Synthesis and applications of 
$N$-Metallo ketene imines

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Abstract

As an important class of intermediates for the preparation of a wide range of organic compounds, N-metallo ketene imines are a recent attractive class of intermediates for organic chemists. Our research group has been engaged in the preparation and application of the N-silyl ketene imines (SKIs). In this frame we have studied the uncatalyzed reaction of SKIs with isocyanates to give the corresponding malonamides.

The reaction works with satisfactory yields and a range of the corresponding amides has been obtained. It has been demonstrated that the use of SKIs, instead of simple lithium anion of nitriles, is essential for the success of the reaction. A possible explanation assumes that this new reaction proceeds via a silatropism. In the course of our studies, reported in this thesis, the synthesis and the reactivity of N-silyl ketene imines in the preparation of 2,2-diaryl-3,4-dihydroxy-alcanonitrile in an uncatalyzed adol-type reaction has been performed.

Our conception has been to use a chiral aldehyde to introduce asymmetric induction at the β-position and at the α-quaternary stereogenic center in the new forming diols. To achieve this goal, in a study case, we used diphenylacetonitrile as the substrate to form the corresponding N-trimethylsilylketene-imines to be reacted with (S)-lactic aldehyde with different protecting groups on the hydroxyl functionality. A number of 2,2-diaryl-3,4-dihydroxy-pentanenitrile were prepared with good to excellent stereo-control at β-position and satisfactory yields. Extension of this protocol to other metallo-ketene imines was performed. Accordingly, the preparation of tin ketene imines was attempted in analogy of the corresponding silyl ketene imine. The reaction of tin ketene imines with aldehydes was tested as a new tool for the synthesis of β-hydroxynitriles starting from carbonyl compounds (aldehydes and/or ketones). Dialkyl(aryl)silyl nitriles and dialkyl(aryl)tin nitriles presents different reactivity. Finally, aluminium-ketene imines, as nucleophilic partner in the opening reaction of epoxides were studied. Preliminary positive results foster us to continue our studies in enlightening the scope and the limitations of this new reaction.
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**Chapter 1. Introduction**

Imines are kinds of important intermediates widely used in organic synthesis. As a special case of imine, ketene imines, belonging to the more general class of compounds known as cumulene, molecules presenting at least two or more cumulative double bonds, were first reported by Staudinger as long ago 1919.\(^1\) They can be represented by the resonance structures 1 and 2, which emphasize the nucleophile properties of the heteroatom and the β-carbon, and by structure 3, which accounts for the electrophilic nature of the α-carbon (Scheme 1.1).

According to theoretical calculations and experimental practice, except in the case of ketene imines with a linear or nearly linear moiety, this structure is characterized by dihedral angles of 90° between carbon and nitrogen substituents, CNC angles close to 120°, and the average bond length of C=N is 1.27Å.\(^3\) It presents characteristic IR absorption at around 2030 cm\(^{-1}\) and a \(^1\)C-NMR of α-C at around 180 ppm. The N-substituent may be -alkyl, -aryl, -hydrogen, -phosphorus, -nitroso and a metal as silicon, aluminium, tin, and so on. For the sake of simplicity, we classify them as \(N\)-organo ketene imines and \(N\)-metallo ketene imines respectively.

\(N\)-organo ketene imines, in which ketene imines were stabilized by conjugation with organic functional groups, such as vinyl, aryl, carbonyl, sulfonyl etc,\(^3\) which can be prepared though several pathways. For example: Synthesis of \(N\)-organo ketene imines via Wittig\(^4\) and aza-Wittig reactions,\(^2,5\) coupling reaction between carbenes and isonitriles\(^6\) and though some multicomponent reactions (MCR).\(^7\)\(^9\)\(^10\) Other preparation and applications of \(N\)-organo ketene imines have been summarized by some available reviews.\(^3\)\(^5\)\(^11\)\(^13\) \(N\)-organo ketene imines can undergo several types of reactions. Among them \(N\)-organo ketene imines have been widely used on heterocyclic addition reactions for formation of heterocyclic compounds.\(^5\) Excellent reviews on this aspect are available for the interested readers.\(^3\)\(^5\)

\(N\)-Metallo ketene imines are a kind of \(N\)-metalated nitriles (Scheme 1.2); in some specific cases they are relatively stable and can be isolated. Meanwhile, some \(N\)-Metallo ketene imines are
not enough stable for isolation; they were considered as active intermediates in organic reactions and the existence of these species were partly traced by IR, X-ray diffusion, and other methods. In the coming section, the development of N-Metallo ketene imines will be reviewed in these two aspects: stable isolable N-Metallo ketene imines, and unstable N-Metallo ketene imines as intermediates in organic synthetic procedures.

\[
\begin{align*}
R_2 & \xrightarrow{\text{C=N-M(L)n}} \\
R_1 & \\
\end{align*}
\]

\(R_1, R_2 = \text{aryl, alkyl, organometallic, H et al}
M = \text{Silyl, Mg, Cr, In et al}
L = \text{alkyl, aryl}

Scheme 1.2 N-Metallo ketene imines

1.1 Synthesis and applications of stable N-Metallo ketene imines.

For methalated nitriles, the methalation on carbon and nitrogen are always competitive, and the stability of the resulting nitrogen methalated nitrile 4 (N-Metallo ketene imines, Scheme 1.2) can be influenced by several factors: the property of group \(R_1, R_2\), the very nature of metal atom and its L groups. Combination effect of these factors made the prediction of this issue very difficult. In general, the more electronegativity and more bulky of \(R_1, R_2\) L groups, more stable the N-Metallo ketene imines is. The influence of the property of metal atom has been rarely discussed.

\[
\begin{align*}
\text{CN} & \xrightarrow{\text{n-BuLi, Et}_2\text{O}, -78^\circ\text{C}} \text{Ph}_2\text{CN} \\
\text{Et}_2\text{O} & \underset{\text{Et}_2\text{O}}{\xrightarrow{\text{Li}}} \text{Ph}_2\text{CN} \\
\text{Ph} & \underset{\text{Me}_2\text{MCl}, \text{Et}_2\text{O}}{\xrightarrow{\text{Me}_2\text{MCl}}} \text{Ph}_2\text{CN} \\
\text{Ph} & \\
\end{align*}
\]

Scheme 1.3 preparation of N-In and N-Ga ketene imines

\(N\)-In and \(N\)-Ga ketene imines were reported by Iravani and co-workers.\textsuperscript{14} Initially they were studying the trimerization of acetonitrile by Me\textsubscript{3}In. When diphenylacetonitrile was used, the expected trimerization product was not formed, instead, a dimer of \(N\)-methalated nitriles (Ketene imine) were found and confirmed by IR, NMR and X-ray structure analyses, while the reactivity and applications of these two species were not mentioned by the authors. The preparation of \(N\)-In
ketene imine through direct reaction between diphenylacetonitrile and Me$_3$In require a long time (48h) despite the presents of CsF as catalyst, a modified procedure, as shown in Scheme 1, 3, $N$-In and $N$-Ga ketene imines were prepared by methalation of diphenylacetonitrile, then trap with Me$_2$InCl or Me$_2$GaCl in diethyl ether, a shorter time (10h for $N$-In ketene imine, 15h for $N$-In ketene imine) a higher yields were achieved. It is worth to mention that the intermediate 5 was identified from IR absorption, which was remarkably shifted from 2030 cm$^{-1}$ to 2167 cm$^{-1}$ 6a and 2188 cm$^{-1}$ 6b respectively.

Scheme 1.4 preparation of N-Magnesium ketene imine

Attracted by alkaline earth metal complexes, several $N$-metallo ketene imines have been prepared through elimination reaction between magnesium organometallics and acetonitriles, the structure of them has been determined by ESR and IR spectroscopy. Metals like Mg, Ba, Sr were included, the IR absorption of $N$-Mg, $N$-Ba, $N$-Sr ketene imines were 2088 cm$^{-1}$, 2075 cm$^{-1}$, 2080cm$^{-1}$ respectively. Complex 8 was chosen as an example to show the preparation procedures (Scheme 1.4), some analogues of compound 8 were used in catalyzed ring-opening polymerization of $L$ and rac-lactides.\(^{15,16}\)

Scheme 1.5 preparation and application of $N$-Zr ketene imine
Zirconacycles like zirconacyclopentadienes 9, zirconacyclopentenes 10, and azazirconacycloallenenes 12 were proved to be a versatile reagent against acetonitrile.\textsuperscript{17-19} Compound 12 was treated with nitriles to give 5-Azaindoles through a multicomponent reaction,\textsuperscript{17} thanks to the acidity $\alpha$-proton of diphenylacetonitrile, $N$-Zr ketene imine 11 and 13 were formed unexpectedly, they have been isolated and identified by NMR and X-ray. Two specific $^{13}$C NMR peaks at $\delta$ 180.49 and 57.29 ppm were unambiguously assigned to the ketene imine structure. For a further investigation, propargyl bromide (or chloride) was treated with 13: halogenated Zirconocenes and $\alpha$-alkylated diphenylacetonitrile 14 were obtained from this reaction (Scheme 1.5 eq. 2). In our knowledge this reaction is, so far, the first example of nitrile alkylation by $N$-Zr ketene imine.

Palladium compounds play a remarkable role in C-C bond formation reactions, when it acts as catalyst. In case of palladium catalysed nitrile anion coupling reaction by aryl halide, Culkin and co-workers\textsuperscript{20} have tried efforts on figure out the intermediate of this reaction. Interestingly, $N$-Pd ketene imine was found to be one of them. Generally speaking, nitrile anions could coordinate the metal in three different ways: 1st): on $\alpha$-carbon; 2nd): cyano nitrogen; and 3rd): bridge two metals in a $\mu^2$ C-N fashion;\textsuperscript{20} most of aryl palladium cyanoalkyl complexes were bound to $\alpha$-carbon, only in the case the palladium was ligated by larger, more donating ligands, a nitrogen binding product($N$-Pd ketene imine 15) can be found as a reaction intermediate (Scheme 1.6).

Considering the content of this thesis, the stable $N$-silyl ketene imine will be summarized in Chapter 2 and $N$-Ge ketene imine will be discussed in Chapter 2.

1.2 The preparation and applications of unstable $N$-Metallo ketene imines as reaction intermediates.

As shown in 1.7, a practical procedure for producing $\omega$-alkoxyanilines 19 through $N$-Cr ketene imine was established by Merlic and co-workers.\textsuperscript{21-23} Chromium carbine 16 can be thermally or
photochemically elaborated into 19 by electro cyclic ring closure via ketene imine formation (Scheme 1.7). In this procedure, Chromium can be substituted by Tungsten (W), but Chromium has been proved to be the best element in comparison to other transition metal elements. Systematic studies have been made for confronting these coordinated metallo ketene imines, including computational and experimental ones. 

Scheme 1.7 Preparation of \( o \)-alkoxyanilines through \( N \)-Cr ketene imine

This reaction has been successfully applied for preparation of several organic cyclic compounds: eg total synthesis of calphostins, preparation of analogues of natural products indolocarbazole, and the synthesis of highly functionalized indazoles.

Scheme 1.8 Asymmetric \( N \)-Copper ketene imine Aldol type and Mannich type reactions.

The generation of nucleophile by decarboxylation-reaction typically appears in biosynthesis. Recently, Liang and co-workers established a catalytic asymmetric aldol and Mannich type reactions by decarboxylation of nitriles (Scheme 1.8). In this procedure, \( N \)-Cu ketene imine was deduced to be the key intermediate. It was generated from an anion exchange between

\[ \text{Ligand 1} = \begin{array}{c} \text{R}_2P \ N^- \ K \ R^+ \\ \text{Ligand 2} = \begin{array}{c} \text{P(Ar)}_2 \ O \ P(Ar)_2 \ O \end{array} \end{array} \]
Chapter 1

the chiral copper acetate complex (For aldol type reaction: CuOAc – TANIAPHOS, For Mannich type reaction: CuOAc - (R)DTBM-SEGPHOS) and cyanoacetic acid 20, followed by extrusion of CO₂. The fresh formed but not isolated N-Cu ketene imines (21 and 24) acted as intermediates in a catalytic cycle. The formation of nucleophilic ketene imine was proved to be essential factor for the taking place of the reaction.

Scheme 1.9 Enantioselective Cyanation/Brook Rearrangement/C-Acylation Reactions of Acylsilanes Catalyzed by Chiral Metal Alkoxides

N-Al ketene imine 27 has been obtained from an aluminum salen complex 26 by Nicewicz and co-workers on 2004.³⁰, ³¹ As shown in Scheme 1.9, starting from acyl silane, an in situ generated (salen)aluminum alkoxide((Salen)Al-CN 26 was obtained. This α-metallo ester silane nitrile underwent a Brook rearrangement reaction with the formation N-Al ketene imine 27. Reaction with benzyl cyanoformate resulted in the formation of the target product 28 in good yields and enantioselectivity (from 82:18 to 91:9).

In summary, as reviewed above, a wide range of organo-metals have been used in the preparation of N-Metallo ketene imines, including Main group IV metals like Gallium, ¹⁴ Indium, ¹⁴ Alkaline Earth Metals: ¹⁵ Magnesium, Barium, Strontium; and transition metals as Zirconium, ¹⁸, ¹⁹ Iridium.³² These N-Metallo ketene imines were prepared and identified for the seeking of catalysts or material usage metallo complexes. In few cases the reactivity was investigated and focused on developing a practical organic synthetic method. Alternatively, N-Cr, N-Cu, N-Al ketene imines were demonstrated as reactive intermediates in practical synthetic procedures. In some cases, stereoselectivity control was successfully achieved. The usage of metals from main group IV, like Germanium,³³ Tin,³⁴ Palladium ²⁰ and Silicon will be discussed in below chapters.

Inspiriting by the reviews above, the main content of this thesis will be focused on developing new method for preparation of nitrogen containing compounds based on N-metallo ketene imines, either as an isolated starting material or as an active intermediates during the process.
Chapter 1

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Chapter 2. Synthesis and applications of N-silyl ketene imines

2.1 Introduction

N-Silyl ketene imine was first prepared by Prober in 1956 from sodium methalated acetonitrile and trimethylsilyl chloride. Following this approach other N-silyl ketene imines, from primary to secondary nitriles, were prepared and identified. The understanding of influence of the substituent-groups on α-carbon position and on silicon atom were discussed by Llonch at 1973, and, more recently, proved by Mermerian and Fu (Scheme 2.1).

![Scheme 2.1 Silylation of nitrile anions.]

Generally speaking, N-silyl ketene imine can be prepared from a methalated nitrile followed by the trapping of the methalated nitrile by suitable alkyl silyl chloride. N-Silyl ketene imines present IR absorption around 2030 cm\(^{-1}\) and a \(^{13}\)C-NMR of α-carbon at around 180 ppm. Other physical properties, like the configurational stability of N-silyl ketene imine were well discussed in review.4,5 The applications of N-silyl ketene imines will be briefly summarized in the coming two sections.

2.1.1 Reactions of N-silyl ketene imines

In the early studies about N-silyl ketene imines (SKIs), very few reports have appeared in literature describing their usage as nucleophiles.6,7 Cazeau and co-workers reported the addition of SKIs to acyl chlorides, aldehydes and ketones.8 Meier reported the acylation reactions of N-trimethylsilyl
ketene imines with different acyl halides in the synthesis of N-acyl ketene imines 7 (Scheme 2.2) and/or α-cyano ketones 6 (Scheme 2.2), depending from the reaction conditions. N-silyl ketene imine derived from allylic nitriles, have been used in several types of cycloaddition reactions with olefinic dienophiles in the presence of KF, and with acetylenic dienophiles formed substituted anilines 8 (Scheme 2.2) without any promoter. These applications of N-silyl ketene imine were summarized in Scheme 2.2.

Scheme 2.2 N-silyl ketene imines as nucleophile react with different electrophiles

2.1.2 Asymmetric reactions of N-silyl ketene imines

N-silyl ketene imines were not used in asymmetric synthesis until 2005, when Fu and Mermerian established a catalytic asymmetric acylation reaction by a chiral (4-(pyrrolidino) pyridine) derivative. Some other catalytic asymmetric reactions were developed: Notte and co-workers developed a catalytic Mannich reaction of N-silyl ketene imines by a chiral silicon derivative; Guin and co-workers developed an asymmetric protonation of N-Silyl ketene imines by chiral phosphoric acids catalysts (11 and 12).

Our interest has been directed towards the asymmetric aldol reactions of N-silyl ketene imines for the preparation of β-hydroxyl nitriles. Catalytic asymmetric aldol type reactions have appeared in recent years. Denmark and coworkers developed an asymmetric aldol type reaction in 2007: the reaction was promoted by SiCl₄ and the co-catalyst catalyst 9.
Figure 2.1 catalyst for asymmetric reactions of N-silyl ketene imines.

With the same catalyst, an asymmetric conjugate reaction between N-silyl ketene imines and unsaturated carbonyl compounds was successful established,\textsuperscript{16} catalytic asymmetric conjugate reaction between N-silyl ketene imines and α, β un-saturated aldehydes and ketones were developed with catalyst 18 as well.\textsuperscript{5} Even α-Vinyl N-silyl ketene imines were successfully applied.\textsuperscript{17}

Scheme 2.3 Lewis base catalyzed asymmetric reactions of N-silyl ketene imines.

Catalytic asymmetric Mannish type reactions of N-silyl ketene imines have been successfully established. Zhao and co-workers reported a procedure for preparation of β-Amino nitriles through Sc\textsuperscript{III} catalyzed three component reaction.\textsuperscript{18} A chiral silane Lewis acid was found to be an efficient catalyst for enantio selective Mannich type reactions of N-silyl ketene imines
reacting with acylhydrazone,\textsuperscript{13, 19} as a kind of interesting heterocyclic compounds. Pyrrolidines were prepared through this procedure.\textsuperscript{19}

In the course of this thesis, uncatalyzed reactions of \textit{N}-silyl ketene imines with unreported electrophile like isocyanate, and an uncatalyzed aldol type reaction with optically pure aldehydes, will be reported.

\section*{2.2 Present work}

\subsection*{2.2.1 Synthesis of \textit{N}-silyl ketene imines}

\textit{N}-trimethylsilyl ketene imines will be one object of this thesis. The preparation of \textit{N}-silyl ketene imine starts from a diphenyl- or diarylnitriles, methalated by lithium organometallic reagent as lithium diisopropyl amine or lithium hexamethyldisilyl amide at -78°C and then traps of the generated carbanion with silyl chloride. The so prepared diphenyl (or diaryl) \textit{N}- silyl ketene imines \textsuperscript{20} (Scheme 2.4) have been used \textit{in-situ} or, in some cases, purified by removal all the reaction solvents, dissolving with anhydrous pentane, filtering, and then removing of pentane. The final residues, constituted by the \textit{N}-silyl ketene imines were fully identified by IR, \textsuperscript{1}H- and \textsuperscript{13}C-NMR.

\begin{eqnarray*}
\text{Scheme 2.4 preparation of } \textit{N}-\text{silyl ketene imines.}
\end{eqnarray*}

\subsection*{2.2.2 Synthesis of \textit{\alpha}-cyano-carboxyamides (malonamides) through an un-catalyzed amidation reaction of \textit{N}-silyl ketene imines with isocyanates.}

There are only few applications between isocyanate as an electrophile and ketene imines\textsuperscript{20, 21} and no paper has been published by using SKIs and isocyanates in an uncatalyzed reaction before our work.\textsuperscript{20}

The reaction between these two reactants should generate malonic amide derivatives bearing a quaternary carbon centre. Taking into account the versatility and the wide range of functionalities that are easily achieved through manipulation of the nitrile group and the amide group, the importance of these intermediates as starting materials for the elaboration of more complex scaffolds is evident.\textsuperscript{22-24} As shown in Fig 2.2, Loperamide \textsuperscript{21} and \textsuperscript{22}, originally
developed by Janssen Pharmaceutica and used against diarrhea, and Varapamil 23 (Figure 2.2) show a malonamide scaffold.

Figure 2.2 Malonamide analogues drugs.

2.2.2.1 Reaction of N-silylketene imines and isocyanates: Synthesis of malonamides

Silyl ketene imines 20a are easily generated by the reaction of a nitrile with a silylating agent,6, 7, 21 in the presence of a base such as lithium diisopropylamide (LDA) or n-butyllithium. Following removal of diisopropylamine under vacuum, the reaction mixture was treated with isocyanate 24a in toluene to produce the target nitrile malonic amides 25a.

Scheme 2.5 Procedure for reaction of N-silylketene imines and isocyanates.

In a study case with diphenylacetonitrile and p-methoxyphenyl isocyanate, different experimental conditions were tested to achieve the best condition in term of reactions yields. First of all, a blank experiment, using only metallated nitrile as nucleophile was tested. Generation of nitrile anion with n-butyllithium in tetrahydrofuran, in the absence of trimethylsilyl chloride, resulted in the formation of the target compound, but in lower yields, and concomitant with the formation of significant quantities of side products (Table 2.1, entry 1, Method A).
Table 2.1 The reactivity of diphenyl N-silyl ketene imine versus isocyanates.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Bases</th>
<th>Method</th>
<th>R'-Cl</th>
<th>Yield(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>n-Butyl lithium</td>
<td>A</td>
<td>--</td>
<td>35.5</td>
</tr>
<tr>
<td>2</td>
<td>n-Butyl lithium</td>
<td>B TMS-Cl</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>LDA</td>
<td>C TMS-Cl</td>
<td>71</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>n-Butyl lithium</td>
<td>D TBS-Cl</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Addition of trimethylsilyl chloride to the lithium diphenylacetonitrile (Table 2.1, entry 2, Method B), prior to treatment with the electrophile, led to an increased yield of the target product. This indicates that the formation of the intermediate N-trimethylsilyl ketene imine plays an important role in the overall process. The use of tert-butyldimethylsilyl chloride (TBDMSCl) instead of trimethylsilyl chloride failed to give the corresponding N-tert-butyldimethylsilyl ketene imine (Table 2.1, entry 4, Method D), presumably because of steric reasons.

Scheme 2.6 N-silyl ketene imine reacts with different isocyanates.

Table 2.2 N-silyl ketene imines react with different isocyanates 24b-24f

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ketene imines(20)</th>
<th>R₁</th>
<th>R₂</th>
<th>Method$^5$</th>
<th>Products</th>
<th>Yield (%)$^k$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(20a)Ph Ph</td>
<td>(24b)Ph</td>
<td>B</td>
<td>25a</td>
<td>67.9</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>(20a)Ph Ph</td>
<td>(24c)Bn</td>
<td>B</td>
<td>25j</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>(20a)Ph Ph</td>
<td>(24d)Si(Me)$_3$</td>
<td>B</td>
<td>25a</td>
<td>No reaction</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>(20a)Ph Ph</td>
<td>(24e)SO$_2$Cl</td>
<td>B</td>
<td>25a</td>
<td>Trace</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>(20a)Ph Ph</td>
<td>(24b)Ph</td>
<td>C</td>
<td>25i</td>
<td>73</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>(20a)Ph Ph</td>
<td>(24f)1-methyl Benzyl</td>
<td>B</td>
<td>25k</td>
<td>78</td>
<td></td>
</tr>
</tbody>
</table>

$: Method B: n$-BuLi, TMSCl, isocyanate, THF, toluene. Method C: LDA, TMSCl, isocyanate, toluene. Method D: LDA, TBDMSCl, isocyanate, toluene. $^@$: Yields of isolated pure products.
Then, a wide range of aromatic nitriles, prepared according literature procedure if not commercially available, were used in generating the corresponding N-silyl ketene imines and reacted with isocyanate 24a (Scheme 2.7). The relative results are reported in Table 2.3.

Table 2.3 Reaction of ketene imines 20a-20j with isocyanates 24a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ketene imines(20) &amp;&lt;sub&gt;4&lt;/sub&gt;</th>
<th>R&lt;sub&gt;3&lt;/sub&gt; &amp;&lt;sub&gt;5&lt;/sub&gt;</th>
<th>Method</th>
<th>Product</th>
<th>Yield&lt;sup&gt;8&lt;/sup&gt; (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(20a)Ph</td>
<td>Ph</td>
<td>(24a) 4-OMeC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>B</td>
<td>25a</td>
</tr>
<tr>
<td>2</td>
<td>(20b)4-BrC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>Ph</td>
<td>(24a) 4-OMeC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>C</td>
<td>25b</td>
</tr>
<tr>
<td>3</td>
<td>(20c)3-MeC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>Ph</td>
<td>(24a) 4-OMeC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>C</td>
<td>25c</td>
</tr>
<tr>
<td>4</td>
<td>(20d)2-MeC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>Ph</td>
<td>(24a) 4-OMeC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>C</td>
<td>25d</td>
</tr>
<tr>
<td>5</td>
<td>(20e)4-MeC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>Ph</td>
<td>(24a) 4-OMeC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>C</td>
<td>25e</td>
</tr>
<tr>
<td>6</td>
<td>(20f)4-OMeC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>Ph</td>
<td>(24a) 4-OMeC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>B</td>
<td>25f</td>
</tr>
<tr>
<td>7</td>
<td>(20g)2-ClC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>Ph</td>
<td>(24a) 4-OMeC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>B</td>
<td>25g</td>
</tr>
<tr>
<td>8</td>
<td>(20h)Pyridine-3-yl</td>
<td>Ph</td>
<td>(24a) 4-OMeC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>B</td>
<td>25h</td>
</tr>
<tr>
<td>9</td>
<td>(20i)4-OMeC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>4-OMeC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>(24a) 4-OMeC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>B</td>
<td>25i</td>
</tr>
</tbody>
</table>

#: The nitriles 19b (44%), 19c (76%), 19d (68%), 19e (67%), 19f (57%), 19g (47%), 19h (73%) and 19i (46%) were prepared from the corresponding ketones using tosylmethyl isocyanide (TosMIC), &sup: Yields of isolated pure products.

2.2.2.2 Reaction of phenyl alkyl N-silyl ketene imines with isocyanates.

The good experimental conditions for un-catalyzed amidation reaction of α, α-diaryl ketene imine by isocyanates, were applied to some α,α aryl alkyl substituted ketene imines to enlarge the reaction scope and versatility of this reaction.

Following the general procedure for preparation of N-silyl ketene imines and starting from phenyl alkyl nitriles, treatment of these compounds with a base followed by trapping with trimethyl silyl chloride, alkyl-aryl N-trimethylsilyl ketene imines 27 (Scheme 2.8) were obtained.
In situ treatment of these reactants with isocyanate, according a one pot procedure, gave the expected target 29 with low yield (Scheme 2.8).

\[
\begin{align*}
\text{CN} & \quad \text{n-BuLi,TMS-Cl} \\
\text{Ph} & \quad \text{Et} \\
26 & \quad \text{Ph} = \text{C} = \text{N} - \text{TMS} \\
& \quad \text{TMS} - \text{CN} \\
27 & \quad \text{21a} \\
& \quad \text{O} = \text{C} = \text{N} - \text{Ph} \quad \text{Et} \quad \text{O} \\
& \quad \text{O} = \text{C} = \text{N} - \text{Ph} \quad \text{Et} \quad \text{O} \\
29 & \quad \text{Yield 12\%} \\
& \quad \text{No Reaction}
\end{align*}
\]

Scheme 2.8 α,α aryl alkyl substituted ketene imines react with isocyanate

In order to get a stable phenyl alkyl N-silyl ketene imine, a more bulky group, such as TBS (tert-butyldimethyl silyl), TIPS (Trisopropyl silyl), on silicon must be used. Accordingly, we prepared, α, α’ phenyl ethyl N-TBS ketene imine 27’ (Scheme 2.9), and then treated with p-methoxyphenyl isocyanate. No reaction took place pointing out that trimethylsilyl group is crucial for this kind of catalyst free amidation reactions.

\[
\begin{align*}
\text{CN} & \quad \text{n-BuLi,TMS-Cl} \\
\text{Ph} & \quad \text{Et} \\
26 & \quad \text{Ph} = \text{C} = \text{N} - \text{Si} \\
& \quad \text{N} \quad \text{Me3} \\
27’ & \quad \text{O} = \text{C} = \text{N} - \text{Ph} \quad \text{Et} \quad \text{O} \\
& \quad \text{No Reaction}
\end{align*}
\]

Scheme 2.9 α, α’ phenyl ethyl N-TBS ketene imine react with isocyanate.

2.2.2.3 Results and discussion

Considering the reactivity of different N-silyl ketene imines, N-TBS present the lowest reactivity, probably due to the very bulky nature of the tert-butyldimethylsilyl group. In order to enlighten this aspect some speculations on the reaction mechanism are below reported.

\[
\begin{align*}
\text{C} = \text{N} - \text{SiMe3} & \quad \text{R1} \quad \text{R2} \quad \text{R3} \\
\text{C} = \text{O} & \quad \text{N} \quad \text{R1} \quad \text{R2} \quad \text{R3} \\
\text{R1} & \quad \text{CN} \quad \text{R2} \quad \text{R3} \\
& \quad \text{CONHR3}
\end{align*}
\]

Scheme 2.10 The supposed pathway of un-catalyzed N-trimethyl ketene imine amidation by isocyanates
First of all, from the above results, it appears clear that, in this catalyst-free amidation, the presence of the trimethylsilyl group was essential for the success of the reaction. A possible explanation assumes that the reaction proceeds via a silatropism, probably by the pathway depicted in Scheme 2.10. As key step, the isocyanate oxygen desilylates the ketene imine moiety to generate an incipient nitrile anion and subsequent attack to the isocyanate carbon center. The resulting intermediate 30 affords, after aqueous work-up, the target product (Scheme 2.10) 31. Whether this proposed step is concerted or not is hard to predict at this stage of studies. Density functional theory (DFT) calculations, in order to clarify the mechanistic aspects, are in progress and preliminary results are below reported.

As a matter of fact, to have a further insight on the mechanism of the reaction between ketene imines and isocyanates, DFT calculations at B3LYP 6-31G* level were performed on diphenyl N-trimethylsilyl ketene imine and phenyl isocyanate (Scheme 2.10). As shown in Fig 2.3, calculations showed a preliminary formation of an electrostatic complex EC, whose energy was taken as the zero point. Then a first transition state TS1 is formed in which an incipient formation of a C—C bond (1.78 Å, 0.63 bond order) between the β-carbon of the SKI and the isocyanate carbonyl is shown. This transition state evolves to a dipolar intermediate Int1, whose geometry and energy are very similar to that of TS1. A second transition state TS2 at higher energy, which
is characterized by the silatropism from the SKI nitrogen to the isocyanate oxygen (N—Si bond 2.09 Å 0.34 bond order, O—Si bond 2.15 Å 0.26 bond order), is therein formed. Finally, this transition state evolves to the final neutral sililoxy nitrile Fin. From the energetic profile, depicted into Figure 2.3, it is allowed to speculate that, despite the presence of two transition states, this reaction cannot be considered a two-step reaction, but rather a very asynchronous one step reaction, in which the nucleophilic attack of the SKI on isocyanate is preliminarier to the silyl tropism from nitrogen to oxygen. This is the very difference with the analogous reaction of SKI with aldehydes, in which the two processes are contemporary leading to a synchronous reaction.

2.2.3 Un-catalyzed asymmetric aldol type reaction of N-silyl ketene imines with optically pure aldehydes

These studies were focused on un-catalyzed aldol reaction of diphenyl N-silyl ketene imine and deal with a catalyst free asymmetric synthetic procedure by using some chiral aldehydes bearing a changeable protecting group of hydroxyl functionality on α-position (Scheme 2.11). The resulting β-hydroxyl nitriles are useful organic intermediates for asymmetric synthesis because of the cyano group is a functional precursor group of amino and carbonyl groups.22,27

![Scheme 2.11 Strategies of catalyst free asymmetric aldol type reaction of N-trimethylsilyl ketene imines](image)

As shown in Scheme 2.12, first we tested whether simple metallated diphenyl acetonitrile 19a’, obtained by reaction of 19a with LDA in THF, would form an aldol adduct by reaction with aldehydes 31a and 31b (Table 2.4, entry 1). After 2 days at room temperature, none of addition product but only starting materials was detected in the crude reaction mixture. The next step of our study was to attempt a catalyst-free reaction of N-(tert-Butyldimethylsilyl) ketene imine 20a’, prepared according to a literature procedure,28 with the aldehyde 31a. The reaction was performed starting from –78 °C and allowing the reaction mixture to warm spontaneously to room temperature. After 2 days, once again, no reaction had occurred. Substitution of the protecting group on the hydroxyl functionality of the aldehyde with a less hindered one (i.e., the benzyl group in 31b) gave the same results (Table 2.4, entries 2 and 3). The simple substitution of N-TBS-
ketene imine $20a'$ with less hindered $N$-trimethylsilyl ketene imine $20a$ allowed the reaction to take place (Table 2.4, entry 4).

![Chemical structure](image-url)

**Scheme 2.12** Reaction of different nucleophiles with aldehydes. (31. Reagents and Conditions. $i$: THF, LDA, -78 °C; $a$: THF, 31a, -78 °C to r.t. 2 days; $b$: THF, TBDMSI, -78 °C, r.t 10 min and after add 31a or 31b at r.t. 2 d.; $c$: THF, TMSCI, -78 °C, 10 min r.t. and after see Table 2.4 and experimental section.)

**Table 2.4** Reaction of aldehydes 31a-31d with different aldehydes

<table>
<thead>
<tr>
<th>Entry</th>
<th>Nucleophile</th>
<th>Aldehyde</th>
<th>Products</th>
<th>$\text{Dr}^{\text{A}}(32/33)$</th>
<th>Total Yields(%)</th>
<th>$J_{\text{H}_3-\text{H}_4}$</th>
<th>$\delta_{\text{H}_3-\text{H}_4}$</th>
<th>$J_{\text{H}_4-\text{H}_5}$</th>
<th>$\delta_{\text{H}_4-\text{H}_5}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>19a'</td>
<td>31a</td>
<td>No reaction</td>
<td>-</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>20a'</td>
<td>31a</td>
<td>No reaction</td>
<td>-</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>20a'</td>
<td>31b</td>
<td>No reaction</td>
<td>-</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>20a</td>
<td>31a</td>
<td>32a 33a</td>
<td>97:3</td>
<td>65</td>
<td>0.8</td>
<td>4.43-4.16</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>45:55</td>
<td>70</td>
<td>0.8</td>
<td>4.66-3.99</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>20a</td>
<td>31b</td>
<td>32b 33b</td>
<td>100:0</td>
<td>83</td>
<td>4.4</td>
<td>4.52-3.68</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>68:32</td>
<td>75</td>
<td>5.2</td>
<td>4.60-3.07</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>20a</td>
<td>31c</td>
<td>32c 33c</td>
<td>70:30</td>
<td>75</td>
<td>2.4</td>
<td>4.53-4.31</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5:95</td>
<td>85</td>
<td>0.8</td>
<td>4.77-4.02</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>20a</td>
<td>31d</td>
<td>32d 33d</td>
<td>65:35</td>
<td>62</td>
<td>1.6</td>
<td>4.50-4.08</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1:99</td>
<td>67</td>
<td>0.0</td>
<td>4.89-3.92</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

#: Method A: Adding the aldehyde 31a-c to the imine 20a at room temperature. $\$: Method B: Adding the aldehyde 31a-31d to the ketene imine 20a at -78°C and after 3 hrs at this temperature, it was left to reach r.t spontaneously.

From a stereochemical point of view, as far as the formation of the new chiral centre is concerned, the highest stereocontrol was achieved using (S)-2-(benzyloxy)propanal derivative 31b at room temp. In this case, an adduct with a $\text{syn}$ relationship between the benzyloxy group and the new TMS-protected hydroxy functionality (Table 2.4, entry 5) was obtained. On the other hand, a
complete anti selectivity (for the assignment of the stereochemistry, see below) was achieved by using an aldehyde bearing an extremely hindered protecting group (i.e., TBDPhS, tert-butylidiphenylsilyl, in 31d) and a reaction temperature of −78 °C (Table 2.4, entry 7). The value of J_{3,4} (Table 2.4) did not give conclusive information on the stereochemical relationship of the two hydroxyl functionalities. Thus, the stereochemistry was ascertained by transformation of the diastereomeric products (i.e., 32a and 33a) into their acetonide derivatives 35a and 35b (Scheme 2.13) and studying these compounds by NOE based studies. The transformation of 32a and 33a into the corresponding diols (i.e., 34a and 34b) was performed by treatment with hydrogen chloride (1 M) in acetonitrile. The diols were then converted into acetonides 35a and 35b by reacting them with 2,2-dimethoxypropane in the presence of pyridinium p-toluenesulfonate (PPTS).

![Scheme 2.13 Preparation of acetonides 35a and 35b from 32a and 33a. Reagents and Conditions: i: HCl (1N), ACN, 30 min, r.t.; ii: Pyridin-p-toluensulphonate (2 eq.), 2, 2-dimethoxypropane, acetone, overnight, r.t.](image)

The assignment of the relative stereochemistry of the substituents at positions 3,4 of the dioxolane rings of 35a and 35b based on the results of NOE experiments was straightforward (Scheme 2.13). For compound 35a, the NOE’s between CH₃ and 5-H and between CH₃ and 4-H were almost of the same magnitude, which is consistent with a trans configuration, according to geometric analysis. For compound 35b, the NOE effect between CH₃ and 5-H was about ten times larger than the NOE effect between CH₃ and 4-H, and so the relative configuration between the two substituents on C-4 and C-5 must be assigned as cis. Accordingly the syn configuration was assigned to compound 32a, and the anti-configuration was assigned to compound 33a.
Chapter 2

Scheme 2.1.4 Preparation of diol 34a from 32b, 32c, 32d respectively. *Reagents and Conditions: i*: Pd/C, Pd(OAc)$_2$, MeOH; *ii*: HCl$_aq$(1N), CH$_3$CN, r.t.)

The configuration of compounds 32b, 32c, and 32d was assigned by transforming them into the corresponding diol (i.e., 34a). Compound 32b was transformed into the corresponding dihydroxy derivative (i.e., 34a) by hydrogenolysis over a mixture of Pd/C and Pd(OAc)$_2$ (Scheme 2.1.4).

Scheme 2.1.5 Reaction of aldehydes 31e-31k with ketene imine 20a i) THF, r.t., overnight.

This aldol-type reaction has been applied to a range of O-protected α-hydroxy aldehydes. The results are reported in Scheme 2.1.5 and Table 2.5. At room temperature, a good diastereomeric excess were obtained, as shown in table 2.5. One exception is aldehyde 31f (table 2.5, entry 2): with much hindered α-hydroxy protecting group associated to a bulky R$_3$ group, no reaction took place. The configurations of compounds 32e and 32g were identified by their transformation into the corresponding acetonide derivatives (i.e., 38 and 40, respectively; Scheme 2.1.6).
Scheme 2.16 Preparation of products 38, 40 from 32e and 32g respectively. Reagents and Conditions: i: Pd/C (10%)/Pd(OAc)$_2$, MeOH, H$_2$; ii: HCl$_{aq}$, 1N, CH$_3$CN, r.t., 30 min. iii: PPTS, 2,2-dimethoxypropane, acetone,r.t.

Table 2.5 Reaction of aldehydes 31e-31k with keteneimine 20a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde</th>
<th>Product*</th>
<th>de</th>
<th>Yield (%)</th>
<th>$J_{H_3-H_4}$</th>
<th>$\delta_{H_3-H_4}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>31e</td>
<td>32e</td>
<td>&gt;98</td>
<td>68</td>
<td>4.4</td>
<td>4.69-3.37</td>
</tr>
<tr>
<td>2</td>
<td>31f</td>
<td>32f</td>
<td>&gt;98*</td>
<td>65</td>
<td>1.2</td>
<td>5.02-3.30</td>
</tr>
<tr>
<td>3</td>
<td>31g</td>
<td>32g</td>
<td>&gt;98</td>
<td>78</td>
<td>2.4</td>
<td>5.10-4.78</td>
</tr>
<tr>
<td>4</td>
<td>31h</td>
<td>32h</td>
<td>&gt;98*</td>
<td>73</td>
<td>2.8</td>
<td>4.95-4.62</td>
</tr>
<tr>
<td>5</td>
<td>31i</td>
<td>32i</td>
<td>&gt;98*</td>
<td>68</td>
<td>2.8</td>
<td>4.01-4.72</td>
</tr>
<tr>
<td>6</td>
<td>31j</td>
<td>32j</td>
<td>81</td>
<td>80</td>
<td>8.0</td>
<td>4.58-4.15</td>
</tr>
<tr>
<td>7</td>
<td>31k</td>
<td>32k</td>
<td>--</td>
<td>0</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

*: For the sake of simplicity, only one diastereoisomer was reported in the table

The configuration of 32f was assigned by comparison the value of the $J_{3.4}$ of di-hydroxy derivative 42 with the corresponding $J$ value of compound 40 (Scheme 2.17).

Scheme 2.17 Preparation of products 42 from 32f. Reagents and Conditions: i: Pd/C (10%)/Pd(OAc)$_2$, MeOH, H$_2$; ii: HCl$_{aq}$, 1N, CH$_3$CN, r.t., 30 min.
The configurations of 32h and 32i were assigned by simply comparing the values of their \( J_{3,4} \) values with that of product 32g (Table 2.5, entries 3–5). Finally the configurations of 32j and 33j were inferred by literature data of the corresponding mono-hydroxy derivatives 43 and 44\(^{29,30} \) (Scheme 2.18).

![Scheme 2.18 Preparation of products 43 and 44. Reagents and Conditions: \( i: \) KF/HF(50%),CH\(_2\)Cl\(_2\)/ACN (9/1), r.t.](image)

To further investigate the scope of this reaction, nitriles with different aromatic substituents were used (Scheme 2.19 and Table 2.6). The addition of the corresponding \( N \)-trimethylsilyl ketene imines, prepared as described above, to \( \alpha \)-\( O \)-protected hydroxyl aldehydes 31b and 31g was examined. Generally speaking, the aldol products were isolated in satisfactory yields, and both electron-poor and electron-rich ketene imines could be used.

![Scheme 2.19 Reaction of different aldehydes 31 with different asymmetric SKIs 20](image)

The main drawback in this last series was the lack of selectivity in the formation of the quaternary stereocentre bearing the cyano group, even though complete stereoselectivity in the formation of the C-3 stereocentre was retained. For the sake of simplicity, only a few examples of the products were fully characterized by X-ray single crystal analysis (Figure 2.4). For the other products, the configuration of the C-2 stereocentre was assigned arbitrarily.
Table 2.6. Different aldehydes 31 with asymmetric SKIs 20

<table>
<thead>
<tr>
<th>Entry</th>
<th>SKI#</th>
<th>R₁</th>
<th>Aldehyde</th>
<th>Products</th>
<th>dr(17/18)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>20b</td>
<td>4-BrC₆H₄</td>
<td>31b</td>
<td>45d/46d₇</td>
<td>55/45</td>
<td>54</td>
</tr>
<tr>
<td>2</td>
<td>20c</td>
<td>3-MeC₆H₄</td>
<td>31b</td>
<td>45b/46b₈,₉</td>
<td>52/48</td>
<td>65</td>
</tr>
<tr>
<td>3</td>
<td>20d</td>
<td>2-MeC₆H₄</td>
<td>31b</td>
<td>45c/46c</td>
<td>70/30</td>
<td>54</td>
</tr>
<tr>
<td>1</td>
<td>20e</td>
<td>4-MeC₆H₄</td>
<td>31b</td>
<td>45a/46a₈,₉</td>
<td>50/50</td>
<td>58</td>
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<tr>
<td>5</td>
<td>20f</td>
<td>4-OtMeC₆H₄</td>
<td>31b</td>
<td>45e/46e</td>
<td>50/50</td>
<td>65</td>
</tr>
<tr>
<td>9</td>
<td>20g</td>
<td>2-ClC₆H₄</td>
<td>31b</td>
<td>45i/46i</td>
<td>80/20</td>
<td>44</td>
</tr>
<tr>
<td>8</td>
<td>20h</td>
<td>3-pyridine</td>
<td>31b</td>
<td>45h/46h</td>
<td>65/35</td>
<td>67</td>
</tr>
<tr>
<td>6</td>
<td>20k</td>
<td>4- CF₃C₆H₄</td>
<td>31b</td>
<td>45f/46f₈</td>
<td>60/40</td>
<td>61</td>
</tr>
<tr>
<td>7</td>
<td>20j</td>
<td>4- NO₂C₆H₄</td>
<td>31b</td>
<td>45g/46g</td>
<td>64/36</td>
<td>57</td>
</tr>
<tr>
<td>12</td>
<td>20c</td>
<td>3-MeC₆H₄</td>
<td>31g</td>
<td>45j/46j₈</td>
<td>50/50</td>
<td>85</td>
</tr>
<tr>
<td>13</td>
<td>20h</td>
<td>3-Pyridine</td>
<td>31g</td>
<td>45k/46k</td>
<td>80/20</td>
<td>40</td>
</tr>
</tbody>
</table>

₇: The corresponding nitriles 19b (44%), 19c (76%), 19d (68%), 19e (67%), 19f (57%), 19g (47%), 19h (73%), 19j (78%), 19k (61%) and were prepared from the corresponding ketones by TosMic methodology. ₈: Because the lack of diastereo-selectivity and the difficulty in isolating the pure diastereoisomer by column chromatography, no effort was taken to attributed for each compound the right configuration. ₉: Identified as the corresponding mono-hydroxide derivatives 45a and 46a. ₈,₉: Identified as the corresponding mono-hydroxide derivatives 45b and 46b.

In conclusion we have developed a catalyst-free aldol-type reaction between a N-trimethylsilyl ketene imine and an O-protected 2-hydroxy aldehyde. The aldol products, already protected on the newly-formed hydroxy functionality as TMS-ethers, were isolated in high yields and with excellent selectivities under well-established reaction conditions, at least for the C-3 stereocentre. The transfer of the TMS-group from the ketene imine to the aldol product avoids any retro-reaction, which is well known to constitute a severe drawback in similar reactions. Even when a lower diastereoselectivity for the asymmetric C-2 quaternary carbon was observed, the stereochemical induction for C-3 remained very high.
Chapter 2

Figure 2.4 X-Ray structures of compounds 45e, 45i, 45k, 46g, 46h-monohydroxide derivative and 47

2.3 Conclusion

N-trimethylsilyl ketene imine has been successfully used in an un-catalyzed amidation reaction with isocyanates to prepare very useful α,α diaryl malonamides with reasonable to good yields; furthermore, a catalyst free asymmetric aldol procedure has been well established for preparation of optically pure β-hydroxyl nitriles with satisfied yield and, in some cases, excellent stereo control were achieved.
2.4 Experimental section

2.4.1 General method

Column chromatography was performed using Merck KGaA Silicagel 60 (230-400 Mesh-ASTM). Melting points were obtained using a Stuart Scientific SMP3 Melting Point apparatus. Optical rotations were obtained using a Unipol L1700 Schmidt+Haensch polarimeter. IR spectra were recorded on a Nicolet 380 FT-IR infrared spectrometer and Alpha Fourier-T Infrared Analysis Spectrometer (Bruker). NMR spectroscopy was performed on a Varian-Mercury 400 spectrometer using the residual signal of the solvent as the internal standard. The chemical shifts are reported in ppm and coupling constants (J) are reported in Hz. GC–MS spectra were recorded using Agilent Technologies 6850 and 5975 GC-Mass instrumentation. LC–MS spectra were obtained using an Agilent Technologies MSD1100 single-quadrupole mass spectrometer. The diastereomeric ratios reported into Tables 1, 2 and 3 have been calculated by HPLC (Agilent, Poroshell 120. SB-C18. 2.7µm, 3.0 x 100 mm) and ^1H NMR on the crude reaction mixture taking into account the undoubtful peaks of each diatereomer. Elemental analyses were obtained using Flash 2000, series CHNS/O Analyzer (Thermo Scientific).

2.4.2 Literature preparation of starting nitriles.

\[
\begin{align*}
\text{Scheme 2.20 Preparation of TOSMIC:} \\
\text{The preparation of N-(tosylmethyl)formamide 2'}
\end{align*}
\]

A stirred mixture of sodium p-toluenesulfinate (534 g, 3 mol), 1.5 L of water, 35% formaldehyde in water (700 ml, 4.4 mol), formamide (1.2 L, 30 mol), and formic acid(488g, 10.6mol) was heated to 90°C for 2 hours. Then the mixture was cooled to room temperature and then in ice-salt with continued stirring, then cooled to -20°C for overnight. The next day, white solid precipitate was
filtered, and then washed thoroughly with water, dried by vacuum at 70°C, g(yield 40%) product were obtained. The crude product was used to next step without purification.

\[ \text{N-(tosylmethyl)formamide } 2' \]

\[ \begin{align*}
2': {} & {} & \begin{align*}
\text{H NMR (400 MHz, CDCl}3\text{)} & \delta 8.08 (s, 1H), 7.79 (dd, J = 8.5, 2.0 Hz, 2H), 7.37 (d, J = 8.0 Hz, 2H), 6.34 (s, 1H), 4.70 (d, J = 6.9 Hz, 2H), 2.45 (s, 3H). \end{align*} \\
\text{13C NMR (100 MHz, CDCl}3\text{)} & \delta 159.98, 145.73, 133.44, 130.45, 130.04, 128.80, 58.63, 21.74. 
\end{align*} \]

The preparation of TOSMIC 3'

A stirred suspension (of crude N-tosylmethylformamide (214 g, 1mol), 500 ml of DME, 200 ml of anhydrous diethyl ether, and 700 ml(2.5 mol)of triethyl amine was cooled in ice-salt to -5°C. A solution of POCl₃ (100 ml.1.1 mol) in 60 ml of DME was added dropwise while keeping the temperature between-5 and 0 °C (about 1.5 h). During the dropping, brown suspension was generated. After stirring for 30min at 0 °C, 2.5 L. of ice--water was added with continued stirring. After 1hour stirring, the brown, crystalline solid was collected by filter, the crude product was dissolved into 600 ml toluene, removed the water by separating funnel, dried over Na₂SO₄, filter, the filtrate were warmed to 60°C, then petroleum ether was dropped to the hot toluene solution until the appearing of suspension from the solution. After 3 hours, g (yield 76%) of fine, light yellow solid was collected.

\[ \text{3': } \begin{align*}
\text{H NMR (400 MHz, CDCl}3\text{)} & \delta 7.89 (d, J = 8.4 Hz, 1H), 7.45 (dd, J = 8.6, 0.6 Hz, 1H), 4.58 (s, 1H), 2.50 (s, 2H). \end{align*} \\
\text{13C NMR (100 MHz, CDCl}3\text{)} & \delta 146.87, 132.00, 130.35, 129.43, 61.05, 21.81. 
\end{align*} \]

Scheme 2.21 Preparation of nitriles
Solid t-BuOK was added to a stirred and cooled solution of ketones and TosMIC in a mixture of DME(or DMSO) and 10 ml of EtOH(99%) while keeping the temperature under 10°C. Stirring was continued, the suspension thus obtained was cooled to room temperature with stirring for 18-24 hours. The precipitate (TosK) was removed and extracted with ether, the combined solutions were concentrated to and purified by flushing silicon chromatography with cyclohexane: acetone=100:1.

The preparation of 2-(4-bromophenyl)-2-phenylacetonitrile (19b)

Following general procedure, product 2-(4-bromophenyl)-2-phenylacetonitrile (19b) was prepared, yield: 44%. Known product. See ref\textsuperscript{31}. mp: 77-78 °C (ref\textsuperscript{31} 79-81 °C).

The preparation of 2-phenyl-2-(m-tolyl)acetonitrile (19c)

19c: Following general procedure, 2-phenyl-2-(m-tolyl)acetonitrile (19c) were prepared, yield: 76%. Known product. See ref\textsuperscript{32}. Semi-melted solid (ref\textsuperscript{32} m.p 26 °C): \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \( \delta \) 7.43 – 7.31 (m, 4H), 7.30 (s, 1H), 7.29 – 7.27 (m, 1H), 7.21 – 7.12 (m, 3H), 5.12 (s, 1H), 2.37 (s, 3H).

The preparation of 2-phenyl-2-(o-tolyl)acetonitrile (19d)

Following general procedure, 2-phenyl-2-(o-tolyl)acetonitrile (19d) were prepared, yield: 68%. 19d: Known product. See ref\textsuperscript{33}. Viscous material \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \( \delta \) 7.41 – 7.31 (m, 4H), 7.30 – 7.25 (m, 4H), 7.23 – 7.18 (m, 1H), 5.30 (s, 1H), 2.29 (s, 3H). \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) \( \delta \) 135.95, 133.61, 131.24, 129.08, 128.77, 128.56, 128.11, 127.74, 126.83, 39.90, 19.47.
The preparation of 2-phenyl-2-([p]-tolyl) acetonitrile (19e)

19e: Following general procedure, 2-phenyl-2-([p]-tolyl) acetonitrile (19e) were prepared, yield: 67%. Known product. See ref34. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.50 – 7.35 (m, 4H), 7.35 – 7.30 (m, 2H), 7.27 (d, $J = 8.0$ Hz, 2H), 5.20 (s, 1H), 2.44 (s, 3H).

The preparation of 2-(4-methoxyphenyl)-2-phenylacetonitrile (19f)

19f: Following general procedure, 2-(4-methoxyphenyl)-2-phenylacetonitrile (9f) were prepared, yield: 57%. Known product. See ref35. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.40 – 7.31 (m, 4H), 7.27 (d, $J = 3.8$ Hz, 1H), 7.25 – 7.22 (m, 1H), 6.96 – 6.80 (m, 2H), 5.10 (s, 1H), 3.80 (s, 3H).

The preparation of 2-(2-chlorophenyl)-2-phenylacetonitrile (19g)

Following general procedure, 2-(2-chlorophenyl)-2-phenylacetonitrile (19g) were prepared, yield: 50%.

19g: Known product. See ref34. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.54 – 7.47 (m, 1H), 7.45 – 7.41 (m, 1H), 7.39 – 7.29 (m, 7H), 5.65 (s, 1H).

The preparation of 2-phenyl-2-(pyridin-3-yl)acetonitrile (19h)

19h: Following general procedure, 2-phenyl-2-(pyridin-3-yl)acetonitrile (9h) were prepared, yield: 73%. Known product. See ref36. mp.63–65°C(ref. 60–61°C). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.64 – 8.55 (m, 2H), 7.72 – 7.64 (m, 1H), 7.45 – 7.27 (m, 6H), 5.18 (s, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$)
δ 152.10, 149.45, 148.68, 141.80, 132.02, 129.90, 129.41, 128.63, 128.24, 127.56, 123.92, 118.63, 40.17.

The preparation of 2,2-bis(4-methoxyphenyl)acetonitrile (19i)
Following general procedure, 2,2-bis(4-methoxyphenyl)acetonitrile (9i) were prepared, yield: 46%.

19i: Known product. See ref37. mp.149-151°C (ref. 148-149°C). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.25 – 7.20 (m, 4H), 6.92 – 6.84 (m, 4H), 5.05 (s, 1H), 3.80 (s, 6H).

The preparation of 2-(4-nitrophenyl)-2-phenylacetonitrile (19j)
Following general procedure, 2-(4-nitrophenyl)-2-phenylacetonitrile (19j) were prepared, yield: 78%.

19j: Known product. See ref38. mp.68-70°C (ref. 70-72°C). $^1$H NMR (400 MHz, CDCl$_3$) δ 8.28 – 8.19 (m, 2H), 7.55 (d, $J$ = 8.5 Hz, 2H), 7.47 – 7.29 (m, 5H), 5.25 (s, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 142.72, 134.38, 129.57, 128.90, 128.70, 127.69, 124.38, 118.44, 42.30.

The preparation of 2-phenyl-2-(4-(trifluoromethyl)phenyl)acetonitrile (19k)
Following general procedure, 2-phenyl-2-(4-(trifluoromethyl)phenyl)acetonitrile (19k) were prepared, yield: 61%.

19k: Known product. See ref39. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.64 (t, $J$ = 7.4 Hz, 2H), 7.49 (dd, $J$ = 8.1, 0.5 Hz, 2H), 7.44 – 7.31 (m, 5H), 5.20 (s, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 134.93, 129.42, 128.65, 128.13, 127.70, 126.22, 118.90, 42.37.
(S)-2-(tert-butyldimethylsilyloxy)propanal (3a), (S)-2-(benzoyloxy)propanal (3b), (S)-2-(triisopropylsilyloxy)propanal (3c), (S)-2-(tert-butyldiphenylsilyloxy)propanal (3d), (S)-2-(benzoyloxy)-3-methylbutanal (3e) and (S)-2-(tert-butyldimethylsilyloxy)-2-phenylacetaldehyde (3i) were prepared according to the general procedure of our group’s previous.40, 41 (R)-1-(2,2-dimethyl-1,3-dioxolan-4-yl)ethanone (3h) was prepared according to the reported procedure.42 2-(benzoyloxy)-3,3-dimethylbutanal (3g), 2-(tert-butyldimethylsilyloxy)-3,3-dimethylbutanal (3f), 2-(tert-butyldimethylsilyloxy)-2-(4-chlorophenyl)acetalddehyde (3j), 2-(tert-butyldimethylsilyloxy)-2-(4-methoxyphenyl)acetalddehyde (3k) were prepared according to the general procedure by Mildland41

2.4.3 Reaction of N-silylketene imines with isocyanates

**Method A; Typical Procedure**

2,2-Diphenylacetonitrile (19a) (193 mg, 1.0 mmol) in THF (2 ml) was added dropwise to a solution of n-BuLi (0.52 ml of a 2.5 M solution in n-hexane, 1.3 mmol) in THF (3 ml) at −78 °C. After 15 min, a solution of isocyanate 24a (164 mg, 1.1 mmol) in toluene (4 ml) was added dropwise at the same temperature. The resulting mixture was stirred at −78 °C for 2 h and then allowed to warm to r.t. over 6 h. Next, the reaction mixture was added dropwise to ice-cold sat. NH₄Cl solution (10 ml), and then extracted with EtOAc (3 × 20 ml). The combined organic phase was dried (Na₂SO₄), filtered and concentrated under vacuum. The crude residue was purified by flash chromatography (cyclohexane: Et₂O, 4:1) to give malonic amide 25a (120 mg, 35%) as a white solid.

**Method B; Typical Procedure**

2,2-Diphenylacetonitrile (19a) (193 mg, 1.0 mmol) in THF (1 ml) was added dropwise to a solution of n-BuLi (0.44 ml of a 2.5 M solution in n-hexane, 1.1 mmol) in THF (3 ml) at −78 °C. Next, a solution of TMSCl (120 mg, 1.1 mmol) in THF (1 ml) was added dropwise at −78 °C. After 15 min, a solution of isocyanate 24a (164 mg, 1.1 mmol) in toluene (1 ml) was added dropwise at −78 °C and the mixture allowed to warm to r.t. over 6–8 h. The reaction mixture was quenched by its addition to ice-cold sat. NH₄Cl solution (10 ml), and then extracted with EtOAc (3 × 20 ml). The combined organic phase was dried (Na₂SO₄), filtered and concentrated under vacuum. The crude residue was purified by flash chromatography (cyclohexane–Et₂O, 4:1) to give malonamide 25a (29 mg, 65%).
Method C; Typical Procedure
2,2-Diphenylacetonitrile (19a) (193 mg, 1.0 mmol) in THF (1 ml) was added dropwise to a solution of LDA (1.3 mmol), previously prepared from n-BuLi (0.52 ml of a 2.5 M solution in n-hexane, 1.3 mmol) and diisopropylamine (131 mg, 1.3 mmol) in THF (3 ml) at –78 °C. After 15 min, a solution of TMSCl (120 mg, 1.1 mmol) in THF (1 ml) was added dropwise to –78 °C. The resulting mixture was stirred for a further 15 min and then the solvent was removed in vacuo. The residue was dissolved in toluene (6 ml) at –78 °C and the isocyanate 24a (164 mg, 1.1 mmol) in toluene (2 ml) was added dropwise at the same temperature. The reaction temperature was maintained at –78 °C for 2 h and then allowed to warm to r.t. over 6–8 h. The reaction mixture was quenched by its addition to ice-cold sat. NH₄Cl solution (10 ml), and then extracted with EtOAc (3 × 20 ml). The combined organic phase was dried (Na₂SO₄), filtered and concentrated under vacuum. The crude residue was purified by silica gel column chromatography (cyclohexane–EtOAc, 95:5) to give 25a (243 mg, 71%).

Method D; Typical Procedure
A solution of n-BuLi (0.40 ml of a 2.5 M solution in n-hexane, 1.0 mmol) was added dropwise to a solution of diisopropylamine (100 mg, 1.0 mmol) in THF (3 ml) at –78 °C. After 5 min, a solution of 2,2-diphenylacetonitrile (19a) (193 mg, 1.0 mmol) in THF (1 ml) was added dropwise at –78 °C, followed by a solution of TBDMSCl (166 mg, 1.1 mmol) in THF (1 ml) at the same temperature. The mixture was stirred for 20 min at –78 °C and then allowed to warm to r.t. The solvent was removed in vacuo and the residue dissolved in anhydrous toluene (3 ml). After cooling to –78 °C, a solution of isocyanate 24a (164 mg, 1.1 mmol) in toluene (1 ml) was added dropwise at –78 °C. The resulting mixture was stirred at –78 °C for 6–8 h, then allowed to warm to r.t. and stirred at this temperature for 2 days. The reaction mixture was quenched by its addition to ice-cold sat. NH₄Cl solution (10 ml), and then extracted with EtOAc (3 × 20 ml). The combined organic phase was dried (Na₂SO₄), filtered and concentrated under vacuum. The starting nitrile 19a (97 mg, 61%) was recovered by flash chromatography (cyclohexane–Et₂O, 4:1). No trace of the target amide 25a was evident in the crude reaction mixture according to TLC, ¹H NMR and HPLC analyses.
The preparation of 2-Cyano-N-(4-methoxyphenyl)-2,2-diphenylacetamide (25a)

25a: White solid. mp: 99–110 °C. IR (KBr): 1043, 1692 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 3.80\) (s, 3 H), 6.86–6.90 (m, 2 H), 7.41–7.49 (complex pattern, 12 H), 7.78 (bs, 1 H, NH). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta = 55.66, 60.36, 94.42, 120.47, 110.17, 128.39, 129.24, 129.31, 129.82, 136.25, 157.14, 163.71\). GC–MS: \(m/z = 342\) [M\(^+\)]. Elemental Analysis: Calcd for C\(_{10}\)H\(_{18}\)N\(_2\)O\(_2\): C, 77.17; H, 5.30. Found: C, 77.32; H, 5.31.

The preparation of 2-(4-Bromophenyl)-2-cyano-N-(4-methoxyphenyl)-2-phenylacetamide (25b)

Starting from 2-(4-bromophenyl)-2-phenylacetonitrile (19b) (272 mg, 1.0 mmol) and isocyanate 24a white solid. (164 mg, 1.1 mmol), following Method C, malonamide 25b was obtained, after flash chromatography (cyclohexane–EtOAc, 4:1), as a light-yellow solid (273 mg, 65%).

25b: White solid. mp: 147–153 °C. IR (KBr): 1041, 1667 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 3.81\) (s, 3 H), 6.85–6.91 (m, 2 H), 7.33–7.41 (m, 2 H), 7.40–7.50 (complex pattern, 7 H), 7.54–7.58 (m, 2 H), 7.85 (bs, 1 H, NH). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta = 55.60, 59.57, 94.38, 120.02, 110.29, 92.58, 128.18, 129.42, 129.61, 130.10, 132.28, 135.33, 135.73, 157.48, 163.19\). LC–MS: \(m/z = 49\) [M + 1\(^+\)]. Elemental Analysis: Calcd for C\(_{10}\)H\(_{17}\)BrN\(_2\)O\(_2\): C, 62.72; H, 4.07. Found: C, 62.82; H, 4.08.

The preparation of 2-Cyano-N-(4-methoxyphenyl)-2-phenyl-2-(m-tolyl)acetamide (25c)

Starting from 2-phenyl-2-(m-tolyl)acetonitrile (19c) (207 mg, 1.0 mmol) and isocyanate 24a (164 mg, 1.1 mmol), following Method C, malonamide 25c was obtained, after flash chromatography (cyclohexane–EtOAc, 12:1), as a white solid (206 mg, 58%).
25c: White solid. mp 133–134 °C. IR (KBr): 1041, 1663 cm\(^{-1}\). \(^1^H\) NMR (400 MHz, CDCl\(_3\)): \(\delta = 2.31\) (s, 3 H), 3.73 (s, 3 H), 6.79–6.82 (m, 2 H), 7.15–7.17 (m, 2 H), 7.24 (d, \(J = 7.2\) Hz, 2 H), 7.34–7.41 (complex pattern, 7 H), 7.71 (bs, 1 H, NH). \(^1^3^C\) NMR (100 MHz, CDCl\(_3\)): \(\delta = 9.65, 55.62, 60.36, 94.37, 120.52, 110.14, 125.40, 128.39, 128.91, 129.14, 129.15, 129.85, 130.02, 136.07, 136.31, 139.25, 157.37, 163.80\). LC–MS: \(m/z = 357 [M + 1]^+\). Elemental Analysis: Calcd for C\(_{12}\)H\(_{20}\)N\(_2\)O\(_2\): C, 77.51; H, 5.66. Found: C, 77.63; H, 5.67.

The preparation of 2-Cyano-N-(4-methoxyphenyl)-2-phenyl-2-(o-tolyl)acetamide (25d)

Starting from 2-phenyl-2-(o-tolyl)acetonitrile (19d) (207 mg, 1.0 mmol) and isocyanate 24a (164 mg, 1.1 mmol), following Method C, malonamide 25d was obtained, after flash chromatography (cyclohexane: EtOAc, 12:1), as a light-yellow solid (108 mg, 64%).

25d: White solid. mp 125–129 °C. IR (KBr): 1045, 1686 cm\(^{-1}\). \(^1^H\) NMR (400 MHz, CDCl\(_3\)): \(\delta = 2.37\) (s, 3 H), 3.79 (s, 3 H), 6.87 (d, \(J = 8.8\) Hz, 2 H), 6.95 (d, \(J = 8.0\) Hz, 1 H), 7.17–7.19 (m, 1 H), 7.26–7.30 (m, 2 H), 7.39–7.55 (complex pattern, 7 H), 7.69 (bs, 1 H, NH). \(^1^3^C\) NMR (100 MHz, CDCl\(_3\)): \(\delta = 9.09, 55.66, 59.81, 94.45, 99.60, 110.10, 126.69, 128.12, 129.13, 129.33, 129.48, 129.51, 129.87, 132.82, 134.55, 135.08, 137.98, 157.43, 163.94\). LC–MS: \(m/z = 357 [M + 1]^+\). Elemental Analysis: Calcd for C\(_{12}\)H\(_{20}\)N\(_2\)O\(_2\): C, 77.51; H, 5.66. Found: C, 77.62; H, 5.67.

The preparation of 2-Cyano-N-(4-methoxyphenyl)-2-phenyl-2-(p-tolyl)acetamide (25e)

Starting from 2-phenyl-2-(p-tolyl)acetonitrile (19e) (207 mg, 1.0 mmol) and isocyanate 24a (164 mg, 1.1 mmol), following Method C, malonamide 25e was obtained, after flash chromatography (cyclohexane–EtOAc, 9:1), as a light-yellow solid (267 mg, 75%).

25e: White solid. mp 107–93 °C. IR (KBr): 1042, 1671 cm\(^{-1}\). \(^1^H\) NMR (400 MHz, CDCl\(_3\)): \(\delta = 2.12\) (s, 3 H), 3.63 (s, 3 H), 6.72–6.79 (m, 2 H), 7.07–7.09 (m, 2 H), 7.18–7.20 (m, 2 H), 7.25–7.32 (complex pattern, 7 H), 7.64 (bs, 1 H, NH). \(^1^3^C\) NMR (100 MHz, CDCl\(_3\)): \(\delta = 9.17, 55.57, 60.08, 94.32, 120.47, 110.12, 128.19, 128.31, 129.09, 129.19, 129.85, 129.94, 133.24, 136.38, 139.24,
The preparation of 2-Cyano-N,2-bis(4-methoxyphenyl)-2-phenylacetamide (25f)
Starting from 2-(4-methoxyphenyl)-2-phenylacetonitrile (19f) (104 mg, 1.0 mmol) and isocyanate 24a (164 mg, 1.1 mmol), following Method B, malonamide 25f was obtained, after flash chromatography (cyclohexane–EtOAc, 4:1), as a white solid (260 mg, 70%).

25f: White solid. mp: 96–120 °C.IR (KBr): 1043, 1666 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ = 3.80 (s, 3 H), 3.83 (s, 3 H), 6.87 (d, J = 8.8 Hz, 2 H), 6.95 (d, J = 8.8 Hz, 2 H), 7.36–7.49 (complex pattern, 9 H), 7.79 (bs, 1 H, NH). ¹³C NMR (100 MHz, CDCl₃): δ = 55.50, 55.60, 94.35, 94.59, 120.54, 110.12, 128.09, 128.26, 129.12, 129.64, 129.85, 136.51, 157.34, 160.9, 164.03. LC–MS: m/z = 373 [M + 1]+. Elemental Analysis: Calcd for C₁₂H₂₀N₂O₂: C, 77.51; H, 5.66. Found: C, 77.61; H, 5.67.

The preparation of 2-(2-Chlorophenyl)-2-cyano-N-(4-methoxyphenyl)-2-phenylacetamide (25g)
Starting from 2-(2-chlorophenyl)-2-phenylacetonitrile (19g) (107 mg, 1.0 mmol) and isocyanate 24a (164 mg, 1.1 mmol), following Method B, malonamide 25g was obtained, after flash chromatography (cyclohexane–EtOAc, 10:1), as a yellow solid (256 mg, 68%).

25g: White solid. mp: 167–169 °C. IR (KBr): 1042, 1670 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ = 3.80 (s, 3 H), 6.77 (dd, J₁ = 1.2 Hz, J₂ = 7.6 Hz, 1 H), 6.87–6.89 (m, 2 H), 7.20 (dt, J₁ = 1.2 Hz, J₂ = 7.2 Hz, 1 H), 7.37 (dt, J₁ = 1.2 Hz, J₂ = 7.2 Hz, 1 H), 7.42–7.45 (m, 2 H), 7.50–7.54 (m, 4 H), 7.68–7.70 (m, 2 H), 7.94 (bs, 1 H, NH). ¹³C NMR (100 MHz, CDCl₃): δ = 55.61, 59.08, 94.39, 98.80, 110.42, 127.19, 128.31, 129.61, 129.66, 129.92, 130.64, 131.01, 133.57, 134.78, 157.40, 163.12. GC–MS: m/z = 376 [M]+. Elemental Analysis: Calcd for C₁₀H₁₅ClN₂O₂: C, 70.12; H, 4.55. Found: C, 70.26; H, 4.56.
**The preparation of 2-Cyano-N-(4-methoxyphenyl)-2-phenyl-2-(pyridin-3-yl)acetamide (25h)**

Starting from 2-phenyl-2-(pyridin-3-yl)acetonitrile (19h) (194 mg, 1.0 mmol) and isocyanate 24a (164 mg, 1.1 mmol), following Method B, malonamide 25h was obtained, after flash chromatography (cyclohexane : EtOAc, 4:1), as a white solid (274 mg, 80%).

25g: White solid. mp: 91–95 °C. IR (KBr): 1046, 1697 cm⁻¹. \(^1\)H NMR (400 MHz, CDCl₃): \(\delta = 3.80\) (s, 3 H), 6.86–6.90 (m, 2 H), 7.34 (dd, \(J_1 = 4.8\) Hz, \(J_2 = 7.6\) Hz, 1 H), 7.45 (m, 7 H), 7.75 (m, 1 H), 8.16 (bs, 1 H, NH), 8.62 (dd, \(J_1 = 1.6\) Hz, \(J_2 = 4.8\) Hz, 1 H), 8.67 (d, \(J = 2.0\) Hz, 1 H). \(^{13}\)C NMR (100 MHz, CDCl₃): \(\delta = 55.46, 57.76, 94.26, 99.39, 110.30, 92.44, 127.88, 129.44, 132.39, 135.00, 136.10, 149.19, 149.97, 157.42, 162.71\). GC–MS: \(m/z = 344\) [M + 1]. Elemental Analysis: Calcd for C₁₀₆H₁₇N₁₂O₂: C, 73.45; H, 4.99. Found: C, 73.56; H, 5.00.

**The preparation of 2-Cyano-N,2,2-triphenylacetamide (25i)**

Starting from 2,2-diphenylacetonitrile (19a) (193 mg, 1.0 mmol) and isocyanate 24b (131 mg, 1.1 mmol), following Method C, malonamide 25i was obtained, after flash chromatography (cyclohexane : EtOAc, 4:1), as a white solid (108 mg, yield 73%).

25i: White solid. mp: 99–110 °C. IR (KBr): 1046, 1703 cm⁻¹. \(^1\)H NMR (400 MHz, CDCl₃): \(\delta = 7.10\) (m, 1 H), 7.34–7.43 (m, 2 H), 7.43–7.53 (complex pattern, 12 H), 7.85 (bs, 1 H, NH). \(^{13}\)C NMR (100 MHz, CDCl₃): \(\delta = 60.56, 120.31, 120.37, 125.71, 128.40, 129.31, 129.33, 129.35, 136.12, 136.78, 163.85, 178.88\). LC–MS: \(m/z = 313\) [M + 1]. Elemental Analysis: Calcd for C₉H₁₇N₂O: C, 80.75; H, 5.16. Found: C, 80.83; H, 5.17.

**The preparation of N-Benzyl-2-cyano-2,2-diphenylacetamide (25j)**
Starting from 2,2-diphenylacetonitrile (19a) (193 mg, 1 mmol) and isocyanate 24c (146 mg, 1.1 mmol), following Method B, malonamide 25j was obtained, after flash chromatography (cyclohexane: EtOAc, 4:1), as a white solid (164 mg, 50%).

25j: White solid. mp: 131–132 °C. IR (KBr): 1047, 1665 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ = 4.44 (d, J = 6.0 Hz, 2 H, CH₂), 6.64 (bs, 1 H, NH), 7.12–7.43 (complex pattern, 15 H). ¹³C NMR (100 MHz, CDCl₃): δ = 44.84, 59.61, 120.45, 127.81, 127.99, 128.31, 128.97, 128.31, 128.97, 129.05, 129.14, 136.31, 137.09, 165.84. LC–MS: m/z = 327 [M + 1]⁺. Elemental Analysis: Calcd for C₁₀H₁₈N₂O: C, 80.96; H, 5.56. Found: C, 80.88; H, 5.55.

The preparation of 2-Cyano-2,2-diphenyl-N-(1-phenylethyl)acetamide (25k)

Starting from 2,2-diphenylacetonitrile (19a) (193 mg, 1 mmol) and isocyanate 24d (162 mg, 1.1 mmol), following Method B, malonamide 25k was obtained, after flash chromatography (cyclohexane:EtOAc=4:1), as a white solid (265 mg, 78%).

25k: White solid. mp: 92–95 °C. IR (KBr): 2129, 1663 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ = 1.54 (d, J = 6.8 Hz, 3 H), 5.17 (quintet, J = 7.2 Hz, 1 H, CH), 6.54 (d, J = 7.6 Hz, 1 H, NH), 7.25–7.40 (complex pattern, 15 H). ¹³C NMR (100 MHz, CDCl₃): δ = 9.67, 50.53, 120.53, 126.12, 127.82, 128.24, 128.29, 128.90, 128.98, 129.05, 129.10, 136.31, 136.38, 142.13, 164.87. GC–MS: m/z = 340 [M]⁺. Elemental Analysis: Calcd for C₁₂H₂₀N₂O: C, 81.15; H, 5.92. Found: C, 81.03; H, 5.91.

The preparation of N-Benzyl-2-cyano-2-(4-methoxyphenyl)-2-phenylacetamide (25l)

Starting from 2-(4-methoxyphenyl)-2-phenylacetonitrile (19f) (104 mg, 1.0 mmol) and isocyanate 24c (146 mg, 1.1 mmol), following Method B, malonamide 25l was obtained, after flash chromatography (cyclohexane–EtOAc, 4:1), as a white solid (144 mg, 40%).

25l: White solid. mp: 132–134 °C. IR (KBr): 1042, 1658 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ = 3.82 (s, 3 H), 4.53 (d, J = 5.6 Hz, 2 H, CH₂), 6.63 (bs, 1 H, NH), 6.90–6.92 (m, 2 H), 7.12–7.42 (complex pattern, 12 H). ¹³C NMR (100 MHz, CDCl₃): δ = 44.79, 55.48, 58.98, 94.46, 120.58,
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127.79, 127.95, 128.9, 128.94, 128.96, 129.10, 129.57, 136.61, 137.15, 159.99, 166.16. LC–MS: $m/z = 357$ [M + 1]$^+$. Elemental Analysis: Calcd for C$_{12}$H$_{20}$N$_2$O$_2$: C, 77.51; H, 5.66. Found: C, 77.28; H, 5.65.

The preparation of 2-Cyano-\text{-}N\text{-}(2\text{-}methylphenyl)-2\text{-}phenyl-2\text{-}(pyridin\text{-}3\text{-}yl)acetamide (25m)

Starting from 2-phenyl-2\text{-}(pyridin\text{-}3\text{-}yl)acetonitrile (19h) (194 mg, 1.0 mmol) and 1-isocyanato-2-methylbenzene (24e) (133 mg, 1.1 mmol), following Method B, malonamide 25m was obtained, after flash chromatography (CH$_2$Cl$_2$–Et$_2$O, 5:1), as a white solid (1712 mg, 53%).

25m: White solid. mp: 120–125 °C. IR (neat): 2128, 1698 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$): $\delta =$ 2.15 (s, 3 H), 7.14–7.27 (m, 3 H), 7.35–7.38 (m, 1 H), 7.47–7.54 (m, 5 H), 7.79–7.85 (m, 2 H), 7.98 (bs, 1 H, NH), 8.65 (dd, $J_1 = 1.2$ Hz, $J_2 = 4.0$ Hz, 1 H), 8.73 (dd, $J_1 = 1.5$ Hz, $J_2 = 0.4$ Hz, 1 H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta =$ 17.28, 58.10, 99.39, 110.64, 92.52, 126.39, 126.39, 126.39, 126.98, 127.88, 129.41, 129.57, 129.61, 130.71, 132.34, 134.37, 135.03, 136.09, 149.24, 150.08, 162.90. LC–MS: $m/z = 328$ [M + 1]$^+$. Elemental Analysis: Calcd for C$_9$H$_{17}$N$_2$O: C, 77.04; H, 5.12. Found: C, 77.26; H, 5.24.

The preparation of 2-Cyano-N,2,2-tris(4-methoxyphenyl)acetamide (25n)

Starting from 2,2-bis(4-methoxyphenyl)acetonitrile (19i) (253 mg, 1.0 mmol) and isocyanate 24a (164 mg, 1.1 mmol), following Method B, malonamide 25n was obtained, after flash chromatography (cyclohexane–EtOAc, 4:1), as a white solid (244 mg, 61%).

25n: White solid. mp: 133–135 °C. IR (KBr): 1041, 1666 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$): $\delta =$ 3.80 (s, 3 H), 3.83 (s, 6 H), 6.85–6.88 (m, 2 H), 6.92–6.95 (m, 4 H), 7.36–7.43 (complex pattern, 6 H), 7.74 (bs, 1 H, NH). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta =$ 55.53, 55.63, 59.14, 94.38, 94.59, 120.71, 110.08, 128.43, 129.58, 129.93, 157.34, 160.09, 164.37. LC–MS: $m/z = 403$ [M + 1]$^+$. Elemental Analysis: Calcd for C$_{24}$H$_{10}$N$_2$O$_4$: C, 71.63; H, 5.51. Found: C, 71.87; H, 5.52.
The preparation of 2-cyano-N-(4-methoxyphenyl)-2-phenylbutanamide (29)
Starting from 2-phenylbutanenitrile (26) (145 mg, 1.0 mmol) and isocyanate 24a (164 mg, 1.1 mmol), following Method B, malonamide 29 was obtained, after flash chromatography (cyclohexane–EtOAc, 6:1), as a white solid (yield 12%).

29: White solid. mp: 73-74 °C. IR (KBr): 1042, 1667 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ 7.80 (d, J = 24.3 Hz, 1H), 7.67 – 7.58 (m, 2H), 7.51 – 7.30 (m, 5H), 6.91 – 6.76 (m, 2H), 3.77 (s, 3H), 2.77 – 2.43 (m, 1H), 2.33 – 2.08 (m, 1H), 1.10 (t, J = 7.4 Hz, 3H).

13C NMR (100 MHz, CDCl₃) δ 164.09, 157.02, 134.98, 129.69, 129.16, 128.79, 126.03, 122.25, 119.83, 114.05, 55.70, 55.35, 31.51, 9.87.

LC–MS: m/z = 295 [M + 1]⁺. Elemental Analysis: Calcd for . Found: C, 73.45; H, 6.16; N, 9.52; O, 10.87. Found: C, 73.59; H, 6.16.

2.4.4 Uncatalyzed asymmetric aldol reaction of N-silyl ketene imines

(S)-2-(tert-butyldimethylsilyloxy)propanal (3a), (S)-2-(benzylxoxy)propanal (3b), (S)-2-(triisopropylsilyloxy)propanal (3c), (S)-2-(tert-butyldiphenyl silyloxy)propanal (3d), (S)-2-(benzylxoxy)-3-methylbutanal (3e) and (S)-2-(tert-butyldimethylsilyloxy)-2-phenylacetalddehyde (3i) were prepared according to the general procedure of our group’s previous.⁴⁰, ⁴¹ (R)-1-(2,2-dimethyl-1,3-dioxolan-4-yl)ethanone (3h) was prepared according to the reported procedure.⁴² 2-(benzylxoxy)-3,3-dimethylbutanal (3g), 2-(tert-butyldimethyl silyloxy)-3,3-dimethylbutanal (3f), 2-(tert-butyldimethylsilyloxy)-2-(4-chloro phenyl)acetaldehyde (3j), 2-(tert-butyldimethylsilyloxy)-2-(4-methoxy phenyl) acetaldehyde (3k) were prepared according to the general procedure by Mildland⁴¹ except benzyl bromide was usedinstead of benzyl chloride in the preparation of aldehyde 3g.

The preparation of N-(2,2-diphenylvinylidene)-1,1,1-trimethylsilanamine 20a.
Trimethylsilyl ketene imine 20a was prepared according literature procedure.²,⁶,⁴³ In detail BuLi (1.23 mmol, 0.49 ml of 2.5M in n-hexane) was added to a THF solution (3 ml) of diisopropylamine (1.35 mmol, 0.19 ml) at -78°C under nitrogen atmosphere. Diphenylacetonitrile (238 mg, 1.23 mmol), dissolved in 1 ml of THF, was dropped into the base solution at -78°C. The colour of the reaction became yellow. After 5min, a solution of TMSCl (1.35 mmol, 0.17 ml) in
THF (1 ml) was added to the reaction mixture. A sample of the resulting keteneimine 20a was characterized by its IR, $^1$H and $^{13}$C NMR spectra.

**20a: IR (neat):** 2038 cm$^{-1}$. $^1$H NMR (400 MHz, C$_6$D$_6$): $\delta = 0.22$ (s, 9H), 7.12-7.24 (complex pattern, 2H), 7.37 (m, 4H), 7.62 (m, 4H). $^{13}$C NMR (100 MHz, C$_6$D$_6$): $\delta = -0.30$, 61.27, 124.74, 127.08, 129.24, 136.61, 180.63.

The Preparation of (3S, 4S)/(3R, 4S)-4-(tert-butyldimethylsilyloxy)-2,2-diphenyl-3-(trimethylsilyloxy)pentanenitriles 32a/33a from 20a.

**Method A:**
To the ketene imine 20a, a solution of (S)-2-(tert-butyldimethylsilyloxy)propanal 31a (231 mg, 1.23 mmol) in THF (1 ml) was added at r.t. The reaction was kept at r.t. overnight. The solvent was removed under vacuum to get the crude mixture which was purified by the flash chromatography (n-hexane: AcOEt= 50:1) to give 32a and 33a (32a: 285 mg, 33a: 9 mg, ratio: 32a/33a=97/3, overall yields 65%).

**Method B:**
To the ketene imine 20a, a solution of (S)-2-(tert-butyldimethylsilyloxy)propanal 31a (231 mg, 1.23 mmol) in THF (1 ml) was added at -78°C. The reaction was kept at this temperature for 3hrs, then it was left to reach r.t. spontaneously and kept overnight. The solvent was removed under vacuum to get the crude product which was purified by flash chromatography (n-hexane: AcOEt= 50:1) to give 32a and 33a (32a: 175 mg, 33a: 215 mg, ratio: 32a/33a=45/55, overall yields 70%).

Spectral data for (3S, 4S)-4-(tert-butyldimethylsilyloxy)-2,2-diphenyl-3-(trimethylsilyloxy)pentanenitrile 32a as follows:

32a: White solid. mp: 106-107 °C. $[\alpha]_D^20$: -16.80 (c: 1.0g/100 mg, CHCl$_3$). IR (neat): 2242 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$): $\delta = -0.16$ (s, 9H), -0.13 (s, 3H), -0.07 (s, 3H), 0.85 (s, 9H), 1.21 (d, $J = 6.4$ Hz, 3H), 3.42 (s, 3H), 7.22 (m, 4H), 7.42 (m, 4H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = -0.30$, 61.27, 124.74, 127.08, 129.24, 136.61, 180.63. 

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Hz, 3H), 4.16 (dq, J=2.8 Hz, J=6.4 Hz, 1H), 4.43 (d, J=2.8 Hz, 1H), 7.24-7.36 (m, 6H), 7.50 (d, J=7.2 Hz, 2H), 7.70 (d, J=7.6 Hz, 2H). $^{13}$C NMR (100 MHz, CDCl$_3$): δ =-4.41, -4.17, 0.12, 18.20, 22.00, 26.12, 57.35, 69.37, 81.88, 121.31, 127.62, 127.86, 128.16, 127.43, 127.50, 127.63, 127.86, 128.16, 127.43, 127.50, 127.50, 138.63, 139.04.

MS (EI): m/z= 438 [M-CH$_3$]. Elemental Analysis: Calcd. for C$_{26}$H$_{39}$NO$_2$Si$_2$: C, 68.82; H, 8.66; N, 3.09; Si, 12.38; Found: C, 68.92; H, 8.67;

The Preparation of (3S, 4S)-4-(tert-butyldimethylsilyloxy)-2,2-diphenyl-3-(trimethylsilyloxy)pentanenitrile 33a as follows:

33a: Colourless oil. $[a]$_D$^2$; +8.72 (c: 1.0g/100 mg, CHCl$_3$). IR (neat): 2242 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$): δ = -0.08 (s, 9H), -0.02 (s, 6H), 0.90 (s, 9H), 1.21 (d, J=7.0 Hz, 3H), 3.99 (dq, J=7.0 Hz, J=0.8 Hz, 1H), 4.66 (d, J=0.8 Hz, 1H), 7.23-7.41 (complex pattern, 6H), 7.49-7.57 (m, 4H). $^{13}$C NMR (100 MHz, CDCl$_3$): δ =-4.79, -4.20, -0.04, 17.98, 18.00, 25.89, 57.01, 69.90, 82.34, 121.27, 127.55, 127.67, 127.85, 128.04, 128.33, 128.84, 138.08, 138.85. MS (EI): m/z= 438 [M-CH$_3$]. Elemental Analysis: Calcd. for C$_{26}$H$_{39}$NO$_2$Si$_2$: C, 68.82; H, 8.66; N, 3.09; Si, 12.38; Found: C, 68.94; H, 8.68;

Spectral data for (3R, 4S)-4-(tert-butyldimethylsilyloxy)-2,2-diphenyl-3-(trimethylsilyloxy)pentanenitrile 33a as follows:

The Preparation of (3S, 4S)/(3R, 4S)-4-(benzyloxy)-2,2-diphenyl-3-(trimethylsilyloxy)pentanenitriles 32b and 33b

Following Method A starting from diphenylacetonitrile (193 mg, 1.0 mmol) and (S)-2-(Benzyloxy)propanal 31b (164 mg, 1.0 mmol), product 32b (356 mg, yield: 83%) was isolated as single diastereoisomer after the flash chromatography (cyclohexane: ether= 7:1). Following Method B starting from diphenylacetonitrile (193 mg, 1.0 mmol) and (S)-2-(Benzyloxy)propanal 31b (164 mg, 1.0 mmol), 32b and 33b were obtained as the crude reaction mixture. This mixture was purified by flash chromatography (cyclohexane: ether= 7:1). From this step 32b was isolated as siloxyl derivative (219 mg, yield: 51%), whereas 33b was isolated as the corresponding mono-hydroxide derivative 33b$^1$ (86 mg, yield: 24%, ratio: 32b/33b$^1$=68/32). As a matter of fact, hydrolysis of the trimethylsilyloxy group occurred during the flash chromatography. It must be stressed out that this one was a single case
Spectral data for (3S, 4S)-4-(benzyl oxy)-2,2-diphenyl-3-(trimethylsilyloxy)pentanenitrile 32b as follow:

32b: White solid, mp: 93-94 ºC. [α]D 20°: +10.36 (c: 1.1g/100 mg, CHCl3). IR (neat): 2246 cm⁻¹. ¹H NMR (400 MHz, CDCl3): δ =-0.22 (s, 9H), 1.11 (d, J=6.4 Hz, 3H), 3.68 (m, 1H), 4.26 (d, J=12.0 Hz, 1H), 4.38 (d, J=12.0 Hz, 1H). 4.52 (d, J=4.4 Hz, 1H), 7.19-7.35 (m, 11H), 7.44 (d, J=7.2 Hz, 2H), 7.70 (d, J=7.6 Hz, 2H). ¹³C NMR (100 MHz, CDCl3): δ = 0.15, 17.31, 57.21, 71.02, 76.07, 81.46, 121.47, 127.23, 127.66, 127.80, 127.88, 128.09, 128.14, 128.59, 128.69, 137.99, 138.39, 138.70. MS (ESI): m/z = 430 [M+H⁺]. Elemental Analysis: Calcd. for C₂₇H₃₃NO₂Si: C, 75.48, H, 7.27, N, 3.26, Si, 6.54, Found: C, 75.78, H, 7.29.

Spectral data for (3R, 4S)-4-(benzyl oxy)-2,2-diphenyl-3-hydroxy pentanenitrile 33b

33b: Colourless oil. [α]D 20°: +131.1 (c:10 g/100 mg, CHCl3). IR (neat): 2238 cm⁻¹. ¹H NMR (400 MHz CDCl3): δ =1.18 (d, J=6.4 Hz, 3H), 3.49 (d, J=9.2 Hz, 1H, OH), 3.55 (dq, J₁=2.0 Hz, J₂=6.4 Hz, 1H), 4.39 (dd, J₁=2.0 Hz, J₂=8.8 Hz,1H), 4.41 (d, J=10.8 Hz, 1H), 4.51 (d, J=10.8 Hz, 1H), 7.27-7.39 (m, 13H), 7.56 (d, J=8.8 Hz, 2H). ¹³C NMR (100 MHz, CDCl3): δ = 17.96, 56.94, 71.17, 72.58, 77.47, 120.85, 127.27, 127.83, 127.85, 128.00, 128.02, 128.19, 128.35, 128.66, 129.02, 137.39, 138.59, 139.22. MS (ESI): m/z =380 [M+Na⁺]. Elemental Analysis: Calcd. for C₂₄H₂₃NO₂: C, 80.64, H, 6.49, N, 3.92, Found: C, 80.88, H, 6.51.

The Preparation of (3S, 4S)/(3R, 4S)-2,2-diphenyl-4-(triisopropylsilyloxy)-3-(trimethylsilyloxy)pentanenitriles 32c/33c.

Method A: BuLi (1.1 mmol, 0.44ml of 2.5M in n-hexane) was added into a solution of diisopropylamine (1.21 mmol, 0.155ml) in 3 ml of THF at -78ºC. Then a solution of diphenylacetonitrile (212 mg, 1.1 mmol) in THF (1 ml) was dropped into the base solution at -78ºC. The colour of the reaction becomes yellow. After 5 min, a solution of TMSCl (0.14ml, 1.1
mmol) in 1 ml of THF was added to the reaction. The reaction mixture was allowed to reach r.t. spontaneously. A solution of (S)-2-(triisopropylsilyloxy)propanal 31c (253 mg, 1.1 mmol) in THF (1 ml) was dropped. The reaction was kept at r.t. overnight. The solvent was removed under vacuum to get a crude mixture which was purified by flash chromatography (hexane: CH₂Cl₂ = 7:1) to get pure compounds 32c and 33c (32c: 381, 33c: 163 g, total yield: 75%, ratio: 32c/33c = 70/30)

**Method B:** Following this method a 5/95 ratio 32c/33c in 85% overall yields were obtained.

Spectral data for (3S, 4S)-2,2-diphenyl-4-(triisopropylsilyloxy)-3-(trimethylsilyloxy)pentanenitrile 32c as follow:

32c: White solid; mp: 67-73 °C. [α]_D^20 = -12.0 (c: 1.0 g/100 mg, CHCl₃). IR (neat): 2239 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ = -0.16 (s, 9H), 0.97-1.01 (Complex pattern, 21H), 1.26 (d, J=6.4 Hz, 3H), 4.31 (dq, J₁=2.4 Hz, J₂=6.4 Hz, 1H), 4.53 (d, J=2.4 Hz, 1H), 7.22-7.36 (complex pattern, 6H), 7.51 (m, 2H), 7.54 (m, 2H). ¹³C NMR (100 MHz, CDCl₃): δ = 0.07, 13.09, 18.09, 18.15, 18.23, 21.26, 57.14, 70.32, 81.63, 121.15, 127.58, 127.63, 127.90, 128.10, 128.41, 128.45, 128.60, 139.13. MS: m/z = 495 [M]. Elemental Analysis: Calcd. for C₂₉H₄₅NO₂Si₂: C, 70.25; H, 9.15; N, 2.82; O, 6.45; Si, 11.33; Found: C, 70.38; H, 9.17.

Spectral data for (3R, 4S)-2,2-diphenyl-4-(triisopropylsilyloxy)-3-(trimethylsilyloxy)pentanenitriles 33c.

33c: Colourless oil. [α]_D^20 = -7.4 (c: 1.0 g/100 mg, CHCl₃). IR (neat): 2238 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ = -0.06 (s, 9H), 1.01 (Complex pattern, 21H), 1.25 (d, J=6.4 Hz, 3H), 4.02 (dq, J₁=0.8 Hz, J₂=6.4 Hz, 1H), 4.77 (d, J=0.8 Hz, 1H), 7.29-7.38 (complex pattern, 6H), 7.51 (m, 2H), 7.56 (m, 2H). ¹³C NMR (100 MHz, CDCl₃): δ = 0.13, 12.44, 18.05, 18.15, 18.21, 57.34, 69.85, 82.46, 121.27, 127.44, 127.77, 127.94, 127.80, 128.43, 128.88, 137.98, 138.57. MS: m/z = 495 [M]. Elemental Analysis: Calcd. for C₂₉H₄₅NO₂Si₂: C, 70.25; H, 9.15; N, 2.82; O, 6.45; Si, 11.33; Found: C, 70.42; H, 9.17.
The Preparation of \((3S, 4S)/(3R, 4S)-4-(\textit{tert}-\text{butyldiphenylsilyloxy})-2,2\text{-diphenyl}-3-(\textit{trimethylsilyloxy})\text{pentanenitrile} \ 32d/33d\).

**Method A:** Following Method A, starting from diphenylacetonitrile (386 mg, 2.0 mmol) and \((S)-2-(\textit{tert}-\text{butyldiphenylsilyloxy})\text{propanal} \ 31d\) (624 mg, 2.0 mmol), products \(32d\) and \(33d\) were obtained by the flash chromatography (petroleum ether:ether = 20:1) \((32d: 750 \text{ mg}, 33d: 404 \text{ mg}, \text{ total yield: } 62\%, \text{ ratio: } 32d/33d=65/35)\).

**Method B:** Following this method a 1/99 ratio \(32d/33d\) in 67% overall yields were obtained.

Spectral data for \((3S, 4S)-4-(\textit{tert}-\text{butyldiphenylsilyloxy})-2,2\text{-diphenyl}-3-(\textit{trimethylsilyloxy})\text{pentanenitrile} \ 32d\) as follow:

\(32d:\) White solid. mp:112-116\(^\circ\)C. \([\alpha]_D^{20} = -7.10 \ (c: 1.0g/100 \text{ mg, CHCl}_3). \text{ IR (neat): } 2248 \text{ cm}^{-1}.^1\text{H NMR (400 MHz, CDCl}_3): \delta = -0.23 \ (s, 9H), 0.87 \ (d, J=6.8 \text{ Hz, 3H}), 0.94 \ (s, 9H), 4.08 \ (dq, J_1=1.6 \text{ Hz, } J_2=6.8 \text{ Hz, 1H}), 4.50 \ (d, J=1.6 \text{ Hz, 1H}), 7.19-737 \ (\text{complex pattern, 15H}), 7.57-7.71 \ (m, 5H). ^{13}\text{C NMR (100 MHz, CDCl}_3): \delta = 0.04, 19.17, 20.86, 26.78, 57.67, 71.09, 81.47, 121.11, 12719, 127.53, 127.63, 127.64, 127.75, 127.78, 128.63, 129.29, 129.47, 133.28, 134.90, 135.57, 135.99, 138.22, 139.73. \text{ MS: m/z=600 [M+Na}^+]. \text{ Elemental Analysis: Calcd. For C}_{36}\text{H}_{43}\text{NO}_2\text{Si}_2: C, 74.82; H, 7.50; N, 2.42; Si, 9.72; Found: C, 75.04; H, 7.52.

Spectral data for \((3R, 4S)-4-(\textit{tert}-\text{butyldiphenylsilyloxy})-2,2\text{-diphenyl}-3-(\textit{trimethylsilyloxy})\text{pentanenitrile} \ 33d\) as follow:

\(33d:\) White solid. mp:142-145\(^\circ\)C. \([\alpha]_D^{20} = -2.80 \ (c: 1.0g/100 \text{ mg, CHCl}_3). \text{ IR (neat): } 2240 \text{ cm}^{-1}.^1\text{H NMR (400 MHz, CDCl}_3): \delta = 0.05 \ (s, 9H), 1.08 \ (d, J=6.4 \text{ Hz, 3H}), 1.10 \ (s, 9H), 3.92 \ (q, J=6.0 \text{ Hz, 1H}), 4.89 \ (s, 1H), 7.11-7.59 \ (m, 20H). ^{13}\text{C NMR (100 MHz, CDCl}_3): \delta = 0.14, 17.89, 19.00, 27.06, 57.51, 71.10, 82.17, 121.02, 127.35, 127.40, 127.49, 127.66, 127.72, 127.82, 128.39, 128.78, 129.63, 133.47, 133.71, 135.71, 135.85, 135.97, 137.34, 138.91. \text{ MS: m/z= 600 [M+Na}^+].
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Elemental Analysis: Calcd. for C$_{36}$H$_{43}$NO$_2$Si$_2$: C, 74.82; H, 7.50; N, 2.42; Si, 9.72; Found: C, 75.00; H, 7.52.

The Preparation of (3S, 4S)-3,4-dihydroxy-2,2-diphenyl pentanenitrile 34a;
1 ml of 1M HCl was added into a solution of (3S, 4S)-4-(tert-butyldimethylsilyloxy)-2,2-diphenyl-3-(trimethylsilyloxy)pentanenitrile 32a (180 mg, 0.4 mmol) in acetonitrile (6ml). The reaction mixture was kept at r.t for 0.5hr. Then the solvent was removed under vacuum to get pure 34a as colourless oil (110 mg, yield: 95%)

34a: Colorless oil. [$\alpha$]$_D$: +78.45 (c: 1.1g/100 mg, CHCl$_3$). IR (neat): 2239 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$):$\delta$ =1.22 (d, J=6.4 Hz, 3H), 1.92 (bs, 1H, OH), 3.37 (bs, 1H, OH), 4.00 (dq, $J_1$=6.4 Hz, $J_2$=1.2 Hz, 1H), 4.39 (d, $J$=1.2 Hz, 1H), 7.31-7.45 (m, 8H), 7.56 (m, 2H). $^{13}$C NMR (100 MHz, CD$_3$OD): $\delta$ =21.65, 58.36, 67.61, 77.68, 122.89, 128.59, 128.91, 129.11, 129.21, 129.84, 130.12, 140.77, 141.77. MS (ESI): m/z=290 [M+Na$^+$]. Elemental Analysis: Calcd. for C$_{17}$H$_{17}$NO$_2$: C, 76.38; H, 6.41; N, 5.24; O, 11.97; Found: C, 76.50; H, 6.42.

The Preparation of (3R, 4S)-3,4-dihydroxy-2,2-diphenylpentanenitrile 34b
Starting from (3R,4S)-4-(tert-butyldimethylsilyloxy)-2,2-diphenyl-3-(trimethylsilyloxy) pentanenitrile 33a (30 mg, 0.07 mmol), following the same procedure for preparing compound 34a, compound 34b was obtained (16 mg, yield:89%).

34b: Colorless oil. [$\alpha$]$_D$: -69.60 (c: 1.0g/100 mg, CHCl$_3$). IR (neat): 2243 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 1.35 (d, J=6.4 Hz, 3H), 1.69 (bs, 1H, OH), 2.50 (bs, 1H, OH), 3.77 (dq, $J_1$=4.0 Hz, $J_2$=6.4 Hz, 1H), 4.69(d, $J$=4.0 Hz, 1H), 7.30-7.46 (complex pattern, 8H), 7.60 (m, 2H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ =17.94, 55.83, 68.32, 77.58, 120.61, 127.07, 127.61, 128.27, 128.31, 129.05, 129.19, 137.36, 138.24. MS (ESI): m/z= 290 [M+Na$^+$]. Elemental Analysis: Calcd. for C$_{17}$H$_{17}$NO$_2$: C, 76.38; H, 6.41; N, 5.24; O, 11.97; Found: C, 76.48; H, 6.42.

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The Preparation of 2,2-diphenyl-2-[(4S, 5S)-2,2,5-trimethyl-1,3-dioxolan-4-yl]acetonitrile 35a

(3S, 4S)-3,4-dihydroxy-2,2-diphenylpentanenitrile 34a (0.44 mmol, 117 mg), PPTS (0.88 mmol, 220 mg) and 2,2-dimethoxypropane (1.0 ml) were mixed together into 5 ml of anhydrous acetone. The reaction mixture was kept stirring at r.t. overnight, decomposed with saturated NH₄Cl solution, extracted with AcOEt (15 ml × 3). The organic phase was dried with anhydrous Na₂SO₄ and concentrated under vacuum to get the crude product which was purified by flash chromatography (cyclohexane : ether = 4:1) to get product 35a (86 mg, yield: 63%).

35a: White solid. mp: 120-124°C. \([\alpha]_D^{20} +3.30\) (c: 1.0 g/100 mg, CHCl₃). IR (KBr): 2247 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): \(\delta = 0.57\) (d, \(J = 6.0\) Hz, 3H), 1.49 (s, 3H), 1.52 (s, 3H), 4.20 (dq, \(J_1 = 6.0\) Hz, \(J_2 = 8.4\) Hz, 1H), 4.41 (d, \(J = 8.4\) Hz, 1H), 7.30-7.41 (complex pattern, 8H), 7.53 (m, 2H). ¹³C NMR (100 MHz, CDCl₃): \(\delta = 18.47, 26.73, 27.83, 55.56, 74.93, 83.71, 109.18, 120.29, 127.25, 128.13, 128.25, 128.76, 129.00, 137.03, 138.92\). MS: m/z = 330 [M+Na⁺]. Elemental Analysis: Calcd. for C₂₀H₂₁NO₂: C, 78.15, H, 6.89, N, 4.56, Found: C, 78.29, H, 6.90

The Preparation of 2,2-diphenyl-2-[(4R, 5S)-2,2,5-trimethyl-1,3-dioxolan-4-yl]acetonitrile 35b

(3R, 4S)-3,4-dihydroxy-2,2-diphenyl pentanenitrile 34b (0.15 mmol, 41 mg), PPTS (0.30 mmol, 75 mg) and 2,2-dimethoxypropane (0.6 ml) were mixed together into 5 ml of anhydrous acetone. The reaction mixture was processed as for 35a. The crude product was purified by flash chromatography (cyclohexane : ether = 4:1) to get product 35b (35 mg, yield: 74%).

35b: White solid. mp: 107-110°C. \([\alpha]_D^{20} +99.4\) (c: 1.0 g/100 mg, CHCl₃). IR (KBr): 2247 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): \(\delta = 1.17\) (d, \(J = 6.4\) Hz, 3H), 1.43 (s, 3H), 1.64 (s, 3H), 4.38 (quintet, \(J = 6.4\) Hz, 1H), 5.07 (d, \(J = 6.4\) Hz, 1H), 7.25-7.40 (complex pattern, 6H), 7.56 (m, 4H). ¹³C NMR (100 MHz, CDCl₃): \(\delta = 16.75, 25.63, 27.77, 53.37, 74.39, 80.28, 108.75, 120.96, 127.23, 127.51, 128.13, 128.25, 128.76, 129.00, 137.03, 138.92\). MS: m/z = 330 [M+Na⁺]. Elemental Analysis: Calcd. for C₂₀H₂₁NO₂: C, 78.15, H, 6.89, N, 4.56, Found: C, 78.29, H, 6.90

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127.98, 128.42, 128.81, 129.27, 137.45, 140.35. MS: m/z=330 [M+Na⁺]. Elemental Analysis: Calcd. for C₂₀H₂₁NO₂: C, 78.15; H, 6.89; N, 4.56; O, 10.41; Found: C, 78.26; H, 6.90

**The Preparation of (3S, 4S)-4-hydroxy-2,2-diphenyl-3-(trimethylsilyloxy)pentanenitrile 34a from 32b.**

(3S, 4S)-4-(benzylxy)-2,2-diphenyl-3-(trimethylsilyloxy)pentanenitrile 32b (90 mg), Pd/C 10% (90 mg) and Pd(AcO)₂ (40 mg) were mixed into 20 ml of anhydrous MeOH. The reaction mixture was kept under H₂ (50psi) for 1 hour. Then the reaction mixture was filtered and the solvent was removed to get crude product. This crude product was directly mixed with 2 ml of acetonitrile and 1 ml of HClₐq (1N). The reaction was kept at r.t for 30mins. Then the solvent was removed under vacuum to give a colourless oil product which showed a superimposable spectral data with the authentic 34a obtained as previously described (see above).

**The Preparation of (3S, 4S)-4-hydroxy-2,2-diphenyl-3-(trimethylsilyloxy)pentanenitrile 34a from 34c and 32d**

1 ml of 1M HCl was added into a solution of 32c (198 mg, 0.4 mmol) in acetonitrile (6ml). The reaction mixture was kept at r.t for 0.5hr. Then the solvent was removed under vacuum to get pure 34a as colourless oil (100 mg, yield: 87%). Starting from 32d (230 mg, 0.4 mmol) following the same procedure above described compound 34a was obtained (95 mg, 82%).

**The Preparation of (3S, 4S)-4-(benzylxy)-5-methyl-2,2-diphenyl-3-(trimethylsilyloxy)hexanenitrile 32e.**

Following Method A, starting from diphenylacetonitrile (193 mg, 1.0 mmol) and (S)-2-(benzyloxy)-3-methylbutanal 31e (211 mg, 1.1 mmol), (3S, 4S)-4-(benzylxy)-5-methyl-2,2-diphenyl-3-(trimethylsilyloxy)hexanenitrile 32e was obtained after flash chromatography (hexane : ether =8:1) (311 mg; yield:68%).
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Spectral data for (3S, 4S)-4-(benzoyloxy)-5,5-dimethyl-2,2-diphenyl-3-(trimethylsilyloxy)hexanenitrile 32e as follow:

32e: White solid; mp: 86-93 °C. [α]D20: +3.80(c: 1.0g/100 mg, CHCl3). IR (neat): 2240 cm⁻¹. ¹H NMR (400 MHz, CDCl3): δ = -0.20 (s, 9H), 0.80 (d, J=6.4 Hz, 3H), 0.93 (d, J=6.4 Hz, 3H), 1.62 (m, 1H), 3.37 (dd, J₁=4.4 Hz, J₂=5.6 Hz, 1H), 4.33 (d, J=11.6 Hz, 1H), 4.47 (d, J=11.6 Hz, 1H), 4.69 (d, J=4.4 Hz, 1H), 7.18-7.37 (Complex pattern, 11H), 7.49 (m, 2H), 7.75 (m, 2H). ¹³C NMR (100 MHz, CDCl3): δ = 0.42, 17.41, 20.41, 31.06, 58.57, 73.77, 79.00, 83.39, 121.01, 127.59, 127.86, 127.98, 128.02, 128.54, 128.58, 128.80, 137.79, 138.22, 139.00. MS (EI): m/z=458 [M+1]. Elemental Analysis: Calcd. for C₂₉H₅₆NO₂Si: C, 76.10; H, 7.71; N, 3.06; Si, 6.14; Found: C, 76.37; H, 7.74

The Preparation of (3S*, 4S*)-4-(benzoyloxy)-5,5-dimethyl-2,2-diphenyl-3-(trimethylsilyloxy)hexanenitrile 32g.

Following Method A, starting from diphenylacetonitrile (290 mg, 1.5 mmol) and 2-(benzoyloxy)-3,3-dimethylbutanal 31g (309 mg, 1.5 mmol), (3S*, 4S*)-4-(benzoyloxy)-5,5-dimethyl-2,2-diphenyl-3-(trimethylsilyloxy)hexanenitrile 32g was obtained after purification by the flash chromatography (hexane : ether = 9:1) (459 mg; yield:65%)

Spectral data for (3S*, 4S*)-4-(benzoyloxy)-5,5-dimethyl-2,2-diphenyl-3-(trimethylsilyloxy)hexanenitrile 32g as follow:

32g: Colourless oil. IR (neat): 2238 cm⁻¹. ¹H NMR (400 MHz, CDCl3): δ = -0.16 (s, 9H), 0.97 (s, 9H), 3.30 (d, J=1.2 Hz, 1H), 3.99 (d, J=11.2 Hz, 1H), 4.18(d, J=11.2 Hz, 1H), 5.02 (d, J=1.2 Hz, 1H), 7.19-7.38 (Complex pattern, 11H), 7.47 (m, 2H), 7.83 (m, 2H). ¹³C NMR (100 MHz, CDCl3): δ = 1.10, 27.18, 37.01, 58.96, 73.96, 77.42, 84.06, 122.24, 126.66, 126.75, 127.83, 128.04, 128.28, 128.36, 128.51, 128.74, 129.27, 136.64, 139.02, 139.66. MS (EI): m/z=472 [M+1]. Elemental Analysis: Calcd. for C₃₀H₇₀NO₂Si: C, 76.39; H, 7.91; N, 2.97; Si, 5.95; Found: C, 76.52; H, 7.92

The Preparation of (R)-3-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-diphenyl-3-(trimethylsilyloxy)propanenitrile 4h and (S)-3-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-diphenyl-3-(trimethylsilyloxy)propanenitrile 33h.

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Following Method A, starting from diphenylacetonitrile (290 mg, 1.5 mmol) and (R)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde 31h (195 mg, 1.5 mmol), a mixture of (R)-3-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-diphenyl-3-(trimethylsilyloxy)propanenitrile 32h and (S)-3-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-diphenyl-3-(trimethylsilyloxy)propanenitrile 33h was obtained after flash chromatography (petroleum ether : ether = 5:1) (480 mg in a ratio, determined by $^1$H NMR, 32h/33h of 9:1). Crystallization (CH$_3$CN/MeOH/H$_2$O) allowed to give pure 32h and 33h.

Spectral data for (R)-3-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-diphenyl-3-(trimethylsilyloxy)propanenitrile 32h as follow:

32h: White solid. mp: 110-114 °C. $[\alpha]_D^2$ = -67.1 (c: 1.0g/100 mg, CHCl$_3$). IR (neat): 2246 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = -0.04 (s, 9H), 1.30 (s, 3H), 1.39 (s, 3H), 3.17 (dd, $J_1$ = 8.4 Hz, $J_2$ = 9.2 Hz, 1H), 3.28 (dd, $J_1$ = 5.2 Hz, $J_2$ = 8.4 Hz, 1H), 4.15 (m, 1H), 4.58 (d, $J$ = 8.0 Hz, 1H), 7.27-7.45 (m, 8H), 7.64 (d, $J$ = 7.6 Hz, 2H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 0.32, 25.73, 26.56, 57.11, 66.10, 78.35, 78.85, 108.04, 120.78, 127.54, 127.82, 128.04, 128.38, 128.65, 128.80, 129.05, 129.17, 137.11, 137.20. MS (ESI): m/z = 418 [M+Na$^+$]. Elemental Analysis: Calcd. for C$_{23}$H$_{29}$NO$_3$Si: C, 69.84; H, 7.39; N, 3.54; O, 12.13; Si, 7.10; Found: C, 69.92; H, 7.40.

Spectral data for (S)-3-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-diphenyl-3-(trimethylsilyloxy)propanenitrile 33h as follow:

33h: White solid. mp: 100-106 °C. $[\alpha]_D^2$ = -21.4 (c: 1.0g/100 mg, CHCl$_3$). IR (neat): 2241 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = -0.13 (s, 9H), 1.24 (s, 3H), 1.45 (s, 3H), 3.71 (dd, $J_1$ = 6.4 Hz, $J_2$ = 8.0 Hz, 1H), 3.99 (t, $J$ = 8.0 Hz, 1H), 4.33 (ddd, $J_1$ = 6.8 Hz, $J_2$ = 1.2 Hz, $J_3$ = 0.4 Hz, 1H), 5.02 (d, $J$ = 1.2 Hz, 1H), 7.30-7.41 (m, 6H), 7.49-7.54 (m, 4H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 0.13, 24.60, 26.29, 57.21, 63.76, 76.60, 77.67, 107.71, 121.22, 127.62, 127.88, 127.99, 128.25, 128.40, 128.85, 129.25.
129.22, 129.34, 137.68, 137.98. MS (ESI): m/z= 418 [M+Na\(^+\)]. Elemental Analysis: Calcd. for C\(_{23}\)H\(_{29}\)NO\(_2\)Si: C, 69.84; H, 7.39; N, 3.54; O, 12.13; Si, 7.10; Found: C, 69.80; H, 7.39.

The Preparation of (3S, 4S)-4-(tert-butyldimethylsilyloxy)-2,2,4-triphenyl-3-(trimethylsilyloxy)butanenitrile 32i.

Following Method A, starting from diphenylacetonitrile (193 mg, 1.0 mmol) and (S)-2-(tert-butyldimethylsilyloxy)-2-phenylacetaldehyde 31i (250 mg, 1.0 mmol), (3S, 4S)-4-(tert-butyldimethylsilyloxy)-2,2,4-triphenyl-3-(trimethylsilyloxy)butanenitrile 32i was obtained after flash chromatography (hexane : ether = 98:2)(402 mg; yield:78%).

Spectral data for (3S, 4S)-4-(tert-butyldimethylsilyloxy)-2,2,4-triphenyl-3-(trimethylsilyloxy)butanenitrile 32i as follow:

32i: White solid; mp: 135-137 °C. \([\alpha]_D^{20}: -4.45 \) (c: 1.1g/100 mg, CHCl\(_3\)). IR (neat): 2247 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 0.49\) (s, 9H), \(-0.46\) (s, 3H), \(-0.28\) (s, 3H), \(0.91\) (s, 9H), \(4.77\) (d, \(J=2.4\) Hz, 1H), \(5.08\) (d, \(J=2.4\) Hz, 1H), \(7.27\) - \(7.37\) (m, 11H), \(7.56\) (d, \(J=8.4\) Hz, 2H), \(7.75\) (d, \(J=7.6\) Hz, 2H). \(^13\)C NMR (100 MHz, CDCl\(_3\)): \(\delta =-4.89, -4.29, 0.35, 18.25, 26.23, 57.72, 75.07, 82.70, 120.63, 127.66, 127.68, 127.79, 127.88, 128.67, 128.80, 138.96, 138.97, 142.57. MS (EI): m/z=515 [M]. Elemental Analysis: Calcd. for C\(_{31}\)H\(_{41}\)NO\(_2\)Si\(_2\): C, 73.00; H, 8.03; N, 10.89; Si, 10.89; Found: C, 73.00; H, 8.03.

The Preparation of (3S\(^*\), 4S\(^*\))-4-(tert-butyldimethylsilyloxy)-4-(4-chlorophenyl)-2,2-diphenyl-3-(trimethylsilyloxy)butanenitrile 32j.

Following Method A, starting from diphenylacetonitrile (232 mg, 1.2 mmol) and 2-((tert-butyldimethylsilyloxy)-2-(4-chlorophenyl)acetaldehyde 31j (341 mg, 1.2 mmol), (3S\(^*\),4S\(^*\))-4-(tert-butyldimethylsilyloxy)-4-(4-chlorophenyl)-2,2-diphenyl-3-(trimethylsilyloxy)butanenitrile 32j was obtained by the flash chromatography ((petroleum ether :ether = 97:3)(481 mg; yield:73%).
Spectral data for \((3S^*, 4S^*)\)-4-(tert-butyldimethylsilyloxy)-4-(4-chlorophenyl)-2,2-diphenyl-3-(trimethylsilyloxy)butanenitrile 32j as follow:

32j: White solid. mp: 156-163 °C. IR (neat): 2251 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = -0.55 (s, 9H), -0.53 (s, 3H), -0.36 (s, 3H), 0.79 (s, 9H), 4.62 (d, \(J = 2.8\) Hz, 1 H), 4.95 (d, \(J = 2.8\) Hz, 1 H), 7.12-7.27 (m, 10H), 7.42 (d, \(J = 8.0\) Hz, 2H), 7.61(d, \(J = 7.2\) Hz, 2H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta = -4.91, -4.25, -0.27, 18.21, 26.17, 57.54, 74.94, 82.45, 120.56, 127.68, 127.79, 127.84, 128.01, 128.35, 128.66, 128.79, 129.02, 133.40, 138.42, 138.74, 140.98. MS: \(m/z = 572\) [M+Na\(^+\)].

Elemental Analysis: Calcd. for C\(_{31}\)H\(_{40}\)ClNO\(_2\)Si\(_2\): C, 67.66; H, 7.33; Cl, 6.44; N, 2.55; O, 5.82; Si, 10.21; Found: C, 67.84; H, 7.35.

The Preparation of \((3S^*, 4S^*)\)-4-(tert-butyldimethylsilyloxy)-4-(4-methoxyphenyl)-2,2-diphenyl-3-(trimethylsilyloxy)butanenitrile 32k

Following Method A, starting from diphenylacetonitrile (193 mg, 1.0 mmol) and 2-((tert-butyldimethylsilyl)oxy)-2-(4-methoxyphenyl)acetaldehyde 31k (280 mg, 1.0 mmol), \((3S^*, 4S^*)\)-4-(tert-butyldimethylsilyloxy)-4-(4-methoxyphenyl)-2,2-diphenyl-3-(trimethylsilyloxy)butanenitrile 32k was obtained after flash chromatography ((petroleum ether :ether =50:1)(371 mg; yield:68%).

Spectral data for \((3S^*, 4S^*)\)-4-(tert-butyldimethylsilyloxy)-4-(4-methoxyphenyl)-2,2-diphenyl-3-(trimethylsilyloxy)butanenitrile 32k

32k: White solid; mp: 118-123 °C. IR (neat): 2245 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = -0.46 (s, 9H), -0.44 (s, 3H), -0.28 (s, 3H), 0.87 (s, 9H), 3.80 (s, 3H), 4.72 (d, \(J = 2.8\) Hz, 1H), 5.01 (d, \(J = 2.8\) Hz, 1H), 6.81(d, \(J = 9.2\) Hz, 2H), 7.18 (d, \(J = 8.8\) Hz, 2H), 7.24-7.37 (m, 6H), 7.53 (d, \(J = 8.0\) Hz, 2H), 7.73 (d, \(J = 8.0\) Hz, 2H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta = -4.84, -4.26, -0.23, 18.26, 26.24, 55.22, 57.57, 74.94, 82.80, 113.22, 120.67, 127.69, 127.73, 127.88, 128.22, 128.61, 128.70, 128.81, 129.16, 134.52, 138.68, 139.06, 159.22. MS (ESI): \(m/z = 568\) [M+Na\(^+\)]. Elementil Analysis: Calcd. for C\(_{32}\)H\(_{43}\)NO\(_3\)Si\(_2\): C, 70.41; H, 7.94; N, 2.57; O, 8.79; Si, 10.29; Found: C, 70.27; H, 7.2.
The Preparation of (3S, 4S)-3-hydroxy-5-methyl-2,2-diphenyl-4-(trimethylsilyloxy)hexanenitrile 36

(3S, 4S)-4-(benzyloxy)-5-methyl-2,2-diphenyl-3-(trimethylsilyloxy)hexanenitrile 32e (130 mg), Pd/C 10% (130 mg) and Pd(OAc)$_2$ (75 mg) were mixed into 15 ml of MeOH. The reaction mixture was kept under H$_2$ (50 psi) for 4 hours. Then the reaction mixture was filtered and the solvent was removed to get crude product which was purified by flash chromatography (n-hexane: ether=10:1) to get (3S, 4S)-3-hydroxy-5-methyl-2,2-diphenyl-4-(trimethylsilyloxy)hexanenitrile 36 (65 mg, yield: 63%).

36: Colourless oil. [α]$_D^{20}$ = +68.2 (c: 1.0g/100 mg, CHCl$_3$). IR (neat): 3452, 2239 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$): δ = 0.17 (s, 9H), 0.63 (d, $J$=6.4 Hz, 3H), 0.90 (d, $J$=6.8 Hz, 3H), 1.57 (m, 1H), 3.73 (dd, $J_1$=1.2 Hz, $J_2$=7.6 Hz, 1H), 4.09 (d, $J$=8.0 Hz, OH), 4.46 (dd, $J_1$=0.8 Hz, $J_2$=8.0 Hz, 1H), 7.27-7.44 (m, 8H), 7.62 (m, 2H). $^{13}$C NMR (100 MHz, CDCl$_3$): δ = 0.46, 16.47, 17.44, 33.90, 57.82, 71.14, 73.41, 120.89, 127.52, 127.57, 127.74, 127.97, 128.29, 128.58, 128.83, 135.73, 135.88, 138.40, 139.12. MS (ESI): m/z=368 [M+1].

Elemental Analysis: Calcd. for C$_{22}$H$_{29}$NO$_2$Si: C, 71.89, H, 7.95, N, 3.81, Si, 7.64, Found: C, 71.96, H, 7.96, N, 3.81, Si, 7.64.

The Preparation of (3S, 4S)-3,4-dihydroxy-5-methyl-2,2-diphenylhexanenitrile 37

Following the same procedure for preparing compound 34a, starting from (3S, 4S)-3-hydroxy-5-methyl-2,2-diphenyl-4-(trimethylsilyloxy)hexanenitrile 36 (45 mg, mmol), (3S,4S)-3,4-dihydroxy-5-methyl-2,2-diphenylhexanenitrile 37 was obtained as colourless oil (28 mg, yield: 72%).

37: [α]$_D^{20}$ = +78.3 (c: 1.0g/100 mg, CHCl$_3$). IR (neat): 3400 (b), 2240 cm$^{-1}$. $^1$H NMR (400 MHz, CD$_3$OD): δ = 0.80 (d, $J$=6.4 Hz, 3H), 0.85 (d, $J$=6.4 Hz, 3H), 1.72 (octet, $J$=6.4 Hz, 1H), 3.00 (dd, $J_1$=6.4 Hz, $J_2$=0.2 Hz, 1H), 4.65 (d, $J$=0.2 Hz, 1H), 7.28 (m, 2H), 7.35 (m, 4H), 7.44 (m, 2H), 7.59 (m, 2H). $^{13}$C NMR (100 MHz, CD$_3$OD): δ = 18.78, 19.35, 33.07, 58.55, 74.11, 75.57, 122.67, 128.33, 128.67, 129.03, 129.65, 129.96, 140.12, 140.53. MS (ESI): m/z = 318 [M+Na$^+$. Elemental Analysis: Calcd. for C$_{19}$H$_{21}$NO$_2$: C, 77.26, H, 7.17, N, 4.74, Found: C, 77.34, H, 7.18.
The Preparation of 2-((4S, 5S)-5-isopropyl-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-diphenylacetonitrile 38

Following the same procedure for preparing compound 35a, starting from (3S, 4S)-3,4-dihydroxy-5-methyl-2,2-diphenylhexanenitrile 37 (10 mg, 0.07 mmol), 2-((4S,5S)-5-isopropyl-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-diphenylacetonitrile 38 was obtained as white solid (10 mg, yield: 90%).

38: mp: 172-174 °C. $[\alpha]_D^20$ = +94.8 (c: 1.0g/100 mg, CHCl₃). IR (neat): 2247 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ = 0.37 (m, 1H), 0.69 (d, J=6.8 Hz, 3H), 0.73 (d, J=6.8 Hz, 3H), 1.47 (s, 3H), 1.48 (s, 3H), 4.02 (dd, $J_1=2.8$ Hz, $J_2=8.0$ Hz, 1H), 4.59 (d, J=7.6 Hz, 1H), 7.28-7.41 (m, 8H), 7.55 (m, 2H). ¹³C NMR (100 MHz, CDCl₃): δ = 14.68, 20.58, 27.23, 27.83, 28.45, 56.28, 79.36, 83.07, 109.64, 120.62, 127.18, 128.04, 128.39, 129.48, 128.71, 128.89, 137.24, 139.15. MS (ESI): m/z=336 [M+1]. Elemental Analysis: Calcd. for C₂₂H₂₅NO₂: C, 78.77; H, 7.51; N, 4.18; O, 9.54. Found: C, 79.01; H, 7.53.

The Preparation of (3S, 4S)-3,4-dihydroxy-2,2,4-triphenylbutanenitrile 39

Following the same procedure for preparing compound 34a, starting from (3S,4S)-4-(tert-butyldimethylsilyloxy)-2,2,4-triphenyl-3-(trimethylsilyloxy)butanenitrile 32i (100 mg, 0.35 mmol), (3S, 4S)-3,4-dihydroxy-2,2,4-triphenylbutanenitrile 39 was obtained as colourless oil (62 mg, yield: 97%).

39: $[\alpha]_D^20$ = +66.73 (c: 1.1g/100 mg, CHCl₃). IR (neat): 3420 (b), 2239 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ = 2.63 (bs, OH), 3.50 (bm, OH), 4.55 (d, J=8.0 Hz, 1H), 4.65 (bs, 1H), 7.04-7.45 (complex pattern, 17h). ¹³C NMR (100 MHz, CDCl₃): 57.18, 71.23, 77.60, 121.06, 125.73, 127.36, 127.85, 128.03, 128.30, 128.57, 128.86, 129.20, 138.05, 138.38, 141.65. MS (ESI): m/z = 352 [M+Na⁺]. Elemental Analysis: Calcd. for C₂₂H₁₉NO₂: C, 80.22; H, 5.81; N, 4.25; O, 9.71. Found: C, 80.44; H, 5.83.
The Preparation of 2-[(4S, 5S)-2,2-dimethyl-5-phenyl-1,3-dioxolan-4-y]-2,2-diphenylacetonitrile 40

Following the same procedure for preparing compound 35a, starting from (3S, 4S)-3,4-dihydroxy-2,2,4-triphenylbutanenitrile 39 (55 mg, 0.17 mmol), 2-[(4S,5S)-2,2-dimethyl-5-phenyl-1,3-dioxolan-4-yl]-2,2-diphenylacetonitrile 40 was obtained as white solid (54 mg, yield: 86%)

40: mp: 218-220 °C. \([\alpha]_D^{20} = +52.30 \) (c: 1.00 g/100 mg, CHCl₃). IR (neat): 2238 cm⁻¹. ¹H NMR (400 MHz, C⁶D₆): δ = 1.51 (s, 3H), 1.65 (s, 3H), 4.89 (d, \( J = 8.0 \) Hz, 1H), 5.21 (d, \( J = 8.0 \) Hz, 1H), 6.64-7.12 (complex pattern, 13H), 7.56 (m, 2H). ¹³C NMR (100 MHz, CDCl₃): 27.00, 27.95, 55.76, 81.47, 84.44, 110.42, 120.21, 127.10, 127.35, 127.76, 127.86, 128.02, 128.06, 128.19, 128.46, 128.76, 135.94, 136.83, 139.19. MS (ESI): \( m/z = 369 \) [M]. Elemental Analysis: Calcd. for C₂₅H₂₃NO₂: C, 81.27; H, 6.27; N, 3.79; O, 8.66. Found: C, 81.41; H, 6.28;

The Preparation of (3S*, 4S*)-3-hydroxy-5,5-dimethyl-2,2-diphenyl-4-(trimethylsilyloxy)hexanenitrile 41

Starting from (3S*, 4S*)-4-(benzyloxy)-5,5-dimethyl-2,2-diphenyl-3-(trimethylsilyloxy)hexanenitrile 32f (120 mg, 0.25 mmol), Pd/C (10%) (120 mg) and Pd(OAc)₂ (35 mg) were mixed in 20ml of anhydrous MeOH. The reaction mixture was kept under H₂ (50 Psi) for 1 hr. After the reaction completed, it was filtered and concentrated under vacuum. (3S*, 4S*)-3-hydroxy-5,5-dimethyl-2,2-diphenyl-4-(trimethylsilyloxy)hexanenitrile 41 was obtained after flash chromatography (cyclohexane: ether=4:1) (95 mg, yield: 98% )

41: Colourless oil. IR (neat): 3445, 2239 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ= 0.27 (s, 9H), 0.65 (s, 9H), 3.57 (d, \( J = 1.2 \) Hz, 1H), 4.25 (d, \( J = 7.6 \) Hz, 1H, OH), 4.53 (dd, \( J_1 = 1.2 \) Hz, \( J_2 = 7.2 \) Hz, 1H), 7.23-7.40 (complex pattern, 8H), 7.62 (m, 2H). ¹³C NMR (100 MHz, CDCl₃): δ = 1.21, 25.84, 35.50, 58.04, 70.79, 77.20, 121.49, 127.77, 128.00, 128.07, 128.56, 128.64, 128.71, 138.26,
138.45. MS (ESI): m/z=382 [M+1]. Elemental Analysis: Calcd. for C_{23}H_{31}NO_{2}Si: C, 72.39; H, 8.19; N, 3.67; O, 8.39; Si, 7.36, Found: C, 72.63; H, 8.22

\[
\begin{align*}
\text{NC} & \quad \text{Ph} \quad \text{OH} \\
\text{Ph} & \quad \text{OH}
\end{align*}
\]

The Preparation of (3S*, 4S*)-3,4-dihydroxy-5,5-dimethyl-2,2-diphenylhexanenitrile 42

(3S*, 4S*)-3-hydroxy-5,5-dimethyl-2,2-diphenyl-4-(trimethylsilyloxy)hexanenitrile 41 (107 mg, 0.28 mmol) was mixed with 2 ml of acetone and PPTS (104 mg, 0.56 mmol). The reaction mixture was kept at r.t. for 24hrs. Then it was filtered and concentrated under vacuum to get the crude product which was purified by Lichroprep® (RP-18, 40-63 μm) chromatography (MeOH: H_{2}O=70:30) to get pure (3S*, 4S*)-3,4-dihydroxy-5,5-dimethyl-2,2-diphenylhexanenitrile 42 (82 mg, yield: 95%).

42: White solid. mp: 63-70 °C. IR (neat): 3440 (b), 2242 cm^{-1}. ^1H NMR (400 MHz, CDCl_3): δ = 0.82 (s, 9H), 1.99 (d, J=5.2 Hz, 1H, OH), 3.50 (d, J=4.4 Hz, 1H), 3.85(d, J=8.0 Hz, 1H, OH), 4.70 (d, J=8.4 Hz, 1H), 7.28-7.48 (complex pattern, 8H), 7.60 (d, J=7.6 Hz, 2H). ^13C NMR (100 MHz, CDCl_3): δ=25.84, 35.01, 58.08, 71.28, 75.27, 121.84, 127.86, 128.18, 128.23, 128.91, 129.04, 138.10, 138.17. MS (ESI): m/z=310 [M+1]. Elemental Analysis: Calcd. for C_{20}H_{23}NO_2: C, 77.64; H, 7.49; N, 4.53; O, 10.34; Found: C, 77.89; H, 7.49;

The Preparation of (R)-3-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-hydroxy-2,2-diphenylpropanenitrile 43 and (S)-3-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-hydroxy-2,2-diphenylpropanenitrile 44

A crude mixture of 32j and 33j (150 mg, 0.38 mmol, ratio 32j: 33j=1:9) was dissolved into 5 ml of CH_2Cl_2/acetonitrile (9:1), KF (22 mg, 0.38 mmol) and HF_{aq} (50%, 1 ml) were added into the solution. The reaction was kept at r.t. for 1hr. Then it was decomposed with 3ml of NaHCO_3 and extracted with CH_2Cl_2 (15ml ×3). The organic phase was washed with NH_4Cl and brine, dried with Na_2SO_4 and removed under vacuum to get the crude product which was purified after flash chromatography (Cyclohexane : ether =3:2) to get pure (S)-3-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-hydroxy-2,2-diphenylpropanenitrile 43 (60 mg, yield: 49%) and (R)-3-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-hydroxy-2,2-diphenylpropanenitrile 44 (6 mg, yield:5%).

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43: White solid. mp: 104-108 °C. \( [\alpha]_D^{10} = -103.6 \) (c: 0.5 g/100 mg, CHCl3). IR (KBr): 3431, 2252 cm\(^{-1}\). 
\( ^1H \) NMR (400 MHz, CDCl3): \( \delta = 1.32 \) (s, 3H), 1.45 (s, 3H), 3.21 (dd, \( J_1 = 6.0 \) Hz, \( J_2 = 8.8 \) Hz, 1H), 3.39 (d, \( J = 5.2 \) Hz, 1H, OH), 3.46 (dd, \( J_1 = 6.0 \) Hz, \( J_2 = 8.8 \) Hz, 1H), 4.16 (q, \( J = 6.0 \) Hz, 1H), 4.45 (t, \( J = 5.2 \) Hz, 1H), 7.31-7.41 (m, 8H), 7.57 (m, 2H). 
\( ^13C \) NMR (100 MHz, CDCl3): \( \delta = 25.32, 26.57, 57.09, 67.07, 74.25, 75.27, 109.97, 120.41, 127.52, 128.25, 128.67, 128.94, 129.27, 137.45, 138.54. \) MS (ESI): \( m/z = 346 \) [M+Na\(^+\)]. Elemental Analysis: Calcd. for C\(_{20}\)H\(_{21}\)NO\(_3\): C, 74.28; H, 6.55; N, 4.33; O, 14.84; Found: C, 74.13; H, 6.54.

44: White solid. mp: 137-139 °C. \( [\alpha]_D^{10} = +67.6 \) (c: 0.5 g/100 mg, CHCl3). IR (KBr): 3439, 2252 cm\(^{-1}\). 
\( ^1H \) NMR (400 MHz, CDCl3): \( \delta = 1.25 \) (s, 3H), 1.40 (s, 3H), 2.56 (d, \( J = 3.2 \) Hz, 1H, OH), 3.87 (dd, \( J_1 = 6.0 \) Hz, \( J_2 = 8.4 \) Hz, 1H), 3.99 (dt, \( J_1 = 2.8 \) Hz, \( J_2 = 6.4 \) Hz, 1H), 4.14 (dd, \( J_1 = 6.8 \) Hz, \( J_2 = 8.4 \) Hz, 1H), 4.90 (t, \( J = 2.8 \) Hz, 1H), 7.33-7.42 (m, 8H), 7.57 (m, 2H). 
\( ^13C \) NMR (100 MHz, CDCl3): \( \delta = 25.28, 26.44, 55.26, 63.68, 74.23, 76.11, 108.50, 120.46, 127.25, 127.88, 128.47, 128.53, 129.06, 129.35, 137.52, 137.71. \) MS: \( m/z = 346 \) [M+Na\(^+\)]. Elemental Analysis: Calcd. for C\(_{20}\)H\(_{21}\)NO\(_3\): C, 74.28; H, 6.55; N, 4.33; O, 14.84; Found: C, 74.21; H, 6.54.

The Preparation of \((2S, 3S, 4S)/(2R, 3S, 4S)-4-(benzyloxy)-2-phenyl-2-p-tolyl-3-(trimethylsilyloxy)pentanenitrile 45a/46a\) (identified as the corresponding monohydroxy derivatives 45a\(^1\) and 46a\(^1\) see below)

BuLi(1.0 mmol, 0.4 ml of 2.5M in n-hexane) was added into a solution of diisopropylamine (1.1 mmol, 0.155 ml) in THF (3 ml) at -78°C. Then a solution of 2-phenyl-2-p-tolylacetonitrile (2e) (207 mg, 1.0 mmol) in THF (1 ml) was dropped into the base solution at -78°C. The color of the reaction became yellow. After 5mins, a solution of TMSCl (0.14 ml, 1.1 mmol) in THF (1 ml) was added to the reaction. The reaction mixture was allowed to reach r.t. \((S)-2-(Benzyloxy)propanal 3b\) (180 mg, 1.1 mmol) in THF (1 ml) was added at r.t. After the reaction was completed (t.l.c. test), the solvent was removed. The crude product so obtained was dissolved into 1 ml of 1 N
HCl\textsubscript{aq} and 5 ml of acetonitrile. The resulting homogeneous solution was kept at r.t. for 30 mins and neutralized with iced saturated solution of NaHCO\textsubscript{3} to adjust the pH at 6.0. The solvent was removed under vacuum, the residue dissolved in 10 ml of water and extracted with ether (20 ml \times 3). The organic phase was dried with anhydrous Na\textsubscript{2}SO\textsubscript{4}, the solvent removed under vacuum. The residue was purified by flash chromatography (silica gel, hexane/ether 4/1) to get an inseparable mixture of products 45a\textsuperscript{1} and 46a\textsuperscript{1} in 58\% overall yields (214 mg) and in a ratio of 50/50 as determined by HPLC and \textsuperscript{1}H NMR spectra. The inseparable diastereomeric mixture arising from flash chromatography was crystallized from ACN:H\textsubscript{2}O=99:1 allowing the separation of a pure isomer to which has been attributed, arbitrarily, the structure 45a\textsuperscript{1} while the 46a\textsuperscript{1} remained in the mother liquorin mixture with 45a\textsuperscript{1}. Because an easily retro reaction takes place no further efforts were made to isolate pure 46a\textsuperscript{1} and its spectral data were deducted from the mixture.

\begin{figure}
\centering
\includegraphics[width=0.5\textwidth]{structure.png}
\caption{Structure of compounds 45a\textsuperscript{1} and 46a\textsuperscript{1}.}
\end{figure}

\textbf{45a}\textsuperscript{1}: White solid; mp: 95-98°C. [\alpha]\textsubscript{D}\textsuperscript{20} =+99.5 (c: 1.0g/100 mg, CHCl\textsubscript{3}). IR (neat): 2238 cm\textsuperscript{-1}. \textsuperscript{1}H NMR (400 MHz, CD\textsubscript{3}OD): \(\delta\) =1.20 (d, \(J=6.8\) Hz, 3H), 2.30 (s, 3H), 3.37 (dq, \(J\textsubscript{1}=2.0\) Hz, \(J\textsubscript{2}=6.4\) Hz, 1H), 4.17 (d, \(J=11.6\) Hz, 1H), 4.45 (d, \(J=11.6\) Hz, 1H), 4.48 (d, \(J=1.6\) Hz, 1H), 7.13(d, \(J=11.6\) Hz, 2H), 7.24-7.40 (complex pattern, 10H), 7.56 (m,2H). \textsuperscript{13}C NMR (100 MHz, CD\textsubscript{3}OD): \(\delta\) =16.80, 20.95, 57.81, 72.00, 74.77, 78.05, 122.82, 128.23, 128.33, 128.43, 128.62, 128.87, 128.94, 129.09, 129.14, 129.56, 129.87, 130.20, 130.50, 137.20, 138.95, 139.48, 141.97. MS (EI): m/z=357 [M-CH\textsubscript{3}+H]. Elemental Analysis: Calcd. for C\textsubscript{25}H\textsubscript{25}NO\textsubscript{2}: C, 80.83; H, 6.78; N, 3.77; O, 8.61; Found: C, 81.03; H, 6.80.

\textbf{46a}\textsuperscript{1}: IR (neat): 2238 cm\textsuperscript{-1}. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): \(\delta\) =1.19 (d, \(J=6.8\) Hz, 3H), 2.26 (s, 3H), 3.65 (d, \(J= 9.6\) Hz, 1H, OH), 3.53 (dq, \(J\textsubscript{1}=2.0\) Hz, \(J\textsubscript{2}=6.4\) Hz, 1H), 4.38 (dd, \(J\textsubscript{1}=2.0\) Hz, \(J\textsubscript{2}=9.6\) Hz, 1H), 4.41 (d, \(J=10.8\) Hz, 1H), 4.52 (d, \(J=10.8\) Hz, 1H), 7.16 (d, \(J=7.6\) Hz, 2H), 7.29-7.40 (complex pattern, 10H), 7.46 (m, 2H). \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): \(\delta\) =17.95, 20.98, 56.68, 71.22, 72.67,
77.50, 121.00, 127.25, 127.81, 128.09, 128.19, 128.57, 129.00, 129.72, 136.28, 137.48, 137.87, 139.45. MS (EI): m/z=357 [M-CH₃+H].

The Preparation of (2S, 3S, 4S) /(/2R, 3S, 4S)-4-(benzyloxy)-2-phenyl-2-m-tolyl-3-(trimethylsilyloxy)pentanenitrile 45b/46b (identified as the corresponding monohydroxyderivatives 45b₁ and 46b₁) (see below)

Following the same procedure of 45a₁/46a₁, starting from 2-phenyl-2-m-tolylacetonitrile (207 mg, 1.0 mmol) and (S)-2-(benzyloxy)propanal 31b (180 mg, 1.1 mmol), an inseparable mixture of (2S, 3S, 4S)-4-(benzyloxy)-2-phenyl-2-m-tolyl-3-(trimethylsilyloxy)pentanenitrile 45b₁ and (2R, 3S, 4S)-4-(benzyloxy)-2-phenyl-2-m-tolyl-3-(trimethylsilyloxy)pentanenitrile 46b₁ was obtained (288 mg, ratio:52/48, overall yield: 65%) after column chromatography on silica gel (hexane/ether: 6/1). Spectral data were deducted from the mixture and the major set of signals arbitrarily attributed to 46b₁.

\[ \text{45b₁: Colorless oil. IR(neat): 2238 cm}^{-1}. \text{ }^1\text{H NMR (400 MHz, (CD}_3\text{)}_2\text{SO/D}_2\text{O): }\delta =1.13 \text{ (d, } J=6.4 \text{ Hz, } 3\text{H), 2.17 (s, } 3\text{H), 3.14 (dq, } J_1=6.0 \text{ Hz, } J_2=1.2 \text{ Hz, } 1\text{H), 3.85 (d, } J=12.0 \text{ Hz, } 1\text{H), 4.36 (d, } J=12.0 \text{ Hz, } 1\text{H), 4.58 (d, } J=1.2 \text{ Hz, } 1\text{H), 7.11 (m, } 1\text{H), 7.18-7.38 (complex pattern, } 13\text{H). }^{13}\text{C NMR (100 MHz, (CD}_3\text{)}_2\text{SO/D}_2\text{O): }\delta =16.09, 21.48, 56.56, 70.19, 74.90, 75.67, 122.07, 125.02, 127.38, 128.56, 127.85, 128.20, 128.28, 128.51, 128.85, 129.06, 138.29, 138.76, 139.26, 141.15. MS (EI): m/z=357 [M-CH₃+H]. \]

\[ \text{46b₁: Colorless oil. IR(neat): 2238 cm}^{-1}. \text{ }^1\text{H NMR (400 MHz, (CD}_3\text{)}_2\text{SO/D}_2\text{O): }\delta =1.13 \text{ (d, } J=6.0 \text{ Hz, } 3\text{H), 2.28 (s, } 3\text{H), 3.14 (dq, } J_1=6.0 \text{ Hz, } J_2=1.2 \text{ Hz, } 1\text{H), 3.89 (d, } J=12.0 \text{ Hz, } 1\text{H), 4.33(d, } J=12.0 \text{ Hz, } 1\text{H), 4.56 (d, } J=1.2 \text{ Hz, } 1\text{H), 7.08(m, } 2\text{H), 7.23-7.38 (complex pattern, } 10\text{H), 7.54 (d, } J=7.6 \text{ Hz, } 2\text{H). }^{13}\text{C NMR (100 MHz, (CD}_3\text{)}_2\text{SO/D}_2\text{O): }\delta =16.01, 21.30, 56.59, 70.25, 74.10, 75.67, \]
The Preparation of (2S, 3S, 4S)/(2R, 3S, 4S)-4-(benzyloxy)-2-phenyl-2-o-tolyl-3-(trimethylsilyloxy)pentanenitrile 45c/46c

Following the same procedure of Method A, starting from 2-phenyl-2-o-tolylacetonitrile 19e (207 mg, 1.0 mmol) and (S)-2-(benzyloxy)propanal 31b (460 mg, 1.1 mmol), (2S, 3S, 4S)-4-(benzyloxy)-2-phenyl-2-o-tolyl-3-(trimethylsilyloxy)pentanenitrile 45c and (2R, 3S, 4S)-4-(benzyloxy)-2-phenyl-2-o-tolyl-3-(trimethylsilyloxy)pentanenitrile 46c were obtained by the flash chromatography (n-hexane: ether= 98:2) (239 mg, ratio:70/30, overall yield: 54%). The stereo attribution at each isomer was determined by X-Ray analysis of the corresponding acetonide 47.

45c: White solid; mp: 61-65 °C. \([\alpha]_D^{20}: +96.90\ (c: 1.0g/100\ mg, CHCl_3)\). IR (neat): 2237 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)): δ =-0.03 (s, 9H), 1.20 (d, J=6.4 Hz, 3H), 2.13 (s, 3H), 3.75 (m, 1H), 4.35 (d, J=12.0 Hz, 1H), 4.39 (d, J=4.0 Hz, 1H), 4.58 (d, J=12.0 Hz, 1H), 7.14-7.39 (complex pattern, 12H), 7.95 (m, 2H). \(^13\)C NMR (100 MHz, CDCl\(_3\)): δ =0.69, 18.78, 21.53, 55.68, 70.98, 75.33, 82.58, 121.06, 125.34, 127.18, 127.42, 127.63, 128.14, 128.26, 128.41, 128.73, 132.82, 135.68, 138.29, 138.43, 138.75. MS (EI): m/z=443 [M]. Elemental Analysis: Calcd. for C\(_{28}\)H\(_{33}\)NO\(_2\)Si: C, 75.80; H, 7.50; N, 3.16; O, 7.21; Si, 6.33; Found: C, 76.00; H, 7.52.

46c: Colorless oil. \([\alpha]_D^{20}: -57.90\ (c: 1.0g/100\ mg, CHCl_3)\). IR (neat): 2237 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)): δ =-0.11 (s, 9H), 1.18 (d, J=6.0 Hz, 3H), 2.20 (s, 3H), 3.85 (dq, J\(_1\)=4.4 Hz, J\(_2\)=6.0 Hz, 1H), 4.35 (d, J=12.0 Hz, 1H), 4.46 (d, J=12.0 Hz, 1H), 4.63 (d, J=4.4 Hz, 1H), 7.12-7.32 (complex pattern, 11H), 7.42 (m, 2H), 7.52 (m,1H). \(^13\)C NMR (100 MHz, CDCl\(_3\)): δ =0.32, 18.20, 21.77, 55.48, 71.11, 76.47, 80.45, 120.89, 125.41, 127.21, 127.53, 127.55, 128.03, 128.07, 128.28,
128.59, 133.04, 135.97, 137.65, 138.44, 138.58. MS (EI): m/z=443[M]. Elemental Analysis: Calcd. for C_{28}H_{33}NO_2Si: C, 75.80; H, 7.50; N, 3.16; O, 7.21; Si, 6.33; Found: C, 75.94; H, 7.51.

The Preparation of (2S, 3S, 4S)/(2R, 3S, 4S)-4-(benzyl)oxy)-2-(4-bromophenyl)-2-phenyl-3-(trimethylsilyloxy)pentanenitrile 45d/46d

Following the same procedure of Method A, starting from 2-(4-bromophenyl)-2-phenylacetonitrile 19b (271 mg, 1.0 mmol) and (S)-2-(benzyl)oxy)propanal 31b (164 mg, 1.0 mmol), a mixture of (2S, 3S, 4S)-4-(benzyl)oxy)-2-(4-bromophenyl)-2-phenyl-3-(trimethylsilyloxy)pentanenitrile 45d and (2R, 3S, 4S)-4-(benzyl)oxy)-2-(4-bromophenyl)-2-phenyl-3-(trimethylsilyloxy)pentanenitrile 46d was obtained after flash chromatography (n-hexane: ether= 9:1) (274 mg, ratio:45/55, Overall yield: 54%). No further efforts to isolate pure 45d from 46d were taken. To 45d was arbitrarily attributed the stereochemistry reported and its spectral data were deducted from the mixture reporting the major set of signals.

45d: colorless oil. IR(neat): 2239 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)): δ =0.00 (s, 9H), 1.3 (d, J=6.4 Hz, 3H), 3.90 (dq, J\(_1\)=4.4 Hz, J\(_2\)=6.4 Hz, 1H), 4.45(d, J=11.6 Hz, 1H), 4.60 (d, J=11.6 Hz, 1H), 4.66(d, J=4.0 Hz, 1H), 7.36-7.62 (complex pattern, 10H), 7.67 (m, 2H), 7.80(m, 2H). \(^13\)C NMR (100 MHz, CDCl\(_3\)): δ =0.00, 17.10, 58.99, 70.87, 75.94, 81.50, 121.91, 127.14, 127.49, 127.79, 127.93, 128.57, 129.22, 131.52, 136.63, 137.59, 138.02, 144.75.MS (EI): m/z=530 [M+Na\(^+\)]. Elemental Analysis: Calcd. for C\(_{27}\)H\(_{30}\)BrNO\(_2\)Si: C, 63.77; H, 5.95; Br, 15.71; N, 2.75; O, 6.29; Si, 5.52; Found: C, 63.71; H, 5.94.

46d: colorless oil. IR(neat): 2239 cm\(^{-1}\). \(^1\)H NMR (400 MHz,CDCl\(_3\)): δ =0.01 (s, 9H),1.35 (d, J=6.0 Hz, 3H), 3.83 (dq, J\(_1\)= 4.4 Hz, J\(_2\)=6.0 Hz, 1H), 4.44 (d, J=12.0 Hz, 1H), 4.65 (d, J=12.0 Hz, 1H), 4.68 (d, J=4.4 Hz, 1H),7.36-7.62 (complex pattern, 12H), 7.85(m, 2H). \(^13\)C NMR (100 MHz,
CDCl$_3$: $\delta =$0.00, 16.79, 58.95, 70.52, 75.35, 81.01, 121.10, 127.12,127.47, 127.49, 128.79, 127.93, 128.57, 129.22, 131.39, 136.63, 137.59, 138.02, 144.75. MS (EI): m/z=530 [M+Na$^+$$]$. 

The Preparation of (2S, 3S, 4S)/(2R, 3S, 4S)-4-(benzzyloxy)-2-(4-methoxyphenyl)-2-phenyl-3-(trimethylsilyloxy)pentanenitrile 45e/46e

Following the same procedure of Method A, starting from 2-(4-methoxyphenyl)-2-phenylacetonitrile 19f (223 mg, 1.0 mmol) and (S)-2-(benzzyloxy)propanal 31b (164 mg, 1.0 mmol), (2S, 3S, 4S)-4-(benzzyloxy)-2-(4-methoxyphenyl)-2-phenyl-3-(trimethylsilyloxy)pentanenitrile 45e and (2R, 3S, 4S)-4-(benzzyloxy)-2-(4-methoxyphenyl)-2-phenyl-3-(trimethylsilyloxy)pentanenitrile 46e were obtained after flash chromatography (petroleum ether : ether= 9:1) (298 mg, ratio:50/50, overall yield:65 %)

45e: White solid. Mp: 65-71 °C. $[\alpha]_D^{20}+15.89$ (c:8.75 g/100 ml, CHCl$_3$). IR (neat): 2242 cm$^{-1}$. $^1$H NMR (400 MHz,CDCl$_3$): $\delta =$0.01 (s, 9H), 1.32 (d, $J$=6.4 Hz, 3H), 3.84 (dq, $J_1$=6.4 Hz, $J_2$=4.4 Hz, 1H), 3.98 (s, 3H), 4.46 (d, $J$=12.0 Hz, 1H), 4.58 (d, $J$=12.0 Hz, 1H), 4.65 (d, $J$=4.4 Hz, 1H), 7.00 (d, $J$=9.6 Hz, 2H), 7.38-7.54 (m, 8H), 7.60 (m, 2H), 7.81 (m, 2H). $^{13}$C NMR (100 MHz,CDCl$_3$): $\delta$ =0.17, 17.27, 55.29, 56.19, 71.00, 76.26, 81.73, 113.79, 121.81, 127.62,127.68, 128.07, 128.62 , 129.55, 138.44, 139.24 , 159.12. MS (EI): m/z= 459 [M]. Elemental Analysis: Calcd. for C$_{28}$H$_{33}$NO$_3$Si: C, 73.16; H, 7.24; N, 3.05; O, 10.44; Si, 6.11, Found: C, 73.26; H, 7.25.

46e: Colorless oil. $[\alpha]_D^{20}+ 3.5$(c: 1.0g/100 mg, CHCl$_3$). IR (neat): 2242 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$): $\delta =$-0.17 (s, 9H), 1.13 (d, $J$=6.4 Hz, 3H), 3.70 (dq, $J_1$=6.4 Hz, $J_2$=4.0 Hz, 1H), 3.79 (s, 3H), 4.32 (d, $J$=12.4 Hz, 1H), 4.42 (d, $J$=12.4 Hz, 1H), 4.50 (d, $J$=4.0 Hz, 1H), 6.85 (d, $J$=9.2 Hz,
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2H), 7.22-7.41 (complex pattern, 10H), 7.65 (m, 2H). 13C NMR (100 MHz, CDCl3): δ = 0.19, 17.35, 55.30, 56.61, 71.00, 75.90, 81.35, 113.97, 121.60, 127.21, 127.71, 127.75, 128.00, 128.08, 128.54, 128.80, 130.63, 138.42, 138.52, 158.98. MS (EI): m/z=459 [M]. Elemental Analysis: Calcd. for C28H33NO3Si: C, 73.16; H, 7.24; N, 3.05; O, 10.44; Si, 6.11, Found: C, 73.30; H, 7.25

The Preparation of (2S, 3S, 4S)/(2R, 3S, 4S)-4-(benzyloxy)-2-phenyl-2-(4-(trifluoromethyl)phenyl)-3-(trimethylsilyloxy)pentanenitrile 45f/46f

Following the same procedure of Method A, starting from 2-phenyl-2-(4-(trifluoromethyl)phenyl)acetonitrile 19j (261 mg, 1.0 mmol) and (S)-2-(benzyloxy)propanal 31b (164 mg, 1.0 mmol), a mixture of (2S, 3S, 4S)-4-(benzyloxy)-2-phenyl-2-(4-(trifluoromethyl)phenyl)-3-(trimethylsilyloxy)pentanenitrile 45f and (2R, 3S, 4S)-4-(benzyloxy)-2-phenyl-2-(4-(trifluoromethyl)phenyl)-3-(trimethylsilyloxy)pentanenitrile 46f was obtained after flash chromatography (petroleum ether : AcOEt=14:1) (303 mg, ratio:40/60, yield: 61 %). No further efforts to isolate pure 45f from 46f were taken. To 45f was arbitrarily attributed the stereochemistry reported and its spectral data were deducted from the mixture reporting the major set of signals.

45f: IR(neat): 2239 cm⁻¹. 1H NMR (400 MHz, CDCl3): δ = 0.10 (s, 9H), 1.25 (d, J=6.4 Hz, 3H), 3.87 (dq, J₁=4.4 Hz, J₂=6.4 Hz, 1H), 4.36 (d, J=11.6 Hz, 1H), 4.52 (d, J=11.6 Hz, 1H), 4.63 (d, J=4.4 Hz, 1H), 7.25-7.53 (complex pattern, 9H), 7.66 (m, 3H), 7.97 (d, J=8.0 Hz, 2H). 13C NMR (100 MHz, CDCl3): δ = 0.27, 17.44, 57.11, 70.75, 71.22, 76.24, 81.91, 121.26, 125.54, 125.70, 127.55, 127.85, 128.28, 128.37, 129.00, 129.07, 130.46, 137.30, 138.10, 138.23, 141.98. MS (EI): m/z=497 [M]. Elemental Analysis: Calcd. for C28H30F3NO2Si: C, 67.58; H, 6.08; F, 11.45; N, 2.81; O, 6.43; Si, 5.64, Found: C, 67.66; H, 6.09.
46f: IR(neat): 2239 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ =-0.08 (s, 9H), 1.29 (d, J=6.4 Hz, 3H),
3.74 (dq, J₁=4.0 Hz, J₂=6.4 Hz, 1H), 4.32 (d, J=12.0 Hz, 1H), 4.57 (d, J=12.0 Hz, 1H), 4.66 (d, J=4.0 Hz, 1H), 7.25-7.53 (complex pattern, 9H), 7.66 (m, 3H), 7.79 (m, 2H).
¹³C NMR (100 MHz, CDCl₃): δ = 0.27, 16.97, 57.09, 70.75, 71.22, 75.62, 81.45, 121.12, 125.54, 125.70, 127.55, 127.85, 128.28, 128.37, 129.00, 129.07, 130.43, 137.30, 138.10, 138.23, 141.97. MS (EI): m/z=497 [M].

The Preparation of (2S, 3S, 4S)/(2R, 3S, 4S)-4-(benzyloxy)-2-(4-nitrophenyl)-2-phenyl-3-(trimethylsilyloxy)pentanenitrile 45g/46g
Following the same procedure of Method A, starting from 2-(4-nitrophenyl)-2-phenylacetonitrile 19k (238 mg, 1.0 mmol) and (S)-2-(benzyloxy)propanal 31b (164 mg, 1.0 mmol), ((2S, 3S, 4S) -4-(benzyloxy)-2-(4-nitrophenyl)-2-phenyl-3-(trimethylsilyloxy)pentanenitrile 45g and (2R, 3S, 4S)-4-(benzyloxy)-2-(4-nitrophenyl)-2-phenyl-3-(trimethylsilyloxy)pentanenitrile 46g were obtained by the flash chromatography (petroleum ether : AcOEt=10:1) (270 mg, ratio:36/64, yield: 57%)

45g: Colorless oil. [α]⁺²⁰: +26.08 (c: 1.3g/100 mg, CHCl₃). IR (neat): 2243cm⁻¹. ¹H NMR (400 MHz,CDCl₃): δ =-0.17 (s, 9H), 1.19 (d, J=6.4 Hz, 3H), 3.87 (dq, J₁=6.4 Hz, J₂=4.0 Hz, 1H), 4.22 (d, J=12.0 Hz, 1H), 4.42 (d, J=12.0 Hz, 1H), 4.54 (d, J=4.0Hz, 1H), 7.12 (m, 2H), 7.24 (m, 3H), 7.35 (m, 5H), 7.93 (d, J=9.2 Hz, 2H), 8.15 (d, J=9.2 Hz, 2H). ¹³C NMR (100 MHz,CDCl₃): δ =-0.00, 17.06, 56.75, 70.90, 75.81, 81.89, 120.75, 123.13, 127.23, 127.48,127.55, 127.88, 128.27, 128.84, 129.52, 137.54, 137.64, 144.67, 145.05. MS (EI): m/z=475 [M+H]. Elemental Analysis: Calcd. for C₂₇H₃₀N₂O₄Si: C, 68.33; H, 6.37; N, 5.90; O, 13.48; Si, 5.92, Found: C, 68.13; H, 6.35.

46g: White solid. mp: 130-133 °C. [α]⁺²⁰: +18.47 (c: 1.1g/100 mg, CHCl₃). IR (neat): 2242 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ =-0.12 (s, 9H), 1.26 (d, J=6.4 Hz, 3H), 3.66 (dq, J₁=6.4 Hz, J₂=4.0
Hz, 1H), 4.21 (d, J=12.0 Hz, 1H), 4.52 (d, J=12.0 Hz, 1H), 4.62 (d, J=4.0 Hz, 1H), 7.26 (m, 4H), 7.42 (m, 4H), 7.66 (d, J=8.8 Hz, 2H), 7.71 (d, J=8.0 Hz, 2H), 8.13 (d, J=8.8 Hz, 2H).

13C NMR (100 MHz, CDCl3): δ = 0.15, 16.57, 57.11, 70.49, 75.46, 81.10, 120.68, 123.57, 127.46, 127.65, 127.74, 128.13, 128.56, 128.84, 129.00, 136.69, 137.74, 145.64, 146.05. MS (EI): m/z=475 [M+H]. Elemental Analysis: Calcd. for C27H30N2O4Si: C, 68.33; H, 6.37; N, 5.90; O, 13.48; Si, 5.92, Found: C, 68.26; H, 6.36.

The Preparation of (2S, 3S, 4S)/(2R, 3S, 4S)-4-(benzyloxy)-2-phenyl-2-(pyridin-3-yl)-3-(trimethylsilyloxy)pentanenitrile 45h/46h

Following the same procedure of Method A, starting from 2-phenyl-2-(pyridin-3-yl)acetonitrile 19h (194 mg, 1.0 mmol) and (S)-2-(benzyloxy)propanal 31b (164 mg, 1.0 mmol), (2S, 3S, 4S)-4-(benzyloxy)-2-phenyl-2-(pyridin-3-yl)-3-(trimethylsilyloxy)pentanenitrile 45h and (2R, 3S, 4S)-4-(benzyloxy)-2-phenyl-2-(pyridin-3-yl)-3-(trimethylsilyloxy)pentanenitrile 46h were obtained after flash chromatography (n-hexane : ether=3:2) (288 mg, ratio:65/35, yield: 67%)

45h: Colorless oil. [α]D20 = +18.40 (c: 1.0g/100 mg, CHCl3). IR (neat): 2240 cm⁻¹. ¹H NMR (400 MHz, CDCl3): δ =-0.04 (s, 9H), 1.28 (d, J=6.4 Hz, 3H), 3.90 (dq, J₁=6.4 Hz, J₂=4.0 Hz, 1H), 4.38 (d, J=11.6 Hz, 1H), 4.55 (d, J=11.6 Hz, 1H), 4.67 (d, J=4.0 Hz, 1H), 7.31–7.58 (complex pattern, 11H), 8.19 (m, 1H), 8.67 (dd, J₁=1.2 Hz, J₂=4.4 Hz, 1H), 9.13 (m, 1H). ¹³C NMR (100 MHz, CDCl3): δ =-0.17, 17.27, 55.48, 71.04, 75.92, 81.58, 120.62, 1223.15, 127.31, 127.66, 128.11, 128.26, 128.96, 133.89, 136.28, 137.78, 138.08, 148.95, 149.42. MS (EI): m/z= 430 [M]. Elemental Analysis: Calcd. for C26H30N2O2Si: C, 72.52; H, 7.02; N, 6.51; O, 7.43; Si, 6.52, Found: C, 72.72; H, 7.04.

46h: White solid. mp: 59–64 °C. [α]D20 = +12.80 (c: 1.1g/100 mg, CHCl3). IR (neat): 2242 cm⁻¹. ¹H NMR (400 MHz, CDCl3): δ =-0.04 (s, 9H), 1.33 (d, J=6.0 Hz, 3H), 3.78 (dq, J₁=6.0 Hz, J₂=4.4
Hz, 1H), 4.35 (d, J=11.6 Hz, 1H), 4.59 (d, J=11.6 Hz, 1H), 4.68(d, J=4.4 Hz,1H), 7.31-7.58 (complex pattern, 11H), 7.83 (d, J=7.6 Hz, 2H), 7.91 (m, 1H), 8.63 (dd, J=1.2 Hz, J=4.8 Hz, 1H), 8.85 (d, J=2.0 Hz, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$): δ =0.09, 16.83, 55.41, 70.70, 75.75, 81.28, 120.66, 123.30, 127.36, 127.65, 128.10, 128.33, 128.86, 134.76, 135.47, 136.64, 137.99, 148.77, 148.88. MS (EI): m/z= 430 [M].

Elemental Analysis: Calcd. for C$_{26}$H$_{30}$N$_2$O$_2$Si: C, 72.52; H, 7.02; N, 6.51; O, 7.43; Si, 6.52. Found: C, 72.69; H, 7.04.

The Preparation of (2$S$, 3$S$, 4$S$)/(2$R$, 3$S$, 4$S$)-4-(benzyloxy)-2-(2-chlorophenyl)-2-phenyl-3-(trimethylsilyloxy)pentanenitrile 45i/46i

Following the same procedure of Method A, starting from 2-(2-chlorophenyl)-2-phenylacetonitrile 19g (227 mg, 1.0 mmol) and (S)-2-(benzyloxy)propanal 31b (164 mg, 1.0 mmol), (2$S$, 3$S$, 4$S$)-4-(benzyloxy)-2-(2-chlorophenyl)-2-phenyl-3-(trimethylsilyloxy)pentanenitrile 45i and (2$R$, 3$S$, 4$S$)-4-(benzyloxy)-2-(2-chlorophenyl)-2-phenyl-3-(trimethylsilyloxy)pentanenitrile 46i were obtained by the flash chromatography (n-hexane : toluene=1:1) (203 mg, ratio:80/20, yield: 44%). The absolute configuration of the isomer 45i was established by X-Ray analysis.

45i: White solid. mp: 75-80 °C. $[\alpha]_{D}^{20}$: +73.50 (c: 1.0g/100 mg, CHCl$_3$). IR (neat): 2240 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$): δ =-0.11 (s, 9H), 1.21 (d, J=6.4 Hz, 3H), 3.92 (dq, J$_1$=6.4 Hz, J$_2$=3.2 Hz, 1H) , 4.33 (d, J=11.6 Hz, 1H), 4.40 (d, J=3.2 Hz, 1H), 4.55 (d, J=11.6 Hz, 1H), 7.20-7.36 (complex pattern, 13H), 8.16(m, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$): δ = 0.46, 18.95, 56.32, 71.20, 75.33, 82.67, 120.25, 126.05, 127.23, 127.52, 127.67, 128.11, 128.20, 128.27, 129.27, 131.46, 131.62, 134.89, 137.82, 138.46. MS (EI): m/z= 448 [M-CH$_3$]. Elemental Analysis: Calcd. for C$_{27}$H$_{30}$ClNO$_2$Si: C, 69.88; H, 6.52; Cl, 7.64; N, 3.02; O, 6.90; Si, 6.05. Found: C, 69.74; H, 6.51.

46i: Colorless oil. $[\alpha]_{D}^{20}$: +46.90 (c: 1.8g/100 mg, CHCl$_3$). IR (neat): 2240 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$): δ =-0.04 (s, 9H), 1.21 (d, J=6.4 Hz, 3H), 3.58 (dq, J$_1$=6.4 Hz, J$_2$=4.0 Hz, 1H), 4.14 (d,
$J=11.6 \text{ Hz, 1H}$, 4.42 (d, $J=11.6 \text{ Hz, 1H}$), 5.10 (d, $J=4.0 \text{ Hz, 1H}$), 7.14-7.38 (complex pattern, 11H), 7.54 (m, 1H), 7.64 (d, $J=6.8 \text{ Hz, 2H}$). $^{13}$C NMR (100 MHz, CDCl$_3$): δ = 0.45, 16.99, 56.38, 70.79, 76.53, 78.51, 120.63, 126.64, 127.18, 127.38, 128.00, 128.08, 128.30, 129.07, 129.28, 131.77, 131.93, 133.31, 135.90, 136.79, 138.46. MS (EI): m/z = 448 [M-CH$_3$]. Elemental Analysis: Calcd. for $\text{C}_{27}\text{H}_{30}\text{ClNO}_2\text{Si}$: C, 69.88; H, 6.52; Cl, 7.64; N, 3.02; O, 6.90; Si, 6.05; Found: C, 70.00; H, 6.53.

**The Preparation of (2S, 3S, 4S)/(2R, 3S, 4S)-4-(tert-butyldimethylsilyloxy)-2,4-diphenyl-2-m-toly1-3-(trimethylsilyloxy)butanenitrile 45j/46j**

Following the same procedure of A, starting from 2-phenyl-2-m-tolylacetonitrile 19c (207 mg, 1.0 mmol) and (S)-2-(tert-butyldimethylsilyloxy)-2-phenylacetaldehyde 31i (250 mg, 1.0 mmol), a mixture products 45j and 46j was obtained by the flash chromatography (cyclohexane: ether=99:1) (429 mg, ratio:50/50, yield: 85%)

![Molecule Structure](image)

45j: IR(neat): 2245 cm$^{-1}$. $^1$H NMR (400 MHz, CD$_3$OD): δ = -0.59 (s, 9H), -0.55 (s, 3H), -0.38 (s, 3H), 0.06 (s, 9H), 2.32 (s, 3H), 4.95 (d, $J=2.0 \text{ Hz, 1H}$), 5.16 (d, $J=1.6 \text{ Hz, 1H}$), 7.06 (d, $J=11.6 \text{ Hz, 1H}$), 7.20-7.45 (complex pattern, 9H), 7.53 (m, 2H), 7.74 (m, 2H). $^{13}$C NMR (100 MHz, CDCl$_3$): δ = -4.85, -4.28, -0.36, 18.16, 21.44, 26.90, 57.68, 74.85, 82.46, 120.62, 124.44, 127.62, 127.68, 127.74, 128.33, 128.49, 128.61, 128.79, 138.29, 138.85, 138.97, 142.74. MS (EI): m/z = 529 [M]. Elemental Analysis: Calcd. for $\text{C}_{32}\text{H}_{43}\text{NO}_2\text{Si}_2$: C, 72.54; H, 8.18; N, 2.64; O, 6.04; Si, 10.60; Found: C, 72.74; H, 8.20.
46j: (50%) IR(neat): 2245 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CD\(_3\)OD); \(\delta =-0.59\) (s, 9H), -0.54 (s, 3H), -0.38 (s, 3H), 0.06 (s, 9H), 2.36 (s, 3H), 4.93 (d, \(J=2.0\) Hz, 1H), 5.15 (d, \(J=1.2\) Hz, 1H), 7.13 (d, \(J=11.6\) Hz, 1H), 7.20-7.45 (complex pattern, 9H), 7.53 (m, 2H), 7.74 (m, 2H). \(^13\)C NMR (100 MHz, CDCl\(_3\)); \(\delta =-4.94\), -4.27, -0.35, 18.25, 21.53, 26.23, 57.77, 74.95, 82.60, 120.68, 124.56, 127.66, 127.71, 127.86, 128.42, 128.56, 128.67, 138.85, 138.97, 142.74. MS (EI): m/z=529 [M].

The Preparation of (2S, 3S, 4S)/(2R, 3S, 4S)-4-(tert-butyldimethylsilyloxy)-2,4-diphenyl-2-(pyridin-3-yl)-3-(trimethylsilyloxy)butanenitrile 45k/46k

Following the same procedure of Method A, starting from 2-phenyl-2-(pyridin-3-yl)acetonitrile 19h (194 mg, 1.0 mmol) and (S)-2-(tert-butyldimethylsilyloxy)-2-phenylacetaldehyde 31i (250 mg, 1.0 mmol), (2S, 3S, 4S)-4-(tert-butyldimethylsilyloxy)-2,4-diphenyl-2-(pyridin-3-yl)-3-(trimethylsilyloxy)butanenitrile 45k and (2R, 3S, 4S)-4-(tert-butyldimethylsilyloxy)-2,4-diphenyl-2-(pyridin-3-yl)-3-(trimethylsilyloxy)butanenitrile 46k were obtained by the flash chromatography (CH\(_2\)Cl\(_2\) : ether=99:1) (197 mg, ratio:80/20, yield: 40%). The absolute configuration of the isomer 45k was established by X-Ray analysis.

45k: White solid. mp:104-107\(^\circ\)C. [\(\alpha\)]\(_D\)\(^{19C}\): + 3.1(c: 1.0g/100 mg, CHCl\(_3\)). IR (neat): 2246 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)); \(\delta =-0.47\) (s, 9H), -0.41 (s, 3H), -0.27 (s, 3H), 0.86 (s, 9H), 4.71 (d, \(J=2.4\) Hz, 1H), 5.13 (d, \(J=2.4\) Hz, 1H), 7.23-7.45 (complex patern, 11H), 8.05 (m, 1H), 8.51 (dd, \(J_1=1.6\) Hz, \(J_2=4.8\) Hz, 1H), 9.05 (d, \(J=2.1\) Hz, 1H). \(^13\)C NMR (50M, CDCl\(_3\)); \(\delta =-4.89\), -4.37, -0.32, 18.21, 26.15, 55.49, 75.69, 83.37, 120.14, 123.20, 127.61, 127.84, 127.96, 128.25, 128.98, 136.40, 138.48, 141.74, 148.57, 149.51. MS (ESI): m/z= 517 [M+H]. Elemental Analysis: Calcd. for C\(_{30}\)H\(_{40}\)N\(_2\)O\(_2\)Si\(_2\): C, 69.72; H, 7.80; N, 5.42; O, 6.19; Si, 10.87; Found: C, 69.80; H, 7.81.
**Chapter 2**

46k: White solid. mp: 88-92 °C. $[\alpha]_D^{20} + 18.3$ (c: 1.0 g/100 mg, CHCl$_3$). IR (neat): 2246 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$): $\delta = -0.39$ (s, 3H), -0.38 (s, 9H), -0.27 (s, 3H), 0.87 (s, 9H), 4.77 (d, $J$ = 2.8 Hz, 1H), 5.08 (d, $J$ = 2.8 Hz, 1H), 7.21-7.41 (m, 11H), 7.67 (m, 2H), 7.96 (m, 1H), 8.52 (m, 1H), 8.79 (s, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = -4.69, -4.17, -0.18, 18.30, 26.20, 58.02, 76.24, 82.33, 119.80, 124.02, 127.76, 127.81, 128.07, 128.25, 128.45, 128.77, 129.13, 136.20, 137.82, 141.16, 148.72, 149.50$. MS (ESI): m/z = 517 [M+1]. Elemental Analysis: Calcd. for C$_{30}$H$_{40}$N$_{2}$O$_{2}$Si$_{2}$: C, 69.72; H, 7.80; N, 5.42; O, 6.19; Si, 10.87; Found: C, 69.51; H, 7.77.

The Preparaton of (2S, 3S, 4S)-3,4-dihydroxy-2-phenyl-2-o-tolypentanenitrile 47

(2S, 3S, 4S)-4-(benzyloxy)-2-phenyl-2-o-tolyl-3-(trimethylsilyloxy)pentanenitrile 45c (120 mg) and Pd/C 10% (120 mg) were mixed into 10 ml of anhydrous MeOH. The reaction mixture was kept under H$_2$ (50psi) for overnight. Then the reaction mixture was filtered and concentrated to get crude product which was purified by flash chromatography (cyclohexane : ether= 3:2) to give pure compound 47 (45 mg, yield: 59%).

47: colourless oil. $[\alpha]_D^{20} +126.18$ (c: 1.1 g/100 mg, CHCl$_3$). IR (neat): 3444 (b), 2241 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 1.10$ (d, $J$ = 6.8 Hz, 3H), 2.07 (s, 3H), 2.13 (d, $J$ = 4.8 Hz, 1H, OH), 3.69 (d, $J$ = 8.4 Hz, 1H, OH), 3.76 (m, 1H), 4.27 (dd, $J_1$ = 1.2 Hz, $J_2$ = 8.4 Hz, 1H), 7.13 (d, $J$ = 7.6 Hz, 1H), 7.25-7.37 (complex pattern, 7H), 7.80 (d, $J$ = 8.0 Hz, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 21.07, 21.68, 55.53, 65.18, 76.68, 120.25, 126.06, 127.05, 128.06, 128.42, 129.03, 133.09, 136.05, 136.99, 138.36$. MS (ESI): m/z=281 [M]. Elemental Analysis: Calcd. for C$_{18}$H$_{19}$NO$_2$: C, 76.84; H, 6.81; N, 4.98; O, 11.37; Found: C, 76.85; H, 6.81.

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The Preparation of \((S)-2\text{-phenyl}-2\text{-o-tolyl}-2-((4S,5S)-2,2,5\text{-trimethyl-1,3-dioxolan-4-y})\text{-acetonitrile 48}

Following the same procedure for preparing compound 35a, starting from \((2S, 3S, 4S)-3,4\text{-dihydroxy-2-phenyl-2-o-tolylpentanenitrile 47 (23 mg, 0.08 mmol)}, PPTS (41 mg, 0.16 mmol) and 2,2\text{-dimethoxypropane (1 ml)} compound 48 was obtained (24 mg, yield: 92\% as white solid.

48: mp: 95-99°C. \(\lbrack \alpha \rbrack^\circ : +126.94 \text{ (c: 1.6 g/100 mg, CHCl}_3\rbrack\). IR (neat): 2239 cm\(^{-1}\). \text{H NMR (400 MHz, CDCl}_3\rbrack: \delta =0.34 \text{ (d, } J=5.2 \text{ Hz, 3H)}, 1.54 \text{ (s, 3H)}, 1.57 \text{ (s, 3H), 2.07 (s, 3H), 4.27 (dq, } J_1=5.2 \text{ Hz, } J_2=7.6 \text{ Hz, 1H), 4.34 (d, } J=8.0 \text{ Hz, 1H), 7.13 (d, } J=7.2 \text{ Hz, 1H,} \text{ 7.26-7.37 (complex pattern, 7H), 7.82 (dd, } J_1=7.6 \text{ Hz, } J_2=0.8 \text{ Hz, 1H). 13C NMR (100 MHz, CDCl}_3\rbrack: \delta =18.41, 20.89, 26.85, 27.94, 54.46, 74.78, 84.73, 109.24, 119.01, 126.12, 127.13, 127.63, 128.40, 128.52, 129.00, 132.76, 135.78, 136.17, 137.95. MS (EI): \text{m/z}= 321 \text{ [M]. Elemental Analysis: Calcd. for C}_{21}\text{H}_{23}\text{NO}_2: C, 78.47; H, 7.21; N, 4.36; O, 9.96, Found: C, 78.49; H, 7.21.}
References

Chapter 2

Chapter 3

Chapter 3. Synthesis and applications of N-tin ketene imines and α-trimethyltin nitriles

3.1 Introduction: State of the art.

Metalated nitriles are versatile synthetic intermediates for preparing α,β-functionalized nitriles. Metal cations and solvent modulate the structure of these anionic chameleons that can be predicatably varied between C-metalated nitriles 1, N-metalated nitriles 2, and nitrile-stabilized carbanions 3 (Scheme 3.1).1,3

\[ \text{Scheme 3.1} \]

Lithiated nitriles (lithium reagents are widely used for α-deprotonation of nitriles4) demonstrate an inherent propensity for planar, nitrogen coordinated dimers in the solid state and solutions.6,7 C-Lithiated nitriles, although less popular than the corresponding N-lithiated, have been characterized by crystallography in a lithiated cyclopropane and were fully identified.8,9 In contrast to lithium, several metals exhibit a preference for coordination to the formally anionic carbon of metallated nitriles. Magnesiated nitrile, e.g., has been reported to present a preference for coordination to carbon.10,11 From the solid-state structures of transition metal-bound alkynitriles, there is a roughly equal preference for N- and C- metalation. In the case of silylated nitriles, C-silylated prevail over N-silylated mainly as a function of the steric demanding of the ligands on silicon atom.3 In an oversimplification the metallo derivative of a nitrile presents two reactive basic centers: one on the α-carbon of the CN group and one on the nitrogen atom. In the frame of this work-thesis on the synthesis and reactivity of N-metallo ketene imines we will discuss in this section the reactivity of lithium metallated nitriles versus an electrophile as...
chlorotrialkyl tin compounds. Analogies and differences with the previous discussed synthesis and reactivity of \(N\)-silyl ketene imines will be emphasized.

Tin and germanium belong, with silicon, to the same group (group 4a metal) of the Mendeleev Table. We have already discussed about the reactivity of lithiated nitriles with chloroalkyl silyl electrophiles in the previous section. Alkyl germanium halides have been used in germylation of methalated nitrile anions by Belousova and co-workers\(^{12}\). From this reaction, a mixture of products containing \(N\)-germanium ketene imine and \(\alpha\)-carbon germylated nitrile (table 3.1) were formed with ratio 90:10. No mention to their reactivity has been reported. In the case of tin, at our knowledge, no studies have appeared on stannylation of nitrile anion\(^{13, 14}\). The corresponding \(N\)-tin ketene imines have been prepared through rearrangement reactions\(^{15, 16}\).

As above anticipated, in the frame of our studies on \(N\)-metallo imines and \(N\)-metallo ketene imines, one of the goals of this thesis has been the study on the synthesis and reactivity of \(N\)-metallo-ketene imines. Considering the similarity between Silicon and Tin, in order to enlighten their analogies and/or differences with the corresponding \(N\)-silyl and \(N\)-tin ketene imines, even in terms of relative stability, we started a study on these new compounds. Accordingly, the preparation of \(N\)-tin-ketene imines, starting from lithiated nitrile in analogy to the preparation of \(N\)-silyl ketene imines, was first considered. The results obtained and the relative discussions are reported in the following section.

### 3.2 Present work

#### 3.2.1 Synthesis and application of \(N\)-tin ketene imines

##### 3.2.1.1 Synthesis of \(N\)-tin ketene imines

The first attempt to prepare \(N\)-tin ketene imines was based on the protocol used for the preparation of \(N\)-silyl ketene imines (see Chapter 2). In a preliminary study, diphenylacetonitrile was treated with lithium diisopropyl amide at -78 °C in a suitable solvent. The corresponding carbanion was treated with different trialkyl tin chlorides. The results are reported in Table 3.1. IR analyses, performed on the crude reaction mixture or, in some cases after distillation, compound 3aa-d showed a stretching band around 2102 cm\(^{-1}\) consistent with the presence of a cumulene double bond. The preparation of different \(N\)-trisubstituted tin ketene imine was then attempted, even
with a very bulky alkyl tin moiety (dibutyl tert-butyl tin) (Table 3.1 4ad, 4bd). This study needs some comments.

Scheme 3.2 Synthesis and stability of N-tin ketene imines

Table 3.1 The identification of N-tin ketene imine according to the literature data.

<table>
<thead>
<tr>
<th>Known products</th>
<th>Prepared products</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketene imine</td>
<td>α-tin nitrile</td>
</tr>
<tr>
<td>Structures</td>
<td>3aa</td>
</tr>
<tr>
<td>IR(cm⁻¹)</td>
<td>2038</td>
</tr>
<tr>
<td>Structures</td>
<td>3ab</td>
</tr>
<tr>
<td>IR(cm⁻¹)</td>
<td>2068</td>
</tr>
<tr>
<td>Structures</td>
<td>3ac</td>
</tr>
<tr>
<td>IR(cm⁻¹)</td>
<td>-</td>
</tr>
<tr>
<td>Structures</td>
<td>3ad</td>
</tr>
<tr>
<td>IR(cm⁻¹)</td>
<td>2034</td>
</tr>
</tbody>
</table>

As in the case of N-silyl ketene imine, the stability of N-tin ketene imines depends from the property of the aryl/alkyl substituents on the beta-position of CN group and on the very nature, in
term of acidity, basicity and steric hindrance of the substituents on the tin. As a matter of fact, as anticipated in the case of germanium and silyl by other authors, a mixture of N-tin and C-tin may be present in the reaction medium (Scheme 3.2), arising from a tropism of the metal from the nitrogen to the carbon.

\( \text{N-Tin ketene imines} \) (Scheme 3.2 table 3.1) showed to be less stable than the corresponding N-silyl ketene imines. In the case of 3aa-d (table 3.1), keeping the reaction mixture at low temperature, IR spectrum showed a predominant presence of the N-Tin ketene imines over the C-Sn derivative. In contrast, IR spectra of other compounds (4ba-d) obtained from different nitriles show the predominance of the C-Sn derivative (for discussion on the equilibrium C-Sn and N-Sn see below).

From the data reported, the IR spectra suggest that at first a N-tin ketene imine is formed. This compound, depending from the reaction conditions, may undergo to a tin-tropism with the break of the N-Tin bond and the formation of a new \( \alpha \)-Carbon-Tin bond. As for the silyl and germanium, the two species may be in equilibrium. The predominance of one over the other depends from different factors: the nature of substituents of ketene imine, the steric hindrance of the substituents on tin and the experimental conditions. With stabilized nitrile-carbanions, as that obtained from diphenylacetonitrile, we can assume, from IR data, that N-tin ketene imines are predominant. On the contrary, with less stabilized carbanion the tin-tropism is favoured. In other words the same factors influencing the equilibrium between N-silyl ketene imines and \( \alpha \)-C-silyl compounds play an important role even in this case. The real and extremely important differences between the tin and the silicon derivatives is that the \( \alpha \)-C-tin compounds behave exactly as the corresponding N-tin compounds when reacted with carbonyl compounds as electrophilic partners (see below), whereas in the case of silyl the \( \alpha \)-C silyl are completely unreactive versus electrophiles unless a catalyst is used. If this reactivity, in the case of tin compounds, depends from equilibrium between the two species and/or from other factors is not completely understood at this time of our knowledge. In a working hypothesis we can assume that the reactive specie is the ketene imine and that the equilibrium between the \( C \)–tin and the \( N \)-tin is shifted versus the more reactive species \( N \)-tin. Following are the results obtained with different carbonyl electrophiles and different nucleophilic tin-derivatives.

3.2.1.2 Application of \( N \)-tin ketene imines and/or \( \alpha \)-tin nitriles in aldol type reaction with aldehydes, ketones and \( \alpha, \beta \) unsaturated carbonyl compounds

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Due to their broad range of applications, β-hydroxy nitriles play an important role in organic chemistry. Their synthesis is usually achieved by reaction of a metallated nitriles and an aldehyde or a ketones. As base sodium amide in liquid ammonia, butyl lithium, LDA have been used. The main drawback of this aldol type reaction lies into the possibility of a retro reaction, generally catalysed by a base, giving rise to the starting materials. As a matter of fact, although the main driving force in such carbonyl addition reaction of carbanions is considered to be the formation of a weaker base or nucleophile, an additional driving force can arise from the counter cation of the forming alkoxy derivatives.

![Scheme 3.3](image)

Scheme 3.3 N-tin ketene imines as an in-situ intermediate react with normal aldehydes

### Table 3.2 N-tin ketene imine 3ba as an in-situ intermediate on aldol type reaction with normal aldehydes

<table>
<thead>
<tr>
<th>Entry</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>5</td>
</tr>
<tr>
<td>6</td>
</tr>
<tr>
<td>7</td>
</tr>
</tbody>
</table>

The first carbonyl compounds we considered were simple aldehydes (Scheme 3.3). N-tin ketene imine and α-trimethyltin nitriles react with a wide range of aliphatic aldehydes (table 3.2.
entries 1-2), aromatic aldehydes (table 3.2 entries 3-5), and heterocyclic aldehydes (table 3.2 entries 6-7) with good yields and diastereoselectivity.

Taking the very interesting 2-furaldehydes (entries 1, 2, 4) and very common benzaldehyde (entry 3), different phenyl alkyl nitriles have been used in this reaction (Scheme 3.4, table 3.3). Dialkyl acetonitrile failed to react. The reasons of this failure, at this time of studies, are difficult to understand.

Scheme 3.4 N-tin ketene imines as an in-situ intermediate react with aldehydes.

Table 3.3 N-tin ketene imines from different nitriles react with aldehydes.

<table>
<thead>
<tr>
<th>Entry</th>
<th>N-tin ketene imine</th>
<th>aldehydes</th>
<th>products</th>
<th>Yield (%)</th>
<th>ratio (6:7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>R₁=Ph, R₂=i-pr(3ca)</td>
<td>R₃= 2-fural(5g)</td>
<td>6h, 7h</td>
<td>69</td>
<td>86:14</td>
</tr>
<tr>
<td>2</td>
<td>R₁=Ph, R₂=Allyl(3da)</td>
<td>R₃= 2-fural(5g)</td>
<td>6i, 7i</td>
<td>67</td>
<td>84:16</td>
</tr>
<tr>
<td>3</td>
<td>R₁=Ph, R₂=Allyl(3da)</td>
<td>R₃= phenyl(5c)</td>
<td>6j, 7j</td>
<td>54</td>
<td>76:24</td>
</tr>
<tr>
<td>4</td>
<td>R’=Ph, R₂=i-Butyl(3ea)</td>
<td>R₃= 2-fural(5g)</td>
<td>6k, 7k</td>
<td>64</td>
<td>85:15</td>
</tr>
<tr>
<td>5</td>
<td>Cyclohexyl(3fa)</td>
<td>R₃= 2-fural(5g)</td>
<td>-</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

# : the corresponding N-tin ketene imine was not isolated; the starting nitriles were prepared according to known procedure. ²⁴$: isolated yield; & : determined by HPLC and ¹H NMR, the configuration were determined by comparison with known compounds.

N-tin ketene imines were also reacted with α,β-unsaturated carbonyl compounds (Scheme 3.5): cinnamaldehyde (table 3.4, entries 2, 4) and crotonaldehyde (table 3.4, entry 1) to give 1,2 addition products, while 2-cyclohexenone (table 3.4, entry 3) gave, predominately, the 1, 4 addition products(8a).
Scheme 3.5 N-tin ketene imines as an in-situ intermediate react with α,β-unsaturated carbonyl compounds

Table 3.4 N-tin ketene imines as an in-situ intermediate react with α,β-unsaturated carbonyl compounds

<table>
<thead>
<tr>
<th>Entry</th>
<th>N-tin ketene imine</th>
<th>Aldehyde(R1, R4)</th>
<th>Products</th>
<th>Yield (%)</th>
<th>Ratio&lt;sup&gt;x&lt;/sup&gt; (6:7)</th>
<th>Ratio&lt;sup&gt;x&lt;/sup&gt; (6,7:8a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>R&lt;sub&gt;1&lt;/sub&gt;=Me(3ba)</td>
<td>R&lt;sub&gt;1&lt;/sub&gt;=H, R&lt;sub&gt;4&lt;/sub&gt;=Me(5h)</td>
<td>6l, 7l</td>
<td>70</td>
<td>60:40</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>R&lt;sub&gt;1&lt;/sub&gt;=Me(3ba)</td>
<td>R&lt;sub&gt;1&lt;/sub&gt;=H, R&lt;sub&gt;4&lt;/sub&gt;=Ph(5i)</td>
<td>6m, 7m</td>
<td>78</td>
<td>62:38</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>R&lt;sub&gt;1&lt;/sub&gt;=Me(3ba)</td>
<td>(5j)</td>
<td>6n, 7n, 8a</td>
<td>53</td>
<td>-</td>
<td>1:24</td>
</tr>
<tr>
<td>4</td>
<td>R&lt;sub&gt;1&lt;/sub&gt;=Ph(3ba)</td>
<td>R&lt;sub&gt;1&lt;/sub&gt;=H, R&lt;sub&gt;4&lt;/sub&gt;=Ph(5i)</td>
<td>6o</td>
<td>33</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

#: the corresponding N-tin ketene imine was not isolated; $: isolated yield; & : determined by HPLC and ¹HNMR, the configuration were determined by comparison with known compounds.

Ketones were also used as electrophiles. Some ketones, such as cyclohexanone, cyclopentanone, and acetophenone (table 3.5, entries 1-3) were successfully, while benzophenone (table 3.5 entry 4) was not reactive, probably because steric problems.

Scheme 3.6 N-tin ketene imines as an in-situ intermediate react with ketones.
Table 3.5 $N$-tin ketene imines as an in-situ intermediate react with ketones.

<table>
<thead>
<tr>
<th>Entry</th>
<th>$N$-tin ketene imine#</th>
<th>Ketones(5k-n)</th>
<th>Products</th>
<th>Reaction time(h)</th>
<th>Yield$^\dagger$(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>R’=Me(3ba)</td>
<td>Cyclohexanone(5k)</td>
<td>6p</td>
<td>2h</td>
<td>74</td>
</tr>
<tr>
<td>2</td>
<td>R’=Me(3ba)</td>
<td>Cyclopentanone(5l)</td>
<td>6q</td>
<td>2h</td>
<td>67</td>
</tr>
<tr>
<td>3</td>
<td>R’=Allyl(3da)</td>
<td>Cyclohexanone(5k)</td>
<td>6r</td>
<td>2h</td>
<td>89</td>
</tr>
<tr>
<td>4</td>
<td>R’=Me(3ba)</td>
<td>Acetophenone(5m)</td>
<td>6s, 7s$^&amp;$</td>
<td>4h</td>
<td>73</td>
</tr>
<tr>
<td>5</td>
<td>R’=Me(3ba)</td>
<td>Benzophenone(5n)</td>
<td>-</td>
<td>48h</td>
<td>0</td>
</tr>
</tbody>
</table>

#: the corresponding $N$-tin ketene imine was not isolated; $\dagger$: isolated yield; $\&$: the absolute configuration of diastereoisomer 6s, 7s were not assigned, the ratio between 6s and 7s is 50:50..

3.2.1.3 Application of $N$-tin ketene imines, generated in situ from lithium enolate of diphenyl acetonitrile and trimethyl tin chloride to the synthesis of Carbon sugar analogues through aldol type reaction with $\alpha$-hydroxy protected aldehydes.

Some optically pure aldehydes were attractive substratum for this aldol type reaction with $N$-tin ketene imines as nucleophilic counterpart.

![Scheme 3.7 $N$-tin ketene imines as an in-situ intermediate react with optically pure aldehydes]

In a logical extension of this protocol and in analogy to the studies performed on the silyl ketene imines, diphenyl $N$-tin ketene imine, identified by IR at low temperature, was reacted with optically pure aldehydes, in one pot reaction, as shown in Scheme 3.7 and table 3.6. From the diastereo control of this reaction, it is similar to the case of silyl ketene imine, in which the better stereo selectivity may be obtained with a more bulky protecting group (entry 3, table 3.6) on $\alpha$-position of optically pure aldehyde.25
Scheme 3.8 One pot reaction between N-tin ketene imines with different glyceraldehydes.

Among the previous optically aldehydes, we were mostly attracted by glyceraldehyde (table 3.6, entry 4), because the aldol additional products bearing three hydroxyl groups vicinal to a versatile functional cyano group, which can be a precursor of the very interesting carbon sugar analogues. In order to study the diastereoselectivity control of the reaction, different experimental parameters were tested. First, different bases were used in this one pot reaction: no significative difference was found between n-butyllithium and lithium bis-trimethylsilylamide.

Table 3.6 N-tin ketene imines as an in-situ intermediate react with optically pure aldehydes

<table>
<thead>
<tr>
<th>Entry</th>
<th>N-tin ketene imine#</th>
<th>Aldehyde(R’’,R’’’’’)</th>
<th>Products</th>
<th>Yield (%)</th>
<th>Ratio(^\circ) (10:11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3aa</td>
<td>R’’=Bn, R’’’’=methyl(9a)</td>
<td>10a, 11°</td>
<td>71</td>
<td>80:20</td>
</tr>
<tr>
<td>2</td>
<td>3ba</td>
<td>R’’=Bn, R’’’’=methyl(9a)</td>
<td>10b, 11°</td>
<td>55</td>
<td>64:36</td>
</tr>
<tr>
<td>3</td>
<td>3aa</td>
<td>R’’=TBS, R’’’’=methyl(9b)</td>
<td>11c</td>
<td>45</td>
<td>99:1</td>
</tr>
<tr>
<td>4</td>
<td>3aa</td>
<td></td>
<td>10d, 11d</td>
<td>61</td>
<td>77:23</td>
</tr>
</tbody>
</table>

#: the corresponding N-tin ketene imine was not isolated; $: isolated yield; &: determined by HPLC and \(^{1}\)HNMR, the configuration were determined by comparison with known compounds.

In contrast, changing the countercation of the base (sodium vs lithium), a dramatic change in diastemeric control was found (table 3.7, entry 5). No dedicated studies have been performed, so far, on the very reasons of this behaviour. In an oversimplification we feel that it may be attributed to the formation of chelated intermediated due to the different chelation propensity of the lithium vs sodium to give chelated complexes with nitrogen and oxygen containing compounds.

Then, different tin chloride were used for formation of different tin ketene imines. Among them, N-trimethyl tin ketene imine (3aa) gave the best results on isolated yields and
diastereoselectivity (table 3.7, entry 3). Moreover, with a bulky protecting group on glyceraldehyde (aldehyde 9b), the diastereoselectivity was improved.

**Table 3.7** Condition modification for aldol reaction of N-tin ketene imine with glyceraldehyde.

| Entry | Base       | N-tin ketene imine | Aldehyde(R’9) | Products   | Yield(|) | Ratio (10:11) |
|-------|------------|--------------------|---------------|------------|--------|---------------|
| 1     | n-BuLi     | R=Ph, 3ac          | R’=i-Pr (9a)  | 10d, 11d   | 44     | 56:44         |
| 2     | n-BuLi     | R=Bu, 3ab          | R’=i-Pr (9a)  | 10d, 11d   | 44     | 71:29         |
| 3     | n-BuLi     | R=Me, 3aa          | R’=i-Pr (9a)  | 10d, 11d   | 61     | 77:23         |
| 4     | LiHMDS     | R=Me, 3aa          | R’=i-Pr (9a)  | 10d, 11d   | 47     | 86:14         |
| 5     | NaHMDS     | R=Me, 3aa          | R’=i-Pr (9a)  | 10d, 11d   | 61     | 24:76         |
| 6     | n-BuLi     | R=Me, 3aa          | R’=c-Hex (9b) | 10e 11e    | 79     | 91:9          |

#: the corresponding N-tin ketene imine was not isolated; $: isolated yield; &: determined by HPLC and 1H NMR, the configuration were determined by comparison with known compounds.

**Scheme 3.9** Different diaryl N-tin ketene imines react with glyceraldehyde.

Different diaryl N-tin ketene imines were prepared *in-situ* and reacted with glyceraldehyde (Scheme 3.9). Aldehyde 9b (cyclohexane protected glyceraldehyde), did not give good yields and diastereoselectivity probably because steric effects due to the bulky protecting group when it reacts with substituted diaryl nitriles. The configuration of compound 10d and 11d were inferred by literature data (see chapter 2 compound 43, 44) and conformed by NOE’s (Nuclear Overhauser Effect) on compound 12 (Scheme 3.10). The configurations of other diaryl derivatives were attributed by comparison of chemical shift and coupling constant J. Compounds 10f-10l and 11f-11l are diastereomeric mixture, the absolute configuration of each isomer, so far, has not assigned.
Table 3.8 Different diaryl N-tin ketene imine react with glyceraldehydes.

<table>
<thead>
<tr>
<th>Entry</th>
<th>N-tin ketene imines $^d$</th>
<th>Products</th>
<th>Yield% $^s$</th>
<th>Ratio $^a$ (10:11)</th>
<th>Ratio $^b$ (Isomer B : Isomer A)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\text{Ar}_1=\text{Ph},$&lt;br&gt;$\text{Ar}_2=\text{4-MePh}(3\text{ga})$</td>
<td>$i$-$\text{Pr}(9\text{a})$</td>
<td>10f, 11f</td>
<td>41</td>
<td>85:15</td>
</tr>
</tbody>
</table>
| 1     | $\text{Ar}_1=\text{Ph},$
$\text{Ar}_2=\text{4-MePh}(3\text{ga})$
$\text{Ar}_1=\text{Ph},$
$\text{Ar}_2=\text{4-MePh}(3\text{ga})$
$\text{Ar}_1=\text{Ph},$
$\text{Ar}_2=\text{4-OMePh}(3\text{ha})$
$\text{Ar}_1=\text{Ph},$
$\text{Ar}_2=\text{3-MePh}(3\text{ia})$
$\text{Ar}_1=\text{4-OMePh},$
$\text{Ar}_2=\text{4-OMePh}(3\text{ja})$
$\text{Ar}_1=\text{Ph},$
$\text{Ar}_2=\text{4-NO}_2\text{Ph}(3\text{ka})$
$\text{Ar}_1=\text{Ph},$
$\text{Ar}_2=\text{3-Py}(3\text{la})$ | $i$-$\text{Pr}(9\text{a})$ | 10h, 11h | 21 | 82:18 | 54:46 | 63:37 |
| 2     | $c$-$\text{Hex}(9\text{b})$ | 10g, 11g | 17 | 86:14 | 78:32 | 50:50 |
| 3     | $i$-$\text{Pr}(9\text{a})$ | 10i, 11i | 28 | 70:30 | 54:46 | 50:50 |
| 4     | $i$-$\text{Pr}(9\text{a})$ | 10j, 11j | 28 | 73:27 | - | - |
| 5     | $c$-$\text{Hex}(9\text{b})$ | 10k, 11k | 13 | 60:40 | 77:23 | 53:47 |
| 6     | $i$-$\text{Pr}(9\text{a})$ | 10l, 11l | 48 | 62:38 | 74:26 | 62:38 |

$^#$: the corresponding N-tin ketene imine was not isolated, the starting nitriles 3g-3l were prepared as the same procedure reported in chapter 2; $^s$: isolated yield; $^\&$: determined by HPLC and $^1$HNMR, the configuration were determined by comparison with known compounds. $^*$: two diastereoisomers in products were not separated.

3.2.2 Synthesis and application of α- tin nitriles

3.2.2.1 Synthesis of α- trimethyltin nitriles

α- tin nitriles were prepared from acetonitriles 1 (Scheme 3.10), methalated by lithium reagent (LDA), and then trap with tin chloride, the reaction mixture were warmed to r.t for 2 hours. The reaction solvents were removed under vacuum, the residues was dissolved into pentane, filter under N$_2$, the filtrate was removed all the solvent, the crude products were distilled under vacuum. As discussed at the beginning of this chapter, when one of the R$_1$, R$_2$ was alkyl group, α- tin nitriles will be the exclusive final isolatable products, which is more thermal stable than the corresponding N-tin ketene imine, but it was also unstable and can be hydrolysed very fast when exposing to the air, this has been proved by the disappearing of its characterized IR absorption at around 2102 cm$^{-1}$ and appearing the strong signal of starting nitrile’s absorption at 2242 cm$^{-1}$ by shaking the sample on the air.
Chapter 3

Scheme 3.10 synthesis of α- tin nitriles

3.2.2.2 Uncatalyzed aldol type reaction of α- trimethyltin nitriles

To investigate the reactivity of α- tin nitriles, α-silyl nitriles were considered as a model of thinking, which have been found to be a useful nucleophiles in carbonyl addition reactions, but in this reaction, generally, an extra catalyst or an additive reagents were needed. In the other hand, organotin compounds are well-known processor for Carbon-Carbon bond formation through Stille coupling reaction and organostannyl addition to carbonyl compounds. So the aldol type reactions with carbonyl compounds were chosen for investigating the reactivity of α- tin nitriles. As a result, not only N-tin ketene imine, but also α- trimethyltin nitriles were successfully used in an uncatalyzed aldol type reaction, and this could be considered as one of the main discovery of this thesis.

Scheme 3.11 α- trimethyltin nitriles react with carbonyl compounds

First, α- trimethyltin nitriles 4ba-4ea were treated with aldehydes at -78°C, in order to have a comparison with the one pot reaction in which N-tin ketene imine as intermediate, a mixture solvents (THF:Toluene=50:50) was used (Scheme 3.11). In general, this reaction could complete in 2 hours, and then decompose the reaction with acidic solution. Compare to one pot reactions, when aldehydes were used as electrophiles, isolated α-trimethyl tin nitrile gives better yield, but the diastereoselectivity were decreased (table 3.9 entries 1-4), while in the case of ketone, the reaction yield were conspicuously decreased (entries 5-6), this phenomenon may point to our prediction that the N-tin ketene imine are more reactive and more steric sensitive than the correspond α- tin nitriles.
### Table 3.9 \( \alpha \)-trimethyltin nitriles react with carbonyl compounds

<table>
<thead>
<tr>
<th>Entry</th>
<th>4</th>
<th>5</th>
<th>product</th>
<th>Yield(^#)</th>
<th>Yield(^$)</th>
<th>Rati(^*) (6:7)</th>
<th>Ratio(^&amp;) (6:7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>R(_1)=Ph, R(_2)=Me(4ba)</td>
<td>R(_3)=2Furan, R(_4)=H(5g)</td>
<td>6g, 7g</td>
<td>72</td>
<td>71</td>
<td>72:18</td>
<td>85:15</td>
</tr>
<tr>
<td>2</td>
<td>R(_1)=Ph, R(_2)=Allyl(4da)</td>
<td>R(_3)=2-Furan, R(_4)=H(5g)</td>
<td>6i, 7i</td>
<td>78</td>
<td>67</td>
<td>60:40</td>
<td>84:16</td>
</tr>
<tr>
<td>3</td>
<td>R(_1)=Ph, R(_3)=i-Pr(4ca)</td>
<td>R(_3)=2-Furan, R(_4)=H(5g)</td>
<td>6h, 7h</td>
<td>89</td>
<td>69</td>
<td>73:27</td>
<td>86:14</td>
</tr>
<tr>
<td>4</td>
<td>R(_1)=Ph, R(_3)=i-Bu(4ea),</td>
<td>R(_3)=2-Furan, R(_4)=H(5g)</td>
<td>6k, 7k</td>
<td>69</td>
<td>64</td>
<td>60:40</td>
<td>85:15</td>
</tr>
<tr>
<td>5</td>
<td>R(_1)=Ph, R(_2)=Me(4ba)</td>
<td>Acetophenone(5l)</td>
<td>6s, 7s</td>
<td>21</td>
<td>73</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>R(_1)=Ph, R(_2)=Me(4ba)</td>
<td>Cyclohexanone(5j)</td>
<td>6p</td>
<td>25</td>
<td>74</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>Cyclohexyl(4fa)</td>
<td>R(_3)=2-Furan, R(_4)=H(5g)</td>
<td>No reaction</td>
<td>0</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

\#: isolated yields of one pot reactions in which \(N\)-tin ketene imines were considered as intermediates; \$: isolated yields. \&: determined by HPLC and \(^1\)HNMR; ratio of one pot reactions in which \(N\)-tin ketene imines were considered as intermediates; 

\*: determined by HPLC and \(^1\)HNMR.

### 3.3 Conclusion

In conclusion, \(N\)-tin ketene imines obtained by trapping lithium enolate of nitrile with tin chloride showed similar reactivity compared to the silyl homologous whereas the corresponding \(C\)-tin compounds, derived from a tin-ketene imines via a tin tropism show a very high reactivity versus electrophiles, like carbonyl compounds, compared to the homologous \(C\)-silyl derivatives. The different reactivity is currently under scouting with the help of theoretical calculations.

### 3.4 Experimental Section

The configurations of aldol addition products were assigned by comparison the chemical shift of known similar products. As shown in table 3.10, proton number 3° and 11° were picked out for comparison, compound 6c and 7c were known products reported by Denmark\(^{31}\) and Yin.\(^{32}\) The major product 7c has proton 3° higher chemical shift than compound 6c, more polar than 6c according to TLC and HPLC. The similar structures 6d, 7d, 6e, 7e, 6f, 7f, 6j, 7j followed this trend. In table 3.11 compound 6g was reported by Denmark, with the same trick, the configuration
of compound 6h, 7h, 6j, 7j, 6k, and 7k can be assigned. Compound 6a is known product from the paper by Yin,\textsuperscript{32} compound 6b and 7b can be identified accordingly, the configuration of 6l, 7l, 6m, 7m were assigned according to reference 33.\textsuperscript{33}

Table 3.10 Aromatic aldehydes: Identification of aromatic aldehyde

<table>
<thead>
<tr>
<th>Products</th>
<th>Products</th>
<th>(^1^H\text{δ }3^o,\ ^1^H\text{δ }12^o</th>
<th>Polarity</th>
</tr>
</thead>
<tbody>
<tr>
<td>7c</td>
<td><img src="image" alt="Image of 7c" /></td>
<td>(^1^H\text{δ }3^o: 4.834) (^1^H\text{δ }12^o: 1.864)</td>
<td>More polar</td>
</tr>
<tr>
<td>6c</td>
<td><img src="image" alt="Image of 6c" /></td>
<td>(^1^H\text{δ }3^o: 4.878) (^1^H\text{δ }12^o: 1.608)</td>
<td>Less polar</td>
</tr>
<tr>
<td>7d</td>
<td><img src="image" alt="Image of 7d" /></td>
<td>(^1^H\text{δ }3^o: 4.841) (^1^H\text{δ }13^o: 3.767)</td>
<td>More polar</td>
</tr>
<tr>
<td>6d</td>
<td><img src="image" alt="Image of 6d" /></td>
<td>(^1^H\text{δ }12^o: 1.588) (^1^H\text{δ }13^o: 3.807)</td>
<td>Less polar</td>
</tr>
<tr>
<td>7e</td>
<td><img src="image" alt="Image of 7e" /></td>
<td>(^1^H\text{δ }3^o: 4.962) (^1^H\text{δ }12^o: 1.891)</td>
<td>More polar</td>
</tr>
<tr>
<td>6e</td>
<td><img src="image" alt="Image of 6e" /></td>
<td>(^1^H\text{δ }3^o: 5.032) (^1^H\text{δ }12^o: 1.668)</td>
<td>Less polar</td>
</tr>
<tr>
<td>7f</td>
<td><img src="image" alt="Image of 7f" /></td>
<td>(^1^H\text{δ }3^o: 4.818) (^1^H\text{δ }12^o: 1.857)</td>
<td>More polar</td>
</tr>
<tr>
<td>6f</td>
<td><img src="image" alt="Image of 6f" /></td>
<td>(^1^H\text{δ }3^o: 4.879) (^1^H\text{δ }12^o: 1.593)</td>
<td>Less polar</td>
</tr>
<tr>
<td>7i</td>
<td><img src="image" alt="Image of 7i" /></td>
<td>(^1^H\text{δ }3^o: 4.885) (^1^H\text{δ }12^o: a: 3.182) (^1^H\text{δ }12^o: b: 2.953)</td>
<td>More polar</td>
</tr>
<tr>
<td>6i</td>
<td><img src="image" alt="Image of 6i" /></td>
<td>(^1^H\text{δ }3^o: 4.936) (^1^H\text{δ }12^o: a: 2.785) (^1^H\text{δ }12^o: b: 2.597)</td>
<td>Less polar</td>
</tr>
</tbody>
</table>
### Table 3.11 2-furan aldehyde products $^1$HNMR

<table>
<thead>
<tr>
<th>Resource</th>
<th>Product</th>
<th>$\delta^1$H 3', 5', 6', 12'</th>
<th>Polarity</th>
</tr>
</thead>
<tbody>
<tr>
<td>7g</td>
<td>(2R*, 3R*)</td>
<td>$\delta^1$H 3': 4.887</td>
<td>More polar</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$\delta^1$H 5': 6.13 (d, J = 3.2 Hz)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>$\delta^1$H 6': 6.25 (dd, J = 3.6, 2.0 Hz)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>$\delta^1$H 12': 1.91</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>$\delta^1$H 3': 4.930 (s)</td>
<td></td>
</tr>
<tr>
<td>6g</td>
<td>(2R*, 3S*)</td>
<td>$\delta^1$H 3': 4.846 (d, J = 3.2 Hz)</td>
<td>Less polar</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$\delta^1$H 5': 6.40 (dd, J = 3.2, 2.0 Hz)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>$\delta^1$H 6': 6.17 (dd, J = 3.2, 1.6 Hz)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>$\delta^1$H 12': 1.68</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>$\delta^1$H 3': 4.839 (d, J = 6.8 Hz)</td>
<td></td>
</tr>
<tr>
<td>7k</td>
<td>(2R*, 3R*)</td>
<td>$\delta^1$H 3': 5.351 (d, J = 7.6 Hz)</td>
<td>More polar</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$\delta^1$H 5': 6.04 (d, J = 3.2 Hz)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>$\delta^1$H 6': 6.241 (dd, J = 3.2, 1.6 Hz)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>$\delta^1$H 12': 2.613</td>
<td></td>
</tr>
<tr>
<td>6k</td>
<td>(2R*, 3S*)</td>
<td>$\delta^1$H 3': 5.345 (d, J = 6.0 Hz)</td>
<td>Less polar</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$\delta^1$H 5': 6.04 (d, J = 3.2 Hz)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>$\delta^1$H 6': 6.240 (dd, J = 3.2, 1.6 Hz)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>$\delta^1$H 12': 2.693</td>
<td></td>
</tr>
<tr>
<td>7i</td>
<td>(2R*, 3R*)</td>
<td>$\delta^1$H 3': 5.15 (d, J = 1.2 Hz)</td>
<td>More polar</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$\delta^1$H 5': 6.078 (d, J = 3.2 Hz)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>$\delta^1$H 6': 6.209 (dd, J = 3.2, 2.0 Hz)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>$\delta^1$H 12': 3.179 b. 2.907</td>
<td></td>
</tr>
<tr>
<td>6i</td>
<td>(2R*, 3S*)</td>
<td>$\delta^1$H 3': 5.15 (d, J = 1.2 Hz)</td>
<td>Less polar</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$\delta^1$H 5': 6.439 (d, J = 3.2 Hz)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>$\delta^1$H 6': 6.389 (dd, J = 3.2, 2.0 Hz)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>$\delta^1$H 12': 2.822, b. 2.659</td>
<td></td>
</tr>
</tbody>
</table>
### Chapter 3

Table 3.12 Aliphatic aldehydes products $^1$HNMR

<table>
<thead>
<tr>
<th>Resource</th>
<th>Product</th>
<th>$^1$H δ 3°, $^1$H δ 11°</th>
<th>Polarity</th>
</tr>
</thead>
<tbody>
<tr>
<td>7a</td>
<td><img src="image" alt="Structure" /></td>
<td>$^1$H δ 3°: 3.64, $^1$H δ 11°: 1.769</td>
<td>Less polar</td>
</tr>
<tr>
<td>6a</td>
<td><img src="image" alt="Structure" /></td>
<td>$^1$H δ 4°: 1.619-1.695</td>
<td>More polar</td>
</tr>
<tr>
<td>7b</td>
<td><img src="image" alt="Structure" /></td>
<td>$^1$H δ 3°: 3.660, $^1$H δ 12°: 1.876</td>
<td>Less polar</td>
</tr>
<tr>
<td>6b</td>
<td><img src="image" alt="Structure" /></td>
<td>$^1$H δ 3°: 3.614, $^1$H δ 12°: 1.984</td>
<td>More polar</td>
</tr>
</tbody>
</table>

Table 3.13 α,β- unsaturated aldehydes products $^1$HNMR

<table>
<thead>
<tr>
<th>Resource</th>
<th>Product</th>
<th>$^1$H δ 3°, $^1$H δ 11°</th>
<th>Polarity</th>
</tr>
</thead>
<tbody>
<tr>
<td>7l</td>
<td><img src="image" alt="Structure" /></td>
<td>$^1$H δ 3°: 4.240, $^1$H δ 11°: 1.785</td>
<td>More polar</td>
</tr>
<tr>
<td>6l</td>
<td><img src="image" alt="Structure" /></td>
<td>$^1$H δ 3°: 4.214, $^1$H δ 11°: 1.655</td>
<td>Less polar</td>
</tr>
<tr>
<td>7m</td>
<td><img src="image" alt="Structure" /></td>
<td>$^1$H δ 3°: 4.462, $^1$H δ 11°: 1.825</td>
<td>More polar</td>
</tr>
<tr>
<td>6m</td>
<td><img src="image" alt="Structure" /></td>
<td>$^1$H δ 3°: 4.442, $^1$H δ 11°: 1.707</td>
<td>Less polar</td>
</tr>
</tbody>
</table>
3.4.1. General method

Column chromatography was performed using Merck KGaA Silicagel 60 (230-400 Mesh-ASTM). Melting points were obtained using a Stuart Scientific SMP3 Melting Point apparatus. Optical rotations were obtained using a Unipol L1700 Schmidt+Haensch polarimeter. IR spectra were recorded on a Nicolet 380 FT-IR infrared spectrometer and Alpha Fourier-T Infrared Analysis Spectrometer (Bruker). NMR spectroscopy was performed on a Varian-Mercury 400 spectrometer using the residual signal of the solvent as the internal standard. The chemical shifts are reported in ppm and coupling constants \( J \) are reported in Hz. GC–MS spectra were recorded using Agilent Technologies 6850 and 5975 GC-Mass instrumentation. LC–MS spectra were obtained using an Agilent Technologies MSD1100 single-quadrupole mass spectrometer. The diastereomeric ratios reported into Tables 1, 2 and 3 have been calculated by HPLC (Agilent, Poroshell 120. SB-C18. 2.7µm, 3.0 x 100 mm) and \(^1\)H NMR on the crude reaction mixture taking into account the undoubtful peaks of each diastereomer. Elemental analyses were obtained using Flash 2000, series CHNS/O Analyzer (Thermo Scientific).

3.4.2. Procedure for one-pot aldol type reaction through N-tin ketene imine and/or \( \alpha \)-tin nitrile

Procedure A:

\( n \)-BuLi was added into a solution of diisopropylamine in THF at -78 °C. Then a solution of starting nitrile 1 in was dropped into the base solution at -78 °C. After 5 min, a solution of trimethyltin chloride in toluene was dropped into the reaction. After maintaining at -78 °C for 15min, the reaction mixture was allowed to reach r.t and keep stirring for 2 hours, then remove all the solvents, dissolve the residue to anhydrous pentane or cyclohexane, filter, remove the solvents of filtrate, the residue were used for next step reaction without further purification. This product was identified by IR in some cases for relative stable \( N \)-tin ketene imine, such as 3aa showed IR at 2102cm\(^{-1}\). Then the prepared product was cooled to -78 °C and a solution of aldehyde (5 or 9) in toluene was slowly dropped into the reaction, after 2 hours, the reaction was quenched by an acidic solution of 1M HCl (0.5 ml) in saturated \( \text{NH}_4\text{Cl} \) solution (15 ml) at -78°C, then 20 ml ethyl acetate was added at same temperature, the mixture was allowed to reach r.t spontaneously, then extract with ethyl acetate(20 ml*2), washed organic phase by
brine, dried by anhydrous Na$_2$SO$_4$, remove all the solvent, made a silicon gel chromatography for purification.

Procedure B:
n-BuLi was added into a solution of diisopropyl amine in THF at -78 °C. Then a solution of starting nitrile 1 in was dropped into the base solution at -78 °C. After 5 min, a solution of trimethyltin chloride in toluene was dropped into the reaction. After maintaining at -78 °C for 15 min, then a solution of aldehyde 5 in toluene was slowly dropped into the reaction, after 2 hours, the reaction was quenched by an acidic solution of 1M HCl (2 ml) in methanol (2 ml) at -78 °C, then 20 ml ethyl acetate was added at same temperature, the mixture was allowed to reach r.t spontaneously, then extract with ethyl acetate(20 ml*2), washed organic phase by brine, dried by anhydrous Na$_2$SO$_4$, remove all the solvent, made a silicon gel chromatography for purification.

Procedure C

$n$-BuLi was added into a solution of starting nitrile 1 in was dropped into the base solution at -78 °C. After 5 min, a solution of trimethyltin chloride in toluene was dropped into the reaction. After maintaining at -78 °C for 15 min, then a solution of aldehyde 9 in toluene was slowly dropped into the reaction, after 16-18 hours, the reaction was quenched by an acidic solution of 1M HCl (0.5 ml) in saturated NH$_4$Cl solution(15 ml) at -78 °C, then 20 ml ethyl acetate was added at same temperature, the mixture was allowed to reach r.t spontaneously, then extract with ethyl acetate(20 ml*2), washed organic phase by brine, dried by anhydrous Na$_2$SO$_4$, remove all the solvent, made a silicon gel chromatography for purification.

The preparation of (2R*, 3R*) 3-hydroxy-2,4-dimethyl-2-phenylpentanenitrile(7a) and (2R*,3S*)-3-hydroxy-2,4-dimethyl-2-phenylpentanenitrile$^{32}$ (6a)

Following the procedure B, n-BuLi (0.44 ml, 1.1 mmol) was added into a solution of diisopropyl ethyl amine(0.15 ml, 1.1 mmol) in THF at -78 °C. A solution of 1b (131 mg, 1.0 mmol) in THF, trimethyltin chloride (219 mg, 1.1 mmol) in toluene were successively added, then aldehyde 5a (86 mg, 1.2 mmol) in toluene was dropped in to reaction. Made the column by Cyclohexane : Ethyl acetate = 4:1, get a diastereomixture 130 mg, yield: 64%. Then separate two diastereo isomer by silicon gel chromatography with dichloromethane : ether = 100:1 for identification.
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Colorless Oil. IR (KBr): 2243 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 7.55 – 7.53\) (m, 2H), \(7.43 – 7.40\) (m, 2H), \(7.39 – 7.34\) (m, 1H), 3.66 (dd, \(J = 8.0, 3.2\) Hz, 1H), 2.08-2.01 (m, 1H), 1.77 (s, 3H), 1.43 (bs, 1H, OH), 1.03 (d, \(J = 7.2\) Hz, 3H), 0.94 (d, \(J = 6.8\) Hz, 3H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta 138.55, 128.88, 128.13, 126.46, 122.64, 81.31, 47.13, 30.08, 23.57, 22.22, 15.65\). MS (HPLC-MS) [M+Na] 226. Elemental Analysis: Calcd for: C, 76.81; H, 8.43; N, 6.89; O, 7.87. Found: C, 76.99; H, 8.44.

White solid .mp. 61-64 °C. IR (KBr): 2243 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 7.47-7.45\) (m, 2H), \(7.43 – 7.37\) (m, 2H), \(7.34 – 7.31\) (m, 1H), 3.66 (dd, \(J = 8.0, 3.2\) Hz, 1H), 1.86 (bs, 1H, OH), 1.85 (s, 3H), 1.70 – 1.62 (m, 1H), 0.96 (d, \(J = 6.8\) Hz, 3H), 0.88 (d, \(J = 6.8\) Hz, 3H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta 138.41, 129.03, 128.00, 125.92, 122.13, 81.49, 48.02, 29.98, 25.95, 21.85, 15.17\). MS (HPLC-MS) [M+Na] 226. Elemental Analysis: Calcd for: C, 76.81; H, 8.43; N, 6.89; O, 7.87. Found: C, 76.98; H, 8.43.

The preparation of \((2R^*,3R^*)-3\)-hydroxy-2,4,4-trimethyl-2-phenylpentanenitrile (7b) and \((2R^*,3S^*)-3\)-hydroxy-2,4,4-trimethyl-2-phenylpentanenitrile (6b)

Following the procedure B, n-BuLi (0.44 ml, 1.1 mmol) was added into a solution of diisopropyl ethyl amine(0.15 ml, 1.1 mmol) in THF at -78 °C. A solution of 1b (131 mg, 1.0 mmol) in THF, trimethyltin chloride (219 mg, 1.1 mmol) in toluene were successively added, then aldehyde 5b (103 mg, 1.2 mmol) in toluene was dropped in to reaction. Made the column by Cyclohexane : Ethyl acetate = 4:1, get a diastereomixture 130 mg, yield: 54%. Then made a column with dichloromethane : ether = 100 :1 for identification.
White solid. mp: 60-62 °C. IR (neat): 2243 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ 7.60 (d, J = 7.6 Hz, 2H), 7.40-7.31 (m, 3H), 3.66 (d, J = 6.0 Hz, 1H), 1.95 (d, J = 6.0 Hz, 1H, OH), 1.88 (s, 3H), 0.94 (s, 9H). ¹³C NMR (100 MHz, CDCl₃) δ 138.60, 128.72, 128.07, 126.83, 123.19, 83.38, 46.64, 37.31, 27.53, 27.01. MS (HPLC-MS) [M+Na]: 240. Elemental Analysis: Calcd for C₁₄H₁₉NO: C, 77.38; H, 8.81; N, 6.45; O, 7.36. Found: C, 77.52; H, 8.82.

Light yellow oil. IR (neat): 2242 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ 7.39 – 7.20 (m, 8H), 7.17 -7.07 (m, 2H), 4.83 (s, 1H), 2.46 (bs, 1H, OH), 1.86 (s, 3H).¹³C NMR (100 MHz, CDCl₃) δ 138.17, 136.81, 128.51, 128.44, 128.13, 127.79, 127.22, 126.91, 121.95, 79.83, 49.08, 22.07. MS (HPLC-MS) [M+Na]:260. Elemental Analysis: Calcd for C₁₆H₁₅NO: C, 80.98; H, 6.37; N, 5.90; O, 6.74. Found: C, 81.10; H, 6.39.
White solid: mp. 96-98 °C. IR (KBr): 2242 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.49 – 7.23 (m, 10H), 7.41 (m, 3H), 7.36 – 7.28 (m, 5H), 4.88 (s, 1H), 2.26 (bs, 1H, OH), 1.61 (s, 3H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 137.75, 137.51, 128.90, 128.86, 128.41, 128.12, 127.56, 126.73, 121.72, 79.92, 49.51, 22.60. MS (HPLC-MS) \([\text{M}+\text{Na}]\). Calcd for C\(_{16}\)H\(_{15}\)NO: C, 80.98; H, 6.37; N, 5.90; O, 6.74. Found: C, 81.19; H, 6.38.

The preparation of (2R*, 3R*)-3-hydroxy-3-(4-methoxyphenyl)-2-methyl-2-phenylpropanenitrile (7d) and (2S*,3R*)-3-hydroxy-3-(4-methoxyphenyl)-2-methyl-2-phenylpropanenitrile (6d)

Following the procedure B, n-BuLi (0.44 ml, 1.1 mmol) was added into a solution of diisopropyl amine(0.15 ml, 1.1 mmol) in THF at -78 °C. A solution of 1b (131 mg, 1.0 mmol) in THF, trimethyltin chloride (219 mg, 1.1 mmol) in toluene were successively added, then aldehyde 5d (163 mg, 1.2 mmol) in toluene was dropped in to reaction. Made the column by Cyclohexane : Ethyl acetate = 4:1, get a diastereomixture 195 mg, yield: 73 %. Then separate two diastereo isomer by silicon gel chromatography with dichloromethane : ether = 100 :1 for identification.

White solid. mp.110-112 °C. IR (KBr): 2240 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.30-7.29 (m, 5H), 7.02 (d, \(J = 8.4\) Hz, 2H), 6.74 (d, \(J = 8.4\) Hz, 2H), 4.81 (d, \(J = 2.8\) Hz, 1H), 3.77 (s, 3H), 2.24 (d, \(J = 2.8\) Hz, 1H, OH), 1.85 (s, 3H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 159.69, 136.97, 130.35, 128.48, 128.44, 128.12, 126.98, 122.12, 113.23, 79.61, 55.20, 49.22, 22.10. MS: HPLC-MS[M+Na]: 290. Elemental Analysis: Calcd for C\(_{17}\)H\(_{17}\)NO\(_2\): C, 76.38; H, 6.41; N, 5.24; O, 11.97. Found: C, 76.52; H, 6.42.
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White solid. mp: 115-117 °C. IR (KBr): 2240 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ 7.48 (d, J = 7.6 Hz, 2H), 7.42-7.36 (m, 3H), 7.23 (d, J = 8.4 Hz, 2H), 6.85 (d, J = 8.4 Hz, 2H), 4.82 (s, 1H), 3.81 (s, 3H), 2.31 (s, 1H, OH), 1.59 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 159.93, 137.63, 129.94, 128.79, 128.71, 126.71, 121.87, 113.46, 79.50, 55.25, 49.62, 22.63. MS (HPLC-MS) [M+Na]: 290. Elemental Analysis: Calcd for C₁₇H₁₇NO₂: C, 76.38; H, 6.41; N, 5.24; O, 11.97. Found: C, 76.50; H, 6.42.

The preparation of (2R*, 3R*)-3-hydroxy-2-methyl-3-(4-nitrophenyl)-2-phenylpropanenitrile (7e) and (2S*, 3R*)-3-hydroxy-2-methyl-3-(4-nitrophenyl)-2-phenylpropanenitrile (6e)

Following the procedure B, n-BuLi (0.44 ml, 1.1 mmol) was added into a solution of diisopropylamine (0.15 ml, 1.1 mmol) in THF at -78 °C. A solution of 1b (131 mg, 1.0 mmol) in THF, trimethyltin chloride (219 mg, 1.1 mmol) in toluene were successively added, then aldehyde 5e (181 mg, 1.2 mmol) in toluene was dropped in to reaction. Made the column by Cyclohexane : Ethyl acetate = 4:1, get a diastereomixture 158 mg, yield: 56 %. Then separate two diastereo isomer by silicon gel chromatography with dichloromethane : ether = 100 :1 for identification.

White solid. mp: 130-132 °C. IR (KBr): 2245 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ 8.07 (d, J = 8.8 Hz, 2H), 7.44 - 7.27 (m, 7H), 4.96 (s, 1H), 2.62 (bs, 1H, OH), 1.89 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 148.18, 145.19, 136.16, 128.92, 128.24, 126.71, 122.90, 121.07, 78.98, 49.11, 21.96. MS (HPLC-MS): [M+Na].305. Elemental Analysis: Calcd for C₁₆H₁₄N₂O₃: C, 68.08; H, 5.00; N, 9.92; O, 17.00. Found: C, 68.7; H, 5.01.

White solid. mp: 174-175 °C. IR (KBr): 2245 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ 8.15 (d, J = 8.8 Hz, 2H), 7.44 – 7.40 (m, 7H), 5.03 (d, J = 3.2 Hz, 1H), 2.59 (d, J = 3.2 Hz, 1H, OH), 1.67
The preparation of (2R*,3R*)-3-hydroxy-2-methyl-2-phenyl-3-(pyridin-3-yl)propanenitrile (7f) and (2S*,3R*)-3-hydroxy-2-methyl-2-phenyl-3-(pyridin-3-yl)propanenitrile (6f)

Following the procedure B, n-BuLi (0.44 ml, 1.1 mmol) was added into a solution of diisopropyl amine (0.15 ml, 1.1 mmol) in THF at -78 °C. A solution of 1b (131 mg, 1.0 mmol) in THF, trimethyltin chloride (219 mg, 1.1 mmol) in toluene were successively added, then aldehyde 5f (128 mg, 1.2 mmol) in toluene was dropped in to reaction. Made the column by Cyclohexane : Ethyl acetate = 4:1, get a diastereomixture 133 mg, yield: 56 %. Then separate two diastereo isomer by silicon gel chromatography with dichloromethane : ether = 100 :3 for identification.

White solid. mp.160-162 °C. IR (neat): 2246 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ 8.36 (bs, 1H), 8.00 (bs, 1H), 7.56 (d, J = 7.6 Hz, 1H), 7.32 – 7.18 (m, 5H), 7.16 – 7.14(m, 1H), 4.82 (s, 1H), 3.51 (bs, 1H, OH), 1.86 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 148.73, 148.13, 136.30, 135.42, 129.00, 128.67, 126.62, 123.68, 121.29, 77.76, 49.43, 22.48. MS(HPLC-MS). [M+Na] 261. Elemental Analysis: Calcd for C₁₆H₁₄N₂O: C, 75.61; H, 5.92; N, 11.76; O, 6.71. Found: C, 75.88; H, 5.94.

White solid. mp.154-156 °C. IR (neat): 2246 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ 8.41 (bs, 1H), 8.22 (bs, 1H), 7.67 (d, J = 7.6 Hz, 1H), 7.41-7.33 (m, 5H), 7.22 (dt, J= 4.8, 3.6 Hz, 1H), 4.88 (s, 1H), 3.66 (bs, 1H, OH), 1.59 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 149.69, 148.75, 136.69, 135.31, 128.99, 128.68, 126.78, 123.25, 121.57, 77.38, 49.42, 21.98. MS(HPLC-MS).
The preparation of (2SR*,3S*)-3-(furan-2-yl)-3-hydroxy-2-methyl-2-phenylpropanenitrile (7g) and (2R*,3R*)-3-(furan-2-yl)-3-hydroxy-2-methyl-2-phenylpropanenitrile (6g)

Following the procedure B, n-BuLi (0.44 ml, 1.1 mmol) was added into a solution of diisopropyl ethyl amine (0.15 ml, 1.1 mmol) in THF at -78 °C. A solution of 1b (131 mg, 1.0 mmol) in THF, trimethyltin chloride (219 mg, 1.1 mmol) in toluene were successively added, then aldehyde 5g (115 mg, 1.2 mmol) in toluene was dropped in to reaction. Made the column by Cyclohexane: Ethyl acetate = 4:1, get a diastereomixture 161 mg, yield: 71%. Then separate two diastereo isomer by preparative HPLC for identification.

7g

Colorless oil. IR (neat): 2242 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.45 – 7.29 (m, 6H), 6.25 (dd, \(J = 3.6, 2.0\) Hz, 1H), 6.13 (d, \(J=3.2, 1H\)), 4.89 (s, 1H), 2.48 (bs, 1H, OH), 1.91 (s, 3H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 151.26, 142.34, 131.20, 128.63, 128.26, 126.44, 121.51, 110.35, 108.73, 74.14, 48.76, 22.97. MS(HPLC-MS). [M+Na] 250, [M+H\(_2\)O] 245. Elemental Analysis: Calcd for C\(_{14}\)H\(_{14}\)NO\(_2\): C, 73.99; H, 5.77; N, 6.16; O, 14.08. Found: C, 74.22; H, 5.79.

6g

White solid. mp.123-125 °C. IR (neat): 2242 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7. 36 (m, 6H), 6.46 (d, \(J = 3.2\) Hz, 1H), 6.40 (dd, \(J = 3.2, 2.0\) Hz, 1H), 4.93 (d, \(J = 4.8\) Hz, 1H), 2.33 (bs, 1H, OH), 1.68 (s, 3H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 151.50, 142.48, 137.27, 128.86, 128.60, 126.40, 128.40, 121.49, 110.63, 108.86, 74.09, 49.09, 22.45. MS(HPLC-MS). [M+Na] 250. Elemental Analysis: Calcd for C\(_{14}\)H\(_{13}\)NO\(_2\): C, 73.99; H, 5.77; N, 6.16; O, 14.08. Found: C, 74.19; H, 5.78.

[M+Na] 261. Elemental Analysis: Calcd for C\(_{13}\)H\(_{14}\)N\(_2\)O: C, 75.61; H, 5.92; N, 11.76; O, 6.71. Found: C, 75.84; H, 5.94.
The preparation of (R*)-2-((S*)-furan-2-yl(hydroxy)methyl)-3-methyl-2-phenylbutanenitrile (7h) and (2R*, 3R*)-2-(furan-2-yl(hydroxy)methyl)-3-methyl-2-phenylbutanenitrile (6h)

Following the procedure B, n-BuLi (0.44 ml, 1.1 mmol) was added into a solution of diisopropyl ethyl amine(0.15 ml, 1.1 mmol) in THF at -78 °C. A solution of 1c (159 mg, 1.0 mmol) in THF, trimethyltin chloride (219 mg, 1.1 mmol) in toluene were successively added, then aldehyde 5g (115 mg, 1.2 mmol) in toluene was dropped in to reaction. Made the column by Cyclohexane: Ethyl acetate = 4:1, get a diastereomixture 176 mg, yield: 69%. Then separate two diastereo isomer by preparative HPLC for identification.

7h

White solid. mp. 76-78 °C. IR (KBr): 2243 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ 7.29 - 7.17 (m, 6H), 6.24 (dd, J = 3.2, 1.6 Hz, 1H), 6.04 (d, J = 3.2 Hz, 1H), 5.35 (d, J = 7.6 Hz, 1H), 2.65-2.58 (m, 1H), 2.39 (d, J = 7.6 Hz, 1H, OH), 1.30 (d, J = 6.8 Hz, 3H), 0.91 (d, J = 6.8 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 151.69, 142.44, 135.58, 128.90, 128.32, 127.00, 119.54, 110.72, 108.96, 74.81, 54.04, 43.12, 25.36, 23.98, 22.75. MS (HPLC-MS) [M+Na].278. Elemental Analysis: Calcd for C₁₆H₁₇NO₂: C, 75.27; H, 6.71; N, 5.49; O, 12.53. Found: C, 75.46; H, 6.72.

6h

White solid. mp.86-88 °C. IR (KBr): 2243 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ 7.42 – 7.31 (m, 5H), 7.19 (t, J = 0.8 Hz, 1H), 6.24 (dd, J = 3.2, 1.6 Hz, 1H), 6.09 (d, J = 3.2 Hz, 1H), 5.34 (d, J = 6.0 Hz, 1H), 2.69 (m, 1H), 2.49 (d, J = 6.4 Hz, 1H, OH), 1.26 (d, J = 6.4 Hz, 3H), 0.86 (d, J = 6.8 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 151.78, 141.92, 134.23, 128.26, 128.06, 127.63, 119.54, 110.35, 108.38, 70.29, 59.36, 32.22, 18.68, 18.41. MS (HPLC-MS) [M+Na].278. Elemental Analysis: Calcd for C₁₆H₁₇NO₂: C, 75.27; H, 6.71; N, 5.49; O, 12.53. Found: C, 75.34; H, 6.71.

The preparation of (R*)-2-((S*)-furan-2-yl(hydroxy)methyl)-2-phenylpent-4-enenitrile (7i) and (R*)-2-((R*)-furan-2-yl(hydroxy)methyl)-2-phenylpent-4-enenitrile (6i)
Following the procedure B, n-BuLi (0.44 ml, 1.1 mmol) was added into a solution of diisopropyl ethyl amine (0.15 ml, 1.1 mmol) in THF at -78 °C. A solution of 1d (157 mg, 1.0 mmol) in THF, trimethyltin chloride (219 mg, 1.1 mmol) in toluene were successively added, then aldehyde 5g (115 mg, 1.2 mmol) in toluene was dropped in to reaction. Made the column by Cyclohexane: Ethyl acetate = 4:1, get a diastereomixture 170 mg, yield: 67%. Then separate two diastereo isomer by preparative HPLC for identification.

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\text{IR (neat): } 2243 \text{ cm}^{-1}. \quad ^1\text{H NMR (400 MHz, CDCl}_3\text{)} \delta 7.31 - 7.27 (m, 6H), 6.21 (dd, J = 3.2, 2.0 Hz, 1H), 6.08 (d, J = 3.2 Hz, 1H), 5.68 - 5.58 (m, 1H), 5.23 (dd, J = 17.2, 1.6 Hz, 1H), 5.13 (d, J = 10.4 Hz, 1H), 4.97 (d, J = 6.4 Hz, 1H), 3.18 (dd, J = 14.0, 8.0 Hz, 1H), 2.91 (dd, J = 14.0, 6.8 Hz, 1H), 2.57 (d, J = 6.8 Hz, 1H, OH). \quad ^{13}\text{C NMR (100 MHz, CDCl}_3\text{)} \delta 151.37, 142.38, 134.76, 131.11, 128.74, 128.50, 128.35, 127.13, 126.96, 120.18, 120.01, 110.64, 109.00, 73.10, 54.62, 39.33. \quad \text{MS (HPLC-MS). [M+Na] 276, [M+H}_{2}\text{O] 271. Elemental Analysis: Calcd for C}_{16}\text{H}_{15}\text{NO}_2: C, 75.87; H, 5.97; N, 5.53; O, 12.63. Found: C, 75.98; H, 5.98.}
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\text{IR (neat): } 2243 \text{ cm}^{-1}. \quad ^1\text{H NMR (400 MHz, CDCl}_3\text{)} \delta 7.47 - 7.35 (m, 6H), 6.44 (d, J = 3.2 Hz, 1H), 6.39 (dd, J = 3.2, 2.0 Hz, 1H), 5.62 - 5.51 (m, 1H), 5.15 (d, J = 1.2 Hz, 1H), 5.11-5.03 (m, 2H), 2.82 (dd, J = 14.0, 6.4 Hz, 1H), 2.66 (dd, J = 14.0, 7.2 Hz, 1H), 2.33 (d, J = 4.8 Hz, ^{13}\text{C NMR (100 MHz, CDCl}_3\text{)} \delta 151.32, 142.49, 134.76, 131.12, 128.83, 128.45, 127.17, 120.27, 120.00, 110.72, 109.06, 73.19, 54.70, 39.40. \quad \text{MS. [M+Na] 276, [M+H}_{2}\text{O] 271. Elemental Analysis: Calcd for C}_{16}\text{H}_{15}\text{NO}_2: C, 75.87; H, 5.97; N, 5.53; O, 12.63. Found: C, 75.97; H, 5.98.}
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**The preparation of (R*)-2-(((R*)-hydroxy(phenyl)methyl)-2-phenylpent-4-enenitrile (7j) and (R*)-2-(((S*)-hydroxy(phenyl)methyl)-2-phenylpent-4-enenitrile (6j)**

Following the procedure B, n-BuLi (0.44 ml, 1.1 mmol) was added into a solution of diisopropyl amine (0.15 ml, 1.1 mmol) in THF at -78 °C. A solution of 1d (131 mg, 1.0 mmol) in THF, trimethyltin chloride (219 mg, 1.1 mmol) in toluene were successively added, then
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aldehyde 5c (127 mg, 1.2 mmol) in toluene was dropped in to reaction. Made the column by Cyclohexane : Ethyl acetate = 4:1, get a diastereomixture 139 mg, yield: 54%. Then separate two diastereo isomer by silicon gel chromatography with dichloromethane : ether = 100 :3 for identification.

White solid. mp. 80-82 °C. IR (KBr): 2240 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ 7.38 – 7.35 (m, 3H), 7.32-7.32 (m, 5H), 7.17-7.17 (m, 2H), 5.69 – 5.59 (m, 1H), 5.22 (dd, J = 17.2, 1.6 Hz, 1H), 5.11 (dd, J = 10.8, 0.8 Hz, 1H), 4.89 (d, J = 3.6 Hz), 3.18 ( dd, J = 14.4, 7.6 Hz, 1H), 2.95 (dd, J = 14.4, 6.4 Hz, 1H), 2.63 (d, J = 3.6 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃) δ 138.27, 134.42, 131.86, 128.49, 128.41, 128.03, 127.80, 127.52, 127.22, 120.33, 119.94, 79.55, 55.35, 39.75. MS (HPLC-MS) [M+Na] 286. Elemental Analysis: Calcd for C₁₈H₁₇NO: C, 82.10; H, 6.51; N, 5.32; O, 6.08. Found: C, 82.21; H, 6.51.

White solid. mp. 127-129 °C. IR (KBr): 2240 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ 7.43 – 7.28 (m, 8H), 7.26-7.23 (m, 2H), 5.59-5.49 (m, 1H), 5.10 – 5.02 (m, 2H), 4.94 (d, J = 3.2 Hz, 1H), 2.78 (dd, J = 14.0, 6.4 Hz, 1H), 2.60 (dd, J = 14.0, 7.6 Hz, 1H), 2.21 (d, J = 3.2 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃) δ 137.84, 134.76, 131.38, 128.93, 128.73, 128.37, 128.13, 127.66, 120.11, 79.15, 55.16, 39.59. IR (KBr, cm⁻¹): 2240. MS (HPLC-MS). [M+Na] 286. Elemental Analysis: Calcd for C₁₈H₁₇NO: C, 82.10; H, 6.51; N, 5.32; O, 6.08. Found: C, 82.28; H, 6.52.

The preparation of (4g) (R*)-2-((S*)-furan-2-yl(hydroxy)methyl)-4-methyl-2-phenylpentanenitrile (7k) and (R*)-2-((R*)-furan-2-yl(hydroxy)methyl)-4-methyl-2-phenylpentanenitrile (6k)

Following the procedure B, n-BuLi (0.44 ml, 1.1 mmol) was added into a solution of diisopropyl ethyl amine(0.15 ml, 1.1 mmol) in THF at -78 °C. A solution of 1e (173 mg, 1.0 mmol) in THF, trimethyltin chloride (219 mg, 1.1 mmol) in toluene were successively added, then aldehyde 5g (115 mg, 1.2 mmol) in toluene was dropped in to reaction. Made the column
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by Cyclohexane: Ethyl acetate = 4:1, get a diastereomixture 172 mg, yield: 64%. Then separate two diastereo isomer by preparative HPLC for identification.

IR (neat): 2242 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.50-7.30 (m, 6H), 6.17 (dd, \(J = 3.2, 1.6\) Hz, 1H), 6.00 (d, \(J = 3.2\) Hz, 1H), 4.84 (d, \(J = 6.8\) Hz, 1H), 2.67 (d, \(J = 4.4\) Hz, 1H, OH), 2.42 (dd, \(J = 14.0, 7.6\) Hz, 1H), 2.08 (dd, \(J = 14.0, 5.6\) Hz, 1H), 1.56 – 1.51 (m, 1H), 1.02 (d, \(J = 6.8\) Hz, 3H), 0.69 (d, \(J = 6.8\) Hz, 3H). MS (HPLC-MS). [M+Na] 292, [M+H\(_2\)O] 287. Elemental Analysis: Calcd for C\(_{17}\)H\(_{19}\)NO\(_2\): C, 75.81; H, 7.11; N, 5.20; O, 11.88. Found: C, 75.97; H, 7.12.

The preparation of (2R,3R)-3-hydroxy-2-methyl-2-phenylhex-4-enenitrile (7l) and (2R,3S)-3-hydroxy-2-methyl-2-phenylhex-4-enenitrile (6l)

Following the procedure B, \(n\)-BuLi (0.44 ml, 1.1 mmol) was added into a solution of diisopropyl ethyl amine(0.15 ml, 1.1 mmol) in THF at -78 °C. A solution of 1b (131 mg, 1.0 mmol) in THF, trimethyltin chloride (219 mg, 1.1 mmol) in toluene were successively added, then aldehyde 5h (84 mg, 1.2 mmol) in toluene was dropped in to reaction. Made the column by Cyclohexane: Ethyl acetate = 4:1, get a diastereomixture 141 mg, yield: 70%. Then made a column with dichloromethane : ether = 100 :1 for identification.
Colorless oil. IR (neat): 2236 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.44 – 7.37 (m, 5H), 5.72 – 5.58 (m, 1H), 5.39 (dd, \(J = 15.6, 7.2\) Hz, 1H), 4.24 (d, \(J = 7.2\) Hz, 1H), 1.99 (bs, 1H, OH), 1.79 (s, 3H), 1.63 (d, \(J = 6.4\) Hz, 3H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 137.33, 132.31, 131.27, 128.86, 128.68, 128.19, 128.06, 127.77, 126.61, 126.49, 122.06, 78.12, 48.41, 23.14, 22.05, 17.83, 17.71. MS (HPLC-MS): [M+Na]=224, [M+H\(_2\)O]=219. Elemental Analysis: Calcd for C\(_{13}\)H\(_{15}\)NO: C, 77.58; H, 7.51; N, 6.96; O, 7.95. Found: C, 77.78; H, 7.53.

The preparation of (2S,3S)-3-hydroxy-2-methyl-2,5-diphenylpent-4-enenitrile (7m) and (2R,3S)-3-hydroxy-2-methyl-2,5-diphenylpent-4-enenitrile (6m)

Following the procedure B, n-BuLi (0.44 ml, 1.1 mmol) was added into a solution of diisopropyl ethyl amine (0.15 ml, 1.1 mmol) in THF at -78 °C. A solution of 1b (131 mg, 1.0 mmol) in THF, trimethyltin chloride (219 mg, 1.1 mmol) in toluene were successively added, then aldehyde 5i (158 mg, 1.2 mmol) in toluene was dropped in to reaction. Made the column by Cyclohexane: Ethyl acetate = 4:1, get a diastereomixture 205 mg, yield: 78%. Then made a column with dichloromethane : ether = 100 :1 for identification.
Colorless oil. IR (neat): 2244 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.52 – 7.21 (m, 10H), 6.54 (d, \(J = 15.96\) Hz, 1H), 6.06 (dd, \(J = 15.6, 6.4\) Hz, 1H), 4.46 (d, \(J = 6.0\) Hz, 1H), 2.06 (bs, 1H, OH), 1.83 (s, 3H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 137.02, 135.79, 134.18, 128.86, 128.58, 128.31, 128.22, 126.67, 126.65, 125.68, 121.94, 78.14, 48.51, 21.97. MS (HPLC-MS): [M+Na]=286. Elemental Analysis: Calcd for C\(_{18}\)H\(_{17}\)NO: C, 82.10; H, 6.51; N, 5.32; O, 6.08. Found: C, 82.22; H, 6.52.

White solid. mp.148-150 °C. IR (neat): 2244 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.52 (d, \(J = 8.0\) Hz, 2H), 7.47 – 7.21 (m, 8H), 6.68 (d, \(J = 16.0\) Hz, 1H), 6.22 (dd, \(J = 16.0, 7.2\) Hz, 1H), 4.44 (d, \(J = 7.2\) Hz, 1H), 2.06 (bs, 1H, OH), 1.71 (s, 3H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 137.17, 135.70, 135.08, 128.97, 128.65, 128.38, 126.78, 126.56, 125.35, 121.84, 78.58, 48.60, 22.69. (HPLC-MS): [M+Na]=286. Elemental Analysis: Calcd for C\(_{18}\)H\(_{17}\)NO: C, 82.10; H, 6.51; N, 5.32; O, 6.08. Found: C, 82.28; H, 6.52.

The preparation of 2-(3-oxocyclohexyl)-2-phenylpropanenitrile (8a)

Following the procedure B, n-BuLi (0.44 ml, 1.1 mmol) was added into a solution of diisopropyl ethyl amine(0.15 ml, 1.1 mmol) in THF at -78 °C. A solution of 1b (131 mg, 1.0 mmol) in THF, trimethyltin chloride (219 mg, 1.1 mmol) in toluene were successively added, then ketone 5j (115 mg, 1.2 mmol) in toluene was dropped in to reaction. Made the column by Cyclohexane: Ethyl acetate = 4:1, get a diastereomixture 120 mg, yield: 53%. Then made a column with dichloromethane : ether = 100 :1 for identification.

Colorless oil. IR (neat): 2235, 1709 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.42 – 7.29 (m, 5H), 2.65 (d, \(J = 13.6\) Hz, 1H), 2.48 – 2.64 (m, 7H), 1.68 (s, 3H), 1.64 – 1.41 (m, 2H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 209.54, 139.10, 138.36, 128.96, 128.00, 125.57, 121.42, 47.92, 43.68.
40.79, 27.11, 26.81, 25.37, 24.73. MS (HPLC-MS): [M+Na]=250. Elemental Analysis: Calcd for C_{15}H_{17}NO: C, 79.26; H, 7.54; N, 6.16; O, 7.04. Found: C, 79.39; H, 7.55.

**Preparation of 3-hydroxy-2,2,5-triphenylpent-4-enenitrile (6o)**

Following the procedure B, n-BuLi (0.44 ml, 1.1 mmol) was added into a solution of diisopropyl ethyl amine (0.15 ml, 1.1 mmol) in THF at -78 °C. A solution of 1a (131 mg, 1.0 mmol) in THF, trimethyltin chloride (219 mg, 1.1 mmol) in toluene were successively added, then aldehyde 5i (158 mg, 1.2 mmol) in toluene was dropped in to reaction. Made the column by Cyclohexane: Ethyl acetate = 4:1, get a diastereomixture 108 mg, yield: 33%.

Colorless oil. IR (neat): 2237 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.79 (d, \(J = 7.2\) Hz, 3H), 7.61 – 7.34 (m, 12H), 6.84 (d, \(J = 16.0\) Hz, 1H), 6.41 (dd, \(J = 16.0, 6.8\) Hz, 1H), 5.42 (d, \(J = 5.6\) Hz, 1H), 2.35 (s, 1H). \(^1\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 137.48, 135.84, 134.77, 128.98, 128.87, 128.54, 128.21, 127.92, 127.53, 126.73, 125.65, 120.68, 109.99, 75.74, 59.39. MS (HPLC-MS): [M+Na]=348. Elemental Analysis: Calcd for C_{23}H_{19}NO: C, 82.10; H, 6.51; N, 5.32; O, 6.08. Found: C, 82.30; H, 6.53.

**Preparation of 2-(1-hydroxycyclohexyl)-2-phenylpropanenitrile\(^{34}\) (6p)**

Following the procedure B, n-BuLi (0.44 ml, 1.1 mmol) was added into a solution of diisopropyl ethyl amine (0.15 ml, 1.1 mmol) in THF at -78 °C. A solution of 1b (131 mg, 1.0 mmol) in THF, trimethyltin chloride (219 mg, 1.1 mmol) in toluene were successively added, then aldehyde 5k (118 mg, 1.2 mmol) in toluene was dropped in to reaction. Made the column by Cyclohexane: Ethyl acetate = 4:1, get a diastereomixture 169 mg, yield: 74%.

Colorless oil. IR (neat): 2237 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.50 (d, \(J = 7.6\) Hz, 2H), 7.40 – 7.34 (m, 3H), 1.81 (s, 3H), 1.69 – 1.52 (m, 7H), 1.47 – 1.33 (m, 4H). \(^1\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 136.88, 128.23, 127.97, 127.91, 123.44, 74.48, 51.87, 33.04, 32.17, 26.89, 25.00,
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The preparation of 2-(1-hydroxycyclopentyl)-2-phenylpropanenitrile (6q)

Following the procedure B, n-BuLi (0.44 ml, 1.1 mmol) was added into a solution of diisopropyl ethyl amine (0.15 ml, 1.1 mmol) in THF at -78 °C. A solution of 1b (131 mg, 1.0 mmol) in THF, trimethyltin chloride (219 mg, 1.1 mmol) in toluene were successively added, then aldehyde 5l (100 Mg, 1.2 mmol) in toluene was dropped in to reaction. Made the column by Cyclohexane: Ethyl acetate = 4:1, get a diastereomixture 144 mg, yield: 67%. Then made a column with dichloromethane : ether = 100 :1 for identification.

6q

Colorless oil. IR (neat): 2237 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 7.55 (d, J=7.6 Hz, 2H), 7.48 – 7.29 (m, 3H), 2.13 – 1.96 (m, 2H), 1.85 (s, 3H), 1.82 – 1.61 (m, 5H), 1.19 (m, 2H). ¹³C NMR (100 MHz, CDCl₃): δ 137.47, 128.413, 127.35, 123.42, 85.45, 49.71, 37.71, 36.10, 23.74, 23.44, 21.17. MS (HPLC-MS): [M+H₂O]=233, [M+Na]=238. Elemental Analysis: Calcd for C₁₄H₁₇NO: C, 78.10; H, 7.96; N, 6.51; O, 7.43. Found: C, 78.24; H, 7.97.

The preparation of 2-(1-hydroxycyclohexyl)-2-phenylpent-4-enenitrile (6r)

Following the procedure B, n-BuLi (0.44 ml, 1.1 mmol) was added into a solution of diisopropyl ethyl amine (0.15 ml, 1.1 mmol) in THF at -78 °C. A solution of 1b (131 mg, 1.0 mmol) in THF, trimethyltin chloride (219 mg, 1.1 mmol) in toluene were successively added, then aldehyde 5k (118 mg, 1.2 mmol) in toluene was dropped in to reaction. Made the column by Cyclohexane: Ethyl acetate = 4:1, get a diastereomixture 226 mg, yield: 89%. Then made a column with dichloromethane : ether = 100 :1 for identification.

6r

Colorless oil. IR (neat): 2237 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ 7.47 (d, J= 7.4 Hz, 2H), 7.40-7.31 (m, 3H), 5.66-5.50 (m, 1H), 5.17 (d, 16.8 Hz, 1H), 5.04 (d, J = 10.0 Hz, 1H), 3.09
(dd, J = 14.6, 6.8 Hz, 1H), 2.89 (dd, J = 14.6, 7.2 Hz, 1H), 1.92 (d, J = 10.4 Hz, 1H), 1.68 – 1.30 (m, 8H). 0.86(d, J=7.2 Hz,1H). 13C NMR (100 MHz, CDCl₃) δ 134.10, 132.69, 128.65, 128.30, 127.98, 122.01, 119.53, 75.04, 58.16, 36.76, 35.86, 33.20, 32.88, 25.08, 21.73, 21.50. MS (HPLC-MS): [M+H₂O]=273. Elemental Analysis: Calcd for C₁₇H₁₇NO: C, 79.96; H, 8.29; N, 5.49; O, 6.27. Found: C, 79.17; H, 8.31.

The preparation of (2R, 3S)-3-hydroxy-2-methyl-2,3-diphenylbutanenitrile (6s) and (2S, 3S)-3-hydroxy-2-methyl-2,3-diphenylbutanenitrile (7s)

Following the procedure B, n-BuLi (0.44 ml, 1.1 mmol) was added into a solution of diisopropyl ethyl amine(0.15 ml, 1.1 mmol) in THF at -78 °C. A solution of 1b (131 mg, 1.0 mmol) in THF, trimethyltin chloride (219 mg, 1.1 mmol) in toluene were successively added, then aldehyde 5m ( mg, 1.2 mmol) in toluene was dropped in to reaction. Made the column by Cyclohexane: Ethyl acetate = 4:1, get a diastereomixture 183 mg, yield: 73%. The diastereo ratio between two isomers are 50:50, so no further attempts on purification and identification have been performed. Two diastereo isomer were tentatively attributed by COSY experiment. The attempts on confirming the absolute of each isomer was not made.

![Diastereomixture 6s or 7s](image)

Isomer 1: IR (neat): 2238 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ 7.37 – 7.27 (m, 5H), 7.23 (m, 5H), 1.68 (s, 3H), 1.62 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 141.84, , 136.64, , 128.29, 127.75, 127.64, 127.29, 126.68, 123.33, 52.52, 26.72, 21.57. MS (HPLC-MS): [M+H₂O]=269, [M+Na]=274. Elemental Analysis Calcd for C₁₇H₁₇NO: C, 81.24; H, 6.82; N, 5.57; O, 6.37. Found: C, 81.43; H, 6.83.

Isomer 2: IR (neat): 2238 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ 7.47 – 7.36 (m, 5H), 7.11 (m, 5H), 1.76 (s, 3H), 1.75 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) 141.29, 136.41, 128.21, 128.11, 128.29, 127.72, 127.04, 123.15, 51.73, 26.37, 21.20. MS (HPLC-MS): [M+H₂O]=269, [M+Na]=274. Elemental Analysis Calcd for C₁₇H₁₇NO: C, 81.24; H, 6.82; N, 5.57; O, 6.37. Found: C, 81.40; H, 6.83.
The preparation of (3S,4S)-4-(benzyl oxy)-3-hydroxy-2,2-diphenylpentanenitrile (10a) and (3R,4S)-4-(benzyl oxy)-3-hydroxy-2,2-diphenylpentanenitrile (11a)

Following the procedure C, to a well dried schlenk flask, BuLi(1.1 mmol, 0.44 ml of 2.5M in n-hexane) was added into a solution of 2,2-diphenylacetonitrile 1a (193 mg, 1.0 mmol) in THF at -78°C. After 10 mins, a solution of trimethyltin chloride (219 mg, 1.1 mmol) in 2 ml of toluene was dropped into the reaction at -78°C. Then the reaction mixture was allowed to go to r.t and stirring for 1 hour. A solution of (S)-2-(benzyl oxy) propanal (1.2 mmol, 197 mg) in 3 ml of toluene was cooled to -78°C, after kept at -78°C and stirring for 18 hrs, the reaction was decomposed by saturated NH₄Cl solution and adjust PH to 7 at -78°C, then extract with ethyl acetate, washed by brine, dried over sodium sulfate, remove all the solvent, the crude product was purified by the flash chromatography (cyclohexane: ether = 8:1) to get pure compound 10a (188 mg), and 11a (66 mg), yield 71%.

10a

White solid. mp: 156-159°C. [α]D: +16. (c: 1.0g/100 mg, CHCl₃). IR(neat): 2242 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ 7.58-7.56 (m, 2H), 7.42 – 7.27 (m, 11H), 7.19-7.16 (m, 2H), 4.76 (dd, J = 3.6, 3.2 Hz, 1H), 4.46 (d, J = 11.6 Hz, 1H), 4.25 (d, J = 11.6 Hz, 1H), 3.50 – 3.42 (m, 1H), 2.52 (d, J=3.2 Hz, 1H, OH), 1.34 (d, J = 6.4 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 139.20, 138.55, 137.36, 129.00, 128.63, 128.32, 128.17, 128.00, 127.81, 127.25, 120.84, 77.45, 72.55, 71.15, 56.92, 17.94. MS (GC-MS): [M+1]=358. Elemental Analysis: Calcd for C₂₄H₂₃NO₂: C, 80.64; H, 6.49; N, 3.92; O, 8.95. Found: C, 80.84; H, 6.50.

11a

White solid. mp: 148-151°C. [α]D: -27. (c: 1.0g/100 mg, CHCl₃). IR(neat): 2242 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ 7.46 (d, J = 8.0 Hz, 2H), 7.31 – 7.12 (m, 13H), 4.40 (d, J = 11.2 Hz, 1H), 4.30 (d, J = 6.4 Hz, 1H), 3.46 (d, J = 6.4 Hz, 1H), 3.39 (d, J = 6.4 Hz, 1H, OH), 1.07 (d, J = 6.4
Hz, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 139.20, 138.55, 137.35, 129.00, 128.63, 128.32, 128.16, 127.98, 127.81, 127.24, 120.83, 77.45, 72.55, 71.15, 56.92, 17.94. MS (GC-MS): [M+1]=358. Elemental Analysis: Calcd for C$_{24}$H$_{23}$NO$_2$: C, 80.64; H, 6.49; N, 3.92; O, 8.95. Found: C, 80.80; H, 6.49.

The preparation of (3R,4S)-4-(benzyloxy)-3-hydroxy-2-methyl-2-phenylpentanenitrile (10b, 10b’, 11b, 11b’)

Following the procedure C, to a well dried schlenk flask, BuLi(1.1 mmol, 0.44 ml of 2.5M in n-hexane) was added into a solution of 2,2-diphenylacetonitrile 1b (131 mg, 1.0 mmol) in THF at -78°C. After 10mins, a solution of trimethyltin chloride (219 mg 1.1 mmol,) in 2 ml of toluene was dropped into the reaction at -78°C. Then the reaction mixture was allowed to go to r.t and stirring for 1 hour. A solution of (S)-2-(benzyloxy)propanal 9a (1.2 mmol, 197 mg) in 3 ml of toluene was cooled to -78°C, after kept at -78°C and stirring for 18hrs, the reaction was decomposed by saturated NH$_4$Cl solution and adjust PH to 7 at -78°C, then extract with ethyl acetate, washed by brine, dried over sodium sulfate, remove all the solvent, the crude product was purified by the flash chromatography (cyclohexane: ether = 8:1) to get a diastereoisomer mixture 162 mg, yield 55%.

(10b, 10b’, 11b, 11b’ (absolute configuration were not assigned))

**Isomer a):** IR(neat): 2238 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.44 (d, $J = 7.2$ Hz, 2H), 7.37 – 7.10 (m, 6H), 7.00 (s, 2H), 4.30 (m, 1H), 4.00 (t, $J = 16$ Hz, 1H), 3.59 (dd, $J = 28.8$, 21.6 Hz, 2H), 3.02 (d, c, 1H), 1.71 (s, 3H), 1.37 – 1.15 (d, $J = 5.8$ Hz 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 137.24, 137.19, 128.63, 128.27, 128.00, 127.95, 127.82, 126.68, 122.70, 79.74, 72.51, 70.48, 46.53, 23.30, 17.93. HPLC-MS: [m+23]=318.

**Isomer b):** IR(neat): 2238 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.50 – 7.28 (m, 10H), 4.47 (dd, $J = 29.2$, 11.2 Hz, 2H), 3.55 (d, $J = 6.4$ Hz, 1H), 3.39 (q, $J = 6.4$ Hz, 1H), 3.20 (d, $J = 8.8$ Hz, 1H), 1.87 (s, 3H), 1.07 (d, $J = 6.4$ Hz, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 138.20, 137.39,
129.07, 128.36, 128.25, 128.04, 127.83, 126.02, 121.62, 80.52, 72.29, 71.04, 47.78, 25.93, 17.57. HPLC-MS: [m+23]=318.

**Isomer c):** IR(neat): 2238 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)) δ 7.53 (d, J = 7.3 Hz, 2H), 7.46 – 7.27 (m, 8H), 4.58 (d, J = 11.2 Hz, 1H), 4.45 (d, J = 11.2 Hz, 1H), 3.92 (s, 1H), 3.79 – 3.67 (m, 1H), 1.78 (s, 3H), 1.27 (d, J = 6.4 Hz, 3H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) δ 138.39, 138.00, 129.02, 128.55, 128.31, 127.96, 127.87, 126.65, 122.24, 110.18, 78.83, 70.94, 46.85, 24.48, 15.42. HPLC-MS: [m+23]=318.

**Isomer d):** IR(neat): 2238 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)) δ 7.45 – 7.27 (m, 8H), 7.20 (d, J = 7.2 Hz, 2H), 4.47 – 4.37 (m, 1H), 4.27 (d, J = 11.6 Hz, 1H), 4.02 (s, 1H), 3.27 – 3.12 (m, 1H), 2.64 (s, 1H), 1.85 (s, 3H), 1.25 (d, J = 6.4 Hz, 3H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) δ 137.90, 137.59, 129.20, 128.50, 128.27, 127.89, 126.05, 121.67, 78.23, 74.77, 70.64, 45.90, 26.39, 13.61. HPLC-MS: [m+23]=318.

The preparation of (3R,4S)-4-((tert-butyldimethylsilyl)oxy)-3-hydroxy-2,2-diphenylpentanenitrile (10c)

Following the procedure C, to a well dried schlenk flask, BuLi(1.1 mmol, 0.44ml of 2.5M in n-hexane ) was added into a solution of 2,2-diphenylacetonitrile 1a (193 mg, 1.0 mmol) in THF at -78°C. After 10mins, a solution of trimethylin tin chloride (219 mg 1.1 mmol,) in 2 ml of toluene was dropped into the reaction at -78°C. Then the reaction mixture was allowed to go to r.t and stirring for 1 hour. A solution of (S)-2-(benzyloxy)propanal (1.2 mmol, 197 mg) in 3 ml of toluene was cooled to -78°C, after kept at -78°C and stirring for 18hrs, the reaction was decomposed by saturated NH\(_4\)Cl solution and adjust PH to 7 at -78°C, then extract with ethyl acetate, washed by brine, dried over sodium sulfate, remove all the solvent, the crude product was purified by the flash chromatography (cyclohexane: ether = 8:1) to get pure compound 10c (170 mg), yield 45%.

![10c](image)

White solid. mp: 99-101°C. [\(\alpha\)]\(^{20}\)D\(_{c}\): -75. (c: 1.0g/100 mg, CHCl\(_3\)). IR(KBr): 2244 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)) δ 7.58 (d, J = 8.0 Hz, 2H), 7.42 – 7.29 (m, 8H), 4.57 (d, J = 2.4 Hz, 1H),
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3.58 – 3.55 (m, 1H), 2.89 (bs, 1H, OH), 1.25 (d, J = 6.4 Hz, 3H), 0.85 (s, 9H), -0.05 (s, 3H), -0.07 (s, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 139.60, 137.41, 128.99, 128.74, 128.17, 127.94, 127.81, 127.02, 120.40, 68.88, 54.34, 25.74, 17.91, 16.94, -4.72, -4.97. MS (GC-MS): [M+1]=382. Elemental Analysis: Calcd for C$_{23}$H$_{31}$NO$_2$Si: C, 72.40; H, 8.19; N, 3.67; O, 8.39; Si, 7.36. Found: C, 72.61; H, 8.20.

The preparation of (R)-3-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-hydroxy-2,2-diphenylpropanenitrile 11d and (S)-3-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-hydroxy-2,2-diphenylpropanenitrile (10d)

Following the procedure C, to a well dried schlenk flask, BuLi (1.1 mmol, 0.44 ml of 2.5M in $n$-hexane) was added into a solution of 2,2-diphenylacetonitrile 1a (193 mg, 1.0 mmol) in THF at -78°C. After 10mins, a solution of trimethyltin chloride (219 mg 1.1 mmol,) in 2 ml of toluene was dropped into the reaction at -78°C. Then the reaction mixture was allowed to go to r.t and stirring for 1 hour. A solution of (R)-2,2-dimethyl-1,3-dioxolan-4-carbaldehyde 9c (1.2 mmol, 156 mg) in 3 ml of toluene was cooled to -78°C, after kept at -78°C and stirring for 18hrs, the reaction was decomposed by saturated NH$_4$Cl solution and adjust PH to 7 at -78°C, then extract with ethyl acetate, washed by brine, dried over sodium sulfate, remove all the solvent, the crude product was purified by the flash chromatography (cyclohexane: ethyl acetate = 8:1) to get pure compound 11d (41 mg) and 10d (156 mg), yield 61%.

![11d]

White solid. mp: 104-108 °C. [$$\alpha$$_D$$]$$^2$$0 = -103.6 (c: 0.5g/100 mg, CHCl$_3$). IR (KBr): 2252 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.58 – 7.56 (m, 2H), 7.40 – 7.31 (m, 8H), 4.44 (t, $J = 5.2$ Hz, 1H), 4.15 (q, $J = 5.2$ Hz, 1H), 3.45 (dd, $J = 8.8$, 6.4 Hz, 1H), 3.38 (d, $J = 5.2$ Hz, 1H, OH), 3.20 (dd, $J = 8.8$ 6.4 Hz, 1H), 1.44 (s, 3H), 1.31 (s, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 138.37, 137.29, 129.12, 128.77, 128.51, 128.09, 127.36, 120.25, 109.80, 75.11, 74.09, 66.91, 56.31, 26.41, 25.16. MS (ESI): m/z=346 [M+Na$^+$]. Elemental Analysis: Calcd. for C$_{20}$H$_{21}$NO$_3$: C, 74.28; H, 6.55; N, 4.33; O, 14.84; Found: C, 74.45; H, 6.56.
White solid. mp: 137-139 °C. [α]D: +67.6 (c: 0.5 g/100 mg, CHCl₃). IR (KBr): 2252 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ 7.57 – 7.55 (m, 2H), 7.44 – 7.32 (m, 8H), 4.92 (t, J = 2.8 Hz, 1H), 4.16 (dd, J = 8.8, 6.8 Hz, 1H), 4.02 (d, q, J = 6.4, 2.8 Hz, 1H), 3.89 (dd, J = 8.8, 6.4 Hz, 1H), 2.58 (d, J = 2.8 Hz, 1H, OH), 1.41 (s, 3H), 1.27 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 137.42, 137.10, 129.19, 128.91, 128.32, 127.71, 127.09, 119.96, 108.34, 75.95, 73.85, 63.63, 55.09, 26.30, 25.13. MS: m/z=346 [M+Na⁺]. Elemental Analysis: Calcd. for C₂₀H₂₁NO₃: C, 74.28; H, 6.55; N, 4.33; O, 14.84; Found: C, 74.34; H, 6.56.

The preparation of (R)-3-hydroxy-2,2-diphenyl-3-((R)-1,4-dioxaspiro[4.5]decan-2-yl)propanenitrile (11e) and (S)-3-hydroxy-2,2-diphenyl-3-((R)-1,4-dioxaspiro[4.5]decan-2-yl)propanenitrile (10e)

Following the procedure C, to a well dried schlenk flask, BuLi (1.1 mmol, 0.44 ml of 2.5M in n-hexane) was added into a solution of 2,2-diphenylacetonitrile 1a (193 mg, 1.0 mmol) in THF at -78°C. After 10 mins, a solution of trimethyltin chloride (219 mg 1.1 mmol) in 2 ml of toluene was dropped into the reaction at -78°C. Then, the reaction mixture was allowed to go to r.t and stirring for 1 hour. A solution of (R)-1,4-dioxaspiro[4.5]decane-2-carbaldehyde 9b (204.0 mg 1.2 mmol) in 3 ml of toluene was cooled to -78°C, after kept at -78°C and stirring for 18hrs, the reaction was decomposed by saturated NH₄Cl solution and adjust PH to 7 at -78°C, then extract with ethyl acetate, washed by brine, dried over sodium sulfate, remove all the solvent, the crude product was purified by the flash chromatography (cyclohexane: ethyl acetate = 8:1) to get pure compound 10e (234 mg), and 11e (21 mg), yield 70%.
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132.40, 130.05, 129.18, 129.07, 128.73, 128.17, 127.71, 127.44, 120.31, 110.51, 74.60, 73.76, 66.53, 56.94, 36.10, 34.58, 24.99, 23.92, 23.69. GC-MS: [M+H]=364. Elemental Analysis: Calcd. for C_{23}H_{25}NO_3: C, 76.01; H, 6.93; N, 3.85; O, 13.21. Found: C, 76.12; H, 6.94.

**White solid.** mp: 132-135°C. \([\alpha]_D^{20^\circ} +64.4\) (c: 5 mg/ ml, CHCl_3). IR (neat): 2253 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl_3) \(\delta\) 7.57 (d, \(J = 7.8\) Hz, 2H), 7.44 – 7.31 (m, 8H), 4.92 (d, \(J = 2.4\) Hz, 1H), 4.10 (dd, \(J = 8.0, 0.5\) Hz, 1H), 4.06 – 3.96 (m, 1H), 3.89 (dd, \(J = 8.0, 2.0\) Hz, 1H), 2.56 (d, \(J = 2.4\) Hz, 1H, OH), 1.61 – 1.45 (complex pattern, 10H). \(^13\)C NMR (100 MHz, CDCl_3) \(\delta\) 137.54, 137.35, 129.11, 128.86, 128.29, 128.27, 127.76, 127.13, 120.30, 109.04, 75.57, 74.09, 63.45, 55.18, 35.96, 34.61, 24.98, 23.80, 23.66. LC-MS: [M+H]=364. Elemental Analysis: Calcd. for C_{20}H_{21}NO_3: C, 76.01; H, 6.93; N, 3.85; O, 13.21. Found: C, 76.10; H, 6.93.

The preparation of (3S)-3-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-hydroxy-2-phenyl-2-(p-tolyl)propanenitrile (10f) and (3R)-3-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-hydroxy-2-phenyl-2-(p-tolyl)propanenitrile (11f)

Following the procedure C, to a well dried schlenk flask, n-BuLi(1.1 mmol, 0.44 ml of 2.5M in n-hexane) was added into a solution of 2-(4-methyl)-2-phenylacetonitrile 3g (207 mg, 1.0 mmol) in THF at -78°C. After 10mins, a solution of trimethyltin chloride (219 mg 1.1 mmol) in 2 ml of toluene was dropped into the reaction at -78°C. Then the reaction mixture was allowed to go to r.t and stirring for 1 hour. A solution of (R)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde 9a (1.2 mmol, 156.0 mg) in 3 ml of toluene was cooled to -78°C, after kept at -78°C and stirring for 18hrs, the reaction was decomposed by saturated NH_4Cl solution and adjust PH to 7 at -78°C, then extract with ethyl acetate, washed by brine, dried over sodium sulphate, remove all the solvent, the crude product was purified by the flash chromatography (cyclohexane: ethyl acetate = 8:1) to get pure compound 10f (121 mg), and 11f (18 mg), yield 41%. Spectral data were deducted from the mixture of each isomer and arbitrarily attributed to isomer A and isomer B.
Isomer A: IR (neat): 2240 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.57 – 7.55 (m, 1H), 7.44 (d, $J = 8.4$ Hz, 1H), 7.41 – 7.28 (m, 5H), 7.25 - 7.17 (m, 2H), 4.41 (t, $J = 5.2$ Hz, 1H), 4.18 – 4.11 (m, 1H), 3.46 – 3.44 (m, 1H), 3.36 (d, $J = 5.2$ Hz, 1H, OH), 3.20 (dd, $J = 8.8, 6.4$ Hz, 1H), 2.34 (s, 3H), 1.44 (s, 3H), 1.31 (s, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 138.54, 137.93, 135.40, 129.78, 129.08, 128.43, 128.00, 127.29, 120.37, 109.75, 75.18, 74.17, 66.96, 56.64, 26.42, 25.20, 20.98. LC-MS: [M+Na]= 360. Elemental Analysis: Calcd. for C$_{21}$H$_{23}$NO$_3$: C, 74.75; H, 6.87; N, 4.15; O, 14.22.

Isomer B: IR (neat): 2240 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.57 – 7.55 (m, 1H), 7.44 (d, $J = 8.4$ Hz, 1H), 7.41 – 7.28 (m, 4H), 7.25 - 7.17 (m, 2H), 4.41 (t, $J = 5.2$ Hz, 1H), 4.18 – 4.11 (m, 1H), 3.46 – 3.44 (m, 1H), 3.36 (d, $J = 4.8$ Hz, 1H, OH), 3.20 (dd, $J = 8.8, 6.4$ Hz, 1H), 2.34 (s, 3H), 1.44 (s, 3H), 1.31 (s, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 138.47, 137.47, 134.43, 129.46, 128.74, 128.43, 127.89, 127.19, 120.37, 109.75, 75.15, 74.13, 66.90, 56.64, 26.42, 25.17, 20.96. LC-MS: [M+Na]= 360. Elemental Analysis: Calcd. for C$_{21}$H$_{23}$NO$_3$: C, 74.75; H, 6.87; N, 4.15; O, 14.22.
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(m, 1H), 2.55 (bs, 1H, OH), 2.33 (s, 3H), 1.42 (s, 3H), 1.27 (s, 3H), 1.27 (s, 1.5H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 138.29, 137.80, 134.53, 129.58, 129.11, 128.27, 128.19, 127.53, 127.04, 120.39, 108.29, 75.96, 74.10, 63.53, 54.84, 26.27, 25.13, 20.93. LC-MS: [M+Na]$^+$ = 360. Elemental Analysis: Calcd. for C$_{21}$H$_{23}$NO$_3$: C, 74.75; H, 6.87; N, 4.15; O, 14.22. Found: C, 74.89; H, 6.88.

The preparation of (3S)-3-hydroxy-2-phenyl-3-((R)-1,4-dioxaspiro[4.5]decan-2-yl)-2-(p-tolyl)propanenitrile (10g) and (3R)-3-hydroxy-2-phenyl-3-((R)-1,4-dioxaspiro[4.5]decan-2-yl)-2-(p-tolyl)propanenitrile (11g)

Following the procedure C, to a well dried schlenk flask, BuLi(1.1 mmol, 0.44 ml of 2.5M in n-hexane) was added into a solution of 2-(4-methyl)-2-phenylacetonitrile 3g (207 mg, 1.0 mmol) in THF at -78°C. After 10 mins, a solution of trimethyltin chloride (219 mg 1.1 mmol) in 2 ml of toluene was dropped into the reaction at -78°C. Then the reaction mixture was allowed to go to r.t and stirring for 1 hour. A solution of (R)-1,4-dioxaspiro[4.5]decan-2-carbaldehyde 9b (204 mg 1.2 mmol) in 3 ml of toluene was cooled to -78°C, after kept at -78°C and stirring for 18 hrs, the reaction was decomposed by saturated NH$_4$Cl solution and adjust PH to 7 at -78°C, then extract with ethyl acetate, washed by brine, dried over sodium sulfate, remove all the solvent, the crude product was purified by the flash chromatography (cyclohexane: ethyl acetate = 8:1) to get pure compound 10g (55 mg), and 11g (15 mg), yield 17%.

Isomer A: IR (neat): 2249 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.57 – 7.54 (m, 1H), 7.47 – 7.16 (m, 8H), 4.40 (t, J = 4.8 Hz, 1H), 4.18 – 4.12 (m, 1H), 3.52 – 3.50 (m, 1H), 3.36 (d, J = 5.4 Hz, 1H, OH), 3.28 – 3.23 (m, 1H), 2.36 (s, 3H), 1.73 – 1.32 (complex pattern, 10H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 138.28 , 137.87, 134.44, 129.63, 128.45, 127.29, 127.18, 127.01, 120.88, 109.89, 75.73, 74.01, 63.36, 54.78, 34.52, 25.14, 23.67, 21.43. LC-MS: [M+Na]$^+$ = 400. Elemental Analysis: Calcd. for C$_{24}$H$_{27}$NO$_3$: C, 76.36; H, 7.21; N, 3.71; O, 12.71. Found: C, 76.66; H, 7.23.
Isomer B: IR (neat): 2249 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)) δ 7.57 – 7.54 (m, 1H), 7.47 – 7.16 (m, 8H), 4.40 (t, J = 4.8 Hz, 1H), 4.18 – 4.12 (m, 1H), 3.52 – 3.50 (m, 1H), 3.36 (bs, 1H, OH), 3.28 – 3.23 (m, 1H), 2.36 (s, 3H), 1.73 – 1.32 (complex pattern, 10H). \(^13\)C NMR (100 MHz, CDCl\(_3\)) δ 138.00, 137.76, 134.34, 129.90, 127.45, 126.89, 126.81, 126.99, 120.88, 109.89, 75.63, 74.21, 63.39, 54.88, 34.55, 25.12, 23.69, 21.45. LC-MS: [M+Na] = 400. Elemental Analysis: Calcd. for C\(_{24}\)H\(_{27}\)NO\(_3\): C, 76.36; H, 7.21; N, 3.71; O, 12.71. Found: C, 76.66; H, 7.23.

Isomer A: IR (neat): 2249 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)) δ 7.58 – 7.18 (m, 9H), 4.90 – 4.89 (m, 1H), 4.10 (dd, J = 8.4, 6.8 Hz, 1H), 4.05 – 3.96 (m, 1H), 3.88 (dd, J = 8.4, 6.0 Hz, 1H), 2.59 (d, J = 2.8 Hz, 1H, OH), 2.34 (s, 3H), 1.74 – 1.32 (complex pattern, 10H). \(^13\)C NMR (100 MHz, CDCl\(_3\)) δ 138.38, 137.90, 134.54, 129.94, 128.96, 128.34, 127.88, 127.14, 120.58, 109.11, 75.75, 74.24, 63.51, 54.95, 34.81, 25.16, 23.83, 21.08. LC-MS: [M+Na] = 400. Elemental Analysis: Calcd. for C\(_{24}\)H\(_{27}\)NO\(_3\): C, 76.36; H, 7.21; N, 3.71; O, 12.71. Found: C, 76.66; H, 7.23.

Isomer B: IR (neat): 2249 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)) δ 7.58 – 7.18 (m, 9H), 4.90 – 4.89 (m, 1H), 4.10 (dd, J = 8.4, 6.8 Hz, 1H), 4.05 – 3.96 (m, 1H), 3.88 (dd, J = 8.4, 6.0 Hz, 1H), 2.57 (d, J = 2.8 Hz, 1H, OH), 2.33 (s, 3H), 1.74 – 1.32 (complex pattern, 10H). \(^13\)C NMR (100 MHz, CDCl\(_3\)) δ 138.33, 137.72, 134.70, 129.71, 129.20, 128.35, 128.34, 127.76, 127.27, 120.58, 109.17, 75.76, 74.33, 63.65, 55.11, 34.78, 25.16, 23.69, 21.08. LC-MS: [M+Na] = 400. Elemental Analysis: Calcd. for C\(_{24}\)H\(_{27}\)NO\(_3\): C, 76.36; H, 7.21; N, 3.71; O, 12.71. Found: C, 76.66; H, 7.23.

The preparation of (3S)-3-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-hydroxy-2-(4-methoxyphenyl)-2-phenylpropanenitrile (10h) and (3R)-3-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-hydroxy-2-(4-methoxyphenyl)-2-phenylpropanenitrile (11h)

Following the procedure C, to a well dried schlenk flask, BuLi(1.1 mmol, 0.44ml of 2.5M in n-hexane) was added into a solution of 2-(4-methoxyl)-2-phenylacetonitrile 1h (223 mg, 1.0

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mmol) in THF at -78°C. After 10mins, a solution of trimethyltin chloride (219 mg 1.1 mmol,) in 2 ml of toluene was dropped into the reaction at -78°C. Then the reaction mixture was allowed to go to r.t and stirring for 1 hour. A solution of (R)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde 9a (1.2 mmol, 156.0 mg) in 3 ml of toluene was cooled to -78°C, after kept at -78°C and stirring for 18hrs, the reaction was decomposed by saturated NH₄Cl solution and adjust PH to 7 at -78°C, then extract with ethyl acetate, washed by brine, dried over sodium sulfate, remove all the solvent, the crude product was purified by the flash chromatography (cyclohexane: ethyl acetate = 8:1) to get pure compound 10h (68 mg), and 11h (5 mg), yield 21%.

Isomer A: IR (neat): 2238 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ 7.54 (d, J= 7.6Hz, 1H), 7.47 - 7.38 (m, 6H), 6.88 (d, J = 6.0 Hz, 2H), 4.88 – 4.86 (m, 1H), 4.20 – 4.08 (m, 1H), 4.06 – 3.96 (m, 1H), 3.92 – 3.83 (m, 1H), 3.80 (s, 3H), 2.57 (bs, 1H, OH), 1.42 (s, 3.0H), 1.28 (s, 3H). HPLC-MS: [M+Na]=376. Elemental Analysis: Calcd. for C₂₁H₂₅NO₄: C, 71.37; H, 6.56; N, 3.96; O, 18.11. Found: C, 71.68; H, 6.59.

Isomer B: IR (neat): 2238 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ 7.54 (d, J= 7.6Hz, 1H), 7.47 - 7.38 (m, 6H), 6.88 (d, J = 6.0 Hz, 2H), 4.88 – 4.86 (m, 1H), 4.20 – 4.08 (m, 1H), 4.06 – 3.96 (m, 1H), 3.92 – 3.83 (m, 1H), 3.80 (s, 3H), 2.57 (bs, 1H, OH), 1.41 (s, 3H), 1.27 (s, 3H). HPLC-MS: [M+Na]=376. Elemental Analysis: Calcd. for C₂₁H₂₅NO₄: C, 71.37; H, 6.56; N, 3.96; O, 18.11. Found: C, 71.68; H, 6.59.

**Isomer B:** IR (neat): 2238 cm^{−1}. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.65 (d, \(J= 7.6\) Hz, 1H), 7.51 – 7.29 (m, 6H), 6.98 – 6.78 (m, 2H), 4.88 (s, 1H), 4.16 – 4.12 (m, 4. 1H), 4.09 – 3.98 (m, 1H), 3.90 – 3.81 (m, 1H), 3.81 (s, 3H), 2.54 (bs, 1H, OH), 1.44 (s, 3H), 1.28 (s, 3H). HPLC-MS: [M+Na]=376. Elemental Analysis: Calcd. for C_{21}H_{23}NO_3: C, 71.37; H, 6.56; N, 3.96; O, 18.11. Found: C, 71.62; H, 6.58.

The preparation of (3R)-3-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-hydroxy-2-phenyl-2-(m-tolyl)propanenitrile (11i) and (3S)-3-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-hydroxy-2-phenyl-2-(m-tolyl)propanenitrile (10i)

Following the procedure C, to a well dried schlenk flask, BuLi(1.1 mmol, 0.44 ml of 2.5M in n-hexane) was added into a solution of 2-(3-methyl)-2-phenylacetonitrile (207 mg, 1.0 mmol) in THF at -78°C. After 10mins, a solution of trimethyltin chloride (219 mg 1.1 mmol,) in 2 ml of toluene was dropped into the reaction at -78°C. Then the reaction mixture was allowed to go to r.t and stirring for 1 hour. A solution of (R)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde 9a (1.2 mmol, 156.0 mg) in 3 ml of toluene was cooled to -78°C, after kept at -78°C and stirring for 18hrs, the reaction was decomposed by saturated NH\(_4\)Cl solution and adjust PH to 7 at -78°C, then extract with ethyl acetate, washed by brine, dried over sodium sulfate, remove all the solvent, the crude product was purified by the flash chromatography (cyclohexane: ethyl acetate = 8:1) to get pure compound 11i (22 mg), and 10i (72 mg), yield 28%.

![11i](image-url)

**Isomer A:** IR (neat): 2238 cm^{−1}. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.58 – 7.55 (m, 1H), 7.46 –7.11 (m, 8H), 4.42 (t, \(J= 5.2\) Hz, 1H), 4.20 – 4.07 (m, 1H), 3.47 – 3.41 (m, 1H), 3.38 (d, \(J= 2.4\) Hz, 1H, OH), 3.19 (m, 1H), 2.35 (s, 3H), 1.44 (s, 3H), 1.31 (s, 3H), \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 139.03, 138.18, 137.29, 129.26, 128.87, 128.46, 128.01, 127.84, 124.96, 120.34, 109.80, 75.18, 74.07, 66.89, 56.85, 30.15, 25.18, 21.50. HPLC-MS: [M+Na]=360. Elemental Analysis: Calcd. for C_{21}H_{23}NO_3: C, 74.75; H, 6.87; N, 4.15; O, 14.22. Found: C, 74.96; H, 6.88.
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Isomer B: IR (neat): 2238 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.58 – 7.55 (m, 1H), 7.46 – 7.22 (m, 7H), 7.15 – 7.11 (m, 1H), 4.43 (t, \(J = 5.2\) Hz, 1H), 4.20 – 4.07 (m, 1H), 3.44 (ddd, \(J = 8.7, 6.2, 4.5\) Hz, 1H), 3.37 (d, \(J = 2.4\) Hz, 1H, OH), 3.21 - 3.18 (m, 1H), 2.33 (s, 3H), 1.44 (s, 3H), 1.31 (s, 3H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 139.03, 138.43, 137.10, 129.10, 128.74, 128.04, 127.28, 124.41, 120.23, 109.74, 75.18, 74.07, 66.94, 57.81, 31.05, 26.42, 21.57. HPLC-MS: [M+Na]=360. Elemental Analysis: Calcd. for C\(_{21}\)H\(_{23}\)NO\(_3\): C, 74.75; H, 6.87; N, 4.15; O, 14.22. Found: C, 74.96; H, 6.88.

Isomer A: IR (neat): 2238 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.53 (d, \(J = 7.7\) Hz, 1H), 7.45 – 7.15 (m, 7H), 7.11 (d, \(J = 3.2\) Hz, 1H), 4.89 (d, \(J = 2.6\) Hz, 1H), 4.217 – 4.13 (m, 1H), 4.01 - 3.96 (m, 1H), 3.90 - 3.85 (m, 1H), 2.52 (d, \(J = 2.8\) Hz, 1H, OH), 2.32 (s, 3H), 1.40 (s, 3H), 1.25 (s, 3H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 138.81, 137.66, 136.99, 129.17, 129.03, 128.79, 128.31, 128.24, 127.02, 124.05, 120.38, 108.29, 75.96, 74.03, 66.46, 55.00, 26.28, 25.14, 21.55. HPLC-MS: [M+Na]=360. Elemental Analysis: Calcd. for C\(_{21}\)H\(_{23}\)NO\(_3\): C, 74.75; H, 6.87; N, 4.15; O, 14.22. Found: C, 74.89; H, 6.87.

Isomer B: IR (neat): 2238 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.53 (d, \(J = 7.7\) Hz, 1H), 7.45 – 7.15 (m, 8H), 4.89 (d, \(J = 2.6\) Hz, 1H), 4.15 (dd, \(J = 7.2, 7.2\) Hz, 1H), 4.01 - 3.96 (m, 1H), 3.90 - 3.85 (m, 1H), 2.55 (d, \(J = 2.8\) Hz, 1H, OH), 2.32 (s, 3H), 1.38 (s, 3H), 1.24 (s, 3H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 139.10, 137.40, 137.18, 129.16, 129.10, 128.88, 128.33, 127.67, 127.02, 124.51, 120.37, 108.29, 75.96, 74.08, 63.54, 55.17, 26.31, 25.19, 21.56. HPLC-MS: [M+Na]=360. Elemental Analysis: Calcd. for C\(_{21}\)H\(_{23}\)NO\(_3\): C, 74.75; H, 6.87; N, 4.15; O, 14.22. Found: C, 74.96; H, 6.88.

The preparation of (3R)-3-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-hydroxy-2-phenyl-2-(m-tolyl)propanenitrile (11j) and (3S)-3-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-hydroxy-2-phenyl-2-(m-tolyl)propanenitrile (10j)
Following the procedure C, to a well dried schlenk flask, BuLi(1.1 mmol, 0.44ml of 2.5M in n-hexane ) was added into a solution of 2,2-bis(4-methoxyphenyl)acetonitrile 1j (253 mg, 1.0
mmol) in THF at -78°C. After 10mins, a solution of trimethyltin chloride (219 mg 1.1 mmol) in 2 ml of toluene was dropped into the reaction at -78°C. Then the reaction mixture was allowed to go to r.t and stirring for 1 hour. A solution of (R)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde 9a (1.2 mmol, 156.0 mg) in 3 ml of toluene was cooled to -78°C, after kept at -78°C and stirring for 18hrs, the reaction was decomposed by saturated NH₄Cl solution and adjust PH to 7 at -78°C, then extract with ethyl acetate, washed by brine, dried over sodium sulfate, remove all the solvent, the crude product was purified by the flash chromatography (CH₂Cl₂:ether) to get pure compound 11j (14 mg), and 10j (98 mg), yield 28%.

IR (neat): 2241 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ 7.46 (d, J = 8.8 Hz, 2H), 7.30 – 7.23 (m, 2H), 6.87 (dd, J = 13.6, 8.8 Hz, 4H), 4.33 (t, J = 5.2 Hz, 1H), 4.18 – 4.10 (m, 1H), 3.80 (s, 3H), 3.79 (s, 3H), 3.47 (dd, J = 8.8, 6.4 Hz, 1H), 3.34 (d, J = 4.9 Hz, 1H, OH), 3.21 (dd, J = 8.8, 6.4 Hz, 1H), 1.58 (s, 1H), 1.44 (s, 3H), 1.31 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 159.45, 159.14, 130.64, 129.56, 129.21, 128.52, 120.59, 114.33, 114.06, 109.70, 75.24, 74.42, 66.99, 55.48, 55.32, 55.30, 26.43, 25.20. HPLC-MS: [M+Na]=406. Elemental Analysis: Calcd. for C₂₂H₂₅NO₅: C, 68.91; H, 6.57; N, 3.65; O, 20.86. Found: C, 69.05; H, 6.58.

IR (neat): 2241 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ 7.44 (t, J = 6.0 Hz, 2H), 7.31 (t, J = 6.0 Hz, 2H), 6.97 – 6.77 (m, 4H), 4.82 (s, 1H), 4.11 (dd, J = 8.4, 2.4 Hz, 1H), 4.02 (td, J = 6.4, 2.4 Hz, 1H), 3.84 (dd, J = 8.4, 6.0 Hz, 1H), 3.80 (s, 6H), 2.51 (d, J = 2.0 Hz, 1H, OH), 1.42 (s, 3H), 1.28 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 159.33, 129.64, 129.58, 128.97, 128.30, 120.66, 114.44, 114.14, 108.26, 76.00, 74.27, 63.44, 55.33, 55.31, 53.54, 26.34, 25.17. HPLC-MS: [M+Na]=406. Elemental Analysis: Calcd. for C₂₂H₂₅NO₅: C, 68.91; H, 6.57; N, 3.65; O, 20.86. Found: C, 69.00; H, 6.58.
The preparation of \((3R)-3-((R)-2,2\text{-dimethyl}-1,3\text{-dioxolan}-4\text{-yl})-3\text{-hydroxy}-2-(4\text{-nitrophenyl})-2\text{-phenylpropanenitrile} (11k)\) and \((3S)-3-((R)-2,2\text{-dimethyl}-1,3\text{-dioxolan}-4\text{-yl})-3\text{-hydroxy}-2-(4\text{-nitrophenyl})-2\text{-phenylpropanenitrile} (10k)\)

Following the procedure C, to a well dried schlenk flask, BuLi (1.1 mmol, 0.44 ml of 2.5 M in \(n\text{-hexane}\)) was added into a solution of 2-(4-nitrophenyl)-2-phenylacetonitrile 1k (238 mg, 1.0 mmol) in THF at -78°C. After 10 mins, a solution of trimethyltin chloride (219 mg, 1.1 mmol) in 2 ml of toluene was dropped into the reaction at -78°C. Then the reaction mixture was allowed to go to r.t and stirring for 1 hour. A solution of (R)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde 9a (1.2 mmol, 156.0 mg) in 3 ml of toluene was cooled to -78°C, after kept at -78°C and stirring for 18 hrs, the reaction was decomposed by saturated \(\text{NH}_4\text{Cl}\) solution and adjust PH to 7 at -78°C, then extract with ethyl acetate, washed by brine, dried over sodium sulfate, remove all the solvent, the crude product was purified by the flash chromatography (\(\text{CH}_2\text{Cl}_2\):ether) to get pure compound 11k (32 mg), and 10k (14 mg), yield 13%.

Isomer A: IR (neat): 2251 cm\(^{-1}\). \(^1\text{H NMR} (400 \text{ MHz, CDCl}_3) \delta 8.26 – 8.22 (m, 2), 7.78 – 7.75 (m, 1H), 7.65 – 7.63 (m, 1H), 7.57 – 7.51 (m, 1H), 7.43 – 7.37 (m, 4H), 4.52 – 4.50 (m, 1H), 4.10 – 4.06 (m, 1H), 3.79 (dd, \(J = 8.8, 6.8 \text{ Hz}, 1H\)), 3.61 (dd, \(J = 8.4, 6.0 \text{ Hz}, 1H\)), 3.30 (d, \(J = 6.8 \text{ Hz}, 1H, \text{OH}\)), 1.45 (s, 3H), 1.30 (s, 3H).

\(^{13}\text{C NMR} (100 \text{ MHz, CDCl}_3) \delta 147.40, 145.51, 142.96, 135.97, 134.52, 129.04, 128.82, 128.17, 124.41, 124.11, 119.63, 110.35, 74.42, 73.53, 66.99, 56.41, 42.31, 26.19, 24.98.\)


Isomer B: IR (neat): 2251 cm\(^{-1}\). \(^1\text{H NMR} (400 \text{ MHz, CDCl}_3) \delta 8.26 – 8.22 (m, 2), 7.78 – 7.75 (m, 2H), 7.43 – 7.37 (m, 5H), 4.46 (t, \(J = 5.2 \text{ Hz}, 1H\)), 4.15 (q, \(J = 5.8 \text{ Hz}, 1H\)), 3.53 (dd, \(J = 8.4, 6.4 \text{ Hz}, 1H\)), 3.47 (d, \(J = 6.0 \text{ Hz}, 1H, \text{OH}\)), 3.25 (dd, \(J = 8.8, 6.0 \text{ Hz}, 1H\)), 1.45 (s, 3H), 1.32 (s, 1H).

\(^{13}\text{C NMR} (100 \text{ MHz, CDCl}_3) \delta 147.40, 145.51, 142.96, 135.97, 134.28, 129.59, 129.13, 128.70, 124.41, 123.79, 119.26, 110.11, 74.73, 74.04, 66.85, 56.89, 29.68, 26.34, 25.02.
Isomer A: IR (neat): 2251 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.26 – 8.22 (m, 2H), 7.78 – 7.76 (m, 1H), 7.68 – 7.66 (m, 1H), 7.57 – 7.54 (m, 1H), 7.45 – 7.39 (m, 4H), 4.91 (t, \(J = 2.5\) Hz, 1H), 4.15 – 4.11 (m, 1H), 4.0 – 3.85 (complex pattern, 3H), 2.58 (bs, 1H, OH), 1.34 (s, 3H), 1.26 (s, 3H). 

Isomer B: IR (neat): 2251 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.26 – 8.22 (m, 2H), 7.57 – 7.54 (m, 2H), 7.45 – 7.41 (m, 5H), 4.91 (t, \(J = 2.5\) Hz, 1H), 4.22 (dd, \(J = 8.4, 6.0\) Hz, 1H), 4.0 – 3.85 (complex pattern, 3H), 2.78 (bs, 1H, OH), 1.34 (s, 3H), 1.26 (s, 3H). 

The preparation of (3R)-3-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-hydroxy-2-phenyl-2-(pyridin-3-yl)propanenitrile (11l) and (3S)-3-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-hydroxy-2-phenyl-2-(pyridin-3-yl)propanenitrile (10l)

Following the procedure C, to a well dried schlenk flask, BuLi(1.1 mmol, 0.44ml of 2.5M in n-hexane) was added into a solution of 2-(pyridin-3-yl)-2-phenylacetonitrile \(\text{I1} \) (194 mg, 1.0 mmol) in THF at -78°C. After 10mins, a solution of trimethyltin chloride (219 mg 1.1 mmol,) in 2 ml of toluene was dropped into the reaction at -78°C. Then the reaction mixture was allowed to go to r.t and stirring for 1 hour. A solution of (R)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde \(\text{9a} \) (1.2 mmol, 156.0 mg) in 3 ml of toluene was cooled to -78°C, after kept at -78°C and stirring for 18hrs, the reaction was decomposed by saturated NH\(_4\)Cl solution and
adjust PH to 7 at -78°C, then extract with ethyl acetate, washed by brine, dried over sodium sulfate, remove all the solvent, the crude product was purified by the flash chromatography (CH₂Cl₂:ether) to get pure compound 11 (43 mg), and 10 (114 mg), yield 48%.

![Structure of 11](image)

**Isomer A:** IR (neat): 2249 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ 8.66 (d, J = 0.8 Hz, 1H), 8.60 – 8.58 (m, 1H), 7.79 – 7.31 (m, 7H), 4.50 (d, J = 4.4 Hz, 1H), 4.15 – 4.10 (m, 1H), 3.76 (dd, J = 8.8, 6.4 Hz, 1H), 3.57 (dd, J = 8.4, 6.4 Hz, 1H), 3.30 (bs, 1H, OH), 1.43 (s, 3H), 1.30 (s, 3H).

¹³C NMR (100 MHz, CDCl₃) δ 149.44, 148.80, 136.70, 135.99, 129.49, 128.95, 128.69, 128.18, 123.62, 119.53, 110.38, 76.08, 74.67, 73.67, 67.04, 53.99, 26.25, 25.10. HPLC-MS: [M+Na]=347. Elemental Analysis: Calcd. for C₁₉H₂₀N₂O₃: C, 70.35; H, 6.21; N, 8.64; O, 14.80. Found: C, 70.57; H, 6.23.

**Isomer B:** IR (neat): 2249 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ 8.73 (d, J = 1.6 Hz, 1H), 8.56 – 8.53 (m, 1H), 7.79 – 7.31 (m, 7H), 4.88 (d, J = 4.0 Hz, 1H), 4.20 – 4.16 (m, 1H), 3.96 (dd, J = 6.4, 3.2 Hz, 1H), 3.83 (dd, J = 6.4, 3.2 Hz, 1H), 3.30 (bs, 1H, OH), 1.35 (s, 3H), 1.26 (s, 3H).

¹³C NMR (100 MHz, CDCl₃) δ 149.06, 148.55, 135.45, 134.13, 129.18, 128.81, 128.57, 127.86, 123.57, 119.53, 108.89, 76.08, 74.27, 64.56, 53.99, 26.25, 24.95. HPLC-MS: [M+Na]=347. Elemental Analysis: Calcd. for C₁₉H₂₀N₂O₃: C, 70.35; H, 6.21; N, 8.64; O, 14.80. Found: C, 70.57; H, 6.23.
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**Isomer B:** IR (neat): 2249 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.81 (d, \(J = 1.6\) Hz, 1H), 8.57 – 8.54 (m, 1H), 7.88 (q, \(J = 2.4\) Hz, 1H), 7.42 – 7.34 (m, 5H), 4.45 (d, \(J = 5.2\) Hz, 1H), 3.97 – 3.96 (m, 1H), 3.75 (bs, 1H, OH), 3.51 (dd, \(J = 8.4, 6.0\) Hz, 1H), 3.25 (dd, \(J = 8.8, 6.0\) Hz, 1H), 1.44 (s, 3H), 1.28 (s, 3H). \(\delta\) \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 149.04, 148.78, 136.23, 136.13, 134.20, 129.40, 128.93, 127.40, 123.49, 119.42, 108.56, 75.80, 73.84, 63.66, 53.57, 26.33, 25.10. HPLC-MS: [M+Na]=347. Elemental Analysis: Calcd. for C\(_{19}\)H\(_{20}\)N\(_2\)O\(_3\): C, 70.35; H, 6.21; N, 8.64; O, 14.80. Found: C, 70.46; H, 6.22.

### 3.4.3. Preparation of α- (phenylalkyltin) nitriles

**General procedure for preparation the preparation α-trimethyltin nitriles (4ba-4fa)**

![Scheme 3.12 preparation of α- (phenylalkyltin) nitriles](image)

\(n\)-BuLi (1.1 mmol, 0.44ml of 2.5M in n-hexane) was added into a solution of diisopropyl ethyl amine (1.1 mmol, 0.15ml) in 3 ml of THF at -78°C. Then a solution of 2-phenylpropanenitrile 1b (131 mg, 1.0 mmol) in THF (1 ml) was dropped into the base solution at -78°C. After 5 min, a solution of trimethyltin chloride (119 mg, 1.1 mmol) in 1ml of toluene was dropped into the reaction. After maintaining at -78°C for 15min, the reaction mixture was allowed to reach r.t. spontaneously and kept for 2hours. Then remove all the solvents under vacuum, dissolve the residues into 5 ml of pentane, filter under N\(_2\), the filtrate was removed all the solvent, the product were distilled under vaccum.

**The preparation of 2,2-diphenyl-2-(trimethylstannyl)acetonitrile (4aa)**

Following the general procedure, 2,2-diphenyl-2-(trimethylstannyl)acetonitrile (4aa) was prepared with yield 60%.
Colorless oil. IR (neat): 2207 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.35 – 7.15 (m, 10H), 0.26 (s, 9H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 138.56, 129.15, 128.94, 128.21, 127.69, 127.26, 126.45, 26.89, -6.77. MS (GC-MS): [M+1]=358. Elemental Analysis: Calcd. for C\(_{17}\)H\(_{19}\)NSn: C, 57.35; H, 5.38; N, 3.93; Sn, 33.34. Found: C, 57.52; H, 5.39.

The preparation of 2-phenyl-2-(trimethylstannyl)propanenitrile (4ba)

Following the general procedure, 2-phenyl-2-(trimethylstannyl)propanenitrile (4ba) was prepared with yield 73%.

![formula](Me)_3SnCN Ph 4ba

Colorless oil. IR (neat): 2202 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.23 (t, \(J = 7.2\) Hz, 3H), 7.14 (t, \(J = 7.2\) Hz, 2H), 1.88 (s, 3H), 0.40 – 0.25 (m, 9H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) 137.19, 129.25, 128.91, 126.81, 125.64, 121.66, 31.37, 20.38, -9.09. MS (GC-MS): [M+1] 296. Elemental Analysis: Calcd. for C\(_{12}\)H\(_{17}\)NSn: C, 49.03; H, 5.83; N, 4.76; Sn, 40.38. Found: C, 49.16; H, 5.84.

The preparation of 3-methyl-2-phenyl-2-(trimethylstannyl)butanenitrile (4ca)

Following the general procedure, 3-methyl-2-phenyl-2-(trimethylstannyl)butanenitrile (4ca) was prepared with yield 65%.

![formula](Me)_3SnCN Ph 4ca

Colorless oil. IR (neat): 2207 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.44 (t, \(J = 7.2\) Hz, 2H), 7.37 (d, \(J = 8.0\) Hz, 2H), 7.26 (t, \(J = 7.2\) Hz, 1H), 2.86 – 2.53 (m, 1H), 1.38 (d, \(J = 6.8\) Hz, 3H), 1.02 (d, \(J = 6.4\) Hz, 3H), 0.40 – 0.18 (m, 9H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 137.04, 129.10, 128.18, 126.65, 125.49, 121.51, 31.22, 24.99, 21.43, 20.23, -9.24. MS (GC-MS): [M+1]=323. Elemental Analysis: Calcd. for C\(_{14}\)H\(_{21}\)NSn: C, 52.22; H, 6.57; N, 4.35; Sn, 36.86. Found: C, 52.42; H, 6.58.

The preparation of 4-methyl-2-phenyl-2-(trimethylstannyl)pentanenitrile (4da)
Following the general procedure, 4-methyl-2-phenyl-2-(trimethylstannyl)pentanenitrile (4da) was prepared with yield 67%.

Colorless oil. IR (neat): 2205 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.38 – 7.32 (m, 2H), 7.30 – 7.25 (m, 2H), 7.20 – 7.14 (m, 1H), 5.96 – 5.69 (m, 1H), 5.36 – 5.01 (m, 2H), 3.13 – 2.92 (m, 1H), 2.92 – 2.74 (m, 1H), 0.33 – 0.16 (m, 9H). \(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 138.17, 128.94, 128.67, 125.64, 124.86, 124.61, 123.82, 118.82, 37.91, 31.90, -8.66. MS (GC-MS) [M+1]=322.

Elemental Analysis: Calcd. for C\(_{14}\)H\(_{19}\)NSn: C, 52.54; H, 5.98; N, 4.38; Sn, 37.09. Found: C, 52.71; H, 5.99.

**The preparation of 4-methyl-2-phenyl-2-(trimethylstannyl)pentanenitrile (4ea)**

Following the general procedure, preparation of 4-methyl-2-phenyl-2-(trimethylstannyl)pentanenitrile (4ea) was prepared with yield 59%.

Colorless oil. IR (neat): 2204 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.31 (t, \(J = 7.6\) Hz, 2H), 7.25 (d, \(J = 8.0\) Hz, 2H), 7.12 (t, \(J = 7.2\) Hz, 1H), 2.38 – 2.11 (m, 1H), 2.03 – 1.76 (m, 2H), 1.00 (d, \(J = 5.6\) Hz, 3H), 0.81 (d, \(J = 5.6\) Hz, 3H), 0.30 – 0.11 (m, 9H). \(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 138.29, 128.98, 128.64, 125.06, 124.46, 120.88, 35.42, 27.09, 23.63, 22.29, -9.00. MS (GC-MS): [M+1]=337. Elemental Analysis: Calcd. for C\(_{15}\)H\(_{23}\)NSn: C, 53.61; H, 6.90; N, 4.17; Sn, 35.32. Found: C, 53.86; H, 6.91.

**The preparation of 1-(trimethylstannyl) cyclohexane-1-carbonitrile (4fa)**

Following the general procedure, preparation of 1-(trimethylstannyl) cyclohexane-1-carbonitrile (4fa) was prepared with yield 80%.

Colorless oil. IR (neat): 2195 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 1.95 (d, \(J = 12.8\) Hz, 2H), 1.81 – 1.57 (m, 5H), 1.53 – 1.50 (m, 2H), 1.34 – 1.19 (m, 1H), 0.35 – 0.14 (m, 9H). \(^13\)C NMR
(100 MHz, CDCl$_3$): $\delta$ 32.46, 26.08, 24.23, 11.76, -10.61. MS (GC-MS) [M+1]=274. Elemental Analysis: Calcd. for: C$_{10}$H$_{19}$NSn: C, 44.16; H, 7.04; N, 5.15; Sn, 43.65. Found: C, 44.33; H, 7.05.

3.4.4. Procedure for aldol type reaction of $\alpha$-(phenylalkyltin)nitriles

Procedure C:
$\alpha$-trimethyltin nitrile was dissolved into toluene at -78 °C under argon, then a solution of carbonyl compounds (5a-n) in THF was slowly dropped into the reaction, after 2 hours, the reaction was quenched by an acidic solution of 1M HCl (0.5 ml) in saturated NH$_4$Cl solution (15 ml) at -78 °C, then 20 ml ethyl acetate was added at same temperature, the mixture was allowed to reach r.t spontaneously, then extract with ethyl acetate(20 ml*2), washed organic phase by brine, dried by anhydrous Na$_2$SO$_4$, remove all the solvent, made a silicon gel chromatography for purification as previous reported for each product.
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Chapter 4. Synthesis of N-aluminum ketene imines and application in epoxide ring opening reaction

4.1 Introduction:

N-aluminium imines are stable intermediates, easily obtainable via reduction of alkyl or aryl nitrile by dialkyl aluminium hydride (Scheme 4.1).\(^1\)-\(^5\) The possibility of a back donation from nitrogen to aluminium makes these intermediates particularly stable.\(^6\) Limited researches have been focused on N-aluminum ketenes, including some physical property investigations,\(^7\) moreover, N-aluminum ketenes as intermediates in practical catalytic acylation reactions have been established as well.\(^8\),\(^9\)

Having available such information, we decided to prepare the corresponding N-aluminum ketene imines according the general procedure so far adopted for the preparation of N-silyl and N-tin ketene imines. The final goal of these studies is to add new information on the synthesis and reactivity of N-metallo ketene imines. In particular, for the N-aluminium ketene imines, we anticipated to use them in the preparation of $\gamma$-hydroxy nitriles. As a matter of fact $\gamma$-hydroxyl nitriles have a wide range of applications in organic synthesis,\(^10\)-\(^12\) particularly as intermediates of $\gamma$-keto-nitrile and lactons, which are precursors of bioactive products. $\gamma$-hydroxy nitriles have been prepared by deprotonated nitriles react with epoxides,\(^12\),\(^13\) while the reaction gave lactone and cyclic iminoester as side products, or in an extreme case, no expected $\gamma$-hydroxyl nitriles were formed,\(^13\) the use of N-aluminium ketene imines are expected to overcome this defect.

![Scheme 4.1 preparation of N-Al imines](image)

4.2 Present work

Among different classes of organic compounds of the most interesting and easily available from market or in house preparation is that of epoxides. The fact that recent methodologies by Sharpless allow the preparation of epc (enantiomerically pure compounds) derivatives renders this class of compounds very interesting.\(^14\),\(^15\) Application of epoxides as stable electrophiles is particularly
challenging, opening of the epoxides by nucleophiles is a quite old reaction: one of the most popular is the opening of epoxides by acid halides to obtain the corresponding epi-halohydrines the nucelophiles are appearing for overcoming this issue.\textsuperscript{16–20} Meanwhile, the enantiomeric epoxide ring opening by catalysts is remaining as a hot field.\textsuperscript{21–23} As a matter of fact their reactions with C-nucleophiles open the stream to an almost numberless differently functionalized derivatives. The regiochemistry of the reaction depends from the steric demanding of the substituents of epoxides, from the reaction conditions and, last but not least, from the presence of a catalyst. At this stage of our preliminary studies we chose to use terminal epoxides since, for steric reasons, only one regioisomer is usually obtained.

Two were the main goal in this project: avoid the formation of side products with the straightforward synthesis of the $\gamma$-hydroxyl nitriles and use the ketene imines as alkylating agents in order to confer extra functionalities to the starting epoxides. To reach these aims, the first action has been, of course, the preparation of $N$-dialkyl aluminium ketene imine from the corresponding nitrile in analogy to what studied in the case of $N$-silyl and $N$-tin ketene imines.

4.2.1 Synthesis of $N$-Aluminum ketene imines

Based on the information above reported and taking advantage of our own experiences on the aluminum-imines we felt that the corresponding ketene imines could be stable intermediates and could be prepared from the corresponding alkali metal ketene imines (alkali= Li, Na, K) by a suitable exchange of the alkali metal with a dialkyl aluminium halides, in analogy to what has been done for the preparation of $N$-silyl and $N$-tin ketene imines (Scheme 4.2).\textsuperscript{24, 25}

\begin{equation}
\text{Scheme 4.2 proposed method for preparation of } N\text{-Al ketene imines}
\end{equation}

Following the above reported working plane, we started with the preparation of suitable aluminium imines from commercially available nitrile and dialkyl aluminium halides. Accordingly, the 2-phenyl-propane nitrile \textbf{1a} was treated with LDA (Lithium diisopropyl amide) to give the corresponding nitrile anion which was treated \textit{in situ} with commercially available diethyl aluminium chloride to give the corresponding aluminium ketene imine, identified by its IR
stretching at 2087 cm\(^{-1}\) (characteristic of C=C=N functional moiety) (Scheme 4.3). No further studies were performed, at this very preliminary stage, for fully identify the aluminium ketene imine.

\[
\begin{align*}
\text{CN} & \quad \text{LDA} \\
\text{Ph} & \quad \text{M=Li, Na, k} \\
\text{Me} & \\
\end{align*}
\]

\[
\begin{align*}
\text{Me} & \quad \text{C=N} \\
\text{Ph} & \\
\end{align*}
\]

Scheme 4.3 preparation of N-Al ketene imines

4.2.2 Uncatalyzed chemo, regio-selective epoxide ring opening reaction by N-aluminum ketene imines: Synthesis of γ-hydroxyl nitriles.

The reaction of alkali metal nitriles and terminal epoxides has been already reported and results in a mixture of cyclic and acyclic products (Scheme 4.4).\(^{12}\) Product 7a (a diastereo mixture of 11a 12a) arise from a classical opening reaction whilst products 5a and 6a arise from a, difficult to avoid (in the basic reaction conditions present), subsequent cyclization to imino ester 5a and/or lactone 6a, derived in turn, from the imino hydrolysis. The factors influencing the reaction and the possible solution have been discussed and reported in literature.

\[
\begin{align*}
\text{Ph} & \quad \text{CN} \\
\text{H}_2\text{C} & \\
\text{LiN(SiMe}_3\text{)}_2 & \quad \text{-78°C} \\
\end{align*}
\]

\[
\begin{align*}
\text{Ph} & \quad \text{CN} \\
\text{R}_2 & \\
\end{align*}
\]

Scheme 4.4 alkali metal nitriles react with terminal epoxides

Before testing the reactivity of N-aluminium ketene imines versus epoxides we performed different experiments to test the reactivity of terminal epoxide with silyl ketene imines. Accordingly, \(N\)-(2,2-diphenylvinylidene)-1,1,1-trimethylsilanamine and 2-methyloxirane were used.

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No reaction took place. (Scheme 4.5 and Table 4.1). Using different aluminium Lewis acids as catalyst, only traces of the target were obtained except the case in which diethylaluminium chloride was used as catalyst (Table 4.1 entry 3, 4). Taking advantage of this information we decide to start a dedicated study on the opening of epoxides by \( N \)-aluminum ketene imines.

Ascertained that neutral silylketene imines are inert “versus” epoxides, our next attempt was to check the reactivity of aluminium ketene imines, prepared as above reported, “versus” terminal epoxides:

\[
\begin{align*}
\text{Table 4.1 } \text{N-silyl ketene imine used in epoxide ring opening reaction} \\
\end{align*}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>N-Silyl ketenimine</th>
<th>Epoxide</th>
<th>Catalyst$</th>
<th>Reaction</th>
<th>Yield&amp;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8a</td>
<td>4a</td>
<td>--</td>
<td>72h</td>
<td>Trace</td>
</tr>
<tr>
<td>2</td>
<td>8a</td>
<td>4a</td>
<td>(Salen)AlCl</td>
<td>72h</td>
<td>Trace</td>
</tr>
<tr>
<td>3</td>
<td>8a</td>
<td>4a</td>
<td>Et(_2)AlCl</td>
<td>18h</td>
<td>35% 10a</td>
</tr>
<tr>
<td>4</td>
<td>8a</td>
<td>4a</td>
<td>Et(_2)AlCl</td>
<td>72h</td>
<td>35% 10a</td>
</tr>
<tr>
<td>5</td>
<td>8a</td>
<td>4a</td>
<td>Et(_2)AlOTf</td>
<td>72h</td>
<td>Trace</td>
</tr>
<tr>
<td>6</td>
<td>8a</td>
<td>4a</td>
<td>(Salen)AlOTf</td>
<td>72h</td>
<td>Trace</td>
</tr>
<tr>
<td>7</td>
<td>8a</td>
<td>4a</td>
<td>(Salen)CrCl</td>
<td>72h</td>
<td>Trace</td>
</tr>
</tbody>
</table>

$: 0.1M$ catalysts were used. &: measured by Chiral HPLC (CHIRALPAK® AD).

We anticipated that aluminium ketene imines must be more reactive than the corresponding silyl ketene imines due to the enhanced oxophile character of aluminium in comparison with silyl. It was extremely gratifying to find out that the reaction between aluminium ketene imine 3a and 2-methyloxirane 4a was successful according the mechanism reported in scheme 4.6 (table 4.2, entry 1). It must be stressed out that a quaternary carbon centre in the final target is generated and no cyclization product of any nature has been found in the reaction mixture. Having established good experimental conditions for this novel epoxide opening by \( N \)-aluminium ketene imines, we
decided to employ aluminium ketene imines 3a and 3b, with 2-methylxirane 4a, the results are shown in table 4.2.

As we can see, there are satisfactory formation of final adducts, but a low diastereoselectivity. In order to check if there is any affection in the yield and the diastereoselectivity by the solvent, toluene, instead of THF, was adopted for the reaction (table 4.2, entry 3). Only a slight improvement on the diastereo-selectivity was observed whereas more side products appeared in the reaction mixture. No effect, so far, has been experienced with the use of Al-salen catalyst (table 4.2, entry 4).

![Scheme 4.6 reaction between aluminium ketene imine 3a, 3b and 2-methylxirane (4a)]

**Table 4.2. Reactions between different nucleophiles and epoxide 4a.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Nucleophile</th>
<th>Product#</th>
<th>Ratio 11/12</th>
<th>Solvent</th>
<th>Method</th>
<th>Yield(%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3b</td>
<td>11b</td>
<td>-</td>
<td>THF</td>
<td>A</td>
<td>58</td>
</tr>
<tr>
<td>2</td>
<td>3a</td>
<td>11a, 12a</td>
<td>50:50</td>
<td>THF</td>
<td>A</td>
<td>60</td>
</tr>
<tr>
<td>3</td>
<td>3a</td>
<td>11a, 12a</td>
<td>40/60</td>
<td>Toluene</td>
<td>B</td>
<td>40</td>
</tr>
<tr>
<td>4</td>
<td>3a</td>
<td>11a, 12b</td>
<td>40/60</td>
<td>Toluene</td>
<td>C&amp;</td>
<td>50</td>
</tr>
</tbody>
</table>

$: for the sake of simplicity, only two diastereomers were reported in the table. &: in method C, L-salen Chloride were used as catalyst. *: isolated yields.
Scheme 4.7 \(N\)-Al ketene imine 3a reacts with epoxides 4b-g.

To test the reaction scope, we treated different epoxide with the \(N\)-Al ketene imine arising from \(\alpha\)-methyl phenylacetonitrile. All the epoxides underwent moderate yields and good regioselectivities since \(\gamma\)-hydroxyl nitrile has been found as the single product. In all entries, only styrene oxide gives a moderate stereoselectivity (Table 4.3 Entry 2), probably due to the steric effect of phenyl group on \(\alpha\)-position, on \(\text{syn}\) and \(\text{anti}\) products.

Table 4.3 reaction of ketene imine 25a with different epoxide

<table>
<thead>
<tr>
<th>Entry</th>
<th>Epoxides (4) *</th>
<th>Product</th>
<th>Dr(^{#}) (12 / 11)</th>
<th>Yield (%)$^5$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4b</td>
<td>11c, 12c</td>
<td>50:50</td>
<td>28</td>
</tr>
<tr>
<td>2</td>
<td>(R_3=\text{Ph}) 4c</td>
<td>11d, 12d</td>
<td>25:75</td>
<td>49</td>
</tr>
<tr>
<td>3</td>
<td>(R_3=\text{CH}_2\text{CH}_3) 4d</td>
<td>11e, 12e</td>
<td>50:50</td>
<td>41</td>
</tr>
<tr>
<td>4</td>
<td>(R_3=(\text{CH}_2)_3\text{CH}_3) 4e</td>
<td>11f, 12f</td>
<td>50:50</td>
<td>40</td>
</tr>
<tr>
<td>5</td>
<td>(R_3=(\text{CH}_2)_3\text{CH}_3) 4f</td>
<td>11g, 12g</td>
<td>50:50</td>
<td>41</td>
</tr>
<tr>
<td>6</td>
<td>(R_3=(\text{CH}_2)_3\text{CH}_3) 4g</td>
<td>11h, 12h</td>
<td>50:50</td>
<td>29</td>
</tr>
</tbody>
</table>

* epoxides 4d-4g were prepared according to reference.\(^{26}\) #: for the sake of simplicity, only two diastereomers were reported in the table, the ratio was determined by \(^1\)H NMR and HPLC; S: isolated yields.
Chapter 4

Then different $N$-Al ketene imines were prepared and treated with styrene oxide ($4b$), with ketene imine $3d$, the yield were increased and the diastereo selectivity remained (table 4.4, entry 3), and on other substrate, both of yield and diastereo selectivity decreased.

![Scheme 4.8](image)

Scheme 4.8 different $N$-Al ketene imines react with epoxide $4b$.

| Entry | $N$-Al ketene imine $R_1$ | Product | Dr$^\gamma$ | Yield (%)$^\kappa$
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$R_1 = \text{Ph (3b)}$</td>
<td>11i</td>
<td>--</td>
<td>50</td>
</tr>
<tr>
<td>2</td>
<td>$R_1 = \text{Isopropyl (3c)}$</td>
<td>11j, 12j</td>
<td>50:50</td>
<td>47</td>
</tr>
<tr>
<td>3</td>
<td>$R_1 = \text{Ally (3d)}$</td>
<td>11k, 12k</td>
<td>30:70</td>
<td>45</td>
</tr>
<tr>
<td>4</td>
<td>$R_1 = \text{Pyridine (3e)}$</td>
<td>11l, 12l</td>
<td>40:60</td>
<td>38</td>
</tr>
<tr>
<td>5</td>
<td>$R_1 = \text{isobutyl (3f)}$</td>
<td>11m, 12m</td>
<td>27:73</td>
<td>52</td>
</tr>
</tbody>
</table>

$#$: for $3c$, $3d$, $3f$ the corresponding starting nitriles were prepared according to reference;$^{27}$ starting nitrile $3e$ were prepared according to reference; $^{28}$,$^{29}$ $S$: for the sake of simplicity, only two diastereomers were reported in the table, the ratio was determined by $^1$H NMR and HPLC; $\&$: isolated yields.

4.3 Conclusion

In summary, $N$-aluminium ketene imines have been prepared and react with terminal epoxides in a moderate yield, in the case of styrene oxide, a stereoselectivity were achieved without any induction. The $N$-aluminium ketene imines described herein react with epoxide give $\gamma$-hydroxyl nitriles as only one product, compare to the existing procedure, this methodology does not need a robust condition, and the ketene imines species bearing a potential for chirality constructions. The usage of this method in stereoselective reactions is present on progressing.
4.4 Experimental section

4.4.1 General method

Column chromatography was performed using Merck KGaA Silicagel 60 (230–400 Mesh-ASTM). Melting points were obtained using a Stuart Scientific SMP3 Melting Point apparatus. Optical rotations were obtained using a Unipol L1700 Schmidt+Haensch polarimeter. IR spectra were recorded on a Nicolet 380 FT-IR infrared spectrometer and Alpha Fourier-T Infrared Analysis Spectrometer (Bruker). NMR spectroscopy was performed on a Varian-Mercury 400 spectrometer using the residual signal of the solvent as the internal standard. The chemical shifts are reported in ppm and coupling constants (\(J\)) are reported in Hz. GC–MS spectra were recorded using Agilent Technologies 6850 and 5975 GC-Mass instrumentation. LC–MS spectra were obtained using an Agilent Technologies MSD1100 single-quadrupole mass spectrometer. The diastereomeric ratios reported into Tables 1, 2 and 3 have been calculated by HPLC (Agilent, Poroshell 120. SB-C18. 2.7µm, 3.0 x 100 mm) and \(^1\)H NMR on the crude reaction mixture taking into account the undoubtful peaks of each diastereomer. Elemental analyses were obtained using Flash 2000, series CHNS/O Analyzer (Thermo Scientific).

The Preparation of 4-hydroxy-2,2-diphenylpentanenitrile 11b

**Method A**: diphenylacetonitrile (290 mg, 1.5 mmol) in THF (1ml) was added into a solution of LiN(SiMe\(_3\))\(_2\) (1.5 mmol, 1.5 ml of 1.0 M in n-hexane) in THF (5 ml) at -78\(^\circ\)C under nitrogen atmosphere. After 10mins, diethyl aluminium chloride (1.5 mmol, 1.5 ml of 1.0 M in n-hexane) was added to the reaction. This reaction mixture was kept at -78\(^\circ\)C for 30mins. A solution of 2-methyloxirane (87 mg, 1.5 mmol) in THF (1 ml) was added. The reaction was kept at -78 \(^\circ\)C for 30mins. Then it was left spontaneously to reach r.t and kept overnight. The reaction was decomposed by saturated NH\(_4\)Cl\(_aq\) and potassium sodium tartrate tetrahydrate and kept stirring for 1hr at r.t. It was extracted by AcOEt (3×15ml). The organic phase was collected, dried and concentrated under *vacuum* to get the crude mixture which was purified by the flash chromatography (cyclohexane: AcOEt= 4:1) to give pure product 11b (118 mg, yield: 58%).
11b: White solid. mp: 88-92 °C. IR(neat): 2244 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 1.25\) (d, \(J=6.0\) Hz, 3H), 1.61 (bs, 1H, OH), 2.51(dd, \(J_1=2.8\) Hz, \(J_2=14.4\) Hz, 1H), 2.68 (dd, \(J_1=7.6\) Hz, \(J_2=14.0\) Hz, 1H), 3.98 (m, 1H), 7.29-7.45 (complex pattern, 10H). \(^13\)C NMR (100 MHz, CDCl\(_3\)): \(\delta = 24.39, 48.17, 49.53, 65.27, 122.63, 126.91, 126.95, 128.01, 128.09, 128.98, 129.01, 139.89, 140.36\). MS (ESI): \(m/z = 252\) [M+1].

The preparation of 2,2-diphenyl-4-((trimethylsilyl)oxy)pentanenitrile 10a

N-silyl ketene imine 8a was prepared according to a general procedure reported in Chapter 2 is-situ, a solution of 2-methyloxirane (87 mg, 1.5 mmol) in THF (1 ml) was added at -78 °C, after 1° min 0.1M of diethyl aluminium chloride were added into the reaction; The reaction was kept at -78 °C for 30mins. Then the reaction was left spontaneously to reach r.t and kept overnight. The reaction was decomposed by saturated NH\(_4\)Cl\(_\text{aq}\) and potassium sodium tartrate tetrahydrate, this mixture was kept stirring for 1h and extracted by AcOEt (3X15ml). The organic phase was collected, dried and concentrated under vacuum to get the crude mixture which was purified by the flash chromatography (cyclohexane: ether = 18:1) to give a product 10a (113 mg, yield: 35%).

10a: IR(neat): 2237 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = -0.10\) (s, 9H), 1.22(d, \(J=6.0\) Hz, 1H), 1.79 (s, 3H), 2.44 (dd, \(J_1= 3.6\) Hz, \(J_2= 14.0\) Hz, 1H), 2.77(dd, \(J_1=7.2\) Hz, \(J_2=14.0\) Hz, 1H), 3.94 - 3.99 (m, 1H), 7.48-7.28(complex pattern, 10H). \(^13\)C NMR (100 MHz, CDCl\(_3\)): \(\delta = -0.29, 24.84, 48.55, 59.33, 65.97, 121.25, 126.63, 127.21, 128.20, 128.84, 128.98, 129.06, 130.23, 137.12\). HPLC-MS: [M+Na]= 346 [M+23].

The Preparation of (2S\*, 4R\*)-4-hydroxy-2-methyl-2-phenylpentanenitrile 11a and (2R\*, 4R\*)-4-hydroxy-2-methyl-2-phenylpentanenitrile 12a

Preparation of diethylaluminium ketene imine 3a
Diethylaluminium ketene imine 3a was prepared according the same literature procedure for the preparation of silyl ketene imines. In detail, α-methyl acetonitriles (197 mg, 1.5 mmol) was added into a solution of LiN(SiMe₃)₂ (1.5 mmol, 1.5 ml of 1.0 M in n-hexane) in THF (5 ml) at -78°C under nitrogen atmosphere. After 10mins, a solution of diethyl aluminium chloride (1.5 mmol, 1.5 ml of 1.0 M in n-hexane) was added to the reaction mixture. A sample of the resulting ketene imine 3a was characterized by its IR spectra. The IR spectra indicated that there is a strong absorption at 2087 cm⁻¹ which is the characteristic signal of the cumulene absorption.

Following Method A, to the solution of ketene imine 3a which was prepared as described above, a solution of 2-methyloxirane (87 mg, 1.5 mmol) in THF (1 ml) was added at -78 °C. The reaction was kept at -78 °C for 30mins. Then the reaction was left spontaneously to reach r.t and kept overnight. The reaction was decomposed by saturated NH₄Claq and potassium sodium tartrate tetrahydrate, this mixture was kept stirring for 1hr and extracted by AcOEt (3X15ml). The organic phase was collected, dried and concentrated under vacuum to get the crude mixture which was purified by the flash chromatography (cyclohexane: AcOEt= 2:1) to give a inseparable mixture of product 11a and 12a (170 mg, ratio: 50:50, total yield: 60%). Spectral data were deducted from the mixture and arbitrarily attributed to 11a and 12a.

**11a**: IR(neat): 2237 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ =1.15(d, J=6.4 Hz, 3H), 1.68 (bs, 1H, OH), 1.79 (s, 3H), 1.98 (dd, J₁= 2.8 Hz, J₂= 13.6 Hz, 1H), 2.16(dd, J₁=8.8 Hz, J₂=13.6 Hz, 1H), 3.85 (m, 1H), 7.31-7.53(complex pattern, 5H). ¹³C NMR (100 MHz, CDCl₃): δ =24.37, 28.11, 40.89, 50.52, 65.58, 123.70, 125.61, 127.98, 129.15, 139.93. MS (ESI): m/z=190 [M+1].

**12a**: IR(neat): 2237 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ =1.23(d, J=6.4 Hz, 3H), 1.68 (bs, 1H, OH), 1.80 (s, 3H), 2.04 (dd, J₁= 3.6 Hz, J₂= 13.6 Hz, 1H), 2.16(dd, J₁=4.0 Hz, J₂=13.6 Hz, 1H), 3.99 (m, 1H), 7.31-7.53(complex pattern, 5H). ¹³C NMR (100 MHz,CDCl₃): δ =24.82, 28.94, 40.96, 50.83, 65.58, 123.89, 125.63, 128.19, 129.28, 140.23. MS (ESI): m/z=190 [M+1].
**Method B:** \(\alpha\)-methyl acetonitriles (197 mg, 1.5 mmol) in toluene (1 ml) was added into a solution of LiN(SiMe\(_3\))\(_2\) (1.5 mmol, 1.5 ml of 1.0 M in n-hexane) in toluene (5 ml) at -78°C under nitrogen atmosphere. After 10 mins, diethyl aluminium chloride (1.5 mmol, 1.5 ml of 1.0 M in n-hexane) was added to the reaction. This reaction mixture was kept at -78°C for 30 mins and filtered. The filtrate was added to a solution of 2-methyloxirane (87 mg, 1.5 mmol) in toluene (1 ml) at -78°C and kept for 30 mins at this temperature. Then the reaction was left spontaneously to reach r.t. for overnight. It was decomposed by saturated NH\(_4\)Cl\(_aq\) and potassium sodium tartrate tetrahydrate, kept stirring for 1 hr at r.t. and extracted by AcOEt (3 \(\times\) 15 ml). The organic phase was collected, dried and concentrated under vacuum to get the crude mixture which was purified by the flash chromatography (cyclohexane: AcOEt = 2:1) to give an inseparable mixture of product 11a and 12a (113 mg, ratio: 40:60, total yield: 40%).

**Method C:** \(\alpha\)-methyl acetonitriles (197 mg, 1.5 mmol) in THF (1 ml) was added into a solution of LiN(SiMe\(_3\))\(_2\) (1.5 mmol, 1.5 ml of 1.0 M in n-hexane) in THF (3 ml) at -78°C under nitrogen atmosphere. After 10 mins, diethyl aluminium chloride (1.5 mmol, 1.5 ml of 1.0 M in n-hexane) was added to the reaction. The reaction was diluted with 20 ml of toluene, kept at -78°C for 30 mins and filtered. (S,S)-N,N-bis(3,5-di-tertbutylsalicylidene)-1,2-cyclohexanedi amino aluminium chloride (135 mg) in THF (1 ml) was added into the filtrate at -78°C and kept for 10 mins. A solution of 2-methyloxirane (87 mg, 1.5 mmol) in toluene (1 ml) was added at -78°C. The reaction was at -50°C for overnight. It was decomposed by saturated NH\(_4\)Cl\(_aq\) and potassium sodium tartrate tetrahydrate, kept stirring for 1 hr at r.t. and extracted by AcOEt (3X15 ml). The organic phase was collected, dried and concentrated under vacuum to get the crude mixture which was purified by the flash chromatography (cyclohexane: AcOEt = 2:1) to give an inseparable mixture of product 11a and 12a (141 mg, ratio: 40:60, total yield: 50%).

**The Preparation of (2S*)-2-((2S*)-2-hydroxy cyclohexyl)-2-phenylpropanenitrile 11c and (2R*)-2-((2S*)-2-hydroxy cyclohexyl)-2-phenylpropanenitrile 12c**

\(\alpha\)-methyl acetonitriles (197 mg, 1.5 mmol) in THF (1 ml) was added into a solution of LiN(SiMe\(_3\))\(_2\) (1.5 mmol, 1.5 ml of 1.0 M in n-hexane) in THF (3 ml) at -78°C under nitrogen atmosphere. After 10 mins, diethyl aluminium chloride (1.5 mmol, 1.5 ml of 1.0 M in n-hexane) was added to the reaction. The reaction was kept at r.t. for 1 hr and concentrated. 10 ml of toluene was added to the residue and filtered. The filtrate was added into a solution of 7-oxabicyclo[4.1.0]heptanes (147 mg, 1.5 mmol) in toluene (1 ml) at -78°C. Then the reaction was left spontaneously to reach r.t. for...
overnight. It was decomposed by saturated NH$_4$Cl$_{aq}$ and potassium sodium tartrate tetrahydrate, kept stirring for 1hr at r.t. and extracted by AcOEt (3 × 15ml). The organic phase was collected, dried and concentrated under vacuum to get the crude mixture which was purified by the flash chromatography (cyclohexane: AcOEt = 4:1) to give an inseparable mixture of product 11c and 12c (113 mg, ratio: 50:50, total yield: 33%). Spectral data were deducted from the mixture and arbitrarily attributed to 11c and 12c.

11c: IR(neat): 2236 cm$^{-1}$, $^1$H NMR (400 MHz, CDCl$_3$): δ = 0.90-1.44 (co mlex pattern, 8H), 1.83 (s, 3H), 1.92 (m, 1H), 3.53 (m, 1H), 7.30-7.55 (complex pattern, 5H). $^{13}$C NMR (100 MHz, CDCl$_3$): δ = 11.08, 24.64, 24.87, 25.60, 25.91, 27.33, 28.07, 37.55, 53.01, 72.91, 123.45, 126.16, 127.64, 127.92, 128.52, 128.97, 140.50. MS (ESI): m/z=230 [M+1].

12c: IR(neat): 2236 cm$^{-1}$, $^1$H NMR (400 MHz, CDCl$_3$): δ = 0.90-1.44 (co mlex pattern, 8H), 1.85 (s, 3H), 1.92 (m, 1H), 3.68 (dt, $J_1=4.4$ Hz, $J_2=14.4$ Hz, 1H), 7.30-7.55 (complex pattern, 5H). $^{13}$C NMR (100 MHz, CDCl$_3$): δ = 11.08, 24.67, 24.88, 25.66, 26.43, 27.93, 36.54, 45.44, 53.26, 73.33, 123.99, 126.43, 127.89, 128.30, 128.87, 141.01. MS (ESI): m/z=230 [M+1].

The Preparation of (2S*, 4R*)-4-hydroxy-2-methyl-2,4-diphenylbutanenitrile 11d and (2R*, 4R*)-4-hydroxy-2-methyl-2,4-diphenylbutanenitrile 11d

Following Method A, stating from α-methyl acetonitriles (197 mg, 1.5 mmol), 2-phenyloxirane (180 mg, 1.5 mmol), (2S*, 4R*)-4-hydroxy-2-methyl-2,4-diphenylbutanenitrile 11d and (2R*, 4R*)-4-hydroxy-2-methyl-2,4-diphenylbutanenitrile 12d were obtained after flash chromatography (cyclohexane : AcOEt =4:1) (184 mg, ratio: 11d/12d=25/75, total yield: 49%).
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**11d:** white solid. mp: 78-82 °C. IR(neat): 2236 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta =1.50\) (s, 3H), 1.58 (bs, 1H, OH), 3.24 (dd, \(J_1=4.8\) Hz, \(J_2=10.0\) Hz, 1H), 3.68 (dd, \(J_1=4.4\) Hz, \(J_2=11.6\) Hz, 1H), 4.25 (t, \(J=10.4\) Hz, 1H), 7.35-7.51 (complex pattern, 8H) 7.57 (m, 2H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta =27.26, 45.19, 57.50, 63.16, 122.01, 125.11, 128.31, 128.50, 129.13, 129.25, 129.57, 136.80, 139.73\). MS (ESI): \(m/z=252\) [M+1].

![Chemical Structure](image)

**12d:** IR(neat): 2236 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta =1.52\) (bs, 1H, OH), 1.88 (s, 3H), 3.25 (dd, \(J_1=5.2\) Hz, \(J_2=9.2\) Hz, 1H), 4.14 (dd, \(J_1=11.6\) Hz, \(J_2=9.6\) Hz, 1H), 4.25 (dd, \(J_1=6.0\) Hz, \(J_2=11.6\) Hz, 1H), 7.00 (m, 2H), 7.17-7.28 (complex pattern, 8H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta =25.83, 45.20, 57.62, 63.17, 122.78, 126.48, 127.94, 127.97, 128.48, 128.54, 129.53, 136.49, 138.58\). MS (ESI): \(m/z=252\) [M+1].

The Preparation of (25\(^*\), 4\(R^*\))-5-tert-butoxy-4-hydroxy-2-methyl-2-phenylpentanenitrile 11e and (2\(R^*\), 4\(R^*\))-5-tert-butoxy-4-hydroxy-2-methyl-2-phenylpentanenitrile 12e

Following Method A, stating from \(\alpha\)-methyl acetonitriles (197 mg, 1.5 mmol), 2-(tert-butoxymethyl)oxirane (195 mg, 1.5 mmol), an inseparable mixture of products 11e and 12e was obtained after flash chromatography (cyclohexane : AcOEt=4:1) (164 mg, ratio: 50:50, total yield: 42%) Spectral data were deducted from the mixture and arbitrarily attributed to 11e and 12e.

![Chemical Structure](image)

**11e:** IR(neat): 2236 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta =1.40\) (s, 9H), 1.82 (s, 3H), 1.95 (dd, \(J_1=3.2\) Hz, \(J_2=14.4\) Hz, 1H), 2.14 (dd, \(J_1=8.4\) Hz, \(J_2=14.4\) Hz, 1H), 2.56 (bs, 1H, OH), 3.09 (dd, \(J_1=7.2\) Hz, \(J_2=8.8\) Hz, 1H), 3.22 (dd, \(J_1=8.8\) Hz, \(J_2=11.2\) Hz, 1H), 3.79 (m, 1H), 7.32 (m, 1H), 7.40 (m, 2H), 7.50 (m, 2H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta =27.58, 28.60, 41.04, 45.33, 65.65, 68.33, 73.42, 123.65, 125.63, 127.91, 129.03, 140.51\). MS (ESI): \(m/z=262\) [M+1].
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12e: IR(neat): 2236 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ =1.64 (s, 9H), 1.81 (s, 3H), 2.03 (dd, $J_1$= 4.0 Hz, $J_2$= 14.4 Hz, 1H), 2.11 (dd, $J_1$=7.6 Hz, $J_2$=14.4 Hz, 1H), 2.38 (bs, 1H, OH), 3.22 (dd, $J_1$=8.8 Hz, $J_2$=4.0 Hz, 1H), 3.36 (dd, $J_1$=3.6 Hz, $J_2$=8.8 Hz, 1H), 3.73 (m, 1H), 7.32 (m, 1H), 7.40 (m, 2H), 7.50 (m, 2H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ =27.54, 27.61, 40.46, 45.24, 65.75, 67.92, 73.50, 123.99, 125.82, 127.96, 129.05, 140.03. MS (ESI): m/z=262 [M+1].

The Preparation of (2$S^*$, 4$R^*$)-5-(2-ethyldodecyl oxy)-4-hydroxy-2-methyl-2-phenylpentanenitrile 11f and (2$R^*$, 4$R^*$)-5-(2-ethyldodecyl oxy)-4-hydroxy-2-methyl-2-phenylpentanenitrile 12f

Following Method A, starting from $\alpha$-methyl acetonitriles (131 mg, 1.0 mmol), 2-((2-ethyldodecyl oxy)methyl)oxirane (186 mg, 1.0 mmol), an inseparable mixture of products 11f and 12f was obtained after flash chromatography (cyclohexane: AcOEt=8:1) (200 mg, ratio: 50:50, total yield: 50%) Spectral data were deduced from the mixture and arbitrarily attributed to 11f and 12f.

11f: IR(neat): 2236 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ =0.87 (t, $J_1$=7.6 Hz, 3H), 0.89 (m, 3H), 1.29(m, 8H), 1.46(m, 1H), 1.81(s, 3H), 2.05 (dd, $J_1$= 4.0 Hz, $J_2$= 14.4 Hz, 1H), 2.20 (bs, 1H, OH), 2.11 (dd, $J_1$=7.2 Hz, $J_2$=14.4 Hz, 1H), 3.29 (m, 3H), 3.41 (m, 1H), 3.83 (m, 1H), 7.32 (m, 1H), 7.41 (m, 2H), 7.51 (m, 2H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ =11.24, 14.23, 23.20, 27.79, 29.23, 30.65, 39.76, 40.53, 45.22 67.73, 74.38, 74.67, 123.89, 125.79, 128.06, 129.11, 140.43. MS (ESI): m/z=424 [M+Na].

12f: IR(neat): 2236 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ =0.88 (m, 6H), 1.29 (m, 8H), 1.59 (m, 1H), 1.83 (s, 3H), 2.05 (dd, $J_1$= 2.8 Hz $J_2$= 14.8 Hz, 1H), 2.13 (dd, $J_1$=7.6 Hz, $J_2$=14.8 Hz, 1H), 2.42 (bs, 1H, OH), 3.15 (m, 1H), 3.29 (m, 3H), 3.83 (m, 1H), 7.32 (m, 1H), 7.41 (m, 2H), 7.51 (m, 2H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ =11.11, 14.23, 23.98, 28.66, 29.23, 30.72, 39.76, 41.02, 45.17, 68.07, 74.38, 74.83, 123.66, 125.63, 127.96, 129.13, 139.98. MS (ESI): m/z=424 [M+Na].
The Preparation of (2S*, 4S*)-4-hydroxy-2-methyl-2-phenyltetradecanenitrile 11g and (2R*, 4S*)-4-hydroxy-2-methyl-2-phenyltetradecanenitrile 12g

Following Method A, stating from α-methyl acetonitriles (131 mg, 1.0 mmol), 2-decyloxirane (184 mg, 1.0 mmol), an inseparable mixture of products 11g and 12g was obtained after flash chromatography (cyclohexane : AcOEt=8:1) (158 mg, ratio: 50:50, total yield: 50%) Spectral data were deducted from the mixture and arbitrarily attributed to 11g and 12g.

11g: IR(neat): 2236 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)): δ =0.89 (t, \(J=7.6\) Hz, 3H), 1.20-1.45 (m, 18H), 1.79 (s, 3H), 2.05 (dd, \(J_1=2.8\) Hz, \(J_2= 14.4\) Hz, 1H), 2.14 (dd, \(J_1=8.4\) Hz, \(J_2=14.4\) Hz, 1H), 3.81 (m, 1H), 7.33 (m, 1H), 7.41 (m, 2H), 7.51 (m, 2H). \(^1\)C NMR (100 MHz, CDCl\(_3\)): δ =14.23, 22.79, 25.39, 27.95, 28.94, 29.42, 29.58, 29.66, 29.69, 32.01, 38.13, 41.08, 49.52, 123.77, 125.60, 127.91, 129.10, 140.17. MS (ESI): m/z=316 [M+1].

12g: IR(neat): 2236 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)): δ =0.89 (t, \(J=7.6\) Hz, 3H), 1.20-1.45 (m, 18H), 1.80 (s, 3H), 1.99 (dd, \(J_1=2.4\) Hz, \(J_2= 14.8\) Hz, 1H), 2.11 (dd, \(J_1=6.8\) Hz, \(J_2=14.8\) Hz, 1H), 3.62 (m, 1H), 7.33 (m, 1H), 7.41 (m, 2H), 7.48 (m, 2H). \(^1\)C NMR (100 MHz, CDCl\(_3\)): δ =14.23, 22.79, 25.33, 27.95, 28.94, 29.56, 29.62, 29.67, 29.70, 32.01, 38.48, 40.98, 49.00, 123.97, 125.65, 128.13, 129.23, 140.37. MS (ESI): m/z= 316 [M+1].

The Preparation of (2S*, 4S*)-4-hydroxy-2-methyl-2-phenyloctanenitrile 11h and (2R*, 4S*)-4-hydroxy-2-methyl-2-phenyloctanenitrile 12h

α-methyl acetonitriles (197 mg, 1.5 mmol) in THF (1ml) was added into a solution of LiN(SiMe\(_3\))\(_2\) (1.5 mmol, 1.5 ml of 1.0 M in n-hexane) in THF (3 ml) at -78°C under nitrogen atmosphere. After 10mins, diethyl aluminium chloride (1.5 mmol, 1.5 ml of 1.0 M in n-hexane) was added to the reaction. The reaction was kept at r.t. for 20mins and concentrated. 20 ml of CH\(_2\)Cl\(_2\) was added to the residue and filtered. The filtrate was cooled to -78 °C. A solution of 2-butyloxirane (150 mg, 1.5 mmol) in CH\(_2\)Cl\(_2\) (1 ml) was added at -78 °C. Then the reaction was left spontaneously to reach r.t for overnight. It was decomposed by saturated NH\(_4\)Cl\(_{aq}\) and potassium
sodium tartrate tetrahydrate, kept stirring for 1 hr at r.t. and extracted by AcOEt (3X15 ml). The organic phase was collected, dried and concentrated under vacuum to get the crude mixture which was purified by the flash chromatography (cyclohexane: AcOEt= 6:1) to give an inseparable mixture of products 11h and 12h (107 mg, ratio: 50:50, total yield: 31%). Spectral data were deduced from the mixture and arbitrarily attributed to 11h and 12h.

**11h**: IR(neat): 2237 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta =0.86 \text{ (t, } J=7.2 \text{ Hz, } 3\text{H}), 1.22-1.49 \text{ (m, } 6\text{H}), 1.80(s, } 3\text{H}), 1.99 \text{ (dd, } J_1=2.4 \text{ Hz, } J_2=14.8 \text{ Hz, } 1\text{H}), 2.11 \text{ (dd, } J_1=9.2 \text{ Hz, } J_2=14.8 \text{ Hz, } 1\text{H}), 3.63 \text{ (m, } 1\text{H}), 7.28-7.53 \text{ (complex pattern, } 5\text{H}). \(^1\)C NMR (100 MHz, CDCl\(_3\)): \(\delta = 14.09, 22.62, 27.46, 28.91, 38.15, 40.97, 48.98, 69.27, 123.76, 125.58, 127.89, 128.10, 129.08, 140.36. MS(ESI) m/z = 232 [M+1].

**12h**: IR(neat): 2237 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta =0.89 \text{ (t, } J=8.0 \text{ Hz, } 3\text{H}), 1.22-1.49 \text{ (m, } 6\text{H}), 1.79 \text{ (s, } 3\text{H}), 2.05 \text{ (dd, } J_1=2.8 \text{ Hz, } J_2=14.4 \text{ Hz, } 1\text{H}), 2.11 \text{ (dd, } J_1=8.2 \text{ Hz, } J_2=14.4 \text{ Hz, } 1\text{H}), 3.81 \text{ (m, } 1\text{H}), 7.28-7.53 \text{ (complex pattern, } 5\text{H}). \(^1\)C NMR (100 MHz, CDCl\(_3\)): \(\delta = 14.05, 22.62, 27.52, 27.91, 37.77, 41.04, 49.47, 69.27, 123.95, 125.63, 128.09, 129.11, 140.16. MS(ESI) m/z = 232 [M+1].

The Preparation of 4-hydroxy-2,2,4-triphenylbutanenitrile (11i)
Following Method A, stating from diphenylacetonitriles (1b) (193 mg, 1.0 mmol), 2-phenyloxirane 4a (120 mg, 1.0 mmol), 4-hydroxy-2,2,4-triphenylbutanenitrile (11i) were obtained after flash chromatography (cyclohexane : AcOEt =4:1). (157 mg, yield: 50%)

**11i**: white solid. mp: 117-118 °C. IR(neat): 2236 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)): 3.89 (dd, \(J = 10.4, 3.6 \text{ Hz, } 1\text{H}), 4.04 (d, \(J = 10.4 \text{ Hz, } 1\text{H}), 4.21 (t, \(J = 10.8 \text{ Hz, } 1\text{H}), 7.06 – 6.93
The Preparation of (2R*,4S*)-4-hydroxy-2-isobutyl-2-phenylpentanenitrile (11j) and (2R*,4R*)-4-hydroxy-2-isobutyl-2-phenylpentanenitrile (12j)

Following Method A, stating from 2-phenyl-4-methylpentanenitrile (1c) (173 mg, 1.0 mmol), 2-phenyloxirane 4b (120 mg, 1.0 mmol), (2R*,4S*)-4-hydroxy-2-isobutyl-2-phenylpentanenitrile (11j) and (2R*,4R*)-4-hydroxy-2-isobutyl-2-phenylpentanenitrile (12j) were obtained after flash chromatography (cyclohexane : AcOEt = 4:1). (163 mg, yield: 47%)

**11j:** IR(neat): 2236 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 0.64 (d, \(J = 6.7\) Hz, 3H), 0.97 (s, 3H), 1.17 (d, \(J = 6.3\) Hz, 3H), 1.67 – 1.53 (m, 1H), 1.86 – 1.83 (m, 1H), 1.88 (d, \(J = 6.0\) Hz, 1H, OH), 2.01 – 1.96 (m, 1H), 2.17 – 2.15 (m, 1H), 3.78 – 3.51 (m, 1H), 4.09 – 3.82 (m, 1H), 7.50 – 7.31 (m, 5H). \(^1^3\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 23.18, 23.70, 23.90, 25.30, 44.97, 45.06, 49.57, 51.05, 64.83, 126.01, 127.55, 128.71, 128.93, 138.24. MS(ESI) \(m/z\) = 232 [M+1].

**11i:** IR(neat): 2236 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 0.62 (d, \(J = 6.7\) Hz, 3H), 0.96 (d, \(J = 6.7\) Hz, 3H), 1.17 (d, \(J = 6.3\) Hz, 3H), 1.67 – 1.53 (m, 1H), 1.86 – 1.83 (m, 1H), 1.88 (d, \(J = 6.0\) Hz, 1H, OH), 2.01 – 1.96 (m, 1H), 2.17 – 2.15 (m, 1H), 3.78 – 3.51 (m, 1H), 4.09 – 3.82 (m, 1H), 7.50 – 7.31 (m, 5H). \(^1^3\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 23.36, 23.68, 24.40, 25.42, 45.35, 49.73, 50.89, 65.17, 123.03, 126.02, 127.55, 128.75, 137.83. MS(ESI) \(m/z\) = 232 [M+1].

The Preparation of (R*)-2-((R*)-2-hydroxy-2-phenylethyl)-2-phenylpent-4-enenitrile (11k) and (R*)-2-((R*)-2-hydroxy-2-phenylethyl)-2-phenylpent-4-enenitrile (12k)

Following Method A, stating from 2-phenylpent-4-enenitrile (1d) (236 mg, 1.5 mmol), 2-phenyloxirane 4b (180 mg, 1.5 mmol), (R*)-2-((R*)-2-hydroxy-2-phenylethyl)-2-phenylpent-4
enenitrile (11k) and (R*)-2-((R*)-2-hydroxy-2-phenylethyl)-2-phenylpent-4-enenitrile (12k) were obtained after flash chromatography (cyclohexane : AcOEt =4:1), (185 mg, yield: 45%). Spectral data were deducted from the mixture and arbitrarily attributed to 11k and 12k.

11k: IR(neat): 2236 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ 1.49 (s, 1H), 2.37 (dd, J = 14.0, 7.6 Hz, 1H), 2.64 (dd, J = 14.4, 6.8 Hz, 1H), 3.53 (q, J = 6.8 Hz, 1H), 3.66 (d, J = 11.0 Hz, 1H), 4.10–4.11 (m, 1H), 4.39 (dd, J = 11.0, 4.8 Hz, 1H), 4.96 (t, J = 12.4 Hz, 1H), 5.46–5.29 (m, 1H), 7.05–6.97 (m, 4H), 7.18 (s, 2H), 7.33–7.27 (m, 2H), 7.46–7.37 (m, 2H). ¹³C NMR (100 MHz, CDCl₃) δ 43.35, 50.51, 56.93, 62.94, 119.90, 120.43, 126.36, 127.67, 128.14, 128.39, 129.03, 131.05, 136.19, 136.91. MS(ESI) m/z= 278 [M+1].

12k: IR(neat): 2236 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ 1.56 (s, 1H), 2.91 (dd, J = 14.0, 6.4 Hz, 1H), 3.05 (dd, J = 14.0, 7.6 Hz, 1H), 3.46–3.33 (m, 2H), 4.12–4.14 (m, 1H), 5.19 (dd, J = 32.8, 13.6 Hz, 2H), 5.70–5.51 (m, 1H), 7.23–7.18 (m, 4H), 7.27 (d, J = 6.8 Hz, 2H), 7.49 (dd, J = 14.0, 6.8 Hz, 2H), 7.56 (t, J = 12.0 Hz, 2H). ¹³C NMR (100 MHz, CDCl₃) δ 42.20, 50.71, 56.40, 63.34, 120.11, 121.27, 127.17, 127.69, 128.20, 128.24, 129.44, 131.62, 135.58, 136.60. MS(ESI) m/z= 278 [M+1].

The Preparation of (2R*,4R*)-4-hydroxy-2,4-diphenyl-2-(pyridin-3-yl)butanenitrile(11l) and (2S*,4R*)-4-hydroxy-2,4-diphenyl-2-(pyridin-3-yl)butanenitrile(12 l)

Following Method A, stating from 2-phenyl-2-(pyridin-3-yl)acetonitrile (1e) (291 mg, 1.5 mmol), 2-phenyloxirane 4b (180 mg, 1.5 mmol), (2R*,4R*)-4-hydroxy-2,4-diphenyl-2-(pyridin-3-yl)butanenitrile(11 l) and (2S*,4R*)-4-hydroxy-2,4-diphenyl-2-(pyridin-3-yl)butanenitrile (12 l) were obtained after flash chromatography (cyclohexane : AcOEt =1:3), (12l) 100 mg and (11l) 77 mg, yield: 38%. Spectral data were deducted from the mixture and arbitrarily attributed to 11 l and 12 l.
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11: IR(neat): 2242 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 1.44 (s, 1H), 3.98 (dd, \(J = 10.0, 2.8\) Hz, 1H), 4.12 (d, \(J = 12.4\) Hz, 2H), 4.31 (t, \(J = 10.7\) Hz, 1H), 7.05 – 6.92 (m, 1H), 7.22 (d, \(J = 4.8\) Hz, 2H), 7.25 (t, \(J = 2.4\) Hz, 2H), 7.36-7.38 (m, 3H), 7.56 – 7.42 (m, 2H), 7.70 (d, \(J = 8.0\) Hz, 2H), 8.30 (d, \(J = 4.4\) Hz, 1H), 8.38 (s, 1H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 54.70, 63.62, 77.36, 120.42, 127.19, 127.78, 128.02, 128.46, 128.85, 128.90, 129.02, 129.24, 129.65, 129.77, 135.86, 137.25. MS(ESI) m/z = 315 [M+1].

11: IR(neat): 2242 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 1.56 (s, 3H), 4.00 (dd, \(J = 10.0, 3.9\) Hz, 1H), 4.11 (td, \(J = 11.8, 5.5\) Hz, 1H), 4.32 (dd, \(J = 11.3, 10.1\) Hz, 1H), 7.15 – 7.08 (m, 4H), 7.23 – 7.17 (m, 3H), 7.29 – 7.23 (m, 3H), 7.38 (dd, \(J = 8.1, 4.7\) Hz, 1H), 7.99 (dd, \(J = 8.1, 2.5\), \(1.5\) Hz, 1H), 8.61 (dd, \(J = 4.7, 1.2\) Hz, 1H), 8.99 (d, \(J = 2.4\) Hz, 1H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 54.20, 63.38, 77.20, 123.71, 126.82, 127.72, 128.01, 128.32, 128.52, 128.56, 128.59, 129.53, 135.02, 148.27, 149.38, 151.05. MS(ESI) m/z = 315 [M+1].

**The Preparation of (R\(^*\))\()-2\-((R\(^*\))\)-2-hydroxy-2-phenylethyl)-2-phenylpent-4-enenitrile (11m) and (R\(^*\))\)-2\-((R\(^*\))\)-2-hydroxy-2-phenylethyl)-2-phenylpent-4-enenitrile (12 m)**

Following Method A, stating from 2-phenylpent-4-enenitrile (1f) (260 mg, 1.5 mmol), 2-phenyloxirane 4g (180 mg, 1.5 mmol), (R\(^*\))\)-2\-((R\(^*\))\)-2-hydroxy-2-phenylethyl)-4-methyl-2-phenylpentanenitrile (11 m) and (R\(^*\))\)-2\-((R\(^*\))\)-2-hydroxy-2-phenylethyl)-4-methyl-2-phenylpentanenitrile (12 m) were obtained after flash chromatography (cyclohexane : AcOEt =4:1), (227 mg, yield: 52%). Spectral data were deducted from the mixture and arbitrarily attributed to 11 m and 12 m.
11m: IR(neat): 2238 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ 7.52 (d, J = 7.2 Hz, 2H), 7.42 (d, J = 7.6 Hz, 1H), 7.35 (d, J = 7.2 Hz, 1H), 7.24 – 7.18 (m, 2H), 7.19 – 7.17 (m, 2H), 7.10 (s, 2H), 4.06 – 3.95 (m, 1H), 3.55 – 3.41 (m, 1H), 3.20 (d, J = 6.0 Hz, 1H), 1.79 (dd, J = 4.4, 14 Hz, 1H), 1.43 (dt, J = 14.4, 6.0 Hz, 2H), 1.41 – 1.31 (m, 1H), 1.27 (s, 1H), 0.80 (d, J = 6.5 Hz, 3H), 0.55 (d, J = 6.6 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 136.92, 136.48, 129.22, 129.13, 128.47, 128.45, 128.21, 126.46, 121.63, 63.18, 58.70, 49.23, 47.38, 25.26, 24.18, 22.75. MS(ESI) m/z= 294 [M+1].

11m: white solid. IR(neat): 2238 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ 7.56 (t, J = 7.2 Hz, 1H), 7.43-7.45 (m, 1H), 7.37 (dd, J = 14.0, 7.2 Hz, 1H), 7.24 – 7.18 (m, 1H), 7.17 – 7.12 (m, 3H), 7.11-7.13 (m, J = 3.2 Hz, 1H), 6.96-6.97 (m, 2H), 4.32-4.33 (m, 1H), 4.22 – 4.11 (m, 1H), 3.26 – 3.22 (m, 1H), 2.15 (dd, J = 19.2, 14.4, 6.4 Hz, 2H), 1.56-1.57 (m, 1H), 1.51 (d, J = 7.2 Hz, 1H), 0.99 (d, J = 6.8 Hz, 3H), 0.72 (d, J = 6.8 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 136.60, 136.52, 129.52, 129.20, 128.37, 128.31, 127.06, 122.05, 66.49, 63.35, 58.58, 49.86, 46.69, 25.92, 24.31, 22.97.
Chapter 4

References

Chapter 5 Conclusion

In conclusion, we have studied the synthesis and applications of three kinds of N-metallo ketene imines: N-silyl ketene imines (SKIs), N-tin ketene imines (TKIs) and N-aluminum ketene imines (AKIs). N-metallo ketene imines were prepared starting from acetonitrile, then metalated by lithium (or sodium) reagents, then trap with alkyl metallo halide. Based on this frame, N-silyl ketene imines have been successfully used in catalyst free amidation by isocyanates (Scheme 5.1 eq1), formed a series of malolimides which are interesting for preparation of some drug analogues, by using a wide range of diarylacetonitrile and isocyanates (15 examples, yields: 50-80%). N-silyl ketene imines also have been used in an un-catalysed efficient asymmetric aldol type reaction (Scheme 5.1 eq2), in some cases, with proper protecting group in α-position of optically pure aldehydes, an excellent stereoselectivity were obtained (24 examples, Yield: 63-85%, de: 5-99%).

Scheme 5.1

As well as in the preparation of N-tin ketene imine and its applications in aldol type reaction with carbonyl compounds (Scheme 5.1 eq3) were discussed in detail among this thesis, including aldehydes, ketones and α,β-unsaturated carbonyl compounds (14 examples, Yield: 37-74%, de: 30-72%), the use of aldehydes characterized by the presence of a stereogenic center and the stereo-induction obtained, were reported as well (12 examples, Yield: 13-79%, de: 34-82%). In this part,
the stannylation of nitrile anion was well discussed, there were big difference between nitrile silylation and stannylation, the stability of resulting C or N methalated products were obvious, but according to us, the real and extremely important differences between the tin and the silicon is that the a-C-tin compounds behave exactly as the corresponding N-tin compounds, whereas in the case of silyl the a-C silyl are completely unreactive versus electrophiles.

Another branch of the researches on the synthesis and use of N-metallo ketene imines is constituted by the preparation of N-aluminium ketene imines and their application on the formation of C-C bond via epoxides-opening reaction (Scheme 5.1 eq 4) for furnishing γ-hydroxyl nitriles. The reaction gave a high regio and chemo selectivities, furnishing γ-hydroxyl nitrile as single target product with satisfactory yields (13 examples, Yield: 28-66%, de: 0-50%).
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Publications during PhD studying


Courses, posters and oral presentations

Schools and conferences attendance


*European school of medicinal chemistry* (XXXII advanced course of medicinal chemistry and “E. Duranti” national seminar for PhD students), Urbino, Italy, July 2-7, 2012.

*XII Giornata della Chimica dell’Emilia Romagna*, Ferrara, Italy 17th Dec 2012.


*XIII Giornata della Chimica dell’Emilia-Romagna*, Bologna, Italy. 18th Dec 2013.

Presentations
