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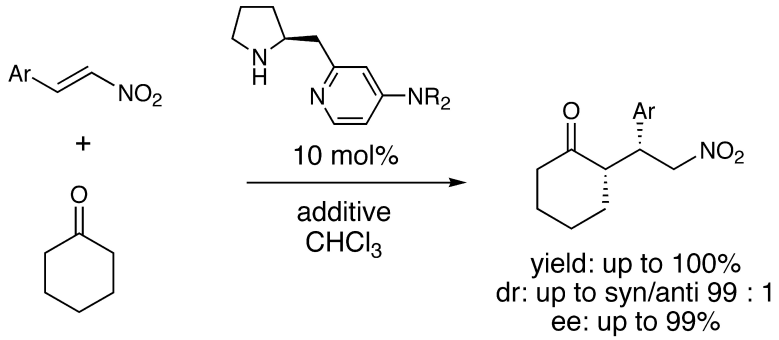

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A New Class of Chiral Pyrrolidine−Pyridine Conjugate Base Catalysts for Use in Asymmetric Michael Addition Reactions

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The Michael addition reaction is widely recognized as one of the most important carbon−carbon bond-forming reactions in organic synthesis.[1] Several reagent systems for this type of transformation that rely on asymmetric catalysts have been developed to date.[2] However, due to the growing need for its transformation to an environment-friendly nonmetal-catalyzed asymmetric synthesis, considerable attention has recently been focused on the development of efficient small-molecule chiral organocatalysts,[3] e.g., pyrrolidine-type chiral amine catalysts. For example, Hanessian,[4] List,[5] and Enders[6] described L-proline-catalyzed asymmetric Michael addition reactions. Barbas[7] and Alexakis[8] have shown that aminomethylpyrrolidine and 2,2′-bipyrrolidine derivatives could serve as useful asymmetric catalysts. Furthermore, Jørgensen[9] reported an asymmetric Michael addition reaction catalyzed by chiral imidazoline catalysts. Although these catalytic processes provide a unique methodology in asymmetric Michael addition reactions, development of new, effective catalysts is still desired.[10]

In our own work directed toward devising highly enantioselective catalysts for the addition of ketones to nitroolefins,[11] we have designed a new class of chiral pyrrolidine catalysts with a pyridine base component adjacent to a stereogenic carbon center. We anticipated that the incorporation of this base function should facilitate enamine formation from ketone precursors via α-hydrogen abstraction. In addition, the resulting pyridinium ring should effectively shield one side of an enamine double bond, which would make nitroolefin acceptors approach from the nonshielded side to give the desired Michael adducts in high enantio- and diastereoselectivity. We describe here the ability of our new bifunctional organocatalysts in performing asymmetric Michael addition reactions.

A variety of chiral pyrrolidine−pyridine conjugate base catalysts **3** were prepared from the cyclic sulfamate **1**[12] by a one-pot reaction in yields of 50−87%: coupling reaction with appropriate pyridyllithium reagents (1.2 equiv) followed by acid hydrolysis of sulfamic acid salts **2** (Scheme 1). These new catalysts were then tested in the asymmetric Michael addition reaction of cyclohexanone (**4**) to *β*-nitrostyrene (**5**).

Scheme 1

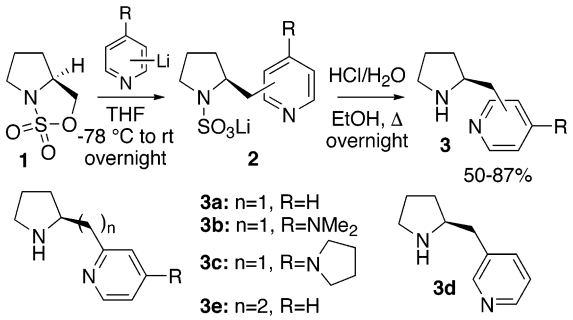
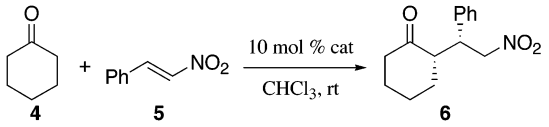


Table 1. Catalytic Asymmetric Michael Addition of Cyclohexanone (**4**) to Nitrostyrene **5** under Various Conditions[a]



entry	cat.	solvent	time (h)	yield[b] (%)	dr[c] (*syn*/*anti*)	ee (%)[d] (*syn*)
1	**3a**	$CHCl_3$	24	82	95/5	63
2[e]	**3a**	$CHCl_3$	36	76	97/3	86
3	**3b**	$CHCl_3$	36	78	95/5	88
4[e]	**3b**	$CHCl_3$ (+ acid[f])	36	99	97/3	94
5[e]	**3b**	**$CHCl_3$ (+acid[g])**	**20**	**98**	**98/2**	**95**
6[e]	**3c**	$CHCl_3$ (+acid[f])	24	97	97/3	95
7[e]	**3c**	**$CHCl_3$ (+acid[g])**	**24**	**95**	**98/2**	**99**
8	**3d**[h]	$CHCl_3$	48	66	91/9	56
9	**3e**[h]	$CHCl_3$	48	55	92/8	55

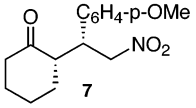
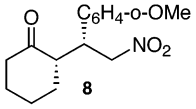
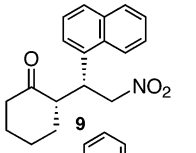
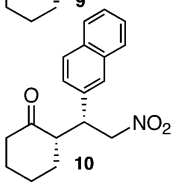
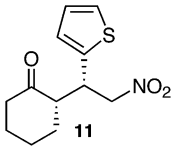
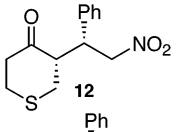
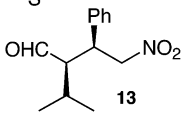
[a] Unless otherwise noted, all reactions were conducted in $CHCl_3$ (2 mL) using **4** (0.5 mL, 20 equiv) and **5** (0.25 mmol) in the presence of 10 mol % of the catalyst. [b] Isolated yield. [c] Determined by ^1H NMR of the crude mixture. [d] Determined by chiral HPLC analysis (Chiralpak AD, hexane/2-propanol = 90:10). [e] At 0 °C. [f] 2,4-Dinitrobenzenesulfonic acid (10 mol %) was added. [g] 2,4-Dinitrobenzenesulfonic acid (5 mol %) was added.

As can be seen from the results summarized in Table 1, the catalytic and enantioselective activities of **3a**−**e** differ significantly. While the use of catalyst **3a** gave only a moderate result at room temperature (entry 1), a decrease in temperature to 0 °C led to a significant improvement in the enantioselectivity (entry 2). To our delight, the introduction of a dimethylamino- or a pyrrolidino-group on the pyridine ring at the 4-position (catalysts **3b** and **3c**) increased dramatically the catalytic activity (entries 3−7), and upon the addition of 2,4-dinitrobenzenesulfonic acid (5 mol %)[13] the reaction went to completion with a nearly perfect stereo- and enantiocontrol. Thus, when a mixture of **4** (20 equiv)[14] and **5** was reacted at 0 °C in $CHCl_3$ in the presence of 10 mol % of **3c** and 5 mol % of 2,4-dinitrobenzenesulfonic acid, the desired product **6** was obtained with an excellent selectivity (entry 7). The lower efficiencies of the isomeric catalyst **3d** and the one-carbon homologue **3e** indicate the importance of proximity of a pyrrolidine−pyridine bifunctionality system (entries 8 and 9).[15]

With the optimal conditions in hand, we then examined a variety of ketones and nitroolefins to establish the general utility of this asymmetric transformation (Table 2).[16] All reactions were performed in $CHCl_3$ at 0 °C in the presence of 10 mol % of **3b** or **3c** and 5 mol % of 2,4-dinitrobenzenesulfonic acid. Various styrene-type nitroolefins were reacted smoothly with **4** in excellent diastereoselectivity (up to 99:1) and high enantioselectivity (up to 98%) (entries 1−10). Tetrahydrothiopyran-4-one was also a suitable substrate as a Michael donor (entries 11 and 12). Isovaleraldehyde provided also the desired adduct **13**, but in very low enantioselec-

10.1021/ja046871g CCC: $27.50

Table 2. Catalytic Asymmetric Michael Addition of Ketones to Nitroolefins[a]

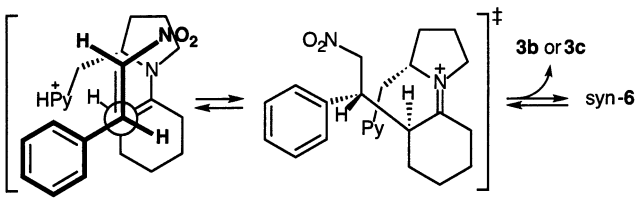
entry	time	product	yield (%)	dr (*syn*/*anti*)	ee (%) (*syn*)
1[b]	46 h	 **7**	97	97 / 3	93
2[c]	24 h		100	97 / 3	96
3[b]	21 h	 **8**	100	98 / 2	92
4[c]	24 h		99	98 / 2	93
5[b]	50 h	 **9**	92	97 / 3	98
6[c]	36 h		100	97 / 3	93
7[b]	24 h	 **10**	99	99 / 1	94
8[c]	8 h		99	98 / 2	93
9[b]	29 h	 **11**	92	94 / 6	88
10[c]	48 h		98	93 / 7	90
11[b]	68 h	 **12**	95	99 / 1	96
12[c]	24 h		98	98 / 2	92
13[b]	6 d	 **13**	45	97 / 3	7
14[c]	6 d		42	96 / 4	9
15[d]	48 h		93	98 / 2	22

[a] All reactions were performed in $CHCl_3$ (2 mL) at 0 °C using ketone (20% vol) and nitroolefin (0.25 mmol) in the presence of 10 mol % of **3** and 5 mol % of 2,4-dinitrobenzenesulfonic acid. [b] **3b** was used. [c] **3c** was used. [d] **3a** was used.

tivity (entries 13 and 14); in this case the use of catalyst **3a** gave a better result (entry 15).

To account for the present high enantio- and diastereoselective Michael addition reactions, we propose an acyclic synclinal transition state, in which the pyridinium ring must effectively shield the *si*-face of an enamine double bond, as depicted in Scheme 2 based on Seebach's model.[17]

Scheme 2



In conclusion, we have developed a new direct method for the asymmetric Michael addition reaction of ketones to nitroolefins using new pyrrolidine−pyridine conjugate base catalysts, which are easily prepared from L-prolinol. The reaction was highly efficient in terms of productivity (up to 100%), enantioselectivity (up to 99% ee), and *syn*-diastereoselectivity (up to *syn/anti* 99:1), and might be useful for preparing enantiomerically enriched γ-nitroketone derivatives. Further studies to extend the scope of this reaction are now in progress.

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Supporting Information Available: Experimental procedures and spectral data for the catalyst **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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