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Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 18 (2007) 2828–2840

Enantioselective addition of dialkylzinc reagents to *N*-(diphenylphosphinoyl)imines catalyzed by β-aminoalcohols with the prolinol skeleton

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Received 26 October 2007; accepted 7 November 2007

Dedicated to the memory of Professor Al Meyers

Abstract—Several β-aminoalcohols with the prolinol framework are shown to be very efficient catalysts for the enantioselective addition of dialkylzinc reagents to *N*-(diphenylphosphinoyl)imines. The use of 0.5 equiv of the catalyst leads to the expected addition products in good yields and with ee up to 94% in a reaction time of only 4 h at room temperature. This ee is the highest value reported so far using 0.5 equiv of an aminoalcohol as a promoter. High enantioselectivities are obtained in the addition of dialkylzincs to both aromatic and aliphatic imines. The amount of the catalyst can be reduced to 0.25 equiv with a slight decrease in the ee. A very interesting effect of the addition rate and temperature on the enantioselectivity was also observed.

1. Introduction

In recent years, there has been great interest in the development of methodologies for the asymmetric preparation of optically active amines, since they are important compounds which are extensively used as resolving agents,[1] starting materials for the preparation of biologically active substances[2] and chiral auxiliaries in asymmetric synthesis.[3] The addition of organometallic reagents to imines is a valuable method for the synthesis of primary and secondary amines.[4,5] However, it presents some problems due to the low electrophilic character of the C=N bond and to the tendency of enolizable imines to undergo α-deprotonation instead of addition. The low electrophilicity of the imine can be overcome by introducing an electron-withdrawing group attached to the nitrogen atom. Amongst the activated imines, *N*-phosphinoylimines[6] are very attractive since the phosphinoyl group can be easily removed from the addition products under mild reaction conditions leading to the free amines.[7] *N*-Phosphinoylimines have found a variety of synthetic applications, including asymmetric processes.[5] Concerning the carbon nucleophiles, dialkylzinc reagents are very useful since organozinc reagents[8] bearing several functional groups can be easily prepared,[9] and can lead to polyfunctionalized organic compounds. However, the reaction of *N*-phosphinoylimines with dialkylzincs is very slow, leading to low yields of addition products in very long reaction times. An improvement of both reaction rate and yield has been achieved by using some additives, such as β-aminoalcohols,[7,10] iminoalcohols,[10j] hydroxyoxazolines[11] and copper,[12] zirconium[13] or nickel[14] complexes. Concerning chiral β-aminoalcohols, there is a trend to believe that a rigid backbone in the ligand is generally required to obtain high enantioselectivity.[7,10c,e–g] However, the synthesis of structurally rigid aminoalcohols often involves a multistep process, which makes the procedure inconvenient and expensive. The development of easily accessible and inexpensive chiral ligands is thus very interesting. We have prepared several aminoalcohols with the prolinol skeleton and various substituents at different positions of the pyrrolidine ring and the carbinol carbon atom. Herein we report our results on their use as catalysts for the enantioselective addition of dialkylzinc reagents to both aromatic and aliphatic *N*-(diphenylphosphinoyl)imines.[15] By fine tuning of the ligand structure, an enantioselectivity of up to 94% has been achieved, which is the highest

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doi:10.1016/j.tetasy.2007.11.006

reported so far using 0.5 equiv of an aminoalcohol as a promoter of the same reaction.

2. Results and discussion

We decided to start by testing *N*-benzyl-L-prolinol **1c** (Fig. 1) as a promoter of the addition of dialkylzincs to *N*-(diphenylphosphinoyl)benzaldimine. The reasons that led us to choose this ligand were (a) the prolinol substructure can be found in ligands with the 2-azanorbornylmethanol framework **2** (Fig. 1) that have been successfully applied as catalysts for the same reaction,[10c,e,g] (b) ligands with a prolinol skeleton have given good enantioselectivities in several asymmetric processes[16] and (c) ligand **1** is commercially available and inexpensive and can be easily prepared in two steps from the readily accessible natural aminoacid L-proline.

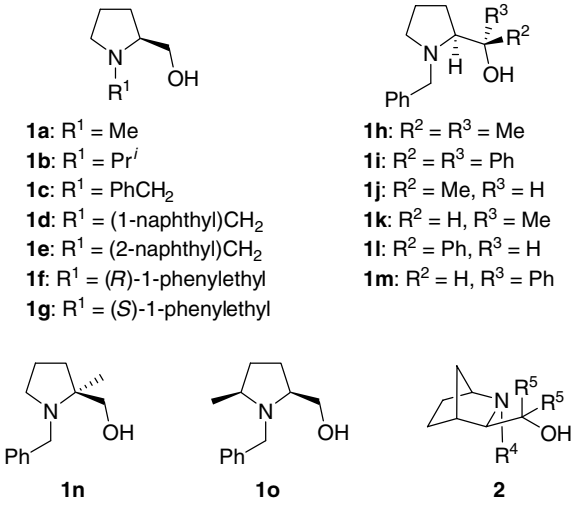
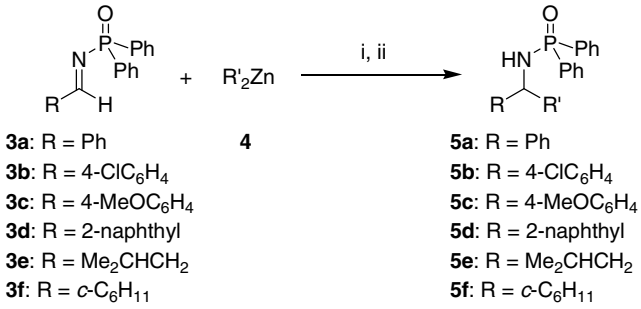


Figure 1.

In the first experiment, diethylzinc (3 equiv) was added dropwise to a solution of benzaldimine **3a** (Scheme 1) and ligand **1c** (1 equiv) in toluene at 0 °C over ca. 10 min. The reaction was stirred allowing the temperature to rise to room temperature and, after 24 h, a disappointing 74% ee was obtained (Table 1, entry 1), which was lower than the one reported for the analogous ligand with 2-azanorbornylmethanol skeleton **2** ($R^4 = PhCH_2$, $R^5 = H$; 91% ee).[10c,17] However, when diethylzinc was slowly added over 3 h using a syringe pump, the ee increased to 86% (Table 1, entry 2). Gratifyingly surprised by this result, we decided to screen the reaction conditions further. Since yields were only moderate in both cases, we repeated the reaction using 9 equiv of diethylzinc instead of 3 equiv and the yield improved to 84% with almost the same enantioselectivity as before, with the time needed for completion of the reaction being much shorter (8 h; Table 1, entry 3).

Next, we studied the effect of temperature. When the addition of diethylzinc (9 equiv in 3 h) to imine **3a** in the presence of ligand **1c** (1 equiv) was stirred for 24 h at 0 °C, the reaction did not go to completion and the ee decreased to



Scheme 1. Reagents and conditions: (i) ligand **1** (0.25–1 equiv), toluene, T; (ii) NH_4Cl (aq).

58% (Table 1, entry 4). However, when the addition of diethylzinc was performed at room temperature, the expected addition product was obtained after only 4 h in 89% yield and 92% ee, which was slightly higher than the one reported for the rigid ligand **2** ($R^4 = PhCH_2$, $R^5 = H$; 91% ee).[10c] Since the reaction was fast under these conditions, we thought about reducing the amount of diethylzinc. Setting up the reaction with 3 equiv and maintaining the addition rate, the same ee of 92% was obtained in 4 h, although the yield decreased to 60% (Table 1, entry 6). Since we had observed before that the addition rate was very important for the enantioselectivity, we repeated the last experiment with addition times of 10 min and 2 h. In the first case, the reaction was completed in 4 h and the addition product was isolated in 79% yield and 92% ee (Table 1, entry 7). Lengthening the addition time to 2 h caused a decrease in both yield and ee (Table 1, entry 8). When the reaction under the conditions of entry 7 was set up at 50 °C (oil bath temperature) instead of room temperature, it was complete in only 1 h, affording the expected product in 96% yield and 90% ee (Table 1, entry 9). We were pleased by this result, since, to the best of our knowledge, this is the fastest addition reaction of diethylzinc to imine **3a** that has ever been reported using an aminoalcohol as a promoter.

In all cases, although a stoichiometric amount of ligand **1c** was used, up to 85% of it could be recovered by column chromatography and reused without loss of chiral induction. For instance, ligand **1c**, which was isolated from the reaction of entry 7 in Table 1, was used as a promoter of another addition reaction of diethylzinc to imine **3a** and the expected addition product **5aa** was obtained in 78% yield and 92% ee.

The possibility of using a substoichiometric amount of the ligand was then investigated. We were delighted to see that we obtained the same result using either 0.5 or 1 equiv of ligand **1c** (compare entries 7 and 10 in Table 1). The ee of 92% is almost equal to the highest ee reported so far using this amount of an aminoalcohol (93%)[10j] and our reaction was much faster (4 h instead of 48 h). With 0.25 equiv of the ligand, the reaction time increased to 20 h and the ee decreased to 80%. However, when the reaction temperature was 50 °C instead of 25 °C, the same results were achieved and the reaction was finished after only 3 h (compare entries 11 and 12 in Table 1). It is worth

Table 1. Enantioselective addition of diethylzinc to *N*-(diphenylphosphinoyl)imine **3a** in the presence of aminoalcohol **1c**: Optimization of the reaction conditions

Entry	Equiv of Et_2Zn	Equiv of **1c**	*T* (°C)	Add. time[a] (h)	Time (h)	Product **5aa**		
						Yield[b] (%)	ee[c] (%)	Configuration[d]
1	3	1	0–25	0.2	24	52	74	(*R*)
2	3	1	0–25	3	24	48	86	(*R*)
3	9	1	0–25	3	8	84	84	(*R*)
4	9	1	0	3	24	45	58	(*R*)
5	9	1	25	3	4	89	92	(*R*)
6	3	1	25	1	4	60	92	(*R*)
7	3	1	25	0.2	4	79	92	(*R*)
8	3	1	25	2	4	48	76	(*R*)
9	3	1	50	0.2	1	96	90	(*R*)
10	3	0.5	25	0.2	4	79	92	(*R*)
11	3	0.25	25	0.2	20	76	80	(*R*)
12	3	0.25	50	0.2	3	75	80	(*R*)

[a] Period of time during which the dropwise addition of diethylzinc to the solution of **1c** and **3a** was performed.
[b] Isolated yield after column chromatography (silica gel, pentane/acetone) based on the starting imine **3a**. All isolated compounds were ⩾95% pure (GC and/or 300 MHz ^{1}H NMR).
[c] Enantiomeric excess determined by HPLC using a ChiralCel OD-H column.
[d] The absolute configuration of the major enantiomer was determined by comparison of the specific rotation of the free primary amine with the one reported in the literature.

noting that, to the best of our knowledge, this is the fastest reaction of this type reported so far using 0.25 equiv of an aminoalcohol as the catalyst with the ee obtained close to the highest ee reported in the literature for that amount of ligand (85%).[10c]

The versatility of our procedure concerning the dialkylzinc reagent was also studied. Dimethyl-, diisopropyl- and dibutylzinc were used as nucleophiles for the addition to imine **3a** under the reaction conditions of entry 10 in Table 1. As previously reported,[7,10c] dimethylzinc turned out to be much less reactive than diethylzinc. The use of 9 equiv was necessary to obtain a moderate yield of the addition product in 3 days at room temperature, but a 90% ee was obtained (Table 2, entry 2). Setting up the reaction at 50 °C led to an improved yield (74%) in only 1 day with a very slight decrease in the ee (Table 2, entry 3). Diisopropylzinc was as efficient as diethylzinc giving good yield and enantioselectivity in a reaction time of only 4 h (Table 2, entry 4). The reaction with dibutylzinc also required a longer reaction time to reach completion affording the addition product in 64% yield and 90% ee (Table 2, entry 5). The same reaction at 50 °C improved both the reaction rate and yield with almost the same enantioselectivity (Table 2, entry 6).

Next, we decided to investigate the scope of this reaction by testing some other imine substrates **3b–f** (Scheme 1). All imines **3** were prepared from the corresponding aldehydes according to the literature procedures.[12g,18] Ligand **1c**

Table 2. Enantioselective addition of dialkylzinc reagents to *N*-(diphenylphosphinoyl)imines **3** in the presence of *N*-benzyl-L-prolinol **1c**[a]: Preparation of compounds **5**

Entry	Imine	R′	Equiv	*T* (°C)	Time (h)	Product			
						No.	Yield[b] (%)	ee[c] (%)	Configuration[d]
1	**3a**	Et	3	25	4	**5aa**	79	92	(*R*)
2	**3a**	Me	9	25	72	**5ab**	51	90	(*R*)
3	**3a**	Me	9	50	24	**5ab**	74	88	(*R*)
4	**3a**	Pr^i	3	25	4	**5ac**	80	90	(*R*)
5	**3a**	Bu^n	3	25	24	**5ad**	64	90	(*R*)
6	**3a**	Bu^n	3	50	4	**5ad**	86	88	(*R*)
7	**3b**	Et	3	25	4	**5b**	80	90	(*R*)
8	**3c**	Et	3	25	12	**5c**	71	92	(*R*)
9	**3d**	Et	3	25	4	**5d**	86	90	(*R*)
10	**3e**	Et	3	25	4	**5e**	60	58	(*R*)
11	**3f**	Et	3	25	4	**5f**	36	90	(*R*)

[a] All reactions were performed by the dropwise addition of the dialkylzinc reagent over ca. 10 min to a stirred solution of imine **3** (0.5 mmol) and ligand **1c** (0.25 mmol) in anhydrous toluene (3 mL) under argon and stirring was continued for the time indicated.
[b] Isolated yield after column chromatography (silica gel, pentane/acetone) based on the starting imine **3**. All isolated compounds **5** were ⩾95% pure (GC and/or 300 MHz ^{1}H NMR).
[c] Enantiomeric excess determined by HPLC using a ChiralCel OD-H column or a Chiralpak AD column.
[d] The absolute configuration of the major enantiomer was determined by comparison of the specific rotation of the free primary amine with that reported in the literature.

(0.5 equiv) was used as a promoter of the addition of diethylzinc to imines **3b–f** under the reaction conditions of entry 10 in Table 1 and the results are listed in Table 2. As can be seen, all imines derived from aromatic aldehydes gave very good ees regardless of the electronic nature of the substituents on the aromatic ring (Table 2, entries 7–9). Although the reaction with imine **3c**, which has an electron-donating group at the *para* position of the benzene ring, was slower (reaction time of 12 h instead of 4 h), a very high ee of 92% was observed in the addition product **5c** (Table 2, entry 8). Our ligand **1c** could also effectively catalyze the addition of diethylzinc to aliphatic imines **3e** and **3f**. The ee obtained with imine **3e**, derived from isobutyraldehyde, was only moderate (58%, Table 2, entry 10), but we were pleased to see that the ee of the addition product to imine **3f**, derived from cyclohexanecarbaldehyde, was of the same level as those obtained with the aromatic imines (90%, Table 2, entry 11).

We also tried to use the activated ketimine **6** (Fig. 2) as the substrate. The reaction of this imine with diethylzinc (3 equiv) in the presence of aminoalcohol **1c** (0.5 equiv) at room temperature gave the reduction product **7a** (Fig. 2) exclusively. We assumed that the reduction process took place via a β-hydride transfer from diethylzinc to the imine carbon atom. Thus, we decided to test dimethylzinc, which lacks hydrogen atoms at the β position. The use of this nucleophile (9 equiv) led to the formation of the expected addition product **7b** (Fig. 2) after stirring at room temperature for 24 h in 40% yield, but with a disappointing 18% ee.

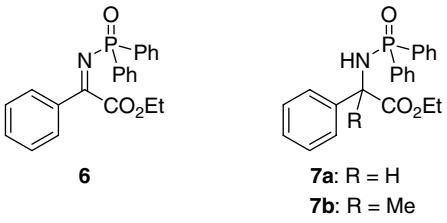
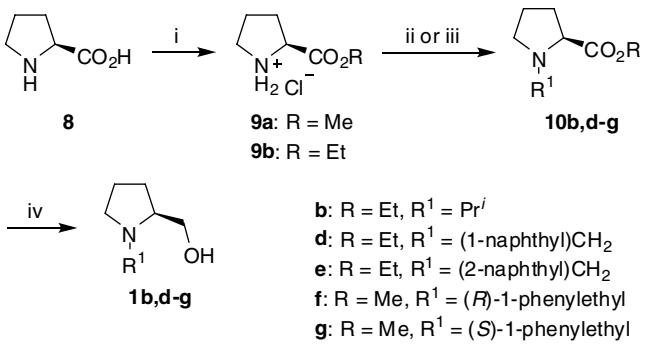


Figure 2.

As described above, by proper choice of the reaction conditions, *N*-benzyl-L-prolinol was shown to be a catalyst for the addition of dialkylzinc reagents to *N*-(diphenylphosphinoyl)aldimines and even more effective than the analogous bicyclic ligand **2**. It is worth noting that the enantiomer of ligand **1c** is also commercially available, which provides the opportunity of preparing both enantiomers of the final amine products.

Having established that compound **1c** with the prolinol skeleton was an efficient catalyst for this reaction, we thought about studying the effect of different ligand substituents on the enantioselectivity. Figure 1 shows all the substituted prolinols **1** which have been tested as catalysts for the addition of diethylzinc to imine **3a**. *N*-Methyl prolinol **1a** was also commercially available. Aminoalcohols **1b**, **1d** and **1e** were prepared from L-proline as described in Scheme 2. L-Proline ethyl ester hydrochloride **9b** was alkylated at nitrogen by reaction with the corresponding



Scheme 2. Reagents and conditions: (i) 2 M HCl in EtOH, reflux (for compound **9b**); (ii) Pr^iBr, K_2CO_3, 18-crown-6 (cat.), NaI, MeCN, reflux, 55% (two steps) (for compound **10b**); (iii) (1-naphthyl)CH_2Cl (for compound **10d**) or (2-naphthyl)CH_2Br (for compound **10e**) or PhCH(Me)Br (for compounds **10f** and **10g**), Et_3N, $CHCl_3$, reflux, 64% (for **10d**, two steps), 74% (for **10e**, two steps) and 70% (for **10f** + **10g**, ^1H NMR ratio **10f**:**10g** = 1:1); (iv) $LiAlH_4$, Et_2O, 0 °C, 68%, 49%, 33%, 82% and 85%, respectively.

alkyl halide in the presence of a base, giving esters **10b**, **10d** and **10e** in 55%, 64% and 74% yields, respectively. The final reduction with $LiAlH_4$ afforded the expected N-alkylated prolinols **1b**, **1d** and **1e**. On the other hand, commercially available L-proline methyl ester hydrochloride **9a** was alkylated at nitrogen by reaction with 1-bromo-1-phenylethane in the presence of triethylamine, giving a mixture of the diastereomeric esters **10f** and **10g** in an overall yield of 70% (1:1 ratio by ^1H NMR). Aminoesters **10f** and **10g** could be separated by flash chromatography and reduction with $LiAlH_4$ afforded aminoalcohols **1f** and **1g** in 82% and 85% yield, respectively. To determine the absolute stereochemistry of the *sec*-phenethyl substituent of compound **10f**, its ester moiety was transformed into a diphenylcarbinol centre by reaction with an excess of PhMgBr. X-ray diffraction analysis of the obtained aminoalcohol showed an (*R*) stereochemistry for the substituent at nitrogen (Fig. 3).[19]

Compounds **1h** and **1i**, which have a tertiary carbinol centre, were synthesized by the reaction of the commercially available *N*-benzyl-L-proline ethyl ester **11** with the corresponding Grignard reagents (Scheme 3). The two epimers **1j** and **1k** were prepared from *N*-benzyl-L-prolinol **1c**, which was converted into aldehyde **12** by a Swern oxidation (Scheme 4). The addition of MeMgBr to **12** in the presence of $CeCl_3$ gave a mixture of products **1j** and **1k**, which could be separated by flash chromatography. Following the same procedure, but using PhMgBr instead of MeMgBr, the two epimers **1l** and **1m** were obtained and could be separated by flash chromatography. The absolute stereochemistry of ligand **1j** was determined by comparison of its physical and spectroscopic data with that reported in the literature.[20] The absolute stereochemistry of the carbinol site of ligand **1m** could be determined by X-ray diffraction analysis (Fig. 4).[21]

Commercially available aminoacid **13** was used as the starting material for the synthesis of ligand **1n** (Scheme 5). The transformation of **13** into its ethyl ester hydrochloride followed by benzylation of the nitrogen atom afforded

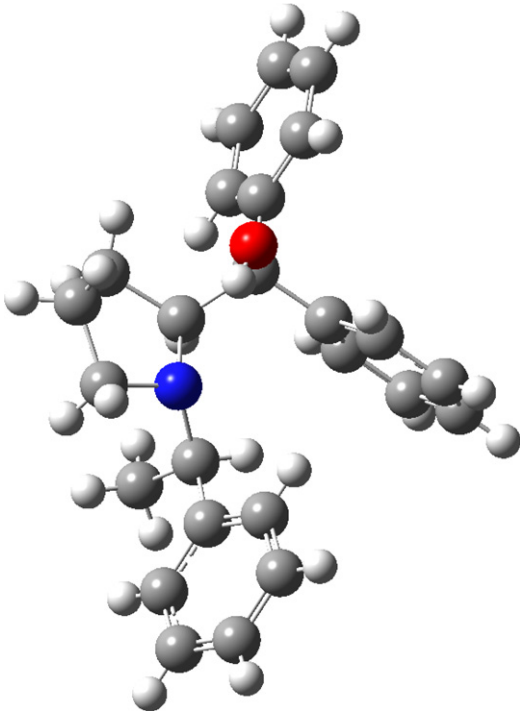
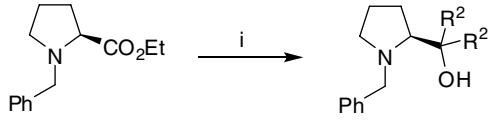
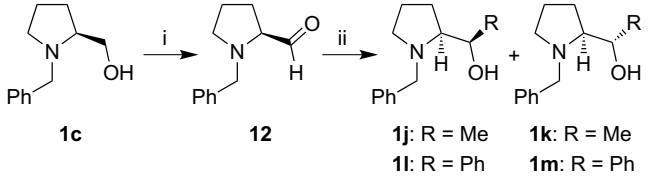


Figure 3. X-ray structure of the diphenylcarbinol derived from **10f**.



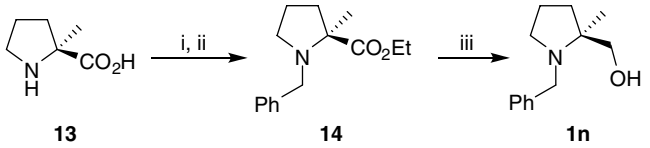
Scheme 3. Reagents and conditions: (i) MeMgBr (for compound **1h**) or PhMgBr (for compound **1i**), THF, −78 °C to rt, 99% and 50%, respectively.



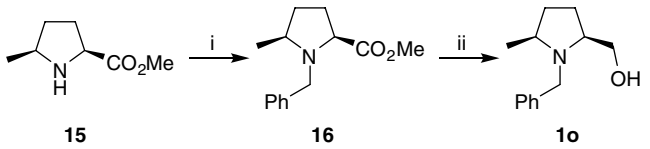
Scheme 4. Reagents and conditions: (i) ClCOCOCl, DMSO, Et_3N, CH_2Cl_2, −78 °C; (ii) MeMgBr (for compounds **1j** and **1k**) or PhMgBr (for compounds **1l** and **1m**), $CeCl_3$, Et_2O, −78 °C, 81% (for **1j** + **1k**, two steps, ^1H NMR ratio **1j**:**1k** = 1:3) and 77% (for **1l** + **1m**, two steps, ^1H NMR ratio **1l**:**1m** = 3:7).

aminoester **14** in 80% yield. Treatment of **14** with $LiAlH_4$ led to aminoalcohol **1n** in 76% yield.

Finally, ligand **1o** was prepared from the *cis*-5-methyl proline methyl ester **15** (Scheme 6), which was synthesized in a sequence of several steps from methyl *N*-Boc-(*S*)-pyroglutamate according to the literature.[22] N-Benzylation of **15** followed by reduction with $LiAlH_4$ afforded the expected ligand **1o**.



Scheme 5. Reagents and conditions: (i) 2 M HCl in EtOH, reflux; (ii) $PhCH_2Br$, Et_3N, $CHCl_3$, reflux, 80% (two steps); (iii) $LiAlH_4$, Et_2O, 0 °C, 76%.



Scheme 6. Reagents and conditions: (i) $PhCH_2Br$, Et_3N, $CHCl_3$, reflux, 30%; (ii) $LiAlH_4$, Et_2O, 0 °C, 92%.

With all aminoalcohols **1** in hand, we decided to test them as catalysts for the addition of diethylzinc to benzaldimine **3a** using 0.5 equiv of ligand **1** under the reaction conditions of entry 10 in Table 1. The results of these reactions are collected in Table 3. It seems that the enantioselectivity improves with the size of the nitrogen substituent. The ee increased upon going from methyl (Table 3, entry 1) to isopropyl (Table 3, entry 2). The presence of an aromatic ring in R^1 seems to be important, since ligand **1c**, which has an *N*-benzyl group, gave 92% ee (Table 3, entry 3). Substitution of the phenyl group by a 2-naphthyl group afforded

Table 3. Enantioselective addition of diethylzinc to *N*-(diphenylphosphinoyl)benzaldimine **3a** in the presence of aminoalcohols **1**[a]

Entry	Ligand	Time (h)	Product **5aa**		
			Yield[b] (%)	ee[c] (%)	Configuration[d]
1	**1a**	18	43	62	(*R*)
2	**1b**	4	80	84	(*R*)
3	**1c**	4	79	92	(*R*)
4	**1d**	4	70	80	(*R*)
5	**1e**	4	85	90	(*R*)
6	**1f**	6	66	60	(*R*)
7	**1g**	4	80	94	(*R*)
8	**1h**	24	45	60	(*R*)
9	**1i**	48	30	20	(*R*)
10	**1j**	4	73	94	(*R*)
11	**1k**	24	35	66	(*R*)
12	**1l**	7	76	88	(*R*)
13	**1m**	24	54	12	(*R*)
14	**1n**	4	86	90	(*R*)
15	**1o**	6	62	60	(*R*)

[a] All reactions were performed by dropwise addition of Et_2Zn (3 equiv) over ca. 10 min to a stirred solution of imine **3a** (0.5 mmol) and ligand **1** (0.25 mmol) in anhydrous toluene (3 mL) under argon at room temperature and stirring was continued for the time indicated.

[b] Isolated yield after column chromatography (silica gel, pentane/acetone) based on the starting imine **3a**. All isolated compounds were ⩾95% pure (GC and/or 300 MHz ^1H NMR).

[c] Enantiomeric excess determined by HPLC using a ChiralCel OD-H column.

[d] The absolute configuration of the major enantiomer was determined by comparison of the specific rotation of the free primary amine with that reported in the literature.

almost the same enantioselectivity (Table 3, entry 5), whereas a 1-naphthylmethyl substituent at the nitrogen atom gave a lower ee (80%; Table 3, entry 4). The introduction of a methyl group on the α-carbon atom of the benzylic substituent at nitrogen also affected the enantioselectivity. The stereochemistry of this new asymmetric carbon atom has proven to be very important. The (*S*)-1-phenylethyl substituent of ligand **1g** led to an increase of the ee to 94% (Table 3, entry 7), whereas the (*R*)-1-phenylethyl substituent gave an ee of 60% (Table 3, entry 6), lower than the one obtained with the unsubstituted benzyl group. The ee of 94% obtained in the reaction catalyzed by **1g** is, to the best of our knowledge, the highest ee reported so far using 0.5 equiv of an aminoalcohol as a promoter of this reaction.

As was previously observed,[7,10c] a decrease in the enantioselectivity was obtained upon increasing the size of the R^2 substituent (compare entries 3, 8 and 9 in Table 3). Moreover, the reactions promoted by the ligands with a tertiary alcohol, **1h** and **1i**, were much slower (reaction times of 24 and 48 h, respectively). Since it had been reported that the introduction of a stereogenic centre at the carbinol site could improve the enantioselectivity of these reactions,[10e] we tested aminoalcohols **1j** and **1k**. A comparison of entries 10 and 11 in Table 3 shows the importance of the stereochemistry at this carbinol centre: ligand **1j**, which has an (*R*)-configuration, gave product **5aa** in good yield and with 94% ee in a fast reaction, whereas the ligand with a (*S*)-carbinol carbon **1k** needed 24 h to give a low yield of the addition product in only 66% ee. The same trend was observed for the pair of epimeric ligands **1l** and **1m** (Fig. 4), having a phenyl group at the carbinol site, concerning both reaction rate and enantioselectivity, the ees being lower than the ones obtained with the ligands **1j** and **1k** bearing a methyl group at the carbinol carbon atom.

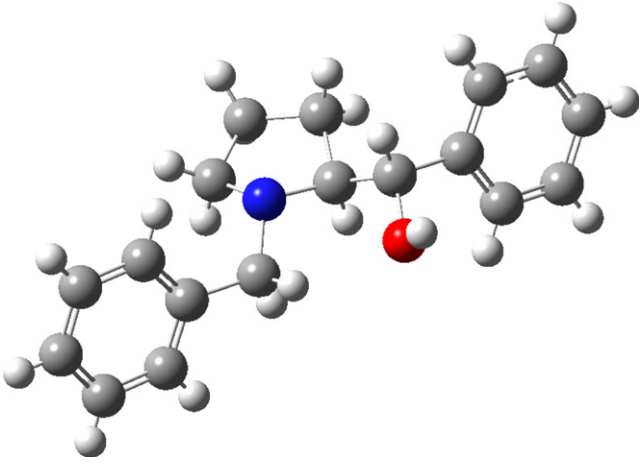


Figure 4. X-ray structure of ligand **1m**.

To determine if further steric bulkiness close to the nitrogen atom would improve the enantioselectivity, aminoalcohols **1n**, having a methyl group at C2 of the pyrrolidine ring, and **1o**, bearing a methyl group at C5 of the pyrrolidine ring, were tested as catalysts. No additional benefits were achieved by the introduction of the methyl group at C2, since the ee (90%, Table 3, entry 14) was slightly lower than the one obtained with *N*-benzyl-L-prolinol **1c**. The introduction of the methyl group at C5 was detrimental to the enantioselectivity, giving only 60% ee (Table 3, entry 15).

The results shown in Table 3 could be rationalized assuming that the addition reaction takes place through a transition state like the one depicted in Figure 5 for the addition of dimethylzinc to imine **3a** promoted by ligand **1c**.[23] The configuration of the stereocentre on the pyrrolidine ring and the coordination between Zn_A and the nitrogen atom of the ligand would force the benzyl group to be in the position indicated in Figure 5. Another molecule of dimethylzinc (Me_2Zn_B) would be coordinated to the oxygen atom of the ligand and the oxygen atom of the imine would coordinate to Zn_A. The transfer of one methyl group from Me_2Zn_B to the carbon of the imine would render the (*R*)-enantiomer of the addition product, which is the major one in all the cases.

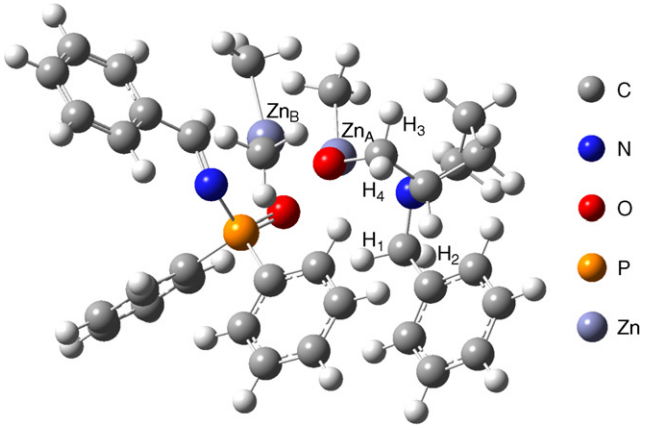


Figure 5.

For the ligands with a primary hydroxymethyl moiety, **1a–g**, **1n** and **1o**, the presence of an aromatic ring on the R^1 substituent seems to be beneficial for the enantioselectivity (Table 3, entries 3, 5, 7 and 14). π–π interactions between the aromatic ring of the R^1 substituent and one of the phenyl groups on the phosphorus atom could stabilize the depicted transition state to some extent, which could also explain the higher enantioselectivities observed. The ee decreased when H_1 of the ligand (Fig. 5) was changed by a methyl group (compare entries 3 and 6 in Table 3). The steric hindrance introduced by this methyl group could make coordination to the imine more difficult, leading to a lower enantioselectivity. The change of H_2 (Fig. 5) to a methyl group (ligand **1g**) afforded the highest enantioselectivity obtained with this kind of ligands (Table 3, entry 7). The introduction of a methyl group at C2 of the pyrrolidine ring (ligand **1n**) did not cause any detrimental effect on the enantioselectivity (compare entries 3 and 14 in Table 3). However, a *cis* methyl group at C5 decreased the ee. This could be due to the steric hindrance between this methyl group and the methyl group on Zn_A, which would

disfavour the formation of the well-ordered transition state.

The change of H_3 (Fig. 5) by a methyl group slightly improves the enantioselectivity (compare entries 3 and 10 in Table 3). A phenyl group instead of H_3 gave only a slight decrease in the ee. Thus, it seems that the effect caused by a substituent at this position (R^2 in Fig. 1) on the enantioselectivity is small, probably because this substituent would point away from the imine. However, changing H_4 (Fig. 5) with a substituent (ligands **1k** and **1m**) led to a decrease of the ee. Bigger the substituent at this position, lower the ee (compare entries 3, 11 and 13 in Table 3). The repulsive interaction between this substituent (R^3 in Fig. 1) and both the aromatic ring of the phosphinoyl group of the imine and one methyl group of Me_2Zn_B would disfavour the formation of the depicted transition state. When the ligand has a tertiary carbinol site (**1h** and **1i**), the substituent located at R^3 seems to be responsible for the decrease observed in the enantioselectivity, since the ee values are very similar to the ones obtained with ligands **1k** and **1m** (compare entry 8 with 11 and 9 with 13 in Table 3).

3. Conclusions

In conclusion, we have reported that several β-aminoalcohols with the prolinol skeleton are very efficient catalysts for the addition of dialkylzinc reagents to *N*-(diphenylphosphinoyl)imines. Fast enantioselective addition reactions can be achieved using 0.5 equiv of the ligand. Our results show the importance of carefully screening the reaction conditions to obtain high levels of enantioselectivity. A proper choice of the addition rate and the temperature turned out to be crucial for obtaining high ee values. Moreover, it is possible to improve both the reaction rates and yields by setting up the experiments at 50 °C with only a very slight decrease in the enantioselectivity. The selectivity can be improved upon by introduction of a stereogenic centre at either the carbinol carbon atom or at the substituent on the nitrogen atom of the ligand. The absolute configuration of this stereogenic centre determines if the enantioselectivity increases or decreases. Another important conclusion that can be drawn from our results is that a rigid structure in the ligand is not always a requisite to obtain high enantioselectivities in this reaction.

4. Experimental

4.1. General

For general experimental information, see Ref. 14. Imines **3** were prepared according to the literature procedures.[12g,18] When mentioned, purification by flash chromatography on deactivated silica gel means that, before adding the reaction crude to the column, the latter was eluted with a mixture of 5% triethylamine in hexane until the eluent coming from the column was basic according to the pH paper. When mentioned, an R_f value measured on deactivated silica gel means that the TLC plate was eluted with a mixture of 5% triethylamine in hexane and dried before applying the sample. Commercially available compounds **1a** {Aldrich, 96%, $[\alpha]_D^{19} = -49.5$ (*c* 5.0, MeOH)}, **1c** {Aldrich, 99%, $[\alpha]_D^{20} = -72.2$ (neat)}, **11** {Aldrich, 97%, $[\alpha]_D^{20} = -62.0$ (neat)} and **13** (Aldrich, ⩾98%) were used as received. Optical rotations were measured on a Perkin–Elmer 341 polarimeter. HPLC analyses were performed at 25 °C on a JASCO apparatus, equipped with a PU-2089 Plus pump, a MD-2010 Plus detector and an AS-2059 Plus automatic injector. The HRMS (EI) were performed by the Technical Services of the University of Alicante on a Finnigan MAT 95S apparatus. The X-ray diffraction analyses were carried out by the Technical Services of the University of Alicante on a Bruker CCD-Apex instrument equipped with an X-ray tube with a Mo anode and a KRYOFLEX low temperature equipment.

4.2. Synthesis of L-proline ethyl ester hydrochloride 9b

$SOCl_2$ (3.5 mL, 52 mmol) was added dropwise to a solution of L-proline (5.0 g, 43 mmol) in EtOH (56 mL) at 0 °C. When the addition was complete, the mixture was refluxed for 6 h. After cooling to room temperature, the solvent was evaporated under reduced pressure. The resulting residue was redissolved in Et_2O and the solvents were evaporated again. This process was repeated twice to remove EtOH completely. The resultant L-proline ethyl ester hydrochloride **9b** was obtained in 98% yield and was used in the alkylation step without further purification.

4.2.1. L-Proline ethyl ester hydrochloride 9b.[24] Colourless oil; R_f 0.32 (ethyl acetate; deactivated silica gel); $[\alpha]_D^{20} = -30.0$ (*c* 3.3, EtOH); *ν* (film) 3404 (NH), 1757 (C=O), 1231 cm^{-1} (CO); δ_H 1.33 (3H, t, $J = 7.2$ Hz, Me), 2.00–2.28, 2.39–2.51 (3H and 1H, respectively, 2m, CH_2CH_2CH), 3.47–3.70 (2H, m, CH_2N), 4.29 (2H, q, $J = 7.2$ Hz, CH_2O), 4.46–4.58 (1H, m, CH); δ_C 13.8 (Me), 23.4, 28.5 (CH_2CH_2CH), 45.9 (CH_2N), 59.1 (CH_2O), 62.6 (CH), 168.6 (CO); *m/z* 144 ($M^+-35.5$, <1%), 143 (2), 70 (100).

4.3. Preparation of *N*-isopropyl L-proline ethyl ester 10b

Ester **9b** (3.0 g, 21 mmol), Pr^iBr (20 mL, 210 mmol), NaI (6.3 g, 42 mmol) and 18-crown-6 (576 mg, 2.4 mmol) were dissolved in anhydrous MeCN (117 mL). K_2CO_3 (4.4 g, 32 mmol) was added and the reaction mixture was refluxed for 3 days. The solvent was evaporated, after which water (20 mL) was added and the resulting mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried over Na_2SO_4. After filtration and evaporation of the solvents, the crude residue was purified by flash chromatography (silica gel, pentane/Et_2O), giving product **10b** in 55% yield.

4.3.1. (*S*)-Ethyl 1-isopropylpyrrolidine-2-carboxylate 10b. Yellow oil; R_f 0.34 (ethyl acetate); $[\alpha]_D^{20} = -54.9$ (*c* 1.2, $CHCl_3$); *ν* (film) 1731 (C=O), 1162 cm^{-1} (CO); δ_H 1.08 (6H, d, $J = 6.4$ Hz, Me_2CH), 1.27 (3H, t, $J = 7.1$ Hz, $MeCH_2$), 1.75–2.18 (4H, m, CH_2CH_2CH), 2.57–2.64, 2.76–2.84 (1H each, 2m, CH_2N), 3.06–3.16 (1H, m, CHMe), 3.39–3.43 (1H, m, CHCO), 4.18 (2H, q, $J = 7.1$ Hz, CH_2O); δ_C 14.1 ($MeCH_2$), 20.0, 21.4 (Me_2CH),

23.4, 30.0 (CH_2CH_2CH), 50.0 ($CHMe$), 52.1 (CH_2N), 60.2 ($CHCO$), 62.7 (CH_2O), 175.2 (CO); *m/z* 185 (M^+, 2%), 112 (100), 70 (42); HRMS: M^+ found 185.1428, $C_{10}H_{19}NO_2$ requires 185.1416.

4.4. Synthesis of N-substituted L-proline esters 10d–g. General procedure

A solution of the L-proline ester hydrochloride **9a** (for **10f** and **10g**) or **9b** (for **10d** and **10e**) (7 mmol), Et_3N (2.3 mL, 16 mmol) and the corresponding alkylating agent [7 mmol, (1-naphthyl)CH_2Cl for **10d**, (2-naphthyl)CH_2Br for **10e** or PhCH(Me)Br for **10f** and **10g**] in $CHCl_3$ (27 mL) was refluxed for 6 h. After cooling to room temperature, an aqueous 1 M NaOH solution (27 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over $MgSO_4$. After filtration and evaporation of the solvents, the crude residue was purified by flash chromatography (silica gel, hexane/acetone), giving products **10d** and **10e** in 64% and 74% yield (from L-proline), respectively. In the reaction between **9a** and PhCH(Me)Br, a 1:1 mixture of epimers **10f** and **10g** was obtained, which could be separated by flash chromatography (silica gel, hexane/acetone) and were isolated in pure form in 13% and 20% yield, respectively. The corresponding physical, spectroscopic and analytical data for compounds **10d**–**g** follow.

4.4.1. (*S*)-Ethyl 1-(1-naphthylmethyl)pyrrolidine-2-carboxylate 10d. Yellow oil; R_f 0.70 (hexane/diethyl ether: 2:1); $[\alpha]_D^{20} = -26.9$ (*c* 1.1, $CHCl_3$); *v* (film) 3072, 3065, 3044, 1597, 1510 (HC=C), 1740 (C=O), 1179 cm^{-1} (CO); δ_H 1.22 (3H, t, $J = 7.1$ Hz, Me), 1.68–1.88, 1.91–2.03, 2.09–2.21 (2H, 1H and 1H, respectively, 3m, CH_2CH_2CH), 2.40 (1H, q, $J = 8.3$ Hz, 1 × CH_2CHHN), 2.88–2.95 (1H, m, 1 × CH_2CHHN), 2.28 (1H, dd, $J = 6.4$ and 2.2 Hz, CHCO), 3.82, 4.45 (1H each, 2d, $J = 12.5$ Hz each, CH_2Ar), 4.10 (2H, q, $J = 7.1$ Hz, CH_2O), 7.27–7.58, 7.74–7.84 (5H and 2H, respectively, 2m, ArH); δ_C 14.2 (Me), 22.9, 29.4 (CH_2CH_2CH), 53.4, 57.2 (2 × CH_2N), 60.4 (CH_2O), 66.1 ($CHCO$), 124.9, 125.0, 125.6 (2C), 125.9, 127.2, 128.0, 128.2, 132.5, 133.7 (ArC), 174.2 (CO); *m/z* 283 (M^+, 1%), 211 (12), 210 (70), 142 (13), 141 (100), 115 (17); HRMS: M^+ found 283.1570, $C_{18}H_{21}NO_2$ requires 283.1572.

4.4.2. (*S*)-Ethyl 1-(2-naphthylmethyl)pyrrolidine-2-carboxylate 10e. Yellow oil; R_f 0.65 (hexane/diethyl ether: 2:1); $[\alpha]_D^{20} = -55.4$ (*c* 1.0, $CHCl_3$); *v* (film) 3082, 3053, 1606, 1508 (HC=C), 1743 (C=O), 1178 cm^{-1} (CO); δ_H 1.18 (3H, t, $J = 7.1$ Hz, Me), 1.69–2.19 (4H, m, CH_2CH_2CH), 2.40 (1H, q, $J = 8.5$ Hz, 1 × CH_2CHHN), 2.98–3.11 (1H, m, 1 × CH_2CHHN), 3.27 (1H, dd, $J = 6.2$ and 2.5 Hz, CHN), 3.68 (1H, d, $J = 12.8$ Hz, 1 × $CHHAr$), 3.99–4.15 (3H, m, CH_2O and 1 × $CHHAr$), 7.39–7.53, 7.73–7.81 (3H and 4H, respectively, 2m, ArH); δ_C 14.1 (Me), 22.9, 29.2 (CH_2CH_2CH), 53.2, 58.8 (2 × CH_2N), 60.3 (CH_2O), 65.3 ($CHCO$), 125.4, 125.7, 127.3, 127.5 (2C), 127.6, 127.7, 132.6, 133.2, 136.1 (ArC), 174.0 (CO); *m/z* 283 (M^+, 1%), 211 (13), 210 (77), 142 (13), 141 (100), 115 (17); HRMS: M^+ found 283.1573, $C_{18}H_{21}NO_2$ requires 283.1572.

4.4.3. (2*S*)-Methyl 1-[(*R*)-1-phenylethyl]pyrrolidine-2-carboxylate 10f. Colourless oil; R_f 0.52 (hexane/diethyl ether: 1:1); $[\alpha]_D^{20} = -60.0$ (*c* 1.0, $CHCl_3$); *v* (film) 3085, 3058, 3026, 1629, 1493 (HC=C), 1733 (C=O), 1160 cm^{-1} (CO); δ_H 1.40 (3H, d, $J = 6.8$ Hz, $MeCH$), 1.75–2.13 (4H, m, CH_2CH_2CH), 2.47–2.53, 3.12–3.17 (1H each, 2m, CH_2N), 3.43–3.47 (1H, m, $CHCO$), 3.45 (3H, s, MeO), 3.63 (1H, q, $J = 6.6$ Hz, $CHPh$), 7.19–7.34 (5H, m, ArH); δ_C 21.6 ($MeCH$), 23.5, 30.2 (CH_2CH_2CH), 51.3 (CH_2N), 51.9 (MeO), 63.3, 63.8 (2 × CHN), 127.1, 127.8 (2C), 128.0 (2C), 144.3 (ArC), 175.4 (CO); *m/z* 233 (M^+, 2%), 218 (10), 175 (13), 174 (100), 105 (88), 103 (11), 79 (11), 77 (13), 70 (74); HRMS: M^+ found 233.1407, $C_{14}H_{19}NO_2$ requires 233.1416.

4.4.4. (2*S*)-Methyl 1-[(*S*)-1-phenylethyl]pyrrolidine-2-carboxylate 10g. Colourless oil; R_f 0.57 (hexane/diethyl ether: 1:1); $[\alpha]_D^{20} = -95.4$ (*c* 1.1, $CHCl_3$); *v* (film) 3078, 3061, 3026, 1630, 1492 (HC=C), 1733 (C=O), 1158 cm^{-1} (CO); δ_H 1.39 (3H, d, $J = 6.6$ Hz, $MeCH$), 1.71–1.79, 1.82–1.94, 2.01–2.12 (1H, 2H and 1H, respectively, 3m, CH_2CH_2CH), 2.55–2.61, 2.96–3.01 (1H each, 2m, CH_2N), 3.30 (1H, dd, $J = 9.3$ and 4.2 Hz, $CHCO$), 3.68 (3H, s, MeO), 3.74 (1H, q, $J = 6.8$ Hz, $CHPh$), 7.22–7.34 (5H, m, ArH); δ_C 22.2 ($MeCH$), 23.1, 29.9 (CH_2CH_2CH), 50.5 (CH_2N), 51.5 (MeO), 61.7, 62.8 (2 × CHN), 127.0, 127.5 (2C), 128.1 (2C), 143.5 (ArC), 175.6 (CO); *m/z* 233 (M^+, 3%), 175 (14), 174 (100), 105 (86), 103 (12), 79 (11), 77 (14), 70 (64); HRMS: M^+ found 233.1430, $C_{14}H_{19}NO_2$ requires 233.1416.

4.4.5. Determination of the absolute configuration of compound 10f. PhMgBr (1.89 mmol, 0.63 mL of a 3 M solution in Et_2O) was added dropwise to a stirred solution of compound **10f** (97 mg, 0.42 mmol) in anhydrous THF (2 mL) under Ar at room temperature. After stirring overnight at the same temperature, water (10 mL) was added and the resulting mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over Na_2SO_4. After filtration and evaporation of the solvents, the crude residue was purified by flash chromatography (silica gel, hexane/ethyl acetate), giving the corresponding tertiary alcohol in 91% yield. The white solid obtained was recrystallized in hexane and the crystals obtained were studied by X-ray diffraction analysis, giving the (*R*)-configuration for the *sec*-phenethyl substituent at the nitrogen atom (Fig. 3).[19]

4.4.6. {(2*S*)-1-[(*R*)-1-Phenylethyl]pyrrolidin-2-yl}diphenylmethanol. White solid; R_f 0.26 (hexane/ethyl acetate: 9:1); mp 111 °C (hexane); $[\alpha]_D^{20} = +54.0$ (*c* 0.5, $CHCl_3$); *v* (KBr) 3457 (OH), 3098, 3065, 3031, 1602, 1495 (HC=C), 1088 cm^{-1} (CO); δ_H 1.23 (3H, d, $J = 6.8$ Hz, Me), 1.48–1.72, 1.81–1.90 (3H and 1H, respectively, 2m, CH_2CH_2CH), 2.50–2.55, 2.71–2.77 (1H each, 2m, CH_2CH_2N), 3.35 (1H, q, $J = 6.8$ Hz, $CHMe$), 4.30 (1H, dd, $J = 5.3$ and 3.5 Hz, CH_2CHN), 5.13 (1H, s, OH), 7.08–7.30 (11H, m, 11 × ArH), 7.61, 7.78 (2H each, 2d, $J = 8.2$ Hz each, 4 × ArH); δ_C 9.4 (Me), 24.8, 30.3, 46.7 ($CH_2CH_2CH_2N$), 56.2 ($CHMe$), 67.0 (CHN), 77.4 (CO), 125.4 (4C), 126.1, 126.4, 126.5, 127.4 (2C), 127.9 (2C), 128.0 (2C), 128.2 (2C), 143.8, 146.8, 148.6 (ArC); *m/z* 339

(M^+-18, 5%), 182 (23), 174 (68), 105 (100), 77 (28), 70 (42). HRMS: M^+-18 found 339.1945, $C_{25}H_{25}N$ requires 339.1987.

4.5. Reduction of esters 10b,d–g. General procedure

A solution of amino ester **10b**,**d**–**g** (12.6 mmol) in anhydrous Et_2O (25 mL) was added dropwise for ca. 10 min to a stirred suspension of $LiAlH_4$ (1.7 g, 37.8 mmol) in anhydrous Et_2O (50 mL) under Ar at 0 °C. The reaction mixture was stirred for 3 h, allowing the temperature to rise to room temperature. Then, the reaction was quenched following a literature procedure.[25] Evaporation of the solvents gave the expected aminoalcohols **1b**,**d**–**g** in pure form in 68%, 49%, 33%, 82% and 85% yield, respectively. The corresponding physical, spectroscopic and analytical data for compounds **1b**,**d**–**g** follow.

4.5.1. [(2*S*)-1-Isopropylpyrrolidin-2-yl]methanol 1b.[26] Yellow oil; R_f 0.28 (ethyl acetate); $[\alpha]_D^{20} = -27.2$ (*c* 1.0, $CHCl_3$); *v* (film) 3384 (OH), 1043 cm^{-1} (CO); δ_H 0.99, 1.11 (3H each, 2d, $J = 6.5$ Hz each, 2 × Me), 1.65–1.90 (4H, m, CH_2CH_2CH), 2.52–2.60 (1H, m, 1 × CH_2CHHN), 2.85–3.32 (3H, m, 1 × CH_2CHHN and 2 × CH), 3.13 (1H, br s, OH), 3.33 (1H, dd, $J = 10.4$ and 2.8 Hz, 1 × $CHHO$), 3.53 (1H, dd, $J = 10.4$ and 4.5 Hz, 1 × $CHHO$); δ_C 16.6, 22.2 (2 × Me), 24.2, 29.0 (CH_2CH_2CH), 47.7 ($CHMe$), 49.9 (CH_2N), 60.0 (CH_2O), 63.2 ($CHCH_2$); *m*/*z* 143 (M^+, 3%), 142 (12), 128 (18), 113 (10), 112 (100), 70 (82).

4.5.2. [(2*S*)-1-(1-Naphthylmethyl)pyrrolidin-2-yl]methanol 1d.[27] Yellow oil; R_f 0.80 (hexane/ethyl acetate: 1:1); $[\alpha]_D^{20} = -30.6$ (*c* 1.1, $CHCl_3$); *v* (film) 3429 (OH), 3071, 3057, 3045, 1597, 1510 (HC=C), 1045 cm^{-1} (CO); δ_H 1.56–1.75, 1.77–1.88, 1.92–1.99 (2H, 1H and 1H, respectively, 3m, CH_2CH_2CH), 2.31–2.43 (1H, m, 1 × CH_2CHHN), 2.69 (1H, br s, OH), 2.77–2.87 (1H, m, CHN), 2.87–2.95 (1H, m, 1 × CH_2CHHN), 3.42 (1H, d, $J = 10.8$ Hz, 1 × $CHHO$), 3.64 (1H, dd, $J = 10.8$, 2.7 Hz, 1 × $CHHO$), 3.78, 4.40 (1H each, 2d, $J = 12.9$ Hz each, CH_2Ar), 7.37–7.54 (4H, m, 4 × ArH), 7.76, 7.84, 8.17 (1H each, 3d, $J = 8.2$ Hz each, 3 × ArH); δ_C 21.1, 23.8 (CH_2CH_2CH), 55.2, 57.1 (2 × CH_2N), 62.5 (CH_2O), 65.1 (CHN), 123.9, 125.3, 125.7, 125.8, 126.2, 127.0, 128.1, 128.7, 132.2, 135.2 (ArC); *m*/*z* 241 (M^+, 1%), 210 (45), 142 (13), 141 (100), 115 (14).

4.5.3. [(2*S*)-1-(2-Naphthylmethyl)pyrrolidin-2-yl]methanol 1e.[27] White solid; R_f 0.62 (hexane/ethyl acetate: 1:1); mp 80 °C; $[\alpha]_D^{20} = -34.4$ (*c* 1.0, $CHCl_3$); *v* (KBr) 3333 (OH), 3057, 3043, 3014, 1598, 1508 (HC=C), 1046 cm^{-1} (CO); δ_H 1.65–2.03 (5H, m, CH_2CH_2CH and OH), 2.29–2.38 (1H, m, 1 × CH_2CHHN), 2.75–2.82 (1H, m, CHN), 2.95–3.01 (1H, m, 1 × CH_2CHHN), 3.45 (1H, dd, $J = 7.1$ and 0.6 Hz, 1 × $CHHO$), 3.72 (1H, dd, $J = 7.1$ and 3.6 Hz, 1 × $CHHO$), 3.51, 4.12 (1H each, 2d, $J = 13.0$ Hz each, CH_2Ar), 7.42–7.49, 7.72–7.84 (3H and 4H, respectively, 2m, ArH); δ_C 23.6, 27.9 (CH_2CH_2CH), 54.7, 58.9 (2 × CH_2N), 62.0 (CH_2O), 64.5 (CHN), 125.8, 126.2, 127.15, 127.2, 127.8 (2C), 128.2, 132.8, 133.5, 137.0 (ArC); *m*/*z* 241 (M^+, 3%), 210 (38), 142 (18), 141 (100), 115 (16).

4.5.4. {(2*S*)-1-[(*R*)-1-Phenylethyl]pyrrolidin-2-yl}methanol 1f. Colourless oil; R_f 0.24 (ethyl acetate); $[\alpha]_D^{20} = +5.0$ (*c* 1.0, $CHCl_3$); *v* (film) 3405 (OH), 3091, 3065, 3025, 1609, 1489 (HC=C), 1040 cm^{-1} (CO); δ_H 1.40 (3H, d, $J = 6.8$ Hz, Me), 1.66–1.76, 1.83–1.93 (3H and 1H, respectively, 2m, CH_2CH_2CH), 2.55–2.61 (1H, m, 1 × $CHHN$), 2.67 (1H, br s, OH), 2.89–3.03 (3H, m, 1 × $CHHN$, CHCO and 1 × $CHHO$), 3.13 (1H, dd, $J = 10.4$ and 2.0 Hz, 1 × $CHHO$), 3.75 (1H, q, $J = 6.6$ Hz, $CHMe$), 7.22–7.37 (5H, m, ArH); δ_C 17.7 (Me), 24.4, 29.4 (CH_2CH_2CH), 50.5 (CH_2N), 60.9, 62.0 (2 × CHN), 63.4 (CH_2O), 127.1, 127.4 (2C), 128.3 (2C), 144.8 (ArC); *m*/*z* 205 (M^+, <1%), 190 (12), 175 (10), 174 (75), 106 (10), 105 (100), 103 (11), 79 (12), 77(14), 70 (82); HRMS: M^+ found 205.1475, $C_{13}H_{19}NO$ requires 205.1467.

4.5.5. {(2*S*)-1-[(*S*)-1-Phenylethyl]pyrrolidin-2-yl}methanol 1g. Colourless oil; R_f 0.22 (ethyl acetate); $[\alpha]_D^{20} = -20.0$ (*c* 1.1, $CHCl_3$); *v* (film) 3386 (OH), 3091, 3065, 3018, 1602, 1502 (HC=C), 1032 cm^{-1} (CO); δ_H 1.44 (3H, d, $J = 6.9$ Hz, Me), 1.54–1.89 (4H, m, CH_2CH_2CH), 2.34–2.42 (1H, m, 1 × $CHHN$), 2.86–3.00 (2H, m, 1 × $CHHN$ and CHCO), 3.11 (1H, br s, OH), 3.39 (1H, dd, $J = 10.4$ and 2.3 Hz, 1 × $CHHO$), 3.65 (1H, dd, $J = 10.4$ and 4.2 Hz, 1 × $CHHO$), 3.78 (1H, q, $J = 6.9$ Hz, $CHMe$), 7.22–7.40 (5H, m, ArH); δ_C 21.9 (Me), 24.0, 29.3 (CH_2CH_2CH), 51.0 (CH_2N), 60.1, 60.8 (2 × CHN), 63.7 (CH_2O), 127.0, 127.7 (2C), 128.1 (2C), 142.8 (ArC); *m*/*z* 205 (M^+, <1%), 175 (11), 174 (80), 105 (100), 103 (11), 79 (12), 77 (14), 70 (77); HRMS: M^+ found 205.1451, $C_{13}H_{19}NO$ requires 205.1467.

4.6. Preparation of ligands 1h and 1i

MeMgBr (15.0 mmol, 5 mL of a 3 M solution in THF, for **1h**) or PhMgBr (15.0 mmol, 5 mL of a 3 M solution in Et_2O, for **1i**) was added dropwise to a solution of the commercially available aminoester **11** (1.2 g, 5.0 mmol) in anhydrous THF (25 mL) under Ar at −78 °C and the reaction was stirred overnight allowing the temperature to rise to room temperature. Then, water (25 mL) was added and the resulting mixture was extracted with Et_2O (2 × 50 mL). The combined organic layers were washed with brine (10 mL) and dried ($MgSO_4$). After filtration and evaporation of the solvents, compound **1h** was obtained in pure form in quantitative yield. Compound **1i** was purified by crystallization with hexane, giving a 50% yield. The corresponding physical and spectroscopic data for compounds **1h** and **1i** follow.

4.6.1. 2-[(2*S*)-1-Benzylpyrrolidin-2-yl]propan-2-ol 1h.[28] Yellow oil; R_f 0.30 (hexane/ethyl acetate: 9:1); $[\alpha]_D^{20} = -42.1$ (*c* 2.5, CH_2Cl_2); *v* (film) 3446 (OH), 3093, 3071, 3022, 1602, 1494 (HC=C), 1071 cm^{-1} (CO); δ_H 1.17, 1.26 (3H each, 2s, 2 × Me), 1.65–1.94 (4H, m, CH_2CH_2CH), 2.37–2.45 (1H, m, 1 × CH_2CHHN), 2.65 (1H, br s, OH), 2.75 (1H, dd, $J = 5.1$ and 3.6 Hz, CHN), 2.86–2.93 (1H, m, 1 × CH_2CHHN), 3.59, 4.14 (1H each, 2d, $J = 13.9$ Hz each, CH_2Ar), 7.21–7.37 (5H, m, ArH); δ_C 25.25, 25.3 (2 × Me), 27.9, 28.8 (CH_2CH_2CH), 55.5, 63.2 (2 × CH_2N), 72.8 (C), 73.0 (CH), 126.9, 128.2 (2C), 128.4 (2C), 140.6 (ArC); *m*/*z* 219 (M^+, <1%), 161 (17), 160 (100), 91 (86).

4.6.2. [(2*S*)-1-Benzylpyrrolidin-2-yl]diphenylmethanol 1i.[29] White solid; R_f 0.60 (hexane/ethyl acetate: 9:1); mp 121 °C (hexane); $[\alpha]_D^{20} = +87.5$ (*c* 1.0, $CHCl_3$); *v* (KBr) 3435 (OH), 3085, 3051, 3025, 1607, 1493 (HC=C), 1099 cm^{-1} (CO); δ_H 1.55–1.85, 1.88–2.02 (3H and 1H, respectively, 2m, CH_2CH_2CH), 2.29–2.42, 2.87–2.93 (1H each, 2m, CH_2CH_2N), 3.01, 3.21 (1H each, 2d, $J = 12.6$ Hz, CH_2Ph), 3.97 (1H, dd, $J = 4.8$ and 4.5 Hz, CHN), 4.92 (1H, s, OH), 6.90–7.41 (11H, m, 11 × ArH), 7.59, 7.73 (2H each, 2d, $J = 7.3$ Hz each, 4 × ArH); δ_C 24.3, 29.9 (CH_2CH_2CH), 55.7, 60.7 (2 × CH_2N), 70.8 (CHN), 78.1 (CO), 125.7 (2C), 125.8 (2C), 126.4, 126.5, 127.0, 128.2 (2C), 128.25 (2C), 128.3 (2C), 128.7 (2C), 139.8, 146.8, 148.2 (ArC); *m*/*z* 343 (M^+, <1%), 161 (13), 160 (100), 91 (51).

4.7. Oxidation of *N*-benzylprolinol 1c to the corresponding aldehyde 12

DMSO (2.1 mL, 37.0 mmol) was added to a solution of oxalyl chloride (1.5 mL, 17.0 mmol) in anhydrous CH_2Cl_2 (95 mL) at −78 °C for ca. 10 min. The reaction mixture was stirred for 15 min and then a solution of aminoalcohol **1c** (3 g, 15.7 mmol) in anhydrous CH_2Cl_2 (25 mL) was added over a period of 10 min. The reaction mixture was stirred for 15 min and triethylamine (9 mL, 68.0 mmol) was added over a period of 10 min. The reaction mixture was stirred allowing the temperature to reach room temperature and then it was washed with brine (100 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried over $MgSO_4$. After filtration and evaporation of the solvent, the crude aldehyde **12** was used in the next step, due to decomposition when its purification was attempted.

4.8. Synthesis of ligands 1j–m. General procedure

MeMgBr (45 mmol, 15 mL of a 3 M solution in THF, for **1j** and **1k**) or PhMgBr (45 mmol, 15 mL of a 3 M solution in Et_2O, for **1l** and **1m**) was added dropwise to a suspension of dry $CeCl_3$ (10.0 g, 45 mmol) in Et_2O (56 mL) at −78 °C. After stirring for 1 h at that temperature, aldehyde **12** (2.8 g, 15 mmol) in Et_2O (28 mL) was added. The reaction mixture was allowed to reach room temperature overnight. The solvent was removed under reduced pressure and the residue was dissolved in CH_2Cl_2 (200 mL) and washed with water (100 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried over $MgSO_4$. The residue obtained after filtration and evaporation of the solvent was a mixture of epimers **1j/1k** (81% combined yield, 1:3 ratio by ^1H NMR) or **1l/1m** (77% combined yield, 3:7 ratio by ^1H NMR). The two pairs of epimers could be separated by flash chromatography (deactivated silica gel, hexane/ethyl acetate), affording pure compounds **1j**, **1k**, **1l** and **1m** in 26%, 40%, 20% and 26% yield, respectively. The absolute stereochemistry of ligand **1j** was determined by comparison of its physical and spectroscopic data with the ones reported in the literature.[20] Compound **1m** was recrystallized in hexane and the crystals obtained were studied by X-ray diffraction analysis, giving the (*S*)-configuration for the carbinol site (Fig. 4).[21] The corresponding physical, spectroscopic and analytical data for compounds **1k**–**m** follow.

4.8.1. (*S*)-1-[(2*S*)-1-Benzylpyrrolidin-2-yl]ethanol 1k. Yellow oil; R_f 0.51 (hexane/ethyl acetate: 1:1); $[\alpha]_D^{20} = -12.6$ (*c* 0.7, $CHCl_3$); *v* (film) 3415 (OH), 3085, 3061, 3027, 1602, 1495 (HC=C), 1074 cm^{-1} (CO); δ_H 1.17 (3H, d, $J = 6.2$ Hz, Me), 1.49–1.58, 1.62–1.81, 1.87–2.00 (1H, 2H and 1H, respectively, 3m, CH_2CH_2CH), 2.38–2.47 (1H, m, 1 × CH_2CHHN), 2.66–2.72 (1H, m, CHN), 2.84–2.91 (1H, m, 1 × CH_2CHHN), 3.36–3.45 (1H, m, CHO), 3.56, 3.98 (1H each, 2d, $J = 13.2$ Hz each, CH_2Ph), 3.58 (1H, br s, OH), 7.21–7.36 (5H, m, ArH); δ_C 20.2 (Me), 24.5, 28.0 (CH_2CH_2CH), 53.9, 62.0 (2 × CH_2N), 69.8 (CHN), 70.6 (CHO), 127.1, 128.4 (2C), 128.7 (2C), 139.7 (ArC); *m*/*z* 205 (M^+, <1%), 161 (13), 160 (100), 91 (90). HRMS: M^+ found 205.1416, $C_{13}H_{19}NO$ requires 205.1467.

4.8.2. (*R*)-[(2*S*)-1-Benzylpyrrolidin-2-yl](phenyl)methanol 1l.[30] Yellow oil; R_f 0.75 (hexane/ethyl acetate: 1:1); $[\alpha]_D^{20} = -69.2$ (*c* 1.3, $CHCl_3$); *v* (film) 3442 (OH), 3085, 3058, 3027, 1615, 1495 (HC=C), 1116 cm^{-1} (CO); δ_H 1.20–1.43, 1.56–1.79 (1H and 3H, respectively, 2m, CH_2CH_2CH), 2.33 (1H, q, $J = 8.5$ Hz, 1 × CH_2CHHN), 2.85–2.91 (1H, m, CHCO), 3.00–3.06 (1H, m, 1 × CH_2CHHN), 3.46, 4.19 (1H each, 2d, $J = 13.0$ Hz each, CH_2Ph), 3.73 (1H, br s, OH), 4.90 (1H, d, $J = 2.9$ Hz, CHO), 7.21–7.39 (10H, m, ArH); δ_C 23.1, 23.9 (CH_2CH_2CH), 54.6, 58.2 (2 × CH_2N), 69.1 (CHN), 70.1 (CHO), 125.4 (2C), 126.7, 127.1, 128.1 (2C), 128.4 (2C), 128.7 (2C), 139.0, 141.5 (ArC); *m*/*z* 267 (M^+, <1%), 161 (12), 160 (100), 91 (70).

4.8.3. (*S*)-[(2*S*)-1-Benzylpyrrolidin-2-yl](phenyl)methanol 1m.[30] White solid; R_f 0.67 (hexane/ethyl acetate: 1:1); mp 75 °C (hexane); $[\alpha]_D^{20} = +101.8$ (*c* 1.1, $CHCl_3$); *v* (KBr) 3150 (OH), 3085, 3056, 3027, 1489 (HC=C), 1070 cm^{-1} (CO); δ_H 1.71–1.83, 1.89–2.04 (3H and 1H, respectively, 2m, CH_2CH_2CH), 2.35–2.47, 2.93–3.00 (1H each, 2m, CH_2CH_2N), 3.06–3.12 (1H, m, CHN), 3.35, 3.66 (1H each, 2d, $J = 12.9$ Hz each, CH_2Ph), 4.40 (1H, d, $J = 4.5$ Hz, CHO), 7.20–7.40 (10H, m, ArH); δ_C 24.2, 29.3 (CH_2CH_2CH), 54.2, 61.2 (2 × CH_2N), 70.1 (CHN), 75.2 (CHO), 126.1 (2C), 127.0, 127.1, 128.2 (2C), 128.3 (2C), 128.6 (2C), 139.4, 143.7 (ArC); *m*/*z* 267 (M^+, <1%), 216 (12), 161 (13), 160 (100), 91 (74).

4.9. Preparation of *N*-benzyl aminoester 14

Compound **14** was prepared from the commercially available aminoacid **13** by the same sequence esterification–N-alkylation described above for the synthesis of aminoesters **10d**–**g**. The overall yield of **14** was 80%. Its corresponding physical, spectroscopic and analytical data follow.

4.9.1. (*S*)-Ethyl 1-benzyl-2-methylpyrrolidine-2-carboxylate 14. Yellow oil; R_f 0.69 (hexane/diethyl ether: 4:1); $[\alpha]_D^{20} = +42.8$ (*c* 1.0, $CHCl_3$); *v* (film) 3085, 3062, 3027, 1604, 1494 (HC=C), 1724 (C=O), 1179 cm^{-1} (CO); δ_H 1.30 (3H, t, $J = 7.1$ Hz, $MeCH_2$), 1.40 (3H, s, MeC), 1.71–1.89, 2.20–2.29 (3H and 1H, respectively, 2m, CH_2CH_2C), 2.69–2.75, 2.80–2.86 (1H each, 2m, CH_2CH_2N), 3.51, 3.83

(1H each, 2d, $J = 13.4$ Hz each, CH_2Ph), 4.13–4.24 (2H, m, CH_2O), 7.19–7.36 (5H, m, ArH); δ_C 14.4 (*Me*CH_2), 21.6 (*Me*C), 21.5, 37.7 (*C*H_2*C*H_2C), 51.3, 53.6 ($2 \times CH_2N$), 60.1 (CH_2O), 67.5 (*C*Me), 126.6, 128.1 (2C), 128.3 (2C), 140.4 (ArC), 175.4 (CO); *m*/*z* 247 (M^+, <1%), 175 (13), 174 (100), 91 (57); HRMS: M^+−Et found 218.1178, $C_{15}H_{21}NO_2$ requires 218.1181.

4.10. Reduction of aminoester 14. Synthesis of ligand 1n

The reduction of **14** was carried out in the same way as for compounds **10b**,**d**–**g**. The isolated yield of **1n** was 76%. Its corresponding physical, spectroscopic and analytical data follow.

4.10.1. [(2*S*)-1-Benzyl-2-methylpyrrolidin-2-yl]methanol 1n. Yellow oil; R_f 0.24 (ethyl acetate); $[\alpha]_D^{20} = -35.7$ (*c* 1, $CHCl_3$); *v* (film) 3423 (OH), 3085, 3062, 3027, 1602, 1495 (HC=C), 1050 cm^{-1} (CO); δ_H 0.99 (3H, s, Me), 1.51–1.78, 2.07–2.16 (3H and 1H, respectively, 2m, CH_2CH_2C), 2.40–2.48, 2.88–2.94 (1H each, 2m, CH_2CH_2N), 3.21, 3.78 (1H each, 2d, $J = 12.8$ Hz each, CH_2Ph), 3.32, 3.44 (1H each, 2d, $J = 10.4$ Hz each, CH_2O), 7.21–7.36 (5H, m, ArH); δ_C 17.4 (Me), 21.8, 35.3 (*C*H_2*C*H_2C), 51.3, 52.5 ($2 \times CH_2N$), 63.6 (C), 65.1 (CH_2O), 127.0, 128.4 (2C), 128.6 (2C), 139.9 (ArC); *m*/*z* 205 (M^+, <1%), 175 (13), 174 (100), 91 (80). HRMS: M^+ found 205.1464, $C_{13}H_{19}NO$ requires 205.1467.

4.11. Preparation of *N*-benzyl aminoester 16

The *cis*-5-methyl proline methyl ester **15** was prepared according to a literature procedure.[31] Benzylation of **15** was performed in the same way as for the synthesis of compounds **10d**–**g**. The isolated yield of **16** was 30%. Its corresponding physical, spectroscopic and analytical data follow.

4.11.1. (2*S*,5*S*)-Methyl 1-benzyl-5-methylpyrrolidine-2-carboxylate 16. Yellow oil; R_f 0.26 (hexane/diethyl ether: 4:1); $[\alpha]_D^{20} = -11.5$ (*c* 1.2, $CHCl_3$); *v* (film) 3085, 3062, 3027, 1604, 1494 (HC=C), 1747 (C=O), 1197 cm^{-1} (CO); δ_H 1.18 (3H, d, $J = 5.8$ Hz, *Me*CH), 1.50–1.65, 1.81–1.98 (1H and 3H, respectively, 2m, CH_2CH_2CH), 2.62–2.73, 3.23–3.28 (1H each, 2m, $2 \times$ CHN), 3.47 (3H, s, MeO), 3.62, 3.94 (1H each, 2d, $J = 13.7$ Hz each, CH_2Ph), 7.20–7.31 (5H, m, ArH); δ_C 19.5 (*Me*CH), 27.7, 32.2 (*C*H_2*C*H_2CH), 51.5 (MeO), 56.5 (CH_2N), 59.5, 66.0 ($2 \times$ CHN), 126.9, 127.9 (2C), 129.5 (2C), 137.7 (ArC), 174.9 (CO); *m*/*z* 233 (M^+, < 1%), 175 (14), 174 (100), 91 (77). HRMS: M^+ found 233.1406, $C_{14}H_{19}NO_2$ requires 233.1416.

4.12. Reduction of aminoester 16. Synthesis of ligand 1o

The reduction of **16** was carried out in the same way as for compounds **10b**,**d**–**g**. The isolated yield of **1o** was 92%. Its corresponding physical and spectroscopic data follow.

4.12.1. [(2*S*,5*S*)-1-Benzyl-5-methylpyrrolidin-2-yl]methanol 1o.[32] Yellow oil; R_f 0.52 (ethyl acetate); $[\alpha]_D^{20} = +39.2$ (*c* 1.0, $CHCl_3$); *v* (film) 3417 (OH), 3091, 3061, 3027, 1596, 1494 (HC=C), 1075 cm^{-1} (CO); δ_H 1.07 (3H, d, $J = 6.0$ Hz, Me), 1.33–1.45, 1.68–1.87 (1H and 3H, respectively, 2m, CH_2CH_2CH), 2.51 (1H, br s, OH), 2.77–2.84, 2.86–2.92 (1H each, 2m, $2 \times$ CHN), 3.21–3.28 (2H, m, CH_2O), 3.63, 3.82 (1H each, 2d, $J = 13.5$ Hz each, CH_2Ph), 7.21–7.35 (5H, m, ArH); δ_C 20.6 (Me), 26.8, 32.8 (*C*H_2*C*H_2CH), 56.8 (CH_2N), 60.5, 65.3 ($2 \times$ CHN), 62.5 (CH_2O), 127.0, 128.2 (2C), 128.8 (2C), 139.4 (ArC); *m*/*z* 205 (M^+, <1%), 175 (14), 174 (100), 91 (85).

4.13. Addition of dialkylzinc reagents to imines 3 catalyzed by ligands 1. Preparation of compounds 5. General procedure

The dialkylzinc reagent (1.5 mmol) was added dropwise over ca. 10 min to a stirred solution of imine **3** (0.5 mmol) and ligand **1** (0.25 mmol) in anhydrous toluene (3 mL) under argon at room temperature. After stirring for the time indicated in Tables 2 and 3, the reaction was hydrolyzed with an aqueous saturated solution of NH_4Cl (5 mL). Water (5 mL) was added and the mixture was extracted with ethyl acetate (3×20 mL). The combined organic layers were washed with brine (5 mL) and then dried (Na_2SO_4). After filtration and evaporation of the solvents, the crude residue was purified by column chromatography (silica gel, pentane/acetone), to give products **5** in the yields and enantiomeric excesses indicated in Tables 2 and 3. Compounds **5aa**,[7] **5ab**,[7] **5ad**,[14] **5b**,[7] **5c**,[10j] **5e**[33] and **5f**[33] were characterized by comparison of their physical and spectroscopic data with the ones reported in the literature. These products were analyzed by HPLC on a ChiralCel OD-H column using a 254 nm UV detector, 10% *i*-PrOH in hexane as eluent and a flow rate of 0.5 mL/min or on a Chiralpak AD column using a 254 nm UV detector, 20% *i*-PrOH in hexane as eluent and a flow rate of 1.0 mL/min. The retention times were 13.7 (*R*) and 18.0 (*S*) for **5aa** (OD-H column), 14.8 (*R*) and 19.6 (*S*) for **5ab** (OD-H column), 21.2 (*R*) and 26.0 (*S*) for **5ac** (OD-H column, 5% *i*-PrOH in hexane as eluent), 11.8 (*R*) and 19.8 (*S*) for **5ad** (OD-H column, 5% *i*-PrOH in hexane as eluent), 12.2 (*R*) and 14.3 (*S*) for **5b** (AD column), 11.1 (*R*) and 13.8 (*S*) for **5c** (AD column), 9.3 (*R*) and 12.9 (*S*) for **5d** (AD column), 7.6 (*S*) and 11.0 (*R*) for **5e** (AD column), 18.2 (*S*) and 22.3 (*R*) for **5f** (AD column, 10% *i*-PrOH in hexane as eluent). The absolute configuration of the major enantiomer of **5aa** was determined by hydrolysis of it[7] and comparison of the specific rotation of the free amine obtained with the reported data.[7] The absolute configuration of the major enantiomer of **5ab**–**ad** was tentatively assigned according to the order of elution of the two enantiomers in the HPLC analysis on the analogy of product **5aa**. For addition products **5b**–**d**, the absolute configuration of the major enantiomer was tentatively assigned according to the HPLC data described in the literature for similar compounds under the same conditions.[33] The retention times of the two enantiomers of compounds **5e** and **5f** have already been described.[33] The corresponding physical and spectroscopic data for compounds **5ac** and **5d** follow.

4.13.1. *N*-(2-Methyl-1-phenylpropyl)-*P*,*P*-diphenylphosphinic amide 5ac[14]**.** White solid; R_f 0.38 (ethyl acetate); mp 166 °C; $[\alpha]_D^{20} = +14.6$ (*c* 1.0, $CHCl_3$) 90% ee; *v* (KBr) 3443 (NH), 3088, 3060, 3028, 1503 (HC=C), 1165 cm^{-1}

(P=O); δ_H 0.82, 1.01 (3H each, 2 d, $J = 6.9$ Hz each, 2 × Me), 1.90–2.11 (1H, m, C*H*Me), 3.33 (1H, m, NH), 3.80–3.99 (1H, m, CHN), 7.00–7.11, 7.15–7.54, 7.59–7.73, 7.77–7.91 (2H, 9H, 2H and 2H, respectively, 4 m, ArH); δ_C 19.2, 19.3 (2 × Me), 35.7 (d, $J = 4.3$ Hz, *C*HMe), 61.3 (CN), 126.8, 126.9, 128.0, 128.1, 128.2, 128.4, 128.5, 131.7, 131.8, 131.9, 132.6, 132.7, 142.9 (d, $J = 3.9$ Hz) (ArC); *m/z* 349 (M^+, <1%), 307 (22), 306 (100), 201 (50).

4.13.2. *N*-[1-(2-Naphthyl)propyl]-*P*,*P*-diphenylphosphinic amide 5d.[14] White solid; R_f 0.29 (ethyl acetate); mp 105 °C; $[\alpha]_D^{20} = +27.5$ (*c* 1.0, $CHCl_3$) 86% ee; *v* (KBr) 3127 (NH), 3040, 3026, 3012, 1598 (HC=C), 1114 cm^{-1} (P=O); δ_H 0.81 (3H, t, $J = 7.4$ Hz, Me), 1.88–2.17 (2H, m, CH_2), 3.27–3.46 (1H, m, NH), 4.21–4.34 (1H, m, CHN), 7.21–7.30, 7.32–7.57, 7.65–7.93 (2H, 8H and 7H, respectively, 3m, ArH); δ_C 10.6 (Me), 32.3 (d, $J = 4.0$ Hz, CH_2), 57.3 (CN), 124.5, 125.5, 125.7, 126.1, 127.6, 127.8, 128.2, 128.3, 128.4, 128.5, 131.65, 131.7, 131.75, 131.8, 131.9, 132.5, 132.6, 132.7, 133.2, 140.7 (d, $J = 5.4$ Hz) (ArC); *m/z* 386 (M^++1, 2%), 385 (M^+, 6), 357 (25), 356 (100), 202 (16), 201 (89), 185 (13), 184 (83), 154 (13), 77 (17).

Acknowledgements

This work was generously supported by the Dirección General de Enseñanza Superior (DGES) of the current Spanish Ministerio de Educación y Ciencia (MEC; Grant No. CSD2007-00006) and the Generalitat Valenciana (GV/2007/036). R.A. thanks the Spanish Ministerio de Educación y Ciencia for a predoctoral fellowship. We also thank MEDALCHEMY S.L. for a gift of chemicals.

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