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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.

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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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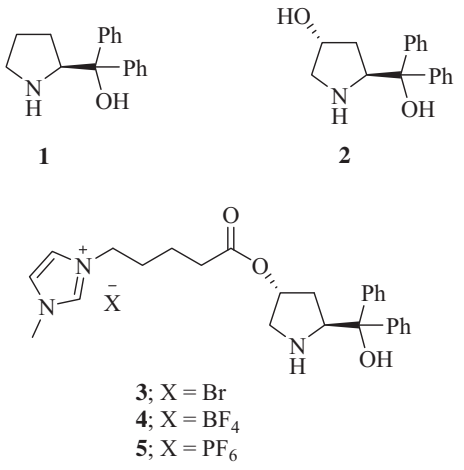


Fig. 1. Structures of α,α-diphenyl-L-prolinol and its ionic liquids.

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%).[= −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, $CDCl_3$): δ = 145.9, 143.3, 127.8

(2C), 127.4 (2C), 127.1 (2C), 127.08 (2C), 81.5, 80.6, 68.5, 64.6, 52.7, 36.3, 33.6, 32.4, 28.7, 28.1, 24.7 ppm.

2.7. Synthesis of 3-(6-((3R,5S)-1-(tert-butoxycarbonyl)-5-(hydroxydiphenylmethyl) pyrrolidin-3-yl) hexyl)-1-methyl-1H-imidazol-3-ium bromide (13)

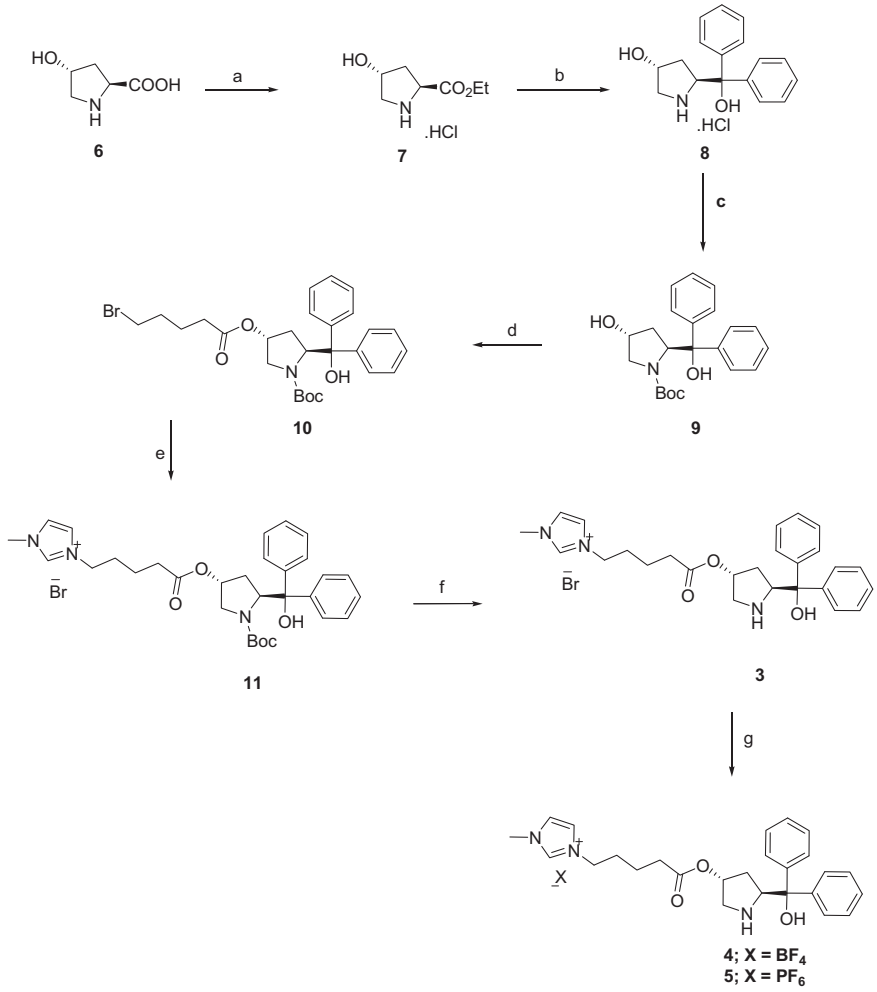
Compound 12 (1.034 g, 2 mmol) and 1-methyl imidazole (1.2eq, 0.191 mL, 2.4 mmol) was heated at 100 °C for 30 min, cooled to room temperature and washed with diethyl ether (5 × 5 mL) to remove excess 1-methyl imidazole. The obtained product was dried under reduced pressure to afford light yellowish solid (1.15 g, 96%). [= −67.2 (c 2.2, dichloromethane); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.59 (s, 1H), 7.38–7.25 (m, 12H), 4.95 (s, 1H), 4.13 (brs, 2H), 3.90 (brs, 4H), 3.49–3.47 (m, 2H), 3.21–3.19 (m, 2H), 2.07 (brs, 2H), 1.82 (brs, 2H), 1.48–1.19 (m, 13H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.3, 143.2, 137.4, 129.6 (2C), 127.9 (2C), 127.5 (2C), 127.1 (2C), 123.8, 122.06, 81.8, 80.9, 67.8, 65.6, 52.8, 49.5, 36.3, 36.1, 29.8, 28.8, 28.2, 22.8 ppm.

2.8. Synthesis of 3-(6-((3R,5S)-5-(hydroxydiphenylmethyl) pyrrolidin-3-yl) hexyl)-1-methyl-1H-imidazol-3-ium bromide (14)

Compound 13 (1.0 g, 1.67 mmol) was dissolved in dry dichloromethane (7.5 mL), trifluoroacetic acid (1.5 mL) was added under inert atmosphere. The reaction mixture was allowed to stir for 4 h at r.t. The solvent was evaporated by rotavapor and crude product was washed with diethyl ether (5 mL). The product 14 was obtained as light yellowish liquid (0.730 g, 88%). [= −11.5 (c 0.68, dichloromethane); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.21 (s, 1H), 7.54 (d, 2H, J = 7.63 Hz), 7.38–7.21 (m, 10H), 4.80 (dd, 1H, J = 12.21, 6.10 Hz), 4.24 (t, 2H, J = 6.87 Hz), 4.02–3.93 (m, 5H), 3.34–3.28 (m, 2H), 3.16 (d, 1H, J = 12.21 Hz), 1.92–1.81 (m, 2H), 1.63–1.55 (m, 2H), 1.43–1.35 (m, 2H), 1.25 (brs, 2H), 1.18–1.10 (m, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.1, 139.9, 128.6 (2C), 128.4 (2C), 127.7, 125.9 (2C), 125.3 (2C), 123.4, 122.0, 85.9, 78.8, 68.6, 67.4, 53.4, 49.9, 35.8, 29.5, 28.8, 22.7 ppm.

2.9. Synthesis of 3-(6-((3R,5S)-5-(hydroxydiphenylmethyl) pyrrolidin-3-yl) hexyl)-1-methyl-1H-imidazol-3-ium hexaflourophosphate (15)

Compound 14 (0.500 g, 1 mmol) was dissolved in the mixture of methanol (7 mL) and water (20 mL). An aqueous solution of KPF_6 (0.36 g, 2 mmol, 10 mL) was added to the above solution. MeOH was removed at reduced pressure by rotavapor to give transparent solution. The aqueous phase was decanted off and the residue was dissolved in CH_2Cl_2 (35 mL), washed with 0.1 M solution of KPF_6 (2 × 10 mL) and dried over Na_2SO_4. The solvent was evaporated and residue was dried under reduced pressure to afford compound 15 (0.463 g, 82% yield). [= −18.5 (c 0.3, dichloromethane); ^{1}H NMR



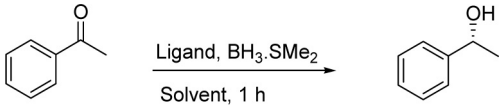
Scheme 1. (a) $SOCl_2$, ethanol, reflux, 4 h, 94%, (b) PhMgBr, Et_2O, reflux, 5 h, 70%, (c) $(Boc)_2O$, Et_3N, CH_2Cl_2, reflux, 1 h, 94%, (d) DCC, DMAP, 5-bromovalleric acid, CH_2Cl_2, reflux, 1.5 h, 96%, (e) 1-Methyl imidazole, 100 °C, 10 min, 98%, (f) TFA, CH_2Cl_2, 2 h, 85%, (g) KPF_6, MeOH/H_2O, 80%, and (h) $NaBF_4$, H_2O, 90%.

(400 MHz, $CDCl_3$): δ = 8.54 (s, 1H), 7.52 (d, 2H, J = 7.63 Hz), 7.37–7.20 (m, 11H), 4.79 (dd, 1H, J = 10.68, 4.58 Hz), 4.10 (t, 2H, J = 6.87 Hz), 4.02–3.99 (t, 1H, J = 5.34 Hz), 3.92 (dd, 1H, J = 12.21, 5.34 Hz), 3.84 (s, 3H), 3.37–3.28 (m, 2H), 3.15 (d, 1H, J = 12.21 Hz), 1.87–1.81 (m, 2H), 1.57–1.52 (m, 2H), 1.41–1.34 (m, 2H), 1.25 (brs, 2H), 1.15–1.08 (m, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.0, 139.9, 128.6 (2C), 128.4 (2C), 127.7, 125.9 (2C), 125.3 (2C), 123.4, 122.0, 85.9, 78.8, 68.6, 67.4, 53.4, 49.9, 35.8, 29.5, 28.8, 22.7 ppm.

3. Results and discussion

The α,α-diphenyl-(L)-prolinol modified with imidazolium ionic liquids (ILs) with tetrafluoroborate and hexafluorophosphate anions (4 and 5) were synthesized in a 80–90% yields by the reaction of α,α-diphenyl-(L)-prolinol @ IL imidazolium bromide (3) with $NaBF_4$ and KPF_6 (Scheme 1). The α,α-diphenyl-(L) prolinol @ IL imidazolium bromide (3) was obtained in a 83.3% yield in a two steps by the reaction of (2*S*,4*R*)-*tert*-butyl-4-((5-bromopentanoyl) oxy)-2-(hydroxydiphenylmethyl) pyrrolidine-1-carboxylate (10) and 1-methyl imidazole at 100 °C and followed by *N*-Boc deprotection using trifluoroacetic acid (TFA). The ester (10) was synthesized in a 95% yield by the reaction of (2*S*,4*R*)-*tert*-butyl-4-hydroxy-2-(hydroxydiphenylmethyl) pyrrolidine-1-carboxylate (9) and 5-bromopentanoic acid in the presence of DCC/DMAP in CH_2Cl_2. (2*S*,4*R*)-*tert*-butyl 4-hydroxy-2-(hydroxydiphenylmethyl) pyrrolidine-1-carboxylate (9) was synthesized from *trans*-4-hydroxy-L-proline in sequence reaction, first *trans*-4-hydroxy-(L)-proline was converted to its ethyl ester (**7**) and then react with phenylmagnesium bromide to give (3R,5S)-5-(hydroxydiphenylmethyl) pyrrolidin-3-ol hydrochloride (8) [48]. Later, the amino group was protected as *N*-Boc by using di-*tert*-butyl dicarbonate and triethylamine. The total yield for the α,α-diphenylprolinol modified with ionic liquids (IL) **3–5** were 39.5–49%, starting from *trans*-4-hydroxy-(*L*)-proline.

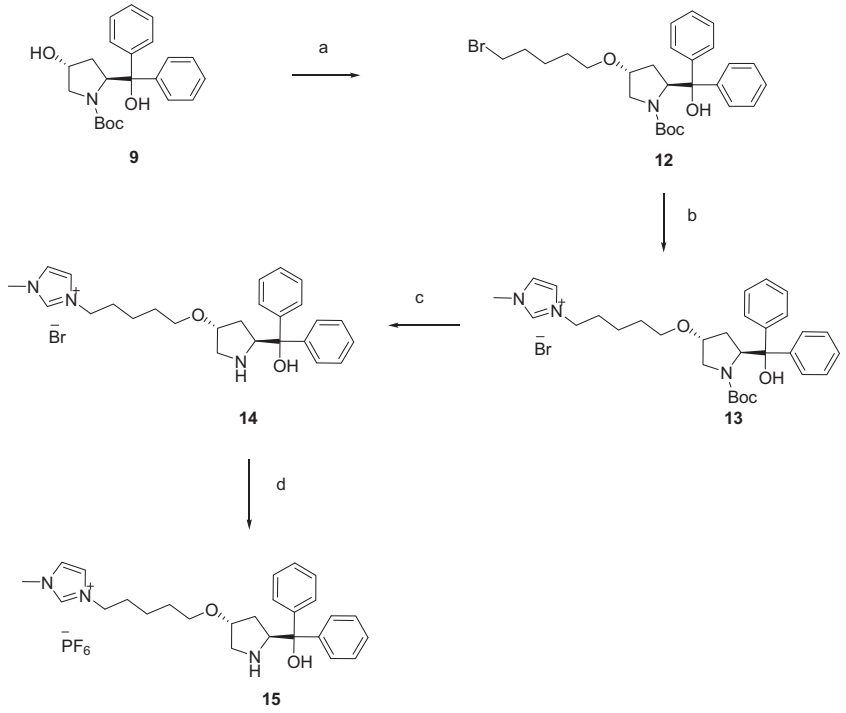
Table 1
Optimization of reaction conditions for asymmetric reduction of acetophenone.[a]



Entry	Ligand	Solvent	T (°C)	Yield (%)[b]	*Ee* (%)[c,d]
1	1	THF	70	96	91
2	2	THF	70	94	91
3	3	THF	70	85	53
4	4	THF	70	92	60
5	5	THF	70	99	84
6	5	Neat	70	90	53
7	5	Hexane	70	79	35
8	5	Diethyl ether	Refluxing	75	13
9	5	Dichloromethane	Refluxing	95	43
10	5	Toluene	110	97	61
11	5	THF	25	75	3
12	5	THF	40	80	13
13	5	THF	50	87	20
14	5	THF	60	85	43
15	5	THF	70	94	65[e]
16	5	THF	70	99	86[f]

[a] Ligands 1–5 (10 mol%) was taken in Schlenk tube, solvent (1 mL), $BH_3{\cdot}SMe_2$ (0.55 mmol) were added and heated or refluxed for specified temperature for 30 min, solution of acetophenone (0.5 mmol in THF (0.5 mL)) was added within 30 min.
[b] Isolated yield after purification by column chromatography.
[c] The ee was determined by HPLC using Chiralcel OD–H column.
[d] The absolute configuration was determined by comparing the optical rotation with literature and found to be (*R*).
[e] IL 5 (5 mol%) was used.
[f] IL 5 (15 mol%) was used.

We screened the different IL's 3–5 (10 mol%) for asymmetric reduction of acetophenone with $BH_3{\cdot}SMe_2$ (2M in THF) at 70 °C under inert atmosphere. 1,3,2-Oxazaborolidine of IL 5 gave an excellent yield (99%) and 84% enantiomeric excess (ee) compared to the other IL's (4) and (3) which have corresponding tetrafluoroborate and bromide anions (Table 1, entries 3–5). We have also used α,α-diphenyl-(L)-prolinol (1) and *trans*-α,α-diphenyl-4-hydroxy-



Scheme 2. Synthesis of (L)-prolinol modified with ether linker ionic liquid. (a) TEA, Dry DCM, 1,5dibromopentane, KOH, 65%, (b) 1-Methyl imidazole, 100 °C, 30 min, 96%, (c) TFA, CH_2Cl_2, 4 h, 88%, and (d) KPF_6, $MeOH/H_2O$, 82%.

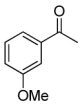
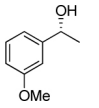
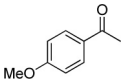
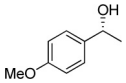
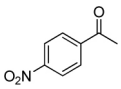
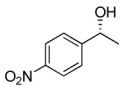
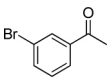
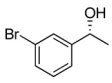
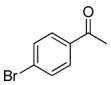
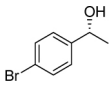
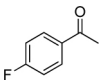
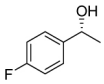
(L)-prolinol (2) under similar reaction conditions, gave 94–96% yields and 91% enantiomeric excesses (ee's) (Table 1, entries 1and 2). Screening of the different solvents for asymmetric reduction of acetophenone using IL 5 (10 mol%) with $BH_3{\cdot}SMe_2$ at 70 °C or reflux temperature. Asymmetric reduction of acetophenone in hexane, diethyl ether and dichloromethane, afforded poor ee's (Table 1, entries 7–9) and moderate ee (61%) was observed in case of toluene as solvent (Table 1, entry 10). The best solvent system for reduction was found to be THF. Effect of temperature on asymmetric reduction was also studied, the reaction temperature varied in range 70–25 °C and ee's were dropped from 86% to 3% (Table 1, entries 5 and 11–14). We have also varied the loading of IL 5 (5–15 mol%), increasing the catalyst loading improved the ee of the product (Table 1, entries 5, 15 and 16).

The asymmetric reduction of a variety of prochiral ketones were carried out using IL 5 (10 mol%) and $BH_3{\cdot}SMe_2$ in THF at 70 °C under inert atmosphere and the results were given in Table 2. The asymmetric reduction of 2-methoxy, 3-methoxy and 4-methoxy acetophenone gave corresponding products in 81–92% yields and 69–86% ee's (Table 2, entries 1–3). Substrate 2-nitro acetophenone gave poor ee (40%) compared to the 4-nitro acetophenone (81% ee) (Table 2, entries 4 and 5). 2-Bromo, 3-bromo and 4-bromo acetophenone afforded 91–94% yields and 64–88% ee's (Table 2, entries 6–8). Substrates 2-fluoro and 4-fluoro acetophenone gave corresponding products in a 90–92% yields and 78–81% ee's (Table 2, entries 9 and 10). These results indicate that 4-substituent on acetophenone provides better ee compared to the other acetophenone derivatives. Asymmetric reduction of propiophenone gave 92% yield with 81% ee (Table 2, entry 11). We have also investigated the asymmetric reduction of aliphatic ketones like cyclopropyl methyl ketone and methyl ethyl ketone afforded 88–91% yields and 48–62% ee's (Table 2, entries 12 and 13).

The recycling and reusability of 1,3,2-oxazaborolidine of IL 5 was carried out for the asymmetric reduction of acetophenone. After completion of fresh catalytic cycle, the solvent (THF) was removed under reduced pressure and a mixture of diethyl ether and hexane (5 mL, 1:1) was added and 1,3,2-oxazaborolidine of IL 5 was precipitated as viscous oil and the product was removed by syringe. The recovered catalyst was used for next catalytic run. The conversions of the products were comparable but enantiomeric excesses (ee's) gradually decreased (Table 3). ^{1}H NMR of IL 5, its 1,3,2-oxazaborolidine and recovered 1,3,2-oxazaborolidine (SI, Figure 6) show that the peak at 2.35 ppm (—CH_2—COO) was disappeared and new peak appears at 3.33 ppm for —CH_2OH due to reduction of ester linkage to alcohol. The reduction of ester in IL 5 was also confirmed by HRMS, show peak at 270.1493 $[M+H]^+$ and 169.1336 $[M]^+$ corresponding to (L)-prolinol (2) and hydroxyl ionic liquid (SI, Scheme 1).

To enhance the stability of catalyst, IL 15 with ether linker was synthesized according to Scheme 2. *N*-boc-*trans*-4-hydroxy-(L)-prolinamide (9) was reacted with 1,5-dibromopentane in presence of KOH at room temperature gave the compound 12 in a 65% yield. The compound 12 was further reacted with 1-methylimidazol at 100 C for 30 min yielded compound 13 and Boc deprotection by trifluroacetic acid gave the IL 14 with bromide anion. The anion exchange of compound 14 by using KPF_6 gave ionic liquid 15. The ionic liquid 15 was tested for the catalytic asymmetric reduction of acetophenone and recovered and reused up to 4 cycles with retention of conversions of product and slightly decrease in ee's (87–81%) were observed (Table 3). The ^{1}H NMR of fresh 1,3,2-oxazaborolidine of IL 15 and recovered 1,3,2-oxazaborolidine of IL 15 were found to be similar, indicated that complex is stable during the reaction. The HRMS data of the recovered ionic liquid 15 was also similar to the fresh ionic liquid 15 (SI, Figs. 7 and 8)

Table 2
Asymmetric reduction of a variety of prochiral ketones using IL 5 and $BH_3{\cdot}SMe_2$.[a]

Entry	Substrates	Products	Yield (%)[b]	Ee[c,d]
1			88	79
2			81	69
3			92	86
4			84	40
5			93	81
6			94	64
7			91	84
8			92	88
9			90	81
10			92	78
11			92	81
12			88	62
13			91	48

[a] The IL 5 (10 mol%) was taken in Schlenk tube, THF (1 mL), $BH_3{\cdot}SMe_2$ (0.55 mmol) were added and heated at 70 °C for 30 min, solution of acetophenone derivatives (0.5 mmol in THF (0.5 mL)) was added to it within 30 min.
[b] Isolated yield after purification by column chromatography.
[c] The ee was determined by HPLC using Chiralcel OD–H/AD–H column.
[d] The absolute configuration was determined by comparing the optical rotation with literature and found to be *R*.

Table 3
Recycling of the catalyst generated from IL 5 and $BH_3{\cdot}SMe_2$ for asymmetric reduction of acetophenone.[a]

Entry	Cycles[a]	Yield[b]	Ee[c]
1 (2)	0	99 (99)	84 (87)[d]
3 (4)	1	95 (99)	73 (85)
5 (6)	2	95 (96)	73 (82)
7 (8)	3	91 (94)	60 (81)
9 (10)	4	90 (94)	55 (81)

[a] Recycling procedure are given in experimental.
[b] Isolated yield after purification by column chromatography.
[c] The ee was determined by HPLC using Chiralcel OD–H column.
[d] Results in parenthesis were given for IL 15.

4. Conclusion

In conclusion we have developed 1,3,2-oxazaborolidine from α,α-diphenyl-4-hydroxy-(L)-prolinol modified with ionic liquids and $BH_3{\cdot}SMe_2$ as a recoverable and reusable catalyst for the asymmetric reduction of prochiral ketones. The asymmetric reduction of acetophenone and its derivatives gave excellent yields of the products and good to moderate ee's except 2-nitro acetophenone. The reduction of aliphatic ketones afforded good yields of the products with moderate ee's. The 1,3,2-oxazaborolidine of α,α-diphenyl-4-hydroxy-(L)-prolinol modified with ionic liquids having ether linkage found to be stable compared to ester linkage in presence of $BH_3.SMe_2$ during the asymmetric reduction. 1,3,2-oxazaborolidine of ionic liquid with ether linkage was recovered and reused up to 4 cycles for the reduction of acetophenone and conversions of the products were comparable and also enantiomeric excess (ee's) slightly decreased.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.molcata 2014.12.009.

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