Enantioselective Addition of Dialkylzinc Reagents to *N*-(Diphenylphosphinoyl) Imines Promoted by 2-Azanorbornylmethanols

David Guijarro, Pedro Pinho, and Pher G. Andersson*

Department of Organic Chemistry, Uppsala University, Box 531, S-751 21 Uppsala, Sweden

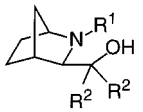
Received September 30, 1997

A set of new β-amino alcohols **2**, with the 2-azanorbornyl framework, has been prepared and evaluated as promoters for the enantioselective addition of dialkylzinc reagents to *N*-(diphenylphosphinoyl) imines **1**. By variation of the substitution pattern in the ligand, ee's up to 92% could be obtained. Although a stoichiometric amount of the ligand was used, about 90% of it could be recovered during the workup. Amino alcohol **2b**, that gave the best enantioselectivities in the stoichiometric reaction, was also applied in a catalytic process, and ee's up to 85% were achieved using 0.25 equiv of the ligand, which is the highest ee obtained so far using that catalytic amount of the ligand. Addition products **3** could be converted into the free amines **4** without racemization by acidic hydrolysis. The utility of ligands **2** as catalysts in the addition of diethylzinc to benzaldehyde has also been investigated, and ee's up to 75% were achieved.

Introduction

The carbon−carbon bond-forming reaction is one of the most fundamental operations for constructing organic molecules. Addition of organometallic reagents to carbonyl compounds is among the most common reaction for this purpose, and its asymmetric version is particularly useful. Among various organometallic compounds, diorganozinc reagents serve as excellent alkyl nucleophiles, and the enantioselective addition of these reagents to prochiral aldehydes has been studied extensively.[1] These asymmetric addition reactions are catalyzed by chiral β-amino alcohols often prepared from the corresponding α-amino acids. Proline has showed to be especially useful as precursor for the preparation of highly effective catalysts.[2,3]

Chiral bicyclic β-amino alcohols have also been successfully used as catalysts for the above-mentioned reaction. By variation of the bicyclic structure, several highly enantioselective catalysts have been prepared.[4] Moderate to good ee's were attained in the alkylation of aromatic and aliphatic aldehydes catalyzed by 2-azanorbornylmethanols.[5a,b] These sterically constrained β-amino alcohols and their bicyclo[2.2.1] ring system may block the approach of the attacking species to one of the enantiotopic faces of the aldehyde. Finally, using a set of ligands containing the octahydro-cyclopenta[*b*]pyrrole system, ee's up to 99% were achieved.[5c]



2a: R^1 = Me; R^2 = H
2b: R^1 = Et; R^2 = H
2c: R^1 = *i*-Pr; R^2 = H
2d: R^1 = $PhCH_2$; R^2 = H
2e: R^1 = $PhCH_2$; R^2 = Me
2f: R^1 = $PhCH_2$; R^2 = *i*-Pr
2g: R^1 = $PhCH_2$; R^2 = Ph

Figure 1.

In the last years, we have been interested in the use of chiral ligands with the 2-azanorbornyl skeleton in asymmetric synthesis. Some bicyclic analogues of proline were applied as ligands for the Cu-catalyzed asymmetric allylic oxidation of olefins.[6] The rigid structure of these unnatural amino acids led to ee's up to 65% in the oxidation of cyclic olefins, the highest observed so far using an amino acid as chiral ligand. In another project, we have recently studied the addition of dialkylzinc reagents to *N*-(diphenylphosphinoyl) imines in the presence of stoichiometric or catalytic amounts of some new chiral aziridino alcohols,[7] and high enantioselectivities were attained (ee up to 94%). One drawback with this system is its low activity when used in catalytic amounts.[8] Therefore, we found it interesting to test some bicyclic β-amino alcohols **2** (Figure 1), having the 2-azanorbornyl framework, in the above-mentioned addition reaction.

(1) For a review, see: (a) Noyori, R.; Kitamura, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 49. (b) Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833.

(2) (a) Soai, K.; Ookawa, A. *J. Chem. Soc., Chem. Commun.* **1986**, 412. (b) Ookawa, A.; Soai, K. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1465.

(3) (a) Soai, K.; Ookawa, A.; Kaba, T.; Ogawa, K. *J. Am. Chem. Soc.* **1987**, *109*, 7111. (b) Corey, E. J.; Hannon, F. J. *Tetrahedron Lett.* **1987**, *28*, 5233. (c) Corey, E. J.; Yuen, P.; Hannon, F. J.; Wierda, D. A. *J. Org. Chem.* **1990**, *55*, 784. (d) Shi, M.; Satoh, Y.; Makihara, T.; Masaki, Y. *Tetrahedron: Asymmetry* **1995**, *6*, 2109.

(4) (a) Kitamura, M.; Suga, S.; Kawai, K.; Noyori, R. *J. Am. Chem. Soc.* **1986**, *108*, 6071. (b) Smaardijk, A. A.; Wynberg, H. *J. Org. Chem.* **1987**, *52*, 135. (c) Oppolzer, W.; Radinov, R. N. *Tetrahedron Lett.* **1988**, *29*, 5645. (d) Tanaka, K.; Ushio, H.; Suzuki, H. *J. Chem. Soc., Chem. Commun.* **1989**, 1700.

(5) (a) Nakano, H.; Kumagai, N.; Kabuto, C.; Matsuzaki, H.; Hongo, H. *Tetrahedron: Asymmetry* **1995**, *6*, 1233. (b) Nakano, H.; Kumagai, N.; Matsuzaki, H.; Kabuto, C.; Hongo, H. *Tetrahedron: Asymmetry* **1997**, *8*, 1391. (c) Wilken, J.; Kossenjans, M.; Gröger, H.; Martens, J. *Tetrahedron: Asymmetry* **1997**, *8*, 2007.

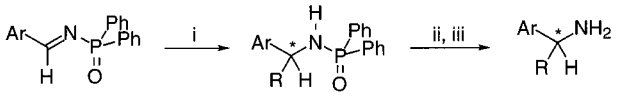
(6) Södergren, M. J.; Andersson, P. G. *Tetrahedron Lett.* **1996**, *37*, 7577.

(7) (a) Andersson, P. G.; Guijarro, D.; Tanner, D. *Synlett* **1996**, 727. (b) Andersson, P. G.; Guijarro, D.; Tanner, D. *J. Org. Chem.* **1997**, *62*, 7364.

(8) For earlier results on this subject, see ref 7b.

S0022-3263(97)01809-4 CCC: $15.00
Published on Web 03/28/1998

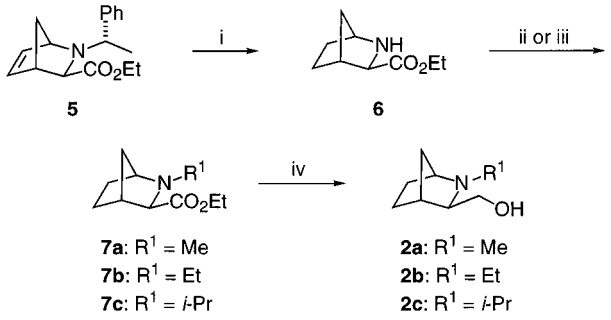
Scheme 1[a]



1 3 4

[a] Key: (i) R_2Zn, ligand **2** (see Figure 2), toluene, 0 °C to rt; (ii) 1.5 M HCl in MeOH, rt; (iii) 15% NaOH.

Scheme 2[a]



7a: R^1 = Me
7b: R^1 = Et
7c: R^1 = *i*-Pr

2a: R^1 = Me
2b: R^1 = Et
2c: R^1 = *i*-Pr

[a] Key: (i) H_2 (100 psi), 5% Pd-C (20 wt %), EtOH, rt, 98%; (ii) MeI, MeCN, reflux, 34% (for compound **7a**); (iii) R^1Br (R^1 = Et, *i*-Pr), K_2CO_3, 18-crown-6 (cat.), NaI (only for R^1 = *i*-Pr), MeCN, reflux, 80 and 82%, respectively; (iv) $LiAlH_4$, THF, 0 °C, 76% (for **2a**), 60% (for **2b**) and 80% (for **2c**).

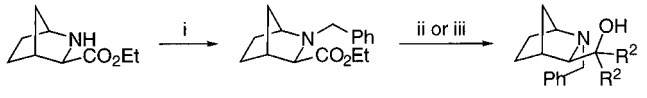
One of the features of those ligands that prompted us to choose them was the fact that both enantiomers are equally available. This is obviously not the case when using proline or camphor derived ligands, where the unnatural stereoisomer is much more expensive than the other one.[9] The bicyclic ring system of ligands **2** can be constructed via an aza-Diels−Alder reaction between cyclopentadiene and an iminium ion derived from (*S*)-1-phenylethylamine and ethyl glyoxylate.[10] Since the amine used as chiral auxiliary is readily available in both enantiomeric forms, either of the two enantiomeric ligands can be prepared.

In this paper, we present the application of some new bicyclic *β*-amino alcohols **2**[11] (Figure 1) to the addition of dialkylzinc reagents to *N*-(diphenylphosphinoyl) imines (Scheme 1). By fine-tuning of the ligand structure, ee's up to 92% could be obtained. Full experimental details about the preparation of the ligands and the addition reaction are given. The utility of some of the ligands **2** as catalysts in the same reaction has also been studied. Acidic hydrolysis of the addition products **3** afforded the free amines **4** without loss of enantiomeric purity (Scheme 1). Ligands **2** were also evaluated as catalysts for the well studied addition of diethylzinc to benzaldehyde, leading to ee's up to 75%.

Results and Discussion

The common precursor for all the ligands was the Diels−Alder adduct **5** (Scheme 2). It was prepared by a diastereoselective aza-Diels−Alder reaction between cyclopentadiene and an iminium ion derived from ethyl glyoxylate and (*S*)-1-phenylethylamine according to a literature procedure.[10] It turned out to be crucial to deactivate the silica gel with Et_3N before purifying the adduct **5** by flash chromatography in order to get good yields, presumably due to decomposition on the otherwise slightly acidic silica. Pd-catalyzed hydrogenolysis of **5** led to the NH ester **6**. The optical purity of **6** was determined to be 98% by HPLC analysis of the *N*-benzoyl ester (see Experimental Section). *N*-Alkylation of **6** furnished the *N*-protected esters **7**. Treatment of **6** with MeI in refluxing acetonitrile afforded the *N*-methyl ester **7a**. Reaction of **6** with ethyl or isopropyl bromide in the presence of K_2CO_3 and a catalytic amount of 18-crown-6 yielded the corresponding *N*-ethyl or *N*-isopropyl esters **7b** or **7c**, respectively. In the case of **7c**, NaI (2 equiv) was added to the reaction mixture in order to facilitate the substitution reaction by in situ generation of *i*-PrI. The esters **7** were then converted into the ligands **2a**−**c** by reduction with $LiAlH_4$.

Scheme 3[a]

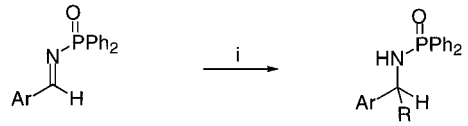


6 8

2d: R^2 = H
2e: R^2 = Me
2f: R^2 = *i*-Pr
2g: R^2 = Ph

[a] Key: (i) $PhCH_2Br$, K_2CO_3, MeCN, rt, 78%; (ii) $LiAlH_4$, THF, 0 °C, 74% (for compound **2d**); (iii) R^2MgBr (R^2 = Me, *i*-Pr, Ph), THF, -30 °C to rt, 84% (for **2e**), 20% (for **2f**) and 47% (for **2g**).

Scheme 4[a]



1a: Ar = Ph
1b: Ar = 1-Naphthyl

3a: Ar = Ph; R = Et
3a': Ar = Ph; R = Me
3b: Ar = 1-Naphthyl; R = Et

[a] Key: (i) R_2Zn (3 equiv), ligand **2** (1 equiv), toluene, 0 °C to rt.

For the synthesis of ligands **2d**−**g**, the *N*-benzyl amino ester **8** was required (Scheme 3). It was prepared by reaction of the NH amino ester **6** with benzyl bromide in acetonitrile in the presence of K_2CO_3. Reduction of **8** with $LiAlH_4$ resulted in ligand **2d**. The rest of the ligands, **2e**−**g**, were synthesized by addition of the corresponding Grignard reagents to the ester **8** in THF. The addition of *i*-PrMgBr to **8** gave only a low yield (20%) of the adduct **2f**, due to the formation of several unidentified byproducts.

The bicyclic amino alcohols **2** were tested as promoters for the addition of dialkylzinc reagents to *N*-(diphenylphosphinoyl) imines **1** (Scheme 4), which were prepared from the corresponding aldehydes according to the literature.[12] Toluene, a nonpolar solvent, was chosen as reaction medium in order to maximize the rate difference between the catalyzed and the noncatalyzed reaction. As a general procedure, the dialkylzinc reagent (3 equiv) was added dropwise to the stirred solution of the imine **1** and the ligand **2** (1 equiv) in dry toluene, under Ar, at 0 °C.

(9) For example, the unnatural D-proline is 24 times more expensive than the natural L-proline.

(10) (a) Stella, L.; Abraham, H.; Feneau-Dupont, J.; Tinant, B.; Declercq, J. P. *Tetrahedron Lett.* **1990**, *31*, 2603. (b) Waldmann, H.; Braun, M. *Liebigs Ann. Chem.* **1991**, 1045.

(11) For the preparation of the enantiomer of ligand **2g** and its evaluation in the enantioselective addition of Et_2Zn to aldehydes, see ref 5b.

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

Table 1. Addition Reaction of R_2Zn to 1 Promoted by the Ligands 2

entry	imine	ligand (equiv)	R	product	yield (%)[a]	ee (%)[b]	config[c]
1	**1a**	**2a** (1)	Et	**3a**	50	75	*S*
2	**1a**	**2b** (1)	Et	**3a**	43	92	*S*
3	**1a**	**2c** (1)	Et	**3a**	59	85	*S*
4	**1a**	**2d** (1)	Et	**3a**	63	91	*S*
5	**1a**	**2d** (0.25)	Et	**3a**	46	85	*S*
6	**1a**	**2d** (0.10)	Et	**3a**	38	68	*S*
7	**1b**	**2d** (1)	Et	**3b**	65	92	*S*
8	**1a**	**2e** (1)	Me[d]	**3a′**	32	83	*S*
9	**1a**	**2e** (1)	Et	**3a**	65	88	*S*
10	**1a**	**2f** (1)	Et	**3a**	52	43	*S*
11	**1a**	**2g** (1)	Et[e]	**3a**	33	16	*S*

[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 Experimental Section). [d] Six equiv of Me_2Zn were used, and the reaction was run for 6 days at room temperature. [e] The reaction was run for 4 days at room temperature.

After allowing the reaction mixture to slowly reach rt, it was stirred until completion according to TLC (2 days). It was then quenched with saturated aqueous NH_4Cl, and extractive workup afforded the secondary amines **3** (Scheme 4, Table 1).

The yields and ee's obtained are summarized in Table 1. Both imines **1a** and **1b** showed to be good substrates for the addition reaction (Table 1, entries 4 and 7). The effect of varying the substituents R^1 and R^2 (Figure 1) on the selectivity was explored. In accordance to our previous observations with the aziridino alcohol ligands,[7] a primary alcohol on the side chain led to a very high level of enantioselection. Enantiomeric excesses of 91 and 92% were obtained when ligand **2d** was used as promoter for the addition of Et_2Zn to **1a** and **1b**, respectively (Table 1, entries 4 and 7). The ee decreased upon increasing the size of the R^2 substituent in the ligand (compare entry 4 with 9−11). When R^2 = Ph, the reaction was much slower than in the other cases. Only 33% yield of the addition product was isolated after 4 days at room temperature. The ee dropped down to 16%, probably due to competition between the rate of the catalyzed and the noncatalyzed reaction. In the case of the other ligands, the catalyzed reaction was faster than the noncatalyzed one,[13] indicating a ligand acceleration effect.[14]

Concerning the substituent on the nitrogen, R^1, a more sterically demanding alkyl group seems to result in a beneficial effect (Table 1, entries 2−4). The best results were obtained using either the *N*-ethyl (**2b**) or the *N*-benzyl ligand (**2d**), which gave the addition products in 92 and 91% ee, respectively (entries 2 and 4).

Me_2Zn turned out to be much less reactive than Et_2Zn. When Me_2Zn was used as nucleophile, only 32% yield of the addition product was obtained after 6 days of reaction time (Table 1, entry 8). However, a high level of asymmetric induction was still observed (83% ee with ligand **2e**, entry 8).

In all cases, when a stoichiometric amount of the chiral ligand was used, up to 90% of it could be recovered during the workup in a typical experiment. Addition products **3** were converted into the free amines **4** without racemization by acidic hydrolysis (see Experimental Section).

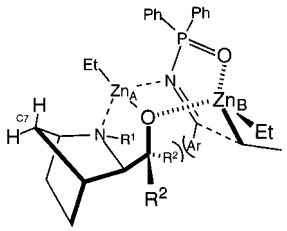
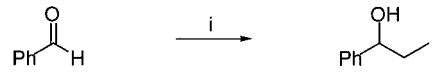


Figure 2.

Scheme 5[a]



9 **10**

[a]Key: (i) Et_2Zn, (2.2 equiv), ligand **2** (0.05 equiv), toluene, 0 °C.

According to our earlier observations,[7b] a transition state like the one depicted in Figure 2 could be used to rationalize the stereochemical outcome of the addition reactions. The steric hindrance brought about by the methylene bridge of the ligand (C7, Figure 2) determines the position of Zn_B and, therefore, the configuration of Zn_A. Coordination of the imine to both zinc atoms (N−Zn_A and O−Zn_B) would lead to a bicyclic transition state like the one shown. The presence of a small R^2 group in the ligand seems to be very important in order to get high selectivities. The steric hindrance between one of the R^2 groups of the ligand and the Ar group of the imine carbon would disfavor the formation of the well-ordered bicyclic transition state, leading to a decrease in the enantioselectivity, which has been observed experimentally (compare entry 4 with 9−11 in Table 1). The transfer of one of the ethyl groups of Zn_B to the imine would give the addition products with the observed stereochemistry.

Prompted by the good enantioselectivities obtained with ligand **2d**, we decided to explore its application as a catalyst in the same transformation. The addition of Et_2Zn to **1a** was run with 0.25 and 0.10 equiv of the ligand **2d** (Table 1, entries 5 and 6) under identical reaction conditions as for the stoichiometric process. Again, a ligand acceleration effect[14] was apparent, since both the yield and the ee dropped down when the amount of ligand was reduced. However, the ee's obtained when using substoichiometric amounts of the ligand are very promising. Only a small loss of enantioselectivity was found with 0.25 equiv of **2d** (compare entries 4 and 5). As a matter of fact, the ee given in entry 5 is the highest value reported so far with that amount of ligand.[15] The value of 68% obtained when using 10 mol % of the ligand, although still moderate, is also very promising.

Ligands **2** were also evaluated as catalysts for the addition of Et_2Zn to benzaldehyde (Scheme 5). In a typical experiment, Et_2Zn (2.2 equiv) was added to the solution of the chiral ligand **2** (0.05 equiv) in dry toluene, under Ar, at 0 °C. After 20 min, PhCHO was added dropwise, and the reaction was stirred at 0 °C for 24 h. After hydrolysis with saturated aqueous NH_4Cl and

(13) The rate of the addition of Et_2Zn to **1a** promoted by **2d** was estimated to be 2.5 times the rate of the reaction in the absence of the ligand.

(14) For a review on this subject see: Berrisford, D. J.; Bolm, C.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1059.

(15) For previous work on the catalytic addition of R_2Zn to *N*-(diphenylphosphinoyl) imines, see: (a) Soai, K.; Hatanaka, T.; Miyazawa, T. *J. Chem. Soc., Chem. Commun.* **1992**, 1097. (b) Reference 7.

Table 2. Addition Reaction of Et_2Zn to 9 Catalyzed by the Ligands 2

entry	ligand	yield (%)[a]	ee (%)[b]	config[c]
1	**2a**	62	24	*R*
2	**2b**[d]	59	48	*S*
3	**2c**[d]	63	53	*S*
4	**2d**[d]	59	75	*S*
5	**2e**[d]	47	24	*S*
6	**2f**	81	28	*R*
7	**2g**[e]	46	49	*R*

[a] Isolated yield after flash chromatography (silica gel, pentane/Et_2O). [b] Determined by HPLC analysis on a chiral column (ChiralCel OD-H). [c] Determined by comparison of the optical rotation with that given in the literature (see Experimental Section). [d] The reaction was run for 1 day at 0 °C and one more day at room temperature. [e] Values given according to the data reported in the literature (ref 5b).

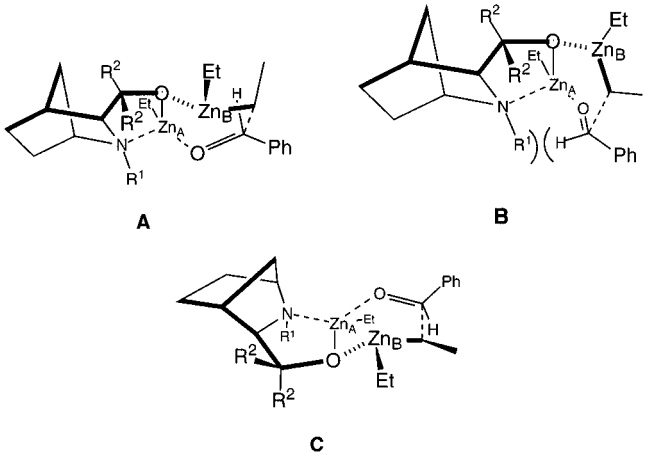


Figure 3.

extractive workup, the expected 1-phenyl-1-propanol was isolated with the yields and ee's shown in Table 2.

As it was the case in the addition to imines **1**, ligand **2d** showed the highest level of chiral induction, giving an ee of 75%. The enantioselectivity dropped upon decreasing the steric bulk of the substituent at nitrogen (Table 2, entries 2−4). A change in the absolute configuration of the product was observed when R^1 = Me (entry 1). These results could be rationalized assuming that **A** and **B** (Figure 3) are two possible transition states involved in the addition reaction. When R^1 is a large group, complex **A** is favored over **B** due to the steric interaction between R^1 and the H of the aldehyde. As a result, the *S* enantiomer of the addition product is preferably formed. When the size of R^1 is reduced, the participation of **B** becomes important and, consequently, the ee is lowered (compare entries 2−4). In the case of R^1 = Me, it seems that **B** begins to be preferred over **A**, therefore changing the configuration of the major enantiomer of the addition product (entry 1).

Once more, the preference for the *S* enantiomer was diminished when increasing the steric bulk of the R^2 group of the ligand (Table 2, entries 4−7). This could be explained assuming that, as the size of R^2 is increased, steric interactions between one of the R^2 groups and the Et_2Zn_B moiety would force Zn_B to change its position from below to above the five-membered ring, provoking thus a change in the configuration of Zn_A (complex **C**, Figure 3). The competition between complexes **A** and **C** would make the ee to drop (compare entries 4 and 5) and even favor the formation of the other enantiomer (entries 6 and 7) as R^2 becomes larger.

Ligands **2b**−**e** showed to be less catalytically active than **2a**, **2f** and **2g**. After 24 h at 0 °C, a low conversion was achieved when those ligands were employed as catalysts. It was necessary to stir the reactions for an additional 24 h at room temperature in order to achieve full conversion of the starting material.

Conclusions

In this paper, we have shown that 2-azanorbornylmethanols **2** can effectively be used as promoters for the enantioselective addition of dialkylzinc reagents to *N*-(diphenylphosphinoyl) imines **1**. High enantioselectivities were obtained in both the stoichiometric and the catalytic processes. It should be noted that these type of ligands can be further refined, i.e. by the introduction of only one R^2 group on the hydroxymethyl carbon, thus providing an additional chiral center. These studies are currently under investigation.

Experimental Section

For general experimental information, see ref 16. 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). When mentioned, deactivated silica gel means that it was treated with 5% Et_3N in pentane, and the column was eluted with the same solvent mixture until the coming eluent was basic according to pH paper. TLC analysis was performed on precoated TLC plates, SIL G-60 UV_{254}, which were purchased from Macherey-Nagel. When mentioned, deactivated silica gel means that the TLC plate was eluted with 5% Et_3N in pentane and dried before applying the sample. Unless otherwise mentioned, [α] values were measured in $CHCl_3$. HPLC analysis were carried out on a chiral column (ChiralCel OD-H), using a 254 nm UV detector and a flow rate of 0.5 mL/min. ^1H 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.[12] PhCHO was purchased from Aldrich Co. and distilled before use.

Ethyl (1*S*,3*R*,4*R*)-2-[(*S*)-1-Phenylethylamino]-2-azabicyclo[2.2.1]hept-5-ene-3-carboxylate (5). Compound **5** was prepared via an aza-Diels−Alder reaction between cyclopentadiene and an iminium ion derived from ethyl glyoxylate and (*S*)-1-phenylethylamine, following a literature procedure.[10] Purification by flash chromatography (deactivated silica gel, pentane/Et_2O: 95/5 to 80/20) gave 60% yield. All the physical and spectroscopic data for compound **5** were in complete agreement with the reported data for its enantiomer,[10] except for the sign of the optical rotation.

Ethyl (1*S*,3*R*,4*R*)-2-Azabicyclo[2.2.1]heptane-3-carboxylate (6). A solution of the Diels−Alder adduct **5** (7.869 g, 29.0 mmol) in absolute ethanol (50 mL) was stirred under a hydrogen pressure of 100 psi at room temperature for 48 h in the presence of 5% Pd−C (1.574 g, 20 wt %). Pd−C was removed by filtration through Celite and evaporation of the solvent yielded 4.809 g (98%) of the pure NH amino ester **6**: R_f 0.53 (pentane/acetone: 1/1; deactivated silica gel); $[\alpha]^{24}_D$ = −28.2 (*c* = 1.26); IR (neat, cm^{-1}) 3310, 1728 and 1206; ^1H NMR δ 1.21 (1 H, br d, *J* = 9.8 Hz), 1.25 (3 H, t, *J* = 7.1 Hz), 1.34−1.66 (5 H, m), 2.18 (1 H, br s), 2.59, 3.27, 3.50 (1 H each, 3 br s), 4.15 (2 H, q, *J* = 7.1 Hz); ^{13}C NMR δ 14.2, 28.4, 31.1, 35.7, 41.7, 56.2, 61.0, 63.6, 174.5; MS (EI) *m/z* (rel intensity) 169 (M^+, 8%), 131 (26), 73 (23), 69 (100), 57 (25), 55 (40). Anal.

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

Calcd for $C_9H_{15}NO_2 \cdot 0.1H_2O$:[17] C, 63.21; H, 8.96; N, 8.19. Found: C, 62.98; H, 9.06; N, 8.11.

The NH ester **6** was *N*-benzoylated by reaction with benzoyl chloride in the presence of Et_3N. Analysis by HPLC, using 20% *i*-PrOH in hexane as eluent and a flow rate of 0.4 mL/min, gave an optical purity of 98%. The retention times for the two enantiomers of the benzamide were 15.0 (minor) and 22.9 min (major).

Ethyl (1*S*,3*R*,4*R*)-2-Methyl-2-azabicyclo[2.2.1]heptane-3-carboxylate (7a). The solution of the ester **6** (339 mg, 2.0 mmol) and MeI (0.21 mL, 3.4 mmol) in MeCN (10 mL) was refluxed under Ar for 19 h. Solvent was evaporated, and the resulting residue was dissolved in CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$. The aqueous phase was extracted twice with CH_2Cl_2 and the combined organic layers were dried. Removal of the solvent by rotary evaporation gave a residue that was purified by flash chromatography (pentane/acetone: 4/1), to afford 123 mg (34%) of the *N*-Me ester **7a**: R_f 0.54 (pentane/acetone: 1/1); $[\alpha]^{25}_D = +13.2$ (c = 1.21, CH_2Cl_2); IR (neat, cm^{-1}) 1740, 1179; ^{1}H NMR δ 1.25 (3 H, t, J = 7.1 Hz), 1.22−1.35 (3 H, m), 1.56−1.67, 1.78−1.92 (1 and 2 H, respectively, 2 m), 2.39 (3 H, s), 2.44 (1 H, s), 2.53−2.56 (1 H, m), 3.30 (1 H, br s), 4.09−4.21 (2 H, m); ^{13}C NMR δ 14.3, 21.6, 29.2, 37.2, 37.8, 42.4, 60.5, 62.2, 71.3, 173.4; MS (EI) *m*/*z* (rel intensity) 183 (M$^+$, 2%), 131 (24), 73 (21), 69 (100), 57 (21), 55 (36). Anal. Calcd for $C_{10}H_{17}NO_2$: C, 65.54; H, 9.35; N, 7.64. Found: C, 65.26; H, 9.35; N, 7.55.

Alkylation of the NH Ester 6. Preparation of Products 7b,c. General Procedure. The NH amino ester **6** (339 mg, 2.0 mmol), the corresponding alkyl bromide (10.0 mmol), and 18-crown-6 (53 mg, 0.2 mmol) were dissolved in dry MeCN (10 mL). Anhydrous K_2CO_3 (335 mg, 2.4 mmol) was added, and the reaction mixture was refluxed for 24 h. Solvent was evaporated, water was added, and the resultant mixture was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine and dried.

Ethyl (1*S*,3*R*,4*R*)-2-Ethyl-2-azabicyclo[2.2.1]heptane-3-carboxylate (7b). Flash chromatography (pentane/acetone: 95/5 to 6/1) yielded 317 mg (80%) of the *N*-ethyl ester **7b**: R_f 0.25 (pentane/acetone: 4/1); $[\alpha]^{25}_D = -11.7$ (c = 1.08); IR (neat, cm^{-1}) 1748, 1174; ^{1}H NMR δ 1.01 (3 H, t, J = 7.3 Hz), 1.23 (3 H, t, J = 7.1 Hz), 1.21−1.34, 1.56−1.67, 1.79−1.89 (3, 1 and 2 H, respectively, 3 m), 2.47−2.50 (1 H, m), 2.50 (1 H, br s), 2.56 (2 H, q, J = 7.3 Hz), 3.43 (1 H, br s), 4.14 (2 H, q, J = 7.1 Hz); ^{13}C NMR δ 14.21, 14.22, 22.1, 29.2, 36.5, 42.6, 45.8, 60.3, 60.5, 70.3, 174.0; MS (EI) *m*/*z* (rel intensity) 197 (M$^+$, 6%), 131 (34), 124 (51), 96 (65), 69 (100), 68 (36). Anal. Calcd for $C_{11}H_{19}NO_2$: C, 66.97; H, 9.71; N, 7.10. Found: C, 66.85; H, 9.76; N, 7.04.

Ethyl (1*S*,3*R*,4*R*)-2-Isopropyl-2-azabicyclo[2.2.1]heptane-3-carboxylate (7c). NaI (600 mg, 4.0 mmol) was added to the reaction mixture before refluxing it, to facilitate the substitution reaction by in situ generation of *i*-PrI. Purification by flash chromatography (pentane/acetone: 99/1 to 9/1) afforded 346 mg (82%) of the *N*-isopropyl ester **7c**: R_f 0.37 (pentane/acetone: 4/1); $[\alpha]^{25}_D = +3.0$ (c = 1.09), $[\alpha]^{25}_{302} = -36.0$ (c = 1.09); IR (neat, cm^{-1}) 1750, 1174; ^{1}H NMR δ 0.97, 1.09 (3 H, each, 2 d, J = 6.2 Hz each), 1.25 (3 H, t, J = 7.1 Hz), 1.22−1.38, 1.59−1.69, 1.78−1.97 (3, 1 and 2 H, respectively, 3 m), 2.42−2.45 (1 H, m), 2.55 (1 H, septet, J = 6.2 Hz), 2.63 (1 H, s), 3.60−3.63 (1 H, m), 4.17 (2 H, q, J = 7.1 Hz); ^{13}C NMR δ 14.2, 21.8, 22.2, 22.8, 29.6, 36.1, 43.2, 50.8, 58.2, 60.4, 70.5, 174.5; MS (EI) *m*/*z* (rel intensity) 211 (M$^+$, 4%), 138 (86), 131 (31), 110 (89), 69 (100), 55 (28). Anal. Calcd for $C_{12}H_{21}NO_2$: C, 68.21; H, 10.02; N, 6.63. Found: C, 68.08; H, 10.08; N, 6.60.

Ethyl (1*S*,3*R*,4*R*)-2-Benzyl-2-azabicyclo[2.2.1]heptane-3-carboxylate (8). Anhydrous K_2CO_3 (335 mg, 2.4 mmol) was added to the solution of **6** (339 mg, 2.0 mmol) and benzyl bromide (0.29 mL, 2.4 mmol) in MeCN (10 mL) at room temperature, and the reaction mixture was stirred for 32 h. Then, solvent was evaporated, water was added, and the resultant mixture was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine and dried. Flash chromatography (pentane/Et_2O: 99/1 to 95/5) gave 407 mg (78%) of the *N*-benzyl ester **8**: R_f 0.53 (pentane/Et_2O: 1/1); $[\alpha]^{25}_D = -0.9$ (c = 1.06), $[\alpha]^{25}_{365} = -8.1$ (c = 1.06); IR (neat, cm^{-1}) 1742, 1155; ^{1}H NMR δ 1.13 (3 H, t, J = 7.1 Hz), 1.24 (1 H, dt, J = 9.4, 1.4 Hz), 1.30−1.44, 1.61−1.71, 1.92−2.05 (2, 1 and 2 H, respectively, 3 m), 2.50−2.54 (1 H, m), 2.67 (1 H, s), 3.31−3.33 (1 H, m), 3.72, 3.76 (1H each, 2 d, J = 12.9 Hz each), 4.00 (2 H, q, J = 7.1 Hz), 7.18−7.37 (5 H, m);^{13}C NMR δ 14.2, 22.4, 29.3, 36.6, 42.4, 55.5, 59.6, 60.2, 69.9, 126.8, 128.1, 129.0, 139.4, 173.5; MS (EI) *m*/*z* (rel intensity) 259 (M$^+$, <1%), 186 (39), 158 (32), 91 (100), 65 (21). Anal. Calcd for $C_{16}H_{21}NO_2$: C, 74.10; H, 8.16; N, 5.40. Found: C, 73.89; H, 8.17; N, 5.37.

Reduction of Esters 7 and 8. General Procedure. To a stirred suspension of $LiAlH_4$ (111 mg, 2.8 mmol) in dry THF (6 mL), under Ar, cooled to 0 °C, the solution of the corresponding amino ester **7**−**8** (1.4 mmol) in dry THF (3 mL) was added dropwise during ca. 10 min. The reaction mixture was stirred for 2 h at 0 °C and then quenched following a literature procedure.[18]

(1*S*,3*R*,4*R*)-3-(Hydroxymethyl)-2-methyl-2-azabicyclo[2.2.1]heptane (2a). Evaporation of the solvent yielded 150 mg (76%) of pure **2a**: R_f 0.08 ($CHCl_3$/MeOH: 95/5); $[\alpha]^{25}_D = -27.7$ (c = 1.03); IR (neat, cm^{-1}) 3384; ^{1}H NMR δ 1.19−1.36, 1.54−1.64, 1.71−1.76, 1.86−1.98 (3, 1, 1, and 2 H, respectively, 4 m), 2.13−2.16 (1 H, m), 2.35 (3 H, s), 3.19 (1 H, br s), 3.32 (1 H, br s), 3.36 (1 H, dd, J = 10.8, 5.4 Hz), 3.47 (1 H, dd, J = 10.8, 5.8 Hz); ^{13}C NMR δ 21.5, 29.4, 36.6, 37.7, 40.9, 62.1, 64.5, 70.5; MS (EI) *m*/*z* (rel intensity) 141 (M$^+$, 2%), 83 (26), 71 (25), 69 (100), 57 (32), 55 (59). Anal. Calcd for $C_8H_{15}NO$: C, 68.04; H, 10.71; N, 9.92. Found: C, 68.38; H, 10.78; N, 9.58.

(1*S*,3*R*,4*R*)-2-Ethyl-3-(hydroxymethyl)-2-azabicyclo[2.2.1]heptane (2b). Purification by flash chromatography (deactivated silica gel, pentane/acetone/MeOH: 100/100/5 and then acetone MeOH: 9/1) afforded 130 mg (60%) of the expected product **2b**: R_f 0.22 (acetone/MeOH: 95/5; deactivated silica gel); $[\alpha]^{25}_D = -14.4$ (c = 1.00); IR (neat, cm^{-1}) 3384; ^{1}H NMR δ 1.06 (3 H, t, J = 7.2 Hz), 1.19−1.34, 1.54−1.62, 1.71−1.76, 1.81−1.89 (3, 1, 1 and 1 H, respectively, 4 m), 2.02−2.06, 2.14−2.17 (1 H each, 2 m), 2.52, 2.65 (1H each, 2 dq, J = 12.0, 7.2 Hz each), 3.35 (1 H, dd, J = 10.7, 4.5 Hz), 3.35−3.38 (2 H, m), 3.44 (1 H, dd, J = 10.7, 6.3 Hz); ^{13}C NMR δ 14.4, 21.7, 29.2, 36.0, 41.0, 45.1, 58.6, 64.4, 69.8; MS (EI) *m*/*z* (rel intensity) 155 (M$^+$, 11%), 124 (35), 96 (100), 95 (27), 69 (62), 68 (59), 67(29). Anal. Calcd for $C_9H_{17}NO \cdot H_2O$:[17] C, 62.39; H, 11.05; N, 8.08. Found: C, 62.67; H, 10.99; N, 8.09.

(1*S*,3*R*,4*R*)-3-(Hydroxymethyl)-2-isopropyl-2-azabicyclo[2.2.1]heptane (2c). The residue obtained after evaporation of the solvent was chromatographed (deactivated silica gel, pentane/acetone: 1/1 and then pentane/acetone/MeOH: 100/100/5 to 0/100/5) and 190 mg (80%) of **2c** were isolated: R_f 0.34 (pentane/acetone: 1/1; deactivated silica gel); $[\alpha]^{25}_D = -24.6$ (c = 1.02); IR (neat, cm^{-1}) 3356; ^{1}H NMR δ 1.06, 1.09 (3H each, 2 d, J = 6.3 Hz each), 1.19−1.37, 1.56−1.65, 1.79−1.91 (3, 1 and 2 H, respectively, 3 m), 2.21−2.25 (2 H, m), 2.66 (1 H, septet, J = 6.3 Hz), 3.39 (1 H, dd, J = 10.6, 3.6 Hz), 3.43 (1 H, dd, J = 10.6, 6.6 Hz), 3.52 (1 H, br s), 3.92 (1 H, br s); ^{13}C NMR δ 22.2, 22.5, 23.1, 28.6, 35.6, 42.0, 50.6, 58.7, 64.9, 68.8; MS (EI) *m*/*z* (rel intensity) 169 (M$^+$, 2%), 138 (88), 110 (100), 96 (25), 68 (61), 67 (34). Anal. Calcd for $C_{10}H_{19}NO \cdot 0.6H_2O$:[17] C, 66.70; H, 11.31; N, 7.78. Found: C, 67.10; H, 11.27; N, 7.41.

(1*S*,3*R*,4*R*)-2-Benzyl-3-(hydroxymethyl)-2-azabicyclo[2.2.1]heptane (2d). Flash chromatography (pentane/acetone: 4/1) afforded 225 mg (74%) of the amino alcohol **2d**: R_f 0.20 (pentane/acetone: 1/1); $[\alpha]^{25}_D = -0.6$ (c = 1.06), $[\alpha]^{25}_{302} = -80.7$ (c = 1.06); IR (neat, cm^{-1}) 3384; ^{1}H NMR δ 1.17 (1 H, br d, J = 9.6 Hz), 1.25−1.37, 1.56−1.66, 1.74−1.80, 1.95−2.05 (2, 1, 1 and 1 H, respectively, 4 m), 2.17−2.22

(17) The product was very hygroscopic.

(18) Micovic, V. M.; Mihailovic, M. L. *J. Org. Chem.* **1953**, *18*, 1190.

(2 H, m), 2.50 (1 H, br s), 3.21 (1 H, br s), 3.24 (1 H, dd, J = 10.7, 3.9 Hz), 3.29 (1 H, dd, J = 10.7, 5.6 Hz), 3.67, 3.71 (1H each, 2 d, J = 13.1 Hz each), 7.20−7.39 (5 H, m); ^{13}C NMR δ 22.1, 29.6, 36.3, 41.7, 54.9, 59.1, 64.1, 69.0, 127.0, 128.3, 128.8, 139.9; MS (EI) m/z (rel intensity) 217 (M^+, <1%), 186 (50), 158 (39), 91 (100), 65 (21). Anal. Calcd for $C_{14}H_{19}NO\cdot 0.3H_2O$:[17] C, 75.50; H, 8.87; N, 6.29. Found: C, 75.50; H, 8.83; N, 6.33.

Addition of Grignard Reagents to 8. Preparation of Amino Alcohols 2e−g. General Procedure. The solution of the amino ester **8** (1.5 mmol) in dry THF, under Ar, was cooled to −30 °C, and the solution of the corresponding Grignard reagent (3.75 mmol) in dry Et_2O (4 mL) was added dropwise. The reaction was stirred for 7 h, allowing the temperature to rise to room temperature. Then, water was added, and the mixture was extracted with ethyl acetate (3 × 20 mL). After drying and evaporation of the solvent, the residue was purified by flash chromatography.

(1*S*,3*R*,4*R*)-2-Benzyl-3-(2-hydroxy-2-propyl)-2-azabicyclo[2.2.1]heptane (2e). Flash chromatography (pentane/acetone: 95/5) gave 311 mg (84%) of product **2e**: R_f 0.40 (pentane/acetone: 4/1); mp = 48−50 °C; $[\alpha]^{25}_D$ = +31.5 (c = 1.09); IR (KBr, cm^{-1}) 3482; ^{1}H NMR δ 1.07 (1 H, br d, J = 9.5 Hz), 1.21, 1.23 (3 H each, 2 s), 1.19−1.30, 1.57−1.66, 1.83−1.89, 2.01−2.09 (2, 1, 1 and 1 H, respectively, 4 m), 2.01 (1 H, s), 2.38−2.42 (1 H, m), 3.12 (1 H, br s), 3.18 (1 H, br s), 3.70, 4.02 (1H each, 2 d, J = 14.0 Hz each), 7.22−7.38 (5 H, m); ^{13}C NMR δ 22.1, 26.5, 29.8, 30.3, 36.0, 39.5, 55.5, 58.0, 71.2, 76.3, 126.8, 128.3 (4 C), 140.0; MS (EI) m/z (rel intensity) 230 (M^+ − 15, 2%), 186 (56), 158 (45), 91 (100), 65 (18). Anal. Calcd for $C_{16}H_{23}NO$: C, 78.32; H, 9.45; N, 5.71. Found: C, 78.34; H, 9.42; N, 5.69.

(1*S*,3*R*,4*R*)-2-Benzyl-3-(3-hydroxy-2,4-dimethyl-3-pentyl)-2-azabicyclo[2.2.1]heptane (2f). Flash chromatography (pentane/acetone: 99/1 to 95/5) afforded 90 mg (20%) of the amino alcohol **2f**: R_f 0.66 (pentane/Et_2O: 1/1); mp = 73−74 °C; $[\alpha]^{25}_D$ = +42.5 (c = 1.00); IR (KBr, cm^{-1}) 3448; ^{1}H NMR δ 1.021, 1.022, 1.04, 1.12 (3 H each, 4 d, J = 7.1 Hz each), 1.04−1.08, 1.16−1.32, 1.58−1.66, 1.92−2.11 (1, 2, 1 and 2 H, respectively, 4 m), 2.02 (1 H, septet, J = 7.1 Hz), 2.16 (1 H, septet, J = 7.1 Hz), 2.44 (1 H, br s), 2.47−2.50 (1 H, m), 3.12 (1 H, br s), 3.14 (1 H, br s), 3.64, 4.03 (1H each, 2 d, J = 14.1 Hz each) and 7.21−7.36 (5 H, m); ^{13}C NMR δ 18.4, 18.8, 19.1, 19.6, 22.3, 29.7, 32.0, 35.0, 35.7, 40.3, 55.3, 57.7, 70.7, 77.2, 126.7, 128.2, 128.3 and 140.1; MS (EI) m/z (rel intensity) 258 (M^+ − 43, 13%), 186 (92), 158 (40), 91 (100) and 65 (13). Anal. Calcd for $C_{20}H_{31}NO$: C, 79.68; H, 10.36; N, 4.65. Found: C, 79.57; H, 10.39; N, 4.67.

(1*S*,3*R*,4*R*)-2-Benzyl-3-(hydroxydiphenylmethyl)-2-azabicyclo[2.2.1]heptane (2g). Flash chromatography (pentane/Et_2O: 95/5) yielded 261 mg (47%) of the expected product **2g**. All the physical and spectroscopic data of **2g** were in complete agreement with the data reported for its enantiomer,[5b] except for the sign of the optical rotation.

Addition Reaction of Dialkylzinc Reagents to 1 Promoted by the Ligands 2. General Procedure. The phosphinoyl imine **1** (76 mg, 0.25 mmol) and the amino alcohol **2** (0.25 mmol) were dissolved in dry toluene (1.5 mL) under Ar, and the mixture was stirred for 10 min at room temperature. The solution was cooled to 0 °C, R_2Zn (0.75 mL 1.0 M solution in hexane, 0.75 mmol) was added dropwise, and the reaction was stirred, allowing the temperature to rise slowly to room temperature (3−4 h) and then for 2 days. 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 (pentane/acetone: 6/1 to 1/1). The resultant solid was analyzed by HPLC, using 10% *i*-PrOH in hexane as eluent. The retention times are: **3a**:[7b] 13.6 (*R*) and 17.7 min (*S*); **3a′**:[7b] 14.7 (*R*) and 18.6 min (*S*); **3b**:[7b] 16.3 (*R*) and 19.8 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[7b] and comparison of the optical rotation of the obtained amine with the reported data.[7b]

Addition Reaction of Et_2Zn to PhCHO Catalyzed by the Ligands 2. General Procedure. Et_2Zn (2.2 mL 1.0 M solution in hexane, 2.2 mmol) was added dropwise to the solution of the ligand **2** (0.05 mmol) in dry toluene (1.5 mL), under Ar, at 0 °C. After 20 min, PhCHO (0.10 mL, 1.0 mmol) was added dropwise, and the resulting solution was stirred for 1 day at 0 °C. The reaction was quenched with saturated aqueous NH_4Cl (10 mL), and the mixture was extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with water (10 mL) and brine (10 mL) and dried. Evaporation of the solvents and flash chromatography (pentane/Et_2O: 9/1) afforded the expected product **10**, that was analyzed by HPLC, using 5% *i*-PrOH in hexane as eluent. The retention times are 15.6 (*R*) and 17.7 min (*S*). Yields and ee's are given in Table 2. The absolute configuration of the major isomer was determined by comparison of the optical rotation with the reported data.[19]

Acknowledgment. We thank the Wenner-Gren Foundation (postdoctoral stipend to D. G.), the Swedish Natural Science Research Council, and the Foundation for Strategic Research (SSF) for financial support.

JO9718096

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