Development of Novel Chiral Urea Catalysts for the Hetero-Michael Reaction

Yoshihiro Sohtome, Aya Tanatani, Yuichi Hashimoto, and Kazuo Nagasawa*

Institute of Molecular and Cellular Biosciences, The University of Tokyo; 1–1–1 Yayoi, Bunkyo-ku, Tokyo 113–0032, Japan. Received December 1, 2003; accepted January 24, 2004; published online January 29, 2004

Chiral urea compounds 10a—g were synthesized as catalysts for conjugate addition of pyrrolidine (2) to γ-crotonolactone (3). In the presence of a catalytic amount of the chiral ureas, this hetero-Michael reaction was greatly accelerated. Asymmetric induction was observed with the catalysts 10e, 10f, and 10g.

Key words organoctatalyst; chiral urea catalyst; hetero-Michael reaction

Michael addition to α,β-unsaturated carbonyl compounds is one of the fundamental bond-forming processes and offers an extremely powerful tool for the synthesis of highly functionalized organic molecules.[1] Thus, development of efficient chiral catalysts for this reaction is still an exciting topic in synthetic organic chemistry.[2,3] Various types of catalysts have been developed so far. Among them, organocatalysts are especially attractive since they do not require strictly controlled reaction conditions, and are not considered to have much unfavorable environment effect compared to the metal-containing catalysts.[4,5] We have recently developed the novel C_2-symmetrical chiral cyclic guanidine compounds **1** as new organocatalysts,[6—9] whose structure was inspired by the marine guanidine alkaloid ptilomycalin A[10—12] and its analogs (Fig. 1).[13,14]

These catalysts were found to accelerate the hetero-Michael reaction depending upon their cavity size.[7] One of the catalyst **1b** works as phase-transfer catalyst for the alkylation of Schiff base imine with high enantioselectivity.[8] Although **1** possesses wide possibility to be developed as superior organocatalyst, it also have some deficiencies, *i.e.*, requirement for relatively long steps preparation, and no asymmetric induction at the hetero-Michael reaction.[7] To overcome these issues, we focused our attention on urea and/or thiourea compounds, which can be grasped as core structure of **1**, as prototype of new efficient and practical organocatalysts. Herein we wish to report the preliminary/basic results of a novel urea-type catalyst **10** for the hetero-Michael reaction, including results on an asymmetric version of this conjugate addition reaction.

Results and Discussion

Urea and thiourea groups are known to coordinate to a carbonyl group as guanidine group, and to activate it by lowering the LUMO energy *via* partial protonation. Thus, various carbonyl group reactions catalyzed by urea or thiourea compounds have been developed.[15—22] At the outset of our studies for developing new chiral urea and/or thiourea catalyst of the hetero-Micahel reaction, we investigated the reaction of pyrrolidine (**2**) with γ-crotonolactone (**3**) in the presence of the simple ureas **5** and **7**,[17] thioureas **6** and **8**,[17] and guanidine **9** as catalysts (Fig. 2).

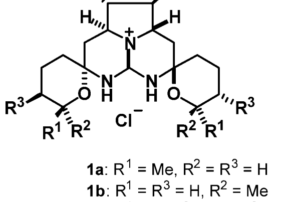
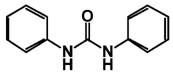
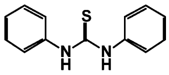

1a: R^1 = Me, R^2 = R^3 = H
1b: R^1 = R^3 = H, R^2 = Me
1c: R^1 = H, R^2 = Me, R^3 = Ph

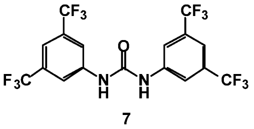
Fig. 1. Structure of Pentacyclic Guanidine Compound **1**

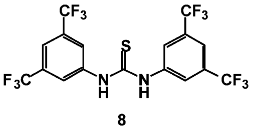
These reactions were performed under Mendoza's conditions,[23—26] *i.e.*, the ratio of **2**, **3** and catalyst was 1 : 1 : 0.1, and the concentrations of the substrate **2** and **3** were set at 0.3 M in $CDCl_3$. The accelerating activities of the catalysts for this hetero-Michael reaction were determined by measuring the $t_{1/2}$ (monitored by ^{1}H-NMR), and the results are summarized in Table 1.

The urea **5** and thiourea **6** accelerated this conjugate addition reaction 3.0 and 2.6-fold, respectively, over the uncatalyzed reaction as expected. From the consideration of the reaction mechanism (vide infra), introduction of EWGs on the aromatic rings of **5** and/or **6** was expected to increase their catalytic activity. In fact, catalysts **7** and **8**, which have trifluoromethyl groups at the 3,5-positions of the aromatic ring of **5** and **6**, the reaction rate was greatly increased by more than 24-fold over the uncatalyzed reaction. In the case of the guanidine **9**, which resembles **7** and **8**, the reaction was accelerated 6.9-fold. Thus, urea and thiourea compounds are realized to be effective for hetero-Michael reaction as cata-


5


6


7


8

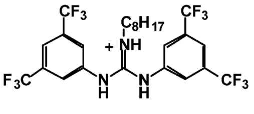
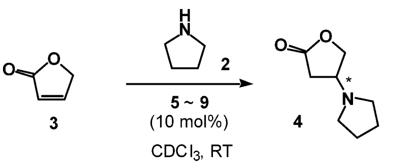

9

Fig. 2. Structures of Urea, Thiourea and the Guanidine Catalysts

* To whom correspondence should be addressed. e-mail: nagasawa@iamu-tokyo.ac.jp

Table 1. Hetero-Michael Reaction Catalysed by **5**—**9**



Entry	Catalyst	$t_{1/2}$ (min)	Rel. increase (fold)
1	None	96	
2	**5**	32	3.0
3	**6**	37	2.6
4	**7**	<4	>24
5	**8**	<4	>24
6	**9**	14	6.9

lysts.

To verify the mechanism of the catalytic activity, *i.e.*, activation of lactone **3** by interaction with the catalysts, the ^{1}H-NMR experiments were conducted with a 1 : 1 mixture of catalyst **7** and lactone **3** in $CDCl_3$. The chemical shifts of the C-2 and C-3 protons of **3** were shifted downfield by 0.03 and 0.04 ppm, respectively, in the presence of the potent catalyst **7** (the original chemical shifts were 6.18 and 7.57, respectively). On the other hand, a smaller downfield shift (0.01 ppm) of the C-3 protons of **3** was observed when the less potent catalyst **5** was used instead of **7**. Moreover, the chemical shifts did not change in CD_3OD under these conditions. These results indicate that 1) the catalytic activity of these urea compounds is correlated with their ability to alter the chemical shifts of protons adjacent to the lactone, and 2) the urea catalysts **5** and **7** interact with the lactone **3** through hydrogen bonding and increase its reactivity simultaneously. The latter led us consider molecular recognition by incorporation of the chirality into **7**, which could be expected to give us new efficient chiral urea-type organocatalysts for the hetero-Michael reaction.

Under such circumstances, the chiral urea **10** was designed. The compound **10** can be prepared from 3,5-bis-trifluoromethylaniline and (*R*,*R*)-1,2-cyclohexyldiamine, and was chosen as a mother skeleton. A range of substituents *R* was incorporated on the 1,2-cyclohexyldiamine moiety as shown in Chart 1 (**10a**—**g**). We expected that the *R* group control the nucleophilic attack of **2** to **3**, and to induce the chirality of **4**. Various types of chiral urea compounds **10a**—**g** were synthesized *via* urea formation and condensation of carboxylic acids in moderate to good yields.[27]

With these chiral urea compounds **10a**—**g** in hand, the hetero-Michael reaction of pyrrolidine (**2**) with γ-crotonolactone (**3**) was examined. The relative reaction rates of the conjugate addition in the presence of these catalysts **10a**—**g** are summarized in Table 2.

Compound **10a** accelerated the hetero-Michael reaction 5.6-fold, and **10b** and **10c**, with aromatic substituents (*R* group), showed similar reaction rate enhancements. In the case of **10d**, which contained a Boc-(L)-Pro moiety, the reaction rate was decreased compared with that of **10a**. In contrast, **10e**, lacking the Boc group of **10d**, and **10g**, a C_2 symmetric chiral urea, accelerated the reaction significantly compared with **10a**. The imidazole-containing catalyst **10f** gave similar acceleration, although it showed poor solubility. Thus **10a**—**g** were revealed to be effective for the reaction acceleration. Next, we examined the asymmetric induction of the reaction using superior catalysts **10e**, **10f** and **10g** (Table 3).

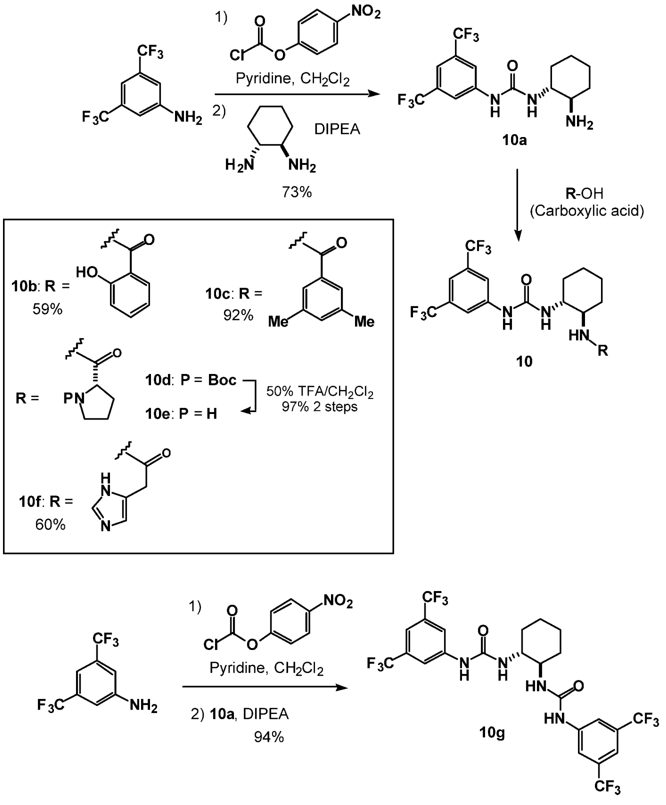
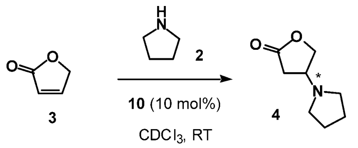


Chart 1. Synthesis of Chiral Urea Compounds **10**

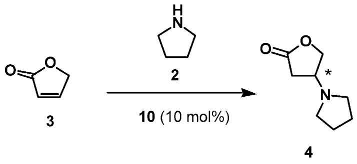
Table 2. Hetero-Michael Reaction with Urea Catalysts **10**



Entry	Catalyst	$t_{1/2}$	Rel. rate increase
1	**10a**	17	5.6
2	**10b**	16	6.0
3	**10c**	19	5.1
4	**10d**	25	3.8
5	**10e**	10	9.6
6	**10f**	17	5.6
7	**10g**	12	8.0

Firstly, in the presence of catalyst **10e** (10 mol%) the reaction of γ-crotonolactone (**3**) with pyrrolidine (**2**) was examined in dichloromethane at 0 °C, but no asymmetric induction was observed. When the reaction temperature was decreased to -40 °C, the conjugate addition product **4** was obtained with 4% ee (t_1).[28] Changing the solvent from dichloromethane to toluene improved the asymmetric induction to 19% ee (t_1). In contrast, in the presence of the catalyst **10f**, the product **4** was obtained with 10% ee (t_2), but with asymmetric induction in the opposite sense, suggesting the possibility of control of enantioselectivity by changing the *R* group. In this case, asymmetric induction was also improved to 15% ee (t_2) in toluene as a solvent. In the case of catalyst

Table 3. Asymmetric Hetero-Michael Reaction with Urea **10e**, **10f** and **10g**



Entry	Catalyst	Solvent	Temp. (°C)	Time (h)	Yield (%)$^{b)}$	ee (%)$^{c,d)}$
1	**10e**	CH_2Cl_2	0	1	75	0
2	**10e**	CH_2Cl_2	−40	10	80	4 (t_1)
3	**10e**	Toluene	−40	4	49	19 (t_1)
4	**10f**	CH_2Cl_2	−40	10	78	10 (t_2)
5	**10f**	Toluene	−40	7	52	15 (t_2)
6	**10g**	CH_2Cl_2	−40	9	77	5 (t_2)
7	**10g**	Toluene	−40	8	53	8 (t_2)

a) The reaction was conducted with lactone (1 eq) and pyrrolidine (3 eq) in the presence of catalyst (10 mol%). *b*) Isolated yield. *c*) The enantiomeric excesses of **3** were determined by HPLC analysis using a Chiralpak AD-H column with hexane/2-propanol, 95 : 5, 1.0 ml/min, t_1=15.1 min, t_2=18.1 min. *d*) The absolute configuration was not determined.

10g, low chiral induction was observed with 5% ee (t_2) in CH_2Cl_2 and 8% ee (t_2) in toluene. Though these data are preliminary results, they indicate that the newly generated chiral center of the product **4** can be controlled by the *R* group in **10**. Thus, further improvement of the asymmetric induction in this reaction can be expected by changing the *R* group.

Conclusion

We have designed and synthesized the new type of chiral urea **10** as a catalyst for the hetero-Michael reaction. With these catalysts, the reaction can be accelerated 5—9-fold. Moreover some of the catalysts, **10e**, **10f**, and **10g** exhibited asymmetric induction in this conjugate addition reaction for the first time. Possibility of asymmetric induction control for desired configuration by changing the structure of the side chain moiety was also demonstrated. Thus, the chiral urea **10** was shown to be a superior prototype asymmetric organocatalyst.

Experimental

General Flash chromatography was performed using Silica gel 60 (spherical, particle size 0.040—0.100 mm; Kanto Co., Inc., Japan). Melting points were determined on a MP-J3 melting point apparatus (Yanaco, Japan) and are uncorrected. Optical rotations were measured with a JASCO DIP polarimeter 370. IR spectra were measured with JASCO VALOR-III FT-IR spectrophotometer. ^{1}H- and ^{13}C-NMR spectra were recorded on JEOL ALPHA500 instrument. Mass spectra were recorded on JEOL JMA-HX110 spectrometer.

Compound 10a To a mixture of 3,5-bis(trifluoromethyl)aniline (0.70 ml, 4.52 mmol) and pyridine (0.40 ml, 4.95 mmol) in dichloromethane (15 ml) was added 4-nitrophenylchloroformate (906 mg, 4.50 mmol) at room temperature. The mixture was stirred for 5 min, then added to a solution of (1*R*,2*R*)-(−)-1,2-diaminocyclohexane (1.54 g, 13.5 mmol) in dichloromethane (5 ml) at room temperature. Subsequently *N*,*N*-diisopropylethylamine (1.0 ml, 13.5 mmol) was added, and the whole mixture was stirred for an additional 15 min at room temperature. Next saturated $NaHCO_3$aq was added, followed by dilution with dichloromethane. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (chloroform/methanol, 40 : 1, 9 : 1, 3 : 1) to give **10a** (1.23 g, 73%) as yellow crystals. mp=80—81 °C (decomposition). $[\alpha]_D^{25}=-4.22°$ (c=1.03, $CHCl_3$). IR (KBr) 3303, 3093, 2940, 2864, 1671, 1573, 1475, 1442, 1389, 1278, 1181, 1129, 1034 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.87 (s, 2H), 7.42 (s, 1H), 3.35 (br s, 1H), 2.58 (m, 1H), 1.97 (br d, J=11.5 Hz, 1H), 1.87 (br d, J=11.5 Hz, 1H), 1.69 (br s, 2H), 1.30—1.21 (m, 2H), 1.15 (m, 2H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 156.43, 141.18, 131.90 (J_{CF}=33.1 Hz), 123.20 (J_{CF}=273.1 Hz), 118.18 (J_{CF}=4.1 Hz), 115.15 (J_{CF}=4.1 Hz), 56.09, 35.10, 32.71, 24.85, 24.54. HR-MS (FAB, M+H) Calcd for $C_{15}H_{18}F_6N_3O$ 370.1354, Found 370.1398.

Compound 10b To a mixture of **10a** (31.9 mg, 0.0864 mmol), salicylic acid (18.0 mg, 0.130 mmol) and DMAP (32.0 mg, 0.262 mmol) in DMF (1 ml) was added EDCI (33.1 mg, 0.173 mmol) and the resulting mixture was stirred at room temperature for 24 h. It was then diluted with EtOAc and the organic layer was washed with H_2O and brine, and dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate, 8 : 1, 4 : 1) to give **10b** (25.1 mg, 59%) as a colorless solid. mp=223—236 °C (decomposition). $[\alpha]_D^{24}=+33.9°$ (c=1.09, CH_3OH). IR (KBr) 3336, 3265, 2920, 2859, 1646, 1594, 1560, 1484, 1450, 1386, 1282, 1246, 1185, 1127 cm^{-1}. ^{1}H-NMR (500 MHz, CD_3OD) δ: 7.85 (s, 2H), 7.70 (dd, J=8.2, 1.5 Hz, 1H), 7.40 (s, 1H), 7.27 (m, 1H), 6.77 (m, 2H), 3.88 (m, 1H), 3.71 (m, 1H) 2.08 (br s, 2H), 1.83 (br s, 2H), 1.41 (m, 4H). ^{13}C-NMR (125 MHz, CD_3OD) δ: 171.28, 161.40, 157.56, 143.13, 134.71, 132.95 (J_{CF}=33.1 Hz), 128.61, 124.80 (J_{CF}=273.1 Hz), 119.86, 119.10 (br), 118.38, 116.65, 115.50 (J_{CF}=4.1 Hz), 55.47, 54.71, 33.78, 32.96, 26.12, 25.94. HR-MS (FAB, M+H) Calcd for $C_{22}H_{22}F_6N_3O_3$ 490.1565, Found 490.1587.

Compound 10c As described for **10b**, the reaction of **10a** (33.3 mg, 0.0902 mmol) and 3,5-dimethylbenzoic acid (20.3 mg, 0.135 mmol) afforded **10c** (41.4 mg, 92%) as a yellow solid. mp=248—250 °C (decomposition). $[\alpha]_D^{25}=+39.7°$ (c=1.05, $CHCl_3$). IR (KBr) 3348, 2937, 2858, 1650, 1634, 1602, 1560, 1471, 1445, 1389, 1340, 1280, 1185, 1134, 1035 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 8.10 (s, 1H), 7.40 (s, 2H), 7.26 (m, 1H), 6.81 (br s, 2H), 3.88 (br s, 2H), 2.26 (br s, 1H), 2.15 (br s, 1H) 2.11 (s, 6H), 1.94 (br, 2H), 1.51—1.41 (m, 4H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 170.02, 156.16, 141.06, 133.97 (J_{CF}=33.1 Hz), 131.75, 131.49, 131.22, 124.22, 124.11 (J_{CF}=272.0 Hz), 117.39 (br), 114.72 (J_{CF}=4.1 Hz), 56.39, 52.82, 33.16, 32.43, 29.69, 25.31, 25.16, 20.67. HR-MS (FAB, M+H) Calcd for $C_{24}H_{26}F_6N_3O_2$ 502.1929, Found 502.1934.

Compound 10d To a mixture of **10** (39.0 mg, 0.106 mmol), *N*-(*tert*-butoxycarbonyl)-L-proline (34.1 mg, 0.158 mmol), HOBt (28.6 mg, 0.212 mmol) and Et_3N (45 μl, 0.321 mmol) in DMF (2 ml) was added EDCI (40.6 mg, 0.212 mmol) at 0 °C and the mixture was stirred for 10 min. After warming to room temperature, the reaction mixture was stirred for 21 h. It was then diluted with EtOAc, and the organic layer was washed with H_2O and brine, and dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate, 1 : 1, 1 : 3) to give **10d** (58.8 mg, 98%) as a colorless oil. $[\alpha]_D^{25}=-23.8°$ (c=0.92, $CHCl_3$). IR (neat) 3329, 3111, 2979, 2937, 2862, 2862, 1651, 1568, 1475, 1389, 1279, 1173, 1132, 1036 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 8.62 (s, 1H), 7.89 (s, 2H), 7.40 (s, 1H), 6.69 (br s, 1H), 6.11 (br s, 1H), 4.19 (br s, 1H), 3.66 (br s, 2H), 3.45 (br s, 1H), 3.32 (br s, 1H), 2.16 (br, 1H), 2.02 (br, 2H), 1.85 (br, 2H), 1.45 (s, 9H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 174.46, 155.47, 141.57, 131.95 (J_{CF}=33.1 Hz), 123.25 (J_{CF}=273.1 Hz), 117.37 (br), 114.71 (br), 80.77, 60.37, 54.64, 47.08, 33.34, 32.34, 29.64, 28.22, 25.08, 24.88, 20.98, 20.85. HR-MS (FAB, M+H) Calcd for $C_{25}H_{33}F_6N_4O_4$ 567.2406, Found 567.2429.

Compound 10e Urea **10d** (137.8 mg, 0.243 mmol) was dissolved in 50% TFA in dichloromethane (2 ml). The reaction mixture was stirred at room temperature for 2 h, and the resulting mixture was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (chloroform/methanol, 40 : 1, 9 : 1) to give **10e** (111.8 mg, 99%) as a colorless solid. mp=185—187 °C (decomposition). $[\alpha]_{\mathrm{D}}^{23}=+8.38^\circ$ ($c=1.00$, CH_3OH). IR (KBr) 3284, 3093, 2940, 2863, 1671, 1570, 1475, 1439, 1389, 1281, 1185, 1131, 1037 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 10.58 (br s, 1H), 8.66 (br s, 1H), 7.85 (s, 2H), 7.75 (s, 1H), 7.41 (s, 1H), 6.09 (br s, 1H), 4.17 (br s, 1H), 3.62 (br s, 2H), 3.41 (br s, 2H), 3.31 (br s, 1H), 2.17—1.77 (m, 8H), 1.27 (m, 4H). ^{13}C-NMR (125 MHz, CD_3OD) δ: 169.57, 157.07, 143.40, 133.17 ($J_{CF}=33.1$ Hz), 124.83 ($J_{CF}=273.1$ Hz), 118.87 (br), 115.45 ($J_{CF}=4.1$ Hz), 61.16, 54.99, 54.36, 47.37, 33.95, 33.06, 31.20, 25.84, 25.75, 25.06. HR-MS (FAB, M+H) Calcd for $C_{20}H_{25}F_6N_4O_2$ 467.1882, Found 467.1885.

Compound 10f As described for **10b**, **10a** (33.3 mg, 0.0902 mmol) and imidazole-4-acetic acid monohydrochloride (28.6 mg, 0.176 mmol) were allow to react to give **10f** (33.3 mg, 60%) as a colorless solid. mp=228—232 °C (decomposition). $[\alpha]_{\mathrm{D}}^{24}=+43.1^\circ$ ($c=1.10$, CH_3OH). IR (KBr) 3341, 3129, 2936, 2862, 1703, 1638, 1561, 1475, 1442, 1393, 1274, 1227, 1179, 1141 cm^{-1}. ^{1}H-NMR (500 MHz, CD_3OD) δ: 7.95 (s, 2H), 7.52 (s, 1H), 7.46 (s, 1H), 6.87 (s, 1H), 3.65 (m, 1H), 3.53 (m, 1H), 3.47 (s, 2H), 2.05 (br d, $J=11.1$ Hz, 1H), 1.95 (br d, $J=6.4$ Hz, 1H), 1.76 (br s, 2H) 1.35 (m, 4H). ^{13}C-NMR (125 MHz, CD_3OD) δ: 173.04, 157.07, 143.45, 136.21, 133.10 ($J_{CF}=33.1$ Hz), 133.03, 124.91 ($J_{CF}=273.1$ Hz), 118.89 (br), 118.03, 115.40 ($J_{CF}=4.1$ Hz), 54.96, 54.38, 49.86, 35.46, 34.05, 33.14, 25.87. HR-MS (FAB, M+H) Calcd for $C_{20}H_{22}F_6N_5O_2$ 478.1678, Found 478.1690.

Compound 10g To a mixture of 3,5-bis(trifluoromethyl)aniline (61.1 μl, 0.394 mmol) and pyridine (55 μl, 0.680 mmol) in dichloromethane (2 ml) was added 4-nitrophenylchloroformate (90.3 mg, 0.448 mmol) at room temperature. The mixture was stirred for 5 min, the resulting mixture was added to a solution of **10a** (82.6 mg, 0.224 mmol) in dichloromethane (1 ml). To this was added *N*,*N*-diisopropylethylamine (39 μl, 0.224 mmol), and the whole mixture was stirred for an additional 20 h at room temperature. Then saturated $NaHCO_3$aq was added, followed by dilution with dichloromethane. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate, 3 : 1, 2 : 1) to give **10g** (132.1 mg, 94%) as a yellow solid. mp=249—252 °C (decomposition). $[\alpha]_{\mathrm{D}}^{23}=+36.4^\circ$ ($c=1.00$, CH_3OH). IR (KBr) 3357, 1614, 1593, 1498, 1389, 1336, 1289, 1183, 1128, 1113 cm^{-1}. ^{1}H-NMR (500 MHz, CD_3OD) δ: 7.82 (s, 4H), 7.31 (s, 2H), 3.56 (br s, 2H), 2.01 (br s, 2H), 1.79 (br s, 2H), 1.37 (m, 4H). ^{13}C-NMR (125 MHz, CD_3OD) 157.55, 143.10, 132.92 ($J_{CF}=33.1$ Hz), 124.67 ($J_{CF}=273.0$ Hz), 118.67 (br), 115.36 (br), 55.71, 33.65, 26.11. HR-MS (FAB, M+H) Calcd for $C_{24}H_{21}F_{12}N_4O_2$ 625.1473, Found 625.1470.

Typical Procedure for the Asymmetric Hetero-Michael Reaction To a mixture of γ-crotonolactone (**1**) (9.6 μl, 0.131 mmol) and **10f** (6.3 mg, 0.0132 mmol) in toluene (1.3 ml) was added pyrrolidine (**2**) (33.1 μl, 0.397 mmol) at −40 °C. The resulting mixture was stirred vigorously at −40 °C for 7 h. Then saturated NH_4Claq was added, and the organic layer was extracted with chroloform/methanol (=40 : 1) solution. The extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*, and the residue was purified by column chromatography on silica gel (chroloform/methanol, 1 : 0, 40 : 1) to give **3** (10.7 mg, 52%). The enantiomeric excess of **3** was determined by the use of chiral HPLC analysis (Chiralpak AD-H column, 0.46 cm (ϕ)×25 cm (L), *n*-hexane/2-propanol 95 : 5, flow rate=1.0 ml/min, minor; 15.1 min (t_1), major; 18.1 min (t_2).

Acknowledgements We are grateful for financial support in the form of an Award in Synthetic Organic Chemistry from Toray Co., Ltd., Japan and a grant from the Pharmacy Research Encouragement Foundation. This research was also supported in part by a Grant-in Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

References and Notes

1) Pelmutter P., "Conjugate Addition Reactions in Organic Synthesis," Pergamon Press, Oxford, 1992.
2) For recent reviews see: Kanai M., Shibasaki M., "Catalytic Asymmetric Synthesis," 2nd ed., ed. by Ojima I., Wiley, New York, 2000.
3) For recent reviews see: Tomioka K., Nagaoka Y., "Comprehensive Asymmetric Catalysis," Vol. 3, Chap. 31.1, ed. by Jacobsen E. N., Pfaltz A., Yamamoto H., Springer Verlag, Berlin, 1999.
4) For recent reviews see: Dalko P. I., Moisan L., *Angew. Chem. Int. Ed.*, **40**, 3726—3748 (2001).
5) For recent reviews see: Jarvo E. R., Miller S. J., *Tetrahedron*, **58**, 2481—2495 (2002).
6) Nagasawa K., Georgieva A., Takahashi H., Nakata T., *Tetrahedron*, **56**, 187—192 (2000).
7) Nagasawa K., Georgieva A., Takahashi H., Nakata T., *Tetrahedron*, **57**, 8959—8964 (2001).
8) Kita T., Georgieva A., Hashimoto Y., Nakata T., Nagasawa K., *Angew. Chem. Int. Ed.*, **41**, 2832—2834 (2002).
9) Nagasawa K., Hashimoto Y., *Chem. Rec.*, **3**, 201—211 (2003).
10) Kashman Y., Hirsh S., McConnell O. J., Ohtani I., Kusumi T., Kakisawa H., *J. Am. Chem. Soc.*, **111**, 8925—8926 (1989).
11) Ohtani I., Kusumi T., Kakisawa H., Kashman Y., Hirsh S., *J. Am. Chem. Soc.*, **114**, 8472—8479 (1992).
12) Ohtani I., Kusumi T., Kakisawa H., *Tetrahedron Lett.*, **33**, 2525 (1992).
13) Jares-Erijman E. A., Ingrum A. L., Carney J. R., Rinehart K. L., Sakai R., *J. Org. Chem.*, **58**, 4805—4808 (1993).
14) Berlinck R. G. S., Braekman J. C., Daloze D., Bruno I., Riccio R., Ferri S., Spampinato S., Speroni E., *J. Nat. Prod.*, **56**, 1007—1015 (1993).
15) Curran D. P., Kuo L. H., *Tetrahedron Lett.*, **36**, 6647—6650 (1995).
16) Schreiner P. R., Wittkopp A., *Org. Lett.*, **4**, 217—220 (2002).
17) Wittkopp A., Schreiner P. R., *Chem. Eur. J.*, **9**, 407—414 (2003).
18) Vachal P., Jacobsen E. N., *Org. Lett.*, **2**, 867—870 (2000).
19) Vachal P., Jacobsen E. N., *J. Am. Chem. Soc.*, **124**, 10012—10014 (2002).
20) Wenzel A. G., Jacobsen E. N., *J. Am. Chem. Soc.*, **124**, 12964—12965 (2002).
21) Okino T., Hoashi Y., Takemoto Y., *Tetrahedron Lett.*, **44**, 2817—2821 (2003).
22) Okino T., Hoashi Y., Takemoto Y., *J. Am. Chem. Soc.*, **125**, 12672—12673 (2003).
23) Alcazar V., Moran J. R., de Mendoza J., *Tetrahedron Lett.*, **36**, 3941—3944 (1995).
24) Howard-Jone A., Murphy P. J., Thomas D. A., *J. Org. Chem.*, **64**, 1039—1041 (1999).
25) Martin-Portugues M., Alcazar V., Prados P., de Mendoza J., *Tetrahedron*, **58**, 2951—2955 (2002).
26) Allingham M. T., Howard-Jones A., Murphy P. J., Thomas D. A., Caulkett P. W. R., *Tetrahedron Lett.*, **44**, 8677—8680 (2003).
27) Quite recently, Takemoto and co-workers also reported a very similar type of chiral thiourea catalyst for the Michael reaction of malonates to nitroolefins.[22]
28) The ee values of **4** were determined by HPLC using a Chiralpak AD-H column. The absolute configuration of **4** is under investigation.