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Pyrrolidine-based amino alcohols: novel ligands for the enantioselective alkylation of benzaldehyde

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Abstract

A series of easily obtained pyrrolidine-based β-amino alcohols derived from tartaric acid and primary amines was synthesized and used as chiral ligands in the enantioselective alkylation of benzaldehyde. Using diethylzinc, 1-phenyl-1-propanol was obtained with enantiomeric excesses of up to 80% when (3*S*,4*S*)-*N*-(1-naphthylmethyl)-3,4-dihydroxypyrrolidine was used. The nature of the *N*-substituent on the ligand, as well as the reaction temperature proved to significantly influence reaction product distribution as well as the enantiomeric excess of the chiral alcohol.

Keywords: Enantioselective alkylation; β-Amino alcohols; Diethylzinc; Pyrrolidinoalcohols; Benzaldehyde

1. Introduction

Studies on the catalytic enantioselective addition of dialkylzinc reagents to aldehydes mediated by chiral ligands have grown considerably since the initial studies of Oguni and Omi [1]. This synthetic process, involving the enantioselective carbon–carbon bond formation, has become a promising and versatile method for obtaining chiral secondary alcohols with very high levels of enantioselection [2–5].

Different types of chiral ligands, namely diols, diamines and their derivatives, amino alcohols, have been explored in enantioselective alkylations. So far it seems that amino alcohols, especially β-amino alcohols, are the most efficient catalysts in these reactions. β-Amino alcohols react with dialkylzinc to form a five-membered zinc alkoxide chelate. The stability and rigidity of this chelate, which is believed to be the true catalytic species, and of the subsequent six-membered transition state which is formed with another dialkylzinc unit and the aldehyde, contribute to the efficient catalytic process with high levels of chiral induction [6–8]. When the backbone skeleton of the chiral ligand itself presents a certain degree of rigidity, namely when it is cyclic, and when there are bulky substituents at or close to the nitrogen and oxygen, there are additional contributions to the formation of a well defined species and consequently more efficient control is attained in the enantioselective alkylation process [9,10].

We have been interested in the enantioselective transfer hydrogenation of carbon–carbon double bonds using pyrrolidine diphosphines with general structure **1** [11,12]. In the synthesis of those chiral ligands, pyrrolidinoalcohols are key intermediates.

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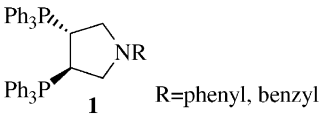


1 R=phenyl, benzyl

Having several structures of this type, which are actually β-amino alcohols, we decided to test their efficiency as ligands in enantioselective alkylations.

In this paper we describe the synthesis and characterization of a range of β-amino alcohols (**3a**–**3f**) easily obtained through the reaction of naturally occurring (L)-tartaric acid with primary amines, as well as their application in the enantioselective alkylation of benzaldehyde. The advantage of our approach is that we can attach to the nitrogen on the rigid pyrrolidine backbone structure a diversity of substituents, both aromatic and aliphatic. The effect of these structural characteristics on the catalyst efficiency, as well as that of other parameters, such as reaction temperature, on the activity and selectivity of the alkylation of benzaldehyde will be discussed.

2. Experimental

2.1. General

All solvents were dried prior to use following standard procedures. Reactions were carried out in an inert atmosphere using standard Schlenk-type techniques. Diethyl zinc (Aldrich) was used as a 1 M solution in hexane. Benzaldehyde was distilled prior to use and stored over 4 Å molecular sieves. Commercially acquired benzylamine, aniline, 4-methoxyphenylamine and cyclohexylamine were stored over KOH. 1-Naphthylamine was purified as described below. 1-Naphthylmethylamine was prepared from 1-naphthylacetic acid, according to the procedure described below.

Melting points were determined using a Leitz–Wetzler 799 microscope, with a heated plate (values are uncorrected). Optical rotations were measured with an Optical Activity AA-5 polarimeter. NMR spectra were recorded on a Bruker AMX 300 (300 and 75.5 MHz, for ^{1}H and ^{13}C, respectively). TMS was used as the internal standard. Chemical shifts are referred in δ and coupling constants, *J*, in Hz. Elemental analyses were carried out on a Fisons Instrument EA 1108 CHNS-O elemental analyzer. GC analyses were recorded on a HP 5890A instrument coupled to an HP 3396A integrator using a capillary column (Supelcowax 10, 30 m, 0.25 i.d., 0.25 μm).

X-ray data were collected at room temperature on an Enraf-Nonius MACH3 diffractometer using graphite monochromated Cu Kα radiation ($\lambda = 1.54184$ Å). A total of 2599 reflections were measured up to $\theta = 72.4^{\circ}$, 2215 independent of which 2185 had $I > 2\sigma$. The structure was solved by direct methods using SHELXS-97 [13] and refined using SHELXL-97 [14].

Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 180818. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk).

Alkylation reaction products were identified by comparison with authentic commercially acquired samples and by GC–MS analysis. Catalytic experiments were repeated in order to confirm results. Enantiomeric excesses were calculated by using the reported value $[\alpha]_D^{22} = +47 \pm 1$ (*c*2.2, hexane) (Fluka Catalogue), for the optically pure enantiomer, (*R*)-1-phenyl-1-propanol, and the absolute configuration was determined by comparing the sign of the optical rotation with an authentic sample.

2.2. Purification of 1-naphthylamine

Commercial 1-naphthylamine was purified by treating a solution of the amine in diethyl ether with HCl. The corresponding amine hydrochloride was filtered as a white solid. Prior to use, the hydrochloride was suspended in xylene and treated with NaOH, 15% until the solid dissolved completely. The organic phase was separated, dried over anhydrous $MgSO_4$, filtered and used directly for the preparation of **2e**.

2.3. 1-Naphthylmethylamine

1-Naphthylacetic acid (0.1 mol, 18.62 g) and thionyl chloride (55 ml) were placed in a round-bottomed flask equipped with a reflux condenser and calcium chloride tube and the mixture was refluxed for 2 h. The excess thionyl chloride was removed under reduced pressure and to the resulting acid chloride 100 ml of

dry toluene were added. After the addition of sodium azide (9.75 g, 0.15 mol) the solution was refluxed in an inert atmosphere for 20 h. After cooling, excess sodium azide was filtered off and washed with toluene. Concentrated HCl (50 ml) was added to the solution, which was refluxed for an additional 3–4 h. The resulting amine hydrochloride precipitated upon cooling, was filtered and washed with toluene to give 11.95 g (62%) of the product. ^{1}H NMR (DMSO): 4.53 (approx. t, 2 H, *J* 5.6); 7.49–7.76 (m, 4 H); 7.92 (t, 2 H, *J* 7.3); 8.11 (d, 1 H, *J* 8.3); 8.77 (bs, 3 H).

To obtain the free 1-naphthylmethylamine, the hydrochloride was suspended in xylene and treated with NaOH, 15%, until the solid dissolved completely. The organic phase was then separated, dried over anhydrous $MgSO_4$, filtered and used directly for the preparation of **2c**.

2.4. General procedure for the synthesis of (3R,4R)-N-substituted-3,4-dihydroxy-2,5-dioxopyrrolidines

To a suspension of tartaric acid (45 g, 0.3 mol) in 200 ml of xylene the amine (0.3 mol) was added and the mixture was refluxed with stirring in a round-bottomed flask equipped with a Dean–Stark apparatus. The reaction was complete when the appropriate amount of water was collected (10.8 ml, 0.6 mol). After cooling the reaction mixture, the product was filtered and purified.

*2.4.1. (3R,4R)-N-Benzyl-3,4-dihydroxy-2,5-dioxopyrrolidine (**2a**)*

The product was recrystallized from ethanol to give 59.8 g (90%) of a yellow solid, m.p. 200–201 °C (196–8 °C) [15]. Anal. calcd. for $C_{11}H_{11}N_1O_4$: C, 59.73; H, 5.01; N, 6.33. Found: C, 59.48; H, 5.05; N, 6.14. $[\alpha]_D = +137.5$ (*c*2, MeOH). ^{1}H NMR ($CDCl_3$/DMSO): 4.40 (s, 2 H); 4.58 (d, 1 H, *J* 14.4, *AB system*); 4.62 (d, 1 H, *J* 14.4, *AB system*); 6.3 (sl, 2 H); 7.23–7.31 (m, 5 H). ^{13}C NMR ($CDCl_3$/DMSO): 41.4, 74.7, 127.5, 127.9, 128.3, 135.5, 174.3.

*2.4.2. (3R,4R)-N-Cyclohexyl-3,4-dihydroxy-2,5-dioxopyrrolidine (**2b**)*

The product was recrystallized from ethyl acetate/petroleum ether to give 39.6 g (62%) of a yellow solid, m.p. 140–141 °C. Anal. calcd. for $C_{10}H_{15}N_1O_4 \cdot 1/2H_2O$: C, 54.04; H, 7.26; N, 6.30. Found: C, 54.22; H, 6.99; N, 6.07. $[\alpha]_D = +95$ (*c*1, MeOH). ^{1}H NMR ($CDCl_3$/DMSO): 1.23–1.35 (m, 4 H); 1.62–1.86 (m, 5 H); 2.06–2.14 (m, 2 H); 4.38 (s, 2 H).

*2.4.3. (3R,4R)-N-(1-Naphthylmethyl)-3,4-dihydroxy-2,5-dioxopyrrolidine (**2c**)*

The product was recrystallized from ethyl acetate/petroleum ether to give 11 g (66%, from 61.73 mmol) of a yellow solid, m.p. 174–176 °C. Anal. calcd. for $C_{15}H_{13}N_1O_4$: C, 66.40; H, 4.83; N, 5.17. Found: C, 65.95; H, 4.85; N, 5.13. $[\alpha]_D = +120$ (*c*1, MeOH). ^{1}H NMR (CD_3OD): 4.55 (s, 2 H); 5.12 (s, 2 H); 7.41–7.55 (m, 4 H); 7.79–7.89 (m, 2 H); 8.22–8.25 (m, 1 H). ^{13}C NMR ($CDCl_3$/DMSO): 65.13, 74.61, 122.87, 124.86, 125.54, 125.95, 126.15, 128.01, 128.27, 130.19, 130.49, 133.14, 174.38.

*2.4.4. (3R,4R)-N-Phenyl-3,4-dihydroxy-2,5-dioxopyrrolidine (**2d**)*

The product was washed with xylene and cold acetone. After drying under vacuum 58 g (93%) of a pale yellow solid was obtained. Physical and spectroscopic data are identical to those previously described [12].

*2.4.5. (3R,4R)-N-(1-Naphthyl)-3,4-dihydroxy-2,5-dioxopyrrolidine (**2e**)*

The product was recrystallized from ethanol to give 74.1 g (96%) of a pale yellow solid, m.p. 239–241 °C. Anal. calcd. for $C_{14}H_{11}N_1O_4$: C, 65.37; H, 4.31; N, 5.44. Found: C, 65.27; H, 4.25; N, 5.59. $[\alpha]_D = +130$ (*c*1, MeOH). ^{1}H NMR ($CDCl_3$/DMSO): 4.73 (s, 1 H); 4.87 (s, 1 H); 6.50 (bs, 2 H); 6.97 (d, 2 H, *J* 8.9); 7.22 (d, 2 H, *J* 8.9). ^{13}C NMR ($CDCl_3$/DMSO): 74.62, 75.14, 121.72, 124.97, 125.84, 126.22, 126.71, 127.91, 128.05, 128.82, 129.37, 133.37, 174.06, 174.09.

*2.4.6. (3R,4R)-N-(p-Methoxyphenyl)-3,4-dihydroxy-2,5-dioxopyrrolidine (**2f**)*

The product was recrystallized from ethanol to give 66.83 g (94%) of a greyish solid, m.p. 237–239 °C. Anal. calcd. for $C_{11}H_{11}N_1O_5$: C, 55.70; H, 4.67; N, 5.90. Found: C, 55.85; H, 4.62; N, 5.89. $[\alpha]_D = +140$ (*c*0.5, DMSO). ^{1}H NMR ($CDCl_3$/DMSO): 3.82 (s, 3 H); 4.59 (bs, 2 H); 6.46 (bs, 2 H); 6.97 (d, 2 H, *J* 8.9); 7.22 (d, 2 H, *J* 8.9). ^{13}C NMR ($CDCl_3$/DMSO): 55.06, 74.51, 113.86, 123.85, 127.32, 158.90, 173.88.

2.5. General procedure for the reduction of (3R,4R)-N-alkyl-3,4-dihydroxy-2,5-dioxopyrrolidines to (3S,4S)-N-alkyl-3,4-dihydroxypyrrolidines

Lithium aluminum hydride (0.23 mol, 8.7 g) was slowly added to the (3*R*,4*R*)-*N*-alkyl-3,4-dihydroxy-2,5-dioxopyrrolidine (0.1 mol) in diethyl ether (400 ml) in an ice bath. The system was refluxed for 48 h. At 0 °C, ethyl acetate was slowly added, followed sequentially by water (8.7 ml), NaOH, 15% (8.7 ml) and water (26.1 ml). The resulting mixture was stirred for 1 h, filtered with Celite and dried over anhydrous $MgSO_4$. After evaporation of the solvent under reduced pressure, the resulting oil was crystallized.

By further stirring the aluminum salts residue in ethyl acetate for 2–3 h, an additional batch of product may be obtained.

2.5.1. (3S,4S)-N-Benzyl-3,4-dihydroxypyrrolidine (**3a**)

Crystallization was carried out in ethyl acetate to give 8.7 g (45%) of a white solid, m.p. 100–101 °C (100 °C) [15]. Anal. calcd. for $C_{11}H_{15}N_1O_2$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.24; H, 7.77; N, 7.10. $[\alpha]_D = +31$ (*c*4.2, MeOH) [+32.4 (*c*4.2, MeOH)[13]]. ^{1}H NMR ($CDCl_3$/DMSO): 2.44 (dd, 2 H, *J* 4.1, 10.0); 2.89 (dd, 2 H, *J* 5.8, 10.0); 3.55 (d, 1 H, *J* 12.9, *AB system*); 3.64 (d, 1 H, *J* 12.9, *AB system*); 4.04 (m, 2 H); 4.58 (sl, 2 H); 7.21–7.33 (m, 5 H). ^{13}C NMR ($CDCl_3$/DMSO): 60.0, 60.1, 77.9, 126.5, 127.7, 128.5, 138.2.

2.5.2. (3S,4S)-N-Cyclohexyl-3,4-dihydroxypyrrolidine (**3b**)

Crystallization was carried out in ethyl acetate/petroleum ether originating 3.7 g (20%) of an off-white solid, m.p. 124–126 °C. Anal. calcd. for $C_{10}H_{19}N_1O_2$: C, 64.83; H, 10.34; N, 7.56. Found: C, 64.35; H, 10.66; N, 7.36. $[\alpha]_D = +35$ (*c*1, MeOH). ^{1}H NMR ($CDCl_3$/DMSO): 1.14–1.26 (m, 5 H); 1.58–1.61 (m, 1 H); 1.71–1.75 (m, 2 H); 1.87–1.91 (m, 2 H); 2.04–2.07 (m, 1 H); 2.53 (dd, 2 H, *J* 4.2, 10.0); 3.00 (dd, 2 H, *J* 5.9, 10.0); 4.06 (approx. t, 2 H, *J* 4.3); 4.2 (bs, 2 H). ^{13}C NMR ($CDCl_3$/DMSO): 24.83, 24.89, 25.96, 31.08, 31.17, 57.92, 63.12, 77.50.

2.5.3. (3S,4S)-N-(1-Naphthylmethyl)-3,4-dihydroxypyrrolidine (**3c**)

Crystallization was carried out in acetone originating 2.26 g (23%, from 40.66 mmol) of the product, m.p. 128–129 °C. Anal. calcd. for $C_{15}H_{17}N_1O_2$: C, 74.05: H, 7.04; N, 5.76. Found: C, 74.00; H, 6.97; N, 5.83. $[\alpha]_D = +30$ (*c*1, MeOH). ^{1}H NMR ($CDCl_3$/DMSO): 2.51 (m, 2 H); 2.96 (m, 2 H); 3.18 (bs, 2 H); 3.99 (m, 4 H); 7.35–7.55 (m, 4 H); 7.72–7.81 (m, 2 H); 8.22 (bs, 1 H). ^{13}C NMR ($CDCl_3$/DMSO): 57.62, 60.04, 77.64, 123.81, 124.58, 124.88, 125.10, 126.06, 127.02, 127.64, 131.50, 132.98, 134.05.

X-ray data for **3c**: orthorhombic, $P2_12_12_1$, pale yellow crystal, $a = 6.0773(2)$ Å, $b = 8.2433(3)$ Å, $c = 24.9246(7)$ Å, $Z = 4$, $R = 0.0319$, $wR = 0.0889$, GOF = 1.055, 2215 reflections, 166 parameters. H atoms were refined as riding on their parent atoms.

2.6. General procedure for the reduction of (3R,4R)-N-aryl-3,4-dihydroxy-2,5-dioxopyrrolidines to (3S,4S)-N-aryl-3,4-dihydroxypyrrolidines

Lithium aluminum hydride (0.23 mol, 8.7 g) and ethyl ether (400 ml) were placed in a round-bottomed flask equipped with a Soxhlet containing the (3*R*,4*R*)-*N*-aryl-3,4-dihydroxy-2,5-dioxopyrrolidine (0.1 mol). The system was refluxed until the reagent had been consumed. At 0 °C, ethyl acetate was slowly added, followed sequentially by water (8.7 ml), NaOH, 15% (8.7 ml) and water (26.1 ml). The resulting mixture was stirred for 1 h, filtered with Celite and dried over anhydrous $MgSO_4$. After evaporation of the solvent under reduced pressure, the resulting oil was crystallized.

By further stirring the aluminum salts residue in ethyl acetate for 2–3 h, an additional batch of product may be obtained.

2.6.1. (3S,4S)-N-Phenyl-3,4-dihydroxypyrrolidine (**3d**)

The resulting oil was crystallized from ethyl acetate/petroleum ether giving a brownish yellow solid (7.2 g, 40%). Physical and spectroscopic data are in agreement with the previously described [12].

*2.6.2. (3S,4S)-N-(1-Naphthyl)-3,4-dihydroxypyrrolidine (**3e**)*

Crystallization was carried out in acetone/water to give 4.6 g (20%) of a brownish solid, m.p. 50–52 °C. Anal. calcd. for $C_{14}H_{15}N_1O_2{\cdot}H_2O$: C, 68.00; H, 6.93; N, 5.66. Found: C, 67.87; H, 6.59; N, 5.85. $[\alpha]_D = +31.5$ (*c*1, MeOH). ^{1}H NMR ($CDCl_3$/DMSO): 3.32 (dd, 2 H, *J* 3.3, 10.01); 3.80 (dd, 2 H, *J* 4.8, 10.0); 4.27 (bs, 2 H); 4.80 (bs, 2 H); 6.90 (dd, 1 H, *J* 1.2, 7.2); 7.30–7.45 (m, 4 H); 7.75–7.78 (m, 1 H); 8.20–8.24 (m, 1 H). ^{13}C NMR ($CDCl_3$/DMSO): 57.98, 76.21, 110.52, 120.40, 123.71, 124.46, 125.09, 125.53, 127.07, 127.72, 134.54, 146.82.

*2.6.3. (3S,4S)-N-(p-Methoxyphenyl)-3,4-dihydroxypyrrolidine (**3f**)*

The resulting oil was crystallized from ethyl acetate/petroleum ether affording 7.2 g (40%) of a brownish yellow solid, m.p. 121–123 °C. Anal. calcd. for $C_{11}H_{15}N_1O_3{\cdot}H_2O$: C, 58.14; H, 7.54; N, 6.16. Found: C, 57.85; H, 7.32; N, 6.43. $[\alpha]_D = +30$ (*c*0.5, DMSO). ^{1}H NMR ($CDCl_3$/DMSO): 3.82 (d, 2 H, *J* 9.8); 3.48 (dd, 2 H, *J* 4.37, 9.8); 4.10 (bs, 2 H); 4.75 (bs, 2 H); 6.37 (d, 2 H, *J* 5.2); 6.70 (d, 2 H, *J* 5.2). ^{13}C NMR ($CDCl_3$/DMSO): 53.05, 54.78, 74.68, 111.07, 113.85, 141.94, 149.47.

2.7. General procedure for enantioselective alkylation reactions

2.7.1. Method A

To the chiral ligand **3** (0.045 mmol) and benzaldehyde (3 mmol) in an inert atmosphere, cyclohexane (12 ml) was added. The temperature of the reaction mixture was lowered to 0 °C and diethylzinc (6 mmol, as a 1 M hexane solution) was added. The reaction was stirred at this temperature for 24 h. After this time a saturated ammonium chloride solution (3 ml) followed by 2 M HCl (3 ml) were added and the reaction mixture was extracted with diethyl ether. The organic phases were washed with water and brine and then dried over anhydrous $MgSO_4$. Removal of the solvent under reduced pressure originated an oily product, which was submitted to purification by preparative thin layer chromatography (hexane/ethyl acetate, 5:1) in order to isolate the chiral alcohol. The ee was determined by comparing the specific rotation with that of the pure enantiomer. The absolute configuration was deduced from the sign of the optical rotation.

2.7.2. Method B

The procedure used was identical to Method A except that, after the addition of the diethyl zinc at 0 °C, the reaction remained at this temperature for 1 h and then was raised to room temperature to complete the 24 h period.

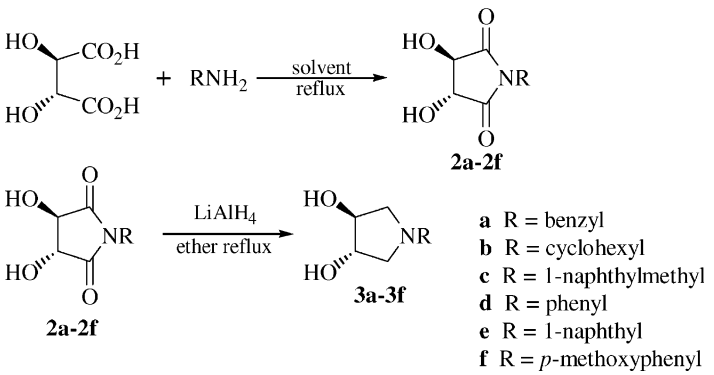
3. Results and discussion

3.1. Synthesis of chiral ligands

A series of pyrrolidine-based β-amino alcohols was prepared according to a two-step synthetic sequence using (L)-tartaric acid and several primary amines (Scheme 1).

The first step involves the reflux of tartaric acid with the appropriate amine in xylene, using Dean–Stark conditions. The reaction is complete when the theoretical amount of water is collected. Using benzyl [15], cyclohexyl, 1-naphthylmethyl, phenyl [12] 1-naphthyl, and 4-methoxyphenyl amines, under these reaction conditions, the corresponding dioxopyrrolidines **2a**–**2f** were obtained in high yield.

The second step of the synthetic sequence involves the reduction of dioxopyrrolidines (*R*,*R*)-**2a**–**2f** to the corresponding pyrrolidines (*S*,*S*)-**3a**–**3f** with lithium aluminum hydride. Two different procedures were adopted for the reduction, depending on the type of substituent on the nitrogen atom. When in the presence aliphatic groups, as in the cases of (*R*,*R*)-**2a**–**2c**, reduction was carried out by the slow addition of the reducing agent to a suspension of the dioxopyrrolidine in diethyl ether, followed by a 48 h reflux. Contrary to these cases, when aromatic groups are directly bonded to the nitrogen atom, as in (*R*,*R*)-**2d**–**2f**, quite a few problems arose. The previously described process furnishes secondary products in significant quantities, requiring other reduction conditions [11,12], namely, the use of a Soxhlet, with slow addition of the substrate to the hydride in diethyl ether.



Scheme 1.

3.2. Enantioselective alkylations

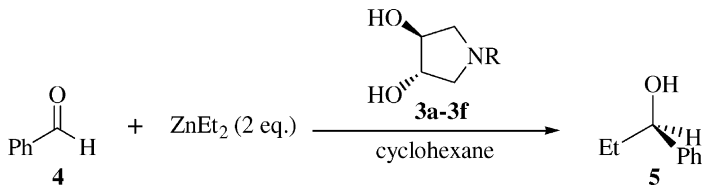
The pyrrolidine-based amino alcohols **3a**–**3f** were used as ligands in the enantioselective alkylation of benzaldehyde **4** with diethyl zinc, Scheme 2.

Initially, reactions were carried out at 0 °C for 24 h in cyclohexane using 2 eq. of diethylzinc and 15 mol% of the ligand. The results are summarized in Table 1. Using the prescribed reaction conditions, ligands **3a**–**3c** proved to be efficient catalysts for the alkylation, with conversions greater than 90% being observed. In the other cases values are significantly lower. In all cases, besides the desired chiral alcohol 1-phenyl-1-propanol **5**, benzyl alcohol is formed as a by-product; in some cases it exists in significant quantities, becoming the main reaction product in the presence of ligands **3d**–**3f**. The formation of benzyl alcohol has been observed by others and is the result of a secondary process in which benzaldehyde is reduced by the zinc alkoxide of the ethylation product, 1-phenyl-1-propanoxide [6].

The substituents on the nitrogen or adjacent atoms as well as those on the carbinol carbon seem to significantly influence the formation of the catalytic species and of the transition state [8–10,16,17]. The presence of alkyl groups is said to favor stable catalytic complexes and thus efficient reactions. While bulky groups allow for a better distinction of the enantiotopic faces of the aldehyde, excessively large substituents, may inhibit the formation of the transition state and thus lower the overall efficiency of the reaction.

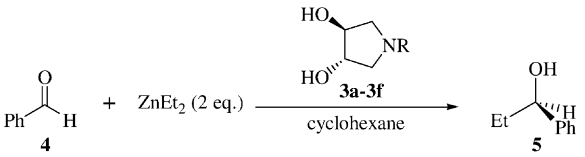
Our results fit into the above observations. There are basically two sets of results, the first including reactions carried out with ligands **3a**–**3c** and the second, with the remaining ligands **3d**–**3f**. The *N*-substituents in the former case are all alkyl, and in the latter are aromatic. With the first group of ligands high conversions were achieved and, with the exception of **3c**, only small amounts of by-product were formed.

With the ligands that make up the second group, alkylations were inefficient, only low conversions and considerable amounts of by-product being observed. This seems to be an indication that the catalytic species is not properly formed. This may be due to the lower nucleophilicity of the aromatic nitrogen atoms relatively to the alkyl nitrogen. This may imply that a weaker catalytic complex results in the presence of



Scheme 2.

Table 1
Enantioselective addition of diethylzinc to benzaldehyde in the presence of **3**[a]



Ligand	Conversion (%)[b]	1-Phenyl-1-propanol (%)[b,c]	ee (%)[d] (absolute configuration)
(*S*,*S*)-**3a**	99	93	72 (*R*)
(*S*,*S*)-**3b**	97	94	75 (*R*)
(*S*,*S*)-**3c**	93	67	80 (*R*)
(*S*,*S*)-**3d**	66	18	–[e]
(*S*,*S*)-**3e**	36	43	–[e]
(*S*,*S*)-**3f**	56	27	–[e]

[a] Reactions were carried out at 0 °C for 24 h after the addition of a 1 M hexane solution of diethylzinc (6 mmol) to **3** (0.45 mmol) and benzaldehyde (3 mmol) in cyclohexane.
[b] Determined by GC.
[c] Relatively to converted benzaldehyde.
[d] Determined by comparing the specific rotation of the isolated product with the value for the pure enantiomer [(*R*)-1-phenyl-1-propanol, $[\alpha]_D = +47$ (*c*2.2, hexane)].
[e] Enantiomeric excesses were not determined due to the very low yields observed.

aromatic nitrogens. This situation is less favorable for the formation of the alcohol product, consequently favoring greater quantities of the secondary product, benzyl alcohol.

Enantiomeric excesses for 1-phenyl-1-propanol obtained in the reactions catalyzed by **3a**–**3c** are listed in Table 1. The highest ee, 80%, resulted when ligand **3c** was used in the alkylation. In this particular reaction a significant amount of by-product was formed.

In order to try to overcome the formation of benzyl alcohol in these reactions, some of the parameters were varied, which included the addition of the substrate in several portions, an increase in the relative quantity of diethylzinc and the change in reaction temperature. No measurable changes were observed in the outcome of the reaction in any of these cases.

In contrast, when the reaction was carried out at 0 °C for 1 h and left at room temperature for 24 h, significant changes were detected in the extension of substrate conversion, in product distribution and in the enantioselectivity of the alkylation, Table 2.

At room temperature, **3d**–**3f** showed greater activity for the alkylation process. These reactions, which at 0 °C essentially gave benzyl alcohol, behaved differently at room temperature, forming 1-phenyl-1-propanol as the major product. The by-product, although much less, still constituted more than 20% of the converted substrate.

Ligand **3c** (which at 0 °C gave good conversion of the substrate, but a significant quantity of benzyl alcohol) under these new reaction conditions showed complete conversion of the substrate and a high percentage of secondary alcohol.

When **3a** and **3b** were used at room temperature, no significant changes were observed in substrate conversion or in product distribution with respect to the results obtained at 0 °C.

With all the ligands marked decreases were found in the enantioselectivity of the alkylation. In the alkylation with **3c**, the ee went from 80% at 0 °C to 30% at room temperature.

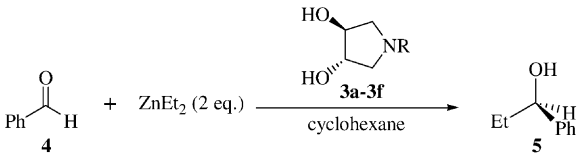
An additional alkylation was attempted using **3a** at an intermediate temperature. After 1 h at 0 °C, the reaction was brought to 10 °C and maintained at this temperature for the remainder of the 24 h. The results (83% conversion, 89% 1-phenyl-1-propanol and an ee of 16%) showed no improvement under these reaction conditions.

3.3. X-Ray crystallography

The structure of ligand **3c**, which exhibited the most efficient chiral induction, was determined by X-ray crystallography, Fig. 1.

The pyrrolidine ring has a twisted half-chair conformation with a local pseudo two-fold axis running

Table 2
Enantioselective addition of diethylzinc to benzaldehyde in the presence of **3**[a]



Ligand	Conversion (%)[b]	1-Phenyl-1-propanol (%)[b,c]	ee (%)[d] (absolute configuration)
(*S*,*S*)-**3a**	97	81	20 (*R*)
(*S*,*S*)-**3b**	97	74	21 (*R*)
(*S*,*S*)-**3c**	>99	94	30 (*R*)
(*S*,*S*)-**3d**	86	77	0
(*S*,*S*)-**3e**	89	61	4 (*R*)
(*S*,*S*)-**3f**	62	77	0

[a] Reactions were carried out at 0 °C for 1 h and brought to room temperature for the remainder of the 24 h, after the addition of a 1 M hexane solution of diethylzinc (6 mmol) to **3** (0.45 mmol) and benzaldehyde (3 mmol) in cyclohexane.
[b] Determined by GC.
[c] Relatively to converted benzaldehyde.
[d] Determined by comparing the specific rotation of the isolated product with the value for the pure enantiomer [(*R*)-1-phenyl-1-propanol, $[\alpha]_D = +47$ (*c*2.2 hexane)].

through C4 and the middle of the N1–C2 bond. The two-fold asymmetry parameter ΔC_2 [N1–C2] is 7.89(13)°. The Cremer and Pople [19] puckering parameters are $q_2 = 0.432(1)$ Å, $\varphi_2 = 12.26(19)°$, the pseudorotation parameters are $\phi = 173.8(1)°$, $\tau_m = 46.2(1)°$ for the reference N1–C2 bond. Atoms N1 and C2 are on opposite sides of the plane passing through C3, C4 and C5 at 0.452(3) Å and –0.238(3) Å, respectively. Bond lengths and angles within the pyrrolidine ring are unexceptional. The geometry around the N1 atom is pyramidal with average N–C bond length of 1.470(2) Å and C–N–C valence angle of 109(6)°.

The fused rings of the naphthyl group are planar within 0.02 Å, with a weighed average C–C bond length of 1.4000(7) Å. The angle between the least-squares planes of the naphthyl and pyrrolidine rings is 61.40(8)°. The torsion angles N1–C6–C7–C8 and C5–N1–C6–C7 are 14.2(2)° and 76.78(16)°, respectively.

The hydroxyl groups are each involved in one hydrogen bond with neighbor molecules, forming an infinite two-dimensional H-bonding network. The N1 atom acts as an acceptor of one of these bonds, the other hydrogen bond bridges two hydroxyls.

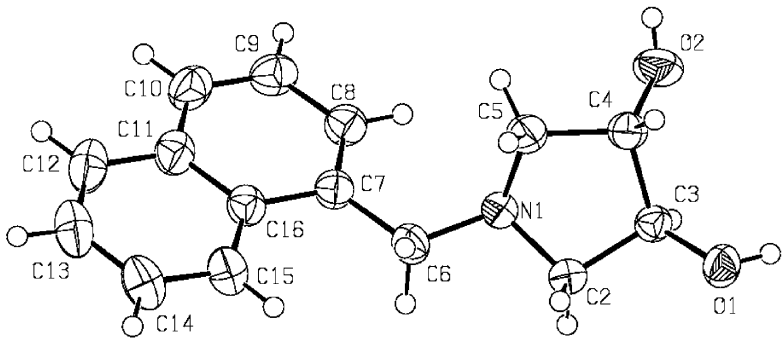


Fig. 1. ORTEPII [18] plot of molecule of compound **3c**. Displacement ellipsoids are drawn at the 50% level.

Clarification of the structure of **3c** is an aid in the interpretation of the greater degree of chiral induction observed with this β-amino alcohol. The bulk of the 1-naphthylmethyl substituent, as confirmed by the X-ray diffraction, must impose considerable limitations on the geometry of approach of benzaldehyde to the coordinated β-amino alcohol in order to form the 6-membered transition state. These limitations will be greater than those observed when less bulky *N*-substituents such as benzyl [20] or cyclohexyl[1] are present. With ligands **3d**–**3f**, the steric effect is not as relevant, probably because the nitrogen atom is directly bonded to the aromatic group, imposing a quasi-planar relationship between the aromatic group and the –C2–N–C5– portion of the pyrrolidine ring [12]. The consequent reduced amount of steric crowding allows for an unrestricted approach of the aldehyde molecule and therefore, an unselective alkylation.

In all of the enantioselective alkylations carried out, the major product had the (*R*) absolute configuration. The preferential formation of this enantiomer is possibly due to the steric hindrance imposed by the *N*-substituent upon the zinc alkoxide catalytic species thus forcing the phenyl group of the aldehyde to preferentially assume a position that is furthest away from it in the six-membered transition state.

4. Conclusions

Synthetic procedures for the preparation of a new class of chiral *N*-aryl and *N*-alkyl pyrrolidine-based β-amino alcohols for enantioselective alkylation reactions are presented in this paper. The catalytic activity of these ligands was tested in the enantioselective alkylation of benzaldehyde. The studies herein described show that the nature of the substituent on the pyrrolidine nitrogen of the β-amino alcohols which we prepared have a significant influence on the ability of these ligands to catalyze the enantioselective addition of diethylzinc to benzaldehyde. Under our optimized reaction conditions (0 °C, 24 h, cyclohexane–hexane) the β-amino alcohols having *N*-alkyl groups were found to display the best overall results, namely with respect to catalytic activity and enantioselectivity. The application of these chiral β-amino alcohols to other enantioselective reactions will be explored.

[1] Unpublished X-ray crystallography results.

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