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Chiral pyrrolidine quaternary derivatives as organocatalysts for asymmetric Michael additions

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Abstract A series of chiral pyrrolidine quaternary derivatives were designed and synthesized. It was found that these derivatives are highly efficient organocatalysts for the asymmetric Michael addition reactions of aldehydes and ketones to nitroolefins with high yields (up to 96%), high enantioselectivities (up to 99% ee), and high diastereoselectivities (up to 97:3 dr). Furthermore, catalyst **7a** could be recycled without remarkable loss of catalytic activity and stereoselectivity.

Keywords Chiral pyrrolidine quaternary derivatives · Asymmetric Michael additions · Organocatalysts · Nitrostyrenes

Introduction

In recent years, the asymmetric Michael addition reactions have draw much attention because it is one of the most important carbon–carbon bond-forming reactions in organic chemistry [1–6]. The organocatalytic asymmetric Michael addition of ketone to nitroolefins was first reported by List [7] and Barbas [8], independently. Since then, there has been a tremendous increase in research activities concerning this area, and many effective organocatalysts have been widely developed [9–17].

Among the various organocatalysts, proline and its derivatives have been demonstrated to make up a successful class of organocatalysts in enamine chemistry. Some of them have been developed for asymmetric Michael reactions of ketones to nitroolefins with high enantioselectivity and diastereoselectivity. Unfortunately, these organocatalysts have some drawbacks. One major disadvantage is that they cannot be easily recycled [18].

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Room temperature ionic liquids (RTILs) can be easily separated from organic reaction systems [19–22]. As a result, quaternary ammonium groups have been introduced into chiral catalysts [23–31], in which pyrrolidine-type imidazolium ILs and pyridinium ILs all provided corresponding products with encouraging results for the Michael additions of ketones or aldehydes to nitroolefins.

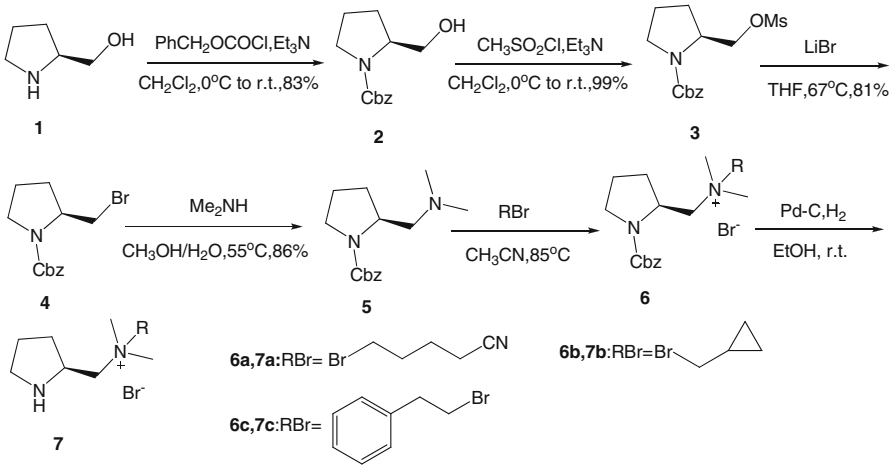
In our previous work, several pyrrolidine-based quaternary alkylammonium ionic liquids were reported, and the structure of these ionic liquids could be easily adjusted to obtain better catalytic capability by changing each of the alkyl groups [32]. However, these alkyl groups were all straight-chain alkyl groups. Further research on the influence of functional groups and branched-chain alkyl groups is needed.

Based on the above considerations, a series of chiral pyrrolidine quaternary derivatives were designed and synthesized, which were used as catalysts in asymmetric Michael additions of cyclohexanone to nitroalkenes with high enantioselectivities and diastereoselectivities. **7a** was designed to study the impact of the cyano group. **7b** and **7c** were designed to study the effect of three-membered ring and benzene ring. Furthermore, they could be easily recycled.

Results and discussion

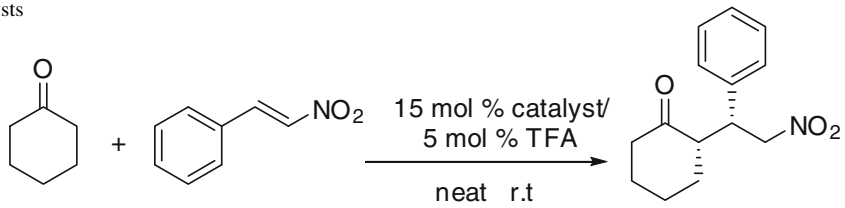
The synthesis of these chiral pyrrolidine quaternary derivatives is shown in Scheme 1. They were synthesized from commercially available starting material (S)-(2-hydroxymethyl) pyrrolidine 1 in six steps. The synthesis of compounds **1**–**5** was described in our previous work [32]. These catalysts are immiscible in hexane, Et_2O, and EtOAc, but are soluble in polar solvent, such as MeOH, DMSO, CH_3CN, and H_2O. The difference of solubility between EtOAc and H_2O allowed them to be easily isolated.

The reaction of cyclohexanone and *trans*-nitrostyrene was explored as a model reaction. Initially, these chiral ionic liquids were used as catalysts in this reaction.



Scheme 1 Synthesis of chiral pyrrolidine quaternary derivatives

Table 1 The asymmetric Michael additions of cyclohexanone to *trans*-nitrostyrene over different catalysts



9a

Entry	Cat.	Cyclohexanone (eq)	Time (h)	Yield[a] (%)	dr[b] (syn/anti)	ee[c] (syn)
1	**7a**	20	96	96	97:3	99
2	**7b**	20	96	94	96:4	94
3	**7c**	20	96	93	96:4	97
4[d]	**7a**	20	120	83	97:3	99
5[e]	**7a**	20	216	71	96:4	98

[a] Isolated yield

[b] Determined by HPLC using Chiralpak As-H column

[c] Determined by HPLC using Chiralpak As-H column

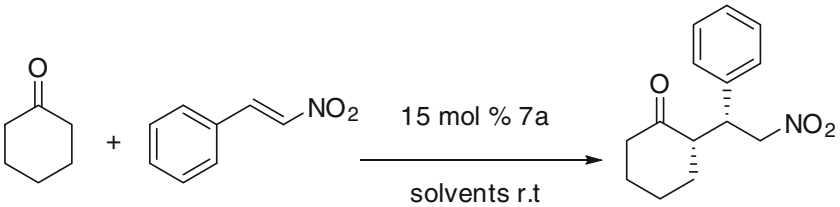
[d] Second cycle of catalyst **7a**

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

As shown in Table 1, all the catalysts exhibited good catalytic performance to yield the corresponding products in good to excellent yields. As **7a** showed the best catalytic activity among the ILs, it was selected as the organocatalyst for the following studies. The recyclability of **7a** was studied, and the results showed that **7a** could be easily recovered from the reaction mixture only by filtration after ethyl ether was added to the reaction mixture. And the Michael addition in the presence of the recovered **7a** yielded similar results but required longer reaction time (entries 4–5). Perhaps the descended purity and the loss of the catalyst **7a** in the recycling process reduced the catalytic activity of the recycled **7a**.

Then, **7a** was used as the catalyst of the asymmetric Michael reactions in different solvents and with different acids. As shown in Table 2, the substantial changes of acids had significant impact on the yield and stereoselectivity. Better enantioselectivity was obtained in the presence of TFA or CH_3COOH rather than CH_3SO_3H and p-TsOH (entries 7–9). What is more, when TFA was used as an additive in the asymmetric Michael reaction, the yield and stereoselectivity were better than when no acid was used (entry 10, Table 2). Therefore, TFA afforded the best yield and stereoselectivity among those acids. The reason why acidic additives had a significant impact may be explained as follows. A proper acidity was helpful to form the enamine. The acidity of TFA was stronger than CH_3COOH but weaker than CH_3SO_3H and p-TsOH. So, when TFA was used as an acidic additive, the reaction system could attain more appropriate acidity than CH_3SO_3H and p-TsOH, and without acidic additive. So, TFA was selected as the acidic additive for the following studies.

Table 2 The influence of solvents and acids to the reaction of cyclohexanone and *trans*-nitrostyrene



Entry[a]	Solvent	Acid (eq)	Time (h)	Yield[b] (%)	dr[c] (syn/anti)	ee[d] (%)(syn)
1	MeOH	TFA/0.1	144	77	94:6	93
2	DMF	TFA/0.1	144	81	97:2	96
3	DMSO	TFA/0.1	120	66	99:1	99
4	EA	TFA/0.1	168	72	94:6	89
5	THF	TFA/0.1	168	73	91:9	88
6	CH_2Cl_2	TFA/0.1	168	75	89:11	89
7	Neat	CH_3SO_3H/0.1	216	43	96:4	77
8	Neat	p-TsOH/0.1	240	49	95:5	73
9	Neat	CH_3CO_2H/0.1	96	53	94:6	91
10	Neat	NO	216	79	95:5	89

[a] 20 equiv of ketone

[b] Isolated yield

[c] Determined by HPLC using Chiralpak As-H column

[d] Determined by HPLC using Chiralpak As-H column

As shown in Table 2, the effects of solvents on the asymmetric Michael reaction were significant. The reactions in different solvents showed different stereoselectivity and different yields (entries 1–6). In polar solvents, such as MeOH, DMSO, and DMF, the reaction demonstrated higher stereoselectivity than in EtOAc, THF, and CH_2Cl_2. The reason was that the catalysts could be better dissolved in MeOH, DMSO, and DMF than in EtOAc, THF, and CH_2Cl_2.

Based on the above work, a variety of other ketones and nitroolefins with different substituents were investigated to establish a general scope of this asymmetric transformation. The results are summarized in Table 3. It was found that nitroolefins with either electron-rich or electron-deficient substituents on the benzene ring reacted smoothly with cyclohexanone to give the Michael adducts (entries 1–6), but the reaction yields, stereoselectivity, and enantioselectivities were different. The differences were caused by the electron cloud density of the benzyl position of substituted nitroolefins and the space hindrance. The electron-withdrawing group on the benzene ring of nitroolefin decreased the electron cloud density of the benzyl position, which was beneficial to the Michael reaction. So **9d** and **9f** were obtained in higher yield and stereoselectivity than **9c** and **9g** (entries 2, 3, 5, and 6). The large substituent group of nitroolefin hindered the nitroolefin to approach the enamine structure. So **9b** and **9e** were obtained in low reaction yield

Table 3 The asymmetric Michael addition of ketones and aldehydes to *trans*-nitrostyrenes catalyzed by **7a**

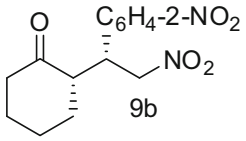
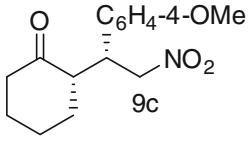
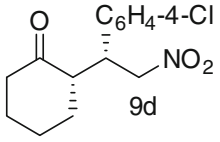
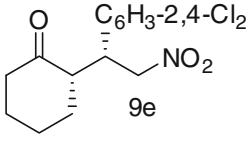
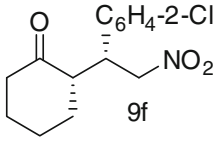
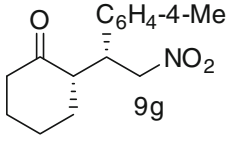
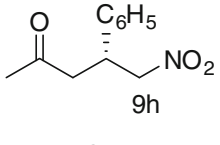
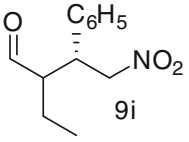
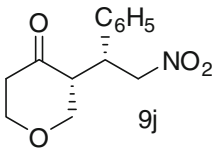
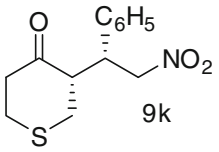
Entry[a]	Product	Time (h)	Yield[b] (%)	dr[c] (syn/anti)	ee[d] (%)(syn)
1	 9b	96	57	94:6	96
2	 9c	168	71	95:5	94
3	 9d	120	81	95:5	97
4	 9e	120	67	96:4	99
5	 9f	120	82	96:4	98
6	 9g	96	75	97:3	95
7	 9h	144	–	–	–
8	 9i	96	82	95:5	97

Table 3 continued

Entry[a]	Product	Time (h)	Yield[b] (%)	dr[c] (syn/anti)	ee[d] (%)(syn)
9	 9j	120	61	93:7	94
10	 9k	120	67	94:6	94

[a] 20 equiv of ketone

[b] Isolated yield

[c] Determined by HPLC using Chiralpak As-H column

[d] Determined by HPLC using Chiralpak As-H column

(entries 1 and 4). Moreover, the results indicated that butyraldehyde, tetrahydro-4H-pyran-4-one, and tetrahydrothiopyran-4-one were also suitable Michael donors (entries 8–10). However, the reactivity of acetone is lower than cyclohexanone and butyraldehyde, so it is not a suitable Michael donor for our catalysts. Therefore, the reaction of acetone to *trans*-nitrostyrene did not obtain the expected products, and by-products were not isolated and identified (entry 7).

Conclusions

In conclusion, a new series of chiral pyrrolidine-type quaternary alkyl ammonium ILs were synthesized, which can be used as efficient catalysts for the asymmetric Michael reactions of aldehydes and ketones to nitroolefins. These chiral ILs catalysts can easily be synthesized. All these chiral ILs catalysts are environmentally friendly, and can easily be recovered and reused to provide desired Michael adducts with high diastereoselectivities and enantioselectivities. Further investigation on the applications of these new ILs to other asymmetric reactions and the structure–activity relationship of catalysts are presently being carried out in our laboratory.

Experimental

General information

Unless specified, Commercial solvents and reagents were used without further purification.

Analytical thin layer chromatography (TLC) was used for monitoring the reactions. Column chromatography was performed with silica gel (200–300 mesh). ^{1}H and ^{13}C NMR were recorded by Varian Inova 500 MHz. Mass spectra were recorded using electrospray ionization (ESI) on LCQ Advanced MAX Mass instruments. HPLC analysis was measured using ChiralPak AS-H column at 254 nm.

General procedure for the preparation of compounds **6a–6c**

Compound **5** (2.6 g, 10.0 mmol), corresponding alkyl bromide (30 mmol) and CH_3CN (40 mL) were added to a 100-mL single neck bottle. After being dissolved, the reaction mixture was stirred under refluxing and monitored by analytical thin layer chromatography (PE:EA = 1:1). After removal of CH_3CN under vacuum, the mixture was diluted with 20 mL EtOAc, and then the resulting mixture was extracted with water (20 mL ×3). The combined water layer was concentrated under vacuum. The resulting residue was purified by silica gel chromatography (CH_3OH:CH_2Cl_2 = 1:20) to get the corresponding compound **6**.

*(S)-N-((1-(benzyloxycarbonyl)pyrrolidin-2-yl)methyl)-4-cyano-N,N-dimethylbutan-1-aminium bromide (**6a**)*

Colorless oil. Yield: 58%; ^{1}HNMR (500 MHz, $CDCl_3$): δ = 1.54–1.73 (8H,m), 1.86–1.88 (2H,m), 3.24–3.40 (12H,m), 3.96–3.99 (2H,m), 5.06–5.08 (2H,m), 7.38–7.47 (5H,m).

*(S)-1-(1-(benzyloxycarbonyl)pyrrolidin-2-yl)-N-(cyclopropylmethyl)-N,N-dimethylmethanaminium bromide (**6b**)*

Colorless oil. Yield: 69%; ^{1}HNMR (500 MHz, CD_3OD): δ = 0.29–0.32 (1H,m), 0.45–0.47 (2H,m), 0.69–0.70 (1H,m), 0.81–0.83 (1H,m), 1.91–2.00 (4H,m), 2.95–3.10 (3H,m), 3.20–3.30 (5H,m), 3.33–3.50 (5H,m), 5.14–5.19 (2H,m), 7.31–7.45 (5H,m).

*(S)-N-((1-(benzyloxycarbonyl)pyrrolidin-2-yl)methyl)-N,N-dimethyl-2-phenylethanaminium bromide (**6c**)*

Colorless oil. Yield: 53%; ^{1}HNMR (500 MHz, $CDCl_3$): δ = 1.67–1.73 (3H,m), 1.96–2.00 (1H,s), 3.10–3.16 (3H,m), 3.45–3.50 (8H,m), 3.74–3.76 (1H,m), 3.76–3.84 (1H,s), 3.84–3.95 (1H,s), 4.21–4.29 (1H,s), 5.07–5.15 (2H,m), 7.31–7.37 (10H,m).

General procedure for the preparation of compounds **7a–7c**

Ten percent Pd/C was added to the solution of the corresponding compound **6** in EtOH. The reaction mixture was stirred for 24 h at ambient temperature under 1 atm H_2. After filtrating the Pd/C, the solution was concentrated under vacuum to give the product. The corresponding catalyst **7** was obtained.

*(S)-4-cyano-N,N-dimethyl-N-(pyrrolidin-2-yl methyl)butan-1-aminium bromide (**7a**)*

Colorless oil. Yield: 98%; ^{1}HNMR (500 MHz, $CDCl_3$): $\delta = 1.22–1.25$ (2H,m), 1.37–1.41 (1H,m), 1.63–1.69 (1H,m), 1.81–1.85 (7H,m), 2.42–2.87 (2H,m), 3.03–3.08 (1H,m), 3.37–3.52 (6H,s), 3.69–3.89 (1H,m), 3.90–3.97 (2H,m); ^{13}CNMR (125 MHz, CD_3OD): $\delta = 119.53, 67.95, 64.14, 57.15, 53.35, 46.76, 31.35, 25.16, 22.31, 17.25, 15.89$; MS (ESI) m/z: calcd. for $C_{12}H_{24}N_3$ 210.34 (positive ion), found 210.2 (positive ion).

*(S)-1-cyclopropyl-N,N-dimethyl-N-(pyrrolidin-2-ylmethyl)methanaminium bromide (**7b**)*

Colorless oil. Yield: 85%; ^{1}HNMR (500 MHz, $CDCl_3$): $\delta = 0.58–0.63$ (2H,m), 0.80–0.85 (2H,m), 1.07–1.12 (1H,m), 1.38–1.45 (1H,m), 1.65–1.72 (1H,m), 1.79–1.85 (1H,m), 2.08–2.15 (1H,m), 2.87–2.92 (1H,m), 3.02–3.07 (1H,m), 3.44–3.57 (6H,s), 3.59–3.60 (1H,m), 3.62–3.67 (3H,m), 3.85–3.90 (1H,m); ^{13}CNMR (125 MHz, CD_3OD): $\delta = 70.11, 68.37, 53.38, 50.52, 46.74, 31.01, 25.06, 4.51, 4.01$; MS (ESI) m/z: calcd. for $C_{11}H_{23}N_2$ 183.31 (positive ion), found 183.1 (positive ion).

*(S)-N,N-dimethyl-2-phenyl-N-(pyrrolidin-2-ylmethyl)ethanaminium bromide (**7c**)*

Colorless oil. Yield: 99%; ^{1}HNMR (500 MHz, $CDCl_3$): $\delta = 1.67–1.73$ (3H,m), 1.96–2.00 (1H,s), 3.11–3.15 (3H,m), 3.45–3.51 (8H,m), 3.73–3.75 (1H,m), 3.77–3.83 (1H,s), 3.85–3.97 (1H,s), 4.21–4.29 (1H,s), 5.07–5.15 (2H,m); ^{13}CNMR (500 MHz, CD_3OD): $\delta = 136.01, 129.07, 128.81, 127.16, 67.87, 66.07, 53.46, 50.97, 46.77, 31.35, 28.85, 25.17$; MS (ESI) m/z: calcd. for $C_{15}H_{25}N_2$ 233.37 (positive ion), found 233.1 (positive ion).

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