Alma Mater Studiorum – Università di Bologna

DOTTORATO DI RICERCA IN

Scienze Chimiche
Ciclo XXVI

Settore Concorsuale di afferenza: 03/C1

Settore Scientifico disciplinare: CHIM/06

Synthesis and applications of N-Metallo ketene imines

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Esame finale anno 2014

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*-trimethylsylilketene-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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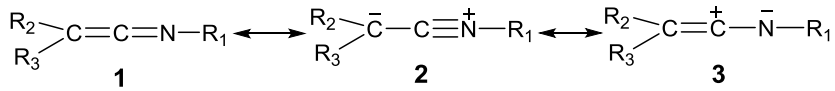
Chapter 1. Introduction

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 as 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 3 (Scheme 1.1).



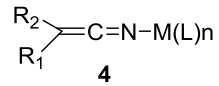
Scheme 1.1 Resonance structure of ketene imine

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^o between carbon and nitrogen substituents, CNC angles close to 120^o, and the average bond length of C=N is 1.27Å.[3] It presents characteristic IR absorption at around 2030 cm^{-1} and a ^{13}C-NMR of α-C at around 180ppm. 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.



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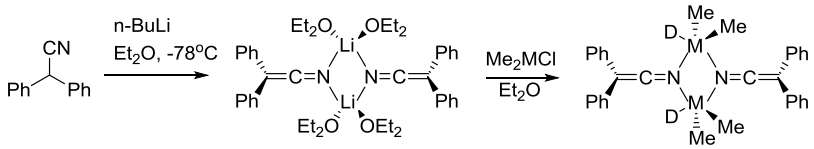
R_1,R_2=aryl, alkyl, organometallic, H et, al
M=Silyl, Mg, Cr, In et al
L=alkyl, aryl

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 mades 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.



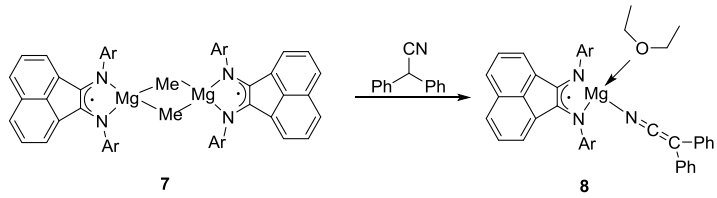
5 **6**

6a: M=In, D=THF
6b: M=Ga, D=none

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

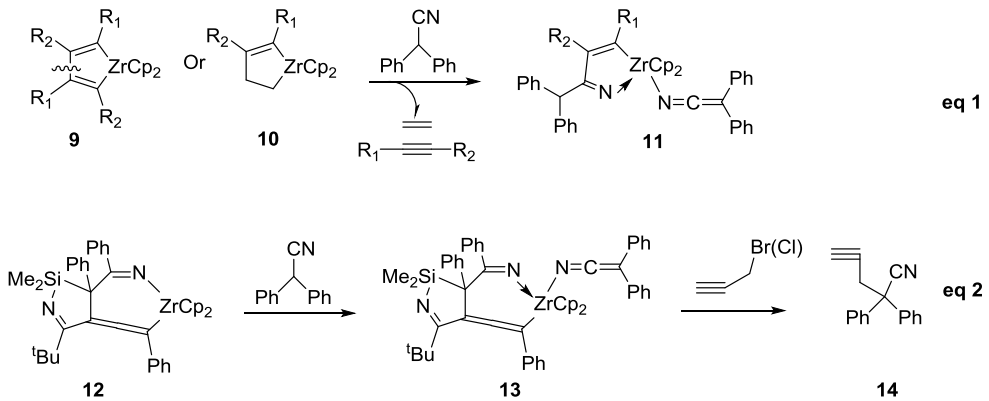
N-In and *N*-Ga ketene imines were reported by Iravani and co-workers.[14] Initially they were studying the trimerization of acetonitrile by Me_3In. When diphenylacetonitrile was used, the expected trimerization product was not formed, instead, a dimer of *N*-methalated nitriles (Ketene imine) were found 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_3In 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_2InCl or Me_2GaCl 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

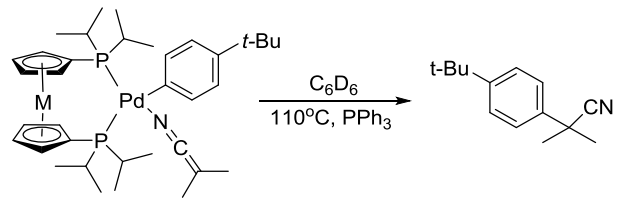
Attracted by alkaline earth metal complexes, several *N*-metallo ketene imines have been prepared through elimination reaction between magnesium organometallics and acetonitriles, the structure of them has been determined by ESR and IR spectroscopy. Metals like Mg, Ba, Sr were included,[15] the IR absorption 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 azazirconacycloallenes **12** were proved to be a versatile reagent against acetonitrile.[17-19] Compound **12** was treated with nitriles to give 5-Azaindoles through a multicomponent reaction,[17] thanks to the acidity α-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 δ 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 α-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[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 α-carbon; 2nd): cyano nitrogen; and 3rd): bridge two metals in a μ^2 C-N fashion;[20] most of aryl palladium cyanoalkyl complexes were bound to α-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).



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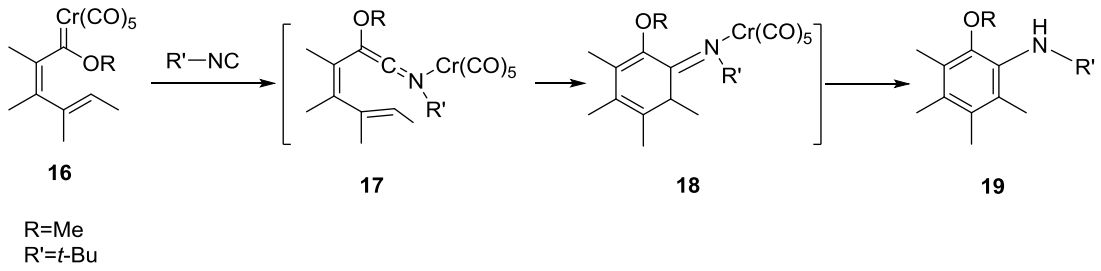
Scheme 1.6 Palladium ketene imine alkylation reaction

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.

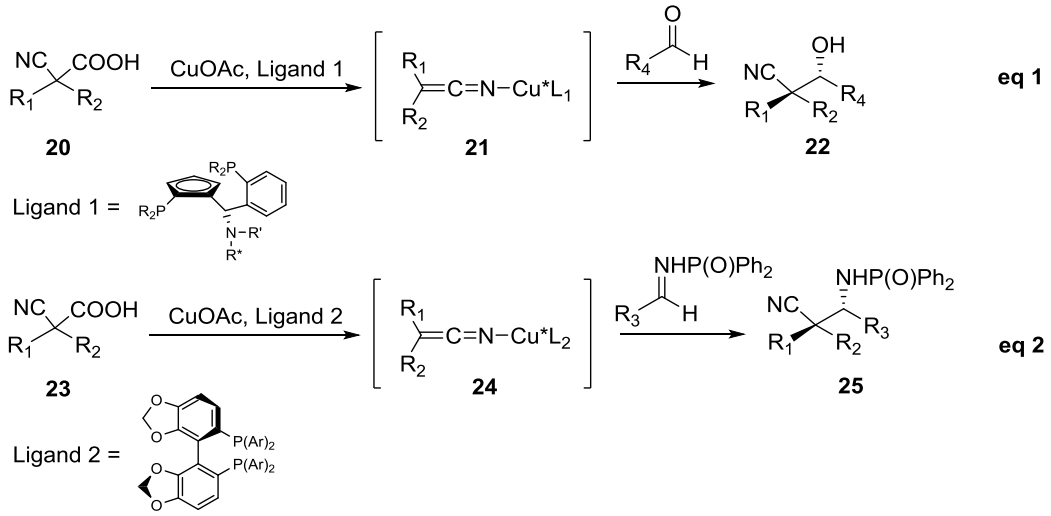
As shown in 1.7, a practical procedure for producing *o*-alkoxyanilines **19** through *N*-Cr ketene imine was established by Merlic and co-workers.[21-23] Chromium carbine **16** can be thermally or

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.[24] Systematic studies have been made for confronting these coordinated metallo ketene imines, including computational and experimental ones.[23, 25]



Scheme 1.7 Preparation of *o*-alkoxyanilines through *N*- Cr ketene imine

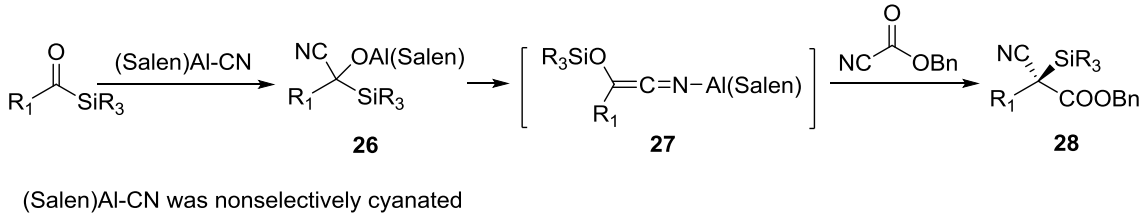
This reaction has been successfully applied for preparation of several organic cyclic compounds: *eg* total synthesis of calphostins,[26] preparation of analogues of natural products indolocarbazole, [27]and the synthesis of highly functionalized indazoles.[24]



Scheme 1.8 Asymmetric *N*-Copper ketene imine Aldol type and Mannich type reactions.

The generation of nucleophile by decarboxylation-reaction typically appears in bio-synthesis. Recently, Liang and co-workers established a catalytic asymmetric aldol and Mannich type reactions by decarboxylation of nitriles (Scheme 1.8).[28, 29] In this procedure, *N*-Cu ketene imine was deduced to be the key intermediate. It was generated from an anion exchange between

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 CO_2. 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.

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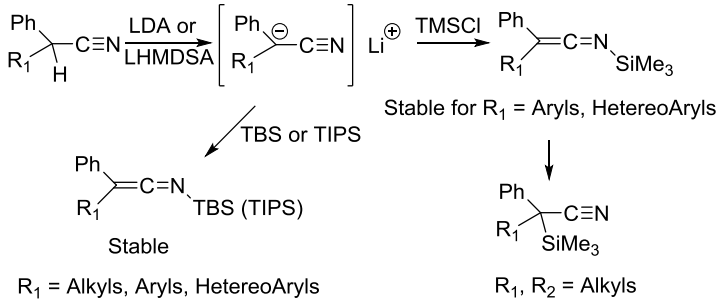
Chapter 2. Synthesis and applications of N-silyl ketene imines

2.1 Introduction

N-Silyl ketene imine was first prepared by Prober in 1956 from sodium methalated acetonitrile and trimethylsilyl chloride.[1] 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,[2] and, more recently, proved by Mermerian and Fu (Scheme 2.1).[3]



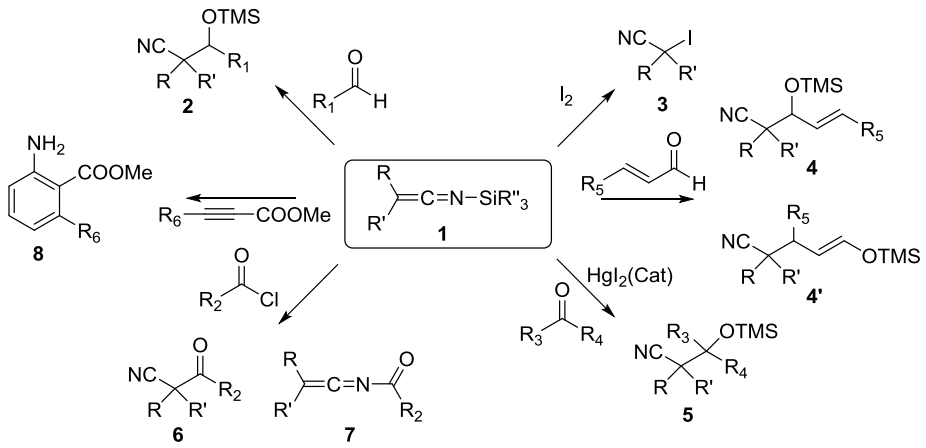
Scheme 2.1 Silylation of nitrile anions.

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.[9] *N*-silyl ketene imine derived from allylic nitriles, have been used in several types of cycloadditional reactions with olefinic dienohiles in the presence of KF,[10, 11] and with acetylenic dienophiles formed substituted anilines **8** (Scheme 2.2) without any promoter.[12] 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**9**.[3] Some other catalytic asymmetric reactions were developed: Notte and co-workers[13] developed a catalytic Mannich reaction of *N*-silyl ketene imines by a chiral silicon derivative **10**; Guin and co-workers[14] 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[15] developed an asymmetric aldol type reaction in 2007: the reaction was promoted by $SiCl_4$ and the co-catalyst catalyst **9**.

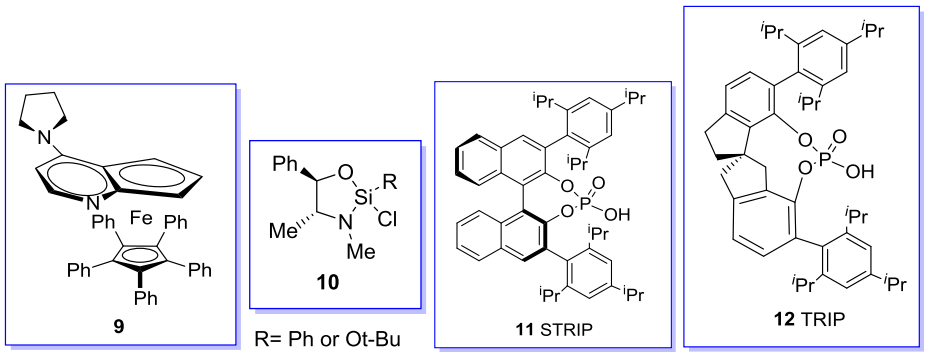
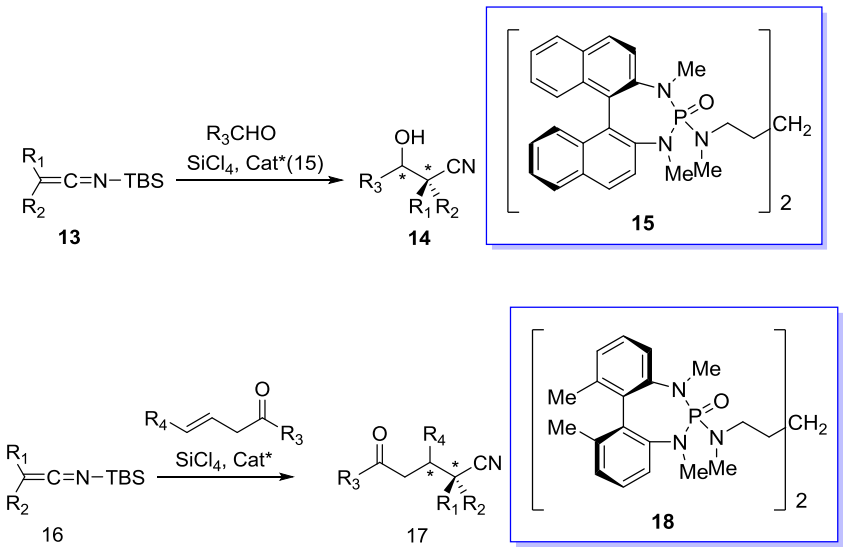


Figure 2.1 catalyst for asymmetric reactions of *N*-silyl ketene imines.

With the same catalyst, an asymmetric conjugate reaction between *N*-silyl ketene imines and unsaturated carbonyl compounds was successful established,[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.[5] Even α-Vinyl *N*-silyl ketene imines were successfully applied.[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^{III} catalyzed three component reaction.[18] A chiral silane Lewis acid was found to be an efficient catalyst for enantio selective Mannich type reactions of *N*-silyl ketene imines

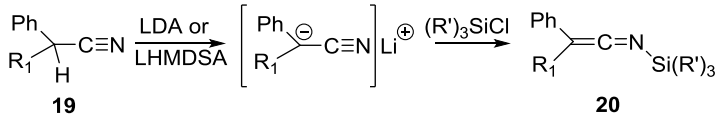
reacting with acylhydrazone,[13, 19] as a kind of interesting hetereocyclic compounds. Pyrrolidines were prepared through this procedure.[19]

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

2.2 Present work

2.2.1 Synthesis of N-silyl ketene imines

N-trimethylsilyl ketene imines will be one object of this thesis. The preparation of *N*-silyl ketene imine starts from a diphenyl- or diarylnitriles, methalated by lithium organometallic reagent as lithium diisopropyl amine or lithium hexamethyldisiyl amide at -78^{o}C and then traps of the generated carbanion with silyl chloride. The so prepared diphenyl (or diaryl) *N*- silyl ketene imines **20** (Scheme 2.4) have been used *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 *N*-silyl ketene imines were fully identified by IR, ^{1}H- and ^{13}C-NMR.



19 **20**

Scheme 2.4 preparation of *N*-silyl ketene imines.

2.2.2 Synthesis of α-cyano-carboxyamides (malonamides) through an un-catalyzed amidation reaction of N-silyl ketene imines with isocyanates.

There are only few applications between isocyanate as an electrophile and ketene imines[20, 21] and no paper has been published by using SKIs and isocyanates in an uncatalyzed reaction before our work.[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.[22-24] As shown in Fig 2.2, Loperamide **21** and **22**, originally

developed by Janssen Pharmaceutica and used against diarrhea, and Varapamil **23** (Figure 2.2) show a malonamide scaffold.[24]

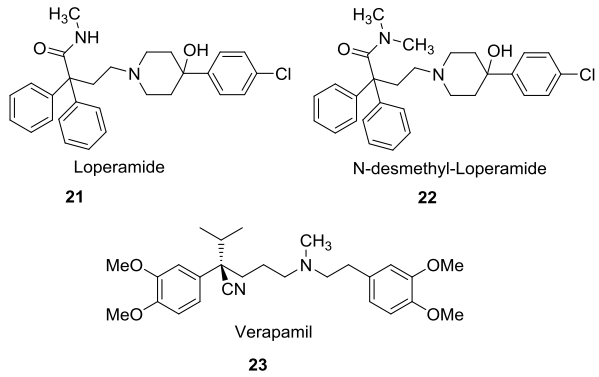
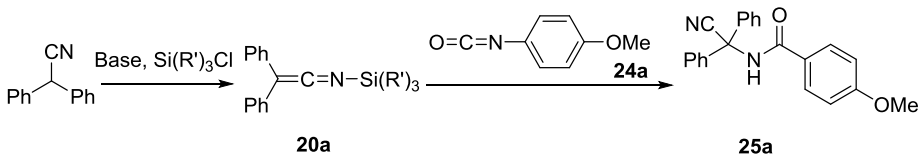


Figure 2.2 Malonamide analogues drugs.

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**.



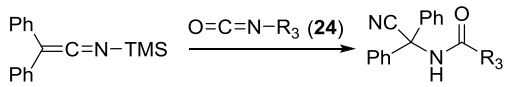
Scheme 2.5 Procedure for reaction of *N*-silylketene imines and isocyanates.

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.

Entry	Bases	Method	R'-Cl	Yield(%)
1	n-Butyl lithium	A	--	35.5
2	n-Butyl lithium	B	TMS-Cl	65
3	LDA	C	TMS-Cl	71
4	n-Butyl lithium	D	TBS-Cl	0

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 steric reason.



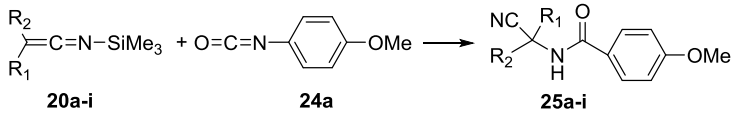
20a **25**

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

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

Entry	Ketene imines(**20**)		R_3	Method[$]	Products	Yield (%)[&]
	R_1	R_2				
1	(**20a**)Ph	Ph	**(24b)**Ph	B	**25a**	67.9
2	(**20a**)Ph	Ph	(**24c**)Bn	B	**25j**	50
3	(**20a**)Ph	Ph	**(24d)**$Si(Me)_3$	B	**25a**	No reaction
4	(**20a**)Ph	Ph	**(24e)**SO_2Cl	B	**25a**	Trace
5	(**20a**)Ph	Ph	(**24b**)Ph	C	**25i**	73
6	(**20a**)Ph	Ph	(**24f**)1-methyl Benzyl	B	**25k**	78

$: 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.



20a-i **24a** **25a-i**

Scheme 2.7 Reaction of different *N*-silyl ketene imines with isocyanate **24**.

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**

Entry	Ketene imines(20)#		R_3§	Method	Product	Yield& (%)
	R_1	R_2				
1	(**20a**)Ph	Ph	(**24a**) 4-OMeC_6H_4	B	**25a**	65
2	(**20b**)4-BrC_6H_4	Ph	(**24a**)4-OMeC_6H_4	C	**25b**	65
3	(**20c**)3-MeC_6H_4	Ph	(**24a**)4-OMeC_6H_4	C	**25c**	58
4	(**20d**)2-MeC_6H_4	Ph	(**24a**)4-OMeC_6H_4	C	**25d**	64
5	(**20e**)4-MeC_6H_4	Ph	(**24a**)4-OMeC_6H_4	C	**25e**	75
6	(**20f**)4-OMeC_6H_4	Ph	(**24a**)4-OMeC_6H_4	B	**25f**	70
7	(**20g**)2-ClC_6H_4	Ph	(**24a**)4-OMeC_6H_4	B	**25g**	68
8	(**20h**)Pyridine-3-yl	Ph	(**24a**)4-OMeC_6H_4	B	**25h**	80
9	(**20i**)4-OMeC_6H_4	4-OMeC_6H_4	(**24a**)4-OMeC_6H_4	B	**25i**	61

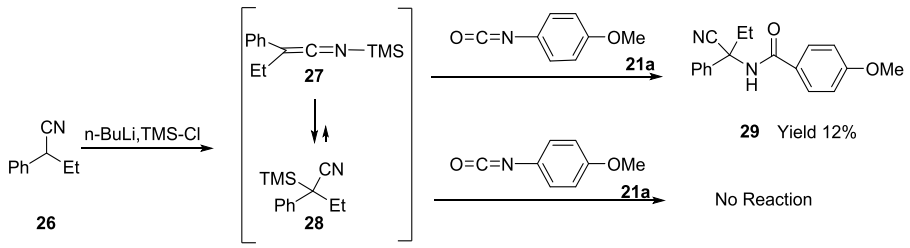
#: The nitriles **19b** (44%), **19c** (76%), **19d** (68%), **19e** (67%), **19f** (57%), **19g**, (47%), **19h** (73%) and **19i** (46%) were prepared from the corresponding ketones using tosylmethyl isocyanide (TosMIC).[25] &: Yields of isolated pure products.

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.

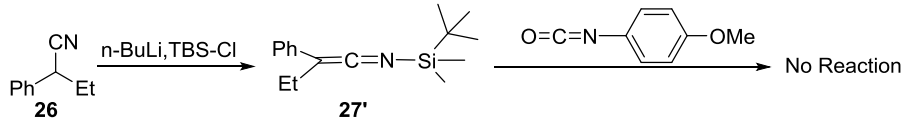
Following the general procedure for preparation of *N*-silyl ketene imines and starting from phenyl alkyl nitriles, treatment of these compounds with a base followed by trapping with trimethyl silyl chloride, alkyl-aryl *N*-trimethylsilyl ketene imines **27** (Sccheme 2.8) were obtained.

In situ treatment of these reactants with isocyanate, according a one pot procedure, gave the expected target **29** with low yield **(**Scheme 2.8**)**.



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

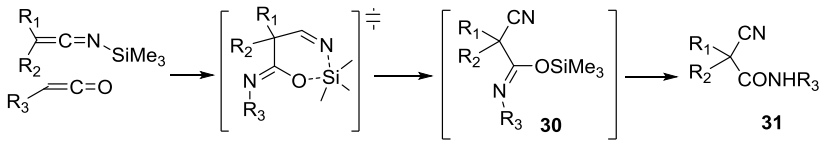
In order to get a stable phenyl alkyl *N*-silyl ketene imine, a more bulky group, such as TBS (*tert*-buthyldimethyl silyl), TIPS (Triisopropyl silyl), on silicon must be used. Accordingly, we prepared, α, α' phenyl ethyl *N*-TBS ketene imine **27'** (Scheme 2.9), and then treated with p-methoxyphenyl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



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.



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**.[26] 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.

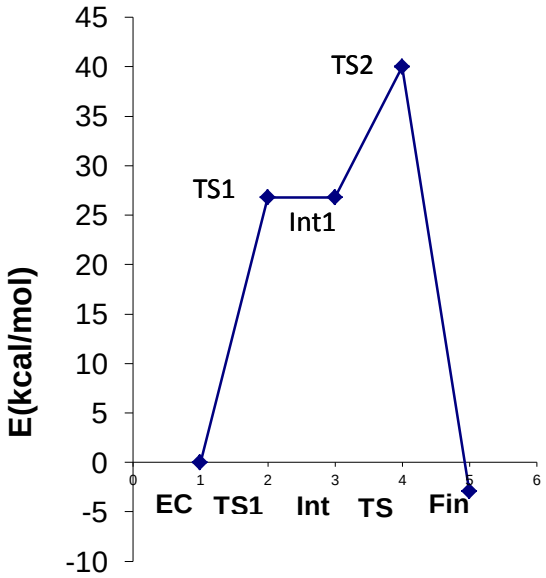


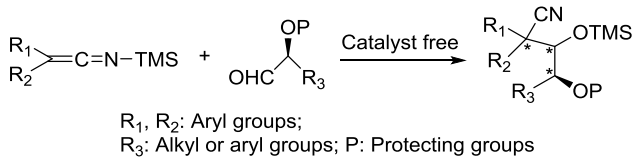
Figure 2.3 DFT calculations of the transition states.

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 nucleopilic 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

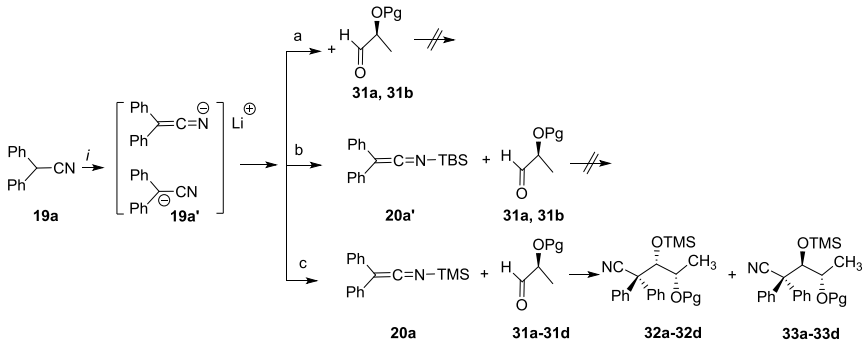
These studies were focused on un-catalyzed aldol reaction of diphenyl *N*-silyl ketene imine and deal with a catalyst free asymmetric synthetic procedure by using some chiral aldehydes bearing a changeable protecting group of hydroxyl functionality on α-position (Scheme 2.11). The resulting β-hydroxyl 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

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 ℃ 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).



31a: Pg=TBDMS; **31b**: Pg=Bn; **31c**: Pg=TIPS; **31d**:Pg=TBDPhS; **32a**, **33a**: Pg=TBDMS; **32b**, **33b**: Pg=Bn; **32c**, **33c**: Pg=TIPS; **32d**, **33d**: Pg=TBDPhS;

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

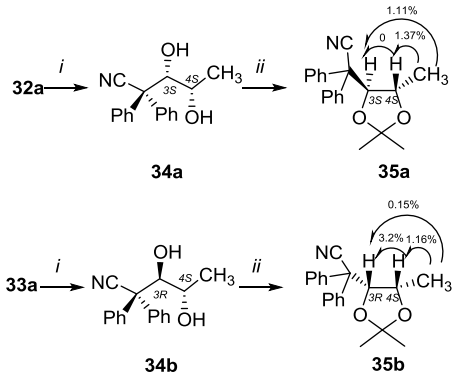
Table 2.4 Reaction of aldehydes 31a-31d with different aldehydes

Entry	nucleophile	Aldehyde	Products		Dr[#,$](32/33)	Total Yields(%)	J H_3-H_4 J H_3-H_4	δH_3-H_4 δH_3-H_4
1	**19a'**	**31a**	No reaction		-	0	-	-
2	**20a'**	**31a**	No reaction		-	0	-	-
3	**20a'**	**31b**	No reaction		-	0	-	-
4	**20a**	**31a**	**32a**	**33a**	97:3[a]	65	0.8	4.43-4.16
					45:55[b]	70	0.8	4.66-3.99
5	**20a**	**31b**	**32b**	**33b**	100:0[a]	83	4.4	4.52-3.68
					68:32[b]	75	5.2	4.60-3.07
6	**20a**	**31c**	**32c**	**33c**	70:30[a]	75	2.4	4.53-4.31
					5:95[b]	85	0.8	4.77-4.02
7	**20a**	**31d**	**32d**	**33d**	65:35[a]	62	1.6	4.50-4.08
					1:99[b]	67	0.0	4.89-3.92

#: 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 ℃ and after 3 hrs at this temperature, it was left to reach r.t spontaneously.

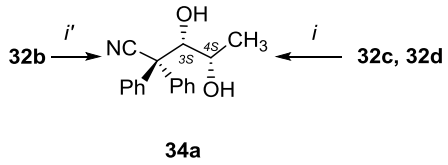
From a stereochemical point of view, as far as the formation of the new chiral centre is concerned, the highest stereocontrol was achieved using (*S*)-2-(benzyloxy)propanal derivative **31b** at room temp. In this case, an adduct with a *syn* relationship between the benzyloxy group and the new TMS-protected 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-butyldiphenylsilyl, in **31d**) and a reaction temperature of –78 ℃ (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.

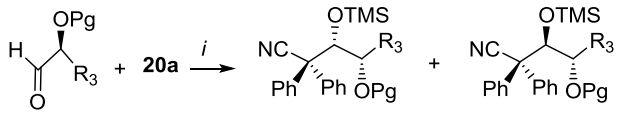
The assignment of the relative stereochemistry of the substituents at positions 3,4 of the dioxolane rings of **35a** and **35b** based on the results of NOE experiments was straightforward (Scheme 2.13). For compound **35a,** the NOE's between CH_3 and 5-H and between CH_3 and 4-H were almost of the same magnitude, which is consistent with a *trans* configuration, according to geometric analysis. For compound **35b**, the NOE effect between CH_3 and 5-H was about ten times larger than the NOE effect between CH_3 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**.



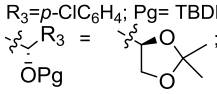
34a

Scheme 2.14 Preparation of diol **34a** from **32b**, **32c**, **32d** respectively. *Reagents and Conditions: i'*: Pd/C, $Pd(OAc)_2$, MeOH: *i*: HCl_{aq}(1N), CH_3CN, 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 2.14).

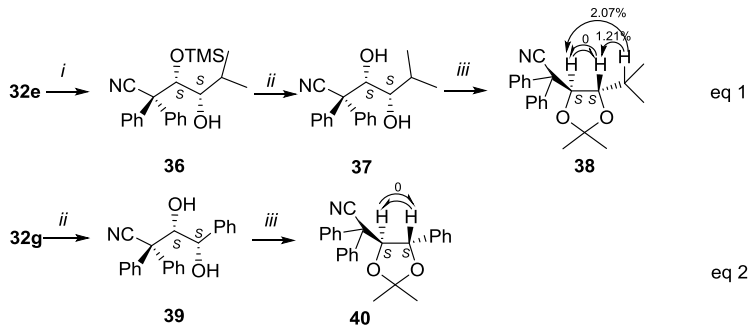


31e-31k **32e-32k** **33e-33k**

31e, **32e**: R_3= *i*-*Pr*; Pg= Bn; **31f**, **32f** : R_3= *t*-Bu; Pg= Bn; **31g**, **32g**: R_3= Ph; Pg= TBDMS; **31h**,**32h**: R_3=*p*-ClC_6H_4; Pg= TBDMS; **31i**, **32i**: R_3=*p*-$MeOC_6H_4$; Pg= TBDMS **31j**, **32j**, **33j**:  = ; **31k**, **32k**: R_3= *t*-Bu; Pg= TBDMS;

Scheme 2.15 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 2.15 and Table 2.5. At room temperature, a good diastereo 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 2.16).



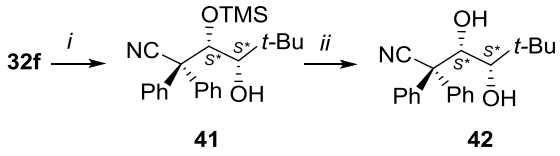
Scheme 2.16 Preparation of products **38, 40** from **32e** and **32g** respectively. *Reagents and Conditions: i:* Pd/C (10%)/$Pd(OAc)_2$, MeOH, H_2; *ii*: HCl_{aq}, 1N, CH_3CN, r.t., 30 min. *iii:* PPTS, 2,2-dimethoxypropane, acetone,r.t.

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

Entry	Aldehyde	Product*	de	Yield (%)	*J* H_3-H_4	δ H_3-H_4
1	**31e**	**32e**	>98	68	4.4	4.69-3.37
2	**31f**	**32f**	>98*	65	1.2	5.02-3.30
3	**31g**	**32g**	>98	78	2.4	5.10-4.78
4	**31h**	**32h**	>98*	73	2.8	4.95-4.62
5	**31i**	**32i**	>98*	68	2.8	4.01-4.72
6	**31j**	**32j**	81	80	8.0	4.58-4.15
7	**31k**	**32k**	--	0	--	--

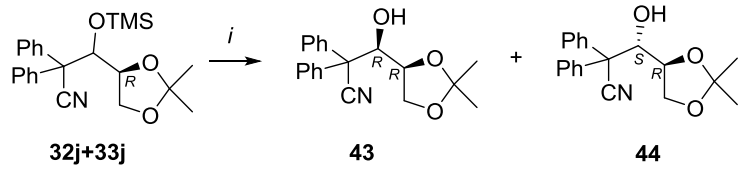
*: For the sack of simplicity, only one diastereo isomer was reported in the table

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_3CN, r.t., 30 min.

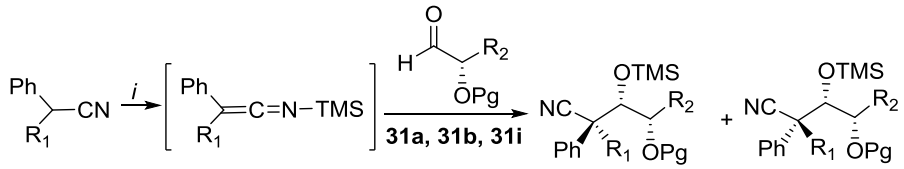
The configurations of **32h** and **32i** were assigned by simply comparing the values of their $J_{3,4}$ values with that of product **32g** (Table 2.5, entries 3–5). Finally the configurations of **32j** and **33j** were inferred by literature data of the corresponding mono-hydroxy derivatives **43** and **44**[29, 30] (Scheme 2.18).



32j+33j **43** **44**

Scheme 2.18 Preparation of products **43** and **44.** *Reagents and Conditions: i:* KF/HF(50%),CH_2Cl_2/ACN (9/1), r.t.

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 α-*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.



19b-19k **20b-20k** **45a-45k** **46a-46k**

Scheme 2.19 Reaction of different aldehydes **31** with different asymmetric SKI**s 20**

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

Entry	SKI[#]	R_1	Aldehyde	Products	dr(**17/18**)	Yield (%)
4	**20b**	4-BrC_6H_4	**31b**	**45d/46d**[&]	55/45	54
2	**20c**	3-MeC_6H_4	**31b**	**45b/46b**[&,$$]	52/48	65
3	**20d**	2-MeC_6H_4	**31b**	**45c/46c**	70/30	54
1	**20e**	4-MeC_6H_4	**31b**	**45a/46a**[&,$]	50/50	58
5	**20f**	4- $OMeC_6H_4$	**31b**	**45e/46e**	50/50	65
9	**20g**	2-ClC_6H_4	**31b**	**45i/46i**	80/20	44
8	**20h**	3-pyridine	**31b**	**45h/46h**	65/35	67
6	**20k**	4- $CF_3C_6H_4$	**31b**	**45f/46f**[&]	60/40	61
7	**20j**	4- $NO_2C_6H_4$	**31b**	**45g/46g**	64/36	57
12	**20c**	3-MeC_6H_4	**31g**	**45j/46j**[&]	50/50	85
13	**20h**	3-Pyridine	**31g**	**45k/46k**	80/20	40

[#]**:** 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. [&]: 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. [$]: Identified as the corresponding mono-hydroxide derivatives **45a** and **46a**. [$$]**:** 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.

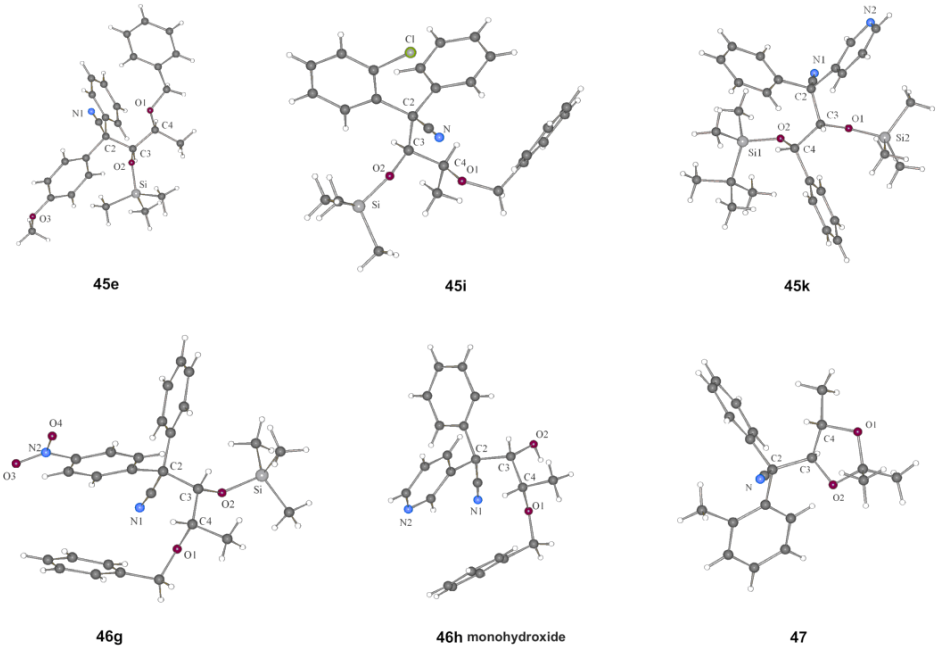


Figure 2.4 X-Ray structures of compounds **45e**, **45i**, **45k**, **46g**, **46h**-monohydroxide derivative and **47**

2.3 Conclusion

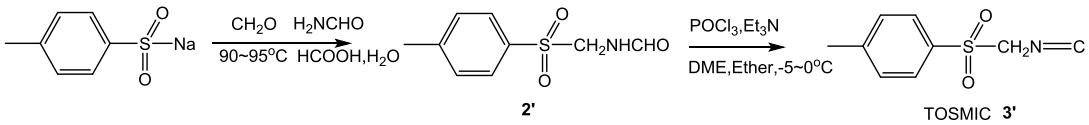
N-trimethylsilyl ketene imine has been successfully used in an un-catalyzed amidation reaction with isocyanates to prepare very useful α,α diaryl malonamides with reasonable to good yields; furthermore, a catalyst free asymmetric aldol procedure has been well established for preparation of optically 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 ^{1}H 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.

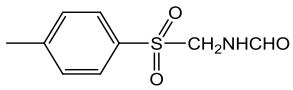


Scheme 2.20 Preparation of TOSMIC*:*

The preparation of N-(tosylmethyl)formamide 2'

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^{o}C for 2 hours. Then the mixture was cooled to room temperature and then in ice-salt with continued stirring, then cooled to -20^{o}Cfor 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.

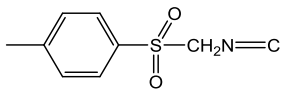


N-(tosylmethyl)formamide 2'

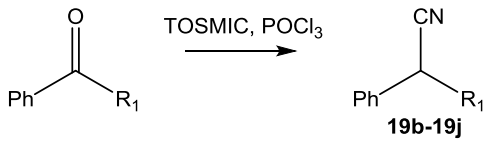
2': ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (s, 1H), 7.79 (dd, *J* = 8.5, 2.0 Hz, 2H), 7.37 (d, *J* = 8.0 Hz, 2H), 6.34 (s, 1H), 4.70 (d, *J* = 6.9 Hz, 2H), 2.45 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ 159.98, 145.73, 133.44, 130.45, 130.04, 128.80, 58.63, 21.74.

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 $POCl_3$ (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 Na_2SO_4, 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.

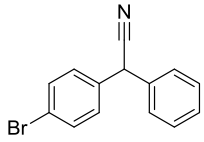


3': ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.4 Hz, 1H), 7.45 (dd, *J* = 8.6, 0.6 Hz, 1H), 4.58 (s, 1H), 2.50 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.87, 132.00, 130.35, 129.43, 61.05, 21.81.



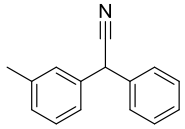
Scheme 2.21 Preparation of nitriles

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 18-24hours. 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.



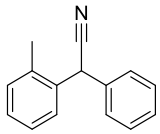
The preparation of 2-(4-bromophenyl)-2-phenylacetonitrile (19b)

Following general procedure, product 2-(4-bromophenyl)-2-phenylacetonitrile (19b) were prepared, yield: 44%. Known product. See ref[31]. mp:77-78 ℃ (ref[31] 79-81 ℃).



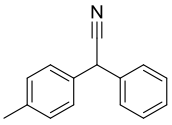
The preparation of 2-phenyl-2-(m-tolyl)acetonitrile (19c)

19c: Following general procedure, 2-phenyl-2-(m-tolyl)acetonitrile (19c) were prepared, yield: 76%.Known product. See ref[32]. Semi-melted solid (ref[32]. m.p 26 ℃): ^{1}H NMR (400 MHz, $CDCl_3$) δ 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).



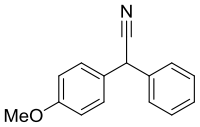
The preparation of 2-phenyl-2-(*o*-tolyl)acetonitrile (19d)

Following general procedure, 2-phenyl-2-(*o*-tolyl)acetonitrile (19d) were prepared, yield: 68%. **19d**: Known product. See ref[33]. Viscous material ^{1}H NMR (400 MHz, $CDCl_3$) δ 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). ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.95, 133.61, 131.24, 129.08, 128.77, 128.56, 128.11, 127.74, 126.83, 39.90, 19.47.



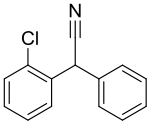
The preparation of 2-phenyl-2-(*p*-tolyl) acetonitrile (19e)

19e: Following general procedure, 2-phenyl-2-(*p*-tolyl) acetonitrile (19e) were prepared, yield: 67%.Known product. See ref[34]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 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)

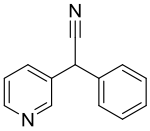
19f: Following general procedure, 2-(4-methoxyphenyl)-2-phenylacetonitrile (9f) were prepared, yield: 57%. Known product. See ref[35]. ^{1}H NMR (400 MHz, CDCl3) δ 7.40 – 7.31 (m, 4H), 7.27 (d, J = 3.8 Hz, 1H), 7.25 – 7.22 (m, 1H), 6.96 – 6.80 (m, 2H), 5.10 (s, 1H), 3.80 (s, 3H).



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

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

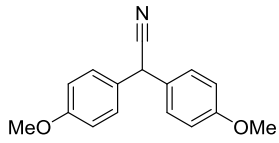
19g: Known product. See ref[34]. ^{1}H NMR (400 MHz, CDCl3) δ 7.54 – 7.47 (m, 1H), 7.45 – 7.41 (m, 1H), 7.39 – 7.29 (m, 7H), 5.65 (s, 1H).



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 ref[36].mp.63-65^{o}C(ref. 60-61 ^{o}C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$)

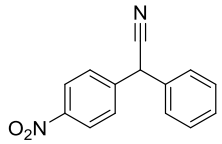
δ 152.10, 149.45, 148.68, 141.80, 135.23, 134.58, 132.02, 129.90, 129.41, 128.63, 128.24, 127.56, 123.92, 118.63, 40.17.



The preparation of 2,2-bis(4-methoxyphenyl)acetonitrile (19i)

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

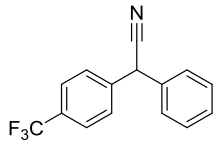
19i: Known product. See ref[37].mp.149-151°C(ref. 148-149 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 – 7.20 (m, 4H), 6.92 – 6.84 (m, 4H), 5.05 (s, 1H), 3.80 (s, 6H).



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 ref[38].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 ref[39]. ^{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-(benzyloxy)propanal (**3b**), (*S*)-2-(triisopropylsilyloxy)propanal (**3c**), (*S*)-2-(*tert*-butyldiphenylsilyloxy)propanal (**3d**), (*S*)-2-(benzyloxy)-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-(benzyloxy)-3,3-dimethylbutanal (**3g**), 2-(*tert*-butyldimethylsilyloxy)-3,3-dimethylbutanal (**3f**), 2-(*tert*-butyldimethylsilyloxy)-2-(4-chlorophenyl)acetaldehyde (**3j**), 2-(*tert*-butyldimethylsilyloxy)-2-(4-methoxyphenyl)acetaldehyde (**3k**) were prepared according to the general procedure by Mildland[41]

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 ℃. 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 ℃ 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. NH_4Cl_{aq} (10 ml), and then extracted with EtOAc (3 × 20 ml). The combined organic phase was dried (Na_2SO_4), filtered and concentrated under *vacuum*. The crude residue was purified by flash chromatography (cyclohexane: Et_2O, 4:1) to give malonic amide **25a** (120 mg, 35%) as a white solid.

Method B; Typical Procedure

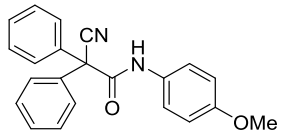
2,2-Diphenylacetonitrile (**19a**) (193 mg, 1.0 mmol) in THF (1 ml)was added dropwise to a solution of *n*-BuLi (0.44 ml of a 2.5 M solution in*n*-hexane, 1.1 mmol) in THF (3 ml) at –78 ℃. Next, a solution of TMSCl (120 mg, 1.1 mmol) in THF (1 ml) was added dropwise at–78 ℃. After 15 min, a solution of isocyanate **24a** (164 mg, 1.1 mmol)in toluene (1 ml) was added dropwise at –78 ℃ 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. NH_4Cl solution (10 ml), and then extracted with EtOAc (3 × 20 ml). The combined organic phase was dried (Na_2SO_4), filtered and concentrated under *vacuum*. The crude residue was purified by flash chromatography (cyclohexane–Et_2O, 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 ℃. After 15 min, a solution of TMSCl (120 mg, 1.1 mmol) in THF (1 ml) was added dropwise to –78 ℃. 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 ℃ 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 ℃ 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.NH_4Cl solution (10 ml), and then extracted with EtOAc (3 × 20 ml).The combined organic phase was dried (Na_2SO_4), 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%).

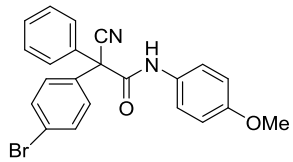
Method D; Typical Procedure

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 ℃. After 5 min, a solution of 2,2-diphenylacetonitrile (**19a**) (193 mg, 1.0 mmol) in THF (1 ml) was added dropwise at –78 ℃, 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 ℃ 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 ℃, a solution of isocyanate **24a** (164 mg, 1.1 mmol) in toluene (1 ml) was added dropwise at –78 ℃. The resulting mixture was stirred at –78 ℃ 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. NH_4Cl solution (10 ml), and then extracted with EtOAc (3 × 20 ml). The combined organic phase was dried (Na_2SO_4), filtered and concentrated under vacuum. The starting nitrile 1**9a** (97 mg, 61%) was recovered by flash chromatography (cyclohexane–Et_2O, 4:1). No trace of the target amide **25a** was evident in the crude reaction mixture according to TLC, ^{1}H NMR and HPLC analyses.



The preparation of 2-Cyano-*N*-(4-methoxyphenyl)-2,2-diphenylacetamide (25a)

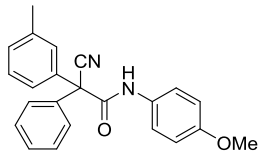
25a: White solid. mp: 99–110 ℃. IR (KBr): 1043, 1692 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.80 (s, 3 H), 6.86–6.90 (m, 2 H), 7.41–7.49 (complex pattern, 12 H), 7.78 (bs, 1 H, NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.66, 60.36, 94.42, 120.47, 110.17, 128.39, 129.24, 129.31, 129.82, 136.25, 157.14, 163.71. GC–MS: *m*/*z* = 342 $[M]^+$. Elemental Analysis: Calcd for $C_{10}H_{18}N_2O_2$: 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 24**a** 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%).

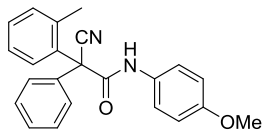
25b: White solid. mp.147–153 ℃. IR (KBr): 1041, 1667 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.81 (s, 3 H), 6.85–6.91 (m, 2 H), 7.33–7.41 (m, 2 H), 7.40–7.50 (complex pattern,7 H), 7.54–7.58 (m, 2 H), 7.85 (bs, 1 H, NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.60, 59.57, 94.38, 120.02, 110.29, 92.58, 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 $C_{10}H_{17}BrN_2O_2$: 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%).

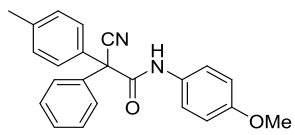
25c: White solid. mp.133–134 ℃. IR (KBr): 1041, 1663 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.31 (s, 3 H), 3.73 (s, 3 H), 6.79–6.82 (m, 2 H), 7.15–7.17 (m, 2 H), 7.24 (d, *J* = 7.2 Hz, 2 H), 7.34–7.41 (complex pattern, 7 H), 7.71(bs, 1 H, NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 9.65, 55.62, 60.36, 94.37, 120.52, 110.14, 125.40, 128.39, 128.91, 129.14, 129.15, 129.12, 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 $C_{12}H_{20}N_2O_2$: 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 ℃. IR (KBr): 1045, 1686 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 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). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 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 $C_{12}H_{20}N_2O_2$: C, 77.51; H, 5.66. Found: C, 77.62; H, 5.67.

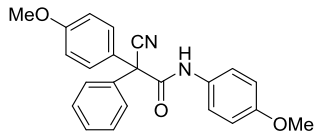


The preparation of 2-Cyano-*N*-(4-methoxyphenyl)-2-phenyl-2-(*p*-tolyl)acetamide (25e)

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 ℃. IR (KBr): 1042, 1671 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 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). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 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,

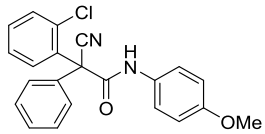
157.31, 163.90. LC–MS: *m*/*z* = 357 $[M + 1]^+$. Elemental Analysis: Calcd for $C_{12}H_{20}N_2O_2$: C, 77.51; H, 5.66. Found: C, 77.61; H, 5.67.



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%).

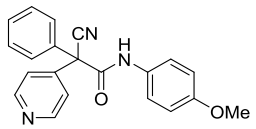
25f: White solid. mp:96–120 ℃. IR (KBr): 1043, 1666 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.80 (s, 3 H), 3.83 (s, 3 H), 6.87 (d, *J* = 8.8 Hz, 2 H), 6.95 (d, *J* = 8.8 Hz, 2 H), 7.36–7.49 (complex pattern, 9 H), 7.79 (bs, 1 H, NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.50, 55.60, 94.35, 94.59, 120.54, 110.12, 128.09, 128.26, 129.12, 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 $C_{12}H_{20}N_2O_3$: C, 74.18; H, 5.41. Found: C, 74.33; H, 5.42.



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%).

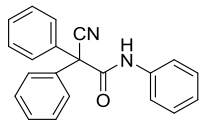
25g: White solid. mp:167–169 ℃. IR (KBr): 1042, 1670 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.80 (s, 3 H), 6.77 (dd, J_1 =1.2 Hz, J_2 = 7.6 Hz, 1 H), 6.87–6.89 (m, 2 H), 7.20 (dt, J_1 = 1.2 Hz, J_2 = 7.2 Hz, 1 H), 7.37 (dt, J_1 = 1.2 Hz, J_2 = 7.2Hz, 1 H), 7.42–7.45 (m, 2 H), 7.50–7.54 (m, 4 H),7.68–7.70 (m, 2 H), 7.94 (bs, 1 H, NH). ^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{10}H_{17}ClN_2O_2$: 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%).

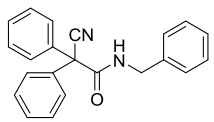
25g: White solid. mp:91–95 ℃. IR (KBr): 1046, 1697 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.80 (s, 3 H), 6.86–6.90 (m, 2 H), 7.34 (dd, J_1 = 4.8 Hz, J_2 = 7.6 Hz, 1 H), 7.45 (m, 7 H), 7.75 (m, 1 H), 8.16 (bs, 1 H, NH), 8.62 (dd, J_1 = 1.6 Hz, J_2 = 4.8 Hz, 1 H), 8.67 (d, J = 2.0 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 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 $C_9H_{17}N_{12}O_2$: 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%).

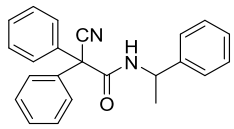
25i: White solid. mp:99–110 ℃. IR (KBr): 1046, 1703 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.10 (m, 1 H), 7.34–7.43 (m, 2 H), 7.43–7.53 (complex pattern, 12 H), 7.85 (bs, 1 H, NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 60.56, 120.31, 120.37, 125.71, 128.40, 129.31, 129.33, 129.35, 136.12, 136.78, 163.85, 178.88. LC–MS: *m*/*z* = 313 $[M + 1]^+$. Elemental Analysis: Calcd for $C_9H_{16}N_2O$: 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%).

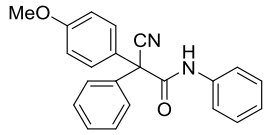
25j: White solid. mp: 131–132 ℃. IR (KBr): 1047, 1665 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 4.44 (d, *J* = 6.0 Hz, 2 H, CH_2), 6.64 (bs, 1 H, NH), 7.12–7.43 (complex pattern, 15 H).13C NMR (100 MHz, $CDCl_3$): δ = 44.84, 59.61, 120.45, 127.81, 127.99, 128.31, 128.97, 129.05, 129.14, 136.31, 137.09, 165.84. LC–MS: *m*/*z* = 327 $[M + 1]^+$. Elemental Analysis: Calcd for $C_{10}H_{18}N_2O$: 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 ℃.IR (KBr): 2129, 1663 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): 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). ^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{12}H_{20}N_2O$: C, 81.15; H, 5.92. Found: C, 81.03; H5.91.

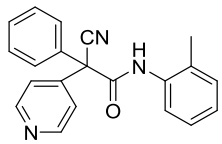


The preparation of *N*-Benzyl-2-cyano-2-(4-methoxyphenyl)-2-phenylacetamide (25l)

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 ℃. IR (KBr): 1042, 1658 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.82 (s, 3 H), 4.53 (d, *J* = 5.6 Hz, 2 H, CH_2), 6.63 (bs, 1 H, NH), 6.90–6.92 (m, 2 H), 7.12–7.42 (complex pattern, 12 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 44.79, 55.48, 58.98, 94.46, 120.58,

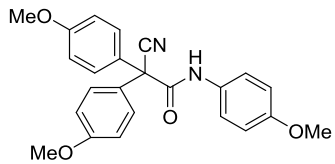
127.79, 127.95, 128.9, 128.94, 128.96, 129.10, 129.57, 136.61, 137.15, 159.99, 166.16. LC–MS: *m*/*z* = 357 $[M + 1]^+$. Elemental Analysis: Calcd for $C_{12}H_{20}N_2O_2$: C, 77.51; H, 5.66. Found: C, 77.28; H, 5.65.



The preparation of 2-Cyano-*N*-(2-methylphenyl)-2-phenyl-2-(pyridin-3-yl)acetamide (25m)

Starting from 2-phenyl-2-(pyridin-3-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_2Cl_2–Et_2O, 5:1), as a white solid (1712 mg, 53%).

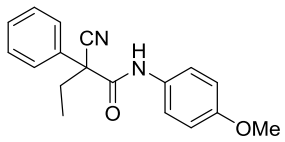
25m: White solid. mp: 120–125 ℃. IR (neat): 2128, 1698 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.15 (s, 3 H), 7.14–7.27 (m,3 H), 7.35–7.38 (m, 1 H), 7.47–7.54 (m, 5 H),7.79–7.85 (m, 2 H), 7.98 (bs, 1 H, NH), 8.65 (dd, J_1 = 1.2 Hz,J_2 = 4.0 Hz, 1 H), 8.73 (dd, J_1 = 1.5 Hz, J_2 = 0.4 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.28, 58.10, 99.39, 110.64, 92.52, 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 $C_9H_{17}N_{12}O$: 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 ℃.IR (KBr): 1041, 1666 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 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, $CDCl_3$): δ = 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 $C_{24}H_{10}N_2O_4$: 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 ℃. IR (KBr): 1042, 1667 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) 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, $CDCl_3$) 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: $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52; O, 10.87. Found: C, 73.59; H, 6.16.

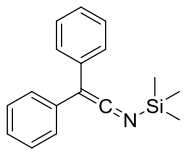
2.4.4 Uncatalyzed asymmetric aldol reaction of N-*silyl ketene imines*

(*S*)-2-(*tert*-butyldimethylsilyloxy)propanal (**3a**), (*S*)-2-(benzyloxy)propanal (**3b**), (*S*)-2-(triisopropylsilyloxy)propanal (**3c**), (*S*)-2-(*tert*-butyldiphenyl silyloxy)propanal (**3d**), (*S*)-2-(benzyloxy)-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-(benzyloxy)-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 Mildland[41] except benzyl bromide was used insted 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_6D_6): δ =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_6D_6): δ =-0.30, 61.27, 124.74, 127.08, 129.24, 136.61, 180.63.

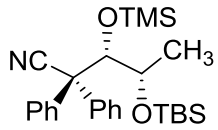
The Preparation of (*3S, 4S*)/(*3R, 4S*)-4-(*tert*-butyldimethylsilyloxy)-2,2-diphenyl-3-(trimethylsilyloxy)pentanenitriles 32a/33a from 20a.

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:

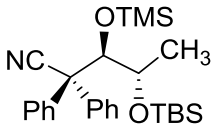
To the ketene imine **20a**, a solution of (*S*)-2-(*tert*-butyldimethylsilyloxy)propanal **31a** (231 mg, 1.23 mmol) in THF (1 ml) was added at-78^{o}C. The reaction was kept at this temperature for 3hrs, then it was left to reach r.t. spontaneously and kept overnight. The solvent was removed under *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 ^{o}C. $[\alpha]_D^{20}$: -16.80 (*c*: 1.0g/100 mg, $CHCl_3$). IR (neat): 2242cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ =-0.16 (s, 9H), -0.13 (s, 3H), -0.07 (s, 3H), 0.85 (s, 9H), 1.21 (d, *J*=6.4

Hz, 3H), 4.16 (dq, J_1=2.8 Hz, J_2=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, 138.63, 139.04. MS (EI): m/z= 438 [M-CH_3]. Elemental Analysis: Calcd. for $C_{26}H_{39}NO_2Si_2$: C, 68.82; H, 8.66; N, 3.09; Si, 12.38; Found: C, 68.92; H, 8.67;



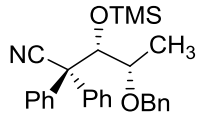
Spectral data for **(*3R, 4S*)-4-(*tert*-butyldimethylsilyloxy)-2,2-diphenyl-3-(trimethylsilyloxy)pentanenitrile 33a** as follows:

33a: Colourless oil**.** $[\alpha]_D^{20}$: +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_1=7.0 Hz, J_2=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 $C_{26}H_{39}NO_2Si_2$: C, 68.82; H, 8.66; N, 3.09; Si, 12.38; Found: C, 68.94; H, 8.68;

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

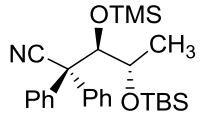
Following ***Method A*** starting from diphenylacetonitrile (193 mg, 1.0 mmol) and (*S*)-2-(Benzyloxy)propanal **31b** (164 mg, 1.0 mmol), product **32b** (356 mg, yield: 83%) was isolated as single diastereoisomer after the flash chromatography (cyclohexane: ether= 7:1).

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-(benzyloxy)-2,2-diphenyl-3-(trimethylsilyloxy)pentanenitrile 32b** as follow:

32b: White solid, mp: 93-94 ^{o}C. $[\alpha]_D^{20}$: +10.36 (*c*: 1.1g/100 mg, $CHCl_3$). IR (neat): 2246 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): 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). ^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{27}H_{31}NO_2Si$: 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-(benzyloxy)-2,2-diphenyl-3-hydroxy pentanenitrile 33b**

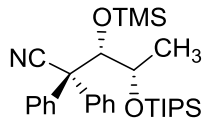
33b: Colourless oil. $[\alpha]_D^{20}$: +131.1 (*c*:10 g/100 mg, $CHCl_3$). IR (neat): 2238 cm^{-1}. ^{1}H NMR (400 MHz $CDCl_3$,): δ =1.18 (d, *J*=6.4 Hz, 3H), 3.49 (d, *J*=9.2 Hz, 1H, OH), 3.55 (dq, J_1=2.0 Hz, J_2=6.4 Hz, 1H), 4.39 (dd, J_1=2.0 Hz, J_2=8.8 Hz,1H), 4.41 (d, *J*=10.8 Hz, 1H), 4.51 (d, *J*=10.8 Hz, 1H), 7.27-7.39 (m, 13H), 7.56 (d, *J*=8.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$):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 $C_{24}H_{23}NO_2$: 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 -78^{o}C. Then a solution of diphenylacetonitrile (212 mg, 1.1 mmol) in THF (1 ml) was dropped into the base solution at -78^{o}C. The colour of the reaction becomes yellow. After 5 min, a solution of TMSCl (0.14ml, 1.1

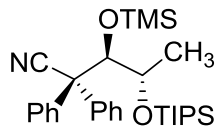
mmol) in 1ml of THF was added to the reaction. The reaction mixture was allowed to reach r.t. spontaneously. A solution of (*S*)-2-(triisopropylsilyloxy)propanal **31c** (253 mg, 1.1 mmol) in THF (1 ml) was dropped. The reaction was kept at r.t. overnight. The solvent was removed under *vacuum* to get a crude mixture which was purified by flash chromatography (hexane: CH_2Cl_2= 7:1) to get pure compounds **32c** and **33c** (**32c**: 381, **33c**: 163g, 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. $[\alpha]_D^{20}$: -12.0 (*c*: 1.0g/100 mg, $CHCl_3$).IR (neat): 2239 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ =-0.16 (s, 9H), 0.97-1.01 (Complex pattern, 21H), 1.26 (d, *J*=6.4 Hz,3H), 4.31(dq, J_1=2.4 Hz, J_2=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). ^{13}C NMR (100 MHz, $CDCl_3$): 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, 138.60, 139.13. MS: m/z= 495 [M]. Elemental Analysis: Calcd. for $C_{29}H_{45}NO_2Si_2$: C, 70.25; H, 9.15; N, 2.82; O, 6.45; Si, 11.33; Found: C,70.38; H, 9.17.



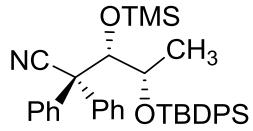
Spectral data for **(*3R, 4S*)-2,2-diphenyl-4-(triisopropylsilyloxy)-3-(trimethylsilyloxy)pentanenitriles 33c.**

33c: Colourless oil**.** $[\alpha]_D^{20}$: -7.4 (c: 1.0g/100 mg, $CHCl_3$). IR (neat): 2238 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ =-0.06 (s, 9H), 1.01 (Complex pattern, 21H), 1.25 (d, *J*=6.4 Hz, 3H), 4.02(dq, J_1=0.8 Hz, J_2=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). ^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{29}H_{45}NO_2Si_2$: 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-(*tert*-butyldiphenylsilyloxy)-2,2-diphenyl-3-(trimethylsilyloxy)pentanenitrile 32d/33d.

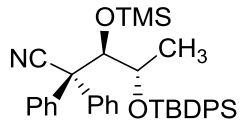
Method A: Following Method A, starting from diphenylacetonitrile (386 mg, 2.0 mmol) and (*S*)-2-(*tert*-butyldiphenylsilyloxy)propanal **31d** (624 mg, 2.0 mmol), products **32d** and **33d** were obtained by the flash chromatography (petroleum ether :ether = 20:1) (**32d**: 750 mg, 33**d**: 404 mg, total yield: 62%, 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-(*tert*-butyldiphenylsilyloxy)-2,2-diphenyl-3-(trimethylsilyloxy)pentanenitrile 32d** as follow:

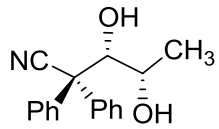
32d: White solid. mp:112-116^{o}C. $[\alpha]_D^{20}$: -7.10 (*c*: 1.0g/100 mg, $CHCl_3$). IR (neat): 2248 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ =-0.23 (s, 9H), 0.87 (d, *J*=6.8 Hz, 3H), 0.94 (s, 9H), 4.08 (dq, J_1=1.6 Hz, J_2=6.8 Hz, 1H), 4.50 (d, *J*=1.6 Hz, 1H), 7.19-7.37 (complex pattern, 15H), 7.57-7.71 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ =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. MS: m/z=600 [M+Na^+]. Elemental Analysis: Calcd. For $C_{36}H_{43}NO_2Si_2$: C, 74.82; H, 7.50; N, 2.42; Si, 9.72; Found: C, 75.04; H, 7.52.



Spectral data for **(3*R*, 4*S*)-4-(*tert*-butyldiphenylsilyloxy)-2,2-diphenyl-3-(trimethylsilyloxy)pentanenitrile 33d** as follow:

33d: White solid. mp:142-145^{o}C. $[\alpha]_D^{20}$: -2.80 (*c*: 1.0g/100 mg, $CHCl_3$). IR (neat): 2240 cm^{-1}.^1H NMR (400 MHz, $CDCl_3$): δ =0.05 (s, 9H), 1.08 (d, *J*=6.4 Hz, 3H), 1.10 (s, 9H), 3.92 (q, *J*=6.0 Hz, 1H), 4.89 (s, 1H), 7.11-7.59 (m, 20H). ^{13}C NMR (100 MHz, $CDCl_3$): δ =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.MS: m/z= 600 [M+Na^+].

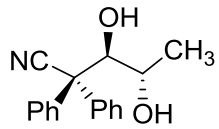
Elemental Analysis: Calcd. for $C_{36}H_{43}NO_2Si_2$: C, 74.82; H, 7.50; N, 2.42; Si, 9.72; Found: C, 75.00; H, 7.52.



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%)

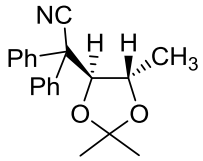
34a: Colorless oil. $[\alpha]_D^{20}$: +78.45(*c*: 1.1g/100 mg, $CHCl_3$). IR (neat): 2239 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$):δ =1.22 (d, *J*=6.4 Hz, 3H), 1.92 (bs, 1H, OH), 3.37 (bs, 1H, OH), 4.00 (dq, J_1=6.4 Hz, J_2=1.2 Hz, 1H), 4.39 (d, *J*=1.2 Hz, 1H), 7.31-7.45 (m, 8H), 7.56 (m, 2H). ^{13}C NMR (100 MHz, CD_3OD): δ =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 %).

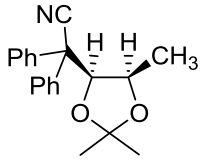
34b: Colorless oil. $[\alpha]_D^{20}$: -69.60 (*c*: 1.0g/100 mg, $CHCl_3$). IR (neat): 2243 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.35 (d, *J*=6.4 Hz, 3H), 1.69 (bs, 1H, OH), 2.50 (bs, 1H, OH), 3.77 (dq, J_1=4.0 Hz, J_2=6.4 Hz, 1H), 4.69(d, *J*=4.0 Hz, 1H), 7.30-7.46 (complex pattern, 8H), 7.60 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ =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.



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 5ml of anhydrous acetone. The reaction mixture was kept stirring at r.t. overnight, decomposed with saturated NH_4Cl solution, extracted with AcOEt (15ml×3). The organic phase was dried with anhydrous Na_2SO_4 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*: 1.0g/100 mg, $CHCl_3$). IR (KBr): 2247 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$):δ = 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). ^{13}C NMR (100 MHz, $CDCl_3$): δ =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 $C_{20}H_{21}NO_2$: 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 (0.6ml) were mixed together into 5ml 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*: 1.0g/100 mg, $CHCl_3$). IR (KBr): 2247cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$):δ = 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). ^{13}C NMR (100 MHz, $CDCl_3$): δ =16.75, 25.63, 27.77, 53.37, 74.39, 80.28, 108.75, 120.96, 127.23, 127.51,

127.98, 128.42, 128.81, 129.27, 137.45, 140.35. MS: m/z=330 [M+Na^+]. Elemental Analysis: Calcd. for $C_{20}H_{21}NO_2$: 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.

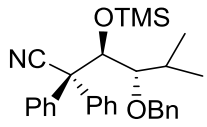
(*3S, 4S*)-4-(benzyloxy)-2,2-diphenyl-3-(trimethylsilyloxy)pentanenitrile **32b** (90 mg), Pd/C 10% (90 mg) and $Pd(AcO)_2$ (40 mg) were mixed into 20 ml of anhydrous MeOH. The reaction mixture was kept under H_2 (50psi) for 1 hour. Then the reaction mixture was filtered and the solvent was removed to get crude product. This crude product was directly mixed with 2 ml of actonitrile and 1 ml of HCl_{aq} (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-(benzyloxy)-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-(benzyloxy)-5-methyl-2,2-diphenyl-3-(trimethylsilyloxy)hexanenitrile **32e** was obtained after flash chromatography (hexane : ether =8:1) (311 mg; yield:68%).

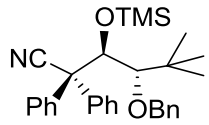


Spectral data for **(*3S, 4S*)-4-(benzyloxy)-5-methyl-2,2-diphenyl-3-(trimethylsilyloxy)hexanenitrile 32e** as follow:

32e: White solid; mp: 86-93 ^{o}C. $[\alpha]_D^{20}$: +3.80(*c*: 1.0g/100 mg, $CHCl_3$). IR (neat): 2240 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$):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, J_1=4.4 Hz, J_2=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). ^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{29}H_{35}NO_2Si$: 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-(benzyloxy)-5,5-dimethyl-2,2-diphenyl-3-(trimethylsilyloxy)hexanenitrile 32g.**

Following ***Method A***, starting from diphenylacetonitrile (290 mg, 1.5 mmol) and 2-(benzyloxy)-3,3-dimethylbutanal **31g** (309 mg, 1.5 mmol), (*3S*, 4S**)-4-(benzyloxy)-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%)

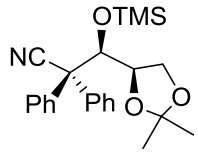


Spectral data for **(*3S*, 4S**)-4-(benzyloxy)-5,5-dimethyl-2,2-diphenyl-3-(trimethylsilyloxy)hexanenitrile 32g** as follow:

32g: Colourless oil**.** IR (neat): 2238 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$):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). ^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{30}H_{37}NO_2Si$: C, 76.39; H, 7.91; N, 2.97; Si, 5.95; Found: C, 76.52; H, 7.92

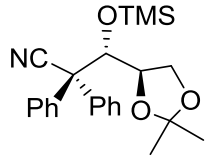
The Preparation of (*R*)-3-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-diphenyl-3-(trimethylsilyloxy)propanenitrile 4h and (*S*)-3-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-diphenyl-3-(trimethylsilyloxy)propanenitrile 33h.

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_3CN/MeOH/H_2O) 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 ℃. $[\alpha]_D^{20}$: -67.1 (*c*: 1.0g/100 mg, $CHCl_3$). IR (neat): 2246 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ =-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_1= 7.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 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 $C_{23}H_{29}NO_3Si$: C, 69.84; H, 7.39; N, 3.54; O, 12.13; Si, 7.10; Found: C, 69.92; H, 7.40.



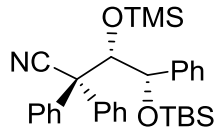
Spectral data for **(*S*)-3-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-diphenyl-3-(trimethylsilyloxy)propanenitrile 33h** as follow:

33h: White solid. mp: 100-106 ℃. $[\alpha]_D^{20}$: -21.4 (*c*: 1.0g/100 mg, $CHCl_3$). IR (neat): 2241 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ =-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, $CDCl_3$): δ = 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,

129.22, 129.34, 137.68, 137.98. MS (ESI): m/z= 418 [M+Na^+]. Elemental Analysis: Calcd. for $C_{23}H_{29}NO_3Si$: 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%).

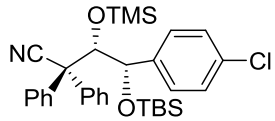


Spectral data for **(*3S, 4S*)-4-(*tert*-butyldimethylsilyloxy)-2,2,4-triphenyl-3-(trimethylsilyloxy)butanenitrile 32i** as follow:

32i: White solid; mp: 135-137 ^oC. $[\alpha]_D^{20}$: -4.45 (*c*: 1.1g/100 mg, $CHCl_3$). IR (neat): 2247 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$):δ =-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, $CDCl_3$): δ =-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 $C_{31}H_{41}NO_2Si_2$:C, 72.18; H, 8.01; N, 2.72; 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*-butyldimethylsilyl)oxy)-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%).

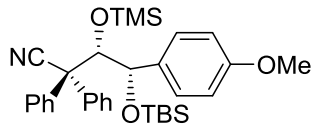


Spectral data for **(*3S*, 4S**)-4-(*tert*-butyldimethylsilyloxy)-4-(4-chlorophenyl)-2,2-diphenyl-3-(trimethylsilyloxy)butanenitrile 32j** as follow:

32j: White solid. mp:156-163 ^{o}C. IR (neat): 2251 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$):δ = -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, $CDCl_3$): δ =-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 $C_{31}H_{40}ClNO_2Si_2$: 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.

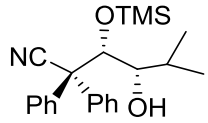
The Preparation of (*3S*, 4S)-4-(tert-butyldimethylsilyloxy)-4-(4-methoxyphenyl)-2,2-diphenyl-3-(trimethylsilyloxy)butanenitrile 32k**

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**

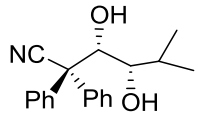
32k: White solid; mp: 118-123 ^{o}C. IR (neat): 2245 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$):δ = -0.46 (s, 9H), -0.44 (s, 3H), -0.28 (s, 3H), 0.87 (s, 9H), 3.80 (s, 3H), 4.72 (d, *J*=2.8 Hz, 1H), 5.01 (d, *J*=2.8 Hz, 1H), 6.81(d, *J*=9.2 Hz, 2H), 7.18 (d, *J*=8.8 Hz, 2H), 7.24-7.37 (m, 6H), 7.53 (d, *J*=8.0 Hz, 2H), 7.73 (d, *J*=8.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = -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^{+}]. Elemental Analysis: Calcd. for $C_{32}H_{43}NO_3Si_2$: 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 mixted into 15ml of MeOH. The reaction mixture was kept under H_2 (50psi) 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%.)

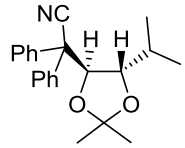
36: Colourless oil. $[\alpha]_D^{20}$: +68.2(*c*: 1.0g/100 mg, $CHCl_3$). IR (neat): 3452, 2239 cm^{-1}. ^1H NMR(400 MHz, $CDCl_3$):δ =0.17 (s, 9H), 0.6 3(d, *J*=6.4 Hz, 3H), 0.90 (d, *J*=6.8 Hz, 3H), 1.57 (m, 1H), 3.73 (dd, J_1=1.2 Hz, J_2=7.6 Hz, 1H), 4.09 (d, *J*=8.0 Hz, OH), 4.46 (dd, J_1=0.8 Hz, 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 $C_{22}H_{29}NO_2Si$: C, 71.89, H, 7.95, N, 3.81, Si, 7.64, Found: C, 71.96, H, 7.96,



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%).

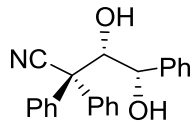
37: $[\alpha]_D^{20}$: +78.3 (*c*: 1.0g/100 mg, $CHCl_3$). IR(neat): 3400 (b), 2240 cm^{-1}. ^1H NMR (400 MHz, CD_3OD): δ= 0.80 (d, *J*=6.4 Hz, 3H), 0.85 (d, *J*=6.4 Hz, 3H), 1.72 (octet, J_1=6.4 Hz, 1H), 3.00 (dd, J_1=6.4 Hz, J_2=0.2 Hz, 1H), 4.65 (d, *J*=0.2 Hz, 1H), 7.28 (m, 2H), 7.35 (m, 4H), 7.44 (m, 2H), 7.59 (m, 2H). ^{13}C NMR (100 MHz, CD_3OD): 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%).

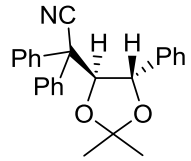
38: mp: 172-174 ^{o}C. $[\alpha]_D^{20}$: +94.8 (*c*: 1.0g/100 mg, $CHCl_3$). IR (neat): 2247 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$):δ = 0.37 (m, 1H), 0.69 (d, *J*=6.8 Hz, 3H,), 0.73 (d, *J*=6.8 Hz, 3H), 1.47 (s, 3H), 1.48(s, 3H), 4.02 (dd, J_1=2.8 Hz, J_2=8.0 Hz, 1H), 4.59 (d, *J*=7.6 Hz, 1H), 7.28-7.41 (m, 8H), 7.55 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{22}H_{25}NO_2$: 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, $CHCl_3$). IR (neat): 3420 (b), 2239 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): 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). ^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{22}H_{19}NO_2$: C, 80.22; H, 5.81; N, 4.25; O, 9.71. Found: C, 80.44; H, 5.83



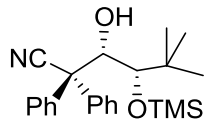
The Preparation of 2-[(*4S, 5S*)-2,2-dimethyl-5-phenyl-1,3-dioxolan-4-yl]-2,2-diphenylacetonitrile 40

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 ^{o}C. $[\alpha]_D^{20}$: +52.30 (*c*: 1.0g/100 mg, $CHCl_3$). IR (neat): 2238 cm^{-1}. ^{1}H NMR (400 MHz, C_6D_6): 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). ^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{25}H_{23}NO_2$: C, 81.27; H, 6.27; N, 3.79; O, 8.66. Found: C, 81.41; H, 6.28;

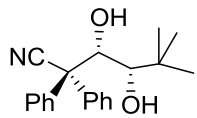
The Preparation of (*3S*, 4S)-3-hydroxy-5,5-dimethyl-2,2-diphenyl-4-(trimethylsilyloxy)hexanenitrile 41**

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 H_2 (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}. ^{1}H NMR (400 MHz, $CDCl_3$): 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). ^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{23}H_{31}NO_2Si$: C, 72.39; H, 8.19; N, 3.67; O, 8.39; Si, 7.36, Found: C, 72.63; H, 8.22



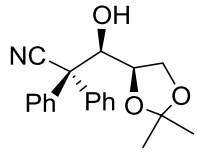
The Preparation of (*3S*, 4S)-3,4-dihydroxy-5,5-dimethyl-2,2-diphenylhexanenitrile 42**

(*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_2O= 70:30) to get pure (*3S*, 4S**)-3,4-dihydroxy-5,5-dimethyl-2,2-diphenylhexanenitrile **42** (82 mg, yield: 95%)

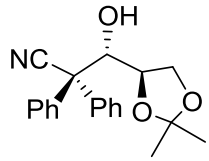
42: White solid. mp: 63-70 ^oC. IR (neat): 3440 (b), 2242 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.82 (s, 9H), 1.99 (d, *J*=5.2 Hz, 1H, OH), 3.50 (d, *J*=4.4 Hz, 1H), 3.85(d, *J*=8.0 Hz, 1H, OH), 4.70 (d, *J*=8.4 Hz, 1H), 7.28-7.48 (complex pattern, 8H), 7.60 (d, *J*=7.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 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%).



43: White solid. mp: 104-108 °C. $[\alpha]_D^{20}$:-103.6 (*c*: 0.5g/100 mg, $CHCl_3$). IR (KBr): 3431, 2252 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ =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). ^{13}C NMR (100 MHz, $CDCl_3$): δ =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.

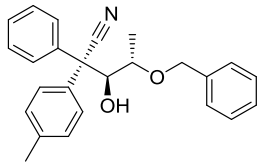


44: White solid. mp: 137-139 °C. $[\alpha]_D^{20}$: +67.6 (*c*: 0.5 g/100 mg, $CHCl_3$). IR (KBr): 3439, 2252 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ =1.25 (s, 3H) , 1.40 (s, 3H), 2.56 (d, *J*=3.2 Hz, 1H, OH), 3.87 (dd, J_1=6.0 Hz, J_2 =8.4 Hz, 1H), 3.99 (dt, J_1=2.8 Hz, J_2=6.4 Hz, 1H), 4.14 (dd, J_1=6.8 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). ^{13}C NMR (100 MHz, $CDCl_3$): δ =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.

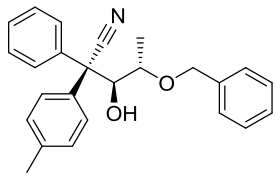
The Preparation of (*2S, 3S, 4S*)/(*2R, 3S, 4S*)-4-(benzyloxy)-2-phenyl-2-*p*-tolyl-3-(trimethylsilyloxy)pentanenitrile 45a/46a (identified as the corresponding monohydroxy derivatives 45a[1] and 46a[1] see below)

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℃. Then a solution of 2-phenyl-2-*p*-tolylacetonitrile (**2c**) (207 mg, 1.0 mmol) in THF (1 ml) was dropped into the base solution at -78℃. 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_{aq} and 5 ml of acetonitrile. The resulting homogeneous solution was kept at r.t. for 30 mins and neutralized with iced satured solution of $NaHCO_3$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 × 3). The organic phase was dried with anhydrous Na_2SO_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**[1] and **46a**[1] in 58% overall yields (214 mg**)** and in a ratio of 50/50 as determined by HPLC and ^{1}H NMR spectra. The inseparable diastereomeric mixture arising from flash chromatography was crystalyzed from ACN:H_2O=99:1 allowing the separation of a pure isomer to which has been attributed, arbitrarly, the structure **45a**[1] while the **46a**[1] remained in the mother liquorin mixture with **45a**[1]. Because an easily retro reaction takes place no further efforts were made to isolate pure **46a**[1] and its spectral data were deducted from the mixture.



45a[1]: White solid; mp: 95-98°C. $[\alpha]_D^{20}$: +99.5 (*c*: 1.0g/100 mg, $CHCl_3$). IR (neat): 2238 cm^{-1}. ^{1}H NMR (400 MHz, CD_3OD): δ =1.20 (d, *J*=6.8 Hz, 3H), 2.30 (s, 3H), 3.37 (dq, J_1=2.0 Hz, J_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). ^{13}C NMR (100 MHz, CD_3OD): δ =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_3+H]. Elemental Analysis: Calcd. for $C_{25}H_{25}NO_2$: C, 80.83; H, 6.78; N, 3.77; O, 8.61; Found: C, 81.03; H, 6.80.

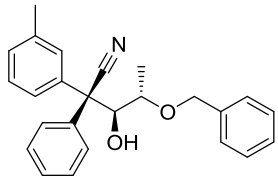


46a[1]: IR (neat): 2238 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ =1.19 (d, *J*=6.8 Hz, 3H), 2.26 (s, 3H), 3.65 (d, *J*= 9.6 Hz, 1H, OH), 3.53 (dq, J_1=2.0 Hz, J_2=6.4 Hz, 1H), 4.38 (dd, J_1=2.0 Hz, J_2=9.6 Hz, 1H), 4.41 (d, *J*=10.8 Hz, 1H), 4.52 (d, *J*=10.8 Hz, 1H), 7.16 (d, *J*=7.6 Hz, 2H), 7.29-7.40 (complex pattern, 10H), 7.46 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ =17.95, 20.98, 56.68, 71.22, 72.67,

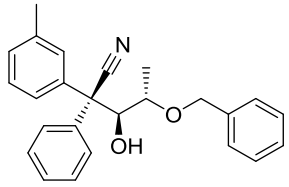
77.50, 121.00, 127.25, 127.81, 127.94, 128.09, 128.19, 128.57, 129.00, 129.72, 136.28, 137.48, 137.87, 139.45. MS (EI): m/z=357 [M-CH_3+H].

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 monohydroxydertivatives 45b[1] and 46b[1](see below)

Following the same procedure of **45a[1]**/**46a[1]**, 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 **45b[1]** and (*2R, 3S, 4S*)-4-(benzyloxy)-2-phenyl-2-*m*-tolyl-3-(trimethylsilyloxy)pentanenitrile **46b[1]** 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 arbitrarly attributed to **46b[1]**.



45b[1]: Colorless oil. IR(neat): 2238 cm^{-1}. ^{1}H NMR (400 MHz, $(CD_3)_2SO/D_2O$): δ =1.13 (d, *J*=6.4 Hz, 3H), 2.17 (s, 3H), 3.14 (dq, J_1=6.0 Hz, J_2=1.2 Hz, 1H), 3.85 (d, *J*=12.0 Hz, 1H), 4.36 (d, *J*=12.0 Hz, 1H), 4.58 (d, *J*=1.2 Hz, 1H), 7.11 (m, 1H), 7.18-7.38 (complex pattern, 13H). ^{13}C NMR (100 MHz, $(CD_3)_2SO/D_2O$): δ= 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-CH_3+H].

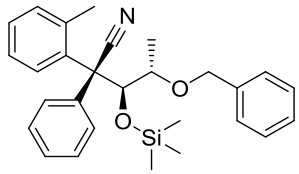


46b[1]: Colorless oil. IR(neat): 2238 cm^{-1}. ^{1}H NMR (400 MHz, $(CD_3)_2SO/D_2O$): δ =1.13 (d, *J*=6.0 Hz,3H), 2.28 (s, 3H), 3.14 (dq, J_1=6.0 Hz, J_2=1.2 Hz, 1H), 3.89 (d, *J*=12.0 Hz, 1H), 4.33(d, *J*=12.0 Hz, 1H), 4.56 (d, *J*=1.2 Hz, 1H), 7.08(m, 2H), 7.23-7.38 (complex pattern, 10H), 7.54 (d, *J*=7.6 Hz, 2H). ^{13}C NMR (100 MHz, $(CD_3)_2SO/D_2O$): δ=16.01, 21.30, 56.59, 70.25, 74.10, 75.67,

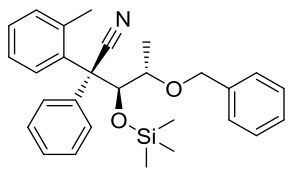
121.98, 124.27, 127.03, 127.44, 127.74, 127.90, 128.26, 128.34, 128.76, 128.92, 138.04, 138.70, 139.13, 140.99. MS (EI): m/z=357 [M-CH_3+H].

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}. ^1H 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 $C_{28}H_{33}NO_2Si$: C, 75.80; H, 7.50; N, 3.16; O, 7.21; Si, 6.33; Found: C, 76.00; H, 7.52.

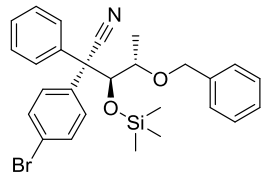


46c: Colorless oil. $[\alpha]_D^{20}$: -57.90 (*c*: 1.0g/100 mg, $CHCl_3$). IR (neat): 2237cm^1. ^1H NMR (400 MHz, $CDCl_3$): δ=-0.11 (s, 9H), 1.18 (d, *J*=6.0 Hz, 3H), 2.20 (s, 3H), 3.85 (dq, J_1=4.4 Hz, J_2=6.0 Hz, 1H), 4.35 (d, *J*=12.0 Hz, 1H), 4.46 (d, *J*=12.0 Hz, 1H), 4.63 (d, *J*=4.4 Hz, 1H), 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,

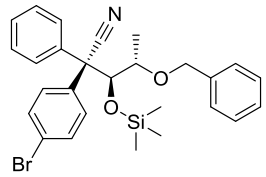
128.59, 133.04, 135.97, 137.65, 138.44, 138.58. MS (EI): m/z=443[M]. Elemental Analysis: Calcd. for $C_{28}H_{33}NO_2Si$: C, 75.80; H, 7.50; N, 3.16; O, 7.21; Si, 6.33; Found: C, 75.94; H, 7.51.

The Preparation of (*2S, 3S, 4S*)/(*2R, 3S, 4S*)-4-(benzyloxy)-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-(benzyloxy)propanal **31b** (164 mg, 1.0 mmol), a mixture of (*2S, 3S, 4S*)-4-(benzyloxy)-2-(4-bromophenyl)-2-phenyl-3-(trimethylsilyloxy)pentanenitrile **45d** and (*2R, 3S, 4S*)-4-(benzyloxy)-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 arbitrarly 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}. ^1H 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 $C_{27}H_{30}BrNO_2Si$: 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.

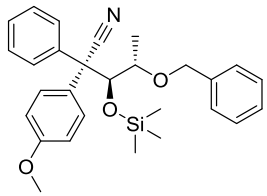


46d: colorless oil. IR(neat): 2239 cm^{-1}. ^1H NMR (400 MHz,$CDCl_3$): δ =0.01 (s, 9H),1.35 (d, *J*=6.0 Hz, 3H), 3.83 (dq, J_1= 4.4 Hz, J_2=6.0 Hz, 1H), 4.44 (d, *J*=12.0 Hz, 1H), 4.65 (d, *J*=12.0 Hz, 1H), 4.68 (d, *J*=4.4 Hz, 1H),7.36-7.62 (complex pattern, 12H), 7.85(m, 2H). ^{13}C NMR (100 MHz,

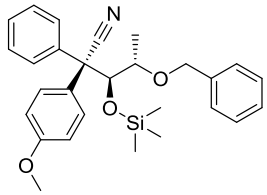
$CDCl_3$): δ =0.00, 16.79, 58.95, 70.52, 75.35, 81.01, 121.10, 127.12,127,47, 127.49, 128.79, 127.93, 128.57, 129.22, 131.39, 136.63, 137.59, 138.02, 144.75. MS (EI): m/z=530 [$M+Na^+$].

The Preparation of (*2S, 3S, 4S*)/(*2R, 3S, 4S*)-4-(benzyloxy)-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-(benzyloxy)propanal **31b** (164 mg, 1.0 mmol), (*2S, 3S, 4S*)-4-(benzyloxy)-2-(4-methoxyphenyl)-2-phenyl-3-(trimethylsilyloxy)pentanenitrile **45e** and (*2R, 3S, 4S*)-4-(benzyloxy)-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 ^oC. $[\alpha]_D^{20}$:+15.89 (*c*:8.75 g/100 ml, $CHCl_3$). IR (neat): 2242 cm^{-1}. ^1H NMR (400 MHz,$CDCl_3$): δ =-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,$CDCl_3$): δ =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 $C_{28}H_{33}NO_3Si$: C, 73.16; H, 7.24; N, 3.05; O, 10.44; Si, 6.11, Found: C, 73.26; H, 7.25.

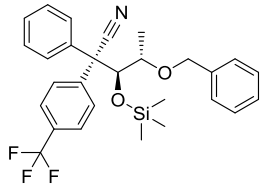


46e: Colorless oil. $[\alpha]_D^{20}$: + 3.5(*c*: 1.0g/100 mg, $CHCl_3$). IR (neat): 2242 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ =-0.17 (s, 9H), 1.13 (d, *J*=6.4 Hz, 3H), 3.70 (dq, J_1=6.4 Hz, J_2=4.0 Hz, 1H), 3.79 (s, 3H), 4.32 (d, *J*=12.4 Hz, 1H), 4.42 (d, *J*=12.4 Hz, 1H), 4.50 (d, *J*=4.0 Hz, 1H), 6.85 (d, *J*=9.2 Hz,

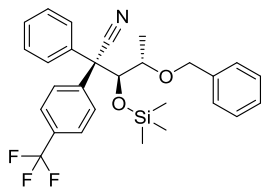
2H), 7.22-7.41 (complex pattern, 10H), 7.65 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ =0.19, 17.35, 55.30, 56.61, 71.00, 75.90, 81.35, 113.97, 121.60, 127.21, 127.71, 127.75, 128.00, 128.08, 128.54, 128.80, 130.63, 138.42, 138.52, 158.98. MS (EI): m/z=459 [M]. Elemental Analysis: Calcd. for $C_{28}H_{33}NO_3Si$: 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 arbitrarly attributed the stereochemistry reported and its spectral data were deducted from the mixture reporting the major set of signals.



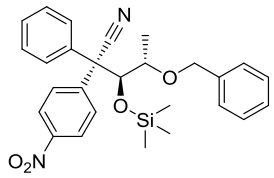
45f: IR(neat): 2239 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ =-0.10 (s, 9H), 1.25 (d, *J*=6.4 Hz, 3H), 3.87 (dq, J_1=4.4 Hz, J_2=6.4 Hz, 1H), 4.36 (d, *J*=11.6 Hz, 1H), 4.52 (d, *J*=11.6 Hz, 1H), 4.63 (d, *J*=4.4 Hz, 1H), 7.25-7.53 (complex pattern, 9H), 7.66 (m, 3H), 7.97 (d, *J*=8.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{28}H_{30}F_3NO_2Si$: 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.



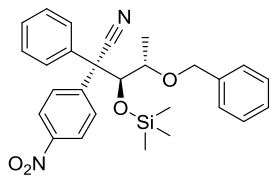
46f: IR(neat): 2239 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ =-0.08 (s, 9H), 1.29 (d, *J*=6.4 Hz, 3H), 3.74 (dq, J_1=4.0 Hz, J_2=6.4 Hz, 1H), 4.32 (d, *J*=12.0 Hz, 1H), 4.57 (d, *J*=12.0 Hz, 1H), 4.66 (d, *J*=4.0 Hz, 1H), 7.25-7.53 (complex pattern, 9H), 7.66 (m, 3H), 7.79 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 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. $[\alpha]_D^{20}$: +26.08 (*c*: 1.3g/100 mg, $CHCl_3$). IR (neat): 2243cm^{-1}. ^1H NMR (400 MHz,$CDCl_3$): δ =-0.17 (s, 9H), 1.19 (d, *J*=6.4 Hz, 3H), 3.87 (dq, J_1=6.4 Hz, J_2=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). ^{13}C NMR (100 MHz,$CDCl_3$): 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 $C_{27}H_{30}N_2O_4Si$: C, 68.33; H, 6.37; N, 5.90; O, 13.48; Si, 5.92, Found: C, 68.13; H, 6.35.

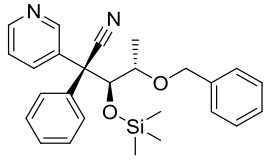


46g: White solid. mp: 130-133 °C. $[\alpha]_D^{20}$: +18.47 (*c*: 1.1g/100 mg, $CHCl_3$). IR (neat): 2242 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ =-0.12 (s, 9H), 1.26 (d, *J*=6.4 Hz, 3H), 3.66 (dq, J_1=6.4 Hz, J_2=4.0

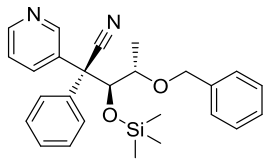
Hz, 1H), 4.21 (d, *J*=12.0 Hz, 1H), 4.52 (d, *J*=12.0 Hz, 1H), 4.62 (d, *J*=4.0 Hz, 1H), 7.26 (m, 4H), 7.42 (m, 4H), 7.66 (d, *J*=8.8 Hz, 2H), 7.71 (d, *J*=8.0 Hz, 2H), 8.13 (d, *J*=8.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ =0.15, 16.57, 57.11, 70.49, 75.46, 81.10, 120.68, 123.57, 127.46, 127.65, 127.74, 127.97, 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 $C_{27}H_{30}N_2O_4Si$: 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. $[\alpha]_D^{20}$: +18.40 (*c*: 1.0g/100 mg, $CHCl_3$). IR (neat): 2240 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ =-0.04 (s, 9H), 1.28 (d, *J*=6.4 Hz, 3H), 3.90 (dq, J_1=6.4 Hz, J_2=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, J_1=1.2 Hz, J_2=4.4 Hz, 1H), 9.13 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{26}H_{30}N_2O_2Si$: C, 72.52; H, 7.02; N, 6.51; O, 7.43; Si, 6.52, Found: C, 72.72; H, 7.04.

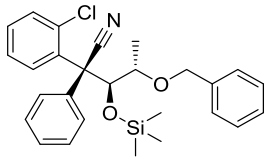


46h: White solid. mp: 59-64 ^{o}C. $[\alpha]_D^{20}$: +12.80 (*c*: 1.1g/100 mg, $CHCl_3$). IR (neat): 2242 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ =-0.04 (s, 9H), 1.33 (d, *J*=6.0 Hz, 3H), 3.78 (dq, J_1=6.0 Hz, J_2 =4.4

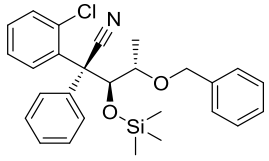
Hz, 1H), 4.35 (d, *J*=11.6 Hz, 1H), 4.59 (d, *J*=11.6 Hz, 1H), 4.68(d, *J*=4.4 Hz,1H), 7.31-7.58 (complex pattern, 11H), 7.83 (d, *J*=7.6 Hz, 2H), 7.91 (m, 1H), 8.63 (dd, J_1=1.2 Hz, J_2=4.8 Hz, 1H), 8.85 (d, *J*=2.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ =0.09, 16.83, 55.41, 70.70, 75.75, 81.28, 120.66, 123.30, 127.36, 127.65, 128.10, 128.13, 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 $C_{26}H_{30}N_2O_2Si$: 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 (*2S, 3S, 4S*)/(*2R, 3S, 4S*)-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), (*2S, 3S, 4S*)-4-(benzyloxy)-2-(2-chlorophenyl)-2-phenyl-3-(trimethylsilyloxy)pentanenitrile **45i** and (*2R, 3S, 4S*)-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 $C_{27}H_{30}ClNO_2Si$: 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.

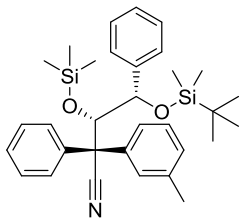


46i: Colorless oil. $[\alpha]_D^{20}$: +46.90 (*c*: 1.8g/100 mg, $CHCl_3$). IR (neat): 2240 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ =-0.04 (s, 9H), 1.21 (d, *J*=6.4 Hz, 3H), 3.58 (dq, J_1=6.4 Hz, J_2=4.0 Hz, 1H), 4.14 (d,

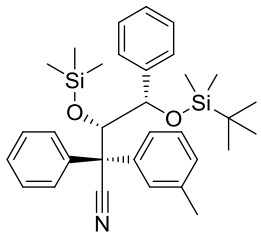
J=11.6 Hz, 1H), 4.42 (d, *J*=11.6 Hz, 1H), 5.10 (d, *J*=4.0 Hz, 1H), 7.14-7.38 (complex pattern, 11H), 7.54 (m, 1H), 7.64 (d, *J*=6.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ =0.45, 16.99, 56.38, 70.79, 76.53, 78.51, 120.63, 126.64, 127.18, 127.38, 128.00, 128.08, 128.30, 129.07, 129.28, 131.77, 131.93, 133.31, 135.90,136.79, 138.46. MS (EI): m/z= 448 [M-CH_3]. Elemental Analysis: Calcd. for $C_{27}H_{30}ClNO_2Si$: 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*-tolyl-3-(trimethylsilyloxy)butanenitrile 45j/46j

Following the same procedure of A, starting from2-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%)



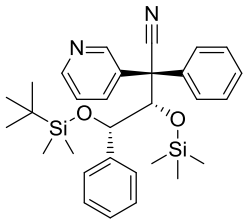
45j: IR(neat): 2245 cm^{-1}. ^{1}H NMR (400 MHz, CD_3OD): δ =-0.59 (s, 9H), -0.55 (s, 3H), -0.38 (s, 3H), 0.06 (s, 9H), 2.32(s, 3H), 4.95 (d, *J*=2.0 Hz, 1H), 5.16 (d, *J*=1.6 Hz, 1H), 7.06 (d, *J*=11.6 Hz, 1H), 7.20-7.45 (complex pattern, 9H), 7.53 (m, 2H), 7.74 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{32}H_{43}NO_2Si_2$: C, 72.54; H, 8.18; N, 2.64; O, 6.04; Si, 10.60; Found: C, 72.74; H, 8.20.



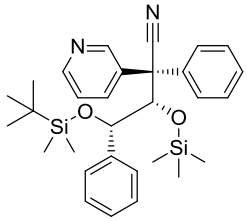
46j: (50%) IR(neat): 2245 cm^{-1}. ^1H NMR (400 MHz, CD_3OD): δ =-0.59 (s, 9H), -0.54 (s, 3H), -0.38 (s, 3H), 0.06 (s, 9H), 2.36 (s, 3H), 4.93 (d, *J*=2.0 Hz, 1H), 5.15 (d, *J*=1.2 Hz, 1H), 7.13 (d, *J*=11.6 Hz, 1H), 7.20-7.45 (complex pattern, 9H), 7.53 (m, 2H), 7.74 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ =-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, 138.54, 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_2Cl_2 : ether=99:1) (197 mg, ratio:80/20, yield: 40%). The absolute configuration of the isomer **45k** was established by X-Ray analysis.



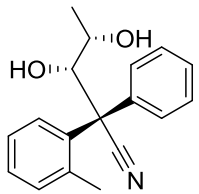
45k: White solid. mp:104-107°C. $[\alpha]_D^{20}$: + 3.1(*c*: 1.0g/100 mg, $CHCl_3$). IR (neat): 2246 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ =-0.47 (s, 9H), -0.41 (s, 3H), -0.27 (s, 3H), 0.86 (s, 9H), 4.71 (d, *J*= 2.4 Hz, 1H), 5.13 (d, *J*= 2.4 Hz, 1H), 7.23-7.45 (complex patern, 11H), 8.05 (m, 1H), 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, $CDCl_3$): δ =-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 $C_{30}H_{40}N_2O_2Si_2$: C, 69.72; H, 7.80; N, 5.42; O, 6.19; Si, 10.87; Found: C, 69.80; H, 7.81.



46k: White solid. mp: 88-92 °C. $[\alpha]_D^{20}$: + 18.3 (*c*: 1.0g/100 mg, $CHCl_3$). IR (neat): 2246 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ =-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, $CDCl_3$): δ =-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 $C_{30}H_{40}N_2O_2Si_2$: C, 69.72; H, 7.80; N, 5.42; O, 6.19; Si, 10.87; Found: C, 69.51; H, 7.77.

The Prearation of (*2S, 3S, 4S*)-3,4-dihydroxy-2-phenyl-2-*o*-tolylpentanenitrile 47

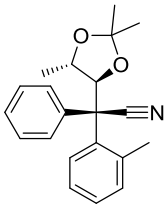
(*2S, 3S, 4S*)-4-(benzyloxy)-2-phenyl-2-o-tolyl-3-(trimethylsilyloxy)pentanenitrile **45c** (120 mg) and Pd/C 10% (120 mg) were mixted into 10 ml of anhydrous MeOH. The reaction mixture was kept under H_2 (50psi) for overnight. Then the reaction mixture was filtered and concentrated to get crude product 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*: 1.1g/100 mg, $CHCl_3$). IR (neat): 3444 (b), 2241 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ =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, $CDCl_3$): δ = 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.

The Prearation of (*S*)-2-phenyl-2-*o*-tolyl-2-((*4S,5S*)-2,2,5-trimethyl-1,3-dioxolan-4-yl)acetonitrile 48

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



48: mp: 95-99 ℃. $[\alpha]_D^{20}$: +126.94 (*c*: 1.6 g/100 mg, $CHCl_3$). IR (neat): 2239 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ =0.34 (d, *J*=5.2 Hz, 3H), 1.54 (s, 3H), 1.57 (s, 3H), 2.07 (s, 3H), 4.27 (dq, J_1=5.2 Hz, J_2=7.6 Hz, 1H), 4.34 (d, *J*=8.0 Hz, 1H), 7.13 (d, *J*=7.2 Hz, 1H) , 7.26-7.37 (complex pattern, 7H), 7.82 (dd, J_1=7.6 Hz, J_2=0.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ =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): m/z= 321 [M]. Elemental Analysis: Calcd. for $C_{21}H_{23}NO_2$: C, 78.47; H, 7.21; N, 4.36; O, 9.96, Found: C, 78.49; H, 7.21.

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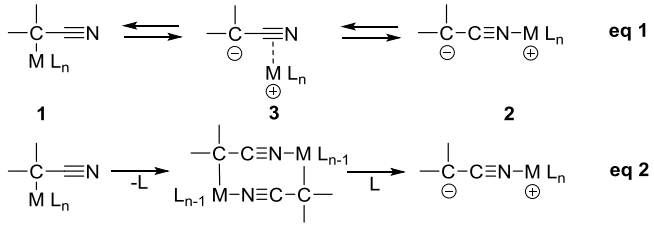
Chapter 3. Synthesis and applications of N-tin ketene imines and α-trimethyltin nitriles

3.1 Introduction: State of the art.

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



Scheme 3.1 the prediated methalated nitrile anionic chameleons.

Lithiated nitriles (lithium reagents are widely used for α-deprotonation of nitriles[4]) demonstrate an inherent propensity for planar, nitrogen coordinated dimers in the solid state[5] 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 alkylnitriles, 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 enphasized.

Tin and germanium belong, with silicon, to the same group (group 4a metal) of the Mendelev Table. We have already discussed about the reactivity of lithiated nitriles with chloro alkyl 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*-germannium ketene imine and α-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.

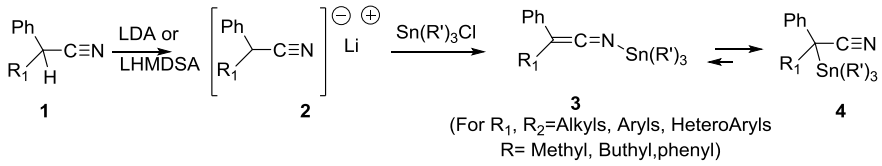
3.2 Present work

3.2.1 Synthesis and application of N-tin ketene imines

3.2.1.1 Synthesis of *N*-tin ketene imines

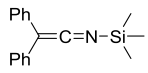
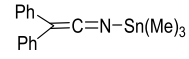
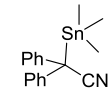
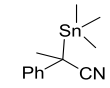
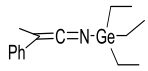
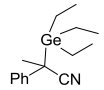
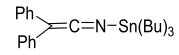
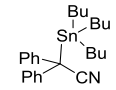
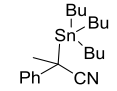
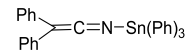
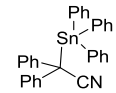
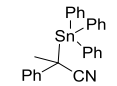
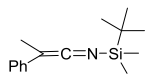
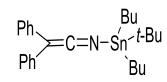
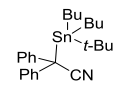
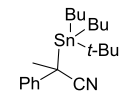
The first attempt to prepare *N*-tin ketene imines was based on the protocol used for the preparation of *N*-silyl ketene imines (see Chapter 2). In a preliminary study, diphenylacetonitrile was treated with lithium diisopropyl amide at -78 ℃ in a suitable solvent. The corresponding carbanion was treated 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*-trisustituted tin ketene imine was then attempted, even

with a very bulkyl 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.

	Known products		Prepared products		
	Ketene imine	α-tin nitrile	Ketene imine	α-tin nitrile	
Structures					
			3aa	**4aa**	**4ba**
IR(cm^{-1})	2038	2215	2102	2207	2202
Structures					
			3ab	**4ab**	**4bb**
IR(cm^{-1})	2068	2218	2104	2206	2194
Structures					
	-	-	**3ac**	**4ac**	**4bc**
IR(cm^{-1})	-	-	2107	2209	2207
Structures					
		-	**3ad**	**4ad**	**4bd**
IR(cm^{-1})	2034	-	2089	2207	2203

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

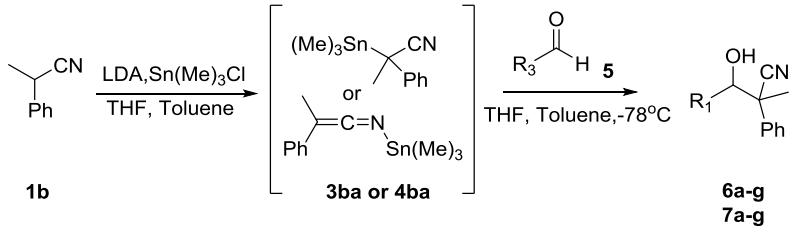
term of acidity, basicity and steric hindrance of the substituents on the tin. As a matter of fact, as anticipated in the case of germanium[12] and silyl by other authors,[17] a mixture of *N*-tin and *C*-tin may be present in the reaction medium (Scheme 3.2), arising from a tropism of the metal from the nitrogen to the carbon.

N-Tin ketene imines **3 (**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 α-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 *α-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 α-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 α-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 α-tin nitriles in aldol type reaction with aldehydes, ketones and α, β unsaturated carbonyl compounds

Due to their broad range of applications, β-hydroxy nitriles play an important role in organic chemistry.[18] Their synthesis is usually achieved by reaction of a metallated nitriles and an aldehyde or a ketones.[19] 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.[20] 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 *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

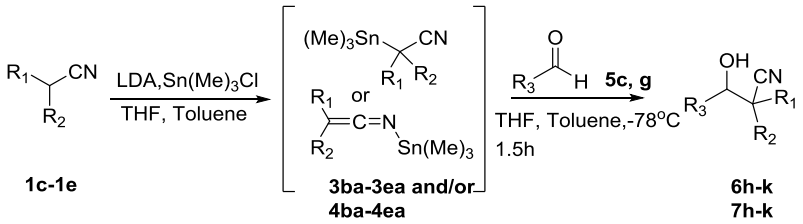
Entry	*N*-tin ketene imine[#]	Aldehydes	Products	Yield[$](%)	6:7[&]
1	**3ba**	R_3= *i*-propyl**(5a)**	**6a, 7a**	64	83:17
2	**3ba**	R_3= *t*-butyl**(5b)**	**6b, 7b**	54	85:15
3	**3ba**	R_3= phenyl**(5c)**	**6c, 7c**	70	85:15
4	**3ba**	R_3= 4-$MeOC_6H_4$**(5d)**	**6d, 7d**	73	85:15
5	**3ba**	R_3= 4-$NO_2C_6H_4$**(5e)**	**6e, 7e**	56	65:35
6	**3ba**	R_3=3-Pyridine**(5f)**	**6f, 7f**	56	77:23
7	**3ba**	R_3= 2-fural**(5g)**	**6g, 7g**	71	85:15

: 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.

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 (table3.2 entries 3-5), and hetereocyclic 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.



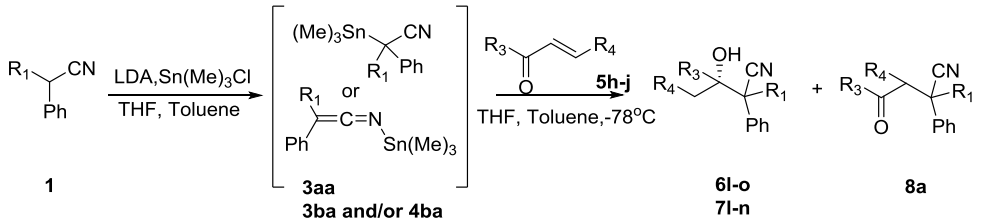
Scheme 3.4 *N*-tin ketene imines as an in-situ intermediate react with aldehydes.

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

Entry	*N*-tin ketene imine[#]	aldehydes	products	Yield[$] (%)	ratio[&] (**6** : **7**)
1	R_1=Ph, R_2=*i*-pr**(3ca)**	R_3= 2-fural**(5g)**	**6h, 7h**	69	86:14
2	R_1=Ph, R_2=Allyl**(3da)**	R_3= 2-fural**(5g)**	**6i, 7i**	67	84:16
3	R_1=Ph, R_2=Allyl**(3da)**	R_3= phenyl**(5c)**	**6j, 7j**	54	76:24
4	R'=Ph, R_2=*i*-Butyl**(3ea)**	R_3= 2-fural**(5g)**	**6k, 7k**	64	85:15
5	Cyclohexyl**(3fa)**	R_3= 2-fural**(5g)**	-	0	0

: 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 ^{1}HNMR, 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, predomintaly, the 1, 4 addition products(**8a**).



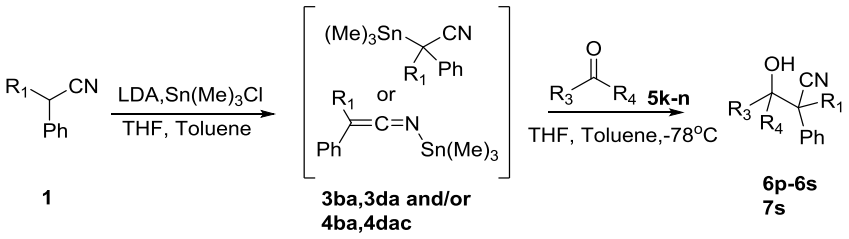
Scheme 3.5 *N*-tin ketene imines as an in-situ intermediate react with α,β-unsaturated carbonyl compounds

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

Entry	*N*-tin ketene imine[#]	Aldehyde(R_3, R_4)	Products	Yield[$] (%)	Ratio[&] (**6** : **7**)	Ratio[&] (**6**,**7**:**8a**)
1	R_1=Me**(3ba)**	R_3=H, R_4=Me**(5h)**	**6l, 7l**	70	60:40	-
2	R_1=Me**(3ba)**	R_3=H, R_4=Ph**(5i)**	**6m, 7m**	78	62:38	-
3	R_1=Me**(3ba)**	 **(5j)**	**6n, 7n** **8a**	53	-	1:24
4	R_1=Ph**(3ba)**	R_3=H R_4=Ph**(5i)**	**6o**	33	-	-

#: 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.

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.

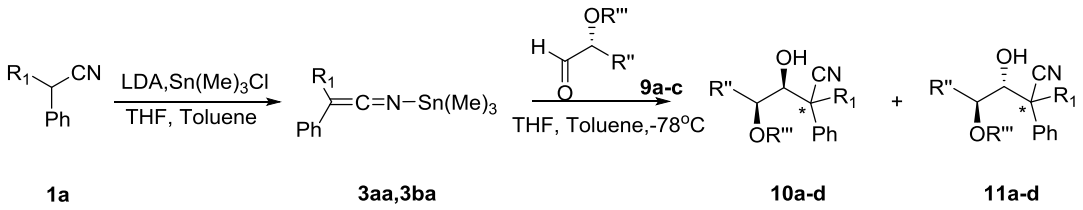
Table 3.5 *N*-tin ketene imines as an in-situ intermediate react with ketones.

Entry	*N*-tin ketene imine[#]	Ketones(5k-n)	Products	Reaction time(h)	Yield[$] (%)
1	R'=Me**(3ba)**	Cyclohexanone(**5k**)	**6p**	2h	74
2	R'=Me**(3ba)**	Cyclopentanone(**5l**)	**6q**	2h	67
3	R'=Allyl**(3da)**	Cyclohexanone(**5k**)	**6r**	2h	89
4	R'=Me**(3ba)**	Acetophenone(**5m**)	**6s, 7s**[&]	4h	73
5	R'=Me**(3ba)**	Benzophenone(**5n**)	-	48h	0

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

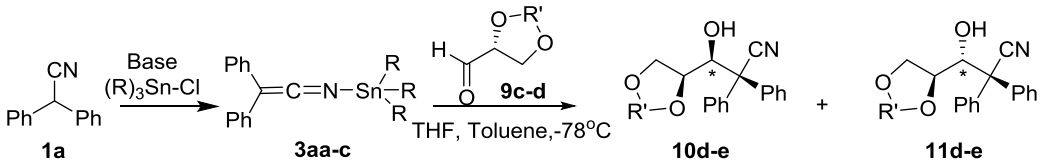
3.2.1.3 Application of *N*-tin ketene imines, generated in situ from lithium enolate of diphenyl acetonitrile and trimethyl tin chloride to the synthesis of Carbon sugar analogues through aldol type reaction with α-hydroxy protected aldehydes.

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 α-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, enty 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.[26] 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*-butylliuthium and lithium bis-trimethylsilylamide.

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

Entry	*N*-tin ketene imine[#]	Aldehyde(R'', R''')	Products	Yield[$] (%)	Ratio[&] (**10**:**11**)
1	**3aa**	R''=Bn ,R'''=methyl**(9a)**	**10a, 11 °**	71	80:20
2	**3ba**	R''=Bn, R'''=methyl**(9a)**	**10b, b'** **11b, b'**	55	64:36
3	**3aa**	R''=TBS, R'''=methyl**(9b)**	**11c**	45	99:1
4	**3aa**	 **(9c)**	**10d,** **11d**	61	77:23

#: 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.

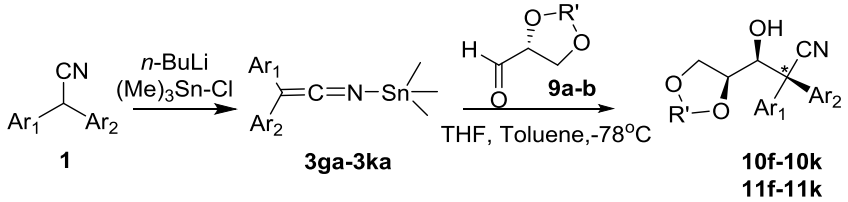
Then, different tin chloride were used for formation of different tin ketene imines. Among them, *N*-trimethyl tin ketene imine **(3aa)** gave the best results on isolated yields and

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 ^{1}HNMR, 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**)[27, 28] 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.

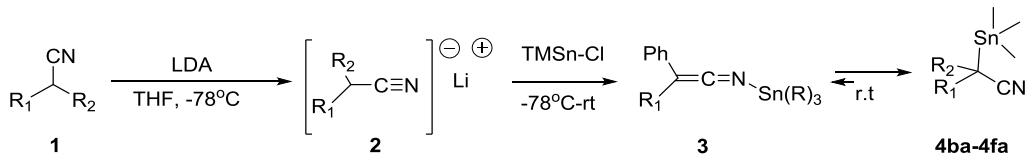
Entry	*N*-tin ketene imines[#]	**9**	Products	Yield%[$]	Ratio[&] (**10**:**11**)	Ratio[&*] (**Ismer B : Isomer A**)	
						In minor	In major
1	Ar_1=Ph, Ar_2=4-MePh**(3ga)**	*i*-Pr**(9a)**	**10f, 11f**	41	85:15	50:50	54:46
2	Ar_1=Ph, Ar_2=4-MePh**(3ga)**	*c*-Hex**(9b)**	**10g, 11g**	17	86:14	78:32	50:50
3	Ar_1=Ph, Ar_2=4-OMePh**(3ha)**	*i*-Pr**(9a)**	**10h, 11h**	21	82:18	54:46	63:37
4	Ar_1=Ph, Ar_2=3-MePh**(3ia)**	*i*-Pr**(9a)**	**10i, 11i**	28	70:30	54:46	50:50
5	Ar_1=4-OMePh, Ar_2=4-OMePh**(3ja)**	*i*-Pr(**9a)**	**10j, 11j**	28	73:27	-	-
6	Ar_1=Ph, Ar_2=4-NO_2Ph**(3ka)**	*c*-Hex**(9b)**	**10k, 11k**	13	60:40	77:23	53:47
7	Ar_1=Ph, Ar_2=3-Py**(3la)**	*i*-Pr**(9a)**	**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; $: 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

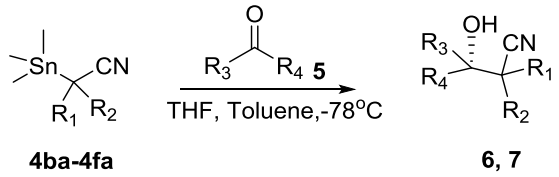
α- tin nitriles were prepared from acetonitriles **1** (Scheme 3.10), methalated by lithium reagent (LDA), and then trap with tin chloride, the reaction mixture were warmed to r.t for 2 hours. The reaction solvents were removed under vacuum, the residues was dissolved into pentane, filter under N_2, 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.



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,[14, 23] 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[29] and organostannyl addition to carbonyl compounds.[30] 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 (enties 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 α- trimethyltin nitriles react with carbonyl compounds

Entry	**4**	**5**	product	Yield[#]%	Yield[$]%	Rati[&] (**6** :**7**)	Ratio[*] (**6** : **7**)
1	R_1=Ph, R_2=Me**(4ba)**	R_3=2Furan, R_4=H**(5g)**	**6g, 7g**	72	71	72:18	85:15
2	R_1=Ph, R_2=Allyl**(4da)**	R_3=2-Furan, R_4=H**(5g)**	**6i, 7i**	78	67	60:40	84:16
3	R_1=Ph, R_2= *i*-Pr**(4ca)**	R_3=2-Furan, R_4=H**(5g)**	**6h, 7h**	89	69	73:27	86:14
4	R_1=Ph, R_2=*i*-Bu**(4ea)**,	R_3=2-Furan, R_4=H**(5g)**	**6k, 7k**	69	64	60:40	85:15
5	R_1=Ph, R_2=Me**(4ba)**	Acetophenone**(5l)**	**6s, 7s**	21	73	-	-
6	R_1=Ph, R_2=Me**(4ba)**	Cyclohexanone**(5j)**	**6p**	25	74	-	-
7	Cyclohexyl**(4fa)**	R_3=2-Furan, R_4=H**(5g)**	**No reaction**	0	0	-	-

#: 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^o 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,[32] compound **6b** and **7b** can be identified accordingly, the configuration of **6l, 7l, . 6m, 7m** were assigned according to reference 33.[33]

Table 3.10 Aromatic aldehydes: Identification of aromatic aldehyde

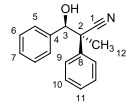
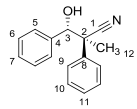
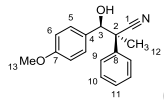
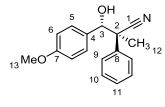
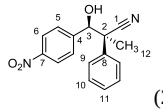
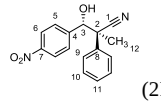
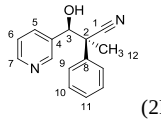
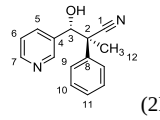
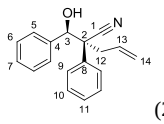
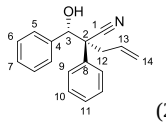
Products	Products	^{1}H δ 3^o, ^{1}H δ 12^o	Polarity
7c	 (2R*, 3R*)	^{1}H δ 3^o: 4.834 ^{1}H δ 12^o: 1.864	More polar
6c	 (2R*, 3S*)	^{1}H δ 3^o: 4.878 ^{1}H δ 12^o: 1.608	Less polar
7d	 (2R*, 3R*)	^{1}H δ 3^o: 4.814 ^{1}H δ 12^o: 1.854 ^{1}H δ 13^o: 3.767	More polar
6d	 (2R*, 3S*)	^{1}H δ 3^o: 4.824 ^{1}H δ 12^o: 1.588 ^{1}H δ 13^o: 3.807	Less polar
7e	 (2R*, 3R*)	^{1}H δ 3^o: 4.962 ^{1}H δ 12^o: 1.891	More polar
6e	 (2R*, 3S*)	^{1}H δ 3^o:5.032 ^{1}H δ 12^o: 1.668	Less polar
7f	 (2R*, 3R*)	^{1}H δ 3^o: 4.818 ^{1}H δ 12^o: 1.857	More polar
6f	 (2R*, 3S*)	^{1}H δ 3^o: 4.879 ^{1}H δ 12^o: 1.593	Less polar
7i	 (2R*, 3R*)	^{1}H δ 3^o: 4.885 ^{1}H δ 12^o: a: 3.182 b: 2.953	More polar
6i	 (2R*, 3S*)	^{1}H δ 3^o: 4.936 ^{1}H δ 12^o:a: 2.785 b: 2.597	Less polar

Table 3.11 2-furan aldehyde products ^{1}HNMR

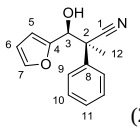
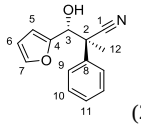
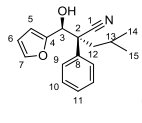
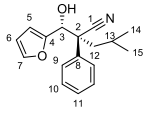
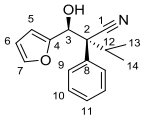
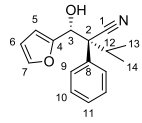
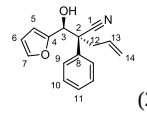
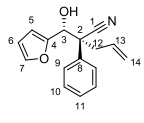
Resource	Product	δ ^{1}H 3°, 5°, 6° 12°	Polarity
7g	 (2R*, 3R*)	δ ^{1}H 3°: 4.887 δ ^{1}H 5°: 6.13 (d, *J* = 3.2 Hz) δ ^{1}H 6°: 6.25(dd, *J* = 3.6, 2.0 Hz) δ ^{1}H 12°: 1.91	More polar
6g	 (2R*, 3S*)	δ ^{1}H 3°: 4.930(s) δ ^{1}H 5°: 6.446 (d, *J* = 3.2 Hz) δ ^{1}H 6°:6.40 (dd, *J* = 3.2, 2.0 Hz) δ ^{1}H 12°:1.68	Less polar
7k	 (2R*, 3R*)	δ ^{1}H 3°: 4.839 (d, *J* = 6.8 Hz) δ ^{1}H 5°: 6.00 (d, *J* = 3.2 Hz) δ ^{1}H 6°: 6.17 (dd, *J* = 3.2, 1.6 Hz) δ ^{1}H 12°:a.2.42, b. 2.67	More polar
6k	 (2R*, 3S*)	δ ^{1}H 3°:4.914 (d, *J* = 2.4 Hz) δ ^{1}H 5°:6.512 (d, *J* = 3.2 Hz) δ ^{1}H 6°:6.41 (dd, *J* = 3.2, 2.0 Hz) δ ^{1}H 12°:a.2.017, b.1.64	Less polar
7h	 (2R*, 3R*)	δ ^{1}H 3°: 5.351. (d, *J*=7.6 Hz) δ ^{1}H 5°: 6.04 (d, *J* = 3.2 Hz) δ ^{1}H 6°: 6.241 (dd, *J* = 3.2, 1.6 Hz) δ ^{1}H 12°:2.613	More polar
6h	 (2R*, 3S*)	^{1}H 3°: 5.345 (d, *J* = 6.0 Hz) δ ^{1}H 5°: 6.089 (d, *J* = 3.2Hz) δ ^{1}H 6°: 6.240 (dd, *J* = 3.2, 1.6 Hz) δ ^{1}H 12°:2.693	Less polar
7i	 (2R*, 3R*)	δ ^{1}H 3°: 4.972 (d, *J* = 6.4 Hz) δ ^{1}H 5°: 6.078 (d, *J* = 3.2 Hz) δ ^{1}H 6°: 6.209 (dd, *J* = 3.2, 2.0 Hz) δ ^{1}H 12°: a. 3.179 b. 2.907	More polar
6i	 (2R*, 3S*)	δ ^{1}H 3°: 5.15 (d, *J* = 1.2 Hz) δ ^{1}H 5°: 6.439 (d, *J* = 3.2 Hz) δ ^{1}H 6°: 6.389 (dd, *J* = 3.2, 2.0 Hz) δ ^{1}H 12°: a. 2.822, b. 2.659	Less polar

Table 3.12 Aliphatic aldehydes products ^{1}HNMR

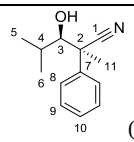
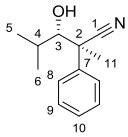
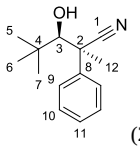
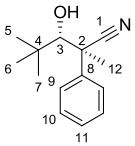
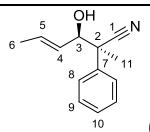
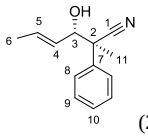
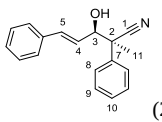
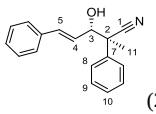
Resource	Product	^{1}H δ 3°, ^{1}H δ 12°	Polarity
7a	 (2R*, 3R*)	^{1}H δ 3°: 3.64 ^{1}H δ 11°: 1.769 ^{1}Hδ 4°: 2.024-2.066	Less polar
6a	 (2R*, 3S*)	^{1}H δ 3°:3.65 ^{1}H δ 11°: 1.849 ^{1}H δ 4°: 1.619-1.695 ^{1}H δ 5° 0.961 ^{1}H δ 6° 0.882	More polar
7b	 (2R*, 3R*)	^{1}H δ 3°: 3.660 ^{1}H δ 12°: 1.876 ^{1}H δ 5,6,7°: 0.943	Less polar
6b	 (2R*, 3S*)	^{1}H δ 3°: 3.614 ^{1}H δ 12°: 1.984 ^{1}H δ 5,6,7°: 0.864	More polar

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

Resource	Product	^{1}H δ 3°, ^{1}H δ 11°	Polarity
7l	 (2R*, 3R*)	^{1}H δ 3°: 4.240 ^{1}H δ 11°: 1.785	More polar
6l	 (2R*, 3S*)	^{1}H δ 3°: 4.214 ^{1}H δ 11°: 1.655	Less polar
7m	 (2R*, 3R*)	^{1}H δ 3°: 4.462 ^{1}H δ 11°: 1.825	More polar
6m	 (2R*, 3S*)	^{1}H δ 3°: 4.442 ^{1}H δ 11°: 1.707	Less polar

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 diatereomer. 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 α- tin nitrile

Procedure A:

n-BuLi was added into a solution of diisopropylamine in THF at -78 ^{o}C. Then a solution of starting nitrile **1** in was dropped into the base solution at -78 ^{o}C. After 5 min, a solution of trimethyltin chloride in toluene was dropped into the reaction. After maintaining at -78 ^{o}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 ^{o}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 NH_4Cl solution (15 ml) at -78^{o}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_2SO_4, remove all the solvent, made a silicon gel chromatography for purification.

Procedure B:

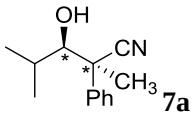
n-BuLi was added into a solution of diisopropyl amine in THF at -78 ^oC. Then a solution of starting nitrile **1** in was dropped into the base solution at -78 ^oC. After 5 min, a solution of trimethyltin chloride in toluene was dropped into the reaction. After maintaining at -78 ^oC for 15 min, then 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 ^oC, 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_2SO_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 ^oC. After 5 min, a solution of trimethyltin chloride in toluene was dropped into the reaction. After maintaining at -78 ^oC 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_4Cl solution(15 ml) at -78 ^oC, 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_2SO_4, remove all the solvent, made a silicon gel chromatography for purification.

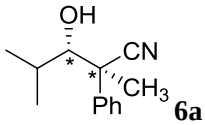
The preparation of (2R*, 3R*) 3-hydroxy-2,4-dimethyl-2-phenylpentanenitrile(7a) and (2R*,3S*)-3-hydroxy-2,4-dimethyl-2-phenylpentanenitrile[32] (6a)

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 ^oC. 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.



7a

Colorless Oil. IR (KBr): 2243 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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.

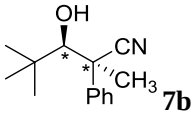


6a

White solid .mp. 61-64 ^{o}C. IR (KBr): 2243 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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.

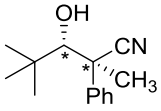
The preparation of (2R*,3R*)-3-hydroxy-2,4,4-trimethyl-2-phenylpentanenitrile (7b) and (2R*,3S*)-3-hydroxy-2,4,4-trimethyl-2-phenylpentanenitrile (6b)

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 ^{o}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** (103 103 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.



7b

White solid. mp: 60-62 °C. IR (neat): 2243 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) 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). ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{14}H_{19}NO$: C, 77.38; H, 8.81; N, 6.45; O, 7.36. Found: C, 77.52; H, 8.82.

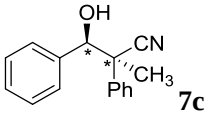


6b

White solid. mp: 116-118 °C. IR (KBr): 2243 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, *J* = 7.6 Hz, 2H), 7.36 (m, 3H), 3.61 (s, 1H), 1.98 (bs, 1H, OH), 1.88 (s, 3H), 0.86 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.38, 128.81, 128.02, 126.49, 122.61, 83.75, 47.05, 37.42, 27.67, 27.52. MS (HPLC-MS) [M+Na]: 240. Elemental Analysis: Calcd for $C_{14}H_{19}NO$: C, 77.38; H, 8.81; N, 6.45; O, 7.36. Found: C, 77.49; H, 8.82.

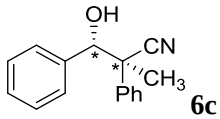
The preparation of (2R*, 3R*)-3-hydroxy-2-methyl-2,3-diphenylpropanenitrile (7c) and (2S*,3R*)-3-hydroxy-2-methyl-2,3-diphenylpropanenitrile[31 32] (6c)

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 **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 167 mg, yield: 70%. Then separate two diastereo isomer by silicon gel chromatography with dichloromethane: acetonitrile = 100:1 for identification.



7c

Light yellow oil. IR (neart): 2242 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) 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).^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{16}H_{15}NO$: C, 80.98; H, 6.37; N, 5.90; O, 6.74. Found: C, 81.10; H, 6.39.

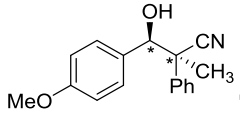


6c

White solid: mp. 96-98 °C. IR (KBr): 2242 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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) [M+Na].260. 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.

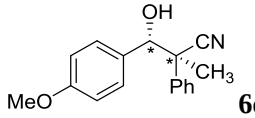
The preparation of (2R*, 3R*)-3-hydroxy-3-(4-methoxyphenyl)-2-methyl-2-phenylpropanenitrile (7d) and (2S*,3R*)-3-hydroxy-3-(4-methoxyphenyl)-2-methyl-2-phenylpropanenitrile[31] (6d)

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.



7d

White solid. mp.110-112 °C. IR (KBr): 2240 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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.

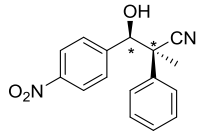


6d

White solid. mp.115-117 ^{o}C. IR (KBr): 2240 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) 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). ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24; O, 11.97. Found: C, 76.50; H, 6.42.

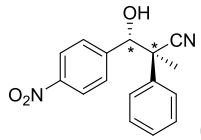
The preparation of (2R*, 3R*)-3-hydroxy-2-methyl-3-(4-nitrophenyl)-2-phenylpropanenitrile (7e) and (2S*, 3R*)-3-hydroxy-2-methyl-3-(4-nitrophenyl)-2-phenylpropanenitrile (6e)

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 ^{o}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.



7e

White solid. mp: 130-132 ^{o}C. IR (KBr): 2245 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) 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). ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{16}H_{14}N_2O_3$: C, 68.08; H, 5.00; N, 9.92; O, 17.00. Found: C, 68.7; H, 5.01.



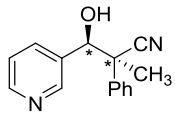
6e

White solid. mp: 174-175 ^{o}C. IR (KBr): 2245 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) 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

(s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.89, 145.21, 136.17, 128.93, 128.60, 128.25, 126.73, 122.92, 121.08, 78.99, 49.13, 21.97. MS (HPLC-MS) [M+Na].305. Elemental Analysis: Calcd for $C_{16}H_{14}N_2O_3$: C, 68.08; H, 5.00; N, 9.92; O, 17.00. Found: C, 68.13; H, 5.00.

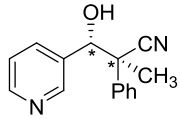
The preparation of (2R*,3R*)-3-hydroxy-2-methyl-2-phenyl-3-(pyridin-3-yl)propanenitrile (7f) and (2S*,3R*)-3-hydroxy-2-methyl-2-phenyl-3-(pyridin-3-yl)propanenitrile (6f)

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 ^{o}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.



7f

White solid. mp.160-162 ^{o}C. IR (neat): 2246 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) 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). ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{15}H_{14}N_2O$: C, 75.61; H, 5.92; N, 11.76; O, 6.71. Found: C, 75.88; H, 5.94.



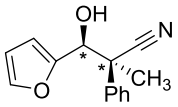
6f

White solid. mp.154-156 ^{o}C. IR (neat): 2246 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) 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). ^{13}C NMR (100 MHz, $CDCl_3$) 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).

[M+Na] 261. Elemental Analysis: Calcd for $C_{15}H_{14}N_2O$: C, 75.61; H, 5.92; N, 11.76; O, 6.71. Found: C, 75.84; H, 5.94.

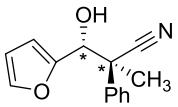
The preparation of (2SR*,3S*)-3-(furan-2-yl)-3-hydroxy-2-methyl-2-phenylpropanenitrile (7g) and (2R*,3R*)-3-(furan-2-yl)-3-hydroxy-2-methyl-2-phenylpropanenitrile[31] (6g)

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 ^oC. 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}. ^1H NMR (400 MHz, $CDCl_3$) 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, $CDCl_3$) δ 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_2O] 245. Elemental Analysis: Calcd for $C_{14}H_{13}NO_2$: $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16; O, 14.08. Found: C, 74.22; H, 5.79.

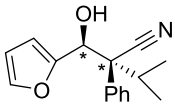


6g

White solid. mp.123-125 ^oC. IR (neat): 2242 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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.

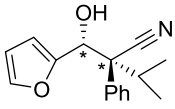
The preparation of (R*)-2-((S*)-furan-2-yl(hydroxy)methyl)-3-methyl-2-phenylbutanenitrile (7h) and (2R*, 3R*)2-(furan-2-yl(hydroxy)methyl)-3-methyl-2-phenylbutanenitrile (6h)

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 ^{o}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 ^{o}C. IR (KBr): 2243 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) 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). ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.69, 142.44, 135.58, 128.90, 128.32, 127.00, 120.71, 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 $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.49; O, 12.53. Found: C, 75.46; H, 6.72.

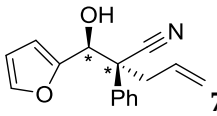


6h

White solid. mp.86-88 ^{o}C. IR (KBr): 2243 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) 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). ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.49; O, 12.53. Found: C, 75.34; H, 6.71.

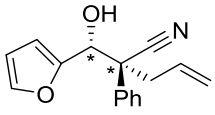
The preparation of (R*)-2-((S*)-furan-2-yl(hydroxy)methyl)-2-phenylpent-4-enenitrile (7i) and (R*)-2-((R*)-furan-2-yl(hydroxy)methyl)-2-phenylpent-4-enenitrile (6i)

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 ^{o}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.



7i

IR (neat): 2243 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 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). 13C NMR (100 MHz, $CDCl_3$) δ 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. MS (HPLC-MS). [M+Na] 276, [M+H_2O] 271. Elemental Analysis: Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53; O, 12.63. Found: C, 75.98; H, 5.98.



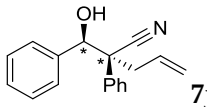
6i

IR (neat): 2243 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 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}C NMR (100 MHz, $CDCl_3$) δ 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. MS. [M+Na] 276, [M+H_2O] 271. Elemental Analysis: Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53; O, 12.63. Found: C, 75.97; H, 5.98.

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)

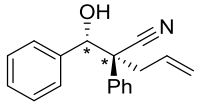
Following the procedure B, n-BuLi (0.44 ml, 1.1 mmol) was added into a solution of diisopropyl amine(0.15 ml, 1.1 mmol) in THF at -78 ^{o}C. A solution of **1d** (131 mg, 1.0 mmol) in THF, trimethyltin chloride (219 mg, 1.1 mmol) in toluene were successively added, then

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.



7j

White solid. mp. 80-82 ^{o}C. IR (KBr): 2240 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.35 (m, 3H), 7.32-7.32 (m, 5H), 7.17-7.15 (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). ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{18}H_{17}NO$: C, 82.10; H, 6.51; N, 5.32; O, 6.08. Found: C, 82.21; H, 6.51.



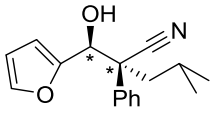
6j

White solid. mp. 127-129 ^{o}C. IR (KBr): 2240 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) 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). ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{18}H_{17}NO$: C, 82.10; H, 6.51; N, 5.32; O, 6.08. Found: C, 82.28; H, 6.52.

The preparation of (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)

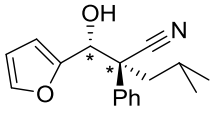
Following the procedure B, n-BuLi (0.44 ml, 1.1 mmol) was added into a solution of diisopropyl ethyl amine(0.15 ml, 1.1 mmol) in THF at -78 ^{o}C. A solution of **1e** (173 mg, 1.0 mmol) in THF, trimethyltin chloride (219 mg, 1.1 mmol) in toluene were successively added, then aldehyde **5g** (115 mg, 1.2 mmol) in toluene was dropped in to reaction. Made the column

by Cyclohexane: Ethyl acetate = 4:1, get a diastereomixture 172 mg, yield: 64%. Then separate two diastereo isomer by preparative HPLC for identification.



7k

IR (neat): 2242 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 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_2O] 287. Elemental Analysis: Calcd for $C_{17}H_{19}NO_2$: $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11; N, 5.20; O, 11.88. Found: C, 75.97; H, 7.12.

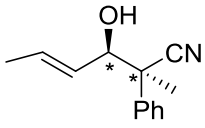


6k

IR (neat): 2242 cm^{-1}.^1H NMR (400 MHz, $CDCl_3$) δ 7.64 – 7.35 (m, 6H), 6.51 (d, *J* = 3.2 Hz, 1H), 6.41 (dd, *J* = 3.2, 2.0 Hz, 1H), 4.91 (d, *J* = 2.4 Hz, 1H), 2.26 (s, 1H, OH), 2.02 (dd, *J* = 14.0, 5.2 Hz, 1H), 1.64 (dd, *J*=14.0 8.0 Hz, 1H), 1.58 – 1.50 (m, 1H), 0.93 (d, *J* = 6.8 Hz, 3H), 0.68 (d, *J* = 6.8 Hz, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ 151.69, 142.44, 135.58, 128.90, 128.32, 127.00, 120.71, 110.72, 108.96, 74.81, 54.04, 43.12, 25.36, 23.98, 22.75. MS (HPLC-MS). [M+Na] 292, [M+H_2O] 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, 75.98; H, 7.12.

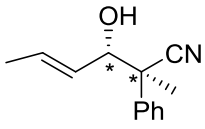
The preparation of (2R,3R)-3-hydroxy-2-methyl-2-phenylhex-4-enenitrile (7l) and (2R,3S)-3-hydroxy-2-methyl-2-phenylhex-4-enenitrile (6l)

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 ^oC. 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.



7l

Colorless oil. IR (neat): 2236 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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_2O]=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.

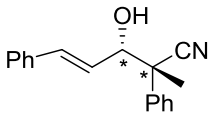


6l

Colorless oil. IR (neat): 2236 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, *J* = 7.8 Hz, 2H), 7.43-7.33 (m, 3H), 5.85 (dq, *J* = 13.6, 6.4 Hz, 1H), 5.59 (dd, *J* = 15.6, 8.0 Hz, 1H), 4.21 (d, *J* = 7.6 Hz, 1H), 1.83 (bs, 1H,OH), 1.76 (d, *J* = 6.4 Hz, 3H), 1.66 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.45, 132.31, 128.86, 128.19, 127.77, 126.49, 121.82, 78.56, 48.44, 23.13, 17.83. MS (HPLC-MS) M+Na] 224, [M+H_2O] 219. Elemental Analysis: Calcd for $C_{13}H_{15}NO$: C, 77.58; H, 7.51; N, 6.96; O, 7.95. Found: C, 77.79; H, 7.52.

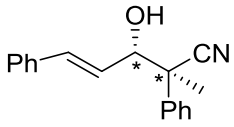
The preparation of (2S,3S)-3-hydroxy-2-methyl-2,5-diphenylpent-4-enenitrile (7m) and (2R,3S)-3-hydroxy-2-methyl-2,5-diphenylpent-4-enenitrile (6m)

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 ^oC. 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.



7m

Colorless oil. IR (neat): 2244 cm^{-1} . ^1H NMR (400 MHz, $CDCl_3$) δ 7.52 – 7.21 (m, 10H), 6.54 (d, *J* = 15.96Hz, 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, $CDCl_3$) δ 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.

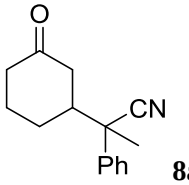


6m

White solid. mp.148-150 °C. IR (neat): 2244 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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.



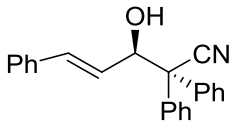
8a

Colorless oil.IR (neat): 2235, 1709 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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 ^{o}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 aldehy **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%.

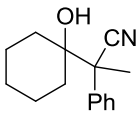


6o

Colorless oil.IR (neat): 2237 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 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). 13C NMR (100 MHz, $CDCl_3$) δ 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 ^{o}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%.



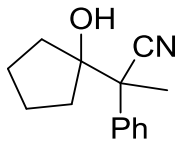
6p

Colorless oil.IR (neat): 2237 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 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). ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.88, 128.23, 127.97, 127.91, 123.44, 74.48, 51.87, 33.04, 32.17, 26.89, 25.00,

21.65, 21.50, 20.30. MS (HPLC-MS): $[M+H_2O]$=247. Elemental Analysis: Calcd for $C_{15}H_{19}NO$: C, 78.56; H, 8.35; N, 6.11; O, 6.98. Found: C, 78.77; H, 8.36.

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 ^{o}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.

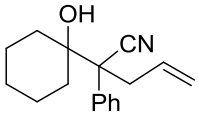


6q

Colorless oil.IR (neat): 2237 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (d, *J*=7.6Hz, 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). ^{13}C NMR (100 MHz, $CDCl_3$): 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): $[M+H_2O]$=233, [M+Na]=238. Elemental Analysis: Calcd for $C_{14}H_{17}NO$: 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 ^{o}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.



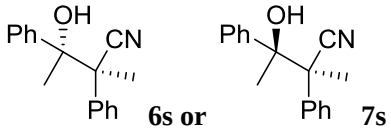
6r

Colorless oil.IR (neat): 2237 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) 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, $CDCl_3$) 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 $C_{17}H_{21}NO$: 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 ^oC. 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.



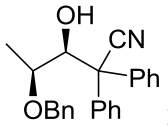
6s or **7s**

Isomer 1: IR (neat): 2238 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.27 (m, 5H), 7.23 (m, 5H), 1.68 (s, 3H), 1.62 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) 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+H_2O]=269, [M+Na]=274. Elemental Analysis Calcd for $C_{17}H_{17}NO$: 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, $CDCl_3$) δ 7.47 – 7.36 (m, 5H), 7.11 (m, 5H), 1.76 (s, 3H), 1.75 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) 141.29, 136.41, 128.21, 128.11, 128.06, 127.72, 127.04, 123.15, 51.73, 26.37, 21.20. MS (HPLC-MS): [M+H_2O]=269, [M+Na]=274. Elemental Analysis Calcd for $C_{17}H_{17}NO$: C, 81.24; H, 6.82; N, 5.57; O, 6.37. Found: C, 81.40; H, 6.83.

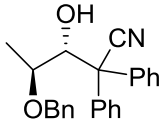
The preparation of (3S,4S)-4-(benzyloxy)-3-hydroxy-2,2-diphenylpentanenitrile (10a) and (3R,4S)-4-(benzyloxy)-3-hydroxy-2,2-diphenylpentanenitrile (11a)

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^{o}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^{o}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^{o}C, after kept at -78^{o}C and stirring for 18hrs, the reaction was decomposed by saturated NH_4Cl solution and adjust PH to 7 at -78^{o}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^{o}C. $[\alpha]_D^{20}$: +16. (*c*: 1.0g/100 mg, $CHCl_3$). IR(neat): 2242 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) 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). ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{24}H_{23}NO_2$: C, 80.64; H, 6.49; N, 3.92; O, 8.95. Found: C, 80.84; H, 6.50.



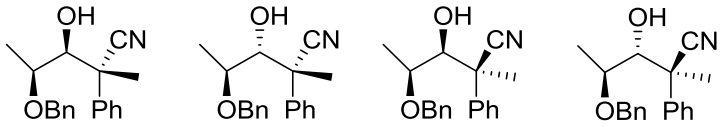
11a

White solid. mp: 148-151^{o}C. $[\alpha]_D^{20}$: -27. (*c*: 1.0g/100 mg, $CHCl_3$). IR(neat): 2242 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) 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, 0.44ml 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^{o}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^{o}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^{o}C, after kept at -78^{o}C and stirring for 18hrs, the reaction was decomposed by saturated NH_4Cl solution and adjust PH to 7 at -78^{o}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 diasteroisomer 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,

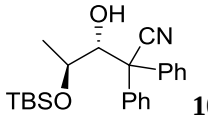
129.07, 128.36, 128.25, 128.04, 127.83, 126.02, 121.62, 80.52, 72.29, 71.04, 47.78, 25.93, 17.57. HPLC-MS: [m+23]=318.

Isomer c): IR(neat): 2238 cm^{-1}. ^1H 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}. ^1H 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 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 (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_4Cl 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%.



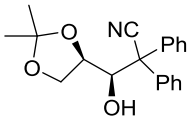
10c

White solid. mp: 99-101°C. $[\alpha]_D^{20}$: -75. (*c*: 1.0g/100 mg, $CHCl_3$). IR(KBr): 2244 cm^{-1}. ^1H 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),

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, $CDCl_3$) δ 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 $C_{23}H_{31}NO_2Si$: C, 72.40; H, 8.19; N, 3.67; O, 8.39; Si, 7.36. Found: C, 72.61; H, 8.20.

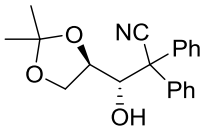
The preparation of (R)-3-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-hydroxy-2,2-diphenylpropanenitrile 11d and (S)-3-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-hydroxy-2,2-diphenylpropanenitrile (10d)

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^{o}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^{o}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 **9c** (1.2 mmol, 156 mg) in 3 ml of toluene was cooled to -78^{o}C, after kept at -78^{o}C and stirring for 18hrs, the reaction was decomposed by saturated NH_4Cl solution and adjust PH to 7 at -78^{o}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 ^{o}C. $[\alpha]_D^{20}$: -103.6 (*c*: 0.5g/100 mg, $CHCl_3$). IR (KBr): 2252 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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.

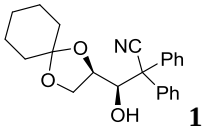


10d

White solid. mp: 137-139 ^{o}C. $[\alpha]_D^{20}$: +67.6 (*c*: 0.5 g/100 mg, $CHCl_3$). IR (KBr): 2252 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) 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). ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{20}H_{21}NO_3$: 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)

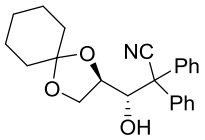
Following the procedure C, to a well dried schlenk flask, BuLi(1.1 mmol, 0.44ml of 2.5M in *n*-hexane) was added into a solution of 2,2-diphenylacetonitrile **1a** (193 mg, 1.0 mmol) in THF at -78^{o}C. After 10mins, a solution of trimethyltin chloride (219 mg 1.1 mmol,) in 2 ml of toluene was dropped into the reaction at -78^{o}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^{o}C, after kept at -78^{o}C and stirring for 18hrs, the reaction was decomposed by saturated NH_4Cl solution and adjust PH to 7 at -78^{o}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%.



11e

mp: colrless oil. $[\alpha]_D$: -114.3 (C: 0.5 mg/ 1 ml, $CHCl_3$) IR (neat): 2253 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 – 7.78 (m, 2H), 7.62 – 7.29 (m, 8H), 4.43 (t, *J* = 5.0 Hz, 1H), 4.15 (q, *J* = 6.0 Hz, 1H), 3.52 (dd, *J* = 11.4, 6.4 Hz, 1H), 3.37 (d, *J* = 5.6 Hz, 1H, OH), 3.25 (dd, J = 8.4, 6.4 Hz, 1H), 1.75 – 1.47 (complex pattern, 10H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.36, 137.48,

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.

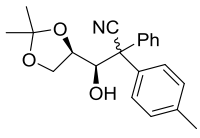


10e

White solid. mp: 132-135^{o}C. $[\alpha]_D^{20}$: +64.4 (*c*: 5 mg/ ml, $CHCl_3$). IR (neat): 2253 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 7.8 Hz, 2H), 7.44 – 7.31 (m, 8H), 4.92 (d, *J* = 2.4 Hz, 1H), 4.1.0 (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, $CDCl_3$) δ 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)

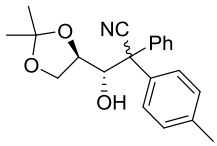
Following the procedure C, to a well dried schlenk flask, *n*-BuLi(1.1 mmol, 0.44ml of 2.5M in *n*-hexane) was added into a solution of 2-(4-methyl)-2-phenylacetonitrile **3g** (207 mg, 1.0 mmol) in THF at -78^{o}C. After 10mins, a solution of trimethyltin chloride (219 mg 1.1 mmol,) in 2 ml of toluene was dropped into the reaction at -78^{o}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^{o}C, after kept at -78^{o}C and stirring for 18hrs, the reaction was decomposed by saturated NH_4Cl solution and adjust PH to 7 at -78^{o}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 arbitrarly attributed to **isomer A** and **isomer B**.



11f

Isomer A: IR (neat): 2240 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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. C, 74.86; H, 6.87.

Isomer B: IR (neat): 2240 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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. C, 74.86; H, 6.87.



10f

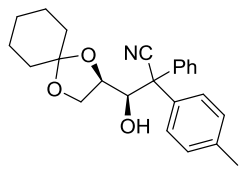
Isomer A: IR (neat): 2240 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 – 7.52 (m, 1H), 7.47 – 7.40 (m, 2H), 7.40 – 7.28 (m, 4H), 7.23 – 7.15 (m, 2H), 4.90 (d, *J* = 2.0 Hz, 1H), 4.19 – 4.14 (m, 1H), 4.03 – 4.00 (m, 1H), 3.88 (dd, *J* = 8.8, 6.4, 1H), 2.56 (bs, 1H, OH), 2.34 (s, 3H), 1.42 (s, 3 H), 1.41 (s, 3H), 1.28 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) 138.20, 137.74, 134.53, 129.85, 129.83, 128.19, 127.64, 126.91, 120.39, 108.24, 75.96, 74.02, 63.41, 54.84, 26.29, 25.16, 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. C, 74.89; H, 6.88.

Isomer B: IR (neat): 2240 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 - 7.28 (m, 7H), 7.23 – 7.15 (m, 2H), 4.90 (d, *J* = 2.0 Hz, 1H), 3.88 (dd, *J* = 8.8, 6.4, 1H), 4.03 – 4.00 (m, 1H), 3.91 – 3.84

(m, 1H), 2.55 (bs, 1H, OH), 2.33 (s, 3H), 1.42 (s, 3 H), 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. 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)

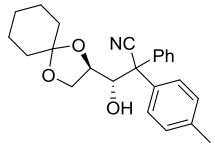
Following the procedure C, to a well dried schlenk flask, BuLi(1.1 mmol, 0.44ml of 2.5M in *n*-hexane) was added into a solution of 2-(4-methyl)-2-phenylacetonitrile **3g** (207 mg, 1.0 mmol) in THF at -78^{o}C. After 10mins, a solution of trimethyltin chloride (219 mg 1.1 mmol,) in 2 ml of toluene was dropped into the reaction at -78^{o}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 mg 1.2 mmol) in 3 ml of toluene was cooled to -78^{o}C, after kept at -78^{o}C and stirring for 18hrs, the reaction was decomposed by saturated NH_4Cl solution and adjust PH to 7 at -78^{o}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%.



11g

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.



10g

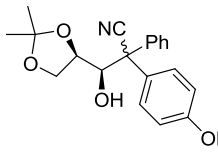
Isomer A: IR (neat): 2249 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 – 7.18 (m, 9H), 4.90 - 4.89 (m, 1H), 4.10 (dd, *J* = 8.4, 6.8 Hz, 1H), 4.05 – 3.96 (m, 1H), 3.88 (dd, *J* = 8.4, 6.0 Hz, 1H), 2.59 (d, *J* = 2.8 Hz, 1H, OH), 2.34 (s, 3H), 1.74 – 1.32 (complex pattern, 10H). ^{13}C NMR (100 MHz, $CDCl_3$) 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 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-methoxylyl)-2-phenylacetonitrile **1h** (223 mg, 1.0

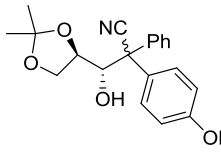
mmol) in THF at -78°C. After 10mins, a solution of trimethyltin chloride (219 mg 1.1 mmol,) in 2 ml of toluene was dropped into the reaction at -78°C. Then the reaction mixture was allowed to go to r.t and stirring for 1 hour. A solution of (R)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde **9a** (1.2 mmol, 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 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%.



11h

Isomer A: IR (neat): 2238 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) 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 $C_{21}H_{23}NO_4$: 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, $CDCl_3$) 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 $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96; O, 18.11. Found: C, 71.68; H, 6.59.



10h

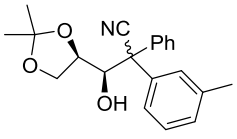
Isomer A: IR (neat): 2238 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J*= 7.6 Hz, 1H), 7.51 – 7.29 (m, 6H), 6.98 – 6.78 (m, 2H), 4.88 (s, 1H), 4.16 – 4.12 (m, 1H), 4.09 – 3.98 (m, 1H), 3.90 – 3.81 (m, 1H), 3.81 (s, 3H), 2.54 (bs, 1H, OH), 1.42 (s, 3H), 1.29 (s, 3H). HPLC-MS:

[M+Na]=376. Elemental Analysis: Calcd. for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96; O, 18.11. Found: C, 71.62; H, 6.58.

Isomer B:IR (neat): 2238 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 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 $C_{21}H_{23}NO_4$: 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)**

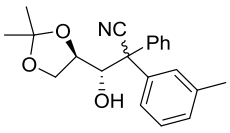
Following the procedure C, to a well dried schlenk flask, BuLi(1.1 mmol, 0.44ml of 2.5M in *n*-hexane) was added into a solution of 2-(3-methyl)-2-phenylacetonitrile (207 mg, 1.0 mmol) in THF at -78^{o}C. After 10mins, a solution of trimethyltin chloride (219 mg 1.1 mmol,) in 2 ml of toluene was dropped into the reaction at -78^{o}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^{o}C, after kept at -78^{o}C and stirring for 18hrs, the reaction was decomposed by saturated NH_4Cl solution and adjust PH to 7 at -78^{o}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

Isomer A: IR (neat): 2238 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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.

Isomer B: IR (neat): 2238 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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.



10i

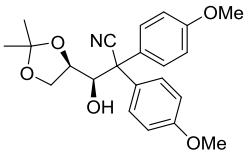
Isomer A: IR (neat): 2238 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 7.7 Hz, 1H), 7.45 – 7.15 (m, 7H), 7.11 (d, *J* = 3.2 Hz, 1H), 4.89 (d, *J* = 2.6 Hz, 1H), 4.217 – 4.13 (m, 1H), 4.01 - 3.96 (m, 1H), 3.90 - 3.85 (m, 1H), 2.52 (d, J = 2.8 Hz, 1H, OH), 2.32 (s, 3H), 1.40 (s, 3H), 1.25 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 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}. ^1H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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 C21H23NO3: 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)

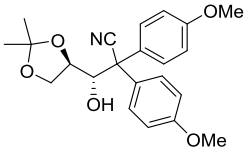
Following the procedure C, to a well dried schlenk flask, BuLi(1.1 mmol, 0.44ml of 2.5M in *n*-hexane) was added into a solution of 2,2-bis(4-methoxyphenyl)acetonitrile **1j** (253 mg, 1.0

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 NH_4Cl 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 (CH_2Cl_2:ether) to get pure compound **11j** (14 mg), and **10j** (98 mg), yield 28%.



11j

IR (neat): 2241 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) 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). ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{22}H_{25}NO_5$: C, 68.91; H, 6.57; N, 3.65; O, 20.86. Found: C, 69.05; H, 6.58.

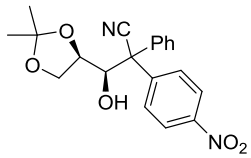


10j

IR (neat): 2241 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) 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). ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{22}H_{25}NO_5$: 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-dimethyl-1,3-dioxolan-4-yl)-3-hydroxy-2-(4-nitrophenyl)-2-phenylpropanenitrile (11k) and (3S)-3-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-hydroxy-2-(4-nitrophenyl)-2-phenylpropanenitrile (10k)

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-nitrophenyl)-2-phenylacetonitrile**1k** (238 mg, 1.0 mmol) in THF at -78^{o}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^{o}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^{o}C, after kept at -78^{o}C and stirring for 18hrs, the reaction was decomposed by saturated NH_4Cl solution and adjust PH to 7 at -78^{o}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 (CH_2Cl_2:ether) to get pure compound **11k** (32 mg), and **10k** (14 mg), yield 13%.

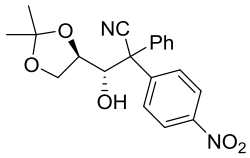


11k

Isomer A: IR (neat): 2251 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 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 Hz, 1H), 3.61 (dd, *J* = 8.4, 6.0 Hz, 1H), 3.30 (d, *J* = 6.8 Hz, 1H, OH), 1.45 (s, 3H), 1.30 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.40, 145.51, 144.60, 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. HPLC-MS: [M+Na]=391. Elemental Analysis: Calcd. for $C_{20}H_{20}N_2O_5$: C, 65.21; H, 5.47; N, 7.60; O, 21.71. Found: C, 65.46; H, 5.49.

Isomer B: IR (neat): 2251 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 – 8.22 (m, 2), 7.78 – 7.75 (m, 2H), 7.43 – 7.37 (m, 5H), 4.46 (t, *J*= 5.2 Hz, 1H), 4.15 (q, *J* = 5.8 Hz, 1H), 3.53 (dd, *J* = 8.4, 6.4 Hz, 1H), 3.47 (d, *J* = 6.0 Hz, 1H, OH), 3.25 (dd, *J* = 8.8, 6.0 Hz), 1.45 (s, 3H), 1.32 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 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.

HPLC-MS: [M+Na]=391. Elemental Analysis: Calcd. for $C_{20}H_{20}N_2O_5$: C, 65.21; H, 5.47; N, 7.60; O, 21.71. Found: C, 65.46; H, 5.49.



10k

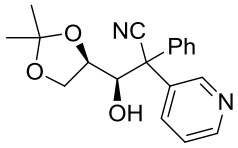
Isomer A: IR (neat): 2251 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.26 – 8.22(m, 2H), 7.78 – 7.76 (m, 1H), 7.68 – 7.66 (m, 1H), 7.57 – 7.54 (m, 1H), 7.45 – 7.39 (m, 4H), 4.91 (t, *J* = 2.5 Hz, 1H), 4.15 – 4.11 (m, 1H), 4.0 – 3.85 (complex pattern, 3H), 2.58 (bs, 1H, OH), 1.34 (s, 3H), 1.26 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.98, 144.59, 136.12, 129.66, 129.37, 129.06, 128.54, 127.66, 126.93, 124.05, 123.86, 119.37, 109.99, 108.92, 75.91, 74.25, 63.50, 56.81, 49.08, 26.22, 24.85. HPLC-MS: [M+Na]=391. Elemental Analysis: Calcd. for $C_{20}H_{20}N_2O_5$: C, 65.21; H, 5.47; N, 7.60; O, 21.71. Found: C, 65.40; H, 5.48.

Isomer B: IR (neat): 2251 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 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). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.70, 134.36, 129.60, 129.10, 128.71, 127.71, 126.93, 124.42, 123.86, 119.31, 118.44, 109.99, 108.66, 75.59, 64.29, 54.54, 49.08, 26.35, 25.03. HPLC-MS: [M+Na]=391. Elemental Analysis: Calcd. for $C_{20}H_{20}N_2O_5$: C, 65.21; H, 5.47; N, 7.60; O, 21.71. Found: C, 65.40; H, 5.48.

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**1l** (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 **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

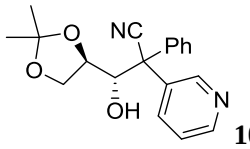
adjust PH to 7 at -78°C, then extract with ethyl acetate, washed by brine, dried over sodium sulfate, remove all the solvent, the crude product was purified by the flash chromatography (CH_2Cl_2:ether) to get pure compound **11l** (43 mg), and **10l** (114 mg), yield 48%.



11l

Isomer A: IR (neat): 2249 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) 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). ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{19}H_{20}N_2O_3$: 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, $CDCl_3$) 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). ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{19}H_{20}N_2O_3$: C, 70.35; H, 6.21; N, 8.64; O, 14.80. Found: C, 70.57; H, 6.23.



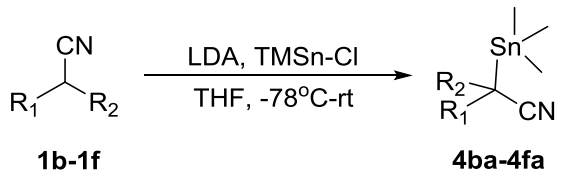
10l

Isomer A: IR (neat): 2249 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.83 (d, *J* = 2.4 Hz, 1H), 8.57 – 8.54 (m, 1H), 7.90 - 7.34 (m, 7H), 4.90 (d, *J* = 2.8 Hz, 1H), 4.26 – 4.12 (m, 2H), 3.99 – 3.96 (m, 1H), 3.75 (bs, 1H, OH), 1.43 (s, 3H), 1.32 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.14, 148.74, 136.28, 136.26, 134.73, 129.50, 128.80, 127.06, 123.49, 119.50, 109.96, 75.80, 74.93, 66.83, 55.40, 26.35, 25.17. HPLC-MS: [M+Na]=347. Elemental Analysis: Calcd. for $C_{19}H_{20}N_2O_3$: C, 70.35; H, 6.21; N, 8.64; O, 14.80. Found: C, 70.46; H, 6.22.

Isomer B: IR (neat): 2249 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 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). δ ^{13}C NMR (100 MHz, $CDCl_3$) δ 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 $C_{19}H_{20}N_2O_3$: 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)



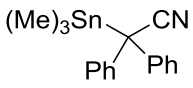
1b-1f **4ba-4fa**

Scheme 3.12 preparation of α- (phenylalkyltin) nitriles

***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%.

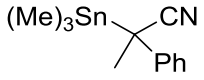


4aa

Colorless oil. IR (neat):2207 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.15 (m, 10H), 0.26 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 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%.

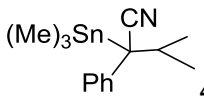


4ba

Colorless oil. IR (neat): 2202 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 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%

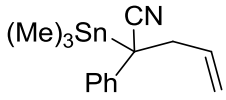


4ca

Colorless oil. IR (neat): 2207 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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%.

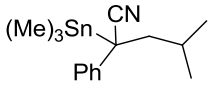


4da

Colorless oil. IR (neat): 2205 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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%.

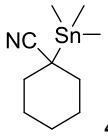


4ea

Colorless oil. IR (neat): 2204 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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%.



4fa

Colorless oil. IR (neat): 2195 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$): δ 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 α-(phenylalkyltin)nitriles

Procedure C:

α-trimethyltin nitrile was dissolved into toluene at -78 ^oC 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_4Cl solution (15 ml) at -78 ^oC, 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_2SO_4, remove all the solvent, made a silicon gel chromatography for purification as previous reported for each product.

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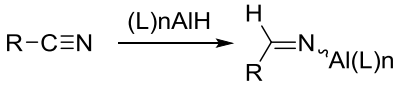
Chapter 4. Synthesis of N-aluminum ketene imines and application in epoxide ring opening reaction

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*-siyl 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 γ-hydroxy nitriles. As a matter of fact γ-hydroxyl nitriles have a wide range of applications in organic synthesis,[10-12] particularly as intermediates of γ-keto-nitrile and lactons, which are precursors of bioactive products. γ-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 γ-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

4.2 Present work

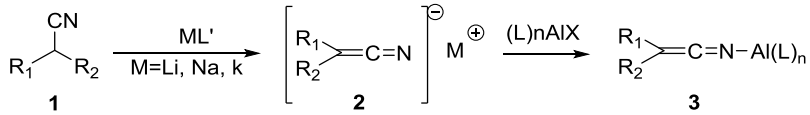
Among different classes of organic compounds of the most interesting and easily available from market or in house preparation is that of epoxides. The fact that recent methodologies by Sharpless allow the preparation of *epc* (enantiomerically pure compounds) derivatives renders this class of compounds 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.[16-20] Meanwhile, the enantiomeric epoxide ring opening by catalysts is remaining as a hot field. [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 γ-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

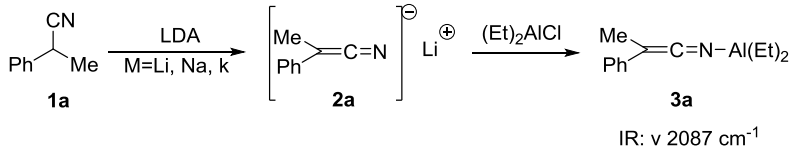
Based on the information above reported and taking advantage of our own experiences on the aluminum-imines we felt that the corresponding ketene imines could be stable intermediates and could be prepared from the corresponding alkali metal ketene imines (alkali= Li, Na, K) by a suitable exchange of the 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).[24, 25]



Scheme 4.2 proposed method for preparation of *N*-Al ketene imines

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 **1a** was treated with LDA (Lithium diisopropyl amide) to give the corresponding nitrile anion which was treated *in situ* with commercially available diethyl aluminium chloride to give the corresponding aluminium ketene imine, identified by its IR

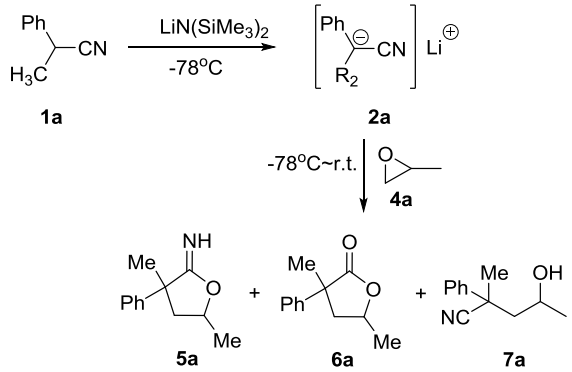
stretching at 2087 cm^{-1} (characteristic of C=C=N functional moiety) (Scheme 4.3). No further studies were performed, at this very preliminary stage, for fully identify the aluminium ketene imine.



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.

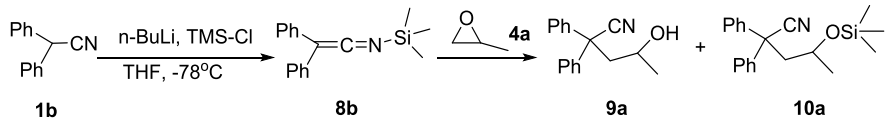
The reaction of alkali metal nitriles and terminal epoxides has been already reported and results in a mixture of cyclic and acyclic products (Scheme 4.4).[12] Product **7a** (a diastereo mixture of **11a 12a**) arise from a classical opening reaction whilst products **5a** and **6a** arise from a, difficult 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.



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.

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 diethylaluminum chloride was used as catalyst (Table 4.1 entrys 3,4). Taking advantage of this information we decide to start a dedicated study on the opening of epoxides by *N*-aluminum ketene imines.



Scheme 4.5 *N*-silyl ketene imine used in epoxide ring opening reaction

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:

Table4.1 *N*-silyl ketene imine used in epoxide ring opening reaction

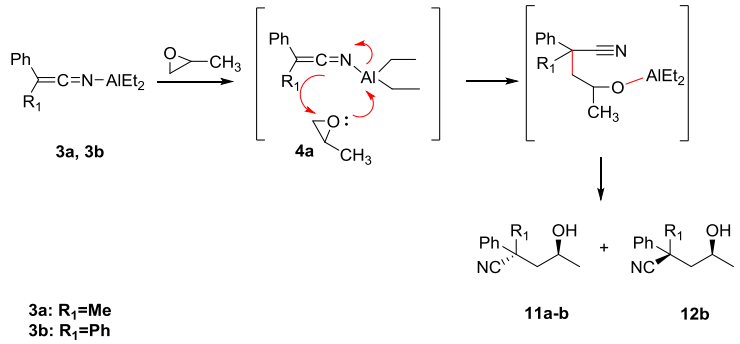
Entry	N-Silyl ketenimine	Epoxide	Ctalyst$	Reaction	Yield&
1	**8a**	**4a**	--	72h	Trace
2	**8a**	**4a**	(Salen)AlCl	72h	Trace
3	**8a**	**4a**	Et_2AlCl	18h	35% **10a**
4	**8a**	**4a**	Et_2AlCl	72h	35% **10a**
5	**8a**	**4a**	Et_2AlOTf	72h	Trace
6	**8a**	**4a**	(Salen)AlOTf	72h	Trace
7	**8a**	**4a**	(Salen)CrCl	72h	Trace

$: 0.1M catalysts were usesd. &: 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*-alluminium ketene imines, we

decided to employ aluminium ketene imines **3a** and **3b**, with 2-methyloxirane **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 diastereo-selectivity 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).

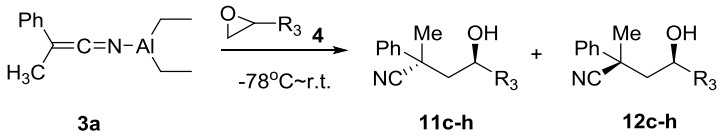


Scheme 4.6 reaction between aluminium ketene imine **3a, 3b** and 2-methyloxirane (**4a**)

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

Entry	Nucleophile	Product#	Ratio **11/12**	Solvent	Method	Yield(%)*
1	**3b**	**11b**	-	THF	A	58
2	**3a**	**11a, 12a**	50:50	THF	A	60
3	**3a**	**11a, 12a**	40/60	Toluene	B	40
4	**3a**	**11a, 12b**	40/60	Toluene	C&	50

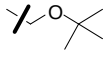
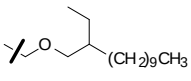
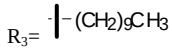
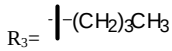
$: for the sack of simplicity, only two diastereomers were reported in the table. &: in method C, L-salen Chloride were used as catalyst. *: isolated yields.



Scheme 4.7 *N*-Al ketene imine **3a** reacts with epoxides **4b-g**.

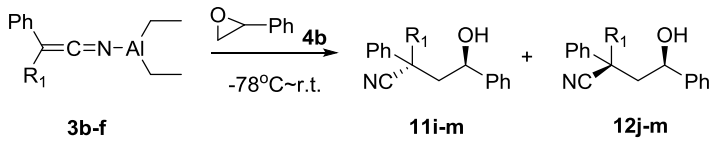
To test the reaction scope, we treated different epoxide with the *N*-Al ketene imine arising from α-methyl phenylacetonitrile. All the epoxides underwent moderate yields and good regioselectivities since γ-hydroxyl nitrile has been found as the single product. In all entries, only styrene oxide gives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

Table 4.3 reaction of ketene imine 25a with different epoxide

Entry	Epoxides(**4**) *	Product	Dr[#] **12 / 11**	Yield (%)[$]
1	 **4b**	11c, 12c	50:50	28
2	R_3=Ph **4c**	11d, 12d	25:75	49
3	R_3=  **4d**	11e, 12e	50:50	41
4	R_3=  **4e**	11f, 12f	50:50	40
5	R_3=  **4f**	11g, 12g	50:50	41
6	R_3=  **4g**	11h, 12h	50:50	29

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

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 different *N*-Al ketene imines react with epoxide **4b**.

Table 4.4. different α-substituted phenylacetonitriles react with epoxides

Entry	*N*-Al ketene imine R_1[#]	Product	Dr[$] **12 / 11**	Yield (%)[&]
1	R_1 = Ph (**3b**)	**11i**	--	50
2	R_1 = Isopropyl (**3c**)	**11j, 12j**	50:50	47
3	R_1 = Ally (**3d**)	**11k, 12k**	30:70	45
4	R_1 = Pyridine (**3e**)	**11l, 12l**	40:60	38
5	R_1 = isobutyl (**3f**)	**11m, 12m**	27:73	52

#: for **3c, 3d, 3f** the corresponding starting nitriles were prepared according to reference,[27] starting nitrile **3e** were prepared according to reference; [28, 29] $: for the sack 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 steoreoselectivity were achieved without any induction. The *N*-aluminium ketene imines described herein react with epoxide give γ-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.

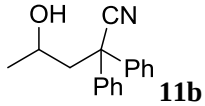
4.4 Experimental section

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 diatereomer. 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^{o}C under nitrogen atmosphere. After 10mins, diethyl aluminium choloride (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^{o}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 ^{o}C for 30mins. Then it was left spontaneously to reach r.t and kept overnight. The reaction was decomposed by saturated NH_4Cl_{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%).

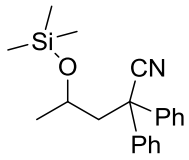


11b

11b: White solid. mp: 88-92 ^{o}C. IR(neat): 2244 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ =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, $CDCl_3$): δ = 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 ^{o}C, after 1 ° min 0.1M of diethyl aluminium chloride were added into the reaction; The reaction was kept at -78 ^{o}C for 30mins. Then the reaction was left spontaneously to reach r.t and kept overnight. The reaction was decomposed by saturated NH_4Cl_{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%).



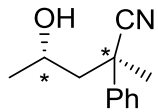
10a: IR(neat): 2237 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ =-0.10(s, 9H), 1.22(d, *J*=6.0 Hz, 1H), 1.79 (s, 3H), 2.44 (dd, J_1= 3.6 Hz, J_2= 14.0 Hz, 1H), 2.77(dd, J_1=7.2 Hz, J_2=14.0 Hz, 1H), 3.94 - 3.99 (m, 1H), 7.48-7.28(complex pattern, 10H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = -0.29, 24.84, 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**

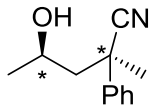
Preparation of diethylaluminium ketene imine 3a

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 $LiN(SiMe_3)_2$ (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 choloride (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 NH_4Cl_{aq} 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}. ^{1}H NMR (400 MHz, $CDCl_3$): δ =1.15(d, *J*=6.4 Hz, 3H), 1.68 (bs, 1H, OH), 1.79 (s, 3H), 1.98 (dd, J_1= 2.8 Hz, J_2= 13.6 Hz, 1H), 2.16(dd, J_1=8.8 Hz, J_2=13.6 Hz, 1H), 3.85 (m, 1H), 7.31-7.53(complex pattern, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): 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}. ^{1}H NMR (400 MHz, $CDCl_3$): δ =1.23(d, *J*=6.4 Hz, 3H), 1.68 (bs, 1H, OH), 1.80 (s, 3H), 2.04 (dd, J_1= 3.6 Hz, J_2= 13.6 Hz, 1H), 2.16(dd, J_1=4.0 Hz, J_2=13.6 Hz, 1H), 3.99 (m, 1H), 7.31-7.53(complex pattern, 5H). ^{13}C NMR (100 MHz,$CDCl_3$): 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].

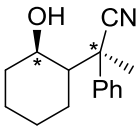
Method B: α-methyl acetonitriles (197 mg, 1.5 mmol) in toluene (1ml) was added into a solution of $LiN(SiMe_3)_2$ (1.5 mmol, 1.5 ml of 1.0 M in n-hexane) in toluene (5 ml) at -78°C under nitrogen atmosphere. After 10mins, diethyl aluminium choloride (1.5 mmol, 1.5 ml of 1.0 M in n-hexane) was added to the reaction. This reaction mixture was kept at -78°C for 30mins 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 30mins at this temperature. Then the reaction was left spontaneously to reach r.t for overnight. It was decomposed by saturated NH_4Cl_{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= 2:1) to give a inseparable mixture of product **11a** and **12a** (113 mg, ratio: 40:60, total yield: 40%).

Method C: 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 choloride (1.5 mmol, 1.5 ml of 1.0 M in n-hexane) was added to the reaction. The reaction was diluted with 20ml of toluene, kept at -78°C for 30mins and filtered. (*S*,*S*)-N,N-bis(3,5-di-tertbutylsalicylidene)-1,2-cyclohexanediamino aluminium chloride (135 mg) in THF (1 ml) was added into the filtrate at -78°C and kept for 10mins. 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_4Cl_{aq} and potassium sodium tartrate tetrahydrate, kept stirring for 1hr at r.t. 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** (141 mg, ratio: 40:60, total yield: 50%).

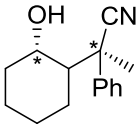
The Preparation of (*2S)-2-((*2S**)-2-hydroxycyclohexyl)-2-phenylpropanenitrile 11c and (*2R**)-2-((*2S**)-2-hydroxycyclohexyl)-2-phenylpropanenitrile 12c**

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 choloride (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 1hr 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_4Cl_{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 arbitrarly attributed to **11c** and **12c**.



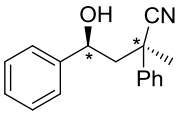
11c: IR(neat): 2236 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ =0.90-1.44 (co mlex pattern, 8H), 1.83 (s, 3H), 1.92(m, 1H), 3.53 (m, 1H), 7.30-7.55 (complex pattern, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.08, 24.64, 24.87, 25.60, 25.91, 27.33, 28.07, 37.55, 53.01, 72.91, 123.45, 126.16, 127.64, 127.92, 128.52, 128.97, 140.50. MS (ESI): m/z=230 [M+1].



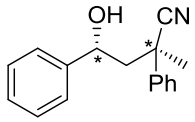
12c: IR(neat): 2236 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ =0.90-1.44 (co mlex pattern, 8H), 1.85 (s, 3H), 1.92(m, 1H), 3.68 (dt, J_1=4.4 Hz, J_2=14.4 Hz, 1H), 7.30-7.55 (complex pattern, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.08, 24.67, 24.88, 25.66, 26.43, 27.93, 36.54, 45.44, 53.26, 73.33, 123.99, 126.43, 127.89, 128.30, 128.87, 128.96, 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%)



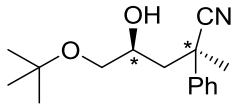
11d: whilte solid. mp: 78-82 °C. IR(neat): 2236 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ =1.50 (s, 3H), 1.58 (bs, 1H, OH), 3.24 (dd, J_1= 4.8 Hz, J_2= 10.0 Hz, 1H), 3.68 (dd, J_1=4.4 Hz, J_2=11.6 Hz, 1H), 4.25 (t, J=10.4 Hz, 1H), 7.35-7.51 (complex pattern, 8H) 7.57 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ =27.26, 45.19, 57.50, 63.16, 122.01, 125.77, 128.31, 128.50, 129.13, 129.25, 129.57, 136.80, 139.73. MS (ESI): m/z=252 [M+1].



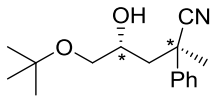
12d: IR(neat): 2236 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ =1.52 (bs, 1H, OH), 1.88 (s, 3H), 3.25 (dd, J_1= 5.2 Hz, J_2= 9.2 Hz, 1H), 4.14 (dd, J_1=11.6 Hz, J_2=9.6 Hz, 1H), 4.25 (dd, J_1=6.0 Hz, J_2=11.6 Hz, 1H), 7.00 (m, 2H), 7.17-7.28 (complex pattern, 8H). ^{13}C NMR (100 MHz, $CDCl_3$): δ =25.83, 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 (*2S*, 4R)-5-*tert*-butoxy-4-hydroxy-2-methyl-2-phenylpentanenitrile 11e and (*2R*, 4R**)-5-*tert*-butoxy-4-hydroxy-2-methyl-2-phenylpentanenitrile 12e**

Following Method A, stating from α-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 arbitrarly attributed to **11e** and **12e.**



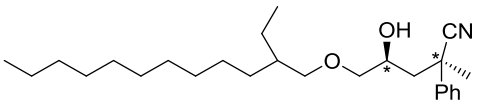
11e: IR(neat): 2236 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ =1.40 (s, 9H), 1.82 (s, 3H), 1.95 (dd, J_1= 3.2 Hz, J_2= 14.4 Hz, 1H), 2.14 (dd, J_1=8.4 Hz, J_2=14.4 Hz, 1H), 2.56 (bs, 1H, OH), 3.09 (dd, J_1=7.2 Hz, J_2=8.8 Hz, 1H), 3.22 (dd, J_1=8.8 Hz, J_2=11.2 Hz, 1H),3,79 (m, 1H), 7.32 (m, 1H), 7.40 (m, 2H), 7.50 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ =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].



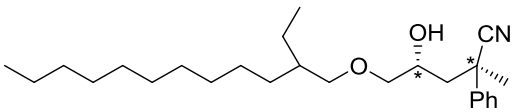
12e: IR(neat): 2236 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ =1.64 (s, 9H), 1.81 (s, 3H), 2.03 (dd, J_1= 4.0 Hz, J_2= 14.4 Hz, 1H), 2.11 (dd, J_1=7.6 Hz, J_2=14.4 Hz, 1H), 2.38 (bs, 1H, OH), 3.22 (dd, J_1=8.8 Hz, J_2=4.0 Hz, 1H), 3.36 (dd, J_1=3.6 Hz, J_2=8.8 Hz, 1H), 3.73 (m, 1H), 7.32 (m, 1H), 7.40 (m, 2H), 7.50 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ =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 (*2S, *4R**)-5-(2-ethyldodecyloxy)-4-hydroxy-2-methyl-2-phenylpentanenitrile 11f and (*2R**, *4R**)-5-(2-ethyldodecyloxy)-4-hydroxy-2-methyl-2-phenylpentanenitrile 12f**

Following Method A, stating from α-methyl acetonitriles (131 mg, 1.0 mmol), 2-((2-ethyldodecyloxy)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 deducted from the mixture and arbitrarly attributed to **11f** and **12f**.



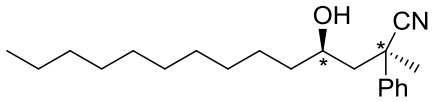
11f: IR(neat): 2236 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ =0.87 (t, J=7.6 Hz, 3H), 0.89 (m, 3H), 1,29(m, 8H), 1.46(m, 1H), 1.81(s, 3H), 2.05 (dd, J_1= 4.0 Hz, J_2= 14.4 Hz, 1H), 2.20 (bs, 1H, OH), 2.11 (dd, J_1=7.2 Hz, J_2=14.4 Hz, 1H), 3.29 (m, 3H), 3.41 (m, 1H), 3.83 (m, 1H), 7.32 (m, 1H), 7.41 (m, 2H), 7.51 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ =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].



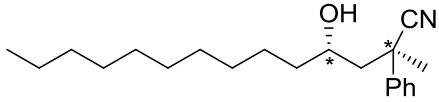
12f: IR(neat): 2236 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ =0.88 (m, 6H), 1.29 (m, 8H), 1.59 (m, 1H), 1.83 (s, 3H), 2.05 (dd, J_1= 2.8 Hz J_2= 14.8 Hz, 1H), 2.13 (dd, J_1=7.6 Hz, J_2=14.8 Hz, 1H), 2.42 (bs, 1H, OH), 3.15 (m, 1H), 3.29 (m, 3H), 3.83 (m, 1H), 7.32 (m, 1H), 7.41 (m, 2H), 7.51 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ =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, 128.00, 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 arbitrarly attributed to **11g** and **12g**.



11g: IR(neat): 2236 cm^{-1}. ^1H 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). ^{13}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].

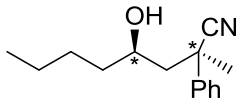


12g: IR(neat): 2236 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ =0.89 (t, *J*=7.6 Hz, 3H), 1.20-1.45 (m, 18H), 1.80 (s, 3H), 1.99 (dd, J_1=2.4 Hz, J_2= 14.8 Hz, 1H), 2.11 (dd, J_1=6.8 Hz, J_2=14.8 Hz, 1H), 3.62 (m, 1H), 7.33 (m, 1H), 7.41 (m, 2H), 7.48 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ =14.23, 22.79, 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].

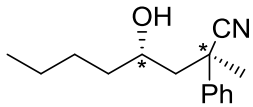
The Preparation of (*2S*, 4S)-4-hydroxy-2-methyl-2-phenyloctanenitrile 11h and (*2R*, 4S**)-4-hydroxy-2-methyl-2-phenyloctanenitrile 12h**

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^oC under nitrogen atmosphere. After 10mins, diethyl aluminium choloride (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_2Cl_2 was added to the residue and filtered. The filtrate was cooled to -78 ^oC. A solution of 2-butyloxirane (150 mg, 1.5 mmol) in CH_2Cl_2 (1 ml) was added at -78 ^oC. Then the reaction was left spontaneously to reach r.t for overnight. It was decomposed by saturated NH_4Cl_{aq} and potassium

sodium tartrate tetrahydrate, kept stirring for 1hr at r.t. 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= 6:1) to give an inseparable mixture of products **11h** and **12h** (107 mg, ratio: 50:50, total yield: 31%). Spectral data were deducted from the mixture and arbitrarly attributed to **11h** and **12h.**



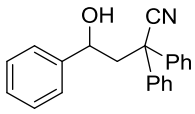
11h: IR(neat): 2237cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ =0.86 (t, *J*=7.2 Hz, 3H), 1.22-1.49 (m, 6H), 1.80(s, 3H), 1.99 (dd, J_1=2.4 Hz, J_2= 14.8 Hz, 1H), 2.11 (dd, J_1=9.2 Hz, J_2=14.8 Hz, 1H), 3.63 (m, 1H), 7.28-7.53 (complex pattern, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.09, 22.62, 27.46, 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): 2237cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ =0.89 (t, *J*=8.0 Hz, 3H), 1.22-1.49 (m, 6H), 1.79 (s, 3H), 2.05 (dd, J_1=2.8 Hz, J_2= 14.4 Hz, 1H), 2.11 (dd, J_1=8.2 Hz, J_2=14.4 Hz, 1H), 3.81 (m, 1H), 7.28-7.53 (complex pattern, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 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%)

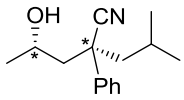


11i: whilte solid. mp: 117-118 ^{o}C. IR(neat): 2236 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ1.50 (s, 1H), 3.89 (dd, *J* = 10.4, 3.6 Hz, 1H), 4.04 (d, *J* = 10.4 Hz, 1H), 4.21 (t, *J* = 10.8 Hz, 1H), 7.06 – 6.93

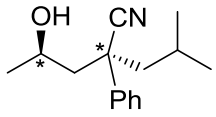
(m, 5H), 7.14 – 7.07 (m, 3H), 7.20 – 7.14 (m, 2H), 7.27-7.29 (m, 1H), 7.39 – 7.32 (m, 2H), 7.65 – 7.57 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 54.49, 55.15, 63.59, 121.17, 126.83, 127.12, 127.31, 127.85, 128.24, 128.30, 128.49, 129.15, 129.62, 136.24, 138.30, 138.74.MS(ESI) m/z= 314 [M+1].

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, $CDCl_3$) δ 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_1 = 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). ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.18, 23.70, 23.90, 25.30, 44.97, 45.06, 49.57, 51.05, 64.83, 126.01, 127.55, 127.81, 128.93, 138.24. MS(ESI) m/z= 232 [M+1].

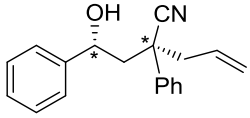


11i: IR(neat): 2236 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.62 (d, *J* = 6.7 Hz, 3H), 0.96 (d, *J* = 6.7 Hz, 3H), 1.17 (d, *J* = 6.3 Hz, 3H), 1.67 – 1.53 (m, 1H), 1.86 – 1.83 (m, 1H), 1.88 (d, J_1 = 6.0 Hz, 1H, OH), 2.01 – 1.96 (m, 1H), 2.17 – 2.15 (m, 1H), 3.78 – 3.51 (m, 1H), 4.09 – 3.82 (m, 1H), 7.50 – 7.31 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 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].

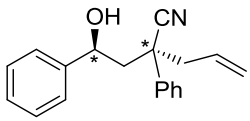
The Preparation of (R*)-2-((R*)-2-hydroxy-2-phenylethyl)-2-phenylpent-4-enenitrile (11k) and **(R*)-2-((R*)-2-hydroxy-2-phenylethyl)-2-phenylpent-4-enenitrile (12k)**

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 arbitrarly attributed to **11k** and **12k.**



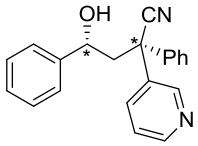
11k: IR(neat): 2236 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.49 (s, 1H), 2.37 (dd, *J* = 14.0, 7.6 Hz, 1H), 2.64 (dd, *J* = 14.4, 6.8 Hz, 1H), 3.53 (q, *J* = 6.8 Hz, 1H), 3.66 (d, *J* = 11.0 Hz, 1H), 4.10-4.11 (m, 1H), 4.39 (dd, *J* = 11.0, 4.8 Hz, 1H), 4.96 (t, *J* = 12.4 Hz, 1H), 5.46 – 5.29 (m, 1H), 7.05 – 6.97 (m, 4H), 7.18 (s, 2H), 7.33 – 7.27 (m, 2H), 7.46 – 7.37 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) 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].



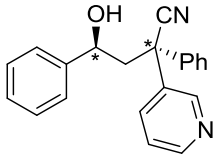
11k: IR(neat): 2236 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.56 (s, 1H), 2.91 (dd, *J* = 14.0, 6.4 Hz, 1H), 3.05 (dd, *J* = 14.0, 7.6 Hz, 1H), 3.46 – 3.33 (m, 2H), 4.12-4.14 (m, 1H), 5.19 (dd, *J* = 32.8, 13.6 Hz, 2H), 5.70 – 5.51 (m, 1H), 7.23 – 7.18 (m, 4H), 7.27 (d, *J* = 6.8 Hz, 2H), 7.49 (dd, *J* = 14.0, 6.8 Hz, 2H), 7.56 (t, *J* = 12.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) 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 arbitrarly attributed to **11 l** and **12 l.**



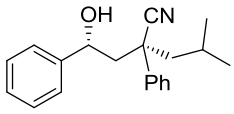
11l: IR(neat): 2242 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44 (s, 1H), 3.98 (dd, *J* = 10.0, 2.8 Hz, 1H), 4.12 (d, *J* = 12.4 Hz, 2H), 4.31 (t, *J* = 10.7 Hz, 1H), 7.05 – 6.92 (m, 1H), 7.22 (d, *J* = 4.8 Hz, 2H), 7.25 (t, *J* = 2.4 Hz, 2H), 7.36-7.38 (m, 3H), 7.56 – 7.42 (m, 2H), 7.70 (d, *J* = 8.0 Hz, 2H), 8.30 (d, *J* = 4.4 Hz, 1H), 8.38 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 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].



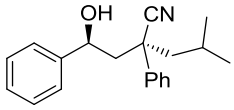
11l: IR(neat): 2242 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.56 (s, 3H), 4.00 (dd, *J* = 10.0, 3.9 Hz, 1H), 4.11 (td, *J* = 11.8, 5.5 Hz, 1H), 4.32 (dd, *J* = 11.3, 10.1 Hz, 1H), 7.15 – 7.08 (m, 4H), 7.23 – 7.17 (m, 3H), 7.29 – 7.23 (m, 3H), 7.38 (dd, *J* = 8.1, 4.7 Hz, 1H), 7.99 (ddd, *J* = 8.1, 2.5, 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, $CDCl_3$) δ 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 arbitrarly attributed to **11 m** and **12 m.**



11m: IR(neat): 2238 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) 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). ^{13}C NMR (100 MHz, $CDCl_3$) 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: whilte solid. IR(neat): 2238 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) 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 (ddd, *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). ^{13}C NMR (100 MHz, $CDCl_3$) 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.

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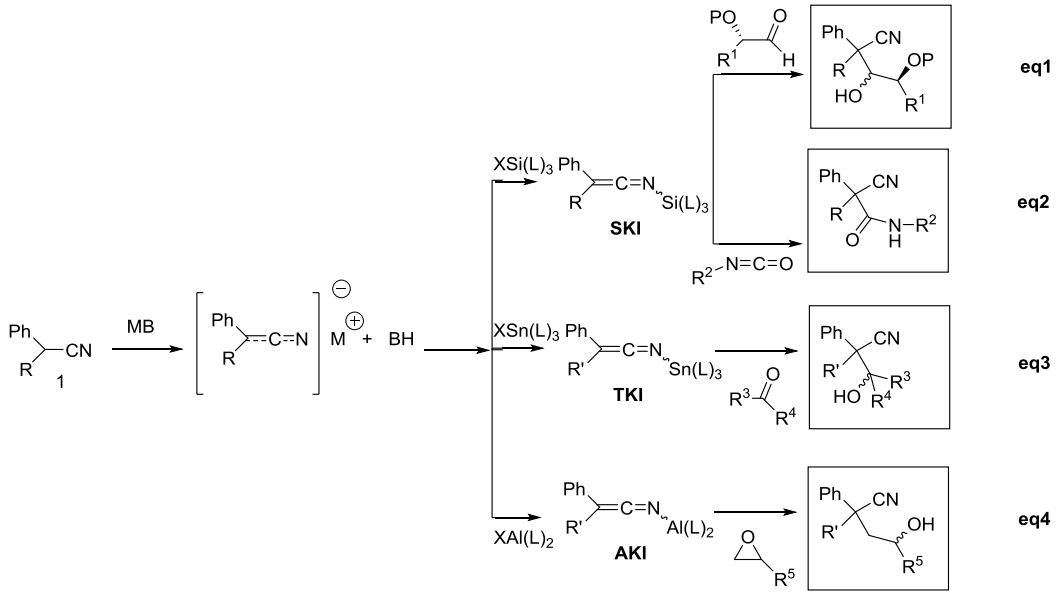
Chapter 5 Conclusion

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 methalated 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(15examples, 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%).

Acknowledgment

It would not have been possible to finish my PhD study without the help and support of the kind people around me, to only some of whom it is possible to give particular mention here.
Above all, I would like to thank my parents and brother for the many years supporting, it is difficult to find an expression for my thanks.

This thesis would not possible to finish without the help, support and patience of my virtual supervisor, Professor. Mauro Panunzio, his advice and knowledge of organic synthesis were the main courses of my PhD period. Furthermore, the lessons I've taken from Professor Panunzio were not only from scientific field, but also the life issues, which made me more confident and mature. Here, I have to thank Professor. Daria Giacomini as well, with her kind supporting; I could smoothly complete my PhD study. Also, I will thank Professor. Alessandro Bongini and Dr. Stefano Biondi for their theoretical support and kind discussion for the problems during my study.

I would like to acknowledge the financial support of China Scholarship Council. And the academic, technical support of University of Bologna, 'G. Ciamician', and its staff of technician, library facilities. I also thank the ISOF institute of National Research Council of Italy, for its financial and technical supporting.

I am grateful to my colleague Sha Long for her help, especially at the beginning of my studying in Italy, and more important the co-working of two years research. I also thank Dr. Matteo Pori and Roberto Soldati; it was wonderful to work with them in the same lab, the fun of my research not only comes from chemistry, but also from these two guys and their temporary students. And other professors, students, technicians from department of Organic chemistry are gratefully acknowledged, especially thank Professor. Diego Savoia, for his providing of accommodation during these three years.

Furthermore, I will thank all of my old teachers, supervisors and friend during my school and university studying before I come to Italy; it's difficult to find a word to say how important they are. Finally, I will thank my friends in Bologna, their accompanying made my study time easier and happier.

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Presentations

1. **Posters** on the conference "*XII Giornata della Chimica dell'Emilia Romagna*", Ferrara, Italy. 17 Dicember 2012. a) **Qin wenling,** Long Sha, Panunzio Mauro. *a,a*-Di-aryl nitriles as precursors of 2,2-disubstituted β-hydroxy nitriles via *N*-tin ketene imines. b) Long Sha, **Qin Wenling**, Bongini Alessandro, and Panunzio Mauro. Synthesis and reactivity of *N*-metallo-kerenimines.
2. **Oral presentation** during summer school *XXXVIII edition of the* "*Attilio Corbella*", in Gargnano (BS), from June 17 to June 21, 2013. **Qin Wenling**, Long Sha, Panunzio Mauro. Synthesis and Applications of *N*-tin and *N*-Aluminum Ketene Imines.