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Diastereoselective Addition of Higher Order Cuprates and Zinc-Copper Reagents to Imines Derived from (*S*)-1-Phenylethylamine

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Abstract

The diastereoselective addition of higher order (H.O.) cuprates and zinc-copper reagents to aliphatic and aromatic chiral imines derived from (*S*)-1-phenylethylamine was examined. Aliphatic chiral imines react with $(Allyl)_2CuCNLi_2$ and $(n\text{-}Bu)_2Cu(CN)Li_2$ in the presence of $BF_3{\cdot}Et_2O$ and Me_3SiCl in high diastereoselection, while $c\text{-}C_6H_{11}Cu(CN)ZnI$ and $AllylCu(CN)ZnBr$ afford chiral amines in comparable yields without additives. Moreover the synthesis of a key intermediate towards a δ-amino-acid was reported.

Keywords: imines, higher order cuprates, zinc-copper reagents, diastereoselection, chiral amines

Introduction

Amines bearing a stereogenic centre in the α-position play a crucial role establishing pharmacological properties in pharmaceutically active compounds. The development of a diastereo- and enantioselective synthesis of amines is an important goal in modern organic synthesis.[1] In this context the preparation of amines, by addition of nucleophilic reagents to chiral imines, is one of most the important methodologies.[2] The inexpensive and commercially available (*R*) and (*S*)-1-phenylethylamine are widely used as auxiliaries due to the simple removal of the arylethyl group. The addition of organometallic reagents to aliphatic and aromatic imines was widely studied by our group[3] and by other authors.[4] In particular lithium, copper, magnesium and zinc reagents, in the presence of Lewis acids such as cerium salts and $BF_3{\cdot}Et_2O$ were already reported, giving high diastereoisomeric ratio. A possible strategy to synthesize functionalized amines could be the employment of H.O. cuprates[5] and zinc-copper reagents. [6] To the best of our knowledge studies as the addition of these organometallic reagents to imines have not been reported. Here we present a full account of our studies.

Results and Discussion

Chiral imines (**1a-g**) were prepared by addition of 1-(*S*)-phenylethylamine to the corresponding aldehyde in CH_2Cl_2 in the presence of anhydrous $MgSO_4$. The imines were easily isolated after filtration, removing the solvent at reduced pressure and used without purification (Scheme 1).

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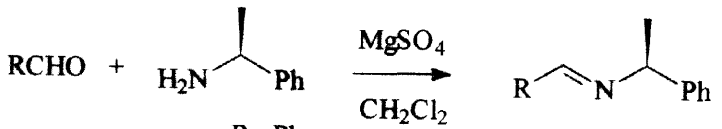


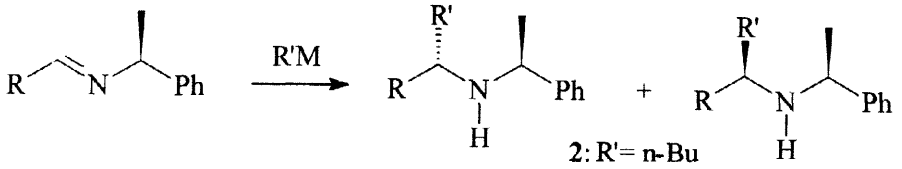
(*S*)-**1**

a: R= i-Pr **e:** R= Ph
b: R= Et **f:** R= n-C_5H_{11}
c: R= n-C_7H_{15} **g:** R=CO_2Me
d: R= c-C_6H_{11}

Scheme 1

The H.O. cuprates $(n\text{-}Bu)_2Cu(CN)Li_2$, and $(Allyl)_2Cu(CN)Li_2$ were prepared as described in the experimental section and used at once in the reaction with imines. All the reactions were performed in dry THF at -78°C and the slurry was allowed to warm to room temperature over 24 hrs. The results obtained are summarized in Table 1.

Table 1. Addition of H.O. Cuprates to imines



(*S*)-**1** (*S,S*) (*R,S*)

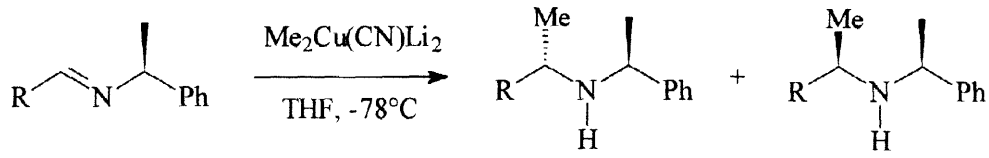
Entry	Imine[a]	R'M	Amine	Yield %[g]	*S,S* / *R,S*[i]
1	**1a**	$(n\text{-}Bu)_2Cu(CN)Li_2$[b]	**2a**	34	76:24
2	**1c**	" "[b]	**2c**	49	80:20
3	**1e**	" "[b]	**2e**	35	72:28
4	**1a**	" "[b]	**2a**	50[h]	90:10
5	**1c**	" "[c]	**2c**	60[h]	86:14
6	**1e**	" "[c]	**2e**	30	65:35
7	**1d**	" "[c]	**2d**	57[h]	87:13
8	**1a**	" "[d]	**2a**	66	78:28
9	**1c**	" "[d]	**2c**	82	87:13
10	**1a**	" "[e]	**2a**	53	85:15
11	**1c**	" "[e]	**2c**	52	82:18
12	**1a**	$(Allyl)_2Cu(CN)Li_2$[f]	**3a**	>90	80:20
13	**1b**	" "	**3b**	>90	19:81
14	**1c**	" "	**3c**	>90	26:74
15	**1e**	" "	**3e**	>90	36:64

[a] All the reactions were carried out on 0.5-1.5 mmol of imines. [b] The reaction was performed in the presence of 1 eq. of $BF_3{\cdot}Et_2O$. [c] The reaction was carried out in the presence of 1 eq. of $BF_3{\cdot}Et_2O$ and 1 eq. of Me_3SiCl. [d] The reaction was carried out in the presence of 1 eq. of $BF_3{\cdot}Et_2O$ and 1 eq. of PPh_3. [e] The reaction was carried out in the presence of 1 eq. of $BF_3{\cdot}Et_2O$ and 1 eq. of bipyridine. [f] All the reactions with allyl H.O. cyanocuprates were performed in the presence of 1 eq. of $BF_3{\cdot}Et_2O$. [g] The yield reported was evaluated by GC or GC-MS analysis, the rest being starting material. [h] Isolated yield of purified amine. [i] The dr was determined by GC or GC-MS analysis.

To enhance the reactivity either of the imines or of the organometallic reagents, Lewis acids and other additives were employed. In fact, the best results were obtained by the addition of $(n\text{-}Bu)_2Cu(CN)Li_2$ to **1a**, **1c** and **1d** in the presence of $BF_3{\cdot}Et_2O$ and Me_3SiCl (entries 4,5 and 7). These conditions allowed us to prepare the chiral amines **2a,c,d** with a notable diastereoselection (90:10).[7] The low reactivity of aromatic imines with copper reagents has been already reported[3a] and appeared to be independent of the nature of the copper salt. In our case this was also confirmed (entries 3 and 6, Table 1), but high yields were observed with the more reactive H.O. allyl-cuprate (entries 12-15, yield >90%). Moreover, the collective results clearly show a significant sensitivity of the diastereoselection to the nature of both the copper reagents and imines. In fact, an inversion of the stereoselection in the reaction between the H.O. allyl cuprate and the aromatic imine **1e** was observed.[3e]

The configuration of the diastereoisomers **3a,b** and **3e** was unambiguously determined on the isolated products by comparison with authentic (*S,S*)-**3a**[6], (*R,S*)-**3b**[8] and (*S,S*)-**3e**[6] while the configuration of the *anti*-diastereoisomer **3c** was assumed on the basis of the results obtained with the imines **1a,b,e** reported above.

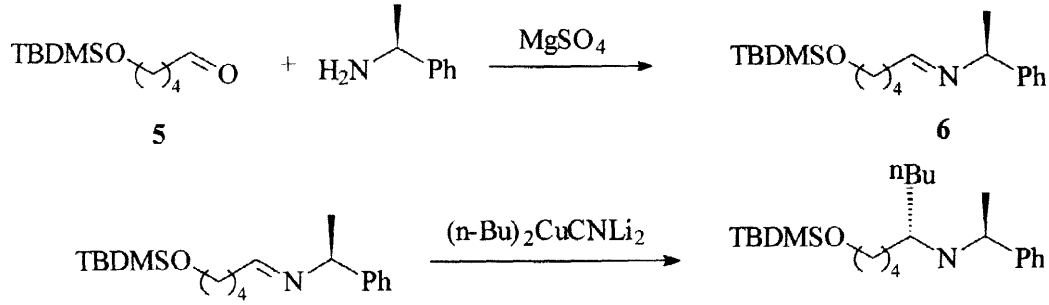
Moreover, the configuration of the prevalent *anti* diastereoisomers **2a**, **2c**, **2d** and **2e** was assigned by analogy with the retention times of the (*S,S*)-**4e,f**[3a] and (*R,S*)-**4e,f**[3a] prepared by the addition of $Me_2Cu(CN)Li_2$ to **1e** and **1f** (Scheme 2). All *anti* diastereoisomers eluted prior to the *syn* ones.



(*S*)-**1e,f** (*S,S*)-**4e,f** (*R,S*)-**4e,f**

Scheme 2

To show the high potential of our method, we have employed it to synthesize the functionalized amine **7**, key intermediate for the synthesis of biologically active products. Adding the imine **6** to $(n\text{-}Bu)_2Cu(CN)Li_2$, we obtained **7** in good yield (45%) and high diastereoisomeric ratio (90:10) (Scheme 3). The procedure was further simplifiedv by preparing the imine *in situ*, simply by stirring in a flask with a sintered glass filter the aldehyde **5**, (*S*)-phenylethylamine and anhydrous $MgSO_4$, then the mixture was directly filtered at low temperature into the flask containing the H.O. cuprate. This method avoids the isolation and storage of sensitive imines. The amine **7** could be a useful precursor of δ-amino-acids after reductive cleavage of the auxiliary, deprotection of the hydroxyl group and finally oxidation of the primary alcohol.[9]



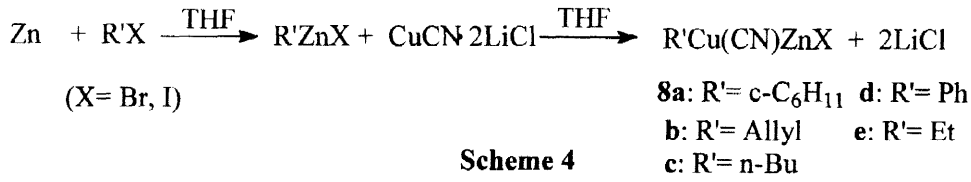
5 **6**

6 **7**

Overall yield= 45%
(*S,S*) : (*R,S*) 90:10

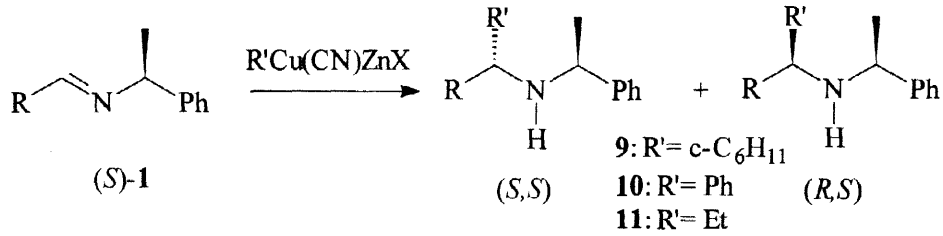
Scheme 3

The development of methods allowing the preparation of organometallic zinc-copper reagents is of special importance due to the utility of these compounds in carbon-carbon bond-forming processes.[6] One of the most widely used preparation of organozinc halides is represented by the oxidative addition of zinc metal to organic halides. Nevertheless, organozinc halides, even diorganozincs, are relatively unreactive with respect to many electrophiles,[6] thus their transmetallation to more reactive organometallics is often required. In fact, the treatment of zinc derivatives with CuCN affords a large variety of highly reactive zinc copper species. The reagents mentioned above, undergo reactions with electrophiles such as aldehydes, ketones and α,β-unsaturated compounds.[6] However, until now, the addition of zinc-copper reagents to imines was not reported. Herein we describe an effective approach to a wide range of enantiomerically enriched amines, employing these highly reactive organocopper species. The Zn-Cu reagents R'Cu(CN)ZnX (**8a-e**) were prepared according to the conditions described by Knochel[10] (Scheme 4) and employed in the addition to **1a**, **1c**, **1e** and **1g**. The results obtained are summarized in Table 2.



Scheme 4

Table 2. Addition of Zinc-Copper Reagents to the imines[a] **1a**, **1c**, **1e** and **1g**



Entry	Imine	R	R'-Cu(CN)ZnX	Amine	Yield %[b]	*S,S* / *R,S*[c]
1	**1a**	i-Pr	AllylCu(CN)ZnBr	**3a**	60	80:20
2	**1c**	n-C_7H_{15}	" "	**3c**	75	18:82
3	**1e**	Ph	" "	**3e**	51	30:70
4	**1e**	Ph	c-C_6H_{11}Cu(CN)ZnI	**9e**	60	80:20
5	**1g**	CO_2Me	" "	**9g**	43	70:30[d]
6	"	"	PhCu(CN)ZnI	**10g**	40	55:45[d]

[a] The reactions were carried out on 0.5-1 mmol of imines following the procedures reported in the experimental section. [b] The yield was evaluated by GC and GC-MS analysis. [c] The dr was determined by GC and GC-MS analysis. The dr does not change during the course of the reaction.[d] The absolute configurations were not assigned.

While aliphatic imines (**1a, 1c**) showed good reactivity with respect to allyl zinc-copper reagent **8b** (Table 2 entries 1,2), they were not so reactive with alkyl analogue **8a**. Aromatic imines instead showed notable reactivity with alkyl zinc-copper organometallics (Table 2, entry 4).[11] On the contrary, activated chiral imine **1g**[12] derived from methyl glyoxylate showed a satisfactory reactivity with alkyl and aryl zinc-copper reagents (Table 2, entries 5,6). The diastereoisomeric ratios were determined by GC-MS and the reaction showed good diastereoselectivity (up to 80:20) with the chiral imines. The configuration of the diastereoisomers (**3a,c,e** and

9e) was assigned by analogy to the chiral amines achieved by employing the corresponding H.O. cuprate reagents. In the case of **9g**, the absolute configuration of the most abundant diastereoisomer was assigned on the basis of the results obtained with the imines **1a,c,e**. The dependence of the diastereoselection on the nature of the substrate with allyl zinc-copper reagents was also observed (entry 3, *anti:syn* 30:70).

A model for the asymmetric addition of copper reagents to chiral imines activated by $BF_3{\cdot}Et_2O$ was recently proposed.[2a] The attack of the nucleophile occurs at the less hindered *Si*-face to give an intermediate d-π^* complex **A** (Figure 1). However, the possibility of a direct addition of the copper reagents to form an intermediate copper (III) **B** can be also considered. On the other hand, these models do not consider the possible isomerization of the iminic double bond when the imino group is complexed to the Lewis acid as recently reported by Jørgensen.[13]

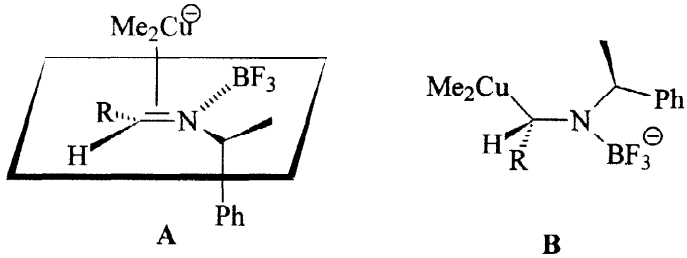


Figure 1

Conclusions

The study performed on the addition of zinc-copper reagents and H.O. cuprates to chiral imines, prepared from (*S*)-phenylethylamine and aldehydes, allows determination of conditions for significant chemo- and diastereoselectivity. This method can be used as an alternative to the use of other organometallics to add alkyl and allyl groups to a variety of chiral imines. High anti diastereoselectivity has been obtained for the first time in the addition of zinc-copper reagents to imines. Functional group tolerance is also exhibited in the process. Finally, it must be mentioned that useful compounds such as an enantiopure functionalized amine can be easily obtained in highly a diastereoselective way with our one-step strategy.

Experimental Section

General information.

IR spectra of neat compounds are expressed by wavenumber (cm^{-1}). Optical rotations were measured on a digital polarimeter in $CHCl_3$ solution in a 1-dm cell. Chemical shifts of ^{1}H-NMR spectra were taken at 300 and at 200 MHz in $CDCl_3$, and are indicated as s, singlet; t, triplet; q, quartet; m, multiplet; br, broad peak. GC-MS analyses were performed at an ionizing voltage of 70eV. Chromatographic purification was done with 240-400 mesh silica gel. Elemental analyses were carried out by using a EACE 1110 CHNS analyzer. The organometallic reactions were performed in flame-dried apparatus under an N_2 atmosphere. Solvents were distilled N_2 atmosphere prior to use: THF over Na-Ph_2CO ketyl, and CH_2Cl_2 over P_2O_5. The imines **1a-b**,[4a] **1c**,[14a] **1d-1e**,[14b] **1g**[12] and the amines **2a**,[3b] **3a**,[3c] **3b**,[8] **3e**,[6] **4d**,[2] **4f**,[2] are known compounds.

Synthesis of the imines 1a-f. General Procedure.

To a solution of (*S*)-1-Phenylethylamine (1.0 mL, 8 mmol) in freshly distilled CH_2Cl_2 (12 mL) were added, under N_2 atmosphere, the desired aldehyde (8 mmol) and anhydrous $MgSO_4$ (3.9 g, 16 mmol). The mixture was stirred at room temperature overnight. The insoluble residue was removed by filtration and the organic phase was evaporated under reduced pressure giving a crude oil. The imine obtained was used without purification. Analytical data were recorded after a carefully Kugelrohr distillation.

(*S*)-N-Isopropylmethylidene-1-phenylethylamine 1a: (pale yellow oil), $[\alpha]_D^{25}$ = -78 (c 1.5, $CHCl_3$), bp 115-120 °C, 18 Torr (lit.[4a] 80 °C, 5 Torr). CG-MS m/z (relative intensity) 105 (100), 106(14), 77 (14), 79 (11), 103 (9), 147 (7), 104 (6); 132 (4). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.60 (1H, t, *J* 5.5 Hz, NH), 7.38-7.20 (5H, m, Ph), 4.26 (q, 1H, *J* 6.8 Hz, PhCHN=CH), 2.52 (1H, sept, *J* 7.5 Hz, CHCH=N), 1.55 (3H, d, *J* 6.8 Hz, CHMe), 1.19 (6H, t, *J* 7.5 Hz, 2 Me). IR (neat) 1665 cm^{-1}. Anal. Calcd for $C_{12}H_{17}N$: C, 82.23; H, 9.79; N, 7.98. Found: C, 82.10; H, 9.71; N, 8.19.

Addition of $(Allyl)_2Cu(CN)Li_2$ to chiral imines. General procedure.
In a flask was placed CuCN (1.6 mmol) and THF (1.5 mL). The resulting slurry was cooled to -78°C, then 3.2 mmol of MeLi (1.6 M, Et_2O) were added dropwise and the mixture warmed to 0°C and stirred until homogeneous. The solution was cooled to -78°C then allyltributyltin (1.6 mmol) was added. The solution was warmed to 0°C and stirred for 30 min then cooled to -78°C. The imine (**1a-c, 1e**) was added, followed by $BF_3{\cdot}Et_2O$ (1.6 mmol). The reaction mixture was allowed to warm to room temperature during 24 hrs, then quenched with an aqueous solution of NH_4Cl (5 mL). The organic phase was separated and the aqueous phase extracted with Et_2O (3 X 5 mL). The combined organic phases were dried, concentrated under reduced pressure and purified by chromatography on silica gel.

3c. (orange oil). R_f (20% Et_2O/Cycloehxane). GC-MS m/z (relative intensity): 114 (100), 218 (76), 106 (74), 79 (10), 70 (7). ^{1}H-NMR (200 MHz, $CDCl_3$) (most abundant diastereoisomer) δ 7.40-7.15 (5H, m, Ph), 5.86-5.70 (1H, m, C<u>H</u>=CH_2), 5.15-4.99 (2H, m, CH=C<u>H</u>$_2$), 3.88 (1H, q, *J* 6.5 Hz, PhC<u>H</u>NH), 2.44-2.25 (1H, m, C<u>H</u>Me), 1.32 (3H, d, *J* 6.5 Hz, CH<u>Me</u>), 2.20 (2H, m, CH_2CH=CH_2), 1.31-1.10 (12H, m, C<u>H</u>$_2$), 0.86 (3H, t, *J* 6.0 Hz, Me), [*syn* diastereoisomer : δ 4.10 (1H, q, *J* 6.3 Hz, PhC<u>H</u>NH)]; ^{13}C-NMR (50 MHz, $CDCl_3$) (most abundant diastereoisomer): δ 146.3, 128.3, 126.8, 126.5, 117.0, 109.1, 54.9, 53.6, 37.6, 34.7, 31.8, 29.3, 27.3, 25.3, 24.6, 22.6, 14.1; [*syn* diastereoisomer : δ 53.4 (NH<u>C</u>HCH$_2$)]. IR (neat) 3385, 1639 cm^{-1}. Anal. Calcd for $C_{19}H_{31}N$: C, 83.45; H, 11.43; N, 5.12. Found: C, 83.37; H, 11.33; N, 5.19.

Preparation of aldehyde 5.[15]
To a solution of 1,4-butanediol (20 mmol, 1.8 mL) in THF (25 mL) was added NaH (20 mmol, 0.48 g) and the resulting mixture was stirred at room temperature for 24 hrs. *t*-BuSiMe_2Cl (20 mmol, 3 g) was added and the resulting mixture stirred for 30 min, then quenched with water and diluted with Et_2O (7 mL). The organic phase was separated, and the aqueous phase extracted with Et_2O (3 X 15 mL). The combined organic phases were dried over sodium sulphate, concentrated under reduced pressure and purified by flash chromatography (60% Et_2O/Cyclohexane) (yield 46%). The protected 4-*O*-silyl-butan-1-ol was oxidized under Swern conditions: to a solution of $(COCl)_2$ (3.45 mmol, 0.3 mL) in CH_2Cl_2 (12 mL) at -60°C was added DMSO (7.2 mmol, 0.51 mL) and the mixture was stirred for 10 min. The protected 4-*O*-silyl-butan-1-ol (3 mmol, 0.611 g) was dissolved in CH_2Cl_2 (2 mL) and added to the reaction mixture dropwise at -60°C. The resulting mixture was stirred 10 min at -60°C then Et_3N (2.1 mL) was added and the reaction mixture was warmed to room temperature and stirred 15 min. The reaction was quenched with water (10 mL). The organic phase was separated and the aqueous phase extracted with CH_2Cl_2 (3 X 10 mL). The combined organic phases were dried over sodium sulphate and evaporated under reduced pressure to leave a oil, purified by flash chromatography (50% Et_2O/Cyclohexane).
Yield 50%. (pale yellow oil). GC-MS m/z (relative intensity) 105 (100), 147 (31), 77 (18), 104 (17), 79 (15), 132 (12), 188 (5); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.26 (1H, s, C<u>H</u>O), 3.62 (2H, t, *J* 6.4 Hz, C<u>H</u>$_2$OSi), 2.52 (2H, t, *J* 6.4 Hz, C<u>H</u>$_2$CHO), 1.92-1.80 (4H, m, CH_2), 0.88 (9H, s, C<u>Me</u>$_3$), 0.28 (6H, s, Si<u>Me</u>$_2$). IR (neat) 1730 cm^{-1}. Anal. Calcd for $C_{11}H_{24}O_2Si$: C, 61.06; H, 11.18; N, 11.18. Found: C, 60.98; H, 11.08; N, 11.02.

Addition of $(n\text{-}Bu)_2Cu(CN)Li_2$ to 6: synthesis of 7.
The imine **6** was prepared *in situ* in THF (2 mL) by stirring **5** (0.2 g, 1 mmol) with (*S*)-phenylethylamine (0.127 mL, 1 mmol) in the presence of anhydrous $MgSO_4$ (0.6 g). The progress of the reaction was monitored by GC-MS. In another flask CuCN (1.6 mmol) was gently flamed under vacuum, followed by flushing with nitrogen. THF was added (1.5 mL) and the resulting slurry was cooled to -78°C. BuLi (0.150 mL, 2.72 mmol) was added dropwise and the mixture warmed to 0°C and stirred until a homogeneous solution was obtained. The mixture of H.O. n-Butyl cuprate was cooled to -78°C then the slurry containing the imine **6** was filtered into the H.O. cuprate, then $BF_3{\cdot}Et_2O$ (0.190 mL, 1.5 mmol) and Me_3SiCl (0.19 mL, 1.5 mmol) were added. The reaction mixture was allowed to warm to room temperature during 24 hrs, then quenched with aqueous saturated NH_4Cl (5 mL). The organic phase was separated and the aqueous phase extracted with Et_2O (3 X 5 mL). The combined organic phases were dried, concentrated under reduced pressure and purified by chromatography on silica. R_f (40% Et_2O/Cycloehxane). Overall yield 45%, maroon oil. GC-MS m/z (relative intensity) 105 (100), 190 (50), 70 (50), 306 (38), 207 (18); ^{1}H-NMR (200 MHz, $CDCl_3$) (most abundant diastereoisomer) δ 7.39-7.18 (5H, m, Ph), 3.86 (1H, q, *J* 6.6 Hz, PhC<u>H</u>NH), 3.60 (2H, m, C<u>H</u>$_2$OSi), 2.36 (1H, m, C<u>H</u>NH), 1.32 (3H, d, *J* 6.6 Hz, CH<u>Me</u>), 1.57-1.19 (12H, m, CH_2), 0.91 (9H, s, C<u>Me</u>$_3$), 0.89 (3H, s, CH_2<u>Me</u>), 0.27 (6H, s, Si<u>Me</u>$_2$); ^{13}C-NMR (75 MHz, $CDCl_3$) (most abundant diastereoisomer): δ 146.3, 128.2, 127.5, 126.6, 63.5, 54.9, 53.7, 34.5, 30.9, 29.5, 28.4, 28.0, 26.0, 24.9, 22.9, 18.4, 14.1, -5.2. Anal. Calcd for $C_{23}H_{43}NOSi$: C, 73.14; H, 11.48; N, 3.71. Found: C, 73.05; H, 11.38; N, 3.66.

Preparation of $c\text{-}C_6H_{11}Cu(CN)ZnI$ (8a).[16] General procedure for the addition of 8a to 1e and 1g.
A flask under nitrogen was charged with cut zinc (1.8 mmol). A few drops of dibromoethane were added followed by THF (1 mL). The suspension was heated with a heatgun until boiling of the solvent was observed. The zinc suspension was stirred for a few minutes and the procedure was repeated three times. A few drops of Me_3SiCl were added to the mixture. The cut zinc turned grey and after 10 min stirring cyclohexyl iodide (0.194 mL, 1.5 mmol) was added. The mixture was stirred at 40°C and the completion of the reaction was checked by GC. Another flask was charged with lithium chloride (0.127 g, 3 mmol) and the lithium chloride was heated at 130°C under vacuum (0.2 mmHg) for 2 hrs. The dried lithium chloride was cooled to room temperature then CuCN (0.154 g, 1.5 mmol) and dry THF (2 mL) were added. The resulting solution was cooled to -40°C and the zinc reagent was transferred by cannula to the $CuCN(LiCl)_2$ complex. The mixture was then warmed to 0°C and stirred for 15 min. The resulting grey white solution was cooled to -78°C then the imine (0.8 mmol) and $BF_3{\cdot}Et_2O$ (0.15 mL, 1.2 mmol) were added and the reaction was allowed to warm to room temperature during 24 hrs. After the usual work-up the reaction mixture was analyzed by GC-MS (see Table 2).

(*S*)-N-Ethylmethylidene-1-phenylethylamine 1b: (colourless oil), $[\alpha]_D^{25}$ = -106 (c 1.08, $CHCl_3$), bp 82-87 °C, 12 Torr (lit.[4a] 64 °C, 3.5 Torr). CG-MS m/z (relative intensity) 105 (100), 77 (15), 106 (14), 91 (7), 146 (5), 161 (4), 51. ^{1}H-NMR (200 MHz, $CDCl_3$) δ 7.91 (1H, s, NH), 7.42-7.20 (5H, m, Ph), 4.40 (1H, q, *J* 6.6 Hz, PhCHN=CH), 2.43-2.26 (2H, m, CH_2), 1.53 (3H, d, *J* 6.6 Hz, CHMe), 1.06 (3H, t, *J* 7.4 Hz, CH_2Me). IR (neat) 1665 cm^{-1}. Anal. Calcd for $C_{11}H_{15}N$: C, 81.94; H, 9.38; N, 8.64. Found: C, 82.16; H, 9.70; N, 8.14.

(*S*)-N-Heptylmethylidene-1-phenylethylamine 1c: (pale yellow oil), $[\alpha]_D^{25}$ = -52.4 (c 2.0, $CHCl_3$), bp 133-138 °C, 1.5 Torr. GC-MS m/z (relative intensity) 147 (100), 105 (65), 132 (38), 77 (22), 202 (11). ^{1}H-NMR (200 MHz, $CDCl_3$) δ 7.74 (1H, t, *J* 5.5 Hz, NH), 7.40-7.20 (5H, m, Ph), 4.30 (1H, q, *J* 6.6 Hz, PhCHN=CH), 1.55 (3H, d, *J* 6.6 Hz, CHMe), 1.48-1.20 (12H, m, CH_2), 0.90 (3H, t, *J* 6.2 Hz, CH_2Me). IR (neat) 1675 cm^{-1}. Anal. Calcd for $C_{16}H_{25}N$: C, 83.06; H, 10.89; N, 6.05. Found: C, 82.98; H, 10.80; N, 6.22.

(*S*)-N-Cyclohexylmethylidene-1-phenylethylamine 1d: (pale yellow oil), $[\alpha]_D^{25}$ = -55 (c 1.5, $CHCl_3$), bp 132-140 °C, 4 Torr (lit.[14b] 130 °C, 4 Torr). CG-MS m/z (relative intensity) 105 (100), 147 (43), 77 (17), 79 (16), 56 (15), 104 (13), 200 (10). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.59 (1H, t, *J* 5.5 Hz, NH), 7.40-7.20 (5H, m, Ph), 4.26 (1H, q, *J* 6.7 Hz, PhCHN=CH), 2.25 (1H, m, CHCH=N), 1.47 (3H, d, *J* 6.7 Hz, CHMe), 1.95-1.60 (6H, m, CH_2), 1.45-1.10 (4H, m, CH_2). IR (neat) 1680 cm^{-1}. Anal. Calcd for $C_{15}H_{21}N$: C, 83.67; H, 9.83; N, 6.50. Found: C, 83.52; H, 9.74; N, 6.74.

(*S*)-N-Phenylmethylidene-1-phenylethylamine 1e: (yellowish oil), $[\alpha]_D^{25}$ = +74 (c 0.8, $CHCl_3$), bp 128-135 °C, 5 Torr (lit.[14b] 106 °C, 0.1 Torr). CG-MS m/z (relative intensity)105 (100), 209 (20), 77 (20), 79 (11), 51(10), 147 (7); 167 (5); 165 (5). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.30 (1H, s, NH), 7.72 (2H, m, Ph), 7.41-7.10 (8H, m, Ph), 4.49 (1H, q, *J* 6.7 Hz, PhCHN=CH), 1.53 (3H, d, *J* 6.7 Hz, CHMe). IR (neat) 1630 cm^{-1}. Anal. Calcd for $C_{15}H_{15}N$: C, 86.08; H, 7.22; N, 6.70. Found: C, 86.01; H, 7.16; N, 6.83.

(*S*)-N-Pentylmethylidene-1-phenylethylamine 1f: (pale yellow oil), $[\alpha]_D^{25}$ = -55 (c 1.5, $CHCl_3$), bp 120-125 °C, 4 Torr. CG-MS m/z (relative intensity) 105 (100), 147 (31), 77 (18), 104 (17), 79 (15), 132 (12), 188 (5). ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.70 (1H, t, *J* 5.5 Hz, NH), 7.40-7.20 (5H, m, Ph), 4.24 (1H, q, *J* 6.6 Hz, PhCHN=CH), 2.23 (2H, m, CH_2CH=N), 1.47 (3H, d, *J* 6.6 Hz, CHMe), 1.55-1.20 (6H, m, CH_2), 0.85 (3H, t, *J* 6.2 Hz, CH_2Me). IR (neat) 1670 cm^{-1}. Anal. Calcd for $C_{14}H_{21}N$: C, 82.70; H, 10.41; N, 6.89. Found: C, 82.59; H, 10.32; N, 7.09.

Addition of $(n\text{-}Bu)_2Cu(CN)Li_2$ to 1a,1c-d. General procedure. In a flask was placed CuCN (0.269 g, 3 mmol) and THF (7 mL). The suspension was cooled to -78°C under nitrogen, then n-BuLi (3.75 mL, 6 mmol) was added. The mixture was warmed to 0°C, stirred 5 min until a green solution was obtained and then cooled to -78°C. The chiral imine (**1a**, **1c-d**) (1.5 mmol) dissolved in THF (2 mL) was added dropwise to the H.O. cuprate at -78°C, then BF_3-Et_2O (0.225 mL, 2.25 mmol) and Me_3SiCl (0.283, 2.25 mmol) were added. The solution became orange and was maintained at -78°C for 1-2 hrs, then allowed to warm to room temperature overnight. The organometallic reagent gradually decomposed giving a black colour. The mixture was quenched with an aqueous solution of NH_4OH (5 mL.). The organic phase was separated and the aqueous phase extracted with Et_2O (3 X 5 ml). Finally, the organic phases were combined, dried over anhydrous Na_2SO_4, concentrated, chromatographed and analyzed by GC or GC- MS.

2a. Yield 50% (pale yellow oil). R_f (30% Et_2O/Cycloehxane). GC-MS m/z (relative intensity) 105 (100), 190 (45), 77 (88), 72 (14). ^{1}H-NMR (200 MHz, $CDCl_3$) (most abundant diastereoisomer): δ 7.39-7.18 (5H, m, Ph), 3.87 (1H, q, *J* 6.6 Hz, PhCHNH), 2.15 (1H, m, CHNH), 1.98-1.81 (1H, m, $CHMe_2$), 1.08 (3H, d, *J* 6.9 Hz, CHMe), 1.38-1.06 (6H, m, CH_2), 1.08 (3H, d, *J* 6.9 Hz, CHMe), 0.91 (3H, t, *J* 6.8 Hz, Me), 0.86 (3H, d, *J* 6.9 Hz, Me), 0.79 (3H, d, *J* 6.9 Hz, Me); ^{13}C-NMR (50 MHz, $CDCl_3$) (most abundant diastereoisomer): δ 146.6, 128.3, 126.9, 126.7, 59.1, 55.3, 29.9, 29.1, 28.8, 24.6, 23.0, 19.1, 17.0, 14.2. IR (neat) 3325, 3072, 3037, 1489 cm^{-1}. Anal. Calcd for $C_{16}H_{27}N$: C, 82.34; H, 11.66; N. 6.00. Found: C, 82.21; H, 11.56; N, 6.10.

2c. Yield 60% (orange oil). R_f (20% Et_2O/Cycloehxane). GC-MS m/z (relative intensity) 105 (100), 190 (45), 77 (88), 72 (14); ^{1}H-NMR (200 MHz, $CDCl_3$) (most abundant diastereoisomer): δ 7.42-7.18 (5H, m, Ph), 3.88 (1H, q, *J* 6.6 Hz, PhCHNH), 2.29 (1H, m, CHNH), 1.35 (3H, d, *J* 6.6 Hz, CHMe), 1.45-1.01 (18H, m, CH_2), 0.95 (3H, t, *J* 7.0 Hz, Me), 0.91 (3H, t, *J* 6.9 Hz, Me); ^{13}C-NMR (50 MHz, $CDCl_3$) (most abundant diastereoisomer): δ 146.3, 128.2, 127.0, 126.6, 54.9, 54.0, 34.4, 33.8, 31.9, 29.4, 28.0, 27.4, 25.9, 24.8, 23.0, 22.8, 15.2, 14.1. IR (neat) 3325, 3072, 3038, 1488 cm^{-1}. Anal. Calcd for $C_{20}H_{35}N$: C, 82.98; H, 12.19; N, 4.83. Found: C, 82.91; H, 12.09; N. 5.00.

2d. Yield 57% (pale yellow oil). R_f (20% Et_2O/Cycloehxane). GC-MS m/z (relative intensity) 105 (100), 88 (95), 190 (70), 77 (19), 55 (19), 216 (11), ^{1}H-NMR (200 MHz, $CDCl_3$) (most abundant diastereoisomer): δ 7.41-7.13 (5 H, m, Ph), 3.84 (1H, q, *J* 6.6 Hz, PhCHNH), 2.15-2.05 (1H, m, CHNH), 1.28 (3H, d, *J* 6.6 Hz, CHMe), 1.87-1.08 (17H, m), 0.65 (3H, t, *J* 6.9 Hz, Me), [*syn* diastereoisomer : δ 4.08 (1H, q, *J* 6.5 Hz, PhCHNH)]; ^{13}C-NMR (50 MHz, $CDCl_3$) (most abundant diastereoisomer): δ 146.6, 128.1, 126.8, 126.6, 58.8, 55.4, 40.2, 30.9, 29.6, 28.6, 27.9, 26.9, 26.8, 26.7, 24.7, 22.8, 14.1. IR (neat) 2924, 2854, 1448 cm^{-1}. Anal. Calcd for $C_{19}H_{31}N$: C, 83.45; H, 11.43; N, 5.12. Found: C, 83.37; H, 11.33; N, 5.21.

Preparation of AllylCu(CN)ZnBr (8b). General procedure for the addition of 8b to 1a, 1c and 1e.

The allyl zinc reagent was prepared by stirring allylbromide (0.173 mL, 2 mmol) with cut zinc (0.157 g, 2 mmol) in THF (2 mL). Another flask was charged with lithium chloride (4 mmol) and it was heated at 130°C under vacuum (0.2 mmHg) for 2 hrs. The dried lithium chloride was cooled to room temperature then CuCN (0.179 g, 2 mmol) and dry THF (2 mL) were added. The resulting solution was cooled to -40°C and the zinc reagent was transferred by cannula to the $CuCN(LiCl)_2$ complex. The resulting mixture was warmed to 0°C and stirred for 15 min. The green solution was cooled to -78°C then the imine (**1a**, **1c**, **1e**) (0.8 mmol) and $BF_3{\cdot}Et_2O$ (0.2 mL, 1.6 mmol) were added and the reaction was allowed to warm to room temperature during 24 hrs. After the usual work-up the reaction mixture was analyzed by GC-MS (see Table 2).

9g. Yield 43%. (pale yellow oil). GC-MS m/z (relative intensity) 105 (100), 216 (56), 112 (60), 192 (15), 260 (12), ^{1}H-NMR (300 MHz, $CDCl_3$) (most abundant diastereoisomer): δ 7.26-7.17 (5H, m, Ph), 3.88 (1H, q, *J* 6.0 Hz, NHC<u>H</u>CO_2Me), 3.80 (1H, q, *J* 6.0 Hz, PhC<u>H</u>NH), 3.52 (3H, s, <u>Me</u>O), 1.29 (3H, d, *J* 6.0 Hz, CH<u>Me</u>), 1.85-1.58 (11H, m, Cy).Anal. Calcd for $C_{17}H_{25}NO_2$: C, 74.14; H, 9.15; N, 5.09. Found: C, 74.07; H, 9.07; N, 5.01.

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