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Highly Enantioselective Michael Addition of Ketones to Nitroolefins with a Pyrrolidine-Based Phthalimide as an Enamine-Type Organocatalyst

Shu-rong Ban,*[a][‡] Hong-yu Xie,[a][‡] Xi-xia Zhu,[a] and Qing-shan Li*[a]

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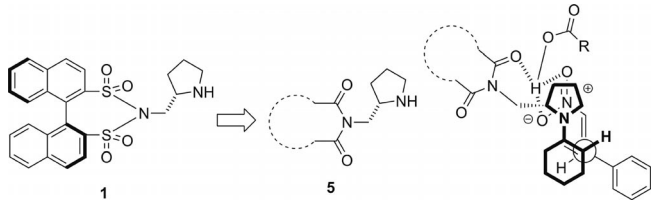
A new type of pyrrolidine-based phthalimide and other analogous imide catalysts **5a–c** were found to be efficient organocatalysts for the asymmetric Michael reaction of ketones to nitroalkenes. After fine optimization of solvents, temperature, and the additive, good to excellent enantioselectivities and diastereoselectivities (up to 99 % *ee*, up to >99:1 *dr*) can be achieved.

Introduction

In recent years, organocatalysis has been the subject of intensive development, and many organocatalysts have been applied in a variety of asymmetric reactions.[1,2] The comparable advantages, including the mild reaction conditions, environmentally benign reaction, and facile recovery of catalysts, render the organocatalytic reaction to possess some features of green chemistry.[3] Enamine catalysis,[4] imine catalysis,[5] hydrogen-bond activation,[6] carbene catalysis,[7] and phase-transfer catalysis[8] are often mentioned in the literature and are deeply researched in the asymmetric organocatalytic reaction. Among the organocatalysts used currently, a great number of pyrrolidine-type organocatalysts have been reported in an asymmetric reaction such as the Aldol reaction,[9] Mannich reaction,[10] Michael addition,[11] and Diels–Alder reaction.[12]

The asymmetric Michael addition of ketones to *trans*-β-nitrostyrene, which provides optically active nitroalkane derivatives of synthetic and biological importance, was pioneered by List[13] and Barbas[14] independently, and since then great effort has been devoted to the development of more selective and efficient catalytic systems for this synthetically useful transformation.[15] Despite the excellent results that have been achieved by these systems, the design and development of novel backbones and efficient chiral organocatalysts remain major challenges in synthetic organic chemistry.

In our previous work, the pyrrolidine-based binaphthyl sulfonimide **1** was synthesized and found to be efficient in the asymmetric Michael reaction of ketones to nitroalkenes.[16] Further, the chirality of binaphthyl did not affect the configuration of the addition product, and it has no obvious impact on enantioselectivity. In addition, the backbone of binaphthyl sulfonimide **1** is somewhat complicated, which makes it "high-carbon economic" and not easily obtained. On the basis of the above facts, we presented the optimized strategy to replace the sulfonimide with the simpler cyclic imide unit, and the possible transition state is shown in Scheme 1: the imide carbonyl oxygen atom and the co-additive proton anchor the nitroalkenes together. To the best of our knowledge, such cyclic imide organocatalysts are not reported in an asymmetric reaction. In this communication, we describe the study of a pyrrolidine-based phthalimide and other analogous imide catalysts **5a–c** that catalyze highly enantioselective Michael addition reactions of ketones with nitroolefins.



Scheme 1. Strategy to simplify the binaphthyl sulfonimide catalyst **1** and the possible transition state of **5**.

Results and Discussion

Cyclic imide catalysts **5a–c** were readily prepared by a straightforward route from the corresponding cyclic anhydride **2** and (*S*)-*tert*-butyl-2-(aminomethyl)pyrrolidine-1-carboxylate (**3**) in two steps with 25.6–68.9 % overall yields (Scheme 2).

[a] School of Pharmaceutical Science, Shanxi Medical University, Taiyuan 030001, People's Republic of China
Fax: +86-351-4690322
E-mail: qingshanl@yahoo.com
shurongban@163.com

[‡] These two authors contributed equally to this work

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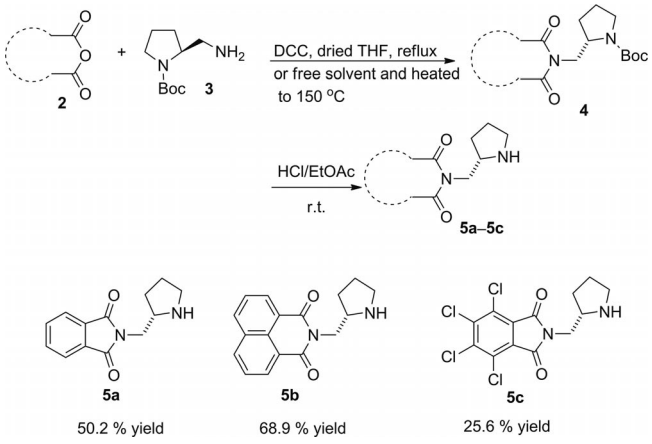
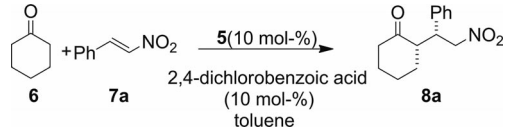


Scheme 2. Synthesis of imide catalysts **5a**–**c**.

With the desired catalysts in hand, we immediately began to optimize the reaction conditions. Using **5a** as the catalyst, a number of parameters were screened in the model asymmetric Michael addition of cyclohexanone to β-nitrostyrene. The results are summarized in Table 1. Initially, the conjugate addition was examined in a few solvents at room temperature with benzoic acid as the additive. Among the various organic solvents tested, dichloromethane, toluene, and no solvent were better in terms of both the diastereoselectivity and enantioselectivity, with 93% *ee*, 96% *ee* and 95% *ee* in enantioselectivity, respectively (Table 1, Entries 1, 2, and 5). When the reaction proceeded in polar solvents (THF and EtOH), the yields of **8a** were very poor (Table 1, Entries 3 and 4). Toluene was then selected as the solvent in the study of the influence of the additive, catalyst, and temperature. The additive carboxylic acid was found to be an essential factor for this reaction. In the absence of any carboxylic acid or in the presence of CF_3COOH, no product was obtained (Table 1, Entries 9 and 10). Almost the same level of enantioselectivity was observed for substituted benzoic acid as for benzoic acid (Table 1, Entry 2, 96% *ee*): 4-bromobenzoic acid (Table 1, Entry 6, 96% *ee*), 4-methylbenzoic acid (Table 1, Entry 7, 96% *ee*), and 2,4-dichlorobenzoic acid (Table 1, Entry 8, 97% *ee*). 2,4-Dichlorobenzoic acid is the best choice because of the higher diastereoselectivity and reaction rate.

Other chiral catalysts **5b**–**c** were screened by employing these optimized conditions (Table 1, Entry 8), and the results are summarized in Table 2. Compounds **5a**–**c** facilitated the asymmetric Michael addition of cyclohexanone to nitrostyrene with good to excellent stereoselectivities and yields. Moreover, **5a** is the best catalyst (Table 2, Entry 1, >99:1 *dr*, 97% *ee*). We also found that for catalyst **5a**, the stereoselectivity increases as the reaction temperature decreases from 20 to 0 °C (Table 2, Entry 4, >99:1 *dr*, 98% *ee*). To our delight, the above results show that imide catalyst **5a** has a higher catalytic performance than binaphthyl sulfonimide **1** for this model reaction.[16]

Table 2. Screening of the catalysts.[a]

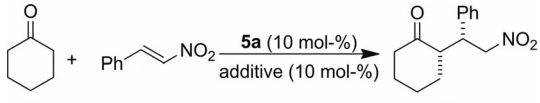


Entry	Catalyst	*T* [°C]	Time [h]	Yield [%][b]	*dr* [*syn*/*anti*][c]	*ee* [%][c]
1	**5a**	20	12	98	>99:1	97
2	**5b**	20	12	91	98:2	97
3	**5c**	20	12	75	97:3	90
4	**5a**	0	24	98	>99:1	98

[a] All reactions were carried out with cyclohexanone (**6**; 100 mg, 1.0 mmol) and nitrostyrene (**7a**; 18.7 mg, 0.13 mmol) in the presence of catalyst **5** (10 mol-%). [b] Yield of the isolated product after chromatography on silica gel. [c] Determined by chiral HPLC on a Chiralpak AS-H column with *n*-hexane and 2-propanol as eluents.

With the optimized reaction conditions in hand, a variety of nitrostyrenes bearing different substitutions were investigated, and the results are summarized in Table 3. Various

Table 1. Screening of reaction conditions for the conjugate addition of cyclohexanone to β-nitrostyrene.[a]

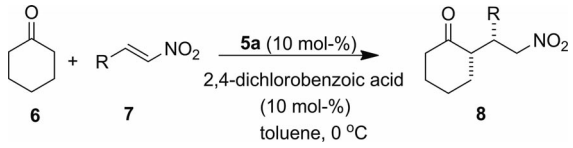


Entry	Additive	Solvent	*T* [°C]	Time [h]	Yield [%][b]	*dr* [*syn*/*anti*][c]	*ee*[%][c]
1	benzoic acid	DCM	20	12	82	98:2	93
2	benzoic acid	toluene	20	12	93	>99:1	96
3	benzoic acid	THF	20	12	23	99:1	92
4	benzoic acid	EtOH	20	12	trace	–	–
5	benzoic acid	neat	20	12	84	98:2	95
6	4-bromobenzoic acid	toluene	20	12	98	99:1	96
7	4-methylbenzoic acid	toluene	20	12	93	99:1	96
8	2,4-dichlorobenzoic acid	toluene	20	12	98	>99:1	97
9	trifluoroacetic acid	toluene	20	12	0	–	–
10	No additive	toluene	20	12	0	–	–

[a] All reactions were carried out with cyclohexanone (**6**; 100 mg, 1.0 mmol) and nitrostyrene (**7a**; 18.7 mg, 0.13 mmol) in the presence of catalyst **5a** (10 mol-%). [b] Yield of the isolated product after chromatography on silica gel. [c] Determined by chiral HPLC on a Chiralpak AS-H column with *n*-hexane and 2-propanol as eluents.

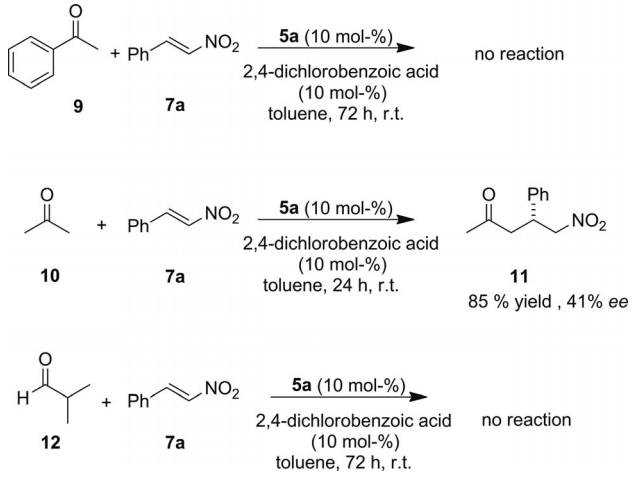
styrene-type nitroalkenes reacted smoothly with cyclohexanone to provide the corresponding adducts in moderate to excellent yields with excellent diastereoselectivities and enantioselectivities (Table 3, Entries 1–11). Excellent diasteroselectivities (up to >99:1 *dr*) and enantioselectivities (93–99% *ee*) were observed regardless of the electronic nature of the aromatic substituent R. The nature of the substituent on the benzene ring slightly influences the reaction rate and yield. When an electron-donating substituent was introduced to the benzene ring, low to moderate yields were obtained (Table 3, Entries 9). In addition, thiophenyl- or furyl-containing nitroalkenes as Michael acceptors gave low yields (Table 3, Entries 10 and 11). Aliphatic aldehyde derived nitroalkenes also appear to be good candidates for this asymmetric Michael addition reaction (Table 3, Entry 12 and 13).

Table 3. Catalytic asymmetric Michael addition of ketones to nitroalkenes.[a]



Entry	R	Time [h]	Yield [%][b]	*dr* [*syn*/*anti*][c]	*ee* [%][c]
1	Ph	24	98	>99:1	98
2	4-MeC_6H_4	36	99	98:2	96
3	2,4-$Cl_2C_6H_4$	48	92	>99:1	99
4	4-BrC_6H_4	48	95	99:1	98
5	3-$NO_2C_6H_4$	48	99	97:3	97
6	2-ClC_6H_4	48	99	>99:1	95
7	4-ClC_6H_4	48	99	98:2	96
8	4-FC_6H_4	72	99	98:2	97
9	3,4-$(MeO)_2C_6H_3$	120	52	93:7	93
10	2-thiophenyl	108	50	97:3	94
11	2-furyl	72	86	98:2	93
12	$PhCH_2CH_2$[d]	72	50	98:2	98
13	*i*Pr[d]	72	80	75:25	92

[a] All reactions were carried out with cyclohexanone (**6**; 100 mg, 1.0 mmol) and nitrostyrene (**7**; 0.13 mmol) in the presence of catalyst **5a** (10 mol-%). [b] Yield of the isolated product after chromatography on silica gel. [c] Determined by chiral HPLC on a Chiralpak AS-H column with *n*-hexane and 2-propanol as eluents. [d] These reactions were carried out at room temperature.



Scheme 3. Michael addition of ketones and aldehyde to **7a**.

Acetophenone, acetone, and isobutyraldehyde were subsequently examined in the **5a**-catalyzed Michael addition with nitrostyrene (**7a**). Unfortunately, as depicted in Scheme 3, the results are not satisfactory. Acetone gave a moderate yield (85%) and enantioselectivity (41% *ee*), and no product was obtained for acetophenone or isobutyraldehyde as a nucleophile.

Conclusions

We have successfully prepared new pyrrolidine-based phthalimide and other analogous imide catalysts **5** as highly efficient and stereoselective organocatalysts for the asymmetric Michael addition of ketones to nitroalkenes. Moderate to excellent diastereoselectivities and enantioselectivities were obtained for the addition of ketones to a variety of nitroalkenes under the catalysis of **5a**. The presence of a Brønsted acid with proper acidity, such as 2,4-dichlorobenzoic acid, proved to be critical for the excellent performance of this catalyst system. The application of this new type of organocatalyst in other asymmetric reactions is underway in our laboratory.

Experimental Section

***N*-{[(*S*)-Pyrrolidin-2-yl]methyl}phthalimide (5a):** The mixture of *o*-phthalic anhydride (148 mg, 1.0 mmol) and (*S*)-*tert*-butyl 2-(aminomethyl) pyrrolidine-1-carboxylate (210 mg, 1.04 mmol) was heated to 150 °C for 10 min and then separated directly by silica gel column chromatography to give the white solid, which was then dissolved in a mixture of concentrated HCl (2 mL) and EtOAc (10 mL) and stirred for 4 h at room temperature. The pH of the mixture was adjusted to about 8 with saturated $NaHCO_3$, after which extraction with dichloromethane was carried out (3 × 20 mL). The solution was dried with anhydrous Na_2SO_4. After removal of the solvent, the product was obtained as white solid (115.5 mg, 50.2% yield). M.p. 96.8–97.5 °C. $[\alpha]_D^{20}$ = –18.0 (*c* = 0.2, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85 (dd, *J* = 3.03 and 5.44 Hz, 2 H), 7.72 (dd, *J* = 3.07 and 5.46 Hz, 2 H), 3.72–3.66 (m, 2 H), 3.51–3.48 (m, 1 H), 3.23 (br. s, 1 H), 3.05–3.00 (m, 1 H), 2.90–2.84 (m, 1 H), 1.92–1.69 (m, 3 H), 1.49–1.43 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.63, 133.88, 132.00, 123.23, 57.50, 46.43, 43.60, 29.61, 25.37 ppm. IR (KBr): $\tilde{\nu}$ = 3456, 3213, 2962, 2817, 1717, 1694, 1645, 1614, 1431, 1398, 1132, 1051, 721 cm^{-1}. HRMS: *m*/*z* = 231.11204 [M + H]$^+$ (calcd. for $C_{13}H_{15}N_2O_2$ 231.11280).

***N*-{[(*S*)-Pyrrolidin-2-yl]methyl}-1,8-naphthalimide (5b):** Compound **5b** was prepared according to the method used for **5a** with 1,8-naphthalic anhydride (198 mg, 1.0 mmol) and (*S*)-*tert*-butyl 2-(aminomethyl) pyrrolidine-1-carboxylate (210 mg, 1.04 mmol). A white solid was obtained (192.9 mg, 68.9% yield). M.p. 157.7–158.9 °C. $[\alpha]_D^{20}$ = –0.3 (*c* = 0.5, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.56 (d, *J* = 6.65 Hz, 2 H), 8.18 (d, *J* = 8.31 Hz, 2 H), 7.72 (t, *J* = 7.77 Hz, 2 H), 4.27–4.25 (m, 2 H), 3.63–3.59 (m, 1 H), 3.12–3.06 (m, 1 H), 2.89–2.83 (m, 1 H), 2.68 (br. s, 1 H), 1.99–1.69 (m, 3 H), 1.58–1.50 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.68,

133.98, 131.52, 131.17, 128.23, 126.90, 122.58, 57.94, 46.51, 44.23, 30.00, 25.38 ppm. IR (KBr): $\tilde{\nu}$ = 3442, 3207, 2949, 2858, 1724, 1666, 1645, 1624, 1589, 1436, 1379, 1357, 1323, 1236, 1165, 1097, 781 cm^{-1}. HRMS: calcd. for $C_{17}H_{17}N_2O_2$ 281.12845 $[M + H]^+$; found 281.12832.

***N*-{[(*S*)-Pyrrolidin-2-yl]methyl}-3,4,5,6-tetrachlorophthalimide (5c):** The reaction mixture of tetrachlorophthalic anhydride (286 mg, 1.0 mmol), dicyclohexylcarbodiimide (DCC, 200 mg, 1 mmol), and (*S*)-tert-butyl 2-(aminomethyl) pyrrolidine-1-carboxylate (210 mg, 1.04 mmol) in dried THF (10 mL) was heated at reflux for 12 h, and the mixture was separated directly by silica gel column chromatography to give a white solid, which was then dissolved in a mixture of concentrated HCl (2 mL) and EtOAc (10 mL) and stirred for 4 h at room temperature. The pH of the mixture was adjusted to about 8 with saturated $NaHCO_3$, after which extraction with dichloromethane was carried out (3 × 20 mL). The solution was dried with anhydrous Na_2SO_4. After removal of the solvent, the product was obtained as a white solid (94.2 mg, 25.6% yield). M.p. decomposed at 280 °C. $[\alpha]_D^{20}$ = +8.7 (*c* = 0.5, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ = 4.68–2.86 (m, 6 H), 2.23–1.44 (m, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.70, 133.97, 129.67, 127.80, 53.45, 48.95, 40.90, 30.96, 23.49 ppm. IR (KBr): $\tilde{\nu}$ = 3465, 3227, 2941, 2858, 1774, 1717, 1681, 1651, 1633, 1435, 1398, 1371, 1298, 1200, 1060, 737 cm^{-1}. HRMS: calcd. for $C_{13}H_{11}C_{l4}N_2O_2$ 366.95691 $[M + H]^+$; found 366.95843.

General Procedure for the Asymmetric Michael Addition of Ketones to Nitroalkenes Catalyzed by 5: A solution of the catalyst **5** (0.013 mmol) and cyclohexanone (0.1 mL, 0.1 mmol) in toluene (0.2 mL) was stirred at room temperature for 30 min. 2,4-Dichloridebenzoic acid (2.5 mg, 0.013 mmol) was then added, and the reaction mixture was stirred for 15 min. To the resulting mixture was added nitroalkene (0.13 mmol) at the required temperature. After the reaction was completed (monitored by TLC), the mixture was purified by column chromatography on silica gel (200–300 mesh, petroleum ether/ethyl acetate = 10:1) to afford the product.

Supporting Information (see footnote on the first page of this article): Experimental details for the products of the catalytic asymmetric Michael addition reactions are presented. ^1H and ^{13}C NMR spectra, IR spectra and mass spectra are also given for all the compounds.

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