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# Synthesis and evaluation of a range of enantiopure β-aminoalcohols derived from tartaric acid for asymmetric hydrogen transfer reduction of prochiral ketones

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**Abstract**

Various (*2R*,*3R*)-3-amino- and (alkylamino)-1,4-bis(benzyloxy)butan-2-ol have been prepared from readily available (+)-diethyl tartrate. These enantiopure β-aminoalcohols have been used in association with Ru(II) or Ir(I) complexes as ligands in the hydrogen transfer reduction of various aryl alkyl ketones; ee up to 80% have been obtained using the ruthenium complex.


*Keywords:* Enantiopure aminoalcohols; Asymmetric transfer hydrogenation; Ketones; Ruthenium; Iridium

## 1. Introduction

Catalytic asymmetric transfer hydrogenation of ketones using isopropanol as the hydrogen donor has recently emerged as one of the most attractive route for the preparation of chiral secondary alcohols [1]. This reduction, occurring under very mild conditions and giving very high enantioselectivities in some examples is a very useful alternative to the classical catalytic reduction of ketones using molecular hydrogen. One of the best catalyst is the ruthenium(II) complex associated with chiral monoarylsulfonated-1,2-diamine or β-aminoalcohols, enantioselectivities greater than 90% being obtained in the reduction of ketones [2,3].

Intense exploration of ruthenium(II)/β-aminoalcohol systems has been performed; this is due to the ready availability and easy functionalization of these substrates, as well as the very height enantioselectivities and activities obtained using these compounds as ligands. Various β-aminoalcohols have been used as ligands by the groups of Noyori [3], Wills [4], Andersson [5], van Leeuwen [6], Knochel [7], and Mortreux [8] with the view of designing more efficient ligands. Despite these developments, it is highly desirable to have access to a wide variety of catalysts in order to optimize the reaction, and also to have an easy access to a large family of modulable chiral ligands. We present here the preparation of a family of chiral aminoalcohols derived from tartaric acid and their applications in hydrogen transfer reduction of various prochiral ketones.

## 2. Experimental

Solvents were purified by standard methods and dried if necessary. All commercially available reagents were used as received. Flash column chromatography was

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performed on silica gel 60 (230–240 mesh, Merck). Melting points were determined with a capillary melting point apparatus Büchi SMP-20. Optical rotation values were recorded using a Perkin-Elmer 241 polarimeter. The NMR spectra were recorded on a Bruker 300 at 300.13 MHz ($^1$H), and 75.47 MHz ($^{13}$C). $^1$H and $^{31}$C NMR chemical shifts were reported as $\delta$ ppm relative to $Me_4Si$ and $CDCl_3$, respectively. Conversion and enantiomeric excesses were determined by GC using a capillary Quadrex OV1 column (30 m × 0.25 mm) and a capillary Cyclodex-β column (30 m × 0.25 mm), respectively.

### 2.1. (1S,2S)-3-(benzyloxy)-1-[(benzyloxy)methyl]-2-hydroxypropyl methanesulfonate (2)

Diol **1** [9] (6.8 g, 22.5 mmol) was dissolved in $C_5H_5N$ (21 mL) at 0°C. Methanesulfonyl chloride (1.6 mL, 22.5 mmol) was slowly added. After stirring for 12 h, cold water (68 mL) was added, and the resulting mixture was extracted with $CH_2Cl_2$ (3× 35 mL). The combined organic phases were washed with a saturated aqueous solution of copper sulfate (2× 10 mL), and dried over sodium sulfate. Evaporation of the solvent under reduced pressure afforded an oil that was purified by flash chromatography on silica gel using petroleum ether/ethyl acetate (1:1) as eluent to afford monomesylate **2** as an oil (3.85 g, 45% yield); $R_f$ 0.6 (petroleum ether/ethyl acetate 1/1); $[\alpha]_D^{25}$ −4.7 (*c* 0.15, $CHCl_3$); $^1$H NMR ($CDCl_3$): $\delta$ 2.58 (d, 1H, *J* = 5.6 Hz, OH), 3.07 (s, 3H, $CH_3$), 3.58 (dd, 1H, *J* = 9.6, 6.0 Hz, $CH_2O$), 3.63 (dd, 1H, *J* = 9.6, 4.9 Hz, $CH_2O$), 3.77 (d, 2H, *J* = 4.9 Hz, $CH_2O$), 4.06 (dddd, 1H, *J* = 6.0, 5.6, 4.9, 4.1 Hz, C*H*OH), 4.51 (d, 1H, *J* = 11.7 Hz, C*H*$_2$C$_6$H$_5$), 4.52 (d, 1H, *J* = 11.7 Hz, C*H*$_2$C$_6$H$_5$), 4.58 (d, 1H, *J* = 11.9 Hz, C*H*$_2$C$_6$H$_5$), 4.60 (d, 1H, *J* = 11.9 Hz, C*H*$_2$C$_6$H$_5$), 4.90 (dt, 1H, *J* = 4.9, 4.1 Hz, CHOMs), 7.26–7.34 (m, 10H, $H_{arom}$); $^{13}$C NMR ($CDCl_3$); $\delta$ 38.9, 70.1, 70.3, 70.7, 73.9, 74.0, 81.9, 128.3, 128.4, 128.9, 137.7, 137.9.

### 2.2. (2R,3R)-3-azido-1,4-bis(benzyloxy)butan-2-ol (3)

A mixture of monomesylated derivative **2** (5.17 g, 13.6 mmol) and sodium azide (1.25 g, 19.8 mmol) in DMF (35 mL) was stirred at reflux for 4 h. The solution was cooled at rt, the suspension was diluted with water (17 mL), and the mixture was extracted with diethylether (3× 17 mL). The combined organic phases were dried over $Na_2SO_4$. The solvent was evaporated under reduced pressure and the residual oil was purified by flash chromatography on silica gel using petroleum ether/ethyl acetate (1:1) as eluent to give azidoalcohol **3** as an yellow oil (3.25 g, 73% yield); $R_f$ 0.9 (petroleum ether/ethyl acetate 1/1); $[\alpha]_D^{25}$ = −10.5 (*c* 0.4, $CHCl_3$); $^1$H NMR ($CDCl_3$): $\delta$ 2.75 (d, 1H, *J* = 5.6 Hz, OH), 3.58 (d, 2H, *J* = 5.6 Hz, $CH_2O$), 3.70–3.80 (m, 3H, $CH_2O$, CHO), 3.98 (m, 1H, $CHN_3$), 4.58 (s, 2H, OC*H*$_2$Ph), 4.60 (s, 2H, OC*H*$_2$Ph), 7.30–7.50 (m, 10H, $H_{arom}$); $^{13}$C NMR ($CDCl_3$): 62.7, 70.5, 71.3, 73.9, 128.0, 128.1, 128.2, 128.3, 128.4, 128.9, 138.0, 138.1. Anal. calcd for $C_{18}H_{21}N_3O_3$: C, 66.04; H, 6.47; N, 12.84. Found: C, 65.82; H, 6.40; N, 12.39.

### 2.3. (2R,3R)-3-amino-1,4-bis(benzyloxy)butan-2-ol (4)

A solution of azidoalcohol **3** (1.8 g, 5.5 mmol) in ethanol (12 mL) was hydrogenated at rt for 48 h in the presence of Pd/C 10% (180 mg). The catalyst was removed by filtration over Celite. Evaporation of the solvent under reduced pressure afforded aminoalcohol **4** as a white solid (1.5 g, 91% yield) that was directly used for the next step; mp 55–57 °C; $[\alpha]_D^{25}$ = +1.4 (*c* 1.1, $CHCl_3$); $^1$H NMR ($CDCl_3$): $\delta$ 2.09 (bs, 3H, $NH_2$, OH), 3.14–3.17 (m, 1H, CHN), 3.44–3.80 (m, 5H, C*H*$_2$OBn, CHO), 4.53 (s, 2H, OC*H*$_2$Ph), 4.55 (s, 2H, OC*H*$_2$Ph), 7.26–7.37 (m, 10H, $H_{arom}$). The spectral data are in agreement with the literature [10].

### 2.4. Synthesis of aminoalcohols (5a–g)

Method A: A solution of aminoalcohol **4** (5.85 mmol) and aldehyde (8.77 mmol) in ethanol (10 mL) was stirred for 1.5 h at rt. $NaBH_4$ (630 mg, 16.65 mmol) was added, and the mixture was stirred at rt for 12 h. The solution was diluted with water (8 mL) and $CHCl_3$ (50 mL). Separation of the organic phase followed by evaporation of the solvent under reduced pressure gave a residue that was purified by flash-chromatography on silica using the appropriate solvent.

Method B: A mixture of aminoalcohol **4** (0.07 mmol), aldehyde (0.077 mmol), and $MgSO_4$ (1.25 mg, 0.077 mmol) in toluene (50 μL) was stirred at 80 °C for 6 h. The solvent was evaporated, and $CH_3OH$ (75 μL), acetic acid (15 μL), and $NaCNBH_3$ (8.56 mg, 0.14 mmol) were added. After being stirred for 12 h, aqueous 0.1 NaOH (1 mL) was added. Extraction of the mixture with ethyl acetate (5 mL), followed by evaporation of the solvent under reduced pressure gave a residue that was purified by flash-chromatography on silica using the appropriate solvent.

#### 2.4.1. (2R,3R)-3-(benzylamino)-1,4-bis(benzyloxy)butan-2-ol (5a)

80% yield (method A); oil; $R_f$ 0.6 (ethyl acetate); $[\alpha]_D^{25}$ = −4.2 (*c* 1.1, $CHCl_3$); $^1$H NMR ($CDCl_3$): $\delta$ 1.86 (bs, 2H, OH, NH), 2.95 (dt, 1H, *J* = 5.3, 5.2 Hz, CHN), 3.60 (d, 2H, *J* = 5.3 Hz, C*H*$_2$OBn), 3.61 (d, 2H, *J* = 5.3 Hz, C*H*$_2$OBn), 3.81 (d, 1H, *J* = 12.6 Hz, C*H*$_2$NH), 3.83 (d, 1H, *J* = 12.6 Hz, C*H*$_2$NH), 3.98 (dt, 1H, *J* = 5.3, 5.2 Hz, CHO), 4.49 (s, 2H, OC*H*$_2$Ph), 4.54 (s, 2H, OC*H*$_2$Ph), 7.28–7.40 (m, 15H, $H_{arom}$); $^{13}$C NMR ($CDCl_3$): $\delta$ 51.8, 58.6, 69.2, 70.1, 72.0, 73.7, 73.9, 127.4, 128.1, 128.2, 138.4, 138.5, 140.8. Anal. calcd for $C_{25}H_{29}NO_3$: C, 76.70; H, 7.47. Found: C, 76.89; H, 7.40.