ORIGIN OF DIASTEREOSELECTIVITY IN THE ADDITION OF ORGANOMETALLIC REAGENTS TO CHIRAL IMINIUM IONS

INTRODUCTION

1-Substituted tetrahydroisoquinoline alkaloids have been intensive targets for organic synthesis because of their ubiquitous occurrence in nature and diverse physiological and pharmacological actions.1 Appropriately substituted benzylisoquinolines such as 1-(3',4',5'-trimethoxybenzyl)-6,7-dihydroxy tetrahydroisoquinoline 1 are potent \( \beta \)-adrenergic agonists, involved in the mobilization of free fatty acids in adipose tissues. The same compound is also a potent tracheal relaxation agent and an effective bronchodilator.

![Image of molecule 1]

The new alkaloid (+)-demethylcoclaurine 2 is found significantly to relax the smooth muscles and uterine strips.

![Image of molecule 2]

Chiral iminium ions form an important class of electrophiles among the various precursors for the synthesis of 1-substituted tetrahydroisoquinolines by the enantioselective and diastereoselective methods. These have been used for diastereoselective nucleophilic addition of carbon nucleophiles and metal
hydrides to C=N bond for the synthesis of 1-substituted tetrahydroisoquinolines. The use of chiral iminium ions for the synthesis of tetrahydroisoquinoline alkaloid saisolidine 6 by the diastereoselective addition of hydride ion to C=N bond has been reported by Kametani et al. Chiral iminium ions 3a-c were reduced with NaBH₄ at 0 °C to give a diastereomeric mixture of 1-substituted tetrahydroisoquinolines 4a-c and 5a-c. Despite of excellent yield, diastereoselective output was poor even after changing methyl group to more bulky ethyl group and phenyl to somewhat sterically demanding naphthyl group. The configuration of C-1 during asymmetric induction has been assigned as S by correlation with (S)-(-)-saisolidine obtained after the debenzylation of the major diastereomer 4a (Scheme 1).

Scheme 1

\[
\begin{align*}
3 & \quad \text{Ar= Ph, R = Me} \\
3b & \quad \text{Ar = Ph, R = Et} \\
3c & \quad \text{Ar= Np, R = Me}
\end{align*}
\]
An interesting modification in Kametani's method was described by Polniaszek\(^4\) to achieve better diastereoselectivity by carrying out the reduction of iminium ion \(3a\) at \(-78\) °C instead at \(0\) °C. The diastereoselectivity of hydride reduction increased from 72:28 (at \(0\) °C) to 94:06 (at \(-78\) °C). Again the \(S\) configuration has been assigned for C-1 with respect to \(6\) obtained after debenzylation of the major diastereomer. Further improvement regarding diastereoselectivity up to 98:02 has been reported by changing phenyl to somewhat more hindered 2-chlorophenyl and 2,6-dichlorophenyl. Net shielding of one of the \(\pi\)-faces of C=N bond in iminium ion \(7\) by these bulkier moieties resulted in an increase in diastereoselectivity during hydride reduction at \(-78\) °C (Scheme 2).

\[
\begin{align*}
\text{Scheme 2}
\end{align*}
\]
After the energy calculations of the most stable conformations of these iminium ions during transition state by this group, the reaction was assumed to proceed via conformation B to give the major diastereomer because of decreased steric interactions as compared to conformation A, where the Me-Me and Me-Cl interactions are prominent and thus make this conformation highly energetic (Scheme 3). \(^5\)

A chirally complementary modification of the strategy developed by Kametini and Polniaszek has been reported by Kibayashi et al\(^6\) describing the reduction of isoquinolinium salts 8 bearing a proline derived hydrazonium moiety attached to nitrogen as a chiral directing auxiliary. The configuration for C-1 has been assigned as \(R\) on the basis of \((R)\)-salsolidine obtained after removal of hydrazonium moiety from major diastereomer 9a (Scheme 4). The preferential formation of one of the major diastereomer has been rationalized on the basis of the pyramidal stability of the trivalent nitrogen of the chiral pyrrolidine ring. The perpendicular approach of the hydride ion occurs from sterically less hindered bottom face of conformer C to give the major diastereomer.

**Scheme 3**

---

\(^5\)  Chapter 1

---

\(^6\)  Chapter 1

---

\(^{4}\)  Chapter 1
Kang has reported the synthesis of 1-substituted tetrahydroisoquinolines by borane mediated reduction of chiral activated azomethines\(^7\). These azomethines have been generated \textit{in situ} by the coordination of a chiral Lewis acid with the nitrogen lone pair of the dihydroisoquinoline. Thiazacicolidine complex 10a and 10b\(^8\), TADDOL-Ti complex 11\(^9\) and Ohno's catalyst 12\(^10\) have been used as chiral Lewis acids and it was found that zinc complex 10a gave the product in optimal enantioselectivity (\textbf{Figure 1}).
Two transition states D and E have been considered during the coordination of Lewis acid 10a with nitrogen of the imine (Scheme 5). Transition state D is disfavoured one because of the repulsive interactions between methyl group on the imine and ethyl group on zinc, as compared to transition state E in which the anti relationship between C=N in the
dihydroisoquinoline and the C-Zn bond in Lewis acid catalyst makes it more favourable than D. BH₃·THF has been assumed to be a better hydride source as compared to other hydrides for achieving high enantiomeric excess. (S)-salsolidine has been obtained after the addition of hydride through conformation E.

Cortes et al have reported the synthesis of benzyl tetrahydroisoquinoline 14 as the main diastereomer by diastereoselective reduction of dihydroisoquinolinium salt 13, incorporating (R)-phenylglycinol as chiral auxiliary for synthesis of the dopaminergic alkaloid (S)-IBTHIQ 15 (Scheme 6).¹¹

Rodrigues¹² has reported the synthesis of (+)-cularine 17a, (+)-O-demethylcularine 17b, (+)-sarcocapnidine 17c and (+)-sarcocapnine 17d, a class of cularine alkaloids by diastereoselective hydride reduction of chiral iminium ion 16 having (+)-8-phenylmenthyl group as the directing moiety. The phenyl group of this auxiliary shields one face of the iminium ion and the attack of hydride occurs from the other side to give the product having S configuration (Scheme 7).
Marazano\textsuperscript{13} has reported hydride reduction of chiral iminium ion 18 to give a diastereomeric mixture of 19a and 19b for the enantioselective synthesis of (-)-argemonine, a natural pavine alkaloid (Scheme 8).
Carbon nucleophiles such as Grignard reagents have also been used for the diastereoselective addition to C=N bond of chiral iminium ions for the synthesis of 1-substituted tetrahydroisoquinolines. Polniaszek has reported the diastereoselective addition of Grignard reagents to C=N of chiral iminium ions having a stereogenic centre attached to nitrogen. Iminium ions were prepared by POCl₃ cyclization of N-formyl derivatives prepared from secondary amines with the aid of formyl pivaloyl anhydride as a formylating reagent (Scheme 9).

![Scheme 9](image)

The major diastereomer 23 formed by addition of MeMgBr has S configuration for C-1. The diastereoselectivities obtained were not as good as with hydride reduction reactions. The relative stabilities of different conformers F and G have been calculated theoretically to deduce the conformational preferences of iminium ions. Conformation G was assumed to be more stable than F and the nucleophilic attack occurs from the least hindered face of G.
where the non-bonded repulsive interactions and other strain factors are minimized to give the major diastereomer (Scheme 10).

Scheme 10

Synthesis of (S)-(+) -cryptostyline has been described as a beautiful application of this methodology since only single diastereomer was obtained after the addition of 3,4-methylenedioxyphenylmagnesium bromide to iminium

Scheme 11

(S)-Cryptostyline
ion derived from 20c, thus indicating the S configuration for C-1 during asymmetric induction (Scheme 11).

Apart from Grignard reagent additions, Polniaszek\textsuperscript{14} has also reported the addition of \textit{cis} and \textit{trans} crotyl trimethylsilane to C=N bond of iminium ion 25 as an application for the enantioselective synthesis of indolizidine alkaloids (-)-26a and 26b (Scheme 12).

\begin{center}
\includegraphics[width=0.8\textwidth]{scheme_12}
\end{center}

Polniaszek\textsuperscript{15} has also reported the allylation addition reactions to C=N bond of acyliminium ions 27 for the synthesis of allyl lactams (Scheme 13). The configuration of C-1 stereogenic centre generated during asymmetric
induction has been assigned as $S$ by correlation with (S)-(+)2-pyrrolidine-5-acetic acid prepared from major diastereomer.

![Diagram](image)

**Scheme 13**

Efficient asymmetric induction has also been reported by Kibayashi *et al.* for the diastereoselective addition of carbon nucleophiles to chiral hydrazonium ions 28a-c. MeLi, MeMgBr and Me$_3$Al were employed as sources of required carbon nucleophiles. The configuration of chiral centre for C-1 has been assigned as $R$ on the basis of (R)-salsolidine obtained after removing hydrazine moiety from the major diastereomer 29a (Scheme 14).
Kibayashi\textsuperscript{16} has further reported an alternative pathway for the generation of chiral hydrazonium ions for the addition of Grignard reagents for the synthesis of tetrahydroisoquinolines. This is based on the Lewis acid (Grignard reagents in this case) assisted preferential cleavage of C-O bond in cyclic N, O-acetals \textsuperscript{30} regarded as masked activated azomethine species. The reverse stereochemical results have been obtained in this case in contrast to hydrazonium ions. The reverse stereochemical results observed in Grignard-Lewis acid combination have been explained as being a consequence of $S_N^1$ type attack of the nucleophile to the more exposed si face of hydrazonium ion \textsuperscript{31} to give (S)-salsolidine (\textbf{Scheme 15}).
In a new variation, the author has disclosed an alkylation, which occurs with Me₃Al and displays concentration dependence reversal in the configuration of the stereogenic centre at C-1. The cleavage of the N, O-acetal with the organoaluminium reagent leads to the formation of a tight ion pair between the aluminate complex and the hydrazonium ion. If the proportion of Me₃Al is low (1.1 equiv), intramolecular delivery of the methyl group from the re-face produced the R-enantiomer. In case an excess amount of Me₃Al being employed, shielding of the re-face preferentially produced the S-enantiomer through an intermolecular si-face attack (Figure 2).
Yamato\textsuperscript{17} has reported a base assisted intramolecular cyclization of 3,4-dihydroisoquinolinium salt 34 for the highly diastereomeric synthesis of chiral oxazolo-(2,3-\(\alpha\))-tetrahydroisoquinolines 35\(\alpha\)-b. Isoquinolinium salt 34 was prepared by condensation of (S)-phenylglycinol 33 and bromo aldehyde 32. Further ring opening of the oxazolidines 35\(\alpha\)-b during attack with MeMgI produced the activated iminium ions as previously reported by Kibayashi, thus resulting in the formation of a diastereomeric mixture of 36\(\alpha\) and 36\(\beta\) after addition of MeMgI. The sense of asymmetric induction for C-1 has been assigned as S since (S)-salsolidine was obtained after reductive cleavage of the major diastereomer 36\(\alpha\) (Scheme 16).

Optically active isoquinolinium salts, form another class of chiral activated azomethines for the diastereoselective nucleophilic addition of organometallic compounds to C=\(\text{N}\) bond for the synthesis of tetrahydroisoquinolines. Potier \textit{et al.}\textsuperscript{18} have reported a synthesis of salsolidine by the addition of MeMgCl to C=\(\text{N}\) bond of isoquinolinium salt 37.

The sense of asymmetric induction for C-1 has been assigned as S since (S)-salsolidine was obtained after debenzylation of the major product (Scheme 17).
Scheme 16
Chapter 1

Comin\textsuperscript{10} has reported the diastereoselective addition of vinyl ether 39, to chiral iminium ion 38, for the synthesis of (-)-laudanosine and addition of enol ether 40 for the synthesis of (+)-glaucine (Scheme 18). In these addition reactions, (-)-8-phenyl menthyl have been used as a controlling auxiliary. One face of the iminium ion 38 is blocked by the phenyl group of the phenylmenthyl auxiliary and attack of the nucleophile occurs from the other side to give the product in good diastereoselectivity (Figure 3).

Scheme 17

Comin\textsuperscript{10} has reported the diastereoselective addition of vinyl ether 39, to chiral iminium ion 38, for the synthesis of (-)-laudanosine and addition of enol ether 40 for the synthesis of (+)-glaucine (Scheme 18). In these addition reactions, (-)-8-phenyl menthyl have been used as a controlling auxiliary. One face of the iminium ion 38 is blocked by the phenyl group of the phenylmenthyl auxiliary and attack of the nucleophile occurs from the other side to give the product in good diastereoselectivity (Figure 3).
Shono\textsuperscript{30} has reported zinc promoted reductive coupling reactions of iminium salts with alkyl halides for the synthesis of benzylisoquinoline, phthalidyl isoquinoline and protoberberine alkaloids (Scheme 19).
Murahashi\textsuperscript{21} has reported addition of optically active (R)-(+)- and (S)-(-)-methyl p-tolyl sulfoxide anion \textsuperscript{41} to 3,4-dihydroisoquinoline N-oxide \textsuperscript{42} for the synthesis of 1-substituted tetrahydroisoquinolines. Treatment of 6,7-dihydroisoquinoline N-Oxide \textsuperscript{42} with (R)-(+)-methyl p-tolyl sulfoxide anion \textsuperscript{41} in THF at \(-78\) °C gave a diastereomeric mixture of 1-sulfinyl hydroxyl amine.
43a and 43b with poor diastereoselectivity. The addition of lithium salt of quinidine 44 improved the diastereoselectivity during reaction. The higher diastereoselectivity obtained has been ascribed to the formation of a facial discriminating organometallic reagent derived from quinidine and α-sulfinyl carbanion 41 and re-face attack is there to give the major product (Scheme 20).

Ukaji\textsuperscript{22} has reported the synthesis of (R)-salsolidine by the addition of dimethylzinc to nitrone 45 mediated by alkaoxide 46, derived from tartaric acid.
series to increase the diastereoselective output. The sense of asymmetric induction for C-1 has been assigned as $R$ on the basis of (R)-salsolidine resulting from the reductive removal of zinc complex of major diastereomer (Scheme 21).

Recently addition of optically active benzyl naphthyl sulfoxide 47 to C=N bond of $N$-oxide 48 has been reported for the formation of hydroxylamine 49 as a precursor for the synthesis of (R)-(−)-norlaudanosine (Scheme 22). 23
Wanner et al have also reported the synthesis of R-homolaudanosine by addition of silyl enol ether of acetophenone derivative 50 to C=N bond of chiral N-acyl-3, 4-dihydroisoquinolinium salt 51 (Scheme 23).²⁴
Addition of chiral dithiane 52, having a menthyl chiral auxiliary, to C=N of hydrastinine chloride 53 have also been reported for the synthesis of (S)-corydalisol 54 (Scheme 24).25
These examples illustrate that the addition reactions across C=N bond of chiral iminium ions have a fundamental role of these precursors for the synthesis of a large number of isoquinoline alkaloids. Their easy formation, high reactivity and desirable selectivity during additions coupled with biological activity of these isoquinoline alkaloids have made these methods of choice for their synthesis.

Despite the ever increasing methods being developed for the diastereoselective synthesis of isoquinoline core, the understanding towards the predictability of diastereoselective addition to C=N for generating a chiral centre at C1 is lacking. In order to understand the diastereoselectivity of these addition reactions and to optimize the chiral auxiliary to give addition products in high diastereoselectivity a project was initiated in our laboratory whose results are described in the next section.
RESULTS AND DISCUSSION

In our laboratory, chiral Schiff bases of type 55 have been investigated theoretically and experimentally for the diastereoselective addition of organolithium compounds (Scheme 25).

![Scheme 25](image)

An increase in diastereoselectivity of the reaction product was observed on increasing the size of alkyl group on stereogenic centre on the Schiff base from methyl to ethyl and further to isopropyl and decreases with change of phenyl to o-toluyl. Based on these experimental and theoretical studies, conceptually a new model has been developed to understand the origin of diastereoselectivity during these addition reactions. The major diastereomer is formed by a preferential attack of the nucleophile from the side of phenyl group in the configuration shown (Figure 4) in which the hydrogen on stereogenic centre is syn to allylic hydrogen to minimize 1,3-allylic strain.

![Figure 4](image)

Similarly isoelectronic oxocarbenium ions have also been investigated and have been shown to follow a similar pattern. By understanding the conformational preference of oxocarbenium ions, we have been able to develop highly diastereoselective allylation and acetate aldol reactions. These two systems fall in the category of 1,3-allylic strain.
In this chapter details of studies carried out to understand the conformation of stereogenic centre responsible for the origin of diastereoselectivity during addition of various organometallic reagents to C=N bond of chiral iminium ions of type 56 have been described. Optimization for the chiral auxiliary leading to high diastereoselectivity for the synthesis of various 1-alkyl-N-substituted tetrahydroisoquinolines have also been explored (Scheme 26).

This system in addition to 1,3-allylic interactions also has two 1,3-syn pentane type interactions (Figure 5). This analysis clearly indicates the additional complexity in this system as compared to the previous two studies. It was not possible to apply previous models directly to substrate 56. In order to understand the intricacy of this system, a theoretical study was undertaken.

Since the real system is large for *ab initio* or density functional level of calculations, a model system representing the key features of interaction of the
chiral centre was envisioned. The *ab initio* and density functional calculations have been carried out on B (Figure 5) using GAUSSIAN98W package. Optimizations have been carried out at HF/3-21G level and single point energies have been obtained at HF/6-31+G*, MP2/6-31+G* and B3LYP/6-31+G* levels. To obtain the potential energy surface of the N2-C3 bond rotation, the dihedral angle of phenyl was fixed at 0° and then rotated by 30°. The potential energy curve thus obtained (Figure 6) showed three energy minima separated by energy differences as shown in Table 1.

Table 1: Relative energies (kcal/mol) of N2-C3 bond rotation of B.

<table>
<thead>
<tr>
<th>Dihedral angle</th>
<th>HF/3-21G</th>
<th>HF/6-31+G*</th>
<th>MP2/6-31+G*</th>
<th>B3LYP/6-31+G*</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.033</td>
<td>0.035</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>30</td>
<td>0</td>
<td>0</td>
<td>0.454</td>
<td>0.088</td>
</tr>
<tr>
<td>60</td>
<td>1.863</td>
<td>0.899</td>
<td>1.764</td>
<td>1.187</td>
</tr>
<tr>
<td>90</td>
<td>1.739</td>
<td>0.902</td>
<td>1.276</td>
<td>0.794</td>
</tr>
<tr>
<td>120</td>
<td>0.476</td>
<td>0.158</td>
<td>0.179</td>
<td>0.129</td>
</tr>
<tr>
<td>150</td>
<td>2.494</td>
<td>2.553</td>
<td>2.348</td>
<td>2.134</td>
</tr>
<tr>
<td>180</td>
<td>4.532</td>
<td>4.504</td>
<td>4.082</td>
<td>3.799</td>
</tr>
<tr>
<td>210</td>
<td>2.151</td>
<td>1.545</td>
<td>1.443</td>
<td>1.485</td>
</tr>
<tr>
<td>240</td>
<td>0.980</td>
<td>0.066</td>
<td>0.204</td>
<td>0.078</td>
</tr>
<tr>
<td>270</td>
<td>2.941</td>
<td>1.395</td>
<td>1.729</td>
<td>1.286</td>
</tr>
<tr>
<td>300</td>
<td>3.421</td>
<td>2.861</td>
<td>3.757</td>
<td>3.057</td>
</tr>
<tr>
<td>330</td>
<td>1.696</td>
<td>1.796</td>
<td>2.153</td>
<td>1.765</td>
</tr>
</tbody>
</table>

Figure 6
Chapter 1

The three minima correspond to the conformation in which phenyl, hydrogen and methyl of chiral centre (C3) occupy almost syn position with respect to C-1 hydrogen (Figure 7). There is very little energy difference between the absolute energies of these three energy minima and all of these could react with nucleophile.

![Figure 7]

The close examination of the minimized structures of conformations A and B reveals that phenyl and methyl are positioned in such a way that they give steric hindrance to the incoming nucleophile. The structure C on the other hand is relatively free from such hindrance for the approach of nucleophile. Additionally, the orientation of three groups of the chiral centre in confirmation C has lot of resemblance with the most stable structure of Schiff base D. In conformation C, the orientation of the phenyl group is similar to the orientation of phenyl group as in Schiff base D. Thus one would expect phenyl group to act as smaller group than the methyl group. If this is true, then changing methyl to sterically more demanding alkyl groups should result in enhanced diastereoselectivity. It has also been shown by Polniaszek that changing the phenyl to 2,6-dichlorophenyl group also enhances the diastereoselectivity.

With these logics and also keeping in mind the results of Polniaszek that replacing the phenyl with 2,6-dichlorophenyl results in the enhancement of diastereoselectivity, various chiral amines 57a-f (Figure 8) with varying size of R group were prepared for the construction of chiral iminium ions 56. In few cases, phenyl was also replaced with 2-chloro or 2,6-dichlorophenyl group.
Optically active amines 57a and 57b are commercially available. Amines 57c and 57d were prepared using Hart’s method by the addition of four equiv. isopropyl magnesium bromide and 1.1 equiv. of tert-butyl lithium respectively to N-trimethylsilyl imine 58 in THF (obtained by reaction of benzaldehyde with lithium hexamethyldisilazane at 0 °C). Addition of tert-butyllithium was carried out at −78 °C for the synthesis of amine 57d and refluxing was required after the addition of isopropyl magnesium bromide for the synthesis of amine 57c (Scheme 27).
Optically active amine 57e was prepared in 32% yield by the directed ortho metallation of the \(N\)-trimethylsilyl derivative 59 of optically active amine 57c (obtained by the reaction of amine with one equivalent \(n\)-butyllithium followed by reaction of the resulting lithium amide with one equivalent chlorotrimethylsilane at 0 °C) with three equiv. of \(n\)-butyllithium at room temperature and reaction of the resulting carbanion 60 with two equivalents of hexachloroethane by using protocol developed by Polniaszek (Scheme 28).29 However the preparation of optically active amine 57f by using the ortho metallation of \(N\)-trimethylsilyl derivative 61 of optically active amine 57e with \(n\)-BuLi and \(s\)-BuLi did not give the desired product (Scheme 28).

![Scheme 28](image-url)
Amine 57f in racemic form was prepared in 40% yield by the addition of isopropyllithium (prepared from 2-chloropropane and lithium in pentane) at -78 °C to C=N bond of N-trimethylsilyl imine 62 which in turn was obtained from 2,6-dichlorobenzaldehyde and lithium hexamethyldisilazane at -78 °C in THF. Addition of two equivalent of isopropylmagnesium bromide instead of isopropyllithium resulted in the formation of complex mixture of products from which the desired amine could not be isolated (Scheme 29).

![Scheme 29](image)

Resolution of racemic amine 57f was attempted with (R)-(-)-camphor-10-sulphonic acid, tartaric acid and N-acetyl-L-leucine respectively. In all the cases fine crystals were obtained in water. These crystals after three recrystallizations from water were hydrolysed with 4N aqueous sodium hydroxide. The amine obtained was in racemic form as confirmed by its zero optical rotation and from the ¹H NMR of corresponding Mosher amide 63a/b with (R)-(+)−α-Methoxy−α-trifluoromethylpherylacetyl chloride which showed two methoxy proton peaks at δ 3.45 and 3.44 of equal intensity (Scheme 30). Changing solvent from water to ethanol also gave the racemic amine even after several recrystallizations.
Chapter 1

1-Phenyl-2-methylpropylamine 57c was resolved using (1R)-(−)-camphor-10-sulphonic acid. Reaction of the racemic amine with (1R)-(−)-camphor-10-sulphonic acid gave the diastereomeric salt 64 (Scheme 31).

White shining crystals having a constant specific rotation [α]D25 = -28.3° (c 0.5, MeOH) were obtained after three recrystallisations from water. Optically active amine was obtained by hydrolysis of this salt with 4N sodium hydroxide having specific rotation [α]D25 = +13.2 (c 4.75, CHCl₃). The configuration of the chiral centre was assigned as R by comparison with the literature value (lit.[α]D25 = -11.5° (c 1, CHCl₃) for S enantiomer).³¹

1-Phenyl-2,2-dimethylpropyl amine 57d was resolved by N-acetyl-L-leucine in water.⁷ Reaction of the racemic amine with N-acetyl-L-leucine gave

Scheme 30

Scheme 31
the diastereomeric salt 65 (Scheme 32). White shining crystals having a constant specific rotation $[\alpha]_D^{25} = -4.2^\circ$ (c 0.64, MeOH) were obtained after four recrystallisations from water. The optically active amine was obtained after the hydrolysis of this salt with 4N aqueous sodium hydroxide having specific rotation $[\alpha]_D^{25} = +4.3$ (c 1, MeOH). The configuration of the chiral centre was assigned as $R$ by comparison with literature value (lit. $[\alpha]_D^{25} = +2.5^\circ$ (c 4, MeOH) for the $R$ enantiomer).  

\[ \begin{align*}
\text{57d (dl)} & \quad + \quad \text{NHAc} \\
& \quad \downarrow \\
\text{NHAc} & \quad \text{CO}_2 \quad \text{H}_2\text{N} \quad \text{phenyl}
\end{align*} \]

\[ \text{ Scheme 32 } \]

The enantiomeric excess of these optically active amines was determined by Mosher’s method by diastereomeric amide formation with one equivalent of (R)-(+)-$\alpha$-Methoxy-$\alpha$-trifluoromethylphenylacetyl chloride in dichloromethane using triethylamine as a base. From the integration of methoxy protons at $\delta$ 3.3 and 3.4 ppm for amide 66a/b of amine 57c and 3.47 and 3.42 ppm for amide 67a/b for amine 57d corresponding to the major and minor diastereomer in their 400 MHz $^1$H NMR, $ee$ was calculated (Scheme 33).  

Enantiomeric excess obtained for 1-phenyl-2-methylpropylamine 57c was 98% and that for 1-phenyl-2,2-dimethylpropylamine 57d was 99%.

\[ [\alpha]_D^{25} = -4.2^\circ \text{ (c 0.64, MeOH)}. \]

Enantiomeric excess obtained for 1-phenyl-2-methylpropylamine 57c was 98% and that for 1-phenyl-2,2-dimethylpropylamine 57d was 99%.
All of these optically active amines 57a-e and racemic 57f were condensed with 3,4-dimethoxyphenylacetic acid in the presence of DCC and catalytic amount of DMAP in dichloromethane to give the corresponding amides 68a-f as white solids except that of amide 68f which was obtained as a viscous oil (Scheme 34 and Table 2).33

Table 2: Reaction of amines 57a-f and 3,4-dimethoxyphenyl acetic acid to give amides 68a-f.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar</th>
<th>R</th>
<th>Yield(%)</th>
<th>$[\alpha]_{D}^{25}$ CHCl$_3$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>Me</td>
<td>70</td>
<td>+11.0 °(c 0.54)</td>
</tr>
<tr>
<td>2</td>
<td>Ph</td>
<td>Et</td>
<td>75</td>
<td>+ 6.9 °(c 1.59)</td>
</tr>
<tr>
<td>3</td>
<td>Ph</td>
<td>iPr</td>
<td>75</td>
<td>-20.2 °(c 1.05)</td>
</tr>
<tr>
<td>4</td>
<td>Ph</td>
<td>iBu</td>
<td>79</td>
<td>-36.7 °(c 2.91)</td>
</tr>
<tr>
<td>5</td>
<td>2-CIC$_6$H$_4$</td>
<td>iPr</td>
<td>65</td>
<td>+ 13.7 °(c 5.24)</td>
</tr>
<tr>
<td>6</td>
<td>2,6-Cl$_2$C$_6$H$_3$</td>
<td>iPr</td>
<td>72</td>
<td>(d)</td>
</tr>
</tbody>
</table>
the coupling of NH protons with the neighboring protons and characteristic IR peak of amides was obtained at 1641 cm$^{-1}$. All of these amides also gave molecular ion peak in their mass spectra.

The amides 68a-f (1 equiv) were reduced with BH$_3$SMe$_2$ (4-5 equiv) in refluxing THF in the presence of BF$_3$OEt$_2$ (0.1 equiv) to give the corresponding secondary amines 69a-f (Scheme 35 and Table 3). The reduction was also tried with 3 equiv of lithium aluminium hydride in refluxing THF but the yield in some cases was poor. The reduction using DIBAL-H (2 equiv) in dichloromethane at 0 °C gave multiple products.

![Scheme 35](image)

Table 3: The reduction of amides 68a-f with BH$_3$SMe$_2$ to give the secondary amines 69a-f.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar</th>
<th>R</th>
<th>Yield (%)</th>
<th>$[\alpha]_D^{25}$ CHCl$_3$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>Me</td>
<td>80</td>
<td>-41.5 °(c 0.72)</td>
</tr>
<tr>
<td>2</td>
<td>Ph</td>
<td>Et</td>
<td>75</td>
<td>-38.7 °(c 0.73)</td>
</tr>
<tr>
<td>3</td>
<td>Ph</td>
<td>$^3$Pr</td>
<td>75</td>
<td>+ 38.3 °(c 0.74)</td>
</tr>
<tr>
<td>4</td>
<td>Ph</td>
<td>$^1$Bu</td>
<td>65</td>
<td>+ 41.4 °(c 1.52)</td>
</tr>
<tr>
<td>5</td>
<td>2-CIC$_6$H$_4$</td>
<td>$^3$Pr</td>
<td>70</td>
<td>-29.5 °(c 1.01)</td>
</tr>
<tr>
<td>6</td>
<td>2,6-CIC$_6$H$_3$</td>
<td>$^3$Pr</td>
<td>78</td>
<td>(d)</td>
</tr>
</tbody>
</table>

The products were identified by mass spectra showing molecular ion peak, $^1$H NMR showed multiplets for benzylic protons and protons adjacent to NH (Ar-CH$_2$-CH$_2$-NH-) between δ 2-3 ppm and IR showed broad band at 3450 cm$^{-1}$ for NH.

These secondary amines 69a-f were $N$-formylated with acetic formic anhydride (Scheme 36 and Table 4).
Table 4: Formylation of secondary amine 69a-f to N-formyl derivatives 70a-f.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar</th>
<th>R</th>
<th>Yield (%)</th>
<th>$[\alpha]_D^{25}$ CHCl$_3$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>Me</td>
<td>90</td>
<td>-30.2 ° (c 0.35)</td>
</tr>
<tr>
<td>2</td>
<td>Ph</td>
<td>Et</td>
<td>90</td>
<td>-23.3 ° (c 1.15)</td>
</tr>
<tr>
<td>3</td>
<td>Ph</td>
<td>t-Pr</td>
<td>89</td>
<td>+36.7 ° (c 0.65)</td>
</tr>
<tr>
<td>4</td>
<td>Ph</td>
<td>t-Bu</td>
<td>97</td>
<td>+2.0 ° (c 0.680)</td>
</tr>
<tr>
<td>5</td>
<td>2-CIC$_6$H$_5$</td>
<td>t-Pr</td>
<td>91</td>
<td>+39.4 ° (c 1.16)</td>
</tr>
<tr>
<td>6</td>
<td>2,6-CIC$_6$H$_4$</td>
<td>t-Pr</td>
<td>94</td>
<td>(dl)</td>
</tr>
</tbody>
</table>

The N-formyl derivatives 70a-f were cyclized by refluxing with excess of POCl$_3$ in benzene to give the iminium ions 71a-f.\(^{38}\) Cyclization was confirmed by disappearance of starting material and appearance of a spot at the base of TLC plate. These iminium ions were obtained as green fluorescent viscous oil and were used as such without purification and characterization for the
addition of MeMgl to give the diastereomeric mixture of 1-alkyl-N-substituted
tetrahydroisoquinolines 72a/a'-f/ (Scheme 37).5

The addition was carried out at -78 °C in THF. In diethyl ether, the
solubility of the iminium ion was problematic and it resulted in the formation of
precipitates of the iminium salt. In toluene, the reaction was not clean,
therefore all the addition reactions were carried out in THF. Lowering the
temperature upto -90 °C did not improve diastereoselectivity over the one
obtained at -78 °C. The diastereomeric ratio was determined by the
integration ratio of protons of (MeO^ArH group resonating between δ 6-7 ppm
for the major and minor diastereomers by 400 MHz 1H NMR. In some cases,
the diastereoselectivity was ascertained by HPLC analysis using Hichrom
RPB(250x 4.6mm), 5 Microns column with mobile phase A:0.01M KH2PO4 (pH
5.5), B:CH3CN with a flow rate of 1.0 mL/min. The results have been compiled
in Table 5.
Table 5: Diastereoselective addition of MeMgl to iminium ions 71a-f to give 1-substituted tetrahydroisoquinolines 72a/a’-ff’.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar</th>
<th>R</th>
<th>Diastereoselectivity</th>
<th>Configuration of iminium ion</th>
<th>Configuration of new chiral centre</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>Me</td>
<td>69:31</td>
<td>S</td>
<td>R</td>
</tr>
<tr>
<td>2</td>
<td>Ph</td>
<td>Et</td>
<td>70:30</td>
<td>S</td>
<td>R</td>
</tr>
<tr>
<td>3</td>
<td>Ph</td>
<td>'Pr</td>
<td>81:19</td>
<td>R</td>
<td>S</td>
</tr>
<tr>
<td>4</td>
<td>Ph</td>
<td>tBu</td>
<td>96:04</td>
<td>R</td>
<td>S</td>
</tr>
<tr>
<td>5</td>
<td>2-CIC₆H₄</td>
<td>'Pr</td>
<td>85:15</td>
<td>R</td>
<td>S</td>
</tr>
<tr>
<td>6</td>
<td>2,6-CI₂C₆H₃</td>
<td>'Pr</td>
<td>99:01</td>
<td>dl</td>
<td>-</td>
</tr>
</tbody>
</table>

The results obtained clearly indicate that there is an increase in the diastereoselectivity as the R group is increased from methyl to ethyl to isopropyl and further to tert-butyl in analogy to alkyl lithium addition to Schiff bases and maximum diastereoselectivity was achieved by changing phenyl to 2,6-dichlorophenyl on one example studied (Table 5, entry 6). The increase in diastereoselectivity with increase in the size of the alkyl group can be explained due to the increase in the differential interaction of the incoming nucleophile with phenyl and alkyl groups of the chiral centre. However, in the case when phenyl is replaced with 2,6-dichlorophenyl and methyl is changed to isopropyl, the increase in diastereoselectivity could not be explained as substitution on second and sixth position of the phenyl group could increase the steric hindrance for the incoming nucleophile. These results suggest that other factors in addition to steric factors are also responsible for the observed diastereoselectivity. In the case of oxocarbenium ion, we have evaluated the effect of negative hyperconjugative stabilization of the developing lone pair on oxygen by the different groups on the chiral center. A similar interaction between the developing lone pair and groups on the chiral center was evaluated in iminium ion system using NBO analysis. The developing lone pair is expected to be deformed because the electron density of the developing lone pair would like to be away from the incoming electron rich nucleophile. For negative hyperconjugation to be effective, the lone pair and the sigma...
bond should be in anti-periplanar conformation. Keeping these in mind, three conformations were considered for this study (Figure 9).

![Figure 9](image)

Ar = phenyl; 2,6-dichlorophenyl

Figure 9

NBO analysis at HF/6-31+G* on phenethylamine suggests that $E^{(2)}$ for $n_N \rightarrow \sigma^*_{C,Ph}$ is 7.65 kcal/mol, $n_N \rightarrow \sigma^*_{C,Me}$ is 7.40 kcal/mol and $n_N \rightarrow \sigma^*_{C,H}$ is 3.93 kcal/mol and for 2,6-dichlorophenethylamine $E^{(2)}$ for $n_N \rightarrow \sigma^*_{C,Ph}$ is 9.19 kcal/mol, $n_N \rightarrow \sigma^*_{C,Me}$ is 8.20 kcal/mol and $n_N \rightarrow \sigma^*_{C,H}$ is 2.28 kcal/mol. The close examination of these results indicated that methyl and phenyl groups show similar stabilization of the developing lone pair by negative hyperconjugation. However, 2,6-dichlorophenyl group showed enhanced stabilization of the developing lone pair. This can explain the enhanced observed diastereoselectivity when phenyl is replaced with 2,6-dichlorophenyl group. This also indicates stabilization of developing lone pair by 2,6-dichlorophenyl group by negative hyperconjugation. Thus negative hyperconjugation has more positive influence on diastereoselectivity than the negative effect of increase in its size.

The structures of the major product were predicted on the basis of proposed model. To confirm the structure of the major diastereomer configuration of newly generated chiral centre at C1 in the products 72a-f had to be determined. It was then planned to remove the chiral auxiliary because the resulting product is a known natural product. The comparison of optical rotation with natural product would confirm the configuration of the newly generated chiral centre. This was not possible for the product 72f obtained from iminium ion 71f ($R = \Pr$, Ar = 2,6-Cl$_2$Ph) because we started with racemic amine.

Reductive removal of the chiral group was achieved for substrate 72a-72c using Pd/C under hydrogen pressure. However the substrate 72d did not undergo reductive removal of chiral auxiliary under various conditions tried. First, the hydrogenolysis of amine 72d was carried out with 10% Pd/C in
ethanol under a balloon pressure of hydrogen. This led to the formation of some byproducts which could not be identified. Further the hydrogenation reaction was carried out at 80 psi pressure of hydrogen in a Parr apparatus in methanol but this led to the formation of a number of spots on TLC. The reaction with 10% Pd/C along with 4 equiv. ammonium formate as a source of hydrogen in refluxing methanol gave back the starting material. The reaction was also carried out with 1.5 equiv. of 1-chloroethylchloroformate in DCM (0 °C) and then refluxing in MeOH. This also gave starting amine even after prolonged refluxing. Reductive removal of the benzyl group with Na-liquid ammonia at -33 °C in THF gave some non-polar spot and the starting amine. Finally the structure of 72d and 72f have been assigned by comparison of their 1H NMR with that of amines 72a-c.

Hydrogenation of amine 72b/b' obtained from iminium ion 71b (R = Et, Ar = Ph) with 10% Pd/C in ethanol under a balloon pressure of hydrogen gave S-salsclidine having $[\alpha]_D^{25} = -23.8^\circ$ (c 0.15, EtOH) by comparison with literature value (lit. $[\alpha]_D^{25} = -59.5^\circ$ (c 4.39, EtOH) for S enantiomer). So the (S)-1-phenylpropylamine 57b gave S-salsolidine in 40% ee (Scheme 38).

![Scheme 38](image)

Similar result has been reported by Polniaszek for the removal of 1-phenylethyl group from amine 72a obtained during hydride reduction reactions (Scheme 39).
In order to further explore the utility of the above study, iminium ion 71d was selected over 71f because we could also prepare it in optically active form from optically pure amine 57d and get the final product in high diastereoselectivity. Addition of various Grignard reagents to iminium ion 71d was carried out in THF at −78 °C to give a diastereomeric mixture of various 1-substituted tetrahydroisoquinolines 73a/b - 77a/b (Scheme 40).

![Scheme 40](image)

Ethylmagnesium bromide, isopropylmagnesium bromide and n-butyllmagnesium bromide were prepared by the addition of respective bromides to magnesium turnings in diethyl ether at 0 °C. 3,4-methylenedioxy phenylmagnesium bromide was prepared by the addition of 4-bromo-3,4-(methylenedioxy) benzene to 5 equiv. magnesium turnings in refluxing THF. Benzylmagnesium bromide was prepared by the addition of benzyl bromide to 5 equiv. magnesium turnings in THF at room temperature but for the initiation of the reaction, some heating was required. All the additions were carried out at −78 °C in THF using 5-7 equiv. of the respective Grignard reagents. The results have been compiled in Table 6. Strangely, very erratic results were obtained with other Grignard reagents and lower diastereoselectivity was observed in comparison to methylmagnesium iodide addition, except for the addition of 3,4-methylenedioxyphenyl group which resulted in the formation of product with complete diastereoselection.
Table 6: Diastereoselective addition of various Grignard reagents to iminium ion 71d to give a mixture of 1-substituted-tetrahydroisoquinolines 73a/b-77a/b.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Diastereoselectivity</th>
<th>([\alpha]_D^{25}) CHCl₃</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Et</td>
<td>83:17</td>
<td>-34.2° (c 0.40)</td>
<td>73a/b</td>
</tr>
<tr>
<td>2</td>
<td>(^{3})Pr</td>
<td>58:42</td>
<td>+21.0° (c 0.45)</td>
<td>74a/b</td>
</tr>
<tr>
<td>3</td>
<td>n-Bu</td>
<td>83:17</td>
<td>-30.8° (c 0.25)</td>
<td>75a/b</td>
</tr>
<tr>
<td>4</td>
<td>3,4-methylene-dioxyphenyl</td>
<td>100:00</td>
<td>-16.0° (c 0.90)</td>
<td>76a/b</td>
</tr>
<tr>
<td>5</td>
<td>Benzyl</td>
<td>91:09</td>
<td>-17.0° (c 0.55)</td>
<td>77a/b</td>
</tr>
</tbody>
</table>

In order to improve the diastereoselectivity for the addition of other nucleophiles to iminium ion 71d and to get consistent diastereoselectivity irrespective of the nature of nucleophiles, different organometallic reagents were explored. The addition of butyl group was considered for this model study. Copper based reagents have found many applications in organic synthesis therefore various butyl copper reagents were investigated for this purpose. First of all Cul catalysed Grignard addition was explored. The reagent was prepared by the addition of titrated etheral solution of butylmagnesium bromide (1.4M solution in ether) to calculated amount of dry anhydrous copper iodide in ether at -78 °C. Treatment of iminium ion 71d in THF to the slurry formed was carried out at -78 °C (Scheme 41 and Table 7).

![Scheme 41](image-url)
A slight increase in diastereoselectivity was observed when the addition of butylmagnesium bromide was carried out in the presence of 0.5 equiv of Cul and there is a decrease in diastereoselectivity when 1 equiv. of Cul was used. The higher diastereoselectivity obtained with 0.5 equiv Cul may be due to formation of Bu₂CuMgBr, a bulkier homodicuprate species as compared to BuCuMg resulting from stoichiometric use of BuMgBr and Cul.

The additions of n-BuLi and its complexes with other metal salts (CeCl₃, Cul) were also investigated (Scheme 42). BuCeLi was prepared by the addition of 1 equiv of n-BuLi to a slurry of 1 equiv dry CeCl₃ in THF at −78 °C. Bu₂CuLi was prepared by the addition of 2 equiv. of n-BuLi to a slurry of 1 equiv. Cul in ether at −40 °C. The addition of these reagents to iminium ion 71d were carried out at −78 °C in THF. The results are compiled in Table 8.

### Table 7: Diastereoselective addition of BuMgBr to iminium ion 71d in the presence of various equivalents of Cul

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cul used</th>
<th>Diastereoselectivity</th>
<th>Yield(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.1 equiv</td>
<td>88:12</td>
<td>80</td>
</tr>
<tr>
<td>2</td>
<td>0.5 equiv</td>
<td>90:10</td>
<td>79</td>
</tr>
<tr>
<td>3</td>
<td>1 equiv</td>
<td>84:16</td>
<td>80</td>
</tr>
</tbody>
</table>

BuCeLi was prepared by the addition of 1 equiv of n-BuLi to a slurry of 1 equiv dry CeCl₃ in THF at −78 °C. Bu₂CuLi was prepared by the addition of 2 equiv. of n-BuLi to a slurry of 1 equiv. Cul in ether at −40 °C. The addition of these reagents to iminium ion 71d were carried out at −78 °C in THF. The results are compiled in Table 8.
Table 8: Diastereoselective addition of various organolithiums to iminium ion 71d.

<table>
<thead>
<tr>
<th>Entry</th>
<th>RM</th>
<th>Diastereoselectivity</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>n-BuLi</td>
<td>68:32</td>
<td>80</td>
</tr>
<tr>
<td>2</td>
<td>BuLi.CeCl₃</td>
<td>93:7</td>
<td>75</td>
</tr>
<tr>
<td>3</td>
<td>Bu₂CuLi</td>
<td>98:2</td>
<td>79</td>
</tr>
</tbody>
</table>

Maximum diastereoselectivity was achieved with the addition of dibutylcuprate lithium (Gilman’s reagent) as compared to n-BuLi and CeCl₃ complex, butyllithium and dialkyl magnesio cuprate (Normant’s reagent) additions.

A similar study was also carried out for the nucleophilic addition of various benzyl organometallic reagents to iminium ion 71d (Scheme 43), because benzyl group has lot of potential in this method for the synthesis of various types of isoquinoline alkaloids.

Scheme 43
Benzyl magnesiumcerate was prepared by the addition of 1 equiv of benzylmagnesium bromide (0.2 M solution in THF) to a slurry of 1 equiv. anhydrous cerium chloride in THF at 0 °C. Lithium dibenzylcuprate was prepared by transmetalation reaction of benzyl tributyltin 79 with 1.1 equiv. methylolithium in THF at −78 °C and the reaction of the resulting benzyllithium 80 with 0.5 equiv. anhydrous Cul at −78 °C in ether. Benzyltributyltin in turn was obtained from benzyl methane sulfonate 78 (prepared from 1.0 equiv benzyl alcohol, 1.2 equiv methanesulphonyl chloride and 1.5 equiv triethylamine in DCM at 0 °C) and tributyltin anion prepared by deprotonation of tributyltin hydride with 1.05 equiv of LDA in THF at 0 °C (Scheme 44). The results have been compiled in Table 9.

Table 9: Diastereoselective addition of various benzyl organometallic reagents to iminium ion 71d.

<table>
<thead>
<tr>
<th>Entry</th>
<th>PhCH$_2$M</th>
<th>Metal used (equiv.)</th>
<th>Diastereoselectivity</th>
<th>Yield(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhCH$_2$MgBr</td>
<td>Cul (0.1)</td>
<td>89:11</td>
<td>70</td>
</tr>
<tr>
<td>2</td>
<td>PhCH$_2$MgBr</td>
<td>Cul (0.5)</td>
<td>88:12</td>
<td>65</td>
</tr>
<tr>
<td>3</td>
<td>PhCH$_2$MgBr</td>
<td>Cul (1.0)</td>
<td>85:15</td>
<td>63</td>
</tr>
<tr>
<td>4</td>
<td>PhCH$_2$MgBr</td>
<td>CeCl$_3$ (1.0)</td>
<td>91:09</td>
<td>70</td>
</tr>
<tr>
<td>5</td>
<td>PhCH$_2$Li</td>
<td>Cul (0.5)</td>
<td>97:03</td>
<td>69</td>
</tr>
</tbody>
</table>
There is a decrease in diastereoselectivity upon addition of benzylmagnesium bromide with increase in the amount of Cul (Table 9, compare entry 1-3). Addition of benzyl Grignard in the presence of 1 equiv. CeCl$_3$ improved the diastereoselectivity over Cul. The maximum diastereoselectivity was achieved with dibenzylcuprate addition.

Taking cue from the superior diastereoselectivities for dialkylcuprate additions over the addition of Grignard or alkylcerium reagents, addition of different dialkylcuprates to iminium ion 71d were carried out (Scheme 45).

![Scheme 45](image_url)

Various cuprate reagents were prepared by treatment of 2 equiv of alkyl lithium with 1 equiv. of anhydrous Cul in ether at appropriate temperature (Scheme 46) under argon atmosphere. Allyllithium was prepared by treating allyltributyltin with 1 equiv of MeLi in THF at $-78^\circ$C. The result of various cuprate addition reactions to iminium ion 71d are depicted in Table 10.
Table 10: Diastereoselective addition of various dialkyl cuprates to iminium ion 71d.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R₂CuLi</th>
<th>Diastereoselectivity</th>
<th>Yield(%)</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me₂CuLi</td>
<td>98:02</td>
<td>70</td>
<td>72d/d'</td>
</tr>
<tr>
<td>2</td>
<td>Et₂CuLi</td>
<td>92:08</td>
<td>75</td>
<td>73a/b</td>
</tr>
<tr>
<td>3</td>
<td>'Pr₂CuLi</td>
<td>H-Reduction</td>
<td>80</td>
<td>81</td>
</tr>
<tr>
<td>4</td>
<td>Bu₂CuLi</td>
<td>98:02</td>
<td>72</td>
<td>75a/b</td>
</tr>
<tr>
<td>5</td>
<td>(Allyl)₂CuLi</td>
<td>94:06</td>
<td>79</td>
<td>82a/b</td>
</tr>
<tr>
<td>6</td>
<td>(Benzyl)₂CuLi</td>
<td>97:03</td>
<td>80</td>
<td>77a/b</td>
</tr>
</tbody>
</table>

In each case diastereoselectivity of addition product is superior to Grignard addition product. However, addition of diisopropyl lithium cuprate gave the reduced product which probably formed by the transfer of hydride by β-hydrogen elimination of the diisopropyl lithium cuprate.
Chapter 1

In conclusion, we have developed a model using the power of computational chemistry supported by experiments, to predict the diastereoochemical outcome of addition of organometallic reagents to isoquinolinium ions having N-chiral centre. We have also identified a chiral auxiliary to give addition products in high diastereoselectivity and a variety of groups have been incorporated at C1 position of iminium ions. This methodology has applications in the synthesis of isoquinoline alkaloids having therapeutic values.
General method for the preparation of methylmagnesium iodide, ethylmagnesium bromide, isopropylmagnesium bromide and butylmagnesium bromide.
Magnesium turnings (1.6 equiv) and freshly distilled ether (10 mL) were placed in a flame dried two necked round bottomed flask fitted with a reflux condenser under nitrogen atmosphere. Alkyl halide (1 equiv) in freshly distilled ether (2 mL) was added dropwise over a period of 15 min. The mixture was stirred vigorously at 0 °C during addition and further at room temperature for half an hour. The reflux condenser was removed and the cloudy Grignard reagent was stored under nitrogen atmosphere in refrigerator. The Grignard reagent was titrated using 1,10-phenanthroline prior to use.47

Preparation of benzylmagnesium bromide.
Magnesium turnings (1.2g, 52.0 mmol) and freshly distilled THF (10 mL) were placed in a flame dried two necked round bottomed flask fitted with a reflux condenser under nitrogen atmosphere. Neat benzyl bromide (1.2 mL, 10.4 mmol) was added dropwise at room temperature. The mixture was stirred at room temperature for one hour after the addition was over, resulting in the formation benzylmagnesium bromide. The Grignard reagent was titrated using 1,10-phenanthroline prior to use.47

Preparation of 3,4-methylenedioxyphenylmagnesium bromide.
Magnesium turnings (1.1g, 48.5 mmol) and freshly distilled THF (10 mL) were placed in a flame dried two necked round bottomed flask fitted with a reflux condenser under nitrogen atmosphere. A few crystals of iodine were also added. Neat 4-bromo-1, 2-(methylenedioxy)benzene (1.16 mL 9.7 mmol) was added dropwise with refluxing. The mixture was stirred further at room temperature for one hour after the completion of addition. 3,4-methylenedioxyphenylmagnesium bromide was obtained as a cloudy solution. The Grignard reagent was titrated using 1,10-phenanthroline prior to use.47
Chapter 1

Preparation of ethyllithium.
Molecularised lithium (1 g, 0.14 mol) and freshly distilled pentane (15-20 mL) were placed in a flame dried two necked round bottomed flask fitted with a reflux condenser under nitrogen atmosphere. Neat 1-bromoethane (0.3 mL) was added and the mixture was heated to gentle reflux. After 20 min. the solution became violet in colour. Heating was stopped to bring the reaction mixture to room temperature. A solution of 1-bromoethane (5.2 mL, 0.07 mol) in freshly distilled pentane (10 mL) was added dropwise at room temperature with vigorous stirring. The mixture was stirred at room temperature for one hour after the completion of addition and it was stored in refrigerator under nitrogen atmosphere. EtLi was decanted with the help of a cannula and titrated with 1,10-phenanthroline and secondary butanol prior to use.

Preparation of isopropyllithium: This was prepared from isopropyl chloride following the above procedure used for the preparation of ethyllithium.

Titration of organolithium and organomagnesium reagents: In a flame dried round bottomed flask under nitrogen atmosphere were placed a few crystals of 1,10-phenanthroline. Organometallic reagent (2 mL) was added with a syringe at -20 °C to give a reddish-brown solution. Secondary butanol was added dropwise until the colour of the charge transfer complex was discharged (reddish-brown to light yellow). The molarity of organometallic reagent was determined from the following equation.

\[
\text{mmol of (RLi or RMgX)} = \frac{\text{mmol (sBuOH)}}{\text{mw of sBuOH} \times \text{mL of sBuOH used}} = 0.803/74.12 \times \text{mL sBuOH used}
\]

Preparation of 1-Phenyl-2-methylpropylamine (57c).
To a flame dried two necked round bottomed flask fitted with a reflux condenser under nitrogen atmosphere were taken 1,1,1,3,3,3-hexamethyldisilazane (27 mL, 0.13 mol) and freshly distilled THF (20 mL). n-BuLi (75 mL, 1.6M solution in hexane, 0.12 mol) was added at 0 °C via cannula. The reaction mixture was stirred at 0 °C for 30 min and then a solution of benzaldehyde (10.1 mL, 0.10 mol) in freshly distilled THF (15 mL) was added dropwise. The mixture was stirred at 0 °C for 30 min and the
formation of the $N$-trimethylsilyl imine 58 was monitored by TLC. Isopropylmagnesium bromide (224 mL, 0.89M solution in ether, 0.2 mol) was added at 0 °C via cannula. The mixture was refluxed at 80 °C for 6-10 h and the progress of the reaction was monitored by TLC. After the completion of reaction, the reaction mixture was quenched with a saturated aqueous solution of ammonium chloride (30 mL) very slowly. The product was extracted with ethyl acetate (3×100 mL). The combined organic extracts were dried over anhydrous Na$_2$SO$_4$, filtered and concentrated in vacuo. The crude yellow oil obtained was vacuum distilled to afford amine 57c as a colourless oil (13 g, 87%).

$^1$H NMR (200 MHz, CDCl$_3$): δ 7.36-7.22 (m, 5H), 3.60 (d, $J = 7.3$ Hz, 1H), 1.90-1.77 (m, 1H), 1.55 (s, 2H), 0.98 (d, $J = 6.3$ Hz, 3H), 0.77 (d, $J = 6.8$ Hz, 3H).

$^{13}$C NMR (75 MHz, CDCl$_3$): δ 145.3, 128.0, 126.8, 126.6, 62.3, 35.3, 19.6, 18.7.

IR (neat): 3378, 3361, 2959, 1602, 1453, 1360, 877, 758, 701 cm$^{-1}$.

MS-CI (m/z): 150 (M$^+$+1), 133 (base peak).

Resolution of 1-Phenyl-2-methylpropylamine. To a hot solution of (1R)-(−)-camphor-10-sulphonic acid (7.94 g, 34.2 mmol) in distilled water (15 mL) racemic amine 57c (5 g, 33.5 mmol) was added dropwise. The mixture was heated for sometime and the formation of amine-acid salt was confirmed by TLC. The solution was cooled to room temperature and kept in a refrigerator for two days. Shining crystals formed were collected (2.2 g, 37%) by decantation and were washed with ice cold water. These crystals were further recrystallized from water till a constant optical rotation $[a]_D^{25} = -28.3$ ° (c 0.5, MeOH) was obtained. The crystals were hydrolysed with 4N NaOH solution. Free amine was extracted with benzene (3×50 mL). The combined organic extracts were dried over anhydrous Na$_2$SO$_4$, filtered and concentrated in vacuo to afford amine 57c (800 mg, 32%). $[a]_D^{25} = +13.2$ ° (c 4.75, CHCl$_3$).

Preparation of 1-phenyl-2, 2-dimethylpropylamine (57d). tert-BuLi (69 mL, 1.5M solution in pentane, 103 mmol) was added to N-trimethylsilylimine 58 (1 equiv. prepared according to above procedure from benzaldehyde, 9.5 mL,
94.2 mmol) at -78 °C under nitrogen atmosphere. The yellow coloured solution was warmed to room temperature and quenched with a saturated solution of ammonium chloride (20 mL). The product was extracted with ethyl acetate (3×100 mL). The combined organic extracts were dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The yellow oil obtained was purified by column chromatography on silica gel (100-200 mesh) using 70% EtOAc/hexane as eluent to afford amine 57d which was further purified by distillation under vacuum as a colourless oil (14g, 85% yield).

1H NMR (300 MHz, CDCl₃): δ (ppm) 7.16-7.04 (m, 5H), 3.59 (s, 1H), 1.46 (s, 2H), 0.80 (s, 9H).

13C NMR (75 MHz, CDCl₃): δ (ppm) 128.2, 127.4, 126.7, 65.3, 34.2, 26.5.

IR (neat): 3385, 3380, 2954, 1603, 1452, 1362, 897, 777, 702 cm⁻¹.

MS-CI (m/z): 164 (M⁺+1), 147 (base peak).

Resolution of 1-Phenyl-2, 2-dimethylpropylamine. To a hot solution of N-acetyl-L-leucine (5.84 g, 0.033 mol) in water (60 mL) was added racemic amine 57d (5 g, 0.030 mol) dropwise with stirring. The hot solution was filtered and fine crystals were allowed to grow overnight at room temperature. The crystals were collected by filtration, and recrystallised three times from water. The crystals (2 g, 40%) were collected having a constant optical rotation [a]D₂₅ = -4.2 ° (c 0.64, MeOH). These crystals were hydrolysed with 4N NaOH solution. The amine was extracted with benzeze (3×50 mL). The combined organic extracts were dried over anhydrous Na₂SO₄ and concentrated in vacuo to afford amine 57d (900 mg, 45%). [a]D₂₅ = +4.3 ° (c 1, MeOH).

General method for the determination of enantiomeric excess of resolved amines 57c and 57d. Triethylamine (0.018 mL, 0.134 mmol) was added to a solution of 1-phenyl-2-methylpropylamine 57c (10 mg, 0.067 mmol) in dichloromethane (0.5 mL), under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 15 min and then neat (R)-(−)-(α-methoxy-α-trifluoromethyl)-phenylacetyl chloride (0.0125 mL, 0.067 mmol) was added. The mixture was stirred at room temperature for 30 min and then quenched with a saturated solution of sodium bicarbonate (1 mL). The amide was
extracted with dichloromethane (2×10 mL). The combined organic extracts were dried over anhydrous Na$_2$SO$_4$, filtered and concentrated in vacuo to give the Mosher amide as a white solid. Amines 57c and 57d were obtained in 98% and 99% ee respectively.

$R$-$N$-(α-isopropylbenzyl)-(R)-2-methoxy-2-trifluoromethyl-2-phenylacetamide (66a/b).

$^1$H NMR (400 MHz, CDCl$_3$): δ (ppm) 7.67-7.22 (m, 10H), 6.95 (d, $J = 8.8$ Hz, 1H), 4.75 (t, $J = 8.3$ Hz, 1H), 3.44 (s, 3H), 3.37 (s, 3H), 2.08-2.01 (m, 1H), 0.86 (d, $J = 6.7$ Hz, 3H).

$R$-$N$-(α-tert. butylbenzyl)-(R)-2-methoxy-2-trifluoromethyl-2-phenylacetamide (67a/b).

$^1$H NMR (400 MHz, CDCl$_3$): δ (ppm) 7.40-7.21 (m, 10H), 7.10 (d, $J = 2.1$ Hz, 1H), 4.78 (d, $J = 9.4$ Hz, 1H), 3.46 (s, 3H), 0.94 (s, 9H).

Preparation of $R$-(+)-1-(2-Chlorophenyl)-2-methylpropylamine (57e). To a flame dried round bottomed flask under nitrogen atmosphere, were placed (R)-(+) -1-phenyl-2-methylpropylamine 57c (4 g, 26.8 mmol) and freshly distilled ether (10 mL). n-BuLi (16.7 mL, 1.6M solution in hexane, 26.8 mmol) was added at 0 °C via cannula. The light yellow suspension was stirred at 0 °C for 15 min and then chlorotrimethylsilane (3.4 mL, 26.8 mmol) was added dropwise. The mixture was stirred for 30 min at 0 °C and then n-BuLi (50.2 mL, 1.6M solution in hexane, 80.4 mmol) was added dropwise via cannula at 0 °C. The mixture was stirred at 0 °C for 1 h and then warmed to room temperature. After 24 h, the mixture was cooled to −78 °C and then a solution of hexachloroethane (12.6 g, 53.6 mmol) in freshly distilled ether (20 mL) was added dropwise at such a rate so that the internal temperature of the reaction mixture did not exceed −68 °C. The addition took 2 h. The resulting pale yellow solution was then gradually warmed to −45 °C and stirred at this temperature for 1 h. The reaction mixture was quenched with a saturated solution of ammonium chloride (10 mL) and the product was extracted with ethyl acetate (3×100 mL). The combined organic extracts were dried over
anhydrous Na$_2$SO$_4$, filtered and concentrated \textit{in vacuo} to afford a brown oil.

The crude product obtained was purified by column chromatography on silica gel (100-200 mesh) using 30% EtOAc/hexane as eluent. The amine \textit{57e} was further purified by Kugelrohr distillation as a colourless oil (2g, 32%).

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ (ppm) 7.45-7.08 (m, 4 H), 4.15 (d, $J = 6.9$ Hz, 1H), 2.01-1.90 (m, 1H), 1.68 (bs, 1H), 0.97 (d, $J = 6.9$ Hz, 3 H), 0.86 (d, $J = 6.9$ Hz, 3H).

$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ (ppm) 142.8, 133.1, 129.4, 127.8, 127.6, 126.7, 57.6, 34.0, 19.9, 17.9.

IR (neat): 3377, 3360, 2958, 1601, 1449, 1359, 870, 750, 703 cm$^{-1}$.

MS-CI (m/z): 167, 184 (base peak, M$^+$+1).

$[\alpha]_D^{25} = -18.4^\circ$ (c 1.63, CHCl$_3$).

Attempted preparation of (R)-(+)\-1\-(2,6-dichlorophenyl)-2-methylpropylamine (\textit{57f}) from (R)-(+)\-1\-(2-chlorophenyl)-2-methylpropylamine (\textit{57e}). To a solution of (R)-(+)\-1\-(2-chlorophenyl)-2-methylpropylamine \textit{57e} (800 mg, 4.37 mmol) in freshly distilled ether (10 mL) at $-78$ °C under argon atmosphere was added n-BuLi (2.7 mL, 1.6M solution in hexane, 4.37 mmol). After 30 min, chlorotrimethylsilane (0.55 mL, 4.37 mmol) was added dropwise, the mixture was warmed to 0 °C and allowed to stir at 0 °C for 30 min. The mixture was cooled to $-25$ °C and n-BuLi (8.19 mL, 1.6M solution in hexane, 13.1 mmol) was added via cannula at such a rate so that the internal temperature of the reaction mixture did not exceed $-20$ °C. The mixture was stirred between $-10$ ° and $-15$ °C for 40 min and then cooled to $-78$ °C. A solution of hexachloroethane (2.06 g, 8.74 mmol) in freshly distilled ether (10 mL) was added slowly via cannula at such a rate so as to maintain the internal temperature of the reaction vessel $-70$ °C. The addition took 1.5 h. The mixture was warmed to $-45$ °C and stirred at this temperature for 1 h and quenched with a saturated solution of ammonium chloride (4 mL) and warmed to room temperature. The product was extracted with ethyl acetate (2×20 mL). The combined organic extracts were dried over anhydrous Na$_2$SO$_4$, filtered and concentrated \textit{in vacuo} to afford a brown oil consisting of
the starting amine 57e and a non-polar spot (not the required one) at the top of TLC.

Preparation of 1-(2,6-dichlorophenyl)-2-methylpropylamine (57f) by Hart’s method. To a flame dried two necked round bottomed flask under nitrogen atmosphere, were taken 1,1,1,3,3,3-hexamethyldisilazane (7.78 mL, 37.05 mmol) and freshly distilled THF (10 mL). n-BuLi (21.3 mL, 1.6M solution in hexane, 34.2 mmol,) was added at 0 °C with syringe. The mixture was stirred at 0 °C for 30 min and then cooled to −78 °C. A solution of 2,6-dichlorobenzaldehyde (5 g, 28.5 mmol) in freshly distilled THF (10 mL) was added dropwise and the stirring was continued at this temperature for half an hour. Isopropyllithium (28 mL, 2M solution in pentane, 57 mmol) was added slowly via cannula. The mixture was warmed to room temperature and then quenched with a saturated solution of ammonium chloride (10 mL). The product was extracted with ethylacetate (2×100 mL). The combined organic extracts were dried over anhydrous Na2SO4, filtered and concentrated in vacuo. The crude product obtained was purified by column chromatography on silica gel (100-200 mesh) using 20% EtOAc/hexane as eluent to afford amine 57f as a brown oil (2 g, 40 %).

1H NMR (300 MHz, CDCl3): δ (ppm) 7.15 (m, 2H), 7.00 (m, 1H), 4.15 (d, J = 10.0 Hz, 1H), 2.55 (bs, 2H), 2.35 (m, 1H), 1.10 (d, J = 6.5 Hz, 3H), 0.65 (d, J = 6.8 Hz, 3H).

13C NMR (75 MHz, CDCl3): δ (ppm) 140.2, 130.1, 128.5, 127.9, 60.1, 32.3, 20.7, 20.0.

IR (neat): 3397, 3350, 2961, 1434, 1383, 873, 757, 703 cm⁻¹.

MS-CI (m/z): 220, 218 (M⁺+1, base peak).

Attempted resolution of 1-(2,6-Dichlorophenyl)-2-methylpropylamine (57f). Racemic amine 57f in three sets each consisting of (500 mg, 2.30 mmol), was added to a hot solution of (1R)-camphor-10-sulphonic acid (588 mg, 2.53 mmol) in water (7 mL), (D)-tartaric acid (379 mg, 2.53 mmol) in hot water (5 mL) and N-acetyl-L-leucine (438 mg, 2.53 mmol) in hot water (10 mL) respectively. The mixture in each case was heated for 10-15 min and the
formation of amine-acid salt was confirmed by TLC. Fine crystals were allowed to grow at room temperature slowly for 3-4 days in each case. The crystals were collected by filtration and recrystallised two times from water. A constant optical rotation $[\alpha]_D^{25} = -20.2^\circ$ (c 1.05, MeOH), $+17.5^\circ$ (c 0.98, MeOH) and $-11.5^\circ$ (c 1.6, MeOH) was obtained after every crystallisation for camphorsulphonic acid, tartaric acid and N-acetyl-L-leucine. The crystals obtained (20% yield) were hydrolysed with 5N NaOH to afford amine 57f. The optical rotation of amine 57f obtained was $[\alpha]_D^{25} = +0.01^\circ$ (c 0.7, CHCl3), $-0.02^\circ$ (c 0.2, CHCl3) and $+0.00^\circ$ (c 0.1, CHCl3) for the respective acids.

**R-N-(α-isopropyl-α-(2,6-dichlorophenyl)-(R)-2-methoxy-2-trifluoromethyl-2-phenylacetamide (63a/b).**

$^1$H NMR (400 MHz, CDCl3): δ (ppm) 7.72-7.53 (m, 3H), 7.40-7.09 (m, 5 H), 6.60-5.29 (m, 1H), 3.45 (s, 3H), 3.44 (s, 3H), 2.56-2.41 (m, 1H), 1.15 (d, J = 6.7 Hz, 3H), 0.89 (d, J = 6.4 Hz, 3H), 0.82 (d, J = 6.9 Hz, 3H), 0.77 (d, J = 6.7 Hz, 3H).

**General method for the formation of amides (68a-f).** To a solution of DCC (6.6 mmol, 1.2 equiv.) and DMAP (catalytic amount) in freshly distilled DCM (20 mL) was added 3, 4-dimethoxyphenylacetic acid (6.4 mmol, 1.2 equiv.) at 0 °C. After half an hour, a solution of amine (5.4 mmol, 1 equiv.) in freshly distilled DCM (10 mL) was added at 0 °C. The mixture was warmed to room temperature and the progress of the reaction was monitored by TLC. After 12 h, the solution was filtered through a sintered funnel and the filtrate was washed with 10% citric acid solution, saturated sodium bicarbonate solution and water respectively. The organic layer was collected, dried over anhydrous Na$_2$SO$_4$ and concentrated in vacuo to afford the crude amides. The crude amides were purified by column chromatography on silica gel (100-200 mesh) using 30% EtOAc/hexane as eluent.

**(S)-N-[1-Phenylethyl]-2-(3,4-dimethoxyphenyl)acetamide (68a).** The amide 68a was obtained as a white crystalline solid (1 g, 70 %) from amine 57a (658...
Chapter 1
mg, 5.4 mmol), DCC (1.3 g, 6.4 mmol), DMAP (catalytic amount) and 3,4-dimethoxyphenylacetic acid (1.2 g, 6.8 mmol).
Mp 102-104 °C.

\[ ^1H \text{NMR} \ (300 \text{ MHz, } \text{CDCl}_3): \delta (\text{ppm}) \ 7.31-7.16 \ (m, \ 5H), \ 6.85-6.75 \ (m, \ 3H), \ 5.74 \ (d, \ J = 7.5 \text{ Hz, } 1H), \ 5.12 \ (m, \ 1H), \ 3.87 \ (s, \ 3H), \ 3.83 \ (s, \ 3H), \ 3.51 \ (s, \ 2H), \ 1.39 \ (d, \ J = 6.7 \text{ Hz, } 3H). \]

\[ ^{13}C \text{NMR} \ (75 \text{ MHz, } \text{CDCl}_3): \delta (\text{ppm}) \ 170.2, \ 148.6, \ 147.6, \ 143.1, \ 128.1, \ 127.4, \ 126.7, \ 125.6, \ 121.0, \ 111.9, \ 111.0, \ 55.4, \ 55.3, \ 48.3, \ 42.6, \ 21.5. \]

IR (CCl4): 2938, 1664, 1514, 1263, 1149, 1028, 756, 702 cm\(^{-1}\).

MS-CI (m/z): 300 (M\(^+\)1, base peak).
\([\alpha]_{D}^{25} = +11.0 ^\circ \ (c \ 0.54, \text{CHCl}_3)\]

\((S)-N-[1-Phenylpropyl]-2-(3,4-dimethoxyphenyl)acetamide (68b).\) The amide 68b was obtained as a white crystalline solid (1.2 g, 75 %) from amine 57b (730 mg, 5.4 mmol), DCC (1.3 g, 6.4 mmol), DMAP (catalytic amount) and 3,4-dimethoxyphenylacetic acid (1.2 g, 6.4 mmol).
Mp 111-113 °C.

\[ ^1H \text{NMR} \ (200 \text{ MHz, } \text{CDCl}_3): \delta (\text{ppm}) \ 7.32-7.12 \ (m, \ 5H), \ 6.87-6.74 \ (m, \ 3H), \ 5.71 \ (d, \ J = 8.0 \text{ Hz, } 1H), \ 4.88 \ (q, J = 7.8 \text{ Hz, } 1H), \ 3.88 \ (s, \ 3H), \ 3.82 \ (s, \ 3H), \ 3.52 \ (s, \ 2H), \ 1.77-1.63 \ (m, \ 2H), \ 0.81 \ (t, \ J = 7.3 \text{ Hz, } 3H). \]

\[ ^{13}C \text{NMR} \ (75 \text{ MHz, } \text{CDCl}_3): \delta (\text{ppm}) \ 170.5, \ 149.3, \ 148.3, \ 142.1, \ 128.5, \ 128.2, \ 127.4, \ 127.2, \ 126.3, \ 121.6, \ 112.3, \ 111.5, \ 55.9, \ 55.8, \ 54.6, \ 43.5, \ 29.1, \ 10.5. \]

IR (CCl4): 3316, 2934, 1641, 1513, 1260, 1234, 1163, 1024, 700 cm\(^{-1}\).

MS-CI (m/z): 314 (M\(^+\)1, base peak).
\([\alpha]_{D}^{25} = +6.9 ^\circ \ (c \ 1.59, \text{CHCl}_3).\]

\((R)-N-[1-Phenyl-2-methylpropyl]-2-(3,4-dimethoxyphenyl)acetamide (68c).\) The amide 68c was obtained as a white crystalline solid (1.76 g, 75 %) from amine 57c (804 mg, 5.4 mmol), DCC (1.3 g, 6.4 mmol), DMAP (catalytic amount) and 3,4-dimethoxyphenylacetic acid (1.2 g, 6.8 mmol).
Mp 115-120 °C.

\[ ^1H \text{NMR} \ (200 \text{ MHz, } \text{CDCl}_3): \delta (\text{ppm}) \ 7.30-7.05 \ (m, \ 5H), \ 6.89-6.74 \ (m, \ 3H), \ 5.73 \ (d, \ J = 8.5 \text{ Hz, } 1H), \ 4.74 \ (t, J = 7.7 \text{ Hz, } 1H), \ 3.90 \ (s, \ 3H), \ 3.83 \ (s, \ 3H), \ 3.59 \ (d, \ J
**Chapter 1**

\[ = 16.3 \text{ Hz, 1H}, \ 3.49 (d, J = 16.3 \text{ Hz, 1H}), \ 1.94-1.80 (m, 1H), \ 0.77 (\text{two merging d, } J = 6.7 \text{ Hz, 6H}) \]

\[ ^{13}\text{C NMR} \ (75 \text{ MHz, CDCl}_3): \ \delta \ (\text{ppm}) \ 170.4, \ 149.3, \ 148.3, \ 128.3, \ 127.4, \ 127.0, \ 126.6, \ 121.6, \ 112.2, \ 111.5, \ 58.7, \ 55.9, \ 55.8, \ 43.5, \ 33.3, \ 19.6, \ 18.3 \]

\[ \text{IR} \ (\text{CCl}_4): \ 3298, \ 2932, \ 1641, \ 1514, \ 1262, \ 1233, \ 1154, \ 1029 \text{ cm}^{-1} \]

\[ \text{MS-CI} \ (m/z): \ 328 \ (M'^{+}1, \ \text{base peak}) \]

\[ [\alpha]^{25}_{D} = -20.2 ^{\circ} \ (c \ 1.05, \ \text{CHCl}_3) \]

\textbf{(R)-N-[(1-Phenyl-2,2-dimethylpropyl)-2-(3,4-dimethoxyphenyl) acetamide (68d).} \ The amide 68d was obtained as a white crystalline solid (1.2 g, 79 %) from amine 57d (880 mg, 5.4 mmol), DCC (1.3 g, 6.4 mmol), DMAP (catalytic amount) and 3,4-dimethoxyphenylacetic acid (1.2 g, 6.8 mmol).

\[ \text{Mp 140-143} \ ^{\circ} \text{C} \]

\[ ^{1}\text{H NMR} \ (200 \text{ MHz, CDCl}_3): \ \delta \ (\text{ppm}) \ 7.24 (d, J = 8.3 \text{ Hz, 3H}), \ 7.00-6.75 \text{ (m, 5H)}, \ 5.98 (d, J = 9.4 \text{ Hz, 1H}), \ 4.75 (d, J = 9.6 \text{ Hz, 1H}), \ 3.92 (s, 3H), \ 3.85 (s, 3H), \ 3.59 (d, J = 16.0 \text{ Hz, 1H}), \ 3.49 (d, J = 16.0 \text{ Hz, 1H}), \ 0.76 (s, 9H) \]

\[ ^{13}\text{C NMR} \ (75 \text{ MHz, CDCl}_3): \ \delta \ (\text{ppm}) \ 170.1, \ 149.3, \ 148.3, \ 139.8, \ 127.8, \ 127.6, \ 127.4, \ 126.9, \ 121.6, \ 112.4, \ 112.3, \ 111.5, \ 61.2, \ 55.9, \ 55.8, \ 48.9, \ 48.4, \ 43.5, \ 34.7, \ 33.9, \ 25.5, \ 24.8, \]

\[ \text{IR} \ (\text{CCl}_4): \ 3303, \ 2956, \ 1624, \ 1516, \ 1262, \ 1231, \ 1152, \ 1027 \text{ cm}^{-1} \]

\[ \text{MS-CI} \ (m/z): \ 342 \ (M'^{+}1, \ \text{base peak}) \]

\[ [\alpha]^{25}_{D} = -36.7 ^{\circ} \ (c \ 2.91, \ \text{CHCl}_3) \]

\textbf{(R)-N-[(1-2-Chlorophenyl)-2-methylpropyl]-2-(3,4-dimethoxyphenyl) acetamide (68e).} \ The amide 68e was obtained as a white crystalline solid (1.6 g, 65 %) from amine 57e (988 mg, 5.4 mmol), DCC (1.3 g, 6.4 mmol), DMAP (catalytic amount) and 3,4-dimethoxyphenylacetic acid (1.2 g, 6.8 mmol).

\[ \text{Mp 100-105} \ ^{\circ} \text{C} \]

\[ ^{1}\text{H NMR} \ (200 \text{ MHz, CDCl}_3): \ \delta \ (\text{ppm}) \ 7.31-7.02 \text{ (m, 4H)}, \ 6.99-6.70 \text{ (m, 3H)}, \ 6.08 (d, J = 9.0 \text{ Hz, 1H}), \ 4.90 (t, J = 9.0 \text{ Hz, 1H}), \ 3.88 (s, 3H), \ 3.82 (s, 3H), \ 3.57 (d, J = 16.0 \text{ Hz, 1H}), \ 3.44 (d, J = 16.0 \text{ Hz, 1H}), \ 2.09-2.02 \text{ (m, 1H)}, \ 0.78 (d, J = 8.3 \text{ Hz, 3H}), \ 0.75 (d, J = 8.3 \text{ Hz, 3H}) \]
**13C NMR** (75 MHz, CDCl₃): δ (ppm) 170.4, 149.3, 148.3, 138.8, 132.7, 130.1, 129.2, 128.2, 127.3, 126.6, 121.6, 112.3, 111.5, 57.6, 55.9, 55.8, 43.4, 31.7, 19.9, 18.3.

**IR** (CCl₄): 3309, 2966, 1639, 1513, 1262, 1233, 1154, 1024 cm⁻¹.

**MS-CI** (m/z): 362 (M⁺+1, base peak).

[α]DRT = +13.7 ° (c 5.24, CHCl₃).

W-[1-(2,6-Dichlorophenyl)-2-methylpropyl]-2-(3,4-dimethoxyphenyl) acetamide (68f). The amide 68f was obtained as a viscous oil (1.4 g, 72 %) from amine 57f (1.1 g, 5.4 mmol), DCC (1.3 g, 6.4 mmol), DMAP (catalytic amount) and 3,4-dimethoxyphenylacetic acid (1.2 g, 6.8 mmol).

**1H NMR** (200 MHz, CDCl₃): δ (ppm) 7.27-7.04 (m, 3H), 6.88-6.73 (m, 3H), 6.46 (d, J = 9.5 Hz, 1H), 5.54 (t, J = 10.4 Hz, 1H), 3.89 (s, 3H), 3.83 (s, 3H), 3.58 (d, J = 16.4 Hz, 1H), 3.47 (d, J = 16.0 Hz, 1H), 2.30-2.21 (m, 1H), 0.96 (d, J = 6.5 Hz, 3H), 0.73 (d, J = 6.8 Hz, 3H).

**13C NMR** (75 MHz, CDCl₃): δ (ppm) 170.3, 149.2, 148.2, 136.2, 129.4, 128.7, 128.5, 127.0, 121.7, 112.3, 111.4, 55.9, 55.8, 55.7, 43.2, 30.9, 19.9, 19.1.

**IR** (neat): 3335, 2964 1660, 1514, 1262, 1238, 1156, 1028 cm⁻¹.

**MS-CI** (m/z): 396 (M⁺+1, base peak).

**General method for the preparation of secondary amines (69a-f).** In a flame dried two necked round bottomed flask fitted with a reflux condenser under nitrogen atmosphere was placed amide (3 mmol, 1 equiv.) and freshly distilled THF (12 mL). BF₃·OEt₂ (0.6 mL, 0.2 mL/mmol) was added with syringe and the mixture was heated to gentle reflux and BH₃·SMe₂ (0.7 mL, 6 mmol, 2 equiv.) was added very slowly dropwise. The mixture was refluxed at 80 °C for 2 h, cooled to 0 °C and quenched with 4.5N HCl (20 mL) very slowly drop after a drop. The pH of the solution was monitored by a pH paper so that it is sufficiently acidic. The mixture was stirred at 0 °C for 1 h and then at room temperature for additional 1 h. The contents were transferred to a separatory funnel and washed with ether (50 mL). The acidic aqueous layer was separated from organic layer and it was further washed with ether (50 mL) so that all the non-basic impurities were removed from the product. The aqueous
layer was basified with solid NaOH. The product was extracted with ethyl acetate (3x70 mL). The combined organic extracts were dried over anhydrous Na$_2$SO$_4$, filtered and concentrated in vacuo to afford the amine. The product was purified by column chromatography on silica gel (100-200 mesh) using 20% EtOAc/hexane as eluent.

(S)-N-[2-(3,4-Dimethoxyphenyl)ethyl]-1-phenylethylamine (69a). The amine 69a was obtained as a viscous light yellow oil (683 mg, 80%) from amide 68a (897 mg, 3 mmol), BF$_3$.OEt$_2$ (0.6 mL) and BH$_3$.SMe$_2$ (0.7 mL, 6 mmol).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ (ppm) 7.32-7.20 (m, 5H), 6.79-6.67 (m, 3H), 3.85 (s, 3H), 3.83 (s, 3H), 3.67 (q, $J = 6.7$ Hz, 1H), 2.75-2.67 (m, 4H), 1.48 (bs, 1H), 1.32 (d, $J = 6.7$ Hz, 3H).

$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ (ppm) 148.7, 147.3, 145.2, 132.4, 128.3, 126.8, 126.5, 120.5, 111.7, 111.1, 58.1, 55.8, 55.7, 48.7, 35.7, 24.1.

IR (neat): 3457, 2932, 1514, 1455, 1262, 1237, 1140, 1029, 762, 702 cm$^{-1}$.

MS-CI (m/z): 286 (M$^+$+1, base peak).

$[\alpha]_{D}^{25}$ = -41.5° (c 0.72, CHCl$_3$).

(S)-N-[2-(3,4-Dimethoxyphenyl)ethyl]-1-phenylpropylamine (69b). The amine 69b was obtained as a viscous light yellow oil (672 mg, 75%) from amide 68b (939 mg, 3 mmol), BF$_3$.OEt$_2$ (0.6 mL) and BH$_3$.SMe$_2$ (0.7 mL, 6 mmol).

$^1$H NMR (200 MHz, CDCl$_3$): $\delta$ (ppm) 7.34-7.19 (m, 5H), 6.79-6.66 (m, 3H), 3.85 (s, 3H), 3.83 (s, 3H), 3.48 (t, $J = 5.9$ Hz, 1H), 2.69 (s, 4H), 1.79-1.51 (m, 2H), 0.75 (t, $J = 7.3$ Hz, 3H).

$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ (ppm): 148.8, 147.3, 143.9, 132.6, 128.2, 127.2, 126.8, 120.5, 111.8, 111.1, 64.9, 55.8, 55.7, 48.7, 35.7, 30.8, 10.7.

IR (neat): 3227, 2932, 1515, 1450, 1260, 1140, 1030, 758, 700 cm$^{-1}$.

MS-CI (m/z): 301(M$^+$+2, base peak).

$[\alpha]_{D}^{25}$ = -38.7° (c 0.73, CHCl$_3$).

(R)-N-[2-(3,4-Dimethoxyphenyl)ethyl]-1-phenyl-2-methylpropylamine (69c). The amine 69c was obtained as a viscous light yellow oil (704 mg, 75%)
from amide 68c (981 mg, 3 mmol), BF₃.OEt₂ (0.6 mL) and BH₃.SMe₂ (0.7 mL, 6 mmol).

\(^1\)H NMR (200 MHz, CDCl₃): \(\delta\) (ppm) 7.32-7.16 (m, 5H), 6.80-6.67 (m, 3H), 3.85 (s, 3H), 3.83 (s, 3H), 3.30 (d, \(J = 6.8\) Hz, 1H), 2.71-2.60 (m, 4H), 1.87-1.77 (m, 1H), 1.25 (bs, 1H), 0.90 (d, \(J = 6.5\) Hz, 3H), 0.69 (d, \(J = 6.5\) Hz, 3H).

\(^1\)C NMR (75 MHz, CDCl₃): \(\delta\) (ppm) 148.8, 147.3, 142.8, 132.8, 127.9, 127.8, 126.6, 120.5, 111.9, 111.1, 69.5, 55.8, 55.7, 49.0, 35.8, 34.3, 19.6, 19.3.

IR (neat): 3342, 2956, 1514, 1461, 1202, 1141, 1030, 756, 703 cm\(^{-1}\).

MS-CI (m/z): 314 (M\(^{+}+\)1, 100%).

\([\alpha]\)\(^D\)\(^{25}\) = +38.3° (c 0.74, CHCl₃).

(R)-N-[2-(3,4-Dimethoxyphenyl)ethyl]-1-phenyl-2,2-dimethylpropylamine (69d). The amine 69d was obtained as a viscous light yellow oil (637 mg, 65%) from amide 68d (975 mg, 3 mmol), BF₃.OEt₂ (0.6 mL) and BH₃.SMe₂ (0.7 mL, 6 mmol).

\(^1\)H NMR (200 MHz, CDCl₃): \(\delta\) (ppm) 7.25-7.20 (m, 5H), 6.80-6.67 (m, 3H), 3.85 (s, 3H), 3.83 (s, 3H), 3.30 (s, 1H), 2.66-2.55 (m, 4H), 1.25 (brs, 1H), 0.83 (s, 9H).

\(^1\)C NMR (75 MHz, CDCl₃): \(\delta\) (ppm) 129.0, 127.3, 126.6, 120.6, 112.0, 111.2, 72.7, 55.9, 55.7, 49.4, 35.7, 34.7, 27.0.

IR (neat): 3450, 2950, 1515, 1453, 1262, 1150, 1030, 739, 704 cm\(^{-1}\).

MS-CI (m/z): 328 (M\(^{+}+\)1).

\([\alpha]\)\(^D\)\(^{25}\) = +41.4° (c 1.52, CHCl₃).

(R)-N-[2-(3,4-Dimethoxyphenyl)ethyl]-1-(2-chlorophenyl)-2-methylpropylamine (69e). The amine 69e was obtained as a viscous light yellow oil (672 mg, 70%) from amide 68e (1 g, 3 mmol), BF₃.OEt₂ (0.6 mL) and BH₃.SMe₂ (0.7 mL, 6 mmol).

\(^1\)H NMR (200 MHz, CDCl₃): \(\delta\) (ppm) 7.33-7.12 (m, 4H), 6.80-6.67 (m, 3H), 3.95 (d, \(J = 6.8\) Hz, 1H), 3.85 (s, 3H), 3.83 (s, 3H), 2.71-2.62 (m, 4H), 1.88-1.66 (m, 1H), 0.92 (d, \(J = 6.5\) Hz, 3H), 0.78 (d, \(J = 6.8\) Hz, 3H).
Chapter 1

$^{13}\text{C NMR}$ (75 MHz, CDCl$_3$): $\delta$ (ppm) 148.8, 140.9, 134.4, 132.7, 129.3, 128.5, 127.5, 126.6, 120.6, 111.9, 111.2, 64.1, 55.9, 55.7, 48.7, 35.8, 33.8, 19.7, 18.7.

IR (neat): 3480, 2956, 1514, 1465, 1262, 1141, 1031, 756 cm$^{-1}$.

$\text{MS-Cl}$ (m/z): 348 (M$^+$+1, base peak).

$[\alpha]_{D}^{\text{RT}} = -29.5^\circ$ (c 1.01, CHCl$_3$).

$N$-[2-(3,4-Dimethoxyphenyl)ethyl]-1-(2,6-dichlorophenyl)-2-methylpropylamine ($69f$). The amine $69f$ was obtained as a viscous light yellow oil (689 mg, 78%) from amide $68f$ (1 g, 3 mmol), BF$_3$·OEt$_2$ (0.6 ml) and BH$_3$·SMe$_2$ (0.7 ml, 6 mmol).

$^1\text{H NMR}$ (200 MHz, CDCl$_3$): $\delta$ (ppm) 7.31-7.02 (m, 3H), 6.77-6.65 (m, 3H), 4.19 (d, $J = 10.3$ Hz, 1H), 3.84 (s, 3H), 3.81 (s, 3H), 2.77-2.53 (m, 4H), 2.37-2.26 (m, 1H), 1.18 (d, $J = 6.3$ Hz, 3H), 0.67 (d, $J = 6.8$ Hz, 3H).

$^{13}\text{C NMR}$ (75 MHz, CDCl$_3$): $\delta$ (ppm) 148.6, 147.2, 138.0, 137.2, 133.7, 132.9, 129.8, 128.3, 127.9, 120.6, 111.9, 111.0, 66.4, 55.8, 55.7, 49.1, 36.1, 31.4, 21.3, 19.9.

IR (neat): 3480, 2957, 1514, 1464, 1262, 1145, 1631, 738, 703 cm$^{-1}$.

$\text{MS-Cl}$ (m/z): 382 (M$^+$+1, base peak).

General method for the formylation of amines 69a-f. A mixture of acetic anhydride (7 mmol) and formic acid (4 mmol) was heated at 60 °C for 2 h under nitrogen atmosphere. A solution of amine (1 mmol) in freshly distilled THF (2 mL) was added dropwise to the above mixture. The heating at 60 °C was required for the formylation of amine $69f$ having 2,6-dichlorophenyl moiety. For all other amines the reaction was carried out at room temperature stirring. The progress of the reaction was monitored by TLC. After 3-4 h, the reaction mixture was quenched with a saturated solution of sodium bicarbonate (5 mL). The product was extracted with ethyl acetate, dried over anhydrous Na$_2$SO$_4$, filtered and concentrated in vacuo to afford the N-formyl derivatives. These were further purified by column chromatography on silica gel (100-200 mesh) using 50% EtOAc/hexane as eluent to afford the product as colourless viscous oil.
(S)-N-1-Phenylethyl-N-[2-{3,4-dimethoxyphenyl}ethyl]formamide (70a).
The N-formyl 70a was obtained as a viscous oil (281 mg, 90%) from amine 69a (285 mg, 1 mmol), acetic anhydride (0.6 mL, 7 mmol) and formic acid (0.15 mL, 4 mmol).

$^1$H NMR (75 MHz, CDCl$_3$): $\delta$ (ppm) 8.40 (s, 1H), 8.02 (s, 1H), 7.40-7.25 (m, 5H), 6.75-6.39 (m, 3H), 5.78 (q, $J = 7.2$ Hz, 1H), 4.69 (q, $J = 6.0$ Hz, 1H), 3.83 (s, 3H), 3.81 (s, 3H), 3.39-3.31 (m, 4H), 2.76-2.45 (m, 4H), 1.60 and 1.59 (two merging d, $J = 7.2$ Hz, 3H).

IR (neat): 2938, 1664, 1514, 1456, 1416, 1263, 1236, 1028 cm$^{-1}$.

MS-CI (m/z): 314 (M$^+$1, base peak).

$[^2]$d$_{25} = -30.2 ^\circ$ (c 0.35, CHCl$_3$).

(S)-N-1-Phenylpropyl-N-[2-{3,4-dimethoxyphenyl}ethyl]formamide (70b).
The N-formyl 70b was obtained as a viscous oil (294 mg, 90%) from amine 69b (299 mg, 1 mmol), acetic anhydride (0.6 mL, 7 mmol) and formic acid (0.15 mL, 4 mmol).

$^1$H NMR (200 MHz, CDCl$_3$): $\delta$ (ppm) 8.40 (s, 1H), 8.05 (s, 1H), 7.40-7.26 (m, 5H), 6.81-6.34 (m, 3H), 5.51 (t, $J = 7.8$ Hz, 1H), 4.34 (t, $J = 7.8$ Hz, 1H), 3.87 (s, 3H), 3.83 (s, 3H), 3.51-2.64 (m, 4H), 2.39-1.95 (m, 2H), 0.96 (t, $J = 7.3$ Hz, 3H).

IR (neat): 2933, 1665, 1514, 1456, 1410, 1240, 1020 cm$^{-1}$.

MS-CI (m/z): 328 (M$^+$1, base peak).

$[^2]$d$_{25} = -23.3 ^\circ$ (c 1.15, CHCl$_3$).

(R)-N-1-Phenyl-2-methylpropyl-N-[2-{3,4-dimethoxyphenyl}ethyl]formamide (70c).
The N-formyl 70c was obtained as a viscous oil (303 mg, 89%) from amine 69c (313 mg, 1 mmol), acetic anhydride (0.6 mL, 7 mmol) and formic acid (0.15 mL, 4 mmol).

$^1$H NMR (200 MHz, CDCl$_3$): $\delta$ (ppm) 8.37 (s, 1H), 7.98 (s, 1H), 7.44-7.20 (m, 5H), 6.73 (d, $J = 8.3$ Hz, 1H), 6.44-6.34 (m, 2H), 5.12 (d, $J = 11.4$ Hz, 1H), 3.98 (d, $J = 11.2$ Hz, 1H), 3.83 (s, 3H), 3.81 (s, 3H), 3.69-3.54 (m, 1H), 3.34-3.26
Chapter 1

(m, 1H), 3.03-2.39 (m, 3H), 2.30-1.70 (m, 4H), 0.99 and 0.98 (two merging d, J = 6.5 Hz, 3H) 0.89 and 0.88 (two merging d, J = 6.3 Hz, 3H)

IR (neat): 2962, 1665, 1515, 1453, 1417, 1263 (cm⁻¹).

MS-CI (m/z): 343 (M⁺+2, base peak).

[α]D²⁵ = +36.7 ° (c 0.65, CHCl₃).

(R)-N-1-Phenyl-2,2-dimethylpropyl-N-[2-(3,4-dimethoxyphenyl)ethyl]formamide (70d). The N-formyl 70d was obtained as a viscous oil (344 mg, 97%) from amine 69d (327 mg, 1 mmol), acetic anhydride (0.6 mL, 7 mmol) and formic acid (0.15 mL, 4 mmol).

¹H NMR (200 MHz, CDCl₃): δ (ppm) 8.48 (s, 1H), 8.15 (s,1H), 7.55-7.26 (m, 5H), 6.75-6.32 (m, 3H), 4.16 (s, 1H), 3.82 (s, 6H), 3.76-3.23 (m, 2H), 2.84-2.70 (m, 1H), 1.92-1.78 (m,1H), 1.07 (s, 9H).

IR (neat): 2957, 1665, 1515, 1464, 1417, 1263, 1236, 1028 cm⁻¹.

MS-CI (m/z): 356 (M⁺+1, base peak).

[α]D²⁵ = +2.0 ° (c 0.68, CHCl₃).

(N)-N-[1-(2-Chlorophenyl)-2-methylpropyl]-N-[2-(3,4-dimethoxyphenyl)ethyl]formamide (70e). The N-formyl 70e was obtained as a viscous oil (341 mg, 91%) from amine 69e (347 mg, 1 mmol), acetic anhydride (0.6 mL, 7 mmol) and formic acid (0.15 mL, 4 mmol).

¹H NMR (200 MHz, CDCl₃): δ (ppm) 8.41 (s, 1H), 8.02 (s,1H), 7.47-7.20 (m, 4H), 6.70 (d, J = 8.1 Hz, 1H), 6.40 (m, 2H), 5.20 (d, J = 11.2 Hz, 1H), 4.50 (d, J = 10.9 Hz, 1H), 3.82 (s, 6H), 3.69-3.55 (m, 1H), 2.92-2.29 (m, 4H), 1.76-1.30 (m, 1H), 1.01 and 1.00 (two merging d, J = 6.4 Hz, 3H), 0.89 and 0.88 (two merging d, J = 6.4 Hz, 3H).

IR (neat): 2964, 1669, 1515, 1467, 1416, 1263, 1238, 1029 cm⁻¹.

MS-CI (m/z): 376 (M⁺+1, base peak).

[α]D²⁵ = +39.4 ° (c 1.16, CHCl₃).

N-[1-(2,6-Dichlorophenyl)-2-methylpropyl]-N-[2-(3,4-dimethoxyphenyl)ethyl]formamide (70f). The N-formyl 70f was obtained as
a viscous oil (384 mg, 94%) from amine 69f (381 mg, 1 mmol), acetic anhydride (0.6 mL, 7 mmol) and formic acid (0.15 mL, 4 mmol).

1H NMR (200 MHz, CDCl3): δ (ppm) 8.60 (s, 1H), 7.39-7.14 (m, 3H), 6.78-6.72 (m, 3H), 4.80 (d, J =11.2 Hz, 1H), 3.85 (s, 3H), 3.83 (s, 3H), 3.75-2.91 (m, 4H), 2.71-2.60 (m, 1H), 1.11 (d, J = 6.3 Hz, 3H), 0.80 (d, J = 6.3 Hz, 3H).

IR (neat): 2970, 1663, 1515, 1417, 1264, 1237, 1029 cm⁻¹.

MS-CI (m/z): 412, 410(M⁺+1, base peak).

General method for cyclization of N-formyl derivatives to iminium ions and addition of MeMgl.

1-Methyl-2-[(1S)-1-phenylethyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (72a/a').

A round bottomed flask was charged with a stir bar, N-formyl 70a (50 mg, 0.15 mmol), and a reflux condenser and the system was purged with nitrogen. Benzene (2 mL) and POCI₃ (1 mL, 5.4 mmol) were added and the reaction mixture was heated to reflux at 90 °C for 4 h. After TLC, revealed total consumption of the N-formyl derivative, the volatiles were removed from the flask on a rotary evaporator to afford the cyclised product as green viscous oil. This viscous oil was dissolved in freshly distilled THF (2 mL). The flask was cooled to −78 °C and MeMgl (5-7 equiv 1M solution in ether) was added dropwise under nitrogen atmosphere. The progress of the reaction was monitored by TLC. The mixture was stirred at this temperature for half an hour and then quenched with a saturated solution of ammonium chloride (5-10 mL). The product was extracted with ether (3×10 mL). The combined organic extracts were dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to afford the crude addition product. The crude product was purified on a small column of silica gel (100-200 mesh) using 5% EtOAc/hexane as eluent to afford a mixture of 72a and 72a' (44 mg, 90%) in diastereomeric ratio 69:31.

1H NMR (400 MHz, CDCl₃): δ (ppm) 7.40-7.22 (m, 5H), 6.57 and 6.56 (two s in the ratio 69:31, 1H), 6.47 and 6.45 (two s in the ratio 69:31, 1H), 3.94 and 3.81 (two q in the ratio 69:31, Jmajor = 6.7 Hz, 3H), 3.84 and 3.82 (two s in the ratio 69:31, 3H), 3.83 and 3.81 (two s in the ratio 31:69, 3H), 3.80 and 3.75 (two q in the ratio 31:69, Jmajor = 6.4 Hz, 1H), 3.01-2.42 (m, 4H), 1.41 and 1.40 (two
merging d in the ratio 31:69, $J_{\text{major}} = 6.7$ Hz, 3H), 1.32 and 1.28 (two d in the ratio 69:31, $J_{\text{major}} = 6.7$ Hz, 3H)

$^1$H NMR (peaks corresponding to major isomer, 75 MHz, CDCl$_3$): $\delta$ (ppm) 147.4, 128.5, 127.6, 127.3, 111.4, 110.6, 77.2, 59.6, 55.9, 53.5, 39.8, 25.4, 22.1, 21.2, 19.8.

IR (neat): 2927, 1516, 1270, 1244, 1140 cm$^{-1}$.

MS-CI (m/z): 105, 192, 296 (base peak), 312 ($M^+ + 1$).

$[\alpha]_D^{25} = -12.9^\circ$ (c 0.55, CHCl$_3$).

1-Methyl-2-[(1S)-1-phenylpropyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (72b/b'). Reaction of N-formyl derivative 70b (50 mg, 0.15 mmol) with POCl$_3$ (0.5 mL, 5.5 mmol) and MeMgl (1.1 mL, 1M solution in ether, 1.05 mmol) afforded a mixture of 72b and 72b' (40 mg, 82%) in diastereomeric ratio 70:30.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ (ppm) 7.30-7.22 (m, 5H), 6.55 and 6.53 (two s in the ratio 70:30, 1H), 3.93 and 3.82 (two q in the ratio 70:30, $J_{\text{major}} = 6.7$ Hz, 1H), 3.83 and 3.81 (two s in the ratio 70:30, 3H), 3.79 and 3.78 (two s in the ratio 70:30, 3H), 3.62 and 3.48 (two m, 1H), 3.01-2.36 (m, 4H), 2.05-1.99 (m, 2H), 1.30 and 1.27 (two d in the ratio 30:70, $J_{\text{major}} = 6.7$ Hz, 3H), 0.71 and 0.61 (two t in the ratio 30:70, $J_{\text{major}} = 7.2$ Hz, 3H).

$^{13}$C NMR (peaks corresponding to major diastereomer, 75 MHz, CDCl$_3$): $\delta$ (ppm) 147.1, 128.7, 128.4, 128.0, 127.9, 126.8, 111.3, 110.6, 77.2, 66.0, 55.8, 39.8, 29.6, 26.2, 25.4, 22.6, 19.5, 10.4.

IR (neat): 2965, 1514, 1254, 1228, 1138 cm$^{-1}$.

MS-CI (m/z): 326 ($M^+ + 1$, base peak).

$[\alpha]_D^{25} = -6.9^\circ$ (c 1.45, CHCl$_3$).

1-Methyl-2-[(1R)-1-phenyl-2-methylpropyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (72c/c'). Reaction of N-formyl derivative 70c (60 mg, 0.17 mmol) with POCl$_3$ (0.6 mL, 6.1 mmol) and MeMgl (1.1 mL, 1M solution in ether, 1.19 mmol) afforded a mixture of 72c and 72c' (50 mg, 85%) in diastereomeric ratio 81:19.
**Chapter 1**

**1H NMR** (400 MHz, CDCl₃): δ (ppm) 7.31-7.21 (m, 5H), 6.56 and 6.52 (two s in the ratio 81:19, 1H), 6.49 and 6.43 (two s in the ratio 19:81, 1H), 3.88 and 3.70 (two q in the ratio 81:19, 3H), 3.84 and 3.81 (two s in the ratio 81:19, 3H), 3.80 and 3.79 (two s in the ratio 19:81, 3H), 3.52 and 3.51 (two merging d in the ratio 81:19, J_major = 3.7 Hz, 1H), 3.01-2.31 (m, 4H), 1.40 and 1.25 (two d in the ratio 19:81, J_major = 6.9 Hz, 3H), 0.80 and 0.79 (two merging d in the ratio 81:19, J_major = 6.7 Hz, 3H).

**13C NMR** (peaks corresponding to major diastereomer, 75 MHz, CDCl₃): δ (ppm) 147.2, 140.3, 132.6, 129.6, 127.3, 126.7, 111.5, 110.7, 96.1, 69.6, 55.8, 53.5, 39.7, 27.9, 25.6, 21.1, 19.5, 15.6;

**IR** (neat): 2962, 1517, 1262, 1229, 1135 cm⁻¹.

**MS-CI** (m/z): 296 (base peak), 340 (M⁺+1).

\[ [\alpha]_{D}^{25} = -7.2^\circ \] (c 0.55, CHCl₃).

1-Methyl-2-[(1R)-1-phenyl-2,2-dimethylpropyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (72d/d'). Reaction of N-formyl derivative 70d (69 mg, 0.19 mmol) with POCI₃ (0.6 ml, 6.8 mmol) and MeMgl (1.3 ml, MW solution in ether, 1.3 mmol) afforded a mixture of 72d and 72d' (58 mg, 85%) in diastereomeric ratio 96:04 from 1H NMR and HPLC profile (KH₂PO₄:CH₃CN (gradient conditions), 1.0 mL/min, 5 micron RPB displayed two diastereomeric peaks at rt = 35.68 min (3.98%) and 36.8 min (94.04%) indicating diastereomeric ratio 96:04.

**1H NMR** (400 MHz, CDCl₃): δ (ppm) 7.37-7.17 (m, 5H), 6.50 and 6.45 (two s in the ratio 96:04, 1H), 6.45 and 6.41 (two s in the ratio 4:96, 1H), 4.08 (q, J = 6.4 Hz, 1H), 3.81 (s, 6H), 3.48 and 3.46 (two s in the ratio 96:04, 1H), 3.28-3.25 (m, 1H), 2.98-2.84 (m, 2H), 2.50-2.46 (m, 1H), 1.15 and 1.14 (two merging d in the ratio 4:96, J_major = 6.4 Hz, 3H), 1.06 (s, 9H).

**13C NMR** (Peaks corresponding to major diastereomer, 75 MHz, CDCl₃): δ (ppm) 147.0, 146.7, 141.1, 134.2, 130.5, 127.4, 126.3, 111.3, 109.9, 59.1, 55.9, 55.7, 41.0, 37.6, 29.6, 29.0, 28.4, 19.1.

**IR** (neat): 2928, 1542, 1265, 1229, 1139 cm⁻¹.
**Chapter 1**

**MS-CI** (m/z): 354 (M$^+$ + 1, base peak).

$[\alpha]_D^{25} = -54.2 \degree$ (c 0.50, CHCl$_3$).

1-Methyl-2-[(1R)-1-(2-chlorophenyl)-2-methylpropyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (72e'). Reaction of N-formyl derivative 70e (70 mg, 0.18 mmol) with POCI$_3$ (0.6 mL, 6.4 mmol) and MeMgl (1.2 mL, 1 M solution in ether, 1.2 mmol) afforded a mixture of 72e and 72e' (59 mg, 85%) in diastereomeric ratio 85:15.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ (ppm) 7.58 (d, $J = 5.9$ Hz, 1H), 7.42-7.30 (m, 1H), 7.21-7.12 (m, 2H), 6.53 and 6.52 (two s in the ratio 85:15, 1H), 6.52 and 6.47 (two s in the ratio 15:85, 1H), 4.29 and 4.26 (two d in the ratio 15:85, $J_{\text{major}} = 5.1$ Hz, 1H), 3.92 and 3.73 (two q in the ratio 85:15, $J_{\text{major}} = 6.9$ Hz, 1H), 3.83 and 3.61 (two s in the ratio 85:15, 3H), 3.82 and 3.79 (two s in the ratio 85:15, 3H), 3.08-2.67 (m, 4H), 1.41 and 1.25 (two d in the ratio 85:15, $J_{\text{major}} = 6.4$ Hz, 3H). 1.24 and 0.98 (two d in the ratio 85:15, $J_{\text{major}} = 6.7$ Hz, 3H), 0.84 and 0.78 (two d in the ratio 85:15, $J_{\text{major}} = 6.9$ Hz, 3H).

$^{13}$C NMR (peaks corresponding to major diastereomer, 75 MHz, CDCl$_3$): $\delta$ (ppm) 135.6, 130.5, 129.5, 129.2, 127.7, 126.0, 111.5, 110.5, 96.2, 64.1, 55.9, 41.1, 39.8, 29.4, 22.6, 20.1, 18.5, 16.7

IR (neat): 2964, 1514, 1259, 1226, 1140 cm$^{-1}$.

**MS-CI** (m/z): 374 (M$^+$ + 2), 358, 330 (base peak).

$[\alpha]_D^{25} = +37.5 \degree$ (c 1.12, CHCl$_3$).

1-Methyl-2-[(1-(2,6-Dichlorophenyl)-2-methylpropyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (72f'). Reaction of N-formyl derivative 70f (55 mg, 0.13 mmol) with POCI$_3$ (0.4 mL, 4.68 mmol) and MeMgl (0.9 mL, 1 M solution in ether, 0.90 mmol) afforded a mixture of 72f and 72f' (46 mg, 87%) in diastereomeric ratio 99:01.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ (ppm) 7.23-7.19 (m, 2H), 6.99 (t, $J = 7.1$ Hz, 1H), 6.53 and 6.48 (two s in the ratio 99:01, 1H), 6.44 and 6.39 (two s in the ratio 99:01, 1H), 4.47 (d, $J = 10.2$ Hz, 1H), 3.81 (s, 3H), 3.79 (s, merging with q, 3H), 3.79 (q, $J = 6.4$ Hz, 1H), 3.26-2.80 (m, 3H), 2.56-2.50 (m, 1H), 1.39 (d, $J = 6.7$ Hz, 3H), 1.25 (m, 1H), 1.11 (d, $J = 6.1$ Hz, 3H), 0.68 (d, $J = 6.7$ Hz, 3H).
$^{13}$C NMR (peaks corresponding to major diastereomer, 75 MHz, CDCl$_3$) $\delta$ (ppm): 146.8, 136.4, 135.8, 130.3, 130.2, 127.8, 127.6, 127.5, 111.3, 111.2, 110.1, 67.1, 55.9, 55.8, 55.7, 39.9, 27.2, 22.9, 20.6, 18.7.
IR (neat): 2965, 1580, 1275, 1141 cm$^{-1}$.
MS-Cl (m/z): 408 (M$^{+}$1, base peak), 366, 364.

1-Ethyl-2-[(1R)-1-phenyl-2,2-dimethylpropyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (73a/b). Reaction of N-formyl derivative 70d (50 mg, 0.14 mmol) with POCl$_3$ (0.3 mL, 5.04 mmol) and EtMgI (1.0 mL, 0.98 M solution in ether, 0.98 mmol) afforded a mixture of 73a and 73b (41 mg, 80%) in diastereomeric ratio 83:17.
$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ (ppm) 7.26-7.22 (m, 2H), 7.12-7.07 (m, 3H), 6.45 and 6.42 (two s in the ratio 17:83, 1H), 6.23 and 6.22 (two s in the ratio 17:83, 1H), 3.79 and 3.78 (two s in the ratio 17:83, 1H), 3.78 and 3.75 (two s in the ratio 17:83, 1H), 3.76 and 3.67 (two t in the ratio 17:83, $J_{\text{major}} = 6.7$ Hz, 1H), 3.48 and 3.46 (two s in the ratio 17:83, 1H), 3.25-3.21 (m, 2H), 2.97-2.90 (m, 1H), 2.44-2.38 (m, 1H), 1.64 (m, 2H), 1.06 and 0.98 (two s in the ratio 17:83, 9H), 0.94 and 0.93 (two merging t, $J_{\text{major}} = 7.5$ Hz, 3H).
$^{13}$C NMR (peaks corresponding to major diastereomer, 75 MHz, CDCl$_3$): $\delta$ (ppm) 146.8, 146.1, 141.6, 132.9, 130.1, 127.1, 126.4, 126.2, 111.4, 110.4, 62.4, 55.9, 55.7, 43.6, 37.5, 29.7, 29.3, 29.1, 28.6, 26.0, 12.2.
IR (neat): 2924, 1508 cm$^{-1}$.
MS-Cl (m/z): 310 (base peak), 368 (M$^{+}$+1).
$[\alpha]_{D}^{25} = -34.2^\circ$ (c 0.4, CHCl$_3$).

1-Isopropyl-2-[(1R)-1-phenyl-2,2-dimethylpropyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (74a/b). Reaction of N-formyl derivative 70d (60 mg, 0.15 mmol) with POCl$_3$ (0.5 mL, 5.4 mmol) and $^3$PrMgBr (1.2 mL, 0.89 M solution in ether, 1.05 mmol) afforded a mixture of 74a and 74b (45 mg, 70%) in diastereomeric ratio 58:42.
$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ (ppm) 7.12-7.02 (m, 5H), 6.42 and 6.25 (two s in the ratio 58:42, 1H), 6.42 and 5.92 (two s in the ratio 42:58, 1H), 3.81 and 3.79 (two s in the ratio 58:42, 3H), 3.79 and 3.76 (two s in the ratio 58:42, 3H), 3.68 and 3.69 (two s in the ratio 58:42, 3H).
and 3.87 (two s in the ratio 42:58, 1H), 3.45-3.24 (m, 2H), 3.12 (d, $J = 8.3$, 1H), 2.85-2.81 (m, 1H), 2.46-2.38 (m, 1H), 2.00 (m, 1H), 1.06 and 1.05 (two merging d, $J_{\text{major}} = 5.3$ Hz, 3H), 1.05 and 1.03 (two s in the ratio 42:58, 9H), 0.74 and 0.72 (two merging d, $J_{\text{major}} = 5.3$ Hz, 3H).

$^{13}$C NMR (peaks corresponding to major diastereomer, 75 MHz, CDCl$_3$): $\delta$ (ppm) 146.9, 145.7, 145.2, 142.2, 139.8, 130.6, 129.9, 126.5, 126.2, 112.4, 111.3, 75.9, 66.0, 55.8, 55.7, 44.0, 36.8, 33.3, 29.2, 29.0, 24.0, 21.0, 18.6.

IR (neat): 2953, 1515, 1464, 1362, 1126, 1107 cm$^{-1}$.

MS-Cl (m/z): 382 (M$^+$+1, base peak).

$[\alpha]_D^{RT} = +21.0^\circ$ (c 0.45, CHCl$_3$).

1-Butyl-2-[(1R)-1-phenyl-2,2-dimethylpropyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (75a/b). Reaction of N-formyl derivative 70d (50 mg, 0.14 mmol) with POCI$_3$ (0.46 mL, 5.04 mmol) and $^t$BuMgBr (0.7 mL, 1.4M solution in ether, 0.98 mmol) afforded a mixture of 75a and 75b (47 mg, 85%) in diastereomeric ratio 83:17.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ (ppm) 7.26-7.23 (m, 2H), 7.12-7.10 (m, 3H), 6.46 and 6.43 (two s in the ratio 17:83, 1H), 6.40 and 6.21 (two s in the ratio 17:83, 1H), 3.79 and 3.78 (two s in the ratio 17:83, 3H), 3.78 and 3.74 (two s in the ratio 17:83, 3H), 3.73 and 3.72 (two merging t in the ratio 17:83, $J_{\text{major}} = 6.1$ Hz, 1H), 3.45 and 3.44 (two s in the ratio 83:17, 1H), 3.24-3.21 (m, 2H), 2.85 (m, 1H), 2.44 and 2.42 (two s in the ratio 17:83, 6H), 1.01 and 0.98 (two s in the ratio 83:17, 9H), 0.85 and 0.84 (two merging t, $J_{\text{major}} = 7.2$ Hz, 3H).

$^{13}$C NMR (peaks corresponding to major diastereomer, 75 MHz, CDCl$_3$): $\delta$ (ppm) 146.8, 146.1, 141.6, 133.1, 130.1, 127.1, 126.2, 111.3, 110.2, 61.2, 55.9, 55.5, 43.4, 37.4, 36.1, 29.7, 28.6, 26.0, 23.0, 14.0.

IR (neat) 2953, 1515, 1464, 1385, 1124, 1100.

MS-Cl (m/e, relative intensity) 396 (M$^+$+1, base peak).

$[\alpha]_D^{RT} = -30.8^\circ$ (c 0.25, CHCl$_3$).

1-(3,4-Methylenedioxyphenyl)-2-[(1R)-1-phenyl-2,2-dimethylpropyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (76a/b). Reaction of N-formyl derivative 70d (80 mg, 0.22 mmol) with POCI$_3$ (0.7 mL, 7.92 mmol) and 3, 4-
methylenedioxy phenyl magnesium bromide (3.8 mL, 0.4M solution in THF, 7.92 mmol) afforded a mixture of 76a and 76b (47 mg, 85%) in diastereomeric ratio 100:00.

\[ \text{H NMR (400 MHz, CDCl}_3\text{): } \delta (\text{ppm}) \text{ 7.05-6.88 (m, 5H), 6.64 (m, 3H), 6.56 (s, 1H), 6.16 (s, 1H), 5.86 (d, } J = 9.1 \text{ Hz, 1H), 5.87 (d, } J = 9.1 \text{ Hz, 1H), 4.86 (s, 1H), 3.83 (s, 3H), 3.65 (s, 3H), 3.61 (s, 1H), 3.21-2.93 (m, 3H), 2.59 (m, 1H), 1.03 (s, 9H).} \]

\[ \text{13C NMR (75 MHz, CDCl}_3\text{): } \delta (\text{ppm}) \text{ 147.4, 147.3, 146.8, 146.3, 140.4, 139.2, 130.0, 126.9, 128.0, 122.6, 111.5, 110.9, 109.6, 107.3, 100.6, 74.1, 66.0, 55.8, 55.7, 42.3, 37.6, 28.8, 27.8, 27.0.} \]

IR (neat): 2928, 1508, 1465, 1342, 1228, 1043 cm\(^{-1}\).

\[ \text{MS-CI (m/z): 460 (M}^+\text{1, base peak).} \]

\[ [\alpha]_D^{25} = -16.0 ^\circ \text{ (c 0.90, CHCl}_3\text{).} \]

1-Benzyl-2-[(1R)-1-phenyl-2,2-dimethylpropyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (77a/b). Reaction of N-formyl derivative 70d (100 mg, 0.28 mmol) with POCl\(_3\) (0.9 mL, 10.0 mmol) and benzylmagnesium bromide (9.8 mL, 0.2M solution in THF, 1.96 mmol) afforded a mixture of 77a and 77b (90 mg, 78%) in diastereomeric ratio 91:09.

\[ \text{H NMR (400 MHz, CDCl}_3\text{): } \delta (\text{ppm}) \text{ 7.36-6.57 (m, 10H), 6.48 and 6.38 (two s in the ratio 91:09, 1H), 5.73 and 5.45 (two s in the ratio 9:91, 1H), 4.01 (m, 1H), 3.79 and 3.77 (two s in the ratio 91:09, 3H), 3.62 and 3.58 (two s in the ratio 91:09, 1H), 3.39 and 3.34 (two s in the ratio 9:91, 3H), 3.38 (m, 1H), 3.20-2.90 (m, 3H), 2.62 (m, 1H), 2.51 (m, 1H), 0.99 and 0.95 (two s in the ratio 9:91, 9H).} \]

\[ \text{13C NMR (peaks corresponding to major diastereomer, 75 MHz, CDCl}_3\text{): } \delta (\text{ppm}) \text{ 146.9, 145.1, 141.1, 140.5, 131.1, 130.5, 130.1, 128.1, 127.8, 126.5, 125.9, 125.7, 111.0, 110.6, 78.0, 65.9, 55.6, 55.2, 42.6, 40.9, 37.8, 29.7, 29.4, 28.4, 27.6.} \]

IR (neat): 2953, 1503, 1452, 1229, 1096, 1014 cm\(^{-1}\).

\[ \text{MS-CI (m/z): 338 (base peak), 430 (M}^+\text{1).} \]

\[ [\alpha]_D^{25} = -17.0 ^\circ \text{ (c 0.55, CHCl}_3\text{).} \]
Addition of butylmagnesium bromide to iminium ion 71d in the presence of 0.1 equiv, 0.5 equiv and 1 equiv Cul. In three flame-dried two-necked round-bottomed flasks under argon atmosphere was placed dry Cul (18 mg, 0.1 equiv), (90 mg, 0.47 mmol, 0.5 equiv) and (180.9, 0.95 mmol, 1 equiv) respectively. Freshly distilled ether (2 mL) was added to each round-bottomed flask. The suspension in each case was cooled to -78 °C and n-BuMgBr (0.67 mL, 1.4M solution in ether, 0.95 mmol) was added to each round-bottomed flask dropwise to give the blackish cuprates. The mixtures were stirred at -78 °C for 0.5 h and then a solution of iminium ion 71d (1 equiv derived from N-formyl 70d, 70 mg, 0.19 mmol) in THF (2 mL) was added to each round-bottomed flask. The mixture were stirred at -78 °C for 1 h and then quenched with saturated solution of ammonium chloride (3-5 mL). The product was extracted with ether (3×20 mL) in each case. The combined organic extracts were dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to afford crude products. Crude products were purified by column chromatography on silica gel (100-200 mesh) using 10% EtOAc/hexane as eluent to afford a mixture of 75a and 75b as a colourless viscous oil (62 mg, 80% for 0.1 equiv Cul in diastereomeric ratio 88:12, 60 mg, 79% for 0.5 equiv Cul in diastereomeric ratio 90:10 and 62 mg, 80% for 1 equiv. Cul in diastereomeric ratio 84:16.

Addition of n-butyllithium to iminium ion 71d. To a solution of iminium ion 71d (1 equiv. derived from 20 mg, 0.056 mmol of N-formyl derivative 70d) in freshly distilled THF (1 mL) under nitrogen atmosphere, was added n-BuLi (0.1 mL, 1.6M solution in hexane, 0.169 mmol) at -78 °C. The light pink coloured solution was stirred at this temperature for 0.5 h and then quenched with a saturated solution of ammonium chloride (5-8 mL). The product was extracted with ether (15 mL) and concentrated in vacuo to give the addition product as an orange oil which was purified by column chromatography on silica gel (100-200 mesh) using 10% EtOAc/hexane as eluent to afford a mixture of 75a and 75b as a colourless oil (17.6 mg, 80%) in diastereomeric ratio 68:32.

Addition of butylceric lithium to iminium ion 71d. To a flame-dried two-necked round-bottomed flask, anhydrous CeCl₃ (388 mg, 1.57 mmol) was
taken under argon atmosphere. It was further dried at 140 °C under vacuum for 1 h, cooled to room temperature and flushed with argon. Freshly distilled THF (3 mL) was added and the suspension was stirred at room temperature for 2 h and then cooled to −78 °C. n-BuLi (0.98 mL, 1.6 M solution in hexane 1.57 mmol) was added to this slurry at −78 °C dropwise and the mixture was stirred at this temperature for 1 h. A solution of iminium ion 71d (prepared from N-formyl derivative 70d, 80 mg, 0.23 mmol) in freshly distilled THF (1.5 mL) was added dropwise at −78 °C. The stirring was continued at this temperature for 1 h and then the reaction mixture was quenched with a saturated solution of ammonium chloride (4 mL). The product was extracted with ether (3×20 mL). The combined organic extracts were dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The crude amine was purified by column chromatography on silica gel (100-200 mesh) using 2:98, 5:95, 10:90 EtOAc/hexane as eluent to afford a mixture of 75a and 75b (66 mg, 75%) as a viscous oil in diastereomeric ratio 93:7.

**Addition of lithium-di-n-butylcucurate to iminium ion 71d.** To a flame dried round bottomed flask under argon atmosphere, was placed dry Cul, (67 mg, 0.35 mmol) and freshly distilled ether (2.5 mL). The suspension was cooled to −40 °C and n-BuLi (0.43 mL, 1.6 M solution in hexane, 0.70 mmol) was added to give a blackish solution. The mixture was stirred at −40 °C for 30 min and then cooled to −78 °C. A solution of iminium ion 71d (prepared from 50 mg, 0.14 mmol of N-formyl derivative 70d) in THF (1 mL) was added dropwise. The mixture was stirred at this temperature for 1 h and then quenched with a saturated solution of ammonium chloride (5 mL). The product was extracted with ether (3×20 mL). The combined organic extracts were dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (100-200 mesh) using 10% EtOAc/hexane as eluent to afford a mixture of 75a and 75b (43 mg, 79%) in diastereomeric ratio 98:02 from ¹H NMR and HPLC profile (KH₂PO₄:CH₃CN (gradient conditions), 1.0 mL/min, 5 micron RPB displayed two diastereomeric peaks at rt = 18.06 min (84.31%) and 19.58 min (2.18%) indicating diastereomeric ratio 97:03.
Chapter 1

Addition of benzylimagnesium bromide to iminium ion 71 in the presence of Cul. Three two-necked round bottomed flasks were flame dried and flushed with argon. Dry Cul (11 mg, 0.1 equiv), (54 mg, 0.28 mmol, 0.5 equiv) and (107 mg, 0.56 mmol, 1 equiv) was placed in first, second and third round bottomed flask under argon quickly. Freshly distilled ether (1.7 mL) was added to each round bottomed flask. The suspension was cooled to −78 °C in each case and benzylimagnesium bromide (2.80 mL, 0.2 M solution in THF, 0.56 mmol) was added to each round bottomed flask dropwise to give the light yellow coloured cuprates. The mixtures were stirred at −78 °C for 0.5 h and then a solution of iminium ion 71d (1 equiv derived from N-formyl derivative 70d, 40 mg, 0.11 mmol) in THF (1 mL) was added dropwise to each round bottomed flask at −78 °C. The mixtures were stirred at this temperature for 1 h and then quenched with saturated solution of ammonium chloride (3 mL). The product was extracted with ether (3×15 mL) in each case. The combined organic extracts were dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to give yellow oils. Crude products were purified by column chromatography on silica gel (100-200 mesh) using 10% EtOAc/hexane as eluent to afford a mixture of 77a and 77b as colourless viscous oil (31 mg, 70% for 0.1 equiv Cul in diastereomeric ratio 89:11, 29 mg, 65% for 0.5 equiv Cul in diastereomeric ratio 88:12 and 28.3 mg, 63% for 1 equiv. Cul in diastereomeric ratio 85:15 from ¹H NMR).

Addition of lithium dimethylcuprate to iminium ion 71d. To a flame dried round bottomed flask under argon atmosphere was placed dry Cul (33 mg, 0.17 mmol) and freshly distilled ether (2.0 mL). The suspension was cooled to 0 °C and methylolithium (0.50 mL, 0.65M solution in ether, 0.33 mmol) was added dropwise to give a clear solution. The solution was stirred at 0 °C for 30 min and then cooled to −78 °C. A solution of iminium ion 71d (1 equiv. prepared from 30 mg, 0.08 mmol of N-formyl derivative 70d) in THF (1.5 mL) was added dropwise. The solution was stirred at this temperature for 0.5 h and then quenched with a saturated solution of ammonium chloride (3 mL). The amine was extracted with ether (3×15 mL). The combined organic
extracts were dried over anhydrous Na$_2$SO$_4$, filtered and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (100-200 mesh) using 5% EtOAc/hexane as eluent to afford a mixture of the 72d and 72d' as a colourless oil (23 mg, 70%) in diastereomeric ratio 98.02 from NMR and HPLC profile (KH$_2$PO$_4$:CH$_3$CN (gradient conditions), 2.5 mL/min, 3 micron C18 displayed two diastereomeric peaks at rt = 13.27 min (92.24%) and 13.84 min (4.88%) indicating diastereomeric ratio 98.02.

**Addition of lithium diethylcuprate to iminium ion 71d.** To a flame dried round bottomed flask under argon atmosphere, dry Cul (21 mg, 0.11 mmol) was placed and freshly distilled ether (2.0 mL) was added and the suspension was cooled to -78 °C. Ethyllithium (0.30 mL, 0.7M solution in pentane, 0.22 mmol) was added to give a blackish coloured mixture. The mixture was stirred at -78 °C for 30 min and a solution of iminium ion 71d (1 equiv. prepared from 20 mg, 0.056 mmol of N-formyl derivative 70d) in freshly distilled THF (1.5 mL) was added dropwise. The mixture was stirred at this temperature for 0.5 h and then quenched with a saturated solution of ammonium chloride (5 mL). The amine was extracted with ether (3×15 mL). The combined organic extracts were dried over anhydrous Na$_2$SO$_4$, filtered and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (100-200 mesh) using 10% EtOAc/hexane as eluent to afford a mixture of 73a and 73b as a colourless oil (16 mg, 75%) in diastereomeric ratio 92:08 from $^1$H NMR and HPLC profile (KH$_2$PO$_4$:CH$_3$CN (gradient conditions), 1.0 ml/min, 5 micron RP18 displayed two diastereomeric peaks at rt = 13.27 min (92.24%) and 13.84 (4.88%) indicating diastereomeric ratio 92.08.

**Addition of lithium diisopropylcuprate to iminium ion 71d.** To a flame dried round bottomed flask under argon atmosphere, was placed dry Cul (38 mg, 0.20 mmol) and freshly distilled ether (2.0 mL). The suspension was cooled to -78 °C and isopropyllithium (0.40 mL, 1M solution in pentane, 0.4 mmol) was added dropwise to give a blackish coloured solution. The solution was stirred at -78 °C for 30 min and a solution of iminium ion 71d (1 equiv. prepared from 38 mg, 0.10 mmol of N-formyl derivative 70d) in freshly distilled
Chapter 1

THF (1.5 mL) was added dropwise. The reaction mixture was stirred at this temperature for 0.5 h and then quenched with a saturated solution of ammonium chloride (5 mL). The amine was extracted with ether (3×15 mL). The combined organic extracts were dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (100-200 mesh) using 10% EtOAc/hexane as eluent to afford hydride reduced amine 81 as a colourless oil (28 mg, 80%).

1H NMR (400 MHz, CDCl₃): δ (ppm) 7.31-7.24 (m, 5H), 6.48 (s, 1H), 6.44 (s, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 3.67-3.51 (m, 2H), 3.36 (s, 1H), 3.14 (m, 1H), 2.83 (m, 1H), 2.65 (m, 1H), 2.32 (m, 1H), 1.07 (s, 9H).

MS-CI (m/z): 340 (M⁺+1), 282 (base peak).

1-Allyl-2-[(1R)-1-phenyl-2,2-dimethylpropyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (82a/b). In a flame dried round bottomed flask under argon atmosphere were taken allyltributyltin (0.3 mL, 0.98 mmol) and freshly distilled THF (3 mL). The solution was cooled to -78 °C and MeLi (1.50 mL, 0.65 M solution in ether, 0.98 mmol) was added dropwise. The orange coloured solution was stirred at -78 °C for 3 h and transferred via cannula to another round bottomed flask containing dry Cu(I)I, (93 mg, 0.49 mmol) in THF (2 mL) under argon atmosphere at -78 °C. The blackish coloured solution was stirred at -78 °C for 0.5 h. A solution of iminium ion 71d (1 equiv. prepared from 50 mg, 0.14 mmol of N-formyl derivative 70d) in THF (1.5 mL) was added dropwise. The mixture was stirred at this temperature for 0.5 h and then quenched with 6N HCl (4 mL). The contents were transferred to a separatory funnel and were shaken vigorously. The aqueous acidic layer was separated and washed with ether (10 mL) so that all the non-basic impurities are removed from the acidic layer. The acidic layer was basified with 5N NaOH solution. The amine was extracted with ether (3×20 mL). The combined organic extracts were dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (100-200 mesh) using 10% EtOAc/hexane as eluent to afford a mixture of 82a and 82b as a colorless oil (42 mg, 79%) in diastereomeric ratio 94:06.

76
\[ \text{\textsuperscript{1}H NMR (400 MHz, CDCl}_3\text{): } \delta \text{ (ppm) 7.32-7.12 (m, 5H), 6.46 and 6.42 (two s in the ratio 94:06, 1H), 6.42 and 6.32 (two s in the ratio 6.94, 1H), 5.83 (m, 1H), 4.89 (m, 1H), 4.88 (m, 1H), 3.90 (two merging t, } J_{\text{major}} = 6.4 \text{ Hz, 1H), 3.81 and 3.80 (two s in the ratio 6.94, 3H), 3.79 and 3.78 (two s in the ratio 6.94, 3H), 3.59 and 3.51 (two s in the ratio 6.94, 1H), 2.96 (m, 1H), 2.53 (m, 2H), 2.25 (m, 1H), 1.05 and 0.97 (two s in the ratio of 6.94, 9H).} \]

\[ \text{\textsuperscript{13}C NMR (peaks corresponding to major diastereomer, 75 MHz, CDCl}_3\text{): } \delta \text{ (ppm) 147.1, 146.1, 141.2, 137.5, 132.1, 130.4, 130.3, 127.5, 127.4, 126.5, 126.3, 115.7, 111.4, 110.5, 96.1, 62.6, 55.9, 55.7, 43.2, 40.2, 37.7, 29.7, 28.6, 27.2.} \]

\[ \text{IR (neat): 2927, 1514, 1465, 1384, 1263, 1228 cm}^{-1}. \]

\[ \text{MS-Cl (m/z): 380 (M}^+{1), 338 (base peak).} \]

\[ [\alpha]_{D}^{25} = -28.3^\circ \text{ (c 0.55, CHCl}_3). \]

\textbf{Preparation of benzyltributyltin (79).} Triethyl amine (4 mL, 28.8 mmol) was added to the solution of benzyl alcohol (2 mL, 19.2 mmol) in freshly distilled DCM (15 mL) at 0 °C. The solution was stirred at this temperature for 15 min and then methanesulphonyl chloride (1.78 mL, 23 mmol) was added at 0 °C. The ice bath was removed and the reaction mixture was stirred at room temperature for 40 min. A saturated solution of ammonium chloride (20 mL) was added. The product was extracted with DCM (2 x 20 mL). The organic layer was further washed with water and brine. The extracts were dried over anhydrous Na\textsubscript{2}SO\textsubscript{4}, filtered and concentrated \textit{in vacuo} to afford the corresponding mesylate derivative 78 (2.7 g, 80%).

\textsuperscript{2} mL, 14.5 mmol) was taken in a flame dried round bottomed flask under nitrogen atmosphere. Freshly distilled THF (6 mL) was added and the solution was cooled to 0 °C. n-BuLi (9.9 mL, 1.6M solution in hexane, 15.9 mmol) was added dropwise. The solution was stirred at 0 °C for 30 min and then the solution of the above formed mesylate 78 (2.7 g, 14.5 mmol) in freshly distilled THF (8 mL) was added at 0 °C. The mixture was stirred at 0 °C for 1 h. The progress of the reaction was monitored by TLC. After the completion of the reaction, a saturated solution of ammonium chloride
was added and the product was extracted with hexane. The combined organic extracts were dried over anhydrous Na$_2$SO$_4$, filtered and concentrated in vacuo to afford the product as an oil. The crude product was purified by column chromatography on silica gel (100-200 mesh) using hexane as an eluent to afford 79 as a colourless oil (2 g, 40%).

$^1$H NMR (200 MHz, CDCl$_3$): $\delta$ (ppm) 7.25-6.95 (m, 5H), 2.30 (m, 2H), 1.53-1.16 (m, 12H), 0.89-0.63 (m, 15H).

**Preparation and addition of lithium dibenzylcuprate to iminium ion 71d.**

In a flame dried round bottomed flask under argon atmosphere were placed benzyltributyltin 79 (373 mg, 0.98 mmol) and freshly distilled THF (6 mL). The solution was cooled to $-78$ °C and MeLi (1.50 mL, 0.65/M solution in ether, 0.98 mmol) was added dropwise. The orange coloured solution was stirred at $-78$ °C for 3 h and transferred via cannula to another round bottomed flask under argon atmosphere containing dry Cu(I)I (94 mg, 0.49 mmol) in freshly distilled THF (2 mL) at $-78$ °C. The blackish colored solution was stirred at $-78$ °C for 0.5 h and a solution of iminium ion 71d (1 equiv. prepared from 50 mg, 0.14 mmol of N-formyl derivative 70d) in freshly distilled THF (1.5 mL) was added dropwise. The reaction mixture was stirred at this temperature for 0.5 h and then quenched with 6N HCl (4 mL). The contents were transferred to a separatory funnel and were shaken vigorously. The aqueous acidic layer was separated and washed with ether (10 mL) so that all the non-basic impurities are removed from the acidic layer. The acidic layer was basified with 5N NaOH solution so that the solution is basic according to pH paper. The amine was extracted with ether (3×20 mL). The combined organic extracts were dried over anhydrous Na$_2$SO$_4$, filtered and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (100-200 mesh) using 10% EtOAc/hexane ml) as eluent to afford a mixture of 77a and 77b as a colourless oil (48 mg, 80%) in diastereomeric ratio 97:03.

**Attempted hydrogenolysis of amine 72d.**

A 10 mL round bottomed flask was charged with a stirr bar and 10% Pd/C (99 mg). EtOH (2 mL) was added. A solution of amine 72d (90 mg) in EtOH (0.5 mL) was added with a syringe.
The whole system was evacuated by applying a minor vacuum and then purged with a balloonful of hydrogen. The reaction mixture was stirred at room temperature for 24 h. TLC revealed the disappearance of amine 72d. The mixture was filtered through a small pad of celite. The combined organic extracts were dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. ¹H NMR of the product indicated the formation of some unwanted products.

**Attempted hydrogenolysis under acidic medium.** A 10 mL round bottomed flask was charged with a stirr bar and 10% Pd/C (50 mg). EtOH (1.5 mL) and 10% HCl (25 drops) were added and the system was purged with a balloonful of hydrogen. The mixture was stirred for 21 h and then a solution of amine 72d (100 mg) in EtOH (1 mL) was added with syringe. The whole system was evacuated by applying a minor vacuum and was purged with hydrogen balloon. The mixture was stirred at room temperature for 24 h and then filtered through a small pad of celite. The filterate was concentrated in vacuo. Water (0.5 mL) was added and the solution was made basic by the addition of solid NaOH. The product was extracted with DCM (3×10 mL). The combined organic extracts were dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. ¹H NMR of the brown oil obtained again revealed the formation of some unwanted product.

**Hydrogenolysis under 80 psi pressure of hydrogen.** Solution of amine 72d (250 mg) in EtOH (70 mL) was taken in 250 mL hydrogenation flask. 10% Pd/C (100-200 mg) was added and the flask was immediately fitted with a cork. The flask was fitted to Par apparatus, pressure of hydrogen (80 psi) was applied and maintained for 12 h. TLC indicated the disappearance of the starting amine. The solution was filtered through a sintered funnel having a bed of celite. The filterate was concentrated. TLC (20% MeOH/CHCl₃) indicated 5-6 spots. ¹H NMR of the crude mixture revealed a complex spectra of unwanted materials.
Hydrogenolysis with ammonium formate. A 25 mL round bottomed flask was fitted with a reflux condenser. A solution of amine 72d (50 mg, 0.56 mmol) in MeOH (2.5 mL) was added. Ammonium formate (40 mg, 0.59 mmol, made anhydrous by azeotropic removal of water with benzene) was added followed by 10% Pd/C (50 mg). The system was evacuated by applying a small vacuum and purged with nitrogen. The mixture was heated to reflux at 60 °C for 3-4 h. TLC indicated the disappearance of starting amine. The solution was cooled to 0 °C so as to precipitate out unused ammonium formate. The solution was filtered through a small pad of celite. The contents were completely transferred with DCM. The combined organic extracts were dried over anhydrous Na2SO4, filtered and concentrated in vacuo. 1H NMR of the crude product revealed the formation of some unwanted products.

Attempted debenzylation with 1-chloroethylformate. To a solution of amine 72d (52 mg, 0.14 mmol) in DCM (1.5 mL) was added 1-chloroethylchloroformate (0.015 mL, 0.14 mmol) at 0 °C. The mixture was stirred at this temperature for 3-4 h and TLC indicated the formation of a streak. DCM was evaporated by rotary evaporator. MeOH (2 mL) was added and the mixture was heated to reflux at 60 °C for 12 h. TLC revealed the starting amine without any spot of the required product.

Attempted debenzylation by reductive method with Na-liquid ammonia. To a flame dried two necked round bottomed flask fitted with a liquid ammonia condenser (cooled to −78 °C by acetone/liquid nitrogen slurry) was added dry liquid ammonia (20 mL, distilled from sodium). Sodium metal pieces (5-7 equiv) were added at −33 °C so that the solution is completely blue. A solution of amine 72d (100 mg) in freshly distilled THF (3 mL) was added. The mixture was stirred at −33 °C for 5-6 h and then quenched with a saturated solution of ammonium chloride (5-10 mL). Excess of ammonia was evaporated and the product was extracted with ethyl acetate (3×15 mL). The combined organic extracts were dried over anhydrous Na2SO4, filtered and concentrated in vacuo. TLC indicated the presence of a non-polar spot and the starting amine.
\( ^1 \text{H NMR of the crude product did not reveal the formation of debenzylated product.} \)