Ionic Liquid-Supported (ILS) (*S*)-Pyrrolidine Sulfonamide for Asymmetric Michael Addition Reactions of Aldehydes with Nitroolefins

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Abstract: A class of ionic liquid supported (ILS) (S)-pyrrolidine sulfonamide organocatalyst (**1c)**, which was developed earlier in our lab, has been applied to a wider range of Michael addition reaction, involving various aryl-substituted nitroolefins and a series of aldehydes. Catalyst **1c** catalyzes Michael additions in which only 2 equivalents of aldehydes to each equivalent of nitroolefin are required. With 10 mol% of ILS catalyst **1c** loading, moderate to excellent yields (51-98%) with moderate enantioselectivities (28-83% ee) and high diastereoselectivities (*syn/anti* ratio up to 97/3) were obtained. Moreover, the catalyst **1c** could be easily recycled and reused for at least 5 times with slightly reduced activities.

Keywords: Aldehydes, asymmetric catalysis, ionic liquid, michael addition, nitroolefins.

INTRODUCTION

The organocatalytic asymmetric Michael reaction has been one of the most powerful synthetic methodologies in modern chemistry for the construction of C-C bonds with simultaneous generation of two contiguous stereocenters in a single step [1]. The products of the Michael reaction are versatile synthetic building blocks for a wide variety of important biological and pharmaceutical compounds [2]. Since the pioneering work of List and Barbas in 2001 [3], a great deal of effort has been devoted to the development of more selective and catalytic protocols for this cornerstone type transformation, and significant progress has been made in recent years [4]. A major problem associated with this reaction however, is that most organocatalytic systems that are typically used require high loadings (normally 10-30 mol%) and a large excess of Michael donor sources (normally 5-20 equivalents) to complete the reactions in reasonable timescales and give good stereoselectivity. As a result, there are high costs associated with these reactions and their applications are limited. Such limitations are of practical significance, especially in the pharmaceutical industry. Despite the effort invested in the development of highly effective organocatalysts aimed at lowering catalyst loading and reducing the quantity of donor sources, only limited success has been achieved [5].

An alternative strategy is to develop recyclable and reusable chiral organocatalysts. Methods for immobilizing homogeneous organocatalysts have only been developed in recent years [6]. For example, insoluble polymer supported proline was used as organocatalyst for the asymmetric Michael addition of ketones and aldehydes to nitroolefins and the catalyst was easily separated and could be recycled [6b]. A large excess of the Michael donor, up to 20 equivalents, is required in order to increase the reaction conversion, this becomes a serious limitation for reactions where Michael donors that are not commercially available. The group of Wang has described fluorous (S)-pyrrolidine sulfonamide promoted enantioselective Michael addition of ketones and aldehydes to nitroolefins [6a]. Again, the same drawback is that 10 equivalents of Michael donor source are needed, and the expensive fluorous silica gel is required for catalyst recovery. Therefore, the development of the high catalytic activity of catalysts, which integrate the advantages of homogeneous and heterogeneous catalysis with easy separation and convenience of recycling the catalysts from the reaction mixture, as well as with low Michael donors loading, are of tremendous importance.

Recently, the use of ionic liquids (ILs) as supports for homogeneous catalyst has attracted much attention due to their attractive physical properties; they include lack of measurable vapor pressure, have high chemical and thermal stability, and they exhibit high ionic conductivity [7]. Most important, the solubility of ionic liquids can be fine-tuned by modification of their cation and anion so that they can be separated easily from organic solvents as well as aqueous media due to solubility differences. ILS chiral pyrrolidine organocatalysts have been used recently to promote the direct asymmetric Michael addition of ketones to nitroolefins with high stereoselectivity. However, a large excess of ketones or aldehydes (10-20 equivalents) is still required to drive the reaction to completion in reasonable timescales [6d-e]. As a result, it is desirable to design and develop efficient ILS organocatalysts, which catalyze Michael reactions with low Michael donor source loading. We have developed a series of ILS pyrrolidine sulfonamide, shown in Fig. (**1**), and it was shown that **1c** served as a recyclable organocatalyst for Michael reactions of ketones to nitroolefins in *i*-PrOH at room temperature affording

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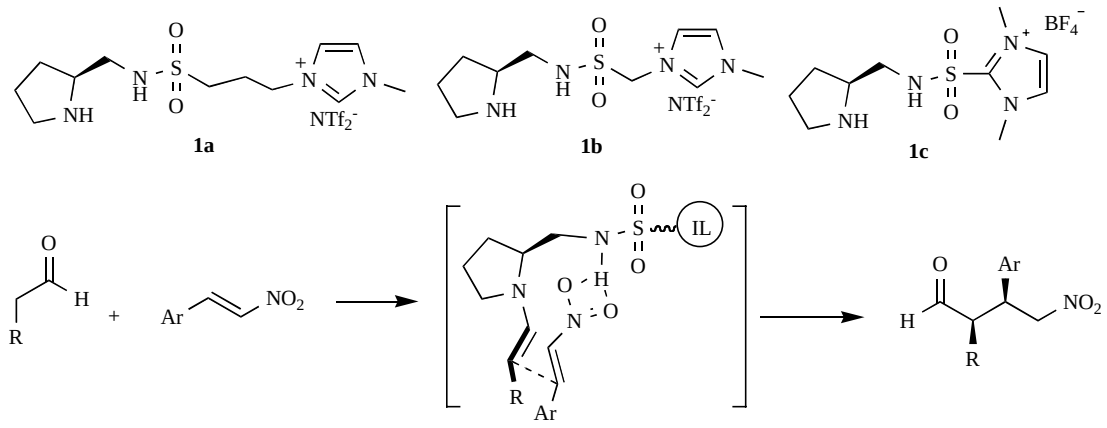


Fig. (1). ILS pyrrolidine sulfonamide organocatalysts used for Michael addition.

Michael adducts in high levels of enantioselectivities (up to 99% ee) and diastereoselectivities (*syn*/*anti* ratio from 92/8 to 99/1) [6i].

Herein, we report the results of studies aimed at exploring the use of ILS organocatalyst **1c** for a wide scope of Michael reactions involving aldehydes. Based on the mechanism proposed for Michael addition to nitroolefins involving the pyrrolidine sulfonamide organocatalysts shown in Fig. (**1**), the acidic N-H hydrogen is believed to stabilize the transition state through hydrogen bonds that allow the preferential enamine addition to the less hindered face of the nitroolefins to induce the outcome of the stereoselectivity. Therefore, subtle changes that affect the acidity of N-H of the catalyst can be utilized to improve catalytic activity and selectivity in a dramatic way.

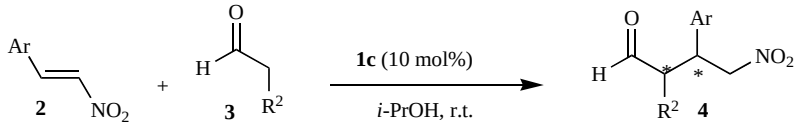
RESULTS AND DISCUSSION

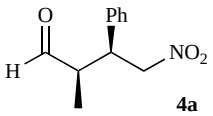
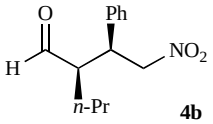
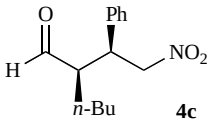
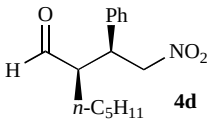
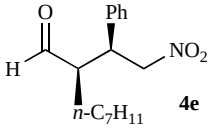
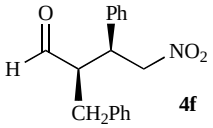
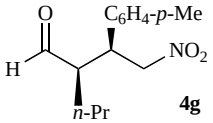
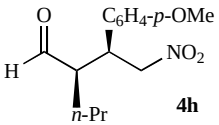
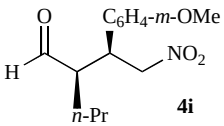
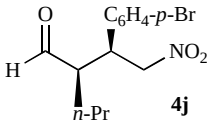
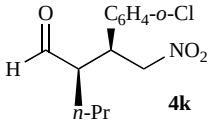
Earlier, we reported on the Michael addition of aldehydes to nitroolefins catalyzed by ILS catalysts **1a** and **1b**, and it was shown that the catalytic activity of **1b** is higher, compared to that of **1a** [6g]. Under the optimized reaction conditions, the conjugate addition reaction of aldehydes (6 equiv) to nitroolefins catalyzed by 20 mol% of **1a** afforded the product in moderate yields (29-70%) with 54-84% ee after 6 days, whereas the reaction is complete within 2-3 days by using **1b** (20 mol%) in excellent yields (82-99%) with 41-85% ee. Since ILS catalyst **1c** was found to exhibit superior catalytic activity for the Michael addition of ketones to nitroolefins, compared to catalyst **1a** and **1b** [6i], we tested it as a catalyst for the Michael addition of aldehydes to nitroolefins; this should result in the use of reduced aldehydes, with respect to the nitroolefin. To test this hypothesis, we used only 2 equivalents of the aldehydes and carried out the reaction in *i*-PrOH at room temperature with 10 mol% of ILS catalyst **1c** loading, the results are summarized in Table **1** [8]. From these results, it is obvious that all aldehydes tested can efficiently undergo Michael addition reactions with a wide range of aryl-substituted nitroolefins to afford the Michael adducts **4a-q** in moderate to excellent yields (51-98%) with moderate enantio- (28-83% ee) and high diastereoselectivities (*syn/anti* ratio up to 97/3). As demonstrated in Table **1**, the length of the chain attached to the aldehydes can influence the yields and enantioselectivities. It was observed that the long chain of the linear aldehydes gave the Michael adducts with relatively higher enantioselectivities and diastereoselectivities, compared to the short chain (Table **1**, entries 1-5). However, for the case of 3-phenylpropionaldehyde, a low enantioselectivity and reaction rate was observed (Table **1**, entry 6).

Next, the reactions of various substituted nitroolefins and the linear aldehyde *n*-pentanal were studied. Generally, the nature of the substituents on the aryl group has a slight influence on the yields and enatioselectivities. For nitroolefins with electron-rich groups (methyl and methoxy), the reaction proceeded smoothly to afford Michael adduct **4g-i** in excellent yields with enantio- (38-46% ee) and diastereoselectivities (*syn/anti* up to 93/7) (Table **1**, entries 7-9). For nitroolefins with electron-deficient groups, the Michael adducts **4j-n** were also obtained in moderate to high yields (70-98%) with moderate enantioselectivities (35-44%), but relative low reaction rate for the NO_2 and CF_3 substituted compounds (Table **1**, entries 10-14). The branched aldehyde isovaleraldehyde was also found to be a suitable substrate as Michael donor affording the product **4o** in high yield with 69% ee and excellent diastereoselectivity (*syn*/*anti*: 97/3) (Table **1**, entry 15). In addition, α,α-disubstituted aldehydes, isobutyraldehyde and cyclopentanecarboxaldehyde, are also suitable Michael donors and afforded adducts **4p**-**q**, which simultaneously generated quaternary carbon centers, in 51-65% yields with good enantioselectivities (75-83%) (Table **1**, entries 16-17).

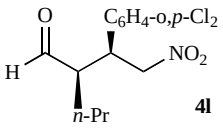
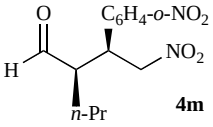
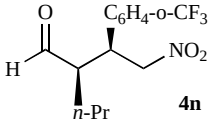
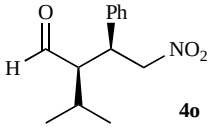
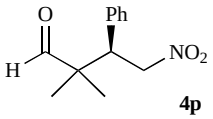
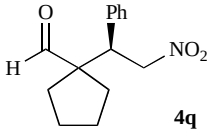
Since the best results for the Michael reaction were obtained using catalyst ILS **1c** (20 mol% of **1c** was used), we chose that reaction to examine the recyclability of the catalyst. We decided to use the reaction of *trans*-β-nitrostyrene and isovaleraldehyde, under standard reaction conditions, as the model reaction. When the first run of 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 simple phase separation. The ethyl acetate phase was combined, concentrated and further purified by flash silica gel column to give the Michael adduct **4o**. The catalyst was recovered, dried and reused for the next run of the reaction. As shown in Table **2**, catalyst **1c** could be recycled and reused for at least 5 times without significant loss of

Table 1. Michael Addition of Aldehydes to Nitroolefins Catalyzed by ILS 1c[a]



Entry	Product	Time (h)	Yield (%)[b]	ee (%)[c]	dr (*syn*/*anti*)[d]
1	 **4a**	4	95	38	81/19
2	 **4b**	3	93	44	91/9
3	 **4c**	2	97	48	94/6
4	 **4d**	2	96	49	95/5
5	 **4e**	3	98	50	96/4
6	 **4f**	24	85	28	87/13
7	 **4g**	4	91	46	91/9
8	 **4h**	5	93	40	93/7
9	 **4i**	5	98	38	89/11
10	 **4j**	4	91	43	84/16
11	 **4k**	3	98	44	89/11

(Table 1). Contd…..

Entry	Product	Time (h)	Yield (%)[b]	ee (%)[c]	dr (*syn/anti*)[d]
12	 **4l**	3	91	35	93/7
13	 **4m**	30	70	37	75/25
14	 **4n**	24	82	40	86/14
15	 **4o**	15	96	69	97/3
16	 **4p**	50	65	75	-
17	 **4q**	50	51	83	-

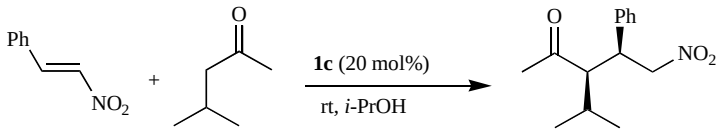
[a]2 equiv of aldehydes was used. [b]Isolated yield. [c]Determined by chiral HPLC. [d]Determined by ^{1}HNMR.

stereoselectivity (ee > 68%; *syn/anti* > 96/4) despite some slight decreasing of activity observed in cycles 3-5.

CONCLUSION

In conclusion, a class of ionic liquid supported (ILS) (S)-pyrrolidine suflonamide organocatalyst (**1c)**, which was developed earlier in our lab, has been applied to a wider range of Michael addition reaction involving various aryl-substituted nitroolefins and a series of aldehydes. We have demonstrated that catalyst **1c** catalyzes Michael additions of aldehydes to nitroolefins using only 2 equivalents of aldehydes and low catalyst loading. Moderate to excellent yields (51-98%) with moderate enantio- (28-83% ee) and high diastereoselectivities (*syn/anti* ratio up to 97/3) were obtained. Moreover, the catalyst **1c** could be easily recycled and reused for at least 5 times with slightly reduced activities.

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



4o

cycle	time (h)	yield (%)[b]	ee (%)[c]	syn/anti[d]
1	10	97	69	97/3
2	10	95	68	97/3
3	12	95	69	96/4
4	20	90	69	97/3
5	36	86	68	96/4

[a]2 equiv of aldehydes was used. [b]Isolated yield. [c]Determined by chiral HPLC. [d]Determined by ^{1}HNMR.

ACKNOWLEDGEMENTS

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[8] Typical experimental procedure for Michael addition of aldehydes to nitroolefins. Synthesis of (R)-2,2-Dimethyl-4-nitrophenylbutanal **4a** [4k]. To a solution of catalyst **1c** (7 mg, 0.02 mmol, 0.1 equiv) in *i*-PrOH (0.5 mL) was added propionaldehyde (23 mg, 0.4 mmol). After stirring for 10 min at room temperature, *trans*-ß-nitrostyrene (30 mg, 0.2 mmol) was added and the reaction mixture was continued to stirring for 4 h. the reaction mixture was concentrated in vacuum and the residue was diluted with ethyl acetate (or ether) to precipitate the catalyst. The organic layer was separated and purified by flash silica gel column (eluent: hexane : ethyl acetate = 9 : 1) to give the Michael adduct **4a** (39 mg, 95%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.72 (d, *J* = 1.6 Hz, 1H), 7.40-7.12 (m, 5H), 4.83-4.64 (m, 2H), 3.87-3.77 (m, 1H), 2.86-2.73 (m, 1H), 1.00 (d, *J* = 7.2 Hz, 3H); *syn*/*anti*: 81/19; ee = 38%. HPLC (Chiralcel OD-H, *i*-propanol/hexane = 9:91, flow rate 1 mL/min, λ = 237 nm): t_{minor} = 24.7 min, t_{major} = 35.8 min.