# PREPARATION AND EVALUATION OF SOME CHIRAL CATALYSTS FOR ALDOL REACTIONS IN ORGANIC AND AQUEOUS MEDIA

THESIS SUBMITTED TO THE

**UNIVERSITY OF PUNE**

FOR THE DEGREE OF

**DOCTOR OF PHILOSOPHY**

IN

**CHEMISTRY**

BY

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**MARCH 2013**

**To**

**My beloved Parents and Teachers…**

**NATIONAL CHEMICAL LABORATORY**

**(Council of Scientific and Industrial Research)**

**Dr. Homi Bhabha road, Pune- 411 008, INDIA.**

## CERTIFICATE

This is to certify that the work incorporated in the thesis entitled "**Preparation and evaluation of some chiral catalysts for aldol reactions in organic and aqueous media**" has been carried out under my supervision at the National Chemical Laboratory, Pune, India and is a bonafide work of **Revannath L. Sutar**. Acknowledgements have been made wherever the work described is based on the findings of the others.

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## DECLARATION

I hereby declare that the work incorporated in thesis entitled **"Preparation and evaluation of some chiral catalysts for aldol reactions in organic and aqueous media"** submitted for Ph.D. degree to the University of Pune has been carried out at National Chemical Laboratory, Pune, under the supervision of **Dr. N. N. Joshi**. This work is original and has not been submitted in part or full by me for any degree or diploma of any university.

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*Revannath*

# *CONTENTS*

# Abbreviations

| | |
|---|---|
| Ac | Acetyl |
| Anhy. | Anhydrous |
| aq. | Aqueous |
| Ar | Aryl |
| BINAM | 2,2'-Diamino-1,1'-binaphthyl |
| BINAP | 2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl |
| BINOL | 2,2'-Dihydroxy-1,1'-binaphthyl |
| Bn | Benzyl |
| Boc | *t*-Butyloxycarbonyl |
| *n*-Bu | *n*-Butyl |
| *t*-Bu | *tert*-Butyl |
| Bz | Benzoyl |
| Cbz | Carbobenzyloxy |
| Conf. | Configuration |
| $^{o}C$ | Temperature in degrees Centigrades |
| CTAB | Cetyl trimethyl ammonium bromide |
| $D_2O$ | Deuterium Oxide |
| DBU | 1,8-Diazabicyclo[5.4.0]undec-7-ene |
| DCC | *N*,*N'*-Dicyclohexylcarbodiimide |
| DCM | Dichloromethane |
| DEPT | Distortionless enhancement by polarization transfer |
| DMAP | *N*,*N*-Dimethylamino pyridine |
| DMA | *N*,*N*-Dimethylacetamide |
| DME | Dimethoxy ethane |
| DMF | *N*,*N*-Dimethylformamide |
| DMSO | Dimethyl sulfoxide |
| dr | Diastereomeric ratio |
| equiv. | Equivalent |
| Et | Ethyl |
| *ee* | Enantiomeric excess |
| g | Gram(s) |

| | |
|---|---|
| GC | Gas chromatography |
| h | Hour(s) |
| HPLC | High performance liquid chromatography |
| HMPA | Hexamethylphosphoramide |
| Hz | Hertz |
| IR | Infrared |
| LC-MS | Liquid chromatography-mass spectrometry |
| LDA | Lithium diisopropylamide |
| M | Molar |
| Me | Methyl |
| mg | Milligram(s) |
| min. | Minute(s) |
| Ms | Methanesulfonyl |
| mL | Milliliter(s) |
| mmol | Millimole(s) |
| MTBD | 7-Methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene |
| nd | Not determined |
| NHC | *N*-Heterocyclic carbene |
| NOBIN | 2-Amino-2'-hydroxy-1,1'-binaphthyl |
| NMR | Nuclear magnetic resonance |
| NMO | *N*-Methylmorpholine-*N*-oxide |
| NR | No reaction |
| PEG | Polyethylene glycol |
| Ph | Phenyl |
| Pv | Pivaloyl |
| *i*-Pr | Isopropyl |
| ppm | Parts per million |
| rt | Room temperature (23–30 $^{o}$C) |
| SDS | Sodium dodecyl sulfate |
| TADDOL | α,α,α,α-Tetraaryl-1,3-dioxolane-4,5-dimethanol |
| TBAF | Tetrabutylammonium fluoride |
| TBAI | Tetrabutylammonium iodide |

| | |
|---|---|
| TBD | 1,5,7-Triazabicyclo[4.4.0]dec-5-ene |
| TBS | *t*-Butyldimethylsilyl |
| THAI | Tetraheptylammonium iodide |
| TMS | Tetramethylsilane |
| TMS- | Trimethylsilyl |
| Tf | Trifluomethanesulfonyl |
| TFA | Trifluoroacetyl |
| THF | Tetrahydrofuran |
| TLC | Thin layer chromatography |
| Ts | *p*-Toluenesulfonyl |
| TS | Transition state |
| TTMPP | Tris(2,4,6-trimethoxyphenyl)phosphine |
| vs. | Verses |

## General Remarks

- Independent numbers have been used for the compounds, schemes, figures and references etc. in the abstract and each Chapter (1−3).
- All reactions were carried out under argon atmosphere using freshly distilled solvents, unless otherwise specified. Petroleum ether used was of the 60−80 °C boiling range. Yields refer to the isolated products. Column chromatographic separations were carried out on silica gel (100−200 or 230−400 mesh) by gradient elution.
- TLC was performed on E-Merck pre-coated silica gel 60 F254 plates and the spots were rendered visible by exposing to UV light, iodine and charring or staining with ninhydrin, *p*-anisaldehyde or phosphomolybdic acid solutions.
- All the melting points were recorded using Buchi B-540 electro thermal melting point apparatus and are uncorrected
- IR spectra were recorded on Shimadzu FTIR instrument using nujol or chloroform for forming films of solids while that of liquids were recorded as neat and are measured in $cm^{-1}$.
- All $^{1}H$ NMR spectra were recorded on Bruker AV 200 MHz spectrometer using tetramethylsilane (TMS) as an internal standard in $CDCl_3$. Chemical shifts have been expressed in ppm on δ scale downfield from TMS. The abbreviations s, br s, d, t, q, quin., sep. and m refer to the singlet, broad singlet, doublet, triplet, quartet, quintet, septet and multiplet respectively.
- All $^{13}C$ NMR spectra were recorded at 50 MHz with $CDCl_3$ (δ 77 ppm) or MeOH (δ 49 ppm) as the reference.
- Micro analysis was done on Carlo-Erba CHNS-O EA 1108 Elemental Analyzer.
- LCMS were recorded on Thermo Finnigan Surveyor MSQ LC-MS while HRMS were recorded on Thermoscientific *Q EXACTIVE* mass spectrometer.
- Optical rotations were obtained on Bellingham & Stanley ADP-220 Polarimeter. Specific rotations, $[\alpha]_D$ are reported in degree, and the concentration (*c*) is given in g/100 mL in the specific solvent.
- Preliminary enantiomeric excesses were determined by comparison of the optical rotations with literature values which were then confirmed by HPLC analysis (performed on Simadzu instrument) using a chiral column and reverse phase technique. The peaks are integrated as the area% values.

# Synopsis of the thesis

## Introduction

Due to the environmental concerns and some beneficial effects of water on few of the organic reactions, organic synthesis in water is of contemporary interest. Though the rare earth metal salts act as water compatible Lewis acids in aqueous media, traditional Lewis acids are of very little use. Therefore other types of catalysts like Lewis bases, Brønsted acids and organocatalysts which are stable to water and air seems to be good alternatives. Amongst asymmetric C−C bond forming reactions, Lewis base catalyzed enantioselective Mukaiyama-type aldol reaction of trimethylsilyl enolates is not much explored. Thus the development of a general chiral Lewis base catalyst for this reaction acting through trimethylsilyl enolate activation is an important endeavor. This will also lead to the catalysis of other C–C bond forming reactions based on hypervalent silicon chemistry using trimethylsilyl nucleophiles. Further the ligands used to prepare Lewis base catalysts bearing an amino group can be used for catalyzing the well known direct aldol reaction.

The present work is a systematic study of the effect of catalyst design and the reaction medium on these two aldol variants. This thesis is divided into three chapters.

**Chapter 1: Development of catalytic asymmetric aldol reaction- a brief literature survey.**

This chapter provides background for the present study through a brief review of the literature on the catalytic asymmetric aldol reactions.

**Chapter 2: Preparation and evaluation of chiral Lewis base catalysts for the Mukaiyama-type aldol reaction**.

This chapter gives the details of our work on the chiral Lewis base catalyzed Mukaiyama-type aldol reaction. It is further subdivided in to the three sections.

**Section 2A: Preparation of chiral Lewis base catalysts**

Based on the hypothesis shown in Figure 1, variety of chiral Lewis bases having different coordination and sterics were designed and prepared. The required chiral ligands were prepared from easily accessible starting materials and were converted to Lewis bases or Lewis acid-Lewis base complexes.

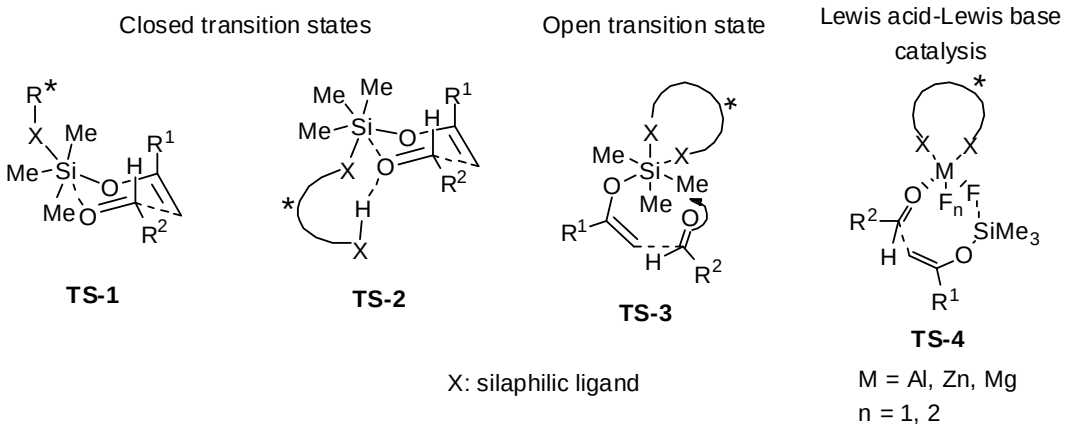



**Figure 1.** Possible activation modes.

## 2A.1. Preparation of Ligands

Monodentate, bidentate, tridentate and lipophilic chiral ligands were prepared from different classes of chiral compounds having variations in p*K*a, sterics, electronics, number and acidity of hydrogen bond donors etc.

### Amino acid derivatives

Various α-amino acid derivatives such as **1**–**6** were prepared in good yields.

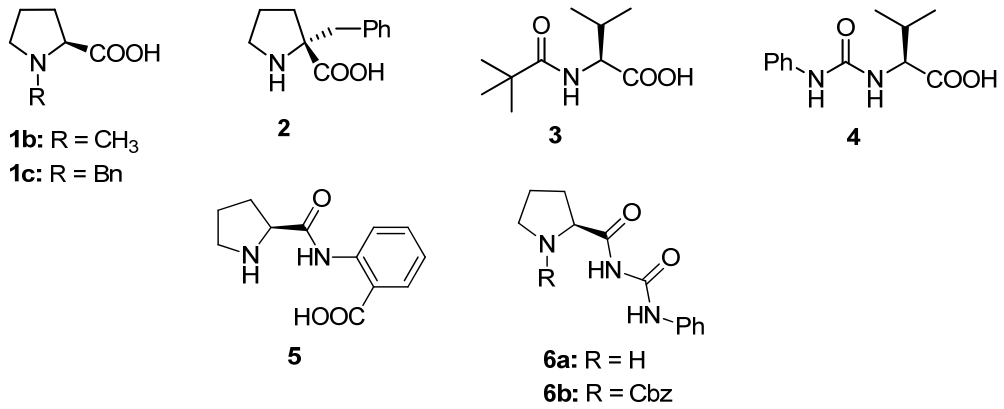



**Figure 2.** Amino acid derived ligands.

### Binaphthyl derivatives

A few binaphthyl derivatives (**7**–**9**) were obtained using simple procedures.

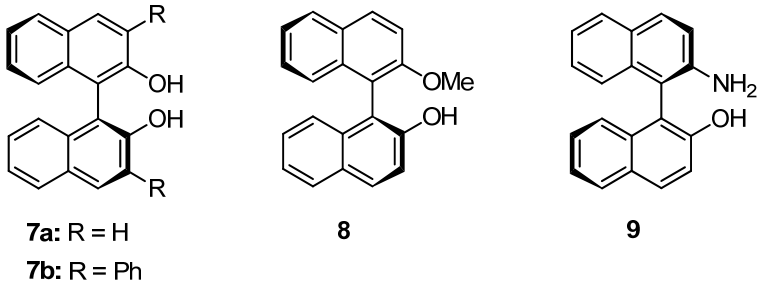
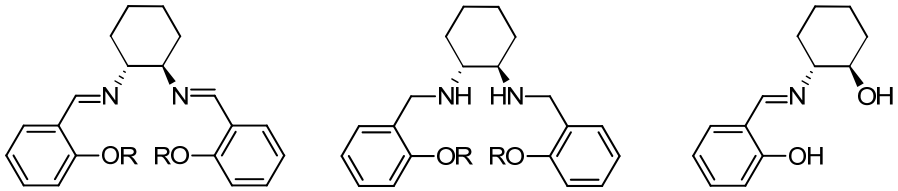



**Figure 3.** Binaphthyl derived ligands.

**Salen derivatives**

Salen derivatives (**10**–**12**) were prepared as precursors of the possible Lewis base catalysts. Few of them can also act as the ligands for the preparation of Lewis acid-Lewis base complexes of metal fluorides.



**10a:** R = H
**10b:** R = Me

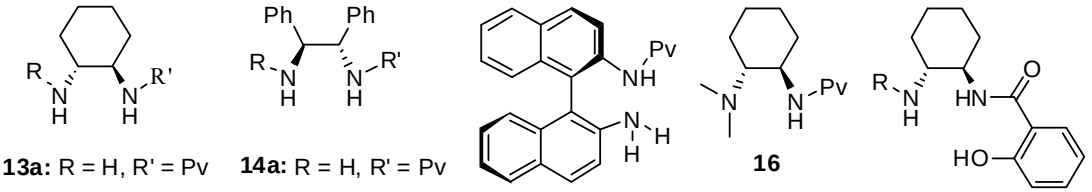
**11a:** R = H
**11b:** R = Me

**12**

**Figure 4.** Salen derived ligands.

**Mono- and diamides of symmetrical diamines**

A variety of ligands containing mono- and diamide functionality were obtained from the corresponding chiral diamines.



**13a:** R = H, R' = Pv
**13b:** R = H, R' = Ac
**13c:** R = H, R' = Bz
**13d:** R = H, R' = Ts
**13e:** R = R' = Pv
**13f:** R = R' = Ts
**13g:** R = Ac, R' = Ts

**14a:** R = H, R' = Pv
**14b:** R = H, R' = Ac
**14c:** R = H, R' = Bz
**14d:** R = H, R' = TFA
**14e:** R = H, R' = Ms
**14f:** R = R' = Pv
**14g:** R = R' = Ms
**14h:** R = R' = TFA

**15**

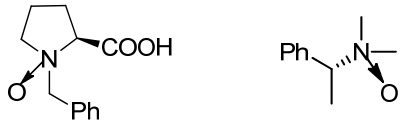
**16**

**17a:** R = H
**17b:** R = Pv

**Figure 5.** Amides derived from symmetrical diamines.

***N*-oxides**

A few of the chiral *N*-oxides were also prepared to study their behavior as Lewis bases and ligands.



**18**

**19**

**Figure 6.** Chiral *N*-oxides.

**Lipophilic ligands**

To study this reaction in aqueous media, a few of the chiral lipophilic ligands (**20**–**23**) were prepared.

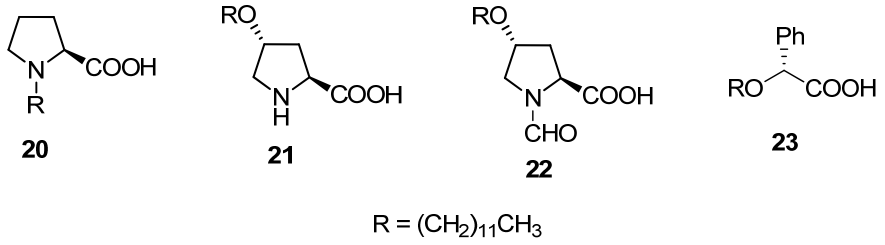



**Figure 7.** Lipophilic carboxylic acids.

**2A.2. Preparation of salts**

Mono salts of above mentioned ligands were prepared by using equimolar amounts of corresponding Brønsted bases. Similarly, few appropriate ligands were converted into the di salts.

**2A.3. Lewis acid-Lewis base complexes**

Chiral complexes containing Lewis acidic metal and Lewis basic fluoride in the same catalyst were prepared from metal fluorides like $ZnF_2.2H_2O$ and $AlF_3.3H_2O$.

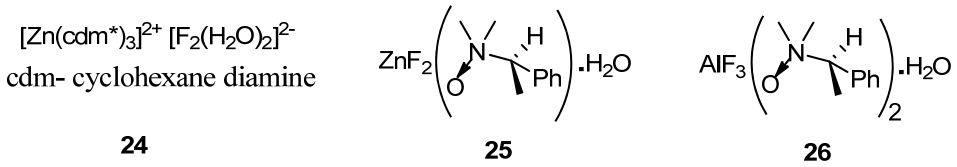
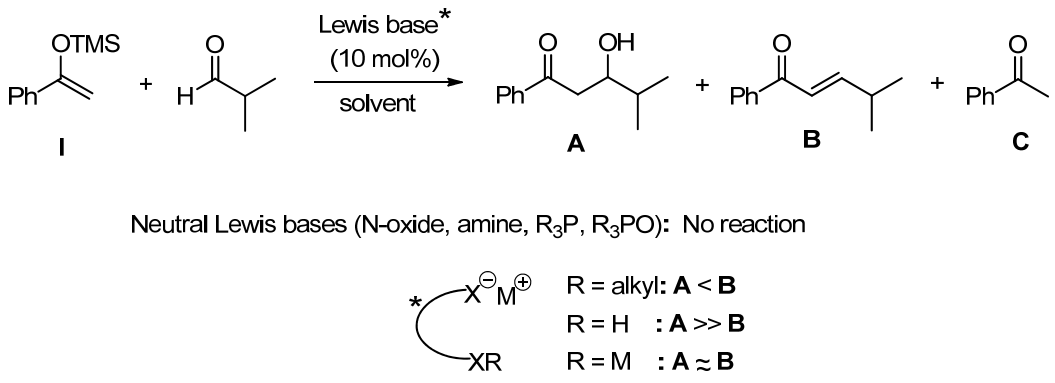



**Figure 8.** Chiral metal fluoride complexes.

**Section 2B: Study of Mukaiyama-type aldol reaction in organic media**

Trimethylsilyl enolate of acetophenone and isobutyraldehyde were selected as the preliminary reactants for screening of above catalysts.

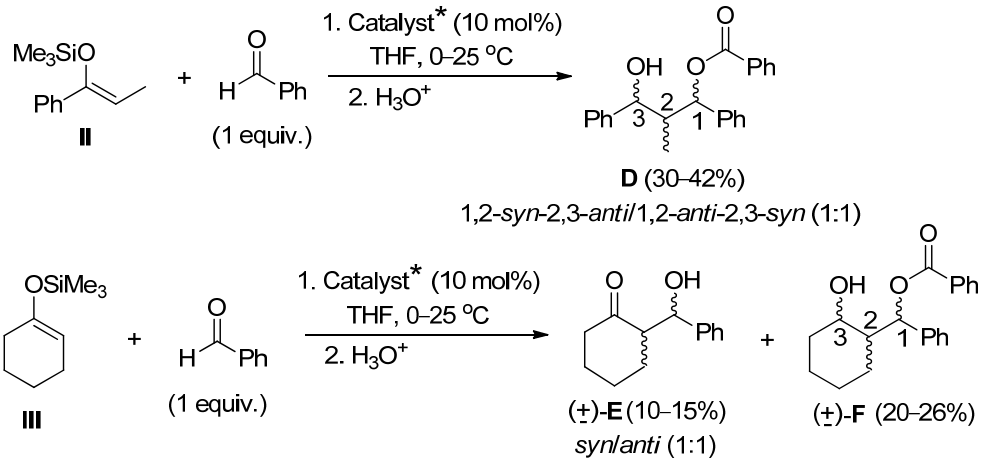



**Scheme 1.** Lewis base catalyzed Mukaiyama-type aldol reaction.

It was observed that the trimethylsilyl enolate (**I**) does not get activated by the non-ionic Lewis bases such as tertiary amines, *N*-oxides, phosphine oxides etc. Similarly our early attempts using anionic salts were disappointing. One of the major problems was their low solubility in commonly used organic solvents like THF and $CH_3CN$. While polar solvents like DMF, DMSO and water led to the side reactions such as hydrolysis of enolate (product **C**) and elimination (product **B**). Few of them such as BINOLate salts are soluble in THF, toluene and $CH_3CN$ but provided considerable amounts of elimination product (**B**) which is due to their strong Brønsted basicity.

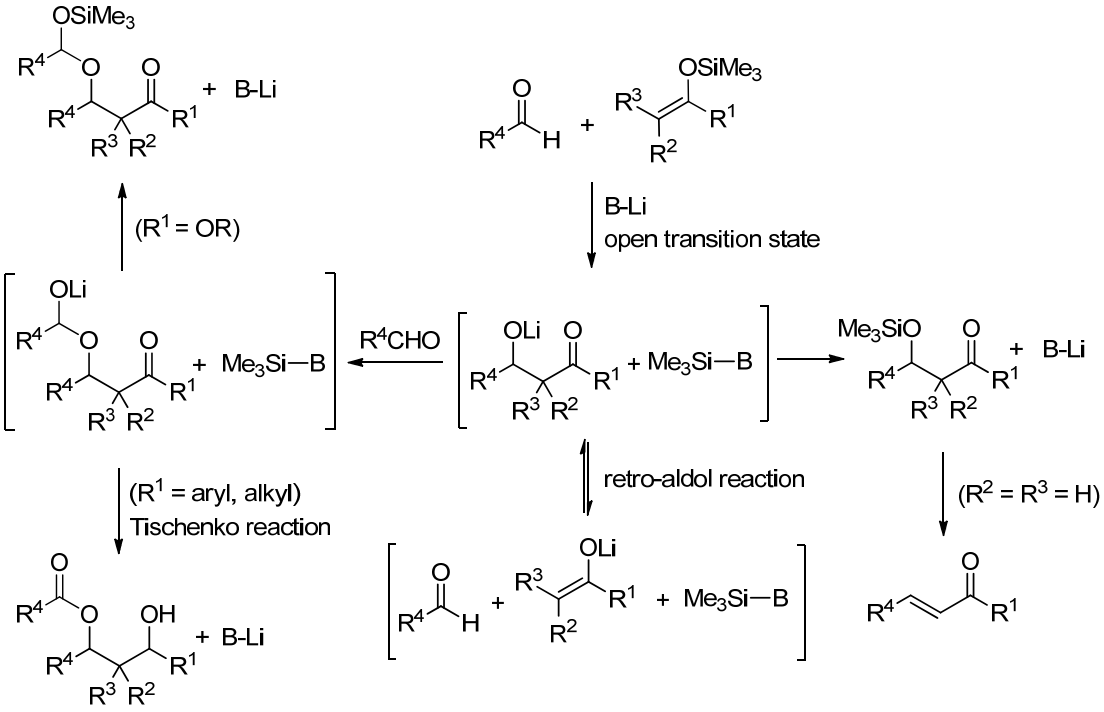
Contrary to the earlier reports with trimethoxysilyl enolates, in this reaction mono salts of the bidentate ligands gave good yields than the di salts. Though the yields were low, it was noted that presence of hydrogen bonding functionalities in the catalysts or reaction medium minimizes the formation of elimination product (**B**). Therefore efficient catalysts (lithum salts of monoamide derivatives of symmetrical diamines) with built in hydrogen bonding sites were designed and prepared. These catalysts effectively suppressed the associated side reactions. However despite of changing several parameters such as sterics and electronics of the catalyst, number and acidities of hydrogen bonding sites or reaction medium, selectivities does not improved.

Therefore the mechanism of anionic Lewis base catalyzed Mukaiyama-type aldol reaction was reinvestigated. The reactions of stereodefined trimethylsilyl enolates (**II** and **III**) in the presence of catalysts with and without hydrogen bonding sites (lithium salts of **13a** and **16**) indicated that this reaction goes through the open transition state even though the catalyst bears a hydrogen bonding site.




**Scheme 2.** Reactions of stereodefined trimethylsilyl enolates with benzaldehyde.

Formation of aldol-Tischenko products confirms the generation of metal aldolate intermediate which will be in equilibrium with the metal enolate. Direct transmetalation of trimethylsilyl enolate with these Lewis bases was ruled out from the $^1$H NMR experiments. This indicated the open transition state and the retro-aldolization of metal aldolate intermediate are responsible for the observed low selectivities. In this reaction Lewis base promotes the trimethylsilyl enolate activation as well as silylation of metal aldolate intermediate.




**Scheme 3.** Revised mechanism of lithium salt catalyzed aldol reaction of trimethylsilyl enolate.

**Section 2C: Mukaiyama-type aldol reaction in aqueous media**

The retro-aldolization, detrimental for the selectivity can be avoided by rapid hydrolysis of the aldolate intermediate using some protic additive such as alcohol or water (catalytic as well as cosolvent). But not unexpectedly it always resulted in the hydrolysis of the Lewis base activated trimethylsilyl enolate. This indicated us the use of micelles of cationic surfactant such as CTAB could be useful.

It was observed that for the reactions catalyzed by lithium salts in water, the addition of CTAB is sufficient to avoid the hydrolysis but for sodium salt, addition of brine is required. Chiral amphiphilic salts prepared from the lipophilic ligands were also examined as possible catalysts, out of which only the sodium salt of **20** gave good yield indicating the requirement of proper ionic character and more lipophilic

environment near the Lewis basic site. The reactions under reverse micellar conditions showed inferior results than in the normal micelles. In many cases it promoted hydrolysis. But the central idea of rapid hydrolysis of aldolate also failed to give good selectivity, indicating that both open transition state and retro-aldolization are responsible for the low selectivity.

**Chapter 3: Preparation and application of new chiral organocatalysts for the direct aldol reaction.**

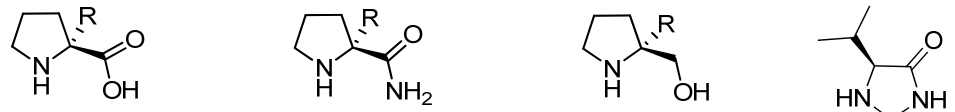
To overcome the drawbacks associated with the direct use of amino acids and chiral amines as catalysts, new organocatalysts are continuously developed. But there is no systematic rational explanation of the effect of simplest possible modifications. This chapter gives the details of our work on the development of simple organocatalytic systems for the direct aldol reaction. It is divided in to three sections.

**Section 3A: Preparation of some new pyrrolidine derived chiral organocatalysts**

To study the effect of variations in catalyst structures on the outcome of direct aldol reaction, several organocatalysts were synthesized from α-amino acids.

**Pyrrolidine derivatives with and without α,α-disubstituents**

Catalysts (**27**–**30**) were prepared to study the effect of α,α-disubstituent of the pyrrolidine derivatives on this reaction.




**27a:** R = H
**27b:** R = Me
**27c:** R = Bn

**28a:** R = H
**28b:** R = Bn

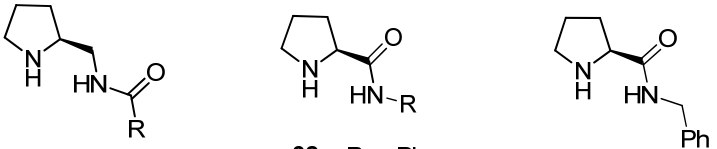
**29a:** R = H
**29b:** R = Bn

**30**

**Figure 9.** Pyrrolidine derived catalysts.

**Prolinamides with variations in the position of amide carbonyl**

To study the effect of position of amide carbonyl on the outcome of this reaction, catalysts **31**–**33** were selected.




**31a:** R = Ph
**31b:** R = *t*-Bu

**32a:** R = Ph
**32b:** R = *t*-Bu

**33**

**Figure 10.** Chiral amides selected to study the effect of position of amide carbonyl.

**Prolinamides with variations in the acidities of hydrogen bonding sites**

To study the effect of increased acidity of hydrogen bonding sites of the prolinamide derivatives on rate and enantioselectivity of direct aldol reaction, organocatalysts **34**–**36** were prepared from L-proline.

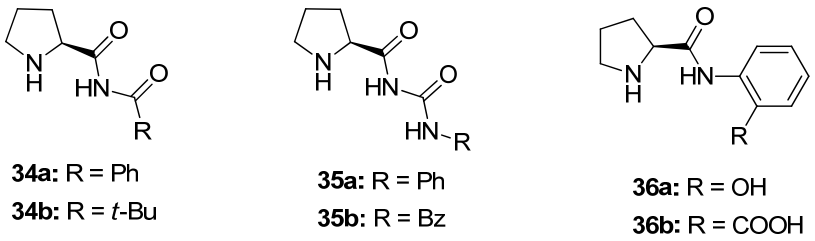
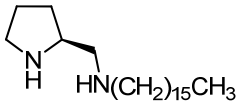



**Figure 11.** Organocatalysts with variations in the acidities of hydrogen bond donors.

**Diamine with long alkyl chain**

A chiral diamine (**37**) possessing pyrrolidine methylamine unit was also prepared from L-proline.

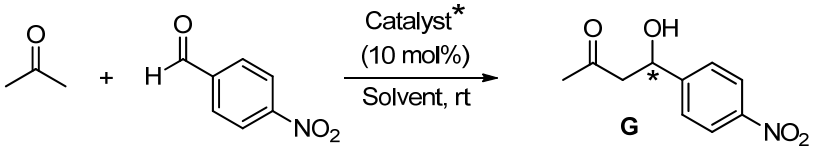


**37**

**Figure 12.** Pyrrolidine derived diamine.

**Section 3B: Systematic evaluation of pyrrolidine derivatives as organocatalysts**

Above series of pyrrolidine containing organocatalysts were then systematically screened to study the effect of several factors on the outcome of direct aldol reaction in organic and aqueous media. Acetone and *p*-nitrobenzaldehyde were used as the preliminary reactants.




**Scheme 4.** Representative example of direct aldol reaction.

It was observed that sterics at the α-position is detrimental. Also simple prolinamides were found to be better than the amides of pyrrolidine methylamine. But no correlation has been found between the acidity of hydrogen bonding sites and the catalytic activity. An enantioswitch of the outcome from '*R*' to '*S*' was observed when the size of the transition state increases from 7 to 8-membered.

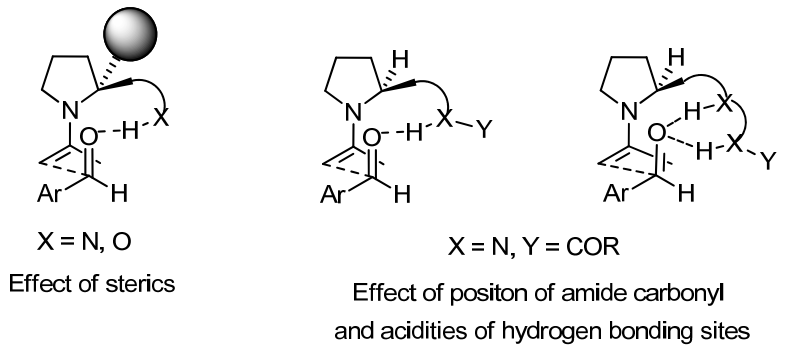
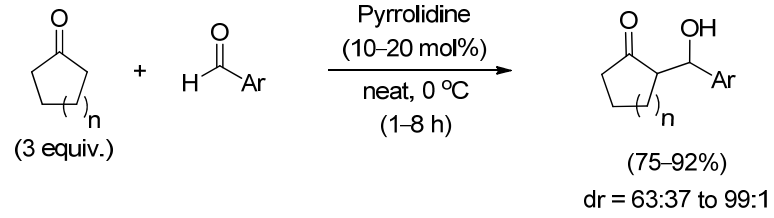



**Figure 13.** Effect of structure of organocatalyst on the direct aldol reaction.

**Section 3C: Some chiral addition complexes for the direct aldol reaction**

Use of simple additives to improve the efficiencies of the well known organocatalysts is another option for developing a catalytic system for this reaction. But the detailed role of these additives in the transitions state is not yet clear. We have systematically studied the requirements of such type of addition complexes.

During the standardization of control experiment, a pyrrolidine catalyzed highly diastereoselective direct aldol reaction of cyclic ketones with aromatic aldehydes (both electron rich and deficient) has been realized under neat conditions.




**Scheme 5.** Pyrrolidine catalyzed direct aldol reaction of cyclic ketones.

Therefore the addition compounds of pyrrolidine with chiral acidic additives such as BINOL, *N*-methyl-L-proline and **13f** were examined as possible catalysts. The enantioselectivity was disappointing in all the cases. From this study it was turned out that for enantioselective outcome, generation of chiral enamine is necessary and not the face selective activation of aldehydes. Accordingly a series of simple addition complexes of chiral amines (**38**–**42**) with achiral acids were systematically screened as possible catalysts for this reaction.

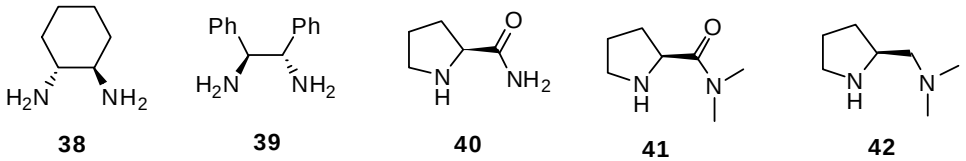
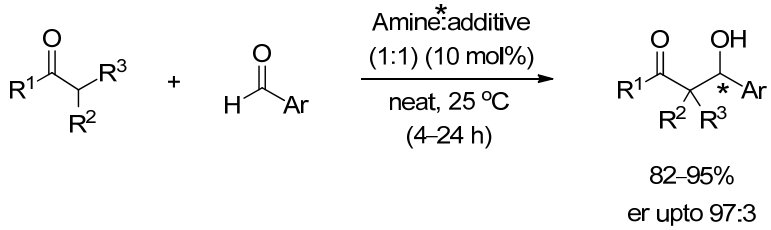



**Figure 14.** Chiral amines used to study the role of chiral enamine.

Good yields were obtained in all the cases but with only modest enantioselectivity. Therefore acid and amine partners involved in the complex formation were changed to chiral α-amino acid and achiral amine. It was realized that a chemical entity that selectively and strongly binds to the carboxylic acid group interacts with L-proline changing its solution properties and reactivity and also alters the binding in the transition state. Amongst the various additives examined, 2-amino phenol and 8-hydroxy quinoline gave promising results. Later combination also gave good enantioselectivities with a variety of donors and acceptors under neat conditions.




**Scheme 6.** Direct aldol reaction catalyzed by chiral amine:additive complex.

**List of Publications**

1. Systematic evaluation of a few proline derivatives as catalysts for aldol reaction **R. L. Sutar**; N. N. Joshi *Tetrahedron Asymmetry* **2013**, *23*, 43−49.
2. A study of Lewis base catalyzed Mukaiyama-type aldol reaction of trimethylsilyl enolates **R. L. Sutar**; N. N. Joshi manuscript communicated.
3. Role of additives in the chiral amine catalyzed direct aldol reaction **R. L. Sutar**; N. N. Joshi manuscript communicated..

**Poster presentations**

1. Presented a poster '**New L-proline derived organocatalysts for enantioselective direct aldol reaction**' on National Science Day celebration at NCL in Feb. 2011.
2. Presented a poster '**Chiral Lewis base catalyzed Mukaiyama-type aldol reaction**' on National Science Day celebration at NCL in Feb. 2012.

*Chapter 1*

# Development of catalytic asymmetric aldol reaction- a brief literature survey

## 1. Introduction

Aldol reaction is one of the fundamental methods for creating C–C bonds with stereo- as well as enantiocontrol.[1] Acid catalyzed dimerization of acetone to mesityl oxide reported by Kane in 1838 is the first example of this reaction.[2a] It is named after the product "aldol" first recognized by Wurtz as a combination of aldehyde and alcohol.[2b] The aldol unit is a widely occurring subunit in many natural products and pharmaceutical agents. This reaction has ability to generate two adjacent stereocenters in a single step therefore control of its stereochemical outcome becomes an important and crucial task. Thus the development of highly diastereo- and enantioselective aldol reaction continues as an active field of the research.

## 2. Directed aldol reaction

The traditional crossed aldol reaction is successful only when applied within the framework of limited substitution patterns. Generation of preformed enolates emerged closely with the chemistry of lithium amides lead to the development of modern aldol reactions.[3] These methods were further rationalized for the preparation of stereodefined enolates[4a] and their kinetically controlled additions.[4b] These methodologies offered a general solution to the problem of diasteroselectivity.

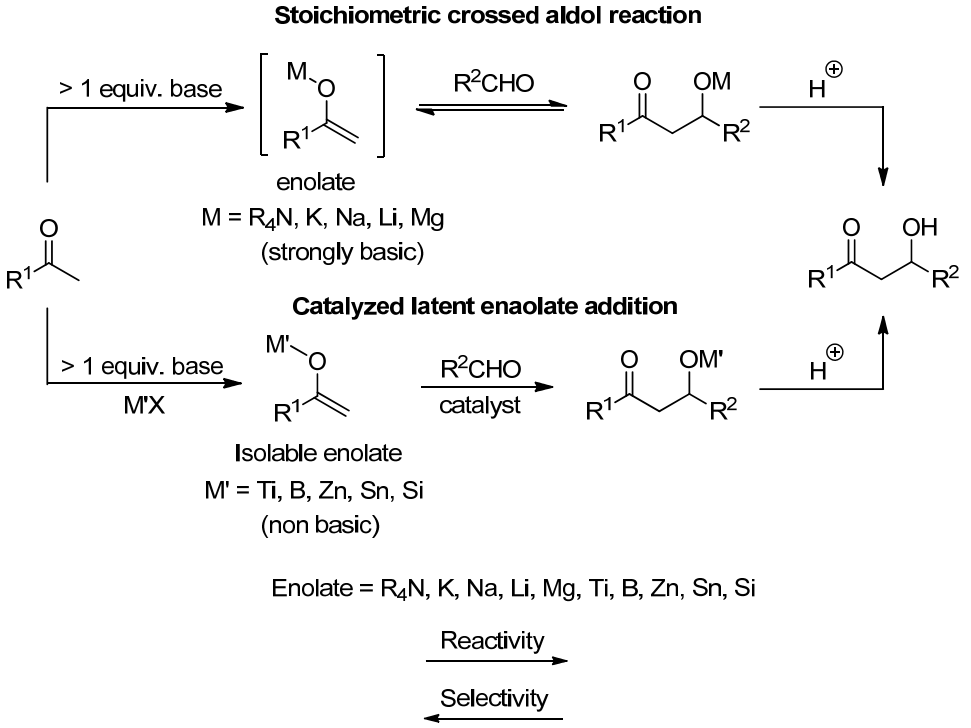



**Figure1.** Directed aldol reaction.

Amongst the enolates of group 1 and 2 metals, those of Li, Na and Mg are widely used for synthetic purposes due to their high reactivity and possibility of irreversible additions under kinetic control. Different transition state models such as 'closed' (Zimmerman-Traxler) and 'open' have been proposed to explain the stereochemical outcome of the reaction which is governed by groups attached to the substrates as well as metal center of the enolate or catalyst.[4b,c]

## 2.1. Chiral auxiliary based aldol reactions

These methods are diverse, extremely general and provide high selectivities by the virtue of highly ordered, closed transition states resulting from the structure of chiral auxiliary and organizational features of the metal. This translates the pre-existing chiral information of one of the auxiliary modified reactants to the newly formed C−C bond. These approaches are summarized in Figure 2.[1d,5] Double stereodifferentiation is also achieved using chiral auxiliaries in both the reactants.[6]

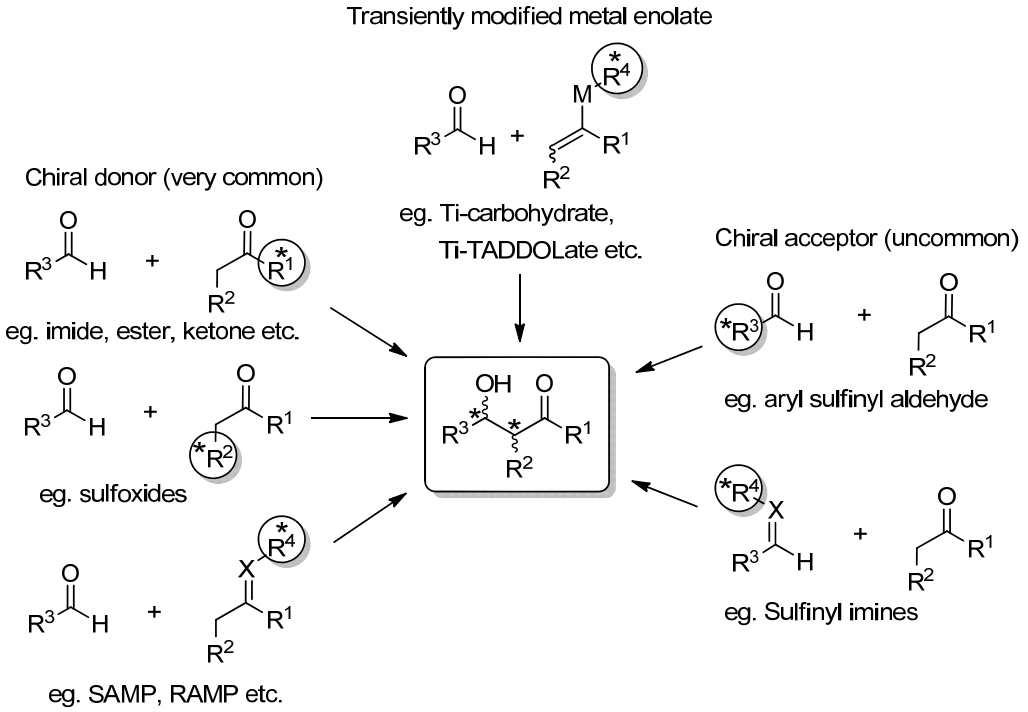



**Figure 2.** Modes of chiral auxiliary attachment.

Diastereoselectivity of the products depends on several factors including enolate geometry, metal ion and the reaction conditions. Generally chiral auxiliaries that perform well in diastereoselective propionate aldol reactions, give unsatisfactory results in the acetate aldol. The use of chiral auxiliaries with conformational rigidity and/or highly crowded environments, the use of enolates with reductively removable

groups like α-halo, thio etc. or α-silyloxy groups and the use of chiral metal carboxylates are the few solutions.[1d] Generally aldehydes are used as electrophiles while additions to ketones are scarcely reported e.g. addition of enolates containing Evans's oxazolidinones,[7] oxazolidinethiones[8] and Braun's auxiliaries[9] etc. Such additions are usually less diastereoselective than analogous additions to aldehydes and are not systematically surveyed for their generality.

In general high reliability, broad substrate tolerance and other practical advantages of these methods outweighs their common drawbacks such as requirements of large excess of metal salts, extra steps for the attachment and detachment of chiral auxiliary etc. Recent work by several groups has demonstrated ease in the synthesis of all possible diastereomers. Also the success of acetate aldol addition has proved to be a solution to some of the long standing problems. Unfortunately these reactions have yet to be made catalytic.[10a]

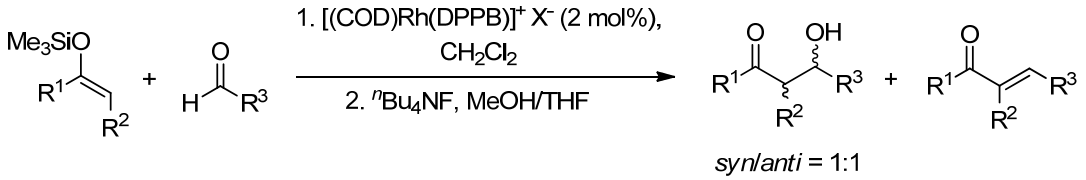
### 2.2. Catalyzed aldol additions of latent enolates (silicon enolates)

Aldol reactions of alkali and alkaline earth metal enolates are reversible therefore catalyzed reactions rely mostly on the latent enolates. These enolates are generated by pre-existing stoichiometric methodologies with some latent metal source in a separate and distinct chemical operation (Figure 1).[1a] Majority of them are weakly nucleophilic reagents and thus cannot react with carbonyl compounds directly. Therefore their reactions require activation of electrophile[1a] or nucleophile[10b] with an activator, acting as a means of influencing reaction stereoselection. Out of these, enolates of silicon are easy to prepare, relatively more stable to air and moisture and have unique moderate reactivities. Few of them can undergo uncatalyzed aldol additions due to the enhanced reactivities arising from the presence of nucleophilic substituents[11] or increased Lewis acidity of silicon.[10,12] Also high pressure,[13a] elevated temperature,[13b,c] molecular sieves[13d,e] or polar solvents such as DMF, DMA, DMSO,[14a] water[14b,c] and ionic liquids[14d] facilitates aldol additions via the more favored concerted mechanism.[15]

#### 2.2.1. Reactions through transmetalation

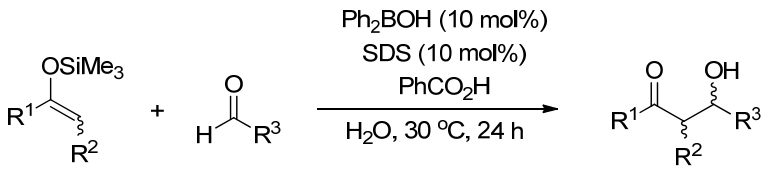
Transmetalation of silyl enolates with some metal salts also increases their reactivity.[16] Intermediacy of rhodium enolate was first recognized by Matsuda et al. in the reaction of trimethylsilyl enolate with aldehydes.[16a] Scope of their nucleophilicity was then studied in the reactions with acetals, ketals and orthoesters under neutral

conditions.[16b] Later Bergman and Heathcock demonstrated the actual intermediate as Rh(I) enolate.[16c]




**Scheme 1.** Aldol reaction through transmetalation of silyl enolate with Rh(I) salts.

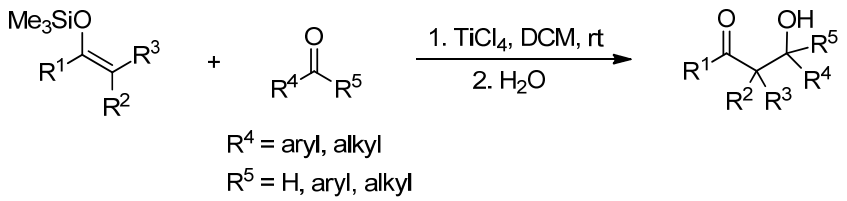
Kobayashi et al. used a catalytic combination of diphenylboronic acid and benzoic acid for the reaction of trimethylsilyl enolates with aldehydes in the micellar media of SDS.[16d,e] Benzoic acid behaves as a weak Brønsted acid additive and accelerates the rate determining Si–B exchange, by protonating the boronic acid. Stereochemical outcome consistent with the traditional boron enolate mediated aldol reactions suggests its intermediacy.[16d] Other metals undergoing transmetalation with silyl enolates include Pd,[17a] Cu,[17b] Ru[17c] etc.




**Scheme 2.** Aldol addition of silyl enolates via boron enolate.

### 2.2.2. Lewis acid catalysis

Use of Lewis acids in the additions of less reactive silyl enolates to aldehydes was first recognized by T. Mukaiyama,[18a] in the form of stoichiometric amount of $TiCl_4$ and later the method became familiar as Mukaiyama aldol reaction. Nucleophilicity of silyl enolates in this catalytic system arises from the electron donation ($\sigma_{O-Si} \rightarrow \pi^*_{C-C}$) followed by stabilization through β-silicon effect.[18b]




**Scheme 3.** Mukaiyama aldol reaction.

Lewis acid activation of the carbonyl group of aldehyde or ketone facilitates enolate addition and subsequent transfer of silicon residue to the aldolate oxygen allows a catalytic process. Stoichiometric amounts of Lewis acids[19] eg. $TiCl_4$,

$BF_3.OEt_2$, $SnCl_4$ etc. used in the original methods were later replaced by catalytic protocols with those bearing soft Lewis basic anions[20] such as $ClO_4^-$ or $TfO^-$. Their catalytic ability depends on the rate of intra- or intermolecular silyl transfer to the aldolate oxygen and their simultaneous liberation.

Although succeeding investigations revealed the mechanism of reaction as stepwise and significantly more complex,[21] Mukaiyama's initial explorations provided a basis for the design and development of chiral catalysts for this and related reactions.[22] Generation of facially discriminated aldehyde electrophiles using chiral Lewis acids which is like their transient asymmetric modification was introduced. Exchange of halides or alkoxides of conventional Lewis acids with enantiopure ligands provided an easy access to the well defined chiral metal species with reduced electrophilicity and increased sterics. Variety of Lewis acid catalysts containing early and late transition metals and chiral ligands bearing *N*, *O* and *P* donors have been developed.[1,22] Their early applications in the aldol additions were largely limited to this reaction and normally provided high selectivities.

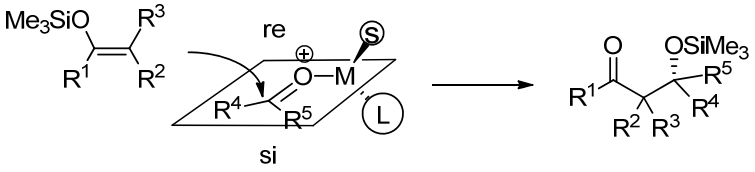



**Figure 3.** Facial discrimination in the asymmetric Mukaiyama aldol reaction.[1a]

Reetz et al. were the first to report the asymmetric Mukaiyama aldol reaction using catalytic amount of (*S*)-BINOL-Ti(IV) dichloride complex[23] (later known as Mikami's catalyst)[24] and few Al and B-based chiral catalysts. A chiral Ti(IV) complex comprising of NOBIN derived tridentate hemisalen ligand developed by Carreira et al., required relatively low loading (0.5–5 mol%) and is a very general catalyst.[25] Chiral oxazaborolidine promoted Mukaiyama aldol reaction initially reported by Kiyooka et al. as stiochiometric;[26] was later modified as a catalytic protocol by several groups.[27] Similarly in 1989, Mukaiyama et al. reported $Sn(OTf)_2$-chiral diamine as a stoichiometric promoter for the enantioselective aldol reaction of ethanethioate derived silyl enolate with aldehydes and ketones.[28] This protocol was later modified to include diamines[29a,b] as well as bisoxazolidinone ligands.[29c,d]

The enantioselective Mukaiyama aldol reaction in aqueous media is another important challenge due to the instabilities of traditional Lewis acids, enolates and usual metal complexes in the presence of water.[30] Both transition and rare earth

metals upon coordination with multidentate chiral ligands have proved to be efficient Lewis acid catalysts in aqueous media.[31] Also few metal salts behave as water tolerant Lewis acids.[32] Besides these, the newly introduced Lewis acid-surfactant-combined catalysts (LASC) in combination with chiral chelating ligands provided good results.[33]

Thus the Lewis acid catalyzed aldol reaction of silyl enolates is a viable strategy[10a] with a few significant advantages over the other aldol variants such as mild reaction conditions, non-reversibility, flexibility of directing both the reactants, regio- and chemoselectivity etc.[34] Therefore it is the subject of interest for almost four decades.[1,35] However it is less general and since it proceeds through the open transition state, selectivity is mostly dominated by van der Waals interactions. Requirement of strictly anhydrous conditions for usual Lewis acids, instability of various functional groups and often formation of *syn* products irrespective of the enolate geometry are the few other limitations.

### 2.2.3. Lewis base catalysis

Although several Lewis bases are used as cocatalysts or ligands in the Lewis acid catalyzed reactions, their direct use as catalysts[36] is relatively less explored. It requires involvement of an element capable of expanding its valency in the presence of a Lewis base eg. silicon.[37] Although silicon species with coordination number > 4 are known from 1809, reported independently by Gay-Lussac[38a] and J. Davy;[38b] first kinetic evidence for the slow formation of reactive pentacoordinate silicon intermediate was provided by Corriu et al. in 1975.[39] Lewis theory of acid-base interactions is the basis of this behavior.[40] Binding of a Lewis base to these elements (eg. Si) through n–σ* interactions, leads to the polarization of adjacent bonds with decrease in electron density at the central atom and increase in electron density at the peripheral atoms. Thus it creates a unique reactivity pattern where electrophilicity and nucleophilicity of adduct are simultaneously enhanced.[41] It also causes ionization and generally exists as an equilibrium with hypervalent species. Depending on the ligands attached to silicon, ionization may lead to two different tetracoordinated silicon species eg. Lewis base activation of enolate can produce Lewis base-silicon adducts along with nascent nonsilicon enolates or cationic siliconium ions from enolates (Figure 4).

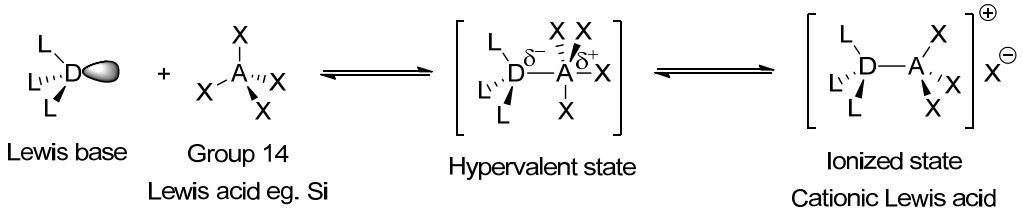



**Figure 4.** Electronic redistribution in Lewis acid-base adducts of group 14 elements.[37]

**Reason for hypervalency of silicon**

Ability of silicon to break the Langmuir-Lewis octet rule was initially explained by considering the involvement of its 3d orbitals in the hybridization, by an analogy of transition metal complexation.[42a] Thus it was believed that in pentacoordinated species, silicon would have $sp^3d$ hybridization with trigonal bipyramidal geometry, while in the hexacoordinated species it would be $sp^3d^2$ with octahedral geometry. The reduced 's' character of silicon orbitals in these species explains their enhanced Lewis acidity and transfer of electron density to the ligands.

However silicon is not a transition metal and its 3d orbitals are too much diffused to involve in meaningful bonding.[42b] Thus second hypothesis rules out their participation and proposes that this is due to the ability of its 3p orbitals to engage in electron rich three-center-four-electron bonding.[42c,d]

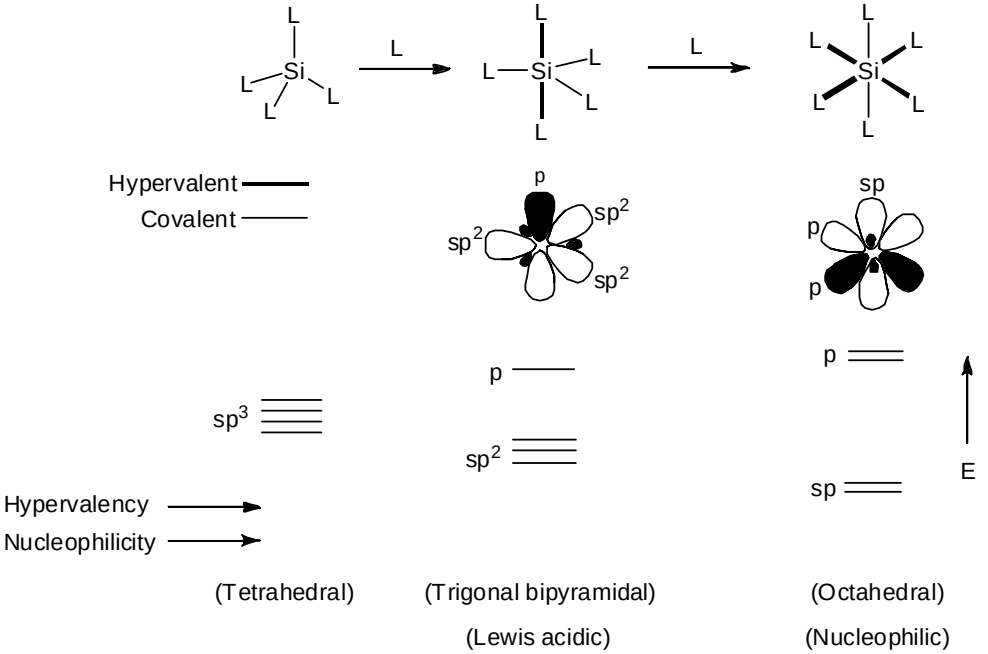



**Figure 5.** Hybridization and orbital picture of hypervalent silicon complexes.

Accordingly, the formation of a penta- or hexacoordinated silicon species would involve 1 or 2 three-center-four-electron molecular bonds, formed by one 'p' orbital

of silicon and two 'p' orbitals from the two electronegative ligands and would thus have $sp^2$ or sp hybridization of silicon respectively (Figure 5). This results in the non-equivalence of ligand positions. The σ-acceptors prefer hypervalent bonds and σ-donors prefer normal covalent bonds with their relative trans-disposition. This helps in predicting the positions of all the ligands around silicon. Gordon et al. supported this hypothesis by theoretical calculations after studying the binding of chloride ion to $SiCl_4$ in the formation of penta- and hexacoordinate silicates at 6-311++G(d,p) level of theory.[43a] They observed changes in the bond lengths and electron density consistent with the Gutmann's analysis.[37] Similar trends were also observed by Sakurai et al. in the allyltrifluorosilanes and corresponding fluorosilicates.[43b]

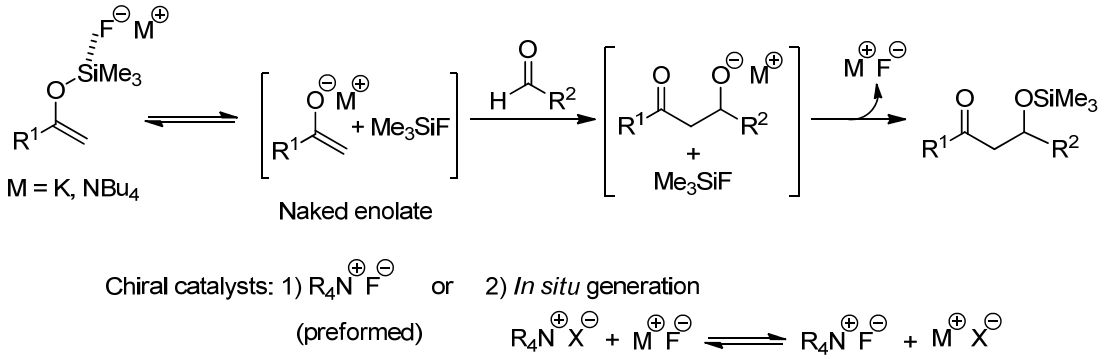
Both the theories explain fundamental properties of hypervalent silicon species that distinguishes them from tetra coordinated silicon compounds. Molecular orbital analysis of these species together with the Gutmann's analysis supports intimate relationship between hypervalent and ionized intermediates.

Most fundamental difference between the Lewis acid and Lewis base catalysis lies in the distribution of electron density in the resulting adducts. The former results in the net transfer of electron density away from the substrate, while the later transfers it towards the substrate. Lewis base activation of silyl enolates is thus a more interesting and challenging option[10,44] and can proceed via formation of nascent enolate[45] or hypervalent silicon intermediates.[10b] There are also few advantages associated with their use such as more stability, ease of preparation and handling etc. Catalytic Lewis acid systems leading to *anti* aldols are less developed; while enolate activation creates possibility of accessing both *syn* or *anti* product from appropriate enolate by proper tuning of the activator.

#### 2.2.3.1. Reactions through the nascent enolate

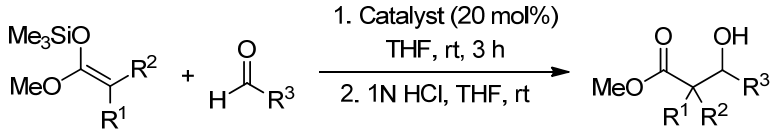
Due to the extremely high enthalpy of Si–F bond (135 kcal $mol^{-1}$), fluorides act as effective promoters for a wide variety of silicon based reactions. Kuwajima et al. first demonstrated their use in the activation of silyl enolates.[46a] Later Heathcock et al. used stoichiometric amounts of these species for a highly *anti* selective reaction between ketone derived silyl enolates and aldehydes.[46b] The Kuwajima's and Noyori's research groups then developed catalytic, fast and high yielding *syn* selective aldol reactions.[47] Intermediacy of quaternary ammonium enolate rather than a hypervalent fluorosilicate was supported by later studies on the reactivity of isolated

ammonium enolates.[48] Their reactions require addition of silylating agents for obtaining high conversions due to the reversibility of C−C bond formation step. This supports the generation of trimethylsilyl fluoride acting as a silylating agent in the quaternary ammonium fluoride catalyzed reactions. A variety of chiral quaternary ammonium fluorides were then designed for the catalytic enantioselective aldol additions of silyl enolates under phase transfer conditions.[45c,47b,c]



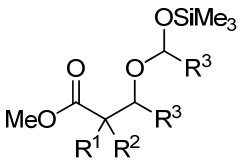

**Scheme 4.** General outline of fluoride catalyzed Mukaiyama-type aldol reaction.

Ability of few neutral Lewis bases to interact with electrophilic trialkylsilyl species has been carefully studied by Stout et al.[49a] From the changes in $^{29}$Si NMR chemical shifts and dissociation equilibrium constants, the order of relative Lewis basicity was established as: *N*-methylimidazole > DMAP > HMPA > dimethylimidazolone > *N*-methylpyridone > pyridine-*N*-oxide > $Ph_3PO$ > DMPU > DMF > pyridine > $Et_3N$. Imamoto et al. surveyed these and related Lewis bases as promoters in the aldol addition of silyl ketene acetals.[49b]




**Catalytic activity:** TTMPP > $Ph_3P$ > $Cy_3P$ > $^nBu_3P$ > 1,2-bis(diphenylphosphino)ethane > DMAP > HMPA > $^tBu_3P$ > $Cy_3PO$ > $Et_3N$ > $Ph_3PO$ > $(PhO)_3P$

$R^1 = R^2 = Me$, $R^3$ = aryl: 68–93%
$R^1 = R^2 = Me$, $R^3$ = alkyl: 50%
$R^1 = H$, $R^2 = Me$, $R^3 = Ph$: 60%
$R^1 = Me$, $R^2 = H$, $R^3 = Ph$: 67%
} *syn*/*anti* = 67:33


Side product

**Scheme 5.** Phosphane catalyzed aldol reactions of silyl ketene acetals.

Out of these, the electron-rich tris(2,4,6-trimethoxyphenyl)phosphine afforded high yields. Low *syn* selectivity obtained from the reactions of both propionate

derived (*E*)- and (*Z*)-enolates led authors to propose an open transition state. Silylated acetal observed as side product similar to that in the fluoride catalyzed aldol additions[47b] suggests analogous generations of naked enolate. However enantioselective Mukaiyama aldol reaction of trimethylsilyl enolates catalyzed by phosphanes is not yet reported.

### 2.2.3.2. Reactions through the hypervalent silicon intermediates

Formation of activated coordinate complexes of silicon with Lewis bases is another approach. In the synthetically useful processes these species are commonly generated *in situ*, in the activation step by the reaction of tetracoordinated silicon compounds with Lewis base.

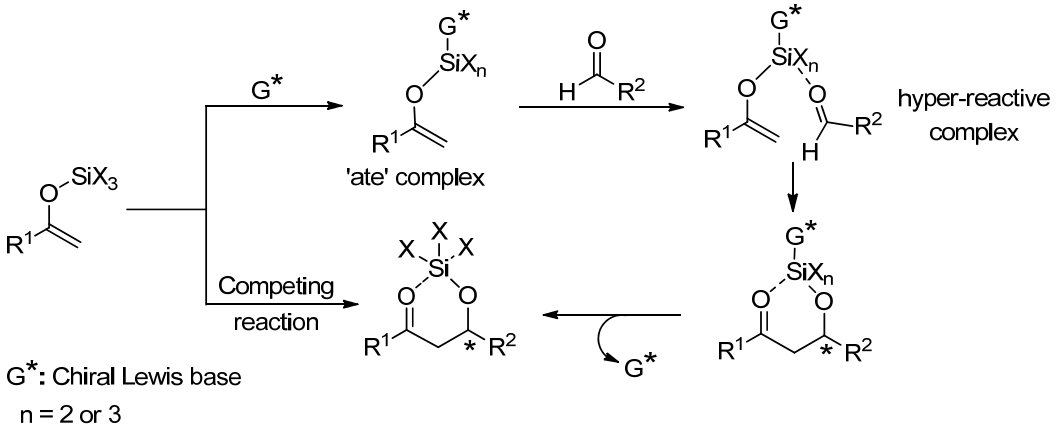
**Possible mechanisms**

Three general mechanisms can be invoked based on the role of hypervalent species.

1. It can act as a Lewis acid, coordinating and activating the substrate towards the attack of an external nucleophile.
2. It can transfer a nucleophilic ligand to the substrate not coordinated to silicon.
3. It can simultaneously coordinate and transfer a nucleophilic ligand to the other substrate.

Though selectivities can be achieved in the first two cases through open transition states, in the last case the peculiar properties of hypervalent silicon species are simultaneously exploited. Thus in the aldol reaction, it generates an ordered preassembly of silyl enolate, aldehyde and chiral Lewis base for the maximum asymmetric influence through a closed transition state. There are few requirements for the development of such type of catalytic process (Scheme 6).

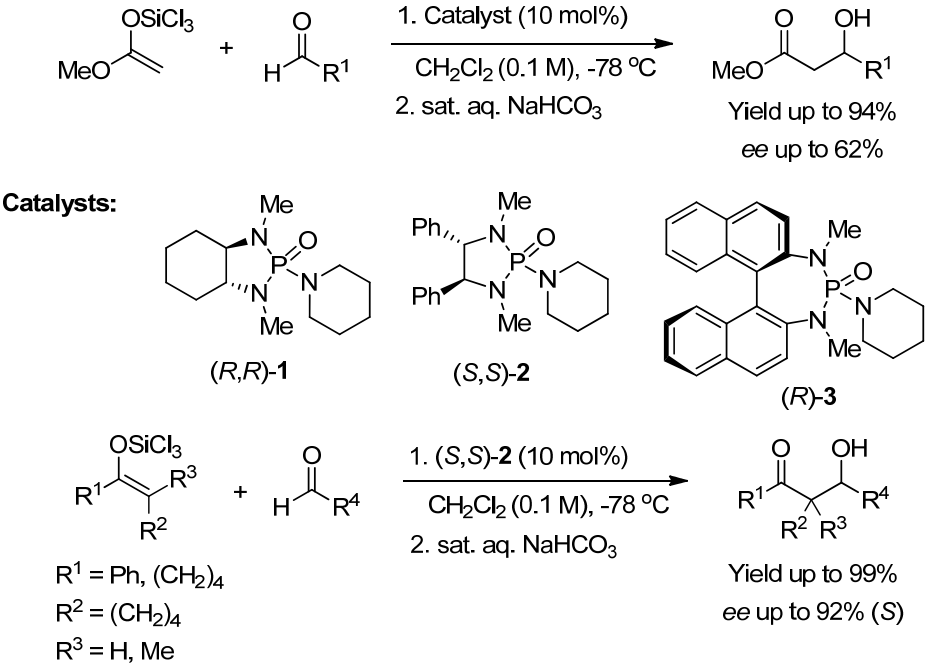
1. To avoid competing reaction, the ‘ate’ complex must be more reactive than enolate.
2. This ‘ate’ complex should activate aldehyde to produce a hyper-reactive complex.
3. The hyper-reactive complex should react through a closed transition state with high degree of chiral information transfer to give a silyl aldolate product.
4. The silyl aldolate should undergo expulsion of Lewis base with the formation of chelated or nonchelated aldolate product.




**Scheme 6.** Asymmetric aldol reaction via hypervalent silicon intermediate of enolate.

### 2.2.3.2.1. Reactions via the cationic siliconium ion of enolate

It occurs by the mechanism of type-3 and provides powerful electrophilic activation with reliable control on selectivity. While studying the reaction of acetate derived trichlorosilyl enolates with aldehydes, Denmark et al. observed that HMPA accelerates the reaction with sterically hindered pivalaldehyde which unlike other aldehydes does not undergo uncatalyzed aldol addition.[10a] The succeeding optimizations of this observation lead to the development of a general protocol using chiral phosphoramides.[10,36,44]

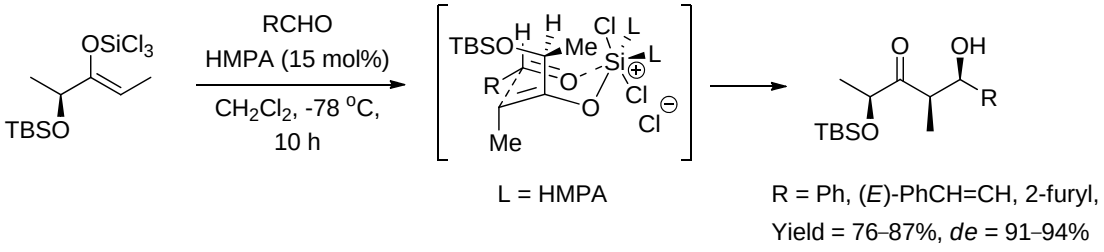



**Scheme 7.** Chiral phosphoramide catalyzed aldol reaction of trichlorosilyl enolates.

Moderate Level of asymmetric induction was initially achieved with limited substrate scope. The reactions of ketone derived trichlorosilyl enolates showed more

improvements.[13e,50] Additions to aromatic aldehydes gave excellent selectivities but those to aliphatic and α,β-unsaturated aldehydes (1,2-adducts) provided moderate selectivities with 2-monosubstituted enolates. While the additions of 2,2-disubstituted and unsubstituted enolates are slow and provide low selectivities.

Uncatalyzed reactions of the substrates bearing stereogenic centers were studied for obtaining diastereoselectivities. It was noted that the reactions of methyl ketone derived trichlorosilyl enolates results in low selectivities. Addition of HMPA or a proper achiral or chiral phosphoramide dramatically accelerates the rate as well as diastereoselectivity.[51] The high selectivities (*syn*,*syn* adducts) obtained in the HMPA catalyzed reaction of homochiral (*Z*)-enolate with various aldehydes was explained by the chair-like cationic transition state.[51b]




**Scheme 8.** HMPA catalyzed aldol reaction of trichlorosilyl enolate.[51b]

A range of efficient $C_2$-symmetric and asymmetric chiral phosphoramides[10b,45] including polymer supported ones[52] were introduced for enantioselective additions of trichlorsilyl enolates and a detailed mechanistic investigation was carried out.[53] Uncatalyzed reaction proceeds through a closed boat like transition state involving unionized hypervalent silane with tbp-configuration of silicon and aldehyde binding at its apical position. It provides high *syn* selectivities with (*E*)-enolates and low *anti* selectivities with (*Z*)-enolates.[13d,50]

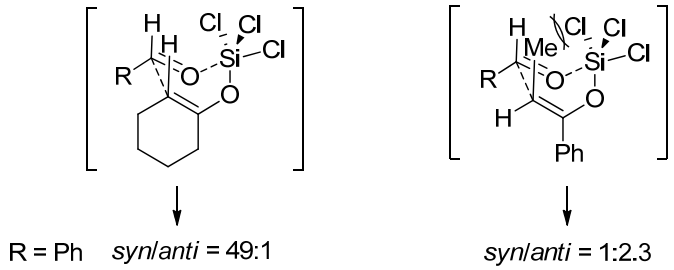



**Figure 6.** Transition states of uncatalyzed aldol addition of trichlorosilyl enolates.

While in the presence of phosphoramide, it displaces one of the chloride from silicon generating cationic siliconium ion; formation of which is supported by the rate

acceleration in the presence of Hunig,s base. It then activates aldehyde through a closed transition state.

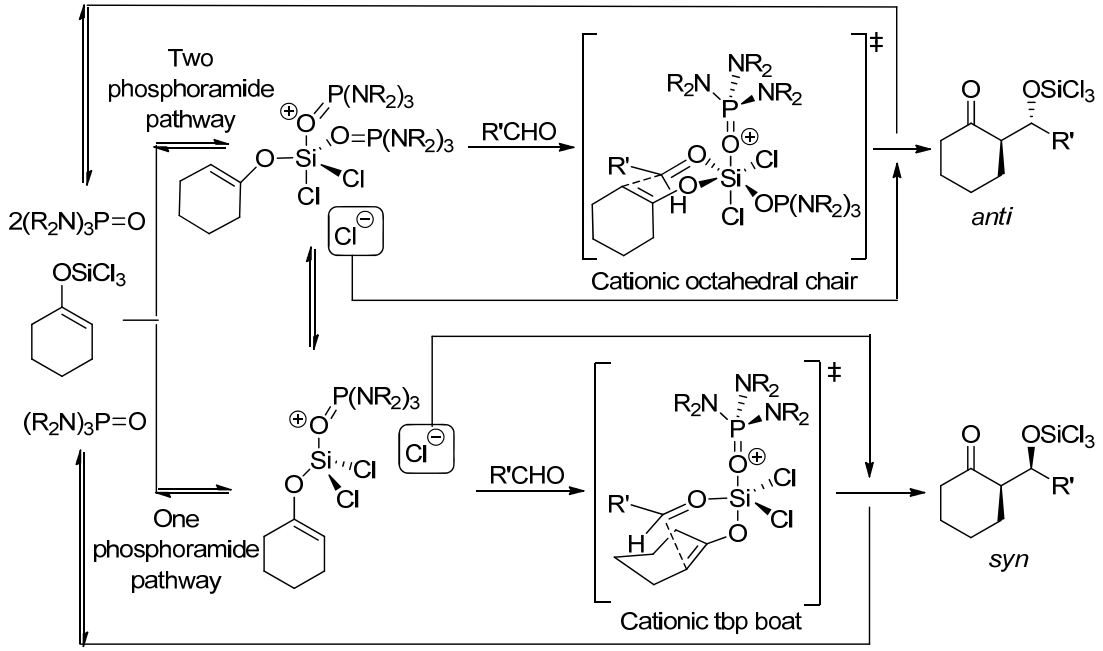
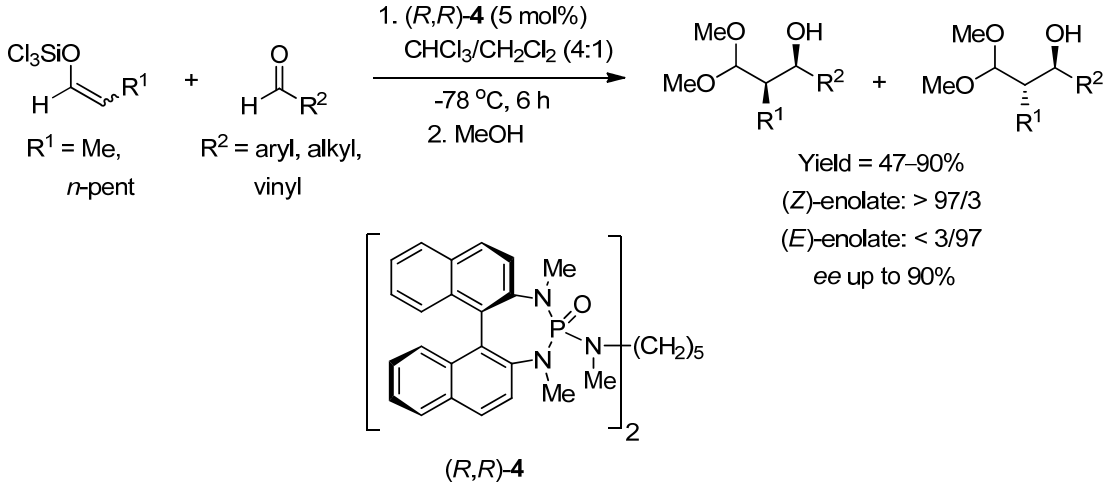



**Figure 7.** Unified mechanism of phosphoramide catalyzed aldol reaction.

When the phosphoramide is less bulky and monodentate, two of these molecules coordinate with silicon and the reaction proceeds via a cyclic chair like transition state. The (*Z*)-enolate gives *syn* product and (*E*)-enolate gives *anti* product in modest enantioselectivities. While in the case of bulky monodentate activator, coordination of second catalyst molecule is precluded by sterics. The reaction then proceeds via a cationic boat like transition state involving pentacoordinate silicon and diastereoselectivity is reversed retaining high enantioselectivities. Thus diastereoselectivity mainly depends on the structure and loading of catalyst.[54] With increasing steric bulk of the *N*-substituent, *syn* selectivity increases while increasing the loading of catalysts promotes reaction via two phosphoramide pathway and diminishes the *syn* selectivity. It thus suggests the use of bisphosporamides for getting higher rates and selectivities.

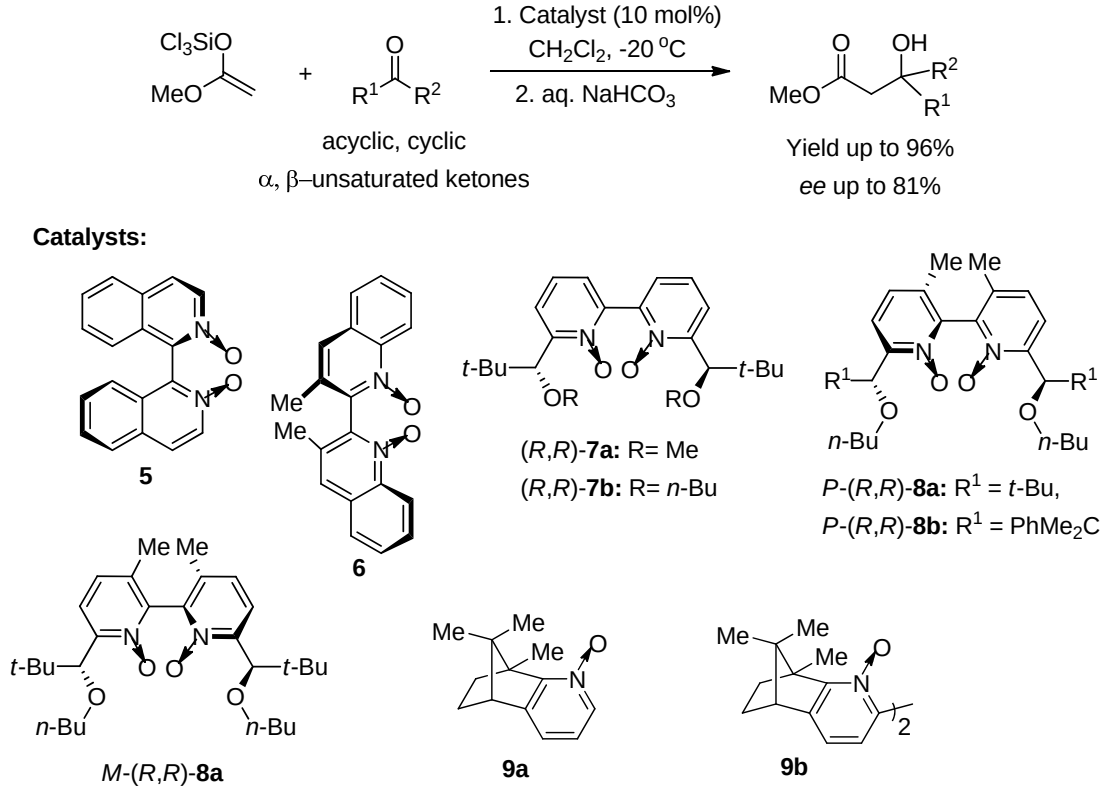
Several general procedures were also developed for the preparation of trichlorosilyl enolates eg. direct enolsilylation with trichlorosilyl triflate, electrophilic substitution of *O*-silyl, α-*C*-silyl- or stannyl carbonyl compounds[10] and most useful direct transsilylation of trimethylsilyl enolates with $SiCl_3OTf$ or $SiCl_4$ (in the presence of $Hg(OAc)_2$).[55] First catalytic diastereo- and enantioselective crossed aldol reaction

of aldehydes was achieved using their stereodefined trichlorosilyl enolates in the presence of dimeric phosphoramide.[56]




**Scheme 9.** Catalytic crossed aldol reaction of aldehydes.

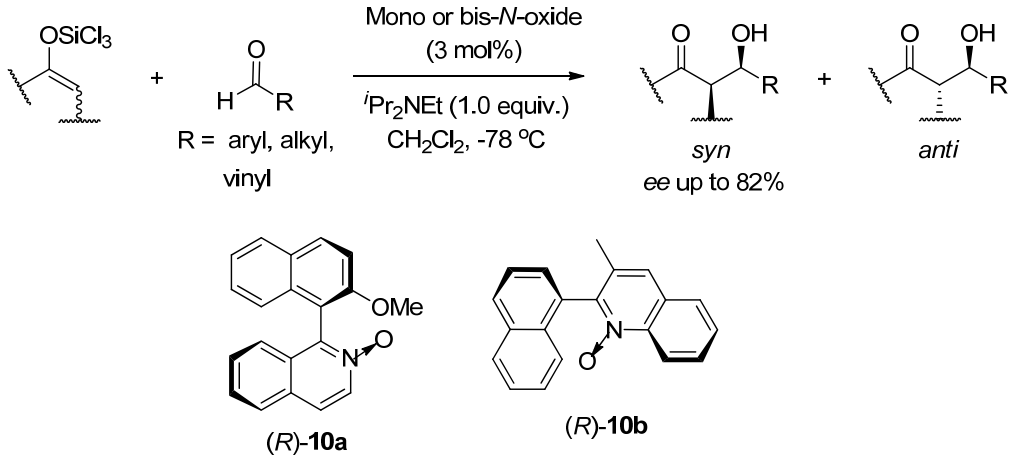
A high yielding and highly selective addition of trichlorosilyl ketene acetal (unsubstituted enolates) to ketones was achieved using pyridine-bis-*N*-oxides;[57a,b] while phosphoramides and mono *N*-oxide (**9a**) gave poor selectivities.




**Scheme 10.** Bis-*N*-oxide catalyzed aldol addition of trichlorosilyl enolates to ketones.

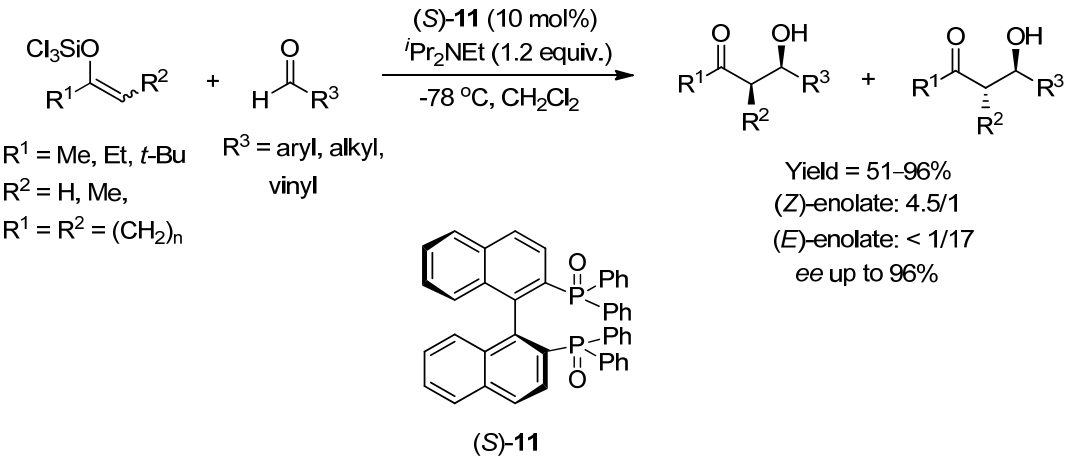
This is due to the ability of aromatic *N*-oxides to balance the higher reactivity of these trichlorosilyl enolates and lower reactivity of ketones towards the nucleophilic attack. In the absence bis-*N*-oxide slow addition takes place even at higher temperature (0 °C). Amongst the aromatic bis-*N*-oxides, those from 2,2'-bipyridine especially *M*-(*R*,*R*)-**8a**, provides good results while those derived from (+)-(*R*)-camphor gives poor yields and selectivities. The ketones bearing enolizable protons also provide aldol products in high yields and enantioselectivities.

Nakajima et al. further developed this concept for the efficient activation of several trichlorosilyl enolates of ketones in their additions to aromatic aldehydes using both bis-*N*-oxides and monodentate *N*-oxides.[57c] In the presence of *N*,*N*´-dioxides, *anti* adducts were obtained from (*E*)-enolates and *syn* adducts from (*Z*)-enolates in decent diastereoselectivity and moderate enantioselectivity. Whereas monodentate *N*-oxides predominantly gave the *syn* adducts. Based on this, a cationic chair like transition state for bis-*N*-oxide catalyzed reaction and a boat like transition state for monodentate *N*-oxide catalyzed reaction were proposed.




**Scheme 11.** *N*-oxide catalyzed aldol additions of trichlorosilyl enolates to aldehydes.

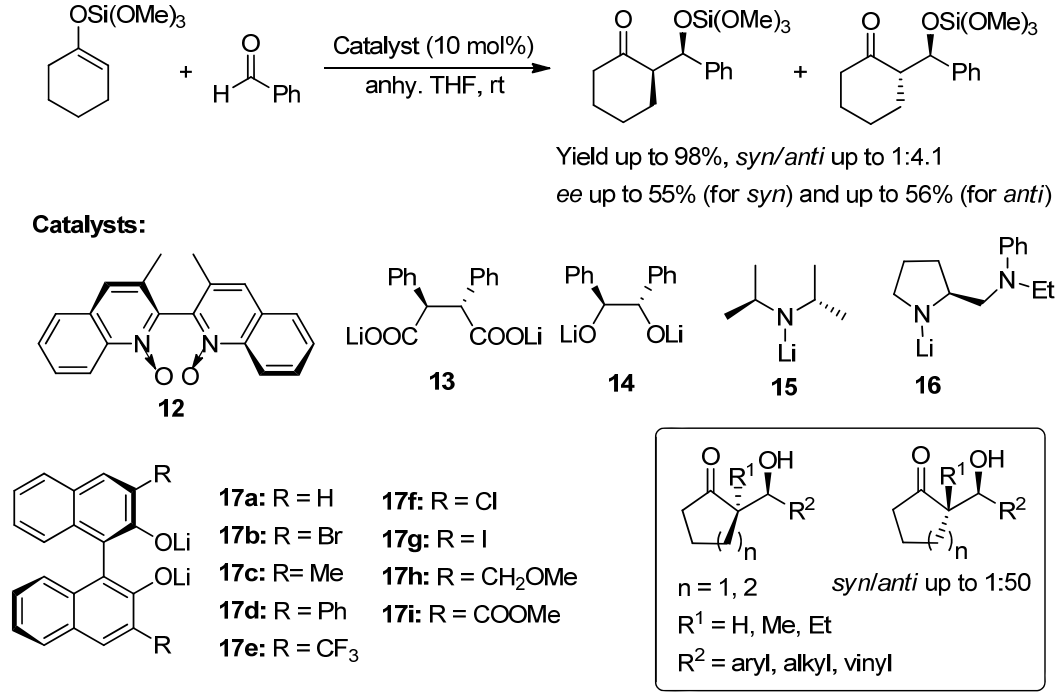
It was also shown that chiral phosphine oxide (BINAPO) also catalyzes the addition of trichlorosilyl enolates to aldehydes in moderate yield and diastereoselectivity but with high enantioselectivity.[58] Addition of Hünig's base increases both chemical and stereochemical efficiency by neutralizing the generated HCl and promoting the dissociation of phosphine oxide from silicon intermediate. The *anti* adducts obtained from (*E*)-silanes and *syn* adducts from (*Z*)-silanes suggests the mechanism similar to bisphosphoramide catalysis.




**Scheme 12.** Aldol additions of trichlorosilyl enolates catalyzed by BINAPO.

Although the use of moisture sensitive trichlorosilyl enolates does not seem practical, it provided a direction for employing easily accessible and more stable silyl enolates as substrates for the Lewis base catalyzed reactions. Later it has been demonstrated that conjugate bases of various oxygen and nitrogen based functional groups get associated with organosilicon pronucleophiles and promote their additions to carbonyl groups.

Application of much stable trimethoxysilyl enolates in the aldol reaction was reported by Nakajima et al. using lithium salts of binaphthol derivatives, amines and diols as catalysts.[59]




**Scheme 13.** Mukaiyama-type aldol reaction of trimethoxysilyl enolates.

Binaphthol salts, especially those having 3,3'-dichloro and dibromo substituents (**17b** and **17f**), gave good diastereo- and enantioselectivities at room temperature which further improved by lowering the temperature (-45 $^{o}$C). Aromatic *N*-oxides and weak carboxylates were unable to catalyze this reaction. A mechanism involving siliconium ion, similar to the Lewis base catalyzed reaction of trichlorosilyl enolates, was proposed under anhydrous conditions. This methodology was further utilized for the enantioselective formation of quaternary carbon centers using 2,2-disubstituted enolates as the substates.[59c] Interestingly in the presence of equimolar amounts of water (1.5 equiv.), from (*E*)-enolates (1.5 equiv.) *syn* products were formed with considerable improvement in the rate and enantioselectivities. On the basis of this and quick decomposition of enolate in the presence of catalyst and water, authors proposed an open transition state involving coordination of water with silicon.

Trichloro[10] and trimethoxy[59a] silyl enolates possess more Lewis acidity at the silicon center than more common trialkylsilyl enolates. After coordination of Lewis base, they loses one of the chloride or methoxide anion generating a cationic siliconium ion which still being Lewis acidic, activates aldehyde through a highly ordered closed transition state and provides reliable control on selectivity. According to the general mechanism this is like a Lewis base catalyzed-silicon Lewis acid mediated process. Formation of cationic siliconium ion is not possible from the dialkyl or trialkylsilyl enolates. That's why an asymmetric Lewis base catalysis using these enolates is difficult and not reported till date. However there are several reports describing their racemic aldol additions.

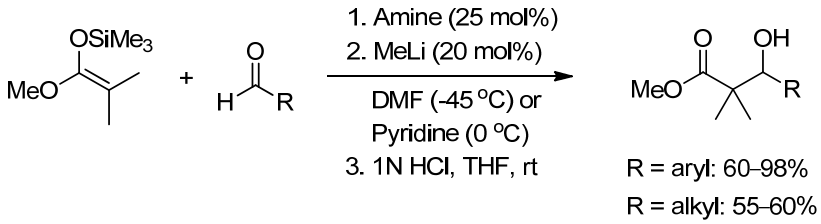
#### 2.2.3.2.2. Catalysis through activated silicon enolate

Based on the catalyst used, these reactions can be grouped into the two types.

**Anionic activation**

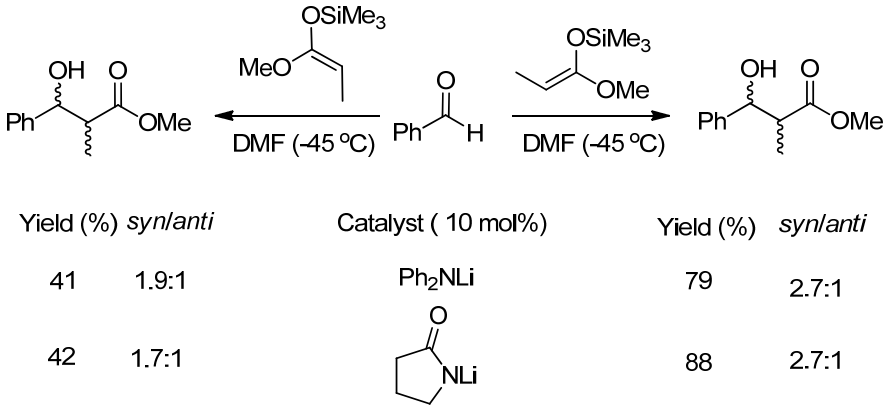
Extensive studies by Mukaiyama et al. have demonstrated the ability of lithium salts of hindered secondary amines to promote the addition of trimethylsilyl ketene acetals to aldehydes.[60a] Among these lithium diphenylamide acts as the most effective promoter. Solvent screening showed that THF as a solvent requires stoichiometric amounts of catalyst and gives a mixture of free aldol (major) and *O*-silyl aldolate; while DMF (at -78 $^{o}$C) and pyridine (at 0 $^{o}$C) enabled a catalytic process and provided good yields of the later (most by NMR integrations). Based on the several control experiments, authors showed the actual catalyst is lithium amide and no involvement

of lithium enolate intermediate. A difficulty in the separation of diphenyl amine from the reaction mixture after workup was later solved by using lithium salt of 2-pyrrolidone as a catalyst having a close p*K*a of N–H;[60b,c] again in DMF and pyridine. Although the p*K*a value of succinimide N–H is much lower than that of diphenylamine or pyrrolidone, its lithium salt effectively activated the enolate.




**Scheme 14.** Aldol reaction of trimethylsilyl enolates using lithium amide catalysts.

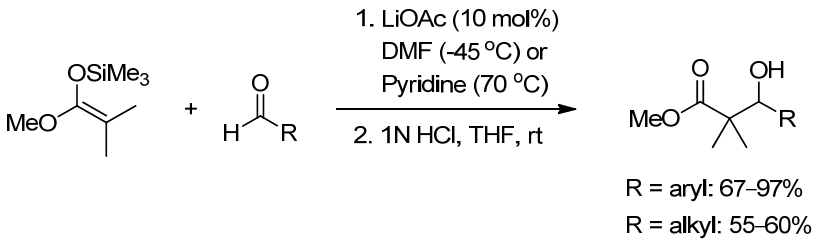
The reactivity of (*E*)-enolates was found to be lower than that of (*Z*)-enolates. Their reactions are less *syn* selective and diastereoconvergent suggesting an open transition structure.




**Scheme 15.** Diastereoselectivity in lithium amide catalyzed reactions.

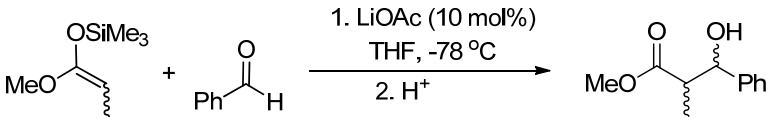
Milder and readily available lithium salts of carboxylic acids eg. acetic acid, isobutyric acid, pivalic acid and various substituted benzoic acids also catalyze this reaction in DMF at -45 °C.[61a,b] But the reaction does not proceed at 0 °C in pyridine and gives high yields at 70 °C. Authors suggested this is to be the weak Lewis basicity of carboxylate salts but that does not rationalize the reactions in DMF. Also in the absence of catalyst, only 14% of product was formed even at 70 °C in pyridine indicating the simultaneous participation of carboxylate salt and solvent in the transition state. Aromatic aldehydes with electron donating groups (*N* or *O*-donors) react smoothly while those with electron withdrawing groups and aliphatic aldehydes give moderate yields in DMF; suggesting a cooperative effect of electron donors. The

problem of low yields from these aldehydes was later solved by using aq. DMF (1:50) as the solvent albeit 2 equiv. of enolate is required.[61c] Sterically hindered triethylsilyl enolate of methyl isobutyrate gives very poor yield (4%). Interestingly 2-pyridinecarboxaldehyde which does not react with enolates under Lewis acidic conditions also give high yields of aldol adducts.




**Scheme 16.** Lithium acetate catalyzed Mukaiyama-type aldol reaction.

The reactivities of both the (*E*)- and (*Z*)-enolates were found to be nearly same and both give products with moderate *syn* selectivity. But the selectivity decreases in aqueous DMF which may be due to the rapid isomerization of lithium aldolate intermediate. The amount of catalyst does not significantly influence the yield and their catalytic activity depends on the nucleophilicity.




| | Solvent | Temp (°C) | Time (h) | Yield (%) | *syn*/*anti* |
|---|---|---|---|---|---|
| (*E*)-enolate | DMF | -45 | 3 | 78 | 1.8:1 |
| | Pyridine | 70 | 2 | 88 | 1.5:1 |
| (*Z*)-enolate | DMF | -45 | 3 | 79 | 2.7:1 |
| | Pyridine | 70 | 2 | 94 | 1.9:1 |

**Scheme 17.** Diastereoselectivity in lithium acetate catalyzed reactions.

Formation of silylated acetal similar to fluoride[47b] or phosphine[49b] catalyzed reactions was observed. Its yield increases when the catalysts are sodium acetate, potassium acetate, lithium succinimide or potassium phthalimide and decreases when the catalyst is lithium pivalate or pyridine is the solvent. The α,β-unsaturated ketones preferentially gives Michael adducts in the presence of both amide and carboxylate salts.[62a] Also *N*-tosylaldimines gives a Mannich-type adducts.[62b]

Authors suggested a similar mechanism (type-2) for both the lithium amide and carboxylate catalyzed reactions in DMF, with a minor modification in the case of lithium carboxylate catalysis to account the formation of small amount of acetal

adduct. As a consequence of a strong solvent effect, the authors invoke a hexacoordinate adduct of the silyl enolate with anionic Lewis base and a solvent molecule. But as in fluoride activated reactions, there is a mechanistic ambiguity in the actual role of the added agent either as an initiator or a catalytic species.[45]

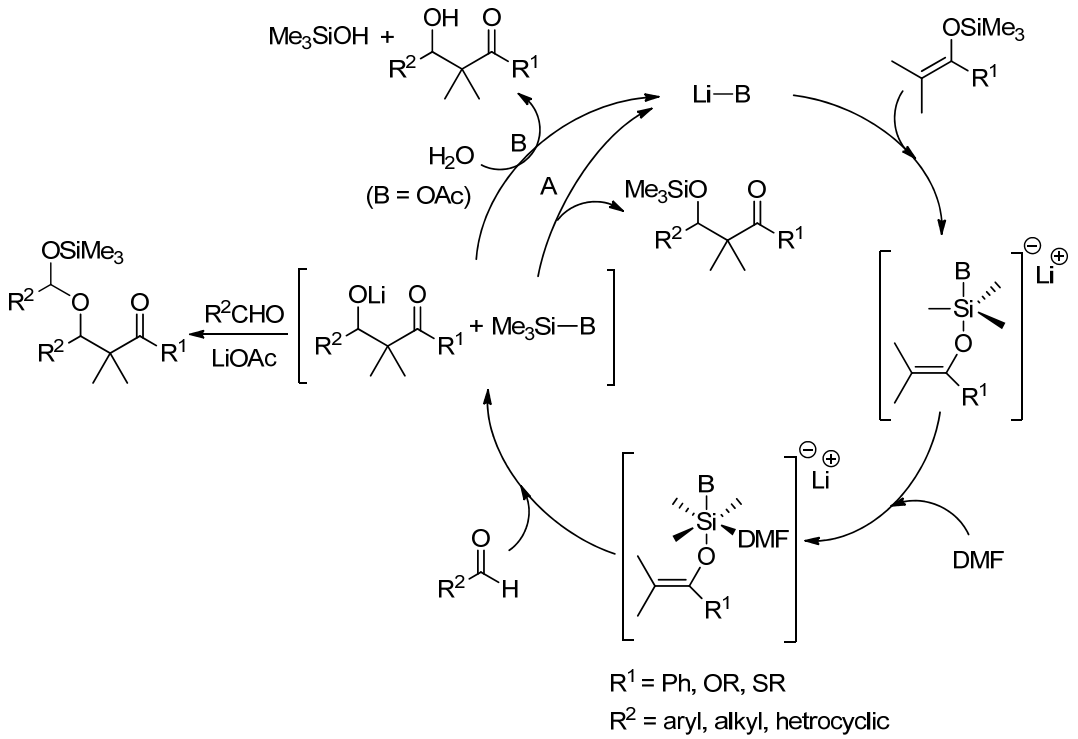
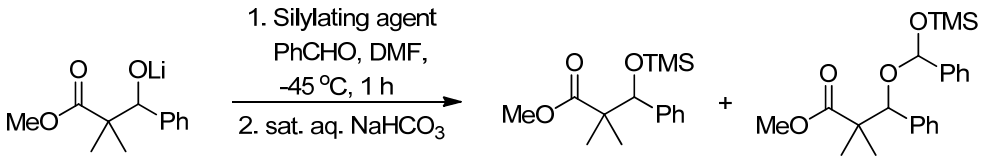



**Figure 8.** Mechanism of aldol reaction catalyzed by lithium salts of amines and carboxylic acids: (A) in the absence of water and (B) in the presence of water (lithium carboxylate).

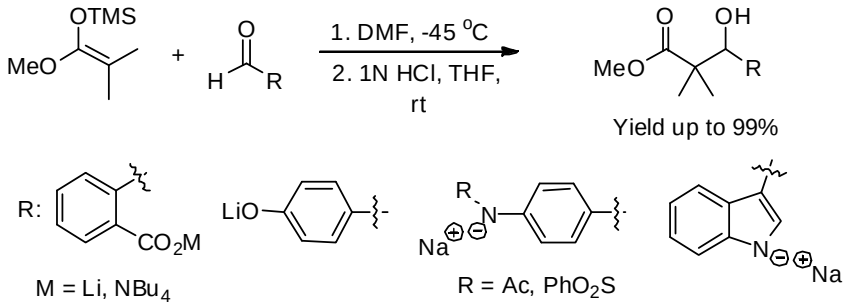
In anhydrous solvents, the lithium aldolate product undergoes silylation with the TMS-Lewis base adducts with regeneration of Lewis base. It was supported by silylation of independently generated lithium aldolate intermediate by both TMS-carboxylate and *N*-TMS-2-pyrrolidinone. However this does not prove the suggested catalyst turnover step. In the lithium carboxylate catalyzed reaction in aqueous DMF, this lithium aldolate undergoes hydrolysis to free aldol.




| Silylating agent | | |
|---|---|---|
| $CH_3CO_2TMS$ | 80 | 20 |
| *N*-TMS-2-pyrrolidinone | 100 | 0 |

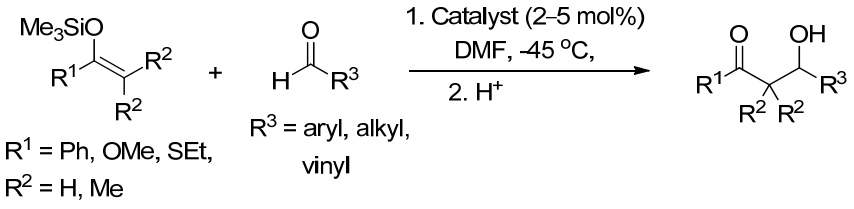
**Scheme 18.** Silylation of preformed lithium aldolate.

Aldehydes bearing Lewis base moieties (carboxylate or amide salts) activates and reacts smoothly with trimethylsilyl enolates of esters to afford the corresponding aldol products in good to high yields.[63a] Various functionalized aldols can be directly obtained without requiring the protection of proper functional groups of aldehydes by simply converting them to salts.

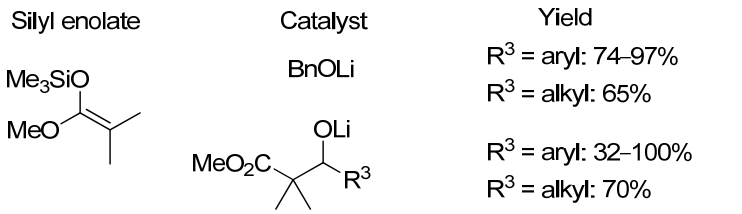



**Scheme 19.** Self-promoted aldol reaction of aldehydes having Lewis base moiety.

Conjugate bases of variety of alcohols acts as effective catalysts at low loading (2–5 mol%) out of which lithium salts were found to be the most effective.[63b] Lithium benzyloxide was selected by the authors and showed good yields in the reactions of 2,2-disubstituted silyl acetals with variety of aldehydes while the unsubstituted silyl enolates gave low yields. As aldol product itself is an alkoxide, a product catalyzed reaction was also reported using catalytic amount of lithium aldolate as initiator catalyst.[63b] A closer examination of this reaction reveals that it operates by Lewis base initiated product catalyzed pathway, as reported for few fluoride catalyzed reactions.[45]



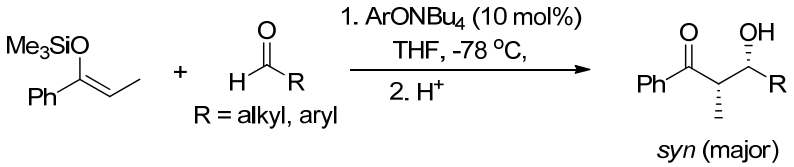

**Catalysts:** BnOLi, MeONa, EtONa, $^t$BuOLi, $^t$BuOK, PhOLi, PhONBu$_4$



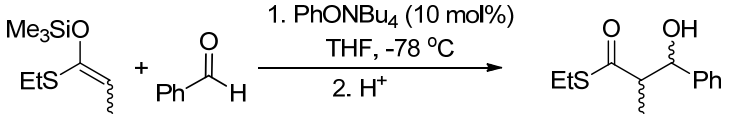

**Scheme 20.** Alkoxide and product catalyzed aldol reaction.

Lithium phenoxide and benzyloxide afford low yields in the corresponding reactions of ketone derived trimethylsilyl enolates. While the tetrabutylammonium

salts especially those of phenol and *p*-methoxyphenol provide high yields and high *syn* selectivities of the products in THF.[64a] Both (*E*) and (*Z*)-enolates showed similar reactivity and similar *syn* selectivity; from which authors proposed acyclic transition state similar to lithium amide or carboxylate catalyzed reaction.



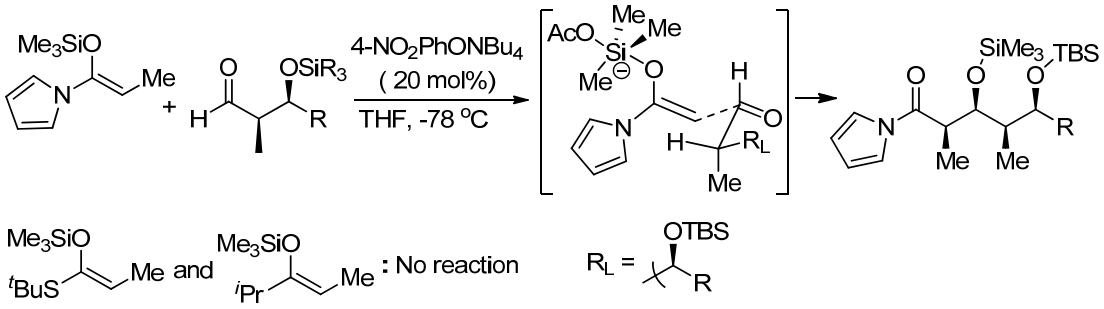

**Ar:** Ph, 2-MeOPh, 3-MeOPh, 4-MeOPh, 4-ClPh, 2-Naphth.




| | Time (h) | Yield (%) | *syn*/*anti* |
|---|---|---|---|
| (*Z*)-enolate | 1.5 | 78 | 93:07 |
| (*E*)-enolate | 1 | 88 | 94:06 |

**Scheme 21.** $ArONBu_4$ catalyzed aldol additions of trimethylsilyl enolates.

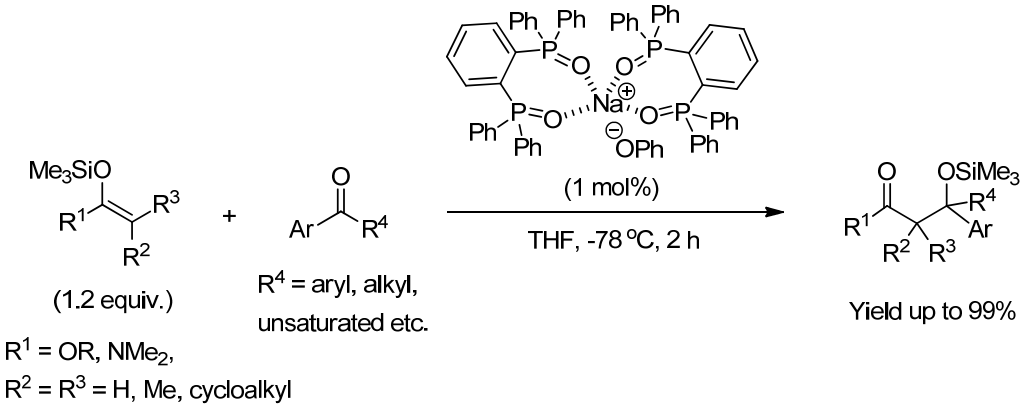
Nelsson et al. applied tertrabutylammonium *p*-nitrophenoxide as a catalyst for the reaction of amide derived trimethylsilyl enolate with α-substituted aldehydes in the total synthesis of Erythronolide-B to get all-*syn* aldol adducts.[64b] From the control experiments it has been revealed that *p*-nitrophenoxide possesses correct Lewis basicity to promote efficient silyl enolate addition; without base promoted epimerization of α-substituted aldehydes. However trimethylsilyl enolates of thioesters and ketones do not react under the identical conditions.




**Scheme 22.** 4-$NO_2PhONBu_4$ catalyzed *syn* selective Mukaiyama-type aldol reaction.

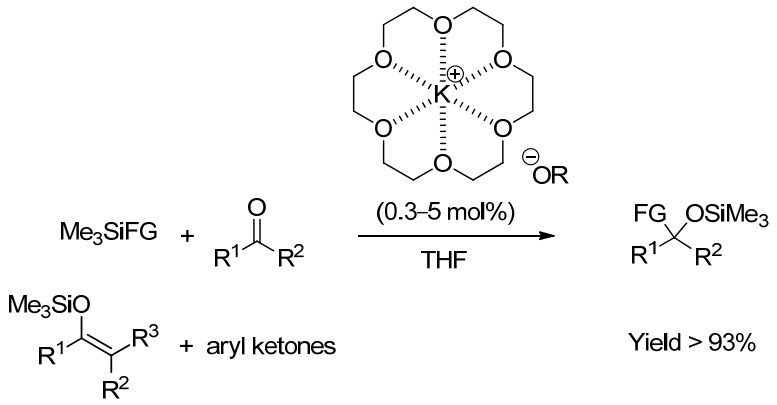
A highly efficient reaction of trimethylsilyl enolates of esters and amides with ketones in the presence of phenoxide-phosphine oxide complex was developed by Ishihara et al.[65a] Phosphine oxide especially bidentate 1,2-$(OPPh_2)_2C_6H_4$ remarkably accelerates the catalytic activity of phenoxide. Amongst the alkali metal phenoxides,

sodium salt showed high reactivity even in a low loading though the reaction becomes slow. A variety of aromatic ketones and aldimines undergo enolate additions in good to excellent yields with minimum competing retro-aldol reaction.



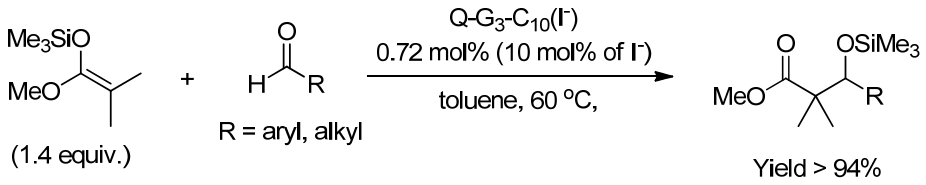

**Scheme 23.** Sodium phenoxide-phosphine oxide as activators.

A potassium alkoxide-crown ether complex was developed as catalyst for the reaction of variety of silyl nucleophiles with ketones and aldimines.[65b] This catalyst has been found to be more efficient than the earlier one. The reactivity order of different complexes was found as: KOPh-18-crown-6 > NaOPh-15-crown-5 >> LiOPh-12-crown-4.



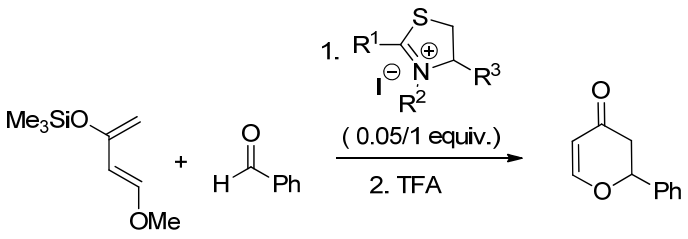

**Scheme 24.** Potassium alkoxide-crown ether complex as a catalyst.

Kaneda et al. used quaternary ammonium dendrimers containing iodide counter ions as Lewis base catalysts in the reaction of trimethylsilyl acetal with aromatic and aliphatic aldehydes in toluene.[66] High activity of dendrimers over TBAI and THAI could be due to the highly polar environment within the dendrimers which acts as a nano reactor.




**Scheme 25.** Quaternary ammonium dendrimers as catalysts.

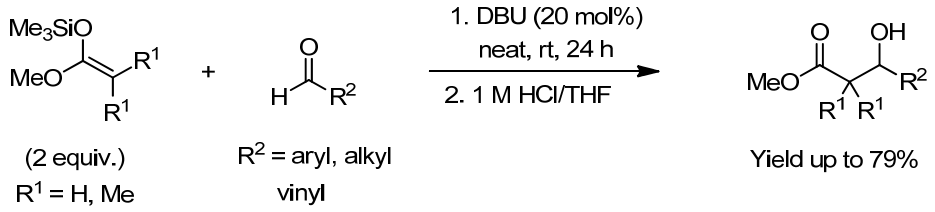
Gaumont et al. used a series of thiazolinium iodides for the aldol reaction of Danishefsky's diene with benzaldehyde.[67] Only the aldol products are formed without any hetero Diels-Alder reaction. These salts can be recycled for more than 10 times without loss of activity.




**Scheme 26.** Thiazolinium salt catalyzed reactions.

**Activation by neutral Lewis bases and weak anions**

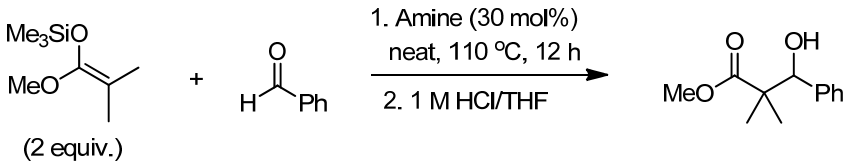
Loh et al. reported a DBU catalyzed aldol reaction of ketene silyl acetals with various aldehydes in good yields under solvent- and metal-free conditions.[68a] Low yields were obtained in solvents such as MeOH, THF, DMF, DCM etc. Under these conditions, α,β-unsaturated cyclic ketones give Mukaiyama-Michael adducts.




**Scheme 27.** DBU catalyzed Mukaiyama-type aldol reaction.

Two years later a systematic screening of various amines as catalysts in the aldol reaction of ketene silyl acetals was carried out by Srivastava and he showed that the yield of reaction increases with the increase in basicity of amine.[68b]

**Table 1.** Screening of various amines for Mukaiyama-type aldol reaction.




| No | Amine | p*K*a[a] | Yield (%) |
|---|---|---|---|
| 1 | None | -- | 0 |
| 2 | Pyridine *N*-oxide | -- | 36 |
| 3 | Pyridine | 5.2 | 27 |
| 4 | DMAP | 9.7 | 45 |
| 5 | Imidazole | 7.0 | 39 |
| 6 | *N*-methyl imidazole | -- | 48 |
| 7 | TBD | -- | 53 |
| 8 | MTBD | 13.0 | 65 |
| 9 | DBU | 11.9 | 60 |

[a] p*K*a values for the aqueous solution of the corresponding conjugate acids.

Based on this they have developed a heterogeneous Lewis base, 1,5,7-Triazabicyclo[4.4.0]dec-5-ene functionalized SBA-15 and was found to be the efficient catalyst. Aromatic and aliphatic aldehydes react smoothly with trimethylsilyl ketals. It gives Michael adduct with the α,β-unsaturated cyclic ketones but aldol product with α,β-unsaturated aldehydes. High catalytic activity, mild reaction conditions, easy recovery and reusability are the few advantages of this catalyst.

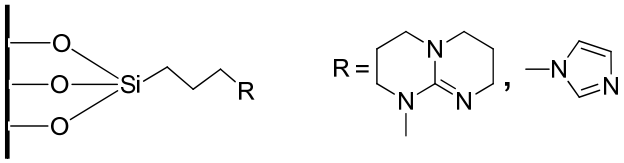
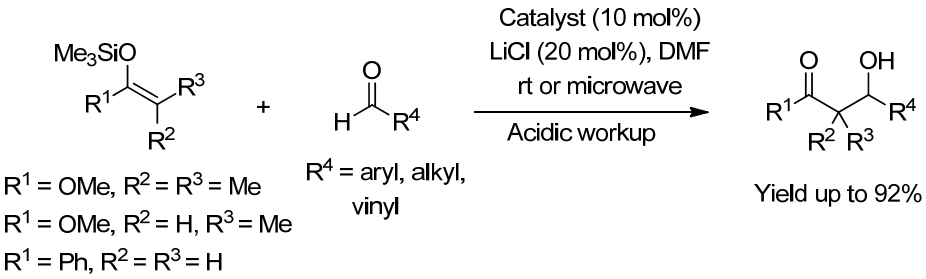



**Figure 9.** Organic base functionalized SBA-15.

In 2005 Hagiwara et al. showed that in the presence of lithium chloride, relatively less basic amines like DMAP, *N*-methyl imidazole and few *N*-oxides[35d,69] also catalyze the reaction of various trimethylsilyl enolates with aldehydes in DMF. As predicted by the Lewis basicity scale of Stout et al.,[49a] *N*-methyl imidazole showed excellent catalytic activity than pyridine *N*-oxide. Conditions are mild enough to tolerate the functional groups like OH, OAc, OTHP, OTBS, SMe, pyridyl, olefin etc.

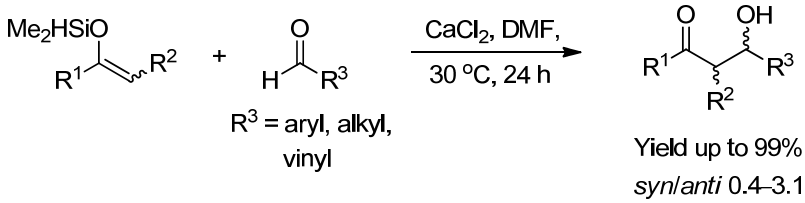
Microwave irradiation at 90 $^{o}$C accelerated the reaction without dehydration of the product. Though the yields were low, LiCl (44%), *N*-methyl imidazole (68%), DMAP (27%), pyridine *N*-oxide (55%)[35d] themselves catalyzes the reaction indicating a co-operative effect of the two catalysts. However participation of the solvent cannot be ruled out.




**Catalysts:** *N*-methylimidazole, Pyridine *N*-oxide, DMAP, DMAP *N*-oxide, $Me_3N$-oxide

**Scheme 28.** LiCl accelerated amine catalyzed aldol reactions.

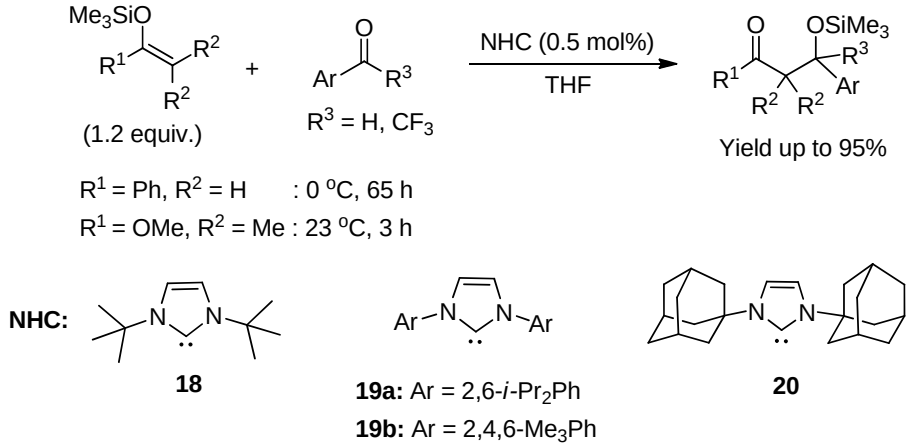
Hosomi et al. reported that an uncatalyzed reaction of dimethylsilyl enolates with aldehydes in aq.DMF gets accelerated by the addition of catalytic amount of $CaCl_2$.[70] The corresponding reaction of trimethylsilyl enolate was found to be quite slow and author suggested less sterics in dimethylsilyl enolates as a reason for their increased reactivity.




**Scheme 29.** $CaCl_2$ promoted aldol addition of dimethylsilyl enolates.

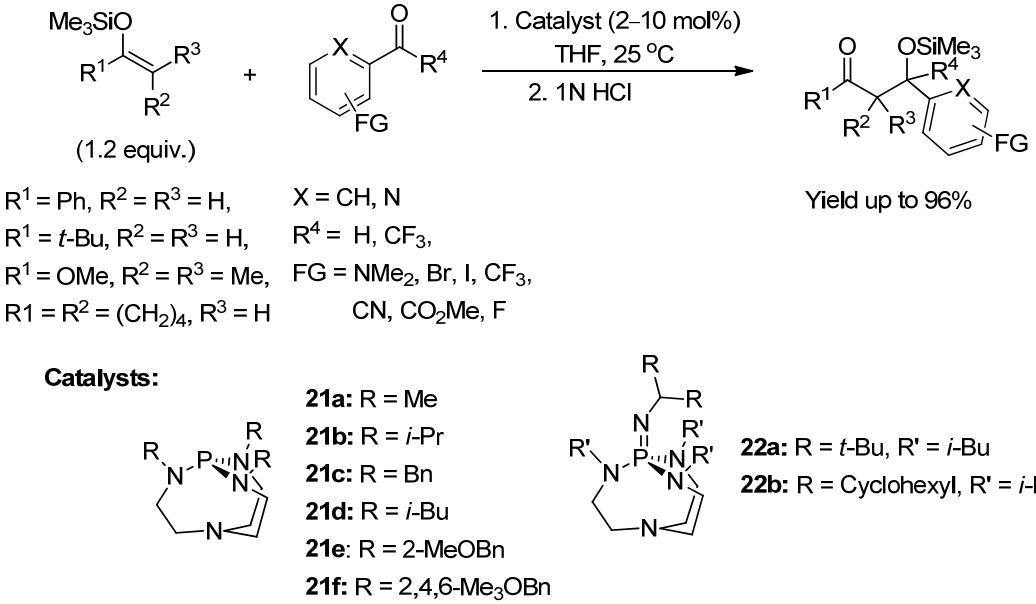
After screening various salts eg. LiCl, $Li_2SO_4$, $Li_2CO_3$, NaCl, $Na_2CO_3$, $MgCl_2$, $Bu_4NCl$, $CaI_2$, $CaCl_2$, LiI, NaI, KI, $Bu_4NI$, LiOTf etc., it was observed that rate accelerating ability of salt increases with intrinsic nucleophilicity of counteranions: $TfO^- < I^- \leq Br^- < Cl^-$. Rate and yield of $CaCl_2$ catalyzed reaction was found better. DMF, DMSO, aq. DMF and water are the best solvents while in MeOH the dehydrated product was observed as the major. On the basis of weak Lewis acidity of $CaCl_2$ and catalytic effect of tetrabutylammonium chloride, authors concluded that there is no involvement of electrophilic activation of aldehyde and reaction occurs through the activation of enolate by chloride ion.

Song et al. have shown that *N*-heterocyclic carbenes are highly effective catalysts in low loading (0.5 mol%).[71] Bulky adamantly substituted carbene exhibited good catalytic activity, while aryl substituted imidazol-2-ylidenes were found to be the less effective for this reaction. Various aldehydes and 2,2,2-trifluoroacetophenone underwent aldol reactions with trimethylsilyl acetals at 23 °C and with trimethylsilyl enolate of acetophenone at 0 °C in THF to afford the aldol adducts in high yields. Extremely mild, operationally simple reaction conditions and tolerance of various functional groups are the few advantages.




**Scheme 30.** NHC catalyzed Mukaiyama-type aldol reaction.

Verkade et al. reported a proazaphosphatrane catalyzed reaction of variety of trimethylsilyl enolates with aldehydes and activated ketone (2,2,2-trifluoroacetophenone) in THF.[72]




**Scheme 31.** Proazaphosphatranes and iminoproazaphosphatranes as catalysts.

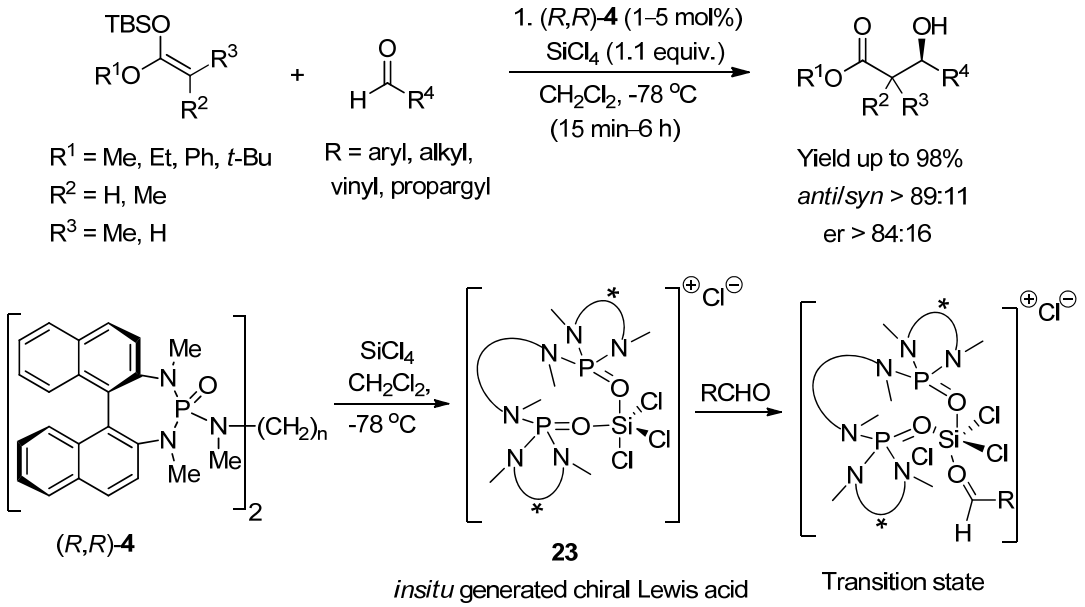
Out of the various proazaphosphatranes and iminoproazaphosphatranes, **21c** worked as a very efficient catalyst. The mild and operationally simple reaction conditions, tolerance of a variety of aryl functional groups and better or comparable yields than those reported earlier are the few advantages.

### 2.2.4. Lewis base-Lewis acid catalysis

Two types of mechanisms can be invoked based on the role played by Lewis base. It can activate a weak Lewis acid or in the presence of Lewis acidic metal cation, can activate silyl enolate.

#### 2.2.4.1. Lewis base activated Lewis acid catalysis

The intriguing demonstration of chiral Lewis base modified siliconium cation as effective catalyst was further reinvestigated with a weak Lewis acid $SiCl_4$, by Denmark et al.[73] Its combination with strongly Lewis basic chiral phosphoramide undergoes *in situ* generation of cationic siliconium ion (type-1 mechanism) similar to trichlorosilyl enolates. Generally other Lewis acids forms covalent adducts with chiral Lewis bases and often decreases their reactivities, whereas Lewis base complexation with group 13 and 14 Lewis acids eg. $SiCl_4$ enhances their Lewis acidity and avoids competing background reactions. This counter-intuitive situation is anticipated by a set of Gutmann's empirical rules.[41]

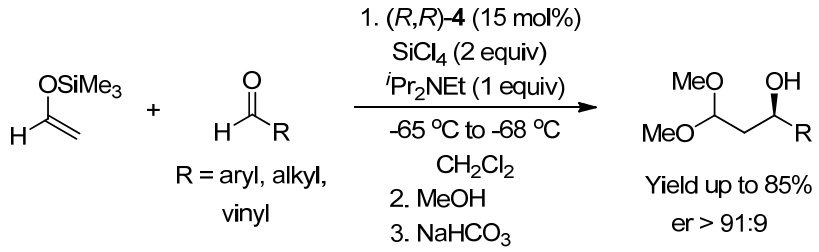



**Scheme 32.** $SiCl_4$/phosphoramide catalyzed aldol reaction of trialkylsilyl enolates.

As preformation of chiral Lewis acid complex is not required, it avoids problem associated with catalysts turnover. It catalyzes the aldol reaction of several

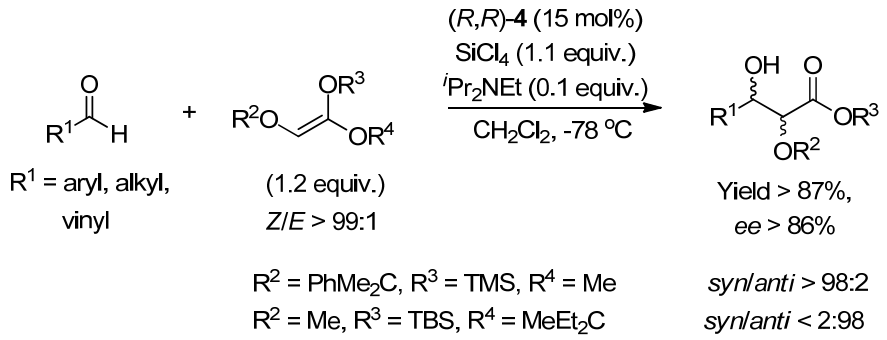
trialkylsilyl enolates of esters with aldehydes. The reaction is found to be stereoconvergent, *anti* selective with selectivities dependent on the steric bulk of alkoxy substituent: Me < Et < Ph << *t*-Bu. On the basis of these results, authors proposed an open transition state where steric interactions between the silyl cation complex and the approaching nucleophile are dominant.[73]

It was later more generalized in the aldol additions of trimethylsilyl enolate of acetaldehyde.[50d,74] Aldol adducts (chlorohydrins) can be trapped as β-hydroxyacetals, aldols or lactones and provides opportunity for stereoselective formation of multiple C−C bonds. Opposite diastereoselectivities to those of aldol additions of corresponding trichlorosilyl enolates were observed.




**Scheme 33.** $SiCl_4$/phosphoramide catalyzed cross-coupling of aldehydes.

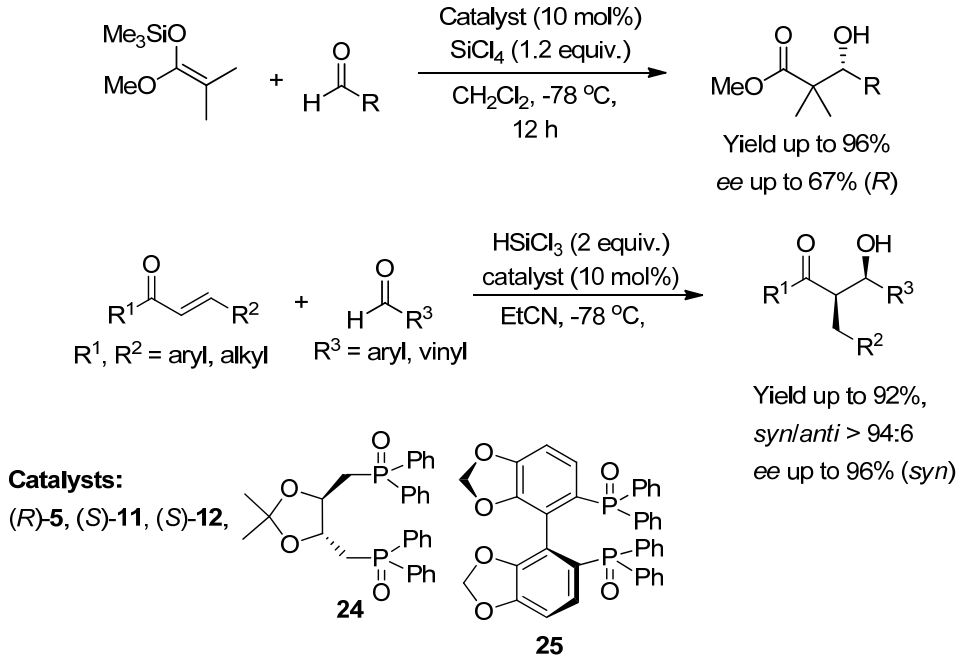
A glycolate aldol reaction is reported for the preparation of stereodefined 1,2-diols.[74c] Diastereoselectivity has been found to be dependent on the size of substituents present on the silyl ketene acetal. Thus both *syn* and *anti*-1,2-diols can be obtained under the same catalytic system in high diastereo- and enantioselectivity.




**Scheme 34.** $SiCl_4$/Phosphoramide catalyzed glycolate aldol reaction.

Later Nakajima et al. screened several phosphine oxides for the enantioselective addition of trimethylsilyl acetals to aldehydes, out of which (*S*)-BINAPO (**11**) provided moderate enantioselectivities in the reactions of aromatic aldehydes.[75a] While aliphatic and α,β-unsaturated aldehydes do not react under these conditions. *In situ* generation of similar activated silicon Lewis acid was achieved via $HSiCl_3$/Lewis

base reduction of α,β-unsaturated ketones which then reacts with aldehydes and gives high *syn* selectivities and high enantioselectivities of aldols.[75b,c] Again out of the several phosphine oxides, (*S*)-(**11**) was found to be a superior activator.



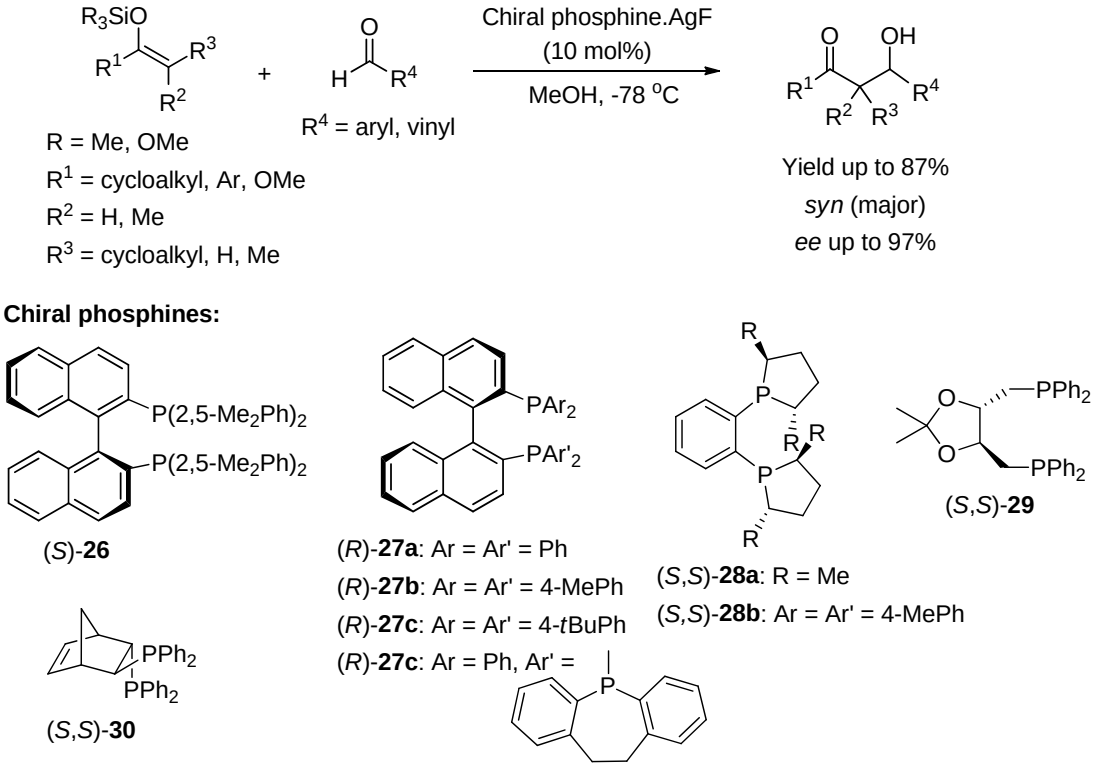

**Scheme 35.** BINAPO activated silicon Lewis acids as catalysts.

Despite of the high selectivity observed with these systems, majority of them are still limited to aromatic and conjugated aldehydes. While the reduced reactivity of aliphatic aldehydes may be due to the unproductive formation of α-chlorosilyl ethers.[72a]

### 2.2.4.2. Combined Lewis base and Lewis acid catalysis

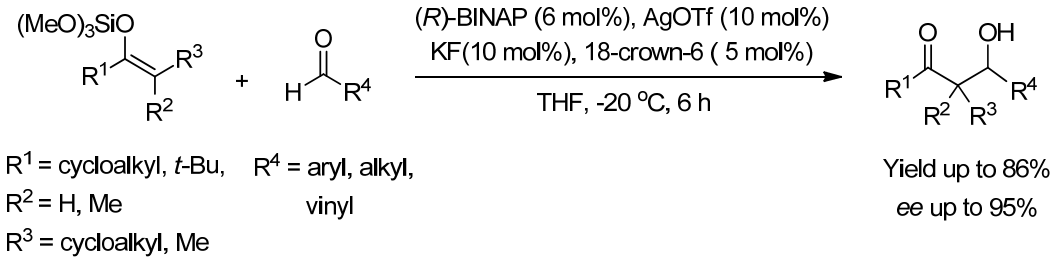
Simultaneous activation of enolate and electrophile by combining the achiral n–σ* catalysis of fluorides with the traditional chiral Lewis acid catalysis is another strategy. Yamamoto et al. have developed a Mukaiyama-type aldol reaction using chiral phosphine.AgF as a dual activator.[76] Out of the several chiral phosphines, (*R*)-*p*-Tol-BINAP (**27b**) gave promising results in the reactions of silyl enolates with aromatic and α,β-unsaturated aldehydes (1,2-adducts) in methanol while aliphatic aldehydes do not react. Trimethylsilyl enolates give low yield while the corresponding trimethoxysilyl enolates provide good yields. On the basis of moderate to high *syn* selectivity obtained irrespective of the enolate geometry, author proposed two different transition states. (*E*)-Enolate follows a boat like while (*Z*)-enolate follows a chair like transition state. A flip between these two transition states (although does not

rationalize the observed results) was proposed to account the observed diastereoconvergence. Authors proposed the formation of a hypervalent silicate that may or may not remain associated with the silver complex which then undergoes aldol addition through an open transition state (Figure 10, (a)).




**Scheme 36.** Chiral phosphine.AgF complex catalyzed aldol reaction.

Yamaguchi et al. have shown that the nature of anionic ligand in the silver complex has a strong impact in the reaction of trimethylsilyl enolates. Coordinating anions such as acetate and chloride behave similarly while weakly coordinating tetrafluoroborate show different reactivity pattern.[77a] An alternative catalyst system consisting of BINAP/ AgOTf/KF/18-crown-6 was developed to allow the reaction in aprotic solvents such as THF with equal high levels of enantioselectivities.[77b]




**Scheme 37.** BINAP/AgOTf/KF/18-crown-6 catalyzed aldol addition.

Unlike the reactions with AgF catalysts, this system can be used for aliphatic aldehydes also. The reactions are diastereodivergent suggesting a closed chair like transition state. Fluoride most likely still acts as an activator of the trialkoxysilyl enolate, but by different interactions (Figure 10, (b)).

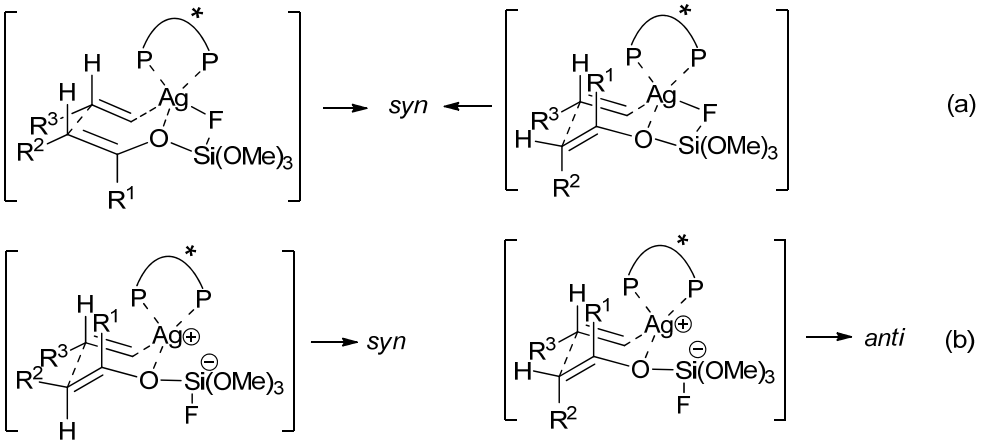
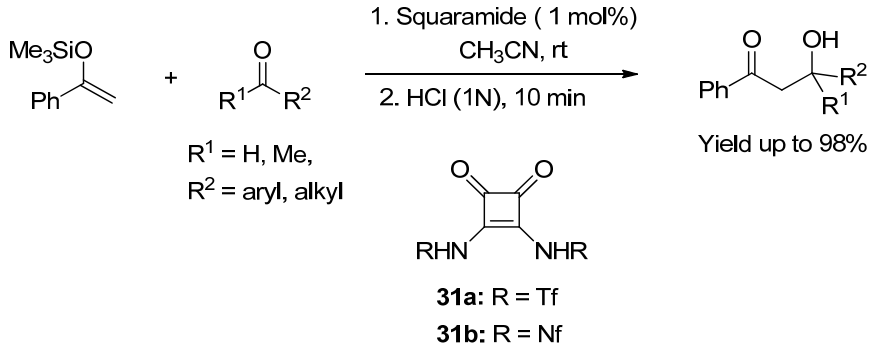



**Figure 10.** Proposed T.S. for catalysis by different Ag(I).phosphine complexes.

### 2.2.5. Brønsted acid catalysis

Enantioselective Mannich-type reaction of trimethylsilyl enolates catalyzed by relatively strong chiral Brønsted acids having distinct chiral pockets and acting merely through hydrogen bonding is well documented.[78] But these catalysts could not activate unfunctionalized aldehydes. Yamamoto et al. developed squaramides (**31a** and **31b**); bench stable Brønsted acids having higher solubility in common organic solvent; as catalysts for the reaction of trimethylsilyl enolates with aldehydes. They act in the low loading (0.1 mol%) without loss of any catalytic activity.[79a] While in the presence of squaric acid complete hydrolysis of enolate occurs.

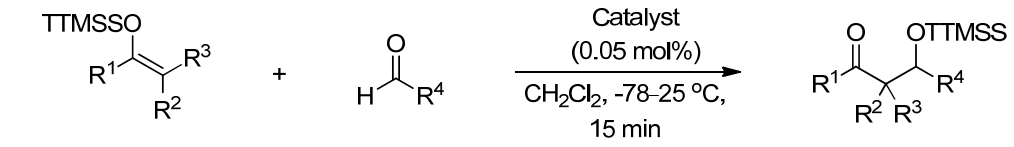



**Scheme 38.** Squaramide catalyzed Mukaiyama-type aldol reaction.

Two mechanisms can be invoked based on the role of Brønsted acid. It may directly activate the aldehyde or get silylated with silyl enolate forming a silicon

Lewis acid which will then activate the aldehyde. On the basis of control experiments using a proton scavenger (2,6-di-*t*-butyl-4-methylpyridine), authors propose simultaneous involvement of both the Lewis acid and Brønsted acid pathways out of which later may be much faster than the former.[79b]

Application of tris(trimethylsilyl)silyl enol ethers in the diastereoselective aldol reaction in the presence of $HNTf_2$ as a Brønsted acid catalyst was reported by Yamamoto et al.[80] Identical results obtained in the presence of its super silylated adduct $(TTMSSNTf)_2$ indicating that it is likely to be the actual catalyst. Due to the extraordinarily bulky tris(trimethylsilyl)silyl (TTMSS) unit it provides high *syn* selectivities of the aldol products in the reactions of β-chiral aldehydes.

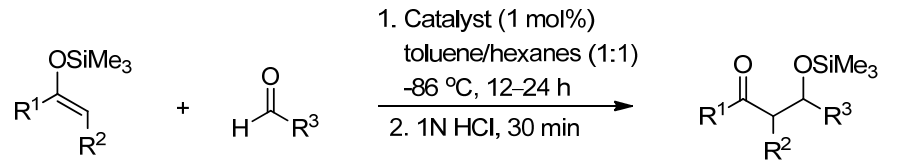



$R^1$ = H, $R^2$ = H, $R^3$ = $CH_3$, $R^4$ = 1°, 2°, 3°-alkyl,
$R^1$ = H, $R^2$ = $R^3$ = H, benzyl, vinyl, γ,δ-unsaturated
$R^1$ = $CH_3$, $R^2$ = $R^3$ = H,
$R^1$ = $R^2$ = $(CH_2)_4$, $R^3$ = H

**Catalysts:** $NHTf_2$, $TTMSSNTf_2$

**Scheme 39.** Addition of super silyl enolates to aldehydes.

First Brønsted acid catalyzed asymmetric aldol reaction of trimethylsilyl enolates derived from various aryl methyl ketones using *N*-Triflylthiophos-phoramide was reported by Yamamoto et al.[81]

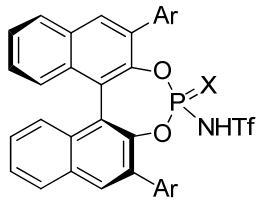



$R^1$ = aryl
$R^2$ = H, alkyl

$R^3$ = aryl. vinyl, heterocyclic

Yield up to 96%
er up to 96:4 (*syn* major)

**Catalysts:**

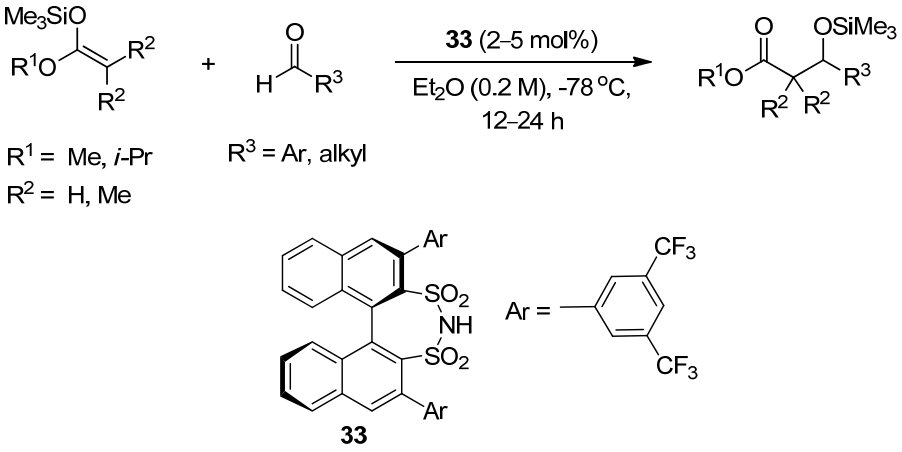



**32a**: X = O, Ar = 2,4,6-($^i$Pr)$_3$Ph
**32b**: X = S, Ar = 2,6-($^i$Pr)$_2$Ph
**32c**: X = S, Ar = 2,4,6-($^i$Pr)$_3$Ph
**32d**: X = S, Ar = 2,6-($^i$Pr)$_2$-4-$^t$BuPh
**32e**: X = S, Ar = 2,6-($^i$Pr)$_2$-4-(2,4,6-($^i$Pr)$_3$Ph)-Ph
**32f**: X = S, Ar = 2,6-($^i$Pr)$_2$-4-(9-anthryl)-Ph
**32g**:X = Se, Ar = 2,4,6-($^i$Pr)$_3$Ph

**Scheme 40.** *N*-Triflylthiophosphoramide catalyzed Mukaiyma-type aldol reaction.

Out of the various catalysts; **32f** gave best results. Aromatic aldehydes with electron withdrawing groups show less reactivity due to diminished basicity and those with bulky substituent at 2-position gives low enantioselectivities. Authors proposed and proved that two different mechanisms are operative depending on the reaction temperature. The reaction does not proceed in the presence of a proton scavenger DTBP at -86 $^{o}$C while it gives same yield and enantioselectivity at room temperature. Also the silylated Brønsted acid generated separately provides the aldol adduct in the same yield and enantioselectivity at room temperature. However it cannot catalyzes the reaction at low temperature indicating that at room temperature the actual catalyst is silylated Lewis acid whereas at -86 $^{o}$C; it is Brønsted acid itself.

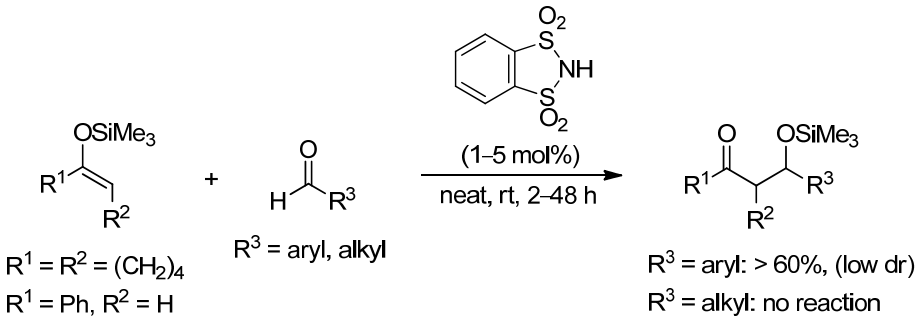
List et al. reported the reaction of ketene silyl acetals with aldehydes using 3,3'-disubstituted 2,2'-binaphthyldisulfonimide (**33**) as a buried $C_2$-symmetric acid catalyst.[82a] Aromatic and α,β-unsaturated aldehydes (1,2-adducts) provide good yield while aliphatic aldehydes result in moderate yields. Aldehydes bearing α-substituent give high enantioselectivities. High turnover numbers (up to 8800) were obtained. A Lewis acid catalyzed mechanism involving *N*-silyl disulfonimide intermediate was proposed and supported by NMR studies.




**Scheme 41.** Disulfonimide as Brønsted acid catalysts.

Barbero et al. reevaluated the mechanism using similar disufonimide catalyst in the reaction of trimethylsilyl enolate of cyclohexanone and acetophenone with various aldehydes.[82b] In the presence of a proton scavenger; (2,6-di-*t*-butyl-4-methylpyridine), the reaction does not go to completion. The formation of *N*-trimethylsilyl sulfonimide was confirmed by NMR and which was less catalytically active than the parent imide. This supports the Brønsted acid catalysis than the Lewis acid. The possible reason

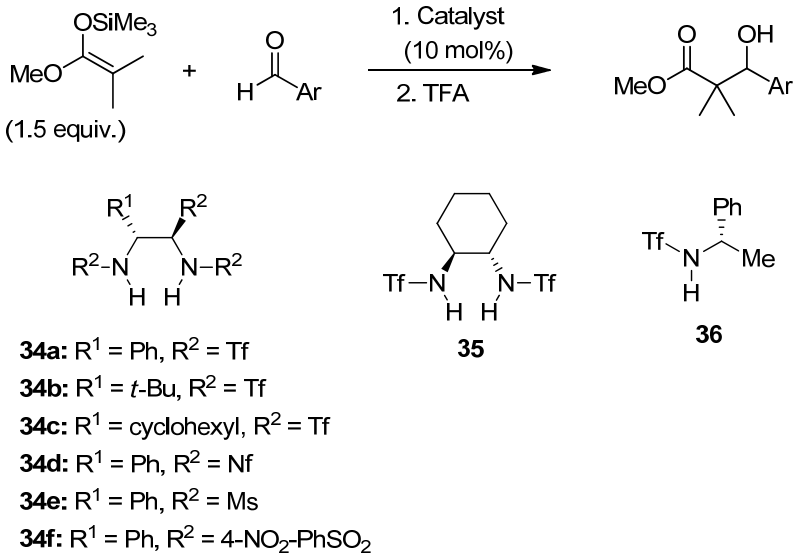
was proposed as the low nucleophilicity of its conjugate base preventing intra- and intermolecular silyl transfer.




**Scheme 42.** *o*-Benzenedisulfonimide catalyzed Mukaiyama-type aldol reaction.

### 2.2.6. Hydrogen bonding catalysis

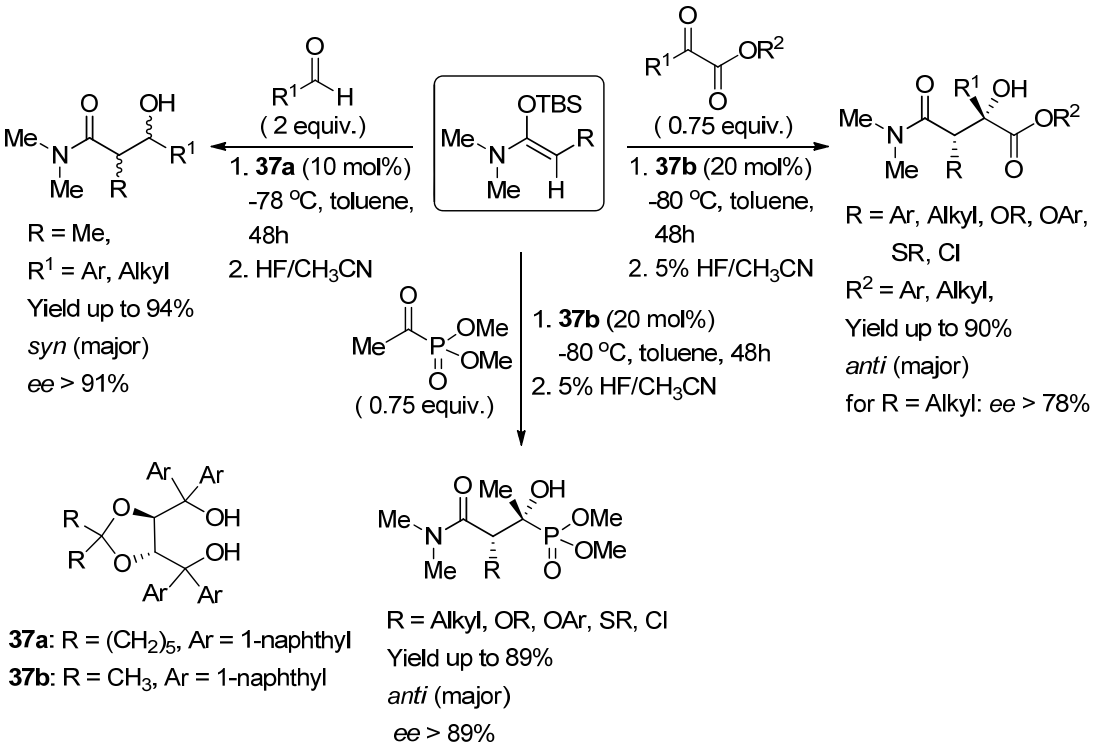
Activation of aldimines through multiple hydrogen bonding is well reported.[83] First addition of trimethylsilyl acetals to aromatic aldehydes activated through double hydrogen bonding was achieved by Jorgenson et al.[84a] Hydrogen bond donors having hydroxyl group eg. BINOL undergoes significant silylation. The problem was later resolved by using chiral bis-sulfonamides.




**Scheme 43.** Aldol additions through face-selective activation of aldehydes.

Though high yields were achieved with 4-nitrobenzaldehyde in the presence of few of the above catalysts in $CHCl_3$, only with **34d** moderate *ee* (43 %) was observed even at -24 $^oC$. Aldehydes bearing basic group (pyridyl) give high yields through a cooperative Lewis base-hydrogen bonding catalysis while unsubstituted benzaldehyde gives low yield.

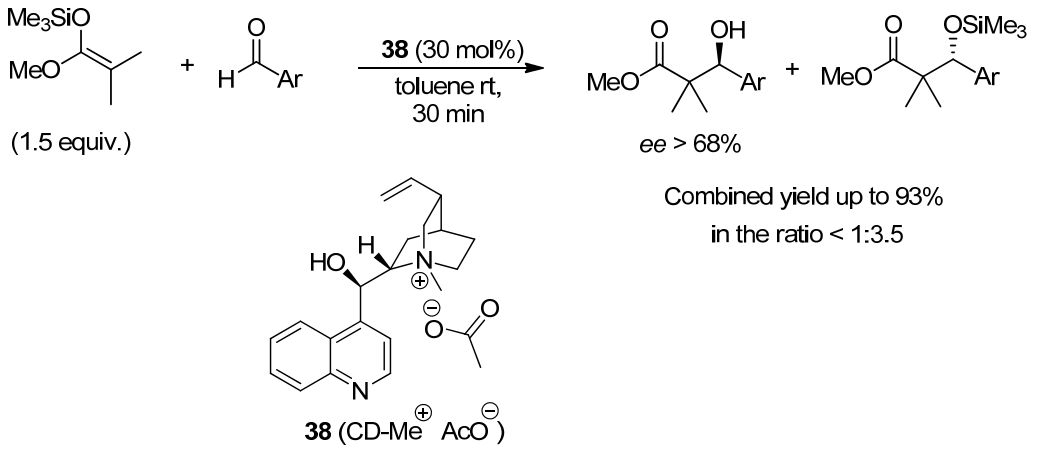
Rawal et al. have achieved face selective activation of aldehydes,[84b] α-hydroxy phosphonates[84c] and pyruvate[84d] esters using tetra-1-naphthyl-TADDOL derivatives at low temperature in the reactions of more nucleophilic and bulky TBS enolates. Though the reactions are quite slow, high selectivities were achieved. Several hydrogen bond donors were screened for the enantioselective reaction of TBS enolates with phosphonates out of which TADDOL derivatives provided the best results.




**Scheme 44.** Hydrogen bond-promoted addition of trimethylsilyl enolates.

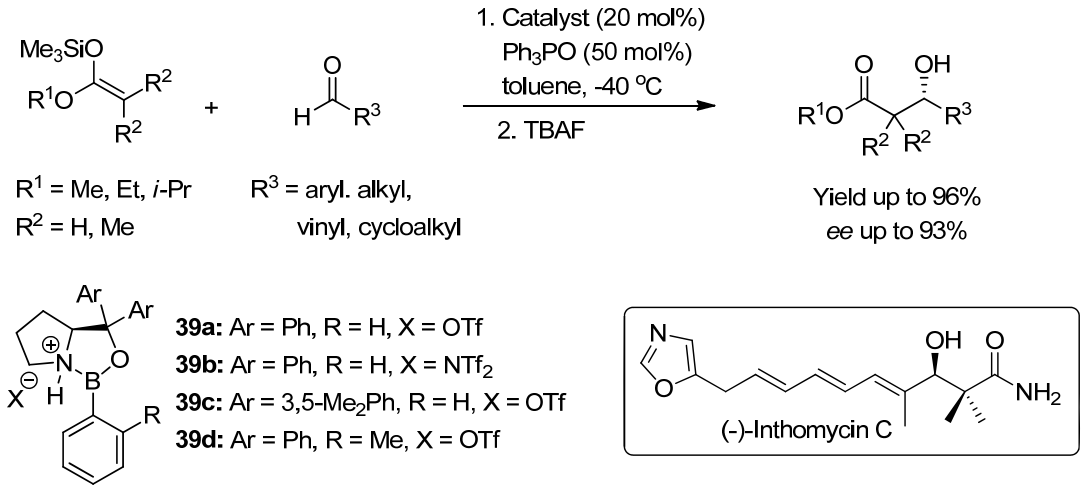
### 2.2.7. Brønsted acid- Brønsted base salts as catalysts

An enantioselective Mukaiyama aldol reaction of trimethylsilyl enolates is reported considering it as a two step process.[85] The enantioselectivity arises from the silylation step and not from the C−C bond formation step. Due to the different reactivities of diasteromeric salts with silyl source (silyl ketene acetal), one alkoxide gets preferentially silylated while other remains as a salt resulting in the enantiomeric enrichment of alcohol product. However the yields of this enriched alcohol are poor as compared to the less enriched silylated product.




**Scheme 45.** Mukaiyama aldol reaction as a two step process.

A cationic oxazaborolidinium ion catalyzed asymmetric addition of ketene silyl acetals to various aldehydes was reported by Ryu et al.[86] The mechanism involving Lewis acid activation of aldehyde by boron was predicted. $Ph_3PO$ additive has an essential role in suppressing the competing achiral pathway of carbonyl activation by cationic silicon species. The synthetic utility of this methodology was demonstrated in the total synthesis of (-)-Inthomycin C.

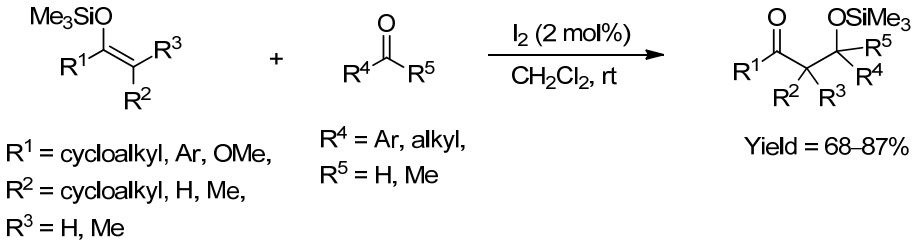



**Scheme 46.** Oxazaborolidinium ion catalyzed Mukaiyama aldol reaction.

### 2.2.8. Halogen catalyzed Mukaiyama aldol reaction

Phukan reported iodine catalyzed reaction of silyl enolates with aldehydes, ketones and acetals in good yield with preferential *anti* selectivity.[87a] Mild and neutral reaction conditions not requiring strictly anhydrous provisions is the important advantage. A mechanism involving initial coordination of iodine with aldehyde followed by electron transfer from silyl enol ether to aldehyde was proposed similar to that observed by Sato et al.[87b] It was later reported that mechanism of halogen

catalyzed Mukaiyama-type aldol reaction may be stepwise or concerted depending on the substituent on silicon.[87c]

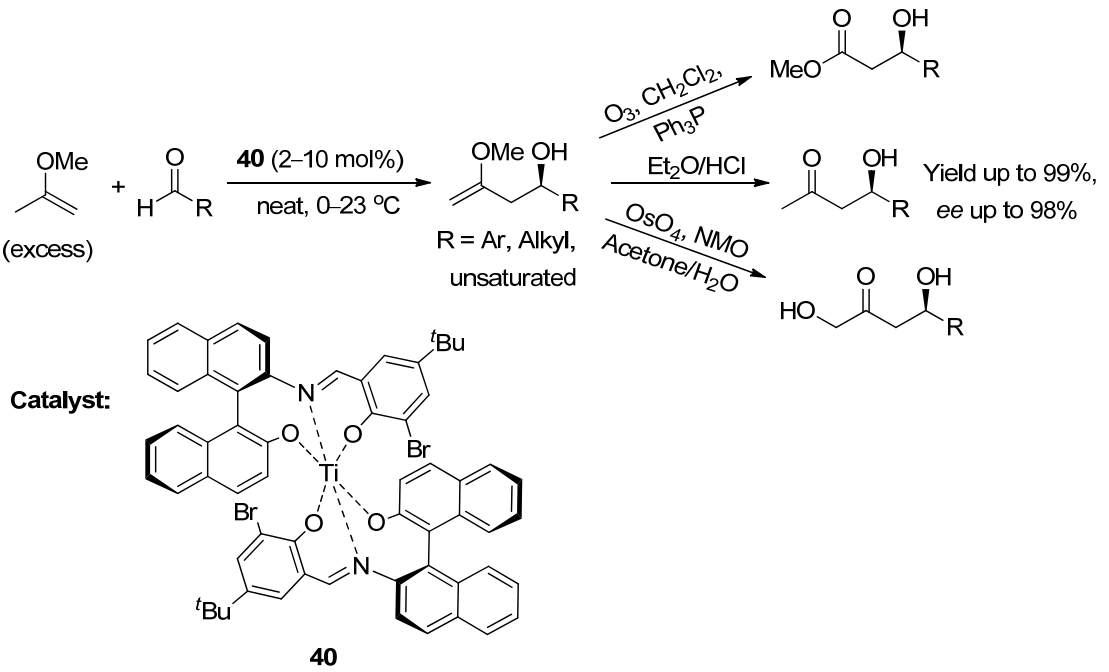



**Scheme 47.** Aldol addition of trimethylsilyl enolates catalyzed by iodine.

The directed enolate additions give impressive results in many cases. However requirement of stoichiometric amounts of base and or adjunct reagents for prior irreversible generation of enolate (insitu or separate) are the major limitations which decrease the atom economy of process. Though the recent works of Evans and Downey[88] has shown the possibility of aldol reaction catalytic in silicon using TMSOTf; the asymmetric reactions are limited to auxiliary based approach.[88a] The detailed mechanism of silicon promoted direct aldol-type reactions is not clear yet.

### 2.3. *O*-alkyl enol ether as enolate equivalent

As an alternative to the preparation of silyl enolates, the use of commercially available 2-methoxy propene in the presence of Ti(IV) complex provided aldol adducts in good yields and useful level of enantioselectivity.[89]




**Scheme 48.** Lewis acid catalyzed aldol reaction of 2-methoxy propene.

However it is limited only to the 2-methoxy propene as the nucleophile.

### 3. Direct aldol reaction

The asymmetric direct aldol reaction being an atom economical process is the most important version of this reaction. An important challenge in its development is the simultaneous control on the regio-, diastereo- and enantioselectivity.[90] The reaction involving α-unsubstituted aldehydes is again a tedious task due to the problem in differentiating the α-protons of donor ketone and acceptor aldehyde. Three general approaches have been attempted for this reaction- biocatalysis, metal catalysis and organocatalysis.

#### 3.1. Biocatalysis

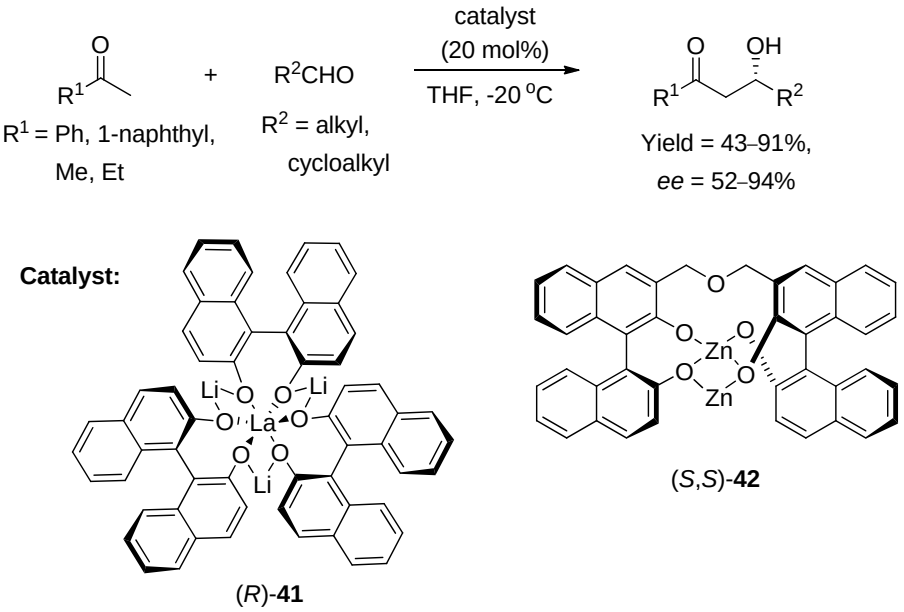
Virtually all the biochemical aldol reactions use unmodified donors and acceptors and takeplace under enzymatic control (lyases) which catalyze reversible and selective crossed aldol additions.[20b,91] As a result of high selectivities under mild conditions in the aqueous media at or near neutral pH, enzymes are synthetically useful. There are two types of catalytic enzymes: (1) The aldolases, a group of naturally occurring enzymes that catalyze aldol reaction under typically mild, in vivo conditions eg. fructose-1,6-bisphosphate and dihydroxyacetone phosphate (DHAP) and (2) catalytic antibodies that have been developed in the recent years to mimic the aldolases with improved substrate specificity. The mechanism of aldolases involves cocatalysis by $Zn^{2+}$ ion and basic functional group in the enzyme's active site. However these have narrow substrate scope and the isolation of products from water becomes difficult. In the recent years extensive study has been carried out to provide the synthetic alternatives for enzymatic direct aldol reactions.

#### 3.2. Metal catalysis

First metal catalyzed asymmetric direct aldol reaction of unmodified ketones with aldehydes inspired by type-II aldolases was developed by Shibasaki et al. using bifunctional Lewis acid-Brønsted base catalyst.[92a] He suggested that a catalyst for a direct aldol reaction should have the combination of Lewis acidity and Brønsted basicity[92b] and emphasized on the use of heterobimetallic catalysts as the best way to achieve the required balance of acid-base properties.

Out of the several heteropolymetallic complexes tested, $LaLi_3$tris(binaph-thoxide) (LLB) gave the promising results. It bears the central Lewis acidic lanthanum and the Brønsted basic lithium binaphthoxide which simultaneously

activates electrophilic aldehyde and nucleophilic ketone respectively. This cooperative mode of action allows efficient asymmetric aldol reaction without their preconversion.

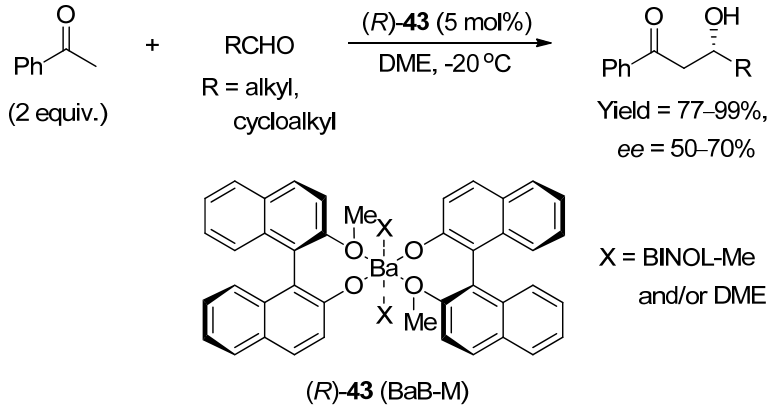



**Scheme 49.** Direct catalytic asymmetric aldol reaction promoted by LLB catalyst.

In the presence of LLB, methyl ketones (including acetone whose direct aldol reactions are difficult to control) react with aldehydes in THF providing aldol adducts in good yields and moderate to high enantioselectivities. The efficiency with respect to aldehydes decreases in the order: highly-α-branched > less-α-branched > unbranched ≈ aromatic. The catalytic activity of LLB gets enhanced by the incorporation of KOH (*in situ* generated from KHMDS and $H_2O$). It catalyzes the aldol reaction of α-hydroxy acetophenone with various aldehydes in lower loading (3–8 mol %)[93] and preferentially gives *anti*-α,β-dihydroxy ketones in high enantioselectivities.[93b] Mechanistic studies suggests that deprotonation of ketone is rate determining and water molecules may coordinate to Li and K during the reaction. The preferential activation of the aldehyde by Lewis acidic lanthanum facilitates addition of hypothetical LLB enolate and results in enantioselectivity. The complementary *syn*-α,β-dihydroxy ketones can be obtained by using (*S*,*S*)-Zn-Zn-linked-BINOL complex.[93b,c] Requirement of excess ketone, long reaction times and limited applicability to methyl ketones are the few shortcomings.

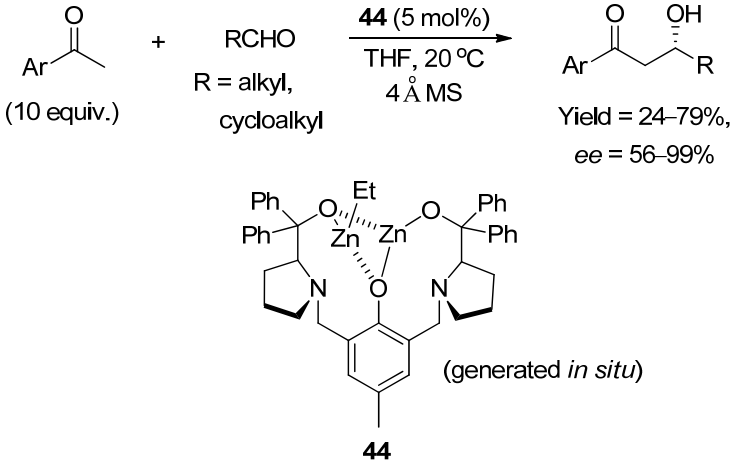
To overcome these limitations, same group has developed a barium phenoxide derived BaB-M catalyst which is a monometallic bifunctional catalyst and possesses

the functions of Lewis acid and Brønsted base.[94] Tertiary as well as secondary aldehydes with acidic α-hydrogen atoms also give cross aldol products without formation of self aldol adducts in excellent yields and modest enantioselectivities.




**Scheme 50.** BaB-M catalyzed direct asymmetric aldol reaction.

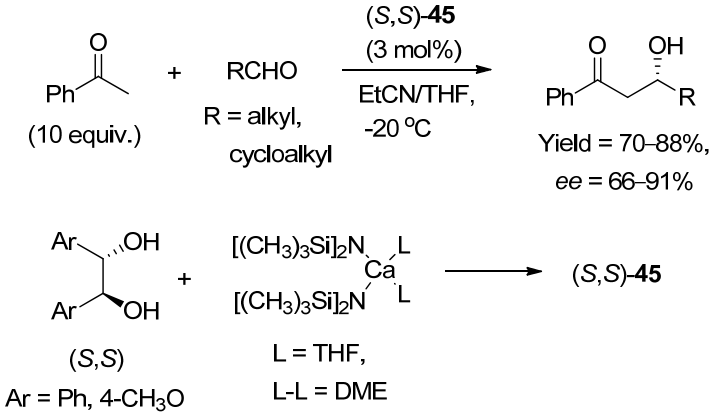
Trost et al. used novel ligands to prepare dimetallic species as catalysts for this reaction.[95a] The structure of catalyst was supported from the equivalents of diethyl zinc used and the ethane evolved. The two proximal zinc species acts as both; a source of zinc atom for the generation of requisite enolate and a Lewis acid. This catalyst is also used for the direct aldol reaction of α-hydroxy ketones and allows use of nearly stoichiometric amounts of both reactants.[95b] A second generation of dinuclear zinc catalysts is also developed for the reaction of acetone with aldehydes.[95c]




**Scheme 51.** Dimetallic-Zn catalyzed direct aldol reaction.

Noyori et al. have developed a highly reactive chiral (hydrobenzoin)Ca complex as a catalyst for the reaction of acetophenone with aliphatic aldehydes which give

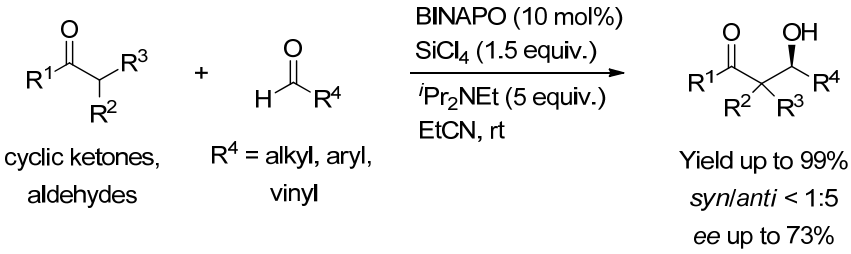
corresponding aldol products in *ee* up to 91%.[96] A notable nonlinear relationship between the enantiomeric excess of the hydrobenzoin and the product was reported. Although the detailed structure of catalyst is unclear, an oligomeric species is proposed as the major one.




**Scheme 52.** Direct aldol reaction catalyzed by chiral (hydrobenzoin)Ca complex.

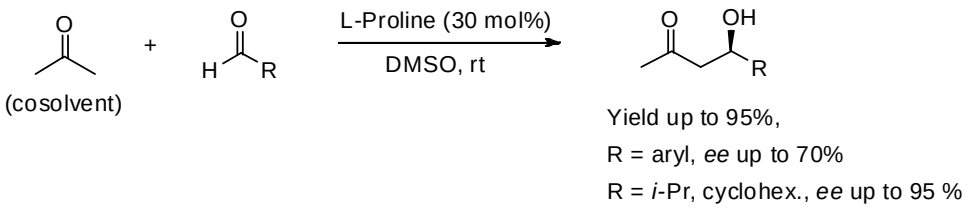
### 3.3. Organocatalysis

Nakajima et al. developed a BINAPO catalyzed direct aldol reaction of cyclic ketones with aldehydes involving *in situ* generation of silicon enolates.[97a] Though the methodology gives good yields only for the reactions of aromatic aldehydes, it has been extended to the crossed aldol reaction between two different aldehydes. Similarly Benaglia et al. have recently screened a series of proline derived diphenyl phosphine oxides for the stereoselective aldol reaction of activated thioesters.[97b]




**Scheme 53.** BINAPO catalyzed aldol reaction via *in situ* generation of silyl enolate.

The discovery of proline catalyzed Hajos-Parrish-Eder-Sauer-Wiechert reaction[98] has introduced the use of small organic molecules as catalysts. In 2000 List, Lerner and Barbas reevaluated this as an intermolecular reaction.[99a] Proline acts as a small enzyme mimic and activates donor through its HOMO-raising by the formation of an enamine; a mechanism reminiscent of the Type-I aldolases.




**Scheme 54.** L-Proline catalyzed direct aldol reaction (First report).

Later its utility was demonstrated in a highly regio- and diasteroselective aldol reaction between hydroxyacetone and aldehydes to give *anti*-1,2-diols with excellent enantioselectivities.[99b]


**Scheme 55.** Proline catalyzed aldol reaction for the preparation of *anti*-1,2-diols.

Among all the organocatalysts reported so far, proline stands out as the first choice considering its low cost and ready availability. Although the direct use of free α-amino acids[98] and easily accessible chiral amines[100] as catalysts is much preferable, they have several limitations. These include rather narrow applicability, unsatisfactory catalytic activities, low solubility in common organic solvents and side reactions such as oxazolidinone formation, parasitic equilibria with substrates, decarboxylation and subsequent [3+2] cycloaddition reactions etc.[101] Therefore high loading of catalyst and large excess of ketone are normally employed to achieve acceptable conversions.[102] Proline catalyzes aldol reaction in water without side products, although with low enantioselectivity.[103]

Development of new chiral organocatalysts is a most common way to overcome these issues. Various primary and secondary amines have been continuously developed as new organocatalysts.[104] Significant synthetic efforts directed for this generally results in proposing a next generation of more active catalysts based on the original designs. As for aldehydes, ketones and imines as electrophiles additional assistance for catalysis is required, a suitably positioned hydrogen bond donors in the catalysts are required. This results in the simultaneous activation of both nucleophiles and electrophiles[105] and also controls the stereochemical outcome. If these sites are sufficiently acidic as a carboxylic acid groups in amino acids, then they also assist the

formation of enamine. Additional hydrogen bonding is also reported to have a beneficial effect on the outcome of the reaction.[105]

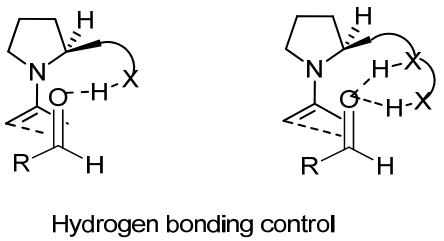



**Figure 11.** Mechanisms of enamine catalysis of organocatalytic direct aldol reaction.

The detailed study of enzymes, particularly efficient biological catalysts is another way to get new organocatalysts. It leads to the improvement of catalytic efficiencies of small organic molecules.[106a] Very recently a nice combination of both the methods is reported.[106b] Although impressive catalysts have been developed by these approaches, time consuming nature of these iterative methods is a major limitation. However the rational design and synthesis of efficient enamine catalysts is still receiving considerable attention.[111] It is well known that addition of a proper acid additive increases the efficiency of a known catalyst both in terms of yield as well as selectivity.[107] Thus the later approach is clearly beneficial.[108]

## Summary and outlook

Broad range of methods have been developed for the asymmetric aldol reaction, the most interesting and successful are those using preformed silyl enolates and direct aldol reaction. Besides the chiral promoter, solvent and temperature the reactivity of enol silane which depends on electron density around the silicon plays an important role in their aldol additions. Under Lewis base activation, trialkylsilanes exhibited enhanced nucleophilic character, whereas trihalosilanes exhibit enhanced nucleophilic and/or electrophilic character. The minimum background reactions and highly ordered closed cyclic transition states associated with the siliconium cation catalysis are the main reasons for the high selectivities. Though the racemic aldol additions of trimethylsilyl enolates using Lewis bases are well known, the known mechanism has a few ambiguities. Its asymmetric version could be achieved through the proper catalyst design and detailed mechanistic studies. Thus understanding the mechanism in more details and developing simple enantioselective catalyst systems for aldol reaction remains an enduring task.

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*Chapter 2*

# Preparation and evaluation of chiral Lewis base catalysts for the Mukaiyama-type aldol reaction

## Introduction

We set ourselves with a goal of studying aldol reaction of trimethylsilyl enolates with aldehydes in the presence of catalytic amounts of chiral Lewis bases (both neutral and anionic). As seen in the previous chapter, coordination of a proper Lewis base with silyl enolate generates a hypervalent silicon species with both increased Lewis acidity at silicon center and nucleophilicity of the enolate part. Though several advantages are associated with the use of trimethylsilyl enolates and Lewis bases, a proper study of catalyzed asymmetric aldol reaction employing them is not reported till date.

Mechanism reported for this reaction involving the use of anionic Lewis base catalysts does not provide several details.[1] Actual role played by these Lewis bases either as an initiator or catalyst is unclear. Generation of alkali metal or tetraalkylammonium aldolate intermediates was proposed to explain the formation of *O*-TMS acetals, however the possibility of their retro-aldolization is not stated. Also the formation *O*-TMS acetal is reported when the trimethylsilyl enolates of esters such as methyl isobutyrate are the substrates but not when trimethylsilyl enolates of ketones are involved. Indeed it shows probability to develop aldol-Tishchenko-type reaction. If the enolate is unsubstituted, formation of elimination product is also possible from the resulting aldolate. The solvent has a pivotal role and most of the catalytic reactions are reported in the silicon activating solvents such as DMF or pyridine. Although at low temperature they do not activate trimethylsilyl enolates, the possibility of cooperative catalysis or side reactions remains due to their involvement in the transition state. Thus a proper study of all these factors governing the net outcome of the reaction is needed. The information gained will be useful for developing asymmetric versions of other reactions using trimethylsilyl nucleophiles as the substrates.

From the literature precedence we hypothesized an asymmetric version of this reaction in a non-activating solvent through either of the transition states shown in the Figure 1. If the Lewis base is monodentate, then the reaction will follow a closed transition state **TS-1**.[2] Similarly if the catalyst bears a hydrogen bond donor site, then the activation of aldehyde by it could lead to another closed transition state; **TS-2**.[3a] Although this reaction is reported to be a two step process, rapid silylation of aldolate intermediate could be achieved by using a proper solvent and catalyst which will shift

the equilibrium to product.[3b] Moreover if the catalyst bears sufficient sterics, possibility of asymmetric outcome through the open transition state (**TS-3**)[3b] cannot be ruled out. The simultaneous activation of both the reactants is also feasible through dual activation in the presence of chiral bifunctional metal complexes possessing both Lewis acidic and Lewis basic sites.[3c] Thus the transition states **TS-1**, **TS-2** and **TS-4** will activate both the reactants through an ordered assembly while **TS-3** will involve steric control.

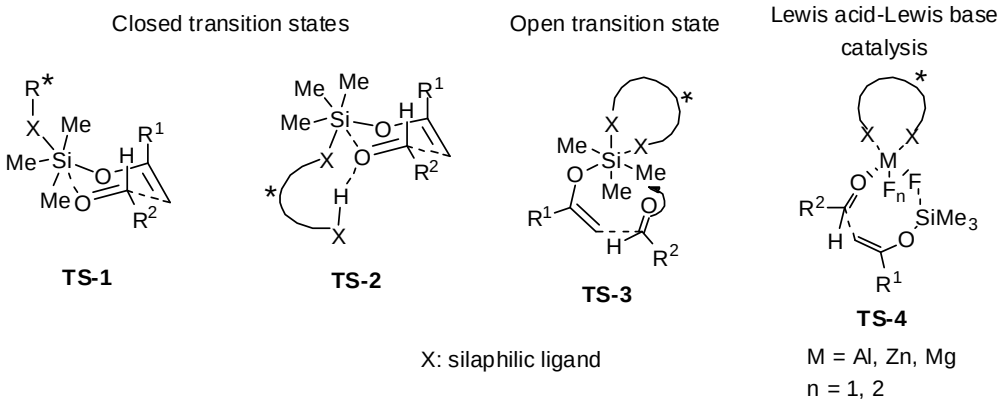



**Figure 1.** Possible activation modes.

The proposed metal aldolate intermediate responsible for various side reactions could be rapidly hydrolyzed in the presence of water without much harming the reactants and catalyst. It will eliminate the problems of retro-aldolization and elimination. This type of reactions can be carried out in the presence of chiral Lewis basic salts either by using aqueous organic solvents or micellar reaction media.[4] The salts of chiral acids bearing a lipophilic group will behave as Lewis base-surfactant-combined catalysts and seems to be good alternatives to the individual use of Lewis base catalysts and surfactants.

This chapter deals with the detailed study of all these aspects. To support the observed results, few mechanistic studies are also included. It is organized in the three sections.

**Section 2A:** Preparation of chiral Lewis base catalysts.

**Section 2B:** Study of Mukaiyama-type aldol reaction in organic media.

**Section 2C:** Mukaiyama-type aldol reaction in aqueous media.

# Section 2A

## Preparation of chiral Lewis base catalysts

### Introduction

There are few requirements for a Lewis base to act as an efficient catalyst for this reaction which should be addressed during the development of such type of catalysis.

1. It must be able to activate trimethylsilyl enolate without direct cleavage of Si–O bond.
2. It should stabilize electron density on silicon after the formation of hypervalent species.
3. It should provide effecient asymmetric environment in the transition state.
4. For a catalytic reaction, it should get regenerated after the formation of trimethylsilyl aldolate.
5. To avoid the role of solvents, it must be soluble in non-activating solvents.

The possible chiral Lewis bases could be neutral or anionic silaphilic ligands bearing a lone pair of electrons.

**1. Neutral Lewis bases**

As seen from the Chapter 1, pyridine *N*-oxide and amines like *N*-methyl imidazole, DMAP, DBU etc. are good activators of trimethylsilyl enolates under certain conditions.[5] Therefore chiral *N*-oxides or tertiary amines could be the possible neutral chiral catalysts. They can be mono- or multidentate.

**2. Anionic Lewis bases**

The conjugate bases of achiral compounds having nitrogen and oxygen based functional groups such as NH, OH and COOH etc. acts as efficient activators of trimethylsilyl enolates.[1] Therefore the salts of chiral acids, phenols and amides can be used as chiral anionic activators. Commercially available chiral mono- or dicarboxylic acids such as α-amino-, α-hydroxy- or tartaric acid and amino alcohols such as ephedrine derivatives can be used as precursors for the preparation of such Lewis bases. However as seen from the Figure 1, the chiral Lewis base coordinated to silicon is quite away from the newly forming C–C bond. Therefore proper tuning of catalyst structure in terms of sterics, electronics, number of coordination and hydrogen

bonding sites etc. is necessary for obtaining asymmetric induction. Thus modification of these chiral ligands becomes essential.

These Lewis bases could be of the following different types.

**2.1. Monodentate Lewis bases**

They can be obtained from the chiral compounds having a single acidic functionality. A few of the bidentate ligands can be converted to monodentate Lewis bases by making other coordination site electron deficient either by attaching an electron withdrawing group such as carbonyl or by the coordination of metal such as lithium.

**2.2. Bidentate Lewis bases**

As $C_2$-symmetry axis within the chiral auxiliary reduces the number of possible diastereomeric transition states, these types of catalysts will be more useful. They can be obtained as disalts from $C_2$-symmetric ligands having two acidic protons eg. BINOLs, salens, diamides and TADDOL derivatives etc.

**2.3. Anionic Lewis bases with hydrogen bonding sites**

Salts of ligands bearing hydrogen bond donor functionalities such as primary or secondary amide, urea, thiourea etc. close to the Lewis basic group are the possible catalysts of this type. The mono lithium salts of bidentate ligands such as BINOLs, salen derivatives, amino alcohols and monoamides of diamines bearing proton on the other coordinating group will also act as catalysts of this type.

**2.4. Amphiphilic Lewis bases**

Amphiphilic Lewis bases could be obtained from the chiral lipophilic acids in the form of their alkali metal salts especially sodium or lithium. Besides acting as Lewis bases, they will also solublize the organic compounds in water.

**3. Bifunctional metal complexes**

Complexes of metal fluorides eg. $AlF_3$, $ZnF_2$ and $MgF_2$ etc. with chiral ligands can act as bifunctional Lewis acid-Lewis base catalysts. For this chiral diamines or amino alcohols will be the suitable ligands.

## Results and discussion

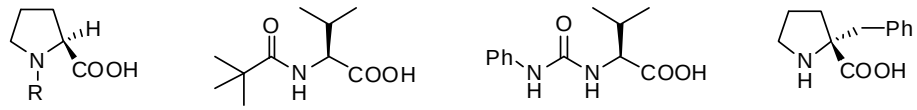
As discussed above, a variety of new chiral ligands were designed and prepared from the easily accessible chiral starting materials. These were converted into the corresponding conjugate bases as alkali metal (Li, Na and K) or tetraalkylammonium salts. Also few *N*-oxides and metal fluoride complexes were prepared from appropriate ligands.

### 1. Synthesis of chiral ligands

Different types of chiral compounds such as α-amino- or α-hydroxy acids, diamines, binaphthyls etc. were selected as the starting materials for the synthesis of these ligands. The variations are in p*K*a, sterics, electronics, number and acidity of hydrogen bond donors etc.

#### *1.1.* Amino acid derivatives

Various α-amino acid derivatives with modifications at the *N*- or *C* terminal or α-carbon were designed and prepared. To study the effect of *N*-substitution and N−H acidity on the outcome of this reaction, *N*-alkyl derivatives of proline (**1a**[6a] and **1b**[6b]) and *N*-acyl derivative of valine (**2**) [6c] respectively were prepared. To study the effect of extra hydrogen bonding site, a valine derived urea (**3**) was prepared.[6d,e] While to understand the effect of α-sterics, α-benzyl proline (**4**) was prepared from proline.[6f]

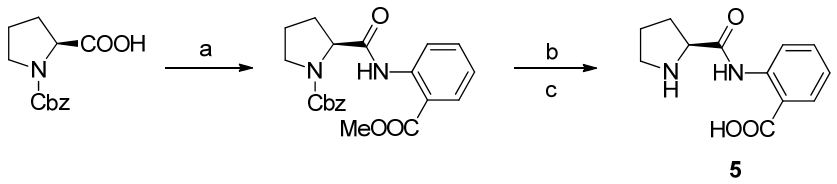



**1a:** R = $CH_3$
**1b:** R = Bn

**2** **3** **4**

**Figure 2.** Amino acid derived ligands.

A prolinamide derivative **5** was prepared to know the effect of position of carboxylic acid group. Pearson et al. have reported its preparation by coupling benzyl anthranilate with *N*-Cbz-L-proline.[7b] But the preparation of benzyl anthranilate itself requires a separate synthetic operation. Therefore it was prepared by using commercially available methyl anthranilate with a modified procedure as shown in the Scheme 1.




**Scheme 1.** (a) (i) EtOCOCl, $Et_3N$, $CHCl_3$, 0 $^oC$, 0.5 h; (ii) methyl 2-aminobenzoate, 0 $^oC$, 1 h, 77%; (b) LiOH, MeOH, rt, 15 h; (c) $H_2$, Pd/C, MeOH, 3 h, 84% (over 2 steps).

### *1.2.* **Binaphthyl derivatives**

Binaphthyl derivatives either as ligands[8a] or their salts as Lewis bases[8b,c] are well known for inducing high levels of selectivities in the variety of reactions. To study the behavior of these Lewis basic salts (either mono or di) in this reaction, a few representative ligands (**6**−**8**) were prepared.[9]

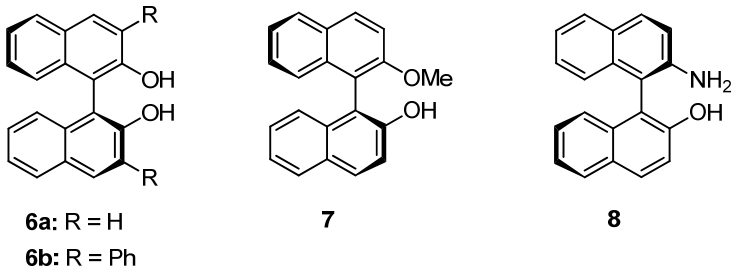



**Figure 3.** Binaphthyl derived ligands.

### *1.3.* **Salen derivatives**

Monolithium salts of salen derivatives act as efficient Lewis bases in the enantioselective addition of TMSCN to aldehydes.[8c,d] Therefore **9a**,[10a] **10a**[10b] and a tridentate hemisalen (**11**)[10c] were prepared as precursors of the possible Lewis base catalysts. The *O*-methyl salen derivatives, **9b**[10a] and **10b**[10b] which can be used as ligands for the preparation of chiral Lewis acid-Lewis base complexes from the metal fluorides were also prepared.

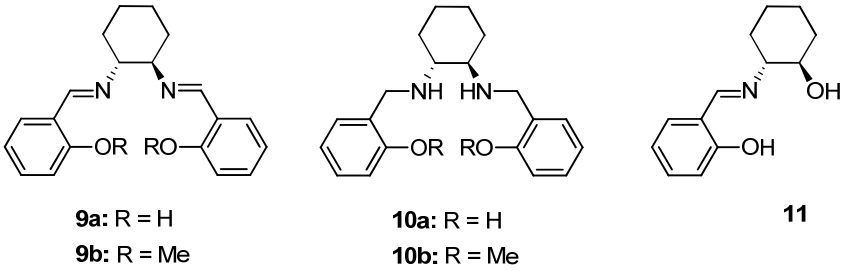
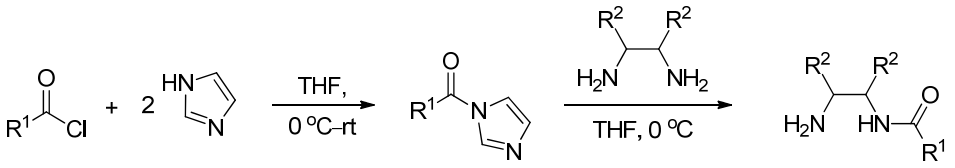



**Figure 4.** Salen derived ligands.

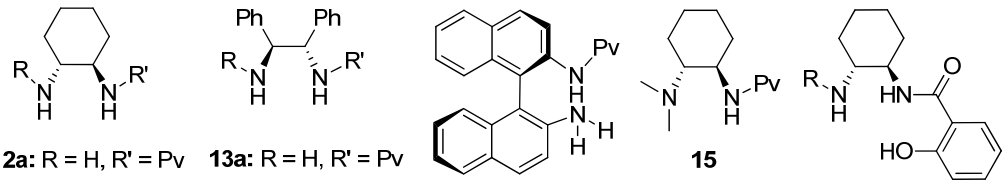
### *1.4.* Mono- and diamides of symmetrical diamines

A variety of chiral ligands containing mono- or diamide unit were obtained from a few symmetrical diamines. The monoamides of symmetrical 1,2-diamines were prepared by modification of the procedure recently reported by Kaushik et al.[11a,b] Efficient monoacylation of 1,2-diamines was reported by using them in the form of disalts and utilizing acyl imidazoles as hindered acylating agents in aqueous ethanol. We found that by using THF as a solvent, monoacylation by acylimidazole can be achieved with free 1,2-diamine itself at 0 $^{o}$C while at 25 $^{o}$C it resulted in the diacylated product along with unreacted diamine (Scheme 2). The yield of diacylated product was improved by employing 2 equivalents of acylating agent.




**Scheme 2.** Imidazole catalyzed direct monoacylation of symmetrical 1,2-diamines.

By this method a series of monoacyl derivatives of (1*R*,2*R*)-cyclohexane-1,2-diamine and (1*S*,2*S*)-1,2-diphenylethane-1,2-diamine[11c] eg. **12a–c**, **13a–d**, **16a** etc. and diacylated derivatives eg. **12e**, **13f**, **13h** etc. were prepared (Figure 5). The required acyl imidazoles were generated in THF from the corresponding acid chlorides, except for trifluoroacetyl one (in the preparation of **13d** and **13 h**) corresponding anhydride was utilized.



**12a:** R = H, R' = Pv
**12b:** R = H, R' = Ac
**12c:** R = H, R' = Bz
**12d:** R = H, R' = Ts
**12e:** R = R' = Pv
**12f:** R = R' = Ts
**12g:** R = Ac, R' = Ts

**13a:** R = H, R' = Pv
**13b:** R = H, R' = Ac
**13c:** R = H, R' = Bz
**13d:** R = H, R' = TFA
**13e:** R = H, R' = Ms
**13f:** R = R' = Pv
**13g:** R = R' = Ms
**13h:** R = R' = TFA

**14**

**15**

**16a:** R = H
**16b:** R = Pv

**Figure 5.** Mono- and diacyl diamines.

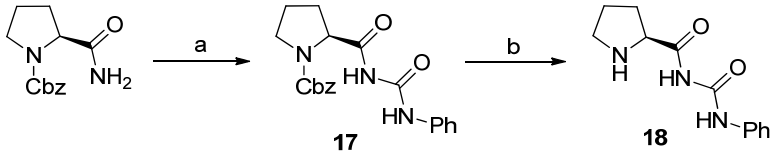
Unfortunately these conditions were found unsuitable for monotosylation/ mesylation. Also, BINAM does not react with any of the acyl imidazoles even by

increasing the temperature or polarity of solvent (DMF). Monotosylate of (1*R*,2*R*)-cyclohexane-1,2-diamine (**12d**),[12a] and monomesylate of (1*S*,2*S*)-1,2-diphenylethane-1,2-diamine (**13e**)[12b] were therefore prepared by reported procedures with moderate yields and monopivalamide of (*R*)-BINAM (**14**) was prepared by using pivaloyl chloride in the presence of pyridine as a base.

Ditosylate (**12f**) and dimesylate (**13g**)[12c] were also prepared to compare the behavior of their salts with those of BINOL and salen. Further to check the role of hydrogen bonding, **15** was prepared from **12a** by Eschweiler-Clarke methylation[12d] and to check the role of acidity of hydrogen bonding site, mixed diamide **12g** with difference in the acidity of amide protons was prepared from monotosylate **12d**. Also an amide ligand with phenolic OH group (**16a**) was prepared by using *O*-benzyl salicyloyl chloride derived acyl imidazole followed by *O*-debenzylation. The ligand **16b** possessing phenolic OH and diamide group was prepared by acylation of *O*-Bn-**16a** with pivaloyl chloride followed by hydrogenolysis.

### 1.5. Urea derivatives

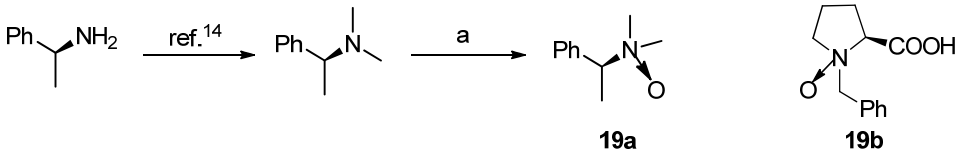
A chiral monoacyl urea derivative **18** having a more acidic N–H was prepared from *N*-Cbz-L-prolinamide[13] by reacting with phenyl isocyanate under reflux followed by Cbz-deprotection.




**Scheme 3.** (a) PhNCO, toluene, reflux, 40 h, 81%; (b) $H_2$, Pd/C, MeOH, 4 h, 91%.

### 1.6. *N*-oxides

A chiral *N*-oxide **19a** was prepared from (*S*)-*N*,*N*-dimethyl-1-phenylethanamine which was obtained from (*S*)-2-methyl benzylamine by Eschweiler-Clarke methylation.[14] It can be used as a neutral Lewis base or ligand for the preparation of complexes of metal fluorides. Also **19b** was prepared from *N*-benzyl-L-proline using the reported procedure.




**Scheme 4.** (a) 30% $H_2O_2$, MeOH, 25 $^oC$, 36 h, quant.

### 1.7. Lipophilic acids

To study this reaction in aqueous media, a few of the chiral acids bearing a long alkyl chain as a lipophilic group were prepared from α-amino and α-hydroxy acids by their *N*- or *O*-alkylation. The *n*-dodecyl group was selected as the common alkyl chain. For example the proline derivatives **20**[15a] and **21**[15c] with and without *N*-alkyl substituent were prepared from L-proline and (2*S*,4*R*)-4-hydroxy-L-proline respectively.

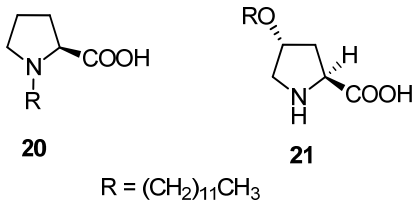
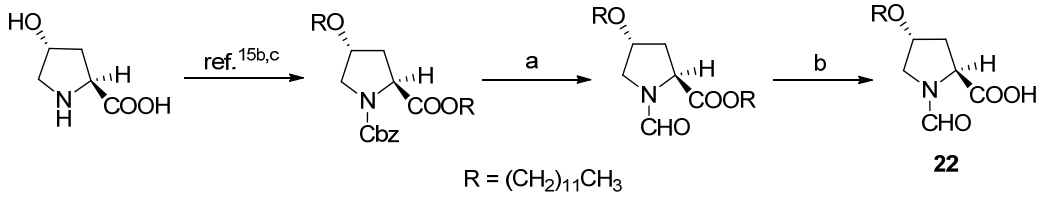


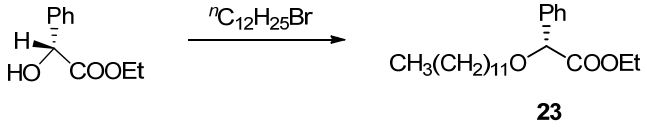

**Figure 6.** Proline derived lipophilic ligands.

Also a lipophilic carboxylic acid (**22**) having *N*-formyl group and also a *n*-dodecyl chain at 4-position was prepared from (2*S*,4*R*)-4-hydroxy proline (Scheme 5).




**Scheme 5.** (a) (i) $H_2$, Pd/C, EtOH, 4 h, 92%; (ii) $HCOONH_4$, $CH_3CN$, reflux, 8 h, 95%; (b) KOH, 1,4-dioxane, rt, 0.5 h, 90%.

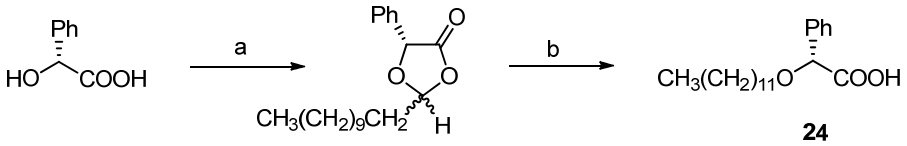
For the preparation of a (*R*)-(-)-mandelic acid derived lipophilic carboxylic acid **24**, simple etherification of its ethyl ester with dodecyl bromide was attempted under basic (NaH, KO$^t$Bu etc.) as well as neutral conditions (KF/alumina) (Scheme 6). However even after several optimizations the reaction resulted in poor yield.




**Scheme 6.** Etherification of ethyl mandelate.

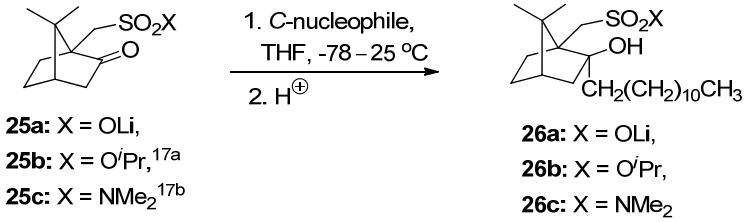
Haung et al. have reported the direct *O*-alkylation of *N*-Boc-4-hydroxy proline in the presence of KOH in anhydrous DMSO.[16a] Under these conditions direct etherification of mandelic acid with *n*-dodecyl bromide was achieved in good yield

but with partial racemization. Therefore an alternative route reported for the synthesis of *O*-alkyl derivatives of lactic acid[16b] was utilized with slight modification. The 1,3-dioxolone-4-one intermediate was obtained with high 2,5-*syn*-selectivity (97:3) which was subsequently cleaved with *t*-BuMgCl in diethyl ether. Due to the presence of long alkyl chain, we were unable to determine the optical purity of **24** by chiral HPLC or $^1$H NMR of its diastereomeric amides, esters etc. Finally it was accomplished by chiral HPLC of its benzyl amide (*ee* > 99%).




**Scheme 7.** (a) Dodecanal, 5 mol% PTSA, 4Å Molecular sieves, $CHCl_3$, reflux, 6 h, 61%; (b) 3 equiv. *t*-BuMgCl, $Et_2O$, 0 $^oC$, 2 h, 75%.

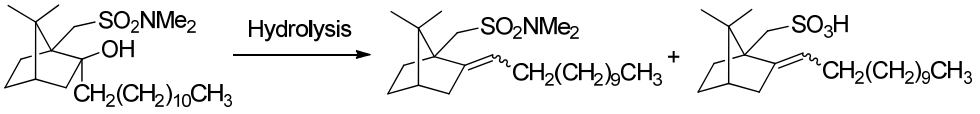
Sulfonate salts are weak Lewis bases but those of lipophilic sulfonic acids act as anionic surfactants. Therefore to study this reaction in the micellar media of chiral sulfonate salts, preparation of a lipophilic sulfonic acid was attempted from (-)-camphor-10-sulfonic acid. Its direct reaction with excess of *n*-dodecyl lithium or *n*-dodecyl magnesium bromide resulted in the formation of complex reaction mixture while it did not react with the Wittig reagent ($CH_3(CH_2)_{10}CH{=}PPh_3$). Its suitably protected derivatives (**25a**–**c**) also showed similar behavior except the reaction of **25c** with dodecyl lithium.[17a–c] This is because of the much hindered nature of the carbonyl group of camphor derivatives.




**Scheme 8.** Alkylation of camphor-10-sulfonic acid derivatives with $C_{12}$-nucleophiles.

Although low yield of alkylated product (30%) was obtained from the reaction of *n*-dodecyl lithium with **25c**, its hydrolysis was attempted. However it always showed preference for dehydration rather than hydrolysis (Table 1). Though it is against the Bredt's rule, from $^1$H NMR splitting of the peak of olefinic proton (triplet) the dehydrated product was confirmed to have exocyclic double bond.

**Table 1.** Hydrolysis of *N*,*N*-dimethyl camphor-10-sulfonamide.



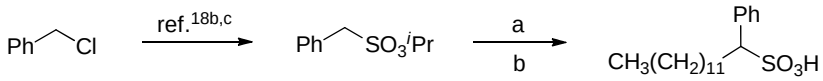

**26c** **27a** **27b**

| No | Reagent | Solvent | Temp ($^oC$) | Time | **27a** (%) | **27b** (%) |
|---|---|---|---|---|---|---|
| 1 | 1 N $H_2SO_4$ | 1,4-Dioxane | Reflux | 10 h | 59 | 15 |
| 2 | 6 N $H_2SO_4$ | $H_2O$ | Reflux | 40 h | 95 | -- |
| 3 | 2 N KOH | PEG-400 | 100 | 10 | -- | -- |
| 4 | 36 N $H_2SO_4$ | PEG-400 | 100 | 20 | Charring. | |
| 5 | 40% $H_2SO_4$ | Acetic acid | 50 | 24 | 90 | -- |
| 6[a] | 25% $H_2SO_4$ | $H_2O$ | -- | 1 min | Charring. | |
| 7 | 50% $H_2SO_4$ | $H_2O$ | 25 | 2 | 93 | -- |
| 8[b] | 1 N $H_2SO_4$ | $H_2O$ | 140 | 15 | Complex mix. | |

[a] Microwave heating was used. [b] Reaction was carried out in the steel bomb.

The sulfonamides of aromatic amines are reported to undergo facile cleavage.[17d] Therefore the starting material was changed to *N*-methyl-*N*-phenyl and *N*,*N*-diphenyl camphor-10-sulfonamide. But they too showed similar reactivity as that of **25c**, with *n*-dodecyl lithium in alkylation and also with various acids and bases during deprotection.

Therefore as an alternative, racemic sulfonic acid **28** was synthesized in superior yield from benzyl chloride via α-alkylation of sulfonate ester intermediate.[18a] However due to high lipophilicity, this acid did not provided crystallizable diastereomeric salt with any of the chiral amine.




(±)-**28**

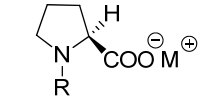
**Scheme 9.** (a) *n*-BuLi, *n*-$C_{12}H_{25}Br$ (1.5 equiv.), THF, HMPA, -78–0 $^oC$, 74%; (b) $H_2O$, reflux, 2 h, 90%.

## 2. Preparation of Lewis base catalysts

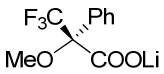
Salts of acid derivatives and phenols which are quite stable were prepared separately while those of amide derivatives were generated *in situ*.

## 2.1. Mono salts

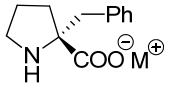
Suitable ligands having one acidic proton were converted into their Lewis basic salts by reaction with the equimolar amounts of the corresponding Brønsted bases. Though it is quite difficult to get exclusive mono salts from the bidentate ligands such as BINOL and salen derivatives; they are reported for their high catalytic activities. Therefore this type of catalysts were also prepared by using one equivalent of the corresponding Brønsted base. The monolithium salts of diamine derived monoamides will be the good alternatives to these mono salts of bidentate ligands.



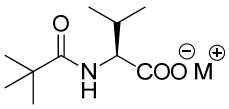
**29a:** R = H, M = Li
**29b:** R = Me, M = Li
**29c:** R = H, M = Na
**29d:** R = Me, M = Na
**29e:** R = Bn, M = Na



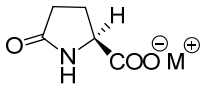
**33**



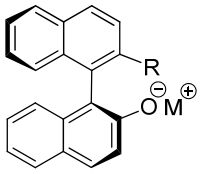
**30a:** M = Li
**30b:** M = Na



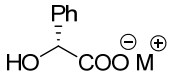
**34a:** M = Li
**34b:** M = $NBu_4$



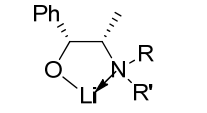
**31a:** M = Li
**31b:** M = Na,
**31c:** M = $NBu_4$



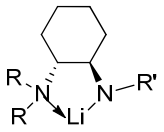
**35a:** R = OH, M = Li
**35b:** R = OMe, M = Li
**35c:** R = $NH_2$, M = Li
**35d:** R = OH, M = Na
**35e:** R = OMe, M = Na
**35f:** R = $NH_2$, M = Na



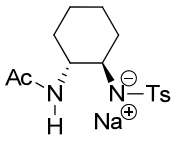
**32a:** M = Li
**32b:** M = Na
**32c:** M = $NBu_4$



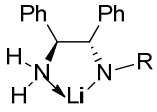
**36a:** R = R' = H
**36b:** R = Me, R' = H
**36c:** R = R' = Me



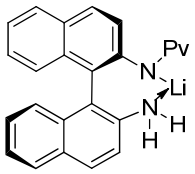
**37a:** R = H, R' = Pv
**37b:** R = Me, R' = Pv
**37c:** R = H, R' = Ts



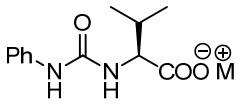
**38**



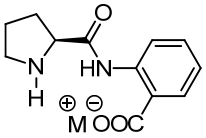
**39a:** R = Pv
**39b:** R = Ms
**39c:** R = TFA



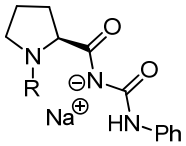
**40**



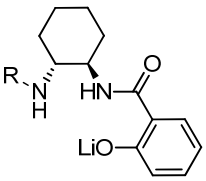
**41a:** M = Li
**41b:** M = $NBu_4$



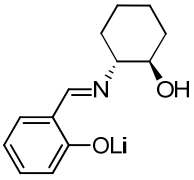
**42a:** M = Li
**42b:** M = Na
**42c:** M = $NBu_4$



**43a:** R = H
**43b:** R = Cbz

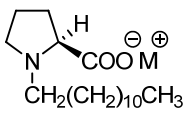


**44a:** R = H
**44b:** R = Pv

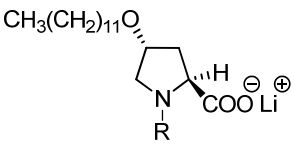


**45**

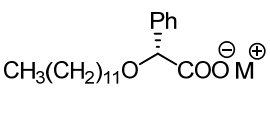
### Mono salts of lipophilic ligands



**46a:** M = Li
**46b:** M = Na



**47a:** R = H
**47b:** R = CHO



**48a:** M = Li
**48b:** M = Na

**Figure 7.** Lewis bases containing mono salts.

## 2.2. Di salts

Appropriate bidentate ligands were also converted into their di salts.

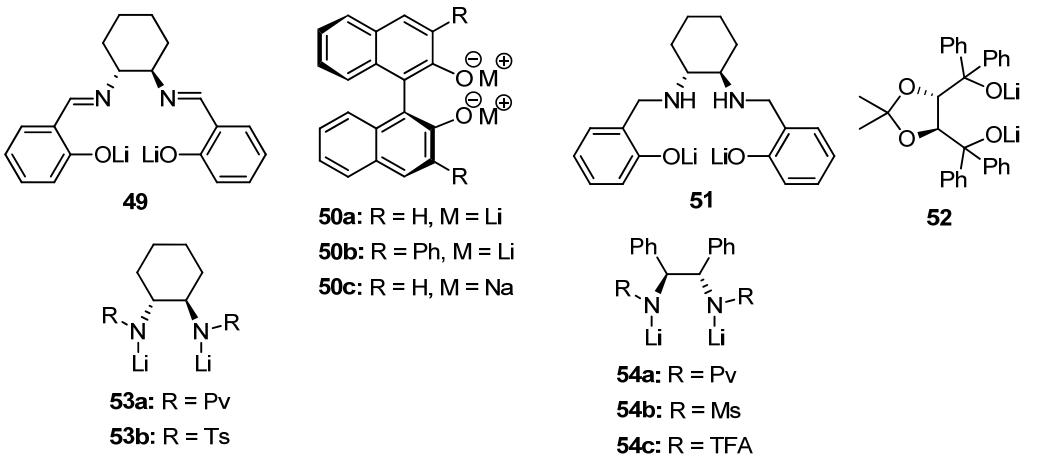



**Figure 8.** Lewis bases containing di salts.

## 2.3. Lewis acid-Lewis base complexes

Kobayashi et al. have reported zinc fluoride-chiral diamines as efficient catalysts for the enantioselective addition of trimethylsilyl enolates to α-hydrazono esters.[3c] Though they were unable to get crystals of the resulting complex, based on the observed high selectivities a double activation mechanism was proposed. Activation of enolate and α-hydrazono ester by fluoride and zinc respectively is believed. Although Hursthouse et al. have reported the preparation of a complex of zinc fluoride with ethylenediamine which is soluble in common organic solvents; fluorine is outside the coordination sphere of zinc.[19] We have also tried preparation of complexes from metal fluorides like $AlF_3.3H_2O$, $ZnF_2.2H_2O$ and $MgF_2.2H_2O$ with variety of chiral ligands. Unfortunately only in few cases (Figure 9) we were able to break metal-fluorine network. As with ethylenediamine,[19] a soluble complex of zinc fluoride (**55**) was obtained with (1*R*,2*R*)-cyclohexane-1,2-diamine only when 3 equivalent of the ligand was used. This indicated complete coordination of zinc with diamine ligands. Our efforts to crystallize it were unsuccessful. Also the complexes **56** and **57**, soluble in organic solvents were obtained using (*S*)-*N*,*N*-dimethyl-1-phenylethanamine-*N*-oxide as the ligand.

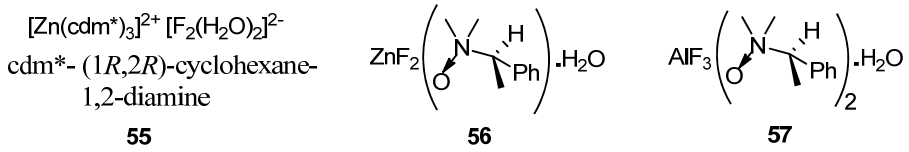


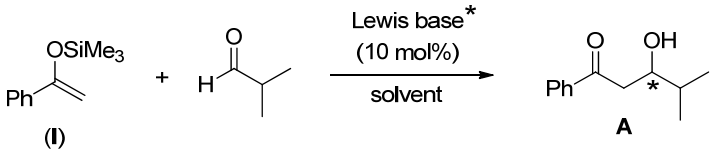

**Figure 9.** Chiral metal fluoride complexes.

## Section 2B

## Study of Mukaiyama-type aldol reaction in organic media

### Introduction

As seen from the Figure 1, for a catalytic reaction through the closed transition states such as **TS-1**, **TS-2** or **TS-4** the reactivity of both the substrates should be low. According to the Mayr's scale of $\pi$-nucleophilicity,[20] trimethylsilyl enolate of acetophenone (**I**)[21a] is 103 times less reactive than that of methyl isobutyrate[21b] which is a most oftenly used enolate in the achiral Lewis base catalyzed aldol and related reactions. Therefore to have fewer background reactions it was selected as the starting material. The required enolate was prepared by the slight modification of the reported procedure.[21a]




**Scheme 10.** Mukaiyama-type aldol reaction.

Also a more stable and less reactive aldehyde (isobutyraldehyde) having sufficient sterics for enantiotopic discrimination was selected as an electrophile. To avoid the participation of solvents such as DMF and DMSO in the transition state we have decided to use less polar solvents or their combinations with minimum amounts of some highly polar solvent.

## Results and discussion

We have first examined several nonionic Lewis bases (both chiral and achiral) as catalysts eg. tertiary amines, *N*-oxide (**19a**), NMO, $Ph_3PO$, HMPA etc. using THF as the solvent. It was noted that as the Lewis basicity of these catalysts is very low. Some of these do not catalyze the reaction while others gave trace amounts of aldol product (**A**).[22a] Therefore we decided to use anionic Lewis bases as catalysts. Initially few of the salts of easily accessible chiral compounds like proline derivatives, binaphthyls, ephedrines and salen derivatives (Figure 10) were examined.

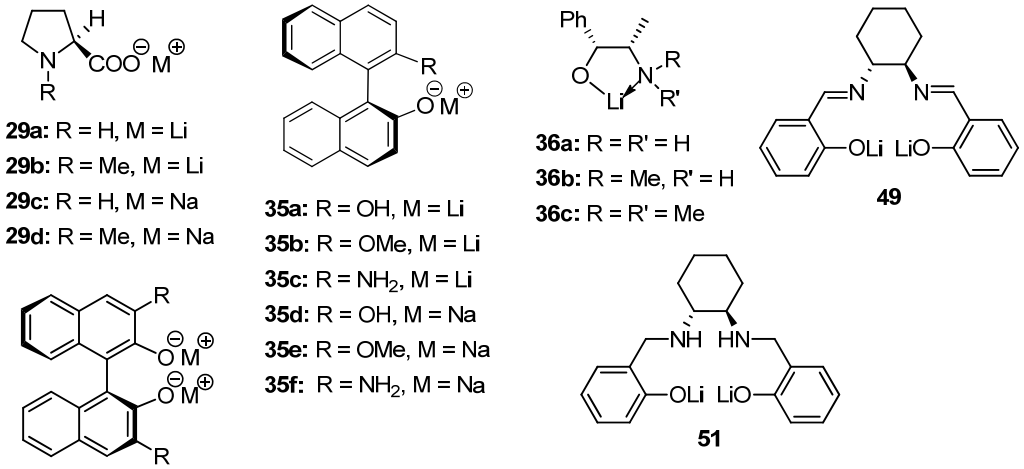
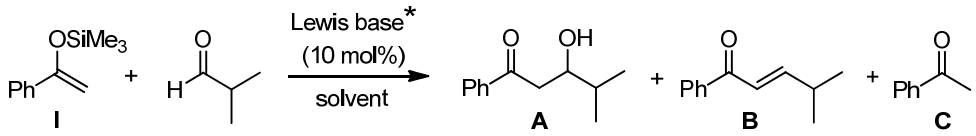



**Figure 10.** Mono and dimetallic salts of bidentate ligands.

Our preliminary findings with few of them were disappointing. One of the problems encountered is their low solubility in commonly used organic solvents such as THF, $CH_3CN$, $Et_2O$ and toluene. On the other hand polar solvents like DMF, DMSO and water led to the side reactions such as hydrolysis of enolate (**C**) and elimination (**B**).[22d] It is well known that lithium salts form aggregate structure;[8b] also one of the lithium salt (**35b**) also showed similar aggregate structure by $^1$H NMR. Therefore a few less acidic protic additives such as alcohols, diamines (both racemic and chiral), diols and water (catalytic as well as cosolvent) which can either increase the solubility or break the aggregate structure of catalyst in solution[8b] were utilized. These additives increased the solubility of above salts in common organic solvents and also suppressed the formation of elimination product (**B**) (e.g. Table 2, entry 3 vs.

2). However not unexpectedly, they always led to the substantial amount of hydrolysis product (**C**). Also few of the above salts mainly gave the elimination product (**B**).

**Table 2.** Examination of mono- and dimetallic salts of bidentate ligands as catalysts.




| No | Catalyst | Solvent | Temp ($^{o}$C) | Time (h) | Yield (%)[a] |
|---|---|---|---|---|---|
| 1 | **29a** | DMF/THF[b] | 25 | 1 | 60 |
| 2 | **29b** | THF | 25 | 24 | Elimination |
| 3 | **29b**[c] | THF | 25 | 6 | 43 |
| 4 | **29c** | DMF | 0 | 1 | Mixture[d] |
| 5 | **29d** | DMF | 25 | 3 | Elimination |
| 6 | **35a** | DMF/THF[b] | 25 | 24 | 54 |
| 7 | **35b** | THF | 25 | 3 | Mixture[d] |
| 8 | **35c** | THF | 0 | 6 | 59 |
| 9 | **35d** | THF | 0 | 10 | 60 |
| 10 | **35e** | THF | 0 | 3 | 63 |
| 11 | **35f** | THF | 0 | 4 | 52 |
| 12 | **36a** | Toluene | 25 | 48 | Mixture[d] |
| 13 | **36b** | Toluene | 25 | 36 | Mixture[d] |
| 14 | **36c** | Toluene | 25 | 36 | Mixture[d] |
| 15 | **49** | $Et_2O$ | 25 | 24 | Trace |
| 16 | **50a** | THF | 0 | 4 | 52 |
| 17 | **50a**[c] | THF | 25 | 14 | No reaction |
| 18 | **50b** | THF | 25 | 10 | 36 |
| 19 | **50b**[e] | THF | 25 | 24 | 73 |
| 20 | **50c** | THF[f] | 25 | 0.5 | 26 |
| 21 | **51** | THF | 25 | 24 | Trace |

[a] Isolated yield of **A** (In all cases *ee* was < 10 % as shown by comparison of the optical rotation with literature value[22a]). [b] DMF:THF (1:9). [c] 10 mol % of ethylenediamine as additive. [d] Mixture of **A**, **B** and **C**. [e] 10 mol% *i*-PrOH as additive. [f] Bottle grade THF.

Thus products (**A**–**C**) are formed in varying ratios depending on the nature of Lewis base and reaction medium used. The Brønsted basicity is responsible for the abstraction of acidic α-proton from the aldolate intermediate after 1,3-silicon migration resulting in the elimination product **B**, while the product **C** is due to the hydrolysis of Lewis base activated trimethylsilyl enolate. It indicated to us that a proper balance between Lewis basicity and Brønsted basicity as well as anhydrous reaction medium is required to improve the yield of expected aldol product (**A**). We did not observed the formation of *O*-acylated product from this reaction in the presence of any of the catalysts, may be because of its less stability. As trace amount of it though formed, may get rapidly decomposed to the aldol product.

It was interesting to observe that the carboxylate salts **29b** and **29d** provided only the elimination product (Table 2, entries 2 and 5) while their analogues with free NH (**29a** and **29c**) showed slight improvement in the yield of desired product (**A**) (Table 2, entries 1 and 4). The lithium salts of binaphthyl derived ligands also showed similar behavior (Table 2, entry 7 vs. 6 and 8). These results indicated the involvement of hydrogen bonding interactions in the transition states of monometallic salt catalyzed reactions as that reported for TMSCN additions to aldehydes.[3a]

The possible role of hydrogen bonding site in these reactions was initially hypothesized as shown in the Figure 11. The proton present in the catalyst structure balances Brønsted basicity of the catalyst through intramolecular hydrogen bonding and suppresses elimination reaction. The catalyst without these features will not involve such type of extra stabilization and shows more Brønsted basic character. This leads to the abstraction of α-proton from the trimethylsilyl aldolate generating substantial amount of elimination product (**B**).

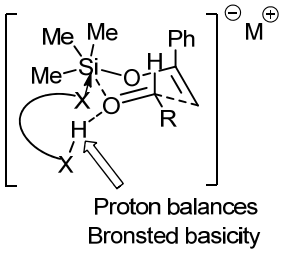



**Figure 11.** Mechanistic hypothesis of using salts bearing hydrogen bonding site.

The lithium salts of ephedrine derivatives (**36a** and **36b**) even though bearing an N−H proton gave substantial amounts of elimination product (Table 2, entries 12 and 13). This is because of their strong Brønsted basic character compared to carboxylates

and phenoxides. Amongst several sodium salts, only the mono sodium salts of binaphthyl derivatives (**35d**–**35f**) are soluble in THF and $CH_3CN$ and gave appreciable yields of the aldol product (**A**). The catalyst **35e** with OMe group showed slightly higher reactivity and yield than those with free NH or OH (**35d** and **35f**) due to its higher solubility in THF. But the enantioselectivity was low and the formation of elimination product was always observed.

We have also evaluated the dimetallic salts of BINOL derivatives (**50a**–**c**) as catalysts. However they gave lower yields than monometallic salts. The elimination product (**B**) was formed predominantly (Table 2, entries 16–20) and enantioselectivities were again poor. The dilithium salt of salen (**49**) also showed similar behavior. The catalyst **51** despite of high solubility in commonly used organic solvents, provided similar results. Dilithium salt of 3,3'-diphenyl BINOL (**50b**) showed improvement in the yield of product although in low *ee* in the presence of catalytic amount of isopropanol as additive (Table 2, entry 19 vs. 18). The low enantioselectivity could be attributed to the reaction proceeding through an open transition state with silicon fully saturated by chelation. These results differ from those with trimethoxysilyl enolates;[23,24d] where one of the methoxy group gets removed after chelation providing Lewis acidic pentavalent silicon species.[1a,23]

The monolithium salts of salen derivatives give better results in the TMSCN additions to aldehydes than the dilithium salts.[8c,d] Therefore we used the monolitihium salt of **9a** as the catalyst. Unlike the monolithium salt of BINOL (**35a**), it resulted in the trace amount of product. Also the monolithium salt of **10a** having extra hydrogen bonding site was used hoping that free NH and OH will avoid the formation of oligomeric structures of lithium salts responsible for their low solubility and also achiral reactions arising from the improper coordination of lithium. But this strategy too failed because of the complete coordination of lithium which resulted in the significant decrease in Lewis basicity of the catalyst. Also the lithium salt of hemisalen (**45**), despite of having an OH group showed the similar results. The comparision of results of salen salts with the binaphthyl salts indicates the superiority of later in this reaction. It indicates that trimethylsilyl enolate is less reactive than TMSCN and does not get activated easily with this type of weak Lewis bases.

We then examined salts of other chiral acids having variations in the α-sterics and acidity of hydrogen bonding site etc. as the catalysts (Table 3). The sterics at the α-position of proline (**30a**) decreased the rate as well as yield of the aldol product.

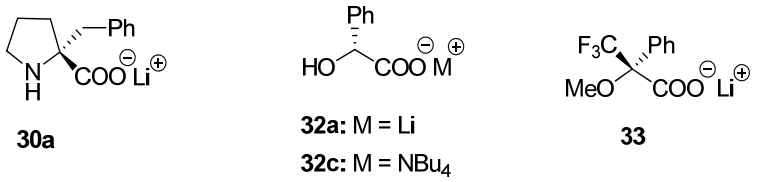
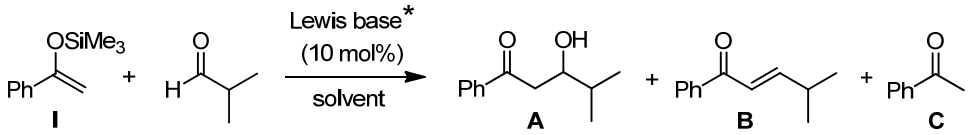



**Figure 12.** Salts of chiral carboxylic acid having different substituents at chiral center.

Similar results were observed when the hydrogen bonding site was OH (**32a**). The tetrabutylammonium salt (**32c**) showed the formation of elimination product only. The lithium salt of (*R*)-(-)-Mosher's acid (**33**) does not activated the trimethylsilyl enolate may be due to its weak Lewis basicity resulting from the presence of electron withdrawing trifluoromethyl group.

**Table 3.** Effect of sterics and electronics of the carboxylate salts.




| No | Catalyst | Solvent | Temp ($^{o}$C) | Time (h) | Yield (%)[a] |
|---|---|---|---|---|---|
| 1 | **30a** | DMF/THF | 25 | 4 | 36 |
| 2 | **32a** | DMF/THF | 25 | 10 | 40 |
| 3 | **32c** | DCM | 0 | 1 | Elimination |
| 4 | **33** | DMF/THF | 25 | 15 | No reaction |

[a] Isolated yield of **A** (In all cases *ee* was < 10 % as shown by comparison of the optical rotation with literature value[22a]). [b] DMF:THF (1:9). [d] Mixture of **A**, **B** and **C**.

We then studied the effect of acidity of hydrogen bonding sites on the outcome of this reaction. A series of catalysts with chirality close to either Lewis basic or hydrogen bonding site were examined (Figure **13**). It has been observed that the catalyst with increased acidity of N−H proton shows inferior results.

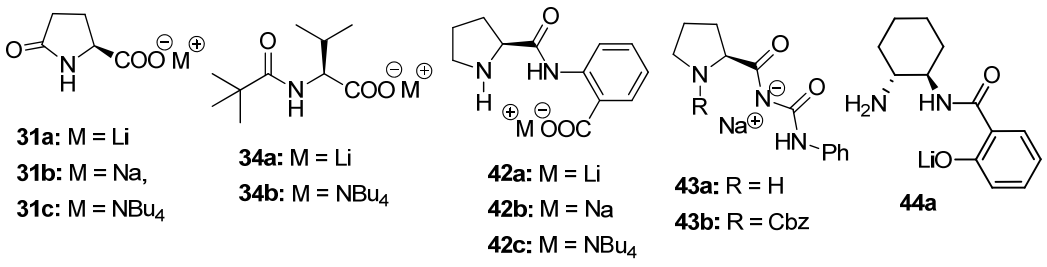



**Figure 13.** Salts with variations in the acidities of hydrogen bonding site.

In most of the cases no formation of product was observed. Only the sodium salt of urea derivatives (**43a** and **43b**) gave moderate yield (≈ 60%) but the racemic product. It seems that due to the increased Brønsted acidities of the hydrogen bonding sites the net Lewis basicity of the catalyst gets significantly reduced.

We have observed that majority of the sodium salts of above listed ligands have low solubility in THF and $CH_3CN$ while in the mixed solvent DMF/THF (1:9) though they are soluble; the reaction resulted in the side products (**B** and **C**). Therefore more soluble tetrabutylammonium salts of a few of the ligands were used. However these always provided appreciable amounts of elimination product (**B**). Therefore lithium salts were preferentially used as catalysts for the rest of study.

The present study indicated that hydrogen bonding sites like NH or OH present in the monometallic salts suppresses the formation of elimination product. However the salts of acids like hydroxy acids and amino acids are of little use as these present solubility problems. Also as seen from Table 2, the yields with mono metallic salts of binaphthyl derivatives were not impressive. An alternate option was therefore conceived which involved using the salts of monoamides of diamines.

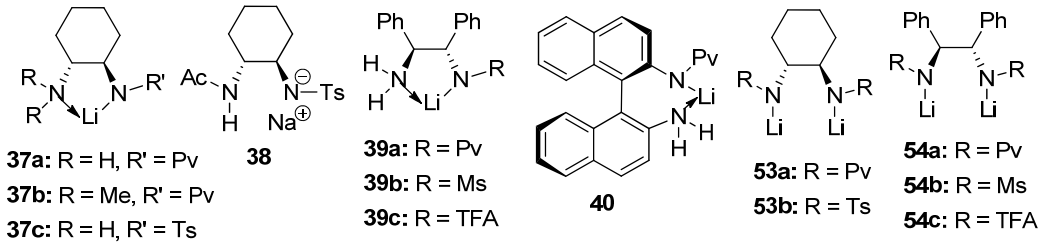
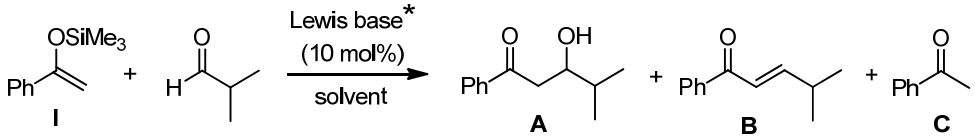



**Figure 14.** Salts of amide derivatives of symmetrical diamines.

It was interesting to find that salts of monoamides exhibited catalytic behavior of amino acid carboxylates. For example **37a** gave good yield while **37b** promoted elimination reaction (Table 4, entry 1 vs. 3). This explains the desirable effect of hydrogen bonding site present in the catalyst structure. In most cases, good yields were realized in short period of time, though the enantioselectivities were low. Out of these catalysts, **39c** with electron withdrawing fluorine atoms was found to be the best one (Table 4, entry 10). In general, mono metallic salts were found to be better than dimetallic salts. Screening of various solvents showed that THF and DME are the solvents of choice for this reaction.

**Table 4.** Evaluation of lithium salts of amides.




| No | Catalyst | Solvent | Temp ($^oC$) | Time (h) | Yield (%)[a] |
|---|---|---|---|---|---|
| 1 | **37a** | THF | 0 | 4 | 76 |
| 2[b] | **37a** | $Et_2O$ | 25 | 7 | 38 |
| 3 | **37b** | $Et_2O$ | 25 | 15 | Mixture |
| 4 | **37c** | THF | 0 | 1 | 72 |
| 5[b] | **38** | THF | 0 $^oC$ | 5 | 68 |
| 6 | **39a** | $Et_2O$ | 25 | 4 | 53 |
| 7[b] | **39a** | Toluene | 25 | 18 | No reaction |
| 8 | **39a** | DME | 25 | 14 | 71 |
| 9 | **39b** | THF | 25 | 3 | 59 |
| 10[b] | **39c** | THF | 0 | 12 | 84 |
| 11 | **40** | THF | 25 | 5 | 66 |
| 12 | **53a** | THF | 0 | 8 | 59 |
| 13 | **53b** | THF | 0 | 5 | 68 |
| 14 | **54a** | THF | 0 | 8 | 68 |
| 15 | **54b** | *i*-PrOH/THF[c] | 25 | 18 | 47 |
| 16 | **54c** | THF | 0 | 3 | 71 |

[a] Isolated yield of **A** (*ee* < 10 % in most cases as shown by the comparison of optical rotation with literature values[22a,b]). [b] Benzaldehyde as electrophile. [c] *i*-PrOH/THF (1:4).

To study the effect of additional hydrogen bonding site present in the catalyst structure, a few of the salts shown in Figure 15 were examined as possible catalysts.

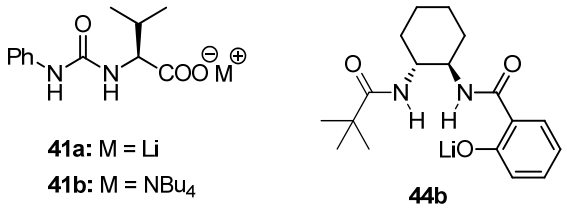
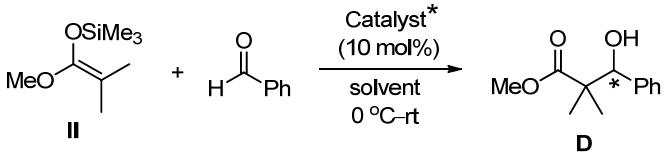



**Figure 15.** Monometallic salts of tridentate ligands.

Poor yield and enantioselectivities were obtained indicating that additional hydrogen bonding has no significant effect. Also the reaction was tried in the presence of organocatalysts **17** and **18** hoping that they will activate aldehyde through hydrogen bonding and enloate will attack on this activated aldehyde. Unfortunately this strategy too failed to give the product. The mixed dibasic lewis bases, having neutral and anionic basic sites (salts of **19b**) do not showed good rates and yields of this reaction.

Few of the catalysts (**37a**, **39a**, **39c**, **40**, **52** and **54a**) were then used to study the substrate scope. The aromatic aldehydes showed increased reactivities than aliphatic ones, while the α,β-unsaturated aldehydes eg. cinnamaldehyde gave 1,4-adducts similar to that reported with other anionic catalysts such as lithium pyrrolidinone.[5b] Also few of these catalysts efficiently activated trimethylsilyl enolates of aliphatic esters. For example the trimethylsilyl enolate of methyl isobutyrate provided good yield of the expected aldol product (Table 5) though in low enantioselectivity. But the trimethylsilyl enolates derived from phenyl esters[21c] eg. phenyl acetate underwent facile cleavage to phenol along with the formation of expected aldol product though in low yield.

**Table 5.** Aldol reaction of trimethylsilyl enolates of methyl isobutyrate.



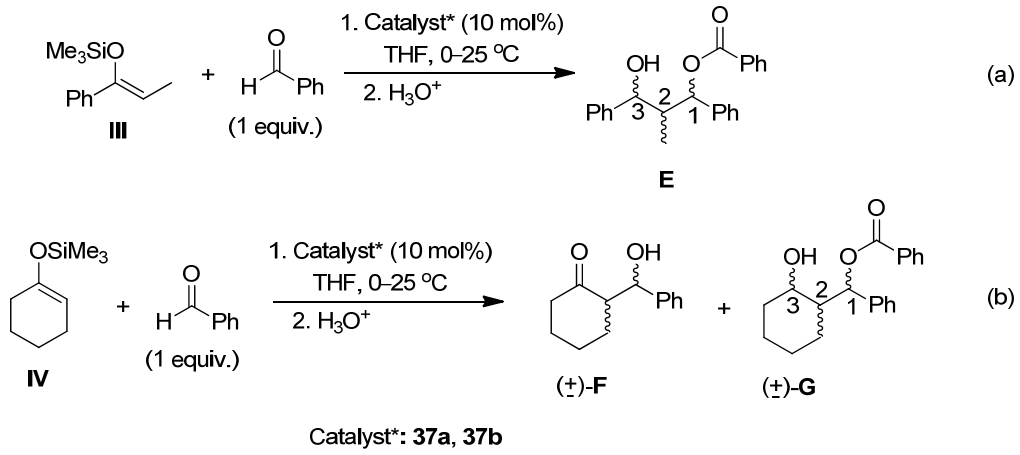

| No | Catalyst | Solvent | Time (h) | Yield (%)[a] | *ee* (%)[b] |
|---|---|---|---|---|---|
| 1 | **39a** | THF | 48 | 77 | 14 |
| 2 | **39a** | *i*-PrOH/THF[c] | 48 | 72 | < 5 |
| 3 | **52** | THF | 36 | 82 | < 5 |
| 4 | **54a** | THF | 48 | 73 | < 5 |

[a] Isolated yield of aldol product (**D**). [b] Determined by the comparison of optical rotation with literature value.[22c] [c] 1 equiv. of *i*-PrOH as additive.

## Mechanistic studies

Through the present study we could optimize the yield of aldol product, the enantioselectivity was disappointing. Therefore mechanism of this reaction was reinvestigated. Although aldol product is not isolated as a sole trimethylsilyl aldolate from the reaction of trimethylsilyl enolate of acetophenone, it was obtained in good yields (> 84%) from the reaction of trimethylsilyl enolate of methyl isobutyrate. This indicates a catalytic process. Also large amounts of elimination products formed in the presence of alkoxides reduces the possibility of metal aldolate acting as catalyst at least in this system. Furthermore the low selectivities from the reactions catalyzed by monolithium salts of tetradentate ligand (**9a** and **10a**) indicate that lithium is not promoting the achiral reaction.

To know whether the hydrogen bond donor present in the catalysts favors the reaction through a closed transition state, aldol additions of stereodefined enolates were carried out in the presence of catalysts with and without hydrogen bond donors (**37a** and **37b**). Surprisingly, aldol-Tishchenko product was the sole product from the reaction of *Z*-enolate (**III**) derived from propiophenone[21d] (Scheme 11, (a)).




**Scheme 11.** Reactions of stereodefined trimethysilyl enolates with benzaldehyde.

The 1,2-*syn*-2,3-*anti* and 1,2-*anti*-2,3-*syn* products (**E**)[24a,b] were obtained in the 1:1 ratio in the presence of both the catalysts **37a** and **37b** (Table 6, entries 1 and 2).

**Table 6.** Addition of stereodefined trimethysilyl enolates to benzaldehyde.

| No | Enolate | Catalyst | Time (h) | Yield (%)[a] | dr[b] |
|---|---|---|---|---|---|
| 1 | **III** | **37a** | 18 | 30 | 1:1[c] |
| 2 | **III** | **37b** | 14 | 42 | 1:1[c] |
| 3 | **IV** | **37a** | 24 | 26[d] | 1:1[e] |
| 4 | **IV** | **37b** | 24 | 20[d] | 1:1[e] |

[a] Isolated yield. [b] Determined by $^1$H NMR and HPLC analysis. [c] Of 1,2-*syn*-2,3-*anti*/1,2-*anti*-2,3-*syn*-**D**. [d] Of aldol product **E**. [e] Of *syn*/*anti*-**E** (found to be racemic by chiral HPLC).

Initially it was thought to be due to the 1,3-benzoate migration from the more favored 1,2-*anti*-2,3-*syn* diastereomer. However from the reaction of cyclohexanone derived enolate (**IV**),[21a] the aldol products (**F**)[24c] (though racemic) were obtained in the same diastereomeric ratio (Table 6, entries 4 and 5). Along with **F**, all the diastereomers of aldol-Tishchenko product (**G**, although racemic) were obtained in the varying ratios (Scheme 11 (b)).[24b,c] Lack of diastereoselectivity in the first step that is aldol reaction, indicates that it proceeds through an open transition state.

Similar type of aldol-Tishchenko reaction is recently reported with trimethoxysilyl enolates.[24d] Formation of aldol-Tishchenko product indicates the generation of metal aldolate intermediate from the aldol reaction of either metal enolate produced by transmetalation or Lewis base activated silyl enolate with aldehyde. Although transmetalation is not reported between the lithium amides and trimethylsilyl enolates, it is based on the trace amounts of product formed in the reaction of sterically hindered triethylsilyl enolate of methyl isopropionate.[1c,d] More direct support to this is provided by $^1$H NMR of the mixture of trimethylsilyl enolate of cyclohexanone and catalysts **35b**. No peak of olefinic proton corresponding to the lithium enolate[24e] was observed. Thus the metal aldolate is generated through the aldol reaction of Lewis base activated trimethylsilyl enolate according to the reported mechanism.[1] Its equilibrium with the metal enolate through retro-aldolization is thus responsible for the observed low enantioselectivities. Though good yields are obtained in this reaction with a few of the catalysts, it is due to the rapid silylation of metal aldolate intermediate as reported by Ishihara et al.[3b]

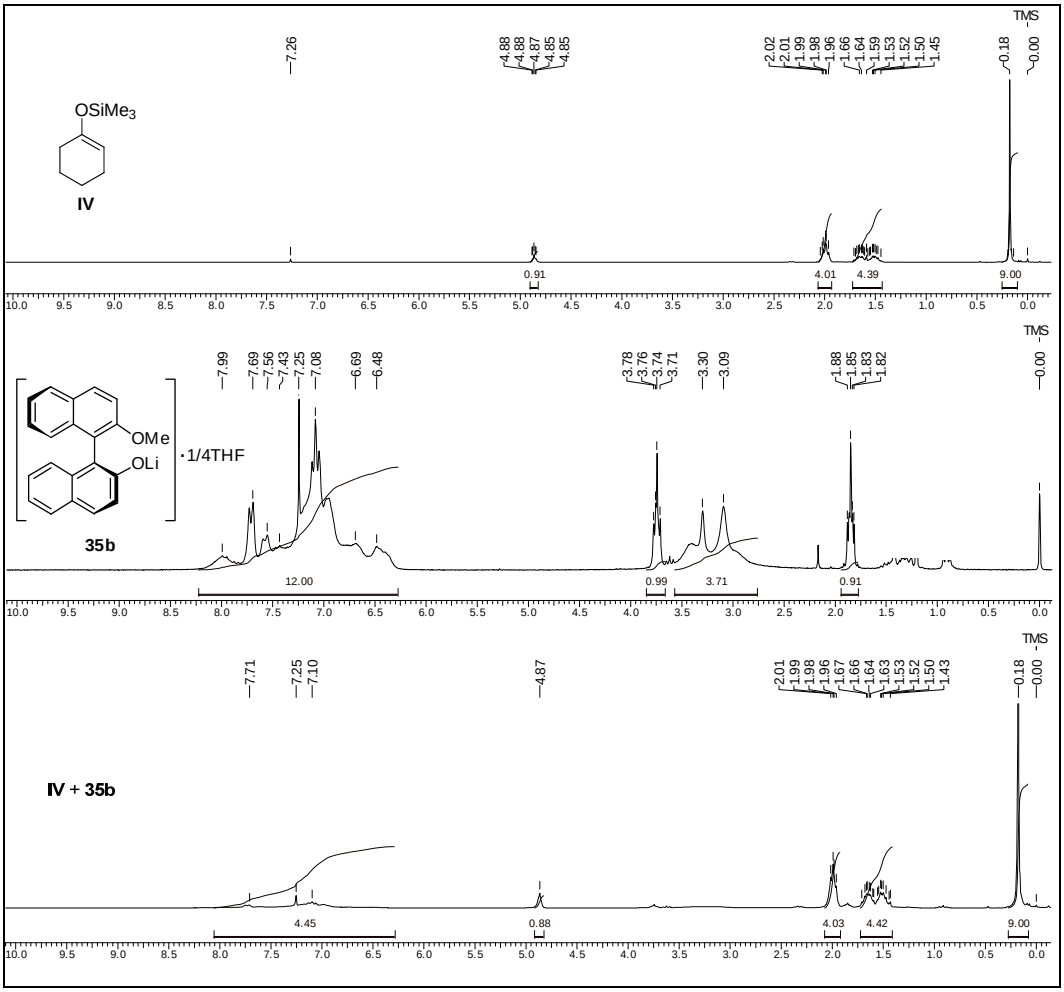



**Figure 16.** $^{1}$H NMR study of the reaction mass showing no transmetalation.

We believe that the Lewis base acts as the mediator for both the enolate activation and silylation of the metal aldolate. Thus Lewis base catalyzed reaction of trimethylsilyl enolates with aldehydes is a two step process.[25] The aldolate intermediate can undergo further reaction with aldehyde or TMS-Lewis base adduct. It is observed that the reaction of metal aldolate with aldehyde is more facile when aldolate has α-substituent.

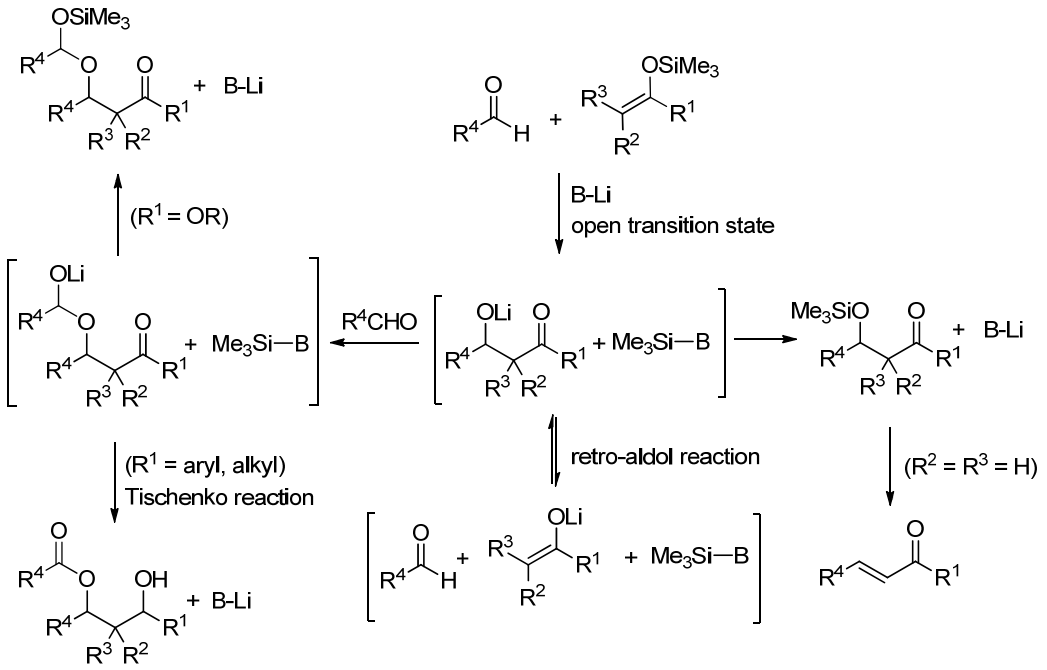



**Figure 17.** Revised mechanism of lithium salt aldol catalyzed reaction of trimethylsilyl enolate.

We have also used few of the chiral Lewis acid-Lewis base complexes derived from the metal fluorides (**55**–**57**) for this reaction. Out of these, the catalyst **55** showed good catalytic activity (Yield = 78%). But as fluorine is outside the coordination sphere of zinc, the achiral fluoride activates the enolate which undergoes direct reaction with the aldehyde and results in no selectivity. Unfortunately other chiral metal fluorides with *N*-oxide ligands do not catalyzed the reaction. Also we have unsuccessfully tried catalytic combinations of zinc fluoride and several chiral diamines eg. **10b**, (1*R*,2*R*)-cyclohexane-1,2-diamine and (1*S*,2*S*)-1,2-diphenylethane-1,2-diamine etc.

# Section 2C

## Mukaiyama-type aldol reaction in aqueous media

### Introduction

Organic reactions in aqueous media are of more interest due to the environmental concerns and the beneficial effects of water on few of the organic reactions.[26] However because of the instability of many common Lewis acids in the presence of water, the development of catalytic asymmetric versions of these reactions, especially C–C bond forming ones in aqueous media is still in the preliminary stage. Recently several water compatible Lewis acids and surfactant combined-Lewis acids etc. have been developed as solution to these problems.[4] Unlike Lewis acids, Lewis bases are more stable to moisture and air. Therefore they can be conveniently used as catalysts under these conditions.

As seen in the previous section, the Lewis basic salts have more solubility in polar solvents and are also stable to air and moisture. Thus they will be good catalysts in aqueous media. This will also generate a monomeric catalytic species especially in the case of lithium salts. Also the metal or quaternary ammonium aldolate formed as intermediates in the aldol reactions of trimethylsilyl enolates catalyzed by these Lewis bases will undergo rapid hydrolysis in the presence of water. This will avoid the problem of retro-aldolization and related side reactions arising from it.

But the Lewis base activated enolate being very reactive is less stable under aqueous conditions and undergoes facile decomposition to its starting material. Also low solubility of organic compounds in water is another problem. Thus a proper selection of aqueous reaction medium is required to overcome these issues. We have decided to apply following three strategies for this study.

1. Use of aqueous organic solvents.
2. Use of micellar media.
3. Reactions through transmetalation.

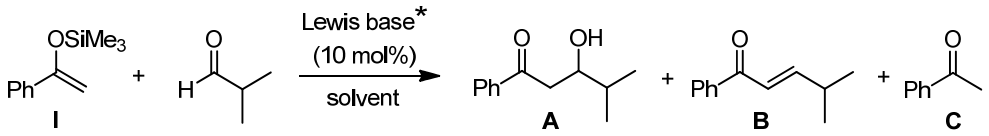
Our studies to avoid hydrolysis of enolate in the wet solvents as well as water are summarized below.

## Results and discussion

The aldol reaction of trimethylsilyl enolates in the aqueous organic solvents (aqueous ethanol and THF) promoted by water tolerant Lewis acids is well reported from the research groups of Kobayashi and others.[26,27] For this the Lewis acid should have some peculiar properties such as its water exchange rate constant (WERC) should be $\geq 3.2 \times 10^6$ $M^{-1}S^{-1}$ and its hydrolysis constant (p*K*h) should be in the range of 4 to 10.08.[28]

But for Lewis base catalysts, such type of study is not reported. We have used a few of the above Lewis bases as catalysts in the aqueous THF as solvent.

**Table 7.** Reactions in water as a cosolvent.[a]




| No | Catalyst | Time (h) | Yield (%)[b] |
|---|---|---|---|
| 1 | **29a** | 2 | Hydrolysis |
| 2 | **29b** | 11 | Hydrolysis |
| 3 | **56** | 0.5 | 26 |
| 4 | **10a** + $\mathbf{ZnF_2}$ | 20 | No reaction |
| 5 | **10a** + $\mathbf{AlF_3}$ | 18 | No reaction |
| 6 | **10b** + $\mathbf{ZnF_2}$ | 12 | No reaction |
| 7 | **10b** + $\mathbf{ZnF_2}$[c] | 36 | 16 |

[a] $H_2O$/THF (1:9) as the solvent . [b] Isolated yield of the aldol product (A). [c] 10 mol% TfOH as additive.

Low yields of the aldol product were obtained in all the cases. This indicated that in the aqueous organic solvents, though the formation of elimination product was avoided by the rapid hydrolysis of the aldolate, the Lewis base activated enolate undergoes facile hydrolysis that decreases the yield of aldol product. Therefore for this reaction in aqueous media use of surfactants could be useful.

Accordingly a few of the chiral monometallic salts were used along with achiral surfactants in water as the solvent. As these catalysts are Lewis basic, a cationic surfactant (CTAB) was employed for this study.

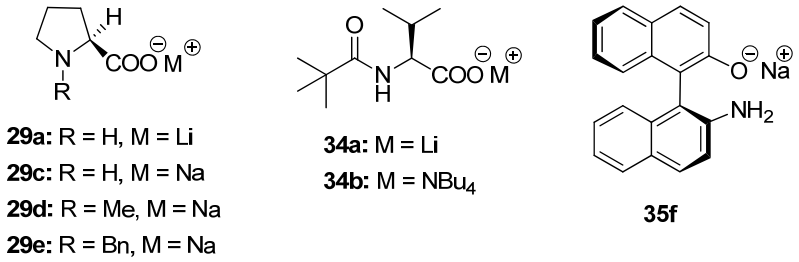
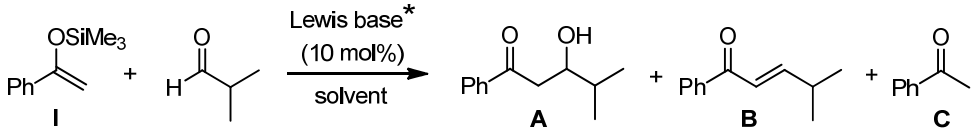



**Figure 18.** Catalysts used to study the reaction in aqueous organic solvents.

**Table 8.** Application of CTAB to avoid the hydrolysis of enolate.




| No | Catalyst | Solvent[a] | CTAB (mol %) | Time (h) | Yield (%)[b] |
|---|---|---|---|---|---|
| 1 | **29a** | $H_2O$ | 0 | 2 | Hydrolysis |
| 2 | **29a** | $H_2O$ | 1 | 60 | Trace |
| 3 | **29a** | $H_2O$ | 10 | 36 | 52 |
| 4 | **29a** | Cyclohexane[c] | 10 | 36 | No reaction |
| 5 | **29c** | $H_2O$ | 0 | 0.5 | Hydrolysis |
| 6 | **29c** | $H_2O$ | 10 | 2 | Hydrolysis |
| 7 | **29c** | Brine | 10 | 4 | 42 |
| 8 | **29c** | Cyclohexane[c] | 10 | 2 | Hydrolysis |
| 9 | **29d** | $H_2O$ | 0 | 24 | Hydrolysis |
| 10 | **29d** | $H_2O$ | 10 | 3 | 54 |
| 11 | **29e** | $H_2O$ | 0 | 24 | Hydrolysis |
| 12 | **29e** | $H_2O$ | 10 | 18 | Hydrolysis |
| 13 | **29e** | Brine | 10 | 15 | Trace |
| 14 | **34a** | $H_2O$ | 10 | 2 | Hydrolysis |
| 15 | **34b** | $H_2O$ | 10 | 2 | Hydrolysis |
| 16 | **35f** | $H_2O$ | 10 | 2 | 36 |
| 17 | **35f** | Cyclohexane[c] | 10 | 12 | Trace |

[a] Concentration of reactants as a 1 M solution. [b] Isolated yield of aldol product (A) (In all cases *ee* was < 10 % as determined by the comparison of optical rotation with the literature value[22a]). [c] 10 mol% water as the additive.

It was found that the use of CTAB minimizes hydrolysis of the enolate in lithium salt (**29a**) catalyzed reaction but not in the sodium salt (**29c**) catalyzed reaction (Table 8, entry 2 vs. 5). In this case, the use of brine as the reaction medium was found to be more effective (Table 8, entry 6). This is due to the salting out effect of brine bringing the catalyst and reactants in a single phase. In the presence of sodium salt of *N*-methyl-L-proline (**29d**) in water, hydrolysis of enolate took place while in the presence of CTAB it gave good yield. However the sodium salt of *N*-benzyl proline (**29e**) showed the formation of trace amount of product even in the presence of CTAB in brine. This may be due to the increased sterics at the Lewis basic site of the catalyst. Reactions under the reverse micellar conditions using cyclohexane water system indicated that normal micelles are better than the reverse ones. (Table 8, entry 4 vs. 3 and entry 7 vs. 8).

It was also observed that the rate of reaction increases with an increase in the concentration of CTAB. At CMC of CTAB (0.92–1.0 mM) the reaction is very slow while its rate at/ or > 10 mol% concentration were found to be almost similar. Therefore 10 mol% concentration was selected as the optimum concentration. The lipophilic lithium salt, **34a** and tetrabutylammonium salt, **34b** promoted the hydrolysis of enolate even in the presence of CTAB while the more lipophilic sodium salt of NOBIN (**35f**) gave the aldol product in water in the moderate yield. While under the reverse micellar conditions, it showed smilar trace amount of product.

We have also used our amphiphilic catalysts (**46a**–**48b**) prepared from lipophilic ligands in the water as well as aqueous organic solvents. The catalysts **46a**, **48a** and **48b** do not activated the enolate (Table 9, entries 1, 9 and 10). Stability of enolate under these Lewis basic conditions in water indicates that the substrates are deep inside the lipophilic environment of catalyst, thus there is no direct contact between them. Out of these catalysts, the sodium salt of amino acid derivative (**46b**) catalyzed the reaction very effectively giving good yields of the aldol product under both normal as well as reverse micellar conditions (Table 9, entries 2–4).

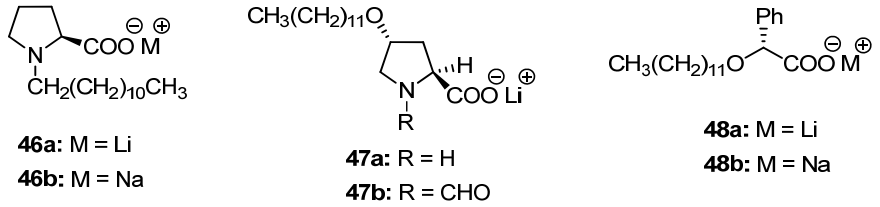
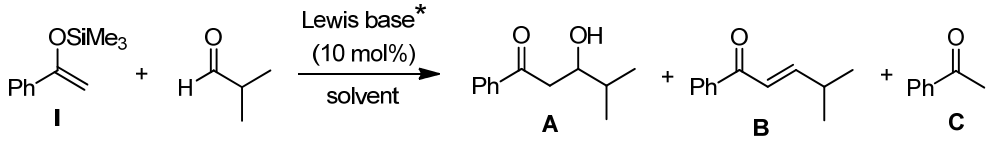



**Figure 19.** Salts of lipophilic ligands.

Hydrolysis of enolate in the presence of **29d** and **29e** under identical conditions indicates the desirable effect of long alkyl chain (Table 8, entries 9 and 11). Also it indicates the requirement of proper ionic character and basicity to activate the enolate (Table 9, entry 2 vs. 1).

**Table 9.** Use of surfactant type-Lewis base catalysts.[a]

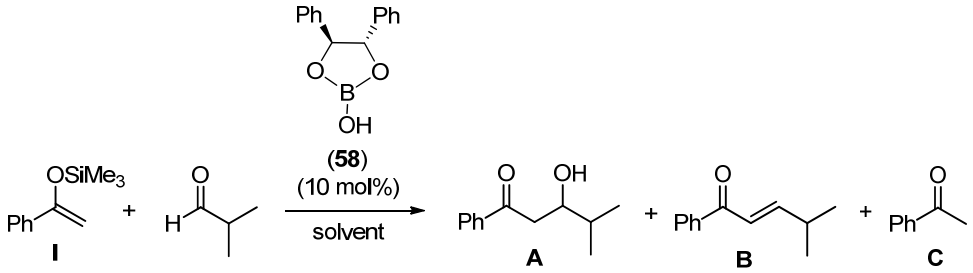



| No | Catalyst | Solvent | Time (h) | Yield (%)[b] |
|---|---|---|---|---|
| 1 | **46a** | $H_2O$ | 21 | No reaction |
| 2 | **46b** | $H_2O$ | 1 | 53 |
| 3 | **46b** | Cyclohexane[c] | 2 | 57 |
| 4 | **46b** | $CHCl_3$[c] | 3 | 44 |
| 5 | **47a** | $H_2O$ | 24 | No reaction |
| 6 | **47b** | $H_2O$ | 2 | Hydrolysis |
| 7 | **47b** | Brine | 15 | Hydrolysis |
| 8 | **47b** | Cyclohexane[c] | 15 | No reaction |
| 9 | **48a** | $H_2O$ | 15 | No reaction |
| 10 | **48b** | $H_2O$ | 15 | No reaction |

[a] All reactions were carried out in water as the solvent at a concentration of 1 M solution. [b] Isolated yield (In all cases *ee* was < 20 % as determined by the comparison of optical rotation with the literature value[22a]). [c] 10 mol% water as the additive.

Contrarily the sodium salt having lipophilic group at 4-position (eg. **47a**) does not catalyze the reaction even by changing the solvent to brine. Also the catalyst **47b** having two Lewis basic sites promoted facile hydrolysis. This indicates the effect of position of the alkyl group in the catalyst. The more lipophilic environment near the more ionic Lewis basic site present in the catalyst **46b** helps to bring both the reactants in close proximity in the stern layer of its micelles, while in the case of catalysts **47a** and **47b** it is likely that the enolate gets activated at the stern layer which then reacts with water present at the periphery and not with the aldehyde which is deep insides the micelles.

Kobayashi et al. have reported a boron enolate mediated stereoselective aldol reaction of trimethylsilyl enolates in the micellar media of SDS in the presence of catalytic amounts of diphenyl boronic acid and benzoic acid.[28] We have used the borate ester prepared from chiral diol ((1*S*,2*S*)-1,2-diphenylethane-1,2-diol) and boronic acid as the boron source. Unfortunately the reactions under identical conditions and also in THF resulted in the hydrolysis of enolate.




**Scheme 12.** Aldol reaction though transmetalation.

Thus we were able to avoid the hydrolysis of the enolate under certain conditions to get good yield of the desired product, but the expected increase in the selectivity by avoiding the retro-aldolization through hydrolysis of the metal or tetraalkylammonium aldolate is not achieved.

## Conclusions

- Being a nucleophilic activation, the outcome of Lewis base catalyzed addition of trimethylsilyl enolates to aldehydes depends on several factors such as enolate, nature of catalyst, solvent, temperature etc. Amongst these the most important is basicity of catalyst which in turn is governed by structure of the ligand.
- New Lewis bases with built-in OH/NH sites were designed and prepared. We have shown that mild Brønsted bases with these sites are efficient Lewis base catalysts for the reactions of trimethylsilyl enolates.
- The open transition state and retro-aldolization of the metal aldolate intermediate are shown to be responsible for the observed low enantioselectivities of the aldol products; out of which former seems to have more impact.
- Based on the observed results, a possibility to develop catalytic enantioselective aldol-Tishchenko-type reaction is revealed.
- For the first time Lewis base catalyzed Mukaiyama-type aldol reaction was successfully carried out in aqueous medium.

# Experimental section

## General

All reagents and solvents were purified and dried according to the literature procedures.[29] *N*-Cbz-L-proline,[7a] *N*-Cbz-L-prolinamide,[13] *N*-Cbz-4-hydroxy-L-proline,[15b] (*S*)-*N*,*N*-dimethyl-1-phenylethanamine[14] and (1*S*,2*S*)-1,2-diphenylethane-1,2-diamine[11c] were prepared according to the literature reports. Similarly the trimethylsilyl enolates of methyl isobutyrate (**II**),[21b] phenyl acetate[21c] and *Z*-enolate of propiophenone (**III**)[21d] were obtained by following the literature procedures.

(**Note:** Compound No. **24** and **28** showed upfield shift of their acidic protons in the $^1$H NMR, due to the presence of long alkyl chain)

## 1. Preparation of ligands

### 1.1. Synthesis of (*S*)-2-(pyrrolidine-2-carboxamido) benzoic acid (5)

*1.1.1. (S)-Benzyl 2-((2-(methoxycarbonyl)phenyl)carbamoyl)pyrrolidine-1-carboxylate.*

A solution of *N*-Cbz-L-proline (1.25 g, 5 mmol) and triethylamine (0.7 mL, 5 mmol) in anhydrous $CHCl_3$ (5 mL) was cooled to 0 $^oC$. Ethyl chloroformate (0.48 mL, 5 mmol) was added to it dropwise and the resulting white suspension was stirred at 0–5 $^oC$ for 0.5 h. Methyl anthranilate (0.65 mL, 5 mmol) was then added and stirring continued for additional 0.5 h at the same temperature. The reaction mixture was gradually warmed to room temperature and monitored by TLC. After completion of the reaction (1 h), it was diluted with dichloromethane (20 mL) and was washed successively with 1 M HCl (10 mL), saturated aqueous $NaHCO_3$ (10 mL) and water (10 mL). Organic layer was dried over anhydrous $Na_2SO_4$ and concentrated. The residue was purified by column chromatography using ethyl acetate/petroleum ether (1:5) as the eluent.

**Yield** : 1.5 g (78%, sticky mass).

**TLC data** : $R_f$(20 % ethyl acetate /petroleum ether): 0.2

**$[\alpha]_D^{25}$** : -133.33 (*c* 1.23, $CHCl_3$).

**IR (Nujol) v/cm$^{-1}$** : 3268, 2953, 1699 (C=O str.), 1603, 1586 (Ar C=C str.).

**$^1$H NMR ($CDCl_3$) ppm** : δ 1.85–2.40 (m, 4H, $(CH_2)_2$), 3.50–3.90 (m, 5H, $OCH_3$ and $NCH_2$), 4.37–4.59 (m, 1H, CH), 4.95–5.31 (m, 2H, $OCH_2Ph$), 6.99–7.60 (m, 7H, Ar H), 8.01 (d, *J* = 7.83

Hz, 1H, Ar H), 8.74 (t, *J* = 8.50 Hz, 1H, Ar H), 11.48 and 11.61 (br s, 1H, CONH, rotamers).

**$^{13}$C NMR ($CDCl_3$) ppm** : δ 23.6 and 24.2 ($CH_2$), 30.3 and 31.4 ($CH_2$), 46.9 and 47.3 ($CH_2$), 52.2 ($OCH_3$), 62.3 (CH), 67.0 and 67.1 ($OCH_2$), 115.3, 120.0, 120.1, 122.6, 127.7, 128.0, 128.3, 130.7, 134.4, 136.2, 136.6, 140.7, 140.9 (Ar C), 154.6 and 155.4 (CO), 168.0 and 168.4 (CO), 171.3 and 171.7 (CO) rotamers.

**HRMS (ESI$^+$) for** : $C_{21}H_{22}N_2O_5$

**Calculated $[M+H]^+$** : 383.1601

**Found** : 383.1606 (100%).

*1.1.2. (S)-2-(1-((Benzyloxy) carbonyl) pyrrolidine-2-carboxamido) benzoic acid (N-Cbz-**5**)*

To the solution of (*S*)-benzyl 2-((2-(methoxycarbonyl)phenyl)carbamoyl)-pyrrolidine-1-carboxylate (1.45 g, 3.8 mmol) in methanol (8 mL), lithium hydroxide monohydrate (319 mg, 7.6 mmol) was added and the solution was stirred at room temperature. After completion of the reaction (15 h) as indicated by TLC, solvent was removed on rotavapor and the residue was acidified to pH ≈ 4 using 2 M HCl. It was extracted with ethyl acetate (3 x 10 mL). Organic layer was washed with brine (10 mL), dried over anhydrous $Na_2SO_4$ and concentrated to obtain crude product. Its purification was done through column chromatography using ethyl acetate as the eluent.

**Yield** : 1.3 g (93%, white solid).

**Melting point** : 62–64 $^oC$.

**TLC data** : $R_f$(ethyl acetate): 0.3

**$[\alpha]_D^{25}$** : -126.42 (*c* 1.25, $CHCl_3$).

**IR (Nujol) v/cm$^{-1}$** : 3186, 2928, 1689 (C=O str.), 1603, 1588 (Ar C=C str.).

**$^1$H NMR ($CDCl_3$) ppm** : δ 1.85–2.40 (m, 4H, $(CH_2)_2$), 3.50–3.87 (m, 2H, $NCH_2$), 4.40–4.80 (m, 2H, CH and $^+$NH, zwitterion), 4.97–5.39 (m, 2H, $OCH_2Ph$), 6.90–7.33 (m, 6H, Ar H), 7.34–7.67 (m, 1H, Ar H), 7.87 and 8.06 (d, *J* = 7.71 Hz, 1H, Ar H, rotamers), 8.75 (dd, *J* = 8.34, 4.17 Hz, 1H, Ar H), 11.58

(d, $J$ = 7.57 Hz, 1H, CONH).

**$^{13}$C NMR ($CDCl_3$) ppm** : δ 23.5 and 24.2 ($CH_2$), 29.6, 30.6 and 31.4 ($CH_2$), 47.0 and 47.4 ($CH_2$), 62.3 (CH), 67.4 and 67.6 ($OCH_2$), 114.5, 115.0, 120.0, 122.8, 122.9, 127.8, 128.0, 128.12, 128.4, 131.6, 131.7, 135.0, 135.9, 136.2 (Ar C), 141.03 and 141.3 (CO), 155.1 and 155.9 (CO), 171.2 and 171.7 (CO) rotamers.

**HRMS ($ESI^+$) for** : $C_{20}H_{20}N_2O_5$.

**Calculated $[M+H]^+$** : 369.1445

**Found** : 369.1442 (100%).

*1.1.3. (S)-2-(Pyrrolidine-2-carboxamido) benzoic acid (***5***)*

To a solution of above described *N*-Cbz derivative (1.29 g, 3.5 mmol) in methanol (20 mL), 10% Pd/C (80 mg) was added and stirred vigorously under the balloon-pressure of hydrogen. After completion of the reaction (6 h) as indicated by TLC, argon was bubbled through the reaction mixture and it was filtered through a small pad of celite. Filtrate and washings were concentrated and the resulting crude product was purified by filtration column chromatography using methanol/dichloromethane (1:4) as the eluent.

**Yield** : 750 mg (92%, white solid).

**Melting point** : 240–242 $^oC$ (Lit.[7b] 225–227 $^oC$).

**TLC data** : $R_f$(20% methanol/dichloromethane): 0.3

**$[\alpha]_D^{25}$** : -84.48 (*c* 1.04, $H_2O$).

**IR (Nujol) v/cm$^{-1}$** : 3359, 2948, 1690 (C=O str.), 1626 (Ar C=C str.), 1041.

**$^1$H NMR ($D_2O$) ppm** : δ 2.01–2.30 (m, 3H) and 2.42–2.65 (m, 1H) $(CH_2)_2$, 3.35–3.51 (m, 2H, $NCH_2$), 4.55 (t, $J$ = 7.20 Hz, 1H, CH), 7.23 (dt, $J$ = 7.58, 0.88 Hz, 1H, Ar H), 7.46 (dt, $J$ = 7.58, 1.52 Hz, 1H, Ar H), 7.86 (dd, $J$ = 7.84, 1.39 Hz, 1H, Ar H), 8.02 (d, $J$ = 7.83 Hz, 1H, Ar H).

**$^{13}$C NMR ($D_2O$) ppm** : δ 23.9 ($CH_2$), 29.3 ($CH_2$), 46.5 ($CH_2$), 60.9 (CH), 122.0, 125.2, 131.2, 133.5, 137.2 (Ar C), 167.5 (NCO), 171.7 (COO).

**Analysis for** : $C_{12}H_{14}N_2O_3$.

**Calculated (%)** : C, 61.53; H, 6.02; N, 11.96

**Found** : C, 61.47; H, 6.16; N, 11.86.

### 1.2. General procedure for monoacylation of 1,2-diamines

In an oven dried 10 mL round-bottom flask, imidazole (450 mg, 6.6 mmol) was dissolved in anhydrous THF (5 mL). The solution was cooled to 0 $^{o}$C and the acid chloride (3 mmol) was added to it dropwise. The resulting white suspension was stirred at 0 $^{o}$C for 30 min and then gradually warmed to room temperature. After stirring further for 30 min, the precipitated imidazole hydrochloride was filtered under argon and residue was washed with anhydrous THF (2 x 5 mL). The filtrate and washings were combined and added dropwise to the ice cold solution of 1,2-diamine (3 mmol) in anhydrous THF (5 mL). Stirring was continued at 0 $^{o}$C and the reaction was monitored by TLC. After completion of the reaction (5–10 h), solvent was evaporated on rotavapor and the residue was redissolved in DCM (20 mL). It was washed with water (10 mL), brine (10 mL) and dried over anhydrous $Na_2SO_4$. After evaporation of solvent, the crude product obtained was purified by flash column chromatography to get the desired product.

#### *1.2.1. N-((1R,2R)-2-Aminocyclohexyl)pivalamide (**12a**)*

**Yield** : 404 mg (68%, white solid).

**Melting point** : 96–97 $^{o}$C.

**TLC data** : $R_f$ (10% methanol/dichloromethane): 0.4

**$[\alpha]_D^{25}$** : -32.32 (*c* 1.0, $CHCl_3$).

**IR (Nujol) v/cm$^{-1}$** : 3344, 2922, 1634 (NC=O str.), 1207.

**$^{1}$H NMR ($CDCl_3$) ppm** : δ 1.03–1.44 (m, 13H, $C(CH_3)_3$ and $(CH_2)_2$), 1.67–1.80 (m, 4H, $CH_2$ and $NH_2$), 1.90–2.04 (m, 2H, $CH_2$), 2.4 (dt, *J* = 10.48, 3.79 Hz, 1H, CH), 3.42–3.62 (m, 1H, CH), 5.56 (d, *J* = 6.82 Hz, 1H, CONH).

**$^{13}$C NMR ($CDCl_3$) ppm** : δ 24.9 ($CH_2$), 27.5 ($CH_3$), 32.2 ($CH_2$), 35.0 ($CH_2$), 38.6 (C), 55.3 (CH), 55.7 (CH), 178.7 (CO).

**Analysis for** : $C_{11}H_{22}N_2O$

**Calculated (%)** : C, 66.62; H, 11.18; N, 14.13

**Found** : C, 67.01; H, 11.13; N, 13.94.

*1.2.2. N-((1R,2R)-2-Aminocyclohexyl)acetamide (**12b**)*

**Yield** **:** 180 mg (38%, white hygroscopic solid).[30]

**Melting point** **:** 104–105 $^{o}$C.

**TLC data** **:** $R_f$ (10% methanol/dichloromethane): 0.3

**$[\alpha]_D^{25}$** **:** -22.78 (*c* 0.79, $CHCl_3$).

**IR (Nujol) v/cm$^{-1}$** **:** 3353, 3283, 2923, 1634 (NC=O str.).

**$^1$H NMR ($CDCl_3$) ppm** **:** δ 1.00–1.45 (m, 4H, $(CH_2)_2$), 1.41–1.60 (m, 4H, $CH_2$ and $NH_2$), 1.90–2.07 (m, 5H, $CH_3$ and $CH_2$), 2.30–2.46 (dt, *J* = 10.29, 4.12 Hz, 1H, CH), 3.53 (dq, *J* = 10.0, 3.9 Hz, 1H, CH), 5.55 (d, *J* = 5.69 Hz, 1H, CONH).

*1.2.3. N-((1R,2R)-2-Aminocyclohexyl)benzamide (**12c**)*

**Yield** **:** 510 mg (78%, white solid).[31]

**Melting point** **:** 175–177 $^{o}$C (Lit.[31] 176–179 $^{o}$C).

**TLC data** **:** $R_f$ (5% methanol/dichloromethane): 0.3

**$[\alpha]_D^{25}$** **:** -48.28 (*c* 1.0, $CHCl_3$).

**IR (Nujol) v/cm$^{-1}$** **:** 3339, 3222, 2948, 1646 (NC=O str.), 1600 (Ar C=C str.).

**$^1$H NMR ($CDCl_3$) ppm** **:** δ 1.10–1.48 (m, 4H, $(CH_2)_2$), 1.50–1.84 (m, 4H, $CH_2$ and $NH_2$), 1.98–2.03 (m, 1H) and 2.05–2.16 (m, 1H) $CH_2$, 2.50 (dt, *J* = 10.29, 3.51 Hz, 1H, CH), 3.73 (dt, *J* = 10.67, 4.01 Hz, 1H, CH), 6.16 (d, *J* = 7.20 Hz, 1H, CONH), 7.40−7.54 (m, 3H, Ar H), 7.79 (dd, *J* = 7.28, 2.03 Hz, 2H, Ar H).

*1.2.4. N-((1S,2S)-2-Amino-1,2-diphenylethyl)pivalamide (**13a**)*

**Yield** **:** 660 mg (74%, white solid).

**Melting point** **:** 135.6–136.8 $^{o}$C.

**TLC data** **:** $R_f$ (40% ethyl acetate/hexane): 0.5

**$[\alpha]_D^{25}$** **:** -39.0 (*c* 1.23, $CHCl_3$)

**IR (Nujol) v/cm$^{-1}$** **:** 3415, 3389, 2922, 1642 (NC=O str.), 1603 (Ar C=C str.).

**$^1$H NMR ($CDCl_3$) ppm** **:** δ 1.13 (s, 9H, $C(CH_3)_3$), 1.45 (br s, 2H, $NH_2$), 4.47 (d, *J* = 2.91 Hz, 1H, CH), 5.10 (dd, *J* = 7.70, 2.78 Hz, 1H,

CH), 7.07 (d, *J* = 7.20 Hz, 1H, CONH), 7.2–7.46 ( m, 10H, Ar H).

**$^{13}$C NMR ($CDCl_3$) ppm** : δ 27.4 ($CH_3$), 38.7 (C), 57.9 (CH), 59.1 and 59.6 (CH), 126.1, 126.3, 127.1, 127.4, 128.2, 128.4, 128.5, 139.1, 140.7, 141.9 (Ar C), 177.6 and 179.3 (CO) rotamers.

**Analysis for** : $C_{19}H_{24}N_2O$

**Calculated (%)** : C, 76.99; H, 8.16; N, 9.45

**Found** : C, 77.24; H, 8.01; N, 9.43.

*1.2.5. N-((1S,2S)-2-Amino-1,2-diphenylethyl)acetamide (**13b**)*

**Yield** : 720 mg (94%, white solid)[32]

**Melting point** : 85–87 °C

**TLC data** : $R_f$ (dichloromethane): 0.2

**$[\alpha]_D^{25}$** : +30.22 (*c* 1.39, $CHCl_3$)

**IR (Nujol) v/cm$^{-1}$** : 3310, 2922, 1639 (NC=O str.), 1601 (Ar C=C str.), 767.

**$^1$H NMR ($CDCl_3$) ppm** : δ 1.54 (br s, 2H, $NH_2$), 1.96 (s, 3H, $CH_3$), 4.42 (d, *J* = 3.28 Hz, 1H, CH), 5.14 (dd, *J* = 8.09, 3.29 Hz, 1H, CH), 6.80 (d, *J* = 7.71 Hz, 1H, CONH), 7.20–7.45 (m, 10 H, Ar H).

*1.2.6. N-((1S,2S)-2-Amino-1,2-diphenylethyl)benzamide (**13c**)*

**Yield** : 680 mg (72%, white solid)[33]

**Melting point** : 181–182 °C (Lit.[33] 181–182 °C).

**TLC data** : $R_f$ (40% ethyl acetate/hexane): 0.4

**$[\alpha]_D^{25}$** : +5.6 (*c* 1.06, $CHCl_3$) (Lit.[33] + 6.25 (*c* 1.0, $CHCl_3$))

**IR (Nujol) v/cm$^{-1}$** : 3339, 2948, 1629 (NC=O str.), 1601 (Ar C=C str.), 699.

**$^1$H NMR ($CDCl_3$) ppm** : δ 1.57 (br s, 2H, $NH_2$), 4.54 (d, *J* = 2.90 Hz, 1H, CH), 5.31 (dd, *J* = 7.66, 3.09 Hz, 1H, CH), 7.20–7.55 (m, 13H, Ar H), 7.65 (d, *J* = 7.45 Hz, 1H, CONH), 7.78 (dd, *J* = 8.09, 1.77 Hz, 2H, Ar H).

*1.2.7. N-((1S,2S)-2-Amino-1,2-diphenylethyl)trifluoroacetamide (**13d**)*

**Yield** : 720 mg (78%, white solid)[34a]

**Melting point** : 263–264 °C.

**TLC data** : $R_f$ (5% methanol/dichloromethane): 0.4

**$[\alpha]_D^{25}$** **:** -36.2 (*c* 1.2, MeOH) (Lit.[34a] -0.39 (*c* 1.0, MeOH))

**IR (Nujol) v/cm$^{-1}$** **:** 3410, 3304, 2948, 1694 (NC=O str.), 1591 (Ar C=C str.).

**$^1$H NMR (DMSO-d6/ $CDCl_3$) ppm** **:** δ 2.75 (br s, 2H, $NH_2$), 4.40 (d, *J* = 4.39 Hz, 1H, CH), 5.66 (ABq, *J* = 8.46, 4.43 Hz, 1H, CH), 7.09–7.48 (m, 8H, Ar H), 7.89 (d, *J* = 8.34 Hz, 1H, Ar H), 8.04–8.09 (m, 1H, Ar H), 9.51 (d, *J* = 7.34 Hz, 1H, CONH).

*1.2.8. N-((1R,2R)-2-Aminocyclohexyl)-2-hydroxybenzamide (**16a**)*

*1.2.8.1. N-((1R,2R)-2-Aminocyclohexyl)-2-(benzyloxy)benzamide*

**Yield** **:** 610 mg (63%, sticky mass)

**TLC data** **:** $R_f$ (5% methanol/dichloromethane): 0.3

**$[\alpha]_D^{25}$** **:** -42.2 (*c* 1.46, $CHCl_3$)

**IR ($CHCl_3$) v/cm$^{-1}$** **:** 3379, 3015, 2938, 1644 (NC=O str.), 1601 (Ar C=C str.).

**$^1$H NMR ($CDCl_3$) ppm** **:** δ 0.62–2.25 (m, 6H, $(CH_2)_3$), 2.80–2.99 (m, 2H, $CH_2$), 3.06 (br s, 2H, $NH_2$), 3.59–3.82 (m, 1H, CH), 4.18–4.36 (m, 1H, CH), 5.13 (d, *J* = 2.40 Hz) and 5.25 (s, 2H, $CH_2Ph$) rotamers, 7.02–7.16 (m, 2H, Ar H), 7.34–7.55 (m, 6H, Ar H), 7.85 (d, *J* = 8.08 Hz, 1H, CONH), 7.97–8.27 (m, 1H, Ar H).

*1.2.8.2. N-((1R,2R)-2-Aminocyclohexyl)-2-hydroxybenzamide(**16a**)*

The procedure described above for the hydrogenolysis of *N*-Cbz-**5** was followed for *N*-((1*R*,2*R*)-2-aminocyclohexyl)-2-(benzyloxy)benzamide (486 mg, 1.5 mmol) using 10% Pd/C (30 mg), 1 M HCl (6 mL) and methanol (10 mL). After 8 h stirring and usual workup, the residue obtained was redissolved in ethyl acetate (20 mL) and washed with saturated aqueous $NaHCO_3$ (20 mL) and brine (10 mL). The organic layer was dried over anhydrous $Na_2SO_4$ and concentrated to get crude product which was purified by column chromatography using methanol/dichloromethane (5:95) as the eluent.

**Yield** **:** 300 mg (85%, yellow solid). [34b]

**Melting point** **:** 62–64 $^oC$.

**TLC data** **:** $R_f$ (5% methanol/dichloromethane): 0.2

**$[\alpha]_D^{25}$** **:** -8.22 (*c* 1.30, MeOH).

**IR (Nujol) v/cm$^{-1}$** **:** 3379, 3115, 2938, 1660 (NC=O str.), 1603 (Ar C=C str.).

**$^1$H NMR ($CDCl_3$) ppm** **:** δ 1.07–2.20 (m, 8H, $(CH_2)_4$), 2.05 (br s, 2H, $NH_2$), 3.05–3.18 (m, 1H, CH), 3.58–3.84 (m, 1H, CH), 6.75–7.01 (m, 3H, Ar H and ArOH), 7.31–7.54 (m, 3H, Ar H and CONH).

### 1.3. General procedure for diacylation of 1,2-diamines

The procedure described above for the monoacylation of 1,2-diamines was followed using 2 equiv. of the acylating agent. After addition of acyl imidazole, the reaction mixture was brought to room temperature and was monitored by TLC. The ususal workup and purification by column chromatography gave the desired product.

*1.3.1. N, N'-((1R,2R)-Cyclohexane-1,2-diyl)bis(2,2-dimethylpropanamide (**12e**)*

**Yield** **:** 670 mg( 80%, white solid)[35a]

**Melting point** **:** 240–241 $^oC$ (Lit.[35a] 239–240 $^oC$).

**TLC data** **:** $R_f$ (3 % methanol/dichloromethane): 0.3

**$[\alpha]_D^{25}$** **:** +46.33 (*c* 1.32, $CHCl_3$) (Lit.[35a] + 44.0 (*c* 1.2, $CHCl_3$))

**IR (Nujol) v/cm$^{-1}$** **:** 3328, 2918, 2857, 1631 (NC=O str.).

**$^1$H NMR ($CDCl_3$) ppm** **:** δ 1.15 (s, 18H, $2C(CH_3)_3$), 1.18–1.40 (m, 4H, $(CH_2)_2$), 1.68–1.83 (m, 2H, $CH_2$), 1.98–2.14 (m, 2H, $CH_2$), 3.52–3.72 (m, 2H, 2CH), 6.14 (br s, 2H, 2CONH).

*1.3.2. N,N'-((1S,2S)-1,2-Diphenylethane-1,2-diyl)bis(2,2-dimethylpropanamide) (**13f**)*

**Yield** **:** 960 mg (84%, white solid)[35b]

**Melting point** **:** 210–212 $^oC$.

**TLC data** **:** $R_f$ (10% ethyl acetate/petroleum ether): 0.2

**$[\alpha]_D^{25}$** **:** +44.85 (*c* 1.41, $CHCl_3$)

**IR (Nujol) v/cm$^{-1}$** **:** 3394, 2928, 1641 (NC=O str.), 1601 (Ar C=C str.), 701.

**$^1$H NMR ($CDCl_3$) ppm** **:** δ 1.17 (s, 18H, $2C(CH_3)_3$), 5.14 (ABq, 2H, 2CH), 6.98 (br s, 2H, 2CONH), 7.02–7.45 (m, 10H, Ar H).

*1.3.3. N,N'-((1S,2S)-1,2-Diphenylethane-1,2-diyl)bis(2,2,2-trifluoroacetamide) (**13h**)*

**Yield** **:** 960 mg (79%, white solid)

**Melting point** : 274–275 $^{o}$C.

**TLC data** : $R_f$ (10% ethyl acetate/hexane): 0.2

**$[\alpha]_D^{25}$** : +34.6 (*c* 1.01, MeOH)

**IR (Nujol) v/cm$^{-1}$** : 3305, 2924, 1693 (NC=O str.), 1598 (Ar C=C str.), 1178.

**$^1$H NMR (DMSO-d6/ $CDCl_3$) ppm** : δ 5.25–5.38 (m, 2H, 2CH), 6.90–7.07 (m, 10H, Ar H), 9.31 (d, *J* = 7.32 Hz, 2H, CONH).

**$^{13}$C NMR (DMSO-d6/ $CDCl_3$) ppm** : δ 56.1 (CH), 125.8, 126.1, 126.7, 127.3, 136.7 (Ar C), 155.2 (CO), 156.0 (CO) rotamers.

**Analysis for** : $C_{18}H_{14}F_6N_2O_2$

**Calculated (%)** : C, 53.47; H, 3.49; N, 6.93

**Found** : C, 53.05; H, 3.42; N, 6.49.

### 1.4. Preparation of *N,N'*-((1*R*,2*R*)-cyclohexane-1,2-diyl)bis(4-methylbenzene-sulfonamide) (12f)

In a 100 ml two necked round-bottom flask equipped with a gas outlet bubbler, (1*R*,2*R*)-(+)-1,2-Diaminocyclohexane L-tartrate (1.32 g, 5 mmol) and $K_2CO_3$ (2.073 g, 15 mmol) were suspended in methanol (30 mL). The mixture was cooled to 0 $^{o}$C and tosyl chloride (2.1 g, 11 mmol) was added to it portion-wise. It was warmed to room temperature and monitored for the evolution of $CO_2$. After completion of the reaction (1.5 h) as indicated by ceasing of $CO_2$ evolution, solvent was evaporated and the residue was dried under vacuum. It was suspended in DCM (30 mL) and washed with brine (2 x 10 mL). The solution was dried over anhydrous $Na_2SO_4$ and concentrated to get a crude product which was crystallized from toluene to yield **12f**.

**Yield** : 1.56 g (74%, white solid)

**Melting point** : 168–169.4 $^{o}$C (Lit.[36] 168–170 $^{o}$C)

**TLC data** : $R_f$ (10% methanol/dichloromethane): 0.5

**$[\alpha]_D^{25}$** : +2.9 (*c* 2.1, pyridine) (Lit.[36] +2.6 (*c* 2.33, pyridine))

**IR (Nujol) v/cm$^{-1}$** : 3288, 2953, 2857, 1596, 1156 (S=O), 1091.

**$^1$H NMR ($CDCl_3$) ppm** : δ 0.95–1.27 (m, 4H, $(CH_2)_2$), 1.46–1.62 (m, 2H, $CH_2$), 1.75–1.95 (m, 2H, $CH_2$), 2.44 (s, 6H, $2CH_3$), 2.62–2.82 (m, 2H, 2CH), 4.81 (br s, 2H, $2SO_2NH$), 7.32 (d, *J* = 8.09 Hz, 4H, Ar H), 7.76 (d, *J* = 8.21 Hz, 4H, Ar H).

### 1.5. Preparation of *N*-((1*R*,2*R*)-2-(4-methylphenylsulfonamido)cyclohexyl)acetamide (12g)

A solution of *N*-((1*R*,2*R*)-2-aminocyclohexyl)-4-methylbenzenesulfonamide (**12d**) 537 mg (2 mmol) and pyridine (0.8 mL, 10 mmol) in anhydrous DCM (4 mL) was cooled to 0 $^{o}$C. Acetyl chloride (0.16 mL, 2.2 mmol) was added to it dropwise and stirring continued at the same temperature. After completion of the reaction (2 h) as indicated by TLC, 2 M HCl (20 mL) was added. Organic layer was separated and aqueous layer was extracted with DCM (2 x 10 mL). Combined organic layer was washed with saturated aqueous $NaHCO_3$ (10 mL), brine (10 mL) and dried over anhydrous $Na_2SO_4$. It was concentrated and the crude product was crystallized from toluene.

| | |
|---|---|
| **Yield** | **:** 570 mg (90%, white crystals). |
| **Melting point** | **:** 190–190.6 $^{o}$C. |
| **TLC data** | **:** $R_f$ (50% ethyl acetate/petroleum ether):0.5 |
| $[\alpha]_D^{25}$ | **:** +37.04 (c = 1.07, $CHCl_3$) |
| **IR (Nujol) v/cm$^{-1}$** | **:** 3394 (NH str.), 3115, 2948, 1657 (NC=O str.), 1596 (Ar C=C str.), 1161, 1078, 661. |
| **$^{1}$H NMR ($CDCl_3$) ppm** | **:** δ 1.0–1.35 (m, 4H, $(CH_2)_2$), 1.6–2.06 (m, 7H, $CH_3$ and 2($CH_2$)), 2.42 (s, 3H, $ArCH_3$), 2.81–3.01 (m, 1H, CH), 3.51–3.71 (m, 1H, CH), 5.61 (br s, 1H, $SO_2NH$), 5.65 (br s, 1H, CONH), 7.29 (d, *J* = 8.85 Hz, 2H Ar H), 7.74 (d, *J* = 8.21 Hz, 2H, Ar H). |
| **$^{13}$C NMR ($CDCl_3$) ppm** | **:** δ 21.4 ($CH_3$), 23.1 ($ArCH_3$), 24.4 ($CH_2$), 24.6 ($CH_2$), 32.3 ($CH_2$), 33.8 ($CH_2$), 52.7 (CH), 58.4 (CH), 126.7, 129.5, 138.4, 142.9 (Ar C), 171.4 (CO). |
| **Analysis for** | **:** $C_{15}H_{22}N_2O_3S$ |
| **Calculated (%)** | **:** C, 58.04; H, 7.14; N, 9.02: S, 10.33. |
| **Found (%)** | **:** C, 57.73; H, 7.08; N, 9.20; S, 10.59. |

### 1.6. Preparation of *N*-((*R*)-2'-amino-[1,1'-binaphthalen]-2-yl)pivalamide (14)

The procedure described above for the preparation of **12g** was followed using (*R*)-BINAM (1.42 g, 5 mmol), pivaloyl chloride (0.61 mL, 5 mmol) and pyridine (4 mL, 40 mmol). After stirring for (8 h) followed by usual workup gave the crude

product which was purified by flash column chromatography using ethyl acetate/petroleum ether (8:92) as the eluent.

**Yield** **:** 530 mg (29%, white solid)

**Melting point** **:** 79.2–83.5 $^{o}$C.

**TLC data** **:** $R_f$ (20% ethyl acetate/hexane): 0.4

**$[\alpha]_D^{25}$** **:** +82.47 (*c* 1.19, $CHCl_3$)

**IR (Nujol) v/cm$^{-1}$** **:** 3465, 3399, 3359, 2948, 1674 (NC=O str.), 1618, 1593 (Ar C=C str.), 1285.

**$^1$H NMR ($CDCl_3$) ppm** **:** δ 0.81 (s, 9H, $C(CH_3)_3$), 3.72 (br s, 2H, $NH_2$), 6.89–7.00 (m, 1H, Ar H), 7.09–7.48 (m, 7H, Ar H), 7.76–8.05 (m, 4H, Ar H), 8.67 (d, *J* = 9.09 Hz, 1H, CONH).

**$^{13}$C NMR ($CDCl_3$) ppm** **:** δ 26.9 ($CH_3$), 39.5 (C), 110.2, 117.9, 120.6, 122.7, 123.4, 124.9, 125.2, 126.8, 127.3, 128.0, 129.1, 130.3, 131.1, 133.4, 135.1, 142.7 (Ar C), 176.8 (CO).

**Analysis for** **:** $C_{25}H_{24}N_2O$

**Calculated (%)** **:** C, 81.49; H, 6.57; N, 7.60

**Found** **:** C, 81.12; H, 6.58; N, 7.14.

### 1.7. 2-Hydroxy-N-((1*R*,2*R*)-2-pivalamidocyclohexyl)benzamide (16b)

The procedure described above for the preparation of **12g** was followed for *N*-((1*R*,2*R*)-2-aminocyclohexyl)-2-(benzyloxy)benzamide (650 mg, 2 mmol) using pivaloyl chloride (0.27 mL, 2.2 mmol) and pyridine (0.8 mL, 10 mmol). After stirring at rt for 3 h follwed by ususal workup the crude product was dissolved in methanol (5 mL) and *O*-benzyl deprotection was carried out using the procedure reported for the hydrogenolysis of *N*-Cbz-**5**. It on usual workup followed by purification on column chromatography using ethyl acetate/petroleum ether (1:4) as the eluent provided the required product.

**Yield** **:** 460 mg (73%, white solid)

**Melting point** **:** 238–239 $^{o}$C.

**TLC data** **:** $R_f$ (30% ethyl acetate/hexane): 0.3

**$[\alpha]_D^{25}$** **:** +42.0 (*c* 1.23, $CHCl_3$)

**IR (Nujol) v/cm$^{-1}$** **:** 3374, 3293, 2948, 2927, 1649 and 1633 (NC=O str.), 1592 (Ar C=C str.), 1365, 750.

**$^1$H NMR ($CDCl_3$) ppm** : δ 1.10 (s, 9H, $C(CH_3)_3$), 1.20–1.51 (m, 4H, $(CH_2)_2$), 1.73–1.90 (m, 2H, $CH_2$), 1.94–2.10 (m, 1H) and 2.19–2.35 (m, 1H, $CH_2$), 3.63–3.97 ( m, 2H, 2(CH)), 5.85 (d, *J* = 7.45 Hz, 1H, CONH), 6.78–6.98 (m, 2H, Ar H), 7.30–7.49 (m, 2H, Ar H), 7.57 (d, *J* = 6.69 Hz, 1H, ArCONH), 12.54 (s, 1H, ArOH).

**$^{13}$C NMR ($CDCl_3$) ppm** : δ 24.4 ($CH_2$), 24.8 ($CH_2$), 27.3 ($CH_3$), 31.9 ($CH_2$), 32.1 ($CH_2$), 38.6 (C), 52.3 (CH), 55.9 (CH), 114.0, 118.2, 118.7, 126.2, 134.0, 161.5 (Ar C), 170.3 (CO), 184.2 (CO).

**Analysis for** : $C_{18}H_{26}N_2O_3$

**Calculated (%)** : C, 67.90; H, 8.23; N, 8.80

**Found** : C, 67.66; H, 8.33; N, 8.34.

### 1.8. Preparation of *N*-((1*R*,2*R*)-2-(dimethylamino)cyclohexyl)pivalamide (15)

A 10 mL round-bottom flask was charged with (**12a**) (198 mg, 1 mmol) and cooled to 0 $^oC$. A 90 % solution of formic acid (0.21 mL, 5 mmol) followed by 30 % solution of formaldehyde (0.185 mL, 2.2 mmol) was added to it. The mixture was gradually brought to 70 $^oC$ and heating continued. After completion of the reaction (3 h) as indicated by TLC, it was cooled to room temperature. The reaction mixture was neutralized by cautious addition of $NaHCO_3$ solution and saturated with brine. It was extracted with DCM (3 x 15 mL), dried over anhydrous $Na_2SO_4$ and concentrated to get crude product. Further purification was achieved through column chromatography using methanol/dichloromethane (3:97) as the eluent to get **15**.

**Yield** : 220 mg (97%, white solid).

**Melting point** : 60.5–62.3 $^oC$.

**TLC data** : $R_f$ (5% methanol/dichloromethane): 0.3

**$[\alpha]_D^{25}$** : -74.14 (*c* 1.16, $CHCl_3$).

**IR (Nujol) v/cm$^{-1}$** : 3374, 2933, 2857, 2826, 2781, 1638 (NC=O str.), 1532.

**$^1$H NMR ($CDCl_3$) ppm** : δ 0.92–1.37 (m, 13H, $C(CH_3)_3$ and $(CH_2)_2$), 1.60–2.10 (m, 4H, 2($CH_2$)), 2.22 (s, 6H, $(N(CH_3)_2$), 2.27–2.57 (m, 1H, CH), 3.30–3.47 (m, 1H, CH), 6.52 (br s, 1H, CONH).

**$^{13}$C NMR ($CDCl_3$) ppm** : δ 21.2 ($CH_2$), 24.5 ($CH_2$), 25.3 ($CH_2$), 27.5 ($CH_3$), 32.5 ($CH_2$), 38.7 (C), 39.6 ($NCH_3$), 51.3 (CH), 66.31 (CH), 179.1 (CO).

**Analysis for** : $C_{13}H_{26}N_2O$.

**Calculated (%)** : C, 68.98; H, 11.58; N, 12.38

**Found** : C, 68.82; H, 11.49; N, 11.98.

### 1.9. Preparation of (*S*)-*N*-(phenylcarbamoyl)pyrrolidine-2-carboxamide (18)

*1.9.1. (S)-Benzyl 2-((phenylcarbamoyl)carbamoyl)pyrrolidine-1-carboxylate (**17**).*

In an oven dried 10 mL side-arm flask equipped with reflux condenser, *N*-Cbz-L-prolinamide (496 mg, 2 mmol) was suspended in anhydrous toluene (4 mL). Phenyl isocyanate (0.22 mL, 2 mmol) was added under argon atmosphere and the solution was refluxed. After completion of the reaction (40 h) as indicated by TLC, solvent was evaporated to get white residue, which was purified by column chromatography using ethyl acetate/petroleum ether (1:4) as the eluent to give **17**.

**Yield** : 600 mg (81%, white solid).

**Melting point** : 173–174 $^{o}$C.

**TLC data** : $R_f$ (20% ethyl acetate/hexane): 0.2

**$[\alpha]_D^{25}$** : -105.26 (*c* 1.11, $CHCl_3$).

**IR (KBr) v/cm$^{-1}$** : 3242, 3188, 2953, 1728, 1702; 1667 (NC=O str.), 1603 (Ar C=C str.), 1553, 1218, 1183.

**$^{1}$H NMR ($CDCl_3$) ppm** : δ 1.86–2.42 (m, 4H, $(CH_2)_2$), 3.40–3.71 (m, 2H, $CH_2$), 4.30–4.58 (m, 1H, CH), 5.17 (ABq, *J* = 12.26, 10.73 Hz, 2H, $CH_2Ph$), 7.05–7.55 (m, 10H, Ar H), 8.71 and 9.21 (br s, 1H, CONH, rotamers), 10.36 (br s, 1H, CONH).

**$^{13}$C NMR ($CDCl_3$) ppm** : δ 23.7 and 24.4 ($CH_2$), 29.3 and 31.2 ($CH_2$), 47.0 and 47.4 ($CH_2$), 61.2 (CH), 67.5 ($CH_2$), 120.3, 128.0, 128.1, 128.4, 128.9, 136.0, 136.9 (Ar C), 151.1 (CO), 154.4 and 155.8 (CO), 174.1 and 174.8 (CO) rotamers.

**Analysis for** : $C_{20}H_{21}N_3O_4$.

**Calculated (%)** : C, 65.38; H, 5.76; N, 11.44

**Found** : C, 65.67; H, 5.48; N, 11.60.

*1.9.2. (S)-N-(Phenylcarbamoyl)pyrrolidine-2-carboxamide (**18**).*

The procedure described above for the hydrogenolysis of *N*-Cbz-**5** was followed for **17** (368 mg, 1 mmol) using 10% Pd/C (30 mg) and methanol (5 mL) as solvent. After stirring for 8 h, followed by usual workup and purification gave **18**.

**Yield** : 210 mg (91%, white solid).

**Melting point** : 78.1–78.8 $^{o}$C.

**TLC data** : $R_f$ (40% ethyl acetate/hexane): 0.2

**$[\alpha]_D^{25}$** : -72.46 (*c* 1.09, $CHCl_3$).

**IR (Nujol) v/cm$^{-1}$** : 3344, 3234, 2954, 2926, 2859, 1702, 1690 (NC=O str.), 1600 (Ar C=C str.), 1222.

**$^1$H NMR ($CDCl_3$) ppm** : δ 1.65–2.35 (m, 5H, $(CH_2)_2$ and NH), 2.91–3.15 (m, 2H, $CH_2$), 3.87 (dd, *J* = 9.35, 5.95 Hz, 1H, CH), 7.10 (tt, *J* = 7.32, 1.33 Hz, 1H, Ar H), 7.25–7.37 (m, 2H, Ar H), 7.47–7.57 (m, 2H, Ar H), 9.86 (br s, 1H, CONH), 10.44 (br s, 1H, CONH).

**$^{13}$C NMR ($CDCl_3$) ppm** : δ 26.0 ($CH_2$), 30.7 ($CH_2$), 47.1 ($CH_2$), 60.5 (CH), 120.1, 124.0, 128.8, 137.2 (Ar C), 150.2 (CO), 177.4 (CO).

**Analysis for** : $C_{12}H_{15}N_3O_2$.

**Calculated (%)** : C, 61.79; H, 6.48; N, 18.01

**Found** : C, 61.73; H, 6.49; N, 18.04.

## 1.10. Preparation of (2*S*,4*R*)-4-(dodecyloxy)-1-formylpyrrolidine-2-carboxylic acid (22)

The procedure described above for the hydrogenolysis of *N*-Cbz-**5** was followed for (2*S*,4*R*)-1-benzyl 2-dodecyl 4-(dodecyloxy)pyrrolidine-1,2-dicarboxylate[15c] (1.2 g, 2 mmol) using 10% Pd/C (60 mg) and methanol (5 mL). After 6 h of stirring and usual work up, the required product was obtained as sticky mass. The crude product was dissolved in acetonitrile (6 mL) and ammonium formate (190 mg, 3 mmol) was added to it.[37] The reaction mixture was refluxed and monitored by TLC. After completion of the reaction (10 h) solvent was removed under vacuum. The residue was redissolved in water and extracted with ethyl acetate (3 × 15 mL). Organic layer was washed with brine (10 mL), dried over anhydrous $Na_2SO_4$ and concentrated to get

viscous oil. It was then dissolved in 1,4-dioxane (3 mL) and solution of KOH (100 mg, 1.8 mmol) in water (1 mL) was added to it. Reaction mass was stirred at room temperature. After completion of the reaction (30 min) as indicated by TLC, dioxane was removed on rotavapor and residue was dissolved in water. It was washed with ethyl acetate (10 mL); acidified to pH ≈ 2 and extracted with ethyl acetate (3 × 10 mL). Organic layer was washed with brine (10 mL) and dried over $Na_2SO_4$. It was concentrated to get sticky mass which was purified by column chromatography using ethyl acetate as the eluent.

**Yield** **:** 410 mg (63%, sticky mass).

**TLC data** **:** $R_f$ (ethyl acetate): 0.2

**$[\alpha]_D^{25}$** **:** -75.0 (*c* 0.78, $CHCl_3$).

**IR ($CHCl_3$) v/cm$^{-1}$** **:** 3319, 2926, 2855, 1738 (OC=O str.), 1674 (NC=O str.), 1385, 1101.

**$^1$H NMR ($CDCl_3$) ppm** **:** δ 0.88 (t, *J* = 6.82 Hz, 3H, $CH_3$), 1.18–1.38 (m, 18H, $(CH_2)_9$), 1.44–1.63 (m, 2H, $CH_2$), 2.22–2.33 (m, 2H, $CH_2$), 3.31–3.55 (m, 2H, $NCH_2$), 3.57–3.84 (m, 2H, $OCH_2$)), 4.03–4.22 (m, 1H, OCH), 4.48–4.66 (m, 1H, CH), 5.93 (br s, 1H, OH), 8.27 (s, 1H, NCHO).

**$^{13}$C NMR ($CDCl_3$) ppm** **:** δ 14.1 ($CH_3$), 22.6 ($CH_2$), 26.1 ($CH_2$), 29.3 ($CH_2$), 29.5 ($CH_2$), 29.6 ($CH_2$), 31.9 ($CH_2$), 49.4 ($CH_2$), 52.1 ($CH_2$), 69.3 ($OCH_2$), 76.0 (NCH), 76.5 (OCH), 167.5 (NCO), 176.3 (COO).

**HRMS for** **:** $C_{18}H_{33}NO_4$.

**Calculated [M]$^+$** **:** 327.2410

**Found** **:** 327.2413 (93%).

### 1.11. Preparation of (*R*)-2-(dodecyloxy)-2-phenylacetic acid (24)

*1.11.1. (5R)-2-Dodecyl-5-phenyl-1,3-dioxolan-4-one*

To a solution of freshly prepared crude *n*-dodecanal (920 mg, 5 mmol) (obtained from the oxidation of *n*-dodecanol) in $CHCl_3$ (25 mL), PTSA (100 mg, 0.5 mmol) and (*R*)-mandelic acid (840 mg, 5.5 mmol) were added. The suspension was heated to reflux using a soxhlet extractor containing activated 4Å molecular seives. A clear solution was formed after 30 min. After completion of the reaction (6 h) as

indicated by TLC, it was cooled to room temperature and solvent was evaporated. The residue was redissolved in diethyl ether (10 mL), cooled to 0 $^{o}$C and treated with Jones reagent (4 mL). After consumption of unreacted aldehyde (1 h), organic layer was separated and aqueous layer was extracted with diethyl ether (2 × 10 mL). Combined organic layer was washed with saturated aqueous $NaHCO_3$ (10 mL), brine (10 mL) and dried over anhydrous $Na_2SO_4$. It was concentrated to get crude product which was purified by column chromatography using ethyl acetate/petroleum ether (2:98) as the eluent.

| | |
|---|---|
| **Yield** | **:** 970 mg (61%, sticky mass); mixture of 2,5-*syn*/*anti* (97:03). |
| **TLC data** | **:** $R_f$ (3% ethyl acetate/hexane): 0.3. |
| **$[\alpha]_D^{25}$** | **:** -23.08 (*c* 1.03, $CHCl_3$). |
| **IR (Neat) v/cm$^{-1}$** | **:** 2926, 2855, 1798 (OC=O str.), 1606 (Ar C=C str.), 1208, 1194, 758. |
| **$^{1}$H NMR ($CDCl_3$) ppm** | **:** δ 0.88 (t, *J* = 6.4 Hz, 3H, $CH_3$), 1.18–1.43 (m, 16H, $(CH_2)_8$), 1.45–1.70 (m, 2H, $CH_2$), 1.86–2.02 (dt, *J* = 9.68, 4.53 Hz, 2H, $CH_2$), 5.24 (d, *J* = 1.01 Hz) and 5.30 (s, 1H, CH), 5.70 (dt, *J* = 4.80, 1.14 Hz) and 6.09 (t, *J* = 5.06 Hz, 1H, CH), 7.33–7.50 ( m, 5H, Ar H). |
| **$^{13}$C NMR ($CDCl_3$) ppm** | **:** δ 14.1 ($CH_3$), 22.7 ($CH_2$), 22.8 ($CH_2$), 29.2 ($CH_2$), 29.3 ($CH_2$), 29.4 ($CH_2$), 29.5 ($CH_2$), 29.6 ($CH_2$), 31.9 ($CH_2$), 34.1 ($CH_2$), 76.7 (PhCH), 104.6 ($O_2CH$), 126.8, 128.7, 129.1, 133.6 (Ar C), 171.7 (CO). |
| **LCMS for** | **:** $C_{20}H_{30}O_3$ |
| **Calculated $[M]^+$** | **:** 318.22 |
| **Found** | **:** 318.28 (18%). |

*1.11.2. (R)-2-(Dodecyloxy)-2-phenylacetic acid (**24**)*

In an oven dried 25 mL round-bottom flask, (5*R*)-2-dodecyl-5-phenyl-1,3-dioxolan-4-one (954 mg, 3 mmol) was dissolved in anhydrous diethyl ether (6 mL). The solution was cooled to 0 $^{o}$C and treated with dropwise addition of 1.1 M solution of *t*-BuMgCl in diethyl ether (9 mL, 9.9 mmol) over a period of 10 min. After completion of the reaction as indicated by TLC (3 h), it was quenched with aqueous

$NH_4Cl$ solution. Product was extracted with ethyl acetate (20 mL) and organic layer was washed with brine. It was dried over anhydrous $Na_2SO_4$ and concentrated to get crude product which was purified by column chromatography using ethyl acetate/ petroleum ether (1:5) as the eluent.

**Yield** **:** 720 mg (75%, low melting solid)

**TLC data** **:** $R_f$ (20% ethyl acetate/hexane): 0.2.

**$[\alpha]_D^{25}$** **:** -59.0 (*c* 1.0, $CHCl_3$).

**IR (Neat) v/cm$^{-1}$** **:** 3360, 2922, 2853, 1738 (OC=O str.), 1595 (Ar C=C str.), 1057, 727.

**$^1$H NMR ($CDCl_3$) ppm** **:** δ 0.88 (t, *J* = 6.7 Hz, 3H, $CH_3$), 1.15–1.41 (m, 18H, $(CH_2)_9$), 1.65 (q, *J* = 6.95 Hz, 2H, $CH_2$), 3.40–3.60 (m, 2H, $CH_2$), 4.87 (s, 1H, CH), 6.08 (br s, 1H, COOH), 7.28–7.52 ( m, 5H, Ar H).

**$^{13}$C NMR ($CDCl_3$) ppm** **:** δ 14.1 ($CH_3$), 22.6 ($CH_2$), 25.9 ($CH_2$), 29.3 ($CH_2$), 29.4 ($CH_2$), 29.5 ($CH_2$), 29.6 ($CH_2$), 29.7 ($CH_2$), 31.9 ($CH_2$), 70.0 ($CH_2$), 80.5 (CH), 127.1, 128.6, 128.8, 135.9 (Ar C), 175.8 (CO).

**LCMS for** **:** $C_{20}H_{32}O_3$

**Calculated [M]$^+$** **:** 320.24

**Found** **:** 320.30 (38%).

*1.11.3. (R)-N-Benzyl-2-(dodecyloxy)-2-phenylacetamide*

The solution of **24** (320 mg, 1 mmol), *N*, *N*-dicyclohexyl carbodimide (206 mg, 1.1 mmol) and 1-Hydroxybenzotriazole (135 mg, 1 mmol) in the anhydrous acetonitrile/DCM (3:5, 5 mL) was cooled to 0 $^oC$. Benzylamine (0.11 mL, 1 mmol) was added to it and the reaction was gradually brought to room temperature. After completion of the reaction as indicated by TLC (3 h), it was diluted with petroleum ether (15 mL) and filtered through Whatman filter paper. Filtrate and washings were combined, concentrated and the residue was purified by column chromatography using ethyl acetate/petroleum ether (1:5) as the eluent.

**Yield** **:** 350 mg (86%, white solid)

**Melting Point** **:** 38–41 $^oC$.

**TLC data** **:** $R_f$ (20% ethyl acetate/hexane): 0.4.

| | |
|---|---|
| **$[\alpha]_D^{25}$** | **:** -69.03 (*c* 1.13, $CHCl_3$). |
| **IR (Neat) v/cm$^{-1}$** | **:** 3421, 3062, 1681 (NC=O str.), 1595 (Ar C=C str.). |
| **$^1$H NMR ($CDCl_3$) ppm** | **:** δ 0.85 (t, *J* = 6.69 Hz, 3H, $CH_3$), 1.15–1.38 (m, 18H $(CH_2)_9$), 1.50–1.64 (m, 2H, $CH_2$), 3.45 (dt, *J* = 6.65, 2.02 Hz, 2H, $CH_2$), 4.47 (q, *J* = 2.95 Hz, 2H, $CH_2$), 4.77 (s, 1H, CH), 7.02–7.15 (m, 1H, CONH), 7.20–7.47 (m, 10H, Ar H). |
| **$^{13}$C NMR ($CDCl_3$) ppm** | **:** δ 14.1 ($CH_3$), 22.7 ($CH_2$), 24.2 ($CH_2$), 26.1 ($CH_2$), 27.4 ($CH_2$), 29.1 ($CH_2$), 29.3 ($CH_2$), 29.5 ($CH_2$), 29.6 ($CH_2$), 30.5 ($CH_2$), 31.9 ($CH_2$), 42.9 ($CH_2$), 53.9 ($CH_2$), 56.1 ($CH_2$), 69.9 ($CH_2$), 67.8 and 82.1 (CH), 126.8, 127.4, 127.6, 128.2, 128.5, 128.7, 137.6, 138.2 (Ar C), 170.9 and 178.6 (NCO) rotamers. |
| **LCMS for** | **:** $C_{27}H_{39}NO_2$. |
| **Calculated $[M+Na]^+$** | **:** 432.29 |
| **Found** | **:** 432.19 (20%). |
| **HPLC** | **:** Column: Chiralcel OD; Mobile phase: *i*-PrOH: petroleum ether (0.3:99.7); Flow rate: 1.0 mL/min.; UV: 200 nm; Retention time: $t_R$ (*R*-isomer): 105.02 min, $t_R$ (*S*-isomer): 122.48 min. |

## 1.12. Preparation of ((1*R*,4*S*)-2-dodecylidene-7,7-dimethylbicyclo[2.2.1]heptan-1-yl)methanesulfonic acid (27b)

### *1.12.1. 1-((1R,2S,4S)-2-Dodecyl-2-hydroxy-7,7-dimethylbicyclo[2.2.1]heptan-1-yl)-N,N- dimethylmethanesulfonamide (**26c**)*

The solution of 1-((1*R*,4*S*)-7,7-dimethyl-2-oxobicyclo[2.2.1] heptan-1-yl)-*N*,*N*-dimethylmethanesulfonamide[17b] (1.3 g, 5 mmol) in anhydrous THF (10 mL) was cooled to -78 $^oC$. The solution of 0.7 M *n*-dodecyl lithium in diethyl ether (8 mL, 5.6 mmol prepared from *n*-dodecyl chloride and lithium metal[38]) was added to it dropwise over the period of 20 min. The mixture was stirred at the same temperature for 10 min (solid formation) and was gradually brought to room temperature. After 24 h (no further progress) it was cooled to 0 $^oC$ and quenched with saturated aqueous $NH_4Cl$ (10 mL). Solvent was evaporated and the residue was extracted with ethyl acetate (3 ×

10 mL). The organic layer was washed with brine (10 mL), dried over anhydrous $Na_2SO_4$ and concentrated to get crude product which was purified by column chromatography using ethyl acetate/petroleum ether (7:93) as the eluent, along with the 40% recovery of starting material.

**Yield** **:** 650 mg (30%, sticky mass)

**TLC data** **:** $R_f$ (10% ethyl acetate/hexane): 0.3.

**$[\alpha]_D^{25}$** **:** -19.7 (*c* 1.0, $CHCl_3$).

**IR (Neat) v/cm$^{-1}$** **:** 3448, 2934, 2853, 1462, 1454 (S=O str.), 1151.

**$^1$H NMR ($CDCl_3$) ppm** **:** δ 0.80–0.94 (m, 6H, $2CH_3$), 1.15 (s, 3H, $CH_3$), 1.20–1.33 (m, 18H, $(CH_2)_9$), 1.34–1.66 (m, 7H, $3(CH_2)_2$ and CH), 1.89–2.12 (m, 2H, $CH_2$), 2.16–2.40 (m, 2H, $CH_2$), 2.46 (br s, 1H, OH), 2.62 and 3.26 (d, *J* = 13.69 Hz, 2H, $CH_2S$), 2.90 (s, 6H, $N(CH_3)_2$).

### *1.12.2. 1-((1R,4S)-2-Dodecylidene-7,7-dimethylbicyclo[2.2.1]heptan-1-yl)-N,N-dimethylmethanesulfonamide (**27a**)*

To a solution of **26c** (620 mg, 1.4 mmol) in 1,4-dioxane (5 mL), 1N $H_2SO_4$ (3 mL) was added and it was refluxed. After completion of the reaction (10 h) as indicted by TLC, solvent was evaporated to get red coloured gummy mass which was purified by flash column chromatography using ethyl acetate: petroleum ether (5:95) as the eluent to get **27a** and methanol/ethyl acetate (1:5) as the eluent to get **27b**.

**Yield (27a)** **:** 340 mg (59%)

**TLC data** **:** $R_f$ (10% ethyl acetate/hexane): 0.4.

**$[\alpha]_D^{25}$** **:** -34.29 (*c* 1.0, $CHCl_3$).

**IR (Neat) v/cm$^{-1}$** **:** 2924, 2853, 1462, 1454, 1338 (S=O str.), 1151.

**$^1$H NMR ($CDCl_3$) ppm** **:** δ 0.77 (s, 3H, $CH_3$), 0.88 (t, *J* = 6.69 Hz, 3H, $CH_3$), 0.96 (s, 3H, $CH_3$), 1.12–1.44 (m, 20H, $(CH_2)_{10}$), 1.61–2.00 (m, 5H, $(CH_2)_2$ and CH), 2.18–2.40 (m, 2H, $CH_2$), 2.88 and 3.10 (d, *J* = 14.15 Hz, 2H, $CH_2S$), 2.91 (s, 6H, $N(CH_3)_2$), 5.45 (t, *J* = 7.07 Hz, 1H, C=CH).

*1.12.3. ((1R,4S)-2-Dodecylidene-7,7-dimethylbicyclo[2.2.1]heptan-1-yl)methane-sulfonic acid (**27b**)*

**Yield** : 85 mg (15%) (sticky mass, observed as sodium salt)

**TLC data** : $R_f$ (20% methanol/ethyl acetate): 0.3.

**$[\alpha]_D^{25}$** : -50.0 (*c* 1.0, EtOH).

**IR ($CHCl_3$) v/cm$^{-1}$** : 3445, 3019, 2925, 2854, 1645 (C=C str.), 1467 (S=O str.).

**$^1$H NMR ($CDCl_3$) ppm** : δ 0.72 (s, 3H, $CH_3$), 0.88 (t, *J* = 6.69, 3H, $CH_3$), 0.94 (s, 3H, $CH_3$), 1.10–1.35 (m, 20H, $(CH_2)_{10}$), 1.40–1.60 (m, 1H, CH), 1.62–1.95 (m, 4H, $(CH_2)_2$), 2.15–2.45 (m, 2H, $CH_2$), 3.04 and 3.25 (d, *J* = 14.9 Hz, 2H, $CH_2S$), 5.47 (t, *J* = 6.82 Hz, 1H, C=CH).

**$^{13}$C NMR ($CDCl_3$) ppm** : δ 14.1 ($CH_3$), 19.4 ($CH_3$), 19.6 ($CH_3$), 22.7 ($CH_2$), 28.2 ($CH_2$), 28.7 ($CH_2$), 29.4 ($CH_2$), 29.6 ($CH_2$), 29.7 ($CH_2$), 29.8 ($CH_2$), 29.9 ($CH_2$), 31.9 ($CH_2$), 34.6 ($CH_2$), 44.3 (CH), 49.0 (C), 51.8 ($CH_2$), 60.4 (C), 119.0 (HC=), 147.0 (>C=).

**LCMS for** : $C_{22}H_{39}O_3SNa$

**Calculated [M+Na]$^+$** : 429.24 (sodium adduct of sodium salt)

**Found** : 429.15 (45%).

## 1.13. Preparation of 1-phenyltridecane-1-sulfonic acid (28)

*1.13.1. Isopropyl 1-phenyltridecane-1-sulfonate*

A solution of isopropyl phenylmethanesulfonate[18c] (642 mg, 3 mmol) in anhydrous THF (6 mL) was cooled to -78 $^oC$ and 1.9 M solution of *n*-BuLi in cyclohexane (3.3 mmol, 1.74 mL) was dropwise added to it. After stirring for 30 min at the same temperature, *n*-dodecyl bromide (1.1 mL, 4.5 mmol) diluted with anhy. HMPA (2 mL) was added. The reaction mass was stirred at the same temperature for 1 h and then gradually brought to 0 $^oC$. The reaction was quenched with saturated aqueous $NH_4Cl$ and THF was evaporated. The residue was extracted with ethyl acetate (3 × 10 mL). Organic layer was washed with brine (10 mL) and dried over anhydrous $Na_2SO_4$. It was concentrated to get crude product which was purified by column chromatography using ethyl acetate/petroleum ether (1:9) as the eluent.

**Yield** : 850 mg (74%, light yellow solid)

**Melting point** : 48–50 $^{o}$C.

**TLC data** : $R_f$ (10% ethyl acetate/ petroleum ether): 0.3.

**IR ($CHCl_3$) v/cm$^{-1}$** : 2920, 2852, 1640 (Ar C=C str.), 1467 and 1454 (S=O str.).

**$^{1}$H NMR ($CDCl_3$) ppm** : δ 0.88 (t, *J* = 6.69 Hz, 3H, $CH_3$), 1.10 (d, *J* = 6.19 Hz, 3H $CH_3$), 1.14–1.28 (m, 20H, $(CH_2)_{10}$), 1.31 (d, *J* = 6.19 Hz, 3H, $CH_3$), 2.00–2.45 (m, 2H, $CH_2$), 4.10 (dd, *J* = 11.24, 3.95 Hz, 1H, CH), 4.62 (sep., *J* = 6.32 Hz, 1H, CH), 7.30–7.45 (m, 5H, Ar H).

**$^{13}$C NMR ($CDCl_3$) ppm** : δ. 14.0 ($CH_3$), 22.4 ($CH_3$), 22.6 ($CH_2$), 23.3 ($CH_3$), 26.6 ($CH_2$), 28.9 ($CH_2$), 29.1 ($CH_2$), 29.2 ($CH_2$), 29.3 ($CH_2$), 29.4 ($CH_2$), 29.5 ($CH_2$), 29.7 ($CH_2$), 31.8 ($CH_2$), 67.8 (OCH), 77.5 (CH), 128.6, 128.8, 129.5, 132.8 (Ar C).

**LCMS for** : $C_{22}H_{38}O_3S$

**Calculated $[M+H]^+$** : 383.26

**Found** : 383.60 (20%).

*1.13.2. 1-Phenyltridecane-1-sulfonic acid (**28**)*

A suspension of isopropyl 1-phenyltridecane-1-sulfonate (764 mg, 2 mmol) in deionized water (5 mL) was refluxed. After completion of the reaction as indicated by TLC (2 h), water was evaporated and the residue was dried under vacuum to get white solid.

**Yield** : 720 mg (99%)

**Melting point** : 61–64 $^{o}$C

**TLC data** : $R_f$ (ethyl acetate): 0.2.

**IR ($CHCl_3$) v/cm$^{-1}$** : 3428, 2922, 2852, 1634 (Ar C=C str.), 1463, 1377 (S=O str.).

**$^{1}$H NMR ($CDCl_3$) ppm** : δ 0.87 (t, *J* = 6.65 Hz, 3H, $CH_3$), 1.02–1.38 (m, 20H, $(CH_2)_{10}$), 2.05–2.40 (m, 2H, $CH_2$), 2.84 (br s, 1H, $SO_3H$), 3.81–4.01 (m, 1H, CH), 7.14–7.42 (m, 5H, Ar H).

**$^{13}$C NMR ($CDCl_3$) ppm** : δ 14.1 ($CH_3$), 22.7 ($CH_2$), 27.3 ($CH_2$), 29.4 ($CH_2$), 29.7

($CH_2$), 29.8 ($CH_2$), 30.6 ($CH_2$), 31.9 ($CH_2$), 66.0 (CH), 127.6, 128.4, 129.4, 136.6 (Ar C).

**LCMS for** **:** $C_{19}H_{32}O_3S$

**Calculated $[M+Na]^+$** **:** 363.20

**Found** **:** 363.44 (30%).

## 2. Preparation of Lewis bases

### *2.1. Anionic Lewis bases*

Carboxylate salts (**29**–**34**, **41**–**42** and **46**−**48**) were prepared by reacting 1 mmol of carboxylic acid with exactly 1 mmol of corresponding hydroxide in methanol (2 mL) at room temperature. After completion of the reaction as indicated by TLC (approx. 30 min), solvent was evaporated and the residue was dried under vacuum. Salts of binaphthyl derivatives were prepared by similar procedure using standard solutions of *n*-BuLi (2 M in cyclohexane) or sodium ethoxide (1 M in THF) as the Brønsted base. These salts are stable and can be stored in a desiccator. The salts of ephedrine derivatives, salen and amides were generated *in situ* using dilute solutions of *n*-BuLi (0.5 M in cyclohexane) or sodium ethoxide (0.5 M in THF) at 0 $^oC$.

### *2.2. (S)-N,N-Dimethyl-1-phenylethanamine-N-oxide (**19a**)*

To an ice cold solution of (*S*)-*N*,*N*-dimethyl-1-phenylethanamine[14] (300 mg, 2 mmol) in methanol (2 mL), 30% aq. hydrogen peroxide (0.8 mL, 6 mmol) was added dropwise. The solution was brought to room temperature and monitored by TLC. After completion of the reaction (36 h), solvent was evaporated under vacuum to get a sticky mass. It was used as catalysts and ligand without further purification.

### *2.3. Metal fluoride complexes*

Catalyst **56** was prepared by refluxing the suspension of $ZnF_2.2H_2O$ (280 mg, 2 mmol) and (1*R*,2*R*)-cyclohexane-1,2-diamine (685 mg, 6 mmol) in methanol (5 mL). The almost clear solution obtained after 30 h was cooled to room temperature, filtered through sintered glass funneland concentrated to get white residue. While the catalysts **57** and **58** were prepared by stirring the suspension of $ZnF_2.2H_2O$ and $AlF_3.3H_2O$ using 1 and 2 equivalents of (*S*)-*N*,*N*-dimethyl-1-phenyl ethanamine-*N*-oxide respectively in methanol for 1 h. A partly soluble suspension was then evaporated on rotavapor to get white residue. These complexes were used as catalyst without further purification.

**3. General procedure for the preparation of trimethylsilyl enolates of ketones**

An oven dried 500 mL two necked round-bottom flask equipped with reflux condenser was charged with chlorotrimethylsilane (18.75 ml, 150 mmol) and anhydrous DMF (40 mL). Triethylamine (33.45 mL, 240 mmol) was then gradually introduced in it. To the resulting pale yellow suspension, ketone (100 mmol) was added dropwise and resultant mixture was stirred vigorously at room temperature for 15 h. It was then stirred at 60$^{o}$C with monitoring the reaction by IR. After completion of the reaction (18 h), it was cooled to room temperature and diluted with petroleum ether (300 mL). To the resulting brown slurry, ice cold water (100 mL) was added and organic layer was separated. It was washed with cold 1N HCl (100 mL), cold aqueous $NaHCO_3$ (2 x 150 mL) and finally with ice cold water (100 mL). The organic layer was dried over anhydrous $Na_2SO_4$ and concentrated to obtain crude product, which was purified by vacuum distillation after discarding the initial fraction (approx. 1 mL).

*3.1. Trimethylsilyl enolate of acetophenone*

**Yield** **:** 16 g (84%, G.C. purity > 95%).

**Boiling point:** 92 $^{o}$C (12 mm of Hg) (Lit.[21a] 89–91 $^{o}$C at 12 mm of Hg).

*3.2. Trimethylsilyl enolate of cyclohexanone*

**Yield** **:** 9.5 g (80%, G.C. purity > 95%).

**Boiling point:** 73 $^{o}$C (20 mm of Hg) (Lit.[21a] 74–75 $^{o}$C at 20 mm of Hg).

**4. General procedure for Mukaiyama-type aldol reaction**

In an oven dried 10 mL side-arm flask, 0.2 mmol of catalyst was dissolved in appropriate solvent under argon atmosphere. The solution was cooled to 0 $^{o}$C and enolate (2 mmol, 0.4 mL) followed by aldehyde (2 mmol, 0.2 mL) was added to it dropwise. The reaction mixture was stirred at 0 $^{o}$C and monitored by TLC. (When it did not show any progress at 0 $^{o}$C, it was warmed to room temperature). After completion of the reaction, it was quenched with aqueous $NH_4Cl$ (2 mL). The solvent was removed on rotavapor and the residue was extracted with ethyl acetate (3 x 5 mL). Combined organic layer was washed with brine (5 mL) and dried over anhydrous $Na_2SO_4$. It was concentrated to get crude product which was purified by flash column chromatography using ethyl acetate/petroleum ether as the eluent.

*4.1. 3-Hydroxy-4-methyl-1-phenylpentan-1-one (**A**)*[22a]

**Appearance** : White solid.

**Melting point** : 52–53 $^{o}$C

**TLC data** : $R_f$ (10% ethyl acetate/hexane): 0.2.

**IR (Nujol) v/cm$^{-1}$** : 3480, 2963, 2877, 1680 (CO str.), 1596 (Ar C=C str.), 1209.

**$^{1}$H NMR ($CDCl_3$) ppm** : δ 1.00 (dd, *J* = 6.82, 4.42 Hz, 6H, $2CH_3$), 1.65–1.9 (h, *J* = 6.57 Hz, 1H, CH), 2.95–3.26 (m, 3H, $CH_2$ and OH), 3.95–4.05 (m, 1H, CH), 7.42–7.65 (m, 3H, Ar H), 7.94–8.03 (m, 2H, Ar H).

*4.2. (E)-4-Methyl-1-phenylpent-2-en-1-one (**B**)*[22d]

**Appearance** : Colourless oil.

**TLC data** : $R_f$ (5% ethyl acetate/hexane): 0.4.

**IR (Neat) v/cm$^{-1}$** : 2961, 2868, 1677 (C=O str.),

**$^{1}$H NMR ($CDCl_3$) ppm** : δ 1.14 (d, *J* = 6.67 Hz, 6H, $2CH_3$), 2.57 (ddq, *J* = 6.69, 6.63, 1.38 Hz, 1H, CH), 6.8 (dd, *J* = 15.42, 1.36 Hz, 1H, CH), 6.97 (dd, *J* = 15.38, 6.54 Hz, 1H, CH), 7.39−7.60 (3H, Ar H), 7.83−8.02 (m, 2H, Ar H).

*4.3. 3-Hydroxy-1,3-diphenylpropan-1-one (Table 4 entry 2)*

**Appearance** : White solid.

**Melting point** : 48–50 $^{o}$C (Lit.[22b] 48–50 $^{o}$C)

**TLC data** : $R_f$ (10% ethyl acetate/hexane): 0.3.

**IR (Nujol) v/cm$^{-1}$** : 3465, 3064, 1679 (C=O str.), 1596 (Ar C=C str.), 1209.

**$^{1}$H NMR ($CDCl_3$) ppm** : δ 3.38 (d, *J* = 6.07 Hz, 2H, $CH_2$), 3.61 (d, *J* = 2.90 Hz, 1H, OH), 5.35 (dt, *J* = 6.06, 2.78 Hz, 1H, CH), 7.28–7.65 (m, 8H, Ar H), 7.90–8.00 (m, 2H, Ar H)

*4.4. Methyl 3-hydroxy-2,2-dimethyl-3-phenylpropanoate (**D**)*[22c]

**Appearance** : White solid.

**Melting point** : 58–59 $^{o}$C

**TLC data** : $R_f$ (10% ethyl acetate/hexane): 0.3.

**IR (Nujol) v/cm$^{-1}$** : 3445, 2922, 1699 (OC=O str.), 1596 (Ar C=C str.), 1059.

**$^{1}$H NMR ($CDCl_3$) ppm** : δ 1.11 (s, 3H, $CH_3$), 1.15 (s, 3H, $CH_3$), 3.07 (d, *J* = 4.04

Hz, 1H, OH), 3.73 (s, 3H, $OCH_3$), 4.9 (d, $J$ = 3.79 Hz, 1H, CH), 7.31(m, 5H, Ar H).

*4.5. 2-Methyl-3-oxo-1,3-diphenylpropyl benzoate (**E**)* [24b]

**Appearance** : Colourless oil, mixture of 1,2-*anti*-2,3-*syn* (dia.1) and 1,2-*syn*-2,3-*anti* (dia.2).

**TLC data** : $R_f$ (10% ethyl acetate/hexane): 0.4.

**IR (Neat) v/cm$^{-1}$** : 3481, 3064, 1714 (OC=O str.), 1601 (Ar C=C str.), 1272.

**$^1$H NMR ($CDCl_3$) ppm** : δ 0.66 (dd, $J$ = 12.88, 7.07 Hz, 3H, $CH_3$), 2.20–2.50 (m, 1H, CH), 2.78 (d, $J$ = 4.04 Hz, (dia.1)) and 3.15 (d, $J$ = 3.16 Hz, (dia.2), 1H, OH), 4.43 (dd, $J$ = 9.4, 2.9 Hz, (dia.2)) and 5.10 (t, $J$ = 2.96 Hz, (dia.1), 1H, CH), 6.06 (d, $J$ = 9.85 Hz, (dia.1)) and 6.76 (d, $J$ = 1.89 Hz, (dia.2), 1H, CH), 7.15–7.70 (m, 13H, Ar H), 8.05–8.14 (m, 1H, Ar H), 8.15–8.24 (m, 1H, Ar H).

*4.6. 2-(Hydroxy(phenyl)methyl)cyclohexanone (**F**)* [24c]

**Appearance** : Colourless oil as the 1:1 mixture of *syn* and *anti* (racemic).

**TLC data** : $R_f$ (10% ethyl acetate/hexane): 0.2.

**IR (Neat) v/cm$^{-1}$** : 3450, 2963, 2882, 1732 (C=O str.), 1603 (Ar C=C str.).

**$^1$H NMR ($CDCl_3$) ppm** : δ 1.4–2.52 (m, 7H, $(CH_2)_3$ and CH), 2.70 (br s, (*syn*)) and 4.55 (br s, (*anti*), 1H, OH), 4.70 (d, $J$ = 9.10 Hz, (*anti*)) and 5.28 (d, $J$ = 2.40 Hz, (*syn*), 1H, CH), 7.20−7.40 (m, 5H, ArH).

*4.7. 2-(Hydroxy(phenyl)methyl)cyclohexanol (hydrolysis product of **G**)* [24b,c]

Crude aldol-Tischenko product (**G**) was saponified using KOH in methanol at rt (15 h). After usual evaporation of the solvent, residue was dissolved in water and washed with ethyl acetate (10 mL). Aqueous layer was neutralized with 1N HCl and extracted with ethyl acetate. After evaporation of the solvent, crude product was purified by column chromatography using ethyl acetate/petroleum ether (1:3) as the eluent.

**Appearance** : Sticky mass mixture containing all four diastereomers (racemic).

**TLC data** : $R_f$ (30% ethyl acetate/hexane): 0.2.

**IR ($CHCl_3$) v/cm$^{-1}$** : 3364, 2928, 2857, 1601 (Ar C=C str.), 701.

**$^1$H NMR ($CDCl_3$) ppm** : δ 0.50–2.09 (m, 8H, $(CH_2)_4$), 2.78, 3.75 and 4.02 (br s, 1H, OH) diastereomers, 3.50 (dt, $J$ = 10.20, 4.42 Hz) and 3.66 (t, $J$ = 9.52 Hz, 1H, CH), 4.12 (d, $J$ = 7.33 Hz), 4.37 (m), 4.51 (d, $J$ = 9.22 Hz), 4.76 (d, $J$ = 4.04 Hz) and 4.94 (d, $J$ = 3.03 Hz, 1H, CH), 7.28–7.44 (m, 5H, Ar H).

**HPLC** : Column: Chiralcel OD-H, mobile phase: *i*-PrOH:*n*-hexane (10:90); flow rate: 1.0 mL/min; UV: 220 nm; $t_R$ (dia.1): 7.95 min and 9.78 min, $t_R$ (dia.2): 12.87 min and 14.0 min, $t_R$ (dia.3): 22.88 min and 37.79 min, $t_R$ (dia.4): 31.86 min and 44.83 min.

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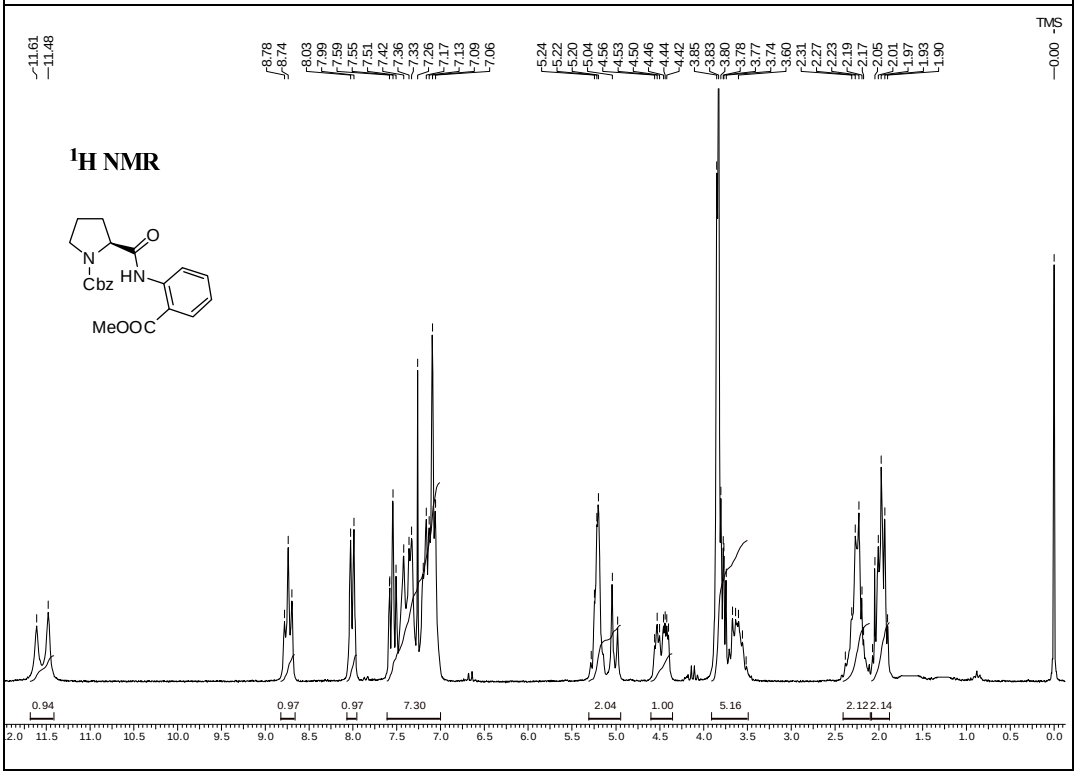
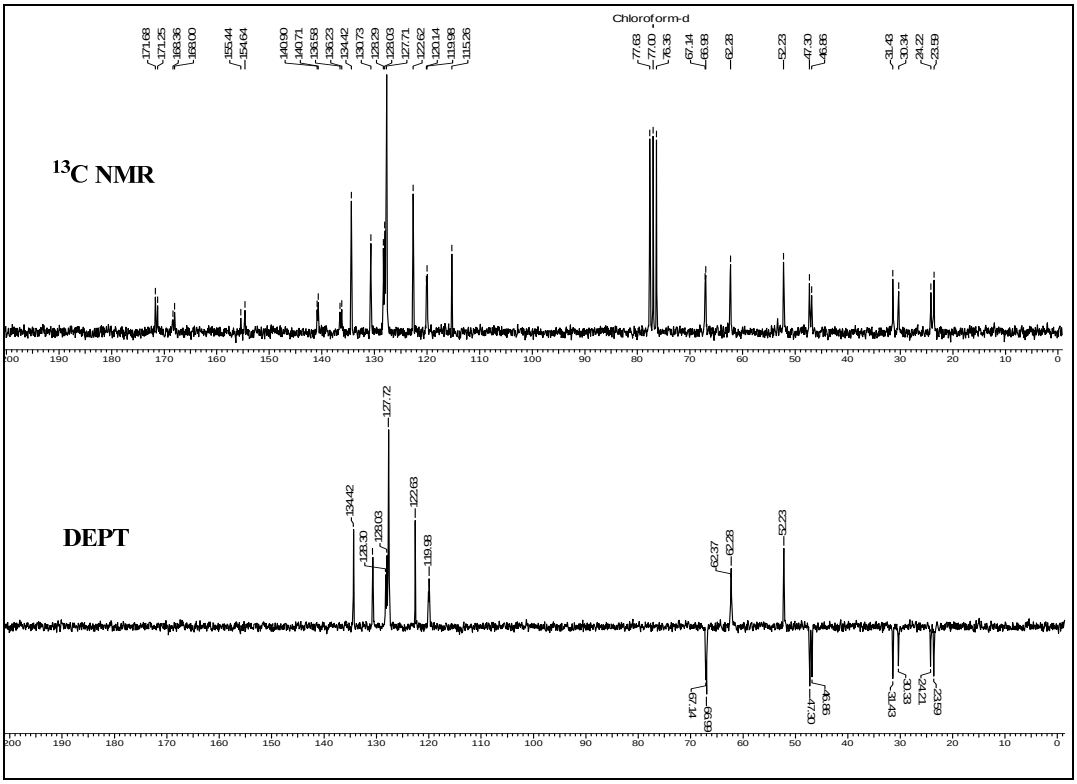
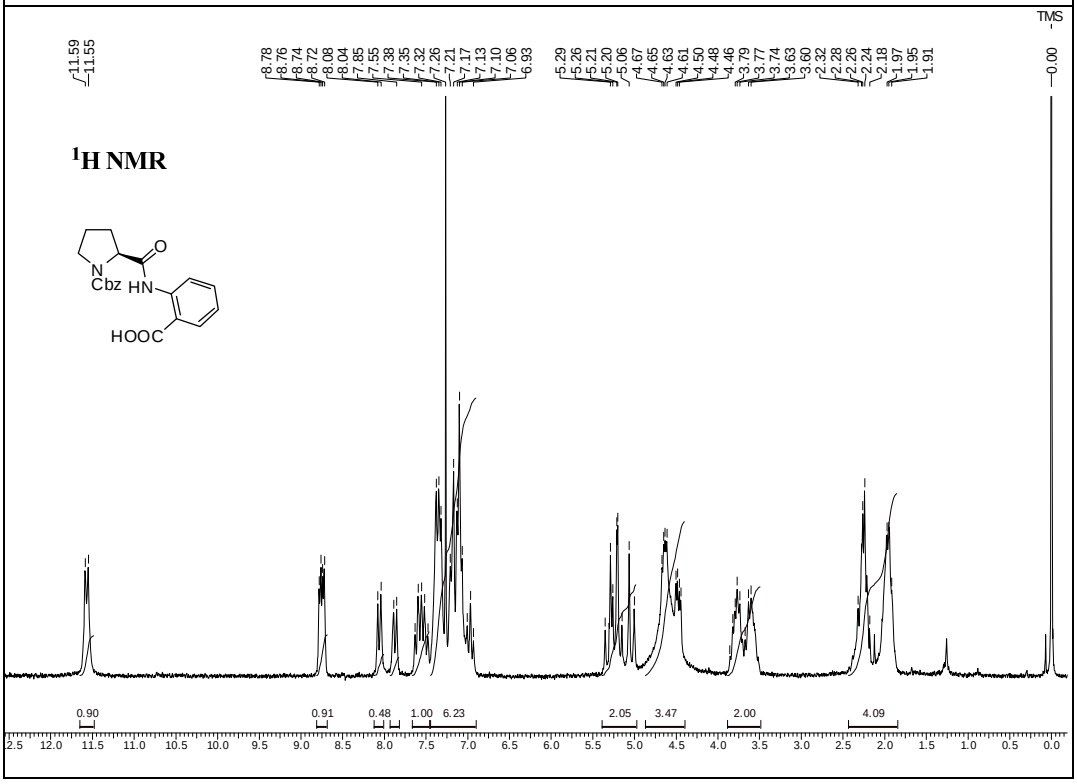
## Spectra and chromatograms

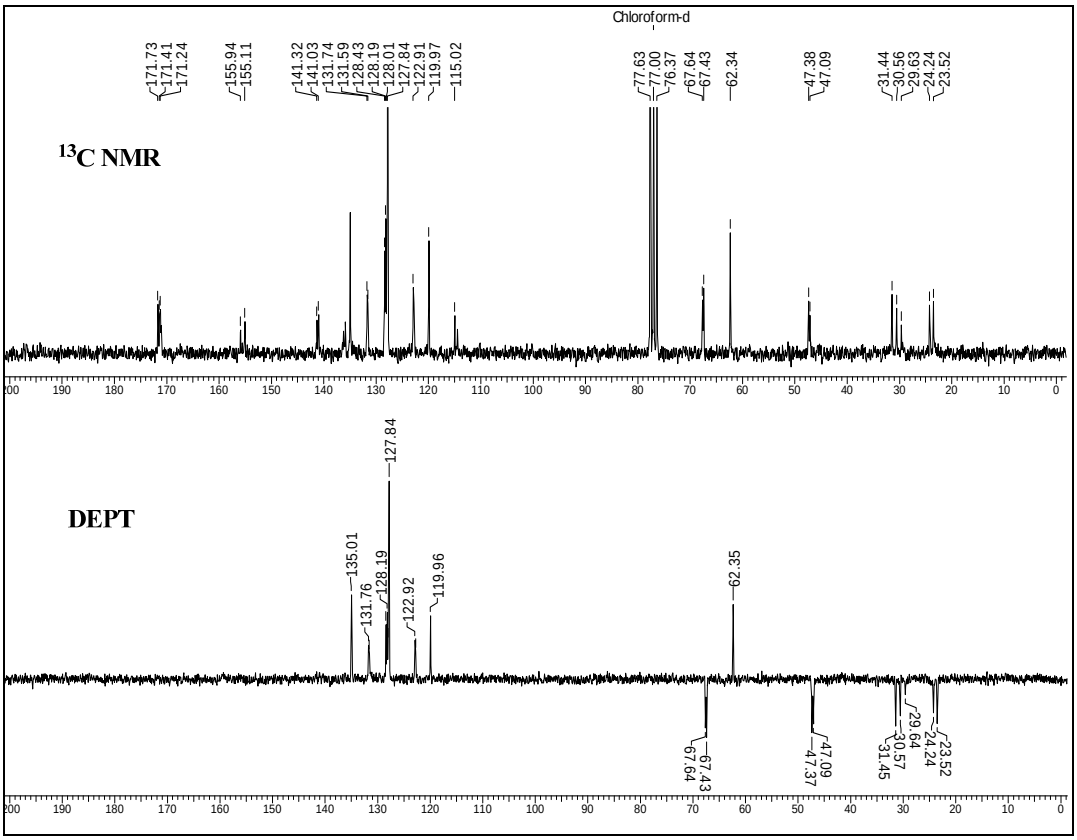
NMR spectra of Methyl ester of *N*-Cbz-**5** ($CDCl_3$)



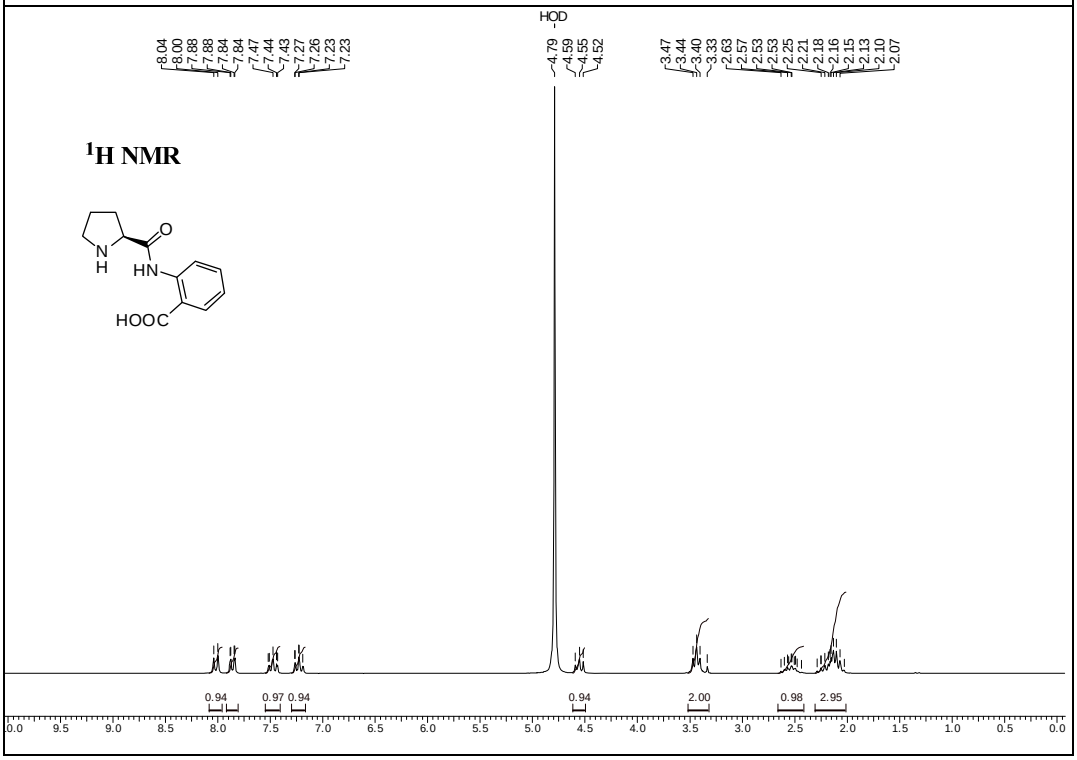



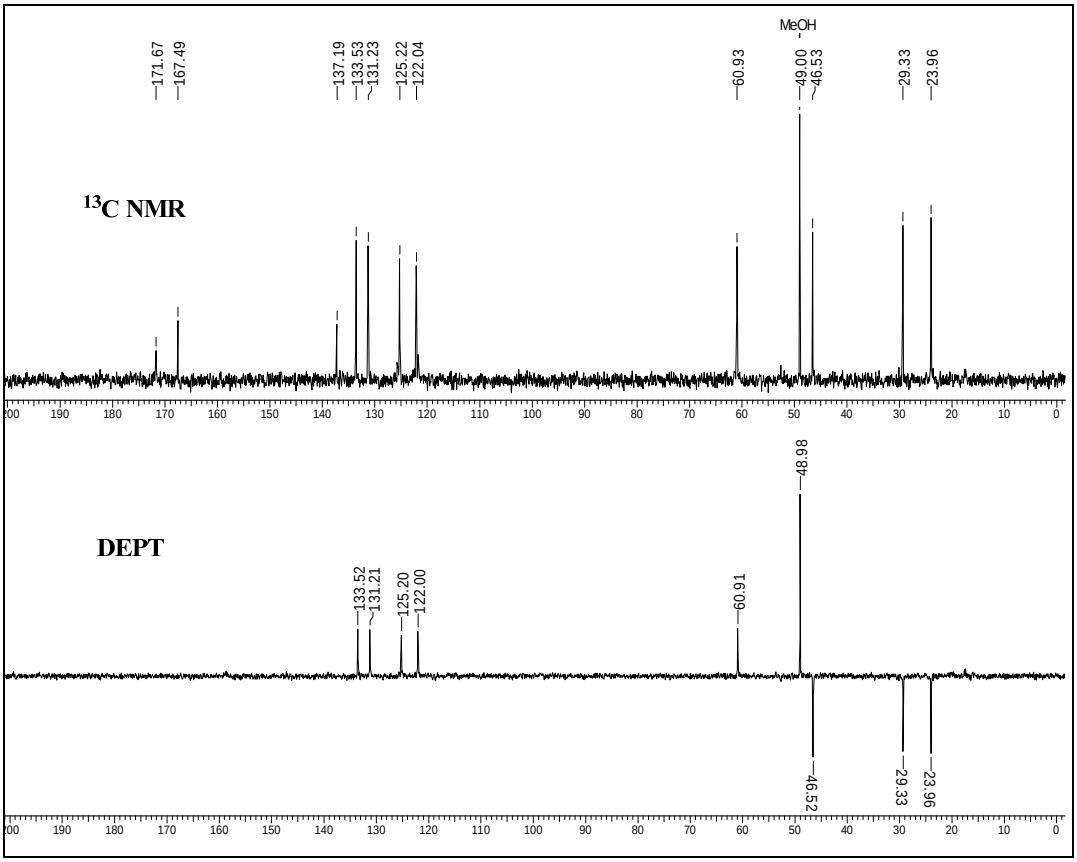
NMR spectra of *N*-Cbz-**5** ($CDCl_3$)



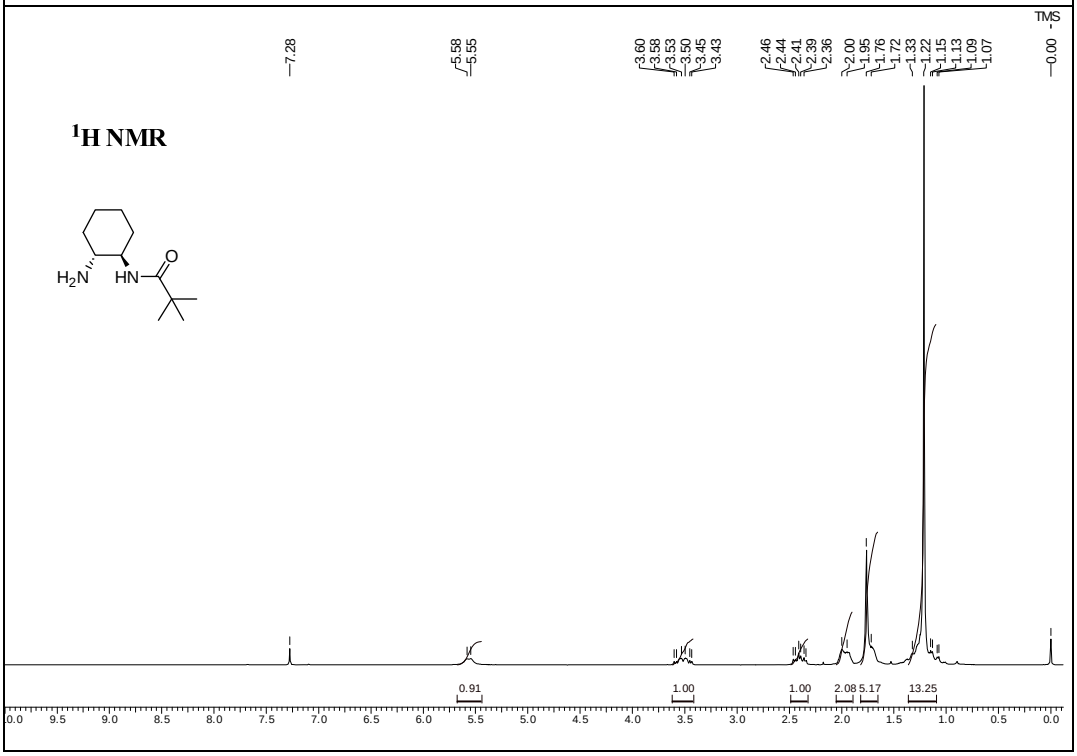



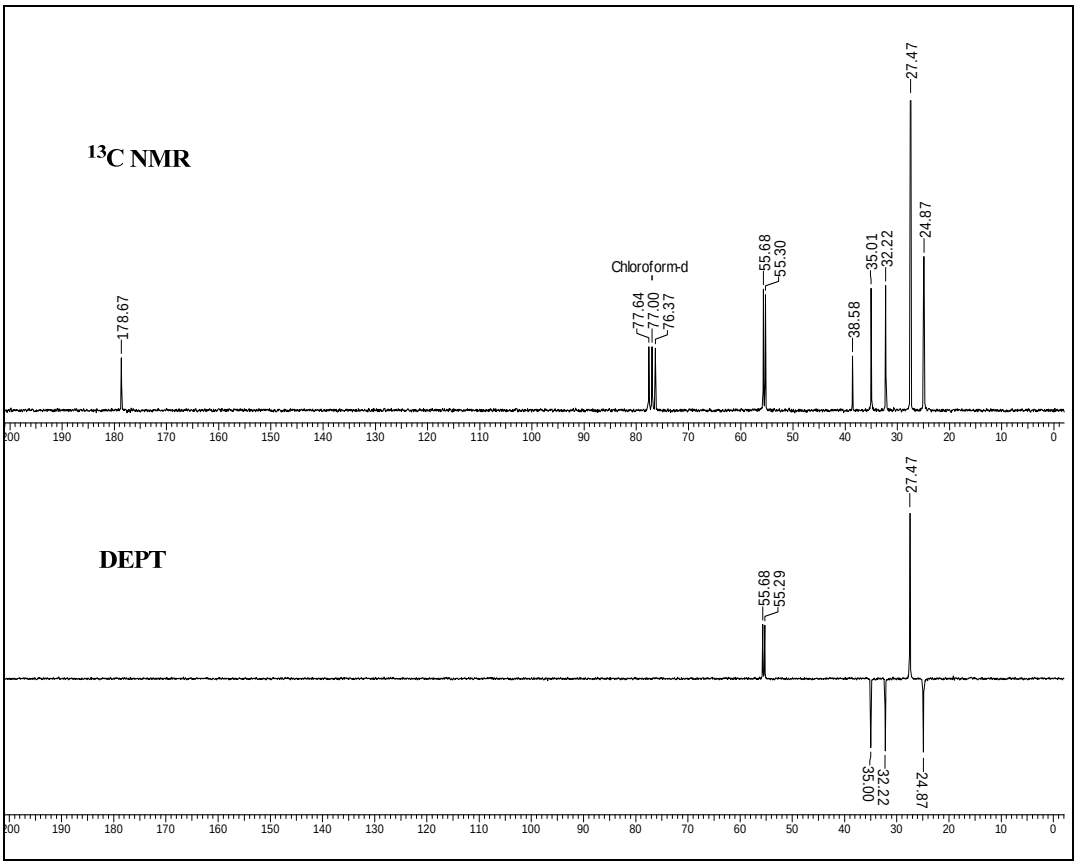
NMR spectra of **5** ($D_2O$)



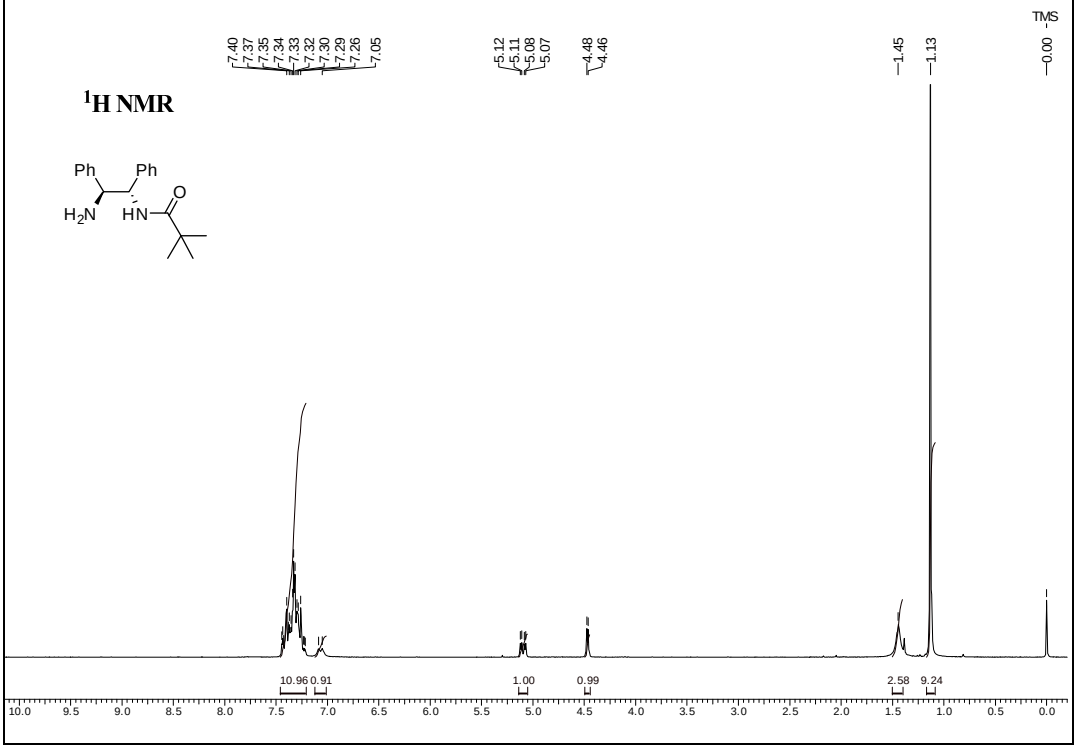



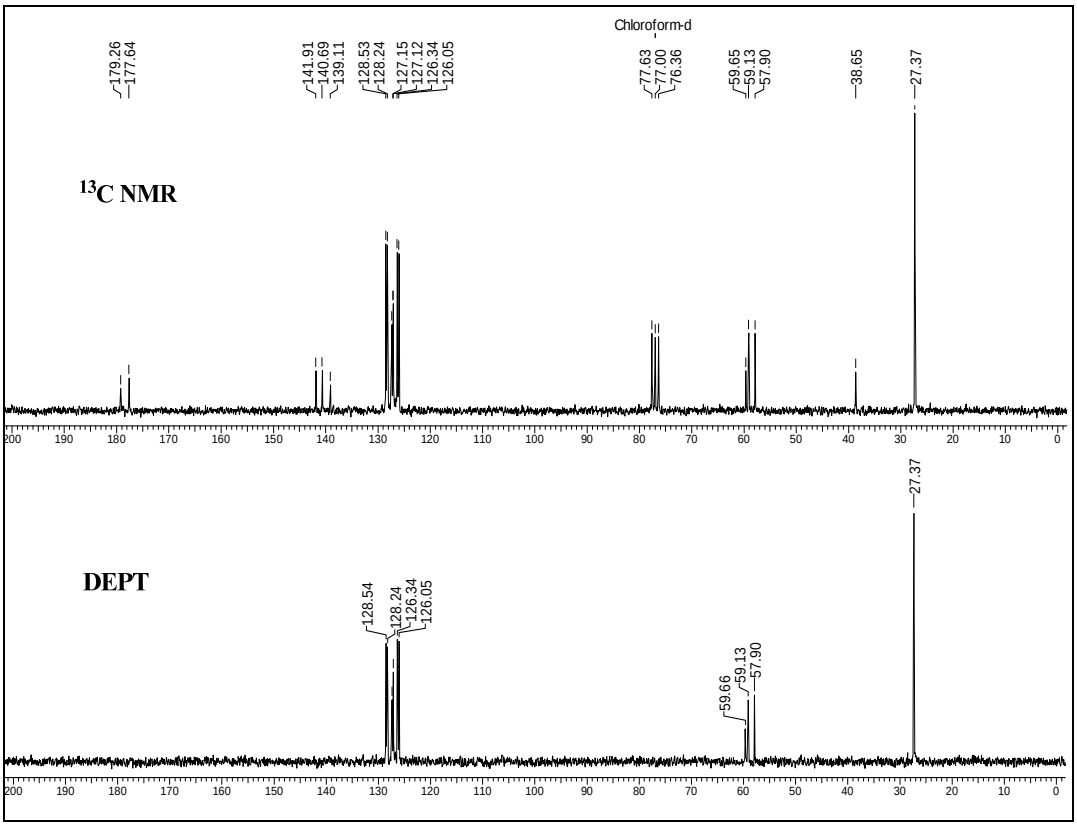
NMR spectra of **12a** ($CDCl_3$)



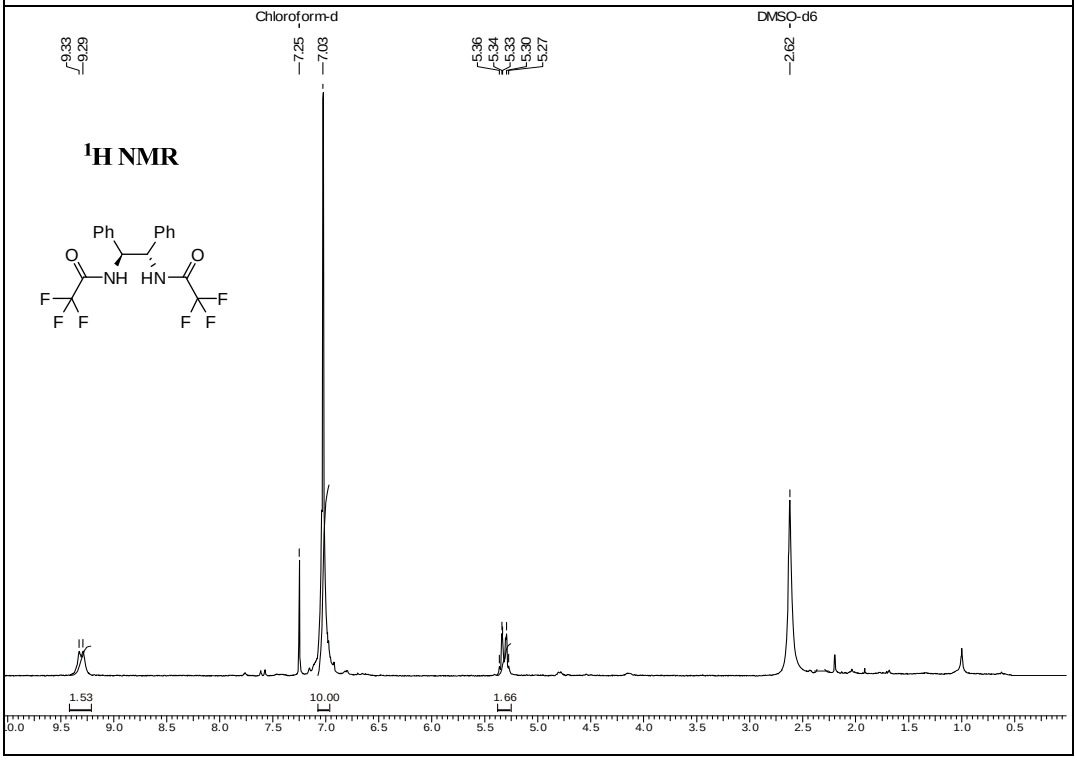



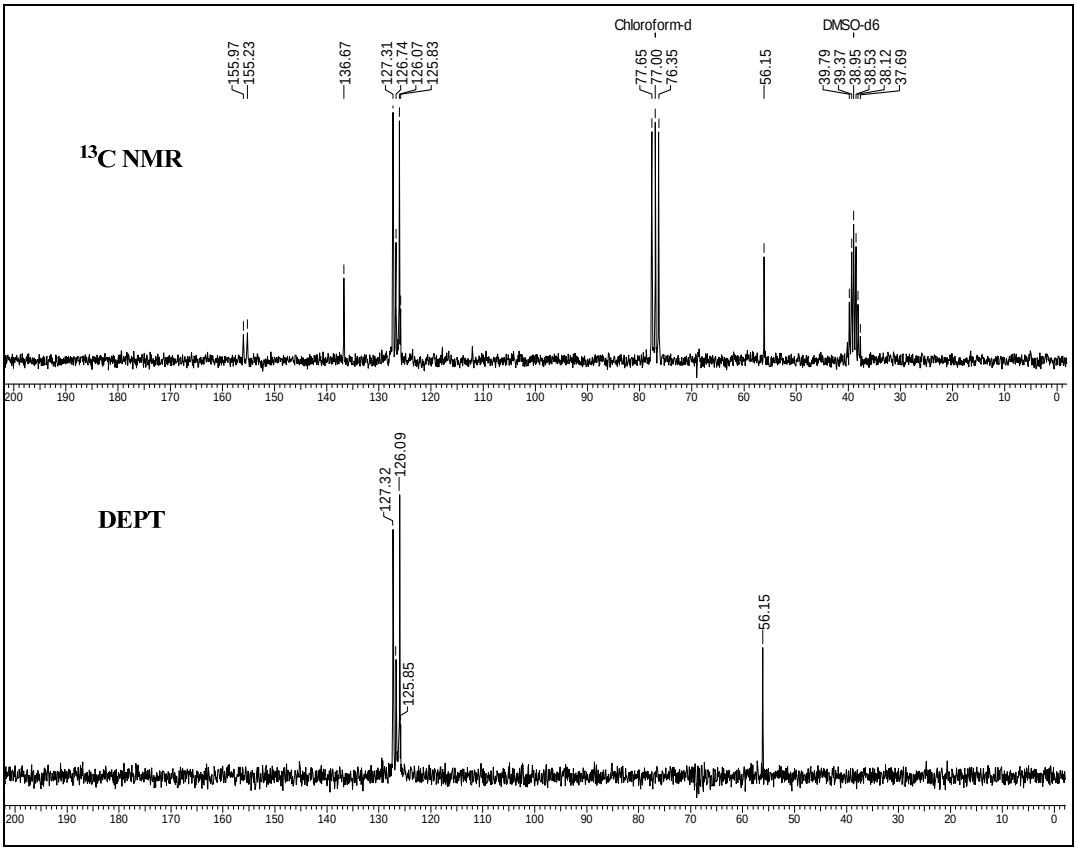
NMR spectra of **13a** ($CDCl_3$)



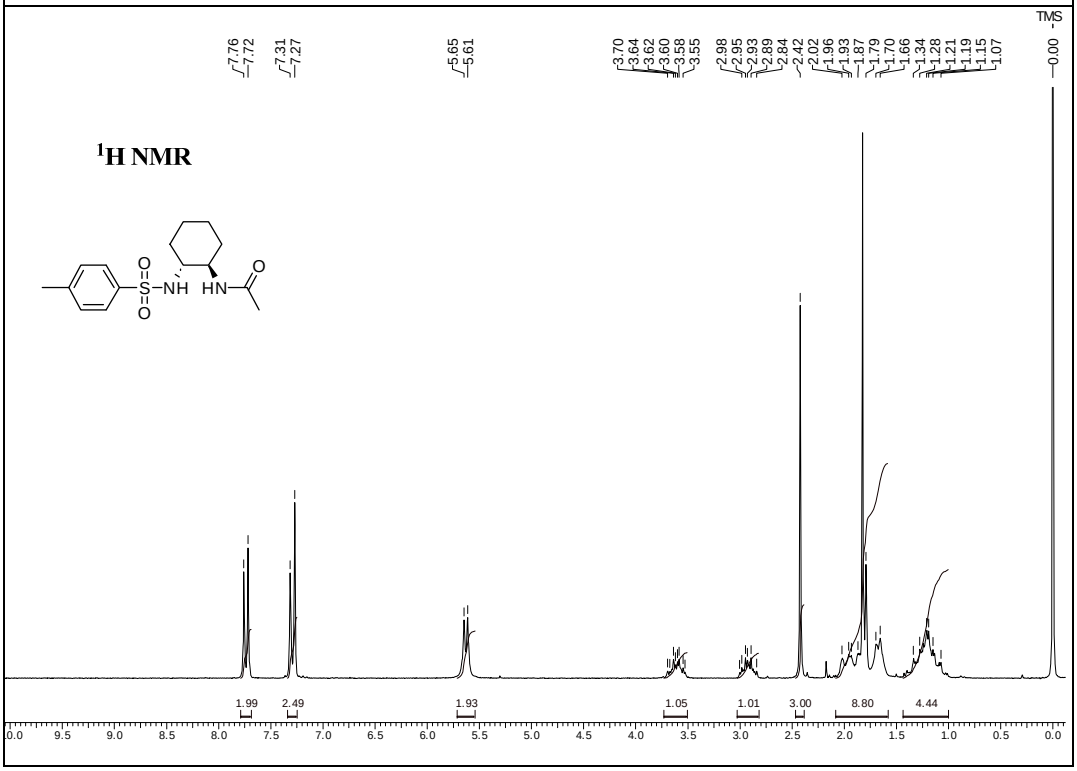



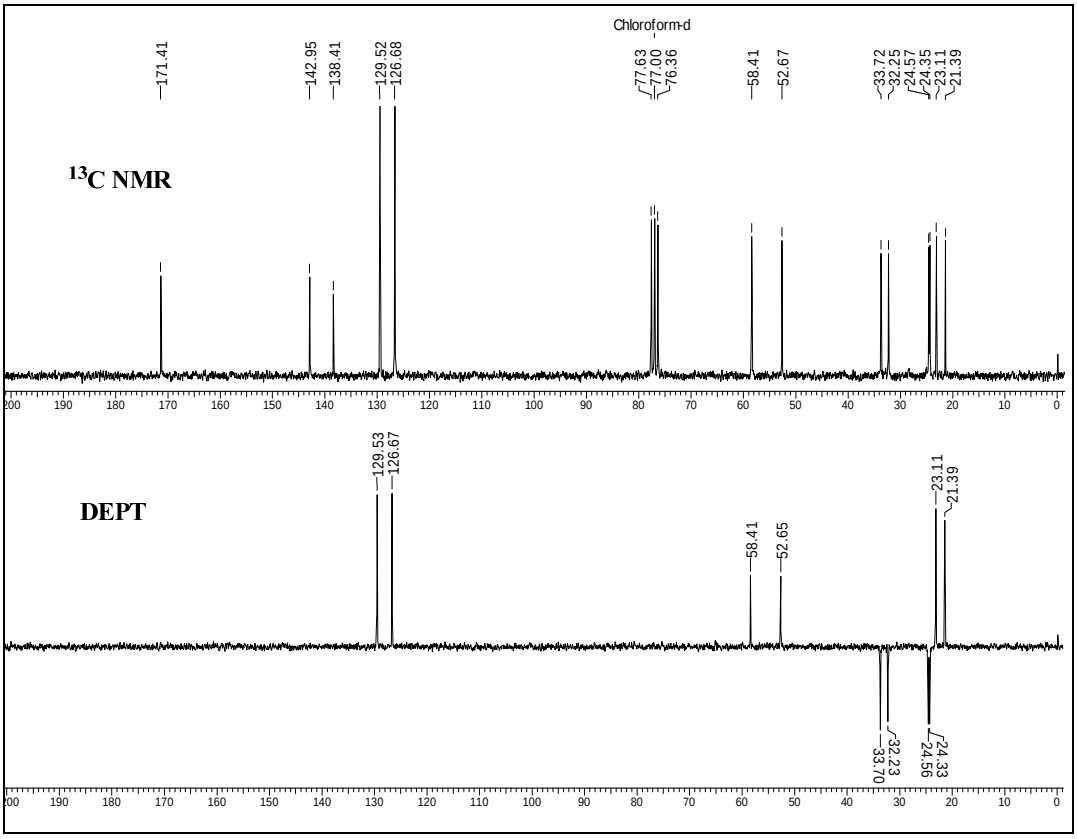
NMR spectra of **13h** (DMSO-d6/$CDCl_3$)



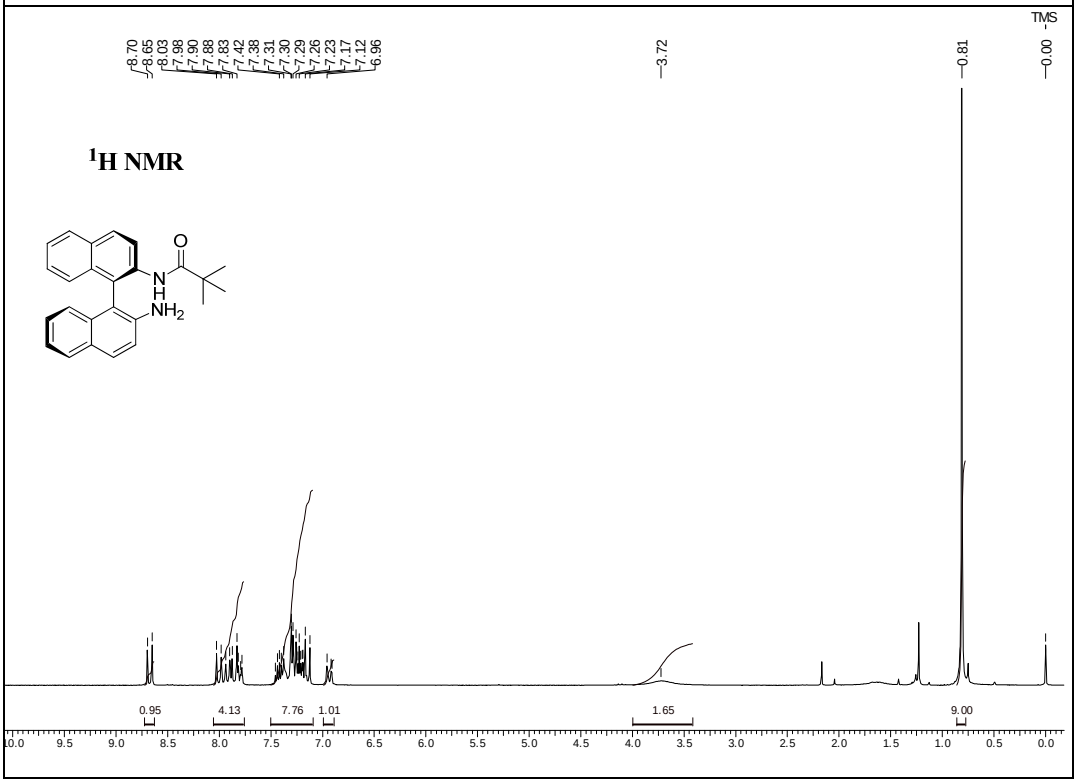



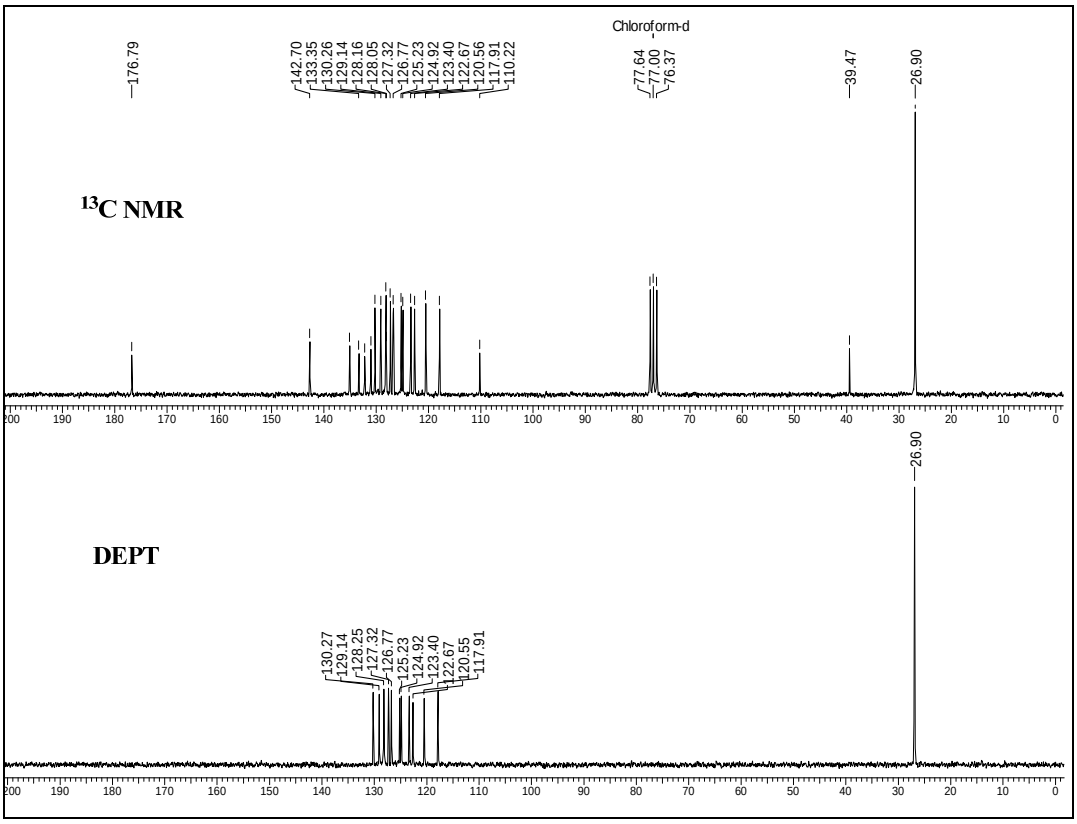
NMR spectra of **12g** ($CDCl_3$)



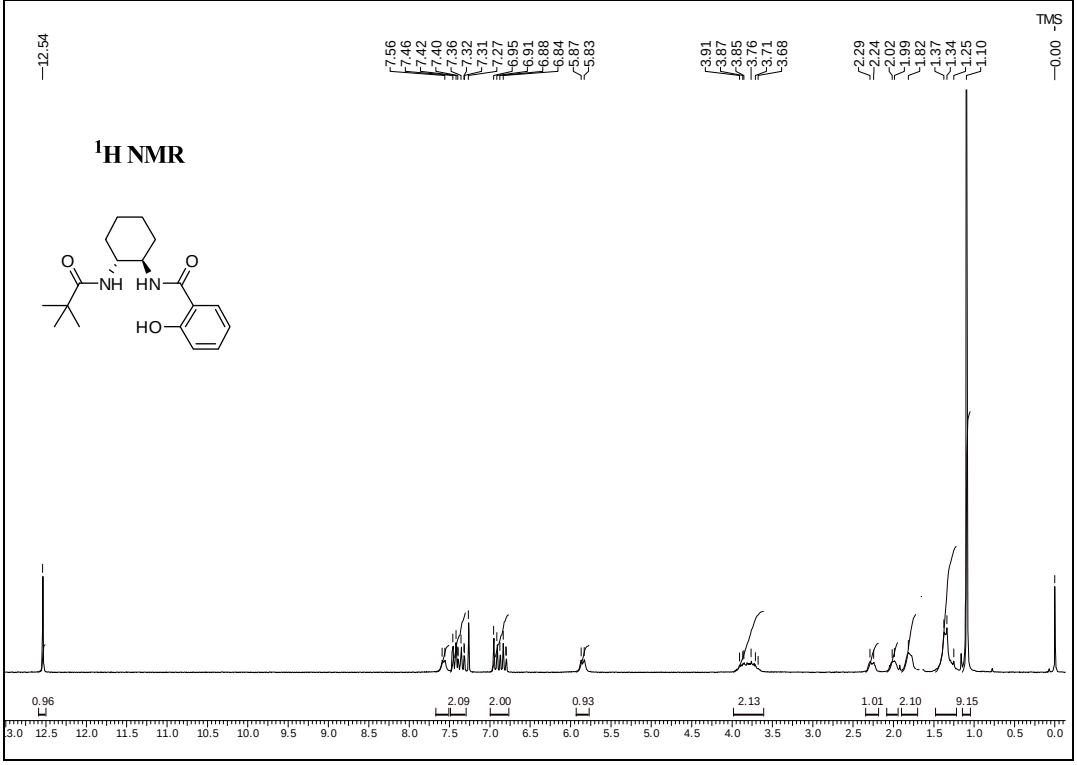



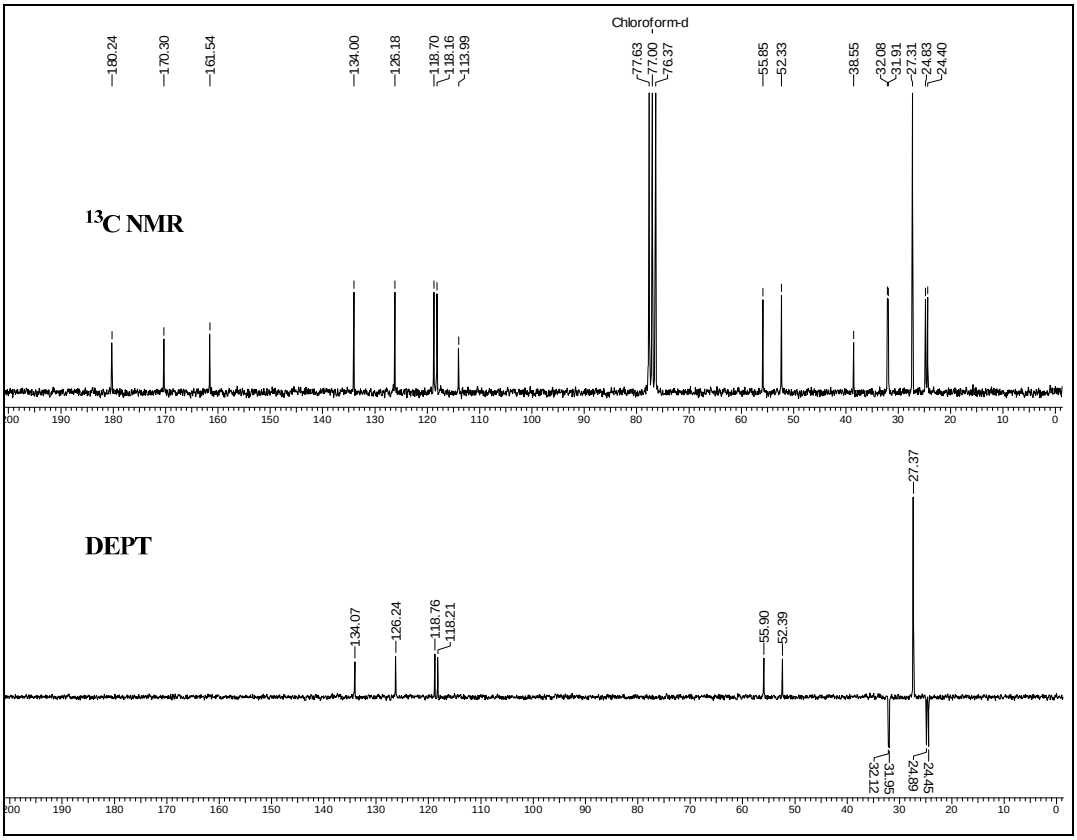
NMR spectra of **14** ($CDCl_3$)



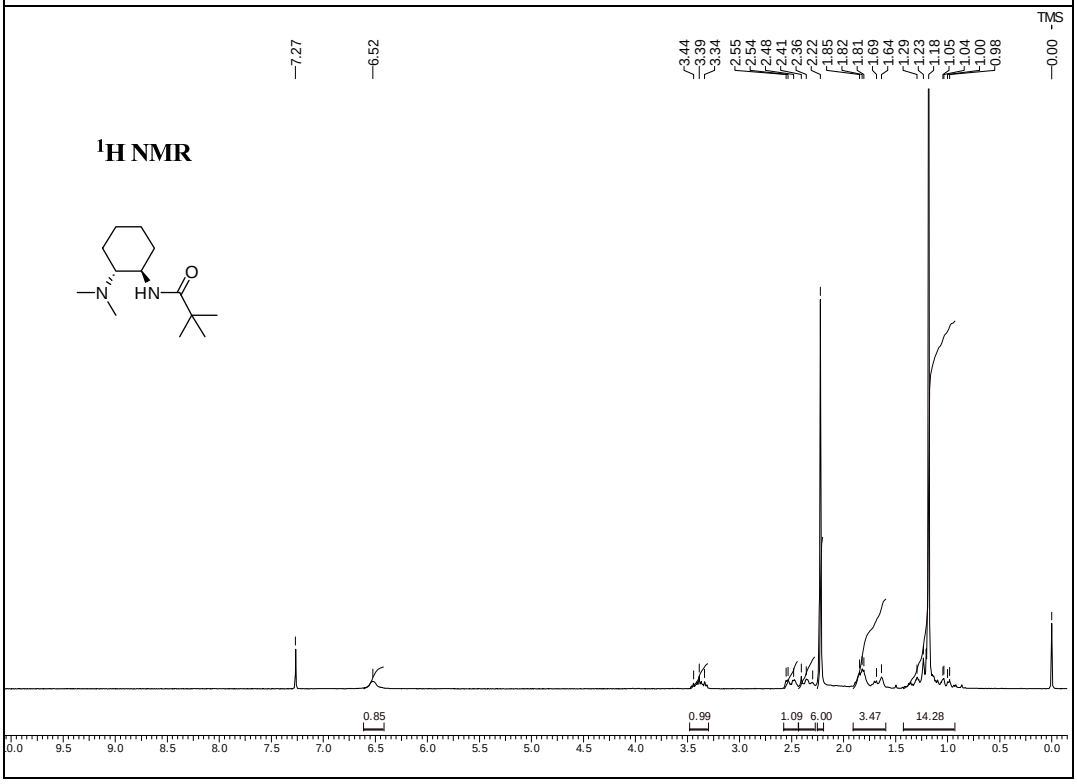



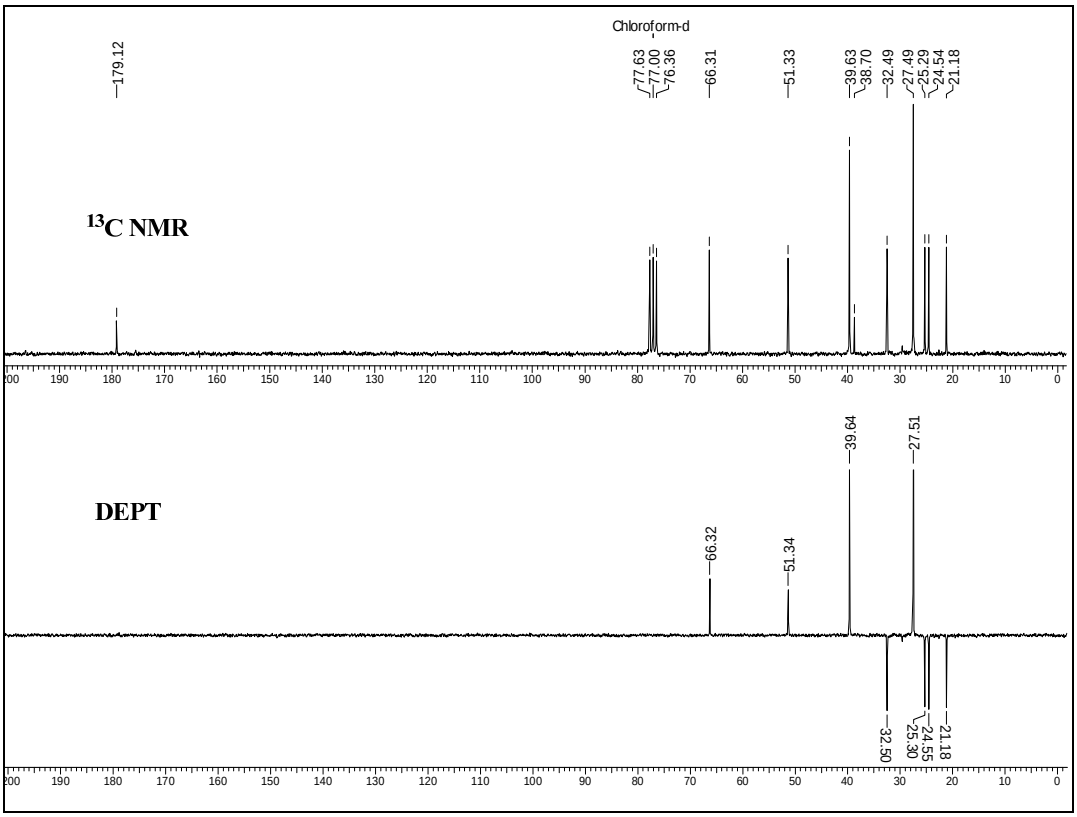
NMR spectra of **16b** ($CDCl_3$)



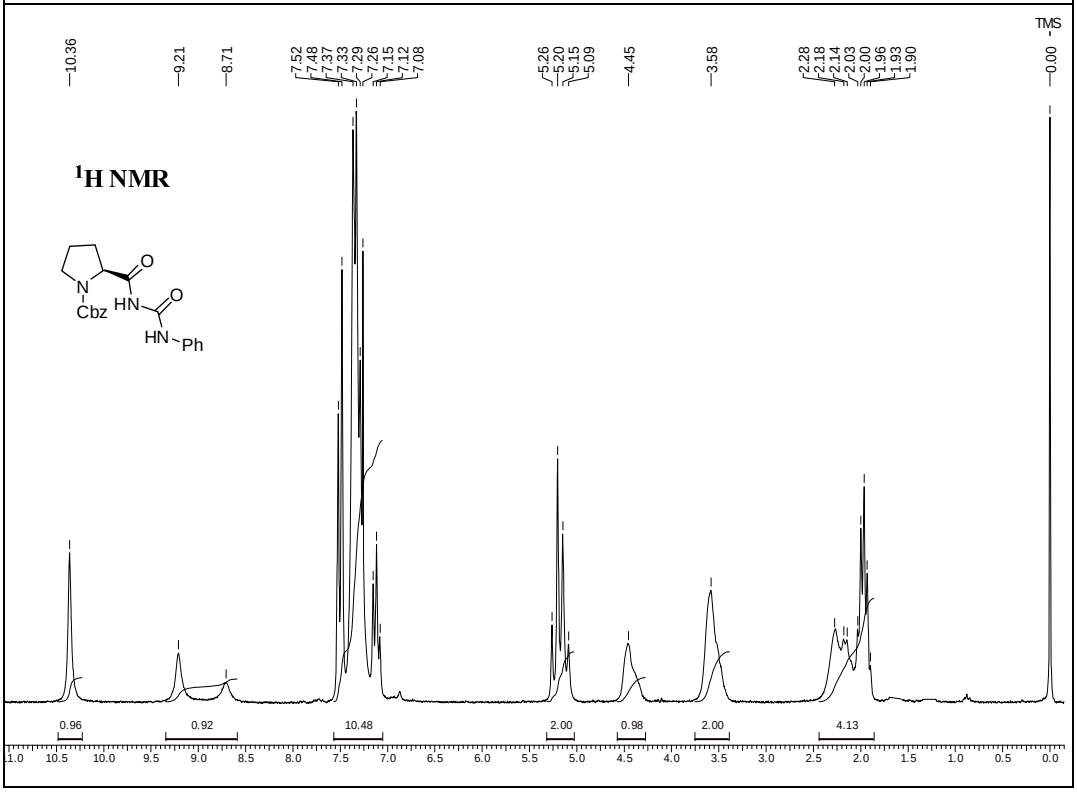



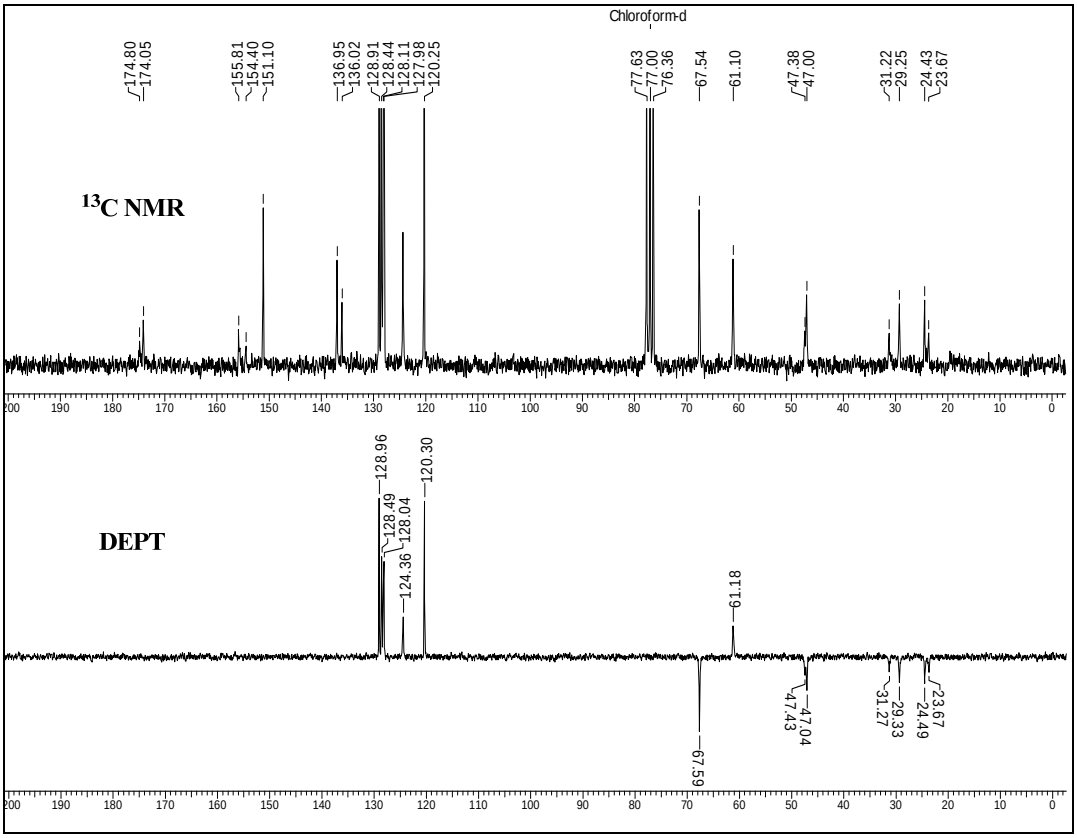
NMR spectra of **15** ($CDCl_3$)



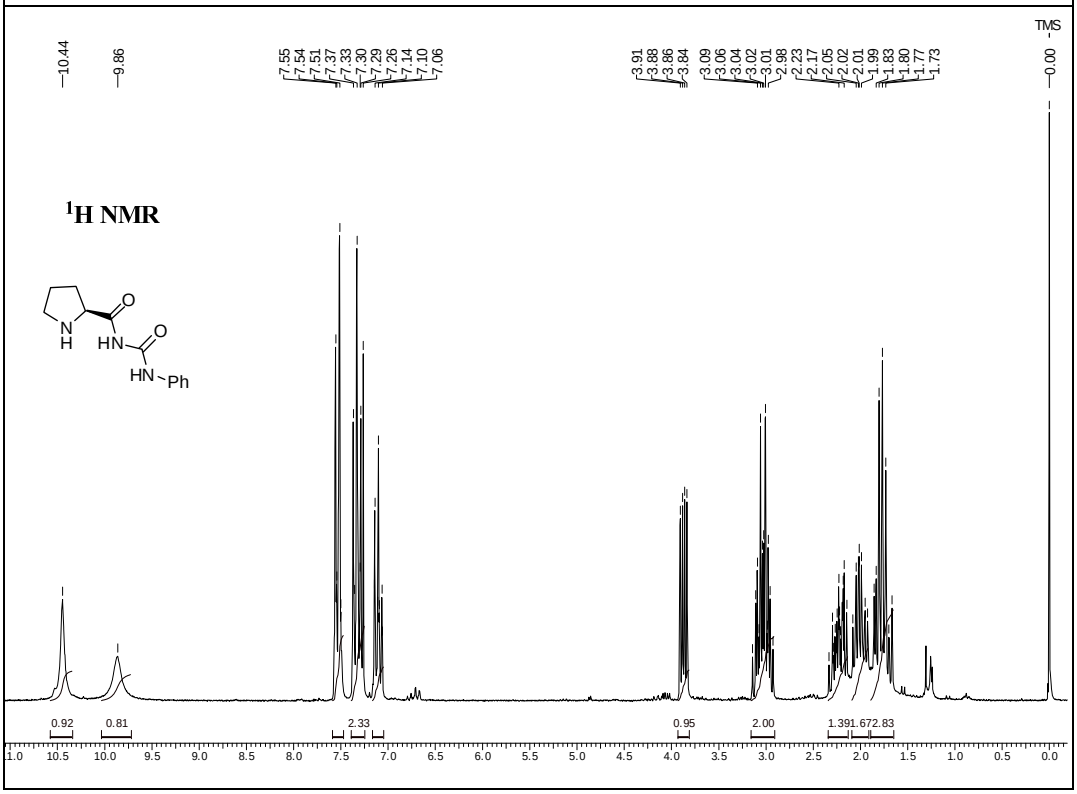



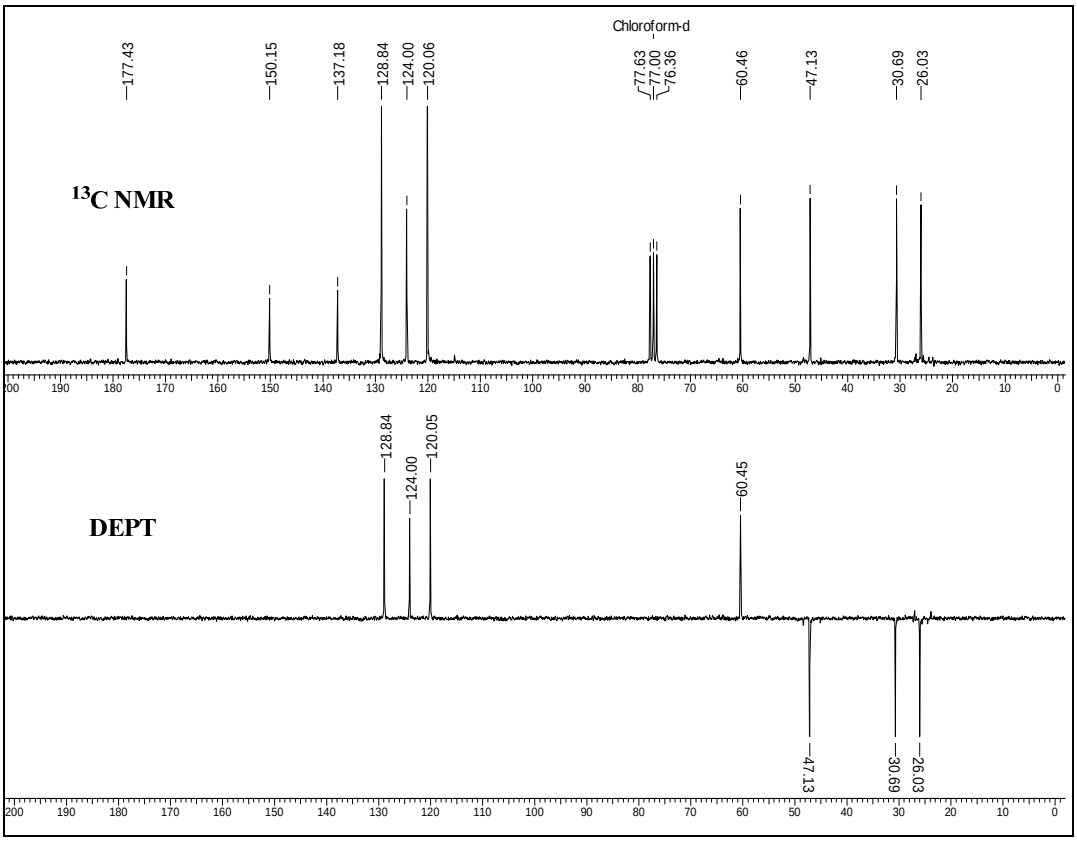
NMR spectra of **17** ($CDCl_3$)



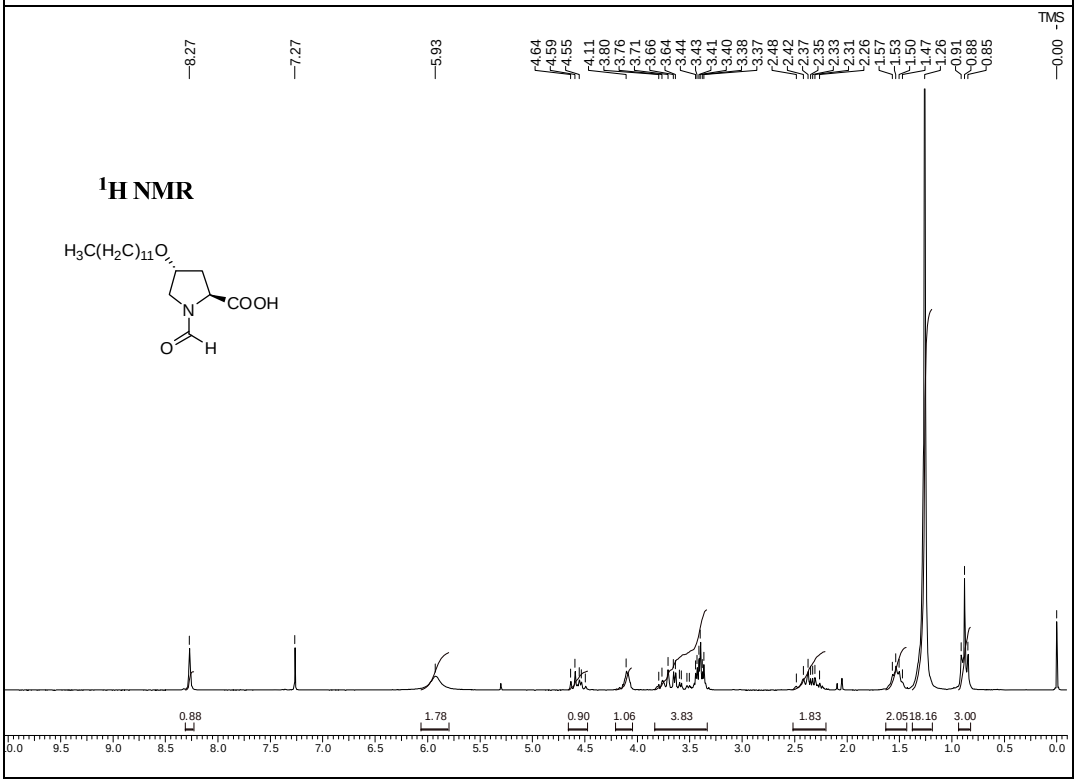



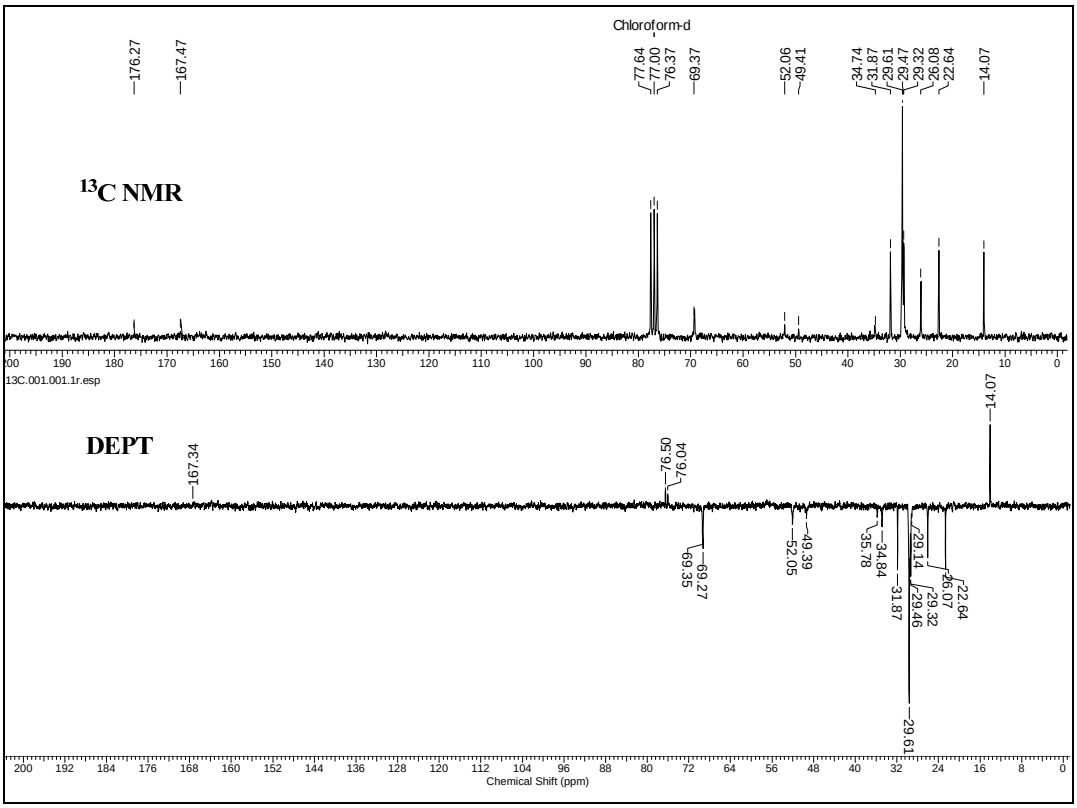
NMR spectra of **18** ($CDCl_3$)



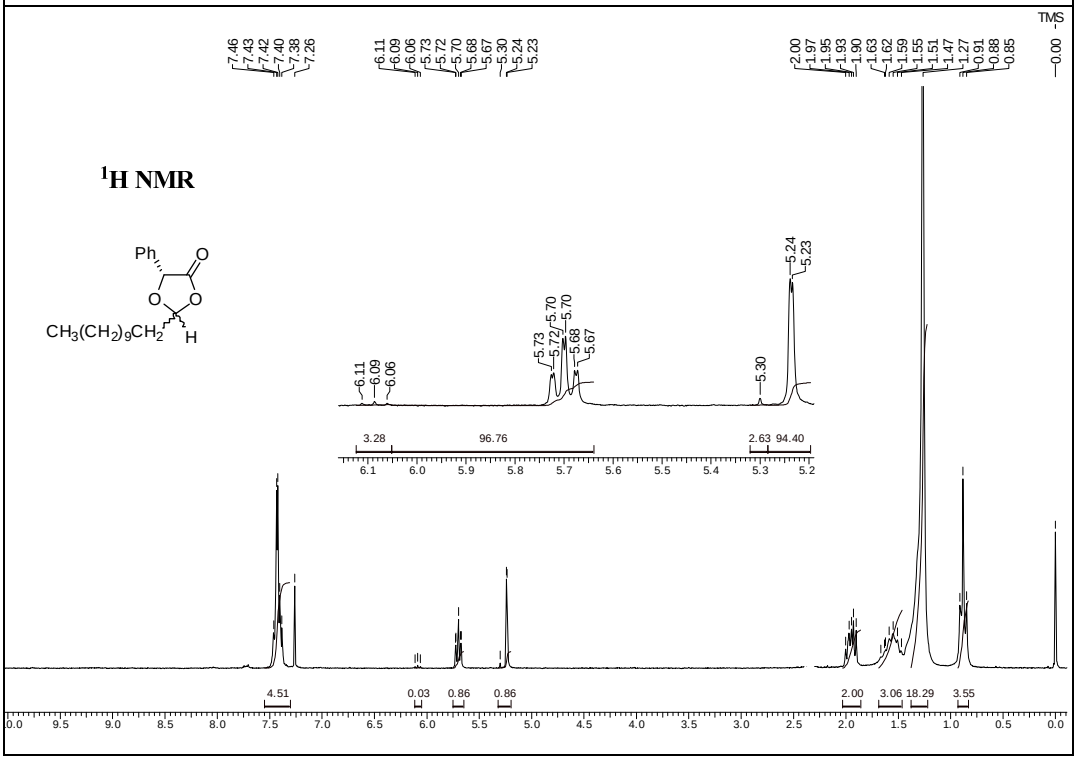



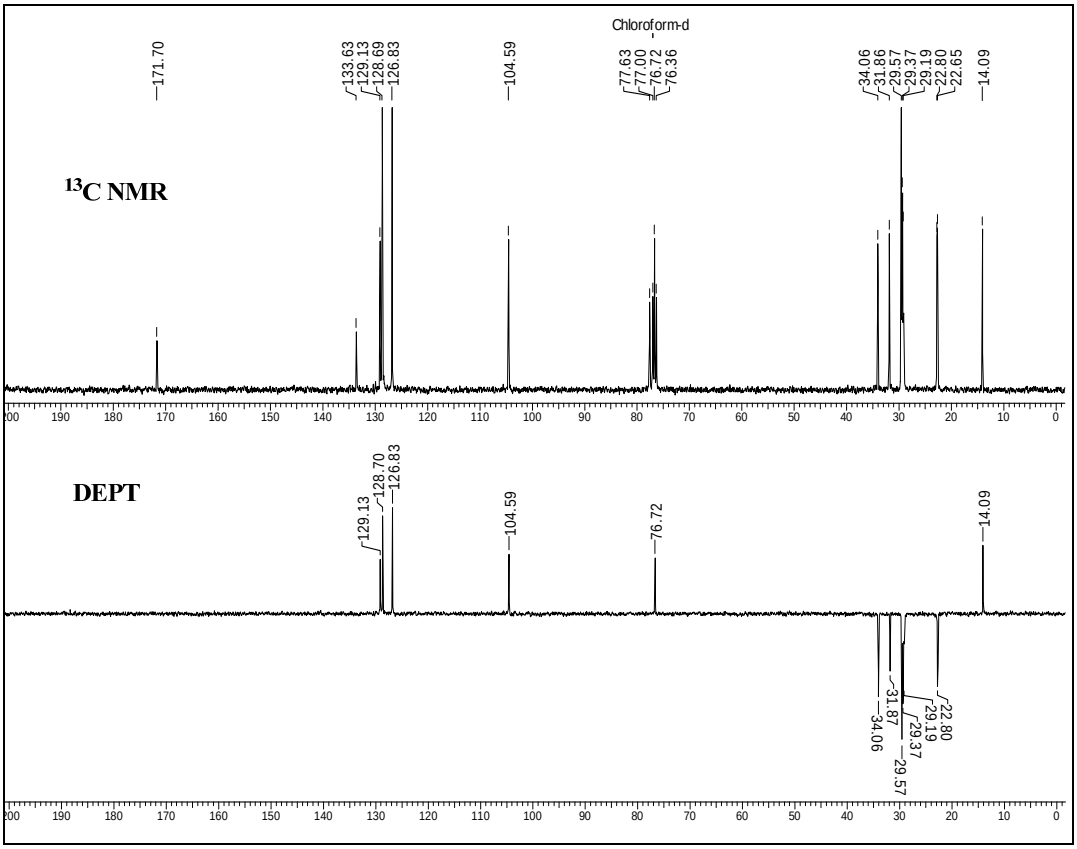
NMR spectra of 2**2** ($CDCl_3$)



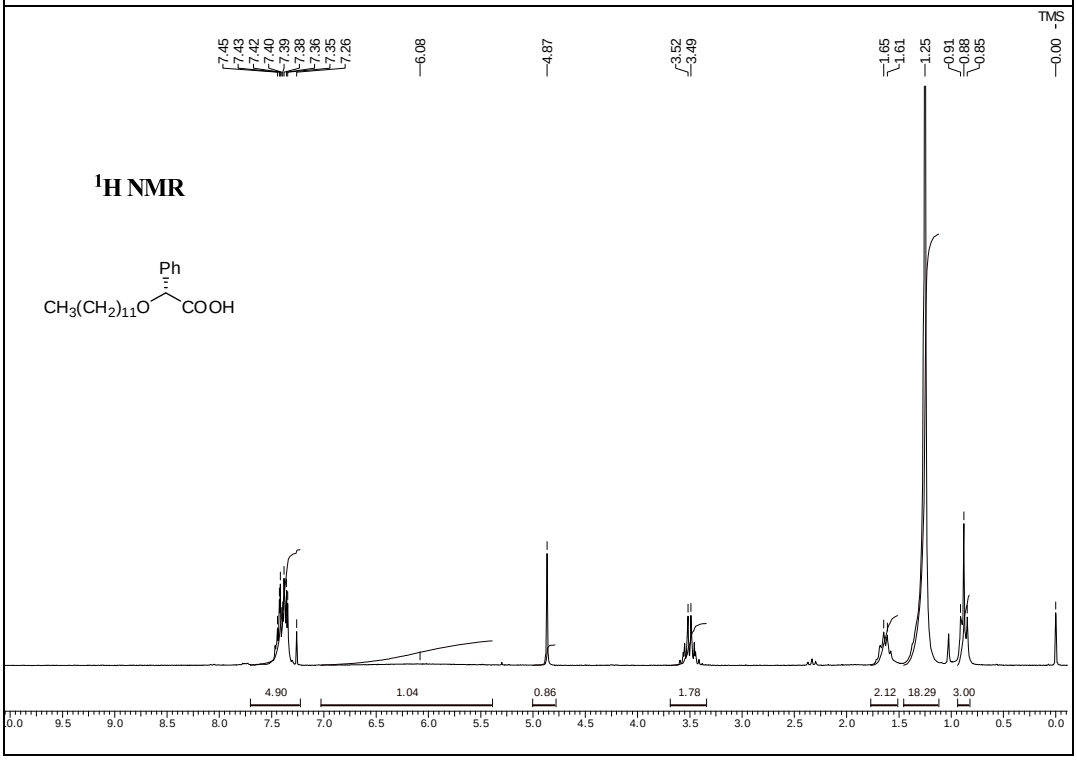



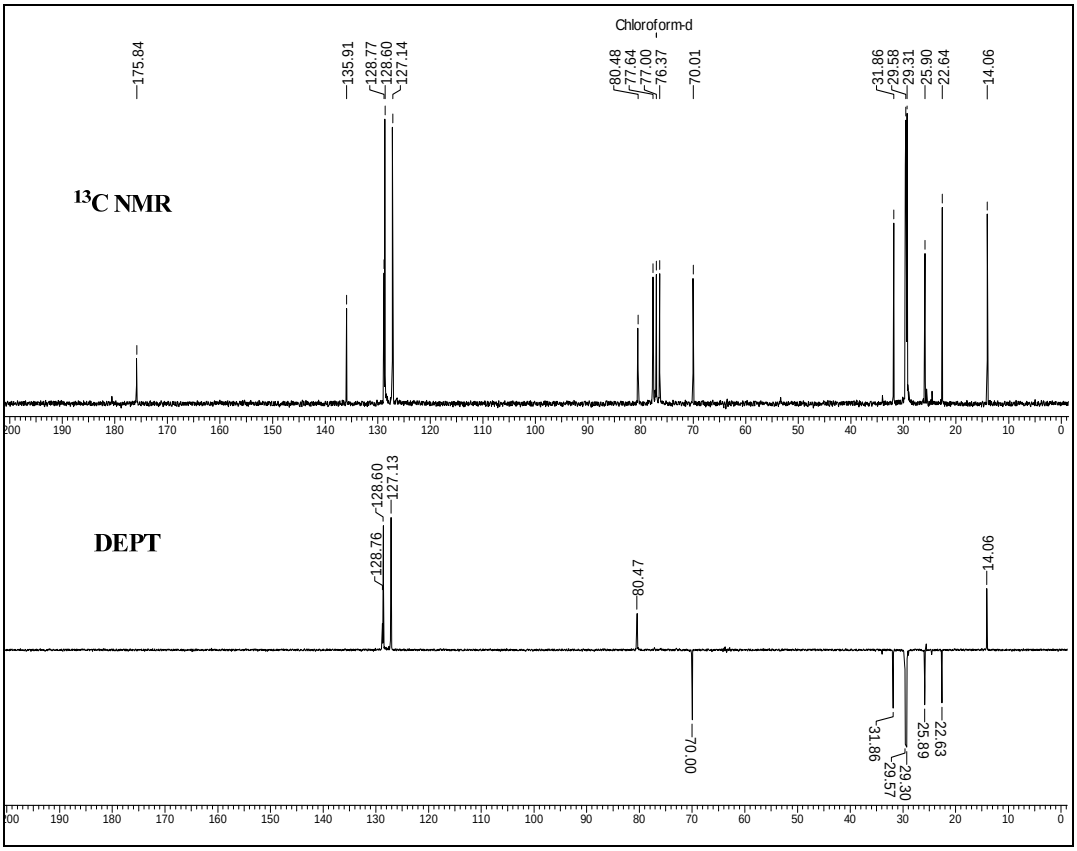
NMR spectra of (5*R*)-2-dodecyl-5-phenyl-1,3-dioxolan-4-one ($CDCl_3$)



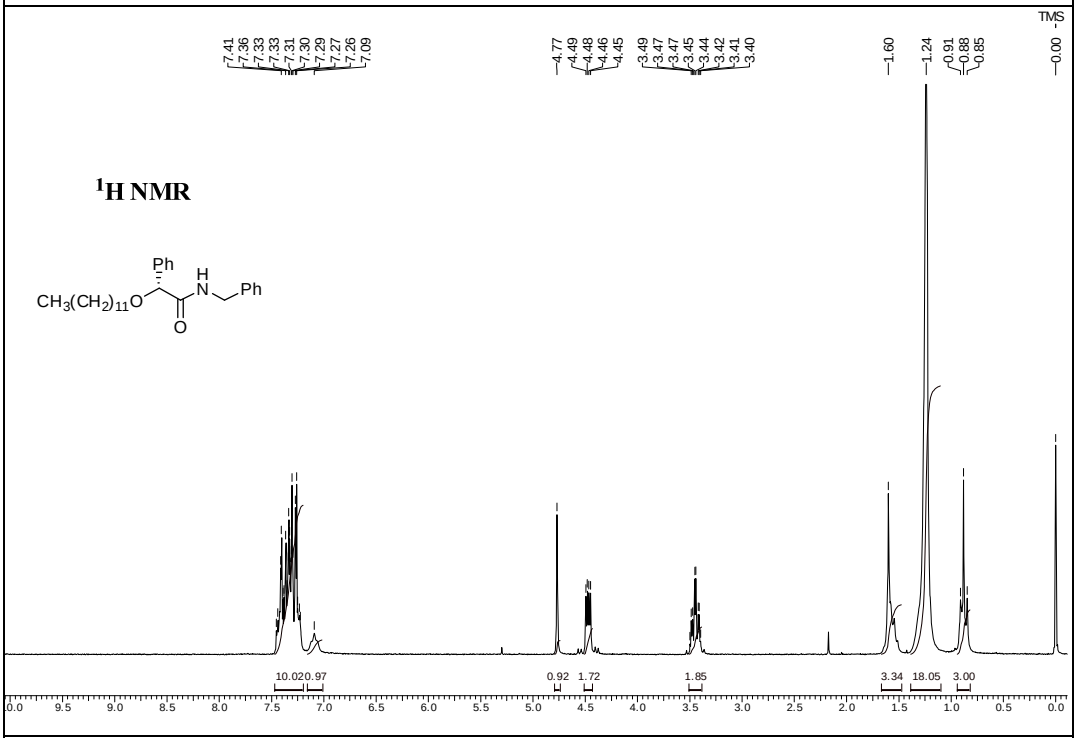



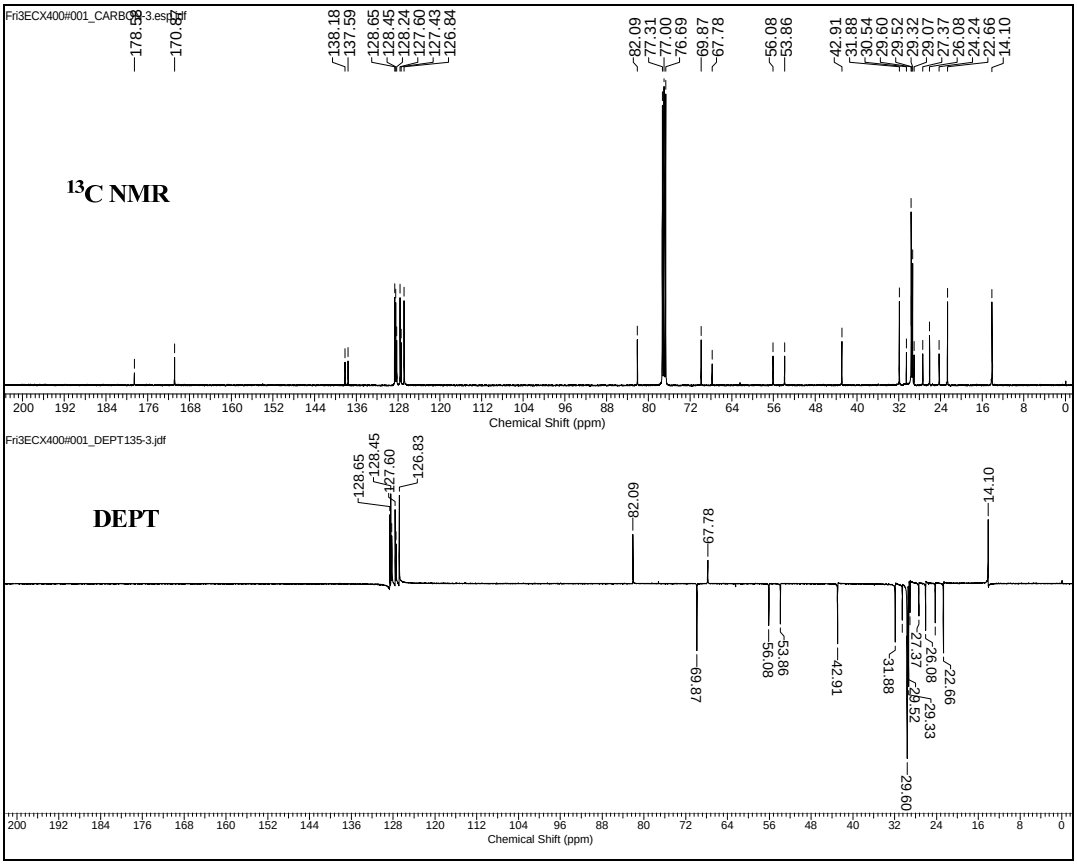
NMR spectra of **24** ($CDCl_3$)



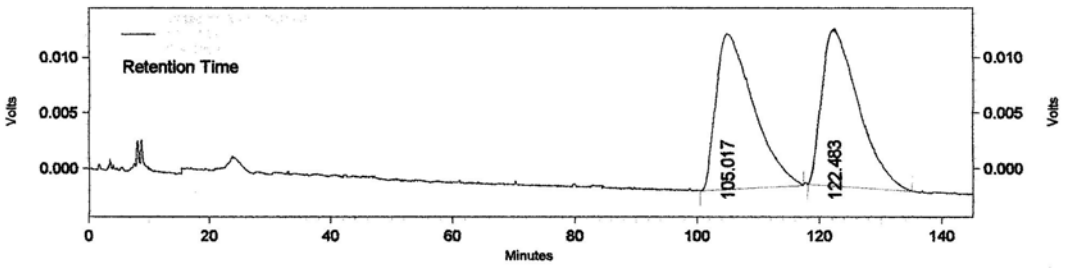



NMR spectra of (*R*)-N-benzyl-2-(dodecyloxy)-2-phenylacetamide ($CDCl_3$)



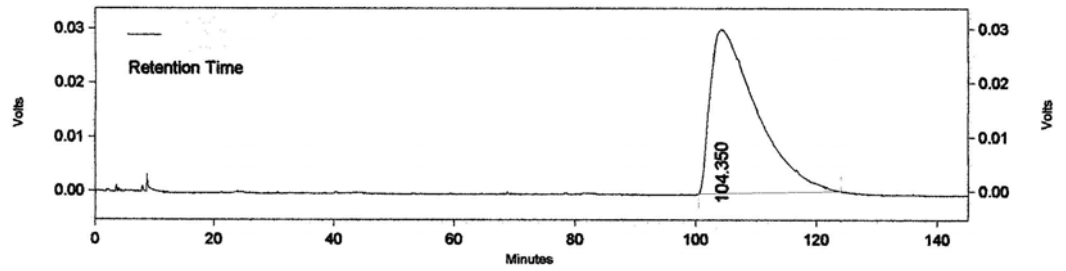
HPLC chromatogram of racemic amide




**Detector A - 1 (220nm)**

| Retention Time | C Area | Area % |
|---|---|---|
| 105.017 | 5964640 | 50.356 |
| 122.483 | 5880195 | 49.644 |
| Totals | 11844835 | 100.000 |

HPLC chromatogram of (-) amide

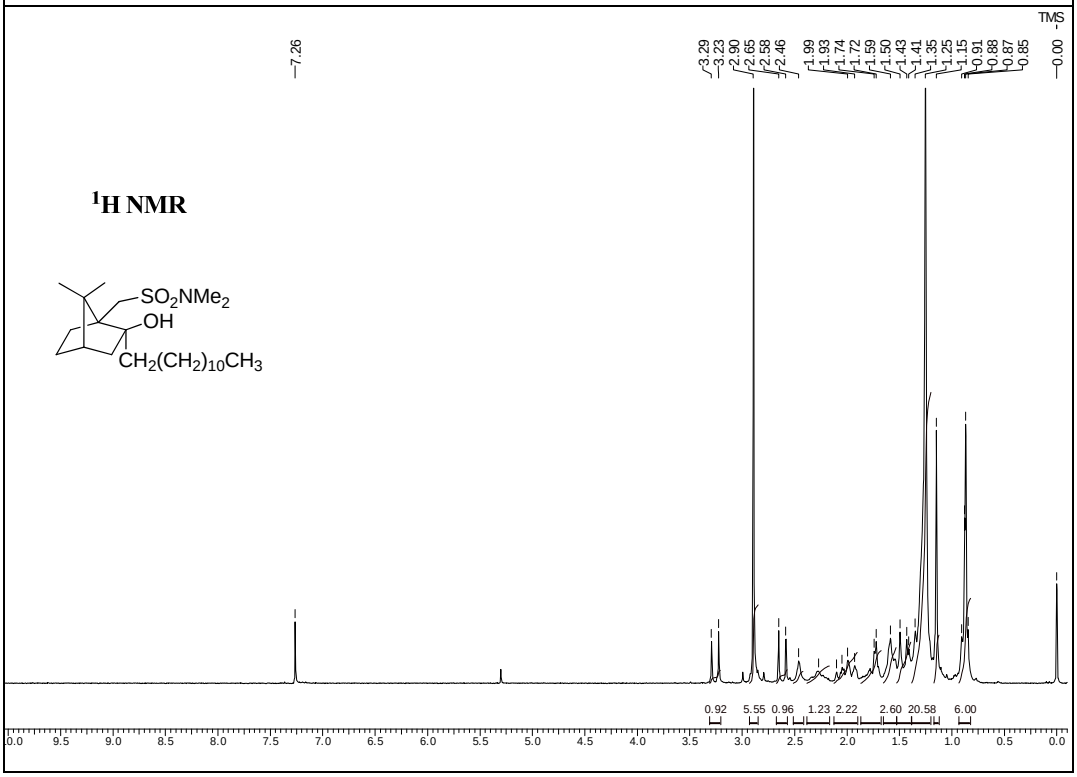



**Detector A - 1 (220nm)**

| Retention Time | C Area | Area % |
|---|---|---|
| 104.350 | 16079368 | 100.000 |
| Totals | 16079368 | 100.000 |

Column: Chiralcel OD; Mobile phase: *i*-PrOH:petroleum ether (0.3:99.7); Flow rate: 1.0 mL/min.; UV: 200 nm. Retention time: $t_R$ (*R*-isomer): 105.02 min, $t_R$ (*S*-isomer): 122.48 min.

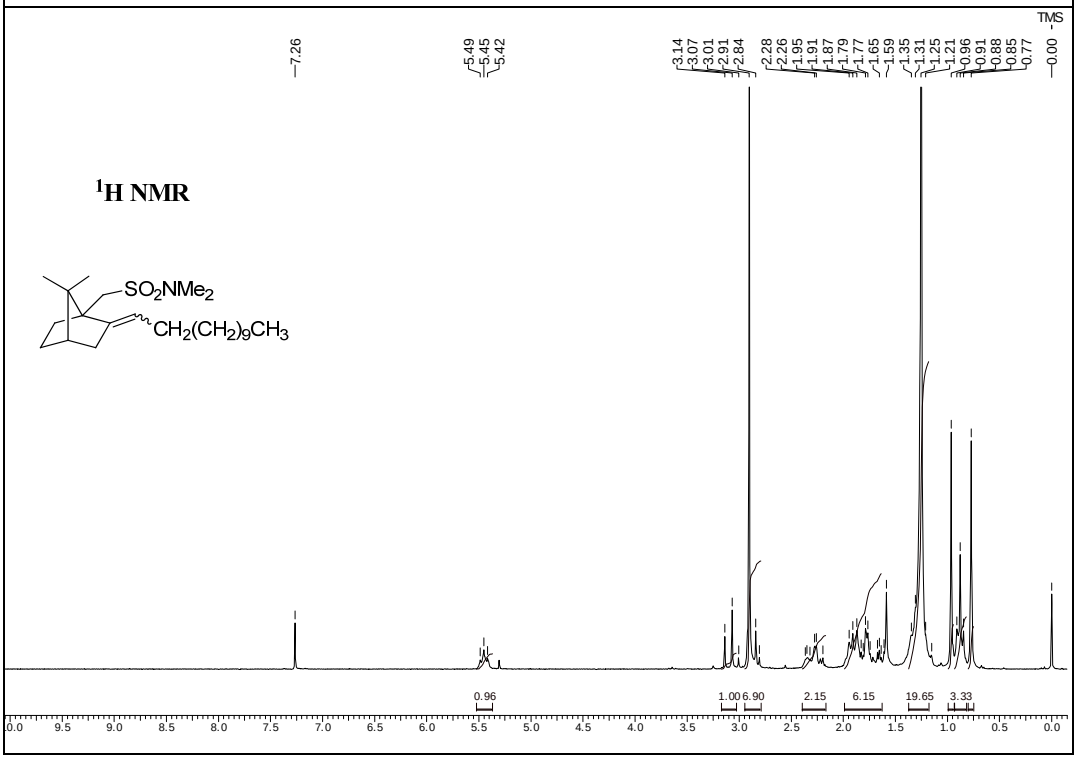
NMR spectra of **26c** ($CDCl_3$)




**$^1$H NMR**

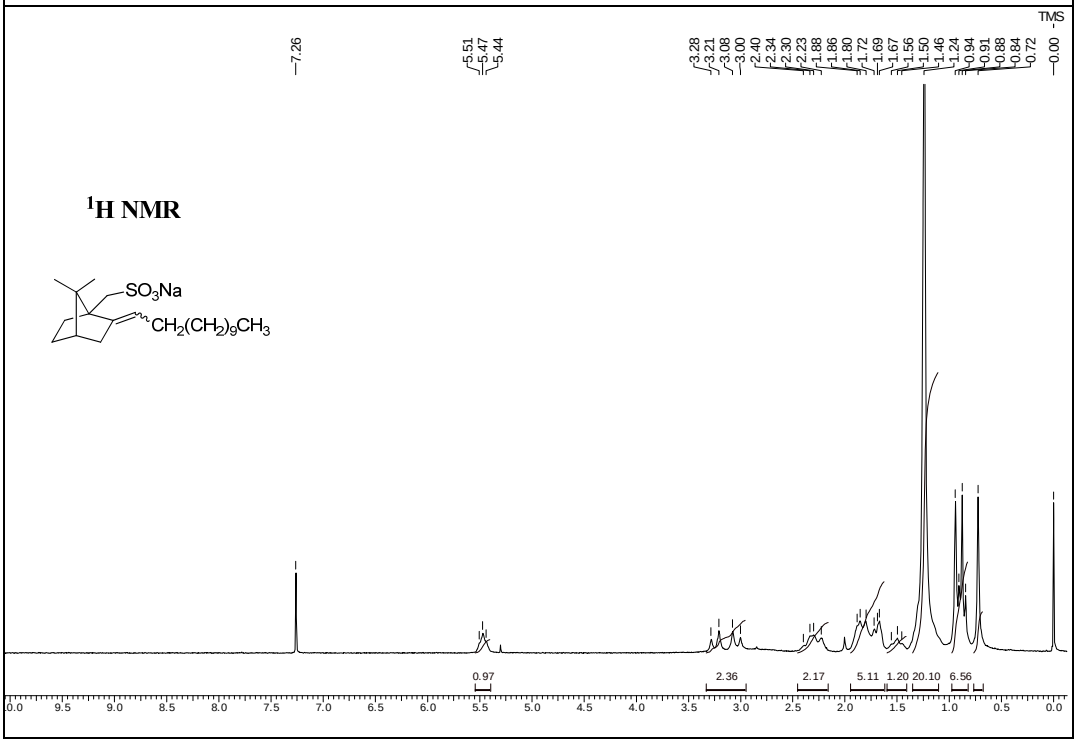


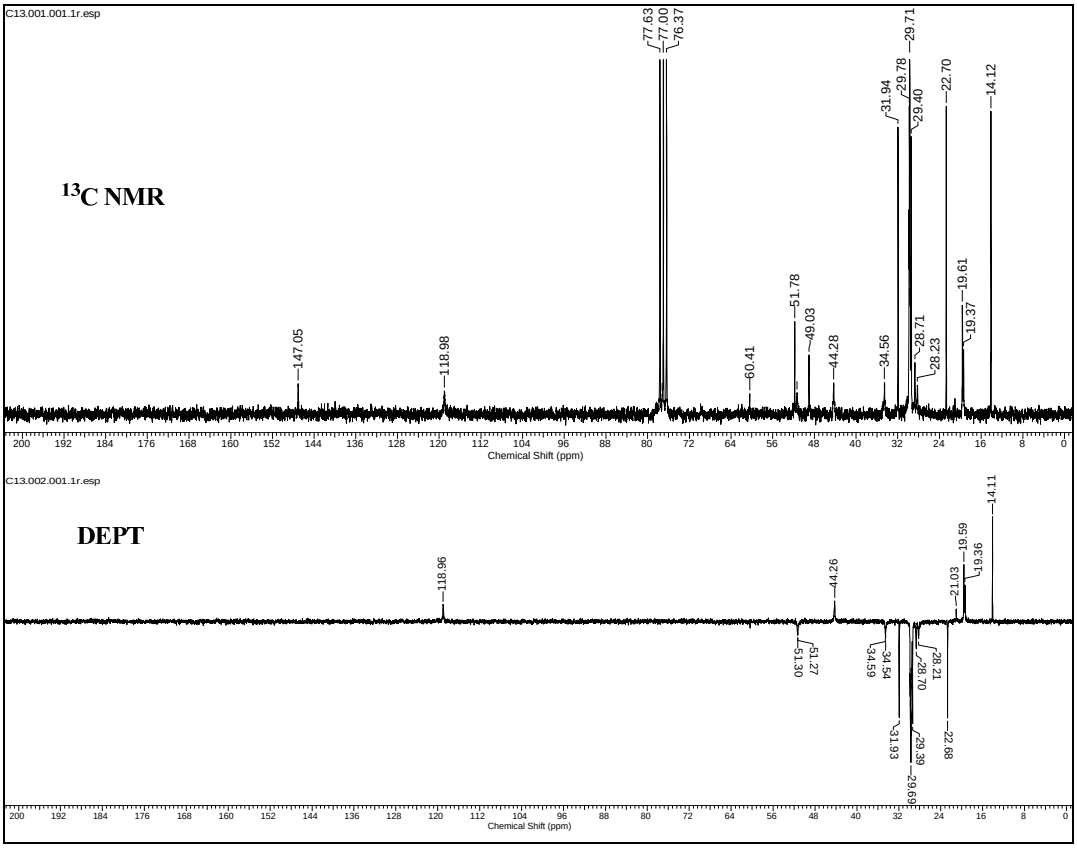

NMR spectra of **27a** ($CDCl_3$)



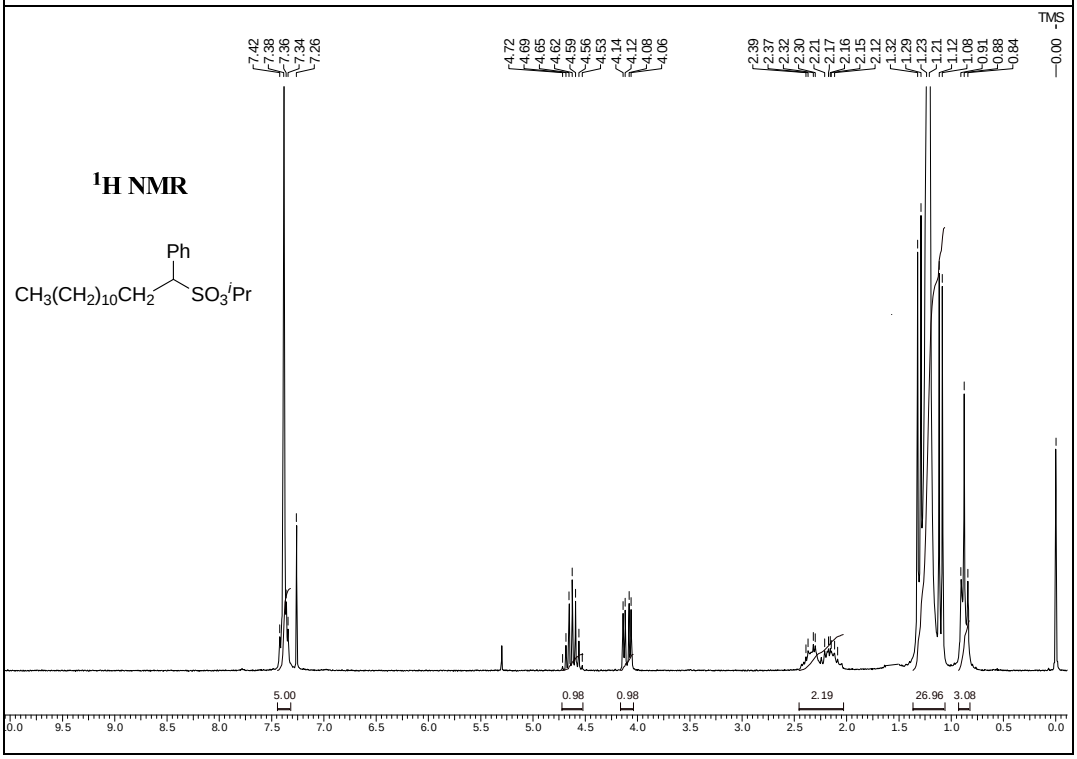

**$^1$H NMR**

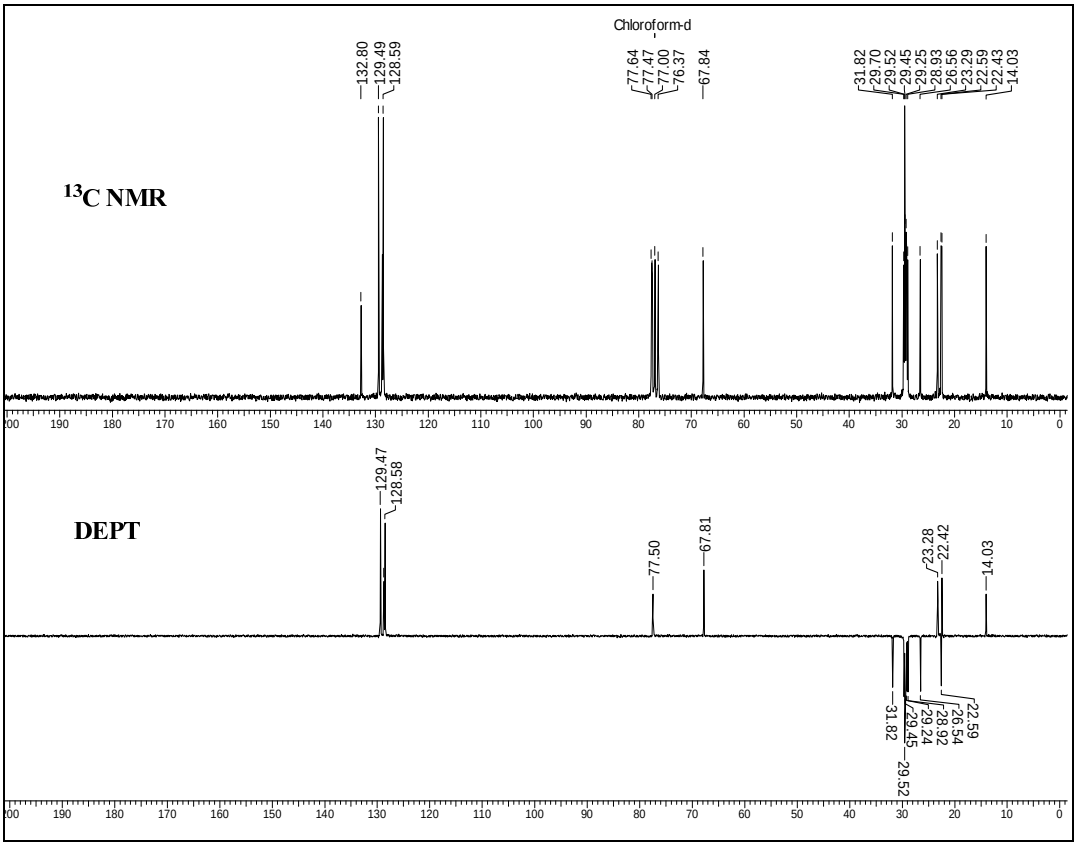
NMR spectra of **27b** ($CDCl_3$)



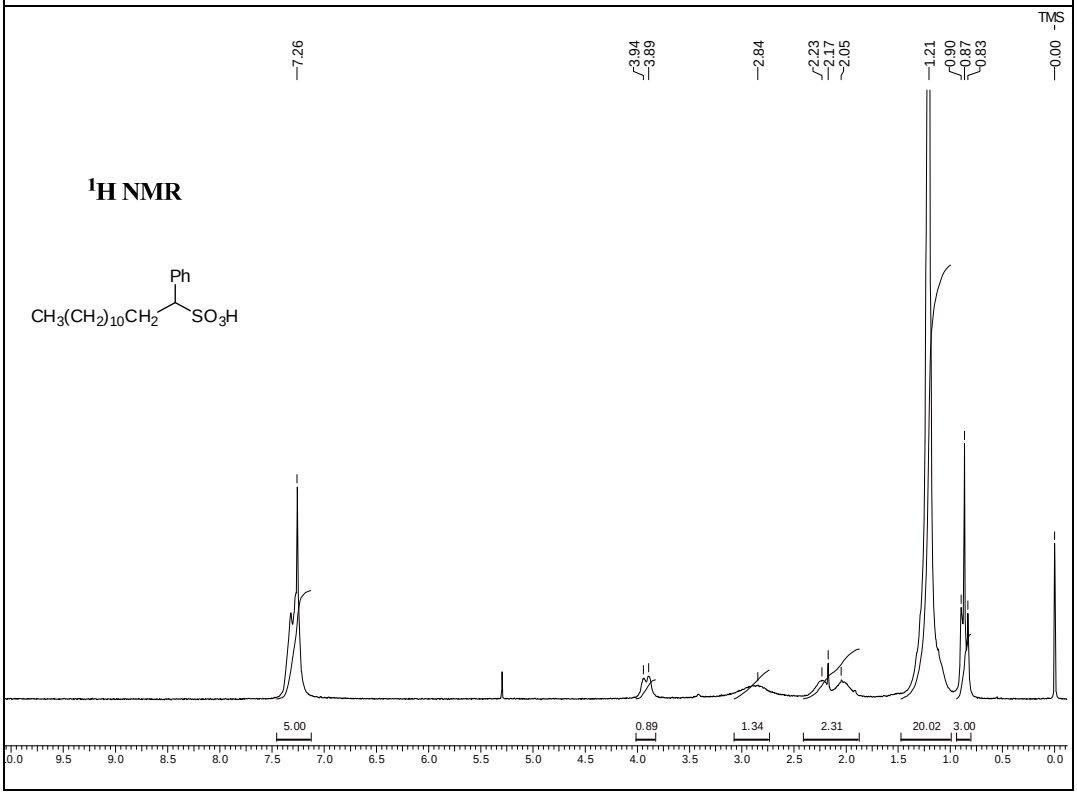



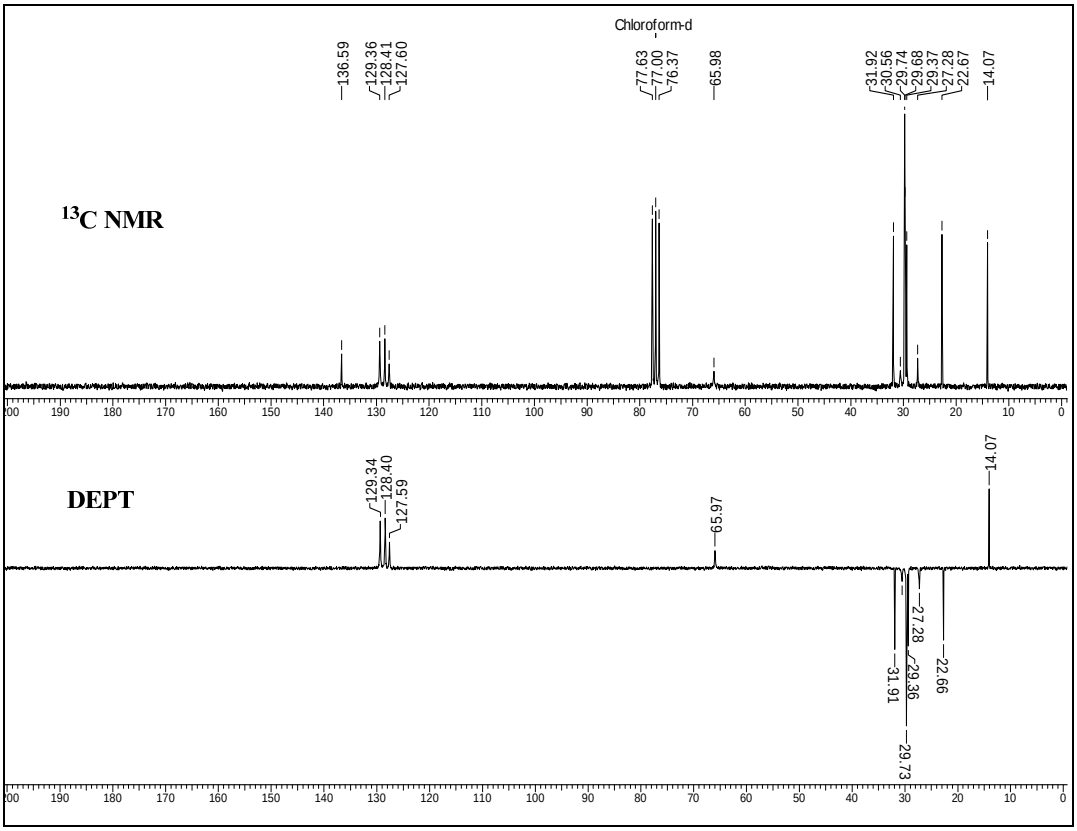
NMR spectra of *i*-propyl ester of **28** ($CDCl_3$)



NMR spectra of **28** ($CDCl_3$)



*Chapter 3*

# Preparation and application of new chiral organocatalysts for the direct aldol reaction

## Introduction

Since the discovery of L-proline catalyzed intermolecular aldol reaction,[1] asymmetric organocatalysis has received growing attention.[2] As catalysts, free α-amino acids[1,3] and easily accessible chiral amines[4] have several limitations.[5] Therefore their simple modifications have become an expedient choice.[6] The development of an efficient chiral organocatalysts is a difficult task and significant efforts are being directed to it. These involve design, synthesis and evaluation of novel organocatalysts. Methods used for their design are based on computer aided techniques,[7] detailed study of enzymes[8] (biologically efficient catalysts) or modifications of already reported organocatalysts. The required organic molecules are then synthesized through the tedious synthetic methods. This makes these custom-made catalysts more valuable than the starting chiral compound (eg. L-proline) which otherwise also acts as organocatalyst.

Recently it has been revealed that the addition of a proper additive increases the efficiency of a known organocatalyst both in the terms of yield as well as selectivity.[9] This method is therefore more beneficial and makes available libraries of catalysts systems simply by changing the additive of choice.[10]

We decided to study a few of these aspects in details in order to develop a simple and efficient organocatalytic system for this reaction. Our emphasis was to understand the effect of simplest possible modifications in the structures of original organocatalysts on the direct aldol reaction, in order to get guidelines for the design of new nearly ideal organocatalyst. Also the requirements of the nature of amine and additive are systematically studied. This study is complied in the following three sections.

**Section 3A:** Preparation of some new pyrrolidine derived chiral organocatalysts.

**Section 3B:** Systematic evaluation of pyrrolidine derivatives as organocatalysts.

**Section 3C:** Some chiral addition complexes for the direct aldol reaction.

# Section 3A

## Preparation of some new pyrrolidine derived chiral organocatalysts

### Introduction

The structural requirements for an amine to act as efficient enamine catalyst indicates that not for all but for less basic nucleophilic amines, Lewis or Brønsted acidic additives are needed to assist the enamine formation.[9] Reactivity of enamines follows the order: pyrrolidine-derived > acyclic amine-derived > piperidine-derived enamines.[9] Therefore a vast majority of successful enamine catalysts are developed based on the pyrrolidine skeleton. The generated enamine reacts readily with reactive electrophiles and controls its approach through the steric interactions.

However for relatively unreactive electrophiles such as aldehydes, ketones and imines, additional assistance for catalysis is required which is generally provided by suitably positioned hydrogen bond donors of the catalyst.[11b–c] This results in the simultaneous activation of both nucleophiles and electrophiles. If these hydrogen bonding sites are sufficiently acidic as the carboxylic acid groups of amino acids then they also assist the formation of enamine. Thus for enantioselective enamine catalysis, the presence of a properly positioned steric bulk or a substituent carrying at least one hydrogen bonding site are essential (Figure 1).[12] The multiple hydrogen bonding sites are also reported to have a beneficial effect on the selectivity of the direct aldol reaction. As a result various bifunctional catalysts have been continuously developed for this reaction.[13,14]

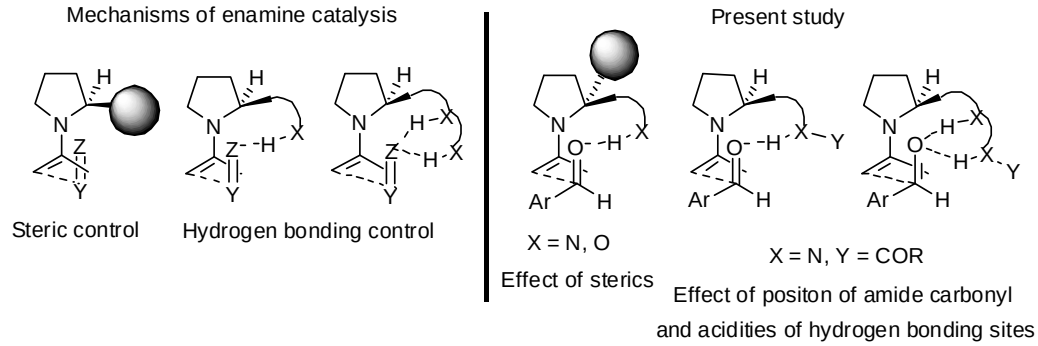



**Figure 1.** Transition states of enamine catalysis.

Most of the successful enamine catalysts reported for the direct aldol-type reaction are the amide derivatives of L-proline or diamines with or without additional hydrogen bonding sites[14] or are the derivatives of 4-hydroxy L-proline.[15] Recently

catalysts with modifications at both of these sites that is, hydroxy and carboxylate group of 4-hydroxy L-proline are also reported.[16] Strategies used for their modification are mainly focused on the variations in electronic and or steric properties of the groups in the side chains.

Thus the rational design of efficient enamine catalysts is still receiving considerable attention.[2] Despite of the recently reported theoretical calculations on the comparison of various organocatalysts for direct aldol reaction,[17] there is no systematic and practical screening of simple chiral pyrrolidine derivatives as the catalysts. Such information could explain the effect of sterics at the chiral center, effect of position of carbonyl group and the effect of acidities of hydrogen bonding sites on the outcome of this reaction. It will be useful in the development of new organocatalysts for this and related reactions.

## Results and discussion

A series of the pyrrolidine derived organocatalysts with variations in the α-sterics, position of amide carbonyl, number and acidities of the hydrogen bonding sites etc. were designed and prepared.

### 1. Pyrrolidine derivatives with and without α,α-disubstituents

There are only few reports of α,α-disubstituted pyrrolidines as the catalysts for this reaction eg. α-methyl-L-proline, thiazolidinium derivatives etc.[3a] It is reported that the reaction catalyzed by α-methyl-L-proline (**1b**) gives low yield and enantioselectivity of the aldol product than that catalyzed by L-proline.[3a]

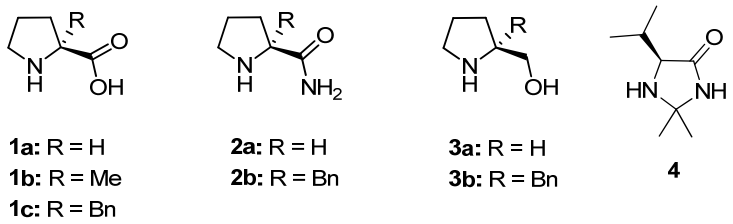
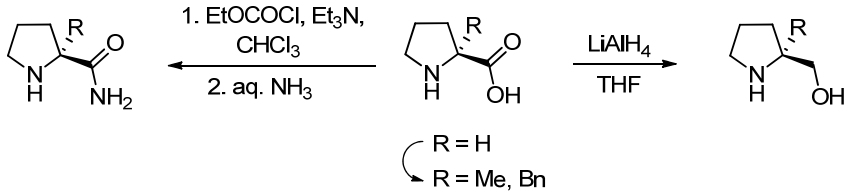



**Figure 2.** Pyrrolidine derivatives selected to study the effect of α-sterics.

To further study the effect of sterics of the α-substituents of L-proline derivatives on the outcome of this reaction, we replaced methyl group in **1b** by benzyl (**1c**).[18a] Also a few easily accessible L-proline derivatives with and without substituents at the chiral carbon (**2a**–**3b**)[18b–d] were prepared following the literature reports (Scheme 1).



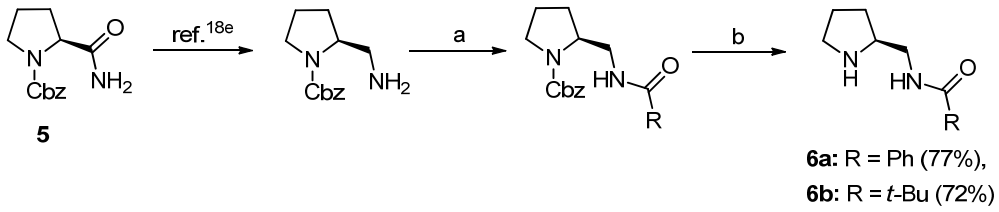

**Scheme 1.** General outline for the preparation of organocatalysts (**1a**–**3b**).

To check the catalytic behavior of imidazolidin-4-ones, generally observed as intermediates in the organocatalytic reactions catalyzed by L-proline derived amides,[20a] an imidazolidin-4-one derivative (**4**) was prepared in good yield by the acid catalyzed condensation of L-valinamide[18g] with acetone.

### 2. Pyrrolidine derivatives to study the effect of position of carbonyl group

The majority of enamine organocatalysts containing amide functionality are derived from L-proline carboxylate due to the ease of their synthesis eg. **7a**, **7b** and

**8**[19] (Figure 3). For this reason prolinamide organocatalysts are of contemporary interest. We were curious to know the behavior of amides obtained from chiral pyrrolidine methylamine and achiral acids. One such sulfonamide derived from *N*-Cbz-L-prolinamide **5** has been used for Michael reaction.[18e] Amides of this type (**6a** and **6b**) were prepared therefore from (*S*)-benzyl 2-(aminomethyl)pyrrolidine-1-carboxylate, obtained by the reduction of *N*-Cbz-L-prolinamide (**5**).




**Scheme 2.** (a) RCOCl, pyridine, $CHCl_3$, 0 $^oC$, 1 h; (b) $H_2$, Pd/C, MeOH.

Comparision of the catalytic activity of these catalysts with the analogous catalysts (**7**–**8**)[19] will provide information about the effect of position of amide carbonyl.

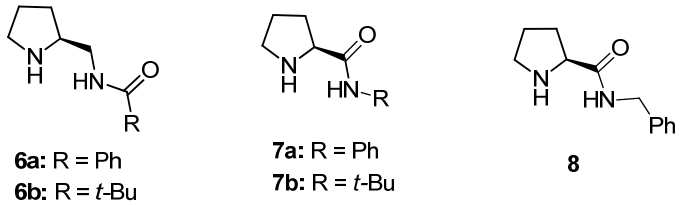



**Figure 3.** Chiral amides used to study the effect of position of carbonyl group.

### 3. Prolinamides with variations in the acidities of hydrogen bonding sites

It is generally accepted that the strength of hydrogen bonding interactions increases with the acidity of involved heteroatom–hydrogen bond. Unlike other pyrrolidine derivatives, N–H of L-proline carboxamides are weak hydrogen bond donors and in the majority of cases extra hydrogen bonding,[14] addition of water or external acids[20b-c] are employed for getting better selectivities. However the effect of acidity of different hydrogen bond donors on their catalytic activity and selectivity in this reaction has not been investigated in details.[21] Therefore the imides **9a** and **9b**[18f] were prepared to study the effect of increased acidity of carboxamide N–H and urea derivatives **10a** and **10b** were selected to evaluate the effect of additional hydrogen bonding site and its acidity.

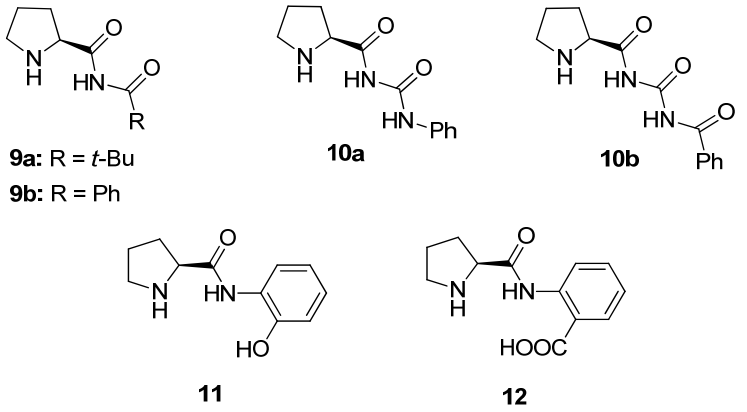
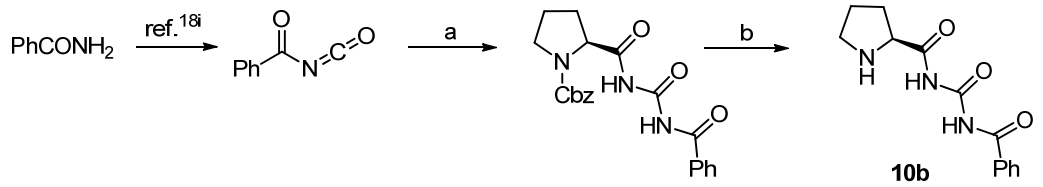



**Figure 4.** Organocatalysts with variations in the acidities of hydrogen bond donors.

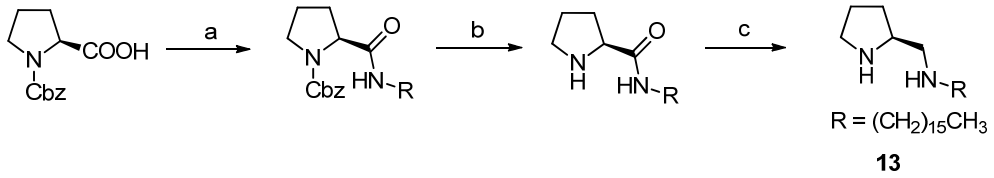
The amide derivatives **11**[19b] and **12** would also provide the information about more acidity of additional hydrogen bonding site. Out of the required organocatalysts, pyrrolidine derived diacyl urea (**10b**) was prepared from *N*-Cbz-L-prolinamide as described for **10a** in the Chapter **2** (compound no. **18**).




**Scheme 3.** (a) **5**, toluene, reflux, 3 h, 89%; (b) $H_2$, Pd/C, EtOH, 87%.

## 4. Diamine with long alkyl chain

Barbas et al. have used a TFA salt of pyrrolidine derived secondary-tertiary diamine as an efficient catalyst for the direct aldol reaction in water.[20b] Though the exclusive formation of monotrifluoroaceate salt of the tertiary amine is impossible, it has been reported as the reason for the observed high yield and selectivity. Also their catalyst contains a tertiary amine group bearing two long alkyl chains. This type of simple catalytic entity with the required free pyrrolidine can be exclusively obtained by using a pyrrolidine derived secondary diamine bearing a long alkyl chain and a lipophilic acid by taking the advantage of their lipophile-lipophile interactions. Accordingly a chiral diamine (**13**) possessing pyrrolidine methylamine unit and a *n*-hexadecyl group was prepared from L-proline following the reaction sequence described in the Scheme 4 in 59% overall yield.




**13**

**Scheme 4.** (a) (i) EtOCOCl, $Et_3N$, $CHCl_3$, 0 $^oC$, 0.5 h; (ii) $CH_3(CH_2)_{15}NH_2$, rt, 15 h, 79%; (b) $H_2$, Pd/C, EtOH, 92%; (c) $BH_3$.DMS, THF, reflux, 6 h, 82%.

## Section 3B

## Systematic evaluation of pyrrolidine derivatives as organocatalysts

### Introduction

Although the mechanism of proline catalyzed direct aldol reaction is not fully understood, the one involving single molecule of proline is well supported by theoretical and kinetic studies (Scheme 6).[22a] It has been revealed that the rate of proline mediated direct aldol reaction depends on the concentration of both the donor ketone and electrophilic aldehyde.[22b] Thus the rate determining step could not be enamine formation but is the C–C bond formation (formation of product iminium species) and was supported from the observed kinetics and deuterium isotope effects. However from the theoretical calculation, Boyd et al.[17a] have reported that the initial reaction between acetone and pyrrolidine nitrogen is the rate determining. Thus it presents a mechanistic ambiguity.

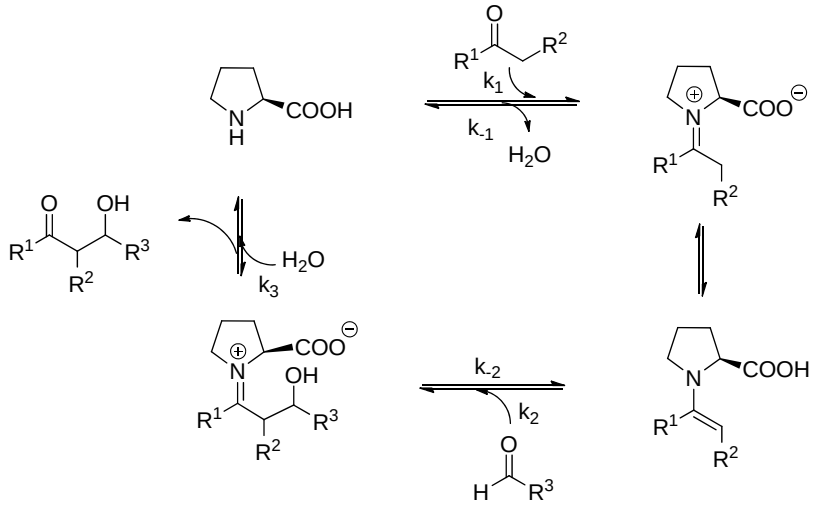
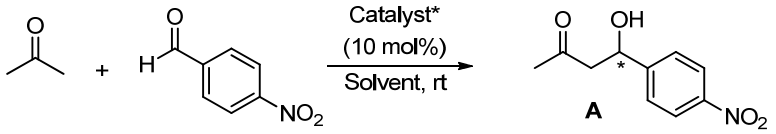



**Figure 5:** Proposed mechanism for the proline catalyzed direct aldol reaction.[21b]

Generally the oxazolidinone is observed as a side product in the proline catalyzed direct aldol reactions. It can be overcome by using aqueous solvents or by employing derivatives of proline such as amides etc. as the catalysts. Based on the above mechanism, behavior of nearly all enamine organocatalyts is explained as the transient source of chiral enamine with minor modifications to explain the effect of extra hydrogen bonding and solvent etc. But the effect of these and other factors on the rate determining step or the stereochemical outcome is not explained in any case.

## Results and discussion

Our study started with a careful survey of a large set of experiments carried out by us and other groups. A series of pyrrolidine derivatives were evaluated as the catalysts for direct aldol reaction in organic and aqueous media. For easy comparison, acetone and *p*-nitrobenzaldehyde were selected as the preliminary reactants.




**Scheme 5:** Representative example of direct aldol reaction.

It was observed that the rate as well as enantioselectivity decreases considerably (Table 1, entries 1, 3 and 4) with an increase in the steric hindrance at the α-position of L-proline derivatives (**1c** > **1b** > **1a**). However under neat conditions (1 M solution of aldehyde in acetone), **1c** could not catalyze the reaction while **1a** gave moderate yield and enantioselectivity (Table 1, entries 5 vs. 2).

**Table 1.** Screening of the pyrrolidine derivatives to study the effect of α-sterics.

| No | Catalyst | Solvent | Time (h) | Yield (%)[a] | *ee* (%)[b] |
|---|---|---|---|---|---|
| 1[c] | **1a** | DMSO | 2 | 68 | 76 |
| 2[c] | **1a** | -- | 24 | 60 | 67 |
| 3[c] | **1b** | DMSO | 2 | 26 | 61 |
| 4 | **1c** | DMSO | 72 | 57 | 36 |
| 5 | **1c** | -- | 96 | Trace | -- |
| 6 | **1c** | aq. DMF[d] | 48 | Trace | -- |
| 7[e] | **2a** | -- | 24 | 81 | 33 |
| 8 | **2b** | -- | 72 | Trace | -- |
| 9[f] | **3a** | -- | 15 | 89[g] | 36[h] |
| 10[f] | **3b** | -- | 18 | No reaction | -- |

[a] Isolated yield of aldol product (**A**). [b] Of '*R*' enantiomer determined by chiral HPLC analysis. [c] Reported (*Ref. 3a*) using 20 mol% of catalyst. [d] 3 vol.% water in DMF. [e] Reported (*Ref. 19a*) using 20 mol% of catalyst. [f] Cyclopentanone and benzaldehyde were used as reactants. [g] *syn*/*anti* (80:20). [h] Of major (*syn*) diastereomer.

To rule out the possibility of oxazolidinone formation as the side reaction,[21c] aqueous DMF was examined as the solvent. However similar results were realized (Table 1, entry 6). Therefore for rest of the study, neat reaction conditions were employed. The catalytic reactivity pattern of prolinamides **2a** and **2b** was similar to L-proline derivatives **1a**–**1c**. Further evidence for the detrimental effect of α-substituent was provided by the L-proline derivatives **3a** and **3b**. In this case acetone was replaced with cyclopentanone to rule out the possibility of imidazolidinone formation from the reaction with amino alcohol. However similar results were realized. The reaction of cyclopentanone with benzaldehyde was catalyzed by **3a** but not by **3b** (Table 1, entries 9 and 10). We also changed the aldehyde to more reactive *p*-nitrobenzaldehyde, but it did not make any difference.

The present study indicated that in proline derivatives, substitution of the α-hydrogen by bulky group adversely affects the outcome of direct aldol reaction. It retards the initial reaction of pyrrolidine nitrogen with acetone as its bulkiness increases from methyl to benzyl. With catalysts having large α-sterics (benzyl group), the reactivity vanishes completely under neat conditions. These results are in accordance with the theoretical calculations by Boyd et al.[17a] which indicates that the initial reaction between proline and acetone requires substantial energy and would inhibit further progress of the reaction. It was also indicated by Maruoka et al. as one of the reasons for the increased reactivity of their bifunctional binaphthyl based secondary amine catalyst.[13a] In this case, the absence of substituent α- to the secondary amine group decreases steric repulsion in the enamine intermediate. Though the rate determining step of proline catalyzed aldol reaction is the C–C bond formation,[21b] our results indicate that with sterically hindered catalysts the enamine formation is sufficiently slowed down and thus it becomes rate determining step. Thus the rate determining step shifts from C–C bond formation to enamine formation.

We then studied the effect of position of amide carbonyl of pyrrolidine derivatives on the outcome of direct aldol reaction under neat conditions. Amides **6a** and **6b** were selected as catalysts and the results were compared with those reported for analogous catalysts; **7a**, **7b** and **8**[22a] (Figure 3). It was observed that both the rate as well as enantioselectivity decreased considerably (Table 2, entry 3 vs. 1 and entry 4 vs. 2) as the carbonyl group goes away from the pyrrolidine ring. It can be thus concluded that for pyrrolidine derived amide organocatalysts, the carbonyl part should be from L-proline.

**Table 2.** Pyrrolidine derivatives with different positions of the amide carbonyl.[a]

| No | Catalyst | Time (h) | Yield (%)[b] | *ee* (%)[c] |
|---|---|---|---|---|
| 1 | **6a** | 60 | 65 | 10 |
| 2 | **6b** | 60 | 68 | 5 |
| 3[d] | **7a** | 24 | 88 | 37 |
| 4[d] | **7b** | 24 | 55 | 15 |
| 5[d] | **8** | 24 | 82 | 21 |

[a] All reactions under neat conditions at 1 M concentration of aldehyde in acetone. [b] Isolated yield of aldol product (**A**). [c] Of '*R*' enantiomer determined by chiral HPLC analysis. [d] Reported (*Ref. 19a*) using 20 mol% of catalyst.

We have then studied the effect of increased acidity of hydrogen bonding site on the catalytic activity. The catalysts **9a**–**10b** (Figure 4) were used in the direct aldol reaction and the results were compared with those of analogous catalysts **7a** and **7b**.[19a] It was observed that with increasing acidity of amide proton (**7a** vs. **9a**), the rate as well as enantioselectivity decreased considerably (Table 3, entry 3 vs. 1).

**Table 3.** Comparison of catalysts with varying acidities of hydrogen bonding sites.

| No | Catalyst | Solvent | Time (h) | Yield (%)[a] | *ee* (%)[b] (*conf.*) |
|---|---|---|---|---|---|
| 1[c] | **7a** | -- | 24 | 55 | 15 (*R*) |
| 2[c] | **7b** | -- | 24 | 88 | 37 (*R*) |
| 3 | **9a** | -- | 36 | 59 | < 5 (*R*) |
| 4 | **9b** | -- | 120 | No reaction | -- |
| 5 | **10a** | -- | 24 | 89 | 31 (*R*) |
| 6 | **10a** | aq.DMF[d] | 72 | 79 | 39 (*R*) |
| 7 | **10b** | -- | 48 | No reaction | -- |
| 8 | **10b** | aq.DMF[d] | 48 | No reaction | -- |
| 9[e] | **11** | -- | 48 | 21 | 62 (*R*) |
| 10 | **12** | -- | 48 | 48 | 52 (*S*) |
| 11 | **12** | aq.DMF[d] | 28 | 53 | 32 (*S*) |

[a] Isolated yield of aldol product (**A**). [b] Determined by chiral HPLC analysis. [c] Reported (*Ref. 19a*) using 20 mol% of catalyst. [d] 3 vol.% water in DMF. [e] Reported (*Ref. 19b*) using 20 mol% of catalyst.

Similarly the imide **9b** does not catalyze the reaction while the amide **7b** gave good yield (Table 3, entry 4 vs. 2). This finding is contrary to the common understanding that the more acidic N–H bond in the imides could provide better catalytic efficiency than the corresponding amides. This may be due to the complete delocalization of the imide proton forming a stable six-membered intramolecular hydrogen bonding with carbonyl groups. Such arrangement would lead to loss of the catalytic activity. However good yield of the aldol product obtained in the reaction catalyzed by monoacyl urea **10a** (Table 3, entry 5 and 6) rules out such possibility.

Unexpectedly, the corresponding diacyl derivative **10b** did not catalyze the reaction (Table 3, entry 7 and 8). In contrast to the L-proline derived sulfonamide[18f] and N-sulfinyl prolinamides,[18h] increased acidity of the N–H of carboxamides and urea derivatives had an adverse effect on either the yield or selectivity. These results support that the effect of hydrogen bond donors in the organocatalytic reactions is dependent on the substrates and the reaction conditions as observed by Yan et al.[21]

Few of these organocatalysts were also used employing aqueous DMF as the solvent, which lead to only marginal improvement in the enantioselectivity (Table 3, entry 6). With the catalysts **11** and **12** possessing more acidic proton for hydrogen bonding, the results did not provide any convincing information. It was notable that as the size of the transition state increases from 7 to 8 membered ring, the absolute configuration of the product changes from '*R*' to '*S*'.

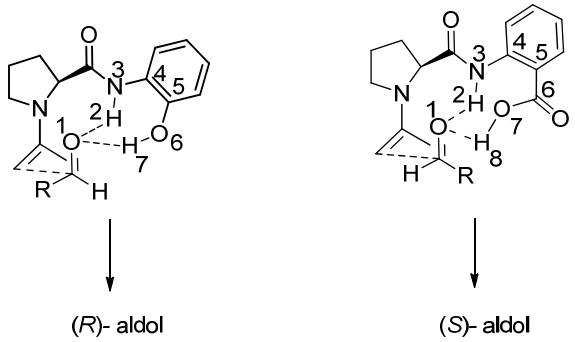



**Figure 6.** Stereochemical outcome and the ring size of the transition state.

Mono salt of Diamine **13** with a lipophilic sulfonic acid (4-dodecylbenzene sulfonic acid) was used as the catalyst. Under neat conditions using bottle grade acetone gave the aldol product in good enantioselectivity but moderate yield. It was thought that the low yield may be due to the presence of large excess of acetone, disturbing the micelles formed. Therefore the solvent was changed to brine. However

no improvement in the yield was observed. Contrarily, it reduced the enantioselectivity (Table 4, entry 2). To check whether the high solubility of acetone in brine is the reason for low yield, it was replaced with isobutyraldehyde. But it resulted in both decrease in the yield as well as selectivity. The reaction under the reverse micellar conditions using cyclohexane and 3 equivalents of water as additive resulted in only trace amount of product.

Formation of a thick emulsion from the reaction in water indicates the catalyst is DBSA salt formed through the lipophile-lipophile interactions (Figure 7). To confirm that the catalyst is a salt with free pyrrolidine NH and not just an adduct, equimolar amount of benzoic acid was added as an additive. It was observed that due to the formation of disalt, the catalyst gets completely quenched (Table 4, entry 5). However in the presence of water, a partial dissociation of benzoic acid salt provides the trace amount of required product (Table 4, entry 6).

**Table 4.** Diamine salt (**13**.DBSA) catalyzed direct aldol reaction.

| No | Solvent | Time (h) | Yield (%)[a] | *ee* (%)[b] |
|---|---|---|---|---|
| 1 | -- | 60 | 59 | 81 |
| 2 | Brine | 48 | 55 | 47 |
| 3[c] | $H_2O$ | 96 | 54 | 23 |
| 4[c] | Cyclohexane[d] | 48 | Trace | -- |
| 5[c,e] | -- | 48 | No reaction | |
| 6[c,e] | $H_2O$ | 48 | Trace | -- |

[a] Isolated yield of aldol product (**A**), [b] Of (*R*)-enantiomer determined by chiral HPLC analysis. [c] Isobutyraldehyde was used as the donor. [d] 3 equiv. of water as additive. [e] Benzoic acid (10 mol%) as the additive.

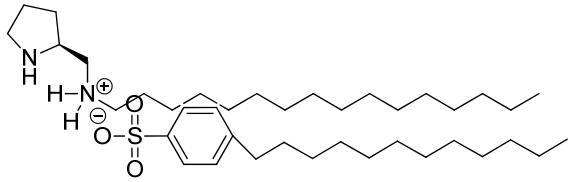


**Figure 7:** Structure of **13**.DBSA.

# Section 3C

## Some chiral addition complexes for the direct aldol reaction

### Introduction

As custom-made catalyst becomes more valuable than the chiral starting material, it is beneficial to improve the efficiencies of the known organocatalysts by addition of inexpensive additives.[23] In this direction it has been shown that the addition of substoichiometric amounts of water improves the outcome of organocatalytic reactions, especially L-proline catalyzed direct aldol reaction.[23a] The 3 vol.% water in DMF was found to be the best solvent for stoichiometric reaction with acceptable rate. Similarly the use of camphorsulfonic acid as additive in the L-proline catalyzed direct aldol reaction in aqueous media, enhances its yield as well as selectivity.[24] Shan et al. have shown that the addition of a catalytic amounts (1 mol%) of diols, BINOL (chiral or racemic) also gives good yield and selectivity in DMSO at 0 $^{o}$C.[25] The host-guest complexes of L-proline with diaryl thiourea bearing electron withdrawing trifluorormethyl groups developed by Demir et al., gives good results in the direct aldol even at room temperature.[26] Recently it has been shown that guanidine salts also increases diastereo- and enantioselectivity of the L-proline catalyzed aldol reaction under neat conditions at 0 $^{o}$C. [27]

In all of these studies, chiral amines particularly L-proline is used as the source of enamine. But the reactions of achiral enamines with aldehydes activated through the face selective activation are not studied. The role played by these additives in the reaction mechanism has not yet been clearly understood. It is likely that a network of hydrogen bonding interactions between the carboxylate group of L-proline, the corresponding additive and the substrates is formed in the transition state at least in less polar solvents.

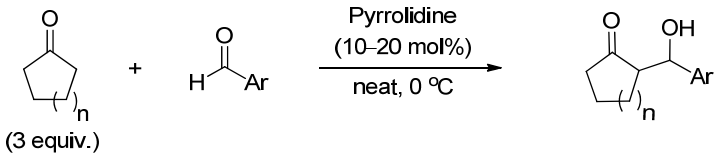
In the present study, the requirements for such type of addition complexes are systematically studied.

## Results and discussion

To understand the exact role of additives in the transition state, we have first selected the reaction of achiral enamine with chiral Brønsted acid activated aldehyde.[28] Pyrrolidine was selected as the simplest source of achiral enamine. Its use as catalyst in the direct aldol reaction of various ketones and α,α-dialkyl aldehydes with aromatic aldehydes is well documented.[29] A high concentration of pyrrolidine (20–40 mol%) is generally used and the formation of side products is reduced by using additives like *p*-nitrophenol[29b] and catechol.[29d] Though water seemed to be the best alternative both as additive and solvent from environmental point of view, moderate diastereoselectivities were reported in it.[29e] During the standardization of control experiments using 10 mol% of pyrrolidine and without drying the reactants, we realized good yields and good to excellent diastereoslectivities in the reactions of cyclic ketones with aromatic aldehydes (both bearing electron withdrawing and electron donating groups) at 0 $^{o}$C under neat conditions (Table 5). However selectivity dramatically decreased along with the formation of small amount of side products, when temperature was raised to 25 $^{o}$C (Table 5, entry 3). For aromatic aldehydes with electron withdrawing groups, 10 mol% of pyrrolidine was found sufficient while for others, 20 mol% of pyrrolidine was required to catalyze the reaction. However substantial amount of side products (up to 30%) were observed in the corresponding reactions of acetone even at 0 $^{o}$C.

As pyrrolidine is a symmetric molecule and does not contain any sterics, the possible reason for observed diastereoselectivity seems to be the strong association between enamine and dissociated pyrrolidine at 0 $^{o}$C.[30]

**Table 5.** Pyrrolidine catalyzed direct aldol reaction of cyclic ketones.




| No. | n | Ar | Time (h) | Yield (%)[a] | dr (*syn*/*anti*)[b] |
|---|---|---|---|---|---|
| 1 | 1 | 4-$NO_2$Ph | 2 | 86 | 72:28 |
| 2 | 2 | 4-$NO_2$Ph | 5 | 91 | 11:89 |
| 3[c] | 2 | 4-$NO_2$Ph | 1 | 75 | 46:54 |
| 4 | 1 | 4-ClPh | 3 | 90 | 94:6 |
| 5 | 2 | 4-ClPh | 6 | 82 | 29:71 |
| 6 | 1 | 4-$CH_3$Ph | 3 | 90 | 98:2 |
| 7 | 1 | 4-$OCH_3$Ph | 3 | 88 | 63:37 |
| 8 | 1 | 2-$NO_2$Ph | 2 | 88 | 98:2 |
| 9 | 1 | 2-ClPh | 2 | 89 | 94:6 |
| 10 | 1 | 2-$CH_3$Ph | 2 | 92 | 83:17 |
| 11 | 1 | 2-$OCH_3$Ph | 2 | 90 | 99:1 |
| 12 | 1 | Ph | 3 | 90 | 79:21 |
| 13 | 1 | 1-Napth | 2 | 91 | 99:1 |
| 14 | 1 | 2-Napth | 2 | 87 | 79:21 |

[a] Isolated yield. [b] Determined by HPLC analysis. [c] Reaction was done at rt.

Encouraged by these results, we tried the reaction with chiral pyrrolidine derivative (L-prolinol). A decreased reaction rate with conservation of diastereoselectivity and moderate enantioselectivity was realized at 25 $^{o}$C. Low enantioselectivity is due to the less stereochemical differentiation of aldehyde by prolinol derived enamine.

Addition compounds of pyrrolidine with a range of chiral acid additives eg. (*R*)-mandelic acid, (*R*)-camphor-10-sulfonic acid, 2,3-dibenzoyl-D-tartaric acid, (*S*)-BINOL, *N*-methyl-L-proline[31a] and *N*,*N*'-((1*R*,2*R*)-cyclohexane-1,2-diyl)bis(4-methylbenzene-sulfonamide)[31b] were then examined as the possible catalysts in the reaction of acetone with *p*-nitrobenzaldehyde under neat conditions. In many cases good yields (> 90%) were obtained but the enantioselectivites were disappointing. From the rate of the reaction we concluded that these are being catalyzed by

pyrrolidine itself with little or no influence of acid additives. It is thus clear that an enantioselective aldol reaction must proceed through chiral enamine intermediate.

The combinations of few easily accessible chiral amines (**14** and **15**)[18b,32a] bearing a neutral amide functionality and achiral acids were evaluated as catalysts under neat conditions (Table 6). Addition of benzoic acid significantly enhanced the rate of prolinamide catalyzed reaction but the enantioselectivity decreased (Table 6, entry 2 vs. 1).

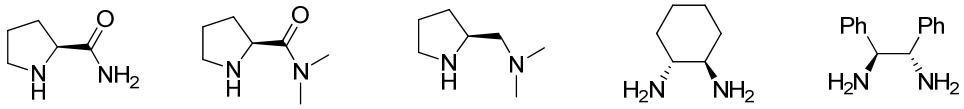



**Figure 8.** Chiral amines used to study the role of chiral enamine.

However stronger acid like PTSA formed stable salt with pyrrolidine N–H of **14** and thus eliminated its catalytic activity.[23e] Salicyclic acid bearing additional hydrogen bonding site decreased both the yield and selectivity. Selectivity further decreased with benzoic acid salt of **15**. Therefore monosalts of diamines (**16–18**) seemed as possible alternatives. Several sulfonate salts of diamines were reported to give high yields and enantioselectivities in the direct aldol reaction eg. monosalts of pyrrolidine derivatives,[10] disalts of 1,2-diphenylethane-1,2-diamine[33] etc. Selectivities get enhanced in protic solvents. When adducts of diamines **16**,[32b] **17** and **18**[32c] were used under neat conditions, good yields with low enantioselectivities were obtained (Table 6, entries 7–11). Selectivities did not improve even though acid additives bear additional hydrogen bonding sites (salicylic acid and BINOL).

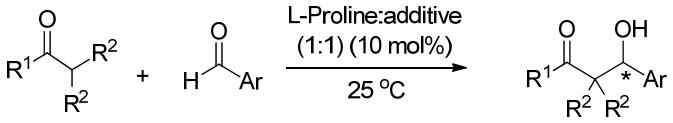
**Table 6.** Chiral amine:achiral acid complexes as catalysts.[a]


| No | Catalyst[b] | Time (h) | Yield (%)[c] | *ee* (%)[d] |
|---|---|---|---|---|
| 1[e] | **14** | 48 | 80 | 30 (*R*) |
| 2 | **14** + **A** | 1 | 86 | 17 (*R*) |
| 3 | **14** + **B** | 24 | No reaction | -- |
| 4 | **14** + **C** | 72 | 88 | < 5 |
| 5 | **15** + **A** | 2 | 81 | 6 (*R*) |
| 6 | **16** + **C** | 24 | 79 | < 5 |
| 7 | **16** + **D** | 36 | 55 | < 5 |
| 8 | **17** + **A** | 48 | 81 | 22 (*S*) |
| 9 | **17** + **B** | 15 | 90 | 33 (*S*) |
| 10 | **17** + **C** | 8 | 74 | 17 (*S*) |
| 11 | **18** + **C** | 48 | 49 | < 5 |

[a] Reactions were carried out in neat acetone at concentrations of 0.4 M solution. [b] 10 mol% chiral amine achiral acid combination (1:1). [c] Isolated yield. [d] Determined by chiral HPLC analysis. [e] Reported (*Ref. 22a*) using 20 mol% of catalyst. **A**: benzoic acid, **B**: PTSA, **C**: salicylic acid, **D**: (±)-BINOL.

Low enantioselectivities may be due to the weak interactions of acid additives in the transition state as compared to sulfonic acids. Thus the additives altered the rate and selectivities of chiral amine catalyzed reaction but a strong acid additive or protic medium is required to get high enantioselectivities. A simple and mild adduct could be obtained by changing the acid and amine partners involved in the complex formation. We anticipated that a chemical entity which selectively and strongly binds to the carboxylic acid group will interact with L-proline altering its solution properties and reactivity and could lead to improved selectivities. Based on this idea, various additives were examined and it was found that 8-hydroxy quinoline provides promising results (Table 7).

**Table 7.** Achiral additive and solvent screening for proline catalyzed aldol reaction.[a]



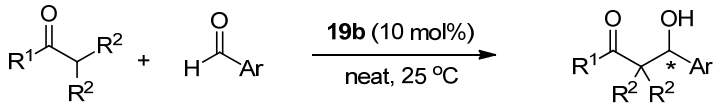

| No | $R^1$ | $R^2$ | Ar | Additive | Solvent | Time (h) | Yield (%)[b] | *ee* (%)[c] |
|---|---|---|---|---|---|---|---|---|
| 1[d] | $CH_3$ | H | 4-$NO_2$Ph | -- | -- | 24 | 60 | 67 |
| 2 | $CH_3$ | H | 4-$NO_2$Ph | **A** | -- | 18 | 74 | 57 |
| 3 | H | $CH_3$ | 4-$NO_2$Ph | **A** | $H_2O$ | 24 | NR | -- |
| 4 | $CH_3$ | H | 4-$NO_2$Ph | **B** | -- | 10 | 90 | 72 |
| 5 | $CH_3$ | H | 4-$NO_2$Ph | **B** | aq. DMF[e] | 24 | Trace | nd |
| 6 | H | $CH_3$ | 4-$NO_2$Ph | **B** | MeOH | 48 | 58 | 73 |
| 7 | H | $CH_3$ | 4-$NO_2$Ph | **B** | $CHCl_3$ | 48 | NR | -- |
| 8 | H | $CH_3$ | 4-$NO_2$Ph | **B** | THF | 48 | Trace | nd |
| 9 | $CH_3$ | H | Ph | **B** | $H_2O$ | 48 | NR | -- |
| 10 | $CH_3$ | H | Ph | **B** | DMSO | 36 | Mixture | -- |

[a] 10 equiv. of donor were used under neat conditions while in solvents 2 equiv. of donor were used. [b] Isolated yield. [c] Of '*R*' enantiomer determined by chiral HPLC analysis. [d] Reported (*Ref. 3a*) using 30 mol% of L-proline. [e] 3 vol.% water in DMF.
**A**: 2-amino phenol, **B**: 8-hydroxy quinoline.

L-Proline:2-amino phenol adduct (**19a**) increased the rate but enantioselectivity was lower than L-proline itself, while L-proline:8-hydroxy quinoline adduct (**19b**) increased both the rate as well as enantioselectivity (Table 7, entries 2 and 3 vs. 1). However it was found that the complex is only a weak adduct and requires large excess of acetone (10 equiv.) to form a clear solution. Therefore different solvents were examined. In water, the reaction did not take place because the adduct dissociates with L-proline dissolving in water and 8-hydroxy quinoline in the liquid reactants. In aqueous DMF, although a clear solution was obtained, the catalytic activity of complex was reduced. The same was the case with THF and methanol. In $CHCl_3$, this complex underwent facile dissociation with complete precipitation of L-proline. Though this complex is very soluble in DMSO (250 mg/ml), it provided mixture of products. Therefore neat conditions (using excess ketone) were used for the other substrates (Table 8). Good yields were achieved in the reactions of acetone

with various aldehydes. However 2-butanone and acetophenone did not react with 4-nitrobenzaldehyde (Table 8, entries 5 and 6). Less reactive isobutyraldehyde reacts very slowly with reactive 4-nitrobenzaldehyde but does not react with benzaldehyde (Table 8, entries 7 and 8) while hydroxyacetone gave mixture of products with 4-nitrobenzaldehyde (Table 8, entry 9).

**Table 8.** Direct aldol reaction catalyzed by **19b**.[a]

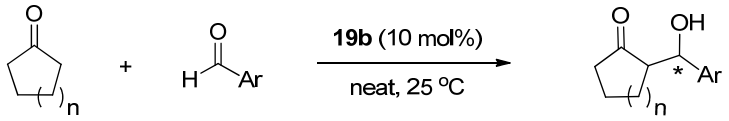



| No | $R^1$ | $R^2$ | Ar | Time (h) | Yield (%)[b] | *ee* (%)[c] |
|---|---|---|---|---|---|---|
| 1 | $CH_3$ | H | 2-$NO_2$Ph | 6 | 93 | 83 |
| 2 | $CH_3$ | H | 3-$NO_2$Ph | 7 | 95 | 54 |
| 3 | $CH_3$ | H | 4-ClPh | 15 | 83 | 68 |
| 4 | $CH_3$ | H | Ph | 48 | 79 | 63 |
| 5 | Et | H | 4-$NO_2$Ph | 48 | No reaction | -- |
| 6 | Ph | H | 4-$NO_2$Ph | 15 | No reaction | -- |
| 7 | H | $CH_3$ | 4-$NO_2$Ph | 48 | <10 | nd |
| 8 | H | $CH_3$ | Ph | 48 | No reaction | -- |
| 9 | $CH_2OH$ | H | 4-$NO_2$Ph | 24 | Mixture | -- |

[a] 10 equiv. of donor were used. [b] Isolated yield. [c] Of '*R*' enantiomer determined by chiral HPLC analysis.

Reactions of a few cyclic ketones were then tried under the same conditions and was noted that they are needed in lesser amounts (< 2.5 equiv.) to form the clear solution. Hence the rate of reaction increased significantly. While earlier methods using addition complexes of L-proline employed large excess of cyclic ketones too.[24–27] Rate as well as enantioselectivity was found to be higher in the reactions of cyclopentanone than cyclohexanone (Table 9, entry 2 vs. 1). Aromatic aldehydes even with electron donating groups underwent reactions in shorter time giving good yields (Table 9). Though the diasteroselectivities were low in few cases, good enantioselectivities were observed in many cases. To check the effect of temperature, the reaction of cyclopentanone was repeated at 0 $^oC$. At this temperature the complex precipitated out and reaction became very sluggish.

**Table 9.** Diastereoselective direct aldol reaction catalyzed by **19b.**[a]




| No | n | Ar | Time (h) | Yield (%)[b] | dr (*syn*/*anti*)[c] | *ee* (%)[d] *syn* | *ee* (%)[d] *anti* |
|---|---|---|---|---|---|---|---|
| 1 | 1 | 4-$NO_2$Ph | 2 | 95 | 66:34 | 85 | 86 |
| 2 | 2 | 4-$NO_2$Ph | 4 | 93 | 19:81 | 22 | 77 |
| 3 | 1 | 4-ClPh | 8 | 94 | 81:19 | 68 | 86 |
| 4 | 1 | 4-$CH_3$Ph | 12 | 91 | 96:4 | 9 | 78 |
| 5 | 1 | 4-$OCH_3$Ph | 30 | 82 | 10:90 | 54 | 54 |
| 6 | 1 | 2-$NO_2$Ph | 4 | 94 | 61:39 | 58 | 94 |
| 7 | 1 | 2-ClPh | 3 | 92 | 57:43 | 13 | 88 |
| 8 | 1 | 2-$CH_3$Ph | 28 | 93 | 57:43 | 5 | 85 |
| 9 | 1 | 2-$OCH_3$Ph | 15 | 93 | 99:1 | 28 | -- |
| 10 | 1 | Ph | 15 | 93 | 70:30 | 27 | 47 |
| 11 | 1 | 1-Napth | 24 | 92 | 60:40 | 14 | 57 |
| 12 | 1 | 2-Napth | 13 | 94 | 83:17 | 18 | 71 |

[a] 2.5 equiv. of ketone was used when aldehyde is solid and 2.2 equiv. when aldehyde is liquid. [b] Isolated yield. [c] Determined by HPLC analysis. [d] Determined by chiral HPLC analysis.

To understand the bonding between L-proline and 8-hydroxy quinoline, crystallization of **19b** was tried under different conditions. Being a weak adduct, our all efforts were unsuccessful. We have observed the disappearance of phenolic OH in the $^1$H NMR of adduct and the reaction mixture indicating that there is an interaction between L-proline and 8-hydroxy quinoline. We have also carried out a series of powder XRD and DSC studies of this adduct to know the exact structure of the adduct. However it was found that the adduct is very weak one and behaves like a mixture of two components.

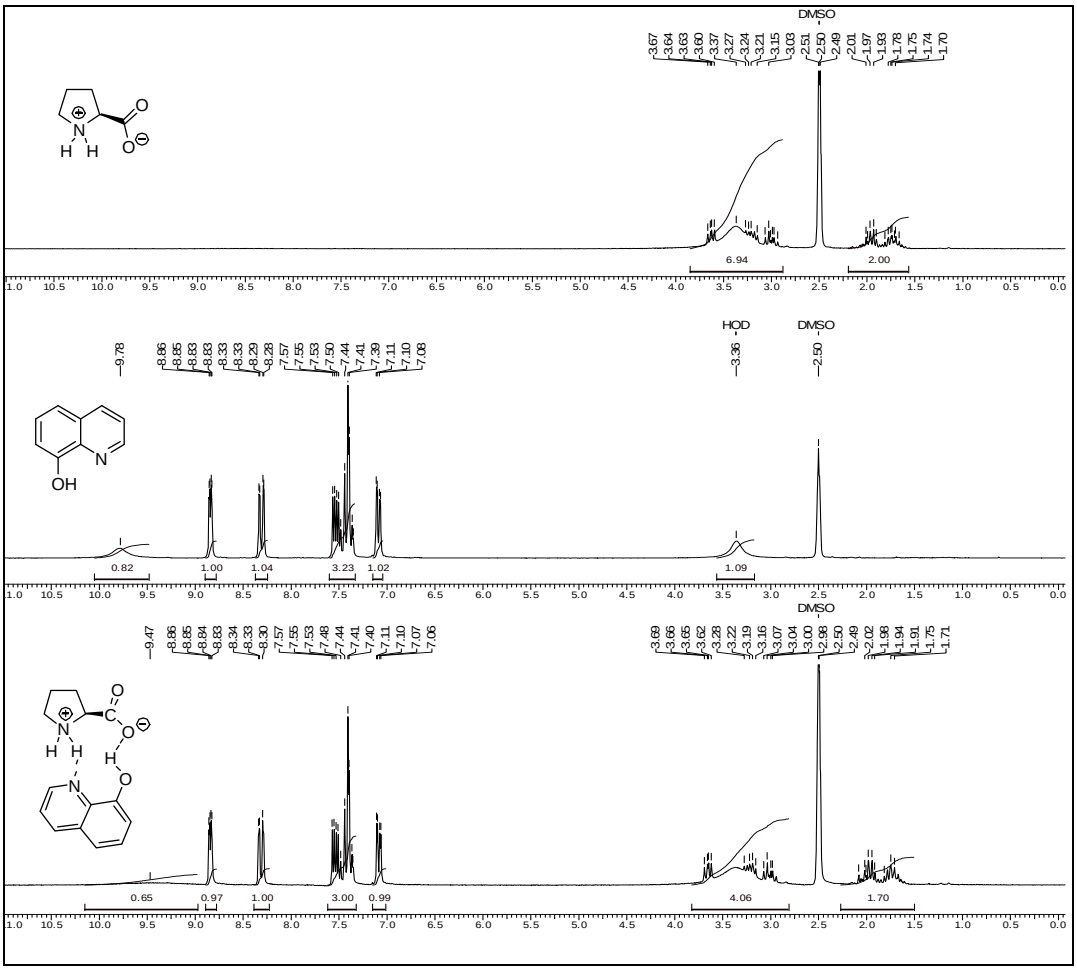



**Figure 9.** $^{1}$H NMR showing interaction among L-proline and 8-hydroxy quinoline.

A possible role of 8-hydroxy quinoline in the transition state is shown in the Figure 10. It seems that it increases the rate of enamine formation. Also due to its association with L-proline, it is more likely that aldehyde is getting activated by OH of 8-hydroxy quinoline and not by the carboxylic acid of L-proline.

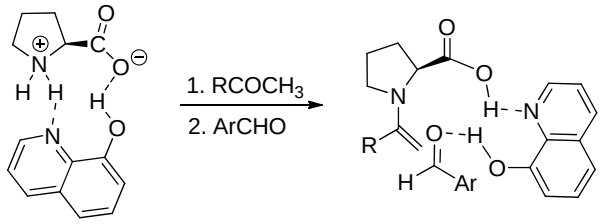



**Figure 10.** Possible interactions of L-proline:8-hydroxy quinoline in the reaction.

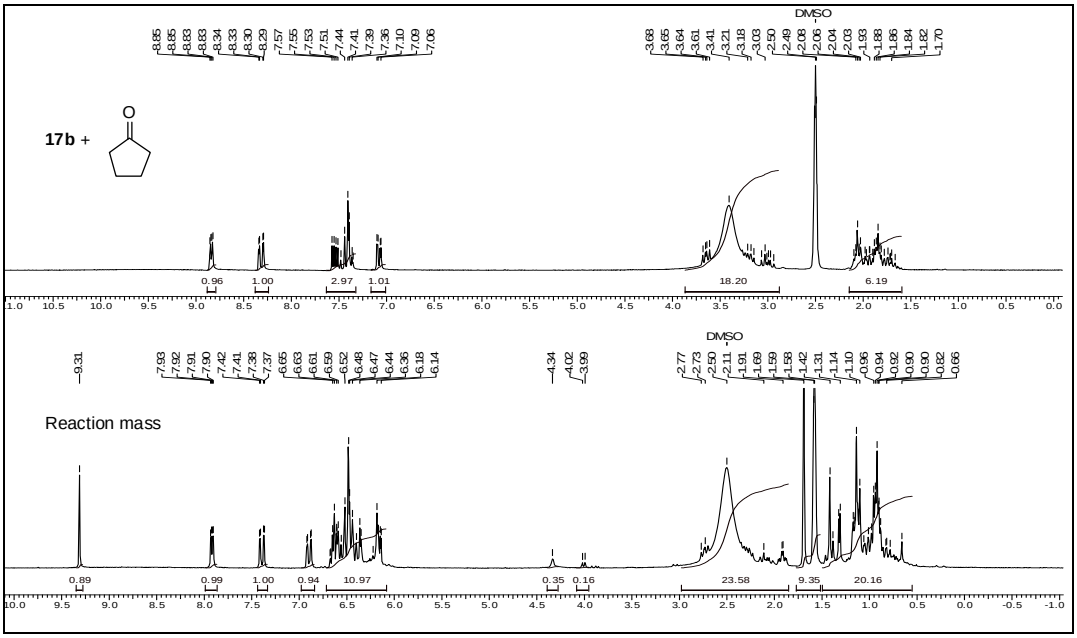



**Figure 11.** $^{1}$H NMR of the reaction mass.

## Conclusions

- A series of L-proline derived organocatalysts were prepared and examined as catalysts for the direct aldol reaction.
- The study revealed that the presence of α-substituent is detrimental for the enantioselective outcome.
- An enantio-switch was observed when the size of transition state increases from the 7 to 8 membered.
- A pyrrolidine-catalyzed highly diastereoselective direct aldol reaction was developed under solvent free conditions.
- An aldol reaction catalyzed by a series of chiral adducts of amines and acids showed that for the enantioselective outcome, chiral enamine and not the face selective activation of aldehyde is needed.
- It was shown that addition of aminophenols increases the catalytic activity of L-proline. Simple adduct of L-proline with 8-hydroxyquinoline was found to be a good catalyst.

# Experimental section

## General

All reagents and solvents were purified and dried according to the literature procedures.[34] Organocatalysts **1c**,[18a] **2a**,[18b] **2b**,[18c] **3a**,[18d] **9a**, **9b**,[18f] **14**,[18b,] **15**,[32a] **18**,[32c] *N*-Cbz-L-prolinamide,[18b] (*S*)-benzyl 2-(aminomethyl)pyrrolidine-1-carboxylate[18e] and L-valinamide[18g] were prepared according to the reported procedures. Diamine **16** was prepared by borane reduction of *N*-Cbz-**15** followed by hydrogenolysis and data has been found in good agreement with the reported one.[32b]

## 1. Preparation of organocatalysts

### 1.1. Preparation of (*R*)-(2-benzylpyrrolidin-2-yl)methanol (3b)

In an oven dried 25 mL side-arm flask equipped with reflux condenser, $LiAlH_4$ (230 mg, 5 mmol) was taken. It was cooled to 0 $^oC$ and freshly distilled anhydrous tetrahydrofuran (10 mL) was added under argon atmosphere. To the resulting suspension, (*R*)-2-benzylpyrrolidine-2-carboxylic acid[18a] (615 mg, 3 mmol) was added portion-wise through a solid addition funnel. The mixture was then heated to reflux. After completion of the reaction (5 h) as indicated by TLC, it was cooled to 0 $^oC$, diluted with THF (10 mL) and quenched by dropwise addition of 1 M NaOH (2 mL). The white solid was removed by filtration. The filtrate and tetrahydrofuran washings were combined together, dried over anhydrous $Na_2SO_4$ and concentrated to get crude product. The residue was purified by column chromatography using methanol/dichloromethane (1:9) as the eluent to obtain **3b**.

**Yield** : 530 mg (92%, white hygroscopic solid).

**Melting point** : 110–112 $^oC$.

**TLC data** : $R_f$ (10% methanol/dichloromethane): 0.3

**$[\alpha]_D^{25}$** : +20.47 (*c* 1.27, $CHCl_3$).

**IR (Nujol) v/cm$^{-1}$** : 3325 (NH and OH str.), 2956, 2871, 1604 (Ar C=C str.).

**$^1$H NMR ($CDCl_3$) ppm** : δ 1.40–1.86 (m, 4H, $(CH_2)_2$), 2.46 (br s, 1H, NH), 2.54 (br s, 1H, OH), 2.67–3.05 (m, 4H, $NCH_2$ and $OCH_2$), 3.2–3.34 (m, 2H, $CH_2Ph$), 7.14–7.36 (m, 5H, Ar H).

**$^{13}$C NMR ($CDCl_3$) ppm** : δ 25.6 ($CH_2$), 32.1 ($CH_2$), 42.3 ($CH_2$), 45.7 ($CH_2$), 65.5 ($CH_2$), 65.9 (C), 126.4, 128.2, 130.2, 137.6 (Ar C).

**HRMS (ESI$^+$) for** : $C_{12}H_{17}NO$.

**Calculated $[M+H]^+$** **:** 192.1383

**Found** **:** 192.1384 (100%).

### 1.2. Preparation of (*S*)-5-isopropyl-2,2-dimethylimidazolidin-4-one (4)

To a solution of free valinamide (348 mg, 3 mmol) (obtained by neutralization of its acetate salt[17g]) and PTSA (57 mg) in methanol ( 6 mL), acetone (1 mL, 15 mmol) was added and solution was heated to reflux. After completion of the reaction as indicated by TLC (18 h), reaction mixture was cooled to room tempareture. Solvents were removed on rotavapor and residue was purified by column chromatography using methanol/dichloromethane (5:95) as the eluent to get **4**.

**Yield** **:** 400 mg (85%, white solid)

**Melting point** **:** 88–89 $^oC$

**TLC data** **:** $R_f$ (10% methanol/dichloromethane): 0.3

**$[\alpha]_D^{25}$** **:** -21.64 (*c* 1.06, $CHCl_3$).

**IR (Nujol) v/cm$^{-1}$** **:** 3338, 3263, 2958, 2922, 1707 (NC=O str.), 1206, 1173.

**$^1$H NMR ($CDCl_3$) ppm** **:** δ 0.94 (d, *J* = 6.82 Hz, 3H, $CH_3$), 1.05 (d, *J* = 6.95 Hz, 3H, $CH_3$), 1.43 (d, *J* = 7.20 Hz, 6H, $2CH_3$), 1.88 (br s, 1H, NH), 2.05–2.30 (m, 1H, CH), 3.56 (d, *J* = 3.79 Hz, 1H, CH), 7.18 (br s, 1H, CONH).

**$^{13}$C NMR ($CDCl_3$) ppm** **:** δ 16.4 ($CH_3$), 19.5 ($CH_3$), 28.6 (CH), 29.5 ($CH_3$), 29.7 ($CH_3$), 63.9 (CH), 71.8 (C), 177.1 (CO).

**Analysis for** **:** $C_8H_{16}N_2O$

**Calculated (%)** **:** C, 61.50; H, 10.32; N, 17.93

**Found** **:** C, 61.22; H, 9.95; N, 17.43.

### 1.3. Preparation of (*S*)-*N*-(pyrrolidin-2-ylmethyl)benzamide (6a)

#### *1.3.1. (S)-Benzyl 2-(benzamidomethyl)pyrrolidine-1-carboxylate (N-Cbz-**6a**)*

A solution of (*S*)-benzyl 2-(aminomethyl)pyrrolidine-1-carboxylate (470 mg, 2 mmol) and pyridine (0.8 mL, 10 mmol) in anhydrous $CHCl_3$ (4 mL) was cooled to 0 $^oC$. Freshly distilled benzoyl chloride (0.27 mL, 2.2 mmol) was added dropwise and stirring continued. After completion of the reaction (30 min) as indicated by TLC, 1N HCl (10 mL) was added. Organic layer was separated and aqueous layer was extracted with dichloromethane (2 x 10 mL). Combined organic layer was successively washed with aqueous $NaHCO_3$ (10 mL) followed by brine (10 mL) and

dried over anhydrous $Na_2SO_4$. The solution was concentrated and the residue was purified by column chromatography using ethyl acetate/petroleum ether (1:3) as the eluent to obtain the required product.

**Yield** **:** 580 mg (86%, sticky mass)

**TLC data** **:** $R_f$ (30 % ethyl acetate/hexane): 0.4

**$[\alpha]_D^{25}$** **:** +27.87 (*c* 1.22, $CHCl_3$).

**IR (Nujol) v/cm$^{-1}$** **:** 3334, 3065, 2953, 2883, 1697 and 1659 (C=O str.), 1538 (Ar C=C str.), 1414, 1104.

**$^1$H NMR ($CDCl_3$) ppm** **:** δ 1.70–2.22 (m, 4H, $(CH_2)_2$), 3.31–3.72 (m, 4H, 2($CH_2$)), 4.09–4.34 (m,1H, CH), 5.05–5.32 (m, 2H, $OCH_2Ph$), 7.22–7.55 (m, 8H, Ar H), 7.85 (d, *J* = 6.32 Hz, 2H, Ar H), 8.25 (br s, 1H, CONH).

**$^{13}$C NMR ($CDCl_3$) ppm** **:** δ 23.9 ($CH_2$), 29.6 ($CH_2$), 46.6 ($CH_2$), 47.0 ($CH_2$), 56.9 (CH), 67.2 ($CH_2$), 127.0, 127.7, 128.0, 128.3, 128.4, 131.1, 134.0, 136.3 (Ar C), 157.2 (CO), 167.4 (CO).

**LCMS for** **:** $C_{20}H_{22}N_2O_3$.

**Calculated $[M+H]^+$** **:** 339.16

**Found** **:** 339.19 (30%).

*1.3.2.* (*S*)*-N-(Pyrrolidin-2-ylmethyl)benzamide (**6a**)*

To a solution of (*S*)-benzyl 2-(benzamidomethyl)pyrrolidine-1-carboxylate (545 mg, 1.6 mmol) in methanol (10 mL), 10% Pd/C (80 mg) was added and stirred vigorously under the balloon-pressure of hydrogen. After completion of the reaction (8 h) as indicated by TLC, argon was bubbled through the reaction mixture and it was filtered through a small pad of celite. Filtrate and washings were concentrated and the resulting crude product was purified by filtration column chromatography using methanol/dichloromethane (1:4) as the eluent to obtain **6a**.

**Yield** **:** 300 mg (92%, sticky mass)

**TLC data** **:** $R_f$ (methanol): 0.3

**$[\alpha]_D^{25}$** **:** +29.0 (*c* 1.0, $CHCl_3$)

**IR (Nujol) v/cm$^{-1}$** **:** 3303, 3060, 2958, 2871, 1639 (NC=O str.), 1603 (Ar C=C str.), 1538, 1303.

**$^1$H NMR ($CDCl_3$) ppm** **:** δ 1.35–2.05 (m, 4H, $(CH_2)_2$), 2.94 (t, *J* = 6.69 Hz, 2H,

$CH_2$), 3.19–3.52 (m, 3H, $CH_2$ and NH), 3.55–3.70 (m, 1H, CH), 7.24 (br s, 1H, CONH), 7.35–7.55 (m, 3H, Ar H), 7.83 (dd, *J* = 6.66, 1.64 Hz, 2H, Ar H).

**$^{13}$C NMR ($CDCl_3$) ppm** : δ 25.6 ($CH_2$), 28.9 ($CH_2$), 43.5 ($CH_2$), 46.1 ($CH_2$), 57.9 (CH), 127.0, 128.3, 131.3, 134.3 (Ar C), 167.6 (CO).

**HRMS (ESI$^+$) for** : $C_{12}H_{16}N_2O$.

**Calculated $[M+H]^+$** : 205.1335

**Found** : 205.1334 (100%).

### 1.4. Preparation of (*S*)-*N*-(pyrrolidin-2-ylmethyl) pivalamide (6b)

*1.4.1. (S)-Benzyl-2-(pivalamidomethyl)pyrrolidine-1-carboxylate (N-Cbz-**6b**)*

The procedure described above for the preparation *N*-Cbz-**6a** was followed using (*S*)-benzyl 2-(aminomethyl) pyrrolidine-1-carboxylate (470 mg, 2 mmol) and pivaloyl chloride (0.28 mL, 2.2 mmol). After 30 min of stirring followed by usual workup gave a crude product, which was purified by column chromatography using ethyl acetate/petroleum ether (1:3) as the eluent to get *N*-Cbz-**6b**.

**Yield** : 550 mg (86%, sticky mass)

**TLC data** : $R_f$ (40 % ethyl acetate/hexane): 0.4

**$[\alpha]_D^{25}$** : -53.73 (*c* 1.34, $CHCl_3$).

**IR (Nujol) v/cm$^{-1}$** : 3359, 2963, 1697 and 1659 (C=O str.), 1528 (Ar C=C str.), 1412, 1106.

**$^1$H NMR ($CDCl_3$) ppm** : δ 1.15 (s, 9H, $(CH_3)_3$), 1.60–2.15 (m, 4H, $(CH_2)_2$), 3.07–3.60 (m, 4H, 2($CH_2$)), 4.00–4.20 (m, 1H, CH), 5.14 (ABq, *J* = 12.38, 6.19 Hz, 2H, $OCH_2Ph$), 7.27–7.50 (m, 6H, Ar H and NH).

**$^{13}$C NMR ($CDCl_3$) ppm** : δ 23.9 ($CH_2$), 27.5 ($CH_3$), 29.5 ($CH_2$), 38.5 (C), 46.0 ($CH_2$), 46.9 ($CH_2$), 56.9 (CH), 67.1 ($CH_2$), 127.8, 128.0, 128.5, 136.5 (Ar C), 156.9 (CO), 179.2 (CO).

**HRMS (ESI$^+$) for** : $C_{18}H_{26}N_2O_3$.

**Calculated $[M+H]^+$** : 319.2016

**Found** : 319.2010.

*1.4.2. (S)-N-(Pyrrolidin-2-ylmethyl)pivalamide (**6b**)*

The procedure described above for the hydrogenolysis of *N*-Cbz-**6a** was followed for *N*-Cbz-**6b** (510 mg, 1.6 mmol). After stirring for 10 h, the usual workup and purification by column chromatography using methanol/dichloromethane (1:3) as the eluent gave **6b**.

**Yield** **:** 250 mg (85%, sticky mass)

**TLC data** **:** $R_f$ (methanol): 0.4

**$[\alpha]_D^{25}$** **:** +8.85 (*c* 1.21, $CHCl_3$).

**IR (Nujol) v/cm$^{-1}$** **:** 3338, 2956, 2873, 1640 (NC=O str.), 1535, 1402, 1212.

**$^1$H NMR ($CDCl_3$) ppm** **:** δ 1.20 (s, 9H, $(CH_3)_3$), 1.29–1.53 (m, 1H) and 1.59–1.98 (m, 3H, $(CH_2)_2$), 2.76 (br s, 1H, NH), 2.92 (t, *J* = 6.44 Hz, 2H, $CH_2$), 3.00–3.16 (m, 1H, CH), 3.22–3.47 (m, 2H, $CH_2$), 6.35 (br s, 1H, NH).

**$^{13}$C NMR ($CDCl_3$) ppm** **:** δ 25.6 ($CH_2$), 27.5 ($CH_3$), 28.7 ($CH_2$), 38.6 (C), 42.9 ($CH_2$), 43.0 ($CH_2$), 46.1 ($CH_2$), 57.9 (CH), 179.0 (CO).

**Analysis for** **:** $C_{10}H_{20}N_2O$.

**Calculated (%)** **:** C, 65.18; H, 10.94; N, 15.20

**Found** **:** C, 65.40, H, 10.63, N, 15.42.

**1.5. Preparation of (*S*)-*N*-(benzoylcarbamoyl)pyrrolidine-2-carboxamide (10b)**

*1.5.1. (S)-Benzyl 2-((benzoylcarbamoyl)carbamoyl)pyrrolidine-1-carboxylate (N-Cbz-**10b**)*

The procedure described in the Chapter 2 (compound no **18**) for the preparation of **10a** was followed using *N*-Cbz prolinamide (496 mg, 2 mmol) and benzoyl isocyanate[22a] (0.25 mL, 2 mmol). After reflux for 2 h, followed by usual workup and column chromatography using ethyl acetate/petroleum ether (1:2) as the eluent, gave the desired product.

**Yield** **:** 700 mg (89%, white solid).

**Melting point** **:** 63–66 $^oC$.

**TLC data** **:** $R_f$ (35 % ethyl acetate/hexane): 0.2

**$[\alpha]_D^{25}$** **:** -81.71 (*c* 1.05, $CHCl_3$).

**IR (Nujol) v/cm$^{-1}$** **:** 3189, 2947, 1774, 1703,1675 (C=O str.), 1599 (Ar C=C

str.), 1181.

**$^1$H NMR ($CDCl_3$) ppm** : δ 1.87–2.45 (m, 4H, $(CH_2)_2$), 3.42–3.80 (m, 2H, $CH_2$), 4.44–4.69 (m, 1H, CH), 4.98–5.28 (m, 2H, $OCH_2Ph$), 7.09–7.70 (m, 8H, Ar H), 7.77–8.00 (m, 2H, Ar H), 10.38 (br s, 1H, CONH), 10.78 (br s, 1H, CONH).

**$^{13}$C NMR ($CDCl_3$) ppm** : δ 23.6 and 24.4 ($CH_2$), 29.4 and 29.6 ($CH_2$), 47.0 and 47.4 ($CH_2$), 61.6 (CH), 67.5 ($CH_2$), 127.3, 127.9, 128.1, 128.4, 128.9, 132.0, 133.5, 136.1 (Ar C), 149.4 (CO), 154.3 and 155.8 (CO), 166.1 (CO), 173.7 (CO).

**Analysis for** : $C_{21}H_{21}N_3O_5$.

**Calculated (%)** : C, 63.79; H, 5.35; N, 10.63

**Found** : C, 63.94; H, 5.48; N, 10.85.

*1.5.2. (S)-N-(Benzoylcarbamoyl)pyrrolidine-2-carboxamide (**10b**)*

The procedure described for the hydrogenolysis of *N*-Cbz-**6a** was followed for *N*-Cbz-**10b** (672 mg, 1.7 mmol). After completion of the reaction (6 h), usual workup followed by column chromatographic purification using ethyl acetate/petroleum ether (1:2) as the eluent, **10b** was obtained.

**Yield** : 380 mg (87%, white solid)

**Melting point** : 94–96 $^oC$.

**TLC data** : $R_f$ (40% ethyl acetate/petroleum ether): 0.2

**$[\alpha]_D^{25}$** : -76.36 (*c* 1.27, $CHCl_3$).

**IR (Nujol) v/cm$^{-1}$** : 3373, 3175, 3061, 2951, 2922, 1758, 1728, 1710, 1658 (C=O str.), 1624 (Ar C=C str.), 1230.

**$^1$H NMR ($CDCl_3$) ppm** : δ 1.65–2.34 (m, 5H, $(CH_2)_2$ and NH), 3.15–3.30 (m, 1H) and 3.62–3.77 (m, 1H) $CH_2$, 4.135 (dd, $J$ = 9.10, 7.45 Hz, 1H, CH), 6.14 (br s, 1H, CONH), 7.40–7.62 (m, 3H, Ar H), 7.78–7.88 (m, 2H, Ar H), 8.53 (br s, 1H, CONH).

**$^{13}$C NMR ($CDCl_3$) ppm** : δ 27.0 ($CH_2$), 27.2 ($CH_2$), 45.1 ($CH_2$), 64.6 (CH), 127.3, 128.4, 131.8, 133.2 (Ar C), 161.0 (CO), 170.1 (CO), 175.1 (CO).

**Analysis for** : $C_{13}H_{15}N_3O_3$.

**Calculated (%)** : C, 59.76; H, 5.79; N, 16.08

**Found** : C, 59.88; H, 6.09; N, 16.04.

### 1.6. Preparation of (*S*)-*N*-(pyrrolidin-2-ylmethyl)hexadecan-1-amine (13)

#### *1.6.1. (S)-Benzyl 2-(hexadecylcarbamoyl)pyrrolidine-1-carboxylate*

The solution of *N*-Cbz-L-proline (1.25 g, 5 mmol) and triethylamine (0.7 mL, 5 mmol) in anhydrous $CHCl_3$ (5 mL) was cooled to 0 $^oC$. Ethyl chloroformate (0.48 mL, 5 mmol) was added to it dropwise and the resulting white suspension was stirred at 0–5 $^oC$ for 0.5 h. *n*-Hexadecylamine (1.21g, 5 mmol) was then added and stirring continued for 0.5 h at the same temperature. The reaction mixture was gradually warmed to room temperature and monitored by TLC. After completion of the reaction (15 h), it was diluted with dichloromethane (20 mL) and washed successively with 1 M HCl (10 mL), saturated aqueous $NaHCO_3$ (10 mL) and water (10 mL). Organic layer was dried over anhydrous $Na_2SO_4$ and concentrated. The residue was purified by column chromatography using ethyl acetate/petroleum ether (3:5) as the eluent.

**Yield** **:** 2 g (86%, white solid)

**Melting point** **:** 85–87 $^oC$.

**TLC data** **:** $R_f$ (30% ethyl acetate/petroleum ether): 0.3

**$[\alpha]_D^{25}$** **:** -61.16 (*c* 1.21, $CHCl_3$).

**IR (Nujol) v/cm$^{-1}$** **:** 3309, 2948, 1723, 1694 (NC=O str.), 1646 (Ar C=C str.).

**$^1$H NMR ($CDCl_3$) ppm** **:** δ 0.88 (t, *J* = 6.32, 3H, $CH_3$), 1.11–1.56 (m, 28 H, $(CH_2)_{14}$), 1.80–2.50 (m, 4H, $(CH_2)_2$), 3.04–3.31 (m, 2H, $NCH_2$), 3.35–3.64 (m, 2H, $NCH_2$), 4.31 (t, *J* = 6.19 Hz, 1H, CH), 5.01–5.27 (m, 2H, $OCH_2Ph$), 5.90 and 6.71 (br s, 1H, CONH, rotamers), 7.28–7.44 (m, 5H, Ar H).

#### *1.6.2. (S)-N-Hexadecylpyrrolidine-2-carboxamide*

The procedure described for the hydrogenolysis of *N*-Cbz-**6a** was followed for (*S*)-*benzyl 2-(hexadecylcarbamoyl)pyrrolidine-1-carboxylate* (1.9 g, 4 mmol). After completion of the reaction (3 h), usual workup followed by filtration column chromatographic purification using methanol/dichloromethane (1:9) as the eluent gave the desired product.

**Yield** **:** 1.2 g (89%, white solid).

**Melting point** **:** 52–54 $^oC$.

**TLC data** : $R_f$ (20% methanol/ dichloromethane): 0.2

**$[\alpha]_D^{25}$** : -35.3 (*c* 2.08, $CHCl_3$).

**IR ($CHCl_3$) v/cm$^{-1}$** : 3313 (N–H str.), 2923, 2853, 1654 (NC=O str.).

**$^1$H NMR ($CDCl_3$) ppm** : δ 0.88 (t, *J* = 6.44 Hz, 3H, $CH_3$), 1.20–1.38 (m, 26H, $(CH_2)_{13}$), 1.40–1.59 (m, 3H, $CH_2$ and NH), 1.71 (quin., *J* = 6.58 Hz, 2H, $CH_2$), 1.82–2.25 (m, 2H, $CH_2$), 2.83–3.10 (m, 2H, $CH_2$), 3.22 (q, *J* = 6.57 Hz, 2H, $NCH_2$), 3.75 (dd, *J* = 5.30, 3.67 Hz, 1H, CH), 7.60 (br s, 1H, CONH).

**$^{13}$C NMR ($CDCl_3$) ppm** : δ 14.1 ($CH_3$), 22.6 ($CH_2$), 26.1 ($CH_2$), 26.9 ($CH_2$), 29.2 ($CH_2$), 29.3 ($CH_2$), 29.6 ($CH_2$), 30.7 ($CH_2$), 31.9 ($CH_2$), 38.9 ($CH_2$), 60.4 (CH), 174.8 (CO).

**LCMS for** : $C_{21}H_{42}N_2O$.

**Calculated $[M+H]^+$** : 339.33

**Found** : 339.33 (100%).

*1.6.3. (S)-N-(Pyrrolidin-2-ylmethyl)hexadecan-1-amine (**13**)*

To an ice cold solution of (*S*)-*N*-hexadecylpyrrolidine-2-carboxamide (676 mg, 2 mmol) in anhydrous THF (5 mL), solution of $BH_3$.DMS (0.56 mL, 6 mmol) was added dropwise. The reactiom mixture was gradually warmed to room temperature and heated to reflux. After completion of the reaction as indicated by TLC (2 h), it was cooled to 0 $^oC$ and treated with slow addition of methanol (10 mL). It was then refluxed for 3 h and cooled to room temperature. Evaporation of solvent on the rotavapor furnished the residue. It was then dissolved in diethyl ether (25 mL) and washed with saturated $NaHCO_3$ (2 × 10 mL). Organic layer was dried over $Na_2SO_4$, concentrated and the residue was purified by filtration column using methanol/dichloromethane (1:5) as the eluent.

**Yield** : 400 mg (62%, yellow liquid)

**TLC data** : $R_f$ (40% methanol/dichloromethane): 0.2

**$[\alpha]_D^{25}$** : -5.32 (*c* 1.53, $CHCl_3$).

**IR (Neat) v/cm$^{-1}$** : 3412 (N–H str.), 2919, 2851, 1642.

**$^1$H NMR ($CDCl_3$) ppm** : δ 0.88 (t, *J* = 6.44 Hz, 3H, $CH_3$), 0.98 and 1.11 (d, *J* = 6.57 Hz, 2H, $CH_2$), 1.16–1.40 (m, 26 H, $(CH_2)_{13}$), 1.40–

1.55 (m, 2H, $CH_2$), 1.59–2.05 (m, 6H, $2CH_2$ and 2(NH)), 2.40–2.70 (m, 2H, $CH_2$), 2.92 (quin., $J$ = 6.19 Hz, 2H, $CH_2$), 3.14–3.33 (m, 1H, CH),

**$^{13}$C NMR ($CDCl_3$) ppm** : δ 14.1 ($CH_3$), 16.7, 22.6, 22.2, 22.6, 23.6, 25.5, 27.3, 29.3, 29.6, 29.9. 31.9, 46.3, 47.8, 50.2, 50.4, 50.7, 54.7 ($CH_2$), 58.2 (CH).

**LCMS for** : $C_{21}H_{44}N_2$.

**Calculated $[M+H]^+$** : 325.35

**Found** : 325.32 (45%).

### 1.7. Preparation of salts.

Adducts of pyrrolidine and chiral acids were generated in situ using acetone as the solvent. While the salts of amines (**13**−**18**) and L-proline with achiral additives were prepared separately by reacting amine (1 mmol) and additive (1 mmol) in methanol at room temperature. After stirring for 15 min, solvent was evaporated on rotavapor and residue was dried under vacuum. These salts are stable and can be stored indefinitely in a desiccator.

### 2. Pyrrolidine catalyzed diastereoselective aldol reaction.

A 10 mL round-bottom flask was charged with aldehyde (2 mmol) and ketone (0.5 mL, 6 mmol) and flask was cooled to 0 $^oC$. Pyrrolidine (0.2–0.3 mmol) was added to it and stirring continued at the same temperature. It was monitored by TLC for the disappearance of aldehyde. After completion of the reaction, it was quenched with 1N HCl (2 mL) and extracted with ethyl acetate (10 mL). Organic layer was separated and washed with saturated aqueous $NaHCO_3$ (5 mL) and brine (5 mL). It was dried over anhydrous $Na_2SO_4$ and concentrated to get crude product which was purified by column chromatography using ethyl acetate/pet ether as the eluent. Diastereomeric ratio was determined by $^1$H NMR and also by HPLC analysis. The respective *syn* and *anti* configurations were assigned by comparing $^1$H NMR and retention times in HPLC.[19b−d]

### 3. General procedure for direct aldol reaction.

In a 10 mL round bottom flask, 0.2 mmol of catalyst (amine: additive (1:1)) was dissolved in ketone (0.5 mL, 6 mmol) at room temperature. After 5 min, aldehyde (2 mmol) was added. The reaction mixture was stirred and monitored by TLC for

aldehyde. After completion of the reaction, volatiles were removed on rotavapor and residue was redissolved in ethyl acetate (10 mL). Organic layer was washed with water (5 mL) and brine (5 mL). It was dried over anhydrous $Na_2SO_4$ and concentrated to get crude product which was purified by column chromatography using ethyl acetate/pet ether as the eluent. Diastereomeric ratio was determined by $^1$H NMR and also by HPLC analysis and the respective *syn* and *anti* configurations was assigned by comparing $^1$H NMR and retention times in HPLC.[19] While enantiomeric excess was determined by chiral HPLC analysis.

*3.1. 4-Hydroxy-4-(4-nitrophenyl)butan-2-one (**A**, Table 7, entry 4)*

**Yield** : 380 mg (90%, light yellow solid)

**Melting point** : 60–62 $^o$C (Lit.[35] 60–62 $^o$C)

**TLC data** : $R_f$ (20% ethyl acetate/petroleum ether): 0.2

**$[\alpha]_D^{25}$** : +44.90 (*c* 1.30, $CHCl_3$)

**IR (Nujol) v/cm$^{-1}$** : 3414, 2922, 2856, 1710 (C=O str.), 1596 (Ar C=C str.).

**$^1$H NMR ($CDCl_3$) ppm** : δ 2.23 (s, 3H, $CH_3$), 2.84−2.88 (m, 2H, $CH_2$), 3.7 (br s, 1H, OH), 5.27 (t, *J* = 6.07 Hz, 1H, CH ), 7.55 (d, *J* =8.85 Hz, 2H, Ar H), 8.22 (d, *J* =8.71 Hz, 2H, Ar H).

***ee*** : 72%.

**HPLC** : Column: Chiralcel OJ-H (250 x 4.6 mm); Mobile phase: *i*-PrOH:petroleum ether (30:70); Flow rate: 0.5 mL/min; UV: 254 nm; Retention time: $t_R$ (*R*-isomer): 19.38 min, $t_R$ (*S*-isomer): 21.33 min.

*3.2. 3-Hydroxy-2,2-dimethyl-3-(4-nitrophenyl)propanal (Table 7, entry 6)*

**Yield** : 260 mg (58%, yellow solid)

**Melting point** : 110–112 $^o$C.

**TLC data** : $R_f$ (20% ethyl acetate/petroleum ether): 0.2

**$[\alpha]_D^{25}$** : +19.20 (*c* 1.25, $CHCl_3$)

**IR (Nujol) v/cm$^{-1}$** : 3389, 2922, 2856, 1719 (C=O str.), 1603 (Ar C=C str.).

**$^1$H NMR ($CDCl_3$) ppm** : δ 0.9 (s, 3H, $CH_3$), 1.07 (s, 3H, $CH_3$), 2.91 (br s, 1H, OH), 5.05 (s, 1H, CH), 7.52 (td, *J* = 8.59, 2.28 Hz, 2H, Ar H), 8.22 (td, *J* = 8.85, 2.4 Hz, 2H, Ar H), 9.62 (s, 1H, CHO).

***ee*** **:** 73%.

**HPLC** **:** Column: Chiralpak AS-H (250 x 4.6 mm); Mobile phase: *i*-PrOH:petroleum ether (15:85); Flow rate: 0.5 mL/min; UV: 254 nm; Retention time: $t_R$ (*R*-isomer): 38.90 min, $t_R$ (*S*-isomer): 43.28 min.

*3.3. 4-Hydroxy-4-(2-nitrophenyl)butan-2-one (Table 8, entry 1)*

**Yield** **:** 390 mg (93%, light yellow solid)

**Melting point** **:** 65–67 $^{o}$C (Lit.[35] 65–68 $^{o}$C)

**TLC data** **:** $R_f$ (20% ethyl acetate/petroleum ether): 0.2

**$[\alpha]_D^{25}$** **:** +119.0 (*c* 1.80, $CHCl_3$)

**IR (Nujol) v/cm$^{-1}$** **:** 3384, 2922, 2851, 1697 (C=O str.), 1605 (Ar C=O str.).

**$^1$H NMR ($CDCl_3$) ppm** **:** δ 2.24 (s, 4H, $CH_3$ and OH), 2.73 (dd, *J* = 17.81, 9.35 Hz, 1H) and 3.15 (dd, *J* = 17.81, 2.15 Hz, 1H, $CH_2$), 5.68 (dd, *J* = 9.47, 2.14 Hz, 1H, CH), 7.44 (dt, *J* = 8.46, 1.51 Hz, 1H, Ar H), 7.67 (dt, *J* = 7.46, 1.27 Hz, 1H, Ar H), 7.94 (ddd, *J* = 13.01, 8.09, 1.39 Hz, 2H, Ar H).

***ee*** **:** 83%.

**HPLC** **:** Column: Chiralpak AS-H (250 x 4.6 mm); Mobile phase: *i*-PrOH:petroleum ether (30:70); Flow rate: 0.5 mL/min; UV: 254 nm; Retention time: $t_R$ (*S*-isomer): 18.54 min, $t_R$ (*R*-isomer): 25.01 min.

*3.4. 4-Hydroxy-4-(3-nitrophenyl)butan-2-one (Table 8, entry 2)*

**Yield** **:** 400 mg (95%, oil)[35]

**TLC data** **:** $R_f$ (20% ethyl acetate/petroleum ether): 0.2

**$[\alpha]_D^{25}$** **:** +41.20 (*c* 1.20, $CHCl_3$)

**IR (Nujol) v/cm$^{-1}$** **:** 3490, 2922, 2857, 1705 (C=O str.), 1580 (Ar C=C str.).

**$^1$H NMR ($CDCl_3$) ppm** **:** δ 2.24 (s, 3H, $CH_3$), 2.94 (m, 2H, $CH_2$ ), 3.64 (br s, 1H, OH), 5.27 (t, *J* = 5.55 Hz, 1H, CH), 7.53 (t, *J* = 7.83 Hz, 1H, Ar H), 7.72 (d, *J* = 7.71 Hz, 1H, Ar H), 8.1−8.27 (m, 2H, Ar H).

***ee*** **:** 54%.

**HPLC** **:** Column: Chiralcel OJ-H (250 x 4.6 mm); Mobile phase: *i*-PrOH:petroleum ether (20:80); Flow rate: 1.0 mL/min, UV: 254 nm; Retention time: $t_R$ (*R*-isomer) 16.45 min, $t_R$ (*S*-isomer) 18.35 min**.**

*3.5. 4-(4-Chlorophenyl)-4-hydroxybutan-2-one (Table 8, entry 3)*

**Yield** **:** 330 mg (83%, low melting white solid)[35]

**TLC data** **:** $R_f$ (10% ethyl acetate/petroleum ether): 0.2

**$[\alpha]_D^{25}$** **:** +21.19 (*c* 1.51, $CHCl_3$)

**IR (Nujol) v/cm$^{-1}$** **:** 3425, 3050, 2882, 1702 (C=O str.), 1595 (Ar C=C str.).

**$^1$H NMR ($CDCl_3$) ppm** **:** δ 2.20 (s, 3H, $CH_3$), 2.79−2.86 (m, 2H, $CH_2$), 3.10 (br s, 1H, OH), 5.08–5.18 (dd, *J* = 7.46, 4.80 Hz, 1H, CH), 7.23−7.53 (m, 4H, Ar H).

***ee*** **:** 68%.

**HPLC** **:** Column: Chiralpak AS-H (250 x 4.6 mm); Mobile phase: *i*-PrOH:petroleum ether (15:85); Flow rate: 0.5 mL/min; UV: 257 nm; Retention time: $t_R$ (*R*-isomer): 22.35 min, $t_R$ (*S*-isomer): 26.76 min.

*3.6. 4-Hydroxy-4-phenylbutan-2-one (Table 8, entry 4)*

**Yield** **:** 260 mg (79%, colourless oil).

**TLC data** **:** $R_f$ (10% ethyl acetate/petroleum ether): 0.3.

**$[\alpha]_D^{25}$** **:** +40.0 (*c* 1.30, $CHCl_3$)

**IR (Neat) v/cm$^{-1}$** **:** 3416, 3056, 2923, 1706 (C=O str.), 1598 (Ar C=C str.).

**$^1$H NMR ($CDCl_3$) ppm** **:** δ 2.19 (s, 3H, $CH_3$), 2.83−2.89 (m, 2H, $CH_2$), 3.3 (br s, 1H, OH), 5.15 (q, *J* = 4.17 Hz, 1H, CH), 7.25−7.4 (m, 5H, Ar H).

***ee*** **:** 63%.

**HPLC** **:** Column: Chiralpak AS-H (250 x 4.6 mm); Mobile phase: *i*-PrOH:petroleum ether (15:85); Flow rate: 0.5 mL/min; UV: 257 nm; Retention time: $t_R$ (*R*-isomer ): 21.62 min, $t_R$ (*S*-isomer): 24.78 min.

*3.7. 2-(Hydroxy(4-nitrophenyl)methyl)cyclopentanone (Table 9, entry 1)*

**Yield** : 450 mg (95%, faint yellow solid) mixture of *syn* and *anti* (66:34).

**Melting point** : 102–114 $^{o}$C.

**TLC data** : $R_f$ (20% ethyl acetate/petroleum ether): 0.2

**IR (Nujol) v/cm$^{-1}$** : 3440, 2948, 2922, 1727 (C=O str.), 1601 (Ar C=C str.).

**$^{1}$H NMR ($CDCl_3$) ppm** : δ 1.46–2.58 (m, 7 H, $(CH_2)_3$ and CH), 2.74−2.84 (m, (*syn*)) and 4.78 (s, (*anti*), 1H, OH), 4.85 (d, *J* = 9.10 Hz (*anti*)) and 5.43 (t, *J* = 3.41 Hz (*syn*), 1H, CH), 7.53 (2 d, *J* = 8.71 Hz, 2H, Ar H), 8.215 (d, *J* = 8.72 Hz, 2H, Ar H).

***ee*** : *syn*: 85%, *anti*: 86%

**HPLC** : Column: Chiralpak AS-H (250 x 4.6 mm); Mobile phase: *i*-PrOH:petroleum ether (25:75); Flow rate: 0.5 mL/min; UV: 254 nm; Retention time: $t_R$ (*syn*, major): 24.86 min, $t_R$ (*anti*, minor): 26.45 min, $t_R$ (*anti*, major): 33.82 min, $t_R$ (*syn*, minor): 65.14 min.

*3.8. 2-(Hydroxy(4-nitrophenyl)methyl)cyclohexanone (Table 9, entry 2)*

**Yield** : 460 mg (93%, white solid), mixture of *syn* and *anti* (19:81).

**Melting point** : 145–151 $^{o}$C.

**TLC data** : $R_f$ (20% ethyl acetate/petroleum ether): 0.2

**IR (Nujol) v/cm$^{-1}$** : 3506, 2948, 1692 (C=O str.), 1603 (Ar C=C str.), 1517.

**$^{1}$H NMR ($CDCl_3$) ppm** : δ 1.25−1.9 (m, 5H, $(CH_2)_2$ and CH), 2.12−2.2 (m, 1H) and 2.27−2.7 (m, 3H, $(CH_2)_2$, 3.20 (d, *J* = 3.28 Hz (*syn*)) and 4.095 (d, *J* = 3.03 Hz (*anti*), 1H, OH), 4.90 (dd, *J* = 8.34, 2.91 Hz (*anti*)) and 5.45−5.53 (m, (*syn*), 1H, CH), 7.50 (2d, *J* = 8.34 Hz, 2H, Ar H), 8.22 (d, *J* = 8.06 Hz, 2H, Ar H).

***ee*** : *syn*: 22%, *anti*: 77%

**HPLC** : Column: Kromasil 5-CelluCoat (250 x 4.6 mm); Mobile phase: *i*-PrOH:petroleum ether (4:96); Flow rate: 1.0 mL/min; UV: 254 nm; Retention time: $t_R$ (*syn*, minor):

34.15 min, $t_R$ (*syn*, major): 39.20 min, $t_R$ (*anti*, major): 41.58 min, $t_R$ (*anti*, minor): 59.73 min.

*3.9. 2-((4-Chlorophenyl)(hydroxy)methyl)cyclopentanone (Table 9, entry 3)*

**Yield** : 420 mg (94%, white solid) mixture of *syn* and *anti* (81:19).

**Melting point** : 91–103 $^{o}$C.

**TLC data** : $R_f$ (10% ethyl acetate/petroleum ether): 0.2

**IR (Nujol) v/cm$^{-1}$** : 3359, 2953, 2859, 1725(C=O str.), 1593 (Ar C=C str.).

**$^1$H NMR ($CDCl_3$) ppm** : δ 1.4–2.6 (m, 8H, $(CH_2)_3$, CH and OH (*syn*)), 4.60 (br s, (*anti*) OH), 4.69 (d, $J$ = 9.09 Hz (*anti*)) and 5.26 (d, $J$ = 2.9 Hz (*syn*), 1H, CH), 7.22−7.36 (m, 4H, Ar H).

***ee*** : *syn*: 68%, *anti*: 86%

**HPLC** : Column: Chiralpak AS-H (250 x 4.6 mm); Mobile phase: *i*-PrOH:petroleum ether (15:85); Flow rate: 0.5 mL/min; UV: 254 nm; Retention time: $t_R$ (*syn*, major): 19.30 min, $t_R$ (*anti*, minor): 22.29 min, $t_R$ (*anti*, major): 25.40 min, $t_R$ (*syn*, minor): 30.79 min.

*3.10. 2-((4-Chlorophenyl)(hydroxy)methyl)cyclohexanone (Table 5, entry 5)*

**Yield** : 390 mg (92%, white solid) mixture of *syn* and *anti* (29:71).

**Melting point** : 84–87 $^{o}$C.

**TLC data** : $R_f$ (10% ethyl acetate/petroleum ether): 0.2

**IR (Nujol) v/cm$^{-1}$** : 3430, 2922, 2852, 1697(C=O str.), 1591 (Ar C=C str.).

**$^1$H NMR ($CDCl_3$) ppm** : δ 1.14–1.19 (m, 5H, $(CH_2)_2$ and CH), 2.20–2.22 (m, 1H) and 2.25–2.65 (m, 3H, $(CH_2)_2$), 3.08 (d, $J$ = 3.06 Hz (*syn*)) and 4.01 (d, $J$ = 2.65 Hz (*anti*)) OH), 4.77 (dd, $J$ = 8.72, 2.53 Hz) and 5.36 (t, $J$ = 2.79 Hz, 1H, CH), 7.19–7.38 (m, 4H, Ar H).

**HPLC** : Column: Kromasil 5-Amy Coat (250 x 4.6 mm); Mobile phase: *i*-PrOH:petroleum ether (30:70); Flow rate: 0.5 mL/min; UV: 220 nm; Retention time: $t_R$ (*syn*): 11.08 min, $t_R$ (*syn*): 12.13 min, $t_R$ (*anti*): 14.39 min, $t_R$ (*anti*):

15.92 min.

*3.11. 2-(Hydroxy(p-tolyl)methyl)cyclopentanone (Table 9, entry 4)*

**Yield** **:** 370 mg (91%, white solid) mixture of *syn* and *anti* (96:4).

**Melting point** **:** 72–77 $^{o}$C.

**TLC data** **:** $R_f$ (10% ethyl acetate/petroleum ether): 0.2

**IR (Nujol) v/cm$^{-1}$** **:** 3465, 2953, 2857, 1725 (C=O str.), 1601 (Ar C=C str.).

**$^{1}$H NMR ($CDCl_3$) ppm** **:** δ 1.58–2.52 (m, 11H, $(CH_2)_3$, CH, OH (*syn*) and $CH_3$), 4.99 (br s, OH (*anti*)), 4.67 (d, $J$ = 8.84 Hz, (*anti*)) and 5.26 (t, $J$ = 3.53 Hz, (*syn*) 1H, CH), 7.10−7.27 (m, 4H, Ar H).

***ee*** **:** *syn*: 9%, *anti*: 78%

**HPLC** **:** Column: Kromasil 5-AmyCoat (250 x 4.6 mm); Mobile phase: *i*-PrOH:petroleum ether (15:85); Flow rate: 0.5 mL/min; UV: 254 nm; Retention time: $t_R$ (*syn*, major): 14.12 min, $t_R$ (*syn*, minor): 16.03 min, $t_R$ (*anti*, major): 17.23 min, $t_R$ (*anti*, minor): 18.79 min.

*3.12. 2-(Hydroxy(4-methoxyphenyl)methyl)cyclopentanone (Table 9, entry 5)*

**Yield** **:** 360 mg (82%, white solid) mixture of *syn* and *anti* (10:90).

**Melting point** **:** 47–55 $^{o}$C.

**TLC data** **:** $R_f$ (10% ethyl acetate/petroleum ether): 0.2

**IR (Nujol) v/cm$^{-1}$** **:** 3465, 2963, 2877, 1720 (C=O str.), 1611 (Ar C=C str.).

**$^{1}$H NMR ($CDCl_3$) ppm** **:** δ 1.4–2.53 (m, 7H, $(CH_2)_3$ and CH), 2.61 (s, (*syn*)) and 4.5 (s, (*anti*), 1H, OH), 3.80 ( s, 3H, $OCH_3$), 4.65 (d, $J$ = 9.10 Hz (*anti*)) and 5.23 (t, $J$ = 3.55 Hz, (*syn*) 1H, CH), 6.83−6.93 (m, 2H, Ar H), 7.21−7.34 (m, 2H, Ar H).

***ee*** **:** *syn*: 54%, *anti*: 54%

**HPLC** **:** Column: Kromasil 5-AmyCoat (250 x 4.6 mm); Mobile phase: *i*-PrOH:petroleum ether (10:90); Flow rate: 0.5 mL/min; UV: 264 nm; Retention time: $t_R$ (*syn*, major): 27.48 min, $t_R$ (*syn*, minor): 32.98 min, $t_R$ (*anti*, major):

37.66 min, $t_R$ (*anti*, minor): 41.08 min.

*3.13. 2-(Hydroxy(2-nitrophenyl)methyl)cyclopentanone (Table 9, entry 6)*

**Yield** : 440 mg (92%, yellow solid) mixture of *syn* and *anti* (61:39).

**Melting point** : 120–122 $^{o}$C.

**TLC data** : $R_f$ (20% ethyl acetate/petroleum ether): 0.3

**IR (Nujol) v/cm$^{-1}$** : 3430, 2963, 2938, 1727 (C=O str.), 1605, (Ar C=C str.).

**$^1$H NMR ($CDCl_3$) ppm** : δ 1.6–2.82 (m, 8H, $(CH_2)_3$, CH and OH), 5.45 (d, $J$ = 8.72 Hz (*anti*)) and 5.92 (d, $J$ = 3.04 Hz, (*syn*) 1H, CH), 7.44 (dt, $J$ = 7.07, 1.39 Hz, 1H, Ar H), 7.66 (tt, $J$ = 7.83, 1.77 Hz, 1H, Ar H), 7.76–7.93 (m, 1H, Ar H), 8.00 (dd, $J$ = 8.09, 1.26 Hz, 1H, Ar H).

***ee*** : *syn*: 58%, *anti*: 94%

**HPLC** : Column: Chiralcel OD-H (250 x 4.6 mm); Mobile phase: *i*-PrOH:petroleum ether (10:90); Flow rate: 0.5 mL/min; UV: 254 nm; Retention time: $t_R$ (*syn*, minor): 17.15 min, $t_R$ (*syn*, major): 21.08 min, $t_R$ (*anti*, major): 27.25 min, $t_R$ (*anti*, minor): 29.03 min.

*3.14. 2-((2-Chlorophenyl)(hydroxy)methyl)cyclopentanone (Table 9, entry 7)*

**Yield** : 410 mg (94%, colourless oil) mixture of *syn* and *anti* (57:43).

**Melting point** : 65–78 $^{o}$C.

**TLC data** : $R_f$ (10% ethyl acetate/petroleum ether): 0.2

**IR (Nujol) v/cm$^{-1}$** : 3455, 3065, 2968, 1732 (C=O str.), 1631 (Ar C=C str.).

**$^1$H NMR ($CDCl_3$) ppm** : δ 1.52–2.76 (m, 8H, $(CH_2)_3$, CH and OH (*syn*)), 4.54 (br s, (*anti*) OH), 5.3 (d, $J$ = 9.22 Hz (*anti*)) and 5.68 (m, (*syn*), 1H, CH), 7.14−7.37 (m, 3H, Ar H), 7.54–7.64 (m, 1H, Ar H).

***ee*** : *syn*: 13%, *anti*: 88%

**HPLC** : Column: Kromasil 5-AmyCoat (250 x 4.6 mm); Mobile phase: *i*-PrOH:*n*-hexane (10:90); Flow rate: 0.5 mL/min; UV: 220 nm; Retention time: $t_R$ (*syn*, major): 15.48 min, $t_R$

(*syn*, minor): 18.85 min, $t_R$ (*anti*, major): 20.83 min, $t_R$ (*anti*, minor): 21.88 min.

*3.15. 2-(Hydroxy(o-tolyl)methyl)cyclopentanone (Table 9, entry 8)*

**Yield** **:** 380 mg (93%, white solid) mixture of *syn* and *anti* (57:43).

**Melting point** **:** 84–87 $^{o}$C.

**TLC data** **:** $R_f$ (10% ethyl acetate/petroleum ether): 0.2

**IR (Nujol) v/cm$^{-1}$** **:** 3460, 2963, 2882, 1727 (C=O str.), 1605 (Ar C=C str.).

**$^{1}$H NMR ($CDCl_3$) ppm** **:** δ 1.37–2.67 (m, 11H, $(CH_2)_3$, CH, OH (*syn*) and $CH_3$), 4.52 (s, (*anti*), OH), 5.00 (d, $J$ = 9.47 Hz (*anti*)) and 5.54 (s, (*syn*), 1H, CH), 7.06−7.27 (m, 3H, Ar H), 7.35−7.56 (m, 1H, Ar H).

**$^{13}$C NMR ($CDCl_3$) ppm** **:** δ 18.8 and 19.5 ($CH_3$), 20.4 ($CH_2$), 22.4 ($CH_2$), 26.9 ($CH_2$), 38.6 ($CH_2$), 39.1 ($CH_2$), 54.0 and 54.8 (CH), 67.7 and 70.8 (CH), 125.4, 126.0, 126.3. 126.8, 127.0, 127.6, 130.2, 130.4, 133.4, 135.3, 139.1 (Ar C) and 141.0 (CO) diastereomers.

***ee*** **:** *syn*: 5%, *anti*: 85%

**HPLC** **:** Column: Kromasil 5-AmyCoat (250 x 4.6 mm); Mobile phase: *i*-PrOH:petroleum ether (10:90); Flow rate: 0.5 mL/min; UV: 264 nm; Retention time: $t_R$ (*syn*, major): 17.08 min, $t_R$ (*syn*, minor): 18.75 min, $t_R$ (*anti*, major): 22.13 min, $t_R$ (*anti*, minor): 25.83 min.

*3.16. 2-(Hydroxy(2-methoxyphenyl)methyl)cyclopentanone (Table 9, entry 9)*

**Yield** **:** 410 mg (93%, white solid) mixture of *syn* and *anti* (99:1).

**Melting point** **:** 122–114 $^{o}$C.

**TLC data** **:** $R_f$ (10% ethyl acetate/petroleum ether): 0.2

**IR (Nujol) v/cm$^{-1}$** **:** 3420, 2953, 2928, 1717 (C=O str.), 1601 (Ar C=C str.).

**$^{1}$H NMR ($CDCl_3$) ppm** **:** δ 1.60–2.7 (m, 8H, $(CH_2)_3$, CH and OH), 3.82 (s, 3H, $OCH_3$), 5.54−5.82 (m, 1H, CH), 6.85 (d, $J$ = 7.95 Hz, 1H, Ar H), 6.97 (dt, $J$ = 7.58, 6. 03 Hz, 1H, Ar H),

7.19−7.31 (m, 1H, Ar H), 7.44 (dd, *J* = 7.33, 1.38 Hz, 1H, Ar H).

***ee*** **:** 28%

**HPLC** **:** Column: Kromasil 5-AmyCoat (250 x 4.6 mm); Mobile phase: *i*-PrOH:petroleum ether (6:94); Flow rate: 0.5 mL/min; UV: 220 nm; Retention time: $t_R$ (*syn*, minor): 36.53 min, $t_R$ (*syn*, major): 45.38 min.

*3.17. 2-(Hydroxy(phenyl)methyl)cyclopentanone (Table 9, entry 10)*

**Yield** **:** 350 mg (94%, colourless oil) mixture of *syn* and *anti* (70:30).

**TLC data** **:** $R_f$ (10% ethyl acetate/petroleum ether): 0.2

**IR (Nujol) v/cm$^{-1}$** **:** 3450, 2963, 1732 (C=O str.), 1603 (Ar C=C str.), 1452.

**$^1$H NMR ($CDCl_3$) ppm** **:** δ 1.4–2.52 (m, 7H, $(CH_2)_3$ and CH), 2.70 (br s, (*syn*)) and 4.55 (br s, (*anti*), 1H, OH), 4.70 (d, *J* = 9.10 Hz, (*anti*)) and 5.28 (d, *J* = 2.40 Hz (*syn*), 1H, CH), 7.20–7.40 (m, 5H, Ar H).

***ee*** **:** *syn*: 27%, *anti*: 47%

**HPLC** **:** Column: Chiralcel OD-H (250 x 4.6 mm); Mobile phase: *i*-PrOH:petroleum ether (10:90): Flow rate: 0.5 mL/min; UV: 213 nm; Retention time: $t_R$ (*syn*, minor): 16.22 min, $t_R$ (*syn*, major): 17.63 min, $t_R$ (*anti*, major): 22.44 min, $t_R$ (*anti*, minor): 25.91 min.

*3.18. 2-(Hydroxy(naphthalen-1-yl)methyl)cyclopentanone (Table 9, entry 11)*

**Yield** **:** 440 mg (92%, sticky mass) mixture of *syn* and *anti* (60:40).

**TLC data** **:** $R_f$ (10% ethyl acetate/petroleum ether): 0.2

**IR (Nujol) v/cm$^{-1}$** **:** 3450, 3050, 2963, 1727 (C=O str.), 1582 (Ar C=C str.).

**$^1$H NMR ($CDCl_3$) ppm** **:** δ 1.36–2.9 (m, 8H, $(CH_2)_3$, CH and OH (*syn*)), 4.75 (br s, OH (*anti*), 5.42 (d, *J* = 9.34 Hz, (*anti*)) and 6.10−6.17 (m, (*syn*) CH), 7.39–7.58 (m, 3H, Ar H), 7.67–7.80 (m, 3H, Ar H), 8.25–8.40 (m, 1H, Ar H).

***ee*** **:** *syn*: 14%, *anti*: 57%.

**HPLC** **:** Column: Kromasil 5-AmyCoat (250 x 4.6 mm); Mobile phase: *i*-PrOH:petroleum ether (10:90); Flow rate: 0.5 mL/min; UV: 264 nm; Retention time: $t_R$ (*syn*, major): 19.61 min, $t_R$ (*syn*, minor): 24.85 min, $t_R$ (*anti*, major): 34.33 min, $t_R$ (*anti*, minor): 36.47 min.

*3.19. 2-(Hydroxy(naphthalen-2-yl)methyl)cyclopentanone (Table 9, entry 12)*

**Yield** **:** 450 mg (94%, white solid) mixture of *syn* and *anti* (83:17)

**Melting point** **:** 86–94 $^{o}$C.

**TLC data** **:** $R_f$ (10% ethyl acetate/petroleum ether): 0.2

**IR (Nujol) v/cm$^{-1}$** **:** 3409, 2948, 2857, 1722 (C=O str.), 1601 (Ar C=C str.).

**$^{1}$H NMR ($CDCl_3$) ppm** **:** δ 1.60−2.65 (m, 8H, $(CH_2)_3$, CH and OH (*syn*)), 4.65 (br s, OH (*anti*)), 4.88 (d, $J$ = 9.10 Hz, (*anti*)) and 5.47 (t, $J$ = 3.92 Hz, 1H, CH), 7.36−7.56 (m, 3H, Ar H), 7.75−7.90 (m, 4H, Ar H).

***ee*** **:** *syn*: 18%, *anti*: 71%.

**HPLC** **:** Column: Kromasil 5-AmyCoat (250 x 4.6 mm); Mobile phase: *i*-PrOH:petroleum ether (10:90); Flow rate: 0.5 mL/min; UV: 264 nm; Retention time: $t_R$ (*syn*, major): 24.57 min, $t_R$ (*syn*, minor): 29.22 min, $t_R$ (*anti*, major): 36.23 min, $t_R$ (*anti*, minor): 39.07 min.

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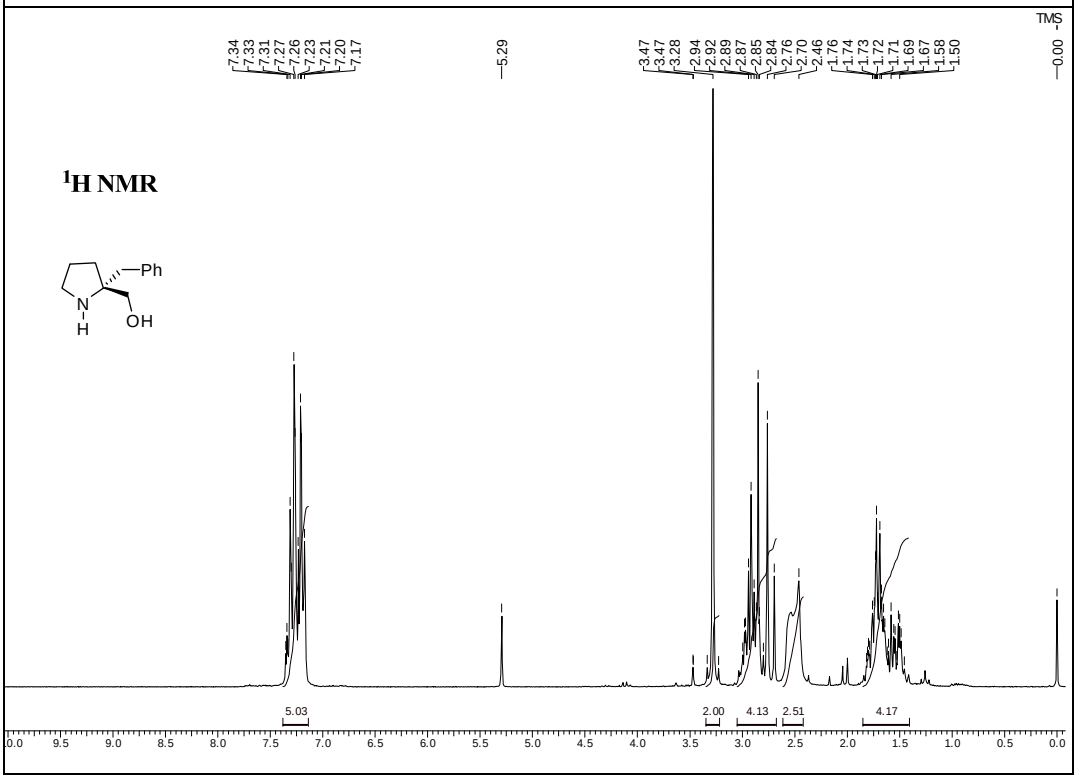
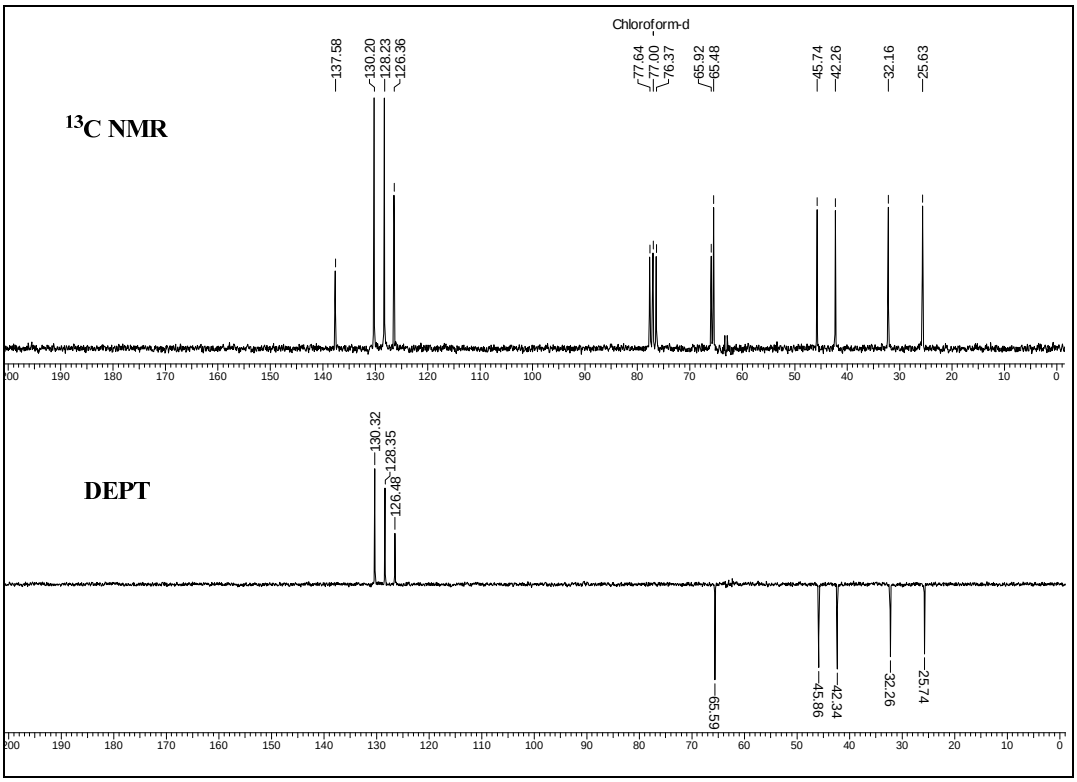
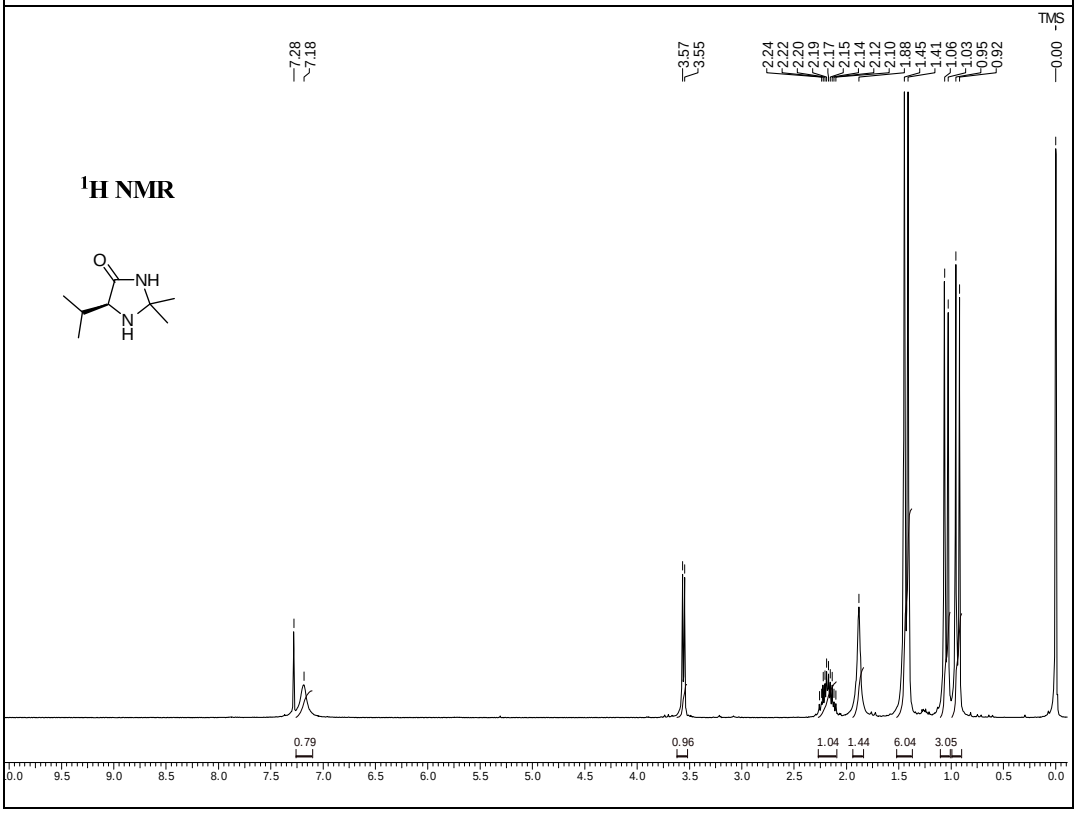
# Spectra and chromatograms

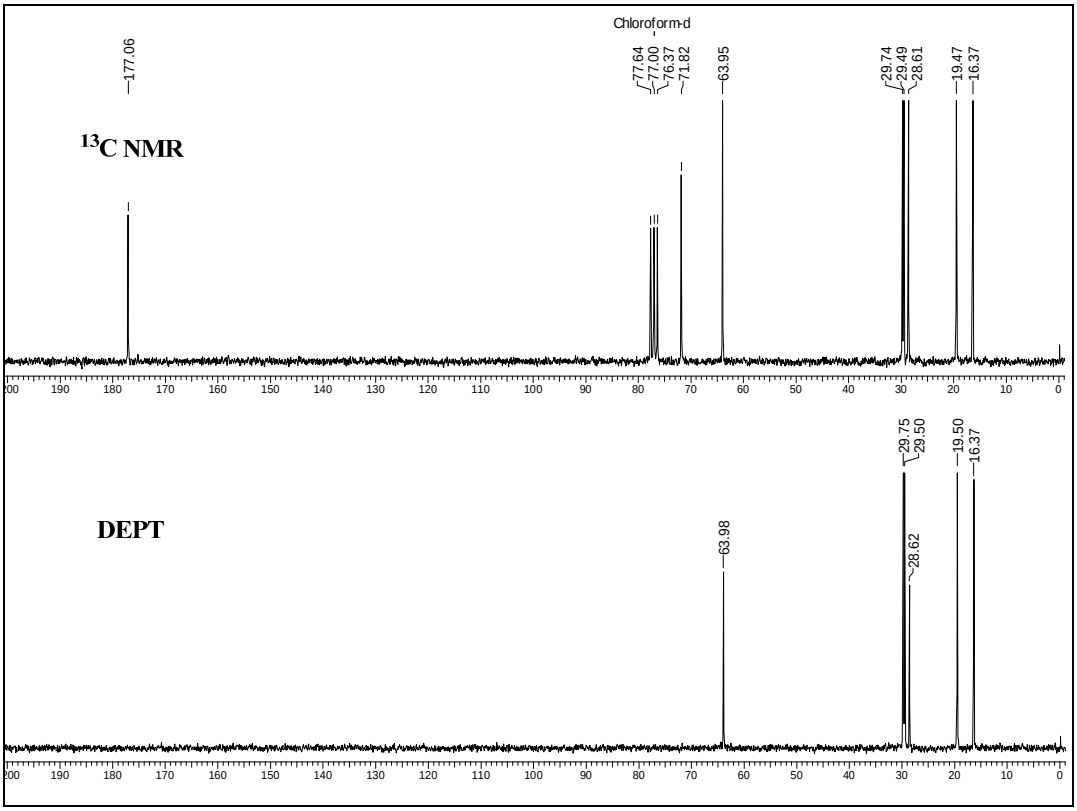
NMR spectra of **3b** ($CDCl_3$)



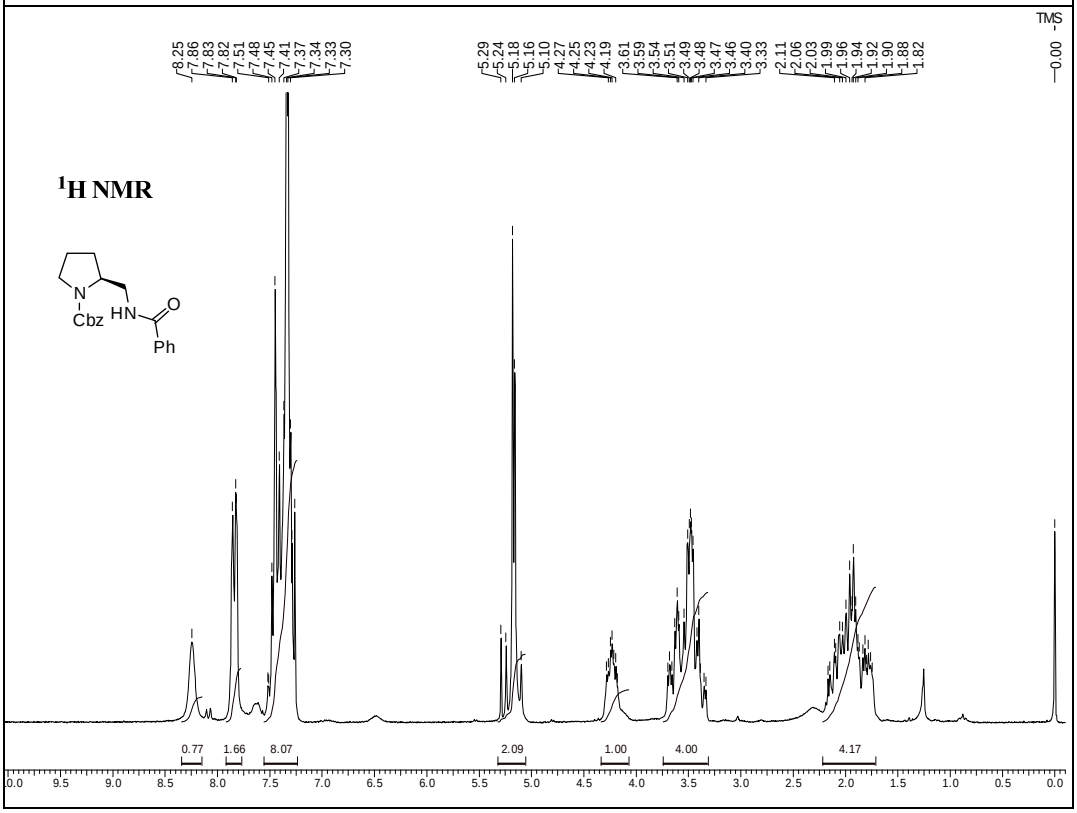



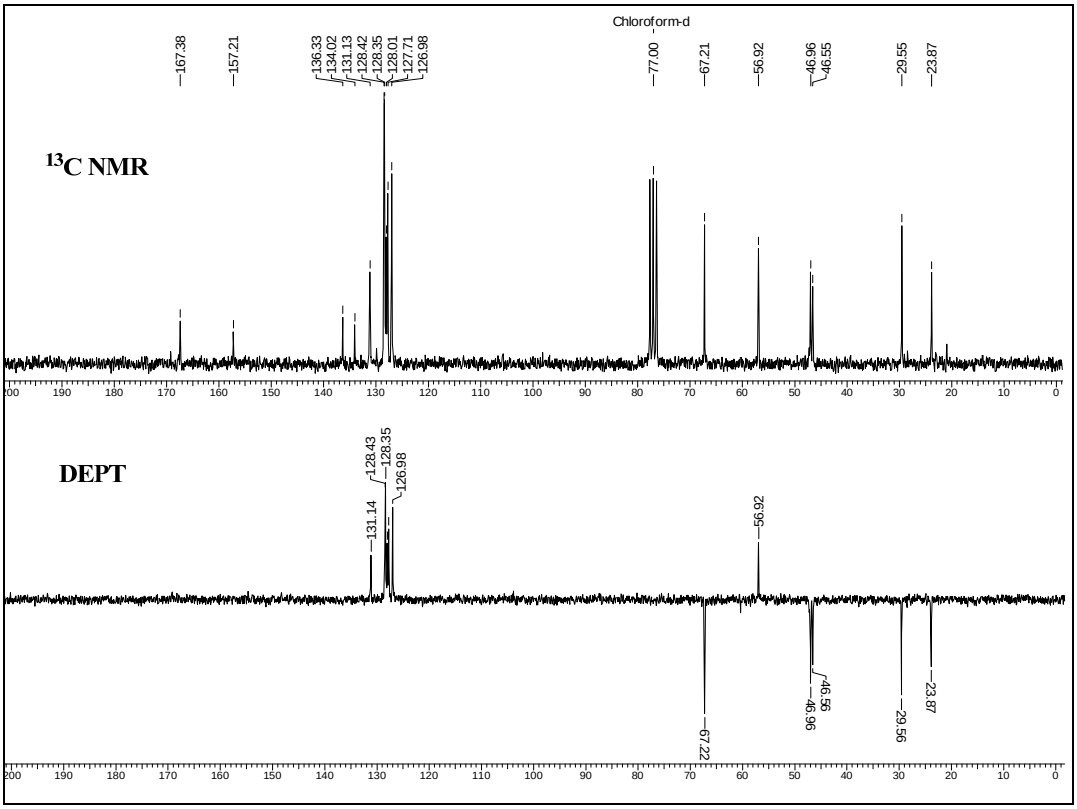
NMR spectra of **4** ($CDCl_3$)



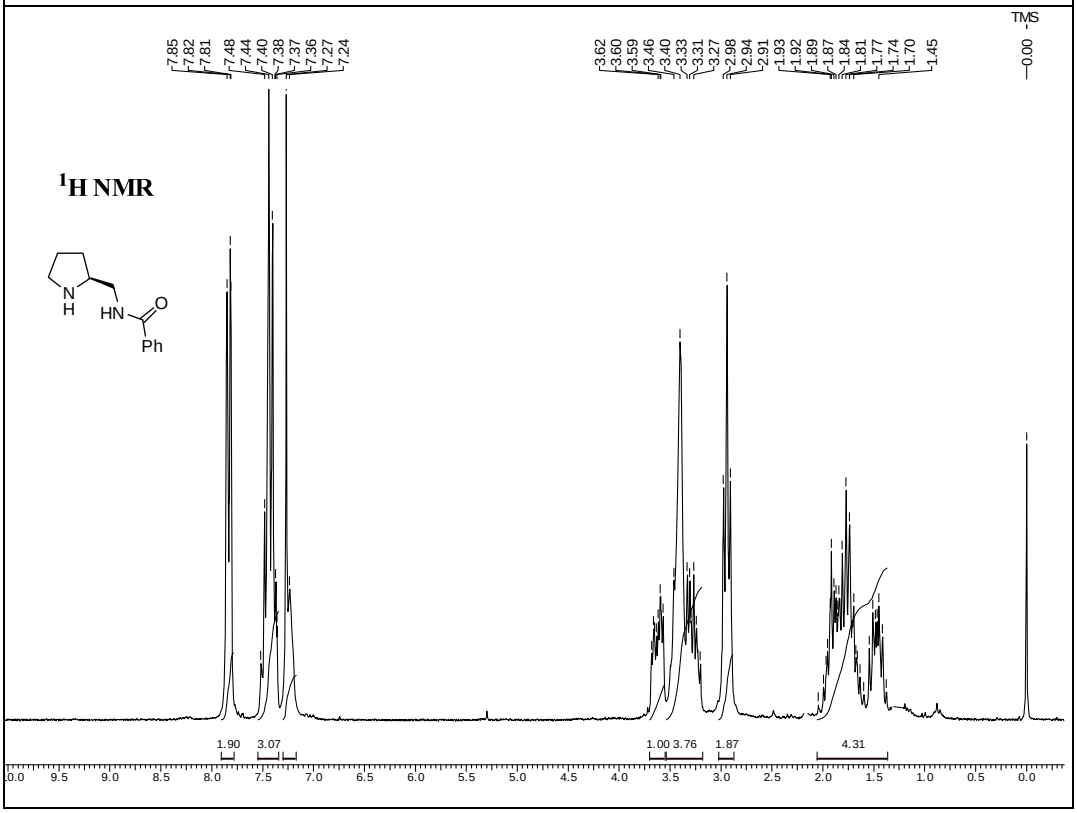



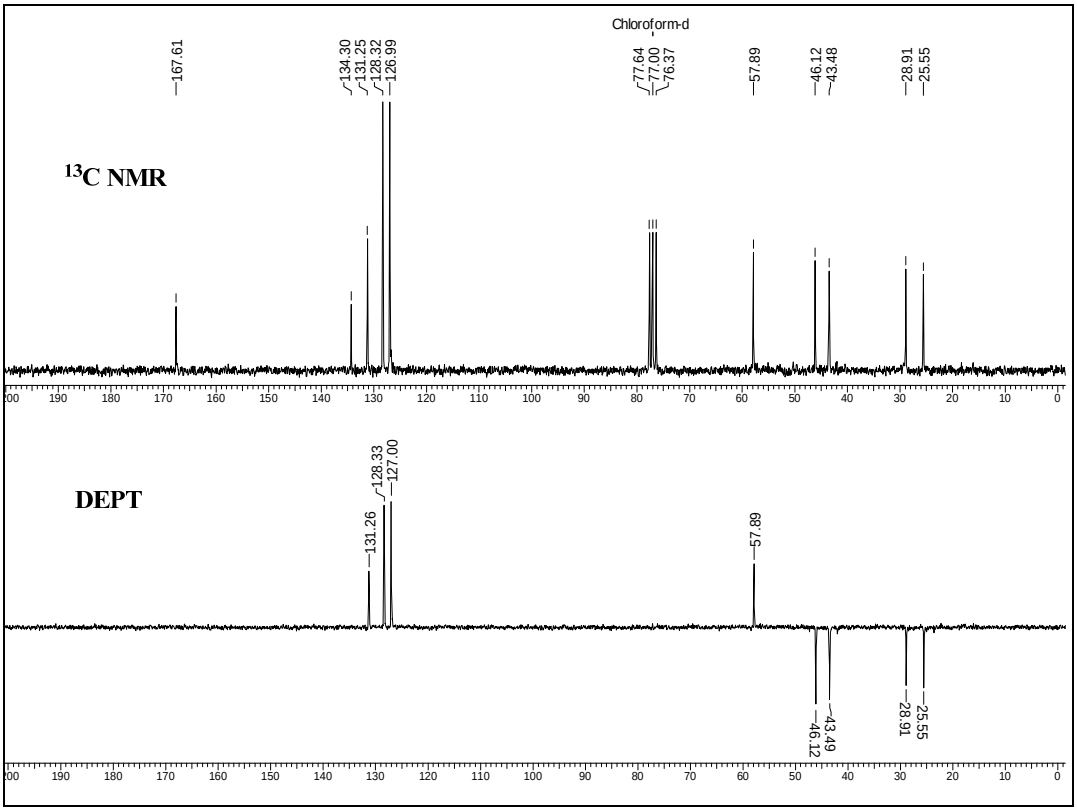
NMR spectra of *N*-Cbz-**6a** ($CDCl_3$)



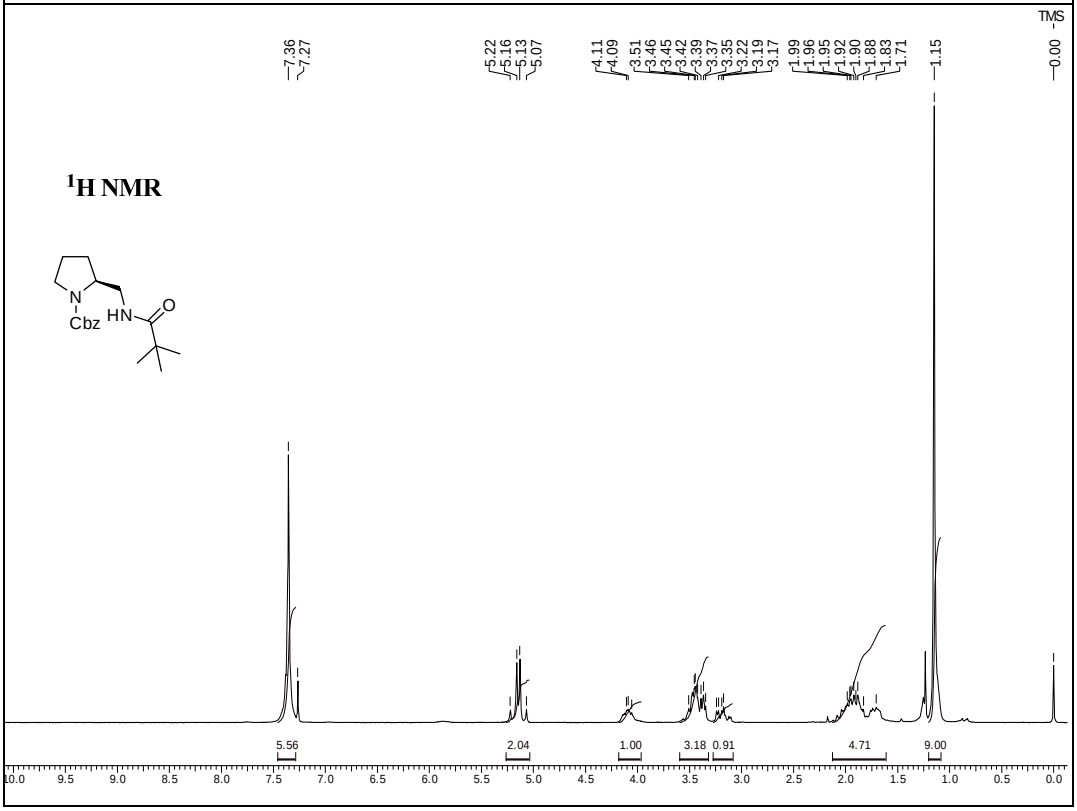



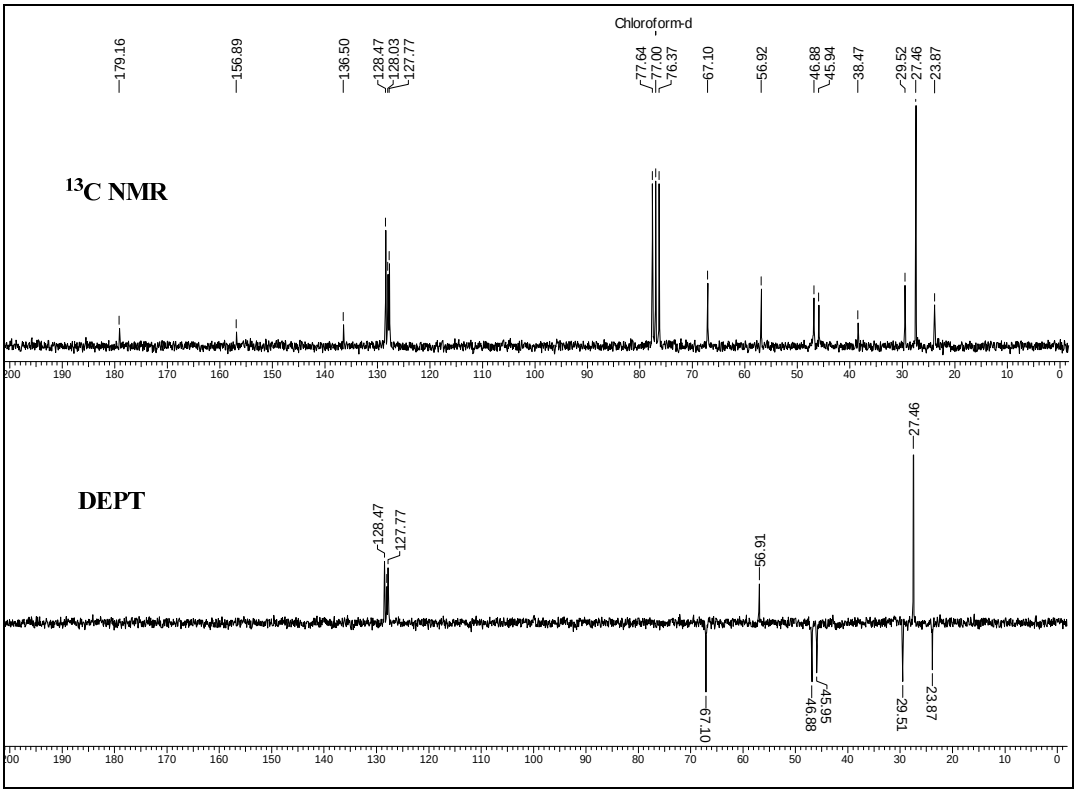
NMR spectra of **6a** ($CDCl_3$)



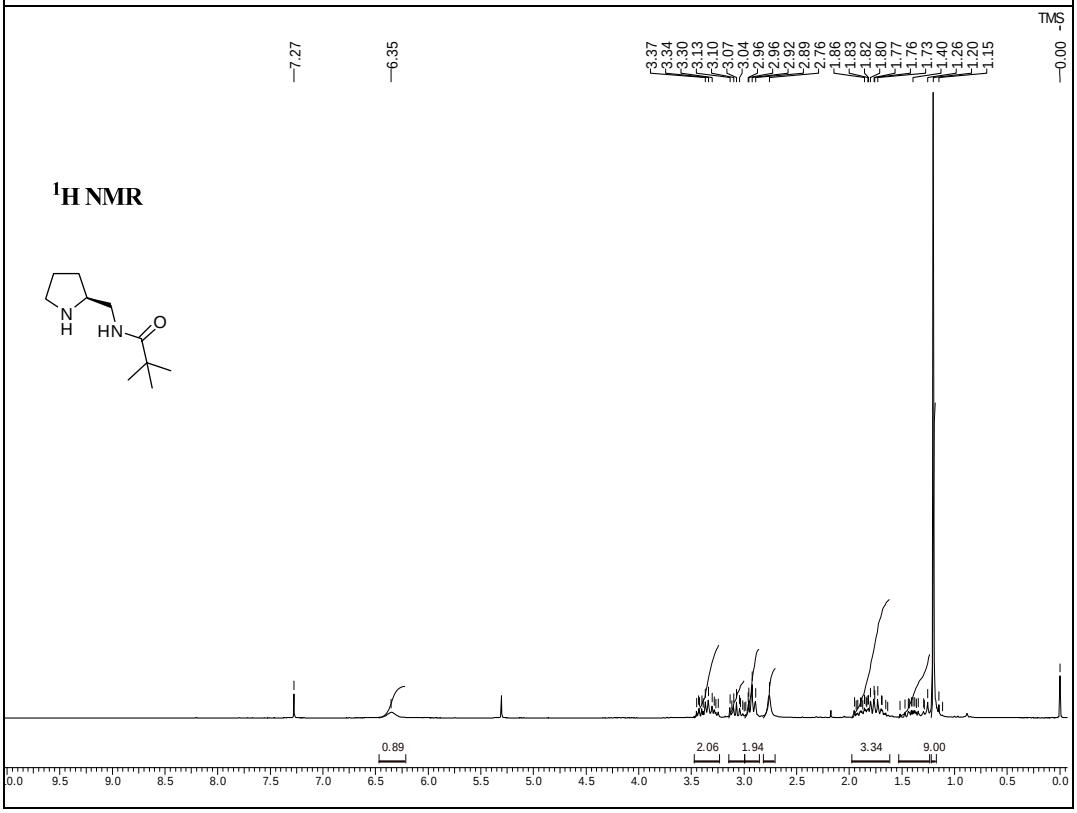



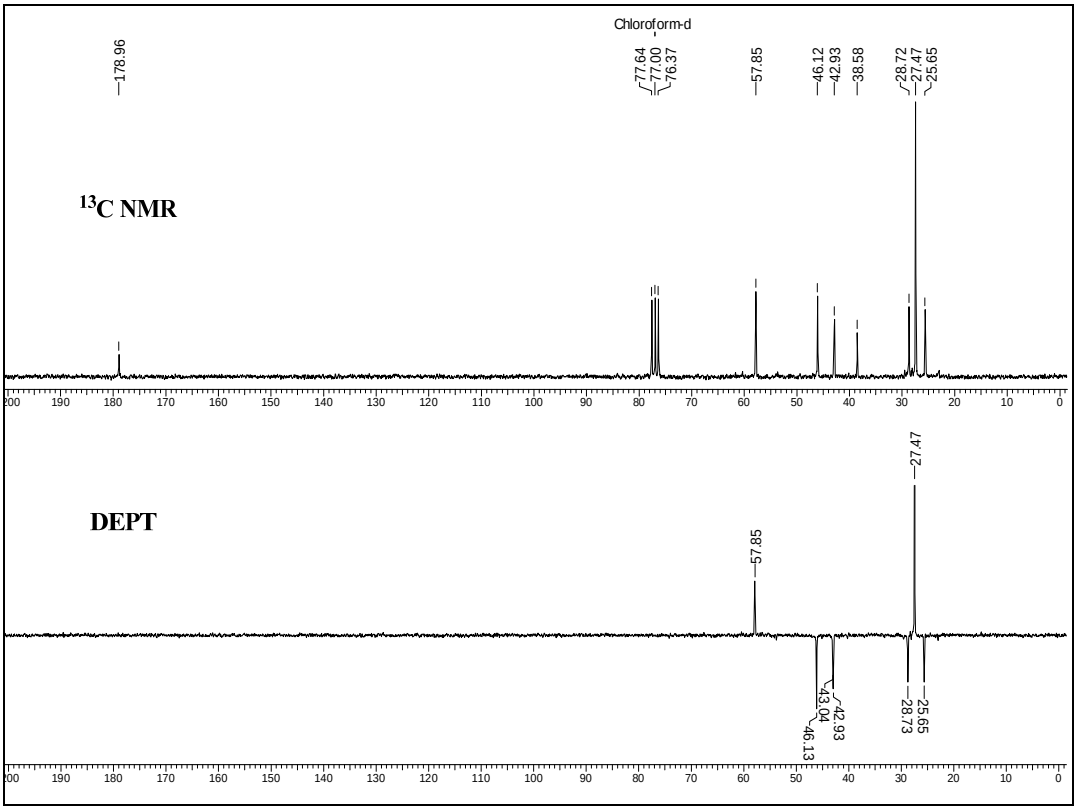
NMR spectra of *N*-Cbz-**6b** ($CDCl_3$)



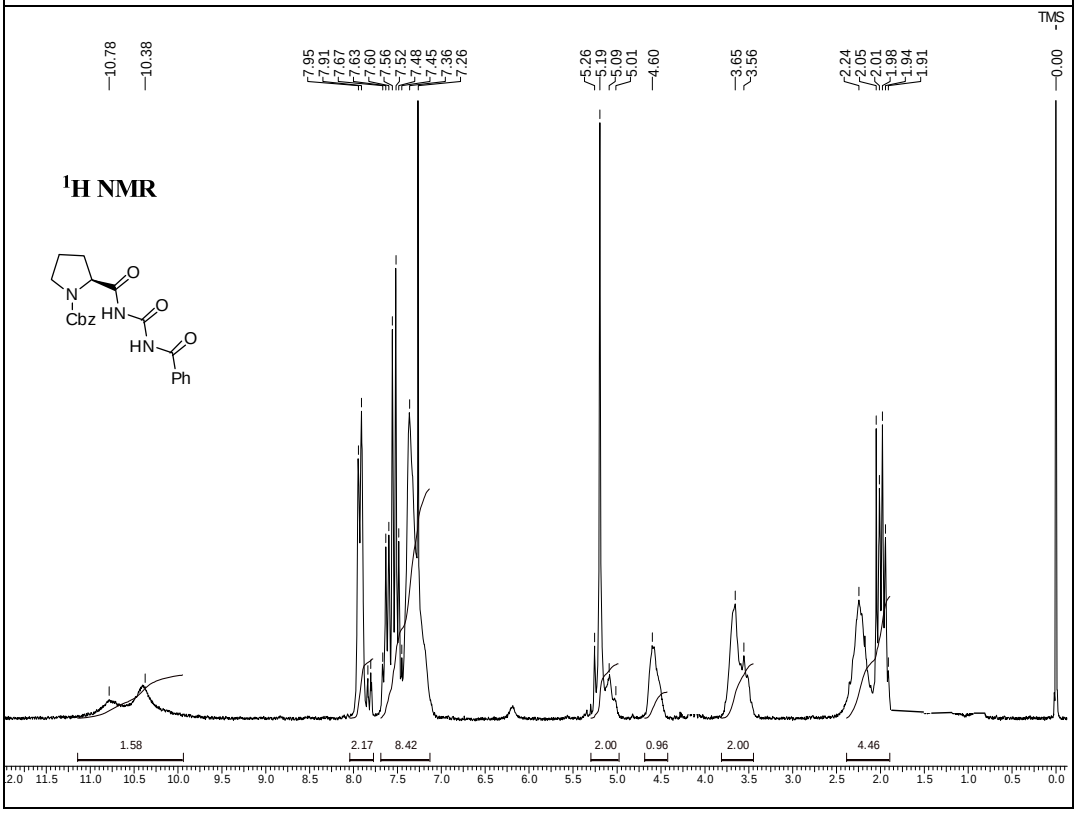



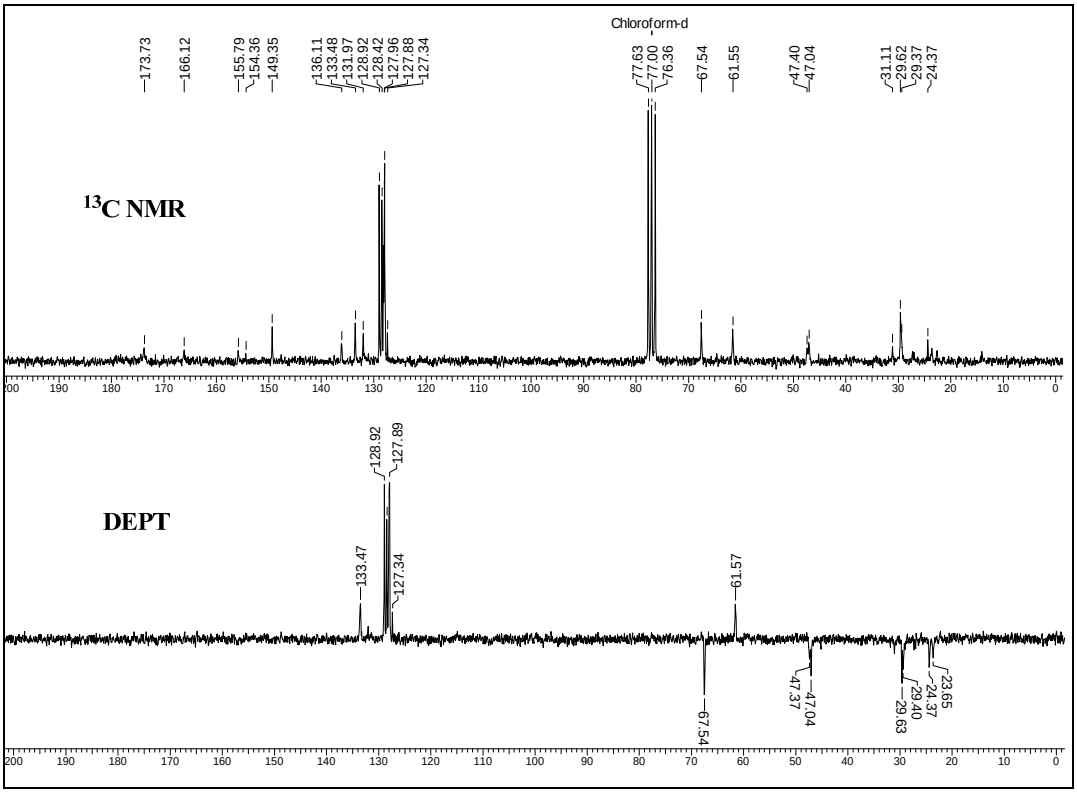
NMR spectra of **6b** ($CDCl_3$)



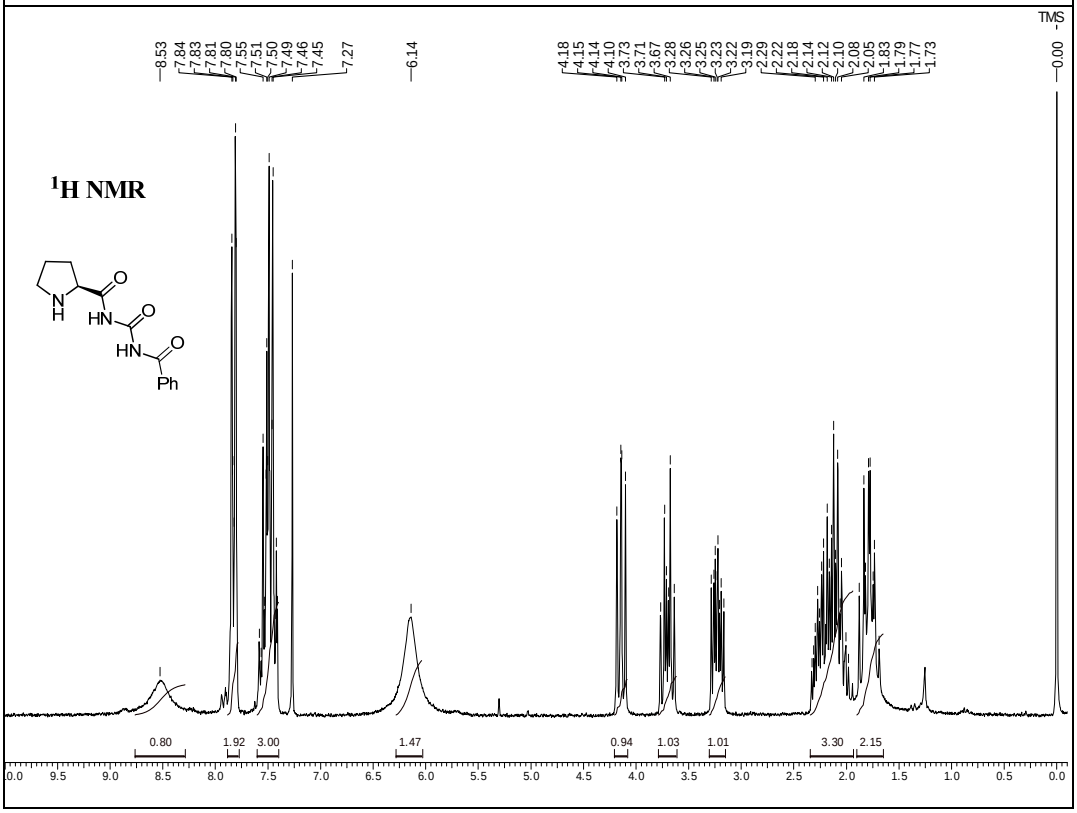



NMR spectra of *N*-Cbz-**10b** ($CDCl_3$)

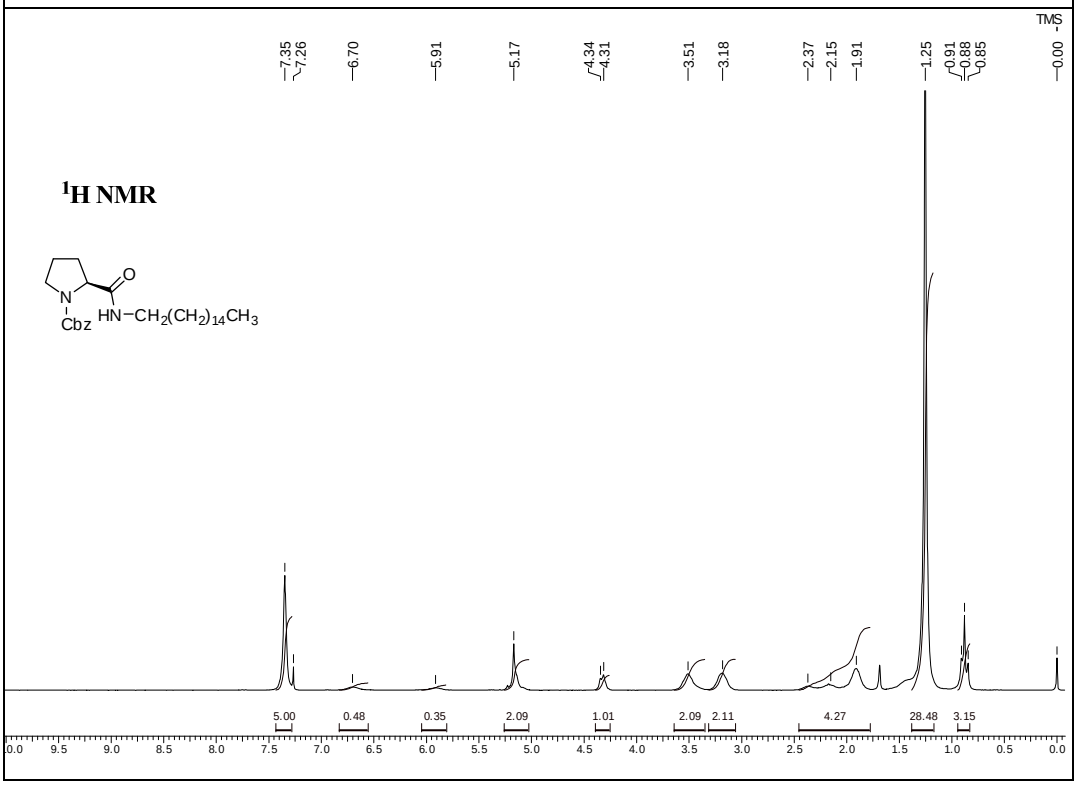


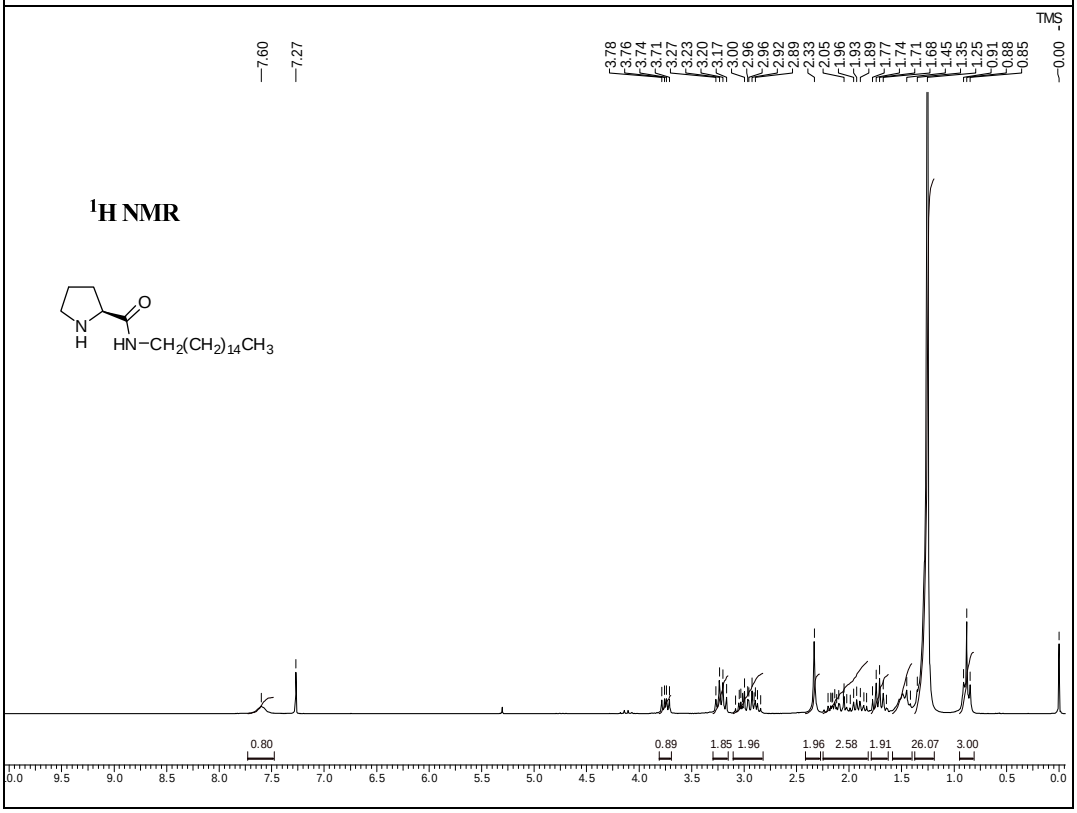
NMR spectra of **10b** ($CDCl_3$)

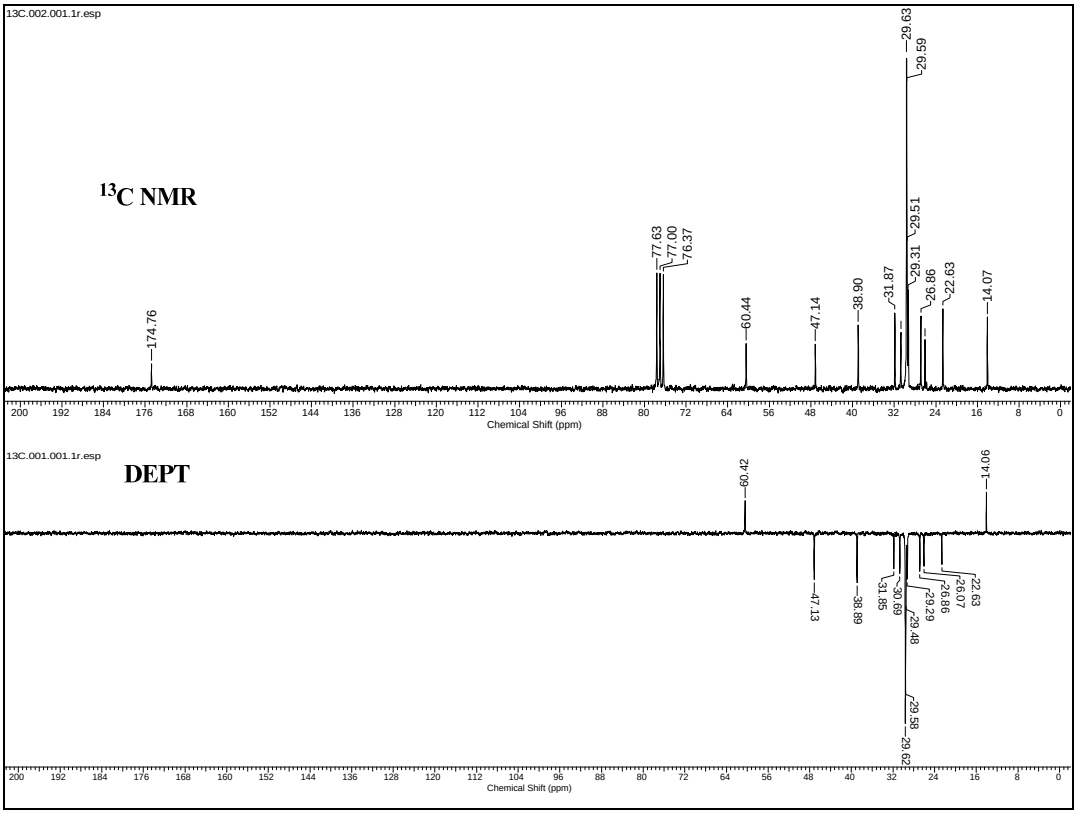


NMR spectra of (*S*)-benzyl 2-(hexadecylcarbamoyl)pyrrolidine-1-carboxylate($CDCl_3$)

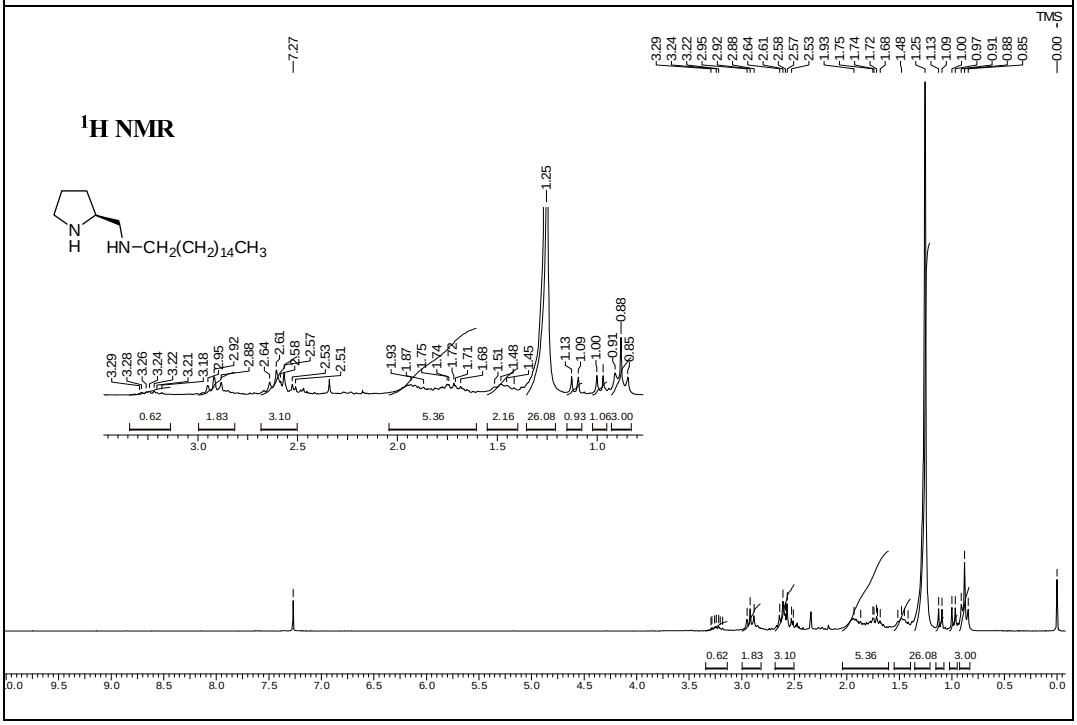


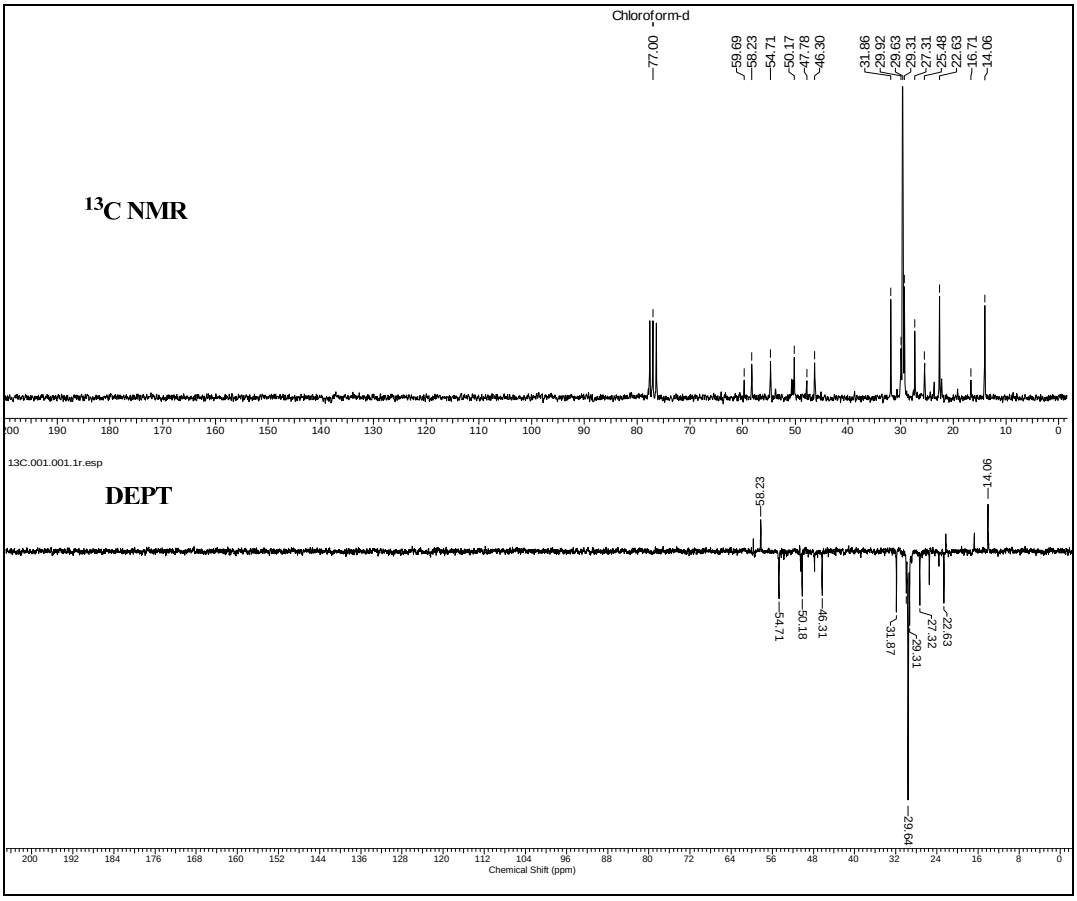
NMR spectra of (*S*)-*N*-hexadecylpyrrolidine-2-carboxamide ($CDCl_3$)



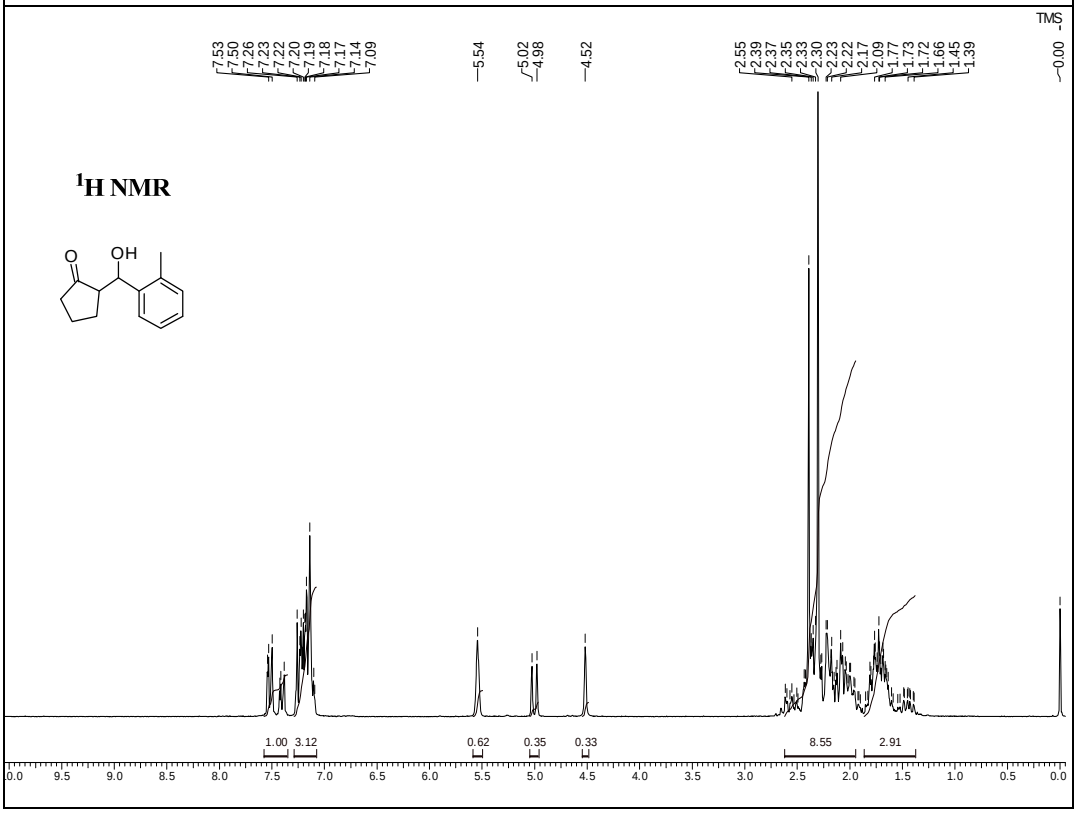



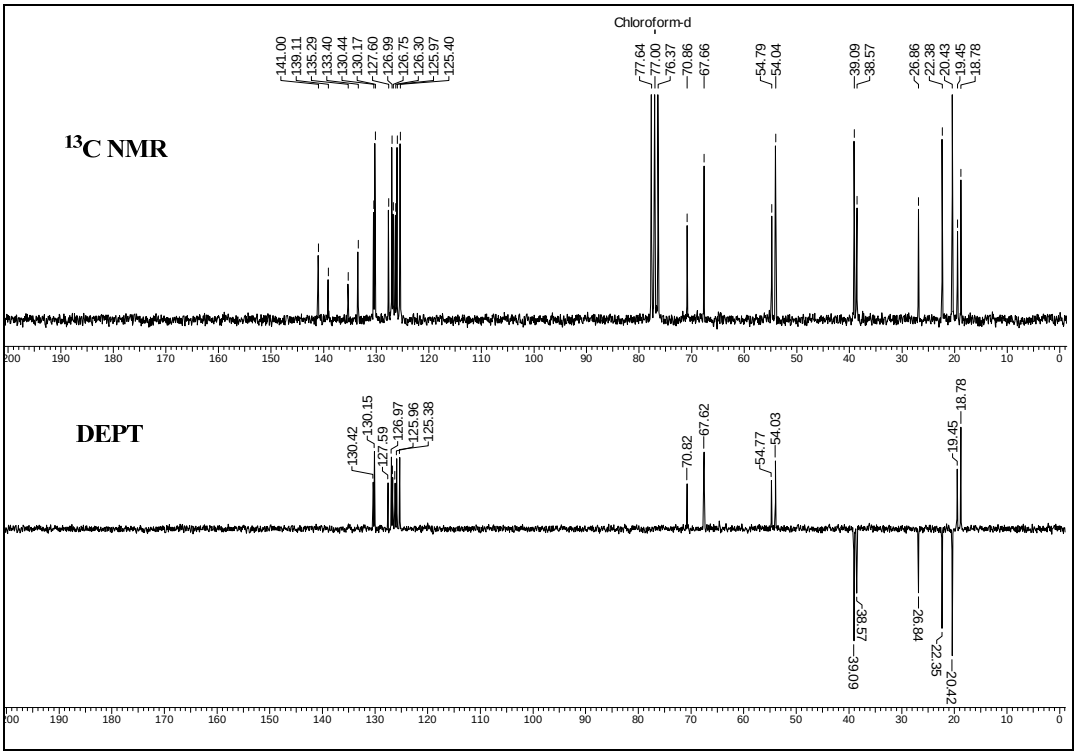
NMR spectra of **13** ($CDCl_3$)

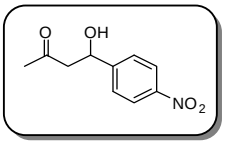


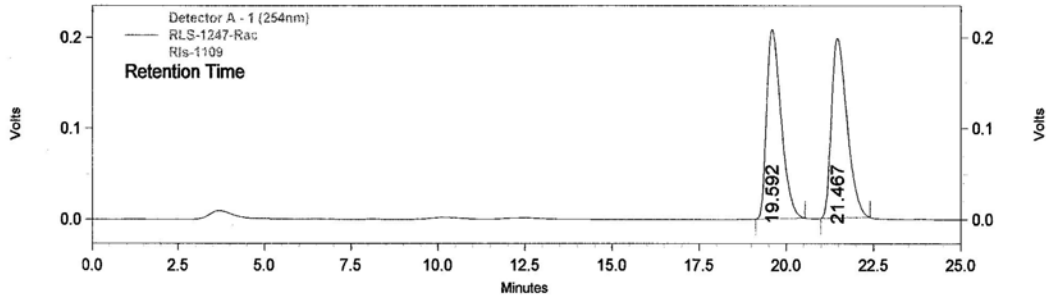
NMR spectra of 2-(hydroxy(*o*-tolyl)methyl)cyclopentanone ($CDCl_3$)





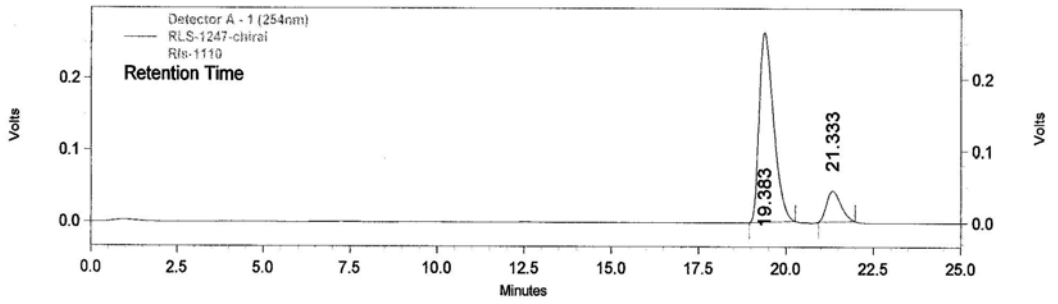

**racemic**




**Detector A - 1 (254nm)**

| Retention Time | C Area | Area % |
|---|---|---|
| 19.592 | 5998521 | 49.364 |
| 21.467 | 6153066 | 50.636 |
| Totals | 12151587 | 100.000 |

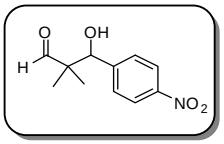
**Table 7, entry 4**



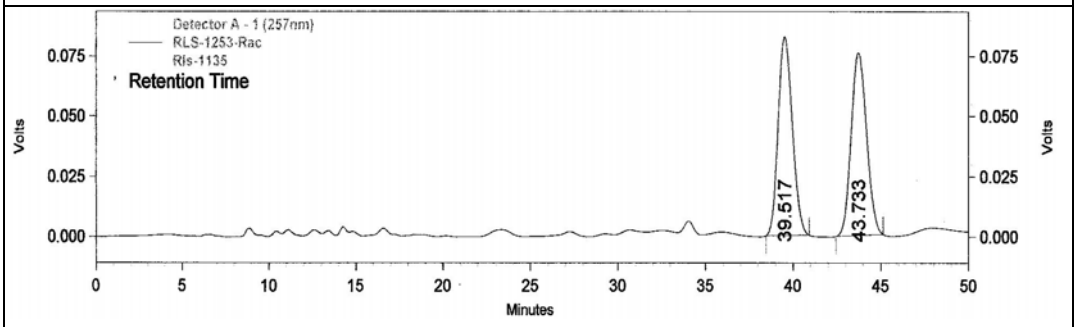

**Detector A - 1 (254nm)**

| Retention Time | C Area | Area % |
|---|---|---|
| 19.383 | 7600000 | 86.106 |
| 21.333 | 1226349 | 13.894 |
| Totals | 8826349 | 100.000 |

Column: Chiralcel OJ-H (250 x 4.6 mm); Mobile phase: *i*-PrOH:petroleum ether (30:70); Flow rate: 0.5 mL/min; UV: 254 nm; Retention time: $t_R$ (*R*-isomer): 19.38 min, $t_R$ (*S*-isomer): 21.33 min.



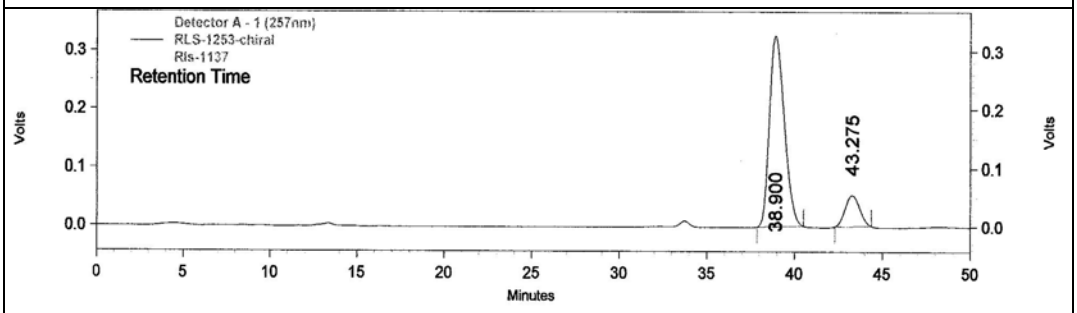

**racemic**




**Detector A - 1 (257nm)**

| Retention Time | C Area | Area % |
|---|---|---|
| 39.517 | 4660641 | 50.042 |
| 43.733 | 4652785 | 49.958 |
| Totals | 9313426 | 100.000 |

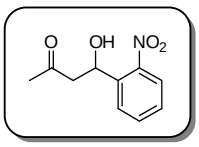
**Table 7, entry 6**



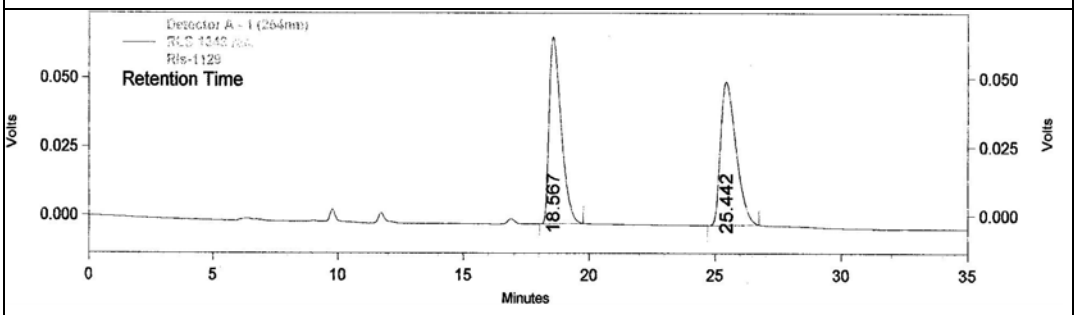

**Detector A - 1 (257nm)**

| Retention Time | C Area | Area % |
|---|---|---|
| 38.900 | 19365893 | 86.302 |
| 43.275 | 3073904 | 13.698 |
| Totals | 22439797 | 100.000 |

Column: Chiralpak AS-H (250 x 4.6 mm); Mobile phase: *i*-PrOH:petroleum ether (15:85); Flow rate: 0.5 mL/min; UV: 254 nm; Retention time: $t_R$ (*R*-isomer): 38.90 min, $t_R$ (*S*-isomer): 43.28 min.



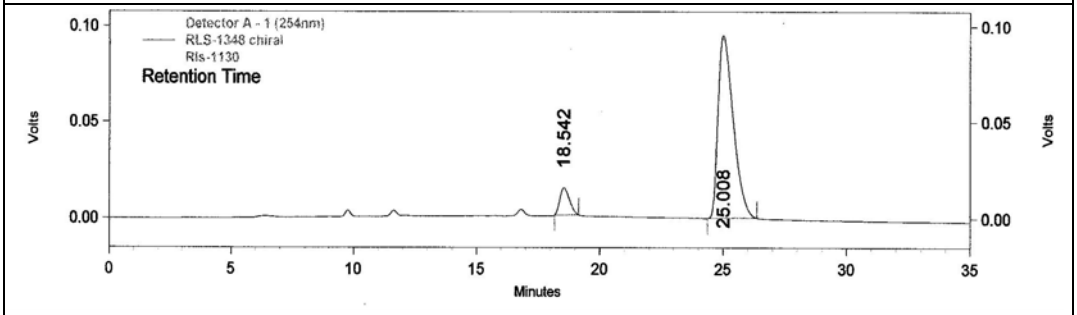

**racemic**




**Detector A - 1 (254nm)**

| Retention Time | C Area | Area % |
|---|---|---|
| 18.567 | 2255869 | 50.156 |
| 25.442 | 2241841 | 49.844 |
| Totals | 4497710 | 100.000 |

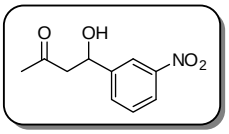
**Table 8, entry 1**



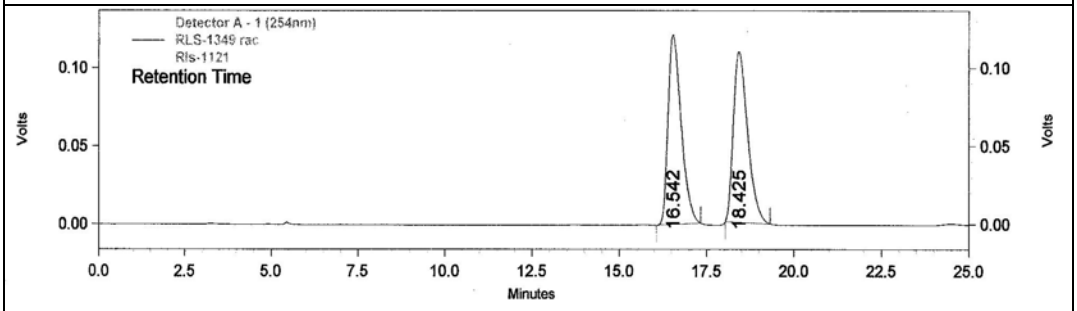

**Detector A - 1 (254nm)**

| Retention Time | C Area | Area % |
|---|---|---|
| 18.542 | 384516 | 8.587 |
| 25.008 | 4093587 | 91.413 |
| Totals | 4478103 | 100.000 |

Column: Chiralpak AS-H (250 x 4.6 mm); Mobile phase: *i*-PrOH:petroleum ether (30:70); Flow rate: 0.5 mL/min; UV: 254 nm; Retention time: $t_R$ (*S*-isomer): 18.54 min, $t_R$ (*R*-isomer): 25.01 min.



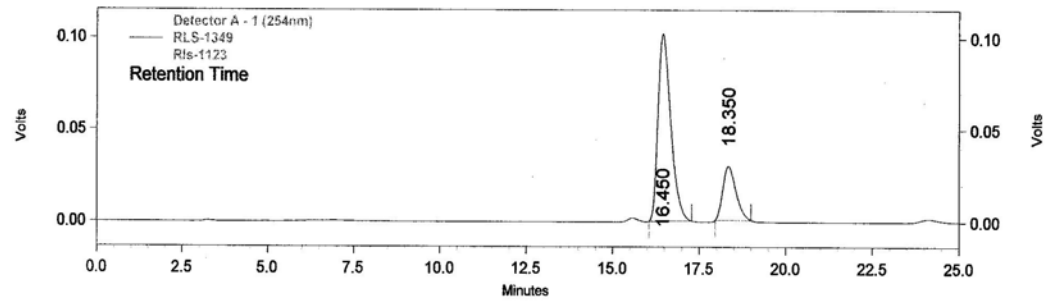

**racemic**




**Detector A - 1 (254nm)**

| Retention Time | C Area | Area % |
|---|---|---|
| 16.542 | 3186693 | 50.549 |
| 18.425 | 3117421 | 49.451 |
| Totals | 6304114 | 100.000 |

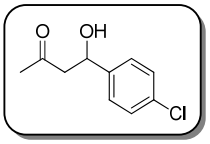
**Table 8, entry 2**



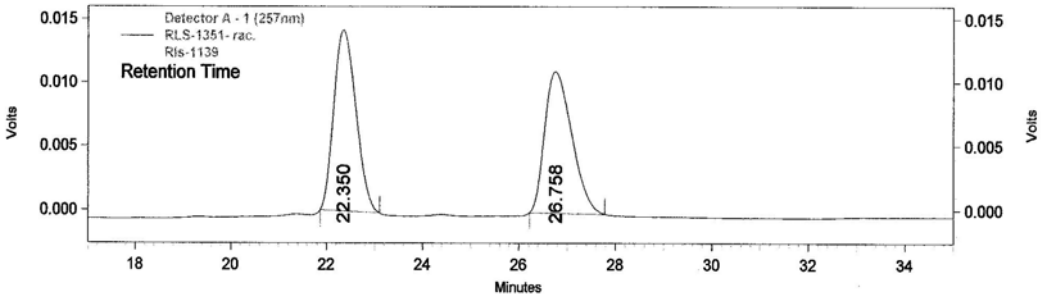

**Detector A - 1 (254nm)**

| Retention Time | C Area | Area % |
|---|---|---|
| 16.450 | 2623541 | 77.166 |
| 18.350 | 776343 | 22.834 |
| Totals | 3399884 | 100.000 |

Column: Chiralcel OJ-H (250 x 4.6 mm); Mobile phase: *i*-PrOH:petroleum ether (20:80); Flow rate: 1.0 mL/min, UV: 254 nm; Retention time: $t_R$ (*R*-isomer) 16.45 min, $t_R$ (*S*-isomer) 18.35 min**.**



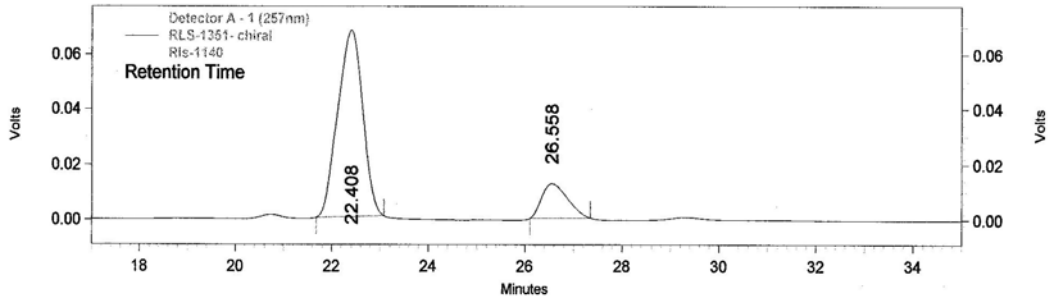

**racemic**




**Detector A - 1 (257nm)**

| Retention Time | C Area | Area % |
|---|---|---|
| 22.350 | 455264 | 51.087 |
| 26.758 | 435897 | 48.913 |
| Totals | 891161 | 100.000 |

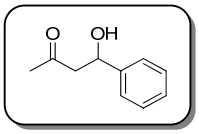
**Table 8, entry 3**



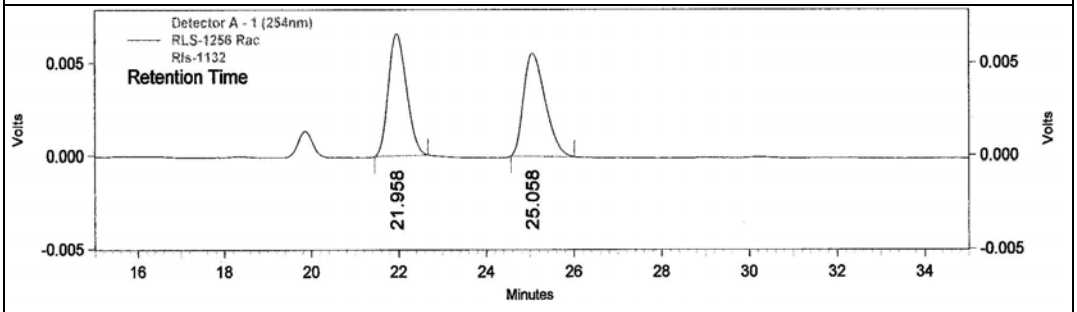

**Detector A - 1 (257nm)**

| Retention Time | C Area | Area % |
|---|---|---|
| 22.408 | 2433827 | 83.949 |
| 26.558 | 465342 | 16.051 |
| Totals | 2899169 | 100.000 |

Column: Chiracel AS-H (250 x 4.6 mm); Mobile phase: *i*-PrOH:petroleum ether (15:85); Flow rate: 0.5 mL/min; UV: 257 nm; Retention time: $t_R$ (*R*-isomer): 22.35 min, $t_R$ (*S*-isomer): 26.76 min.



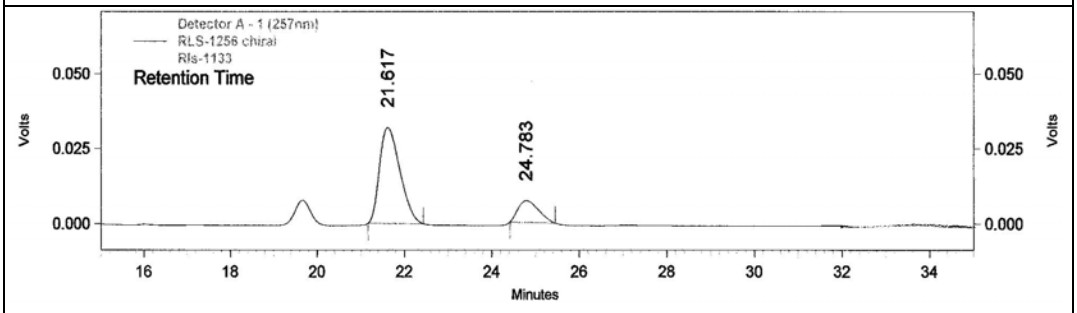

**racemic**




**Detector A - 1 (254nm)**

| Retention Time | C Area | Area % |
|---|---|---|
| 21.958 | 190334 | 49.943 |
| 25.058 | 190766 | 50.057 |
| Totals | 381100 | 100.000 |

**Table 8, entry 4**




**Detector A - 1 (257nm)**

| Retention Time | C Area | Area % |
|---|---|---|
| 21.617 | 1042385 | 81.535 |
| 24.783 | 236073 | 18.465 |
| Totals | 1278458 | 100.000 |

Column: Chiralpak AS-H (250 x 4.6 mm); Mobile phase: *i*-PrOH:petroleum ether (15:85); Flow rate: 0.5 mL/min; UV: 257 nm; Retention time: $t_R$ (*R*-isomer ): 21.62 min, $t_R$ (*S*-isomer): 24.78 min.

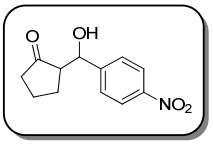
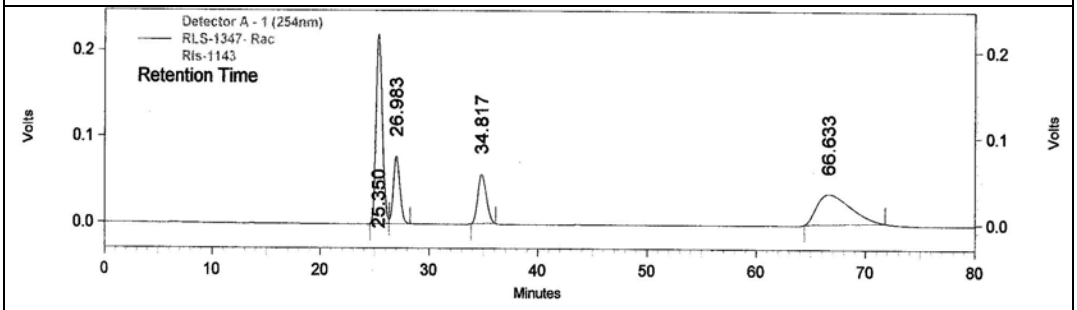


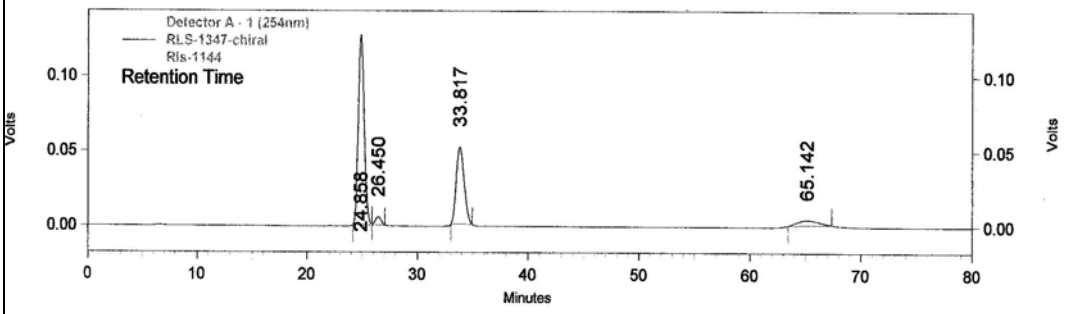

**Table 5, entry 1 (racemic)**




**Detector A - 1 (254nm)**

| Retention Time | C Area | Area % |
|---|---|---|
| 25.350 | 8926282 | 38.962 |
| 26.983 | 3277755 | 14.307 |
| 34.817 | 3134831 | 13.683 |
| 66.633 | 7571417 | 33.048 |
| Totals | 22910285 | 100.000 |

**Table 9, entry 1**




**Detector A - 1 (254nm)**

| Retention Time | C Area | Area % |
|---|---|---|
| 24.858 | 4753788 | 59.679 |
| 26.450 | 191901 | 2.409 |
| 33.817 | 2550010 | 32.013 |
| 65.142 | 469888 | 5.899 |
| Totals | 7965587 | 100.000 |

Column: Chiralpak AS-H (250 x 4.6 mm); Mobile phase: *i*-PrOH:petroleum ether (25:75); Flow rate: 0.5 mL/min; UV: 254 nm; Retention time: $t_R$ (*syn*, major): 24.86 min, $t_R$ (*anti*, minor): 26.45 min, $t_R$ (*anti*, major): 33.82 min, $t_R$ (*syn*, minor): 65.14 min.

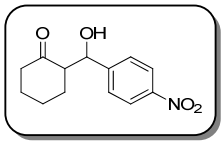
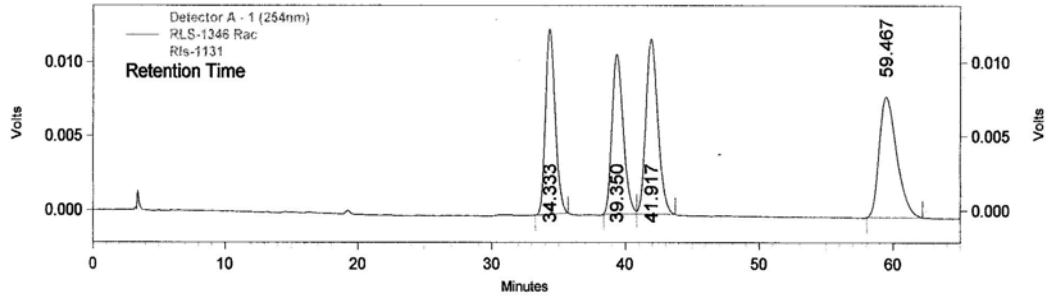


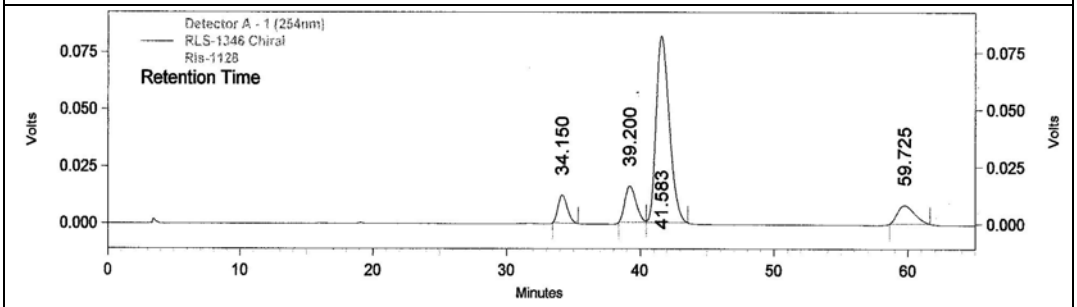

**Table 5, entry 3 (racemic)**




**Detector A - 1 (254nm)**

| Retention Time | C Area | Area % |
|---|---|---|
| 34.333 | 632798 | 23.058 |
| 39.350 | 630567 | 22.977 |
| 41.917 | 739773 | 26.956 |
| 59.467 | 741254 | 27.010 |
| Totals | 2744392 | 100.000 |

**Table 9, entry 2**




**Detector A - 1 (254nm)**

| Retention Time | C Area | Area % |
|---|---|---|
| 34.150 | 590773 | 7.544 |
| 39.200 | 928591 | 11.858 |
| 41.583 | 5605521 | 71.581 |
| 59.725 | 706105 | 9.017 |
| Totals | 7830990 | 100.000 |

Column: Kromasil 5-CelluCoat (250 x 4.6 mm); Mobile phase: *i*-PrOH:petroleum ether (4:96); Flow rate: 1.0 mL/min; UV: 254 nm; Retention time: $t_R$ (*syn*, minor): 34.15 min, $t_R$ (*syn*, major): 39.20 min, $t_R$ (*anti*, major): 41.58 min, $t_R$ (*anti*, minor): 59.73 min.

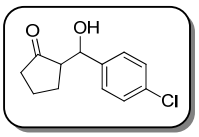
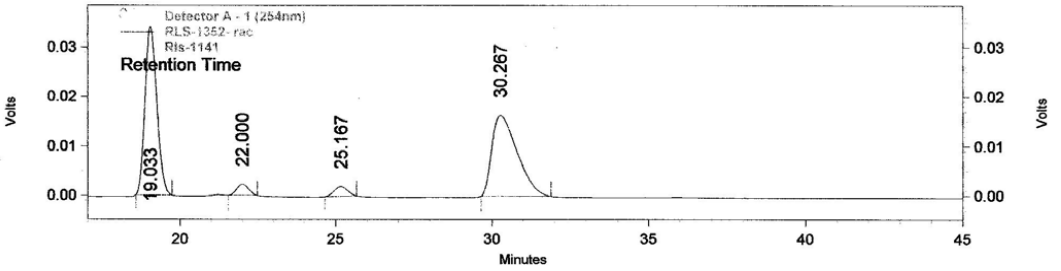


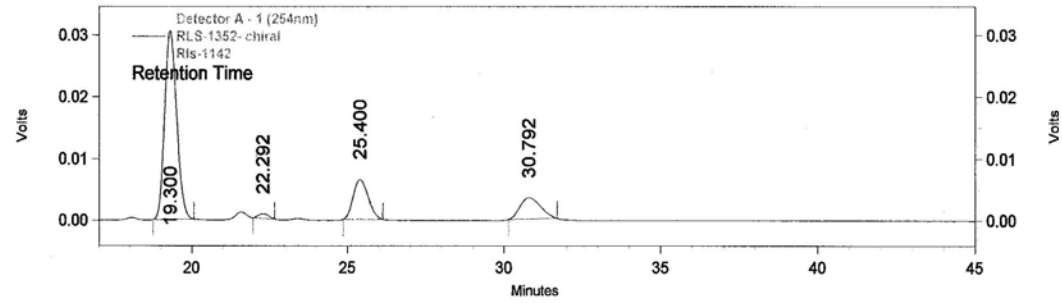

**Table 5, entry 4 (racemic)**




**Detector A - 1 (254nm)**

| Retention Time | C Area | Area % |
|---|---|---|
| 19.033 | 905868 | 46.634 |
| 22.000 | 59338 | 3.055 |
| 25.167 | 58070 | 2.989 |
| 30.267 | 919249 | 47.322 |
| Totals | 1942525 | 100.000 |

**Table 9, entry 3**




**Detector A - 1 (254nm)**

| Retention Time | C Area | Area % |
|---|---|---|
| 19.300 | 825672 | 68.069 |
| 22.292 | 16184 | 1.334 |
| 25.400 | 214186 | 17.658 |
| 30.792 | 156956 | 12.940 |
| Totals | 1212998 | 100.000 |

Column: Chiralpak AS-H (250 x 4.6 mm); Mobile phase: *i*-PrOH:petroleum ether (15:85); Flow rate: 0.5 mL/min; UV: 254 nm; Retention time: $t_R$ (*syn*, major): 19.30 min, $t_R$ (*anti*, minor): 22.29 min, $t_R$ (*anti*, major): 25.40 min, $t_R$ (*syn*, minor): 30.79 min.

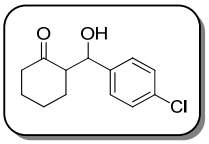
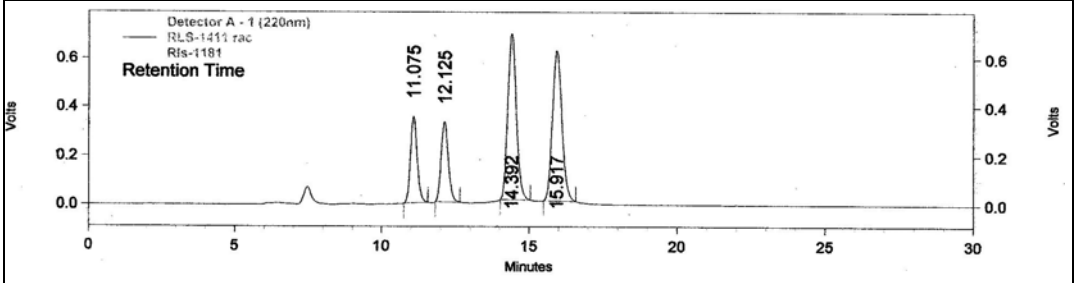



**Table 5, entry 5 (racemic)**




**Detector A - 1 (220nm)**

| Retention Time | C Area | Area % |
|---|---|---|
| 11.075 | 5618838 | 14.493 |
| 12.125 | 5544784 | 14.302 |
| 14.392 | 13776920 | 35.536 |
| 15.917 | 13828599 | 35.669 |
| Totals | 38769141 | 100.000 |

Column: Kromasil 5-Amy Coat (250 x 4.6 mm); Mobile phase: *i*-PrOH:petroleum ether (30:70); Flow rate: 0.5 mL/min; UV: 220 nm; Retention time: $t_R$ (*syn*): 11.08 min, $t_R$ (*syn*): 12.13 min, $t_R$ (*anti*): 14.39 min, $t_R$ (*anti*): 15.92 min.

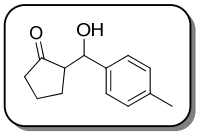
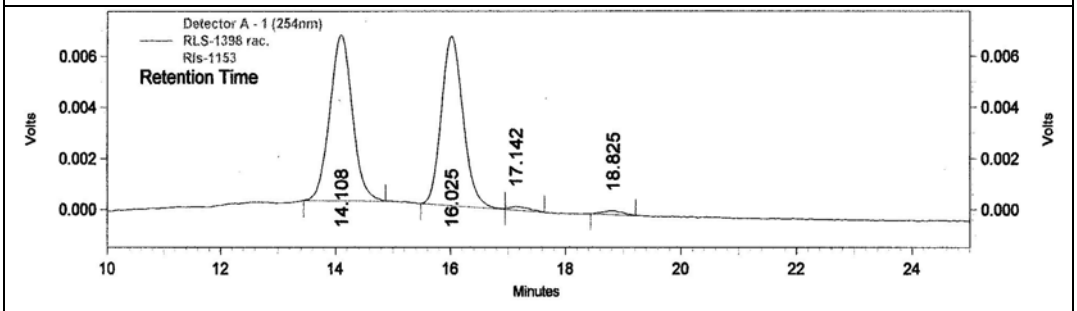


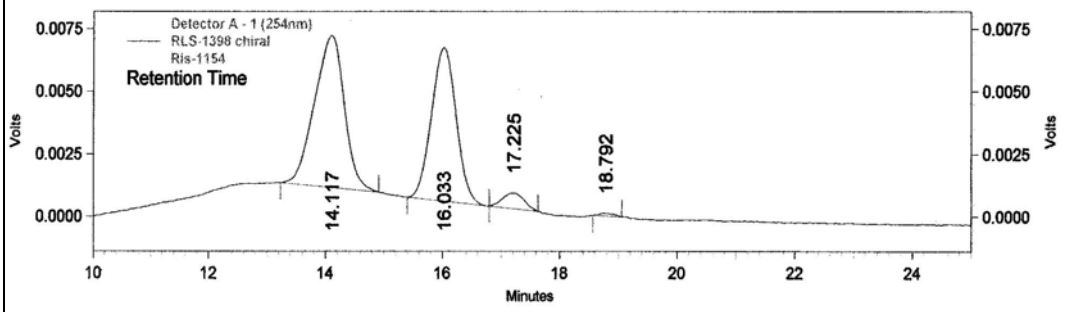

**Table 5, entry 6 (racemic)**




**Detector A - 1 (254nm)**

| Retention Time | C Area | Area % |
|---|---|---|
| 14.108 | 177481 | 49.501 |
| 16.025 | 173872 | 48.494 |
| 17.142 | 3439 | 0.959 |
| 18.825 | 3751 | 1.046 |
| Totals | 358543 | 100.000 |

**Table 9, entry 4**




**Detector A - 1 (254nm)**

| Retention Time | C Area | Area % |
|---|---|---|
| 14.117 | 215057 | 51.996 |
| 16.033 | 180484 | 43.637 |
| 17.225 | 16068 | 3.885 |
| 18.792 | 1990 | 0.481 |
| Totals | 413599 | 100.000 |

Column: Kromasil 5-AmyCoat (250 x 4.6 mm); Mobile phase: *i*-PrOH:petroleum ether (15:85); Flow rate: 0.5 mL/ min; UV: 254 nm; Retention time: $t_R$ (*syn*, major): 14.12 min, $t_R$ (*syn*, minor): 16.03 min, $t_R$ (*anti*, major): 17.23 min, $t_R$ (*anti*, minor): 18.79 min.

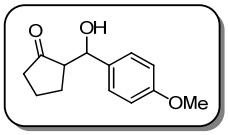
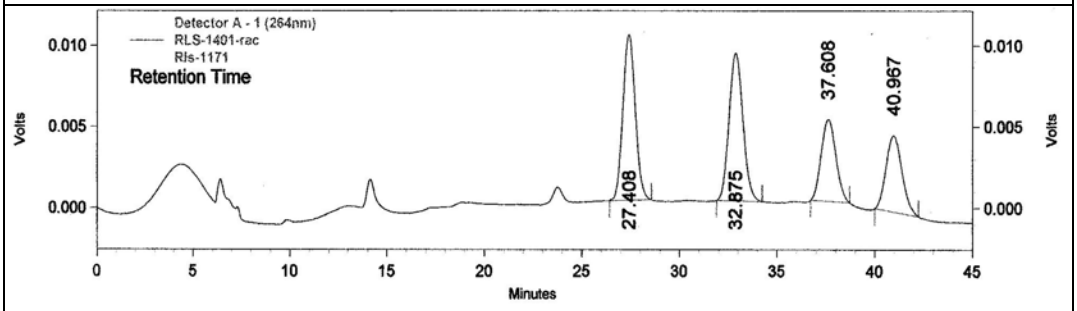


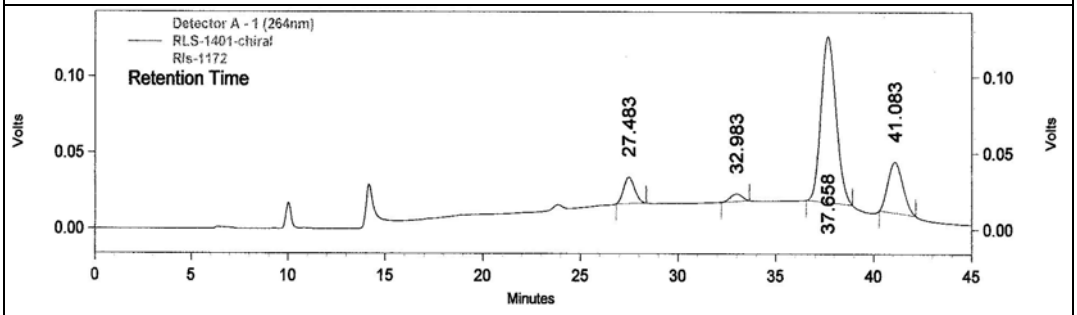

**Table 5, entry 7 (racemic)**




**Detector A - 1 (264nm)**

| Retention Time | C Area | Area % |
|---|---|---|
| 27.408 | 451570 | 31.473 |
| 32.875 | 451109 | 31.441 |
| 37.608 | 264480 | 18.434 |
| 40.967 | 267617 | 18.652 |
| Totals | 1434776 | 100.000 |

**Table 9, entry 5**




**Detector A - 1 (264nm)**

| Retention Time | C Area | Area % |
|---|---|---|
| 27.483 | 682251 | 8.032 |
| 32.983 | 203874 | 2.400 |
| 37.658 | 5838651 | 68.740 |
| 41.083 | 1769027 | 20.827 |
| Totals | 8493803 | 100.000 |

Column: Kromasil 5-AmyCoat (250 x 4.6 mm); Mobile phase: *i*-PrOH:petroleum ether (10:90); Flow rate: 0.5 mL/ min; UV: 264 nm; Retention time: $t_R$ (*syn*, major): 27.48 min, $t_R$ (*syn*, minor): 32.98 min, $t_R$ (*anti*, major): 37.66 min, $t_R$ (*anti*, minor): 41.08 min.

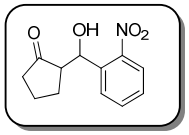
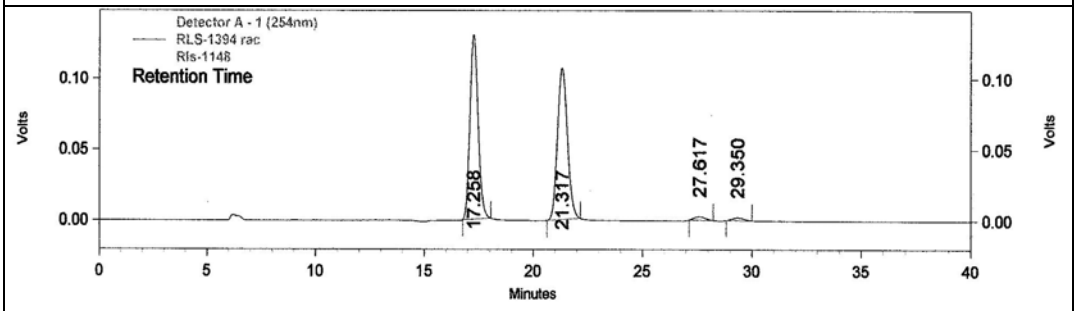


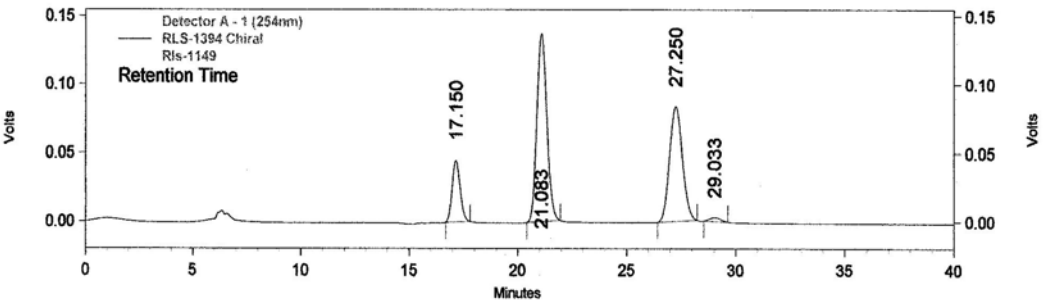

**Table 5, entry 8 (racemic)**




**Detector A - 1 (254nm)**

| Retention Time | C Area | Area % |
|---|---|---|
| 17.258 | 3389769 | 48.801 |
| 21.317 | 3397600 | 48.913 |
| 27.617 | 85830 | 1.236 |
| 29.350 | 72958 | 1.050 |
| Totals | 6946157 | 100.000 |

**Table 9, entry 6**




**Detector A - 1 (254nm)**

| Retention Time | C Area | Area % |
|---|---|---|
| 17.150 | 1147982 | 12.643 |
| 21.083 | 4386426 | 48.308 |
| 27.250 | 3445606 | 37.947 |
| 29.033 | 100057 | 1.102 |
| Totals | 9080071 | 100.000 |

Column: Chiralcel OD-H (250 x 4.6 mm); Mobile phase: *i*-PrOH:petroleum ether (10:90); Flow rate: 0.5 mL/min; UV: 254 nm; Retention time: $t_R$ (*syn*, minor): 17.15 min, $t_R$ (*syn*, major): 21.08 min, $t_R$ (*anti*, major): 27.25 min, $t_R$ (*anti*, minor): 29.03 min.

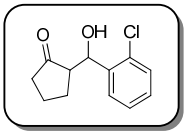
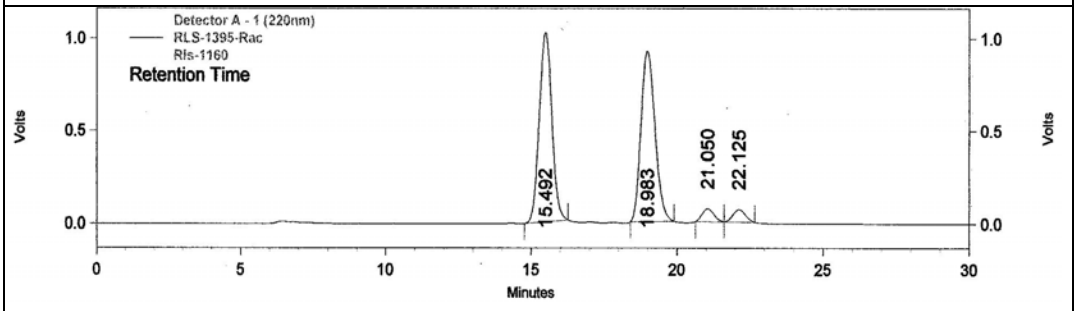


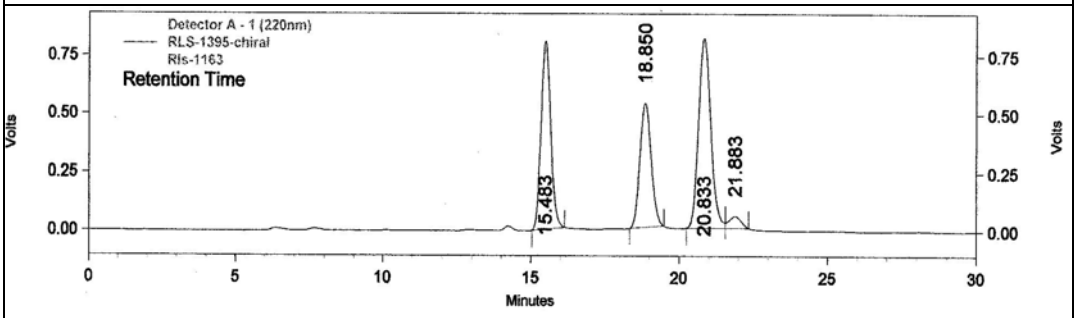

**Table 5, entry 9 (racemic)**




**Detector A - 1 (220nm)**

| Retention Time | C Area | Area % |
|---|---|---|
| 15.492 | 30767026 | 46.994 |
| 18.983 | 30774244 | 47.005 |
| 21.050 | 1939188 | 2.962 |
| 22.125 | 1989297 | 3.038 |
| Totals | 65469755 | 100.000 |

**Table 9, entry 7**




**Detector A - 1 (220nm)**

| Retention Time | C Area | Area % |
|---|---|---|
| 15.483 | 18226470 | 31.923 |
| 18.850 | 14070852 | 24.645 |
| 20.833 | 23367676 | 40.928 |
| 21.883 | 1429666 | 2.504 |
| Totals | 57094664 | 100.000 |

Column: Kromasil 5-AmyCoat (250 x 4.6 mm); Mobile phase: *i*-PrOH:*n*-hexane (10:90); Flow rate: 0.5 mL/min; UV: 220 nm; Retention time: $t_R$ (*syn*, major): 15.48 min, $t_R$ (*syn*, minor): 18.85 min, $t_R$ (*anti*, major): 20.83 min, $t_R$ (*anti*, minor): 21.88 min.

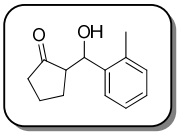
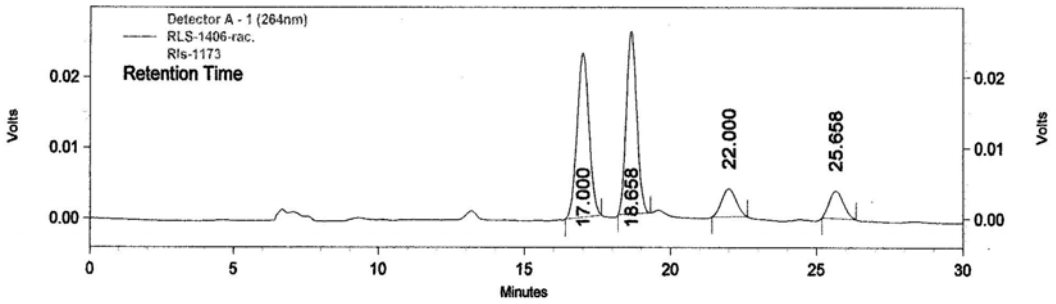


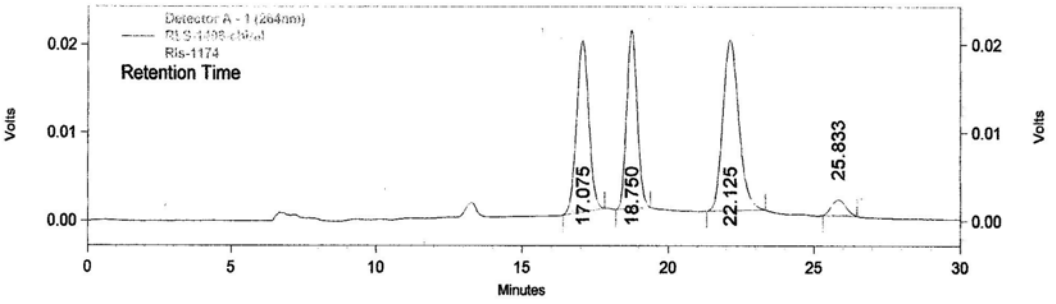

**Table 5, entry 10 (racemic)**




**Detector A - 1 (264nm)**

| Retention Time | C Area | Area % |
|---|---|---|
| 17.000 | 661630 | 41.940 |
| 18.658 | 644975 | 40.884 |
| 22.000 | 138906 | 8.805 |
| 25.658 | 132058 | 8.371 |
| Totals | 1577569 | 100.000 |

**Table 9, entry 8**




**Detector A - 1 (264nm)**

| Retention Time | C Area | Area % |
|---|---|---|
| 17.075 | 567285 | 30.075 |
| 18.750 | 510780 | 27.079 |
| 22.125 | 745622 | 39.529 |
| 25.833 | 62571 | 3.317 |
| Totals | 1886258 | 100.000 |

Column: Kromasil 5-AmyCoat (250 x 4.6 mm); Mobile phase: *i*-PrOH:*n*-hexane (10:90); Flow rate: 0.5 mL/min; UV: 264 nm; Retention time: $t_R$ (*syn*, major): 17.08 min, $t_R$ (*syn*, minor): 18.75 min, $t_R$ (*anti*, major): 22.13 min, $t_R$ (*anti*, minor): 25.83 min.

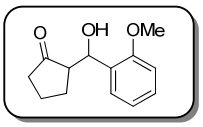
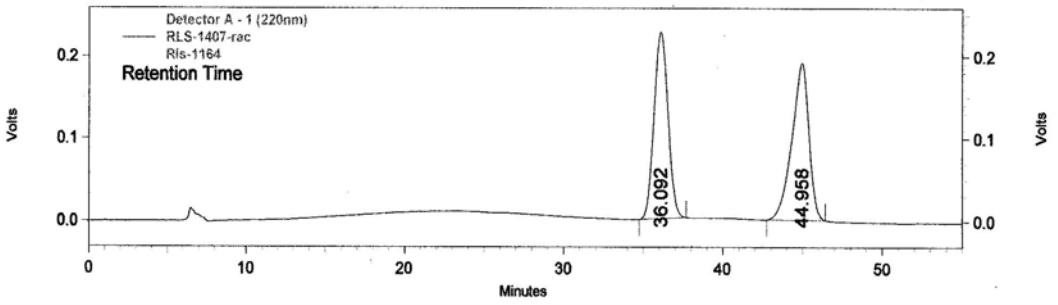


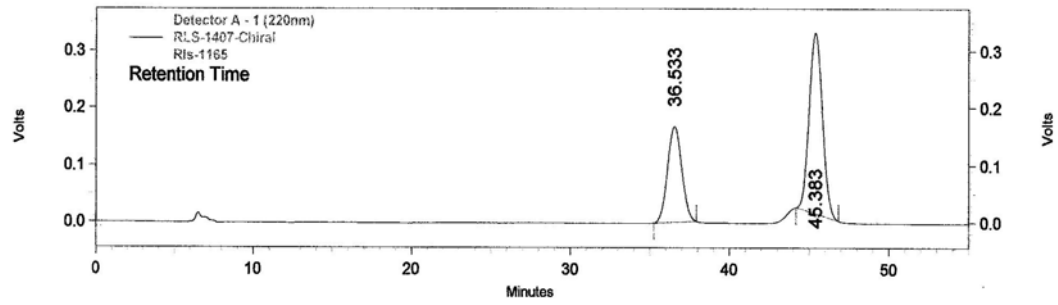

**Table 5, entry 11 (racemic)**




**Detector A - 1 (220nm)**

| Retention Time | C Area | Area % |
|---|---|---|
| 36.092 | 13849082 | 49.543 |
| 44.958 | 14104745 | 50.457 |
| Totals | 27953827 | 100.000 |

**Table 9, entry 9**




**Detector A - 1 (220nm)**

| Retention Time | C Area | Area % |
|---|---|---|
| 36.533 | 10437317 | 36.221 |
| 45.383 | 18378087 | 63.779 |
| Totals | 28815404 | 100.000 |

Column: Kromasil 5-AmyCoat (250 x 4.6 mm); Mobile phase: *i*-PrOH:petroleum ether (6:94); Flow rate: 0.5 mL/min; UV: 220 nm; Retention time: $t_R$ (*syn*, minor): 36.53 min, $t_R$ (*syn*, major): 45.38 min.

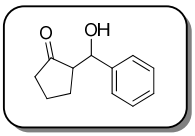
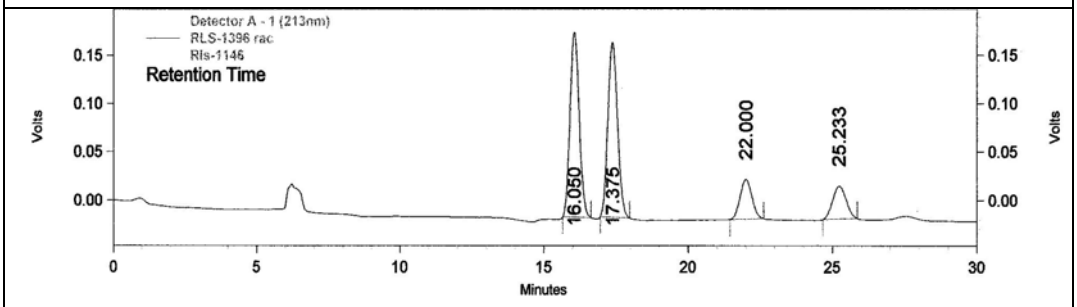


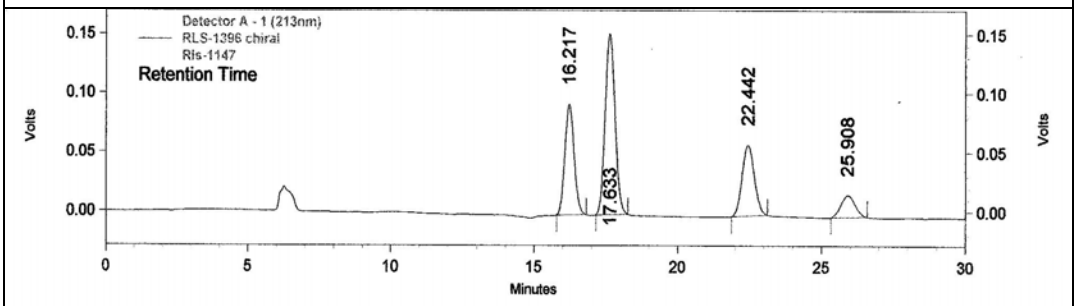

**Table 5, entry 12 (racemic)**




**Detector A - 1 (213nm)**

| Retention Time | C Area | Area % |
|---|---|---|
| 16.050 | 4235503 | 39.412 |
| 17.375 | 4219090 | 39.260 |
| 22.000 | 1176091 | 10.944 |
| 25.233 | 1115980 | 10.384 |
| Totals | 10746664 | 100.000 |

**Table 9, entry 10**




**Detector A - 1 (213nm)**

| Retention Time | C Area | Area % |
|---|---|---|
| 16.217 | 2101172 | 25.707 |
| 17.633 | 3651534 | 44.675 |
| 22.442 | 1778754 | 21.762 |
| 25.908 | 642161 | 7.857 |
| Totals | 8173621 | 100.000 |

Column: Chiralcel OD-H (250 x 4.6 mm); Mobile phase: *i*-PrOH:petroleum ether (10:90): Flow rate: 0.5 mL/min; UV: 213 nm; Retention time: $t_R$ (*syn*, minor): 16.22 min, $t_R$ (*syn*, major): 17.63 min, $t_R$ (*anti*, major): 22.44 min, $t_R$ (*anti*, minor): 25.91 min.

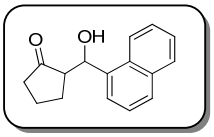
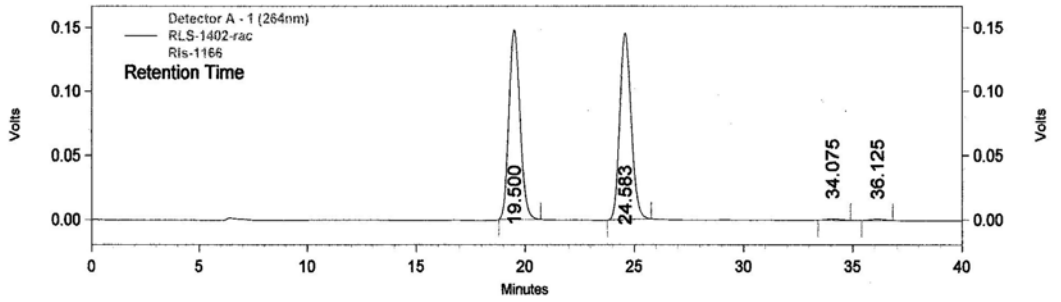


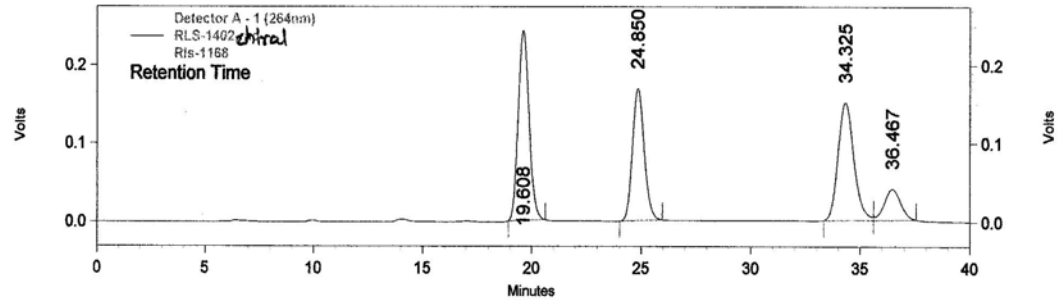

**Table 5, entry 13 (racemic)**




**Detector A - 1 (264nm)**

| Retention Time | C Area | Area % |
|---|---|---|
| 19.500 | 5232051 | 49.343 |
| 24.583 | 5276567 | 49.763 |
| 34.075 | 48746 | 0.460 |
| 36.125 | 46132 | 0.435 |
| Totals | 10603496 | 100.000 |

**Table 9, entry 11**




**Detector A - 1 (264nm)**

| Retention Time | C Area | Area % |
|---|---|---|
| 19.608 | 8398809 | 34.590 |
| 24.850 | 6290440 | 25.907 |
| 34.325 | 7534443 | 31.030 |
| 36.467 | 2057288 | 8.473 |
| Totals | 24280980 | 100.000 |

Column: Kromasil 5-AmyCoat (250 x 4.6 mm); Mobile phase: *i*-PrOH:petroleum ether (10:90); Flow rate: 0.5 mL/ min; UV: 264 nm; Retention time: $t_R$ (*syn*, major): 19.61 min, $t_R$ (*syn*, minor): 24.85 min, $t_R$ (*anti*, major): 34.33 min, $t_R$ (*anti*, minor): 36.47 min.

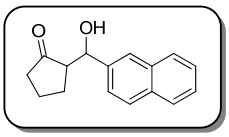
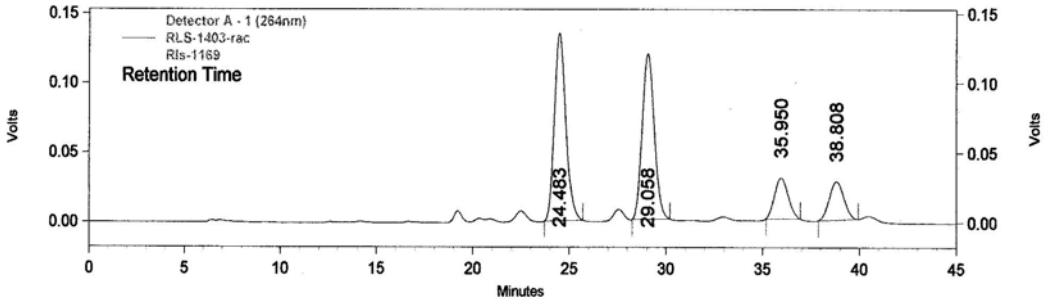


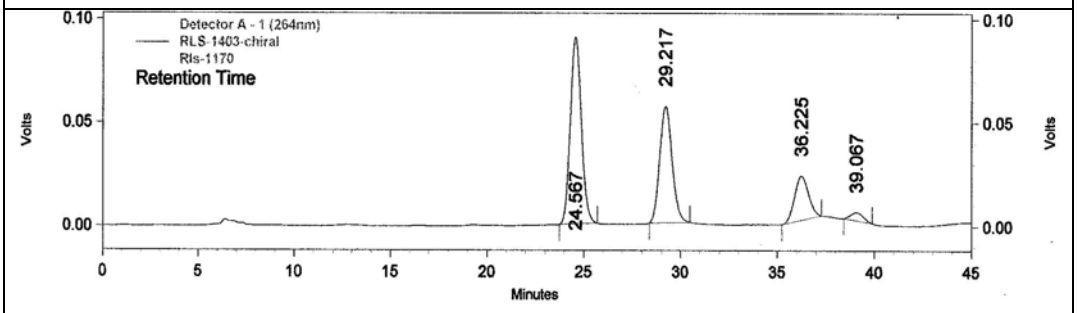

**Table 5, entry 14 (racemic)**




**Detector A - 1 (264nm)**

| Retention Time | C Area | Area % |
|---|---|---|
| 24.483 | 5552105 | 40.754 |
| 29.058 | 5174991 | 37.986 |
| 35.950 | 1446326 | 10.616 |
| 38.808 | 1450122 | 10.644 |
| Totals | 13623544 | 100.000 |

**Table 9, entry 12**




**Detector A - 1 (264nm)**

| Retention Time | C Area | Area % |
|---|---|---|
| 24.567 | 3572551 | 48.797 |
| 29.217 | 2503889 | 34.201 |
| 36.225 | 1063836 | 14.531 |
| 39.067 | 180903 | 2.471 |
| Totals | 7321179 | 100.000 |

Column: Kromasil 5-AmyCoat (250 x 4.6 mm); Mobile phase: *i*-PrOH:petroleum ether (10:90); Flow rate: 0.5 mL/ min; UV: 264 nm; Retention time: $t_R$ (*syn*, major): 24.57 min, $t_R$ (*syn*, minor): 29.22 min, $t_R$ (*anti*, major): 36.23 min, $t_R$ (*anti*, minor): 39.07 min.