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Design, Synthesis and Characterization of *N*-Containing Organic Compounds

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Contents

Thesis' purpose

The needed of new intermediates/products for screening mainly in the fields of drug discovery and material science is the driving force behind the development of new methodologies and technologies for the rapid synthesis of simple moieties or for the assembly of more complicated structures. Among organic scaffolds which constitute one of the privileged target of the organic chemists, a priority place has to be attributed to the organic compounds, cyclic as well as acyclic ones, containing the nitrogen atom. That said it is clear to the reader that any new methodology, which will allow the introduction of the nitrogen atom for the synthesis of an established target or for the curiosity driven research, will be welcome.

The main research theme of the group joined by the Applicant during the thesis period, has been the development of new methodologies for the above.

More in detail, the objectives of this PhD thesis are:

(1). Preparation of new heterocycles, presenting the *N*-Heteroarylmethyl 3-carboxy-5-hydroxy piperidine scaffold, as potential and selective α-glucosidase Inhibitors.

(2). Synthesis of *enantiomerically* pure 1, 4-dihydropyridine using "solid" ammonia (magnesium nitride).

(3). Use of *N*-trialkylsilylimines in the synthesis of *N*-containing heterocycles *via* a Hetero Diels-Alder strategy.

(4). *N*-Metallo-ketene imines (metallo= Si, Sn, Al) in the preparation of highly functionalized derivatives as possible building blocks in the preparation of nitrogen containing targets.

Chapter 1.

N-Heteroarylmethyl 3-carboxy-5-hydroxy piperidine: A Novel Scaffold for the Design of Potent and Selective α-glucosidase Inhibitors

1.1 Introduction:

Owing to the success of α-glucosidase inhibitors as antidiabetic agents and the postulated involvement of this enzyme in tumorigenesis[1] and viral infection,[2] the interest in the discovery and development of novel, structurally different inhibitors is much alive. Several of the compounds described in the literature are natural products from plants used in the folk medicine around the world as remedy against diabetes.[3] Fewer α-glucosidase inhibitors have originated through rational drug design and novel chemical synthesis.[4,5] None has thus far supplanted the use of Acarbose or the other clinically tested inhibitors.

Iminosugars are a rich fount of glycosidase inhibitors.[6,7] Since the discovery in the mid sixties of nojirimicin,[8] the first identified natural α-glucosidase inhibitor, a large number of synthetic mimetics based on the same scaffold or that of azasugars[9] and aminocyclitols[10], have been evaluated. As in nojirimycin, the prototypical iminosugar and transition state analogues, a protonated nitrogen in these compounds is responsible for the formation of a stable electrostatic interaction with the critical carboxylate ion located within the catalytic pocket of the α-glucosidase. It is postulated that the ammonium ion, by mimicking the positively charged oxycarbenium ion in the pyranose ring of the natural substrate during catalysis, accounts for the competitive mechanism of inhibition of the compounds.[3] As a consequence of the fact that most glycosidases utilize the carboxylate ion as a catalytic group, the poor specificity of iminosugars and the related scaffolds toward α-glucosidase, is a limiting factor for their development as drugs.

Compounds in which the protonable nitrogen is substituted or is replaced by another atom have also been evaluated. Of these, emiglitate, a synthetic analogue of deoxynojirimycin,[11] and salacinol, a naturally occurring thiasugar,[9] display remarkable potency both in vitro and in vivo. Interestingly in these compounds, the protonable nitrogen carries a substituent harboring an electron dense region, a structural feature that is uncommon in natural and synthetic iminosugars or in α-glucosidase inhibitors in general. Likewise there is little information on the effect of replacing the hydroxyl residues decorating the iminosugar pyranose ring with different substituents. Conceivably this may drastically affect the inhibitory activity since key features of the natural substrate are removed. However the recent report[12] that 4,5 dihydroxy-1,2 cyclohexane dicarboxylic acids are endowed with α-glucosidase inhibitory activity, challenges this view. Given these premises, and provided the aim of this thesis on the design and synthesis of new nitrogen containing heterocyclic compounds with a potentially useful bio-activity, we embarked, in

collaboration with Glyconova (Colleretto Giacosa, Italy) and Innovative Chemistry (Milano, Italy), in a chemical programaimed at synthesizing and evaluating, as glycosidases inhibitors, a novel series of azasugars embedding in their structure some of the non-canonical features discussed above. In the course of our studies we found that a series of new compounds, characterized by a piperidine scaffold bearing in position 3 of the heterocycle carboxy functionality, and by the presence of a heteromethylaryl appendance, directly linked on the nitrogen atom, act as potent α-glucosidase inhibitors. Unlike acarbose and the other main α-glucosidase inhibitors, the compounds sound to act through a reversible uncompetitive mechanism of inhibition which makes them attractive as candidate for drug development.

1.2 Present work

1.2.1 Chemistry

The scaffold 1-heteroarylmethyl-4-hydroxy-piperidine-3-carboxylic acids **7a-7d** (Chart 1)[13] was prepared with slight modifications of the literature procedures. In detail the commercially available ethyl 1-benzyl-4-oxo-3-piperidine carboxlate hydrochloride **1** (from Aldrich), after neutralization by TEA (triethylamine) was reduced by sodium borohydride to give an inseparable mixture of the corresponding alcohol **2 (SL34/14/1)** (mixture of *cis*- and *trans*- isomers).[14] This mixture was treated with *tert*-butyldimethylsilyl chloride (TBSCl) in the presence of imidazole in DMF to give the TBS-ether **5** and the *cis*-isomer of alcohol **2b**.[15] Column chromatography on silica gel furnished pure alcohol **2b**. Removal of *N*-benzyl protecting group by means of palladium on carbon (10%) in ethanol, followed by alkylation of the chlorohydrate by means of Hüning base in acetonitrile[16] in the presence of alkylating halides, furnished the targets**7a-7d**. Sample **(SL34/81/1)** was prepared by simple NaOH/MeOH mediated hydrolysis of sample **2 (SL34/14/1)**.

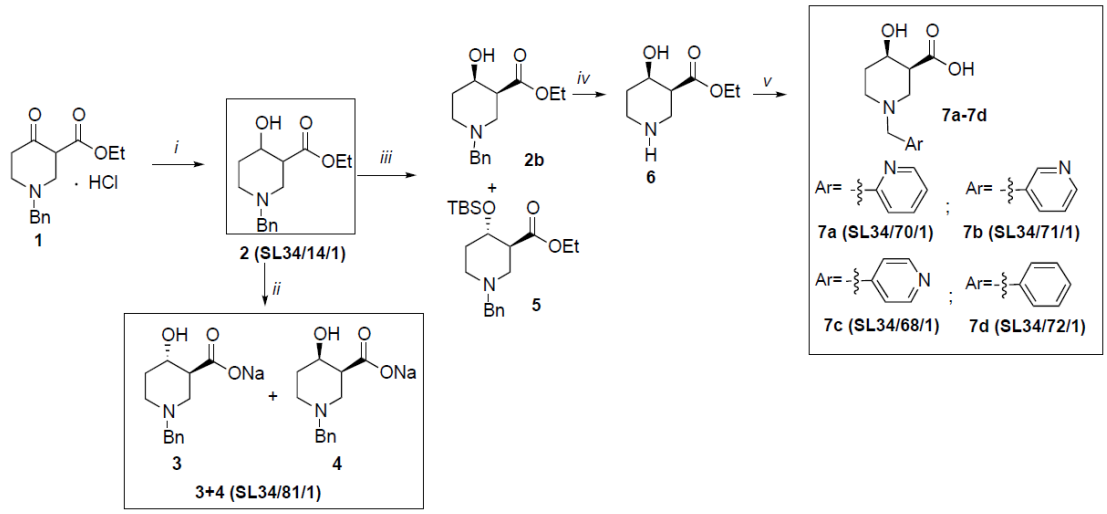

Chart 1. *Reagents and Conditions*. *i*: NEt_3, $NaBH_4/CH_3OH$. *ii*: $NaOH_{aq}$2M/MeOH (1/10). *iii*: TBDMSCl/Imidazole/DMF. *iv*: Pd/C (10%), EtOH; *v*: CH_3CN, base, $ArCH_2X$; and then *ii.*

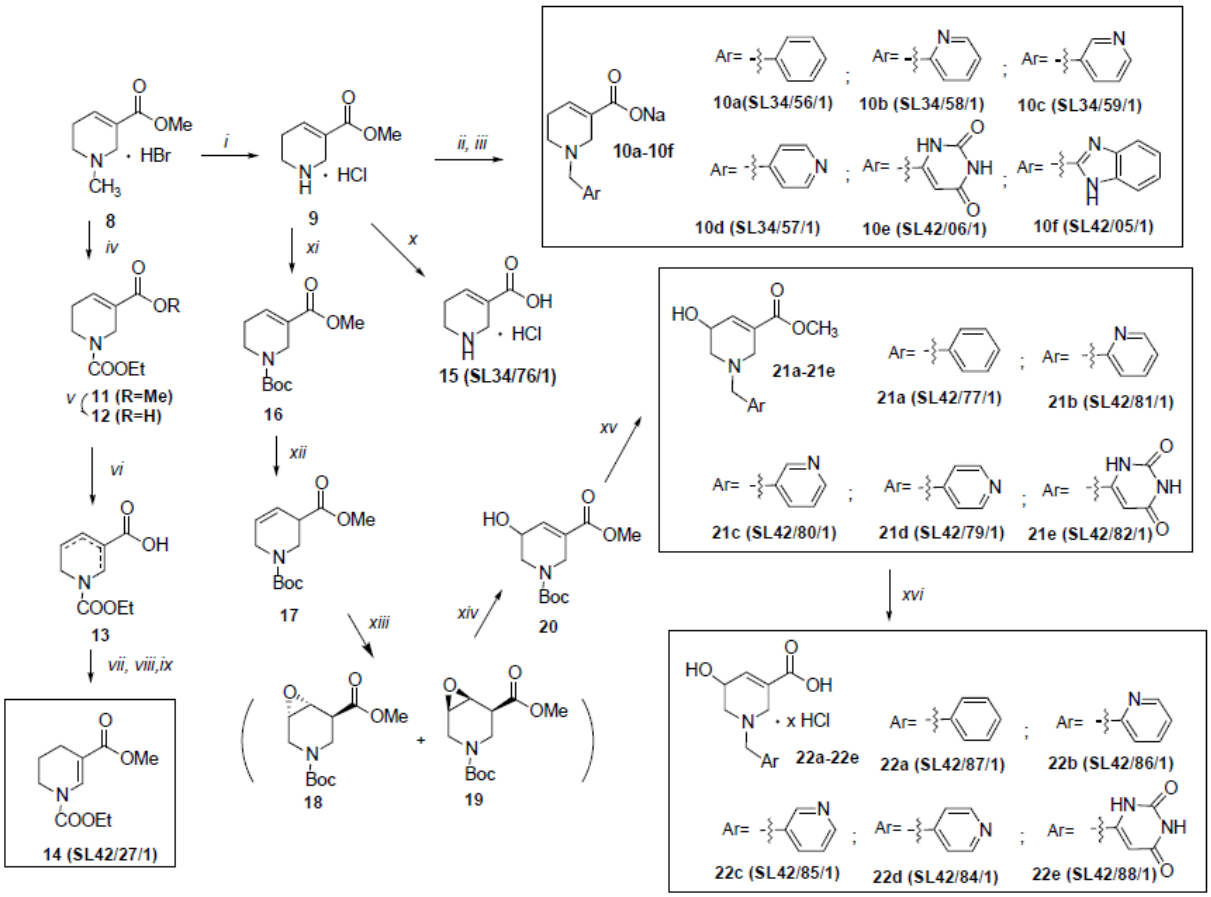

Chart 2. *Reagents and Conditions. i:* ACE-Cl, Toluene then MeOH; *ii:* (*for* **10a-10d)** $NaHCO_3$, EtOH, $ArCH_2X$ then *iii* $NaOH_{aq}$ 2M/MeOH (1/10); (*for* **10e-10f**) CH_3CN, base, $ArCH_2X$ then *iii* $NaOH_{aq}$ 2M/MeOH (1/10); *iv*: ClCOOEt, Toluene, Reflux; *v*: $NaOH_{aq}$ 5M/ Toluene, 50°C; *vi*: LDA, THF, HMPA (mixture of 2-3, 3-4, 4-5 *ene*-isomers **13**); *vii*: HCl_{aq} (1N); *viii:* $SOCl_2$/MeOH; *ix*: Flash chromatography; *x*: $NaOH_{aq}$ 2M/ Toluene,refulx. HCl/ether; *xi:* $NaOH_{aq}$, $(Bu^tOCOO)O_2$, Bu^tOH; *xii:* LDA, THF. *xiii*: MCPA/DCM; *xiv* : KOH/MeOH; *xv*: (a) TFA, DCM, (b) ACN, base, $ArCH_2X$; *xvi*: HCl (1N).

Preparations of samples **10a-10f** were realized as outlined into Chart 2[17] starting from commercially available arecoline hydrobromide **8**. Accordingly, demethylation of arecoline was performed by known procedure.[18] Product **15 (SL34/76/1)** was obtained from **9** by its hydrolysis and tested as such. The demethylated product **9**, in turn, was alkylated by the suitable alkyl halide in the presence of bicarbonate,[19] followed by hydrolysis with sodium hydroxide, to give the targets **10a (SL34/56/1)**, **10b (SL34/58/1)**, **10c (SL34/59/1)** and **10d (SL34/57/1)**.Targets **10e (SL42/06/1)** and **10f (42/05/1)** were synthetized by adopting, as alkylating procedure, that above described followed by hydrolysis by $NaOH_{aq/MeOH}$.[16] In order to test the potential activity of other double bond isomer, product **14 (SL42/27/1)** was prepared *via* an alternative demethylation procedure of arecoline with chloroformiate followed by isomerization of the resulting carbamate **12** (see Chart 2) with LDA, in the presence of hexametapol (HMPA), and SO_2Cl_2 mediated esterification with MeOH. The *N*-Boc protected 5-hydroxy guvacine scaffold **20** was obtained by means of oxidation of product **17** (see Chart 2) by meta-chloroperbenzoic acid followed by elimination to give intermediate **20**. After removal of *N-Boc* protecting group, the corresponding alkylation[16] furnished targets **21a (SL42/77/1)**, **21b (SL42/81/1)**, **21c (SL42/80/1)**, **21d (SL42/79/1)** and **21e (SL42/82/1)**. Hydrolysis of

the said products with hydrogen chloride furnished the end products **22a (SL42/87/1)**, **22b (SL42/86/1)**, **22c (SL42/85/1)**, **22d (SL42/84/1)** and **22e (SL42/88/1)** (see Chart 2).

1.2.2 Screening of the glycosidase activity

All the compounds underwent initial testing at 100 µM level. Given the presence of a carboxyl residue in sp^2 configuration on the azasugar mimicking the transition state of uronic acid, in addition to α-glucosidase the compounds were also tested on α-glucuronidase and hyluronidase (Table 1).

Table 1*: Effect of a series of compounds tested at 100 µM on a set of glycolytic enzymes.

	β-glucosidase (Almonds)	*β-glucuronidase (Helixpomatia)*	*α-glucosidase S.cereviasie*	*Hyaluronidase (Bovinetestes)*	*β-mannosidase (Jackbean)*	*β-mannosidase (Helixpomatia)*
SL34/14/1	-	95	100	103	-	-
SL34/56/1	-	89	97	100	-	-
SL34/57/1	-	95	99	99	-	-
SL34/58/1	-	96	95	101	-	-
SL34/59/1	-	102	102	99	-	-
SL34/68/1	-	108	85	100	-	-
SL34/70/1	-	103	95	100	-	-
SL34/71/1	-	104	97	100	-	-
SL34/72/1	-	102	82	100	-	-
SL34/81/1	-	102	82	100	-	-
SL42/05/1	-	100	93	100	-	-
SL42/06/1	-	100	97	102	-	-
SL42/27/1	88.7	96.3	109	100	104	97
SL42/77/1	71.7	93	92	99	84	100
SL42/79/1	83.3	105	94	99	98	107
SL42/80/1	86.8	102	105	99	104	111
SL42/81/1	82.3	103	97	100	93	78
SL42/82/1	87.4	97	95	100	101	71
SL42/84/1	99.2	103	3	104	78	89
SL42/85/1	96.5	100	2	102	94	117
SL42/86/1	90.4	103	2	101	79	96
SL42/87/1	99.6	97	95	101	104	97
SL42/88/1	111.3	102	3	100	85	96

*: The compounds were dissolved in DMSO not to exceed 1% of the total volume. The results were computed as percent of the enzymatic activity measured in the presence of DMSO alone. Details on the individual assays are given in the text.

None displayed activity toward these two enzymes. On the other hand, **SL42/84/1**, **SL42/85/1**, **SL42/86/1** and **SL42/88/1** were identified as potent α-glucosidase inhibitors. The IC50 of these compounds, evaluated over a concentration ranging between 0.1 to 100 µM, fell between 2 and 12 µM. Compound **SL42/85/1** displayed the highest inhibitory activity with IC_{50} of 2.2 µM. An inspection of the structure of the active compounds points to key features that are required for activity. Beside the critical presence of the 5-hydroxy residue not replaceable by the same substituent in 4 position as in **SL34/70/1**, **SL34/71/1**, **SL34/68/1**, a 3-carboxylate residue on the piperidine ring appears crucial since its esterification, as in compounds **SL42/79/1**, **SL42/80/1**, **SL42/81/1** and **SL42/82/1**, lead to loss of activity. By the same token, the presence of an *N*-substituent carrying an electron-dense region, appears critical given the absence of activity of **SL42/87/1** in which the pyridine or the 1,3-diazacyclohexan-2,6-dione rings are replaced by a benzene ring. The remarkable inhibitory activity of these compounds in spite of the reduced protonability of the tertiary amine and the other major structural changes introduced in comparison to the known α-glucosidase inhibitors, such as the reduced hydroxylation of the piperidine ring, lead us to consider the

possibility they could act through a different mechanism than that of the canonical transition state analogue of the D-glucosyl cabocation. Studies are currently on the way to confirm this hypothesis.

1.2.3 Conclusions

In the present investigation, a series of *N*-heteroarylmethyl 3-carboxy-5-hydroxy piperidine compounds was found endowed with potent α-glucosidase inhibitory activity. Distinctly from acarbose and the other clinically available inhibitors, the compounds displayed uncompetitive modality of enzyme inhibition which makes them good candidates for *in vivo* testing. The results from the biological evaluation of compounds whose structure is comprised within a rather limited chemical space have allowed the identification of structural features that are critical for the activity of this novel class of α-glucosidase inhibitors. A carboxylate and single hydroxyl residues properly positioned on the azasugar ring along with a suitable aglicone attached to the protonable nitrogen, were found to be necessary as well as sufficient for activity. The simple scaffold and the significant inhibitory activity observed are good starting points for further structural investigations on these molecules. The data gathered fill, at least in part, the inadequacy of information on the structure-activity relationship of uncompetitive α-glucosidase inhibitors and should serve as basis for the design and development of novel therapeutics for the treatment of diabetes mellitus and other diseases in which α-glucosidase is involved.

1.3 Experimental section

1.3.1 Chemistry: Material and Methods

All starting materials, unless otherwise stated, were purchased and used without any further purification. The starting material for the 4-hydroxy-piperidine-3-carboxylic acid scaffold was the commercially available ethyl 1-benzyl-4-oxopiperidine-3-carboxylate from Sigma Aldrich. For the compounds reported into Chart 2 the starting material was the commercially available Arecoline hydrobromide from Qingdao Sicemo, LTD, Qingdao, China. Solvents were distilled and dried according to standard procedures. 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. IR spectra were recorded on a Nicolet 380 FT-IR infrared spectrometer. 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*) 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. Elemental analyses were obtained at Laboratorio Scienze Ambientali (Ravenna, Italy) using a Flash 2000, series CHNS/O Analyzer (Thermo Scientific).

Preparation of ethyl 1-benzyl-4-hydroxypiperidine-3-carboxylate 2 (SL34/14/1)

Ethyl 1-benzyl-4-oxo-3-piperidine carboxlate hydrochloride **1** (5 g, 16.8 mmol) was dissolved into 130 mL methanol. NEt_3 (2.3 mL, 16.8 mmol) was dropped into this solution at 0℃ and kept stirring for 10

min at this temperature. $NaBH_4$ (2.1 g, 3.0 eq) was added into the reaction mixture in portions. The reaction mixture was kept at 0℃ for 2hrs. HCl_{aq} (5M) was added to adjust the pH =2~3. The solvent was partially removed to small volume under vacuum and the residue was neutralized by saturated $NaHCO_3$ solution. This mixture was extracted by CH_2Cl_2 (30mL×3). The organic phase was dried (Na_2SO_4) and the solvent removed under vacuum to get 3.64 g of yellow liquid as a mixture of two diastereomers which was purified by flash chromatography (AcOEt: cyclohexane =3:2) to give product **2** (**SL34/14/1**) (3.64 g, ratio: *trans/cis*=4/7, yield: 82.7%).

Spectra for (*3S*, 4S)-ethyl 1-benzyl-4-hydroxypiperidine-3-carboxylate 2a**

IR (film): 1731 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ= 1.18 (t, *J*=7.2 Hz, 3H), 1.57 (m, 1H), 1.87 (m, 1H), 2.03 (m, 2H), 2.53 (m, 1H), 2.78 (m, 1H), 3.04 (m, 1H), 3.45 (q_{AB}, *J*=13.6 Hz, 2H), 3.71 (m, 1H), 4.08 (m, 2H), 7.15-7.27 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ= 14.12, 32.57, 49.64, 51.33, 53.41, 60.88, 62.24, 69.67, 127.8, 128.28, 128.96, 173.38; MS (EI) m/z =263 [M]; Elemental Analysis: Calcd. for $C_{15}H_{21}NO_3$: C, 68.42; H, 8.04; N, 5.32; O, 18.23; Found: C, 68.64; H, 8.07; N, 5.34

Spectra for (*3S*, 4R)-ethyl 1-benzyl-4-hydroxypiperidine-3-carboxylate 2b**

IR (film): 1731 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ= 1.16 (t, *J*=7.2 Hz, 3H), 1.71 (m, 1H), 1.80 (m, 1H), 2.41 (m, 2H), 2.58 (m,1H), 2.68 (m, 2H), 3.41 (q_{AB}, *J*=13.2 Hz, 2H), 4.01 (m, 1H), 4.08 (m, 2H), 7.15-7.26 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ= 14.08, 31.51, 46.17, 50.62, 60.76, 62.70, 77.50, 127.19, 128.24, 129.08, 173.70; MS (EI) m/z = 263 [M].

Preparation of sodium 1-benzyl-4-hydroxypiperidine-3-carboxylates 3 and 4 (SL34/81/1)

Compound **2** (150 mg, 0.57 mmol) was mixed with $NaOH_{aq}$ (0.32 mL, 2 M) and MeOH (3 mL) for 3 hrs at r.t. After the reaction completed, the solvent was removed under vacuum. The residue was treated with anhydrous MeOH and filtered. The filtrate was concentrated under vacuum to get the mixture of two diastereomers (**SL34/81/1)** (140 mg, ratio: *trans*/*cis*= 2:3, yield: 95%)

Spectral data of mixture SL34/81/1

Sodium (3*S, 4*S**)-1-benzyl-4-hydroxypiperidine-3-carboxylate 3**

IR (film): 1644 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ=1.57 (dq, J_1=4.0 Hz, J_2=10.8 Hz, 1H), 1.88 (m, 1H), 2.05 (m, 2H), 2.31 (ddd, J_1=4.0 Hz, J_2=1.2 Hz, J_2=10.0 Hz,1H), 2.88 (m, 1H), 3.15 (m, 1H), 3.54 (q_{AB}, *J*=12.8 Hz, 2H), 3.61 (dt, J_1=4.8 Hz, J_2=10.8 Hz, 1H), 7.30 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ= 33.94, 49.43, 53.01, 55.88, 63.68, 71.89, 128.32, 129.25, 130.75, 138.61, 181.01; MS (ESI) m/z =234 $[M\text{-}Na]^-$; Elemental Analysis: Calcd. for $C_{13}H_{16}NNaO_3$: C, 60.69; H, 6.27; N, 5.44; Na, 8.94; O, 18.66; Found: C, 60.85; H, 6.29; N,5.45.

Sodium (3*S, 4*R**)-1-benzyl-4-hydroxypiperidine-3-carboxylate 4 (for the spectra of corresponding acid derivative see product 7d)**

IR (film): 1644 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ=1.75 (m, 2H), 2.44(m, 1H), 2.52 (m, 3H), 2.86 (m, 1H), 3.54 (q_{AB}, J=12.8 Hz, 2H), 4.11 (m, 1H), 7.30 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ= 32.16, 49.63, 52.57, 55.87, 64.22, 66.87, 128.26, 129.21, 130.65, 138.55, 181.56; MS (ESI) m/z =234 $[M\text{-}Na]^-$.

Preparation of (*3S*, 4R)-ethyl 1-benzyl-4-hydroxypiperidine-3-carboxylate 2b and (*3S*, 4S**)-ethyl 1-benzyl-4-(*ter*-butyldimethylsilyloxy)piperidine-3-carboxylate 5.**

The inseparable mixture of two diastereomers **2** (2.5 g, 9.5 mmol), was treated with imidazole (0.36 g, 5.2 mmol) and TBDMSCl (0.72 g, 4.75 mmol) in anhydrous DMF (16 mL) at r.t. After stirring for 5hrs the reaction mixture was decomposed with ice/water and extracted with CH_2Cl_2 (3×30 mL). The organic phase was washed by brine, dried by sodium sulphate and the solvent removed under vacuum to get yellow oil (3.3 g). Purification by flash chromatography (Ether : Cyclohexane=1:1) gave **2b** (1.17 g) and **5** (1.31 g) in 85% overall yields. Spectral data as follow:

(*3S*, 4R)-ethyl 1-benzyl-4-hydroxypiperidine-3-carboxylate 2b（for spectral data see compound 2）**

(*3S*, 4S)-ethyl-1-benzyl-4-(ter-butyldimethylsilyloxy)piperidine-3-carboxylate 5**

IR (film): 1732 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ= 0.01 (s, 3H), 0.04 (s, 3H), 0.85 (s, 9H), 1.23 (t, J= 7.2 Hz, 3H), 1.65 (m, 1H), 1.84 (m, 1H), 2.16 (t, J=12.0 Hz, 1H), 2.28 (t, J=12.0 Hz, 1H), 2.62 (dt, J_1=2.8 Hz, J_2=12.0 Hz, 1H), 2.80 (m, 1H), 2.89 (d, J=10.8 Hz, 1H), 3.52 (s, 2H), 3.90 (ddd, J_1=4.0 Hz, J_2=4.4 Hz, J_3=5.6 Hz, 1H), 4.09 (m, 2H), 7.20-7.31(m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ= 14.13, 20.26, 32.57, 44.42, 46.92, 60.80, 66.08, 173.82; MS (EI) m/z =377 [M]; Elemental Analysis: Calcd. for $C_{21}H_{35}NO_3Si$: C, 66.80; H, 9.34; N, 3.71; O, 12.71; Si, 7.44; Found: C,66.98; H, 9.37; N, 3,72.

Preparation of (*3S*, 4R)-ethyl 4-hydroxypiperidine-3-carboxylate hydrochloride 6**

Product **2b** (1.03 g, 3.9 mmol), Pd/C 10% (1.0 g) and EtOH (100 mL) were mixed together and left to react in Parr apparatus for 1.5 hrs under hydrogen pressure (15 psi). The reaction mixture was filtered through celite. The filtrate was concentrated under vacuum to obtain, as yellow oil, compound **6** (0.65 g, Yield: 96%). Spectral data were superimposable with literature data.[20]

Synthesis of (3*S, 4*R**)-4-hydroxy-1-(heteroarylmethyl)piperidine-3-carboxylic acids:**

Preparation of (3*S, 4*R**)-4-hydroxy-1-(pyridin-2-yl-methyl)piperidine-3-carboxylic acid 7a (SL34/70/1) as general procedure.**

Compound **6** (87 mg, 0.5 mmol), 2-(bromomethyl)-pyridine hydrobromide (126 mg, 0.5 mmol), *N*,*N*-diisopropyl ethyl amine (0.35 mL, 2.0 mmol) and CH_3CN (10 mL) were mixed together at 0℃. The reaction was kept at r.t. for 5 hrs. After the reaction completed (t.l.c. test) the solvent was concentrated under vacuum and the residue was dissolved in 20 mL CH_2Cl_2. The organic phase was washed by saturated $NaHCO_3$. The aqueous phase was extracted by CH_2Cl_2 (15 mL×2). The organic phase was collected, dried with sodium sulphate and the solvent removed under vacuum to afford a residue which was purified by

flash chromatograph (AcOEt: MeOH=1:1) to get pure compound **7a** (**SL34/70/1)** (100 mg, yield: 75.8%) identified as ethyl ester. Spectral data as follow

Ethylester of (3*S, 4*R**)-4-hydroxy-1-(pyridin-2-yl-methyl)piperidine-3-carboxylic acid 7a**

IR (film): 1728 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ= 1.17 (t, *J*=6.4 Hz, 3H), 1.81 (m, 2H), 2.51 (m, 2H), 2.71(m, 2H), 3.38 (bs, 1H, OH), 3.64 (q_{AB}, *J*=14.4 Hz, 2H), 4.11(m, 3H), 7.11(m, 1H), 7.34 (d, *J*=8.0 Hz, 1H), 7.59 (dt, J_1=2.0 Hz, J_2=7.6 Hz, 1H), 8.50 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ= 14.05, 31.71, 46.30, 47.13, 50.32, 60.61, 64.26, 65.74, 121.98, 122.98, 136.35, 149.10, 158.49, 173.56; MS (EI) m/z =264 [M]; Elemental Analysis: $C_{14}H_{20}N_2O_3$ C, 63.62; H, 7.63; N, 10.60; O, 18.16; Found: C, 63.81; H, 7.65; N, 10.63.

Product **7a** (**L34/70/1**) was obtained by treatment of the corresponding ester (100 mg, 0.43 mmol) with $NaOH_{aq}$ (0.32 mL, 2 M) and MeOH (2.5 mL) at r.t. for 5 hrs. The solvent was removed under *vacuum* to get a crude mixture which was purified by flash chromatography (AcOEt: acetone: H_2O: CH_3COOH= 5:3:2:2) to get pure **7a** (87 mg, yield: 92%)

IR (film): 1658 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ= 1.79 (m, 2H), 2.48 (m, 1H), 2.55 (m, 2H), 2.70 (bs, 2H), 3.61 (q_{AB}, *J*=13.6 Hz, 2H), 4.05 (bs, 1H), 7.33 (m, 1H), 7.30 (m, 1H), 7.54 (d, *J*=7.6 Hz, 1H), 7.81 (dt, J_1=1.2 Hz, J_2=7.6 Hz, 1H), 8.48 (m, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ= 32.57, 49.63, 49.85, 53.10, 65.09, 66.74, 123.78, 125.20, 138.60, 149.70, 159.44, 181.52; MS (EI) m/z =235 $[M-H]^-$; Elemental Analysis: Calcd. for $C_{12}H_{16}N_2O_3$: C, 61.00; H, 6.83; N, 11.86; O, 20.32; Found: C, 61.15; H, 6.85; N, 11.89.

Preparation of (3*S, 4*R**)-4-hydroxy-1-(pyridin-3-ylmethyl)piperidine-3-carboxylic acid 7b (SL34/71/1).**

This product was prepared following the above reported procedure for **SL34/70/1**. Starting from compound **6** (87 mg, 0.5 mmol), 3-(bromomethyl)-pyridine hydrobromide (126 mg, 0.5 mmol), the ethyl ester of **7b** was obtained after the flash chromatography (AcOEt: MeOH=1:1) (95 mg, yield: 72%).

IR (film): 1728 m^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ= 1.17 (t, *J*=7.2 Hz, 3H), 1.76 (m, 1H), 1.82 (m, 1H), 2.46 (m, 2H), 2.67 (m, 2H), 3.50 (bs, 1H), 3.50 (q_{AB}, *J*=13.6 Hz, 2H), 4.10 (m, 3H), 7.21 (dd, J_1=4.8 Hz, J_2=7.6 Hz,1H), 7.62 (d, *J*=7.6 Hz, 1H), 8.46 (d, *J*=14.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ= 14.05, 31.76, 46.33, 48.12, 50.93, 59.95, 60.66, 65.94, 123.28, 133.77, 136.59, 148.42, 150.19, 173.41; MS (EI) m/z =264 [M]; Elemental Analysis: Calcd. for $C_{14}H_{20}N_2O_3$: C, 63.62; H, 7.63; N, 10.60; O, 18.16; Found: C, 63.80; H, 7.65; N, 10.63.

Following the same procedure for the preparation of compound **SL34/70/1**, the ethyl ester of compound **7b** (95 mg, 0.41 mmol) was treated with $NaOH_{aq}$ (0.31 mL, 2 M) and MeOH (2.5 mL). After chromatography (AcOEt: acetone: H_2O: CH_3COOH= 5:3:2:2) **7b** was obtained (85 mg, yield: 94.4%)

IR (film): 1654 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ= 1.75 (m, 2H), 2.49 (m, 3H), 2.73 (m, 1H), 3.58 (q_{AB}, J=13.6 Hz, 2H), 4.10 (m, 1H), 7.40 (dd, J_1=5.6 Hz, J_2=8.0 Hz, 1H), 7.84 (dt, J_1=1.6 Hz, J_2=8.0 Hz, 1H), 8.43 (dd, J_1=1.2 Hz,J_2=4.8 Hz, 1H), 8.51 (d, J=1.6 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ= 32.49, 49.43, 49.63, 51.32, 51.32, 61.05, 66.78, 125.03, 125.07, 135.60, 139.35, 148.92, 151.00, 181.46; MS (EI) m/z =235 $[M-H]^-$; Elemental Analysis: Calcd. for $C_{12}H_{16}N_2O_3$: C, 61.00; H, 6.83; N, 11.86; O, 20.32; Found: C, 61.16; H, 6.85; N, 11.89.

Preparation of (3*S, 4*R**)-4-hydroxy-1-(pyridin-4-ylmethyl)piperidine-3-carboxylic acid 7c (SL34/68/1).**

This product was prepared following the above reported procedure for **SL34/70/1**. Starting from compound **6** (87 mg, 0.5 mmol), 4-(bromomethyl)-pyridine hydrobromide (126 mg, 0.5 mmol), ethyl ester of **7c** was obtained after the flash chromatography (AcOEt: MeOH=1:1) (100 mg, yield: 75.8%)

IR (film): 1728 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ= 1.17 (t, J=7.2 Hz, 3H), 1.79 (m, 2H), 2.45 (m, 2H), 2.66 (m, 2H), 3.48 (q_{AB}, J=14.8 Hz, 2H), 3.66 (bs, 1H, OH), 4.08 (q, J=7.2 Hz, 2H), 4.13(m, 1H), 7.21 (d, J=6.0 Hz, 2H), 8.45 (dd, J_1=1.2 Hz, J_2=4.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ= 14.06, 31.86, 46.41, 48.02, 51.03, 60.63, 61.47, 65.11, 123.67, 147.87, 149.50, 149.54, 173.29; MS (EI) m/z =264 [M]; Elemental Analysis: Calcd. for $C_{14}H_{20}N_2O_3$: C, 63.62; H, 7.63; N, 10.60; O, 18.16; Found: C, 63.79; H, 7.65; N, 10.63.

Following the same procedure for the preparation of compound **SL34/70/1**, starting from the corresponding ethyl ester of **7c** (100 mg, 0.43 mmol), $NaOH_{aq}$ (0.33 mL, 2 M) and MeOH (2.5 mL), compound **7c** was obtained after chromatography (AcOEt: acetone: H_2O: CH_3COOH= 5:3:2:2) (80 mg, yield: 84.6%)

IR (film): 1658 cm^{-1}; ^{1}H NMR (200 MHz, CD_3OD) δ= 1.77 (m, 2H), 2.58 (m, 4H), 3.57 (s, 2H), 4.06 (s, 1H), 7.40 (m, 2H), 8.40 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ= 32.59, 49.45, 49.66, 52.83, 62.58, 66.81, 125.80, 125.84, 149.94, 150.02, 150.42, 181.49; MS (EI) m/z =235 $[M-H]^-$; Elemental Analysis: Calcd. for $C_{12}H_{16}N_2O_3$: C, 61.00; H, 6.83; N, 11.86; O, 20.32 ; Found: C, 61.14; H, 6.85; N, 11.89.

Preparation of (3*S, 4*R**)-1-benzyl-4-hydroxypiperidine-3-carboxylic acid 7d (SL34/72/1)**

Compound **7d** (**SL34/72/1)** was obtained by hydrolysis of compound **2b** (100 mg, 0.43 mmol), $NaOH_{aq}$ (0.33 mL, 2 M) and MeOH (2.5 mL), removal of the solvent and flash chromatography of the residue (AcOEt: acetone: H_2O: CH_3COOH= 5:3:1:1) (88 mg, yield: 93.6%).

IR (film): 1644 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ= 1.76 (m, 2H), 2.44 (m, 1H), 2.53 (m, 3H), 2.83 (m, 1H), 3.54 (q_{AB}, J=13.2, 2H), 4.10 (m, 1H), 7.22-7.35 (m, 5H); ^{13}C NMR (100 MHz, CD_3OD) δ= 34.77, 51.86, 52.08, 52.29, 66.90. 69.82, 130.94, 131.89, 133.46, 141.24, 184.22; MS (EI) m/z = 234 $[M-H]^-$;

Elemental Analysis: Calcd. for $C_{13}H_{17}NO_3$:C, 66.36; H, 7.28; N, 5.95; O, 20.40; Found: C, 66.58; H, 7.30; N, 5.97.

Preparation of methyl 1,2,5,6-tetrahydropyridine-3-carboxylate hydrochloride 9

The pH of a solution of arecoline hydrobromide **8** (Qingdao Sicemo, LTD, Qingdao, China) (15.0 g) in water (30 mL) was adjusted to pH=13~14 by saturated Na_2CO_3 solution. This solution was extracted by ether (50 mL×3). The yellow oil (Arecoline, 9.8 g) was obtained after drying and removing the solvent.

Arecoline (1.55 g, 10 mmol) was dissolved into 35mL CH_2Cl_2. A mixture of ACE-Cl (1.2 mL, 11mmol) and $ClCH_2CH_2Cl$ (2 mL) was dropped into the reaction mixture at 0 °C and kept stirring for 15 min. The temperature was risen to 100 °C and the mixture refluxed for 6 hrs (monitor by TLC). The solvent was removed under vacuum. The residue was dissolved into 25 mL methanol. This reaction mixture was kept refluxing at 110 °C for 6 hrs until the reaction completed (monitor by TLC: AcOEt : Cyclohexane=3:2). Then the solvent was removed to get compound **9** (0.83 g, two steps overall yield: 58.5%). This product is directly used in the next step without any further purification.

IR (film): 1710 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ= 1.72 (s, 1H, NH), 2.19 (m, 2H), 2.87 (t, *J*=5.7 Hz, 2H), 3.49 (m, 2H), 3.68 (s, 3H), 6.99 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ= 26.15, 41.83, 44.02, 51.40, 130.26, 138.22, 166.41; MS (EI) m/z =141 [M-HCl]; Elemental Analysis: Calcd. for $C_7H_{12}ClNO_2$: C, 47.33; H, 6.81; Cl, 19.96; N, 7.89; O, 18.01; Found: C, 47.48; H, 6.83; N, 7.92.

Synthesis of sodium-1-(heteroarylmethyl)-1,2,5,6-tetrahydropyridine-3-carboxylates:

Preparation of sodium-1-benzyl-1,2,5,6-tetrahydropyridine-3-carboxylate 10a (SL34/56/1) as general procedure.

$NaHCO_3$ (179 mg, 2.24 mmol) and EtOH (20 mL) were mixed together and keeping stirring at 0 °C for 5mins. Then product **9** (100 mg, 0.56 mmol) and (bromomethyl)-benzene (96.6 mg, 0.56 mmol) were added into the mixture at 0° C. The reaction mixture was refluxed at 110 °C for 5 hrs until the reaction was completed (t.l.c. test). The solvent was removed under vacuum and the residue was dissolved with 20 mL CH_2Cl_2. The organic phase was washed by saturated $NaHCO_3$. The aqueous phase was extracted by CH_2Cl_2 (15mL×3). The organic phase was collected, dried with sodium sulphate and concentrated under vacuum to get crude product. This crude product was purified by flash chromatography (AcOEt: cyclohexane = 1:4) to get **10a-methyl ester** (50 mg, yield: 55.7%) which was identified by its spectral data.

IR (KBr): 1722 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ= 2.33 (m, 2H), 2.54 (t, *J*=5.6 Hz, 2H), 3.24 (m, 2H), 3.66 (s, 2H), 3.73 (s, 3H), 7.02 (m, 1H), 7.25-7.37 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ= 26.55, 48.30, 51.47, 51.62, 62.44, 127.12, 128.28, 129.05, 138.00, 166.35; MS (EI) m/z =231 [M]; Elemental Analysis: Calcd. for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06; O, 13.83; Found: C, 72.90; H, 7.43; N, 6.08.

Methyl ester derivative of **10a** (45 mg) was dissolved in 1 mL of MeOH. Then 0.145 mL of $NaOH_{aq}$ (2 M) was added. This reaction mixture was kept at 50 °C for 2.5 hrs. After the reaction completed, the

solvent was removed under vacuum to get the crude product. This crude product was dissolved into the anhydrous MeOH and filtered. The filtrate was concentrated under vacuum to get the pure **10a** (**SL34/56/1**) (40 mg, yield: 85%)

IR (film): 1700 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ= 2.63 (m, 2H), 3.31 (m, 4H), 4.44 (s, 2H), 7.21 (m, 1H), 7.44-7.59 (m, 5H); ^{13}C NMR (100 MHz, CD_3OD) δ= 23.91, 60.79, 125.41, 130.26, 130.39, 131.29, 132.41, 138.05, 138.08, 166.65; MS (ESI) m/z = 216 $[M\text{-}Na]^-$; Elemental Analysis: Calcd.for$C_{13}H_{14}NNaO_2$: C, 65.26; H, 5.90; N, 5.85; Na, 9.61; O, 13.37; Found: C, 65.48; H, 5.92; N, 5.87.

Preparation of sodium 1-(pyridin-2-ylmethyl)-1,2,5,6-tetrahydropyridine-3-carboxylate 10b (SL34/58/1)

Following the same procedure for the preparation of compound (**SL34/56/1**), starting from $NaHCO_3$ (239 mg, 2.84 mmol), EtOH (20 mL), product **9** (126 mg, 0.71 mmol) and 2-(bromomethyl)pyridine hydrobromide (179 mg, 0.71 mmol), compound **10b-methyl ester** was obtained after flash chromatography (AcOEt : MeOH =9 :1) (127 mg, yield: 77.0%)

IR (film): 1722 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ= 2.36 (m, 2H), 2.61 (t, J=5.6 Hz, 2H), 3.28 (q_{AB}, J= 2.8 Hz, 2H), 3.71 (s, 3H), 3.80 (s, 1H), 7.02 (m, 1H), 7.17 (m, 1H), 7.42 (d, J=8.0 Hz, 1H), 8.44 (dt, J_1=1.2 Hz, J_2=7.6 Hz, 1H), 8.57 (d, J=4.8 Hz , 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ= 26.46, 48.73, 51.62, 63.96, 122.07, 122.99, 128.93, 136.45, 137.94, 149.25, 158.48, 166.79; MS (EI) m/z =232[M]; Elemental Analysis: Calcd. for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.06; O, 13.78; Found: C, 67.46; H, 6.96; N, 12.10.

Following the same procedure for the preparation of compound (**SL34/56/1**), starting from the corresponding ester of **10b** (87 mg, 0.38 mmol), and 0.28 ml of $NaOH_{aq}$ (2 M), compound **10b** (**SL34/58/1**) was obtained (72 mg, yield: 80%)

IR (film): 1662 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ= 2.29 (m, 2H), 2.57 (t, J=5.6 Hz, 2H), 3.27 (dd, J_1=2.8 Hz, J_2=4.8 Hz, 2H), 3.79 (s, 2H), 6.69 (m, 1H), 7.32 (dddd, J_1=1.2 Hz, J_2=4.8 Hz, J_3=7.6 Hz, 1H), 7.56 (dt, J_1=7.6 Hz, J_2=1.2 Hz, 1H), 7.83 (dt, J_1=2.0 Hz, J_2=7.6 Hz, 1H), 8.50 (m, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ= 26.85, 50.30, 54.39, 64.61, 123.92, 125.24, 132.14, 135.78, 138.70, 149.65, 159.21, 174.70; MS (ESI) m/z = 217 $[M\text{-}Na]^-$; Elemental Analysis: Calcd. for $C_{12}H_{13}N_2NaO_2$: C, 60.00; H, 5.45; N, 11.66; Na, 9.57; O, 13.32; Found: C, 60.17; H, 5.47; N, 11.69.

Preparation of sodium 1-(pyridin-3-ylmethyl)-1,2,5,6-tetrahydropyridine-3-carboxylate 10c (SL34/59/1)

Following the same procedure for the preparation of compound **SL34/56/1**, starting from $NaHCO_3$ (239 mg, 2.84 mmol), EtOH (20 mL), product **9** (126 mg, 0.71 mmol) and 3-(bromomethyl)pyridine hydrobromide (179 mg, 0.71 mmol), compound (**SL34/59/1-methyl ester**) was obtained after flash chromatography (AcOEt : MeOH =98:2) (70 mg, yield: 42.4%)

IR (film): 1712 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ= 2.31 (m, 2H), 2.53 (t, *J*=5.6 Hz, 2H), 3.20 (m, 2H), 3.63 (s, 2H), 3.70 (s, 3H), 7.00 (m, 1H), 7.24 (m, 1H), 7.67 (d, *J*= 8.0 Hz, 1H), 8.50 (d, *J*= 4.4 Hz, 1H), 8.55 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ= 26.44, 48.35, 51.53, 51.56, 59.58, 123.36, 128.79, 133.52, 136.56, 137.90, 148.68, 150.30, 166.17; MS (EI) m/z =232 [M]; Elemental Analysis: Calcd. for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.06; O, 13.78; Found: C,67.38; H, 6.96; N,12.09.

Following the same procedure for the preparation of compound (**SL34/56/1**), starting from the **SL34/59/1-methyl ester** (70 mg, 0.30 mmol), and 0.23 ml of $NaOH_{aq}$ (2 M), compound **10c** (**SL34/59/1**) was obtained (60 mg, yield: 83%)

IR (film): 1663 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ= 2.30 (m, 2H), 2.60 (t, *J*=5.6 Hz, 2H), 3.21 (dd, J_1=2.4 Hz, J_2=4.4 Hz, 2H), 3.70 (s, 2H), 6.69 (m, 1H), 7.41 (dddd, J_1=0.8 Hz, J_2=5.2 Hz, J_3=7.6 Hz, 1H), 7.89 (dt, J_1=1.6 Hz, J_2=8.0 Hz, 1H), 8.45 (dd, J_1=1.6 Hz, J_2=4.8 Hz, 1H), 8.53 (m, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ= 26.80, 50.11, 54.11, 60.57, 125.12, 125.14, 132.04, 132.16, 135.36, 135.61, 139.51, 148.99, 151.12, 174.59; MS (ESI) m/z =217 $[M\text{-}Na]^-$; Elemental Analysis: Calcd. for $C_{12}H_{13}N_2NaO_2$: C, 60.00; H, 5.45; N, 11.66; Na, 9.57; O, 13.32; Found: C, 60.19; H, 5.47; N, 11.70.

Preparation of sodium 1-(pyridin-4-ylmethyl)-1,2,5,6-tetrahydropyridine-3-carboxylate 10d (SL34/57/1)

Following the same procedure for the preparation of compound **SL34/56/1**, starting from $NaHCO_3$ (239 mg, 2.84 mmol), EtOH (20 mL), product **9** (126 mg, 0.71 mmol) and 4-(bromomethyl)pyridine hydrobromide (179 mg, 0.71 mmol), compound (**SL34/57/1-methyl ester**) was obtained after flash chromatography (AcOEt : MeOH =8:1) (80 mg, yield: 48.5%)

IR (film): 1710 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ= 2.35 (m, 2H), 2.52 (m, 2H), 3.22 (m, 2H), 3.64 (s, 2H), 3.72 (s, 3H), 7.02 (m, 1H), 7.28 (d, *J*= 6.0 Hz, 2H), 8.54 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ= 26.44, 48.59, 51.51, 51.65, 61.12, 123.67, 128.81, 137.88, 147.50, 149.83, 165.15; MS (EI) m/z =232 [M]; Elemental Analysis: Calcd. for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.06; O, 13.78; Found: C, 67.41; H, 6.96; N, 12.09.

Following the same procedure for the preparation of compound (**SL34/56/1**), starting from **SL34/57/1-methyl ester** (150 mg, 0.56 mmol), and 0.70 ml of $NaOH_{aq}$ (2 M), compound **10d** (**SL34/57/1**) was obtained (114 mg, yield: 85%)

IR (film): 1666 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ= 2.31 (m, 2H), 2.55 (t, *J*=6.0 Hz, 2H), 3.22 (dd, J_1=2.4 Hz, J_2=4.8 Hz, 2H), 3.70 (s, 2H), 6.69 (m, 1H), 7.46 (d, *J*=7.2 Hz, 2H), 8.46 (d, *J*=7.2 Hz, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ= 26.84, 50.31, 54.30, 62.24, 125.93, 125.96, 132.03, 132.14, 135.68, 149.99, 150.07, 174.61; MS (EI) m/z =217 $[M\text{-}Na]^-$; Elemental Analysis: Calcd. for $C_{12}H_{13}N_2NaO_2$: C, 60.00; H, 5.45; N, 11.66; Na, 9.57; O, 13.32; Found: C, 60.18; H, 5.47; N,11.69.

Preparation of sodium 1-((2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)methyl)-1,2,5,6-tetrahydropyridine-3-carboxylate 10e (SL42/06/1)

Product **9** (150 mg, 0.85 mmol), 6-(chloromethyl)uracil (137 mg, 0.85 mmol) and diisopropyl ethyl amine (0.739 mL, 4.25 mmol) were mixed in 15 mL of CH_3CN. This reaction mixture was kept at r.t. for 3 hrs. After the reaction completed (t.l.c testing), the solvent was removed under vacuum to get the crude product. This crude product was purified after flash chromatography (AcOEt : MeOH =3:1) to get **SL42/06/1-methyl ester** (150 mg, yield: 66.7%)

IR (film): 1733, 1716, 1700, 1653 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ= 2.40 (m, 2H), 2.58 (t, *J*=6.0 Hz, 2H), 3.23 (q_{AB}, *J*=2.8 Hz, 2H), 3.42 (d, *J*= 1.2 Hz, 2H), 3.73 (s, 3H), 4.35 (s, 1H), 7.03 (m, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ= 27.19, 41.27, 48.37, 52.21, 58.66, 100.40, 129.61, 139.33, 155.35, 167.64; MS (EI) m/z = 266 [M+1]; Elemental Analysis: Calcd. for $C_{12}H_{15}N_3O_4$: C, 54.33; H, 5.70; N, 15.84; O, 24.13; Found: C, 54.43; H, 5.71; N, 15.87.

The **SL42/06/1-methyl ester** (50 mg, 0.18 mmol) was treated with $NaOH_{aq}$ (2 M, 0.43 mL) at 50°C for 3 hrs. After the hydrolysis was completed, the solvent was removed under vacuum. The residue was dissolved in anhydrous MeOH (5 mL). The mixture was filtered. The solution was concentrated under vacuum to give **10e** (**SL42/06/1**) (25 mg, 48 %)

IR (film): 1715, 1670 cm^{-1}; ^1H NMR (400 MHz, D_2O) δ= 2.50 (m, 2H), 3.03 (m, 2H), 3.59 (m, 2H), 3.85 (m, 2H), 5.92 (m, 1H), 6.77 (m, 1H); ^{13}C NMR (100 MHz, D_2O) δ= 23.61, 48.36, 51.35, 56.09, 102.44, 130.12, 133.00, 149.98, 152.81, 166.53, 172.85; MS (ESI) m/z =274 [M+H]; Elemental Analysis: Calcd. for $C_{11}H_{12}N_3NaO_4$: C, 48.36; H, 4.43; N, 15.38; Na, 8.41; O, 23.42; Found: C, 48.46; H, 4.44; N, 15.41.

Preparation of sodium 1-((1*H*-benzo[*d*]imidazol-2-yl)methyl)-1,2,5,6-tetrahydropyridine-3-carboxylate 10f (SL42/05/1)

Following the same procedure for the preparation of **SL42/06/1**, starting from **9** (150 mg, 0.85 mmol), 2-(chloromethyl)-benzimidazole (142 mg, 0.85 mmol) and diisopropyl ethyl amine (0.443 mL, 2.55 mmol), compound **SL42/05/1-methyl ester** (50 mg, yield: 21.7%) was obtained after flash chromatography (AcOEt : cyclohexane = 3:1)

IR (film): 1709 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ= 2.33 (m, 2H), 2.64 (t, *J*=5.2 Hz, 2H), 3.31 (q_{AB}, *J*=2.8 Hz, 2H), 3.70 (s, 3H), 3.96 (s, 2H), 7.01 (m, 1H), 7.22 (m, 2H), 7.57(m, 2H), 10.42 (bs, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ= 26.30, 48.90, 51.63, 51.72, 55.85, 12.38, 137.82, 152.09, 166.05; MS (EI) m/z = 240 [M-OCH_3]; Elemental Analysis: Calcd. for $C_{15}H_{17}N_3O_2$: C, 66.40; H, 6.32; N, 15.49; O, 11.79; Found: C, 66.57; H, 6.34; N, 15.53.

Following the same procedure for the preparation of compound **SL42/06/1**, starting from **SL42/05/1-methyl ester** (50 mg, 0.18 mmol), and 0.14 ml of $NaOH_{aq}$ (2 M), compound **10f** (**SL42/05/1**) was obtained (30 mg, yield: 60%)

IR (film): 1663 cm^{-1}; ^1H NMR (400 MHz, D_2O) δ= 2.42 (m, 2H), 2.96 (m, 2H), 3.55 (m, 2H), 4.22 (m, 2H), 6.70 (m, 1H), 7.32 (m, 2H), 7.61 (m, 2H); ^{13}C NMR (100 MHz, D_2O) δ= 23.73, 47.94, 51.06, 52.63,

115.02, 123.30, 130.54, 132.58, 147.06, 173.10; MS (ESI) m/z =280 [M+H]; Elemental Analysis: Calcd. for $C_{14}H_{14}N_3NaO_2$: C, 60.21; H, 5.05; N, 15.05; Na, 8.23; O, 11.46; Found: C, 60.43; H, 5.07; N,15.10.

Preparation of 1-ethyl 3-methyl 5,6-dihydropyridine-1,3(2*H*)-dicarboxylate 11

The pH of a solution of arecoline hydrobromide **8** (Qingdao Sicemo, LTD, Qingdao, China) (15.0 g) in water (30 mL) was adjusted to 13~14 by saturated Na_2CO_3 solution. This solution was extracted by ether (50 mL×3). The yellow oil (Arecoline, 9.8 g) was obtained after drying and removing the solvent.

Arecoline (6.59 g, 42.5 mmol) was dissolved into 80ml toluene at 0℃. A mixture of ClCOOEt (12.24 mL, 11 mmol) and toluene (20 mL) was dropped into the reaction mixture at 0 ℃ in 1 hour and kept stirring for 15 min at this temperature. Then the temperature was increased to 100 ℃ and refluxed for 2.5 hrs. This reaction was decomposed with ice water and the pH adjusted to 2-3 with HCl_{aq} (1 M). The mixture was extracted by AcOEt (20 mL×3). The organic phase was washed by NaHCO3 and brine, dried and the solvent removed under vacuum to get **11** as yellow oil (5.8 g, yield: 64%)

IR (film): 1704 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ= 1.26 (t, J=7.1 Hz, 3H), 2.31(m, 2H), 3.52 (t, J=5.6 Hz, 2H), 3.75(s, 3H), 4.16 (m, 4H), 7.07 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ= 14.65, 25.37, 39.19, 42.49, 51.69, 61.44, 128.96, 137.78, 155.54, 165.64; MS (EI) m/z =213 [M]; Elemental Analysis: Calcd. for $C_{10}H_{15}NO_4$: C, 56.33; H, 7.09; N, 6.57; O, 30.01; Found: C, 56.54; H, 7.12; N,6.59.

Preparation of 1-(ethoxycarbonyl)-1,2,5,6-tetrahydropyridine-3-carboxylic acid 12

Product **11** (462 mg, 2.0 mmol) was dissolved into 10 ml toluene at 0 °C. A solution of $NaOH_{aq}$ (0.6 mL, 5 M) was dropped into the reaction mixture at 0 °C. Then the temperature was rose to 50 °C for 5.5 hrs. The reaction mixture was decomposed with ice water, adjusted the pH to 2-3 with HCl_{aq} (1 M) and extracted with AcOEt (25 mL × 3). The organic phase was collected, dried with Na_2SO_4 and the solvent removed under vacuum to get compound **12** (390 mg, 98%). This product was directly used for the next step without any further purification.

IR (film): 1705, 1687 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ= 1.28 (t, J=8.8 Hz, 3H), 2.32 (m, 2H), 3.53 (t, J=5.6 Hz, 2H), 3.76 (m, 4H), 7.08(s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ= 14.60, 25.51, 42.24, 48.11, 61.74, 127.87, 140.23, 157.89, 169.91; MS (EI) m/z =199 [M]; Elemental Analysis: Calcd. for $C_9H_{13}NO_4$: C, 54.26; H, 6.58; N, 7.03; O, 32.13; Found: C, 54.44; H, 6.60; N,7.05.

Preparation of 1-ethyl 3-methyl 5,6-dihydropyridine-1,3(4H)-dicarboxylate 14 (SL42/27/1)

BuLi (2.2 mL, 2.5M in THF, 5.5 mmol) was added into a solution of diisopropyl ethyl amine (0.70 mL, 5.0 mmol) in THF (20 mL) at -78 °C. The temperature was rose to -10 °C and 4 ml of HMPA were added at this temperature. This reaction mixture was kept at this temperature for 30mins and then cooled

down to -78 °C again. A solution of compound **12** (500 mg, 2.5 mmol) in THF (5 mL) was dropped into the base solution at -78 °C. This reaction mixture was kept at -78 °C for 3 hrs, then poured into a cold saturated NH_4Cl_{aq} (20 mL). The pH was adjusted to pH=2-3 and the mixture was extracted with AcOEt (30 mL × 3). The organic phase was washed with HCl (1 M) and brine, dried with Na_2SO_4 and evaporated to get crude product which was purified by flash chromatography (AcOEt : Cyclohexane =3:1) to get a mixture of *ene*-isomers **13**. This mixture was processed in the next step without any purification.

The mixture of isomers **13** (360 mg, 1.81 mmol) was directly dissolved into 1 mL of MeOH. This solution was added into a solution of SO_2Cl_2 (2.88 mL) in MeOH (20 mL) at 0^oC. This reaction mixture was kept at 0 ^oC for 1hr. After the reaction completed, the solvent was removed to get the crude product which was purified by column chromatography (AcOEt : cyclohexane= 1:4) to give pure compound **14** (**SL42/27/1)**.

IR (film): 1724, 1700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ= 1.34 (t, *J*=6.8 Hz, 3H), 1.85 (m, 2H), 2.32 (dt, *J*=1.2 Hz, *J*=6.0 Hz, 2H), 3.61 (m, 2H), 3.74(s, 3H), 4.27 (q, *J*=6.8 Hz, 1H), 8.03 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ= 14.45, 20.63, 20.89, 42.16, 51.32, 62.76, 102.12, 135.47, 153.36, 167.96; MS (EI) m/z =213 [M]; Elemental Analysis: Calcd. for $C_{10}H_{15}NO_4$: C, 56.33; H, 7.09; N, 6.57; O, 30.01; Found: C, 56.50; H, 7.11; N, 6.59.

Preparation of 1,4,5,6-tetrahydropyridine-3-carboxylic acid hydrochloride 15 (SL34/76/1)

Product **9** (500 mg, 2.82 mmol) was dissolved into 10ml toluene at 0 °C. A solution of $NaOH_{aq}$ (8.6 mL, 2 M) was dropped into the reaction mixture at 0 °C. Then the temperature was rose to 110 °C and kept for 6 hrs (monitoring by tlc: AcOEt/ acetone/ water/ acetic acid=5:3:2:2). The reaction mixture was decomposed with ice water and the pH adjusted to 2-3 with HCl_{aq} (3 M). The solvent was removed under vacuum. The residue was treated with ethereal hydrogen chloride and filtered to get pure **15**[21,22](330 mg, 92%).

mp: 305 °C (Decomp).IR (film): 1665 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ= 2.27 (m, 2H), 2.92 (t, *J*=6.0 Hz, 2H), 3.56 (m, 2H), 6.75 (m, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ= 24.32, 41.00, 44.13, 130.86, 134.50, 173.12.

Preparation of 1-*tert*-butyl 3-methyl 5,6-dihydropyridine-1,3(2H)-dicarboxylate 16

Compound **9** (5.49 g, 31.0 mmol) was mixed with triethylamine (5.65 mL, 40.3 mmol) and di-*tert*-butyl dicabonate (10.14 g, 46.5 mmol) in 60 mL of anhydrous methanol at r.t. The reaction mixture was kept overnight. After removing the solvent under vacuum, 60 mL of water were added to the residue. The pH of the mixture was adjusted to 4-5 and extracted with ethyl acetate (80 mL×3). The collected organic phase were dried and evaporated to get the compound **16** (11.08 g, Yield: 79%). Spectral data were superimposable with literature data.[23]

Preparation of 1-*tert*-butyl 3-methyl 2,3-dihydropyridine-1,3(6*H*)-dicarboxylate 17

BuLi (8.96 mL, 2.5 M in THF) was added into a solution of diisopropyl ethyl amine (3.15 mL, 22.41 mmol) in THF (35 mL) at -78°C. Then the temperature was rose to -10 °C for 30 min and then cooled down to -78°C. A solution of compound **16** (3 g, 12.45 mmol) in THF (10 mL) was dropped into the base solution and kept for 3 min. The reaction mixture was poured into a cold NH_4Cl solution (1M, 80 mL) and extracted with ether (60 mL × 3). The organic phase was collected, dried and evaporated to get crude product which was purified by flash chromatography (AcOEt : Cyclohexane =1:4) to give pure compound **17** (1.48 g, yield: 49.3%). Spectral data were superimposable with literature data.[23]

Preparation of (1*S,5*S**,6*R**)-3-*tert*-butyl 5-methyl 7-oxa-3-azabicyclo[4.1.0]heptane-3,5-dicarboxylate 18 and (1*R**,5*S**,6*S**)-3-*tert*-butyl 5-methyl 7-oxa-3-azabicyclo[4.1.0]heptane-3,5-dicarboxylate 19**

Product **17** (250 mg, 1.03 mmol) was dissolved into anhydrous CH_2Cl_2 (20 mL). 3-Chloroperbenzoic acid (MCPA, 357 mg, 2.06 mmol) was added. The reaction mixture was kept at r.t for 3 hrs, then an extra 1 eq. of MCPA (179 mg, 1.03 mmol) was added and the mixture left overnight. The reaction was decomposed with $Na_2S_2O_5$ and extracted with AcOEt (15 mL × 3). The organic phase was collected, washed with $Na_2S_2O_5$, brine, dried with Na_2SO_4 and evaporated to get a crude mixture of **18** and **19** which was purified by flash chromatography (AcOEt : cyclohexane =1:4) (175 mg, overall yield: 66%).

An aliquot of the mixture was further purified to get pure isolated **18** and **19**. Spectral data as follow

18: White solid. Mp: 70-74°C; IR (film): 1738, 1698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ= 1.45 (s, 9H), 3.00 (m, 2H), 3.34 (m, 1H), 3.42 (d, *J*=15.2 Hz, 1H), 3.61 (d, *J*=4.0 Hz, 1H), 3.76 (s, 3H), 3.84-4.20 (m, 2H); ^{13}C NMR (100 MHz,$CDCl_3$) δ= 28.33, 38.10, 38.92, 41.28, 50.89, 51.22, 52.17, 80.30, 154.32, 170.88. MS (EI) m/z =242 [M-CH_3]; Elemental Analysis: Calcd. for $C_{12}H_{19}NO_5$: C, 56.02; H, 7.44; N, 5.44; O, 31.09; Found: C, 56.15; H, 7.46; N, 5.45.

19: Oil. IR (film): 1738, 1698 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ=1.41 (s, 9H), 3.03 (d, *J*=19.2 Hz 1H), 3.23 (d, *J*=20.8 Hz 1H), 3.44 (m, 1H), 3.48 (dd, J_1=4.0 Hz, J_2=1.2 Hz, 1H), 3.57 (m, 1H), 3.71(s, 3H), 3.78 (m, 1H); ^{13}C NMR (100 MHz,$CDCl_3$) δ= 28.26, 39.80, 40.35, 42.03, 50.00, 50.90, 52.14, 80.13,154.75, 171.48. MS (EI) m/z =242 [M-CH_3]; Elemental Analysis: Calcd. for $C_{12}H_{19}NO_5$: C, 56.02; H, 7.44; N, 5.44; O, 31.09; Found: C, 56.17; H, 7.46; N, 5.46.

Preparation of 1-*tert*-butyl 3-methyl 5-hydroxy-5,6-dihydropyridine-1,3(2*H*)-dicarboxylate 20.

A mixture of compounds **18** and **19** (500 mg, 2.02 mmol) and KOH solid (226 mg, 4.04 mmol) were dissolved in 20 mL of MeOH. The reaction mixture was kept at r.t for 30 min. The pH of the reaction was adjusted to 6-7 by HCl_{aq} (2 M). The solvent was removed under vacuum. The residue was mixed with 20 mL of water and extracted with AcOEt (15 mL × 3). The organic phase was collected, dried with Na_2SO_4

and evaporated. The crude product was purified by flash chromatography (AcOEt : cyclohexane =2:3) to get pure compound **20** (350 mg, yield: 67%).

White solid. Mp: 78-85 ^{o}C; IR (film): 1699 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ=1.47 (s, 9H), 3.49-3.51(m, 1H), 3.65-3.73 (m, 1H), 3.78 (s, 3H), 3.97 (dt, J_1=18.4 Hz, J_2=2.4 Hz, 1H), 4.18 (dt, J_1=18.4 Hz, J_2=2.0 Hz, 1H), 4.26 (m, 1H), 6.92 (m, 1H); ^{13}C NMR (100 MHz,$CDCl_3$) δ= 28.43, 42.78, 46.16, 52.05, 63.46, 80.72, 129.34, 139.79, 154.95, 165.66. MS (EI) m/z =257 [M]; Elemental Analysis: Calcd. for $C_{12}H_{19}NO_5$: C, 56.02; H, 7.44; N, 5.44; O, 31.09; Found: C, 56.17; H, 7.46; N, 5.46.

Synthesis of methyl 1-(heteroarylmethyl)-5-hydroxy-1,2,5,6-tetrahydropyridine-3-carboxylates:

Preparation of methyl 1-benzyl-5-hydroxy-1,2,5,6-tetrahydropyridine-3-carboxylate 21a (SL42/77/1) and 1-benzyl-5-hydroxy-1,2,5,6-tetrahydropyridine-3-carboxylic acid hydrochloride 22a (SL42/87/1) (as general procedure).

Compound **20** (100 mg, 0.39 mmol) was dissolved in 3 mL of CH_2Cl_2. TFA (3 mL) was added into this solution at 0 ^{o}C. The reaction mixture was kept at 0 ^{o}C for 20mins. The solvent was removed under vacuum. The crude residue was dissolved in 10 ml of CH_3CN. (Bromomethyl)benzene (67 mg, 0.389 mmol) and diisopropyl ethyl amine (0.27 mL, 1.56 mmol) were added into the solution at 0 ^{o}C. This reaction mixture was kept at r.t. for 3hrs. After the reaction completed, the solvent was removed under vacuum. The residue was dissolved with CH_2Cl_2 and washed with brine. The organic phase was separated, dried and the solvent was removed. This crude product was purified by flash chromatography (AcOEt : cyclohexane = 2:3) to get pure compound **21a** (**SL42/77/1**) (20 mg, 21%)

IR (film): 1718 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ= 2.36 (bs, 1H, OH), 2.53 (dd, J_1=11.6 Hz, J_2=3.2 Hz, 1H), 2.75 (dd, J_1=11.6 Hz, J_2=3.6 Hz, 1H), 2.99 (d, J=17.2 Hz, 1H), 3.43 (d, J=16.8 Hz, 1H), 3.68 (q_{AB}, J=12.8 Hz, 2H), 3.75 (s, 3H), 4.21 (m, 1H), 7.31 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ= 51.69, 51.85, 56.39, 62.00, 63.97, 127.51, 128.45, 129.09, 131.29, 137.50, 166.03. MS (EI) m/z =247 [M]; Elemental Analysis: Calcd. for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66; O, 19.41; Found: C, 68.18; H, 6.95; N, 5.67.

Preparation of 22a (SL42/87/1).

Compound **21a** (20 mg) was dissolved into 2ml of HCl_{aq} (1 M). After refluxing for 4.5 hrs at 110 ^{o}C, the solvent was removed under vacuum to get compound **22a** (**SL42/87/1**) (20 mg, yield: 91%).

IR (film): 1708 cm^{-1}; ^{1}H NMR (400 MHz, D_2O) δ= 3.31-3.62 (m, 2H), 3.76-4.25 (m, 2H), 4.50 (m, 2H), 4.67 (m, 1H), 7.11(m, 1H), 7.55 (m, 5H) ; ^{13}C NMR (100 MHz, D_2O) δ= 48.91, 54.14, 59.63, 60.08, 126.53, 127.88, 129.33, 129.49, 130.36, 131,13, 135.87, 166.76. MS (ESI) m/z = 269 [M]; Elemental Analysis: Calcd. for $C_{13}H_{16}ClNO_3$: C, 57.89; H, 5.98; Cl, 13.14; N, 5.19; O, 17.80; Found: C, 58.07; H, 6.00; N, 5.21.

Synthesis of methyl 5-hydroxy-1-(pyridin-2-ylmethyl)-1,2,5,6-tetrahydropyridine-3-carboxylate 21b (SL42/81/1) and the corresponding acid 5-hydroxy-1-(pyridin-2-ylmethyl)-1,2,5,6-tetrahydropyridine-3-carboxylic acid hydrochloride 22b (SL42/86/1)

Following the procedure of **SL/42/77/1** and starting from **20** (90 mg, 0.35 mmol), 2-(bromomethyl)-pyridine hydrobromide (87 mg, 0.35 mmol) and diisopropyl ethyl amine (0.24 mL, 1.4 mmol) compound **21a** (**SL42/81/1**) was obtained (36 mg, yield: 41%) after flash chromatography (AcOEt :MeOH=5:1).

IR (film): 1710 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ= 2.56 (d, J=11.6 Hz, 1H), 2.71 (dd, J_1=11.6 Hz, J_2=3.6 Hz, 1H), 2.99 (d, J=16.8 Hz, 1H), 3.38 (d, J=16.8 Hz, 1H), 3.66 (s, 3H), 3.74 (m, 2H), 4.20 (m, 2H), 4.70 (s, 1H, OH), 6.90 (m, 1H), 7.12 (m, 1H), 7.30 (d, J=4.8 Hz, 1H), 7.60 (m, 1H), 8.45 (d, J=4.4 Hz, 1H); ^{13}C NMR (100 MHz, $(CD_3)_2CO$) δ= 51.00, 51.53, 56.57, 62.87, 63.93, 122.19, 122.86, 131.15, 136.71, 139.82, 149.11, 158.41, 165.51; MS (ESI) m/z =249 $[M+1]^+$; Elemental Analysis: Calcd. for $C_{13}H_{16}N_2O_3$: C, 62.89; H, 6.50; N, 11.28; O, 19.33; Found: C, 63.09; H, 6.52; N, 11.32.

Preparation of 22b (SL42/86/1)

Compound **SL42/81/1** (15.0 mg) was dissolved into 2 ml of HCl_{aq} (1 M). The reaction was refluxed for 3 hrs at 110 ^oC. The solvent was removed under vacuum to get compound **22b** (**SL42/86/1**) (15 mg, yield: 81%).

IR (film): 1708 cm^{-1}; ^1H NMR (400 MHz, D_2O) δ= 3.52 (m, 2H), 4.00 (m, 2H), 4.74 (m, 2H), 7.13 (m, 1H), 8.00 (m, 2H), 8.45 (m, 1H), 8.83 (d, J=5.6 Hz, 1H); ^{13}C NMR (100 MHz, D_2O) δ= 49.50, 54.54, 57.75, 60.47, 126.37, 126.72, 127.74, 136.92, 143.61, 146.11, 146.14, 166.92; MS (EI) m/z = 269 $[M\text{-}HCl\text{-}H]^-$; Elemental Analysis: Calcd. for $C_{12}H_{16}Cl_2N_2O_3$: C, 46.92; H, 5.25; Cl, 23.08; N, 9.12; O, 15.63; Found: C, 47.04; H, 5.26; N, 9.14.

Synthesis of methyl 5-hydroxy-1-(pyridin-3-ylmethyl)-1,2,5,6-tetrahydropyridine-3-carboxylate 21c(SL42/80/1) and the corresponding acid 5-hydroxy-1-(pyridin-3-ylmethyl)-1,2,5,6-tetrahydropyridine-3-carboxylic acid hydrochloride 22c (SL42/85/1)

Following the procedure of **SL/42/77/1** and starting from **20** (90 mg, 0.35 mmol), 3-(bromomethyl)-pyridine hydrobromide (87 mg, 0.35 mmol) and diisopropyl ethyl amine (0.24 mL, 1.4 mmol), compound **21c** (**SL42/80/1**) was obtained after flash chromatography (AcOEt :MeOH=5:1)(75 mg, yield: 87%).

IR (film): 1685 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ= 2.56 (dd, J_1=11.2 Hz, J_2=2.4 Hz, 1H), 2.76(dd, J_1=3.6 Hz, J_2=11.2 Hz, 1H), 2.99 (d, J=16.4 Hz, 1H), 3.42 (d, J=16.8 Hz, 1H), 3.70 (q_{AB}, J=13.6 Hz, 2H), 3.76 (s, 3H), 4.24 (m, 1H), 4.76(s, 1H, OH), 6.98 (m, 1H), 7.72 (dd, J_1=11.2 Hz, J_2=3.6 Hz, 1H), 8.57 (m, 2H), 8.60 (s, 1H); ^{13}C NMR (100 MHz, $(CD_3)_2CO$) δ= 51.93, 52.07, 57.36, 59.62, 65.13, 124.19, 130.58, 134.65, 137.32, 140.87, 149.40, 151.10, 166.49; MS (ESI) m/z =249 [M+1]; Elemental Analysis: Calcd. for $C_{13}H_{16}N_2O_3$: C, 62.89; H, 6.50; N, 11.28; O, 19.33; Found: C, 63.02; H, 6.51; N, 11.30.

Preparation of 22c (SL42/85/1)

Compound **SL42/80/1** (20 mg) was dissolved into 2ml of HCl_{aq} (1 M). This reaction was refluxed for 5 hrs at 110 ^{o}C. The solvent was removed under vacuum to get compound **22c** (**SL42/85/1**) (23 mg, yield: 92%).

IR (film): 1707 cm^{-1}; ^{1}H NMR (400 MHz, D_2O) δ= 3.55 (dd, J_1=4.0Hz, J_2=12.4 Hz, 1H), 3.62 (dd, J_1=4.4 Hz, J_2=12.8 Hz, 1H), 4.02 (dt, J_1=2.4 Hz, J_2=16.8 Hz, 1H), 4.17 (d, J=15.6 Hz, 1H), 4.86 (m, 2H), 7.14 (m, 1H), 8.25 (dd, J_1=5.6 Hz, J_2=8.0 Hz, 1H), 8.88 (dt, J_1=1.2 Hz, J_2=8.4 Hz, 1H), 8.99 (d, J=5.6 Hz, 1H), 9.12 (s, 1H); ^{13}C NMR (100 MHz, D_2O) δ= 49.21, 54.19, 55.67, 60.07, 126.02, 128.04, 128.78, 136.55, 143.22, 143.79, 149.33, 166.91; MS (EI) m/z =269 $[M\text{-}HCl\text{-}H]^{-}$; Elemental Analysis: Calcd. for $C_{12}H_{16}Cl_2N_2O_3$: C, 46.92; H, 5.25; Cl, 23.08; N, 9.12; O, 15.63; Found: C, 47.03; H, 5.26; N, 9.14.

Synthesis of methyl 5-hydroxy-1-(pyridin-4-ylmethyl)-1,2,5,6-tetrahydropyridine-3-carboxylate 21d (SL42/79/1) and the corresponding acid 5-hydroxy-1-(pyridin-4-ylmethyl)-1,2,5,6-tetrahydropyridine-3-carboxylic acid hydrochloride 22d (SL42/84/1)

Following the procedure of **SL/42/77/1** and starting from **20** (100 mg, 0.37 mmol), 4-(bromomethyl)-pyridine hydrobromide (94 mg, 0.37 mmol) and diisopropyl ethyl amine (0.27 mL, 1.56 mmol), compound **21d** (**SL42/79/1**) was obtained after flash chromatography (AcOEt :MeOH=5:1) (70 mg, yield: 78%).

IR (film): 1685 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ= 2.57 (dd, J_1=12.0 Hz, J_2= 2.8 Hz, 1H), 2.74 (dd, J_1=4.0 Hz, J_2=12.0 Hz, 1H), 3.01 (d, J=16.4 Hz, 1H), 3.42 (d, J=16.8 Hz, 1H), 3.68 (q_{AB}, J=14.0 Hz, 2H), 3.76 (s, 3H), 4.25 (m, 1H), 4.76 (bs, 1H, OH), 6.98 (m, 1H), 7.32 (m, 2H), 8.59 (m, 2H); ^{13}C NMR (100 MHz, $(CD_3)_2CO$) δ= 51.93, 52.19, 57.50, 61.06, 65.18, 124.48, 130.64, 140.77, 148.59, 150.56, 166.47; MS (ESI) m/z =249 [M+1]; Elemental Analysis: Calcd. for $C_{13}H_{16}N_2O_3$: C, 62.89; H, 6.50; N, 11.28; O, 19.33; Found: C, 63.10; H, 6.52; N, 11.32.

Preparation of 22d (SL42/84/1)

Compound **SL42/79/1** (20 mg) was dissolved into 2 ml of HCl_{aq} (1 M). This reaction was refluxed for 5 hrs at 110 ^{o}C. The solvent was removed under vacuum to get compound **22d** (**SL42/84/1**) (17 mg, yield: 68%).

IR (film): 1707 cm^{-1}; ^{1}H NMR (400 MHz, D_2O) δ= 3.51 (dd, J_1=4.0 Hz, J_2=12.8 Hz, 1H), 3.63 (dd, J_1=4.0 Hz, J_2=12.8 Hz, 1H), 4.05 (dt, J_1=1.2 Hz, J_2=16.4 Hz, 1H), 4.02 (d, J=16.4 Hz, 1H), 4.91 (m, 2H), 7.17 (m, 1H), 8.33 (d, J=6.4 Hz,1H), 8.98 (d, J=6.4Hz, 1H); ^{13}C NMR (100 MHz, D_2O) δ= 49.80, 54.62, 57.52, 60.04, 125.92, 129.14, 136.64, 142.35, 148.66, 166.77; MS (EI) m/z =269 $[M\text{-}HCl\text{-}H]^{-}$; Elemental Analysis: Calcd. for $C_{12}H_{16}Cl_2N_2O_3$: C, 46.92; H, 5.25; Cl, 23.08; N, 9.12; O, 15.63; Found: C, 47.05; H, 5.26; N, 9.15.

Synthesis of methyl 1-((2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)methyl)-5-hydroxy-1,2,5,6-tetrahydropyridine-3-carboxylate 21e (SL42/82/1) and the corresponding acid1-((2,6-dioxo-1,2,3,6-

tetrahydropyrimidin-4-yl)methyl)-5-hydroxy-1,2,5,6-tetrahydropyridine-3-carboxylic acid hydrochloride 22e (SL42/88/1)

Following the procedure of **SL/42/77/1** and starting from **20** (105 mg, 0.39 mmol), 6-(chloromethyl) uracil (63 mg, 0.39 mmol) and diisopropyl ethyl amine (0.20 mL, 1.17 mmol), compound **21e** (**SL42/82/1**) was obtained after flash chromatography (AcOEt : MeOH=9:1) (50 mg, yield: 46%).

IR (film): 1716 cm^{-1}; ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ= 2.64 (dd, J_1=4.4 Hz, J_2=11.6 Hz, 1H), 2.78 (dd, J_1=4.4 Hz, J_2=11.6 Hz, 1H), 3.11 (d, J=16.4 Hz, 1H), 3.30 (d, J=16.4 Hz, 1H), 3.56 (q_{AB}, J=15.2 Hz, 2H), 3.71 (s, 3H), 4.32 (m, 1H), 4.42 (d, J=1.2 Hz, 1H, OH), 5.63 (m, 1H), 6.89 (m, 1H), 10.02 (m, 2H, NH); ^{13}C NMR (100 MHz, $(CD_3)_2CO$) δ= 51.75, 52.03, 57.56, 58.15, 64.67, 97.38, 100.23, 130.68, 139.65, 152.66, 165.11, 166.42. MS (ESI) m/z =282 [M+H]; Elemental Analysis: Calcd. for $C_{12}H_{15}N_3O_5$: C, 51.24; H, 5.38; N, 14.94; O, 28.44; Found: C, 51.42; H, 5.40; N,15.00.

Preparation of 22e (SL42/88/1)

Compound **SL42/82/1** (22 mg) was dissolved into 2ml of HCl_{aq} (1 M). The reaction was refluxing for 4 hrs at 110 ^{o}C. The solvent was removed under vacuum to get compound **22e** (**SL42/88/1**) (20 mg, yield: 69%).

IR (film): 1712 cm^{-1}; ^{1}H NMR (400 MHz, D_2O) δ= 3.45 (m, 2H), 3.89 (dt, J_1=2.0 Hz, J_2=16.4 Hz, 1H), 4.06 (d, J=16.8 Hz, 1H), 4.23 (m, 3H), 6.22 (s, 1H), 7.19 (m, 1H); ^{13}C NMR (100 MHz, D_2O) δ= 49.58, 54.80, 55.19, 59.98, 105.22, 125.62, 136.76, 144.15, 152.34, 165.85, 166.56; MS (EI) m/z = 398 $[M+Na]^+$; Elemental Analysis: Calcd. for $C_{11}H_{16}Cl_3N_3O_5$: C, 35.08; H, 4.28; Cl, 28.24; N, 11.16; O, 21.24; Found: C, 35.17; H, 4.29; N,11.19.

1.3.2 Biology: Material and Methods

1.3.2.1 Chemicals and Reagents

The newly synthesized compounds were weighted and dissolved in DMSO as 100 mM stock solution and aliquots stored at -80°C till the time of use. The chemical reagents and the enzymes α-glucosidase (EC 3.2.1.20) from Saccharomyces cerevisiae, β-glucuronidase (E.C. 3.2.1.31) from bovine liver and hyaluronidase (E.C. 3.2.1.35) from bovine testes were purchased from Sigma (St. Louis, MO). From the same supplier were purchased the chromogenic substrates 4-Nitrophenyl derivative of α-glucopyranoside, phenolphthalein β-glucuronide, and hyaluronic acid from bovine vitreous humor. The cell vitality Alamar Blue dye were obtained through Invitrogen (Carlsbad, CA).

1.3.2.2 In vitro enzymatic assays

α-glucosidase activity was measured by a kinetic end-point assay.[24] A mix consisting of 50 µL deionizated water, 0.35 µL of α-glucosidase (0.175 U/mL) and 1 µL of the compound stock solution in DMSO, was pre-incubated 20 minutes at 37°C followed by the addition of 50 µL phosphate buffered saline (140 mM) pH 7.2, 1.35 µL reduced glutathione (9 mM) and 12 µL 4-nitrophenyl-α-glucopyranoside (0.9

mM) as substrate. The cocktail was further incubated 45 minutes at 37°C and the color development monitored at 400 nm on a Benchmark Plus spectrophotometer plate reader (BioRad). The percent effect of the compound on the α-glucosidase enzymatic activity was calculated by the following formula: % Inhibition/Activation = [(AC - AS)/AC] ×100, where AC is the absorbance of the control (samples with DLSO alone) and AS is the absorbance of the tested sample. Each experiment was performed in triplicates, along with appropriate blanks.

β-glucuronidase activity was assayed by monitoring the quantity of phenolphthalein liberated by alkalinization of the reaction mix at the end of the incubation. Hyaluronidase was assayed by the nephelometric procedure.

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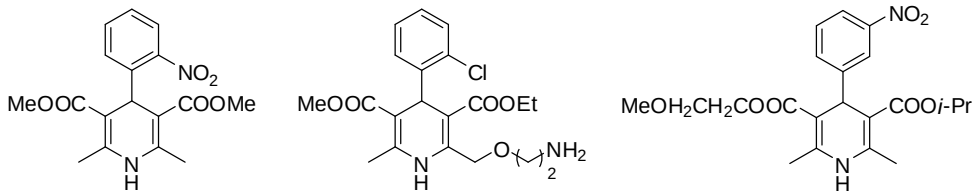
Chapter 2.

Synthesis of enantiomerically pure 1, 4-dihydropyridine using "solid" ammonia (magnesium nitride)

2.1 Introduction

1,4-dihydropyridine derivatives has attracted significant attention due to their wide spectrum of biological activity. These compounds containing the 1,4-dihydropyridine moiety have been found to act as calcium modulators,[1-3] BACE-1 inhibitors,[4] drugs in the treatment of vasodilatation,[5] mineral corticoid receptor antagonist,[6] hepatoprotection, neuromodulatory, anti-atherosclerosis, anti-diabetes, antioxidant, antimutagenic and antitumoragents.[7-9] 1,4-Dihydropyridines such as nifedipine, (Adalat®, Procardia®), amlodipine and nimodipine (Figure 1) are widely prescribed as antihypertensive drugs.[10] In addition, the dihydropyridine moiety has found application as an NADH analogue.[11-14]

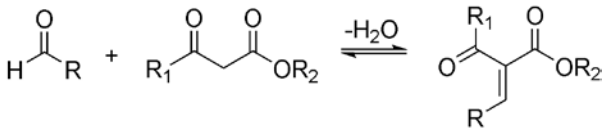


nifedipine amlodipine nimodipine

Figure 1. Some typical antihypertensive drugs based on 1,4-dihydropyridine scaffold

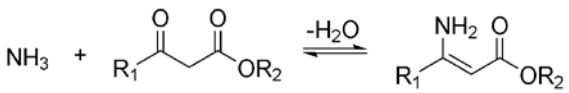
The most classic method to prepare dihydropyridines was discovered by Hantzsch in 1882[15] and consists of a multicomponent reaction (MCR) between an aldehyde, a β-keto ester and a 30% aqueous ammonia solution as the nitrogen source.[6-10,16]

There are many pathways to generate Hantzsch esters. For simplicity, usually they are described as four discrete steps. The first step can be visualized as proceeding through a Knoenenagel condensation product as key intermediate (Scheme 1):



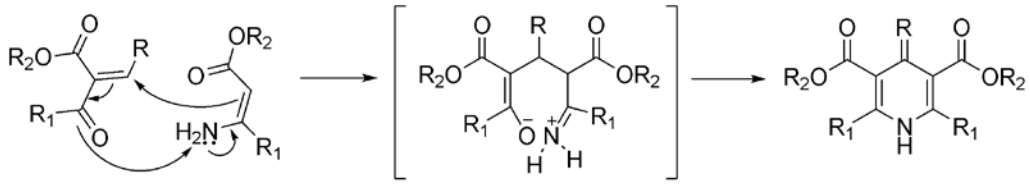
Scheme1

A second key intermediate is an ester enamine, which is produced by condensation of the second equivalent of the β-ketoester with ammonia (scheme 2):



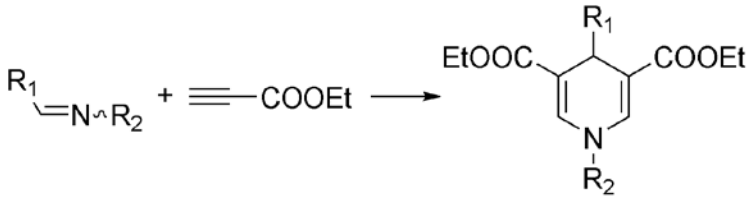
Scheme 2

Further condensation between these two intermediate gives the final derivatives (scheme 3):



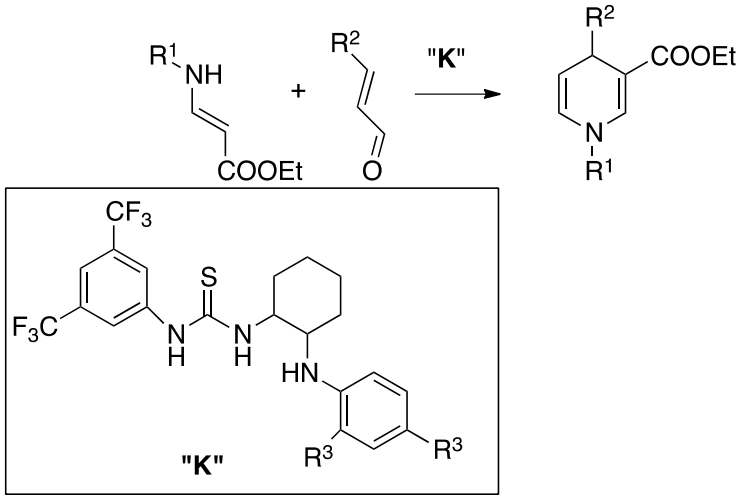
Scheme 3

But due to the modest yield reported, a lot of improvements on this method have been developed, including the use of catalysts such as boronic acids,[17,18] metal triflates,[19] molecular iodine,[20] TMS iodide,[21] Bu_4NHSO_4,[22] bakers' yeast,[23] ceric ammonium nitrate,[24] in situ generated HCl,[25] and silica-supported acids.[26,27] Solvent free[28] and microwave irradiation conditions[29,30] have also been reported. Some authors have described the use of ultrasounds, microwaves and solvent free conditions has recently been published reporting shorter reaction time and higher yield[31-34] Several authors have prepared polycyclic systems containing the 1,4-dihydropyridine ring using dimedone and different acid catalysis.[35-37] An environmentally friendly synthesis of 1,4-dihydropyridine derivatives was developed by the one-pot reaction of aldehydes, ethyl acetoacetate and ammonia in water under refluxing conditions in moderate yield.[38] Silica supported 12-tungstophosphoric acid catalysts has afforded 1,4-dihydropyridines under solvent-free conditions in high yields.[39] An interesting synthesis of 1,4-DHP in variable yields using aldimines and propiolate ester in the presence of a catalytic amount of Scandium(III) triflate has been reported (Scheme 4).[40]



Scheme 4

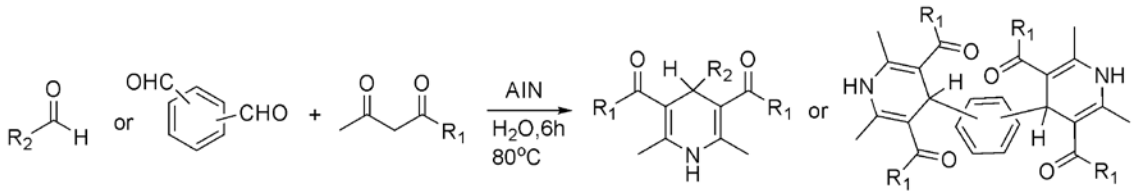
As far is concerned the synthesis of enantiomerically pure 1,4-DHP, several methods for synthesis of chiral DHPs have been reported, including asymmetric induction, resolution of racemic mixture, or chemoenzymatic method. Asymmetric Michael addition using α-methyl benzylamine as chiral inducer has been reported as well. By this synthetic startegy better results have been recently obtained by Yamamoto[41] on an asymmetric synthesis of (+)- and (-)-6-dimethoxymethyl-1,4-dihydropyridine-3-carboxylic acid derivatives using *t*-butylester of *L*-valine as a chiral auxiliary. The asymmetric synthesis of 4-*N*-substituted 4-aryl-3-carbethoxy 1,4-DHP has been achieved in good yield and moderate enantio-selectivity using bifunctional thiourea-ammonium salts as catalyst (scheme 5).[42]



Scheme 5

A Lewis acid (Zn[(L)proline]$_2$) catalyzed one pot synthesis of Hantzsch 1,4-dihydropyridine (DHP) derivatives under solvent-free condition by conventional heating and microwave irradiation has been reported.[43] The Lewis acid catalyst Zn[(L)proline]$_2$ used in this reaction afford 1,4-DHP in moderate to good yield. The catalyst is reusable up to five cycles without appreciable loss of its catalytic activity.

Ammonia is the reagent of choice as a source of nitrogen in organic chemistry, as well as in the Hantzsch reaction, yet its use can be hampered by handling issues, especially on a small scale. Among the modifications recently been reported, special emphasis warrants the use of substitutes of aqueous ammonia with reagents able to produce ammonia in situ (e.g. urotropine, metallo-nitrides, etc, etc). Nano aluminum nitride in the presence of water acts as solid source of ammonia, which is used for the preparation of 1,4-dihydropyridines and bis-(1,4-dihydropyridines). An efficient and simple procedure for the one-pot synthesis of 1,4-dihydropyridine and bis-(1,4-dihydropyridine) derivatives was achieved by combination of methyl acetoacetate or ethyl acetoacetate with aldehydes or dialdehydes and aluminum nitride at 80 ^{o}C in water in high purity and good yields (scheme 6).[44]



Scheme 6 synthesis of 1,4-dihydropyridines using nano aluminum nitride as solid source

Magnesium nitride (Figure 2), a commercially available, bench-stable solid, has been largely ignored by the synthetic community to date. It has been known to release ammonia in the presence of protic solvent, such as water and alcohol.[45-48] Taking this information into account, considering the property of magnesium nitride and the easier operation as a solid material in handling, magnesium nitride could be considered as an alternative of ammonia in the organic synthesis. Recently, it has been utilized by Steven V. Ley's group as a source to release ammonia in presence of protic solvents for the preparation of different

N-containing compounds.[48-50] In this chapter we will report our own results in using magnesium nitride as ammonia source and optically active ester of acetoacetate as counterpart in the condensation reaction. Actually, the need of enantiomerically pure 1,4-dihydropyridines for biotest[6,51-55] is a well known problem and we feel that a contribution to this problem is welcomed among the research groups involved in the field of synthesis and bio-activity of dihydropyridines.

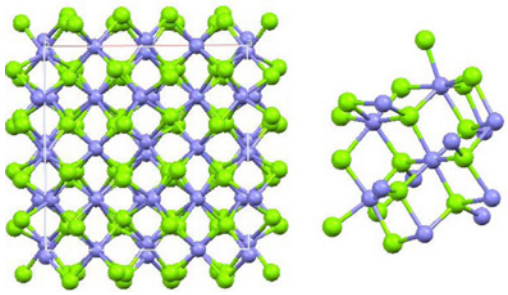
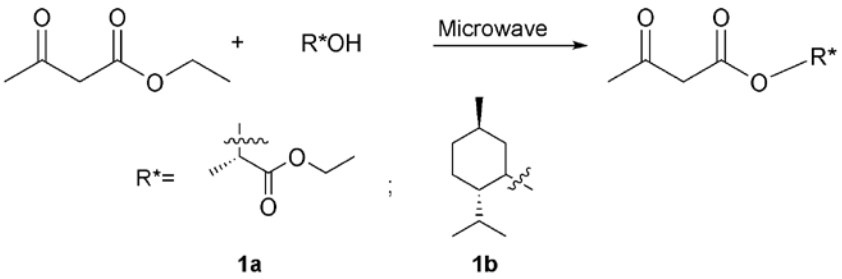


Figure 2. Mg_2N_3 cubic cell: green: Mg, blue: N

2.2 Present work

2.2.1 Preparation of enantiomerically pure acetoacetate ester

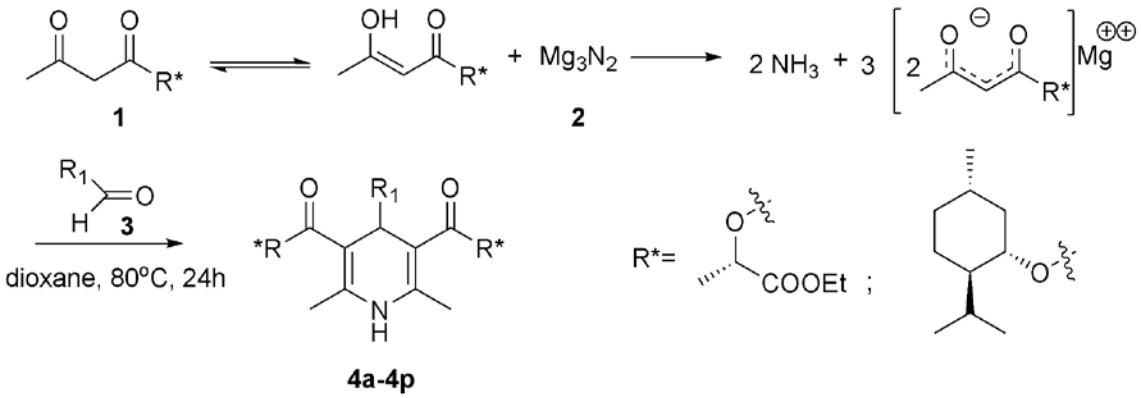
The suitable starting acetoacetate, to be used in the Hantzsch reaction as the source of chirality in the final DHPs were been easily prepared from a commercially available ethyl acetonacetate. It was ri-functionalized by introducing a chiral alchoxy functionality, *e.g.* natural menthol or (*S*)-2-hydroxy-propanol (lactic ester), *via* a MAOS (Microwave Assisted Organic Synthesis) mediated trans-esterification in absence of any catalyst. (Scheme 7)



Scheme 7. Preparation of enatiomerically pure acetoacetate ester

2.2.2 Preparation of target DHPs

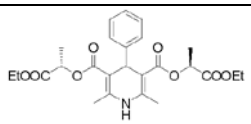
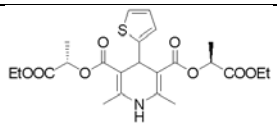
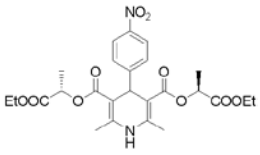
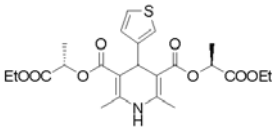
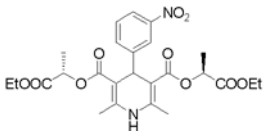
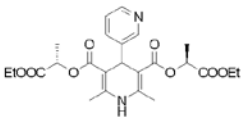
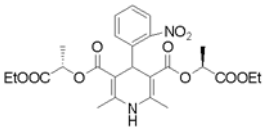
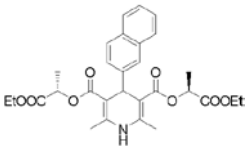
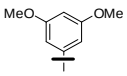
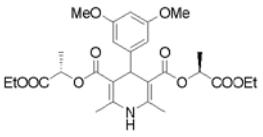
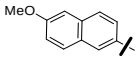
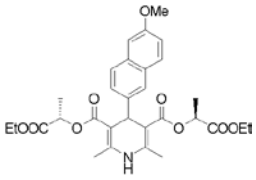
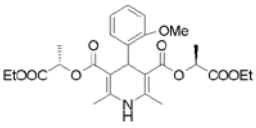
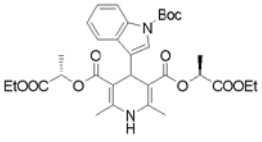
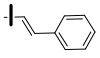
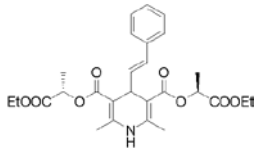
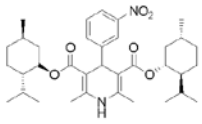
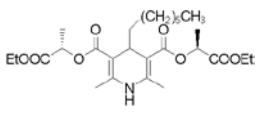
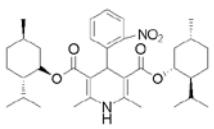
A series of *enantiomerically* 1,4-dihydropyridines were synthesized *via* the one-pot condensation of an aldehyde, a β-keto ester, which was prepared as above described, and magnesium nitride in 1,4-dioxane. (Scheme 8 and Table 1)



Scheme 8. Preparation of 1,4-diydropyridines **4a**-**4p**

It must be stressed out that, from synthetic point of view, a reasonable difference with the already published results, is based on the use of the aprotic dioxane, instead of protic ethanol as reported by Ley, as solvent. By this way a slow decomposition of magnesium nitride, by the enolic form of the acetoacetate, takes place allowing the use of a stoichiometric amount of magnesium nitride, acetoacetate and aldehyde. A series of the title compounds have been synthesized *via* one-pot condensation of aldehyde, β-ketoester and magnesium nitride in dioxane (Scheme 8 and Table 1). The starting optically active acetoacetate esters (**2a**) and (**2b**) were prepared in good yield by a MAOS (Microwave Assisted Organic Synthesis) mediated trans-esterification in absence of any catalyst.[56] Any attempt to obtain the dihydropyridines (**4a-q**) under MAOS conditions partially failed. In fact, even in the best cases, the yields obtained were lower than those obtained by convective heating whereas the time needed to complete the reaction was of the same order of running the reaction under convective heating. In summary, in this chapter we propose an easy protocol for the preparation of optically active Hantzch esters in satisfactory yields.

Table 1. Synthesis of optically active Hantzch esters from aldehydes **3** and acetoacetate **1**

Entry	R_1	Product	Yield (%)	Entry	R_1	Product	Yield (%)
1		 **4a**	95	9		 **4i**	28
2		 **4b**	66	10		 **4j**	73
3		 **4c**	66	11		 **4k**	58
4		 **4d**	46	12		 **4l**	52
5		 **4e**	41	13		 **4m**	26
6		 **4f**	43	14		 **4n**	22
7		 **4g**	65	15		 **4o**	50
8	$CH_3(CH_2)_6$–	 **4h**	58	16		 **4p**	25

2.3 Experimental section

All starting materials, unless otherwise stated, were purchased and used without any further purification. Solvents were distilled and dried according to standard procedures. All the reactions were run in a sealed tube under a nitrogen atmosphere. 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 and are not corrected. Optical rotations were obtained using a Perkin Elmer 343 polarimeter. IR spectra were recorded on a Nicolet 380 FT-IR infrared spectrometer. 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. Elemental analyses were performed at CNR-ISMAR, Bologna, Italy.

(2*S*)-1-Ethoxy-1-oxopropan-2-yl 3-Oxobutanoate (1a)

(*S*)-(–)-Ethyl lactate (0.3 mol, 35 mL) and ethyl acetoacetate (0.15 mol, 19.5 mL), in a 50 mL flask, were heated at reflux temperature in a microwaves oven (Milestone/MicroSynth) at 500 W for 3 h. During this time the EtOH produced during the transesterification was removed by side-arm distillation. The excess (*S*)-(–)-ethyl lactate was removed by rotary evaporation. The residue was found to consist of 24.2 g (80% conversion) of the target compound. The analytical data (including the optical rotation) were analogous with the literature.[56]

(1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl 3-Oxobutanoate (1b)

The title product was prepared using the previously reported microwave-assisted organic synthesis technique. The analytical data (including the optical rotation) were analogous with the literature.[56]

Bis[(2*S*)-1-ethoxy-1-oxopropan-2-yl]2,6-Dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (4a); Typical Procedure

A mixture of benzaldehyde (**3a**) (0.203 mL, 2 mmol), β-keto ester **1a** (0.836 g, 4 mmol) and Mg_3N_2 (**2**) (0.100 g, 1 mmol) in anhydrous 1,4-dioxane (3 mL) in a 5 mL sealed tube was stirred for 24 h at 80 °C. The mixture was cooled, dissolved in ice-cold H_2O (10 mL), and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layer was dried over $MgSO_4$, the solvent removed in vacuo and the product purified by flash chromatography on silica gel (EtOAc–cyclohexane, 35:65).

Yellow oil; yield: 0.896 g (95%); $[\alpha]_D^{20}$: +133.43 (*c* 0.7, $CHCl_3$). IR (film): 1740, 1695 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.14 (t, *J* = 7.1 Hz, 3 H), 1.25 (t, *J* = 7.1 Hz, 3 H), 1.42 (d, *J* = 6.9 Hz, 3 H), 1.46 (d, *J* = 6.9 Hz, 3 H), 2.34 (s, 3 H), 2.35 (s, 3 H), 4.07 (m, 2 H), 4.18 (m, 2 H), 4.96 (q, *J* = 7.1 Hz, 1 H), 5.03 (q, *J* = 6.9 Hz, 1 H), 5.07 (s, 1 H), 5.97 (s, 1H, NH), 7.13–7.31 (m, 5 H, Ar). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.96, 14.06, 16.87, 17.04, 19.51, 19.85, 39.45, 60.94, 61.13, 68.24, 68.44, 103.15, 103.88, 126.11, 127.73,

128.14, 145.27, 147.45, 166.65, 166.70, 171.20, 171.47. MS (ESI): *m*/*z* = 474 [M + H^+]$^+$. Elemental Analysis: Calcd. for $C_{25}H_{31}NO_8$: C, 63.41; H, 6.60; N, 2.96. Found: C, 63.60; H, 6.62.

Bis[(2*S*)-1-ethoxy-1-oxopropan-2-yl]2,6-Dimethyl-4-(4-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (4b)

The product was prepared according to the typical procedure from 4-nitrobenzaldehyde (**3b**) (0.302 g, 2 mmol), β-keto ester **1a** (0.836 g, 4 mmol) and Mg_3N_2 (**2**) (0.100 g, 1 mmol). The crude mixture was extracted with EtOAc (3 × 10 mL), dried over Na_2SO_4 and purified by flash chromatography (EtOAc–cyclohexane, 35:65).

Yellow solid; yield: 0.681 g (66%); mp: 55 °C; $[\alpha]_D^{20}$: +63.64 (*c* 1.1, $CHCl_3$). IR (film): 1735, 1701 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.13 (t, *J* = 7.2 Hz, 3 H), 1.25 (t, *J* = 7.2 Hz, 3 H), 1.42 (d, *J* = 6.8 Hz, 3 H), 1.48 (d, *J* = 6.8 Hz, 3 H), 2.26 (s, 3 H), 2.38 (s, 3 H), 4.05 (m, 2 H), 4.20 (m, 2 H), 4.96 (q, *J* = 6.8 Hz, 1 H), 5.00 (q, *J* = 6.8 Hz, 1 H), 5.15 (s, 1 H), 6.43 (s, 1 H), 7.47 (d, *J* = 9.6 Hz, 2 H), 8.07 (d, *J* = 9.6 Hz, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.94, 14.03, 16.90, 17.01, 19.34, 19.56, 39.83, 61.02, 61.37, 68.33, 68.55, 101.83, 102.61, 123.17, 129.08, 145.64, 146.55, 154.79, 166.10, 166.15, 170.95, 171.46. MS (ESI): *m*/*z* = 519 [M + H^+]$^+$. Elemental Analysis: Calcd. for $C_{25}H_{30}N_2O_{10}$: C, 57.91; H, 5.83; N, 5.40. Found: C, 58.03; H, 5.84.

Bis[(2*S*)-1-ethoxy-1-oxopropan-2-yl]2,6-Dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (4c)

The product was prepared according to the typical procedure from 3-nitrobenzaldehyde (**3c**) (0.302 g, 2 mmol), β-keto ester **1a** (0.836 g, 4 mmol) and Mg_3N_2 (**2**) (0.100 g, 1 mmol). The crude mixture was extracted with EtOAc (3 × 10 mL), dried over Na_2SO_4 and purified by flash chromatography (EtOAc–cyclohexane, 35:65).

Yellow oil; yield: 0.684 g (66%); $[\alpha]_D^{20}$: +60.9 (*c* 1.1, $CHCl_3$). IR (film): 1738, 1701 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.12 (t, *J* = 6.8 Hz, 3 H), 1.24 (t, *J* = 6.8 Hz, 3 H), 1.44 (d, *J* = 6.8 Hz, 3 H), 1.49 (d, *J* = 6.8 Hz, 3 H), 2.37 (s, 3 H), 2.41 (s, 3 H), 4.04 (m, 2 H), 4.20 (m, 2 H), 4.97 (q, *J* = 6.8 Hz, 1 H), 5.00 (q, *J* = 7.2 Hz, 1 H), 5.16 (s, 1 H), 6.17 (s, 1 H, NH), 7.39 (t, *J* = 7.8 Hz, 1 H), 7.68 (dt, *J* = 1.4 Hz, *J* = 7.7 Hz, 1 H), 8.01 (ddd, *J* = 1.0 Hz, *J* = 1.4 Hz, *J* = 8.2 Hz, 1 H), 8.14 (s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.88, 14.02, 16.82, 16.95, 19.13, 19.37, 39.85, 60.90, 61.45, 68.23, 68.53, 101.83, 102.73, 121.25, 123.44, 128.58, 134.80, 145.71, 146.78, 147.83, 149.81, 166.09, 166.22, 170.91, 171.74. MS (ESI): *m*/*z* = 541 [M + Na^+]$^+$. Elemental Analysis: Calcd. for $C_{25}H_{30}N_2O_{10}$: C, 57.91; H, 5.83; N, 5.40. Found: C, 59.59; H, 5.99.

Bis[(2*S*)-1-ethoxy-1-oxopropan-2-yl]2,6-Dimethyl-4-(2-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (4d)

The product was prepared according to the typical procedure from 2-nitrobenzaldehyde (**3d**) (0.151 g, 1 mmol), β-keto ester **1a** (0.404 g, 2 mmol) and Mg_3N_2 (**2**) (0.50 g, 0.5 mmol). The crude mixture was

extracted with EtOAc (3 × 10 mL), dried over Na_2SO_4 and purified by flash chromatography (EtOAc–cyclohexane, 35:65).

Yellow oil; yield: 0.236 g (46%); $[\alpha]_D^{20}$: +55.0 (*c* 1.0, $CHCl_3$). IR (film): 1735, 1701 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.03 (t, *J* = 6.8 Hz, 3 H), 1.26 (t, *J* = 6.8 Hz, 3 H), 1.41 (d, *J* = 7.2 Hz, 3 H), 1.45 (d, *J* = 7.6 Hz, 3 H), 2.26 (s, 3 H), 2.41 (s, 3 H), 3.96 (m, 2 H), 4.19 (m, 2 H), 4.92 (q, *J* = 6.8 Hz, 1 H), 5.01 (q, *J* = 7.2 Hz, 1 H), 6.09 (s, 1 H), 6.77 (bs, 1 H, NH), 7.25 (t, *J* = 8.4 Hz, 1 H), 7.48 (t, *J* = 8.0 Hz, 1 H), 7.56 (d, *J* = 7.6 Hz, 1 H), 7.82 (d, *J* = 8.0 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): d = 13.00, 13.05, 14.96, 15.26, 15.46, 33.34, 59.73, 60.37, 67.47, 67.55, 101.48, 102.00, 123.19, 125.98, 131.05, 132.02, 142.16, 145.20, 145.63, 146.10, 165.37, 165.89, 170.09, 171.16. MS (ESI): *m*/*z* = 519 $[M + H^+]^+$. Elemental Analysis: Calcd. for $C_{25}H_{30}N_2O_{10}$: C, 57.91; H, 5.83; N, 5.40. Found: C, 59.71; H, 6.01.

Bis[(2*S*)-1-ethoxy-1-oxopropan-2-yl]4-(3,5-Dimethoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (4e)

The product was prepared according to the typical procedure from 3,5-dimethoxybenzaldehyde (**3e**) (0.332 g, 2 mmol), β-keto ester **1a** (0.836 g, 4 mmol) and Mg_3N_2 (**2**) (0.100 g, 1 mmol). The crude mixture was extracted with EtOAc (3 × 10 mL), dried over Na_2SO_4 and purified by flash chromatography (EtOAc–cyclohexane, 35:65).

Yellow oil; yield: 0.441 g (41%); $[\alpha]_D^{20}$: +40.0 (*c* 1.1, $CHCl_3$). IR (film): 1740, 1698 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.17 (t, *J* = 7.0 Hz, 3 H), 1.25 (t, *J* = 7.2 Hz, 3 H), 1.44 (d, *J* = 6.8 Hz, 3 H), 1.49 (d, *J* = 7.6 Hz, 3 H), 2.34 (s, 3 H), 2.35 (s, 3 H), 3.75 (s, 6 H), 4.14 (m, 4 H), 5.00 (q, *J* = 7.2 Hz, 1 H), 5.06 (q, *J* = 7.2 Hz, 1 H), 5.07 (s, 1 H), 5.84 (s, 1 H, NH), 6.27 (s, 1 H), 6.50 (s, 1 H), 6.51 (s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): d = 13.74, 13.89, 16.82, 16.93, 18.88, 19.20, 39.31, 54.94, 60.82, 61.08, 68.02, 68.29, 97.51, 102.13, 102.98, 106.47, 145.04, 146.08, 149.92, 160.05, 166.66, 170.01, 171.59. MS (ESI): *m*/*z* = 534 $[M + H^+]^+$. Elemental Analysis: Calcd. for $C_{27}H_{35}NO_{10}$: C, 60.78; H, 6.61; N, 2.63. Found: C, 60.96; H, 6.63.

Bis[(2*S*)-1-ethoxy-1-oxopropan-2-yl]4-(2-Methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (4f)

The product was prepared according to the typical procedure from 2-methoxybenzaldehyde (**3f**) (0.272 g, 2 mmol), β-keto ester **1a** (0.808 g, 4 mmol) and Mg_3N_2 (**2**) (0.100 g, 1 mmol). The crude mixture was extracted with EtOAc (3 x 10 mL), dried over MgSO4 and purified by flash chromatography (EtOAc–cyclohexane, 35:65).

Yellow oil; yield: 0.431 g (43%); $[\alpha]_D^{20}$: +55.56 (*c* 0.9, $CHCl_3$). IR (film): 1740, 1691 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.03 (t, *J* = 7.1 Hz, 3 H), 1.25 (t, *J* = 7.1 Hz, 3 H), 1.40 (d, *J* = 6.9 Hz, 3 H), 1.45 (d, *J* = 6.9 Hz, 3 H), 2.21 (s, 3 H), 2.32 (s, 3 H), 3.72 (s, 3 H), 3.95 (m, 2 H), 4.19 (m, 2 H), 4.87 (q, *J* = 7.1 Hz, 1 H), 4.98 (q, *J* = 7.1 Hz, 1 H), 5.28 (s, 1 H), 6.65 (bs, 1 H, NH), 6.78 (m, 2 H), 7.08 (dt, *J* = 1.8 Hz, *J* = 7.4 Hz, 1 H), 7.21 (dd, *J* = 1.8 Hz , *J* = 7.5 Hz , 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.79, 13.99, 16.76,

16.80, 18.86, 19.23, 35.36, 55.08, 60.64, 61.10, 67.80, 67.99, 101.31, 102.13, 110.51, 119.67, 127.16, 131.26, 135.37, 145.04, 146.08, 157.24, 167.05, 167.27, 171.36, 172.11. MS (ESI): *m*/*z* = 504 $[M + H^+]^+$. Elemental Analysis: Calcd. for $C_{26}H_{33}NO_9$: C, 62.02; H, 6.61; N, 2.78. Found: C, 62.20; H, 6.63.

Bis[(2*S*)-1-ethoxy-1-oxopropan-2-yl]2,6-Dimethyl-4-styryl-1,4-dihydropyridine-3,5-dicarboxylate (4g)

The product was prepared according to the typical procedure from *trans*-cinnamaldehyde (**3g**) (0.264 g, 2 mmol), β-keto ester **1a** (0.836 g, 4 mmol) and Mg_3N_2 (**2**) (0.100 g, 1 mmol). The crude mixture was extracted with EtOAc (3 x 10 mL), dried over Na_2SO_4 and purified by flash chromatography (EtOAc–cyclohexane, 35:65).

Yellow oil; yield: 0.645 g (65%); $[\alpha]_D^{20}$: +44.55 (*c* 0.9, $CHCl_3$). IR (film): 1741, 1698 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.19 (t, *J* = 6.8 Hz, 3 H), 1.26 (t, *J* = 6.8 Hz, 3 H), 1.51 (d, *J* = 6.4 Hz, 3 H), 1.53 (d, *J* = 6.4 Hz, 3 H), 2.32 (s, 3 H), 2.33 (s, 3 H), 4.16 (m, 4 H), 4.69 (d, *J* = 6.0 Hz, 1 H), 5.08 (q, *J* = 6.8 Hz, 1 H), 5.12 (q, *J* = 7.2 Hz, 1 H), 5.99 (s, 1 H, NH), 6.36 (m, 2 H), 7.14–7.31 (m, 5 H, Ar). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.02, 14.08, 17.05, 17.11, 19.46, 19.60, 36.33, 61.05, 61.15, 68.25, 68.36, 100.54, 101.23, 126.25, 126.78, 128.28, 128.37, 128.73, 131.76, 137.83, 145.49, 146.18, 166.63, 166.74, 171.33, 171.49. MS (ESI): *m*/*z* = 500 $[M + H^+]^+$. Elemental Analysis: Calcd. for $C_{27}H_{33}NO_8$: C, 64.92; H, 6.66; N, 2.80. Found: C, 65.18; H, 6.69.

Bis[(2*S*)-1-ethoxy-1-oxopropan-2-yl]4-Heptyl-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (4h)

The product was prepared according to the typical procedure from octanal (**3h**) (0.256 g, 2 mmol), β-keto ester **1a** (0.836 g, 4 mmol) and Mg_3N_2 (**2**) (0.100 g, 1 mmol). The crude mixture was extracted with EtOAc (3 x 10 mL), dried over Na_2SO_4 and purified by flash chromatography (EtOAc–cyclohexane, 35:65).

Yellow oil; yield: 0.572 g (58%); $[\alpha]_D^{20}$: +52.00 (*c* 0.9, $CHCl_3$). IR (film): 1741, 1696 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.83 (t, *J* = 7.0 Hz, 3 H), 1.19–1.41 (complex pattern, 18 H), 1.48 (d, *J* = 7.2 Hz, 3 H), 1.49 (d, *J* = 6.8 Hz, 3 H), 2.23 (s, 3 H), 2.26 (s, 3 H), 3.95 (t, *J* = 5.6 Hz, 1 H), 4.18 (m, 4 H), 5.05 (q, *J* = 7.2 Hz, 1 H), 5.06 (q, *J* = 6.8 Hz, 1 H), 6.32 (s, 1 H, NH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.03, 14.06, 16.95, 16.98, 19.12, 19.16, 22.62, 24.70, 29.39, 29.92, 31.92, 32.70, 36.95, 60.94, 61.12, 68.05, 68.09, 101.93, 102.47, 146.00, 146.39, 167.11, 167.41, 171.58, 171.71. MS (ESI): *m*/*z* = 496 $[M + H^+]^+$. Elemental Analysis: Calcd. for $C_{26}H_{41}NO_8$: C, 63.01; H, 8.34; N, 2.83. Found: C, 63.17; H, 8.36.

Bis[(2*S*)-1-ethoxy-1-oxopropan-2-yl]2,6-Dimethyl-4-(thien-2-yl)-1,4-dihydropyridine-3,5-dicarboxylate (4i)

The product was prepared according to the typical procedure from thiophene-2-carbaldehyde (**3i**) (0.332 g, 2 mmol), β-keto ester **1a** (0.836 g, 4 mmol) and Mg_3N_2 (**2**) (0.100 g, 1 mmol). The crude mixture was extracted with EtOAc (3 x 10 mL), dried over Na_2SO_4 and purified by flash chromatography (EtOAc–cyclohexane, 35:65).

Yellow oil; yield: 0.268 g (28%); $[\alpha]_D^{20}$: +33.08 (*c* 1.3, $CHCl_3$). IR (Nujol): 1737, 1697 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.21 (t, *J* = 7.6 Hz, 3 H), 1.26 (t, *J* = 7.1 Hz, 3 H), 1.48 (d, *J* = 7.1 Hz, 3 H), 1.50 (d, *J* = 7.1 Hz, 3 H), 2.36 (s, 3 H), 4.19 (m, 4 H), 5.06 (q, *J* = 7.1 Hz, 1 H), 5.10 (q, *J* = 7.1 Hz, 1 H), 5.42 (s, 1 H), 6.01 (s, 1 H, NH), 6.86 (m, 2 H), 7.05 (dd, *J* = 1.4 Hz, *J* = 5.0 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.04, 14.08, 16.96, 17.07, 19.52, 19.79, 34.25, 61.06, 61.17, 68.45, 68.59, 102.89, 103.31, 123.13, 123.46, 126.41, 144.96, 145.64, 151.34, 166.38, 166.44, 171.23, 171.37. MS (ESI): *m*/*z* = 480 $[M + H^+]^+$. Elemental Analysis: Calcd. for $C_{23}H_{29}NO_8S$: C, 57.61; H, 6.10; N, 2.92. Found: C, 57.80; H, 6.30.

Bis[(2*S*)-1-ethoxy-1-oxopropan-2-yl]2,6-Dimethyl-4-(thien-3-yl)-1,4-dihydropyridine-3,5-dicarboxylate (4j)

The product was prepared according to the typical procedure from thiophen-3-carbaldehyde (**3j**) (0.332 g, 2 mmol), β-keto ester **1a** (0.836 g, 4 mmol) and Mg_3N_2 (**2**) (0.100 g, 1 mmol). The crude mixture was extracted with EtOAc (3 x 10 mL), dried over Na_2SO_4 and purified by flash chromatography (EtOAc–cyclohexane, 35:65).

Yellow oil; yield: 0.704 g (73%); $[\alpha]_D^{20}$: +52.35 (*c* 1.7, $CHCl_3$). IR (film): 1740, 1698 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.21 (t, *J* = 7.0 Hz, 3 H), 1.26 (t, *J* = 6.6 Hz, 3 H), 1.45 (d, *J* = 7.2 Hz, 3 H), 1.50 (d, *J* = 7.2 Hz, 3 H), 2.32 (s, 3 H), 2.33 (s, 3 H), 4.17 (m, 4 H), 5.03 (q, *J* = 6.8 Hz, 1 H), 5.06 (q, *J* = 7.2 Hz, 1 H), 5.20 (s, 1 H), 6.15 (bs, 1 H, NH), 6.98 (m, 1 H), 7.06 (dd, *J* = 1.2 Hz, *J* = 5.0 Hz,1 H), 7.12 (dd, *J* = 3.0 Hz, *J* = 4.9 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.05, 14.07, 16.96, 17.08, 19.43, 19.63, 34.33, 61.07, 61.20, 68.30, 68.46, 102.43, 103.00, 120.55, 124.49, 127.69, 145.22, 145.81, 147.50, 166.66, 166.72, 171.35, 171.49. MS (ESI): *m*/*z* = 480 $[M + H^+]^+$. Elemental Analysis: Calcd. for $C_{23}H_{29}NO_8S$: C, 57.61; H, 6.10; N, 2.92. Found: C, 57.80; H, 6.30.

Bis[(2*S*)-1-ethoxy-1-oxopropan-2-yl]2,6-Dimethyl-4-(pyridin-3-yl)-1,4-dihydropyridine-3,5-dicarboxylate (4k)

The product was prepared according to the typical procedure from pyridine-3-carbaldehyde (**3k**) (0.332 g, 2 mmol), β-keto ester **1a** (0.836 g, 4 mmol) and Mg_3N_2 (**2**) (0.100 g, 1 mmol). The crude mixture was extracted with EtOAc (3 x 10 mL), dried over Na_2SO_4 and purified by flash chromatography (EtOAc–cyclohexane, 9:1).

White solid; yield: 0.549 g (58%); mp 127 °C; $[\alpha]_D^{20}$: +74.00 (*c* 1.0, $CHCl_3$). IR (film): 1741, 1699 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): d = 1.11 (t, *J* = 7.0 Hz, 3 H), 1.24 (t, *J* = 6.8 Hz, 3 H), 1.43 (d, *J* = 7.1 Hz, 3 H), 1.48 (d, *J* = 7.1 Hz, 3 H), 2.33 (s, 3 H), 2.36 (s, 3 H), 4.04 (m, 2 H), 4.18 (m, 2 H), 4.95 (q, *J* = 7.1 Hz, 1 H), 5.00 (q, *J* = 7.1 Hz, 1 H), 5.04 (s, 1 H), 6.90 (s, 1 H, NH), 7.16 (dd, *J* = 4.7 Hz, *J* = 7.7 Hz, 1 H), 7.64 (m, 1 H), 8.36 (m, 1 H), 8.52 (d, *J* = 2.0 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.95, 14.05, 16.89, 17.02, 19.19, 19.41, 37.55, 60.97, 61.29, 68.26, 68.48, 101.99, 102.74, 123.04, 135.92, 143.19, 145.69, 146.59, 147.14, 149.65, 166.28, 166.29, 171.02, 171.51. MS (ESI): *m*/*z* = 475 $[M + H^+]^+$. Elemental Analysis: Calcd. for $C_{24}H_{30}N_2O_8$: C, 60.75; H, 6.37; N, 5.90. Found: C, 60.91; H, 6.39.

Bis[(2*S*)-1-ethoxy-1-oxopropan-2-yl]2,6-Dimethyl-4-(naphthalen-2-yl)-1,4-dihydropyridine-3,5-dicarboxylate (4l)

The product was prepared according to the typical procedure from naphthalene-2-carbaldehyde (**3l**) (0.312 g, 2 mmol), β-keto ester **1a** (0.808 g, 4 mmol) and Mg_3N_2 (**2**) (0.100 g, 1 mmol). The crude mixture was extracted with EtOAc (3 x 10 mL), dried over MgSO4 and purified by flash chromatography (EtOAc–cyclohexane, 35:65).

Yellow oil; yield: 0.543 g (52%); $[\alpha]_D^{20}$: +49.60 (*c* 1.0, $CHCl_3$). IR (film): 1744, 1699 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.95 (t, *J* = 7.1 Hz, 3 H), 1.20 (t, *J* = 7.1 Hz, 3 H), 1.39 (d, *J* = 7.1 Hz, 3 H), 1.44 (d, *J* = 7.1 Hz, 3 H), 2.36 (s, 6 H), 3.95 (m, 2 H), 4.16 (m, 2 H), 4.90 (q, *J* = 7.1 Hz, 1 H), 5.02 (q, *J* = 7.1 Hz, 1 H), 5.23 (s, 1 H), 5.87 (s, 1 H, NH), 7.36 (m, 2 H), 7.49 (dd, *J* = 1.8 Hz, *J* = 8.7 Hz, 1 H), 7.68–7.77 (complex pattern, 4 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.53, 13.93, 16.82, 16.93, 18.98, 19.30, 39.70, 60.72, 61.18, 68.01, 68.35, 102.34, 103.26, 124.94, 125.37, 126.52, 127.12, 127.21, 127.28, 127.67, 132.19, 133.16, 144.98, 145.09, 146.07, 166.71, 171.19, 171.79. MS (ESI): *m*/*z* = 524 $[M + H^+]^+$. Elemental Analysis: Calcd. for $C_{29}H_{33}NO_8$: C, 66.53; H, 6.35; N, 2.68. Found: C, 66.71; H, 6.37.

Bis[(2*S*)-1-ethoxy-1-oxopropan-2-yl]2,6-Dimethyl-4-(6-methoxynaphthalen-2-yl)-1,4-dihydropyridine-3,5-dicarboxylate (4m)

The product was prepared according to the typical procedure from 6-methoxynaphthalene-2-carbaldehyde (**3m**) (0.300 g, 1.6 mmol), β-keto ester **1a** (0.649 g, 3.2 mmol) and Mg_3N_2 (**2**) (0.083 g, 0.8 mmol). The reaction mixture was stirred for 29 h at 90–100 °C, and then at r.t. for an additional 48 h. The crude mixture was extracted with CH_2Cl_2 (3 x 15 mL), dried over MgSO4 and purified by flash chromatography (EtOAc–cyclohexane, 35:65).

Yellow oil; yield: 0.224 g (26%); $[\alpha]_D^{20}$: +54.27 (*c* 1.0, $CHCl_3$). IR (film): 1740, 1691 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.97 (t, *J* = 7.1 Hz, 3 H), 1.23 (t, *J* = 7.1 Hz, 3 H), 1.42 (d, *J* = 7.1 Hz, 3 H), 1.47 (d, *J* = 7.1 Hz, 3 H), 2.35 (s, 3 H), 2.38 (s, 3 H), 3.89 (s, 3 H), 3.94 (m, 2 H), 4.18 (m, 2H), 4.91 (q, *J* = 7.1 Hz, 1 H), 5.01 (q, *J* = 7.1 Hz, 1 H), 5.19 (s, 1 H), 6.16 (s, 1 H, NH), 7.01–7.13 (m, 2 H), 7.46 (dd, *J* = 1.8 Hz, *J* = 8.5 Hz, 1 H), 7.61 (m, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.72, 14.03, 16.90, 17.03, 18.40, 19.74, 39.52, 55.23, 60.85, 61.16, 68.15, 68.42, 102.96, 103.81, 105.51, 118.17, 126.12, 126.41, 127.73, 128.74, 129.27, 133.18, 142.91, 144.38, 145.44, 157.11, 166.72, 166.78, 171.20, 171.61. MS (ESI): *m*/*z* = 554 $[M + H^+]^+$. Elemental Analysis: Calcd. for $C_{30}H_{35}NO_9$: C, 65.09; H, 6.37; N, 2.53. Found: C, 65.30; H, 6.39.

Bis[(2*S*)-1-ethoxy-1-oxopropan-2-yl]4-[1-(*tert*-Butoxycarbonyl)-1*H*-indol-3-yl]-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (4n)

The product was prepared according to the typical procedure from *tert*-butyl-3-formyl-1*H*-indole-1-carboxylate (**3n**) (0.492 g, 2.0 mmol), β-keto ester **1a** (0.808 g, 2.0 mmol) and Mg_3N_2 (**2**) (0.100 g, 1.0 mmol). The reaction mixture was stirred for 29 h at 90–100 °C, and then at r.t. for an additional 48 h. The

crude mixture was extracted with CH_2Cl_2 (3 x 15 mL), dried over $MgSO_4$ and purified by flash chromatography (EtOAc–cyclohexane, 35:65).

Yellow oil; yield: 0.272 g (22%); $[\alpha]_D^{20}$: +38.34 (*c* 0.8, $CHCl_3$). IR (film): 1732, 1699 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.96 (t, *J* = 7.1 Hz, 3 H), 1.24 (t, *J* = 7.1 Hz, 3 H), 1.36 (d, *J* = 7.1 Hz, 3 H), 1.43 (d, *J* = 7.1 Hz, 3 H), 1.64 (s, 9 H), 2.28 (s, 3 H), 2.35 (s, 3 H), 3.80–3.99 (complex pattern, 2 H), 4.19 (m, 2 H), 4.91 (q, *J* = 7.1 Hz, 1 H), 5.00 (q, *J* = 7.1 Hz, 1 H), 5.34 (s, 1 H), 6.59 (bs, 1 H, NH), 7.02 (d, *J* = 2.4 Hz, 1 H), 7.15–7.24 (complex pattern, 2 H), 7.38 (s, 1 H), 7.67 (d, *J* = 7.9 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.60, 13.98, 16.82, 16.89, 19.07, 19.47, 28.13, 30.70, 60.76, 61.20, 68.11, 68.38, 83.24, 102.72, 110.87, 114.80, 120.44, 121.98, 123.55, 124.40, 129.66, 144.48, 145.69, 166.78, 171.14, 171.80. MS (ESI): *m*/*z* = 613 $[M + H^+]^+$. Elemental Analysis: Calcd. for $C_{32}H_{40}N_2O_{10}$: C, 62.73; H, 6.58; N, 4.57. Found: C, 62.91; H, 6.60.

Bis[(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl]2,6-Dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (4o)

The product was prepared according to the typical procedure from 3-nitrobenzaldehyde (**3c**) (0.302 g, 2 mmol), β-keto ester **1b** (0.960 g, 4 mmol) and Mg_3N_2 (**2**) (0.100 g, 1 mmol). The mixture was stirred for 28 h at 90–100 °C. The crude mixture was extracted with CH_2Cl_2 (3 × 10 mL), dried over MgSO4 and purified by flash chromatography (Et_2O–cyclohexane, 30:70).

Yellow solid; yield: 0.589 g (50%); mp 151 °C; $[\alpha]_D^{20}$: 20 –26.25 (*c* 0.8, $CHCl_3$). IR (Nu*J*ol): 1700 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.49 (d, *J* = 7.1 Hz, 3 H), 0.58 (d, *J* = 7.1 Hz, 3 H), 0.76 (d, *J* = 6.9 Hz, 3 H), 0.84 (d, *J* = 6.5 Hz, 3 H), 0.90 (d, *J* = 6.5 Hz, 3 H), 0.94 (d, *J* = 7.1 Hz, 3 H), 0.72–2.08 (complex pattern, 18 H), 2.33 (s, 3 H), 2.43 (s, 3 H), 4.67 (dt, *J* = 4.3 Hz, *J* = 11.2 Hz, 2 H), 5.10 (s, 1 H), 5.64 (bs, 1 H, NH), 7.38 (t, *J* = 8.1 Hz, 1 H), 7.62 (dt, *J* = 1.4 Hz, *J* = 8.1 Hz, 1 H), 8.01 (ddd, *J* = 1.0 Hz, *J* = 2.4 Hz, *J* = 5.9 Hz, 1 H), 8.14 (t, *J* = 2.2 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.64, 16.87, 19.61, 20.91, 22.06, 22.85, 23.91, 25.52, 31.46, 34.35, 39.96, 41.05, 41.58, 47.27, 47.54, 3.33, 74.10, 103.19, 104.10, 121.23, 123.39, 128.68, 134.60, 144.25, 145.37, 148.05, 150.13, 166.69. MS (ESI): *m*/*z* = 595 $[M + H^+]^+$. Elemental Analysis: Calcd. for $C_{35}H_{50}N_2O_6$: C, 70.68; H, 8.47; N, 4.71. Found: C, 70.93; H, 8.50.

Bis[(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl]2,6-Dimethyl-4-(2-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (4p)

The product was prepared according to the typical procedure from 2-nitrobenzaldehyde (**3d**) (0.302 g, 2 mmol), β-keto ester **1b** (0.960 g, 4 mmol) and Mg_3N_2 (**2**) (0.100 g, 1 mmol). The mixture was stirred for 24 h at 90–100 °C, then at 120 °C for 8 h, and then at r.t. for an additional 48 h. The crude mixture was extracted with CH_2Cl_2 (3 x 10 mL), dried over MgSO4 and purified by flash chromatography (Et2O–cyclohexane, 30:70).

Yellow solid; yield: 287 mg (25%); mp 93 °C; $[\alpha]_D^{20}$: 20 +20.87 (*c* 1.0, $CHCl_3$). IR (film): 1687 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.46 (d, *J* = 7.1 Hz, 3 H), 0.51 (d, *J* = 7.1 Hz, 3 H), 0.65 (d, *J* = 6.7 Hz, 3

H), 0.82 (d, *J* = 6.7 Hz, 6 H), 0.88 (d, *J* = 7.1 Hz, 9 H), 0.90–1.94 (complex pattern, 12 H), 2.27 (s, 3 H), 2.34 (s, 3 H), 4.64 (dq, *J* = 4.3 Hz, *J* = 9.8 Hz, 2 H), 5.78 (bs, 1 H, NH), 5.96 (s, 1 H), 7.23 (m, 1 H), 7.46 (dt, *J* = 1.2 Hz, *J* = 7.1 Hz, 1 H), 7.56 (dd, *J* = 1.2 Hz, *J* = 7.9 Hz, 1 H), 7.81 (dd, *J* = 1.2 Hz, *J* = 8.3 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.58, 16.34, 19.71, 19.99, 20.62, 20.99, 20.98, 22.84, 23.54, 25.24, 26.33, 31.42, 31.50, 34.08, 34.18, 39.68, 40.22, 40.72, 46.14, 46.40, 73.37–73.42, 74.16–74.21, 103.92, 104.45, 124.21, 126.61, 131.60, 132.76, 143.45, 143.76, 145.00, 147.42, 166.80, 166.97. MS (ESI): *m*/*z* = 595 $[M + H^+]^+$. Elemental Analysis: Calcd. for $C_{35}H_{50}N_2O_6$: C, 70.68; H, 8.47; N, 4.71. Found: C, 70.96; H, 8.80.

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Chapter 3.

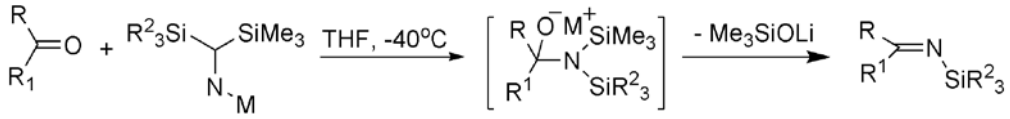
Use of N-trialkylsilylimines in the synthesis of N-containing heterocycles via a Hetero Diels-Alder strategy

3.1 Introduction:

Imines chemistry has achieved a dramatic development in the past decades. Due to their importance in organic synthesis, many *N*-substituted imines have been developed and applied for the syntheses of amino acids, β-lactams, heterocycles, alkaloids, aziridines, and amines.[1,2] Among the reported imines, variously substituted *N*-trialkylsilylimines in general and *N*-trimethylsilylimines, in particular, play a prominent role as a result of their easy preparation and use in a plethora of synthetic applications.[3] Some of these researches' studies have been developed in the laboratories where this thesis' study has been realized.[4-12]

3.1.1 Preparation of N-trimethylsilyl imines

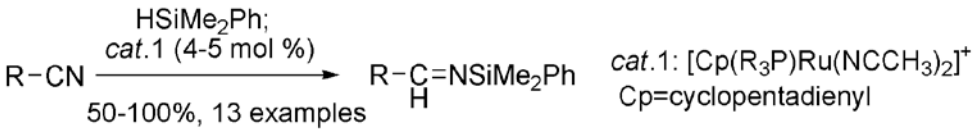
N-trimethylsilyl imines are useful intermediate in the organic synthesis. They can be prepared in several ways. One of the simplest and high efficient method for the preparation is based on the addition-elimination reaction of an alkaline metallo hexamethyldisilylamines to aldehydes and ketones (Scheme 1).



R=alkyl or aryl; R_1=H, aryl; COOEt; R_2=Me; *t*-Bu; *i*-Pr

Scheme 1: Preparation of *N*-(trialkylsilyl)imines

Recently an interesting alternative to this procedure appeared in literature: Nikonov and coworkers[13] reported an elegant preparation of silyl-aldimines via a chemoselective hydrosilylation of nitriles catalyzed by Ruthenium complex (Scheme 2). For other methods for the preparation of silylimines the reader may refers to reported reviews.[3,4]



Scheme 2

As above anticipated, *N*-trialkylsilylimines have found useful application in the synthesis of a large variety of organic compounds presenting a nitrogen atom in their scaffold, including heterocycles. Accordingly, in this chapter will be reported the studies on the synthesis of piperidine scaffold starting from suitable decorated *N*-trimethyl silyl imines. As a matter of fact six-member nitrogen containing

heterocyclic rings constitute a framework very frequently encountered in natural products. Among them piperidine ring is one of the most common and continues to be highly used moiety in pharmaceutical research.[14-18] There is special emphasis towards the preparation of piperidines bearing an hydroxyalkyl side chain at β-position of the nitrogen atom, since such scaffold may be identified as such or suitably elaborated in alkaloids with important bioactivity,[19,20] for examples Conhydrine, (-)-Castanospermine, (-)-slaframine, and (-)-swainsonine (Fig. 1).

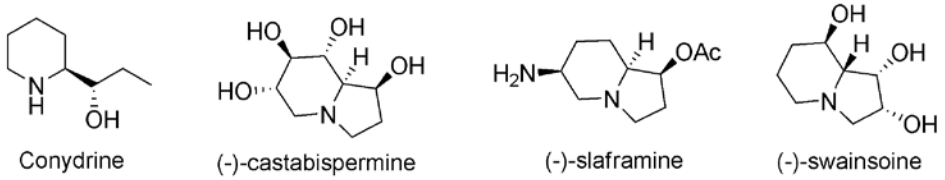
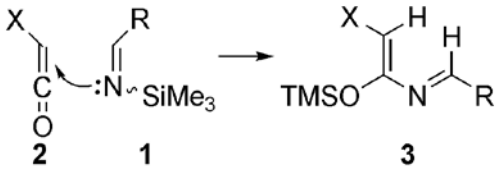


Figure 1.

Numbers of very valuable synthetic methods for the preparation of this backbone, particularly those associated with conhydrines,[21] have been already appeared in literature. However, to our knowledge, very few of them are based on a hetero Diels–Alder strategy.[15-18,22-25] In order to apply this strategy, using as suitable starting material a silyl imine, the latter must be converted into a diene. For the sake of easy reading and understanding, in the following section are reported the protocol to convert silyl imine into the corresponding azadiene and the basic properties of these interesting intermediates.

3.1.2 Preparation of electrophilic azadienes from N-Silylimines

Acylimines are good synthons for the hetero Diels–Alder (HDA) strategy to prepare heterocycles and natural products.[26-32] An important part of this strategy involves the use of imino Diels Alder reaction which provides an efficient route to the construction of functionalized six-member nitrogen-containing heterocyclic structures,[33] with control of regio-, diastereo- and enantioselectivity.[34] The HDA adducts have been used as such for the synthesis of complex cyclic structures as new heterocycles or open-chain compounds. The synthetic scope of azadienes (Scheme 3) in the preparation of important intermediates in organic synthesis is well documented.[4,7,10,35,36]



Scheme 3

Reaction of *N*-trimethylsilylimine with an acylating agent such as acyl chlorides in the presence of a base gives rise to the formation of a 3-trialkylsilyloxy-2-aza-1,3-diene **3** (Scheme 3). After the pioneering work by the Ghosez group[37,38] such intermediates have been proved, *inter alia*, to be useful starting materials in hetero Diels-Alder reaction, with carbonyl compounds as dienophiles.[39] The formation of the

azadiene has been supposed to happen via a nucleophilic attack of the imine's nitrogen lone pair to the ketene as represented in Scheme 3. The ketene **2** is formed *in situ* in the reaction pot, adding triethylamine to the corresponding acyl chloride. The 3-trialkylsilyloxy-2-aza-1,3-dienes **3** with various substitution patterns are obtained in variable yields. Their stability largely depends on the said substitution pattern. The **X** group on ketene may be an hydrogen,[38,40], alkyl/aryl groups,[38] or a heterogroups as an amidic one: it is possible to isolate and spectroscopically characterise the azadienes deriving from ketenes carrying in the α-position amido groups, halogens or sulphidic substituents. The stability is mostly conferred by the nature of the silylimines **1** utilized. The most stable 3-trialkylsilyoxy-2-aza-1,3-dienes are the triisopropyl- and *tert*-butyl-dimethyl silyloxy ones because the triisopropyl- and *tert*-butyl-dimethylsilyl groups are not easily labile. It is even possible to purify by flash chromatography on a short silica gel-column the azadienes carrying an amidic substituent in position 4 and a *tert*-butyl-dimethylsilyl group on the oxygen.[36,41] The configuration of the isolated and purified azadienes has been determined by a serie of NOE experiments. In the Figure 2, the results obtained for two stable azadienes **A** and **B** are reported as examples. Observing the increment values obtained, it can be deducted that the configuration of these azadienes is *s-cis-ZE*.[10,36,42]

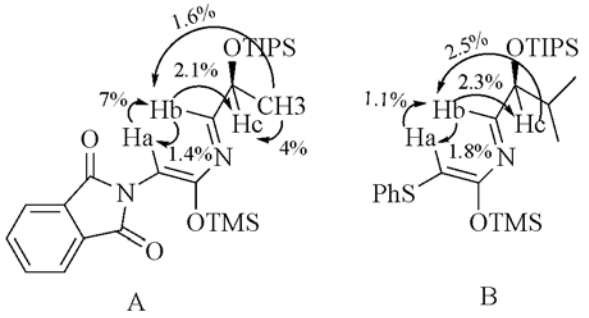


Figure 2

In order to give a paramount sight on the preparation it must be underlined that an alternative route for the preparation of 3-trialkylsilyloxy-2-azadienes, is the Pinner-Ghosez procedure.[38] Azadienes of type **1** have been used as dienophile counterparts in hetero Diels-Alder reaction.

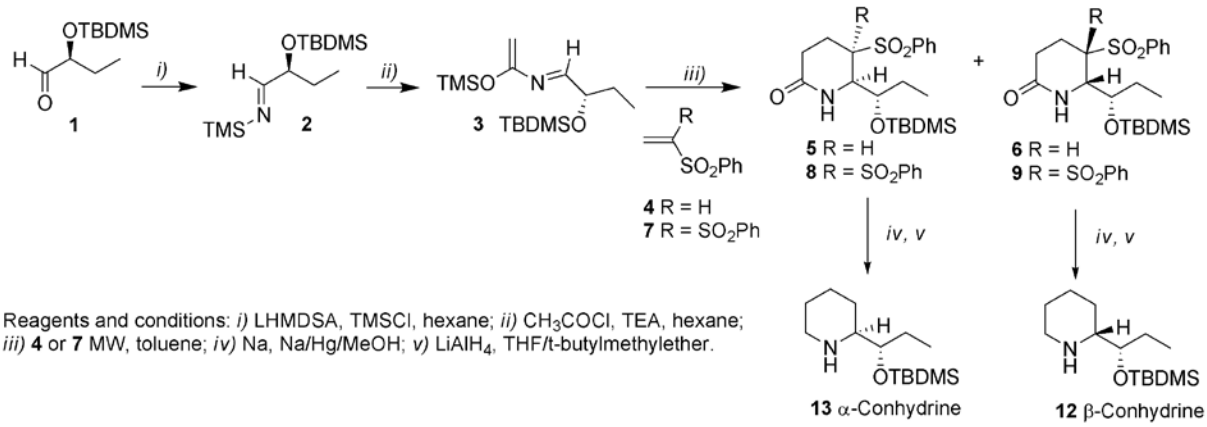
3.1.3 Reactivity of trialkylsilyloxy-2-aza-1,3-dienes: six-member ring formation via Hetero-Diels Alder reactions between azadienes and an appropriate dienophile.

The hetero Diels-Alder (HDA) reaction using heterodienes and/or heterodienophiles is a very useful method for constructing heterocyclic rings and is widely used as a key step in the synthesis of natural products.[28,43-46]

3-Trialkylsilyloxy-2-aza-1,3-dienes have been used in HDA reactions with a variety of dienophiles furnishing pyridones, isoquinolones, tetrahydropyridones, piperidones, pyrimidones, tetrahydrooxazinones with various substitution patterns.[3] This chemistry has been mainly developed by Ghosez's and our groups. Ghosez has demonstrated the importance of the trialkylsilyloxy group at C-3 in doing this diene a good enophile, because it increases the nucleophilicity of the diene at C-4 by raising the energy of the HOMO and increasing its coefficient at C-4. In fact, according to the FMO theory,[47] the cycloaddition of the

carbonyl dienophile to 1,3-dienes is a $HOMO_{diene}$ $LUMO_{dienophile}$ controlled process. The presence of the trialkylsilyloxy group at C-3 also decreases the energy barrier between the *cisoid* and *transoid* conformation of the diene, thus favouring the cycloaddition over reactions on the nitrogen atom.[48,49]

Among the several applications of hetero Diels-Alder reaction using azadienes generated from aldimines that concerning the synthesis of *Conhydrine*, a biologically active piperidine derivative[5] found with *Conine* in the poison hemlock (*Conium maculatum*, popularly known as *Cicuta*, the Socrates poison) is worth of mention since constitutes the prodrome of the work performed during this thesis and which will be the object of the following section. The synthetic strategy involved the reaction of a chiral azadiene **3**[50] with vinylsulfone **4** or **7** that afforded the Diels Alder adducts **5** and **6** or **8** and **9** respectively (see Scheme 4). The use of the more dienophile **7** resulted in better yields.[51] In particular, when the reaction was carried out using microwaves afforded the expected HAD-adduct in 82% chemical yields and 1/1 diastereomeric ratio. The synthetic utility of this methodology has been demonstrated by converting the cyclic adducts **8** and **9** to corresponding conhydrines **12** and **13** in two steps (Scheme 4).[52]



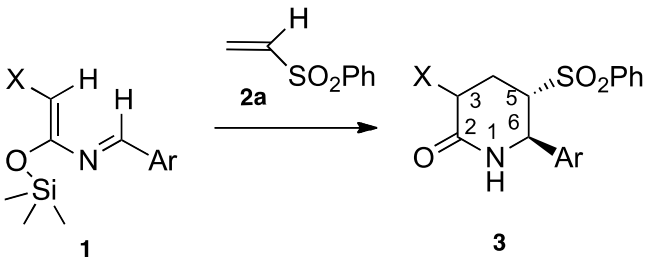
Scheme 4

3.2 Present work

3.2.1 Preparation of 6-Aromatic- and Heteroaromatic-Substituted Piperidin-2-one Scaffold by Hetero Diels-Alder (HDA) Strategy.[53]

As above anticipated, functionalized 2-azadienes have been shown to be versatile intermediates for the preparation of five- and six-member heterocycles.[33,35,54,55] Moreover the azadiene system has been used for an electrocyclization reaction to give[4,48,56-59] different heterocyclic compounds such as β-lactam rings *via* a two step Staudinger's reaction,[7,6] tetramic acid scaffold,[40] perhydrooxazin-2-ones, cyclic intermediates in the synthesis of α-amino-β-hydroxy-acids,[59,60] β-hydroxy-carboxylic acids[40] and 1,3-aminols.[8,9,28,61] Recently, as above reported, the HDA-approach has been used for the synthesis of *Conhydrine*, a poisonous alkaloid present in *conium maculatum* and characterized by a piperidine scaffold.[5] By the present work we report the natural prosecution of our studies in this stream by extending the preparative utility of this novel approach to piperidine-2-one heterocyclic rings substituted in position 6 by an aromatic or heteroaromatic group.[15,17,18,22-24] The synthetic protocol for the preparation of the starting azadiene **1** (scheme 5) was that

already published: synthesis of a *N*-trimethylsilylimine[62] and coupling of this intermediate with a suitable acyl chloride in the presence of a base such as triethylamine (TEA).[38] In order to obtain the target piperidine-2-one scaffold the azadiene thus prepared was reacted with a dienophilic moiety bearing two carbon atoms to allow the formation of a six-member heterocyclic ring (Scheme 5). The intrinsic characteristic flexibility of a sulfonyl group, which may be easily removed, according well established literature protocol, or elaborated to more complex decorations of the heterocyclic ring, drove our choice towards the vinylsulfone **2a** (Scheme 5) which presents, additionally, the necessary electron-poor nature for a normal electron demand hetero Diels-Alder reaction.



Scheme 5. Reaction of azadiene **1(a-e)** with dienophiles **2a**

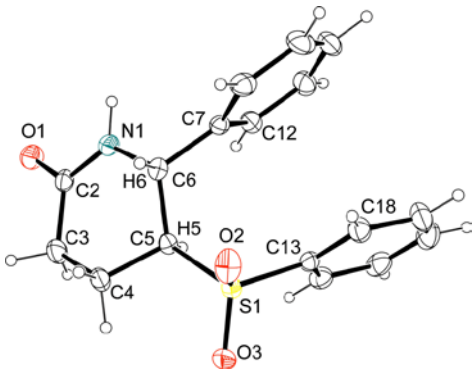


Fig. 3 X-ray crystal structure of **3a** with partial atomic numbering scheme. The atomic displacement parameters are drawn at the 30% probability level.

Reaction of the azadiene **1a** with the vinylsulphone **2a** in anhydrous toluene at reflux for seven hrs (Scheme 5 and Table 1 entry 1) or at 110°C under microwave irradiation for 20 min. (Table 1 entry 2) gave rise to the formation of the piperidin-2-one **3a** in 38% and 50% yields, respectively, and occurs with full *exo* selectivity in analogy to the already reported results by Ghosez's group, some of them supported by X-Ray structures determination.[63-65] Since better yields were obtained using MAOS technique, this procedure was adopted for all the examples reported in Table 1. As previously pointed out the *trans* relationship between the positions 5 and 6 is observed.[63-65] The structural relationship between the substituents in 5 and 6 positions of the piperidin-2-one ring has been confirmed by an X-ray diffraction study, carried out in order to unequivocally determine the correct structure of **3a**. This analysis shows that the piperidinone ring adopts a distorted half-chair conformation with the hydrogens bound to C5 and C6 in *trans* position [H5C5C6H6 torsion angle of 176(1)°, see Figure 3]. In addition π-π interactions are present between the

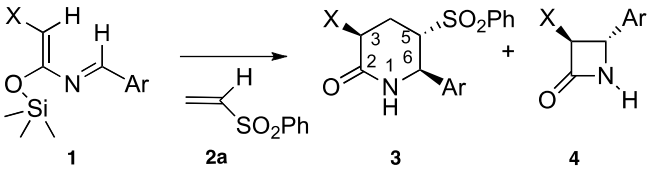
two phenyl rings. Moreover the sole cyclic product obtained is that arising from a [4+2] HDA reaction, although in moderate-low yields (Table 1).

Table 1. Synthesis of piperidin-2ones **3a-e**

Entry	**Diene 1**	**X**	**Ar**	**3**(Y%)
1[a]	**1a**	H	Ph	**3a(**38**)**
2[b]	**1a**	H	Ph	**3a(**50)
3[b]	**1b**	H	*p*-MeO-Ph	**3b**(26)
4[b]	**1c**	H	*p*-NO_2-Ph	**3c**(13)
5[b]	**1d**	H	Thienyl	**3d**(25)
6[b]	**1e**	H	3-Pyridyl	**3e**(18)

[a]: Convective heating. [b]: Dielectric heating

On the contrary, using azadienes **1(f-h),** characterized by the presence of a substituent X on the 4-position, a β-lactam ring **4** is also detected in the crude reaction mixture, (Scheme 6 and Table 2) independently from the reaction conditions adopted (convective or dielectric heating, Table 2 entries 1 and 2), thus showing a competitive electrocyclization reaction of the diene itself with the formation of the corresponding β-lactam ring **4**.



Scheme 6. Reaction of azadiene **1(f-h)** with dienophiles **2a**

From a stereochemical point of view the stereo relationship between the substituents in 3 and 5 and in 5 and 6 positions of the piperidine-2-one ring 3 are *trans* as well as invariably *trans* is the stereo-relationship of the substituents in 3 and 4 positions of the β-lactam **4**.

Table 2. Reaction of azadiene **1(f-h)** with dienophiles **2a**

Entry	**Diene 1**	**X**	**Ar**	**3** (Y%)	**4** (Y%)
1[a]	**1f**	Cl	Ph	**3f** (11)	**4f** (30)[6]
2[b]	**1f**	Cl	Ph	**3f** (17)	**4f** (38)
3[b]	**1g**	Br	Ph	**3g** (16)	**4g** (42)[6]
4[b]	**1h**	Ph-S-	Ph	**3h** (3)	**4h** (16)[7]

[a]Convective heating. [b] Dielectric heating

This competition between a [2+2EC] electrocyclic reaction and a [4+2] cycloaddition has been already observed by our group using the same diene-scaffold and a carbonyl compound as dienophile. Theoretical studies by Density Functional computations[66] showed that the competition between the formation of a perhydrooxazinone (arising from a 4+2 HDA reaction) and/or a β-lactam (arising from a [2+2EC] Staudinger reaction) is governed by a delicate interplay between temperature and the very nature of the substituents of the diene and dienophile, respectively. Similar computational studies have also been performed in the present case where the competition is between the piperidin-2-one **3f** and the β-lactam **4f** formation. The example of entry 1 of Table 2, yielding the compounds **3f** and **4f** (X=Cl, Ar=Ph) has been used as study case. In order to have the most complete overview of the reaction profile, we took in exam, from theoretical point of view, both the 5-6 *cis* (arising from an endo attack) and 5-6 *trans* (arising from an exo attack) possible stereo relationships of the substituents. Figure 4 shows the energy profiles, Figure 5 the geometries of the corresponding transition states and Figure 6 the variation of the $G^{\#}$ energy barriers against temperature. From Figure 4 it may anticipated that HDA reaction is favoured in comparison with the formation of the [2+2EC] electrocyclic ring closure. In particular, the HDA exo1 approach has the lowest energy barrier (Fig. 4). However, careful analysis from Figure 6, shows that, on the basis of the variation of the $G^{\#}$ barriers, the formation of the β-lactam is possible only at high temperature conditions. As the matter of fact, from experimental point of view, the formation of the β-lactam ring takes place at toluene reflux temperature (110 °C) whereas at low temperature (25 °C) only traces of the six-member ring are detected by NMR analysis after 5 hrs. The slope of the data in Figure 6, obtained through linear regression, indicates that exo1 reaction is higher than the electrocyclic closure (0.048 against 0.0035), and that the two lines intersect at 488 T[K]. This intersection temperature indicates qualitatively when the mechanism changes thus suggesting that only at high temperatures it is possible to obtain the β-lactam product. Figure 4 shows the energy profiles of the two possible endo pathways, which have been called respectively endo1 (C), and endo2stack (B) (Fig. 5). Endo2stack (B) is due to the stacking interaction between the phenyl group of the diene with the phenyl group of the $-SO_2Ph$ substituent of the dienophile (see the corresponding transition states geometries in Fig. 5)

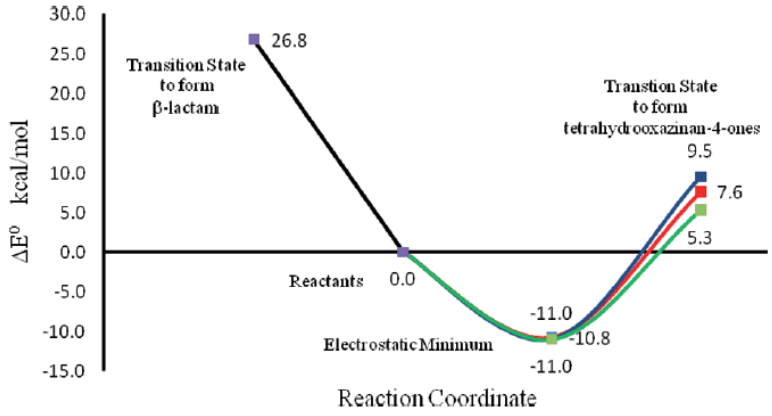


Figure 4. E^0 energy profiles for the 2+2EC (black line), *exo1* (green line), *endo1*(red line) and *endo2stack* (blue line) pathways.

Against the three different electrostatic minima with almost identical energy, the *exo1* (**A**) (Fig. 5) approach is favoured compared with both the *endo* pathways. Among them the *endo2stack* (**B**) approach has a slightly higher barrier than *endo1*(**C**). The stabilizing stacking interaction probably does not compensate the strain at which the molecule is forced to maximize the non-bonded interaction. In fact, linear regression of the $G^{\#}$ data in Figure 6, shows that *endo2stack* (**B**) has a higher slope (0.06) than *exo1* (**A**) and *endo1*(**C**) (~0.048) due to a destabilizing entropy effect. [67]

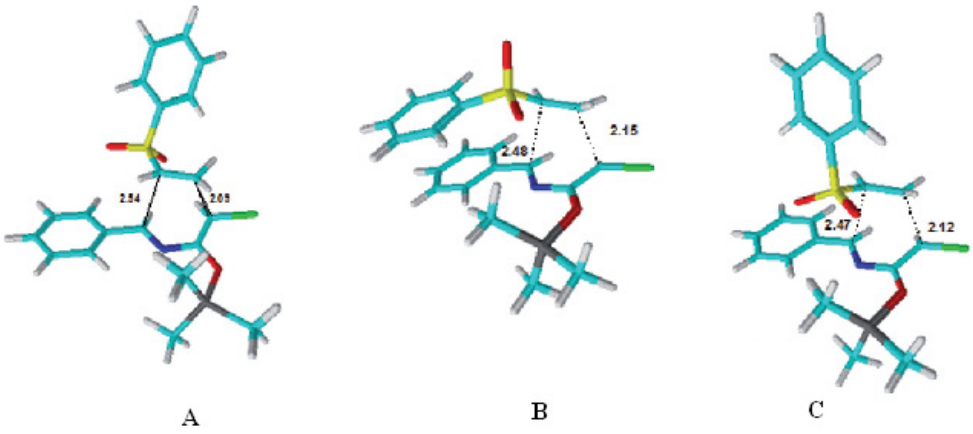


Figure 5. Optimized transition states geometries: (A) *exo1*, (B) *endo2stack* and (C) *endo1* mechanisms.

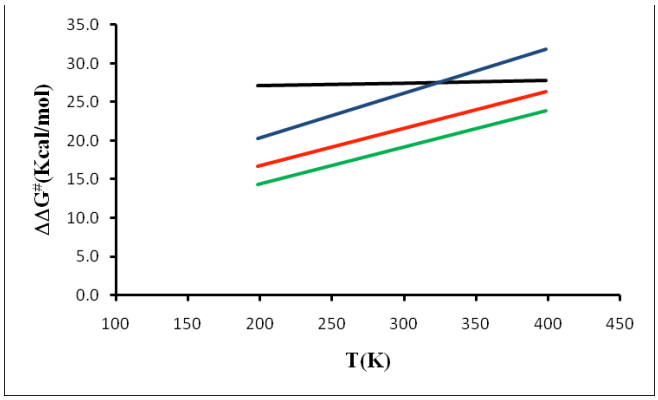
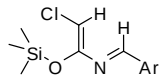
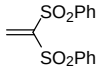


Figure 6. Variation of the $G^{\#}$ energy barriers of the 2+2EC (black line) and HDA (*endo1*, red line, *endo2stack*, blu line and *exo1*, green line) reactions against temperature.

Taking advantage of the results reported by De Lucchi[51] on the reactivity of the sulfones in Diels-Alder reaction, the next step of our studies was to consider a new reaction pathway in which the electron demanding nature of the dienophile was increased by adding an extra sulfone group in its scaffold. To support this choice and before studying the mechanism from a theoretical point of view, we have analyzed the global electrophilic indices of **1f**, **2a** and **2b** through the conceptual DFT descriptors.[67-70] The results of this theoretical investigation have been reported in Table 3. Both the dienophiles **2a** and **2b** have a high index but **2b** is higher than **2a** and consequently a better reactivity in the HDA reaction which should further disfavour the formation of the β-lactam side product. This result has been tested from a theoretical point of view investigating the reaction of the diene **1f** with the dienophile **2b** (Scheme 7). For this reaction

we have detected two different HDA transition states: *no-stack1* and *stack1* (see Figure 7 for the geometries of the corresponding transition states). Because *stack1*, which has the corresponding stacking interaction described in the **1f** + **2a** reaction, due to a destabilizing entropy effect, is not favoured, we have limited our discussion to the *no-stack1* pathway.

Table 3. Electrophilic indice of **1f**, **2a** and **2b**

			
	1f	**2a**	**2b**
μ	0.15	0.17	0.18
x	3.99	4.65	4.89
η	0.22	0.31	0.28
S	4.47	3.25	3.55
△Nmax	0.66	0.55	0.64
ω	1.31	1.29	1.56
△ω		-0.02	0.25

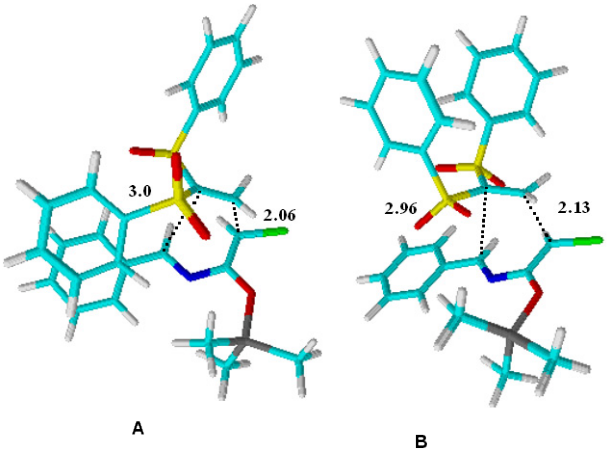


Figure 7. Optimized transition states geometries: (A) *stack1* and (B) *no-stack1* mechanisms.

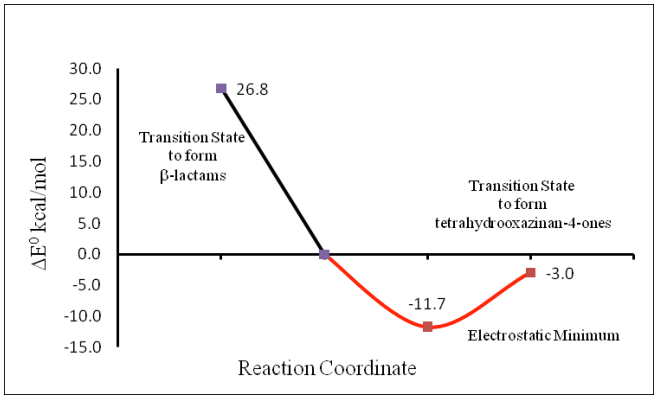


Figure 8. E^0 energy profiles for the 2+2EC (black line) and *no-stack1* (red line) pathways.

In Figure 8, together with the 2+2EC pathway, is reported the energy profile of the *no-stack1* mechanism and in Figure 8 the variation of the $G^{\#}$ energy barrier of the *no-stack1* reaction against temperature. Figure 8 shows that the HDA pathway is even more stabilized in comparison with the 2+2EC mechanism. This disulfone system forms an electrostatic minimum stabilized of 11.7 kcal/mol. The energy barrier to form the HDA product is now reduced by half compared to the mono-sulfone case (8.7 against 16.3 kcal/mol.), being lower than the stabilization due to the electrostatic interaction. Diagram in Figure 9 shows that, despite a higher slope (~0.06), the intersection temperature becomes 524 *T*[K]. In other words, this qualitative diagram indicates that is necessary a higher temperature to form the β-lactam.

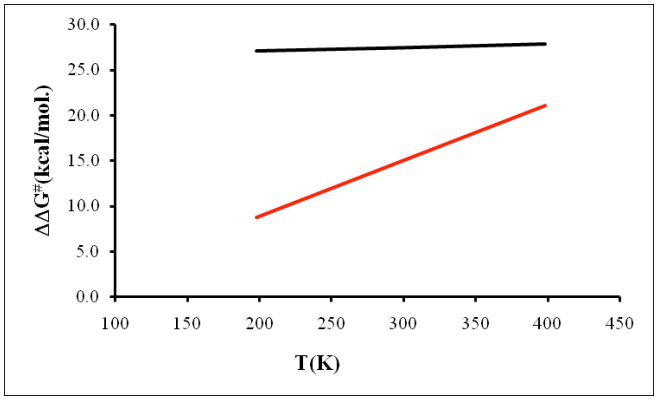
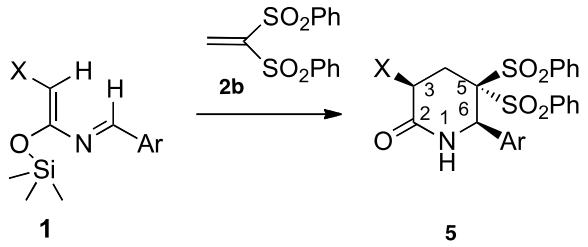


Figure 9. Variation of the $G^{\#}$ energy barriers of the 2+2EC (black line) and HDA *no-stack1*(red line) reactions against temperature.

Having in mind the theoretical simulations, we increased the reactivity of the dienophile introducing a second sulfone moiety into the vinylsulfone scaffold (Scheme 7). As predicted a higher yielding HDA reaction took place and no traces of a β-lactam compound was present in the crude reaction mixture (Scheme 7 and Table 4).

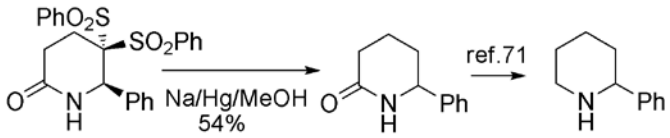


Scheme 7. Reaction of azadiene **1** with dienophiles **2b**.

Once again the stereo relationship between the substituents on the C-3 (if present) and C-6 positions (piperidine numbering) was in a mutual *cis* relationship as dictated by an HDA mechanism. To test the practicability and synthetic utility of the protocol herein reported, the elaboration of compound **5a** to the racemic (±)-2-phenyl-piperidine was explored and proved to be relatively straightforward (Scheme 8). The protocol to elaborate **5a** to the corresponding **6**[71] was identified in the use of a popular desulphonation by means of sodium amalgam in methanol. Elaboration of **6** to the 2-phenyl-piperidine **7** by means of $LiAlH_4$ has been already reported.[71]

Table 4. Synthesis of Piperydin-2-ones **5** from azadiene **1** and dienophile **2b**

Entry	Diene **1**	R	Ar	**5** (Y%)	**4** (Y%)
1	1a	H	Ph	**5a** (61)	**4a** (0)
2	1c	H	*p*-NO_2-Ph	**5c** (30)	**4c** (0)
3	1d	H	Thienyl	**5d** (38)	**4d** (0)
4	1e	H	3-Pyridyl	**5e** (75)	**4e** (0)
5	1f	Cl	Ph	**5f** (64)	**4f** (0)
6	1h	Ph-S-	Ph	**5h** (25)	**4h** (0)
7	1i	Cl	p-F-Ph	**5i** (96)	**4i** (0)



Scheme 8. Synthesis of 2-phenylpiperidine.

3.2.2 Conclusions

From the results reported we have demonstrated that the reactivity of azadiene of type **1** may be extended to the preparation of an important scaffold as is that of piperidine. Application of this strategy to the preparation of other bio-important compounds, presenting different decorations on the ring, is currently under studies. Theoretical studies addressed to disclose the main parameters which favours the [4+2] reaction *versus* the competitive [2+2] have been carried out and the relative results reported.

3.3 Experimental Section

General: All the reactions were conducted under N_2 atmosphere. NMR spectra were recorded with a Varian instrument at 400 MHz (^{1}H) and 100 MHz (^{13}C). Chemical shifts (δ) for ^{1}H and ^{13}C NMR spectra and *J* value are reported in ppm. All chemical shifts are quoted relative to deuterated solvent signals. Optical rotations were measured at 25 °C with a Perkin–Elmer Polarimeter 141. Mass spectra were recorded with a Finnigan MAT GCQ spectrometer in the electron impact mode at 70 eV and are reported as *m*/*z*. The infrared spectra were recorded with a Perkin Elmer Spectrum BX spectrometer; wave numbers are reported in cm^{-1}. Elemental analyses were performed at CNR-ISMAR, Bologna, Italy. Solvents were distilled and dried according to the standard procedure.

Reaction of the azadiene **1a** with the sulphone **2a**, under convective heating (Entry 1 Table 1).

Azadiene **1a** (1 mmol) was dissolved in 10 mL of anhydrous toluene and phenyl vinylsulfone **2a** (0.17 g, 1 mmol) was added in one portion under magnetic stirrer. The solution was warmed at reflux temperature for 7 hrs then was cooled at room temperature. The solvent was removed in vacuo and the

crude reaction mixture was purified by crystallization with ethanol Product **3a** (0.12 g) was obtained in 38% yield.

Reaction of the azadiene **1a** with the sulphone **2a**, under MAOS conditions (Entry 2 Table 1)

Azadiene **1a** (1 mmol) was dissolved in 10 mL of anhydrous toluene and was put in a flask for microwave oven synthesis (Milestone). Phenyl vinylsulfone (0.17 g, 1 mmol) was added and the mixture was submitted to microwave irradiation for 20' at 500 Watt power. The solvent was evaporated and the pure product **3a** (0.16 g) was obtained by crystallization of the crude reaction mixture with ethanol in 50% yield.

(5*S, 6*R**)-6-phenyl-5-(phenylsulfonyl)piperidin-2-one 3a:** white solid; m.p.= 229°C. IR ($CHCl_3$): 1668 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.81 (m, 2H, Ar), 7.62 (m, 1H, Ar), 7.16 (m, 2H, Ar), 7.27 (m, 3H, Ar), 7.12 (m, 2H, Ar), 5.73 (bs, 1H, NH), 5.15(dd, J_1 = 3.2 Hz, J_2 = 4.4 Hz, 1H, 6-H), 3.42 (q, J = 5.6 HZ, 1H, 5-H), 2.79 (dt, J_1 =8.0 Hz, J_2= 18.0 Hz, 1H, 3-H_A), 2.48 (dt, J_1 =6.4Hz, J_2= 18.0 Hz, 1H, 3-H_B), 2.22 (m, 2H, 4-CH_2) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 170.54, 139.77, 137.62, 134.09, 129.41, 129.11, 126.87, 128.53, 126.44, 63.76, 55.20, 28.05, 18.47 ppm. Ms *(m/z*): 316, 174, 173, 158, 144. $C_{17}H_{17}NO_3S$ (315.09) calculated: C 64.74, H 5.43, N 4.44; found: C 64.80, H 5.44, N 4.44.

X-ray Crystallography for **3a**

The X-ray intensity data for **3a** were measured on a Bruker SMART Apex II diffractometer equipped with a CCD area detector using a graphite monochromated Mo-K_α radiation source (λ = 0.71073 Å). Cell dimensions and the orientation matrix were initially determined from a least-squares refinement on reflections measured in three sets of 20 exposures, collected in three different ω regions, and eventually refined against all data. For all crystals, a full sphere of reciprocal space was scanned by 0.3°ω steps. The software SMART.[72] was used for collecting frames of data, indexing reflections and determination of lattice parameters. The collected frames were then processed for integration by software[72] and an empirical absorption correction was applied with SADABS.[73] The structure was solved by direct methods (SIR 97)[74] and subsequent Fourier syntheses and refined by full-matrix least-squares calculations on F^2 (SHELXTL)[75] attributing anisotropic thermal parameters to the non-hydrogen atoms. All hydrogen atoms were located in the Fourier map. The methylene and aromatic hydrogens were placed in calculated positions and refined with isotropic thermal parameters *U(H)* = 1.2 *Ueq*(C), and allowed to ride on their carrier carbons whereas the methine and aminic H atoms were located in the Fourier map and refined isotropically.

$C_{17}H_{17}NO_3S$, **3a**, M = 315.38, monoclinic, space group *P2₁/c (*No. 14), *a* = 15.9096(11), *b* = 5.7746(4), *c* = 17.2601(12) Å, β = 17.2601(12)°, V = 1516.49(18) $Å^3$, *Z* = 4, T = 293(2) K, Dc = 1.381gcm–1, μ(Mo-Kα) = 0.226 mm^{-1}, F(000) = 664 crystal size = 0.20 x 0.2510 x 0.05 mm, 16370 reflections collected [R(int) = 0.0353], 3707 unique. Final R [I > 2σ(I)] = 0.0402, wR2[I σ 2σ(I)] =0.0937, and for all data R (all data) = 0.0643, wR2 (all data) = 0.1055.

CCDC-829176 contains the supplementary crystallographic data for compound **3a**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Reaction of the azadiene **1b-h** with the sulphone **2a**, under MAOS conditions: General procedure.

Azadiene **1b-h** (1 mmol) was dissolved in 10 mL of anhydrous toluene and was put in a flask for microwave oven synthesis (Milestone). Phenyl vinylsulphone (0.17 g, 1 mmol) was added and the mixture was submitted to microwave irradiation for 20' at 500 *Watt* power. The solvent was evaporated and the residue was purified by flash chromatography (eluent CH_2Cl_2/ethylacetate, 75/25) to afford the products **3b-h** and the β-lactams **4f-h** in the yields and ratios reported in Table 1 and in Table 2.

(5*S, 6*R**)-6-(4-methoxyphenyl)-5-(phenylsulfonyl)piperidin-2-one 3b:** white solid; m.p =160-165°C. IR ($CHCl_3$): 1667 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.75 (m, 2H, Ar), 7.59 (m, 1H, Ar), 7.46 (m, 2H, Ar), 6.97 (d, J = 8.8 Hz, 2H, Ar), 6.72 (d, J = 8.8 Hz, 2H, Ar), 6.48 (bs, 1H, NH), 5.01 (dd, J_1 = 1.6 Hz, J_2 = 4.4 Hz, 1H, 6-H), 3.72 (s, 3H, OMe), 3.36 (dt, J_1= 4.8 Hz, J_2 = 6.0 Hz, 1H, 5-H), 2.70 (m, 1H, 3-H_A), 2.40 (m, 1H, 3-H_B), 2.16 (m, 2H, 4-CH_2) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 170.63, 159.49, 137.68, 133.81, 131.51, 129.21, 128.35, 127.64, 114.21, 63.78, 55.20, 54.60, 28.06, 18.41 ppm. Ms (*m/z*): 345, 329, 203, 188, 172, 134, 92, 77. $C_{18}H_{19}NO_4S$ (345.10) calculated: C 62.59, H 5.54, N 4.06; found: C 62.55, H 5.55, N 4.05.

(5*S, 6*R**)-6-(4-nitrophenyl)-5-(phenylsulfonyl)piperidin-2-one 3c:** yellow solid. m.p.= 225-230°C. IR ($CHCl_3$): 1675 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ =8.17 (d, J = 8.8 Hz, 2H, Ar), 7.84 (d, J = 8.8 Hz, 2H, Ar), 7.69 (m, 1H, Ar), 7.56 (m, 2H, Ar), 7.39 (m, 2H, Ar), 6.41 (bs, 1H, NH), 5.31 (dd, J_1 = 2.4 Hz, J_2 = 4.4 Hz, 1H, 6-H), 3.38 (dt, J_1= 4.8 Hz, J_2 = 6.8 Hz, 1H, 5-H), 2.77 (m, 1H, 3-H_A), 2.47 (m, 1H, 3-H_B), 2.24-2.08 (m, 2H, 4-CH_2) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ =170.52, 147.97, 147.02, 137.05, 134.51, 129.63, 128.59, 127.70, 124.30, 63.58, 54.58, 28.06, 19.07 ppm. Ms (*m/z*): 360, 359, 299, 227, 218, 201, 171, 115, 91, 78. $C_{17}H_{16}N_2O_5S$ (360.08) calculated: C 56.60, H 4.47, N 7.77; found: C 56.85, H 4.48, N 7.79.

(5*S, 6*R**)-5-(phenylsulfonyl)-6-(thiophen-3-yl)piperidin-2-one 3d:** yellow solid. m.p = 190°C. IR ($CHCl_3$): 1672 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.83 (m, 2H, Ar), 7.64 (m, 1H, Ar), 7.53 (m, 2H, Ar), 7.18 (m, 1H, Th), 6.86 (m, 2H, Th), 6.29 (bs, 1H, NH), 5.38 (dd, J_1 = 2.8 Hz, J_2 = 4.8 Hz, 1H, 6-H), 3.50 (ddd, J_1=J_2= 4.8 Hz, J_3 = 6.8 Hz, 1H, 5-H), 2.73 (m, 1H, 3-H_A), 2.45 (m, 1H, 3-H_B), 2.38-2.20 (m, 2H, 4-CH_2) ppm . ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 170.16, 143.79, 137.62, 134.11, 129.40, 128.52, 127.13, 126.18, 125.99, 64.35, 51.37, 28.21, 19.00 ppm. Ms (*m/z*): 321, 305, 179, 164, 150, 110. $C_{15}H_{15}NO_3S_2$ (321.05) calculated: C 56.05, H 4.70, N 4.36; found: C 56.22, H 4.68, N 4.37.

(5*S, 6**R***)-5-(phenylsulfonyl)-6-(pyridin-3-yl)piperidin-2-one 3e:** white solid. m.p. = 205°C. IR ($CHCl_3$): 1674 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.55 (d, J = 2.0 Hz, 1H, Py), 8.53 (dd, , J_1=1.6 Hz, J_2 = 4.8 Hz, 1H, Py), 7.80 (m, 2H, Ar), 7.70 (m, 1H, Py), 7.66 (m, 1H, Ar), 7.53 (m, 1H, Ar), 7.33 (dd,

J_1=5.2 Hz, J_2 = 8.0 Hz, 1H, Py), 6.34 (bs, 1H, NH), 5.20 (dd, J_1 = 2.0 Hz, J_2 = 6.4 Hz, 1H, 6-H), 3.52 (q, J= 6.4, 1H, 5-H), 2.75 (m,1H, 3-H_A), 2.52 (m, 1H, 3-H_B), 2.22 (m, 2H, 4-CH_2) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 170.50, 149.47, 148.07, 137.29, 134.83, 134.34, 129.57, 128.51, 123.89, 63.47, 53.43, 28.34, 19.15 ppm. Ms (*m/z*): 316, 175, 141, 78. $C_{16}H_{16}N_2O_3S$ (316.09) calculated: C 60.74, H 5.10, N 8.85; found: C 60.56, H 5.12, N 8.87.

(3*S, 5*S**, 6*R**)-3-chloro-6-phenyl-5-(phenylsulfonyl)piperidin-2-one 3f:** white solid. m.p = 150°C. IR ($CHCl_3$): 1686 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.69 (m, 2H, Ar), 7.57 (m, 1H, Ar), 7.43 (m, 2H, Ar), 7.25 (m, 3H, Ar), 7.16 (m, 2H, Ar), 5.98 (bs, 1H, NH), 5.03 (dd, J_1= 1.6 Hz, J_2= 7.2 Hz, 1H, 6-H), 4.71 (t, J = 5.2 Hz, 1H, 3-H), 3.87 (ddd, J_1= 4.4 Hz, J_2= 7.2 Hz, J_3= 8.8 Hz, 1H, 5-H), 2.67 (m, 2H, 4-CH_2) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 166.03, 138.39, 137.42, 134.14, 129.34, 129.11, 129.05, 128.33, 127.13, 61.05, 56.43, 51.16, 29.43 ppm. Ms (*m/z*): 349, 314, 258, 208, 158, 91, 77. $C_{17}H_{16}ClNO_3S$ (349.05) calculated: C 58.37, H 4.61, N 4.00; found: C 58.19, H 4.59, N 4.02.

(3*S, 5*S**, 6*R**)-3-bromo-6-phenyl-5-(phenylsulfonyl)piperidin-2-one 3g:** Yellow oil. IR ($CHCl_3$): 1672 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.64 (m, 2H, Ar), 7.56 (m, 1H, Ar), 7.40 (m, 2H, Ar), 7.24 (m, 5H, Ar), 6.20 (bs, 1H, NH), 5.04 (dd, J_1 = 2.0 Hz, J_2 = 8.4 Hz, 1H, 6-H), 4.73 (t, J = 5.2 Hz, 1H, 3-H), 3.97 (q, J_1= 6.8 Hz, 1H, 5-H), 2.72 (dd, J_1= 5.2 Hz, J_2= 6.8 Hz, 2H, 4-CH_2) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ =166.39, 138.23, 137.57, 134.02, 129.25, 129.15, 129.04, 128.24, 127.37, 61.23, 56.81, 40.67, 29.98 ppm. Ms (*m/z):* 395, 393, 314, 254, 252, 141, 77. $C_{17}H_{16}BrNO_3S$ (393.00) calculated: C 51.79, H 4.09, N 3.55; found: C 51.67, H 4.11, N 3.54.

(3*S,5*S**,6*R**)-6-phenyl-5-(phenylsulfonyl)-3-(phenylthio)piperidin-2-one 3h:** Yellow oil. IR ($CHCl_3$): 1672 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.71 (m, 2H,Ar), 7.61 (m, 1H, Ar), 7.46 (m, 2H, Ar), 7.34 (m, 4H, Ar), 7.20 (m, 4H, Ar), 6.95 (m, 2H, Ar), 6.42 (bs, 1H, NH), 5.07 (dd, J_1 = 2.4 Hz, J_2 = 5.6 Hz, 1H, 6-H), 4.19 (dd, J_1 = 5.6 Hz, J_2 = 8.0 Hz, 1H, 3-H), 3.65 (ddd, J_1= 4.4 Hz, J_2= 5.6 Hz, J_3= 7.2 Hz, 1H, 5-H), 2.44 (ddd, J_1= 5.6 Hz, J_2= 7.2 Hz, J_3= 12.4 Hz, 1H, 4-H_A), 2.32 (ddd, J_1= 4.4 Hz, J_2= 8.0 Hz, J_3= 12.4 Hz, 1H, 4-H_B) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ=168.85, 139.07, 137.33, 134.66, 134.08, 133.23, 129.37, 129.32, 128.99, 128.79, 128.64, 128.42, 126.69, 62.36, 55.53, 45.31, 25.77 ppm. Ms (*m/z*): 423, 326, 281, 248, 204, 172, 144, 129, 91, 77. $C_{23}H_{21}NO_3S_2$ (423.10) calculated: C 65.22, H 5.00, N 3.31; found: C 65.48, H 5.02, N 3.30.

Reaction of the azadiene **1a, c-f, h-i** with the sulphone **2b**, under MAOS conditions as general procedure.

Azadiene **1a**, **c-f**, **h-i** (1 mmol) was dissolved in 10 mL of anhydrous toluene and was put in a flask for microwave oven synthesis (Milestone). 1,1-Bis(phenylsulfonyl)ethylene **2b** (0.31 g, 1 mmol) was added and the mixture was submitted to microwave irradiation for 20' at 500 Watt power. The solvent was evaporated and the residue was purified by flash chromatography (eluent CH_2Cl_2/ethylacetate, 80/20) to afford the products **5a**, **c-f**, **h-i**.

6-phenyl-5,5-bis(phenylsulfonyl)piperidin-2-one 5a: m.p. = 218°C. IR ($CHCl_3$): 1641 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.19 (m, 2H, Ar), 7.76 (m, 1H, Ar), 7.64 (m, 2H, Ar), 7.55 (m, 1H, Ar), 7.48 (m, 2H, Ar), 7.36-7.22 (m, 7H, Ar), 6.53 (bs, 1H, NH), 5.25 (d, *J* = 3.6 Hz, 1H, 6-H), 2.94 (m, 3H, 3-CH_2, 4-H_A), 2.80 (m, 1H, 4-H_B) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 169.62, 138.41, 136.99, 136.23, 135.19, 134.12, 131.27, 130.67, 130.20, 129.17, 128.44, 128.31, 90.24, 58.48, 27.74, 23.36 ppm. Ms (*m/z*): 454, 313, 171, 143, 115, 95, 77. $C_{23}H_{21}NO_5S_2$ (455.09) calculated: C 60.64, H 4.65, N 3.05; found: C 60.47, H 4.67, N 3.05.

6-(4-nitrophenyl)-5,5-bis(phenylsulfonyl)piperidin-2-one 5c: white solid. m.p. = 160°C. IR ($CHCl_3$): 1676 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.15 (m, 4H, Ar), 7.80 (m, 1H, Ar), 7.73 (m, 2H, Ar), 7.67 (m, 3H, Ar), 7.49 (m, 4H, Ar), 6.74 (bs, 1H, NH), 5.28 (d, *J* = 2.8 Hz, 1H, 6-H), 3.05 (m, 1H, 3-H_A), 2.86 (m, 3H, 4-CH_2, 3-H_B) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 169.83, 148.17, 143.22, 138.18, 136.24, 135.61, 134.86, 131.15, 130.99, 130.98, 129.52, 128.58, 123.40, 89.71, 57.95, 29.69, 23.47 ppm; Ms (*m/z*): 499, 438, 359, 218, 78.$C_{23}H_{20}NO_7S_2$ (500.07) calculated: C 55.19, H 4.03, N 5.60; found: C 55.39, H 4.01, N 5.62.

5,5-bis(phenylsulfonyl)-6-(thiophen-2-yl)piperidin-2-one 5d: white solid; m.p. = 225°C; IR ($CHCl_3$): 1676 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ [ppm] = 8.13 (d, 2H, *J*=7.2 Hz, Ar), 7.73 (m, 3H, Ar), 7.62 (m, 3H, Ar), 7.45 (m, 2H, Ar), 7.29 (d, 1H, *J*=5.2 Hz, Th), 7.17 (d, 1H, *J*=3.6 Hz, Th), 6.92 (dd, J_1 = 3.6 Hz, J_2 = 5.2 Hz, 1H, Th), 6.12 (bs, 1H, NH), 5.55 (d, *J* = 3.2 Hz, 1H, 6-H), 3.05 (m, 1H, 3-H_A), 2.83 (m, 1H, 3-H_B), 2.76 (m, 2H, 4-CH_2) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 169.64, 138.68, 138.46, 136.89, 135.29, 134.42, 131.32, 130.93, 130.72, 129.26, 128.48, 127.99, 126.53, 89.75, 54.64, 29.69, 24.40 ppm. Ms (*m/z*): 461, 369, 351, 319, 254, 177, 153, 135, 125, 111, 97, 77. $C_{21}H_{19}NO_5S_3$ (461.04) calculated: C 54.64, H 4.15, N 3.03; found: C 54.45, H 4.14, N 3.05.

5,5-bis(phenylsulfonyl)-6-(pyridin-3-yl)piperidin-2-one 5e: white solid. m.p. = 215°C; IR ($CHCl_3$): 1677 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.55 (dd, J_1 = 2.0 Hz, J_2 = 4.8 Hz, 1H, Py), 8.51 (d, *J* = 2.0, 1H, Py), 8.16 (m, 2H, Ar), 7.79 (m, 1H, Ar), 7.72 (m, 1H, Py), 7.66 (m, 5H, Ar), 7.45 (m, 2H, Ar), 7.23 (dd, J_1 = 4.8 Hz, J_2 = 8.0 Hz, 1 H, Py), 6.26 (bs, 1H, NH), 5.25 (d, *J* = 3.2 Hz, 1H, 6-H), 2.98 (m, 1H, 3-H_A), 2.88 (m, 1H, 3-H_B), 2.82 (m, 2H, 4-CH_2) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 170.24, 150.41, 149.29, 145.21, 137.91, 136.36, 135.40, 134.62, 132.73, 131.04, 130.70, 129.29, 128.51, 123.34, 89.30, 56.02, 27.40, 23.32 ppm. Ms (*m/z*): 456, 315, 174, 77. $C_{22}H_{20}N_2O_5S_2$ (456.08) calculated: C 57.88, H 4.42, N 6.14; found: C 57.70, H 4.43, N 6.17.

(3*S, 6*R**)-3-chloro-6-phenyl-5,5-bis(phenylsulfonyl)piperidin-2-one 5f:** white solid. m.p = 155°C. IR ($CHCl_3$): 1687 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.21 (m, 2H, Ar), 7.80 (m, 1H, Ar), 7.68 (m, 2H, Ar), 7.59 (m, 1H, Ar), 7.52 (m, 2H, Ar), 7.40 (m, 2H, Ar), 7.31 (m, 1H, Ar), 7.26 (m, 4H, Ar), 6.68 (d, *J*=3.6, 1H, NH), 5.14 (d, *J* = 3.6 Hz, 1H, 6-H), 4.99 (dd, J_1 = 8.0 Hz, J_2 = 10.4 Hz, 1H, 3-H), 3.50 (dd, J_1 = 8.0 Hz, J_2 = 14.8 Hz, 1H, 4-H_A), 3.30 (dd, J_1 = 10.4 Hz, J_2 = 14.8 Hz, 1H, 4-H_B). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 166.30, 137.91, 136.03, 135.61, 135.13, 134.45, 131.34, 130.64, 130.15, 129.47, 129.38,

128.64, 128.53, 90.50, 58.85, 50.22, 33.49. Ms (*m/z*): 490, 453, 349, 312, 246, 207, 181, 146, 77. $C_{23}H_{20}ClNO_5S_2$ (489.05) calculated: C 56.38, H 4.11, N 2.86; found: C 56.54, H 4.11, N 2.86.

(3*S, 6*R**)-6-phenyl-5,5-bis(phenylsulfonyl)-3-(phenylthio)piperidin-2-one 5h:** white solid. m.p = 210°C. IR ($CHCl_3$): 1672 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.20 (m, 2H, Ar), 7.77 (m, 1H, Ar), 7.64 (m, 2H, Ar), 7.57 (m, 2H, Ar), 7.49 (m, 1H, Ar), 7.38 (m, 1H, Ar), 7.27 (m, 3H, Ar), 7.21 (m, 3H, Ar), 6.99 (m, 3H, Ar), 6.61 (m, 2H, Ar), 6.23 (d, J = 3.2 Hz, 1H, NH), 5.29 (d, J = 3.2 Hz, 1H, 6-H), 4.38 (dd, J_1 = 7.2 Hz, J_2 = 12.0 Hz, 1H, 3-H), 3.29 (dd, J_1 = 7.2 Hz, J_2 = 14.4 Hz, 1H, 4-H_A), 2.78 (dd, J_1 = 12.0 Hz, J_2 = 14.4 Hz, 1H, 4-H_B) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 167.40, 137.43, 137.31, 136.09, 135.29, 135.25, 133.85, 131.58, 130.70, 130.44, 130.25, 129.33, 129.18, 129.15, 129.08, 128.46, 128.32, 90.86, 58.89, 44.44, 30.93 ppm. Ms (*m/z*): 563, 421, 369, 343, 312, 280, 246, 171, 143, 110, 95, 78.$C_{29}H_{25}NO_5S_3$ (563.09) calculated: C 61.79, H 4.47, N 2.48; found: C 61.58, H 4.48, N 2.48.

(3*S, 6*R**)-3-chloro-6-(4-fluorophenyl)-5,5-bis(phenylsulfonyl) piperidin-2-one 5i:** white solid. m.p. = 200°C. IR ($CHCl_3$): 1694 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.16 (m, 2H, Ar), 7.98 (d, J = 3.6 Hz, 1H, NH), 7.74 (m, 1H, Ar), 7.63 (m, 2H, Ar), 7.55 (m, 3H, Ar), 7.40 (m, 2H, Ar), 7.23 (m, 2H, Ar), 6.90 (m, 2H, Ar), 5.18 (d, J = 3.6 Hz, 1H, 6-H), 4.88 (dd, J_1 = 8.0 Hz, J_2 = 9.6 Hz, 1H, 3-H), 3.50 (dd, J_1 = 8.0 Hz, J_2 = 14.8 Hz, 1H, 4-H_A), 3.26 (dd, J_1 = 10.4 Hz, J_2 = 14.8 Hz, 1H, 4-H_B) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 164.10, 161.61, 137.73, 135.49, 135.40, 134.41 131.86, 131.78, 131.14, 130.97, 130.94, 130.26, 129.27, 128.42, 115.39, 115.17, 89.99, 57.54, 49.91, 32.85 ppm. Ms (*m/z*): 438 (M^+ =508), 366, 349, 330, 264, 225, 199, 164, 150,125, 97, 77. $C_{23}H_{19}ClFNO_5S_2$ (507.04) calculated: C 54.38, H 3.77, N 2.76; found: C 54.24, H 3.75, N 2.77.

Desulfonylation procedure. Preparation of the 6-phenylpiperidin-2-one 6.

Compound **5a** (0.11 g, 1 mmol) was dissolved in methanol (20 mL). KH_2PO_4 (210 mg) and sodium amalgam (Hg 0.44 g, Na 27 mg) were added and the reaction mixture was stirred at r.t for 3h. The mixture was filtered on a Celite pad and the solvent eliminated under *vacuo*. The resulting crude mixture was purified by flash chromatography on silica gel (ethyl acetate/MeOH 95:5) to afford the desired piperidin-2-one **6** in 54% yield.

IR ($CHCl_3$): 1654 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.36 (m, 2H), 7.29 (m, 3H), 5.98 (bs, 1H), 4.54 (dd, J_1 = 4.8 Hz, J_2 = 9.2 Hz, 1H), 2.45 (m, 2H), 2.10 (m, 1H), 1.91 (m, 1H), 1.80 (m, 1H), 1.68 (m, 1H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 172.39, 142.41, 128.83, 127.95, 126.04, 57.79, 32.12, 31.20, 19.63 ppm. Ms (*m/z*): 175, 174, 146, 118, 104, 77. $C_{11}H_{13}NO$ (175.10) calculated: C 75.40, H 7.48, N 7.99; found: C 75.32, H 7.44, N 7.85.

Computational methods

Due to the presence of non-bonded interactions DFT calculations were carried out using the Truhlar's hybrid functional M062X [76] together with the 6-311+G(d,p)[77] basis set within the framework of the Gaussian 09 suite of programs. [77] All the molecular structures were fully optimized using the Berny analytical gradient optimization method and the stationary points characterized by frequency calculation. The intrinsic reaction coordinate (IRC) was used to trace the path of the chemical reactions. The Thermochemical Analysis was performed at different temperatures (198.15, 298.15 and 398.15 K) starting from the frequency calculations. The electrophilicity indices were calculated at the B3LYP/6-31g* computational level to compare the values with the reported classification of electrophilicity. The global index ω is given by the expression $\omega = \mu 2/2\eta$ in terms of the electronic chemical potential μ and the chemical hardness η. The absolute electronegativity χ is the negative of the chemical potential μ, the softness S is the inverse of the hardness and the ΔNmax, $-\mu/\eta$, is the maximum amount of electronic charge that the electrophile system may accept. These quantities were approximated by using the one electron energies of the frontier molecular orbital HOMO and LUMO, εH and εL, as $\mu \sim (\varepsilon H + \varepsilon L)/2$ and $\eta \sim (\varepsilon H - \varepsilon L)/2$, respectively.

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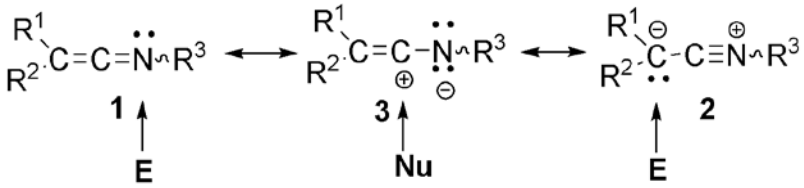
Chapter 4

N-Metallo-ketene imines (metallo= Si, Sn, Al) in the preparation of highly functionalized derivatives as possible building blocks in the preparation of nitrogen containing targets

4.1 Introduction

Ketenimines, belonging to a 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.[1,2] They can be represented by the resonance structures **1** and **2**, which emphasize the nucleophile properties of the heteroatom and the β-carbon, and by structure **3**, which accounts for the electrophilic nature of the α-carbon (Scheme 1). Ketenimines are known with *N*-substituted -alkyl, -aryl, -hydrogen, -phosphorus, -nitroso, and –boron substituent.[1] They can be easily converted to amides, imidates and amidines by reaction with amines, alcohols and water respectively. Because of their property as nucleophiles and/or electrophiles, depending from the reactant/counterpart and from the variability of the substituent groups on the ketenimines, they are widely employed in organic synthesis for the preparation of different heterocyclic compounds, as well as acyclic ones.



Scheme 1

Variously substituted ketene imines can be prepared by several different reactions: (1) substitution reactions using heterocumulenes; (2) alkylation of nitrile anions with suitable electrophilic alkylating reagents; (3) addition reaction of isocyanides; (4) dehydration of secondary amides and (5) rearrangement reactions.[1] Some of the main developments in the study of the chemical behavior of ketenimines, as well of their syntheses, have been summarized in a number of available reviews. [1,3-14]

4.1.1 N-metallo ketene imines

Among classical keteneimines, *N*-metallo keteneimines (MKIs) are a special class of ketene imines bearing as substituent at iminic nitrogen a metal such as Si,[15] Sn,[16] Cu,[17] Ir,[18] and Fe.[19] Because of the very nature of the metal linked to the nitrogen and its alkyl/aryl different groups, the reactivity of such kind of reagents is expected to be completely different on the variation of the said metal and its substituents. In an over simplification, *N*-metallo ketene imine, particularly *N*-silylketene imine, can be considered a stable

neutral form of the corresponding metallated (Li, Na, K) nitrile. Due to their relatively easy preparation and stability, trialkyl(aryl)-silyl-ketene imines are the most popular among metallo-ketene imines and are finding out increasing applications in organic synthesis. One of the most successful application, allowing the construction of a chiral quaternary stereogenic center, has been reported in a serie of elegant papers by Denmark (see below).[15,20] Our interest in such kind of intermediates rose from our previous experience in the corresponding *N*-silylimines.

4.1.2 Synthesis and Applications on N-trialkylsilyl ketene imines

Nitriles play significant roles in the different scope of pharmaceuticals.[21] The nitrile group always appears to play important effect in key bonding with pharmaceuticals: the hydrogen bonding with the blockbuster drug anastrazole[22] (**1**, Figure 1), or the covalent attachment with anti-diabetic drug vildagliptin[21,23,24] (**2**, Figure 1) are among the most significant examples. A lots of nitrile-containing pharmaceuticals, especially those bearing cyano group at the all-carbon quaternary centers, play important roles in the treatment of different diseases, such as Levocabastine[25] (**3**, Figure 1) acting as an antihistamine in the treatment of allergic conjunctivitis, Cilomilast[26] (**4**, Figure 1) for the treatment of respiratory disorders such as asthma and Chronic Obstructive Pulmonary Disease (COPD), Anastrozole[27] in the treatment of breast cancer and Verapamil[28,29] (**5**, Figure 1) an L-type calcium channel blocker using in the treatment of hypertension, angina pectoris, cardiac arrhythmia, and most recently, cluster headaches.

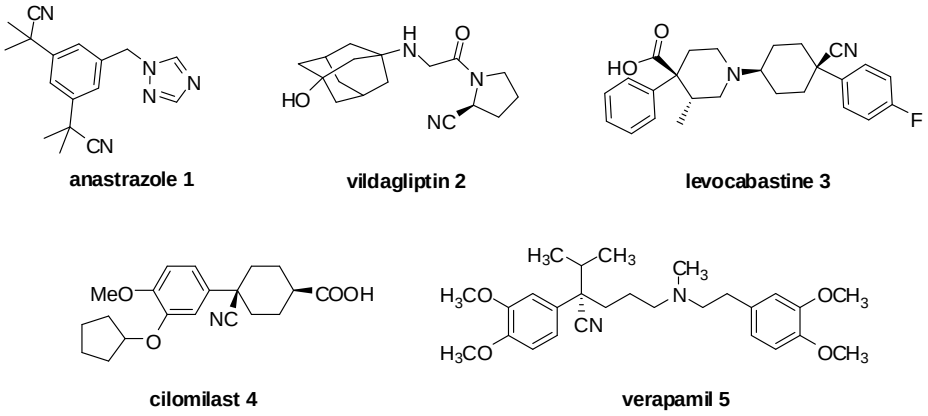


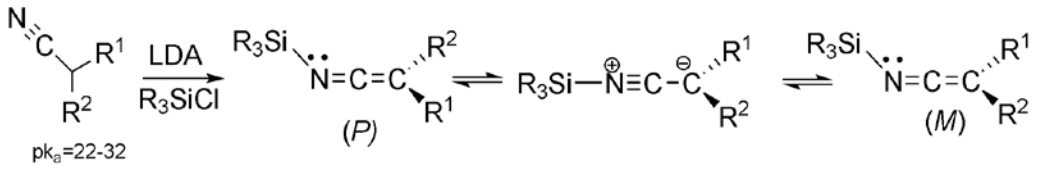
Figure 1

In the past several decades, impressive progress has been made in the field of stereoselective synthesis. However, synthesis of carbon atoms bonded to four different carbon substituents (all-carbon quaternary centers), especially those *enationmerically* enriched quaternary center, is a continuing significant challenge for the organic chemists.[30] The difficulties for the rapid and selective creation of such centers arise from the steric repulsion between the carbon substituents and the steric environments presented by the non-hydrogen substituents.[30]

Aldol-type reaction in promoting C-C bond with the control of the stereoisomery during the formation of a new stereocenter from the original sp^2 carbonyl moiety is a well established methodology and constitutes, from several years, a very powerful tool in the paraphermalia of organic synthesis directed

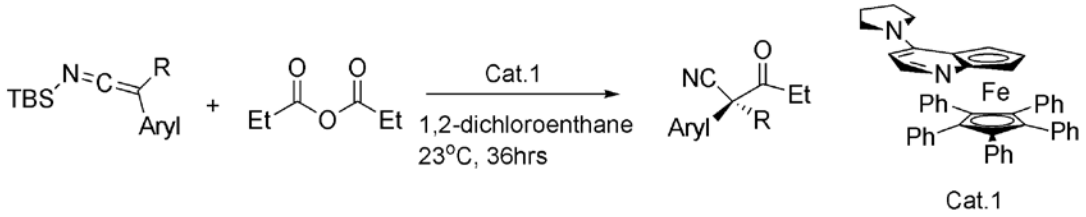
towards the formation of new C-C bond.[31] Although aldol reaction is an useful method in organic synthesis, the application of this reaction in the generation of an all-carbon quaternary stereogenic center is relatively rare because of the lack of need and inability to obtain geometrically defined α,α-disubstituted enolate or enolate equivalents.[30] In order to solve such limitations, Denmark *et al*. developed a catalysts system combining silyl ketene imines (SKIs) as nucleophile with aldehydes in a novel Lewis base catalyzed aldol reaction to obtain excellent diastereo- and enantioselectivities in the construction of quaternary stereogenic centers, beside the new formation of a new stereocenter, bearing an hydroxyl functionality, arising from the original sp^2 of the aldehyde.[32]

Silyl ketene imines (SKIs) can be easily prepared through the *N*-alkylation of metallated nitriles and a suitable silylating reagent (Scheme 2). The characteristic feature of SKIs is the pair of orthogonal substituent planes that imparts an axis of chirality when R_1 and R_2 are dissimilar, and results in the formation of a racemic mixture of *P* and *M* enantiomers (Scheme 2).[15]

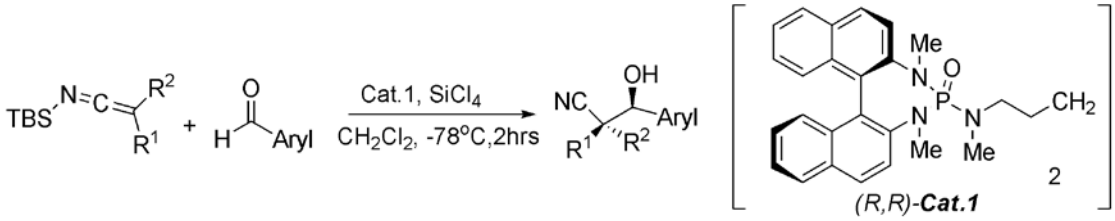


Scheme 2

Because of this unique structure, SKI has the potential to offer significant advantages in the formation of quaternary stereogenic carbon atoms. Despite SKIs were known as nucleophiles, only until recent years they were applied as nucleophiles in the catalytic, asymmetric reactions. Based on their previous researches[33,34], Fu's group applied the SKIs with different electrophiles *via* a catalytic enantioselective intermolecular acylation to construct all-carbon quaternary stereocenters with good enantioselectivity (Scheme 3).[35]

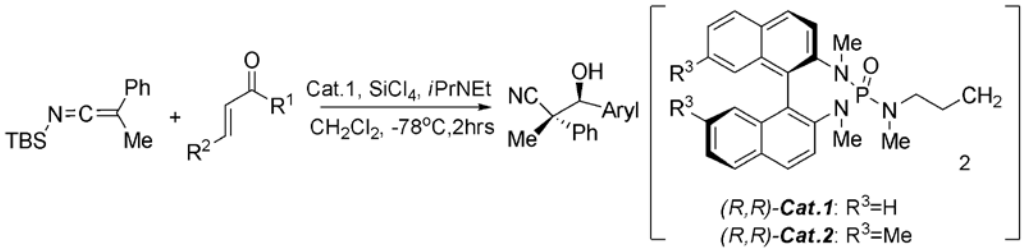


Scheme 3



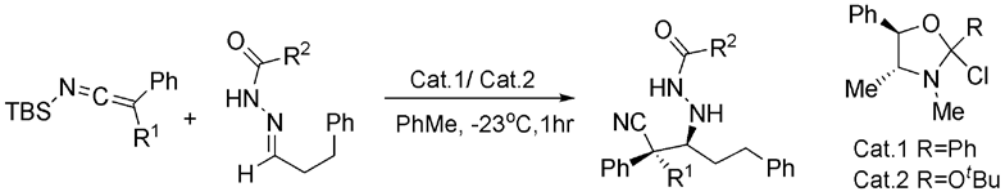
Scheme 4

Then Demark's group reported the enatioselective preparation of quaternary nitriles *via* Lewis base catalyzed additions with SKIs and aldehydes (Scheme 4).[32] Afterwards, their group reported the application of SKIs with unsaturated electrophiles under Lewis base catalyst system to afford the moderate stereoselectivities in the construction of quaternary nitriles (Scheme 5). [36]

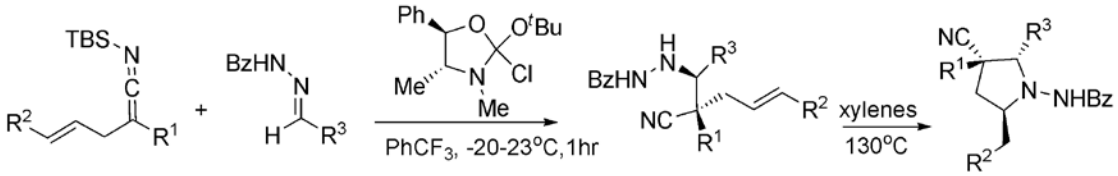


Scheme 5

Leighton and co-workers reported preparation of β-hydrazido nitriles bearing a quaternary stereogenic center by additions of SKIs to acyl hydrazones *via* Mannich reaction with good diastereo- and enantioselectivities (Scheme 6).[37] The method has been applied to the synthesis of pyrrolidines bearing quaternary nitrile (Scheme 7). [38]



Scheme 6



Scheme 7

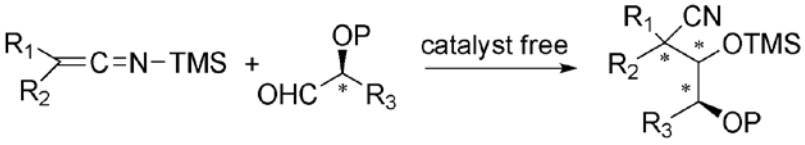
There are also some other applications with SKIs in the catalytic, enantioselective reactions with achieved good diastero- and enatioslectivities.[15,17,39-41]

Generally, two main approaches may be identified for achieving high stereocontrol in this C-C bond forming reaction: one is the use of a catalyst system.[15,42,43] All the examples mentioned above belong to this synthetic approach. Another consists in reaching this goal "*via*" the fishing the proper starting material, [30,44-48] which presents at least one stereogenic center to be used as source of high stereochemical induction. Usually in this approach the proper materials belong to the natural chiral pool and must be easy accessible and of low cost. Although SKIs have been utilized in some uncatalyzed reaction,[49-52] so far, at our acknowledge, there is no applications to the synthesis of enantiomerically pure compounds (*epc*) through the use of SKIs and optically pure starting materials (chiral SKIs or/and chiral electrophiles) in the construction of the quaternary carbon center to achieve the sterocontrol in the final product.[15]

4.2 Present work

4.2.1 ***Section A*** **:** *Reaction of silylketene imines and aldehydes: Synthesis of β-hydroxy nitriles*

Based on the background of SKIs above reported, we started our research, adopting the second strategy, by using silyl ketene imines (SKIs) with *O*-protected α-hydroxy aldehydes, which already present a chiral center in the starting material, in an uncatalyst aldol-type reaction in an effort of generating, in high yields and high stereo induction, β-hydroxy nitriles (Scheme 8). β-hydroxy nitriles are useful organic intermediate for asymmetric synthesis because of the cyano group is a functional precursor group of amino and carbonyl groups.[53] Our purpose on this project is accounting on the chiral source bearing on the starting aldehydes may introduce the stereo-induction on the formation of the new hydroxyl group or even better on the quaternary carbon center (when R_1 and R_2 are different).

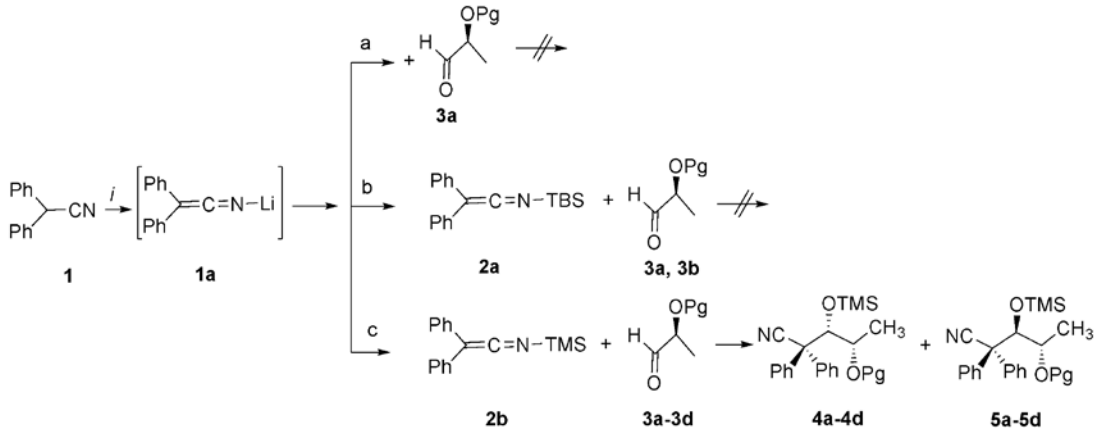


R_1: alkyl or aryl group; R_2: alkyl or aryl group
R_3: alkyl or aryl group; P: Protecting group

Scheme 8

Previous studies have documented that SKIs are easily prepared in high yields by deprotonation with LDA of disubstituted alkyl or aryl nitriles followed by trapping the resulting anion with a trialkylsilyl chloride. The choice of the alkylsilyl groups and the nature of the substituents of the starting nitrile are mandatory for the site of silylation of the lithium anion obtained. In this frame, Frainnet[54] reported that: a) the sole formation of the *N*-trimethylsilyl ketene imines achieved by using diphenylacetonitrile as starting nitrile and TMSCl as silylating agent; b) a mixture of *C*-silylated and *N*-silylated products is obtained by using 2-phenylpropane nitrile and TMSCl; c) almost exclusive *C*-silylation was obtained by using 2-phenyl-butane nitrile or 2-phenylhexane nitrile and TMSCl as silylating agent. On these bases, it has been reported that to avoid the formation of *C*-silylated derivatives, a very bulky silylating agent, like *t*-butyldimethylsilyl (TBDMS) or triisopropylsilyl (TIPS) chloride, must be used.[35,55,56] Being well aware of these drawbacks, the guideline of this study was to ascertain if, with stable diphenyl-*N*-trialkyl silylketene imines, an uncatalyzed aldol-type reaction may be achieved thanks to the possibility of a silatropism from the imine nucleophile to the aldehyde electrophile[57] *via* a Zimmerman-Traxler six-membered ring transition state.[58] Accordingly with this goal, the very first attempt we performed was to test if the metallated diphenylacetonitrile (**1a**), obtained by reaction of diphenylacetonitrile **1** with LDA, gave rise to the formation of an aldol adduct after reaction with (*S*)-2-*tert*-butyldimethylsilyloxypropanal **3a** (Scheme 9, *path a*, Table 1, entry 1). No product but starting materials were detained into the crude reaction mixture after 2 days at room temperature. The next step of our study was to try a *catalyst-free* reaction of *N*-TBDMS-ketene imine (**2a**), prepared according literature procedure, and aldehydes (**3a**). The reaction was

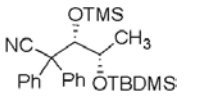
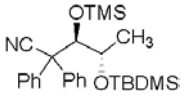
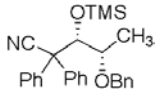
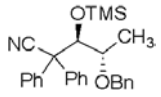
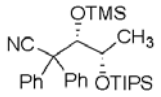
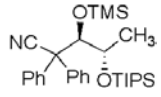
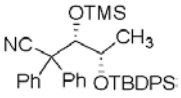
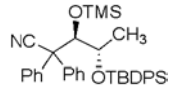
performed starting from -78 °C and leaving the temperature to reach room temperature spontaneously: After 2 days, once again, *no reaction occurred.* The substitution of the protecting group on the hydroxy-functionality of aldehyde with a less hindered one, as the benzyl group (**3b**), gave the same results (Scheme 9 *path b* and Table 1 *entries* 2 and 3). The simple substitution of TBDMS-keteneimine (**2a**) with the less hindered TMS-keteneimine (**2b**) allowed the reaction to happen (Scheme 9, *path c* and Table 1 *entry* 4).



3a: Pg=TBDMS; **3b**: Pg=Bn; **3c**: Pg=TIPS; **3d**:Pg=TBDPhS; **4a**, **5a**: Pg=TBDMS; **4b**, **5b**: Pg=Bn; **4c**, **5c**: Pg=TIPS; **4d**, **5d**: Pg=TBDPhS;

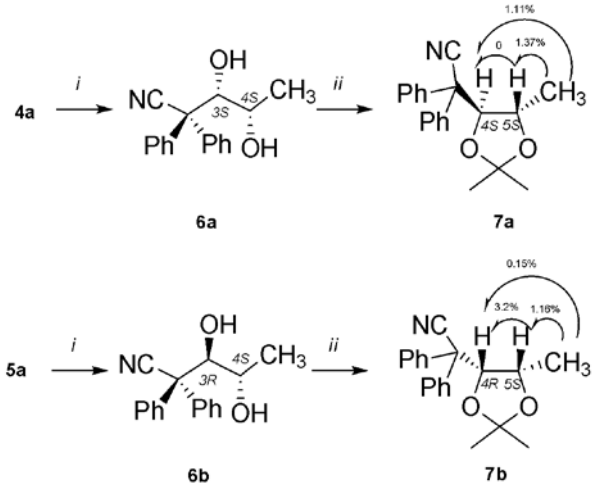
Scheme 9. Reaction of different nucleophiles with aldehydes **3**. *Reagents and Conditions*. *i*: THF, LDA, -78 °C; *a*: THF, **3a**, -78 °C to r.t, 2 days; *b*: THF, TBDMSCl, -78 °C, r.t 10 min and after add **3a** or **3b** at r.t. 2 d.; *c*: THF, TMSCl,-78°C, 10 min r.t. and after see Table 1 and experimental section.

Table 1 Reaction of aldehydes **3a-3d** with diffrent nucleophiles

Entry	nucleophile	Aldehyde	Products	dr[a,b] (4/5)	Total Yields (%)	*J* H_3-H_4**(4)** / *J* H_3-H_4**(5)**	δH_3-H_4**(4)** / δH_3-H_4**(5)**
1	**1a**	**3a**	No reaction	--	0		
2	**2a**	**3a**	No reaction	--	0		
3	**2a**	**3b**	No reaction	--	0		
4	**2b**	**3a**	 **4a**  **5a**	97:3[a] 45:55[b]	65 70	2.8 0.8	4.43-4.16 4.66-3.99
5	**2b**	**3b**	 **4b**  **5b**	100:0[a] 68:32[b]	83 75	4.4 5.2	4.52-3.68 4.60-3.07
6	**2b**	**3c**	 **4c**  **5c**	70:30[a] 5:95[b]	75 85	2.4 0.8	4.53-4.31 4.77-4.02
7	**2b**	**3d**	 **4d**  **5d**	65:35[a] 1:99[b]	62 67	1.6 0.0	4.50-4.08 4.89-3.92

a: Method A: Adding the aldehyde **3a-c** to the imine **2b** at room temperature. b: Method B: Adding the aldehyde **3a-3d** to the

imine **2b** at -78°C and after 3 hrs at this temperature, it was left to reach spontaneously r.t.



Scheme 10. Preparation of acetonides **7a** and **7b** from **4a** and **5a**. *Reagents and Conditions*: *i*: HCl (1N), ACN, 30 min, r.t.; *ii*: Pyridin-*p*-toluensulphonate (2 eq.), 2,2-dimethoxypropane, acetone, overnight, r.t.

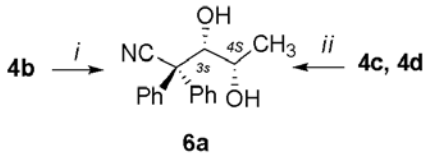


Chart 1. Preparation of diol **6a** from **4b**, **4c**, **4d** respectively. *Reagents and Conditions: i*: Pd/C, $Pd(OAc)_2$, MeOH: *ii*: HCl_{aq}(1N), CH_3CN, r.t.)

From stereochemical point of view, as far as is concerned the formation of the new chiral center, the highest sterocontrol is achieved on using (*S*)-2-(benzyloxy)propanal derivative (**3b**) at r.t.. In this case an adduct with *syn*-relationship between the benzyloxy group and the new TMS-protected hydroxyl functionality (Table 1 *entry* 5) is obtained. On the other hand, a total *anti*-selectivity (for the attribution of the stereorelationship see below) is achieved by the use of an aldehyde bearing an extremely hindered protecting group as TBDPhS (*tert*-butyldiphenylsilyl) (**3d**) and a reaction temperature of -78 °C (Table 1 *entry* 7). The stereorelationship of the two hydroxyl functionalities, due to the doubtful value of the $J\ H_3$-H_4 (Table 1), was deducted and ascertained by the elaboration of the *diastereomeric compounds* **4a** and **5a** to their acetonide derivatives **7a** and **7b** (Scheme 10) and relative NOE's study. In detail the elaboration of **4a** and **5a** to the corresponding diols **6a** and **6b** was performed by treatment with hydrogen chloride 1N in acetonitrile. The diols so obtained were converted into the acetonides **7a** and **7b** by reaction with 2,2-dimethoxypropane in the presence of pyridinium *p*-toluenesulfonate (PPTS). Taking advantage of NOE's experiments, the attribution of the relative stereochemistry of the substituents on the position 4 and 5 of the dioxolane rings **7a** and **7b** was straightforward (see Scheme 10). For compound **7a**, the NOE effects between -CH_3/C-(5)H and -CH_3/C-(4)H are almost of the same value, which is consistent with a *trans*-configuration according to the geometry analysis. Consequentially, for compound **7b**, since the NOE effect between -CH_3/C-(5)H is about ten times larger than the NOE effect between -CH_3/C-(4)H, the relative *cis*-configuration between the two substituents on the C_4 and C_5 must be attributed. Accordingly the *syn-stereoconfiguration* has been attributed to compound **4a** while the *anti-configuration* has been attributed to compound **5a**. The stereorelationship for the other *diastereomeric compounds* (**4b**, **4c** and **4d**) were

assigned by elaborating them to the corresponding diol **6a**. Compound **4b** was elaborated to the corresponding dihydroxy derivatives **6a** *via* hydrogenolysis by means of a mixture of Pd/C and $Pd(AcO)_2$[59] (chart 1) whereas the silyl protected compounds **4c** and **4d** were processed to the diols **6a** by simple hydrogen chloride/acetonitrile treatment. Consequently even the absolute configurations of the isomer **5b, 5c** and **5d** were assigned.

It has been reported that the reaction of an alkali phenyl acetonitrile does not add satisfactorily to benzophenone due to the weakly basic nature of the phenylacetonitrile carbanion.[60,61] However, magnesium and aluminum halide derivatives of phenyl acetonitrile underwent addition to benzophenone. As a matter of fact, it has been presumed that, under the latter conditions, the coordinating capacities of the metallic cations (*e.g.* magnesium or aluminum) play an important role. In our case, in a blank experiment, as we mentioned above, the adduct of the lithium anion of diphenylacetonitrile **1a** and aldehyde **3a** failed to be isolated (see Scheme 9, *path a*. Table 1 entry 1). However, the corresponding TMS-ketene imine **2b** adds spontaneously to aldehyde **3a** to form the final products **4a** and **5a** (see Table1, entry 4). In the light of these results we can presume that, in the actual case, the *N*-silyl group plays an important role in this uncatalyzed reaction because of the silylatropism, from the imine nitrogen to the carbonylic oxygen, generating a stable β-silyloxy derivative (Fig.2).

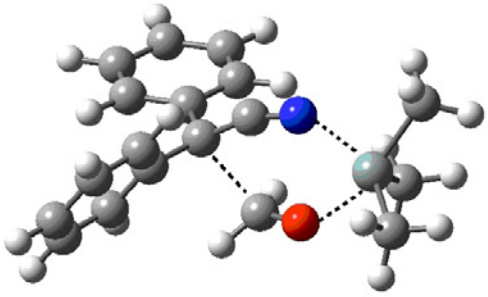
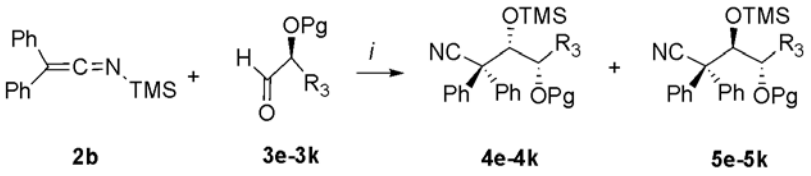


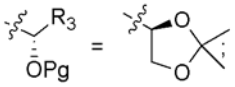
Fig 2: For the sake of simplicity in the figure has been reported the hypothesized transition state between the silylimine and formaldehyde

As above reported and based on this working hypothesis, we envision that the real driving force of this uncatalyzed reaction is represented by the transfer ability of the silyl group from the SKI to the forming hydroxyl group of the aldehyde *via* the formation of a Zimmerman-Traxler type transition state with a hypervalent silicon[57] working as alkylating agent. By this way, two important advantages are reached: to furnish the necessary energy for the reaction-taking place and to obtain a final product already protected on the hydroxyl functionality as TMS-derivative. It must be stressed out that this second advantage avoids a retro reaction which is well known to happen in the presence of a catalytic amount of base.[60] The hindered TBDMS group in the SKI **2a** lowers down the transfer ability of the silyl group resulting in a failure in the formation of the final target (see above Scheme 9, Table 1 entries 2 and 3). These observations should be considered a further robust support of our mechanistic hypothesis.

The aldol type reaction described has been applied to a range of *O*-protected α-hydroxy aldehydes. The results are reported in Scheme 11 and Table 2



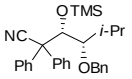
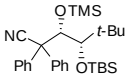
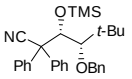
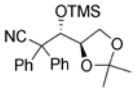
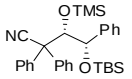
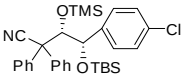
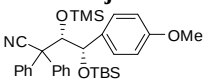
2b **3e-3k** **4e-4k** **5e-5k**

3e, **4e**: R_3= *i*-Pr; Pg= Bn; **3f**, **4f**: R_3= *t*-Bu; Pg= TBDMS; **3g**, **4g** : R_3= *t*-Bu;Pg= Bn; **3h**, **4h**, **5h**:  =

3i, **4i**: R_3= Ph; Pg= TBDMS; **3j**,**4j**: R_3=*p*-ClC_6H_4; Pg= TBDMS; **3k**, **4k**: R_3=*p*-$MeOC_6H_4$; Pg= TBDMS

Scheme 11 Reaction of aldehydes **3e-3k** with ketene imine **2b**

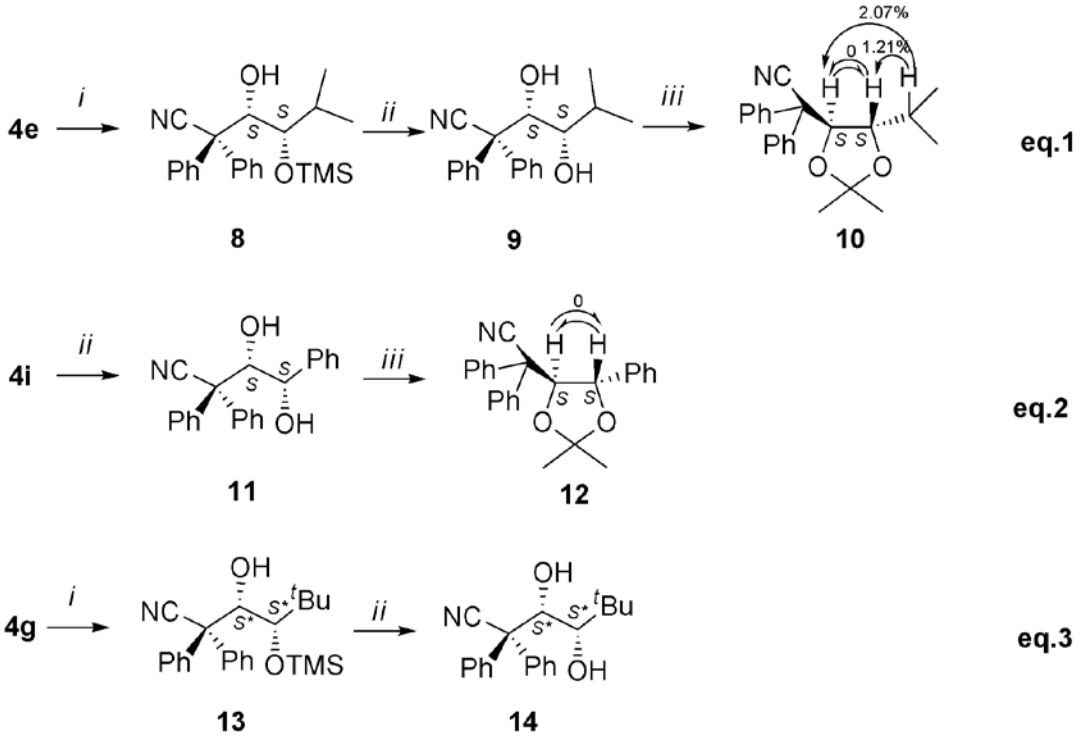
Table 2 Reaction of aldehydes **3e-3k** with keteneimine **2b**

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

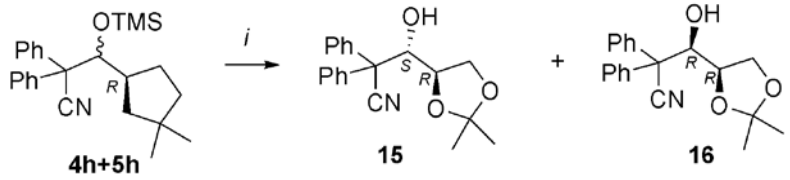
*: For the sack of simplicity, only one diastereomers were reported in the table

These results reported in the Table 2 show a satisfactory formation of the aldol-type adducts. From stereochemical point of view, the trend is similar to that previously observed, except for entry 4. Entry 2 of Table 2 warrants some comments: in this entry is reported the reaction of the aldehyde **3f** presenting two hindered groups on the aldehyde (the alkyl side chain and the TBDMS on the hydroxyl functionality). According to the already discussed intolerance of this reaction to the sterical demanding, it was not surprising that no reaction took place. In fact, the simple substitution of the TBDMS with a less sterical demanding benzyl group allowed the reaction to happen (Table 2 entry 3). The stereorelationship of the two hydroxyl functionalities of the products **4e** and **4i** have been attributed by Noe experiments after their elaboration to the corresponding acetonide **10** and **12** respectively (Scheme 12 eqs 1 and 2). The configuration of **4g** was attributed by comparison the value of the $J_{3\text{-}4}$ of the di-hydroxy derivative **14** with the corresponding *J* of the product **9** (Scheme 12 eq 3). The configurationsof **4j** and **4k** were attributed by

simply comparing the values of their $J_{3\text{-}4}$ with that of product **4i**. Finally the configurations of **4h** and **5h** were inferred by literature data of the corresponding mono-hydroxy derivatives **15** and **16**[62,63] (Scheme 13).



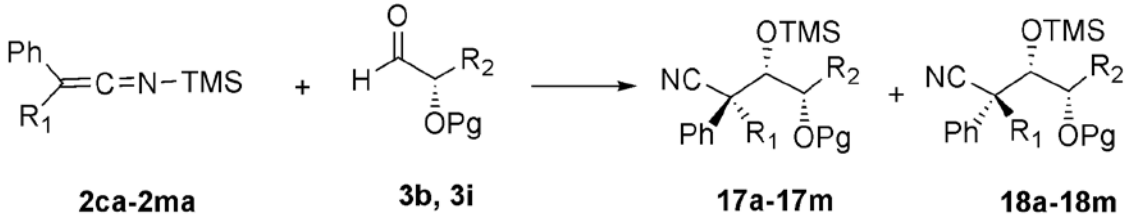
Scheme 12. Preparation of products **10, 12** and **14** from **4e**, **4i** and **4g** respectively. *Reagents and Conditions: i:* Pd/C (10%)/$Pd(OAc)_2$, MeOH, H_2; *ii*: HCl_{aq}, 1N, CH_3CN, r.t., 30 min. *iii:* PPTS, 2,2-dimethoxypropane, acetone, r.t.



Scheme 13. Preparation of products **15** and **16.** *Reagents and Conditions: i:* KF/HF(50%),CH_2Cl_2/ACN (9/1), r.t.

To further elaborate the scope of this reaction, a survey of the nitrile structure, with different aromatic substituents, was undertaken (Scheme 14 and Table 3). The addition of the corresponding *N*-trimethylsilyl ketene imines, prepared as above described, to a number of α-*O*-protected hydroxy aldehydes **3b** and **3i** was examined. Generally speaking the aldol products were isolated in satisfactory yields, electron poor and electron rich ketene imines have been used. The main drawback in this last series was the lack of the selectivity in the formation of the quaternary stereocenter bearing the cyano group whereas a total stereoselectivity in the formation of the C-3 stereocenter remains active. For the sake of simplicity only few examples in the list have been fully characterized by X-Ray analysis. Product **17c** was characterized by the relative acetonide derivative **20** (scheme 15, X-Ray strcture see figure 2). Product **18h** was characterized by the relative mono-hydroxide derivative. Product **17e**, **18g**, **18i** and **17k** were characterized as such (figure

2). For other products in the list an arbitrary attribution of the absolute configuration of the C1 stereocenter has been adopted.



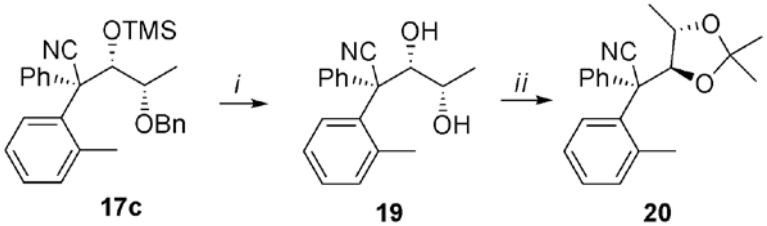
2ca-2ma **3b, 3i** **17a-17m** **18a-18m**

Scheme 14. Reaction of different aldehydes **3** with different asymmetric **SKIs 2**

Table 3. Different aldehydes **3** with asymmetric **SKIs 2**

Entry	SKI[#]	R_1	Aldehyde	Products	dr(**17/18**)	Yield(%)
1	**2ca**	4-C_6H_4	**3b**	**17a/18a**[&,$]	50/50	58
2	**2da**	3- C_6H_4	**3b**	**17b/18b**[&,$$]	52/48	65
3	**2ea**	2- C_6H_4	**3b**	**17c/18c**	70/30	54
4	**2fa**	4-BrC_6H_4	**3b**	**17d/18d**[&]	55/45	54
5	**2ga**	4- OC_6H_4	**3b**	**17e/18e**	50/50	65
6	**2ha**	4- $CF_3C_6H_4$	**3b**	**17f/18f**[&]	60/40	61
7	**2ia**	4- $NO_2C_6H_4$	**3b**	**17g/18g**	64/36	57
8	**2ja**	3-pyridine	**3b**	**17h/18h**	65/35	67
9	**2ka**	2-ClC_6H_4	**3b**	**17i/18i**	80/20	44
12	**2da**	3- C_6H_4	**3i**	**17j/18j**[&]	50/50	85
13	**2j*a***	3-Pyridine	**3i**	**17k/18k**	80/20	40

[#]: The corresponding nitriles **2c** (67%), **2d** (76%), **2e** (68%), **2f** (44%), **2g** (57%), **2h** (61%), **2i** (78%), **2j** (73%), **2k** (47%) 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 **17a**[1] and **18a**[1]. [$$]**:** Identified as the corresponding mono-hydroxide derivatives **17b**[1] and **18b**[1]



17c **19** **20**

Scheme 15. Preparation of acetonide derivative **20** from **17c**. *Reagents and Conditions: i:* Pd/C (10%), MeOH, H_2; *ii*: PPTS, 2,2-dimethoxypropane, acetone, r.t.

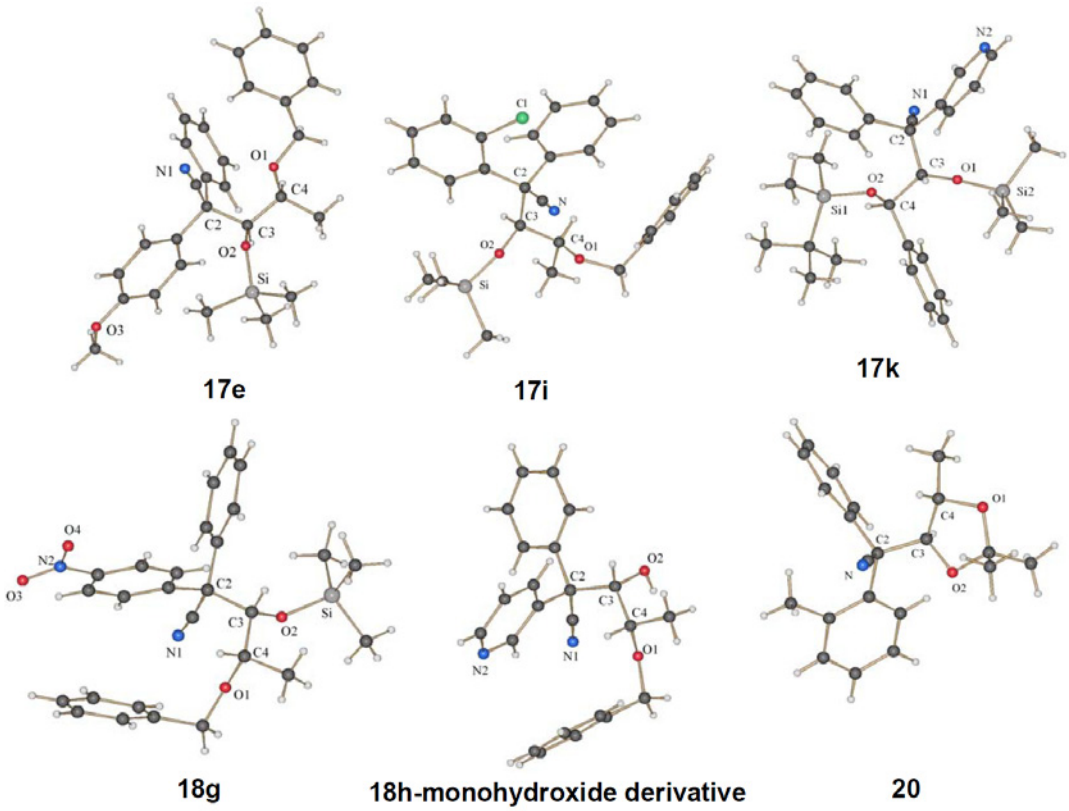


Figure 2. X-Ray structures of compounds **17e**, **17i**, **17k**, **18g**, **18h**-monohydroxide derivative and **20**

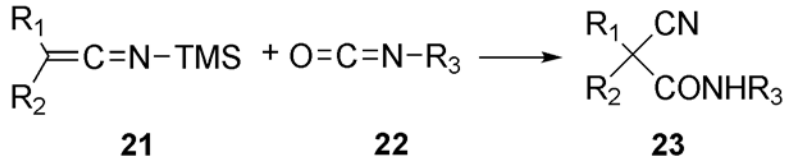
4.2.2 ***Section B****: Reaction of silylketene imines and isocyanates: Synthesis of α-cyano-β-carboxyamides (malonamides)*

Despite silylketene imines are known from a long time,[64] very few reports have appeared in literature describing their use as nucleophile.[65,66] Frainnet reported the addition of SKIs to acyl chlorides, aldehydes and ketones.[49] Würthwein[50] reported the acylation reactions of *N*-trimethylsilyl ketene imines with different acyl halides in the synthesis of *N*-acylketene imines and/or α-cyano ketones, depending from the reaction conditions. Fu et al. have described the enantioselective acylation of SKIs, catalyzed by a chiral 4-(pyrrolidino)pyridine derivative.[35] Chiral silicon Lewis acid mediated asymmetric Mannich reaction of SKIs with acyl hydrazone have been described by Leighton.[67,68] More recently list reported a catalytic asymmetric protonation of SKIs by a chiral phosphoric acid.[69]

In collaboration with other PhD students of the same research group during the period of my PhD thesis, I have participated in a project having as main goal the synthesis of malonimides, with a quaternary stereocenter, from the corresponding malonamide. In the light of our experiences on SKIs, we felt that these reagents may generate malonic amide derivatives by reaction with SKIs. In this section are reported the highlights of the results obtained.[70]

There are only few applications between isocaynate as a electrophlies and ketenimines[71] and no literature has been published by using SKIs and isocyanates in an uncatalyzed reaction.[15] The reaction with these two reactants should generate malonic amide derivatives bearing a quaternary center (when R_1 and R_2

are different) (Scheme 16). 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.[53,72]



Scheme 16

Silyl ketene imines **21** are easily generated by the reaction of a nitrile with a silylating agent,[65,66] in the presence of a base such as lithium diisopropyl amide (LDA) or n-butyllithium. Following removal of diisopropyl amine under vacuum (if necessary), the reaction mixture was treated with isocyanate **22** in toluene to produce the target nitrile malonic amides **23** in reasonable to good yields. (Scheme 16, table 4)

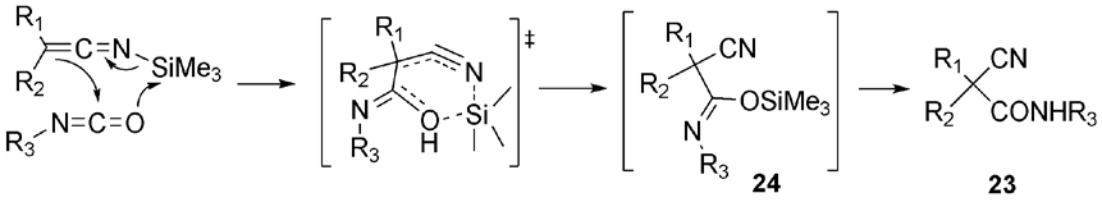
Table 4. Reaction of ketene imine **21** and isocyanate **22**

Entry	Ketene imines [a]		R_3 [b]	Method	Product	Yield[c](%)
	R_1	R_2				
1	(**21a**)Ph	Ph	(**22a**)4-OC_6H_4	A	**23a**	35
2	(**21a**)Ph	Ph	(**22a**) 4-OC_6H_4	B	**23a**	65
3	(**21a**)Ph	Ph	(**22a**)4-OC_6H_4	C	**23a**	71
4	(**21a**)Ph	Ph	(**22a**)4-OC_6H_4	D	**23a**	0
5	(**21b**)4-BrC_6H_4	Ph	(**22a**)4-OC_6H_4	C	**23b**	65
6	(**21c**)3-C_6H_4	Ph	(**22a**)4-OC_6H_4	C	**23c**	58
7	(**21d**)2-C_6H_4	Ph	(**22a**)4-OC_6H_4	C	**23d**	64
8	(**21e**)4-C_6H_4	Ph	(**22a**)4-OC_6H_4	C	**23e**	75
9	(**21f**)4-OC_6H_4	Ph	(**22a**)4-OC_6H_4	B	**23f**	70
10	(**21g**)2-ClC_6H_4	Ph	(**22a**)4-OC_6H_4	B	**23g**	68
11	(**21h**)Pyridine-3-yl	Ph	(**22a**)4-OC_6H_4	B	**23h**	80
12	(**21a**)Ph	Ph	(**22b**)Ph	C	**23i**	73
13	(**21a**)Ph	Ph	(**22c**)Bn	B	**23j**	50
14	(**21a**)Ph	Ph	(**22d**)1-phenylethyl	B	**23k**	78
15	(**21f**)4-OC_6H_4	Ph	(**22c**)Bn	B	**23l**	40
16	(**21h**)Pyridine-3-yl	Ph	(**22e**)2-C_6H_4	B	**23m**	53
17	(**21i**)4-OC_6H_4	4-OC_6H_4	(**22a**)4-OC_6H_4	B	**23n**	61

[a]: The corresing nitriles of **21b** (44%), **21c** (76%), **21d** (68%), **21e** (67%), **21f** (57%), **21g**, (47%), **21h** (73%) and **21i** (46%) were prepared from the corresponding ketonesusing tosylmethyl isocyanide (TosMIC).[73] [b]: Method A: *n*-BuLi, isocyanate, THF, toluene. Method B: *n*-BuLi, TMSCl, isocyanate, THF, toluene. Method C: LDA, TMSCl, isocyanate, toluene. Method D: LDA, TBDMSCl, isocyanate, toluene. [c]: Yields of isolated pure products.

The reactions of nitrile anions generated using *n*-butyllithiumin tetrahydrofuran, in the absence of trimethylsilyl chloride, resulted in formation of the target compounds, but in lower yields, accompanied by the formation of significant quantities of side products (Table 4, entry 1, Method A). Addition of trimethylsilyl chloride to the nitrile anion (Table 4, entry 2, Method B), prior to treatment with the electrophile, led to an increased yield of the target product. This indicates that 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 was expected to give the corresponding *N-tert*-butyldimethylsilyl ketene imine (Table 4, entry 4, Method D). However, the reactivity of the resultant ketene imine was decreased significantly, probably due to the very bulky nature of the *tert*-

butyldimethylsilyl group; this would render the silatropism step, which is thought to be the driving force of the whole process (*vide infra*), difficult. From these results, it was apparent 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* silatropism, probably by way of the pathway depicted in Scheme 17. As the key step, the isocyanate oxygen desilylates the ketene imine moiety to generate an incipient nitrile anion. The resulting intermediate **24** affords, after aqueous work-up, the target product **23**.[74] Whether this proposed step is concerted or not is hard to predict at this stage. Density functional theory (DFT) calculations in order to clarify the mechanistic aspects are in progress and the results will be reported in due course. A wide range of both aromatic nitriles (Table 4, entries 5–11 and 17) and isocyanates (Table 4, entries 11–14 and 16) have been employed in this reaction.

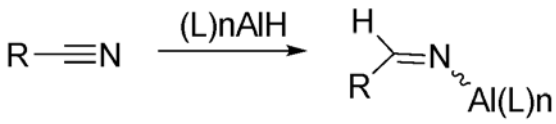


Scheme 17

4.2.3 ***Section C****: Synthesis of other N-metallo ketene imine: Synthesis of γ-hydroxy nitriles from Al-ketene imines and epoxides.*

As anticipated in the introduction of this chapter there are different ketene-imines characterized from a direct linkage between the iminic nitrogen and a metallo[75]: Sn,[76] Cu,[77] Fe,[78] to don't report keteneimine complexes with metal arising from a carbene complexes and isocyanades. Since organometallic complexes are outside the scope of this Thesis they will not be treated. On the metallo ketene imines above reported, few of them have found applications in organic chemistry: We can already anticipated that in the frame of our general program on the synthesis and use of metallo ketene imines we have started a project on tin ketene imines: since the relative results will be the core of the W.L. Qin' thesis, a PhD student of the same research group, no mention will be made on this metallo ketene imine in this Thesis. As far as is concerned in this Thesis, in the following section I will report our very preliminary studies on another class of metallo-ketene imines, at our acknowledge never reported in the literature: *N*-aluminium ketene imines.

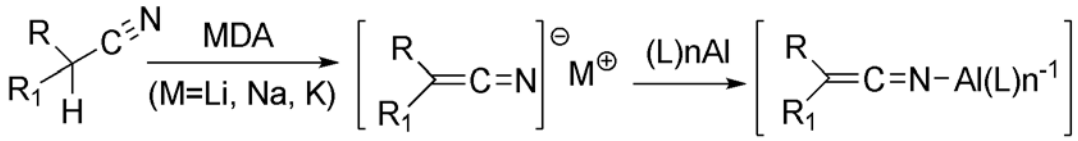
The corresponding aluminium imines are stable intermediates, easily obtainable via reduction of alkyl or aryl nitrile by aluminium hydride (Scheme 18). [79-82]



Scheme 18

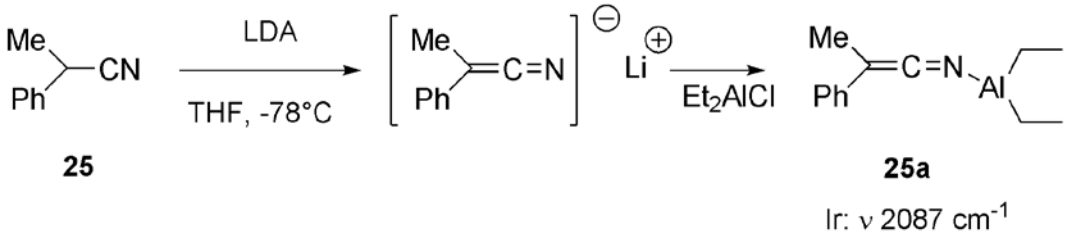
Based on these informations and our own experiences on the aluminium-imines we felt that the corresponding ketene imines could be stable intermediates and could be prepared from the corresponding

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 is done for the preparation of silyl ketene imines (Scheme 19).[64,65]



Scheme 19

Following the above reported working plane, we started, at the very beginning, with the preparation of suitable aluminium imines from commercially available nitrile and dialkyl aluminium halides. Accordingly, the 2-phenyl-propane nitrile **25** was treated with LDA (Lithium diisopropyl amide) to give the corresponding nitrile anion[83-85] 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 20). No further studies were performed, at this very preliminary stage, for fully identify the aluminium ketene imine on the basis of its stability, ^{1}H NMR, Mass, ^{13}C NMR, since, in the light of the scope of our project, we preferred to test its reactivity by a reaction with a suitable electrophiles.

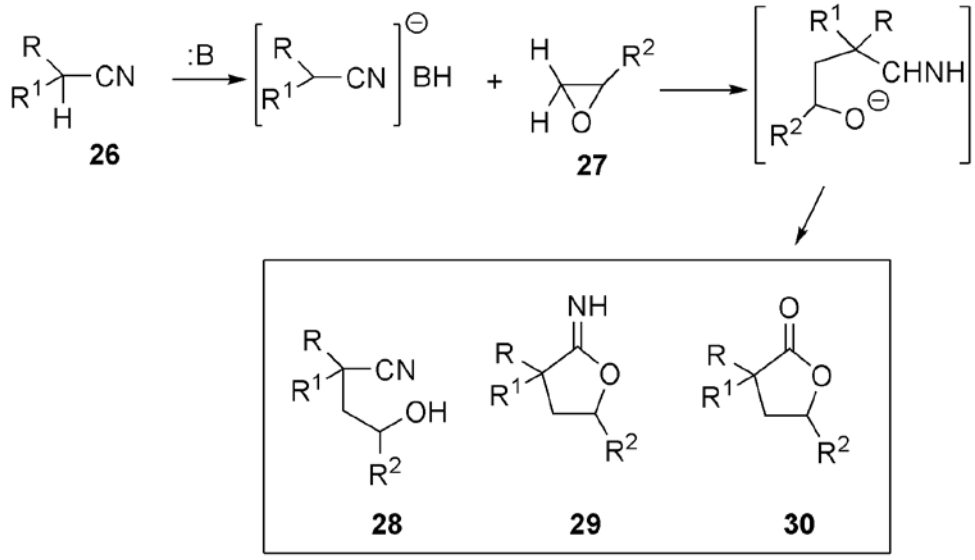


Scheme 20

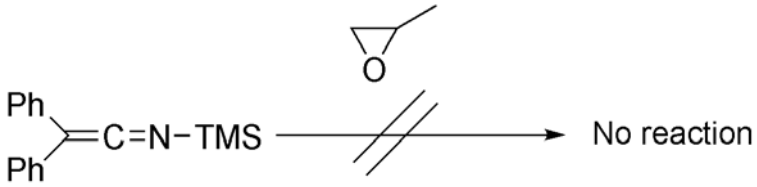
Among different classes of electrophiles available for this purpose one of the most interesting and easily available from market or in house preparation is that of epoxides.[86] The fact that recent methodologies by Sharpless or Jacobsen[87-89] allow the preparation of *epc* (enantiomerically pure compounds) derivatives, renders this class of electrophiles very interesting. As a matter of fact their reactions with C-nucleophiles open the stream to an almost numberless differently functionalized derivative. 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*-halidrines. The regiochemistry of the reaction depends from the sterical 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 studies we chose to use terminal epoxides since, for steric reasons, only one regioisomer is usually obtained.

The reaction of alkali metal nitriles and terminal epoxides, has been already reported and results in a mixture of cyclic and acyclic products (Scheme 21). Product **28** arise from a classical opening reaction whilst products **29** and **30** arise from a, difficult to avoid (in the basic reaction conditions present), subsequent cyclization to imino ester **29** and/or lactone **30**, derived in turn, from the imino hydrolysis.[90] The factors influencing the reaction and the possible solution have been discussed and reported in

literature[91-94]. On the other hand reaction of epoxide with trimethylsilylacetonitrile anion has been reported as well.[95] Well aware of these informations our first concern was to try the opening-reaction of epoxides by a "*neutral*" *N*-trimethylsilyl ketene imines (Scheme 22).



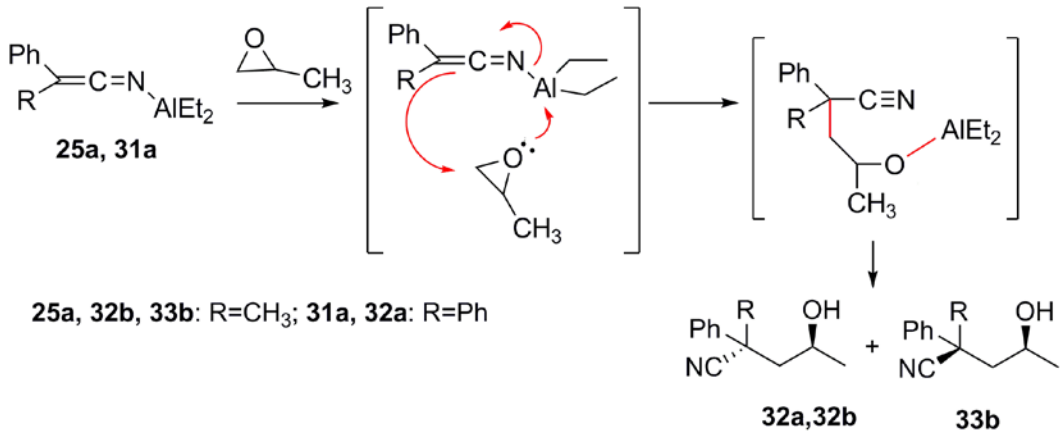
Scheme 21.



Scheme 22

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: We anticipated that aluminium ketene imines must be more reactive than the corresponding silyl ketene imines due to the enhanced oxophile character of aluminum in comparison with silyl. It was extremely gratifying to find out that the reaction between aluminium ketene imine **31a** and 2-methyloxirane was successful according the mechanism reported in scheme 23 (table 5, entry 1). It must be stressed out that no cyclization product of any nature was found in the reaction mixture. Since we found out this reaction taking place at this condition, we decided to employ another aluminium ketene imine **25a**, preparing from asymmetric α-methyl acetonitrile, with 2-methyloxirane in the same reaction, from which should generated a quaternary carbon center in the final target. The result is show in table 5, entry 2. As we can see, there are satisfactory formation of final adducts, but no diastereo-selectivity. In order to check if there is any affection in the yield and the diastereo-selectivity by the solvent, taking place of THF, toluene was adopted for the reaction (table 5, entry 3). It is showed that there was a slight improvement on the diastereo-selectivity. But we found there were more side products appeared in the reaction by using toluene comparing with the reaction in THF. Then an effort to attempt to increase the diastereo-slectivity with Al-salen catalyst was experienced (table 5, entry 4). The result showed that there was no significant

improvement on the diastereo-selectivity with this catalyst. With all these preliminary results obtained, we consider Method A as a suitable condition for the next studies without further optimization at this stage.



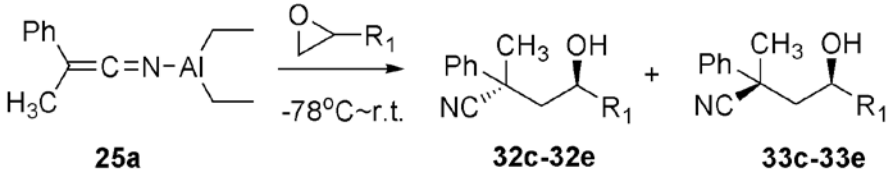
Scheme 23

Table 5. Reactions between different nucleophiles and epoxide

Entry	Nucleophile	Product[a]	dr **32/33**	Solvent	Method	Yield(%)
1	**31a**	**32a**	-	THF	A	58
2	**25a**	**32b** **33b**	50:50	THF	A	60
3	**25a**	**32b**	**33b** 40/60	Toluene	B	40
4	**25a**	**32b**	**33b** 40/60	Toluene	C	50

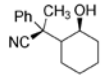
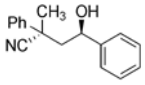
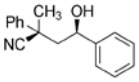
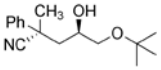
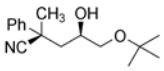
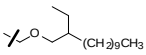
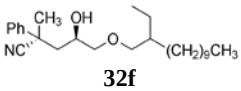
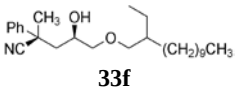
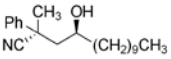
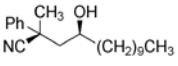
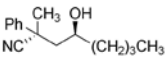
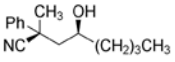
[a]: for the sack of simplicity, only two diastereomers were reported in the table

The results obtained using different epoxides with aluminium ketene imine **25a** are reported (scheme 24, table 6). From table 6, it is evident that the best aluminium ketene imine is that derived from the reaction of lithium ketene imine and diethylaluminum chloride. At this stage it is clear from the results obtained that, whereas the formation of cyclized product has been avoided thanks' to the use of "neutral" nucleophiles as musty be considered aluminium ketene imines, some other important drawbacks must be taken into account: the scarce control in the diastereoselectivity of the reaction and the relatively (if one consider the three step one pot reaction) low yields. Work is under way to solve these problems and to apply this relatively new reaction to *epc* compounds.



Scheme 24

Table 5 reaction of ketene imine **25a** with different epoxides

Entry	R_1	Products[a]		Dr **32**:**33**	Yield (%)
1		 **32c**	 **33c**	50:50	33
2		 **32d**	 **33d**	25:75	49
3		 **32e**	 **33e**	50:50	42
4		 **32f**	 **33f**	50:50	50
5		 **32g**	 **33g**	50:50	50
6		 **32h**	 **33h**	50:50	31

[a]: for the sack of simplicity, only two diastereomers were reported in the table

4.3 Experimental section

All starting materials, unless otherwise stated, were purchased and used without any further purification. Solvents were distilled and dried according to standard procedures. 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. NMR spectroscopy was performed on Varian-Mercury 400 and Varian-Mercury 200 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. Elemental analyses were obtained using a Flash 2000, series CHNS/O Analyzer (Thermo Scientific).

4.3.1 Experimental data for the preparation of β-hydroxy nitriles (Section A.)

(*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.[96,97] (*R*)-1-(2,2-dimethyl-1,3-dioxolan-4-yl)ethanone (**3h**) was prepared according to the reported procedure.[98] 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[97] except benzyl bromide was used insted of benzyl chloride in the preparation of aldehyde **3g**. 2-phenyl-2-*p*-tolylacetonitrile (**2c**), 2-phenyl-2-*m*-tolylacetonitrile (**2d**), 2-phenyl-2-*o*-tolylacetonitrile (**2e**), 2-(3-bromophenyl)-2-phenylacetonitrile (**2f**), 2-(3-methoxyphenyl)-2-phenylacetonitrile (**2g**), 2-phenyl-2-(3-(trifluoromethyl)phenyl)acetonitrile (**2h**), 2-(3-nitrophenyl)-2-phenylacetonitrile (**2i**), 2-phenyl-2-(pyridin-3-yl)acetonitrile (**2j**), 2-(3-chlorophenyl)-2-phenylacetonitrile (**2k**) were prepared from the corresponding ketones by TosMic methodology.[70,73] The diastereomeric ratios reported into Tables 1, 2 and 3 have been calculated by HPLC (Agilent, Poroshell 120. SB-C18. 2.7□ m, 3.0 x 100 mm) and ^{1}H NMR on the crude reaction mixture taking into account the doubtless peaks of each diatereomer. X-Ray was performed on SMART Apex Ⅱ X-Ray diffractomer.

Preparation of *N*-(2,2-diphenylvinylidene)-1,1,1-trimethylsilanamine 2b.

Trimethylsilyl ketene imine **2b** was prepared according literature procedure.[54,99] In detail BuLi (1.23 mmol, 0.49 mL of 2.5M in n-hexane) was added to a THF solution (3 mL) of diisopropyl ethyl amine (1.35 mmol, 0.19 mL) at -78^{o}C under nitrogen atmosphere. Diphenylacetonitrile (238 mg, 1.23 mmol), dissolved in 1 mL of THF, was dropped into the base solution at -78^{o}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 **2b** was characterized by its IR, ^{1}H and ^{13}C NMR spectra.

IR (film): 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.

Preparation of (*3S, 4S*)/(*3R, 4S*)-4-(*tert*-butyldimethylsilyloxy)-2,2-diphenyl-3-(trimethylsilyloxy)pentanenitriles 4a/5a from 2b.

Method A:

To the keteneimine **2b**, a solution of (*S*)-2-(*tert*-butyldimethylsilyloxy)propanal **3a** (231mg, 1.23mmol) 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 **4a** and **5a (4a**: 285 mg, **5a**: 9 mg, ratio: **4a**/**5a**=97/3, overall yields 65%).

Method B:

To the keteneimine **2b**, a solution of (*S*)-2-(*tert*-butyldimethylsilyloxy)propanal **3a** (231mg, 1.23mmol) 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 **4a** and **5a (4a**: 175mg, **5a**: 215 mg, ratio: **4a**/**5a**=45/55, overall yields 70%).

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

White solid. mp: 106-107 °C. $[\alpha]_D^{20}$: -16.80 (*c*: 1.0g/100 mg, $CHCl_3$). IR (film): 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 5a** as follows:

Colourless oil**.** $[\alpha]_D^{20}$: +8.72(*c*: 1.0g/100 mg, $CHCl_3$). IR (film): 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;

Preparation of (*3S, 4S*)/(*3R, 4S*)-4-(benzyloxy)-2,2-diphenyl-3-(trimethylsilyloxy)pentanenitriles 4b and 5b

Following ***Method A*** starting from diphenylacetonitrile (193 mg, 1.0 mmol) and (*S*)-2-(Benzyloxy)propanal **3b** (164 mg, 1.0 mmol), product **4b** (356mg, 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 **3b** (164 mg, 1.0 mmol), **4b** and **5b** were obtained as the crude reaction mixture. This mixture was purified by flash chromatography (cyclohexane: ether= 7:1). From this step **4b** was isolated as siloxyl derivative (219mg, yield: 51%), whereas **5b** was isolated as the corresponding mono-hydroxide derivative **5b^1** (86mg, yield: 24%, ratio: **4b**/**5b^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 4b** as follow:

White solid, mp: 93-94 °C. $[\alpha]_D^{20}$: +10.36 (*c*: 1.1g/100 mg, $CHCl_3$). IR (film): 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 5b**[1]

Colourless liquid. $[\alpha]_D^{20}$: +131.1 (*c*:10 g/100 mg, $CHCl_3$). IR (film): 2238 cm^{-1}. ^{1}HNMR (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}CNMR (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.

Preparation of (*3S, 4S*)/(*3R, 4S*)-2,2-diphenyl-4-(triisopropylsilyloxy)-3-(trimethylsilyloxy)pentanenitriles 4c/5c.

Method A: BuLi (1.1 mmol, 0.44mL of 2.5M in n-hexane) was added into a solution of diisopropyl ethyl amine (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 **3c** (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 **4c** and **5c** (**4c**: 381, **5c**: 163g, total yield: 75%, ratio: **4c**/**5c**=70/30)

Method B: Following this method a 5/95 ratio **4c/5c** in 85% overall yields were obtained.

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

White solid; mp: 67-73 ^{o}C. $[\alpha]_D^{20}$: -12.0 (*c*: 1.0g/100 mg, $CHCl_3$).IR (film): 2239 cm^{-1}. ^{1}H 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 5c.**

Colourless oil**.** $[\alpha]_D^{20}$: -7.4 (c: 1.0g/100 mg, $CHCl_3$). IR (film): 2238 cm^{-1}. ^{1}H 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.

Preparation of (*3S, 4S*)/(*3R, 4S*)-4-(*tert*-butyldiphenylsilyloxy)-2,2-diphenyl-3-(trimethylsilyloxy)pentanenitrile 4d/5d.

Method A: Following Method A, starting from diphenylacetonitrile (386 mg, 2.0 mmol) and (*S*)-2-(*tert*-butyldiphenylsilyloxy)propanal **3d** (624 mg, 2.0 mmol), products **4d** and **5d** were obtained by the flash chromatography (petroleum ether :ether = 20:1) (**4d**: 750 mg, **5d**: 404 mg, total yield: 62%, ratio: **4d**/**5d**=65/35).

Method B: Following this method a 1/99 ratio **4d/5d** in 67% overall yields were obtained.

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

White solid. mp:112-116^oC. $[\alpha]_D^{20}$: -7.10 (*c*: 1.0g/100 mg, $CHCl_3$). IR (film): 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 5d** as follow:

White solid. mp:142-145^oC. $[\alpha]_D^{20}$: -2.80 (*c*: 1.0g/100 mg, $CHCl_3$). IR (film): 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.

Preparation of (*3S, 4S*)-3,4-dihydroxy-2,2-diphenyl pentanenitrile 6a;

1ml of 1M HCl was added into a solution of (*3S, 4S*)-4-(*tert*-butyldimethylsilyloxy)-2,2-diphenyl-3-(trimethylsilyloxy)pentanenitrile **4a** (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 **6a** as colourless oil (110 mg, yield: 95%)

Colorless oil. $[\alpha]_D^{20}$: +78.45(*c*: 1.1g/100 mg, $CHCl_3$). IR (film): 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.

Preparation of (*3R, 4S*)-3,4-dihydroxy-2,2-diphenylpentanenitrile 6b

Starting from *(3R,4S*)-4-(*tert*-butyldimethylsilyloxy)-2,2-diphenyl-3-(trimethylsilyloxy) pentanenitrile **5a** (30 mg, 0.07 mmol), following the same procedure for preparing compound **6a**, compound **6b** was obtained (16 mg, yield:89 %).

Colorless oil. $[\alpha]_D^{20}$: -69.60 (*c*: 1.0g/100 mg, $CHCl_3$). IR (film): 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.

Preparation of 2,2-diphenyl-2-[(*4S,5S*)-2,2,5-trimethyl-1,3-dioxolan-4-yl]acetonitrile 7a

(*3S, 4S*)-3,4-dihydroxy-2,2-diphenylpentanenitrile **6a** (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 **7a** (86 mg, yield: 63 %).

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

Preparation of 2,2-diphenyl-2-[(*4R, 5S*)-2,2,5-trimethyl-1,3-dioxolan-4-yl]acetonitrile 7b

(*3R, 4S*)-3,4-dihydroxy-2,2-diphenyl pentanenitrile **6b** (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 **7a**. The crude product was purified by flash chromatography (cyclohexane : ether = 4:1) to get product **7b** (35 mg, yield: 74 %).

White solid. mp: 107-110^{o}C. $[\alpha]_D^{20}$: +99.4 (*c*: 1.0g/100 mg, $CHCl_3$). IR (KBr): 2247cm^{-1}. ^{1}H 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

Preparation of (*3S, 4S*)-4-hydroxy-2,2-diphenyl-3-(trimethylsilyloxy)pentanenitrile 6a from 4b.

(*3S, 4S*)-4-(benzyloxy)-2,2-diphenyl-3-(trimethylsilyloxy)pentanenitrile **4b** (90 mg), Pd/C 10% (90 mg) and $Pd(AcO)_2$ (40 mg) were mixted 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 **6a** obtained as previously described (see above).

Preparation of (*3S, 4S*)-4-hydroxy-2,2-diphenyl-3-(trimethylsilyloxy)pentanenitrile 6a from 4c and 4d

1ml of 1M HCl was added into a solution of **4c** (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 **6a** as colourless oil (101mg, yield: 87%). Starting from **4d** (230 mg, 0.4 mmol) following the same procedure above described compound **6a** was obtained (95 mg, 82%).

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

Following ***Method A***, starting from diphenylacetonitrile (193 mg, 1.0 mmol) and (*S*)-2-(benzyloxy)-3-methylbutanal **3e** (211 mg, 1.1 mmol), (*3S, 4S*)-4-(benzyloxy)-5-methyl-2,2-diphenyl-3-(trimethylsilyloxy)hexanenitrile **4e** 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 4e** as follow:

White solid; mp: 86-93 ^{o}C. $[\alpha]_D^{20}$: +3.80(*c*: 1.0g/100 mg, $CHCl_3$). IR (film): 2240 cm^{-1}. ^{1}H 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

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

Following ***Method A***, starting from diphenylacetonitrile (290 mg, 1.5mmol) and 2-(benzyloxy)-3,3-dimethylbutanal **3g** (309 mg, 1.5 mmol), (*3S**, *4S**)-4-(benzyloxy)-5,5-dimethyl-2,2-diphenyl-3-(trimethylsilyloxy)hexanenitrile **4g** 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 4g** as follow:

Colourless oil**.** IR (film): 2238 cm^{-1}. ^{1}H 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

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 5h.

Following ***Method A***, starting from diphenylacetonitrile (290 mg, 1.5 mmol) and (*R*)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde **3h** (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 **4h** and (*S*)-3-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-diphenyl-3-(trimethylsilyloxy)propanenitrile **5h** was obtained after flash chromatography (petroleum ether : ether = 5:1) (480 mg in a ratio, determined by ^{1}H NMR, **4h/5h** of 9:1). Crystallization (CH_3CN/MeOH/H_2O) allowed to give pure **4h** and **5h.**

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

White solid. mp: 110-114 °C. $[\alpha]_D^{20}$: -67.1 (*c*: 1.0g/100 mg, $CHCl_3$). IR (film): 2246 cm^{-1}. ^1H 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 5h** as follow:

White solid. mp: 100-106 °C. $[\alpha]_D^{20}$: -21.4 (*c*: 1.0g/100 mg, $CHCl_3$). IR (film): 2241 cm^{-1}. ^1H 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.

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

Following ***Method A***, starting from diphenylacetonitrile (193 mg, 1.0 mmol) and (*S*)-2-(tert-butyldimethylsilyloxy)-2-phenylacetaldehyde **3i** (250 mg, 1.0 mmol), (*3S, 4S*)-4-(tert-butyldimethylsilyloxy)-2,2,4-triphenyl-3-(trimethylsilyloxy)butanenitrile **4i** 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 4i** as follow:

White solid; mp: 135-137 ^oC. $[\alpha]_D^{20}$: -4.45 (*c*: 1.1g/100 mg, $CHCl_3$). IR (film): 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

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

Following ***Method A***, starting from diphenylacetonitrile (232 mg, 1.2 mmol) and 2-((*tert*-butyldimethylsilyl)oxy)-2-(4-chlorophenyl)acetaldehyde **3j** (341 mg, 1.2 mmol), (*3S*,4S**)-4-(*tert*-butyldimethylsilyloxy)-4-(4-chlorophenyl)-2,2-diphenyl-3-(trimethylsilyloxy)butanenitrile **4j** 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 4j** as follow:

White solid. mp:156-163 ^{o}C. IR (film): 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.

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

Following ***Method A***, starting from diphenylacetonitrile (193mg, 1.0 mmol) and 2-((*tert*-butyldimethylsilyl)oxy)-2-(4-methoxyphenyl)acetaldehyde **3k** (280mg, 1.0mmol), (*3S*,4S**)-4-(tert-butyldimethylsilyloxy)-4-(4-methoxyphenyl)-2,2-diphenyl-3-(trimethylsilyloxy)butanenitrile **4k** 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 4k** as follow:

White solid; mp: 118-123 ^{o}C. IR (film): 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.

Preparation of (*3S, 4S*)-3-hydroxy-5-methyl-2,2-diphenyl-4-(trimethylsilyloxy)hexanenitrile 8

(*3S, 4S*)-4-(benzyloxy)-5-methyl-2,2-diphenyl-3-(trimethylsilyloxy)hexanenitrile **4e** (130 mg), Pd/C 10% (130 mg) and $Pd(OAc)_2$(75mg) 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 **8** (65mg, yield: 63%.)

Colourless oil. $[\alpha]_D^{20}$: +68.2(*c*: 1.0g/100 mg, $CHCl_3$). IR (film): 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,

Preparation of (*3S, 4S*)-3,4-dihydroxy-5-methyl-2,2-diphenylhexanenitrile 9

Following the same procedure for preparing compound **6a**, starting from (*3S, 4S*)-3-hydroxy-5-methyl-2,2-diphenyl-4-(trimethylsilyloxy)hexanenitrile **8** (45mg, mmol), (*3S,4S*)-3,4-dihydroxy-5-methyl-2,2-diphenylhexanenitrile **9** was obtained as colourless oil (28 mg, yield: 72%).

$[\alpha]_D^{20}$: +78.3 (*c*: 1.0g/100 mg, $CHCl_3$). IR(film): 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

Preparation of 2-((*4S, 5S*)-5-isopropyl-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-diphenylacetonitrile 10

Following the same procedure for preparing compound **7a**, starting from (*3S, 4S*)-3,4-dihydroxy-5-methyl-2,2-diphenylhexanenitrile **9** (10mg, 0.07 mmol), 2-[(*4S,5S*)-5-isopropyl-2,2-dimethyl-1,3-dioxolan-4-yl]-2,2-diphenylacetonitrile **10** was obtained as white solid (10 mg, yield: 90%).

mp: 172-174 ^oC. $[\alpha]_D^{20}$: +94.8 (*c*: 1.0g/100 mg, $CHCl_3$). IR (film): 2247 cm^{-1}. ^1H 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

Preparation of (*3S, 4S*)-3,4-dihydroxy-2,2,4-triphenylbutanenitrile 11

Following the same procedure for preparing compound **6a**, starting from (*3S,4S*)-4-(*tert*-butyldimethylsilyloxy)-2,2,4-triphenyl-3-(trimethylsilyloxy)butanenitrile **4i** (100 mg, 0.35 mmol), (*3S, 4S*)-3,4-dihydroxy-2,2,4-triphenylbutanenitrile **11** was obtained as colourless oil (62 mg, yield: 97%).

$[\alpha]_D^{20}$: +66.73(*c*: 1.1g/100 mg, $CHCl_3$). IR (film): 3420 (b), 2239 cm^{-1}. ^1H 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

Preparation of 2-[(*4S, 5S*)-2,2-dimethyl-5-phenyl-1,3-dioxolan-4-yl]-2,2-diphenylacetonitrile 12

Following the same procedure for preparing compound **7a**, starting from (*3S, 4S*)-3,4-dihydroxy-2,2,4-triphenylbutanenitrile **11** (55 mg, 0.17 mmol), 2-[(*4S,5S*)-2,2-dimethyl-5-phenyl-1,3-dioxolan-4-yl]-2,2-diphenylacetonitrile **12** was obtained as white solid (54 mg, yield:86%)

mp: 218-220 °C. $[\alpha]_D^{20}$: +52.30 (*c*: 1.0g/100 mg, $CHCl_3$). IR (film): 2238 cm^{-1}. ^1H 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;

Preparation of (*3S*, 4S)-3-hydroxy-5,5-dimethyl-2,2-diphenyl-4-(trimethylsilyloxy)hexanenitrile 13**

Starting from (*3S*, 4S**)-4-(benzyloxy)-5,5-dimethyl-2,2-diphenyl-3-(trimethylsilyloxy)hexanenitrile **4g** (120 mg, 0.25 mmol), Pd/C (10%) (120mg) and $Pd(OAc)_2$ (35mg) 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 **13** was obtained after flash chromatography (cyclohexane: ether=4:1) (95 mg, yield: 98%)

Colourless oil. IR (film): 3445, 2239 cm^{-1}. ^1H 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

Preparation of (*3S*, 4S)-3,4-dihydroxy-5,5-dimethyl-2,2-diphenylhexanenitrile 14**

(*3S*, 4S**)-3-hydroxy-5,5-dimethyl-2,2-diphenyl-4-(trimethylsilyloxy)hexanenitrile **13** (107 mg, 0.28mmol) was mixed with 2 mL of acetone and PPTS (104 mg,0.56mmol). 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 **14** (82 mg, yield: 95%)

White solid. mp: 63-70 ^oC. IR (film): 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;

Preparation of (*R*)-3-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-hydroxy-2,2-diphenylpropanenitrile 15 and (*S*)-3-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-hydroxy-2,2-diphenylpropanenitrile 16

A crude mixture of **4h** and **5h** (150 mg, 0.38 mmol, ratio **4h**: **5h**=1:9) was dissolved into 5 mL of CH_2Cl_2/acetonitrile (9:1), KF (22mg, 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 **15** (60 mg, yield: 49%) and (*R*)-3-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-hydroxy-2,2-diphenylpropanenitrile **16** (6 mg, yield:5%).

15: White solid. mp: 104-108 ^oC. $[\alpha]_D^{20}$:-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.

16: White solid. mp: 137-139 ^oC. $[\alpha]_D^{20}$: +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.

Preparation of (*2S, 3S, 4S*)/(*2R, 3S, 4S*)-4-(benzyloxy)-2-phenyl-2-*p*-tolyl-3-(trimethylsilyloxy)pentanenitrile 17a/18a (identified as the corresponding monohydroxy derivatives 17a[1] and 18a[1] see below)

BuLi(1.0 mmol, 0.4 mL of 2.5M in n-hexane) was added into a solution of diisopropyl ethyl amine (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 **17a[1]** and **18a[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 **17a[1]** while the **18a[1]** remained in the mother liquorin mixture with **17a[1]**. Because an easily retro reaction takes place no further efforts were made to isolate pure **18a[1]** and its spectral data were deducted from the mixture.

17a[1]: White solid; mp: 95-98°C. $[\alpha]_D^{20}$: +99.5 (*c*: 1.0g/100 mg, $CHCl_3$). IR (film): 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.

18a[1]: IR (film): 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].

Preparation of (*2S, 3S, 4S*) /(*2R, 3S, 4S*)-4-(benzyloxy)-2-phenyl-2-*m*-tolyl-3-(trimethylsilyloxy)pentanenitrile 17b/18b (identified as the corresponding monohydroxydertivatives 17b[1] and 18b[1](see below)

Following the same procedure of **17a**[1]/**18a**[1], starting from 2-phenyl-2-*m*-tolylacetonitrile (207 mg, 1.0 mmol) and (*S*)-2-(benzyloxy)propanal **3b** (180 mg, 1.1 mmol), an inseparable mixture of (*2S, 3S, 4S*)-4-(benzyloxy)-2-phenyl-2-*m*-tolyl-3-(trimethylsilyloxy)pentanenitrile **17b**[1] and (*2R, 3S, 4S*)-4-(benzyloxy)-2-phenyl-2-*m*-tolyl-3-(trimethylsilyloxy)pentanenitrile **18b**[1] was obtained (288mg, 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 **18b**[1].

17b[1]: Colorless oil. IR(film): 2238 cm^{-1}. ^1H 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].

18b[1]: Colorless oil. IR(film): 2238 cm^{-1}. ^{1}HNMR (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].

Preparation of (*2S, 3S, 4S*) /(*2R, 3S, 4S*)-4-(benzyloxy)-2-phenyl-2-*o*-tolyl-3-(trimethylsilyloxy)pentanenitrile 17c/18c

Following the same procedure of Method A, starting from 2-phenyl-2-*o*-tolylacetonitrile**2e** (207 mg, 1.0 mmol) and (*S*)-2-(benzyloxy)propanal **3b** (180 mg, 1.1 mmol), (*2S, 3S, 4S*)-4-(benzyloxy)-2-phenyl-2-*o*-tolyl-3-(trimethylsilyloxy)pentanenitrile **17c** and (*2R, 3S, 4S*)-4-(benzyloxy)-2-phenyl-2-*o*-tolyl-3-(trimethylsilyloxy)pentanenitrile **18c** were obtained by the flash chromatography (n-hexane: ether= 98:2) (239mg, ratio:70/30, overall yield: 54%). The stereo attribution at each isomer was determined by X-Ray analysis of the corresponding acetonide **20** .

17c: White solid; mp: 61-65 °C. $[\alpha]_D^{20}$: + 96.90 (*c*: 1.0g/100 mg, $CHCl_3$). IR(film): 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.

18c: Colorless oil. $[\alpha]_D^{20}$: -57.90 (*c*: 1.0g/100 mg, $CHCl_3$). IR (film): 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.

Preparation of (*2S, 3S, 4S*)/(*2R, 3S, 4S*)-4-(benzyloxy)-2-(4-bromophenyl)-2-phenyl-3-(trimethylsilyloxy)pentanenitrile 17d/18d

Following the same procedure of Method A, starting from 2-(4-bromophenyl)-2-phenylacetonitrile **2f** (271 mg, 1.0 mmol) and (*S*)-2-(benzyloxy)propanal **3b** (164 mg, 1.0 mmol), a mixture of (*2S, 3S, 4S*)-4-(benzyloxy)-2-(4-bromophenyl)-2-phenyl-3-(trimethylsilyloxy)pentanenitrile **17d** and (*2R, 3S, 4S*)-4-(benzyloxy)-2-(4-bromophenyl)-2-phenyl-3-(trimethylsilyloxy)pentanenitrile **18d** was obtained after flash chromatography (*n*-hexane: ether= 9:1) (274mg, ratio:45/55, Overall yield: 54%). No further efforts to isolate pure **17d** from **18d** were taken. To **17d** was arbitrarly attributed the stereochemistry reported and its spectral data were deducted from the mixture reporting the major set of signals.

17d: colorless oil. IR(film): 2239 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ =0.00 (s, 9H), 1.3 (d, *J*=6.4 Hz, 3H), 3.90 (dq, J_1=4.4 Hz, J_2=6.4 Hz, 1H), 4.45(d, *J*=11.6 Hz, 1H), 4.60 (d, *J*=11.6 Hz, 1H), 4.66(d, *J*=4.0 Hz, 1H), 7.36-7.62 (complex pattern, 10H), 7.67 (m, 2H), 7.80(m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ =0.00, 17.10, 58.99, 70.87, 75.94, 81.50, 121.91, 127.14, 127.49, 127.79, 127.93, 128.57, 129.22, 131.52, 136.63, 137.59, 138.02, 144.75.MS (EI): m/z=530 [M+Na$^+$]. Elemental Analysis: Calcd. for $C_{27}H_{30}BrNO_2Si$: 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.

18d: colorless oil. IR(film): 2239 cm^{-1}. ^{1}H NMR (400 MHz,$CDCl_3$): δ =0.01 (s, 9H),1.35 (d, *J*=6.0 Hz, 3H), 3.83 (dq, J_1= 4.4 Hz, J_2=6.0 Hz, 1H), 4.44 (d, *J*=12.0 Hz, 1H), 4.65 (d, *J*=12.0 Hz, 1H), 4.68 (d, *J*=4.4 Hz, 1H),7.36-7.62 (complex pattern, 12H), 7.85(m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 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$^+$].

Preparation of (*2S, 3S, 4S*)/(*2R, 3S, 4S*)-4-(benzyloxy)-2-(4-methoxyphenyl)-2-phenyl-3-(trimethylsilyloxy)pentanenitrile 17e/18e

Following the same procedure of Method A, starting from 2-(4-methoxyphenyl)-2-phenylacetonitrile **2g** (223 mg, 1.0 mmol)and (*S*)-2-(benzyloxy)propanal **3b** (164 mg, 1.0 mmol), (*2S, 3S, 4S*)-4-(benzyloxy)-2-(4-methoxyphenyl)-2-phenyl-3-(trimethylsilyloxy)pentanenitrile **17e** and (*2R, 3S, 4S*)-4-(benzyloxy)-2-(4-methoxyphenyl)-2-phenyl-3-(trimethylsilyloxy)pentanenitrile **18e** were obtained after flash chromatography (petroleum ether : ether= 9:1) (298mg, ratio:50/50, overall yield:65 %)

17e: White solid. Mp: 65-71 ^{o}C. $[\alpha]_D^{20}$:+15.89 (*c*:8.75 g/100 mL, $CHCl_3$). IR (film): 2242 cm^{-1}. ^{1}H 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.

18e: Colorless oil. $[\alpha]_D^{20}$: + 3.5(*c*: 1.0g/100 mg, $CHCl_3$). IR (film): 2242 cm^{-1}. ^{1}H 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

Preparation of (*2S, 3S, 4S*)/(*2R, 3S, 4S*)-4-(benzyloxy)-2-phenyl-2-(4-(trifluoromethyl)phenyl)-3-(trimethylsilyloxy)pentanenitrile 17f/18f

Following the same procedure of Method A, starting from 2-phenyl-2-(4-(trifluoromethyl)phenyl)acetonitrile **2h** (261 mg, 1.0 mmol) and (*S*)-2-(benzyloxy)propanal **3b** (164 mg, 1.0 mmol), a mixture of (*2S, 3S, 4S*)-4-(benzyloxy)-2-phenyl-2-(4-(trifluoromethyl)phenyl)-3-(trimethylsilyloxy)pentanenitrile **17f** and (*2R, 3S, 4S*)-4-(benzyloxy)-2-phenyl-2-(4-(trifluoromethyl)phenyl)-3-(trimethylsilyloxy)pentanenitrile **18f** was obtained after flash chromatography (petroleum ether : AcOEt=14:1) (303mg, ratio:40/60, yield: 61 %). No further efforts to isolate pure **17f** from **18f** were taken. To **17f** was arbitrarly attributed the stereochemistry reported and its spectral data were deducted from the mixture reporting the major set of signals.

17f: IR(film): 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.

18f: IR(film): 2239 cm^{-1}. ^{1}H 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].

Preparation of (*2S, 3S, 4S*)/(*2R, 3S, 4S*)-4-(benzyloxy)-2-(4-nitrophenyl)-2-phenyl-3-(trimethylsilyloxy)pentanenitrile 17g/18g

Following the same procedure of Method A, starting from 2-(4-nitrophenyl)-2-phenylacetonitrile **2i** (238 mg, 1.0 mmol) and (*S*)-2-(benzyloxy)propanal **3b** (164 mg, 1.0 mmol), ((*2S, 3S, 4S*) -4-(benzyloxy)-2-(4-nitrophenyl)-2-phenyl-3-(trimethylsilyloxy)pentanenitrile **17g** and (*2R, 3S, 4S*)-4-(benzyloxy)-2-(4-nitrophenyl)-2-phenyl-3-(trimethylsilyloxy)pentanenitrile **18g** were obtained by the flash chromatography (petroleum ether : AcOEt=10:1) (270mg, ratio:36/64, yield: 57%)

17g: Colorless oil. $[\alpha]_D^{20}$: +26.08 (*c*: 1.3g/100 mg, $CHCl_3$). IR (film): 2243cm^{-1}. ^{1}H 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.

18g: White solid. mp: 130-133 ^{o}C. $[\alpha]_D^{20}$: +18.47 (*c*: 1.1g/100 mg, $CHCl_3$). IR (film): 2242 cm^{-1}. ^{1}H 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.

Preparation of (*2S, 3S, 4S*)/(*2R, 3S, 4S*)-4-(benzyloxy)-2-phenyl-2-(pyridin-3-yl)-3-(trimethylsilyloxy)pentanenitrile 17h/18h

Following the same procedure of Method A, starting from 2-phenyl-2-(pyridin-3-yl)acetonitrile **2j** (194 mg, 1.0 mmol) and (*S*)-2-(benzyloxy)propanal **3b** (164 mg, 1.0 mmol), (*2S, 3S, 4S*)-4-(benzyloxy)-2-phenyl-2-(pyridin-3-yl)-3-(trimethylsilyloxy)pentanenitrile **17h** and (*2R, 3S, 4S*)-4-(benzyloxy)-2-phenyl-2-(pyridin-3-yl)-3-(trimethylsilyloxy)pentanenitrile **18h** were obtained after flash chromatography (n-hexane : ether=3:2) (288mg, ratio:65/35, yield: 67%)

17h: Colorless oil. $[\alpha]_D^{20}$: +18.40 (*c*: 1.0g/100 mg, $CHCl_3$). IR (film): 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.

18h: White solid. mp: 59-64 ^{o}C. $[\alpha]_D^{20}$: +12.80 (*c*: 1.1g/100 mg, $CHCl_3$). IR (film): 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.

Preparation of (*2S, 3S, 4S*)/(*2R, 3S, 4S*)-4-(benzyloxy)-2-(2-chlorophenyl)-2-phenyl-3-(trimethylsilyloxy)pentanenitrile 17i/18i

Following the same procedure of Method A, starting from 2-(2-chlorophenyl)-2-phenylacetonitrile **2k** (227 mg, 1.0 mmol) and (*S*)-2-(benzyloxy)propanal **3b** (164 mg, 1.0 mmol), (*2S, 3S, 4S*)-4-(benzyloxy)-2-(2-chlorophenyl)-2-phenyl-3-(trimethylsilyloxy)pentanenitrile **17i** and (*2R, 3S, 4S*)-4-(benzyloxy)-2-(2-chlorophenyl)-2-phenyl-3-(trimethylsilyloxy)pentanenitrile **18i** were obtained by the flash chromatography (n-hexane : toluene=1:1) (203mg, ratio:80/20, yield: 44%). The absolute configuration of the isomer **17i** was established by X-Ray analysis.

17i: White solid**.** mp: 75-80 °C. $[\alpha]_D^{20}$: +73.50 (*c*: 1.0g/100 mg, $CHCl_3$). IR (film): 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.

18i: Colorless oil. $[\alpha]_D^{20}$: +46.90 (*c*: 1.8g/100 mg, $CHCl_3$). IR (film): 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.

Preparation of (*2S, 3S, 4S*)/(*2R, 3S, 4S*)-4-(tert-butyldimethylsilyloxy)-2,4-diphenyl-2-*m*-tolyl-3-(trimethylsilyloxy)butanenitrile 17j/18j

Following the same procedure of A, starting from2-phenyl-2-m-tolylacetonitrile **2d** (207 mg, 1.0 mmol)and (*S*)-2-(tert-butyldimethylsilyloxy)-2-phenylacetaldehyde **3i** (250 mg, 1.0 mmol), a mixture products **17j** and **18j** was obtained by the flash chromatography (cyclohexane: ether=99:1) (429mg, ratio:50/50, yield: 85%)

17j: IR(film): 2245 cm^{-1}. ^1H 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.

18j:(50%) IR(film): 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]

Preparation of (*2S, 3S, 4S*)/(*2R, 3S, 4S*)-4-(tert-butyldimethylsilyloxy)-2,4-diphenyl-2-(pyridin-3-yl)-3-(trimethylsilyloxy)butanenitrile 17k/18k

Following the same procedure of Method A, starting from 2-phenyl-2-(pyridin-3-yl)acetonitrile **2j** (194 mg, 1.0 mmol) and (*S*)-2-(tert-butyldimethylsilyloxy)-2-phenylacetaldehyde **3i** (250 mg, 1.0 mmol), (*2S, 3S, 4S*)-4-(tert-butyldimethylsilyloxy)-2,4-diphenyl-2-(pyridin-3-yl)-3-(trimethylsilyloxy)butanenitrile **17k** and (*2R, 3S, 4S*)-4-(tert-butyldimethylsilyloxy)-2,4-diphenyl-2-(pyridin-3-yl)-3-(trimethylsilyloxy)butanenitrile **18k** were obtained by the flash chromatography (CH_2Cl_2 : ether=99:1) (197mg, ratio:80/20, yield: 40%). The absolute configuration of the isomer **17k** was established by X-Ray analysis.

17k: White solid. mp:104-107°C. $[\alpha]_D^{20}$: + 3.1(*c*: 1.0g/100 mg, $CHCl_3$). IR (film): 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.

18k: White solid. mp: 88-92 °C. $[\alpha]_D^{20}$: + 18.3 (*c*: 1.0g/100 mg, $CHCl_3$). IR (film): 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.

Prearation of (*2S, 3S, 4S*)-3,4-dihydroxy-2-phenyl-2-*o*-tolylpentanenitrile 19

(*2S, 3S, 4S*)-4-(benzyloxy)-2-phenyl-2-o-tolyl-3-(trimethylsilyloxy)pentanenitrile **17c** (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 **19** (45 mg, yield: 59%).

colourless oil. $[\alpha]_D^{20}$: +126.18 (*c*: 1.1g/100 mg, $CHCl_3$). IR (film): 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.

Prearation of (*S*)-2-phenyl-2-*o*-tolyl-2-((*4S,5S*)-2,2,5-trimethyl-1,3-dioxolan-4-yl)acetonitrile 20

Following the same procedure for preparing compound **7a**, starting from (*2S, 3S, 4S*)-3,4-dihydroxy-2-phenyl-2-*o*-tolylpentanenitrile **19** (23 mg, 0.08 mmol), PPTS (41mg, 0.16mmol) and 2,2-dimethoxypropane (1 mL) compound **20** was obtained (24 mg, yield: 92 %) as white solid.

mp: 95-99°C. $[\alpha]_D^{20}$: +126.94 (*c*: 1.6 g/100 mg, $CHCl_3$). IR (film): 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.

4.3.2 Experimental data for the preparation of α-cyano-β-carboxyamides (Section B.)

Method A; Typical Procedure

2,2-Diphenylacetonitrile (**21a**) (193 mg, 1.0 mmol) in THF (2 mL) was added dropwise to a solution of *n*-BuLi (0.52 mL of a 2.5 M solution in *n*-hexane, 1.3 mmol) in THF (3 mL) at –78 °C. After 15 min, a solution of isocyanate **22a** (164 mg, 1.1 mmol) in toluene (4 mL) was added dropwise at the same temperature. The resulting mixture was stirred at –78 °C for 2 h and then allowed to warm to r.t. over 6 h. Next, the reaction mixture was added dropwise to ice-cold sat. 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 **23a** (120 mg, 35%) as a white solid.

Method B; Typical Procedure

2,2-Diphenylacetonitrile (**21a**) (193 mg, 1.0 mmol) in THF (1 mL)was added dropwise to a solution of *n*-BuLi (0.44 mL of a 2.5 M solution in*n*-hexane, 1.1 mmol) in THF (3 mL) at –78 °C. Next, a solution of TMSCl (120 mg, 1.1 mmol) in THF (1 mL) was added dropwise at–78 °C. After 15 min, a solution of isocyanate **22a** (164 mg, 1.1 mmol)in toluene (1 mL) was added dropwise at –78 °C and the mixture allowed to warm to r.t. over 6–8 h. The reaction mixture was quenched by its addition to ice-cold sat. 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 **23a** (221 mg, 65%).

Method C; Typical Procedure

2,2-Diphenylacetonitrile (**21a**) (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 diisopropyl ethyl amine (131 mg, 1.3 mmol) in THF (3 mL) at –78 °C. After 15 min, a solution of TMSCl (120 mg, 1.1 mmol) in THF (1 mL) was added dropwise to –78 °C. The resulting mixture was stirred for a further 15 min and then the solvent was removed *in vacuo*. The residue was dissolved in toluene (6 mL) at –78 °C and the isocyanate **22a** (164 mg, 1.1 mmol) in toluene (2 mL) was added dropwise at the same temperature. The reaction temperature was maintained at –78 °C for 2 h and then allowed to warm to r.t. over 6–8 h. The reaction mixture was quenched by its addition to ice-cold sat.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 **23a** (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 ethyl amine (101 mg, 1.0 mmol) in THF (3 mL) at –78 °C. After 5 min, a solution of 2,2-diphenylacetonitrile (**21a**) (193 mg, 1.0 mmol) in THF (1 mL) was added dropwise at –78 °C, followed by a solution of TBDMSCl (166 mg, 1.1 mmol) in THF (1 mL) at the same temperature. The mixture was stirred for 20 min at –78 °C and then allowed to warm to r.t. The solvent was removed *in vacuo* and the residue dissolved in anhydrous toluene (3 mL). After cooling to –78 °C, a solution of isocyanate **22a** (164 mg, 1.1 mmol) in toluene (1 mL) was added dropwise at –78 °C. The resulting mixture was stirred at –78 °C for 6–8 h, then allowed to warm to r.t. and stirred at this temperature for 2 d. 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 **21a** (117 mg, 61%) was recovered by flash chromatography (cyclohexane–Et_2O, 4:1). No trace of the target amide **23a** was evident in the crude reaction mixture according to TLC, ^1H NMR and HPLC analyses.

2-Cyano-*N*-(4-methoxyphenyl)-2,2-diphenylacetamide (23a)

mp：119–122 °C. IR (KBr): 2243, 1692 cm^{-1}. ^1H 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, 114.42, 120.47, 122.17, 128.39, 129.24, 129.31, 129.82, 136.25, 157.14, 163.71. GC–MS: *m*/*z* = 342 $[M]^+$. Elemental Analysis: Calcd for $C_{22}H_{18}N_2O_2$: C, 77.17; H, 5.30. Found: C, 77.32; H, 5.31.

2-(4-Bromophenyl)-2-cyano-*N*-(4-methoxyphenyl)-2-phenylacetamide (23b)

Starting from 2-(4-bromophenyl)-2-phenylacetonitrile (**21b**) (272 mg, 1.0 mmol) and isocyanate **22a** (164 mg, 1.1 mmol), following Method C, malonamide **23b** was obtained, after flash chromatography (cyclohexane–EtOAc, 4:1), as a light-yellow solid (273 mg, 65%).

mp：147–153 °C. IR (KBr): 2241, 1667 cm^{-1}. ^1H 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, 114.38, 120.02, 122.29, 123.58, 128.18, 129.42, 129.61, 130.10, 132.28, 135.33, 135.73, 157.48, 163.19. LC–MS: *m*/*z* = 421 $[M + 1]^+$. Elemental Analysis: Calcd for $C_{22}H_{17}BrN_2O_2$: C, 62.72; H, 4.07. Found: C, 62.82; H, 4.08.

2-Cyano-*N*-(4-methoxyphenyl)-2-phenyl-2-(*m*-tolyl)acetamide (23c)

Starting from 2-phenyl-2-(*m*-tolyl)acetonitrile (**21c**) (207 mg, 1.0mmol) and isocyanate **22a** (164 mg, 1.1 mmol), following Method C, malonamide **23c** was obtained, after flash chromatography (cyclohexane–EtOAc, 12:1), as a white solid (206 mg, 58%).

mp：133–134 °C. IR (KBr): 2241, 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 = 21.65, 55.62, 60.36, 114.37, 120.52, 122.14, 125.40, 128.39, 128.91, 129.14, 129.15, 129.23, 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 $C_{23}H_{20}N_2O_2$: C, 77.51; H, 5.66. Found: C, 77.63; H, 5.67.

2-Cyano-*N*-(4-methoxyphenyl)-2-phenyl-2-(*o*-tolyl)acetamide (23d)

Starting from 2-phenyl-2-(*o*-tolyl)acetonitrile (**21d**) (207 mg, 1.0mmol) and isocyanate **22a** (164 mg, 1.1 mmol), following Method C, malonamide **23d** was obtained, after flash chromatography (cyclohexane: EtOAc, 12:1), as a light-yellow solid (228 mg, 64%).

mp：125–129 °C. IR (KBr): 2245, 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 = 21.09, 55.66, 59.81, 114.45, 119.60, 122.10, 126.69, 128.23, 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 $C_{23}H_{20}N_2O_2$: C, 77.51; H, 5.66. Found: C, 77.62; H, 5.67.

2-Cyano-*N*-(4-methoxyphenyl)-2-phenyl-2-(*p*-tolyl)acetamide (23e)

Starting from 2-phenyl-2-(*p*-tolyl)acetonitrile (**21e**) (207 mg, 1.0mmol) and isocyanate **22a** (164 mg, 1.1 mmol), following Method C, malonamide **23e** was obtained, after flash chromatography (cyclohexane–EtOAc, 9:1), as a light-yellow solid (267 mg, 75%).

mp：107–113 °C. IR (KBr): 2242, 1671 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.23 (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 = 21.17, 55.57, 60.08, 114.32, 120.47, 122.12, 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 $C_{23}H_{20}N_2O_2$: C, 77.51; H, 5.66. Found: C, 77.61; H, 5.67.

2-Cyano-*N*,2-bis(4-methoxyphenyl)-2-phenylacetamide (23f)

Starting from 2-(4-methoxyphenyl)-2-phenylacetonitrile (**21f**) (224mg, 1.0 mmol) and isocyanate **22a** (164 mg, 1.1 mmol), following Method B, malonamide **23f** was obtained, after flash chromatography (cyclohexane–EtOAc, 4:1), as a white solid (260 mg, 70%).

mp：116–120 °C. IR (KBr): 2243, 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, 114.35, 114.59, 120.54, 122.12, 128.09, 128.26, 129.12, 129.23, 129.64, 129.85, 136.51, 157.34, 160.11, 164.03. LC–MS: *m*/*z* = 373 $[M + 1]^+$. Elemental Analysis: Calcd for $C_{23}H_{20}N_2O_3$: C, 74.18; H, 5.41. Found: C, 74.33; H, 5.42.

2-(2-Chlorophenyl)-2-cyano-*N*-(4-methoxyphenyl)-2-phenylacetamide (23g)

Starting from 2-(2-chlorophenyl)-2-phenylacetonitrile (**21g**) (227mg, 1.0 mmol) and isocyanate **22a** (164 mg, 1.1 mmol), following Method B, malonamide **2g** was obtained, after flash chromatography (cyclohexane–EtOAc, 10:1), as a yellow solid (256 mg, 68%).

mp：167–169 °C. IR (KBr): 2242, 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, 114.39, 118.80, 122.42, 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 $C_{22}H_{17}ClN_2O_2$: C, 70.12; H, 4.55. Found: C, 70.26; H, 4.56.

2-Cyano-*N*-(4-methoxyphenyl)-2-phenyl-2-(pyridin-3-yl)acetamide(23h)

Starting from 2-phenyl-2-(pyridin-3-yl)acetonitrile (**21h**) (194 mg,1.0 mmol) and isocyanate **22a** (164 mg, 1.1 mmol), following Method B, malonamide **23h** was obtained, after flash chromatography (cyclohexane :EtOAc, 4:1), as a white solid (274 mg, 80%).

mp：111–115 °C. IR (KBr): 2246, 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, 114.26, 119.39, 122.30, 123.44, 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 $C_{21}H_{17}N_{23}O_2$: C, 73.45; H, 4.99. Found: C, 73.56; H, 5.00.

2-Cyano-*N*,2,2-triphenylacetamide (23i)

Starting from 2,2-diphenylacetonitrile (**21a**) (193 mg, 1.0 mmol) and isocyanate **22b** (131 mg, 1.1 mmol), following Method C, malonamide **23i** was obtained, after flash chromatography (cyclohexane : EtOAc, 4:1), as a white solid (228 mg, yield 73%).

mp：119–122 °C. IR (KBr): 2246, 1703 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.22 (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 $C_{21}H_{16}N_2O$: C, 80.75; H, 5.16. Found: C, 80.83; H, 5.17.

***N*-Benzyl-2-cyano-2,2-diphenylacetamide (23j)**

Starting from 2,2-diphenylacetonitrile (**21a**) (193 mg, 1 mmol) and isocyanate **22c** (146 mg, 1.1 mmol), following Method B, malonamide **23j** was obtained, after flash chromatography (cyclohexane: EtOAc, 4:1), as a white solid (164 mg, 50%).

mp：131–132 °C. IR (KBr): 2247, 1665 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.44 (d, J = 6.0 Hz, 2 H, CH_2), 6.64 (bs, 1 H, NH), 7.23–7.43 (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 $C_{22}H_{18}N_2O$: C, 80.96; H, 5.56. Found: C, 80.88; H, 5.55.

2-Cyano-2,2-diphenyl-*N*-(1-phenylethyl)acetamide (23k)

Starting from 2,2-diphenylacetonitrile (**21a**) (193 mg, 1 mmol) and isocyanate **22d** (162 mg, 1.1 mmol), following Method B, malonamide **23k** was obtained, after flash chromatography (cyclohexane:EtOAc=4:1), as a white solid (265 mg, 78%).

mp：92–95 °C.IR (KBr): 2239, 1663 cm^{-1}. ^{1}H 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 = 21.67, 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 $C_{23}H_{20}N_2O$: C, 81.15; H, 5.92. Found: C, 81.03; H5.91.

***N*-Benzyl-2-cyano-2-(4-methoxyphenyl)-2-phenylacetamide (23l)**

Starting from 2-(4-methoxyphenyl)-2-phenylacetonitrile (**21f**) (224mg, 1.0 mmol) and isocyanate **22c** (146 mg, 1.1 mmol), following Method B, malonamide **23l** was obtained, after flash chromatography (cyclohexane–EtOAc, 4:1), as a white solid (144 mg, 40%).

mp: 132–134 °C. IR (KBr): 2242, 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), 7.23–7.42 (complex pattern, 12 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 44.79, 55.48, 58.98, 114.46, 120.58, 127.79, 127.95, 128.21, 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 $C_{23}H_{20}N_2O_2$: C, 77.51; H, 5.66. Found: C, 77.28; H, 5.65.

2-Cyano-*N*-(2-methylphenyl)-2-phenyl-2-(pyridin-3-yl)acetamide (23m)

Starting from 2-phenyl-2-(pyridin-3-yl)acetonitrile (**21h**) (194 mg,1.0 mmol) and 1-isocyanato-2-methylbenzene (**22e**) (133 mg, 1.1mmol), following Method B, malonamide **23m** was obtained, after flash chromatography (CH_2Cl_2–Et_2O, 5:1), as a white solid (1723mg, 53%).

mp: 230–235 °C. IR (neat): 2238, 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, 119.39, 122.64, 123.52, 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 $C_{21}H_{17}N_{23}O$: C, 77.04; H, 5.23. Found: C, 77.26; H, 5.24.

2-Cyano-*N*,2,2-tris(4-methoxyphenyl)acetamide (23n)

Starting from 2,2-bis(4-methoxyphenyl)acetonitrile (**21i**) (253 mg,1.0 mmol) and isocyanate **22a** (164 mg, 1.1 mmol), following Method B, malonamide **23n** was obtained, after flash chromatography (cyclohexane–EtOAc, 4:1), as a white solid (244 mg, 61%).

mp: 133–135 °C.IR (KBr): 2241, 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, 114.38, 114.59, 120.71, 122.08, 128.43, 129.58, 129.93, 157.34, 160.09,164.37.LC–MS: *m*/*z* = 403 $[M + 1]^+$. Elemental Analysis: Calcd for $C_{24}H_{22}N_2O_4$: C, 71.63; H, 5.51. Found: C, 71.87; H, 5.52.

4.3.3 Experimental data for the preparation of γ-hydroxy nitriles (Section C.)

The diastereomeric ratios reported into Tables 5 and 6 have been calculated by HPLC (Agilent, Poroshell 120. SB-C18. 2.7m, 3.0 × 100 mm) and ^1H NMR on the crude reaction mixture taking into account the doubtless peaks of each diatereomer.

Preparation of 4-hydroxy-2,2-diphenylpentanenitrile 32a

Method A:. diphenylacetonitrile (290 mg, 1.5 mmol) in THF (1mL) was added into a solution of $LiN(SiMe_3)_2$ (1.5mmol, 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 **32a** (218 mg, yield: 58%).

White solid. mp: 88-92 ^oC. IR(film): 2244 cm^{-1}. ^1H NMR (400 MHz, CDCl3): 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, CDCl3): 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].

Preparation of (*2S*, 4R)-4-hydroxy-2-methyl-2-phenylpentanenitrile 32b and (*2R*, 4R**)-4-hydroxy-2-methyl-2-phenylpentanenitrile 32c**

Preparation of diethylaluminium ketene imine 25a

Diethylaluminium ketene imine **25a** was prepared according the same literature procedure for the preparation of silylketene imines.[54,99] In detail, α-methyl acetonitriles (197 mg, 1.5 mmol) was added into a solution of $LiN(SiMe_3)_2$ (1.5mmol, 1.5 mL of 1.0 M in n-hexane) in THF (5 mL) at -78^oC 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 keteneimine **25a** 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 keteneimine **25a** which was prepared as described above, a solution of 2-methyloxirane (87 mg, 1.5 mmol) in THF (1 mL) was added at -78 ^oC. The reaction was kept at -78 ^oC 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 **32b** and **33b** (170 mg, ratio: 50:50, total yield: 60%). Spectral data were deducted from the mixture and arbitrarly attributed to **32b** and **33b**

32b: IR(film): 2237 cm^{-1}. ^1H 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, 28.21, 40.89, 50.52, 65.58, 123.70, 125.61, 127.98, 129.15, 139.93. MS (ESI): m/z=190 [M+1].

33b: IR(film): 2237 cm^{-1}. ^1H 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 $LiN(SiMe_3)_2$ (1.5mmol, 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 **32b** and **33b** (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 $LiN(SiMe_3)_2$ (1.5mmol, 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 (135mg) in THF (1ml) 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 **32b** and **33b** (141 mg, ratio: 40:60, total yield: 50%).

Preparation of (*2S)-2-((*2S**)-2-hydroxycyclohexyl)-2-phenylpropanenitrile 32c and (*2R**)-2-((*2S**)-2-hydroxycyclohexyl)-2-phenylpropanenitrile 33c**

 α-methyl acetonitriles (197 mg, 1.5 mmol) in THF (1mL) was added into a solution of $LiN(SiMe_3)_2$ (1.5mmol, 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. 10ml 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 **32c** and **33c** (113 mg, ratio: 50:50, total yield: 33%). Spectral data were deducted from the mixture and arbitrarly attributed to **32c** and **33c**.

32c: IR(film): 2236 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ =0.90-1.44 (comlex 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 = 21.08, 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].

33c: IR(film): 2236 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ =0.90-1.44 (comlex 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 = 21.08, 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].

Preparation of (*2S*, 4R)-4-hydroxy-2-methyl-2,4-diphenylbutanenitrile 32d and (*2R*, 4R**)-4-hydroxy-2-methyl-2,4-diphenylbutanenitrile 33d**

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 **32d** and (*2R*, 4R**)-4-hydroxy-2-methyl-2,4-diphenylbutanenitrile **33d** were obtained after flash chromatography (cyclohexane : AcOEt =4:1) (184 mg, ratio:**32d**/**33d**=25/75, total yield: 49%)

32d: whilte solid. mp: 78-82 °C. IR(film): 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].

33d: IR(film): 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].

Preparation of (*2S*, 4R)-5-*tert*-butoxy-4-hydroxy-2-methyl-2-phenylpentanenitrile 32e and (*2R*, 4R**)-5-*tert*-butoxy-4-hydroxy-2-methyl-2-phenylpentanenitrile 33e**

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 **32e** and **33e** 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 **32e** and **33e.**

32e: IR(film): 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].

33e: IR(film): 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), 2.21 (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].

Preparation of (*2S*, 4R)-5-(2-ethyldodecyloxy)-4-hydroxy-2-methyl-2-phenylpentanenitrile 32f and (*2R*, 4R**)-5-(2-ethyldodecyloxy)-4-hydroxy-2-methyl-2-phenylpentanenitrile 33f**

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 **32f** and **33f** 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 **32f** and **33f**.

32f: IR(film): 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), 2.21 (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].

33f: IR(film): 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 =11.21, 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].

Preparation of (*2S*, 4S)-4-hydroxy-2-methyl-2-phenyltetradecanenitrile 32g and (*2R*, 4S**)-4-hydroxy-2-methyl-2-phenyltetradecanenitrile 33g**

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 **32g** and **33g** 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 **32g** and **33g**.

32g: IR(film): 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].

33g: IR(film): 2236 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ =0.89 (t, *J*=7.6 Hz, 3H), 1.20-1.45 (m, 18H), 1.80 (s, 3H), 1.99 (dd, J_1=2.4 Hz, J_2= 14.8 Hz, 1H), 2.11 (dd, J_1=6.8 Hz, J_2=14.8 Hz, 1H), 3.62 (m, 1H), 7.33 (m, 1H), 7.41 (m, 2H), 7.48 (m, 2H). ^{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].

Preparation of (*2S*, 4S)-4-hydroxy-2-methyl-2-phenyloctanenitrile 32h and (*2R*, 4S**)-4-hydroxy-2-methyl-2-phenyloctanenitrile 33h**

 α-methyl acetonitriles (197 mg, 1.5 mmol) in THF (1mL) was added into a solution of $LiN(SiMe_3)_2$ (1.5mmol, 1.5 mL of 1.0 M in n-hexane) in THF (3 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. The reaction was kept at r.t. for 20mins and concentrated. 20ml of CH_2Cl_2 was added to the residue and filtered. The filtrate was cooled to -78 ^{o}C. A solution of 2-butyloxirane (150 mg, 1.5 mmol) in CH_2Cl_2 (1 mL) was added at -78 ^{o}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 (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 **32h** and **33h** (107 mg, ratio: 50:50, total yield: 31%). Spectral data were deducted from the mixture and arbitrarly attributed to **32h** and **33h.**

32h: IR(film): 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].

33h: IR(film): 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, 129.21, 140.16. MS(ESI) m/z= 232 [M+1].

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Publications list

[1] **S. Long**, F. R. Stefani, S Biondi, G Ghiselli, and M. Panunzio. *N*-Heteroarylmethyl 3-carboxy-5-hydroxy piperidine: A Novel Scaffold for the Design of Potent Glucosidase Inhibitors. *Submitted to Bioorganic & Medicinal Chemistry*

[2] W.L. Qin, **S. Long**, M. Panunzio and A. Bongini. Catalyst-Free Amidation of *N*-Trimethylsilyl Ketene Imines with Isocyanates. *Synthesis*, 2012, *44*, 3191-3196

[3] **S. Long**, M. Panunzio, W. L. Qin, A. Bongini, M. Monari. Catalyst-free efficient aldol-type reaction of *O*-protected α-hydroxy aldehydes and N-trimethylsilyl ketene imines. *Manuscript in Preparation.*

[4] M. Panunzio, **S. Long**, W.L. Qin. Synthesis and use of N-(trialkylsilyl)imines (Review). Current Organic Chemistry. *abstrac approved, Manuscript in Preparation.*

[5] **S. Long**, M. Monari, M. Panunzio, E. Bandini, A. D'Aurizio, A. Venturini. Hetero-Diels–Alder (HDA) Strategy for the Preparation of 6-Aryl- and Heteroaryl-Substituted Piperidin-2-one Scaffolds: Experimental and Theoretical Studies. *Eu.J. Org. Chem*. 2011, 2011, 6218.

[6] **S. Long**, M. Panunzio, A. Petroli, W. L. Qin, Z. N. Xia. The Use of Magnesium Nitride for the Synthesis of Enantiomerically Pure 1,4-Dihydropyridines via the Hantzsch Reaction. *Synthesis.* 2011, 1071.

[7] S. Biondi, **S. Long**, M. Panunzio, W. L. Qin. Current Trends in β-Lactam Based β-Lactamases Inhibitors. *Curr. Med. Chem.* 2011, 18, 4223

Courses, posters and oral presentations

Poster: "***Long, Sha*** *and Panunzio, Mauro*. Synthesis of optically active 1,4-Dihydropyridines via Hantzch reaction and "solid ammonia" Mg_3N_2. ***X Giornata della Chimica dell'Emilia Romagna***. 26th Nov. 2010, Parma, Italy

Oral presentation*:* ***Long Sha****, Bongini Alessandro, Qin WenLing and Panunzio Mauro*. Synthesis and Reactivity of N-Silylketenimines, ***FIRB—DAY***. 24th Jan., 2011, Bologna, Italy

Oral presentation: ***Long, Sha****; Qin, WenLing; Panunzio, Mauro.* Synthesis and Reactivity of Silylimines: Preliminary studies on Un-catalyzed Synthesis of 2,2-Diaryl-3,4-dihydroxy-pentanenitrile Starting from N-TMS-Ketenimine. ***XI Giornata della Chimica dell'Emilia Romagna***. 28th Oct. 2011, Modena, Italy

Poster and oral presentation. ***Long, Sha****; Qin, WenLing; Panunzio, Mauro.* Studies on the uncatalyzed aldol-type reaction of *O*-protected α-hydroxy aldehydes and *N*-trimethylsilyl ketene imines. ***XXXVII "A. CORBELLA" SUMMER SCHOOL Seminars in Organic Synthesis Gargnano (BS)***. 18th -22th Jun. 2012**,** Palazzo Feltrinelli**,** Gargnano, Italy;

Poster: "***Long Sha****; Qin, WenLing; Bongini Alessandro* and *Panunzio Mauro.* Synthesis and reactivity of *N*-metallo-keteneimines. ***XII Giornata della Chimica dell'Emilia Romagna***. 17th Dec. 2012, Ferrara, Italy.

Poster: *Qin WenLing*; ***Long Sha*** and *Panunzio Mauro*. α,α-diaryl nitriles as precursors of 2,2-disubstituted β-hydroxy nitriles via *N*-tin ketene imines. ***XII Giornata della Chimica dell'Emilia Romagna.*** 17th Dec. 2012, Ferrara, Italy.