

Communications

Asymmetric Michael Addition of Ketones to Nitroolefins Catalyzed by a Novel Chiral Pyrrolidine-Thiourea in the Ionic Liquid

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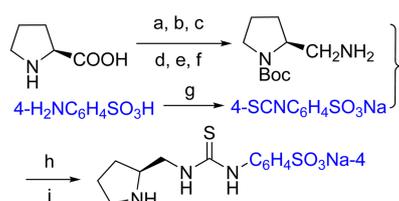
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Organocatalytic asymmetric reactions have proved to be efficient and powerful tools in organic synthesis.¹ Among them, the asymmetric Michael reaction of nitroolefins with carbon nucleophiles is widely recognized as one of the most important and versatile processes for the synthesis of enantioselective C-C and C-X bonds; for the nitroolefins are of special interest as excellent Michael acceptors, and the nitro functionality can be easily transformed into an amine, nitrile oxide, ketone, carboxylic acid, hydrogen, *etc.*, providing a wide range of synthetically interesting compounds.²

Because of the growing need for environment-friendly asymmetric synthesis, considerable attention has been focused on the development of efficient small-molecule chiral organocatalysts for asymmetric reactions; among which, the catalysts typically used for the asymmetric Michael reaction of nitroolefins are proline and its analogues derived secondary amines.³ By now, chiral pyrrolidine-urea(thiourea)-based organocatalysts have been widely used in asymmetric catalysis due to that the bifunctional thiourea catalysts could activate both nitroolefins and nucleophiles simultaneously and control the approach of nucleophiles to nitroolefins. Meanwhile, ionic liquids have been widely used as environmentally benign solvents to replace common organic media. Moreover, they are reusable, allow for simple isolation of products and enable the easy recovery of catalysts. More interesting is the enhancement of reaction efficiency by using ionic liquids as solvents.



Conditions: a. (Boc)₂O/NaOH; b. ClCO₂Et/K₂CO₃/MeOH; c. NaBH₄/LiCl/MeOH; d. TsCl/Py; e. NaN₃/DMF; f. Ph₃P/THF; g. CCl₂/H₂O; h. CF₃CO₂H/DCM; i. NaHCO₃.

Scheme 1. Synthesis of catalyst.

Herein we wish to report a novel ionic liquid-soluble pyrrolidine-thiourea that promotes the asymmetric Michael reaction of nitroolefins in ionic liquid; this reaction system will make the process more environmentally benign and more economical.

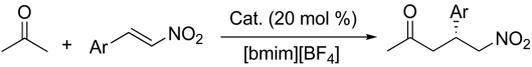
The novel catalyst was synthesized from the “chiral pool” using L-Proline as a starting material (Scheme 1).^{3a,3b,4} The synthetic procedures were quite straightforward and afforded the product in 15% total yield from L-proline (9 steps).⁵ The catalyst obtained is soluble in ionic liquids and water, but insoluble in many organic solvents. These properties, together with the straightforward synthesis, suffice for practical applications in asymmetric synthesis.

We first choose the addition of cyclohexanone to (2-nitrovinyl)-benzene as our research model to evaluate the novel chiral catalysts, and optimize the reaction conditions.⁶ A series of ionic liquid solvents are first examined for the

Table 1. Asymmetric Michael addition of cyclohexanone to *trans*-nitroolefins^a

Entry	Ar	Time (h)	<i>syn/anti</i>	Yield (%) ^b	ee (%) ^c
1	Ph	60	97/3	86	90
2	4-BrC ₆ H ₄	60	96/4	80	79
3	4-ClC ₆ H ₄	60	95/5	86	80
4	4-MeC ₆ H ₄	72	98/2	81	78
5	4-MeOC ₆ H ₄	72	93/7	72	70
6	2-Naphtyl	72	98/2	70	81
7	3,4-OCH ₂ OC ₆ H ₃	72	95/5	68	85
8	2-O ₂ NC ₆ H ₄	48	97/3	86	84
9	3-O ₂ NC ₆ H ₄	48	93/7	81	82
10	2-furyl	60	95/5	72	69

^aThe reaction was carried out on 0.25 mmol scale at 20 °C. ^bIsolated yields after chromatographic purification. ^cDetermined by chiral HPLC analysis.

Table 2. Asymmetric Michael addition of acetone to *trans*-nitroolefins^a


Entry	Ar	Time (h)	Yield (%) ^b	ee (%) ^c
1	Ph	48	88	55
2	4-BrC ₆ H ₄	48	82	42
3	4-MeOC ₆ H ₄	60	78	41
4	4-FC ₆ H ₄	48	85	61
5	3,4-OCH ₂ OC ₆ H ₃	60	72	60
6	2-O ₂ NC ₆ H ₄	60	68	36
7	2-furyl	48	81	48
8	2-Naphthyl	60	68	49

^aThe reaction was carried out on 0.25 mmol scale at 20 °C. ^bIsolated yields after chromatographic purification. ^cDetermined by chiral HPLC analysis.

asymmetric Michael reaction in the presence of 20 mol % of the organocatalyst. In all of the ionic liquid solvents, the Michael reaction could proceed smoothly to give rise to the desired product at room temperature. The best results was obtained when the reaction was carried out in [bmim][BF₄] (Table 1, entry 1). From the results, it could be found that the novel pyrrolidine-thiourea could catalyze the reaction of cyclohexanone with nitroolefins smoothly in good yields with high diastereoselectivities and good enantioselectivities. However, no improvements in enantioselectivities and yields were observed when other reaction conditions were applied, such as changing the catalyst loading or decreasing the reaction temperature and so on.

Having optimized the reaction conditions, we extended the catalytic enantioselective Michael reaction to a wide variety of nitroolefins with different structures. The results obtained are shown in Table 1. Various nitroolefins with both electron-donating and electron-withdrawing substituents could react with cyclohexanone to furnish the desired *syn*-products in good yields with excellent enantio- and diastereoselectivities smoothly.

Similarly, asymmetric Michael addition of acetone with various nitroolefins could be achieved under the same conditions. The results are listed in Table 2. It could be seen from the results that acetone give the desired products in good yields; however, the enantioselectivity of products were low.

With the success of the above reactions, we continued our investigation by exploring the recyclability of the catalytic system. The recycling process was studied starting with cyclohexanone and (2-nitrovinyl)-benzene as starting materials. After the reaction was completed, the resulting mixture was

extracted with Et₂O to give [bmim][BF₄] containing the chiral catalyst. The chiral catalytic system could be used four times with comparable enantioselectivity and yield (Yield: 86, 83, 80, 80%; ee: 90, 89, 88, 88%).

In conclusion, a novel chiral pyrrolidine-thiourea has been developed and successfully applied to the asymmetric Michael addition of ketones with nitroolefins in ionic liquid. The corresponding products could be obtained in good yields with good enantio- and diastereoselectivities of products. In addition, the chiral catalytic system could be reused with comparable catalytic activity and stereoselectivity. Further studies are under way to expand the synthetic utility of this new reaction, as well as the application of this catalytic system in other asymmetric transformations.

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- Data for the catalyst: $[\alpha]_D^{25} = -16.2$ (c = 4, H₂O); ¹H NMR (400 MHz, D₂O) δ 7.84 (d, *J* = 8.4 Hz, 2H), 7.43 (d, *J* = 8.4 Hz, 2H), 3.91-3.70 (m, 3H), 3.40-3.26 (m, 2H), 2.22-2.14 (m, 1H), 2.11-1.96 (m, 2H), 1.81-1.74 (m, 1H); ¹³C NMR (100 MHz, DMSO-*d*₆) δ 181.2, 145.1, 138.9, 126.8, 123.2, 59.3, 45.4, 27.8, 23.5.
- Typical Experimental Procedure.** Nitrostyrene (37 mg, 0.25 mmol) and Cat. (20 mol %) were mixed with cyclohexanone (0.5 mL, 5 mmol) in [bmim]BF₄ (2 mL) at rt. After stirring for 60 h, the reaction mixture was extracted with Et₂O three times. The crude product was purified by column chromatography on silica gel to give the desired product with 86% yield, *syn/anti* = 97:3, 90% ee [by HPLC on a Chiralpak AD-H column, *i*-PrOH/Hexane = 10/90, 0.5 mL/min, *t*_{minor} = 17.618 min, *t*_{major} = 20.329 min.]. All the Michael addition products are known compounds.