Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 18 (2007) 1788–1794

Pyrrolidine–pyridinium based organocatalysts for highly enantioselective Michael addition of cyclohexanone to nitroalkenes

Dan-Qian Xu, Bing-Tao Wang, Shu-Ping Luo, Hua-Dong Yue, Li-Ping Wang and Zhen-Yuan Xu*

State Key Laboratory Breeding Base of Green Chemistry-Synthesis Technology, Zhejiang University of Technology, Hangzhou 310014, China

Received 28 May 2007; accepted 18 July 2007
Available online 24 August 2007

Abstract—A novel class of pyrrolidine–pyridinium based organocatalysts has been developed and demonstrated to efficiently catalyze the asymmetric Michael addition reactions of unmodified cyclohexanone to nitroalkenes in the ionic liquid $BMImBF_4$ with up to 95% yield and nearly 100% ee. The catalytic system could be reused for four times and still retained high enantioselectivity. X-ray crystallographic analysis results suggested that a sterically hindered pyridinium moiety on the catalyst played an important role in the chiral induction.

1. Introduction

Michael addition reactions play an important role in C–C bond forming reactions in organic synthesis. The development of efficient methods for the asymmetric Michael addition is one of the significant goals in asymmetric synthesis.[1] One of the valuable Michael addition reactions is the conjugate addition of a carbon nucleophile to an electron deficient nitroalkene, which is a potentially useful building block in organic synthesis.[1a,2] Since the versatile nitro functionality can be easily transformed into an amine, nitrile oxide, ketone, carboxylic acid, hydrogen, etc., great efforts have been made to improve the diastereoselectivity and enantioselectivity of the process over the last few years.[1,3]

With the development of environmentally friendly organic reactions, asymmetric organocatalysis has emerged as a new field in organic synthesis, due to the great advantages of organocatalysts.[4] Accordingly, more and more attention has been paid to organocatalytic asymmetric Michael addition reactions, although metal-complex-mediated processes afford Michael adducts in high yield with good enantiomeric excess.[3] Since List[5a] and Barbas[5b] reported the enantioselective Michael additions of unmodified ketones using L-proline and (*S*)-1-(2-pyrrolidinylmethyl)-pyrrolidine as organocatalysts, respectively, some new chiral pyrrolidine-type amines have been developed for promoting the efficiency of the process.[6] The pyrrolidine portion of these chiral amines is regarded as a unique backbone for the asymmetric catalysis that facilitates enamine- and imine-based transformations from ketone precursors. Recently, with the development of task specific ionic liquids, there have been reports concerning ionic-liquid-functionalized pyrrolidine-type amines as highly efficient asymmetric organocatalysts.[7] In these types of chiral amines, the pyrrolidine portion is conjugated to the imidazolium-type ionic liquids, so that the former can serve as a catalytic site and the latter as both the phase tag and a chiral-induction group. In our own work, such types of chiral amines have also been designed and applied successfully in chiral discrimination and asymmetric Michael addition to nitroalkenes, in which the pyrrolidine–imidazolium conjugates as organocatalysts combined with ionic liquids (ILs) as reaction media presented a synergistic effect in the improvement of reaction performance of reactivity, enantioselectivity, and recyclability.[8] As part of a program aimed at developing new organocatalysts for asymmetric organic transformations, we herein report the ability of our new pyrrolidine–pyridinium conjugates in performing asymmetric Michael addition reactions, the work of which was encouraged by the success of chiral pyrrolidine–pyridine[6a] and pyrrolidine–imidazolium[7a] conjugates as highly enantioselective organocatalysts (Fig. 1).

* Corresponding author. Tel./fax: +86 571 88320066; e-mail: greenchem@zjut.edu.cn

0957-4166/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2007.07.021

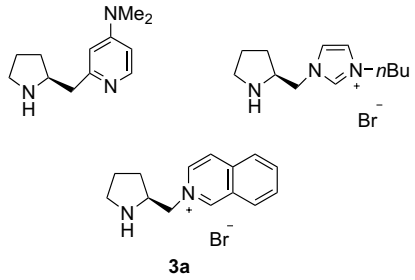
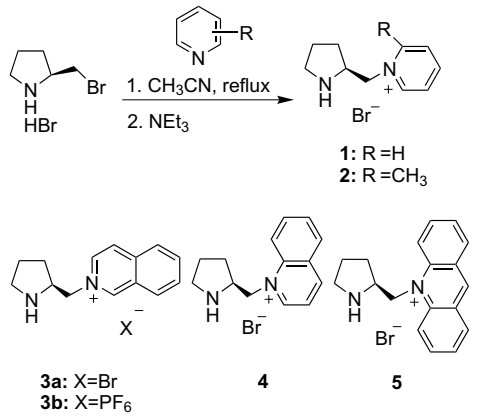


Figure 1. Favored pyrrolidine-type organocatalysts.

2. Results and discussion

The pyrrolidine–pyridinium bromide conjugates **1**–**5** were readily synthesized by treating pyridine or pyridine derivatives with (*S*)-(+)-2-bromomethylpyrrolidine hydrobromide, which was prepared, according to our previous work, from commercially available L-proline by reduction with $NaBH_4$–I_2, a neutralization step and bromination with PBr_3 successively.[8] Anion metathesis of **3a** with KPF_6 afforded **3b** (Scheme 1).

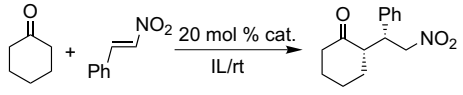


Scheme 1. Synthesis of organocatalysts **1**–**5**.

Based upon our previous work, we initially used these organocatalysts **1**–**5** for the direct asymmetric Michael addition of cyclohexanone **6** to *trans*-β-nitrostyrene **7a** to afford the Michael adduct **8a** using ILs $BMImPF_6$ and $BMImBF_4$ as reaction media, respectively. As shown in Table 1, organocatalysts **1**–**5** were indeed able to catalyze the transformation in ILs, but the activity and enantioselectivity differed significantly. Catalysts **1**–**2** and **4**–**5** gave only poor to moderate results in either ILs (entries 1, 2, 5–8, and 11, 12). While catalyst **3b** still exhibited a poor performance in $BMImPF_6$, the use of $BMImBF_4$ led to a significant improvement in both activity and enantioselectivity with 95% yield and 93% ee value obtained after 20 h (entries 4 and 10). Compound **3a** was a powerful catalyst, providing the desired adducts with a high degree of diastereo- and enantiocontrol in either ILs (entries 3 and 9).

Using pyrrolidine–pyridinium conjugate **3a** as a catalyst, a series of different solvents were screened at room temperature. As evident in Table 2, the reaction yield and enantioselectivity varied significantly in the solvents screened. In general, reactions in traditional solvents were sluggish (48 h) with poor enantioselectivities (0–59%) (entries 1–7) while the use of the substrate cyclohexanone as a solvent led to 91% yield and 63% ee value after 48 h (entry 8). Interestingly, regardless of the solvents used, the reactions exhibited high diastereoselectivity with values in the range of 90/10–96/4. To our delight, decreasing the amount of **3a** from 20 mol % to 10 mol % did not affect the reaction performance in $BMImBF_4$, while further decreasing to 5 mol % still did not affect the diastereoselectivity and enantioselectivity of **8a**, but reduced the chemical yield (entries 9 and 10). Therefore, the use of 10 mol % of catalyst **3a** was optimal to ensure high reaction efficiency (94% yield and 99% ee). In addition, the observation indicated

Table 1. Organocatalyzed direct Michael addition of cyclohexanone **6** to *trans*-β-nitrostyrene **7a** in ILs[a]

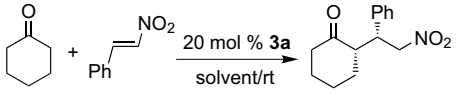


6 **7a** **8a**

Entry	Cat.	IL	Time (h)	Yield[b] (%)	dr[c] (*syn*/*anti*)	ee[d] (%)
1	**1**	$BMImPF_6$	48	93	91/9	28
2	**2**	$BMImPF_6$	48	19	91/9	7
3	**3a**	**$BMImPF_6$**	**48**	**88**	**96/4**	**95**
4	**3b**	$BMImPF_6$	48	90	90/10	41
5	**4**	$BMImPF_6$	48	74	91/9	8
6	**5**	$BMImPF_6$	48	8	91/9	23
7	**1**	$BMImBF_4$	24	94	90/10	68
8	**2**	$BMImBF_4$	48	80	91/9	4
9	**3a**	**$BMImBF_4$**	**20**	**95**	**93/7**	**99**
10	**3b**	**$BMImBF_4$**	**20**	**95**	**96/4**	**93**
11	**4**	$BMImBF_4$	24	92	91/9	17
12	**5**	$BMImBF_4$	48	92	91/9	52

[a] All reactions were carried out in $BMImPF_6$ or $BMImBF_4$ (3 mL) using **6** (2 mmol) and **7a** (1 mmol) in the presence of 20 mol % of **1**–**5**.
[b] Isolated yield.
[c] Determined by GC–MS.
[d] Determined by chiral HPLC analysis with CD detector (Daicel Chiralpak AS-H, hexane/2-propanol = 85/15).

Table 2. Solvent effect for organocatalyzed direct Michael addition reactions[a]



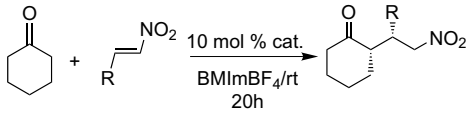
6 7a 8a

Entry	Solvent	Time (h)	Yield[b] (%)	dr[c] (*syn*/*anti*)	ee[d] (%)
1	2-PrOH	48	55	93/7	6
2	MeOH	48	94	92/8	0
3	CH_3CN	48	55	90/10	28
4	$C_6H_5CH_3$	48	95	92/8	31
5	CH_2Cl_2	48	94	92/8	59
6	THF	48	27	93/7	27
7	DMSO	48	37	91/9	24
8	Neat[e]	48	91	90/10	63
9	**$BMImBF_4$**[f]	**20**	**94**	**94/6**	**99**
10	$BMImBF_4$[g]	20	50	93/7	97

[a] Unless otherwise noted, all reactions were carried out in solvent (3 mL) using **6** (2 mmol) and **7a** (1 mmol) in the presence of 20 mol % of **3a**.
[b] Isolated yield.
[c] Determined by GC–MS.
[d] Determined by chiral HPLC analysis with CD detector (Daicel Chiralpak AS-H, hexane/2-propanol = 85/15).
[e] 10 equiv of cyclohexanone was used.
[f] 10 mol % of **3a** was used.
[g] 5 mol % of **3a** was used.

that the catalytic system of pyrrolidine–pyridinium conjugate combined with ionic liquid media presented a synergistic effect in the improvement of the organocatalytic transformation, in which the ionic medium might play an important role in stabilizing the formed iminium-ion transition state, and further **3a**/$BMImBF_4$ was superior to **3a**/$BMImPF_6$. On the other hand, it was noted that acids were not needed in this catalytic system, while it was usually essential to apply Brønsted acids as co-catalysts to improve the chiral amine catalyzed asymmetric Michael additions.[6]

Table 3. Michael addition of **6** to **7** catalyzed by **3a** or **3b** in $BMImBF_4$[a]



6 7 8

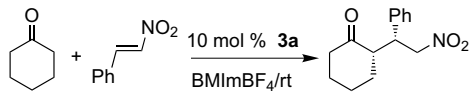
Entry	Cat.	Product	R	Yield[b] (%)	dr[c] (*syn*/*anti*)	ee[d] (%)
1	**3a**	**8a**	C_6H_5	94	94/6	99
2	**3b**			95	96/4	93
3	**3a**	**8b**	*o*-MeO–C_6H_4	95	95/5	82
4	**3b**			95	96/4	97
5	**3a**	**8c**	*m*-MeO–C_6H_4	93	95/5	92
6	**3b**			95	93/7	93
7	**3a**	**8d**	*p*-MeO–C_6H_4	95	92/8	~100
8	**3b**			95	94/6	93
9	**3a**	**8e**	*p*-Me–C_6H_4	94	94/6	87
10	**3b**			94	95/5	98
11	**3b**	**8f**	*p*-Cl–C_6H_4	95	95/5	83
12	**3b**	**8g**	*o*-Br–C_6H_4	95	96/4	81
13	**3b**	**8h**	*m*-Br–C_6H_4	94	92/8	82
14	**3a**	**8i**	*p*-CF_3–C_6H_4	93	95/5	84
15	**3a**	**8j**	*o*-NO_2–C_6H_4	93	95/5	77
16	**3b**	**8k**	2-Naphthyl	95	93/7	82
17	**3a**	**8l**	2-Furanyl	95	90/10	87
18	**3b**			95	91/9	91
19	**3b**	**8m**	2-Thioanyl	95	92/8	75

[a] All reactions were carried out in $BMImBF_4$ (3 mL) using **6** (2 mmol) and **7** (1 mmol) in the presence of 10 mol % of catalyst.
[b] Isolated yield.
[c] Determined by GC analyses.
[d] Determined by chiral HPLC analysis with CD detector (Daicel Chiralpak AS-H, hexane/2-propanol = 85/15).

Encouraged by the above results, the asymmetric addition reactions of cyclohexanone to *trans*-β-nitroalkenes promoted by 10 mol % of catalysts **3a** and/or **3b** were carried out in $BMImBF_4$ at room temperature with the results summarized in Table 3. While the introduction of electron-donating (OCH_3 and CH_3) or electron-withdrawing (Cl, Br, CF_3, and NO_2) groups on the benzene ring of the *trans*-β-nitrostyrene slightly influenced enantioselectivities, the Michael adducts were all formed in excellent yields (93–95%) and good diastereoselectivities (92/8–96/4) without any side products observed (entries 3–15). The *O*- and *S*-heteroaromatic nitroalkenes were also suitable substrates as Michael acceptors (entries 17–19).

One noteworthy feature of the present study was the recyclability of the organoncatalyst, as well as the reaction media. The **3a**/$BMImBF_4$ system could be repeatedly used for four consecutive runs for the addition of **6** to **7a** (Table 4). In each reuse, the organocatalyst retained its high activity and high levels of enantioselectivities (96–99% ee) and diastereoselectivity (94/6) despite some degree of loss of the yields observed in entries 2–4.

Table 4. Recycling study of Michael reaction organocatalyzed by **3a**[a]

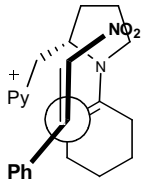


6 **7a** **8a**

Recycle	Time (h)	Yield[b] (%)	dr[c] (*syn*/*anti*)	ee[d] (%)
	20	94	94/6	99
1	24	94	94/6	99
2	24	92	94/6	99
3	24	90	94/6	97
4	24	90	94/6	96

[a] All reactions were carried out in $BMImBF_4$ (3 mL) using **6** (2 mmol) and **7a** (1 mmol) in the presence of 10 mol % of **3a**.
[b] Isolated yield.
[c] Determined by GC–MS.
[d] Determined by chiral HPLC analysis with CD detector (Daicel Chiralpak AS-H, hexane/2-propanol = 85/15).

The Michael adduct **8a** was determined to have a *syn* configuration by X-ray crystallographic analysis.[9] Therefore, based on Seebach's model,[10] pyrrolidine–pyridinium conjugates must catalyze a *Re*-face attack on **6** via an enamine transition state, in which the *Si*-face was shielded by the pyridinium moiety on the catalyst as outlined in Scheme 2. In addition, the ionic liquid $BMImBF_4$ might play a key role in stabilizing the formed iminium-ion transition state, owned a greater charge density than the initial reaction molecules, by operating favorable electrostatic interactions, which led to the enhancement of the overall reaction efficiency.[11]



Scheme 2. Proposed transition state.

To better understand the efficiency of the present model, the relative configurations of the pyrrolidine–pyridinium conjugates **2** and **3a** were also investigated, as shown in Figure 2, by X-ray diffraction of their hydrobromide salts.[9] The results suggested that the isoquinolium-containing arm of **3a** catalyst could shield the *Si*-face of the enamine double bond more completely and thus direct the Michael acceptor approaching the less hindered *Re*-face more efficiently than the methylpyridinium-containing arm of **2** (Fig. 3), which was quite concordant with the observed stereochemistry and the obtained enantiomeric excess values of the Michael adducts.

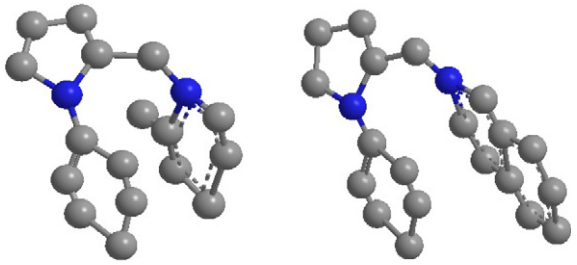


Figure 3. The possible enamine transition states of **2** and **3a** catalyzed Michael addition.

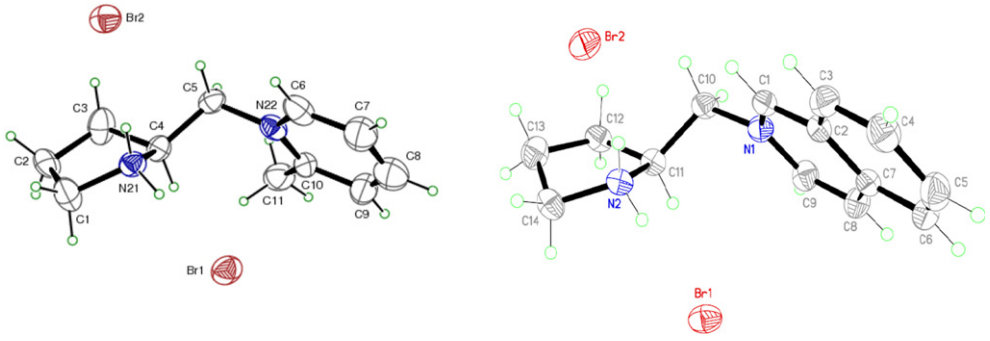


Figure 2. X-ray crystal structures of **2** and **3a**'s hydrobromide salts.

3. Conclusions

In conclusion, pyrrolidine–pyridinium based organocatalysts have been designed and readily synthesized from commercially available L-proline. The **3a**/$BMImBF_4$ catalytic system demonstrated high enantioselectivities (75–100% ee) and yields (93–95%) and recyclability in the Michael addition of cyclohexanone to different aromatic nitroalkenes. X-ray crystallographic analysis results gave clear evidence that a pyridinium-containing arm on the catalyst played an important role in the chiral induction by shielding the *Si*-face of enamine transition state and thus directing the Michael acceptor approaching the less hindered *Re*-face. Further investigations on the application of these catalysts in asymmetric organocatalysis are currently in progress.

4. Experimental

4.1. General

All reactions were carried out directly under air. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker ARX 400. Chemical shifts of ^1H and ^{13}C were given in δ relative to tetramethylsilane (TMS). IR spectra were obtained on a Bruker EQUINOX 55. Electrospray ionization (ESI) mass experiments were performed on a Finnigan LCQ Advantage. ESI-HRMS spectra were obtained on a Bruker APEX III FTICR mass spectrometer. HPLC experiments were carried out using a JASCO LC-2000 Plus system consisting of MD and CD detectors. GC–MS experiments were performed on a Angilent 6890N gas chromatograph with a 5973N mass selective detector.

4.2. Experimental procedures

4.2.1. General procedures for the preparation of organocatalysts 1–5's hydrobromide. To a stirred solution of pyridine or pyridine derivatives (10 mmol) in MeCN (40 mL) was added (*S*)-(+)-2-bromomethylpyrrolidine hydrobromide (10 mmol) at 80 °C and the reaction mixture was stirred at reflux for 20 h. The solvent was removed under reduced pressure and the residue was recrystallized from MeOH to afford organocatalysts **1**–**5** hydrobromide (71–86% yield).

A mixture of **3a** (7 mmol), KPF_6 (7 mmol) and 20 mL of CH_3OH/H_2O was stirred at room temperature for 2 days. Solvents of the mixture were removed under vacuum and the residue was recrystallized from MeOH to afford a white solid **3b** (92% yield).

4.2.2. General procedures for the asymmetric Michael addition reaction. To a stirred solution of catalyst **3a** or **3b** (0.1 mmol) in $BMImBF_4$ (3 mL) at room temperature was added cyclohexanone (2 mmol), triethylamine (0.1 mmol) and after 15 min, nitroalkene (1 mmol). The reaction mixture was stirred at room temperature for the appropriate time by monitoring on GC. After completion of the reaction, water (5 mL) was added to the reaction mixture and the organic layer was extracted with ethyl ether (3×5 mL). The combined extracts were dried over Na_2SO_4 and concentrated. The residue was purified by preparative TLC (hexane/$CHCl_3 = 4/1$) to give the Michael adduct. On the other hand, the remaining catalyst-$BMImBF_4$ system could be reused in subsequent reactions after being dried under vacuum to remove water.

4.3. Spectroscopic data

4.3.1. (*S*)-(+)-1-Pyrrolidin-2-ylmethyl-pyridinium bromide hydrobromide 1. ^1H NMR (400 MHz, DMSO-d_6, δ ppm): 9.29–9.28 (d, 4H), 8.70–8.66 (t, $J = 8.0$ Hz, 1H), 8.26–8.22 (t, $J = 8.0$ Hz, 2H), 5.09 (s, 1H), 3.80–3.67 (m, 2H), 3.38–3.35 (d, $J = 11.6$ Hz, 1H), 3.03–2.98 (t, $J = 11.6$ Hz, 1H), 2.34–2.30 (m, 2H), 2.09–2.05 (m, 1H), 1.87–1.85 (m, 1H); ^{13}C NMR (75 MHz, DMSO-d_6, δ ppm): 147.1, 144.5, 128.8, 64.8, 45.4, 42.6, 28.7, 21.4; IR (KBr): 3440, 2910, 2701, 2477, 1628, 1570, 1487, 1451, 1177 cm^{-1}; MS (ESI, *m*/*z*): 162.9 $[M-HBr-Br]^+$; HRMS (ESI): Calcd for $C_{10}H_{15}N_2^+$: 163.1235. Found: 163.1228.

4.3.2. (*S*)-(+)-2-Methyl-1-pyrrolidin-2-ylmethyl-pyridinium bromide hydrobromide 2. ^1H NMR (400 MHz, DMSO-d_6, δ ppm): 9.32 (s, 2H), 9.19–9.18 (d, $J = 6.4$ Hz, 1H), 8.57–8.52 (t, $J = 8.0$ Hz, 1H), 8.14–8.12 (d, $J = 8.0$ Hz, 1H), 8.06–8.03 (t, $J = 6.4$ Hz, 1H), 5.07–5.04 (m, 2H), 4.13 (s, 1H), 3.38 (m, 1H), 3.16–3.14 (m, 1H), 2.94 (s, 3H), 2.27–2.23 (m, 1H), 2.05–2.02 (m, 1H), 1.96–1.92 (m, 1H), 1.83–1.78 (m, 1H); ^{13}C NMR (75 MHz, DMSO-d_6, δ ppm): 156.7, 146.4, 146.1, 130.8, 126.2, 58.4, 56.8, 45.1, 27.9, 22.5, 20.7; IR (KBr): 3468, 2755, 2472, 1629, 1574, 1511, 1471, 1177 cm^{-1}; MS (ESI, *m*/*z*): 176.9 $[M-HBr-Br]^+$; HRMS (ESI): Calcd for $C_{11}H_{17}N_2^+$: 177.1392. Found: 177.1390.

4.3.3. (*S*)-(+)-2-Pyrrolidin-2-ylmethyl-isoquinolinium bromide hydrobromide 3a. ^1H NMR (400 MHz, DMSO-d_6, δ ppm): 10.27 (s, 1H), 9.20 (s, 2H), 8.94–8.92 (d, $J = 8.0$ Hz, 1H), 8.72–8.70 (d, $J = 8.0$ Hz, 1H), 8.54–8.52 (d, $J = 8.0$ Hz, 1H), 8.42–8.40 (d, $J = 8.0$ Hz, 1H), 8.34–8.30 (t, $J = 8.0$ Hz, 1H), 8.14–8.11 (t, $J = 8.0$ Hz, 1H), 5.21–5.16 (m, 2H), 4.28 (s, 1H), 3.29–3.37 (m, 1H), 3.22–3.21 (m, 1H), 2.27–2.24 (m, 1H), 2.11–2.06 (m, 1H), 1.99–1.84 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6, δ ppm): 151.4, 137.8, 137.7, 135.3, 131.8, 131.1, 127.7, 127.6, 126.5, 60.0, 59.9, 45.4, 27.9, 22.9; IR (KBr): 3421, 2973, 2851, 2719, 2461, 1644, 1510, 1409, 1285, 1185 cm^{-1}; MS (ESI, *m*/*z*): 213.0 $[M-HBr-Br]^+$; HRMS (ESI): Calcd for $C_{14}H_{17}N_2^+$: 213.1392. Found: 213.1388.

4.3.4. (*S*)-(+)-2-Pyrrolidin-2-ylmethyl-isoquinolinium hexafluorophosphate hydrobromide 3b. ^1H NMR (400 MHz, DMSO-d_6, δ ppm): 10.17 (s, 1H), 9.08 (s, 2H), 8.87–8.85 (d, $J = 8.0$ Hz, 1H), 8.70–8.68 (d, $J = 8.0$ Hz, 1H), 8.53–8.51 (d, $J = 8.0$ Hz, 1H), 8.40–8.39 (d, $J = 8.0$ Hz, 1H), 8.33–8.30 (t, $J = 8.0$ Hz, 1H), 8.14–8.10 (t, $J = 8.0$ Hz, 1H), 5.20–5.06 (m, 2H), 4.23 (s, 1H), 3.37–3.34 (m, 1H), 3.22–3.20 (m, 1H), 2.27–2.22 (m, 1H), 2.09–2.05 (m, 1H), 1.99–1.94 (m, 1H), 1.90–1.83 (m, 1H); ^{13}C NMR (75 MHz, DMSO-d_6, δ ppm): 151.4, 137.8, 137.7, 135.3, 131.8, 131.1, 127.7, 127.6, 126.5, 60.0, 59.9, 45.4, 27.9, 22.9; IR (KBr): 3420, 2959, 2747, 1650, 1401, 883, 841, 740, 558 cm^{-1}; MS (ESI, *m*/*z*): 213.0 $[M-HBr-Br]^+$, 145

$[PF_6]^-$; HRMS (ESI): Calcd for PF_6^-: 144.9642. Found: 144.9646.

4.3.5. (*S*)-(+)-1-Pyrrolidin-2-ylmethyl-quinolinium bromide hydrobromide 4. ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 10.29 (s, 1H), 9.26 (s, 2H), 8.96–8.94 (d, $J = 8.0$ Hz, 1H), 8.72–8.70 (d, $J = 8.0$ Hz, 1H), 8.52–8.50 (d, $J = 8.0$ Hz, 1H), 8.41–8.39 (d, $J = 8.0$ Hz, 1H), 8.33–8.29 (t, $J = 8.0$ Hz, 1H), 8.13–8.10 (t, $J = 8.0$ Hz, 1H), 5.22–5.19 (m, 2H), 4.30–4.28 (m, 1H), 3.38–3.34 (m, 1H), 3.22–3.19 (m, 1H), 2.29–2.22 (m, 1H), 2.11–2.04 (m, 1H), 1.98–1.83 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6, δ ppm): 151.4, 137.8, 137.7, 135.4, 131.8, 131.1, 127.7, 127.6, 126.5, 59.9, 59.8, 45.3, 28.0, 22.9; IR (KBr): 3405, 2704, 2394, 1568, 1433, 1210 cm^{-1}; MS (ESI, *m*/*z*): 213.0 $[M-HBr-Br]^+$; HRMS (ESI): Calcd for $C_{14}H_{17}N_2^+$: 213.1392. Found: 213.1388.

4.3.6. (*S*)-(+)-10-Pyrrolidin-2-ylmethyl-acridinium bromide hydrobromide 5. ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 9.99 (s, 1H), 8.88–8.72 (m, 2H), 8.53–8.51 (d, $J = 8.0$ Hz, 2H), 8.41–8.38 (d, $J = 8.0$ Hz, 2H), 8.30–8.26 (t, $J = 8.0$ Hz, 2H), 7.95–7.91 (t, $J = 8.0$ Hz, 2H), 4.48-4.43 (m, 1H), 3.59–3.56 (m, 1H), 3.29–3.15 (m, 2H), 3.00–2.98 (m, 1H), 2.23–2.20 (m, 1H), 1.94–1.85 (m, 2H), 1.75–1.71 (m, 1H); ^{13}C NMR (75 MHz, DMSO-d_6, δ ppm): 148.3, 140.7, 137.4, 130.3, 128.1, 126.2, 120.8, 49.3, 44.4, 42.8, 32.6, 21.7; IR (KBr): 3429, 2995, 2897, 2705, 2415, 1638, 1583, 1467, 1398, 892, 746 cm^{-1}; MS (ESI, *m*/*z*): 263.2 $[M-HBr-Br]^+$; HRMS (ESI): Calcd for $C_{18}H_{19}N_2^+$: 263.1548. Found: 263.1545.

4.3.7. 2-(2-Nitro-1-phenylethyl)cyclohexanone 8a. ee value was determined by HPLC analysis (Daicel Chiralpak AS-H, hexane/2-propanol = 85/15, 1.0 ml/min, 220 nm; t_r(minor) = 14.32 min, t_r(major) = 20.58 min); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 7.34–7.16 (m, 5H), 4.95 (dd, $J = 12.4$, 4.8 Hz, 1H), 4.63 (dd, $J = 12.4$, 10 Hz, 1H), 3.75 (ddd, $J = 10$, 10, 4.8 Hz, 1H), 2.72–1.19 (m, 9H, cycl); MS (EI): 55 (30), 77 (12), 91 (63), 104 (34), 115 (25), 141 (15), 157 (13), 171 (100), 183 (21), 200 (60), 247 (1).

4.3.8. 2-(2-Nitro-1-(2-methoxyphenyl)ethyl)cyclohexanone 8b. The ee value was determined by HPLC analysis (Daicel Chiralpak AS-H, hexane/2-propanol = 85/15, 1.0 ml/min, 220 nm; t_r(minor) = 11.35 min, t_r(major) = 14.90 -min); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 7.24 (dd, $J = 8.4$, 7.6 Hz, 1H), 7.08 (d, $J = 7.6$ Hz, 1H), 6.88 (t, $J = 8.4$ Hz, 2H), 4.88–4.80 (m, 2H), 3.95 (dt, $J = 9.2$, 4.9 Hz, 1H), 3.84 (s, 3H), 3.01–2.94 (m, 1H), 2.49–2.35 (m, 2H), 2.09–2.05 (m, 1H), 1.79–1.56 (m, 4H), 1.25–1.16 (m, 1H); MS (EI): 55 (11), 77 (17), 91 (15), 105 (11), 121 (60), 134 (54), 145 (10), 159 (12), 171 (9), 187 (7), 201 (100), 213 (6), 230 (51), 277 (10).

4.3.9. 2-(2-Nitro-1-(3-methoxyphenyl)ethyl)cyclohexanone 8c. The ee value was determined by HPLC analysis (Daicel Chiralpak AS-H, hexane/2-propanol = 85/15, 1.0 ml/min, 220 nm; t_r(minor) = 12.75 min, t_r(major) = 25.90 min); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 7.25 (t, $J = 8.0$ Hz, 1H), 6.79 (d, $J = 8.0$ Hz, 1H), 6.75 (d, $J = 8.0$ Hz, 1H), 6.71 (s, 1H), 4.92 (dd, $J = 12.0$, 4.0 Hz, 1H), 4.62 (dd, $J = 12.0$, 10.4 Hz, 1H), 3.79 (s, 3H), 3.77–3.70 (m, 1H), 2.70–2.62 (m, 1H), 2.49–2.35 (m, 2H), 2.10–2.07 (m, 1H), 1.81–1.55 (m, 4H), 1.27–1.21 (m, 1H); MS (EI): 55 (5), 77 (16), 91 (26), 103 (14), 121 (39), 134 (27), 147 (11), 159 (18), 171 (10), 187 (14), 201 (100), 213 (33), 230 (38), 277 (19).

4.3.10. 2-(2-Nitro-1-(4-methoxyphenyl)ethyl)cyclohexanone 8d. The ee value was determined by HPLC analysis (Daicel Chiralpak AS-H, hexane/2-propanol = 85/15, 1.0 ml/min, 220 nm; t_r(minor) = 18.76 min, t_r(major) = 20.07 min); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 7.09 (d, $J = 6.7$ Hz, 2H), 6.85 (d, $J = 6.7$ Hz, 2H), 4.90 (dd, $J = 12.4$, 4.6 Hz, 1H), 4.58 (dd, $J = 12.4$, 9.6 Hz, 1H), 3.78 (s, 3H), 3.71 (ddd, $J = 9.6$, 9.6, 4.6 Hz, 1H), 2.72–2.60 (m, 1H), 2.50–2.31 (m, 2H), 2.11–2.02 (m, 1H), 1.77–1.64 (m, 4H), 1.27–1.15 (m, 1H); MS (EI): 55 (4), 77 (6), 91 (14), 103 (5), 121 (39), 134 (74), 147 (6), 176 (5), 187 (7), 201 (100), 213 (6), 230 (54), 277 (3).

4.3.11. 2-(2-Nitro-1-(4-methylphenyl)ethyl)cyclohexanone 8e. The ee value was determined by HPLC analysis (Daicel Chiralpak AS-H, hexane/2-propanol = 85/15, 1.0 ml/min, 220 nm; t_r(minor) = 8.56 min, t_r(major) = 13.33 min); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 7.12 (d, $J = 8.4$ Hz, 2H), 7.04 (d, $J = 8.4$ Hz, 2H), 4.91 (dd, $J = 12$, 4.8 Hz, 1H), 4.60 (dd, $J = 12$, 10 Hz, 1H), 3.75–3.69 (ddd, $J = 10$, 10, 4.8 Hz, 1H), 2.70–2.63 (m, 1H), 2.50–2.35 (m, 2H), 2.33 (s, 3H), 2.10–2.04 (m, 1H), 1.79–1.52 (m, 4H), 1.28–1.18 (m, 1H); MS (EI): 55 (6), 77 (7), 91 (17), 105 (47), 118 (36), 129 (16), 147 (13), 155 (11), 171 (11), 185 (100), 197 (13), 214 (53).

4.3.12. 2-(2-Nitro-1-(4-chlorophenyl)ethyl)cyclohexanone 8f. The ee value was determined by HPLC analysis (Daicel Chiralpak AS-H, hexane/2-propanol = 85/15, 1.0 ml/min, 220 nm; t_r(minor) = 11.18 min, t_r(major) = 17.47 min); ^{1}H NMR (400 MHz, $CDCl_3$, δppm): 7.34 (d, $J = 8.4$ Hz, 2H), 7.15 (d, $J = 8.4$ Hz, 2H), 4.93 (dd, $J = 12.4$, 4.4 Hz, 1H), 4.61 (dd, $J = 12.4$, 10 Hz, 1H), 3.75 (ddd, $J = 10$, 10, 4.4 Hz, 1H), 2.67–2.63 (m, 1H), 2.50–2.34 (m, 2H), 2.10–2.08 (m, 1H), 1.82–1.61 (m, 4H), 1.30–1.19 (m, 1H); MS (EI): 55 (13), 77 (10), 89 (7), 103 (16), 115 (23), 125 (57), 138 (37), 151 (11), 165 (12), 175 (7), 182 (8), 191 (13), 205 (100), 217 (14), 234 (50).

4.3.13. 2-(2-Nitro-1-(2-bromophenyl)ethyl)cyclohexanone 8g. The ee value was determined by HPLC analysis (Daicel Chiralpak AS-H, hexane/2-propanol = 85/15, 1.0 ml/min, 220 nm; t_r(minor) = 10.54 min, t_r(major) = 13.67 min); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 7.47 (dd, $J = 8.1$, 1.2 Hz, 1H), 7.23–7.13 (m, 2H), 7.06–7.00 (m, 1H), 4.87–4.73 (m, 2H), 4.30–4.22 (m, 1H), 2.78 (m, 1H), 2.38–2.28 (m, 2H), 2.03–1.97 (m, 1H), 1.72–1.45 (m, 4H), 1.30–1.26 (m, 1H); MS (EI): 55 (14), 67 (5), 77 (14), 91 (7), 103 (16), 115 (26), 128 (23), 141 (8), 155 (7), 171 (24), 185 (96), 199 (18), 246 (100).

4.3.14. 2-(2-Nitro-1-(3-bromophenyl)ethyl)cyclohexanone 8h. The ee value was determined by HPLC analysis (Daicel Chiralpak AS-H, hexane/2-propanol = 85/15, 1.0 ml/min, 220 nm; t_r(minor) = 12.22 min, t_r(major) = 21.42 min); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 7.27 (s, 1H), 7.19 (d,

$J = 8.0$ Hz, 1H), 7.12 (d, $J = 8.0$ Hz, 1H), 4.95 (dd, $J = 12.8$, 4.8 Hz, 1H), 4.62 (dd, $J = 12.8$, 10 Hz, 1H), 3.77–3.72 (m, 1H), 2.75–1.20 (m, 9H, cycl); MS (EI): 55 (33), 67 (13), 71 (32), 90 (13), 103 (29), 115 (58), 129 (56), 143 (21), 156 (20), 170 (44), 182 (89), 195 (6), 209 (10), 221 (5), 235 (12), 249 (99), 251 (100), 263 (15), 280 (62).

4.3.15. 2-(2-Nitro-1-(4-trifluolomethylphenyl)ethyl)cyclohexanone 8i. The ee value was determined by HPLC analysis (Daicel Chiralpak AS-H, hexane/2-propanol = 85/15, 1.0 ml/min, 220 nm; t_r(minor) = 8.17 min, t_r(major) = 11.75 min); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 8.31 (d, $J = 8.8$ Hz, 2H), 7.59 (d, $J = 8.8$ Hz, 2H), 4.99 (m, 1H), 4.66 (m, 1H), 3.98 (m, 1H), 2.70–1.25 (m, 9H, cycl); MS (EI): 55 (30), 69 (12), 81 (8), 103 (8), 115 (15), 129 (17), 151 (14), 159 (68), 173 (35), 185 (24), 199 (16), 209 (15), 225 (19), 239 (100), 251 (34), 268 (53).

4.3.16. 2-(2-Nitro-1-(2-nitrophenyl)ethyl)cyclohexanone 8j. The ee value was determined by HPLC analysis (Daicel Chiralpak AS-H, hexane/2-propanol = 85/15, 1.0 ml/min, 220 nm; t_r(minor) = 25.38 min, t_r(major) = 30.43 min); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 7.90–7.84 (m, 1H), 7.65–7.54 (m, 1H), 7.47–7.38 (m, 2H), 4.95–4.93 (m, 1H), 4.35–4.30 (m, 1H), 4.13–4.09 (m, 1H), 2.66–1.24 (m, 9H, cycl); MS (EI): 55 (49), 67 (22), 77 (41), 91 (31), 104 (20), 115 (39), 130 (36), 144 (19), 156 (17), 168 (13), 185 (91), 200 (20), 246 (100).

4.3.17. 2-(2-Nitro-1-(2-naphthyl)ethyl)cyclohexanone 8k. The ee value was determined by HPLC analysis (Daicel Chiralpak AS-H, hexane/2-propanol = 85/15, 1.0 ml/min; t_r(minor) = 17.77 min, t_r(major) = 33.86 min); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 7.82–7.27 (m, 7H), 5.01 (dd, $J = 12.4$, 4.4 Hz, 1H), 4.73 (t, $J = 12.4$ Hz, 1H), 3.93 (ddd, $J = 10$, 10, 4.4 Hz, 1H), 2.78–1.19 (m, 9H, cycl); MS (EI): 55 (16), 73 (16), 81 (25), 115 (16), 128 (17), 141 (52), 154 (53), 165 (39), 179 (28), 191 (15), 207 (46), 221 (100), 250 (43), 281 (21), 297 (10).

4.3.18. 2-(2-Nitro-1-(furan-2-yl)ethyl)cyclohexanone 8l. The ee value was determined by HPLC analysis (Daicel Chiralpak AS-H, hexane/2-propanol = 85/15, 1.0 ml/min, 220 nm; t_r(minor) = 10.13 min, t_r(major) = 17.07 min); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 7.34 (s, 1H), 6.29 (s, 1H), 6.18 (s, 1H), 4.80 (dd, $J = 12.4$, 4.8 Hz, 1H), 4.67 (dd, $J = 12.4$, 9.6 Hz, 1H), 3.98 (ddd, $J = 9.6$, 9.6, 4.8 Hz, 1H), 2.79–1.25 (m, 9H, cycl); MS (EI): 55 (11), 65 (9), 77 (14), 81 (29), 91 (15), 94 (33), 108 (10), 121 (9), 134 (9), 147 (14), 161 (100), 190 (63), 237 (1).

4.3.19. 2-(2-Nitro-1-(thioan-2-yl)ethyl)cyclohexanone 8m. The ee value was determined by HPLC analysis (Daicel Chiralpak AS-H, hexane/2-propanol = 85/15, 1.0 ml/min, 220 nm; t_r(minor) = 12.50 min, t_r(major) = 16.10 min); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 7.23–7.21 (m, 1H), 6.95–6.91 (m, 2H), 4.89 (dd, $J = 12.0$, 4.4 Hz, 1H), 4.65 (dd, $J = 12.0$, 8.8 Hz, 1H), 4.13 (ddd, $J = 8.8$, 8.8, 4.4 Hz, 1H), 2.79–1.28 (m, 9H, cycl); MS (EI): 55 (10), 65 (9), 77 (10), 97 (50), 110 (50), 123 (15), 135 (16), 150 (10), 163 (14), 177 (100), 189 (4), 206 (70).

Acknowledgment

We thank Professor Gu Jian-Ming of Zhejiang University for X-ray crystal structure analysis.

References

1. For reviews, see: (a) Sibi, M. P.; Manyem, S. *Tetrahedron* **2000**, *56*, 8033–8061; (b) Krause, N.; Hoffmann-Röder, A. *Synthesis* **2001**, 171–196; (c) Berner, O. M.; Tedeschi, L.; Enders, D. *Eur. J. Org. Chem.* **2002**, 1877–1894.
2. Perlmutter, P. *Conjugate Addition Reaction in Organic Synthesis*; Pergamon: Oxford, 1992.
3. (a) Christoffers, J. *Eur. J. Org. Chem.* **1998**, 1259–1266; (b) Hayashi, T. *Synlett* **2001**, 879–887; (c) Luchaco-Cullis, C. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 8192–8193; (d) Duursma, A.; Minnaard, A. J.; Feringa, B. L. *Tetrahedron* **2002**, *58*, 5773–5778; (e) Rimkus, A.; Sewald, N. *Org. Lett.* **2003**, *5*, 79–80; (f) Zhu, M.-K.; Cun, L.-F.; Mi, A.-Q.; Jiang, Y.-Z.; Gong, L.-Z. *Tetrahedron: Asymmetry* **2006**, *17*, 491–493; (g) Yan, Z.-Y.; Niu, Y.-N.; Wei, H.-L.; Wu, L.-Y.; Zhao, Y.-B.; Liang, Y.-M. *Tetrahedron: Asymmetry* **2006**, *17*, 3288–3293; (h) Vishnumaya; Singh, V. K. *Org. Lett.* **2007**, *9*, 1117–1119.
4. For selected reviews, see: (a) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2001**, *40*, 3726–3748; (b) Berkessel, A.; Gröger, H. *Metal-Free Organic Catalysts in Asymmetric Synthesis*; Wiley-VCH: Weinheim, 2004; (c) 'Special Issue: Asymmetric Organocatalysis', *Acc. Chem. Res.* **2004**, *37*, 487–631; (d) List, B. *Chem. Commun.* **2006**, 819–824; (e) Marigo, M.; Jørgensen, K. A. *Chem. Commun.* **2006**, 2001–2011.
5. (a) List, B.; Pojarliev, P.; Martin, H. J. *Org. Lett.* **2001**, *3*, 2423–2425; (b) Betancort, J. M.; Sakthivel, K.; Thayumanavan, R.; Barbas, C. F., III *Tetrahedron Lett.* **2001**, *42*, 4441–4444.
6. (a) Ishii, T.; Fujioka, S.; Sekiguchi, Y.; Kotsuki, H. *J. Am. Chem. Soc.* **2004**, *126*, 9558–9559; (b) Mase, N.; Thayumanavan, R.; Tanaka, F.; Barbas, C. F., III *Org. Lett.* **2004**, *6*, 2527–2530; (c) Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4212–4215; (d) Mase, N.; Watanabe, K.; Yoba, H.; Takabe, K.; Tanaka, F.; Barbas, C. F., III *J. Am. Chem. Soc.* **2006**, *128*, 4966–4967; (e) Cao, C.-L.; Ye, M.-C.; Sun, X.-L.; Tang, Y. *Org. Lett.* **2006**, *8*, 2901–2904; (f) Zu, L.; Wang, J.; Li, H.; Wang, W. *Org. Lett.* **2006**, *8*, 3077–3079; (g) Palomo, C.; Vera, S.; Mielgo, A.; Gómez-Bengoa, E. *Angew. Chem., Int. Ed.* **2006**, *45*, 5984–5987; (h) Pansare, S. V.; Pandya, K. *J. Am. Chem. Soc.* **2006**, *128*, 9624–9625.
7. (a) Luo, S.; Mi, X.; Zhang, L.; Liu, S.; Xu, H.; Cheng, J.-P. *Angew. Chem., Int. Ed.* **2006**, *45*, 3093–3097; (b) Luo, S.; Mi, X.; Liu, S.; Xu, H.; Cheng, J.-P. *Chem. Commun.* **2006**, 3687–3689.
8. (a) Luo, S.-P.; Xu, D.-Q.; Yue, H.-D.; Wang, L.-P.; Yang, W.-L.; Xu, Z.-Y. *Tetrahedron: Asymmetry* **2006**, *17*, 2028–2033; (b) Xu, D.; Luo, S.; Yue, H.; Wang, L.; Liu, Y.; Xu, Z. *Synlett* **2006**, 2569–2572.
9. CCDC 624624 and CCDC 638972 and CCDC 639742 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.
10. Seebach, D.; Golinski, J. *Helv. Chim. Acta* **1981**, *64*, 1413–1423.
11. Chiappe, C.; Pieraccini, D. *J. Phys. Org. Chem.* **2005**, *18*, 275–297.