A Novel Method for the Asymmetric Synthesis of α,α-Disubstituted Alkylamines *via* Grignard Additions to Ketimines†

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The design of practical methods to prepare optically pure α,α-disubstituted alkylamines remains an important challenge. We now report a new and efficient method for the asymmetric synthesis of α,α-disubstituted amines **2** where R^3 is a nitrogen-containing heterocycle. The method utilizes the diasteroselective addition of a Grignard reagent to ketimine **1**, followed by an oxidative cleavage of the chiral auxiliary to afford the target amines **2** in high enantiomeric excess. A model involving chelation of the imine and heterocyclic nitrogen with Mg is proposed to rationalize the observed diastereoselectivity.

Introduction

The design of practical methods to prepare optically pure α,α-disubstituted alkylamines remains an important challenge.[1] Numerous methods are available for the asymmetric synthesis of α,α-disubstituted amino acids[2] and for α-monosubstituted alkylamines,[3] but few methods are available for the synthesis of acylic α,α-disubstituted alkylamines[4] in optically pure form. We now report a new, efficient method for the asymmetric synthesis of α,α-disubstituted alkylamines where one of the α-substituents is a nitrogen-containing heterocycle. The method utilizes the diastereoselective addition of a Grignard reagent to ketimine **1**, which contains a chiral auxiliary on nitrogen (Scheme 1). Facile oxidative cleavage of the chiral auxiliary results in the formation of the target amines **7** and **8** in high enantiomeric excess. The addition of Grignard reagents to ketimines is not well precedented because imines have a propensity to enolize. In fact, enolizable ketimines are generally inert to Grignard reagents and in their presence will undergo complete enolization.[5] Therefore, the majority of the literature in this field addresses the addition of organometallic reagents to aldimines,[3] but not to ketimines. An additional challenge to this approach is that imines tend to have poor reactivity toward nucleophilic addition and are often activated by the addition of a Lewis acid[6] or through substitution of nitrogen with activating groups such as *N*-acyliminium ions[7] or nitrones.[3e] Finally, ketimines can exist in both the *E* and *Z* conformation, which decreases the chance for a diastereoselective reaction.

Results and Discussion

Our focus has been to design a system for the asymmetric Grignard addition in which chelation to magnesium could control the *E*/*Z* ratio of imine isomers and simultaneously activate the imine toward nucleophilic attack. Our initial experiments utilized the ketimine **1**, derived from (*S*)-phenylglycinol and 2-acetylpyridine, and the Grignard reagent (2-fluorobenzyl)magnesium chloride (**2**). The experiments were carried out by precomplexing the imine **1**[8] with an additive such as $MgBr_2$ in a solvent of choice and then adding an ethereal solution of (*o*-fluorobenzyl)magnesium chloride.[9] Our first experiments were conducted at 0 °C using THF as the solvent, and a variety of additives were examined, such as $MgBr_2$, $CeCl_3$, and $Yb(OTf)_3$. The isomer ratios from these reactions ranged between 2:1 and 3:1 (**5a**/**5b**). Use of (*S*)-phenylglycinol as the auxiliary led to predominantly the (*S*) configuration at the newly formed stereogenic center.[10] Lowering the temperature of the reaction or running the reaction in the absence of $MgBr_2$ gave a lower range of diastereoselectivities.

A great increase in selectivity was observed for this Grignard addition[11] when a noncoordinating solvent was used. In the presence of $MgBr_2$, high de's (diastereomeric

† Dedicated to Professor Yoshito Kishi on the occasion of his 60th birthday.

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(8) A detailed NMR analysis of the imine **1** in CH_2Cl_2 shows four species present in the following ratios: 21.0% (*E* imine), 34.9% and 30.8% (*cis* and *trans* oxazolidines), and 13.2% (*Z* imine). Such ratios were determined only for imine **1**.

(9) Generation of the (*o*-fluorobenzyl)magnesium chloride in either THF of MTBE gave exclusively benzyl dimer.

(10) The absolute configuration of **7** is presumed to be (*S*) based on a correlation with the biological activity of a closely related series for which an X-ray crystal structure was obtained. All other chiral amines are presumed to have the (*S*) configuration based on our model.

(11) We have observed that the yields for the Grignard additions are slightly higher using 3 equiv of the Grignard reagent rather than 2 equiv. The Grignard reagents typically contain 10% of the unreacted alkyl bromide and 10% of the Wurtz homodimer.

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Scheme 1

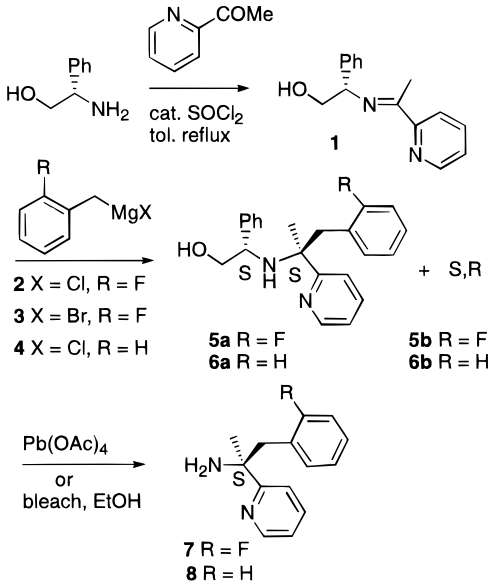


Table 1. Dependence of de on Mg Salt Type and Stoichiomery at rt for the Reaction of Grignard Reagent 2 with Imine 1

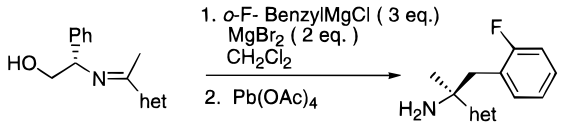
[RMgCl], M	additive	% yield	% de
2.4	none	41	50
2.4	$MgBr_2$/1 equiv	46	84
2.4	$MgBr_2$/2 equiv	46	89
2.4	$MgBr_2$/3 equiv	45	91
1.0	$MgCl_2$/1 equiv	50	78
1.0	$MgCl_2$/2 equiv	50	78
1.0	$MgBr_2$/1 equiv	51	91
1.0	*$MgBr_2$/2 equiv*	*70*	*96*
1.0	MgI_2/2 equiv	38	95

excess) were observed when the reaction was carried out in either toluene or methylene chloride.[12] For example, carrying out this reaction in toluene at 0 °C in the presence of 2 equiv of $MgBr_2$ increased the de of this reaction to 80%. When the reaction was run in methylene chloride at 0 °C with only 1 equiv of $MgBr_2$, a poor de of 34% was observed, but with 2 equiv of $MgBr_2$ the de increased to 84%. Finally, increasing the temperature of the reaction from 0 °C to rt increased the de to 96% with a yield of 70%. From these experiments we concluded that the de increased with reaction temperature and appeared to be related to the amount of $MgBr_2$ present.

We further studied the effect of the stoichiometry and type of Mg salt on the diastereoselectivity (Table 1). These reactions were carried out at rt in methylene chloride using a 2.4 M concentration of the Grignard reagent **2**. It was observed that with no external $MgBr_2$ added to the reaction mixture, a 50% de was obtained, but that the de increased significantly with the addition of 3 equiv of $MgBr_2$. To study a possible counterion effect, $MgBr_2$ was compared with $MgCl_2$ and MgI_2 (Table 1), and these reactions were carried out using a 1.0 M Grignard concentration. The addition of 1 or 2 equiv of $MgCl_2$ resulted in the same de of 78%. Performing the same experiment in the presence of 1 or 2 equiv of $MgBr_2$ afforded a 91% and 96% de respectively. Finally, using MgI_2 as the Lewis acid gave no further improvement. From these experiments it is clear that there is a positive

(12) Keck, G. E.; Andrus, M. B.; Romer, D. R. *J. Org. Chem.* **1991**, *56*, 417.

Scheme 2



het	ee
2-pyridyl	96%
2- thiazolyl	85%
2-thienyl	50%
2-furyl	16%
phenyl	——

correlation between the amount of $MgBr_2$ added to the reaction mixture and the de. We also observed that the bromide counterion is superior to the chloride, and no increased benefit is obtained from the use of the iodide. It is also interesting to note that a lower concentration of the Grignard reagent affords higher diastereoselectivities. A possible explanation for the counterion effect is that the addition of $MgBr_2$ converts the (*o*-fluorobenzyl)magnesium chloride to the (*o*-fluorobenzyl)magnesium bromide *via* the Schlenk equilibrium and the (*o*-fluorobenzyl)magnesium bromide is more diastereoselective than the corresponding chloride.[13]

In order to confirm that the bromobenzyl Grignard reagent is more selective than the chlorobenzyl Grignard, the imine **1** was treated with (*o*-fluorobenzyl)magnesium bromide in the presence of varying amounts of $MgBr_2$. After cleavage of the chiral auxiliary with $Pb(OAc)_4$,[14] the ee's were determined to be 88%, 94%, and 95% with the addition of 0, 0.5, and 1 equiv of $MgBr_2$, respectively.[15] These data demonstrate that the (*o*-fluorobenzyl)magnesium bromide is in fact more diastereoselective than the (*o*-fluorobenzyl)magnesium chloride and that less external $MgBr_2$ is needed to obtain high de's.

We postulate that the key element in controlling the diastereoselectivity of this asymmetric Grignard reaction is chelation of the pyridine and imine nitrogens with $MgBr_2$. If this is the case, replacement of the pyridine with other heterocycles of a lower coordinating ability should result in a decreased diastereoselectivity. Alternative heterocycles examined were 2-thiazole, 2-thiophene, 2-furan, and a substituent containing no heteroatom, phenyl (Scheme 2). In agreement with our postulate, the pyridine affords the highest ee (96%). Thiazole, thiophene, and furan afford ee's of 85%, 50%, and 16%, respectively. Replacement of the pyridine with phenyl afforded no desired product, presumably enolization of the ketimine being the sole course of reaction. In the case of the thiophene and furan, very poor yields of the desired products were isolated due to competing addition of the Grignard reagent directly to the heterocycle.

To define the role of the hydroxyl group in the phenylglycinol auxiliary and to determine whether formation of the magnesium alkoxide is required for the high diastereoselectivity, we prepared the TBS and methyl protected analogs (entry 4 and 5, Table 2). For both the

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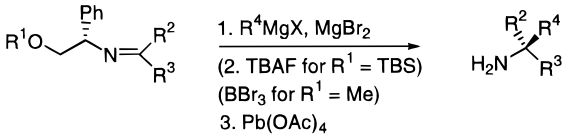
(14) For $Pb(OAc)_4$ oxidation see Pridgen, L. N.; Mokhallalati, M. K. *Synth. Commun.* **1993**, *23*, 2055. An alternative facile method which we have developed is to reflux substrate **5a** or **5b** in a mixture of bleach and EtOH in a sealed vessel. Typical yields for this reaction are 60% and it has the advantage of ease of workup while giving no toxic lead byproducts.

(15) Enantiomeric excesses were determined by chiral HPLC using a chiralpak AD column with hex/IPA/Et_3N (900:100:1) as eluant.

Table 2. Scope of the Asymmetric Grignard Addition



entry	R^1	R^2	R^3	R^4	X	yield, %	ee(de), %	amine
1	H	Et	2-pyr	*o*-F-Bn	Br	23[a]	92	9
2	H	Ph	2-pyr	Benzyl	Cl	72[b]	21	10
3	H	Me	2-pyr	Benzyl	Cl	48[a]	93	8
4	TBS	Me	2-pyr	Benzyl	Cl	50[b]	97	8
5	Me	Me	2-pyr	*o*-F-Bn	Cl	73[b]	92	7
6	TBS	Me	2-pyr	Et	Br	60[b]	(97)	12
7	TBS	Me	2-pyr	C_6H_{11}	Br	65[b]	76	13
8	TBS	Me	2-pyr	allyl	Br	74[b]	(89)	14
9	TBS	Me	2-quinolyl	Benzyl	Cl	64[b]	54	15
10	H	Me	2-thiazolyl	*o*-F-Bn	Cl	48[b]	85	16

[a] Over two steps. [b] For addition only.

methyl[16] and TBS[17] protected ethers, high ee's were obtained for the product amines **7** and **8**, 92% and 97%, respectively, suggesting that magnesium alkoxide is not required for high diastereoselectivity. It should be noted that the oxygen atom in the auxiliary is a required element for this reaction. In fact, we have prepared the ketimine derived from acetylpyridine and (*R*)-(+)-α-methylbenzylamine[18] and have added the Grignard reagent **2** to this substrate. Only a 2:1 ratio of diastereomers was obtained at rt, although a slight increase in selectivity was observed (5:1) at low temperature.

To explore the scope of the asymmetric Grignard reaction we have examined additional ketimines and Grignard nucleophiles (Table 2). The methyl group of the ketimine can be replaced with ethyl, and a high ee of the amine **9** is obtained (entry 1). However, the enantioselectivity is lost if the methyl is replaced with a large phenyl group to afford the amine **10** in only 21% ee. It is interesting to note that the ee's of these reactions can be improved by the use of the TBS protected (*S*)-phenylglycinol. Compare the addition of benzylmagnesium chloride to the imines lacking and containing the TBS group (entries 3 and 4). The ee improves from 93% to 97% with the silyl protecting group. Among other Grignard reagents examined were EtMgBr, cyclohexylmagnesium bromide, and allylmagnesium bromide. Ethylmagnesium bromide is a suitable Grignard reagent for this reaction and gives a 60% yield for the addition with a 97% de. Cyclohexyl and allyl Grignard reagents afford selectivities of 76% and 89%, respectively. As possible replacements for the pyridine ring we examined 2-quinolyl and 2-thiazolyl. 2-Thiazolyl gave the better results of the two with an ee of 85%.

A working model to explain the observed 1,3-asymmetric induction is shown in Figure 1. We propose equilibration of the ketimine to the *E* isomer and then chelation of the pyridine and imine nitrogens with MgX_2.

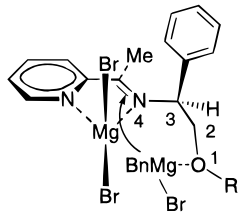


Figure 1.

After chelation, delivery of the nucleophile would then occur from the less hindered *si* face.[19] The delivery of the nucleophile could be oxygen assisted when R = H or Me (Figure 1), but this is less likely for R = TBS. The model described in Figure 1 was shown by molecular modeling to be a low energy conformation.[20] Use of a solvent with a low coordinating ability such as methylene chloride would maximize the complexation of the $MgBr_2$ with the substrate.

In summary, we have demonstrated the first broad method for the asymmetric addition of Grignard reagents to acyclic ketimines and in the majority of the cases which we have studied, enolization is not a significant problem.[21] The necessity for a nitrogen-containing moiety such as pyridine or thiazole as an imine substituent makes this method applicable to many medicinally important compounds. Application of this method to the synthesis of biologically active pharmaceuticals is in progress.

Experimental Section

General Procedures. Proton and ^{13}C NMR spectra were measured at 270 MHz using TMS as the standard. The commercial chemicals were used as received without further purification, and all solvents were dried by standard methods prior to use. Column chromatography was carried out on silica gel 60 (E. Merck, 230−400 mesh).

(16) Methylation of (*S*)-phenylglycinol was carried out according to Meyers, A. I.; Poindexter, G. S.; Brich, Z. *J. Org. Chem.* **1978**, *43*, 892.

(17) Silylation of (*S*)-phenylglycinol was carried out with TBSCl, imidazole, DMF at 0 °C in 83% yield.

(18) Two alternative auxiliaries have been examined, (*S*)-valinol and (1*S*,2*R*)-(+)-norephedrine. (*S*)-Valinol gives similar results to (*S*)-phenylglycinol, but (1*S*,2*R*)-(+)-norephedrine is a less effective auxiliary. For alternative conditions using (*S*)-valinol see Sorcek, R.; Lazer, E.; Wong, H.-C.; Spero, D.; Miao, C.; Potocki, I. U.S. Patent 021581, 1996, also, Miao, C.; Potocki, I., submitted for publication.

(19) Alternatively, Mg could have an octahedral geometry, and the phenylglycinol oxygen could act as one of the ligands. Mechanistic studies and molecular modeling will be the topic of a future publication.

(20) Another low energy conformation places the C_2-O_1 bond of the chiral auxiliary antiperiplanar to the imine N_4-C_3 bond, with the large phenyl group blocking the top face of the molecule.

(21) We speculate that if the mechanism of enolization involves complexation of the Grignard reagent with the imine nitrogen followed by a *syn* elimination, the geometry shown in Figure 1 would prevent deprotonation.

(*S*)-*N*-(1-Phenyl-2-hydroxyethyl)-*N*-(1-pyridin-2-ylethylidene)amine (1). To a solution of (*S*)-phenylglycinol (11.9 g, 86.8 mmol) and 2-acetylpyridine (9.73 mL, 86.8 mmol) in 125 mL of toluene was added thionyl chloride (15 mg), and the mixture was refluxed for 1.45 h using a Dean−Stark trap. The solvent was evaporated under reduced pressure to give the imine as a brown oil (20.85 g, quant). It was used without purification in the next reaction.

(*S*)-1-(2-Fluorobenzyl)-1-(2-pyridyl)-1-aminoethane (7). A solution of imine **1** (69 mg, 0.286 mmol) in dry CH_2Cl_2 (3 mL) was cooled to 0−5 °C in an ice bath. Anhydrous $MgBr_2$ (106 mg, 0.57 mmol) was added. The reaction mixture was stirred at this tempreature for 0.25 h and then for 1 h more at room temperature. An ethereal solution of (2-fluorobenzyl)magnesium chloride (0.7 M, 0.86 mmol) was added at room temperature, and the reaction mixture was stirred for 2 h. A saturated solution of NH_4Cl was added to quench the reaction mixture. The crude product was extracted with CH_2Cl_2, dried over anhydrous Na_2SO_4, and concentrated. The product was purified by silica gel chromatography using ethyl acetate/hexane (1:4) as the eluant to afford amino alcohol **5a** as a light yellow oil (70 mg, 70%).

A solution of amino alcohol **5a** (4.54 g, 13 mmol) in 90 mL of CH_2Cl_2/CH_3OH (2:1) was cooled to 5 °C in an ice bath. Lead tetraacetate (6.32 g, 14.3 mmol) was added in one portion. After stirring for 7 min, the reaction mixture was quenched by addition of 45 mL of 2 N NaOH. After stirring for 1 h at room temperature, the reaction mixture was filtered through Celite. The filtrate was extracted with CH_2Cl_2, dried, and concentrated. The residue was dissolved in 75 mL of ether and treated with 20 mL of 3 N HCl. After stirring for 0.5 h, the aqueous layer was extracted with ether. The ether layer was discarded, and the aqueous layer was made basic with 2 N NaOH, extracted with CH_2Cl_2, and concentrated. The residue was purified by chromatography on a silica gel column and eluted with hexane/acetone (4:1) to give pure product **7** as yellow oil (2.0 g, 67%). $[\alpha]^{25}_D$ + 7.6° (*c* 0.82, EtOH); ^{1}H NMR ($CDCl_3$) δ 1.51 (s, 3H), 1.82 (bs, 2H), 3.14 (s, 2H), 6.78−6.79 (m, 1H), 6.89−7.00 (m, 2H), 7.11−7.17 (m, 2H), 7.33−7.37 (m, 1H), 7.56−7.59 (m, 1H), 8.59−8.62 (1H); ^{13}C NMR ($CDCl_3$) δ 27.8, 43.0, 57.5, 115.00 (J = 25.16 Hz), 119.4, 121.4, 123.3 (J = 3.14 Hz), 124.7 (J = 15.72 Hz), 128.0 (J = 8.18 Hz), 132.5 (J = 4.40 Hz), 136.1, 148.5, 161.5 (J = 244.66 Hz), and 166.1; HRMS calcd for $C_{14}H_{15}FN_2$ 231.1297, found 231.1290. Anal. Calcd for $C_{14}H_{15}FN_2$·HCl: C, 63.03; H, 6.04; N, 10.50. Found: C, 63.03; H, 5.83; N, 10.31. ee = 96%.

Alternative Synthesis of 7 from (*S*)-*N*-(1-Phenyl-2-methoxyethyl)-*N*-(1-pyridin-2-ethylidene)amine. The imine was synthesized from (*S*)-1-amino-1-phenyl-2-methoxyethane[14] and 2-acetylpyridine as described above.

A solution of imine (0.58 g, 2.3 mmol) in dry CH_2Cl_2 (20 mL) was cooled to 0−5 °C in an ice bath. Anhydrous $MgBr_2$ (0.85 g, 4.6 mmol) was added. The reaction mixture was stirred at this temperature for 0.25 h and then for 1 h at room temperature. An ethereal solution of (2-fluorobenzyl)magnesium chloride (1.24 M, 6.9 mmol) was added at room temperature and the reaction mixture was stirred for 2 h. A saturated solution of NH_4Cl was added to quench the reaction mixture. The crude product was extracted with CH_2Cl_2, dried over anhydrous Na_2SO_4, and concentrated. The product was purified by silica gel chromatography using ethyl acetate/hexane (1:4) as the eluant to afford a light yellow oil (0.61 g, 73%). It was used as such in the next step.

A solution of methyl ether (52 mg, 0.143 mmol) in dry CH_2Cl_2 (4 mL) at 0 °C was treated with BBr_3/CH_2Cl_2 (1 M, 0.57 mmol). After stirring the reaction mixture for 20 h at room temperature, it was poured into a saturated solution of $NaHCO_3$ and extracted with CH_2Cl_2. The organic extract was dried over anhydrous Na_2SO_4 and concentrated, and the residue, amino alcohol **5a**, was used in the next step without further purification. **5a** was converted to **7** as described above (24% over two steps). ee = 92%.

(*S*)-1-(2-Fluorobenzyl)-1-(2-pyridyl)-1-aminopropane (9). The imine was synthesized from ethyl-2-pyridyl ketone and (*S*)-2-phenylglycinol as described above in **1**. It was used without further purification in the next step.

The addition of 2-fluorobenzylmagnesium chloride to the imine and the cleavage of chiral auxiliary was accomplished as described for **7**. The product **9** was obtained as light yellow oil (23% over two steps). $[\alpha]^{25}_D$ − 33.9° (*c* 0.66, EtOH); ^{1}H NMR ($CDCl_3$) δ 0.73 (t, 3H, J = 7.3 Hz), 1.75 (m, 1H, J = 7.3 Hz), 2.19 (m, 1H, J = 7.3 Hz), 3.16 (s, 2H), 6.69−6.72 (m, 1H), 6.84−6.97 (m, 2H), 7.10−7.14 (m, 2H), 7.33−7.36 (m, 1H), 7.55−7.58 (m, 1H), 8.58−8.60 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 8.5, 34.5, 42.5, 61.2, 115.5 (J = 23.24 Hz), 121.1, 121.6, 123.8 (J = 3.32 Hz), 125.0 (J = 15.69 Hz), 128.4 (J = 8.15 Hz), 133.0 (J = 4.32 Hz), 136.3, 148.9, 162.1 (J = 244.89 Hz), and 165.2; HRMS calcd for $C_{15}H_{17}FN_2$ 245.1454, found 245.1445, ee = 92%.

(*S*)-1-Ethyl-1-(2-pyridyl)-1-aminoethane (12). The imine was obtained from 2-acetylpyridine and (*S*)-1-(*tert*-butyldimethylsilyloxy)-2-phenylethylamine[15] as described for **1**. It was used without further purification in the next step.

The addition of ethylmagnesium bromide to the imine was carried out as described above. The product was obtained as light yellow oil (60%).

To a solution of the TBS ether (0.15 g, 0.39 mmol) in dry THF (5 mL) at 0 °C was added TBAF/THF (1 M, 0.39 mL). After stirring the solution at this temperature for 1 h, it was diluted with ether , washed with water, dried (anhydrous Na_2SO_4), and concentrated. The chiral auxiliary was cleaved with lead tetraacetate as described above to give **12** as light yellow oil (30 mg, 51% over two steps). ^{1}H NMR ($CDCl_3$) δ 0.74 (t, 3H, J = 7.3 Hz), 1.50 (s, 3H), 1.85 (m, 2H), 7.10−7.14 (m, 1H), 7.39−7.42 (m, 1H), 7.61−7.67 (m, 1H), 8.55−8.56 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 8.9, 28.9, 37.09, 57.3, 119.8, 121.6, 136.6, 148.9, and 167.2; HRMS calcd for $C_9H_{14}N_2$ 151.1235, found 151.1239, ee = 97%.

(*S*)-1-Phenyl-1-(2-pyridyl)phenethylamine (10). The imine was obtained from 2-benzoylpyridine and (*S*)-2-phenylglycinol as described for **1**. Benzylmagnesium chloride was added to this imine followed by the cleavage of the chiral auxiliary as described for **7** to obtain **10** as colorless oil (47% over two steps). $[\alpha]^{25}_D$ + 2.6° (*c* 0.78, EtOH); ^{1}H NMR ($CDCl_3$) δ 3.57 (d, 1H, J = 11.9 Hz), 3.87 (d, 1H, J = 11.9 Hz), 6.77−6.81 (m, 2H), 7.10−7.45 (m, 10H), 7.55−7.59 (m, 1H), 8.57−8.59 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 48.5, 63.5, 121.5, 126.4, 126.6, 126.8, 127.8, 128.1, 130.8, 136.3, 137.3, 147.0, 148.5, and 166.0; HRMS calcd for $C_{19}H_{18}N_2$ 275.1548, found 275.1543, ee = 21%.

(*S*)-1-Methyl-1-(2-pyridyl)phenethylamine (8). The imine was synthesized from 2-acetylpyridine and (*S*)-2-phenylglycinol as described for **1**. Benzylmagnesium chloride was then added to the imine followed by cleavage of the chiral auxiliary with lead tetraacetate as described above to give **8** as yellow oil (48% over two steps). $[\alpha]^{25}_D$ − 24° (*c* 0.23, EtOH); ^{1}H NMR ($CDCl_3$) δ 1.50 (s, 3H), 3.03 (d, 1H, J = 12.7 Hz), 3.16 (d, 1H, J = 12.7 Hz), 6.84−6.88 (m, 2H), 7.10−7.15 (m, 4H), 7.25−7.30 (m, 1H), 7.53−7.59 (m, 1H), 8.59−8.61 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 28.8, 51.1, 57.8, 120.0, 121.8, 126.7, 128.2, 130.8, 136.5, 138.2, 149.0, and 166.9; HRMS calcd for $C_{14}H_{16}N_2$ 213.1392, found 213.1398, ee = 93%.

(*S*)-1-Cyclohexyl-1-(2-pyridyl)ethylamine (13). The imine was obtained from 2-acetylpyridine and (*S*)-1-(*tert*-butyldimethylsilyloxy)-2-phenylethylamine as described for **1**. Cyclohexylmagnesium bromide was added to the imine followed by the cleavage of the chiral auxiliary as described for **7** to give **13** as yellow oil (54% over two steps). ^{1}H NMR ($CDCl_3$) δ 0.89−1.21 (m, 6H), 1.43 (s, 3H), 1.60−1.75 (m, 5H), 7.07−7.11 (m, 1H), 7.36−7.39 (m, 1H), 7.60−7.63 (m, 1H), 8.52−8.54 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 25.9, 26.9, 27.1, 27.7, 48.9, 59.6, 120.4, 121.5, 136.3, 148.7, and 167.2; HRMS calcd for $C_{13}H_{20}N_2$ 205.1704, found 205.1711, ee = 76%.

(*S*)-4-(2-Pyridyl)-4-[(2-phenyl-1-hydroxyethyl)amino]-pent-1-ene (14). The imine was prepared from 2-acetylpyridine and (*S*)-1-(*tert*-butyldimethylsilyloxy)-2-phenylethylamine by the general procedure for **1**. Allylmagnesium bromide was added to the imine as described for **7** followed by the desilylation as described for **12** gave **14** as yellow oil (69% over two steps). $[\alpha]^{25}_D$ + 40.2° (*c* 0.44, EtOH); ^{1}H NMR ($CDCl_3$) δ 1.40 (s, 3H), 2.55−2.60 (m, 2H), 3.40−3.56 (m, 2H), 3.74−3.80 (m, 1H), 4.90−4.97 (m, 2H), 5.45−5.55 (m, 1H), 6.98−7.25 (m, 7H), 7.45−7.51 (m, 1H), 8.39−8.41 (m, 1H); ^{13}C

NMR ($CDCl_3$) δ 25.8, 46.3, 59.8, 60.7, 67.6, 118.2, 121.1, 121.8, 127.2, 127.5, 128.5, 134.8, 136.4, 143.3, 148.8, and 165.7; HRMS calcd for $C_{18}H_{22}N_2O$ 283.1810, found 283.1817, ee = 89%.

(*S*)-1-Methyl-1-(2-quinolyl)phenethylamine (15). The imine was prepared from 2-acetylquinoline and (*S*)-1-(*tert*-butyldimethylsilyloxy)-2-phenylethylamine as described for **1**. Benzylmagnesium chloride was added to this imine, followed by the cleavage of the TBS group, and the chiral auxiliary gave **15** as light yellow oil (57% over two steps). $[\alpha]^{25}_D$ − 9.6° (*c* 0.78, EtOH); ^{1}H NMR ($CDCl_3$) δ 1.60 (s, 3H), 3.13 (d, 1H, J = 13.00 Hz), 3.27 (d, 1H, J = 13.00 Hz), 6.91−6.95 (m, 2H), 7.12−7.16 (m, 3H), 7.48−7.54 (m, 2H), 7.67−7.69 (m, 1H), 7.78−7.81 (m, 1H), 8.04−8.09 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 29.3, 50.0, 58.4, 118.7, 126.4, 126.7, 127.1, 127.7, 128.3, 129.3, 129.6, 130.9, 136.4, 138.0, 147.6, and 167.0; HRMS calcd for $C_{18}H_{18}N_2$ 275.1548, found 275.1549, ee = 54%.

(*S*)-1-(2-Fluorobenzyl)-1-(2-thiazolyl)ethylamine (16). The imine was prepared from 2-acetylthiazole and (*S*)-2-phenylglycinol as described for **1**. (2-Fluorobenzyl)magnesium chloride was added to the imine followed by the cleavage of the chiral auxiliary as described for **7** gave **17** as yellow oil (21% over two steps). $[\alpha]^{25}_D$ − 17.1° (*c* 0.53, EtOH); ^{1}H NMR ($CDCl_3$) δ 1.58 (s, 3H), 3.18−3.30 (m, 2H), 6.90−7.05 (m, 3H), 7.15−7.34 (m, 2H), 7.76 (d, 1H, J = 3.2 Hz); ^{13}C NMR ($CDCl_3$) δ 29.8, 42.7, 57.7, 115.3 (J = 22.64 Hz), 118.8, 123.9 (J = 3.04 Hz), 128.6 (J = 7.88 Hz), 132.6 (J = 3.04 Hz), 142.7, 161.7 (J = 244.14 Hz), and 180.5; HRMS calcd for $C_{12}H_{13}FN_2S$ 237.0862, found 237.0861, ee = 85%.

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Supporting Information Available: Characterization data for compounds **7**, **8**, **9**, **10**, **13**, **14**, **15**, **16** including copies of ^{1}H and ^{13}C NMR data and reverse phase HPLC data (29 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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