Addition of Organozincate Reagents to Imines Derived from (*S*)-1-Phenylethylamine and Ethyl (*S*)-Valinate—Synthesis of (*S*)-1-(2-Pyridyl)alkylamines

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Abstract: Triorganozincates were added to aliphatic aldimines derived from (*S*)-1-phenylethylamine and (*S*)-valine esters in the presence of boron trifluoride to give secondary amines with low diastereoselectivies. From mixed zincates, most alkyl groups (methyl, ethyl, 1-heptynyl, but not *tert*-butyl) could be transferred. No addition to benzaldimines was observed, but the imines prepared from 2-pyridinecarboxaldehyde did not require activation by BF_3 and underwent selective group transfer from mixed zincates at −78 °C. Excellent diastereoselectivities were observed in the reactions of the 2-pyridine imine derived from ethyl (*S*)-valinate with mixed zincates, in which the methyl group was used as nontransferable ligand, allowing the transfer of alkyl and vinyl groups with excellent to complete selectivity. However, dimethyl(aryl)- and dimethyl(1-heptynyl)zincates did not react. (*S*)-1-(2-Pyridyl)alkylamines were prepared with high optical purity by subsequent removal of the chiral auxiliary.

Keywords
amines · asymmetric synthesis · C–C coupling · chiral auxiliaries · imines · zinc

Introduction

We previously reported that aromatic and aliphatic imines derived from (*S*)-1-phenylethylamine, such as **1** and **2** (Figure 1), react with dimethylcuprate–boron trifluoride reagents to give (*S*,*S*) secondary amines with good to excellent diastereoselectivities, superior to that obtained with methyllithium.[1] On the other hand, the 2-pyridine imine **3** reacted sluggishly with dimethylcuprate or dimethylcuprate–BF_3 reagents, but rapidly with alkyllithiums and benzylmagnesium chloride, with the opposite sense of asymmetric induction.[1b] Since we also demonstrated that (*S*)-valine esters are excellent chiral auxiliaries for the preparation of homoallylic amines through the addition of allylmetal reagents to the imines **4**, **5a** and **6a**,[2] we attempted the addition of dimethylcuprate–BF_3 reagents to the same imines, but observed no reaction or obtained complex mixtures of unidentified products with low yields. We now wish to test the reactivities and the diastereoselectivities of triorganozincates towards the same imines,[3] alone or in the presence of a Lewis acid, since it is known that these reagents add to α,β-enones,[4] similarly to cuprates and organocopper–BF_3 reagents, although following a different mechanism.

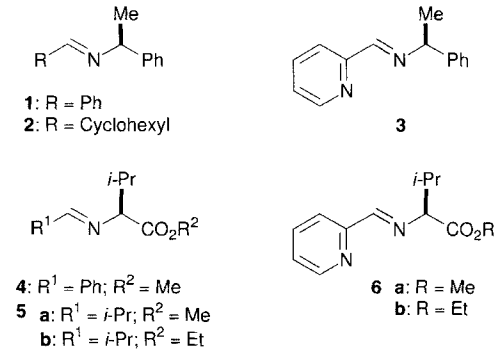

Figure 1. Homochiral imines used in reactions with triorganozincates.

Results and Discussion

We found that the zincate $Et_2MeZnLi$, prepared by the addition of MeLi to Et_2Zn,[5] was unreactive towards the benzaldimines **1** and **4**, even in the presence of one equivalent BF_3; however, it reacted with **2** in the presence of BF_3 transferring both alkyl groups to give **7** and **8** with low diasteroselectivities (Scheme 1). Similarly, the BF_3-promoted addition of lithium diethyl(1-heptynyl)zincate to **2** gave a mixture of diastereomeric products **8** and **9**. The known compound **7** was unambiguously identified by GC-MS analysis, which also allowed the diastereomeric ratio (d.r.) to be determined, as well as the configuration of the diastereomers, with (*S*,*S*)-**7** being eluted first.[1b] The structure and configuration of **8** and **9** were then assigned from the mass

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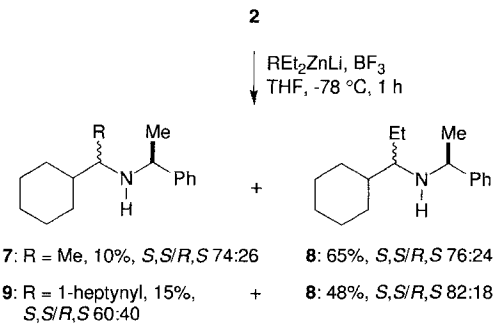
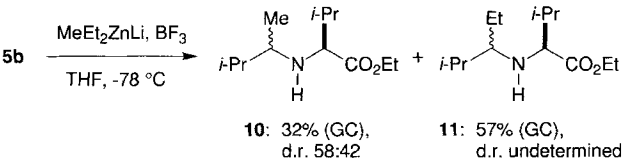


Scheme 1. BF_3-promoted addition of mixed triorganozincates to the imine **2**.

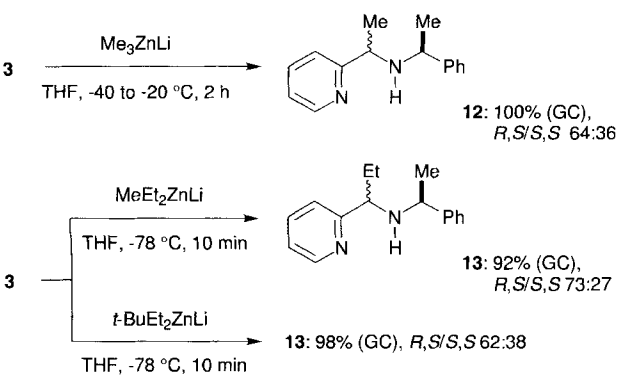
spectral fragmentation patterns and GC retention times, by analogy to **7**.

Similarly, the reaction of the valine-derived aliphatic imine **5b** with $Et_2MeZnLi$ in the presence of BF_3 afforded a mixture of **10** and **11** by methyl and ethyl transfer, respectively, as determined by GC-MS analysis (Scheme 2). The d.r. of **10** could be evaluated by GC-MS analysis and was very low, whereas the diastereomers of **11** were not distinguished by GC-MS or ^1H NMR analysis, owing to the very similar substituents at the newly formed stereocentre.



Scheme 2. BF_3-Promoted addition of a mixed triorganozincate to the imine **5b**.

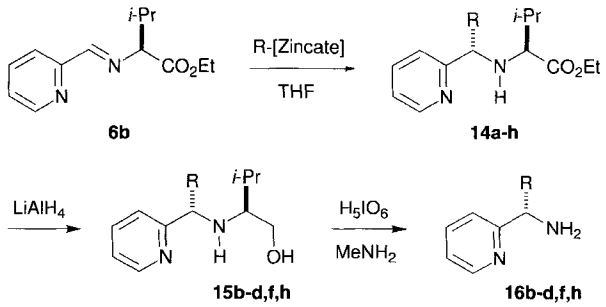
The imine **3** derived from 2-pyridinecarboxaldehyde was quantitatively converted to the amine **12** by treatment with Me_3ZnLi in the absence of BF_3 at -40 to $-20\,^\circ C$ (Scheme 3). The mixed zincates $Et_2MeZnLi$ and $tBuEt_2ZnLi$ reacted rapidly with **3** even at $-78\,^\circ C$ to give **13** by exclusive ethyl transfer.[6] This selectivity is in marked contrast with the BF_3-promoted reaction of $Et_2MeZnLi$ with **1**, where both methyl and ethyl group were transferred (Scheme 1). Moreover, the exclusive formation of **13** by using $Et_2MeZnLi$, prepared from Et_2Zn and MeLi, demonstrated that no product was formed by the addition of free MeLi to **3**. Unfortunately, only a moderate excess of



Scheme 3. Addition of triorganozincates to the imine **3**.

the (*R*,*S*) diastereomers was obtained, and the the d.r. was only slightly affected by the steric properties of the nontransferred alkyl group (Me, *t*Bu). Owing to the low degree of stereocontrol, the amines **12** and **13** were not isolated. The configuration of the major diastereomer in **12** was readily determined as being (*R*,*S*) by GC-MS analysis, by comparison of the spectrum of (*R*,*S*)-**12** previously prepared from **3** by addition of CH_3Li.[1b] Amine **13** was identified exclusively on the basis of the mass spectral fragmentation pattern, and its configuration was assigned by analogy to **12**.

As expected, the valine-derived imine **6b** reacted with triorganozincates in the absence of BF_3 to give the amines **14** with moderate to excellent diastereoselectivity (Scheme 4, Table 1). The zincate prepared from methylmagnesium chloride and Me_2Zn reacted only partially at $-78\,^\circ C$ to give **14a**, despite the fact that two equivalents of the reagent were employed (entry 1). By-products were consistently produced by raising the temperature. The corresponding lithium zincate was unreactive at $-78\,^\circ C$ and gave some **14a** by allowing the reaction mixture to reach room temperature, but the d.r. was only moderate



a: R = Me **e**: R = *t*-Bu
b: R = Et **f**: R = Bn
c: R = *n*-Bu **g**: R = Allyl
d: R = *i*-Pr **h**: R = Vinyl

Scheme 4. Addition of triorganozincates to the imine **6b**. Synthesis of (*S*)-1-(2-pyridyl)alkylamines **16**.

Table 1. Addition of triorganozincate reagents to the imine **6b** [a].

Entry	R-Zincate (equiv)	*T* (°C)	Amine	Yield (%) [b]	(*S*,*S*):(*R*,*S*) [c]
1	$Me_3ZnMgCl$ (2)	−78	**14a**	(50)	92:8
2	Me_3ZnLi (2)	−78 to 20 [d]	**14a**	(50) [e]	77:23
3	$Et_2MeZnMgCl$ (1.1)	−78	**14b**	90	96:4
4	$tBuEt_2ZnMgCl$ (1.1)	−78	**14b**	73 [e]	82:18
5	$nBuMe_2ZnMgCl$ (1.1)	−78	**14c**	86	94:6
6	$nBuMe_2ZnLi$ (1.5)	−78	**14c**	(10)	95:5
7	$iPrMe_2ZnMgCl$ (1.1)	−78	**14d**	90	95:5
8	$tBuMe_2ZnMgCl$ (1.1)	−78	**14e**	(80) [e]	57:43
9	$tBuMe_2ZnLi$ (1.5)	−78	**14e**	(45)	74:26
10	$tBuMe_2ZnLi$ (1.5)	0	**14e**	(75) [e]	75:25
11	$BnMe_2ZnMgCl$ (1.1)	−78	**14f**	88	88:12
12	$allylMe_2ZnMgBr$ (1.1)	−78	**14g**	91	73:27
13	$vinylMe_2ZnMgBr$ (1.1)	−78	**14h**	95	>99:1 [f]

[a] The reactions were performed on 5 mmol of **6b** and quenched after 1 h, although the reaction of the magnesium zincates were generally complete after a few minutes. [b] Yield of product purified by column chromatography on SiO_2; the number in parentheses is the approximate conversion (%) of **6b** to **14**, evaluated by GC-MS analysis; the presence of unreacted **6b** and by-products made product purification difficult. [c] Determined by GC-MS and/or ^1H NMR analysis of the crude reaction product. [d] The temperature was allowed to rise slowly overnight before quenching. [e] Higher-boiling by-products were formed. [f] The minor diastereomer was not detected.

(entry 2). In both cases, owing to the low conversion and the presence of by-products, we could not isolate pure **14a**.

The mixed zincates RMe_2ZnLi or RMe_2ZnMgX, prepared by addition of RLi or RMgX to Me_2Zn, reacted even at the low temperature and the zincates derived from Grignard reagents were more effective than the corresponding lithium zincates (compare entries 1/2, 5/6 and 8/9 in Table 1). Careful GC-MS analyses of the reaction mixtures allowed us to establish that only the R group was transferred from allyl and benzyl zincates (entries 11 and 12); in the case of alkylzincates (R = Et, *n*Bu, *i*Pr, *t*Bu) transfer of R gave the major products, but trace amounts of **14a** (0.5–2%) were produced by methyl transfer. The zincates prepared by adding PhMgBr, 2-furyllithium and 1-heptynyllithium to Me_2Zn proved to be almost unreactive.

The effect of the Li or MgX counterion on the diastereoselectivity was not easily established, because the Grignard- and alkyllithium-derived zincates reacted at different temperatures; however, in the transfer of *t*Bu from the mixed zincates at −78 °C, a better stereocontrol (despite the low yields) was provided by the lithium zincate (entries 8–10). The d.r. was moderately affected by the nature of the R group and decreased in the order vinyl > Et, *i*Pr, *n*Bu > Me > Bn > *t*Bu, allyl. The transfer of the vinyl group was particularly selective (entry 13); only one diastereomer of **13h** was detected by GC-MS and ^{1}H NMR analysis of the crude reaction product. Apart from benzyl, *tert*-butyl and allyl, all the alkyl groups were transferred with similarly high diastereoselectivities. The use of allyl-$Me_2ZnMgCl$ (entry 12) gave no improvement in stereocontrol with respect to allylzinc bromide;[1b] moreover, lower ratios were obtained by using allyl$Et_2ZnMgCl$ and $(allyl)_3ZnMgCl$–2 MgBrCl, prepared from $ZnBr_2$. It should be noted that the use of *t*Bu, rather than Me, as the nontransferable ligand decreased the stereocontrol in the transfer of Et (compare entries 3/4).

The major diastereomer of the allylated product **14g** was assigned the (*S*,*S*) configuration by GC-MS analysis of the crude reaction mixture, based on our previous report.[2b] Since the major diastereomer was eluted first in all the reaction mixtures, the configuration was assumed to be the same for the other new compounds **14**. The ^{1}H NMR spectra of the crude diastereomeric mixtures were also consistent with the assigned configurations, since the absorptions of the C*H*CO_2Et protons in the major diastereomer always occurred at lower frequency with respect to the minor diastereomer, as observed with the α-aryl-substituted homoallylic amines derived from methyl (*S*)-valinate.[2] In the case of the allylic amine **14h**, the minor diastereomer was not detected, but the isolated diastereomer is expected to have the (*S*,*S*) configuration, assuming that the mechanism and the sense of asymmetric induction is the same for all the zincates.

The removal of the auxiliary group of **14b–d,f,h** was carried out following the reported procedure[2] (Scheme 4). The reduction with $LiAlH_4$ in THF in the first step occurred smoothly, when carried out at low temperature (≤ 0 °C). Provided that the intermediate β-amino alcohols **15b–d,f,h** were first purified by column chromatography (69–80% yield), the subsequent oxidative cleavage with H_5IO_6–$MeNH_2$ (solvent of choice: MeOH/THF/H_2O) afforded the optically active primary amines **16b–d,f,h** in over 95% yield and in high purity, so that no further purification was required. Hence, we demonstrated the efficiency of the two-step route to the optically active amines **16** and, at the same time, unambiguously determined the (*S*) configuration of the newly formed stereocentre in **14d,f** by comparison with the optical properties of **16d,f** with those of the authentic (*R*) enantiomers.[7] No attempt was made to prepare the compounds **16a**,[7,8] **16e** or **16g**, because of the low yield and/or diastereomeric purity of their precursors **14a,e,g**; moreover, (*S*)- and (*R*)-**16g** are more conveniently available from **6a** with the appropriate choice of the allylmetal reagent.[2b]

Our results suggest that the reaction takes place through the preliminary formation of a complex between the zincate and the imine **6b**, which is itself involved in *N*,*N*-bidentate or *N*,*N*,*O*-tridentate chelation to the Li or MgX counterion of the zincate. Because magnesium prefers tetracoordination, we assume that here the ester group will not participate in the chelation, as shown in the complex **17** (Figure 2). The auxiliary group, although free to rotate along the N–C* bond, probably adopts an eclipsed orientation of the H–C* and H–C=N hydrogens, as we previously observed in the imine **6a** and in its complexes with $ZnBr_2$ and $SnCl_2$.[2b] Consequently, the magnesium stereocentre in **17** should preferentially form with the larger substituent (RR′ZnMe) *anti* to the *i*Pr group of the auxiliary. Similarly, the lithium zincates can form a bidentate complex analogous to **17**, where lithium is presumably coordinated by a THF molecule. The alternative *N*,*N*,*O*-tridentate complex **18** should be destabilized by steric interactions of the *i*Pr substituent in the fused bicyclic structure.

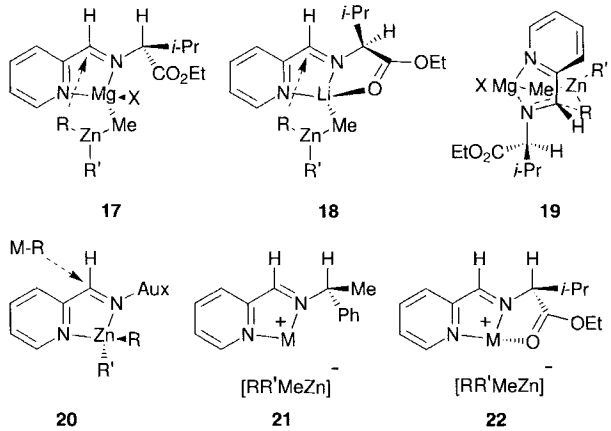


Figure 2. Intermediates and transition states in the reactions of 2-pyridine imines with triorganozincates.

In the complexes derived from mixed methyl–alkyl zincates, it is most probable that the methyl group will link the two metal centres, owing to the superior "bridging" ability of methyl compared to homologous alkyl groups in associated metal alkyls. Then, the carbon–carbon bond-forming step would occur by attack of the R group bound to zinc at the *Si* face of the azomethine function through the six-membered cyclic transition state **19** (Figure 2). Accordingly, the diastereoselectivity is affected by the size of R′, which occupies a pseudoaxial position in the chair transition state, given the sp^2 hybridization for zinc in triorganozincates.[10] Indeed, the d.r. decreased on going from $Me_2RZnMgCl$ (R′ = Me in **19**) and $MeEt_2ZnMgCl$ (R′ = Et) to *t*Bu$Et_2ZnMgCl$ (R′ = *t*Bu). The serious steric interaction of

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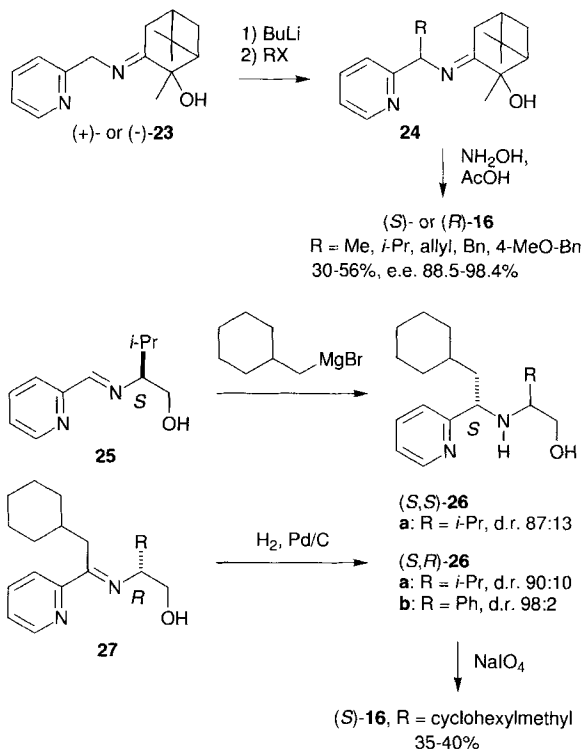
*t*Bu (= R) with the auxiliary in **19** accounts for the low diastereoselectivity obtained in the *t*Bu transfer, because other transition states become accessible.

An alternative pathway involves the formation of an imine–ZnRR′ complex, followed by attack of the organometallic reagent RM at the C=N double bond, as depicted in **20** (Figure 2). This mechanism can, however, be excluded in the light of the experiment performed by adding first Et_2Zn to **3** at −78 °C (no reaction occurred despite the intense red colour observed) and then MeLi: ethyl transfer occurred almost exclusively to produce **13** (>95%, d.r. 62:38 by GC-MS analysis). This indicates that MeLi preferentially attacks the Zn centre of the chelated N,N–Zn complex, followed by formation of the N,N–Li complex.

An ionic mechanism should also be considered, as in our previous report on the imine **3**,[1b] owing to the strong chelating ability of the 2-pyridineimine moiety towards metal cations. Accordingly, both imines **3** and **6b** might be able to promote the ionic dissociation of the zincate reagent to form the ionic couples **21** and **22**, respectively (Figure 2, M = Li or MgX). Consequently, the amines should be produced by attack of R from the *anion* RMe_2Zn^- at the less hindered *Si* face of the imine. The sense of asymmetric induction observed is consistent with both mechanisms. Finally, an SET process may be operative, at least partially, but products that might derive from intermediate radicals or radical anions were never detected in the crude reaction mixtures.

The BF_3-promoted addition of zincates to the unactivated imines **2** and **5b** can proceed through the preliminary coordination of BF_3 to the azomethine nitrogen, providing the necessary activation for the attack by the nucleophile. However, this scenario does not explain the observed lack of group-transfer selectivity and the ineffectiveness of other Lewis acids such as $Ti(OiPr)_4$, $TiCl_4$ and $SnCl_4$. Hence, it is probable that BF_3 affects the structure of the mixed zincate $R_2R'ZnM$, promoting either their dissociation into separated organometallic compounds ($R'M-BF_3+R_2Zn$, and $RM-BF_3+RR'Zn$) and/or their conversion to a mixture of mixed and symmetrical zincates.[11]

The method presented here is a valuable route to (*S*)-1-(2-pyridyl)alkylamines **16**, which are useful bidentate ligands or catalysts in asymmetric synthesis.[12] The preparation of **16h** is particularly attractive, since the vinyl group can undergo further transformations. Two syntheses of such amines have been reported, similarly exploiting the asymmetric induction of an auxiliary (Scheme 5). The alkylation of the lithium carbanion obtained by metalation of the imines **23** derived from (+)- and (−)-2-hydroxypinan-3-one afforded the imines **24**, which were converted to the amines (*S*)- and (*R*)-**16**, including **16a,d,e**, with low to moderate overall yield and excellent enantiomeric excess.[7] (*S*)-1-(2-Pyridyl)-2-cyclohexylethylamine (**16**, R = cyclohexylmethyl) was synthesized through the addition of excess cyclohexylmethylmagnesium bromide to the imine **25**, prepared from 2-pyridinecarboxaldehyde and (*S*)-valinol, giving mainly the (*S*,*S*) diastereomer of the amine **26a**. In addition, the catalytic hydrogenation of the ketimines **27a**, derived from (*R*)-valinol, and especially **27b**, derived from (*R*)-phenylglycinol, gave (*S*,*S*)-**26a,b** with better diastereoselectivity.[13] However, the oxidative cleavage of **26a,b** by sodium periodate gave the primary amine **16** with low yield.



Scheme 5. Other auxiliary-induced stereoselective syntheses of the amines (*S*)- and (*R*)-**16**.

Experimental Section

General methods and the procedure for the preparation of the imines, e.g. **2**, **3**, **5a** and **6a**, were described previously.[1,2]

Ethyl *N*-[(2-Pyridyl)methylidene]-(*S*)-valinate (6b): $[\alpha]_D^{25} = -98.8$ ($c = 2.1$ in $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz, 20 °C): $\delta = 8.65$ (m, 1H; pyridine), 8.35 (s, 1H; CH=N), 8.15 (m, 1H; pyridine), 7.75 (m, 1H; pyridine), 7.34 (m, 1H; pyridine), 4.22 (m, 2H; OCH_2CH_3), 3.74 (d, $J = 7.3$ Hz, 1H; $CHCO_2Et$), 2.40 (m, 1H; $CHMe_2$), 1.28 (t, 3H; OCH_2CH_3), 0.98 (2d, $J = 6.8$ Hz, 6H; $CHMe_2$); MS (70 eV, EI): *m/z* (%): 161 (100), 92 (67), 119 (65), 145 (27), 191 (21), 118 (19).

Preparation of Triorganozincates: The commercially available solution of Me_2Zn (2M in toluene) or Et_2Zn (1M in hexane) was added to an equal volume of anhydrous THF in N_2 atmosphere, and the solution was cooled at −78 °C. Then an equimolar amount of organolithium or Grignard reagent (1.6 M MeLi in Et_2O, 3M MeMgCl in THF, 2M *n*BuMgCl in Et_2O, 2M *i*PrMgBr in THF, 1M *t*BuMgCl in THF, 1.7 M *t*BuLi in pentane, 2M AllylMgCl in THF, 2M BnMgCl in THF, 1M VinylMgBr in THF) was added to the R_2Zn solution, which was magnetically stirred for 20 min prior to use.

Boron Trifluoride-Mediated Addition of Zincates to the Imines 2 and 5b. General Procedure: To the solution of the zincate (1 mmol), prepared as above and cooled to −78 °C, were added a solution of the imine (1 mmol) in THF (2 mL) and then, during 10 min, a solution of BF_3-Et_2O (0.14 mL, 1 mmol) in THF (2 mL). The reaction mixture was stirred for 1 h at −78 °C and then quenched with 10% aq. NaOH (3 mL). The organic layer was separated, the aqueous phase was extracted with Et_2O (10 mL × 3) and the collected organic layers were dried over Na_2SO_4. The composition of the mixture was determined by GC-MS analysis.

***N*-(1-Cyclohexylethyl)-(*S*)-1-phenylethylamine (7)**:[11b] MS (70 eV, EI): *m/z* (%): 105 (100) [$PhCHMe^+$], 148 (76) [M^+ − cyclohexyl].

***N*-(1-Cyclohexylpropyl)-(*S*)-1-phenylethylamine (8)**: MS (70 eV, EI): *m/z* (%): 105 (100) [$PhCHMe^+$], 162 (75) [M^+ − cyclohexyl], 58 (34), 216 (5) [M^+ − Et].

***N*-(1-Cyclohexylhept-2-yn-1-yl)-(*S*)-1-phenylethylamine (9)**: MS (70 eV, EI): *m/z* (%): 105 (100) [PhCHMe$^+$], 124 (68), 228 (49) [M^+ − cyclohexyl].

Ethyl *N*-(3-Methyl-2-butyl)-(*S*)-valinate (10): MS (70 eV, EI): *m/z* (%): 172 (100) [M^+ − *i*Pr], 142 (68) [M^+ − CO_2Et], 98 (62), 72 (52), 200 (2) [M^+ − Me], 214 (<0.5) [M^+ − H].

Ethyl *N*-(2-Methyl-3-pentyl)-(*S*)-valinate (11): MS (70 eV, EI): *m/z* (%): 186 (100) [M^+ − *i*Pr], 112 (63), 156 (47) [M^+ − CO_2Et], 72 (35), 126 (22), 200 (12) [M^+ − Et], 228 (<0.5) [M^+ − H].

General Procedure for the Preparation of Ethyl *N*-[(*S*)-1-(2-Pyridyl)alkyl]-(*S*)-valinate (14): A solution of the imine **6b** (1.10 g, 5 mmol) in anhydrous THF (5 mL) was added over 30 min to a magnetically stirred solution at −78 °C of the triorganozincate (5 mmol), prepared as described above. The reaction mixture was stirred for further 2 h, then quenched with 10% aq $NaHCO_3$ (10 mL). The organic layer was separated and the aqueous phase extracted with Et_2O (3 × 20 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated at reduced pressure. The resulting oil was chromatographed on a SiO_2 column with cyclohexane–EtOAc (90:10) as eluent.

Ethyl *N*-[(*S*)-1-(2-Pyridyl)propyl]-(*S*)-valinate (14b): 1.18 g (90%) by using $Et_2MeZnMgCl$; $[\alpha]_D^{20} = -111.8$ (c = 2.3 in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz, 20 °C): δ = 8.54 (m, 1H; pyridine), 7.65 (m, 1H; pyridine), 7.50 (m, 1H; pyridine), 7.15 (m, 1H; pyridine), 4.20 (m, 2H; OCH_2CH_3), 3.58 (t, 1H; ArC*H*N), 2.77 (d, *J* = 7.3 Hz, 1H; C*H*CO_2Et), 2.05 (broad, 1H; NH), 1.9 (m, 1H; C*H*Me_2), 1.75 (m, 2H; $CHCH_2CH_3$), 1.28 (t, 3H; OCH_2CH_3), 1.0–0.85 (m, 9H; Me); the absorption of the C*H*CO_2Et proton of the minor diastereomer (10%) fell at δ = 3.0; MS (70 eV, EI): *m/z* (%): 120 (100), 121 (50), 191 (45), 106 (27), 92 (24), 221 (20), 161 (17), 235 (15).

Ethyl *N*-[(*S*)-1-(2-Pyridyl)pentyl]-(*S*)-valinate (14c): 1.26 g (86%) by using (*n*Bu)$Me_2ZnMgCl$; $[\alpha]_D^{20} = -87.4$ (*c* = 3.6 in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz, 20 °C): δ = 8.52 (m, 1H; pyridine), 7.65 (m, 1H; pyridine), 7.48 (m, 1H; pyridine), 7.13 (m, 1H; pyridine), 4.18 (m, 2H, OCH_2CH_3), 3.61 (t, ArC*H*N), 2.74 (d, *J* = 6.0 Hz, 1H, C*H*CO_2Et), 2.0 (broad, 1H, NH), 1.85 (m, 1H, C*H*Me_2), 1.68 (m, 2H, $ArCHCH_2$), 1.50–1.0 (m, 4H, CH_2), 1.25 (t, 3H, OCH_2CH_3), 0.96–0.75 (m, 9H, Me); the absorption of the C*H*CO_2Et proton of the minor diastereomer (4%) fell at 2.96 ppm; MS (70 eV, EI): *m/z* (%): 148 (100), 106 (58), 149 (53), 219 (51), 235 (30), 93 (25), 249 (21), 107 (20), 161 (20), 119 (19).

Ethyl *N*-[(*S*)-1-(2-Pyridyl)-2-methylpropyl]-(*S*)-valinate (14d): 1.25 g (90%) by using Me_2(*i*Pr)ZnMgBr; $[\alpha]_D^{20} = -120.9$ (*c* = 2.6 in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz, 20 °C): δ = 8.50 (m, 1H; pyridine), 7.62 (m, 1H; pyridine), 7.46 (m, 1H; pyridine), 7.14 (m, 1H; pyridine), 4.14 (m, 2H; OCH_2CH_3), 3.37 (d, *J* = 6.5 Hz, 1H; ArC*H*N), 2.65 (d, *J* = 6.5 Hz, 1H; C*H*CO_2Et), 2.07–1.63 (m, 3H; C*H*Me_2 and NH), 1.23 (t, 3H; OCH_2CH_3), 1.0–0.75 (m, 12H; CHMe_2); the absorption of the C*H*CO_2Et proton of the minor diastereomer (3%) is at δ = 2.84; MS (70 eV, EI): *m/z* (%): 134 (100), 235 (97), 161 (53), 119 (40), 92 (38), 205 (36), 135 (35), 120 (34), 93 (23), 118 (23).

Ethyl *N*-[(*S*)-1-(2-Pyridyl)-2-phenylethyl]-(*S*)-valinate (14f): 1.37 g (88%) by using $BnMe_2ZnMgBr$; $[\alpha]_D^{20} = -44.2$ (*c* = 2.4 in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz, 20 °C) δ = 8.55 (m, 1H; pyridine), 7.63 (m, 1H; pyridine), 7.42 (m, 1H; pyridine), 7.35-7.08 (m, 6H; aryl), 4.04 (m, 2H; OCH_2CH_3), 3.95 (dd, *J* = 5.5 and 8.9 Hz, 1H; ArC*H*N), 3.11 (dd, *J* = 5.5 Hz and 13.4 Hz, 1H; CH_2Ph), 2.84 (dd, *J* = 8.9 Hz and 13.4 Hz, 1H; CH_2Ph), 2.73 (d, *J* = 6.3 Hz, 1H; C*H*CO_2Et), 2.05 (broad, 1H; NH), 1.80 (m, 1H; C*H*Me_2), 1.14 (t, 3H; OCH_2CH_3), 0.88 and 0.83 (2d, *J* = 6.7 Hz, 6H; CHMe_2); the absorption of the C*H*CO_2Et proton of the minor diastereomer could not be determined with certainty, since it was covered by other signals; MS (70 eV, EI): *m/z* (%): 235 (100), 182 (64), 161 (50), 119 (35), 92 (27), 183 (24), 253 (20), 91 (18), 167 (17), 180 (15).

Ethyl *N*-[(*S*)-1-(2-Pyridyl)-3-buten-1-yl]-(*S*)-valinate (14g): 1.26 g (91%); ^{1}H NMR ($CDCl_3$, 300 MHz, 20 °C): δ = 8.50 (m, 1H; pyridine), 7.65 (m, 1H; pyridine), 7.49 (m, 1H; pyridine), 7.14 (m, 1H; pyridine), 5.85–5.65 (m, 1H; C*H*=CH_2), 5.15–5.05 (m, 2H; CH=CH_2), 4.25–4.05 (m, 2H; OCH_2CH_3), 3.75–3.60 (m, 1H; ArC*H*N), 2.75 (d, *J* = 5.6 Hz, 1H; C*H*CO_2Et), 2.35 (m, 2H, CH_2CHN), 2.3 (broad, 1H; NH), 1.85 (m, 1H; C*H*Me_2), 1.26 (t, 3H; OCH_2CH_3). 0.91 and 0.85 (2d, *J* = 6.9 Hz, 6H; CHMe_2); (*R,S*)-**14g** (27% of the diastereomeric mixture) gave separated absorptions at δ = 2.98 (d, *J* = 5.6 Hz, 1H; C*H*CO_2Et), 2.55 (m, 2H, CH_2CHN), 2.05 (m, 1H; C*H*Me_2), 1.10 (t, 3H; OCH_2CH_3), 0.97 and 0.90 (2d, *J* = 6.9 Hz, 6H; CHMe_2); MS (70 eV, EI): *m/z* (%): 235 (100), 161 (60), 132 (47), 203 (40), 117 (34), 133 (33), 119 (32), 92 (24).

Ethyl *N*-[(*S*)-1-(2-Pyridyl)-2-propen-1-yl]-(*S*)-valinate (14h): 1.24 g (95%) by using Me_2(vinyl)ZnMgCl and avoiding the chromatographic purification; $[\alpha]_D^{20} = -49.1$ (*c* = 2.2 in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz, 20 °C): δ = 8.55 (m, 1H; pyridine), 7.68 (m, 1H; pyridine), 7.49 (m, 1H; pyridine), 7.18 (m, 1H; pyridine), 6.0-5.88 (m, 1H; C*H*=CH_2), 5.32-5.12 (m, 2H; CH=CH_2), 4.31 (d, *J* = 7.5 Hz, 1H; ArC*H*N), 4.20 (m, 2H; OCH_2CH_3), 2.92 (d, *J* = 5.6 Hz, 1H; C*H*CO_2Et), 2.65 (broad, 1H; NH), 2.0 (m, 1H; C*H*Me_2), 1.28 (t, 2H; OCH_2CH_3), 0.96 and 0.93 (2d, *J* = 6.9 Hz, 6H; CHMe_2); no absorption that could be attributed to the minor diastereomer was observed; MS (70 eV, EI): *m/z* (%): 189 (100), 187 (55), 118 (46), 173 (35), 120 (32), 117 (29), 219 (26), 217 (19), 147 (15), 190 (15).

By the same procedure the following amines were prepared from the imines **3** and **6b**, but not isolated, and identified by the mass spectral fragmentation pattern.

***N*-[1-(2-Pyridyl)ethyl]-(*S*)-1-phenylethylamine (12)**:[11b] MS (70 eV, EI): *m/z* (%): 107 (100), 106 (72), 105 (41), 120 (35), 79 (18), 78 (17), 77 (16), 211 (5) [M^+ − Me].

***N*-[1-(2-Pyridyl)propyl]-(*S*)-1-phenylethylamine (13)**: MS (70 eV, EI): *m/z* (%): 107 (100), 105 (97), 121 (74), 120 (74), 106 (72), 79 (32), 77 (25), 78 (20), 211 (14) [M^+ − Et], 225 (5) [M^+ − Me].

Ethyl *N*-[(*S*)-1-(2-Pyridyl)ethyl]-(*S*)-valinate (14a): MS (70 eV, EI): *m/z* (%): 106 (100), 177 (61) [M^+ − CO_2Et], 107 (50), 207 (18) [M^+ − *i*Pr), 78 (18), 72 (8), 235 (<2%) [M^+ − Me].

Ethyl *N*-[(*S*)-1-(2-Pyridyl)-2,2-dimethylpropyl]-(*S*)-valinate (14e: MS (70 eV, EI): *m/z* (%): 235 (100) [M^+ − *t*Bu], 161 (59), 148 (35), 119 (27), 92 (23), 219 (17) [M^+ − CO_2Et], 107 (15), 236 (14), 134 (12), 132 (11).

Preparation of *N*-[(*S*)-1-(2-Pyridyl)alkyl]-(*S*)-valinol (15): To the stirred solution of the previously obtained **14** in THF (10 mL) at −5 °C in N_2 atmosphere was added portionwise $LiAlH_4$ (1 molequiv). After having been stirred for 30 min at −5-0 °C, the mixture was quenched with 1 M KOH (10 mL) and further stirred for 15 min at 20 °C, then filtered. The solid was thoroughly washed with Et_2O, the organic layer was separated, and the aqueous layer was extracted with Et_2O (3 × 25 mL). The collected organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The β-amino alcohol remained as an oil and was chromatographed on a SiO_2 column with cyclohexane/EtOAc (60:40) as eluent, to remove the traces of unreacted **14** and in part or totally the more polar diastereomer (*R,S*)-**15**, which was sometimes detected by ^{1}H NMR spectroscopy.

***N*-[(*S*)-1-(2-Pyridyl)propyl]-(*S*)-valinol (15b)**: 0.80 g (80%); $[\alpha]_D^{20} = -30.3$ (c = 2.2 in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz, 20 °C): δ = 8.60 (m, 1H; pyridine), 7.65 (m, 1H; pyridine), 7.18 (m, 2H; pyridine), 3.63 (m, 1H ArC*H*N and 1H CH_2OH), 3.43 (dd, *J* = 4.3 Hz and *J* = 11 Hz, 1H; CH_2OH), 2.18 (m, 1H; $CHCH_2OH$), 1.90–1.60 (m, 5H; CH_2CH_3, C*H*Me_2, NH and OH), 0.95–0.78 (m, 6H; Me); absorptions of (*R,S*)-**14b** (5%) were observed at δ = 3.85 (t; ArC*H*N) and 2.35 (m; $CHCH_2OH$).

***N*-[(*S*)-1-(2-Pyridyl)pentyl]-(*S*)-valinol (15c)**: 0.990 g, 79%; $[\alpha]_D^{20} = -35.2$ (*c* = 3.2 in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz, 20 °C): δ = 8.55 (m, 1H; pyridine), 7.60 (m, 1H; pyridine), 7.12 (m, 2H; pyridine), 3.63 (t, 1H; ArC*H*N), 3.59 and 3.38 (dd, *J* = 4.1 and *J* = 10.8 Hz, 2H; CH_2OH), 2.10 (m, 1H; $CHCH_2OH$), 2.0 (brs, 1H; OH), 1.8-1.55 (m, 4H; $CHCH_2$, C*H*Me_2, and NH), 1.4-1.0 (m, 4H; CH_2CH_2Me), 1.08 (d, *J* = 6.7 Hz, 3H; Me), 0.80 (m, 9H; Me); the presence of (*R,S*)-**15c** in separated chromatographic fractions was indicated by the signals at δ = 3.86 (t; ArC*H*N) and 2.20 (m; $CHCH_2OH$).

***N*-[(*S*)-1-(2-Pyridyl)-2-methylpropyl]-(*S*)-valinol (15d)**: 0.74 g, 69%; $[\alpha]_D^{20} = -48.7$ (*c* = 2.1 in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz, 20 °C): δ = 8.60 (m,

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1H; pyridine), 7.61 (m, 1H; pyridine), 7.13 (m, 2H; pyridine), 3.61 (dd, $J = 3.9$ and 10.8 Hz, 1H; CH_2OH), 3.43 (dd, $J = 3.6$ and $J = 10.8$ Hz, 1H; CH_2OH), 3.30 (d, $J = 7.6$ Hz, 1H; ArC*H*N), 2.05 (m, 1H; NH), 2.02 (m, 1H; NC*H*CH_2OH), 1.95 (m, 1H; PyCHC*H*Me_2), 1.85 (broad, 1H; OH), 1.60 (m, 1H; C*H*Me_2), 1.08 (d, $J = 6.7$ Hz, 3H; Me), 0.75 (m, 9H; Me); signals that could be assigned to (*R,S*)-**15d** were not observed in the collected chromatographic fractions.

***N*-[(*S*)-1-(2-Pyridyl)-2-phenylethyl]-(*S*)-valinol (15f)**: 0.97 g (77%); $[\alpha]_D^{20} = +4.8$ ($c = 2.3$ in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz, 20 °C): $\delta = 8.60$ (m, 1H; pyridine), 7.55 (m, 1H; pyridine), 7.30–6.95 (m, 7H; aryl), 3.69 (t, 1H; ArCHN), 3.46 (dd, $J = 4.0$ Hz and $J = 11.0$ Hz, 1H; CH_2OH), 3.28 (dd, $J = 4.2$ Hz and $J = 10.7$ Hz, 1H; CH_2OH), 2.98 (m, 2H; CH_2Ph), 2.05 (m, 1H; NH), 2.05 (m, 1H; NC*H*CH_2OH), 2.5–1.8 (broad, 2H; NH and OH), 1.55 (m, 1H; C*H*Me_2), 0.77 and 0.74 (2d, $J = 6.8$ Hz, 6H; CHMe_2); the presence of (*R,S*)-**15f** in separated chromatographic fractions was evidenced by the signal at $\delta = 4.12$ (t; ArC*H*N).

***N*-[(*S*)-1-(2-Pyridyl)prop-2-enyl]-(*S*)-valinol (15h)**: 0.75 g, 75%; $[\alpha]_D^{20} = +49.4$ ($c = 2.0$ in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 200 MHz, 20 °C): $\delta = 8.58$ (m, 1H; pyridine), 7.66 (m, 1H; pyridine), 7.30 (m, 1H; pyridine), 7.19 (m, 1H; pyridine), 6.0–5.84 (m, 1H; C*H*=CH_2), 5.35-5.19 (m, 2H; CH=C*H*$_2$), 4.40 (d, $J = 8.4$ Hz, 1H; ArC*H*N), 3.62 (dd, $J = 4.2$ Hz and $J = 10.7$ Hz, 1H; CH_2OH), 3.36 (dd, $J = 6.7$ Hz and $J = 10.7$ Hz, 1H; CH_2OH), 2.48 (m, 1H; NC*H*CH_2OH), 1.9-1.6 (broad, 1H; OH), 1.83 (m, 1H; C*H*Me_2), 1.2 (broad, 1H; NH), 0.93 and 0.87 (2d, $J = 6.7$ Hz, 6H; CHMe_2).

Preparation of (*S*)-1-(2-Pyridyl)alkylamines 16: To the solution of the previously obtained β-amino alcohol **15** in a MeOH/THF mixture (9:1, 10 mL) was added 40% aq. $MeNH_2$ (1.2 mL per mmol of **15**). Then a solution of H_5IO_6 (0.82 g, 3.6 mmol, per mmol of **15**) in H_2O (10 mL) was added slowly. The mixture was stirred magnetically over 1 h. H_2O (10 mL) was then added and the solid phase filtered off. The aqueous solution was concentrated at reduced pressure to remove most MeOH and was then extracted with Et_2O (3 × 20 mL). The collected organic layers were dried over $MgSO_4$ and then concentrated at reduced pressure (water bath at 50–60 °C) to give the primary amine as an oily residue in almost quantitative yield (≥95%). The pure state of the amine (≥97%) was determined by GC and ^{1}H and ^{13}C NMR analyses.

(*S*)-1-(2-Pyridyl)propylamine (16b): $[\alpha]_D^{20} = -7.0$ ($c = 2.2$ in $CHCl_3$); $[\alpha]_D^{20} = -8.6$ ($c = 2.5$ in EtOH); ^{1}H NMR ($CDCl_3$, 300 MHz, 20 °C): $\delta = 8.57$ (m, 1H; pyridine), 7.24 (m, 1H; pyridine), 7.27 (m, 1H; pyridine), 7.15 (m, 1H; pyridine), 3.87 (t, 1H; CHN),1.85 (broad, 2H; NH_2), 1.9–1.65 (m, 2H; CHC*H*$_2$CH$_3$), 0.88 (t, 3H; CH_3); ^{13}C NMR (300 MHz): $\delta = 162$, 149, 136, 122, 121, 59, 32, 11; MS (70 eV, EI): *m/z* (%): 107 (100); $C_8H_{12}N_2$ (136.2): calcd C 70.55, H 8.88, N 20.57; found C 70.35, H 9.03, N 20.62.

(*S*)-1-(2-Pyridyl)pentylamine (16c): $[\alpha]_D^{20} = -5.4$ ($c = 3.4$ in $CHCl_3$); $[\alpha]_D^{20} = -4.8$ ($c = 2.0$ in EtOH); ^{1}H NMR ($CDCl_3$, 200 MHz, 20 °C): $\delta = 8.50$ (m, 1H; pyridine), 7.60 (m, 1H; pyridine), 7.22 (m, 1H; pyridine), 7.10 (m, 1H; pyridine), 3.87 (t, 1H; CHN),1.85 (broad, 2H; NH_2), 1.70 (m, 2H; CHC*H*$_2$), 1.40–1.05 (m, 4H; CH_2CH_2), 0.81 (t, 3H; CH_3); ^{13}C NMR (300 MHz): $\delta = 161$, 149, 136, 122, 121, 57, 38, 28, 22, 14; MS (70 eV, EI): *m/z* (%): 107 (100), 80 (18); $C_{10}H_{16}N_2$ (164.2): calcd C 73.12, H 9.82, N 17.06; found C 72.98, H 9.85, N 17.17.

(*S*)-1-(2-Pyridyl)-2-methylpropylamine (16d): $[\alpha]_D^{20} = -1.3$ ($c = 3.1$ in $CHCl_3$); $[\alpha]_D^{20} = -3.5$ ($c = 3.3$ in EtOH); lit.:[7] $[\alpha]_D^{20} = +3.42$ (EtOH) for the (*R*) enantiomer; ^{1}H NMR ($CDCl_3$, 300 MHz, 20 °C): $\delta = 8.52$ (m, 1H; pyridine), 7.61 (m, 1H; pyridine), 7.22 (m, 1H; pyridine), 7.12 (m, 1H; pyridine), 3.67 (d, $J = 6.6$ Hz; ArC*H*N), 2.0 (m, 1H; C*H*Me_2), 1.85 (broad, 2H; NH_2), 0.92 and 0.81 (2d, $J = 6.8$ Hz; CHMe_2); ^{13}C NMR (300 MHz): $\delta = 162$, 149, 136, 122, 121, 63, 35, 20, 18; MS (70 eV, EI): *m/z* (%): 107 (100), 80 (18).

(*S*)-1-(2-Pyridyl)-2-phenylethylamine (16f): $[\alpha]_D^{20} = +14.9$ ($c = 3.5$ in $CHCl_3$); $[\alpha]_D^{20} = +31.3$ ($c = 2.1$ in EtOH); lit.:[7] $[\alpha]_D^{20} = -41.22$ (EtOH) for the (*R*) enantiomer; ^{1}H NMR ($CDCl_3$, 200 MHz, 20 °C): $\delta = 8.57$ (m, 1H; pyridine), 7.58 (m, 1H; pyridine), 7.30–7.08 (m, 7H; aryl), 4.22 (dd, $J = 5.5$ and 8.6 Hz, 1H; ArC*H*N), 3.14 (dd, $J = 5.5$ and 13.2 Hz, 1H; CH_2Ph), 2.87 (dd, $J = 8.6$ and $J = 13.2$ Hz, 1H; CH_2Ph), 1.85 (broad, 1H; NH); ^{13}C NMR (300 MHz): $\delta = 163$, 149, 139, 136, 129, 128, 126, 122, 121, 59, 45; MS (70 eV, EI): *m/z* (%): 107 (100), 80 (24), 91 (15).

(*S*)-1-(2-Pyridyl)prop-2-enylamine (16h): $[\alpha]_D^{20} = +18.6$ ($c = 2.1$ in $CHCl_3$); $[\alpha]_D^{20} = +22.2$ ($c = 2.1$ in EtOH); ^{1}H NMR ($CDCl_3$, 200 MHz, 20 °C): $\delta = 8.45$ (m, 1H; pyridine), 7.55 (m, 1H; pyridine), 7.22 (m, 1H; pyridine), 7.18 (m, 1H; pyridine), 6.05–5.85 (m, 1H; C*H*=CH_2), 5.22-5.01 (m, 2H; CH=C*H*$_2$), 4.45 (d, $J = 6.6$ Hz, 1H; CHN), 2.0 (broad, 2H; NH_2); ^{13}C NMR (300 MHz, 20 °C): $\delta = 162$, 149, 141, 137, 122, 121, 145, 59; MS (70 eV, EI): *m/z* (%): 119 (100), 56 (47), 107 (35), 80 (28), 79 (24), 78 (22), 106 (22), 133 (15); $C_8H_{10}N_2$ (134.2): calcd C 71.61, H 7.51, N 20.88; found C 71.22, H 7.45, N 21.33.

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