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Organocatalytic Highly Enantio- and Diastereoselective Mannich Reaction of β-Ketoesters with *N*-Boc-aldimines

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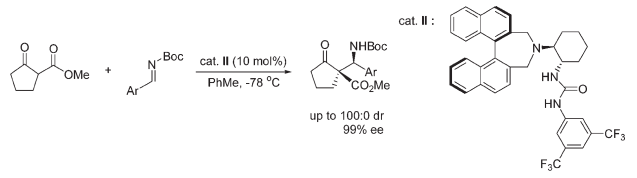

The catalytic enantioselective Mannich reaction promoted by chiral bifunctional organocatalysts is described. The treatment of β-ketoesters with *N*-Boc-aldimines under mild reaction conditions afforded the corresponding β-amino β-ketoesters with excellent diastereoselectivities (up to 100:0 dr) and excellent enantioselectivities (up to 99% ee).

Optically active β-amino acids are fundamental building blocks for the preparation of pharmaceutical and agrochemical target molecules. In addition, these compounds are useful chiral starting materials in the synthesis of bioactive amine containing natural products such as those belonging to the alkaloid family.[1,2] Enantioselective Mannich reactions are efficient and powerful methods to prepare chiral β-amino carbonyl derivatives.[3] Tremendous efforts have been made in the development of efficient chiral catalysts for enantioselective Mannich reactions with preformed enolates[4] and enolizable β-dicarbonyl and related compounds.[5] Highly enantioselective direct Mannich reactions with aldehydes and ketones have also been accomplished with chiral metal complexes and organocatalysts.[6,7]

Recently, several groups presented catalytic asymmetric Mannich reactions of β-ketoesters using organocatalysts to circumvent the problems commonly associated with conventional metal catalysis. For example, Terada et al. have developed a new chiral phosphorodiamidic acid to catalyze the addition of acetylacetates to imines in a highly enantioselective fashion.[8] The Jørgensen and Ricci groups have reported a highly enantio- and diastereoselective Mannich reaction using β-ketoesters catalyzed by cinchona alkaloid-derived catalysts.[9] Also, Schaus et al. have used cinchonine itself to catalyze the highly enantioselective addition of β-ketoesters to imines.[10] More recently, the Dixon, Takemoto, and Deng groups have reported highly enantioselective Mannich reactions of β-ketoesters, catalyzed by bifunctional organocatalysts containing thiourea functionality.[11] Bifunctional organocatalysts possessing a combination of hydrogen-bonding donors and chiral tertiary amines have been developed for activation of both electrophilic and nucleophilic components. They have emerged as powerful tools for

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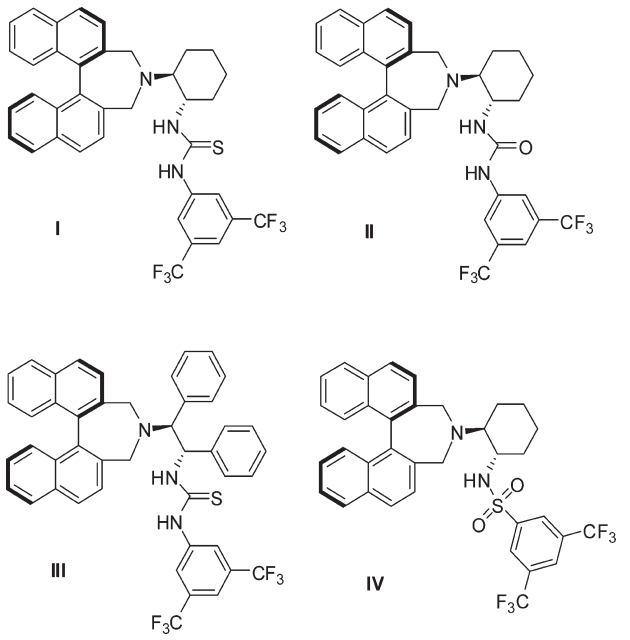


FIGURE 1. Structures of bifunctional organocatalysts.

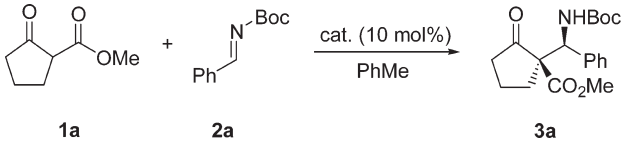
the enantioselective formation of carbon−carbon bonds and carbon−heteroatom bonds.[12]

As part of a research program related to the development of synthetic methods for the enantioselective construction of stereogenic carbon centers,[13] we recently reported chiral amine−thiourea bifunctional organocatalyst **I** (Figure 1) to be a highly selective catalyst for the enantioselective amination of active methines.[14] We envisioned that the assembly of a structurally well-defined chiral 1,2-diamine and binaphthyl scaffold with a thiourea motif could constitute a new class of bifunctional organocatalyst. The rigid binaphthyl structure can serve as an efficient stereocontrolling axial chiral element. Herein, we wish to describe the direct enantioselective Mannich reaction of β-ketoesters with simple *N*-Boc-imines catalyzed by bifunctional organocatalysts bearing both central and axial chiral elements.

A survey of some reaction parameters was performed, and some representative results are presented in Table 1. Our investigation began with the catalytic enantioselective Mannich reaction of methyl cyclopentanone 2-carboxylate (**1a**) with *N*-Boc-benzaldimine (**2a**). When the reaction was performed in toluene at room temperature in the presence of 10 mol % of catalyst **I**, product **3a** was isolated in high yield with 81% ee (Table 1, entry 1). Further tuning of the conditions found the reaction to be optimal when performed in toluene at −78 °C for 90 h, producing **3a** with a high level of diastereocontrol (97:3) and excellent enantioselectivity (97%) (entry 3). We examined the impact of the structure of catalysts **I**−**IV** on the selectivity (Table 1, entries 3−6). Excellent results have been obtained with catalyst **II** (entry 4, 97% yield, 97:3 dr, 99% ee).

We then explored the possibility of using wide range of *N*-Boc-protected para-substituted aromatic and heteroaromatic aldimines **2** with β-ketoester **1a** under the optimized reaction conditions. As shown in Table 2, the products **3a**−**f** were formed in high yields (72−97%), excellent diastereoselectivities (96:4−100:0), and excellent enantioselectivities (97−99%). Furthermore, aliphatic *N*-Boc-aldimine (**2g**) was also an effective substrate for this process (entry 7). The absolute configuration of **3a** was determined by comparing the chiral HPLC data and specific rotation with an authentic sample.[5,9−11]

TABLE 1. Optimization of the Reaction Conditions

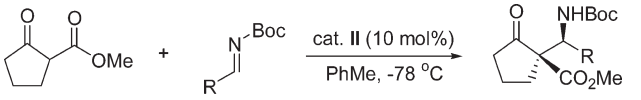


1a **2a** **3a**

entry	cat.	*T* (°C)	time (h)	yield[a] (%)	dr[b]	ee[c] (%)
1	**I**	rt	4	90	90:10	81
2	**I**	−40	10	94	85:15	89
3	**I**	−78	90	95	97:3	97
4	**II**	−78	86	97	97:3	99
5	**III**	−78	43	90	76:24	54
6	**IV**	−78	43	86	77:23	55

[a]Refers to the isolated mixture of diastereomers. [b]Determined by ^{1}H NMR of the crude reaction mixture. [c]Enantiomeric excess of the major diastereomer, determined by chiral HPLC analysis with chiral column (Chiralpak AD-H).

TABLE 2. Variation of the *N*-Boc-imines



1a **2** **3**

entry	**2**, R	time (h)	yield[a] (%)	dr[b]	ee[c] (%)
1	**2a**, Ph	86	**3a**, 97	97:3	99
2	**2b**, 2-furanyl	96	**3b**, 96	100:0	99
3	**2c**, 2-naphthyl	96	**3c**, 90	98:2	99
4	**2d**, *p*-OMe-Ph	80	**3d**, 72	96:4	99
5	**2e**, *p*-Me-Ph	80	**3e**, 96	99:1	97
6	**2f**, *p*-Cl-Ph	90	**3f**, 89	100:0	99
7	**2g**, -CH_2CH_2Ph	100	**3g**, 61	96:4	98

[a]Refers to the isolated mixture of diastereomers. [b]Determined by ^{1}H NMR of the crude reaction mixture. [c]Enantiomeric excess of the major diastereomer, determined by chiral HPLC analysis with chiral column (Chiralpak AD-H).

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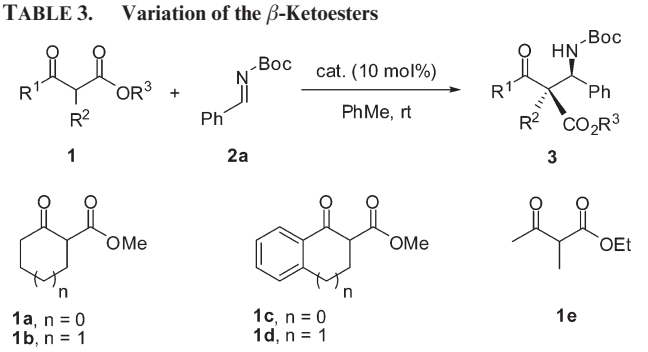
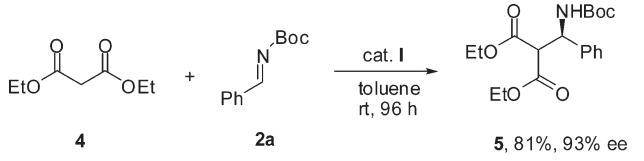
TABLE 3. Variation of the β-Ketoesters



entry	1	cat.	time (h)	yield[a] (%)	dr[b]	ee[c] (%)
1[d]	**1a**	**II**	86	**3a**, 97	97:3	99
2[e]	**1b**	**II**	78	**3h**, 68	94:6	95
3[f]	**1c**	**II**	29	**3i**, 93	80:20	93
4	**1d**	**I**	7	**3j**, 88	99:1	96
5	**1e**	**I**	110	**3k**, 83	63:37	71

[a]Refers to the isolated mixture of diastereomers. [b]Determined by ^{1}H NMR of the crude reaction mixture. [c]Enantiomeric excess of the major diastereomer, determined by chiral HPLC analysis with chiral column (Chiralpak AD-H for **3a**, **3j**, and **3k**, OD-H for **3i**, and Chiralcel OJ for **3h**). [d]Reaction was carried out at −78 °C. [e]Reaction was carried out in Et_2O. [f]Reaction was carried out at −40 °C.

SCHEME 1. Enantioselective Mannich Reaction of Diethyl Malonate with *N*-Boc-aldimine



To examine the generality of the catalytic enantioselective Mannich reaction of β-ketoesters **1** by using new bifunctional organocatalysts **I** and **II**, we studied the addition of various β-ketoesters **1** to *N*-Boc-benzaldimine **(2a)**. As can be seen by the results summarized in Table 3, the corresponding products **3h**−**j** were obtained in high to excellent yields, excellent diastereoselectivities, and excellent enantioselectivities. The cyclic β-ketoester **1b** and cyclic aromatic β-ketoesters **1c**,**d** reacted with *N*-Boc-benzaldimine **(2a)** to give the corresponding Mannich products **3h**−**j** in 68−93% yields and 93−96% ee. In contrast to the cyclic β-ketoesters, unfortunately, the reaction of acyclic β-ketoester **1e** proceeded slowly even to give the Mannich product **3k** in moderate enantioselectivity (entry 5).

We examined the direct enantioselective Mannich reaction of diethylmalonate (**4**) with *N*-Boc-benzaldimine (**2a**) using bifunctional organocatalyst **I** in toluene at room temperature. In the presence of 10 mol % of catalyst **I**, the reaction proceeded to afford the β-aminated product **5** after 96 h with 81% yield and 93% ee (Scheme 1).

Although the reason for the observed enantioselectivity is still unclear, we believe that a carbonyl group of the *N*-Boc-benzaldimine (**2a**) is activated by the urea or thiourea moiety through hydrogen bonding, and the β-ketoester moiety is activated by the basic nitrogen atom in tertiary amine (Figure 2). These interactions control the stereochemical outcome of the reaction and increase the reaction rate.

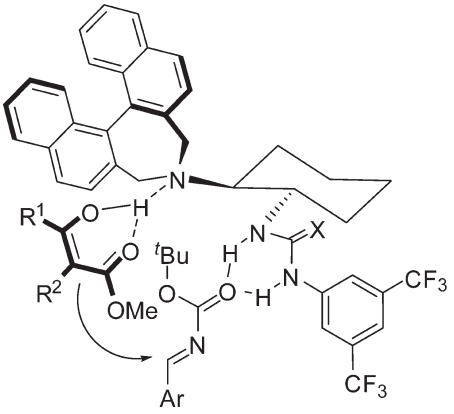


FIGURE 2. Proposed stereochemical model.

In conclusion, we have developed a highly efficient catalytic enantioselective Mannich reaction of β-ketoesters using bifunctional organocatalysts **I** and **II**. The desired β-amino carbonyl compounds were obtained in good to high yields, and excellent diastereoselectivities (up to 100:0) and excellent enantioselectivities (up to 99% ee) were observed. We believe that this method provides an efficient route for the preparation of chiral β-amino acid derivatives, and the availability of these compounds should facilitate medicinal chemical studies in various fields. Further study of these bifunctional organocatalysts in asymmetric reactions is under current investigation.

Experimental Section

General Procedure for the Mannich Reaction of β-Ketoesters. To a stirred solution of β-ketoester (0.3 mmol) and catalyst **I** or **II** (0.03 mmol) in toluene (1.5 mL) was added *N*-Boc-aldimine (72 mg, 0.36 mmol) at the temperature in Table 3. The reaction mixture was stirred for 7−110 h at the indicated temperature. The mixture was diluted with saturated NH_4Cl solution (30 mL) and extracted with ethyl acetate (2 × 30 mL). The combined organic layers were dried over $MgSO_4$, filtered, concentrated, and purified by flash chromatography to afford the β-amino β-ketoester.

Methyl (1*R*)-1-[(*S*)-1-*tert*-Butoxycarbonylaminophenylmethyl]-2-oxocyclopentanecarboxylate (3a). To a stirred solution of β-ketoester **1a** (42 mg, 0.3 mmol) and catalyst **II** (19 mg, 0.03 mmol) in toluene (1.5 mL) was added *N*-Boc-aldimine **2a** (72 mg, 0.36 mmol) at −78 °C. The reaction mixture was stirred for 86 h at −78 °C. The mixture was diluted with saturated NH_4Cl solution (30 mL) and extracted with ethyl acetate (2 × 30 mL). The combined organic layers were dried over $MgSO_4$, filtered, concentrated, and purified by flash chromatography to give compound **3a** (101 mg, 97%). Major diastereoisomer: $[\alpha]^{27}_D$ = −56.2 (c = 0.4, $CHCl_3$, 99% ee); ^{1}H NMR (200 MHz, $CDCl_3$) δ = 7.30−7.23 (m, 5H), 5.87 (brs, 1H), 5.16 (d, J = 9.4 Hz, 1H), 3.67 (s, 3H), 2.54−2.42 (m, 1H), 2.42−2.30 (m, 2H), 2.04−1.80 (m, 3H), 1.38 (s, 9H); ^{13}C NMR (50 MHz; $CDCl_3$) δ = 210.8, 169.8, 155.1, 138.2, 128.3, 128.0, 127.4, 79.7, 64.8, 55.6, 52.6, 37.5, 30.5, 28.1, 18.9; MS (ESI) m/z = 348.0 $[M + H]^+$ 120.9, 123.0, 149.9, 206.6; ESI-HRMS m/z calcd for $C_{19}H_{26}NO_5$ $[M+H]^+$ 348.1811, found 348.1818; t_R HPLC (95:5 *n*-hexane/*i*-PrOH, 220 nm, 1.0 mL/min) Chiralpak AD-H column, t_R = 13.7 min (major), t_R = 38.3 (minor).

Methyl (2*R*)-2-[(*S*)-1-*tert*-Butoxycarbonylaminophenylmethyl]-1-tetralone-2-carboxylate (3j). To a stirred solution of β-ketoester **1d** (61 mg, 0.3 mmol) and catalyst **I** (20 mg, 0.03 mmol) in toluene (1.5 mL) was added *N*-Boc-aldimine **2a**

(72 mg, 0.36 mmol) at room temperature. The reaction mixture was stirred for 7 h at room temperature. The mixture was diluted with a saturated NH_4Cl solution (30 mL) and extracted with ethyl acetate (2 × 30 mL). The combined organic layers were dried over $MgSO_4$, filtered, concentrated, and purified by flash chromatography to give compound **3j** (108 mg, 88%). Major diastereoisomer: $[\alpha]^{26}_D = 26.2$ ($c = 0.8$, $CHCl_3$, 96% ee); ^1H NMR (200 MHz, $CDCl_3$) $\delta = 7.75$ (d, $J = 7.7$ Hz, 1H), 7.44−7.51 (m, 3H), 7.19−7.39 (m, 5H), 5.99 (d, $J = 11.4$ Hz, 1H), 5.33 (d, $J = 11.4$ Hz, 1H), 3.48 (s, 3H), 3.08 (d, $J = 6.23$ Hz, 2H), 2.68−2.75 (m, 1H), 2.22−2.36 (m, 1H), 1.35 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) $\delta = 194.4$, 170.1, 154.9, 142.2, 138.7, 133.6, 132.2, 128.6, 128.2, 128.0, 127.5, 126.6, 125.6, 79.4, 63.0, 57.6, 52.2, 30.2, 28.0, 25.7; MS (ESI): $m/z = 409.8$ $[M + H]^+$ 121.0, 149.9, 206.0; EI-HRMS m/z calcd for $C_{24}H_{27}F_6NO_5$ $[M]^+$ 409.1889, found 409.1886; t_R HPLC (90:10, *n*-hexane/*i*-PrOH, 254 nm, 1.0 mL/min) Chiralpak AD-H column, $t_R = 12.2$ min (major), $t_R = 20.6$ (minor).

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Supporting Information Available: General experimental procedures, ^1H and ^{13}C NMR spectra, characterization data, and HPLC assays. This material is available free of charge via the Internet at http://pubs.acs.org.