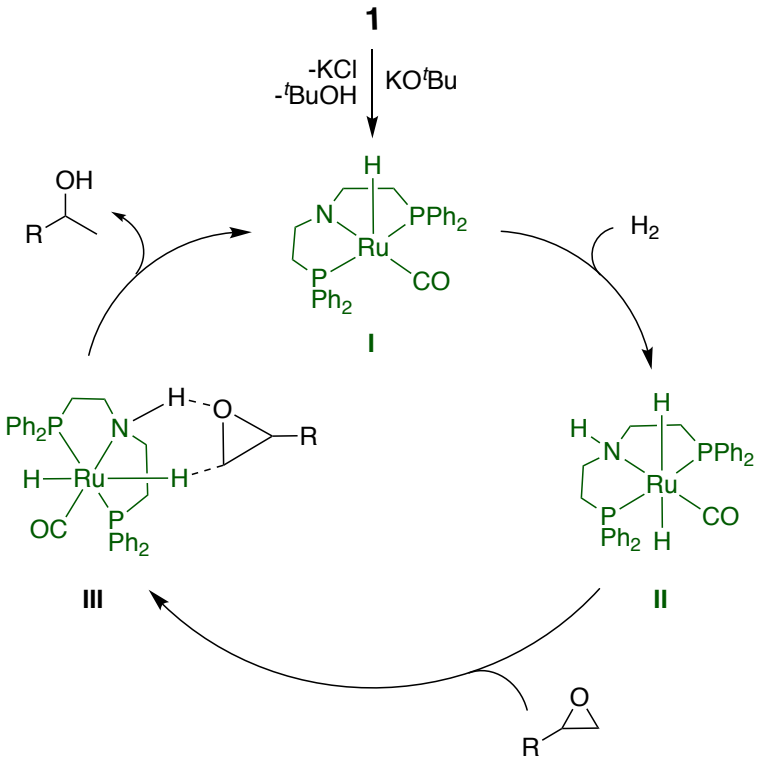
Scheme 6.3 Mechanistic Studies for the Hydrogenation of Terminal Epoxides Catalyzed by 1



On the basis of these experimental observations and our previous reports[12-15,17] involving catalyst **1**, a catalytic cycle for regioselective ring opening of epoxides to secondary alcohols is proposed (Scheme 6.4). The catalyst **1** in the presence of base is converted into reactive unsaturated intermediate **I**.[17b,18] Heterolytic activation of H_2 by **I** involving amine-amide metal-ligand cooperation leads to the formation of saturated ruthenium dihydride intermediate **II**.[19] Perhaps the formation of intermediate **III** upon reaction of **II** with epoxide preferably involves less substituted carbon and oxygen centers of terminal epoxide. Hydrogen pressure is also plays important role in the conversion of epoxide as well as product selectivity. At 10 bar hydrogen pressure, only 40% conversion of epoxide occurred, in which the considerable amount of anti-Markovnikov primary alcohol was formed in 20% (Table 6.1, entry 1) indicating the

involvement of other mechanistic pathways at low pressure. Whereas use of 50 bar hydrogen pressure provided the complete conversion and very high selectivity for the Markovnikov secondary alcohols (Table 6.1, entries 3,9 and Table 6.2) indicating that the high hydrogen pressure is essential for the effective formation of ruthenium dihydride intermediate **II** and its further selective reaction with epoxide. Notably, internal epoxide failed to undergo ring opening when subjected to catalysis (Scheme 6.2b). Thus, preferential approach of metal hydride to less substituted terminal carbon of epoxide, precluding the internal tertiary carbon and interaction of acidic amine proton to epoxide oxygen leads to the selective formation of intermediate **III**. On **III**, metal-hydride and amine proton are concomitantly transferred to epoxide through a six-membered cyclic transition state, resulting in the selective formation of secondary alcohol and regeneration of active intermediate **I** to complete a catalytic cycle.

Scheme 6.4 Plausible Mechanism for the Selective Hydrogenation of Epoxides Catalyzed by 1



6.4 CONCLUSIONS

In conclusion, a ruthenium catalyzed highly Markovnikov selective hydrogenation of epoxides is demonstrated. The catalyst exhibits superior reactivity to control regioselectivity with a wide substrate scope. Diverse aromatic, benzylic, glycidyl, aliphatic terminal epoxides and also diepoxides were well tolerated to provide secondary alcohol products in good to excellent yields. Interestingly, this transformation contrasts the recently reported catalytic anti-Markovnikov selective hydrogenation of epoxides and compliments the efficient and selective synthesis of secondary alcohols from epoxides.[11] Metal-ligand cooperation mediated dihydrogen activation to ruthenium trans-dihydride formation and its preferential reaction with oxygen and less substituted terminal carbon of epoxide is suggested to be the origin of observed Markovnikov selectivity. Concomitant transfer of amine proton and metal-hydride to epoxide through a six-membered cyclic transition state is proposed to provide the selective formation of secondary alcohols. Synthetic utilities of such mechanistic pathway are currently under investigation.

6.5 EXPERIMENTAL SECTION

General Experimental: All catalytic reactions were performed in H_2 atmosphere using Buchi tinyclave steel vessel with a Teflon sleeve (25 mL) high-pressure reactors. All stoichiometric reactions were performed in nitrogen atmosphere MBRAUN glove box. Ru-MACHO **[Carbonylchlorohydrido{bis[2-(diphenylphosphinomethyl)ethyl]amino}ethyl]amino} ruthenium(II)]** and KO^{t}Bu were purchased from Sigma-Aldrich and stored inside glove box. Epoxides were purchased from Acros, Sigma-Aldrich, Alfa-aesar, TCI chemicals and used without further purification. Epoxides required for the secondary alcohol products **6.1c**, **6.1d** and **6.1t** were prepared by epoxidation of corresponding alkenes using *m*-CPBA.[11b] Dry

solvents were prepared according to standard procedures. Infrared (IR) spectra were recorded in Perkin-Elmer FT-IR and Thermo-Nicolet FT-IR spectrophotometers. Mass spectra (ESI-MS) were obtained on Bruker micrOTOF-Q II Spectrometer and are reported as m/z (relative intensity). Nuclear magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded at Bruker AV-400 and JEOL-400 (^{1}H at 400 MHz, ^{13}C at 100.6 MHz). ^{1}H NMR chemical shifts are referenced in parts per million (ppm) with respect to tetramethyl silane (TMS) (δ 0.00 ppm) and ^{13}C {^{1}H} NMR chemical shifts are referenced in parts per million (ppm) with respect to $CDCl_3$ (δ 77.160 ppm). Coupling constants are reported in Hertz (Hz). ^{1}H NMR spectroscopy abbreviations: s, Singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; dt, doublet of triplets; dq, doublet of quartets; td, triplet of doublets; qd, quartets of doublets; ddd, doublets of doublets of doublets; m, multiplet; br, broad. Assignment of spectra was done based on one-dimensional (DEPT-135) NMR techniques.

GC Method: Gas chromatography data were obtained using a gas chromatograph equipped with a SH-Rtx-1 capillary column (30 m × 250 μm). The instrument was set to an injection volume of 1 μL, an inlet split ratio of 10:1, and inlet and detector temperatures of 300 and 330 °C, respectively. The temperature program used for all of the analyses is as follows: 50 °C, 1 min; 12 °C/min to 320 °C, 7 min. Response factor for all of the necessary compounds with respect to standard benzene was calculated from the average of three independent GC runs.

General Optimization Procedure for Regioselective Hydrogenation of Styrene Oxide:

A Buchi tinyclave steel high-pressure reactor containing a Teflon sleeve (25 mL) was equipped with a stirring bar, catalyst **1** (0.01-0.005 mmol), base (0.02-0.01 mmol), styrene oxide (0.5 mmol) and toluene (1.5 mL) under nitrogen atmosphere inside the

glove box. The pressure reactor was taken out of the glove box, charged with H_2 and heated at indicated temperature (using preheated oil bath) with stirring for 24 h. After cooling to room temperature, the H_2 pressure was released. Benzene internal standard (0.5 mmol) was added into the reaction mixture. The conversion of styrene oxide was calculated using GC analysis. Further, the solvent was evaporated and crude reaction mixture was purified by column chromatography over silica-gel (100-200 mesh) using ethyl acetate/hexane mixture as an eluent. Yields were calculated for isolated pure products of **6.1a** and **6.1b**.

Procedure for 1 mmol Scale Reaction of Regioselective Hydrogenation of Styrene Oxide:

A Buchi tinyclave steel high-pressure reactor containing a Teflon sleeve (25 mL) was equipped with a stirring bar, catalyst **1** (0.01 mmol), base (0.02 mmol), styrene oxide (1 mmol) and toluene (1.5 mL) under nitrogen atmosphere inside the glove box. The pressure reactor was taken out of the glove box, charged with H_2 (50 bar) and heated at indicated temperature (using preheated oil bath) with stirring for 24 h. After cooling to room temperature, the H_2 pressure was released. Benzene internal standard (1 mmol) was added into the reaction mixture. The conversion of styrene oxide was calculated using GC analysis. Further, the solvent was evaporated and crude reaction mixture was purified by column chromatography over silica-gel (100-200 mesh) using ethyl acetate/hexane mixture as an eluent. The reaction provided a complete conversion of styrene oxide and 97 % yield isolated as the mixtures **6.1a** and **6.1b** (94:6 selectivity).

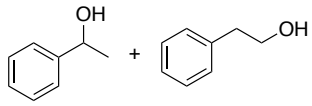
General Procedure for Regioselective Hydrogenation of Epoxides:

A Buchi tinyclave steel high-pressure reactor containing a Teflon sleeve (25 mL) was equipped with a stirring bar, catalyst **1** (0.01 mmol), base (0.02 mmol), epoxide (0.5 mmol) and toluene (1.5 mL) under nitrogen atmosphere inside the glove box. The

pressure reactor was taken out of the glove box, charged with H_2 gas (50 bar) and heated at 75 °C (using preheated oil bath) with stirring for 24 h. After cooling to room temperature, the H_2 pressure was released. Benzene internal standard (0.5 mmol) was added into the reaction mixture. The conversion of epoxides was calculated using GC analysis. Further, the solvent was evaporated and crude reaction mixture was purified by column chromatography over silica-gel (100-200 mesh) using ethyl acetate/hexane mixture as an eluent. Yields were calculated for isolated pure products.

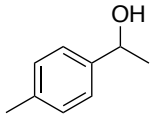
Spectral Data of the Secondary Alcohol Products:

1-Phenylethan-1-ol (6.1a):[20] Purified by silica gel column chromatography using ethyl acetate/hexane (20:80) mixture as an eluent. Colorless liquid. Isolated as a mixture of isomers **6.1a** and **6.1b**, ca. 96:4 ratio. Yield: 60 mg, 99% (for 0.5 mmol scale) and 118 mg, 97% (for 1 mmol scale). IR (DCM): 3413, 3054, 2976, 1452, 1265, 896, 745 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.14-7.26 (m, 5H, ArC*H*), 4.74 (q, *J* = 6.4 Hz, 1H, C*H*-isomer-A), 3.69 (t, *J* = 6.6 Hz, 2H, CH_2-isomer-B), 2.72 (t, *J* = 6.7 Hz, 2H, CH_2- isomer-B), 2.39 (s, 1H, O*H*), 1.36 (d, *J* = 6.5 Hz, 3H, CH_3-isomer-A). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 145.87, 128.47, 127.41, 125.42, 70.29, 63.56, 39.15, 25.15. MS (ESI) m/z calcd for $C_8H_{10}O$ $(M+H)^+$: 123.08, found: 123.08.



6.1a 6.1b

1-(*p*-Tolyl)ethan-1-ol (6.1c):[20] Purified by silica gel column chromatography using ethyl acetate/hexane (20:80) mixture as an eluent. Colorless liquid. Yield: 49 mg, 72%. IR (DCM): 3506, 3026, 2921, 1495, 1217, 911, 729 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.14 (d, *J* = 7.9 Hz, 2H, ArC*H*), 7.04 (d, *J* = 7.8 Hz, 2H, ArC*H*), 4.71 (q, *J* = 6.2 Hz, 1H, C*H*), 2.24 (s, 4H, Ar-CH_3 & O*H*), 1.35 (d, *J* = 6.4 Hz, 3H, CH_3). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 142.98, 137.08, 129.17, 125.44, 70.18, 25.11, 21.13. MS (ESI) m/z calcd for $C_9H_{12}O$ $(M+H)^+$: 137.09, found: 137.09.

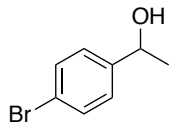


1-(4-(*tert*-Butyl)phenyl)ethan-1-ol (6.1d):[20] Purified by silica gel column chromatography using ethyl acetate/hexane (20:80) mixture as an eluent. Colorless liquid. Yield: 37.4 mg, 42%. IR (DCM): 3419, 3053, 2965, 1265, 1086, 741 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.28-7.33 (m, 2H, ArC*H*), 7.21-7.26 (m, 2H, ArC*H*), 4.80 (q, *J* = 6.5 Hz, 1H, C*H*), 1.83 (s, 1H, O*H*), 1.42 (d, *J* = 6.5 Hz, 3H, CH_3), 1.25 (s, 9H, 3×CH_3). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 150.59, 142.89, 125.54, 125.30, 70.32, 34.63, 31.48, 25.03. MS (ESI) m/z calcd for $C_{12}H_{18}O$ $(M+H)^+$: 179.14, found: 179.14.

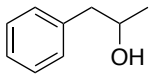
1-(4-Fluorophenyl)ethan-1-ol (6.1e):[20] Purified by silica gel column chromatography using ethyl acetate/hexane (20:80) mixture as an eluent. Colorless liquid. Yield: 67 mg, 96%. IR (DCM): 3425, 3052, 2963, 2905, 1259, 1089, 801, 746 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.22 (dd, J_1 = 7.8 Hz, J_2 = 5.8 Hz, 2H, ArC*H*), 6.92 (t, *J* = 8.6 Hz, 2H, ArC*H*), 4.76 (q, *J* = 6.4 Hz, 1H, C*H*), 2.21 (s, 1H, O*H*), 1.36 (d, *J* = 6.4 Hz, 3H, CH_3). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 163.41, 160.98, 141.64 (d, *J* = 3.1 Hz), 127.15 (d, *J* = 8.0 Hz), 115.31 (d, *J* = 21.3 Hz), 69.80, 25.33. MS (ESI) m/z calcd for C_8H_9FO $(M+H)^+$: 141.07, found: 141.07.

1-(4-Chlorophenyl)ethan-1-ol (6.1f):[20] Purified by silica gel column chromatography using ethyl acetate/hexane (20:80) mixture as an eluent. Colorless liquid. Yield: 31 mg, 40%. IR (DCM): 3446, 3053, 2985, 1492, 1265, 742, 735 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.18 (q, *J* = 8.3 Hz, 4H, ArC*H*), 4.72 (q, *J* = 6.4 Hz, 1H, C*H*), 2.39 (s, 1H, O*H*), 1.34 (d, *J* = 6.4 Hz, 3H, CH_3). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 144.33, 133.06, 128.63, 126.88, 69.70, 25.27. MS (ESI) m/z calcd for C_8H_9ClO $(M+H)^+$: 157.04, found: 157.04.

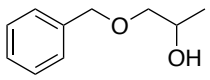
1-(4-Bromophenyl)ethan-1-ol (6.1g):[20] Purified by silica gel column chromatography using ethyl acetate/hexane (20:80) mixture as an eluent. Colorless liquid. Yield: 37 mg,

37%. IR (DCM): 3413, 3053, 2968, 2932, 1435, 1376, 1265, 746 cm^{-1}. 

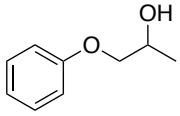
^1H NMR (400 MHz, $CDCl_3$): δ 7.34 (d, J = 8.0 Hz, 2H, ArC*H*), 7.10 (d, J = 8.1 Hz, 2H, ArC*H*), 4.70 (dd, J_1 = 11.0 Hz, J_2 = 4.7 Hz, 1H, C*H*), 2.48 (s, 1H, O*H*), 1.32 (d, J = 6.4 Hz, 3H, CH_3). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 144.78, 131.51, 127.19, 121.09, 69.65, 25.18. MS (ESI) m/z calcd for C_8H_9BrO $(M+H)^+$: 200.99, found: 200.99.

1-Phenylpropan-2-ol (6.1h):[6c] Purified by silica gel column chromatography using ethyl acetate/hexane (20:80) mixture as an eluent. Colorless liquid. Yield: 64.6 mg, 95%. IR (DCM): 3372, 3061, 2967, 2928, 1452, 1120, 741 cm^{-1}. 

^1H NMR (400 MHz, $CDCl_3$): δ 7.19-7.23 (m, 2H, ArC*H*), 7.10-7.15 (m, 3H, ArC*H*), 3.90 (ddd, J_1 = 7.7 Hz, J_2 = 6.2 Hz, J_3 = 5.1 Hz, 1H, C*H*), 2.63 (qd, J_1 = 13.4 Hz, J_2 = 6.4 Hz, 2H, CH_2), 1.81 (s, 1H, O*H*), 1.13 (d, J = 6.2 Hz, 3H, CH_3). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 138.65, 129.48, 128.58, 126.50, 68.91, 45.82, 22.80. MS (ESI) m/z calcd for $C_9H_{12}O$ $(M+H)^+$: 137.09, found: 137.09.

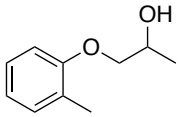
1-(Benzyloxy)propan-2-ol (6.1i):[10a] Purified by silica gel column chromatography using ethyl acetate/hexane (20:80) mixture as an eluent. Colorless liquid. Yield: 81 mg, 98%. IR (DCM): 3446, 3053, 2973, 2863, 1453, 1265, 1096, 743 cm^{-1}. 

^1H NMR (400 MHz, $CDCl_3$): δ 7.18-7.28 (m, 5H, ArC*H*), 4.45 (s, 2H, CH_2), 3.87-3.91 (s, 1H, C*H*), 3.35 (dd, J_1 = 9.4 Hz, J_2 = 3.2 Hz, 1H, CH_2), 3.19 (dd, J_1 = 9.4 Hz, J_2 = 8.0 Hz, 1H, CH_2), 2.69 (s, 1H, O*H*), 1.04 (d, J = 6.4 Hz, 3H, CH_3). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 138.01, 128.47, 127.78, 75.85, 73.28, 66.45, 18.73. MS (ESI) m/z calcd for $C_{10}H_{14}O_2$ $(M+H)^+$: 167.10, found: 167.10.

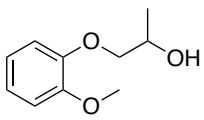
1-Phenoxypropan-2-ol (6.1j):[6c] Purified by silica gel column chromatography using ethyl acetate/hexane (20:80) mixture as an eluent. Colorless liquid. Yield: 74.5 mg, 98%. IR (DCM): 3392, 3054, 2937, 2856, 1447, 1265, 

895, 747 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.19 (t, *J* = 7.8 Hz, 2H, ArC*H*), 6.87 (t, *J* = 7.3 Hz, 1H, ArC*H*), 6.81 (d, *J* = 8.2 Hz, 2H, ArC*H*), 4.05-4.13 (m, 1H, C*H*), 3.82 (dd, J_1 = 9.2 Hz, J_2 = 3.0 Hz, 1H, CH_2), 3.68-3.72 (m, 1H, CH_2), 2.55 (s, 1H, O*H*), 1.18 (d, *J* = 6.4 Hz, 3H, CH_3). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 158.64, 129.58, 121.16, 114.64, 73.29, 66.30, 18.87. MS (ESI) m/z calcd for $C_9H_{12}O_2$ $(M+H)^+$: 153.09, found: 153.09.

1-(*o*-Tolyloxy)propan-2-ol (6.1k):[21] Purified by silica gel column chromatography using ethyl acetate/hexane (20:80) mixture as an eluent. Colorless liquid. Yield: 80.6 mg, 97%. IR (DCM): 3421, 3052, 2975, 2928, 1495, 1265, 1051, 741 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.02-7.10 (m, 2H, ArC*H*), 6.79 (td, J_1 = 7.4 Hz, J_2 = 1.0 Hz, 1H, ArC*H*), 6.68-6.75 (m, 1H, ArC*H*), 4.04-4.23 (m, 1H, C*H*), 3.83 (dd, J_1 = 9.2 Hz, J_2 = 3.5 Hz, 1H, CH_2), 3.71 (dd, J_1 = 9.2 Hz, J_2 = 7.4 Hz, 1H, CH_2), 2.46 (s, 1H, O*H*), 2.15 (s, 3H, CH_3), 1.21 (d, *J* = 6.4 Hz, 3H, CH_3). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 156.65, 130.85, 126.94, 126.77, 120.87, 111.27, 73.31, 66.49, 18.96, 16.33. MS (ESI) m/z calcd for $C_{10}H_{14}O_2$ $(M+H)^+$: 167.10, found: 167.10.



1-(2-Methoxyphenoxy)propan-2-ol (6.1l):[22] Purified by silica gel column chromatography using ethyl acetate/hexane (20:80) mixture as an eluent. Colorless liquid. Yield: 61 mg, 67%. IR (DCM): 3485, 2971, 2931, 2837, 1732, 1504, 1027, 742 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 6.80-6.91 (m, 4H, ArC*H*), 4.08-4.13 (m, 1H, C*H*), 3.92 (dd, J_1 = 9.7 Hz, J_2 = 3.0 Hz, 1H, CH_2), 3.77 (s, 3H, OCH_3), 3.72 (dd, J_1 = 9.6 Hz, J_2 = 8.4 Hz, 1H, CH_2), 2.95 (s, 1H, O*H*), 1.16 (d, *J* = 6.4 Hz, 3H, CH_3). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 150.00, 148.27, 122.20, 121.15, 115.38, 112.04, 75.93, 66.05, 55.90, 18.50. MS (ESI) m/z calcd for $C_{10}H_{14}O_3$ $(M+H)^+$: 183.10, found: 183.10.



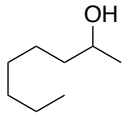
1-(4-Methoxyphenoxy)propan-2-ol (6.1m):[23] Purified by silica gel column chromatography using ethyl acetate/hexane (20:80) mixture as an eluent. Colorless liquid. Yield: 88 mg, 97%. IR (DCM): 3586, 3053, 2934, 2835, 1508, 1265, 1041, 741 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 6.74-6.79 (m, 4H, ArC*H*), 4.07-4.12 (m, 1H, C*H*), 3.82 (dd, J_1 = 9.2 Hz, J_2 = 2.9 Hz, 1H, CH_2), 3.65-3.69 (m, 4H, OCH_3 & CH_2), 2.37 (s, 1H, O*H*), 1.19 (d, J = 6.4 Hz, 3H, CH_3). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 154.24, 152.87, 115.72, 114.82, 74.23, 66.45, 55.85, 18.83. MS (ESI) m/z calcd for $C_{10}H_{14}O_3$ $(M+H)^+$: 183.10, found: 183.10.

1-(2,4-Dibromophenoxy)propan-2-ol (6.1n):[24] Purified by silica gel column chromatography using ethyl acetate/hexane (20:80) mixture as an eluent. Colorless liquid. Yield: 101 mg, 65%. IR (DCM): 3521, 3054, 2983, 2853, 1734, 1244, 1047, 911, 735 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.60 (d, J = 2.4 Hz, 1H, ArC*H*), 7.29 (dd, J_1 = 8.7 Hz, J_2 = 2.4 Hz, 1H, ArC*H*), 6.70 (d, J = 8.7 Hz, 1H, ArC*H*), 4.16 (dqd, J_1 = 13.0 Hz, J_2 = 6.5 Hz, J_3 = 3.2 Hz, 1H, C*H*), 3.92 (dd, J_1 = 9.1 Hz, J_2 = 3.2 Hz, 1H, CH_2), 3.74 (dd, J_1 = 9.0 Hz, J_2 = 7.5 Hz, 1H, CH_2), 2.10 (s, 1H, O*H*), 1.23 (d, J = 6.4 Hz, 3H, CH_3). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 154.26, 135.52, 131.34, 114.83, 113.61, 113.32, 74.86, 66.09, 18.64. MS (ESI) m/z calcd for $C_9H_{10}Br_2O_2$ $(M+H)^+$: 308.91, found: 308.91

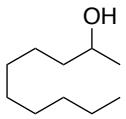
1-([1,1'-Biphenyl]-2-yloxy)propan-2-ol (6.1o):[25] Purified by silica gel column chromatography using ethyl acetate/hexane (20:80) mixture as an eluent. Colorless liquid. Yield: 112 mg, 98%. IR (DCM): 3582, 3053, 2983, 1583, 1434, 1265, 744 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.37-7.40 (m, 2H, ArC*H*), 7.24-7.29 (m, 2H, ArC*H*), 7.14-7.21 (m, 3H, ArC*H*), 6.89-6.94 (m, 1H, ArC*H*), 6.82 (d, J = 8.2 Hz, 1H, ArC*H*), 3.84-3.90 (m, 1H, C*H*), 3.78 (dd, J_1 = 9.2 Hz, J_2 = 3.5 Hz, 1H, CH_2), 3.58-3.63 (m, 1H, CH_2), 2.24 (s, 1H, O*H*), 1.02 (dd, J_1 =

6.4 Hz, J_2 = 2.0 Hz, 3H, CH_3). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 155.44, 138.45, 131.37, 130.89, 129.47, 128.73, 128.09, 127.05, 121.58, 113.31, 74.20, 66.12, 18.72. MS (ESI) m/z calcd for $C_{15}H_{16}O_2$ $(M+H)^+$: 229.12, found: 229.12.

Octan-2-ol (6.1p):[26] Purified by silica gel column chromatography using ethyl acetate/hexane (20:80) mixture as an eluent. Colorless liquid. Yield: 64 mg, 98%. IR (DCM): 3430, 3052, 2987, 1460, 1267, 747 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.68-3.76 (m, 1H, C*H*), 1.85 (s, 1H, O*H*), 1.32-1.41 (m, 2H, CH_2), 1.22-1.30 (m, 8H, CH_2), 1.11 (dd, J_1 = 6.2 Hz, J_2 = 0.6 Hz, 3H, CH_3), 0.81 (t, J = 6.7 Hz, 3H, CH_3). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 68.31, 39.51, 31.96, 29.44, 25.86, 23.60, 22.73, 14.20. MS (ESI) m/z calcd for $C_8H_{18}O$ $(M+H)^+$: 131.14, found: 131.14.



Decan-2-ol (6.1q):[26] Purified by silica gel column chromatography using ethyl acetate/hexane (20:80) mixture as an eluent. Colorless liquid. Yield: 78 mg, 99%. IR (DCM): 3432, 3052, 2928, 2855, 1466, 1264, 909, 731 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.67-3.72 (m, 1H, C*H*), 1.79 (s, 1H, O*H*), 1.31-1.38 (m, 2H, CH_2), 1.20-1.26 (m, 12H, CH_2), 1.10 (d, J = 6.1 Hz, 3H, CH_3), 0.81 (t, J = 6.7 Hz, 3H, CH_3). ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$): δ 68.15, 39.45, 31.97, 29.76, 29.68, 29.37, 25.88, 23.50, 22.75, 14.16. MS (ESI) m/z calcd for $C_{10}H_{22}O$ $(M+H)^+$: 159.17, found: 159.17.



Dodecan-2-ol (6.1r):[26] Purified by silica gel column chromatography using ethyl acetate/hexane (20:80) mixture as an eluent. Colorless liquid. Yield: 91 mg, 98%. IR (DCM): 3446, 3053, 2927, 2854, 1436, 1263, 895, 720 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.69-3.76 (m, 1H, C*H*), 1.96 (s, 1H, O*H*), 1.22-1.46 (m, 17H, CH_2), 1.13 (dd, J_1 = 6.2 Hz, J_2 = 0.9 Hz, 3H, CH_3), 0.84 (t, J = 6.8 Hz, 3H, CH_3). ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$): δ 68.10, 39.44, 31.99, 29.76, 29.71,

29.42, 25.87, 23.47, 22.75, 14.15. MS (ESI) m/z calcd for $C_{12}H_{26}O$ $(M+H)^+$: 187.20, found: 187.20.

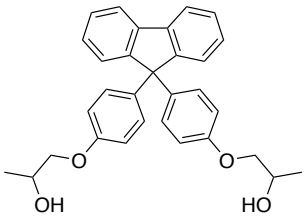
Hexadecan-2-ol (6.1s):[27] Purified by silica gel column chromatography using ethyl acetate/hexane (20:80) mixture as an eluent. Colorless liquid. Yield: 75 mg, 62%. IR (DCM): 3447, 3053, 2927, 2854, 1421, 1265, 895, 738 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.66-3.77 (m, 1H, C*H*), 1.49 (s, 1H, O*H*), 1.30-1.42 (m, 2H, CH_2), 1.19-1.26 (m, 23H, CH_2), 1.11 (d, J = 6.2 Hz, 3H, CH_3), 0.81 (t, J = 6.9 Hz, 3H, CH_3). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 68.32, 39.52, 32.06, 29.80, 29.50, 25.92, 23.59, 22.83, 14.24. MS (ESI) m/z calcd for $C_{16}H_{34}O$ $(M+H)^+$: 243.27, found: 243.27.

2-Phenylpropan-2-ol (6.1t):[28] Purified by silica gel column chromatography using ethyl acetate/hexane (20:80) mixture as an eluent. Colorless liquid. Yield: 31.2 mg, 46%. IR (DCM): 3447, 3058, 3003, 1450, 1267, 895, 747, 703 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.37 -7.39 (m, 2H, ArC*H*), 7.23 (t, J = 7.6 Hz, 2H, ArC*H*), 7.13 (t, J = 7.3 Hz, 1H, ArC*H*), 2.05 (s, 1H, O*H*), 1.47 (s, 6H, CH_3). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 149.22, 128.26, 126.72, 124.48, 72.56, 31.77. MS (ESI) m/z calcd for $C_9H_{12}O$ $(M+H)^+$: 136.08, found: 136.08.

1,1'-((Propane-2,2-diylbis(4,1-phenylene))bis(oxy))bis(propan-2-ol) (6.2a):[29] Purified by silica gel column chromatography using ethyl acetate/hexane (20:80) mixture as an eluent. Colorless liquid. Yield: 170.5 mg, 99%. IR (DCM): 3438, 3052, 2971, 2932, 1607, 1510, 1249, 1306, 744 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.03-7.07 (m, 4H, ArC*H*), 6.70-6.75 (m, 4H, ArC*H*), 4.06-4.10 (m, 2H, C*H*), 3.82 (dd, J_1 = 9.3 Hz, J_2 = 3.3 Hz, 2H, CH_2), 3.69 (dd, J_1 = 9.3 Hz, J_2 = 7.7 Hz, 2H, CH_2), 2.48 (s, 2H, O*H*), 1.55 (s, 6H, CH_3), 1.18 (d, J = 6.4 Hz, 6H, CH_3). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 156.50,

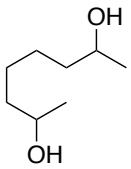
143.66, 127.88, 114.05, 73.37, 66.36, 41.82, 31.13, 18.87. MS (ESI) m/z calcd for $C_{21}H_{28}O_4$ $(M+H)^+$: 345.20, found: 345.20.

1,1'-(((9*H*-Fluorene-9,9-diyl)bis(4,1-phenylene))bis(oxy))bis(propan-2-ol) (6.2b):[30]



Purified by silica gel column chromatography using ethyl acetate/hexane (20:80) mixture as an eluent. Colorless white solid. Yield: 226 mg, 97%. IR (DCM): 3433, 3053, 2977, 2929, 1507, 1265, 1038, 739 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.66 (d, *J* = 7.4 Hz, 2H, ArC*H*), 7.26 (dd, J_1 =14.6 Hz, J_2 =7.5 Hz, 4H, ArC*H*), 7.17 (t, *J* = 7.3 Hz, 2H, ArC*H*), 7.03 (d, *J* = 8.6 Hz, 4H, ArC*H*), 6.67 (d, *J* = 8.6 Hz, 4H, ArC*H*), 3.95-4.23 (m, 2H, C*H*), 3.78 (dd, J_1= 9.2 Hz, J_2 = 2.9 Hz, 2H, CH_2), 3.64 (t, *J* = 8.5 Hz, 2H, CH_2), 2.29 (s, 2H, O*H*), 1.16 (d, *J* = 6.3 Hz, 6H, CH_3). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 157.42, 151.79, 140.06, 138.70, 129.34, 127.83, 127.50, 126.09, 120.28, 114.31, 73.34, 66.36, 64.27, 18.85. MS (ESI) m/z calcd for $C_{31}H_{30}O_4$ $(M+H)^+$: 467.22, found: 467.22.

Octane-2,7-diol (6.2c):[6c] Purified by silica gel column chromatography using ethyl



acetate/hexane (20:80) mixture as an eluent. Colorless liquid. Yield: 71 mg, 97%. IR (DCM): 3470, 3052, 2987, 1572, 1267, 895, 747 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.67-3.70 (m, 2H, C*H*), 2.72 (s, 2H, O*H*), 1.23-1.41 (m, 8H, CH_2), 1.09 (dd, J_1 = 6.2 Hz, J_2 = 1.1 Hz, 6H, CH_3). $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 67.73, 67.64, 39.16, 25.75, 25.66, 23.41. MS (ESI) m/z calcd for $C_8H_{18}O_2$ $(M+H)^+$: 147.14, found: 147.14

6.6 NOTES AND REFERENCES

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^{1}H and ^{13}C NMR Spectra of the Secondary Alcohol Products:

Figure 6.1 ^{1}H NMR spectrum of 1-phenylethan-1-ol (**6.1a**):

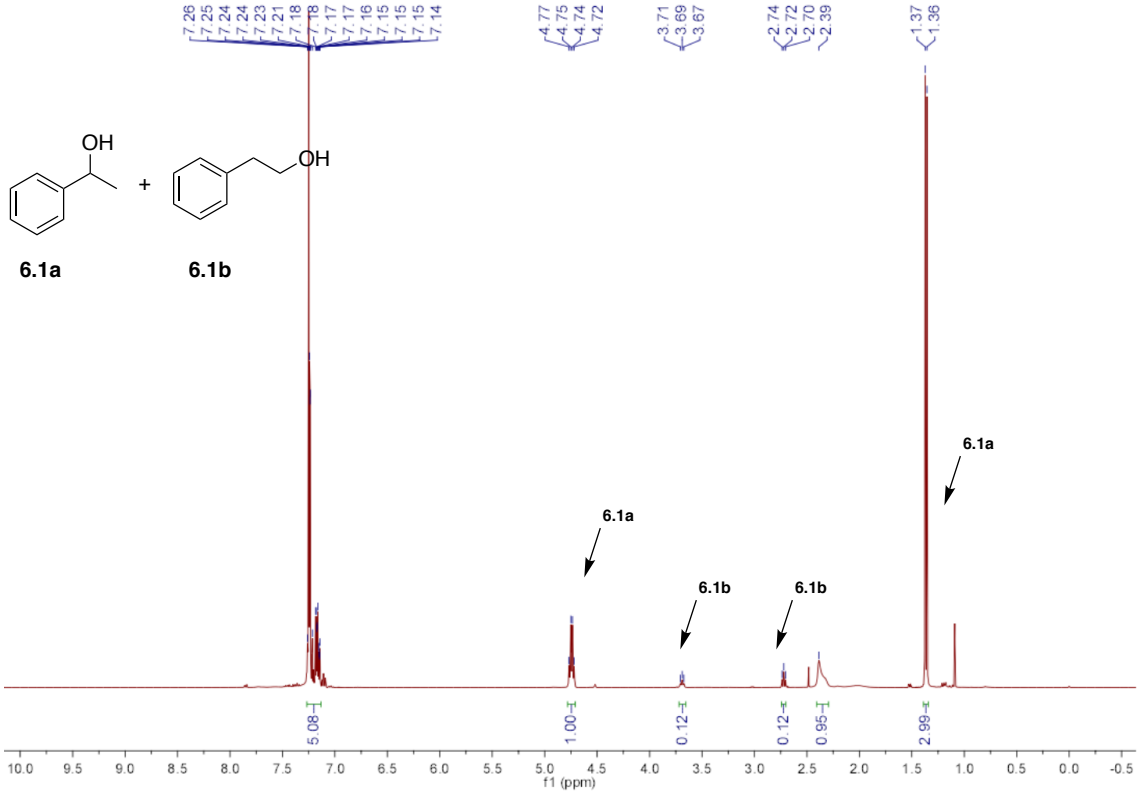


Figure 6.2 ^{13}C NMR spectrum of 1-phenylethan-1-ol (**6.1a**):

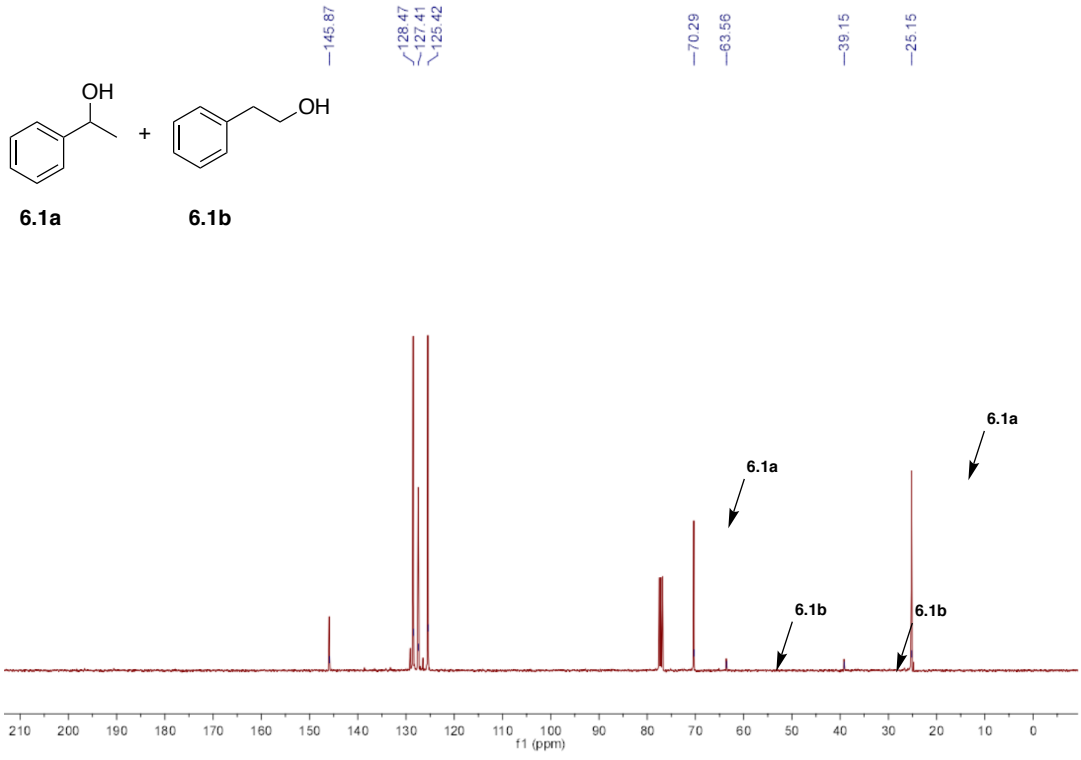


Figure 6.3 ^{1}H NMR spectrum of 1-(2-methoxyphenoxy)propan-2-ol (**6.1l**):

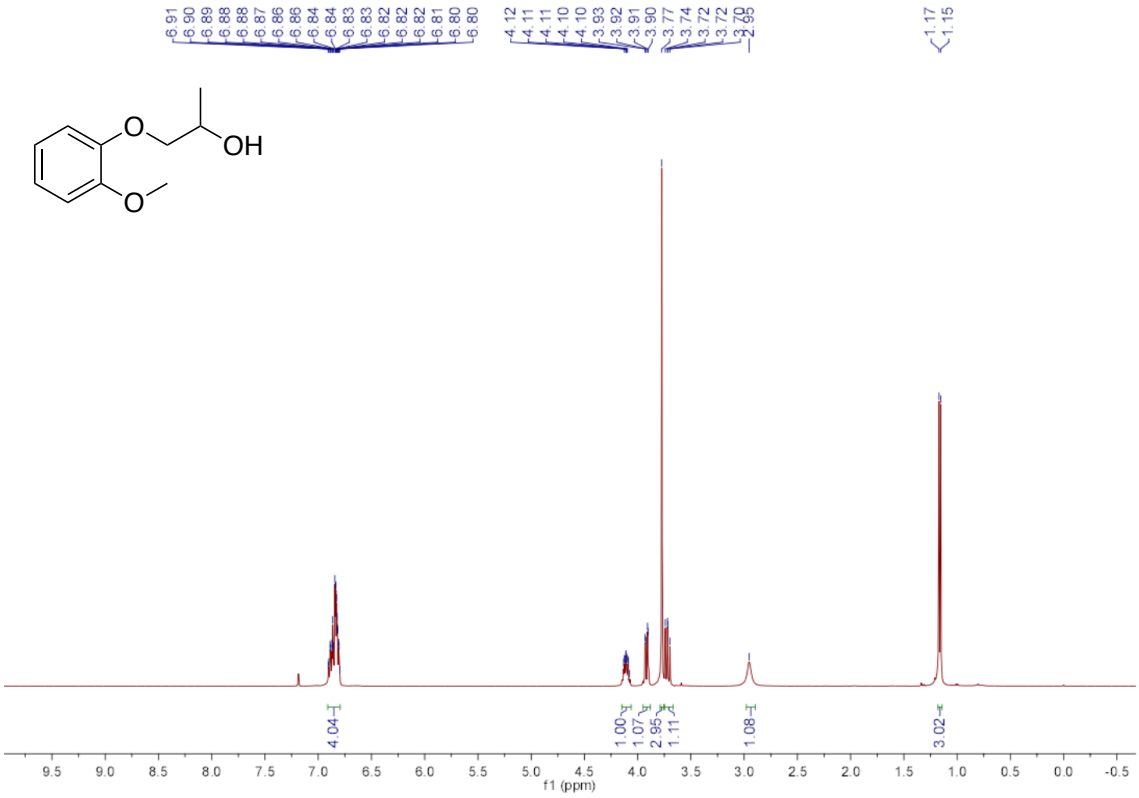


Figure 6.4 ^{13}C NMR spectrum of 1-(2-methoxyphenoxy)propan-2-ol (**6.1l**):

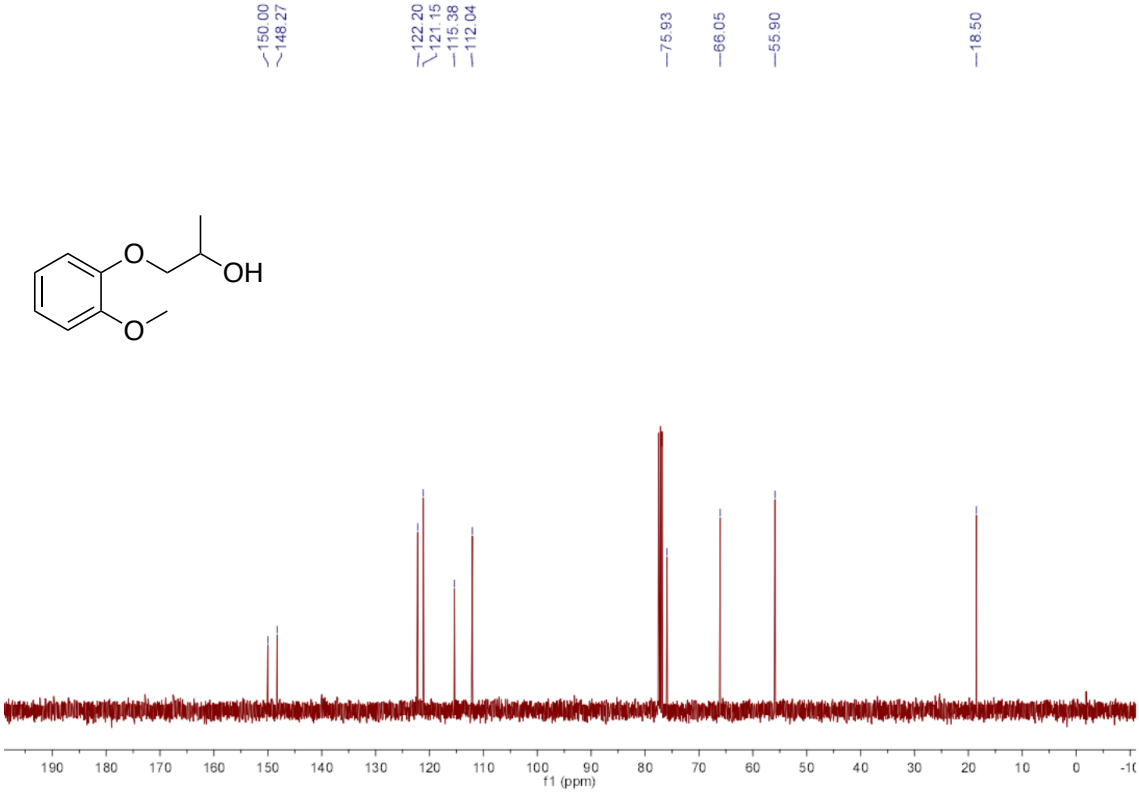


Figure 6.5 ^{1}H NMR spectrum of 1,1'-((propane-2,2-diylbis(4,1-phenylene))bis(oxy))bis(propan-2-ol) (**6.2a**):

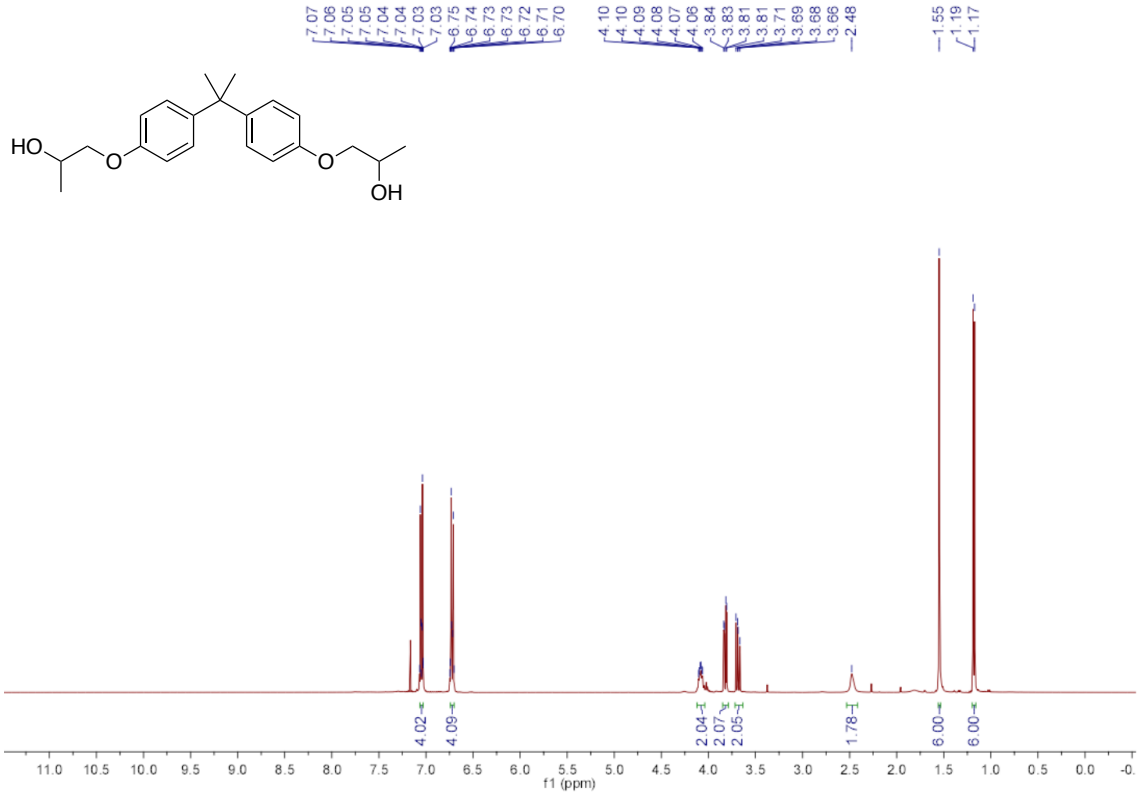
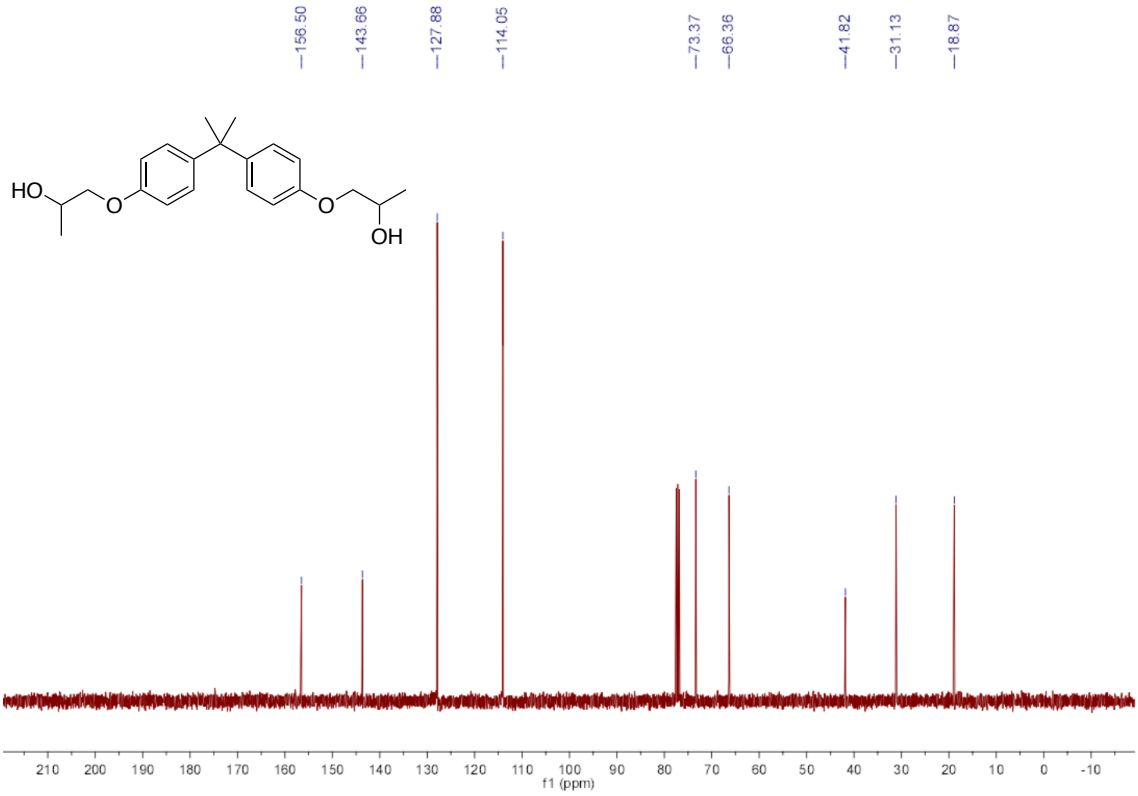


Figure 6.6 ^{13}C NMR spectrum of 1,1'-((propane-2,2-diylbis(4,1-phenylene))bis(oxy))bis(propan-2-ol) (**6.2a**):



Chapter 7

Conclusions

The activation of unreactive chemical bonds by transition metal complexes is an area of utmost importance. In this context, catalytic activation of C–H, N–H and O–H bonds via greener pathway is a challenging task. The classical methodology for the construction of C–C and C–X (X = H, O, N, S, halides, etc.) bonds involves enolate substitution reactions using organometallic reagents or organohalides. However, there are several disadvantages associated with these traditional synthetic methods, including handling of reactive and air-sensitive organometallic reagents and the production of copious salt-based waste during the course of the reactions. Thus, the development of green and sustainable chemical transformations using transition metal catalysis emerged as topic of interest chemical research and strongly desired. In the last two decades, pincer complexes-based catalysts have made tremendous impact in several fundamental chemical transformations and helped achieving greener procedures with high atom efficiency. Pincer ligands having planar framework with presence of bulky substituents on donor atoms covers much coordination sphere around the metal center, which offer control over vacant coordination sites and enhance stability of the resulting pincer complexes. Thus, pincer complexes possess unique balance of stability versus reactivity. As a result, "pincer complexes" once considered, as a favorite adventure for probing reaction mechanism by organometallic chemists became preferred catalysts for various challenging transformations in organic synthesis.

Chapter 1 covered the synthesis, reactivity and previous reports on catalysis by Ru-MACHO (**1**). The unusual reactivity in pincer complexes named, as "Metal-ligand

cooperation" has become an important concept in catalysis for various bond activation reactions in green catalytic pathway. Borrowing hydrogen methodology and acceptorless dehydrogenation concepts allow construction of both C–C and C–N bonds from alcohols and provide an efficient, atom-economical access to an assortment of useful products. On the basis of these two concepts, new C–C, C=C and C–N bond formation reactions were developed using catalyst **1**, which are presented in Chapters 2-6. Further, based on stoichiometric studies, characterization of transient intermediates and labeling experiments the plausible reaction mechanisms for the developed catalytic methods are presented.

Chapter 2 consists of a facile α-alkylation of arylmethyl nitriles with primary alcohols using ruthenium pincer catalyst **1**. An assortment of arylmethyl nitriles can be effectively alkylated using unactivated aliphatic primary alcohols, including challenging ethylation and methylation were also achieved. This green catalytic transformation follows the principle of the borrowing hydrogen methodology and produced water as the only byproduct. Notably, secondary alcohols didn't undergo alkylation reactions. When deuterium-labeled alcohol was used, the expected deuterium transposition occurred, provided both α-alkylation and α-deuteration of arylmethyl nitriles. Further, consumption of nitrile was monitored by GC, which indicated the involvement of first order kinetics. Experimental evidences are suggested the possible mechanistic pathway. The ruthenium catalyst **1** reacts with base and generates an unsaturated reactive intermediate, which reacts with both nitriles and alcohols. Further, oxidation of alcohols to aldehydes and also formed a [2+2] cycloadduct with nitriles that tautomerizes to its enamine intermediate, which further undergo conjugate addition leading to condensation reactions. Subsequent hydrogenation of the intermediate vinyl nitriles (resulted from condensation reactions) provided the selective α-alkylated products.

Overall, an efficient α-alkylation of nitriles using primary alcohols can be attributed to the amine-amide metal-ligand cooperation that is operative in the pincer catalyst **1**, which enables all the catalytic intermediates to remain in +2 oxidation state throughout the catalytic cycle.

In chapter 3, direct coupling of secondary alcohols with nitriles, which delivered β-disubstituted vinyl nitriles, was achieved. Arylmethyl nitriles, heteroarylmethyl nitriles and also aliphatic nitriles were directly coupled with cyclic, acyclic as well as symmetrical and unsymmetrical secondary alcohols, which resulted β-disubstituted vinyl nitriles in good to excellent yields. Notably, liberated H_2 and water are the only byproducts. The acceptorless dehydrogenation of nitriles and alcohols proceeds via amine-amide metal-ligand cooperation that occurs in the activated complex **1**. This new C=C bond formation proceeds through activation of the O–H bond of secondary alcohols via an unsaturated 16-electron intermediate ruthenium pincer complex **1**. Further condensation of in situ formed ketones reaction with nitriles provides expected vinyl nitrile products.

In chapter 4, an unprecedented direct cross coupling of two different secondary alcohols to β-disubstituted ketones was demonstrated. A variety of cyclic, acyclic, symmetrical and unsymmetrical secondary alcohols were selectively coupled with aromatic benzylic secondary alcohols to resulted ketone products. A single catalyst oxidizes both secondary alcohols to provide selectively β-disubstituted ketones. Number of bond activation and bond formation reactions occurs in selective sequence via amine-amide metal-ligand cooperation operative in catalyst **1**. Kinetic and deuterium-labeling experiments suggested that the aliphatic secondary alcohols oxidize faster than benzylic secondary alcohols, which selectively assimilating to provide the cross-coupled ketone products. Interestingly, this new C–C bond forming methodology produces H_2 and H_2O

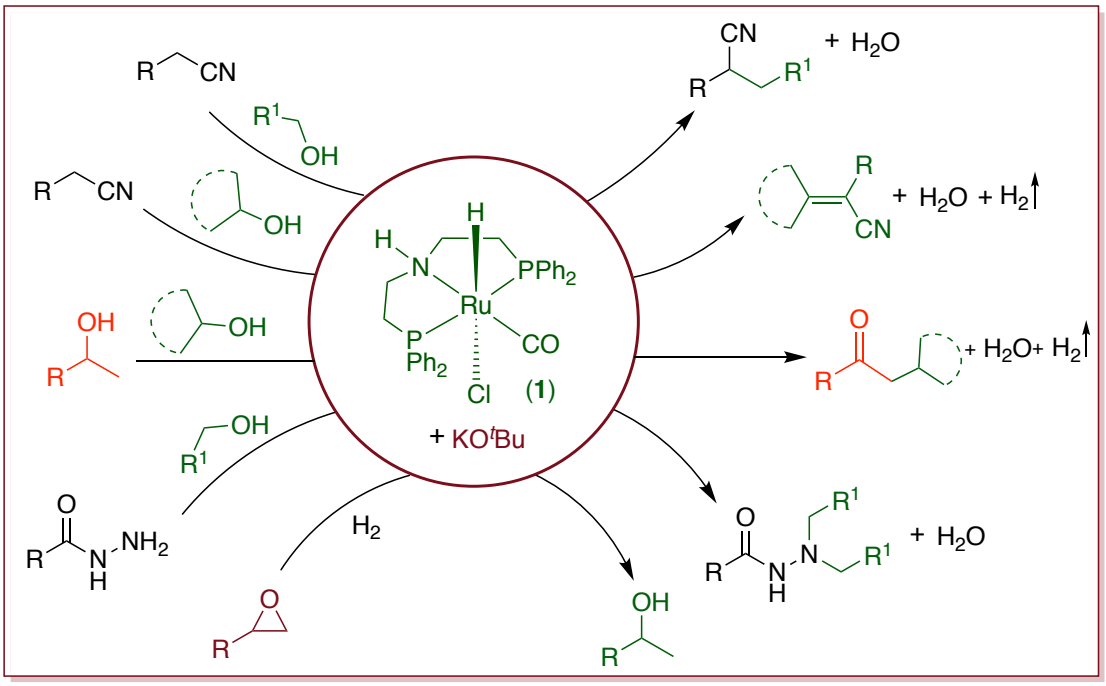
as the only byproducts, which make this protocol greener, atom economical and environmentally benign.

In chapter 5, an unprecedented direct N,N-dialkylation of acylhydrazides using alcohols was reported. This catalytic protocol employs catalyst **1** and provides one-pot synthesis of both symmetrical and unsymmetrical N,N-disubstituted acylhydrazides. Challenging diethylation and dimethylation reactions are performed using ethanol and methanol, respectively as alkylating reagents. Assortment of primary and secondary alcohols can be used with remarkable selectivity and the products were obtained in excellent yields. Interestingly, the use of diols resulted in intermolecular cyclization of acyhydrazides and such products are privileged structures in biologically active compounds. Further, one-pot synthesis of N,N-dialkylated acylhydrazides directly from ester via tandem reaction process also demonstrated. Preliminary mechanistic and deuterium labeling studies indicate that the reaction follows O–H bond activation of alcohols and hydrazone intermediates. Water is the only byproduct, which makes this catalytic protocol sustainable and environmentally benign.

In chapter 6, highly selective Markovnikov hydrogenation of terminal epoxides to secondary alcohols was reported. Diverse aromatic and aliphatic terminal epoxides underwent facile hydrogenation to secondary alcohols with exclusive selectivity and excellent yields. Interestingly, diepoxides also hydrogenated to diols in excellent yields. Notably, internal epoxides did not undergo hydrogenation reactions. Metal-ligand cooperation mediated dihydrogen activation to ruthenium trans-dihydride formation and its preferential reaction with oxygen and less substituted terminal carbon of the epoxide is suggested to be the origin of observed selectivity.

Overall, efficient atom economical and environmentally benign methods are discovered for the range of important products using Ru-MACHO pincer complex (**1**). It is evident

that metal–ligand cooperation stems from aliphatic amine backbone of pincer complex **1**, namely amine-amide metal-ligand cooperation is a powerful approach for bond activation and catalyst design. I believe that future research on amine-amide metal–ligand cooperation would enhance our understanding on fundamental bond activation processes, and also provide new opportunities for the design of sustainable catalytic reactions aimed at solving valuable synthetic problems.



Catalysis Based on Ruthenium Pincer Complexes

The thesis provides a detailed study on the catalytic application of Ru-Macho pincer catalyst (**1**). Metal-ligand cooperation (MLC) operative in these catalytic systems and other catalytic applications reported in the literature are introduced in the first chapter. The second chapter describes the Ru-Macho catalyzed α-alkylation of arylmethyl nitriles using various primary alcohols. This green catalytic alkylation reactions in which alcohols are used as alkylating reagents are facilitated the metal-ligand cooperation. Water is the only byproduct in the reaction. On the basis of kinetic and mechanistic studies the possible mechanistic pathway is proposed.

A unique, ruthenium(II) pincer-catalyzed direct olefination nitrile compounds using secondary alcohols are presented in the chapter 3. An extensive substrate scope with arylmethyl nitriles, heteroaryl-methyl nitriles, and aliphatic nitriles as well as cyclic, acyclic, symmetrical, and unsymmetrical secondary alcohols are explored in the reaction, which provided diverse α-vinyl nitriles.

Chapter 4 describes the discovery of a new catalytic reaction, namely, the cross coupling of secondary alcohols. Cyclic, acyclic, symmetrical, and unsymmetrical secondary alcohols are selectively coupled with aromatic benzylic secondary alcohols to provide β-disubstituted ketones products. The product-induced diastereoselectivity was observed. Kinetic and deuterium labeling experiments suggested that the aliphatic secondary alcohols undergo oxidation reaction faster than benzylic secondary alcohols, selectively assimilating to provide the cross-coupled products. Both olefination of nitrile and cross coupling of secondary alcohols produced H_2 and H_2O as the only byproducts, which make these catalytic protocols greener, atom economical and environmentally benign.

The direct N,N-dialkylation and cyclization of acylhydrazides using alcohols are developed in Chapter 5. This is new catalytic protocol, which provided one-pot synthesis of both symmetrical and unsymmetrical N,N-disubstituted acylhydrazides using variety of primary and secondary alcohols. Products were obtained in with remarkable selectivity and excellent yields. Notably, use of diols resulted in intermolecular cyclization of acylhydrazides. Involvement of hydrazone intermediate in these transformations is established through mechanistic studies.

In chapter 6, ruthenium(II)-catalyzed highly selective Markovnikov hydrogenation of terminal epoxides to secondary alcohols is presented. Benzylic, glycidyl, and aliphatic epoxides as well as diepoxides were subjected hydrogenation to provide secondary alcohols with exclusive selectivity to secondary alcohols. Metal−ligand cooperation-mediated ruthenium trans-dihydride formation and its selective reaction involving oxygen and the less substituted terminal carbon of the epoxide is proposed for the origin of the observed selectivity. Chapter 7 provides the summary of entire thesis.

All the experimental results are published in peer-reviewed journals of international repute. The developed methods will leave a major impact on the way these useful chemicals are synthesized in both laboratory and large scale. The key findings of this thesis will have significant influence on the development of sustainable catalysis.