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Ionic Liquid-Supported (ILS) (*S*)-Pyrrolidine Sulfonamide, a Recyclable Organocatalyst for the Highly Enantioselective Michael Addition to Nitroolefins

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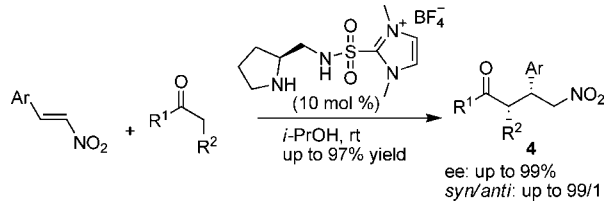
ABSTRACT



A new class of ionic liquid supported (ILS) (*S*)-pyrrolidine sulfonamide organocatalyst has been developed and shown to be a very effective catalyst for the asymmetric Michael addition reactions of ketones and aldehyde to nitroolefins with high enantio- and diastereoselectivities. This ILS organocatalyst is also easily recycled and could be reused at least five times without significant loss of its ability to affect the outcome of the asymmetric reactions.

Over the past few years, there has been a tremendous increase in research activities on the development of organocatalysts for asymmetric carbon−carbon bond-forming reactions,[1] especially for the Michael addition reaction.[2] The conjugate addition of ketones to nitroolefins is of particular importance since it represents an efficient method for the preparation of γ-nitrocarbonyl compounds with two contiguous stereocenters in a single step. These compounds are versatile synthetic building blocks since the nitro and carbonyl groups can be transformed easily into other useful functional groups.[3] As a result, much effort has been devoted toward developing efficient asymmetric catalysts, especially environmentally friendly organocatalysts that are also metal-free for these and similar asymmetric reactions. Proline and its pyrrolidine-based derivatives have been investigated and shown to be effective asymmetric catalysts for the Michael addition of aldehydes and ketones to nitroolefins;[4−6] however, these organocatalysts still have some drawbacks in that

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(2) For reviews, see: (a) Sulzer-Mosse, S.; Alexakis, A. *Chem. Comm.* **2007**, *30*, 3123. (b) Jarvo, E. R.; Miller, S. J. *Tetrahedron* **2002**, *58*, 2481.

(3) For recent reviews, see: (a) Krause, N.; Hoffmann-Roder, A. *Synthesis* **2001**, 171. (b) Berner, O. M.; Tedeschi, L.; Enders, D. *Eur. J. Org. Chem.* **2002**, 1877. (c) Sibi, M. P.; Manyem, S. *Tetrahedron* **2000**, *56*, 8033. (d) Christoffers, J.; Baro, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 1688.

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high catalyst loading (10−30 mol %) is typically required, which will raise the cost and limit its application in the pharmaceutical industry. In addition, low temperature and a large excess of ketone (normally 10−20 equiv) are also generally required to achieve good enantioselection.[7] Therefore, the design and development of highly active organocatalysts aimed at overcoming these limitations have proven to be a significant challenging task and limited success has only been achieved quite recently.[8,9]

One aspect of our research is aimed at the development of recyclable ionic liquid supported (ILS) organocatalysts for asymmetric organic reactions, and we have recently shown that imidazolium ILS pyrrolidine sulfonamides **1a**−**b** (Figure 1) serve as recyclable catalysts for Michael addition

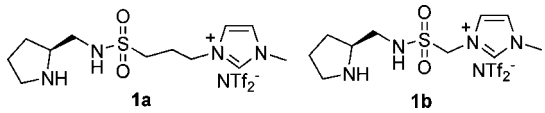
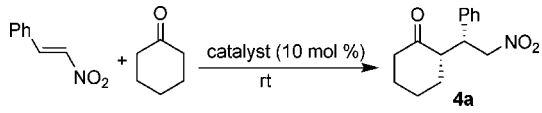


Figure 1. ILS (*S*)-pyrrolidine sulfonamide organocatalysts.

of aldehydes with nitroolefins;[8a,b] these ILS catalysts, however, resulted in moderate reaction rate when cyclohexanone was used as the substrate (see Table 1, entries 6−8).

Table 1. Optimization of the Reaction Conditions[a]

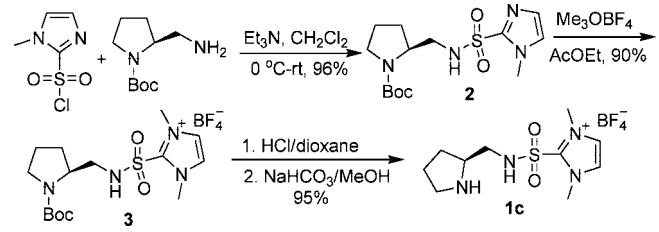


entry	catalyst	solvent	time (h)	yield[b] (%)	ee[c] (%)	syn/anti[d]
1	**1c**	M_eOH	19	95	73	95/5
2	**1c**	***i*-PrOH**	16	91	90	95/5
3	**1c**	CH_3CN	17	81	86	95/5
4	**1c**	neat	14	92	85	99/1
5[e]	**1c**	[BMIM][PF_6]	17	<10	*f*	*f*
6[g]	**1a**	CH_3CN	144	38	88	95/5
7[g]	**1a**	***i*-PrOH**	120	<10	*f*	*f*
8[g,h]	**1b**	MeOH	144	40	90	94/6

[a] Ketone (5 equiv) was used. [b] Isolated yield. [c] Determined by chiral HPLC. [d] Determined by ^{1}H NMR. [e] [BMIM][PF_6] = 1-Butyl-3-methyl imidazolium hexafluorophosphate. [f] Not determined. [g] Catalyst (20 mol %) was used. [h] Trifluoroacetic acid (5 mol %) was used.

For Michael addition reactions involving sulfonamide organocatalysts of this type, it is believed that the acidic N−H hydrogen plays an important role in the stabilization of the transition state via hydrogen bonding.[5k,8a,b] Based on this knowledge, we have designed a new type of ILS pyrrolidine sulfonamide organocatalyst based on subtle structural modifications to catalysts **1a** and **1b** in order to increase the N−H acidity. This new design is based on introducing the sulfonyl group into the C-2 position of the imidazolium cation, which is more electronegative than C-4 or C-5; in addition, the imidazolium cation which serves as an electron-withdrawing group will result in a fairly acidic N−H. The increased acidity will result in stronger hydrogen bonds that are formed in the transition states of these reactions. We believe that such modifications, even though slight, will result in dramatic enhancement of the catalytic activity and selectivity and will avoid the need for an acidic additive. Also, this substitution of imidazolium cation introduces more steric bulk closer to the catalytic site and may improve the stereoselectivity. Herein, we report the synthesis of this new and novel organocatalyst, **1c** (Scheme 1) and the results of the studies

Scheme 1. Synthesis of ILS (*S*)-Pyrrolidine Sulfonamide Organocatalyst **1c**



using **1c** as a recyclable organocatalyst to promote highly enantio- and diastereoselective Michael addition reactions of ketones and aldehyde to nitroolefins.

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(6) For selected other organocatalytic Michael addition reactions, see: (a) Halland, N.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **2002**, *67*, 8331. (b) Halland, N.; Hansen, T.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 4955. (c) Melchiorre, P.; Jørgensen, K. A. *J. Org. Chem.* **2003**, *68*, 4151. (e) Halland, N.; Aburel, P. S.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 1272. (f) Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2001**, *123*, 4370. (g) Li, H.; Wang, Y.; Tang, L.; Deng, L. *J. Am. Chem. Soc.* **2004**, *126*, 9906. (h) Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672.

(7) Only the diamine- and triamine-protonic acid catalysts (ref 5l using 5 equiv of ketone and ref 5m using 2 equiv of ketone) provide good ee for a few substrates at room temperature.

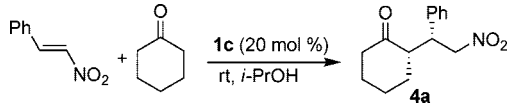
(8) For examples reported recyclable organocatalysts for Michael addition reactions using ionic liquid as support, see: (a) Ni, B.; Zhang, Q.; Headley, A. D. *Green Chem.* **2007**, *9*, 737. (b) Zhang, Q.; Ni, B.; Headley, A. D. *Tetrahedron* **2008**, *64*, 5091. (c) Ni, B.; Zhang, Q.; Headley, A. D. *Tetrahedron Lett.* **2008**, *49*, 1249. (d) Wu, L.-Y.; Yan, Z.-Y.; Xie, Y.-X.; Niu, Y.-N.; Liang, Y.-M. *Tetradedron: Asymmetry* **2007**, *18*, 2086. (e) Luo, S.; Mi, X.; Zhang, L.; Liu, S.; Xu, H.; Cheng, J.-P. *Angew. Chem., Int. Ed.* **2006**, *45*, 3093.

Catalyst **1c** was readily prepared from 1-methyl-2- sufonyl chloride imidazole and (*S*)-2-amino-1-*N*-Boc-pyrrolidine in three steps with 82% overall yield (Scheme 1).

Initially, the Michael reaction of cyclohexanone and *trans*-β-nitrostyrene in various solvents was examined at room temperature using ILS pyrrolidine sulfonamide **1a**−**c** as organocatalysts. As shown in Table 1, the catalyst **1c** displayed excellent catalytic efficiency in protic solvent MeOH at room temperature for 19 h, affording Michael adduct **4a** in 95% yield with moderate enantioselectivity (73% ee) and high diastereoselectivity (*syn/anti* 95/5) (Table 1, entry 1). The enantioselectivity dramatically improved when the solvent *i*-PrOH was used (Table 1, entry 2). When the reaction was carried out in CH_3CN or a neat condition, slightly decreased enantioselectivities were observed (Table 1, entries 3−4). However, using ionic liquid [BMIM][PF_6] as solvent only resulted in low yield (Table 1, entry 5). Noteworthy, catalyst **1c** exhibited superior catalytic activity, compared to catalysts **1a**−**b** (Table 1, entries 6−8). These results are a strong indication that the introduction of the sulfonyl group into the C-2 position of the electron-withdrawing imidazolium cation enhances the acidity of the N−H proton of catalyst **1c** and thus provide a stronger hydrogen-bonding interaction with substrate in the transition state, which results in enhanced catalytic activity and stereochemical control.

Next, we chose the reaction of *trans*-β-nitrostyrene and cyclohexanone as the model under standard reaction conditions to examine the recyclability of catalysts ILS **1c** (20 mol % was used). After the reaction was completed, the reaction mixture was concentrated and the residue was diluted with ethyl acetate to precipitate the catalyst, which was easily recovered (>90%) by the simple phase separation. The catalyst was dried and reused for the next run of the reaction. As shown in Table 2, catalyst **1c** could be recycled

Table 2. Recycling Studies of ILS **1c** Catalyzed Michael Addition of Cyclohexanone to *trans*-β-Nitrostyrene[a]



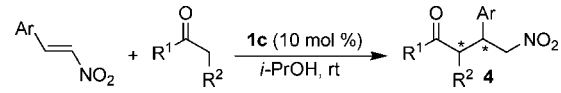
cycle	time (h)	yield[b] (%)	ee[c] (%)	*syn/anti*[d]
1	12	92	90	95/5
2	16	90	90	95/5
3	18	93	90	94/6
4	24	86	89	95/5
5	40	80	88	93/7

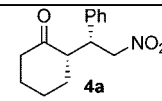
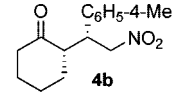
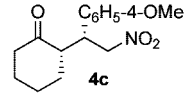
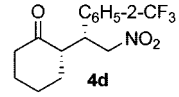
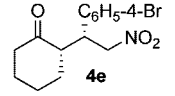
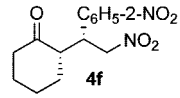
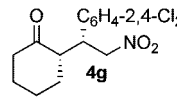
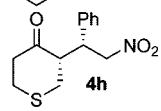
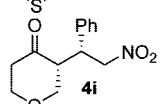
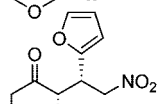
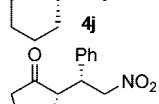
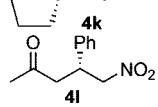
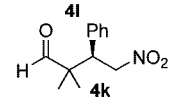
[a] Ketone (5 equiv) was used. [b] Isolated yield. [c] Determined by chiral HPLC. [d] Determined by ^{1}H NMR.

and reused for at least 5 times without significant loss of stereoselectivity (ee > 88%; *syn/anti* > 93/7) despite some slight decreasing of activity observed in cycles 2−5.

Having established the standard reaction conditions for Michael addition of cyclohexanone with *trans*-β-nitrostyrene, we next investigated the scope of the Michael reaction for which catalyst **1c** is effective with a series of ketones and nitroolefins in *i*-PrOH as the solvent, and the results are shown in Table 2. From these results, it is obvious that all 6-membered ring ketones can efficiently undergo Michael reactions with different aryl-substituted nitroolefins in the presence of 10 mol % of catalyst **1c** in *i*-PrOH at room

Table 3. Michael Reaction of Ketones to Nitroolefins[a]



entry	product	time (h)	yield (%)[b]	ee (%)[c]	syn/anti[d]
1	 **4a**	16	91	90	95/5
2	 **4b**	17	90	99	99/1
3	 **4c**	24	83	98	99/1
4	 **4d**	20	90	95	98/2
5	 **4e**	17	87	94	93/7
6	 **4f**	24	96	90	97/3
7	 **4g**	24	96	99	99/1
8[e]	 **4h**	32	85	92	96/4
9[e]	 **4i**	36	94	92	94/6
10	 **4j**	24	97	80	92/8
11	 **4k**	36	10	nd[f]	nd[f]
12	 **4l**	36	75	14	-
13	 **4k**	16	85	75	-

[a] Ketone (5 equiv) was used. [b] Isolated yield. [c] Determined by chiral HPLC. [d] Determined by ^{1}H NMR. [e] Ketone (3 equiv) was used. [f] Not determined.

temperature to give the Michael adducts **4a**−**j** in high yields with excellent enantio- (80−99% ee) and diastereoselectivities (*syn*/*anti* ratio up to 99/1). The results in Table 3 also show that the nature of the substituents on aryl groups slightly influences the yields and enatioselectivities. For nitroolefins with electron-rich groups (methyl and methoxy), the reaction proceeded smoothly to afford Michael adduct **4b**−**c** in excellent enantio- (98−99% ee) and diastereoselectivities (*syn*/*anti* 99/1) (Table 3, entries 2−3). These results are superior to those of the experiments by Wang and co-workers with recyclable fluorous (*S*)-pyrrolidine sulfonamide catalyst (ee: 89−91%; *syn*/*anti* 16/1−50/1).[9a] For nitroolefins with electron-deficient groups, the Michael adducts **4d**−**g** were also obtained in high yields (87−96%) with excellent enantio- (90−99% ee) and diastereoselectivities (*syn*/*anti* ratio up to 99/1) (Table 3, entries 4−7). Tetrahydrothiopyran-4-one, tetrahydro-4H-pyran-4-one, and 2-(2-nitrovinyl)furan were also suitable substrates as Michael donors (Table 3, entries 8−10). However, when cyclopentanone was used as substrate, only poor yield was obtained (Table 3, entry 11). Acetone worked well to give the desired products in good yield, but poor enantioselectivity (14% ee) (Table 3, entry 12). The Michael addition of *i*-butyraldehydes with *trans*-β-nitrostyrene underwent smoothly under catalyst **1c** to afford an adduct containing adjacent quaternary and tertiary carbon centers (Table 3, entry 13).

The absolute stereochemistry of major product **4a** was determined to be 2*S*,3*R* by comparing its optical rotation.[5] The absolute stereochemical results can be explained by related transition state models previous discussed for (*S*)-pyrrolidine sulfonamide catalyzed Michael reactions.[5k]

In conclusion, we have developed a catalytic recyclable ILS (*S*)-pyrrolidine sulfonamide organocatalyst **1c**, which can be used to promote highly efficient, asymmetric Michael addition reactions of ketones and aldehyde to nitroolefins. The main advantages of this catalyst are the ease of synthesis, low catalyst loading (10 mol %), and the use of small excess of ketones (3−5 equiv) for high stereoselectivities (ee up to 99%; *syn*/*anti* up to 99/1) at room temperature. Moreover, the catalyst is readily recovered and reused for at least five times without significant loss of catalytic activity and stereoslectivity. Further studies focusing on the scope of this recyclable catalyst catalyzed asymmetric transformations are currently under investigation and will be reported in due course.

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Supporting Information Available: Experimental procedures, spectral data, HPLC data, and HPLC spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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