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Asymmetric reduction of ketones catalyzed by α,α-diphenyl-(L)-prolinol modified with imidazolium ionic liquid and $BH_3{\cdot}SMe_2$ as a recoverable catalyst

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ABSTRACT

The synthesis of α,α-diphenyl-4-*trans*-hydroxy-(L)-prolinol modified with imidazolium based ionic liquids was carried out with *trans*-α,α-diphenyl-4-hydroxy-(L)-prolinol, 5-bromovaleric acid or 1,5-dibromopentane and imidazole. α,α-Diphenyl-4-hydroxy-(L)-prolinol modified with imidazolium ionic liquid was treated with $BH_3{\cdot}SMe_2$ which generate 1,3,2-oxazaborolidine, that acts as a catalyst for asymmetric reduction of prochiral ketones. α,α-Diphenyl-4-hydroxy-(L)-prolinol modified with imidazolium ionic liquids (PF_6 anion) with $BH_3{\cdot}SMe_2$ found to be an efficient catalyst (10 mol%) for the reduction of the acetophenone, gave 99% yield and 87–84% ee. The catalytic method has wide applicability for a variety of substrates. 1,3,2-oxazaborolidine containing ether linkage ionic liquid was recovered and reused up to 4 cycles with 99–91% yields and 87–81% ee's.

1. Introduction

The enantioselective reduction of prochiral ketones is an important transformation for the synthesis of chiral secondary alcohols [1,2]. Enantiopure secondary alcohols are important intermediates or chiral building blocks for the preparation of natural products, pharmaceuticals and agrochemicals. Alcohol functionality can be converted to other useful functional groups such as chloride [3–6], amine [7,8], azide [9] and fluoride [10–12]. Chiral 1,3,2-oxazaborolidine catalyzed asymmetric reduction of ketones in conjunction with BH_3.THF is one of most popular method which was developed by Hirao et al. and later improved by Corey and co-workers [13–20]. Numerous methods for asymmetric reduction of ketone using chiral 1,3,2-oxazaborolidine have been developed in homogenous medium at room temperature as well as higher temperatures [21–35]. Low molecular weight chiral 1,3,2-oxazaborolidines are difficult to separate from the product, if modified this can be recoverable and reusable for asymmetric reduction of ketones. In the recent past several researchers have been addressed to this issue by using fluorous tags [36], triazole linked dendimers [37], imidazolium-tagged sulfonamide [38], use of C_3-symmetric Tris(β-hydroxyphosphoramide) [39] and sulfonamide [40], and immobilization by covalent bond on polymer beads [41–44]. Maltsev et al., have been reported O-TMS-α,α-diphenyl-L-prolinol modified with an ionic liquid moiety for asymmetric Michael reaction of α,β-enals with dialkyl malonates, nitroalkanes and N-protected hydroxylamine [45–47]. Herein, we report the synthesis of α,α-diphenyl-L-prolinol containing ionic liquids (ILs) with imidazolium cation, and bromide, hexafluorophosphate and tetrafluoroborate anions (Fig. 1) with $BH_3{\cdot}SMe_2$ generate 1,3,2-oxazaborolidine as a catalysts for the asymmetric reduction of prochiral ketones using $BH_3{\cdot}SMe_2$ as hydride source.

2. Experimental

2.1. General details

All the ketones and $BH_3{\cdot}SMe_2$ (2M in THF) were used as recieved from commercial source. Proton and carbon nuclear magnetic resonance spectra (^1H and ^{13}C NMR, respectively) were recorded on 400 MHz (operating frequencies: ^1H, 400.13 MHz; ^{13}C, 100.61 MHz) Jeol-FT-NMR spectrometers at ambient temperature. The chemical shifts (δ) for all compounds are listed in parts per million downfield from tetramethylsilane using the NMR solvent as an

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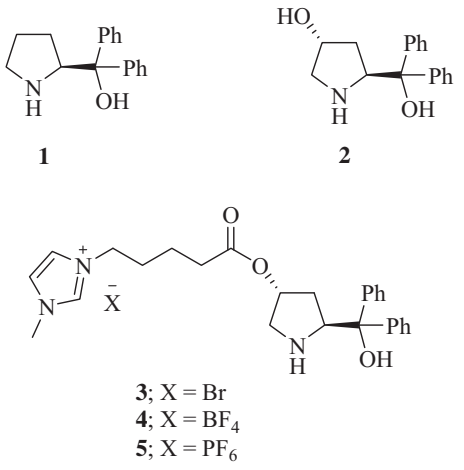

Fig. 1. Structures of α,α-diphenyl-L-prolinol and its ionic liquids.

internal reference. The reference values used for deuterated chloroform ($CDCl_3$) were 7.26 and 77.00 ppm for ^1H and ^{13}C NMR spectra, respectively. HRMS analysis was carried out using QSTAR XL Pro system microTOF-Q-II. Infrared spectra were recorded on a PerkinElmer FT-IR spectrometer. Thin layer chromatography was carried out using Merck Kieselgel 60 F254 silica gel plates. Column chromatography separations were performed using silica gel 230–400 mesh. All the new synthesized compounds were characterized by ^1H, ^{13}C NMR and HRMS and known compounds were characterized by ^1H and ^{13}C NMR. The experimental procedure for the known compounds were followed according to literature reports and given in supporting information (SI). The enantiomeric excess was determined on Shimadzu LC-2010HT using OD–H and AD–H chiral columns. The optical rotation was taken using Rudoplph digipol polarimeter.

2.2. General procedure of asymmetric reduction of ketones

In a schlenk tube, $BH_3{\cdot}SMe_2$ (0.55 mmol, 275 μL) was added in the solution of IL 5 (28 mg, 10 mol%) dissolved in THF (1 mL), under nitrogen atmosphere. The homogenous mixture was stirred and heated at 70 °C for 30 min. Later, a solution of ketone (0.5 mmol in THF (0.5 mL)) was added within 30 min. After the addition was completed, the solvent was evaporated under vacuum. An aqueous solution of 1M HCl (5 mL) was added and the product was extracted with DCM. The solvent was dried on anhydrous sodium sulfate and evaporated under reduced pressure. Crude residue was further purified by column chromatography on silica gel using hexane-ethyl acetate as eluent. Enantiomeric excesses of all alcohols were determined by HPLC analysis using Chiralcel OD–H/AD–H chiral column, isopropanol-*n*-hexane as mobile phase and HPLC conditions are given in SI.

2.3. Procedure for recycling of catalyst

After the fresh catalytic cycle, the solvent was removed under vaccum and hexane:diethyl ether (5 mL, 1:1) was added. The 1,3,2-oxazaborolidine of IL 5 or IL 15 was precipited out as viscous liquid and the product was in the solvent which was removed by syringe. The recovered catalyst was dissolved in THF (1 mL) and $BH_3{\cdot}SMe_2$ (250 μL, 0.50 mmol) was added, and resulting mixture was heated at 70 °C for 30 min. A solution of acetophenone (0.5 mmol in THF (0.5 mL)) was added within 30 min, after the addition was completed, the reaction progress was checked on TLC, and the solvent was evaporated under vacuum. Similar procedure was also followed for next catalytic run.

2.4. Synthesis of (2S,4R)-tert-butyl 4-((5-bromopentanoyl) oxy)-2-(hydroxydiphenylmethyl) pyrrolidine-1-carboxylate (10)

5-Bromopentanoic acid (0.81 g, 4.48 mmol) was added to a solution of *N,N'*-dicyclohexylcarbodiimide (DCC) (0.92 g, 4.48 mmol) and 4-dimethylaminopyridine (DMAP) (0.42 g, 0.1 mmol) in CH_2Cl_2 (20 mL) at 0 °C and then compound 9 (1.29 g, 3.5 mmol) was added in a 10 min. The reaction mixture was stirred at 0 °C for 1 h, later DCC (0.46 g, 2.24 mmol) and 5-bromopentanoic acid (0.40 g, 2.24 mmol) were added and the reaction mixture was refluxed for 30 min, precipitate was filtered off and washed with CH_2Cl_2 (3 × 25 mL). Organic filtrate was washed with conc. HCl (1.65 mL), saturated aqueous $NaHCO_3$ (2 × 15 mL), water (25 mL) and dried over Na_2SO_4. The solvent was evaporated by rotavapor and the product was isolated by column chromatography using a mixture of hexane/Et_2O (8:2) to afford brown solid (1.78 g, 96%). Mp = 108.1 °C; = + 33.9 (c 0.8, chloroform); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.42–7.23 (m, 10H), 5.03 (dd, *J* = 8.79, 5.86 Hz, 1H), 4.72 (brs, 1H), 3.54 (brs, 1H), 3.38 (t, *J* = 6.59 Hz, 2H), 3.01 (brs, 1H), 2.28–2.22 (m, 3H), 2.14–2.11 (m, 1H), 1.87–1.83 (m, 2H), 1.76–1.71 (m, 2H), 1.34 (brs, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.7, 145.2, 143.2, 128.1 (2 C), 127.9 (2 C), 127.7 (2 C), 127.4 (2 C), 81.7, 73.0, 65.2, 53.5, 36.2, 33.3, 33.0, 32.0, 28.3, 23.4 ppm; IR (CH_2Cl_2, film): ν = 3433, 3058, 2963, 1730, 1679, 1407, 1259, 1165, 701 cm^{-1}.

2.5. Synthesis of 3-(5-(((3R,5S)-1-(tert-butoxycarbonyl)-5-(hydroxydiphenylmethyl) pyrrolidin-3-yl) oxy)-5-oxopentyl)-1-methyl-1H-imidazol-3-ium bromide (11)

The mixture of compound 10 (1.59 g, 3 mmol) and 1-methyl-1H-imidazole (0.49 g, 6 mmol) was heated at 100 °C for 10 min and then cooled to room temperature and washed with Et_2O (5 × 6 mL) to separate an excess of 1-methyl-1H-imidazole. The residue was dissolved in MeOH (1.5 mL) and Et_2O (30 mL) was added, ethereal layer was separated and the residue was washed with Et_2O (5 × 6 mL). The obtained product was dried under reduced pressure to afford 11 (1.80 g, 98%) as a brown hygroscopic liquid. = + 16.8 (c 1.6, chloroform); ^1H NMR (400 MHz, $CDCl_3$): δ = 9.74 (s, 1H), 7.37–6.97 (m, 12H), 4.76–4.75 (m, 1H), 4.04–4.01 (m, 2H), 3.73 (s, 3H), 3.52–3.48 (m, 2H), 2.04–2.01 (m, 3H), 1.87–1.84 (m, 1H), 1.64 (d, *J* = 5.86 Hz, 2H), 1.33–1.29 (m, 2H), 1.03 (brs, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.4, 145.7, 136.5, 127.9 (2C), 126.9 (2C), 126.8 (2C), 126.6 (2C), 126.0, 123.5, 122.1, 80.8, 74.6, 63.5, 53.3, 48.3, 35.7, 32.6, 31.2, 28.7, 27.3, 20.8 ppm; IR (CH_2Cl_2, film): ν = 3419, 3108, 2929, 1726, 1676, 1409, 1392, 1232, 1167, 701 cm^{-1}.

2.6. Synthesis of (2R,4R)-tert-butyl4-((5-bromopentyl) oxy)-2-(hydroxydiphenylmethyl) cyclopentanecarboxylate (12)

Compound 9 (2 g, 5.4 mmol) was dissolved in dry dichloromethane (50 mL) and triethylamine (0.904 mL, 6.5 mmol) and 1,5-dibromopentane (0.881 mL, 6.5 mmol) were added and reaction mixture was allowed to stir at r.t. for 15 min, then anhydrous KOH (0.151 g, 2.7 mmol) was added. The resulting heterogeneous reaction mixture was allowed to stir at r.t. for overnight. The residue was diluted with DCM and washed with saturated aq. solution of $NaHCO_3$, water and dried over Na_2SO_4. The solvent was evaporated by rotavapor and product was purified by column chromatography with Hexane/EtOAc (80:20). The product was obtained as light yellowish liquid (1.791 g, 64%).$[\alpha]_D^{25}$ = −23.0 (c 1.26, dichloromethane); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.15 (m, 10H), 4.94 (t, 1H *J* = 7.63 Hz), 3.36–3.28 (t, 3H, *J* = 6.87 Hz), 3.14–3.09 (m, 3H), 2.03–2.0 (m, 2H), 1.79–1.72 (m, 2H,), 1.45–1.24 (m, 13H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$):