Tetrahedron: *Asymmetry* 21 (2010) 2530–2534

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

# Chiral quaternary alkylammonium ionic liquid [Pro-dabco][$BF_4$]: as a recyclable and highly efficient organocatalyst for asymmetric Michael addition reactions

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ARTICLE INFO

*Article history:*
Received 6 September 2010
Accepted 7 October 2010
Available online 4 November 2010

ABSTRACT

A novel series of chiral quaternary ammonium ionic liquids have been synthesized and shown to be very effective catalysts for the asymmetric Michael addition reactions of ketones and aldehydes to nitroolefins with excellent yields (up to 100%), diastereoselectivities (*syn*/*anti* = 99:1), and enantioselectivities (up to 97%). The catalytic system, an ionic liquid organocatalyst in [Bmim][$BF_4$], could be reused five times without a significant loss in catalytic activity or stereoselectivity.



## 1. Introduction

The Michael reaction is widely recognized as one of the most important carbon–carbon bond-forming procedures, and it plays an important role in organic synthesis.[1] The development of organocatalysts that promote asymmetric Michael reactions is an attractive area of research.[2] Over the past few years, there has been a tremendous increase in research activities concerning the development of organocatalysts for asymmetric carbon–carbon bond-forming reactions,[3] especially for the Michael addition reactions.[4] Among the various organocatalysts, proline and its derivatives have been demonstrated to make up a successful class of organocatalysts in enamine chemistry.[5,6] Some of them have been developed for asymmetric Michael reactions of ketones to nitroolefins with high enantioselectivity and diastereoselectivity. Most recently, we have also reported a new class of proline based catalysts, which were very effective catalysts for asymmetric Michael addition reactions of ketones with nitroolefins and chalcones;[7] however, a major disadvantage is that they cannot be easily recovered and recycled. As a result, the design and development of environmentally friendly chiral organocatalysts, which could be easily recovered and recycled for asymmetric Michael reactions with high enantioselectivity remain a major challenge in synthetic organic chemistry.

Over the past decade, room-temperature ionic liquids have received broad attention due to their favorable properties, such as non-inflammability, negligible vapor pressure, reusability, and high thermal stability.[8] They have served as effective reaction media for a wide variety of organic reactions and other applications in chemistry.[9] Among the various ionic liquids, chiral ionic liquids are particularly attractive and important owing to their potential applications to chiral discrimination, such as asymmetric synthesis and the resolution of racemates.[10] Chiral ionic liquids with functional groups have also been applied as soluble and recyclable organocatalysts for asymmetric reaction by attachment of catalytically active chiral groups onto the side chains of ionic liquids. Recently, some functionalized chiral ionic liquids have been designed and used effectively as catalysts for asymmetric reactions, such as Michael additons,[11] Aldol reactions,[12] and borane reductions.[13] There have been cases where imidazolium ionic liquids have been used most successfully for asymmetric Michael reactions with high enantioselectivities. For example, Luo et al.,[11a–c] Headley et al.,[11d–f] Wang et al.,[11i–k] and other teams have reported excellent chiral imidazolium ionic liquid catalysts for asymmetric Michael reactions to nitroolefins. We have also reported an efficient procedure for asymmetric Michael additions of cyclohexanone to chalcones catalyzed by an imidazolium ionic liquid.[11m] However, nearly all chiral ionic liquid catalysts are based on imidazolium, only one example in which chiral pyridinium ionic liquids have been used as catalyst for asymmetric reactions.[14] The application of chiral quaternary alkylammonium ionic liquids as catalysts to achieve asymmetric products has not been reported for Michael addition between nitroolefins with ketones and aldehydes. Herein, we report the design and synthesis of a novel class of chiral quaternary alkylammonium ionic liquids, which are very effective organocatalysts for highly enantioselective Michael additions of cyclic ketones to nitroolefins; in addition, they are easily recovered from the reaction mixture.

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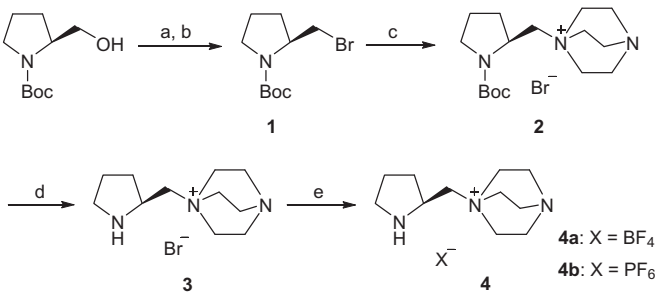
doi:10.1016/j.tetasy.2010.10.009

## 2. Results and discussion

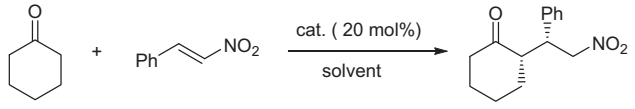
A series of pyrrolidine–DABCO-type chiral ionic liquids were prepared from the "chiral pool" using *N*-Boc-L-prolinol as the starting material (Scheme 1). The synthetic procedures were straightforward: (*S*)-*N*-Boc 2-bromomethylpyrrolidine was prepared in two steps from *N*-Boc-L-prolinol, which was then treated with DABCO at room temperature in ethyl acetate. Anion metathesis of **3** with either $AgBF_4$ or $KPF_6$ afforded **4a** or **4b**.




**Scheme 1.** Synthesis of functionalized chiral ionic liquids. Reagents and conditions: (a) TsCl, $CH_2Cl_2$ 88%; (b) LiBr, acetone, reflux, 91%; (c) DABCO, ethyl acetate, rt, 62%; (d) HBr, $NaHCO_3$ (aq), 95%; (e) $AgBF_4$ or $KPF_6$, $C_2H_5OH$, 100%.

Initially, we used these chiral ionic liquids for the direct asymmetric Michael addition of cyclohexanone **5a** to *trans*-β-nitrostyrene **6a** to afford the Michael adduct **7a** using ILs [Bmim][$BF_4$] as reaction media. As shown in Table 1, all of the catalysts tested exhibited good catalytic activity with the corresponding products, which were obtained in good to excellent chemical yields (Table 1, entries 1–3). Catalyst **4a** was superior to **3** and **4b**, which promoted the Michael addition reaction with higher diastereoselectivity and enantioselectivity (Table 1, entry 2). Catalyst **4a** was used as the catalyst of choice and evaluated in different solvents (Table 1, entries 4–11). The yields and enantioselectivities of the product differed significantly. When THF and $CHCl_3$ were used as the solvent, the product was obtained in low yields (Table 1, entries 4 and 5). When the reaction was carried out in a protic solvent, such as MeOH, $C_2H_5OH$, *i*-PrOH, and *t*-BuOH, moderate to good enantioselectivities were obtained (Table 1, entries 6–9). However, when using water as the solvent, no product was obtained (Table 1, entry 10). The use of [Bmim][$PF_6$] led to a slight decrease in both activity and enantioselectivity with 83% yield and 88% ee value being obtained (Table 1, entry 11). Pyrrolidine–DABCO tetrafluoroborate in [Bmim][$BF_4$] gave the best performances with quantitative yield and high diastereoselectivity (*syn*/*anti* = 96:4) and enantioselectivity (91% ee).

**Table 1**
Optimization of the reaction conditions[a]



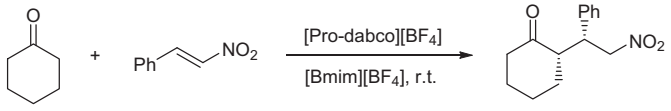

5a 6a 7a

| Entry | Cat. | Solvent | *t* (h) | Yield[b] (%) | dr[c] (*syn*/*anti*) | ee[d] (%) |
|---|---|---|---|---|---|---|
| 1 | **3** | [Bmim][$BF_4$] | 48 | 95 | 88:12 | 85 |
| 2 | **4a** | [Bmim][$BF_4$] | 22 | 100 | 96:4 | 91 |
| 3 | **4b** | [Bmim][$BF_4$] | 48 | 85 | 92:8 | 90 |
| 4 | **4a** | THF | 96 | <5 | — | — |
| 5 | **4a** | $CHCl_3$ | 96 | <5 | — | — |
| 6 | **4a** | MeOH | 48 | 88 | 76:24 | 74 |
| 7 | **4a** | $C_2H_5OH$ | 48 | 84 | 79:21 | 79 |
| 8 | **4a** | *i*-PrOH | 96 | 61 | 78:22 | 81 |
| 9 | **4a** | *t*-BuOH | 48 | 83 | 75:25 | 78 |
| 10 | **4a** | $H_2O$ | 96 | 0 | — | — |
| 11 | **4a** | [Bmim][$PF_6$] | 54 | 83 | 94:6 | 88 |

[a] All reactions were conducted in a solvent (0.5 mL) using **5a** (0.1 mL, 1.0 mmol) and **6a** (15 mg, 0.1 mmol) in the presence of 20 mol % of the catalyst.
[b] Isolated yield.
[c] Determined by $^1H$ NMR spectroscopy.
[d] Determined by HPLC analysis (chiralcel AD-H column).

The recyclability and reusability of the catalyst chiral ionic liquid **4a** and the solvent [Bmim][$BF_4$] were examined for the reaction of cyclohexanone to *trans*-β-nitrostyrene under standard reaction conditions. After the reaction was complete, the reaction mixture was concentrated and the residue was extracted three times with ether. Removal of the solvent and purification by column chromatography gave the Michael adduct **7a**. The catalyst chiral ionic liquid **4a** remained in the solvent [Bmim][$BF_4$]. The catalyst and the solvent were easily recovered in more than 90% yield. After drying, they were reused for the next run of the reaction. As shown in Table 2, catalyst **4a** could be recycled and reused at least five more times without any loss of stereoselectivity (ee >90%; *syn*/*anti* >93:7) but a slight decrease in activity was observed in cycles 2–6.

**Table 2**
Recycling studies of ionic liquid [Pro-dabco][$BF_4$] catalyzed Michael addition of cyclohexanone to *trans*-β-nitrostyrene[a]



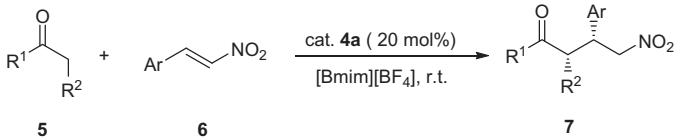

5a 6a 7a

| Cycle | *t* (h) | Yield[b] (%) | dr[c] (*syn*/*anti*) | ee[d] (%) |
|---|---|---|---|---|
| 1 | 22 | 100 | 96:4 | 91 |
| 2 | 29 | 97 | 96:4 | 91 |
| 3 | 35 | 95 | 93:7 | 90 |
| 4 | 41 | 88 | 95:5 | 92 |
| 5 | 43 | 93 | 96:4 | 91 |
| 6 | 62 | 90 | 95:5 | 91 |

[a] All reactions were conducted in [Bmim][$BF_4$] (0.5 mL) using **5a** (0.1 mL, 1.0 mmol) and **6a** (15 mg, 0.1 mmol) in the presence of 20 mol % of the catalyst.
[b] Isolated yield.
[c] Determined by $^1H$ NMR spectroscopy.
[d] Determined by HPLC analysis (chiralcel AD-H column).

Having established the standard reaction conditions for the Michael addition of cyclohexanone to *trans*-β-nitrostyrene, we then examined the reactions of other nitroolefins to establish a general scope of this asymmetric transformation. The results are shown in Table 3. High isolated yields were obtained for all of the six-membered ring ketones, which can efficiently undergo Michael reactions with different aryl-substituted nitroolefins in the presence of 20 mol % of catalyst **4a** in [Bmim][$BF_4$] at room temperature to give the Michael adducts **7a**–**7l** in high yields and with excellent enantioselectivities (87–97% ee) and diastereoselectivities (*syn*/*anti* ratio up to 99:1). Other ketones, such as cyclopentanone and acetone, were also examined in the **4a**-catalyzed Michael addition reaction with **6a**. The reaction with cyclopentanone occurred smoothly and showed moderate diastereoselectivity and enantioselectivity for the *syn* product (Table 3, entry 13). Acetone worked well to give the desired products in good yield but with low enantioselectivity (40% ee) (Table 3, entry 14). The Michael addition of isobutyraldehyde to *trans*-β-nitrostyrene was obtained in moderate yield but with good enantioselectivity (81% ee) (Table 3, entry 15).

**Table 3**
Asymmetric Michael addition reactions of ketones and nitrostyrene[a]




**5** **6** **7**

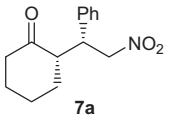
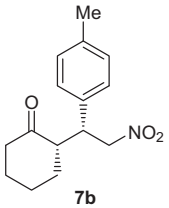
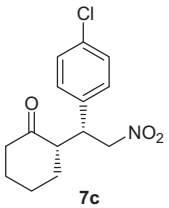
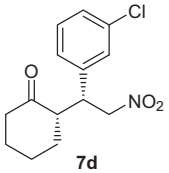
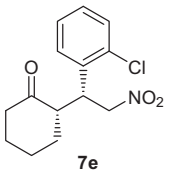
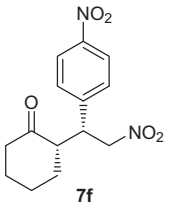
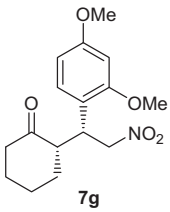
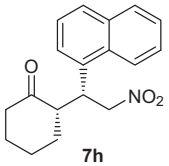
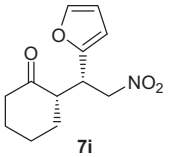
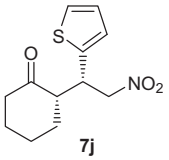
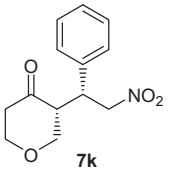
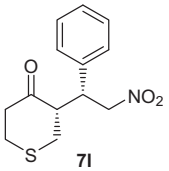
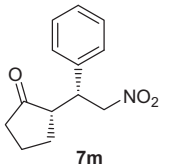
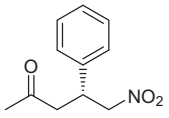
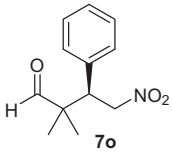
| Entry | Product | *t* (h) | Yield[b] (%) | dr[c] (*syn*/*anti*) | ee[d] (%) |
|---|---|---|---|---|---|
| 1 |  **7a** | 22 | 100 | 96:4 | 91 |
| 2 |  **7b** | 68 | 94 | 99:1 | 93 |
| 3 |  **7c** | 20 | 87 | 98:2 | 93 |
| 4 |  **7d** | 36 | 98 | 97:3 | 87 |
| 5 |  **7e** | 20 | 100 | 99:1 | 97 |
| 6 |  **7f** | 20 | 95 | 94:6 | 91 |
| 7 |  **7g** | 96 | 92 | 97:3 | 92 |
| 8 |  **7h** | 72 | 91 | 98:2 | 97 |

**Table 3** (*continued*)

| Entry | Product | *t* (h) | Yield[b] (%) | dr[c] (*syn*/*anti*) | ee[d] (%) |
|---|---|---|---|---|---|
| 9 |  **7i** | 28 | 97 | 93:7 | 90 |
| 10 |  **7j** | 60 | 93 | 96:4 | 90 |
| 11 |  **7k** | 17 | 100 | 99:1 | 96 |
| 12 |  **7l** | 48 | 96 | 91:9 | 87 |
| 13 |  **7m** | 22 | 95 | 75:25 | 79 |
| 14 |  **7n** | 90 | 81 | — | 40 |
| 15 |  **7o** | 96 | 41 | — | 81 |

[a] All reactions were conducted in solvent (0.5 mL) using **5** (1.0 mmol) and **6** (0.1 mmol) in the presence of 20 mol % of the catalyst.
[b] Isolated yield.
[c] Determined by $^1$H NMR spectroscopy.
[d] Determined by HPLC analysis (chiralcel AD-H or OD-H column).

The stereochemistries of the major products **7** were determined to be (2*S*,3*R*) by comparison of their specific rotations with other previous studies.[5–7] The absolute stereochemical results can be explained by an acyclic synclinal transition state, as proposed by Seebach and Golinski.[15]

## 3. Conclusions

In conclusion, we have designed and prepared the first example of an asymmetric Michael reaction in which chiral quaternary alkylammonium ionic liquids have been used as highly efficient asymmetric organocatalysts. The chiral ionic liquid catalysts were easily prepared from commercially available L-prolinol. They are capable of catalyzing highly enantioselective and diastereoselective nitro-Michael addition reactions. Moreover, the catalyst and

the solvent were readily recovered and reused for at least five times without a significant loss of catalytic activity or stereoselectivity. Further investigation into the applications of this recyclable catalyst in asymmetric catalysis is currently in progress and will be reported in due course.

## 4. Experimental section

### 4.1. General

All the solvents were purified according to standard procedures. The $^1$H NMR spectra were recorded at 300 MHz, $^{13}$C NMR was recorded at 75 MHz. $^1$H and $^{13}$C NMR chemical shifts were calibrated to tetramethylsilane as an external reference. Coupling constants are given in Hertz. The following abbreviations are used to indicate the multiplicity: s, singlet; d, doublet: t, triplet; q, quartet; m, multiplet; HRMS were recorded on an IonSpec FT-ICR mass spectrometer with ESI resource. Melting points were measured on a RY-I apparatus and are reported uncorrected. Optical rotations were measured on a Perkin–Elmer 341 Polarimeter at 20 °C. HPLC analysis was performed on Shimadzu CTO-10AS by using a Chiralpak AD-H or OD-H column purchased from Daicel Chemical Industries.

### 4.2. General procedure for the preparation of ionic liquid catalyst

#### 4.2.1. (*S*)-*tert*-Butyl 2-(bromomethyl)pyrrolidine-1-carboxylate 1[16]

In a 50 mL round-bottomed flask, *N*-Boc-L-prolinol (2.52 g, 12.5 mmol) was dissolved in 25 mL $CH_2Cl_2$, 7.5 mL of pyridine was added and cooled down to 0 °C. Then, *p*-toluenesulfonyl chloride (2.96 g, 15.6 mmol) was added and the mixture was stirred at room temperature for 24 h. After this time, the reaction mixture was diluted with 50 mL of $CH_2Cl_2$ and washed with water, 1 M HCl, saturated $NaHCO_3$ and, finally, brine. The organic layer was dried with sodium sulfate, filtered, and concentrated under reduced pressure, to yield a colorless oil. The crude product was purified by flash chromatography through deactivated silica eluting with petroleum ether–ethyl acetate 8:1. After evaporation of the solvents, colorless oil was obtained (3.91 g, 88%). A solution of the colorless oil *O*-tosyl-*N*-Boc-prolinol (3.55 g, 10 mmol) and lithium bromide (2.58 g, 30 mmol) in acetone (20 mL) was heated at reflux for 6 h during which time the formation of a fine precipitate was observed. On cooling, the volatiles were removed in vacuo and the residual material was partitioned between dichloromethane (20 mL) and distilled water (20 mL) and further extracted with dichloromethane (2 × 20 mL). The combined organic portions were washed with brine (15 mL), dried (magnesium sulfate), filtered, and concentrated in vacuo to yield a colorless oil. The crude product was purified by flash chromatography through deactivated silica eluting with petroleum ether–ethyl acetate 7:1. After evaporation of the solvents, the title compound was obtained as a colorless liquid (2.4 g, 91%). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ (ppm) 1.47 (s, 9H), 1.79–1.90 (m, 2H), 1.94–2.04 (m, 2H), 3.19–3.51 (m, 3H), 3.58–3.63 (m, 1H), 3.91–4.13 (m, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$,): $\delta$ (ppm) 22.62, 28.45, 30.11, 34.84, 46.94, 57.84, 79.70, 154.19; $[\alpha]_D^{20} = -40.5$ (*c* 0.80, $CHCl_3$).

#### 4.2.2. 1-[(*S*)-*tert*-Butyl 2′-methyl pyrrolidine-1′-carboxylate]-4-aza-1-azoniabicyclo[2.2.2]octane bromide 2

In a 100 mL round-bottomed flask, DABCO (3.36 g, 30 mmol) was added to a solution of compound **1** (2.64 g, 10 mmol) in AcOEt (50 mL) at room temperature. The mixture was stirred for 5 days and concentrated in vacuo. The residue was purified by flash chromatography through deactivated silica eluting with petroleum ether–ethyl acetate 1:1. After evaporation of the solvents, the title compound was obtained as a colorless oil (2.33 g, 62%). $^1$H NMR (300 MHz, $D_2O$): $\delta$ (ppm) 1.12–1.30 (m, 2H), 1.42 (s, 9H), 1.57–1.67 (m, 2H), 1.99–2.21 (m, 1H), 2.71–2.82 (m, 2H), 3.02 (t, 6H, *J* = 6.9 Hz), 3.33 (t, 6H, *J* = 8.0 Hz), 3.45–3.56 (m, 3H); $^{13}$C NMR (75 MHz, $D_2O$): $\delta$ (ppm) 22.68, 28.53, 34.64, 46.55, 50.90, 52.68, 57.80, 69.39, 79.42, 154.56; $[\alpha]_D^{20} = -12.0$ (*c* 0.80, $CH_3OH$); HRMS calcd for $C_{16}H_{30}N_3O_2^+$ $M^+$ 296.2333, found 296.2335.

#### 4.2.3. 1-[(*S*)-2′-Methylpyrrolidine]-4-aza-1-azoniabicyclo[2.2.2]octane bromide 3

To a solution of [Boc-pro-dabco][Br] **2** (752 mg, 2 mmol) in $CH_2Cl_2$ (5 mL) was added dropwise HBr (5 mL) at 0 °C. The mixture was warmed to room temperature and stirred overnight. After removal of the organic solvents in vacuo, the residue was dissolved in $CH_2Cl_2$ (5 mL) and then treated with saturated $NaHCO_3$ solution (15 mL) for 1 h at room temperature. The aqueous layer was extracted three times with $CH_2Cl_2$ (3 × 5 mL) and the combined extracts were dried over anhydrous $Na_2SO_4$. Concentration in vacuo after filtration gave the catalyst [Pro-dabco][Br] **3** 524 mg (95% yield). $^1$H NMR (300 MHz, $D_2O$): $\delta$ (ppm) 1.02–1.07 (m, 1H), 1.24–1.36 (m, 1H), 1.53–1.69 (m, 2H), 1.94–2.14 (m, 1H), 2.70–2.78 (m, 2H), 3.11 (t, 6H, *J* = 6.9 Hz), 3.38 (t, 6H, *J* = 8.0 Hz), 3.48–3.55 (m, 3H); $^{13}$C NMR (75 MHz, $D_2O$): $\delta$ (ppm) 24.38, 31.48, 46.35, 51.80, 53.01, 57.54, 69.28; $[\alpha]_D^{20} = +20.5$ (*c* 0.80, $CH_3OH$); HRMS calcd for $C_{11}H_{22}N_3^+$ $M^+$ 196.1808, found 196.1809.

#### 4.2.4. 1-[(*S*)-2′-Methylpyrrolidine]-4-aza-1-azoniabicyclo[2.2.2] octane tetrafluoroborate 4a

To a solution of product **3** (276 mg, 1 mmol) in ethanol (10 mL), was added $AgBF_4$ (195 mg, 1 mmol) solution (in ethanol). The mixture was vigorously stirred at room temperature for 30 min. Filtered to remove the inorganic salts and the filtrate was concentrated in vacuo to afford a pale yellow and clear liquid **4a** 283 mg (100% yield). $^1$H NMR (300 MHz, $D_2O$): $\delta$ (ppm) 1.05–1.12 (m, 1H), 1.27–1.39 (m, 1H), 1.49–1.60 (m, 2H), 1.91–2.10 (m, 1H), 2.71–2.80 (m, 2H), 3.01–3.16 (m, 6H), 3.29–3.38 (m, 6H), 3.50–3.56 (m, 3H); $^{13}$C NMR (75 MHz, $D_2O$): $\delta$ (ppm) 24.79, 31.68, 46.39, 51.88, 53.11, 58.54, 68.25; $[\alpha]_D^{20} = +34.4$ (*c* 0.80, $CH_3OH$); HRMS calcd for $C_{11}H_{22}N_3^+$ $M^+$ 196.1808, found 196.1811.

#### 4.2.5. 1-[(S)-2′-Methylpyrrolidine]-4-aza-1-azoniabicyclo[2.2.2] octane hexafluoro-phosphate 4b

To a solution of product **3** (276 mg, 1 mmol) in acetonitrile and acetone (15 mL, 9:1), was added well-sieved $KPF_6$ (920 mg, 5.0 mmol). The mixture was vigorously stirred at room temperature for 2 days and then filtered to remove the inorganic salts. The filtrate was triturated with $AgPF_6$ solution (in acetonitrile) until no precipitation was formed and then filtered again and concentrated. The combined organic layer was concentrated in vacuo to afford a pale clear yellow liquid **4b** 341 mg (100% yield). $^1$H NMR (300 MHz, $D_2O$): $\delta$ (ppm) 1.03–1.11 (m, 1H), 1.29–1.43 (m, 1H), 1.43–1.56 (m, 2H), 1.93–2.15 (m, 1H), 2.74–2.83 (m, 2H), 2.92–3.13 (m, 6H), 3.24–3.36 (m, 6H), 3.51–3.59 (m, 3H); $^{13}$C NMR (75 MHz, $D_2O$): $\delta$ (ppm) 25.56, 30.82, 45.71, 52.09, 53.14, 59.06, 67.32; $[\alpha]_D^{20} = +27.6$ (*c* 0.80, $CH_3OH$); HRMS calcd for $C_{11}H_{22}N_3^+$ $M^+$ 196.1808, found 196.1803.

### 4.3. Typical experimental procedure for the asymmetric Michael addition to nitroolefins

To a mixture of catalyst **4a** (6 mg, 0.02 mmol) in [Bmim][$BF_4$] (0.5 mL) and cyclohexanone (104 μL, 1.0 mmol), *trans*-β-nitrostyrene (15 mg, 0.1 mmol) was added at room temperature under air. After stirring at room temperature for 22 h, the reaction mixture was extracted with ether and the organic layer was concentrated under reduced pressure. The product was purified by flash

chromatography on silica gel (EtOAc/hexane = 1:5) to afford the Michael adduct **7a** (24.8 mg, 100%) as a white solid: *syn*/*anti* = 98:2 (by $^1$H NMR), The ee was determined by HPLC analysis (Chiralpak AD-H, $\lambda$ = 254 nm, *i*-PrOH/hexane = 10:90, 0.5 mL/min, 254 nm, $t_R$ (minor) = 21.8 min, $t_R$ (major) = 27.0 min), 96% ee; $[\alpha]_D^{25} = -35.8$ (*c* 0.80, $CHCl_3$). After drying, the catalytic system of catalyst **4a** in [Bmim][$BF_4$] was reused for the next run of the reaction.

## Acknowledgments

This work was financially supported by National Basic Research Program of China (973 Program) (No. 2010CB833301) and the Research Fund for the Doctoral Program of Higher Education (No. 20090031110019). We also thank the Nankai University State Key Laboratory of Elemento-Organic Chemistry for support.

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