Chiral-Thiourea-Catalyzed Direct Mannich Reaction

Yousuke Yamaoka, Hideto Miyabe, Yoshizumi Yasui, Yoshiji Takemoto*

Graduate School of Pharmaceutical Sciences, Kyoto University, Yoshida, Sakyo-ku, Kyoto 606-8501, Japan
Fax +81(75)7534569; E-mail: takemoto@pharm.kyoto-u.ac.jp

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Abstract: In the presence of a chiral thiourea as a bifunctional organocatalyst, Mannich reaction of *N*-Boc-imine with prochiral 1,3-dicarbonyl compounds proceeded with excellent enantio- and diastereoselectivities.

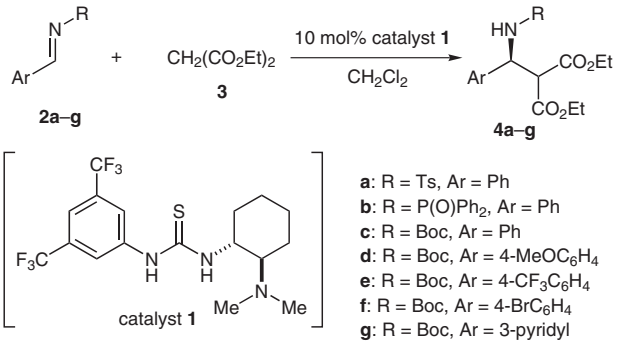
Key words: organocatalyst, thiourea, enantioselective, Mannich reaction, imine

Chiral organocatalysts have become a field of central importance for enantioselective transformations of organic molecules.[1] Recent progress in this area has resulted in the advent and development of various organocatalysts which do not require the strictly controlled reaction conditions compared to many established metal-catalyzed transformations.[1] Recently, our laboratory introduced the chiral thiourea **1** as a bifunctional organocatalyst, which accelerates the aza-Henry reaction and the Michael reaction of nitroolefins or α,β-unsaturated imides as a result of dual activation of electrophile and nucleophile (Scheme 1).[2–4]

In recent years, enantioselective direct Mannich reaction has attracted much attention in approaches toward chiral β-amino acid derivatives.[5,6] Asymmetric Mannich reaction with a symmetric C-nucleophile such as a dialkyl malonate has been wildly investigated. In contrast, the reaction with an unsymmetrical nucleophile allows the generation of two stereogenic centers in a single carbon–carbon bond-forming process; thus, the control of both enantio- and diastereoselectivities is a challenging task.

Cinchona alkaloids having thiourea moiety were recently shown to be effective catalysts for direct Mannich reaction independently by the research groups of Deng[7a] and Dixon.[7b] We became interested in the possibility of the use of simple thiourea **1** in direct Mannich reaction with unsymmetrical prochiral nucleophiles. Herein, we report the highly enantio- and diastereoselective Mannich reaction of a wide range of cyclic 1,3-dicarbonyl compounds catalyzed by chiral thiourea **1**.

Prior to exploring the reaction with prochiral nucleophiles, we first investigated the catalytic activity of thiourea **1** in Mannich reaction. In the presence of thiourea **1** (10 mol%), reactions of aldimines **2a–g** with malonate **3**



Scheme 1

were run in CH_2Cl_2 (Scheme 1). Although the electron-deficient *N*-sulfonylimine **2a** exhibited excellent reactivity toward nucleophilic malonate **3**, no enantioselectivity was observed (Table 1, entry 1). Good control of enantioselectivity was not achieved by using imine **2b** either (entry 2). In contrast, *N*-Boc-imine **2c** worked well to give the product **4c** with 88% ee after stirring at room temperature for 24 hours (entry 3). The degree of selectivity was shown to be dependent on the reaction temperature; thus, changing the temperature from room temperature to 0 °C led to a moderate increase in enantioselectivity to 94% ee (entry 4). Excellent chemical yield and high enantioselectivity were also obtained in the reaction of less reactive *N*-Boc-imine **2d** having an electron-donating methoxy group (entry 5). The reactions of imines **2e** and **2f** having

Table 1 Reaction of Malonate **3** with Imines **2a–g**[a]

Entry	Imine	Temp (°C)	Time (h)	Yield (%)	ee (%)
1	**2a**	r.t.	24	86	0[b]
2	**2b**	r.t.	72	58	10
3	**2c**	r.t.	24	77	88
4	**2c**	0	48	84	94
5	**2d**	–20	72	82	93
6	**2e**	–78	24	91	96
7	**2f**	–78	24	84	98
8	**2g**	–78	48	73	97

[a] All reactions were carried out in CH_2Cl_2 in the presence of thiourea **1** (10 mol%).
[b] Racemic adduct **4a** was obtained.

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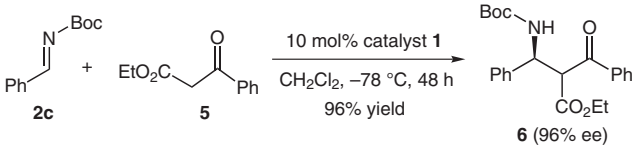
an electron-withdrawing group proceeded smoothly even at –78 °C to give adducts **4e** and **4f** with 96% ee and 98% ee, respectively (entries 6 and 7). The reaction of imine **2g** containing basic pyridine moiety was also successful under similar reaction conditions (entry 8). These observations suggest that thiourea **1** acts as a chiral catalyst for direct Mannich reaction with excellent catalytic activity.

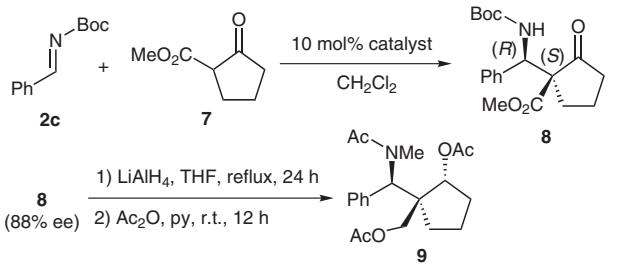
Next, we tried the reaction of *N*-Boc-imine **2c** with prochiral nucleophile **5** (Scheme 2). In the presence of **1** (10 mol%), nucleophile **5** reacted with **2c** at –78 °C to give the adduct **6** in 96% yield with excellent ee. However, valuable diastereoselectivity was not observed, probably because of epimerization.



Scheme 2

On the basis of these results, we next focused on the chiral Mannich reaction with cyclic 1,3-dicarbonyl compounds having a substituent at the 2-position. To test the viability of thiourea **1**, the reaction with prochiral nucleophile **7** was investigated by using several catalysts (Scheme 3, Table 2). In the presence of base such as Et_3N, $(i\text{-}Pr)_2NEt$, or DBU (10 mol%), the *N*-Boc-imine **2c** reacted well with nucleophile **7** with moderate diastereoselectivities; however, the reaction proceeded slowly in the absence of catalyst (Table 2, entries 1–4). As expected, thiourea **1** worked well as an effective catalyst for the control of both enantio- and diastereoselectivities (entry 5). These observations suggest that dual activation of electrophile and nucleophile using the bifunctional thiourea **1** is crucial for successful stereocontrol. In the presence of thiourea **1** (10 mol%), the reaction proceeded at –20 °C to give a 92:8 diastereomeric mixture of the desired adduct **8** in 89% yield with 88% ee (entry 6). The absolute and relative configuration of major product was determined by converting the adduct **8** to the authentic compound **9**.[6c] Thus, a stereoselective construction of quaternary carbon center was achieved by using the simple thiourea catalyst **1**.

The scope of enantio- and diastereoselective reaction catalyzed by thiourea **1** was investigated under the optimized conditions (Scheme 4). At first, we tested the reaction site



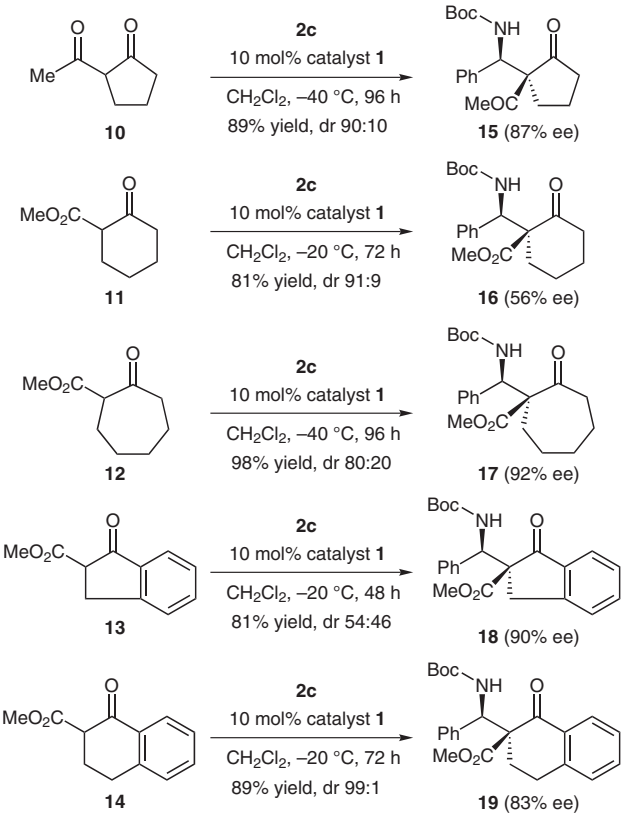
Scheme 3

Table 2 Reaction of β-Keto Ester **7** with Imine **2c**

Entry	Catalyst	Time (h)	Yield (%)	dr	ee (%)
1[a]	none	48	67	68:32	–
2[a]	Et_3N	8	93	60:40	–
3[a]	$(i\text{-}Pr)_2NEt$	8	87	60:40	–
4[a]	DBU	8	86	66:34	–
5[a]	thiourea **1**	9	98	91:9	82[c]
6[b]	thiourea **1**	72	89	92:8	88[c]

[a] Reactions were carried out in CH_2Cl_2 in the presence of catalyst (10 mol%) at r.t.
[b] Reaction was carried out in CH_2Cl_2 in the presence of thiourea **1** (10 mol%) at –20 °C.
[c] The ee given is for the major isomer.

of the 1,3-diketone **10**. As expected, the reaction took place at position 2 of 1,3-diketone **10** to give the product **15** with 87% ee accompanied by a small amount of diastereomer without detection of other adducts. Only a modest enantioselectivity was observed in the reaction with six-membered β-keto ester **11**, although diastereoselectivity still remained high. The seven-membered keto ester **12** also produced adduct **17** with an excellent enantioselectivity. The diastereoselectivity was shown to be dependent on the structure of nucleophiles. The use of five-mem-



Scheme 4

bered β-keto ester **13**, bearing an aromatic ring, as a prochiral nucleophile led to decreased diastereoselectivity. In contrast, a high degree of diastereocontrol was achieved in the reaction of six-membered β-keto ester **14**.

In summary, we have developed the thiourea-catalyzed direct Mannich reaction of *N*-Boc-imine with a wide range of unsymmetrical cyclic 1,3-dicarbonyl compounds. The reaction using simple thiourea **1** as bifunctional catalyst proceeded smoothly to afford the corresponding adducts with good enantio- and diastereoselectivities.

Melting points were taken on a Yanagimoto micromelting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 500 MHz, and 125 MHz, respectively; TMS was used as an internal standard. IR spectra were recorded on a Jasco FT/IR-410 Fourier-transfer IR spectrometer. Optical rotations were recorded on a Jasco DIP-360 polarimeter. Enantiomeric excess was determined by high-performance liquid chromatography (HPLC) analysis. Compound **4c** is a known compound.[4b]

Chiral-Thiourea-Catalyzed Direct Mannich Reaction; General Procedure

To a solution of *N*-Boc-imine **2c**–**g** (0.30 mmol) and thiourea catalyst **1** (12.4 mg 0.03 mmol) in anhyd CH_2Cl_2 (0.6 mL), was added the appropriate 1,3-dicarbonyl compound (0.60 mmol) under argon at the temperature indicated in the text. After stirring at the same temperature, the mixture was concentrated under reduced pressure. Purification of the residue by flash chromatography [hexane–EtOAc (3:1) in the cases of **4c**–**g** and **15**–**19** or hexane–Et_2O (2:1) in the case of **8**] afforded adducts **4c**–**g**, **8** and **15**–**19**.

Diethyl (*S*)-[1-(*tert*-Butoxycarbonylamino)-1-(4-methoxyphenyl)methyl]malonate (4d)

Colorless crystals; mp 89–93 °C (EtOAc–hexane). HPLC (DAICEL Chiralcel OD-H, hexane–propan-2-ol, 97:3, 0.5 mL/min, 210 nm): t_R (minor) = 21.0 min, t_R (major) = 23.2 min. A sample of 93% ee by HPLC analysis gave $[\alpha]_D^{25}$ +3.0 (*c* 1.3, $CHCl_3$).

IR ($CHCl_3$): 3430, 2983, 1726, 1498 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.22 (2 H, d, *J* = 8.6 Hz), 6.84 (2 H, d, *J* = 8.6 Hz), 6.13 (1 H, br m), 5.43 (1 H, br m), 4.26–4.05 (4 H, m), 3.85 (1 H, br m), 3.78 (3 H, s), 1.41 (9 H, s), 1.26 (3 H, t, *J* = 7.0 Hz), 1.16 (3 H, t, *J* = 7.2 Hz).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.2, 167.2, 159.0, 155.0, 131.8, 127.5, 113.9, 79.5, 61.8, 61.5, 57.0, 55.2, 52.9, 28.2, 13.9, 13.8.

MS (FAB$^+$): *m*/*z* (%) = 396 (10, [M + H]$^+$), 180 (100).

HRMS (FAB$^+$): *m*/*z* calcd for $C_{20}H_{30}NO_7$ [M + H]$^+$: 396.2022; found: 396.2016.

Anal. Calcd for $C_{20}H_{29}NO_7$: C, 60.74; H, 7.39; N, 3.54. Found: C, 60.71; H, 7.27; N, 3.47.

Diethyl (*S*)-[1-(*tert*-Butoxycarbonylamino)-1-(4-trifluoromethylphenyl)methyl]malonate (4e)

Colorless oil. HPLC (DAICEL Chiralcel OD-H, hexane–propan-2-ol, 90:10, 1.0 mL/min, 210 nm): t_R (minor) = 12.4 min, t_R (major) = 27.1 min. A sample of 96% ee by HPLC analysis gave $[\alpha]_D^{28}$ +15.3 (*c* 1.1, $CHCl_3$).

IR ($CHCl_3$): 3428, 2983, 1728, 1497 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.51 (2 H, d, *J* = 8.2 Hz), 7.37 (2 H, d, *J* = 8.2 Hz), 6.20 (1 H, br m), 5.46 (1 H, br m), 4.22–3.93 (4 H, m), 3.82 (1 H, br m), 1.34 (9 H, s), 1.19 (3 H, t, *J* = 7.2 Hz), 1.06 (3 H, t, *J* = 7.2 Hz).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 167.9, 166.8, 155.0, 143.8, 129.9 (q, *J* = 32 Hz), 126.8, 125.5, 124.4 (q, *J* = 272 Hz), 80.0, 62.1, 61.7, 56.5, 53.1, 28.1, 13.8, 13.7.

MS (FAB$^+$): *m*/*z* (%) = 434 (12, [M + H]$^+$), 174 (100).

HRMS (FAB$^+$): *m*/*z* calcd for $C_{20}H_{27}F_3NO_6$ [M + H]$^+$: 434.1791; found: 434.1799.

Diethyl (*S*)-[1-(4-Bromophenyl)-1-(*tert*-butoxycarbonylamino)methyl]malonate (4f)

Colorless crystals; mp 61–63 °C (EtOAc–hexane). HPLC (DAICEL Chiralcel OD-H, hexane–propan-2-ol, 97:3, 0.5 mL/min, 210 nm): t_R (minor) = 14.6 min, t_R (major) = 17.4 min. A sample of 98% ee by HPLC analysis gave $[\alpha]_D^{27}$ +6.6 (*c* 1.5, $CHCl_3$).

IR ($CHCl_3$): 3428, 2984, 1728, 1494 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.45 (2 H, d, *J* = 8.3 Hz), 7.20 (2 H, d, *J* = 8.3 Hz), 6.20 (1 H, br m), 5.43 (1 H, br m), 4.27–4.04 (4 H, m), 3.84 (1 H, br m), 1.44 (9 H, s), 1.27 (3 H, t, *J* = 7.2 Hz), 1.16 (3 H, t, *J* = 7.2 Hz).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 167.9, 166.9, 155.0, 138.8, 131.6, 128.1, 121.5, 79.8, 62.0, 61.7, 56.6, 52.9, 28.2, 13.9, 13.8.

MS (FAB$^+$): *m*/*z* (%) = 444 (16, [M + H]$^+$), 446 (15, [M + H]$^+$), 161 (100).

HRMS (FAB$^+$): *m*/*z* calcd for $C_{19}H_{27}{}^{79}BrNO_6$ [M + H]$^+$: 444.1022; found: 444.1007.

Anal. Calcd for $C_{19}H_{26}BrNO_6$: C, 51.36; H, 5.90; N, 3.15; Br, 17.98. Found: C, 51.33; H, 5.82; N, 2.91; Br, 17.95.

Diethyl (*S*)-[1-(*tert*-Butoxycarbonylamino)-1-(3-pyridyl)methyl]malonate (4g)

Colorless oil. HPLC (DAICEL Chiralcel OD-H, hexane–propan-2-ol, 95:5, 0.5 mL/min, 210 nm): t_R (major) = 24.0 min, t_R (minor) = 27.6 min. A sample of 97% ee by HPLC analysis gave $[\alpha]_D^{22}$ +8.9 (*c* 0.9, $CHCl_3$).

IR ($CHCl_3$): 3428, 2984, 1714, 1497 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.52 (1 H, s), 8.44 (1 H, br m), 7.60 (1 H, br d, *J* = 7.9 Hz), 7.20 (1 H, br m), 6.18 (1 H, br m), 5.45 (1 H, br m), 4.22–3.97 (4 H, br m), 3.82 (1 H, br m), 1.34 (9 H, s), 1.20 (3 H, t, *J* = 7.0 Hz), 1.09 (3 H, t, *J* = 7.2 Hz).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 167.8, 166.8, 155.0, 149.0, 148.2, 135.3, 134.2, 123.3, 80.0, 62.1, 61.8, 56.4, 51.5, 28.2, 13.9, 13.7.

MS (FAB$^+$): *m*/*z* (%) = 367 (100, [M + H]$^+$).

HRMS (FAB$^+$): *m*/*z* calcd for $C_{18}H_{27}N_2O_6$ [M + H]$^+$: 367.1869; found: 367.1871.

Ethyl (*S*)-2-Benzoyl-3-(*tert*-butoxycarbonylamino)-3-phenylpropionate (6)

Colorless oil; inseparable 5:3 diastereomeric mixture. HPLC (DAICEL Chiralcel AD-H, hexane–propan-2-ol, 95:5, 0.5 mL/min, 210 nm): t_R (major) = 49.9 and 62.7 min, t_R (minor) = 73.9 and 115.7 min. A sample of 96% ee (5:3 diastereomeric mixture) by HPLC analysis gave $[\alpha]_D^{28}$ +31.9 (*c* 1.1, $CHCl_3$).

IR ($CHCl_3$): 3435, 2983, 1732, 1710, 1497 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.95 (6/8 H, br d, *J* = 7.3 Hz), 7.80 (10/8 H, br d, *J* = 7.3 Hz), 7.62–7.14 (8 H, br m), 6.38 (5/8 H, br m), 6.08 (3/8 H, br m), 5.61 (5/8 H, br m), 5.52 (3/8 H, br m), 4.95 (5/8 H, br m), 4.92 (3/8 H, br m), 4.19–4.05 (2 H, br m), 1.40 (45/8 H, s), 1.36 (27/8 H, br s), 1.20–1.06 (3 H, br m).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 195.1, 193.2, 168.5, 167.7, 155.3, 155.0, 140.3, 140.1, 136.8, 135.7, 133.8, 133.7, 128.9, 128.7, 128.6, 128.5, 128.4, 128.3, 127.6, 127.4, 126.5, 79.5, 61.9, 61.6, 59.2,

57.2, 54.3, 53.6, 28.2, 13.8. Two carbon peaks were missing due to overlapping.

MS (FAB⁻): *m*/*z* (%) = 396 (45, [M – H]⁺), 153 (100).

HRMS (FAB⁻): *m*/*z* calcd for $C_{23}H_{26}NO_5$ [M – H]⁺: 396.1811; found: 396.1814.

Methyl (1*S*)-1-[(*R*)-1-(*tert*-Butoxycarbonylamino)-1-phenylmethyl]-2-oxocyclopentanecarboxylate (8)

Colorless oil; inseparable 92:8 diastereomeric mixture. ^{1}H NMR and HPLC data of major diastereoisomer are given. HPLC (DAICEL Chiralcel AD-H, hexane–propan-2-ol, 97:3, 0.6 mL/min, 210 nm): t_R (major) = 30.6 min, t_R (minor) = 82.8 min.

IR ($CHCl_3$): 3441, 3027, 2981, 1751, 1725, 1497 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.30–7.12 (5 H, m), 5.89 (1 H, br m), 5.14 (1 H, d, *J* = 9.5 Hz), 3.61 (3 H, s), 2.45 (1 H, br m), 2.26 (2 H, br m), 1.98–1.75 (3 H, m), 1.32 (9 H, s).

MS (FAB⁺): *m*/*z* (%) = 348 (2, [M + H]⁺), 106 (100).

HRMS (FAB⁺): *m*/*z* calcd for $C_{19}H_{26}NO_5$ [M + H]⁺: 348.1811; found: 348.1818.

(2*R*)-2-Acetyl-2-[(*R*)-1-(*tert*-butoxycarbonylamino)-1-phenylmethyl]cyclopentanone (15)

Major diastereoisomer was isolated as a colorless oil. HPLC (DAICEL Chiralcel AD-H, hexane–propan-2-ol, 85:15, 0.5 mL/min, 210 nm): t_R (minor) = 13.3 min, t_R (major) = 36.7 min. A sample of 87% ee by HPLC analysis gave $[\alpha]_D^{26}$ –74.1 (*c* 1.1, $CHCl_3$).

IR ($CHCl_3$): 3439, 3029, 2980, 1708, 1496 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.34–7.17 (5 H, m), 5.72 (1 H, br d, *J* = 9.5 Hz), 4.97 (1 H, br m) 2.63 (1 H, br m), 2.37 (3 H, s), 2.15 (1 H, br m), 1.78–1.25 (4 H, m), 1.39 (9 H, s).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 213.2, 202.5, 154.7, 138.3, 128.5, 127.8, 127.4, 80.2, 73.6, 56.8, 39.1, 28.1, 25.4, 19.2. One carbon peak was missing due to overlapping.

MS (FAB⁺): *m*/*z* (%) = 332 (4, [M + H]⁺), 106 (100).

HRMS (FAB⁺): *m*/*z* calcd for $C_{19}H_{26}NO_4$ [M + H]⁺: 332.1862; found: 332.1869.

Methyl (1*S*)-1-[(*R*)-1-(*tert*-Butoxycarbonylamino)-1-phenylmethyl]-2-oxocyclohexanecarboxylate (16)

Colorless oil; inseparable 91:9 diastereomeric mixture. ^{1}H NMR and HPLC data of major diastereoisomer are given. HPLC (DAICEL Chiralcel OJ-H, hexane–propan-2-ol, 98:2, 0.4 mL/min, 210 nm): t_R (major) = 33.7 min, t_R (minor) = 51.2 min.

IR ($CHCl_3$): 3445, 3030, 2951, 1708, 1494 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.36–7.21 (5 H, m), 6.27 (1 H, br d, *J* = 9.5 Hz), 5.25 (1 H, br d, *J* = 9.5 Hz), 3.54 (3 H, s), 2.65 (1 H, br m), 2.48 (1 H, br m), 2.41 (1 H, br m), 2.05–1.85 (4 H, br m), 1.70 (1 H, br m), 1.38 (9 H, s).

MS (FAB⁺): *m*/*z* (%) = 362 (2, [M + H]⁺), 106 (100).

HRMS (FAB⁺): *m*/*z* calcd for $C_{20}H_{28}NO_5$ [M + H]⁺: 362.1968; found: 362.1963.

Methyl (1*S*)-1-[(*R*)-1-(*tert*-Butoxycarbonylamino)-1-phenylmethyl]-2-oxocycloheptanecarboxylate (17)

Major diastereoisomer was isolated as a colorless oil. HPLC (DAICEL Chiralcel OD-H, hexane–propan-2-ol, 95:5, 0.5 mL/min, 210 nm): t_R (minor) = 16.5 min, t_R (major) = 19.3 min. A sample of 92% ee by HPLC analysis gave $[\alpha]_D^{25}$ +45.7 (*c* 1.2, $CHCl_3$).

IR ($CHCl_3$): 3440, 3030, 2937, 1705, 1493 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.33–7.22 (5 H, m), 6.45 (1 H, br d, *J* = 10.1 Hz), 5.21 (1 H, br d, *J* = 10.1 Hz), 3.67 (3 H, s), 2.89 (1 H, br m), 2.45 (1 H, br m), 2.06 (1 H, m), 1.95–1.60 (3 H, br m), 1.70 (1 H, br m), 1.60–1.35 (3 H, m), 1.38 (9 H, s).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 208.9, 172.0, 155.1, 138.2, 128.3, 128.2, 127.8, 79.7, 68.6, 59.7, 52.1, 40.5, 33.5, 30.3, 28.2, 26.6, 25.5.

MS (FAB⁺): *m*/*z* (%) = 376 (3, [M + H]⁺), 106 (100).

HRMS (FAB⁺): *m*/*z* calcd for $C_{21}H_{30}NO_5$ [M + H]⁺: 376.2124; found: 376.2127.

Methyl (2*S*)-2-[(*R*)-1-(*tert*-Butoxycarbonylamino)-1-phenylmethyl]-1-oxo-2-indancarboxylate (18)

Colorless oil; inseparable 54:46 diastereomeric mixture. IR, ^{1}H NMR, MS, and HPLC data of diastereomeric mixture are given. HPLC (DAICEL Chiralcel OD-H, hexane–propan-2-ol, 99:1, 1.0 mL/min, 210 nm): t_R (major) = 37.1 and 43.8 min, t_R (minor) = 53.4 and 63.7 min.

IR ($CHCl_3$): 3438, 3030, 1710, 1497 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.73–7.10 (9 H, m), 6.73 (46/100 H, br m), 6.00 (54/100 H, br m), 5.43 (54/100 H, br m), 5.33 (46/100 H, br m), 3.79 (46/100 H, d, *J* = 17.7 Hz), 3.73 (3 H, br s), 3.48 (54/100 H, d, *J* = 17.7 Hz), 3.25 (46/100 H, d, *J* = 17.7 Hz), 3.23 (54/100 H, d, *J* = 17.7 Hz), 1.38 (9 H, br s).

MS (FAB⁺): *m*/*z* (%) = 396 (1, [M + H]⁺), 106 (100).

HRMS (FAB⁺): *m*/*z* calcd for $C_{23}H_{26}NO_5$ [M + H]⁺: 396.1811; found: 396.1816.

Methyl (2*S*)-2-[(*R*)-1-(*tert*-Butoxycarbonylamino)-1-phenylmethyl]-1-tetralone-2-carboxylate (19)

Major diastereoisomer was isolated as a colorless oil. HPLC (DAICEL Chiralcel AD-H, hexane–propan-2-ol, 90:10, 1.0 mL/min, 210 nm): t_R (minor) = 12.8 min, t_R (major) = 21.7 min. A sample of 83% ee by HPLC analysis gave $[\alpha]_D^{25}$ –32.1 (*c* 1.5, $CHCl_3$).

IR ($CHCl_3$): 3444, 2980, 1730, 1707, 1494 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.01 (1 H, d, *J* = 7.7 Hz), 7.60–7.42 (3 H, m), 7.34–7.17 (5 H, br m), 5.99 (1 H, br m), 5.34 (1 H, d, *J* = 10.4 Hz), 3.48 (3 H, s), 3.08 (2 H, br m), 2.72 (1 H, br m), 2.29 (1 H, br m), 1.36 (9 H, s).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 194.7, 170.4, 155.2, 142.4, 138.8, 133.7, 132.4, 128.7, 128.2, 128.1, 127.6, 126.8, 79.6, 63.2, 57.8, 52.4, 30.4, 28.1, 25.8. One carbon peak was missing due to overlapping.

MS (FAB⁺): *m*/*z* (%) = 432 (4, [M + Na]⁺), 150 (100).

HRMS (FAB⁺): *m*/*z* calcd for $C_{24}H_{27}NO_5$ + Na [M + Na]⁺: 432.1787; found: 432.1783.

Conversion of Adduct 8 into Compound 9

To a solution of the diastereomeric mixture of Mannich product **8** (51 mg, 0.15 mmol, dr 92:8) in THF (2 mL), was slowly added $LiAlH_4$ (168 mg, 4.5 mmol) at r.t. After heating at reflux under argon for 24 h, the mixture was diluted with CH_2Cl_2 (5 mL) at r.t. H_2O (0.16 mL), followed by aq 1 M NaOH (0.16 mL), and again H_2O (0.5 mL) were successively added to this solution at –78 °C. The resulting mixture was gradually warmed to r.t. The mixture was filtered through a Celite pad, washed with CH_2Cl_2 (5 × 10 mL), and the combined CH_2Cl_2 washings were concentrated under reduced pressure to afford the crude product. To a solution of the crude product in pyridine (2.5 mL), was added Ac_2O (1.25 mL) under argon at r.t. After stirring at room temperature for 12 h, the mixture was concentrated under reduced pressure. Purification of the residue by flash chromatography (hexane–EtOAc, 1:1) afforded the desired product **9** (19.6 mg, 37%) as a colorless oil.[6c] Diastereoisomers could not be separated. ^{1}H and ^{13}C NMR data of major diastereoiso-

mer are given. A sample of 92:8 diastereomeric mixture gave $[\alpha]_D^{26}$ –45.8 (*c* 0.9, $CHCl_3$).

^{1}H NMR (500 MHz, $CDCl_3$ at 50 °C): δ = 7.42–7.17 (5 H, m), 6.27 (1 H, s), 5.29 (1 H, m), 4.19 (1 H, d, *J* = 11.9 Hz), 3.89 (1 H, d, *J* = 11.9 Hz), 2.97 (3 H, s), 2.07 (3 H, s), 2.03 (3 H, s), 1.88 (3 H, s), 2.25–1.60 (6 H, m).

^{13}C NMR (125 MHz, $CDCl_3$ at 50 °C): δ = 171.3, 171.0, 170.5, 139.3, 129.6, 128.3, 127.2, 79.2, 65.8, 57.5, 53.0, 34.1, 31.8, 30.9, 22.4, 21.2, 21.1, 20.9.

MS (FAB$^+$): *m*/*z* (%) = 362 (70, $[M + H]^+$), 302 (100).

HRMS (FAB$^+$): *m*/*z* calcd for $C_{20}H_{28}NO_5$ $[M + H]^+$: 362.1968; found: 362.1971.

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References

(1) For recent reviews on organocatalyst chemistry, see: (a) Dalko, P. I.; Moisan, L. *Angew. Chem. Int. Ed.* **2001**, *40*, 3726. (b) Pihko, P. M. *Angew. Chem. Int. Ed.* **2004**, *43*, 2062. (c) Dalko, P. I.; Moisan, L. *Angew. Chem. Int. Ed.* **2004**, *43*, 5138. (d) *Special Issue on Asymmetric Organocatalysis: Acc. Chem. Res.* **2004**, *37*, 487–631. (e) Bolm, C.; Rantanen, T.; Schiffers, I.; Zani, L. *Angew. Chem. Int. Ed.* **2005**, *44*, 1758. (f) *Special Issue on Organocatalysis: Adv. Synth. Catal.* **2004**, *346*, 1007–1249. (g) Seayad, J.; List, B. *Org. Biomol. Chem.* **2005**, *3*, 719. (h) Takemoto, Y. *Org. Biomol. Chem.* **2005**, *3*, 4299. (i) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2006**, *45*, 1520.

(2) The potential of ureas and thioureas to serve as organocatalysts has recently begun to be explored by several groups, see: (a) Curran, D. P.; Kuo, L. H. *J. Org. Chem.* **1994**, *59*, 3259. (b) Curran, D. P.; Kuo, L. H. *Tetrahedron Lett.* **1995**, *36*, 6647. (c) Wilcox, C. S.; Kim, E.; Romano, D.; Kuo, L. H.; Curran, D. P. *Tetrahedron* **1995**, *51*, 621. (d) Sigman, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 4901. (e) Vachal, P.; Jacobsen, E. N. *Org. Lett.* **2000**, *2*, 867. (f) Sigman, M. S.; Vachal, P.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2000**, *39*, 1279. (g) Vachal, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 10012. (h) Wenzel, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 12964. (i) Joly, G. D.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 4102. (j) Taylor, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 10558. (k) Schreiner, P. R.; Wittkopp, A. *Org. Lett.* **2002**, *4*, 217. (l) Wittkopp, A.; Schreiner, P. R. *Chem. Eur. J.* **2003**, *9*, 407.

(3) For examples of urea-catalyzed reactions, see: (a) Sohtome, Y.; Tanatani, A.; Hashimoto, Y.; Nagasawa, K. *Chem. Pharm. Bull.* **2004**, *52*, 477. (b) Maher, D. J.; Connon, S. J. *Tetrahedron Lett.* **2004**, *45*, 1301. (c) Sohtome, Y.; Tanatani, A.; Hashimoto, Y.; Nagasawa, K. *Tetrahedron Lett.* **2004**, *45*, 5589. (d) Yoon, T. P.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2005**, *44*, 466. (e) Taylor, M. S.; Tokunaga, N.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **2005**, *44*, 6700. (f) Fuerst, D. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2005**, *127*, 8964. (g) Raheem, I. T.; Jacobsen, E. N. *Adv. Synth. Catal.* **2005**, *347*, 1701. (h) Berkessel, A.; Cleemann, F.; Mukherjee, S.; Müller, T. N. *Angew. Chem. Int. Ed.* **2005**, *44*, 807. (i) Berkessel, A.; Mukherjee, S.; Cleemann, F.; Müller, T. N. *Chem. Commun.* **2005**, 1898. (j) Li, B.-J.; Jiang, L.; Liu, M.; Chen, Y.-C.; Ding, L.-S.; Wu, Y. *Synlett* **2005**, 603. (k) Vakulya, B.; Varga, A.; Csampai, A.; Soos, T. *Org. Lett.* **2005**, *7*, 1967. (l) McCooey, S. H.; Connon, S. J. *Angew. Chem. Int. Ed.* **2005**, *44*, 6367. (m) Herrera, R. P.; Sgarzani, V.; Bernardi, L.; Ricci, A. *Angew. Chem. Int. Ed.* **2005**, *44*, 6576. (n) Wang, J.; Li, H.; Yu, X.; Zu, L.; Wang, W. *Org. Lett.* **2005**, *7*, 4293. (o) Wang, J.; Li, H.; Duan, W.; Zu, L.; Wang, W. *Org. Lett.* **2005**, *7*, 4713. (p) Berkessel, A.; Cleemann, F.; Mukherjee, S. *Angew. Chem. Int. Ed.* **2005**, *44*, 7466. (q) Ye, J.; Dixon, D. J.; Hynes, P. S. *Chem. Commun.* **2005**, 4481. (r) Tsogoeva, S. B.; Yalalov, D. A.; Hateley, M. J.; Weckbecker, C.; Huthmacher, K. *Eur. J. Org. Chem.* **2005**, 4995. (s) Sohtome, Y.; Hashimoto, Y.; Nagasawa, K. *Adv. Synth. Catal.* **2005**, *347*, 1643. (t) Marcelli, T.; van der Haas, R. N. S.; van Maarseveen, J. H.; Hiemstra, H. *Angew. Chem. Int. Ed.* **2006**, *45*, 929. (u) Dixon, D. J.; Richardson, R. D. *Synlett* **2006**, 81.

(4) For our studies on urea-catalyzed reactions, see: (a) Okino, T.; Hoashi, Y.; Takemoto, Y. *Tetrahedron Lett.* **2003**, *44*, 2817. (b) Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672. (c) Okino, T.; Nakamura, S.; Furukawa, T.; Takemoto, Y. *Org. Lett.* **2004**, *6*, 625. (d) Hoashi, Y.; Okino, T.; Takemoto, Y. *Angew. Chem. Int. Ed.* **2005**, *44*, 4032. (e) Hoashi, Y.; Yabuta, T.; Takemoto, Y. *Tetrahedron Lett.* **2004**, *45*, 9185. (f) Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X.; Takemoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 119. (g) Hoashi, Y.; Yabuta, T.; Yuan, P.; Miyabe, H.; Takemoto, Y. *Tetrahedron* **2006**, *62*, 365. (h) Xu, X.; Furukawa, T.; Okino, T.; Miyabe, H.; Takemoto, Y. *Chem. Eur. J.* **2006**, *12*, 466. (i) Xu, X.; Yabuta, T.; Yuan, P.; Takemoto, Y. *Synlett* **2006**, 137. (j) Inokuma, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2006**, *128*, 9413. (k) Miyabe, H.; Tuchida, S.; Yamauchi, M.; Takemoto, Y. *Synthesis* **2006**, 3295.

(5) For a review of catalytic asymmetric direct Mannich reactions, see: Córdova, A. *Acc. Chem. Res.* **2004**, *37*, 102.

(6) For some recent examples of direct asymmetric Mannich reactions, see: (a) Ting, A.; Lou, S.; Schaus, S. E. *Org. Lett.* **2006**, *8*, 2003. (b) Lou, S.; Taoka, B. M.; Ting, A.; Schaus, S. E. *J. Am. Chem. Soc.* **2005**, *127*, 11256. (c) Hamashima, Y.; Sasamoto, N.; Hotta, D.; Somei, H.; Umebayashi, N.; Sodeoka, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 1525. (d) Uraguchi, D.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 5356. (e) Matsunaga, S.; Yoshida, T.; Morimoto, H.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 8777. (f) Zhuang, W.; Saaby, S.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2004**, *43*, 4476. (g) Cobb, A. J. A.; Shaw, D. M.; Ley, S. V. *Synlett* **2004**, 558. (h) Córdova, A. *Chem. Eur. J.* **2004**, *10*, 1987.

(7) (a) Song, J.; Wang, Y.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 6048. (b) Tillman, A. L.; Ye, J.; Dixon, D. J. *Chem. Commun.* **2006**, 1191.