Preparation and Use of Aziridino Alcohols as Promoters for the Enantioselective Addition of Dialkylzinc Reagents to *N*-(Diphenylphosphinoyl) Imines

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A set of chiral aziridino alcohols **2**−**5** has been synthesized starting from either readily available amino acids (L-serine, L-threonine, and *allo*-L-threonine) or simple olefins (using Sharpless asymmetric aminohydroxylation and dihydroxylation reactions). Chiral ligands **2**−**5** have been tested as promoters for the enantioselective addition of dialkylzinc reagents to *N*-(diphenylphosphinoyl) imines **1**. The influence of the substituents on the aziridine ring and the alcohol moiety on the selectivity has been studied, and in the best case, an enantiomeric excess of up to 94% could be obtained. Acidic hydrolysis of the initially formed *N*-protected amines **6** led to the corresponding free amines **7** without racemization. Although a stoichiometric amount of the ligand was used, about 90% of it could be recovered during the workup and reused without significant loss of chiral induction. The utility of the aziridino alcohols **2**−**5** as catalysts for the same reaction has also been evaluated and enantiomeric excesses of up to 76% were achieved using 0.25 equiv of the chiral ligand. A possible transition state for the addition reaction is also proposed.

Introduction

Nucleophilic addition of organometallic reagents to carbonyl compounds is a very important operation in organic synthesis, and the asymmetric version of this reaction is particularly useful. Several highly enantioselective additions to prochiral aldehydes leading to optically active alcohols have been reported,[1] and among the various organometallic compounds, diorganozincs serve as excellent alkyl nucleophiles. β-Amino alcohols have proved to be one of the most efficient types of catalyst for this reaction, and ee's up to 99% have been achieved.[2]

Although enormous progress has been made in the stereoselective addition of nucleophiles to aldehydes, considerably less attention has been paid to the corresponding enantioselective conversion of imines to chiral amines. Optically active amines are important compounds extensively utilized as resolving agents,[3] starting materials for the preparation of biologically active substances,[4] and chiral auxilliaries in asymmetric synthesis.[5] However, only a few examples of enantioselective alkylation of the imine functionality have been reported,[6] and this is primarily due to the relatively poor electrophilicity of the C=N function and the tendency of enolizable imines to undergo deprotonation instead of addition.

In 1990, Tomioka and co-workers reported the addition of organolithium compounds to *N*-aryl imines in the presence of stoichiometric amounts of chiral amino ethers.[7a] The corresponding secondary amines were isolated with enantiomeric purities ranging from 48 to 75%. Shortly after this report, the same authors developed a catalytic process, using a substoichiometric amount of the chiral ligand.[7b] In 1991, Itsuno and co-workers studied the addition of butyllithium to *N*-silyl imines in the presence of chiral promoters such as alcohols, diols, and amino alcohols.[8a] The same group has reported on the addition of butyllithium to *N*-alumino, *N*-boryl, and *N*-silyl imines in the presence of chiral nitrogen ligands including (−)-sparteine and proline-derived amino alcohols.[8b] Chiral bis(oxazolines) have been applied as promoters for the addition of organolithium reagents to *N*-aryl imines,[9] and ee's of up to 91% were obtained.

Despite the progress in catalytic enantioselective addition of dialkylzinc reagents to aldehydes, the application of the same methodology to *N*-aryl or *N*-silyl imines failed.[8a] These substrates are unreactive with diethylzinc even in the presence of a stoichiometric amount of an amino alcohol at high temperatures. The use of activated *N*-acyl or *N*-phosphinoyl imines has turned out to be crucial, and the first example of enantioselective addition of diethylzinc to the imine function was reported by Katritzky and co-workers in 1992.[10] Diethylzinc was reacted with *N*-(amidobenzyl)benzotriazoles (masked *N*-acyl imines) to afford the corresponding optically active amides in ee's up to 76%. Soon afterward, Soai and co-workers found that dialkylzinc reagents added to *N*-

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(2) For a review, see: (a) Noyori, R.; Kitamura, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 49. (b) Soai, K.; Niwa, S. *Chem. Rev. (Washington, D.C.)* **1992**, *92*, 833.
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(6) For a review, see: (a) Denmark, S. E.; Nicaise, O. J.-C. *J. Chem. Soc., Chem. Commun.* **1996**, 999. (b) Enders, D.; Reinhold: U. *Tetrahedron: Asymmetry* **1997**, *8*, 1895.
(7) (a) Tomioka, K.; Inoue, I.; Shindo, M.; Koga, K. *Tetrahedron Lett.* **1990**, *31*, 6681. (b) Tomioka, K.; Inoue, I.; Shindo, M.; Koga, K. *Tetrahedron Lett.* **1991**, *32*, 3095.
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(10) Katritzky, A. R.; Harris, P. A. *Tetrahedron: Asymmetry* **1992**, *3*, 437.

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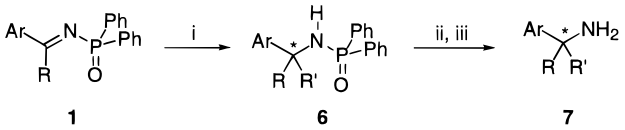
Scheme 1[a]



1 6 7

[a] Key: (i) R'_2Zn, ligand **2**−**5** (see Figure 1), toluene, 0 °C to rt; (ii) 1.5 M HCl in MeOH, rt; (iii) 15% NaOH.

(diphenylphosphinoyl) imines in the presence of catalytic or stoichiometric amounts of chiral *β*-amino alcohols with high enantioselectivities (75−91% ee).[11] Ukaji and coworkers have used a nitrone as the acceptor,[12] reacting dialkylzincs with 3,4-dihydroisoquinoline *N*-oxide derivatives to give the corresponding alkylated hydroxylamines with ee's ranging from 25 to 91%.

For the past few years, we have been exploring the use of chiral aziridines in asymmetric synthesis. Chiral aziridines are available in enantiomerically pure (or highly enriched) form by a variety of procedures,[13] and they are suitable building blocks for the synthesis of biologically active species.[14] The utility of C_2-symmetric aziridines as auxilliaries for asymmetric alkylation and aldol reactions of amide enolates has also been demonstrated.[15] We have evaluated C_2-symmetric bis(aziridines) as ligands for a variety of metal-mediated asymmetric transformations,[16] and in the best cases, ee's of >99% were obtained. The aziridine ligand is unusual in that slow pyramidal inversion introduces a *stereogenic nitrogen*.[13]

Recently, we have reported in a preliminary communication the use of some aziridino alcohols as promoters for the addition of diethylzinc to *N*-(diphenylphosphinoyl) imines[17] (Scheme 1). In this paper we present the extension of this study to some new aziridine ligands **2**−**5** (Figure 1) and substrates. By fine-tuning of the ligand structure, enantioselectivities of up to 94% ee could be obtained. A suggestion about a possible transition state for the addition reaction is proposed. Full experimental details about the preparation of the ligands and the addition reaction are given. We have also evaluated the utility of ligands **2**−**5** as catalysts in the same reaction. Acidic hydrolysis of the addition products **6** afforded the free amines **7**, without loss of enantiomeric purity (Scheme 1).

Synthesis of the Ligands

Figure 1 shows the aziridino alcohols that have been prepared and tested as promoters of the above-mentioned reaction. Three different approaches were used to obtain the ligands in enantiomerically pure form: (a) the use of the chiral pool, (b) Sharpless asymmetric aminohydroxylation,[18] and (c) Sharpless asymmetric dihydroxylation.[19]

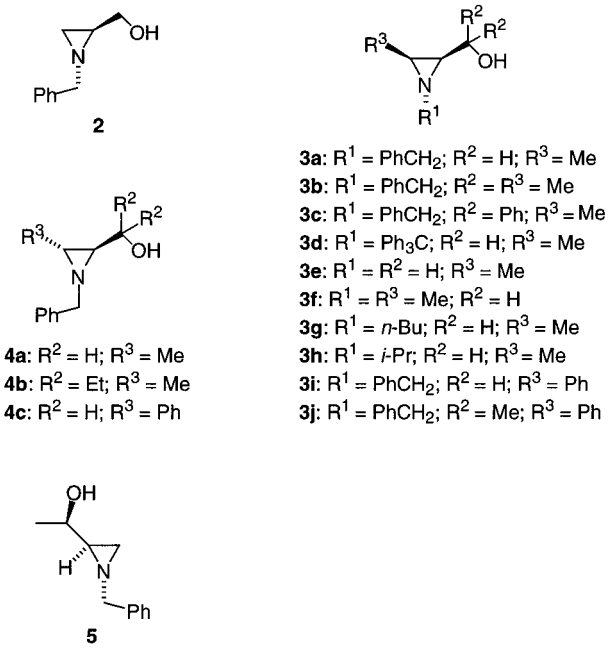
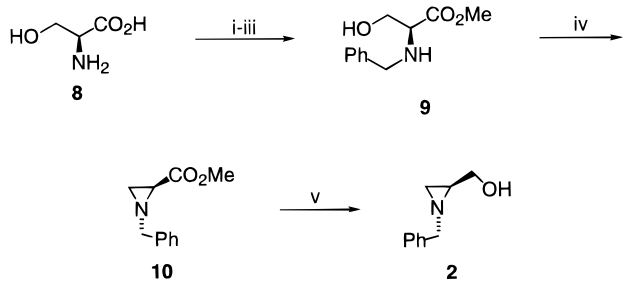


Figure 1.

Scheme 2[a]



[a] Key: (i) 2 M HCl in MeOH, reflux; (ii) Et_3N, PhCHO, MeOH, 0 °C; (iii) $NaBH_4$, 70% (three steps); (iv) PPh_3, CBr_4, Et_3N, CH_2Cl_2/$CHCl_3$, rt and then reflux, 39%; (v) $LiAlH_4$, THF, −40 °C to rt, 74%.

(a) Using the Chiral Pool: Synthesis of the Ligands 2, 3a−h, 4a,b, and 5. The starting materials for the preparation of the aziridino alcohols **2**, **3a**−**h**, **4a**,**b,** and **5** were the readily available amino acids L-serine, L-threonine, and *allo*-L-threonine. The synthesis of aziridino alcohol **2** is shown in Scheme 2. L−Serine **8** was converted into its methyl ester hydrochloride.[20] This was followed by a reductive alkylation,[21] to give the *N*-benzyl amino ester **9**, and reaction of **9** with Ph_3P and CBr_4[22] afforded the aziridino ester **10**. The ligand **2** was then obtained by reduction of **10** with $LiAlH_4$.

Starting from L-threonine **11** and following the same sequence of esterification−reductive alkylation as before,

(11) Soai, K.; Hatanaka, T.; Miyazawa, T. *J. Chem. Soc., Chem. Commun.* **1992**, 1097.
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(13) For a review, see: Tanner, D. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 599.
(14) See, for example: (a) Oppolzer, W.; Flaskamp, E. *Helv. Chim. Acta* **1977**, *60*, 204. (b) Baldwin, J. E.; Adlington, R. M.; Robinson, N. G. *J. Chem. Soc., Chem. Commun.* **1987**, 153. (c) Tanner, D.; Somfai, P. *Tetrahedron Lett.* **1987**, *28*, 1211. (d) Tanner, D.; He, H. M. *Tetrahedron* **1992**, *48*, 6079.
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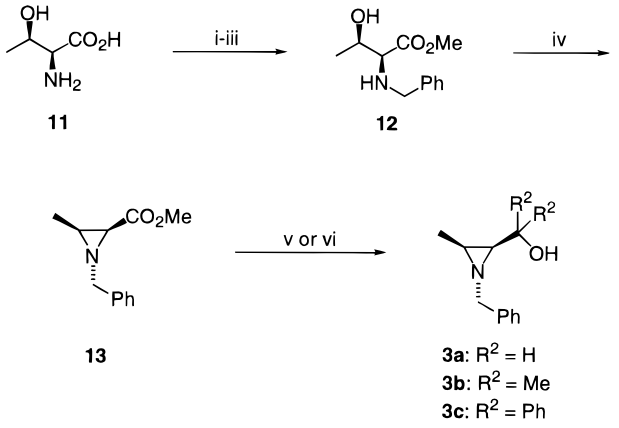
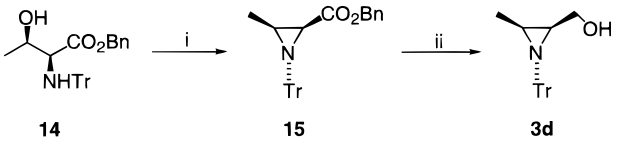
Scheme 3[a]



[a] Key: (i) 2 M HCl in MeOH, reflux; (ii) Et_3N, PhCHO, MeOH, 0 °C; (iii) $NaBH_4$, 69% (three steps); (iv) PPh_3, CCl_4, Et_3N, MeCN, rt, 67%; (v) $LiAlH_4$, THF, 0 °C to rt, 90% (for compound **3a**); (vi) MeLi (for compound **3b**) or PhMgBr (for compound **3c**), THF, −78 °C to rt, 83 and 78%, respectively.

Scheme 4[a]



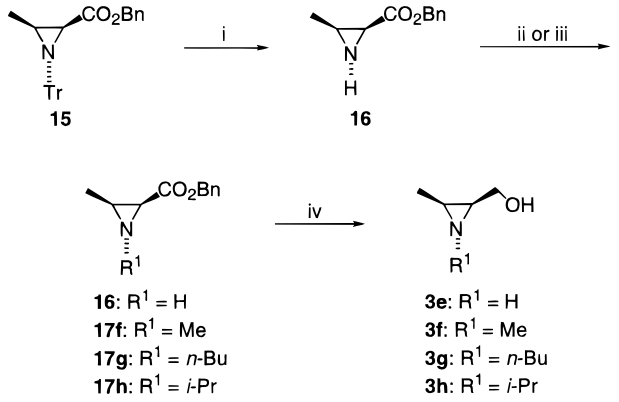
[a] Key: Tr = Ph_3C. (i) SO_2Cl_2, Et_3N, toluene, −50 °C, 72%; (ii) $LiAlH_4$, THF, −40 °C to rt, 78%.

the protected amino ester **12** was obtained (Scheme 3). It was then cyclized to the aziridino ester **13** by reaction with Ph_3P in the presence of CCl_4.[23] Reduction with $LiAlH_4$ led to the aziridino alcohol **3a**. Treatment of **13** with excess of MeLi or PhMgBr afforded the ligands **3b** and **3c**, respectively.

According to a literature procedure,[24] L-threonine was transformed into the *N*-trityl benzyl ester **14** (Scheme 4). This was cyclized to the aziridino ester **15** by reaction with SO_2Cl_2,[25] and **15** was then reduced with $LiAlH_4$ to yield the aziridino alcohol **3d**.

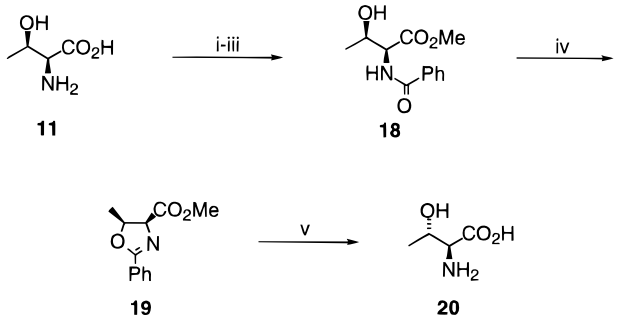
The N−H aziridino ester **16** (Scheme 5) was thought to be a suitable precursor for the synthesis of the ligands **3e**−**h**. The detritylation of **15** was first attempted with HCO_2H in MeOH,[25] but this was unsuccessful. The deblocking was finally achieved by treatment of **15** with CF_3CO_2H.[24a] Reduction of **16** with $LiAlH_4$ then yielded ligand **3e**. The *N*-methyl aziridino ester **17f** was prepared by treatment with K_2CO_3 and MeI in THF in the presence of 18-crown-6.[26] The alkylation procedure used for the preparation of **17f** was also applied to the synthesis of both **17g** and **17h**, but no alkylated product was formed after several days in refluxing THF. However, changing the solvent to MeCN afforded the expected alkylated products **17g** and **17h** in 70 and 85% yield, respectively. In the case of **17h**, a stoichiometric amount

Scheme 5[a]



[a] Key: Tr = Ph_3C. (i) CF_3CO_2H, $CHCl_3$/MeOH (1/1, v/v), −5 °C, 77%; (ii) MeI, K_2CO_3, 18-crown-6 (cat.), THF, rt, 44% (for compound **17f**); (iii) R^1Br (R^1 = *n*-Bu, *i*-Pr), K_2CO_3, 18-crown-6 (cat.), NaI (only for R^1 = *i*-Pr), MeCN, reflux, 70 and 85%, respectively (for compounds **17g,h**); (iv) $LiAlH_4$, Et_2O, 0 °C to rt, 50, 52, 70, and 65%, respectively.

Scheme 6[a]



[a] Key: (i) 2 M HCl in MeOH, reflux; (ii) Et_3N, MeOH, rt; (iii) PhCOCl, 0 °C, 84% (three steps); (iv) $SOCl_2$, 0 °C; (v) 6 M HCl, reflux, 86% (two steps).

of NaI was added to the reaction mixture to aid the substitution reaction by in situ generation of *i*-PrI. The aziridino esters **16** and **17f**−**h** were then reduced with $LiAlH_4$, to yield the desired aziridino alcohols **3e**−**h**.

Each of the ligands **2** and **3a**−**h** were obtained as single invertomers, due to a relatively high inversion barrier at nitrogen.[13] NOE studies on the ligand **3a** showed, as expected, that the benzyl group on the nitrogen and the hydroxymethyl group on the aziridine ring had a trans relationship to each other (see experimental part).

For the preparation of ligands **4a**,**b**, with opposite absolute configuration at C3 in the aziridine ring, the required *allo*-L-threonine was prepared from L-threonine in a five-step sequence.[27] First, L-threonine **11** was converted into its methyl ester hydrochloride.[20] After treatment with Et_3N, it was reacted in situ with PhCOCl, to give the *N*-benzoyl amino ester **18** (Scheme 6). Treatment of **18** with $SOCl_2$[27] gave the expected oxazoline **19**, and hydrolysis in 6 M HCl at reflux[27] yielded *allo*-L-threonine **20** in good overall yield.

allo-L−Threonine was transformed into the aziridino ester **21** according to Scheme 7. Reduction of **21** with $LiAlH_4$ afforded ligand **4a**, which was obtained as a mixture of invertomers at nitrogen in a 7:1 ratio, the major isomer being the one having the benzyl and the methyl groups in a cis relationship (see the Experimental Section). Treatment of **21** with excess of EtMgBr led to

(23) For a similar process, see: Shaw, K. J.; Luly, J. R.; Rapoport, H. *J. Org. Chem.* **1985**, *50*, 4515.

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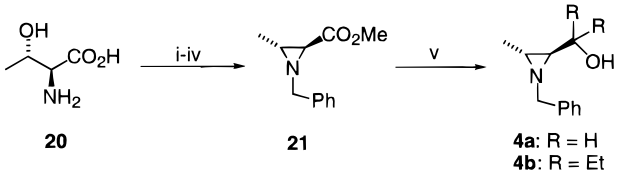
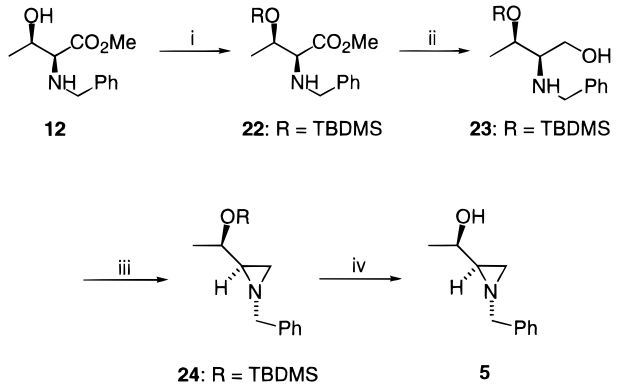
Scheme 7[a]



[a] Key: (i) 2 M HCl in MeOH, reflux; (ii) Et_3N, PhCHO, MeOH, 0 °C; (iii) $NaBH_4$, 84% (three steps); (iv) PPh_3, CCl_4, Et_3N, MeCN, rt, 66%; (v) $LiAlH_4$, THF, 0 °C to rt, 74% (for compound **4a**) or EtMgBr, THF, −78 °C to rt, 82% (for compound **4b**).

Scheme 8[a]



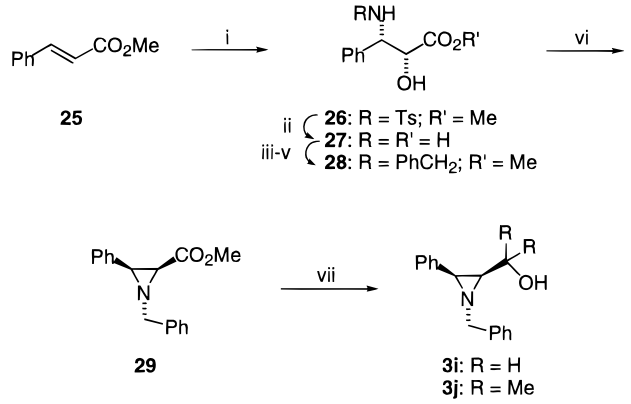
[a] Key: (i) TBDMSCl, imidazole, DMF, rt, 94%; (ii) DIBALH, CH_2Cl_2, 0 °C to rt, 58%; (iii) PPh_3, DEAD, THF, 0 °C to rt, 82%; (iv) $(n\text{-}Bu)_4N^+F^-$, THF, rt, 69%.

the aziridino alcohol **4b**. Only one isomer was detected in this case, with the same stereochemistry as the major invertomer of **4a**.

The ligand **5** was also prepared from L-threonine. The *N*-benzyl amino ester **12** was *O*-protected with *t*-$BuMe_2$-SiCl in the presence of imidazole[16c] (Scheme 8). Reduction with DIBALH afforded the amino alcohol **23**, which was then cyclized to the aziridine **24** under Mitsunobu conditions.[16c] Finally, **24** was *O*-deprotected by reaction with $(n\text{-}Bu)_4NF$,[28] to yield the desired aziridino alcohol **5**.

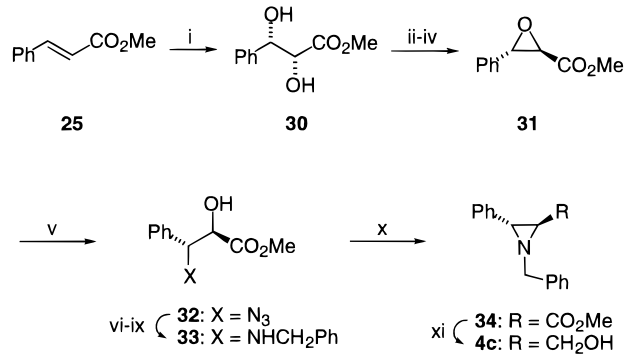
(b) The Aminohydroxylation Approach: Synthesis of the Ligands 3i,j. To investigate the effect of the substituent at C3 in the aziridine ring, ligands **3i**,**j** were prepared. The amino acid **27** was thought to be a good precursor for their synthesis and it was obtained as shown in Scheme 9. First, methyl cinnamate **25** was submitted to Sharpless asymmetric aminohydroxylation,[18] which gave **26** in 97% ee after recrystallization. **26** was transformed into the free amino acid **27** by deprotection with HBr in AcOH.[29] The latter was then converted into the *N*-benzyl amino ester **28** following the sequence esterification-reductive alkylation at nitrogen[21] (vide supra). It was possible to improve the optical purity at this stage, and after recrystallization of **28** from pentane/CH_2Cl_2, only one enantiomer could be detected by HPLC analysis (see the Experimental Section). The method that had been used for the preparation of ligand **3a** was applied for the cyclization step,[23] and the aziridino ester **29** was obtained in 35% overall yield (from **26**). The reduction of the aziridino ester **29** with $LiAlH_4$ afforded the ligand **3i**. Treatment of **29** with excess of MeMgBr then led to the aziridino alcohol **3j**.

Scheme 9[a]



[a] Key: (i) $K_2OsO_2(OH)_4$ (4 mol %), $(DHQ)_2$−PHAL (5 mol %), TsN(Cl)Na·$3H_2O$, *t*-BuOH/H_2O (v/v = 1/1), rt, 51%; (ii) 45% HBr in $MeCO_2H$, PhOH, 75 °C; (iii) 2 M HCl in MeOH, reflux; (iv) Et_3N, PhCHO, MeOH, 0 °C; (v) $NaBH_4$, 41% (four steps); (vi) PPh_3, CCl_4, Et_3N, MeCN, rt, 86%; (vii) $LiAlH_4$, Et_2O, 0 °C to rt, 94% (for compound **3i**) or MeMgBr, THF, −78 to −5 °C, 89% (for compound **3j**).

Scheme 10[a]



[a] Key: (i) $K_2OsO_2(OH)_4$ (0.2 mol %), $(DHQ)_2$−PHAL (0.5 mol %), NMO, *t*-BuOH, rt, 72%; (ii) $Me(OMe)_3$, *p*-TsOH, CH_2Cl_2, rt; (iii) MeCOBr, CH_2Cl_2, −20 °C to rt; (iv) K_2CO_3, MeOH, −20 °C, 76% (three steps); (v) NaN_3, NH_4Cl, MeOH, reflux; 95%; (vi) H_2, 5% Pd−C, MeOH, rt; (vii) 2 M HCl in MeOH, reflux; (viii) Et_3N, PhCHO, MeOH, 0 °C; (ix) $NaBH_4$, 56% (four steps); (x) PPh_3, CCl_4, Et_3N, MeCN, rt, 88%; (xi) $LiAlH_4$, THF, 0 °C to rt, 59%.

(c) The Dihydroxylation Approach: Synthesis of the Ligand 4c. Sharpless asymmetric dihydroxylation protocol[19] was used to establish the required stereochemistry of ligand **4c**. Methyl cinnamate **25** was converted into the diol **30**[30] (Scheme 10), which was obtained in 98% ee after recrystallization. Compound **30** was stereospecifically transformed into the epoxide **31**.[31] Ring opening of the epoxide with NaN_3,[32] followed by hydrogenation and reductive alkylation[21] of the resultant amine, led to the *N*-protected amino ester **33**. Cyclization as previously described for **12** (Scheme 3) and reduction of the ester with $LiAlH_4$ afforded the aziridino alcohol **4c**.

Results and Discussion

The aziridino alcohols **2**−**5** were tested as promoters for the addition of dialkylzinc reagents to several *N*-(diphenylphosphinoyl) imines. The required imines **1**

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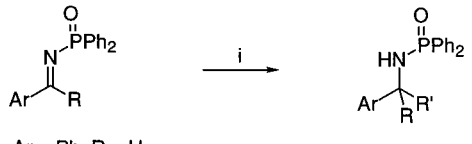
(32) Legters, J.; Thijs, L.; Zwanenburg, B. *Tetrahedron Lett.* **1989**, *30*, 4881.

Scheme 11[a]



1a: Ar = Ph; R = H
1b: Ar = 1-Naphthyl; R = H
1c: Ar = 4-Cl-C_6H_4; R = H
1d: Ar = Ph; R = Me

6aa: Ar = Ph; R = H; R' = Me
6ab: Ar = Ph; R = H; R' = Et
6b: Ar = 1-Naphthyl; R = H; R' = Et
6c: Ar = 4-Cl-C_6H_4; R = H; R' = Et
6d: Ar = Ph; R = Me; R' = Et

[a] Key: (i) R'_2Zn (3 equiv), ligand **2**−**5** (1 equiv), toluene, 0 °C to rt.

Table 1. Addition Reaction of R'_2Zn to 1 Promoted by the Ligands 2−5

entry	imine	ligand	R′	product	yield (%)[a]	ee (%)[b]	config[c]
1	**1a**	**2**	Et	**6ab**	18	12	*R*
2	**1a**	**3a**	Me[d]	**6aa**	68	75	*R*
3	**1a**	**3a**	Et	**6ab**	63	94	*R*
4	**1b**	**3a**	Et	**6b**	59	80	*R*
5	**1c**	**3a**	Et	**6c**	48	82	*R*[e]
6	**1a**	**3b**	Et	**6ab**	92	59	*R*
7	**1a**	**3c**	Et	**6ab**	56	16	*S*
8	**1a**	**3d**	Et	**6ab**	33	3	*S*
9	**1a**	**3e**	Et	***f***			
10	**1a**	**3f**	Et	**6ab**	78	80	*R*
11	**1a**	**3g**	Et	**6ab**	66	83	*R*
12	**1a**	**3h**	Et	**6ab**	72	91	*R*
13	**1a**	**3i**	Et	**6ab**	57	86	*R*
14	**1a**	**3i**[g]	Et	**6ab**	57	50	*R*
15	**1a**	**3j**	Et	**6ab**	60	52	*R*
16	**1a**	**4a**	Me[h]	**6aa**	36	4	*R*
17	**1a**	**4a**	Et	**6ab**	83	5	*R*
18	**1b**	**4a**	Et	**6b**	21	6	*R*
19	**1c**	**4a**	Et	**6c**	59	11	*R*[e]
20	**1d**	**4a**	Et	***i***			
21	**1a**	**4b**	Et	**6ab**	63	44	*S*
22	**1a**	**4c**	Et	**6ab**	63	38	*R*
23	**1a**	**5**	Et	**6ab**	45	55	*R*

[a] Isolated yield after flash chromatography (silica gel, pentane/acetone). [b]Determined by HPLC analysis on a chiral column (ChiralCel OD-H). [c]Determined by comparison of the optical rotation of the free amine with the data given in the literature (see the Experimental Section). [d]Six equivalents of dimethylzinc was used and the reaction was run for 11 days at rt. [e]Tentatively assigned by the retention times of the enantiomers on the HPLC analysis, according to our observations with the products **6a**,**b**. [f]After 7 days at rt, no product was detected (^{1}H NMR). [g]The optical purity of the ligand was 50%. [h] Six equivalents of dimethylzinc was used and the reaction was running for 8 days at rt. [i]After 4 days at rt, no product was detected (^{1}H NMR).

(Scheme 11) were prepared from the corresponding aldehydes or ketones, according to the literature.[33] As a general procedure, the dialkylzinc reagent (3 equiv) was added dropwise to a stirred solution of the imine **1** and the corresponding aziridino alcohol **2**−**5** (1 equiv) in dry toluene, under nitrogen, at 0 °C. The temperature was allowed to rise slowly to rt and then the reaction was stirred for 4 days. After quenching with saturated aqueous NH_4Cl and usual workup, the expected products **6** were obtained (Scheme 11, Table 1).

Table 1 shows the yields and ee's obtained with all the ligands **2**−**5**. The imine **1a** proved to be the best substrate for the addition reaction. Ligand **2**, derived from serine, gave only poor conversion and low ee (Table 1, entry 1). However, introduction of a methyl group as in **3a** resulted in a dramatic increase in both yield and enantioselectivity (Table 1, entry 3). A somewhat lower ee was obtained when the methyl group on the aziridine ring, R^3 (Figure 1), was exchanged for a phenyl group (Table 1, entry 13). When the steric bulk of the side chain bearing the hydroxyl group was varied, a decrease in enantioselectivity was found upon increasing the size of the R^2 substituent in ligands **3** (compare entry 3 with 6 and 7 and entry 13 with 15). Surprisingly, ligand **3c** induced the opposite configuration in the product (Table 1, entry 7) for reasons not yet understood. In the case of the trans ligands **4**, a preference for the *S* enantiomer was observed when R^2 (Figure 1) was changed to a larger group (compare entries 17 and 21).

The size of the substituent on nitrogen is also important. The simplest ligand, **3e**, proved to be unsuitable for promotion of the addition reaction. No reaction product was detected after 7 days at rt (Table 1, entry 9). When R^1 was an alkyl group, however, good selectivities were observed. The ee increased upon going from a primary (Table 1, entries 10 and 11) to a secondary (Table 1, entry 12) alkyl group. According to the result obtained with the ligand **3a**, it seems that the presence of an aromatic ring in R^1 is very important. Ligand **3a**, in which R^1 is a benzyl group, gave the highest enantioselectivity (Table 1, entry 3). Increasing the steric bulk of R^1 resulted in an unexpected inversion of the stereochemical outcome of the reaction. When ligand **3d**, bearing a trityl group on the nitrogen, was used (Table 1, entry 8), the reaction was very sluggish, and we presume that the very large trityl group inhibits coordination between the zinc and the nitrogen.

Comparison of entries 3 and 17 clearly shows the importance of the stereochemistry at C3. Almost racemic product was obtained when ligand **4a**, derived from *allo*-L-threonine, was tested. A similar effect was observed when phenyl was the substituent at C3. The ee dropped from 86% for ligand **3i** (entry 13) to 38% for ligand **4c** (entry 22).

Introduction of a stereocenter at the carbinol site (ligand **5**, entry 23) improved matters somewhat as compared to ligand **2** (Table 1, entry 1), but we have as yet no convincing explanation for the fact that both of these ligands, although having different absolute configuration of the aziridine backbone, induce the same sense of chirality in the product.

Concerning the substrates, imines **1b** and **1c** were shown to be less effective than **1a** in the enantioselective addition reaction, although good selectivities were observed with the ligand **3a** (Table 1, entries 4 and 5). However, imine **1d**, derived from acetophenone, turned out to be inert under the standard reaction conditions. No addition product was detected in the reaction mixture after 4 days at rt (Table 1, entry 20).

Me_2Zn turned out to be much less reactive than Et_2Zn, and a larger excess of the former as well as much longer reaction times were necessary to achieve moderate conversions and low to moderate ee's (Table 1, entries 2 and 16).

In all cases, although a stoichiometric amount of the chiral ligand was used, up to 90% of it could be recovered during the workup in a typical experiment. The recovered ligand could be used in further experiments without loss of chiral induction.[34]

Based on the results in Table 1, the stereochemical outcome of the reaction could be rationalized by assuming that the addition takes place through the transition state depicted in Figure 2 (for ligand **3a** and imine **1a**). The steric bulk of the substituent at C3 on the aziridine ring

(33) (a) Jennings, W. B.; Lovely, C. J. *Tetrahedron* **1991**, *47*, 5561. (b) Krzyzanowska, B.; Stec, W. J. *Synthesis* **1982**, 270.

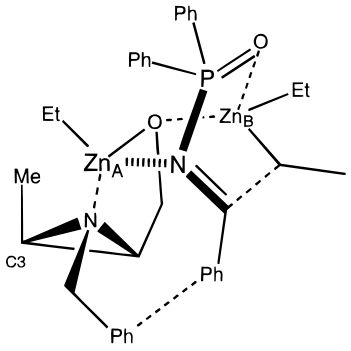
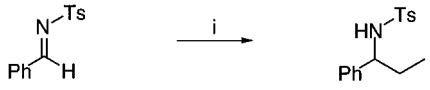


Figure 2.

Scheme 12[a]



35 **36**

[a] Key: (i) Et_2Zn (3 equiv), ligand **3a** (1 equiv), toluene, 0 °C, 45%, racemic.

forces Zn_B to be in the position shown, determining in this way the stereochemistry at Zn_A. The extra coordination between the oxygen of the imine and Zn_B would lead to the formation of a bicyclic transition state. The stereochemistry observed in the product would be obtained if an ethyl group from Zn_B was transferred to the imine carbon. For steric reasons, it appears advantageous to have a small group on the hydroxylic carbon, and this assumption was borne out experimentally. $\pi-\pi$ Interactions between the phenyl group of R^1 and the aromatic group on the imine carbon are expected to stabilize the depicted transition state to some extent, leading to the improved selectivity observed. The loss of enantioselectivity found with ligands **2** and **4**, having no substituent or inverted configuration at C3, might be due to the possibility of forming two different transition states with opposite configuration at Zn_A.

Another imine with a different electron-withdrawing group on the nitrogen was also tested. Et_2Zn (3 equiv) was added dropwise to a stirred solution of the *N*-tosyl imine **35**[33a] and the aziridino alcohol **3a** (1 equiv) in dry toluene, under nitrogen, at 0 °C (Scheme 12). The reaction was complete after 38 h at 0 °C. Workup as for the addition to imines **1** afforded the expected product **36**[35] in 45% isolated yield, but in racemic form. Assuming that the reaction takes place through a transition state similar to the one depicted in Figure 2, the possibility of coordination of both oxygens of the sulfonyl group to Zn_B would allow the imine to aproach the complex between the aziridino alcohol moiety and Et_2Zn in two different ways: the one shown in Figure 2 and another one in which the imine is turned 180° around the $N-Zn_A$ axis. This would explain the obtention of the racemic product in this case.

The good enantioselectivities obtained with some of the ligands prompted us to test them in a catalytic reaction. Ligand **3a** was chosen as catalyst and imine **1a** as substrate for the study, because this pair gave the best ee in the stoichiometric reaction. Several addition reactions of Et_2Zn (3 equiv) to the imine **1a** were set up with different amounts of the ligand **3a** (0.50, 0.25, and 0.10 equiv) under the same conditions as for the stoichiometric reaction. The results are shown in Table 2 (entries 1−3). As can be seen, the ee decreased upon reducing the amount of ligand. When 0.10 equiv of the ligand was used, the reaction was much slower than in the other cases, indicating a ligand acceleration effect.[36] After the normal reaction time (4 days at rt), only 37% of the addition product was isolated after workup, together with some unreacted starting material. However, moderate enantioselectivity was still obtained (Table 2, entry 3). When 0.50 and 0.25 equiv of the ligand were used, conversions obtained were similar to the one observed in the stoichiometric reaction (Table 1, entry 3) and with the same reaction times, although the products were obtained with a slight decrease in the enantioselectivity.

Table 2. Addition Reaction of Et_2Zn to 1a Catalyzed by the Ligands 3−4

entry	ligand	equiv	yield (%)[a]	ee (%)[b]	config[c]	ee cat./ stoich[d]
1	**3a**	0.50	76	87	*R*	0.93
2	**3a**	0.25	68	75	*R*	0.80
3	**3a**	0.10	37	49	*R*	0.52
4	**3b**	0.25	24	33	*R*	0.56
5	**3c**	0.25	50	9	*S*	0.56
6	**3f**	0.25	52	45	*R*	0.56
7	**3g**	0.25	63	60	*R*	0.72
8	**3h**	0.25	60	65	*R*	0.71
9	**3i**	0.50	64	81	*R*	0.94
10	**3i**	0.25	50	76	*R*	0.88
11	**3j**	0.25	50	22	*R*	0.42
12	**4b**	0.25	47	17	*S*	0.39
13	**4c**	0.25	48	28	*R*	0.73

[a] Isolated yield after flash chromatography (silica gel, pentane/acetone). [b]Determined by HPLC analysis on a chiral column (ChiralCel OD-H). [c]Determined by comparison of the optical rotation of the free amine with the data given in the literature (see the Experimental Section). [d] Ratio between the ee obtained in the catalytic and in the corresponding stoichiometric reaction (see Table 1).

Since the ee obtained with 0.25 equiv of the ligand was still relatively good, aziridino alcohols **3b**,**c**,**f**−**j** and **4b**,**c** were also tested in the catalytic reaction (0.25 equiv of the ligand) in order to get some information about the optimum structure for the catalyst. The rest of the ligands were not evaluated because of their inefficiency to induce enantioselectivity in the stoichiometric reaction. The results are summarized in Table 2. To determine which is the ligand structure that leads to the smallest loss of enantioselectivity, the ratio between the ee in the catalytic and in the stoichiometric reactions was calculated (Table 2, last column). As can be seen, that ratio varied from 0.39 to 0.88. Again, ligands with a primary alcohol on the side chain and an α-branched substituent at nitrogen gave less loss of selectivity (Table 2, entries 2, 7, 8, 10, and 13). The presence of an aromatic ring on the substituent at nitrogen seems to give an additional beneficial effect (Table 2, entries 2 and 10), possibly by $\pi-\pi$ stacking in the transition state.[37] Ligand **3i**, with

(34) A sample of ligand **3a** was recovered from two successive stoichiometric reactions and it was used to set up a catalytic (0.50 equiv of **3a**) addition reaction to the imine **1a**. The expected product was isolated in 79% yield and 81% ee, a value that is only slightly lower than the one obtained in the same catalytic reaction but using fresh ligand (Table 2, entry 1).

(35) Sisko, J.; Weinreb, S. M. *J. Org. Chem.* **1990**, *55*, 393.

(36) Berrisford, D. J.; Bolm, C.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1059.

(37) For a similar discussion concerning the AD reaction, see: Kolb, H. C.; Andersson, P. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1994**, *116*, 1278.

(38) Bedekar, A. V.; Koroleva, E. B.; Andersson, P. G. *J. Org. Chem.* **1997**, *62*, 2518.

Table 3. Study on the Variation of the ee with the Reaction Time

reaction time (h)	yield (%)[a]	ee (%)[b]	reaction time (h)	yield (%)[a]	ee (%)[b]
5.0	35	75	47.0	64	76
9.0	44	79	61.0	66	75
22.5	58	76	102.0	69	75
32.5	61	75			

[a] Estimated by ^{1}H NMR on the crude sample before purification by flash chromatography. [b]Determined by HPLC analysis on a chiral column (ChiralCel OD-H).

a phenyl group on the aziridine ring, proved to be the most efficient, giving a loss of ee of only 12% (Table 2, entry 10).

A kinetic study was performed in order to check if there was any degradation of the catalytic system during the reaction time. Imine **1a** was used as substrate and ligand **3a** (0.25 equiv) as catalyst. Aliquots were extracted from the reaction during the whole reaction time. After hydrolysis with saturated aqueous NH_4Cl and extraction with ether, the organic phase was dried over $MgSO_4$. Evaporation of the solvent afforded a residue that was purified by flash chromatography. The product was analyzed by chiral HPLC (see the Experimental Section) and the results obtained are presented in Table 3. Two interesting features of the reaction are apparent. The rate is fast at the beginning and slows down after the first day. The yield of the addition product reaches 58% after 22.5 h and increases only very slightly from that point till the end. On the other hand, the ee is practically constant during the whole reaction time, so the efficiency of the catalytic system in inducing chirality is not impaired during the reaction.

The presence of an excess of Et_2Zn in the reaction medium seems to be beneficial in order to get good selectivities in the catalytic process. The addition reaction indicated in Table 2, entry 2, was repeated, but adding Et_2Zn very slowly (addition time, 26 h) with the aid of a syringe pump. The reaction was quenched and worked up in the usual way 3 h after the addition was complete. Product **6ab** was isolated in 48% yield and 62% ee, which is slightly lower than the one obtained under the standard conditions (Table 2, entry 2). According to previous observations made in the case of the addition to aldehydes,[2b] the ethylzinc amide that is formed after the addition of Et_2Zn to the imine could also form a complex with the chiral catalyst, which might reduce the enantioselectivity of the latter. When an excess of Et_2Zn is present, the chiral complex may be more easily formed between Et_2Zn and the chiral catalyst, securing a stereoselective pathway.

One experiment was performed in order to study the correlation between the optical purity of the ligand and the ee obtained in the addition product. A sample of ligand **3i** of 50% optical purity was prepared from optically pure and racemic **3i**. A stoichiometric addition of Et_2Zn to **1a** was set up with the optically enriched ligand as promoter, giving 57% yield and 50% ee (Table 1, entry 14). If there had been a linear correlation between the ee's of the product and the ligand, a value of 43% [corresponding to 50% of the ee obtained in the stoichiometric reaction with optically pure **3i** (Table 1, entry 13)] would have been expected. Therefore, it can be concluded that there is a small chiral amplification in this case.

Conclusions

A set of new chiral aziridino alcohols **2**−**5** has been synthesized and tested as promoters for the enantioselective addition of dialkylzinc reagents to *N*-(diphenylphosphinoyl) imines **1**. In the best case, an enantioselectivity of up to 94% could be obtained. Acidic hydrolysis of the initially formed *N*-protected amines **6** led to the corresponding free amines **7** without racemization. Although a stoichiometric amount of the ligand was used, about 90% of it could be recovered during the workup and reused without significant loss of chiral induction. The utility of the aziridino alcohols **2**−**5** as catalysts for the same reaction has also been evaluated, and enantioselectivities of up to 76% were achieved using 0.25 equiv of the chiral ligand. To the best of our knowledge, this is the first time that aziridino alcohols have been applied as ligands in the above-mentioned reaction.

Experimental Section

For general experimental information, see ref 38. Unless otherwise noted, final product solutions were dried over $MgSO_4$, filtered, and evaporated. Flash chromatography was performed on silica gel (Matrex 60A, 37−70 μm). TLC analyses were performed on precoated TLC plates, SIL G-60 UV_{254}, which were purchased from Macherey-Nagel. The following chromatography solvent systems were used: A, pentane/Et_2O; B, pentane/Et_2O/MeOH; C, pentane/ethyl acetate; D, pentane/ethyl acetate/MeOH; E, pentane/acetone; F, pentane/$CHCl_3$/MeOH; G, pentane/$CHCl_3$/MeOH/Et_3N; H, $CHCl_3$/MeOH; I, $CHCl_3$/MeOH/Et_3N. Unless otherwise mentioned, R_f values were taken in pentane/Et_2O 1/1, and $[\alpha]_D$ values were measured in CH_2Cl_2. HPLC analysis was carried out on a chiral column (ChiralCel OD-H), using a 254 nm UV detector, 10% *i*-PrOH in hexane as eluent, and a flow rate of 0.5 mL/min. ^{1}H and ^{13}C NMR spectra were recorded at 400 and 100.4 MHz, respectively. Et_2Zn and Me_2Zn were purchased from Aldrich Co. Imines **1** were prepared according to a literature procedure.[33]

[(2*S*)-*N*-Benzyl-2-aziridinyl]methanol (2).[17,39] The aziridino ester **10** was synthesized following a literature procedure.[22] **10** (1.339 g, 7.0 mmol) was dissolved in dry THF (20 mL) under N_2 and cooled to −40 °C. $LiAlH_4$ (7.0 mL 1.0 M solution in THF, 7.0 mmol) was added dropwise and the reaction was stirred for 4 h, allowing the temperature to rise slowly to rt. Then, the reaction was quenched following a literature procedure.[40] After evaporation of the solvent, the resultant residue was purified by flash chromatography (solvent G, 90/10/1/1), yielding 850 mg (74%) of the expected aziridino alcohol **2**: R_f 0.30 (solvent I, 95/5/1); mp 84−85 °C; $[\alpha]^{25}_D = -11.3$ (c = 1.01); IR (KBr, cm^{-1}) 3125; ^{1}H NMR δ 1.45−1.49 (1 H, m), 1.80−1.86 (2 H, m), 3.25 (1 H, br s), 3.36 (1 H, dd, J = 11.8, 5.4 Hz), 3.43, 3.47 (1 H each, 2 d, J = 13.4 Hz each), 3.76 (1 H, dd, J = 11.8, 2.9 Hz), and 7.24−7.37 (5 H, m); ^{13}C NMR δ 31.1, 40.4, 62.5, 64.0, 127.2, 128.0, 128.4, and 138.8; MS (EI) m/z (rel intensity) 91 ($M^+ - 72$, 100), 72 (82), 65 (20), and 44 (56).

***N*-Benzyl-L-threonine Methyl Ester (12).** MeOH (20 mL) was cooled in an ice−NaCl bath and $SOCl_2$ (1.46 mL, 20.0 mmol) was added dropwise. To the resultant solution of HCl in MeOH, L-threonine (2.431 g, 20.0 mmol) was added and the reaction mixture was refluxed for 1 h.[20] After that time, MeOH was evaporated and another 20 mL of a 2 M solution of HCl in MeOH, prepared in the same way as before, was added and the reaction was refluxed for another hour. MeOH was evaporated again and the resultant L-threonine methyl ester hydrochloride was submitted to a reductive alkylation, according to a previously described procedure,[21] to yield 3.084 g (69% from threonine) of the title compound: R_f 0.19; $[\alpha]^{24}_D = -61.3$ (c = 1.05); IR (neat, cm^{-1}) 3444, 1732, 1199; ^{1}H NMR (300

(39) Schwan, A. L.; Refvik, M. D. *Tetrahedron Lett.* **1993**, *34*, 4901.
(40) Micovic, V. M.; Mihailovic, M. L. *J. Org. Chem.* **1953**, *18*, 1190.

MHz) δ 1.20 (3 H, d, J = 6.2 Hz), 2.05 (1 H, br s), 3.04 (1 H, d, J = 7.6 Hz), 3.63−3.70 (2 H, m), 3.72 (3 H, s), 3.84 (1 H, d, J = 12.9 Hz), and 7.22−7.37 (5 H, m); ^{13}C NMR (75.5 MHz) δ 19.3, 51.9, 52.6, 67.3, 68.0, 127.3, 128.3, 128.4, 139.1, and 174.1; MS (EI) m/z (rel intensity) 208 ($M^+ - 15$, <1), 179 (17), 178 (18), 91 (100), and 88 (20). Anal. Calcd for $C_{12}H_{17}NO_3$: C, 64.54; H, 7.69; N, 6.27. Found: C, 64.30; H, 7.73; N, 6.12.

Methyl (2*S*,3*S*)-*N*-Benzyl-3-methyl-2-aziridinecarboxylate (13).[17,41] The *N*-protected amino ester **12** was cyclized to the aziridino ester **13** following a previously described procedure.[23] The isolated yield of **13** was 67%: R_f 0.41; (lit.[41] bp_2 120−122 °C); $[\alpha]^{25}_D = -77.1$ (c = 0.96); IR (neat, cm^{-1}) 1750, 1718, 1195, and 1124; ^{1}H NMR (300 MHz) δ 1.29 (3 H, d, J = 5.7 Hz), 1.97−2.06 (1 H, m), 2.24 (1 H, d, J = 6.0 Hz), 3.56, 3.63 (1 H each, 2 d, J = 13.8 Hz each), 3.73 (3 H, s), and 7.20−7.40 (5 H, m); ^{13}C NMR (75.5 MHz) δ 13.2, 41.8, 42.6, 52.0, 63.6, 127.1, 127.8, 128.3, 137.9, and 170.2; MS (EI) m/z (rel intensity) 205 (M^+, 2), 114 (97), 91 (100), 59 (79), and 54 (26).

[(2*S*,3*S*)-*N*-Benzyl-3-methyl-2-aziridinyl]methanol (3a).[17,42] To a stirred suspension of $LiAlH_4$ (593 mg, 15.0 mmol) in dry THF (20 mL), under N_2, cooled to 0 °C, a solution of the aziridino ester **13** (1.035 g, 5.0 mmol) in dry THF (10 mL) was added dropwise during ca. 10 min. The reaction mixture was stirred for 3 h, allowing the temperature to rise to rt. Then the reaction was quenched following a literature procedure.[40] After evaporation of the solvent, the residue was chromatographed (solvent A, 6/1, 4/1, 1/1 and then solvent B, 50/50/2), giving 798 mg (90%) of the aziridino alcohol **3a**: R_f 0.17 (Et_2O); (lit.[42] $bp_{0.005}$ 94−96 °C); $[\alpha]^{24}_D = +17.3$ (c = 1.04); IR (neat, cm^{-1}) 3383; ^{1}H NMR (300 MHz) δ 1.18 (3 H, d, J = 5.7 Hz), 1.71−1.85 (2 H, m), 2.38 (1 H, br s), 3.47−3.57 (3 H, m), 3.73 (1 H, dd, J = 11.6, 5.0 Hz), and 7.20−7.40 (5 H, m); ^{13}C NMR (75.5 MHz) δ 13.3, 39.3, 44.3, 60.0, 64.2, 127.1, 127.9, 128.4, and 139.1; MS (EI) m/z (rel intensity) 178 ($M^+ + 1$, <1), 177 (M^+, 1), 91 (87), 86 (85), and 58 (100).

3a was obtained as a single invertomer at nitrogen, as shown by the NMR data, and a NOESY experiment[43] was performed in order to establish the absolute configuration at nitrogen. An enhancement of the signal corresponding to the benzylic protons was observed upon irradiation of both aziridine protons. An NOE was also obtained from the hydrogens of the CH_2O group when the methyl group was irradiated. These results confirm that the benzyl group on the nitrogen has a trans relationship to both the methyl and the hydroxymethyl groups on the aziridine ring.

2-[(2*S*,3*S*)-*N*-Benzyl-3-methyl-2-aziridinyl]-2-propanol (3b). The aziridino ester **13** (205 mg, 1.0 mmol) was dissolved in dry THF (5 mL) under N_2 and cooled to −78 °C. Methyllithium (2.5 mL 1.2 M solution in THF, 3.0 mmol) was added dropwise and the reaction was stirred overnight allowing the temperature to rise to rt. Then, water (10 mL) was added and the mixture was extracted with ether (2 × 20 mL). The combined organic layers were washed with brine and dried. Flash chromatography (solvent A, 9/1, 6/1), afforded 170 mg (83%) of the aziridino alcohol **3b** as an oil: R_f 0.40; $[\alpha]^{25}_D = +11.3$ (c = 1.09); IR (neat, cm^{-1}) 3447; ^{1}H NMR (300 MHz) δ 1.03, 1.20 (3 H each, 2 s), 1.36 (3 H, d, J = 5.9 Hz), 1.45 (1 H, d, J = 6.6 Hz), 1.66−1.72 (1 H, m), 2.97 (1 H, br s), 3.44, 3.71 (1 H each, 2 d, J = 13.2 Hz each), and 7.21−7.39 (5 H, m); ^{13}C NMR (75.5 MHz) δ 13.7, 25.6, 31.7, 40.3, 50.3, 64.5, 67.1, 127.1, 128.27, 128.32, and 139.1; MS (EI) m/z (rel intensity) 205 (M^+, 22), 190 (49), 178 (37), 147 (52), and 91 (100). Anal. Calcd for $C_{13}H_{19}NO$: C, 76.04; H, 9.35; N, 6.82. Found: C, 75.82; H, 9.43; N, 6.71.

α-[(2*S*,3*S*)-*N*-Benzyl-3-methyl-2-aziridinyl]-α-phenylbenzyl Alcohol (3c). PhMgBr was prepared by adding a solution of PhBr (0.24 mL, 2.2 mmol) in dry THF (2 mL) to a suspension of Mg (55 mg, 2.3 mmol) in the same solvent (1 mL) under N_2, at such a rate to allow a gentle reflux of THF. The reaction mixture was then refluxed for 2 h. After that time, the reaction was cooled to −78 °C and the solution of the aziridino ester **13** (205 mg, 1.0 mmol) in dry THF (2 mL) was added. The reaction mixture was stirred overnight, allowing the temperature to rise to rt. Water (10 mL) was added and the resultant mixture was extracted with ether (2 × 20 mL). The combined extracts were washed with water and brine and dried. The solvent was evaporated and the residue was chromatographed (solvent A, 9/1), to give 257 mg (78%) of the title compound: R_f 0.65; mp 117−118 °C; $[\alpha]^{25}_D = +60.2$ (c = 1.10); IR (KBr, cm^{-1}) 3366; ^{1}H NMR (300 MHz) δ 1.07 (3 H, d, J = 6.1 Hz), 1.94 (1 H, quintet, J = 6.1 Hz), 2.47 (1 H, d, J = 6.1 Hz), 3.51, 3.78 (1 H each, 2 d, J = 13.4 Hz each), 4.62 (1 H, s), 7.10−7.37, and 7.48−7.54 (13 and 2 H, respectively, 2 m); ^{13}C NMR (75.5 MHz) δ 13.5, 40.3, 51.2, 63.6, 73.6, 125.7, 126.3, 126.4, 126.8, 127.1, 127.8, 128.0, 128.3, 138.5, 145.1, and 149.5; MS (EI) m/z (rel intensity) 329 (M^+, 1), 224 (92), 167 (64), 105 (65), 91 (100), and 77 (63). Anal. Calcd for $C_{23}H_{23}NO$: C, 83.84; H, 7.05; N, 4.25. Found: C, 83.64; H, 7.15; N, 4.20.

[(2*S*,3*S*)-*N*-Trityl-3-methyl-2-aziridinyl]methanol (3d). The aziridino ester **15** was prepared as previously reported.[25] All the physical and spectroscopic data of the product were in complete agreement with the reported data,[25] except for the melting point (140−142 °C; lit.[25] mp 99-101 °C) and the optical rotation {$[\alpha]^{24}_D = -114.3$ (c = 1.55, $CHCl_3$); lit.[25] $[\alpha]^{20}_D = -108.9$ (c = 1.54, $CHCl_3$)}. **15** was reduced in the same way as for the synthesis of **2**. The crude residue was purified by flash chromatography (solvent A, 95/5, 9/1, 6/1), giving 78% of the expected aziridino alcohol **3d**: R_f 0.36; mp 113 °C; $[\alpha]^{24}_D = +13.5$ (c = 1.05); IR (KBr, cm^{-1}) 3436; ^{1}H NMR δ 1.31−1.37 (4 H, m), 1.44−1.49 (1 H, m), 1.76 (1 H, t, J = 5.6 Hz), 3.81 (1 H, dt, J = 11.2, 5.6 Hz), 3.88−3.94 (1 H, m), 7.20−7.32 and 7.47−7.51 (9 and 6 H, respectively, 2 m); ^{13}C NMR δ 13.5, 30.9, 36.3, 61.2, 74.5, 126.7, 127.5, 129.4, and 144.7; MS (EI) m/z (rel intensity) 243 ($M^+ - 86$, 100), 241 (13), 165 (63), 77 (10), and 58 (16). Anal. Calcd for $C_{23}H_{23}NO$: C, 83.84; H, 7.05; N, 4.25. Found: C, 84.03; H, 7.19; N, 4.20.

Benzyl (2*S*,3*S*)-3-Methyl-2-aziridinecarboxylate (16).[25] The detritylation of the aziridino ester **15** was carried out according to a previously described procedure.[24a] The expected N−H aziridino ester was obtained in 77% yield: R_f 0.42 (solvent H, 95/5); mp 55−56 °C; $[\alpha]^{24}_D = -0.6$ (c = 1.08); IR (KBr, cm^{-1}) 3185, 1733, and 1184; ^{1}H NMR δ 1.02 (1 H, br s), 1.29 (3 H, d, J = 5.7 Hz), 2.27−2.35 (1 H, m), 2.68 (1 H, d, J = 6.3 Hz), 5.19, 5.22 (1 H each, 2 d, J = 12.2 Hz each), and 7.31−7.41 (5 H, m); ^{13}C NMR δ 13.1, 34.0, 34.9, 67.1, 128.3, 128.4, 128.6, 135.5, and 170.8; MS (EI) m/z (rel intensity) 100 ($M^+ - 91$, 85), 91 (100), 69 (10), 65 (19), and 45 (46).

Benzyl (2*S*,3*S*)-*N*,3-Dimethyl-2-aziridinecarboxylate (17f). The *N*-methylation of **16** was performed following a literature procedure.[26] The expected product **17f** was obtained in 44% yield: R_f 0.32 (Et_2O); $[\alpha]^{24}_D = -92.2$ (c = 1.27); IR (neat, cm^{-1}) 1746 and 1167; ^{1}H NMR δ 1.22 (3 H, d, J = 5.6 Hz), 1.79 (1 H, dq, J = 6.7, 5.6 Hz), 2.09 (1 H, d, J = 6.7 Hz), 2.40 (3 H, s), 5.14, 5.21 (1 H each, 2 d, J = 12.4 Hz each), and 7.29−7.39 (5 H, m); ^{13}C NMR δ 12.9, 43.0, 43.7, 46.9, 66.6, 128.3, 128.4, 128.5, 135.7, and 169.7; MS (EI) m/z (rel intensity) 114 ($M^+ - 91$, 100), 91 (54), and 65 (15). Anal. Calcd for $C_{12}H_{15}NO_2 \cdot 0.1H_2O$:[44] C, 69.60; H, 7.41; N, 6.77. Found: C, 69.33; H, 7.30; N, 6.57.

Benzyl (2*S*,3*S*)-*N*-(*n*-Butyl)-3-methyl-2-aziridinecarboxylate (17g). The N−H aziridino ester **16** (511 mg, 2.7 mmol), *n*-BuBr (0.45 mL, 4.1 mmol), and 18-crown-6 (72 mg, 0.3 mmol) were dissolved in dry MeCN (15 mL). K_2CO_3 (560 mg, 4.1 mmol) was added and the reaction mixture was refluxed for 3 days. The solvent was evaporated, water was added, and the resultant mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried. Flash chromatography (solvent A, 95/5, 9/1) afforded the desired product **17g** in 70% yield: R_f 0.46; $[\alpha]^{25}_D = -77.5$ (c = 1.10); IR (neat, cm^{-1}) 1747 and 1169; ^{1}H NMR δ 0.89 (3 H, t, J = 7.3 Hz), 1.24 (3 H, d, J = 5.6 Hz), 1.26−1.41, 1.52−1.61 (2 H each,

(41) Bouteville, G.; Gelas-Mialhe, Y.; Vessière, R. *Bull. Soc. Chim. Fr.* **1971**, 3264.

(42) Capeller, R. V.; Griot, R.; Häring, M.; Wagner-Jauregg, T. *Helv. Chim. Acta* **1957**, *40*, 1652.

(43) We are grateful to Dr. Adolf Gogoll for helping to set up the experiment and to interpret the data.

(44) The product was very hygroscopic.

2 m), 1.82 (1 H, dq, J = 6.9, 5.6 Hz), 2.10 (1 H, d, J = 6.9 Hz), 2.27 (1 H, dt, J = 11.4, 7.5 Hz), 2.35−2.43 (1 H, m), 5.16, 5.21 (1 H each, 2 d, J = 12.4 Hz each), and 7.29−7.39 (5 H, m); ^{13}C NMR δ 13.2, 14.0, 20.4, 31.5, 42.0, 42.6, 60.6, 66.5, 128.2, 128.3, 128.5, 135.8, and 169.8; MS (EI) m/z (rel intensity) 156 (M^+ − 91, 100), 91 (70), 84 (46), and 57 (47). Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.83; H, 8.57; N, 5.66. Found: C, 72.85; H, 8.55; N, 5.66.

Benzyl (2*S*,3*S*)-3-Methyl-*N*-isopropyl-2-aziridinecarboxylate (17h). The *N*-isopropylaziridino ester **17h** was prepared in the same way as **17g**, but 10 equiv of *i*-PrBr was used and NaI (2 equiv) was also added to the reaction mixture before reflux. The expected product **17h** was isolated in 85% yield: R_f 0.42; $[\alpha]^{25}_D$ = −64.2 (c = 1.00); IR (neat, cm^{-1}) 1747 and 1166; ^{1}H NMR δ 1.13, 1.15 (3 H each, 2 d, J = 6.4 Hz each), 1.26 (3 H, d, J = 5.6 Hz), 1.57 (1 H, septet, J = 6.4 Hz), 1.87 (1 H, dq, J = 6.7, 5.6 Hz), 2.12 (1 H, d, J = 6.7 Hz), 5.17, 5.20 (1 H each, 2 d, J = 12.3 Hz each), and 7.28−7.38 (5 H, m); ^{13}C NMR δ 13.5, 21.5, 21.7, 41.3, 42.3, 61.3, 66.5, 128.16, 128.22, 128.5, 135.9, and 169.7; MS (EI) m/z (rel intensity) 142 (M^+ − 91, 70), 91 (93), 84 (38), 73 (100), and 70 (52). Anal. Calcd for $C_{14}H_{19}NO_2 \cdot 0.3H_2O$:[44] C, 70.43; H, 8.29; N, 5.87. Found: C, 70.21; H, 8.11; N, 5.70.

Reduction of Esters 16 and 17f−h. General Procedure. The reduction of **16** and **17f−h** was carried out in the same way as for **13**, but in Et_2O instead of THF. After careful evaporation of the solvent, the residue was chromatographed.

[(2*S*,3*S*)-3-Methyl-2-aziridinyl]methanol (3e). Flash chromatography (neutral aluminum oxide; solvent F, 70/30/1, 60/40/2, 50/50/3, 50/50/5) afforded the ligand **3e** in 50% yield: R_f 0.17 (solvent I, 95/5/1); mp 83−85 °C; $[\alpha]^{25}_D$ = +1.3 (c = 1.10); IR (KBr, cm^{-1}) 3260; ^{1}H NMR δ 1.16 (3 H, d, J = 5.8 Hz), 2.22 (1 H, dq, J = 6.6, 5.8 Hz), 2.28 (1 H, ddd, J = 7.4, 6.6, 4.7 Hz), 2.50 (2 H, br s), 3.47 (1 H, dd, J = 11.8, 7.4 Hz), and 3.72 (1 H, dd, J = 11.8, 4.7 Hz); ^{13}C NMR δ 13.7, 29.8, 35.9, and 60.8; MS (EI) m/z (rel intensity) 86 (M^+ − 1, 8), 70 (57), 69 (78), and 54 (100). Anal. Calcd for $C_4H_9NO \cdot 0.1H_2O$:[44] C, 54.01; H, 10.45; N, 15.75. Found: C, 53.84; H, 10.21; N, 15.48.

[(2*S*,3*S*)-*N*,3-Dimethyl-2-aziridinyl]methanol (3f).[45] Flash chromatography (neutral aluminum oxide; solvent D, 80/20/1, 70/30/1) gave 52% yield: R_f 0.29 (solvent I, 95/5/1); $[\alpha]^{25}_D$ = −3.0 (c = 1.07); IR (neat, cm^{-1}) 3358; ^{1}H NMR δ 1.13 (3 H, d, J = 5.8 Hz), 1.46−1.54, 1.56−1.62 (1 H each, 2 m), 2.38 (3 H, s), 3.44 (1 H, dd, J = 11.9, 7.4 Hz), 3.69 (1 H, dd, J = 11.9, 4.5 Hz), and 4.15 (1 H, br s); ^{13}C NMR δ 12.9, 40.1, 46.0, 47.2, and 60.2; MS (EI) m/z (rel intensity) 101 (M^+, <1), 86 (35), 84 (100), and 70 (36).

[(2*S*,3*S*)-*N*-(*n*-Butyl)-3-Methyl-2-aziridinyl]methanol (3g). Flash chromatography (solvent A, 3/1 and then solvent B, 75/25/2, 75/25/4). The isolated yield was 70%: R_f 0.10 (solvent H, 95/5); $[\alpha]^{24}_D$ = +8.1 (c = 1.21); IR (neat, cm^{-1}) 3356; ^{1}H NMR δ 0.90 (3 H, t, J = 7.3 Hz), 1.15 (3 H, d, J = 5.7 Hz), 1.27−1.40 (2 H, m), 1.49−1.63 (4 H, m), 2.27, 2.34 (1 H each, 2 dt, J = 11.6, 7.4 Hz each), 3.00 (1 H, br s), 3.49 (1 H, dd, J = 11.6, 6.6 Hz), and 3.71 (1 H, dd, J = 11.6, 5.1 Hz); ^{13}C NMR δ 13.4, 14.0, 20.5, 32.0, 39.0, 44.3, 59.9, and 60.7; MS (EI) m/z (rel intensity) 128 (M^+ − 15, 14), 112 (100), 58 (38), 57 (49), and 56 (83). Found: M, 143.1288. $C_8H_{17}NO$ requires M, 143.1310.

[(2*S*,3*S*)-3-Methyl-*N*-isopropyl-2-aziridinyl]methanol (3h).[45] Flash chromatography (solvent A, 3/1 and then solvent B, 75/25/2, 75/25/4), yielded 65% of the aziridino alcohol **3h**: R_f 0.16 (solvent H, 95/5); $[\alpha]^{24}_D$ = +12.7 (c = 1.19); IR (neat, cm^{-1}) 3355; ^{1}H NMR δ 1.09, 1.10 (3 H each, 2 d, J = 6.3 Hz each), 1.16 (3 H, d, J = 5.7 Hz), 1.50−1.65 (3 H, m), 2.55 (1 H, br s), 3.51 (1 H, dd, J = 11.5, 6.5 Hz), and 3.68 (1 H, dd, J = 11.5, 5.3 Hz); ^{13}C NMR δ 13.7, 21.9, 22.0, 38.2, 43.9, 60.1, and 60.7; MS (EI) m/z (rel intensity) 129 (M^+, 4), 86 (37), 70 (29), 58 (100), and 56 (42).

Methyl (2*R*,3*S*)-3-(Benzylamino)-2-hydroxy-3-phenylpropionate (28). The *N*-tosyl amino ester **26** was prepared from methyl cinnamate via Sharpless asymmetric aminohydroxylation.[18] The β-amino acid **27**, obtained by deprotection of **26**,[29] was then submitted to the sequence esterification−reductive alkylation at nitrogen used for the synthesis of **12**, giving the *N*-benzyl amino ester **28** in 41% yield (from **26**): R_f 0.32 (solvent A, 1/2); mp 107−108 °C ; $[\alpha]^{24}_D$ = +73.9 (c = 1.04); IR (KBr, cm^{-1}) 3509, 3371, 1725, 1256, and 1105; ^{1}H NMR δ 3.51, 3.77 (1H each, 2 d, J = 13.3 Hz each), 3.71 (3 H, s), 3.96 (1 H, d, J = 3.9 Hz), 4.26 (1 H, d, J = 3.9 Hz), and 7.22−7.41 (10 H, m); ^{13}C NMR δ 50.7, 52.4, 63.5, 74.9, 127.0, 127.7, 127.76, 128.20, 128.3, 128.6, 139.6, 140.0, and 173.8; MS (EI) m/z (rel intensity) 196 (M^+ − 89, 54), 104 (7), 91 (100), 77 (9), and 65 (13). Anal. Calcd for $C_{17}H_{19}NO_3$: C, 71.55; H, 6.72; N, 4.91. Found: C, 71.29; H, 6.58; N, 4.80.

Recrystallization from pentane/CH_2Cl_2 gave the amino ester **28** optically pure, according to HPLC. Analysis by HPLC of racemic **28** (prepared in the same way as the optically active product) showed the retention times 16.5 and 25.5 min for the two enantiomers. In the analysis of the recrystallized product under the same conditions, only the enantiomer at 16.5 min could be detected.

Methyl (2*S*,3*S*)-*N*-Benzyl-3-phenyl-2-aziridinecarboxylate (29). The *N*-protected amino ester **28** was cyclized to the aziridino ester **29** following a literature procedure.[23] The isolated yield of **29** was 86%: R_f 0.50; mp 73−74 °C; $[\alpha]^{24}_D$ = +5.8 (c = 1.20); IR (Nujol, cm^{-1}) 1739 and 1458; ^{1}H NMR δ 2.66 (1 H, d, J = 6.8 Hz), 3.07 (1 H, d, J = 6.8 Hz), 3.48 (3 H, s), 3.67, 3.93 (1 H each, 2 d, J = 13.7 Hz each), 7.20−7.35 and 7.37−7.44 (6 and 4 H, respectively, 2 m); ^{13}C NMR δ 45.9, 47.8, 51.7, 63.6, 127.3, 127.4, 127.7, 127.9, 128.0, 128.4, 135.0, 137.6, and 168.4; MS (EI) m/z (rel intensity) 267 (M^+, 3), 176 (51), 117 (53), 116 (89), and 91 (100). Anal. Calcd for $C_{17}H_{17}NO_2$: C, 76.37; H, 6.42; N, 5.24. Found: C, 76.37; H, 6.41; N, 5.24.

(2*S*,3*S*)-*N*-Benzyl-3-phenyl-2-aziridinemethanol (3i). Compound **29** was reduced in the same way as **13**, but in Et_2O instead of THF. The crude residue was purified by flash chromatography (solvent A, 6/1, 4/1 and then solvent B, 50/50/1), yielding 94% of the aziridino alcohol **3i**: R_f 0.20; $[\alpha]^{24}_D$ = +123.8 (c = 1.00); IR (neat, cm^{-1}) 3383; ^{1}H NMR δ 1.36 (1 H, dd, J = 7.3, 4.9 Hz), 2.16−2.22 (1 H, m), 2.91 (1 H, d, J = 6.6 Hz), 3.28−3.35 (1 H, m), 3.46 (1 H, ddd, J = 11.7, 7.3, 5.8 Hz), 3.69, 3.74 (1 H each, 2 d, J = 13.3 Hz each), and 7.19−7.44 (10 H, m); ^{13}C NMR δ 46.2, 47.0, 60.6, 64.4, 126.9, 127.2, 127.5, 128.09, 128.13, 128.5, 136.6, and 138.9; MS (EI) m/z (rel intensity) 239 (M^+, <1), 148 (62), 91 (100), and 65 (11). Anal. Calcd for $C_{16}H_{17}NO$: C, 80.30; H, 7.16; N, 5.85. Found: C, 80.67; H, 7.26; N, 5.76.

2-[(2*S*,3*S*)-*N*-Benzyl-3-phenyl-2-aziridinyl]-2-propanol (3j). A solution of the aziridino ester **29** (278 mg, 1.0 mmol) in dry THF (5 mL), under N_2, was cooled to −78 °C and MeMgBr (1.4 mL 3.0 M solution in THF, 4.2 mmol) was added dropwise. The reaction was stirred for 2 h at −78 °C and then it was allowed to warm slowly to −5 °C during ca. 6 h. Then, it was quenched with saturated aqueous NH_4Cl and extracted with Et_2O (2 × 20 mL). The combined organic layers were washed with brine and dried. Flash chromatography (solvent A, 9/1) yielded 248 mg (89%) of the aziridino alcohol **3j**: R_f 0.43; mp 62−63 °C; $[\alpha]^{24}_D$ = +106.1 (c = 1.11); IR (KBr, cm^{-1}) 3451; ^{1}H NMR δ 0.97, 1.03 (3 H each, 2 s), 1.87 (1 H, d, J = 6.7 Hz), 2.08 (1 H, s), 2.89 (1 H, d, J = 6.7 Hz), 3.64, 3.88 (1 H each, 2 d, J = 12.7 Hz each), and 7.16−7.46 (10 H, m); ^{13}C NMR δ 25.9, 30.4, 46.6, 53.9, 65.0, 68.8, 126.7, 127.5, 127.7, 128.0, 128.5, 128.8, 137.0, and 138.8; MS (EI) m/z (rel intensity) 252 (M^+ − 15, <1), 176 (82), 91 (100), and 65 (27). Anal. Calcd for $C_{18}H_{21}NO$: C, 80.86; H, 7.92; N, 5.24. Found: C, 80.74; H, 8.02; N, 5.24.

N-Benzoyl-(L)-threonine Methyl Ester (18).[27] L-Threonine was converted into its methyl ester hydrochloride following the same procedure as for the preparation of **12** (first step).[20] The amino ester hydrochloride (210 mmol) was dissolved in 130 mL of MeOH, and Et_3N (88 mL, 630 mmol) was added. After 15 min, the reaction mixture was cooled to 0 °C and PhCOCl (27 mL, 231 mmol) was added dropwise. The reaction was stirred for 2 h at 0 °C. Then, MeOH and the excess Et_3N were evaporated. Water (100 mL) was added and the mixture was extracted with ethyl acetate (3 × 100 mL). The combined organic layers were washed with water (50 mL) and brine (50 mL) and dried. The solvent was

(45) Wartski, L.; Sierra-Escudero, A. *Bull. Soc. Chim. Fr.* **1975**, 1663.

evaporated, and the resulting residue was refluxed for 1 h with stirring in 300 mL of dry ether. After cooling, the white solid was filtered off. A 40.287 g portion of the expected product **18** was obtained. On cooling the mother liquors in the refrigerator, 1.500 g more of product crystallized. The yield of this one-pot procedure was 84%: R_f 0.44 (solvent H, 95/5); mp 97−98 °C; $[\alpha]^{25}_D = +24.0$ ($c = 5.43$, EtOH); IR (KBr, cm^{-1}) 3427, 3360, 1746, 1644, 1526, and 1259; ^{1}H NMR δ 1.27 (3 H, d, $J = 6.4$ Hz), 2.76−2.81 (1 H, m), 3.77 (3 H, s), 4.40−4.48 (1 H, m), 4.81 (1 H, dd, $J = 8.9$, 2.5 Hz), 7.03 (1 H, d, $J = 8.9$ Hz), 7.39−7.45, 7.48−7.53, and 7.82−7.85 (2, 1, and 2 H, respectively, 3 m); ^{13}C NMR δ 20.0, 52.6, 57.7, 68.2, 127.2, 128.6, 131.9, 133.7, 167.9, and 171.6; MS (EI) *m*/*z* (rel intensity) 193 ($M^+ - 44$, 13), 161 (21), 105 (100), 77 (63), and 51 (21).

Methyl (2*S*,3*R*)-*N*-Benzyl-3-methyl-2-aziridinecarboxylate (21).[46] *allo*-L-Threonine **20** was prepared from **18** in 86% yield[27] and transformed into **21** in the same way as for the corresponding L-threonine derivative **13**. The yield of the isolated product was 55% (from **20**). **21** was obtained as a 1:0.7 mixture of invertomers at nitrogen: R_f 0.42; $[\alpha]^{26}_D = -90.3$ (c =1.16); IR (neat, cm^{-1}) 1732 and 1200; ^{1}H NMR δ major invertomer: 1.25 (3 H, d, $J = 5.5$ Hz), 2.34 (1 H, qd, $J = 5.5$, 2.8 Hz), 2.46 (1 H, d, $J = 2.8$ Hz), 3.67 (3 H, s), 3.88, 4.04 (1 H each, 2 d, $J = 13.8$ Hz each), and 7.21−7.39 (5 H, m). Minor invertomer: 1.38 (3 H, d, $J = 6.0$ Hz), 2.04 (1 H, d, $J = 2.8$ Hz), 2.62 (1 H, qd, $J = 6.4$, 2.8 Hz), 3.71 (3 H, s), 3.68, 3.84 (1 H each, 2 d, $J = 14.1$ Hz each), and 7.21−7.39 (5 H, m); ^{13}C NMR δ major invertomer: 17.9, 41.1, 42.8, 51.9, 55.0, 126.8, 128.0, 128.26, 139.3, and 170.1. Minor invertomer: 10.7, 40.1, 44.1, 52.1, 54.7, 126.9, 127.6, 128.33, 138.7, and 171.5; MS (EI) *m*/*z* (rel intensity) 206 ($M^+ + 1$, 2), 205 (M^+, 13), 146 (49), 114 (100), 91 (98), and 59 (63).

[(2*S*,3*R*)-*N*-Benzyl-3-methyl-2-aziridinyl]methanol (4a).[17,42] The title compound was prepared in the same way as for the corresponding serine derivative **2**. The yield of the isolated product was 74%. The product was obtained as a 1:0.15 mixture of invertomers at nitrogen: R_f 0.22 (solvent H, 95/5); mp 72−73 °C; $[\alpha]^{24}_D = +27.7$ ($c = 1.02$); IR (KBr, cm^{-1}) 3357; ^{1}H NMR δ 1.20 (0.45 H, d, $J = 5.5$ Hz), 1.31 (3 H, d, $J = 6.1$ Hz), 1.55 (0.15 H, qd, $J = 5.5$, 3.6 Hz), 1.63 (1 H, dt, $J = 5.5$, 3.4 Hz), 2.01 (0.15 H, dt, $J = 8.6$, 3.6 Hz), 2.16 (1 H, qd, $J = 6.1$, 3.4 Hz), 2.63 (0.15 H, br s), 3.10 (1 H, br s), 3.38 (1 H, m), 3.55 (1 H, d, $J = 13.9$ Hz), 3.65 (0.15 H, d, $J = 14.4$ Hz), 3.67−3.74 (1 H + 0.15 H, m), 3.74 (1 H, d, $J = 13.9$ Hz), 3.84 (0.15 H, d, $J = 14.4$ Hz), 3.84−3.92 (0.15 H, m), and 7.23−7.40 (5 H + 0.75 H, m); ^{13}C NMR δ major invertomer: 11.0, 35.5, 47.0, 54.8, 62.2, 126.9, 127.8, 128.4, and 139.8; MS (EI) *m*/*z* (rel intensity) 176 ($M^+ - 1$, 4), 91 (89), 86 (100), 65 (26), and 58 (60).

A NOESY experiment[43] was carried out at −50 °C in order to establish the absolute configuration at nitrogen for the major invertomer. An enhancement of the signals corresponding to the methyl group and the proton at C2 in the aziridine ring was observed upon irradiation of the benzylic protons. An NOE was also obtained from the hydrogens of the CH_2O group when the hydrogen at C3 in the aziridine ring was irradiated. No enhancement of the signal corresponding to the benzylic protons was observed in the latter case. These results confirm the trans relationship between the benzyl group and the hydroxymethyl groups on the aziridine ring, as well as the cis relationship between the benzyl and the methyl groups. The energy barrier for nitrogen inversion was estimated to be ca. 70 kJ/mol, the value being determined by full line-shape fitting of spectra obtained at various temperatures using the program gNMR 3.6.5 (Cherwell Scientific).[43]

3-[(2*S*,3*R*)-*N*-Benzyl-3-methyl-2-aziridinyl]-3-pentanol (4b). The title compound was prepared from **21** and EtMgBr, following the same procedure as for the synthesis of ligand **3c**. The crude mixture was purified by flash chromatography (solvent A, 9/1, 6/1, 4/1, 2/1, 1/1), to afford the desired aziridino alcohol **4b** in 82% yield: R_f 0.18; $[\alpha]^{24}_D = -35.2$ (c = 1.20); IR (neat, cm^{-1}) 3425; ^{1}H NMR δ 0.82 (3 H, t, $J = 7.5$ Hz), 0.91 (3 H, t, $J = 7.6$ Hz), 1.31 (3 H, d, $J = 6.1$ Hz), 1.36 (2 H, q, 7.5 Hz), 1.44 (1 H, d, 3.4 Hz), 1.47−1.54 (2 H, m), 2.20 (1 H, qd, 6.1, 3.4 Hz), 2.71 (1 H, br s), 3.73 (2 H, s), and 7.24−7.40 (5 H, m); ^{13}C NMR δ 7.8, 8.0, 11.0, 29.3, 32.1, 33.7, 51.0, 54.4, 70.3, 126.8, 128.0, 128.3, and 140.0; MS (EI) *m*/*z* (rel intensity) 233 (M^+, 1), 142 (63), 91 (100), and 56 (20). Anal. Calcd for $C_{15}H_{23}NO$: C, 77.21; H, 9.93; N, 6.00. Found: C, 77.09; H, 10.02; N, 5.99.

Methyl (2*R*,3*R*)-3-(Benzylamino)-2-hydroxy-3-phenylpropionate (33). As previously reported, epoxide **31**[31] was synthesized and ring-opened with NaN_3.[32] The azido alcohol **32** (5.308 g, 24.0 mmol) was dissolved in MeOH (30 mL) and hydrogenated in the presence of 5% Pd−C (228 mg) under 1 atm of hydrogen at rt for 2 days. The catalyst was filtered off and washed with MeOH. Solvent was evaporated and the resultant oily residue was dissolved in a 2 M solution of HCl in MeOH (25 mL) at rt and stirred for 10 min. Solvent was evaporated and the resultant hydrochloride was then submitted to the reductive alkylation process described above for the synthesis of **12**. The crude residue was purified by flash chromatography (solvent A, 1/1, 1/2 and then solvent B, 50/50/2). The *N*-benzyl amino ester **33** was obtained in 56% yield (from **32**): R_f 0.14; mp 98−99 °C; $[\alpha]^{24}_D = -81.5$ ($c = 1.05$); IR (KBr, cm^{-1}) 3467, 3333, 1720, and 1282; ^{1}H NMR δ 2.30, 3.30 (1 H each, 2 br s), 3.60 (3 H, s), 3.62, 3.78 (1 H each, 2 d, J = 13.1 Hz each), 4.07 (1 H, d, $J = 4.2$ Hz), 4.54 (1 H, d, $J = 4.2$ Hz), and 7.23−7.38 (10 H, m); ^{13}C NMR δ 51.0, 52.1, 63.8, 73.6, 127.1, 127.7, 128.0, 128.2, 128.4, 128.5, 137.7, 139.7, and 173.0; MS (EI) *m*/*z* (rel intensity) 226 ($M^+ - 59$, 4), 197 (19), 196 (80), 91 (100), and 65 (32). Anal. Calcd for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.91. Found: C, 71.67; H, 6.71; N, 4.95.

Recrystallization from pentane/CH_2Cl_2 gave the amino ester **33** optically pure, according to HPLC. Analysis by HPLC of racemic **33** (prepared in the same way as the optically active product) showed the retention times 19.6 and 21.3 min for the two enantiomers. In the analysis of the recrystallized product under the same conditions, only the enantiomer at 21.3 min could be detected.

Methyl (2*S*,3*R*)-*N*-Benzyl-3-phenyl-2-aziridinecarboxylate (34).[47] Compound **33** was cyclized to the aziridino ester **34**.[23] The isolated yield of **34** was 88%. The product was obtained as a 1:0.15 mixture of invertomers at nitrogen: R_f 0.57; $[\alpha]^{24}_D = +7.2$ ($c = 1.16$); IR (neat, cm^{-1}) 1730, 1201, and 1174; ^{1}H NMR δ major invertomer: 2.81 (1 H, br s), 3.35 (1 H, br s), 3.72 (3 H, br s), 4.11, 4.27 (1 H each, 2 br d, $J = 13.9$ Hz each), and 7.15−7.45 (10 H, m); ^{13}C NMR δ major invertomer: 44.4, 48.6, 52.1, 54.9, 126.3, 126.9, 127.6, 128.0, 128.3, 128.4, 138.1, 139.1, and 169.2; MS (EI) *m*/*z* (rel intensity) 268 ($M^+ + 1$, <1), 267 (M^+, 5), 176 (83), 117 (48), 116 (100), and 91 (68).

[(2*S*,3*R*)-*N*-Benzyl-3-phenyl-2-aziridinyl]methanol (4c). The aziridino ester **34** was reduced with $LiAlH_4$, following the procedure described above for the synthesis of **3a**. The crude residue was purified by flash chromatography (solvent E, 9/1, 6/1), to afford the ligand **4c** in 59% yield. The product was obtained as a 1:0.36 mixture of invertomers at nitrogen: R_f 0.28 (solvent E, 2/1); $[\alpha]^{24}_D = +31.7$ ($c = 1.13$); IR (neat, cm^{-1}) 3354; ^{1}H NMR δ 1.44 (0.36 H, br s), 2.12 (1 H, t, $J = 6.2$ Hz), 2.42−2.60 (1+0.72 H, m), 3.14, 3.48 (1 H each, 2 d, $J = 13.6$ Hz each), 3.34 (1 H, d, $J = 3.6$ Hz), 3.56−3.64 (1 H, m), 3.85−4.09 (1+1.44 H, m), and 7.15−7.47 (10+3.60 H, m); ^{13}C NMR δ 43.9, 44.0, 45.4, 48.2, 55.4, 55.5, 59.0, 62.3, 126.2, 126.9, 127.5, 127.95, 128.02, 128.1, 128.3, 130.2, 133.1, and 139.3; MS (EI) *m*/*z* (rel intensity) 239 (M^+, 1), 148 (58), and 91 (100). Anal. Calcd for $C_{16}H_{17}NO$: C, 80.30; H, 7.16; N, 5.85. Found: C, 80.07; H, 7.22; N, 5.87.

Methyl *N*-Benzyl-*O*-(*tert*-butyldimethylsilyl)-L-threoninate (22). Methyl *N*-benzyl-L-threoninate **12** (866 mg, 3.9 mmol), *t*-$BuMe_2SiCl$ (1.212 g, 7.8 mmol), and imidazole (1.062 g, 15.6 mmol) were dissolved in DMF (4 mL), and the reaction mixture was stirred at rt for 3 days. The DMF was evaporated, and water (10 mL) and CH_2Cl_2 (20 mL) were added to the resultant residue. The layers were separated, and the

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aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic phases were washed with water (2 × 10 mL) and dried. The solvent was evaporated and the residue was purified by flash chromatography (solvent A, 98/2, 95/5). A 1.238 g (94%) portion of the protected threoninate **22** was obtained: R_f 0.56 (solvent A, 3/1); $[\alpha]^{25}_D = -53.7$ ($c = 1.02$); IR (neat, cm^{-1}) 1745, 1157, 1097, and 836; ^1H NMR (300 MHz) δ −0.01, 0.03 (3 H each, 2 s) 0.86 (9 H, s), 1.25 (3 H, d, $J = 6.2$ Hz), 2.13 (1 H, br s), 3.12 (1 H, d, $J = 3.4$ Hz), 3.62, 3.98 (1 H each, 2 d, $J = 13.4$ Hz each), 3.72 (3 H, s), 4.18 (1 H, dq, 6.2, $J = 3.4$ Hz), and 7.20−7.39 (5 H, m); ^{13}C NMR (75.5 MHz) δ −5.2, −4.4, 17.9, 20.8, 25.7, 51.5, 52.0, 66.2, 69.8, 126.8, 128.17, 128.22, 140.2, and 174.0; MS (EI) *m/z* (rel intensity) 338 ($M^+ + 1$, <1), 337 (M^+, <1), 293 (40), 159 (54), 91 (100), and 73 (49). Anal. Calcd for $C_{18}H_{31}NO_3Si$: C, 64.04; H, 9.27; N, 4.15. Found: C, 63.80; H, 9.28; N, 4.09.

(2*R*,3*R*)-2-(Benzylamino)-3-[(*tert*-butyldimethylsilyl)-oxy]-1-butanol (23). Compound **22** (190 mg, 0.6 mmol) was dissolved in dry CH_2Cl_2 (2.5 mL) under N_2 and cooled to −78 °C. DIBALH (2.0 mL 1.0 M solution in THF, 2.0 mmol) was added and the reaction mixture was stirred overnight, allowing the temperature to rise to rt. Then the reaction was quenched with water (5 mL). KOH (20%, 5 mL) was added and the mixture was extracted with ethyl acetate (3 × 20 mL). The combined organics were washed with water and dried. Flash chromatography (solvent C: 2/1) yielded 101 mg (58%) of the expected amino alcohol **23**: R_f 0.22 (solvent C, 1/1); $[\alpha]^{25}_D = -10.6$ ($c = 1.09$); IR (neat, cm^{-1}) 3364, 1098, and 835; ^1H NMR (300 MHz) δ 0.04, 0.07 (3 H each, 2 s), 0.87 (9 H, s), 1.21 (3 H, d, $J = 6.3$ Hz), 2.58 (1 H, dt, $J = 6.3$, 4.3 Hz), 3.44 (1 H, dd, $J = 10.9$, 4.0 Hz), 3.68 (1 H, dd, $J = 10.9$, 4.6 Hz), 3.79, 3.85 (1 H each, 2 d, $J = 13.2$ Hz each), 3.91 (1 H, quintet, $J = 6.3$ Hz), and 7.20−7.35 (5 H, m); ^{13}C NMR (75.5 MHz) δ −5.0, −4.2, 17.9, 20.5, 25.8, 51.8, 59.9, 64.0, 68.8, 127.0, 128.0, 128.4, and 140.3; MS (EI) *m/z* (rel intensity) 294 ($M^+ - 15$, 2), 278 (24), 150 (100), 91 (92), and 73 (24). Anal. Calcd for $C_{17}H_{31}NO_2Si$: C, 65.95; H, 10.11; N, 4.53. Found: C, 65.91; H, 10.02; N, 4.47.

(*R*)-*N*-Benzyl-2-{(*R*)-1-[(*tert*-butyldimethylsilyl)oxy]-ethyl}aziridine (24). To the solution of the protected amino alcohol **23** (181 mg, 0.6 mmol) in dry THF (6 mL) was added Ph_3P (232 mg, 0.9 mmol). The solution was cooled to 0 °C, and DEAD (0.14 mL, 0.9 mmol) was added dropwise. The ice bath was removed and the reaction was stirred at rt overnight. The solvent was evaporated and the residue was purified by flash chromatography (solvent A, 9/1), affording 139 mg (82%) of the desired aziridine **24**: R_f 0.59; $[\alpha]^{23}_D = +44.4$ ($c = 1.31$); IR (neat, cm^{-1}) 1112, and 836; ^1H NMR (300 MHz) δ 0.01, 0.04 (3 H each, 2 s), 0.88 (9 H, s), 1.13 (3 H, d, $J = 6.4$ Hz), 1.36 (1 H, d, $J = 6.4$ Hz), 1.58−1.69 (2 H, m), 3.21, 3.60 (1 H each, 2 d, $J = 13.0$ Hz each), 3.43 (1 H, quintet, $J = 6.4$ Hz), and 7.20−7.38 (5 H, m); ^{13}C NMR (75.5 MHz) δ −4.8, −4.6, 18.2, 21.2, 25.9, 31.0, 46.0, 64.9, 71.3, 127.0, 128.3, 128.4, and 139.2; MS (EI) *m/z* (rel intensity) 234 ($M^+ - 57$, 29), 115 (32), 91 (100), 75 (59), and 73 (40). Anal. Calcd for $C_{17}H_{29}NOSi$: C, 70.03; H, 10.05; N, 4.81. Found: C, 69.91; H, 10.18; N, 4.73.

(*R*)-1-[(*R*)-*N*-Benzyl-2-aziridinyl]ethanol (5). Compound **24** (114 mg, 0.4 mmol) was dissolved in dry THF (2.5 mL). (n-Bu)$_4$NF (1.2 mL 1.0 M solution in THF, 1.2 mmol) was added and the reaction was stirred at rt for 32 h. Water (10 mL) was added and the mixture was extracted with ether (3 × 20 mL). The combined organic extracts were washed with water and brine and dried. Flash chromatography (solvent A, 6/1 and then Et_2O) gave 48 mg (69%) of the ligand **5**: R_f 0.18 (ethyl acetate); $[\alpha]^{24}_D = -11.5$ ($c = 0.99$); IR (neat, cm^{-1}) 3384; ^1H NMR (300 MHz) δ 1.14 (3 H, d, $J = 6.4$ Hz), 1.49 (1 H, d, $J = 6.6$ Hz), 1.60−1.66 (1 H, m), 1.82 (1 H, d, $J = 3.6$ Hz), 2.59 (1 H, br s), 3.35−3.50 (1 H, m), 3.40, 3.50 (1 H each, 2 d, $J = 13.0$ Hz each), and 7.24−7.37 (5 H, m); ^{13}C NMR (75.5 MHz) δ 20.8, 31.8, 45.0, 64.3, 68.0, 127.3, 128.2, 128.5, and 138.9; MS (EI) *m/z* (rel intensity) 177 (M^+, 3), 91 (100), 86 (51), 65 (20), and 58 (19). Anal. Calcd for $C_{11}H_{15}NO$: C, 74.52; H, 8.55; N, 7.90. Found: C, 74.36; H, 8.65; N, 7.88.

Addition Reaction of Dialkylzinc Reagents to 1 Promoted by the Ligands 2−5. General Procedure. The phosphinoylimine **1** (76 mg, 0.25 mmol) and the aziridino alcohol **2**−**5** (0.25 mmol) were dissolved in dry toluene (1.5 mL) under nitrogen, and the mixture was stirred for 10 min at rt. The solution was cooled to 0 °C, Et_2Zn (0.68 mL 1.1 M solution in toluene, 0.75 mmol) was added, the reaction was stirred, the temperature was allowed to rise slowly to rt (3−4 h), and then the mixture was stirred for 4 days more. The reaction was quenched with saturated aqueous NH_4Cl (10 mL) and the mixture was extracted with CH_2Cl_2 (4 × 10 mL) and dried. Solvents were evaporated and the residue was purified by flash chromatography (solvent E, 6/1, 4/1, 2/1, 1/1). The resultant solid was analyzed by HPLC. The retention times are as follows: **6aa**, 14.7 (*R*) and 18.6 min (*S*); **6ab**, 13.6 (*R*) and 17.7 min (*S*); **6b**, 16.3 (*R*) and 19.8 min (*S*); and **6c**, 14.7 (*R*) and 16.7 min (*S*). Yields and ee's are given in Table 1. The absolute configuration of the major isomer was determined by hydrolysis of the reaction product and comparison of the optical rotation of the obtained amine with the reported data.[48]

General Procedure for the Hydrolysis. The product was stirred overnight at rt in a 1.5 M solution of hydrogen chloride in methanol (2 mL). Then, solvent was evaporated and 2 M aqueous HCl (5 mL) was added. The mixture was extracted with ethyl acetate (2 × 10 mL), and the organic layers were discarded. The aqueous layer was basified with 15% NaOH and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried. Evaporation of the solvent gave the pure amine.

The reported optical rotation for 1-phenylpropylamine was found to be in error. Hydrolysis of **6ab** with 61.5% ee gave the corresponding free amine, with $[\alpha]^{25}_D = +8.8$ ($c = 1.04$, $CHCl_3$). According to the literature,[48a] that value corresponds to 24% ee for the amine. However, the free amine was converted into the corresponding benzamide by reaction with benzoyl chloride in the presence of triethylamine. Analysis by HPLC gave a value of 61.3% ee, which is in very good agreement with the optical purity of the starting amide **6ab**. The retention times for the two enantiomers of the benzamide were 20.5 (*R*) and 32.2 min (*S*).

***N*-(1-Phenylethyl)-*P*,*P*-diphenylphosphinic amide (6aa)**:[11] R_f 0.48 (solvent H, 95/5); mp 166−170 °C (75% ee); $[\alpha]^{24}_D = +28.5$ [$c = 1.01$, 75% ee (*R*)]; IR (KBr, cm^{-1}) 3167 and 1181; ^1H NMR δ 1.57 (3 H, d, $J = 6.7$ Hz), 3.20 (1 H, br s), 4.34−4.46 (1 H, m), 7.20−7.52 and 7.79−7.94 (11 and 4 H, respectively, 2 m); ^{13}C NMR δ 25.9 (d, $J = 3.1$ Hz), 51.1, 125.9, 127.1, 128.3, 128.39, 128.42, 128.51, 128.54, 131.69, 131.72, 131.78, 131.80, 131.9, 132.0, 132.4, 132.5, and 145.1 (d, $J = 6.1$); MS (EI) *m/z* (rel intensity) 321 (M^+, 2), 306 (23), 201 (54), 120 (100), and 77 (45).

***N*-(1-Phenylpropyl)-*P*,*P*-diphenylphosphinic amide (6ab)**:[11] R_f 0.42 (solvent H, 95/5); mp 111−114 °C (45% ee); $[\alpha]^{24}_D = +31.3$ [$c = 1.35$, 81% ee (*R*)]; IR (KBr, cm^{-1}) 3151, 1197, and 1182; ^1H NMR (300 MHz) δ 0.78 (3 H, t, $J = 7.4$ Hz), 1.75−2.09 (2 H, m), 3.24 (1 H, dd, $J = 9.7$, 6.2 Hz), 4.03−4.17 (1 H, m), 7.11−7.52 and 7.70−7.91 (11 and 4 H, respectively, 2 m); ^{13}C NMR (75.5 MHz) δ 10.5, 32.5 (d, $J = 3.3$ Hz), 57.1, 126.5, 127.0, 128.2, 128.3, 128.4, 128.5, 131.6, 131.67, 131.73, 131.79, 131.84, 132.4, 132.5, 132.6, 132.8 and 143.5 (d, $J = 6.0$); MS (EI) *m/z* (rel intensity) 306 ($M^+ - 29$, 100), 202 (12), 201 (72), and 77 (15).

***N*-[1-(1-Naphthyl)propyl]-*P*,*P*-diphenylphosphinic amide (6b)**: R_f 0.25 (hexane/acetone: 2/1); mp 167−169 °C (6% ee); $[\alpha]^{25}_D = -23.3$ [$c = 1.00$, 73% ee (*R*)]; IR (KBr, cm^{-1}) 3197 and 1190; ^1H NMR δ 0.85 (3 H, t, $J = 7.4$ Hz), 2.05−2.13 (2 H, m), 3.42 (1 H, dd, $J = 9.2$, 6.8 Hz), 4.99 (1 H, tt, $J = 9.8$, 6.8 Hz), 7.15−7.21, 7.29−7.55, and 7.66−7.91 (2, 8, and 7 H, respectively, 3 m); ^{13}C NMR δ 10.6, 32.5, 52.7, 122.9, 123.3, 125.3, 125.4, 125.9, 127.6, 128.1, 128.2, 128.4, 128.5, 128.7, 130.6, 131.5, 131.6, 131.75, 131.78, 131.8, 132.3, 132.4, 133.8, and 139.7; MS (EI) *m/z* (rel intensity) 356 ($M^+ - 29$, 75), 201 (100), 184 (38), and 154 (35). Anal. Calcd for $C_{25}H_{24}NOP$: C, 77.89; H, 6.29; N, 3.63. Found: C, 77.79; H, 6.13; N, 3.84.

***N*-[1-(4-Chlorophenyl)propyl]-*P*,*P*-diphenylphosphinic amide (6c)**: R_f 0.53 (solvent H, 95/5); mp 162−164 °C (82%

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ee); $[\alpha]^{25}_D = +44.1$ [$c = 1.02$, 82% ee (*R*)]; IR (KBr, cm^{-1}) 3222 and 1183; ^1H NMR δ 0.79 (3 H, t, $J = 7.4$ Hz), 1.73−1.85 (1 H, m), 1.97 (1 H, dqd, $J = 13.6$, 7.4, 6.1 Hz), 3.25 (1 H, dd, $J = 9.5$, 6.1 Hz), 4.03−4.13 (1 H, m), 7.06−7.10, 7.21−7.25, 7.28−7.35, 7.38−7.51, 7.69−7.76, and 7.81−7.88 (2 H, 2 H, 2 H, 4, 2, and 2 H, respectively, 6 m); ^{13}C NMR δ 10.5, 32.3 (1 C, d, $J = 4.5$ Hz), 56.5, 127.9, 128.2, 128.3, 128.4, 128.5, 131.4, 131.68, 131.71, 131.75, 131.84, 132.38, 132.47, 132.7, 133.7, and 142.1 (2 C, d, $J = 4.6$ Hz); MS (EI) *m*/*z* (rel intensity) 369 (M^+, <1), 340 (66), 201 (100), and 77 (29). Anal. Calcd for $C_{21}H_{21}ClNOP$: C, 68.19; H, 5.73; N, 3.79. Found: C, 67.87; H, 5.65; N, 3.50.

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