Synthesis and Utilization of α, β-Unsaturated Carbonyl Compounds: Access to Functionalized Piperidines and Selective Reduction of Alkylidene β-Keto Esters

A Thesis
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This Thesis is Dedicated to

My Beloved Parents, Sister,

Brother-in-Law and Niece

भारतीय विज्ञान शिक्षा एवं अनुसंधान संस्थान, पुणे

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CERTIFICATE

Certified that the work incorporated in the thesis entitled "*Synthesis and Utilization of α, β-Unsaturated Carbonyl Compounds: Access to Functionalized Piperidines and Selective Reduction of Alkylidene β-Keto Esters*" submitted by **Mr. Lakshmi VR Babu Syamala** was carried out by the candidate, under my supervision. The work presented here or any part of it has not been included in any other thesis submitted previously for the award of any degree or diploma from any other university or institution.

Date: 28th Mar 2018, Pune

Dr. Ramakrishna G. Bhat

(Research Supervisor)

DECLARATION

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List of Abbreviations

(Hmim)OTs	1-methylimidazolium *p*-toluenesulfonate
°C	degree Celsius
Å	angstrom
Ac	Acetyl
Ar	Aryl
Atm	atmosphere
Bn	benzyl ($C_6H_5CH_2$)
Boc	*tert*-butoxycarbonyl
BOX	bisoxazoline
bs	broad singlet
Bu	Butyl
Calcd.	calculated
Cat.	catalytic
Cbz	benzyloxycarbonyl
$CDCl_3$	Deuterated chloroform
COD	cyclooctadiene
DABCO	1,4-Diazabicyclo[2.2.2]octane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	*N,N'*-Dicyclohexylcarbodiimide
DCM	dichloromethane
dd	doublet of doublet
de/dr	diastereomeric excess/diastereomeric ratio
DMBA	*N*, *N*-1, 3-Dimethyl barbituric acid
DMEDA	*N*, *N*-Dimethylethylene diamine
DMF	*N,N*-Dimethyl formamide
DMSO-*d6*	Deuterated dimethyl sulfoxide
ee/er	enantiomeric excess/enantiomeric ratio
equiv.	equivalents

ESI TOF	Electrospray ionisation time-of-flight
ESMS	electrospray mass spectrometry
EtOAc	ethyl acetate
FTIR	Fourier-transform infrared spectroscopy
g	gram(s)
h	hour(s)
HPLC	High Performance Liquid Chromatography
HRMS	High Resolution Mass Spectroscopy
Hz	Hertz
^{i}Pr	isopropyl
J	Spin coupling constant (in NMR spectroscopy)
L	Ligand
LA	Lewis acid
M	molar (mol L^{-1})
m	multiplet (in NMR)
m/z	mass to charge ratio
MA	Meldrum's Acid
MeCN	Acetonitrile
mg	milligram
min	minute(s)
mol	mole(s)
m.p.	melting point
MS	Molecular Sieves
nm	nanometer
NPs	Nanoparticles
Nu	Nucleophile
ppm	parts per million
PyBOX	Pyridine bisoxazoline
q	quartet (NMR)
r.t./rt	room temperature

R$_f$	retention factor (in chromatography)
t-/tert-	Tertiary (branched alkyl chain)
TBAF	tetrabutyl ammonium fluoride
td	triplet of doublet
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TMS	Trimethylsilyl
Ts	tosyl
VT–NMR	Variable Temperature NMR

SYNOPSIS

The thesis entitled "***Synthesis and Utilization of α, β-Unsaturated Carbonyl Compounds: Access to Functionalized Piperidines and Selective Reduction of Alkylidene β-Keto Esters***" comprises of five main chapters.

Chapter 1: Importance of α, β-Unsaturated Carbonyl Compounds in Organic Synthesis

This chapter presents the importance, reactions and synthesis of α, β-unsaturated carbonyl compounds. α, β-Unsaturated carbonyl compounds find a wide variety of applications in pharmaceutical industries and in natural product syntheses. α, β-unsaturated carbonyl compounds are the basic building blocks in organic synthesis. The importance of α, β-unsaturated carbonyl compounds in conjugate addition reactions has been highlighted.
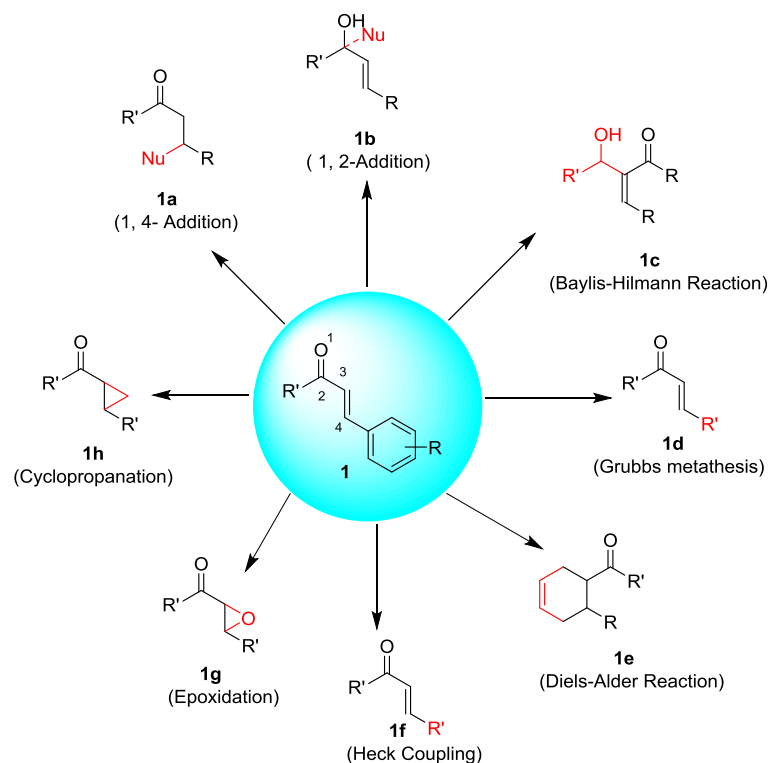

Fig. 1.1: Few synthetic transformations of α, β-unsaturated carbonyl compounds (**1**)

α, β-Unsaturated carbonyl compounds are one of the important class of compounds in organic synthesis with the general structure (O=C−C$^{\alpha}$=C$^{\beta}$−); e.g., enones and enals. Due to the presence of both carbonyl and alkene functionalities, these skeletons are widely used as active intermediates in many organic transformations. α, β-Unsaturated carbonyl compounds are good Michael acceptors and have been used for C-C, C-N, C-S, C-O and other bond formations.

These compounds are the key intermediates and backbone of many natural products and bioactive molecules. These α, β-unsaturated carbonyl compounds (**1**) can be subjected to a wide range of functional group transformations such as 1, 2- or 1, 4-(conjugate) addition (**1** to **1a**, **1b**), Baylis-Hillman reaction (**1** to **1c**), Grubbs' metathesis (**1** to **1d**), cycloadditions (**1** to **1e**), Heck coupling reaction (**1** to **1f**), epoxidation (**1** to **1g**), cyclopropanation (**1** to **1h**) as shown in **Fig 1.1**.

In this chapter, few selected reactions of α, β-unsaturated carbonyl compounds and methods for the synthesis of these compounds have been discussed.

Chapter 2: Organocatalytic Approach for the Synthesis of α, β-Unsaturated Keto Compounds

In this chapter, we present a practical organocatalytic approach for the synthesis of α, β-unsaturated ketones *via* aldol condensation of acetone with various aromatic and aliphatic aldehydes. The chapter begins with a brief overview on the importance of α, β-unsaturated carbonyl compounds and some of the selected methods for their synthesis.

Traditionally, α, β-unsaturated carbonyl compounds are synthesized by Claisen-Schmidt condensation using aldehydes and ketones in presence of stoichiometric amount of strong bases such as NaOH, KOH and Ca(OH)$_2$. However, the use of strong bases limits the scope of the reaction, as they produce a complex mixture of self-condensed side products and formation of large amounts of corrosive solid waste during work-up. These methods have severe drawbacks with especially base-sensitive functional groups. In this chapter, a novel organocatalytic protocol for the synthesis of α, β-unsaturated carbonyl compounds has been described. This organocatalytic protocol utilizes acetone (**2**) and aldehydes (**3**) in presence of catalytic amount of Meldrum's

acid (**5**) (30 mol%) and *N,N'*-dimethylethylenediamine (DMEDA) (**6**) (10 mol%) in ethyl acetate at 55 °C to afford α, β-unsaturated carbonyl compounds **4** (Scheme 2.1).
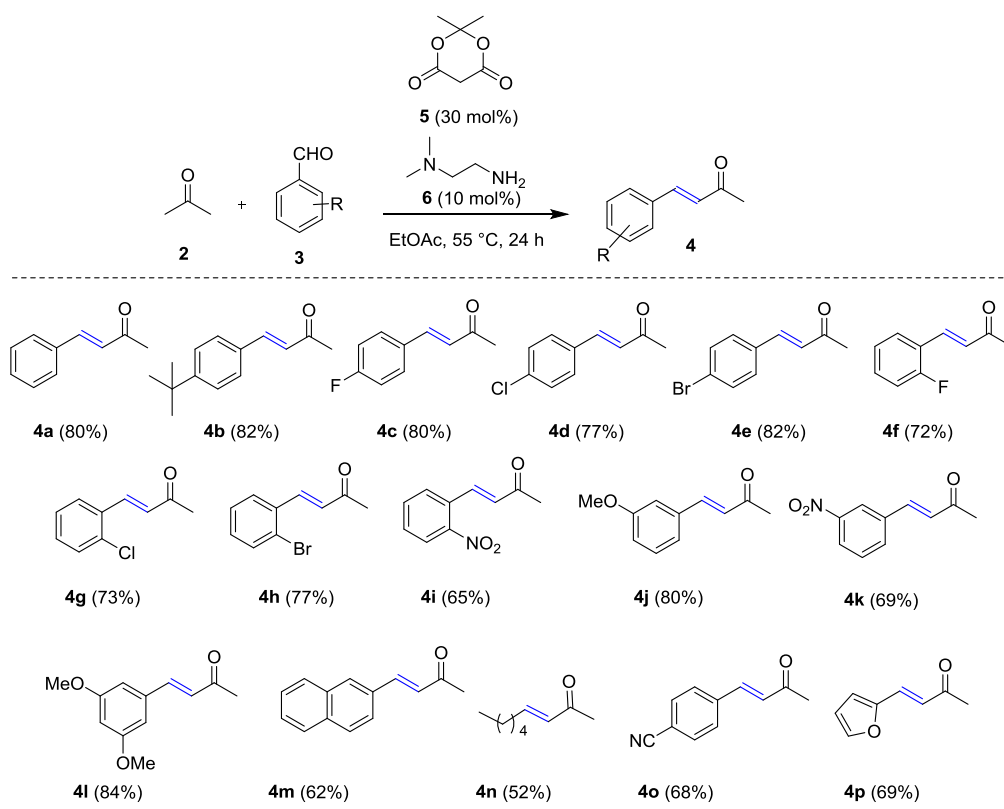
Scheme 2.1: Substrate scope of the protocol

Having optimized reaction conditions in hand, we explored the scope of the method using different aromatic aldehydes (**3a-3p**) and acetone (**2**) as substrates to afford the corresponding products (**4a-4p**) in good yields up to 84% (Scheme 2.1). It was observed that the aromatic aldehydes with electron donating as well as electron withdrawing groups reacted smoothly. Further, in order to show the generality of the protocol, aliphatic (**3n**) and heterocyclic aldehydes (**3p**) were used for the synthesis of α, β-unsaturated ketones (**4n**, **4p**) in moderate to good yields.

In order to further evaluate the practicality of this protocol, we explored this catalyst system for the synthesis of alkylidene β-keto esters (**8**) *via* the reaction of aldehydes (**3**) and methyl acetoacetate (**7**) under the optimized reaction conditions (Scheme 2.2). The reaction of substituted benzaldehydes (**3**) and methylacetoacetate (**7**) afforded the corresponding products (**8a-8d**) in very good yields (up to 84%) (Scheme 2.2). Both electronically activated and deactivated aldehydes reacted smoothly to

afford the corresponding desired products:alkylidene β-keto esters in good yields in 12 h (Scheme 2.2).
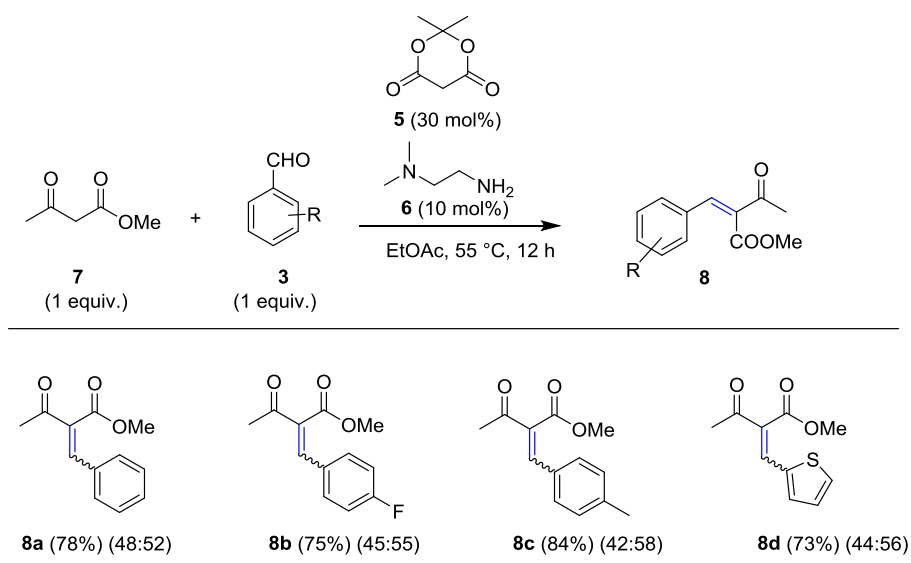
Scheme 2.2: Substrate scope of the reaction with methyl acetoacetate (**7**)

The highlights of this methodology are the use of easily and commercially available less expensive catalysts, high selectivity, functional group tolerance and more importantly method does not yield self condensed side products. In addition, catalytic system proved to be efficient for synthesizing alkylidene β-keto esters in good yields by the reaction of methyl acetoacetate with various aldehydes.

Chapter 3: Iron (III)-Catalyzed Selective Reduction of Alkylidene β-ketoesters

In this chapter, we present a $FeCl_3 \cdot 6H_2O$/triethylsilane composite system for the selective conjugate reduction of carbon-carbon double bond of Michael acceptor-alkylidene β-keto esters under mild reaction conditions. This chapter begins with a brief overview of the importance of selective conjugate reduction of α, β-unsaturated ketones and some of the selected methods for the selective conjugate reduction. The conjugate reduction of α, β-unsaturated ketones and esters commonly suffers from the competitive 1, 2-reduction to afford allylic alcohols. It is also desirable to develop a protocol without the use of any ligands and additives/co-catalysts.

Owing to the importance of the selective conjugate reduction of α, β-unsaturated carbonyl compounds, we explored the catalyst system comprising of FeCl$_3$.6H$_2$O/Et$_3$SiH for the selective conjugate reduction of carbon-carbon double bond of alkylidene β-keto esters under mild conditions. As a model reaction, benzylidene methylacetoacetate **9a** was treated with various Lewis acid catalysts in presence of triethylsilane in DCM at room temperature. Based on the initial screenings, Et$_3$SiH (1.02 equiv.) and FeCl$_3$.6H$_2$O (20 mol%) in DCM at room temperature emerged as optimum reaction condition for the selective reduction of benzylidene methylacetoacetate **9a** to afford the corresponding reduced product **10a** in 85% yield (Scheme 3.1).
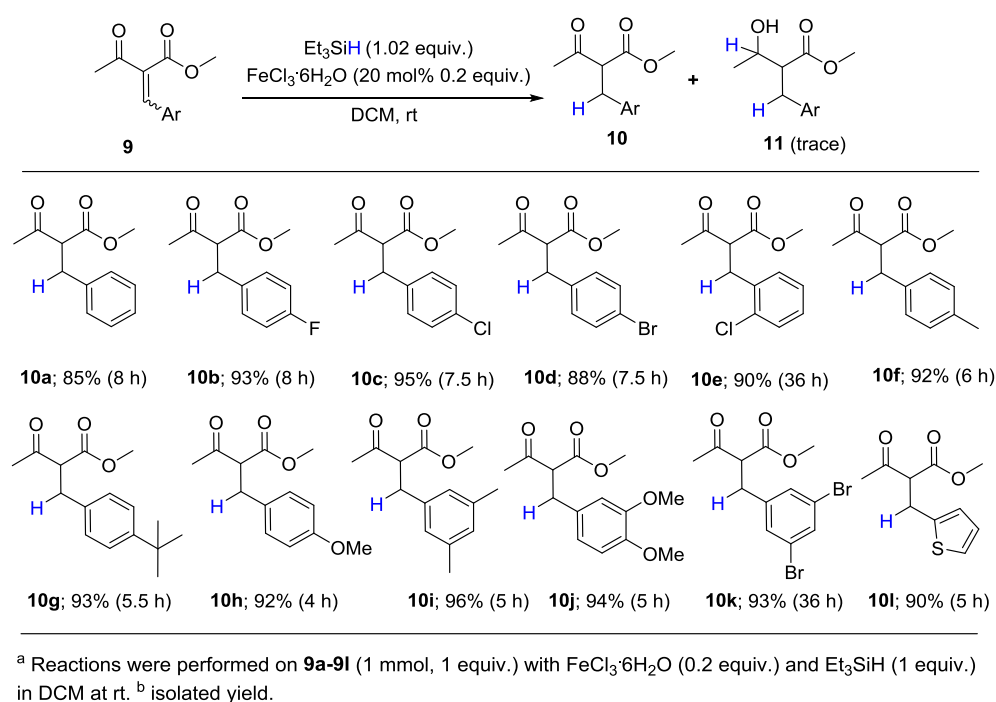
Scheme 3.1: Substrate scope of alkylidene β-ketoesters for the selective reduction[a,b]

Having optimized reaction conditions in hand, we explored the scope of the reaction with various alkylidene β-keto esters (**9a-9l**) as substrates to furnish the corresponding products (**10a-10l**) in good yields (Scheme 3.1). It was observed that the aromatic aldehydes with electron donating as well as electron withdrawing groups reacted smoothly. Later, we explored the selective conjugate reduction of acetylacetone derivatives (**12a-12e**) under optimum reaction conditions to afford the corresponding 1, 4-conjugate reduction products (**13a-13e**) chemoselectively in good to excellent yields.

However, substrate (**12e**) with electron withdrawing group afforded the desired product (**13e**) along with 1, 2-addition product **14e** in trace quantity (Scheme 3.2).
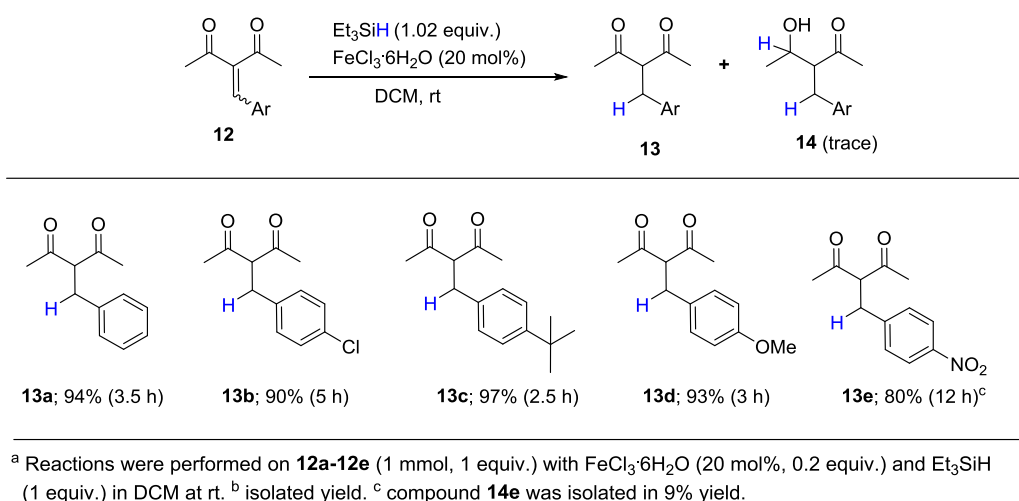
Scheme 3.2: Substrate scope of alkylidene acetylacetones for the selective reduction[a,b]

To expand the scope of this methodology, further, we synthesized few alkylidene Meldrum's acid derivatives (**15a**-**15c**). These compounds under the optimum reaction conditions afforded the corresponding 1, 4-conjugate addition products (**16a**-**16c**) exclusively in almost quantitative yields (Scheme 3.3). Method proved to be highly selective for the 1, 4-conjugate reduction. However, few ketones under the optimum reaction conditions afforded the mixture of 1, 4-conjugate addition as well as 1, 2-reduction products.
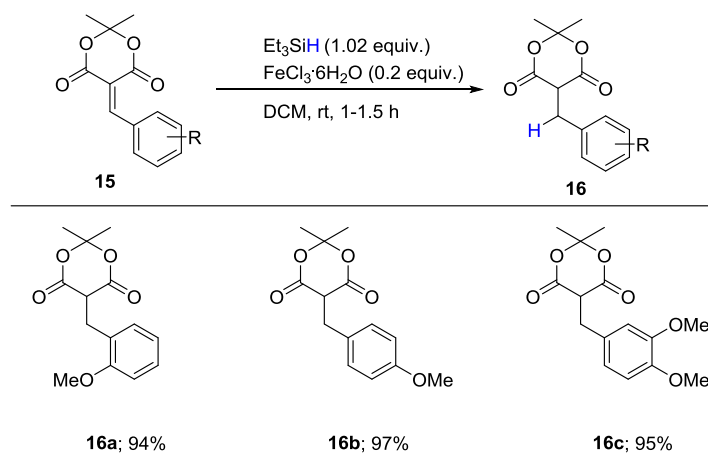
Scheme 3.3: Substrate scope of Meldrum's adducts for the selective reduction[a,b]

Novel reducing system comprising of $FeCl_3 \cdot 6H_2O$/triethylsilane is successfully utilized for the highly selective conjugate reduction of carbon-carbon double bond of alkylidene β-keto esters and β-keto carbonyl compounds under mild conditions. Chemoselective reduction afforded exclusively 1, 4-conjugate reduction products (as major products) and method did not require the use of any base/acid for the desilylation unlike the previous procedures. A broad range of alkylidene derivatives underwent smooth reduction under practical reaction conditions.
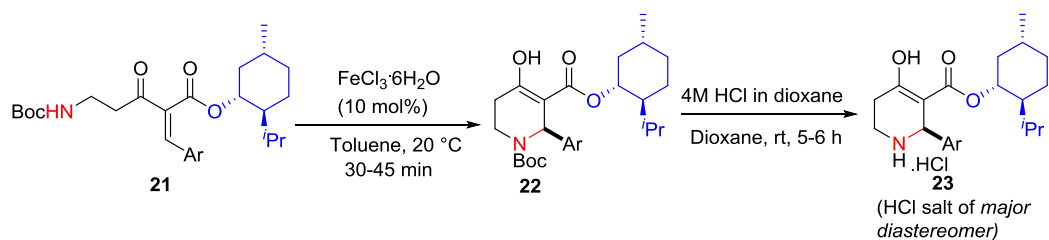
Chapter 4: $FeCl_3 \cdot 6H_2O$ catalyzed diastereoselective synthesis of (L)-menthyl 4-oxo-2-arylpiperidine-3-carboxylates

This chapter begins with a brief account on the importance of substituted piperidine derivatives and their synthesis. An efficient diastereoselective synthesis of substituted piperidines using catalytic amount of $FeCl_3 \cdot 6H_2O$ has been described in this chapter. We explored the intramolecular aza-Michael addition of carbamate on alkylidene β-keto (L)-menthyl esters in presence of catalytic amount of $FeCl_3 \cdot 6H_2O$ in a very short time.

The piperidine ring system is one of the naturally occurring common structural sub-units and is core to many bioactive natural products. Particularly, piperidines bearing the alkyl and/or aryl substituent group at the 2- and/or 2, 6-position on the ring can be found as a core structure in pharmaceuticals and many naturally occurring alkaloids.

Owing to the importance of piperidine moiety and their synthetic value, we became interested in exploring a new protocol for the synthesis of chiral piperidine derivatives. In order to synthesize chiral piperidine derivatives in a stereoselective manner, we chose a suitably activated alkene moiety for the intramolecular aza-Michael addition of carbamate. In this regard, we decided to synthesize suitable alkylidene β-ketoesters starting from β-ketoesters.

We chose (L)-menthol as chiral auxiliary for the desired effective steroinduction, as it is cheap and commercially available. We assumed that activation of the double bond by appropriate Lewis acid would lead to the expected intramolecular cyclization. In order to validate the hypothesis, we synthesized various

alkylidene β-keto (L)-menthyl esters (**21**) starting from (L)-menthyl-β-keto ester (**20**) by condensing with different aldehydes (Scheme 4.1).

Scheme 4.1: Synthesis of β-keto (L)-menthyl ester (**19**) and alkylidene β-keto (L)-menthyl esters (**21, 21'**)

Z (**21a**) and E (**21'a**) isomers were studied independently for the cyclization in different solvents. After screening of various solvents, we found that DCM and toluene were good solvents as Z-isomer cyclized with good diastereoselectivity to afford the cyclized product (**22a**) in excellent yields. However it was observed that the corresponding E-isomer **21'a** reacted slowly under the optimized reaction condition to yield the corresponding cyclized product (**22a**) with lower diastereoselectivity. Therfore, we chose (Z)–isomer as the suitable starting material. After rigorous screening of various solvents and temperature conditions, FeCl$_3$·6H$_2$O (0.1 equiv. or 10 mol%) in toluene at 20 ^{o}C was found to be better optimized reaction condition to give **22a** in 98% yield with dr 21:79.

In order to expand the reaction scope of the method, various (Z)-alkylidene β-keto (L)-menthyl esters (**21d–21q**) were subjected for cyclization under the optimized reaction conditions to afford the corresponding piperidine derivatives (**22d–22q**). It was found that regardless of their electronic nature, functional groups on the substrates tolerated the reaction conditions with excellent yields. We observed moderate to good diastereomeric ratio (up to dr 9:91) for the piperidine derivatives from HPLC studies (Scheme 4.2).

Scheme 4.2: Substrate scope of diastereoselective piperidine derivatives

Entry	Ar-	5[b] dr(%)[b] (% yield)	6[c] (HCl salt) yield (%)	Entry	Ar-	5[b] dr(%)[b] (%yield)	6[c] (HCl salt) yield (%)
1	22a (phenyl)	21:79 (98)	23a (95)	10	22j (4-EtO)	29:71 (95)	23j (88)
2	22b (4-Br)	18:82 (97)	23b (93)	11	22k (4-NC)	15:85 (98)	23k (96)
3	22c (4-O₂N)	15:85 (98)	23c (95)	12	22l (3-O₂N)	14:86 (95)	23l (95)
4	22d (4-F)	19:81 (97)	23d (88)	13	22m (3,5-diMe)	9:91 (96)	23m (96)
5	22e (4-Cl)	17:83 (96)	23e (92)	14	22n (3,5-diOMe)	11:89 (94)	23n (94)
6	22f (3-Cl)	15:85 (95)	23f (93)	15	22o (3,5-diBr)	9:91 (99)	23o (98)
7	22g (4-Me)	20:80 (96)	23g (92)	16	22p (furan)	36:64 (93)	23p (89)
8	22h (4-tBu)	19:81 (95)	23h (94)	17	22q (thiophene)	30:70 (95)	23q (90)
9	22i (4-MeO)	27:73 (95)	23i (85)				

[a] Reactions were performed with 0.1 equiv. (10 mol%) of FeCl₃.6H₂O in toluene at 20 °C and deprotection of Boc group was performed on the major diastereomer with 4M HCl in dioxane, dioxane as solvent. [b] dr was calculated by HPLC using chiralpak IA column. [c] Obtained yield of the product after washing with in *n*-pentane.

To our dismay, we observed that ^{1}H-NMR spectra of the products were highly complex due to peaks arising from both diastereomers and equilibrating rotamers of the corresponding diastereomers. It was evident from the VT-NMR studies that existence of rotamers is due to *N*-Boc group and this observation was further supported by earlier findings. Hence, we isolated the major diastereomer of all the products (**22a-22q**) and were subjected for *N*-Boc deprotection with 4 M HCl in dioxane solution to afford the

corresponding salts (**23a-23q**) in good to excellent yields (Scheme 4.2). ^{1}H NMR spectrum of *N*-Boc-deprotected piperidine derivatives was neat and revealed the existence of enolic form of salt and all peaks were well resolved. It was conclusive from ^{1}H-NMR spectra that all piperidine hydrochloride salts (**23a-23q**) existed mostly in enolic form.

We demonstrated the novel access of diastereoselective piperidine derivatives by exploring the strength of environmentally benign iron (III) chloride (10 mol%) as a catalyst and naturally available (L)-menthol as a chiral auxiliary. Intramolecular cyclization proceeded in diastereoselective manner. Reaction conditions were mild and favored rapid formation of piperidine derivatives in good to excellent yields and with high diastereoselectivity.

Chapter 5: Bis(Oxazoline)-Copper(II) Complex as Chiral Catalyst System for the Enantioselective Synthesis of 2, 3, 4-Trisubstitued Piperidines

In this chapter an efficient method for the enantioselective synthesis of substituted piperidines using catalyst system comprising of copper(II) triflate-bisoxazoline (BOX) chiral ligand has been described. We explored the intramolecular aza-Michael addition of carbamate on alkylidene *β*-keto methyl/benzyl esters to synthesize the various functionalized 4-oxo-2-arylpiperidine-3-carboxylate derivatives with high enantioselectivity (up to *er* 88:12) in good to excellent yields.

Initially, we synthesized few selected starting materials (**25/25'**) (*E*/*Z* ~40:60) from alkyl *β*-ketoesters (**24**) by condensing with various aldehydes by using previously reported protocol (Scheme 5.13).
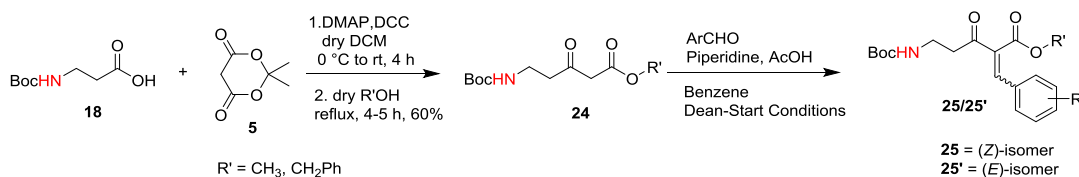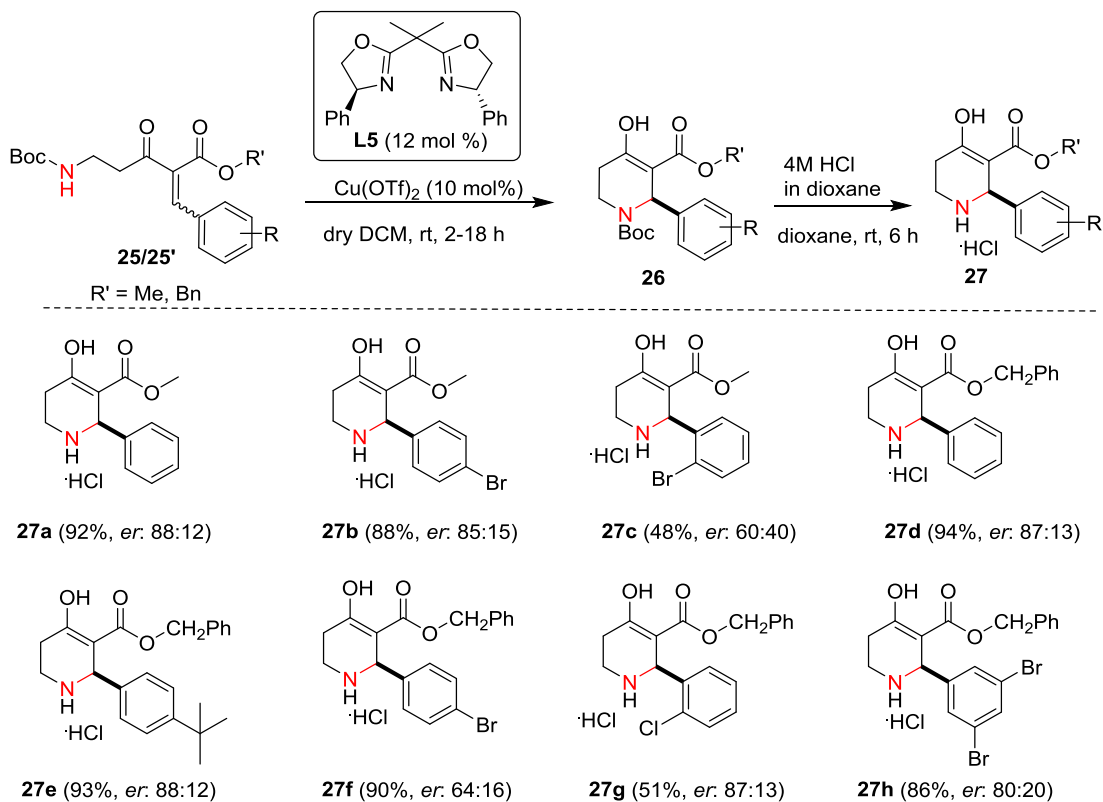

Scheme 5.1: Synthesis of alkylidene *β*-ketoesters

For the initial experiments, (*Z*)–isomer (**25a**) was chosen as a model substrate considering its reactivity based on our previous experience. We screened various

catalyst systems comprising of different BOX ligands (12 mol%) and Lewis acids as catalysts (10 mol%) for inducing the enantioselectivity in the proposed intramolecular aza-Michael conjugate addition reaction (**25a**) (Scheme 5.2). To our delight, the reaction of **25a** with a combination of 10 mol% of Cu(OTf)$_2$ and 12 mol% of chiral BOX ligand **L5** afforded the expected product (**26a**) in 92% yield with very good enatioselectivity (*er* 88:12) in 1.5 h at room temperature.

Having obtained the initial success on the catalyst system, further we carried out experiments to find out the effect of stereochemistry (*E* and *Z*) of starting material on the outcome of enantioselectivity. Interestingly, both (*Z*)– and (*E*)–isomers showed the same pattern of cyclization and afforded the desired product **26a**. However, (*E*)–isomer afforded the product **26a** with slightly lower enantioselectivity (*er* 80:20). Further, we carried out independent reactions of both (*Z*) and (*EZ*)–mixture in different solvents and temperature to understand the outcome of enantioselectivity of the reaction. We observed a slight improvement in enatioselectivity at 0 °C (*er* 92:8) and –25 °C (*er* 92:8). Interestingly, the reaction of (*EZ*)–mixture (**25a/25'a**) under the initial reaction conditions at room temperature afforded the desired product **26a** in very good yield and enantioselectivity (92% yield, *er* 88:12). On the basis of these exhaustive screening results, 10 mol% of Cu(OTf)$_2$ and 12 mol% of chiral BOX ligand **L5** in dry DCM at room temperature emerged as the optimum reaction condition for the effective enantioselective aza-Michael conjugate addition reaction.

In order to extend the scope of the reaction, methyl and benzyl esters of various (*EZ*)–alkylidene *β*-ketoesters (*E*/*Z* ~40:60) (**25/25'**) were subjected to intramolecular aza-Michael conjugate addition reaction under optimized reaction conditions and their subsequent deprotection of *N*-Boc-group with 4 M HCl in dioxane to afford the corresponding piperidine derivatives (**27a-27h**) in very good yields and enantioselectivity (up to 92% yield and *er* up to 88:12) (Scheme 5.2). It was observed that the reaction with *o*-substituted alkylidene derivative (**27c** and **27g**) resulted the cyclized product in lower yields (48%) probably due to the poor reactivity of (*E*)–isomer of (*EZ*)–mixture (**25c/25'c** and **25g/25'g**) under the optimized reaction conditions.

Scheme 5.2: Substrate scope of various (*EZ*)–alkylidene alkyl-*β*-ketoesters (**25/25'**)

We developed an efficient enantioselective synthesis of substituted piperidines using a catalyst system comprising of copper (II) triflate (10 mol%) as a Lewis acid catalyst and bis-oxazoline (BOX) (12 mol%) as chiral ligand. We explored the intramolecular aza-Michael addition of carbamates on alkylidene *β*-keto methyl/benzyl esters to synthesize the various functionalized 4-oxo-2-arylpiperidine-3-carboxylate derivatives with high enantioselectivity (up to *er* 88:12) in good to excellent yields.

(*Numbers of substrates and products in the synopsis are different from those in thesis*)

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List of Publications

1. Lakshmi V. R. Babu Syamala, and Ramakrishna G. Bhat; "FeCl$_3$·6H$_2$O Catalyzed Diastereoselective Synthesis of (L)-Menthyl 4-Oxo-2-arylpiperidine-3-carboxylates" *Tetrahedron Lett.* **2017**, *58*, 4836–4840.

2. Lakshmi V. R. Babu Syamala, Trimbak B. Mete and Ramakrishna G. Bhat; "Iron Chloride Catalyzed Selective Conjugate Reduction of Alkylidene β-keto esters and Alkylidene acetylacetones" *Manuscript is communicated.*

3. Lakshmi V. R. Babu Syamala, Ankit Singh and Ramakrishna G. Bhat; "Bis(Oxazoline)-Copper(II) Complex as Chiral Catalyst System for the Enantioselective Synthesis of 2, 3, 4-Trisubstitued Piperidines" *Manuscript under preparation.*

4. Lakshmi V. R. Babu Syamala, Tushar M. Khopade and Ramakrishna G. Bhat; "Organocatalytic Approach for the Synthesis of α, β-Unsaturated Carbonyl Compounds" *Manuscript is communicated.*

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Importance of *α, β*-Unsaturated Carbonyl Compounds in Organic Synthesis

R = H, Alkyl, X, OR, CN, NO$_2$

α, β-unsaturated Carbonyl Compounds

O N E
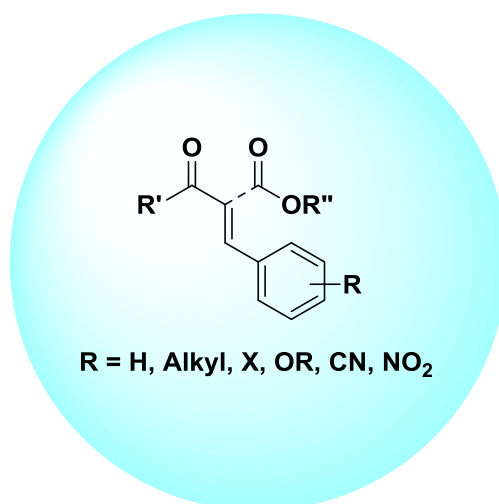
Importance of α, β-Unsaturated Carbonyl Compounds in Organic Synthesis

1

In this chapter the importance, reactions and synthesis of α, β-unsaturated carbonyl compounds have been described. The α, β-unsaturated carbonyl compounds find a wide variety of applications in pharmaceutical industries and in natural product syntheses. These α, β-unsaturated carbonyl compounds are the basic building blocks in synthetic organic chemistry. The importance of α, β-unsaturated carbonyl compounds in conjugate addition reactions has been highlighted.

1.1 Introduction

Reactivity and general properties of *α, β*-unsaturated carbonyl compounds[1] make these compounds as one of the very important and useful class of compounds in organic synthesis[2,3] with the general structure (O=C−C$^\alpha$=C$^\beta$-); e.g., enones and enals. These functionalized molecules are often used as basic intermediates and building blocks in synthetic organic chemistry for the synthesis of various natural products, pharmaceuticals, drugs, and other biologically important molecules.[4-6] Due to the presence of both carbonyl and alkene functionalities, these skeletons are widely used as active intermediates in many of organic transformations. Due to its importance, in recent years, researchers have shown much attention for the stereoselective synthesis of unsaturated carbonyl compounds and their synthetic utility in the diastereoselective as well as enantioselective synthesis of pharmaceuticals and natural products.

1.2 Reactivity of *α, β*-Unsaturated carbonyl compounds

These unsaturated carbonyl compounds contain a carbonyl group which is in conjugation with an alkene moiety, hence they show characteristic properties of both carbonyl and olefinic groups along with some special characteristic reactions.[7] Since the carbonyl group acts as an electron-withdrawing group, *α, β*-unsaturated carbonyl compounds are often attacked by nucleophiles at the *β* carbon to afford conjugate addition products.

However α, β-unsaturated carboxyl derivatives such as acids, esters can also undergo nucleophilic substitution at carbonyl functionality. Generally α, β-unsaturated ketones, acids, esters, and nitriles are less reactive than simple alkenes toward electrophilic reagents like Br_2 and HX. Due to the electron withdrawing nature of carbonyl group in α, β-unsaturated ketone, acid, ester, or nitrile etc., C=C bond is susceptible to undergo nucleophilic addition reactions which is uncommon for the simple olefins. Therefore, the presence of the carbonyl group is not only lowers the reactivity of the C=C double bond towards electrophilic addition, but also controls the orientation of the addition.

In nucleophilic addition of α, β-unsaturated carbonyl compounds, nucleophile generally attacks at the β-carbon depending on the type of nucleophile/conditions and the electrophile adds at the electron rich α-carbon. In case of simple olefins, electrophilic addition takes place to form the most stable carbocation intermediate. In α, β-unsaturated carbonyl compounds (**1**), electrophilic addition takes place via electrophilic attack towards carbonyl end (path a) to give the stable intermediate (**I**), whereas nucleophilic addition of (**1**) involves through attack of nucleophile at the β-carbon (path b) to give stable intermediate (**II**) (Scheme 1.1).
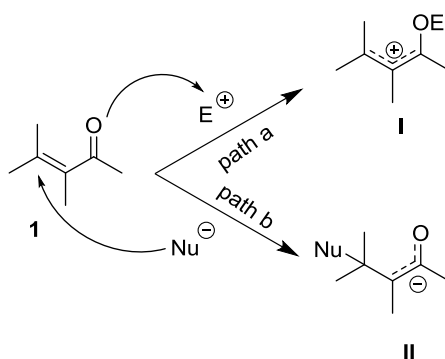
Scheme 1.1: Pathways of electrophilic and nucleophilic attack on (**1**)

The addition of nucleophile in 1, 2- or 1, 4- manner depends on various factors, e.g., condition of the reaction, nature of the unsaturated carbonyl compounds and type of the nucleophile. For example, in general, hard nucleophiles prefer to react with hard electrophiles, and soft nucleophiles react with soft electrophiles. Hard nucleophiles tend to react at the carbonyl carbon (hard) of an enone whereas soft nucleophiles tend to react at the β-carbon (soft) of an enone leading to conjugate addition.

Functionalized α, β-unsaturated carbonyl compounds are the key intermediates and the backbone of many natural products and bioactive molecules, as these α, β-unsaturated

carbonyl compounds can be subjected to a wide range of functional group transformations. These unsaturated carbonyl compounds (**2**) undergo nucleophilic additions via 1, 2- or 1, 4- manner to give the corresponding 1, 2- or 1, 4- (conjugate) addition products (**2a, 2b**).[8,9] In the presence of base such as tertiary amine or phosphine, these carbonyl compounds (**2**) undergo Baylis-Hillman reaction[10] to give β-hydroxy unsaturated carbonyl compounds (**2c**) (Fig. 1.1).
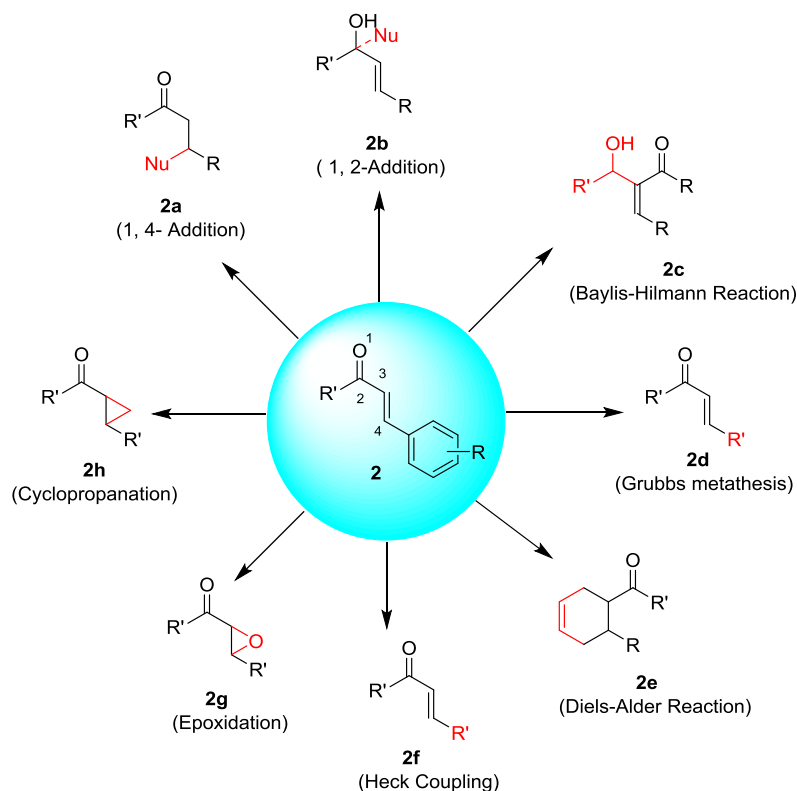

Fig. 1.1: Some of the well-known synthetic transformations of *α, β*-unsaturated carbonyl compounds (**2**)

Unsaturated carbonyl compounds (**2**) react with olefins in presence of Grubbs' catalyst, to give the corresponding cross metathesis[11-13] products (**2d**). Under thermal/light conditions, they undergo various types of transformations including cycloadditions.[14] These unsaturated carbonyl compounds (**2**) undergo Heck coupling reaction[15] in the presence of metal catalysts such as Pd, Ru, Rh complexes to give β-substituted unsaturated carbonyl compounds (**2f**). Likewise, compounds (**2**) can be converted into epoxides (**2g**)[16-18] by using suitable peracids such as *m*-CPBA. Compounds (**2**) also undergo cyclopropanation[19] under Simmons-Smith reaction conditions[20,21] conditions to give cyclopropanation products (**2h**) (Fig. 1.1).

There are plenty of reports on α, β-unsaturated carbonyl compounds that undergo a wide variety of transformations. Herein, few selected reported reactions of α, β-unsaturated carbonyl compounds have been highlighted.

1.3 Selected reactions of α, β-unsaturated carbonyl compounds and α, β-unsaturated esters

Xu *et al.*[22] demonstrated conjugate addition of enones (**3**) with weak nucleophilic carbamates (**4**) by using FeCl$_3$·6H$_2$O as an efficient catalyst in the presence of Me$_3$SiCl to give the conjugate addition product (**5**) (Scheme 1.2).
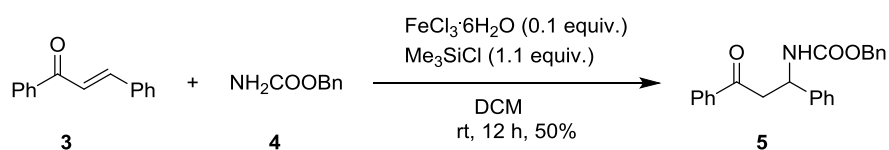
Scheme 1.2: Aza-Michael reaction of carbamate (**4**) with β-phenylenone (**3**)

Han *et al.*[23] synthesized a series of acidic-functionalized ionic liquid catalysts and used them for hetero-Michael addition of ethyl carbamate (**7**) to α, β-unsaturated ketones (**6**) under solvent-free conditions at room temperature to obtain the corresponding β-amino carbonyl compounds (**9**) (Scheme 1.3). 1-methylimidazolium p-toluenesulfonate [(Hmim)OTs] (**8**) was found to be the most efficient catalyst thereby demonstrating a wide substrate scope in good to excellent yields.
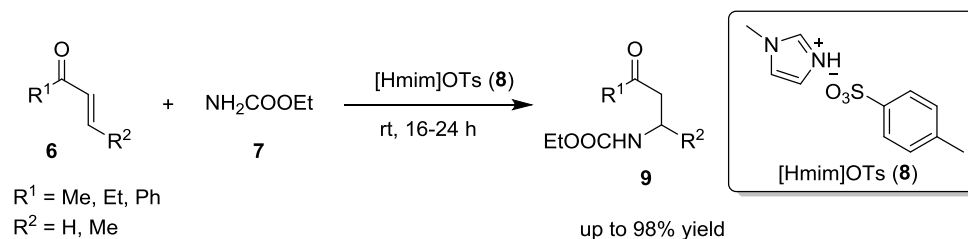

Scheme 1.3: Aza-Michael addition of α, β unsaturated ketones (**6**) with ethyl carbamate (**7**) catalyzed by [Hmim]OTs (**8**)

Ramachary and Mondal[24] reported hydroalkoxylation between alcohols and conjugated olefins (**10**) in the presence of amine as well as acid catalysts. The reactions proceeded in the absence of transition metals at room temperature. Commercially available amines and acids make this as an attractive protocol for the preparation of β-alkoxy ketones (**11**) (Scheme 1.4).
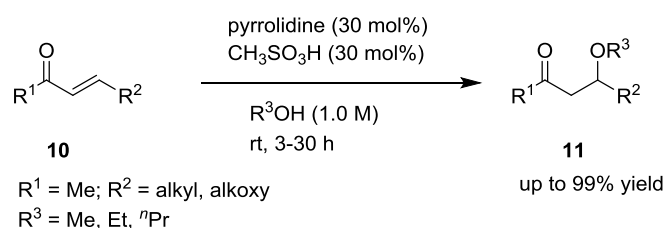
Scheme 1.4: Organocatalytic hydroalkoxylation of enones (**10**)

Chu *et al.*[25] described a 1, 4-addition of thiophenol (**13**) to $\alpha,\ \beta$-unsaturated ketones (**12**) in the presence of a catalytic amount of anhydrous $FeCl_3$ under solvent free conditions to give β-thiophenyl carbonyl compounds (**14**) (Scheme 1.5). These enones exhibit an enhanced reactivity in anhydrous $FeCl_3$ thereby reducing the reaction times and significantly improving the yields. This protocol contributed towards the development of a green strategy for the conjugate addition of thiols to enones.
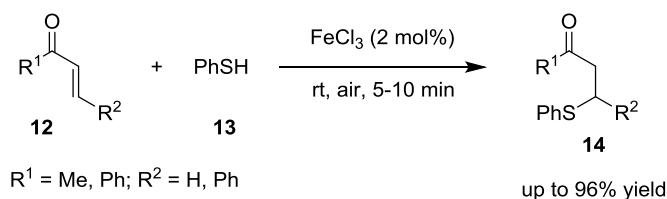
Scheme 1.5: $FeCl_3$-catalyzed conjugate addition of thiophenol (**13**) to unsaturated ketones (**12**)

Chu *et al.*[26] demonstrated an iodine catalyzed 1, 4-conjugate addition reaction of mercaptans (**16**) to $\alpha,\ \beta$-unsaturated ketones (**15**) to afford the corresponding β-thioalkyl carbonyl compounds (**17**) (Scheme 1.6). The highlights of this protocol are operational simplicity, inexpensive reagents, high yields of products, the use of relatively low or nontoxic reagents and solvent-free conditions.
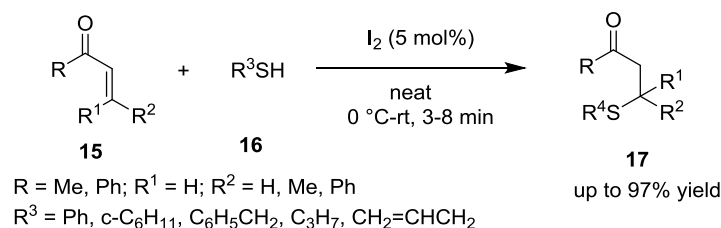

Scheme 1.6: Iodine-catalyzed Michael addition of thiols (**16**) to enones (**15**)

Yuan *et al.*[27] described the formation of 1, 2, 3-triazoles (**20**) from $\alpha,\ \beta$-unsaturated esters (**18**) with azides (**19**) using NHC based catalyst (Scheme 1.7). This protocol offered high yields and good regio-selectivities under metal-free conditions.
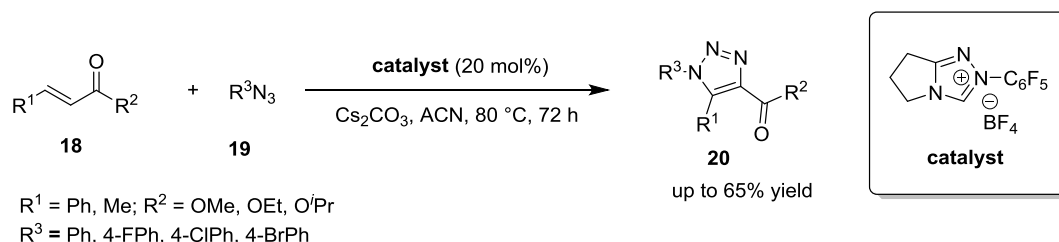
Scheme 1.7: NHC catalyzed cycloaddition of α, β-unsaturated esters (**18**) with azides (**19**)

Li *et al.*[28] demonstrated an iminium catalyzed 1, 3-dipolar cycloaddition reaction of α, β-unsaturated ketones (**21**) with azides (**22**) to furnish 1, 4, 5-trisubstituted 1, 2, 3-triazoles (**23**) in good yields with high levels of regioselectivity (Scheme 1.8).
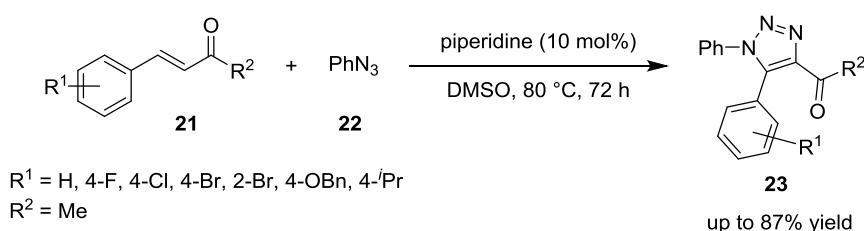

Scheme 1.8: Organocatalytic 1, 3-dipolar cycloaddition reaction of α, β-unsaturated ketones (**21**) with phenylazide (**22**)

Zhang *et al.*[29] reported an efficient Ru-catalyzed conjugate addition reaction of arylboronic acids (**24**) to enones (**25**) under neutral conditions to give conjugate addition products (**26**) (Scheme 1.9). This Ru (II)-catalyzed system efficiently inhibited the β-hydride elimination and protonolysis of arylboronic acids. Further, this protocol does not require any additional ligands.
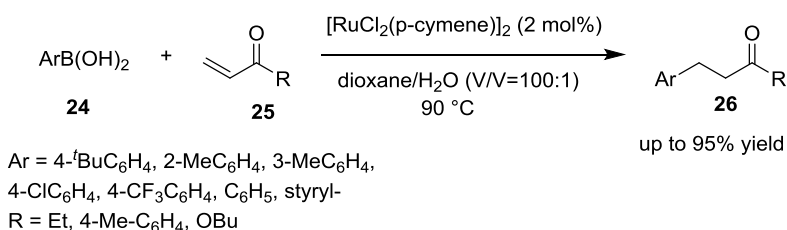

Scheme 1.9: Ru-catalyzed 1, 4-addition of boronic acids (**24**) to conjugated ketone (**25**)

Roscales *et al.*[30] reported trifluoroacetic anhydride catalyzed conjugate addition of arylboronic acids (**27**) to α, β-unsaturated ketones (**28**) under simple and metal-free conditions to afford the corresponding conjugate addition products (**29**) (Scheme 1.10). This protocol demonstrated good substrate scope in high yields.
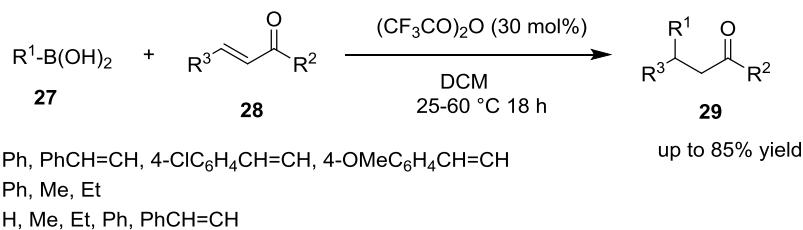
Scheme 1.10: Trifluoroacetic anhydride catalyzed conjugate addition of arylboronic acids (**27**) to unsaturated ketones (**28**)

Bartoli *et al.*[31] reported the first enantioselective organocatalytic Friedel-Crafts alkylation of indoles (**30**) with *α, β*-unsaturated ketones (**31**) in the presence of catalyst to give Friedel-Crafts alkylation/conjugate addition products (**32**) (Scheme 1.11). Novel and highly reactive amine salt catalyst was developed in which both the cation and the anion are chiral.
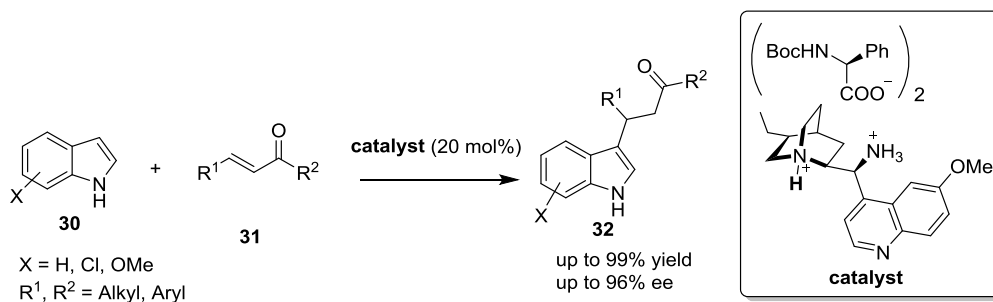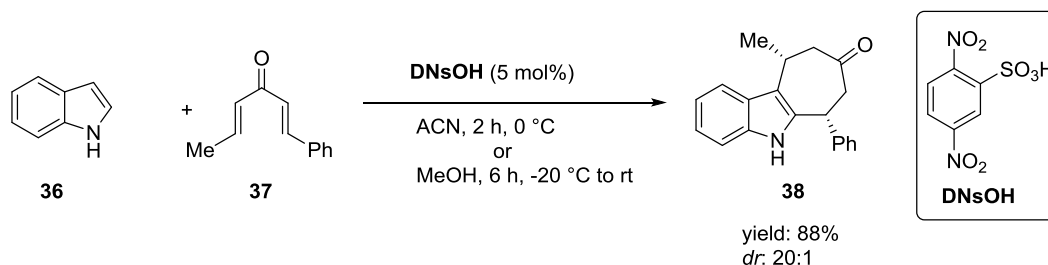

Scheme 1.11: Organocatalytic Friedel-Crafts alkylation of indoles (**30**) with *α, β*-unsaturated ketones (**31**)

Kang *et al.*[32] reported a chiral primary amine catalyzed organocatalytic enantioselective decarboxylative Michael addition reaction of *β*-keto acids (**33**) on unsaturated carbonyl compounds (**34**) in presence of cinchonine catalyst for the synthesis of chiral 1, 5-diketones (**35**) with excellent enantioselectivity (Scheme 1.12).
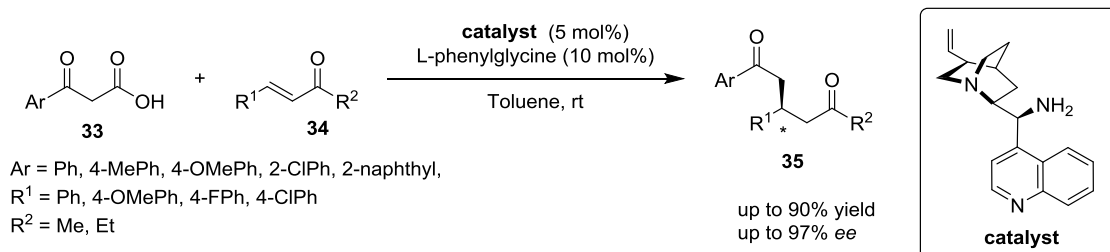

Scheme 1.12: Organocatalytic enantioselective decarboxylative Michael addition of *β*-keto acids (**33**)

Carbery and coworkers[33] described a Brønsted acid (**DNsOH**) catalyzed diastereoselective tandem double Friedel-Crafts reaction of indole (**36**) and non-symmetrical divinyl ketone (**37**) to form fused [6-5-7]-tricyclic indole (**38**) in 88% yield with *dr* 20:1 (Scheme 1.13). This reaction is highly regioselective and affords high levels of *syn*-diastereoselectivity.

Scheme 1.13: Double Friedel-Crafts reaction of indole (**36**) with divinyl ketone (**37**)

Mojzesova *et al.*[34] reported an enantioselective organocatalytic transformation of 3-penten-2-one (**39**) with 4-nitrobenzaldehyde (**40**) to pyranone (**41**) via oxa-Diels–Alder reaction under non-classical reaction conditions (Scheme 1.14). They also conducted the reaction under ultrasonic/microwave irradiation, solvent-free conditions using ball milling technique and flow micro-reactor.
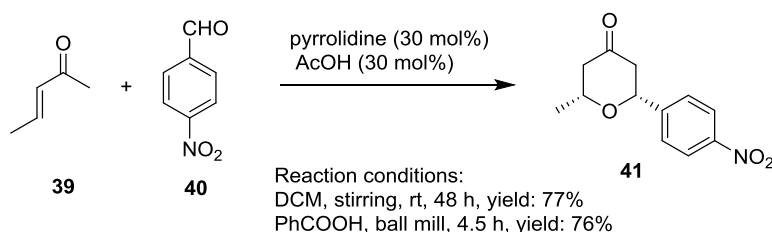
Scheme 1.14: Organocatalytic oxa-Diels–Alder reaction of 3-penten-2-one (**39**) with 4-nitrobenzaldehyde (**40**)

1.4 Applications of *α, β*-unsaturated carbonyl compounds in natural product synthesis

Loh *et al.*[35] demonstrated the application of *α, β*-unsaturated esters by synthesizing a key intermediate (**44**) by a DABCO catalyzed reaction of acetaldehyde (**42**) with methyl acrylate (**43**). The resulted Baylis-Hillman product (**44**) which upon a series of reactions gave Antillatoxin (**45**) (Scheme 1.15).
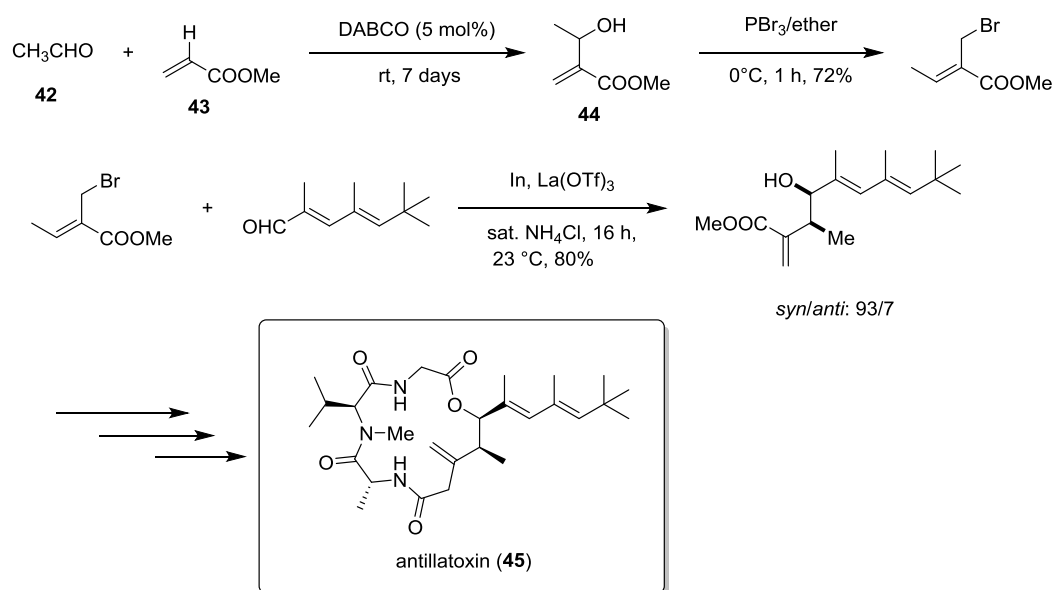
Scheme 1.15: Baylis-Hillman adduct (**44**) as a key intermediate for the synthesis of antillatoxin (**45**)

Smith *et al.*[36] reported an efficient synthesis of bio-active (–)–cylindrocyclophane F (**49**) from cyclobutenone derivative (**46**) via a sequential Danheiser annulation of **47** followed by ring closing metathesis dimerization (Scheme 1.16).
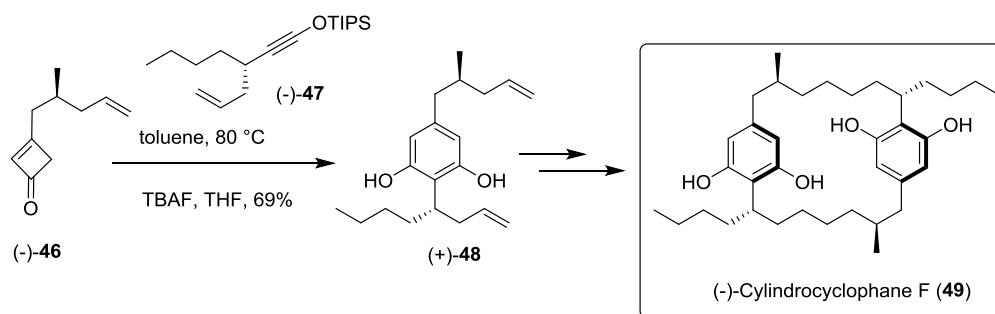
Scheme 1.16: Synthesis of (–)-cylindrocyclophane F (**49**) from cyclobutenone derivative (**46**)

Suzuki *et al.*[37] reported an effective SmI_2-mediated intramolecular reductive coupling of allyl chloride unit with α, β-unsaturated ester part in intramolecularly (**50**) to give precursors of (-)-kainic acid (**51**) and (+)-*allo*-kainic acid (**52**). Further, the oxidation of precursors **51, 52** in presence of CrO_3 afforded the (–)–kainic acid (**53**) and (+)–*allo*-kainic acid (**54**) (Scheme 1.17).
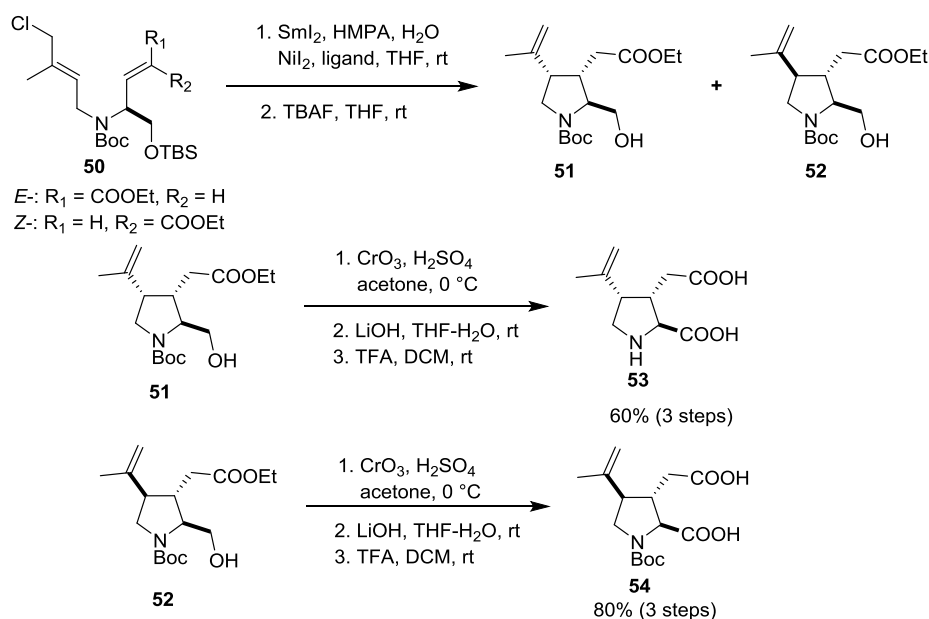
Scheme 1.17: Synthesis of (–)–kainic acid (**53**) and (+)–*allo*-kainic acid (**54**) from (**50**)

Due to their versatility, *α, β*-unsaturated carbonyl compounds have been explored in the synthesis of many bio-active molecules along with a wide range of functional group transformations. Hence, researchers have been focusing on the development of novel and practical methods for the synthesis of *α, β*-unsaturated carbonyl compounds. In this regard, few selected synthesis of *α, β*-unsaturated carbonyl compounds have been described.

1.5 Few selected synthesis of *α, β*-unsaturated carbonyl compounds and *α, β*-unsaturated esters

List and co-workers[38] reported the synthesis of *(E)-α, β*-unsaturated esters (**57**) from aldehydes (**55**) and malonate half esters (**56**) using Doebner-Knoevenagel condensation (Scheme 1.18). Both aromatic and aliphatic aldehydes afforded unsaturated esters (**57**) with good regio- and stereoselectively. This protocol was successfully used for the preparation of *p*-methoxycinnamates used as sunscreen ingredients.
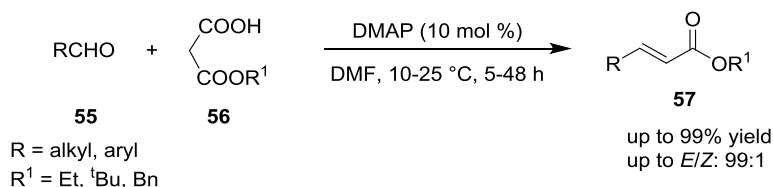

Scheme 1.18: The decarboxylative Knoevenagel-type reaction of malonate half esters (**56**) with aldehyde (**55**)

Claridge *et al.*[39] reported a highly *(E)*-selective Wadsworth-Emmons reaction for the synthesis of variety of unsaturated esters (**60**) through the reaction of various substituted aromatic aldehydes (**59**) with alkyl diethylphosphonoacetate (**58**) and MeMgBr (Scheme 1.19).
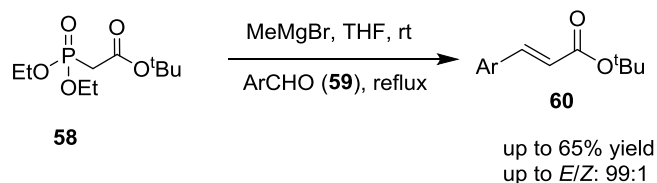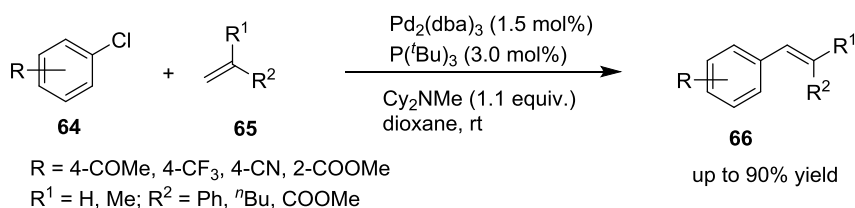

Scheme 1.19: Wadsworth-Emmons reaction of alkyl diethylphosphonoacetate (**60**) with aromatic aldehydes (**59**)

Lummiss *et al.*[40] reported the efficient synthesis of high-value *(E)*-cinnamates and *(E)*-ferulate esters (**63**) from the renewable phenylpropenoids (**61**) and various acrylates (**62**) using Ru-catalyst (Scheme 1.20). Essential-oil phenylpropenoids are transformed *via* acrylate cross-metathesis into potent antioxidants that are extensively used in perfumery and cosmetics, and in treating disorders related with oxidative damage.
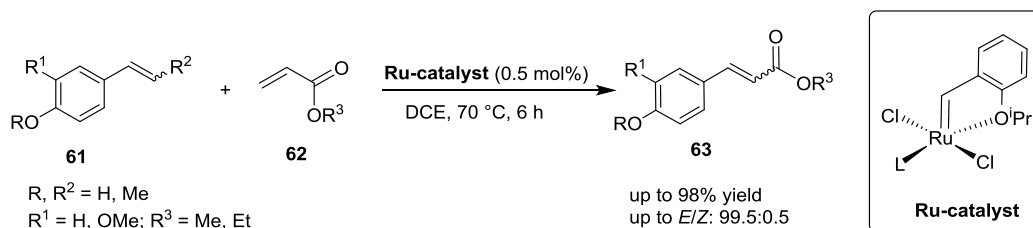

Scheme 1.20: Olefin cross-metathesis of phenylpropenoids (**61**) with acrylates (**62**)

Fu and co-workers[41] demonstrated Heck reaction of aryl chlorides (**64**) with olefins (**65**) catalyzed by a 2nd generation Cy$_2$NMe, Pd/P(^{t}Bu)$_3$ complex to give corresponding arylated products (**66**) with high *E/Z* stereoselectivity (Scheme 1.21). The protocol tolerated sterically and electronically diverse array of aryl bromides, as well as activated aryl chlorides, coupled with a range of mono- and di-substituted olefins at room temperature.


Scheme 1.21: Heck coupling of aryl chlorides (**64**) with olefins (**65**)

Concellon *et al.*[42] described a stereoselective reaction of aldehydes (**67**) with ethyl dibromoacetate (**68**) promoted by SmI_2 or $CrCl_2$ to afford *(E)-α, β*-unsaturated esters (**69**) (Scheme 1.22). The transformation takes place *via* two sequential reactions:an aldol-type reaction followed by *E*-stereoselective *β*-elimination reaction. The stereoselectivity of this reaction was proposed on the basis of the chelation of the Sm^{III} or Cr^{III} centers with both oxygen atoms.

Scheme 1.22: Stereoselective synthesis of *(E)-α, β*-unsaturated esters (**69**) using SmI_2, $CrCl_2$

Nishizawa *et al.*[43] reported a water compatible reaction of *(E)*-selective alkyl-substituted *sec*-ethoxyalkynyl acetate (**70**) catalyzed by $Hg(OTf)_2$ to give *α, β*-unsaturated ester (**71**) in excellent yield under mild conditions (Scheme 1.23). This protocol is particularly noteworthy for giving complete *E*-selectivity higher than the HWE reaction.

Scheme 1.23: Hydration of *sec*-ethoxyalkynyl acetate (**70**) catalyzed by $Hg(OTf)_2$

Puri *et al.*[44] demonstrated $BF_3 \cdot OEt_2$ mediated *syn*-selective Meyer–Schuster rearrangement to give *(Z)-β*-aryl-*α, β*-unsaturated esters (**73**) from phenoxy propargyl alcohols (**72**) under ambient conditions (Scheme 1.24). The reaction mechanism is proposed to involve an electrophilic borylation of an allene intermediate as the key step to kinetically control the stereoselectivity.

Scheme 1.24: *Syn*-selective Meyer–Schuster rearrangement of phenoxypropargyl alcohols (**72**)

Ozeki and co-workers[45] reported the selective synthesis of trisubstituted *(E)-α, β*-unsaturated esters (**77**) *via* a sequential aldol reaction (**74** to **75**), acetylation of the hydroxy group at the *β*-position (**75** to **76**), and an E1cB reaction (**76** to **77**) induced by 1, 8-diazabicyclo[5.4.0]undec-7-ene (DBU) (Scheme 1.25). They also showed that the reaction is suitable for gram scale synthesis.
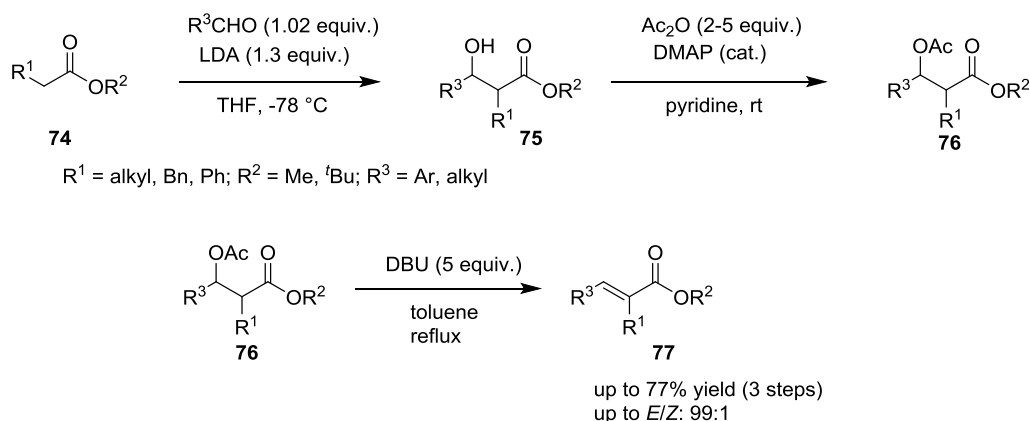

Scheme 1.25: Synthesis of trisubstituted *(E)-α, β*-unsaturated esters (**77**)

Bhat and co-workers[46] described a cost-effective catalytic route for the stereoselective synthesis of *α, β*-unsaturated esters (**80**) starting from alkylidene Meldrum's acids (**78**) and alcohols (**79**) in presence of catalytic amount of $FeCl_3 \cdot 6H_2O$ (Scheme 1.26). This methodology provides an easy and direct access to a range of *α, β*-unsaturated esters, including the synthesis of compound of high industrial value such as octinoxate-a sunscreen filter.
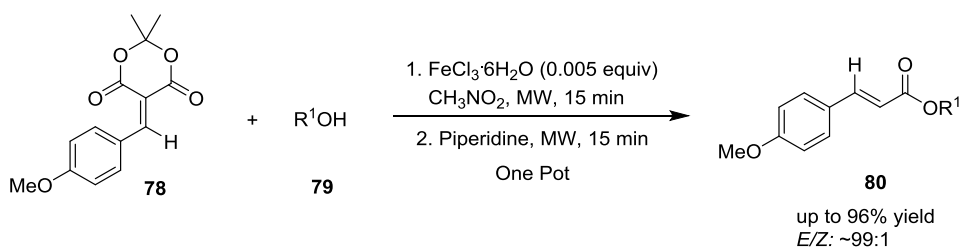

Scheme 1.26: Synthesis of *p*-methoxycinnamates (**80**)

Dheur *et al.*[47] reported the hydroacylation of terminal alkynes (**82**) with aryl boronic acids (**81**) involving rhodium acyl reagents generated under CO pressure to give *(E)-α, β*-unsaturated ketones (**83**) (Scheme 1.27). The reaction proceeded without any additional use of phosphine ligands.
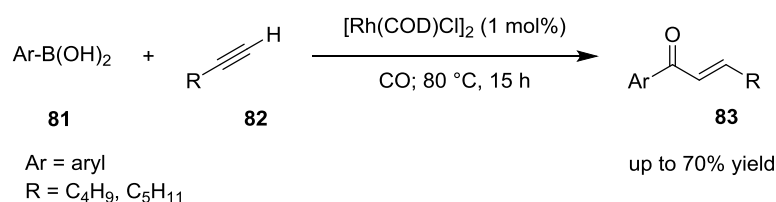
Scheme 1.27: 1, 4-Carbonylative addition of aryl boronic acids (**81**) to terminal alkynes (**82**).

Pennell *et al.*[48] reported Au (I)-catalyzed Meyer–Schuster rearrangement of primary, secondary and tertiary propargylic alcohols (**84**) at room temperature to give enones (**85**) in excellent yields (Scheme 1.28). Small quantities of MeOH or 4-methoxyphenylboronic acid were also required to get optimum results.
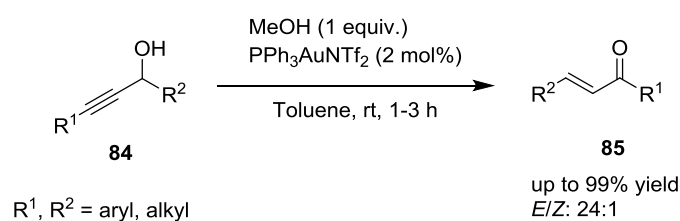
Scheme 1.28: Meyer-Schuster rearrangement of secondary propargylic alcohols (**84**)

Viviano *et al.*[49] developed the synthesis of 4-aryl-3-buten-2-ones (**87**) by using three different continuous flow strategies (Heck (**A**), Wittig (**B**), Aldol condensation (**C**) reactions) from Ar-X (**86**) (Scheme 1.29). They also synthesized few important anti-inflammatory drugs nabumetone, aroma compounds raspberry ketone [4-(4-hydroxyphenyl)-2-butanone] by using this protocol.
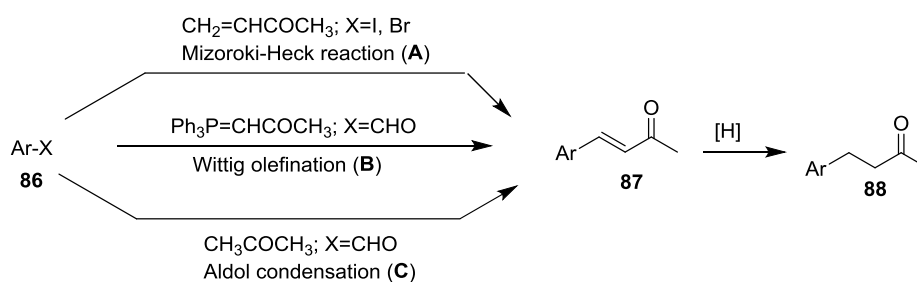
Reaction conditions:
A. 4-OMeC$_6$H$_4$I, Pd(OAc)$_2$, Cs$_2$CO$_3$, DMF/H$_2$O, 74%
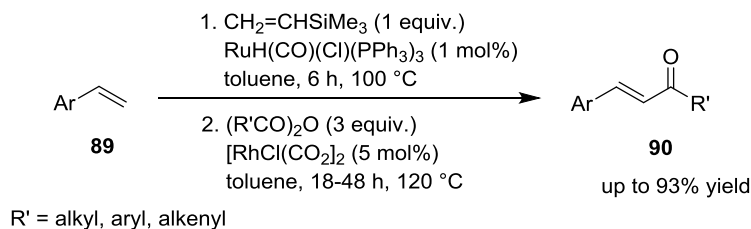**B.** ArCHO, DMF, 210 °C, 10 min, 98-70%
C. ArCHO, NaOH, acetone:H$_2$O (2:1), 97-69%

Scheme 1.29: Mizoroki-Heck reaction (**A**), Wittig reaction (**B**) and Aldol condensation (**C**) under microwave, batch and continuous flow conditions

Pawluc *et al.*[50] developed an efficient Ru- and Rh-catalyzed protocol for the highly stereoselective one-pot synthesis of *(E)*-styryl ketones (**90**) from styrenes (**89**). The reaction

15

involved through a sequential ruthenium-catalyzed silylative coupling[31] followed by rhodium-catalyzed desilylative acylation (Scheme 1.30).

1. CH$_2$=CHSiMe$_3$ (1 equiv.)
   RuH(CO)(Cl)(PPh$_3$)$_3$ (1 mol%)
   toluene, 6 h, 100 °C

2. (R'CO)$_2$O (3 equiv.)
   [RhCl(CO$_2$]$_2$ (5 mol%)
   toluene, 18-48 h, 120 °C

89

90

up to 93% yield

R' = alkyl, aryl, alkenyl

Scheme 1.30: One-pot synthesis of *(E)*-styryl ketones from styrenes

1.6 Conclusions

α, β-Unsaturated carbonyl compounds are very useful scaffolds and intermediates in organic synthesis. α, β-Unsaturated carbonyl compounds are good Michael acceptors and have been used for C-C, C-N, C-S, C-O and other bond formations. Many methods rely on the transition metal catalysts and organometallic reagents for the synthesis of α, β-unsaturated carbonyl compounds. Due to its importance, many methods have been developed for the synthesis of α, β-unsaturated carbonyl compounds and they have been utilized in various applications in organic synthesis. Most of the methods available in the literature are metal catalyzed and indeed it is challenging and demanding to synthesize α, β-unsaturated carbonyl compounds under metal free conditions.

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Chapter 2

Organocatalytic Approach for the Synthesis of α, β-Unsaturated Keto Compounds
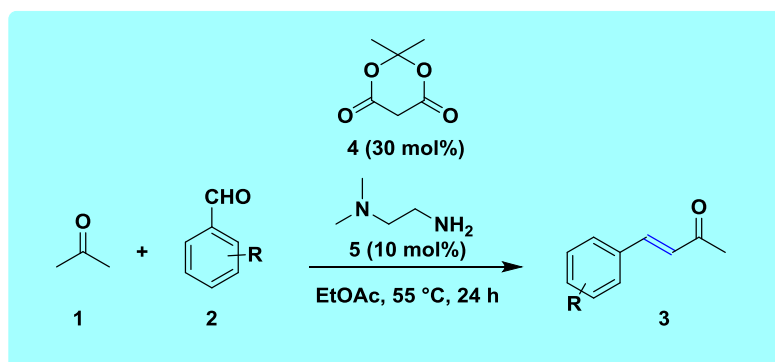
Organocatalytic Approach for the Synthesis of α, β-Unsaturated Keto Compounds

2

In this chapter a practical organocatalytic approach for the synthesis of α, β-unsaturated ketones via Aldol condensation of acetone with various aromatic and aliphatic aldehydes has been described. The highlights of this protocol are the easy availability of catalyst, high selectivity, and functional group tolerance. Reaction is very selective with no side products unlike base mediated reactions. In addition, we have also demonstrated the efficiency of catalyst system for synthesizing alkylidene β-keto esters from methyl acetoacetate with various aldehydes.

2.1 Introduction

α, β-Unsaturated carbonyl compounds and their derivatives are very important building blocks in organic synthesis.[1-3] These α, β-unsaturated ketone derivatives are key intermediates in several fields of organic synthesis,[1] biochemistry,[4] food chemistry and in agrochemicals.[5] However, these are widely used especially in synthetic transformations such as conjugate addition,[1,6-8] oxidation,[9,10] epoxidation,[11-13] peroxidation,[11,14] hydrogenation,[15-21] cycloaddition,[2,22-27] Morita-Baylis-Hillman reaction,[28] Diels-Alder Reaction,[29,30] cyclopropanation[31] as the starting materials.

Traditionally, these molecules are synthesized by Claisen-Schmidt condensation[32-35] using aldehydes and ketones catalyzed by strong bases such as NaOH, KOH and Ca(OH)$_2$ frequently used in stoichiometric amounts. However, the use of strong bases limits the scope of the reaction, as they produce a complex mixture of self-condensed side products and formation of large amounts of corrosive solid waste during work-up, and these methods have severe drawbacks with especially base-sensitive functional groups. In-spite of these

drawbacks, Claisen-Schmidt condensation is one of most common methods to prepare α, β-unsaturated ketone derivatives.

The other widely used methods include Wittig, Horner-Wadsworth-Emmons,[36-40] Peterson olefination,[41] further, these methods not only require strong bases to initiate the reaction but also they generate a stoichiometric amount of phosphorous and silicon containing by-products after the reaction.

As these α, β-unsaturated ketone derivatives are one of the important multi-functional group containing scaffolds, several methods have been developed for their synthesis that include catalytic,[42-46] one-pot,[47] ionic liquids,[48-51] and organometallic catalysts[52-55] to reduce the cost and by-products.

2.2 Some selected examples for the synthesis of α, β-unsaturated carbonyl compounds

Fernandes and co-workers[47] reported one-pot synthesis of β-substituted and β, β-disubstituted α, β-unsaturated methyl ketones (**10**) from homoallyl alcohols (**9**) by sequential PdCl$_2$/CrO$_3$ promoted Wacker process followed by an acid-mediated dehydration reaction (Scheme 2.1). They also explored internal homoallyl alcohols, which resulted in excellent regioselective formation of non-conjugated unsaturated carbonyl compounds under the optimized conditions.

R = H, X, OMe, NO$_2$, OH
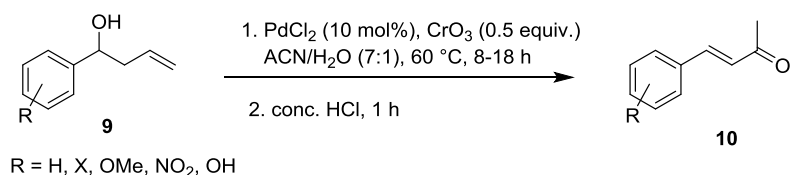
Scheme 2.1: One-pot conversion of secondary homoallyl alcohols (**9**) to β-substituted α, β-unsaturated methyl ketones (**10**)

Bellassoued *et al.*[56] demonstrated the conversion of benzaldehyde (**2a**) into benzylidene acetone (**3a**) in good yield with a high *E*-stereoselectivity using α, α-*bis*(trimethylsilyl) *N-tert*-butyl acetimine (**11**) (Scheme 2.2). The reaction was mediated by a catalytic amount of tetrabutylammonium fluoride (TBAF) under mild conditions. The disilylated reagent is easily generated from *N-tert*-butylacetimine, lithium diisopropylamide (LDA) and chlorotrimethylsilane.
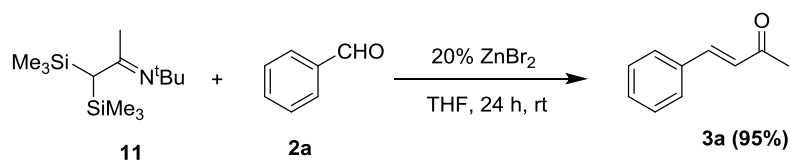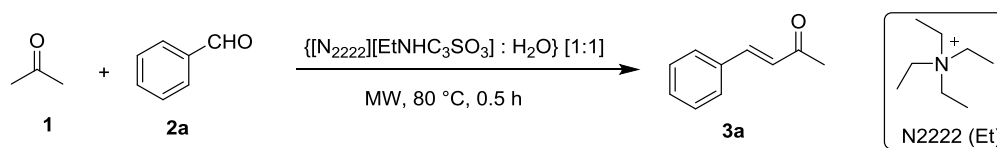
Scheme 2.2: Synthesis of benzylidene acetone (**3a**) using α, α-bis(trimethylsilyl) *N-tert*-butylacetimine (**11**) and $ZnBr_2$

A novel one-pot protocol that provides benzylidene acetone (**3a**) from benzyl amine (**12**) under mild conditions, using catalytic $CuCl_2 \cdot 2H_2O$ and *m*-CPBA as an oxidant was reported by Liu *et al*.[57] A variety of different α, β-unsaturated methyl ketone/nitro compounds were synthesized in moderate yields (Scheme 2.3).
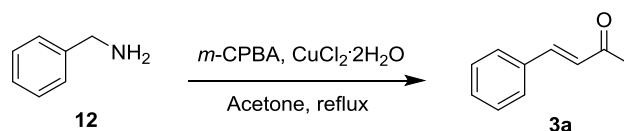
Scheme 2.3: The oxidation of benzylamine (**12**) by *m*-CPBA

Gao *et al*.[49] reported microwave-assisted aldol condensation reaction of benzaldehyde (**2a**) with acetone (**1**) in ionic liquid to afford **3a** in good yields (Scheme 2.4). It was observed that the aldol reaction proceeded more efficiently *via* microwave-assisted heating than through the conventional thermal heating. Further, ionic liquid (IL) was found to be reusable for at least five times without apparent loss of activity.

Scheme 2.4: Ionic liquid-catalyzed Aldol condensation

Xu *et al*.[58] described a practical approach for the synthesis of benzylidene acetone (**3a**), including the symmetrically or dissymmetrically substituted dimethylidene acetone derivatives by employing 5–10 mol% $Ca(OH)_2$ catalyst wherein the reactions were performed simply by using inexpensive and benign dilute aqueous ethanol (20 v/v%) as a solvent (Scheme 2.5). Further, evaporation of solvent directly gave the pure products in the excellent 96% yield.
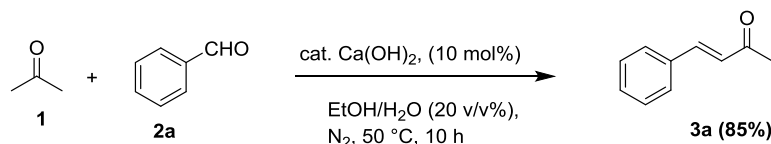
Scheme 2.5: Ca(OH)$_2$-catalyzed Claisen-Schmidt condensation

Nasrollahzadeh *et al.*[59] demonstrated an environmental friendly, phosphine free, highly efficient and stable heterogeneous Pd/CuO nanoparticles (NPs) for the Heck coupling of aryl halides (**13**) with electron withdrawing olefins (**14**) under aerobic conditions to give unsaturated ketones (**15**) (Scheme 2.6). This methodology has the advantages of high yields, phosphine free and easy work-up. Further, after the reaction, catalyst was recovered from the reaction mixture and reused several times without any significant loss of catalytic activity.

R = H, Cl, OH, OMe, CHO etc.
X = I, Br, Cl; Z = COMe, COOMe, CN
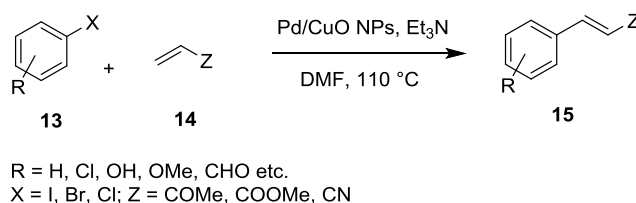
Scheme 2.6: Heck reactions of aryl halides (**13**) and olefins (**14**)

Chen *et al.*[60] developed a new strategy to perform the tandem Aldol condensation/dehydration of aromatic aldehydes (**16**) with acetone (**1**) using D-aminoacylase as biocatalyst and imidazole as co-catalyst in octane (Scheme 2.7). A series of α, β-unsaturated ketones (**17, 18**) was prepared efficiently by the reaction of various aldehydes with ketones using D-aminoacylase and imidazole in 2:1 ratio at 50 °C.

R = H, 2-NO$_2$, 3-NO$_2$, 4-NO$_2$
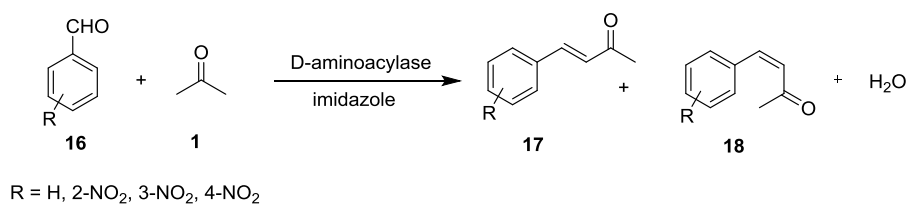
Scheme 2.7: D-aminoacylase and imidazole co-catalyzed tandem Aldol condensation/ dehydration between acetone (**1**) and aldehydes (**16**)

Mikami *et al.*[61] reported an efficient deoxygenation of styrene oxides (**19**) into the corresponding α, β-unsaturated ketones (**20**) catalyzed by hydrotalcite-supported silver nanoparticles (Ag/HT) using CO/H$_2$O as a reductant (Scheme 2.8). Various styrene oxide derivatives were smoothly converted to α, β-unsaturated ketones (**20**) in high yields without

affecting other reducible functionalities. The Ag/HT catalyst was reusable without loss of activity or selectivity.
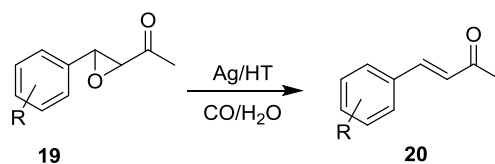
Scheme 2.8: Catalytic deoxygenation of epoxide (**19**) using Ag/HT with CO/H_2O

List *et al.*[62] developed an efficient and practical method for the aldol condensation of acetone (**1**) with aromatic and aliphatic aldehydes (**21**), using morpholinium trifluoroacetate as a catalyst (20 mol%) to give unsaturated ketones (**23**) (Scheme 2.9). The easily available catalyst, high selectivity, and functional group tolerance make this an attractive protocol.
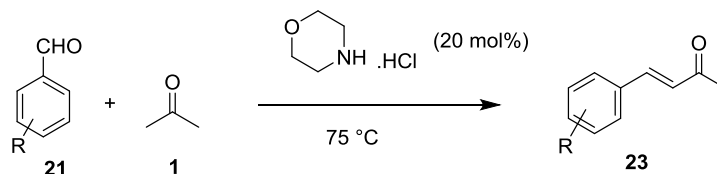
Scheme 2.9: Aldol condensation of aromatic aldehydes (**21**) with acetone (**1**)

In spite of many methods available in the literature, it is very desirable and challenging to develop more efficient practical protocols which afford the desired unsaturated keto compounds in good yields without forming any competing side products. In this regard, we planned to develop a novel organocatalytic protocol.

2.3 Results and Discussion

Initially, we started our study by choosing acetone (**1**) and benzaldehyde (**2a**) as model substrates to optimize the reaction conditions. At first we undertook the screening of different catalysts and co-catalysts. Catalysts such as L-proline, pyrrolidine, *N, N*-dimethylethylene diamine (DMEDA) were used at room temperature with and without the presence of co-catalyst. However, reaction with L-proline, pyrrolidine, *N*, *N*-dimethylethylene diamine (DMEDA) without any co-catalyst (Table 1, entry 1, 2, 5) were failed to give any expected product even after prolonged reaction time (48 h). In next attempts, we added Meldrum's Acid (MA) (**4**) as a co-catalyst (0.1 equiv.) wherein, we observed the formation of desired unsaturated ketone (**3a**) only in 10-20% (entry 3, 4, 6). Later, when the reaction was performed at 90 °C, we observed good conversion of the reaction, however, with the decomposition of Meldrum's Acid (MA) (**4**) during the course of the reaction (entry 7). Later,

we added Meldrum's acid (MA) gradually increasing the amount from 0.1 to 0.3 equivalent with time during the course of the reaction, which resulted in 55% yield. In order to minimize the decomposition of the Meldrum's acid (MA) and to increase yield of the product (**3a**), we planned to optimize the temperature of reaction.

**Table 2.1:** Screening of catalyst and co-catalyst for optimizing the reaction conditions[a]
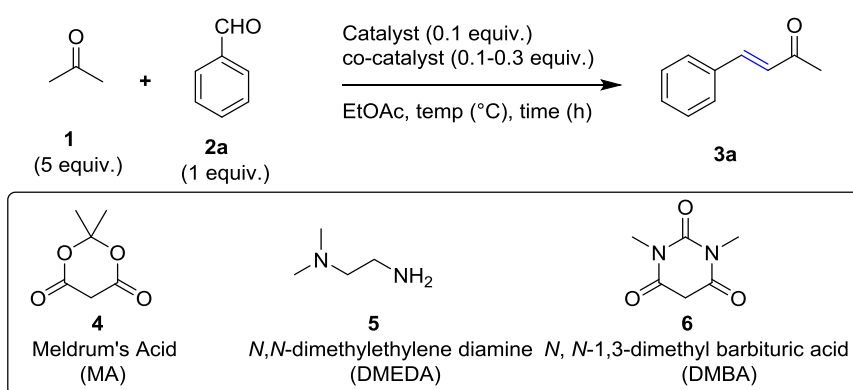
Entry	Catalyst	Co-catalyst	Temp (°C)	Time (h)	Yield (%)[b]
1	L-Proline	-	rt	48	NR
2	Pyrrolidine	-	rt	48	Trace
3	L-Proline	MA (0.1)	rt	48	10
4	Pyrrolidine	MA (0.1)	rt	48	15
5	DMEDA	-	rt	48	Trace
6	DMEDA	MA (0.1)	rt	48	20
7	DMEDA	MA (0.3)	90	48	55
8	DMEDA	MA (0.3)	55	24	80
9	-	MA (0.3)	55	48	NR
10	DMEDA	DMBA (0.1)	55	24	70
11	DMEDA	DMBA (0.3)	55	36	76

[a]Reaction of aldehyde **2a** (4 mmol, 1 equiv.), acetone **1** (20 mmol, 5 equiv.), catalyst (0.1 equiv.) and co-catalyst (0.1-0.3 equiv.) in ethyl acetate as solvent. [b]Isolated yield of the product, purified by column chromatography, reaction progress was monitored by TLC.

To our delight, when we carried out the reaction at 55 °C for 24 h, we observed the formation of benzylidene acetone (**3a**) in 80% yield (entry 8). However, catalytic amount of

Meldrum's acid (MA) (**4**) did not afford any desired product even after prolonged reaction time (48 h) (entry 9). Whereas the combination of *N*, *N*-dimethylethylene diamine (DMEDA) as a catalyst and *N*, *N*-1, 3-dimethyl barbituric acid (**6**) (DMBA, 0.1 equiv.) as a co-catalyst at 55 °C afforded the desired product **3a** in 70% yield in 24 h (entry 10). However, prolonging the reaction time (36 h) and increasing the catalytic amount of DMBA (0.3 equiv.) under similar reaction conditions did not have any significant effect on the yield and rate (Table 1, entry 11).

Table 2.2: Screening of the reaction in solvents[a]
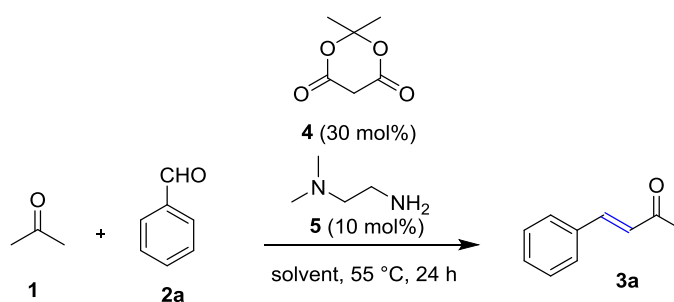
| Entry	Solvent	Time (h)	Yield (%)[b]
1	DCM	48	72
2	CHCl$_3$	48	82
3	Toluene	48	75
4	EtOAc	24	80
5	Neat	48	62
6	ACN	48	73
7	THF	48	78
8	MeOH	48	45
10	DMF	48	Trace
11	DMSO	48	Trace

[a]Reaction of aldehyde **2a** (4 mmol, 1 equiv.), acetone **1** (20 mmol, 5 equiv.), catalyst **5** (DMEDA) (10 mol%) and co-catalyst **4** (MA) (30 mol%) in various solvents. [b]Isolated yield of the product, purified by column chromatography, reaction progress was monitored by TLC.

In order to evaluate the effect of solvents, reactions were carried out with the optimized catalyst **5** (DMEDA, 0.1 equiv.) and co-catalyst **4** (MA, 0.1-0.3 equiv.) using various solvents at 55 °C. Initially, the reactions were carried out using halogenated solvents

such as DCM and CHCl$_3$ to afford the desired products **3a** in 72 and 82% respectively in 48 h (Table 2, entry 1, 2). Whereas the reaction in toluene afforded the desired product **3a** in 75% in 48 h. Neat reaction conditions did not lead to satisfactory result (only 62% yield) (entry 5). We screened several other polar solvents, out of which EtOAc proved to be the optimum solvent by affording **3a** in 80% yield in 24 h (entry 4, 6-8). While solvents such as DMF and DMSO afforded trace amount of products and proved to be inefficient (entry 10, 11). We decided to explore the use of EtOAc as solvent for the further reaction scope instead of CHCl$_3$ based on the environmental considerations. Based on the exhaustive screening DMEDA (**5**) (0.1 equiv.) and Meldrum's acid (MA) (**4**) (30 mol%) in ethyl acetate at 55 ^{o}C proved to be the optimum reaction condition.

Scheme 2.10: Substrate scope of the reaction[a]
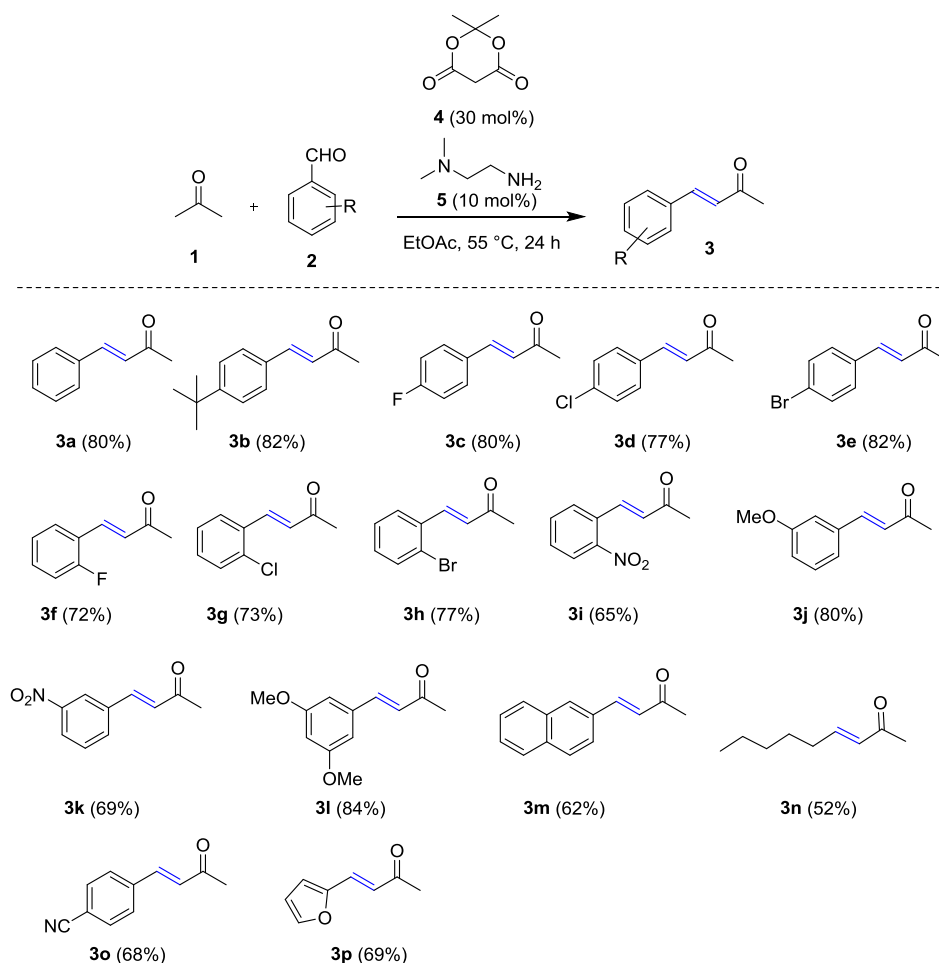
[a]Reaction of aldehyde **2a** (4 mmol, 1equiv.), acetone **1** (20 mmol, 5 equiv.), catalyst **5** (DMEDA) (10 mol%) and co-catalyst **4** (MA) (30 mol%) in EtOAc

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Having optimized the reaction condition in hand, we decided to explore the scope of the reaction using different aromatic aldehydes (**2a-2p**) as substrates under the optimized reaction conditions (Scheme 2.10). It was observed that the aromatic aldehydes with electronically activated as well as electronically deactivated groups reacted smoothly to furnish the corresponding products (**3a-3p**) in good yields (Scheme 2.10). However, in the case of electron deficient aromatic aldehydes reaction found to be sluggish, probably due to the stability of corresponding Knoevenagel intermediate formed during the reaction. Further, in order to show the generality of our protocol, aliphatic (**2n**) and heterocyclic aldehydes (**2p**) were used for the synthesis of *α, β*-unsaturated ketones (**3n**, **3p**) in moderate to good yields.

In order to further evaluate the activity our optimized catalytic system, we explored this catalyst system for the synthesis of alkylidene *β*-keto esters (**8**) via the reaction of aldehydes (**2**) and methyl acetoacetate (**7**) (Scheme 2.11). The reaction comprising of benzaldehyde (**2a**) and methylacetoacetate (**7**) afforded the corresponding product **8a** in 78% yield in 12 h. Both electronically activated and deactivated aldehydes reacted efficiently and afforded the corresponding desired products: alkylidene *β*-keto esters (**8b**-**8d**) in good yields in 12 h.

Scheme 2.11: Substrate scope of the reaction with methyl acetoacetate (**7**)[a]
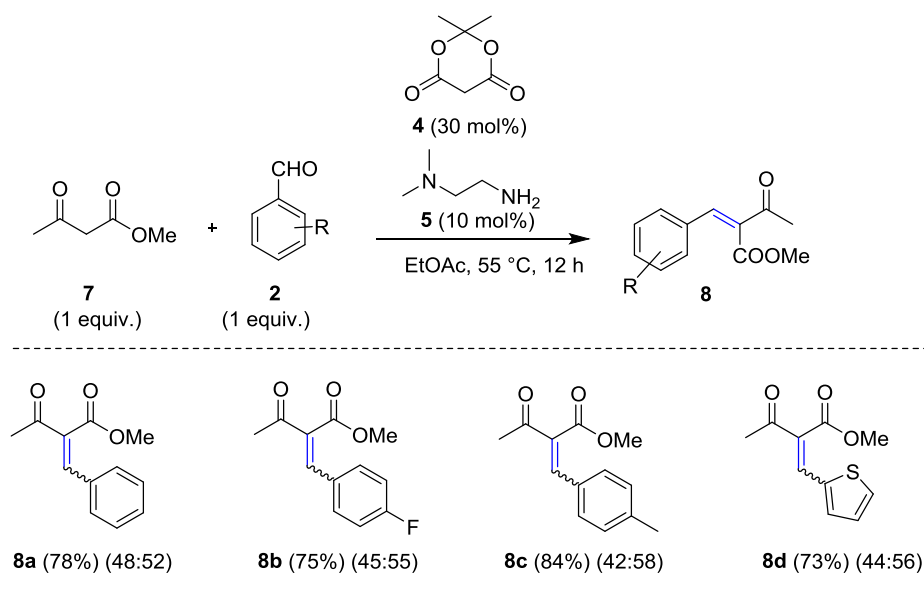
[a]Reaction of aldehyde **2a** (4 mmol, 1equiv.), methyl acetoacetate (4 mmol, 1 equiv.), catalyst **5** (DMEDA) (10 mol%) and co-catalyst **4** (MA) (30 mol%) in EtOAc

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2.4 Plausible mechanism of the reaction

Initially Meldrum's acid (**4**) reacts with aldehyde (**2**) to give corresponding Meldrum's adduct (**A**), which further undergoes conjugate addition with the previously generated enamine of acetone (**B**) to give the conjugate addition product (**C**). In the final step, the conjugate addition product (**C**) might be undergoing retro-Michael reaction to afford the expected unsaturated ketone (**3**) with the elimination of catalyst (**5**) (Scheme 2.13). The reaction is highly selective because it is working under milder, weak basic and organocatalytic conditions. The possibility of bis condensation product such as dibenzalacetone was not observed as the product formed was more stable than simple acetone. Moreover, since the formation of enamine/imine from acetone is more preferable than with the benzylidene acetone. Also, acetone is more electrophilic in nature. Even the reaction with 2 equiv. of aldehyde afforded only mono condensation product.
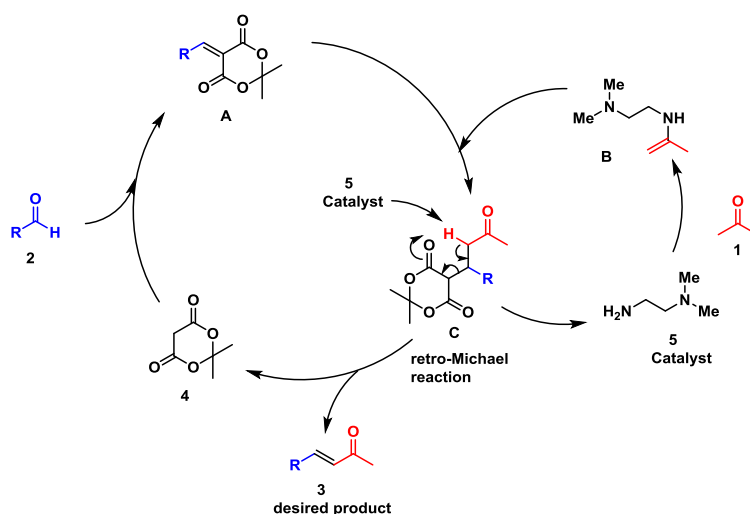
Scheme 2.13: Plausible mechanism for organocatalytic condensation reaction

2.5 Conclusions

In summary, we have developed a practical organocatalytic approach for the synthesis of *α, β*-unsaturated ketones *via* Aldol (Claisen-Schmidt) condensation of acetone with aromatic and aliphatic aldehydes. The easily and commercially available less expensive catalyst, high selectivity, and functional group tolerance are the highlights of this methodology. We did not observe any competing side products from self-condensation. In addition, catalytic system proved to be efficient for synthesizing alkylidene *β*-keto esters in good yields by the reaction of methyl acetoacetate with various aldehydes.

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2.6 Experimental Section

General: All starting materials were obtained from Aldrich, Acros, Merck and were used as obtained unless otherwise mentioned. All reactions were carried out with distilled and dried solvents under an atmosphere of dry N_2 and oven-dried glassware. All solvents CH_2Cl_2, toluene, EtOAc, Pet. ether, *n*-Pentane were purified and dried by using regular procedures using "Purification of Laboratory Chemicals" by Perrin and stored over activated 4 Å molecular sieves. All compounds were purified by using column chromatographic technique on 100-200 mesh size silica gel. Analytical thin-layer chromatography (TLC) was performed using Merck silica gel 60 GF_{254} pre-coated aluminum backed plates (2.5 mm) with spot detection under UV light or ninhydrin, PMA or vanillin. ^1H NMR and ^{13}C NMR were recorded in $CDCl_3$ on 400 MHz (100 MHz for ^{13}C). Chemical shifts in ^1H NMR and ^{13}C NMR spectra are reported as δ in ppm with the solvent resonance as the internal standard, coupling constants (*J*-values) are given in Hz. ^1H NMR data were reported in the order of chemical shift, multiplicity (s, singlet; d, doublet; t, triplet; m, multiplet; dt, doublet of triplet), coupling constant in hertz (Hz) and number of protons. High-Resolution mass spectra were obtained from HRMS-ESI-TOF. IR spectra of neat samples were recorded using FT-IR spectrophotometer and reported in cm^{-1}. All melting points were measured in open glass capillary and values are uncorrected.

General Procedure for the synthesis of unsaturated carbonyl compounds (3):

To a stirred solution of benzaldehyde **2** (4 mmol, 1 equiv.) and acetone **1** (20 mmol, 5 equiv.) in EtOAc (5 mL) were added Meldrum's Acid **4** (1.2 mmol, 30 mol%) and *N, N*-dimethylethylenediamine (DMEDA) **5** (0.4 mmol, 10 mol%) at room temperature. Then the reaction mixture was warmed to 55 °C and stirred for 18-24 h. After completion of reaction (as monitored by TLC), volatiles were evaporated and the residue was purified by silica gel column chromatography using EtOAc/petroleum ether (5-15:95-85) as an eluent to afford the unsaturated carbonyl compounds (**3**).

(*E*)-4-phenylbut-3-en-2-one (3a):
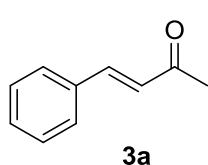
Pale yellow solid (470 mg, 80%); m.p. = 40-42 °C; R_f = 0.6 (5% EtOAc + Pet. ether); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.56 – 7.49 (m, 3H), 7.41– 7.39 (m, 3H), 6.72 (d, *J* = 16.3 Hz, 1H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 198.5, 143.6, 134.5, 130.6, 129.1, 128.4, 127.2, 27.6; HRMS (ESI–TOF) m/z Calcd. for C$_{10}$H$_{10}$O [M + H]$^+$ = 147.0810, observed = 147.0813.

(*E*)-4-(4-(tert-butyl)phenyl)but-3-en-2-one (3b):
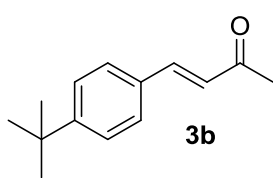
Pale yellow solid (665 mg, 82%); m.p. = 52-53 °C; R_f = 0.7 (5% EtOAc + Pet. ether); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.53 – 7.41 (m, 5H), 6.69 (d, *J* = 16.3 Hz, 1H), 2.38 (s, 3H), 1.33 (s, 9H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 198.7, 154.3, 143.6, 131.8, 128.3, 126.6, 126.1, 35.1, 31.3, 27.5; HRMS (ESI–TOF) m/z Calcd. for C$_{14}$H$_{18}$O [M + H]$^+$ = 203.1436, observed = 203.1440.

(*E*)-4-(4-chlorophenyl)but-3-en-2-one (3d):
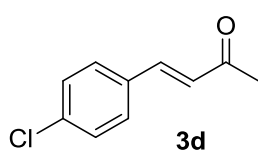
Pale yellow liquid (560 mg, 77%); R_f = 0.5 (5% EtOAc + Pet. ether); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.48 – 7.44 (m, 3H), 7.38 – 7.36 (m, 2H), 6.68 (d, *J* = 16.3 Hz, 1H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 198.2, 142.0, 136.5, 133.0, 129.5, 129.4, 127.6, 27.8; HRMS (ESI–TOF) m/z Calcd. for C$_{10}$H$_9$OCl [M + H]$^+$ = 181.0420, observed = 181.0430.

**(*E*)-4-(4-bromophenyl)but-3-en-2-one (3e):**
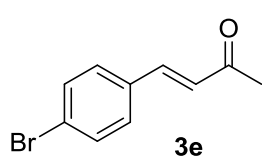
Pale yellow solid (741 mg, 82%); m.p. = 90-91 °C ; R_f = 0.6 (5% EtOAc + Pet. ether); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.54 – 7.52 (m, 2H), 7.46 – 7.39 (m, 3H), 6.70 (d, *J* = 16.2 Hz, 1H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 198.2, 142.1, 133.5, 132.3, 129.7, 127.7, 124.9, 27.8; HRMS (ESI–TOF) m/z Calcd. for C$_{10}$H$_9$OBr [M + H]$^+$ = 224.9915, observed = 224.9918.

(*E*)-4-(2-fluorophenyl)but-3-en-2-one (3f):
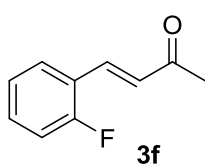
Yellow solid (472 mg, 72%); m.p. = 48-49 °C; R_f = 0.6 (5% EtOAc + Pet. ether); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.67 (d, *J* = 16.5 Hz, 1H), 7.57 (td, *J* = 7.6, 1.6 Hz, 1H), 7.38 (tdd, *J* = 7.2, 5.2, 1.6 Hz, 1H), 7.20 – 7.09 (m, 2H), 6.79 (d, *J* = 16.5 Hz, 1H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 198.6, 162.7, 160.2, 135.8, 135.8, 132.1, 132.0, 129.4, 129.3, 128.8, 128.8, 124.7, 124.7, 122.7, 122.5, 116.4, 116.2, 27.6; HRMS (ESI–TOF) m/z Calcd. for C$_{10}$H$_9$OF [M + H]$^+$ = 165.0715, observed = 165.0726.

(*E*)-4-(2-chlorophenyl)but-3-en-2-one (3g):
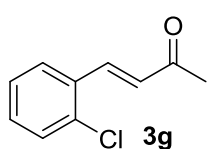
Pale yellow liquid (530 mg, 73%); R_f = 0.6 (5% EtOAc + Pet. ether); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.93 (d, *J* = 16.4 Hz, 1H), 7.65 – 7.63 (m, 1H), 7.44 – 7.42 (m, 1H), 7.35 – 7.27 (m, 2H), 6.67 (d, *J* = 16.4 Hz, 1H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 198.5, 139.3, 135.2, 132.8, 131.4, 130.3, 129.7, 127.7, 127.3, 27.3; HRMS (ESI–TOF) m/z Calcd. for C$_{10}$H$_9$OCl [M + H]$^+$ = 181.0420, observed = 181.0427.

(*E*)-4-(2-bromophenyl)but-3-en-2-one (3h):
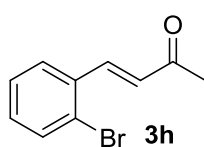
Yellow Liquid (691 mg, 77%); R_f = 0.6 (5% EtOAc + Pet. ether); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.89 (d, *J* = 16.3 Hz, 1H), 7.63 – 7.61 (m, 2H), 7.36 – 7.32 (m, 1H), 7.27 – 7.22 (m, 1H), 6.62 (d, *J* = 16.3 Hz, 1H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 198.4, 142.0, 134.5, 133.6, 131.5, 129.9, 127.9, 127.9, 125.7, 27.3; HRMS (ESI–TOF) m/z Calcd. for C$_{10}$H$_9$OBr [M + H]$^+$ = 224.9915, observed = 224.9923.

**(E)-4-(2-nitrophenyl)but-3-en-2-one (3i):**
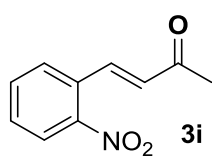
White pluffy solid (500 mg, 65%); R_f = 0.3 (10% EtOAc + Pet. ether); ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.09 – 8.07 (m, 1H), 7.99 (d, J = 16.2 Hz, 1H), 7.68 (qd, J = 7.9, 1.6 Hz, 2H), 7.58 (ddd, J = 8.7, 6.7, 2.2 Hz, 1H), 6.58 (d, J = 16.2 Hz, 1H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 198.2, 148.4, 139.1, 133.8, 132.0, 130.9, 130.6, 129.2, 125.2, 27.2; HRMS (ESI–TOF) m/z Calcd. for C$_{10}$H$_9$NO$_3$ [M + H]$^+$ =192.0660, observed = 192.0662.

(E)-4-(3-methoxyphenyl)but-3-en-2-one (3j):
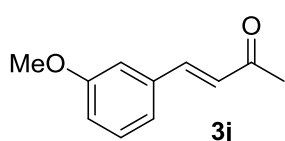
Yellow liquid (566 mg, 80%); R_f =0.5 (15% EtOAc + Pet. ether); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.48 (d, J = 16.3 Hz, 1H), 7.31 (t, J = 7.9 Hz, 1H), 7.14 (d, J = 7.7 Hz, 1H), 7.08 – 7.05 (m, 1H), 6.95 (ddd, J = 8.2, 2.3, 0.6 Hz, 1H), 6.70 (d, J = 16.3 Hz, 1H), 3.84 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 198.6, 160.0, 143.5, 135.9, 130.1, 127.5, 121.1, 116.5, 113.1, 55.4, 27.6; HRMS (ESI–TOF) m/z Calcd. for C$_{11}$H$_{12}$O$_2$ [M + H]$^+$ = 177.0915, observed = 177.0923.

**(E)-4-(3-nitrophenyl)but-3-en-2-one (3k):**
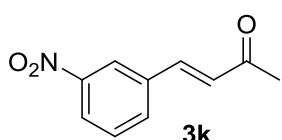
White Powder (530 mg, 69%); m.p. = 106-107 °C; R_f = 0.2 (5% EtOAc + Pet. ether); ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.40 (t, J = 1.8 Hz, 1H), 8.26 – 8.23 (m, 1H), 7.87 (d, J = 7.7 Hz, 1H), 7.63 – 7.54 (m, 2H), 6.84 (d, J = 16.3 Hz, 1H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 197.7, 148.8, 140.3, 136.4, 133.9, 130.1, 129.5, 124.8, 122.7, 28.1; HRMS (ESI–TOF) m/z Calcd. for C$_{10}$H$_9$NO$_3$ [M + H]$^+$ = 192.0660, observed = 192.0664.

**(E)-4-(3,5-dimethoxy phenyl)but-3-en-2-one (3l):**
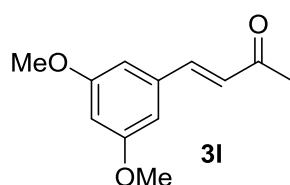
White pluffy solid (530 mg, 84%); R_f = 0.4 (15% EtOAc + Pet. ether); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.42 (d, J = 16.2 Hz, 1H), 6.69 – 6.66 (m, 3H), 6.50 (t, J = 2.3 Hz, 1H), 3.81 (s, 6H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 198.5, 161.1, 143.6, 136.4, 127.7, 106.2, 102.9, 55.5, 27.6; HRMS (ESI–TOF) m/z Calcd. for C$_{10}$H$_{10}$O [M + H]$^+$ = 207.1023, observed = 207.1016.

(*E*)-4-(naphthalen-2-yl)but-3-en-2-one (3m):
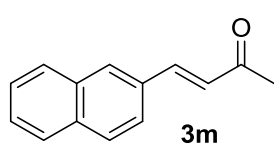
Yellow solid (485 mg, 62%); m.p. = 103-104 °C; R_f = 0.4 (5% EtOAc + Pet. ether); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.94 (s, 1H), 7.86 – 7.82 (m, 3H), 7.69 – 7.65 (m, 2H), 7.53 – 7.50 (m, 2H), 6.82 (d, *J* = 16.3 Hz, 1H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 198.5, 143.6, 134.4, 133.4, 132.0, 130.5, 128.9, 128.7, 127.9, 127.5, 127.4, 126.9, 123.6, 27.7; HRMS (ESI–TOF) m/z Calcd. for C$_{14}$H$_{12}$O [M + H]$^+$ = 197.0966, observed = 197.0972.

(*E*)-non-3-en-2-one (3n):
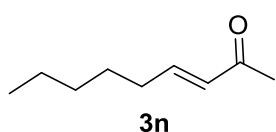
Pale yellow liquid (294 mg, 52%); R_f = 0.8 (5% EtOAc + Pet. ether); ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.81 (dt, *J* = 16.0, 6.9 Hz, 1H), 6.07 (dt, *J* = 16.0, 1.5 Hz, 1H), 2.25 – 2.20 (m, 5H), 1.51 – 1.44 (m, 2H), 1.36 – 1.28 (m, 4H), 0.92 – 0.88 (m, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 198.9, 148.8, 131.4, 32.5, 31.4, 27.8, 26.9, 22.5, 14.0; HRMS (ESI–TOF) m/z Calcd. for C$_9$H$_{16}$O [M + H]$^+$ = 141.1279, observed = 141.1286.

General procedure for the synthesis of alkylidene keto ester compounds (8):

To a stirred solution of benzaldehyde **2** (4 mmol, 1 equiv.) and methylacetoacetate **7** (4 mmol, 1 equiv.) in EtOAc (5 mL) were added Meldrum's Acid **4** (1.2 mmol, 30 mol%) and *N*, *N*-dimethylethylene diamine (DMEDA) **5** (0.4 mmol, 10 mol%) at room temperature. Then the reaction mixture was warmed to 55 °C and stirred for 8-12 h. After completion of reaction (as monitored by TLC), volatiles were evaporated and the residual reaction mixture was purified by silica gel column chromatography using EtOAc/ petroleum ether (5-15:95-85) as an eluent to afford the unsaturated carbonyl compounds (**8**).

**Methyl (*E*)-2-benzylidene-3-oxobutanoate (8a-*E*):**
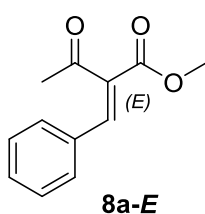
Yellow liquid (307 mg, 48%); R_f = 0.4 (15% EtOAc + Pet. ether); IR (Neat) cm^{-1}: 2954, 1725, 1438, 1254, 1206, 1047, 765, 694; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.70 (s, 1H), 7.39 (s, 5H), 3.84 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 203.5, 165.0, 140.9, 133.7, 132.9, 130.6, 129.8, 129.0, 52.6, 31.3; HRMS (ESI–TOF) m/z Calcd. for C$_{12}$H$_{12}$O$_3$ [M + H]$^+$ = 205.0865, observed = 205.0876.

**Methyl (*Z*)-2-benzylidene-3-oxobutanoate (8a-*Z*):**
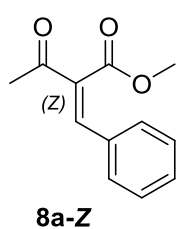
Yellow liquid (333 mg, 52%); R_f = 0.3 (15% EtOAc + Pet. ether); IR (Neat) cm^{-1}: 2952, 1730, 1665, 1436, 1214, 1039, 975, 756, 691; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.58 (s, 1H), 7.42 (tdd, *J* = 7.4, 5.1, 1.7 Hz, 5H), 3.84 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 194.8, 168.4, 141.7, 134.4, 132.9, 130.9, 129.5, 129.0, 52.7, 26.6; HRMS (ESI–TOF) m/z Calcd. for C$_{12}$H$_{12}$O$_3$ [M + H]$^+$ = 205.0865, observed = 205.0862.

Methyl (*E*)-2-(4-fluorobenzylidene)-3-oxobutanoate (8b-*E*):
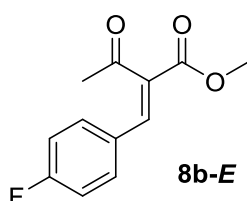
Pale yellow liquid (307 mg, 45%); R_f = 0.35 (15% EtOAc + Pet. ether); IR (Neat) cm^{-1}: 2955, 1734, 1704, 1598, 1509, 1228, 1165, 1049, 835; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.65 (s, 1H), 7.40 (dd, *J* = 8.8, 5.3 Hz, 2H), 7.07 (t, *J* = 8.6 Hz, 2H), 3.85 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 203.5, 165.2, 164.9, 162.7, 139.7, 133.5, 132.0, 131.9, 129.2, 129.1, 116.4, 116.2, 52.7, 31.3; HRMS (ESI–TOF) m/z Calcd. for C$_{12}$H$_{11}$O$_3$F [M + H]$^+$ = 223.0770, observed = 223.0776.

**Methyl (*Z*)-2-(4-fluorobenzylidene)-3-oxobutanoate (8b-*Z*):**
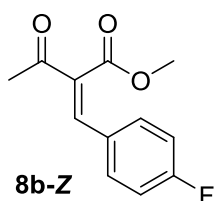
White solid (365 mg, 55%); m.p.=71-73 °C; R$_f$ = 0.3 (15% EtOAc + Pet. ether); IR (Neat) cm^{-1}: 1731, 1665, 1599, 1509, 1227, 1164, 1041, 834; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.56 (s, 1H), 7.47 – 7.41 (m, 2H), 7.09 (dd, *J* = 9.4, 7.8 Hz, 2H), 3.86 (s, 3H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 194.6, 168.3, 165.4, 162.9, 140.5, 134.1, 131.8, 131.7, 129.2, 129.2, 116.5, 116.2, 52.8, 26.7; HRMS (ESI–TOF) m/z Calcd. for C$_{12}$H$_{11}$O$_3$F [M + H]+ = 223.0770, observed = 223.0772.

Methyl (*E*)-2-(4-methylbenzylidene)-3-oxobutanoate (8c-*E*):
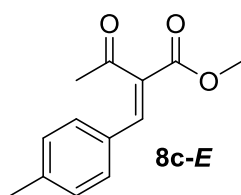
Pale yellow liquid (308 mg, 42%); R_f = 0.5 (15% EtOAc + Pet. ether); IR (Neat) cm^{-1}: 2953, 1701, 1614, 1433, 1254, 1777, 1061, 816; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.66 (s, 1H), 7.29 (d, *J* = 8.2 Hz, 2H), 7.18 (d, *J* = 7.9 Hz, 2H), 3.83 (s, 3H), 2.36 (d, *J* = 3.7 Hz, 6H); ^{13}C NMR

(100 MHz, CDCl$_3$) δ 203.8, 165.1, 141.2, 141.1, 132.7, 130.1, 130.0, 129.9, 129.8, 129.8, 115.2, 52.5, 31.3, 21.5; HRMS (ESI–TOF) m/z Calcd. for C$_{13}$H$_{14}$O$_3$ [M + H]$^+$ = 219.1021, observed = 219.1026.

**Methyl (Z)-2-(4-methylbenzylidene)-3-oxobutanoate (8c-Z):**
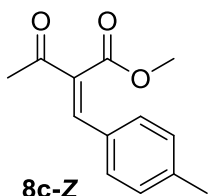
Pale yellow liquid (426 mg, 58%); R_f = 0.4 (15% EtOAc + Pet. ether); IR (Neat) cm^{-1}: 1733, 1664, 1607, 1437, 1386, 1218, 1184, 1042, 976, 812; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.55 (s, 1H), 7.35 – 7.31 (m, 2H), 7.22 – 7.17 (m, 2H), 3.85 (s, 3H), 2.41 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 194.8, 168.6, 141.8, 141.7, 133.5, 130.1, 129.8, 129.7, 52.6, 26.5, 21.6; HRMS (ESI–TOF) m/z Calcd. for C$_{13}$H$_{14}$O$_3$ [M + H]$^+$ = 219.1021, observed = 219.1024.

Methyl (E)-3-oxo-2-(thiophen-2-ylmethylene)butanoate (8d-E):
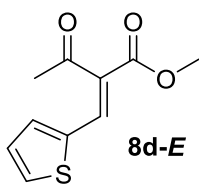
Pale yellow liquid (267 mg, 44%); R_f = 0.45 (15% EtOAc + Pet. ether); IR (Neat) cm^{-1}: 1699, 1607, 1421, 1348, 1251, 1348, 1251, 1204, 1174, 1060, 856, 719; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.81 (t, J = 0.7 Hz, 1H), 7.53 (dt, J = 5.1, 1.0 Hz, 1H), 7.37 (ddd, J = 3.8, 1.2, 0.6 Hz, 1H), 7.09 (dd, J = 5.1, 3.7 Hz, 1H), 3.84 (s, 3H), 2.49 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 202.2, 165.5, 136.1, 135.4, 134.8, 132.4, 129.1, 128.0, 52.5, 31.0; HRMS (ESI–TOF) m/z Calcd. for C$_{10}$H$_{10}$O$_3$S [M + H]$^+$ = 211.0429, observed = 211.0428.

Methyl (Z)-3-oxo-2-(thiophen-2-ylmethylene)butanoate (8d-Z):
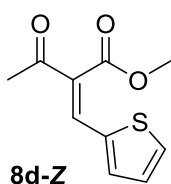
Pale yellow liquid (339 mg, 56%); R_f = 0.3 (15% EtOAc + Pet. ether); IR (Neat) cm^{-1}: 2951, 1725, 1657, 1605, 1426, 1266, 1202, 1048, 974, 931, 854, 718; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.75 (t, J = 0.7 Hz, 1H), 7.58 (dt, J = 5.1, 1.0 Hz, 1H), 7.41 (ddd, J = 3.8, 1.2, 0.6 Hz, 1H), 7.11 (dd, J = 5.1, 3.7 Hz, 1H), 3.95 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 194.4, 167.9, 136.3, 135.6, 134.6, 132.6, 130.1, 128.1, 52.8, 27.0. HRMS (ESI–TOF) m/z Calcd. for C$_{10}$H$_{10}$O$_3$S [M + H]$^+$ = 211.0429, observed = 211.0422.

2.7 Appendix I: ^{1}H and ^{13}C spectral data of representative compounds

Fig AI.1: ^{1}H NMR (400 MHz, CDCl$_3$) spectrum of compound **3a**

Fig AI.2: ^{13}C NMR (100 MHz, CDCl$_3$) spectrum of compound **3a**

7.54
7.54
7.53
7.52
7.46
7.42
7.41
7.41
7.40
7.39
6.72
6.68

2.38

1.98
3.26
1.04

3.00

AI.3: ^{1}H NMR (400 MHz, CDCl$_3$) spectrum of compound **3e**

198.2

142.1
133.5
132.3
129.7
127.7
124.9

27.8

Fig AI.4: ^{13}C NMR (100 MHz, CDCl$_3$) spectrum of compound **3e**

40

AI.5: ^{1}H NMR (400 MHz, CDCl$_3$) spectrum of compound **3k**

Fig AI.6: ^{13}C NMR (100 MHz, CDCl$_3$) spectrum of compound **3k**
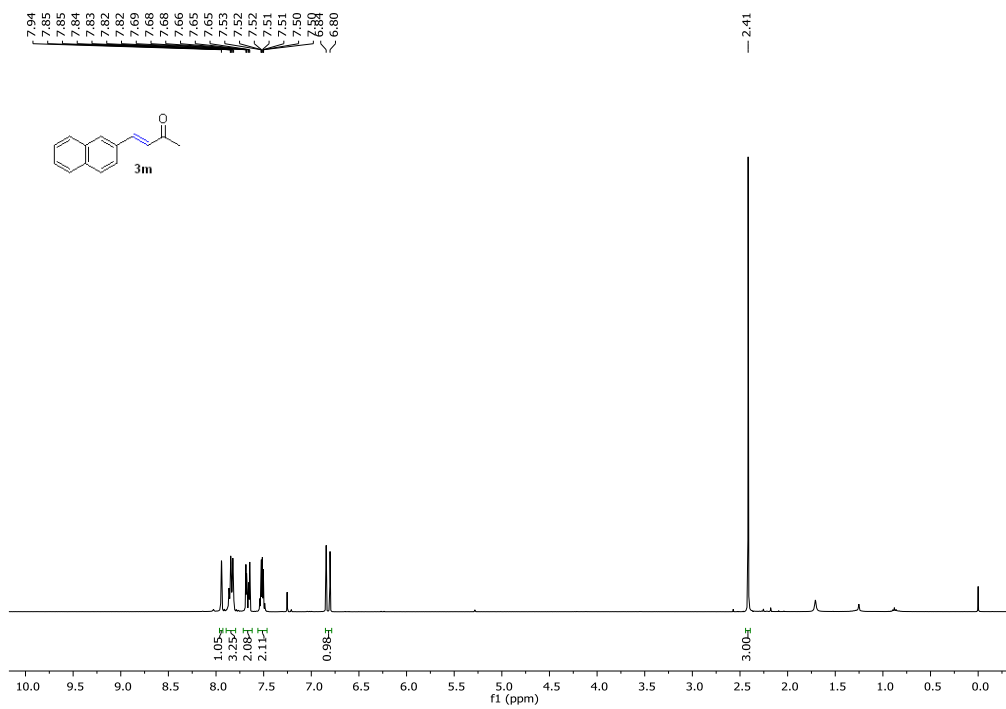
AI.7: ^{1}H NMR (400 MHz, CDCl$_3$) spectrum of compound **3m**
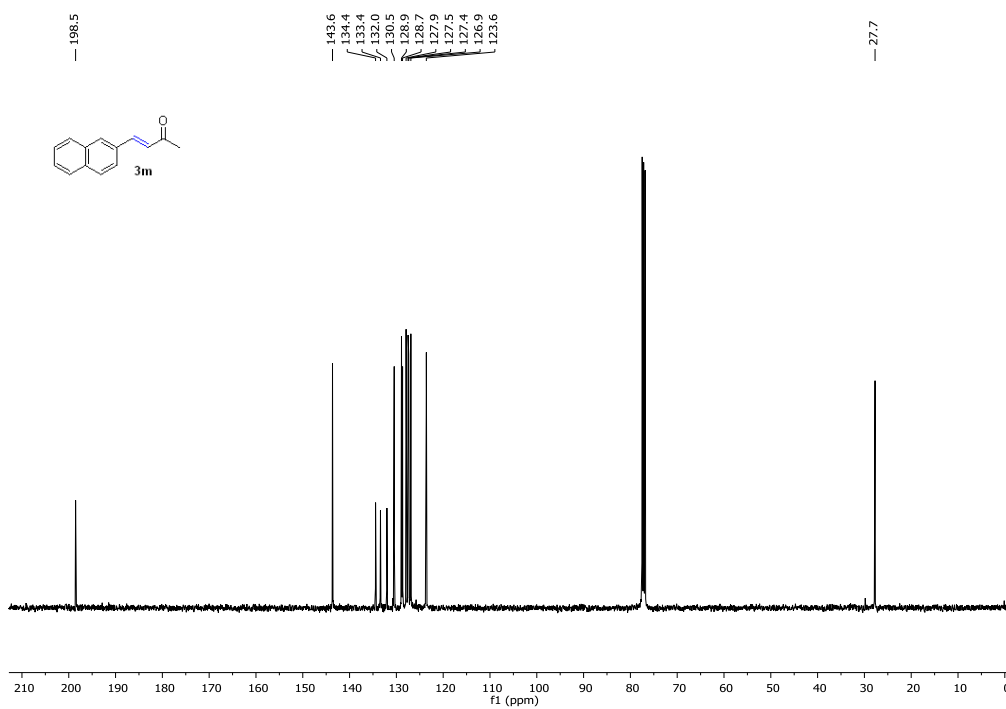
Fig AI.8: ^{13}C NMR (100 MHz, CDCl$_3$) spectrum of compound **3m**
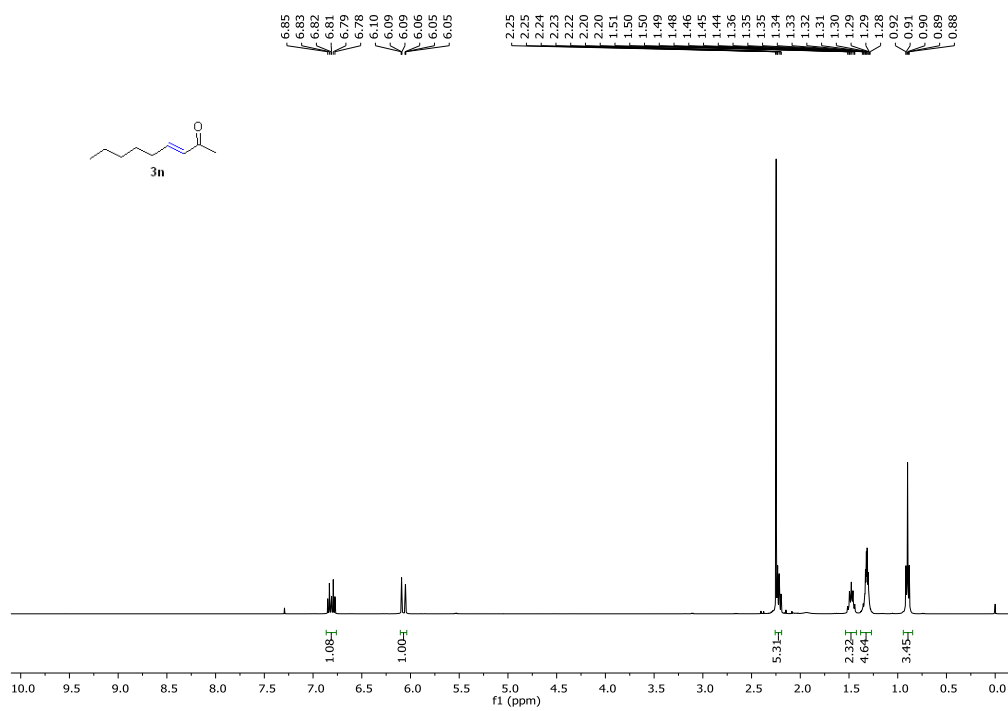
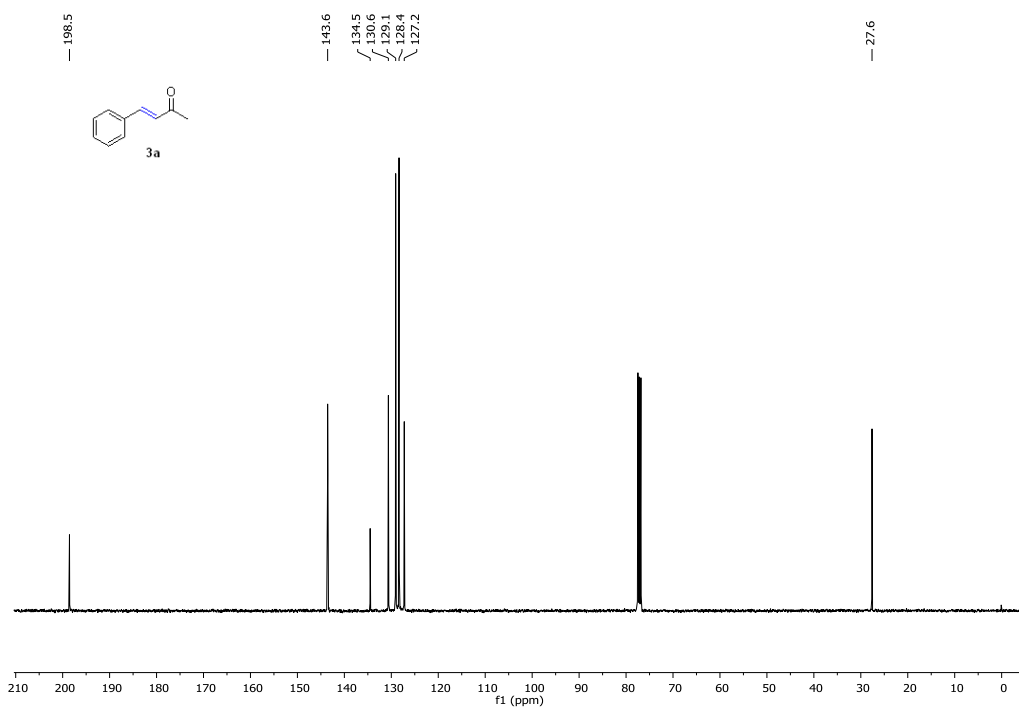**AI.9:** ^{1}H NMR (400 MHz, CDCl$_3$) spectrum of compound **3n**
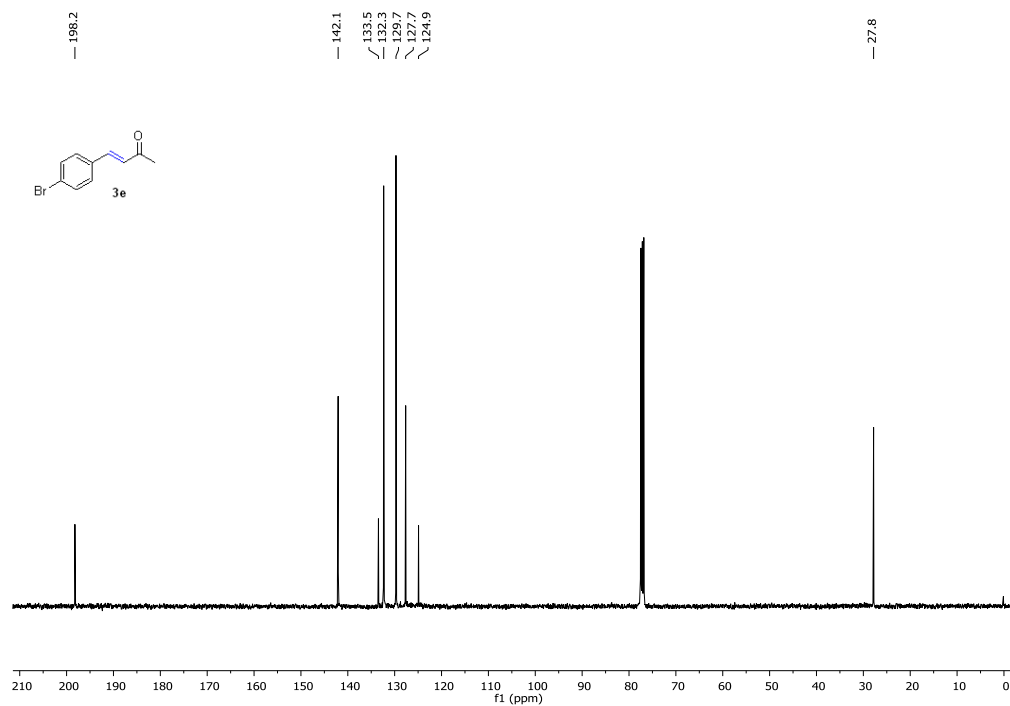

Fig AI.10: ^{13}C NMR (100 MHz, CDCl$_3$) spectrum of compound **3n**

AI.11: ^{1}H NMR (400 MHz, CDCl$_3$) spectrum of compound **8a-*E***

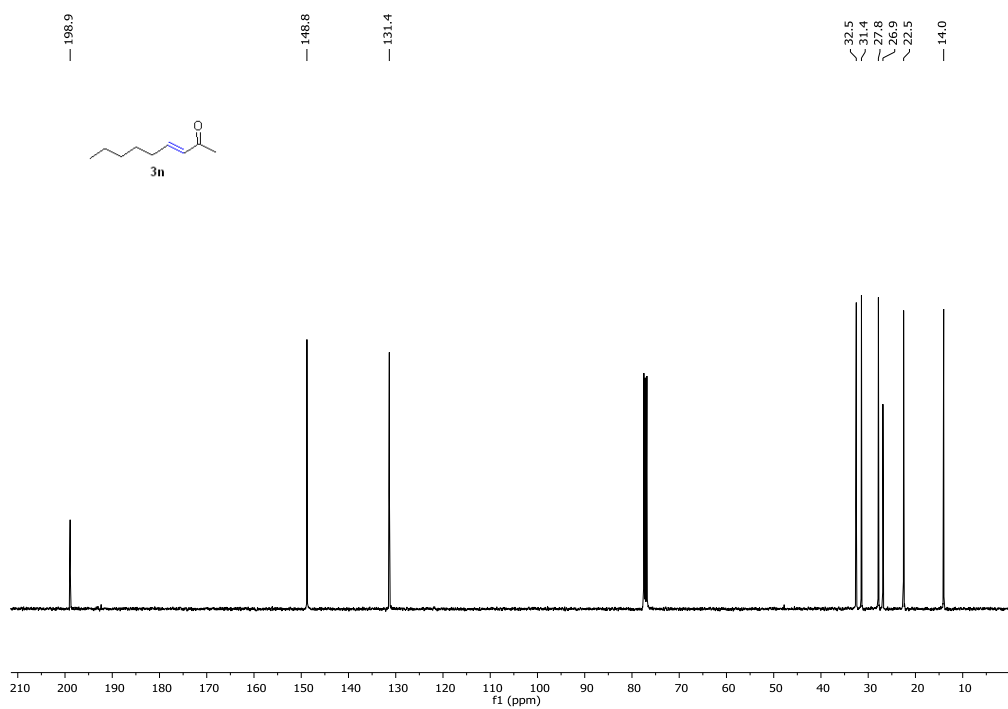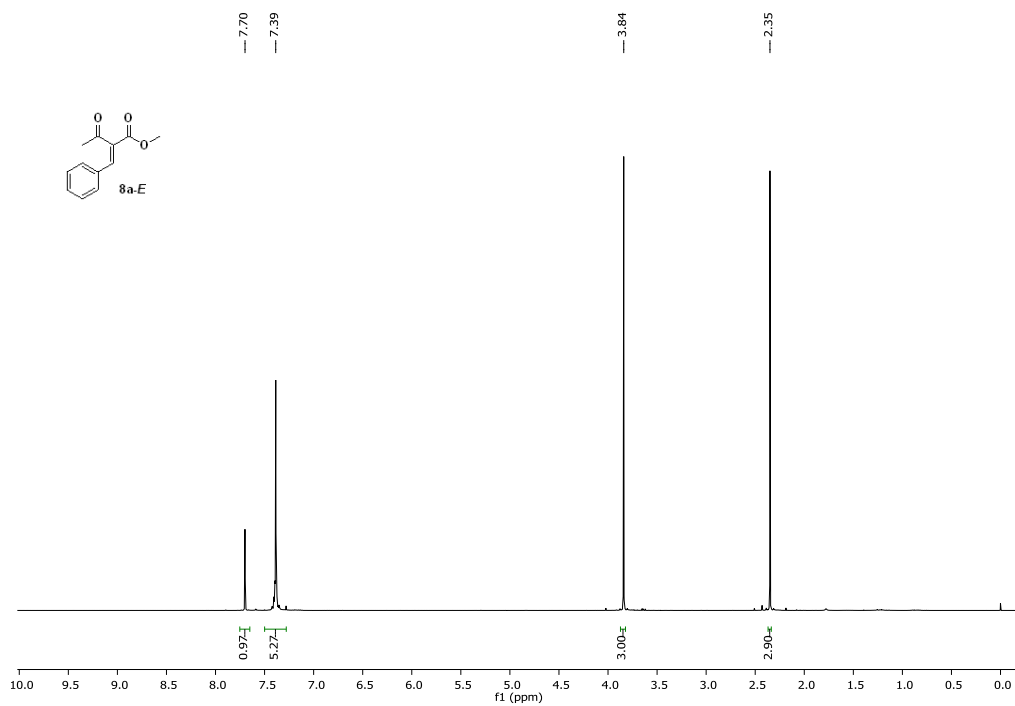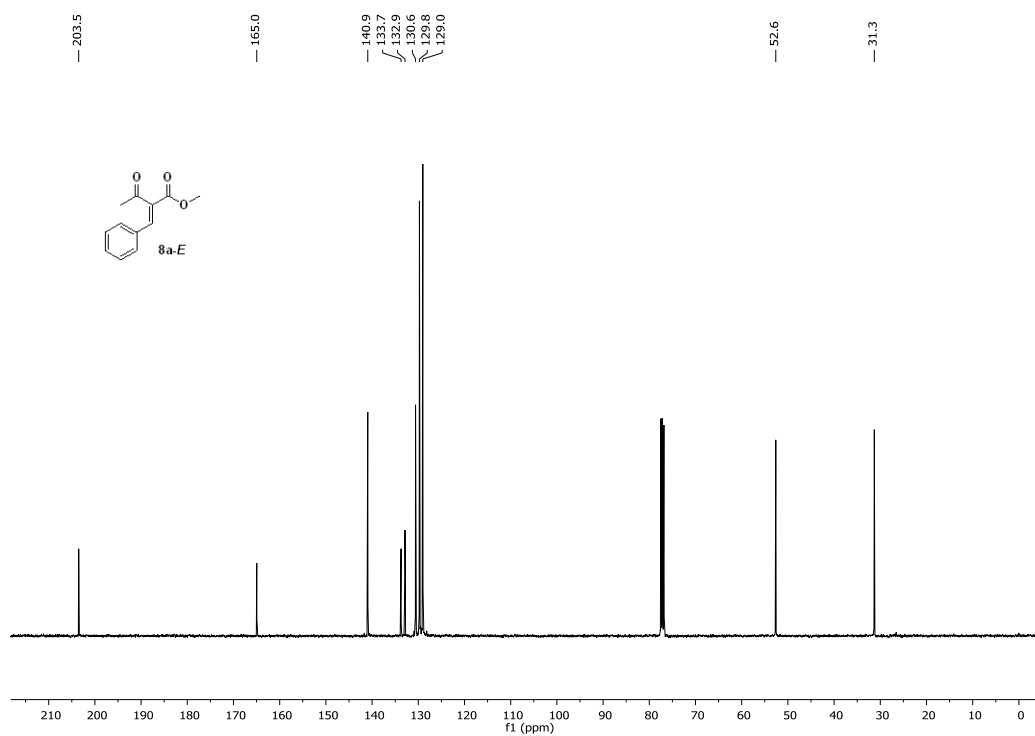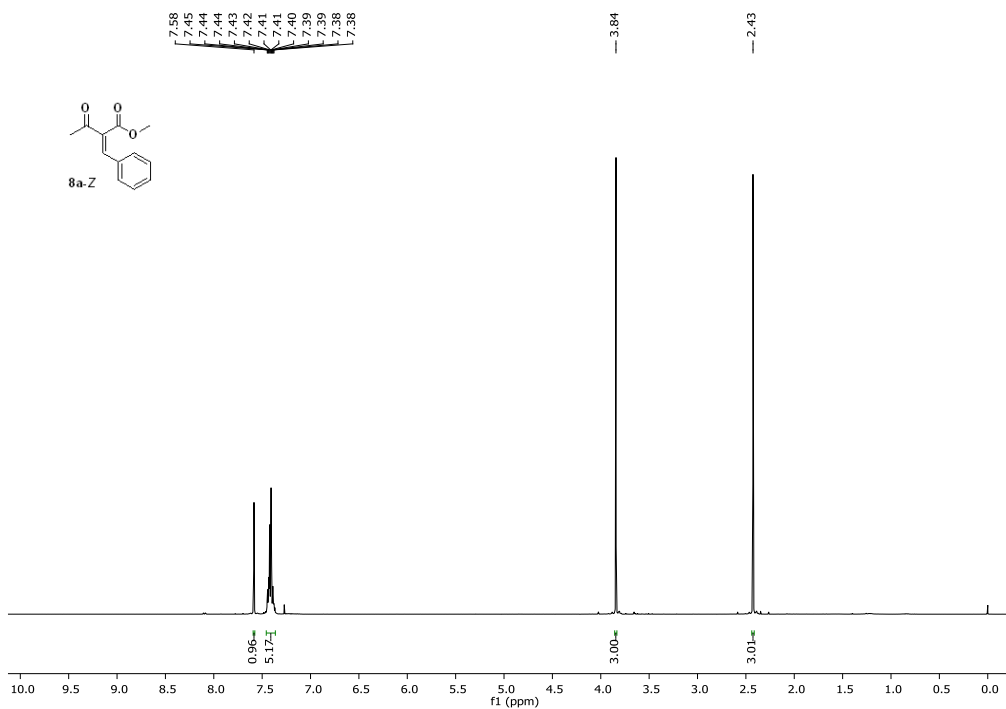**Fig AI.12:** ^{13}C NMR (100 MHz, CDCl$_3$) spectrum of compound **8a-*E***

AI.13: ^{1}H NMR (400 MHz, CDCl$_3$) spectrum of compound **8a-Z**
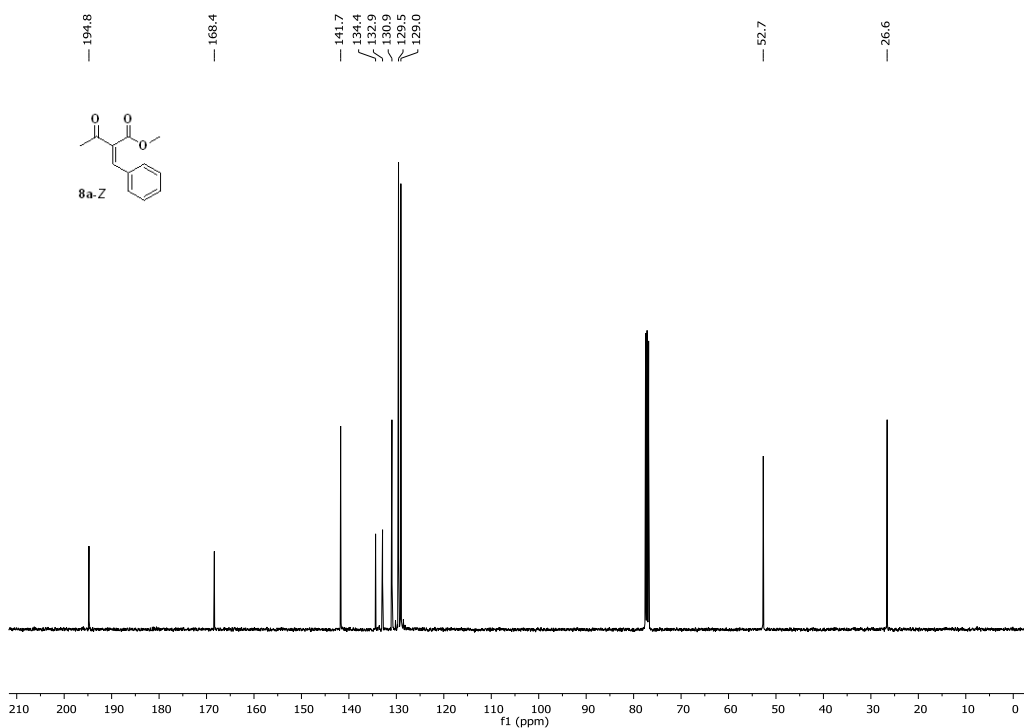
Fig AI.14: ^{13}C NMR (100 MHz, CDCl$_3$) spectrum of compound **8a-Z**

45

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Chapter 3

Iron (III) Catalyzed Selective Reduction of Alkylidene *β*-ketoesters
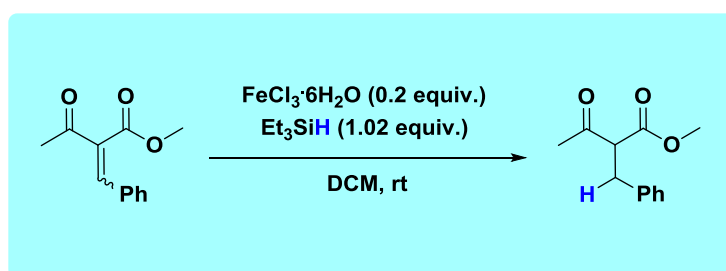
T H R E E

Iron (III) Catalyzed Selective Reduction of Alkylidene β-ketoesters

<div style="text-align:right">**3**</div>

FeCl$_3$.6H$_2$O/triethylsilane composite catalyst system is successfully developed for the selective conjugate reduction of carbon-carbon double bond of Michael acceptor-alkylidene β-keto esters under mild reaction conditions to afford the corresponding saturated β-keto esters. The process involves the iron-catalyzed hydrosilylation, followed by in situ hydrolysis of silyl enol ether. The optimal reaction conditions include 20 mol% of FeCl$_3$.6H$_2$O and triethylsilane in dichloromethane. A broad range of substrates undergoes reduction 1, 4-selective manner to afford the corresponding saturated compounds in excellent yields.

3.1 Introduction

Composite reducing systems comprising of hydrosilanes and transition metal catalysts have been highly successful reduction strategies in organic synthesis.[1-3] Chemoselective reduction of one functionality over another without any side reactions is always a challenge in both chemical and pharmaceutical industries. However, organosilanes unlike organometallic reagents are usually unreactive and inert towards various organic substrates.[4-6] Trialkylsilanes are known to be poor reducing agents and these organosilanes can be activated by appropriate Lewis acids in order to explore their use in organic synthesis.[4-9] Alternatively, transmetallation has also been explored to activate less reactive organosilanes to carry out organic transformations.[10,11] Nowadays, the selective conjugate reduction of α, β-unsaturated ketones has become one of the important functional group transformations for the synthesis of natural products and biologically active compounds under environmentally friendly conditions. The conjugate reduction of α, β-unsaturated ketones and esters commonly suffers from the competitive 1, 2-reduction to afford the corresponding allylic alcohols. It's known in the literature that Et$_3$SiH/EtMe$_2$SiH coupled with the suitable

transition metal reagents lead to conjugate addition of α, β-unsaturated ketones and esters.[12] Metals such as Cu, Ir, Pd, Mo, Rh and other metal complexes have been explored for the hydrosilylation reaction for achieving the conjugate reduction.[13-17] Usually, Rh and Ir features the most common noble metals for the hydrosilylation, however, hydrosilylation methods for the reduction of α, β-unsaturated ketones and esters have been achieved by exploring the use of first row elements[18,19] such as Ti, Zn, Cu, Fe, Ni and early transition element such as Mo.[16] Hydrosilylation strategy has been successfully used for the reduction of compounds such as olefins, carbonyls and imines.[20]

Reduction of conjugate systems is complex and alternative reduction pathways can lead to multiple reduction products. The reduction of compound **I** involve three pathways as shown in Figure 3.1. The selective reduction of **I** such as 1, 2-reduction, 1, 4-reduction and complete competitive reductions are very important and it is a challenging task in organic synthesis.[21] Reduction of **I** leads to a variety of possible products (**Ia**, **Ib**, **Ic**) in varying ratios under most reductive conditions (path a, path b, path c) as shown in Fig 3.1.
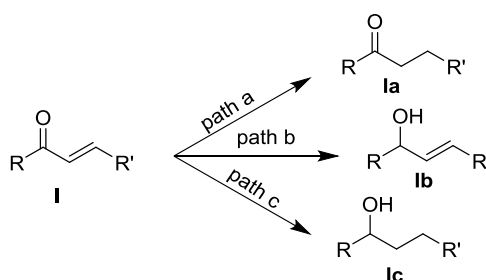
Fig 3.1: Common reductive fates of α, β-unsaturated carbonyl compounds (**I**)

3.2 Some selected literature reports for the selective reduction of α, β-unsaturated carbonyl compounds

Nakajima and co-workers[22] reported a Lewis base catalyzed conjugate reduction of benzylidene acetone (**9**) with trichlorosilane in the presence of HMPA and Ph$_3$PO to give saturated ketone (**10**) (Scheme 3.1). This research group has also demonstrated the reductive Aldol reaction by using this protocol.
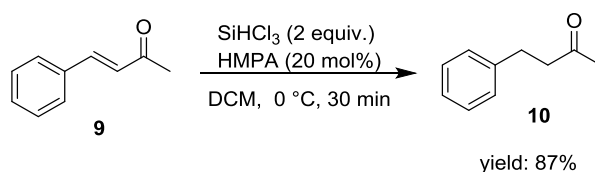
Scheme 3.1: HMPA-catalyzed conjugate reduction of benzylidene acetone (**9**)

Keinan *et al.*[19] demonstrated an efficient catalytic system comprising of Pd(PPh$_3$)$_4$, hydridosilane and ZnCl$_2$ for the conjugate reduction of *α, β*-unsaturated ketones and aldehydes (**11**) to afford the corresponding reduced products (**12**) (Scheme 3.2). The reaction tolerated a broad range of unsaturated ketones and aldehydes, and the protocol was highly selective for Michael acceptors. However, the reduction of *α, β*-unsaturated carboxylic acid derivatives was very sluggish under these conditions.

R^1 = H, Me. aryl
R^2 = R^3 = H, alkyl
R^4 = H, Me, aryl

up to 100% yield
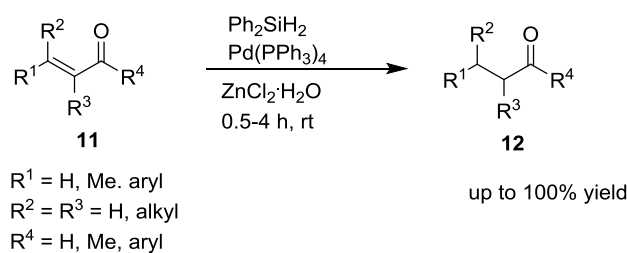
Scheme 3.2: Conjugate reduction of *α, β*-unsaturated ketones and aldehydes (**11**)

Mori *et al.*[23] reported a CuF(PPh$_3$)$_3$·2EtOH catalyzed 1,4-selective reduction of *α, β*-unsaturated ketones (**13**) with HSiPhMe$_2$ in *N, N*-dimethylacetamide (DMA) to give the corresponding saturated ketones (**14**) in excellent yields (Scheme 3.3). However, sterically hindered enones were unreactive towards this catalytic system.

R^1 = Ph, C$_5$H$_{11}$; R^2 = Me, Ph

up to 99% yield

Scheme 3.3: Cu (I) mediated reduction of *α, β*-unsaturated ketones (**13**) with phenyldimethylsilane

Mori *et al.*[13] reported reduction of *α, β*-unsaturated ketones (**15**) with dimethylphenylsilane using CuCl/PPh$_3$/TBAF as an efficient catalytic system. The reaction was found to proceed in a 1, 4-selective manner to give the corresponding saturated ketones (**16**) in very good yield (up to 99%) (Scheme 3.4).

R^1 = Ph, C$_5$H$_{11}$; R^2 = Me, Ph

up to 99% yield
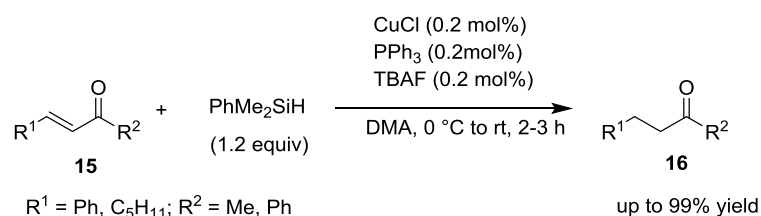
Scheme 3.4: Conjugate reduction of *α, β*-unsaturated carbonyl compounds (**15**)

Shang and co-workers[24] described a new hydride palladium catalyst generated from [PdCl$_2$(PPh$_3$)$_2$] and HSi(OEt)$_3$ for highly efficient isomerization of substituted amide-derived olefins. In addition to *cis–trans* isomerization of double bonds, the selective reduction of activated alkenes (**17**) underwent smoothly to obtain reduced products (**18**) in good yields (Scheme 3.5).
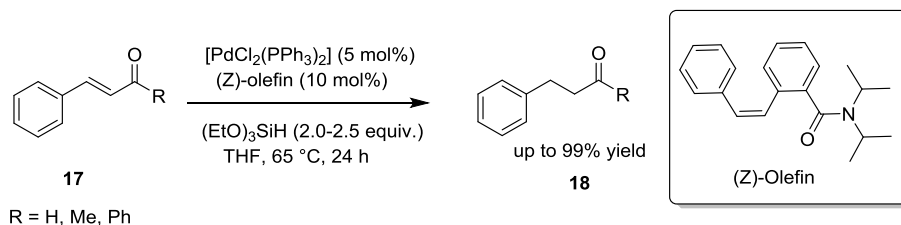
Scheme 3.5: Palladium-catalyzed hydrogenation of olefins (**17**) promoted by amide-derived (*Z*)-olefin

A highly active bimetallic Co/Zr complex (THF)Zr(Mes*N*P^{i}Pr$_2$)$_3$CoN$_2$ (catalyst A) was reported by Thomas and co-workers[18] for the hydrosilylation of benzylidene acetone (**9**) with PhSiH$_3$ to obtain the conjugate reduction product (**10**) in 58% yield and unsaturated alcohol (**19**) in 22% yield (Scheme 3.6). The protocol demonstrated the importance of co-operative reac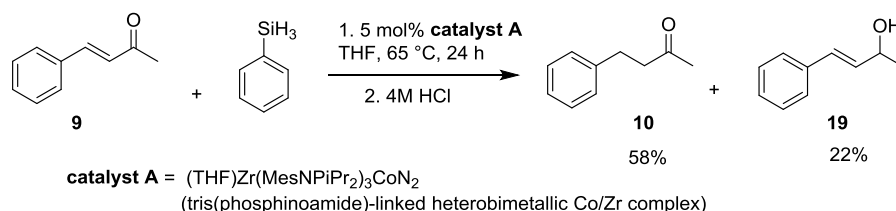tivity between Co and Zr. The highlights of the protocol are the use of inexpensive and naturally abundant metals, and synthetically straightforward ligands.

Scheme 3.6: Reduction of benzylidene acetone (**9**) with phenylsilane catalyzed by bimetallic-complex (**catalyst A**)

Mirza-Aghayan *et al.*[14] reported PdCl$_2$ catalyzed selective hydrogenation of the carbon–carbon double bond of *α, β*-unsaturated ketones (**20**) using Et$_3$SiH as reducing agent to give the corresponding saturated carbonyl compounds (**21**). The reaction were carried out under mild conditions and afforded the desired products in high yields (up to 95%).
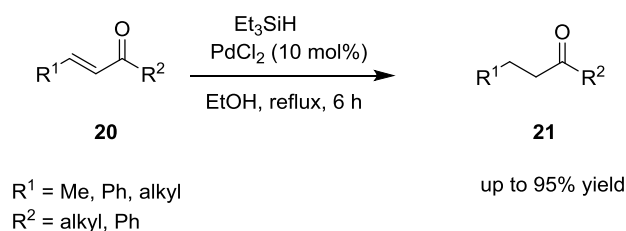
Scheme 3.7: Selective conjugate reduction of *α, β*-unsaturated ketones (**20**) using Et$_3$SiH/PdCl$_2$ system

Kunz and co-workers[25] demonstrated the synthesis of Rh complex (catalyst B) with the dipyrido-anellated NHC ligand dipyrido[1,2-*c*;2',1'-*e*]imidazolin-6-ylidene (dipiy) and used it as catalyst for the hydrosilylation of benzylidene acetone (**9**) to give the conjugate reduction product (**10**) (66%) along with 27% of **19** (Scheme 3.8).
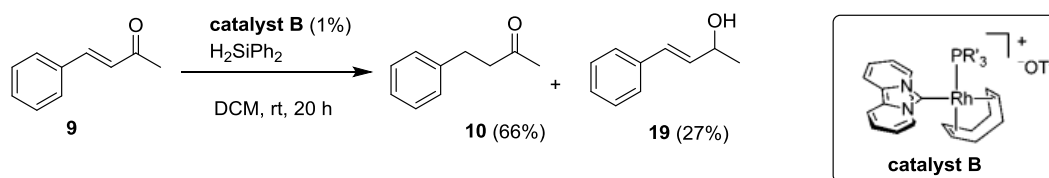
Scheme 3.8: Hydrosilylation of benzylidene acetone (**9**) by diphenylsilane

Ding *et al.*[26] reported an efficient pincer-Pd complex (catalyst C) catalyzed protocol for chemoselective hydrogenation of *α, β*-unsaturated ketones (**22**) using *n*-BuOH as a hydrogen source and solvent. The methodology was found to afford the corresponding conjugate reduction products (**23**) in good to excellent yields (Scheme 3.9). Based on deuterium-labeling experiments, the reaction mechanism has been proposed to occur via a pincer-Pd-hydride intermediate.
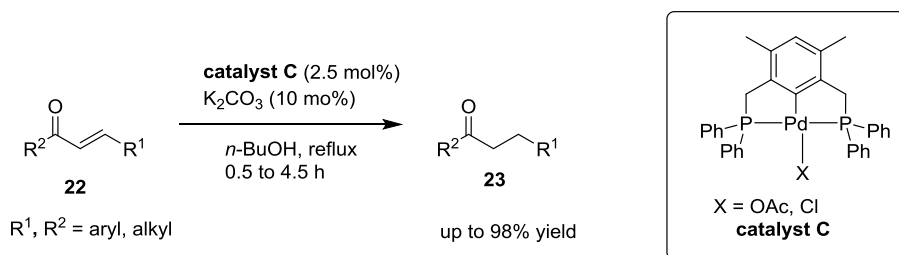
Scheme 3.9: Pincer palladium complex (**catalyst C**) catalyzed chemoselective hydrogenation of *α, β*-unsaturated ketones (**22**)

An efficient method was developed by Zhou *et al.*[27] for the chemoselective conjugate reduction of *α, β*-unsaturated ketones (**24**) with tosylhydrazine to give the corresponding saturated ketones (**25**) in moderate to good yields (Scheme 3.10). This protocol demonstrated

a transition-metal-free, cheap and a convenient alternative method to the traditional catalytic hydrogenation.
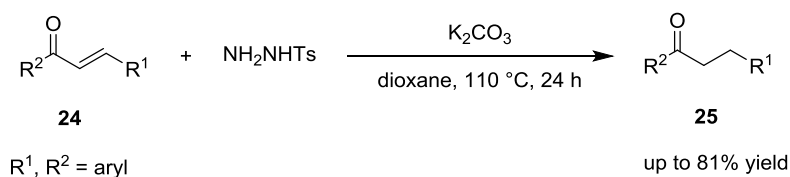
Scheme 3.10: Conjugate reduction of α, β-unsaturated ketones (**24**) with tosylhydrazine

Cordes and co-workers[21] described a convenient alternative method to traditional catalytic hydrogenation using $NaBH_4$ for the selective reduction of α, β-unsaturate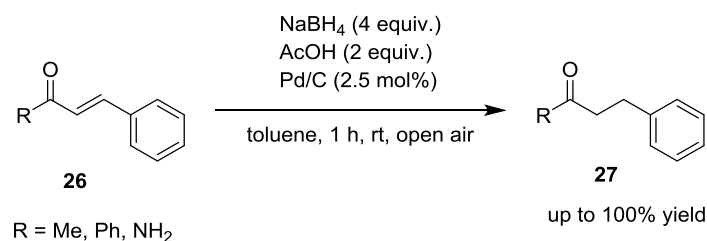d carbonyl compounds (**26**) in a short time to give the corresponding saturated carbonyl compounds (**27**) (Scheme 3.11). Complete conversion with high selectivity was observed even with moderate catalyst loadings.
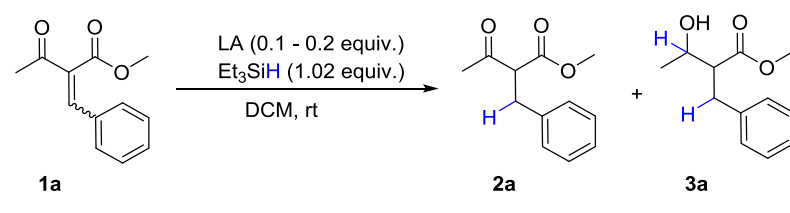
Scheme 3.11: Selective reduction of various α, β-unsaturated carbonyl compounds (**26**)

However, the reduction of a particular functionality is relatively easy compared to selective reduction of a particular functional group without reducing other sensitive moiety. Most of the hydrosilylation methods also required the use of base or acid for the final hydrolyis of silylated intermediates.[11] In contrast, iron based hydrosilylation received limited attention[12] and interestingly there are no reports on iron based conjugate reduction. Interestingly, most of the work on hydrosilylation has been focused on the reduction of ketones or α, β-unsaturated ketones.[13] Surprisingly, there are no reports on the selective reduction/hydrosilylation reaction on the alkylidene β-keto esters. This class of compounds unusually behaves differently even though they are relatively more reactive. It would be interesting to explore the novel catalyst system comprising of simple and commercially available metal catalyst. It is also desirable to develop a protocol without need of any ligands and additives/co-catalysts. Herein, we report the versatility of $FeCl_3.6H_2O/Et_3SiH$ system for the selective conjugate reduction of carbon-carbon double bond of alkylidene β-keto esters under mild conditions.

3.3 Results and Discussion

At the outset, we commenced our work with a model reaction of benzylidene methylacetoacetate **1a** with various Lewis acids in presence of triethylsilane in DCM at room temperature. Compound **1a** did not react with Et$_3$SiH (1 equiv.) in presence of different Lewis acids (entry 1-6, Table 3.1).

Table 3.1: Screening of Lewis acid catalysts for optimizing the reaction conditions[a]

Entry	LA (Catalyst)[a]	Time (h)	Yield[b] (%)
1	CuCl$_2$·2H$_2$O	24	trace
2	MnCl$_2$·6H$_2$O	24	NR
3	NiCl$_2$·6H$_2$O	24	NR
4	Cu(OAc)$_2$	24	NR
5	Zn(OAc)$_2$	24	NR
6	CuSO$_4$·5H$_2$O	24	NR
7	Cu(I)Br	24	27+12[c]
8	CoCl$_2$·6H$_2$O	24	NR
9	FeCl$_3$	4	dec.
10	FeCl$_3$·6H$_2$O	12	74+13[c]
11	FeCl$_3$·6H$_2$O (0.2 equiv.)	8	85+6[c]
12	FeCl$_2$·4H$_2$O	24	Trace
13	CeCl$_3$·7H$_2$O	24	NR
14	SnCl$_2$·2H$_2$O	24	15
15	MgBr$_2$·6H$_2$O	24	NR
16	Cu(NO$_3$)$_2$·3H$_2$O	24	NR
17	Ni(acac)$_2$	24	NR
18	Fe(acac)$_3$	24	NR
19	Fe(ClO$_4$)$_3$·XH$_2$O	24	trace
20	No Catalyst	24	NR

[a]Reactions were performed with 0.1 equiv. of Lewis acids (LA) in DCM. [b]Isolated yield of the product after column chromatography. [c]Yield of alcohol **3a.** dec. = decomposition. NR = No Reaction.

Surprisingly, metal salts which are known to catalyze hydrosilylation of enones did not catalyze effectively the reduction of alkylidene β-keto ester **1a**. Reaction of compound **1a** with anhydrous FeCl$_3$ and Et$_3$SiH in DCM at room temperature led to decomposition (entry 9, Table 3.1). Interestingly, catalytic amount of FeCl$_3$·6H$_2$O (0.1 equiv.) under the reaction condition afforded the desired product **2a** along with corresponding alcohol **3a** as 1, 2-reduction minor product in 13% yield (entry 10, Table 3.1). Gratifyingly, FeCl$_3$·6H$_2$O (20 mol%, 0.2 equiv.) reacted smoothly under the reaction conditions to afford the conjugate reduction product **2a** in 85% yield along with significantly lower amount of alcohol **3a** in 6% yield (entry 11, Table 3.1). While, the treatment of compound **1a** with FeCl$_2$·4H$_2$O (entry 12, Table 3.1) under the reaction conditions led to just a trace amount of desired product. Likewise, compound **1a** did not react with Et$_3$SiH (1.02 equiv.) in presence of other Lewis acids (entry 13-18, Table 3.1). Reaction did not work in the absence of any catalyst (entry 20, Table 3.1).

Table 3.2: Screening of solvents for optimizing the reaction[a]
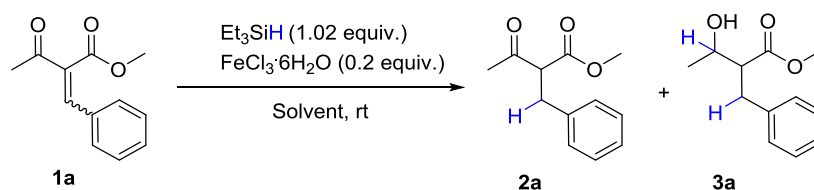
Entry	Solvent	Time (h)	Yield[b] (%)
1	DCM	8	85+6[c]
2	CHCl$_3$	12	54+11
3	Toluene	12	28+8
4	Benzene	12	25+6
5	EtOAc	24	Trace
6	MeOH	12	30+15[c]
7	Acetone	24	Trace
8	THF	24	NR
9	ACN	24	NR
10	DMF	24	NR
11	DMSO	24	NR

[a]Reactions were screened on **1a** (1 mmol) with Et$_3$SiH (1 equiv.) and FeCl$_3$·6H$_2$O (0.2 equiv.) in various solvents. [b]Isolated yield. [c]Yield of alcohol **3a.** NR = No Reaction.

Encouraged by this initial success, we screened various solvents for optimizing the reaction conditions. Non-polar solvents such as chloroform, benzene and toluene afforded the conjugate reduction product **2a** in poor yield (entry 2-4, Table 3.2). While solvents such as ethyl acetate and acetone afforded the product **2a** in trace amounts. Protic solvent such as methanol afforded the mixture of **2a** and **3a**. While, aprotic polar solvents proved to be disadvantageous for the desired transformation. DCM proved to be the optimum solvent for the desired transformation (entry 1, Table 3.2).

In order to explore the most suitable and optimum silyl reducing agent we screened the reaction with triethoxy silane and triphenyl silane in presence of FeCl$_3$·6H$_2$O (see Table 3.3). Reaction of benzylidene methylacetoacetate **1a** with triethoxylsilane in DCM, FeCl$_3$·6H$_2$O (20 mol%) led to an inseparable mixture of products (entry 2, Table 3.3). While, triphenylsilane afforded the mixture of **2a** and **3a** (see entry 3, Table 3.3). Triethylsilane proved to be the most suitable reducing agent affording the corresponding conjugate reduction product **2a** in 85% yield. Based on different screening experiments FeCl$_3$·6H$_2$O (20 mol%), Et$_3$SiH (1 equiv.) in DCM at room temperature proved to be the optimum reaction condition.

Table 3.3: Screening of silane reducing agents for optimizing the reduction reaction[a]
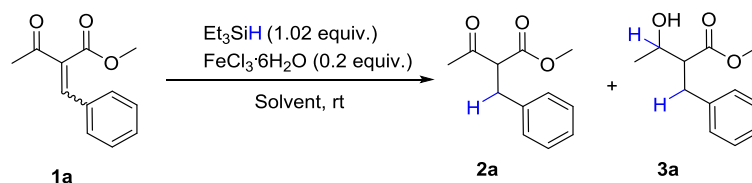
Entry	Silane	Time (h)	Yield[b] (%)
1	Et$_3$SiH	8	85 + 6[c]
2	(EtO)$_3$SiH	12	Inseparable Mixture
3	Ph$_3$SiH	8	66+15[c]

[a]Reactions were screened on **1a** (1 mmol) with silane (1 equiv.) and FeCl$_3$·6H$_2$O (0.2 equiv.) in DCM. [b]Isolated yield. [c]Yield of alcohol **3a.**

Having optimum reaction conditions in hand, we planned to explore the substrate scope for the generality of the method. Various alkylidene methyl acetoacetates (**1b-1l**) under optimum reaction conditions afforded the corresponding 1, 4-conjugate reduction products

(**2b-2l**) in good to excellent yields (see Scheme 3.12). This method proved to be highly chemoselective as it afforded selectively 1, 4-conjugate addition products and we observed only a trace amount of 1, 2-addition products (alcohol). Substrate containing both electron-donating and weak electron withdrawing groups, and heteroaryl derived substrate reacted smoothly under the reaction conditions and the functional groups did not have any significant effect on reaction rate and yields.

Scheme 3.12: Substrate scope of alkylidene *β*-ketoesters for reduction under optimized reaction conditions[a,b]
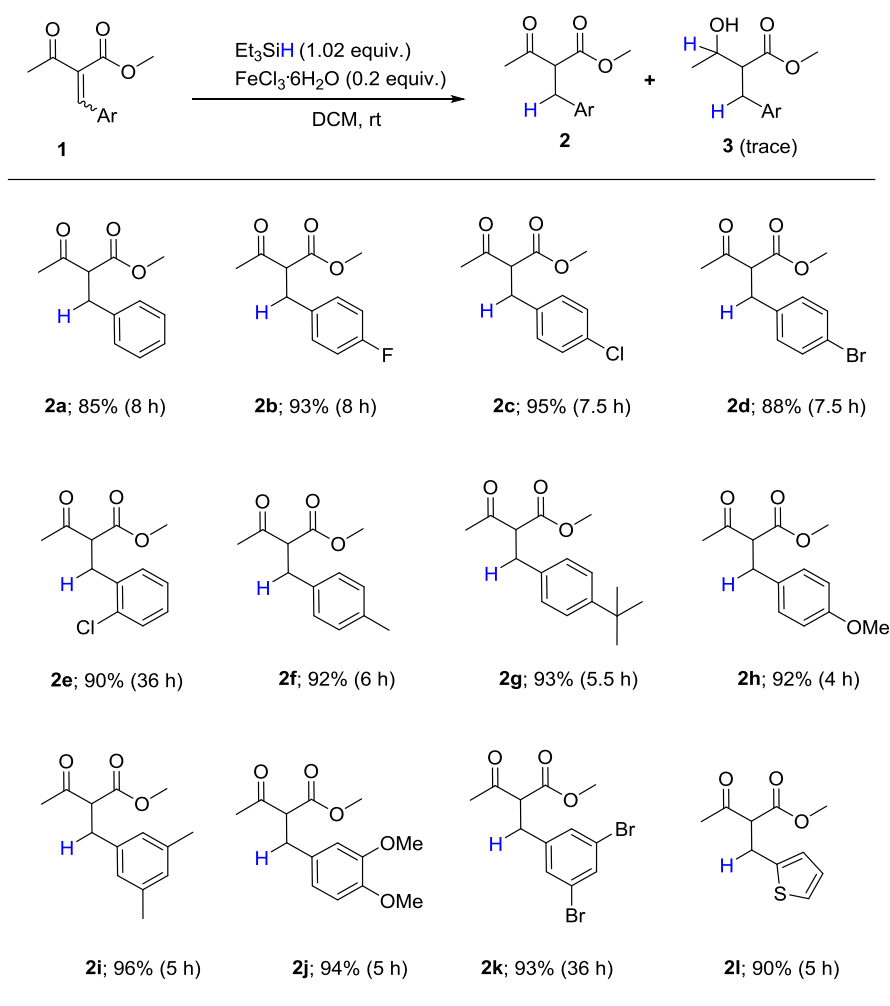
[a] Reactions were performed on **1a-1l** (1 mmol, 1 equiv.) with $FeCl_3 \cdot 6H_2O$ (0.2 equiv.) and Et_3SiH (1 equiv.) in DCM at rt. [b] isolated yield.

Later, we turned our attention towards acetyl acetone derivatives. The alkylidene acetylacetone derivatives (**4a-4e**) under optimum reaction conditions afforded the corresponding 1, 4-conjugate reduction products (**5a-5e**) chemoselectively in good to

excellent yields. However, substrates with electron withdrawing group **4e** afforded the desired product **5e** along with 1, 2-addition product **6e** in smaller quantity (Scheme 3.13).

Scheme 3.13: Substrate scope of reduction with optimized reaction conditions[a,b]
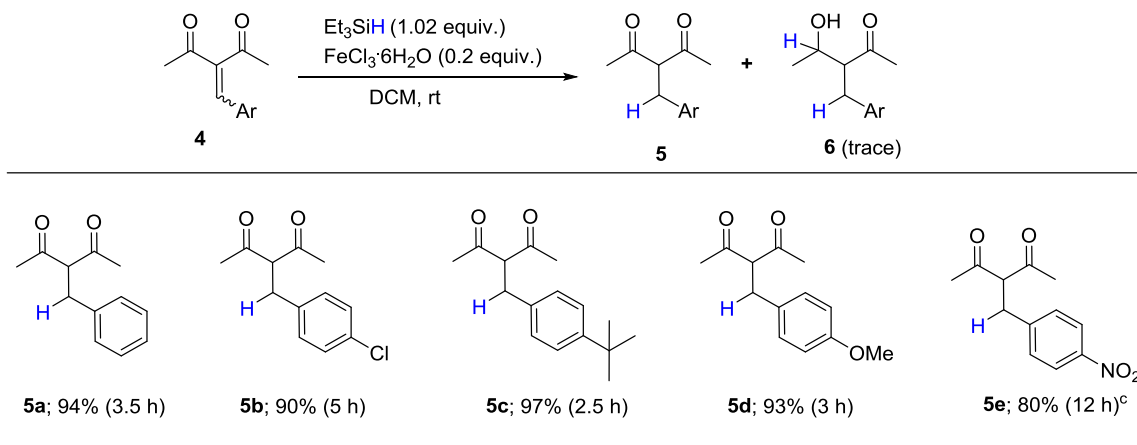
a Reactions were performed on **4a-4e** (1 mmol, 1 equiv.) with FeCl$_3$·6H$_2$O (0.2 equiv.) and Et$_3$SiH (1 equiv.) in DCM at rt. b isolated yield. c compound **6e** was isolated in 9% yield.

To expand the scope of the methodology further we synthesized few alkylidene Meldrum's acid derivatives (**7a-7c**). These compounds under the optimum reaction conditions afforded the corresponding 1, 4-conjugate addition products (**8a-8c**) exclusively in almost quantitative yields (Scheme 3.14). Method proved to be highly selective for the 1,4-conjugate reduction. However, few ketones under the optimum reaction conditions afforded the mixture of 1,4-conjugate addition as well as 1, 2-reduction products.

Scheme 3.14: Substrate scope of reduction with optimized reaction conditions[a,b]
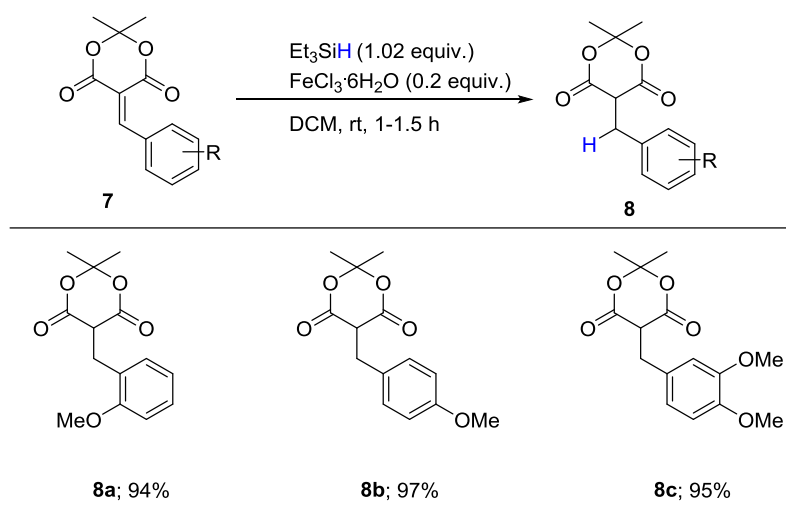
a Reactions were performed on **7a-7c** (1 mmol, 1 equiv.) with FeCl$_3$·6H$_2$O (0.2 equiv.) and Et$_3$SiH (1 equiv.) in DCM at rt. b isolated yield.

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3.4 Conclusions

In conclusion, novel reducing system comprising of $FeCl_3 \cdot 6H_2O$/triethylsilane is successfully developed for the highly selective conjugate reduction of carbon-carbon double bond of alkylidene β-keto esters and β-keto carbonyl compounds under mild condition. Chemoselective reduction afforded exclusively 1, 4-conjugate reduction products as major products and the method did not require the use of any base/acid for the desilylation. A broad range of alkylidene derivatives underwent smooth reduction under practical reaction conditions.

3.5 Experimental Section

General: All starting materials were obtained from Aldrich, Acros, Merck and were used as obtained unless otherwise mentioned. All reactions were carried out with distilled and dried solvents under an atmosphere of dry N_2 and oven-dried glassware. All solvents CH_2Cl_2, toluene, EtOAc, Pet. ether, n-Pentane were purified and dried by using regular procedures using "Purification of Laboratory Chemicals" by Perrin and stored over activated 4 Å molecular sieves. All compounds were purified by using Column Chromatographic technique on 100-200 mesh size silica gel. Analytical thin-layer chromatography (TLC) was performed using Merck silica gel 60 GF_{254} pre-coated aluminum backed plates (2.5 mm) with spot detection under UV light or ninhydrin, PMA or vanillin. ^{1}H NMR and ^{13}C NMR were recorded in $CDCl_3$ on 400 MHz (100 MHz for ^{13}C). Chemical shifts in ^{1}H NMR and ^{13}C NMR spectra are reported as δ in ppm with the solvent resonance as the internal standard, coupling constants (*J*-values) are given in Hz. ^{1}H NMR data were reported in the order of chemical shift, multiplicity (s, singlet; d, doublet; t, triplet; m, multiplet; dt, doublet of triplet), coupling constant in hertz (Hz) and number of protons. High-Resolution mass spectra were obtained from HRMS-ESI-TOF. IR spectra of neat samples were recorded using FT-IR spectrophotometer and reported in cm^{-1}. All melting points were measured in open glass capillary and values are uncorrected.

General Experimental procedure for the reduction of alkylidene *β*-keto esters (1a-1l)

To a stirred solution of *cis*- and *trans*- diastereomeric mixture of alkylidene *β*–keto ester **1a-1l**, (*Z/E*- ratio~60:40) (1 mmol) in DCM (4 mL), finely powdered FeCl$_3$·6H$_2$O (0.054 g, 0.2 mmol) was added at room temperature. After few minutes of stirring, Et$_3$SiH (0.163 mL, 1.02 mmol) was added carefully at room temperature. Then, the resulting reaction mixture was allowed to stir till the completion of reaction as monitored by TLC (see respective Scheme 3.12). After completion of reaction, the crude reaction mixture was purified by column chromatography over silica gel eluting with pet. ether/EtOAc (98:2 to 85:15) to obtain the corresponding 1,4-conjugate reduction products (**2a-2l**). However, NMR spectra revealed that isolated compounds were existed in keto-enol forms.

Methyl 2-benzyl-3-oxobutanoate (2a):
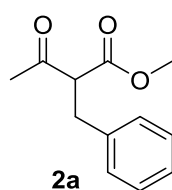
Clear liquid (0.175 g, 85 %); R_f = 0.40 (15% EtOAc + Pet. ether); IR (Neat) cm^{-1}: 2953, 1740, 1715, 1495, 1437, 1357, 1216, 1148, 747, 700; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.29 – 7.25 (m, 2H), 7.22 – 7.16 (m, 3H), 3.80 (t, *J* = 7.6 Hz, 1H), 3.69 (s, 3H), 3.16 (d, *J* = 7.6 Hz, 2H), 2.18 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 202.5, 169.7, 138.2, 128.9, 128.7, 126.8, 61.3, 52.6, 34.2, 29.8; HRMS (ESI–TOF) m/z Calcd. for C$_{12}$H$_{14}$O$_3$Na [M + Na]$^+$ = 229.0840, observed = 229.0841. Isolated compound existed as keto:enol form in 93:7 ratio and NMR values are only given with respect to keto form.

Methyl 2-(4-fluorobenzyl)-3-oxobutanoate (2b):
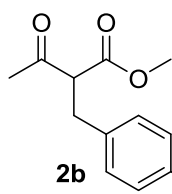
Clear liquid (0.208 g, 93%); R_f = 0.40 (15% EtOAc + Pet. ether); IR (Neat) cm^{-1}: 2954, 1741, 1717, 1509, 1439, 1219, 1154, 837; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.15 – 7.08 (m, 2H), 6.98 – 6.94 (m, 2H), 3.75 (t, *J* = 7.6 Hz, 1H), 3.69 (s, 3H), 3.13 (dd, *J* = 7.6, 1.3 Hz, 2H), 2.19 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 202.2, 174.0, 173.6, 169.5, 163.0, 160.6, 133.9, 133.8, 130.4, 130.4, 129.1, 129.1, 115.7, 115.4, 115.3, 115.1, 99.1, 61.3, 52.6, 51.8, 33.3, 30.9, 29.8, 19.1; HRMS (ESI–TOF) m/z Calcd. for C$_{12}$H$_{13}$O$_3$FNa [M + Na]$^+$ = 247.0746, observed = 247.0745. Isolated compound existed as keto:enol form in 82:18 ratio and ^{1}H NMR values are only given with respect to keto form and ^{13}C NMR values are given for both keto and enol forms.

Methyl 2-(4-chlorobenzyl)-3-oxobutanoate (2c):
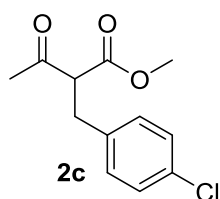
Clear liquid (0.228 g, 95%); R_f = 0.42 (15% EtOAc + Pet. ether); IR (Neat) cm^{-1}: 2953, 1742, 1718, 1492, 1439, 1358, 1249, 1218, 1151, 840, 815; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.27 – 7.22 (m, 2H), 7.09 (dd, J = 14.1, 8.3 Hz, 2H), 3.75 (t, J = 7.6 Hz, 1H), 3.70 (s, 3H), 3.13 (dd, J = 7.6, 2.3 Hz, 2H), 2.20 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 202.1, 174.1, 173.6, 169.4, 139.3, 136.7, 132.7, 130.3, 129.1, 128.9, 128.5, 98.7, 61.1, 52.7, 51.8, 33.4, 31.0, 29.9, 19.2; HRMS (ESI–TOF) m/z Calcd. for C$_{12}$H$_{13}$O$_3$Cl [M + Na]$^+$ = 263.0450, observed = 263.0454. Isolated compound existed as keto:enol form in 85:15 ratio and ^{1}H NMR values are only given with respect to keto form and ^{13}C NMR values are given for both keto and enol forms.
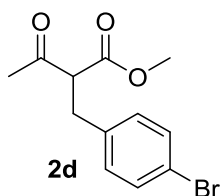
Methyl 2-(4-bromobenzyl)-3-oxobutanoate (2d):

Clear liquid (0.251 g, 88%); R_f = 0.45 (15% EtOAc + Pet. ether); IR (Neat) cm^{-1}: 2952, 1741, 1717, 1488, 1438, 1357, 1248, 1217, 1150, 1106, 1070, 1010, 838, 810; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.39 (d, J = 8.4 Hz, 2H), 7.05 (d, J = 8.4 Hz, 2H), 3.75 (t, J = 7.6 Hz, 1H), 3.70 (s, 3H), 3.11 (dd, J = 7.6, 2.6 Hz, 2H), 2.19 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 202.0, 174.1, 173.5, 169.4, 139.9, 137.2, 131.8, 131.5, 130.7, 129.5, 120.8, 119.7, 98.7, 61.0, 52.7, 51.8, 33.4, 31.1, 29.8, 19.2; HRMS (ESI–TOF) m/z Calcd. for C$_{12}$H$_{14}$O$_3$Br [M + H]$^+$ = 285.0126, observed = 285.0134. Isolated compound existed as keto:enol form in 74:26 ratio and ^{1}H NMR values are only given with respect to keto form and ^{13}C NMR values are given for both keto and enol forms.

**Methyl 2-(2-chlorobenzyl)-3-oxobutanoate (2e):**
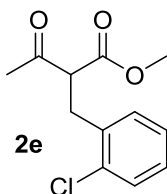
Pale yellow liquid (0.217 g, 90%); R_f = 0.45 (15% EtOAc + Pet. ether); IR (Neat) cm^{-1}: 2954, 1743, 1720, 1475, 1440, 1358, 1253, 1219, 1152, 995, 756; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.36 – 7.34 (m, 1H), 7.25 – 7.14 (m, 3H), 3.97 (t, J = 8 Hz, 1H), 3.69 (s, 3H), 3.33 – 3.21 (m, 2H), 2.22 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 202.3, 174.8, 173.7, 169.5, 137.9, 135.8, 134.1, 131.7, 129.7, 129.4, 128.5, 128.2, 127.3, 127.1, 126.9, 97.1, 58.7, 52.6, 51.8, 32.1, 29.9, 29.2, 19.1; HRMS (ESI–TOF) m/z Calcd. for C$_{12}$H$_{14}$O$_3$Cl [M + H]$^+$ = 241.0631, observed = 241.0629. Isolated compound existed as keto:enol form in 93:7 ratio and ^{1}H NMR values are only given with respect to keto form and ^{13}C NMR values are given for both keto and enol forms.

Methyl 2-(4-methylbenzyl)-3-oxobutanoate (2f):
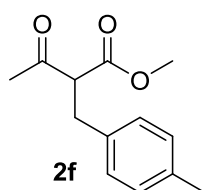
Pale yellow liquid (0.202 g, 92%); R_f = 0.50 (15% EtOAc + Pet. ether); IR (Neat) cm^{-1}: 3008, 2953, 1743, 1718, 1516, 1439, 1358, 1251, 1217, 1151, 1066, 840, 808; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.09 – 7.04 (m, 4H), 3.77 (t, J = 7.7 Hz, 1H), 3.69 (s, 3H), 3.12 (d, J = 7.6 Hz, 2H), 2.30 (s, 3H), 2.17 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 202.7, 173.9, 173.8, 169.8, 137.7, 136.4, 135.5, 135.0, 129.4, 129.1, 128.7, 127.7, 99.2, 61.4, 52.6, 51.8, 33.8, 31.1, 29.8, 21.1, 19.2; HRMS (ESI–TOF) m/z Calcd. for C$_{13}$H$_{17}$O$_3$ [M + H]$^+$ = 221.1177, observed = 221.1177. Isolated compound existed as keto:enol form in 89:11 ratio and ^{1}H NMR values are only given with respect to keto form and ^{13}C NMR values are given for both keto and enol forms.
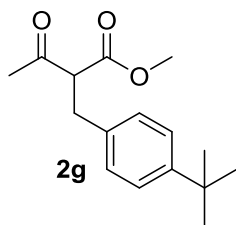
Methyl 2-(4-(tert-butyl)benzyl)-3-oxobutanoate (2g):

Clear liquid (0.243 g, 93%); R_f = 0.55 (15% EtOAc + Pet. ether); IR (Neat) cm^{-1}: 2959, 2871, 1743,1719, 1513, 1438, 1359, 1259, 1216, 1151, 839; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.29 (d, J = 8.3 Hz, 2H), 7.10 (d, J = 8.3 Hz, 2H), 3.79 (t, J = 7.6 Hz, 1H), 3.70 (s, 3H), 3.14 (d, J = 7.6 Hz, 2H), 2.18 (s, 3H), 1.29 (s, 9H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 202.7, 169.8, 149.7, 135.1, 128.5, 125.6, 61.3, 52.6, 34.5, 33.6, 31.5, 29.8, 19.3, 19.2; HRMS (ESI–TOF) m/z Calcd. for C$_{16}$H$_{22}$O$_3$Na [M + Na]$^+$ = 285.1466, observed = 285.1461. Isolated compound existed as keto:enol form in 93:7 ratio and NMR values are only given with respect to keto form.

Methyl 2-(4-methoxybenzyl)-3-oxobutanoate (2f):
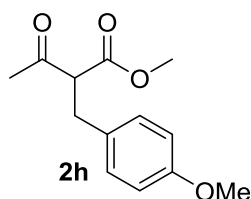
Clear liquid (0.217 g, 92%); R_f = 0.40 Pet. ether: EtOAc (80:20); IR (Neat) cm^{-1}: 2954, 1742, 1716, 1513, 1440, 1246, 1176, 1150, 1032, 834; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.09 (d, J = 8.6 Hz, 2H), 6.81 (d, J = 8.6 Hz, 2H), 3.77 (s, 3H), 3.73 – 3.71 (m, 1H), 3.69 (s, 3H), 3.10 (d, J = 7.6 Hz, 2H), 2.17 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 202.7, 173.8, 169.7, 158.5, 157.9, 132.9, 130.1, 129.9, 128.7, 114.1, 113.8, 99.4, 61.5, 55.4, 55.3, 52.6, 51.7, 33.4, 30.7, 29.9, 19.2; HRMS (ESI–TOF) m/z Calcd. for C$_{13}$H$_{16}$O$_4$Na [M + Na]$^+$ = 259.0946, observed = 259.0952. Isolated compound existed as keto:enol form in 89:11 ratio and ^{1}H NMR values are only given with respect to keto form and ^{13}C NMR values are given for both keto and enol forms.

**Methyl 2-(3, 5-dimethylbenzyl)-3-oxobutanoate (2i):**
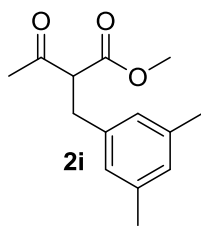
Pale yellow liquid (0.227 g, 96%); R_f = 0.50 (15% EtOAc + Pet. ether); IR (Neat) cm^{-1}: 2953, 1744, 1719, 1607, 1439, 1358, 1251, 1217, 1151, 850, 702; ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.84 (s, 1H), 6.78 (s, 2H), 3.78 (t, J = 7.5 Hz, 1H), 3.70 (s, 3H), 3.08 (d, J = 7.5 Hz, 2H), 2.27 (s, 6H), 2.18 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 202.7, 169.8, 138.2, 138.1, 128.5, 126.6, 61.3, 52.6, 34.0, 29.9, 21.4; HRMS (ESI–TOF) m/z Calcd. for C$_{14}$H$_{19}$O$_3$ [M + H]$^+$ = 235.1334, observed = 235.1324. Isolated compound existed as keto:enol form in 95:5 ratio and NMR values are only given with respect to keto form.

Methyl 2-(3, 5-dimethoxybenzyl)-3-oxobutanoate (2i):
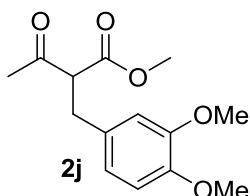
Pale yellow liquid (0.250 g, 94%); R_f = 0.30 (25% EtOAc + Pet. ether); IR (Neat) cm^{-1}: 3001, 2950, 2837, 1740, 1715, 1594, 1448, 1250, 1145, 1027, 857, 808, 765; ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.78 (d, J = 8.0 Hz, 1H), 6.72 (d, J = 1.7 Hz, 1H), 6.70 (s, 1H), 3.85 (d, J = 3.1 Hz, 7H), 3.78 (t, J = 7.5 Hz, 1H), 3.70 (s, 3H), 3.11 (d, J = 7.7 Hz, 2H), 2.19 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 202.7, 169.7, 149.0, 147.8, 130.6, 120.8, 112.0, 111.3, 61.5, 55.9, 52.6, 33.8, 29.9; HRMS (ESI–TOF) m/z Calcd. for C$_{14}$H$_{18}$O$_5$Na [M + Na]$^+$ = 289.1051, observed = 289.1054. Isolated compound existed as keto:enol form in 92:8 ratio and NMR values are only given with respect to keto form.

Methyl 2-(3, 5-dibromobenzyl)-3-oxobutanoate (2j):
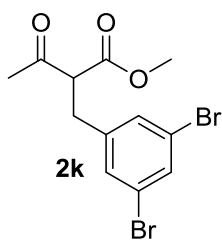
Clear liquid (0.338 g, 93%); R_f = 0.50 (15% EtOAc + Pet. ether); IR (Neat) cm^{-1}: 2952, 1745, 1721, 1554, 1431, 1358, 1249, 1213, 1152, 855, 742; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.52 (t, J = 1.6 Hz, 1H), 7.27 (d, J = 1.5 Hz, 2H), 3.76 – 3.73 (m, 1H), 3.73 (s, 3H), 3.14 – 3.04 (m, 2H), 2.23 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 201.3, 174.6, 173.2, 169.1, 145.0, 142.3, 132.6, 131.8, 130.8, 129.6, 123.1, 123.0, 97.8, 60.7, 52.9, 52.0, 33.1, 31.2, 29.8, 19.3; HRMS (ESI–TOF) m/z Calcd. for C$_{12}$H$_{13}$O$_3$Br$_2$ [M + H]$^+$ = 362.9231, observed = 362.9212. Isolated compound existed as keto:enol form in 66:34 ratio and ^{1}H NMR values are only given with respect to keto form and ^{13}C NMR values are given for both keto and enol forms.

Methyl 3-oxo-2-(thiophen-2-ylmethyl)butanoate (2l):
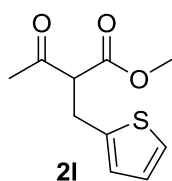
Pale yellow liquid (0.191 g, 90%); R_f = 0.4 (15% EtOAc + Pet. ether); IR (Neat) cm^{-1}: 2954, 1742, 1718, 1436, 1358, 1251, 1215, 1150, 848, 703; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.13 (dd, J = 5.1, 1.2 Hz, 1H), 6.89 (dd, J = 5.1, 3.5 Hz, 1H), 6.81 (dq, J = 3.5, 1.2 Hz, 1H), 3.83 (t, J = 7.4 Hz, 1H), 3.73 (s, 3H), 3.38 (ddd, J = 7.4, 4.5, 0.7 Hz, 2H), 2.23 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 201.9, 174.0, 173.2, 169.2, 144.6, 140.3, 127.0, 126.8, 126.0, 124.3, 124.0, 123.3, 99.7, 61.4, 52.7, 51.8, 29.9, 28.2, 26.5, 19.0; HRMS (ESI–TOF) m/z Calcd. for C$_{10}$H$_{13}$O$_3$S [M + H]$^+$ = 213.0585, observed = 213.0583. Isolated compound existed as keto:enol form in 92:8 ratio and ^{1}H NMR values are only given with respect to keto form and ^{13}C NMR values are given for both keto and enol forms.

General Experimental procedure for the reduction of alkylidene β-diketones (4a-4e) and alkylidene Meldrum's acid adducts (7a-7c):

To a stirred solution of alkylidene β–diketones (**4a-4e, 7a-7c**) (1 mmol) in DCM (4 mL), finely powdered FeCl$_3$·6H$_2$O (0.054 g, 0.2 mmol) was added at room temperature. After few minutes of stirring, Et$_3$SiH (0.163 mL, 1.02 mmol) was added carefully at room temperature. Then, the resulting reaction mixture was allowed to stir till the completion of reaction as monitored by TLC (see Scheme 3.13 and 3.14). After completion of the reaction, the crude reaction mixture was purified by column chromatography over silica gel eluting with pet. ether/EtOAc (98:2 to 85:15) to obtain corresponding 1,4-conjugate reduction products (**5a-5e, 8a-8c**). However, NMR spectra of isolated compounds **5a**-**5e** revealed that compounds existed in keto-enol forms.

(Z)-3-benzyl-4-hydroxypent-3-en-2-one (5a):
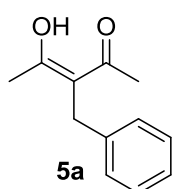
Pale yellow liquid (0.179 g, 94%); R_f = 0.48 (15% EtOAc + Pet. ether); IR (Neat) cm^{-1}: 3027, 2927, 2859, 1702, 1601, 1494, 1419, 1385, 950, 716; ^{1}H NMR (400 MHz, CDCl$_3$) δ 16.82 (s, 1H, enolic-OH), 7.35 – 7.11 (m, 5H), 4.01 (t, J = 7.5 Hz, 0.4H, keto-CH), 3.66 (s, 2H, enolic-CH$_2$), 3.15 (d, J = 7.4 Hz, 0.82H, keto-CH$_2$), 2.13 (s, 3H, keto–enol-CH$_3$), 2.08 (s, 6H, keto–enol-CH$_3$); ^{13}C NMR (100 MHz, CDCl$_3$) δ 203.7, 192.1, 139.8, 138.1, 128.9, 128.8, 128.7, 127.5, 126.9, 126.4, 108.4, 70.1, 34.4, 33.0, 29.9, 23.4; HRMS (ESI–TOF) m/z Calcd. for C$_{12}$H$_{15}$O$_2$ [M + H]$^+$ =

191.1072, observed = 191.1072. Isolated compound existed as keto:enol form in 28:72 ratio and NMR values are given for both enol and keto forms.

(Z)-3-(4-chlorobenzyl)-4-hydroxypent-3-en-2-one (5b):
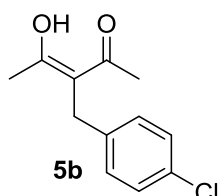
Pale yellow semi solid (0.202 g, 90%); R_f = 0.55 (15% EtOAc + Pet. ether); IR (Neat) cm^{-1}: 2930, 1703, 1599, 1491, 1415, 1359, 1094, 1013, 956, 813; ^{1}H NMR (400 MHz, CDCl$_3$) δ 16.82 (s, 1H, enolic-OH), 7.29 – 7.24 (m, 2H), 7.10 – 7.07 (m, 2H), 3.97 (t, J = 7.5 Hz, 0.33H, keto-CH), 3.63 (s, 2H, enolic-CH$_2$), 3.12 (d, J = 7.7 Hz, 0.7H, keto-CH$_2$), 2.14 (s, 2H, keto–enol-CH$_3$), 2.06 (s, 6H, keto–enol-CH$_3$); ^{13}C NMR (100 MHz, CDCl$_3$) δ 203.3, 192.1, 138.3, 136.6, 132.7, 132.2, 130.2, 129.8, 129.0, 128.9, 128.8, 108.0, 70.0, 33.6, 32.5, 29.9, 23.4; HRMS (ESI–TOF) m/z Calcd. for C$_{12}$H$_{14}$O$_2$Cl [M + H]$^+$ = 225.0682, observed = 225.0683. Isolated compound existed as keto:enol form in 25:75 ratio and NMR values are given for both enol and keto forms.

(Z)-3-(4-(tert-butyl)benzyl)-4-hydroxypent-3-en-2-one (5c):
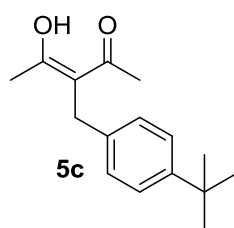
Pale yellow solid (0.240 g, 97%); m.p. = 94-96 °C; R_f = 0.60 (15% EtOAc + Pet. ether); IR (Neat) cm^{-1}:2961, 1703, 1604, 1514, 1416, 1362, 1272, 1015, 942, 820; ^{1}H NMR (400 MHz, CDCl$_3$) δ 16.81 (s, 1H, enolic-OH), 7.33 – 7.26 (m, 2H), 7.09 – 7.06 (m, 2H), 4.01 (t, J = 7.5 Hz, 0.26H, keto-CH), 3.62 (s, 2H, enolic-CH$_2$), 3.13 (d, J = 7.5 Hz, 0.54H, keto-CH$_2$), 2.13 (s, 2H, keto–enol-CH$_3$), 2.08 (s, 6H, keto–enol-CH$_3$), 1.31 (s, 10H, , keto–enol-^{t}Bu), 1.31 (s, 3H, keto–enol-^{t}Bu); ^{13}C NMR (100 MHz, CDCl$_3$) δ 203.9, 192.0, 149.8, 149.3, 136.6, 135.0, 128.4, 127.2, 125.7, 125.7, 108.6, 70.2, 34.5, 33.8, 32.5, 31.5, 31.4, 29.8, 23.5; HRMS (ESI–TOF) m/z Calcd. for C$_{16}$H$_{23}$O$_2$ [M + H]$^+$ = 247.1698, observed = 247.1698. Isolated compound existed as keto:enol form in 20:80 ratio and NMR values are given for both enol and keto forms.

(Z)-4-hydroxy-3-(4-methoxybenzyl)pent-3-en-2-one (5d):
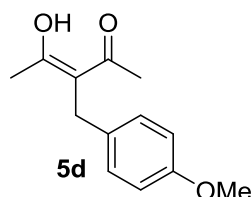
White semi solid (0.205 g, 93%); R_f = 0.40 (15% EtOAc + Pet. ether); IR (Neat) cm^{-1}: 2929, 2837, 1700, 1607, 1509, 1421, 1244, 1176, 1030, 954,815,747; ^{1}H NMR (400 MHz, CDCl$_3$) δ 16.79 (s, 1H, enolic-OH), 7.08 – 7.04 (m, 2H), 6.86 – 6.80 (m, 2H), 3.97 (t, J = 7.7

Hz, 0.37H, keto-CH), 3.79 – 3.77 (m, 5H, keto–enol-OCH$_3$), 3.59 (s, 2H, enolic-CH$_2$), 3.09 (d, J = 7.8 Hz, 0.73H, keto-CH$_2$), 2.12 (s, 3H, keto–enol-CH$_3$), 2.07 (s, 7H, keto–enol-CH$_3$); ^{13}C NMR (100 MHz, CDCl$_3$) δ 203.9, 192.0, 158.5, 158.3, 131.7, 130.0, 129.7, 128.4, 114.2, 114.2, 108.7, 70.4, 55.4, 55.3, 33.6, 32.1, 29.9, 23.4; HRMS (ESI–TOF) m/z Calcd. for C$_{13}$H$_{17}$O$_3$ [M + H]$^+$ = 221.1177, observed = 221.1177. Isolated compound existed as keto:enol form in 27:73 ratio and NMR values are given for both enol and keto forms.

(Z)-4-hydroxy-3-(4-nitrobenzyl)pent-3-en-2-one (5e):
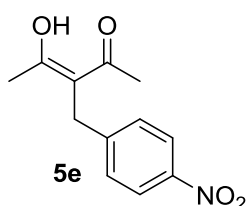
Pale yellow semi solid (0.188 g, 80%); R_f = 0.40 (25% EtOAc + Pet. ether); IR (Neat) cm^{-1}: 2935, 1714, 1599, 1516, 1344, 1166, 1108, 1005, 940, 854, 794, 727; ^{1}H NMR (400 MHz, CDCl$_3$) δ 16.87 (s, 1H, enolic-OH), 8.20 – 8.13 (m, 2H), 7.37 – 7.33 (m, 2H), 4.03 (t, J = 7.4 Hz, 0.35H, keto-CH), 3.78 (s, 3H, enolic-CH$_2$), 3.26 (d, J = 7.4 Hz, 0.54H, enolic-CH$_2$), 2.18 (d, J = 3.5 Hz, 3H, keto–enol-CH$_3$), 2.07 (s, 6H, keto–enol-CH$_3$); ^{13}C NMR (100 MHz, CDCl$_3$) δ 206.8, 202.5, 192.1, 149.1, 147.7, 146.9, 146.6, 146.0, 129.8, 129.4, 128.3, 124.1, 124.0, 123.8, 107.2, 69.4, 44.3, 33.7, 33.1, 30.2, 29.8, 29.4, 23.5; HRMS (ESI–TOF) m/z Calcd. for C$_{12}$H$_{14}$NO$_4$ [M + H]$^+$ = 236.0923, observed = 236.0925. Isolated compound existed as keto:enol form in 20:80 ratio and NMR values are given for both enol and keto forms.

5-(2-methoxybenzyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (8a):
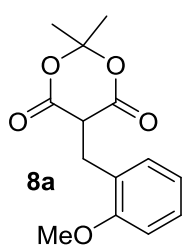
Yellow semi solid (0.248 g, 94%); R_f = 0.35 (25% EtOAc + Pet. ether); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.27 (dd, J = 7.5, 1.6 Hz, 1H), 7.20 – 7.13 (m, 1H), 6.85 (td, J = 7.5, 1.0 Hz, 1H), 6.77 (d, J = 8.2 Hz, 1H), 3.95 (t, J = 5.9 Hz, 1H), 3.75 (s, 3H), 3.32 (d, J = 5.9 Hz, 2H), 1.69 (s, 3H), 1.64 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 165.5, 157.2, 132.0, 128.4, 125.8, 120.7, 110.3, 105.0, 55.3, 46.2, 28.7, 28.1, 26.6; HRMS (ESI–TOF) m/z Calcd. for C$_{14}$H$_{17}$O$_5$ [M + H]$^+$ = 265.1076, observed = 265.1073.

5-(4-methoxybenzyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (8b):
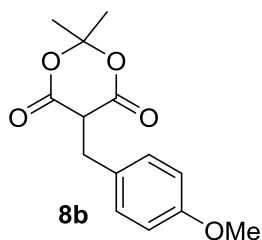
Yellow semi solid (0.256 g, 97%); R_f = 0.40 (25% EtOAc + Pet. ether); ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.22 (d, J = 8.6 Hz, 2H), 6.79 (d, J = 8.6 Hz, 2H), 3.76 – 3.73 (m, 1H), 3.74 (s, 3H), 3.40 (d, J = 4.9 Hz, 2H), 1.70 (s, 3H), 1.47 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 165.5, 158.7, 131.0, 129.1, 113.9, 105.2, 55.2, 48.2, 31.4, 28.4, 27.2; HRMS (ESI–TOF) m/z Calcd. for C$_{14}$H$_{17}$O$_5$ [M + H]$^+$ = 265.1076, observed = 265.1078.

5-(3,4-dimethoxybenzyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (8c):
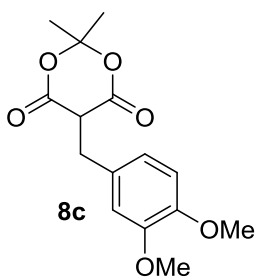
Yellow semi solid (0.279 g, 95%); R_f = 0.20 (25% EtOAc + Pet. ether); ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.86 – 6.82 (m, 2H), 6.75 (d, J = 8.0 Hz, 1H), 3.84 (s, 3H), 3.82 (s, 3H), 3.73 (t, J = 4.8 Hz, 1H), 3.43 (d, J = 4.8 Hz, 2H), 1.71 (s, 3H), 1.47 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 165.6, 148.8, 148.2, 129.6, 122.1, 113.2, 111.2, 105.3, 55.9, 55.9, 48.4, 32.0, 28.6, 27.5; HRMS (ESI–TOF) m/z Calcd. for C$_{15}$H$_{19}$O$_6$ [M + H]$^+$ = 295.1181, observed = 295.1185.

3.6 Appendix III: ^{1}H and ^{13}C spectral data of representative compounds

Compound No.	Fig AIII.X	data	page No.
2a	Fig AIII.1 and AIII.2	^{1}H-^{13}C	73
2d	Fig AIII.3 and AIII.4	^{1}H-^{13}C	74
2l	Fig AIII.5 and AIII.6	^{1}H-^{13}C	75
5a	Fig AIII.7 and AIII.8	^{1}H-^{13}C	76
5c	Fig AIII.9 and AIII.10	^{1}H-^{13}C	77
8b	Fig AIII.13 and AIII.14	^{1}H-^{13}C	78

Fig AIII.1: ^{1}H NMR (400 MHz, CDCl$_3$) spectrum of compound **2a**

Fig AIII.2: ^{13}C NMR (100 MHz, CDCl$_3$) spectrum of compound **2a**

73
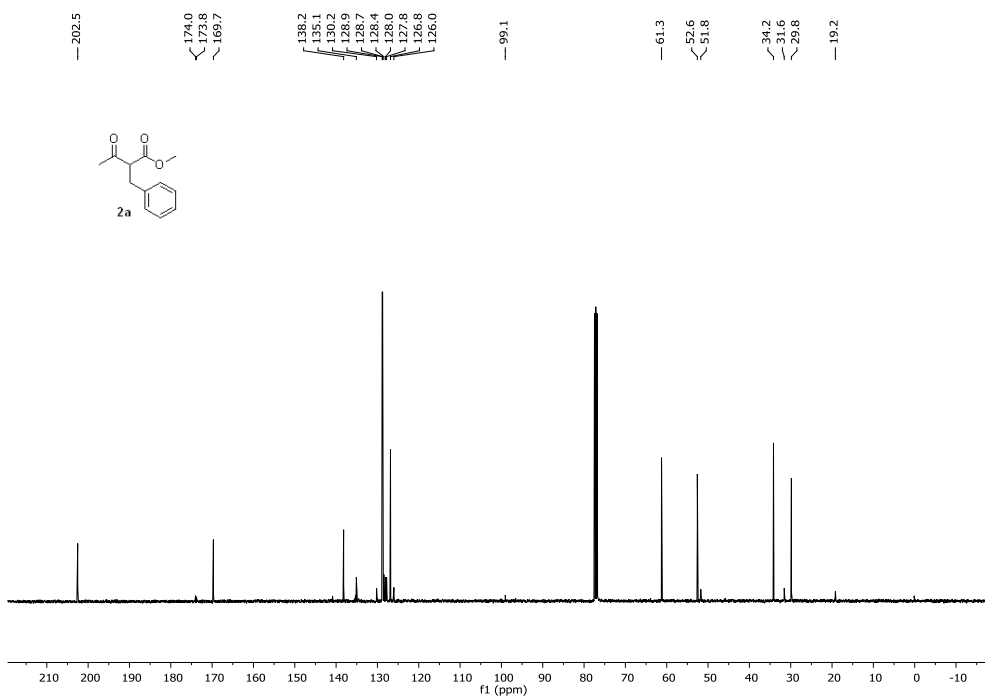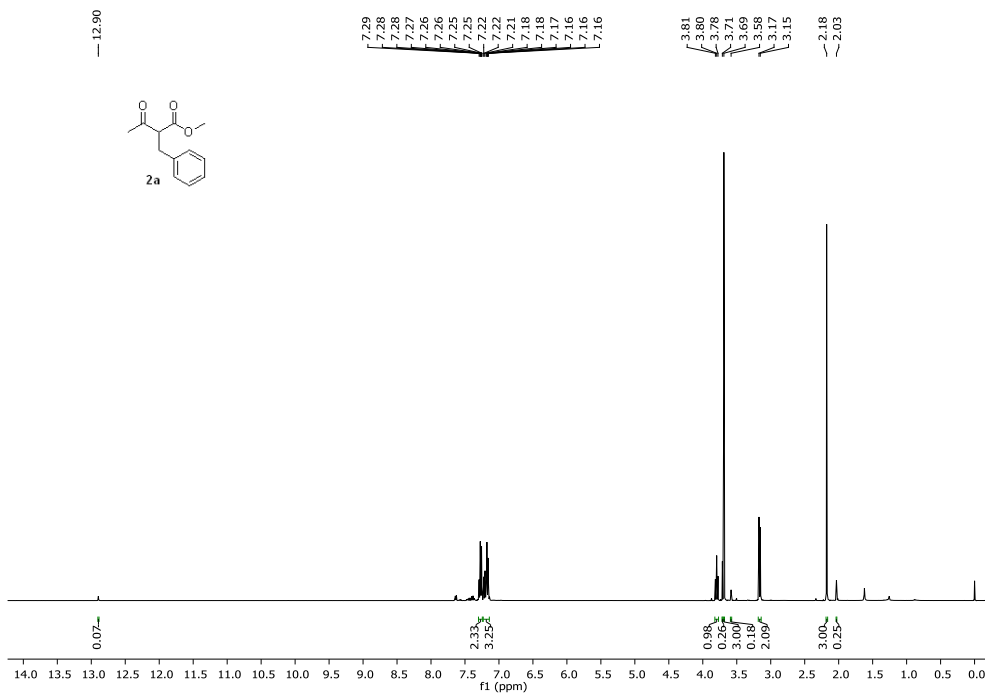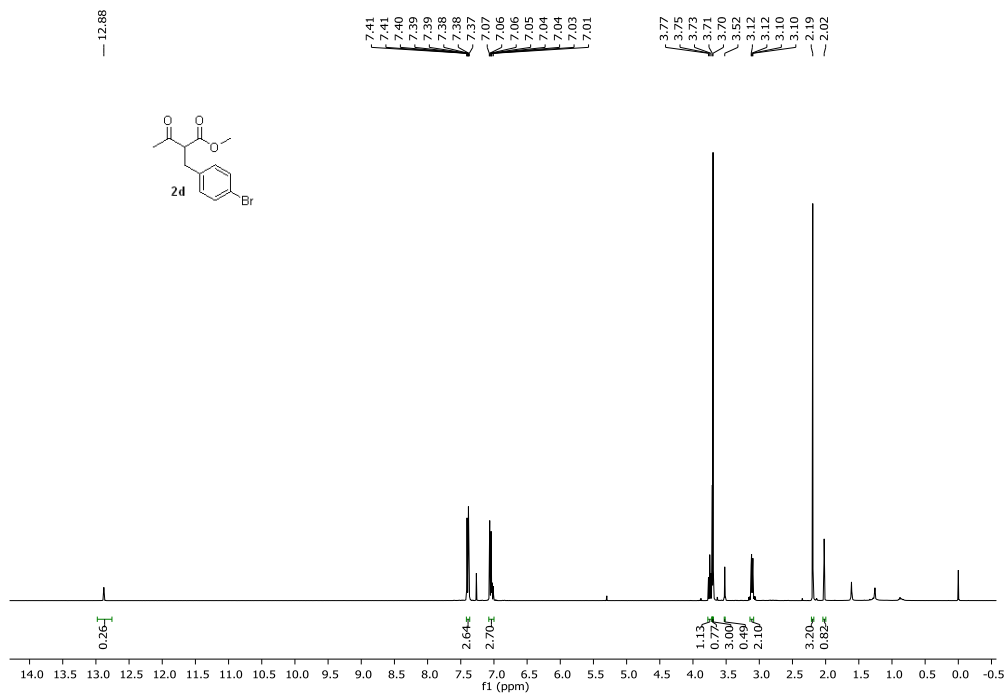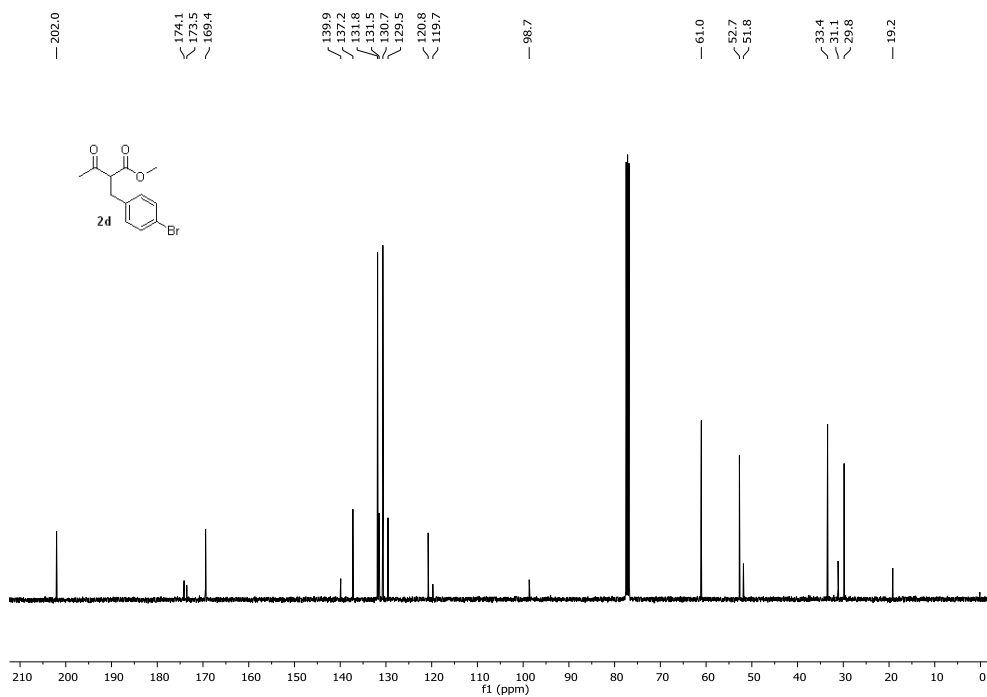
Fig AIII.3: ^{1}H NMR (400 MHz, CDCl$_3$) spectrum of compound **2d**

Fig AIII.4: ^{13}C NMR (100 MHz, CDCl$_3$) spectrum of compound **2d**

74
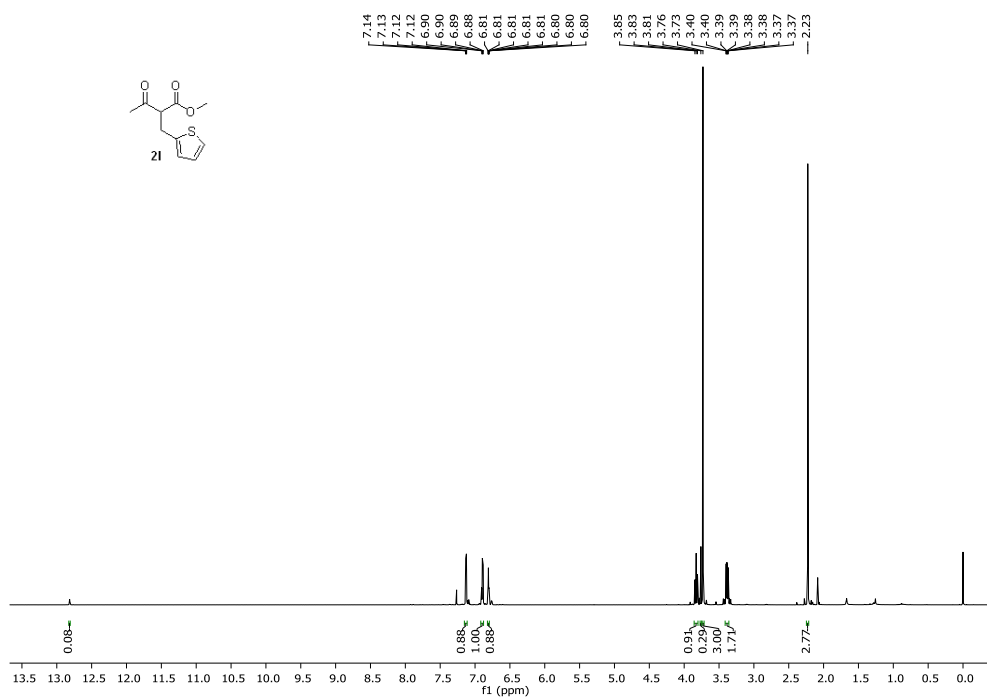
Fig AIII.5: ^{1}H NMR (400 MHz, CDCl$_3$) spectrum of compound **2l**
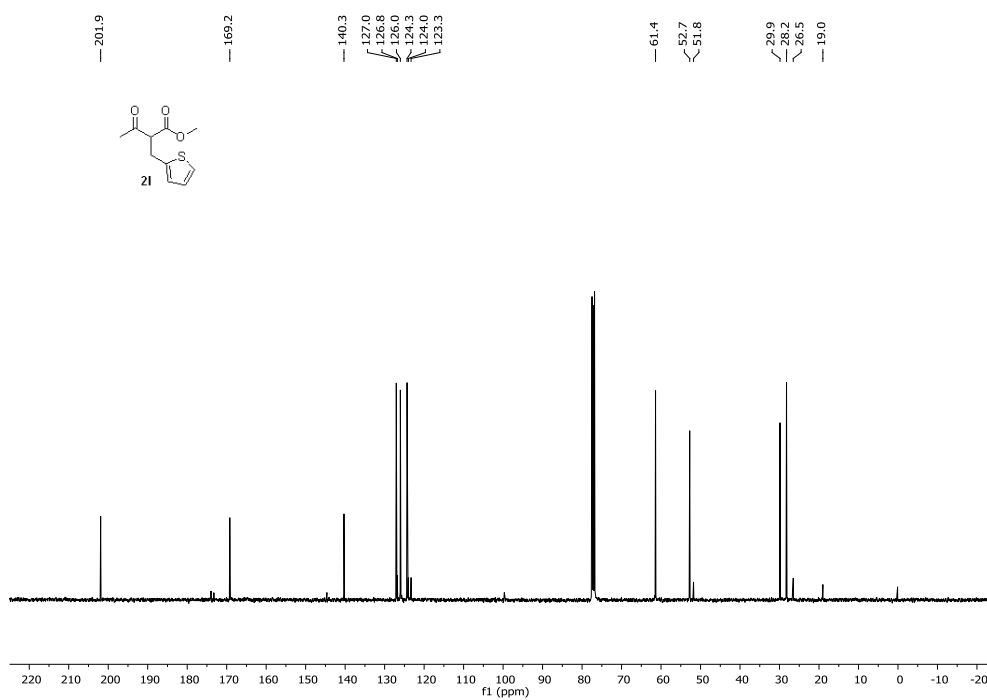
Fig AIII.6: ^{13}C NMR (100 MHz, CDCl$_3$) spectrum of compound **2l**
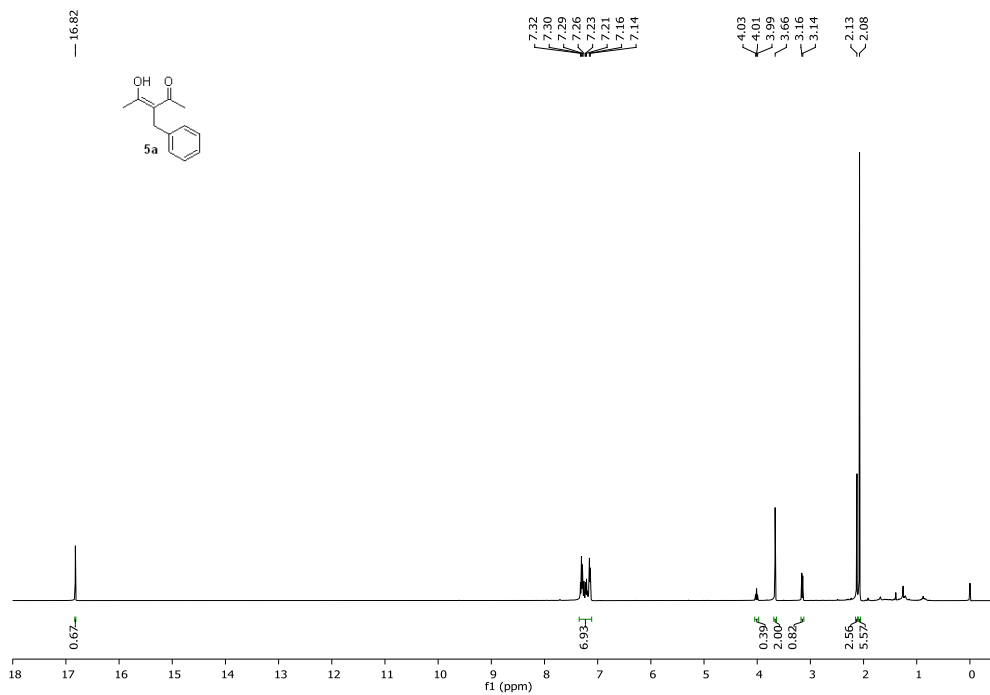
Fig AIII.7: ^{1}H NMR (400 MHz, CDCl$_3$) spectrum of compound **5a**
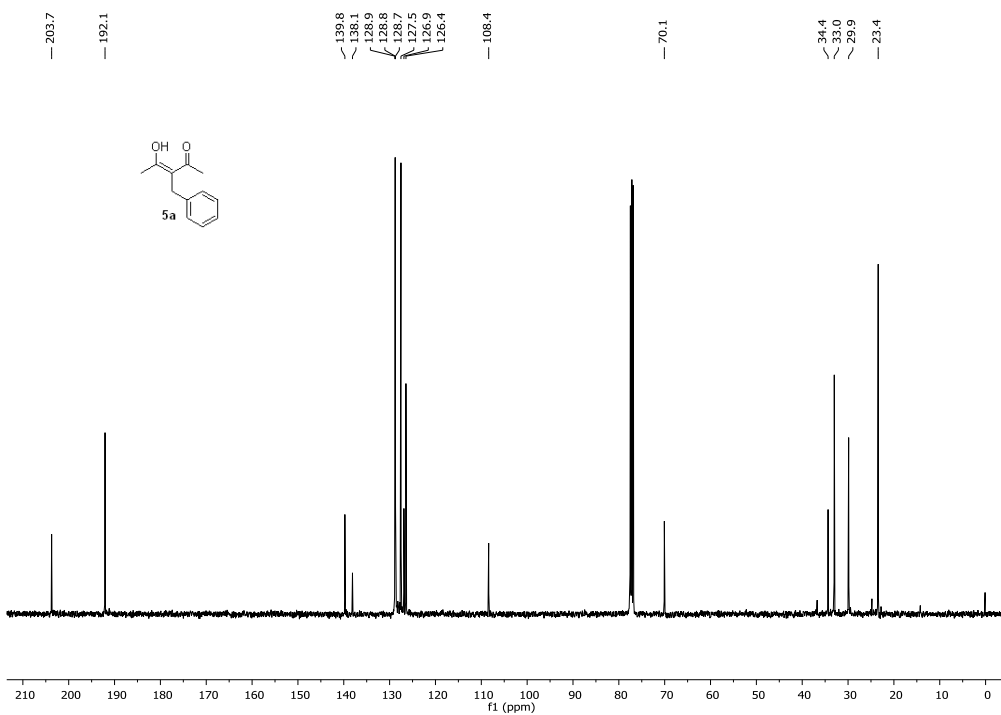
Fig AIII.8: ^{13}C NMR (100 MHz, CDCl$_3$) spectrum of compound **5a**
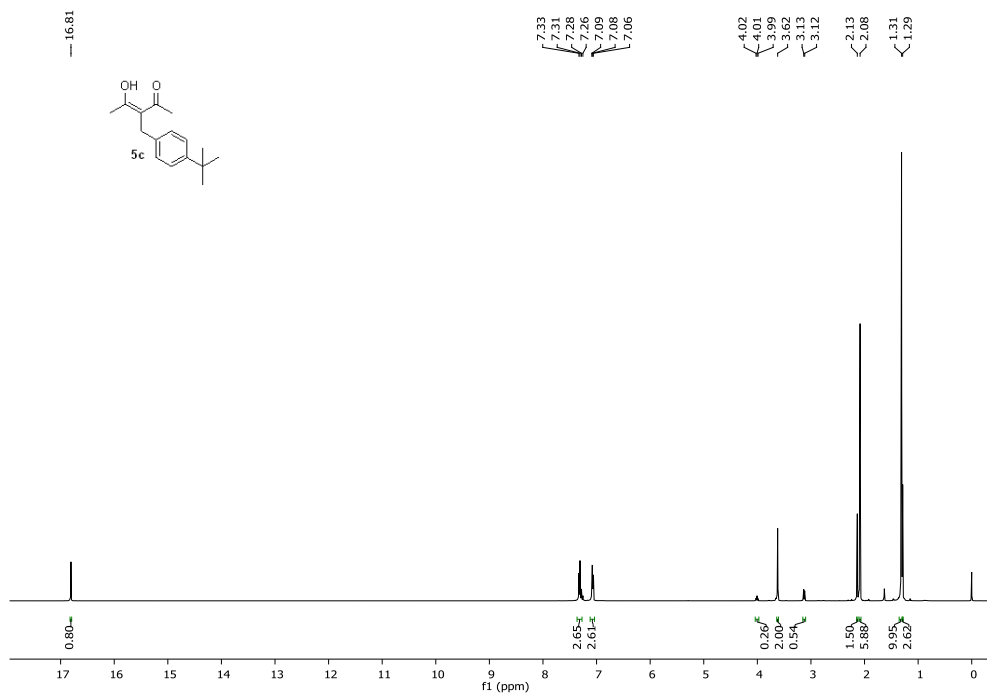
Fig AIII.9: ^{1}H NMR (400 MHz, CDCl$_3$) spectrum of compound **5c**
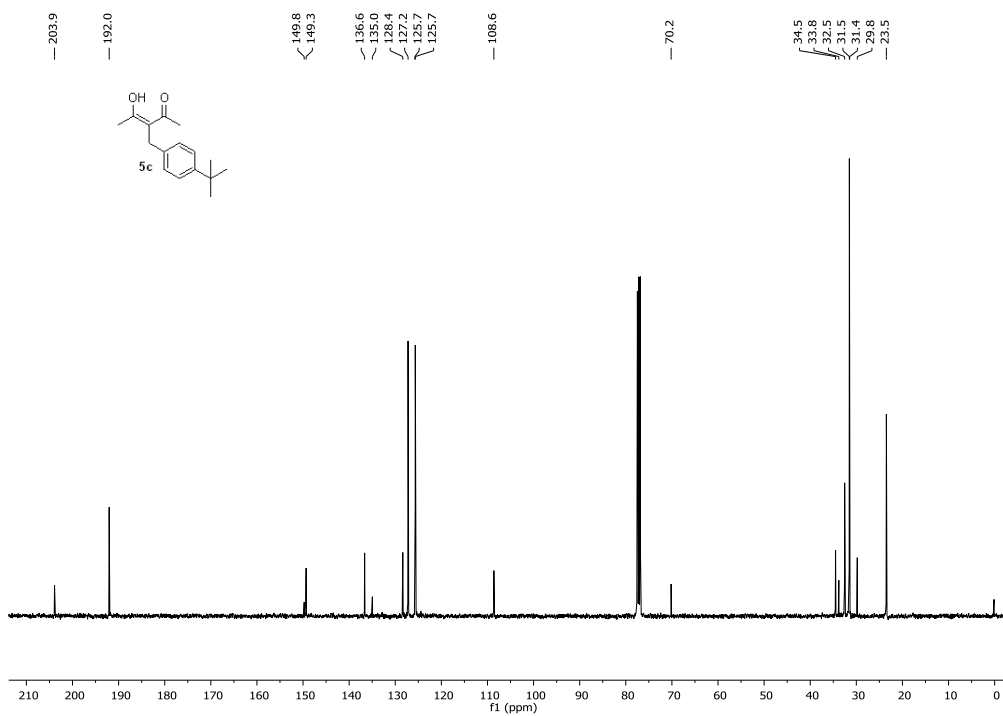
Fig AIII.10: ^{13}C NMR (100 MHz, CDCl$_3$) spectrum of compound **5c**

77
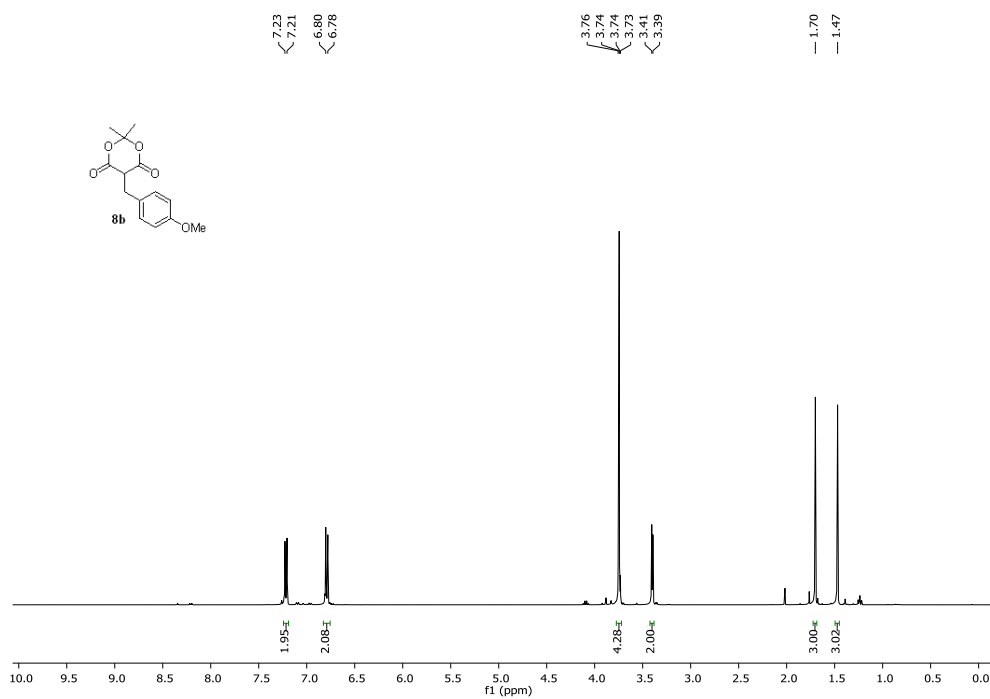
Fig AIII.11: ^{1}H NMR (400 MHz, CDCl$_3$) spectrum of compound **8b**

Fig AIII.12: ^{13}C NMR (100 MHz, CDCl$_3$) spectrum of compound **8b**

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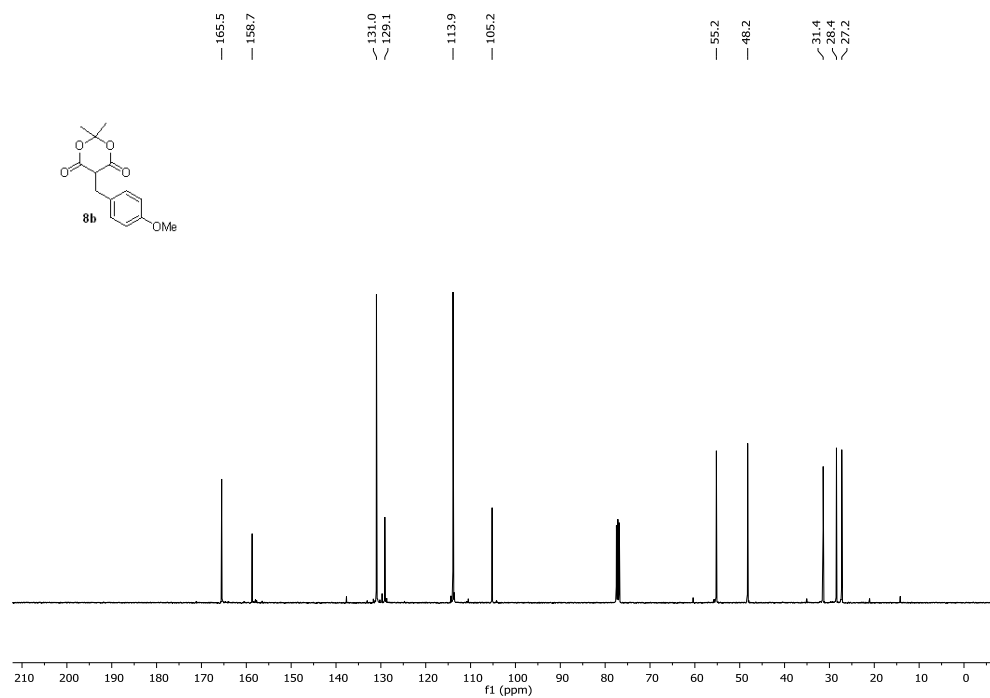
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Chapter 4

FeCl₃·6H₂O Catalyzed Diastereoselective Synthesis of (L)-Menthyl 4-oxo-2-arylpiperidine-3-carboxylates
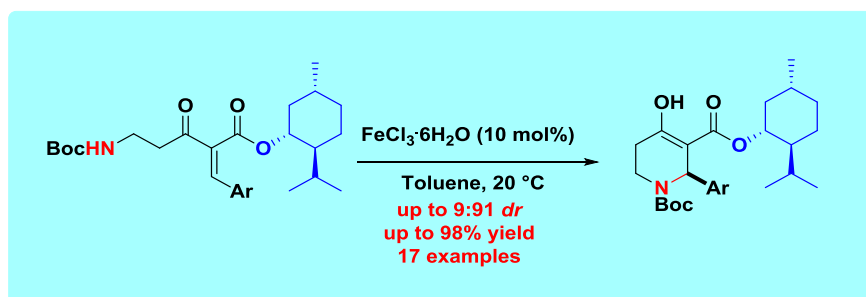
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FeCl$_3$·6H$_2$O Catalyzed Diastereoselective Synthesis of (L)-Menthyl 4-oxo-2-arylpiperidine-3-carboxylates

4

In this chapter an efficient diastereoselective synthesis of substituted piperidines using catalytic amount of FeCl$_3$·6H$_2$O is described. We explored the intramolecular aza-Michael addition of carbamate on alkylidene β-keto (L)-menthyl esters in presence of catalytic amount of FeCl$_3$·6H$_2$O in a very short time. Time dependent ^{1}H-NMR studies were carried out to understand and distinguish peaks arising from diastereomers and rotamers. Reaction conditions were mild and favored the rapid formation of piperidine derivatives in good to excellent yields with high diastereoselectivity.

4.1 Introduction

Alkaloids are group of natural products produced by a large variety of organisms including bacteria, fungi, plants and animals. Most of the alkaloids are found to be biologically active and predominantly used as drugs. The piperidine ring system (**9**) is one of naturally occurring common structural sub-units and is core to many bioactive natural products.[1,2] A number of naturally occurring piperidine alkaloids and synthetic analogues (Fig 4.1) exhibit a wide range of biological properties (necrotic, insecticidal, antibacterial, antifungal, anti-HIV). Because of the known biological activity of these moieties, they have great importance in the pharmaceutical industry.[3a,b] Particularly, piperidines bearing the alkyl and/or aryl substituent group at the 2- and/or 2, 6-position on the ring can be found as a core structure in many naturally occurring alkaloids.[3c,d] For instance, (*S*)-(+)- and (*R*)-(-)-coniine, (-)-lobeline, alkaloid 241D, and (-)-cassine are some of the few simple substituted piperidine rings, which are known to be inhibitors of the ganglionic, neuromuscular, central neuronal nicotinic acetylcholine receptors and HIV-protease.[4]
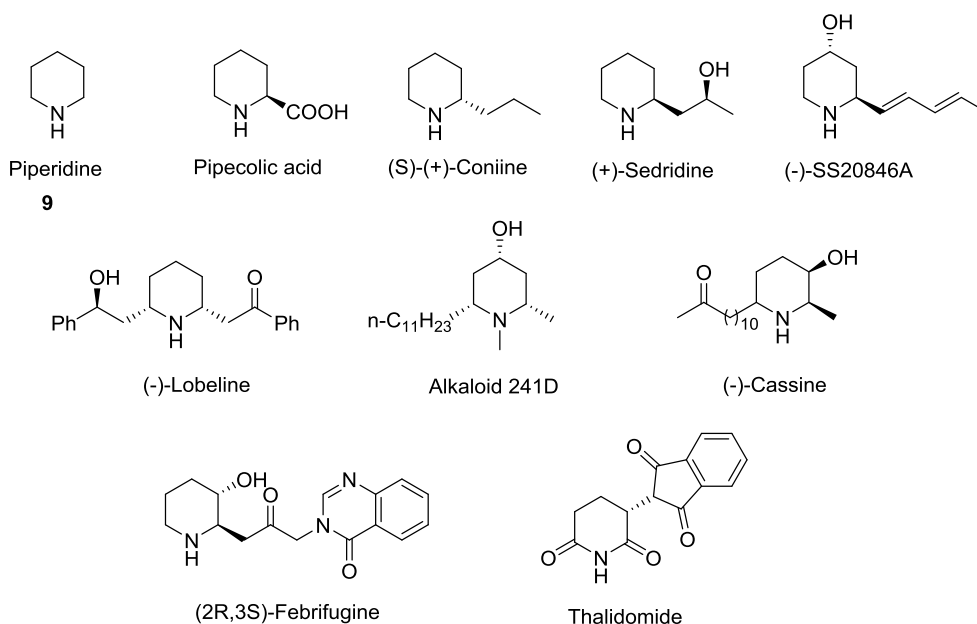
Fig 4.1: Some piperidine alkaloids found in plants and synthetic analogues

As the biological activity of a molecule depends on their absolute configuration, several stereo-controlled synthetic strategies have been developed for substituted piperidines.[5] However, it is important to note that few simple piperidines and their analogue alkaloids have toxic properties, as observed in one of the most well-known examples of a pyridine alkaloid, e.g., nicotine.

Three most successful approaches are: the use of the chiral pool, especially amino acids; the use of reagents that utilizes a chiral catalyst; and the use of chiral auxiliaries in the asymmetric formation or derivatization of the piperidine ring. For the asymmetric synthesis of substituted piperidine derivatives,[5] various methods have been reported.[5a] Particularly, chiral auxiliaries have been employed for the synthesis of piperidine core as one of the strategies.[5b-5e]

Fig 4.2: Solenopsin alkaloid in fire ants (courtesy: Wikipedia)

The 'solenopsins' are piperidine alkaloids derived from the venom of the red fire ant *Solenopsis invicta.* These piperidine alkaloids are known to inhibit angiogenesis via the phosphoinositol-3 kinase (PI3-K) signalling pathway[6] (Fig 4.2). Dart frog found in central and south America secretes many lipophilic alkaloids through their skin as their protecting mechanism against predation.[4]

Several drugs containing piperidine ring as main core are available in the market. For the treatment of attention-deficit-hyperactivity disorder, Ritalin®[7] is used as the drug and Bayrepel® (**10**),[8] the insect repellent also contain a 2-substituted piperidine core (Fig 4.3). Piperidine core is present in many active pharmaceutical ingredients (APIs) and few are listed here (Fig 4.3).

Bayrepel ®
10

Ritalin®
(psychostimulant)

Melperane
(antipscychotic)

Thioridazine
(antipsychotic)

Loperanide opioid

Paroxetine
(antidepressant)
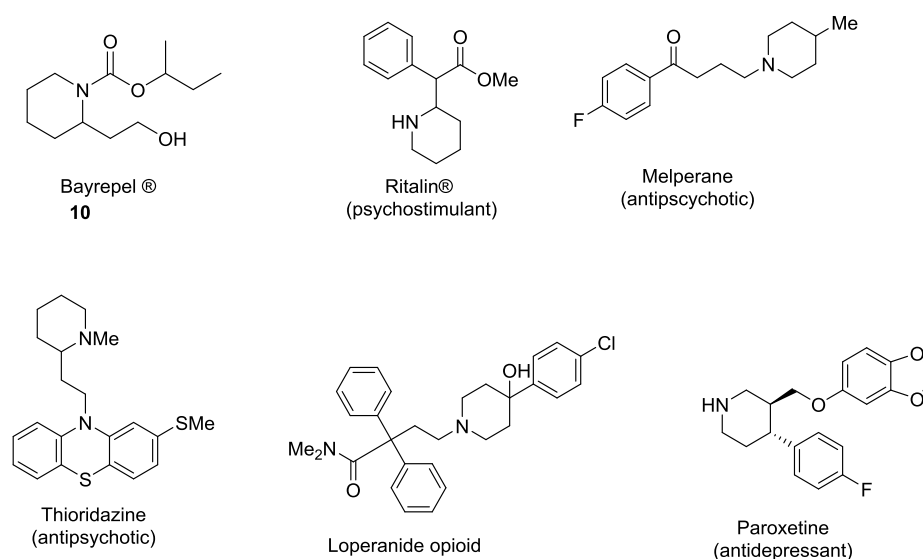
Fig 4.3: Some of the APIs containing piperidine core

Piperidine derivatives have been synthesized by exploring many methods[9] mostly starting from substituted pyridines,[10] amino alcohols,[11] imines.[12] Other methods rely on aldol reaction,[13] reductive amination reaction,[14] ring expansion and heterocyclic rearrangements,[15] aza-conjugate additions. [16] Various metal and acid catalyzed cyclizations,[17] Mannich type reactions and Diels-Alder reactions[18] have been explored. Recently, olefin metathesis,[19] and multicomponent reactions[20] have been employed for the construction of piperidines.

4.2 Selected methods for the synthesis of substituted piperidines

Bols and co-workers[21] have reported the hydrogenation of pyridine derivative (11) in presence of Rh/C to afford the *cis*-5-hydroxy amino acid (12) as the only product. Compound *cis*-5-hydroxy amino acid (12) was further confirmed by the previously reported method wherein, by-product obtained after the hydrogenation of 5-aminonicotinic acid (13) with PtO$_2$ as a catalyst (Scheme 4.1).
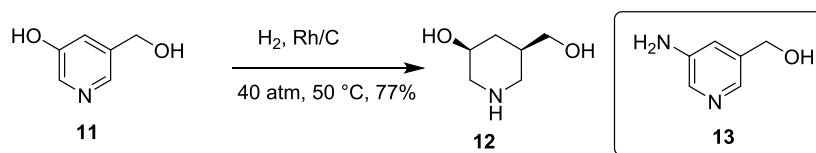
Scheme 4.1: Hydrogenation of pyridine derivative (11)

Wang, Zhou and co-workeres[22] reported a scarce selective homogeneous hydrogenation of pyridinol to piperidinone derivative. A homogeneous iridium catalyst has been utilized for the selective hydrogenation of 3-hydroxypyridinium salts (14, 16) to afford direct 2- and 4-substituted piperidin-3-one derivatives (15, 17) with high yields. The reported protocol is a good practical method for the synthesis of piperidin-3-ones which shows high chemoselectivity under milder reaction conditions with an easy scalability (Scheme 4.2).
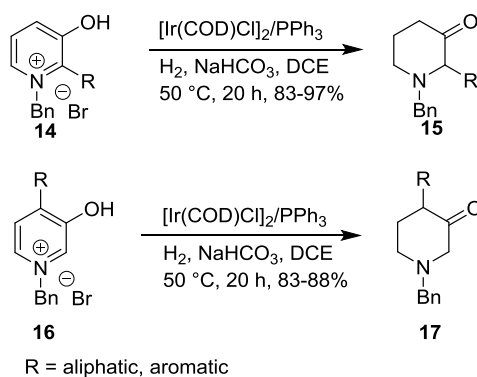
Scheme 4.2: Iridium-catalyzed selective hydrogenation of 3-hydroxypyridinium salts (14, 16)

Ruano *et al.*[23] developed a diastereoselective reduction of α-sulphinyl 2,3,4,5-tetrahydropyridine (18) by using DIBAL-H in the presence of ZnBr$_2$ to yield the corresponding piperidine derivative (19) in 65% yield (Scheme 4.3).
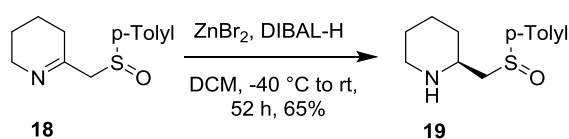
Scheme 4.3: Stereoselective reduction of α-sulfinyl ketimines (18)

The *N*-9-(phenylfluorenyl) (9-PhF-) protected derivative (**20**) upon treatment with excess of LDA at -78 °C, followed by excess ethyl iodide underwent an intramolecular nucleophilic substitution of alkyl iodide with nucleophilic carbon to give the corresponding piperidine derivative (**21**). This pipecolic acid derivative has been used as an intermediate in a synthesis of apovincamine (**22**) (Scheme 4.4).[24]
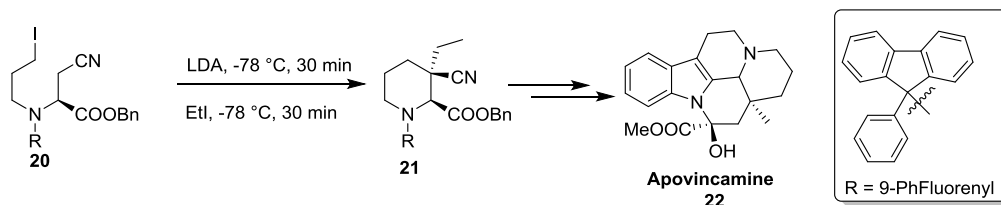
Scheme 4.4: 2, 3-Substituted piperidines (**21**) *via* intramolecular nucleophilic substitution

Bailey and co-workers[25] have attempted an enantio-specific and stereo-selective route to 5-substituted pipecolic acid derivatives (**25**). The attempted method utilizes the naturally occurring (L)-glutamic acid as a chiral source, which further under subsequent steps undergoes nucleophilic substitution of chloro group (**23**) with nitrogen as a key step as described below (Scheme 4.5).
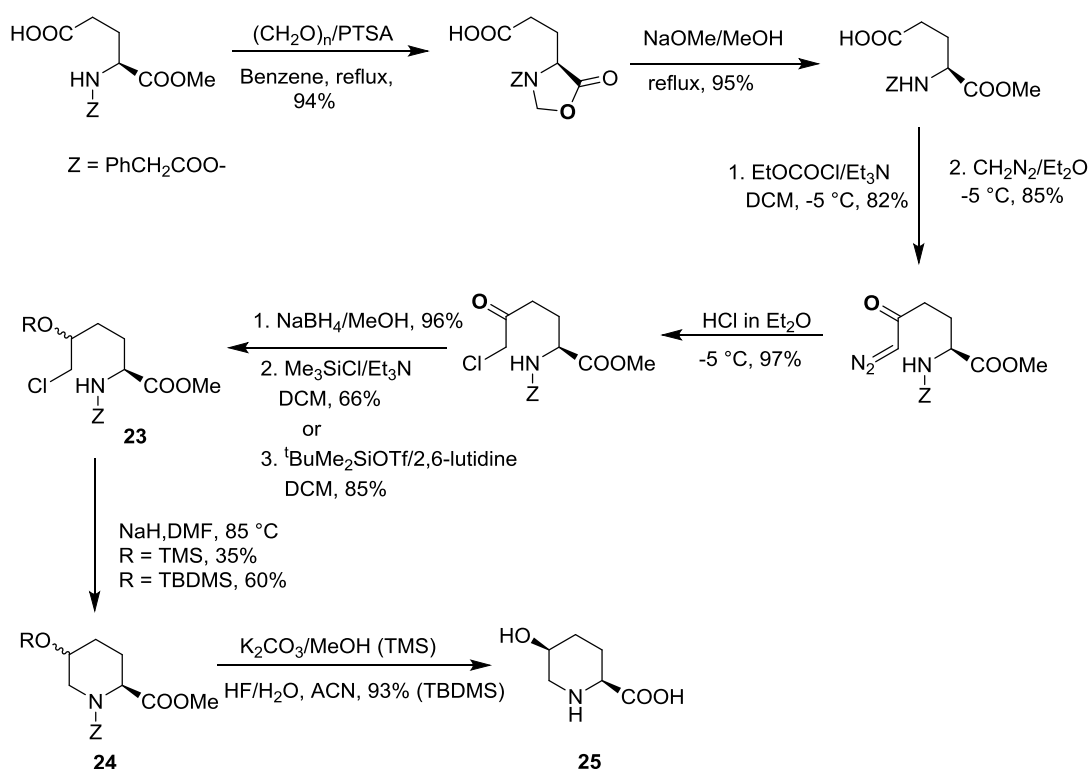
Scheme 4.5: 5-Hydroxy pipecolic acid (**25**) *via* intramolecular nucleophilic substitution with nitrogen

Burger and co-workers[26] have synthesized 4-oxo-, *cis*-4-hydroxy-, and *trans*-4-hydroxy-L-pipecolic acids starting from L-aspartic acid (**26**) and its derivative (**29**) as a homochiral precursors. Initially, this method utilizes the Stille cross-coupling to get the corresponding coupled products (**27, 30**); which further follow the Lewis acid (BF$_3$.Et$_2$O) catalyzed intramolecular aza-Michael addition under refluxing conditions to provide protected derivatives of vicinal amino and carboxylic groups. The resulting vicinal amino and carboxylic groups were deprotected by using ^{i}PrOH/H$_2$O (50:50, v/v) to afford the corresponding 4-oxo-L-pipecolic acid (**28**) or *trans*-6-methyl-4-oxo-L-pipecolic acid (**31**) (Scheme 4.6). However, reaction was unsuccessful when phenyl, methoxycarbonyl or dimethyl substituted enones were treated under similar reaction conditions.
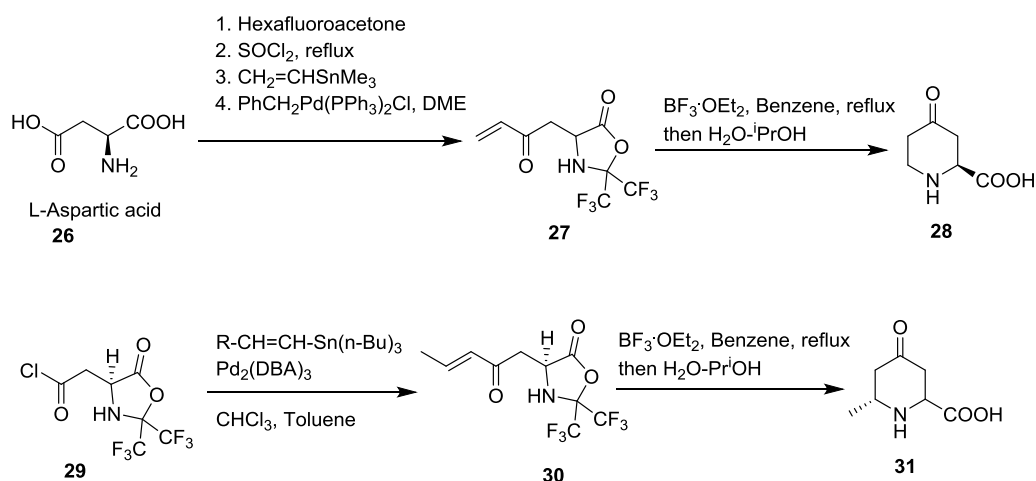
Scheme 4.6: 4-oxo-L-pipecolic acids (**28, 31**) from L-Aspartic acid (**26**) via Michael addition

Hirai and coworkers[27] have described an asymmetric intramolecular Michael reaction of **32** using the chiral base (*R*)-(+)-1-phenylethylamine to afford the piperidine derivative (**33**). The stereochemistry of these products depends on the chiral base employed for the synthesis. However, when the reaction was performed with (*S*)-(−)-1-phenylethylamine as a chiral base, the reaction afforded the opposite isomer of **33** (Scheme 4.7). These chiral bases were recovered in quantitative yield without any loss of optical purity.
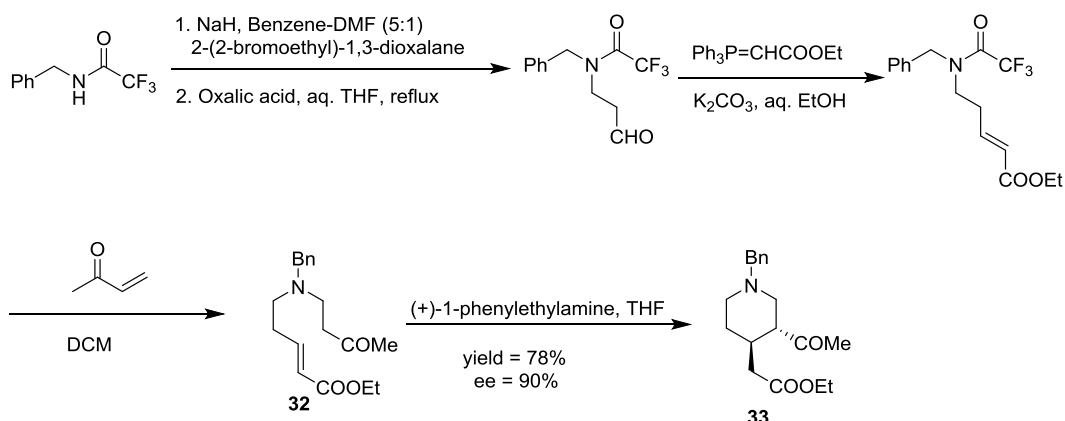
Scheme 4.7: Chiral base catalyzed intramolecular Michael addition

Davis and co-workers[28] have developed a one-pot intramolecular aza-Michael addition followed by a retro-Michael type elimination of **35** to give enantiopure 2,4,5-trisubstituted piperidines **36** starting from an *N*-Sulfinyl δ-amino β-ketoester enaminones (**34**), a sulfinimine-derived chiral building block (Scheme 4.8). This new chiral building block (**35**) is readily prepared by treating *N*-sulfinyl δ-amino β-ketoesters (**34**) with dimethylformamide dimethyl acetal.
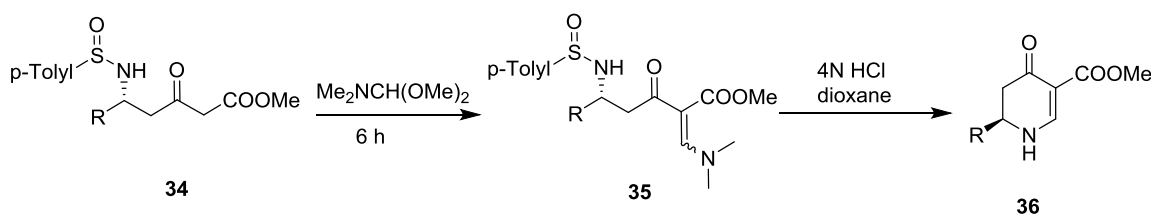
Scheme 4.8: Intramolecular aza-Michael addition followed by retro-Michael type elimination

Recently, Cossy and co-workers[29] have demonstrated a highly efficient diastereoselective protocol for the synthesis of substituted *cis*-2,6-piperidines (**38**) and *cis*-2,6-tetrahydropyrans. This method explored the use of $FeCl_3 \cdot 6H_2O$ as a catalyst in the key step of the reaction (Scheme 4.9). The highlights of the protocol are mild reaction conditions, eco-friendly and selective formation of stable *cis*-isomers. This methodology also tolerated the use of substrates bearing alkyl or ester groups.

X = NPG; R^1, R^2 = H, Alkyl, Aryl
R^3 = H, Ac

dr: 90/10 to >99/1
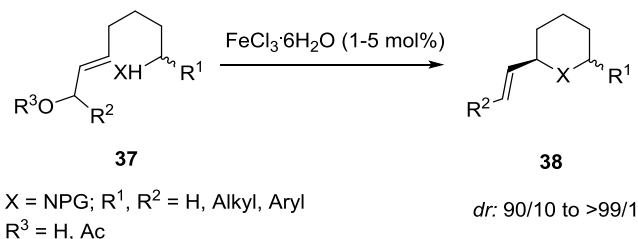
Scheme 4.9: $FeCl_3 \cdot 6H_2O$ catalyzed diastereoselective synthesis of substituted piperidines

Recently, our group developed[30] a two-step one pot synthesis of *trans*-2, 3-disubstituted 4-piperidones by utilizing an intramolecular aza-Michael addition reaction strategy starting from alkylidene β-keto esters (**39**). The reaction involves a cascade type reaction, which uses BF$_3$·Et$_2$O or one pot deprotection of ^{t}Boc group by TFA, then TEA to afford *trans*-2,3-disubstituted piperidines (**41**) via the free amine (**40**) (Scheme 4.10).
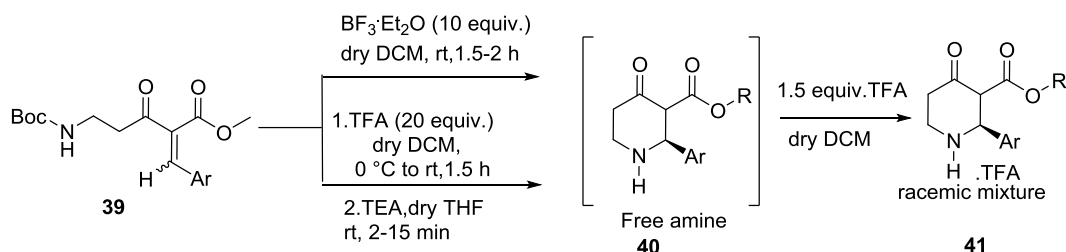
Scheme 4.10: One pot synthesis of *trans*-2, 3-disubstituted 4-piperidones (**41**)

4.3 Results and Discussion

Due to the importance of biological activity of piperidine moiety and their synthetic value, we became interested in exploring a new protocol for the synthesis of chiral piperidine derivatives. In order to synthesize chiral piperidine derivatives in a stereoselective manner, we chose a suitably activated alkene moiety for the intramolecular aza-Michael addition of carbamate. However, the major challenge in achieving good stereoselectivity depends on one or more factors, for instance, choosing a proper chiral starting material, chiral catalyst, chiral auxiliary or solvent.

However, the major challenge is the activation of double bond for the effective and efficient cyclization with good stereoselectivity. As the classic base mediated reactions suffers from undesired side reactions, we thought that the Lewis acid catalyzed Michael addition reactions would serve as better method for the required chemoselective and stereoselctive method. It is well known that generally Lewis acids activate the system by chelation or by coordination,[31] however it is very crucial to choose a particular Lewis acid for the effective transformation for the conjugate addition of carbamates. This prompted us to explore the asymmetric synthesis of piperidine derivatives by using chiral auxiliary under mild Lewis acid catalytic system. In this regard, we decided to synthesize suitable alkylidene β-ketoesters starting from β-ketoesters.

4.4 Synthesis of β-ketoester and alkylidene β-keto esters

Though there are many approaches for the synthesis of β-ketoesters[32] but only few methods are available in literature for the synthesis of β-ketoesters starting from carboxylic acids.[33] It is known in the literature that alcohols can readily react with an intermediate, obtained from the coupling of Meldrum's acid with carboxylic acid to afford the corresponding β-ketoesters.[34] Different alcohols can be used as nucleophiles for the construction of different β-ketoesters.

It is very well established that naturally occuring chiral auxiliaries such as (+)-cinchonine and menthol are very useful in controlling the stereochemical outcome in various transformations. In this regard, initially we chose (+)-cinchonine (**A**) as the chiral auxiliary for the effective stereoinduction. At the outset we synthesized the alkylidene β-keto cinchonine ester (**42a, 42b**) starting from the corresponding β-keto cinchonine ester (**42**) by exploring the Knoevenagel condensation reaction. However, condensation reaction resulted in an inseparable *EZ*-mixture of alkylidene β-keto cinchonine ester (**42a, 42b**). Further, the cyclization of *EZ*-mixture resulted in the mixture of products with lower diastereoselctivity (Scheme 4.11). It is important to note that *E* and *Z* isomers have different rate of cyclization thus leading to products with different diastereoselectivity making it very difficult to ascertain the exact diastereoslectivity of the each product.

Scheme 4.11: Synthesis of alkylidene β-keto cinchonine esters (**42a, 42b**)

Scheme 4.12: Proposed strategy for synthesis of alkylidene β-keto (L)-menthyl esters (**4, 4'**)

Later, we chose (L)-menthol as chiral auxiliary for the desired effective steroinduction, as it is cheap and commercially available. Gratifyingly, isomers (*E* and *Z*) alkylidene *β*-keto menthyl esters (**4**) were separable for the application (Scheme 4.12).

Table 4.1: Synthesis of (L)-menthyl *α*, *β*-unsaturated *β*-keto-*γ*-amino esters using Knoevenagel condensation[a]
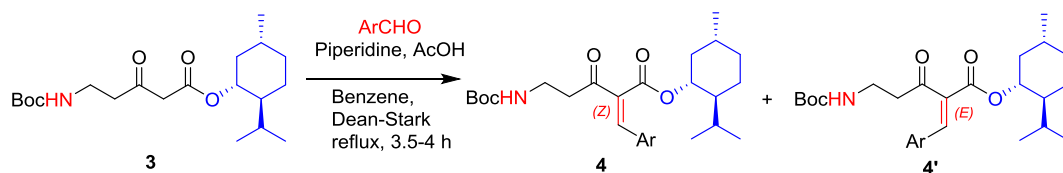
Entry	Ar-	Product (Z:E)[b]	Time(h)	yield (%)[c]	Entry	Ar-	Product (Z:E)[b]	Time(h)	yield (%)[c]
1	**4a:4'a**	60:40	4 h	78	10 EtO	**4j:4'j**	58:42	4.5 h	74
2 Br	**4b:4'b**	56:44	3.5 h	85	11 NC	**4k:4'k**	58:42	4 h	88
3 O_2N	**4c:4'c**	58:42	4 h	90	12 O_2N	**4l:4'l**	60:40	4 h	85
4 F	**4d:4'd**	53:47	3.5 h	80	13	**4m:4'm**	60:40	4 h	85
5 Cl	**4e:4'e**	58:42	3.5 h	82	14 MeO OMe	**4n:4'n**	55:45	4 h	82
6 Cl	**4f:4'f**	57:43	4 h	82	15 Br Br	**4o:4'o**	55:45	3.5 h	85
7	**4g:4'g**	60:40	3.5 h	75	16	**4p:4'p**	60:40	3 h	75
8 ^tBu	**4h:4'h**	56:44	3.5 h	78	17	**4q:4'q**	58:42	3.5 h	70
9 MeO	**4i:4i**	60:40	4.5 h	76					

[a] Reactions were conducted under Dean-Stark conditions as mentioned in the SI. [b] Based on NMR of reaction mixture and Isolated yield of product after column chromatography. [c] Isolated yield of the product after column chromatography.

We assumed that activation of the double bond by appropriate Lewis acid would lead to the expected intramolecular cyclization. In order to explore the idea, we synthesized various alkylidene *β*-keto (L)-menthyl esters (**4**) from the corresponding (L)-menthyl-*β*-keto

ester **3** by condensing β-ketoesters (**3**) with different aldehydes (Scheme 4.12) in good to excellent yields (70–90%, Table 4.1).[35]

The stereochemistry of geometrical isomers (*E-* and *Z-*) was determined by 1d-*nOe* studies of **4a**. In order to study the effect of geometrical isomers on the cyclization, *E* and *Z* isomers of **4** were isolated by column chromatography.

Table 4.2: Screening of Lewis acid catalysts for optimizing the aza-Michael addition reaction
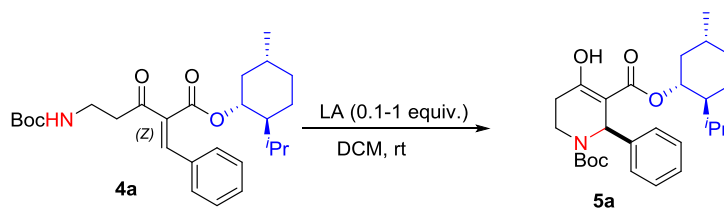
Entry	LA (catalyst)[a]	*dr* (%)[b]	Time (min/h)	Yield[c] (%)
1	FeCl$_3$	51:49	5 min	96
2	CoCl$_2$	—	4	NR
3	CeCl$_3$	—	4	Trace
4	Sc(OTf)$_3$	39:61	2	90
5	Cu(OAc)$_2$	—	4	NR
6	Zn(OAc)$_2$	—	4	NR
7	CuSO$_4$	—	4	NR
8	Cu(I)Br	—	4	NR
9	CoCl$_2$	—	4	NR
10	CuCl$_2$	36:64	3	85
11	FeCl$_3$·6H$_2$O	24:76	10 min	96
12	**FeCl$_3$·6H$_2$O**	**23:77**	**15 min**	**98**
13	FeCl$_2$·4H$_2$O	—	4	Trace
14	CeCl$_3$·7H$_2$O	—	4	Trace
15	RuCl$_3$·XH$_2$O	25:75	4	85
16	RhCl$_3$·XH$_2$O	—	4	Trace
17	LaCl$_3$·7H$_2$O	—	4h	NR
18	DyCl$_3$·7H$_2$O	—	4	NR
19	NdCl$_3$·7H$_2$O	—	4	NR
20	No Catalyst	—	24	NR

[a]Reactions were performed with 1equiv. of Lewis acids (LA) in DCM (entry 1-3, 5-11, 14) and reactions were performed with 0.1 equiv (10 mol%) of LA in DCM (entry 4, 12–13, 15–19). [b]*dr* were calculated by HPLC using chiralpak IA column. [c]Isolated yield of the product after column chromatography, NR = No Reaction occurred. rt ~ 28 °C.

In order to optimize the reaction conditions, we chose *Z*-isomer of (L)-menthyl alkylidene *β*-keto ester **4a** (major isomer) as a model substrate to explore the intramolecular

cyclization by using different Lewis acids in DCM (Table 4.2). In the initial attempts, we screened various anhydrous Lewis acids (0.1-1 equiv.) at room temperature in DCM (see entry 1–10, Table 4.2). Only few Lewis acids facilitated the intramolecular cyclization to give the corresponding piperidine derivative **5a**. Surprisingly, anhydrous $FeCl_3$ (1 equiv.) catalyzed the desired transformation in short time (5 min) to afford the desired piperidine derivative **5a** in excellent yield (96%, see entry 1, Table 4.2). Both $FeCl_3$ and $Sc(OTf)_3$ catalyzed the reaction to give desired product **5a**, however with poor diastereoselectivity. Later, hydrated Lewis acids were explored for the desired transformation. After screening several hydrated Lewis acids (entry 11–19), $FeCl_3 \cdot 6H_2O$ was proved to be a suitable catalyst for providing good diastereoselectivity. It is noteworthy that when we attempted the reaction with lower catalytic loading of (0.1 equiv or 10 mol%) of $FeCl_3 \cdot 6H_2O$ reaction proceeded smoothly (15 min) with an excellent yield with good diastereoselectivity (entry 12). $FeCl_3 \cdot 6H_2O$ was relatively slow in catalyzing the reaction (15 min), however resulted in good diastereoselectivity. We surmise that anhydrous $FeCl_3$, being a strong Lewis acid, was quick in catalyzing the reaction resulting in poor diastereoselectivity. Interestingly $FeCl_2 \cdot 4H_2O$ (entry 13) did not catalyze the reaction. We also observed that reaction did not proceed in the absence of catalyst (entry 20).

Z (**4a**) and E (**4'a**) isomers were studied independently for the cyclization in different solvents.[36] After screening of various solvents (see Table **4.3**), we found that DCM and toluene were good solvents as Z-isomer cyclized with good diastereoselectivity in excellent yields. However it was observed that the corresponding E-isomer **4'a** reacted slowly under the optimized reaction condition to yield the cyclized product with lower diastereoselectivity. We believe that probably the steric and electronic factors are the cause of slow reactivity of E-isomer. Also, we observed that in case of polar solvents like MeOH, EtOH reaction was sluggish and in case of polar aprotic solvents such as DMF and DMSO reaction did not proceed even after prolonged reaction time. In order to find out the scope and limitaions of the reaction, Z- and E- isomers of various alkylidene β-keto menthyl esters (**4b–4q**) were isolated and the corresponding major Z–isomers were used for the reactions.

Table 4.3: Optimization of the reaction for the *E* and *Z*–isomers in different solvents[a]

4a- (*Z*)-isomer OR **4'a**-(*E*)-isomer   **5a**

Entry	Solvent	*dr* (%)[b] Time (min/h) (**4a** to **5a**)	Yield (%)[c]	*dr* (%)[b] Time (min/h) (**4'a** to **5a**)	Yield (%)[c]
1	DCM	23:77 (15 min)	98	66:34 (40 min)	96
2	CHCl$_3$	23:77 (15 min)	98	65:35 (45 min)	94
3	Toluene	22:78 (15 min)	98	70:30 (4 h)	95
4	EA	22:78 (4 h)	70	56:44 (4 h)	62
5	Acetone	21:79 (4 h)	65	60:40 (4 h)	58
6	DMF	NR (12 h)	--	NR (12 h)	--
7	DMSO	NR (12 h)	--	NR (12 h)	--

[a]Reactions were performed with 0.1equiv. (10 mol%) of FeCl$_3$·6H$_2$O. [b]*dr* was calculated by HPLC using chiralpak IA column. [c]Isolated yield of the product after column chromatography, NR = No Reaction occurred. rt ~ 28 ^{o}C

4.5 Effect of Solvent and Temperature

Further, in order to find out suitable solvent and optimal temperature conditions, we treated compounds **4a** (Ph), **4b** (4-Br), **4c** (4-NO$_2$) with FeCl$_3$·6H$_2$O in DCM and toluene at room temperature (~28 °C) to afford the corresponding piperidine derivatives (**5a, 5b, 5c**) with slightly variable diastereoselectivity. However, when the reactions were carried out at 0 to 15 ^{o}C, starting materials did not react even after prolonged reaction time. However, when reactions were carried out at 20 ^{o}C in toluene or DCM, reactions proceeded with improved diastereoselectivity with excellent yields (see Table 4.4). Based on these studies, optimized reaction condition [FeCl$_3$·6H$_2$O (0.1 equiv. or 10 mol%), toluene, 20 ^{o}C] was employed for the further studies.

Table 4.4: Influence of temperature and solvent on diastereoselectivity[a]
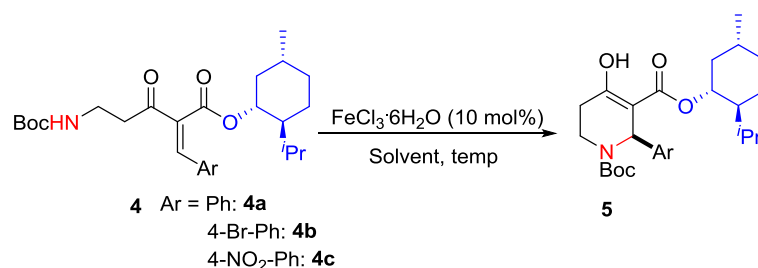
Entry (Ar)	DCM		Toluene	
	at rt*	at 20 °C	at rt*	at 20 °C
5a (Ph)	23:77	21:79	22:78	21:79
5b (4-Br)	21:79	20:80	19:81	17:83
5c (4-NO$_2$)	21:79	21:79	18:82	17:83

[a]Reactions were performed with 0.1 equiv. of FeCl$_3$·6H$_2$O and *dr* were calculated by HPLC using chiralpak IA column. *rt = 28 °C

In order to expand the reaction scope of this method, various (*Z*)-alkylidene *β*-keto (L)-menthyl esters (**4d–4q**) were explored for the cyclization under the optimized reaction conditions to afford the corresponding piperidine derivatives (**5d–5q**). It was found that regardless of their electronic nature, functional groups on the substrates tolerated the reaction conditions with excellent yields. We observed moderate to good diastereomeric ratio (up to *dr* 9:91) for the piperidine derivatives from HPLC studies (see Table 1.5).[37] However, we could not explore the scope of the protocol with *o*-substituted aromatic derivatives and aliphatic alkyledine *β*-ketoesters as they were inseparable mixture of *E* and *Z* isomers.

We believe that steric factor resulting from substituent on benzene ring also played a significant role in enhancing the diastereoselectivity. Alkene bearing *meta*-mono and di-substituted derivatives led to the enhancement in diastereoselectivity in comparison with *para*-substituted derivatives. Both electron-withdrawing and -donating groups did not have any significant effect on the rate of the reaction as well as on the diastereoselectivity. Even the heteroaromatic substituted alkylidene *β*-ketoesters (**4p, 4q**) underwent cyclization with an ease affording the corresponding piperidine derivatives in excellent yields (**5p, 5q,** see Table 1.5). However, we observed that products **5p** and **5q** suffered from moderate diastereoselectivity.

4.6 Confirmation of Diastereomers and Rotamers

To our dismay, we observed that ^{1}H-NMR spectra of the products were highly complex due to peaks arising from both diastereomers and equilibrating rotamers of the corresponding diastereomers. Merging of peaks in ^{1}H-NMR made almost impossible to analyze the spectra in detail. It was clear from the ^{1}H-NMR spectrum of **5o** that two peaks of equal intensity at 12.68 ppm and 12.56 ppm in $CDCl_3$ at room temperature are due to rotamers of corresponding diastereomers. Also the peaks with equal integration did not correspond to the diastereoselectivity (*dr* 9:91) that we observed from HPLC studies. In order to confirm this ambiguity, we subjected the diastereomeric product **5o** for the variable temperature (VT)-NMR (500 MHz) studies. It was indicated from the VT-NMR stacked spectrum that equilibrating rotameric peaks with equal intensity at room temperature (25 $^{\circ}$C) slowly started resolving into two clear set of peaks at variable temperature (–40 to –55 $^{\circ}$C) (Fig. 1.4) and the diastereomeric ratio clearly matched with HPLC data. It was evident from the VT-NMR studies that existence of rotamers is due to *N*-Boc group and this observation was further supported by earlier finding.[38] Hence, we decided to isolate the major diastereomer[39] of **5o** and deprotect the Boc-group to simplify the spectrum there by avoiding rotameric peaks. ^{1}H NMR spectrum of Boc-deprotected piperidine derivative (**6o**) was neat and revealed the existence of enolic form of salt and all peaks were well resolved.

Table 1.5: Substrate scope of diastereoselective piperidine derivatives[a]
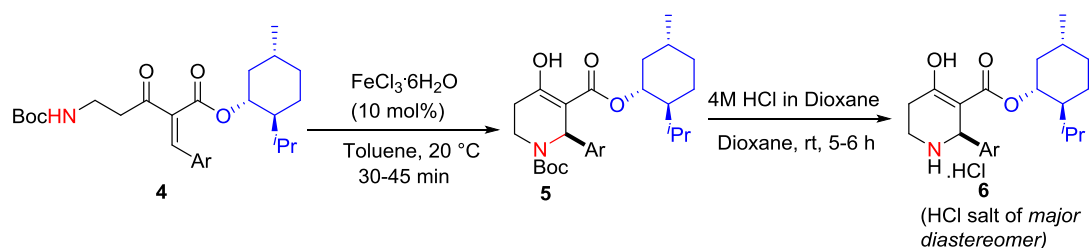
Entry	Ar-	5 dr(%)[b] (% yield)	6 (HCl salt) yield (%)	Entry	Ar-	5 dr(%)[b] (%yield)	6 (HCl salt) yield (%)
1	**5a**	21:79 (98)	**6a** (95)	10	**5j**	29:71 (95)	**6j** (88)
2	**5b**	18:82 (97)	**6b** (93)	11	**5k**	15:85 (98)	**6k** (96)
3	**5c**	15:85 (98)	**6c** (95)	12	**5l**	14:86 (95)	**6l** (95)
4	**5d**	19:81 (97)	**6d** (88)	13	**5m**	9:91 (96)	**6m** (96)
5	**5e**	17:83 (96)	**6e** (92)	14	**5n**	11:89 (94)	**6n** (94)
6	**5f**	15:85 (95)	**6f** (93)	15	**5o**	9:91 (99)	**6o** (98)
7	**5g**	20:80 (96)	**6g** (92)	16	**5p**	36:64 (93)	**6p** (89)
8	**5h**	19:81 (95)	**6h** (94)	17	**5q**	30:70 (95)	**6q** (90)
9	**5i**	27:73 (95)	**6i** (85)				

[a]Cyclization reactions were performed with 0.1 equiv. (10 mol%) of $FeCl_3.6H_2O$ in Toluene at 20 °C and deprotection of Boc group was performed on the major diastereomer with 4M HCl in dioxane, dioxane as solvent. [b]dr was calculated by HPLC using chiralpak IA column. [c]Obtained yield of the product after washing with in n-pentane.

These findings prompted us to isolate the major diastereomers of all the products (**5a-5q**) and were subjected for Boc deprotection to afford the corresponding salts (**6a-6q**) in good to excellent yields (Table 1.5).[40] It was conclusive from ^{1}H-NMR spectra that all piperidine hydrochloride salts (**6a-6q**) existed mostly in enolic form. All the products were characterized by spectroscopic data. Also, we observed from the ^{1}H and ^{13}C-NMR spectra

that final products with electron donating groups on phenyl ring showed slightly equilibrating keto-enol tautomers.
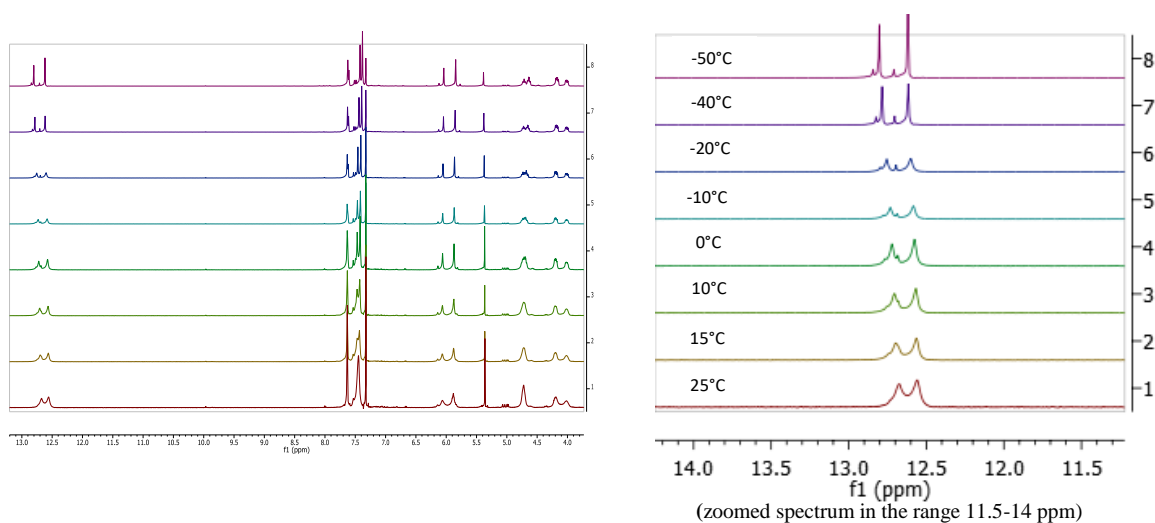
Fig. 1.4 Variable Temperature (VT) NMR study of *N*-Boc derivative of (L)–menthyl ester of 2-(3, 5-dibromophenyl) piperidone (**5o**) derivative.

4.7 Attempts towards the deprotection of menthyl ester

In order to find out the stereochmistry of the synthesized piperidine derivatives, we planned to remove the chiral auxiliary. Unfortunately all the protocols that we attempted towards the removal of chiral auxiliary:menthyl ester were unsuccesful. Many known methods such as deprotection under acidic conditions (conditions A to get 7), transesterification (conditions B to get 8) were attempted for the deprotection of menthyl ester (Scheme 4.13). (see experimental sectionfor the details of various methods). Surprisingly different deprotection methods of menthyl esters known in the literature did not work on menthyl *β*-ketoester scaffold.
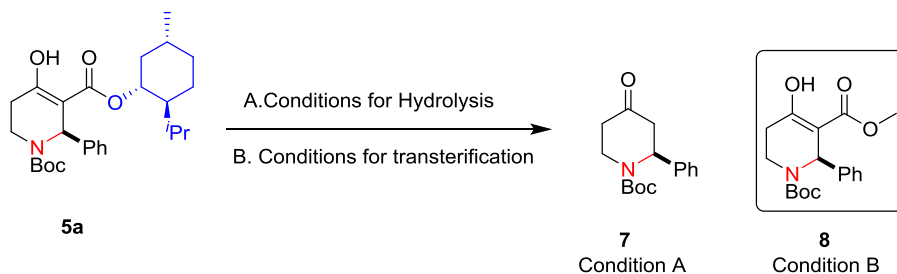
Scheme 4.13: Attempts towards the deprotection of menthyl ester

4.8 Conclusions

In conclusion, we have demonstrated the novel access of diastereoselective piperidine derivatives by exploring the strength of environmentally benign iron (III) chloride (10 mol%) as a catalyst and naturally available (L)-menthol as a chiral auxiliary. Intramolecular cyclization proceeded in diastereoselective manner. Reaction conditions were mild and favored rapid formation of piperidine derivatives in good to excellent yields and with high diastereoselectivity.

4.9 Experimental Section

General: All starting materials were obtained from Aldrich, Acros, Merck and were used as obtained unless otherwise mentioned.All reactions were carried out with distilled and dried solvents under an atmosphere of dry N_2 and oven-dried glassware. All solvents CH_2Cl_2, Toluene, EtOAc, Pet. ether, *n*-Pentane were purified and dried by using regular procedures using "Purification of Laboratory Chemicals" by Perrin and stored over activated 4 Å molecular sieves. All compounds were purified by using Column Chromatographic technique on 100-200 mesh size silica gel. Analytical Thin-layer chromatography (TLC) was performed using Merck silica gel 60 GF_{254} pre-coated aluminum backed plates (2.5 mm) with spot detection under UV light or ninhydrin, PMA or vanillin. ^{1}H NMR and ^{13}C NMR were recorded in $CDCl_3$ on 400 MHz (100 MHz for ^{13}C) and 500 MHz (125 MHz for ^{13}C). Chemical shifts in ^{1}H NMR and ^{13}C NMR spectra are reported as δ in ppm with the solvent resonance as the internal standard, Coupling constants (*J*-values) are given in Hz. ^{1}H NMR data were reported in the order of chemical shift, multiplicity (s, singlet; d, doublet; t, triplet; m, multiplet; dt, doublet of triplet), coupling constant in hertz (Hz) and number of protons. Specific rotations were recorded using $CHCl_3$ as a solvent (Rudolph Analytical Research). High-Resolution mass spectra were obtained from HRMS-ESI-TOF. IR spectra of neat samples were recorded using FT-IR spectrophotometer and reported in cm^{-1}. All melting points were measured in open glass capillary and values are uncorrected. The diastereomeric ratio was calculated by injecting the samples into HPLC using Chiralpak IA column, using n-hexane and IPA as an eluent.

**General procedure for the Synthesis of (L)-menthyl 5-((*tert*-butoxycarbonyl) amino)-3-oxopentanoate (3)**
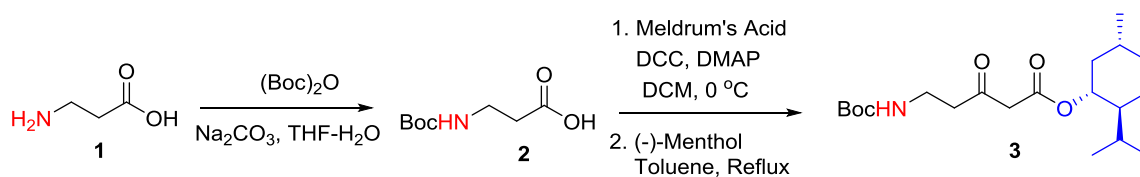
To a well stirred mixture of 3-(*tert*-butoxycarbonyl)amino propanoic acid (**2**) (25 g, 132.2 mmol), Meldrum's acid (19.1 g, 132.2 mmol), *N,N*-dimethylamino pyridine (DMAP) (21 g, 171.86 mmol) in dry DCM (350 mL) at 0 °C was added portion-wise dicyclohexyl carbodiimide (DCC) (30 g, 145.4 mmol) over 20 minutes at 0 °C. Then the reaction mixture was allowed to warm to room temperature and stirred for 4 h. The precipitate formed was removed by filtration through a sintered glass funnel. Filtrate was washed with aqueous 1M $KHSO_4$ solution (2 x 250 mL) then with brine solution (2 x 175 mL) and dried over anhydrous sodium sulfate and concentrated to dryness under reduced pressure to give brownish residue. Then to this brownish residue, (L)-menthol (21.7 g, 138.81 mmol) was added and was dissolved in dry toluene (250 mL) and refluxed for 8 h. After the reaction, crude compound (**3**) was purified by column chromatography over silica gel eluting with Pet. Ether/EtOAc (85:15) affording as a pale yellow oil in overall 60% yield.

Pale yellow oil (22.15 g, 60%); $R_f = 0.40$ Pet. Ether: EtOAc (80:20); $[\alpha]^{25}_D$ −41.6 (c 1, $CHCl_3$); IR (Neat) cm^{-1}: 2955, 2928, 2870, 1712, 1505, 1455, 1366, 1247, 1117, 983; ^1H NMR (400 MHz, $CDCl_3$) δ 4.99 (br s, 1H, NH), 4.72 (td, *J* = 10.9, 4.4 Hz, 1H), 3.43 (s, 2H), 3.37 (q, *J* = 5.8 Hz, 2H), 2.76 (t, *J* = 5.7 Hz, 2H), 2.05–2.00 (m, 1H), 1.84 (dtd, *J* = 14.0, 7.0, 2.7 Hz,, 1H), 1.70–1.69 (m, 1H), 1.66–1.65 (m,1H), 1.53–1.45 (m, 1H), 1.42 (s, *J* = 5.4 Hz, 9H), 1.40–1.33 (m, 2H), 1.10–0.96 (m, 2H), 0.90 (t, *J* = 6.9 Hz, 6H), 0.76 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.6, 166.6, 155.9, 79.5, 75.8, 49.8, 47.0, 43.2, 40.8, 35.1, 34.3, 31.5, 28.5, 26.3, 23.4, 22.1, 20.9, 16.3; HRMS (ESI–TOF) m/z Calcd. for $C_{20}H_{35}NO_5$ $[M + Na]^+$ 392.2407, observed 392.2412.

General Experimental procedure for the Synthesis of (L)-menthyl *α, β*-unaturated *β*-ketoesters 4 (Knoevenagel condensation):

(L)-menthyl 2-benzylidene-5-(*tert*-butoxycarbonylamino)-3-oxopentanoate (4a, 4'a):

To a solution of (L)-menthyl *β*-keto ester (1.85 g, 5.0 mmol), benzaldehyde (0.557 mL, 5.25 mmol) in benzene (80 mL), were added piperidine (0.05 mL, 0.5 mmol, 0.1 equiv.), acetic acid (0.06 mL, 1 mmol, 0.2 equiv.). The reaction mixture was refluxed using Dean-Stark apparatus to remove the water formed during the course of the reaction. After the completion of reaction (3.5–4 h), benzene was evaporated under vacuum and the residue was purified by column chromatography over silica gel eluting with Pet. Ether/EtOAc (97:3 to 90:10) affording **4a:4'a** as pale yellow oil in 78% yield (1.70 g, Z:E = 60:40).
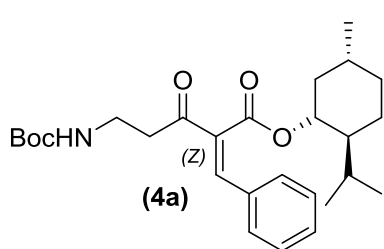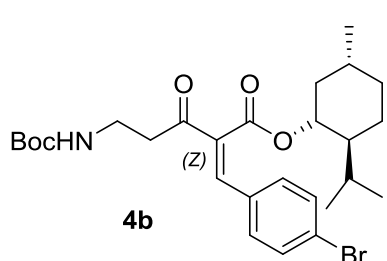

(Z)-Isomer (4a): Pale yellow pluffy solid (1.02 g, 60%); R_f = 0.28 Pet. Ether: EtOAc (85:15); $[\alpha]^{25}_D$ −23.60 (c 1, CHCl$_3$); IR (Neat) cm^{-1}: 3056, 2957, 2931, 2870, 1716, 1667, 1503, 1452, 1391, 1366, 1224, 1176, 980, 755, 694; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.56 (s, 1H), 7.50–7.48 (m, 2H), 7.42–7.34 (m, 3H), 5.14 (br s, 1H, NH), 4.87 (td, *J* = 10.9, 4.4 Hz, 1H), 3.50–3.44 (m, 2H), 2.97 (q, *J* = 5.4 Hz, 2H), 2.22–2.19 (m, 1H), 1.75–1.64 (m, 3H), 1.59–1.48 (m, 1H), 1.43 (s, 9H), 1.39–1.31 (m, 2H), 1.04 (ddd, *J* = 30.1, 15.0, 11.0 Hz, 2H), 0.93 (d, *J* = 6.6 Hz, 3H), 0.76 (dd, *J* = 12.3, 6.9 Hz, 6H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 196.4, 167.4, 156.0, 140.6, 135.0, 132.9, 130.7, 129.6, 128.8, 79.3, 76.3, 46.8, 40.2, 38.6, 35.3, 34.1, 31.5, 28.5, 25.5, 23.0, 22.1, 20.8, 15.9; HRMS (ESI–TOF) m/z Calcd. for C$_{27}$H$_{39}$NO$_5$ [M + Na]$^+$ 480.2720, observed 480.2734.
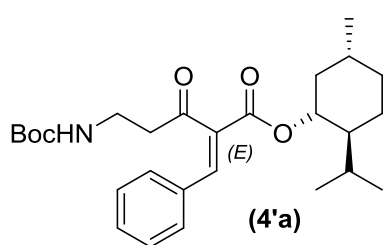
(E)-Isomer (4'a): Pale yellow oil (0.68 g, 40%); R_f = 0.48 Pet. Ether: EtOAc (85:15); $[\alpha]^{25}_D$ −38.40 (c 1, CHCl$_3$); IR (Neat) cm^{-1}: 3057, 2956, 2929, 2870, 1703, 1623, 1499, 1450, 1366, 1253, 1178, 1078, 1011, 961, 767, 693; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.67 (s, 1H), 7.39–7.33 (m, 5H), 5.03 (br s, 1H, NH), 4.88–4.79 (m, 1H), 3.45–3.38 (m, 2H), 2.80–2.74 (dt, *J* = 8.8, 5.5 Hz, 2H), 2.10–2.06 (d, *J* = 12.0 Hz, 1H), 1.89–1.81 (m, 1H), 1.74–1.66 (m, 2H), 1.58–1.46 (m, 1H), 1.42 (s, 9H), 1.28–1.22 (m, 2H), 1.14–0.98 (m, 2H), 0.94–0.89 (dd, *J* = 6.8, 3.8 Hz, 6H), 0.81–0.76 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 205.3, 164.0, 155.9, 140.9, 133.9, 132.9, 130.6, 129.7, 129.1, 79.4, 75.9, 47.1, 43.8, 40.9, 35.1, 34.2, 31.6, 28.6, 26.5,

23.5, 22.1, 20.9, 16.4; HRMS (ESI–TOF) m/z Calcd. for $C_{27}H_{39}NO_5$ [M + Na]$^+$ 480.2720, observed 480.2718.

(L)-menthyl   5-((*tert*-butoxycarbonyl)amino)-2-(4-bromobenzylidene)-3-oxopentanoate (4b, 4'b):


(*Z*)-Isomer (4b): Pale yellow pluffy solid (1.26 g, 56%); R_f = 0.30 Pet. Ether: EtOAc (85:15); [α]^{25}_D −21.80 (c 1, CHCl$_3$); IR (Neat) cm^{-1}: 3058, 2956, 2929, 2870, 1713, 1622, 1586, 1503, 1455, 1366, 1223, 1172,1073, 1010, 980, 956, 816, 780; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.51 (s, 1H), 7.49 (d, *J* = 3.8 Hz, 2H), 7.34 (d, *J* = 8.4 Hz, 2H), 5.07 (br s, 1H, NH), 4.84 (td, *J* = 10.9, 4.3 Hz, 1H), 3.46 (q, *J* = 5.6 Hz, 2H), 2.93 (m, 2H), 2.18–2.15 (m, 1H), 1.69–1.62 (m, 4H), 1.55–1.49 (m, 1H), 1.43 (s, 9H), 1.37–1.30 (m, 2H), 1.03 (ddd, *J* = 29.4, 14.6, 10.9 Hz, 2H), 0.93 (d, *J* = 6.5 Hz, 3H), 0.79 (d, *J* = 7.0 Hz, 3H), 0.73 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 196.2, 167.2, 156.0, 139.3, 135.6, 132.2, 132.0, 131.0, 125.3, 79.5, 76.6, 46.9, 40.3, 38.9, 35.3, 34.2, 31.6, 28.5, 25.6, 23.1, 22.2, 20.9, 16.0; HRMS (ESI–TOF) m/z Calcd. for $C_{27}H_{38}BrNO_5$ [M + H]$^+$ 536.2012, observed 536.2020.
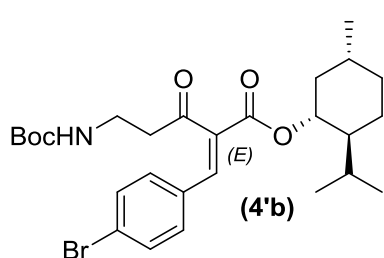
(*E*)-Isomer (4'b): Pale yellow oil (0.99 g, 44%); R_f = 0.52 Pet. Ether: EtOAc (85:15); [α]^{25}_D −37.2 (c 1, CHCl$_3$); IR (Neat) cm^{-1}: 3057, 2956, 2929, 2870, 1703, 1622, 1489, 1455, 1366, 1250, 1177, 1073, 1010, 957, 818, 736; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.59 (s, 1H), 7.51–7.49 (m, 2H), 7.23–7.20 (m, 2H), 5.00 (br s, 1H, NH), 4.83 (td, *J* = 10.9, 4.4 Hz, 1H), 3.42 (q, *J* = 5.6 Hz, 2H), 2.82–2.67 (m, 2H), 2.07–2.02 (m, 1H), 1.83 (pd, *J* = 7.0, 2.7 Hz, 1H), 1.77–1.68 (m, 2H), 1.62 (s, 1H), 1.56–1.47 (m, 1H), 1.43 (s, 9H), 1.25 (s, 1H) 1.13–0.98 (m, 2H), 0.91 (dd, *J* = 6.7, 4.7 Hz, 6H), 0.78 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 205.1, 163.8, 155.9, 139.5, 134.5, 132.4, 131.8, 131.1, 125.2, 79.5, 76.1, 47.1, 43.8, 40.8, 34.2, 31.5, 31.1, 28.6, 26.5, 23.4, 22.1, 20.9, 16.4; HRMS (ESI–TOF) m/z Calcd. for $C_{27}H_{38}BrNO_5$ [M + H]$^+$ 536.2012, observed 536.2015.

(L)-menthyl 5-((*tert*-butoxycarbonyl)amino)-2-(4-nitrobenzylidene)-3-oxopentanoate (4c, 4'c):


4c
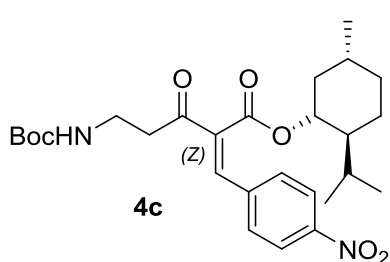
(Z)–Isomer (4c): White solid (1.3 g, 58%); mp 114–116 °C; R_f = 0.35 Pet. Ether: EtOAc (75:25); $[\alpha]^{25}_D$ −27.4 (c 1, CHCl$_3$); IR (Neat) cm^{-1}: 2955, 2929, 2870, 1712,1597, 1522, 1455, 1344, 1224, 1110, 979, 954, 911, 862, 846, 749, 692; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.22 (d, *J* = 8.7 Hz, 2H), 7.62 (d, *J* = 8.7 Hz, 2H), 7.59 (s, 1H), 5.04 (br s, 1H, NH), 4.84 (td, *J* = 10.9, 4.3 Hz, 1H), 3.47 (q, *J* = 5.6 Hz, 2H), 3.05–2.91 (m, 2H), 2.12–2.09 (m, 1H), 1.69–1.61 (m, 2H), 1.58–1.53 (m, 1H), 1.52–1.46 (m, 1H), 1.42 (s, 9H), 1.35–1.24 (m, 1H), 1.08–0.98 (m, 1H), 0.91 (d, *J* = 6.5 Hz, 3H), 0.89–0.80 (m, 2H), 0.75 (d, *J* = 7.1 Hz, 3H), 0.70 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 195.9, 166.4, 156.0, 148.6, 139.5, 137.8, 137.6, 130.2, 124.0, 79.6, 77.0, 46.8, 40.2, 39.2, 35.3, 34.1, 31.5, 28.5, 25.7, 23.0, 22.1, 20.8, 16.0; HRMS (ESI–TOF) m/z Calcd. for C$_{27}$H$_{38}$N$_2$O$_7$ [M + Na]$^+$ 525.2577, observed 525.2574.

(4'c)
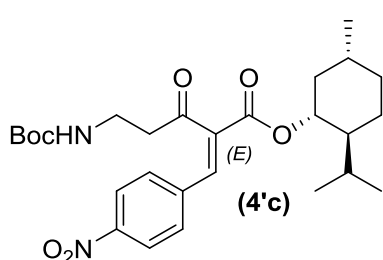
(E)-Isomer (4'c): Pale yellow oil (0.93 g, 42%); R_f = 0.6 Pet. Ether: EtOAc (75:25); $[\alpha]^{25}_D$ −40.0 (c 1, CHCl$_3$); IR (Neat) cm^{-1}: 2956, 2928, 2870, 1699, 1597, 1521, 1455, 1366, 1344, 1248, 1168, 956, 850, 755, 688; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.22 (d, *J* = 8.7 Hz, 2H), 7.68 (s, 1H), 7.52 (d, *J* = 8.8 Hz, 2H), 4.98 (br s, 1H, NH), 4.86 (td, *J* = 10.9, 4.4 Hz, 1H), 3.43 (q, *J* = 5.4 Hz, 2H), 2.84–2.70 (m, 2H), 2.07–2.04 (m, 1H), 1.82 (pd, *J* = 6.9, 2.6 Hz, 1H), 1.73–1.70 (m, 2H), 1.62 (s, 1H), 1.56–1.46 (m, 1H), 1.42 (s, 9H), 1.14–1.00 (m, 2H), 0.94–0.90 (m, 6H), 0.87–0.85 (m, 1H), 0.78 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 204.2, 163.3, 155.9, 148.5, 139.1, 138.0, 137.5, 130.4, 124.2, 79.7, 76.6, 47.1, 44.0, 40.8, 34.9, 34.2, 31.6, 28.5, 26.6, 23.5, 22.1, 20.9, 16.4; HRMS (ESI–TOF) m/z Calcd. for C$_{27}$H$_{38}$N$_2$O$_7$ [M + Na]$^+$ 525.2577, observed 525.2565.

(L)-menthyl 5-((*tert*-butoxycarbonyl)amino)-2-(4-fluorobenzylidene)-3-oxopentanoate (4d, 4'd):
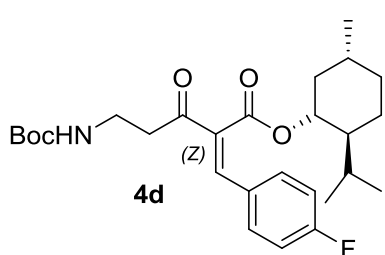
**(Z)-Isomer (4d):** Pale yellow oil (0.95 g, 53%); R_f = 0.24 Pet. Ether: EtOAc (85:15); $[\alpha]^{25}_D$ −18.80 (c 1, CHCl₃); IR (Neat) cm^{-1}: 3068, 2957, 2929, 2871, 1716, 1669, 1601, 1509, 1456, 1392, 1367, 1240, 1162, 959, 832, 650; ^{1}H NMR (400 MHz, CDCl₃) δ 7.51 (s, 1H), 7.49–7.47 (m, 2H), 7.08–7.04 (m, 2H), 5.09 (br s, 1H, NH), 4.86 (td, *J* = 10.9, 4.4 Hz, 1H), 3.47 (q, *J* = 5.4 Hz, 2H), 3.02–2.88 (m, 2H), 2.21–2.17 (m, 1H), 1.73–1.64 (m, 3H), 1.55–1.49 (m, 1H), 1.43 (s, 9H), 1.39–1.31 (m, 1H), 1.25 (s, 1H), 1.11–0.97 (m, 2H), 0.93 (d, *J* = 6.6 Hz, 3H), 0.79 (d, *J* = 7.0 Hz, 3H), 0.74 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, CDCl₃) δ 196.3, 167.4, 165.4, 162.9, 156.1, 139.4, 134.8, 131.9, 131.9, 116.3, 116.1, 79.5, 76.6, 46.9, 40.3, 38.8, 35.3, 34.2, 31.6, 28.5, 25.6, 23.1, 22.2, 20.9, 16.0; HRMS (ESI–TOF) m/z Calcd. for $C_{27}H_{38}FNO_5$ [M + Na]$^+$ 498.2631, observed 498.2630.
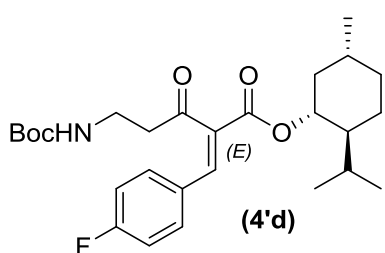
(E)-Isomer (4'd): Pale yellow oil (0.85 g, 47%); R_f = 0.45 Pet. Ether: EtOAc (85:15); $[\alpha]^{25}_D$ −35.20 (c 1, CHCl₃); IR (Neat) cm^{-1}: 2956, 2928, 2870, 1701, 1601, 1508, 1456, 1366, 1253, 1162, 961, 836, 759; ^{1}H NMR (400 MHz, Chloroform–d) δ 7.62 (s, 1H), 7.37–7.33 (m, 2H), 7.07–7.03 (m, 2H), 5.00 (br s, 1H, NH), 4.83 (td, *J* = 10.9, 4.4 Hz, 1H), 3.44–3.40 (m, 2H), 2.82–2.67 (m, 2H), 2.08–2.03 (m, 1H), 1.83 (pd, *J* = 7.0, 2.6 Hz, 1H), 1.71–1.68 (m, 2H), 1.57–1.47 (m, 1H), 1.48–1.44 (m, 1H), 1.42 (s, 9H), 1.27–1.23 (m, 1H), 1.13–1.06 (m, 1H), 1.04–0.97 (m, 1H), 0.91 (dd, *J* = 6.7, 4.6 Hz, 6H), 0.78 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, CDCl₃) δ 205.3, 165.2, 163.9, 162.7, 155.8, 139.6, 133.6, 131.9, 131.8, 116.4, 116.2, 79.5, 76.0, 47.1, 43.9, 40.9, 35.0, 34.2, 31.5, 28.6, 26.5, 23.5, 22.1, 20.9, 16.4; HRMS (ESI–TOF) m/z Calcd. for $C_{27}H_{38}FNO_5$ [M + Na]$^+$ 498.2631, observed 498.2629.

**(L)-menthyl 5-((*tert*-butoxycarbonyl)amino)-2-(4-chlorobenzylidene)-3-oxopentanoate (4e, 4'e):**
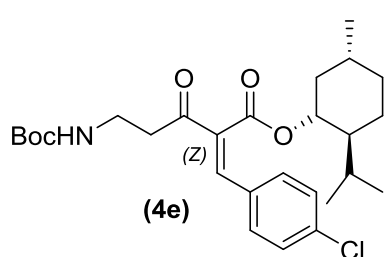
**(Z)-Isomer (4e):** Pale yellow oil (1.11 g, 58%); $R_f = 0.28$ Pet. Ether: EtOAc (85:15); $[\alpha]^{25}_D$ −19.40 (c 1, CHCl$_3$); IR (Neat) cm^{-1}: 3041, 2956, 2929, 2870, 1716, 1624, 1592, 1493, 1455, 1390, 1366, 1224, 1175, 1094, 1014, 820, 760; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.50 (s, 1H), 7.42–7.40 (m, 2H), 7.35–7.33 (m, 2H), 5.07 (br s, 1H, NH), 4.84 (td, $J = 10.9, 4.4$ Hz, 1H), 3.46 (q, $J = 5.5$ Hz, 2H), 3.01–2.88 (m, 2H), 2.18–2.15 (m, 1H), 1.69–1.64 (m, 3H), 1.55–1.48 (m, 1H), 1.42 (s, 9H), 1.37–1.30 (m, 1H), 1.24 (s, 1H), 1.03 (ddd, $J = 28.6, 14.3, 11.0$ Hz, 2H), 0.93 (d, $J = 6.5$ Hz, 3H), 0.78 (d, $J = 7.0$ Hz, 3H), 0.73 (d, $J = 6.9$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 196.2, 167.2, 156.0, 139.2, 136.9, 135.4, 131.5, 130.9, 129.2, 79.9, 76.6, 46.9, 40.2, 38.8, 35.3, 34.2, 31.6, 28.5, 25.6, 23.1, 22.1, 20.9, 16.0; HRMS (ESI–TOF) m/z Calcd. for C$_{27}$H$_{38}$ClNO$_5$ [M + Na]$^+$ 514.2336, observed 514.2330.
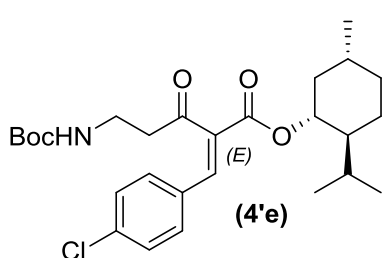
(E)-Isomer (4'e): Pale yellow oil (0.81 g, 42%); $R_f = 0.48$ Pet. Ether: EtOAc (85:15); $[\alpha]^{25}_D$ −34.80 (c 1, CHCl$_3$); IR (Neat) cm^{-1}: 2956, 2930, 2871, 1703, 1623, 1591, 1492, 1455,1390, 1366, 1252, 1178, 1093, 1013, 827, 760; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.61 (s, 1H), 7.36–7.33 (m, 2H), 7.30–7.27 (m, 2H), 5.00 (br s, 1H, NH), 4.83 (td, $J = 10.9, 4.5$ Hz, 1H), 3.44–3.40 (m, 2H), 2.81–2.67 (m, 2H), 2.07–2.02 (m, 1H), 1.82 (pd, $J = 7.0, 2.6$ Hz, 1H), 1.71–1.67 (m, 2H), 1.56–1.49 (m, 1H), 1.42 (s, 9H), 1.40–1.39 (m, 1H), 1.27–1.23 (m, 1H), 1.13–0.96 (m, 2H), 0.91 (dd, $J = 6.8, 4.6$ Hz, 6H), 0.77 (d, $J = 6.9$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 205.1, 163.8, 155.8, 139.4, 136.8, 134.4, 131.3, 131.0, 129.4, 79.5, 76.1, 47.1, 43.9, 40.9, 35.0, 34.2, 31.5, 28.6, 26.5, 23.4, 22.1, 20.9, 16.4; HRMS (ESI–TOF) m/z Calcd. for C$_{27}$H$_{38}$ClNO$_5$ [M + Na]$^+$ 514.2336, observed 514.2333.

(L)-menthyl 5-((*tert*-butoxycarbonyl)amino)-2-(3-chlorobenzylidene)-3-oxopentanoate (4f, 4'f):
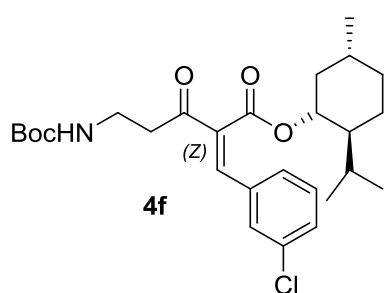
(Z)-Isomer (4f): Pale yellow oil (1.1 g, 57%); R_f = 0.30 Pet. Ether: EtOAc (80:20); $[\alpha]^{25}_D$ −27.50 (c 1, CHCl$_3$); IR (Neat) cm^{-1}: 3070, 2956, 2930, 2870, 1716, 1625, 1565, 1502, 1456, 1390, 1366, 1224, 1175, 957, 784, 687; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.49 (s, 1H), 7.48–7.47 (m, 1H), 7.38 – 7.29 (m, 3H), 5.06 (br s, 1H, NH), 4.87 (td, *J* = 10.9, 4.3 Hz, 1H), 3.46 (q, *J* = 5.1 Hz, 2H), 3.02–2.88 (m, 2H), 2.22–2.18 (m, 1H), 1.74–1.63 (m, 3H), 1.56–1.47 (m, 2H), 1.43 (s, 9H), 1.37–1.30 (m, 1H), 1.28–1.23 (m, 1H), 1.10–0.98 (m, 1H), 0.93 (d, *J* = 6.6 Hz, 3H), 0.80 (d, *J* = 7.0 Hz, 3H), 0.74 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 196.1, 166.9, 156.0, 139.0, 136.1, 135.0, 134.8, 130.7, 130.2, 129.0, 127.9, 79.5, 76.7, 46.8, 40.2, 39.0, 35.3, 34.2, 31.6, 28.5, 25.8, 23.1, 22.1, 20.9, 16.0; HRMS (ESI–TOF) m/z Calcd. for C$_{27}$H$_{38}$ClNO$_5$ [M + H]$^+$ 492.2517, observed 492.2521.
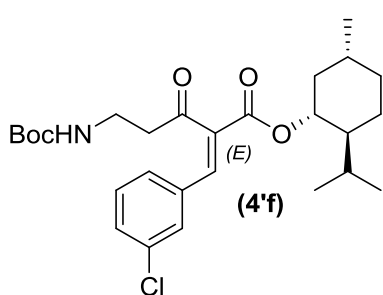
(E)-Isomer (4'f): Pale yellow oil (0.83 g, 43%); R_f = 0.48 Pet. Ether: EtOAc (80:20); $[\alpha]^{25}_D$ −36.60 (c 1, CHCl$_3$); IR (Neat) cm^{-1}: 3065, 2957, 2929, 2870, 1704, 1625, 1564, 1504, 1456, 1366, 1252, 1195, 1162, 961, 788, 686; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.59 (s, 1H), 7.37–7.28 (m, 3H), 7.22–7.21 (m, 1H), 5.01 (br s, 1H, NH), 4.83 (td, *J* = 10.9, 4.4 Hz, 1H), 3.44–3.41 (m, 2H), 2.81–2.66 (m, 2H), 2.07–2.03 (m, 1H), 1.83 (pd, *J* = 6.9, 2.6 Hz, 1H), 1.71–1.67 (m, 2H), 1.57–1.48 (m, 1H), 1.46 (m, 1H), 1.41 (s, 9H), 1.25 (m, 1H), 1.13–0.99 (m, 2H), 0.91 (dd, *J* = 6.8, 4.5 Hz, 6H), 0.78 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 204.8, 163.7, 155.9, 139.1, 135.2, 135.1, 134.7, 130.5, 130.3, 129.7, 127.5, 79.4, 76.2, 47.1, 43.9, 40.8, 35.1, 34.2, 31.5, 28.5, 26.5, 23.4, 22.1, 20.9, 16.4; HRMS (ESI–TOF) m/z Calcd. for C$_{27}$H$_{38}$ClNO$_5$ [M + H]$^+$ 492.2517, observed 492.2520.

(L)-menthyl 5-((*tert*-butoxycarbonyl)amino)-2-(4-methylbenzylidene)-3-oxopentanoate (4g, 4'g):

(*Z*)-Isomer (4g): Pale yellow pluffy solid (1.0 g, 40%); R_f = 0.32 Pet. Ether: EtOAc (85:15); $[\alpha]^{25}_D$ −18.50 (c 1, CHCl$_3$); IR (Neat) cm^{-1}: 3056, 2956, 2928, 2869, 1716, 1606, 1505, 1451, 1366, 1225, 1175, 959, 811; ^{1}H NMR(400MHz, CDCl$_3$): δ (ppm) 7.51 (s, 1H), 7.38 (d, *J*=8.2 Hz, 2H), 7.17 (d, *J*=8.1 Hz, 2H), 5.09 (s, 1H, NH), 4.87 (td, *J*=10.9, 4.3 Hz, 1H), 3.46 (q, *J*=5.4 Hz, 2H), 2.95 (t, *J*=5.7 Hz, 2H), 2.37 (s, 3H), 2.26–2.18 (m, 1H), 1.78–1.64 (m, 2H), 1.58–1.48 (m, 2H), 1.43 (s, 9H), 1.38–1.30 (m, 1H), 1.29–1.21 (m, 1H), 1.10–0.98 (m, 1H), 0.93 (m, 3H), 0.88–0.85 (m, 1H), 0.79–0.74 (m, 6H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 196.5, 167.7, 156.0, 141.6, 140.9, 134.1, 130.1, 129.9, 129.9, 77.4, 76.4, 46.9, 40.2, 38.6, 34.2, 31.6, 28.5, 26.5, 25.5, 23.1, 22.2, 21.7, 20.9, 16.0; HRMS (ESI–TOF) m/z Calcd. for C$_{28}$H$_{41}$NO$_5$ [M + Na]$^+$ 494.2882, observed 494.2879.
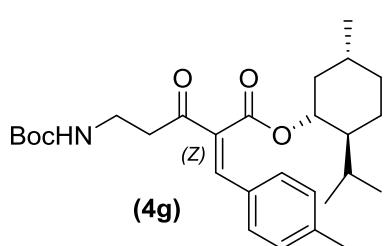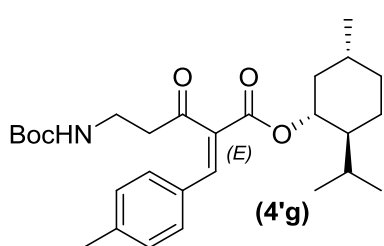

**(*E*)-Isomer (4'g):** Pale yellow oil (0.67 g, 40%); R_f = 0.52 Pet. Ether: EtOAc (85:15); $[\alpha]^{25}_D$ −39.20 (c 1, CHCl$_3$); IR (Neat) cm^{-1}: 3057, 2956, 2928, 2871, 1714, 1621, 1607, 1510, 1455, 1366, 1254, 1180, 961, 815, 759; ^{1}H NMR (400 MHz, CDCl$_3$) (partial conversion of E to Z is observed): δ (ppm) 7.64 (s, 1H), 7.24 (d, *J*=8.2 Hz, 2H), 7.16 (d, *J*=8.1 Hz, 2H), 5.05 (br s, 1H, NH), 4.82 (td, *J*=10.9, 4.4 Hz, 1H), 3.42 (m, 2H), 2.74 (m, 2H), 2.35 (s, 3H), 2.09–2.02 (m, 1H), 1.84 (m, 1H), 1.74–1.66 (m, 2H), 1.57–1.46 (m, 2H), 1.42 (s, 9H), 1.40–1.31 (m, 1H), 1.11–0.97 (m, 2H), 0.93–0.88 (m, 6H), 0.87–0.81 (m, 1H), 0.79–0.76 (m, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 205.6, 164.2, 155.9, 141.2, 141.0, 132.8, 130.1, 129.8, 129.7, 77.4, 75.8, 47.1, 43.7, 40.9, 34.2, 31.5, 31.1, 28.6, 26.5, 23.5, 22.1, 21.6, 20.9, 16.4; HRMS (ESI–TOF) m/z Calcd. for C$_{28}$H$_{41}$NO$_5$ [M + Na]$^+$ 494.2882, observed 494.2879.

(L)-menthyl   5-((*tert*-butoxycarbonyl)amino)-2-(4-tert.   butylbenzylidene)-3-oxopentanoate (4h, 4'h):
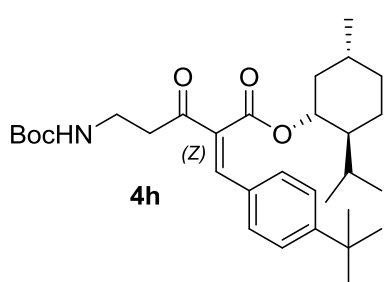
(*Z*)-Isomer (4h): Pale yellow semi solid (1.06 g, 56%); R_f = 0.38 Pet. Ether: EtOAc (85:15); $[\alpha]^{25}_D$ −21.00 (c 1, CHCl$_3$); IR (Neat) cm^{-1}: 3056, 2957, 2933, 2870, 1717, 1666, 1605, 1505, 1455, 1391, 1365, 1222, 1176, 1108, 959, 913, 828, 757; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.53 (s, 1H), 7.43–7.36 (m, 4H), 5.10 (br s, 1H, NH), 4.88 (td, J = 10.9, 4.3 Hz, 1H), 3.47 (q, J = 5.6 Hz, 2H), 2.96 (m, 2H), 2.22–2.19 (m, 1H), 1.77–1.62 (m, 4H), 1.56–1.48 (m, 2H), 1.42 (s, 9H), 1.38–1.34 (m, 1H), 1.31 (s, 9H), 1.05 (qd, J = 13.4, 12.8, 3.7 Hz, 1H), 0.93 (d, J = 6.6 Hz, 3H), 0.76 (dd, J = 6.9, 4.0 Hz, 6H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 196.5, 167.7, 156.0, 154.6, 140.8, 134.2, 130.1, 129.7, 125.9, 79.4, 76.3, 46.9, 40.3, 38.6, 35.3, 35.1, 34.2, 31.6, 31.2, 28.5, 25.5, 23.1, 22.2, 20.9, 16.0; HRMS (ESI–TOF) m/z Calcd. for C$_{31}$H$_{47}$NO$_5$ [M + Na]$^+$ 536.3346, observed 536.3347.
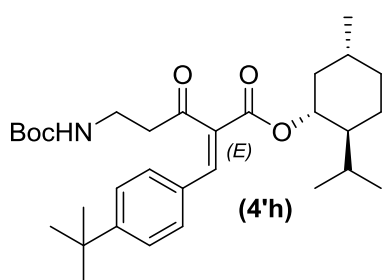
(*E*)-Isomer (4'h): Pale yellow oil (0.84 g, 44%); R_f = 0.55 Pet. Ether: EtOAc (85:15); $[\alpha]^{25}_D$ −34.00 (c 1, CHCl$_3$); IR (Neat) cm^{-1}: 3058, 2957, 2930, 2870, 1703, 1620, 1504, 1456, 1390, 1365, 1253, 1179, 1108, 961, 834, 760; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.63 (s, 1H), 7.38 (d, J = 8.4 Hz, 2H), 7.28 (d, J = 8.5 Hz, 2H), 5.08 (br s, 1H, NH), 4.83 (td, J = 10.9, 4.4 Hz, 1H), 3.45 (q, J = 5.5 Hz, 2H), 2.87–2.73 (m, 2H), 2.08–2.04 (m, 1H), 1.84 (pd, J = 7.0, 2.6 Hz, 1H), 1.71–1.67 (m, 2H), 1.55–1.48 (m, 1H), 1.44 (s, 9H), 1.41–1.39 (m, 1H), 1.30 (s, 9H), 1.14–1.02 (m, 2H), 0.91 (dd, J = 6.8, 4.2 Hz, 7H), 0.78 (d, J = 6.9 Hz, 3H) ; ^{13}C NMR (100 MHz, CDCl$_3$) δ 205.6, 164.2, 156.0, 154.3, 140.9, 132.6, 130.0, 129.9, 126.1, 79.4, 75.8, 47.1, 43.8, 40.9, 35.3, 35.1, 34.3, 31.6, 31.2, 28.6, 26.5, 23.5, 22.1, 20.9, 16.5; HRMS (ESI–TOF) m/z Calcd. for C$_{31}$H$_{47}$NO$_5$ [M + Na]$^+$ 536.3346, observed 536.3355.

(L)-menthyl 5-((*tert*-butoxycarbonyl)amino)-2-(4-methoxybenzylidene)-3-oxopentanoate (4i, 4'i):

(**4i**)
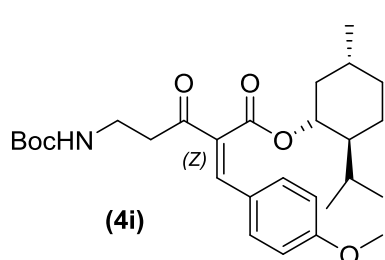
(***Z***)-**Isomer (4i):** Pale Yellow powder (1.0 g, 60%); mp 99–101 °C; R_f = 0.40 Pet. Ether: EtOAc (75:25); $[\alpha]^{25}_D$ −10.00 (c 1, CHCl$_3$); IR (Neat) cm^{-1}: 3070, 2954, 2931, 2870, 1713, 1601, 1511, 1456, 1366, 1260, 1169, 1030, 957, 913, 828, 736; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.48 (s, 1H), 7.47–7.44 (m, 2H), 6.88–6.86 (m, 2H), 5.10 (br s, 1H, NH), 4.89 (td, *J* = 10.9, 4.3 Hz, 1H), 3.83 (s, 3H), 3.48–3.44 (m, 2H), 3.00–2.87 (m, 2H), 2.25–2.23 (m, 1H), 1.84–1.77 (m, 1H), 1.69–1.66 (m, 3H), 1.57–1.50 (m, 1H), 1.42 (s, 9H), 1.37–1.35 (m, 1H), 1.12–0.98 (m, 2H), 0.94 (d, *J* = 6.5 Hz, 3H), 0.79 (t, *J* = 7.3 Hz, 6H).; ^{13}C NMR (100 MHz, CDCl$_3$) δ 196.4, 168.0, 162.0, 156.0 140.5, 132.6, 132.0, 125.3, 114.4, 79.4, 76.3, 55.5, 46.9, 40.3, 38.5, 34.2, 31.6, 31.1, 28.5, 25.6, 23.1, 22.2, 20.9, 16.0; HRMS (ESI–TOF) m/z Calcd. for C$_{28}$H$_{41}$NO$_6$ [M + Na]$^+$ 510.2831, observed 510.2830.
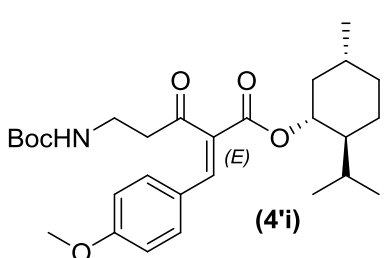

(**4'i**)

(***E***)-**Isomer (4'i):** Pale yellow oil (0.67 g, 40%); R_f = 0.54 Pet. Ether: EtOAc (75:25); $[\alpha]^{25}_D$ −41.20 (c 1, CHCl$_3$); IR (Neat) cm^{-1}: 3075, 2956, 2930, 2870, 1698, 1601, 1511, 1456, 1390, 1366, 1251, 1172, 1031, 960, 832; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.60 (s, 1H), 7.32–7.28 (m, 2H), 6.88–6.86 (m, 2H), 5.06 (br s, 1H, NH), 4.82 (td, *J* = 10.9, 4.4 Hz, 1H), 3.81 (s, 3H), 3.44 (q, *J* = 5.6 Hz, 2H), 2.85–2.70 (m, 2H), 2.08–2.01 (m, 1H), 1.84 (dtd, *J* = 13.8, 6.9, 2.5 Hz, 1H), 1.70–1.66 (m, 3H), 1.56–1.45 (m, 2H), 1.42 (s, 9H), 1.12–0.97 (m, 2H), 0.90 (dd, *J* = 6.8, 3.7 Hz, 6H), 0.77 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 205.9, 164.3, 161.6, 155.9, 140.7, 131.8, 131.2, 125.4, 114.6, 79.3, 75.6, 55.5, 47.1, 43.8, 40.9, 34.2, 31.5, 31.1, 28.6, 26.4, 23.5, 22.1, 20.9, 16.4; HRMS (ESI–TOF) m/z Calcd. for C$_{28}$H$_{41}$NO$_6$ [M + Na]$^+$ 510.2831, observed 510.2824.

(L)-menthyl 5-((*tert*-butoxycarbonyl)amino)-2-(4-ethoxybenzylidene)-3-oxopentanoate (4j, 4'j):
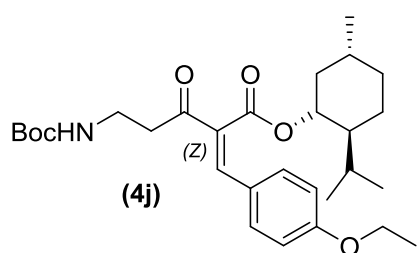
(Z)-Isomer (4j): Yellow powder (0.97 g, 58%); mp 130–132 °C; R_f = 0.42 Pet. Ether: EtOAc (75:25); $[\alpha]^{25}_D$ −5.4 (c 1, CHCl$_3$); IR (Neat) cm^{-1}: 2955, 2929, 2870, 1713,1661, 1600, 1510, 1454, 1391, 1365, 1305, 1257, 1169, 1042, 957, 862, 825; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.48–7.44 (m, 3H), 6.86 (m, 2H), 5.10 (br s, 1H, NH), 4.89 (td, J = 10.8, 4.3 Hz, 1H), 4.05 (q, J = 6.6 Hz, 2H), 3.47–3.46 (m, 2H), 3.02–2.87 (m, 2H), 2.27–2.24 (m, 1H), 1.86–1.79 (m, 1H), 1.70–1.67 (m,1H), 1.60 (s, 1H), 1.55–1.48 (m, 2H), 1.44–1.40 (m, 12H), 1.39–1.36 (m, 1H) 1.12–1.06 (m, 1H), 1.02–0.99 (m, 1H), 0.96–0.94 (m, 3H), 0.82–0.79 (m, 6H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 196.4, 168.1, 161.4, 156.0, 140.6, 132.4, 132.1, 125.1, 114.9, 79.3, 76.3, 63.8, 46.9, 40.3, 38.5, 35.4, 34.2, 31.6, 28.5, 25.6, 23.1, 22.2, 20.9,16.0, 14.8; HRMS (ESI–TOF) m/z Calcd. for C$_{29}$H$_{43}$NO$_6$ [M + Na]$^+$ 524.2987, observed 524.2985.
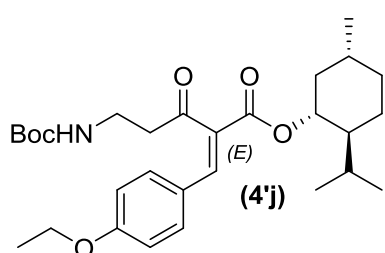

(E)-Isomer (4'j): Pale yellow oil (0.71 g, 42%); R_f = 0.56 Pet. Ether: EtOAc (75:25); $[\alpha]^{25}_D$ −44.6 (c 1, CHCl$_3$); IR (Neat) cm^{-1}: 2956, 2928, 2870, 1702, 1601, 1509, 1455, 1390, 1366, 1304, 1252, 1173, 1041, 960, 919, 835, 758; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.61 (s, 1H), 7.29 (d, J = 8.9 Hz, 2H), 6.86 (d, J = 8.8 Hz, 2H), 5.06 (br s, 1H, NH), 4.82 (td, J = 10.9, 4.4 Hz, 1H), 4.05 (q, J = 6.9 Hz, 2H), 3.44 (q, J = 5.0 Hz, 2H), 2.85–2.71 (m, 2H), 2.09–2.04 (m, 1H), 1.85 (pd, J = 6.9, 2.3 Hz, 1H), 1.71 (br s, 1H), 1.68 (m, 1H), 1.59 (m, 1H), 1.53–1.48 (m, 1H), 1.46–1.40 (m, 12H), 1.31–1.24 (m, 1H), 1.14–0.98 (m, 2H), 0.91 (dd, J = 6.8, 3.9 Hz, 6H), 0.78 (d, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 206.0, 164.4, 161.1, 155.9, 140.8, 131.8, 131.1, 125.3, 115.0, 79.4, 75.7, 63.8, 47.2, 43.8, 41.0, 35.3, 34.3, 31.6, 28.6, 26.5, 23.5, 22.1, 20.9, 16.5, 14.8; HRMS (ESI–TOF) m/z Calcd. for C$_{29}$H$_{43}$NO$_6$ [M + Na]$^+$ 524.2987, observed 524.2983.

(L)-menthyl 5-((*tert*-butoxycarbonyl)amino)-2-(4-cyanobenzylidene)-3-oxopentanoate (4k, 4'k):
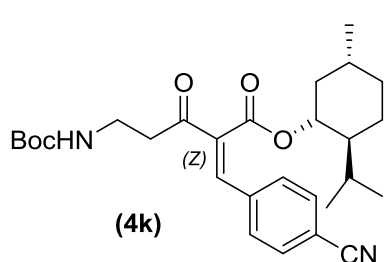
(Z)-Isomer (4k): Pale yellow oil (1.17 g, 58%); R_f = 0.32 Pet. Ether: EtOAc (75:25); $[\alpha]^{25}_D$ −23.00 (c 1, CHCl$_3$); IR (Neat) cm^{-1}: 2956, 2930, 2871, 2229, 1715, 1504, 1455, 1366, 1226, 1175, 956, 828, 758; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.67–7.65 (m, 2H), 7.57 (s, 1H), 7.55–7.54 (m, 2H), 5.03 (br s, 1H, NH), 4.83 (td, *J* = 10.9, 4.4 Hz, 1H), 3.47–3.46 (m, 2H), 3.03 – 2.89 (m, 2H), 2.13–2.08 (m, 1H), 1.69–1.62 (m, 2H), 1.58 (ddd, *J* = 13.8, 7.0, 2.5 Hz, 1H), 1.52–1.46 (m, 1H), 1.43 (s, 9H), 1.35–1.23 (m, 2H), 1.09–0.98 (m, 1H), 0.92 (d, *J* = 6.6 Hz, 3H), 0.87–0.81 (m, 1H), 0.77 (d, *J* = 7.0 Hz, 3H), 0.70 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 195.9, 166.5, 156.0, 138.0, 137.7, 137.4, 132.5, 129.9, 118.2, 113.8, 79.6, 76.9, 46.8, 40.2, 39.2, 35.3, 34.1, 31.5, 28.5, 25.7, 23.0, 22.1, 20.8, 16.0; HRMS (ESI–TOF) m/z Calcd. for C$_{28}$H$_{38}$N$_2$O$_5$ [M + Na]$^+$ 505.2678, observed 505.2677.
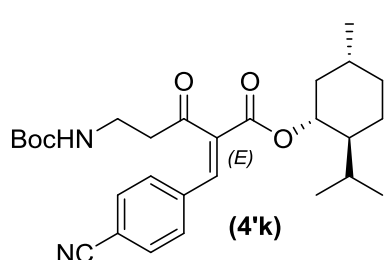

(E)-Isomer (4'k): Pale yellow oil (0.85 g, 42%); R_f = 0.6 Pet. Ether: EtOAc (75:25); $[\alpha]^{25}_D$ −31.80 (c 1, CHCl$_3$); IR (Neat) cm^{-1}: 3090, 2957, 2929, 2871, 2230, 1705, 1505, 1456, 1390, 1366, 1253, 1200, 1175, 960, 839; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.66 (s, 1H), 7.64 (d, *J* = 3.3 Hz, 2H), 7.44 (d, *J* = 8.2 Hz, 2H), 4.96 (br s, 1H, NH), 4.85 (td, *J* = 10.9, 4.3 Hz, 1H), 3.45–3.36 (m, 2H), 2.81–2.66 (m, 2H), 2.06–2.02 (m, 1H), 1.81 (dtd, *J* = 13.8, 6.9, 2.4 Hz, 1H), 1.71–1.69 (m, 2H), 1.57–1.46 (m, 2H), 1.42 (s, 9H), 1.12–0.99 (m, 2H), 0.91 (t, *J* = 6.1 Hz, 6H), 0.77 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 204.2, 163.4, 155.8, 138.4, 137.3, 136.9, 132.7, 130.0, 118.1, 113.8, 79.7, 77.4, 47.1, 43.9, 40.8, 34.9, 34.2, 31.5, 28.6, 26.5, 23.4, 22.1, 20.9, 16.4; HRMS (ESI–TOF) m/z Calcd. for C$_{28}$H$_{38}$N$_2$O$_5$ [M + Na]$^+$ 505.2678, observed 505.2683.

(L)-menthyl 5-((*tert*-butoxycarbonyl)amino)-2-(3–nitrobenzylidene)-3-oxopentanoate (4l, 4'l):
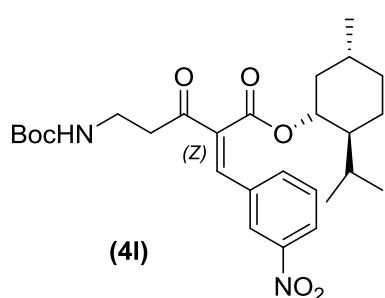
(*Z*)-Isomer (4l): Pale yellow oil (1.22 g, 60%); R_f = 0.28 Pet. Ether: EtOAc (75:25); $[\alpha]^{25}_D$ −31.60 (c 1, CHCl$_3$); IR (Neat) cm^{-1}: 2957, 2931, 2871, 1715, 1534, 1507, 1456, 1391, 1353, 1228, 1176, 980, 957, 823, 735, 6810; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.33–8.32 (m, 1H), 8.27–8.24 (m, 1H), 7.80–7.78 (m, 1H), 7.60 (s, 1H), 7.57–7.54 (m, 1H), 5.05 (br s, 1H, NH), 4.85 (td, *J* = 10.9, 4.4 Hz, 1H), 3.50–3.46 (m, 2H), 3.06–2.91 (m, 2H), 2.17–2.12 (m, 1H), 1.68–1.61 (m, 3H), 1.55–1.47 (m, 1H), 1.43 (s, 9H), 1.39–1.23 (m, 2H), 1.09–0.98 (m, 1H), 0.91 (d, *J* = 6.5 Hz, 3H), 0.87–0.83 (m, 1H), 0.77 (d, *J* = 7.0 Hz, 3H), 0.69 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 195.9, 166.5, 156.0, 148.6, 137.7, 137.3, 135.0, 134.9, 130.0, 125.0, 124.1, 79.6, 77.1, 46.8, 40.3, 39.2, 35.3, 34.1, 31.5, 28.5, 25.8, 23.1, 22.1, 20.8, 15.9; HRMS (ESI–TOF) m/z Calcd. for C$_{27}$H$_{38}$N$_2$O$_7$ [M + Na]$^+$ 525.2576, observed 525.2571.
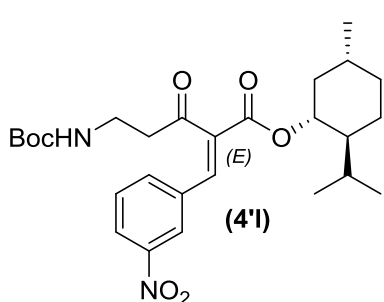

(*E*)-Isomer (4'l): Pale yellow oil (0.82 g, 40%); R_f = 0.54 Pet. Ether: EtOAc (75:25); $[\alpha]^{25}_D$ −39.20 (c 1, CHCl$_3$); IR (Neat) cm^{-1}: 2957, 2928, 2871, 1704, 1630, 1534, 1505, 1456, 1352, 1252, 1202, 1174, 960, 836, 676; ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.25–8.23 (m, 2H), 7.68 (s, 1H), 7.66 (m, 1H), 7.59–7.55 (m, 1H), 5.02 (br s, 1H, NH), 4.86 (td, *J* = 10.9, 4.4 Hz, 1H), 3.43 (q, *J* = 5.3 Hz, 2H), 2.84–2.70 (m, 2H), 2.08–2.04 (m, 1H), 1.83 (dtd, *J* = 13.9, 6.9, 2.6 Hz, 1H), 1.74–1.67 (m, 2H), 1.57–1.49 (m, 1H), 1.44–1.41 (m, 1H), 1.38 (s, 9H), 1.24–1.22 (m, 1H), 1.14–1.00 (m, 2H), 0.92 (dd, *J* = 6.7, 4.9 Hz, 6H), 0.78 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 204.3, 163.4, 155.9, 148.5, 137.9, 136.8, 135.1, 134.5, 130.2, 124.8, 124.3, 79.5, 76.5, 47.1, 44.1, 40.8, 34.9, 34.2, 31.6, 28.5, 26.5, 23.5, 22.1, 20.9, 16.4; HRMS (ESI–TOF) m/z Calcd. for C$_{27}$H$_{38}$N$_2$O$_7$ [M + Na]$^+$ 525.2576, observed 525.2576.

(L)-menthyl   5-((*tert*-butoxycarbonyl)amino)-2-(3,5-dimethylbenzylidene)-3-oxopentanoate (4m, 4'm):

(Z)-Isomer (4m): Pale yellow oil (1.18 g, 60%); R_f = 0.35 Pet. Ether: EtOAc (85:15); $[\alpha]^{25}_D$ −32.60 (c 1, CHCl$_3$); IR (Neat) cm^{-1}: 3056, 2956, 2930, 2870, 1716, 1665, 1660, 1503, 1455, 1390, 1366, 1222, 1172, 958, 846, 757, 691; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.50 (s, 1H), 7.09 (s, 2H), 7.03 (s, 1H), 5.07 (br s, 1H, NH), 4.86 (td, *J* = 10.9, 4.4 Hz, 1H), 3.46 (m, 2H), 3.02–2.87 (m, 2H), 2.30 (s, 6H), 2.26–2.20 (m, 1H), 1.81–1.73 (m, 1H), 1.70–1.63 (m, 2H), 1.59–1.46 (m, 2H), 1.43 (s, 9H), 1.38–1.31 (m, 1H), 1.11–1.00 (m, 1H), 0.93 (d, *J* = 6.5 Hz, 3H), 0.91–0.88 (m, 1H), 0.81 (d, *J* = 7.1 Hz, 3H), 0.75 (d, *J* = 6.9 Hz,3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 196.4, 167.6, 156.0, 141.3, 138.5, 134.6, 132.9, 132.8, 127.5, 79.4, 76.3, 46.8, 40.3, 38.7, 35.4, 34.2, 31.6, 28.5, 25.8, 23.2, 22.2, 21.3, 20.9, 16.1; HRMS (ESI–TOF) m/z Calcd. for C$_{29}$H$_{43}$NO$_5$ [M + Na]$^+$ 508.3038, observed 508.3030.
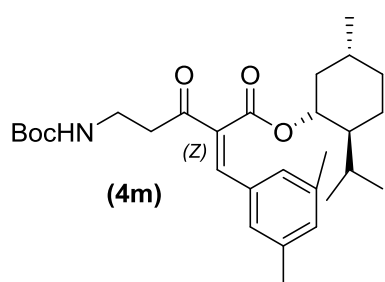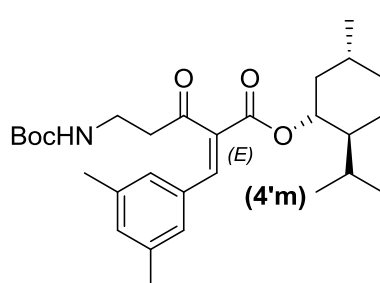

(E)-Isomer (4'm): Pale yellow oil (0.78 g, 40%); R_f = 0.54 Pet. Ether: EtOAc (85:15); $[\alpha]^{25}_D$ −43.20 (c 1, CHCl$_3$); IR (Neat) cm^{-1}: 3057, 2956, 2929, 2870, 1703, 1621, 1503, 1456, 1366, 1235, 1169, 1129, 850, 759, 690; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.62 (s, 1H), 7.01 (s, 1H), 6.94 (s, 2H), 5.06 (br s, 1H, NH), 4.81 (td, *J* = 10.9, 4.3 Hz, 1H), 3.42–3.41 (m, 2H), 2.79–2.65 (m, 2H), 2.29 (s, 6H), 2.07–2.04 (m, 1H), 1.88–1.81 (m, 1H), 1.71–1.67 (m, 2H), 1.57–1.47 (m, 1H), 1.41 (s, 9H), 1.28–1.22 (m, 1H), 1.13–1.00 (m, 2H), 0.91 (dd, *J* = 6.8, 4.0 Hz, 6H), 0.85 (d, *J* = 12.3 Hz,1H), 0.77 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 205.6, 164.1, 155.9, 141.3, 138.7, 133.3, 132.8, 132.5, 127.5, 79.4, 75.8, 47.1, 43.8, 40.9, 35.2, 34.2, 31.5, 28.5, 26.4, 23.5, 22.1, 21.4, 20.9, 16.4; HRMS (ESI–TOF) m/z Calcd. for C$_{29}$H$_{43}$NO$_5$ [M + Na]$^+$ 508.3038, observed 508.3042.

(L)-menthyl 5-((*tert*-butoxycarbonyl)amino)-2-(3,5-dimethoxybenzylidene)-3-oxopentanoate (4n, 4'n):
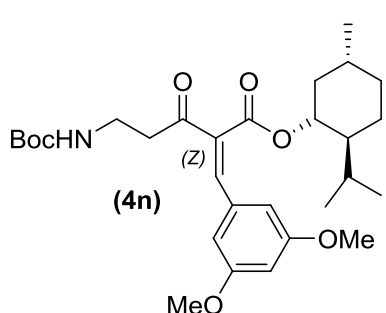
(Z)-Isomer (4n): Pale yellow oil (1.1 g, 55%); R_f = 0.34 Pet. Ether: EtOAc (75:25); $[\alpha]^{25}_D$ −41.20 (c 1, CHCl$_3$); IR (Neat) cm^{-1}: 3056, 2956, 2935, 2870, 1715, 1668, 1591, 1505, 1456, 1390, 1366, 1206, 1158, 1070, 981, 957, 840, 758, 687; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.51 (s, 1H), 6.61 (d, *J* = 2.2 Hz, 2H), 6.48 (m, 1H), 5.06 (br s, 1H, NH), 4.81 (td, *J* = 10.9, 4.4 Hz, 1H), 3.77 (s, 6H), 3.46 (m, 2H), 3.00–2.88 (m, 2H), 2.18–2.14 (m, 1H), 1.67–1.58 (m, 3H), 1.54–1.46 (m, 1H), 1.43 (s, 9H), 1.34–1.23 (m, 2H), 1.08–0.98 (m, 1H), 0.90 (d, *J* = 6.6 Hz, 3H), 0.87–0.80 (m, 1H), 0.76 (d, *J* = 7.0 Hz, 3H), 0.69 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) (partial cis-trans Isomerisation is found) δ 196.3, 161.1, 160.6, 140.9, 107.4, 107.3, 106.2, 103.1, 102.5, 76.0, 74.9, 55.5, 46.9, 40.2, 34.1, 31.5, 31.3, 28.5, 25.7, 23.5, 22.1, 22.0, 20.9, 16.0; HRMS (ESI–TOF) m/z Calcd. for C$_{29}$H$_{43}$NO$_7$ [M + Na]$^+$ 540.2937, observed 540.2930.
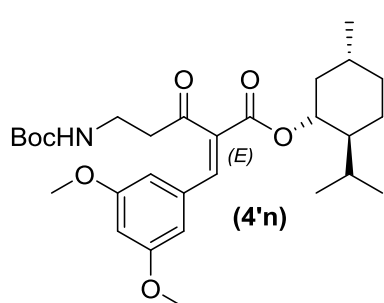
(E)-Isomer (4'n): Pale yellow oil (0.91 g, 45%); R_f = 0.55 Pet. Ether: EtOAc (75:25); $[\alpha]^{25}_D$ −42.80 (c 1, CHCl$_3$); IR (Neat) cm^{-1}: 3057, 2956, 2932, 2871, 1704, 1591, 1505, 1456, 1366, 1237, 1158,1069, 981, 955, 844, 759, 683; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.60 (s, 1H), 6.47 (s, 3H), 5.02 (br s, 1H, NH), 4.82 (td, *J* = 10.9, 4.4 Hz, 1H), 3.76 (s, 6H), 3.40–3.39 (m, 2H), 2.80–2.66 (m, 2H), 2.09–2.04 (m, 1H), 1.88–1.80 (m, 1H), 1.71–1.67 (m, 2H), 1.58–1.45 (m, 2H), 1.41 (s, 9H), 1.25 (m, 1H), 1.13–0.98 (m, 2H), 0.91 (dd, *J* = 6.8, 3.7 Hz, 6H), 0.78 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 205.5, 163.9, 161.1, 155.9, 140.9, 134.7, 134.2, 107.3, 103.1, 79.4, 76.0, 55.5, 47.1, 43.9, 40.9, 35.3, 34.2, 31.5, 28.5, 26.5, 23.5, 22.1, 20.9, 16.4; HRMS (ESI–TOF) m/z Calcd. for C$_{29}$H$_{43}$NO$_7$ [M + Na]$^+$ 540.2937, observed 540.2947.

(L)-menthyl 5-((*tert*-butoxycarbonyl)amino)-2-(3,5-dibromobenzylidene)-3-oxopentanoate (4o, 4'o):
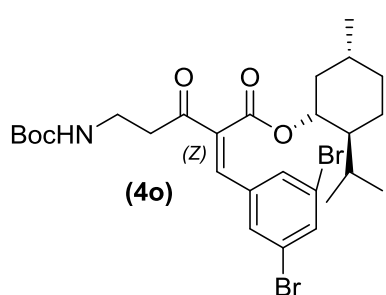
(Z)-Isomer (4o): White powder (1.38 g, 55%); mp 103–105 °C; R_f = 0.34 Pet. Ether: EtOAc (85:15); $[\alpha]^{25}_D$ −35.00 (c 1, CHCl$_3$); IR (Neat) cm^{-1}: 3071, 2955, 2930, 2869, 1714,1547, 1504, 1390, 1366, 1222, 1174, 956, 859, 744, 677; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.69 (t, *J* = 1.7 Hz, 1H), 7.53–7.52 (m, 2H), 7.40 (s, 1H), 5.03 (br s, 1H, NH), 4.86 (td, *J* = 10.9, 4.4 Hz, 1H), 3.46 (q, *J* = 5.8 Hz, 2H), 3.02–2.85 (m, 2H), 2.23–2.17 (m, 1H), 1.76–1.62 (m, 4H), 1.58–1.47 (m, 1H), 1.43 (s, 9H), 1.38–1.30 (m, 1H), 1.28–1.21 (m, 1H), 1.06 (qd, *J* = 13.4, 12.8, 3.6 Hz, 1H), 0.94 (d, *J* = 6.6 Hz, 3H), 0.83 (d, *J* = 7.0 Hz, 3H), 0.76 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 195.8, 166.4, 156.0, 137.2, 137.0, 136.6, 135.8, 130.7, 123.5, 79.5, 77.1, 46.8, 40.3, 39.1, 35.3, 34.2, 31.7, 28.5, 26.0, 23.2, 22.2, 20.9, 16.1; HRMS (ESI–TOF) m/z Calcd. for C$_{27}$H$_{37}$Br$_2$NO$_5$ [M + Na]$^+$ 636.0935, observed 636.0933.
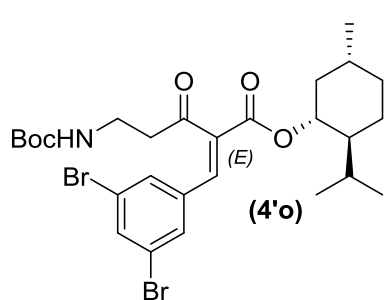

(E)-Isomer (4'o): Pale yellow oil (1.13 g, 45%); R_f = 0.45 Pet. Ether: EtOAc (85:15); $[\alpha]^{25}_D$ −30.00 (c 1, CHCl$_3$); IR (Neat) cm^{-1}: 3066, 2956, 2928, 2870, 1703, 1579, 1546, 1503,1366, 1249, 1196, 1128, 960, 858, 752, 676; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.67 (t, *J* = 1.6 Hz, 1H), 7.50 (s, 1H), 7.42 (d, *J* = 1.7 Hz, 2H), 5.00 (br s, 1H, NH), 4.83 (td, *J* = 10.9, 4.4 Hz, 1H), 3.42 (q, *J* = 5.5 Hz, 2H), 2.81–2.66 (m, 2H), 2.06–2.03 (m, 1H), 1.81 (pd, *J* = 7.0, 2.6 Hz, 1H), 1.72–1.68 (m, 2H), 1.60 (br s, 1H), 1.57–1.48 (m, 1H), 1.41 (s, 9H), 1.27–1.21 (m, 1H), 1.14–0.99 (m, 2H), 0.94–0.89 (m, 6H), 0.77 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 204.3, 163.3, 156.0, 137.4, 136.6, 136.4, 135.7, 131.0, 123.6, 79.5, 76.5, 47.1, 44.1, 40.8, 35.1, 34.2, 31.6, 28.6, 26.5, 23.5, 22.1, 20.9, 16.4; HRMS (ESI–TOF) m/z Calcd. for C$_{27}$H$_{37}$Br$_2$NO$_5$ [M + Na]$^+$ 636.0935, observed 636.0937.

(L)-menthyl 5-((*tert*-butoxycarbonyl)amino)-2-(furan-2-ylmethylene)-3-oxopentanoate(4p, 4'p):
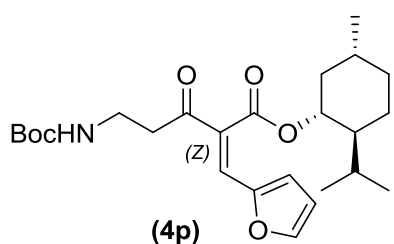
(Z)-isomer (4p): White powder (0.96 g, 60%); mp 78–80 °C; R_f = 0.34 Pet. Ether: EtOAc (75:25); $[\alpha]^{25}_D$ −11.6 (c 1, CHCl$_3$); IR (Neat) cm^{-1}: 3143, 3125, 2955, 2934, 2871, 1717, 1623, 1503, 1470, 1390, 1366, 1239, 1177, 1077, 1021, 958, 751; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.50–7.49 (m, 1H), 7.27 (s, 1H), 6.82 (d, *J* = 3.5 Hz, 1H), 6.51 (dd, *J* = 3.4, 1.8 Hz, 1H), 5.07 (br s, 1H, NH), 4.95 (td, *J* = 10.9, 4.3 Hz, 1H), 3.45 (q, *J* = 5.6 Hz, 2H), 2.97–2.82 (m, 2H), 2.35–2.31 (m, 1H), 1.98 (pd, *J* = 6.9, 2.5 Hz, 1H), 1.74 (m, 1H), 1.69 (m, 2H), 1.60–1.52 (m, 1H), 1.47–1.46 (m, 1H), 1.42 (s, 9H), 1.32–1.23 (m, 1H), 1.16–1.02 (m, 2H), 0.96 (d, *J* = 6.6 Hz, 3H), 0.85 (dd, *J* = 9.8, 7.0 Hz, 6H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 195.7, 167.1, 156.0, 149.1, 146.4, 130.2, 125.8, 119.2, 113.1, 79.4, 76.5, 47.0, 40.5, 38.7, 35.4, 34.3, 31.6, 28.5, 25.8, 23.2, 22.3, 20.9, 16.1; HRMS (ESI–TOF) m/z Calcd. for C$_{25}$H$_{37}$NO$_6$ [M + Na]$^+$ 470.2518, observed 470.2516.
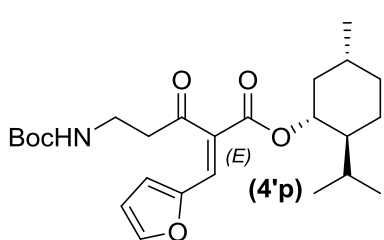
(E)-isomer (4'p): Pale yellow oil (0.64 g, 40%); R_f = 0.48 Pet. Ether: EtOAc (75:25); $[\alpha]^{25}_D$ −35.6 (c 1, CHCl$_3$); IR (Neat) cm^{-1}: 3142, 3125, 2956, 2929, 2870, 1706, 1624, 1504, 1366, 1246, 1210, 1177, 1122,1079, 1018, 961, 855, 755; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.50 (s, 1H), 7.34 (s, 1H), 6.72 (d, *J* = 3.4 Hz, 1H), 6.48–6.47 (m, 1H), 5.15 (br s, 1H, NH), 4.82 (td, *J* = 10.9, 4.4 Hz, 1H), 3.53 (q, *J* = 5.5 Hz, 2H), 2.94–2.91 (m, 2H), 2.06–2.00 (m, 1H), 1.83 (pd, *J* = 7.0, 2.7 Hz, 1H), 1.71 (m, 1H), 1.68–1.66 (m, 1H), 1.54–1.47 (m, 1H), 1.45 (s, 9H), 1.42–1.38 (m, 1H), 1.27–1.24 (m, 1H), 1.12–0.98 (m, 2H), 0.91 (dd, *J* = 6.6, 5.7 Hz, 6H), 0.76 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 203.9, 164.1, 156.0, 149.3, 146.4, 129.5, 126.2, 118.0, 112.8, 79.3, 75.8, 47.2, 43.6, 40.9, 35.1, 34.3, 31.6, 28.6, 26.5, 23.5, 22.1, 20.9, 16.4; HRMS (ESI–TOF) m/z Calcd. for C$_{25}$H$_{37}$NO$_6$ [M + Na]$^+$ 470.2518, observed 470.2516.

(L)-menthyl 5-((*tert*-butoxycarbonyl)amino)-2-(thiophen-2-ylmethylene)-3-oxopentanoate (4q, 4'q):
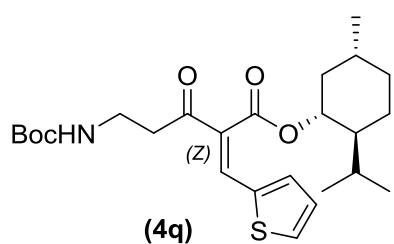
(Z)-isomer (4q): Pale yellow pluffy solid (0.9 g, 58%); R_f = 0.38 Pet. Ether: EtOAc (75:25); $[\alpha]^{25}_D$ −40.0 (c 1, CHCl$_3$); IR (Neat) cm^{-1}: 3100, 3077, 2956, 2931, 2870, 1713, 1663, 1610, 1505, 1391, 1365, 1253, 1203, 1172, 1056, 958, 859, 712; ^{1}H NMR (400 MHz, CDCl$_3$) (partial *cis-trans* isomerization is observed) δ 7.68 (s, 1H), 7.57 (d, J = 5.0 Hz, 1H), 7.44–7.42 (m, 1H), 7.11–7.08 (m, 1H), 5.05 (br s, 1H, NH), 4.94 (td, J = 10.9, 4.3 Hz, 1H), 3.46 (m, 2H), 2.93 (qt, J = 17.9, 5.6 Hz,, 2H), 2.33–2.28 (m, 1H), 1.93 (dtd, J = 13.9, 7.0, 2.5 Hz, 1H), 1.72–1.68 (m, 2H), 1.59–1.51 (m, 1H), 1.43 (s, 9H), 1.41–1.39 (m, 1H), 1.28–1.25 (m, 1H), 1.14–1.04 (m, 2H), 0.96 (d, J = 6.5 Hz, 3H), 0.83 (dd, J = 17.7, 7.0 Hz, 6H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 196.2, 167.2, 156.0, 136.2, 135.0, 133.9, 132.6, 130.7, 128.1, 79.5, 76.7, 47.1, 40.4, 39.1, 35.5, 34.3, 31.7, 28.5, 25.6, 23.2, 22.2, 21.0, 16.2; HRMS (ESI–TOF) m/z Calcd. for C$_{25}$H$_{37}$NO$_5$S [M + Na]$^+$ 486.2289, observed 486.2289.
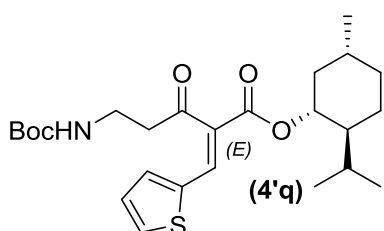

(E)-isomer (4'q): Pale yellow oil (0.65 g, 42%); R_f = 0.58 Pet. Ether: EtOAc (75:25); $[\alpha]^{25}_D$ −44.60 (c 1, CHCl$_3$); IR (Neat) cm^{-1}: 3099, 2957, 2929, 2870, 1699, 1610, 1505, 1365, 1249, 1204, 1122, 1053, 959, 712; ^{1}H NMR (400 MHz, CDCl$_3$) (partial *cis-trans* isomerization is observed) δ 7.76 (s, 1H), 7.49–7.48 (m, 1H), 7.32–7.30 (m, 1H), 7.07 (dd, J = 5.1, 3.7 Hz, 1H), 5.09 (br s, 1H, NH), 4.84 (td, J = 10.9, 4.4 Hz, 1H), 3.49 (q, J = 5.4 Hz, 2H), 3.00–2.89 (m, 2H), 2.07–2.00 (m, 1H), 1.82 (pd, J = 7.0, 2.7 Hz, 1H), 1.71–1.66 (m, 2H), 1.56–1.47 (m, 1H), 1.42 (m, 9H), 1.41–1.38 (m, 1H), 1.27–1.23 (m, 1H), 1.13–1.02 (m, 2H), 0.90 (t, J = 7.0 Hz, 6H), 0.77 (d, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 204.6, 164.3, 155.9, 136.1, 134.9, 134.2, 131.9, 129.5, 128.1, 79.3, 77.4, 47.2, 43.4, 40.9, 35.4, 34.2, 31.6, 28.6, 26.5, 23.5, 22.1, 20.9, 16.4; HRMS (ESI–TOF) m/z Calcd. for C$_{25}$H$_{37}$NO$_5$S [M + Na]$^+$ 486.2289, observed 486.2292.

General Experimental procedure for the aza-Michael addition reaction of Piperidones:

To the stirred solution of Knoevenagel product **4a** (0.8 g, 1.75 mmol) in 10 mL of toluene, finely powdered FeCl$_3$.6H$_2$O (0.047g, 0.175 mmol) was added at 20°C. The reaction mixture was allowed to stir for 30-45 min. After the completion of reaction as monitored by TLC, toluene was evaporated on rotary evaporator and the major diastereomer (**5a**) and minor diastereomer **5'a** were isolated as pale yellow oils by column chromatography over silica gel eluting with Pet. Ether/EtOAc (99:1 to 96:4) (**5a:5'a,** 98% yield).

**General Experimental procedure for the Deprotection of Boc-group:**

To a stirred solution of pure major diastereomer **5a** (0.46 g, 1 mmol) in 4 mL dioxane, 1.5 mL of 4 M HCl in dioxane solution was added at 20 °C, after the addition, reaction mixture was allowed to stir at room temperature for 5-6 hrs. After the completion of reaction as monitored by TLC, dioxane was evaporated on rotary evaporator. Traces of dioxane is removed by using High Vacuum. Then the reaction mixture was washed with dry n-pentane for 4–5 times (6–7 mL for each wash), which afforded **6a** as a white powder (0.375 g) in 95% yield.

(L)-menthyl 4-hydroxy-2-(phenyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (6a):
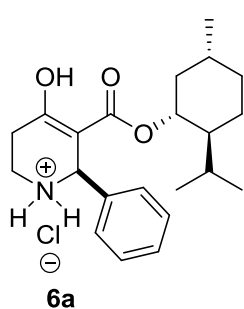
White Powder (0.38 g, 95%); mp 162–164°C; R$_f$ = 0.45 MeOH:CHCl$_3$ (8:92); [α]^{25}$_D$ −35.40 (c 1, CHCl$_3$); IR (Neat) cm^{-1}: 3423 (br), 2956, 2925, 2870, 1657, 1457, 1406, 1302, 1248, 1223, 1182, 1083, 982, 963, 845,830, 757, 699; ^{1}H NMR (400 MHz, CDCl$_3$) (Enolic form) δ 12.51 (s, 1H), 10.40 (s, 1H), 9.58 (s, 1H), 7.36–7.35 (m, 5H), 5.18 (s, 1H), 4.57 (td, J = 10.5, 4.0 Hz, 1H), 3.03 (br s, 1H), 2.82–2.75 (m, 2H), 2.24 (br s, 1H), 1.75–1.73 (m, 1H), 1.57–1.51 (m, 2H), 1.36–1.33 (m, 1H), 1.30–1.24 (m, 1H), 1.06–0.89 (m, 2H), 0.87–0.81 (m, 4H), 0.72 (d, J = 6.5 Hz, 3H), 0.67 (d, J = 6.5 Hz, 3H), 0.63–0.62 (m, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 197.7 (Keto peak from Keto–Enol tautomerization), 169.8, 169.3 (keto form), 165.3 (keto form), 135.6, 132.7 (keto form), 129.6, 129.3 (keto form), 129.2, 129.1 (keto form), 129.0, 96.1, 75.6, 61.9 (keto form), 60.3 (keto form), 54.8, 46.8, 40.5 (keto form), 39.7, 37.2 (keto form), 36.9, 34.1 (keto form), 33.9, 31.4 (keto form), 31.1, 26.3, 25.9, 25.7 (keto form), 23.2, 23.0 (keto form), 22.0 (keto form) 21.8, 20.9, 20.7 (keto form), 16.4, 15.7 (keto form); HRMS (ESI–TOF) m/z Calcd. for C$_{22}$H$_{31}$NO$_3$ [M + H]$^+$ 358.2382, observed 358.2389.

(L)-menthyl   4-hydroxy-2-(4-bromophenyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (6b):
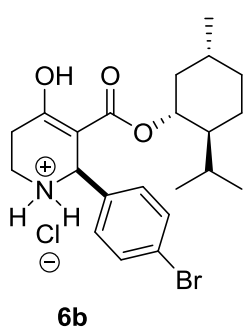
White Powder (0.44 g, 93%); mp 192–194°C; R_f = 0.50 MeOH:CHCl$_3$ (8:92); [α]^{25}$_D$ −27.4 (c 1, CHCl$_3$); IR (Neat) cm^{-1}: 3384 (br), 2956, 2926, 2870, 1655, 1606, 1510, 1455, 1405, 1366, 1299, 1221, 1181, 1091, 981, 912, 833, 755; ^{1}H NMR (400 MHz, CDCl$_3$) (Enolic form) δ 12.53 (s, 1H), 10.43 (s, 1H), 9.72 (s, 1H), 7.53 (s, 2H), 7.34 (s, 2H), 5.17 (s, 1H), 4.62–4.58 (m, 1H), 3.06–2.64 (m, 4H), 1.89–1.86 (m, 1H), 1.73 (s, 1H), 1.57 (m, 2H), 1.38–1.36 (m, 1H), 1.30–1.25 (m,1H), 1.07–0.91 (m, 2H), 0.87–0.86 (m, 3H), 0.74 (d, J = 6.2 Hz, 6H) 0.68–0.65 (m, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 170.1, 169.1, 134.7, 132.2, 131.2, 123.9, 95.8, 75.9, 54.5, 46.8, 39.9, 37.3, 33.9, 31.2, 26.5, 26.0, 23.3, 21.9, 21.0, 16.5; HRMS (ESI–TOF) m/z Calcd. for C$_{22}$H$_{30}$BrNO$_3$ [M + H]$^+$ 436.1487, observed 436.1480.

(L)-menthyl 4-hydroxy-2-(4-nitrophenyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (6c):
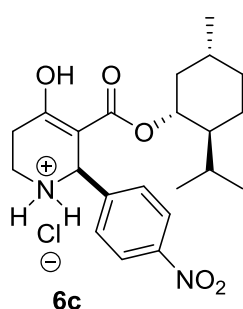
White Powder (0.42 g, 95%); mp 162–163°C; R_f = 0.38 MeOH:CHCl$_3$ (8:92); [α]^{25}$_D$ −16.40 (c 1, CHCl$_3$); IR (Neat) cm^{-1}: 3420 (br), 2956, 2927, 2870, 1656, 1525, 1456, 1406, 1349, 1248, 1225, 1093, 982, 855, 753, 699; ^{1}H NMR (400 MHz, CDCl$_3$) (Enolic form) δ 12.58 (s, 1H), 10.61 (s, 1H), 10.04 (s, 1H), 8.24 (s, 2H), 7.68 (s, 2H), 5.33 (s, 1H), 4.64–4.60 (m, 1H), 3.09 (s, 2H), 2.83 (s, 2H), 1.72 (m, 1H), 1.56 (t, J = 10.9 Hz, 2H), 1.40 (d, J = 11.2 Hz, 1H), 1.28–1.24 (m, 2H), 1.03–0.92 (m, 2H), 0.87 (s, 3H), 0.73 (s, 3H), 0.68 (d, J = 6.4 Hz, 3H), 0.64–0.58 (m, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 170.5, 168.8, 148.8, 142.1, 130.6, 124.1, 95.2, 76.2, 54.1, 46.9, 40.1, 37.4, 33.8, 31.2, 26.5, 25.9, 23.2, 21.8, 21.0, 16.5; HRMS (ESI–TOF) m/z Calcd. for C$_{22}$H$_{30}$N$_2$O$_5$ [M + H]$^+$ 403.2233, observed 403.2240.

(L)-menthyl 4-hydroxy-2-(4-fluorophenyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (6d):
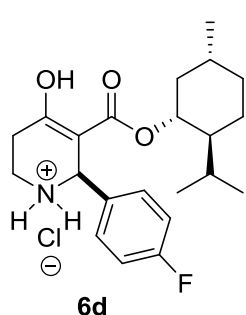
White Powder (0.36 g, 88%); mp 177–179°C ; R_f = 0.45 MeOH:CHCl$_3$ (8:92); $[\alpha]^{25}_D$ −35.40 (c 1, CHCl$_3$); IR (Neat) cm^{-1}: 3431 (br), 2956, 2927, 2870, 1657, 1607, 1511, 1406, 1300, 1248, 1223, 1092, 982, 834; ^{1}H NMR (400 MHz, CDCl$_3$) (Enolic form) δ 12.53 (s, 1H), 10.43 (s, 1H), 9.75 (s, 1H), 7.42 (s, 2H), 7.07 (t, J = 7.1 Hz, 2H), 5.21 (s, 1H), 4.61 (td, J = 10.6, 4.2 Hz, 1H), 3.05–2.77 (m, 4H), 1.74 (m, 1H), 1.59–1.55 (m, 2H), 1.40 (d, J = 11.7 Hz, 1H), 1.32–1.25 (m, 1H), 1.06–1.01 (m, 1H), 0.99–0.92 (m, 1H), 0.89–0.85 (m, 4H), 0.73–0.71 (m, 6H), 0.66–0.64 (m, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 197.2 (Keto peak of Keto–Enol tautomer) 169.9, 169.2, 165.2 (keto form), 164.7, 162.2 (keto form), 131.3, 131.2, 116.1, 115.9, 96.0, 75.9, 54.0, 46.8, 40.0, 36.8, 33.9, 31.2, 26.4, 25.8, 23.2, 21.9, 20.9, 16.4; HRMS (ESI–TOF) m/z Calcd. for C$_{22}$H$_{30}$FNO$_3$ [M + H]$^+$ 376.2288, observed 376.2290.

**(L)-menthyl 4-hydroxy-2(4-chlorophenyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (6e):**
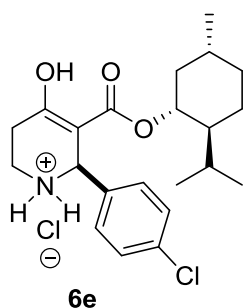
White Powder (0.39 g, 92%); mp 188–189 °C; R_f = 0.46 MeOH:CHCl$_3$ (8:92); $[\alpha]^{25}_D$ −31.0 (c 1, CHCl$_3$); 3430 (br), 2956, 2926, 2870, 1656, 1493, 1455, 1414, 1300, 1248, 1223, 1092, 982, 821 757; ^{1}H NMR (400 MHz, CDCl$_3$) (Enolic form) δ 12.53 (s, 1H), 10.47 (s, 1H), 9.78 (s, 1H), 7.37 (s, 4H), 5.18 (s, 1H), 4.60 (td, J = 10.1, 3.4 Hz, 1H), 3.05–2.90 (m, 2H), 2.80 (m, 2H), 1.73 (s, 1H), 1.57 (m, 2H), 1.38 (d, J = 11.6 Hz, 1H), 1.29–1.25 (m, 1H), 1.07–0.91 (m, 2H), 0.86 (m, 4H), 0.73 (d, J = 6.3 Hz, 6H), 0.67–0.64 (m,1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 170.0, 169.1, 135.8, 134.1, 130.8, 129.2, 95.9, 75.8, 54.3, 46.8, 39.9, 37.1, 33.9, 31.2, 26.4, 25.9, 23.3, 21.9, 21.0, 16.4; HRMS (ESI–TOF) m/z Calcd. for C$_{22}$H$_{30}$ClNO$_3$ [M + H]$^+$ 392.1992, observed 392.2004.

(L)-menthyl 4-hydroxy-2-(3-chlorophenyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (6f):
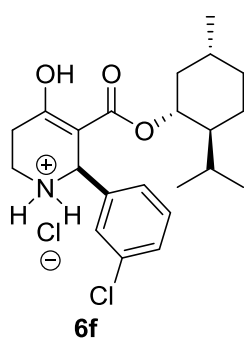
White Powder (0.4 g, 93%); mp 161–162°C; R_f = 0.45 MeOH:CHCl$_3$ (8:92); [α]$^{25}_D$ −22.40 (c 1, CHCl$_3$); IR (Neat) cm^{-1}: 3387 (br), 2956, 2926, 2870, 1656, 1455, 1406, 1312, 1247, 1222, 1182, 1082, 982, 785, 755, 705, 690; ^{1}H NMR (400 MHz, CDCl$_3$) (Enolic form) δ 12.54 (s, 1H), 10.57 (s, 1H), 9.85 (s, 1H), 7.42–7.32 (m, 4H), 5.19 (s, 1H), 4.60 (td, J = 10.7, 4.2 Hz, 1H), 3.08–2.93 (m, 2H), 2.90–2.75 (m, 2H), 1.74–1.72 (m, 1H), 1.59–1.55 (m, 2H), 1.43–1.40 (m, 1H), 1.30–1.25 (m, 1H), 1.03 (t, J = 11.5 Hz, 1H), 0.98–0.91 (m, 2H), 0.88–0.86 (m, 4H), 0.72 (d, J = 6.5 Hz, 6H), 0.67–0.62 (m, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 170.2, 169.1, 137.6, 134.8, 130.5, 129.8, 129.5, 127.5, 95.6, 75.9, 54.1, 46.9, 40.0, 37.0, 33.9, 31.2, 26.4, 25.9, 23.2, 21.9, 20.9, 16.4; HRMS (ESI–TOF) m/z Calcd. for C$_{22}$H$_{30}$ClNO$_3$ [M + H]$^+$ 392.1992, observed 392.2002.

**(L)-menthyl 4-hydroxy-2-(4-methylphenyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (6g):**
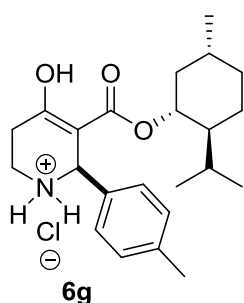
White Powder (0.38 g, 92%); mp 179–180°C; R_f = 0.48 MeOH:CHCl$_3$ (8:92); [α]$^{25}_D$ −34.20 (c 1, CHCl$_3$); IR (Neat) cm^{-1}: 3408 (br), 2955, 2925, 2870, 1745, 1655, 1455, 1413, 1366, 1223, 1092, 981, 912, 813, 752; ^{1}H NMR (400 MHz, CDCl$_3$) (Enolic form) δ 12.48 (s, 1H), 10.33 (s, 1H), 9.52 (s, 1H), 7.27 (s, 2H), 7.16 (s, 2H), 5.18 (s, 1H), 4.57 (dt, J = 10.5, 5.3 Hz , 1H), 3.03 (br s, 1H), 2.81–2.72 (m, 3H), 2.31 (s, 3H), 1.75 (s, 1H), 1.57–1.52 (m, 2H), 1.35–1.24 (m, 2H), 1.04 (t, J = 11.0 Hz, 1H), 0.97–0.90 (m, 1H), 0.88–0.83 (m, 4H), 0.73–0.71 (m, 3H), 0.68 (d, J = 6.4 Hz, 3H), 0.64–0.62 (m, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 197.8 (Keto peak of Keto–Enol Tautomer), 169.5, 169.4, 165.4 (keto form), 140.4 (keto form), 139.6, 132.5, 129.9 (keto form) 129.6, 129.2, 129.1 (keto form), 96.3, 75.5, 61.8 (keto form), 60.4 (keto form), 54.5, 46.8, 40.5 (keto form), 39.8, 34.1 (keto form), 33.9, 31.4 (keto form), 31.1, 26.3, 25.9, 25.7 (keto form), 23.2, 22.0 (keto form), 21.9, 21.4 (keto form), 21.3, 20.9, 16.4, 15.7 (keto form); HRMS (ESI–TOF) m/z Calcd. for C$_{23}$H$_{33}$NO$_3$ [M + H]$^+$ 372.2538, observed 372.2547.

(L)-menthyl 4-hydroxy-2-(4-*tert*. butylphenyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (6h):
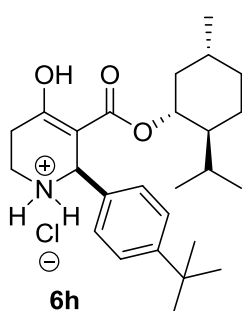
White Powder (0.42 g, 94%); mp 153–155°C; R_f = 0.5 MeOH:CHCl$_3$ (8:92); [α]$^{25}_D$ −23.80 (c 1, CHCl$_3$); IR (Neat) cm^{-1}: 3447 (br), 2956, 2927, 2870, 1656, 1622, 1455, 1413, 1365, 1314, 1249, 1223, 1182, 1080, 982, 829, 755; ^{1}H NMR (500 MHz, CDCl$_3$) (Enolic form) δ 12.46 (s, 1H), 10.39 (s, 1H), 9.55 (s, 1H), 7.36 (d, J = 7.9 Hz, 2H), 7.31 (d, J = 8.1 Hz, 2H), 5.18 (s, 1H), 4.64–4.55 (m, 1H),3.06 (m, 1H), 2.82–2.63 (m, 2H), 2.08 (m, 1H), 1.75–1.68 (m, 1H), 1.60–1.49 (m, 2H), 1.27 (s, 11H), 1.04–0.88 (m, 2H), 0.86–0.80 (m, 4H), 0.71 (d, J = 6.8 Hz, 3H), 0.67–0.63 (m, 3H), 0.62–0.53 (m, 1H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 197.8 (Keto peak of Keto–Enol Tautomer), 169.4, 165.3 (keto form), 153.5 (keto form), 152.8, 132.5, 129.0, 128.7 (keto form), 126.2 (keto form), 125.8, 96.4, 76.1 (keto form), 75.4, 61.5 (keto form), 60.1 (keto form), 54.3, 46.8, 46.7 (keto form), 40.5 (keto form), 39.8, 37.2 (keto form), 36.7 (keto form), 34.9 (keto form), 34.8, 34.1 (keto form), 34.0, 31.4, 31.4 (keto form), 31.1, 26.3, 25.9 (keto form), 25.8 (keto form), 23.2, 23.2 (keto form), 22.0 (keto form), 21.9, 20.9, 20.6 (keto form), 16.4, 15.8 (keto form); HRMS (ESI–TOF) m/z Calcd. for C$_{23}$H$_{39}$NO$_3$ [M + H]$^+$ 414.3008, observed 414.3010.

(L)-menthyl 4-hydroxy-2-(4-methoxyphenyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (6i):
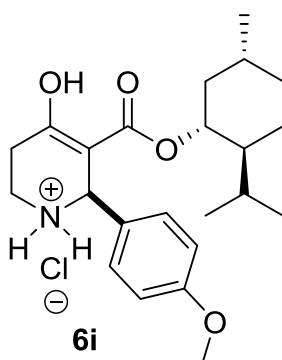
White Powder (0.36 g, 85%); mp 183–185°C; R_f = 0.36 MeOH:CHCl$_3$ (8:92); [α]$^{25}_D$ −33.00 (c 1, CHCl$_3$); IR (Neat) cm^{-1}: 3434 (br), 2955, 2927, 2870, 1656, 1612, 1585, 1516, 1455, 1406, 1367, 1302, 1250, 1181, 1035, 981, 956, 830, 755; ^{1}H NMR(500 MHz, CDCl$_3$) (Enolic form) : δ (ppm) 12.50 (s, 1H), 10.24 (s, 1H), 9.47 (s, 1H), 7.30 (m, 2H), 6.87 (m, 2H), 5.18 (s, 1H), 4.60 (td, J=10.8, 4.3 Hz, 1H), 3.78 (s, 3H), 3.04 (m, 1H), 2.80 (m, 2H), 2.68 (m, 1H), 2.51 (m, 1H), 2.01 (m, 1H), 1.81–1.72 (m, 1H), 1.64–1.49 (m, 2H), 1.45–1.22 (m, 2H), 1.11–1.01 (m, 1H), 0.88–084 (m, 4H), 0.72 (m, 5H), 0.65 (m, 1H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 197.7 (Keto peak of Keto–Enol Tautomer), 169.5, 169.4 (keto form), 165.4 (keto form), 161.0 (keto form), 160.6, 130.5, 127.4, 124.6 (keto form), 114.5 (keto form), 114.3, 96.3, 76.0 (keto form), 75.6, 61.6 (keto form), 60.6, 55.5, 55.4 (keto form), 54.2 (keto form), 46.8, 40.6 (keto form), 39.9, 37.1, 34.1 (keto form), 34.0, 31.5 (keto form), 31.2, 26.3, 25.8

(keto form), 25.7, 23.2, 23.0 (keto form), 22.0 (keto form), 21.9, 20.9, 20.7 (keto form), 16.4, 15.8 (keto form); HRMS (ESI–TOF) m/z Calcd. for $C_{23}H_{33}NO_4$ [M + H]$^+$ 388.2488, observed 388.2491.
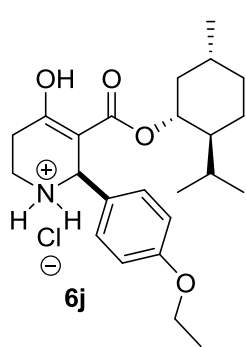
(L)-menthyl 4-hydroxy-2-(4-ethoxyphenyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (6j):
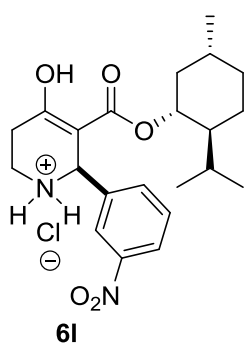
White Powder (0.38 g, 88%); mp 163–165°C; R_f = 0.38 MeOH:CHCl$_3$ (8:92); $[\alpha]^{25}_D$ −31.00 (c 1, CHCl$_3$); IR (Neat) cm^{-1}: 3435 (br), 2956, 2927, 2870, 1656, 1613, 1514, 1455, 1403, 1366, 1300, 1247, 1180, 1091, 1047, 982, 825, 756; ^{1}H NMR (500 MHz, CDCl$_3$) (Enolic form): δ (ppm) 12.49 (s, 1H), 10.27 (s, 1H), 9.53 (s, 1H), 7.31–7.30 (m, 2H), 6.85 (m, 2H), 5.20 (s, 1H), 4.59 (td, J=10.7, 4.1 Hz, 1H), 4.00 (q, J=6.8 Hz, 2H), 3.04 (br s, 1H), 2.88–2.81 (m, 2H), 2.70–2.66 (s, 1H), 2.34–2.21 (m, 1H), 1.77–1.74 (m, 1H), 1.60–1.53 (m, 2H), 1.41–1.37 (m, 4H), 1.31–1.22 (m, 2H), 1.08–1.03 (m, 1H), 0.93 (ddd, J = 22.4, 11.3, 3.1 Hz, 1H), 0.86 (d, J = 7.2 Hz, 3H), 0.73–0.69 (m, 6H), 0.63–0.62 (m, 1H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 197.9 (Keto peak form Keto–Enol Tautomer), 169.5 (keto form), 169.4, 159.9, 130.5, 127.2, 114.8, 96.4, 75.5, 63.7, 54.1, 46.8, 39.9, 36.5, 33.9, 31.2, 26.3, 25.9 (keto form), 23.2, 21.9, 20.9, 16.4, 14.9; HRMS (ESI–TOF) m/z Calcd. for $C_{24}H_{35}NO_4$ [M + H]$^+$ 402.2644, observed 402.2651.

(L)-menthyl 4-hydroxy-2-(4-cyanophenyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (6k):
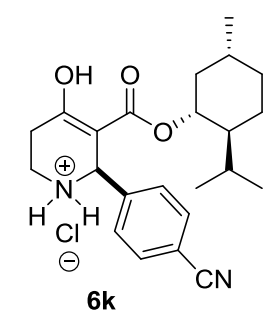
White Powder (0.4 g, 96%); mp 189–190°C; R_f = 0.38 MeOH:CHCl$_3$ (8:92); $[\alpha]^{25}_D$ −17.40 (c 1, CHCl$_3$); 3438 (br), 2956, 2926, 2870, 2231, 1657, 1456, 1415, 1303, 1248, 1224, 1181, 1093, 982, 830, 755; ^{1}H NMR (400 MHz, CDCl$_3$) (Enolic form): δ (ppm) 12.57 (s, 1H), 10.51 (s, 1H), 9.90 (s, 1H), 7.70 (m, 2H), 7.62 (m, 2H), 5.27 (s, 1H), 4.61 (td, J=10.4, 3.9 Hz, 1H), 3.05 (m, 2H), 2.89–2.76 (m, 2H), 1.72–1.71 (m, 1H), 1.59–1.56 (m, 2H), 1.39 (d, J = 11.5 Hz, 1H), 1.32–1.24 (m, 2H), 1.02–0.91 (m, 2H), 0.86 (d, J = 6.0 Hz, 3H), 0.74–0.72 (m, 6H), 0.65–0.63 (m, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 170.4, 168.8, 140.4, 132.7, 130.2, 118.0, 113.8, 95.1, 76.1, 54.3, 46.9, 40.1, 37.2, 33.8, 31.2, 26.5, 25.8, 23.2, 21.9, 20.9, 16.4; HRMS (ESI–TOF) m/z Calcd. for $C_{23}H_{30}N_2O_3$ [M + H]$^+$ 383.2334, observed 383.2339.
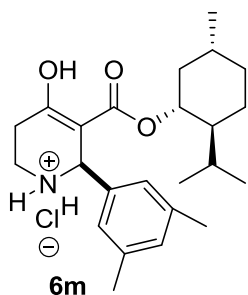
(L)-menthyl 4-hydroxy-2-(3-nitrophenyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (6l):

White Powder (0.42 g, 95%); mp 136–139°C; R_f = 0.35 MeOH:CHCl$_3$ (8:92); $[\alpha]^{25}_D$ −22.40 (c 1, CHCl$_3$); IR (Neat) cm^{-1}: 3430 (br), 2956, 2927, 2870, 1720, 1656, 1532, 1456, 1407, 1351, 1297, 1247, 1095, 981, 954, 820, 754, 693; ^{1}H NMR (400 MHz, CDCl$_3$) (Enolic form): δ 12.59 (s, 1H), 10.61 (s, 1H), 10.09 (s, 1H), 8.27–8.23 (m, 2H), 7.90 (s, 1H), 7.61 (m, 1H), 5.38 (s, 1H), 4.62 (td, J = 10.4, 3.8 Hz, 1H), 3.15 (br s, 2H), 2.95–2.79 (m, 2H), 1.74 (br s, 1H), 1.56 (t, J = 10.8 Hz, 2H), 1.40–1.38 (m, 1H), 1.32–1.24 (m, 2H), 1.03–0.91 (m, 2H), 0.89–0.84 (m, 4H), 0.72 (d, J = 5.5 Hz, 3H), 0.68 (d, J = 6.5 Hz, 3H, 3H), 0.62–0.56 (m, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 170.7, 168.8, 148.4, 137.6, 135.4, 130.2, 124.6, 124.4, 95.1, 76.1, 53.9, 47.0, 40.2, 37.1, 33.8, 31.1, 26.4, 25.9, 23.2, 21.8, 20.9, 16.4; HRMS (ESI–TOF) m/z Calcd. for C$_{22}$H$_{30}$N$_2$O5 [M + H]$^+$ 403.2233, observed 403.2237.

(L)-menthyl 4-hydroxy-2-(3,5-dimethylphenyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (6m):

White Powder (0.41 g, 96%); mp 172–174°C; R_f = 0.50 MeOH:CHCl$_3$ (8:92); $[\alpha]^{25}_D$ −40.60 (c 1, CHCl$_3$); IR (Neat) cm^{-1}: 3381(br), 2955, 2923, 2870, 1656, 1456, 1404, 1344, 1311, 1293, 1245, 1222, 1095, 982, 847, 755; ^{1}H NMR (400 MHz, CDCl$_3$) (Enolic form): δ (ppm) 12.50 (s, 1H), 10.42 (s, 1H), 9.53 (s, 1H), 6.99 (s, 2H), 6.96 (s, 1H), 5.14 (s, 1H), 4.58 (td, J=10.6, 4.2 Hz, 1H), 3.70 (s, 1,4-dioxane peak), 3.01 (br s, 1H), 2.84–2.80 (m, 2H), 2.70–2.65 (m, 1H), 2.28 (s, 6H), 1.77–1.71 (m, 1H), 1.58–1.53 (m, 2H), 1.41–1.38 (m, 1H), 1.32–1.24 (m, 1H), 1.04–0.90 (m, 2H), 0.85 (d, J = 6.7 Hz, 4H), 0.72–0.70 (m, 6H), 0.63–0.57 (m, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 197.9 (Keto peak from Keto–Enol Tautomer), 169.5, 169.5, 165.3 (keto form), 139.0 (keto form), 138.5, 135.3, 132.5 (keto form), 131.9 (keto form), 131.0, 126.9, 126.5 (keto form), 96.3, 75.8 (keto form), 75.6, 67.2 (dioxane peak), 54.5, 46.8, 40.6 (keto form), 39.9, 37.2 (keto form), 36.7, 34.1 (keto form), 34.0, 31.4 (keto form), 31.1, 26.2, 25.9, 25.8 (keto form), 23.2, 23.0 (keto form), 22.0 (keto form), 21.9, 21.3, 20.9, 20.8 (keto form), 16.3 15.6 (keto form); HRMS (ESI–TOF) m/z Calcd. for C$_{24}$H$_{35}$NO$_3$ [M + H]$^+$ 386.2695, observed 386.2694.
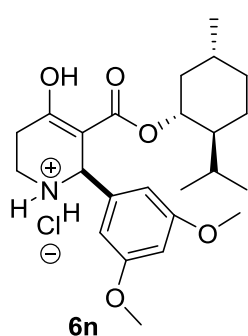
(L)-menthyl 4-hydroxy-2-(3,5-dimethoxyphenyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (6n):

White Powder (0.43 g, 94%); mp 102–104°C; R_f = 0.36 MeOH:CHCl$_3$ (8:92); [α]^{25}$_D$ −49.60 (c 1, CHCl$_3$); IR (Neat) cm^{-1}: 3390 (br), 2955, 2929, 2870, 1655, 1600, 1458, 1431, 1354, 1311, 1244, 1222, 1205, 1158, 1063, 981, 911, 839, 755, 704; ^{1}H NMR (400 MHz, CDCl$_3$) (Enolic form): δ (ppm) 12.54 (s, 1H), 10.45 (s, 1H), 9.67 (s, 1H), 6.59 (s, 2H), 6.42 (s, 1H), 5.21 (s, 1H), 4.64 (td, J=10.7, 4.1 Hz, 1H), 3.79 (s, 6H), 3.05–2.89 (m, 3H), 2.67–2.63 (m, 1H), 1.78–1.75 (m, 1H), 1.59–1.50 (m, 3H), 1.31–1.24 (m, 2H), 1.12–1.06 (m, 1H), 0.87–0.85 (m, 5H), 0.74–0.72 (d, J = 6.3 Hz, 6H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 197.6 (Keto peak form Keto–Enol Tautomer), 169.9, 169.4, 161.2, 137.5, 107.2, 106.5 (keto form), 101.6, 95.9, 75.7, 62.2 (keto form), 60.6 (keto form), 55.8, 55.7 (keto form), 54.4, 46.8, 40.6 (keto form), 40.0, 36.7, 33.9, 31.5 (keto form), 31.2, 26.3, 25.8, 23.2, 21.9, 21.0, 20.7 (keto form), 16.3, 15.6 (keto form), 14.2 (keto form); HRMS (ESI–TOF) m/z Calcd. for C$_{24}$H$_{35}$NO$_5$ [M + H]$^+$ 418.2593, observed 418.2582.

(L)-menthyl 4-hydroxy-2-(3,5-dibromophenyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (6o):
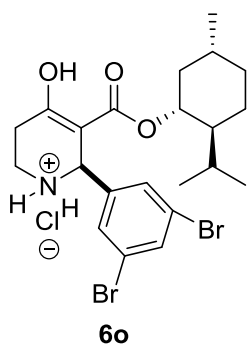
White Powder (0.54 g, 98%); mp 174–176°C; R_f = 0.65 MeOH:CHCl$_3$ (8:92); [α]^{25}$_D$ −31.20 (c 1, CHCl$_3$); IR (Neat) cm^{-1}: 3386 (br), 2956, 2925, 2869, 1656, 1622, 1584, 1418, 1455, 1344, 1306, 1243, 1180, 1090, 981, 857,757, 690; ^{1}H NMR (400 MHz, CDCl$_3$) (Enolic form): δ 12.58 (s, 1H), 10.66 (s, 1H), 10.06 (s, 1H), 7.69 (s, 1H), 7.59 (s, 2H), 5.19 (s, 1H), 4.63 (td, J = 10.6, 5.3 Hz, 1H), 3.10 (s, 2H), 2.93–2.79 (m, 2H), 1.73 (m, 1H), 1.62–1.58 (m, 2H), 1.51–1.48 (m, 1H), 1.34–1.25 (m, 1H), 1.09–1.03 (m, 2H), 0.88 (d, J = 6.5 Hz, 4H), 0.80–0.75 (m, 3H), 0.73 (d, J = 6.4 Hz, 3H), 0.68 – 0.63 (m, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 170.6, 169.0, 139.4, 135.2, 131.3, 123.5, 95.2, 76.2, 53.6, 46.9, 40.3, 37.2, 33.9, 31.2, 26.4, 25.9, 23.2, 21.9, 21.0, 16.3; HRMS (ESI–TOF) m/z Calcd. for C$_{22}$H$_{29}$Br$_2$NO$_3$ [M + H]$^+$ 514.0592, observed 514.0594.

(L)-menthyl 4-hydroxy-2-(2-furyl)-1,2,5,6-tetrahydropyridine-3–carboxylate (6p):
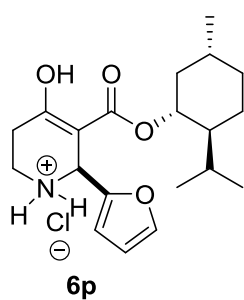
White Powder (0.34 g, 89%); mp 140–142°C; R_f = 0.35 MeOH:CHCl$_3$ (8:92); $[\alpha]^{25}_D$ −7.20 (c 1, CHCl$_3$); IR (Neat) cm^{-1}: 3438 (br), 2956, 2926, 2870, 1657, 1456, 1409, 1366, 1309, 1246, 1222, 1183, 1092, 1013, 982, 823, 745; ^{1}H NMR (500 MHz, CDCl$_3$) (Enolic form): δ (ppm) 12.52 (s, 1H), 10.36 (s, 1H), 10.11 (s, 1H), 7.45 (s, 1H), 6.49 (s, 1H), 6.37 (s, 1H), 5.42 (s, 1H), 4.70 (td, J=10.8, 4.1 Hz, 1H), 3.44 (br s, 1H), 3.19–3.11 (m, 2H), 2.55 (d, J=16.4 Hz, 1H), 1.83–1.81 (m, 1H), 1.65–1.59 (m, 3H), 1.41–1.32 (m, 1H), 1.22–1.17 (m, 1H), 0.99 (qd, J = 14.1, 13.6, 3.5 Hz, 1H), 0.89 (d, J=6.8 Hz, 3H), 0.79 (d, J=6.5 Hz, 3H), 0.75 (d, J = 6.6 Hz, 3H), 0.73–0.70 (m, 1H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 169.8, 169.3, 148.2, 144.1, 112.3, 111.0, 94.4, 75.7, 47.5, 46.9, 40.3, 36.7, 34.0, 31.3, 26.2, 25.7, 23.2, 22.0, 21.0, 16.3; HRMS (ESI–TOF) m/z Calcd. for C$_{20}$H$_{29}$NO$_4$ [M + H]$^+$ 348.2175, observed 348.2180.

**(L)-menthyl 4-hydroxy-2-(2-thiophenyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (6q):**
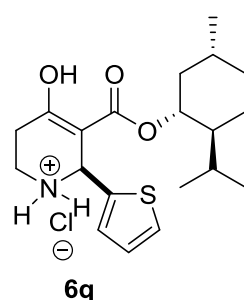
White Powder (0.36 g, 90%); mp 192–194°C; R_f = 0.35 MeOH:CHCl$_3$ (8:92); $[\alpha]^{25}_D$ −13.4 (c 1, CHCl$_3$); IR (Neat) cm^{-1}: 3426 (br), 2955, 2926, 2870, 1655, 1624, 1456, 1407, 1362, 1306, 1246, 1221, 1171, 1088, 981, 843, 753, 706; ^{1}H NMR (500 MHz, CDCl$_3$) (Enolic form): δ (ppm) 12.54 (s, 1H), 10.40 (s, 1H), 9.98 (s, 1H), 7.36 (s, 1H), 7.32 (d, J=4.9 Hz, 1H), 7.05 (s, 1H), 5.61 (s, 1H), 4.69 (td, J=10.7, 4.1 Hz, 1H), 3.28 (br s, 2H), 3.11–3.04 (m, 1H), 2.59 (d, J=17.5 Hz, 1H), 1.83–1.81 (m, 1H), 1.62–1.54 (m, 3H), 1.37–1.30 (m, 1H), 1.17 (t, J = 11.4 Hz, 1H), 0.97 (qd, J = 14.6, 13.9, 3.3 Hz, 1H), 0.89 (d, J=6.7 Hz, 3H), 0.75 (d, J=6.4 Hz, 6H), 0.71–0.66 (m, 1H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 169.7, 169.2, 139.0, 129.6, 128.1, 127.4, 97.2, 75.8, 48.8, 46.8, 39.9, 36.0, 34.0, 31.3, 26.3, 25.8, 23.2, 21.9, 21.0, 16.4; HRMS (ESI–TOF) m/z Calcd. for C$_{20}$H$_{29}$NO$_3$S [M + H]$^+$ 364.1946, observed 364.1946.

Scheme 4.13: Attempted Removal of Chiral Auxiliary (Hydrolysis of menthyl ester)
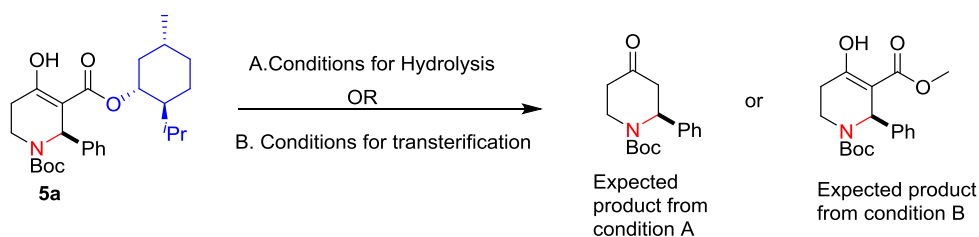
Following different methods were explored for the possible removal of menthyl group by the reported literature protocols for menthyl esters hydrolysis as well as for other esters. Unfortunately all the thirteen (13) different methods were unsuccessful for obtaining the desired product.

*(Note that menthyl ester hydrolysis of *β*-keto ester of such scaffold **5a** is not known in the literature).

A. Conditions for Hydrolysis:

Method 1: TFA/MW/reflux:

Menthyl ester (0.14 g, 0.3 mmol) was dissolved in 2.5 mL of TFA and placed in a microwave reactor for 30 min (10 min warming to 110 °C, followed by 20 min at 110 °C) at 250 *psi.*

Result: After 30 mins, TLC revealed that successful deprotection of Boc group was followed with the decomposition.

Ref: Taber, D. F.; Berry, J. F.; Martin, T. J. *J. Org. Chem.* **2008**, *73*, 9334.

Method 2: Conc. HCl/reflux: Deprotection of Boc followed by decomposition.

A solution of menthyl ester (0.14 g, 0.3 mmol) was refluxed by adding 0.5 mL TFA and 12 N HCl (3 mL) at 150 °C in a pressure tube for 1 day. (Monitored for every one hour)

Result: Easy deprotection of Boc was followed by the decomposition leading to mixture of products.

Ref: Merino, I.; Laxmi, Y. R. S.; Florez, J.; Barluenga, J.; Ezquerra, J.; Pedregal, C. *J. Org. Chem.* **2002**, *67*, 648.

Method 3. Krapcho Decarboxylation:

A Solution of menthyl ester (0.14 g, 0.3 mmol), LiCl (0.015 g, 0.367 mmol), H$_2$O (0.006 g, 0.006 mL, 0.367 mmol), in 3 mL of DMSO was refluxed for 5 h.

Result: After 1 h, TLC was checked, and it was found there was no reaction, however lead to decomposition on prolonged heating.

Ref: Krapcho, A. P.; Gowrikumar, G. *J. Org. Chem.* **1987**, *52*, 1880.

Method 4. KOH, MeOH/reflux

A Solution of menthyl ester (0.14 g, 0.3 mmol) was refluxed with KOH (1g, 18.36 mmol) in MeOH (4 mL) for 5 h.

Result: Decomposition of starting material was observed on prolonged heating.

Ref: Ye, S.; Tang, Y.; Dai, L.-X. *J. Org. Chem.* **2001**, *66*, 5717.

B. Conditions for Transesterification:

Method 5: Use of InI$_3$/reflux:

Menthyl ester (0.14 g, 0.3 mmol) was heated at reflux with a solution of indium triiodide in 2-propanol, prepared in situ by stirring indium metal chunks (53 mg, 1.5 mmol) and iodine (174 mg, 2.25 mmol) in dry 2-propanol (3 mL) at room temperature (25 °C) for half an hour.

Result: After 6 h, TLC was checked, and it was found that there was no reaction, however, prolonged heating lead to decomposition.

Ref: Ranu, B. C.; Duta, P. *J. Org. Chem.* **1982**, *63*, 6027.

Method 6: DBU and Methanol Reflux

In a PTFE seal tube, menthyl ester (0.14 g, 0.3 mmol) and DBU (0.93 g, 0.6 mmol) were dissolved in 4 mL of methanol and heated to reflux for 12 h.

Result: After 2 h, TLC was checked and it was found that there was no reaction, however, prolonged heating lead to decomposition.

Ref: Romanski, J.; Nowak, P., Kosinski, K., Jurczak, J., *Tetrahedron Lett.* **2012**, *53*, 5287.

Method 7: NBS (cat), BuOH, Toluene/100 °C

In a PTFE seal tube, menthyl ester (0.140 g, 0.3 mmol) in 3 mL of dry MeOH and 1 mL of dry toluene, NBS (0.11 g, 0.06 mmol, 0.2 equiv.) was heated at 90-100 °C.

Result: Reaction mixture was decomposed.

Ref: Bandgar, B. P., Uppalla, L. S., Sadavarte, V. S. *Synlett* **2001**, 11, 1715.

Method 8. MeOH/DMAP/heat

In a PTFE seal tube, Menthyl ester (0.140 g, 0.3 mmol) in 3 ml of dry MeOH and 1 ml of dry Toluene, DMAP (0.075 g, 0.03 mmol, 0.2 equiv.) was heated at 90-100 °C.

Result: Reaction mixture was decomposed.

Ref: Taber, D. F.; Amedio, J. C., Jr.; Patel, Y. K. *J. Org. Chem.* **1985**, *50*, 3618;

Christoffers, J, Önal, N. *Eur. J. Org. Chem.* **2000**, 1633.

Method 9: I$_2$/Heat

In a PTFE seal tube, menthyl ester (0.140 g, 0.3 mmol) and I$_2$ (16 mg, 0.06mmol) were dissolved in 3 mL of dry methanol and 1ml of dry toluene and heated to reflux for 24 hr.

Result: After 6 h, TLC was checked, and it was found that there was no reaction, however, prolonged heating lead to decomposition.

Ref: Chavan, S. P.; Kale, R. R.; Shivasankar, K.; Chandake, S. I.; Benjamin, S.B. *Synthesis* **2003**, 17, 2695.

Method 10: Me$_3$SiI/I$_2$/heat in CHCl$_3$

To menthyl ester (0.14 g, 0.3 mmol), Me$_3$SiI (61 mg, 0.3 mmol), I$_2$ (78mg, 0.3 mmol) were dissolved in 3 mL of dry CHCl$_3$ and heated to reflux for 3 h. To this refluxed solution 1.5 mL of dry MeOH is added and refluxed overnight.

Result: Progress of the reaction was checked by TLC, and it was found that there was no reaction, however, prolonged heating lead to decomposition.

Ref: Olah, G. A.; Narang, S. C.; Salem, G. F.; Gupta, B. G. B. *Synthesis* **2001**, 142.

Method 11: Zn and I$_2$ Reflux in methanol

To Menthyl ester (0.14 g, 0.3 mmol) in 3 mL of dry MeOH and 1 mL of dry toluene, Zinc (0.40 g, 0.6 mmol) and Iodine (0.039 g, 0.15 mmol) was added, and the reaction mixture was refluxed for 5 h.

Result: Reaction was monitored by TLC and it was found that there was no reaction, however, prolonged heating lead to decomposition.

Ref: Chavan, S. P.; Shivasankar, K.; Sivappa, R.; Kale, R. *Tetrahedron Letters* **2002**, *43*, 8583.

Method 12. Reflux with HMTA (Hexamethylenetetramine)/Methanol

To Menthyl ester (0.14 g, 0.3 mmol) in 3 mL of dry MeOH and 1 mL of dry toluene, HMTA (0.09 g, 0.061 mmol) was added, and the reaction mixture was refluxed for 8 h.

Result: Reaction was monitored by TLC and it was found that there was no reaction, however, prolonged heating lead to decomposition.

Ref: Ribeiro, R. S.; *de* Souza, R. O. M. A.; Vasconcellos, M. L. A. A.; Oliveira, B. L.; Ferreira, L. C; Aguiar, L. C. S. *Synthesis* **2007**, *1*, 61.

Method 13: LAH Reduction followed by PDC/DMF oxidation:
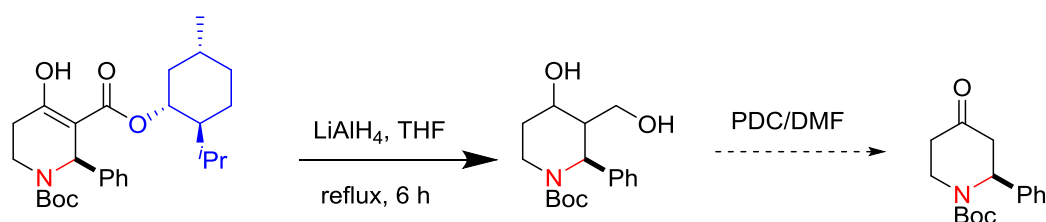
Step 1: To menthyl ester (1g, 2.19 mmol) in 25 mL dry THF, LiAlH$_4$ (0.332 g, 8.74 mmol, 4 equiv) was added pinch-wise for 3 times at 0 °C and the reaction mixture was slowly allowed to rt followed by refluxing for 6 h until the completion of the reaction, as monitored by TLC, after the completion, the reaction mixture was diluted with Et$_2$O, followed by quenching with sat. NH$_4$Cl and evaporation of volatiles resulted in a crude reaction mixture, which was diluted with 20 mL of water and extracted with Et$_2$O. The combined organic layers were washed with brine, dried over Na$_2$SO$_4$ and solvent was evaporated under reduced pressure. The reaction mixture was purified on silica column chromatography using *n*-hexane-EA (30:60) system obtained an yield of 60% (403 mg).

Ref: Ma, X.-P.; Zhu, J.-F.; Wu, S.-Y.; Chen, C.-H.; Zou, N.; Liang, C.; Su, G.-F.; Mo, D.-L. *J. Org. Chem.* **2017**, *82*, 502

Step 2: PDC/DMF oxidation

In an oven dried round bottomed flask containing diol (0.200g, 0.6 mmol) (from step 1) in 3 mL of dry DMF, PDC (1.47 g, 3.90 mmol) was added at rt and stirred for 12 h. (reaction was monitored on hourly basis).

Result: PDC/DMF conditions lead to mixture of complex products

Ref: Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, *20*, 399.

4.10 Appendix III: ^{1}H and ^{13}C spectral data, HPLC chromatograms of representative compounds

Compound No.	Fig AIII.X	data	page No.
3	Fig AIII.1 and AIII.2	^{1}H-^{13}C	133
Z-4a	Fig AIII.3 and AIII.4	^{1}H-^{13}C	134
E-4'a	Fig AIII.5 and AIII.6	^{1}H-^{13}C	135
Z-4o	Fig AIII.7 and AIII.8	^{1}H-^{13}C	136
E-4'o	Fig AIII.9 and AIII.10	^{1}H-^{13}C	137
6a	Fig AIII.11 and AIII.12	^{1}H-^{13}C	138
6o	Fig AIII.13 and AIII.14	^{1}H-^{13}C	139
5a	Fig AIII.15	HPLC	140
5o	Fig AIII.16	HPLC	140
6a	Fig AIII.17	HPLC	141
6o	Fig AIII.18	HPLC	141

Fig AIII.1: ^{1}H NMR (400 MHz, CDCl$_3$) spectrum of compound **3**
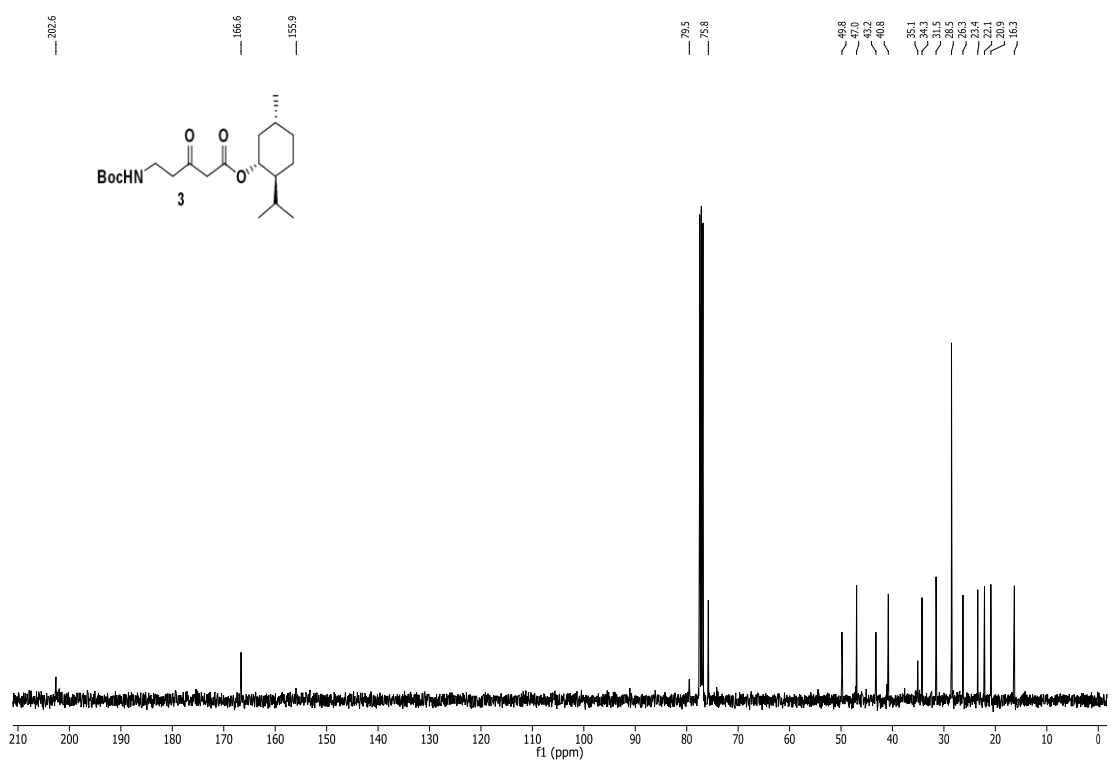
Fig AIII.2: ^{13}C NMR (100 MHz, CDCl$_3$) spectrum of compound **3**

Fig AIII.3: ^{1}H NMR (400 MHz, CDCl$_3$) spectrum of compound **4a**

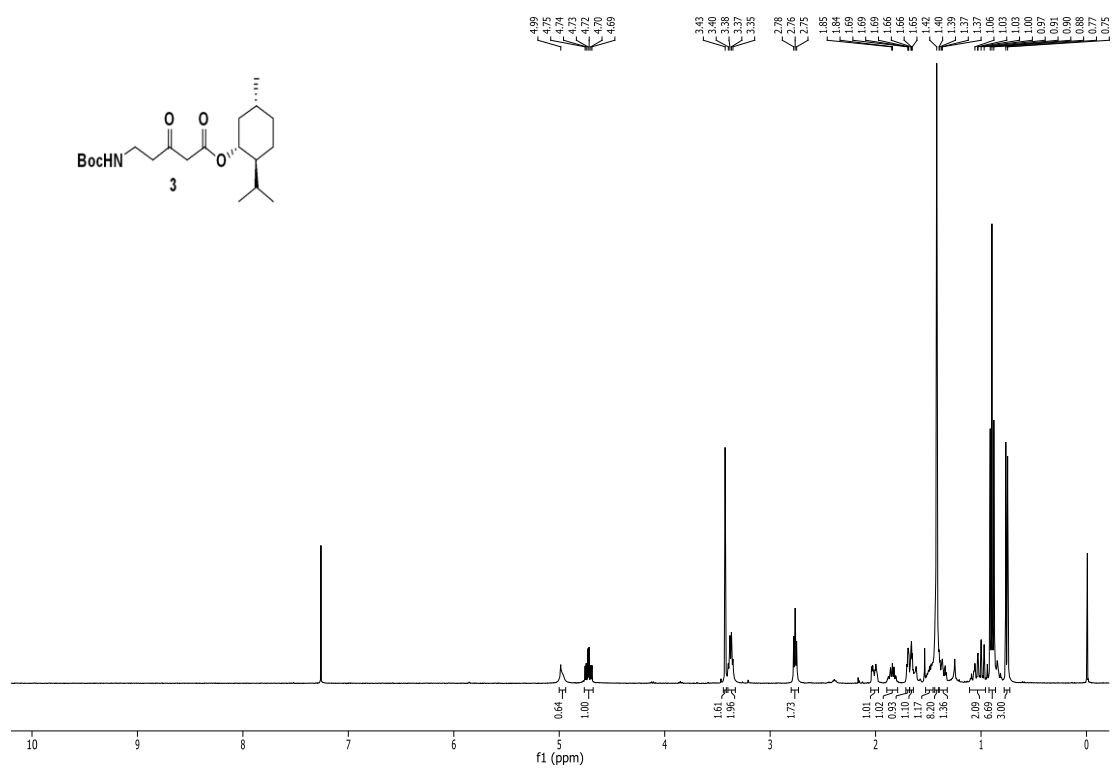**Fig AIII.4:** ^{13}C NMR (100 MHz, CDCl$_3$) spectrum of compound **4a**

134

Fig AIII.5: ¹H NMR (400 MHz, CDCl₃) spectrum of compound **4'a**

AIII.6: ¹³C NMR (100 MHz, CDCl₃) spectrum of compound **4'a**
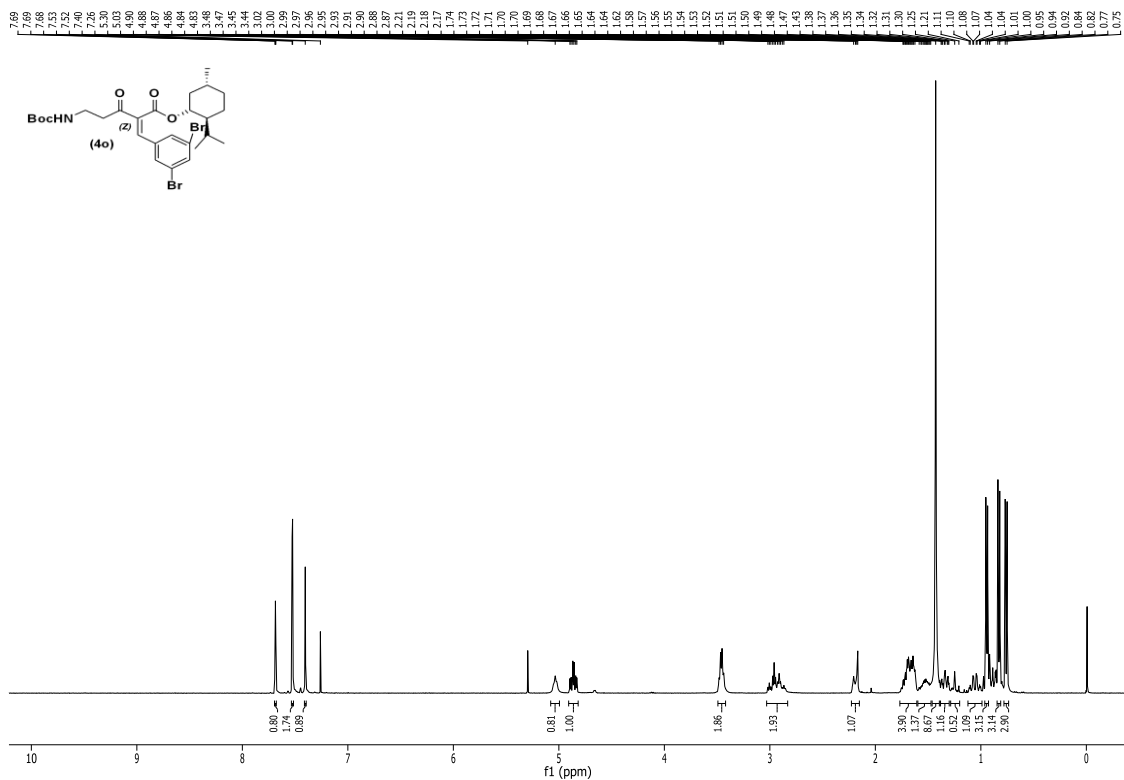
Fig AIII.7: ^{1}H NMR (400 MHz, CDCl$_3$) spectrum of compound **4o**
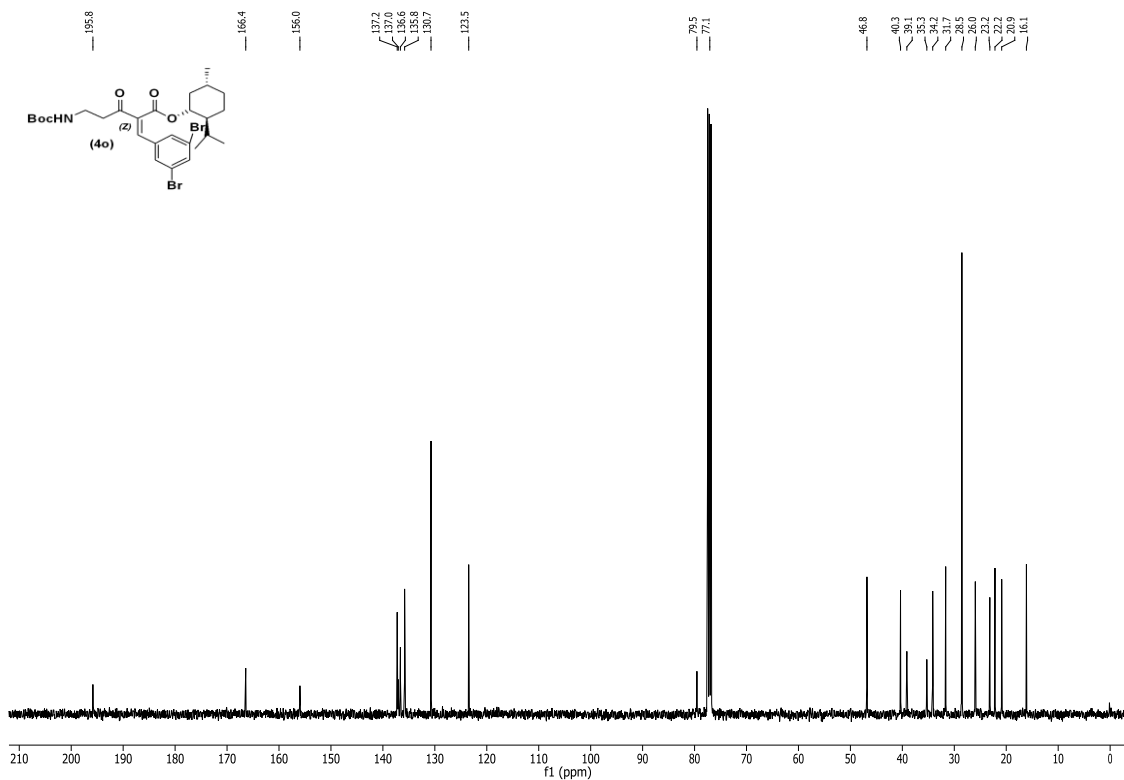
Fig AIII.8: ^{13}C NMR (100 MHz, CDCl$_3$) spectrum of compound **4o**
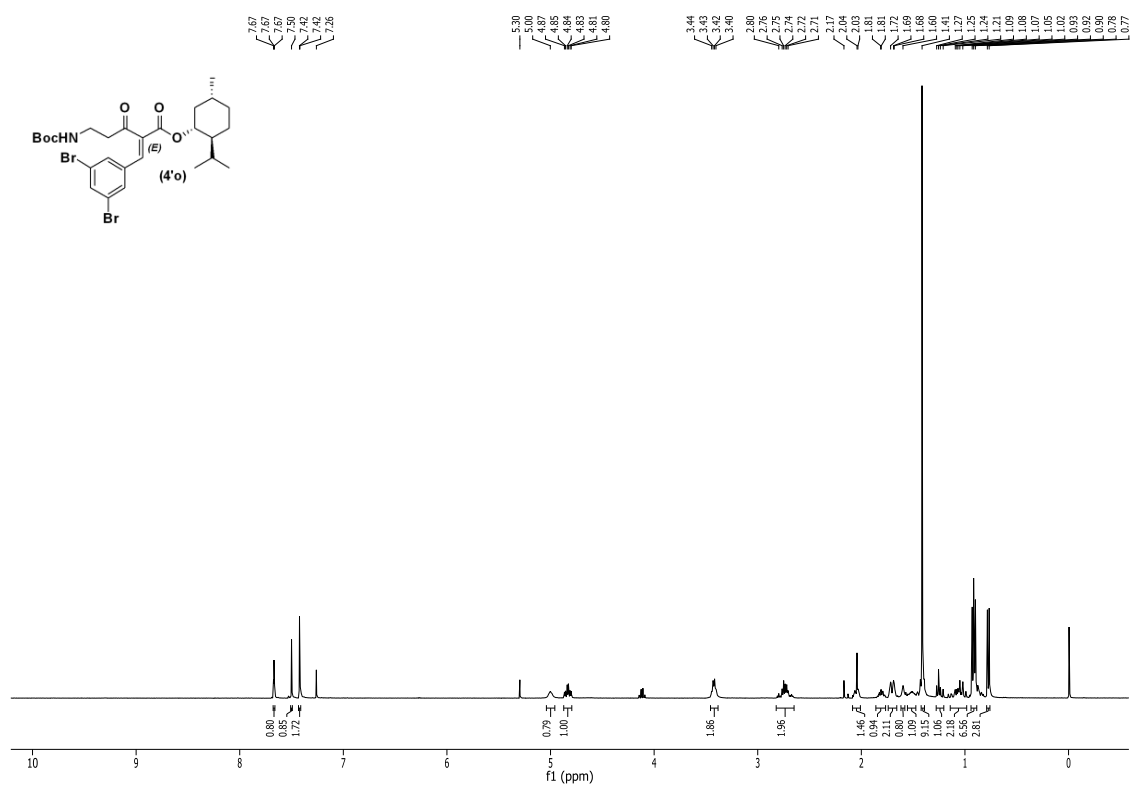
AIII.9: ^{1}H NMR (400 MHz, CDCl$_3$) spectrum of compound **4'o**
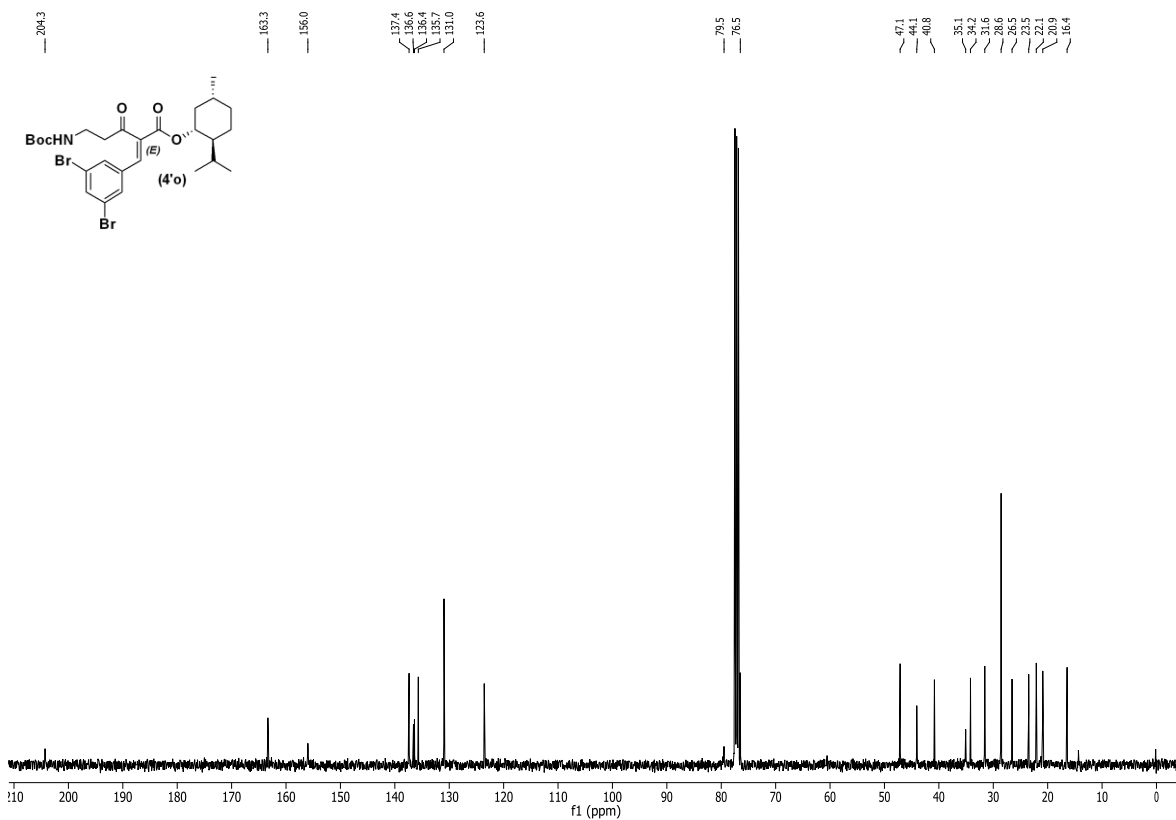
Fig AIII.10: ^{13}C NMR (100 MHz, CDCl$_3$) spectrum of compound **4'o**
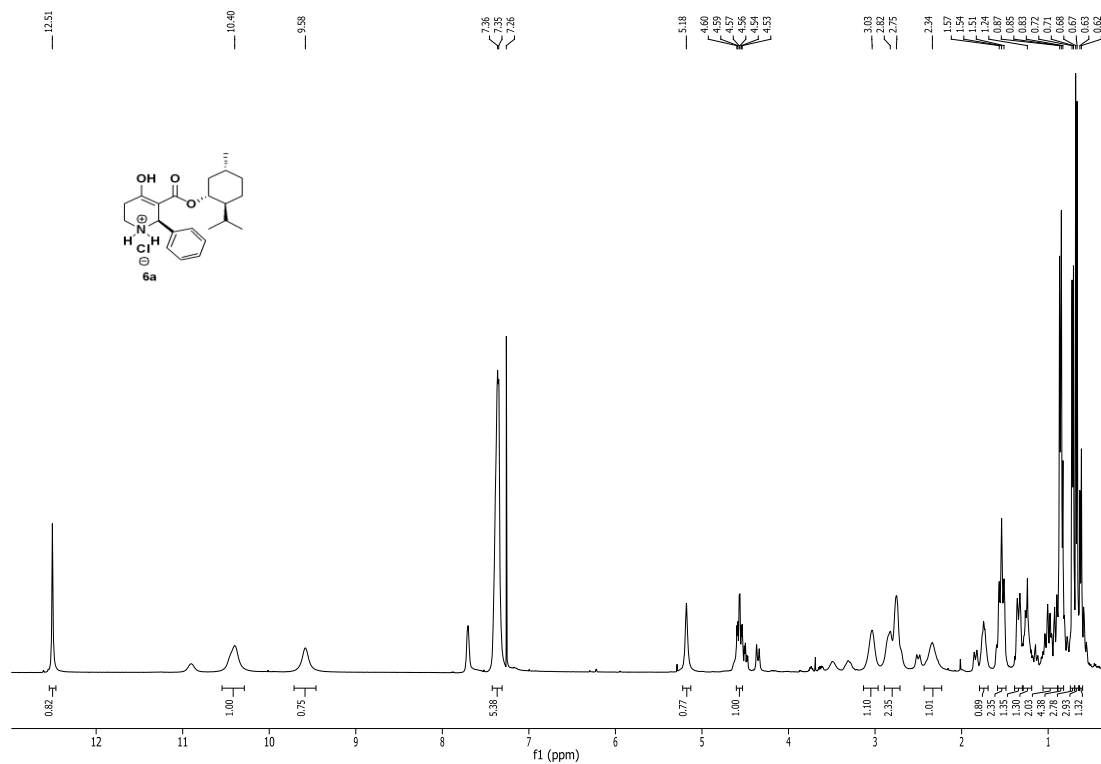
Fig AIII.11: ^{1}H NMR (400 MHz, CDCl$_3$) spectrum of compound **6a**
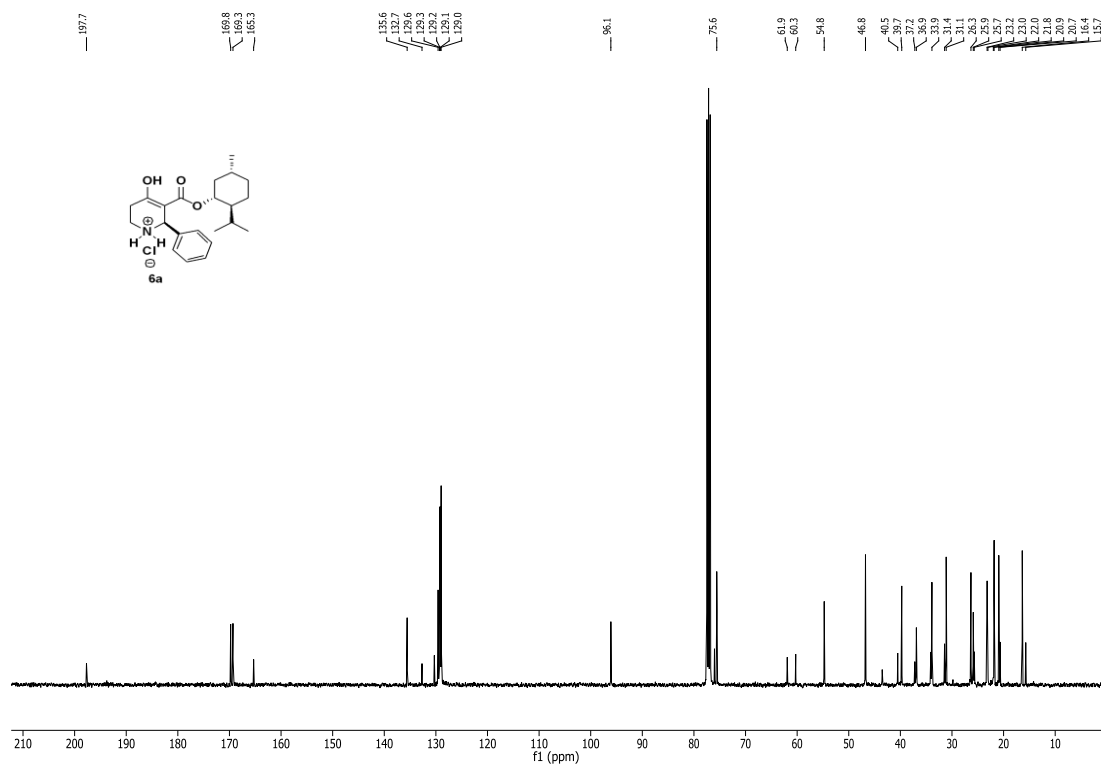
Fig AIII.12: ^{13}C NMR (100 MHz, CDCl$_3$) spectrum of compound **6a**

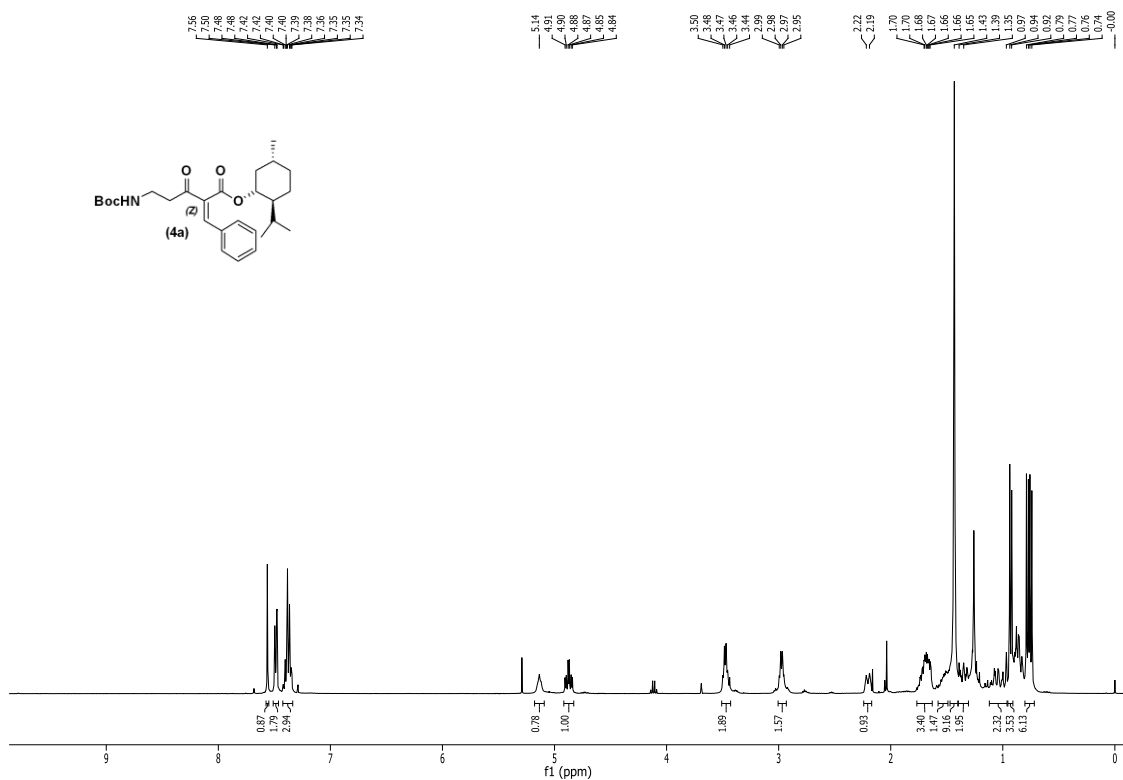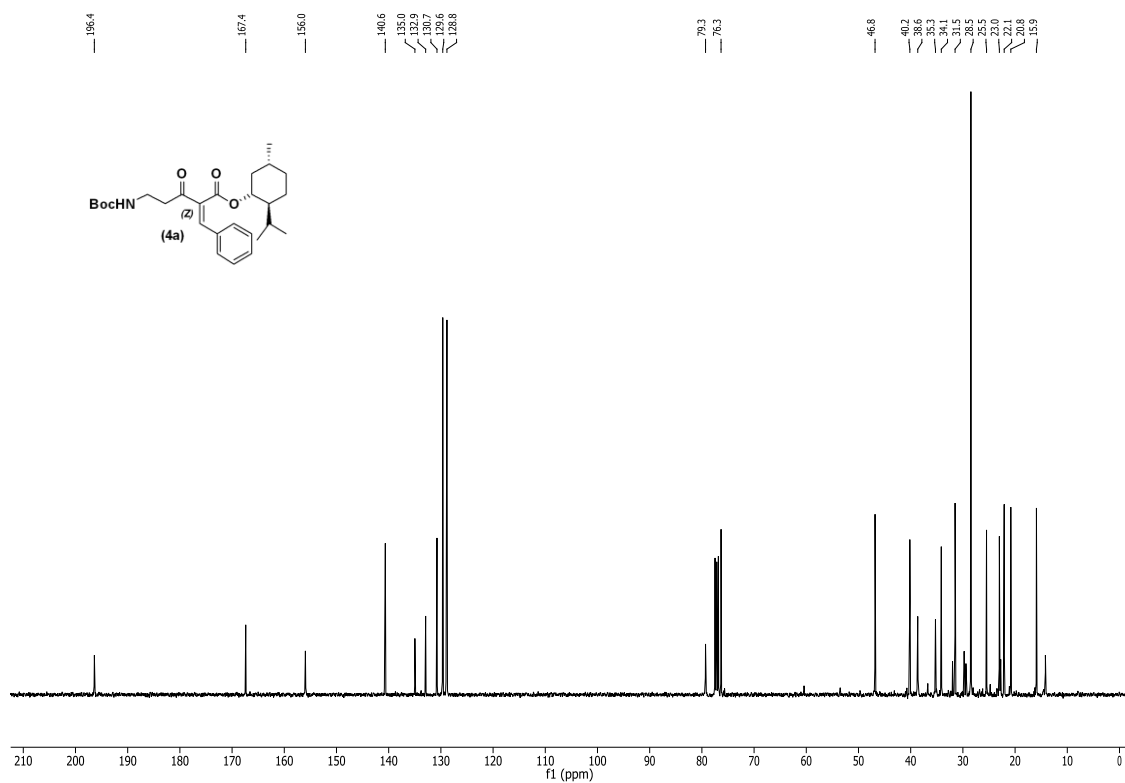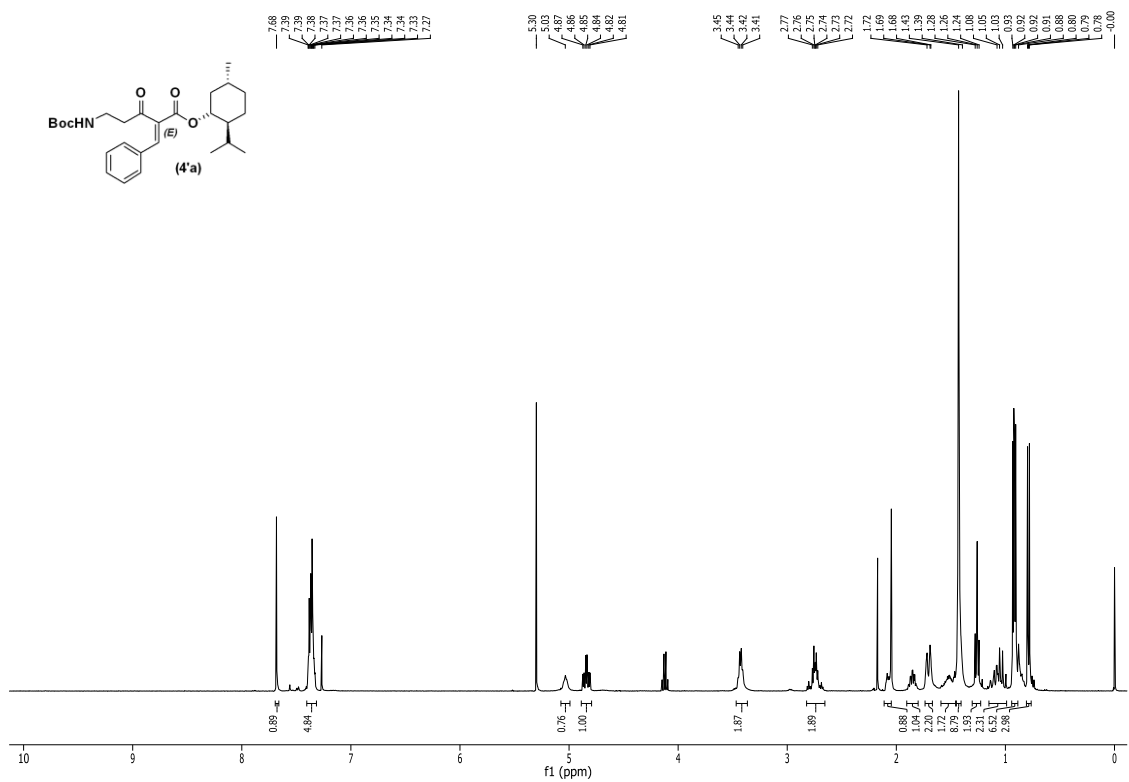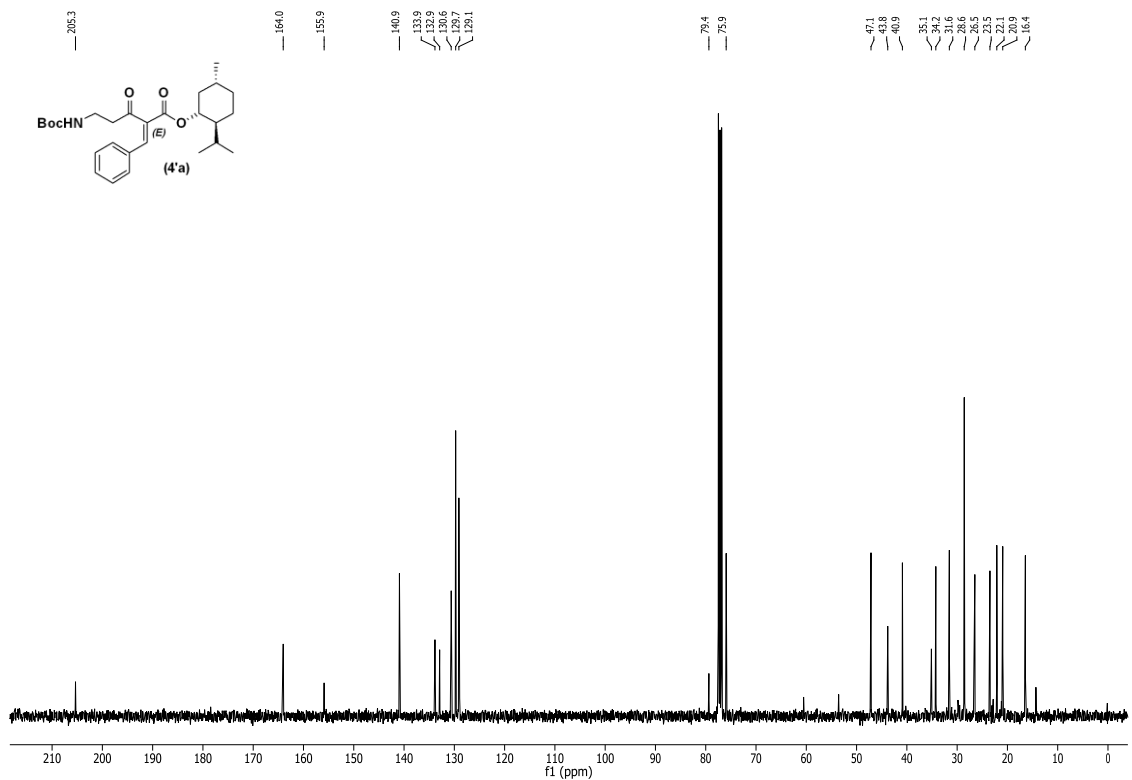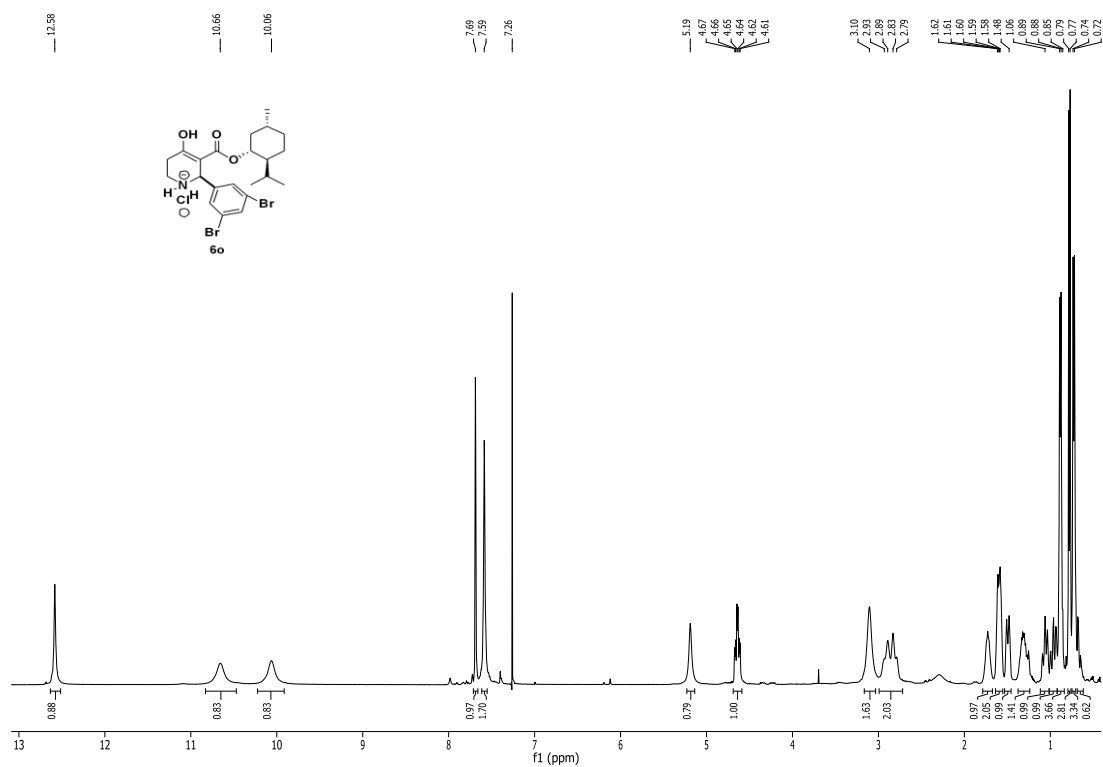**Fig AIII.13:** ^{1}H NMR (400 MHz, CDCl$_3$) spectrum of compound **6o**
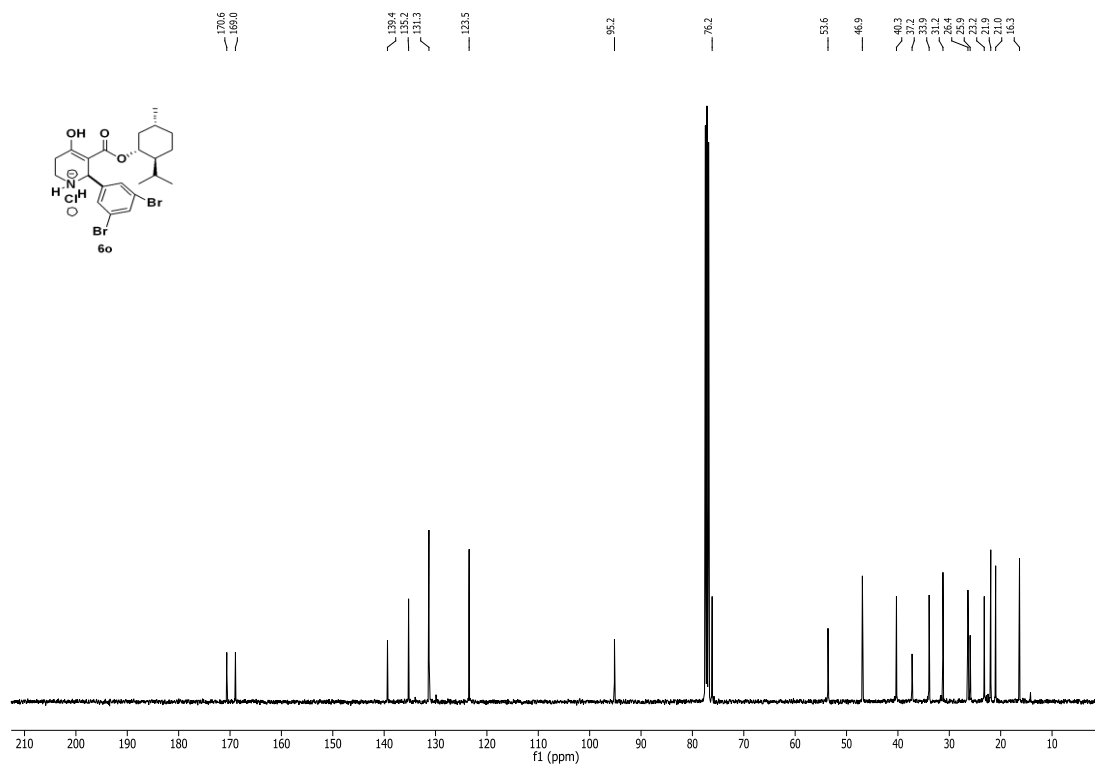
Fig AIII.14: ^{13}C NMR (100 MHz, CDCl$_3$) spectrum of compound **6o**

HPLC Chromatograms of *N*-Boc Piperidines (5)

HPLC analysis was carried using chiralpak IA, eluenet: *n*-hexane+IPA (95:5); Flow rate: 0.5 mL/min, sample was prepared in 5% IPA in *n*-hexane.

HPLC Data:

DAD: Signal A,
250 nm/Bw:4 nm
Results

Retention Time	Area	Area %	Height	Height %
7.607	5410524	20.81	633974	22.59
8.387	20583165	79.19	2172054	77.41
Totals	25993689	100.00	2806028	100.00
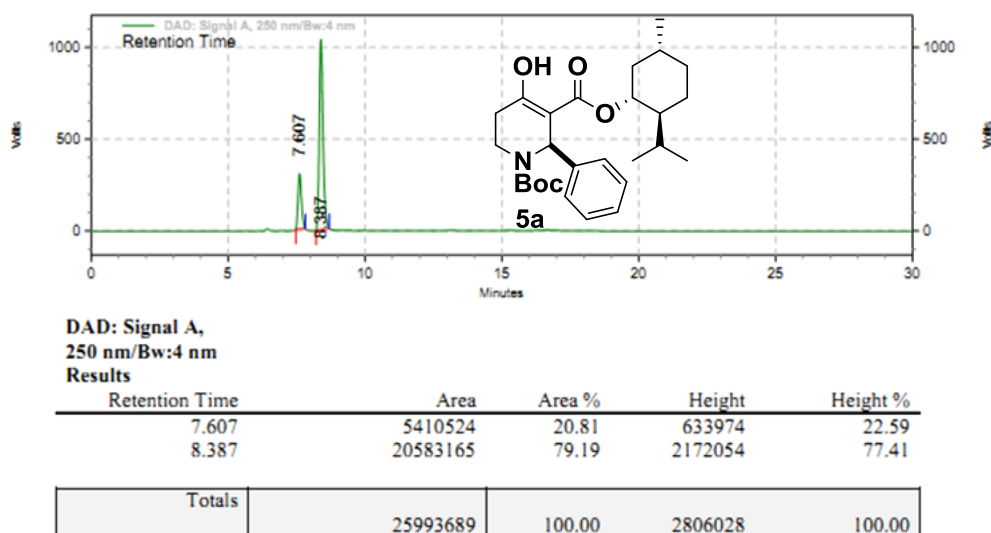
Fig AIII.15: HPLC profile of compound **5a**

DAD: Signal A,
250 nm/Bw:4 nm
Results

Retention Time	Area	Area %	Height	Height %
7.133	1448462	9.05	183838	11.02
8.553	14563937	90.95	1484393	88.98
Totals	16012399	100.00	1668231	100.00
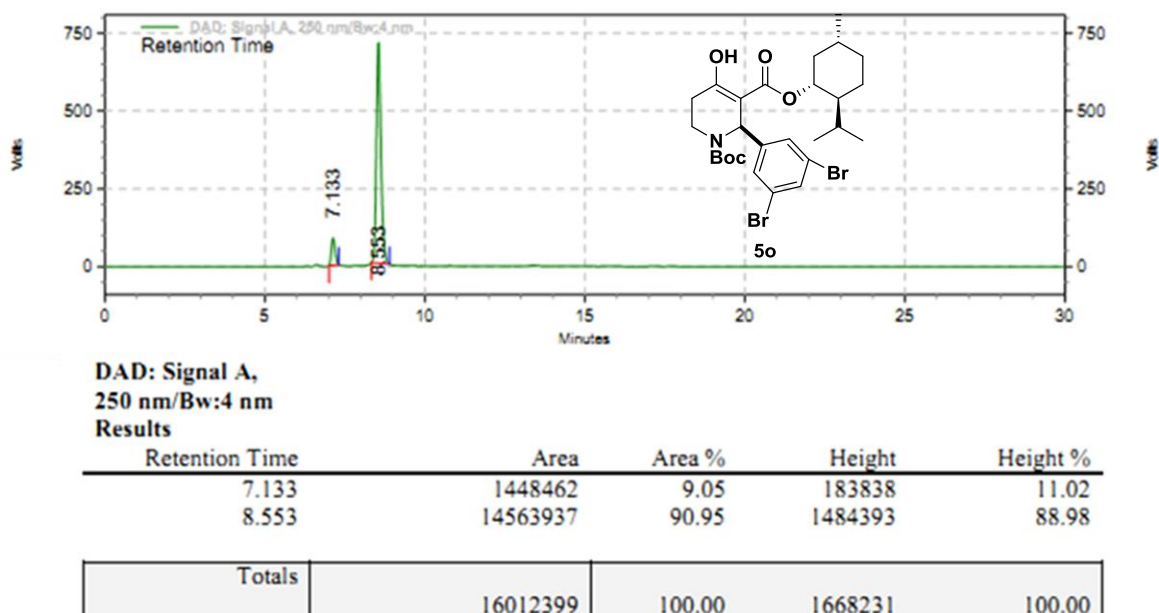
Fig AIII.16: HPLC profile of compound **5o**

HPLC Chromatograms of Piperidine hydrochloride Salts (6)

HPLC analysis was carried using chiralpak IA, Eluent: *n*-hexane + IPA (50:50) Flow rate 0.5mL/min, Sample was prepared in IPA.

DAD: Signal A,
250 nm/Bw:4 nm
Results

Retention Time	Area	Area %	Height	Height %
8.060	754726	7.47	75705	9.74
8.620	9344367	92.53	701730	90.26
Totals	10099093	100.00	777435	100.00
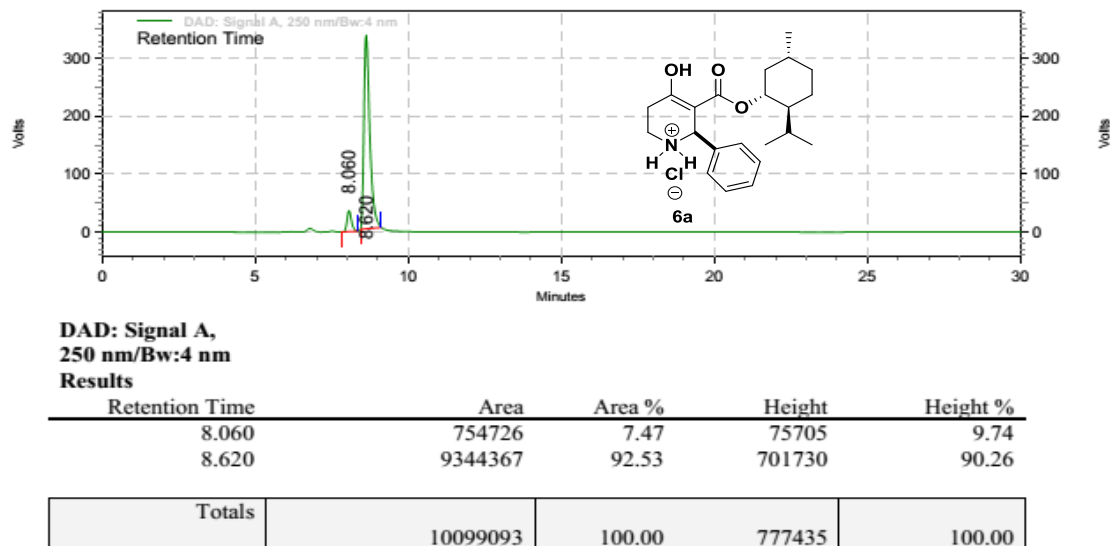
Fig AIII.17: HPLC profile of compound **6a**

(Based on ^{1}H NMR, molecule exists in enolic form, however small amount keto form is expected due keto-enol tautomerism)

DAD: Signal A,
250 nm/Bw:4 nm
Results

Retention Time	Area	Area %	Height	Height %
7.867	52201417	100.00	3426503	100.00
8.233	0	0.00	0	0.00
8.247	0	0.00	0	0.00
Totals	52201417	100.00	3426503	100.00

Fig AIII.18: HPLC profile of compound **6o**

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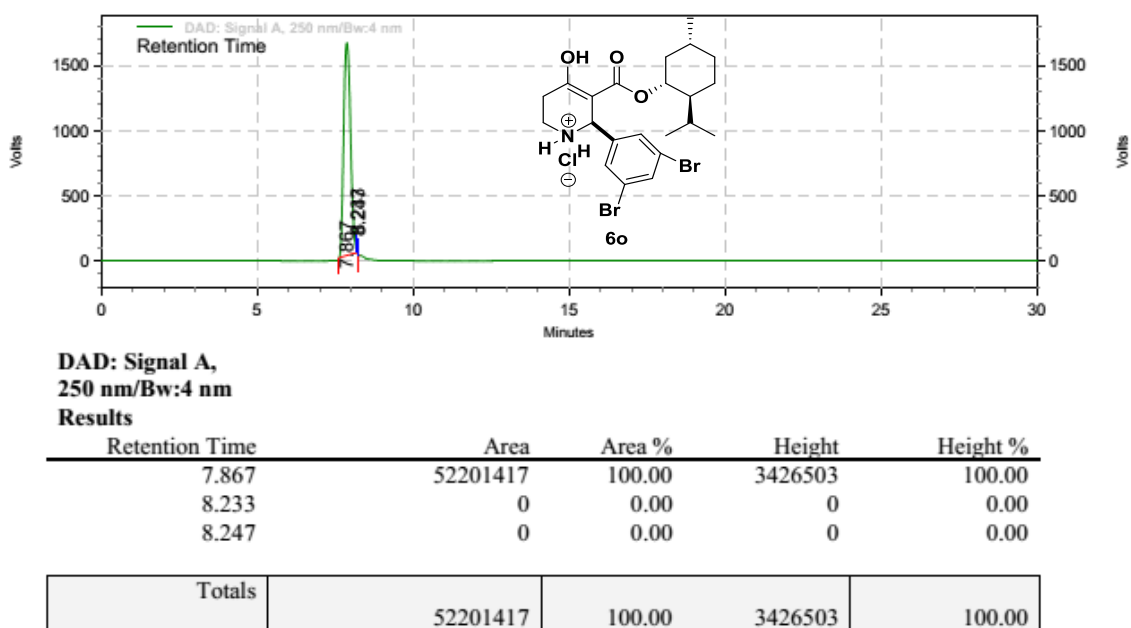
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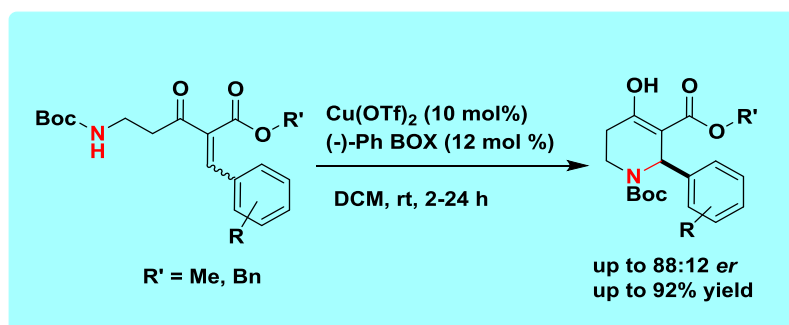24. Christie, B. D.; Rapoport, H. *J. Org. Chem.* **1985**, *50*, 1239.

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35. Various (L)–menthyl alkylidene *β*–keto esters **4** have been synthesized starting from *N*-Boc *β*–alanine **2** which is in turn synthesized starting from *β*–alanine **1** (see supporting information for the details).

36. Reaction containing both *E* and *Z* isomers (mixture) resulted in poor stereoselectivity. Later, *E* and *Z* isomers were separated before the reaction. Isolated *E* and *Z* isomers were confirmed ^{1}H NMR and by 1d nOe. Details and yields are given in supporting information.

37. Diastereomeric ratio was determined by HPLC. Chromatograms of all the products (**5a–5q**) are given in supporting information.

38. A quick literature search revealed numerous examples of VTNMR or other techniques being used for qualitative identification of rotamers with no mention of saturation transfer; for a few examples, see: (a) Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496; (b) Dennis X. Hu, Peter Grice, and Steven V. Ley, *J. Org. Chem.* **2012**, *77*, 5198; (c) Al–Horani, R. A.; Desai, U. R. *Tetrahedron* **2012**, *68*, 2027; (d) Lewis, K. C.; Maxwell, A. R.; McLean, S.; Reynolds, W. F.; Enriquez, R. G. *Magn. Reson. Chem.* **2000**, *38*, 771; (e) Smith, A. B.;

Chruma, J. J.; Han, Q.; Barbosa, J. *Bioorg. Med. Chem. Lett*. **2004**, *14*, 1697; (f) Dransfield, P. J.; Gore, P. M.; Prokes, I.; Shipman, M.; Slawin, A. M. Z. *Org. Biomol. Chem.* **2003**, *1*, 2723.

39. It was difficult to calculate the exact yield of both diastereomers as some amount of diastereomers was isolated as mixture. Hence, the combined yields of the diastereomers are reported.

40. Purity of piperidine hydrochloride salts (**6**) has been confirmed by HPLC studies and they were found to be highly pure (up to 99%, see ESI). [(-)-Menthol of 99% *ee* purity was used for the reactions]

Chapter 5

Bis(Oxazoline)-Copper(II) Complex as Chiral Catalyst System for the Enantioselective Synthesis of 2, 3, 4-Trisubstitued Piperidines

R' = Me, Bn

Cu(OTf)$_2$ (10 mol%)
(-)-Ph BOX (12 mol %)

DCM, rt, 2-24 h

up to 88:12 *er*
up to 92% yield

F I V E

Bis(Oxazoline)-Copper(II) Complex as Chiral Catalyst System for the Enantioselective Synthesis of 2, 3, 4-Trisubstitued Piperidines

5

In this chapter an efficient enantioselective synthesis of substituted piperidines using catalytic amount of copper(II) triflate as a Lewis acid catalyst and bis-oxazoline(BOX) as chiral ligand is described. We explored the intramolecular aza-Michael addition of carbamate on alkylidene β-keto methyl/benzyl esters to synthesize the various functionalized 4-oxo-2-arylpiperidine-3-carboxylate derivatives with high enantioselectivity (up to er 88:12) in good to excellent yields.

5.1 Introduction

Nitrogen containing chiral compounds are key motifs in many biologically active molecules and also find a great utility in synthetic organic chemistry. Chiral amines have also been utilized extensively as chiral ligands in asymmetric synthesis.[1,2] Asymmetric synthesis of enantiomerically pure nitrogen based compounds is of high importance as they are very important scaffolds in fine chemicals, pharmaceuticals, and chiral ligands[2] in asymmetric catalysis.[3] In this regard, catalytic asymmetric synthesis has become one of the forefronts in modern synthetic organic and organometallic chemistry.[4-7]

Several methods such as asymmetric alkylation and hydrogenation of carbon-nitrogen double bonds have been developed to synthesize chiral amine compounds.[8,9] Conjugate amination of carbon-carbon double bonds that are activated by an electron-withdrawing group is one of the important transformations.[10-15] On the other hand, the development of enantioselective catalytic versions of these transformations has faced a great challenge and difficulties. However, a number of chiral auxiliaries and stoichiometric reagents have been explored for the enantioselective 1,4-addition with high stereoselectivity.[16]

Very few catalysts facilitate the facile addition of amine (N-H) to carbon-carbon double bonds (known as hydroamination, or the aza-Michael addition reaction) with high

enantioselectivity. Conjugate addition of hetero nucleophiles (having hetero atoms) to α, β-unsaturated carbonyl compounds are one of the most useful transformations in organic synthesis for accessing heterocycles.[17] Enantioselective conjugate addition of weaker heteroatom nucleophiles such as carbamates to α, β-unsaturated carbonyl compounds is proven to be more difficult than the reactive amines to form a new C-N bond and simultaneously introducing a new stereogenic center.[18,19]

Use of chiral Lewis acid catalysts in the asymmetric synthesis of carbon-carbon bond forming reactions has attracted a great attention of organic chemists.[3,20,21] Transformations such as aldol reaction, Diels–Alder reaction and Michael addition reactions and many more are usually catalyzed by Lewis acid activation of one of the reacting partners. The use of suitable chiral complex catalysts can facilitate the efficient asymmetric version of these reactions. In recent years, asymmetric catalysis with chiral (Lewis acid) metal complexes has become one of the most interesting and effective methods for the synthesis of enantiomerically pure compounds.[3,20] Chiral catalyst systems based on Cu^{II}, Ni^{II}, Zn^{II}, or Co^{II} complexes containing a variety of C2-symmetric chiral bis(oxazoline) (BOX) ligands have been utilized in a variety of transformations such as carbocyclic and hetero Diels–Alder, aldol, Michael, and amination reactions with excellent enantioselectivities. In this regard, C2-symmetric chiral bis(oxazolines) ligands (BOX ligands) have become one of the most popular classes of chiral ligands. The chiral BOX ligands have received a great deal of attention as ligands in coordination chemistry[22,23] and in asymmetric catalysis.[24-28] Oxazolines and their derivatives have been intensely studied and employed in a wide range of applications, particularly in asymmetric catalysis.[24,29-31] Remarkable examples include catalytic oxidations, reductions of olefins and ketones, carbonyl addition reactions insertions, and group transfer reactions.[32] Complexes with a single BOX as the bidentate ligand are the most popular in asymmetric catalysis. Since the discovery of bis(oxazoline) (BOX) ligands around 1990's, their metal complexes have been utilized in a variety of metal-mediated asymmetric catalytic transformations. BOX ligands have quickly established into a high-performance ligand platform and are now classified as "privileged ligands".[33,34] Further, these BOX ligands have been extensively used for the 1, 4-additions of Grignard, dialkylzinc and organolithium reagents to the suitable substrates.[35] Especially, the use of chiral bisoxazoline ligands for the enantioselective hetero-conjugate addition has become one of the crucial transformations for the synthesis of heterocycles.

In view of high efficiency and broad scope of the chiral BOX ligands in asymmetric synthesis, we became interested in exploring the application of chiral BOX ligands for the

intramolecular aza-Michael conjugate addition reaction. Herein, in this chapter we have described the asymmetric synthesis of piperidine derivatives using a catalyst system comprising of Lewis acid and BOX ligand in detail with literature background.

5.2 Some of the selected methods for bisoxazoline (BOX) ligands-catalytic system

Pfaltz and co-workers[36] developed a series of efficient P, N-ligands, also known as oxazoline-phosphite ligands. These were found to be efficient ligands for the enantioselective copper-catalyzed 1, 4-addition of organozinc reagents to enones (**9**). Both cyclic enones (**9**) and acyclic enones showed good enantioselectivity. They found improved enantioselectivity (*ee* up to 94%) with increasing the steric bulk in the 3,3'-position of binaphthyl from simple H to a biphenyl moiety (Scheme 5.1).
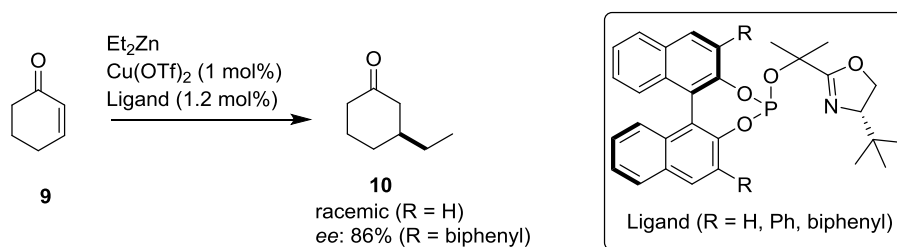

Scheme 5.1: Enantioselective Cu-(oxazoline-phosphite ligands) complex catalyzed 1,4-addition of Et$_2$Zn to cyclohexenone (**9**)

Schinnerl *et al.*[37] demonstrated the first example of an asymmetric ethyl transfer to cyclohexenone (**9**) with ZnEt$_2$ as a reagent using bis(oxazolines) as chiral ligands (**L6** and **L**). In case of **L6**, reaction gave racemic compound, whereas when they used ligand (**L**), the conjugate addition product (**10**) was obtained in 93% yield with 94% *ee* (Scheme 5.2). They illustrated that the high enantioselectivity is due to the strong binding interactions of bimetallic complex formed wherein, the substrate is locked in a two-point binding mode via zinc and copper atoms.
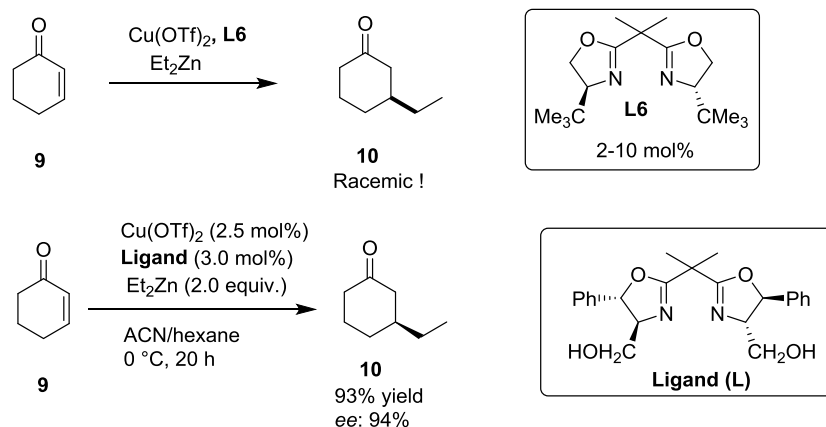
Scheme 5.2: Asymmetric 1, 4-addition of ZnEt$_2$ to cyclohexenone (**9**)

Yamazaki and co-workers[38] reported the enantioselective Friedel-Crafts reaction/Michael addition reactions of indoles (**11**) with highly reactive ethenetricarboxylates (**12**) in the presence of catalytic amounts of chiral bisoxazoline (**L6**, 12 mol%)-copper (II) complex (10 mol%) in THF at room temperature to give alkylated products (**13**) in high yields with very high enantioselectivity (up to 95% *ee*) (Scheme 5.3). Further they explained the high enantioselectivity of resulting products is due to the secondary orbital interaction of indoles with the less hindered side of the ethenetricarboxylates-Cu(II)-ligand complex.
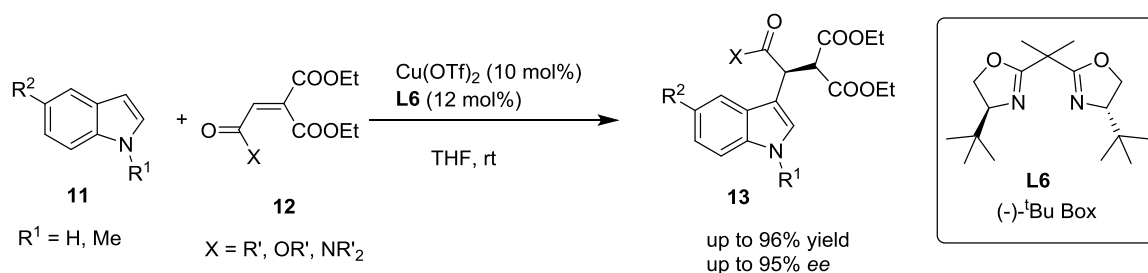
Scheme 5.3: Asymmetric enantioselective Michael addition of indoles (**11**) to ethenetricarboxylates (**12**)

Shizuka *et al.*[39] demonstrated the first enantioselective Hosomi–Sakurai conjugate allylation of cyclic unsaturated ketoester (**14**) with allyltrimethylsilane (**15**) in the presence of 10 mol% of Cu(OTf)$_2$- di(*tert*-butyl)bis(oxazoline) ligand (**L6**) to give **16** in 90% *ee* (Scheme 5.4). The resulting products obtained from these reactions were further functionalized into a variety of useful building blocks for target- and diversity-oriented synthesis.
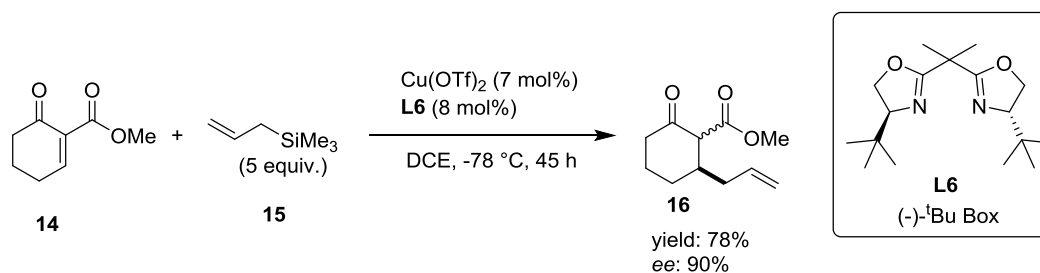
Scheme 5.4: Catalytic enantioselective Hosomi–Sakurai conjugate allylation of **14**

Sibi and co-workers[40] reported the chiral Lewis acid-catalyzed conjugate additions of *O*-benzylhydroxylamine (**18**) to α, β–unsaturated pyrazole amides (**17**) using catalytic amounts of a chiral Lewis acid catalyst derived from MgBr$_2$·OEt$_2$ and a bisoxazoline ligand to afford the corresponding conjugate addition product (**19**) (Scheme 5.5).
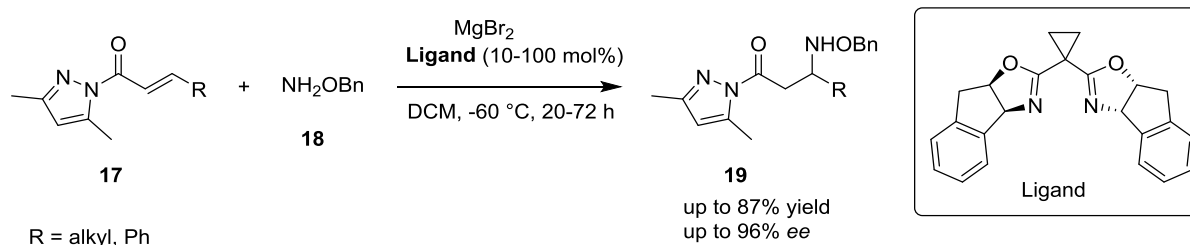
Scheme 5.5: Enantioselective conjugate aza-Michael addition of *O*-Benzylhydroxylamine (**18**) to unsaturated Amides (**17**)

Sibi and co-workers[21] illustrated the temperature dependent enantioselective conjugate addition of amine (**18**) on α, β-unsaturated oxazolidinone derived from 4,4-disubstituted-2-oxazolidinone (**20**) in presence of chiral Lewis acid complex derived from MgBr$_2$·OEt$_2$ and bisoxazoline to give the corresponding conjugate addition product (**21**) (Scheme 5.6). They proved that the face selectivity in these conjugate additions is temperature dependent and was found to be unusually opposite at two different temperatures.
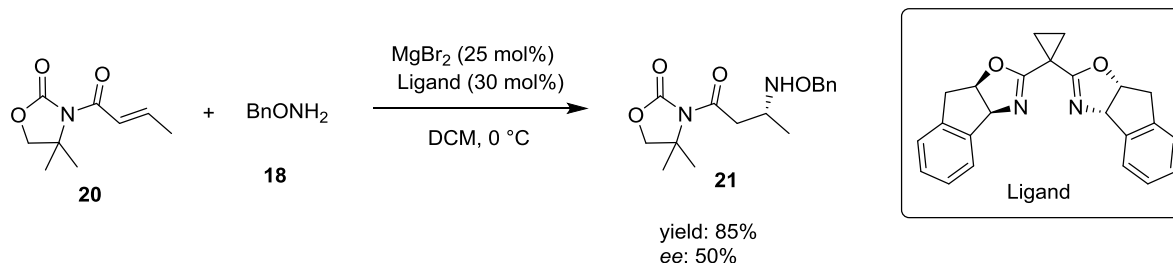
Scheme 5.6: Enantioselective conjugate aza-Michael addition of *O*-benzylhydroxylamine (**18**) to unsaturated oxazolidinone (**20**)

Zhuang *et al.*[41] demonstrated the catalytic enantioselective addition of secondary aromatic amines (**22**) to alkyl oxazolidinones (enones) (**23**) in the presence of a chiral nickel

complex to give compound **24** (Scheme 5.7). This protocol showed an excellent enantioselectivity with good yields. For assigning the absolute configuration of the addition product, one of the obtained products was converted into an optically active amide. A chiral trigonal bipyrimidal nickel complex was proposed as an intermediate based on the absolute configuration.


R[1] = H, Cl, Me, 3-OMe, 4-OMe
R[2] = Me, Bn
R[3] = Me, *n*-Pr, COOEt

up to 93% yield
up to 96% *ee*
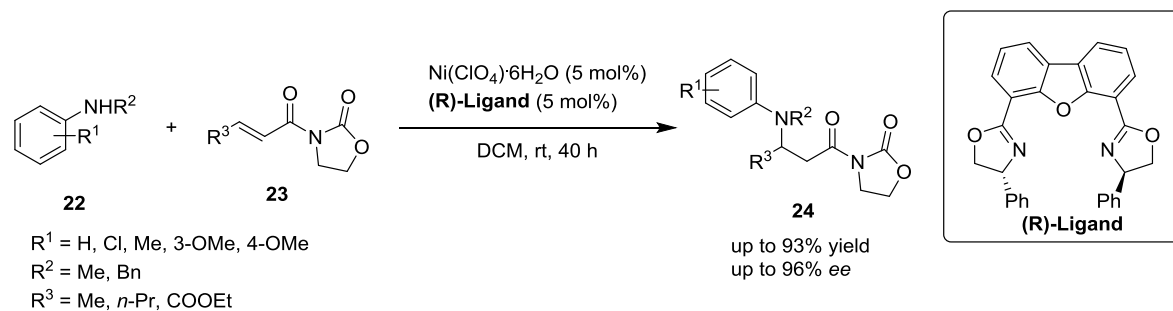
Scheme 5.7: Catalytic enantioselective addition of aromatic amines (**22**) to enones (**23**)

Palomo *et al.*[19] reported the first highly enantioselective conjugate addition reactions of weak carbamates (**25**) to α'-hydroxy enones (**26**) catalyzed by chiral Lewis acid-BOX complex. As hypothesized, α'-hydroxy enones coordinate to bis-(oxazoline)-copper complexes in a very efficient manner through a 1, 4-metal binding pattern to give 1, 4-addition products (**27**) with excellent yields with high enantioselectivity (*ee* up to 98%) (Scheme 5.8).

R = alkyl
R[1] = Bn, alkyl

up to 92% yield
up to 98% *ee*
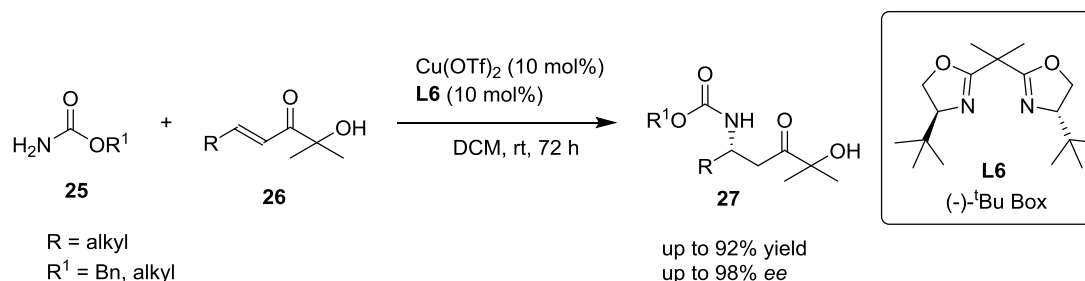
Scheme 5.8: Catalytic enantioselective conjugate addition of carbamates (**25**) to α'-hydroxy enones (**26**)

Aggarwal and co-coworkers[42] demonstrated the asymmetric Nazarov cyclization of divinyl ketones (**28**) bearing α-ester or α-amide groups using catalytic Cu(II)-BOX complexes to give cylopentenones (**29**) with moderate to good enantioselectivity (Scheme 5.9). However, good enantioselectivity was observed in divinyl keto amides when compared to divinyl keto esters.
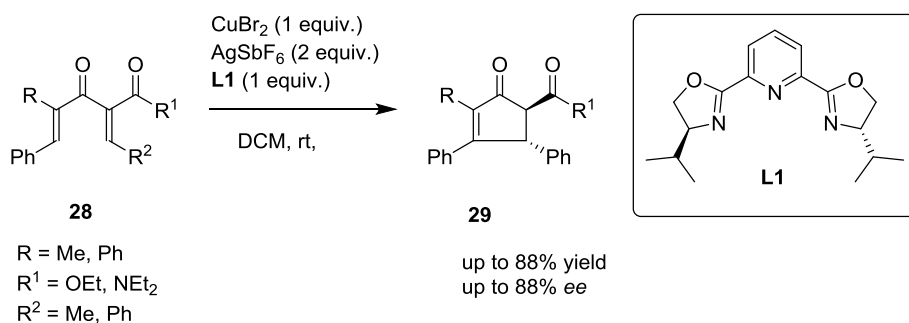
Scheme 5.9: Catalytic asymmetric Nazarov reactions promoted by chiral Lewis acid complexes

Yamazaki and co-workers[43] developed a catalytic enantioselective intermolecular aza-Michael conjugate addition of *N*-methyl aromatic amines (**30**) to the reactive electrophilic olefins (ethenetricarboxylates) (**31**) in presence of chiral Cu(II)-BOX complex in THF at 20 °C for 17 h to give the corresponding conjugate addition product (**32**) in moderate *ee* with high yields (Scheme 5.10). However, it is noteworthy to note that the reaction with aniline and primary aniline resulted in racemic compounds.
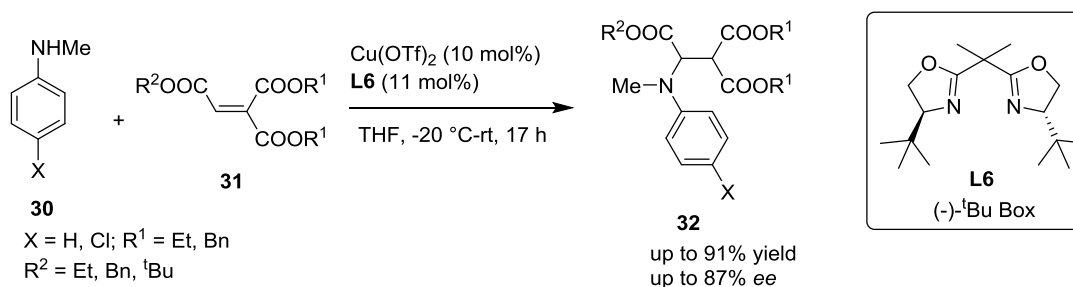
Scheme 5.10: Conjugate addition of aromatic amines (**30**) to ethenetricarboxylates (**31**)

Rasappan *et al.*[44] reported a highly enantioselective Friedel-Crafts alkylation of indoles (**33**) with benzylidene malonates (**34**) in the presence of catalytic Cu(II)-azabis(oxazolines) complex to give the conjugate addition products (**35**) with excellent enantioselectivity up to 99% *ee* (Scheme 5.11). They discovered an interesting observation that a slight excess of chiral ligand results in lowering enantioselectivity which is generally opposite to many asymmetric reactions (metal-BOX) wherein, an excess of chiral ligand (BOX) with respect to the metal reagent generally improves the enantioselectivity as the background reaction due to free metal is suppressed.
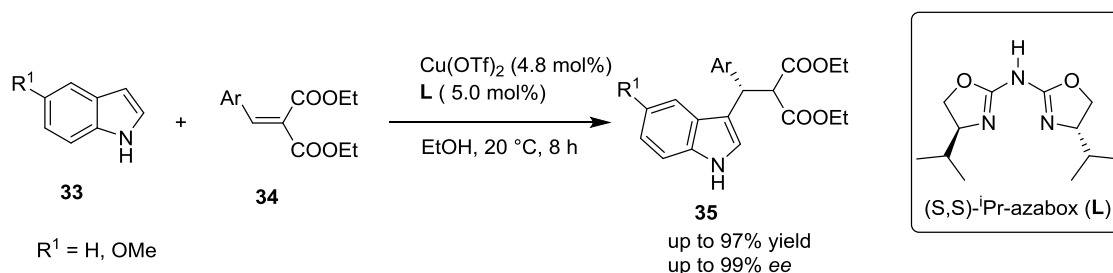
Scheme 5.11: Enantioselective Michael additions of indoles (**33**) to benzylidene malonates (**34**)

Wen *et al.*[45] demonstrated a highly enantioselective Michael addition of indoles (**36**) with trifluoroethylidene malonates (**37**) catalyzed by a catalytic amount of Cu(II)-bis(oxazoline) complex to afford β-CF$_3$-malonate derivatives (**38**) with high enantioselectivity in excellent yields (Scheme 5.12). This is an efficient method for the construction of stereogenic tertiary carbon centers bearing a CF$_3$ group. Further, this method was utilized for the preparation of interesting precursors of biologically active β-CF$_3$-tryptophan and 4-CF$_3$-β-carboline derivatives in high *ee*.
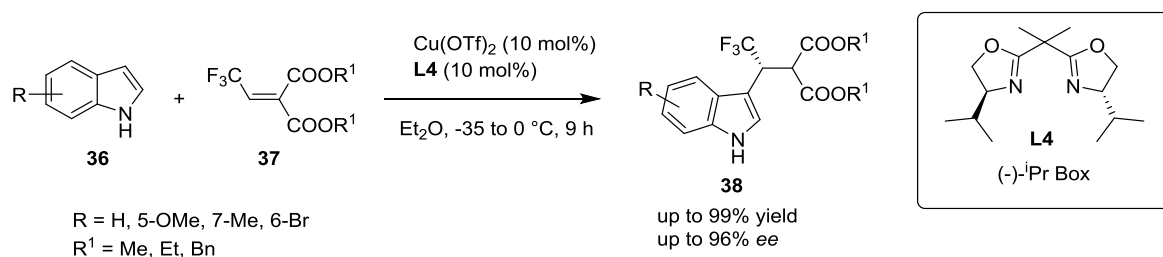
Scheme 5.12: Enantioselective Friedel-Crafts alkylation of indoles (**36**) with trifluoroethylidene malonates (**37**) by Cu-BOX Complexes

5.3 Results and Discussion

Recently, we reported[46] an efficient diastereoselective synthesis of substituted piperidines using catalytic amount of FeCl$_3$·6H$_2$O and (L)-menthol as chiral auxiliary. Surprisingly, different deprotection methods of menthyl esters known in the literature did not work on menthyl β-ketoester scaffold. To overcome this drawback of removal of chiral auxiliary and to improvise the strategy, we planned to develop an efficient methodology for the enantioselective synthesis of various substituted piperidines. In this regard, we developed a method comprising of Cu(OTf)$_2$-BOX complex catalyst system for the enantioselective synthesis of 2,3,4-trisubstituted piperidine derivatives with good enantioselectivity up to *er* 88:12.

In order to validate our strategy, initially, we synthesized few selected starting materials:alkylidene β-ketoesters (**4/4'**) (*E*/*Z* ~40:60) from alkyl β-ketoesters (**2**) by condensing with various aldehydes (**3**). Alkyl β-ketoesters (**2**) was synthesized starting from *N*-Boc-protected β-alanine (**1**) by using our previously reported protocol[47] (Scheme 5.13).
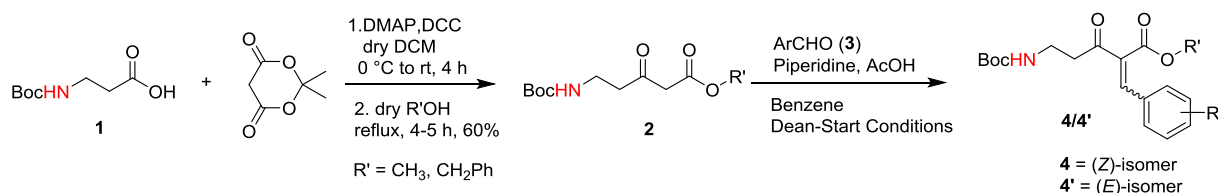
Scheme 5.13: Synthesis of alkylidene β-ketoester
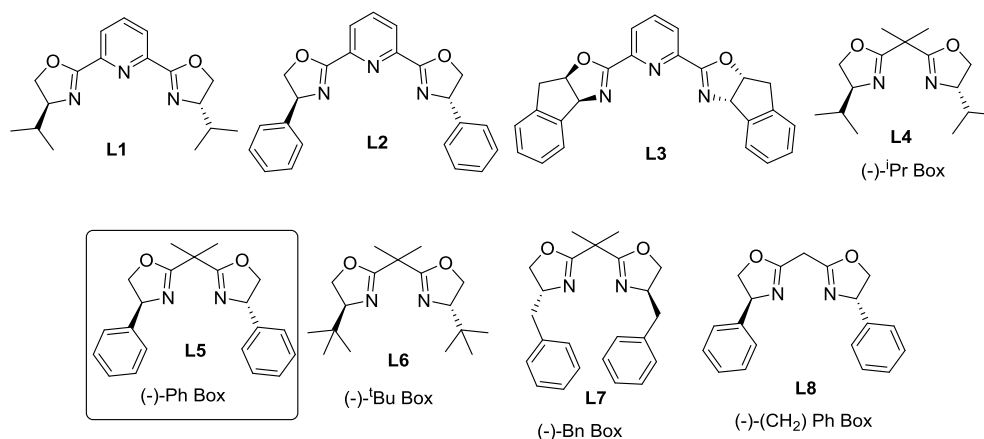
Fig 5.1: Various chiral BOX ligands (**L1** to **L8**) used for screening

For the initial model reactions, considering the advantage of the reactivity of (*Z*)–isomer (**4a**) based on our previous experience (Chapter 4), we chose (*Z*)–isomer (**4a**) as a starting material and BOX (**L1** to **L8**) as chiral ligands for inducing the chirality in the proposed planned reaction. Initially, reactions were screened with PyBOX ligands such as **L1**, **L2**, **L3** (Fig 5.1) as the chiral ligands (12 mol%) and Sc(OTf)$_3$ (10 mol%) as Lewis acid catalyst in dry DCM at room temperature. We observed that the conjugate addition was relatively slow at room temperature and the desired *N*-Boc protected product (**5a**) was formed in moderate to poor enantioselectivity even after prolonged reaction time (18 h) with moderate yields (entries 1-3, Table 5.1).

Table 5.14: Screening of Lewis acid catalysts and ligands for the optimization of aza-Michael conjugate addition reaction[a]

4a → **5a**

catalyst (10 mol%)
ligand (**L**) (12 mol %)

DCM, rt, time
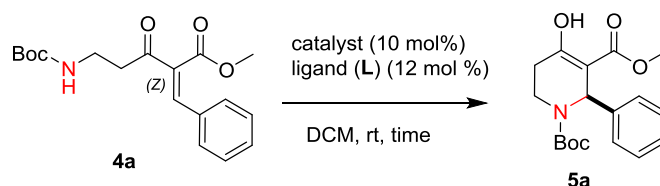
S.No.	Catalyst	BOX (**L**)	Time (h)	Yield (%)[b]	er[c]
1	Sc(OTf)$_3$	L1	18	49	50:50
2	Sc(OTf)$_3$	L2	18	55	48:52
3	Sc(OTf)$_3$	L3	18	85	33:67
4	Cu(OTf)$_2$	L4	3	90	59:41
5	Cu(OTf)$_2$	L5	1.5	95	90:10
6	Cu(OTf)$_2$	L6	8	45	47:53
7	Cu(OTf)$_2$	L7	4	88	36:64
8	Cu(OTf)$_2$	L8	3	89	88:12
9	MgBr$_2$	L5	18	15	42:58
10	Ni(OTf)$_2$	L5	18	82	57:43
11	Zn(OTf)$_2$	L5	18	76	79:21

[a]Reaction of **4a** (0.4 mmol, 1equiv.), catalyst (10 mol%) and ligand (**L**) (12 mol%) in 3-4 mL DCM at room temperature. [b]Isolated yield of the product after column chromatography. [c]er was determined by chiralpak IA column using hexane and IPA as solvents.

Later, we curiously attempted intramolecular aza-Michael conjugate addition reaction with various bisoxazoline (BOX) ligands such as **L4** to **L8** and Cu(OTf)$_2$ as the Lewis acid catalyst at room temperature (Fig 5.1, entries 4 to 8, Table 5.1). To our delight, the reaction of **4a** in presence of 10 mol% of Cu(OTf)$_2$ and 12 mol% of BOX Ligand **L5** afforded the desired product (**5a**) in 95% yield with er 90:10 in 1.5 h (entry 5, Table 5.1). In order to find out the effect of Lewis acid on the rate of the reaction and enantioselectivity, we screened the reaction by using different Lewis acids such as MgBr$_2$, Ni(OTf)$_2$ and Zn(OTf)$_2$ in combination with **L5**. However, in all these cases the desired product (**5a**) was obtained with moderate to good enantioselectivity (up to er 79:21) (entries 9 to 11, Table 5.1).

Having obtained the initial results of catalytic system, in order to find out the influence of stereochemistry (*E* and *Z*) of starting material on the outcome of enantioselectivity of the reaction, we then carried out a reaction on (*E*)–isomer (**4'a**) using the

same reaction conditions that are used for the (*Z*)–isomer (**4a**) (entry 2, Table 5.2). Interestingly, both (*Z*)– and (*E*)–isomers showed the same pattern of cyclization and however, (*E*)–isomer afforded the product (**5a**) with slightly lower enantioselectivity [up to *er* 80:20] (entry 2, Table 5.2). The reaction with a mixture of both (*EZ*)–isomers (~40:60 ratio) showed relatively high enantioselectivity up to 88:12 (entry 3, Table 5.2). Further, in order to understand the effect of solvents on the enantioselectivity, the reaction of (*Z:E* **4a:4'a**)–mixture was explored in various solvents such as THF, ACN, Et$_2$O and Toluene. Solvents such as Et$_2$O and toluene found to be beneficial and useful for the formation of the product (**5a**) with good enantioselectivity (up to *er* 87:13). However, we observed that enantioselectivity slightly dropped in comparison to the reaction in DCM (entries 4 to 7, Table 5.2). On the basis of these initial results, experiments were further carried out to find out the effect of temperature on the enantioselectivity of the conjugate addition reaction.

The reactions were carried out on both (*Z*)-**4a** and (*EZ*)–mixture (**4a/4'a**) at three different temperatures *viz.* 0 °C, –25 °C and –40 °C. Low temperature screenings revealed that reactions of both (*Z*) and (*EZ*)–mixture independently showed that only a slight improvement in enantioselectivity (up to *er* 92:8) at 0 °C and –25 °C. Interestingly, in case of (*EZ*)–mixture at –25 °C, we observed that the reaction of (*Z*)–isomer was facile and only the (*Z*)–isomer underwent reaction smoothly, whereas (*E*)–isomer did not react even after prolonged reaction time (24 h) (entries 8-11, Table 5.2). The reaction of (*EZ*)–mixture (**4a/4'a**) at –40 °C did not undergo even after the prolonged reaction time and the starting materials were recovered (entry 12, Table 5.2).

On the basis of these exhaustive screening results, we found that the reaction of **4a/4'a** (***EZ* mixture)** in presence of 10 mol% of Cu(OTf)$_2$ with 12 mol% **L5** in dry DCM at room temperature gave the desired product **5a** in 95% with enantioselectivity 88:12. Based on these observations 10 mol% of Cu(OTf)$_2$ and 12 mol% of **L5** in dry DCM at room temperature proved to be the optimized reaction conditions for the effective enantioselective aza-Michael conjugate addition reaction.

Table 5.2: Optimization of reaction in various solvents and temperature for aza-Michael conjugate addition reaction[a]
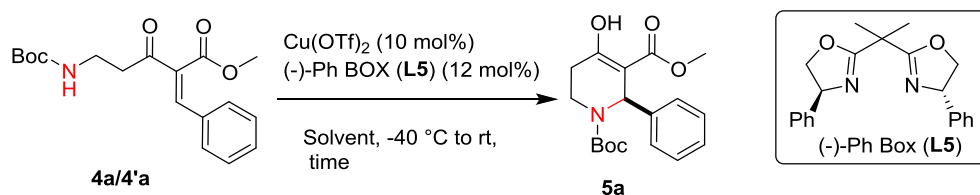
| S.No.	E/Z– (4'a/4a)	Temp (°C)	Solvent	Time (h)	Yield (%)[b]	er[c]
1	Z-Ph	Rt	DCM	1.5	92	90:10
2	E-Ph	rt	DCM	3	85	80:20
3	EZ-Ph	rt	DCM	2	92	88:12
4	EZ-Ph	rt	THF	24	48	83:17
5	EZ-Ph	rt	ACN	24	53	74:26
6	EZ-Ph	rt	Et$_2$O	24	82	87:13
7	EZ-Ph	rt	Toluene	24	86	85:15
8	EZ-Ph	0	DCM	18	77	82:8
9	Z-Ph	0	DCM	5	88	90:10
10	EZ-Ph	–25	DCM	24	46	92:8
11	Z-Ph	–25	DCM	15	84	92:8
12	EZ-Ph	–40	DCM	24	NR	---

[a]Reaction of **4a/4'a** (0.4 mmol, 1 equiv.) with Cu(OTf)$_2$ (10 mol%) and **L5** (12 mol%) in 3-4 mL dry solvent at room temperature. [b]Isolated yield of the product after column chromatography. [c]er was determined by chiralpak IC column using hexane and IPA as solvents.

It was evident from the NMR studies that the existence of rotamers is due to presence of N-Boc group, and this observation was further supported by earlier finding.[38] Hence, we decided to deprotect the Boc-group to simplify the spectrum there by avoiding rotameric peaks. ^{1}H-NMR spectrum of Boc-deprotected piperidine derivative (**6a**) was neat and revealed the existence of enolic form of salt and all peaks were well resolved.

In order to extend the scope and generality of the reaction, various (EZ)–alkylidene methyl β-ketoesters (E/Z ~40:60) (**4a/4'a** to **4c/4'c**) were subjected to intramolecular aza-Michael conjugate addition reaction under the optimized reaction conditions. Further the obtained product was subjected to subsequent deprotection of N-Boc-group with 4M HCl in dioxane to afford the corresponding piperidine derivatives (**6a-6c**) in very good yields up to
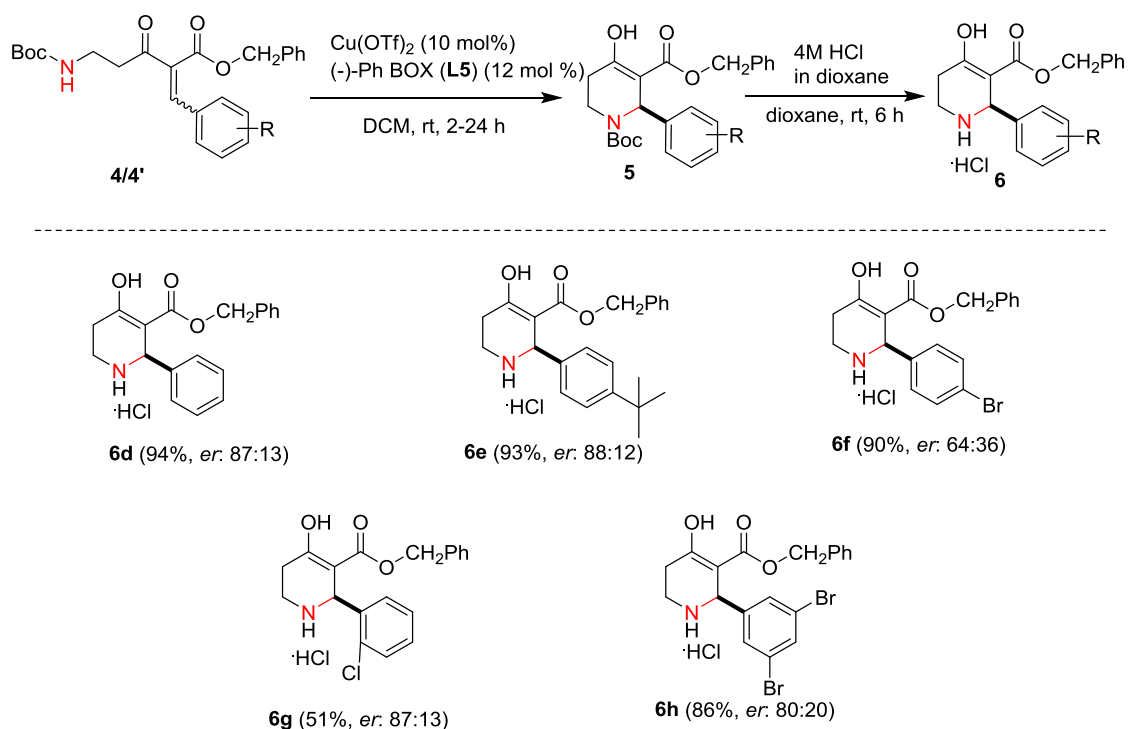
92% with good enantioselectivity (*er* up to 88:12) (Scheme 5.15). However, it was observed that the reaction with *o*-bromo alkylidene derivative (**4c/4'c**) resulted in the corresponding cyclized product (**6c**) in 48% yield. This is probably due to the poor reactivity of (*E*)–isomer (**4'c**) of (*EZ*)–mixture (**4c/4'c**) under the optimized reaction conditions.

Scheme 5.15: Substrate scope of various (*EZ*)–alkylidene methyl-*β*-ketoesters (**4/4'**)
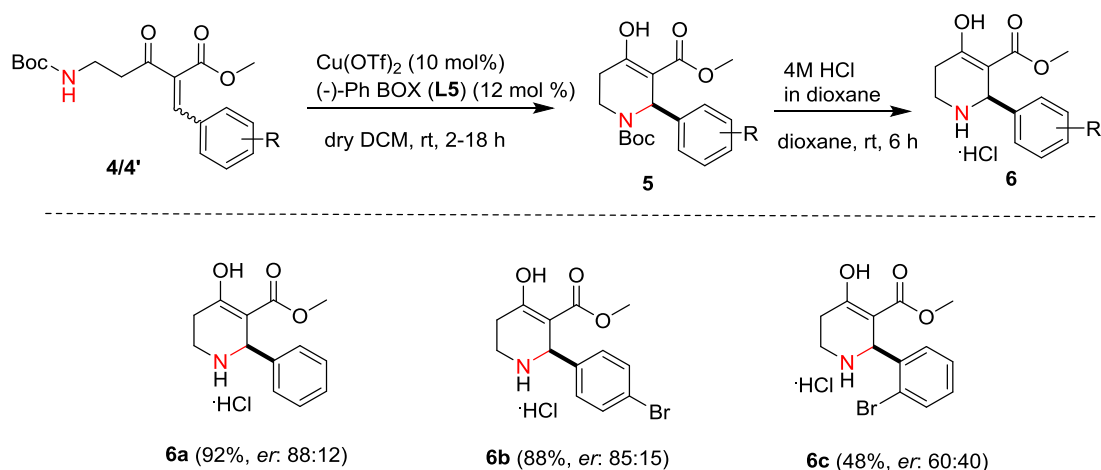

In order to know the effect of ester group on the enantioselectivity, various (*EZ*)–alkylidene benzyl *β*-ketoesters (**4d/4'd** to **4h/4'h**) were synthesized and they were subjected to the intramolecular aza-Michael conjugate addition reaction under the optimized reaction conditions. The corresponding piperidine derivatives (**6d-6h**) were obtained in very good yields and enantioselectivity (up to 94% yield, *er* up to 87:13) (Scheme 5.16). It was observed that the reaction with *o*-chloro alkylidene derivative (**4g/4'g**) resulted in the corresponding cyclized product (**6g**) in 48% yield probably due to the poor reactivity of (*E*)–isomer of (*EZ*)–mixture under the optimized reaction conditions. We also observed that substrates containing *para*-substitution on benzene ring showed good reactivity when compared to other substitutions to give the desired product in good yields and enantioselectivity. We believe that steric factor emanating from *o*-substituent on benzene ring in alkylidene *β*-keto ester plays a significant role in decreasing the reactivity of (*E*)–isomer.

Scheme 5.16: Substrate scope of various (*EZ*)–alkylidene benzyl-*β*-ketoesters (**4/4'**)

6d (94%, *er*: 87:13)

6e (93%, *er*: 88:12)

6f (90%, *er*: 64:36)

6g (51%, *er*: 87:13)

6h (86%, *er*: 80:20)

Further, in order to expand the scope and practicality of the method we also carried out the reaction of corresponding *tert*-butyl ester of alkylidene anthranlilic *β*-ketoester (**7**) under the optimized reaction conditions. However, the starting material **7** was completely unreactive under these reaction conditions. Later, the reaction of **7** in presence of catalytic amount of DBU (10 mol%) under the reaction conditions resulted in racemic quinoline derivative in 92% yield.

Scheme 5.17: Test reaction with *tert*-butyl esters of alkylidene anthranilic *β*-ketoester (**7**)
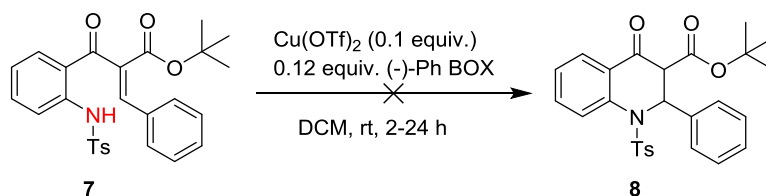
5.4 Conclusions

In conclusion, we have developed an efficient enantioselective synthesis of substituted piperidines using catalytic amount of copper (II) triflate (10 mol%) as a Lewis acid catalyst and bis-oxazoline (12 mol%) as chiral ligand. We explored the intramolecular aza-Michael addition of carbamate on alkylidene *β*-keto methyl/benzyl esters to synthesize various functionalized 4-oxo-2-arylpiperidine-3-carboxylate derivatives with high enantioselectivity (up to *er* 88:12) in good to excellent yields.

5.5 Experimental Section

General: All starting materials were obtained from Aldrich, Acros, Merck and were used as obtained unless otherwise mentioned.All reactions were carried out with distilled and dried solvents under an atmosphere of dry N_2 and oven-dried glassware. All solvents CH_2Cl_2, Toluene, EtOAc, Pet. ether, *n*-Pentane were purified and dried by using regular procedures using "Purification of Laboratory Chemicals" by Perrin and stored over activated 4 Å molecular sieves. All compounds were purified by using Column Chromatographic technique on 100-200 mesh size silica gel. Analytical Thin-layer chromatography (TLC) was performed using Merck silica gel 60 GF_{254} pre-coated aluminum backed plates (2.5 mm) with spot detection under UV light or ninhydrin, PMA or vanillin. ^{1}H NMR and ^{13}C NMR were recorded in CDCl$_3$ or DMSo-*d6* on 400 MHz for ^{1}H and ^{13}C (100 MHz for ^{13}C). Chemical shifts in ^{1}H NMR and ^{13}C NMR spectra are reported as δ in ppm with the solvent resonance as the internal standard, Coupling constants (*J*-values) are given in Hz. ^{1}H NMR data were reported in the order of chemical shift, multiplicity (s, singlet; d, doublet; t, triplet; m, multiplet; dt, doublet of triplet), coupling constant in hertz (Hz) and number of protons. Specific rotations were recorded using CHCl$_3$ as a solvent (Rudolph Analytical Research). High-Resolution mass spectra were obtained from HRMS-ESI-TOF. IR spectra of neat samples were recorded using FT-IR spectrophotometer and reported in cm^{-1}. All melting points were measured in open glass capillary and values are uncorrected. The enantiomeric ratio was calculated by injecting the samples into HPLC using Chiralpak IA column, using n-hexane and IPA as an eluent.

General experimental procedure for the aza-Michael addition reaction of Piperidones: Synthesis of Piperidine derivative (5)

Cu(OTf)$_2$ (10 mol%) and bisoxazoline ligand **L5** (12 mol%) were charged in a dried 25 mL round bottomed flask and evacuated the flask under high vaccum for 30–45 minutes. To this mixture, 2 mL of dry DCM was added under argon atmosphere and stirred the reaction mixture at room temperature for 30-45 minutes. To this stirred solution, Knoevenagel product **4a/4'a** (133 mg, 0.4 mmol) in dry DCM (2 mL) was added under dry condition at room temperature and stirred the resulting reaction mixture till the completition of the reaction (2 h) as monitored by TLC (Scheme 5.15 and 5.16). After completion, the reaction mixture was quenched with H$_2$O (1 mL) and extracted with DCM (2x5 mL). The combined organic layers were dried over Na$_2$SO$_4$ and concentrated under vacuum. The resulting residue was purified by column chromatography over silica gel eluting with Pet. ether/EtOAc (97:3 to 94:6) affording **5a** as a white solid (127 mg, 95%)

General Experimental procedure for the Deprotection of Boc-group:

To a stirred solution of enantiomeric mixture **5a** (116 mg, 0.35 mmol) in 1 mL DCM, 2.5 mL of 4 M HCl in dioxane solution was added at room temperature and the reaction mixture was allowed to stir at room temperature for 5-6 h. After the completion of reaction as monitored by TLC, dioxane was evaporated on rotary evaporator. Traces of dioxane was removed under high vacuum. Then the reaction mixture was washed with dry *n*-pentane for 4–5 times (4–5 mL for each wash), to afford compound **6a** (87 mg) as a white powder in 92% yield.

Methyl-4-hydroxy-2-phenyl-1,2,5,6-tetrahydropyridine-3-carboxylate hydrochloride (6a):
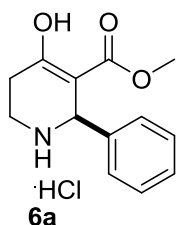
White solid (87 mg, 92%); R_f = 0.65 (20% MeOH + CHCl$_3$); [α]$^{25}_D$ −100.20 (c 1, CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$) δ 12.47 (s, 1H), 10.57 (bs, 1H), 9.79 (bs, 1H), 7.49 – 7.36 (m, 5H), 5.43 (s, 1H), 3.59 (s, 3H), 3.15 – 3.03 (m, 3H), 2.63 (d, J = 13.8 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 170.2, 170.0, 134.6, 129.8, 129.3, 129.1, 95.3, 53.7, 52.2, 35.6, 25.8; HRMS (ESI–TOF) m/z Calcd. for C$_{13}$H$_{16}$NO$_3$ [M + H]$^+$ = 234.1130, observed = 234.1136.

**Methyl-2-(4-bromophenyl)-4-hydroxy-1,2,5,6-tetrahydropyridine-3-carboxylate hydrochloride (6b):**
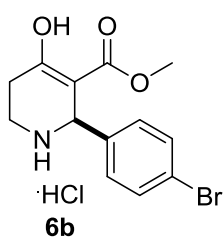
White solid (107 mg, 88%); R_f = 0.60 (20% MeOH + CHCl$_3$); [α]^{25}$_D$ −83.20 (c 1, CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$) δ 12.47 (s, 1H), 10.60 (bs, 1H), 9.89 (bs, 1H), 7.55 (d, J = 7.3 Hz, 2H), 7.38 (d, J = 7.3 Hz, 2H), 5.36 (s, 1H), 3.60 (s, 3H), 3.12 – 3.01 (m, 3H), 2.68 (d, J = 12.8 Hz, 1H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 170.4, 169.8, 133.7, 132.4, 131.0, 124.3, 95.1, 53.3, 52.4, 35.9, 25.9; HRMS (ESI–TOF) m/z Calcd. for C$_{13}$H$_{15}$BrNO$_3$ [M + H]$^+$ = 312.0235, observed = 312.0235.

Methyl-2-(2-bromophenyl)-4-hydroxy-1,2,5,6-tetrahydropyridine-3-carboxylate hydrochloride (6c):
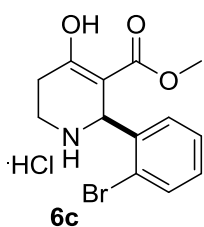
White solid (59 mg, 48%); R_f = 0.55 (20% MeOH + CHCl$_3$); [α]^{25}$_D$ −68.50 (c 1, CHCl$_3$); ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.02 (s, 1H), 11.02 (bs, 1H), 9.16 (bs, 1H), 7.76 (d, J = 7.7 Hz, 1H), 7.43 (m,3H), 5.61 (s, 1H), 3.52 (s, 3H), 3.23 (dd, J = 12.5, 5.6 Hz, 1H), 3.06 – 2.99 (m, 1H), 2.89 – 2.80 (m, 1H), 2.74 – 2.69 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.6, 168.6, 134.5, 133.3, 131.4, 130.8, 128.1 125.1, 95.1, 66.4, 52.1, 52.0, 35.1, 25.5 (NMR spectra of compound contains trace amount of 1,4-dioxane); HRMS (ESI–TOF) m/z Calcd. for C$_{13}$H$_{15}$BrNO$_3$ [M + H]$^+$ = 312.0235, observed = 312.0237.

**Benzyl-4-hydroxy-2-phenyl-1,2,5,6-tetrahydropyridine-3-carboxylate hydrochloride (6d):**
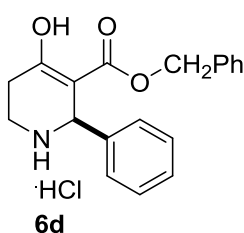
White solid (114 mg, 94%); R_f = 0.55 (10% MeOH + CHCl$_3$); [α]^{25}$_D$ −158.80 (c 1, CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$) δ 12.39 (s, 1H), 10.56 (bs, 1H), 9.77 (bs, 1H), 7.42 – 7.34 (m, 5H), 7.24 – 7.13 (m, 3H), 6.75 (d, J = 7.3 Hz, 2H), 5.36 (s, 1H), 5.11 (d, J = 12.3 Hz, 1H), 4.90 (d, J = 12.3 Hz, 1H), 3.06 – 2.64 (m, 4H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 170.4, 169.3, 134.8, 134.7, 129.7, 129.5, 129.1, 128.5, 128.3, 127.6, 95.5, 66.7, 54.0, 36.0, 26.0. (NMR spectra of compound contains trace amount of 1,4-dioxane); HRMS (ESI–TOF) m/z Calcd. for C$_{19}$H$_{20}$NO$_3$ [M + H]$^+$ = 310.1443, observed = 310.1447.

Benzyl-2-(4-(tert-butyl)phenyl)-4-hydroxy-1,2,5,6-tetrahydropyridine-3-carboxylate hydrochloride (6e):
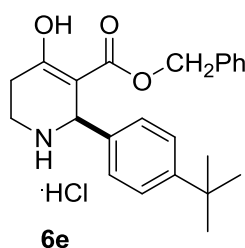
White solid (131 mg, 93%); R_f = 0.45 (8% MeOH + CHCl$_3$); $[\alpha]^{25}_D$ −123.60 (c 1, CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$) δ 12.39 (s, 1H), 10.57 (s, 1H), 9.73 (s, 1H), 7.22 − 7.11 (s, 3H), 6.73 (d, J = 7.3 Hz, 2H), 5.43 (s, 1H), 5.16 (d, J = 12.5 Hz, 1H), 4.87 (d, J = 12.5 Hz, 1H), 3.08 (s, 3H), 2.61 (d, J = 9.9 Hz, 1H), 1.31 (s, 9H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 170.2, 169.4, 152.9, 134.9, 131.6, 129.2, 128.4, 128.2, 127.4, 126.0, 95.6, 66.6, 53.4, 35.6, 34.8, 31.4, 26.0; HRMS (ESI–TOF) m/z Calcd. for C$_{23}$H$_{28}$NO$_3$ [M + H]$^+$ = 366.2069, observed = 366.2065.

**Benzyl-2-(4-bromophenyl)-4-hydroxy-1,2,5,6-tetrahydropyridine-3-carboxylate hydrochloride (6f):**
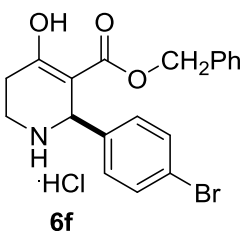
White solid (134 mg, 90%); R_f = 0.65 (10% MeOH + CHCl$_3$); $[\alpha]^{25}_D$ −129.40 (c 1, CHCl$_3$); ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.12 (s, 1H), 10.53 (bs, 1H), 9.53 (bs, 1H), 7.61 (d, J = 8.4 Hz, 3H), 7.44 (d, J = 8.4 Hz, 2H), 7.27 − 7.18(m, 3H), 6.82 (d, J = 7.0 Hz, 2H), 5.43 (s, 1H), 5.16 (d, J = 12.9 Hz, 1H), 4.97 (d, J = 12.9 Hz, 1H), 3.22 − 3.18 (m, 1H), 3.03 − 2.96 (m, 1H), 2.87 − 2.79 (m, 1H), 2.74 − 2.69 (m, 1H); ^{13}C NMR (100 MHz, DMSO) δ 170.3, 168.3, 135.2, 135.1, 131.7, 131.5, 128.1, 127.9, 127.0, 122.6, 95.2, 65.7, 52.2, 35.3, 25.6. HRMS (ESI–TOF) m/z Calcd. for C$_{19}$H$_{19}$BrNO$_3$ [M + H]$^+$ = 344.1053, observed = 344.1057.

Benzyl-2-(2-chlorophenyl)-4-hydroxy-1,2,5,6-tetrahydropyridine-3-carboxylate hydrochloride (6g):
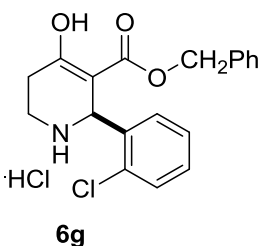
White solid (68 mg, 51%); R_f = 0.55 (8% MeOH + CHCl$_3$); $[\alpha]^{25}_D$ −43.60 (c 1, CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$) δ 12.36 (s, 1H), 10.63 (s, 1H), 9.63 (s, 1H), 7.43 − 7.15 (m, 7H), 6.78 (d, J = 7.2 Hz, 2H), 5.86 (s, 1H), 5.11 (d, J = 12.3 Hz, 1H), 4.88 (d, J = 12.3 Hz, 1H), 3.54 − 2.52 (m, 4H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 170.7, 169.0, 135.3, 134.6, 132.7, 131.1, 130.7, 130.0, 128.4, 128.3, 127.6, 127.3, 95.2, 66.7, 50.4, 36.4, 26.0; HRMS (ESI–TOF) m/z Calcd. for C$_{19}$H$_{19}$ClNO$_3$ [M + H]$^+$ = 379.0742, observed = 379.0746.

Benzyl-2-(3,5-dibromophenyl)-4-hydroxy-1,2,5,6-tetrahydropyridine-3-carboxylate hydrochloride (6h):
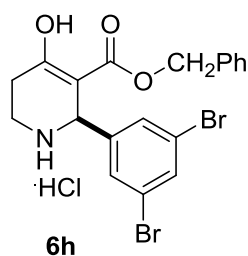
White solid (152 mg, 86%); R_f = 0.50 (10% MeOH + CHCl$_3$); [α]$^{25}_D$ −91.40 (c 1, CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$) δ 12.42 (s, 1H), 10.65 (bs, 1H), 10.03 (bs, 1H), 7.61 (s, 1H), 7.53 (s, 2H), 7.30 – 7.24 (m, 3H), 6.86 (d, J = 6.1 Hz, 2H), 5.29 (s, 1H), 5.20 (d, J = 11.8 Hz, 1H), 4.89 (d, J = 11.8 Hz, 1H), 3.21 – 2.74 (m, 4H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 171.1, 168.8, 138.7, 135.5, 134.3, 131.4, 128.8, 128.7, 127.8, 123.6, 94.6, 67.2, 67.1, 53.0, 36.4, 26.0. (NMR spectra of compound contains trace amount of 1,4-dioxane); HRMS (ESI–TOF) m/z Calcd. for C$_{19}$H$_{18}$Br$_2$NO$_3$ [M + H]$^+$ = 465.9653, observed = 465.9656.

5.6 Appendix IV: ^{1}H and ^{13}C spectral data and HPLC chromatograms of representative compounds

compound No.	Fig AIV.X	data	page No.
6a	Fig AIV.1 and AIV.2	^{1}H-^{13}C	169
6b	Fig AIV.3 and AIV.4	^{1}H-^{13}C	170
6c	Fig AIV.5 and AIV.6	^{1}H-^{13}C	171
6d	Fig AIV.7 and AIV.8	^{1}H-^{13}C	172
6e	Fig AIV.9 and AIV.10	^{1}H-^{13}C	173
5a	Fig AIV.11 and AIV.12	HPLC	174
5h	Fig AIV.13 and AIV.14	HPLC	175
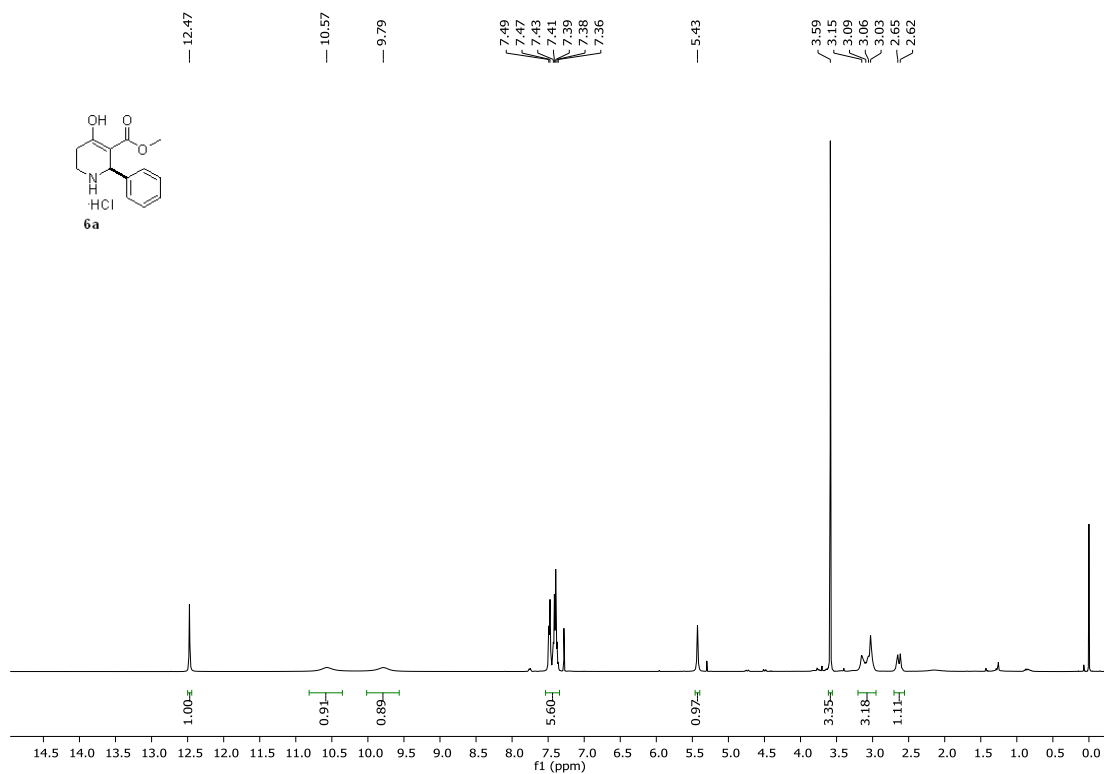
Fig AIV.1: ^{1}H NMR (400 MHz, CDCl$_3$) spectrum of compound **6a**
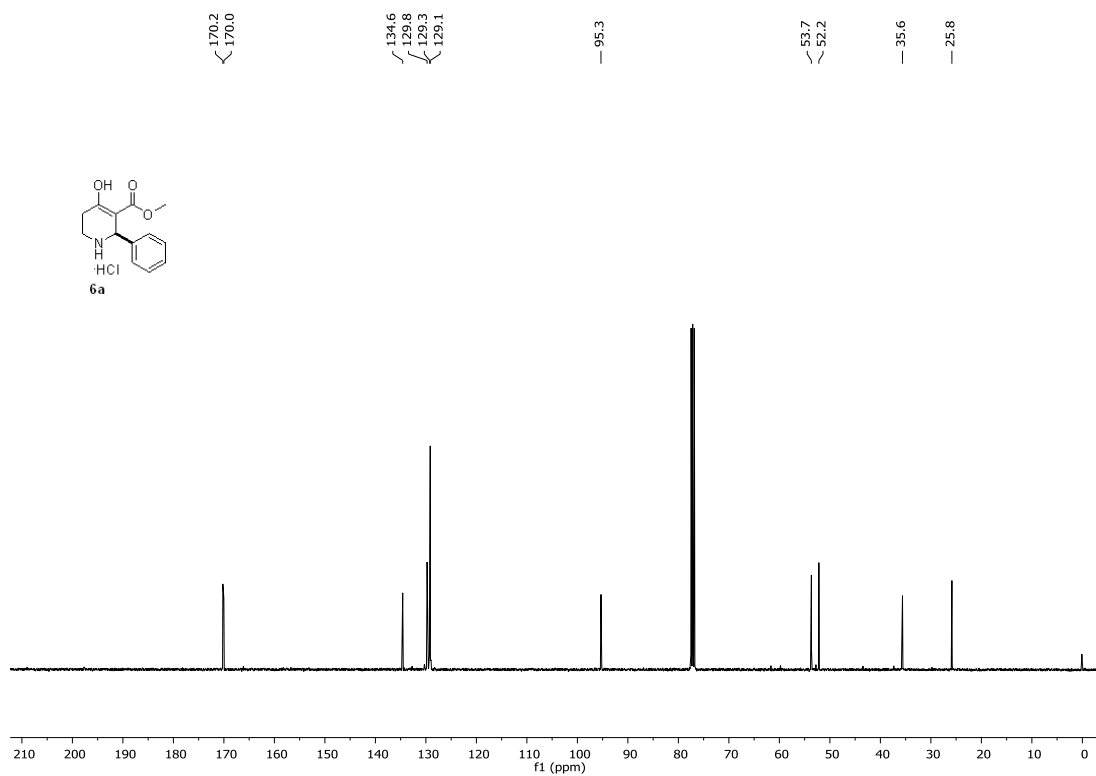
Fig AIV.2: ^{13}C NMR (100 MHz, CDCl$_3$) spectrum of compound **6a**

169

Fig AIV.3: ^{1}H NMR (400 MHz, CDCl$_3$) spectrum of compound **6b**
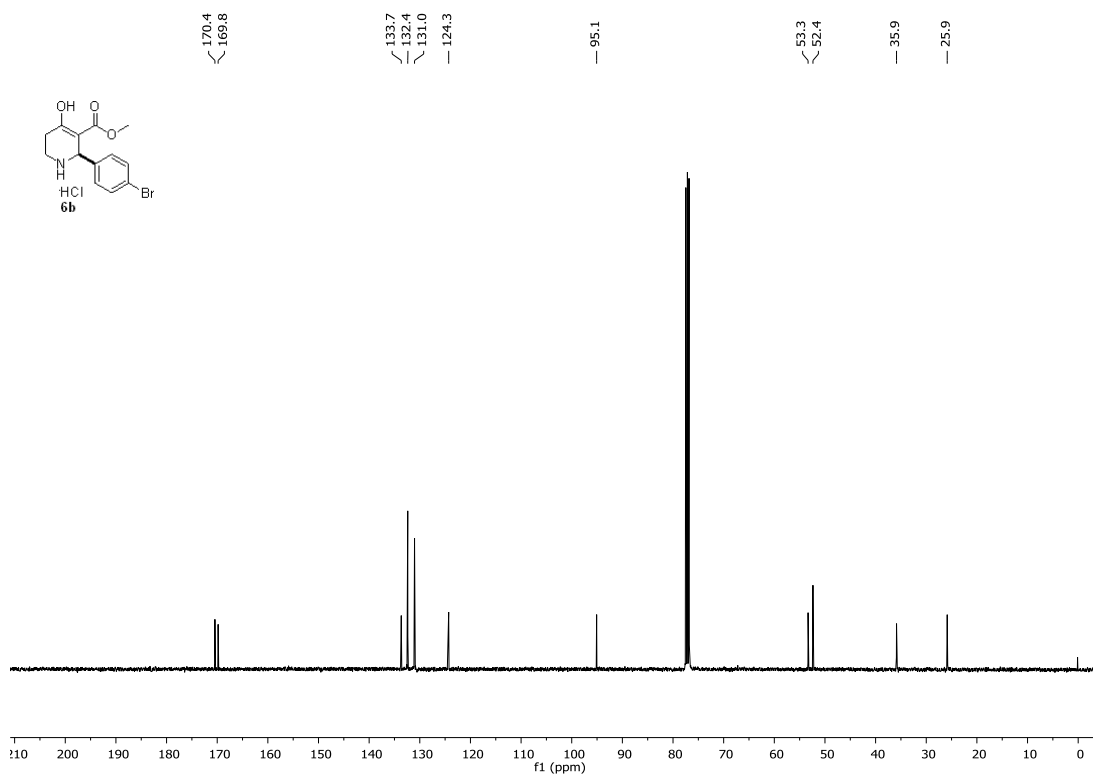
Fig AIV.4: ^{13}C NMR (100 MHz, CDCl$_3$) spectrum of compound **6b**

170
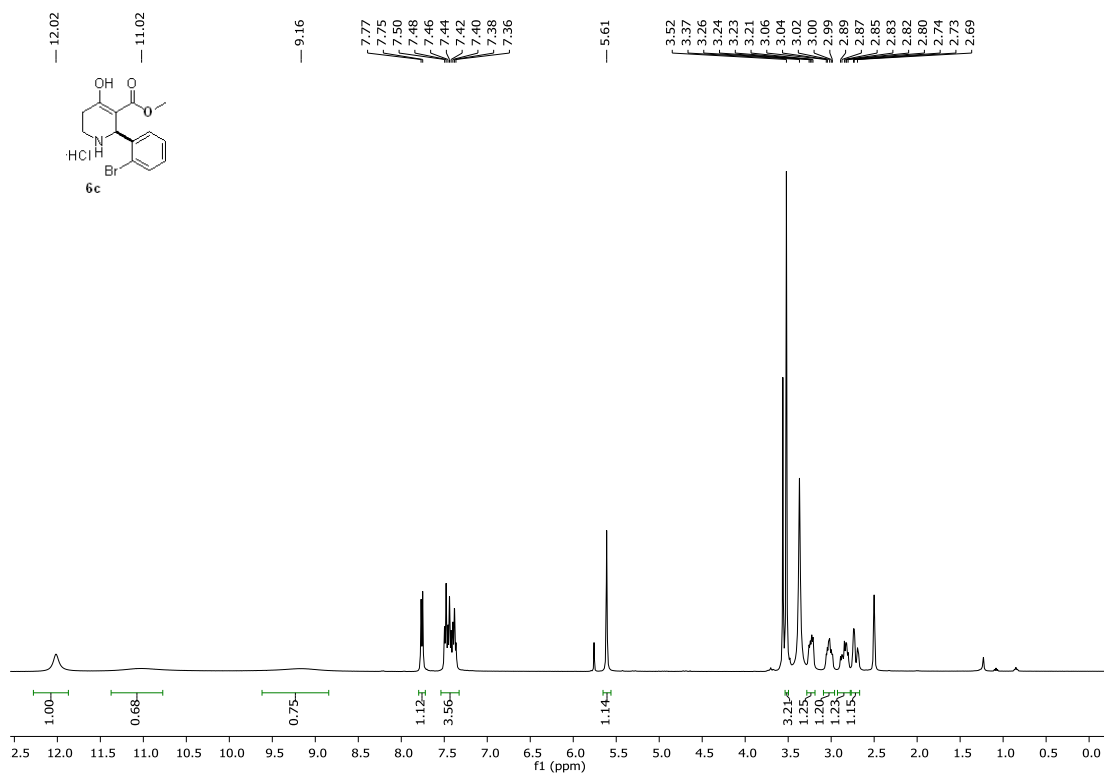
Fig AIV.5: ^{1}H NMR (400 MHz, CDCl$_3$) spectrum of compound **6c**
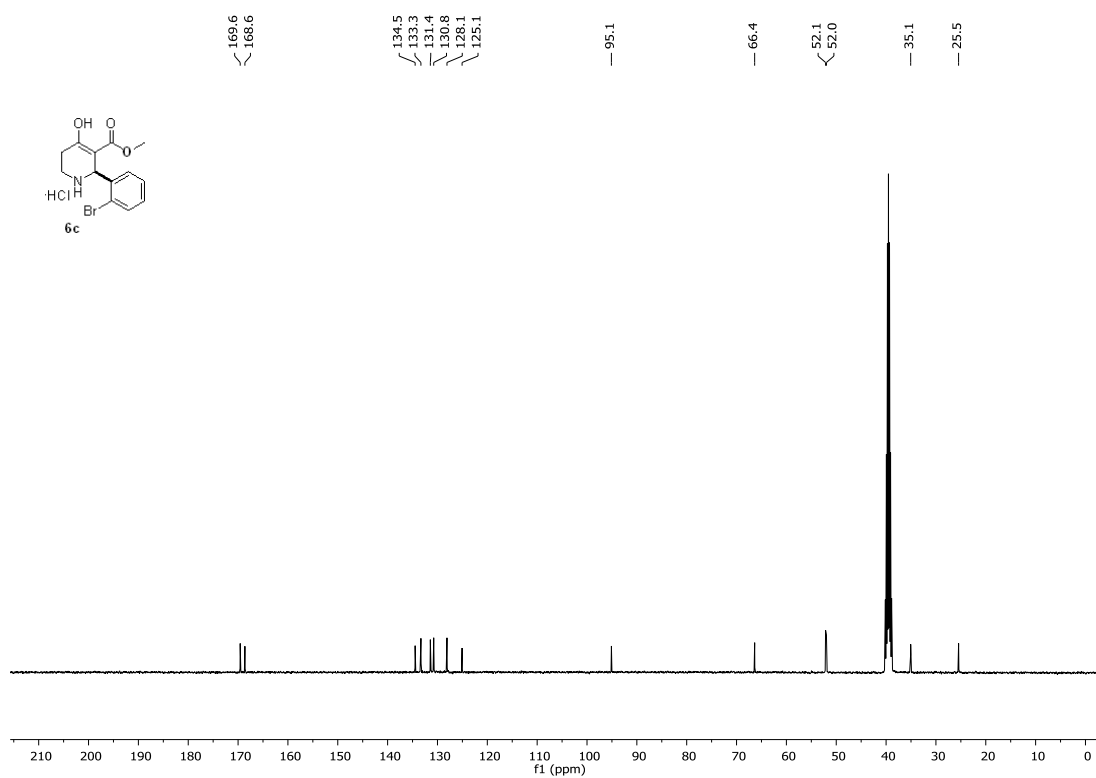
Fig AIV.6: ^{13}C NMR (100 MHz, CDCl$_3$) spectrum of compound **6c**

171
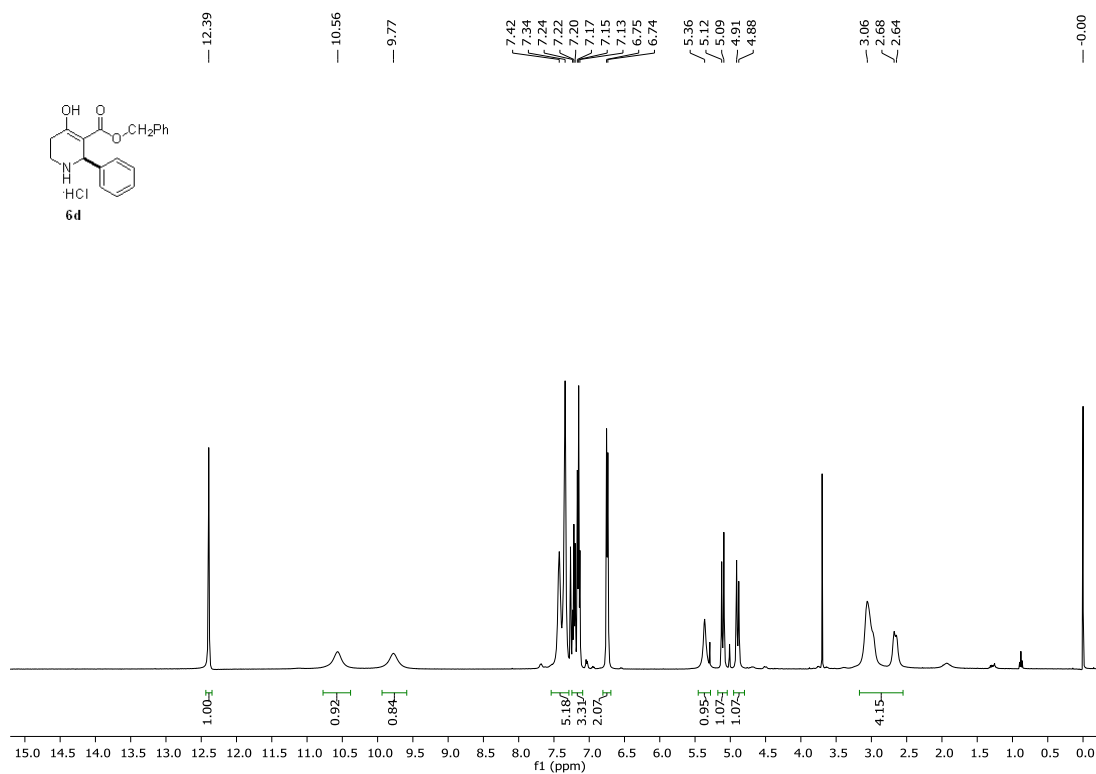
Fig AIV.7: ^{1}H NMR (400 MHz, CDCl$_3$) spectrum of compound **6d**
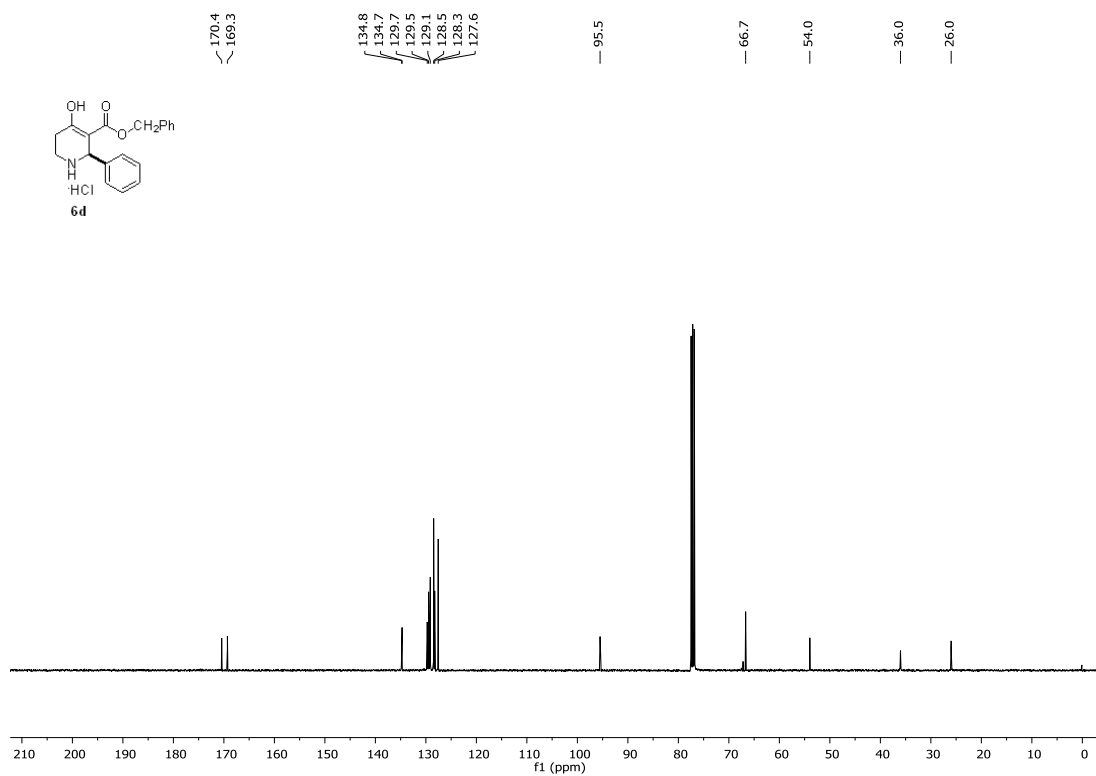
Fig AIV.8: ^{13}C NMR (100 MHz, CDCl$_3$) spectrum of compound **6d**

172
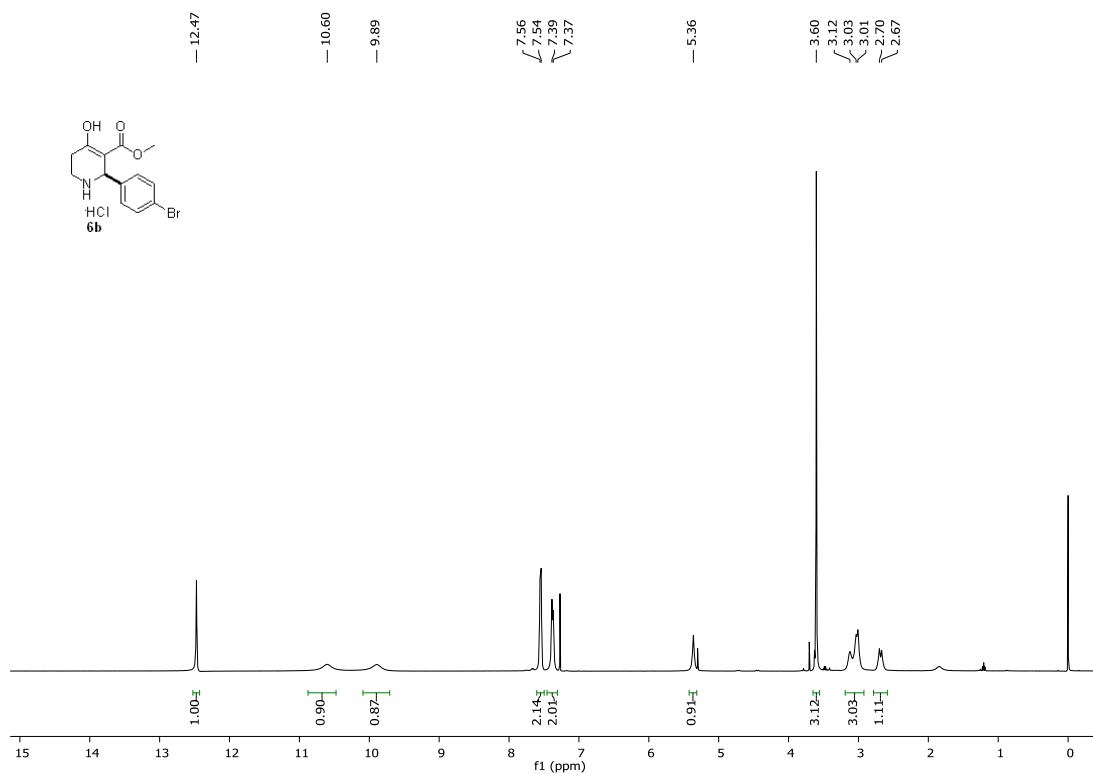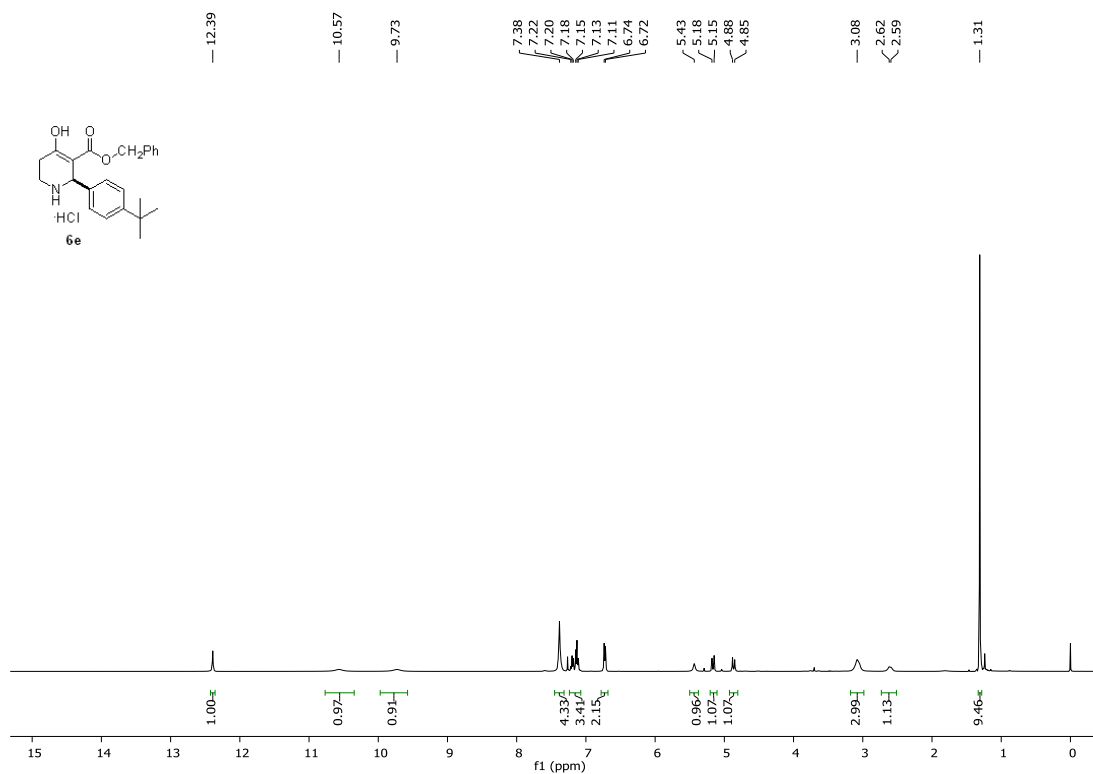
Fig AIV.9: ^{1}H NMR (400 MHz, CDCl$_3$) spectrum of compound **6e**
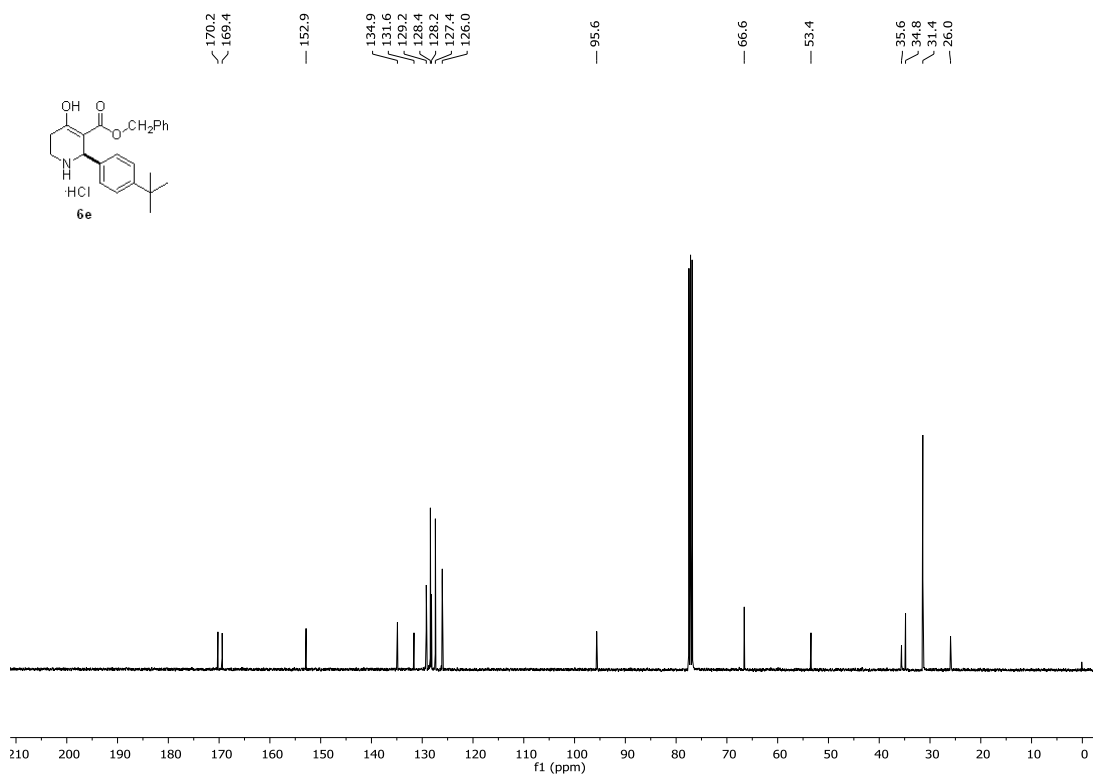
Fig AIV.10: ^{13}C NMR (100 MHz, CDCl$_3$) spectrum of compound **6e**

HPLC Chromatograms of *N*-Boc Piperidines

HPLC analysis was carried by using chiralpak IC, eluenet: *n*-hexane+IPA (90:10); Flow rate: 0.3 mL/min, sample was prepared in 5% IPA in *n*-hexane.

HPLC Data:
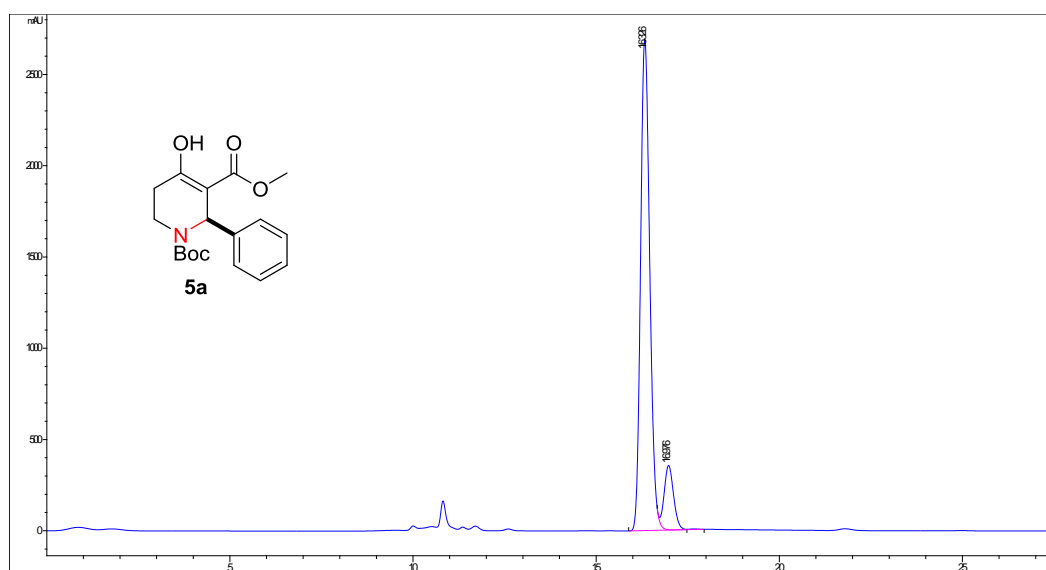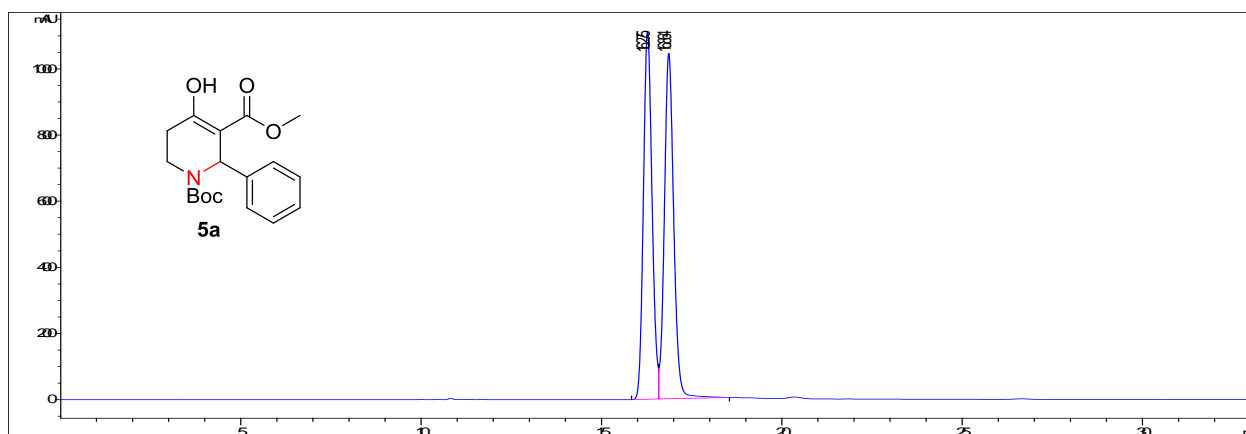
#	Time	Area	Height	Width	Area%	Symmetry
1	16.326	46993.4	2691.9	0.2694	88.288	0.796
2	16.976	6234.1	352.5	0.2743	11.712	0.823

Fig AIV.11: HPLC profile of compound **5a**
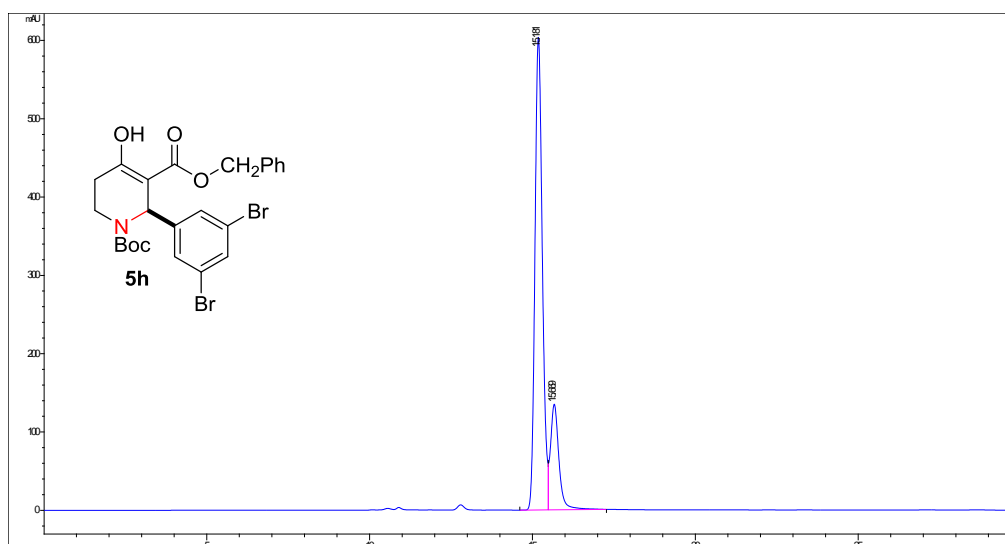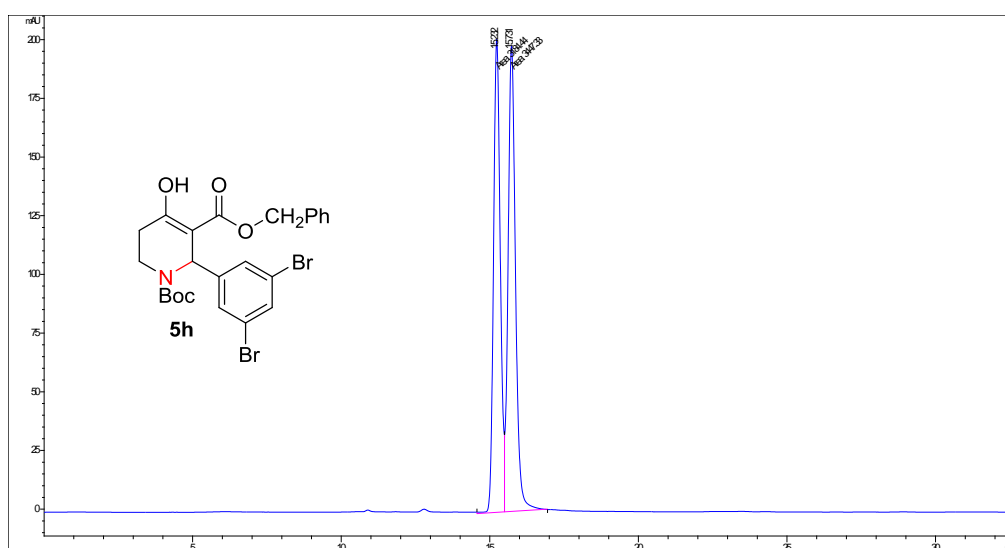
#	Time	Area	Height	Width	Area%	Symmetry
1	15.181	9532.4	603.7	0.2422	79.597	0.821
2	15.669	2443.4	134.9	0.2713	20.403	0.726

Fig AIII.12: HPLC profile of compound **5h**

5.7 References

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FeCl$_3$·6H$_2$O catalyzed diastereoselective synthesis of (L)-menthyl 4-oxo-2-arylpiperidine-3-carboxylates

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ABSTRACT

An efficient diastereoselective synthesis of substituted piperidines is accomplished by using catalytic amount of FeCl$_3$·6H$_2$O via intramolecular aza-Michael addition of carbamate on alkylidene β-keto (L)-menthyl esters in a very short time.

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Introduction

Piperidine ring system is a naturally occurring scaffold and is core to many bioactive natural products.[1,2] It is also the most common structural feature of many drugs and pharmaceutical agents.[3a,3b] Prevalence of piperidine moieties in a wide range of compounds makes them privileged structural scaffolds. Along with their natural counterparts, synthetic analogues particularly 2- and 2,6-disubstituted piperidines are of greater interest in the pharmaceutical industries because these exhibit wide range of biological activities.[3c,3d] Undoubtedly development of stereoselective and eco-friendly stereocontrolled strategies to access substituted piperidines remains a challenge because of their synthetic value. Different methods have been reported for the asymmetric synthesis of substituted piperidine derivatives.[4a] Chiral auxiliaries have been employed for the synthesis of piperidine core as one of the strategies.[4b–4e] Some of the most used protocols are CN (*R, S*) method,[4a,5] use of chiral lactams[6] and aza Diels-Alder methodology.[7] Given the biological importance and synthetic value, we got interested in exploring new strategy for the synthesis of chiral piperidine derivatives. For stereoselective synthesis of substituted piperidines, an intramolecular aza-Michael addition of carbamate to a suitably located and activated alkene moiety appears to be an effective approach. However, major challenge is achieving the effective and efficient cyclization with good stereoselectivity by activating the double bond. Lewis acid catalyzed Michael addition reactions are proved to be more chemoselective and effective compared to classic base mediated reactions as the latter suffer from undesired side reactions. Though it is known that Lewis acids activate the system by chelation or by coordination,[8c] it is tricky to choose a particular Lewis acid for the effective transformation and conjugate addition of carbamates. This prompted us to explore the asymmetric synthesis by using chiral auxiliary under mild Lewis acid catalytic system. Herein, we wish to report the asymmetric synthesis of substituted piperidines catalyzed by FeCl$_3$·6H$_2$O using (L)-menthol as chiral auxiliary.

Results and discussion
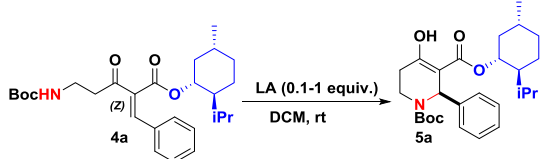
We envisioned that alkylidene β-keto-(L)-menthyl esters with suitably placed carbamate could be used as a precursor for the cyclization. Activation of the double bond by appropriate Lewis acid would initiate the subsequent intramolecular cyclization. It was presumed that natural menthyl ester would control the stereochemical outcome. To validate our assumption we prepared (L)-menthyl alkylidene β-keto ester **4** from the corresponding (L)-menthyl-β-keto ester **3**.[9]

We chose to explore the intramolecular cyclization of *Z*-isomer of (L)-menthyl alkylidene β-keto ester **4a** using different Lewis acids in DCM as a test bed to optimize the process (Table 1). Initially we screened various anhydrous Lewis acids (0.1–1 equiv.) at room temperature in dichloromethane (see entry 1–10, Table 1). We observed that very few Lewis acids facilitated the intramolec-

Table 1
Screening of Lewis acid catalysts for optimizing the aza-Michael addition reaction.

Entry	LA (catalyst)[a]	dr (%)[b]	Time (h)	Yield[c] (%)
1	FeCl$_3$	51:49	5 min	96
2	CoCl$_2$	–	4 h	NR
3	CeCl$_3$	–	4 h	Trace
4	Sc(OTf)$_3$	39:61	2 h	90
5	Cu(OAc)$_2$	–	4 h	NR
6	Zn(OAc)$_2$	–	4 h	NR
7	CuSO$_4$	–	4 h	NR
8	Cu(I)Br	–	4 h	NR
9	CoCl$_2$	–	4 h	NR
10	CuCl$_2$	34:64	3 h	85
11	FeCl$_3$·6H$_2$O	24:76	10 min	96
12	**FeCl$_3$·6H$_2$O**	**23:77**	**15 min**	**98**
13	FeCl$_2$·4H$_2$O	–	4 h	Trace
14	CeCl$_3$·7H$_2$O	–	4 h	Trace
15	RuCl$_3$·XH$_2$O	25:75	4 h	85
16	RhCl$_3$·XH$_2$O	–	4 h	Trace
17	LaCl$_3$·7H$_2$O	–	4 h	NR
18	DyCl$_3$·7H$_2$O	–	4 h	NR
19	NdCl$_3$·7H$_2$O	–	4 h	NR
20	No Catalyst	–	24 h	NR

Initial optimized reaction conditions has been highlighted in bold.
[a] Reactions were performed with 1equiv. of Lewis acids (LA) in DCM (entry 1–3, 5–11, 14) and reactions were performed with 0.1 equiv (10 mol%) of LA in DCM (entry 4, 12–13, 15–19).
[b] dr were calculated by HPLC using chiralpak IA column.
[c] Isolated yield of the product after column chromatography, NR – No Reaction occurred. rt ∼28 °C.

ular cyclization leading to **5a**. Interestingly, FeCl$_3$ (1 equiv.) catalyzed the desired transformation in short time (5 min) to afford the desired piperidine derivative **5a** in excellent yield (96%, see entry 1, Table 1). Although both FeCl$_3$ and Sc(OTf)$_3$ catalyzed the cyclization yet reactions proceeded with poor diastereoselectivity with different reaction times. Later we curiously attempted the reactions with hydrated Lewis acids. Interestingly after screening several hydrated Lewis acids (entry 11–19) FeCl$_3$·6H$_2$O was proved to be a superior catalyst and the cyclization proceeded with good diastereoselectivity. Encouraged by this we attempted the reaction
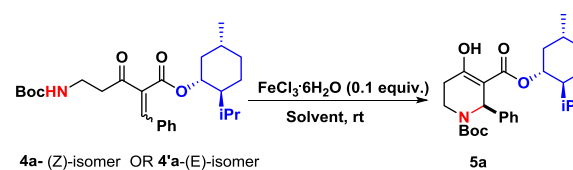
with lower catalytic loading of (0.1 equiv or 10 mol%) of FeCl$_3$·6H$_2$O and it is gratifying to note that reaction proceeded smoothly (15 min) with an excellent yield with good diastereoselectivity (entry 12). FeCl$_3$·6H$_2$O was relatively slow in catalyzing the reaction, however resulted in good diastereoselectivity. We surmise that anhydrous FeCl$_3$, being a strong Lewis acid, was quick in catalyzing the reaction resulting in poor diastereoselectivity. Interestingly FeCl$_2$·4H$_2$O (entry 13) did not catalyze the reaction. We also observed that reaction did not proceed in the absence of catalyst (entry 20). To the best of our knowledge FeCl$_3$·6H$_2$O has been explored for the first time for intramolecular aza-Michael addition.

Cyclization of both Z (**4a**) and E (**4′a**) isomers were studied independently in different solvents.[10] Screening of various solvents (see Table 2) revealed that dichloromethane as well as toluene were the best solvents as Z-isomer cyclized with good diastereoselectivity in excellent yields, however we observed that corresponding E-isomer **4′a** reacted slowly under the optimized reaction condition to yield cyclized product with lower diastereoselectivity. We believe that slow reactivity of E-isomer is probably due to the steric and electronic factors. Reaction was sluggish in polar solvents like MeOH, EtOH and in aprotic polar solvents such as DMF and DMSO reaction did not proceed even after prolonged reaction time. In order to study the reaction scope, various alkylidene β-keto menthyl esters (**4b–4q**) were prepared and the corresponding major Z-isomers were explored for the reactions.

Further, we observed that compounds **4a** (Ph), **4b** (4-Br), **4c** (4-NO$_2$) when treated with FeCl$_3$·6H$_2$O in DCM as well as in toluene at room temperature (∼28 °C) resulted in the corresponding piperidine derivatives (**5a**, **5b**, **5c**) with variable diastereoselectivity. However, when the reactions were carried out at 0 to 15 °C, starting materials did not react even after prolonged reaction time. Gratifyingly when we carried out the reactions at 20 °C in toluene or DCM, reactions proceeded with improved diastereoselectivity with excellent yields (see Appendix-II, ESI). Based on these findings, optimized reaction condition [FeCl$_3$·6H$_2$O (0.1 equiv. or 10 mol%), toluene, 20 °C] was employed for the further studies.

In order to expand the reaction scope and for the generality of this method, various (Z)-alkylidene β-keto menthyl esters were examined for cyclization. Various (L)-menthyl alkylidene β-ketoesters (Z-isomer of **4d–4q**) were subjected to cyclization under optimized reaction conditions to afford the corresponding piperidine derivatives (**5d–5q**) in excellent yields. It was found that regardless of their electronic nature, functional groups on the substrates tolerated the reaction conditions. It is gratifying to note that we

Table 2
Optimization of the reaction for the E and Z–isomers in different solvents.[a]

Entry	Solvent	dr (%)[b] Time (min/h) (**4a–5a**)	Yield (%)[c]	dr (%)[b] Time (min/h) (**4′a–5a**)	Yield (%)[c]
1	DCM	23:77 (15 min)	98	66:34 (40 min)	96
2	CHCl$_3$	23:77 (15 min)	98	65:35 (45 min)	94
3	Toluene	22:78 (15 min)	98	70:30 (4 h)	95
4	EA	22:78 (4 h)	70	56:44 (4 h)	62
5	Acetone	21:79 (4 h)	65	60:40 (4 h)	58
6	DMF	NR (12 h)	–	NR (12 h)	–
7	DMSO	NR (12 h)	–	NR (12 h)	–

[a] Reactions were performed with 0.1equiv. (10 mol%) of FeCl$_3$·6H$_2$O.
[b] dr was calculated by HPLC using chiralpak IA column.
[c] Isolated yield of the product after column chromatography, NR – No Reaction occurred. rt ∼28 °C.

observed moderate to good diastereomeric ratio (up to 9:91) for the piperidine derivatives from HPLC studies (see Table 3).[11] However, we could not explore the scope of the protocol with o-substituted aromatic derivatives and aliphatic alkylidine β-ketoesters as they were inseparable mixture of E and Z isomers.
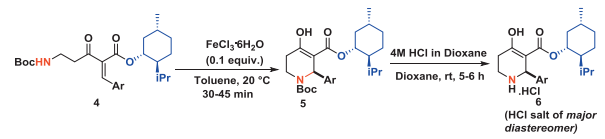
We believe that steric factor resulting from substituent on benzene ring also played a significant role in enhancing the diastereoselectivity. Alkene bearing meta-mono and di-substituted derivatives led to the enhancement in diastereoselectivity in comparison with para-substituted derivatives. Both electron-withdrawing and -donating groups did not have any significant effect on rate of the reaction as well as on the diastereoselectivity. Even the heteroaromatic substituted alkylidene β-ketoesters (4p, 4q) underwent cyclization with an ease affording the corresponding piperidine derivatives in excellent yields (5p, 5q, see Table 3). However, we observed that products 5p and 5q suffered from moderate diastereoselectivity.

To our dismay, we observed that ¹H NMR spectra of the products were highly complex due to peaks arising from both diastereomers and equilibrating rotamers of the corresponding

diastereomers. Also, merging of peaks made almost impossible to analyze the spectra in detail. It was clear from the ¹H NMR spectrum of 5o that two peaks of equal intensity at 12.68 ppm and 12.56 ppm in CDCl₃ at room temperature are due to rotamers of corresponding diastereomers.

Also the peaks with equal integration did not correspond to the diastereoselectivity (dr 9:91) that we observed from HPLC studies. In order to confirm this ambiguity, we subjected the diastereomeric product 5o for the variable temperature (VT)-NMR (500 MHz) studies. It is obvious from the VT-NMR stacked spectrum that equilibrating rotameric peaks with equal intensity at room temperature (25 °C) slowly started resolving into two clear set of peaks at variable temperature (−40 to −55 °C) (Fig. 1) and the diastereomeric ratio clearly matched with HPLC data. It was evident from the VT-NMR studies that existence of rotamers is due to N-Boc group and this observation was further supported by earlier finding.[12] Hence, we decided to isolate the major diastereomer[13] of 5o and deprotect the Boc-group to simplify the spectrum there by avoiding rotameric peaks. ¹H NMR spectrum of Boc-deprotected piperidine derivative (6o) was neat and

Table 3
Synthesis of diastereoselective piperidine derivatives.[a–d]

Entry	Ar-	5 dr(%)[b] (% yield)[c]	6 (HCl salt) yield (%)[d]	Entry	Ar-	5 dr(%)[b] (%yield)[c]	6 (HCl salt) yield (%)[d]
1	5a	21:79 (98)	6a (95)	10	5j (EtO)	29:71 (95)	6j (88)
2	5b (Br)	18:82 (97)	6b (93)	11	5k (NC)	15:85 (98)	6k (96)
3	5c (O₂N)	15:85 (98)	6c (95)	12	5l (O₂N)	14:86 (95)	6l (95)
4	5d (F)	19:81 (97)	6d (88)	13	5m	9:91 (96)	6m (96)
5	5e (Cl)	17:83 (96)	6e (92)	14	5n (MeO, OMe)	11:89 (94)	6n (94)
6	5f (Cl)	15:85 (95)	6f (93)	15	5o (Br, Br)	9:91 (99)	6o (98)
7	5g	20:80 (96)	6g (92)	16	5p	36:64 (93)	6p (89)
8	5h (ᵗBu)	19:81 (95)	6h (94)	17	5q	30:70 (95)	6q (90)
9	5i (MeO)	27:73 (95)	6i (85)				

[a] Cyclization reactions were performed with 0.1equiv. (10 mol%) of FeCl₃·6H₂O in Toluene at 20 °C and deprotection of Boc group was performed on the major diastereomer with 4 M HCl in dioxane, dioxane as solvent.
[b] dr was calculated by HPLC using chiralpak IA column.
[c] Isolated yield after column chromatography.
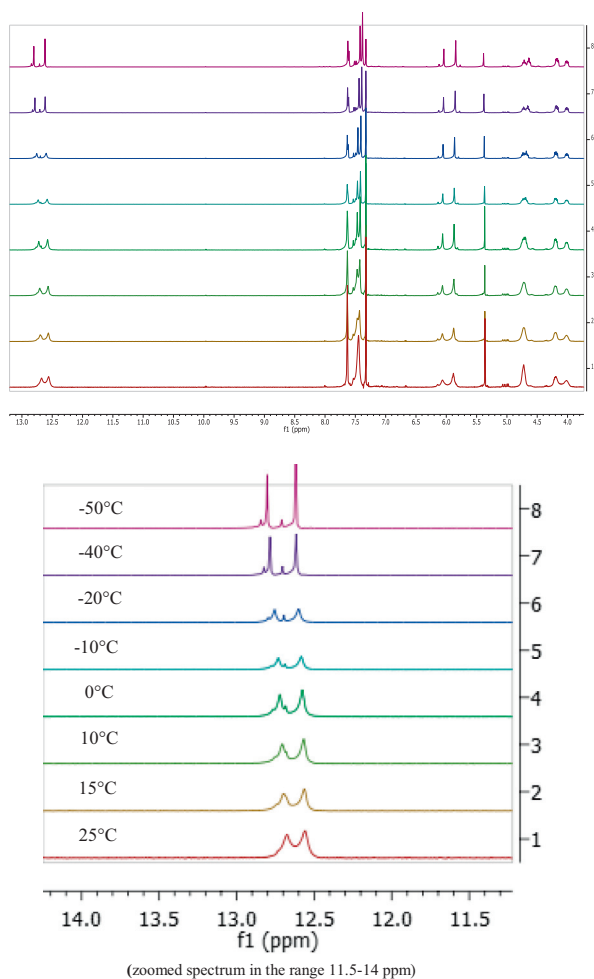[d] Obtained yield of the product after washing with in n-pentane.

Fig. 1. Variable Temperature (VT) NMR study of *N*-Boc derivative of (L)-menthyl ester of 2-(3,5-dibromophenyl) piperidone (**5o**) derivative.

revealed the existence of enolic form of salt and all peaks were well resolved. These findings prompted us to isolate the major diastereomers of all the products (**5a–5q**) and were subjected for Boc deprotection to afford the corresponding salts (**6a–6q**) in good to excellent yields (Table 3).[14] It was conclusive from ^{1}H NMR spectra that all piperidine hydrochloride salts (**6a–6q**) existed mostly in enolic form. All the products were characterized by spectroscopic data. Also, we observed from the ^{1}H and ^{13}C NMR spectra that final products with electron donating groups on phenyl ring showed slightly equilibrating keto-enol tautomers. In quest for the determination of enantioselectivity, we planned to remove the chiral auxiliary. Unfortunately all the protocols that we attempted towards the removal of chiral auxiliary, menthyl ester were unsuccessful (see ESI for the details of various methods). Surprisingly different deprotection methods of menthyl esters known in the literature did not work on menthyl *β*-ketoester scaffold.

Conclusions

In conclusion, we have demonstrated the novel access of diastereoselective piperidine derivatives by exploring the strength of environmentally benign iron (III) chloride (10 mol%) as a catalyst and naturally available (L)-menthol as a chiral auxiliary. Intramolecular cyclization proceeded in diastereoselective manner. Reaction conditions were mild and favored rapid formation of piperidine derivatives in good to excellent yields and with high diastereoselectivity.

A. Supplementary data

Experimental details, ^{1}H, ^{13}C NMR spectra and HPLC profiles of compounds **6** are available in the supporting information. Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.tetlet.2017.11.026.

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9. Various (L)-menthyl alkylidene *β*-keto esters **4** have been synthesized starting from N-Boc *β*-alanine **2** which is in turn synthesized starting from *β*-alanine **1** (see supporting information for the details).
10. Reaction containing both *E* and *Z* isomers (mixture) resulted in poor stereoselectivity. Later, *E* and *Z* isomers were separated before the reaction.

Isolated *E* and *Z* isomers were confirmed ^{1}H NMR and by 1d nOe. Details and yields are given in supporting information.

11. Diastereomeric ratio was determined by HPLC. Chromatograms of all the products (**5a**–**5q**) are given in supporting information.

12. (a) A quick literature search revealed numerous examples of VTNMR or other techniques being used for qualitative identification of rotamers with no mention of saturation transfer; for a few examples, see: Myers AG, Yang BH, Chen H, McKinstry L, Kopecky DJ, Gleason JL. *J Am Chem Soc.* 1997;119:6496;
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13. It was difficult to calculate the exact yield of both diastereomers as some amount of diastereomers was isolated as mixture. Hence, the combined yields of the diastereomers are reported.

14. Purity of piperidine hydrochloride salts (**6**) has been confirmed by HPLC studies and they were found to be highly pure (up to 99%, see ESI). [(-)-Menthol of 99% ee purity was used for the reactions].