Asymmetric Michael additions catalysed by functionalised quaternary alkylammonium ionic liquids

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Some functionalised quaternary alkylammonium ionic liquids were synthesised and examined as organocatalysts for asymmetric Michael additions of aldehydes and ketones to nitroolefins. All of them exhibited excellent enantioselectivities (>99% ee) and diastereoselectivities (> 99/1 d/r). One of the catalysts (*S*)-*N,N*-dimethyl-*N*-pyrrolidin-2-ylmethyl)-2-methylpropan-1-aminium bromide could be recovered for reuse with similar results, and triethylamine was found to be an effective additive to enhance its catalytic activity.

Keywords: asymmetric Michael additions, quaternary alkylammonium ionic liquids, catalysis

Recently, room temperature ionic liquids (RTILs) have been widely studied.[1–2] Due to their particular properties, ILs can easily be separated from reaction systems.[3] So they have been widely used as solvents or catalysts for various organic reactions.[4] Furthermore, it is of considerable interest to obtain functionalised ILs by modifying normal ILs.[5–10]

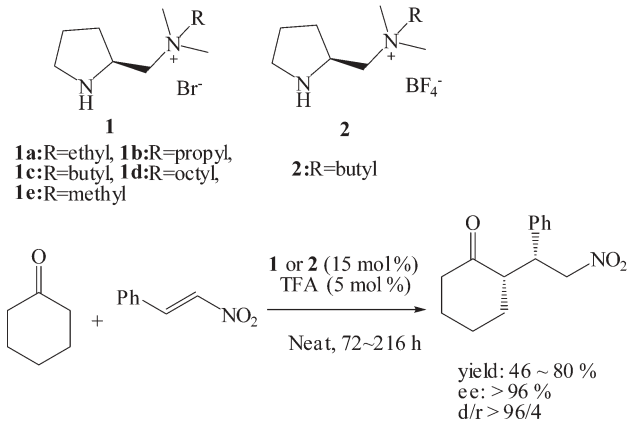
Indeed, many groups have introduced chiral pyrrolidine groups into ILs to obtain chiral ILs which can effectively catalyse asymmetric Michael additions of cyclohexanone to nitroalkenes.[11–22] Encouraging results were seen with some pyrrolidine-type imidazolium ionic liquids, DABCO ionic liquids and pyridinium ionic liquids. But all of those ILs can only be recovered and reused for only a few times. So it would be useful to increase the catalytic activity of recycled catalyst.

We previously reported several chiral pyrrolidine-based quaternary alkylammonium ILs which catalysed asymmetric Michael additions of cyclohexanone to nitroalkenes in moderate yields with excellent stereoselectivity[23] (Scheme 1).

In order to obtain better stereoselectivity and yield of asymmetric Michael additions and to study the structure-activity relationship of catalysts, we designed and synthesised three novel chiral pyrrolidine-based quaternary alkylammonium ILs (Scheme 2). All of them were used as organocatalysts in the asymmetric Michael additions of cyclohexanone to nitroalkenes and the results are reported here.

Results and discussion

In order to improve the stereoselectivity and yield of asymmetric Michael additions, three new pyrrolidine-based chiral quaternary alkylammonium ionic liquids **8a–c** were prepared and their catalytic properties evaluated in the Michael addition of cyclohexanone to *trans*-nitrostyrene. Representative results are summarised in Table 1.



Scheme 1 The Michael reaction catalysed by chiral quaternary alkylammonium ILs reported by Wang *et al.*[23]

Firstly, when compound **8a** was used as a catalyst, excellent enantioselectivity and diastereoselectivity were obtained but yields were only moderate. Also it required much longer reaction time (552 h) than compound **1a** (144 h).[23] A plausible reason is the isopropyl group of **8a** could hinder the approach of *trans*-nitrostyrene to the enamine in the transition state due to its large steric effect, as shown in Scheme 3. In contrast, compound **8b** showed excellent enantioselectivity, diastereoselectivity and yield of Michael addition with a similar reaction time (144 h) to compound **1a**. The reason may be that the branched methyl group of **8b** is at the β-position of the quaternary ammonium N atom which would not hinder the approach of *trans*-nitrostyrene to the enamine in the transition state like **8a**. Compound **8c** showed similar catalytic property to **8b**. But when no TFA was added, the reaction time was prolonged and the reaction yield decreased. This result indicated that the hydroxyl group of compound **8c** could not replace the acidic additive.

Then the recyclability of the catalyst **8b** was examined in the Michael addition of cyclohexanone to *trans*-nitrostyrene (Table 2). The catalyst **8b** could be easily recovered from the reaction mixture by addition of water. The aqueous phase was washed three times with EA, concentrated *in vacuo*, from which **8b** was obtained. When recovered **8b** was used to catalyse Michael addition of cyclohexanone to *trans*-nitrostyrene, similar results were obtained but with a prolonged reaction time. Interestingly, triethylamine was found to be an effective additive to enhance the catalytic activity of recovered **8b**. When triethylamine was added to the reaction mixture, the reaction was complete in much shorter time. In the same reaction time, the reaction with triethylamine exhibited much higher conversion of *trans*-nitrostyrene than the reaction without triethylamine.

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 3. It was reported that acidic additives exhibited important impact on the yield and enantioselectivity of the reaction catalysed by compound **1c**.[23] But when **8b** was used as a catalyst of the Michael reaction, a similar stereoselectivity to TFA was obtained in the presence of AcOH, CH_3SO_3H and p-TsOH (entries 7–9). Also the reaction yield in the presence of CH_3SO_3H was lower than that of TFA, AcOH and p-TsOHFinally, it was found that the Michael reaction could proceed without acidic additive to afford similar results (Entry 10). The effect of solvents on the model reaction catalysed by **8b** was not as significant as that on **1c**. The stereoselectivity and reaction times in different solvents were similar, but yields varied (entries 1–6).

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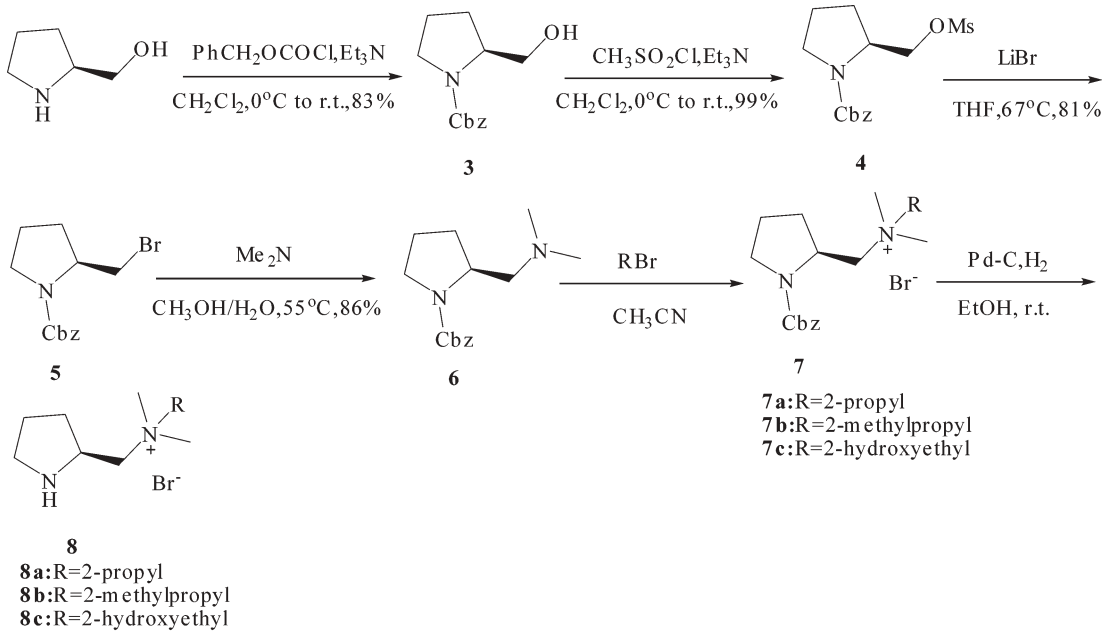
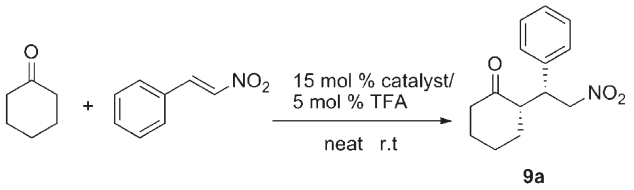


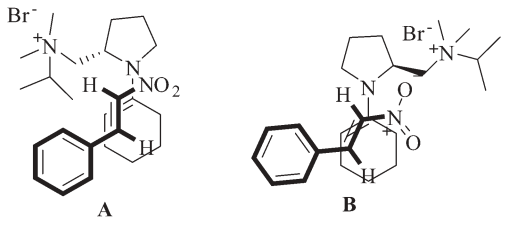
Scheme 2 Synthesis of chiral quaternary alkylammonium ILs.

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



Entry	Cat.	Time /h	Yield [a] /%	*syn* /*anti*[b]	ee (syn)/%[b]
1	**8a**	552	68	96/4	97
2	**8b**	144	92	98/2	96
3	**8c**	168	89	97/3	99
4	**8c**[c]	336	64	99/1	99

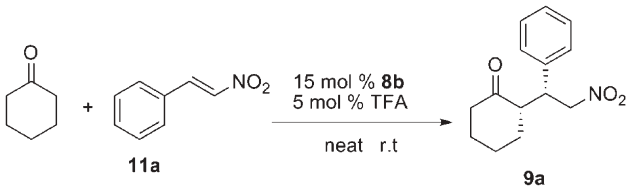
[a] Isolated yield.
[b] Determined by chiral HPLC.
[c] No acid added.



Scheme 3 Plausible transition state.

Next, IL **8b** was used as a catalyst for several Michael reactions of a variety of aldehydes, ketones and nitroolefins. As shown in Table 4, different substituents on nitroolefins gave different catalytic results. When a 4-CH_3O substituted nitroolefin was used as a Michael receptor, the Michael reaction required a much longer reaction time and showed lower enantioselectivies (entry 2). A conceivable reason is that as a strong electron-rich group CH_3O would increase the electron cloud density at the benzyl position, which would be disadvantageous to the Michael reaction. A 2-NO_2 substituted nitroolefin needed the shortest reaction time, but gave a lower yield (entry 1). The reason may be that NO_2 as an electron-deficient group would decrease the electron cloud density at the benzyl position, but the bulk structure of o-NO_2 would hinder the nitroolefin approach to the enamine structure. Other

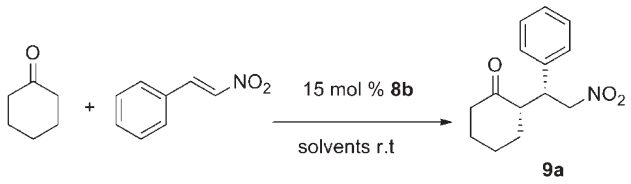
Table 2 Recycling studies of **8b** catalysed Michael addition of cyclohexanone to *trans*-nitrostyrene with or without triethylamine



Entry	Time /h	11a/9a[a]	Yield[b] /%	*syn* /*anti*[c]	ee (*syn*)/%[c]
1[d]	130	1: 6	–	96/4	96
2[e]	130	1: 19	–	96/4	94
3[d]	178	1: 23	–	96/4	95
4[e]	178	1: 41	–	96/4	95
5[d]	240	–	70	96/4	95
6[e]	202	–	79	96/4	95
7[f]	16	9: 1	–	97/3	98
8[g]	16	3: 1	–	96/3	96
9[f]	64	2: 1	–	97/3	96
10[g]	64	1: 1	–	95/5	96
11[f]	184	1: 1	–	96/4	96
12[g]	184	1: 10	–	95/5	95
13[f]	256	1: 3	–	96/4	96
14[g]	256	1: 14	–	95/5	97
15f	760	–	68	95/5	97
16[g]	280	–	70	95/5	97
17[h]	480	–	68	96/4	97

[a] The reaction mixture determined by chiral HPLC.
[b] Isolated yield.
[c] Determined by chiral HPLC.
[d] Second cycle of catalyst **8b**.
[e] Second cycle of catalyst **8b** with 3 mol% triethylamine.
[f] Third cycle of catalyst **8b**.
[g] Third cycle of catalyst **8b** with 6 mol% triethylamine.
[h] Fourth cycle of catalyst **8b** with 12 mol% triethylamine.

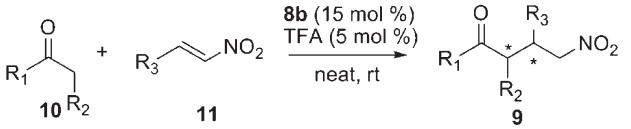
Table 3 The effects of acidic additives and solvents



Entry[a]	Solvent	Acids/ /mol%	Time /h	Yield [b] /%	*syn* /*anti*[c]	ee (*syn*)/%[c]
1	MeOH	TFA/5	240	74	93/7	95
2	DMSO	TFA/5	192	78	97/3	95
3	DMF	TFA/5	216	79	96/4	96
4	CH_2Cl_2	TFA/5	240	94	95/5	95
5	THF	TFA/5	240	95	96/4	95
6	EA	TFA/5	216	62	96/4	95
7	Neat	CH_3SO_3H/5	192	34	96/4	96
8	Neat	p-TsOH/5	192	91	95/5	95
9	Neat	AcOH/5	120	91	99/1	99
10	Neat	Neat	172	77	97/3	97

[a] 20 equiv of ketone.
[b] Isolated yield.
[c] Determined by chiral HPLC.

Table 4 Asymmetric Michael addition of ketones and aldehydes to *trans*-nitrostyrenes catalysed by **7c**



Entry[a]	R_1	R_2	R_3	Time /h	Product	Yield /%[b]	*syn* /*anti*[c]	ee /%[c]
1	-$(CH_2)_4$-		2-NO_2-Ph	48	**9b**	68	97:3	96%
2	-$(CH_2)_4$-		4-OMe-Ph	288	**9c**	90	96:4	88%
3	-$(CH_2)_4$-		4-Cl-Ph	72	**9d**	83	94:6	96%
4	-$(CH_2)_4$-		2,4-Cl-Ph	72	**9e**	88	99:1	99%
5	-$(CH_2)_4$-		2-Cl-Ph	72	**9f**	99	99:1	96%
6	-$(CH_2)_4$-		4-Me-Ph	96	**9g**	76	97:3	95%
7	Me	H	Ph	–	–	–	–	–
8	H	Et	Ph	–	–	–	–	–

[a] 20 equiv. of ketone.
[b] Isolated yield.
[c] Determined by chiral HPLC.

substituents on nitroolefins showed lesser impact on the Michael reaction for the electronic and steric effect of those substituents on the nitroolefin were much weaker. Because of its lower reaction activity, no Michael product was obtained when acetone was used as the Michael donor. Surprisingly, 1-butyraldehyde did not give the Michael product either.

In summary, a series of chiral pyrrolidine-type quaternary alkylammonium ILs have been prepared from (*S*)-(2-hydroxymethyl)pyrrolidine in six steps and used to catalyse the asymmetric Michael addition reactions of cyclohexanone and nitroolefins. IL **8b** could be easily recovered for recycling. When triethylamine is added, the catalytic activity of recycled **8b** was enhanced. Further investigation on the applications of these ILs to other Michael reactions is being undertaken in our laboratory.

Experimental

Commercial reagents were used without purification unless indicated. Analytical TLC was performed with various mixtures of ethylacetate (EA) and petroleum ether (PE) on 0.20 mm silica gel plates and silica gel (200–300 mesh) was used for flash chromatography. Both were 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 could be assigned from first-order splitting patterns. Mass spectra were recorded using electrospray ionization (ESI) on LCQ Advanced MAX Mass instruments. Optical rotations were determined on an Autopol II polarimeter using 1 mL cell with a 1 dm path length. HPLC-UV analysis was carried out using ChiralPak AS-H column at λ = 254 nm.

General procedure

Synthesis of the intermediates: Intermediates **3–6** were obtained following literature procedures.[23–25]

Synthesis of the intermediate **7a**: Under N_2 protection, intermediate **6** (1.3 g, 5.0 mmol) and MeCN (10 mL) was added to an autoclave.[26] After **6** had dissolved, 2-bromopropane (2.3 g, 0.019 mol) was added. The reaction mixture was stirred at 110 ºC until intermediate **6** had disappeared by analytical TLC (EA: PE = 1:1), and MeCN was removed *in vacuo*. The mixture was dissolved in water (10 mL), then NaOH (0.2 g, 5.0 mmol) was added. After NaOH had dissolved, the resulting mixture was extracted with EA (10 mL×3). Then the combined water layers were concentrated *in vacuo*. The residue was purified by flash chromatography (MeOH: CH_2Cl_2 = 1:10) on silica gel to give **7a** as a yellow solid. (0.9 g, 48% yield); ^{1}H NMR (500 MHz, D_2O) δ ppm: 0.96–1.20 (6H, m), 1.75–1.79 (3H, m), 2.00–2.05 (1H, m), 2.52 –2.89 (6H, m), 3.06–3.14 (2H, m), 3.17–3.41 (4H, m), 4.21 (1H, s), 4.92–5.06 (2H, m), 7.26–7.29 (5H, m).

Synthesis of the intermediate **7b**: Under N_2 protection, intermediate **6** (1.6 g 6.2 mmol) and MeCN (12 mL) were added to a single neck bottle.[23] After **6** had dissolved, 1-bromo-2-methylpropane (3.2 g 0.023 mol) was added. The reaction mixture was stirred under reflux until intermediate **6** had disappeared by analytical TLC (EA: PE = 1:1), and MeCN was removed *in vacuo*. The mixture was diluted with EA (10 mL), then the resulting 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 **7b** as a colourless oil (1.7 g, 70% yield). ^{1}H NMR (500 MHz, CD_3OD) δ ppm: 0.86–1.11 (6H, m), 1.90–2.29 (5H, m), 2.91 (1H, s), 2.99 (1H, s), 3.02 (1H, s), 3.18 (3H, s), 3.23 (2H, s), 3.41–3.60 (4H, m), 4.28–4.42 (1H, m), 5.15 (2H, s), 7.32–7.46 (5H, m).

Synthesis of the intermediate **7c**: The procedure was similar to that used for the synthesis of **7b**, with 2-bromoethanol (2.9g 0.023mol) replacing 1-bromo-2-methyl propane. The residue obtained was purified by flash chromatography (MeOH: CH_2Cl_2 = 1:7) on silica gel to give **7c** as a white solid (1.8 g, 74% yield); ^{1}H NMR (500 MHz, CD_3OD) δ ppm: 1.91–2.01 (3H, m), 2.17–2.25 (1H, m), 3.00 (1H, s), 3.07 (1H, s), 3.25 (3H, s), 3.28 (3H, s), 3.44–3.52 (4H, m), 3.56–3.65 (2H, m), 3.80–4.00 (2H, m), 4.38–4.43 (1H, m), 5.15 (2H, s), 7.31–7.47 (5H, m).

Preparation of **8***; general procedure*

To a solution of the corresponding intermediate **7** (3.9 mmol) in EtOH (30 mL), Pd/C (wet, 10%, 0.2g) was added.[23,27] The reaction mixture was stirred at r.t. under 1 atm H_2 overnight. After filtering off 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 solidified. The solid catalyst **8a** was obtained by filtration; **8b**, **8c** as oils were was obtained by pouring off the EA.

8a: Yellow solid, yield 99%). IR (KBr) υ = 2963, 2876, 2079, 1669, 1474, 1117, 905 cm^{-1}; H NMR (500 MHz, D_2O) δ ppm: 1.23–1.26 (6H, m), 1.28–1.35 (1H, m), 1.58–1.67 (2H, m), 1.97–2.01 (1H, m), 2.70–2.75 (1H, m), 2.77–2.82 (1H, m), 2.90 (3H, s), 2.91 (3H, s), 3.19–3.23 (1H, m), 3.33–3.36 (1H, m), 3.40–3.43 (1H, m), 3.61–3.66 (1H, m). ^{13}C NMR (125 MHz, D_2O) δ ppm: 67.0, 66.2, 52.8, 46. 5, 3.6, 24.2, 15.9, 15.9. $[\alpha]_D^{r.t.}$ = +8.4 (c = 1.46, MeOH); HRMS (ESI+) Calcd for $C_{10}H_{23}N_2$, *m/z* 171.1861 (positive ion); found 171.1862 (positive ion

8b: Yellow oil. yield 84%; IR (KBr) υ = 2971, 2871, 2776, 1631, 1470, 964, 553 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD) δ ppm: 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 (125 MHz, CD_3OD) δ ppm: 68.1, 66.8, 53.4, (50.8, 50.8, 50.7, 50.7), 46.7, 31.4, 25.1, 15.9, 9.7. $[\alpha]_D^{r.t.}$ = +12.8 (c = 0.97, MeOH); HRMS (ESI+) Calcd for: $C_{11}H_{25}N_2$, *m/z* 185.2018 (positive ion); found 185.2010 (positive ion).

*Recycled **8b***: Yellow oil. Recycled yield: 92-95%.HRMS (ESI+); found 185.2005 (positive ion).

8c: Colorless oil. yield 97%; IR (KBr) υ = 2963, 2925, 2859, 1731, 1640, 1553, 1461, 1076, 740 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ ppm: 1.38–1.46 (1H, m), 1.67–1.76 (1H, m), 1.80–1.87 (1H, m), 2.09–2.16 (1H, m), 2.88–2.93 (1H, m), 2.96–3.00 (1H, m), 3.25 (3H, s), 3.26 (3H, s), 3.44–3.55 (2H, m), 3.58–3.65 (2H, m), 3.66–3.72 (1H, m), 4.00–4.03 (2H, m); ^{13}C NMR (125 MHz, CD_3OD) δ ppm: 69.2, 69.2, 69.2, 66.3, 66.2, 66.2, 55.8, 53.4, 51.9, 51.9, 51.8, 51.8, 51.8, 51.7, 46.6, 31.4, 25.1.$[\alpha]_D^{r.t.}$ = +12.0 (c = 0.25, MeOH). HRMS (ESI+) Calcd for: $C_9H_{21}N_2O$, *m/z* 173.1654 (positive ion); found 173.1644 (positive ion).

General experimental procedure for the Michael addition of cyclohexanone to nitroalkene by chiral catalyst: TFA (2.85 mg 0.025 mmol) was dropped into a solution of the chiral catalyst (0.075 mmol) in cyclohexanone (1g, 10mmol). [23] After stirring for 1 h, nitroalkene (0.5 mmol) was added, and the solution was stirred at r.t. until nitroalkene had disappeared by Analytical TLC (EA: PE = 1:5). The solution was diluted with water (5 mL), and the resulting mixture was extracted with EA (2 mL×3). The combined organic layers were 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. PE (3 mL) was added to the crude product and the mixture was vibrated by ultrasonic waves 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.[28] The absolute configurations of the product (e.e) were determined by comparison of HPLC retention times catalysed by the racemic proline.[29]

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