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Pyrrolidine-based chiral pyridinium ionic liquids (ILs) as recyclable and highly efficient organocatalysts for the asymmetric Michael addition reactions

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Abstract

A novel series of pyrrolidine-based chiral pyridinium ionic liquids (ILs) have been developed by using commercially available (*S*)-(2-aminomethyl)-1-*N*-Boc-pyrrolidine. These chiral ILs have been found to be recyclable and efficient organocatalysts for the asymmetric catalytic Michael addition reactions of ketones to nitroolefins with high yields, high enantioselectivies, and diastereoselectivies.

Owing to the intriguing properties of ionic liquids (ILs), they have been intensively investigated as solvents for synthetic organic reactions, and most recently for their ability to also act as catalysts for specific reactions.[1] Even though much progress has been achieved in the design and synthesis of new chiral ILs,[2] there has been limited success in them being able to affect the outcomes of asymmetric reactions.[3] There have been cases where imidazolium ionic liquids have been used successfully for asymmetric reactions, for example, Luo et al.[3e,f] reported the reactions of cyclohexanone with nitroolefins catalyzed by pyrrolidine-type chiral imidazolium ILs, in which high diastereo- and enantioselectivity were observed, but there are major problems associated with the use of chiral ILs derived from imidazolium ILs when used as catalysts or solvents for asymmetric reactions. For example, side products often result due to the relatively acidic nature of the C2 hydrogen of the imidazolium ring.[4] Pyridinium derived ionic liquids offer a better alternative since most of the problems encountered in the use of imidazolium ionic liquids can be avoided or minimized in these ionic liquids. Amazingly, chiral pyridinium ILs have been exploited far less.[5] A thorough review of the literature reveals only one example in which chiral pyridinium ILs have been used as solvents for an asymmetric reaction and no enantioselective induction was observed.[5c] Herein, we report the design and synthesis of a novel class of pyrrolidine-based chiral pyridinium ILs, which are very effective organocatalysts for highly enantioselective Michael addition of cyclic ketones to nitroalkenes; in addition, they are easily recoverable for reuse.

It is known that asymmetric Michael addition reaction is among the most powerful and convergent strategies for the enantioselective formation of C–C bonds in organic synthesis.[6] Recently, several efficient small-molecular chiral organocatalysts, such as pyrrolidine-based amine,[7] pyrrolidine–pyridine,[8] aminomethylpyrrolidine,[9] 2,2′-bipyrrolidine,[10] pyrrolidinyltetrazole,[11] pyrrolidine sulfonamide,[12] and pyrrolidine–thiourea,[13] have been developed for the asymmetric Michael reaction of ketones to nitroolefins with high enantioselectivity and diastereoselecivity. These approaches provide a unique methodology in asymmetric Michael addition, but a major disadvantage is that they are not easily recovered and recycled. As a result, the development of environment-friendly and metal-free chiral organocatalysts for asymmetric Michael reaction with high enantioselectivity, as well as efficient catalyst recovery and reuse, remains a challenging task.

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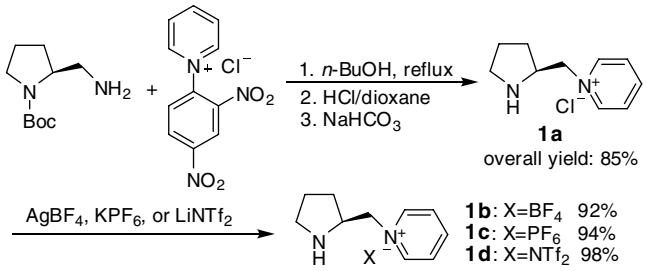
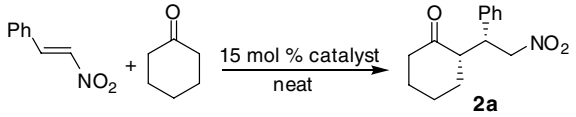


Scheme 1.

The synthesis of pyrrolidine-based chiral pyridinium ILs **1a–d** is outlined in Scheme 1. Starting from commercially available (*S*)-(2-aminomethyl)-1-*N*-Boc-pyrrolidine, using Marazano's reaction with Zincke's salt, and followed by Boc deprotection afforded **1a**, which was subjected to anion exchange to give **1b–d** (Scheme 1). All the chiral ILs synthesized were soluble in polar solvent, such as MeOH, CH_3CN, DMF, and DMSO, but were immiscible in Et_2O, EtOAc, and hexane. Chiral ILs **1a–c** were soluble in H_2O, while the anion NTf_2 **1d** was immiscible in H_2O. The different solubility allows them to be easily extracted for reuse.

As shown in Table 1,[14] all chiral pyridinium ILs **1a–d** catalyzed the asymmetric Michael reaction of cyclohexanone with nitrostyrene. The catalytic and enantioselective activities varied significantly with different anion moieties of chiral ILs and the additive acid. Compound **1a** with Cl^- as anion was used as a catalyst to show the high diastereo- and enantioselectivity with moderate yield at room temperature (entry 1). Interestingly, addition of TFA increased the reaction rate without losing enantioselectivity (entry 2). The anion exchange of Cl^- to BF_4^- (**1b**) provided comparable selectivity with enhanced reaction activity when TFA was added (entry 4). When the reaction was performed at lower temperature (4 °C), the adduct was obtained in high yield (92%) with nearly optically purity (99% ee) and excellent diastereoselectivity (*syn*/*anti* ratio >99%) (entry 5). The slightly low selectivities were observed with PF_6^- (**1c**) and NTf_2^- (**1d**) as anions (entries 6–9). In addition, catalyst **1b** could be recycled two times with only slightly decreased yield (82%) and selectivities in the third cycle (entries 10 and 11). Overall, chiral ILs **1a–b** with Cl^- and BF_4^- as anions gave the best performances with high yields, high diastereo- and enantioselectivity.[15]

Table 1
The effect of catalyst in the Michael reaction of cyclohexanone and nitrostyrene



Entry	Catalyst	TFA[a] (mol %)	*T*	Time (h)	Yield[b] (%)	ee[c] (%) (*syn*)	dr[d] (*syn*/*anti*)
1	**1a**	—	rt	36	74	99	98/2
2	**1a**	**5**	**rt**	**36**	**91**	**99**	**97/3**
3	**1b**	—	rt	36	75	94	>99/1
4	**1b**	5	rt	16	95	98	99/1
5	**1b**	**5**	**4 °C**	**30**	**92**	**99**	**>99/1**
6	**1c**	—	rt	72	90	93	99/1
7	**1c**	5	rt	48	92	86	95/5
8	**1d**	—	rt	43	81	95	96/4
9	**1d**	5	rt	16	95	93	96/4
10[e]	**1b**	5	4 °C	30	90	99	99/1
11[f]	**1b**	5	4 °C	30	82	94	96/4

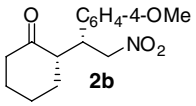
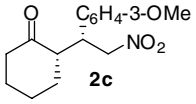
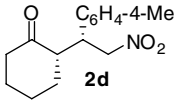
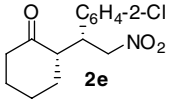
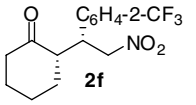
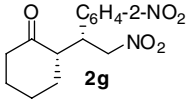
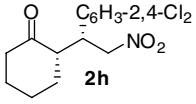
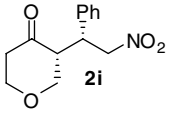
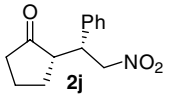
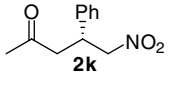
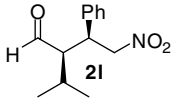
[a] TFA (trifluoroacetic acid).
[b] Isolated yield.
[c] Determined by Chiral HPLC.
[d] Determined by ^1H NMR.
[e] Second cycle of **1b**.
[f] Third cycle of **1b**.

Encouraged by these results, we next probed the conjugate addition of a few cyclic ketones to a variety of nitroolefins with catalysts **1a**/TFA at ambient temperature and **1b**/TFA at 4 °C, respectively (Table 2). The results showed that the reactions proceeded efficiently with cyclohexanone and nitroolefins to give the Michael adducts with high yields (73–100%), excellent levels of diastereoselectivities (*syn*/*anti* ratio up to >99/1) and enantioselectivities (ee up to 99%). More significantly, nitroolefins possessing either electron-rich or electron-deficient substituents reacted smoothly with Michael donors (entries 1–14), including tetrahydro-4*H*-pyran-4-one (entries 15 and 16). Cyclopentanone and acetone also provided the desired adducts **2j** and **2k**, respectively, but in low selectivities; in these two cases, catalyst **1d** showed a higher catalytic activity, compared to **1b** (entries 17–20). Isovaleraldehyde was also a suitable Michael donor and afforded the desired product **2l** with moderate enantioselectivity and good diastereoselectivity (entry 21).

The high diastereo- and enantioselectivities may be explained by an acyclic synclinal transition state **A**, in which the pyridinium ring plays an important role in shielding the *si*-face of enamine double bond.[16] The possible ionic attraction between pyridinium cation and nitro group of the substrate (transition state **B** in Fig. 1) should also contribute to the enantioselectivity observed.

In conclusion, we have designed and synthesized a new class of chiral ILs that serve as efficient catalysts for the asymmetric Michael reaction of cyclic, six-membered ketones to nitroolefines. These pyrrolidine-based chiral pyridinium ILs catalysts are easily prepared from commercially available (*S*)-(2-aminomethyl)-1-*N*-Boc-pyrrolidine in two or three steps. Our chiral ILs are environment-friendly, easy recovery and can be reused as catalysts for a broad range of Michael acceptors and donors with high yields (up to 100%), high diastereoselectivities (*syn*/*anti* up to >99:1) and enantioselectivies (ee up to 99%). The applications of these new ILs to other asymmetric reactions, such as diamination and aminohalogenation, are presently being carried out in our lab.

Table 2
Asymmetric Michael reaction of ketones to nitroolefins catalyzed by **1a**/TFA or **1b**/TFA

Entry	Product	Cat. (*T*)	Time (h)	Yield[a] (%)	ee[b] (%) (*syn*)	dr[c] (*syn*/*anti*)
1	 **2b**	**1a** (rt)	48	73	98	93/7
2		**1b** (4 °C)	48	91	98	>99/1
3	 **2c**	**1a** (rt)	48	75	96	>99/1
4		**1b** (4 °C)	48	98	95	99/1
5	 **2d**	**1a** (rt)	48	77	99	96/4
6		**1b** (4 °C)	36	91	98	97/3
7	 **2e**	**1a** (rt)	36	85	96	99/1
8		**1b** (4 °C)	21	98	96	99/1
9	 **2f**	**1a** (rt)	48	83	96	97/3
10		**1b** (4 °C)	36	92	97	99/1
11	 **2g**	**1a** (rt)	41	94	96	99/1
12		**1b** (4 °C)	24	100	94	99/1
13	 **2h**	**1a** (rt)	36	87	97	>99/1
14		**1b** (4 °C)	24	95	97	>99/1
15	 **2i**	**1a** (rt)	36	76	89	94/6
16		**1b** (4 °C)	36	90	92	94/6
17	 **2j**	**1b** (rt)	36	<10	nd[d]	nd[d]
18		**1d** (rt)	36	69	62/82	53/47
19	 **2k**	**1b** (rt)	72	82	35	—
20		**1d** (rt)	36	90	40	—
21	 **2l**	**1b** (rt)	144	46	42	93/7

[a] Isolated yield.
[b] Determined by Chiral HPLC.
[c] Determined by ^{1}H NMR spectroscopy (400 MHz).
[d] Not determined.

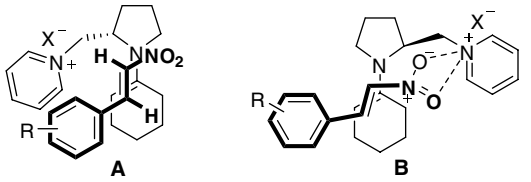


Fig. 1. Transition state for Michael additions.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.12.024.

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14. For the solvent and additive effect of catalyst **1b** for Michael addition see Supplementary data.
15. *Typical procedure*: Catalyst **1b** (8 mg, 15 mol %) was dissolved in MeOH (20 μL). Then cyclohexanone (0.4 mL) and trifluoroacetic acid solution of MeOH (16 μL, 14 μL/mg, 5 mol %). After stirring for 30 min at room temperature, β-nitrostyrene was added and the reaction mixture was stirred at 4 °C for 30 h. Ethyl ether was added to precipitate the catalyst and the organic layer was separated. Removal of the solvent and purification by silica gel column (eluent: hexane–ethyl acetate = 4:1) gave the Michael adduct (45 mg, 92%) as a white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.23 (m, 3H), 7.20–7.14 (m, 2H), 4.94 (dd, $J = 12.4$ and 4.4 Hz, 1H), 6.43 (dd, $J = 12.4$ and 10.0 Hz, 1H), 3.76 (dt, $J = 9.6$ and 4.4 Hz, 1H), 2.74–2.64 (m, 1H), 2.52–2.34 (m, 2H), 2.13–2.03 (m, 1H), 1.83–1.50 (m, 4H), 1.30–1.18 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.9, 137.7, 128.9, 128.2, 127.8, 78.9, 52.5, 43.9, 42.7, 33.2, 28.5, 25.0; $[\alpha]_D^{20}$ −37.0 ($c = 0.48$ in $CHCl_3$); *syn*/*anti* > 99/1; ee = 99%; HPLC (Chiralpak AS-H, *i*-propanol/hexane = 10/90, flow rate 0.7 mL/min, $\lambda = 238$ nm): $t_{minor} = 24.7$ min, $t_{major} = 37.5$ min. The catalyst was dissolved in MeOH and neutralized with $NaHCO_3$ solid. Removal of the solvent left a residue, which was diluted with a mixture solvent (CH_2Cl_2–MeOH = 10:1), and the insoluble was removed by filtration. The filtrate was concentrated and dried to give the catalyst, which was used for the next run reaction.
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