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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 δ 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 ($CDCl_3$): δ 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 ($CDCl_3$); δ 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 ($CDCl_3$): δ 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 ($CDCl_3$): δ 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 ($CDCl_3$): δ 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 ($CDCl_3$): δ 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.

*2.4.2. (2R,3R)-1,4-bis(benzyloxy)-3-[(2-methylbenzyl)amino]butan-2-ol (**5b**)*

57% yield (method A) and 27% yield (method B); oil; R_f 0.4 (petroleum ether/ethyl acetate 2:1); $[\alpha]_D^{25} = -0.3$ (*c* 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 2.30 (s, 3H, CH_3), 2.95 (dt, 1H, *J* = 5.1 Hz, CHN), 3.57 (d, 2H, *J* = 5.1 Hz, C*H*$_2$OBn), 3.59 (d, 2H, *J* = 5.1 Hz, C*H*$_2$OBn), 3.74 (d, 1H, *J* = 12.9 Hz, C*H*$_2$NH), 3.77 (d, 1H, *J* = 12.9 Hz, C*H*$_2$NH), 3.96 (dt, 1H, *J* = 5.1 Hz, C*H*OH), 4.47 (s, 2H, OC*H*$_2$Ph), 4.51 (s, 2H, OC*H*$_2$Ph), 7.14–7.30 (m, 14H, H_{arom}); ^{13}C NMR ($CDCl_3$): δ 19.4, 50.0, 59.2, 69.2, 70.1, 72.3, 73.8, 73.9, 126.3, 127.5, 128.1, 128.2, 128.8, 129.1, 130.7, 136.9, 138.4, 138.5, 138.6. HRMS (EI) calcd for $C_{26}H_{32}NO_3$ $[M+H]^+$: 406.2380, found: 406.2380.

*2.4.3. (2R,3R)-1,4-bis(benzyloxy)-3-[(2-methoxybenzyl)amino]butan-2-ol (**5c**)*

27% yield (method B); yellow oil; R_f 0.1 (petroleum ether/ethyl acetate 2:3); $[\alpha]_D^{25} = +7.6$ (*c* 0.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 3.29 (dt, 1H, *J* = 3.4, 3.4 Hz, CHN), 3.43–3.82 (m, 7H, OCH_3, OC*H*$_2$Bn), 4.15–4.22 (m, 3H, CH_2N, CHO), 4.41–4.55 (m, 4H, OC*H*$_2$Ph), 6.81 (d, 1H, *J* = 8.1 Hz, H_{arom}), 6.91 (dd, 1H, *J* = 7.5 Hz, H_{arom}), 7.25–7.28 (m, 12H, CH_{arom}); ^{13}C NMR ($CDCl_3$): δ 47.3, 55.2, 5.1, 66.1, 67.1, 70.7, 73.5, 73.6, 110.5, 120.8, 127.9, 128.0, 128.1, 128.5, 130.5, 131.2, 137.1, 157.6. HRMS (EI) calcd for $C_{26}H_{32}NO_4$ $[M+H]^+$: 422.2331, found: 422.2330.

*2.4.4. (2R,3R)-1,4-bis(benzyloxy)-3-[(2-bromobenzyl)amino]butan-2-ol (**5d**)*

50% yield (method B); yellow oil; R_f 0.1 (petroleum ether/ethyl acetate 2:3); $[\alpha]_D^{25} = +2.0$ (*c* 0.25, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 2.83 (bs, 2H, NH, OH), 2.98 (dt, 1H, *J* = 5.2 Hz, CHN), 3.56–3.66 (m, 4H, C*H*$_2$OBn), 3.88 (d, 1H, *J* = 13.7 Hz, CH_2N), 3.4 (d, 1H, *J* = 13.7 Hz, CH_2N), 4.02 (dt, 1H, *J* = 5.2 Hz, CHO), 4.49 (s, 2H, OC*H*$_2$Ph), 4.57 (s, 2H, OC*H*$_2$Ph), 7.13 (dd, 1H, *J* = 7.5 Hz, H_{arom}), 7.20–7.40 (m, 12H, CH_{arom}), 7.39 (d, 1H, *J* = 7.5 Hz, H_{arom}); ^{13}C NMR ($CDCl_3$): δ 50.5, 57.3, 67.9, 67.9, 70.5, 72.2, 72.5, 124.5, 127.8, 128.1, 128.2, 128.9, 129.0, 130.6, 133.2, 138.4, 138.5, 139.7. HRMS (EI) calcd for $C_{25}H_{29}BrNO_3$ $[M+H]^+$: 470.1331, found: 470.1331.

*2.4.5. (2R,3R)-1,4-bis(benzyloxy)-3-[(3,5-dimethoxybenzyl)amino]butan-2-ol (**5e**)*

40% yield (method A or method B); oil; R_f 0.1 (petroleum ether/ethyl acetate 1:1); $[\alpha]_D^{25} = -20.4$ (*c* 0.25, $CHCl_3$): ^{1}H NMR ($CDCl_3$): δ 2.93 (dt, 1H, *J* = 5.3, 5.2 Hz, CHN), 3.58 (d, 2H, *J* = 5.3 Hz, C*H*$_2$OBn), 3.60 (d, 2H, *J* = 5.3 Hz, C*H*$_2$OBn), 3.74 (s, 2H, NCH_2), 3.75 (s, 6H, OCH_3), 3.96 (dt, 1H, *J* = 5.3, 5.2 Hz, CHO), 4.47 (s, 2H, OC*H*$_2$Ph), 4.52 (s, 2H, OC*H*$_2$Ph), 6.35 (s, 1H, H_{arom}), 6.48 (s, 2H, H_{arom}), 7.28–7.33 (m, 10H, H_{arom}); ^{13}C NMR ($CDCl_3$): δ 51.8, 55.7, 58.5, 69.2, 70.0, 72.3, 73.8, 73.8, 99.4, 106.3, 128.0, 128.1, 128.2, 128.8, 138.4, 138.5, 143.3, 161.2. Anal. calcd for $C_{27}H_{33}NO_5$: C, 71.82; H, 7.37. Found: C, 71.57; H, 7.25.

*2.4.6. (2R,3R)-1,4-bis(benzyloxy)-3-[(mesitylmethyl)amino]butan-2-ol (**5f**)*

37% yield (method A); oil; R_f 0.6 (petroleum ether/ethyl acetate 1:1); $[\alpha]_D^{25} = +11.8$ (*c* 1.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 2.27 (s, 3H, CH_3), 2.33 (s, 3H, CH_3), 2.42 (s, 3H, CH_3), 3.00 (dt, 1H, *J* = 5.3 Hz, CHN), 3.54–3.77 (m, 6H, CH_2N, C*H*$_2$OBn), 4.01 (dt, 1H, *J* = 5.2 Hz, CHO), 4.49 (s, 2H, OC*H*$_2$Ph), 4.56 (d, 1H, *J* = 12.1 Hz, OC*H*$_2$Ph), 4.57 (d, 1H, *J* = 12.1 Hz, OC*H*$_2$Ph), 6.85 (s, 1H, H_{arom}), 6.89 (s, 1H, H_{arom}), 7.27–7.29 (m, 10H, H_{arom}); ^{13}C NMR ($CDCl_3$): δ 18.3, 18.4, 19.9, 57.9, 58.6, 67.6, 68.4, 70.7, 72.3, 72.4, 126.6, 126.7, 126.8, 127.2, 127.3, 127.9, 128.0, 136.6, 138.7. Anal. calcd for $C_{28}H_{35}NO_3$: C, 77.56; H, 8.14. Found: C, 77.64; H, 8.35.

*2.4.7. (2R,3R)-1,4-bis(benzyloxy)-3-[(2-naphtylmethyl)amino]butan-2-ol (**5g**)*

30% yield (method B); oil; R_f 0.4 (petroleum ether/ethyl acetate 2:3); $[\alpha]_D^{25} = +5.8$ (*c* 0.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 2.99 (dt, 1H, *J* = 5.3, 5.2 Hz, CHN), 3.61 (d, 2H, *J* = 5.2 Hz, C*H*$_2$OBn), 3.62 (d, 2H, *J* = 5.1 Hz, C*H*$_2$OBn), 3.99 (d, 1H, *J* = 10.5 Hz, CH_2N), 3.96 (d, 1H, *J* = 10.5 Hz, CH_2N), 3.98 (d, 1H, *J* = 10.5 Hz, CH_2N), 4.01 (dt, 1H, *J* = 5.3, 5.2 Hz, CHOH), 4.49 (s, 2H, OC*H*$_2$Ph), 4.53 (s, 2H, OC*H*$_2$Ph), 7.28–7.38 (m, 10H, H_{arom}), 7.43–7.50 (m, 3H, H_{arom}), 7.70–7.90 (m, 43H, H_{arom}); ^{13}C NMR ($CDCl_3$): δ 51.9, 58.5, 69.1, 70.1, 72.2, 73.8, 73.9, 125.8, 126.0, 126.3, 126.4, 127.0, 128.1, 128.2, 128.5, 128.9, 133.8, 138.4. HRMS (EI) calcd for $C_{29}H_{32}NO_3$ $[M+H]^+$: 442.2382, found: 442.2380.

*2.5. (2R,3R)-1,4-bis(benzyloxy)-3-[(cyclohexylmethyl)amino]butan-2-ol (**5h**)*

A solution of azide **3** (300 mg, 0.92 mmol) and cyclohexanecarbaldehyde (103 mg, 0.92 mmol) in CH_3OH (12 mL) was stirred under hydrogen in the presence of Pd/C 10% (40 mg) for 48 h. The mixture was filtered on Celite, the solvent was evaporated under reduced pressure, and the residue was purified by flash chromatography on silica gel using petroleum ether/ethyl acetate (2:3) as eluent to give aminoalcohol **5h** as an yellow oil (76.8 mg, 21% yield); R_f 0.1 (petroleum ether/ethyl acetate 2:3); $[\alpha]_D^{25} = +9$ (*c* 0.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.18–1.28 (m, 6H, CH_2, CH), 1.67–1.71 (m, 5H, CH_2), 2.37 (dd, 1H, *J* = 11.2, 6.6 Hz, CH_2N), 2.47 (dd, 1H, *J* = 11.2, 6.6 Hz, CH_2N), 2.84 (dt, 1H, *J* = 5.2, 5.1 Hz, CHN), 3.55 (d, 4H, *J* = 5.2 Hz, C*H*$_2$OBn), 3.91 (dt, 1H, *J* = 5.1 Hz, CHO), 4.48 (s, 2H, OC*H*$_2$Ph), 4.56 (s, 2H, OC*H*$_2$Ph), 7.31–7.37 (m, 10H, H_{arom}); ^{13}C NMR ($CDCl_3$): δ 26.4, 26.5, 27.1, 31.8, 38.8, 54.7, 59.6, 69.3, 69.7, 72.3, 73.7, 73.9, 128.1, 128.2, 128.3, 128.8, 138.0, 138.5. Anal. calcd for $C_{25}H_{35}NO_3$: C, 75.53; H, 8.87. Found: C, 75.69; H, 8.83.

2.6. (2R,3R)-1,4-bis(benzyloxy)-3-(dibenzylamino)butan-2-ol (6)

A mixture of aminoalcohol **5a** (390 mg, 1 mmol), Cs_2CO_3 (325 mg, 1 mmol), and benzyl bromide (187 mg, 1.1 mmol) in toluene (1.5 mL) and acetonitrile (0.5 mL) was stirred at reflux for 1 h. The mixture was cooled at rt. After filtration, the solvent was evaporated under reduced pressure to give a residue that was purified by flash-chromatography using ethyl acetate/petroleum ether (1:5) as eluent affording aminoalcohol **6** as an oil (235 mg, 60% yield); R_f 0.4 (petroleum ether/ethyl acetate 5:1); $[\alpha]_D^{25} = -42$ (*c* 0.5, $CHCl_3$); ^{1}H RMN ($CDCl_3$) δ 2.85 (bs, 1H, OH), 2.99–3.05 (m, 1H, CHN), 3.36 (dd, 1H, *J* = 9.6, 6.5 Hz, C*H*$_2$OBn), 3.72 (d, 2H, *J* = 13.8 Hz, C*H*$_2$OBn), 3.83 (dd, 1H, *J* = 9.6, 3.2 Hz, C*H*$_2$OBn), 3.90 (s, 2H, CH_2N), 3.96 (d, 1H, *J* = 10.9 Hz, CH_2N), 3.97 (d, 1H, *J* = 10.9 Hz, CH_2N), 4.13 (m, 1H, CHO), 4.47 (d, 1H, *J* = 11.9 Hz, OC*H*$_2$Ph), 4.58 (d, 1H, *J* = 11.9 Hz, OC*H*$_2$Ph), 4.60 (d, 1H, *J* = 12.0 Hz, OC*H*$_2$Ph), 4.65 (d, 1H, *J* = 12.0 Hz, OC*H*$_2$Ph), 7.26–7.45 (m, 20H, H_{arom}); ^{13}C NMR ($CDCl_3$) δ 55.7, 58.7, 68.3, 70.2, 73.1, 73.6, 73.8, 127.3, 128.0, 128.1, 128.3, 128.6, 128.7, 128.8, 129.0, 129.6, 138.5, 140.4. Anal. calcd for $C_{25}H_{29}NO_3$: C, 76.70; H, 7.47. Found: C, 76.69; H, 7.26.

2.7. (2S,3R)-3-azido-1,4-bis(benzyloxy)butan-2-ol (7)

To a solution of azide **3** (1.4 g, 4.32 mmol) dissolved in THF (15 mL) was added at 0 °C a solution of $ClCH_2COOH$ (0.82 g, 8.64 mmol) in THF (15 mL). Then a solution of PPh_3 (2.27 g, 8.64 mmol) in THF (7.5 mL) was added and the solution was stirred at 0 °C for 30 min. DEAD (1.34 mL, 8.64 mmol) was slowly added and the solution was stirred at rt for 24 h. Filtration of triphenylphosphine oxide followed by evaporation of the solvent gave the chloroacetic ester that was dissolved in CH_3OH (10 mL). To this solution was added at 0 °C a solution of CH_3ONa (233 mg, 4.32 mmol) in CH_3OH (10 mL), and the mixture was stirred for 12 h at rt. The solvent was evaporated under reduced pressure, a saturated aqueous solution of NaCl (12 mL) was added, and the mixture was extracted with CH_2Cl_2 (3× 12 mL). Evaporation of the solvent gave a residue that was purified by flash-chromatography using ethyl acetate/petroleum ether (1:2) as eluent to give azidoalcohol **7** as an oil (406 mg, 29% yield); R_f 0.6 (petroleum ether/ethyl acetate 2:1); $[\alpha]_D^{25} = -24.8$ (*c* 1.1, $CHCl_3$); ^{1}H RMN ($CDCl_3$): δ 2.75 (d, 1H, *J* = 5.1 Hz, OH), 3.57 (m, 1H, C*H*N_3), 3.72–3.80 (m, 4H, C*H*$_2$OBn), 3.96–3.99 (m, 1H, CHO), 4.57 (s, 2H, OC*H*$_2$Ph), 4.60 (s, 2H, OC*H*$_2$Ph), 7.35–7.39 (m, 10H, H_{arom}). The spectral data are in agreement with the literature [11].

2.8. (2S,3R)-3-amino-1,4-bis(benzyloxy)butan-2-ol (8)

A solution of azidoalcohol **7** (416 mg, 1.21 mmol) in ethanol (10 mL) was hydrogenated at room temperature for 48 h in the presence of Pd/C 10% (42 mg). The catalyst was removed by filtration over Celite. Evaporation of the solvent under reduced pressure afforded aminoalcohol **8** as a white solid (376 mg, 97% yield) that was directly used for the next step; mp 49–52 °C; $[\alpha]_D^{25} = +6.6$ (*c* 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 2.14 (bs, 3H, NH_2, OH), 3.07–3.12 (m, 1H, C*H*NH_2), 3.41–3.58 (m, 4H, C*H*$_2$OBn), 3.69–3.73 (m, 1H, C*H*OH), 4.50 (s, 2H, OC*H*$_2$Ph), 4.52 (s, 2H, OC*H*$_2$Ph), 7.24–7.33 (m, 10H, H_{arom}). The spectral data are in agreement with the literature [12].

2.9. (2S,3R)-3-(benzylamino)-1,4-bis(benzyloxy) butan-2-ol (9)

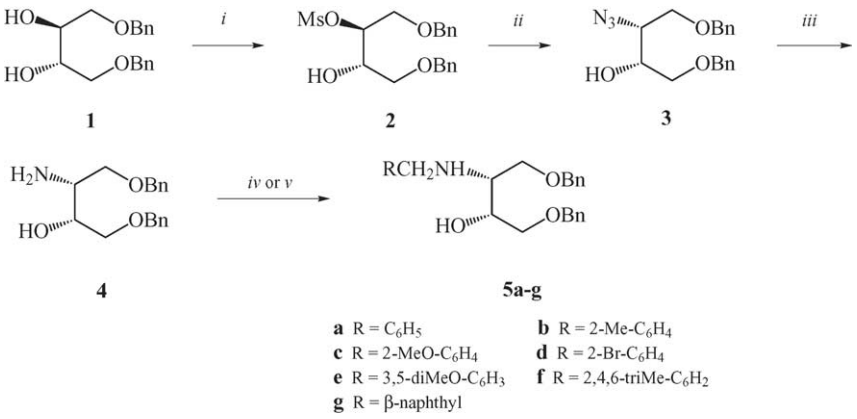
A solution of aminoalcohol **8** (415 mg, 1.4 mmol) and benzaldehyde (0.19 mL, 2.1 mmol) in C_2H_5OH (10 mL) was stirred at rt for 2 h. $NaBH_4$ (149 mg, 3.9 mmol) was added, and the mixture was stirred during 12 h at rt. After addition of water (20 mL), the mixture was extracted with $CHCl_3$ (2× 10 mL). Evaporation of the solvent under reduced pressure gave a residue that was purified by flash-chromatography using ethyl acetate/petroleum ether (1:1) as eluent to afford aminoalcohol **8** as an oil (337 g, 50% yield); R_f 0.5 (petroleum ether/ethyl acetate 1:1); $[\alpha]_D^{25} = -19.6$ (*c* 0.75, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 2.91–2.94 (m, 1H, CHN), 3.45–3.90 (m, 7H, CHO, C*H*$_2$OBn, PhC*H*$_2$N), 4.49 (s, 2H, OC*H*$_2$Ph), 4.54 (s, 2H, OC*H*$_2$Ph), 7.31–7.39 (m, 15H, H_{arom}); ^{13}C NMR ($CDCl_3$): δ 52.3, 58.6, 69.8, 70.4, 72.0, 73.7, 73.8, 127.4–129.0, 138.4, 138.6, 140.6.

2.10. Typical asymmetric hydrogen transfer reduction of ketones

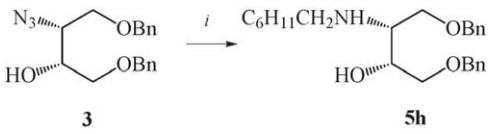
The catalyst was prepared in a Schlenk tube by stirring the organometallic precursor (2.56×10^{-2} mmol) and the ligand (5.12×10^{-2} mmol) in *i*-PrOH (5 mL) at 70 °C for 1 h. To this solution cooled to rt was added a solution of the ketone (0.51 mmol) and KOH (0.13 mmol) in *i*-PrOH (5 mL). The mixture was then stirred at the desired temperature for the time indicated. The conversion and the enantiomeric excess were determined by gas chromatography on the crude mixture using a capillary Quadrex OV1 column and a capillary Cyclodex-β column, respectively.

3. Results and discussion

(*2S,3S*)-1,4-bis(benzyloxy)butane-2,3-diol (**1**) was prepared starting from (+)-diethyl tartrate according to literature procedures in a four step synthesis [9,13]. Mesylation of diol **1** in C_5H_5N at 0 °C using 1 equiv of MsCl afforded monomesylate **2** in 45% yield after column chromatography, together with a very small amount of the bismesylate (less than 5%) (Scheme 1). Reaction of mesylate **2** with sodium azide in DMF at reflux gave azide **3** in 73% yield. Aminoalcohol **4** was obtained in 91% yield by treatment of azide **3** under hydrogen in C_2H_5OH in the presence of Pd/C.



Scheme 1. Reagents and conditions: (i) MsCl, C_5H_5N, 0 °C; (ii) NaN_3, DMF, reflux; (iii) H_2, Pd/C, rt; (iv) for compounds **5a**–**c** and **5e**–**f** RCHO, C_2H_5OH, rt, then $NaBH_4$; (v) for compounds **5b**–**e** and **5g** RCHO, C_2H_5OH, $MgSO_4$, 80 °C, then $Na(CN)BH_3$, CH_3CO_2H, CH_3OH, rt.

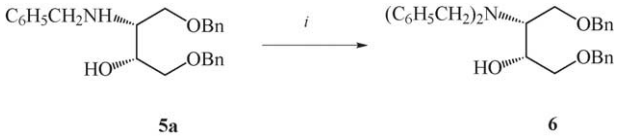


Scheme 2. Reagents and conditions: (i) $C_6H_{11}CHO$, H_2, Pd/C, CH_3OH, rt.

Transformation of aminoalcohol **4** to *N*-alkylated aminoalcohols **5a**–**g** bearing a secondary aminofunction (Scheme 1) was performed by condensation of compound **4** with the appropriate aromatic aldehyde in C_2H_5OH, followed by the in situ reduction of the intermediate oxazoline for **5a**–**b** and **5e**–**f** [14], or by condensation of the appropriate aldehyde in toluene at 80 °C in the presence of $MgSO_4$, followed by the in situ reduction of the intermediate imine by $Na(CN)BH_3$ in CH_3OH for **5c**–**d**, **5e**, and **5g** [15].

Aminoalcohol **5h**, bearing a cyclohexylmethyl substituent, was obtained from azide **3** by condensation with cyclohexanecarbaldehyde in CH_3OH under hydrogen in the presence of Pd/C (Scheme 2) [16].

Condensation of aminoalcohol **5a** with benzyl bromide in the presence Cs_2CO_3 in toluene/CH_3CN afforded *N*,*N*-dibenzyl aminoalcohol in 60% yield (Scheme 3) [17].

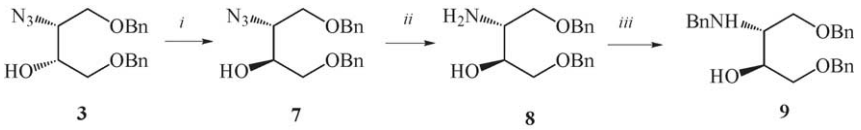


Scheme 3. Reagents and conditions: (i) $C_6H_5CH_2Br$, Cs_2CO_3, toluene/acetonitrile, 90 °C.

Finally (*2R*,*3R*)-3-azido-1,4-bis(benzyloxy)butan-2-ol (**3**) was transformed into (*2S*,*3R*)-3-azido-1,4-bis(benzyloxy) butan-2-ol (**7**) via a Mitsunobu reaction in 29% yield [18] (Scheme 4). Reduction of azide **7** under the above mentioned conditions for azide **3** afforded (*2S*,*3R*)-aminoalcohol **8** in 97% yield. Condensation of aminoalcohol **8** with benzaldehyde in C_2H_5OH, followed by the in situ reduction gave (*2S*,*3R*)-aminoalcohol **9** in 50% yield.

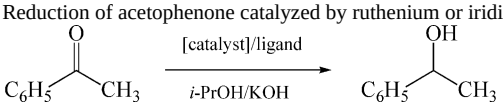
Ligands **4**, **5a**, and **6** were initially studied in the reduction of acetophenone. The ruthenium(II) or iridium(I) complexes were prepared in situ by heating a mixture of $[Ru(p\text{-cymene})Cl_2]_2$ or $[Ir(COD)Cl]_2$ and the appropriate ligand in 2-propanol for 1 h under argon. Then the catalyst solution was cooled to room temperature, and acetophenone in 2-propanol was introduced together with potassium hydroxide. The results are summarized in Table 1.

Reduction of acetophenone at rt in the presence of primary aminoalcohol **4** as the chiral ligand was not quantitative using ruthenium(II) or iridium(I) complex, the highest enantioselectivity (49% ee) being observed with the ruthenium complex (Table 1, entries 1–2). The use of *N*-benzyl aminoalcohol **5a** associated with $[Ru(p\text{-cymene})Cl_2]_2$ gave a more active catalyst, quantitative conversion being obtained at rt after 20 h with ee up to 72% (Table 1, entry 3). Increasing the temperature to 50 °C gave a more active catalyst, but lower enantioselectivity (55% ee) (Table 1, entry 4). With the catalyst obtained by mixing $[Ir(COD)Cl]_2$ and ligand **5a**, lower yields and enantioselectivities were obtained even at 50 °C (Table 1, entries 5 and 6). Finally *N*,*N*-dibenzyl aminoalcohol **6** gave a less active and enantioselective catalyst (49% ee) (Table 1, entry 7).



Scheme 4. Reagents and conditions: (i) PPh_3, DEAD, $ClCH_2CO_2H$, THF, 0 °C, then CH_3ONa, CH_3OH, 0 °C; (ii) H_2, Pd/C, rt; (iii) C_6H_5CHO, C_2H_5OH, rt, then $NaBH_4$.

Table 1
Reduction of acetophenone catalyzed by ruthenium or iridium complexes associated with ligands **4**, **5a** and **6**[a]

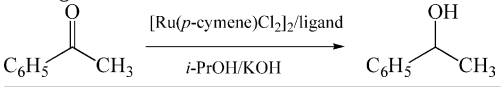


Entry	Complex	Ligand	T (°C)	Time (h)	Conversion (%)[b]	ee (%) (configuration)[c]
1	[Ru(*p*-cymene)Cl_2]$_2$	**4**	25	4	84	49 (*S*)
2	[Ir(COD)Cl]$_2$	**4**	25	3	72	30 (*S*)
3	[Ru(*p*-cymene)Cl_2]$_2$	**5a**	25	20	96	72 (*S*)
4	[Ru(*p*-cymene)Cl_2]$_2$	**5a**	50	2	85	55 (*S*)
5	[Ir(COD)Cl]$_2$	**5a**	25	3	10	16 (*S*)
				120	88	28 (*S*)
6	[Ir(COD)Cl]$_2$	**5a**	50	5	51	19 (*S*)
7	[Ru(*p*-cymene)Cl_2]$_2$	**6**	25	24	52	49 (*S*)

[a] Reactions conditions: [acetophenone] = 0.5 M in *i*-PrOH; [acetophenone]:[metal]:[ligand]:[KOH] = 20:1:2:5.
[b] Determined by capillary GC on a Quadrex OV1 column.
[c] Determined by capillary GC on a Cyclodex-β column and by comparison with an authentic sample.

We then studied the influence of the substituent on the nitrogen on both the activity and the enantioselectivity in the reduction of acetophenone using [Ru(*p*-cymene)Cl_2]$_2$ as the catalyst precursor. Ligands **5b**–**d**, bearing *para*-substituted methyl, methoxy, and bromide group, respectively, gave rise to decrease on reaction rates compared to ligand **5a**, with lower enantioselectivity (9, 45, and 52%, respectively) (Table 2, entries 2–4). The observed lower activities are probably due to steric factors. The same trend (lower activity and enantioselectivity) was observed using ligand **5f**, bearing three methyl groups at position 2, 4, and 6 (Table 2, entry 6). Conversely, ligand **5e**, bearing two *meta*-substituted methoxy groups, gave rise to improved reaction rate, with only minimal effect on the enantioselectivity (66% ee) (Table 2, entry 5). Ligand **5g**, bearing a β-naphtylmethyl group at nitrogen, gave phenylethanol with enantioselectivity up to 73%, but with low conversion (Table 2, entry 7). Finally, ligand **5h**, with a cyclohexylmethyl substituent on the nitrogen, gave a catalyst as enantioselective as that obtained using ligand **5a** (ee up to 60%), but the conversion was again lower (Table 2, entry 8).

Table 2
Reduction of acetophenone catalyzed by [Ru(*p*-cymene)Cl_2]$_2$ associated with ligands **5a**–**h**, **8**, and **9**[a]



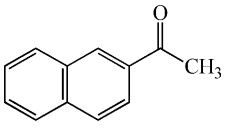
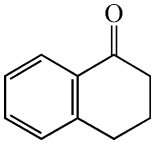
Entry	Ligand	Time (h)	Conversion (%)[b]	ee (%) (configuration)[c]
1	**5a**	20	96	72 (*S*)
2	**5b**	1	15	9 (*S*)
3	**5c**	1	11	36 (*S*)
		22	24	45 (*S*)
4	**5d**	2	25	52 (*S*)
5	**5e**	3	69	66 (*S*)
		24	96	66 (*S*)
6	**5f**	1	18	4 (*S*)
		24	20	3 (*S*)
7	**5g**	1	22	73 (*S*)
		72	74	62 (*S*)
8	**5h**	1	47	60 (*S*)
9	**8**	1	95	37 (*R*)
10	**9**	24	74	46 (*R*)
		72	91	47 (*R*)

[a] Reactions conditions: [acetophenone] = 0.5 M in *i*-PrOH; [acetophenone]:[Ru]:[ligand]:[KOH] = 20:1:2:5.
[b] Determined by capillary GC on a Quadrex OV1 column.
[c] Determined by capillary GC on a Cyclodex-β column and by comparison with an authentic sample.

(*2S*,*3R*)-aminoalcohol **8**, having the reverse configuration at carbon bearing the hydroxyl function, and the *N*-benzyl analogue, were also tested as ligands in the reduction of acetophenone using [Ru(*p*-cymene)Cl_2]$_2$ as the catalyst precursor (Table 2, entries 9 and 10). They gave less enantioselective catalysts (49 and 37% ee, respectively), although the later one showed a very high activity. It is noteworthy that ligands **4** and **5a** gave the (*S*) enantiomer, when ligands **8** and **9** afforded the (*R*) enantiomer; these results showed that the stereogenic centre bearing the hydroxyl function is the predominant one in controlling the absolute reduction stereochemistry, in agreement with previous results [3].

We finally examined the reduction of various ketones using [Ru(*p*-cymene)Cl_2]$_2$ associated with ligands **4** or **5a** (Table 3). In the reduction of alkyl phenyl ketones, the highest enantioselectivities were obtained using *N*-benzyl aminoalcohol **5a** as the ligand; increasing the steric bulk of the alkyl moiety of the ketone from CH_3 to C_2H_5, and *i*-C_3H_7, decreased the enantioselectivity from 72 to 62%, and then 37%, respectively (Table 3, entries 2, 3, and 5). The use of aminoalcohol **4** gave lower enantioselectivities (Table 3, entries 1 and 4). Introduction of a methoxy group on the *para* position of the aromatic ring decreased the enantioselectivity of the reduction (Table 3, entries 6 and 7), whereas a nitro group or a bromide gave almost the same ee (Table 3, entries 8–10). However the presence of a methoxy group at the *ortho* position of the phenyl ring gave almost the same enantioselectivity (65% ee) using **5a** as the chiral ligand (Table 3, entry 11). Finally when β-naphtoacetophenone was reduced with ee up to 57% at rt (Table 3, entry 12), α-tetralone gave the corresponding

Table 3
Reduction of various ketones catalyzed by [Ru(*p*-cymene)Cl_2]$_2$ associated with ligands **4** or **5a**[a]

Entry	Substrate	Ligand	Time (h)	Conversion (%)[b]	ee (%) (configuration)[c]
1	$C_6H_5COCH_3$	**4**	4	84	49 (*S*)
2	$C_6H_5COCH_3$	**5a**	20	96	72 (*S*)
3	$C_6H_5COC_2H_5$	**5a**	20	50	62 (*S*)
4	C_6H_5CO-*i*-C_3H_7	**4**	4	65	25 (*S*)
5	C_6H_5CO-*i*-C_3H_7	**5a**	20	71	37 (*S*)
6	4-$CH_3OC_6H_4COCH_3$	**4**	3	100	16 (*S*)
7	4-$CH_3OC_6H_4COCH_3$	**5a**	4	65	38 (*S*)
			24	81	37 (*S*)
8	4-$NO_2C_6H_4COCH_3$	**4**	1	65	40 (*S*)
9	4-$NO_2C_6H_4COCH_3$	**5a**	24	75	72 (*S*)
10	4-$BrC_6H_4COCH_3$	**5a**	24	62	65 (*S*)
11	2-$CH_3OC_6H_4COCH_3$	**5a**	3	80	65 (*S*)
			22	99	65 (*S*)
12		**5a**	3	16	57 (*S*)
			6[d]	70	26 (*S*)
13		**5a**	24	52	80 (*S*)
			48	64	69 (*S*)

[a] Reactions conditions: [substrate] = 0.5 M in *i*-PrOH [ketone]:[Ru]:[ligand]:[KOH] = 20:1:2:5.
[b] Determined by capillary GC on a Quadrex OV1 column.
[c] Determined by capillary GC on a Cyclodex-β column and by comparison with an authentic sample.
[d] Reaction performed at 40 °C.

alcohol with ee up to 80%, but with lower conversion (Table 3, entry 13).

4. Conclusion

In summary, we have developed a new family of modulable ligands easily accessible and prepared from the readily inexpensive tartaric acid. The catalytic efficiency and enantioselectivity of these ligands have been studied in the hydrogen transfer reduction of various ketones in the presence of Ru(II) and Ir(I) complexes. The *N*-benzyl aminoalcohol associated with the Ru(II) complex gave the highest enantioselectivity, ee up to 80% being reached. Studies are currently in progress in order to optimize these ligands and particularly by modifying the nature of the protecting group.

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