ORGANOCATALYZED ASYMMETRIC SYNTHESIS: CHIRAL INTERMEDIATES AND THEIR APPLICATIONS

By

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As members of the Viva Voce Committee, we certify that we have read the dissertation prepared by **GANGA BABU VAMISETTI** entitled **"ORGANOCATALYZED ASYMMETRIC SYNTHESIS: CHIRAL INTERMEDIATES AND THEIR APPLICATIONS"** 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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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.

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List of publication arising from the thesis

JOURNALS

1. "A highly regio- and enantioselctive organocatalyzed Michael addition of malonates to nitrodienes", Raghunath Chowdhury, **Ganga B. Vamisetti**, Sunil K. Ghosh, *Tetrahedron: Asymmetry*, **2014**, *25*, 516-522.

2. "On water" organocatalyzed [4+2] cycloaddition of enones and nitro dienes for the enantioselective synthesis of densely substituted cyclohexanones", **Ganga B. Vamisetti**, Raghunath Chowdhury, Mukesh Kumar, Sunil K. Ghosh, *Org. Lett*., **2016**, *18*, 1964-1967.

3. "On water" organocatalyzed enatioselective synthesis of highly functinalized cyclohexanones with an all-carbon quaternary centre from allylidene malononitriles and enones", **Ganga B. Vamisetti**, Raghunath Chowdhury, Mukesh Kumar, Sunil K. Ghosh, *Tetrahedron: Asymmetry*, **2017**, *28*, 317-323.

4. "Organocatalytic decarboxylative aldol reaction of β-ketoacids with α-ketophosphonates en route for the enantioselective synthesis of tertiary α-hydroxyphosphonates", **Ganga B. Vamisetti**, Raghunath Chowdhury, Sunil K. Ghosh, *Org. Biomol. Chem*. **2017**, *15*, 3869-3873.

Conferences

1. "On water"organocatalyzed double Michael addition of enones and nitrodienes for the synthesis of highly substituted chiral cyclohexanones", **Ganga B. Vamisetti**, Raghunath Chowdhury, Mukesh, K., Sunil K. Ghosh, in the proceedings of conference **NDCS-2015** held in BITS-Pilani during Oct 16-18, 2015.
2. "Nitrodiene mediated Michael and double Michael addition reactions", **Ganga B. Vamisetti**, Sunil K. Ghosh, in the proceedings of conference **NCC-2015** held in MSU-Vadodara during Dec 18-19, 2015.
3. "Water mediated organocatalysed enantioselective synthesis of highly substituted cyclohexanone *via* [4+2] cycloaddition from enones and nitrodienes", **Ganga B. Vamisetti**, Sunil K. Ghosh, in the proceedings of conference **ISMC-2016** held in BARC, Mumbai during Dec 6-10, 2016.
4. "On water" organocatalyzed formal [4+2] cycloaddition of acyclic enones with allylidene malononitriles for the synthesis of optically active cyclohexanones", **Ganga B. Vamisetti**, Raghunath Chowdhury, Sunil K. Ghosh in the proceeding of conference **ICOS-2016** held in IIT-Bombay during Dec 11-16, 2016.
5. "Organocatalysed asymmetric synthesis: chiral intermediates and their applications", **Ganga B. Vamisetti**, Sunil K. Ghosh, in the proceedings of conference **RSM-2017** held in St. Xavier's College, Mumbai during, Feb 17-18, 2017.

V. Gangababu..

GANGA BABU VAMISETTI

Dedicated to.....

MY Beloved Parents

Sisters & Teachers

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……Ganga Babu Vamisetti

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SYNOPSIS

Organocatalyzed Asymmetric Synthesis: Chiral Intermediates and Their Applications

This thesis describes the development of methods using organocatalysts for the construction of chiral cyclic and acyclic organic molecules with one or more stereogenic centers including chiral quaternary center and heteroatomic functional groups. The content of this thesis has been divided into five chapters.

Chapter 1: Chirality in bio-molecules and asymmetric synthesis using organocatalysis

This chapter presents a brief overview of organocatalysis in terms of recent developments and usefulness. With the aid of small organic molecules, a great variety of transformations can be achieved along with acceleration of the chemical reaction. Organocatalyst is a small and metal-free organic molecule, consisting of carbon, nitrogen, oxygen, sulphure, and phosphorous atoms. The presence of these hetero atoms in the catalyst creates acidic/basic sites. Currently, organocatalysis[1] itself is emerged as a powerful technique because of the various advantages associated with this field. A collection of chiral organocatalysts such as aminoacids, peptide derived compounds, cinchona alkaloids such as cinchonidine, quinine, quinidine and various sugar derived compounds has been employed in the asymmetric synthesis. Chiral amine based organocatalysts have been widely employed for covalent mode of activation in asymmetric transformations till to date. They activate the carbonyl compounds either by enamine formation (raising the HOMO) or α,β-unsaturated carbonyl by iminium-ion formation (lowering the LUMO). Apart from covalent catalysis, bifunctional asymmetric catalysis[2] involves the synergistic activation of

both acidic and basic sites in the substrate. These various modes of activations in organocatalysis lead the construction of complex organic molecules from simple precursors under the same reaction conditions.

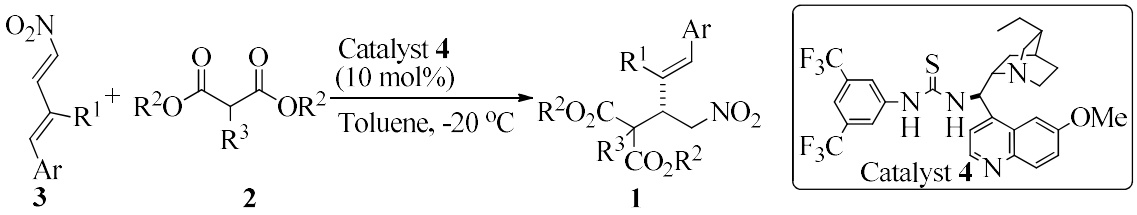
Chapter 2: Organocatalyzed highly regio- and enantioselective Michael addition of malonates to nitrodienes

(*E*)-Dialkyl 2-(1-nitro-4-arylbut-3-en-2-yl)malonates **1** have been employed for the synthesis of various types of organic skeletons such as nitro substituted cyclopropane derivatives, γ-amino carbonyl compounds and heterocyclic compounds. The synthesis of such addition products has drawn extensive attention from the organic community. However, these existing methodologies consist of either usage of transition metal complexes, highly volatile solvents or prolonged reaction time. Thus, the development of more general, operationally simple method for nitro functionalized malonates **1** is highly desirable. This chapter describes an organocatalyzed highly regio- and enantioselective Michael addition of malonates to nitrodienes for the synthesis of (*E*)-dialkyl 2-(1-nitro-4-arylbut-3-en-2-yl)malonates **1.**[3]

Organocatalyzed Michael addition of active methylene compounds containing dicarbonyl functionalities to conjugated nitroolefins has been thoroughly studied to get the Michael adducts with very good selectivities. The same addition of dicarbonyl compounds to nitrodienes has not been explored well with the organocatalysts. We were interested in the Michael addition of active methylene/methyne group of 1,3 dicarbonyl compounds **2** to nitrodienes **3** under purely organocatalyzed conditions. Therefore, we performed a number of initial experiments for screening the various bifunctional thiourea based organocatalysts. Using 0.1 equivalent of catalyst and 2 equivalents of 1,3 dicarbonyl compound **2** with respect to **3**, quinidine derived

thiourea catalyst **4** was found to be superior compared to other catalysts we tried. The Michael addition reaction conditions such as solvent, temperature and catalyst stoichiometry were optimized using catalyst **4**. The optimized conditions was finally established as 2 equiv of 1,3 dicarbonyl compound **2** with respect to nitrodiene **3**, 0.1 equiv of quinidine thiourea catalyst **4** in toluene at a temperature of -20 °C. The reaction provided exclusively the 1,4-addition product **1** (Table 1) and no trace of 1,6-addition product was formed.

Table 1. Michael addition of malonates **2** to nitrodienes **3**



3 **2** **1**

Entry	Ar	R^1	R^2	R^3	Product	Yield (%)	ee (%)
1	Ph	H	Me	H	**1a**	85	88
2	Ph	H	Et	H	**1b**	80	88
3	2-OMePh	H	Me	H	**1c**	75	89
4	4-NO_2Ph	H	Me	H	**1d**	70	76
5	4-BrPh	H	Me	H	**1e**	87	84
6	4-ClPh	H	Me	H	**1f**	93	85
7	4-ClPh	H	Et	H	**1g**	91	80
8	Ph	CH_3	Me	H	**1h**	66	80
9	3-BrPh	H	Me	H	**1i**	95	85
10	Ph	H	Me	$CH_2CH{=}CH_2$	**1j**	45	85

As shown in Table **1**, a number of nitrodienes with electron-withdrawing and electron-donating substituents on aryl components of the nitrodiene were prepared and reacted with various 1,3-dicarbonyl compounds under optimized conditions which

gave the desired (*E*)-dialkyl 2-(1-nitro-4-arylbut-3-en-2-yl)malonates **1** in moderate to excellent yields (45-95%) and high enantioselectivities (76-89%).

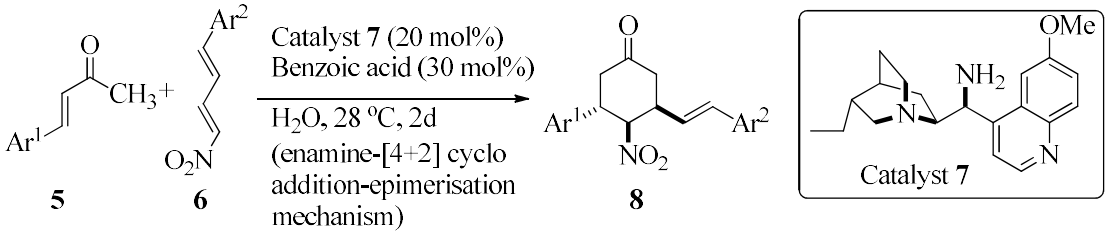
Chapter 3: **Organocatalysed enantioselective synthesis of highly substituted cyclohexanones *via* [4+2] cycloaddition from enones and nitrodienes**

The ubiquity of six membered rings in nature has led to the development of inventive stereoselective synthetic methods. Functionalized 4-nitrosubstituted cyclohexanones are important intermediates for the synthesis of many natural products and biologically active compounds.[4] Several methodologies have been developed to access such compounds, including protection-deprotection of substrates and multistep synthesis. α,β-Unsaturated ketones such as chalcones have received less attention as Michael acceptors probably due to their reduced reactivities compared to enals. Barbas *et al.*[5] were among the first to report the Diels-Alder reaction of nitroolefine and α,β-unsaturated ketones for the synthesis of functionalized 4-nitrocyclohexanones using organocatalysts with moderate enantioselectivities. In addition to that, the use of water as a reaction medium for such reactions has not been studied in detail. In this chapter, an "on-water" highly stereo and enantioselective organocatalytic synthesis of highly substituted cyclohexanones has been described using chalcones and nitrodienes.

The reaction between benzylidene acetone **5a** and 4-phenyl-1-nitrobutadiene **6a** was chosen as the model reaction to optimize the organocatalyst, additive, solvent and reaction conditions that provided 4-nitrosubstituted cyclohexanones. A large number of catalysts were screened and zeroed on the cinchona based primary amine catalysts (*S*)-(8-ethylquinuclidine-2-yl)(6-methoxyquinoline-4-yl)methanamine **7** which offered the product **8a** in moderate yield but with excellent enantioselectivity.

After several experimentation, the optimized conditions were obtained by using 2 equiv of enone **5a** with respect to nitrodiene **6a**, 0.2 equiv of catalyst **7** and 0.3 equiv of benzoic acid as an additive in water at 28 ^{o}C for 2 d. Further, with the established optimal reaction conditions, the substrate scope was explored using variety of enones **5** and nitrodienes **6** having electron-donating and electron-withdrawing functionalities at the aromatic rings of the both components, which offers the desired 4-nitrosubstituted cyclohexanones **8** with the yield upto 80% and excellent selectivities (dr upto 9/1, ee upto 99%) as shown in the Table **2**.[6] A mechanistic studies using ^{1}H NMR revealed that the reaction is proceeding through *endo* [4+2] cycloadditon path instead of a double Michael addition reaction, in which enone moiety acting as a diene system and nitrodiene moiety acting as a dienophile system.

Table 2. Synthesis of cyclohexanones from enones and nitrodienes



Entry	Ar^1	Ar^2	Product	dr	Yield (%)	ee (%)
1	Ph	Ph	**8a**	80:20	75	>98
2	4-ClPh	Ph	**8b**	90:10	70	>94
3	4-FPh	Ph	**8c**	84:16	80	>94
4	4-OMePh	Ph	**8d**	60:40	65	>94
5	4-CF_3Ph	Ph	**8e**	80:20	70	>94
6	3-BrPh	Ph	**8f**	90:10	75	93
7	2-ClPh	Ph	**8g**	84:16	70	>94
8	Ph	4-ClPh	**8h**	75:25	70	94
9	Ph	4-NO_2Ph	**8i**	70:30	60	>94
10	Ph	3-BrPh	**8j**	80:20	64	>95

11	4-ClPh	4-ClPh	**8k**	80:20	65	94
12	3-BrPh	3-BrPh	**8l**	70:30	58	>96

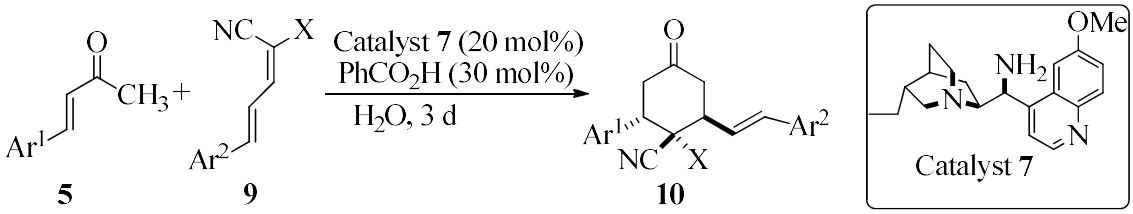
Chapter 4: Organocatalysed enantioselective synthesis of highly substituted cyclohexanones with all-carbon quaternary center from allyliedene malonitrile and enones

Functionalized cyclohexanones with an all carbon quaternary center are important intermediates for the synthesis of many natural products and biologically active compounds. Because of steric encumbrance around the quaternary center, often drastic conditions are required for the generation of the quaternary center resulting in loss of stereocontrol. Besides, combination of electrophiles and nucleophiles those provide the quaternary center are also limited. Therefore, the generation of a quarternary stereocenter in an asymmetric synthesis has created a much more interest in the chemical community.[7] Organocatalyzed double Michael addition reaction or Diels-Alder reaction of enones with a dienophile in pure water leading to highly substituted six member rings were not explored. Recently our group successfully demonstrated an organocatalyzed "on water" *endo* [4+2] cycloaddition with enamine of enone as diene and nitrodiene as dienophile for the construction of 4-nitro-substituted cyclohexanones.[6] This chapter deals with the development of an "on water" *endo* [4+2] cycloaddition of allylidene malononitrile or cyanoacetate leading to an asymmetric synthesis of highly substituted chiral cyclohexanones with an all-carbon quaternary or quaternary stereogenic center.

We chose the reaction between benzylidene acetone **5a** and 3-phenylallylidene malononitrile **9a** as the model reaction. A variety of cinchona based chiral primary amines were screened as catalyst for the reaction and (*S*)-(8-ethylquinuclidine-2-yl)(6-

methoxyquinoline-4-yl)methanamine **7** in combination with benzoic acid as an additive was found to be a good catalytic system for the reaction leading to product **10a**. Further optimizations were performed with respect to solvent and reaction conditions. The optimized conditions was to use enone **5a** (2 equiv) with respect to phenylallylidene malononitrile **9a** (1 equiv), catalyst **7** (0.2 equiv) in combination with benzoic acid (0.3 equiv) and water as the reaction media at room temperature. With these optimized conditions, the reaction was found to be general in terms of enones **5** and allylidene malonates/malonoesters **9** having electron-donating and electron-withdrawing functionalities at the aromatic rings of the both components. Chiral cyclohexanones **10** were formed (Table 3) with three contiguous stereogenic centers including an all-carbon quaternary one in good yield (upto 80%) and with excellent selectivities (dr upto 19/1, ee upto 91%).[8]

Table 3. Synthesis of cyclohexanones from enones and allyliedene malonitrile



5 **9** **10**

Entry	Ar^1	Ar^2	X	Product	dr	Yield (%)	ee (%)
1	Ph	Ph	CN	**10a**	95:5	77	74
2	4-ClPh	Ph	CN	**10b**	nd	80	73
3	4-BrPh	Ph	CN	**10c**	nd	50	76
4	4-OMePh	Ph	CN	**10d**	nd	63	71
5	3-ClPh	Ph	CN	**10e**	nd	53	67
6	Ph	4-FPh	CN	**10f**	nd	55	71
7	Ph	4-OMePh	CN	**10g**	nd	55	66
8	Ph	4-NO_2Ph	CN	**10h**	nd	59	82
9	4-BrPh	4-BrPh	CN	**10i**	nd	52	75

10	Ph	Ph	CO_2Et	**10j**	90:10	50	90
11	Ph	4-BrPh	CO_2Et	**10k**	84:16	51	82
12	Ph	Ph	CO_2Me	**10l**	90:10	45	91

Chapter 5: **Organocatalytic enantioselective synthesis of *tert*-α-hydroxyphosphonates from β-ketoacids and α-ketophosphonates**

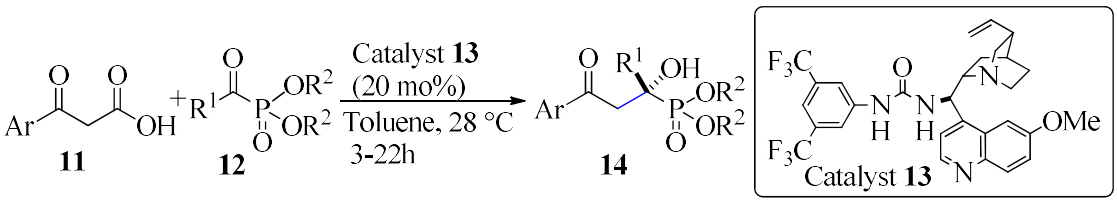
The chiral α-hydroxyphosphonic acid derivatives have important biologically activity. They are widely used as anticancer and antivirus compounds, and also known inhibitors of renin or human immunodeficiency virus (HIV) protease and polymerase. Only a few stereoselective syntheses of α-hydroxyphosphonates were reported including the asymmetric reduction of α-ketophosphonates, asymmetric oxidation of benzylphosphonates and the asymmetric hydrophosphonylation of carbonyl compounds. The reaction of α-ketophosphonates with aromatic ketones such as acetophenones are not explore well. We envisioned that β-aryl β-ketoacids are surrogate of acetophenone enolate. Recently, metal[9] and organocatalyzed[10] asymmetric decarboxylative reactions of β-ketoacids with various electrophiles have been reported. However, the catalytic enantioselective decarboxylative aldol reaction of β-ketoacids to acetyl phosphonates has not been explored using either organocatalysis or metal catalysis. This chapter presents the development of an organocatalysed method for C-C bond formation between β-ketoacids and α-ketophosphonates *via* decorboxylative aldol reaction leading to γ-carbonyl *tert*-α-hydroxyphosphonate having a hydroxyl and phosphonate bearing chiral quaternary center.

Initially, benzoylacetic acid **11a** and diethyl acetylphosphonate **12a** were chosen as the reactants for the model reaction in the presence of various

organocatalysts including bifunctional organocatalysts. Quinidine derived urea catalyst **13** was found to be good for the reaction that generated the product **14a** in 70% yield and with good enantioselectivity (er = 84/16). The reaction conditions were further optimized in terms of solvent, additive, temperature and catalyst concentration and the mode of addition of reagents to improve the yield and selectivity. The optimized reaction conditions was to use of catalysts **13** (0.2 equiv), benzoylacetic acid **11a** (1.3 equiv) with respect to diethyl acetylphosphonate **12a** (1.0 equiv) in dry toluene at 28 °C.

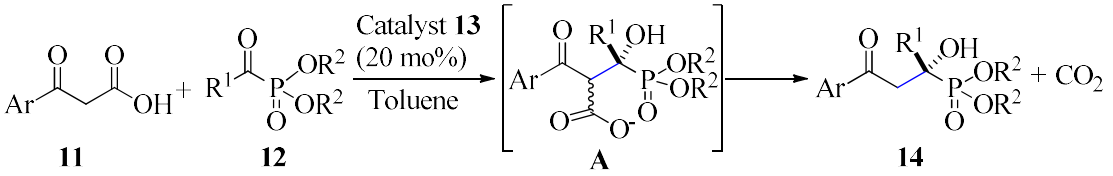
With these optimized reaction conditions the scope of the catalytic decarboxylative aldol reaction was explored with different β-ketoacids **11** and α-ketophosphonates **12** (Table **4**).[11] The size of R^1 and R^2 in α-ketophosphonates had strong influence on both the reactivity and enantioselectivity. The electronic nature as well as the position of the substituent on the aryl rings of the β-ketoacids had influenced the reactivity as well as enantioselectivity of the desired product **14** with the yield upto 84% and er upto 93/7.

Table 4. Synthesis of *tert*-α-hydroxyphosphonates from β-ketoacids and α-ketophosphonates



Entry	Ar	R^1	R^2	Product	Yield (%)	er (%)
1	Ph	CH_3	Et	**14a**	70	84:16
2	Ph	CH_3	Me	**14b**	82	nd
3	Ph	CH_3	^{i}Pr	**14c**	84	85:15
4	Ph	Et	^{i}Pr	**14d**	64	77:23
5	Ph	Ph	Et	**14e**	66	65:35
6	4-FPh	CH_3	^{i}Pr	**14f**	82	79:21
7	4-OMePh	CH_3	^{i}Pr	**14g**	70	78:22
8	3-ClPh	CH_3	^{i}Pr	**14h**	72	83:17
9	3-BrPh	CH_3	^{i}Pr	**14i**	79	93:7
10	2-ClPh	CH_3	^{i}Pr	**14j**	73	92:8
11	2-ClPh	CH_3	Et	**14k**	70	89:11

Mechanistic studies by ^{31}P NMR spectroscopy revealed that the first step is the addition of the enolate of β-ketoacid to the α-ketophosphonate leading to the intermediate **A** which then undergoes decarboxylation offers the product **14** (Scheme**1**).



Scheme 1

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ABBREVIATIONS

AcOH:	Acetic Acid
B. p.:	Boiling Point
Cbz:	Benzyloxycarbonyl
CSA:	Camphorsulfonic Acid
Cy:	Cyclohexyl
DCC:	*N*,*N*-Dicyclohexylcarbodiimide
DIPC:	*N*,*N*-Diisopropylcarbodiimide
DIBAL:	Diisobutylaluminum Hydride
DIPEA:	Diisopropylethylamine
DMAP:	4-Dimethylaminopyridine
DMF:	Dimethylformamide
DMSO:	Dimethylsulphoxide
dr:	Diastereomer Ratio
ee:	Enantiomeric Excess
EtOH:	Ethanol
EtOAc:	Ethyl Acetate
g:	Gram
GC:	Gas Chromatography
HF:	Hydrofluoric Acid
HOMO:	Highest Occupied Molecular Orbital
HPLC:	High Performance Liquid Chromatography

HRMS:	High Resolution Mass Spectroscopy
Hz:	Hertz
IR:	Infrared
LDA:	Lithium Diisopropylamide
LUMO:	Lowest Unoccupied Molecular Orbital
M:	Molar
m:	*meta*
m-CPBA:	*meta*-Chloroperoxybenzoic Acid
mg:	milligram
mL:	milliliter
mmol:	millimole
M. p.:	Melting Point
NMP	*N*-Methylpyrrolidone
NMR:	Nuclear Magnetic Resonance
nOe	Nuclear Overhauser Effect
o:	*ortho*
P:	*Para*
ppm:	Parts Per Million
SOMO:	Singly Occupied Molecular Orbital
TFA:	Trifluoroacetic Acid
THF:	TetrahydroFuran
TMS:	Trimethylsilyl Ether
TLC:	Thin Layer Chromatography

CHAPTER 1

Chirality in bio-molecules and asymmetric synthesis using organocatalysis

1.1 Introduction

1.1.1 Introduction and isolation of chiral compounds

In 1848, French chemist and biologist Louis Pasteur made the fundamental discovery that the sodium ammonium salt of an optically inactive tartaric acid could be manually split into two optically active salts. One of them being identical to the natural tartaric acid.[1a] In 1860, he suggested that preparative chemistry needed some chiral help to create chiral compounds.[2a] Additionally, Pasteur drew the important conclusions that the rotation of plane-polarised light caused by the different tartaric acid salt crystals was a property of chiral molecules. Further, Pasteur correlated the phenomenon of optical activity with an asymmetric grouping of atoms within molecule. When a molecule cannot be superimposed on its mirror image, it is called chiral and the molecules with non-superimposable images are called enantiomers.[1b,c] However, it needed about a century after to understand the phenomenon of chirality. Chirality plays key role on the physical, chemical and biological properties of molecules.[3,4a]

Chirality and chiral molecules play an important role in organic chemistry. However, chirality is not restricted to the presence of a single, configurationally stable chairal center in the molecule. Some structures including cumulene, allenes, spiranes, alkylidenecycloalkanes, atropisomers (biphenyls and similar compounds) which also show chirality due to restricted rotation along a bond.[2b] Emil Fischer identified that a "dissymmetric force" in not required to generate chiral molecules in living organism. He also showed that, the asymmetry in molecules can control the asymmetry in subsequent

reactions and “lock and key” principle provides a mechanism for stereochemical selection in nature.[4b,c]

1.1.2 Importance of chirality in bio-molecules

There is an immense impact of chirality as a fundamental feature of many biomolecules. Many biologically active molecules are chiral, including the naturally occurring amino acids (the building blocks of proteins) and sugars. In biological systems, most of these compounds are of the same chirality: most amino acids are levorotatory (*l*) and sugars are dextrorotatory (*d*). Naturally occurring proteins are made up of L-amino acids, which are essential for structure and chemical transformations in cells, also share a common absolute configuration. Enzymes, which are chiral, often distinguish between the two enantiomers of a chiral substrate. One could imagine an enzyme as having a glove-like cavity that binds a substrate. If this glove is right-handed, then one enantiomer will fit inside and be bound, whereas the other enantiomer will have a poor fit and is unlikely to bind.

Biological compounds (**Figure 1.1**) containing the chiral information interacts with receptors in the body in a stereospecific manner. In 1926, Arthur Cushny reported the difference in pharmacological action of the enantiomers of a molecule.[5a-c] In the early 20th century, drugs possessing chiral centres are sold as racemate based on the assumption that one enantiomer would be pharmacologically active at consistent dose and the other enantiomer would not compile in the body or cause any dangerous side effects. After that guidelines proclaimed by the United States of Food and Drug Administration, drugs

molecules containing a chiral center should be prepared in enantiomerically pure form, or alternatively that full toxicological and pharmacokinetic profiles should be presented for each enantiomer if the drug was sold as a racemate. Therefore, today the preparation of pure stereoisomers or chiral compounds has become a topic of great importance and methods of supplying optically pure materials are being intensively pursued. Nature has provided a variety of enantiomerically pure compounds consider as the chiral pool, which can be subjected to further transformations. Apart from chiral pool synthesis, there are two general methods for obtaining enantio-pure compounds, *viz* resolution of racemic mixture and asymmetric synthesis.

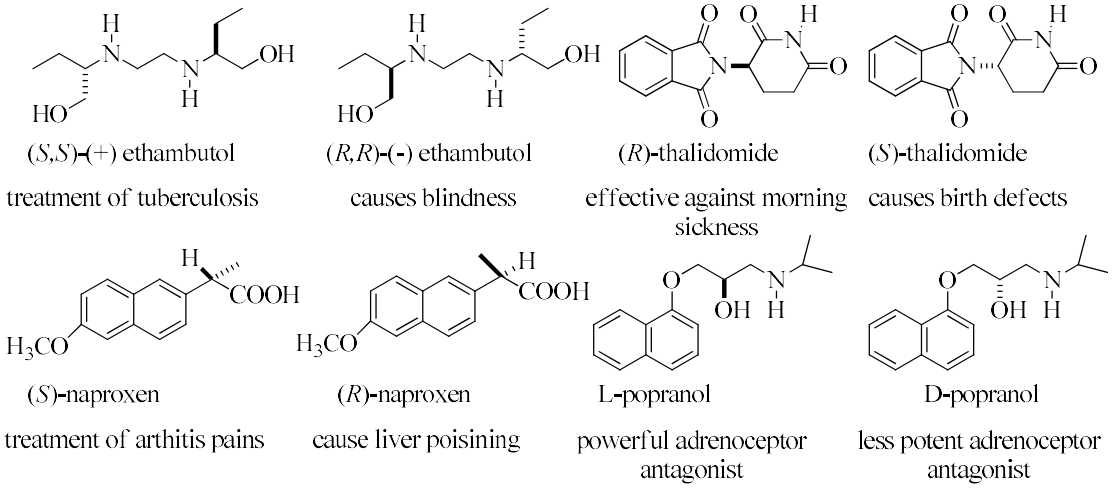
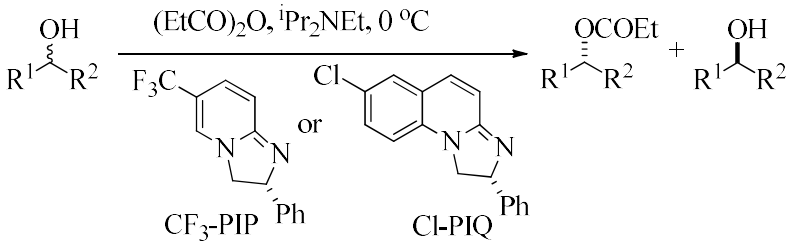


Figure 1.1 Enantiomers with different biological activity

1.1.3 Resolution of racemic mixtures

This is the oldest method for separating a pair of enantiomers. The fact that diastereomers have different physical properties, such as solubility, melting point or boiling point, is used to achieve separation of enantiomers in a racemates. Reaction of racemates with an

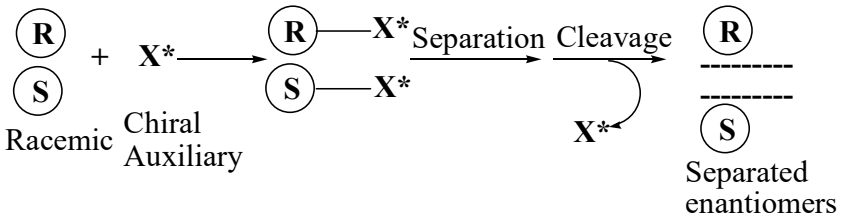
enantiomerically pure reagent gives a mixture of diastereomers, which in principle can be separated.[5d] In addition, chromatographic methods where the stationary phase is a chiral reagent that adsorbs one enantiomer more strongly than other has been in practice. But such resolution seldom have led to both pure enantiomers on a preparative scale.[6] Another class of process in which one enantiomer from the racemic mixture may react rapidly with a chiral reagent there by leaving excess of unreacted enantiomer behind is termed as the kinetic resolution.[7] For example, a class of 2,3-dihydroimidazo-[*1,2-a*]-pyridine (DHIP) and its derivatives CF_3-PIP and Cl-PIQ are employed as enantioselective acylation catalyst (**Scheme 1.1**) to attain kinetic resolution of secondary alcohols.[8]



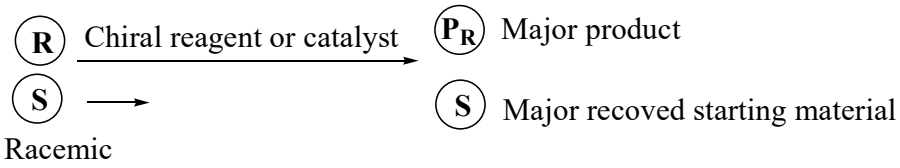
Scheme 1.1 Kinetic resolution of secondary alcohol

The dynamic kinetic resolution (DKR) method is a type of kinetic resolution where a racemic compound can be converted into an enantio-pure compound. In DKR, the chiral center of a particular molecule that can be easily epimerized so that the (*R*) and (*S*) enantiomers can interconvert throughout the reaction process. For the DKR to be possible, the enantiomers in a racemate should be in a dynamic equilibrium. The plausible representations of resolution of racemic mixtures are depicted in **Figure 1.2.**

(a) Stoichiometric method



(b) Kinetic resolution



(c) Dynamic kinetic resolution

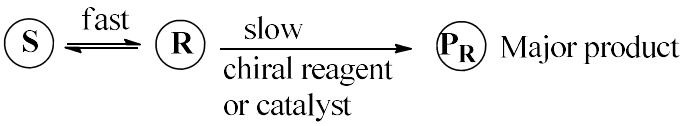


Figure 1.2 Resolution of racemate to prepare enantioenriched compounds

1.1.4 Asymmetric synthesis

In 1904 Marckawald entitled the definition of asymmetric synthesis: "Asymmetric syntheses are those reactions which produce new optically active or chiral unit from an achiral unit in an ensemble of substrate by an incorporation of stoichiometric, substoichiometric or catalytic amount of chiral compound".[9] Later on the definition of asymmetric synthesis was modified in 1971 by Morrison and Mosher[10] as asymmetric synthesis is a reaction in which an achiral unit in an ensemble of substrate molecule

(having either enantiotopic or diastereotopic groups are faces) is converted into a chiral unit in such a manner that unequal amounts of stereoisomers are produced.

Many of naturally occurring or biologically active organic compounds contain chiral centers (**Figure 1.3**). Therefore chirality is the source of diverse phenomenon at the macro and micro level to regulate environment and living organisms.[11] Since biological systems are made up of chiral amino acids, sugars and lipids, they are capable to discriminate the enantiomeric forms of pheromones, pollutants and drug compounds. However, this asymmetric synthesis is employed for the synthesis of complex organic molecules with less complexity in meaningful way.[12]

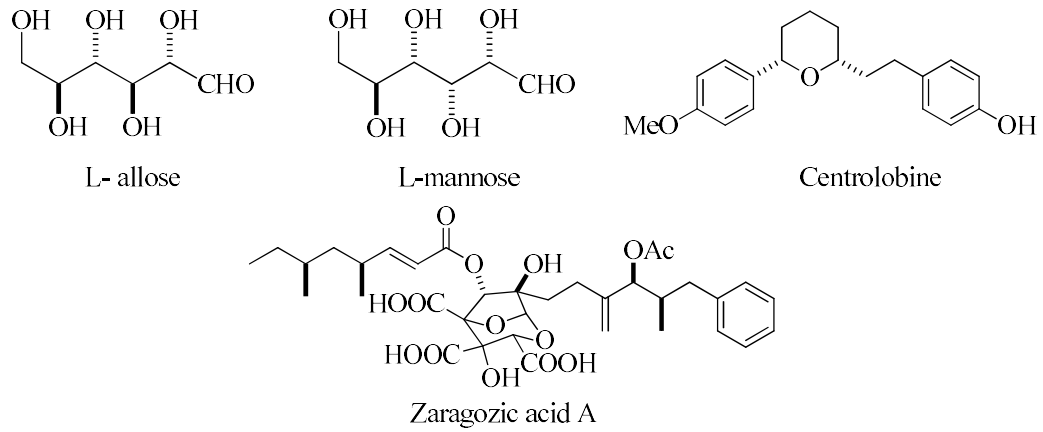


Figure 1.3 Examples of natural products constructed by the use of asymmetric synthesis

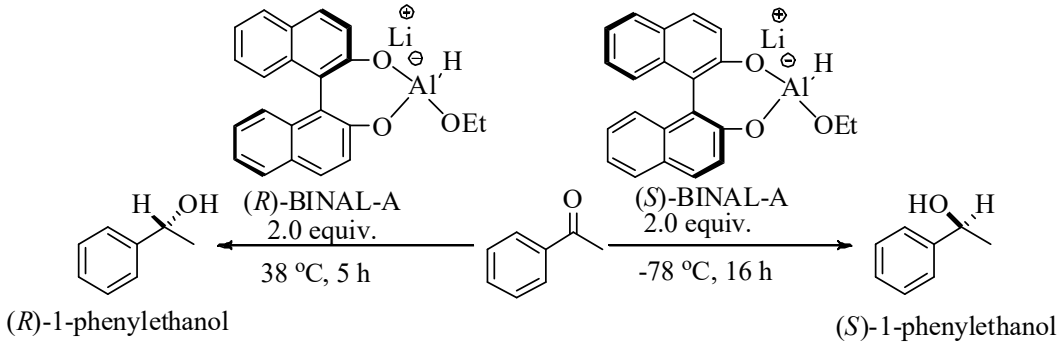
1.1.5 Methods for asymmetric synthesis

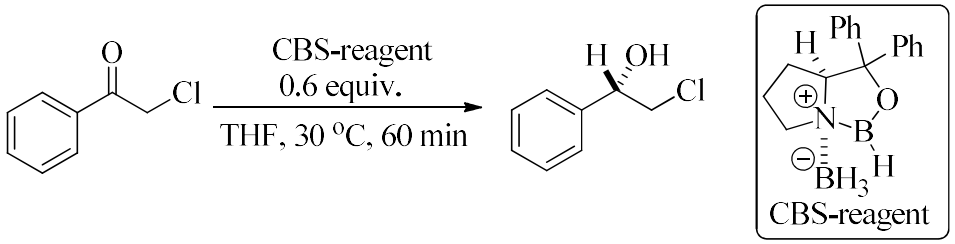
Asymmetric synthesis by virtue is a strategy through which an unequal amount of stereoisomers are produced preferentially with high enantioselectivity. This strategy is

further explored to various classes according to the site in an achiral unit, where the chirality is to be generated.

i. Chiral reagent or chiral solvent induced asymmetric synthesis

This method relies on the incorporation of chiral control element into the structure of the reagent to direct stereochemistry at new stereogenic center of the substrate. Stoichiometric quantity of reagent (**Scheme 1.2**)[13] is generally used and in not recovered for re-use. This is expensive technique because the cost of the enantio-pure reagent is quiet high.



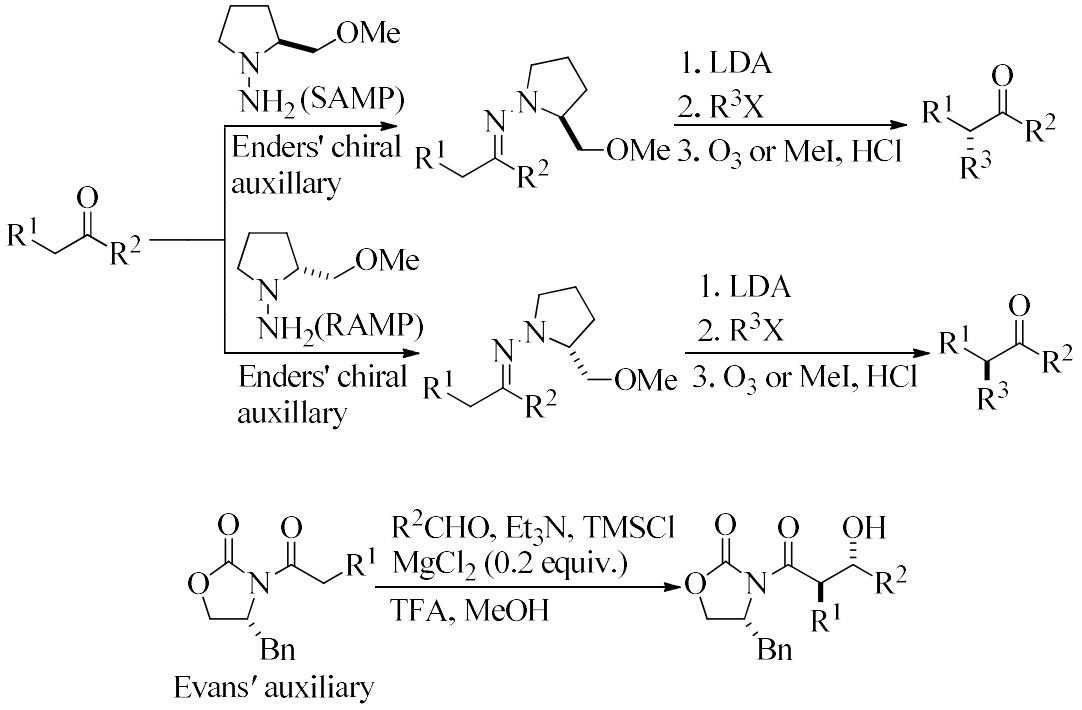


Scheme 1.2 Reagent control enantioselective synthesis of secondary alcohol

ii. Chiral auxiliary induced asymmetric synthesis[14]

This technique involves inclusion of chiral compounds, the auxiliary, into the substrate by a temporary covalent attachment. On reaction with reagent the auxiliary induces diastereoselectivity preferring for one over the other. Subsequent removal of auxiliary offers product with acceptable level of enantioselectivity (**Scheme 1.3**).

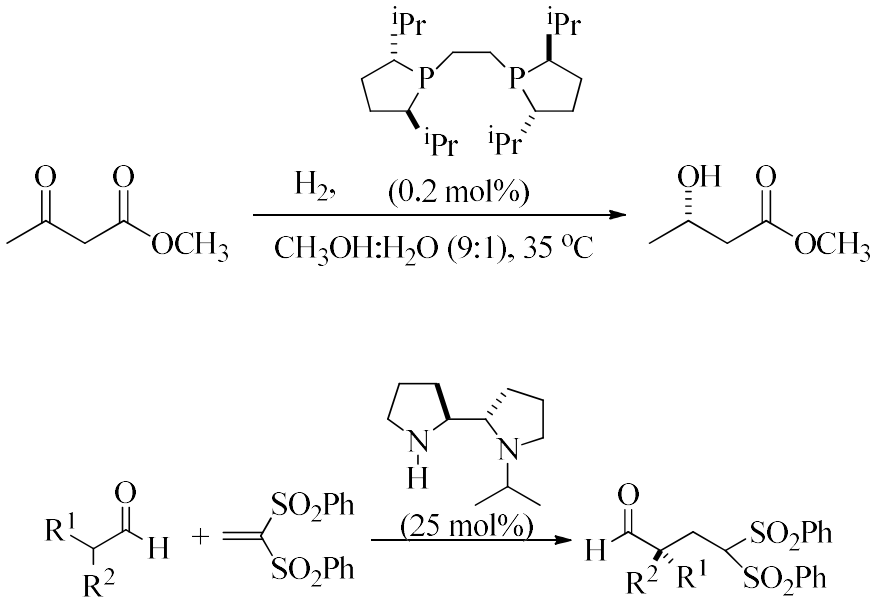
A good chiral auxiliary should be cheap and enantiomerically pure. It should be easy to attach to a substrate. After the reaction, it should help easy purification of diastereomers either by crystallization or chromatography. The auxiliary should be easily removable and without loss of purity of the desired product and if possible it should be recovered for reuse.



Scheme 1.3 Examples for chiral auxiliary assisted asymmetric synthesis

iii. Chiral catalyst induced asymmetric synthesis or asymmetric catalysis

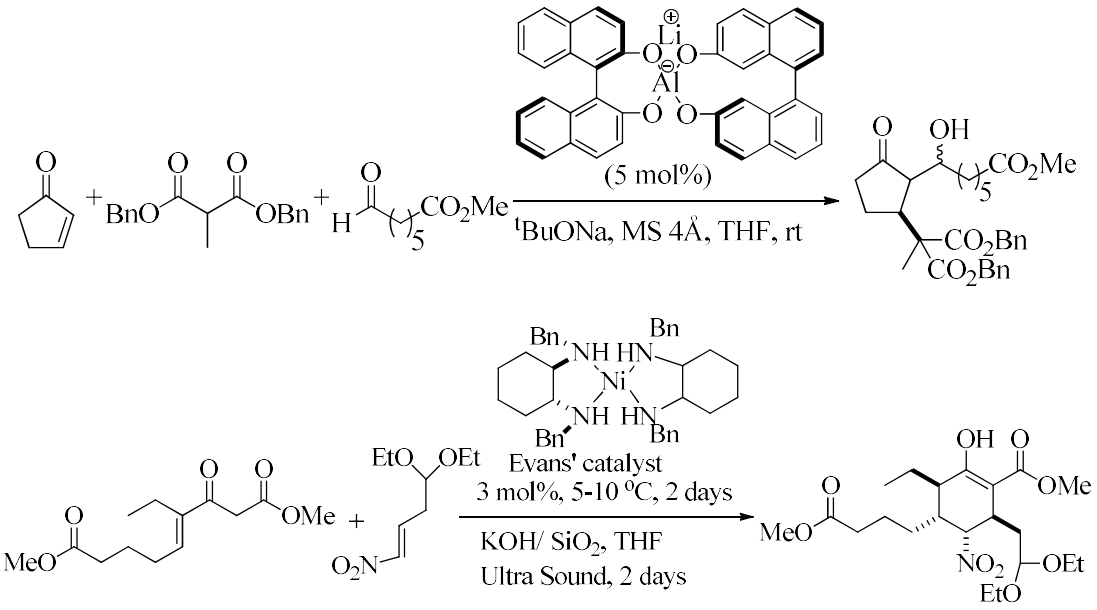
It involves the acceleration of chemical transformations by the addition of substoichiometric amount of a chiral compound, the catalyst into the reaction (**Scheme 1.4**).[15] Due to substrate-catalyst interactions, the diastereomeric transition state having lower energy leads to one enantiomer in excess. The chiral compound may be a purely organic compound or organic-inorganic complex. The use of a purely chiral organic compound is termed as organocatalysis.



Scheme 1.4 Examples for chiral catalyst assisted asymmetric synthesis

The importance of enantioselective reactions has been well recognised for which Nobel Prize has been awarded in 2001 to Knowles,[16] Noyori[17] and Sharpless[18] for their contributions towards the field of metal-mediated asymmetric catalysis. These metal catalysts (**Scheme 1.5**)[19] can mimic the properties of Lewis acid or Lewis base. Various

classes of metal based asymmetric catalytic reactions have been greatly explored till to date.



Scheme 1.5 Examples for metal mediated asymmetric synthesis

But most of the metal catalysed reactions are sensitive to air and moisture. In addition to that some of them are quiet expensive and some of are toxic. Therefore, there is a need of an alternative approach devoiding of these shortcomings. The discovery and the use of simple chiral organic molecule, which are easily available and capable to produce asymmetric transformations in a metal free environment under mild and simple reaction conditions, is emerged as an asymmetric orgnanocatalysis. This field has been experienced an important growth. [20] Currently, asymmetric orgnaocatalysis is recognized as a third independent synthetic tool beside metal and enzyme catalysis for the synthesis of chiral molecules. This asymmetric organocatalysis shows the path to the synthesis of

key steps involved in the complex natural products[21] and other biologically active compounds.

1.2 Asymmetric synthesis by organocatalysis

The term "Organic Catalysis" (Organische Katalysatoren) initially coined by Langenbeck[22] in 1932. Organocatalyst is a small and metal-free organic molecule, consisting of carbon, nitrogen, oxygen, sulphure, and phosphorous atoms, may promote potential transformations. Addition of substoichiometric amount of these catalysts promotes many chemical reactions. The presence of hetero atom (N, O, P and S) in the catalyst creates acidic/basic sites.[23] Today organocatalysis itself is emerged as a powerful technique because of the various advantages[24] associated with this field. Some of them are mentioned below.

i. Some of the organocatalysts are readily available in nature in substantial amount with excellent enantiopurity in both the isomeric forms.

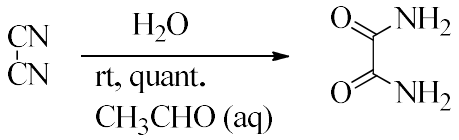
ii. These catalysts are worked as environment friendly, easy to handle because of less sensitive to air, moisture, and metal free and less toxic.

iii. These are low molecular weight compounds and are available at low price.

iv. At the end of the reaction, these catalysts are easily removed from the product. Sometimes these are recovered and can be reused.

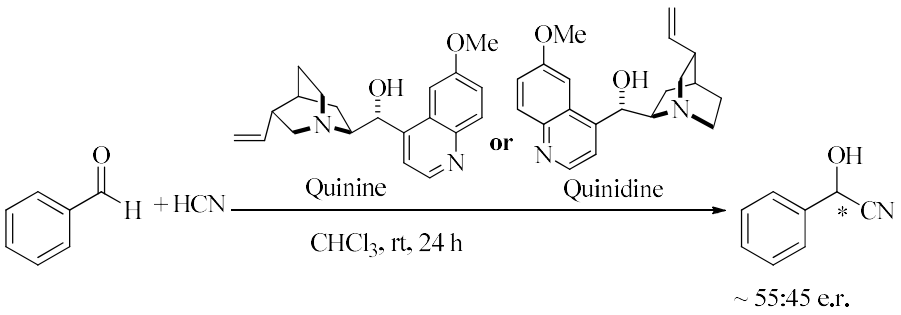
1.2.1 Historical developments in organocatalysis

In the middle of 19th century von Leibig's fortuitously discovered the transformation of dicyane into the oxamide in the presence of an aqueous solution of acetaldehyde. This reaction is considered to be the first organocatalytic reaction (**Scheme 1.6**).[25]



Scheme 1.6 von Leibig's oxamide synthesis

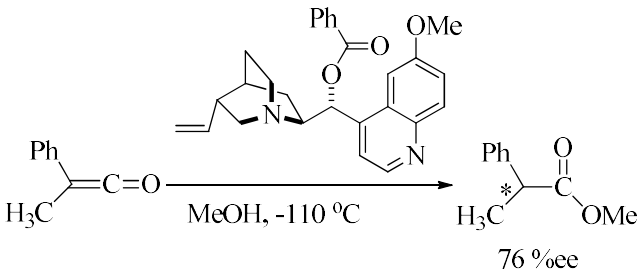
The first well established enantioselective reaction was performed on a prochiral substrate, benzaldehyde with HCN in the presence of catalytic amount of either quinine or quinidine. This contribution came from Bredig' and Fiske,[26] and the cyanohydrin product produced in <9% ee (**Scheme 1.7**) only. But these studies reveal the ground breaking concepts for enantioselective reactions.



Scheme 1.7 Bredig's and Fiske's synthesis of cyanohydrin

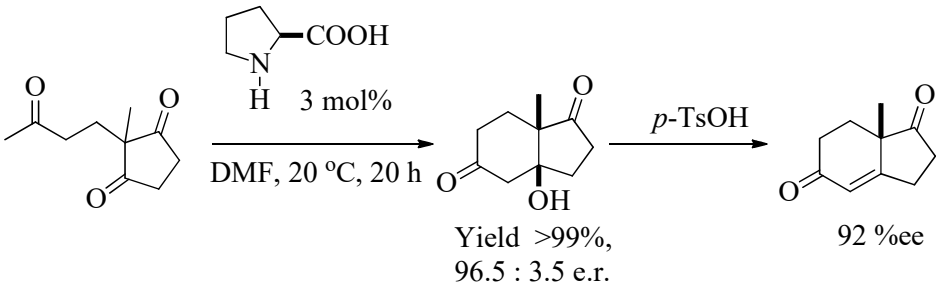
Pracejus[27a] and Maetje[27b] reported temperature dependent synthesis of enantiomerically enriched 2-phenyl propanoate having 76% ee from

phenyl(methyl)ketene and methanol in the presence of benzoyl quinine as the catalyst (**Scheme 1.8)**.



Scheme 1.8 Pracejus and Maetje's synthesis of chiral 2-phenyl propanoate

An inspired orgnaocatalytic highly enantioselective transformation was performed by Hajos, Parrish at Hoffmann-La Roche[28a,b] and Eder, Sauer and Weichert[28c,d] at Schering used (*S*)-proline as a catalyst. Today, this reaction is known as Hajos-Parrish-Eder-Sauer-Weichert reaction (**Scheme 1.9**).



Scheme 1.9 H-P-E-S-W reaction

Research groups of List[29a] and MacMillan[29b] initially demonstrated the enamine and iminium catalysis independently with the development of an asymmetric Diels-Alder reaction. Their pioneering work increases the awareness of employing purely organic

molecules as efficient catalysts for potential asymmetric transformations and is addressed as organocatalysis.

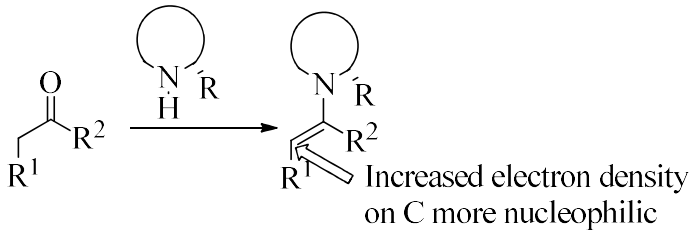
1.3 Different organocatalytic modes of activations

Organocatalytic modes of activation can be classified according to the covalent or non-covalent character of the substrate-catalyst interaction and to the chemical nature (Lewis acid, Lewis base, Brønsted acid, Brønsted base) of the catalyst.[30] The majority of organocatalyst are N, C, O, P and S based Lewis bases. Among these, nitrogen-based organocatalysts are widely employed for asymmetric transformations. It covers the diverse mechanisms and convert substrate into either an activated nucleophiles or electrophiles and this class is referred as amino catalysis[31] and is comes under the category of covalent catalysis. Today's aminocatalytic transformations of carbonyl compounds via iminium ion and enamine intermediates using chiral primary and secondary amines (as well as their salts) as organocatalysts, hinges upon four distinct activation modes and is categorized accordingly in: (i) enamine, (ii) iminium ion, (iii) dienamine and (iv) Singly Occupied Molecular Orbital (SOMO) catalysis.

i. Enamine activation catalysis[32]

It involves the initial acid-promoted condensation of carbonyl compounds with the amine to generate an enamine intermediate (**Scheme 1.10**). This mode of activation results in increased electron density (HOMO level increases) at the reaction center(s). The intermediate product formed is more prone to further transformations and acts as a Lewis base. Due to protonation-deprotonation, there exist a facile equilibrium between enamine

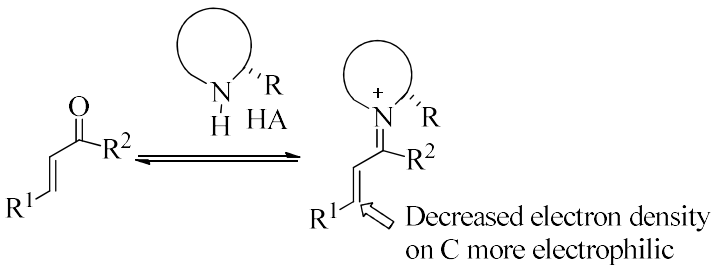
(electron-rich) and iminiun (electron-deficient) states of the same center. Further the reaction condition will direct the chemical transformations entirely in different mechanistic pathways result in different products.



Scheme 1.10 Activation of saturated carbonyl compounds to enamine intermediate

ii. Iminium activation catalysis

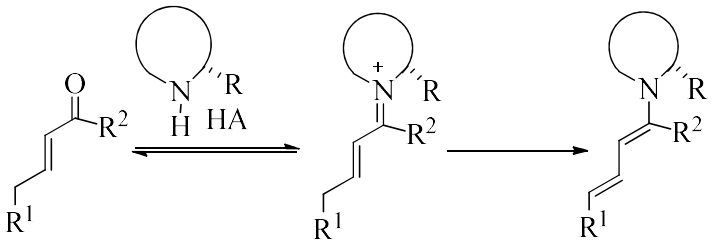
In 1937, Langenbeck[33a] was first reported the iminium catalysis. Later on, this field was advanced by the contribution of Cordes,[33b] Baum,[33c] Jung[33d] and Woodward. It involves the formation of an iminium intermediate by the condensation of α, β-unsaturated carbonyl compounds with the amine (**Scheme 1.11**). The electron density at reaction center is lowered (LUMO-level decreased). The concept of iminium catalysis is more explored by MacMillan[33e] for the last two decades.



Scheme 1.11 Activation of unsaturated carbonyl compounds to iminium intermediate

iii. Dienamine activation catalysis[34]

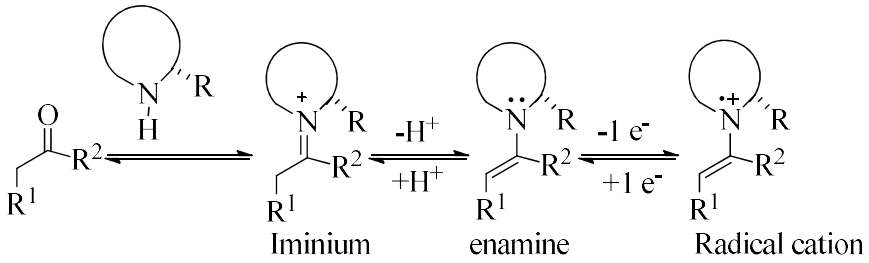
α,β-Unsaturated carbonyl compounds containing γ-hydrogen undergo condensation with the amine catalyst to forms an iminium ion which on subsequent γ-hydrogen deprotonation produce an electron rich dienamine intermediate (**Scheme 1.12**). The *s*-cis conformer of this intermediate undergoes a highly stereoselective [4+2]-cycloaddition reaction. Upon hydrolysis catalyst-product cleavage takes place.



Scheme 1.12 Dienamine intermediate formation from unsaturated carbonyl compounds

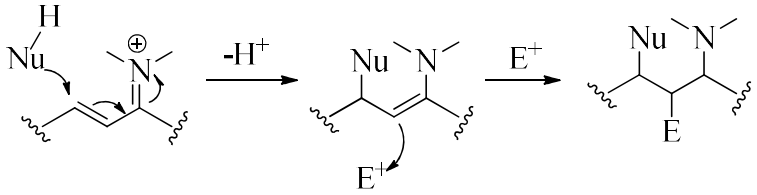
iv. Singly Occupied Molecular Orbital (SOMO) activation catalysis

In 2007, MacMillan and co-workers[35] introduced a new pathway for α-functinalization of carbonyl compounds. This mode of activation involves the condensation of carbonyl compounds with the secondary amine catalyst leads to an iminium ion (2π electrons) followed by enamine (4π electrons). Upon mild oxidation, the enamine is transformed to a cation radical (3π electrons) with a singly occupied molecular orbital (SOMO) as shown in the **Scheme 1.13**.



Scheme 1.13 Radical cation formation from saturated carbonyl compounds

In organocatalysis, enamine and iminium ion catalysis are two divergent reaction modes, though sharing a common ion formation and almost always results in iminium ion formation. Further conjugate addition of a nucleophile to an iminium ion generates an enamine intermediate which can in turn react with another electrophile (**Scheme 1.14**).[32b] The interdependency of these two catalytic intermediates promote several types of transformations based on different activation modes side by side makes aminocatalysis a powerful tool in the construction of complex molecular skeletons in a highly stereocontrolled manner.

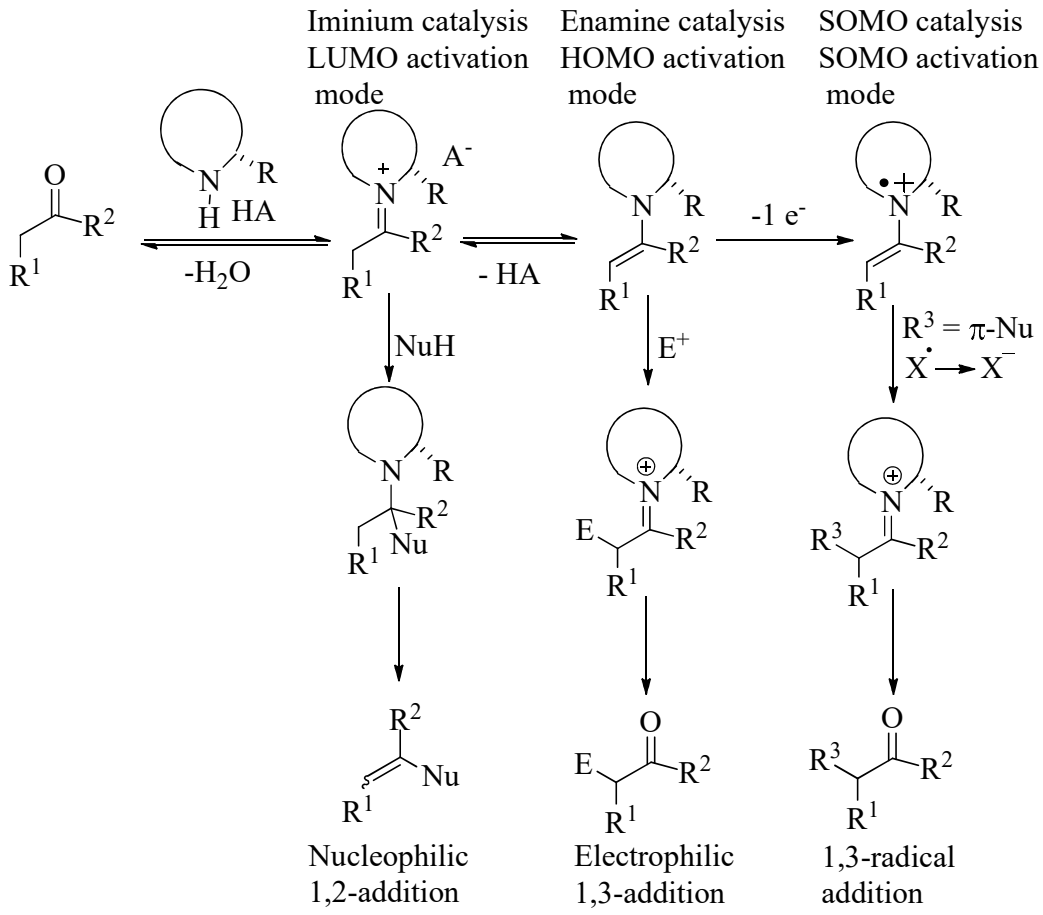


Scheme 1.14 Interdependency representation of enamine and iminium catalysis

In principle, the aminocatalytic activation emulates the mechanism of the activation of carbonyl compounds by Lewis acids. But in metal catalysed reactions of α,β-unsaturated ketones, the steric and electronic similarity of the carbonyl substituents does not permit high levels of discrimination between the free electron lone pairs in the metal-association step, which is essential for attaining high stereocontrol in subsequent

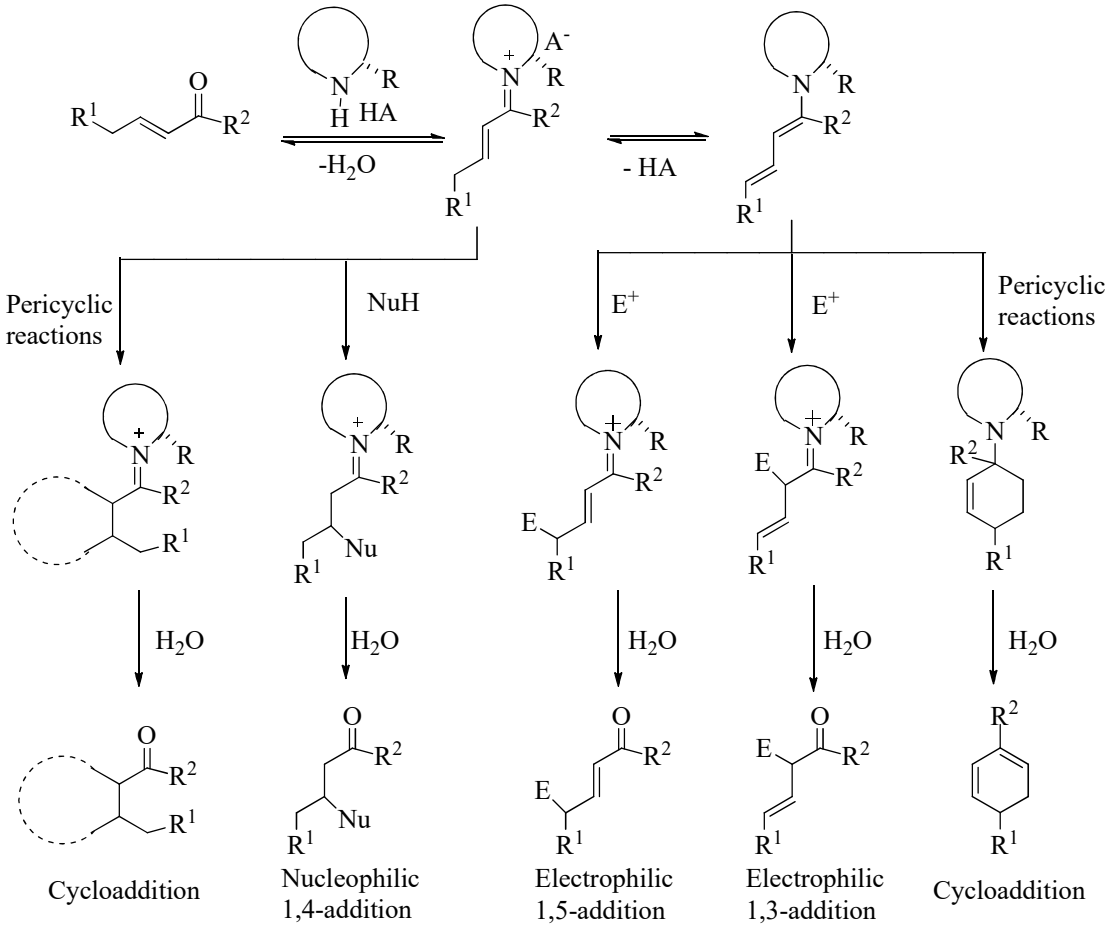
transformation. In aminocatalysis by contrast, iminium ion formation overcomes the necessity of discriminating between the free electron lone pairs.

Divergent reaction pathways of various saturated carbonyl compounds through aminocatalysis are represented in the **Scheme 1.15**.



Scheme 1.15 Aminocatalytic activation modes and divergent reaction pathways with aldehyde and ketones

Divergent reaction pathways of various unsaturated carbonyl compounds such as enals and enones, through aminocatalysis are represented in the **Scheme 1.16**.

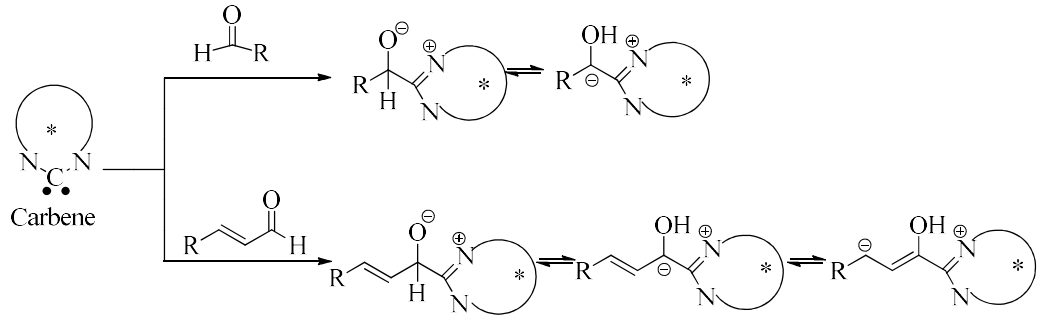


Scheme 1.16 Aminocatalytic activation modes and divergent reaction pathways with enals and enones

v. Carbene activation catalysis[36]

N-Heterocyclic carbenes (NHCs) are a class of Lewis base catalysts. The employment of carbenes is found in the pioneering work of Buchner, Curtius, Staudinger and Kupfer in the early 20th century. The mechanism of NHC involves the inversion of electrophilic carbonyl center to a nucleophilic carbonyl center, popularly known as umpolung

(**Scheme 1.17**). This mode of activation leads to *ipso*-functionalization of saturated carbonyl compounds and α-functinalization of α,β-unsaturated carbonyl compounds.

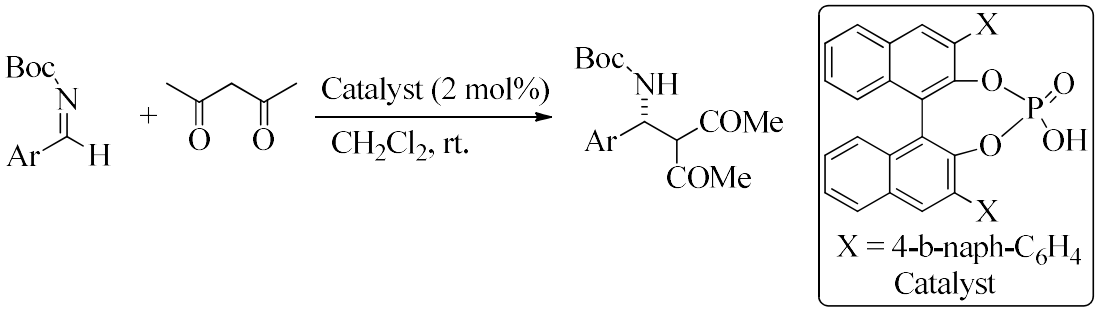


Scheme 1.17 Carbene assisted intermediates formation for *ipso* and α-functinalization of saturated and unsaturated carbonyl compounds

Besides covalent catalysis, non covalent catalysis is also emerged as a potential tool for the asymmetric transformations. It involves the non-bonding interactions of the substrate containing basic functional groups with the catalyst. These non covalent interactions enhance the electrophilicity of the substrate and make it more facile for nucleophilic attack. Based on the degree of proton transfer in the transition-state, one can distinguish hydrogen-bonding activation catalysis[37a,b] and Brønsted acid activation catalysis.[37c,d] Chiral (thio) ureas, chiral amidinium ions, chiral squaramides and chiral diols are the most widely employed H-bonding catalyst.

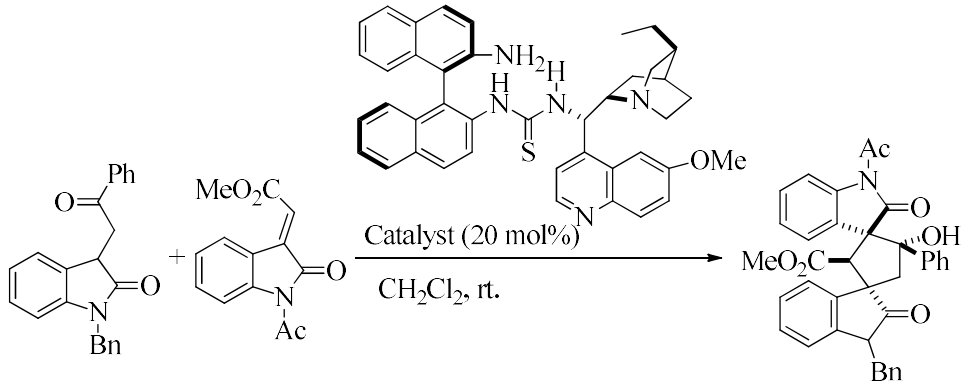
In Brønsted acid activation catalysis, catalyst transfers a proton to a basic center in the substrate and makes it more electrophilic. This field is more dominated by the chiral BINOL-derived phosphoric acids, which promotes the nucleophilic attack of carbonyl compounds through contact ion pair (**Scheme 1.18**). Through the principle of H-

bonding donor catalysis by anion-binding, Jacobsen emphasized the relation between H-bonding and Brønsted acid catalysis.[38-40]



Scheme 1.18 Example for Brønsted acid catalysis

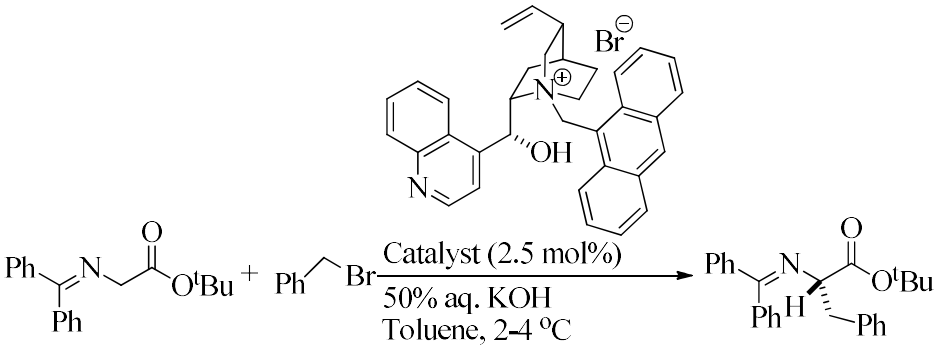
Another class of noncovalent catalysis is the bifunctional asymmetric catalysis. This field was pioneered by Shibasaki and co-workers,[41] involves the synergistic activation of both acidic and basic sites in the substrate (**Scheme 1.19**).[42] This strategy is first developed by Takemoto and co-workers.[43,44]



Scheme 1.19 Example for bifunctional asymmetric catalysis

Asymmetric Phase Transfer Catalysis (PTC) is a class of catalysis involving the contact ion pair mechanism. After the successful application of cinchona alkaloid based

quaternary ammonium salts as PTC catalyst, this field has been more explored to wide range of transformation for the last three decades.[40] Here, the deprotonated neutral pronucleophile forms tight ionic complex at the interface of organic and aqueous phase with the chiral ammonium ion (genetates the asymmetric induction over the nucleophilic anion). This complex is more prone to the electrophilic attach followed by releasing the formed product (**Scheme 1.20**).



Scheme 1.20 Example for phase transfer catalysis

1.4 Summary of the desertion research

The development of novel synthetic organocatalysed methodologies has become wide spread popularity because of its advantages over the other related fields. In the following chapter's significant efforts have been made towards the step wise approaches to meet the target. 1,4-Addition of 1,3-dicarbonyl compounds to nitrodiene through non-covalent interactions mode of catalysis technique has been described in **Chapter 2**. In **Chapter 3**, a stereo selective asymmetric organocatalytic green methodology "on-water" for the construction of highly substituted cyclohexanones has been described. The development of diastereoselective, primary amine catalysed highly substituted cyclohexanone with-all

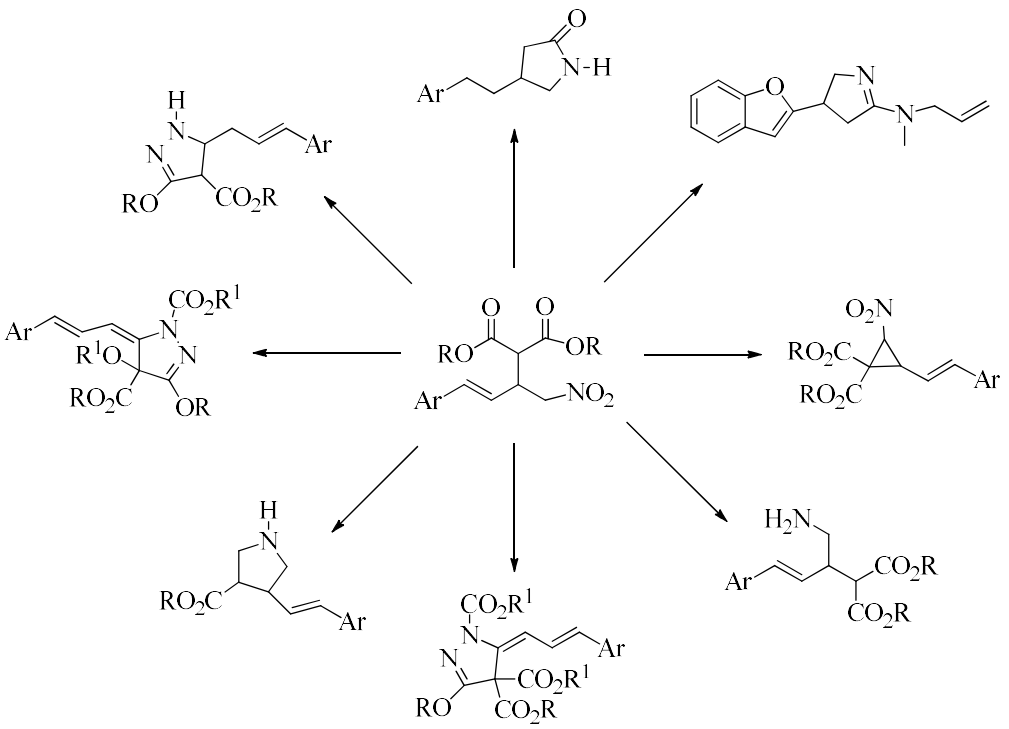
carbon quaternary center has been elaborated in **Chapter 4**. The development of organocatalysed C-C bond formation between β-ketoacids and α-ketophosphonates via decorboxylative aldol reaction has been presented in **Chapter 5**.

CHAPTER 2

Organocatalyzed highly regio- and enantioselective Michael addition of malonates to nitrodienes

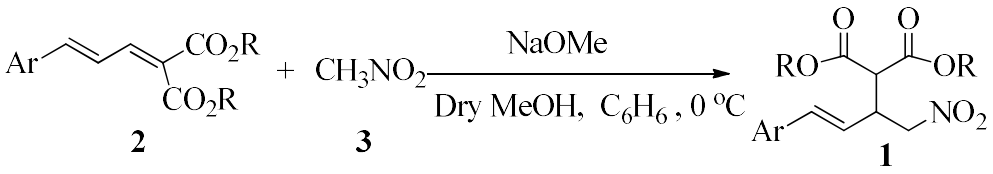
2.1 Introduction

Nitro substituted cyclopropane derivatives,[48] γ-amino carbonyl compounds[49] and heterocyclic compounds[50] are found to be important intermediates for the synthesis of various natural products and biologically active compounds. The synthesis of the variety of active pharmaceutical ingredients have been established starting from γ-amino carbonyl compounds and heterocyclic compounds. (*E*)-Dialkyl 2-(1-nitro-4-arylbut-3-en-2-yl)malonate **1** was chosen as one of the most important intermediate to synthesize the said skeletons as well as various biologically active compounds as shown in the **Scheme 2.1**.[51-55] In addition to this, γ-aminobutyric acid (GABA) derivatives[56] which are known as the major inhibitory neurotransmitters in the mammalian central nervous system could also be derived from the (*E*)-dialkyl 2-(1-nitro-4-arylbut-3-en-2-yl)malonate **1.**



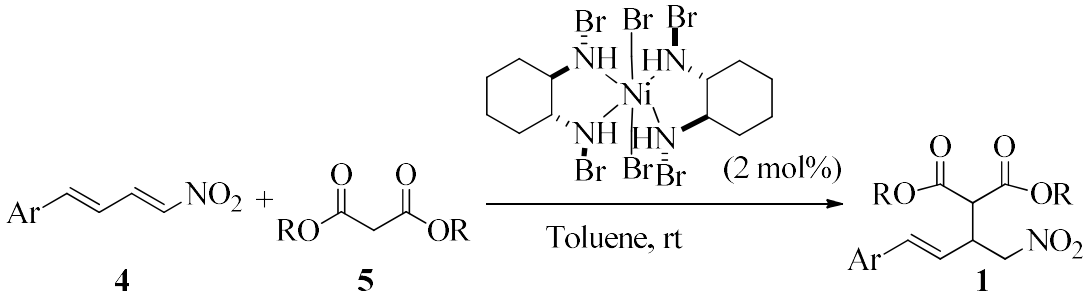
Scheme 2.1 Diverse applications of malonate intermediate **1**

A number of different synthetic approaches have been developed for the synthesis of **1** based on 1,4-addition of appropriate nucleophiles on activated dienes. In 1919, Engel-Brecht and Kohler reported the addition of nitromethane to dienedioates in the presence of sodium methoxide in dry methanol.[57] The intermediate upon neutralisation with AcOH followed by saturated with HCl offers the malonate derivative **1** as shown in the **Scheme 2.2**.



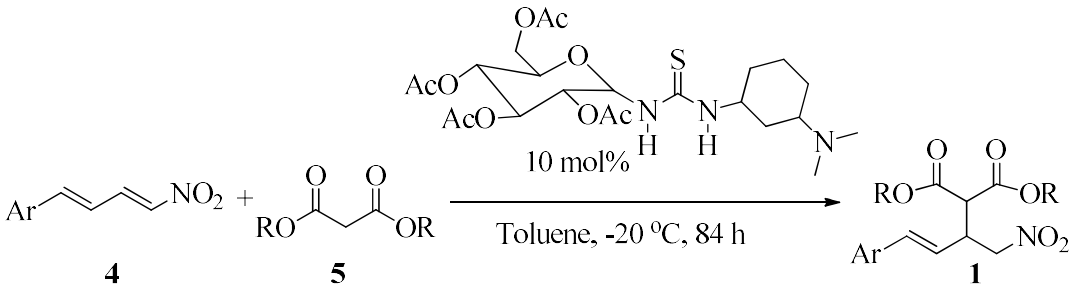
Scheme 2.2 Engel-Brecht and Kohler's synthesis for intermediate **1**

In 2007, Evans and co-workers[58] reported the synthesis of **1** via asymmetric Lewis-acid catalyzed Michael addition of dialkyl malonate to 4-aryl-1-nitrobutadienes (**Scheme 2.3**).



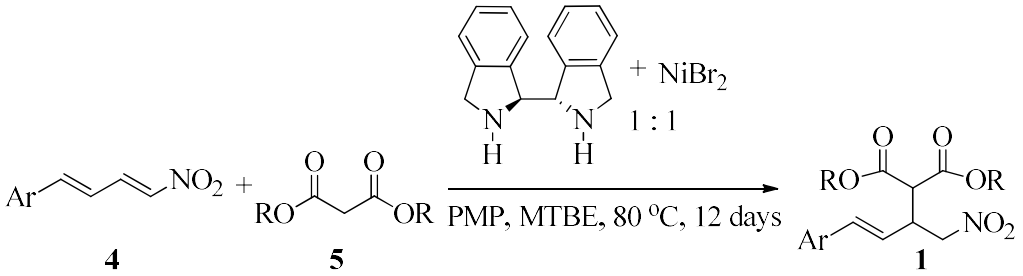
Scheme 2.3 Evans synthesis for intermediate **1**

In 2008, Ma and co-workers[59] reported the Michael addition of malonates to nitrodiene using catalytic amount of saccharide-derived bifunctional thiourea as shown in the **Scheme 2.4**.



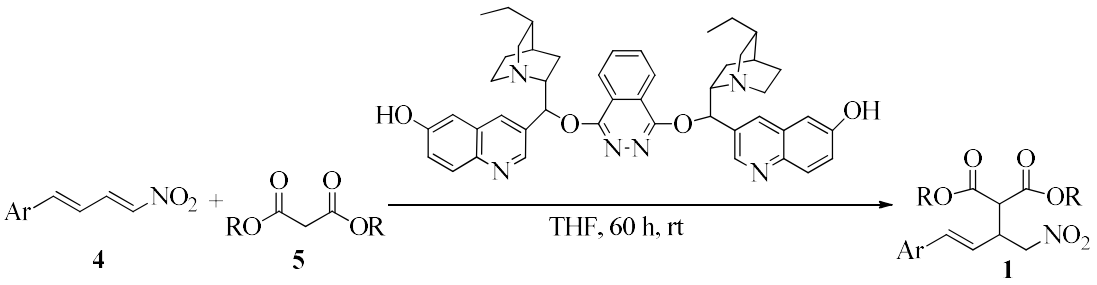
Scheme 2.4 Ma's synthesis for the intermediate **1**

Chungu and co-workers in 2009, reported the synthesis of malonate **1** using biisoindoline and 'Ni' complex based catalyst in presence of 1,2,2,6,6-pentamethylpiperidine (PMP) and *tert*-butylmethyl ether (MTBE) as the solvent for the Michael addition of malonates to nitrodiene (**Scheme 2.5**).[60]



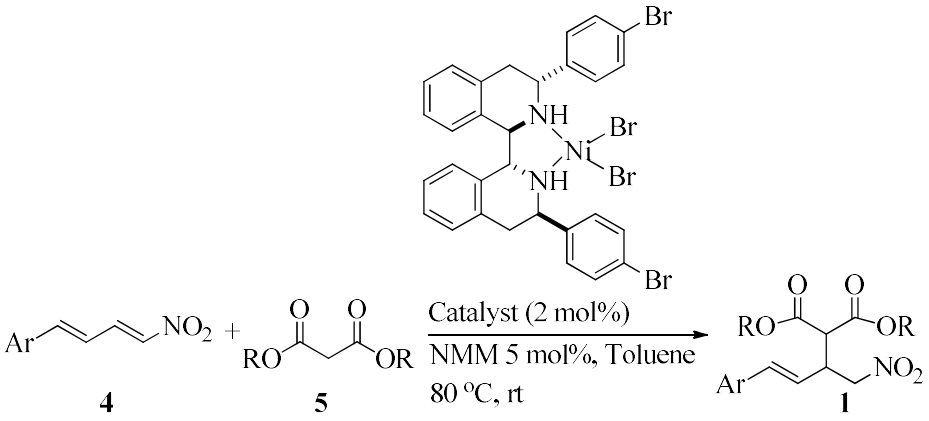
Scheme 2.5 Chungu's synthesis for the intermediate **1**

In 2010, Guoqiang *et al.*[61] reported the formation of Carbon-Carbon between nitrodiene **2** and 1,3-dicarbonyl compounds **3** through Michael addition using chiral diquinidine catalyst (**Scheme 2.6**).



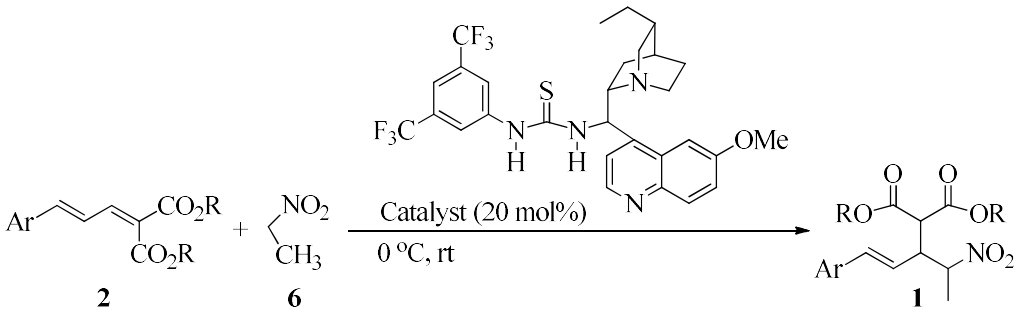
Scheme 2.6 Guoqiang's synthesis for the intermediate **1**

In 2011**,** Czekelius and co-workers[62] demonstrated that chiral C_2-symmetric 1,2-diamine based on a 1,1-bi(tetrahydroisoquinoline) scaffold with Ni^{II} complex in presence of *N*-methylmorpholine (NMM) can be an efficient catalyst for the enantioselective Michael addition of malonic esters to conjugated nitroalkenes and nitrodienes (**Scheme 2.7**).



Scheme 2.7 Czekelius's synthesis for the intermediate **1**

Quintavalla and co-workers[63] in 2012 reported that cinchona alkaloid-derived bifunctional thioureas efficiently catalyze the enantioselective conjugate addition of nitroalkanes to alkylidenemalonates with syn-diastereoselectivity (**Scheme 2.8**). This route opens the pathway to the synthesis of unnatural optically active γ-aminoacid derivatives.



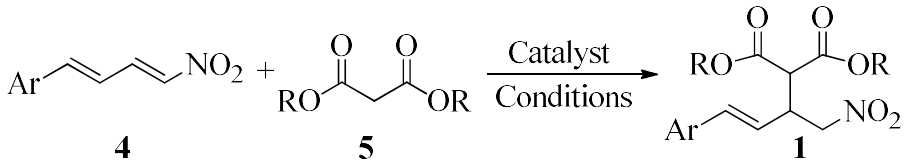
Scheme 2.8 Quintavalla's synthesis for the intermediate **1**

2.2 Present Work

Catalytic asymmetric Michael addition reaction is one of the most commonly used technique for C-C and C-X (X = heteroatom) bond formation in organic synthesis.[64] Today this organocatalysed version of Michael addition reaction is more rejuvenated, because of diverse complex structural molecules are being synthesized in an atom-economic way by the addition of nucleophiles to the Michael acceptors. The repository of electron-deficient simple olefins such as nitro olefins,[65] enones,[66] enals[67] *etc*. are employed as Michael acceptors. Correspondingly, active methylene group containing compounds such as 1,3-dicarbonyl compounds,[68] malonates, malononitriles are acting as Michael donors. Until now, the extended conjugated systems such as activated diens and enynes has been less explored as Michael acceptors. This type of Michael acceptors underwent asymmetric conjugate addition reactions leading to highly functionalized intermediates. This would enhance the utility of the approach in the synthesis of natural products and pharmaceutical intermediates. The presence of the extra conjugation in the Michael acceptor system debates the issue of regio-selectivity over 1,4-addition versus 1,6-addition. But in practice 1,4-addition[69] is favored over 1,6-addition[70] based on the principle of vinilogy.[71] Even though acyclic or cyclic β-ketoesters employed as donors for

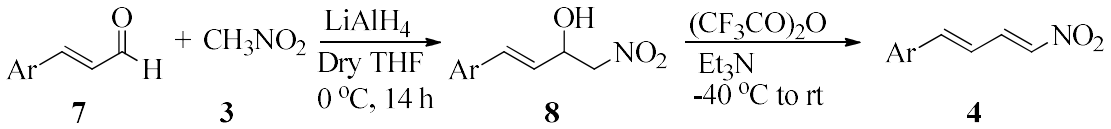
conjugate addition to nitrodienes using chiral guanidines[72] and 6'-OH cinchona alkoloids[73] as a promoters, still now this version of studies is not explored in detail. Nitroenynes have recently been used as substrates in metal-[74] or organo-catalyzed[75] selective 1,4-addition of malonates, β-keto esters and β-diketones.

Therefore, we have undertaken an investigation of new protocol to construct (*E*)-dialkyl 2-(1-nitro-4-arylbut-3-en-2-yl)malonates **1** (**Scheme 2.9**). This process utilises the synthetic convenience of malonates as nucleophiles and nitrodienes as electrophile under mild organocatalysis that follows 1,4-addition path.[76]



Scheme 2.9 Proposed synthesis of the malonate intermediate **1**

Nitrodienes **4** are prepared[82,83] from the commercially available cinnamaldehydes **7** and nitromethane **3** through Henry reaction followed by dehydration (**Scheme 2.10**).



Scheme 2.10 Synthesis of nitrodienes

Chiral bifunctional thiourea catalysts derived from the natural alkaloids and *trans*1,2 diaminocyclohexane have been used as organocatalyst for many reactions including aldol, Michael and Mannich reactions. We have prepared[76-78] seven bifunctional

thiourea catalysts **9-15** (**Figure 2.1**) to examine their ability for the Michael addition of malonate **5** to nitrodiene **4.**

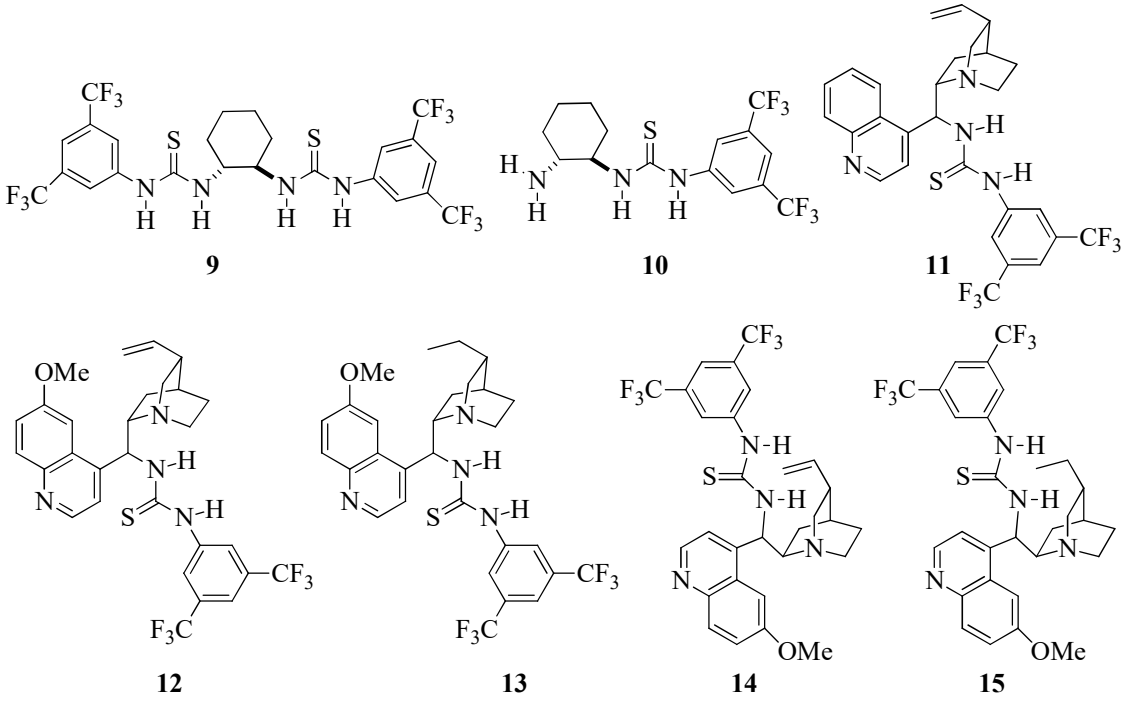


Figure 2.1 Structure of the bifunctional organocatalysts

2.2.1 Optimization of reaction conditions

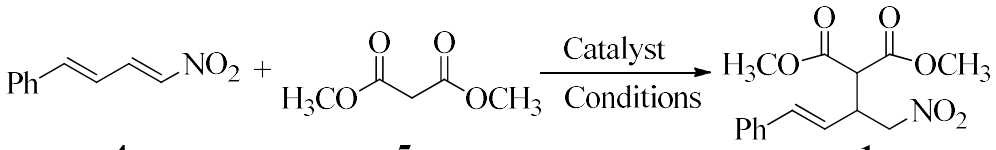
Initially the reaction between nitrodiene [(*1E,3E*)-4-nitrobuta-1,3-dien-1-yl]benzene **4a** and dimethyl malonate **5a** leading to (*E*)-dimethyl 2-(1-nitro-4-phenylbut-3-en-2-yl)malonate **1a** was chosen as the model reaction for the evaluation of thiourea based catalysts. A number of initial experiments were performed to investigate the effect of bifunctional thiourea derived organocatalysts **9**,[77]**10**[78] and **11-15**[79] (**Figure 2.1**) and solvents on formation of Michael addition product malonate **1a.**

For identification of the suitable catalyst, the reaction was performed using 10 mol% each of the catalysts **9-15** in toluene at room temperature (~28 ^{o}C). The *trans*-1,2-diaminocyclohexane based bis-thiourea catalyst **9** failed to produce the desired addition product **1a** (**Table 2.1**, entry 1). The monothiourea catalyst **10** showed modest activity under the same conditions to furnish **1a** in moderate yield and enantioselectivity (**Table 2.1**, entry 2). The *Cinchona* alkaloid-derived catalysts **11-15** showed high catalytic activity under the similar reaction conditions (**Table 2.1**, entries 3-7) and the reactions were complete in all cases. In particular, the catalysts **13** and **15** showed highest yield and enantioselectivity (**Table 2.1**, entries 5 and 7). The enantiopreference with catalysts **11-13** was opposite to that of the catalyst **15** and provided the adduct *ent*-**1a**.

Next we studied the effect of solvents for the formation of the product **1a** using 10 mol% of catalyst **15** (**Table 2.1**, entries 8-12) at the room temperature. Amongst the chosen solvents, dichloromethane and the ethers (Et_2O and THF) produced similar yield and enantioselectivity of the product **1a** as obtained in toluene (**Table 2.1**, entries 8-10). But the reaction rate in Et_2O was comparable to that in toluene. The yield and enantioselectivity were low in polar aprotic solvents such as CH_3CN and DMF (**Table 2.1**, entries 11 and 12). This may be due to loss of H-bonding interaction between the catalyst and the nitrodiene. When the addition reaction was performed using catalyst **15** at lower temperature (-20 °C) in toluene, the enantioselectivity of the addition product **1a** improved significantly (**Table 2.1**, 88% ee, entry 13) but the reaction took longer time to complete. Under all these conditions, the reaction exclusively furnished the 1,4-addition product only. Based on these results, we formulated the optimized reaction conditions as:

nitrodiene **4a** (1 equiv), dimethyl malonate **5a** (2 equiv), catalyst **15 (**10 mol%), toluene as the solvent and the reaction temperature as -20 °C**.**

Table 2.1 Optimization of the asymmetric Michael addition of dimethyl malonate 5**a** to nitrodiene **4a**.[a]



4a **5a** **1a**

Entry	Catalyst (10 mol %)	Solvent	Time (h)	Yield (%)[b] [ee (%)][c]
1	**9**	Toluene	48	n.r.[d]
2	**10**	Toluene	30	55[e] [49]
3	**11**	Toluene	44	72 [-42]
4	**12**	Toluene	24	83 [-50]
5	**13**	Toluene	26	82 [-70]
6	**14**	Toluene	42	88 [38]
7	**15**	Toluene	24	90 [70]
8	**15**	CH_2Cl_2	47	91 [68]
9	**15**	Et_2O	24	89 [62]
10	**15**	THF	48	90 [65]

11	**15**	DMF	72	20[e] [25]
12	**15**	CH_3CN	72	45[e] [54]
13	**15**	Toluene	52	85 [88][f]

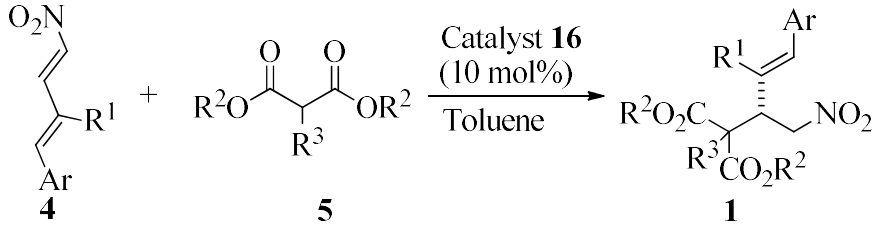
[a]Reactions were performed with nitrodiene **4a (**0.25 mmol) dimethyl malonate and **5a (**0.5 mmol) and in the presence of the respective catalysts (10 mol%) in dry solvents (0.5 mL). [b]Yield of chromatographically homogeneous products. [c]Determined by HPLC analysis on Daicel chiralpak AD-H column. [d]n.r. = no reaction. [e]Incomplete reaction. [f]Reaction performed at -20 °C.

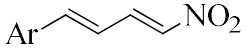
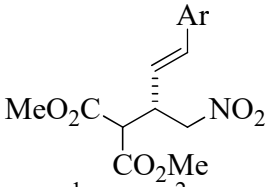
2.2.2 Study of the substrate scope

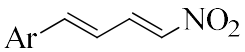
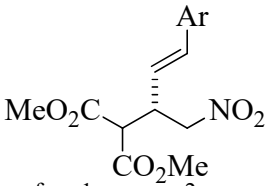
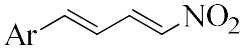
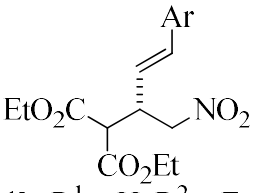
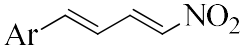
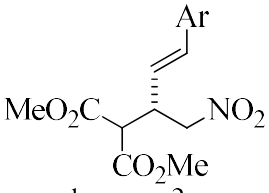
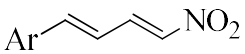
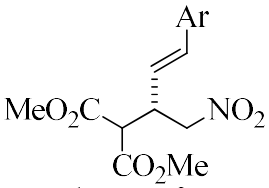
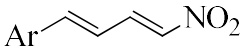
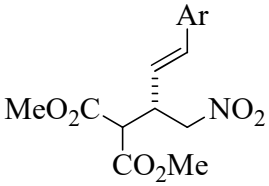
With the optimal reaction conditions in hand, we next examined the generality of this organocatalytic process. To establish the scope of the reaction, different nitrodienes **4a-h** and three different Michael donors *viz* dimethyl malonate **5a**, diethyl malonate **5b** and dimethyl allylmalonate **5c** were employed. The results are summarized in **Table 2.2**. Substituent on the aromatic ring of the 4-aryl-1-nitrobutadienes had minimal effect on the reactivity except for 2-substituted aryl group **4b** where the reaction was slower (**Table 2.2**, entry 4), probably due to the steric factor. The solubility of the nitrodienes **4c-e** in toluene at -20 °C was poor. Hence, their reactions were performed at 0 °C and/ or at room temperature. The nitrodiene **4f** bearing a 3-methyl group also resulted in the formation of the addition product **1h** with acceptable yield and enantioselectivity. But the reaction was sluggish and remained incomplete (80% conversion) presumably due to unfavoured interaction between the substrate and nucleophile. The 4,4-dialkyl substituted nitrodiene

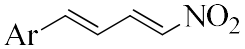
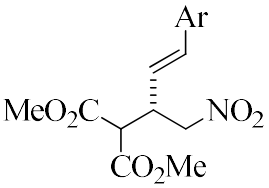
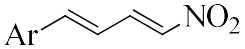
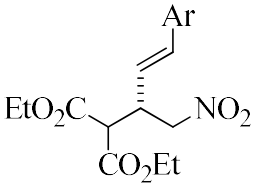
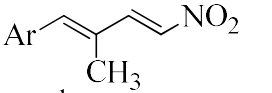
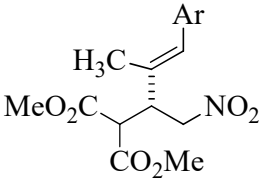
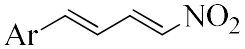
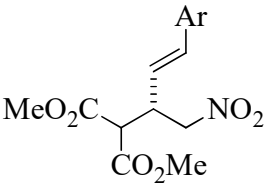
4h also underwent the Michael addition with dimethyl malonate **5a** at room temperature. The corresponding addition product **1j** was obtained in good yield and with good enantioselectivity. The majority of the addition products (**Table 2.2**, 1a-d and 1g) were solids and a few of them after single recrystallization provided the products with improved enantiomeric excess (**Table 2.2**, entries 1, 2, 4 and 8) of the products. The reaction of dimethyl allylmalonate **5c** with nitrodiene **4a** was very slow at -20 °C. Although the reaction rate was enhanced at 0 °C, the reaction remained incomplete (60% conversion) even after 6 d. In all these cases 1,4-addition products **1a-h** were formed exclusively with good to excellent yields and enatioselectivities.

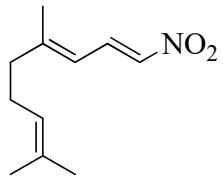
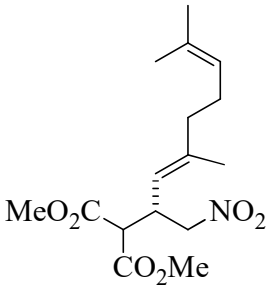
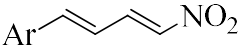
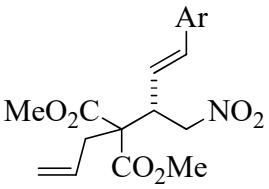
Table 2.2 Michael addition of malonates **5a-c** to nitrodienes **4a-h**.[a]



Entry	Nitrodiene	Temp (°C)/ Time (d)	Product	Yield[b] (%)	ee (%)[c]
1	 **4a**, R^1 = H, Ar = Ph,	-20/3	 **1a**, R^1 = H, R^2 = Me, R^3 = H, Ar = Ph	85 (47)[d]	88 (99)[c]

2	 **4a**, R^1 = H, Ar = Ph,	-20/3	 **1a**[f], R^1 = H, R^2 = Me, R^3 = H, Ar = Ph	85 (48)[d]	88 (99)[c]
3	 **4a**, R^1 = H, Ar = Ph,	-20/6	 **1b**, R^1 = H, R^2 = Et, R^3 = H, Ar = Ph	80	88
4	 **4b**, R^1 = H Ar = 2-OMePh	-20/6	 **1c**, R^1 = H, R^2 = Me, R^3 = H, Ar = 2-OMePh	75[h] (50)[d]	89 (99)[e]
5	 **4c**, R^1 = H Ar = 4-NO_2Ph	28/1.5	 **1d**, R^1 = H, R^2 = Me, R^3 = H, Ar = 4-NO_2Ph	70	76
6	 **4d**, R^1 = H Ar = 4-BrPh	0/1.7	 **1e**, R^1 = H, R^2 = Me, R^3 = H, Ar = 4-BrPh	87	84

7	 **4e**, R^1 = H Ar = 4-ClPh	0/2.5	 **1f**, R^1 = H, R^2 = Me, R^3 = H, Ar = 4-ClPh	93	85
8[g]	 **4e**, R^1 = H Ar = 4-ClPh	0/2.5	 **1g**, R^1 = H, R^2 = Et, R^3 = H, Ar = 4-ClPh	91 (45)[d]	80 (99)[e]
9	 **4f**, R^1 = CH_3, Ar = Ph	-20/6	 **1h**, R^1 = CH_3, R^2 = Me, R^3 = H, Ar = Ph	66[h]	80
10	 **4g**, R^1 = H Ar = 3-BrPh	-20/3	 **1i**, R^1 = H, R^2 = Me, R^3 = H, Ar = 3-BrPh	95	85

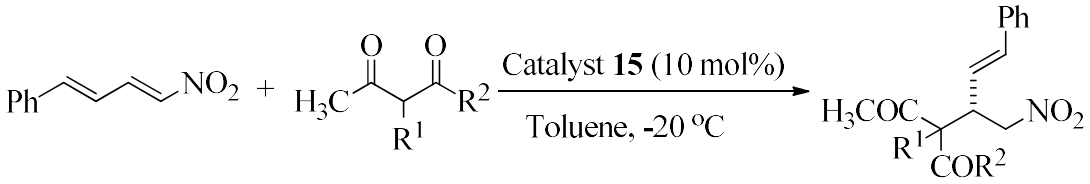
11	 **4h**	28/2	 **1j**, R^2 = Me, R^3 = H	76	72
$12^{i,j}$	 **4a**, R^1 = H, Ar = Ph,	0/6	 **1k**, R^1 = H, R^2 = CH_3 R^3 = $CH_2CH{=}CH_2$, Ar = Ph	45^h	85

[a]Unless otherwise specified, all the reactions were performed with nitrodiene (0.25 mmol) with malonate 3**a** (0.5 mmol) in the presence of 10 mol% of the catalyst **15** in dry toluene (0.5 mL). [b]Yield of chromatographically homogeneous product. [c]Determined by HPLC analysis using a chiral stationary phase. [d]% of yield after single recrystallization. [e]ee after single recrystallization. [f]Catalyst **13** was used instead of catalyst **15**. [g]Malonate **5b** was used. [h] Incomplete reaction. [i]Malonate **5c** was used. [j]20 mol% of catalyst **15** was used.

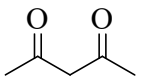
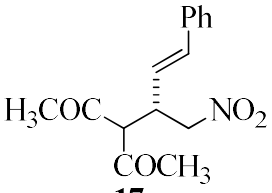
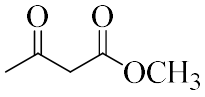
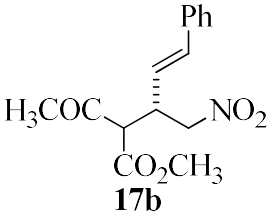
With the fruitful results from above, we further explored the Michael addition of 1,3-dicarbonyl compounds **16a-c** to nitrodiene **4a** under optimized reaction conditions. Acetylacetone **16a** gave the addition product **17a** (**Table 2.3**, entry 1) in excellent yield and high enantioselectivity. The ee of **17a** was significantly improved (>96%) upon

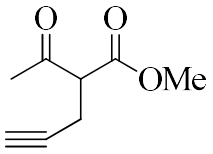
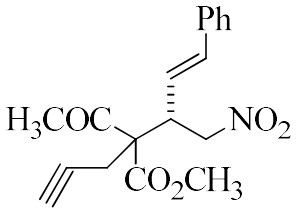
single recrystallization. Similarly, methyl acetoacetate **16b** also underwent 1,4-addition with nitrodiene **4a** to give the Michael adduct **17b** (**Table 2.3**, entry 2) in 90% yield as an inseparable 1/1 mixture of diastereoisomers. Each diastereoisomer was also formed with high enantioselectivity. The methyl 2-propargylacetoacetate **16c** offers the Michael adduct **17c** (**Table 2.3**, entry 3) as an inseparable mixture of diastereoisomers in a ratio of 70/30. Compared to minor diastereioisomer, major one shows the highest enantioselectivity.

Table 2.3 Michael addition of 1,3-dicarbonyl compounds to nitrodiene **4a**.[a]



4a **16** **17**

Entry	Nucleophile	Product	Yield[b] (%)	dr[c]	ee[d] (%)
1	 **16a**	 **17a**	92	-	79 (96)[e]
2	 **16b**	 **17b**	90	1/1	83[f], 81[g]

3	 **16c**	 **17c**	95	7/3	54[f], 80[g]

[a]Unless otherwise specified, all the reactions were performed with nitrodiene 4**a** (0.25 mmol) with the nucleophile (0.5 mmol) in the presence of 10 mol% of the catalyst **15** in dry toluene (0.5 mL) at -20 °C for 24 h. [b]Yield of chromatograhically homogeneous product. [c]Determined from ^{1}H NMR of the crude product. [d]Determined by HPLC analysis using a chiral stationary phase. [e]Improved by single recrystallization. [f]ee for 1st or major diastereoisomer. [g]ee for 2nd or minor diastereoisomer.

To assign the absolute configuration of the Michael adduct **1b,** we recorded the specific rotation value for **1b** and compared with the values reported in the literature indicating (*S*)-configuration to **1b** ($[\alpha]_D^{23}$ = -23.0, *c* = 1, $CHCl_3$; *lit.*[58] $[\alpha]_D^{22}$ = +26.1, *c* = 1.15, $CHCl_3$ for the antipode of **1b** with 95% ee). In analogy with **1b**, the absolute configuration of the other products **1a** and **1c-g** were tentatively assigned as (*S*)-configuration. Further the formation of the (*S*)-**1b** can be explained by dual activation model proposed by Takemoto *et. al.*[80] The NO_2 group in **4a** can complex to the thiourea moiety of the catalyst **15** by two H-bonding interactions while the enol form of dimethyl malonate can form H-bond to bridgehead nitrogen as shown in **TS-1** (**Figure 2.2**). The most favored approach would be at the *Si*-face of the nitrodiene **4a** because of least steric interaction at the transition state for the H-bonding interaction of the enol form of dimethyl malonate **5a** to bridgehead nitrogen leading to *S* configuration in the product **1a.** Another model proposed by Pàpai,[81] in which the NO_2 group in **4a** can complex to the

protonated bridgehead nitrogen as shown in **TS-2** (**Figure 2.2**) while thiourea moiety of the catalyst **15** can participate in two H-bonding interactions with the enolate form of dimethyl malonate. The most favored approach would be at the *Re*-face of the nitrodiene **4a** because of least steric interaction at the transition state for the H-bonding interactions leading to (*S)*-configuration for product **1a**

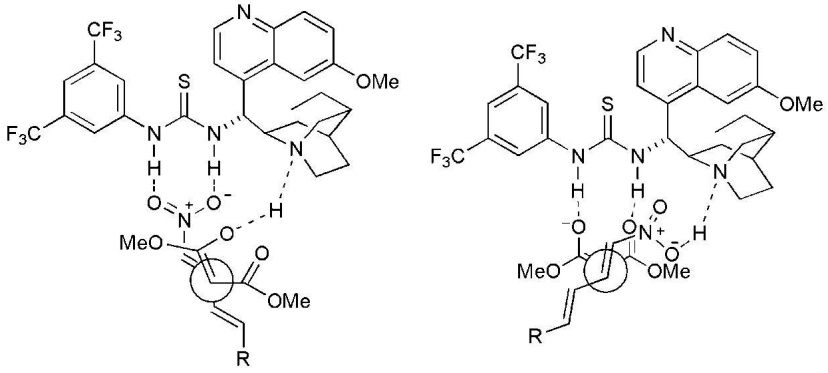
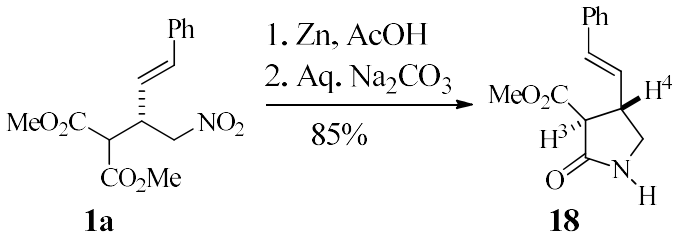


Figure 2.2 Transition state model

To show the utility of the method, we have synthesized the γ-lactam **18** (**Scheme 2.11**) from the addition product **1a.** The chemoselective reduction of the nitro group in **1a** by Zn and acetic acid gave the intermediate amine which upon cyclization furnished the desired lactam **18** in very good yield. The *trans*-relative configuration of lactam **18** was confirmed by ^{1}H-^{1}H ROESY spectra wherein no nOe interaction was observed between H^3 and H^4 (**Scheme 2.11**).



Scheme 2.11 Synthesis of a γ-lactam.

2.3 Conclusion

In summary, we have developed a method for the synthesizing 1,4-addition product from 1,3-dicarbonyl compounds and various substituted nitrodienes using easily accessible *cinchona* alkaloid-based thiourea organocatalysts. These addition reactions offer well to excellent yields and enantioselectivities. The addition products hold promise for the construction of stereo- and regio-chemically diverse heterocyclic skeletons comprised of flexible rings and embedded functionalities.

2.4 Experimental section

General Details: All reactions were performed in oven-dried (120 ^{o}C) or flame-dried glass apparatus under dry N_2 or argon atmosphere.

Solvent purification: The solvents were dried and distilled from the indicated drying agents. Toluene form sodium; THF, Diethylether from sodium/benzophenone; DMF, DCM from CaH_2 and then stored over molecular sieves. DBU was dried from CaH_2 and then stored over Ca metal.

NMR Study: ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker 200 MHz spectrometer. Spectra were referenced to residual chloroform (δ 7.26 ppm, ^{1}H; 77.00 ppm, ^{13}C). Chemical shifts are reported in ppm (δ); multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), quint (pentet), dd (doublet of doublet), m (multiplet) and br (broad). Coupling constants, *J*, are reported in Hertz.

Mass Spectrometry: Mass spectra were recorded on a Fission VG Quatro II mass spectrometer (EI 70 V; CI 30 V). HRMS were recorded in a Waters Micromass Q-TOF Mass Spectrometer.

High Performance Liquid Chromatography: Enantiomeric excess determination were carried out by JASCO HPLC model instrument fitted with a Daicel chiralpak AD-H/OD-H/OJ-H/AS-H column and UV detector with λ fixed at 220 nm/ 254 nm.

IR Study: IR spectra were recorded on a Nicolet Impact 410 FT IR spectrophotometer in NaCl cell or in KBr discs. Peaks are reported in cm^{-1}.

Melting Point: Melting points (mp) were determined on a Fischer John's point apparatus and are uncorrected.

TLC: Analytical thin-layer chromatography was performed using homemade Acme silica gel plates (about 0.5 mm).

Column Chromatography: Column Chromatography was performed using Silica Gel 230-400 mesh (for flash chromatography) obtained from Sisco Research Laboratories Pvt. Ltd.

2.4.1 General procedures and Materials

General Procedure I: Preparation of nitrodienes 4a-h & Catalysts 9-15.

The nitrodienes **4a-h** were prepared[82,83] following the general procedures reported in the literature. The organocatalysts **9**,[76] **10**[77] and **11-15**[78] were prepared following the literature procedures.

Preparation of nitrodiene 4a-h

((*1E,3E*)-4-nitrobuta-1,3-dien-1-yl)benzene 4a

Following the literature[82,83] procedure, a slurry of $LiAlH_4$ (72 mg, 1.5 mmol) in dry THF (75 mL) is stirred for 30 min at 0°C. Add nitromethane (4.1 mL, 75 mmol) to this slurry. After 30 min the corresponding aldehyde (1.98 g, 15.0 mmol) was added in one portion at 0°C. The mixture was stirred at 0°C for 16 hours. Then HCl 1N and water were added to the reaction mixture which was extracted three times with dichloromethane. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to give orange oil of nitro-alcohol which can be used without purification for the next step. Then, to a solution of nitro-alcohol freshly prepared (15.0 mmol), in dry dichloromethane (150 mL) was added at -40°C trifluoroacetic anhydride (2.2 mL, 16.0 mmol) and then NEt_3 (4.4 mL, 31.5 mmol). The reaction mixture was then allowed to warm at room temperature during the appropriate time until completion of the reaction. Then the reaction mixture was diluted in dichloromethane and the organic phases were washed with water, aqueous saturated solution of NH_4Cl and brine. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. Then the resulting oil/solid is purified using a mixture of ethyl acetate and hexane as eluant through column chromatography on silica gel offers the desired product **2a** (1.05 g, 40%) as a brilliant yellow colour solid. mp 44-46°C; IR (film): $\bar{\upsilon}$ = 3101, 1622, 1514, 1494, 1331, 1151, 993, 822, 760, 690 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 6.86-6.81 (1 H, m), 7.12-7.10 (1 H, d, J = 15.4 Hz), 7.20-7.18 (1 H, d, J = 13.2 Hz), 7.38-7.35 (3 H, m), 7.52-7.50 (2 H, m), 7.76-7.73 (1 H, t, J = 12.2 Hz) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 120.4, 127.6 (2 C),

128.9, 130.0, 135.1, 138.4 (2C), 139.1, 145.9 ppm; Elemental analysis calcd (%) for $C_{10}H_9NO$: calcd. C 68.56, H 5.18, N 8.00; found: C 68.54, H 5.20, N 7.97.

1-methoxy-2-((*1E,3E*)-4-nitrobuta-1,3-dien-1-yl)benzene 4b

The nitrodiene **4b** was prepared according to procedure for nitrodiene **4a** from 2-OMe cinnamaldehyde (2.43 g, 15.0 mmol) after column chromatography (eluent: Hexane/EtOAc = 98/2 as eluent) as yellowish viscuous oil, (0.75 g, 25%). IR (film): $\bar{\upsilon}$ = 3092, 2952, 2820, 1621, 1583, 1511, 1481, 1305, 1238, 1213, 1146, 1014, 982, 963, 821, 802, 752, 731, 516 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 3.75 (3 H, s), 6.72-6.70 (1 H, m), 6.90-6.89 (2 H, m), 7.11-7.08 (1 H, d, J = 15.4 Hz), 7.20-7.17 (1 H, d, J = 12.9 Hz), 7.72-7.75 (1 H, t, J = 11.0 Hz), 7.42-7.44 (2 H, m) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 55.3, 114.2, 118.2, 127.7 (2 C), 129.1, 137.1, 139.7, 145.7, 160.3 ppm; Elemental analysis calcd (%) for $C_{11}H_{11}NO_3$: calcd. C 64.38, H 5.40, N 6.83; found: C 64.30, H 5.20, N 7.07.

1-nitro-4-((*1E,3E*)-4-nitrobuta-1,3-dien-1-yl)benzene 4c

The nitrodiene **4c** was prepared according to procedure for nitrodiene **4a** from 4-NO_2 cinnamaldehyde (0.85 g, 5.0 mmol) after column chromatography (eluent: Hexane/EtOAc = 98/2 as eluent) as yellowish viscuous oil, (0.39 g, 35%). IR (film): $\bar{\upsilon}$ = 3122, 2982, 2870, 1631, 1593, 1531, 1491, 1335, 1258, 1243, 1166, 1044, 992, 973, 841, 822, 772, 741 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 8.25-8.19 (m, 2H), 8.05-8.03 (2 H, m), 7.92-7.78 (1 H, d, J = 15.6 Hz), 7.64-7.37 (1 H, d, J = 12.8 Hz), 7.30-7.15 (1 H, t, J = 11.1 Hz), 7.11-7.0 (1 H, m) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 148, 142.1, 139.2 (2 C), 136.1, 134.5, 129.6 (2 C), 128.5, 125.5 ppm; Elemental analysis calcd (%) for $C_{10}H_8N_2O_4$: calcd. C 54.55, H 3.36, N 12.72; found: C 54.45, H 3.45, N 12.62.

1-bromo-4-((*1E,3E*)-4-nitrobuta-1,3-dien-1-yl)benzene 4d

The nitrodiene **4d** was prepared according to procedure for nitrodiene **4a** from 4-Br cinnamaldehyde (1.06 g, 5.0 mmol) after column chromatography (eluent: Hexane/EtOAc = 98/2 as eluent) as brilliant yellow solid (0.48 g, 38%); mp 100-101 °C.; IR (film): $\bar{\upsilon}$ = 3089, 1619, 1567, 1529, 1460, 1329, 1145, 1046, 979, 819, 805, 732 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.20-7.18 (1 H, m), 7.38-7.35(1 H, m), 7.48-7.45 (2 H, m), 7.60-7.57 (3 H, m), 7.85-7.80 (1 H, t, J = 12.2 Hz) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 122.1 (2 C), 128.9, 129.0 (2 C), 134.3, 134.1(2 C), 139.1, 144.0 ppm; Elemental analysis calcd (%) for $C_{10}H_8BrNO_2$: calcd. C 47.27, H 3.17, N 5.51; found: C 47.15, H 3.22, N 5.45.

1-chloro-4-((*1E,3E*)-4-nitrobuta-1,3-dien-1-yl)benzene 4e

The nitrodiene **4e** was prepared according to procedure for nitrodiene **4a** from 4-Cl cinnamaldehyde (0.83 g, 5.0 mmol) after column chromatography (eluent: Hexane/EtOAc = 98/2 as eluent) as brilliant yellow solid (0.38 g, 36%); mp 108-110 °C.; IR (film): $\bar{\upsilon}$ = 3078, 1625, 1577, 1519, 1480, 1349, 1165, 1096, 979, 819, 807, 752 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.21-7.17 (1 H, m), 7.40-7.37 (1 H, m), 7.49-7.45 (2 H, m), 7.65-7.60 (3 H, m), 7.86-7.81 (1 H, t, J = 12.0 Hz) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 122.3, 129.0 (2 C), 128.7, 134.1 (2 C), 134.6, 139.9 (2 C), 144.0 ppm; Elemental analysis calcd (%) for $C_{10}H_8ClNO_2$: calcd. C 57.30, H 3.85, N 6.68; found: C 57.25, H 3.75, N 6.58.

((*1E,3E*)-2-methyl-4-nitrobuta-1,3-dien-1-yl)benzene 4f

The nitrodiene **4f** was prepared according to procedure for nitrodiene **4a** from (*E*)-2-methyl-3-phenylacrylaldehyde (0.73 g, 5.0 mmol) after column chromatography (eluent:

Hexane/EtOAc = 98/2 as eluent) as yellowish viscuous oil, (0.40 g, 42%); IR (film): ῡ = 3082, 2962, 2810, 1616, 1573, 1510, 1471, 1301, 1228, 1218, 1136, 1004, 972, 953, 811, 805, 752, 731cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.21 (3 H, s), 6.86-6.81 (1 H, m), 7.12-7.10 (1 H, d, J = 15.4 Hz), 7.20-7.18 (1 H, d, J = 13.2 Hz), 7.38-7.35 (3 H, m), 7.52-7.50 (2 H, m) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 120.4, 127.6, 128.9, 130.0, 135.1 (2 C), 138.4, 139.1 (2 C), 145.9, 18.2 ppm; Elemental analysis calcd (%) for $C_{11}H_{11}NO_2$: calcd. C 69.83, H 5.86, N 7.40; found: C 69.81, H 5.90, N 7.50.

1-bromo-3-((*1E,3E*)-4-nitrobuta-1,3-dien-1-yl)benzene 4g

The nitrodiene **4g** was prepared according to procedure for nitrodiene **4a** from 3-Br cinnamaldehyde (1.06 g, 5.0 mmol) after column chromatography (eluent: Hexane/EtOAc = 98/2 as eluent) as brilliant yellow solid (0.53 g, 38%); mp 91-93 °C.; IR (film): ῡ = 3079, 1629, 1547, 1519, 1450, 1339, 1125, 1036, 979, 821, 810, 712 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.18-7.15 (1 H, m), 7.33-7.31(1 H, m), 7.41-7.37 (2 H, m), 7.57-7.51 (3 H, m), 7.81-7.79 (1 H, t, J = 12.0 Hz) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 122.4 (2 C), 128.7, 128.9 (2 C), 134.2, 134.2 (2 C), 139.4, 144.4 ppm; Elemental analysis calcd (%) for $C_{10}H_8BrNO_2$: calcd. C 47.27, H 3.17, N 5.51; found: C 47.17, H 3.27, N 5.47.

(*1E,3E*)-4,8-dimethyl-1-nitronona-1,3,7-triene 4h

The nitrodiene **4h** was prepared according to procedure for nitrodiene **4a** from (*E*)-3,7-dimethylocta-2,6-dienal (0.76 g, 5.0 mmol) after column chromatography (eluent: Hexane/EtOAc = 98/2 as eluent) as yellowish viscuous oil (0.40 g, 41%); IR (film): ῡ = 3053, 1575, 1525, 1520, 1430, 1329, 1115, 1056, 969, 811, 805, 706 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ = ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.69 (3 H, s), 1.80 (3 H, s), 1.75 (3

H, s), 1.95 (4 H, t, J = 2.5 Hz), 5.18 (1 H, m), 6.41-6.37 (1 H, m), 7.22-7.19 (1 H, m), 7.56-7.44 (1 H, t, J = 12.0 Hz) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 18.5, 19.1, 23.5, 26.1, 39.1, 123.1, 124.5, 132.1, 134.1, 135.2, 139.2 ppm; Elemental analysis calcd (%) for $C_{11}H_{17}NO_2$: calcd. C 67.66, H 8.78, N 7.17; found: C 67.42, H 8.75, N 7.12.

Preparation of catalysts 9-15

1,1'-((*1R,2R*)-cyclohexane-1,2-diyl)bis(3-(3,5-bis(trifluoromethyl)phenyl)thiourea) 9

Following the literature[77] procedure, A solution of *trans*1,2-diaminocyclohexane (0.60 mL, 5.00 mmol, 1.0 equiv.) in dry DCM (10 mL) was cooled to 0 ^{o}C under an argon atmosphere. A solution of 3,5-*bis*(trifluoromethyl)-phenyl isothiocyanate (1.84 mL, 10.00 mmol, 2.0 equiv.) in dry DCM (10 mL) was added drop wise over 6 h. The resulting yellow solution was kept for overnight stirring. The reaction mixture was concentrated *in vacuo* and the yellow residue purified by column chromatography (70/30 EtOAc/$CHCl_3$) affording the thiourea catalyst **9** (1.38 g, 42%) as a yellow solid, mp 100-102 ^{o}C; IR ($CHCl_3$): $\bar{\upsilon}$ = 1262, 1152, 1147, 1125, 955, 870, 742 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6) δ = 1.15-1.41 (4 H, m), 1.50-1.69 (2 H, m), 1.78-2.15 (2 H, m), 2.42-2.51 (1 H, m), 3.69-3.90 (1 H, m), 7.62 (2 H, s), 8.19 (4 H, s) ppm; ^{13}C NMR (50 MHz, DMSO-d_6) δ = 24.2, 24.4, 30.5, 34.6, 53.5, 59.9, 115.2, 115.4, 121.4, 121.6, 123.1 (4 C, q, $J_{C\text{-}F}$ = 270.2 Hz), 130.0 (4 C, q, $J_{C\text{-}F}$ = 34.2 Hz), 133.0, 133.2, 142.2, 142.4, 180.0, 180.2 ppm; elemental analysis calcd (%) for $C_{24}H_{20}F_{12}N_4S_2$: C, 43.90; H, 3.07; N, 8.53; found: C, 43.73; H, 3.02; N, 8.63.

1-((*1R,2R*)-2-aminocyclohexyl)-3-(3,5-bis(trifluoromethyl)phenyl)thiourea 10

Following the literature[78] procedure, A solution of *trans*1,2-diaminocyclohexane (0.60 mL, 5.00 mmol, 1.0 equiv.) in dry DCM (10 mL) was cooled to 0 ^{o}C under an argon atmosphere. A solution of 3,5-*bis*(trifluoromethyl)-phenyl isothiocyanate (0.92 mL, 5.00 mmol, 1.0 equiv.) in dry DCM (10 mL) was added drop wise over 6 h. The resulting yellow solution was kept for overnight stirring. The reaction mixture was concentrated *in vacuo* and the yellow residue purified by column chromatography (70/30 EtOAc/$CHCl_3$) affording the thiourea catalyst **10** (0.89 g, 46%) as a yellow solid, mp 77-77 ^{o}C; IR (film): $\bar{\upsilon}$ = 1262, 1152, 1147, 1125, 955, 870, 742 cm^{-1}; ^{1}H NMR (200 MHz, DMSO-d_6) δ = 1.05-1.41 (4 H, m), 1.49-1.73 (2 H, m), 1.88-2.13 (2 H, m), 2.32-2.55 (1 H, m), 3.79-3.92 (1 H, m), 7.66 (1 H, s), 8.23 (2 H, s) ppm; ^{13}C NMR (50 MHz, DMSO-d_6) δ = 24.3, 24.6, 30.6, 34.7, 53.7, 58.9, 114.9, 121.9, 122.9 (2 C, q, $J_{C\text{-}F}$ = 269.2 Hz), 129.8 (2 C, q, $J_{C\text{-}F}$ = 32.1 Hz), 133.7, 141.6, 179.2 ppm; elemental analysis calcd (%) for $C_{15}H_{17}F_6N_3S$: C, 46.75; H, 4.45; N, 10.90; found: C, 46.70; H, 4.42; N, 10.93.

1-(3,5-bis(trifluoromethyl)phenyl)-3-(quinolin-4-yl((*1S,2S,4S,5R*)-5-vinylquinuclidin-2-yl)methyl)thiourea 11

Following the literature[79] procedure, a solution of 9-Amino(9-deoxy)epi-cinchonidine **48** (see chapter-**3** for its preparation**,** 0.98 g, 3.4 mmol) in dry THF (10 mL) was slowly added a solution of 3,5-bis(trifluoromethyl)phenyl isothiocyanate (0.92 g, 3.4 mmol) in 5 mL of dry THF at ambient temperature. The mixture was stirred overnight, and the solvent was removed *in vacuo.* The residue was purified by column chromatography on silica gel (EtOAc/MeOH/aq. NH_4OH = 98/2/1 as eluant) affording thiourea **11** (1.34 g, 70%) as an off-white amorphous solid; IR (film): $\bar{\upsilon}$ = 1620, 1505, 1464, 1373, 1269,

1159, 1123, 849, 675 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.84 (1 H, dd, *J* = 13.2, 10.2 Hz), 1.41 (1 H, ddd, *J* = 13.6, 10.6, 2.4 Hz), 1.65 (1 H, br m), 1.69 (2 H, m), 2.32 (1 H, m), 2.69 (1 H, ddd, *J* = 13.4, 4.5, 2.2 Hz), 2.79 (1 H, ddd, *J* = 15.2, 13.4, 4.7 Hz), 3.28 (1 H, dd, *J* = 13.4, 9.8 Hz), 3.36 (1 H, q, *J* = 10.4 Hz), 3.54 (1 H, dddd, *J* = 15.3, 10.2, 7.6, 2.1 H), 4.96 (1 H, dt, *J* = 17.1, 1.3 Hz), 5.01 (1 H, dt, *J* = 10.2, 1.2 Hz), 5.80 (1 H, ddd, *J* = 17.0, 10.2, 6.2 Hz), 6.30 (1 H, d, *J* = 11.2 Hz), 7.42 (1 H, dd, *J* = 9.1, 2.4 Hz), 7.53 (1 H, d, *J* = 4.6 Hz), 7.57 (1 H, br s), 7.93 (1 H, d, *J* = 9.1 Hz), 8.05 (1 H, br d, *J* = 2.4 Hz), 8.10 (2 H, br s), 8.66 (1 H, d, *J* = 4.5 Hz) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 25.7, 27.5, 27.3, 39.7, 41.6, 55.2, 55.6, 60.2, 103.2, 113.8, 116.7 (1 C, sept, $^{3}J_{C\text{-}F}$ = 3.7 Hz), 120.1, 122.4, 122.5, 123.4 (q, $^{1}J_{C\text{-}F}$ = 272.0 Hz, CF_3), 129.0, 130.1, 131.6 (q, $^{2}J_{C\text{-}F}$ = 33.0 Hz), 141.4, 141.9, 144.0, 146.4, 147.2, 158.5, 181.4 ppm; Elemental analysis calcd (%) for $C_{28}H_{26}F_6N_4S$: calcd C 59.57, H 4.64, N 9.92; found: C 59.47, H 4.72, N 9.82; $[\alpha]_D^{25}$ = –107.9 (*c* 0.50 in $CHCl_3$).

1-(3,5-bis(trifluoromethyl)phenyl)-3-((6-methoxyquinolin-4-yl)((*1S,2S,4S,5R*)-5-vinylquinuclidin-2-yl)methyl)thiourea 12

The catalyst **12** was prepared according to procedure for catalyst **11** from 9-Amino(9-deoxy)epi-quinine **47** (see chapter-**3** for its prepration, 1.10 g, 3.4 mmol) after column chromatography (EtOAc/MeOH/ aq. NH_4OH = 98/2/1 as eluent) as a amorphous solid (1.62 g, 74%); IR (film): $\bar{\upsilon}$ = 1630, 1525, 1460, 1370, 1280, 1175, 1126, 862, 678 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.87 (1 H, dd, *J* = 13.2, 10.2 Hz), 1.44 (1 H, ddd, *J* = 13.2, 10.2, 2.4 Hz), 1.61 (1 H, br m), 1.69 (2 H, overlapping br m), 2.35 (1 H, br m), 2.77 (1 H, ddd, *J* = 13.4, 4.5, 2.1 Hz), 2.80 (1 H, ddd, *J* = 15.4, 13.6, 4.7 Hz), 3.27 (1 H, dd, *J*

= 13.4, 9.7 Hz), 3.40 (1 H, br pseudo q, *J* = 10.4 Hz), 3.54 (1 H, dddd, *J* = 15.4, 10.3, 7.4, 2.31 Hz), 4.01 (3 H, OCH_3), 4.78 (1 H, dt, *J* = 17.0, 1.3 Hz), 5.00 (1 H, dt, *J* = 10.3, 1.3 Hz), 5.82 (1 H, ddd, *J* = 17.0, 10.4, 6.0 Hz), 6.30 (1 H, d, *J* = 10.9 Hz), 7.33 (1 H, dd, *J* = 9.2, 2.4 Hz), 7.33 (1 H, dd, *J* = 9.1, 2.4 Hz), 7.53 (1 H, d, *J* = 4.5 Hz), 7.50 (1 H, br s), 7.90 (1 H, d, *J* = 9.1 Hz), 8.05 (1 H, br d, *J* = 2.4 Hz), 8.10 (2 H, br s), 8.65 (1 H, d, *J* = 4.5 Hz) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 25.7, 27.6, 27.7, 39.5, 41.7, 55.3, 55.4, 55.7, 60.4, 103.0, 113.8, 116.5, 120.0, 122.1, 122.2, 123.2, 129.0, 130.0, 131.2, 141.0, 141.8, 144.0, 145.8, 146.8, 157.8, 180.1 ppm; Elemental analysis calcd (%) for $C_{29}H_{28}F_6N_4OS$: calcd C 58.58, H 4.75, N 9.42; found: C 58.50, H 4.70, N 9.37; $[\alpha]_D^{25}$ = –124.5 (*c* 0.50, $CHCl_3$).

1-(3,5-bis(trifluoromethyl)phenyl)-3-(((*1S,2S,4S,5R*)-5-ethylquinuclidin-2-yl)(6-methoxyquinolin-4-yl)methyl)thiourea 13

The catalyst **13** was prepared according to procedure for catalyst **11** from 9-Amino(9-deoxy)epi-hydroquinine **45** (see chapter-**3** for its prepration, 1.11 g, 3.4 mmol) after column chromatography (EtOAc/MeOH/ aq. NH_4OH = 98/2/1 as eluent) as a amorphous solid (1.52 g, 70%); IR (film): $\bar{\upsilon}$ = 1620, 1505, 1484, 1373, 1268, 1171, 1120, 661 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 0.69 (1 H, dd, *J* = 13.1, 10.0 Hz), 0.84 (3 H, t, *J* = 7.1 Hz), 1.3 (1 H, ddd, *J* = 13.1, 10.2, 2.6 Hz), 1.39 (1 H, br m), 1.51 (1 H, br m), 1.69 (2 H, br m), 2.51 (1 H, ddd, *J* = 13.4, 4.3, 2.2 Hz), 2.81 (1 H, ddd, *J* = 15.4, 13.6, 4.8 Hz), 3.28 (1 H, dd, *J* = 13.4, 9.7 Hz), 3.32 (1 H, q, *J* = 10.6 Hz), 3.54 (1 H, dddd, *J* = 15.4, 10.4, 7.6, 2.1 Hz), 4.01 (3 H, s, OCH_3), 6.31 (1 H, d, *J* = 11.1 Hz), 7.43 (1 H, dd, *J* = 9.2, 2.4 Hz) 7.54 (1 H, d, *J* = 4.4 Hz), 7.57 (1 H, br s), 7.90 (1 H, d, *J* = 9.2 Hz), 8.04 (1 H, br d, *J* = 2.4 Hz), 8.06 (2 H, br s), 8.59 (1 H, d, *J* = 4.6 Hz) ppm; ^{13}C NMR (50 MHz,

$CDCl_3$): δ = 11.4, 25.4, 25.6, 27.3, 28.2, 37.2, 41.8, 55.2, 55.2, 57.6, 60.2, 103.1, 116.7 (br signal, $^3J_{C\text{-}F}$ = 3.7 Hz), 120.1, 122.6, 123.4 (q, $^1J_{C\text{-}F}$ = 272.0 Hz, CF_3), 129.1, 130.1, 131.4 (q, $^2J_{C\text{-}F}$ = 33.0 Hz), 142.0, 144.1, 146.4, 147.1, 158.4, 181.3 ppm; Elemental analysis calcd (%) for $C_{29}H_{30}F_6N_4OS$: calcd C 58.38, H 5.07, N 9.39; found: C 58.02, H 5.01, N 9.42; $[\alpha]_D^{25}$ = –128.4 (*c* 0.50 in $CHCl_3$).

1-(3,5-bis(trifluoromethyl)phenyl)-3-((6-methoxyquinolin-4-yl)((*1S,2R,4S,5R*)-5-vinylquinuclidin-2-yl)methyl)thiourea 14

The catalyst **14** was prepared according to procedure for catalyst **11** from 9-Amino(9-deoxy)epi-quininidine (1.10 g, 3.4 mmol) after column chromatography (EtOAc/MeOH/ aq. NH_4OH = 98/2/1 as eluent) as a amorphous solid (1.53 g, 70%); IR (film): $\bar{\upsilon}$ = 1620, 1540, 1515, 1470, 1380, 1280, 1168, 1154, 965, 837, 679 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 1.59 (1 H, unresolved partly overlapping signal), 1.87 (1 H, pseudo sext, *J* = 3.2 Hz), 1.94 (1 H, unresolved partly overlapping signal), 2.03 (1 H, closely coupled m), 2.07 (1 H, closely coupled m), 2.33 (1 H, br m), 2.54 (1 H, ddd, *J* = 15.4, 13.6, 4.7 Hz), 2.69 (1 H, ddd, *J* = 13.4, 4.4, 2.2 Hz), 3.01 (1 H, dd, *J* = 13.4, 9.7 Hz), 3.11 (1 H, dddd, *J* = 15.1, 10.2, 7.3, 2.2 Hz), 3.68 (1 H, br pseudo q, *J* = 10.4 Hz), 4.00 (3 H, s, OCH_3), 5.07 (1 H, dt, *J* = 17.0, 1.3 Hz), 5.12 (1 H, dt, *J* = 10.3, 1.2 Hz), 6.02 (1 H, ddd, *J* = 17.0, 10.3, 6.1 Hz), 6.81 (1 H, d, *J* = 11.1 Hz), 7.40 (1 H, dd, *J* = 9.1, 2.4 Hz), 7.56 (1 H, d, *J* = 4.4 Hz), 7.60 (1 H, br s), 7.92 (1 H, d, *J* = 9.2 Hz), 7.97 (2 H, br s), 8.14 (1 H, br d, *J* = 2.6 Hz), 8.65 (1 H, d, *J* = 4.4 Hz) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 24.2, 27.2, 28.1, 39.7, 41.4, 54.1, 55.6, 56.2, 59.0, 103.0, 114.1, 117.0 (br signal, $^3J_{C\text{-}F}$ = 3.7 Hz), 119.7, 122.7, 123.1, 123.5 (q, $^1J_{C\text{-}F}$ = 271.2 Hz, CF_3), 129.0, 130.1, 131.8 (q, $^2J_{C\text{-}F}$ = 33.2 Hz), 141.4, 141.7, 144.4, 146.2, 147.1, 158.8, 182.1 ppm; Elemental analysis calcd (%) for

$C_{29}H_{28}F_6N_4OS$: calcd C 58.58, H 4.75, N 9.42; found: C 58.36, H 4.45, N 9.35; $[\alpha]_D^{25}$ = +24.2 (*c* 0.50 in $CHCl_3$).

1-(3,5-bis(trifluoromethyl)phenyl)-3-(((*1S,2R,4S,5R*)-5-ethylquinuclidin-2-yl)(6-methoxyquinolin-4-yl)methyl)thiourea 15

The catalyst **15** was prepared according to procedure for catalyst **11** from 9-Amino(9-deoxy)epihydroquinidine **46** (see chapter-**3** for its prepration, 1.11 g, 3.4 mmol) after column chromatography (EtOAc/MeOH/ aq. NH_4OH = 98/2/1 as eluent) as a amorphous solid (1.60 g, 74%); IR (film): $\bar{\upsilon}$ = 1620, 1512, 1470, 1394, 1288, 1170, 1121, 1031, 876, 672cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 1.02 (1 H, dd, *J* = 13.3, 10.4 Hz), 1.21 (1 H, ddd, *J* = 13.2, 10.4, 2.7 Hz), 1.59 (2 H, overlapping br m), 2.34 (1 H, br m), 1.61 (1 H, br m), 3.04 (2 H, m), 3.32 (1 H, pseudo q, *J* = 10.7 Hz), 3.36 (1 H, ddd, *J* = 13.6, 4.7, 2.3 Hz), 3.56 (1 H, dd, *J* = 13.4, 9.8 Hz), 4.02 (3 H, s, OCH_3), 5.14 (1 H, dt, *J* = 17.1, 1.4 Hz), 5.21 (1 H, dt, *J* = 10.4, 1.4 Hz), 5.95 (1 H, ddd, *J* = 17.1, 10.4, 6.1 Hz), 6.34 (1 H, d, *J* = 11.1 Hz), 7.44 (1 H, dd, *J* = 9.2, 2.4 Hz), 7.54 (1 H, d, *J* = 4.4 Hz), 7.58 (1 H, br s), 7.96 (1 H, d, *J* = 9.2 Hz), 8.01 (1 H, br d, *J* = 2.4 Hz), 8.10 (2 H, br s), 8.66 (1 H, d, *J* = 4.4 Hz) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 25.4, 26.2, 27.5, 39.1, 47.4, 49.1, 54.4, 55.4, 60.4, 103.4, 114.1, 116.4, 122.5, 122.6, 123.6 (q, $^1J_{C\text{-}F}$ = 272.0 Hz, CF_3), 129.1, 130.1, 131.7 (q, $^2J_{C\text{-}F}$ = 32.9 Hz), 140.6, 142.0, 144.0, 146.7, 147.0, 158.4, 181.1 ppm; Elemental analysis calcd (%) for $C_{29}H_{30}F_6N_4OS$: calcd C 58.38, H 5.07, N 9.39; found: C 58.02, H 5.01, N 9.42; $[\alpha]_D^{25}$ = +216.3 (*c* 0.50 in $CHCl_3$).

General procedure II. Michael addition of 1,3-dicarbonyl compounds to nitrodienes using DBU as catalyst:

The 1,3-dicarbonyl compound **5a-c** or **16a-c** (0.5 mmol) was added to the corresponding nitrodiene **4a**-**h** (0.25 mmol) in toluene (0.5 mL) and the reaction mixture was stirred for 10 min. DBU (8 µL, 0.05 mmol, 20 mol%) was added to the homogenous reaction mixture and stirring continued at room temperature (~28 °C) until completion of the reaction. The resulting mixture was diluted with EtOAc and washed with water. The organic phase was dried over $MgSO_4$ and evaporated under reduced pressure. The residue was purified by column chromatography over silica gel using hexane/EtOAc as eluent to give the desired addition products *rac*-**1a-k** or *rac*-**17a-c**.

General procedure III. Asymmetric Michael addition of 1,3-dicarbonyl compounds to nitrodienes:

Respective 1,3-dicarbonyl compound 5**a-c** or **16a-c** (0.5 mmol) was added to a stirred solution of the nitrodiene **4a**-**h**(0.25 mmol) and the thiourea catalyst **15** (16 mg, 0.025 mmol, 10 mol%) in toluene (0.5 mL) at -20 °C. The reaction mixture was stirred at the same temperature for 14-144 h, diluted with EtOAc and washed with water. The organic phase was dried over $MgSO_4$ and evaporated under reduced pressure. The residue was purified by column chromatography over silica gel using hexane/EtOAc as eluent to give the desired addition products **1a-k** and **17a-c**.

(*S*)-Methyl 2-carbomethoxy-3-(nitromethyl)-5-phenyl-4-pentenoate 1a

Prepared from **24a** (43.8 mg, 0.25 mmol) and methylmalonate **5a** (0.115 mL, 0.50 mmol) according to *General Procedure* **2.4.III** using catalyst **15.** White solid. Yield: 65mg (85%, 88% ee). Recrystallized from hexane-EtOAc. Yield: 36 mg (47%); m.p. 94-95 °C; IR (KBr): $\bar{\upsilon}$ = 2982, 2877, 2843, 1739, 1554, 1464, 1431, 1256, 1154, 742 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$). δ = 3.73 (3 H, s, OCH_3), 3.76 (3 H, s, OCH_3), 3.73-3.77 (2 H, m,

=CCH_ACH$_B$), 4.62-4.80 (2 H, m, CH_2NO_2), 6.0-6.18 (1 H, m, PhCH=CH_ACH$_2$), 6.57 (1 H, d, J = 15.8 Hz, PhCH_A=CH), 7.26-7.33 (5 H, m, Ph) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 41.2, 52.8, 52.9, 53.3, 76.9, 123.3, 126.6 (2 C), 128.2, 128.6 (2 C), 135.5, 135.8, 167.5, 167.6 ppm; elemental analysis calcd (%) for $C_{15}H_{17}NO_6$: C 58.63, H 5.58, N 4.56, found: C 58.97, H 5.63, N 4.53; $[\alpha]^{24}_D$ = -24.2 (c = 1.2, $CHCl_3$, 99.5% ee); The enantiomeric excess of the recrystallized product was determined by HPLC with a Daicel chiralpak AD-H column [λ = 220 nm], eluent: 2-propanol/ hexane (10/90), flow rate = 0.8 mL/min, t_{minor}= 21.13 min (0.33%), t_{major}= 25.85 min (99.67%).

(*R*)-Methyl 2-carbomethoxy-3-(nitromethyl)-5-phenyl-4-pentenoate *ent*-1a

Prepared frome **4a** (43.8 mg, 0.25 mmol) and methylmalonate **5a** (0.115 mL, 0.50 mmol) according to *General Procedure* **2.4.III** using catalyst **13** instead of catalyst **15**, product *ent*-1a was obtained as white solid. Yield: 65 mg (85%, 88% ee). Recrystallized from hexane-EtOAc. Yield: 37 mg (48%). m.p. 92-93 °C; $[\alpha]_D^{24}$ = +23.3 (c = 1.2, $CHCl_3$, >98% ee). The enantiomeric excess of the recrystallized product was determined by HPLC with a Daicel chiralpak AD-H column [λ = 220 nm], eluent: 2-propanol/ hexane (10/90), flow rate = 0.8 mL/min, t_{major}= 19.04 min (99.35%), t_{minor}= 23.28 min (0.65%).

(*S*)-Ethyl 2-carboethoxy-3-(nitromethyl)-5-phenyl-4-pentenoate 1b

Prepared frome **4a** (43.8 mg, 0.25 mmol) and ethylmalonate **5b** (0.153 mL, 0.50 mmol) according to *General Procedure* **2.4.III** using catalyst **15.** Yellow solid; Yield: 67 mg (80%, 88% ee); m.p. 48-49 °C; IR ($CHCl_3$, film): $\bar{\upsilon}$ = 3026, 2981, 2938, 2874, 1732, 1556, 1465, 1448, 1371, 1030, 970, 784, 694 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.19 (6 H, q, J = 7.2 Hz, 2 x CH_3), 3.62-3.80 (2 H, m, =CCH_ACH$_B$CH$_2$,), 4.13-4.27 (4 H, q, J = 7.2 Hz, 2 x OCH_2CH$_3$), 4.62-4.80 (2 H, m, CH_2NO_2), 6.10 (1 H, dd, J = 9.0, 15.8 Hz,

PhCH=CH_A), 6.56 (1 H, d, J = 15.8 Hz, PhCH_A=CH_A), 7.23-7.33 (5 H, m, Ph) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.0 (2C), 41.2, 53.6, 61.9, 62.0, 77.1, 123.4, 126.6 (2 C), 128.2, 128.6 (2 C), 135.4, 135.8, 167.1, 167.3 ppm; $[\alpha]^{25}_D$ = -23.0 (c = 1.0, $CHCl_3$) 95% ee; The enantiomeric excess was determined by HPLC with a Daicel chiralpak AD-H column [λ = 220 nm], eluent:2-propanol/ hexane (10/90), flow rate = 0.8 mL/min, t_{minor}= 20.57 min (4.88%), t_{major}= 22.55 min (95.12%).

(*S*)-Methyl 2-carbomethoxy-3-(nitromethyl)-5-(2-methoxyphenyl)-4-pentenoate 1c

Prepared frome **4b** (51.4 mg, 0.25 mmol) and methylmalonate **5a** (0.115 mL, 0.50 mmol) according to *General Procedure* **2.4.III** using catalyst **15.** White solid; Yield: 63mg (75%); Recrystallized from hexane-EtOAc; Yield: 42 mg (50%); m.p. 53-55 °C; IR ($CHCl_3$, film): $\bar{\upsilon}$ = 2985, 2877, 1740, 1554, 1465, 1448, 1255, 1030, 970, 784 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.73 (4 H, s, OCH_3, =CHCH_A), 3.76 (4 H, s, OCH_3, COCH_ACO), 3.81 (3 H, s, PhOCH_3), 4.63-4.81 (2 H, m, CH_2NO_2), 6.01-6.17 (1 H, m, ArCH=CH_A), 6.81-6.92 (3 H, m, Ar, ArCH_A=CH), 7.18-7.36 (2 H, m, Ar) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 41.6, 52.8 (2 C), 53.5, 55.4, 77.05, 110.8, 120.6, 123.7, 124.9, 127.0, 129.3, 130.4, 156.7, 167.6, 167.8 ppm; elemental analysis calcd (%) for $C_{16}H_{19}NO_7$: C 56.97, H 5.68, N, 4.15; found: C 57.15, H 5.50, N 4.09; $[\alpha]^{25}_D$ = -12.0 (c = 0.6, $CHCl_3$, >99% ee); The enantiomeric excess was determined by HPLC with a Daicel chiralpak AD-H column [λ = 220 nm], eluent: 2-propanol/ hexane (10/90), flow rate = 0.8 mL/min, t_{minor}= 21.1 min (0.28%), t_{major}= 24.10 min (99.72%).

(*S*)-Methyl 2-carbomethoxy-3-(nitromethyl)-5-(4-nitrophenyl)-4-pentenoate 1d

Prepared from **4c** (55.0 mg, 0.25 mmol) and methylmalonate **5a** (0.115 mL, 0.50 mmol) according to *General Procedure* **2.4.III** using catalyst **15.** Yellow solid; Yield: 62 mg

(70%); m.p. 97-99 °C; IR (KBr): $\bar{\upsilon}$ = 2985, 2843, 1740, 1600, 1552, 1515, 1438, 1348, 1322, 1262, 1163, 973, 745 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 3.71-3.77 (2 H, m, =CCH_ACH_B), 3.74 (3 H, s, OCH_3), 3.77 (3 H, s, OCH_3), 4.71-4.75 (2 H, m, CH_2NO_2), 6.30 (1 H, dd, J = 8.6, 15.8 Hz, ArCH=CH_A), 6.64 (1 H, d, J = 15.8 Hz, ArCH_A=CH), 7.45 (2 H, d, J = 8.8 Hz, Ar), 8.15 (2 H, d, J = 8.8 Hz, Ar) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 41.1, 52.97, 53.02, 53.07, 76.6, 124.0 (2 C), 127.3 (2 C), 128.4, 133.4, 142.0, 147.4, 167.4 (2 C) ppm; HRMS (ESI): m/z: calcd for $C_{15}H_{16}N_2O_8Na$ $[M + Na]^+$: 375.0790; found:375.0799; elemental analysis calcd (%) for $C_{15}H_{16}N_2O_8$: C 51.14, H 4.58, N 7.95; found: C, 50.97; H, 4.58; N, 8.32; $[\alpha]^{25}_D$ = -13.3 (c = 0.75, $CHCl_3$, 76% ee); The enantiomeric excess was determined by HPLC with a Daicel chiralpak OD-H column [λ = 220 nm], eluent:2-propanol/ hexane (10/90), flow rate = 1.0 mL/min, t_{minor}= 80.97 min (12.14%), t_{major}= 87.74 min (87.76%).

(*S*)-Methyl 2-carbomethoxy-3-(nitromethyl)-5-(4-bromophenyl)-4-pentenoate 1e

Prepared from **4d** (63.24 mg, 0.25 mmol) and methylmalonate **5a** (0.115 mL, 0.50 mmol) according to *General Procedure* **2.4.III** using catalyst **15.** Light yellow oil; Yield: 84 mg (87%); IR (film): $\bar{\upsilon}$ = 3025, 2955, 1737, 1556, 1435, 1378, 1162, 1072, 969, 753 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 3.67-3.75 (2 H, m, =CCH_ACH_B), 3.72 (3 H, s, OCH_3), 3.75 (3 H, s, OCH_3), 4.60-4.78 (2 H, m, CH_2NO_2), 6.02-6.15 (1 H, m, ArCH=CH_A), 6.50 (1 H, d, J = 15.8 Hz, ArCH_A=CH), 7.17 (H, d, J = 8.4 Hz, Ar), 7.39-7.43 (3 H, m, Ar) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 41.2, 51.1, 52.9, 52.92, 76.8, 122.1, 124.1, 128.1 (2 C), 131.7 (2 C), 134.3, 134.7, 167.4, 167.5 ppm; elemental analysis calcd (%) for $C_{15}H_{16}BrNO_6$: C 46.65, H 4.18, N 3.63; found: C 46.26, H 4.05, N 3.95; $[\alpha]^{27}_D$ = -11.3 (c = 2.3, $CHCl_3$, 84% ee); The enantiomeric excess was determined by HPLC with a Daicel

chiralpak OD-H column [λ = 220 nm], eluent: 2-propanol/ hexane (10/90), flow rate = 0.8 mL/min, t_{minor}= 31.69 min (8.01%), t_{major}= 41.43 min (91.99).

(*S*)-Methyl 2-carbomethoxy-3-(nitromethyl)-5-(4-chlorophenyl)-4-pentenoate 1f

Prepared from **4e** (52.30 mg, 0.25 mmol) and ethylmalonate **5a** (0.115 mL, 0.50 mmol) according to *General Procedure* **2.4.III** using catalyst **15.** Light yellow oil; Yield: 79 mg (93%); IR (film): $\bar{\upsilon}$ = 2955, 2925, 2847, 1731, 1556, 1492, 1435, 1378, 1093, 972, 753 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 3.67-3.76 (2 H, m, =CCH_ACH_B), 3.72 (3 H, s, OCH_3), 3.76 (3 H, s, OCH_3), 4.61-4.79 (2 H, m, CH_2NO_2), 6.01-6.14 (1 H, m, ArCH=CH_A), 6.52 (1 H, d, J = 15.8 Hz, ArCH_A=CH), 7.18-7.32 (4H, m, Ar) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 41.2, 52.9, 53.2, 76.8, 124.0, 127.8 (2 C), 128.7 (2 C), 129.2 (2 C), 129.3 (2 C), 133.9 (2 C), 134.3 (2 C) 167.5, 167.6 ppm; elemental analysis calcd (%) for $C_{15}H_{16}ClNO_6$: calcd. C 52.72, H 4.72, N 4.10; found: C 52.53, H 4.48, N 4.29; $[\alpha]^{27}_D$ = -15.6 (c = 0.9, $CHCl_3$, 86% ee); The enantiomeric excess was determined by HPLC with a Daicel chiralpak OD-H column [λ = 220 nm], eluent: 2-propanol/ hexane (5/95), flow rate = 0.8 mL/min, t_{minor}= 41.9 min (7.33%), t_{major}= 49.09 min (92.67%).

(*S*)-Ethyl 2-carboethoxy-3-(nitromethyl)-5-(4-cholrophenyl-4-pentenoate 1g

Prepared from **4e** (52.30 mg, 0.25 mmol) and ethylmalonate **5b** (0.153 mL, 0.50 mmol) according to *General Procedure* **2.4.III** using catalyst **15.** Yellow solid; Yield: 85 mg (91%); Recrystallized from hexane-EtOAc; Yield: 42 mg (45%); m.p. 62-64 °C; IR (KBr): $\bar{\upsilon}$ = 2980, 2877, 2843, 1747, 1550, 1472, 1374, 1259, 1154, 1012, 936, 745 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.24 (6 H, q, J = 7.2 Hz, 2 x CH_2 CH_3), 3.62-3.79 (2 H, m, =CCH_AC$H_B$$CH_2$,), 4.16-4.27 (4 H, m, 2 x OC$H_2$$CH_3$), 4.61-4.80 (2 H, m, CH_2NO_2), 6.09 (1 H, dd, J = 8.8, 15.8 Hz, PhCH=CH_A), 6.52 (1 H, d, J = 15.8 Hz, PhCH_A=CH),

7.20 (4 H, m, Ar) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.0 (2 C), 41.2, 53.5, 62.0, 62.1, 77.0, 124.2, 127.8 (2 C), 128.8 (2 C), 133.9, 134.2, 134.3, 167.1, 167.2 ppm; elemental analysis calcd (%) for $C_{17}H_{20}ClNO_6$: C 55.21, H 5.45, N 3.79; found: C 55.60, H, 5.24, N 3.98; $[\alpha]^{26}_D$ = -21.4 (c = 1.4, $CHCl_3$, 99% ee); The enantiomeric excess was determined by HPLC with a Daicel chiralpak OD-H column [λ = 220 nm], eluent: 2-propanol/hexane (5/95), flow rate = 0.8 mL/min, t_{minor}= 21.90 min (0.52%), t_{major}= 25.33 min (99.48%).

Dimethyl 2-(*R*,*E*)-3-methyl-1-nitro-4-phenylbut-3-en-2-yl) malonate 1h

Prepared from **4f** (47.27 mg, 0.25 mmol) and methylmalonate **5a** (0.115 mL, 0.50 mmol) according to *General Procedure* **2.4.III** using catalyst **15.** Colourless oil; Yield: 53 mg (66%); IR (film): $\bar{\upsilon}$ = 2954, 2914, 1735, 1552, 1492, 1435, 1329, 1028, 746 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.86 (3 H, d, J = 1.0 Hz, CH_3=CCH), 3.72 (3 H, s, OCH_3), 3.74-3.76 (2 H, m, =CCH_ACH_B), 3.78 (3 H, s, OCH_3), 4.65-4.82 (2 H, m, CH_2NO_2), 6.43 (1 H, bs, PhCH_A=CHCH$_3$), 7.12-7.14 (2 H, m, Ph), 7.25-7.35 (3 H, m, Ph) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 15.1, 46.5, 52.7, 52.9, 53.0, 75.7, 127.0, 128.1 (2 C), 128.8 (2 C), 131.0 (2 C), 132.3 (2 C), 136.6 (2 C), 167.4, 168.0 ppm; elemental analysis calcd (%) for $C_{16}H_{19}NO_6$: calcd. C 59.81, H 5.96, N 4.36; found: C 59.51, H 6.26, N 4.16. $[\alpha]^{27}_D$ = -20.5 (c = 1.9, $CHCl_3$, 80% ee); The enantiomeric excess was determined by HPLC with a Daicel chiralpak OD-H column [λ = 220 nm], eluent: 2-propanol/hexane (5/95), flow rate = 0.5 mL/min, t_{major}= 47.17 min (90.29%), t_{minor}= 57.25 min (9.71%).

(*S*)-Methyl 2-carboethoxy-3-(nitromethyl)-5-(3-bromophenyl)-4-pentenoate 1i

Prepared from **4g** (63.24 mg, 0.25 mmol) and methylmalonate **5a** (0.115 mL, 0.50 mmol) according to *General Procedure* **2.4.III** using catalyst **15.** Yellow oil; Yield: 91 mg

(95%); IR (film): $\bar{\upsilon}$ = 3026, 2954, 1736, 1557, 1435, 1378, 1161, 1072, 970, 753 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 3.67-3.70 (2 H, m, =CCH_ACH_B), 3.73 (3 H, s, OCH_3), 3.76 (3 H, s, OCH_3), 4.61-4.79 (2 H, m, CH_2NO_2), 6.04-6.19 (1 H, m, ArCH=CH_A), 6.50 (1 H, d, J = 15.8 Hz, ArCH_A=CH), 7.11-7.24 (2 H, m, Ar), 7.35-7.38 (1 H, m, Ar), 7.39-7.45 (1 H, m, Ar) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 41.1, 52.95, 53.0, 53.2, 76.8, 124.9, 125.3, 126.8, 129.4, 130.1, 131.2, 134.1, 137.9, 167.5, 167.5 ppm; elemental analysis calcd (%) for $C_{15}H_{16}BrNO_6$: C 46.65, H 4.18, N, 3.63; found: C 46.56, H 4.04, N 4.11; $[\alpha]^{23}_D$ = -7.7 (c = 2.2, $CHCl_3$, 85% ee); The enantiomeric excess was determined by HPLC with a Daicel chiralpak AD-H column [λ = 220 nm], eluent: 2-propanol/ hexane (10/90), flow rate = 0.8 mL/min,t_{minor}= 22.0 min (7.36%), t_{major}= 34.82 min (92.64%).

(4*E*)-Dimethyl 2-[(*S*)-4,8-dimethyl-1-nitronona-3,7-dien-2-yl)malonate 1j

Prepared from **4h** (48.78 mg, 0.25 mmol) and methylmalonate **5a** (0.115 mL, 0.50 mmol) according to *General Procedure* **2.4.III** using catalyst **15.** Yellow oil; Yield:62 mg (76%); E:Z ~ 6/4; IR (film): $\bar{\upsilon}$ = 2956, 2922, 2856, 1739, 1632, 1556, 1435, 1378, 1257, 1160, 1016, 912, 733 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$, E:Z ~ 6/4): δ = 1.55 (3 H, s, =CCH_3), 1.66 (6 H, s, 2 x =CCH_3), 1.97-2.04 (4 H, m, =CCH_2CH_2), 3.50 (1 H, d, J = 8.0 Hz, COCH_ACO), 3.70 (3 H, s, OCH_3), 3.73 (3 H, s, OCH_3), 3.86-3.92 (1H, m, C=CH_ACH_2), 4.44 (1 H, dd, J = 8.4, 12.2 Hz, $(CH_3)_2$C=CH_ACH_2), 4.62 (1 H, dd, J = 4.9, 12.2 Hz, C=CH_ACH), 4.95-5.04 (2 H, m, CH_2NO_2) ppm; ^{13}C NMR (50 MHz, $CDCl_3$, E:Z ~ 6/4): 16.3, (*E*), 17.5 (*Z*), 17.6 (*E*), 23.4 (*Z*), 25.5 (*E*), 25.6 (*Z*), 26.3, 32.0 (*Z*), 36.3 (*Z*), 36.6 (*E*), 39.7 (*E*), 52.6 (2 C, *Z*), 52.7 (2 C, *E*), 53.4 (*E*), 53.6 (*Z*), 77.3 (*Z*), 77.4 (*E*), 118.7 (*E*), 119.3 (*Z*), 123.4 (*E*), 123.6 (*Z*), 131.9 (*E*), 132.4 (*Z*), 142.8 (*Z*), 143.0 (*E*), 167.7 (*Z*), 167.8 (*E*), 167.9 (*Z*), 168.0 (*E*) ppm; HRMS (ESI): m/z calcd for $C_{16}H_{25}NO_6Na$

[M + Na]$^{+}$: 350.1575; found: 350.1574; $[\alpha]^{27}_{D}$ = -9.0 (*c* 1.0, $CHCl_3$, 72% ee); The enantiomeric excess was determined by HPLC with a Daicel chiralpak AD-H column [λ = 220 nm], eluent: 2-propanol/hexane (5/95), flow rate = 0.5 mL/min, t_{minor}= 12.58 min (14.16%), t_{major}= 14.43 min (85.84%).

Dimethyl 2-allyl-2-((*S*,*E*)-1-nitro-4-phenylbut-3-en-2-yl) malonate 1k

Prepared from **5a** (43.8 mg, 0.25 mmol) and 2-propynoylmalonate **5c** (172.07 mg, 0.50 mmol) according to *General Procedure* **2.4.III** using catalyst **15.** Yellow oil; Yield: 40 mg (45%); IR (film): $\bar{\upsilon}$ = 3081, 3027, 2954, 2846, 1729, 1641, 1556, 1495, 1434, 1378, 970, 920, 748 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.60-2.82 (2 H, m, =CCH_2), 3.69 (1 H, dd, J = 3.0, 10.4 Hz, CH=CHCH_A), 3.76 (3 H, s, OCH_3), 3.80 (3 H, s, OCH_3), 4.50 (1 H, dd, *J* = 10.8, 12.6 Hz, CH_2=CH_A), 4.90 (1 H, dd, J = 2.9, 12.7 Hz, PhCH=CH_A), 5.07-5.18 (2 H, m, CH_2NO_2), 5.62-5.77 (2 H, m, CH=CH_2), 6.54 (1 H, d, J = 15.6 Hz, PhCH_A=CH), 7.24-7.32 (5 H, m, Ph) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 38.5, 44.9, 52.7, 52.8, 59.5, 77.6, 120.1, 122.1, 126.2 (2 C), 128.3, 128.6 (2 C), 131.4, 135.8, 136.9, 169.7, 169.9 ppm; elemental analysis calcd (%) for $C_{18}H_{21}NO_6$: C 62.24, H 6.09, N 4.03; found: C 62.03, H 5.75, N 4.06; $[\alpha]^{23}_{D}$ = +20.9 (*c* = 2.2, $CHCl_3$); The enantiomeric excess was determined by HPLC with a Daicel chiralpak OD-H column [λ = 220 nm], eluent: 2-propanol/ hexane (5/95), flow rate = 0.5 mL/min,t_{minor}= 25.44 min (8.51%), t_{major}= 43.74 min (91.49%).

3-((*S*,*E*)-1-Nitro-4-phenylbut-3-en-2yl) pentane-2,4-dione 17a

Prepared from **4a** (43.8 mg, 0.25 mmol) and acetylacetone **16a** (0.102 mL, 0.50 mmol) according to *General Procedure* **2.4.III** using catalyst **15.** White solid; Yield: 63 mg (92%); Recrystallized from hexane-EtOAc; Yield: 36 mg (53%); m.p. 143-145 °C; IR

(KBr): ῡ = 2985, 2878, 2844, 1729, 1704, 1553, 1356, 1268, 1146, 970, 744 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 2.19 (3 H, s, $COCH_3$), 2.27 (3 H, s, $COCH_3$), 3.64-3.79 (1 H, m, =CHC$H_A$$CH_2$), 4.05 (I H, d, J = 11.0 Hz, COCH_ACO), 4.53 (2 H, d, J = 6.0 Hz, CH_2NO_2), 6.00 (1 H, dd, J = 9.4 Hz, PhCH=CH_A), 6.54 (1 H, d, J = 15.8 Hz, PhCH_A=CH), 7.29-7.31 (5 H, m, Ph) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 29.9, 30.5, 40.9, 68.9, 77.3, 123.1, 126.5 (2 C), 128.4, 128.6 (2 C), 135.5, 135.5, 201.6, 201.8 ppm; elemental analysis calcd (%) for $C_{15}H_{17}NO_4$: C 65.44, H 6.22, N 5.09;found: C 65.39, H 5.88, N 5.05; $[\alpha]^{26}_D$ = -203 (c =1.0, $CHCl_3$, >96% ee); The enantiomeric excess was determined by HPLC with a Daicel chiralpak AD-H column [λ = 220 nm], eluent: 2-propanol/hexane (5/95), flow rate = 0.5 mL/min, t_{minor}= 26.12 min (1.84%), t_{major}= 32.61 min (98.16%).

(3*S*)-Methyl 2-acetyl-3-(nitromethyl)-5-phenylpent-4-enoate 17b

Prepared from **4a** (43.8 mg, 0.25 mmol) and acetylacetone **16b** (0.094 mL, 0.50 mmol) according to *General Procedure* **2.4.III** using catalyst **15.** White solid; Yield: 65.5 mg (90%); IR ($CHCl_3$, film): ῡ = 3348, 3054, 3020, 2951, 1791, 1696, 1490, 1449, 1434, 1346, 1270, 1213, 1168, 1049, 997, 926, 754 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$, ~1:1 mixture of diastereoisomers): δ = 2.26 (3 H, s, $COCH_3$), 2.30 (3 H, s, $COCH_3$), 3.70-3.88 (4 H, m, =CHC$H_A$$CH_2$), 3.71 (3H, s, OCH_3), 3.77 (3 H, s, OCH_3), 4.59-4.76 (4 H, m, CH_2NO_2), 6.02(1 H, dd, J = 3.0, 15.8 Hz, PhCH_A=CH), 6.07 (1 H, dd, J = 3, 15.8 Hz, PhCH=CH_A), 6.55 (2 H, dd, J = 2.0, 16.0 Hz, PhCH_A=CH), 7.27-7.29 (10 H, m, Ph) ppm; ^{13}C NMR (50 MHz, $CDCl_3$, ~1:1 mixture of diastereoisomers): δ = 30.1, 40.5, 40.8, 52.8 (2 C), 60.1, 60.5, 77.1 (2 C), 123.4 (2 C), 126.5 (4 C), 128.2,128.3, 128.6 (4 C), 135.2, 135.5, 135.7, 135.8, 167.8, 168.0, 200.8, 200.9 ppm; HRMS (ESI): m/z calcd for

$C_{15}H_{17}NO_5Na$ $[M + Na]^+$ 314.0994; found: 314.0999; The enantiomeric excess was determined by HPLC with a Daicel chiralpak AS-H column [λ = 220 nm], eluent: 2-propanol/hexane (5/95), flow rate = 0.5 mL/min, $t_{minor\ (diast\text{-}1)}$= 52.00 min (5.17%), $t_{major\ (diast\text{-}2)}$= 69.00 min (41.79%),$t_{minor\ (diast\text{-}2)}$= 77.90 min (3.78%), $t_{major\ (diast\text{-}1)}$= 142.20 min (49.26%).

(3*S*)-Methyl 2-acetyl-3-(nitromethyl)-5-phenyl-2-(prop-2-ynyl) pent-4-enoate 17c

Prepared from **4a** (43.8 mg, 0.25 mmol) and 2-propynylacetylacetate **16c** (154 mg, 0.50 mmol) according to *General Procedure* **2.4.III** using catalyst **15.** Yellow oil; Yield: 78 mg (95%); IR (film): $\bar{\upsilon}$ = 3306, 2955, 2925, 2852, 2255, 1719, 1556, 1449, 1434, 1224, 970, 731 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$, ~7:3 mixture of diastereoisomer): δ = 2.16 (1H, t, J = 1.6H), 2.24 (3 H, s, $COCH_3$), 2.73-2.88 (3 H, m, 1 H major, 2 H minor, ≡CCH_2), 2.99 (1 H, dd, J = 2.6, 17.6 Hz, major, , CH_A≡CCH_2), 3.75 (3 H, s, major, $COCH_3$), 3.83 (3 H, s, minor, $COOCH_3$), 3.84-4.01 (1 H, m,), 4.46 (1 H, dd, J = 10.8, 12.6 Hz), 4.66 (1 H dd, J = 10.8, 12.6 Hz), 4.88-4.98 (1 H, m, CH_2NO_2), 5.80 (1 H, dd, J = 10.2, 15.8 Hz, minor, PhCH=CH_A), 6.00 (1 H, dd, J = 9.8, 15.6 Hz, major, PhCH=CH_A), 6.55 (1 H, d, J = 15.8 Hz, major, PhCH_A=CH), 6.63 (1 H, d, J = 15.8 Hz, minor, PhCH_A=CH), 7.23-7.32 (5 H, m, Ph) ppm; ^{13}C NMR (50 MHz, $CDCl_3$, ~7:3 mixture of diastereoisomers): δ = 22.0 (major), 22.9 (minor), 27.1 (minor), 27.8 (major), 29.6, 43.8 (minor), 45.5 (major), 53.1 (minor), 53.2 (major), 63.7 (minor), 64.4 (major), 73.3, 76.7 (major), 78.5 (minor), 121.6 (minor), 122.2 (major), 126.6 (2 C, major), 126.7 (2 C, minor), 128.3 (major), 128.4 (minor), 128.6 (2 C), 135.7 (minor), 135.8 (major), 136.7 (major), 137.1 (minor), 169.6, 201.0 (minor), 202.0 (major) ppm; HRMS (ESI):

m/z calcd for $C_{18}H_{19}NO_5Na$ $[M + Na]^+$:352.1156; found:352.1155; The enantiomeric excess was determined by HPLC with a Daicel chiralpak AD-H column [λ = 220 nm], eluent: 2-propanol/hexane (5/95), flow rate = 0.5 mL/min, $t_{minor\ (minor\ diast)}$= 27.92 min (2.63%), $t_{major\ (minor\ diast)}$= 29.35 min (24.29%),$t_{minor\ (major\ diast)}$= 30.45 min (16.97%), $t_{major\ (major\ diast)}$= 34.40 min (56.10%).

(3*S*,4*S*)-Methyl 2-oxo-4-styrylpyrrolidine-3-carboxylate 18

Zinc powder (570 mg, 8.8 mmol) was added portion wise to a stirred solution of nitroester **1a** (77 mg, 0.25 mmol, 88% ee) in 2:1 THF/acetic acid (3 mL) at room temperature. After 3 h, the reaction mixture was filtered through a Celite pad and the filtrate was evaporated under reduced pressure followed by high vacuum. The residue was dissolved in dichloromethane (3 mL) and an aqueous saturated solution of sodium bicarbonate (1 mL) was added into it. The reaction mixture was stirred at room temperature for 20 h, extracted with dichloromethane and the organic extract was evaporated under reduced pressure. The residue was purified by column chromatography to give the lactam 13 (52 mg, 85%) as white flakes. m.p. 140-143 °C; IR ($CHCl_3$, film): $\bar{\upsilon}$ = 3348, 3054, 3020, 2951, 1791, 1696, 1490, 1449, 1434, 1346, 1270, 1213, 1168, 1049, 997, 926, 754 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.24 (1 H, t, J = 8.0 Hz, =CHCH_A), 3.35 (1 H, d, J = 9.2 Hz,COC$H_A$$CO_2$), 3.53-3.75 (2 H, m, NCH_2), 3.79 (3 H, s, CO_2CH_3), 6.12 (1 H, dd, J = 7.8, 15.8 Hz, PhCH=CH_A), 6.53 (1H, d, J = 15.6 Hz, PhCH_A=CH), 7.15 (1 H, bs, NH), 7.18-7.36 (5 H, m, Ph) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 42.8, 46.2, 52.8, 53.9, 126.3 (2 C), 127.2, 127.9, 128.6 (2 C), 132.6, 136.1, 169.4, 172.9 ppm; elemental analysis calcd (%) for $C_{14}H_{15}NO_3$: calcd. C 68.56, H 6.16, N 5.71; found: C 68.69, H 6.46, N 5.27. $[\alpha]^{26}_D$ = -127.4 (c = 0.31, $CHCl_3$).

CHAPTER 3

Organocatalysed enantioselective synthesis of highly substituted cyclohexanones via [4+2] cycloaddition from enones and nitrodienes

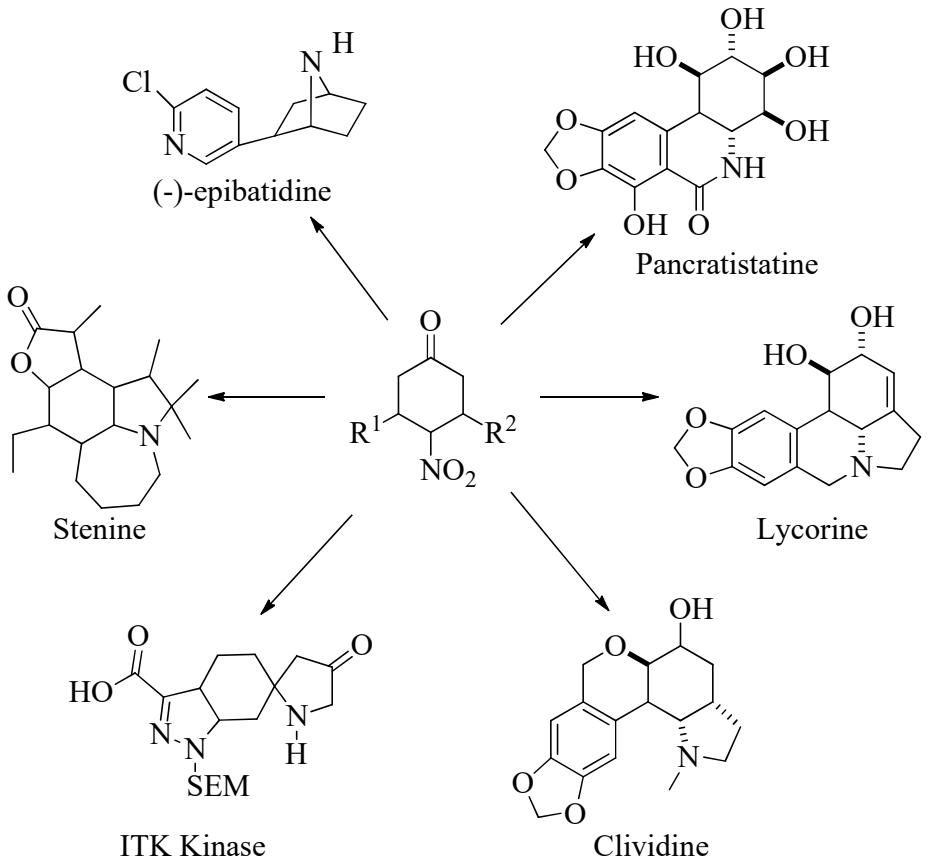
3.1 Introduction

The Diels-Alder reaction is the most synthetically useful strategy for constructing six member ring systems.[84] It offers wide scope in the synthesis of templates for combinatorial libraries. In particular, a [4+2] cycloaddition[29b] strategy offers the possibility of the synthesis of rigid three dimensional cores from the substrates with diverse substituents attached by directionally constrained C-C (or C-X, X = hetero atom) linkages. In this kind of reactions more than one new bond is formed in a one pot reaction. This cycloaddition path involves the rapid conversion of simple prochiral starting materials in to the stereochemically complex product with high stereoselectivity.

Organocatalysis has gained formidable importance because of its green chemistry perspective. One of the most important constituent in a reaction is the solvent which is present in excess. One such solvent system, which obeys this criterion of green chemistry, is 'water'. It is a suitable solvent in various biosynthetic processes inspiring the possibility of using water as a reaction medium in synthetic organic chemistry.[85] In 1980s, Breslow studied Diels-Alder reaction using water as a solvent system which brought major breakthrough in organic synthesis.[86] Later on Sharpless and co-workers[45] introduced the concept of 'on water' for the use of water as reaction medium and it creates major impetus towards research in the green chemistry.

Functionalized 4-nitro substituted cyclohexanones are important class of scaffolds found in the synthesis of natural products and biologically active compounds (**Scheme 3.1**).[87] Consequently, nitrosubstituted cyclohexanones are considered as rich source for

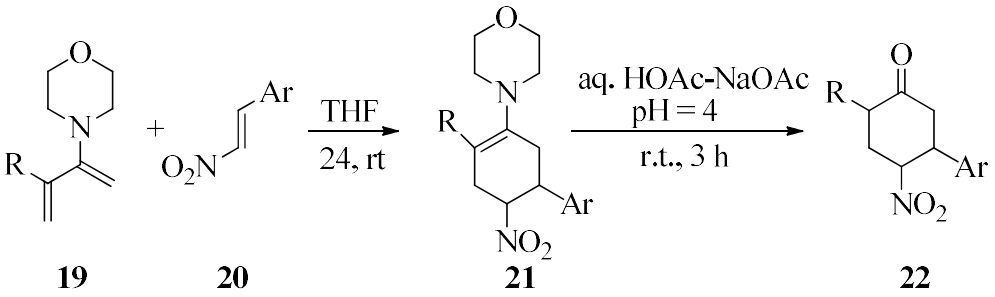
the synthesis of such molecules. Therefore, there is a surge in interest for the development of simple, efficient and environmentally benign method for the synthesis of 4-nitrocyclohexanones using organocatalyst. There are two approaches involving the synthesis of chiral substituted 4-nitrocyclohexanones. They comprised of either double Michael addition reaction carried out between α,β-unsaturated carbonyl compounds and unsaturated nitroolefins or [4+2] cycloaddition with same substrates.[88]



Scheme 3.1 Diverse applications of 4-nitrocyclohexanones

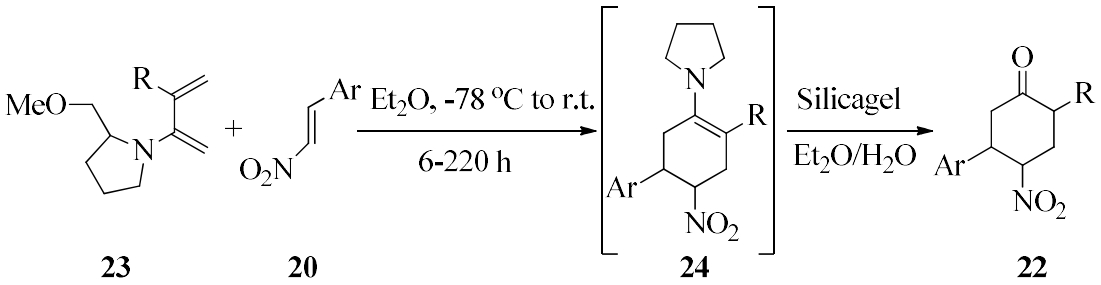
In 1990, José Barluenga[89] reported the [4+2] cycloaddition of that 2-morpholinobutadiene **19** by a step wise [4+2] cycloaddition with β-nitroaryl compounds

20 via intermediate formation of **21**. After hydrolysis of **20** under pH (= 4.0) control gave 4-nitrocyclohexanones **22** (**Scheme 3.2**).



Scheme 3.2 Barluenga's synthesis of 4-nitrocyclohexanones

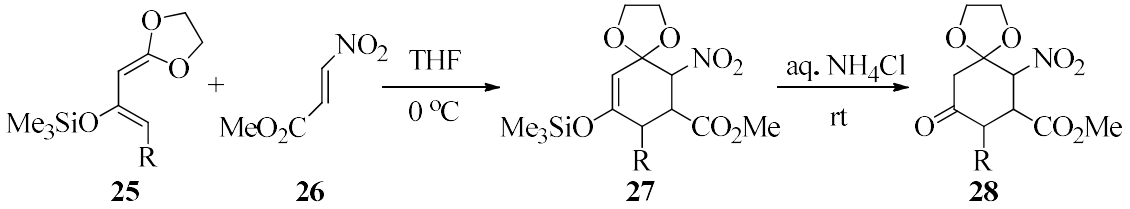
In 1992, Eder *et. al*[90] reported the synthesis of 4-nitrocyclohexanone **22** from 2-amino-1,3- diene **23** and electrophilic nitroolefins **20** *via* [4+2] cycloaddition in ether at low temperature followed by treatment with silica gel and Et_2O/H_2O with good diastereo- and enantioselectivity (**Scheme 3.3**) via enanamine intermediate formation **24**. But the problem associated with this approach is the difficulty in preparation of such diene compounds.



Scheme 3.3 Eder's synthesis of 4-nitrocyclohexanones

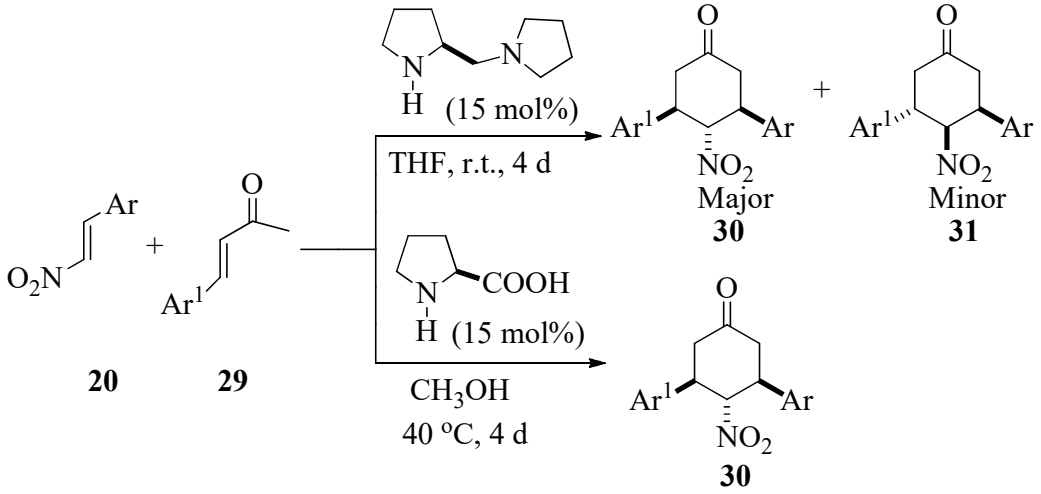
In 2000, Yong –Jin Wu and co-workers[91] prepared the cyclization product of dienic silyl enol ether **25** and methyl (*E*)-2-nitropropenoate **26** via Diels-Alder reaction

via the intermediate **27**. Upon mild hydrolysis, this adduct leads to 4-nitrocyclohexanone **28** (**Scheme 3.4**).



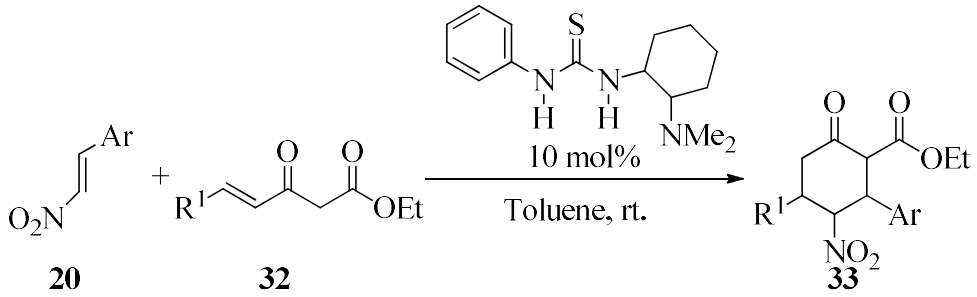
Scheme 3.4 Wu's synthesis of 4-nitrocyclohexanones

Barbas *et.al*[92] reported for the first time that chiral dienamine species derived from α,β-unsaturated ketones **29** can be used in a diastereoselective Diel-Alder type reaction. The 2-amino 1,3-butadiene intermediate act as electron rich diene that undergoes normal electron demand Diels-Alder reaction with nitroolefins **20** to give 4-nitrocyclohexanones **30** and **31**. (L)-Proline or (*S*)-1-(2-pyrrolidinylmethyl) pyrrolidine were found to be good catalysts for the purpose (**Scheme 3.5**).



Scheme 3.5 Barbas synthesis of 4-nitrocyclohexanones

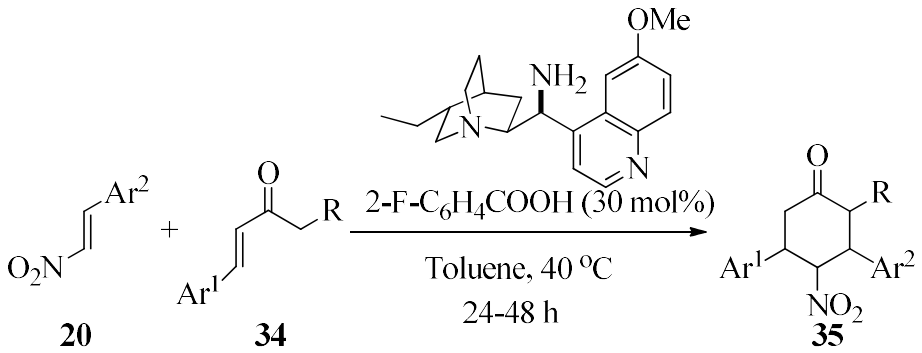
In 2004, Takemoto and co-workers[93] reported the synthesis of highly substituted 4-nitrocyclohexanone derivatives **33** from nitroolefins **20** and γ,δ-unsaturated β-ketoesters **32** by a double Michael addition reaction in presence of bifunctional thiourea catalyst as shown in **Scheme 3.6**.



20 **32** **33**

Scheme 3.6 Takemoto's synthesis of 4-nitrocyclohexanones

In 2009, Melchiorre and his co-workers[93] showed the solution to the issue of activating the α,β-unsaturated ketones **34** towards enamine and iminium tandem sequence. These activated enones undergo sequential double Michael addition with nitroolefins **20** to give 4-nitrocyclohexanones **35**. This approach is complementary to venerable [4+2] cycloaddition (**Scheme 3.7)**.

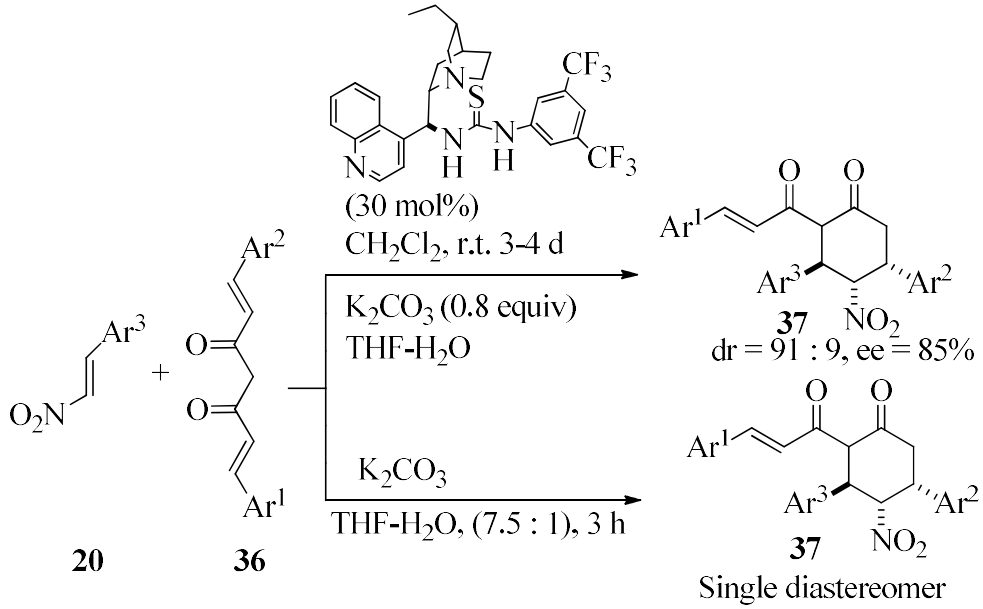


20 **34** **35**

Scheme 3.7 Melchiorre's synthesis of 4-nitrocyclohexanones

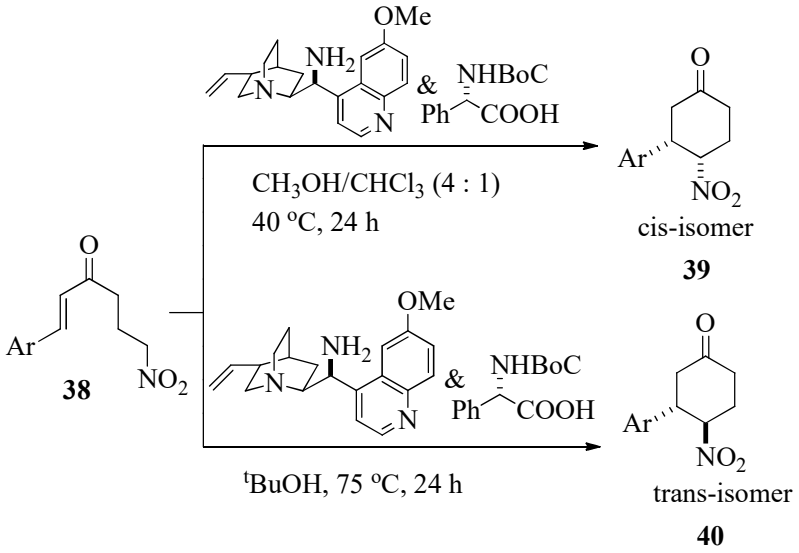
In 2011, Namboothiri *et.al* [94] for the first time reported highly diastereo- and enantioselective approach to the synthesis of highly functionalized 4-nitrocyclohexanones

37 through inter-intramolecular double Michael addition reaction between nitroolefins **20** and curcumin derivatives **36** using the combination of dihydrocinchonine-thiourea organocatalyst and K_2CO_3 (**Scheme 3.8**).



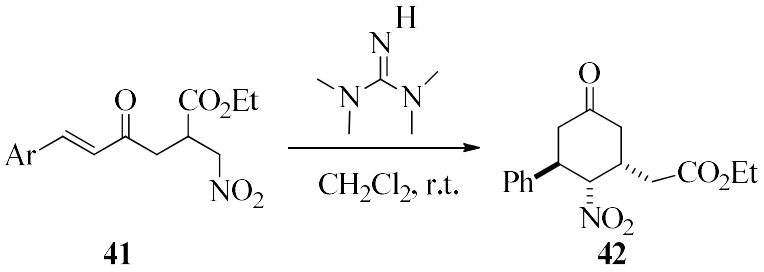
Scheme 3.8 Namboothiri's synthesis of 4-nitrocyclohexanones

In 2012 Jørgensen *et.al*[95] reported a diastereo- and enantioselective reaction leading to the formation of both the *cis* and *trans* diastereoisomers of 4-nitrocyclohexanone derivatives in an intramolecular Michael reaction path using a combination of cinchona based primary amine and phenyl glycine as catalyst. Based on the DFT calculations and ^{1}H-NMR studies, they revealed that *trans* isomer is generated due to catalyst-induced epimerization of the labile nitro bearing stereo center (**Scheme 3.9**).



Scheme 3.9 Jørgensen's synthesis of 4-nitrocyclohexanones

In 2014, Zhihui Shao *et.al*[96] reported the synthesis of 4-nitrosubstituted cyclohexanones **42** via a diastereoselective intramolecular Michael addition of α,β-unsaturated carbonyl compounds **41** in the presence of TMG (1,1,3,3-tetramethylguanidine) base as shown in **Scheme 3.10**.

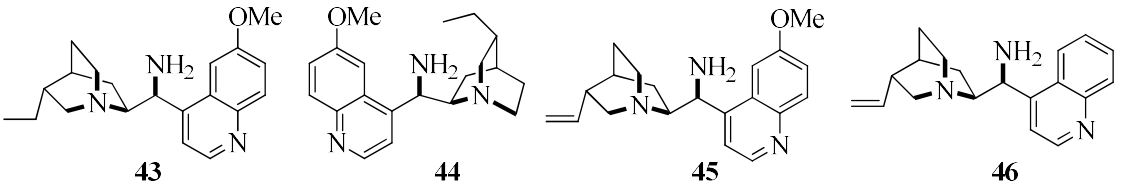


Scheme 3.10 Shao's synthesis of 4-nitrocyclohexanones

3.2 Present work

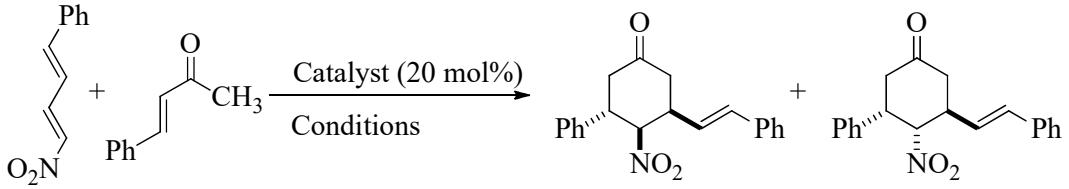
Unlike nitroalkenes, nitrodienes have not been used for double Michael reactions or cycloadditions although nitrodienes are expected to give additional functional group for further chemical manipulations. In many organocatalysed Michael addition reactions,[97] it has been observed that increasing conjugation to the Michael acceptor often shows

altered reactivity and selectivity.[98] So, the reactivity, selectivity and reaction modes of nitrodienes with acyclic enones are yet to be established. Chiral primary amine has recently been extensively used in the enamine activation of aldehydes and ketones.[99] The aim of the present chapter is to use chiral primary amines as catalyst for nitrosubstituted cyclohexanone synthesis from enones and nitrodienes. The enone is expected to form the enamine which then would expected to react with nitrodiene by a double Michael addition or a [4+2] cycloaddition leading to functionalized 4-nitrocyclohexanones. A list of amine organocatalysts[97] (**Figure 3.1**) were chosen for the purpose with a combination of chiral or achiral protic acid for this proposed transformation (**Scheme 3.11**).[100]



43 **44** **45** **46**

Figure 3.1 Structures of catalysts used in this work



4a **29a** **47a** **48a**

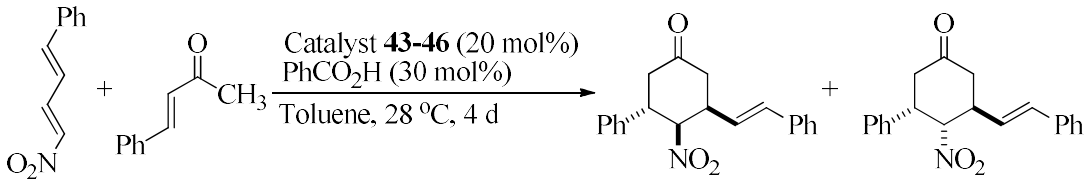
Scheme 3.11 Proposed synthesis of 4-nitrosubstituted cyclohexanones

3.2.1 Optimization of reaction conditions

For the model reaction, 4-phenyl-1-nitrobutadiene **4a** was chosen as the nitrodiene component benzylidene acetone **29a** was chosen as the enone. Initially we screened the cinchona based primary amine catalysts **43-46** (**Figure 3.1)** in combination with benzoic

acid as an additive. Benzoic acid is known to enhances the reactivity or/and the selectivity[101] (including chemo-, regio-, diastereo-, and enantioselectivity) by modification of the reaction pathway. The optimization of catalyst for the reaction between **4a** and **29a** leading to nitro-substituted cyclohexanones **47a** and **48a** in toluene at rt (28 ^{o}C) is presented in **Table 3.1.**

Table 3.1 Screening of catalyst for organocatalysed [4+2] cycloaddition of nitrodiene **4a** and benzylidene acetone **29a**[a].



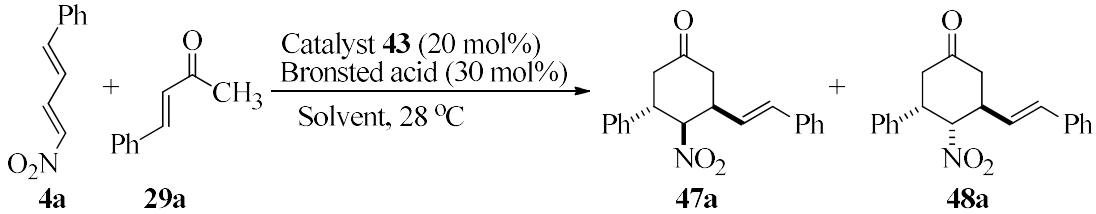
4a **29a** **47a** **48a**

Entry	Catalyst (20 mol%)	**47a/48a**[b]	%Yield of **47a**[c]	%ee of **47a**[d]
1	**43**	65:35	52	99
2	**44**	64:36	46	96[f]
3	**45**	44:56	35	98
4	**46**	40:60	22[e]	96

[a]Unless noted otherwise, all reactions were performed using **4a** (0.2 mmol), **29a** (0.4 mmol), catalyst (0.02 mmol) and benzoic acid (0.03 mmol) in toluene (0.5 mL). [b]Determined by ^{1}H NMR of the crude reaction mixture. [c]Isolated yield of diastereoisomer **47a** after chromatographic purification. [d]Enantiomeric excess of **47a** as determined by HPLC on chiral stationary phase. [e] Incomplete reaction. [f] Product formed with opposite enantioselectivity.

All the catalysts showed positive result (**Table 3.1**, entries 1-4) with the formation of the desired nitro substituted cyclohexanones **47a** and **48a**, but catalyst **43** provided the best result (**Table 3.1,** entry 1). Catalyst **44**, the pseudoenantiomer of catalyst **43**, gave **47a** with a similar level but opposite enantioselectivity (**Table 3.1**, entry 2). We choose catalyst **43** for further optimisation and screened a number of Brønsted acid additives and solvent system. Benzoic acid still remained the additive of choice because of superior yield and selectivities (**Table 3.2**, entry 1). Variation in the polarity of the organic solvents did not improve the yield or selectivities in a meaningful way compared to toluene (**Table 3.2**, entries 5-9). But an exciting result was obtained when water was used as a medium, although none of the reactants and the catalyst was soluble in water (**Table 3.2**, entry 10). The reaction was greatly accelerated (completed in 2 d) resulting in good yield. The diastereoselectivity was improved now to an acceptable level. So, the optimised conditions was to use enone (2 equiv.) with respect to nitrodiene (1 equiv) in the presence of catalyst **43** (20 mol %), benzoic acid (30 mol %) and water at rt (28 ^{o}C) for 2 d.

Table 3.2: Additive and solvent screening using catalysts **43** (20 mol%)[a]



Entry	Additive	Solvent	Time	**47a**/**48a**[b]	%Yield of **47a**[c]	%ee of **47a**[d]
1	Benzoic acid	Toluene	4 d	65:35	52	99

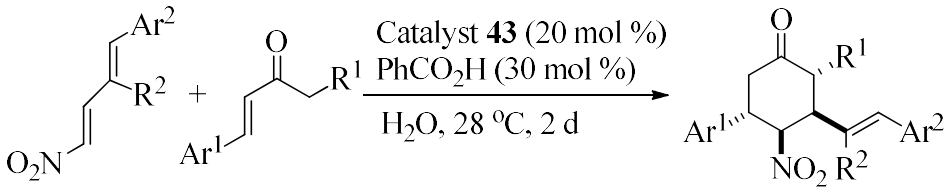
2	3,5-Dinitrobenzoic acid	Toluene	5 d	55:45	16[e]	93
3	4-Nitrobenzoic acid	Toluene	5 d	50:50	21[e]	93
4	2-Fluorobenzoic acid	Toluene	5 d	60:40	35	96
5	Acetic acid	Toluene	5 d	60:40	20[e]	95
6	Benzoic acid	Xylene	5 d	50:50	38	95
7	Benzoic acid	$CHCl_3$	5 d	67:33	42	96
8	Benzoic acid	MTBE[f]	5 d	83:17	39	>99
9	Benzoic acid	THF	5 d	50:50	41	92
10	Benzoic acid	MeOH	5 d	50:50	32	94
11	Benzoic acid	H_2O	2 d	80:20	75	>98

[a]Unless noted otherwise, all reactions were performed using **4a** (0.2 mmol), **29a** (0.4 mmol), catalyst (0.02 mmol) and additive (0.03 mmol) in solvent (0.5 mL). [b]Determined by ^{1}H NMR of the crude reaction mixture. [c]Isolated yield of diastereoisomer **47a** after chromatographic purification. [d]Enantiomeric excess of **47a** as determined by HPLC on chiral stationary phase. [e]Incomplete reaction. [f]MTBE = ^{t}Butyl methyl ether.

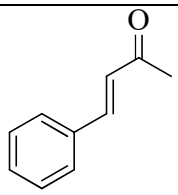
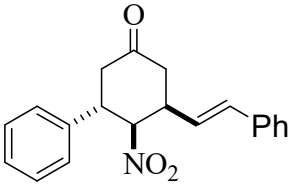
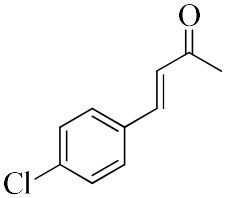
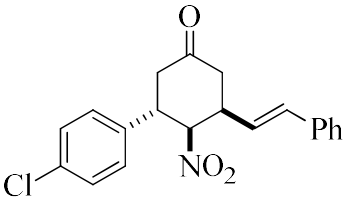
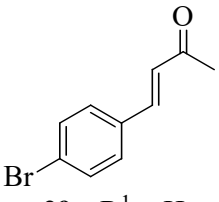
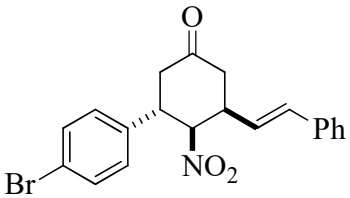
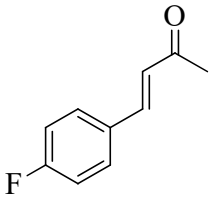
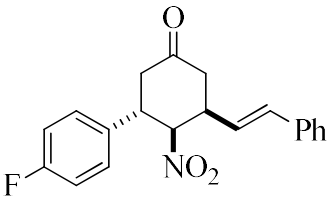
3.2.2 Study of the substrate scope

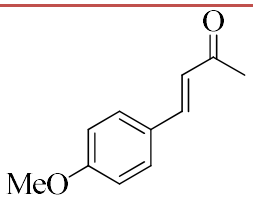
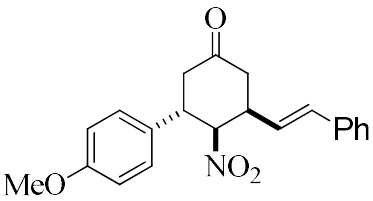
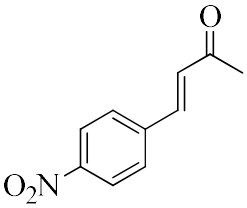
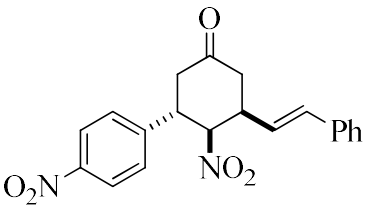
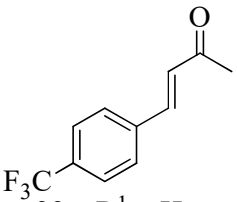
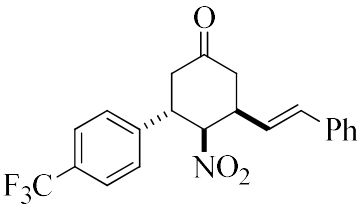
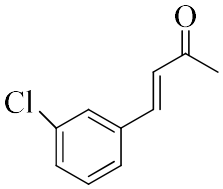
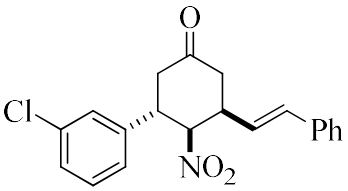
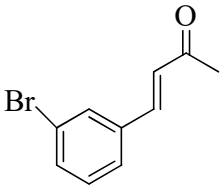
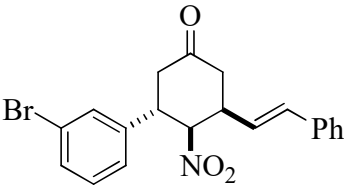
With the established optimal reaction conditions, the substrate scope was explored using variety of nitrodienes **4** and enones **29** having electron-donating and electron-withdrawing functionalities at the aromatic rings of the both components. The products **47a-t**, formed by reaction of various enones and 4-aryl-1-nitrobutadiene, is presented in **Table 3.3**.

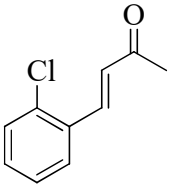
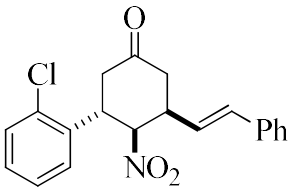
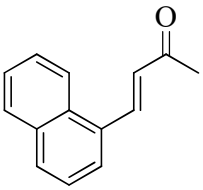
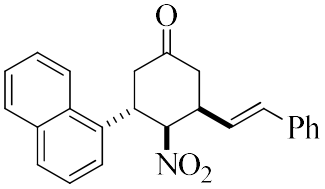
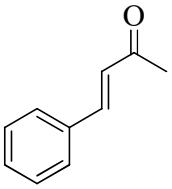
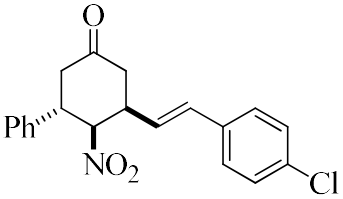
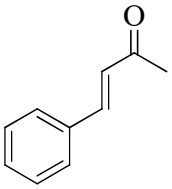
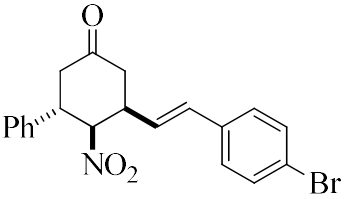
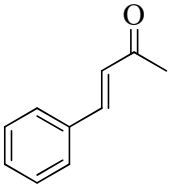
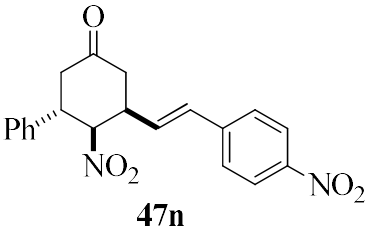
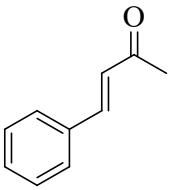
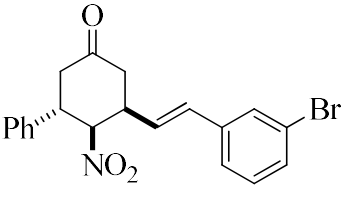
Table 3.3 Synthesis of cyclohexanones **47a-t** from various nitrodienes **4** and enones **29**.

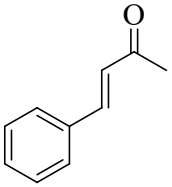
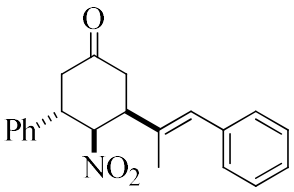
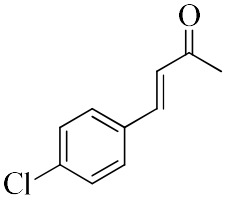
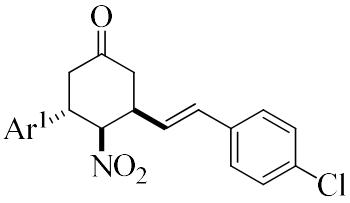
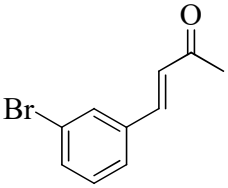
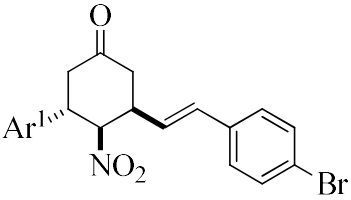
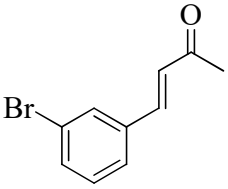
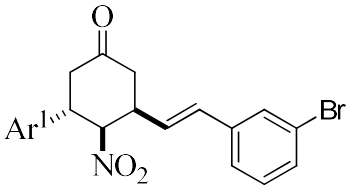
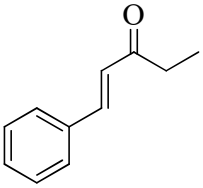
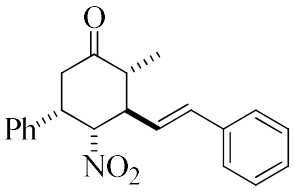


4 **29** **47a-t**

Entry	Enone	Product	dr[a]	Yield[b] (%)	ee (%)[c] of **47a**
1	 **29a**, R^1 = H	 **47a**	80:20	75	>98 (100%)[d]
2	 **29b**, R^1 = H	 **47b**	90:10	70	>94 (100%)[d]
3	 **29c**, R^1 = H	 **47c**	84:16	62	>94 (100%)[d]
4	 **29d**, R^1 = H	 **47d**	84:16	80	>94 (100)[d]

5	 **29e**, R^1 = H	 **47e**	60:40	65[e]	>94 (100%)[d]
6	 **29f**, R^1 = H	 **47f**	84:16	65[f]	>95
7	 **29g**, R^1 = H	 **47g**	80:20	70	>94 (100%)[d]
8	 **29h**, R^1 = H	 **47h**	80:20	65	87 (100%)[d]
9	 **29i**, R^1 = H	 **47i**	90:10	75	93 (100%)[d]

10	 **29j**, R^1 = H	 **47j**	84:16	70	>94 (100%)[d]
11	 **29k**, R^1 = H	 **47k**	79:21	65	>89 (100%)[d]
12	 **29a**, R^1 = H	 **47l**	75:25	70	94 (100%)[d]
13	 **29a**, R^1 = H	 **47m**	75:25	62	>90 (97%)[d]
14	 **29a**, R^1 = H	 **47n**	70:30	60	>94
15	 **29a**, R^1 = H	 **47o**	80:20	64	>95 (100%)[d]

16	 **29a**, R^1 = H	 **47p**	84:16	74[e]	96
17	 **29b**, R^1 = H	 **47q**	80:20	65	94 (>98%)[d]
18	 **29i**, R^1 = H	 **47r**	84:16	70	92 (100%)[d]
19	 **29i**, R^1 = H	 **47s**	70:30	58	>96 (100%)[d]
20	 **29a**, R^1 = CH_3	 **47t**	6:3:1	51[e]	>99

[a]Determined by ^{1}H NMR. [b]Isolated yield of the major diastereoisomer. [c]Determined by major diastereoisomer by HPLC. [d]% ee after recrystallization. [e]Combined isolated yield of both diastereoisomers. [f]Reaction performed at 40 °C.

The reaction worked well irrespective of whether the aromatic ring is functionalized with electron-donating or withdrawing groups at various positions in both the reacting partners. All of the products were solid, and many of them could be made enantiopure just by single recrystallization. The reaction worked well with (*E*)-1-phenylpent-1-en-3-one as enone, providing product **47t** with an additional chiral center (**Table 3.3**, entry 20).

3.2.3 Assignment of absolute configuration

The absolute configuration of 4-nitro substituted cyclohexanone **47g** was established by single crystal X-ray crystallography and was found to be *3S,4R,5S* (**Figure 3.2**). The absolute configuration of the other products **47a-f** and **47h-s** was assigned in analogy.

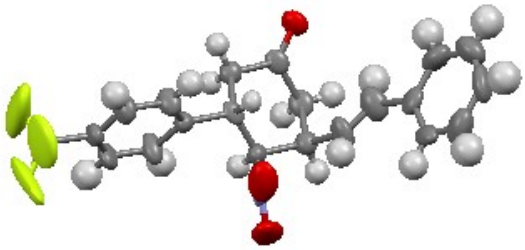
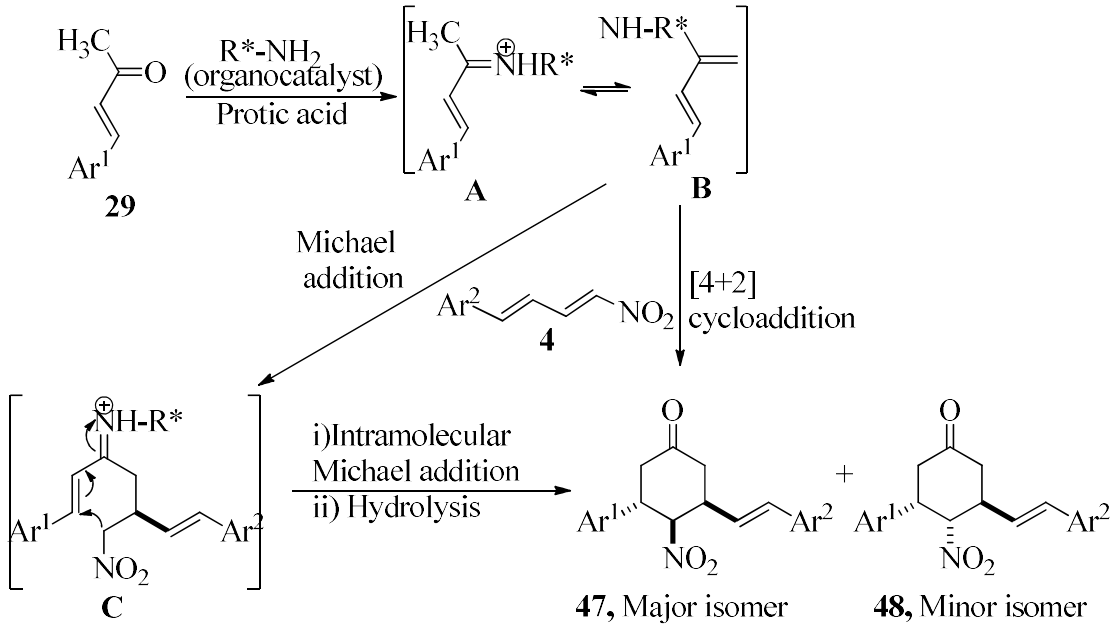


Figure 3.2 ORTEP diagram of **47g**

3.2.4 Proposed mechanism for reaction

A plausible mechanism for the formation of 4-nitrocyclohexanone from nitrodiene **4** and α,β-unsaturated ketone **29** catalyzed by primary amine has been presented in **Scheme 3.12.** Initially, the unsaturated methyl ketone **29** would react with primary amine

organocatalyst in the presence of Brønsted acid to give the iminium **A** which remains in equilibrium with the enamine **B**. The enamine in principle can react with nitrodiene **4** to provide the 3,4,5-trisubstituted cyclohexanone **47/48** either by a double Michael addition or a HOMO raised [4+2] cycloaddition. Here, we found that the major and the minor diastereoisomers **47a** and **48a** have the same enantioselectivity. The major diastereoisomer **47a** was stable towards isomerisation on separate treatment with the catalytic system while the nitro-bearing centre of the minor diastereoisomer **48a** slowly epimerises to the major diastereoisomer 4**7a** under the same conditions.

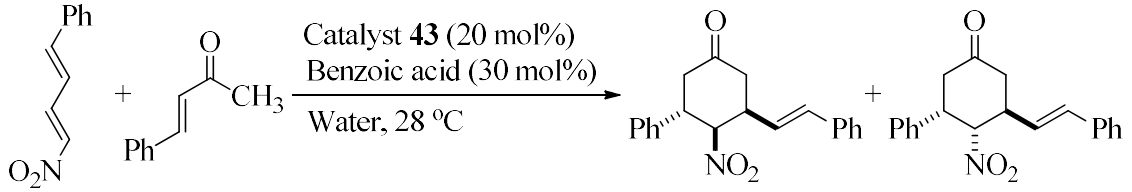


Scheme 3.12 Proposed reaction mechanism for formation of 4-nitrocyclohexanone

The progress of cyclohexanone formation from nitrodiene **4a** and enone **29a** was monitored by ^{1}H NMR spectroscopy. From this study, an interesting change in the ratio of **47a**/**48a** as observed as the time progressed (**Table 3.4**). After 2 h, the diastereoisomer **48a** was almost the sole product in the incomplete reaction. But as the time advanced, the

conversion also progressively increased and the diatereoisomer ratio **47a/48a** was also changed from 4/96 to 80/20 after 2 days. The ratio of **47a/48a** could further be improved to 90/10 if the reaction was left for 6 days at room temperature without any loss of enantioselectivity or yield. These experiments confirm that the diastereoisomer **48a** was initially formed as a kinetic *endo* [4+2] cycloaddition product which over the time isomerises under the reaction conditions to thermodynamically more stable diastereoisomer **47a**. Therefore, we believed that 4-nitrocyclohexanones are formed *via* [4+2] cycloaddition pathway.

Table 3.4 Change in diastereoisomeric ratio with time as monitored by ^{1}H NMR



4a **29a** **47a,** Major isomer **48a,** Minor isomer

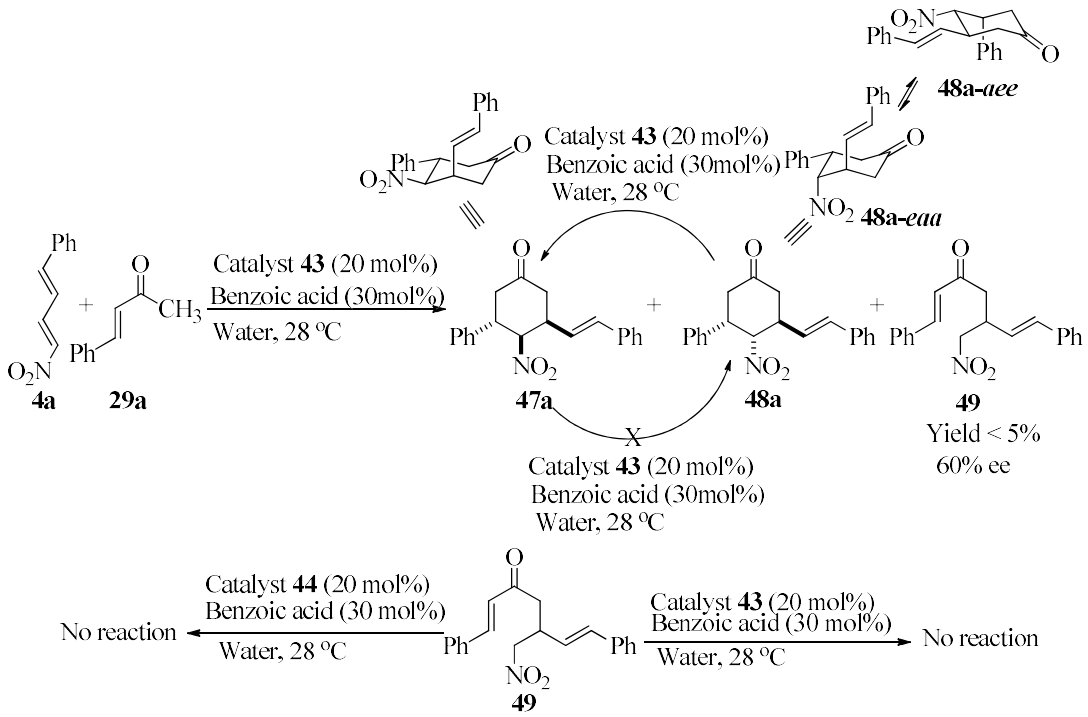
Entry	Time (h)	**47a**/**48a**[a]	yield[b] (%)	ee[c] (%)
1	2	4/96	d	-
2	6	15/85	d	-
3	24	62/38	d	-
4	48	80/20	75	>98
5	168	90/10	82	>98
6	120[e]	90:10	80	94

[a]Determined by ^{1}H NMR of the crude reaction mixture. [b]Isolated yield of diastereoisomer **47a** after chromatographic purification. [c]Determined by HPLC on chiral

stationary phase. [d]Incomplete reaction; yield not determined. [e]Reaction performed for 48 h at rt and then 72 h at 40 ºC.

Further, the ease of epimerisation of **48a** to 4**7a** can be explained by analyzing the conformational preferences for **47a** and **48a** (**Scheme 3.13**). After the cycloaddition and hydrolysis, the product **48a** can have two conformations **48a-*eaa*** and **48a-*aee***. Considering the substituent steric factors (cyclohexane A values), conformer **48a-*eaa*** will be preferred over **48a-*aee***. The NO_2 group in **48a-*eaa*** is axially disposed would thus prefer to become equatorial by α-deprotonation-reprotonation (epimerisation) leading to diastereoisomer **47a** with a conformation where the Ph and NO_2 groups are equatorial as supported by X-ray crystal structure of **47g**. The support in favour of [4+2] cycloaddition pathway was further augmented by appreciable rate acceleration of the reactions in water[102] compared to organic solvents (**Table 3.2**, entry 11).

In addition to diastereoisomers **47a** and **48a**, we have also isolated a very small amount of Michael addition product **49** from the reaction between nitrodiene **4a** and enone **29a** under the optimised conditions in <4% yield and with poor enantioselectivity (60% ee). This adduct did not undergo intramolecular Michael type cycloaddition to give the 4-nitrocyclohexanone(s) **47a/48a** under the optimised conditions using catalyst **43** or **44.** This observation also suggests that [4+2] cycloaddition preferred over a double Michael addition for the current synthesis of densely substituted 4-nitrocyclohecanones.



Scheme 3.13 Mechanistic studies for the formation of major isomer **47a**

3.3 Conclusion

In summary, we have developed an eco-friendly 'on water' organocatalytic [4+2] cycloaddition method for densely substituted cyclohexanones at ambient conditions. Water played key role in rate enhancements as well as diastereo- and enantioselectivities. The observed diastereiosomers are due to the nitro-bearing centre which is epimerisable under acid/base conditions. Mechanistic analysis of the reaction goes in favour of an *endo* [4+2] cycloaddition and the formed 4-nitrosubstituted cyclohexanone derivatives might find important application in complex organic molecule synthesis and natural product synthesis.

3.4 Experimental Section

General details: As described in **Chapter-2**

3.4.1 General methods and Materials

Materials

Benzylidene acetone **29a** was purchased from Spectrochem Private Limited, India. Other arylidene acetones **29** were synthesized from respective aryl aldehydes and acetone following the literature procedures.[106] Nitrodienes **4** were prepared[82,83] from substituted cinnamaldehydes and nitromethanes following the procedure as described in the Chapter **2.** Organocatalysts **43-46** were prepared according to literature.[107]

Preparation of organocatalysts 43-46

9-Amino-(9-deoxy)epihydroquinine 43

Following the literature[107] procedure, hydroquinine (3.26 g, 10.0 mmol, 1.0 equiv) and triphenylphosphine (3.15 g, 12.0 mmol, 1.2 equiv) were dissolved in dry THF (50 mL) and the solution was cooled to 0 °C. Diisopropyl azodicarboxylate (2.43 g, 12.0 mmol, 1.2 equiv) was added into the reaction mixture followed by a solution of diphenyl phosphoryl azide (3.3 g, 12.0 mmol, 1.2 equiv) in dry THF (20 mL) at 0 °C. The mixture was allowed to warm to room temperature and stirred for 12 h. The reaction mixture was heated to 50 °C for 2 h. Triphenylphosphine (3.41 g, 13.0 mmol, 1.3 equiv) was added into it and heating was maintained until the gas evolution has ceased (2 h). The reaction mixture was cooled to room temperature, water (1 mL) was added and stirred for 3 h. Solvents were removed in vacuo and the residue was taken in a biphasic system comprised of CH_2Cl_2 and 10% hydrochloric acid (1:1, 100 mL). The organic phase was

separated and the aqueous phase was extracted with CH_2Cl_2 (4 × 50 mL). The aqueous phase was made alkaline with excess ammonia and was extracted with CH_2Cl_2 (4 × 50 mL). The combined organic phases was dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/MeOH/ aq. NH_4OH = 50/50/1 as eluent) affording the catalyst **43** (2.30 g, 71%) as a yellowish viscuous oil. IR ($CHCl_3$): $\bar{\upsilon}$ = 1622, 1507, 1473, 1433, 1265, 1032, 915, 737, 635 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ = 0.85 (3 H, t, J = 7.3 Hz, CH_2CH_3), 1.35 (2 H, m, CH_2CH_3), 1.47 (1 H, br m), 1.52-1.53 (2 H, m), 1.56 (1 H, br m), 1.59-1.60 (2 H, m), 2.56 (1 H, ddd, J = 2.3, 4.7, 13.6 Hz), 2.79 (1 H, ddd, J = 4.9, 13.8, 15.6 Hz), 3.16 (1 H, q, J = 10.7 Hz), 3.28 (1 H, dd, J = 9.9, 13.6 Hz), 3.32 (1 H, dddd, J = 2.3, 7.8, 10.5, 15.6 Hz), 4.00 (3 H, s, OCH_3), 4.72 (1 H, d, J = 11.0 Hz), 7.45 (1 H, dd, J = 2.6, 9.3 Hz), 7.61 (1 H, d, J = 4.7 Hz), 7.69 (1 H, br s), 7.97 (1 H, d, J = 9.3 Hz) 8.69 (1 H, d, J = 4.7 Hz) ppm; ^{13}C NMR (125 MHz, CD_3OD) δ = 11.4. 25.7, 25.8, 27.6, 28.0, 37.8, 40.8, 51.9, 55.2, 57.8, 62.2, 102.1, 120.2, 122.3, 129.4, 130.6, 144.2, 147.5, 148.3, 158.8 ppm; HRMS (EI) Exact mass calculated for $C_{20}H_{27}N_3O$ $[M]^+$ 325.2154; Found: 325.2160. Anal. Calcd. for $C_{20}H_{27}N_3O$: C, 73.81; H, 8.36; N, 12.91; O, 4.92. Found: C, 73.75; H, 8.30; N, 12.75; $[\alpha]_{23}^{D}$ = +71.0 (c 0.97, $CHCl_3$).

9-Amino-(9-deoxy)epihydroquinidine 44

The catalyst **44** was prepared according to procedure for catalyst **43** from hydroquinidine (3.26 g, 10.0 mmol) after column chromatography (eluent: EtOAc/MeOH/ aq. NH_4OH = 50/50/1 as eluent) as yellowish viscuous oil, (2.30 g, 70%). ^1H NMR (500 MHz, $CDCl_3$): δ = 0.86 (3 H, t, J = 7.2 Hz), 0.91–0.98 (1 H, m), 1.10–1.02 (1 H, m), 1.26–1.64 (7 H, m),

2.07 (2 H, bs), 2.62 (1 H, ddd, J = 2.3, 7.3, 14.1 Hz), 2.84 –3.08 (4 H, m), 3.95 (3 H, s), 4.53–4.77 (1 H, m), 7.37 (1 H, dd, J = 2.7, 9.3Hz), 7.55–7.45 (1 H, m), 8.02 (1 H, d, J = 9.2 Hz), 8.73 (1 H, d, J = 4.5 Hz), 7.63 (1 H, bs) ppm; ^{13}C (125 MHz, $CDCl_3$): δ = 11.9, 23.9, 25.0, 25.6, 26.7, 36.5, 48.9 (2 C), 49.0, 55.2, 62.6, 99.5, 119.5, 121.8, 128.4, 131.4, 143.7, 147.4, 147.8, 157.0 ppm; $[\alpha]_{23}^{D}$ = + 33.5 (c 1.00, $CHCl_3$)

9-Amino-(9-deoxy)epi-quinine 45

The catalyst 4**5** was prepared according to procedure for catalyst **43** from quinine (3.24 g, 10.0 mmol) after column chromatography (EtOAc/MeOH/ aq. NH_4OH = 50/50/1 as eluent) as a yellowish gummy oil, (2.39 g, 74%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.71–0.79 (1 H, m), 1.36–1.45 (1 H, m), 1.48–1.58 (2 H, m), 1.59–1.64 (1 H, m), 1.93– 2.12 (2 H, m), 2.23–2.31 (1 H, m), 2.74–2.84 (2 H, m), 2.98–3.12 (1 H, m), 3.15–3.23 (1 H, m), 3.26 (1 H, dd, J = 10.0, 13.7 Hz), 3.94 (3 H, s), 4.51–4.67 (2 H, m), 4.90– 5.01 (2 H, m), 5.78 (1 H, ddd, J = 7.5, 10.1, 17.3 Hz), 7.36 (1 H, dd, J = 2.8, 9.3 Hz), 7.41–7.46 (1 H, m), 7.64 (1 H, bs), 8.01 (1 H, d, J = 9.4 Hz), 8.73 (1 H, d, J = 4.5 Hz) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 25.6, 27.0, 27.6, 39.6, 40.7, 50.3, 55.5 (2 C), 61.9, 100.2, 114.5, 119.4, 121.5, 128.5, 131.6, 141.6, 143.9, 146.8, 148.0, 157.3 ppm; $[\alpha]_{23}^{D}$ = + 100.5 (c 1.00 in $CHCl_3$).

9-Amino-(9-deoxy)epi-cinchonidine 46

The catalyst **46** was prepared according to procedure for catalyst **43** from cinchonidine (2.93 g, 10.0 mmol) after column chromatography (eluent: EtOAc/MeOH/ aq. NH_4OH = 50/50/1 as eluent) as slightly yellow oil, (2.20 g, 75%); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.95–1.13 (2 H, m), 1.47–1.68 (3 H, m), 2.34 (1 H, q, J = 8.5 Hz), 3.91–2.25 (5 H, m),

4.68 (1 H, d, *J* = 10.2 Hz), 5.06–5.08 (1 H, m), 5.10 (1 H, dt, *J* = 1.6, 13.9, Hz), 5.89 (1 H, ddd, *J* = 6.9, 10.4, 17.3 Hz), 7.38 (1 H, dd, *J* = 2.6, 9.1 Hz), 7.52–7.60 (2 H, m,), 7.91 (1 H, d, *J* = 9.1 Hz), 8.61 (1 H, d, J = 4.6 Hz) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 25.9, 27.1, 29.0, 40.6, 48.1, 50.3, 63.4 (broad), 105.6 (broad), 115.6, 120.6 (broad), 123.7, 130.6, 131.5, 141.2, 144.2, 147.6, 148.3, 158.3 ppm; $[\alpha]_{23}^{D}$ = +80 (c = 1.1, $CHCI_3$).

3.4.2 Experimental procedures and characterizations

General Procedure I: Preparation of trisubstituted *rac*-cyclohexanone derivatives

All the reactions were carried out in normal toluene and no special precautions were taken to exclude water or air from the reaction flask. Pyrrolidine (0.1 mmol) and benzoic acid (6.0 mg, 0.05 mmol) were added to a stirred solution of the nitrodiene **4** (0.2 mmol) enones **29** (0.4 mmol) in toluene (1 mL). Then the reaction mixture was stirred at 50 ºC for 2 d. After that, the solvent was removed under reduced pressure and the resulting residue was directly subjected to column chromatography on silica gel to afford the corresponding products *rac*-4**7a-t.**

General Procedure II: Preparation of trisubstituted chiral cyclohexanone derivatives

All the reactions were carried out in double distilled water and no special precautions were taken to exclude air from the reaction flask. Benzoic acid (7.5 mg, 0.06 mmol, 30 mol %) was added to a heterogeneous mixture of the catalyst **43** (13 mg, 0.04 mmol, 20 mol %) and water (0.5 mL). The resulting heterogeneous mixture was stirred at 40 °C for 10 min in a pre-heated oil bath. After that, the mixture was brought to room temperature and enone **29** (0.4 mmol, 2.0 equiv) was added, followed by the addition of nitrodiene **4**

(0.2 mmol, 1 equiv). The heterogeneous mixture was stirred at 28 °C for 2 d. The reaction mixture was extracted with dichloromethane (3 × 10 mL) and the combined extract was washed with brine, dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography on silica using hexane/EtOAc as eluent to give 4**7a-t**. Except mentioned, each solid product was recrystallized from hexane/EtOAc combined solvent systems to give the corresponding enantiomerically pure cyclohexanone.

(3*S*,4*R*,5*S*)-4-Nitro-3-phenyl-5-styrylcyclohexanone 47a

The product **47a** was obtained following the *General procedure* **3.4.2 II** from nitrodiene **4a** (35 mg, 0.2 mmol, 1.0 equiv) and enone **29a** (58.5 mg, 0.4 mmol, 2.0 equiv) using catalyst **43** (13.0 mg, 0.04 mmol, 20 mol %) and water (0.5 mL)**.** White solid. Yield: 48.0 mg (75%, >98% ee); Recrystallized from hexane-EtOAc; mp: 209-210 °C; IR ($CHCl_3$): $\bar{\upsilon}$ = 1715, 1542, 1493, 1370, 1210, 1027, 968, 907, 757, 695 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ = 2.83-2.61 (2 H, m, =CHCHCH_2), 2.90-2.86 (2 H, m, PhCHCH_2), 3.58-3.47 (1 H, m, =CHC*H*), 3.99-3.86 (1 H, m, PhC*H*), 5.30 (1 H, dd, *J* = 4.4, 9.4 Hz, NO_2C*H*), 6.10 (1 H, dd, *J* = 7.7, 15.9 Hz, PhCH=C*H*), 6.46 (1H, dd, *J* = 0.6, 15.8 Hz, PhC*H*=CH), 7.40-7.25 (10 H, m, 2 x Ph) ppm; ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 41.5, 42.3, 43.2, 45.0, 90.4, 123.6, 126.6 (2 C), 127.1 (2 C), 128.0, 128.3, 128.6 (2 C), 129.2 (2 C), 134.7, 135.8, 139.0, 205.97 ppm; Anal. calcd for $C_{20}H_{19}NO_3$: C, 74.75; H, 5.96; N, 4.36; Found: C, 74.76; H, 6.14; N, 4.22; $[\alpha]_D^{25}$ = -69.9 (*c* 2.00, $CHCl_3$, ee >99.99%); The *ee* was determined by HPLC using a Daicel Chiralpak AD-H [hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 14.05 min, τ_{minor} = 18.73 min, >98% ee.

(3*S*,4*S*,5*S*)-4-Nitro-3-phenyl-5-styrylcyclohexanone 48a

Yellow liquid: Yield: 6.0 mg (9%, >97% ee); IR (film): $\bar{\upsilon}$ = 1711, 1541, 1492, 1372, 1210, 1027, 968, 907, 759, 697 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ = 2.69 (1 H, dd, J = 6.0, 16.0 Hz, =CHCHCH_2), 2.75 (1 H, dd, J = 5.5, 15.5 Hz, =CHCHCH_2), 3.08 (1 H, dd, J = 6.0, 15.5 Hz, PhCHCH_2), 3.40 (1 H, dd, J = 10.8, 15.3 Hz, PhCHCH_2), 3.60 (1 H, quin, J = 6.0 Hz, =CHC*H*), 3.79 (1 H, quin, J = 5.0 Hz, PhC*H*), 5.07 (1 H, t, J = 5.0 Hz, NO_2C*H*), 6.10 (1 H, dd, J = 7.3, 15.8 Hz, PhCH=C*H*), 6.61 (1 H, d, J = 16 Hz, PhC*H*=CH), 7.15 (2 H, d, J = 7.5 Hz, Ph), 7.38-7.29 (8 H, m, Ph) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 41.0, 41.5, 41.7, 42.3, 90.3, 126.2, 126.6 (2 C), 127.4 (2 C), 128.4, 128.7 (2 C), 129.1 (2 C), 134.3, 135.8, 136.9, 207.3 ppm; Anal. calcd for $C_{20}H_{19}NO_3$: C, 74.75; H, 5.96; N, 4.36; Found: C, 74.71; H, 6.11; N, 4.31; ee; $[\alpha]_D^{25}$ = -93.0 (*c* 0.91, $CHCl_3$, ee >97.0%); The *ee* was determined by HPLC using a Daicel Chiralpak AD-H [hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 17.74 min, τ_{minor} = 24.00 min, >97%.

(1*E*,6*E*)-5-(Nitromethyl)-1,7-diphenylhepta-1,6-dien-3-one 49

Yellow liquid: Yield: 2.0 mg (3%, 60% ee); ^1H NMR ($CDCl_3$, 500 MHz): δ = 3.00 (2 H, d, J = 6.5 Hz, OCC*H2*), 3.71-3.64 (1 H, m, NO_2CH_2C*H*), 4.59 (1 H, dd, J = 7. 5, 12.5 Hz, NO_2CH_2), 4.69 (1 H, dd, J = 6.0, 12.5 Hz, NO_2CH_2), 6.15 (1 H, dd, J = 8.5, 16.0 Hz, PhCH=C*H*), 6.58 (1 H, d, J = 15.5 Hz, PhC*H*=CH), 6.76 (1 H, d, J = 16.0 Hz, OCC*H*=CH), 7.26-7.15 (1 H, m, OCCH=C*H*), 7.32-7.29 (2 H, m, Ph), 7.35-7.34 (2 H, m, Ph), 7.42-7.40 (3 H, m, Ph), 7.57-7.55 (2 H, m, Ph), 7.60 (1 H, d, J = 16.5 Hz, Ph) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 37.4, 42.4, 78.8, 125.7, 126.5 (2 C), 128.0, 128.4 (3 C), 128.6 (2 C), 129.0 (2 C), 130.9, 133.4, 134.1, 136.2, 143.7, 196.8 ppm; The *ee* was

determined by HPLC using a Daicel Chiralpak AD-H [hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 24.98 min, τ_{minor} = 32.9 min, 60% ee.

(3*S*,4*R*,5*S*)-3-(4-Chlorophenyl)-4-nitro-5-styrylcyclohexanone 47b

The product **47b** was obtained following the *General procedure* **3.4.2 II** from nitrodiene **4a** (35 mg, 0.2 mmol, 1.0 equiv) and enone **29b** (72.0 mg, 0.4 mmol, 2.0 equiv) using catalyst **43** (13.0 mg, 0.04 mmol, 20 mol %) and water (0.5 mL)**.** White solid**.** Yield**:** 48.0 mg (75%, >94% ee). Recrystallized from hexane-EtOAc; mp: 201-202 °C; IR ($CHCl_3$): ῡ = 1715, 1545, 1493, 1377, 1092, 1015, 969, 837, 750, 694 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ = 2.79-2.56 (2 H, m, =CHCHCH_2), 2.89-2.85 (2 H, m, ArCHCH_2), 3.57-3.49 (1 H, m, =CHC*H*), 3.96-3.83 (1 H, m, PhC*H*), 5.24 (1 H, dd, *J* = 4.6, 9.8 Hz, NO_2C*H*), 6.07 (1 H, dd, *J* = 7.8, 15.8 Hz, PhCH=C*H*), 6.47 (1 H, d, *J* = 15.8 Hz, PhC*H*=CH), 7.35-7.18 (9 H, m, Ph & Ar) ppm; ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 41.6 (2 C), 43.3, 45.1, 90.3, 123.2, 126.7 (2 C), 128.4, 128.5 (2 C), 128.6 (2 C), 129.4 (2 C), 134.0, 135.0, 135.8, 137.4, 205.3 ppm; Anal. calcd for $C_{20}H_{18}ClNO_3$: C, 67.51; H, 5.10; N, 3.94; Found: C, 67.46; H, 4.84; N, 3.66; $[\alpha]_D^{25}$ = -217.9 (*c* 1.54, $CHCl_3$, ee >99.99%); The *ee* was determined by HPLC using a Daicel Chiralpak AD-H [hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 19.10 min, τ_{minor} = 25.36 min, >94% ee.

(3*S*,4*R*,5*S*)-3-(4-Bromophenyl)-4-nitro-5-styrylcyclohexanone 47c

The product **47c** was obtained following the *General procedure* **3.4.2 II** from nitrodiene **4a** (35.0 mg, 0.2 mmol, 1.0 equiv) and enone **29c** (89.5 mg, 0.4 mmol, 2.0 equiv) using catalyst **43** (13.0 mg, 0.04 mmol, 20 mol %) and water (0.5 mL)**.** White solid**.** Yield**:** 50.0 mg (75%, >94% ee). Recrystallized from hexane-EtOAc; mp: 169-170 °C; IR ($CHCl_3$): ῡ = 1715, 1546, 1485, 1373, 1289, 1011, 968, 836, 749, 694 cm^{-1}; ^1H NMR ($CDCl_3$, 500

MHz): δ = 2.64 (1 H, dd, J = 11.0, 15.5 Hz, =CHCHCH_2), 2.83-2.79 (1 H, m, =CHCHCH_2), 2.90-2.84 (2 H, m, ArCHCH_2), 3.58-3.53 (1 H, m, =CHCH), 3.91-3.86 (1 H, m, ArCH), 5.25 (1 H, dd, J = 4.5, 9.5 Hz, NO_2CH), 6.08 (1 H, dd, J = 7.5, 15.5 Hz, PhCH=CH), 6.47 (1 H, d, J = 15.5 Hz, PhCH=CH), 7.15 (2 H, d, J = 8.5 Hz, Ar), 7.35-7.27 (5 H, m, Ph), 7.48 (2 H, d, J = 8.5 Hz, Ar) ppm; ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 41.66, 41.7, 43.3, 45.0, 90.2, 122.1, 123.2, 126.7 (2 C), 122.1, 123.2, 128.4, 128.6 (2 C), 128.8 (2 C), 132.4 (2 C), 135.1, 135.8, 138.0, 205.3 ppm; Anal. calcd for $C_{20}H_{18}BrNO_3$: C, 60.01; H, 4.53; N, 3.50; Found: C, 60.35; H, 4.24; N, 3.36; $[\alpha]_D^{25}$ = -187.9 (*c* 1.30, $CHCl_3$, ee >99.99%); The *ee* was determined by HPLC using a Daicel Chiralpak AD-H [hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 19.36 min, τ_{minor} = 25.80 min, >94% ee.

(3*S*,4*R*,5*S*)-3-(4-Fluorophenyl)-4-nitro-5-styrylcyclohexanone 47d

The product **47d** was obtained following the *General procedure* **3.4.2 II** from nitrodiene **4a** (35 mg, 0.2 mmol, 1.0 equiv) and enone **29d** (65.6 mg, 0.4 mmol, 2.0 equiv) using catalyst **43** (13.0 mg, 0.04 mmol, 20 mol %) and water (0.5 mL)**.** White solid**.** Yield**:** 54.0 mg (80%, >94% ee). Recrystallized from hexane-EtOAc; mp: 216-218 °C; IR ($CHCl_3$): $\bar{\upsilon}$ = 1715, 1544, 1509, 1373, 1224, 1160, 969, 842, 750, 695 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 2.63 (1 H, dd, J = 10.7, 15.5 Hz, =CHCHCH_2), 2.9-2.77 (3 H, m, CH_2COCH), 3.59-3.48 (1 H, m, =CHCH), 3.97-3.84 (1 H, m, ArCH), 5.24 (1 H, dd, J = 4.5, 9.7 Hz, NO_2CH), 6.08 (1 H, dd, J = 7.8, 16.0 Hz, PhCH=CH), 6.46 (1 H, d, J = 15.8 Hz, PhCH=CH), 7.08-6.99 (2 H, m, Ph), 7.34-7.21 (7H, m, Ph & Ar) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 41.6, 43.3, 45.2, 90.6, 116.2 (d, Jc-$_F$ = 22 Hz), 123.3, 126.7 (2 C), 128.4, 128.6 (2 C), 128.8 (d, Jc-$_F$ = 8 Hz), 134.7 (d, Jc-$_F$ = 4 Hz), 134.9, 135.8, 162.2 (d, Jc-$_F$ =

248 Hz), 205.6 ppm; Anal. calcd for $C_{20}H_{18}FNO_3$: C, 70.78; H, 5.35; N, 4.13; Found: C, 70.67; H, 5.01; N, 3.95; $[\alpha]_D^{25}$ = -192.8 (*c* 1.34, $CHCl_3$, ee >99.99%); The *ee* was determined by HPLC using a Daicel Chiralpak AD-H [hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 18.11 min, τ_{minor} = 23.46 min, >94% ee.

(3*S*,4*R*,5*S*)-3-(4-Methoxyphenyl)-4-nitro-5-styrylcyclohexanone 47e

The product **47e** was obtained following the *General procedure* **3.4.2 II** from nitrodiene **4a** (35 mg, 0.2 mmol, 1.0 equiv) and enone **29e** (70.4 mg, 0.4 mmol, 2.0 equiv) using catalyst **43** (13.0 mg, 0.04 mmol, 20 mol %) and water (0.5 mL)**.** White solid**.** Yield**:** 32.0 mg (45%, >95% ee). Recrystallized from hexane-EtOAc; mp: 138-140 °C; IR ($CHCl_3$): ῡ = 1715, 1550, 1514, 1368, 1252, 1180, 1032, 964, 748, 695 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ = 2.66 (1 H, dd, *J* = 10.2, 15.6 Hz, =CHCHC*H*), 2.89-2.78 (3 H, m, CH_2COC*H*), 3.54-3.42 (1 H, m, =CHC*H*), 3.76 (3 H, s, OCH_3), 3.93-3.81 (1 H, m, ArC*H*), 5.22 (1 H, dd, *J* = 4.4, 9.2 Hz, NO_2C*H*), 6.09 (1 H, dd, *J* = 7.7, 15.7 Hz, PhCH=C*H*), 6.45 (1 H, dd, *J* = 0.8, 15.8 Hz, PhC*H*=CH), 6.90-6.82 (2 H, m, Ar), 7.22-7.14 (2 H, m, Ar), 7.35-7.24 (5 H, m, Ph) ppm; ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 41.3, 41.7, 43.2, 45.0, 55.3, 90.8, 114.6 (2 C), 123.8, 126.6 (2 C), 128.2 (3 C), 128.6 (2 C), 130.9, 134.6, 135.9, 159.2, 206.2 ppm; Anal. calcd for $C_{21}H_{21}NO_4$: C, 71.78; H, 6.02; N, 3.99; Found: C, 71.61; H, 5.71; N, 3.88. $[\alpha]_D^{25}$ = -192.0 (*c* 1.28, $CHCl_3$, ee >99.99%); The *ee* was determined by HPLC using a Daicel Chiralpak AD-H [hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 18.51 min, τ_{minor} = 33.03 min, >95%.

(3*S*,4*R*,5*S*)-3-(4-Nitrophenyl)-4-nitro-5-styrylcyclohexanone 47f

The product **47f** was obtained following the *General procedure* **3.4.2 II** from nitrodiene **4a** (35 mg, 0.2 mmol, 1.0 equiv) and enone **29f** (70.4 mg, 0.4 mmol, 2.0 equiv) using

catalyst **43** (13.0 mg, 0.04 mmol, 20 mol %) and water (0.5 mL)**.** Yellow solid**.** Yield**:** 48.0 mg (65%, >95% ee). Recrystallized from hexane-EtOAc; mp: 172-174 °C; ; IR ($CHCl_3$): ῡ = 1719, 1596, 1550, 1520, 1347, 1252, 1016, 855, 748, 695 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz): δ = 2.65 (1 H, dd, *J* = 12.0, 15.6 Hz, =CHCHC*H*), 2.80 (1 H, dd, *J* = 4.8, 15.6 Hz, =CHCHC*H*), 2.96-2.89 (2 H, m, ArCHCH_2), 3.67-3.65 (1 H, m, =CHC*H*), 4.06-4.01 (1 H, m, ArC*H*), 5.36 (1 H, dd, *J* = 4.2, 10.2 Hz, NO_2C*H*), 6.07 (1 H, dd, *J* = 7.8, 15.6 Hz, PhCH=C*H*), 6.50 (1 H, d, *J* = 16.2 Hz, PhC*H*=CH), 7.35-7.26 (5 H, m, Ph), 7.47 (2 H, d, *J* = 9.0 Hz, Ar), 8.22 (2 H, d, *J* = 8.4 Hz, Ar) ppm; ^{13}C NMR ($CDCl_3$, 150 MHz): δ = 41.7, 42.0, 43.4, 45.1, 89.7, 122.4, 124.4 (2 C), 126.6 (2 C), 128.1 (2 C), 128.5, 128.6 (3 C), 135.5, 146.0, 147.5, 204.2 ppm; Anal. calcd for $C_{20}H_{18}N_2O_5$: C, 65.57; H, 4.95; N, 7.65; Found: C, 65.55; H, 5.11; N, 7.74; $[\alpha]_D^{25}$ = -158.0 (*c* 0.92, $CHCl_3$, ee >95%); The *ee* was determined by HPLC using a Daicel Chiralpak AD-H [hexane/*i*-PrOH (80:20)]; flow rate 1.0 mL/min; τ_{major} = 53.09 min, τ_{minor} = 68.35 min, >95% ee.

(3*S*,4*R*,5*S*)-3-(4-Trifluoromethylphenyl)-4-nitro-5-styrylcyclohexanone 47g

The product **47g** was obtained following the *General procedure* **3.4.2 II** from nitrodiene **4a** (35 mg, 0.2 mmol, 1.0 equiv) and enone **29g** (85.6 mg, 0.4 mmol, 2.0 equiv) using catalyst **43** (13.0 mg, 0.04 mmol, 20 mol %) and water (0.5 mL)**.** White solid**.** Yield**:** 55.0 mg (70%, >94% ee). Recrystallized from hexane-EtOAc; mp: 162-164 °C; IR ($CHCl_3$): ῡ = 1717, 1544, 1373, 1327, 1252, 1168, 1131, 1069, 1018, 969, 846, 758, 694 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz): δ = 2.67 (1 H, dd, *J* = 11.4, 15.6 Hz, =CHCHC*H*), 2.82 (1 H, dd, *J* = 5.4, 15.6 Hz, =CHCHC*H*), 2.94-2.88 (2 H, m, ArCHCH_2), 3.62-3.59 (1 H, m, =CHC*H*), 4.00-3.96 (1 H, m, ArC*H,*), 5.33 (1 H, dd, *J* = 4.2, 10.2 Hz, NO_2C*H*), 6.09 (1

H, dd, *J* = 7.8, 15.6 Hz, PhCH=C*H*), 6.49 (1 H, d, *J* = 16.2 Hz, PhC*H*=CH), 7.35-7.27 (5 H, m, Ph), 7.40 (2 H, d, *J* = 8.4 Hz, Ar), 7.62 (2 H, d, *J* = 7.2 Hz, Ar) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 41.85, 41.92, 43.4, 45.1, 90.0, 122.7 (q, *Jc-F* = 270 Hz), 126.3 (q, *Jc-F* = 3.5 Hz), 122.9, 126.7 (3 C), 127.6 (2 C), 128.5, 128.7 (2 C), 130.3 (q, *Jc-F* = 32.6 Hz), 135.3, 135.7, 142.9, 204.9 ppm; HRMS (ESI): *m/z* calcd. For $C_{21}H_{18}F_3NNaO_3$ [M + Na]$^+$ 412.1131, found 412.1126. $[\alpha]_D^{25}$ = -194.0 (*c* 1.07, $CHCl_3$, ee >99.99%); The *ee* was determined by HPLC using a Daicel Chiralpak AD-H [hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 14.50 min, τ_{minor} = 18.66 min, >94% ee.

(3*S*,4*R*,5*S*)-3-(3-Chlorophenyl)-4-nitro-5-styrylcyclohexanone 47h

The product **47h** was obtained following the *General procedure* **3.4.2 II** from nitrodiene **4a** (35.0 mg, 0.2 mmol, 1.0 equiv) and enone **29h** (72.0 mg, 0.4 mmol, 2.0 equiv) using catalyst **43** (13 mg, 0.04 mmol, 20 mol %) and water (0.5 mL)**.** White solid**.** Yield**:** 46.0 mg (65%, 87% ee). Recrystallized from hexane-EtOAc; mp: 170-172 °C; IR ($CHCl_3$): $\bar{\upsilon}$ = 1718, 1574, 1544, 1373, 1207, 1081, 969, 789, 749, 692 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 2.65 (1 H, dd, *J* = 11.4, 15.6 Hz, =CHCHC*H*), 2.82 (1 H, dd, *J* = 5.4, 15.6 Hz, =CHCHC*H*), 2.92-2.86 (2 H, m, ArCHC*H*$_2$), 3.59-3.57 (1 H, m, =CHC*H*), 3.92-3.87 (1 H, m, ArC*H*), 5.28 (1 H, dd, *J* = 4.5, 9.9 Hz, NO_2C*H*), 6.07 (1 H, dd, *J* = 8.4, 16.2 Hz, PhCH=C*H*), 6.48 (1 H, d, *J* = 16.2 Hz, PhC*H*=CH), 7.16-7.15 (1 H, m, Ph), 7.29-7.26 (4 H, m, Ph), 7.36-7.31 (4 H, m, Ar) ppm; ^{13}C NMR ($CDCl_3$, 150 MHz): δ = 41.8 (2 C), 43.3, 45.2, 90.1, 123.1, 125.3, 126.7 (2 C), 127.3, 128.3, 128.4, 128.7 (2 C), 130.5, 135.0, 135.1, 135.7, 140.9, 205.2 ppm; HRMS (ESI): *m/z* calcd. for $C_{20}H_{18}ClNNaO_3$ [M + Na]$^+$ 378.0867, found. 378.0886. $[\alpha]_D^{25}$ = -218 (*c* 1.07, $CHCl_3$, ee >99.99%); The *ee* was

determined by HPLC using a Daicel Chiralpak AD-H [hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 14.54 min, τ_{minor} = 16.74 min, 87% ee.

(3*S*,4*R*,5*S*)-3-(3-Bromophenyl)-4-nitro-5-styrylcyclohexanone 47i

The product **47i** was obtained following the *General procedure* **3.4.2 II** from nitrodiene **4a** (35.0 mg, 0.2 mmol, 1.0 equiv) and enone **29i** (89.5 mg, 0.4 mmol, 2.0 equiv) using catalyst **43** (13.0 mg, 0.04 mmol, 20 mol %) and water (0.5 mL)**.** White solid**.** Yield**:** 60.0 mg (75%, 93% ee). Recrystallized from hexane-EtOAc; mp: 177-179 °C; IR ($CHCl_3$): $\bar{\upsilon}$ = 1717, 1543, 1371, 1208, 1070, 968, 785, 771, 696 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz): δ = 2.63 (1 H, dd, *J* = 11.4, 15.6 Hz, =CHCHC*H*), 2.80 (1 H, dd, *J* = 5.4, 16.2 Hz, =CHCHC*H*), 2.91-2.84 (2 H, m, ArCHCH_2), 3.59-3.56 (1 H, m, =CHC*H*), 3.90-3.85 (1 H, m, ArC*H*), 5.27 (1 H, dd, *J* = 4.2, 9.9 Hz, NO_2C*H*), 6.07 (1 H, dd, *J* = 7.8, 15.6 Hz, PhCH=C*H*), 6.47 (1 H, d, *J* = 15.6 Hz, PhC*H*=CH), 7.22-7.18 (2 H, m, Ar), 7.42-7.23 (7 H, m, Ar & Ph) ppm; ^{13}C NMR ($CDCl_3$, 150 MHz): δ = 41.8 (2 C), 43.4, 45.2, 90.1, 123.1, 123.3, 125.8, 128.4, 128.7 (2 C), 128.4, 130.3, 130.8, 131.3, 135.2, 135.8, 141.2, 205.1 ppm; Anal. calcd for $C_{20}H_{18}BrNO_3$: C, 60.01; H, 4.53; N, 3.50; Found: C, 60.32; H, 4.26; N, 3.36; $[\alpha]_D^{25}$ = -183 (*c* 1.09, $CHCl_3$, ee >99.99%); The *ee* was determined by HPLC using a Daicel Chiralpak AD-H [hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 15.34 min, τ_{minor} = 17.27 min, 93% ee.

(3*S*,4*R*,5*S*)-3-(2-Chlorophenyl)-4-nitro-5-styrylcyclohexanone 47j

The product **47j** was obtained following the *General procedure* **3.4.2 II** from nitrodiene **4a** (35.0 mg, 0.2 mmol, 1.0 equiv) and enone **29j** (72.0 mg, 0.4 mmol, 2.0 equiv) using catalyst **43** (13 mg, 0.04 mmol, 20 mol %) and water (0.5 mL)**.** White solid**.** Yield**: 5**0.0 mg (70%, >94% ee). Recrystallized from hexane-EtOAc; mp: 156-158 °C; IR ($CHCl_3$): $\bar{\upsilon}$

1718, 1574, 1544, 1438, 1372, 1207, 1082, 969, 789, 749, 692 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz): δ = 2.69 (1 H, dd, *J* = 9.0, 15.0 Hz, =CHCHC*H*), 2.82 (1 H, dd, *J* = 5.4, 15.6 Hz, =CHCHC*H*), 3.02-2.94 (2 H, m, ArCHCH_2), 3.47-3.43 (1 H, m, =CHC*H*), 4.46-4.427 (1 H, m, ArC*H*), 5.41 (1 H, m, NO_2C*H*), 6.09 (1 H, dd, *J* = 7.5, 15.9 Hz, PhCH=C*H*), 6.46 (1 H, d, *J* = 15.6 Hz, PhC*H*=CH), 7.32-7.26 (m, Ar & Ph), 7.44-7.42 (1 H, m, Ar) ppm; ^{13}C NMR ($CDCl_3$, 150 MHz): δ = 39.5, 40.9, 42.7, 42.9, 88.0, 123.7, 126.6 (2 C), 127.8, 128.3, 128.6 (2 C), 129.3, 130.7, 133.8, 134.6 (2 C), 135.9, 136.5, 206.2 ppm; HRMS (ESI): *m/z* calcd. for $C_{20}H_{18}ClNNaO_3$ $[M + Na]^+$ 378.0867, found. 378.0890; $[\alpha]_D^{27}$ = -92.0 (*c* 1.00, $CHCl_3$, ee >99.99%); The *ee* was determined by HPLC using a Daicel Chiralpak AD-H [hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 12.54 min, τ_{minor} = 16.37 min, >94% ee.

(3*S*,4*R*,5*S*)-3-(Naphthalene-1-yl)-4-nitro-5-styrylcyclohexanone 47k

The product **47k** was obtained following the *General procedure* **3.4.2 II** from nitrodiene **4a** (35.0 mg, 0.2 mmol, 1.0 equiv) and enone **29k** (78.8 mg, 0.4 mmol, 2.0 equiv) using catalyst **43** (13.0 mg, 0.04 mmol, 20 mol %) and water (0.5 mL)**.** White solid**.** Yield**: 48.0** mg (65%, >89% ee). Recrystallized from hexane-EtOAc; mp: 150-152 °C; IR ($CHCl_3$): $\bar{\upsilon}$ = 1714, 1549, 1367, 1210, 1019, 969, 776, 751, 694 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz): δ = 2.84-2.81 (1 H, m, =CHCHCH_2), 3.16-3.12 (2 H, m, ArCHCH_2), 3.34-3.30 (1 H, m, =CHC*H*), 4.86 (1 H, q, *J* = 6.0 Hz, ArC*H*), 5.40 (1 H, t, *J* = 7.5 Hz, NO_2C*H*), 6.11 (1 H, dd, *J* = 7.2, 15.6 Hz, PhCH=C*H*), 6.40 (1 H, d, *J* = 16.2 Hz, PhC*H*=CH), 7.26-7.23 (1 H, m, Ph), 7.30-7.27 (4 H, m, Ph), 7.36-7.34 (1 H, m, Ar), 7.46 (1 H, t, *J* = 7.5 Hz, Ar), 7.56 (1 H, t, *J* = 7.2 Hz, Ar), 7.66-7.63 (1 H, m, Ar), 7.83 (1 H, d, *J* = 8.4 Hz, Ar), 7.91 (1 H, d, *J* = 7.8 Hz, Ar), 8.15 (1 H, d, *J* = 8.4 Hz, Ar) ppm; ^{13}C NMR ($CDCl_3$, 150 MHz): δ =

38.6, 40.0, 42.2, 43.1, 88.6, 122.1, 123.9, 124.4, 125.3, 126.2, 126.5 (2 C), 127.3, 128.2, 128.5 (2 C), 128.9, 129.4, 130.5, 134.1 (2 C), 135.3, 135.8, 207.1 ppm; HRMS (ESI): *m/z* calcd. for $C_{24}H_{21}NNaO_3$ $[M + Na]^+$ 394.1414, found. 394.1414. $[\alpha]_D^{27}$ = -46.0 (*c* 0.75, $CHCl_3$, ee >99.99%); The ee was determined by HPLC using a Daicel Chiralpak AD-H [hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 13.17 min, τ_{minor} = 14.47 min, >89% ee.

(3*S*,4*R*,5*S*)-3-(4-Chlorostyryl)-4-nitro-5-phenylcyclohexanone 47l

The product **47l** was obtained following the *General procedure* **3.4.2 II** from nitrodiene **4e** (41.8 mg, 0.2 mmol, 1.0 equiv) and enone **29a** (58.5 mg, 0.4 mmol, 2.0 equiv) using catalyst **43** (13.0 mg, 0.04 mmol, 20 mol %) and water (0.5 mL)**.** White solid**.** Yield**: 50.0** mg (70%, 94% ee). Recrystallized from hexane-EtOAc; mp: 180-182 °C; IR ($CHCl_3$): $\bar{\upsilon}$ = 1719, 1547, 1492, 1371, 1303, 1209, 1090, 1011, 970, 816, 773, 699 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ = 2.71 (1 H, dd, *J* = 10.7, 15.2 Hz, =CHCHCH_2), 2.93-2.84 (3 H, m, CH_2COCH_2CHCH=), 3.54-3.50 (1 H, m, =CHC*H*), 3.95-3.90 (1 H, m, PhC*H*), 5.30 (1 H, dd, *J* = 4.5, 9.0 Hz, NO_2C*H*), 6.09 (1 H, dd, *J* = 7.7, 15.7 Hz, ArCH=C*H*), 6.42 (1 H, d, *J* = 16.2 Hz, ArC*H*=CH), 7.31-7.26 (7 H, m, Ph & Ar), 7.38-7.35 (2 H, m, Ar) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 41.5, 42.3, 43.2, 44.9, 90.4, 124.3, 127.1 (3 C), 127.9 (3 C), 128.1, 128.8 (2 C), 129.3, 133.5, 134.1, 134.3, 138.9, 205.8 ppm; Anal. calcd for $C_{20}H_{18}ClNO_3$: C, 67.51; H, 5.10; N, 3.94; Found: C, 67.62; H, 4.74; N, 3.73; $[\alpha]_D^{26}$ = -247.0 (*c* 0.88, $CHCl_3$, ee >99.99%); The *ee* was determined by HPLC using a Daicel Chiralcel OD-H [hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{minor} = 33.95 min, τ_{major} = 52.47 min, 94% ee.

(3*S*,4*R*,5*S*)-3-(4-Bromostyryl)-4-nitro-5-phenylcyclohexanone 47m

The product **47m** was obtained following the *General procedure* **3.4.2 II** from nitrodiene **4d** (50.6 mg, 0.2 mmol, 1.0 equiv) and enone **29a** (58.5 mg, 0.4 mmol, 2.0 equiv) using catalyst **43** (13.0 mg, 0.04 mmol, 20 mol %) and water (0.5 mL)**.** White solid**.** Yield**: 50.0** mg (62%, >97% ee). Recrystallized from hexane-EtOAc; mp: 197-198 °C; IR ($CHCl_3$): ῡ = 1720, 1546, 1487, 1370, 1303, 1210, 1070, 1008, 973, 699 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ = 2.71 (1 H, dd, J = 10.5, 15.2 Hz, =CHCHCH_2), 2.93-2.84 (3 H, m, CH_2COCH_2CHCH=), 3.54-3.50 (1 H, m, =CHCH), 3.95-3.90 (1 H, m, PhCH), 5.30 (1 H, dd, J = 4.5, 9.0 Hz, NO_2CH), 6.10 (1 H, dd, J = 7.75, 16.2 Hz, ArCH=CH), 6.40 (1 H, d, J = 16.5 Hz, ArCH=CH), 7.20 (2 H, d, J = 8.0 Hz, Ph), 7.32-7.27 (3 H, m, Ph), 7.38-7.35 (2 H, m, Ar), 7.44 (2 H, d, J = 8.0 Hz, Ar) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 41.5, 42.3, 43.2, 44.9, 90.3, 122.2, 124.5, 127.1 (2 C), 128.1, 128.2 (2 C), 129.3 (3 C), 131.8, 133.8, 134.8, 138.9, 205.8 ppm; Anal. calcd for $C_{20}H_{18}BrNO_3$: C, 60.01; H, 4.53; N, 3.50; Found: C, 60.34; H, 4.19; N, 3.18; $[\alpha]_D^{26}$ = -211.0 (*c* 0.86, $CHCl_3$, ee >97%); The *ee* was determined by HPLC using a Chiralcel OD-H [hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{minor} = 34.48 min, τ_{major} = 52.01 min, 90% ee.

(3*S*,4*R*,5*S*)-3-(4-nitrostyryl)-4-nitro-5-phenylcyclohexanone 47n

The product **47n** was obtained following the *General procedure* **3.4.2 II** from nitrodiene **4c** (44 mg, 0.2 mmol, 1.0 equiv) and enone **29a** (58.5 mg, 0.4 mmol, 2.0 equiv) using catalyst **43** (13.0 mg, 0.04 mmol, 20 mol %) and water (0.5 mL)**.** White solid**.** Yield**: 44.0** mg (60%, >94% ee). Recrystallized from hexane-EtOAc; mp: 146-148 °C; IR ($CHCl_3$): ῡ = 1719, 1597, 1550, 1516, 1343, 1218, 1109, 864, 826, 745, 700, 637 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ = 2.75 (1 H, dd, J = 10.5, 15.5 Hz, =CHCHCH_2), 2.94-2.87 (3 H,

m, C*H*$_2$COC*H*$_2$CHCH=), 3.60-3.55 (1 H, m, =CHC*H*), 3.97-3.92 (1 H, m, PhC*H*), 5.31 (1 H, dd, *J* = 4.0, 8.8 Hz, NO$_2$C*H*), 6.31 (1 H, dd, *J* = 8.0, 16.5 Hz, ArCH=C*H*), 6.54 (1 H, d, *J* = 16.5 Hz, ArC*H*=CH), 7.33-7.27 (3 H, m, Ph), 7.39-7.36 (2 H, m, Ph), 7.49 (2 H, d, *J* = 9.0 Hz, Ar), 8.19 (2 H, d, *J* = 9.0 Hz, Ar) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 41.4, 42.5, 42.9, 44.8, 90.2, 124.1, 127.1 (3 C), 127.3 (2 C), 128.2, 128.7, 129.3 (2 C), 132.7, 138.7, 142.1, 147.5, 205.4 ppm; Anal. calcd for $C_{20}H_{18}N_2O_5$: C, 65.57; H, 4.95; N, 7.65; Found: C, 65.77; H, 4.93; N, 7.29; $[\alpha]_D^{25}$ = -200.0 (*c* 0.70, $CHCl_3$, ee >94%); The *ee* was determined by HPLC using a Daicel Chiralcel OD-H [hexane/*i*-PrOH (80:20)]; flow rate 0.75 mL/min; τ_{minor} = 75.35 min, τ_{major} = 99.22 min, >94% ee.

(3*S*,4*R*,5*S*)-3-(3-Bromostyryl)-4-nitro-5-phenylcyclohexanone 47o

The product **47o** was obtained following the *General procedure* **3.4.2 II** from nitrodiene **4g** (50.6 mg, 0.2 mmol, 1.0 equiv) and enone **29a** (58.5 mg, 0.4 mmol, 2.0 equiv) using catalyst **43** (13.0 mg, 0.04 mmol, 20 mol %) and water (0.5 mL)**.** White solid**.** Yield**: 51.0** mg (64%, >95% ee). Recrystallized from hexane-EtOAc; mp: 205-206 °C; IR ($CHCl_3$): $\bar{\upsilon}$ = 1720, 1546, 1487, 1370, 1303, 1210, 1070, 1008, 973, 699 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.71 (dd, *J* = 10.5, 16.0 Hz, =CHCHC*H*$_2$), 2.93-2.85 (3 H, m, C*H*$_2$COC*H*$_2$CHCH=), 3.54-3.52 (1 H, m, =CHC*H*), 3.96-3.91 (1 H, m, PhC*H*), 5.30 (1 H, dd, *J* = 4.2, 9.3 Hz, NO$_2$C*H*), 6.12 (1 H, dd, *J* = 8.0, 15.5 Hz, ArCH=C*H*), 6.40 (1 H, d, *J* = 15.5 Hz, ArC*H*=CH), 7.20-7.15 (m, 1 H), 7.31-7.24 (4 H, m, Ph & Ar), 7.40-7.35 (3 H, m, Ph), 7.50 (1 H, br s, Ar) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 41.5, 42.3, 43.1, 44.9, 90.4, 122.8, 125.3, 125.4, 127.1 (2 C), 128.1, 129.3 (2 C), 129.4, 130.1, 131.7, 133.4, 137.9, 138.8, 205.7 ppm; Anal. calcd for $C_{20}H_{18}BrNO_3$: C, 60.01; H, 4.53; N, 3.50; Found: C, 60.30; H, 4.29; N, 3.38; $[\alpha]_D^{26}$ = -212.0 (*c* 0.83, $CHCl_3$, ee >99.99%); The *ee*

was determined by HPLC using a Daicel Chiralcel OD-H [hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{minor} = 39.80 min, τ_{major} = 61.56 min, >95% ee.

(3*S*,4*R*,5*S*)-4-Nitro-3-phenyl-5-[(*E*)-1-phenylprop-1-en-2yl]-cyclohexanone 47p

The product **47p** was obtained following the *General procedure* **3.4.2 II** from nitrodiene **4f** (37.8 mg, 0.2 mmol, 1.0 equiv) and enone **29a** (58.5 mg, 0.4 mmol, 2.0 equiv) using catalyst **43** (13.0 mg, 0.04 mmol, 20 mol %) and water (0.5 mL)**.** gummy liquid**.** Yield**: 50.0** mg (74%, 96% ee); IR (film): $\bar{\upsilon}$ = 1725, 1563, 1535, 1485, 1401, 1379, 1211, 1087, 1021, 965, 845, 824, 768 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ = 1.95 (3 H, s, CH_3), 2.82-2.73 (2 H, m, =CHCHCH_2), 2.94-2.90 (1 H, m, PhCHCH_2), 3.30 (1 H, dd, J = 9.0, 16.0 Hz, PhCHCH_2), 3.45-3.41 (1 H, m, =CHC*H*), 3.87-3.83 (1 H, m, PhC*H*), 5.26 (1 H, dd, J = 4.5, 7.5 Hz, NO_2C*H*), 6.43 (1 H, br s, CH_3CH=C*H*), 7.14-7.13 (2 H, m, =CHC$_6H_5$), 7.26-7.24 (m, =CHC$_6H_5$), 7.36-7.33 (5 H, m, Ph) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 16.5, 41.5, 41.9, 42.3, 45.8, 88.9, 127.1, 127.6 (2 C), 128.2 (2 C), 128.4, 128.9 (2 C), 129.0 (2 C), 129.3, 135.1, 136.6, 136.8, 207.6 ppm; HRMS (ESI): *m/z* calcd. for $C_{21}H_{21}NNaO_3$ $[M + Na]^+$ 358.1414, found. 358.1391; $[\alpha]_D^{25}$ = -17.0 (*c* 1.11, $CHCl_3$, mixture of diasteroisomers); The *ee* was determined by HPLC using a Daicel Chiralcel OD-H [hexane/*i*-PrOH (90:10)]; flow rate 1.00 mL/min; τ_{minor} = 26.81 min, τ_{major} = 30.51 min, 96% ee.

(3*S*,4*R*,5*S*)-3-(4-Chlorostyryl)-5-(4-chlorophenyl)-4-nitrocyclohexanone 47q

The product **47q** was obtained following the *General procedure* **3.4.2 II** from nitrodiene **4e** (41.8 mg, 0.2 mmol, 1.0 equiv) and enone **29b** (72.0 mg, 0.4 mmol, 2.0 equiv) using catalyst **43** (13.0 mg, 0.04 mmol, 20 mol %) and water (0.5 mL)**.** White solid**.** Yield**: 51.0** mg (65%, >95% ee). Recrystallized from hexane-EtOAc; mp: 183-185 °C; IR (film): $\bar{\upsilon}$ =

1717, 1592, 1545, 1491, 1407, 1372, 1213, 1093, 1013, 970, 835, 814, 757 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ = 2.65 (1 H, dd, J = 11.5, 15.5 Hz, =CHCHCH_2), 2.82 (1H, dd, J = 5.0, 16.0 Hz, =CHCHCH_2), 2.88 (2 H, br s, ArCHCH_2), 3.55-3.53 (1 H, m, =CHC*H*), 3.92-3.87 (1 H, m, ArC*H*), 5.29 (1 H, dd, J = 4.25, 9.75 Hz, NO_2C*H*), 6.07 (1 H, dd, J = 8.0, 15.5 Hz, ArCH=C*H*), 6.42 (1 H, d, J = 15.5 Hz, ArC*H*=CH), 7.22-7.20 (2 H, m, Ar), 7.30-7.25 (4 H, m, Ar), 7.35-7.33 (2 H, m, Ar) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 41.6, 41.7, 43.2, 45.0, 90.2, 123.9, 127.8 (2 C), 128.5 (2 C), 128.8 (2 C), 129.5 (2 C), 133.8, 134.0, 134.1, 134.2, 137.3, 205.2 ppm; Anal. calcd for $C_{20}H_{17}Cl_2NO_3$: C, 61.55; H, 4.39; N, 3.59; Found: C, 61.45; H, 4.38; N, 3.52; $[\alpha]_D^{27}$ = -254.0 (*c* 0.87, $CHCl_3$, ee >98%); The *ee* was determined by HPLC using a Daicel Chiralcel OD-H [hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{minor} = 37.16 min, τ_{major} = 60.82 min, 94% ee.

(3*S*,4*R*,5*S*)-3-(4-Bromostyryl)-5-(3-bromophenyl)-4-nitrocyclohexanone 43r

The product **43q** was obtained following the *General procedure* **3.4.2 II** from nitrodiene **4d** (50.6 mg, 0.2 mmol, 1.0 equiv) and enone **29i** (89.5 mg, 0.4 mmol, 2.0 equiv) using catalyst **43** (13.0 mg, 0.04 mmol, 20 mol %) and water (0.5 mL)**.** White solid**.** Yield**: 67.0** mg (70%, 92% ee). Recrystallized from hexane-EtOAc; mp: 210-212 °C; IR (film): $\bar{\upsilon}$ = 1717, 1592, 1548, 1497, 1373, 1207, 1071, 1009, 968, 784, 691 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ = 2.65 (1 H, dd, J = 11.5, 15.5 Hz, =CHCHCH_2), 2.81 (1 H, dd, J = 5.2, 15.8 Hz, =CHCHCH_2), 2.88 (2 H, d, J = 5.0 Hz, ArCHCH_2), 3.57-3.55 (1 H, m, =CHC*H*), 3.90-3.85 (1 H, m, ArC*H*), 5.29 (1 H, dd, J = 4.5, 10.0 Hz, NO_2C*H*), 6.07 (1 H, dd, J = 8.0, 16.0 Hz, ArCH=C*H*), 6.42 (1 H, d, J = 16.0 Hz, ArC*H*=CH), 7.25-7.20 (4 H, m, Ar), 7.45-7.43 (4 H, m, Ar) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 41.8, 42.8, 43.2,

45.1, 90.0, 122.3, 123.3, 123.9, 125.8, 128.2 (2 C), 130.2, 130.8, 131.4, 131.8 (2 C), 133.9, 134.7, 141.1, 205.0 ppm; Anal. calcd for $C_{20}H_{17}Br_2NO_3$: C, 50.13; H, 3.58; N, 2.92; Found: C, 50.43; H, 3.40; N, 2.91; $[\alpha]_D^{27}$ = -211.0 (*c* 0.97, $CHCl_3$, ee >99.99%); The *ee* was determined by HPLC using a Daicel Chiralcel OD-H [hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{minor} = 47.62 min, τ_{major} = 68.53 min, 92% ee.

(3*S*,4*R*,5*S*)-3-(3-Bromostyryl)-5-(3-bromophenyl)-4-nitrocyclohexanone 47s

The product **47s** was obtained following the *General procedure* **3.4.2 II** from nitrodiene **4g** (50.6 mg, 0.2 mmol, 1.0 equiv) and enone **29i** (89.5 mg, 0.4 mmol, 2.0 equiv) using catalyst **43** (13.0 mg, 0.04 mmol, 20 mol %) and water (0.5 mL)**.** White solid**.** Yield**: 56.0** mg (58%, >96% ee). Recrystallized from hexane-EtOAc; mp: 184-186 °C; IR (film): $\bar{\upsilon}$ = 1718, 1592, 1547, 1476, 1372, 1208, 1072, 1013, 970, 758, 692 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ = 2.65 (1 H, dd, *J* = 11.5, 15.5 Hz, =CHCHCH_2), 2.83 (1 H, dd, *J* = 5.5, 15.5 Hz, =CHCHCH_2), 2.88 (2 H, d, *J* = 5.0 Hz, ArCHCH_2), 3.60-3.56 (1 H, m, =CHC*H*), 3.91-3.86 (1 H, m, 1 H ArC*H*), 5.29 (1 H, dd, *J* = 4.5, 9.5 Hz, NO_2C*H*), 6.10 (1 H, dd, *J* = 7.75, 15.8 Hz, ArCH=C*H*), 6.41 (1 H, d, *J* = 16.0 Hz, ArC*H*=CH), 7.27-7.17 (4 H, m, Ar), 7.44-7.40 (3 H, m, Ar), 7.50 (1 H, s, Ar) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 41.8 (2 C), 43.3, 45.2, 90.0, 122.8, 123.3, 124.7, 125.4, 125.8, 125.8, 129.4, 130.15, 130.15, 130.2, 130.8, 131.2, 131.4, 133.8, 137.8, 137.8, 137.8, 141.1, 141.1, 204.9 ppm; Anal. calcd for $C_{20}H_{17}Br_2NO_3$: C, 50.13; H, 3.58; N, 2.92; Found: C, 50.26; H, 3.30; N, 2.79; $[\alpha]_D^{25}$ = -187.0 (*c* 0.87, $CHCl_3$, ee >99.99%); The *ee* was determined by HPLC using a Daicel Chiralcel OD-H [hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{minor} = 46.24 min, τ_{major} = 70.03 min, >96% ee.

(2*R*,3*R*,4*S*,5*S*)-2-Methyl-4-nitro-5-phenyl-3-styrylcyclohexanone 43t

The product **47t** was obtained following the *General procedure* **3.4.2 II** from nitrodiene **4a** (35.0 mg, 0.2 mmol, 1.0 equiv) and enone **29l** (64.0 mg, 0.4 mmol, 2.0 equiv) using catalyst **43** (13.0 mg, 0.04 mmol, 20 mol %) and water (0.5 mL)**.** Yellow gum**.** Yield**: 34.0** mg (51%, >96% ee); IR (film): ῡ = 1714, 1551, 1495, 1453, 1368, 969, 746, 697 cm^{-1}; ^{1}H NMR ($CDCl_3$, 800 MHz): δ = 1.26 (3 H, d, J = 6.4 Hz, CH3), 2.54 (1 H, sex, $CH_3CHCHCH$=), 2.96 (1 H, dd, J = 6.4, 16.0Hz, =CHC*H*), 3.11-3.07 (2 H, m, PhCHCH_2), 4.03 (1 H, q, J = 5.6 Hz, PhC*H*), 5.22 (1 H, dd, J = 5.6, 10.4 Hz, NO_2C*H*), 5.96 (1 H, dd, J = 8.8, 15.2 Hz, PhCH=C*H*), 6.50 (2 H, d, J = 16.0 Hz, PhC*H*=CH & Ph), 7.05 (1 H, t, J = 4.0 Hz, Ph), 7.27-7.25 (1 H, m, Ph), 7.33-7.28 (4H, m, Ph), 7.36-7.35 (3H, m, Ph) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 12.4, 42.5, 43.8, 46.0, 46.1, 91.1, 126.0, 126.4 (2 C), 128.0 (2 C), 128.1, 128.4, 128.6 (2 C), 128.9 (2 C), 135.3, 136.0, 136.8, 208.0 ppm; HRMS (ESI): *m/z* calcd. for $C_{21}H_{21}NNaO_3$ $[M + Na]^+$ 358.1413, found. 358.1371; $[\alpha]_D^{26}$ = -63.0 (*c* 0.59, $CHCl_3$, ee >99.9%); The *ee* was determined by HPLC using a Daicel Chiralpak AD-H hexane/*i*-PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 21.01 min, >99.9% ee.

3.4.3.1 X- ray Crystallographic data

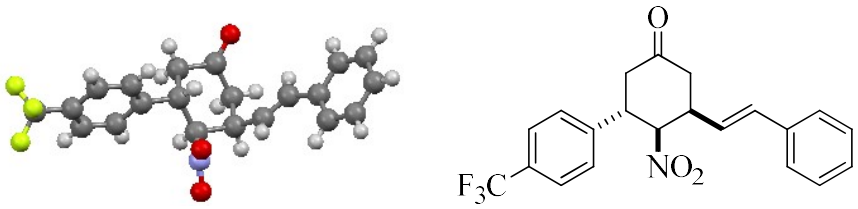


Figure 3.2: X-ray structure of **47g**, CCDC No. **1450559**

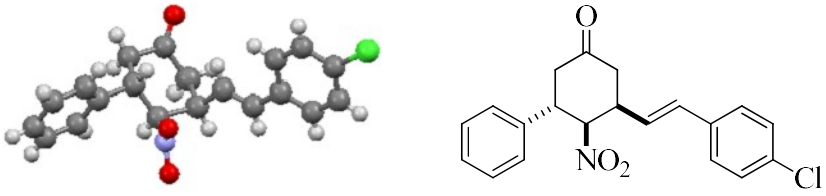


Figure 3.3: X-ray structure of **47l**, CCDC No. **1450560**

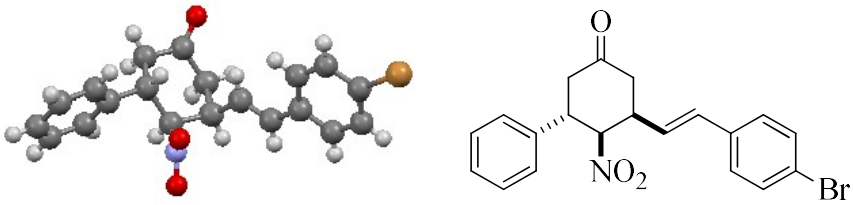


Figure 3.4: X-ray structure of **47m**, CCDC No. **1450561**

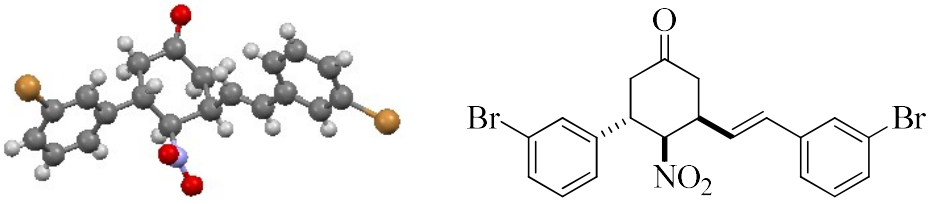


Figure 3.5: X-ray structure of **47s,** CCDC No. **1450562**

Compounds	**47g**	**47l**	**47m**	**47s**
Formula	$C_{21}H_{18}F_3NO_3$	$C_{20}H_{18}ClNO_3$	$C_{20}H_{18}BrNO_3$	$C_{20}H_{17}Br_2NO_3$
Formula Wt	389.36	355.80	400.26	479.17
Crystal System	Orthorhombic	Monoclinic	Monoclinic	Orthorhombic
Space Group	P 21 21 21	P 1 21 1	P 1 21 1	P 21 21 21
T,K	293(2)	293(2)	293(2)	293(2)
Z	4	2	2	4
a, Å	6.0481(3)	5.9375(5)	5.9479(5)	6.04125(16)
b, Å	15.9843(8)	12.3627(14)	12.3464(13)	9.8526(4)
c, Å	19.4099(10)	12.7571(11)	12.9363(12)	31.9892(11)
α, deg	90	90	90	90
β, deg	90	99.297(8)	99.635(8)	90
γ, deg	90	90	90	90
V, $Å^3$	1876.44(16)	924.12(15)	936.59(15)	1904.07(12)
$\rho_{calc,}$ mg/mm^3	1.378	1.279	1.419	1.671
μ, m/mm^{-1}	0.955	1.977	3.138	5.566
θ range, deg	3.571-68.719	3.532-69.987	3.451-60.870	4.686-72.914
GOF (F^2)	1.049	1.003	0.981	1.073
$R_1{}^a$ ($wR_2{}^b$), %	0.0857 (0.2589)	0.0601 (0.1741)	0.0619 (0.1960)	0.0629 (0.1745)

CHAPTER 4

Organocatalysed enantioselective synthesis of highly substituted cyclohexanones with all-carbon quaternary centre from allyliedene malonitrile and enones

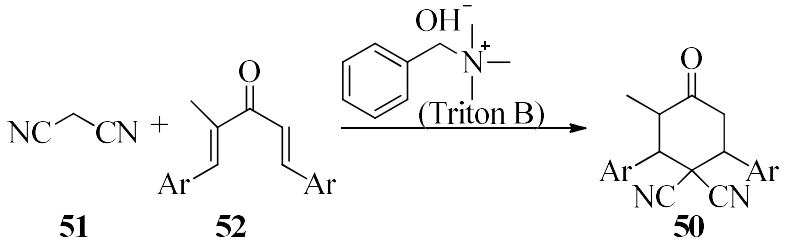
4.1 Introduction

Six-membered carbocycles are common motifs in nature and they can be found in many terpenoid, polyketide, shikimate derived monocyclic and polycyclic molecular architectures.[108] The [4+2] cycloaddition reaction is an effective and rapid tool to access six-membered rings, a route that nature has admirably pursued and chemists have diligently imitated.[109] The cycloaddition approach non-aromatic six-membered carbocycles have generated renewal of interest[110] especially for functionalized six-membered carbocycles.[111] Since the advent of modern organocatalysis at the turn of the 21st century, amine-mediated reactions have been at the center of an explosive growth, and culminated in the implementation of myriad of high-impact organic transformations, including efficient and creative organocatalytic [4+2] cycloadditions.[112] Asymmetric organocatalysed [4+2] cycloaddition reaction mediated by chiral amines greatly facilitated the rapid conversion of simple achiral starting materials in to stereochemically complex products with multiple stereo centers and with very high stereoselectivity. In this context, the development of organocatalytic enantio- and diastereoselective one-pot cycloaddition reactions is a rapidly growing research area.

Functionalized chiral cyclohexanones are an important class of scaffolds found in many bio-active synthetic molecules.[113] They have been considered as a rich source of starting materials for the synthesis of biologically active compounds.[114] Therefore, a considerable attention has been given for the development of simple but efficient methods for the practical synthesis of chiral cyclohexanones using organocatalysts. Organocatalyzed double Michael addition strategy has been frequently employed for the synthesis of substituted cyclohexanones.

The development of synthetic methodologies for the stereoselective construction of quaternary stereocenters remains a significant challenge as many complex molecules and natural products[115] possess quaternary centers. It is also difficult to invert undesired configurations of quaternary centers to the desired ones, so the stereoselectivities of reactions on quaternary carbons often govern the total efficiency of the syntheses.

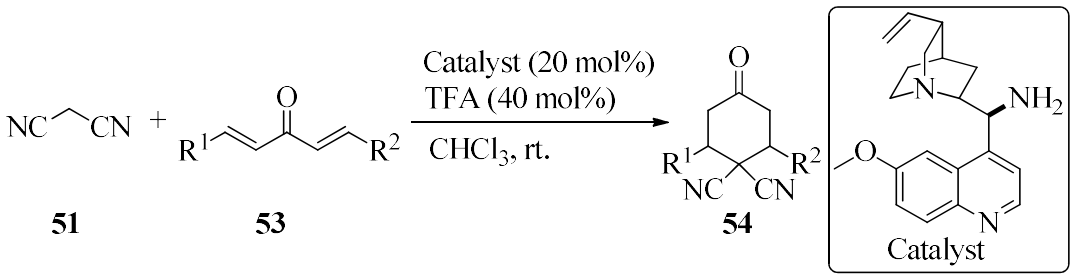
In 2001, Padmavathi *et. al.* reported the synthesis of 1,1-dicyano-4-oxocyclohexane **50** via the double Michael addition of malononitrile **51** to activated bis olefins **52** in presence of triton-B in alcohol and 10% sodium alkoxide as a catalyst (**Scheme 4.1**).[116]



51 **52** **50**

Scheme 4.1 Padmavathi's synthesis of 4,4-dicyanosubstituted cyclohexanones

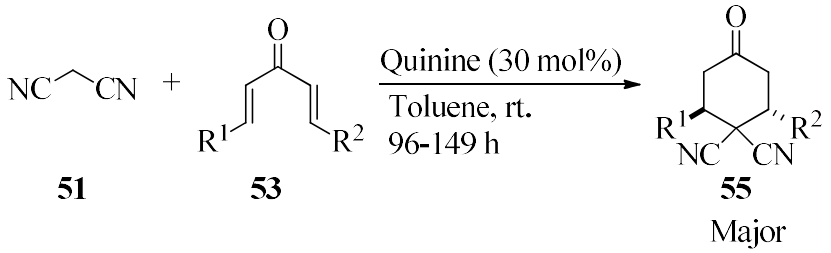
In 2010, Ming Yan *et. al.* reported the double conjugated addition of malononitrile **51** to dienone **53** for the synthesis of 1,1-dicyano-4-oxo-cyclohexanes **54** using 9-amino-9-deoxyepiquinine (**Scheme 4.2**).[117] In this strategy, aliphatic substituents and electron withdrawing groups present on the aromatic rings do not gave fruitful results.



51 **53** **54**

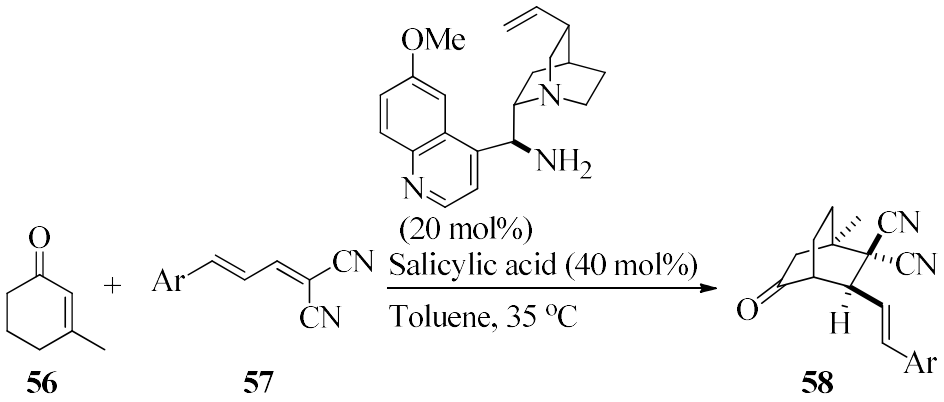
Scheme 4.2 Yan's synthesis of 4,4-dicyanosubstituted cyclohexanone

In 2011, Alessandra *et. al.* reported the synthesis of substituted 1,1-dicyano-4-oxo cyclohexanes **55** using double Michael addition of malanonitrile **51** to 1,5-disubstituted penta diene-3-one **53** catalyzed by quinine (**Scheme 4.3**).[118] This strategy offers moderate to good yield with excellent diastereoselectivities.



Scheme 4.3 Alessandra's synthesis of synthesis of 4,4-dicyanosubstituted cyclohexanone

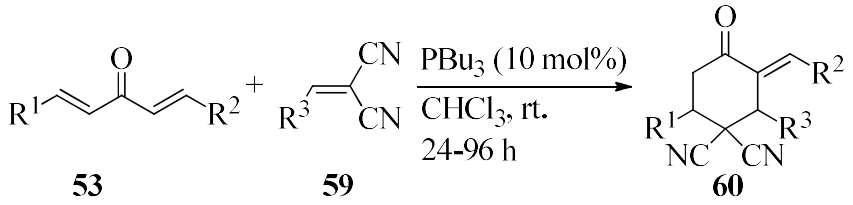
In 2012, Chen, *et.al.* reported the γ-regioselective Michael addition of β-substituted cyclic enones **56** to alkylidenemalononitrile **57** via amine mediated dienamine activation using a quinidine based primary amine. This strategy follows the stepwise Michael-Michael cascade path to produce the desired product **58** (**Scheme 4.4**).[119]



Scheme 4.4 Chen's synthesis of synthesis of 4,4-dicyanosubstituted cyclohexanone

In 2012, He *et. al* reported the phosphine catalyzed [4+2] cycloaddition reaction between 1,4-dien-3-ones **53** and 2-aryl-1,1-dicyano alkenes **59** as double activated

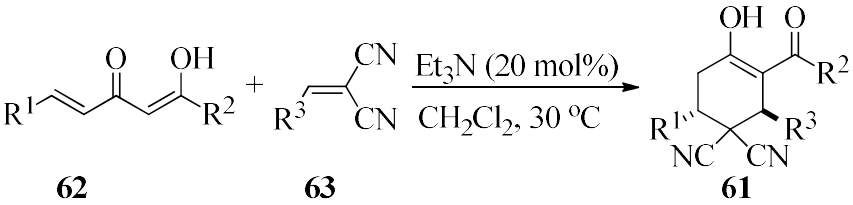
alkenes for the synthesis of poly substituted 1,1-dicyano-4-oxocyclohexane products **60** (**Scheme 4.5**).[120]



53 **59** **60**

Scheme 4.5 He's synthesis of synthesis of 4,4-dicyanosubstituted cyclohexanone

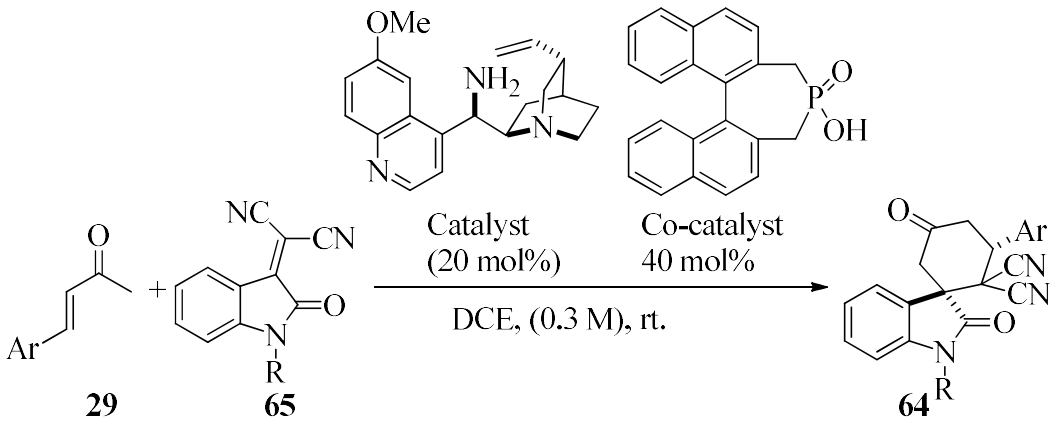
In 2015, Lin *et. al.* reported a diastereoselective synthesis of 1,1-dicyano-4-oxo cyclohexane **61** via a domino double Michael addition of 1-hydroxy-1,4-diene-3-ones **62** to 2-alkalidenemalononitrile **63** in presence of triethylamine (**Scheme 4.6**).[121] This approach introduces the feasibility of synthesis of bioactive molecules.



62 **63** **61**

Scheme 4.6 Lin's synthesis of synthesis of 4,4-dicyanosubstituted cyclohexanone

In 2016, Ramachary *et. al.* reported that Brønsted acids can controll primary amine catalyzed stereoselective asymmetric synthesis of spirooxoindoles **64** from simple aliphatic α,β-unsaturated enones **29** and 2-(2-oxoindolin-3-ylidene)-malononitriles **65.** The reaction was proposed to proceed in a [4+2] cycloaddition fashion between dienamine and the cyano compound (**Scheme 4.7**).[122]



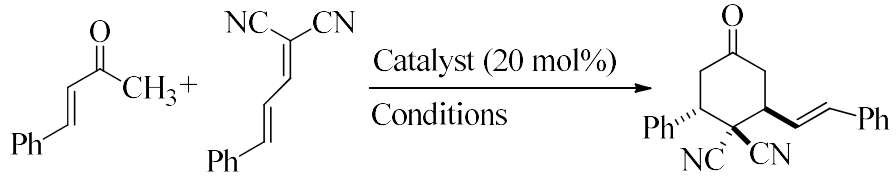
Scheme 4.7 Ramachary's synthesis of synthesis of 4,4-dicyanosubstituted cyclohexanone

4.2 Present work

This chapter describes the development of an asymmetric organocatalytic methodology for the enantioselective synthesis of highly substituted cyclohexanones with all-carbon quaternary centre from allyliedene malonitrile and enones. Generation of a quaternary all carbon chiral centre with high stereocontrol is a challenging and exciting task in organic synthesis.[123] Due to steric encumbrance around the quaternary centre, often drastic conditions are required resulting in loss of stereocontrol. Besides, combination of electrophiles and nucleophiles those provide the quaternary centre with high stereocontrol under mild conditions has been realized using organocatalsyts.[124] A number of strategies including organocatalytic domino/tandem/cascade reactions for the formation of quaternary stereocenters in organic solvents are known. But, such reactions in water as a solvent system are not well explored.

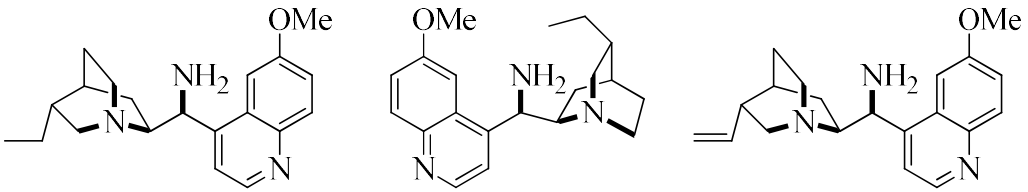
Nature has been using water as reaction medium for myriad of biosynthesis pathways in biological system for highly enantiopure complex organic molecules. Breslow and co-workers[125] revealed an unusual rate enhancement of Diels-Alder reaction,

although poor solubility of most of the organic compounds in water. However, we propose that "on water" concept for the synthesis of highly substituted chiral cyclohexanones with an all-carbon quaternary or quaternary stereogenic (**Scheme 4.8**) *via* [4+2] cycloaddition reactions by utilization of the 3-phenylallylidene malononitrile as dienophiles and enamine intermediate formed from enones with chiral amine catalysts (**Figure 4.1**) as diene system may be applicable in the presence of water as a solvent.[126]

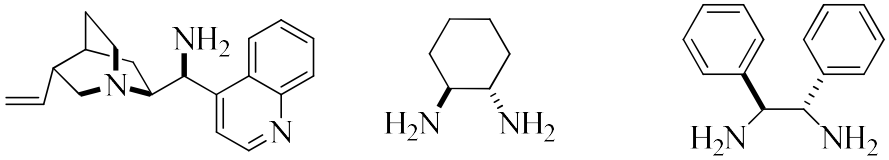


29a **57a** **68a**

Scheme 4.8 Proposed synthesis of 4,4-dicyanosubstituted cyclohexanone



43 **44** **45**



46 **66** **67**

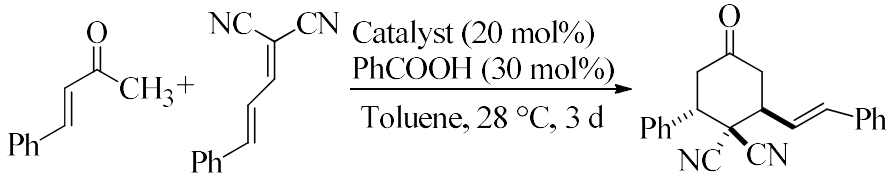
Figure 4.1 Structure of the primary amine organocatalysts

4.2.1 Optimization of reaction conditions

For the model reaction, benzylidene acetone **29a** was chosen as the precursor of the diene and 3-phenylallylidene malononitrile **57a** as the dieneophilic component for the

cycloaddition reaction. Brønsted acids have been used frequently in combination with amine based oraganocatalysts to improve the yield as well as selectivity.[101] Initially we screened the primary amine catalysts **43-46** and **66, 67** (**Figure 4.1**) in combination with benzoic acid as an additive in toluene at room temperature (28 ^{o}C) for the formation of the desired substituted cyclohexanones **68a**. The results are presented in **Table 4.1**.

Table 4.1 Screening of catalyst for organocatalysed [4+2] cycloaddition of benzylidene acetone and 3-phenylallylidene malononitrile[a]



29a **57a** **68a**

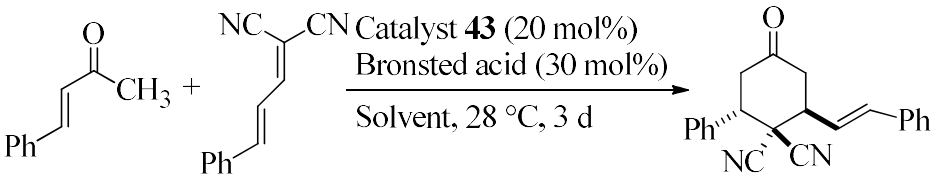
Entry	Catalyst	dr[b]	Yield of **68a**[c]	er[d]
1	**43**	90:10	70	84:16
2	**44**	90:10	38	10:90
3	**45**	80:20	53	78:22
4	**46**	75:25	55	83:17
5	**66**	n.d.[e]	15	45:55
6	**67**	n.d.[e]	21	77:23

[a] Reaction conditions: **29a** (0.2 mmol), **57a** (0.1 mmol), catalyst (0.02 mmol) and solvent (0.25 mL). [b] Determined by ^{1}H NMR. [c] Isolated yield of diastereoisomer **68a**. [e] Not determined.

The cinchona alkaloids derived primary amine catalysts **43-46** gave superior results. The catalyst **43** gave the desired product **68a** in good yield and diastereoselectivity but with moderate enantioselectivity (**Table 4.1**, entry 1). Catalyst **44,** the pseudoenantiomer of catalyst **43**, afforded the enantiomer of product **68a** with similar level of diastereoselectivity but with slightly improved enantioselectivity although the yield was lower than catalyst **43** (**Table 4.1**, entries 1 and 2). Catalysts **45** and **46** offered only moderate to good yield and selectivities (**Table 4.1**, entries 3 and 4). Diamines **66** and **67** were not much effective in this reaction as both yield and enantioselectivity (**Table 4.1**, entries 5 and 6) were inferior.

We choose catalyst **43** for further optimization with Brønsted acid additives and solvent system (**Table 4.2**). 2-Fluorobenzoic acid and salicylic acid provided better enantioselectivity but the yields were poor (**Table 4.2**, entries 2 and 3). Chiral acid additive did not influence the enantioselectivitiy of the reaction (**Table 4.2**, entries 5 and 6). Benzoic acid was found to be the optimal additive and further optimization was done for solvents. Toluene was found to be superior amongst the organic solvent screened (**Table 4.2**, entries 7-11). Interestingly, when the reaction was carried out in neat water both yield and enatioselectivity of **68a** improved (**Table 4.2**, entry 12). Although the catalyst, additive and the reactants were insoluble in water, the reaction progressed smoothly. Therefore, the optimized condition was to use enone **29a** (2 equiv) with respect to phenylallylidene malononitrile **57a** (1 equiv), catalyst **43** (20 mol%) in combination with benzoic acid (30 mol%) in water that gave product **68a** in 77% yield and with acceptable level of diastereo- and enantioselectivity (**Table 4.2**, entry 12).

Table 4.2: Optimization of reaction using catalyst **43** (20 mol%)[a]



29a **57a** **68a**

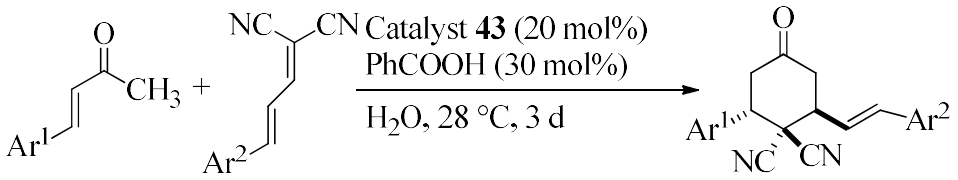
Entry	Solvent	Additive	dr[b]	Yield of **68a**[c]	er[d]
1	Toluene	$PhCO_2H$	90:10	70	84:16
2	Toluene	$2\text{-}FC_6H_4CO_2H$	n.d.[e]	46	86:14
3	Toluene	$2\text{-}OHC_6H_4CO_2H$	85:15	52	87:13
4	Toluene	$3,5\text{-}(NO_2)_2C_6H_3CO_2H$	84:16	45	80:20
5	Toluene	(+) CSA[f]	n.d.[e]	30	82:18
6	Toluene	Boc-D-phg-OH	76:24	65	84:16
7	THF	$PhCO_2H$	88:12	56	72:28
8	MTBE	$PhCO_2H$	85:15	59	80:20
9	$CHCl_3$	$PhCO_2H$	80:20	61	68:32
10	EtOAc	$PhCO_2H$	86:14	54	84:16
11	MeOH	$PhCO_2H$	66:34	42	83:17
12	H_2O	$PhCO_2H$	95:5	77	87:13

[a] Unless noted otherwise, all reactions were performed using **29a** (0.2 mmol), **57a** (0.1 mmol), catalyst (0.02 mmol) and solvent (0.25 mL). [b] Determined by ^1H NMR. [c] Isolated yield of diastereoisomer **68a**. [e] Not determined. [f] Camphor sulphonic acid was used as an additive.

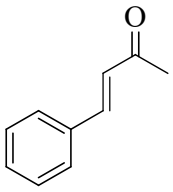
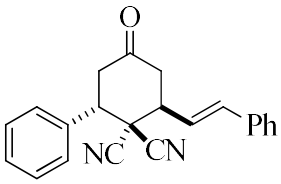
4.2.2 Study of the substrate scope

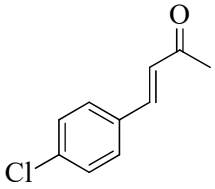
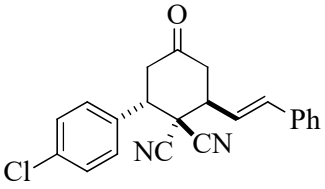
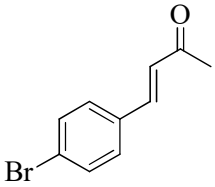
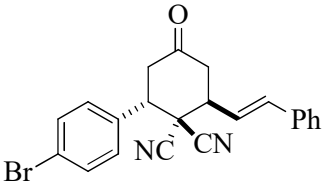
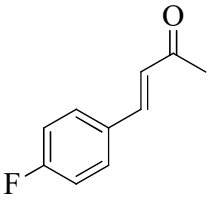
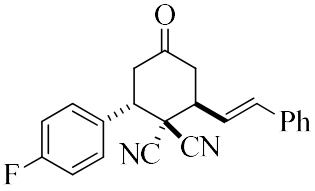
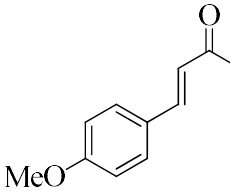
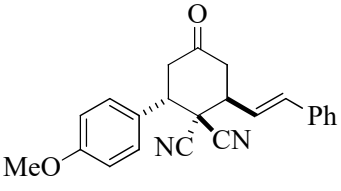
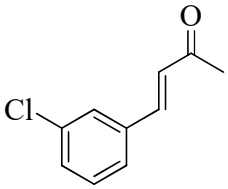
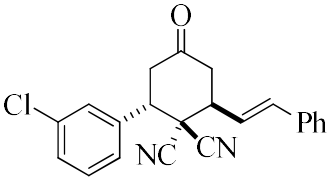
With the established optimal reaction conditions, the substrate scope was explored using variety of enones **29** and allylidene malononitriles **57** having electron-donating and electron-withdrawing functionalities at the aromatic rings of both components (**Table 4.3**). The products **68a-m**, having two stereogenic centres and one all-carbon quaternary centre were obtained in moderate to good yields, high diastereoselctivities and with moderate enantioselectivities. The solid products **68b** and **68c** could be made enantiopure by single recrystalization.

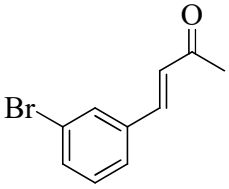
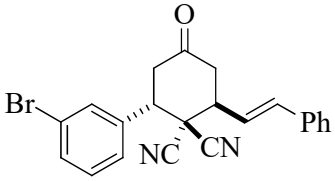
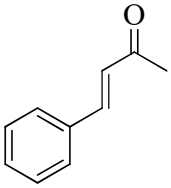
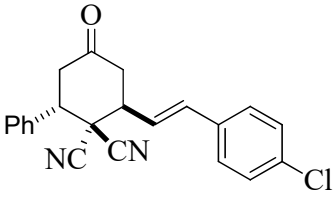
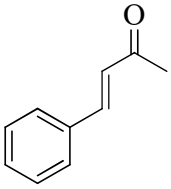
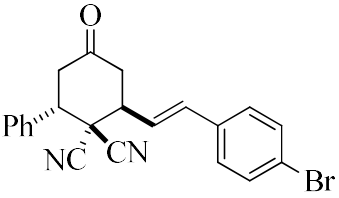
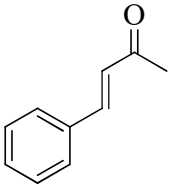
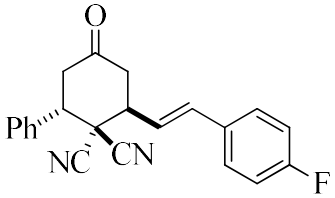
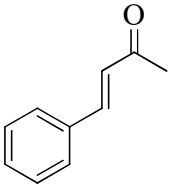
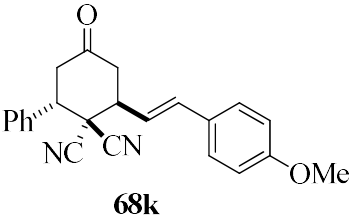
Table 4.3 Reactions of enones **29** and allylidene malononitriles **57** for the synthesis of cyclohexanones **68a-m**

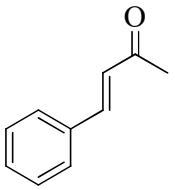
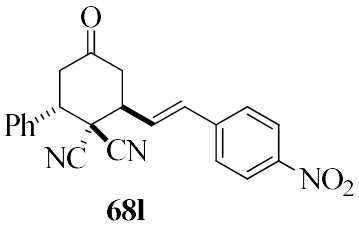
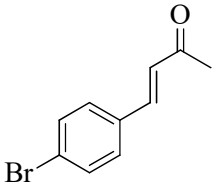
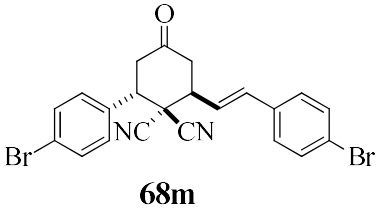


29 **57** **68**

Entry	Enone	Product	dr[a]	Yield[b,c] (%)	ee(%) of **68**
1	 **29a**	 **68a**	95:5	77	74

2	 **29b**	 **68b**	n.d.[b]	80	73 (96% ee)[d]
3	 **29c**	 **68c**	n.d.[b]	50	76 (>99% ee)[d]
4	 **29d**	 **68d**	n.d.[b]	62	72
5	 **29e**	 **68e**	n.d.[b]	63	71
6	 **29h**	 **68f**	n.d.[b]	53	67

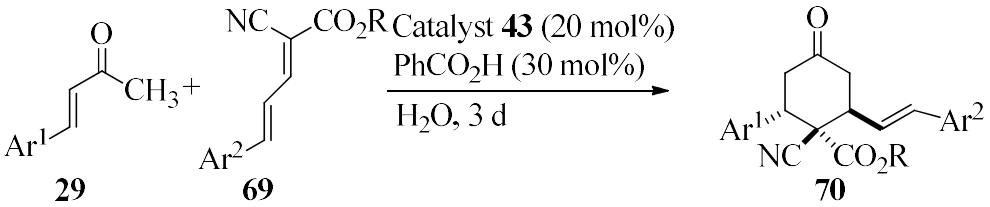
7	 **29i**	 **68g**	n.d.[b]	60	65
8	 **29a**	 **68h**	n.d.[b]	51	70
9	 **29a**	 **68i**	n.d.[b]	62	70
10	 **29a**	 **68j**	n.d.[b]	55	71
11	 **29a**	 **68k**	n.d.[b]	56	66

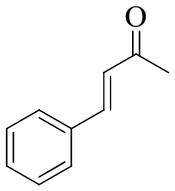
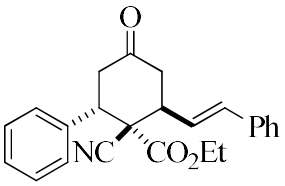
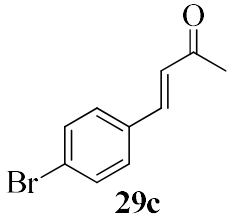
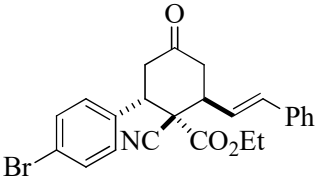
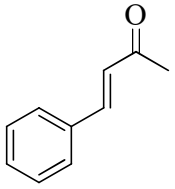
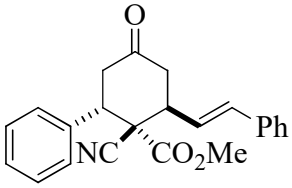
12	 **29a**	 **68l**	n.d.[b]	59	82
13	 **29c**	 **68m**	n.d.[b]	52	75

[a] Reaction conditions: **29** (0.4 mmol), **57** (0.2 mmol), catalyst **43** (0.04 mmol), H_2O (0.5 mL). [b] Other diastereoisomer neither could be detected by ^1H NMR nor isolated. [c] Isolated yield of diastereoisomer shown. [d] ee of **68** as determined by HPLC. [e] ee after single recrystalization.

With these fruitful results, we extended the [4+2] cycloaddition reaction to acyclic enones and allylidene cyanoacetate to produce chiral cyclohexanones with three contiguous stereogenic centres including an all-carbon quaternary one. The primary amine catalyst **43** in combination with benzoic acid catalyzed the reaction of enones **29a** and **29c** with allylidene cyanoacetate **69** in water (**Table 4.4**) to furnish the cyclohexanones **70a-c** in moderate yield, good diasteroselectivities and excellent enantioselectivities.

Table 4.4 Scope of substrates



Entry	Enone	Product	dr[a]	% of Yield[c] (% of conversion)	ee(%)[d] of **70**
1	 **29a**	 **70a**	90**:**10 90:10	50[b] (75) 67[g] (95)	90 85
2	 **29c**	 **70b**	84:16	51[g]	82
3	 **29a**	 **70c**	90:10	45[g]	91

[a] Reaction conditions: **29** (0.4 mmol), **69** (0.2 mmol), catalyst **43** (0.04 mmol) in H_2O (0.5 mL). [b] Reaction was performed at 28 ºC. [c] Isolated yield of diastereoisomer shown. [d] % of conversion of **70.** [e] Determined by ^1H NMR. [f] ee of **70** as determined by HPLC. [g] Reaction was performed at 40 ºC.

4.2.3 Assignment of absolute configuration

The absolute configuration of the product **68b** was established by single crystal X-ray crystallography and found to be 2*S*,6*S* as shown in **Figure 4.2**. The absolute configuration of the other products **68a** and **68c-m** was assigned in analogy.

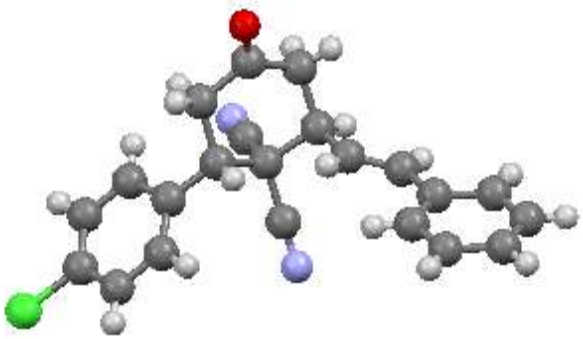
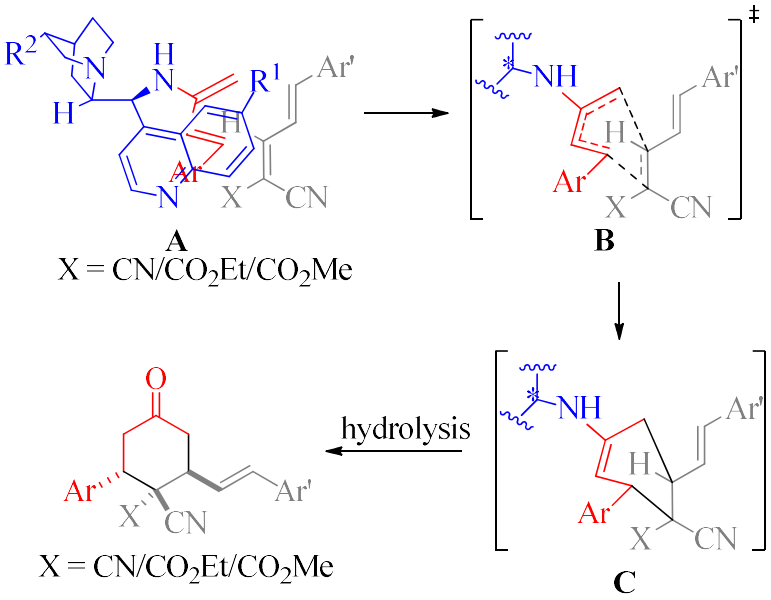


Figure 4.2 ORTEP diagram of **68b**

4.2.4 Proposed mechanism for the reaction

A plausible mechanism for the formation of 4,4-dicyanoclohexanone from α,β-unsaturated ketone **29** and allylidene malononitrile **57** or allylidene cyanoacetate **69** catalyzed by primary amine **43** can be explained *via endo* [4+2] cycloaddition[100] as shown in **Scheme 4.9.** Initially, the unsaturated methyl ketone **29** would react with primary amine organocatalyst **43** in the presence of Brønsted acid to give the enamine intermediate **A.** The dienophile allylidene malononitrile or allylidene cyanoacetate approach the enamine **A**, from the least hindered bottom face as shown in the transition state structure **B** leading to the formation of enamine **C** which on hydrolysis regenerates the amine catalyst and provides the desired product **68** or **70**.



Scheme 4.9 Proposed transition state for the formation of substituted cyclohexanone

4.3 Conclusion

In conclusion, we have developed an organocatalyzed green approach for the synthesis of highly functionalized cyclohexanones with an all-carbon quaternary or quaternary stereogenic centre in aqueous media. The [4+2] cycloaddition reactions probably underwent via the enamine of the enones as diene and allylidene malononitrile or cyanoacetate as dienophile. The products contain 2-3 stereogenic centres thus would find use in organic synthesis of complex molecules.

4.4 Experimental Section

General details: As described in **Chapter-2**

4.4.1 General methods and Materials

Materials

Benzylidene acetone **29a** was purchased from Spectrochem Private Limited, India. Other arylidene acetones **29** were synthesized from respective aryl aldehydes and acetone

following the literature procedures.[105] allylidene malononitrile **57**/allylidene cyanoacetate **69** were prepared from substituted cinnamaldehydes and malononitrile/malonoesters following the procedures reported in the literatures.[127] Organocatalysts **43-46** were prepared according to literature[107] as described in Chapter **3** catalysts **66** and **67** are commercially available.

Preparation of allylidene malononitrile 57/allylidene cyanoacetate 69

(*E*)-2-(3-Phenylallylidene)malononitrile 57a

Following the literature[127] procedure, cinnamaldehyde (0.60 g, 5.0 mmol, 1 equiv), malononitrile (0.66 g, 10.0 mmol, 2 equiv) were dissolved in benzene (25.0 mL). Piperidine benzoate (0.28 g, 1.25 mmol, 0.25 eqiuv) was added to the reaction mixture and refluxed for 4 h. The reaction mixture was acidified with 1 N HCl, diluted with water and extracted three times with dichloromethane. The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (eluent: Hexane/EtOAc = 95/5 as eluent) to give allylidene malononitrile **57a** (0.36, 40%) as a yellow solid. mp 173-175 °C; IR (film): $\bar{\upsilon}$ = 2260, 2241, 1621, 1587, 1093, 761 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.27 (2 H, d, J = 9.6 Hz, Ph), 7.46 (2 H, d, J = 8.0 Hz, Ph), 7.59 (1 H, dd, J = 7.5, 16.6, Hz, CH=), 7.60 (1 H, d, J = 7.60 Hz, CH=), 7.61 (1 H, d, J = 1.6 Hz, Ph), 7.62 (1 H, d, J = 7.60 Hz, CH=) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 84.0, 112.6 (2 C), 122.5, 128.1, 128.6 (2 C), 128.8 (2 C), 135.6, 151.2, 160.8 ppm; Elemental analysis calcd (%) for $C_{12}H_8N_2$: calcd C 79.98, H 4.47, N 15.55; found: C 79.82, H 4.57, N 15.66.

(*E*)-2-(3-(4-Chlorophenyl)allylidene)malononitrile 57b

The allylidene malononitrile **57b** was prepared according to procedure for allylidene malononitrile **57a** from 4-chlorocinnamaldehyde (0.83 g, 5.0 mmol, 1 equiv). After column chromatography (eluent: Hexane/EtOAc = 95/5 as eluent) the product **57b** was obtained as yellow solid, (0.48 g, 45%); mp 185-187 °C; IR (film): $\bar{\upsilon}$ = 2270, 2261, 1641, 1598, 1103, 771 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.33 (2 H, d, J = 9.8 Hz, Ar), 7.52 (2 H, d, J = 8.4 Hz, Ar), 7.59 (1 H, dd, J = 7.6, 16.8 Hz, CH=), 7.64 (1 H, d, J = 7.62 Hz, CH=), 7.68 (1 H, d, J = 7.62 Hz, CH=) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 84.1, 112.3 (2 C), 122.7, 128.3, 128.8 (2 C), 128.9 (2 C), 135.8, 151.4, 161.0 ppm; Elemental analysis calcd (%) for $C_{12}H_7ClN_2$: calcd C 67.15, H 3.29, N 13.05; found: C 67.25, H 3.33, N 13.15.

(*E*)-2-(3-(4-Bromophenyl)allylidene)malononitrile 57c

The allylidene malononitrile **57c** was prepared according to procedure for allylidene malononitrile **57a** from 4-bromocinnamaldehyde (1.06 g, 5.0 mmol, 1 equiv). After column chromatography (eluent: Hexane/EtOAc = 95/5 as eluent) the product **57c** was obtained as yellow solid (0.54 g, 42%); mp 191-193 °C; IR (film): $\bar{\upsilon}$ = 2265, 2258, 1639, 1594, 1098, 761 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.30 (2 H, d, J = 9.2 Hz, Ar), 7.51 (2 H, d, J = 8.3 Hz, Ar), 7.57 (1 H, dd, J = 7.40, 16.6 Hz, CH=), 7.63 (1 H, d, J = 7.60 Hz, CH=), 7.68 (1 H, d, J = 7.60 Hz, CH=) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 83.9, 112.2 (2 C), 122.6, 128.3, 128.6 (2 C), 128.7 (2 C), 135.6, 151.0, 159.7 ppm; Elemental analysis calcd (%) for $C_{12}H_7BrN_2$: calcd C 55.63, H 2.72, N 10.81; found: C 55.72, H 2.85, N 10.91.

(*E*)-2-(3-(4-Fluorophenyl)allylidene)malononitrile 57d

The allylidene malononitrile **57d** was prepared according to procedure for allylidene malononitrile **57a** from 4-fluorocinnamaldehyde (0.75 g, 5.0 mmol, 1 equiv). After column chromatography (eluent: Hexane/EtOAc = 95/5 as eluent) the product **57d** was obtained as yellow solid (0.46 g, 46%); mp 177-179 °C; IR (film): $\bar{\upsilon}$ = 2295, 2287, 1649, 1597, 1102, 781 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.30 (2 H, d, J = 9.2 Hz, Ar), 7.51 (2 H, d, J = 8.3 Hz, Ar), 7.57 (1 H, dd, J = 7.4, 16.6 Hz, CH=), 7.63 (1 H, d, J = 7.60 Hz, CH=), 7.68 (1 H, d, J = 7.60 Hz, CH=) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 84.1, 112.2 (2 C), 116.4 (J_{C-F} = 21.8 Hz), 130.3 (J_{C-F} = 8.6 Hz), 130.8 (J_{C-F} = 2.9 Hz), 132.9, 133.0 (2 C), 135.6, 151.0, 163.3 (J_{C-F} = 248.5 Hz) ppm; Elemental analysis calcd (%) for $C_{12}H_7FN_2$: calcd C 72.72, H 3.56, N 14.13; found: C 72.83, H 3.63, N 14.25.

(*E*)-2-(3-(4-Methoxyphenyl)allylidene)malononitrile 57e

The allylidene malononitrile **57e** was prepared according to procedure for allylidene malononitrile **57a** from 4-methoxycinnamaldehyde (0.81 g, 5.0 mmol, 1 equiv). After column chromatography (eluent: Hexane/EtOAc = 95/5 as eluent) the product **57e** was obtained as yellow solid (0.45 g, 43%); mp 166-167 °C; IR (film): $\bar{\upsilon}$ = 3024, 2265, 2258, 1639, 1594, 1098, 761 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 3.81 (3 H, S, OCH_3), 6.72 (1 H, dd, J = 16.20, 7.60 Hz, CH=), 6.94 (2 H, d, J = 8.80 Hz, Ar), 7.06 (1 H, d, J = 7.60 Hz, CH=), 7.59 (1 H, d, J = 8.80 Hz, CH=), 7.60 (1 H, d, J = 7.60 Hz, Ar), 7.61 (2 H, d, J = 1.6 Hz, Ar) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 55.8, 83.0, 111.9 (2 C), 122.0, 127.1, 127.9 (2 C), 128.3 (2 C), 134.5, 150.2, 159.8 ppm; Elemental analysis calcd (%) for $C_{13}H_{10}N_2O$: calcd C 74.27, H 4.79, N 13.33; found: C 74.53, H 4.63, N 13.45.

(*E*)-2-(3-(4-Nitrophenyl)allylidene)malononitrile 57f

The allylidene malononitrile **57f** was prepared according to procedure for allylidene malononitrile **57a** from 4-nitrocinnamaldehyde (0.89 g, 5.0 mmol, 1 equiv). After column chromatography (eluent: Hexane/EtOAc = 95/5 as eluent) the product **57f** was obtained as yellow solid (0.50 g, 44%); mp 153-155 °C; IR (film): $\bar{\upsilon}$ = 2265, 2268, 1649, 1594, 1560, 1102, 771 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.06 (1 H, d, J = 8.10 Hz, CH=), 7.20 (1 H, d, J = 8.3 Hz, CH=), 7.81 (1 H, dd, J = 7.60, 16.6 Hz, CH=), 8.04 (2 H, d, J = 7.60 Hz, Ar), 8.21 (2 H, d, J = 7.60 Hz, Ar) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 85.1, 113.4 (2 C), 117.2, 131.2, 132.8, 133.3, 134.2 (2 C), 135.8, 152.0, 164.3 ppm; Elemental analysis calcd (%) for $C_{12}H_7N_3O_2$: calcd C 64.00, H 3.13, N 18.66; found: C 64.21, H 3.627, N 18.92.

(*2E,4E*)-Ethyl 2-cyano-5-phenylpenta-2,4-dienoate 69a

The allylidene cyanoacetate **69a** was prepared according to procedure for allylidene malononitrile **57a** from cinnamaldehyde (0.60 g, 5.0 mmol, 1 equiv). After column chromatography (eluent: Hexane/EtOAc = 95/5 as eluent) the product **69a** was obtained as yellow solid (0.57 g, 50%); mp 181-183 °C; IR (film): $\bar{\upsilon}$ = 3120, 3010, 2265, 2268, 1745, 1635, 1594, 1550, 1108, 775 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.32 (3 H, t, J = 6.3 Hz, CH_2CH_3), 4.31 (2 H, m, OCH_2CH_3), 7.17 (2 H, d, J = 9.4 Hz, Ph), 7.26 (2 H, d, J = 9.2 Hz, Ph), 7.60 (1 H, dd, J = 7.5, 16.6 Hz, CH=), 7.67 (1 H, d, J = 9.3 Hz, CH=), 7.69 (1 H, d, J = 1.80 Hz, Ph), 7.72 (1 H, d, J = 9.20 Hz, CH=) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.5, 60.5, 84.0, 111.8 (2 C), 121.6, 127.8, 128.1 (2 C), 128.3 (2 C), 133.4, 140.2, 170.1 ppm; Elemental analysis calcd (%) for $C_{14}H_{13}NO_2$: calcd C 73.99, H 5.77, N 6.16; found: C 74.05, H 5.67, N 6.26.

(*2E,4E*)-Methyl 2-cyano-5-phenylpenta-2,4-dienoate 69b

The allylidene cyanoacetate **69b** was prepared according to procedure for allylidene malononitrile **57a** from cinnamaldehyde (0.60 g, 5.0 mmol, 1 equiv). After column chromatography (eluent: Hexane/EtOAc = 95/5 as eluent) the product **69b** was obtained as yellow solid (0.59 g, 55%); mp 189-191 °C; IR (film): $\bar{\upsilon}$ = 3120, 3010, 2265, 2268, 1745, 1635, 1594, 1550, 1108, 775 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.32 (3 H, s, OCH_3), 7.19 (2 H, d, *J* = 9.2 Hz, Ph), 7.24 (2 H, d, *J* = 9.4 Hz, Ph), 7.62 (1 H, dd, *J* = 7.40, 16.4 Hz, CH=), 7.66 (1 H, d, *J* = 9.40 Hz, CH=), 7.71 (1 H, d, *J* = 1.90 Hz, Ph), 7.74 (1 H, d, *J* = 9.40 Hz, CH=) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 60.5, 85.0, 112.7 (2 C), 122.9, 128.2, 128.6 (2 C), 129.9 (2 C), 134.1, 141.1, 170.6 ppm; Elemental analysis calcd (%) for $C_{13}H_{11}NO_2$: calcd C 73.23, H 5.20, N 6.57; found: C 73.33, H 5.43, N 6.69.

4.4.2 General Procedure I for the preparation of *rac*-substituted cyclohexanone

All the reactions were carried out in normal toluene and no special precautions were taken to exclude water or air from the reaction flask. Pyrrolidine (0.1 mmol) and benzoic acid (6.0 mg, 0.05 mmol) were added to a stirred solution of the enones **29** (0.4 mmol) allylidene malononitriles **57** (0.2 mmol) and in toluene (1 mL). Then the reaction mixture was stirred at 50 ºC for 2 d. After that, the solvent was removed under reduced pressure and the resulting residue was directly subjected to column chromatography on silica gel to afford the corresponding products *rac*-**68a-d**

General Procedure II for the preparation of *rac*-cyclohexanone

The reaction was carried out in double distilled water and no special precautions were taken to exclude air from the reaction flask. Benzoic acid (7.5 mg, 0.06 mmol) was added

to a heterogeneous mixture of the catalyst **43** (6.5 mg, 0.02 mmol) and catalyst **44** (6.5 mg, 0.02 mmol) in water (0.5 mL). The resulting heterogeneous mixture was stirred at 40 °C for 10 min in a pre-heated oil bath. After that, the mixture was brought to room temperature and then corresponding enone **29** (0.4 mmol) was added, followed by the addition of allylidene malononitriles **57** (0.2 mmol)/allylidene cyanoacetate **69** (0.2 mmol). The heterogeneous mixture was stirred at 28 °C for 3 d and extracted with dichloromethane (3 × 10 mL). The combined organic extract was washed with brine, dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography on silica using hexane/EtOAc as eluent to give *rac*- **68e-m** and *rac*-**70a-c**.

General Procedure III for the preparation of chiral cyclohexanone derivatives

All the reactions were carried out in double distilled water and no special precautions were taken to exclude air from the reaction flask. Benzoic acid (7.5 mg, 0.06 mmol) was added to a heterogeneous mixture of the catalyst **43** (13 mg, 0.04 mmol) and water (0.5 mL). The resulting heterogeneous mixture was stirred at 40 °C for 10 min in a pre-heated oil bath. After that, the mixture was brought to room temperature and enone **29** (0.4 mmol, 2 equiv) was added, followed by the addition of allylidene malononitrile **57** (0.2 mmol, 1 equiv) or allylidene cyanoacetate **69.** The heterogeneous mixture was stirred at 28 °C for 3 d. The reaction mixture was extracted with dichloromethane (3 × 10 mL) and the combined extract was washed with brine, dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography on silica using hexane/EtOAc as eluent to give **68a**-**m** and **70a-c**.

(*2S,6S*)-2-Phenyl-4-oxo-6-styrylcyclohexane-1,1-dicarbonitrile 68a

The product **68a** was obtained following the *General procedure* **4.4.2 III** from enone **29a** (58.5 mg, 0.4 mmol, 2 equiv) allylidene malononitrile **57a** (36 mg, 0.2 mmol, 1 equiv) using catalyst **43** (13 mg, 0.04 mmol, 20 mol %) and water (0.5 mL)**.** Yield**:** (50 mg, 77%); IR (film): $\bar{\upsilon}$ = 3033, 2922, 2360, 2241, 1721, 1587, 1093, 761 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 2.93-2.84 (2 H, m, =CHCHCH_2), 3.15-3.09 (2 H, m, PhCHCH_2), 3.60-3.57 (1 H, m, =CHC*H*CH_2), 3.69 (1 H, dd, *J* = 5.0, 10.5 Hz, PhC*H*CH_2), 6.25 (1 H, dd, *J* = 7.5, 15.5 Hz, PhCH=C*H*), 6.73 (1 H, d, *J* = 16 Hz, PhC*H*=CH), 7.39-7.32 (5 H, m, Ph), 7.46-7.43 (5 H, m, Ph) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 41.4, 42.8, 44.4, 44.6, 45.5, 113.6, 113.8, 121.7, 126.9 (2 C), 128.5 (2 C), 128.8 (2 C), 129.0, 129.2 (2 C), 129.6, 134.9, 135.1, 137.8, 203.5 ppm; Elemental analysis calcd (%) for $C_{22}H_{18}N_2O$: calcd C 80.96, H 5.56, N 8.58; found: C 80.96, H 5.56, N 8.56; $[\alpha]_D^{25}$ = -68.6 (*c* 1.70, $CHCl_3$,73% ee); The enantiomeric ratio was determined by HPLC with a Daicel chiralpak AD-H column [λ = 254 nm], eluent: 2-propanol/hexane (20/80), flow rate = 1.0 mL/min, t_{major} = 10.35 min (86.31%), t_{minor} = 15.65 min (13.69%).

***(2S,6S*)-4-Oxo-2-(4-chlorophenyl)-6-styrylcyclohexane-1,1-dicarbonitrile 68b.**

The product **68b** was obtained following the *General procedure* **4.4.2 III** from enone **29b** (72 mg, 0.4 mmol, 2 equiv) allylidene malononitrile **57a** (36 mg, 0.2 mmol, 1 equiv) using catalyst **43** (13 mg, 0.04 mmol, 20 mol %) and water (0.5 mL)**.** Yield: (58 mg, 80%); Recrystallized from hexane-EtOAc; mp: 171-173 °C; IR (film): $\bar{\upsilon}$ = 3030, 2923, 2345, 2225, 1724, 1577, 1073, 751cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 2.84-2.80 (1 H, m, =CHCHCH_2), 2.93-2.89 (1 H, m, =CHCHCH_2), 3.13-3.05 (2 H, m, ArCHCH_2), 3.58

(1 H, q, *J* = 5.5 Hz, =CHC*H*CH_2), 3.65 (1 H, dd, *J* = 4.5, 11 Hz, ArC*H*CH_2), 6.23 (1 H, dd, *J* = 7.0, 16 Hz, PhCH=C*H*), 6.73 (1 H, d, *J* = 16.5 Hz, PhC*H*=CH), 7.37-7.32 (5 H, m, Ph), 7.46-7.43 (4 H, m, Ar) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 41.3, 42.7, 44.3, 44.7, 44.8, 113.4, 113.6, 121.3, 126.9 (2 C), 128.8 (2 C), 129.1, 129.5 (2 C), 129.8 (2 C), 133.3, 135.0, 135.8, 138.0, 203.0 ppm; Elemental analysis calcd (%) for $C_{22}H_{17}ClN_2O$: calcd. C 73.23, H 4.75, N 7.76; found: C 73.24, H 4.83, N 7.87; $[\alpha]_D^{25}$ = -109.1 (*c* 0.62, $CHCl_3$, 96% ee); The enantiomeric ratio was determined by HPLC with a Daicel chiralpak AD-H column [λ = 254 nm], eluent: 2-propanol/hexane (20/80), flow rate = 1.0 mL/min, t_{major} = 10.06 min (86.45%), t_{minor} = 13.47 min (13.55%).

(*2S,6S*)-2-(4-Bromophenyl)-4-oxo-6-styrylcyclohexane-1,1-dicarbonitrile 67c

The product **68c** was obtained following the *General procedure* **4.4.2 III** from enone **29c** (89.5 mg, 0.4 mmol, 2 equiv) allylidene malononitrile **57a** (36 mg, 0.2 mmol, 1 equiv) using catalyst **43** (13 mg, 0.04 mmol, 20 mol %) and water (0.5 mL)**.** Yield: (41 mg, 50%); Recrystallized from hexane-EtOAc; mp: 190-192 °C; IR (film): $\bar{\upsilon}$ = 3027, 2902, 2334, 2241, 1722, 1596, 1093, 752 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.93-2.81 (2 H, m, =CHCHCH_2), 3.13-3.05 (2 H, m, ArCHCH_2), 3.60-3.58 (1 H, m, =CHC*H*CH_2), 3.65-3.63 (1 H, m, ArC*H*CH_2), 6.23 (1 H, dd, *J* = 6.5, 16.0 Hz, PhCH=C*H*), 6.73 (1 H, d, *J* = 16.0 Hz, PhC*H*=CH), 7.35-7.37 (2 H, m, Ph), 7.39-7.36 (3 H, m, Ph), 7.44-7.42 (2 H, m, Ar), 7.44-7.42 (2 H, m, Ar) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 41.3, 42.6, 44.2, 44.7, 44.9, 113.3, 113.6, 121.3, 124.0, 126.9 (2 C), 128.8 (2 C), 129.1, 130.1 (2 C), 132.5 (2 C), 133.8, 135.0, 138.1, 203.0 ppm; Elemental analysis calcd (%) for $C_{22}H_{17}BrN_2O$: calcd. C 65.20, H 4.23, N 6.91; found: C 65.51, H 4.46, N 6.92; $[\alpha]_D^{25}$ = -151.4 (*c* 0.46,

$CHCl_3$, ee >99.9%); The enantiomeric excess was determined by HPLC with a Daicel chiralpak AD-H column [λ = 254 nm], eluent: 2-propanol/hexane (20/80), flow rate = 1.0 mL/min, t_{major} = 10.00 min (88.12%), t_{minor} = 12.35 min (11.88%).

***(2S,6S)*-2-(4-Fluorophenyl)-4-oxo-6-styrylcyclohexane-1,1-dicarbonitrile 68d**

The product **68d** was obtained following the *General procedure* **4.4.2 III** from enone **29d** (65.6 mg, 0.4 mmol, 2 equiv) allylidene malononitrile **57a** (36 mg, 0.2 mmol, 1 equiv) using catalyst **43** (13 mg, 0.04 mmol, 20 mol %) and water (0.5 mL)**.** Yield: (43 mg, 62%); IR ($CHCl_3$ film): $\bar{\upsilon}$ = 3027, 2918, 2375, 2250, 1722, 1587, 1083, 766 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 2.83 (1 H, ddd, J = 1.5, 5.0, 15.5 Hz, =CHCHCH_2), 2.91 (1 H, ddd, J = 1.5, 4.5, 16.0 Hz, =CHCHCH_2), 3.13-3.06 (2 H, m, ArCHCH_2), 3.59 (1 H, q, J = 5.0 Hz, =CHC*H*CH_2), 3.68 (1 H, dd, J = 5.0, 11.5 Hz, ArC*H*CH_2), 6.24 (1 H, dd, J = 7.0, 16.0 Hz, PhCH=C*H*), 6.73 (1 H, d, J = 15.5 Hz, PhC*H*=CH), 7.13 (2 H, t, Ar), 7.39-7.32 (5 H, m, Ph), 7.44-7.42 (2 H, d, J = 10 Hz, Ar) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 41.3, 42.9, 44.5, 44.6, 44.7, 113.4, 113.7, 116.4 ($J_{C\text{-}F}$ = 21.8 Hz), 121.4, 126.9 (3 C), 128.8 (2 C), 129.1, 130.3 ($J_{C\text{-}F}$ = 8.6 Hz), 130.8 ($J_{C\text{-}F}$ = 2.9 Hz), 135.0, 138.0 (2 C), 163.3 ($J_{C\text{-}F}$ = 248.5 Hz), 203.2 ppm; Elemental analysis calcd (%) for $C_{22}H_{17}FN_2O$: calcd. C 76.73, H 4.98, N 8.13; found C 76.63, H 4.92, N 8.11; $[\alpha]_D^{25}$ = -59.3 (*c* 1.00, $CHCl_3$, ee 72%); The enantiomeric excess was determined by HPLC with a Daicel chiralpak AD-H column [λ = 254 nm], eluent: 2-propanol/hexane (20/80), flow rate = 1.0 mL/min, t_{major} = 9.09 min (86.07%), t_{minor} = 13.21 min (13.93%).

***(2S,6S)*-2-(4-Methoxyphenyl)-4-oxo-6-styrylcyclohexane-1,1-dicarbonitrile 68e**

The product **68e** was obtained following the *General procedure* **4.4.2 III** from enone **29e** (70.4mg, 0.4 mmol, 2 equiv) allylidene malononitrile **57a** (36 mg, 0.2 mmol, 1 equiv) using catalyst **43** (13 mg, 0.04 mmol, 20 mol %) and water (0.5 mL)**.** Yield: (45 mg, 63%); $\bar{\upsilon}$ = 3032, 2932, 2325, 2235, 1720, 1581, 1063, 742 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.91-2.82 (2 H, m, =CHCHCH_2), 3.11-3.05 (2 H, m, ArCHCH_2), 3.54 (1 H, q, J = 6.0 Hz, =CHCHCH_2), 3.66 (1 H, dd, J = 5.0, 15.0 Hz, ArCHCH_2), 6.25 (1 H, dd, J = 7.0, 16.0 Hz, PhCH=CH), 6.72 (1 H, d, J = 16.0 Hz, PhCH=CH), 6.95 (2 H, d, J = 9.0 Hz, Ar), 7.31-7.29 (2 H, d, Ar), 7.38-7.31 (3 H, m, Ph), 7.43-7.42 (2 H, m, Ph) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 41.4, 43.0, 44.4, 44.7, 44.9, 55.3, 113.7, 113.9, 114.6, 121.8, 126.88, 126.9 (2 C), 128.8, 128.9, 129.2 (2 C), 129.7, 130.1, 135.1, 137.7, 160.4, 203.7 ppm; Elemental analysis calcd (%) for $C_{23}H_{20}N_2O_2$: calcd. C 77.51, H 5.66, N 7.86; found C 77.50, H 5.66, N 7.85; $[\alpha]_D^{25}$ = -60.5 (c = 1.49, $CHCl_3$, ee 71%); The enantiomeric excess was determined by HPLC with a Daicel chiralpak AD-H column [λ = 254 nm], eluent: 2-propanol/hexane (20/80), flow rate = 1.0 mL/min, t_{major} = 9.88 min (85.62%), t_{minor} = 21.82 min (14.38%).

***(2S,6S)*-2-(3-Chlorophenyl)-4-oxo-6-styrylcyclohexane-1,1-dicarbonitrile 68f**

The product **68f** was obtained following the *General procedure* **4.4.2 III** from enone **29b** (72 mg, 0.4 mmol, 2 equiv) allylidene malononitrile **57a** (36 mg, 0.2 mmol, 1 equiv) using catalyst **43** (13 mg, 0.04 mmol, 20 mol %) and water (0.5 mL)**.** Yield: (38 mg, 53%); IR ($CHCl_3$ film): $\bar{\upsilon}$ = 3042, 2938, 2315, 2255, 1723, 1582, 1053, 745 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.83 (1 H, dd, J = 4.5, 16.0, =CHCHCH_2), 2.91 (1 H, ddd, J= 1.5, 4.5, 6.0 Hz, =CHCHCH_2), 3.14-3.06 (2 H, m, ArCHCH_2), 3.65-3.60 (2 H, m,

=CHC*H*CH_2 & ArC*H*CH_2), 6.23 (1 H, dd, *J* = 7.0, 16 Hz, PhCH=C*H*), 6.74 (1 H, d, *J* = 16.0 Hz, PhC*H*=CH), 7.29 (1 H, d, J = 7.5 Hz, Ph), 7.39-7.32 (4 H, m, Ph), 7.45-7.40 (4H, m, Ar) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 41.2, 42.7, 44.2, 44.8, 44.9, 113.3, 113.5, 121.3, 126.6, 126.9 (2 C), 128.7, 128.9 (2 C), 129.1, 130.0, 130.5, 135.0, 135.3, 136.8, 138.1, 203.0 ppm; Elemental analysis calcd (%) for $C_{22}H_{17}ClN_2O$: calcd. C 73.23, H 4.75, N 7.76; found C 73.48, H 4.75, N 7.77; $[\alpha]_D^{25}$ = -71.2 (*c* = 0.81, $CHCl_3$, ee 67%); The enantiomeric excess was determined by HPLC with a Daicel Chiralcel OD-H column [λ = 254 nm], eluent: 2-propanol/hexane (20/80), flow rate = 1.0 mL/min, t_{major} = 10.00 min (83.29%), t_{minor} = 11.76 min (16.71%).

***(2S,6S)*-2-(3-Bromophenyl)-4-oxo-6-styrylcyclohexane-1,1-dicarbonitrile 68g**

The product **68g** was obtained following the *General procedure* **4.4.2 III** from enone **29i** (89.5 mg, 0.4 mmol, 2 equiv) allylidene malononitrile **57a** (36 mg, 0.2 mmol, 1 equiv) using catalyst **43** (13 mg, 0.04 mmol, 20 mol %) and water (0.5 mL)**.** Yield: (48 mg, 60%); IR ($CHCl_3$ film): $\bar{\upsilon}$ = 3022, 2915, 2355, 2255, 1725, 1584, 1080, 751cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.82 (1 H, ddd, J = 1.5, 4.5, 16.0 Hz, =CHCHC*H*$_2$), 2.91 (1 H, ddd, J = 1.5, 4.5, 16.0 Hz, =CHCHC*H*$_2$), 3.14-3.05 (2 H, m, ArCHC*H*$_2$), 3.64-3.60 (2 H, m, =CHC*H*CH_2 & ArC*H*CH_2), 6.23 (1 H, dd, *J* = 7.0, 15.5 Hz, PhCH=C*H*), 6.74 (1 H, d, *J* = 15.5 Hz, PhC*H*=CH), 7.40-7.31 (5 H, m, Ph), 7.45-7.43 (2 H, m, Ar), 7.53 (1 H, bs, Ar), 7.59-7.57 (1 H, m, Ar) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 41.2, 42.7, 44.2, 44.8, 44.9, 113.3, 113.5, 121.2, 123.3, 126.9 (2 C), 127.0, 128.8 (2 C), 129.1, 130.8, 131.6, 132.9, 135.0, 137.1, 138.1, 202.8 ppm; Elemental analysis calcd (%) for $C_{22}H_{17}BrN_2O$: calcd. C 65.20, H 4.23, N 6.91; found C 65.23, H 4.23, N 6.84; $[\alpha]_D^{25}$ = -35.2 (*c* = 0.68,

$CHCl_3$; ee 65%); The enantiomeric excess was determined by HPLC with a Daicel Chiralpak AD-H column [λ = 254 nm], eluent: 2-propanol/hexane (20/80), flow rate = 1.0 mL/min, t_{major} = 9.98 min (82.61%), t_{minor} = 12.43 min (17.39%).

***(2S,6S)*-2-(4-Chlorostyryl)-4-oxo-6-phenylcyclohexane-1,1-dicarbonitrile 68h**

The product **68h** was obtained following the *General procedure* **4.4.2 III** from enone **29a** (58.5 mg, 0.4 mmol, 2 equiv) allylidene malononitrile **57b** (42.8 mg, 0.2 mmol, 1 equiv) using catalyst **43** (13 mg, 0.04 mmol, 20 mol %) and water (0.5 mL)**.** Yield: (37 mg, 51%); IR ($CHCl_3$ film): $\bar{\upsilon}$ = 3029, 2928, 2365, 2260, 1724, 1597, 1073, 755 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 2.91-2.85 (2 H, m, =CHCHCH_2), 3.15-3.08 (2 H, m, PhCHCH_2), 3.56 (1 H, q, *J* = 5.5 Hz, =CHC*H*CH_2), 3.68 (1 H, dd, *J* = 5.0, 10.5 Hz, PhC*H*CH_2), 6.20 (1 H, dd, *J* = 7.0, 16.5 Hz, ArCH=C*H*), 6.67 (1 H, d, *J* = 16.5 Hz, ArC*H*=CH), 7.34-7.53 (4 H, m, Ph & Ar), 7.38-7.35 (2 H, m, Ar), 7.45-7.44 (3 H, m, Ph) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 41.4, 42.7, 44.3, 44.5, 45.6, 113.5, 113.7, 122.3, 127.8, 128.1 (2 C), 128.5 (2 C), 129.0, 129.3 (2 C), 129.7, 133.5, 134.8, 134.9, 136.6, 203.4 ppm; Elemental analysis calcd (%) $C_{22}H_{17}ClN_2O$: calcd. C 73.23, H 4.75, N 7.76; found C 73.21, H 4.74, N 7.74; $[\alpha]_D^{25}$ = -51.0 (*c* = 1.33, $CHCl_3$, ee 70%); The enantiomeric excess was determined by HPLC with a Daicel Chiralpak AD-H column [λ = 254 nm], eluent: 2-propanol/hexane (20/80), flow rate = 1.0 mL/min, t_{major} = 10.49 min (85.07%), t_{minor} = 15.96 min (14.93%).

***(2S,6S)*-2-(4-Bromostyryl)-4-oxo-6-phenylcyclohexane-1,1-dicarbonitrile 68i**.

The product **68i** was obtained following the *General procedure* **4.4.2 III** from enone **29a** (58.5 mg, 0.4 mmol, 2 equiv) allylidene malononitrile **57c** (51.6 mg, 0.2 mmol, 1 equiv)

using catalyst **43** (13 mg, 0.04 mmol, 20 mol %) and water (0.5 mL)**.** Yield: (50 mg, 62%); IR ($CHCl_3$ film): $\bar{\upsilon}$ = 3026, 2922, 2351, 2280, 1723, 1557, 1073, 755 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 2.91-2.85 (2 H, m, =CHCH*C*H_2), 3.15-3.08 (2 H, m, PhCHC*H*$_2$), 3.57-3.54 (1 H, q, *J* = 6.0 Hz, =CHC*H*CH_2), 3.68 (1 H, dd, *J* = 5.0, 10.0 Hz, PhC*H*CH_2), 6.22 (1 H, dd, *J* = 7.0, 16.0 Hz, ArCH=C*H*), 6.66 (1 H, d, *J* = 15.5 Hz, ArC*H*=CH), 7.30 (2 H, m, Ph), 7.38-7.36 (2 H, m, Ar), 7.45-7.44 (3 H, m, Ph), 7.50 (2 H, d, *J* = 8.5 Hz, Ar) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 41.4, 42.7, 44.3, 44.6, 45.6, 113.5, 113.7, 122.5, 123.1, 128.4 (2 C), 128.5 (2 C), 129.3 (2 C), 129.7, 132.0 (2 C), 134.0, 134.8, 136.6, 203.3 ppm; Elemental analysis calcd for $C_{22}H_{17}BrN_2O$: calcd. C 65.20, H 4.23, N 6.91; found C 65.20, H 4.25, N 6.90; $[\alpha]_D^{25}$ = -42.8 (*c* = 1.25, $CHCl_3$ ee 70%); The enantiomeric excess was determined by HPLC with a Daicel Chiralpak AD-H column [λ = 254 nm], eluent: 2-propanol/hexane (20/80), flow rate = 1.0 mL/min, t_{major} = 12.44 min (85.08%), t_{minor} = 20.45 min (14.92%).

***(2S,6S)*-2-(4-Fluorostyryl)-4-oxo-6-phenylcyclohexane-1,1-dicarbonitrile 68j**

The product **68j** was obtained following the *General procedure* **4.4.2 III** from enone **29a** (58.5 mg, 0.4 mmol, 2 equiv) allylidene malononitrile **57d** (39.6 mg, 0.2 mmol, 1 equiv) using catalyst **43** (13 mg, 0.04 mmol, 20 mol %) and water (0.5 mL)**.** Yield: (38 mg, 55%); IR ($CHCl_3$ film): $\bar{\upsilon}$ = 3040, 2925, 2352, 2243, 1724, 1572, 1053, 744 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 2.90-2.84 (2 H, m, =CHCH*C*H_2), 3.15-3.08 (2 H, m, PhCHC*H*$_2$), 3.56 (1 H, q, *J* = 6.0 Hz, =CHC*H*CH_2), 3.69 (1 H, dd, *J* = 4.5, 10.5 Hz, PhC*H*CH_2), 6.15 (1 H, dd, *J* = 7.0, 16.0 Hz, ArCH=C*H*), 6.68 (1 H, d, *J* = 16.0 Hz, ArC*H*=CH), 7.06 (2 H, t, J = 8.5 Hz, Ph), 7.42-7.38 (4 H, m, Ar & Ph), 7.45-7.44 (3 H,

m, Ar) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 41.5, 42.7, 44.4, 44.6, 45.5, 113.6, 113.7, 115.9 ($J_{C\text{-}F}$ = 21.8 Hz), 121.5, 128.5 (2 C), 128.6, 128.7 (2 C), 129.3 (2 C), 129.7, 131.3 ($J_{C\text{-}F}$ = 2.9 Hz), 134.9, 136.6, 163.1 ($J_{C\text{-}F}$ = 247.5 Hz), 203.5 ppm; Elemental analysis calcd for $C_{22}H_{17}FN_2O$: calcd. C 76.73, H 4.98, N 8.13; found C 76.80, H 4.96, N 8.18; $[\alpha]_D^{25}$ = -36.5 (*c* = 1.66, $CHCl_3$, ee 71%); The enantiomeric excess was determined by HPLC with a Daicel Chiralpak AD-H column [λ = 254 nm], eluent: 2-propanol/hexane (20/80), flow rate = 1.0 mL/min, t_{major} = 10.40 min (85.37%), t_{minor} = 15.62 min (14.63%).

***(2S,6S)*-2-(4-methoxystyryl)-4-oxo-6-phenylcyclohexane-1,1-dicarbonitrile 68k**

The product **68k** was obtained following the *General procedure* **4.4.2 III** from enone **29a** (58.5 mg, 0.4 mmol, 2 equiv) allylidene malononitrile **57e** (42.0 mg, 0.2 mmol, 1 equiv) using catalyst **43** (13 mg, 0.04 mmol, 20 mol %) and water (0.5 mL)**.** Yield: (40.0 mg, 56%); IR ($CHCl_3$ film): $\bar{\upsilon}$ = 3018, 2927, 2347, 2255, 1724, 1573, 1073, 745 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.91-2.83 (2 H, m, =CHCHCH_2), 3.14-3.08 (2 H, m, PhCHCH_2), 3.56 (1 H, q, *J* = 5.5 Hz, =CHC*H*CH_2), 3.67 (1 H, dd, *J* = 4.5, 11.0 Hz, PhC*H*CH_2), 3.83 (3 H, s, OCH_3), 6.09 (1 H, dd, *J* = 7.5, 16.0 Hz, ArCH=C*H*), 6.66 (1 H, d, *J* = 15.5 Hz, ArC*H*=CH), 6.90 (2 H, d, *J* = 8.0 Hz, Ar), 7.40-7.46 (4 H, m, Ar & Ph), 7.44-7.43 (3 H, m, Ph) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 41.5, 42.8, 44.6, 44.8, 45.4, 55.4, 113.6, 113.9, 114.2 (2 C), 119.2, 127.9, 128.3 (2 C), 128.5, 129.2 (2 C), 129.6, 135.0, 137.2 (2 C), 160.3, 203.6 ppm; Elemental analysis calcd for $C_{23}H_{20}N_2O_2$: calcd. C 77.51, H 5.66, N 7.86; found C 77.52, H 5.67, N 7.86; $[\alpha]_D^{25}$ = -77.1 (*c* = 1.19, $CHCl_3$; ee 66%); The enantiomeric excess was determined by HPLC with a Daicel Chiralpak AD-H

column [λ = 254 nm], eluent: 2-propanol/hexane (20/80), flow rate = 1.0 mL/min, t_{major} = 13.47 min (83.01%), t_{minor} = 21.25 min (16.99%).

***(2S,6S)*-2-(4-Nitrostyryl)-4-oxo-6-phenylcyclohexane-1,1-dicarbonitrile 68l**

The product **68l** was obtained following the *General procedure* **4.4.2 III** from enone **29a** (58.5 mg, 0.4 mmol, 2 equiv) allylidene malononitrile **57f** (45.0 mg, 0.2 mmol, 1 equiv) using catalyst **43** (13 mg, 0.04 mmol, 20 mol %) and water (0.5 mL)**.** Yield: (40.0 mg, 56%); IR ($CHCl_3$ film): $\bar{\upsilon}$ = 3016, 2925, 2364, 2242, 1723, 1567, 1053, 750 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 2.94-2.89 (2 H, m, =CHCHCH_2), 3.17-3.11 (2 H, m, PhCHCH_2), 3.59 (1 H, q, J = 6.5 Hz, =CHCHCH_2), 3.70 (1 H, dd, J = 5.0, 9.5 Hz, PhCHCH_2), 6.40 (1 H, dd, J = 7.5, 16.0 Hz, ArCH=CH), 6.79 (1 H, d, J = 16.0 Hz, ArCH=CH), 7.38-7.36 (2 H, m, Ph), 7.46-7.45 (3 H, m, Ph), 7.57 (2 H, d, J = 8.0 Hz, Ar), 8.24 (2H, d, J = 9.0 Hz, Ar) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 41.3, 42.6, 44.1, 44.4, 45.9, 113.3, 113.4, 124.1 (2 C), 126.5, 127.6 (2 C), 128.5 (2 C), 129.3 (2 C), 129.8, 134.6, 135.6, 141.1, 147.9, 203.0 ppm; Elemental analysis calcd for $C_{22}H_{17}N_3O_3$: calcd. C 71.15, H 4.61, N 11.31; found C 71.14, H 4.62, N 11.35; $[\alpha]_D^{25}$ = -62.0 (c = 1.81, $CHCl_3$, ee 82%); The enantiomeric excess was determined by HPLC with a Daicel Chiralpak AD-H column [λ = 254 nm], eluent: 2-propanol/hexane (20/80), flow rate = 1.0 mL/min, t_{major} = 24.66 min (91.15%), t_{minor} = 39.10 min (8.85%).

***(2S,6S)*-2-(4-Bromostyryl)-4-oxo-6-(4-bromophenyl)cyclohexane-1,1-dicarbonitrile 68m**

The product **69m** was obtained following the *General procedure* **4.4.2 III** from enone **29c** (89.5 mg, 0.4 mmol, 2 equiv) allylidene malononitrile **57c** (51.6 mg, 0.2 mmol, 1

equiv) using catalyst **43** (13 mg, 0.04 mmol, 20 mol %) and water (0.5 mL)**.** Yield: (50.0 mg, 52%); IR ($CHCl_3$ film): $\bar{\upsilon}$ = 3015, 2925, 2360, 2275, 1723, 1577, 1075, 749 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 2.84 (1 H, ddd, *J* = 1.5, 5.0, 16.0 Hz, =CHCHCH_2), 2.89 (1 H, ddd, J = 1.5, 5.5, 16.5 Hz, =CHCHCH_2), 3.12-2.91 (2 H, m, ArCHCH_2), 3.57-3.54 (1 H, m, =CHC*H*CH_2), 3.63 (1 H, dd, *J* = 4.5, 11.0 Hz, ArC*H*CH_2), 6.21 (1 H, dd, *J* = 7.0, 16.0 Hz, ArCH=C*H*), 6.66 (1 H, d, *J* = 16.0 Hz, ArC*H*=CH), 7.30-7.25 (4 H, m, Ar), 7.50 (2 H, d, *J* = 8.5 Hz, Ar), 7.58 (2 H, d, *J* = 8.5 Hz, Ar) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 41.2, 42.6, 44.1, 44.6, 45.0, 113.3, 113.4, 122.1, 123.2, 124.1, 128.4 (2 C), 130.0 (2 C), 132.0 (2 C), 132.5 (2 C), 133.7, 133.8, 136.9, 202.8 ppm; Elemental analysis calcd for $C_{22}H_{16}Br_2N_2O$: calcd. C 54.57, H 3.33, N 5.79; found C 54.57, H 3.34, N 5.78; $[\alpha]_D^{25}$ = -97.2 (*c* = 0.50, $CHCl_3$, ee 75%); The enantiomeric excess was determined by HPLC with a Daicel Chiralpak AD-H column [λ = 254 nm], eluent: 2-propanol/hexane (20/80), flow rate = 1.0 mL/min, t_{major} = 22.25 min (87.25%), t_{minor} = 30.77 min (12.75%).

***(1S,2S,6S)*-Ethyl 1-cyano-4-oxo-2-phenyl-6-styrycyclohexanecarboxylate 70a**

The product **70a** was obtained following the *General procedure* **4.4.2 III** from enone **29a** (58.5 mg, 0.4 mmol, 2 equiv) allylidene cyanoacetate **69a** (45.4 mg, 0.2 mmol, 1 equiv) using catalyst **43** (13 mg, 0.04 mmol, 20 mol %) and water (0.5 mL)**.** Yield: (37.0 mg, 50% at 28 ^oC) & (50.0 mg, 67% at 40 ^oC); IR ($CHCl_3$ film): $\bar{\upsilon}$ = 3025, 2918, 2375, 2250, 1749, 1722, 1587, 1223, 1083, 748 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 1.05 (3 H, t, *J* = 7.0 Hz, CH_2CH_3); 2.85-2.83 (2 H, m, =CHCHCH_2), 3.01 (1 H, dd, *J* = 6.5, 16.0 Hz, PhCHCH_2), 3.07 (1 H, dd, *J* = 6.5, 16.0 Hz, PhCHCH_2), 3.58-3.53 (1 H, m, =CHC*H*CH_2), 4.01-3.91 (1 H, m, PhC*H*CH_2 & CH_2CH_3), 6.20 (1 H, dd, *J* = 8.5, 15.5 Hz, PhCH=C*H*),

6.55 (1 H, d, *J* = 16.0 Hz, PhC*H*=CH), 7.15-7.12 (2 H, m, Ph), 7.28-7.29 (1 H, m, Ph), 7.37-7.30 (7 H, m, Ph) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.6, 40.9, 42.1, 42.3, 47.8, 54.3, 62.9, 117.8, 125.3, 126.6 (2 C), 128.3, 128.5 (2 C), 128.6 (2 C), 128.8 (2 C), 134.9 (2 C), 136.0, 136.9, 166.0, 206.6 ppm; Elemental analysis calcd for $C_{24}H_{23}NO_3$: calcd. C 77.19, H 6.21, N 3.75; found C 77.19, H 6.23, N 3.76; HRMS (ESI) calcd for $C_{24}H_{23}NO_3Na$ [M+Na^+]: 396.1570, found: 396.1577; $[\alpha]_D^{25}$ = -75.9 (*c* = 1.41, $CHCl_3$, ee 90%); The enantiomeric excess was determined by HPLC with a Daicel Chiralpak AD-H column [λ = 254 nm], eluent: 2-propanol/hexane (20/80), flow rate = 1.0 mL/min, t_{major} = 8.52 min (95.03%), t_{minor} = 10.19 min (4.97%).

***(1S,2S,6S)*-Ethyl 2-(4-bromophenyl)-1-cyano-4-oxo-6-styrylcyclohexanecarboxylate 70b**

The product **70b** was obtained following the *General procedure* **4.4.2 III** from enone **29a** (89.5mg, 0.4 mmol, 2 equiv) allylidene cyanoacetate **69a** (45.4 mg, 0.2 mmol, 1 equiv) using catalyst **43** (13 mg, 0.04 mmol, 20 mol %) and water (0.5 mL)**.** Yield: (46.0 mg, 51% at 40 ^{o}C); IR ($CHCl_3$ film): $\bar{\upsilon}$ = 3030, 2933, 2365, 2248, 1751, 1724, 1590, 1230, 1090, 755 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.09 (3 H, t, J= 7.0 Hz, CH_2CH_3) 2.85-2.80 (2 H, m, =CHC*H*CH_2), 2.95 (1 H, dd, *J* = 5.5, 16.0 Hz, ArCHCH_2), 3.07 (1 H, dd, *J* = 7.5, 16.5 Hz, ArCHCH_2), 3.54-3.49 (1 H, m, =C*H*CH_2), 3.84 (1 H, t, J = 6.5 Hz, Ar*C*HCH_2), 4.05-3.99 (2 H, m, CH_2CH_3); 6.20 (1 H, dd, *J* = 8.5, 16.0 Hz, PhCH=C*H*), 6.55 (1 H, d, *J* = 15.5 Hz, PhC*H*=CH), 7.04 (2 H, d, *J* = 9.0 Hz, Ar), 7.29-7.26 (1 H, m, Ph), 7.38-7.31 (4 H, m, Ph),7.48 (2 H, d, *J* = 8.5 Hz, Ar) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.7, 41.2, 42.1, 46.9, 54.1, 63.1, 117.6, 122.9, 124.9, 126.6 (2 C), 128.4,

128.7 (2 C), 130.2 (2 C), 132.0 (2 C), 135.2, 135.8, 135.9, 166.0, 206.2 ppm; Elemental analysis calcd for $C_{24}H_{22}BrNO_3$: calcd. C 63.73, H 4.90, N 3.10; found C 63.72, H 4.90, N 3.12; HRMS (ESI) calcd for $C_{24}H_{22}NO_3Br$ [M+H$^+$]: 452.0856, found: 452.0856; $[\alpha]_D^{25}$ = -59.0 (*c* = 3.26, $CHCl_3$, ee 82%); The enantiomeric excess was determined by HPLC with a Daicel Chiralpak AD-H column [λ = 254 nm], eluent: 2-propanol/hexane (20/80), flow rate = 1.0 mL/min, t_{major} = 10.39 min (91.22%), t_{minor} = 14.11 min (8.78%).

***(1S,2S,6S)*-Methyl 1-cyano-4-oxo-2-phenyl-6-styrycyclohexanecarboxylate 70c**

The product **70c** was obtained following the *General procedure* **4.4.2 III** from enone **29a** (58.5 mg, 0.4 mmol, 2 equiv) allylidene cyanoacetate **69a** (41.6 mg, 0.2 mmol, 1 equiv) using catalyst **43** (13 mg, 0.04 mmol, 20 mol %) and water (0.5 mL)**.** Yield: (32.0 mg, 45% at 40 ^oC); IR (film): $\bar{\upsilon}$ = 3025 2933, 2375, 2252, 1748, 1728, 1580, 1225, 1085, 744cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.85-2.83 (2 H, m, =CHCHCH_2), 3.01 (1 H, dd, *J* = 6.0, 16.5 Hz, PhCHCH_2), 3.06 (1 H, dd, *J* = 6.5, 16.0 Hz, PhCHCH_2), 3.54-3.52 (1 H, m, =CHC*H*CH$_2$), 3.56 (3 H, s, OCH_3); 3.93 (1 H, t, J = 6.0 Hz, PhC*H*CH$_2$), 6.20 (1 H, dd, *J* = 7.5, 15.5 Hz, PhCH=C*H*), 6.56 (1 H, d, *J* = 15.5 Hz, PhC*H*=CH), 7.13-7.11 (2 H, m, Ph), 7.28-7.25 (1 H, m, Ph), 7.37-7.30 (7 H, m, Ph) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 40.7, 42.1, 42.3, 47.8, 53.3, 54.2, 117.6, 125.2 126.6 (2 C), 128.3, 128.4 (2 C), 128.6 (2 C), 128.7, 128.9 (2 C), 134.9, 136.0, 136.8, 166.4, 206.5 ppm; Elemental analysis calcd (%) for $C_{23}H_{21}NO_3$: calcd C 76.86, H 5.89, N 3.90; found C 76.85, H 5.89, N 3.90; HRMS (ESI) calcd for $C_{23}H_{21}NO_3Na$ [M+Na$^+$]: 382.1414, found: 382.1416; $[\alpha]_D^{25}$ = -66.9 (*c* 2.28, $CHCl_3$, ee 91%); The enantiomeric excess was determined by

HPLC with a Daicel chiralpak AD-H column [λ = 254 nm], eluent: 2-propanol/hexane (20/80), flow rate = 1.0 mL/min, t_{major} = 10.28 min (95.52%), t_{minor} = 13.35 min (4.48%).

4.4.3.1 X- ray Crystallographic data

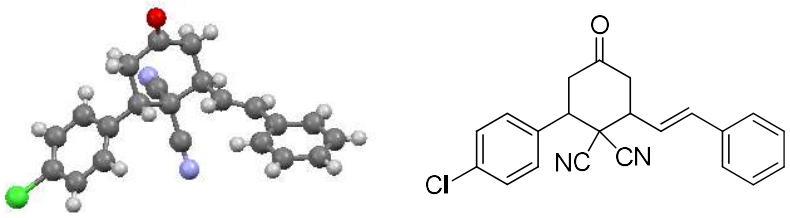


Figure 4.2: X-ray structure of **67b**, CCDC No. **1501137**

Bond precision:	C-C = 0.0161 A		
	Wavelength=1.54184		
Cell:	a=6.8443(3)	b=12.8636(5)	c=21.2586(9)
	alpha=90	beta=90	gamma=90
	Calculated	Reported	
Volume	1871.66(14)	1871.65(13)	
Space group	P 21 21 21	P 21 21 21	
Hall group	P 2ac 2ab	P 2ac 2ab	
Moiety formula	$C_{22}H_{17}ClN_2O$	$C_{22}H_{17}ClN_2O$	
Sum formula	$C_{22}H_{17}ClN_2O$	$C_{22}H_{17}ClN_2O$	
Mr	360.83	360.82	
Dx,g cm^{-3}	1.281	1.281	
Z	4	4	
Mu (mm-1)	1.898	1.898	
F000	752.0	752.0	
F000’	755.39		
h,k,lmax	8,15,26	8,15,26	

Nref	3757[2172]	3537
Tmin,Tmax	0.593,0.872	0.599,0.878
Tmin’	0.423	

Correction method = # Reported T Limits: Tmin=0.599; Tmax=0.878

AbsCorr = GAUSSIAN

Data completeness = 1.63/0.94 Theta(max) = 73.267

R(reflections)= 0.0951(2439) wR2(reflections) = 0.2520(3537)

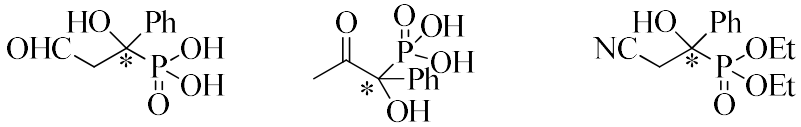
S = 1.186 Npar= 235

CHAPTER 5

Organocatalytic enantioselective synthesis of tert-α-hydroxyphosphonates from β-ketoacids and α-ketophosphonates

5.1 Introduction

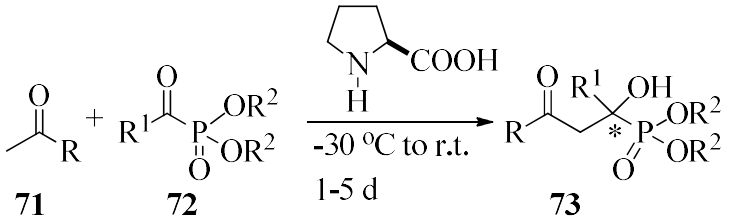
Chiral α-hydroxyphosphonic acids and their derivatives are well known for their biological activities.[128] They are widely used in pharmaceutical preparations, such as anticancer,[129] antivirus activities[130] and are also well known antioxidants. They are known for their excellent inhibitory activities towards a number of important groups of enzymes including HIV protease and polymerase,[131] rennin[132] and a number of protein tyrosine kinases and phosphatises.[133] Due to their relevance to biomedical applications, there have been considerable interests in developing highly enantioselective methods for the synthesis of these compounds in recent years. Besides their biological importance, α-hydroxyphosphonates could be transformed into different α-functionalized compounds.[134] The asymmetric synthesis of α-hydroxyphosphonates mainly relies on the synthesis of secondary α-hydroxyphosphonates by means of enzymatic[135] and chemical methods.[136] On the contrary, the synthesis of more challenging tertiary α-hydroxyphosphonates has received less attention.[137] The biological activity of some of the chiral tertiary α-hydroxyphosphonates are well documented in the literature (**Figure 5.1**).



Anti-cancer | Inhibitor of acetoacetate synthesis | Anti-oxidant

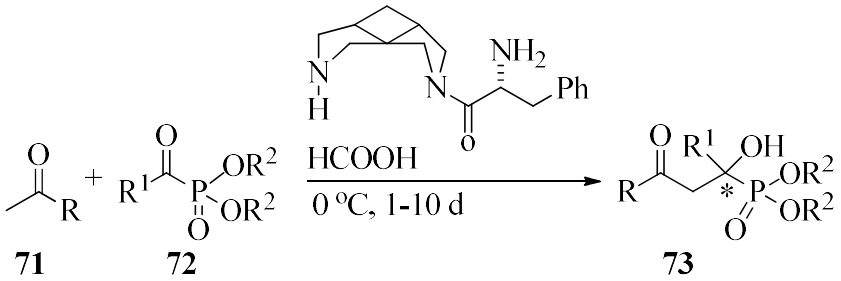
Figure 5.1 Biologically active tertiary α-hydroxyphosphonic acid derivatives

In 2006, Zhao and Samanta[138] reported the synthesis of optically active tertiary α-hydroxyphosphonates **73** *via* proline catalyzed aldol addition of ketone **71** to α-ketophosphonates **72** (**Scheme 5.1**).



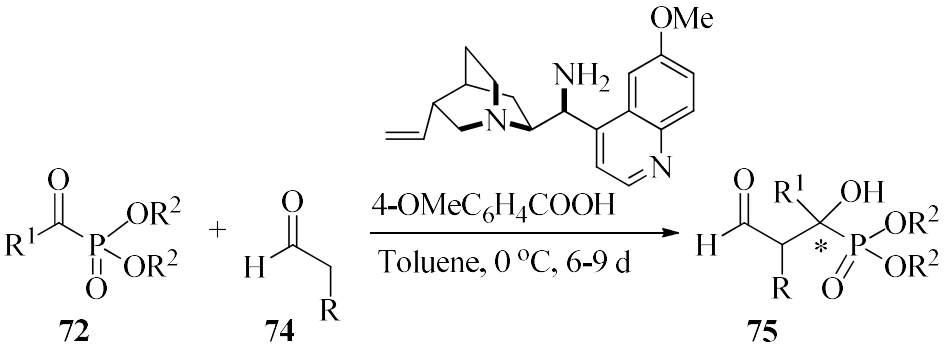
Scheme 5.1 Zhao's synthesis of γ-carbonyl tertiary α-hydroxy phosphonate ester

Hu *et. al.*[139] in 2008 reported the synthesis of tertiary α-hydroxyphosphonates **73** with excellent yield and enantioselectivity by introducing L-phenylalanine amino acid into the bicyclic bispidine frame work, which in turn used as a catalyst and formic acid as an additive for the direct aldol reaction of carbonyl compounds **71** with the α-ketophosphonates **72** (**Scheme 5.2**). Indeed in some cases this approach requires prolonged time for reaction completion.



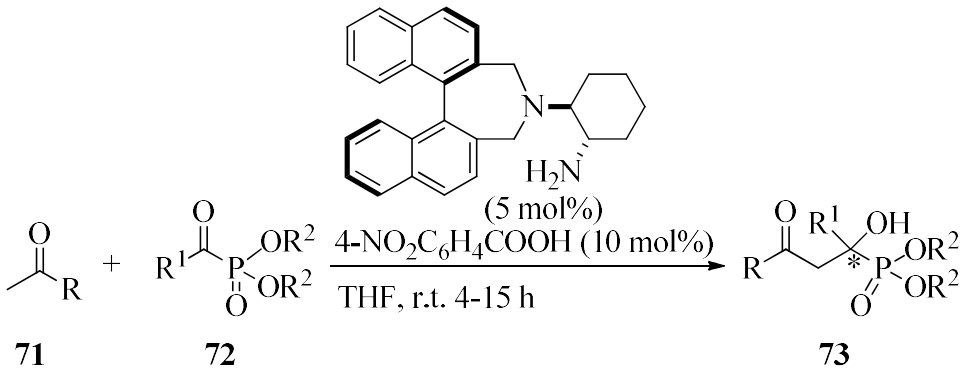
Scheme 5.2 Hu's synthesis of γ-carbonyl tertiary α-hydroxy phosphonate ester

In 2011, Zhao *et. al.*[140] reported crossed aldol reaction between α-ketophosphonates **72** and enolizable aldehydes **74** for the synthesis of β-formyl-α-hydroxyphosphonates **75** using 9-amino-9-deoxyepiquinine as the catalyst and 4-methoxybenzoic acid as an additive (**Scheme 5.3**). The reaction worked well especially with acetaldehyde, which is a difficult substrate for organocatalyzed cross-aldol reactions.



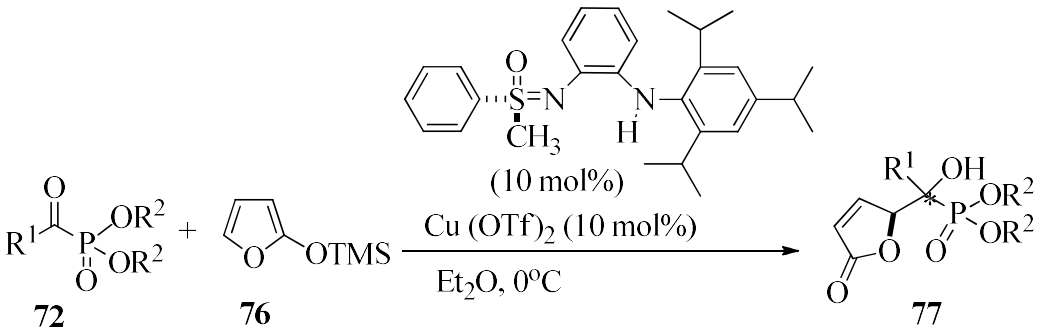
Scheme 5.3 Zhaos' synthesis of γ-carbonyl tertiary α-hydroxyphosphonate ester

Kim *et. al.*[141] in 2011 reported the direct enantioselective aldol reaction between acetone **71** and α-ketophosphonates **72** catalyzed by bifunctional organocatalysts bearing both central and axial chiral elements for the synthesis of optically active tertiary α-hydroxyphosphonates **73** (**Scheme 5.4**).



Scheme 5.4 Kim's synthesis of γ-carbonyl tertiary α-hydroxy phosphonate ester

In 2014, Carsten Bolm *et. al.*[142] reported the synthesis of γ-(hydroxyalkyl)butenolides **77** with the simultaneous construction of up to two adjacent quaternary stereogenic centers by a catalytic asymmetric vinylogous Mukaiyama aldol reaction from α-ketophosphonates **72** and silyloxy furan **76** using chiral copper-sulfoximine catalyst (**Scheme 5.5**).

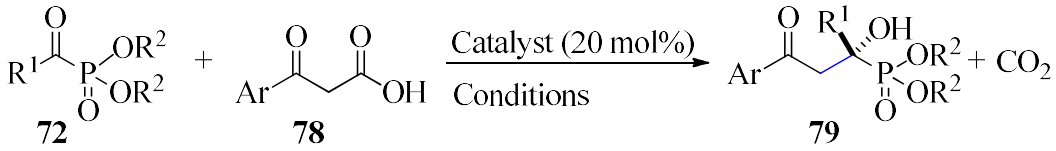


72 76 77

Scheme 5.5 Carsten's synthesis of tertiary α-hydroxyphosphonate ester

5.2 Present work

In the present chapter, the development of an organocatalytic methodology for C-C bond formation between β-ketoacids and α-ketophosphonates *via* decorboxylative aldol reaction leading to γ-carbonyl *tert*-α-hydroxyphosphonate having a hydroxyl and phosphonate bearing chiral quaternary centre is described. The stereoselective synthesis of γ-carbonyl *tert*-α-hydroxyphosphonate in an asymmetric fashion has attracted much attention from the chemical community. Only a few approaches including asymmetric reduction of α-ketophosphonates,[143] asymmetric oxidation of benzyl phosphonates,[144] asymmetric hydrophosphonylation of carbonyl compounds[145] or aldol reaction of enolizable aldehydes/ketones with α-ketophosphonates via covalent catalysis is well explored. The catalytic enantioselective decarboxylative aldol reaction of β-ketoacids to acetylphosphonate via non covalent catalysis (hydrogen bonding) using urea based amines has not been explored. We have undertaken an investigation of new protocol for the synthesis of γ-carbonyl *tert*-α-hydroxyphosphonate **79** *via* decarboxylatative aldol reaction of β-ketoacids **78** with acetyl phosphonates **72** (**Scheme 5.6**).



72 78 79

Scheme 5.6 Proposed synthesis of γ-carbonyl *tert*-α-hydroxyphosphonate

5.2.1 Optimization of reaction conditions

Initially the model reaction between diethyl acetylphosphonate **72a** and benzoylacetic acid **78a,** a surrogate of acetophenone enolate, were chosen as substrates for the decarboxylative aldol addition product phosphonate **79a**. A number of initial experiments were performed to investigate the effect of bifunctional (thio)urea derived organocatalysts **11-15**, **80-81**[81] and naturally occurring cinchona based catalysts **82-84** (**Figure 5.2**) in toluene at room temperature (28 ^{o}C).

We started our investigation with 20 mol% of cinchona based bifunctional thiourea catalyst **11-15** and **80-81**. The desired product **79a** was formed with moderate to good yield and enantioselectivity (**Table 5.1**, entries 1-5). Quinidine based bifunctional urea catalyst **80** offers desired product with good yield and enantioselectivity (**Table 5.1**, entry 6), whereas the catalyst **81** gave moderate yield and enantioselectivity (**Table 5.1**, entry 7) under the similar conditions. With cinchonidine **82** as a catalyst, the desired product **79a** was formed with moderate yield and enantioselectivity (**Table 5.1**, entry 8). Similar results were obtained in the case of quinine **83** and quinidine **84** (**Table 5.1**, entries 9-10). Amongst these, quinidine derived urea catalyst **80** was found to be a superior catalyst for further optimization.

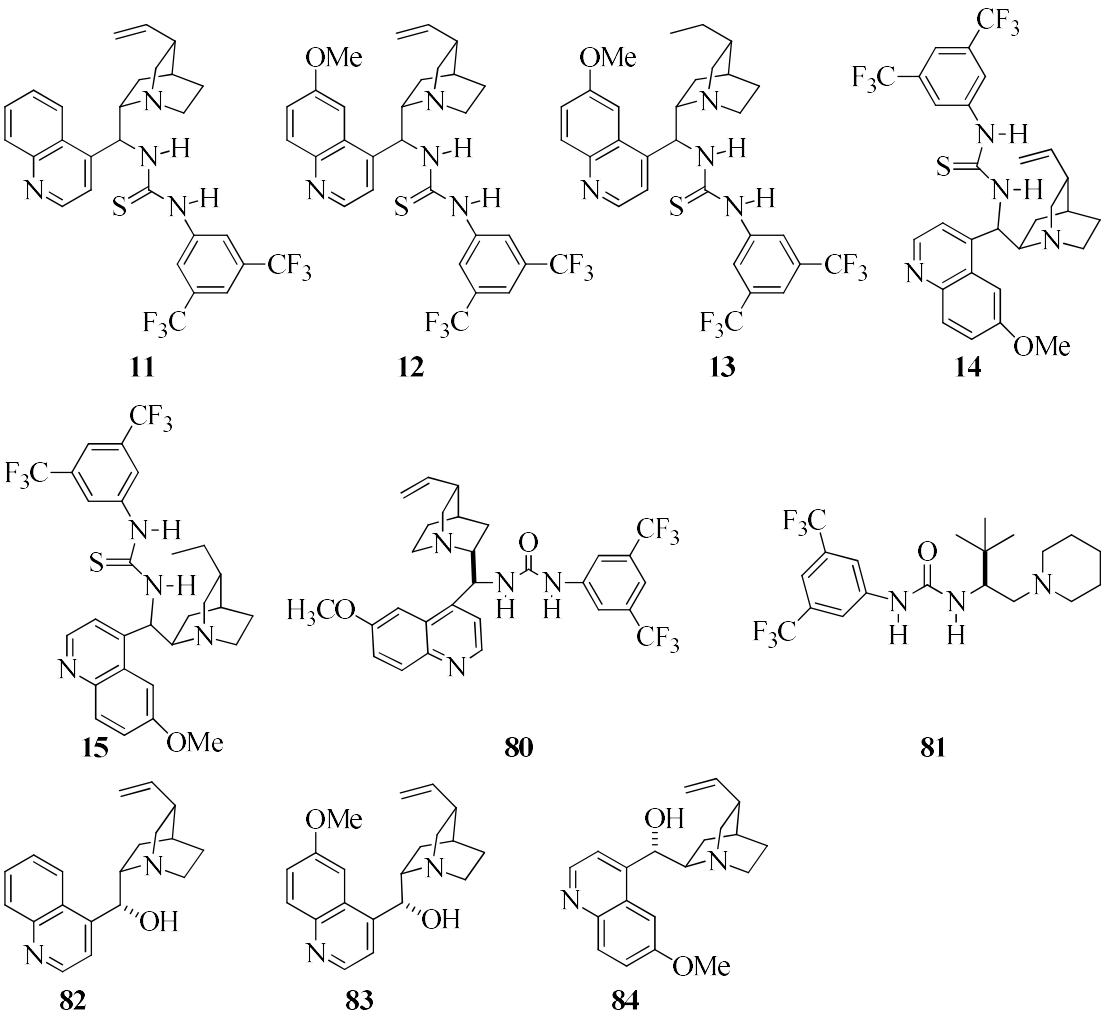
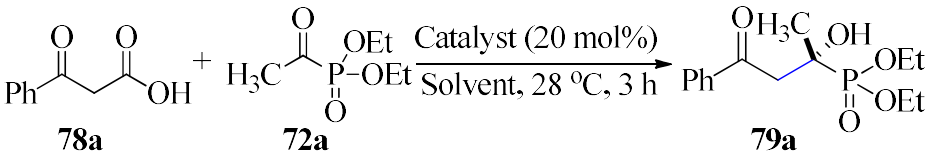


Figure 5.2 Structure of the organocatalysts

Variation in the polarity of the organic solvents (**Table 5.1**, entries 11-16) with the catalyst **80** did not improve the yield or selectivities in a meaningful way compared to toluene (**Table 5.1**, entry 6). When the reaction was carried out in methyl *tert*-butyl ether (MTBE), the yield of product **79a** was higher but enantioselectivity was slightly lower compared to toluene (**Table 5.1**, entry 6 *vs.* 15). A similar result was obtained when the reaction was performed in 1:1 mixture of MTBE/toluene (**Table 5.1**, entry 15 *vs.* 16). Catalyst loading did not affect the enantioselectivity of the reaction but affected the yield of

the reaction (**Table 5.1**, entries 17-18). Lowering the temperature as well as dilution of the reaction, use of additive, reverse addition of reagents and slow addition (via syringe pump) had no beneficial effect on the *er* of **79a**. After detailed studies in the variation of all reaction parameters, the optimized reaction conditions were set as: diethyl acetylphosphonate **72a** (1.0 equiv), benzoylacetic acid **78a** (1.3 equiv), 20 mol% of catalyst **80** and dry toluene as solvent at 28 °C.

Table 5.1 Optimization of the decarboxylative aldol addition of benzoylacetic acid **78a** to diethyl acetylphosphonate **72a.**[a]



Entry	Catalyst (mol%)	Solvent	Yield (%)[b]	e.r.(*R*:*S*)[c]
1	**11**(20)	toluene	80	24:76
2	**12**(20)	toluene	85	23:77
3	**13**(20)	toluene	65	30:70
4	**14**(20)	toluene	84	81:19
5	**15**(20)	toluene	64	79:21
6	**80**(20)	toluene	70	84:16
7	**81**(20)	toluene	67	29:71
8	**82**(20)	toluene	33	55:45
9	**83**(20)	toluene	40	65:35

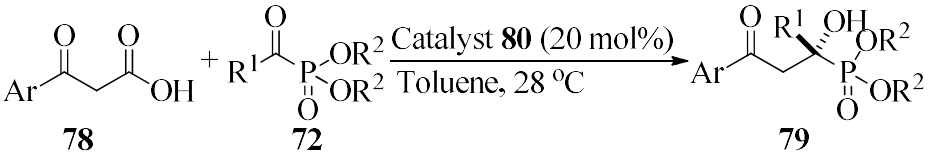
10	**84**(20)	toluene	43	32:68
11	**80**(20)	mesitylene	60	83:17
12	**80**(20)	THF	67	79:21
13	**80**(20)	CH_2Cl_2	60	75:25
14	**80**(20)	EtOAc	63	80:20
15	**80**(20)	MTBE	76	82:18
16	**80**(20)	MTBE/toluene [d]	75	82:18
17[e]	**80**(10)	toluene	65	84:16
18[e]	**80**(5)	toluene	60	84:16

[a]Reaction conditions: **72a** (0.1mmol), **78a** (0.13 mmol), solvent (1.0 mL). [b]Isolated yield. [c]Determined by HPLC using chiral OD-H column. [d] v/v 1:1. [e]Reaction time 4 h.

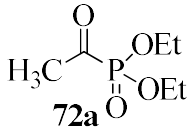
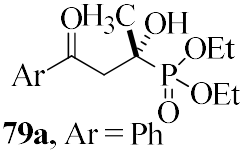
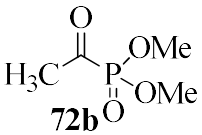
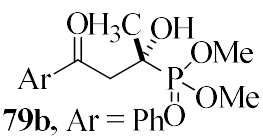
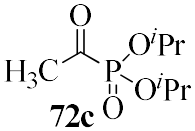
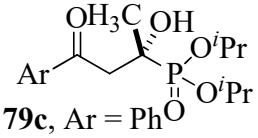
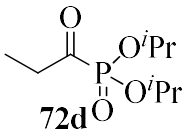
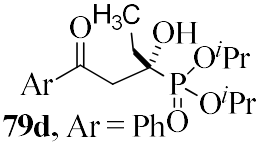
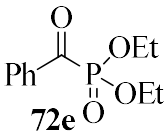
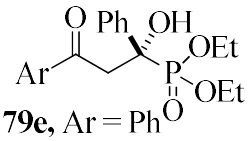
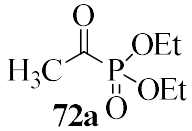
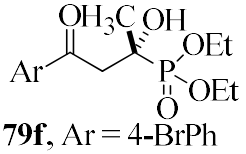
5.2.2 Study of the substrate scope

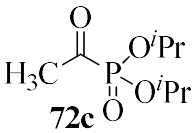
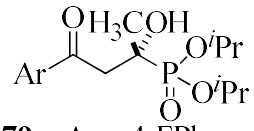
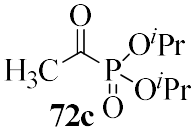
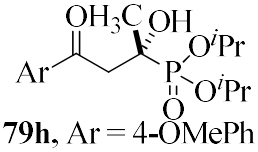
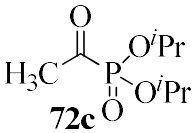
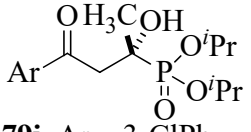
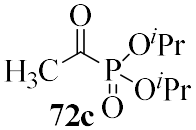
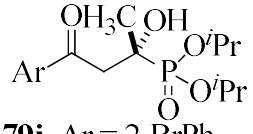
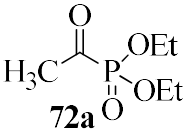
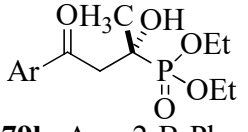
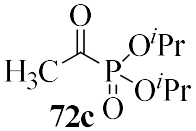
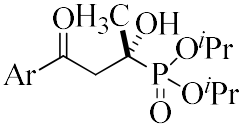
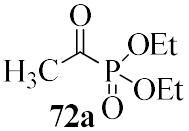
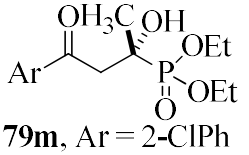
With the established optimal reaction conditions, the substrate scope was explored using variety of α-ketophosphonates **72** with different alkyl and alkoxy substituents and β-ketoacids **78** having electron-donating and electron-withdrawing functionalities at the aromatic ring. The size of R^1 and R^2 in α-ketophosphonates had strong influence on both the reactivity and enantioselectivity. As the size of R^1 increases the enantioselectivity decreases (**Table 5.2**, entry 1 *vs.* 5 and entry 3 *vs.* 4). On the other hand, with the increase in the size of R^2, the reactivity of α-ketophosphonate drops but the enantioselectivity of the products increases (**Table 5.2**, entries 12-15). The products **79a-q** are formed with one quaternary chiral centre in moderate to good yields and enantioselectivities as presented in **Table 5.2.** The solid products **79j** could be made enantiopure by single recrystalization.

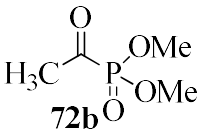
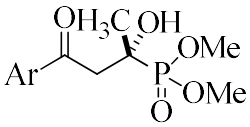
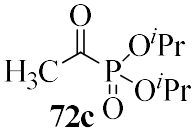
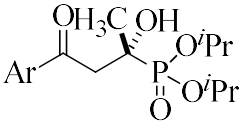
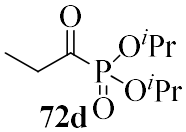
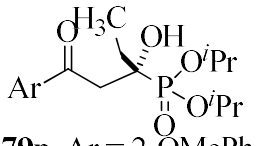
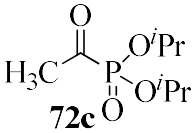
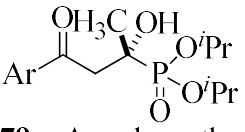
Table 5.2 Scope of various α-ketophosphonates **72** and β-ketoacids **78** for the synthesis of tertiary α-hydroxyphosphonates **79a-q**[a]



78 **72** **79**

Entry	α-Ketophosphonates	Product	Time	Yield[b] (%)	e.r.(%)[c] of **79**
1	 **72a**	 **79a**, Ar = Ph	3 h	70	84:16
2	 **72b**	 **79b**, Ar = Ph	2 h	82	n.d
3	 **72c**	 **79c**, Ar = Ph	18 h	84	85:15
4	 **72d**	 **79d**, Ar = Ph	12 h	64	77:23
5	 **72e**	 **79e,** Ar = Ph	18 h	66	65:35
6	 **72a**	 **79f**, Ar = 4-BrPh	3 h	70	82:18

7	 **72c**	 **79g**, Ar = 4-FPh	21 h	82	79:21
8	 **72c**	 **79h**, Ar = 4-OMePh	48 h	70	78:22
9	 **72c**	 **79i**, Ar = 3-ClPh	22 h	72	83:17
10	 **72c**	 **79j**, Ar = 2-BrPh	24 h	79	93:7
11	 **72a**	 **79k**, Ar = 2-BrPh	4 h	76	92:8
12	 **72c**	 **79l**, Ar = 2-ClPh	22 h	73	92:8
13	 **72a**	 **79m**, Ar = 2-ClPh	4 h	70	89:11

14	 **72b**	 **79n**, Ar = 2-ClPh	3 h	71	85:15
15	 **72c**	 **79o**, Ar = 2-OMePh	22 h	78	85:15
16	 **72d**	 **79p**, Ar = 2-OMePh	26 h	56	79.5:20.5
17	 **72c**	 **79q**, Ar = 1-napth	10 h	64	87:13

[a]Reaction conditions: **72** (0.26 mmol), **78** (0.2 mmol), solvent (2.0 mL). [b]Isolated yield. [c]enantiomers are inseparable. [d]Reaction was carried out in 0.1 mmol scale.

5.2.3 Assignment of absolute configuration

The absolute configuration of the product **79j** was established by single crystal X-ray crystallography and was found to be *R* as shown in the (**Figure 5.3**). The absolute configuration of the other products **79a-i** and **79k-q** was assigned in analogy.

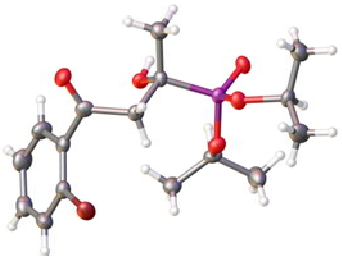
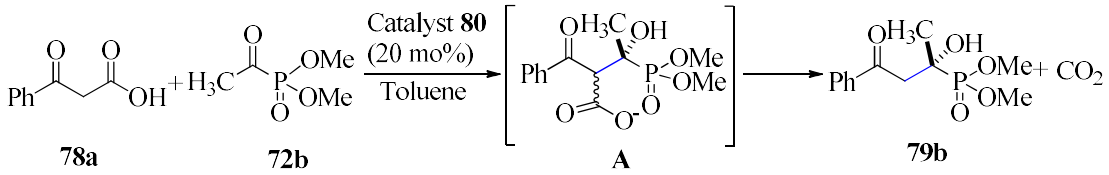


Figure 5.3 ORTEP diagram of **79j**

5.2.4 Proposed mechanism for reaction

A plausible mechanism for the formation of aldol product from α-ketophosphonate **72b** and benzoylacetic acid **78a** in presence of 20 mol% of quinidine based bifunctional catalyst **80** has been presented in **Scheme 5.7**. The enolate form of the benzoylacetic acid undergoes aldol reaction with the acetophosphonate to give the adduct **A** which under the reaction conditions undergoes decarboxylation to give the desired product. The alternative mechanism of first decarboxylation and then aldol known rules out by doing reaction with acetophenone and α-ketophophonate route without any success.



Scheme 5.7 Plausible reaction pathway for the decarboxylative aldol reaction.

To get insight into the reaction pathway, the reaction is monitored by ^{31}P NMR spectroscopy between **72b** and **78a** as shown in the **Figure 5.4**. In general, the ^{31}P NMR peak for α-ketophosphonates are known to appear at δ = -0.73 ppm. After the addition of α-ketophosphonate **72b** to the reaction mixture of benzoylacetic acid **78a** and the catalysts **80** (20 mol%), the desired product **79b** peak in ^{31}P NMR appeared at δ = 27.3 ppm. In addition, two additional peaks at δ = 25.5 ppm and 25.1 ppm were also observed which we believe was due to the two diastereoiosomers of intermediate **A** (**Scheme 5.7**). The peak at 10.83 ppm was assigned to be dimethyl phosphite which was formed due to the decomposition of **72b**. A peak observed at 22.54 ppm which is due to complex formation between **72b** and the catalyst **80**. As the time progressed, the intensity of the peaks at δ = -0.73 ppm (α-ketophosphonate **72b),** δ = 25.46 ppm and 25.1 ppm decreased

while the intensity of the product peak (δ =27.2 ppm) increased. This observation and previous literature reports[146,147] advocate that the first step is the addition of the enolate of β-ketoacid to the α-ketophosphonate leading to the intermediate **A** which then undergoes decarboxylation to the product **79b.**

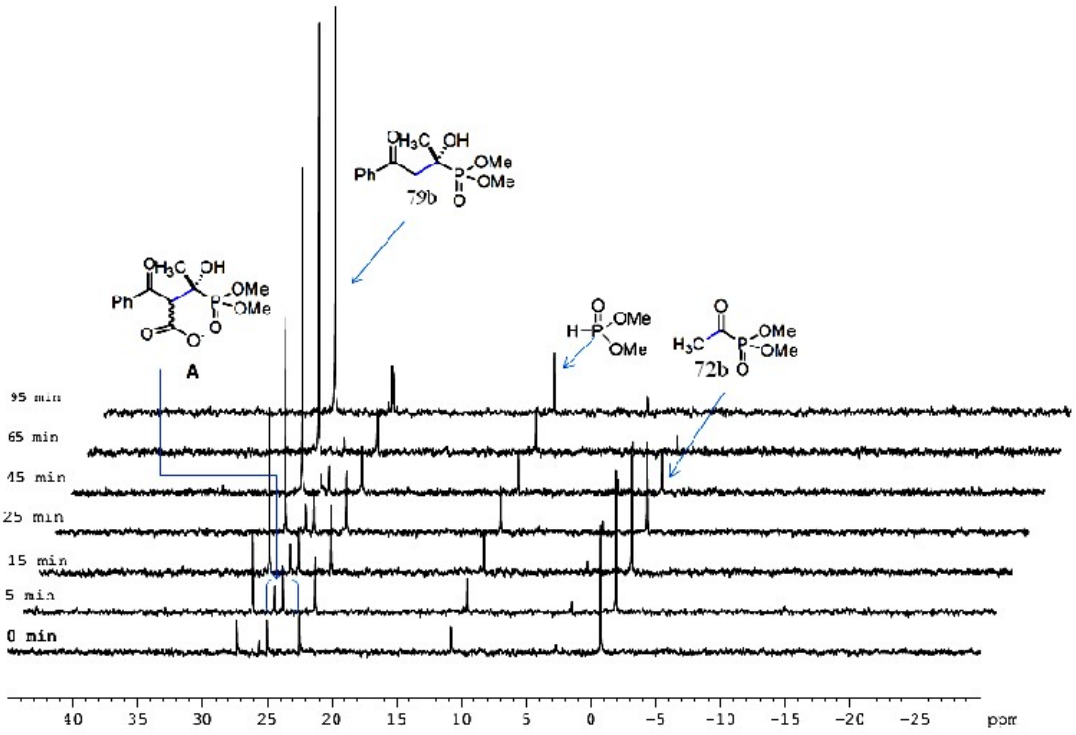


Figure 5.4 Time-elapsed ^{31}P NMR spectra for the synthesis of **79b** in [D_8]-toluene

5.3 Conclusion

In conclusion, we have developed an organocatalyzed decarboxylative aldol reaction of β-ketoacids, surrogates of aromatic ketone enolate, with α-ketophosphonates for the synthesis of γ-carbonyl tertiary α-hydroxy phosphonate ester having a hydroxyl and phosphonate bearing chiral quaternary centre. This approach offers the desired product in

good yield with moderate to good enatioselectivity. The ^{31}P NMR spectroscopy studies reveal the plausible pathway of the reaction.

5.4 Experimental Section

General details: As described in **Chapter-2**

5.4.1 General methods and Materials

The ^{1}H and ^{13}C NMR spectroscopic data were recorded in a 500 MHz (^{1}H NMR: 500 MHz, ^{13}C NMR: 125 MHz) Varian spectrometer. The ^{1}H and ^{13}C chemical shifts are given in ppm (δ scale) and are measured relative to $CHCl_3$ (7.27 ppm) and $CDCl_3$ (77.0 ppm), respectively, as internal standards. ^{31}P NMR spectroscopic data were recorded with 400 MHz (^{31}P NMR: 162 MHz) and 500 MHz (^{31}P NMR: 202 MHz) Bruker spectrometers. High resolution mass spectra were recorded at 60-70 eV with a Q-TOF spectrometer (ESI, Ar). Enantiomeric excess (*ee*) values were determined by HPLC analysis with a JASCO (JASCOPU-2080) instrument fitted with a Daicel Chiralpak AD-H column/Daicel Chiralcel OD-H and UV-2075 detector (λ fixed at 254 nm). Optical rotations were measured with a JASCO DIP polarimeter. Melting points (mp) were measured in a Büchi B-540 apparatus. Elemental analyses (C, H, N) were carried out by Elementar, vario MICRO CHNS instrument. Infrared (IR) spectra were recorded on an FT-IR spectrometer as thin films using NaCl plates. Suitable X-ray quality crystal of **79j** was grown in hexane and X-ray diffraction studies were carried out at specified temperatures.

5.4.1 General procedures

General Procedure I: Preparation of α-ketophosphonates 72a-e, β-ketoacids 78a-i and catalysts 11-15, 80-81 & 87-89

The α-ketophosphonates **72a-e** following the general procedures reported in the literature.[148] The β-ketoacids **78a-i** were prepared following the literature procedure.[149] The organocatalysts **11-15** and **80-81** are prepared following the literature procedure[81] and as described in Chapter 2. Catalysts **82-84** are commercially available.

Preparation of α-ketophosphonates 72a-e

Diethyl acetylphosphonate 72a

Following the literature[148] procedure, triethyl phosphite (1.50 mL, 9.0 mmol) was slowly added to a solution of acetyl chloride (0.70 mL, 9.90 mmol) in CH_2Cl_2 (15 mL) at 0 °C under argon. The mixture was stirred overnight at room temperature and the solvent was removed under vacuum. The residue was purified by column chromatography using hexanes/ethyl acetate as eluent to give **72a** (1.35 g, 84 %) as colorless liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.37 (6 H, t, J = 7.2 Hz, OCH_2CH_3), 2.48 (3 H, d, J = 5.0 Hz, $COCH_3$), 4.24 (4 H, dq, J_{HP} = 7.2 Hz, OCH_2CH_3) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.5, 17.1, 17.7, 64.2 (2 C), 199.7 (d, $^1J_{C\text{-}P}$ = 178.2 Hz, C=O) ppm; ^{31}P NMR (202 MHz, $CDCl_3$) δ = -2.77 ppm.

Dimethyl acetylphosphonate 72b

Following the literature[148] procedure, trimethyl phosphite (1.06 mL, 9.0 mmol) was slowly added to a solution of acetyl chloride (0.70 mL, 9.90 mmol) in CH_2Cl_2 (15 mL) at 0 °C under argon. The mixture was stirred overnight at room temperature and the solvent

was removed under vacuum. The residue was purified by column chromatography using hexanes/ethyl acetate as eluent to give **72a** (1.09 g, 80 %) as colourless liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 2.78 (3 H, s, $COCH_3$), 3.78 (6 H, s, 2 x OCH_3) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.2, 52.3, 52.4, 199.9 (d, $^{1}J_{C\text{-}P}$ = 177.8 Hz, C=O) ppm; ^{31}P NMR (202 MHz, $CDCl_3$) δ = -2.02 ppm;

Diisopropyl acetylphosphonate 72c

Following the literature[148] procedure, triisopropyl phosphite (2.20 mL, 9.0 mmol) was slowly added to a solution of acetyl chloride (0.70 mL, 9.90 mmol) in CH_2Cl_2 (15 mL) at 0 °C under argon. Then the mixture was stirred overnight at room temperature and the solvent was removed under vacuum. The residue was purified by column chromatography using hexanes/ethyl acetate as eluent to give **72c** (1.31 g, 70 %) as colorless liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.48 (6 H, d, $^{3}J_{H\text{-}H}$ = 6.3 Hz, $OCH(CH_3)_2$), 1.50 (6 H, d, $^{3}J_{H\text{-}H}$ = 6.3 Hz, $OCH(CH_3)_2$), 2.78 (3 H, s, $COCH_3$), 4.86 (2 H, m, 2H, $OCH(CH_3)_2$) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 12.1, 26.1 (2 C), 26.8 (2 C), 73.1 (2 C), 199.3 (d, $^{1}J_{C\text{-}P}$ = 177.4 Hz, C=O) ppm; ^{31}P NMR (202 MHz, $CDCl_3$) δ = -2.02 ppm.

Diisopropyl propionylphosphonate 72d

Following the literature[148] procedure, trimethyl phosphite (2.20 mL, 9.0 mmol) was slowly added to a solution of propionyl chloride (0.87 mL, 9.90 mmol) in CH_2Cl_2 (15 mL) at 0 °C under argon. Then the mixture was stirred overnight at room temperature before the solvent was removed under vacuum. The residue was purified by column

chromatography using hexanes/ethyl acetate as eluent to give **72d** (1.31 g, 70 %) as colourless liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.48 (6 H, d, $^{3}J_{H,H}$ = 6.3 Hz, OCH(CH_3)$_2$), 1.50 (6 H, d, $^{3}J_{H,H}$ = 6.3 Hz, OCH(CH_3)$_2$), 2.78 (3 H, s, $COCH_3$), 4.86 (2 H, m, 2H, OC*H*(CH_3)$_2$) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.2, 15.6, 23.6 (2 C, d, $^{3}J_{C\text{-}P}$ = 5.5 Hz), 23.8 (2 C), 72.8 (2 C, d, $^{2}J_{C\text{-}P}$ = 7.4 Hz), 199.3 (d, $^{1}J_{C\text{-}P}$ = 176.9 Hz, C=O) ppm; ^{31}P NMR (202 MHz, $CDCl_3$) δ = -2.20 ppm.

Diethyl benzoylphosphonate 72e

Following the literature[148] procedure, triethyl phosphite (1.50 mL, 9.0 mmol) was slowly added to a solution of benzoyl chloride (1.15 mL, 9.90 mmol) in CH_2Cl_2 (15 mL) at 0 °C under argon. Then the mixture was stirred overnight at room temperature and the solvent was removed under vacuum. The residue was purified by column chromatography using hexanes/ethyl acetate as eluent to give **72e** (1.31 g, 60 %) as colourless liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.29 (6 H, t, J = 7.4 Hz, OCH_2CH_3), 4.54 (4 H, dq, $J_{H\text{-}P}$ = 7.4 Hz, OCH_2CH_3), 7.51 (2 H, t, $^{3}J_{H,H}$ = 7.5 Hz, Ph), 7.63 (1 H, t, $^{3}J_{H,H}$ = 7.5 Hz, Ph), 8.29 (2 H, $^{3}J_{H\text{-}H}$ = 7.5 Hz, Ph) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 17.5, 17.8, 67.5, 67.6, 128.5 (2 C), 129.6 (2 C), 134.3, 135.4 (d, $^{2}J_{C\text{-}P}$ = 62.6 Hz), 199.3 (d, $^{1}J_{C\text{-}P}$ = 177.4 Hz, C=O) ppm; ^{31}P NMR (202 MHz, $CDCl_3$) δ = -2.20 ppm.

Preparation of β-ketoacids 78a-i

3-Oxo-3-phenylpropanoic acid 78a

Following the literature[149] procedure, a solution of acetophenone (1.20 g, 10.0 mmol, 1.0 equiv) in dry THF (10 mL) was added to NaH (1.10 g, 25.0 mmol, 60% in oil, 2.5 equiv) at 28 ^{o}C. Dimethyl carbonate (1.62 g, 18.0 mmol, 1.8 equiv) was then added to the

reaction mixture at the same temperature. The reaction mixture was heated under reflux for 2-3 h. The reaction mixture was cooled to room temperature and quenched with ice water (5 mL). The pH of the solution was adjusted up to 3 using 3 M HCl solution and extracted with ethyl acetate (3 × 10 mL). The Organic layer was dried over Na_2SO_4 filtered and concentrated under reduced pressure. The resulting crude material is purified by column chromatography using a mixture of ethyl acetate and hexane as eluant to give ethyl 3-oxo-3-phenylpropanoate. A solution of 0.5 M NaOH was added to the ester at room temperature and stirred at room temperature for about 12 h. The reaction mixture was acidified with 3 M HCl solution until adjusts pH up to 3. The reaction mixture was extracted with ethyl acetate (3 × 10 mL). The Organic layer was dried over Na_2SO_4 filtered and concentrated under reduced pressure. Then the resulting crude is purified by column chromatography using a mixture of ethyl acetate and hexane to give 3-oxo-3-phenylpropanoic acid **78a** (0.98 g, 60%) as a white solid. mp 81-83 °C; IR (film): $\bar{\upsilon}$ = 3101, 1742, 1710, 1514, 1474, 1311, 1171, 973, 812, 750, 680 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 3.44 (2 H, s, $COCH_2$), 7.18 (3 H, m, Ph), 7.60 (2 H, m, Ph), 10.09 (1 H, br. s, COOH) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 52.22, 121.45, 121.85 128.74, 129.38, 132.77, 169.43, 174.5, 196.62 ppm; Elemental analysis calcd (%) for $C_9H_8O_3$: calcd. C 65.85, H 4.91; found: C 65.58, H 5.01.

3-(4-Bromophenyl)-3-oxopropanoic acid 78b

The β-ketoacids **78b** was prepared following the procedure for β-ketoacids **78a** from 2-bromo acetophenone (1.98 g, 10.0 mmol, 1.0 equiv) as a solid. Yield: **78b** (1.21 g, 50%). mp 121-123 °C; IR (film): $\bar{\upsilon}$ = 3099, 1739, 1708, 1505, 1463, 1315, 1185, 963, 822, 740, 670 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 3.48 (2 H, s, $COCH_2$), 7.41 (3 H, m, Ar), 7.62

(2 H, m, Ar), 10.28 (1 H, s, COOH) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 52.42, 121.55, 129.03, 129.76, 133.75, 169.73, 192.92 ppm; Elemental analysis calcd (%) for $C_9H_7BrO_3$: calcd. C 44.47, H 2.90; found: C 44.62, H 2.80.

3-(4-Fluorophenyl)-3-oxopropanoic acid 78 c

The β-ketoacids **78c** was prepared following the procedure for β-ketoacids **78a** from 2-fluoro acetophenone (1.38 g, 10.0 mmol, 1.0 equiv) as a pale yellow color solid. Yield: **78c** (0.82 g, 45%). mp 141-143 °C; IR (film): $\bar{\upsilon}$ = 3102, 1749, 1717, 1516, 1473, 1325, 1195, 953, 832, 750, 680 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.56 (2 H, s, $COCH_2$), 7.23 (2 H, t, J = 8.4 Hz, Ar), 8.0 (2 H, dd, J = 5.7, 9.2 Hz, Ar), 11.02 (1 H, s, COOH) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 55.8, 116.6 (2 C, d, $J_{C\text{-}F}$ = 22.6 Hz), 132.5 (2 C, d, $J_{C\text{-}F}$ = 9.6 Hz), 133.8, 166.9 (d, $J_{C\text{-}F}$ = 260.1 Hz), 172.8, 198.2 ppm; Elemental analysis calcd (%) for $C_9H_7FO_3$: calcd. C 59.35, H 3.87; found: C 59.55, H 3.97.

3-(4-Methoxyphenyl)-3-oxopropanoic acid 78d

The β-ketoacids **77d** was prepared following the procedure for β-ketoacids **78a** from 4-methoxy acetophenone (1.50 g, 10.0 mmol, 1.0 equiv) as a white color solid. Yield: **78d** (0.78 g, 40%). mp 179-181 °C; IR (film): $\bar{\upsilon}$ = 3142, 1749, 1717, 1516, 1473, 1325, 1195, 953, 832, 750, 682 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.37 (2 H, s, $COCH_2$), 3.78 (3 H, s, OCH_3), 6.73 (2 H, d, J = 9.2 Hz, Ar), 7.82 (2 H, d, J = 9.2 Hz, Ar), 10.89 (1 H, s, COOH) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 53.8, 55.9, 116.7 (2 C), 131.2, 131.4 (2 C), 165.2, 179.4 ppm; Elemental analysis calcd (%) for $C_{10}H_{10}O_4$: calcd. C 61.85, H 5.19; found: C 61.55, H 5.27.

3-(3-Chlorophenyl)-3-oxopropanoic acid 78e

The β-ketoacids **78e** was prepared following the procedure for β-ketoacids **78a** from 3-chloro acetophenone (1.54 g, 10.0 mmol, 1.0 equiv) as a white color solid, Yield: **78e** (0.83 g, 42%). mp 131-133 °C; IR (film): $\bar{\upsilon}$ = 3121, 1735, 1725, 1526, 1454, 1352, 1187, 961, 825, 750, 672 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 3.72 (2 H, s, COCH_2), 7.52 (1 H, t, J = 8.2 Hz, Ar), 7.54 (1 H, d, J = 8.2 Hz, Ar), 7.92 (1 H, d, J = 7.8 Hz, Ar), 7.94 (1 H, s, Ar), 11.05 (1 H, s, COOH) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): 53.8, 127.2, 128.9, 130.8, 134.1, 134.8, 138.9, 172.5, 190.5 ppm; Elemental analysis calcd (%) for $C_9H_7ClO_3$: calcd. C 54.43, H 3.55; found: C 54.64, H 3.67.

3-(2-Bromophenyl)-3-oxopropanoic acid 78f

The β-ketoacids **78f** was prepared following the procedure for β-ketoacids **78a** from 2-bromo acetophenone (1.98 g, 10.0 mmol, 1.0 equiv) as a white color solid. Yield **78f** (0.95 g, 39%). mp 125-127 °C; IR (film): $\bar{\upsilon}$ = 3112, 1745, 1723, 1536, 1464, 1362, 1197, 951, 835, 760, 682 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 3.52 (2 H, s, COCH_2), 7.56 (1 H, t, J = 8.4 Hz, Ar), 7.59 (1 H, d, J = 8.4 Hz, Ar), 7.79 (1 H, d, J = 7.8 Hz, Ar), 7.95 (1 H, s, Ar), 11.06 (1 H, s, COOH) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): 53.9, 128.2, 128.7, 131.0, 134.7, 134.9, 137.9, 173.5, 191.5 ppm; Elemental analysis calcd (%) for $C_9H_7BrO_3$: calcd. C 44.47, H 2.90; found: C 44.67, H 2.72.

3-(2-Chlorophenyl)-3-oxopropanoic acid 78g

The β-ketoacids **78g** was prepared following the procedure for β-ketoacids **78a** from 2-chloro acetophenone (1.54 g, 10.0 mmol, 1.0 equiv) as a white color solid Yield **78g** (0.74 g, 42%). mp 138-140 °C; IR (film): $\bar{\upsilon}$ = 3121, 1735, 1725, 1526, 1454, 1352, 1187, 961, 825, 750, 672 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 3.65 (2 H, s, COCH_2), 7.30 (1 H, td, J = 1.7, 7.8 Hz, Ar), 7.38 (1 H, t, J = 7.5 Hz, Ar), 7.61-7.57 (2 H, m, Ar), 11.12 (1 H, s,

COOH) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 54.2, 126.8 (2 C), 130.5, 132.3, 135.6, 139.1, 172.5, 196.0 ppm; Elemental analysis calcd (%) for $C_9H_7ClO_3$: calcd. C 54.43, H 3.55; found: C 54.77, H 3.66.

3-(2-Methoxyphenyl)-3-oxopropanoic acid 78h

The β-ketoacids **78h** was prepared following the procedure for β-ketoacids **78a** from 2-methoxy acetophenone (1.50 g, 10.0 mmol, 1.0 equiv) as a white colour solid Yield **78h** (0.84 g, 40%). mp 148-151 °C; IR (film): $\bar{\upsilon}$ = 3132, 1732, 1710, 1526, 1463, 1345, 1184, 963, 842, 760, 673 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.84 (2 H, s, COCH_2), 3.90 (3 H, s, OCH_3), 6.95 (1 H, d, J = 8.0 Hz, Ar), 7.00 (1 H, t, J = 7.7 Hz, Ar), 7.47 (1 H, td, J = 1.6, 8.2 Hz, Ar), 7.70 (1 H, dd, J = 1.6, 8.2 Hz, Ar), 11.14 (1 H, s, COOH) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 54.2, 56.1, 112.1, 121.1, 125.2, 132.3,134.7, 159.2, 171.9, 193.1 ppm; Elemental analysis calcd (%) for $C_{10}H_{10}O_4$: calcd. C 61.85, H 5.19; found: C 61.65, H 5.24.

3-(Naphthalen-2-yl)-3-oxopropanoic acid 78i

The β-ketoacids **78i** was prepared following the procedure for β-ketoacids **78a** from 1-(naphthalen-2-yl) ethanone (1.70 g, 10.0 mmol, 1.0 equiv) as a white color solid. Yield: **78i** (0.84 g, 39%). mp 147-149 °C; IR (film): $\bar{\upsilon}$ = 3142, 1742, 1720, 1536, 1473, 1355, 1164, 943, 862, 780, 693 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.80 (2 H, s, COCH_2), 7.60-7.54 (2 H, m, Napthyl), 7.67-7.63 (1 H, m, Napthyl), 7.92 (1 H, d, J = 7.7 Hz, Napthyl), 8.00 (1 H, d, J = 7.7 Hz, Napthyl), 8.12 (1 H, d, J = 8.6 Hz, Napthyl), 8.66 (1 H, d, J = 9.2 Hz, Napthyl), 11.07 (1 H, s, COOH) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 52.9, 124.6, 127.1, 127.8, 128.9, 129.6, 129.8 130.2, 132.6, 135.0, 171.2, 193.2 ppm;

Elemental analysis calcd (%) for $C_{13}H_{10}O_3$: calcd. C 72.89, H 4.71; found: C 72.95, H 4.80.

5.4.2 General Procedure II for the preparation *rac*-79a-q

In an oven and vacuum-dried flask, β-ketoacid **78** (0.13 mmol, 1.3 equiv), a mixture of catalysts **12** (0.01 mmol, 0.1 equiv) and **14** (0.01 mmol, 0.1 equiv) were taken with 0.5 mL of freshly distilled toluene under argon. Then, a solution of α-ketophosphonate **72** (0.1 mmol, 1.0 equiv) in toluene (0.5 mL) was added slowly to the reaction mixture and stirred at 28 ºC. Upon consumption of the α-ketophosphonate (monitored by TLC), the reaction mixture was directly subjected to column chromatography on silica gel to afford the corresponding products *rac*-**79a-q**.

General Procedure III for the preparation chiral tertiary α-hydroxy phosphonate ester 79a-q

In an oven and vacuum-dried flask, β-ketoacid **78** (0.26 mmol, 1.3 equiv) and catalyst **80** (0.02 mmol, 0.2 equiv) were taken with 0.5 mL of freshly distilled toluene under argon. Then, a solution of α-ketophosphonate **72** (0.2 mmol, 1.0 equiv) in toluene (0.5 mL) was added slowly to the reaction mixture and stirred at 28 ºC. Upon consumption of the α-ketophosphonate (monitored by TLC), the reaction mixture was directly subjected to column chromatography on silica gel to afford the corresponding products **79a-q**

(*R*)-Diethyl 2-hydroxy-4-oxo-4-phenylbutan-2ylphosphonate 79a

The product **79a** was obtained following the *General procedure* **5.4.1 III** from α-ketophosphonate **72a** (36.0 mg, 0.2 mmol, 1.0 equiv) β-ketoacid **78a** (42.6 mg, 0.26 mmol, 1.3 equiv) using catalyst **80** (22.6 mg, 0.04 mmol, 20 mol %) and toluene (1.0 mL)**.** Colourless liquid **Yield: 79a** (42.0 mg, 70%); IR (film): $\bar{\upsilon}$ = 3288, 2982, 2360, 2341,

1764, 1597, 1449, 1393, 1049, 1023, 956 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.24 (3 H, t, J = 7.0 Hz, OCH_2CH_3), 1.28 (3 H, t, J = 6.5 Hz, OCH_2CH_3), 1.56 (3 H, d, J = 15.0 Hz, CH_3COH), 3.01 (1 H, t, J = 16.5 Hz, $COCH_2$), 3.65 (1 H, dd, J = 7.5, 16.5 Hz, $COCH_2$), 4.18-4.08 (4 H, m, OCH_2CH_3), 5.00 (1 H, d, J = 11.0 Hz, CO*H*), 7.46 (2 H, t, J = 7.5 Hz, Ph), 7.58 (1 H, t, J = 7.5 Hz, Ph), 7.96 (2 H, d, J = 7.5 Hz, Ph) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.3 (d, $J_{C\text{-}P}$ = 5.6 Hz), 16.4 (d, $J_{C\text{-}P}$ = 4.75 Hz), 23.9 (d, $J_{C\text{-}P}$ = 3.0 Hz), 42.4 (d, $J_{C\text{-}P}$ = 3.0 Hz), 63.0 (d, $J_{C\text{-}P}$ = 7.5 Hz), 63.1 (d, $J_{C\text{-}P}$ = 7.6 Hz), 72.5 (d, $J_{C\text{-}P}$ = 168.8 Hz), 128.4 (2 C), 128.7 (2 C), 133.8, 137.0, 201.0 (d, $J_{C\text{-}P}$ = 7.5Hz) ppm; ^{31}P-NMR (121.5 MHz, $CDCl_3$): δ = 24.6 ppm; $[\alpha]_D^{28}$ = -38.7 (c = 0.80 in CH_3OH); The enantiomeric excess was determined by HPLC with a Daicel Chiralcel OD-H column [λ = 254 nm], eluent: 2-propanol/hexane (3/97), flow rate = 0.5 mL/min, t_{minor} = 33.44 min (15.84%), t_{major} = 35.31 min (84.16%).

(*R*)-Dimethyl 2-hydroxy-4-oxo-4-phenylbutan-2ylphosphonate 79b

The product **79b** was obtained following the *General procedure* **5.4.1 III** from α-ketophosphonate **72b** (30.4 mg, 0.2 mmol, 1.0 equiv) β-ketoacid **78a** (42.6 mg, 0.26 mmol, 1.3 equiv) using catalyst **80** (22.6 mg, 0.04 mmol, 20 mol %) and toluene (1.0 mL)**.** Colourless liquid Yield: **79b** (45 mg, 82%); IR (film): $\bar{\upsilon}$ = 3288, 2982, 2360, 2341, 1764, 1597, 1449, 1393, 1049, 1023, 956 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.58 (3 H, d, J =15.0 Hz, CH_3), 3.07 (1 H, t, J = 17.0 Hz, $COCH_2$), 3.65 (1 H, dd, J = 7.5, 17.0 Hz, $COCH_2$), 3.74 (3 H, d, J = 10.0 Hz, OCH_3), 3.82 (3H, d, J = 10.5 Hz, OCH_3), 5.08 (1 H, bs, OH), 7.50 (2 H, t, J = 7.5 Hz, Ph), 7.61 (1H, t, J = 7.5 Hz, Ph), 7.97 (2 H, d, J = 7.5 Hz, Ph) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 23.9 (d, $J_{C\text{-}P}$ = 3.0 Hz), 42.5 (d, $J_{C\text{-}P}$ = 4.7

Hz), 53.7 (d, $J_{C\text{-}P}$ = 7.6 Hz), 53.8 (d, $J_{C\text{-}P}$ = 7.5 Hz), 72.8 (d, $J_{C\text{-}P}$ = 167.9 Hz), 128.4 (2 C), 128.8 (2 C), 133.8, 137.0, 200.8 (d, $J_{C\text{-}P}$ = 9.5 Hz) ppm; ^{31}P-NMR (202.5 MHz, $CDCl_3$): δ = 26.8 ppm; $[\alpha]_D^{28}$ = -33.13 (*c* = 1.66 in CH_3OH).

(*R*)-Diisopropyl 2-hydroxy-4-oxo-4-phenylbutan-2ylphosphonate 79c

The product **79c** was obtained following the *General procedure* **5.4.1 III** from α-ketophosphonate **72c** (41.6 mg, 0.2 mmol, 1.0 equiv) β-ketoacid **78a** (42.6 mg, 0.26 mmol, 1.3 equiv) using catalyst **80** (22.6 mg, 0.04 mmol, 20 mol %) and toluene (1.0 mL)**.** Colourless liquid Yield: **79c** (55 mg, 84%); IR (film): $\bar{\upsilon}$ = 3285, 2980, 2935, 2342, 1675, 1580, 1105, 987, 752 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.35-1.25 (12 H, m, 2 x $CH(CH_3)_2$), 1.55 (3 H, d, *J* =16.0 Hz, CH_3), 2.99 (1 H, t, *J* = 16.0 Hz, $COCH_2$), 3.65 (1 H, dd, *J* = 7.5, 16.5 Hz, $COCH_2$), 4.78-4.70 (2 H, m, 2 x $OCH(CH_3)_2$), 4.85 (1 H, d, *J* = 10.0 Hz, OH), 7.47 (2 H, t, *J* = 7.5 Hz, Ph), 7.59 (1 H, t, *J* = 7.5 Hz, Ph), 7.98 (2 H, d, *J* = 7.5 Hz, Ph) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 23.8-23.6 (3 C, m), 24.0 (d, $J_{C\text{-}P}$ = 5.5 Hz), 24.1 (d, $J_{C\text{-}P}$ = 1.3 Hz), 42.5 (d, $J_{C\text{-}P}$ = 5.0 Hz), 71.0 (d, $J_{C\text{-}P}$ = 170.3 Hz), 71.5 (d, $J_{C\text{-}P}$ = 5.8 Hz), 71.6 (d, $J_{C\text{-}P}$ = 5.8 Hz), 128.5 (2 C), 128.6 (2 C), 133.6, 137.4, 200.8 (d, $J_{C\text{-}P}$ = 9.5Hz) ppm; ^{31}P-NMR (202.5 MHz, $CDCl_3$): δ = 23.1 ppm; $[\alpha]_D^{28}$ = -31.3 (*c* = 1.34 in CH_3OH); The enantiomeric excess was determined by HPLC with a Daicel Chiralcel OD-H column [λ = 254 nm], eluent: 2-propanol/hexane (3/97), flow rate = 0.5 mL/min, t_{minor} = 19.38 min (14.93%), t_{major} = 35.31 min (85.07%).

(*R*)-Diisopropyl 3-hydroxy-1-oxo-4-phenylpentan-3ylphosphonate 79d

The product **79d** was obtained following the *General procedure* **5.4.1 III** from α-ketophosphonate **72d** (44.4 mg, 0.2 mmol, 1.0 equiv) β-ketoacid **78a** (42.6 mg, 0.26 mmol, 1.3 equiv) using catalyst **80** (22.6 mg, 0.04 mmol, 20 mol %) and toluene (1.0 mL)**.** Colourless liquid Yield: **79d** (44 mg, 64%); IR (film): $\bar{\upsilon}$ = 3292, 2979, 2940, 2880, 2360, 2341, 1675, 1597, 1457, 1049, 1023, 986, 771 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.06 (12 H, m, 2 x $CH(CH_3)_2$), 1.26 (3 H, t, J = 6.5 Hz, CH_2CH_3), 1.90-1.82 (1 H, m, CH_2CH_3), 2.02-1.91 (1 H, m, CH_2CH_3), 2.91 (1 H, dd, J = 16.0, 21.5 Hz, $COCH_2$), 3.60 (1 H, dd, J = 7.0, 16.0 Hz, $COCH_2$), 4.75-4.67 (2 H, m, 2 x $OCH(CH_3)_2$), 5.08 (1 H, d, J = 7.5 Hz, OH), 7.48 (2 H, t, J = 7.5 Hz, Ph), 7.60 (1 H, t, J = 7.5 Hz, Ph), 7.99 (2 H, d, J = 7.5 Hz, Ph) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 7.6 (d, $J_{C\text{-}P}$ = 5.8 Hz), 24.1 (d, $J_{C\text{-}P}$ = 5.8 Hz), 29.6 (d, $J_{C\text{-}P}$ = 3.8 Hz), 39.4 (d, $J_{C\text{-}P}$ = 5.8 Hz), 71.3 (t, $J_{C\text{-}P}$ = 7.8 Hz), 74.4 ($J_{C\text{-}P}$ = 166.9 Hz), 128.5 (3 C), 133.5 (2 C), 137.5, 200.8 (d, $J_{C\text{-}P}$ = 7.6 Hz) ppm; ^{31}P-NMR (202.5 MHz, $CDCl_3$): δ = 23.4 ppm; $[\alpha]_D^{28}$ = -26.12 (c = 1.21 in CH_3OH); The enantiomeric excess was determined by HPLC with a Daicel Chiralcel OD-H column [λ = 254 nm], eluent: 2-propanol/hexane (3/97), flow rate = 0.5 mL/min, t_{minor} = 16.35 min (22.72%), t_{major} = 35.31 min (77.28%).

(*R*)-Diethyl 1-hydroxy-3-oxo-1,3-diphenylpropylphosphonate 79e

The product **79e** was obtained following the *General procedure* **5.4.1 III** from α-ketophosphonate **72e** (48.4 mg, 0.2 mmol, 1.0 equiv) β-ketoacid **78a** (42.6 mg, 0.26 mmol, 1.3 equiv) using catalyst **80** (22.6 mg, 0.04 mmol, 20 mol %) and toluene (1.0 mL)**.** Colourless liquid Yield: **79e** (48 mg, 64%); IR (film): $\bar{\upsilon}$ = 3295, 2985, 2935, 2889, 2366, 2351, 1665, 1587, 1492, 1427, 1041, 1030, 976, 761 cm^{-1}; ^{1}H NMR (500 MHz,

$CDCl_3$): δ = 1.09 (3 H, t, J = 7.0 Hz, OCH_2CH_3), 1.31 (3 H, t, J = 7.0 Hz, OCH_2CH_3), 3.70-3.65 (1 H, m, $COCH_2$), 3.90-3.80 (2 H, m, $COCH_2$, OCH_2CH_3), 4.02 (1 H, dd, J = 10.5, 17.5 Hz, OCH_2CH_3), 4.22-4.13 (2 H, m, OCH_2CH_3), 5.43 (1 H, d, J = 22.0 Hz, OH), 7.28-7.25 (1 H, m, Ph), 7.35 (2 H, t, J = 7.5 Hz, Ph), 7.47 (2 H, t, J = 7.5 Hz, Ph), 7.60 (1 H, t, J = 7.5 Hz, Ph), 7.69-7.67 (2 H, m, Ph), 7.96 (2 H, d, J = 7.5 Hz, Ph) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.2 (d, $J_{C\text{-}P}$ = 4.8 Hz), 16.3 (d, $J_{C\text{-}P}$ = 5.8 Hz), 42.7 (d, $J_{C\text{-}P}$ = 2.9 Hz), 42.7 (d, $J_{C\text{-}P}$ = 2.9 Hz), 63.4 (d, $J_{C\text{-}P}$ = 7.6 Hz), 63.9 (d, $J_{C\text{-}P}$ = 6.6 Hz), 126.1 (d, $J_{C\text{-}P}$ = 3.8Hz), 127.6 (d, $J_{C\text{-}P}$ = 3.8 Hz), 128.1 (d, $J_{C\text{-}P}$ = 2.9 Hz), 128.3 (2 C), 128.7 (2 C), 133.9, 136.8, 136.9, 139.9, 200.8 (d, $J_{C\text{-}P}$ = 12.3 Hz) ppm; ^{31}P-NMR (202.5 MHz, $CDCl_3$): δ = 20.7 ppm; $[\alpha]_D^{28}$ = -16.3 (c = 1.75 in CH_3OH); The enantiomeric excess was determined by HPLC with a Daicel Chiralcel OJ-H column [λ = 254 nm], eluent: 2-propanol/hexane (10/90), flow rate = 0.5 mL/min, t_{minor} = 15.77 min (65.25%), t_{major} = 28.33 min (34.75%).

(*R*)-Diethyl 4-(4-bromophenyl)-2-hydroxy-4-oxobutan- 2-ylphosphonate 79f

The product **79f** was obtained following the *General procedure* **5.4.1 III** from α-ketophosphonate **72a** (36.0 mg, 0.1 mmol, 1.0 equiv) β-ketoacid **78b** (63.2 mg, 0.26 mmol, 1.3 equiv) using catalyst **80** (22.6 mg, 0.04 mmol, 20 mol %) and toluene (1.0 mL)**.** Colourless liquid Yield: **79f** (53 mg, 70%); IR (film): $\bar{\upsilon}$ = 3293, 2982, 2360, 2341, 1677, 1580, 1395, 1049, 1025, 987, 792 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.26 (3 H, t, J = 7.0 Hz, OCH_2CH_3), 1.31 (3 H, t, J = 7.0 Hz, OCH_2CH_3), 1.56 (3 H, d, J = 15.5 Hz, $C(OH)CH_3$), 2.95 (1 H, d, J = 16.5 Hz, $COCH_2$), 3.63 (1 H, dd, J = 7.5, 16.5 Hz, $COCH_2$), 4.20-4.09 (4 H, m, OCH_2CH_3), 4.81 (1 H, d, J = 10.0 Hz, OH), 7.61 (2 H, d, J = 8.5 Hz, Ar), 7.84 (2 H, d, J = 8.0 Hz, Ar) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.3 (d,

$J_{C\text{-}P}$ = 5.8 Hz), 16.4 (d, $J_{C\text{-}P}$ = 5.8 Hz), 23.8 (d, $J_{C\text{-}P}$ = 2.8 Hz), 42.6 (d, $J_{C\text{-}P}$ = 5.6 Hz), 63.0 (d, $J_{C\text{-}P}$ = 7.5 Hz), 63.2 (d, $J_{C\text{-}P}$ = 7.6 Hz), 71.8 (d, $J_{C\text{-}P}$ = 167.9 Hz), 129.1, 129.9 (2 C), 132.0 (2 C), 135.9, 199.6 (d, $J_{C\text{-}P}$ = 9.5 Hz) ppm; ^{31}P-NMR (121.5 MHz, $CDCl_3$): δ = 24.4 ppm; $[\alpha]_D^{28}$ = -5.8 (*c* = 2.17 in CH_3OH); The enantiomeric excess was determined by HPLC with a Daicel Chiralcel OJ-H column [λ = 254 nm], eluent: 2-propanol/hexane (3/97), flow rate = 0.5 mL/min, t_{minor} = 27.76 min (18.11%), t_{major} = 29.40 min (81.89%).

(*R*)-Diisopropyl 4-(4-fluorophenyl)-2-hydroxy-4-oxobutan-2-ylphosphonate 79g

The product **79g** was obtained following the *General procedure* **5.4.1 III** from α-ketophosphonate **72c** (41.6 mg, 0.2 mmol, 1.0 equiv) β-ketoacid **78c** (47.3 mg, 0.26 mmol, 1.3 equiv) using catalyst **80** (22.6 mg, 0.04 mmol, 20 mol %) and toluene (1.0 mL)**.** Colourless liquid Yield: **79g** (57 mg, 82%); IR (film): $\bar{\upsilon}$ = 3293, 2981, 2360, 2341, 1665, 1580, 1395, 1049, 1025, 987, 792 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.30-1.24 (12 H, m, 2 x $CH(CH_3)_2$); 1.52 (3 H, d, *J* = 15.0 Hz, $C(OH)CH_3$), 2.91 (1 H, t, *J* = 16.0 Hz, $COCH_2$), 3.61 (1 H, dd, *J* = 7.5, 15.5 Hz, $COCH_2$), 4.75-4.70 (3 H, m, 2 x $OCH(CH_3)_2$ & O*H*), 7.13 (2 H, t, *J* = 8.2 Hz, Ar), 8.0 (2 H, dd, *J* = 5.5, 9.0 Hz, Ar) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 23.87-23.76 (3 C, m), 24.14-24.08 (2 C, m), 42.6 (d, $J_{C\text{-}P}$ = 5.6 Hz), 71.4 (d, $J_{C\text{-}P}$ = 169.8 Hz), 71.5 (d, $J_{C\text{-}P}$ = 7.6 Hz), 71.6 (d, $J_{C\text{-}P}$ = 7.6 Hz), 115.7 (2 C, d, $J_{C\text{-}F}$ = 21.8 Hz), 131.3 (2 C, d, $J_{C\text{-}F}$ = 9.4 Hz), 133.9, 166.1 (d, $J_{C\text{-}F}$ = 255.1 Hz), 199.0 (d, $J_{C\text{-}P}$ = 9.5 Hz) ppm; ^{31}P-NMR (202.5 MHz, $CDCl_3$): δ = 23.1 ppm; $[\alpha]_D^{28}$ = -5.8 (*c* = 2.17 in CH_3OH); The enantiomeric excess was determined by HPLC with a Daicel Chiralcel OD-H column [λ = 254 nm], eluent: 2-propanol/hexane (3/97), flow rate = 0.5 mL/min, t_{minor} = 15.81 min (21.26%), t_{major} = 16.40 min (78.74%).

(*R*)-Diisopropyl 4-(4-methoxyphenyl)-2-hydroxy-4-oxobutan-2-ylphosphonate 79h

The product **79h** was obtained following the *General procedure* **5.4.1 III** from α-ketophosphonate **72c** (41.6 mg, 0.2 mmol, 1.0 equiv) β-ketoacid **78d** (50.5 mg, 0.26 mmol, 1.3 equiv) using catalyst **80** (22.6 mg, 0.04 mmol, 20 mol %) and toluene (1.0 mL)**.** Colourless liquid Yield: **79h** (62.0 mg, 70%); IR (film): $\bar{\upsilon}$ = 3294, 2980, 2933, 2360, 2341, 1667, 1600, 1225, 1174, 988 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.32-1.25 (12 H, m, 2 x CH(CH_3)$_2$), 1.53 (3 H, d, J = 15.3 Hz, C(OH)CH_3), 2.94 (1 H, t, J = 16.0 Hz, COCH_2), 3.57 (1 H, dd, J = 7.0, 16.0 Hz, COCH_2), 3.88 (3 H, s, OCH_3), 4.77-4.71 (2 H, m, 2 X OCH(CH_3)$_2$), 5.01 (I H, d, J = 11.0 Hz, OH), 6.94 (2 H, d, J = 9.0 Hz, Ar), 7.96 (2 H, d, J = 9.0 Hz, Ar) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 23.90-23.76 (3 C, m), 24.12-24.09 (2 C, m), 41.9 (d, $J_{C\text{-}P}$ = 4.8 Hz), 55.5, 71.3 (d, $J_{C\text{-}P}$ = 5.0 Hz), 71.4 (d, $J_{C\text{-}P}$ = 4.8 Hz), 71.6 (d, $J_{C\text{-}P}$ = 170.4 Hz), 113.8 (2 C), 130.4, 130.9 (2 C), 164.1, 199.4 (d, $J_{C\text{-}P}$ = 9.6 Hz) ppm; ^{31}P-NMR (202.5 MHz, $CDCl_3$): δ = 23.2 ppm; $[\alpha]_D^{28}$ = -24.8 (c = 1.30, CH_3OH); The enantiomeric excess was determined by HPLC with a Daicel Chiralcel OD-H column [λ = 254 nm], eluent: 2-propanol/hexane (3/97), flow rate = 0.5 mL/min, t_{minor} = 30.38 min (22.20%), t_{major} = 32.81 min (77.80%).

(*R*)-Diisopropyl4-(3-chlorophenyl)-2-hydroxy-4-oxobutan-2-ylphosphonate 79i

The product **79i** was obtained following the *General procedure* **5.4.1 III** from α-ketophosphonate **72c** (41.6 mg, 0.2 mmol, 1.0 equiv) β-ketoacid **78e** (51.6 mg, 0.26 mmol, 1.3 equiv) using catalyst **80** (22.6 mg, 0.04 mmol, 20 mol %) and toluene (1.0 mL)**.** Colourless liquid Yield: **79i** (52.0 mg, 72%); IR (film): $\bar{\upsilon}$ = 3292, 2980, 2360, 2341, 1681, 1571, 1385, 1375, 1105, 990cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.31-1.28 (12

H, m, 2 x CH(CH_3)$_2$), 1.53 (3 H, d, J = 15.0 Hz, C(OH)CH_3), 2.90 (1 H, t, J = 15.5 Hz, COCH_2), 3.61 (1 H, dd, J = 8.0, 15.5 Hz, COCH_2), 4.73 (2 H, q, J = 7.5 Hz, 2 x OCH(CH$_3$)$_2$), 7.40 (1 H, t, J = 8.0 Hz, Ar), 7.53 (1 H, d, J = 8.0 Hz, Ar), 7.85 (1 H, d, J = 7.5 Hz, Ar), 7.94 (1 H, s, Ar), the OH proton could not be detected, ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 23.5 (d, $J_{C\text{-}P}$ = 3.0 Hz), 23.74 (d, $J_{C\text{-}P}$ = 5.0 Hz), 23.8 (d, $J_{C\text{-}P}$ = 5.0 Hz), 24.05 (d, $J_{C\text{-}P}$ = 3.2 Hz), 24.07 (d, $J_{C\text{-}P}$ = 3.2 Hz), 43.0 (d, $J_{C\text{-}P}$ = 5.4 Hz), 71.3 (d, $J_{C\text{-}P}$ = 169.6 Hz), 71.8 (2 C, t, $J_{C\text{-}P}$ = 7.5 Hz), 126.6, 128.6, 129.9, 133.3, 134.9, 139.1, 199.1 (d, $J_{C\text{-}P}$ = 9.6 Hz) ppm; ^{31}P-NMR (202.5 MHz, $CDCl_3$): δ = 23.1 ppm; $[\alpha]_D^{28}$ = -2.6 (c = 5.22 in CH_3OH); The enantiomeric excess was determined by HPLC with a Daicel Chiralcel OD-H column [λ = 254 nm], eluent: 2-propanol/hexane (3/97), flow rate = 0.5 mL/min, t_{minor} = 15.13 min (17.26%), t_{major} = 15.72 min (82.74%).

(*R*)-Diisopropyl4-(2-bromophenyl)-2-hydroxy-4-oxobutan-2-ylphosphonate 79j

The product **79j** was obtained following the *General procedure* **5.4.1 III** from α-ketophosphonate **72c** (41.6 mg, 0.2 mmol, 1.0 equiv) β-ketoacid **78f** (63.2 mg, 0.26 mmol, 1.3 equiv) using catalyst **80** (22.6 mg, 0.04 mmol, 20 mol %) and toluene (1.0 mL)**.** Colourless liquid Yield: **79j** (64.0 mg, 79%); IR (film): ῡ = 3280, 2980, 2360, 2341, 1694, 1587, 1385, 1375, 1105, 990, 758 cm^{-1}; ; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.23 (3 H, d, J = 6.5 Hz, CH(CH_3)$_2$), 1.34-1.30 (9 H, m, CH(CH_3)$_2$), 1.53 (3 H, d, J = 15.5 Hz, C(OH)CH_3), 3.09 (1 H, t, J = 16.0 Hz, COCH_2), 3.56 (1 H, dd, J = 7.0, 16.0 Hz, COCH_2), 4.42 (1 H, d, J = 10.5 Hz, OH), 4.81-4.67 (2 H, m, OCH(CH$_3$)$_2$), 7.30 (1 H, td, J = 1.7, 7.8 Hz, Ar), 7.38 (1 H, t, J = 7.5 Hz, Ar), 7.61-7.57 (2 H, m, Ar) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.47 (d, $J_{C\text{-}P}$ = 2.0 Hz), 23.72 (d, $J_{C\text{-}P}$ = 2.8 Hz), 23.76 (d, $J_{C\text{-}P}$ = 2.8

Hz), 24.05 (d, $J_{C\text{-}P}$ = 2.8 Hz), 24.16 (d, $J_{C\text{-}P}$ = 2.8 Hz), 47.3 (d, $J_{C\text{-}P}$ = 4.8 Hz), 71.3 (d, $J_{C\text{-}P}$ = 169.6 Hz), 71.8 (2 C, t, $J_{C\text{-}P}$ = 7.5 Hz), 118.7, 127.4, 129.5, 131.9, 133.6, 141.6, 203.9 (d, $J_{C\text{-}P}$ = 9.6 Hz) ppm; ^{31}P-NMR (202.5 MHz, $CDCl_3$): δ = 22.8 ppm; $[\alpha]_D^{28}$ = -4.8 (*c* = 4.27 in CH_3OH); The enantiomeric excess was determined by HPLC with a Daicel Chiralcel OD-H column [λ = 254 nm], eluent: 2-propanol/hexane (3/97), flow rate = 0.5 mL/min, t_{major} = 18.55 min (93.65%), t_{minor} = 20.54 min (6.35%).

(*R*)-Diethyl4-(2-bromophenyl)-2-hydroxy-4-oxobutan-2-ylphosphonate 79k

The product **79k** was obtained following the *General procedure* **5.4.1 III** from α-ketophosphonate **72a** (36.0 mg, 0.2 mmol, 1.0 equiv) β-ketoacid **78f** (63.2 mg, 0.26 mmol, 1.3 equiv) using catalyst **80** (22.6 mg, 0.04 mmol, 20 mol %) and toluene (1.0 mL)**.** Colourless liquid Yield: 79k (58.0 mg, 76%); IR (film): $\bar{\upsilon}$ = 3282, 2983, 2924, 2360, 2341, 1695, 1587, 1097, 1049, 1023, 757 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): *δ* = 1.33-1.29 (6 H, m, OCH_2CH_3), 1.58 (3 H, d, *J* = 15.5 Hz, $C(OH)CH_3$), 3.13 (1 H, t, *J* = 16.0 Hz, $COCH_2$), 3.58 (1 H, dd, *J* = 7.0, 17.0 Hz, $COCH_2$), 4.22-4.15 (4 H, m, OCH_2CH_3), 4.59 (1 H, d, *J* = 10.0 Hz, OH), 7.31 (1 H, t, *J* = 7.5 Hz, Ar), 7.39 (1 H, t, *J* = 7.5 Hz, Ar), 7.56 (1 H, d, *J* = 7.0 Hz, Ar), 7.61 (1 H, d, *J* = 7.5 Hz, Ar) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): *δ* = 16.4 (d, $J_{C\text{-}P}$ = 5.8 Hz), 23.6 (d, $J_{C\text{-}P}$ = 4.2 Hz), 29.6 (d, $J_{C\text{-}P}$ = 4.8 Hz), 47.2 (d, $J_{C\text{-}P}$ = 5.2 Hz), 63.0 (d, $J_{C\text{-}P}$ = 7.6 Hz), 63.2 (d, $J_{C\text{-}P}$ = 7.6 Hz), 72.0 (d, $J_{C\text{-}P}$ = 167.9 Hz), 118.5, 127.5, 129.4, 132.1, 133.8, 141.2, 203.9 (d, $J_{C\text{-}P}$ = 10.5 Hz) ppm; ^{31}P-NMR (202.5 MHz, $CDCl_3$): *δ* = 24.5 ppm; $[\alpha]_D^{28}$ = -16.8 (*c* = 1.16 in CH_3OH); The enantiomeric excess was determined by HPLC with a Daicel Chiralcel OD-H column [λ

= 254 nm], eluent: 2-propanol/hexane (3/97), flow rate = 0.5 mL/min, t_{major} = 34.95 min (91.69%), t_{minor} = 40.10 min (8.31%).

(*R*)-Diisopropyl 4-(2-chlorophenyl)-2-hydroxy-4-oxobutan-2-ylphosphonate 79l

The product **79l** was obtained following the *General procedure* **5.4.1 III** from α-ketophosphonate **72c** (41.6 mg, 0.2 mmol, 1.0 equiv) β-ketoacid **78g** (51.6 mg, 0.26 mmol, 1.3 equiv) using catalyst **80** (22.6 mg, 0.04 mmol, 20 mol %) and toluene (1.0 mL)**.** Colourless liquid Yield: **79l** (53.0 mg, 73%); IR (film): $\bar{\upsilon}$ = 3277, 2980, 2936, 2874, 2360, 2341, 1697, 1590, 1486, 1386, 1023, 989, 766 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 1.21 (3 H, d, J = 6.5Hz, OCH(CH_3)$_2$), 1.33-1.28 (9 H, m, CH(CH_3)$_2$), 1.52 (3 H, d, J = 15.0 Hz, C(OH)CH_3), 3.07 (1 H, t, J = 16.5 Hz, COCH_2), 3.57 (1 H, dd, J = 7.5, 16.5 Hz, COCH_2), 4.48 (1 H, d, J = 10.0 Hz, OH), 4.71-4.65 (1 H, m, OCH(CH_3)$_2$), 4.79-4.73 (1 H, m, OCH(CH_3)$_2$), 7.34-7.31 (1 H, m, Ar), 7.40-7.38 (2 H, m, Ar), 7.60 (1 H, d, J = 7.0 Hz, Ar) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 23.6 (d, $J_{C\text{-}P}$ = 2.1 Hz), 23.7 (2 C, t, $J_{C\text{-}P}$ = 5.3 Hz), 24.1 (d, $J_{C\text{-}P}$ = 3.1Hz), 24.2 (d, $J_{C\text{-}P}$ = 3.1 Hz), 47.5 (d, $J_{C\text{-}P}$ = 5.6 Hz), 71.3 (d, $J_{C\text{-}P}$ = 7.5 Hz), 71.67 (d, $J_{C\text{-}P}$ = 169.9 Hz), 71.7 (d, $J_{C\text{-}P}$ = 7.6 Hz), 126.9, 129.8, 130.4, 131.0, 132.0, 139.5 (d, $J_{C\text{-}P}$ = 1.8 Hz), 203.4 (d, $J_{C\text{-}P}$ = 10.4 Hz) ppm; ^{31}P-NMR (202.5 MHz, $CDCl_3$): δ = 22.8 ppm; $[\alpha]_D^{28}$ = -1.15 (*c* = 0.64 in CH_3OH); The enantiomeric excess was determined by HPLC with a Daicel Chiralcel OD-H column [λ = 254 nm], eluent: 2-propanol/hexane (3/97), flow rate = 0.5 mL/min, t_{major} = 16.96 min (91.59%), t_{minor} = 18.35 min (8.41%).

(*R*)-Diethyl4-(2-chlorophenyl)-2-hydroxy-4-oxobutan-2-ylphosphonate 79m

The product **79m** was obtained following the *General procedure* **5.4.1 III** from α-ketophosphonate **72a** (36.0 mg, 0.2 mmol, 1.0 equiv) β-ketoacid **78g** (51.6 mg, 0.26 mmol, 1.3 equiv) using catalyst **80** (22.6 mg, 0.04 mmol, 20 mol %) and toluene (1.0 mL)**.** Colourless liquid Yield: **79m** (47.0 mg, 70%); IR (film): $\bar{\upsilon}$ = 3288, 2957, 2854, 2360, 2341, 1693, 1590, 1469, 1053, 1031, 832, 776 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.30 (6 H, q, J = 7.5 Hz, 2 x OCH_2CH_3), 1.56 (3 H, d, J = 15.0 Hz, $C(OH)CH_3$), 3.13 (1 H, t, J = 16.5 Hz, $COCH_2$), 3.60 (1 H, dd, J = 7.0, 16.5 Hz, $COCH_2$), 4.21-4.12 (4 H, m, 2 x OCH_2CH_3), 4.61 (1 H, d, J = 10.5 Hz, OH), 7.36-7.33 (1 H, m, Ar), 7.42-7.39 (2 H, m, Ar), 7.60 (1 H, d, J = 7.5 Hz, Ar) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.4 (2 C, d, $J_{C\text{-}P}$ = 5.4 Hz), 23.7 (d, $J_{C\text{-}P}$ = 2.3 Hz), 47.4 (d, $J_{C\text{-}P}$ = 5.6 Hz), 63.0 (d, $J_{C\text{-}P}$ = 7.5 Hz), 63.1 (d, $J_{C\text{-}P}$ = 7.3 Hz), 72.1 (d, $J_{C\text{-}P}$ = 167.8 Hz), 127.0, 129.7, 130.6, 131.1, 132.2, 139.1 (d, $J_{C\text{-}P}$ = 1.5 Hz), 203.4 (d, $J_{C\text{-}P}$ = 10.0 Hz) ppm; ^{31}P-NMR (202.5 MHz, $CDCl_3$): δ = 24.5 ppm; $[\alpha]_D^{28}$ = -8.6 (c = 1.41 in CH_2Cl_2); The enantiomeric excess was determined by HPLC with a Daicel Chiralcel OD-H column [λ = 254 nm], eluent: 2-propanol/hexane (3/97), flow rate = 0.5 mL/min, t_{major} = 31.60 min (88.88%), t_{minor} = 34.00 min (11.12%).

(*R*)-Dimethyl 4-(2-chlorophenyl)-2-hydroxy-4-oxobutan-2-ylphosphonate 79n

The product **79n** was obtained following the *General procedure* **5.4.1 III** from α-ketophosphonate **72a** (30.4 mg, 0.2 mmol, 1.0 equiv) β-ketoacid **78g** (51.6 mg, 0.26 mmol, 1.3 equiv) using catalyst **80** (22.6 mg, 0.04 mmol, 20 mol %) and toluene (1.0 mL)**.** Colourless liquid Yield: **79n** (44.0 mg, 71%); IR (film): $\bar{\upsilon}$ = 3288, 2957, 2854, 2360, 2341, 1693, 1590, 1469, 1053, 1031, 832, 776 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.57 (3 H, d, J = 15.5 Hz, $C(OH)CH_3$), 3.13 (1 H, t, J = 17.0 Hz, $COCH_2$), 3.57 (1 H, dd,

J = 7.0, 17 Hz, COCH_2), 3.78 (3 H, d, J = 7.0 Hz, OCH_3), 3.80 (1 H, d, J = 7.0 Hz, OCH_3), 4.74 (1 H, d, J = 10.5 Hz, OH), 7.35-7.32 (1 H, m, Ar), 7.41-7.40 (2 H, m, Ar), 7.57 (1 H, d, J = 7.5 Hz, Ar) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 23.8 (d, $J_{C\text{-}P}$ = 1.8 Hz), 47.4 (d, $J_{C\text{-}P}$ = 5.8 Hz), 53.6 (d, $J_{C\text{-}P}$ = 7.5 Hz), 53.7 (d, $J_{C\text{-}P}$ = 6.6 Hz), 72.4 (d, $J_{C\text{-}P}$ = 167.9 Hz), 127.0, 129.5, 130.6, 131.1, 132.3, 138.9, 203.9 (d, $J_{C\text{-}P}$ = 10.5 Hz) ppm; ^{31}P-NMR (202.5 MHz, $CDCl_3$): δ = 24.6 ppm; The enantiomeric excess was determined by HPLC with a Daicel Chiralcel OD-H column [λ = 254 nm], eluent: 2-propanol/hexane (3/97), flow rate = 0.5 mL/min, t_{major} = 57.85 min (85.31%), t_{minor} = 62.00 min (14.69%).

(*R*)-Diisopropyl 4-(2-methoxyphenyl)-2-hydroxy-4-oxobutan-2-ylphosphonate 79o

The product **79o** was obtained following the *General procedure* **5.4.1 III** from α-ketophosphonate **72c** (41.6 mg, 0.2 mmol, 1.0 equiv) β-ketoacid **78h** (50.5 mg, 0.26 mmol, 1.3 equiv) using catalyst **80** (22.6 mg, 0.04 mmol, 20 mol %) and toluene (1.0 mL)**.** Colourless liquid Yield: **79o** (56.0 mg, 78%); IR (film): ῡ = 3288, 2982, 2341, 1661, 1598, 1486, 1465, 1386, 1375, 1105, 991, 756 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.32-1.26 (12 H, m, OCH(CH_3)$_2$), 1.50 (3 H, d, J = 15.5 Hz, C(OH)CH_3), 3.14 (1 H, dd, J = 14.0, 16.5 Hz, COCH_2), 3.62 (1 H, dd, J = 8.0, 16.5 Hz, COCH_2), 3.90 (3 H, s, OCH_3), 4.80-4.67 (2 H, m, OCH(CH_3)$_2$), 4.90 (1 H, d, J = 12.0 Hz, OH), 6.95 (1 H, d, J = 8.0 Hz, Ar), 7.00 (1 H, t, J = 7.5 Hz, Ar), 7.47 (td, J = 1.5, 8.0 Hz, 1 H), 7.70 (1 H, dd, J = 1.5, 8.0 Hz, Ar) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.3, 16.38, 16.4, 16.5, 23.9 (d, $J_{C\text{-}P}$ = 2.8 Hz), 42.3 (d, $J_{C\text{-}P}$ = 3.0 Hz), 62.9 (d, $J_{C\text{-}P}$ = 7.4 Hz, 2 C), 63.2 (d, $J_{C\text{-}P}$ = 7.5 Hz), 71.8 (d, $J_{C\text{-}P}$ = 168.5 Hz), 128.4 (2 C), 128.7 (2 C), 133.8, 137.0, 201.0 (d, $J_{C\text{-}P}$ = 9.5 Hz) ppm; ^{31}P-NMR (202.5 MHz, $CDCl_3$): δ = 23.5 ppm; $[\alpha]_D^{25}$ = -7.6 (c = 3.77 in CH_3OH); The

enantiomeric excess was determined by HPLC with a Daicel Chiralpak AD-H column [λ = 254 nm], eluent: 2-propanol/hexane (20/80), flow rate = 0.25 mL/min, t_{major} = 25.80 min (85.02%), t_{minor} = 27.81 min (14.98%).

(*R*)-Diisopropyl 3-hydroxy-1-(2-methoxyphenyl)-1-oxo-pentan-3ylphosphonate 79p

The product **79p** was obtained following the *General procedure* **5.4.1 III** from α-ketophosphonate **72d** (44.4 mg, 0.2 mmol, 1.0 equiv) β-ketoacid **78h** (50.5 mg, 0.26 mmol, 1.3 equiv) using catalyst **80** (22.6 mg, 0.04 mmol, 20 mol %) and toluene (1.0 mL)**.** Colourless liquid Yield: **79p** (42.0 mg, 56%); IR (film): $\bar{\upsilon}$ = 3288, 2979, 2360, 2341, 1665, 1598, 1486, 1465, 1386, 1375, 1106, 887, 757 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 1.02 (3 H, t, J = 7.5 Hz, CH_2CH_3), 1.25-1.22 (6 H, m, $OCH(CH_3)_2$), 1.29 (6 H, t, J = 6.0 Hz, $OCH(CH_3)_2$), 1.96-1.80 (2 H, m, CH_3CH_2COH), 3.12 (1 H, dd, J = 17.0, 20.0 Hz, $COCH_2$), 3.57 (1 H, dd, J = 7.5, 16.5 Hz, $COCH_2$), 3.91 (3 H, s, OCH_3), 4.76-4.67 (2 H, m, $OCH(CH_3)_2$), 5.16 (1 H, d, J = 8.5 Hz, OH), 6.95 (1 H, d, J = 8.5 Hz, Ar), 7.00 (1 H, t, J = 7.5 Hz, Ar), 7.47 (1 H, td, J = 1.5, 8.5 Hz, Ar), 7.70 (1 H, dd, J = 1.5, 7.0 Hz, Ar) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 7.9 (d, $J_{C\text{-}P}$ = 5.8 Hz), 23.7 (d, $J_{C\text{-}P}$ = 5.8 Hz), 23.8 (d, $J_{C\text{-}P}$ = 4.8 Hz), 24.1 (d, $J_{C\text{-}P}$ = 2.9 Hz, 2 C), 29.7 (d, $J_{C\text{-}P}$ = 3.8 Hz), 44.5 (d, $J_{C\text{-}P}$ = 4.8 Hz), 55.5, 70.9 (d, $J_{C\text{-}P}$ = 7.6 Hz), 71.1 (d, $J_{C\text{-}P}$ = 7.5 Hz), 74.7 (d, $J_{C\text{-}P}$ = 167.0 Hz), 111.6, 120.8, 128.8, 130.7, 130.9, 158.6, 204.0 (d, $J_{C\text{-}P}$ = 8.4 Hz) ppm; ^{31}P-NMR (202.5 MHz, $CDCl_3$): δ = 23.8 ppm; $[\alpha]_D^{25}$ = -1.35 (c = 1.27 in CH_3OH); The enantiomeric excess was determined by HPLC with a Daicel Chiralpak OD-H column [λ = 254 nm], eluent: 2-propanol/hexane (3/97), flow rate = 0.5 mL/min, t_{minor} = 20.51 min (20.51%), t_{major} = 30.18 min (79.49%).

(*R*)-Diisopropyl 2-hydroxy-4-(naphthalen-3-yl)-4-oxo-butan-2ylphosphonate 79q

The product **79q** was obtained following the *General procedure* **5.4.1 III** from α-ketophosphonate **72c** (20.8 mg, 0.1 mmol, 1.0 equiv) β-ketoacid **78i** (27.8 mg, 0.13 mmol, 1.3 equiv) using catalyst **80** (11.3 mg, 0.02 mmol, 20 mol %) and toluene (0.5 mL)**.** Colourless liquid Yield: **79q** (24.0 mg, 64%); IR (film): $\bar{\upsilon}$ = 3283, 2980, 2933, 1671, 1598, 1385, 1374, 1180, 1104, 989, 774 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.32-1.29 (12 H, m, OCH(CH_3)$_2$), 1.60 (3 H, d, J = 15.5 Hz, C(OH)CH_3), 3.14 (1 H, t, J = 16.5 Hz, COCH_2), 3.73 (1 H, dd, J = 7.0, 16.5 Hz, COCH_2), 4.83-4.74 (2 H, m, OCH_2(CH_3)$_2$), 4.91 (1 H, d, J = 10.5 Hz, OH), 7.56-7.50 (2 H, m, Napthyl), 7.63-7.60 (1 H, m, Napthyl), 7.88 (1 H, d, J = 7.5 Hz, Napthyl), 7.98 (1 H, d, J = 7.0 Hz, Napthyl), 8.0 (1 H, d, J = 8.5 Hz, Napthyl), 8.64 (1 H, d, J = 9.0 Hz, Napthyl) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 23.85-23.77 (m, 2 C); 23.9 (d, $J_{C\text{-}P}$ = 2.6 Hz), 24.09 (d, $J_{C\text{-}P}$ = 3.4 Hz), 24.1 (d, $J_{C\text{-}P}$ = 3.4 Hz), 46.3 (d, $J_{C\text{-}P}$ = 5.5 Hz), 74.4 (d, $J_{C\text{-}P}$ = 7.8 Hz), 71.6 (d, $J_{C\text{-}P}$ = 7.6 Hz), 72.3 (d, $J_{C\text{-}P}$ = 169.8 Hz), 124.2, 125.8, 126.6, 128.2, 128.4, 128.7, 130.0, 133.3, 134.0, 136.0 (d, $J_{C\text{-}P}$ = 1.6 Hz), 204.7 (d, $J_{C\text{-}P}$ = 9.6 Hz) ppm; ^{31}P-NMR (202.5 MHz, $CDCl_3$): δ = 23.2 ppm; $[\alpha]_D^{24}$ = -22.9 (c = 0.78 in CH_3OH); The enantiomeric excess was determined by HPLC with a Daicel Chiralpak OD-H column [λ = 254 nm], eluent: 2-propanol/hexane (3/97), flow rate = 0.5 mL/min, t_{minor} = 26.90 min (12.84%), t_{major} = 31.03 min (87.16%).

5.4.3.1 X- ray Crystallographic data

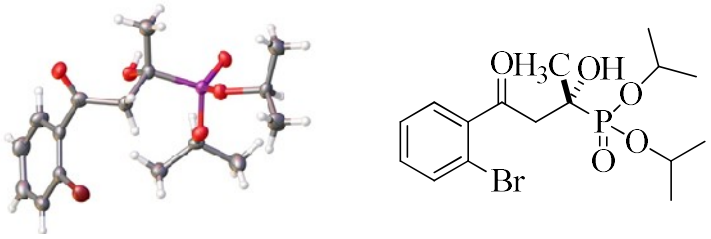


Figure 5.2: X-ray structure of **79j**, CCDC No. **1534803**

Empirical formula	$C_{16}H_{24}BrO_5P$
Formula weight	407.23
Temperature/K	107.8(4)
Crystal system	monoclinic
Space group	C2
a/Å	19.4281(4)
b/Å	8.92102(13)
c/Å	11.7047(2)
α/°	90
β/°	105.986(2)
γ/°	90
Volume/Å^3	1950.19(6)
Z	4
ρ_{calc}g/cm^3	1.387

μ/mm^{-1}	3.826
F(000)	840.0
Crystal size/mm^3	0.643 × 0.393 × 0.366
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection/°	7.858 to 146.226
Index ranges	-23 ≤ h ≤ 24, -10 ≤ k ≤ 10, -14 ≤ l ≤ 13
Reflections collected	7048
Independent reflections	3773 [R_{int} = 0.0549, R_{sigma} = 0.0451]
Data/restraints/parameters	3773/1/214
Goodness-of-fit on F^2	1.136
Final R indexes [I>=2σ (I)]	R_1 = 0.0585, wR_2 = 0.1480
Final R indexes [all data]	R_1 = 0.0644, wR_2 = 0.1709
Largest diff. peak/hole / e $Å^{-3}$	1.32/-0.75
Flack parameter	-0.06(4)

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