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Optically active N-1-phenylethyl derivatives of (1R)-2-amino-1-phenylethanol as chiral auxiliaries in the enantioselective addition of diethylzinc to arylaldehydes.

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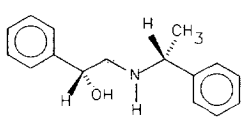
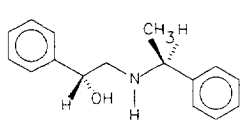
Abstract: The aminoalcohols (1R)-2-N[(R)-1-phenylethyl]amino-1-phenylethanol, (1R)-2-N[(S)-1-phenylethyl]amino-1-phenylethanol, and (1R)-2-N-methyl-N[(R)-1-phenylethyl]amino-1-phenylethanol, synthesized by simple procedures, have been used as chiral catalysts in the enantioselective addition of diethylzinc to arylaldehydes, obtaining optically active 1-arylpropanols in good chemical yields (47 to 95%) and e.e.s up to 88%.

Optically active β-aminoalcohols, having different structures, have proved to be very efficient chiral auxiliaries for asymmetric reactions[1]. In particular, they are the catalysts of choice for the enantioselective addition of Et_2Zn to aldehydes[2] and high extents of enantioselectivity have been reached employing compounds such as DAIB[3] or derivatives of ephedrine and pseudoephedrine[2].
We report here the use of the two optically active diastereomeric aminoalcohols 1a and 1b and the N-methyl derivative 1c as promoters of the enantioselective addition of Et_2Zn to arylaldehydes[a].



1a



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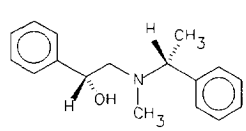


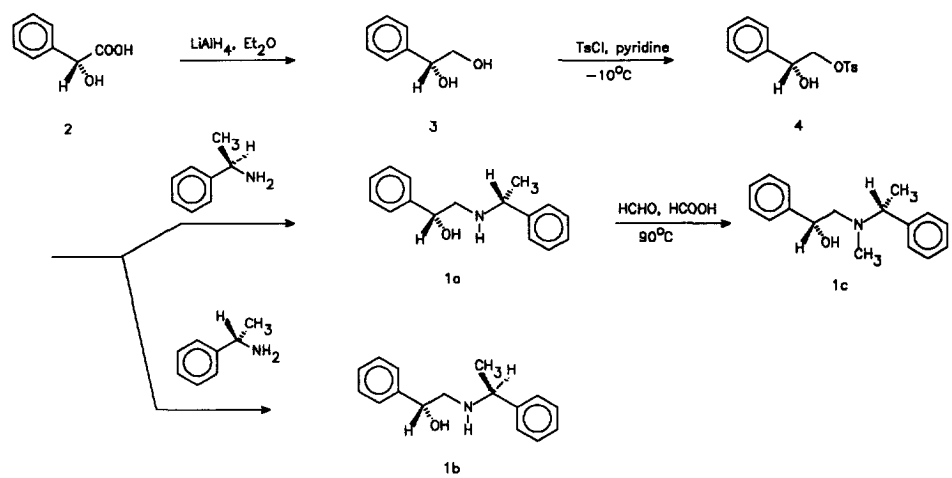
1c

We addressed our attention toward these compounds because they have two stereogenic centers in 1,4 positions, instead of 1,2 like the most common chiral promoters of the asymmetric addition of Et_2Zn to aldehydes[2], and the effect of this structural feature on the outcome of the reaction was the goal of the present investigation. The synthesis of the aminoalcohols was carried out from mandelic acid and 1-phenylethylamine, which are commercially available in the two enantiomeric forms and therefore allow both the diastereoisomers

[a] The compounds 1a and 1b, to the best of our knowledge, have been used in asymmetric organic synthesis only as ligands of $LiAlH_4$[4].

to be obtained. As a matter of fact we employed 1a and 1b to evaluate if the R,R diastereoisomer is more efficient than the R,S one as a catalyst of the alkylation of arylaldehydes. Unlike the report in the literature[4,5], we have performed the synthesis of 1a, 1b and 1c (Scheme) employing a method which, starting from inexpensive commercially available compounds and using simple experimental procedures, provides enantiomerically pure products.

Scheme

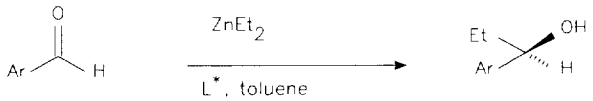


Following the sequence shown in the Scheme, reduction of (R)-mandelic acid by $LiAlH_4$ in Et_2O gives (R)-1-phenylethandiol 2 in almost quantitative yield. Treatment of 2 with tosyl chloride (TsCl) in pyridine at -10°C gives the corresponding 1-hydroxy-2-tosyloxy derivative 3 in 75% yield. By reacting 3 with (R)-α-phenylethylamine at 90°C for 5 hours, the aminoalcohol 1a is obtained in 40% yield, after crystallization from ethyl acetate. By reacting 3 with (S)-α-phenylethylamine the diastereomer 1b is obtained, which is purified by flash chromatography (yield 50%). By Eischweiler-Clarke reaction from 1a, we have synthesized the N-methyl derivative 1c, in 95% yield.

The addition of $ZnEt_2$ to arylaldehydes, promoted by 1a, 1b and 1c was carried out following a standard procedure reported in the literature[6]. It is worthy of note that the reaction affords the secondary alcohol in practice as single product, the presence of the alcohol from reduction being below 4% in all the cases. The absolute configuration of the 1-arylpropanols has been obtained from the elution order in HPLC on Pirkle stationary phase (R)-DNBPG for 1-(2-naphthyl)propanol and 1-(4-methoxyphenyl)propanol[7] and from the sign of the optical rotation for 1-phenylpropanol[8]. The absolute configuration of the dextrorotatory antipode of 1-(4-trifluoromethylphenyl)propanol is reported in the literature[9]. As the assignment has been made on the basis of mechanistic considerations of asymmetric induction in the reduction of prochiral ketones by chiral Grignard reagents, the absolute configuration of the dextrorotatory antipode of this alcohol was confirmed by using the method of induction of a cholesteric mesophase in a nematic liquid cristal[10]. On this basis we have assigned the R absolute configuration to the dextrorotatory antipode of 4-trifluoromethylphenylpropanol: the result

obtained is wholly in accord with the literature[9]. By means of the previously described method, we have confirmed the absolute configuration of the prevailing enantiomer of 1-(4-methoxyphenyl)propanol, already determined from the elution order in HPLC[7].

Table: Enantioselective addition of $ZnEt_2$ to arylaldehydes[a]



L*	Ar	Yield(%)	time(h)	e.e.(%)	A.C.
1a	Phenyl	78	6	88[b]	R[b]
1a	2-naphthyl	75	6	82[c]	R[c]
1a	4-CF_3-phenyl	80	6	82[d]	R[d]
1a	4-methoxyphenyl	50	22	52[c]	R[c]
1b	Phenyl	90	6	78[e]	R[b]
1b	2-napthyl	78	6	68[c]	R[c]
1b	4-CF_3-phenyl	95	6	66[f]	R[d]
1b	4-methoxyphenyl	70	22	33[c]	R[c]
1c	phenyl	65	6	50[g]	R[b]
1c	2-naphthyl	47	6	48[c]	R[c]
1c	4-CF_3-phenyl	79	6	48[h]	R[d]

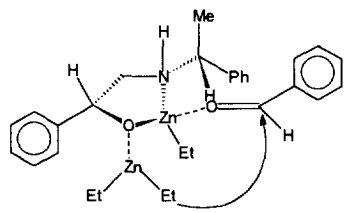
a) reaction conditions: 0.092 mmol of catalyst, 1 mmol of aldehyde, 1.5 mmol of $ZnEt_2$, 8 ml of toluene. b) $[\alpha]_D^{25}$= 38.7 (c=1 $CHCl_3$); lit[8].: $[\alpha]_D^{25}$=-42.2 (c=0.95, $CHCl_3$) 95% e.e., (S) c) Pirkle DNBPG hexane-isopropanol , absolute configuration obtained from elution order[7]. d) $[\alpha]_D^{28}$=26.8 (c=1, $CHCl_3$); $[\alpha]_D^{28}$=32.5 (c=1, $CHCl_3$)[11], absolute configuration obtained from the screw sense of the cholesteric mesophase induced in MBBA nematic liquid crystal[10]. e) $[\alpha]_D^{25}$=34.6 (c=1, $CHCl_3$). f) $[\alpha]_D^{28}$=21.5 (c=1, $CHCl_3$). g) $[\alpha]_D^{25}$=22.1 (c=1, $CHCl_3$). h) $[\alpha]_D^{28}$=15.6 (c=1, $CHCl_3$).

All the results obtained are summarized in the table and show that the aminoalcohols 1a and 1b are good catalysts for the reaction, giving in six hours the alkylation product in good yields and e.e. up to 88%. When the substrate is disactivated toward the nucleophilic addition, as in the case of 4-methoxybenzaldehyde, longer time of reaction is required to obtain the secondary alcohol in satisfactory yield: this result indicates that the rate determining step of the reaction is the ethyl transfer on the carbonyl group[8]. Also the e.e. obtained in these cases are lower, this result being attributable to the presence of the competing uncatalyzed reaction, leading to the racemic product[8]. The chemical yields are higher when the catalyst is 1b while the e.e. are higher when 1a is employed. Therefore 1b accelerates the alkylation reaction more than 1a, which, on the contrary, performs the best chiral discrimination. The N-methyl derivative 1c is a catalyst less efficient than

1a and 1b, giving lower yields and lower e.e. of alkylation product. The absolute configuration of the prevailing enantiomer is (R) in all the examined cases. This result suggests that the stereogenic center responsible of the asymmetric induction is that in 1 position deriving from mandelic acid. The stereogenic center deriving from α-phenylethylamine influences only the extent of the asymmetric induction, the e.e. obtained with 1a being higher than those obtained with 1b. Indeed the (R,R) diastereoisomer gives higher enantioselectivity than the (R,S) diastereoisomer.

Assuming the mechanism proposed by Noyori[3], we can suppose that the aminoalcohol, reacting with $ZnEt_2$ forms a five centers chelate, as described in Figure.

Figure



This assembly allows to razionalize some experimental results above reported:

i) The aldehyde can coordinate to the zinc with the lone pair of the oxygen atom in anti position to its phenyl group[3], approaching also in "anti" manner to the phenyl group at C-1 of the aminoalcohol. In this way the molecule of $ZnEt_2$ coordinated to the oxygen atom, attacks the carbonyl group on the re face, providing a secondary alcohol having the (R) absolute configuration.

ii) In this assembly the absolute configuration of the 1-phenylethylamine moiety does not influence the sense of asymmetric induction.

iii) The presence of the methyl group on the nitrogen atom in 1c makes more difficult the coordination of the aldehyde and hence justifies the lower yields obtained with this aminoalcohol.

In conclusion, the aminoalcohols 1a and 1b have proved to be good promoters of the addition of $ZnEt_2$ to arylaldehydes. We have observed that the presence of two stereogenic centers in 1,4 position is a structural feature suitable to this kind of chiral catalysts, the yields and e.e. being good with substrates not disactivated toward the nucleophilic addition, and the R,R configuration gives the highest extent of asymmetric induction. The simple method of synthesis of 1a, 1b and 1c followed by us, allows easily to obtain these compounds which can be tested as chiral auxiliaries also in others enantioselective reactions.

EXPERIMENTAL

^1H NMR spectra were recorded on a Varian Gemini 200 (200 MHz) spectrometer in deuterated chloroform with TMS as the internal standard. Melting points were taken using a Reichart Thermovar apparatus and are uncorrected. Optical rotations were measured on a Jasco DIP-360 polarimeter in 1 dm tube and the rotations

refer to those of a pure liquid. CD spectra were recorded on a Jasco J-500 spectropolarimeter. Chiral HPLC analyses were performed on a Pirkle DNBPG column (4.6x250 mm) at a flow rate of 1 or 2 ml/min with a Jasco Twincle apparatus equipped with a UV Jasco Uvidec detector. Unless noted, all reagents were obtained from commercial sources. Anhydrous toluene and ether were distilled from Na, under Argon. Pyridine was distilled from KOH under argon. All $ZnEt_2$ runs were performed under Argon atmosphere.

(1R)-1-Phenyl-1,2-dihydroxyethane (3)

Under a N_2 atmosphere, $LiAlH_4$ (1g, 0.0263 mol) and Et_2O (40 ml) are placed in a dried round bottomed flask, equipped with a magnetic stirrer, a dropping funnel and a condenser. To the stirred suspension is added dropwise R-mandelic acid (2g, 0.0263 mol) dissolved in Et_2O, and the resulting suspension is refluxed for 5h and then stirred at r.t. for 12h. Ice cold H_2O is added dropwise to the mixture, then the solid is filtered off and the organic layer is washed with 10% $NaHCO_3$, then with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The crude product is recrystallized from ether-pentane 1:2 to give 3. Yield: 85% (1.54 g, 0.011 mol). M.p. 63°C; $[\alpha]_D^{26}$=-39.4 (c=2.5, EtOH) ; lit[12]: $[\alpha]_D^{13}$= 39.3 (c=3.13, EtOH) for the S enantiomer. ^1H NMR ($CDCl_3$/TMS) δ: 2.2 (s, 1H, OH); 3.15 (s, 1H, OH); 3.6-3.8 (m, 2H, CH_2); 4.8 (dd, 1H, CH); 7.15-7.3 (m, 5H,aromatic).

(1R)-1-hydroxy-1-phenyl-2-tosyloxyethane (4)

To a solution of (1R)-1,2-dihydroxy-1-phenylethane (1.3 g, 9.42 mmol) in dry pyridine (10 ml), is added dropwise a solution of TsCl (1.8 g, 9.47 mmol) in dry pyridine (5 ml) at -10°C. The mixture is stirred at -10°C for 4h, treated with ice-water and extracted with ethyl ether (5x20 ml). The organic layer is washed with 10% HCl, 5% $NaHCO_3$, H_2O, then dried (Na_2SO_4). After evaporation to dryness 2.05 g (7 mmol) are obtained (yield 75%). M.p. 65°C $[\alpha]_D^{25}$=-46.6 (c=2, $CHCl_3$)

^1H NMR ($CDCl_3$/TMS) δ: 2.3 (s, 1H, OH); 2.45 (s, 3H, CH_3); 4-4.2 (m, 2H, CH_2); 5 (dd, 1H, CH); 7.3-7.4 (m, 7H, aromatics); 7.8 (d, 2H, aromatics)

(1R)-2-N[(R)-1-phenylethyl]amino-1phenylethanol (1a)

In a schlenk under N_2 1g (3.48 mmol) of (1R)-1-hydroxy-1-phenyl-2-tosyloxyethane and 0.66ml (5.2 mmol) of (R)-1-phenylethylamine are placed. The mixture is warmed at 90°C for 5h, then cool down to r.t., diluted with a 1M KOH solution and extracted with $CHCl_3$. The organic layer is washed with water, dried (Na_2SO_4) and concentrated under reduced pressure. The crude product is recrystallized from ethyl acetate, giving 0.33g (1.37 mmol) of 1a, yield 40%.

M.p. 145-148°C $[\alpha]_D^{28}$=26.5 (c=1, $CHCl_3$)

^1H NMR ($CDCl_3$/TMS) δ: 1.35 (d, 3H, CH_3); 2.45 (s, 2H, OHand NH); 2.6-2.8 (m, 2H, CH_2); 3.75 (q, 1H, CH); 4.55 (dd, 1H, CH); 7.2-7.4 (m, 10H, aromatics).

(1R)-2-N[(S)-1-phenylethyl]amino-1phenylethanol (1b)

The reaction is carried out starting from (1R)-1-hydroxy-1-phenyl-2-tosyloxyethane and (S)-1-

phenylethylamine as described for 1a. The crude product is purified by flash chromatography (ethyl acetate) obtaining 0.41 g (1.7 mmol) of 1b, yield 50%.

M.p. 80-85°C $[\alpha]_D^{26}$=-111 (c=1, $CHCl_3$).

^1H NMR ($CDCl_3$/TMS) δ: 1.4 (d, 3H, CH_3); 2.5-2.85 (m, 4H, CH_2, NH and OH); 3.85 (q, 1H, CH); 4.75 (dd, 1H, CH); 7.2-7.4 (m, 10H, aromatics).

(1R)-2-N-methyl-N-[(R)-1-phenylethyl]amino-1-phenylethanol (1c)

To 0.5 g (2 mmol) of 1a 1.5 ml of formaldehyde (40% H_2O solution, 20 mmol) and 0.85 ml of 99% formic acid (22 mmol) are added. The mixture is warmed at 90°C for 10h, then cool down to r.t., made basic with a 1M NaOH solution. The resulting suspension is extracted with $CHCl_3$ and the organic layer is washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The crude product is purified by column chromatography (SiO_2, $CHCl_3$) obtaining 0.46 g (1.8 mmol, 90% yield) of 1c as colorless liquid. $[\alpha]_D^{22}$=-20 (c=1, $CHCl_3$).

^1H NMR ($CDCl_3$/TMS) δ: 1.4 (d, 3H, CH_3); 2.25 (s, 3H, CH_3); 2.35 (s, 1H, OH); 2.4-2.65 (m, 2H, CH_2); 3.8 (q, 1H, CH); 4.6 (dd, 1H, CH); 7.2-7.4 (m, 10H, aromatics).

General procedure for the addition of diethylzinc to arylaldehydes catalyzed by 1a, 1b and 1c.

To a solution of the chiral aminoalcohol (0.092 mmol) in toluene (8 ml), Et_2Zn (3 ml, 1M hexane) is added. The mixture is stirred for 30 min, then cooled at 0°C and 1.5 mmol of aldehyde is added. After the mixture is stirred for 6h at r.t., HCl 1M is added to quench the reaction. The mixture is extracted with Et_2O and the organic is washed with 5% $NaHCO_3$, then H_2O, dried (Na_2SO_4) and concentrated under reduced pressure. The secondary alcohol is purified by column chromatography (SiO_2, $CHCl_3$) and the e.e. is determined by HPLC on Pirkle chiral stationary phase or from the optical rotation value.

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