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# Pyrrolidine-Based Chiral Quaternary Alkylammonium Ionic Liquids as Organocatalysts for Asymmetric Michael Additions

**Ge Wang · Huichao Sun · Xiaohui Cao · Ligong Chen**

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**Abstract** A series of chiral pyrrolidine-type quaternary alkylammonium ionic liquids were synthesized and served as efficient catalysts for asymmetric Michael additions of aldehydes and ketones to nitroolefins, and the corresponding adducts were obtained in excellent enantioselectivities (>99% ee) and diastereoselectivities (>99% dr) under solvent-free reaction conditions. Furthermore, the catalyst **7c** could be recovered for next run of the reaction with similar yield and selectivity.

**Keywords** Ionic liquids · Chiral catalyst · Asymmetric Michael additions · Solvent-free reaction

## 1 Introduction

Michael addition is one of the most important organic reactions to form C–C bonds, and asymmetric Michael addition catalyzed by chiral catalyst is a very significative strategy for organic synthesis [1–7]. Since L-proline was reported as a chiral catalyst in Michael addition by List at 2001 [8], lots of pyrrolidine derivatives have been used for the asymmetric Michael additions of ketones or aldehydes to nitroolefins [9–19]. Most of them yielded high enantioselectivity and diastereoselectivity. But it is difficult for them to be recovered and reused.

Normally, room temperature ionic liquids (RTILs) can be easily separated from organic reaction systems [20–24]. Therefore, several groups introduced quaternary ammonium groups into chiral catalysts [25–43]. Thereinto, pyrrolidine-type imidazolium ILs, DABCO ILs and pyridinium ILs all produced encouraging results for the Michael additions of ketones or aldehydes to nitroolefins.

Herein, we designed and synthesized several novel pyrrolidine-based quaternary alkylammonium ILs. And structure of these ionic liquids could be easily adjusted to obtain better catalytic capability by changing each of the alkyl groups. Then all of them were used as organocatalysts in the asymmetric Michael additions of cyclohexanone to nitroalkenes. And the results are summarized and reported here.

## 2 Experimental

### 2.1 General Information

Commercial reagents were used without purification except for otherwise explanation. Analytical thin layer chromatography was performed on 0.20 mm silica gel plates and silica gel (200–300 mesh) was used for flash chromatography both purchased from Qingdao Haiyang Chemistry Company. $^{1}H$ and $^{13}C$ NMR were recorded on Varian-500 instruments. Chemical shifts were reported in ppm down field from internal $Me_4Si$. All the multiplet patterns assigned the first-order splitting patterns. Mass spectra were recorded using electrospray ionization (ESI) on LCQ Advanted MAX Mass instruments. Optical rotations were tested on a WZZ-3 polarimeter using 10 mL cell with a 1 dm path length and Autopol II polarimete using 1 mL cell with a 1 dm path length. HPLC analysis was measured using ChiralPak AS-H column at 254 nm.

G. Wang · H. Sun · X. Cao · L. Chen (✉)
School of Chemical Engineering and Technology, Tianjin University, Tianjin 300072, People's Republic of China
e-mail: lgchen@tju.edu.cn

### 2.2 (*S*)-Benzyl 2-(hydroxymethyl)pyrrolidine-1-carboxylate (**2**)

The compound **2** was obtained following literature procedure [44].

### 2.3 (*S*)-Benzyl 2-((methylsulfonyloxy) methyl)-pyrrolidine-1-carboxylate (**3**)

To a stirred solution of compound **2** (5.5 g, 0.023 mol) in $CH_2Cl_2$ (60 mL), $(Et)_3N$ (3.0 g, 0.030 mol) was dropped at 0 °C [45, 46]. Then a solution of methanesulfonyl chloride (3.2 g, 0.028 mol) in $CH_2Cl_2$ (20 mL) was dropped into the above reaction solution. After naturally increasing the reaction temperature to r. t., the reaction mixture was stirred for 18 h. The mixture was diluted with water (50 mL), and then the resulted mixture was extracted with $CH_2Cl_2$ (20 mL × 3). The combined organic layer was washed with 1 M HCl solution (25 mL × 2) and brine (20 mL × 2), then dried over anhydrous $Na_2SO_4$ and concentrated in vacuo to give the compound **3** as colorless oil. Yield: 99%; $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 1.84–2.02 (4H, m), 2.93 (3H, s), 3.42–3.49 (2H, m), 4.09–4.22 (1H, m), 4.27–4.38 (2H, m), 5.12–5.18 (2H, m), 7.26–7.40 (5H, m); $^{13}$C NMR (500 MHz, $CDCl_3$): $\delta$ = 155.22, 137.71, 136.89, 128.97, 128.88, 128.83, 128.76, 128.64, 128.55, 128.31, 128.13, 69.75, 69.61, 67.49, 67.12, 56.54, 55.87, 47.41, 47.09, 37.22, 37.13, 28.83, 27.99, 24.04, 23.17.

### 2.4 (*S*)-Benzyl 2-(bromomethyl)pyrrolidine-1-carboxylate (**4**)

Under $N_2$ protection, compound **3** (3.1 g, 0.01 mol) and THF (30 mL) was added to a 100 mL single neck bottle [45, 46]. After compound **3** dissolved, $LiBr.H_2O$ (3.2 g, 0.03 mol) was added to the solution. The reaction mixture was stirred for 16 h under refluxing, and THF was removed away in vacuo. The mixture was diluted with water (10 mL), and the resulted mixture was extracted with $CH_2Cl_2$ (10 mL × 3). The combined organic layer was washed with water (10 mL × 2) and brine (20 mL × 2), then dried over anhydrous $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography (EA:PE = 1:4) on silica gel to give the compound **4**, a colorless oil. Yield: 81%; $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 1.81–2.01 (4H, m), 3.27–3.67 (4H, m), 4.10–4.14 (1H, m), 5.11–5.21 (2H, m), 7.32–7.37 (5H, m).

### 2.5 (*S*)-Benzyl 2-((dimethylamino) methyl)pyrrolidine-1-carboxylate (**5**)

In a 250 mL single neck bottle, compound **4** (17 g, 0.058 mol) in MeOH (114 mL) was added to a stirred solution of $Me_2NH$ (7.8 g, 0.18 mol) in water (16 g). After sealing the bottle by a rubber plug, the reaction mixture was stirred for 18 h at 55 °C. Then MeOH was removed in vacuo. The residuary mixture was extracted with EA (20 mL × 3). The combined organic layer was washed with water (30 mL × 2) and brine (30 mL × 2), then dried over anhydrous $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography (MeOH:$CH_2Cl_2$ = 1:20) on silica gel to give the compound **5**, a colorless oil. Yield: 86%; $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 1.86–1.97 (4H, m), 2.19–2.54 (8H, m), 3.41–3.43 (2H, m), 3.92–4.00 (1H, m), 5.10–5.19 (2H, m), 7.28–7.38 (5H, m).

### 2.6 General Procedure for the Preparation of Compounds **6a**–**6e**

Under $N_2$ protection, compound **5** (1.3 g, 5.0 mmol) and MeCN (10 mL) was added to a 100 mL single neck bottle [47]. After compound **5** dissolved, corresponding alkyl bromide (0.019 mol) was added into the solution. The reaction mixture was stirred under refluxing until compound **5** disappeared by analytical thin layer chromatography (EA:PE = 1:1), and MeCN was removed away in vacuo. The mixture was diluted with 10 mL EA, and then the resulted mixture was extracted with water (10 mL × 3). The combined water layer was washed with EA (15 mL × 3) and concentrated in vacuo. The residue was purified by flash chromatography (MeOH:$CH_2Cl_2$ = 1:10) on silica gel to give the corresponding quaternary ammonium **6**.

#### *2.6.1 (S)-N-((1-(Benzyloxycarbonyl)pyrrolidin-2-yl)methyl)-N,N-dimethylethanaminium bromide (**6a**)*

Colorless oil. Yield: 44%; $^1$H NMR (500 MHz, $CD_3OD$): $\delta$ = 1.17–1.40 (3H, m), 1.95–2.01 (3H, m), 2.20–2.24 (1H, m), 2.92–2.93 (2H, m), 3.00–3.01 (2H, m), 3.17–3.57 (10H, m), 4.41 (1H, s), 5.15 (2H, s), 7.31–7.48 (5H, m).

#### *2.6.2 (S)-N-((1-(Benzyloxycarbonyl)pyrrolidin-2-yl)methyl)-N,N-dimethylpropan-1-aminium bromide (**6b**)*

Colorless oil. Yield: 99%; $^1$H NMR (500 MHz, $CD_3OD$): $\delta$ = 0.87–1.01 (3H, m), 1.63–2.01 (5H, m), 2.18–2.26 (1H, m),2.92–3.00 (2H, m), 3.17 (3H, s), 3.20 (3H, s), 3.45–3.55 (4H, m), 4.41 (1H, s), 5.15 (2H, s), 7.31–7.46 (5H, m).

#### *2.6.3 (S)-N-((1-(Benzyloxycarbonyl)pyrrolidin-2-yl)methyl)-N,N-dimethylbutan-1-aminium bromide (**6c**)*

Colorless oil. Yield: 99%; $^1$H NMR (500 MHz, $CD_3OD$): $\delta$ = 0.94–1.03 (3H, m), 1.24–1.41 (2H, m), 1.59–1.82 (2H,

m), 1.91–2.01 (3H, m), 2.18–2.25 (1H, m), 2.92 (1H, s), 3.01 (1H, s), 3.17 (3H, s), 3.20 (3H, s), 3.40–3.56 (4H, m), 4.41 (1H, s), 5.15 (2H, s), 7.31–7.46 (5H, m).

#### 2.6.4 (S)-N-((1-(Benzyloxycarbonyl)pyrrolidin-2-yl)methyl)-N,N-dimethyloctan-1-aminium bromide (**6d**)

Colorless oil. Yield: 99%; $^1$H NMR (500 MHz, $CD_3OD$): $\delta = 0.90$–$0.91$ (3H, m), 1.32–1.77 (12H, m), 1.80–2.02 (3H, m),2.19–2.23 (1H, m), 2.90 (1H, s), 2.98 (1H, s), 3.10–3.19 (4H, m), 3.35–3.55 (7H, m), 4.40 (1H, s), 5.15 (2H, s), 7.31–7.45 (5H, m).

#### 2.6.5 (S)-1-(1-(Benzyloxycarbonyl)pyrrolidin-2-yl)-N,N,N-trimethylmethanaminium bromide (**6e**)

A solution of NaOH (11 g, 0.27 mol) in water (12 mL) was dropped to $Me_3N$.HCl (20 g, 0.21 mol) to produce $Me_3N$ [48]. The $Me_3N$ was bubbled to a solution of compound **4** (3.3 g, 0.011 mol) in EA (20 mL) at 0 °C. After $Me_3N$ (9.6 g, 0.16 mol) was absorbed, the reaction mixture was sealed by a rubber plug and stirred at r.t. for 168 h. The mixture was filtrated, and the filter cake was washed by EA (20 mL) to give the product **6e**, a white solid. Yield: 89%; $^1$H NMR (500 MHz, $CD_3OD$): $\delta = 1.93$–$2.01$ (3H, m), 2.18–2.25 (1H, m), 3.02–3.04 (3H, m), 3.24–3.26 (6H, m), 3.42–3.55 (4H, m), 4.39 (1H, s), 5.15 (2H, s), 7.31–7.47 (5H, m).

### 2.7 General Procedure for the Preparation of Compounds 7a–7e

To the solution of corresponding compound **6** (3.9 mmol) in EtOH (30 mL) [49], 10% Pd/C (0.15 g) was added. The reaction mixture was stirred at r. t. under 1 atm $H_2$ overnight. After filtrating the Pd/C, the solution was concentrated in vacuo to give the crude product. Adding EA (5 mL) to the crude product and vibrating by ultrasonic wave, the product was solidified. The corresponding catalyst **7** was obtained by filtration.

#### 2.7.1 (S)-N,N-Dimethyl-N-(pyrrolidin-2-ylmethyl) ethanaminium bromide (**7a**)

White solid. Yield: 85%; $^1$H NMR (500 MHz, $CD_3OD$): $\delta = 1.38$ (3H, t, $J = 7.5$ Hz), 1.45–1.53 (1H, m), 1.72–1.81 (1H, m),1.84–1.91 (1H, m), 2.13–2.19 (1H, m), 2.95–3.05 (2H, m), 3.17 (3H, s), 3.18 (3H, s), 3.39–3.49 (2H, m), 3.59 (2H, q, $J = 7$ Hz), 3.71–3.75 (1H, m); $^{13}$C NMR (500 MHz, $CD_3OD$): $\delta = 67.22$, 60.98, 53.50, 50.37, 46.70, 31.39, 24.94, 7.63; $[\alpha]_D^{r.t.} = +14.1$ (c = 0.99, MeOH); MS (ESI) *m/z*: calcd. for $C_9H_{21}N_2$ 157.28 (positive ion), found 157.4 (positive ion).

#### 2.7.2 (S)-N,N-Dimethyl-N-(pyrrolidin-2-ylmethyl) propan-1-aminium bromide (**7b**)

White solid. Yield: 72%; $^1$H NMR (500 MHz, $CD_3OD$): $\delta = 1.00$ (3H, t, $J = 7$ Hz), 1.38–1.42 (1H, m), 1.68–1.73 (1H, m),1.78–1.86 (3H, m), 2.07–2.12 (1H, m), 2.87–2.99 (2H, m), 3.15 (3H, s), 3.16 (3H, s), 3.27–3.40 (4H, m), 3.59–3.64 (1H, m); $^{13}$C NMR (500 MHz, $CD_3OD$): $\delta = 68.10$, 66.82, 53.35, (50.80, 50.76, 50.72, 50.69), 46.71, 31.37, 25.14, 15.94, 9.67; $[\alpha]_D^{r.t.} = +12.8$ (c = 0.97, MeOH); MS (ESI) *m/z*: calcd. for $C_{10}H_{23}N_2$ 171.30 (positive ion), found 171.2 (positive ion).

#### 2.7.3 (S)-N,N-Dimethyl-N-(pyrrolidin-2-ylmethyl) butan-1-aminium bromide (**7c**)

White solid. Yield: 65%; $^1$H NMR (500 MHz, $CD_3OD$): $\delta = 1.01$ (3H, t, $J = 7.5$ Hz), 1.39–1.47 (3H, m), 1.70–1.87 (4H, m), 2.09–2.15 (1H, m), 2.90–3.01 (2H, m), 3.16 (3H, s), 3.17 (3H, s), 3.31–3.46 (4H, m), 3.63–3.66 (1H, m); $^{13}$C NMR (500 MHz, $CD_3OD$): $\delta = 68.02$, 65.36, 53.39, 50.77, 46.71, 31.37, 25.11, 24.41, 19.54, 12.75; $[\alpha]_D^{r.t.} = +8.5$ (c = 0.98, MeOH); MS (ESI) *m/z*: calcd. for $C_{11}H_{25}N_2$ 185.33 (positive ion), found 185.2 (positive ion).

Recycled **7c**: Light yellow solid. Recycled yield: 90–95%; $^1$H NMR (500 MHz, $D_2O$): $\delta = 1.02$ (3H, t, $J = 7.5$ Hz), 1.31–1.32 (1H, m), 1.40–1.40 (2H, m), 1.61–1.64 (1H, m),1.72–1.85 (3H, m), 1.93–1.99 (1H, m),2.04–2.09 (1H, m), 2.29–2.38 (2H, m), 3.11–3.20 (6H, m), 3.24–3.35 (2H, m), 3.43–3.46 (2H, m), 3.71–3.81 (1H, m), 4.05–4.06 (1H, m), 7.25–7.32 (1H, m).

#### 2.7.4 (S)-N,N-Dimethyl-N-(pyrrolidin-2-ylmethyl) octan-1-aminium bromide (**7d**)

White solid. Yield: 60%; $^1$H NMR (500 MHz, $CD_3OD$): $\delta = 0.90$ (3H, t, $J = 7.5$ Hz), 1.33–1.46 (11H, m), 1.69–1.87 (4H, m), 2.08–2.14 (1H, m), 2.89–3.00 (2H, m), 3.16 (3H, s), 3.18 (3H, s), 3.31–3.48 (4H, m), 3.60–3.67 (1H, m); $^{13}$C NMR (500 MHz, $CD_3OD$): $\delta = 67.93$, 65.55, 53.41, 50.77, 46.71, 31.71, 31.37, 29.05, 29.02, 26.22, 25.08, 22.50, 22.48, 13.25; $[\alpha]_D^{r.t.} = +14.0$ (c = 1.01, MeOH); MS (ESI) *m/z*: calcd. for $C_{15}H_{33}N_2$ 241.44 (positive ion), found 241.3 (positive ion).

#### 2.7.5 (S)-N,N,N-Trimethyl-1-(pyrrolidin-2-yl) methanaminium bromide (**7e**)

White solid. Yield: 89%; $^1$H NMR (500 MHz, $CD_3OD$): $\delta = 1.75$–$1.81$ (1H, m), 1.90–1.96 (1H, m), 1.98–2.06 (1H, m),2.34–2.40 (1H, m), 3.14 (9H, s), 3.29–3.32 (2H, m), 3.75–3.84 (2H, m), 4.04–4.09 (1H, m); $^{13}$C NMR (500 MHz, $CD_3OD$): $\delta = 71.45$, 71.43, 54.78, 54.53,

54.50, 47.80, 32.42, 26.28, 24.19; $[\alpha]_D^{r.t.} = +7.8$ (c = 0.95, MeOH); MS (ESI) *m/z*: calcd. for $C_8H_{19}N_2$ 143.25 (positive ion), found 143.1 (positive ion).

### 2.8 (*S*)-*N*,*N*-Dimethyl-*N*-(pyrrolidin-2-ylmethyl)butan-1-aminium fluoroboric acid (**8**) [32]

To the solution of corresponding compound **7** (1.7 mmol) in MeCN (33 mL) and acetone (4 mL), $NaBF_4$ (0.95 g, 8.7 mmol) was added. The reaction mixture was stirred at r.t. for 72 h. After filtrating the insoluble solid, a saturated solution of $AgBF_4$ in MeCN was dropped into the solution above until no precipitate produced. After filtrating the insoluble solid, the solution was concentrated in vacuo to give the corresponding product **8**.

Orange solid. Yield: 68%; $^1$H NMR (500 MHz, $CD_3OD$): $\delta = 1.02$ (3H, t, $J = 7.5$ Hz), 1.39–1.47 (2H, m), 1.62–1.70 (1H, m),1.74–1.83 (2H, m), 1.89–1.95 (1H, m), 1.96–2.02 (1H, m), 2.27–2.34 (1H, m), 3.11–3.22 (8H, m), 3.38–3.44 (2H, m), 3.52–3.62 (2H, m), 3.85–3.91 (1H, m); $^{13}$C NMR (500 MHz, $CD_3OD$): $\delta = 65.70$, 65.36, 57.16, 50.41, 50.19, 46.34, 30.91, 24.31, 23.46, 19.40, 12.70; $[\alpha]_D^{r.t.} = +6.7$ (c = 1.03, MeOH); MS (ESI) *m/z*: calcd. for $C_{15}H_{33}N_2$ 185.33 (positive ion), found 185.2 (positive ion).

### 2.9 General Experimental Procedure for the Michael addition of Cyclohexanone to Nitroalkene by Chiral Catalyst

To a solution of the chiral catalyst (0.075 mmol) in cyclohexanone (1 g, 10 mmol), TFA (2.85 mg, 0.025 mmol) was dropped in. After stirring for 1 h, the nitroalkene (0.5 mmol) was added, and the solution was stirred at r.t. for 72 h except for otherwise explanation. The solution was diluted with 5 mL of water, and the resulted mixture was extracted with EA (2 mL × 3). The combined organic layer was washed with water (3 mL × 2) and brine (3 mL × 2), then dried over anhydrous $MgSO_4$ and concentrated in vacuo to give the crude product. Adding PE (3 mL) to the crude product and vibrating by ultrasonic wave for 1 h. The corresponding product was obtained by filtration.

The relative configurations of the products (syn and anti) were determined by comparison of HPLC data with those reported in the literature [13]. The absolute configurations of the product (e.e) were determined by comparison of HPLC retention times catalyzed by the racemic proline [8].

#### *2.9.1 (S)-2-((R)-2-Nitro-1-phenylethyl)cyclohexanone (**9a**)*

$^1$H NMR (500 MHz, $CDCl_3$): $\delta = 1.20$–1.28 (1H, m), 1.27–1.82 (4H, m), 2.06–2.11 (1H, m),2.37–2.51 (2H, m), 2.68–2.72 (1H, m), 3.72–3.80 (1H, m), 4.62–4.66 (1H, m), 4.93–4.96 (1H, m), 7.16–7.34 (5H, m).

#### *2.9.2 (S)-2-((R)-2-Nitro-1-(2-nitrophenyl)ethyl)cyclohexanone (**9b**)*

$^1$H NMR (500 MHz, $CDCl_3$): $\delta = 1.24$–1.32 (1H, m), 1.43–1.73 (3H, m), 1.81–1.84 (1H, m), 2.04–2.14 (1H, m), 2.37–2.39 (1H, m), 2.40–2.51 (1H, m), 2.72–2.77 (1H, m), 3.92–3.96 (1H, m), 4.68–4.73 (1H, m), 5.00–5.03 (1H, m), 7.51–7.68 (2H, m), 8.08–8.16 (2H, m).

#### *2.9.3 (S)-2-((R)-1-(4-Methoxyphenyl)-2-nitroethyl)cyclohexanone (**9c**)*

$^1$H NMR (500 MHz, $CDCl_3$): $\delta = 1.19$–1.28 (1H, m), 1.57–1.82 (4H, m), 2.05–2.11 (1H, m), 2.36–2.42 (1H, m), 2.46–2.50 (1H, m), 2.62–2.68 (1H, m), 3.69–3.74 (1H, m), 3.79 (3H, s), 4.57–4.61 (1H, m), 4.90–4.93 (1H, m), 6.84 (2H, d, $J = 8.5$ Hz), 7.06 (2H, d, $J = 8.5$ Hz).

#### *2.9.4 (S)-2-((R)-1-(4-Chlorophenyl)-2-nitroethyl)cyclohexanone (**9d**)*

$^1$H NMR (500 MHz, $CDCl_3$): $\delta = 1.19$–1.28 (1H, m), 1.57–1.83 (4H, m), 2.08–2.13 (1H, m), 2.35–2.42 (1H, m), 2.46–2.51 (1H, m), 2.63–2.68 (1H, m), 3.74–3.79 (1H, m), 4.59–4.63 (1H, m), 4.92–4.96 (1H, m), 7.11–7.14 (2H, m), 7.29–7.32 (2H, m).

#### *2.9.5 (S)-2-((R)-1-(2,4-Dichlorophenyl)-2-nitroethyl)cyclohexanone (**9e**)*

$^1$H NMR (500 MHz, $CDCl_3$): $\delta = 1.30$–1.38 (1H, m), 1.60–1.86 (4H, m), 2.10–2.15 (1H, m), 2.35–2.42 (1H, m), 2.46–2.51 (1H, m), 2.84–2.92 (1H, m), 4.11–4.24 (1H, m), 4.86–4.92 (2H, m), 7.17 (1H, d, $J = 8.0$ Hz), 7.23 (1H, dd, $J_1 = 8.0$ Hz, $J_2 = 2.0$ Hz), 7.41 (1H, d, $J = 2.0$ Hz).

#### *2.9.6 (S)-2-((R)-1-(2-Chlorophenyl)-2-nitroethyl)cyclohexanone (**9f**)*

$^1$H NMR (500 MHz, $CDCl_3$): $\delta = 1.30$–1.38 (1H, m), 1.59–1.85 (4H, m), 2.09–2.14 (1H, m), 2.37–2.43 (1H, m), 2.47–2.51 (1H, m), 2.90–2.97 (1H, m), 4.27–4.31 (1H, m), 4.87–4.94 (2H, m), 7.20–7.25 (3H, m), 7.38–7.39 (1H, m).

#### *2.9.7 (S)-2-((R)-2-Nitro-1-p-tolylethyl)cyclohexanone (**9g**)*

$^1$H NMR (500 MHz, $CDCl_3$): $\delta = 1.20$–1.28 (1H, m), 1.57–1.81 (4H, m), 2.03–2.11 (1H, m), 2.32 (3H, s), 2.36–2.42 (1H, m), 2.46–2.50 (1H, m), 2.64–2.70 (1H, m),

3.70–3.75 (1H, m), 4.59–4.63 (1H, m), 4.90–4.94 (1H, m), 7.04 (2H, d, $J = 8.0$ Hz), 7.12 (2H, d, $J = 8.0$ Hz).

*2.9.8 (2R,3S)-2-Ethyl-4-nitro-3-phenylbutanal (**9i**)*

$^1$H NMR (500 MHz, $CDCl_3$): $\delta = 0.82$–$0.91$ (3H, m), 1.48–1.55 (2H, m), 2.66–2.72 (1H, m),3.77–3.82 (1H, m), 4.61–4.75 (2H, m), 7.18–7.22 (2H, m), 7.29–7.37 (2H, m), 9.73 (1H, d, $J = 2.5$ Hz).

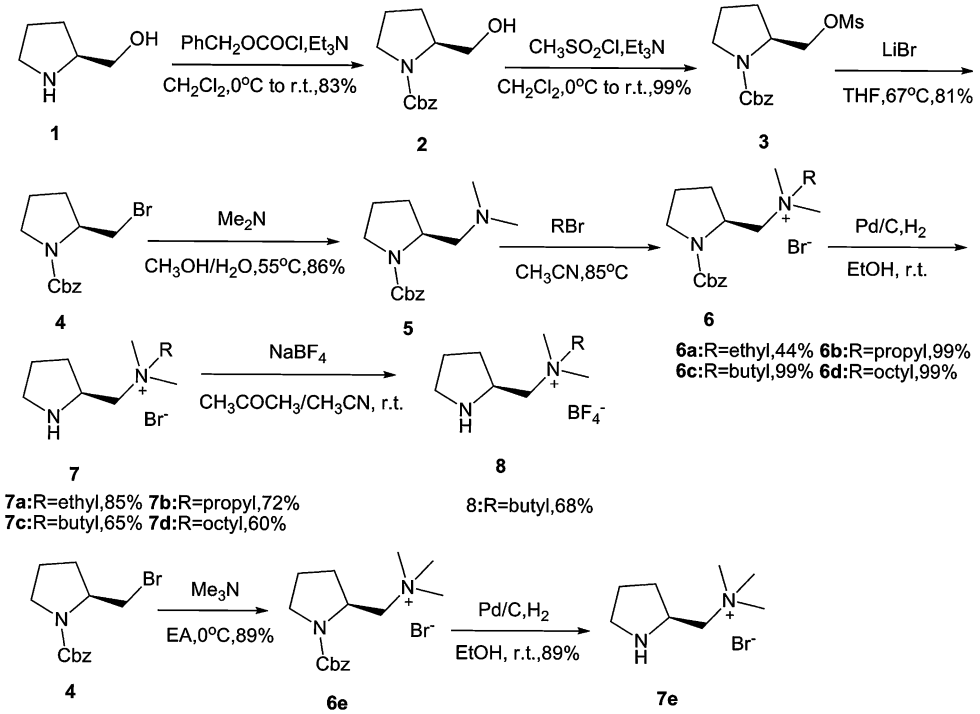
## 3 Results and Discussion

In order to improve the stereoselectivity and yield of asymmetric Michael additions, we designed and prepared pyrrolidine-based chiral quaternary alkylammonium ionic liquids **7a**–**7e** and **8**. At first, the simplest pyrrolidine-based quaternary alkylammonium ionic liquid **7e** was designed. Then **7a**–**7d** was designed to study the impact of alkyl length of ionic liquids on catalytic activity. For studying the effect of anion, compound 8 was designed. All of them were easily prepared from the commercially available (S)-(2-hydroxy-methyl)pyrrolidine 1 in six or seven steps, and the synthetic route were shown in Scheme 1. Then all these ionic liquids were used as organocatalysts for asymmetric Michael additions of cyclohexanone to *trans*-nitrostyrene, and the representative results are summarized in Table 1.

As shown in Table 1, it is obvious that the ratio of cyclohexanone to trans-nitrostyrene played an important role to the model addition. When the ratio was about 20:1, the product was obtained in the highest yield (80%), excellent enantioselectivity (99%) and diastereoselectivity (99:1). Then, the analogs of **7c** were also investigated as the organocatalysts for the model addition. The Michael additions of cyclohexanone to trans-nitrostyrene in the presence of these catalysts afforded similar enantioselectivity and diastereoselectivity, but lower yields (Entries 6–10). These results showed that alkyl length and anion of ionic liquids exhibited little impact on the stereoselectivity, but much impact on the reaction yield and time. A plausible reason was that the solubility of **7a**–**7e** and **8** in cyclohexanone was closed related to their structures. While **7c** could dissolve in cyclohexanone, **7e**, **7b** and **8** could not absolutely dissolve under the same condition.

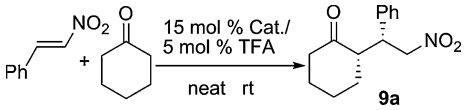
A plausible transition state was proposed to explain the stereochemical results (Scheme 2). In this state, the alkyl chains of the ILs moiety would hinder nitroolefins to approach the si-face of enamine. Perhaps the ionic attraction between the quaternary alkylammonium cation and the nitro group of the nitroolefins would increase the stereoselectivity too [26].

For IL **7c** showed the best catalytic activity among the ILs above when catalyzed the Michael addition of cyclohexanone to *trans*-nitrostyrene, it was selected as the organocatalyst for the following studies. Next, the recyclability of




**Scheme 1** Synthesis of several chiral ILs

**Table 1** Michael additions of cyclohexanone to *trans*-nitrostyrene




| Entry | Cat. | Cyclohexanone (eq) | Time (h) | Yield[a] (%) | syn/anti[b] | ee (syn)[c] (%) |
|---|---|---|---|---|---|---|
| **1** | 7c | 10 | 48 | 46 | 98/2 | 99 |
| **2** | 7c | 15 | 72 | 60 | 98/2 | 98 |
| **3** | 7c | 20 | 72 | 80 | 99/1 | 99 |
| **4** | 7c | 30 | 72 | 60 | 99/1 | 99 |
| **5** | 7c | 40 | 72 | 67 | 99/1 | 99 |
| **6** | 7a | 20 | 144 | 56 | 99/1 | 99 |
| **7** | 7b | 20 | 144 | 42 | 99/1 | 99 |
| **8** | 7d | 20 | 144 | 65 | 99/1 | 99 |
| **9** | 7e | 20 | 96 | 60 | 99/1 | 99 |
| **10** | 8 | 20 | 216 | 74 | 94/6 | 96 |
| **11**[d] | 7c | 20 | 72 | 76 | 99/1 | 98 |
| **12**[e] | 7c | 20 | 480 | 70 | 96/4 | 96 |

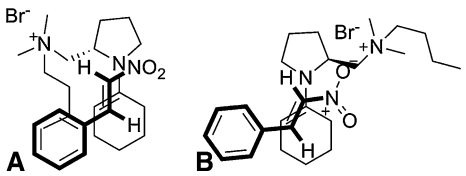
[a] Isolated yield

[b] Determined by chiral HPLC; Column: ChiralPak AS-H; Flowing phase: 2-propanol/hexane = 10/90; Flowing rate: 0.7 mL/min

[c] Determined by chiral HPLC

[d] Second cycle of catalyst **7c**

[e] Third cycle of catalyst **7c**

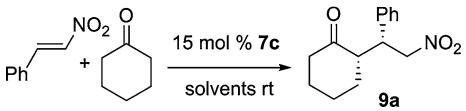



**Scheme 2** Plausible transition state

catalyst **7c** was studied. The result showed that **7c** could be easily recovered from the reaction mixture only by filtration after ethyl ether was added to the reaction mixture in 90–95% yield. And the Michael addition in the presence of the recovered **7c** obtained similar results but required longer reaction time (entries 11–12). The $^{1}$H NMR data of the recycled **7c** showed that the purity of **7c** descended. The descended purity and the loss of the catalyst **7c** in recycled process, perhaps, reduced the catalytic activity of the recycled **7c**.

Encouraged by the results described above, the effects of acidic additives and solvents to the reaction were investigated, and the results are shown in Table 2. It is clear that acidic additives exhibited important impact on the yield and enantioselectivity of the reaction. Better enantioselectivity was obtained in the presence of TFA or AcOH rather than $CH_3SO_3H$ and *p*-TsOH (entries 7–9). TFA afforded the best yield among those protonic acids.

**Table 2** The effects of acidic additives and solvents




| Entry[a] | Solvent | Acids/(mol %) | Time (h) | Yield[b] (%) | syn/anti[c] | ee (syn)[c] (%) |
|---|---|---|---|---|---|---|
| **1** | MeOH | TFA/5 | 142 | 48 | 98/2 | 97 |
| **2** | DMSO | TFA/5 | 142 | 51 | 99/1 | 99 |
| **3** | DMF | TFA/5 | 144 | 56 | 99/1 | 99 |
| **4** | $CH_2Cl_2$ | TFA/5 | 312 | 82 | 96/4 | 98 |
| **5** | THF | TFA/5 | 288 | 73 | 95/5 | 96 |
| **6** | EA | TFA/5 | 288 | 74 | 96/4 | 99 |
| **7** | Neat | $CH_3SO_3H$/5 | 168 | 40 | 99/1 | 76 |
| **8** | Neat | p-TsOH/5 | 168 | 48 | 96/4 | 78 |
| **9** | Neat | AcOH/5 | 72 | 39 | 97/3 | 98 |
| **10** | Neat | neat | 216 | 80 | 99/1 | 99 |

[a] 20 equiv of ketone

[b] Isolated yield

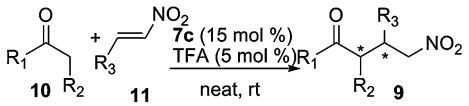
[c] Determined by chiral HPLC

Interestingly, the Michael reaction could proceed slowly without acidic additive to afford similar results (entry 10). The reasons why acidic additives exhibited important impacts may be explained as follows. As shown in Scheme 2 (state B), there was enamine structure in the transition state. A proper acidity was helpful to form the enamine. When TFA was used as an acidic additive, the reaction system could attain more appropriate acidity than $CH_3SO_3H$, p-TsOH, and without acidic additive. When AcOH was used as an additive, it would form a salt with catalyst **7c** which could not absolutely dissolve in cyclohexanone, so the catalytic activity of **7c** descended. So TFA was a better acidic additive than $CH_3SO_3H$, *p*-TsOH, AcOH and without acidic additive. Then TFA was selected as the acidic additive for the following studies.

As shown in Table 2, the impact of solvents on asymmetric Michael reaction was not significant. The reactions proceeded in different solvents showed similar stereoselectivity, but different reaction yields (entries 1–6). A plausible reason was that when a strong polar solvent, such as MeOH, DMSO and DMF, was used, the reaction was accelerated and the by-product was increased. Then the reaction time and yield was decreased.

Finally, IL **7c** was applied to several Michael reactions for a variety of aldehydes, ketones and nitroolefins. The results summarized in Table 3 indicated that different substituents on nitroolefins would yield different results. While Cl or $CH_3$ substituted aryl nitroolefins gave the corresponding products with moderate yields, excellent stereoselectivity (entries 3–6), $CH_3O$ substituted indicated

**Table 3** Asymmetric Michael addition of ketones and aldehydes to *trans*-nitrostyrenes catalyzed by **7c**




| Entry[a] | $R_1$ | $R_2$ | $R_3$ | Time (h) | Product | Yield (%)[b] | Flowing phase | Flowing rate (mL/min) | syn/anti[c] | ee (%)[c] |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | $-(CH_2)_4-$ | | 2-$NO_2$-Ph | 144 | 9b | 55 | 2-propanol:hexane = 7:93 | 0.7 | 97:3 | 96 |
| 2 | $-(CH_2)_4-$ | | 4-OMe-Ph | 144 | 9c | 76 | 2-propanol:hexane = 10:90 | 2 | 99:1 | 78 |
| 3 | $-(CH_2)_4-$ | | 4-Cl-Ph | 168 | 9d | 85 | 2-propanol:hexane = 10:90 | 0.7 | 97:3 | 94 |
| 4 | $-(CH_2)_4-$ | | 2,4-Cl-Ph | 168 | 9e | 68 | 2-propanol:hexane = 10:90 | 0.7 | 99:1 | 99 |
| 5 | $-(CH_2)_4-$ | | 2-Cl-Ph | 168 | 9f | 88 | 2-propanol:hexane = 10:90 | 0.7 | 99:1 | 96 |
| 6 | $-(CH_2)_4-$ | | 4-Me-Ph | 72 | 9g | 73 | 2-propanol:hexane = 10:90 | 0.7 | 99:1 | 94 |
| 7 | Me | H | Ph | 72 | 9h | – | 2-propanol:hexane = 10:90 | 0.7 | – | – |
| 8 | H | Et | Ph | 72 | 9i | 88 | 2-propanol:hexane = 1:99 | 1.0 | 99:1 | 74 |

[a] 20 equiv of ketone

[b] Isolated yield

[c] Determined by Chiral HPLC

lower enantioselectivies (entry 2) and $NO_2$ substituted gave lower yield (entry 1). Furthermore, 1-butyraldehyde was found to be a suitable Michael donor with high yield (88%), diastereoselectivities (99:1) and enantioselectivies (74%). But acetone exhibited low activity, after stirring 240 h under the same reaction conditions, no corresponding adduct was detected (Entries 7, 9). The reasons why the reaction yield and stereoselectivity was different may be explained as follows. One plausible reason was the electron cloud density of the benzyl position of substituted nitroolefins was different. One was the space hindrance of the substituent group on phenyl group of substituted nitroolefins was dissimilar. The other was the activity and structure of aldehydes and ketones were different. The electron-deficient substituent on phenyl group of nitroolefin would decrease the electron cloud density of the benzyl position, which was of benefit to Michael reaction. So **9d** and **9f** were obtained with higher reaction yield and stereoselectivity than **9c** and **9g** (entries 2, 3, 5, 6). The large substituent group on phenyl group of nitroolefin would hinder the nitroolefin to approach the enamine structure. So 9b and 9e were obtained with lower reaction yield (entries 1, 4). The activity and structure of aldehydes and ketones were important factors too. The activity to form enamine structure of acetone was too low to obtain Michael product (entry 8). 1-butyraldehyde could form enamine structure with catalyst **7c**, but this enamine could not hinder nitroolefin to approach the si-face of enamine perfectly because the space hindrance of this enamine was much less than enamine formed by cyclohexanone and **7c**. So **9i** was obtained with higher reaction yield and lower enantioselectivies (entry 7).

## 4 Conclusions

In conclusion, a series of chiral pyrrolidine-type quaternary alkylammonium ILs have been developed, which can be used to promote highly efficient for the asymmetric Michael addition reactions of cyclohexanone to nitroolefins. These chiral ILs catalysts could be easily synthesized from (*S*)-(2-hydroxy-methyl)pyrrolidine in six or seven steps. IL **7c** is easily recovered and reused. Further investigation on the applications of these ILs to other asymmetric reactions and the structure activity relationship of catalysts, are presently underway in our lab.

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