HETEROCYCLES, Vol. 79, 2009, pp. 573 - 582. © The Japan Institute of Heterocyclic Chemistry
Received, 6th September, 2008, Accepted, 22nd October, 2008, Published online, 30th October, 2008.
DOI: 10.3987/COM-08-S(D)18

ASYMMETRIC SYNTHESIS OF 4-SUBSTITUTED 2,6-DIOXOPIPERIDINE-3-CARBONITRILE BY USING THIOUREA-CATALYZED ASYMMETRIC MICHAEL ADDITION†

Tsubasa Inokuma, Yuuki Nagamoto, Shota Sakamoto, Hideto Miyabe, Kiyosei Takasu, and Yoshiji Takemoto*

Graduate School of Pharmaceutical Sciences, Kyoto University, Yoshida, Sakyo-ku, Kyoto 606-8501, Japan
E-mail: takemoto@pharm.kyoto-u.ac.jp

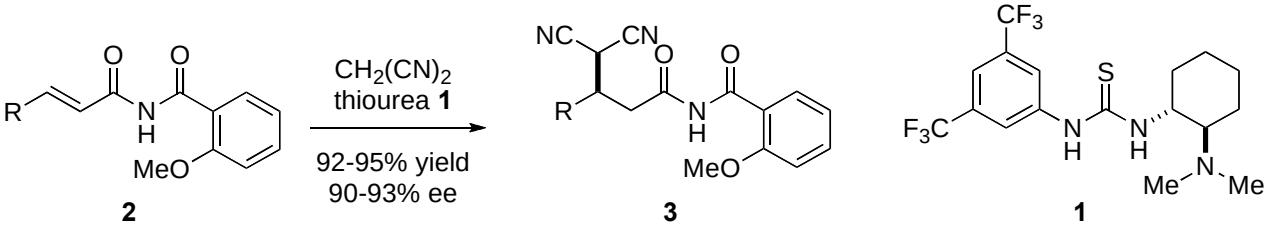
Abstract – An enantioselective Michael addition of several α,β-unsaturated carbonyl compounds with malononitrile catalyzed by a bifunctional thiourea is described. We also demonstrate the transformation of Michael adduct into an enantiomerically enriched functionalized piperidine.

INTRODUCTION

Enantioselective formation of carbon-carbon bonds in a catalytic manner has been the subject of significant interest in the field of synthetic chemistry. Among a lot of excellent efforts on the catalytic enantioselective reactions, an asymmetric Michael reaction of α,β-unsaturated carbonyl compounds with activated methylene compounds, such as nitroalkane, 1,3-diketones and malononitrile, has been extensively studied.[1] We have reported that bifunctinal thiourea catalyst (**1**)[2] promoted the enantioselective Michael reaction of α,β-unsaturated imides with several activated methylene compounds (Scheme 1).[3]

The use of 2-methoxybenzimide **2**, in which an intramolecular hydrogen bond between the methoxy group and the imide proton would be formed, accelerated the reaction rate and achieved excellent

Scheme 1. Asymmetric Michael reaction catalyzed by bifunctional thioures **1**

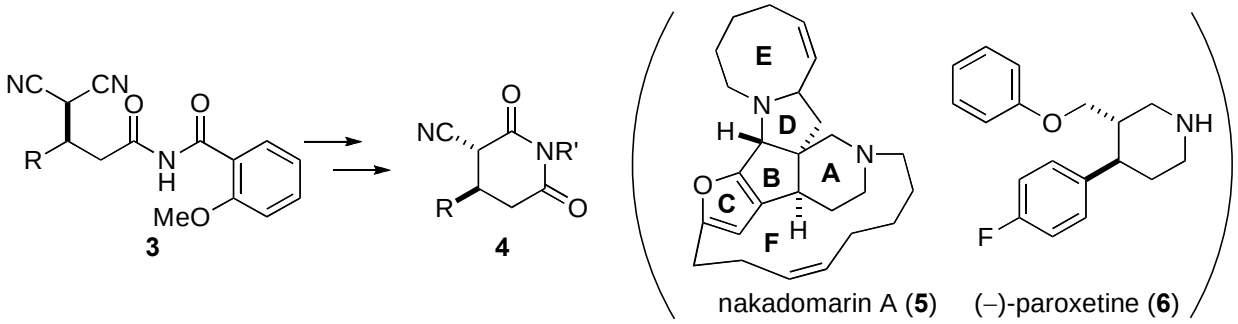


2 **3** **1**

†This paper is dedicated to the memory of Dr. John Daly.

asymmetric induction in the thiourea-catalyzed reaction.[3b] We envisioned that the product **3** might be a precursor of chiral piperidine derivatives such as **4** by the intramolecular cyclization (Scheme 2).[4] A piperidine ring is a ubiquitous molecular skeleton, which often appears in naturally occurring substances such as antimalarial nakadomarin A **5**[5] as well as synthetic pharmaceuticals such as anti-depressive paroxetine **6**.[6] With an aim of the synthesis of **5**, we further explored several substrates **7** bearing a 3-furyl group as the β-substituent to reveal the effect of the substituent (X) of Michael acceptors **7** on the reactivity with malononitrile. In addition, synthetic application of the Michael adducts **8** for the preparation of chiral piperidine-2,6-dione derivative **10** was examined.

Scheme 2. Conversion of the Michael adducts to piperidine derivatives

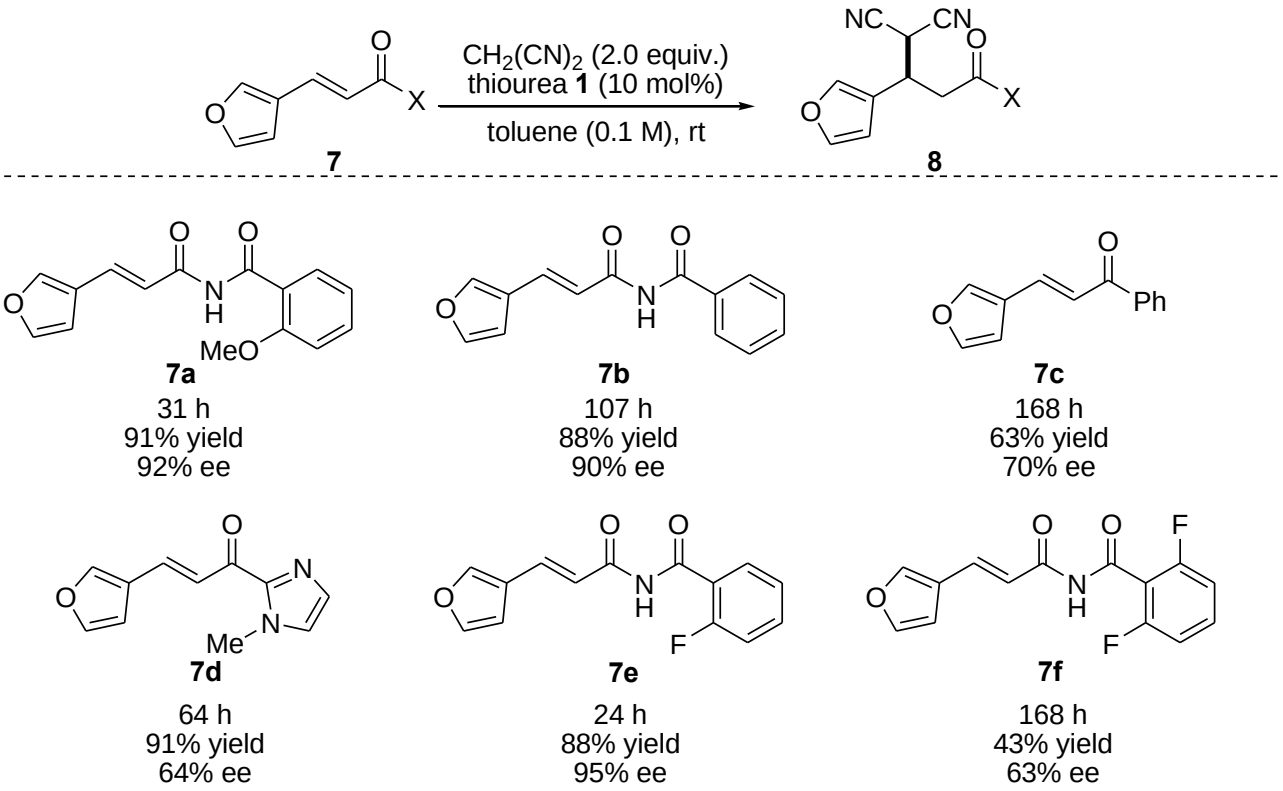


RESULTS AND DISCUSSION

In an initial study, we selected 2-methoxybenzimide **7a** as a substrate for the asymmetric Michael reaction with malononitrile. In contrast to **2** (R = Ph),[3b] the reaction of **7a** proceeded very slowly due to the electron-rich furyl group (Scheme 3). In addition, simple benzimide **7b** was much poorer substrate for this reaction as expected. Then, in order to improve the reactivity of this reaction, we screened several α,β-unsaturated carbonyl compounds **7c** and **7d** together with the imides **7e** and **7f.** The reaction of **7c-f** with malononitrile (2.0 equiv.) was carried out in toluene (0.1 M) at ambient temperature in the presence of 10 mol% of **1** until the substrate was completely consumed or, otherwise, for 1 week (168 h). The results are summarized in Scheme 3. The reaction of phenylketone **7c** took place to give the desired Michael adduct **8c** in 63% yield.[7] However, the reaction did not complete within 168 h and the ee was modelate (70% ee). In a case of **7d** bearing *N*-methyl imidazole as the acyl moiety, the reaction was complete within 64 h to give **8d** in 91% yield with 64% ee.[8] As a result, all these substrates were inferior to **7a** in terms of both the reactivity and the enantioselectivity. Therefore, we reexamined other imides **7e** and **7f**. We speculated that if the methoxy group of **7a** was replaced by the fluoro group, its electron-withdrawing property as well as its potential ability as a proton acceptor would make the substrates **7e** and **7f** more reactive than **7a**. When *o*-fluorobenzimide **7e** was utilized as a substrate for this

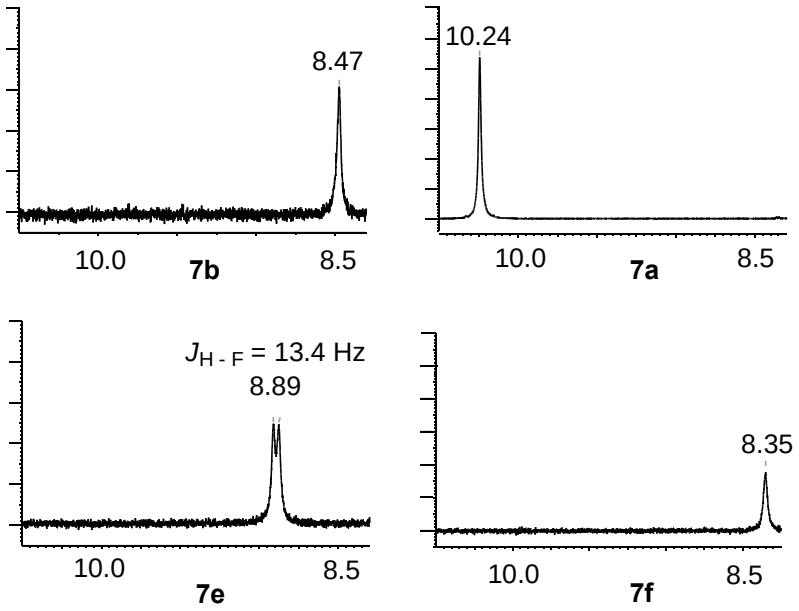
reaction, the reaction was complete within 24 h and desired product **8e** was obtained in good yield with 95% ee. On the other hand, the reaction of 2,6-difluorobenzimide **7f** led to significant decrease in both reactivity and enantioselectivity.

Scheme 3. Thiourea catalyzed asymmetric Michael addition of α,β-unsaturated carbonyl compounds with malononitrile



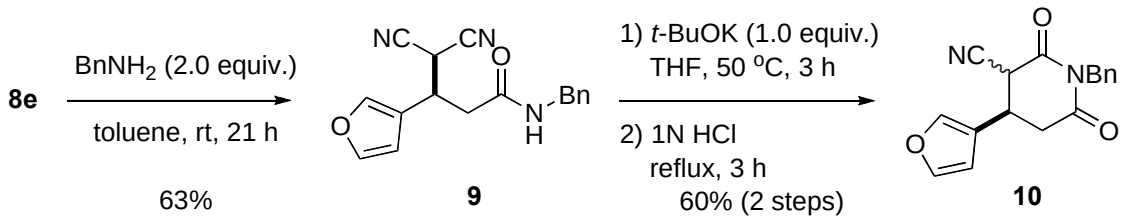
We next elucidated the intramolecular hydrogen bond of the imide substrates by ^{1}H NMR analysis (Figure 1). As reported previously, the chemical shifts ($CDCl_3$ at 25 ^{o}C) of the imide proton of **7a** was observed at significant downfield area (10.24 ppm) compared with **7b**, which undoubtedly indicate that an intramolecular hydrogen bond between the alkoxy oxygen and the imide proton is formed in the compound **7a**. On the other hand, the imide proton of 2-fluorobenzimide **7e** was observed at 8.89 ppm as a doublet peak (J = 13.4 Hz). The observed spin-spin coupling indicated the formation of H-F hydrogen bond.[9] In sharp contrast, no H-F interaction, that is spin-spin coupling of the imide proton, was observed in ^{1}H NMR spectrum of difluorobenzimide **7f**.[9] On the basis of these results, the conformation of **7a** and **7e** should be restricted by the formation of the intramolecular hydrogen bond, and therefore the bifunctional thiourea **1** could appropriately activate them by the formation of intermolecular hydrogen bond network.[10] Consequently, the reaction of **7e** proceeded much faster in a highly enantioselective manner.

Figure 1. ^{1}H-NMR spectrum of imide protons of the **7a, 7b**, **7e** and **7f**



Finally, to transform the obtained Michael adduct **8e** into advanced derivative, we undertook the synthesis of piperidine-2,6-dione **10**, which might be a potential synthetic intermediate for nakadomarin A (**5**). Treatment of benzimide **8e** with benzylamine readily afforded benzylamide **9**. Subsequently the reaction of **9** with *t*-BuOK, followed by HCl hydrolysis, provided the desired piperidine-2,6-dione **10** in 60% yield.

Scheme 4. Transformation of **8e** into piperidine-2,6-dione **10**.



In summary, we have screened several α,β-unsaturated carbonyl compounds for the organocatalytic asymmetric Michael reaction with malononitrile and found that new Michael acceptor **7e** possessed potential property in terms of reactivity and stereoselectivity. Moreover, we have demonstrated the transformation of **8e** into piperidine-2,6-dione **10** bearing 3-furyl group at C(4) position, which corresponds to a partial structure (A or C ring) of nakadomarin A. Further study is in progress towards establishing synthetic routes for the natural product.

EXPERIMENTAL

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 and 126 MHz, respectively. Tetramethylsilane (TMS) was used as an internal standard. IR spectra were recorded on a JASCO FT/IR-410 spectrometer. Low and high resolution mass spectra were obtained by EI or FAB method. Optical rotations were recorded on a JASCO DIP-360 polarimeter with a path length of 1 cm; concentrations are quoted in mg (1 mL). $[\alpha]_D$ values are measured in 10^{-1} deg cm^2 g^{-1}. Enantiomeric excess was determined by high performance liquid chromatography (HPLC) analysis.

Typical procedure for preparation of benzimide 7a.

A 1.58 M solution of ^{n}BuLi in hexane (8.6 mL, 13.6 mmol) was added to a solution of diethyl 2-(2-methoxybenzamido)-2-oxoethylphosphonate[3b,11] (2.23 g, 6.78 mmol) in THF (15 mL) at −78 °C. The resulting solution was stirred at the same temperature for 10 min. After addition of 3-furaldehyde (0.59 mL, 6.78 mmol), the mixture was stirred at ambient temperature for 2 h. After dilution with H_2O and acidification with by 1 N HCl, the resulting mixture was extracted with EtOAc, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting residue was recrystallized from hexane-EtOAc to afford **7a** (1.18 g, 64%) as colorless solids.

***N*-(*E*)-(3-(Furan-3-yl)acryloyl)-2-methoxybenzamide** (**7a**): Colorless solids, mp 119-120 °C (hexane-EtOAc); ^{1}H NMR δ 10.24 (s, 1H), 8.19 (dd, *J* = 7.3, 1.8 Hz, 1H), 7.81 (d, *J* = 15.5 Hz, 1H), 7.71 (s, 1H), 7.58 (d, *J* = 15.5 Hz, 1H), 7.55 (td, *J* = 7.3, 1.8 Hz, 1H), 7.45 (s, 1H), 7.13 (t, *J* = 7.3 Hz, 1H), 7.04 (d, *J* = 7.3 Hz, 1H), 6.74 (d, *J* = 1.2 Hz, 1H), 4.04 (s, 3H); ^{13}C NMR δ 167.6, 164.0, 157.8, 145.2, 144.4, 135.9, 134.7, 132.8, 123.3, 121.7, 120.5, 120.2, 111.7, 107.8, 56.2; IR (KBr) ν 3343, 1697 cm^{-1}; FABMS *m/z* 272 ($M-H^+$, 100); Anal. Calcd for $C_{15}H_{13}NO_4$: C, 66.41; H, 4.83; N, 5.16; Found: C, 66.13; H, 4.77; N, 5.16.

***N*-(*E*)-(3-(Furan-3-yl)acryloyl)benzamide** (**7b**): Colorless solids, mp 142-143 °C (hexane-EtOAc); ^{1}H NMR δ 9.10 (s, 1H), 7.94 (d, *J* = 7.3 Hz, 2H), 7.82 (d, *J* = 15.2 Hz, 1H), 7.72 (s, 1H), 7.61 (t, *J* = 7.3 Hz, 1H), 7.57 (d, *J* = 15.2 Hz, 1H), 7.51 (t, *J* = 7.3 Hz, 2H), 7.45 (s, 1H), 6.73 (s, 1H); ^{13}C NMR δ 167.9, 166.1, 145.5, 144.5, 136.7, 133.2, 133.0, 128.9, 127.9, 123.2, 119.1, 107.8; IR (KBr) ν 3255, 1699 cm^{-1}; EIMS *m/z* 241 (M^+, 5), 105 (100); Anal. Calcd for $C_{14}H_{11}NO_3$: C, 69.70; H, 4.60; N, 5.81; Found: C, 69.78; H, 4.84; N, 5.88.

Typical procedure for preparation of α,β-unsaturated ketone 7c.

A mixture of 3-furaldehyde (45 μL, 0.667 mmol) and $BzCH=PPh_3$ (300 mg, 0.789 mmol) in toluene (4.0 mL) was stirred at 70 °C for 17 h. Then, the resulting mixture was concentrated *in vacuo,* purified with silica gel column chromatography (hexane-EtOAc = 6 : 1) to afford **7c** (78.7 mg, 76%).

(*E*)-3-(Furan-3-yl)-1-phenylprop-2-en-1-one (**7c**): Yellow solids, mp 77-78 °C (hexane-EtOAc); ^{1}H NMR δ 7.99 (td, *J* = 6.9, 1.1 Hz, 2H), 7.74 (s, 1H), 7.72 (d, *J* = 15.0 Hz, 1H), 7.58 (tt, *J* = 6.9, 1.1 Hz, 1H), 7.51 (dd, *J* = 6.3, 1.1 Hz, 1H), 7.48 (dd, *J* = 3.5, 1.7 Hz, 2H), 7.25 (d, *J* = 15.0 Hz, 1H), 6.71 (d, *J* = 1.7 Hz, 1H); ^{13}C NMR δ 190.4, 145.4, 144.5, 138.1, 134.8, 132.7, 128.6, 123.2, 122.0, 107.4; IR (KBr) ν 3144, 1661 cm^{-1}; FABMS *m/z* 199 (M-H$^+$, 100); Anal. Calcd for $C_{13}H_{10}O_2$: C, 78.77; H, 5.09; Found: C, 78.96; H, 5.18.

(*E*)-3-(Furan-3-yl)-1-(1-methyl-1H-imidazol-2-yl)prop-2-en-1-one (**7d**): White solids, mp 103-104 °C (hexane-EtOAc); ^{1}H NMR δ 7.77 (d, *J* = 16.0 Hz, 1H), 7.75 (d, *J* = 2.3 Hz, 1H), 7.73 (d, *J* = 16.0 Hz, 1H), 7.45 (s, 1H), 7.21 (s, 1H), 7.07 (s, 1H), 6.77 (d, *J* = 1.6 Hz, 1H), 4.09 (s, 3H); ^{13}C NMR δ 180.4, 145.5, 144.4, 143.9, 133.4, 129.2, 127.1, 123.4, 122.7, 107.8, 36.3; IR (KBr) ν 3128, 1660 cm^{-1}; FABMS *m/z* 203 (M-H$^+$, 100); Anal. Calcd for $C_{11}H_{10}N_2O_2$: C, 65.34; H, 4.98; N, 13.85; Found: C, 65.10; H, 4.92; N, 13.80.

***N*-(*E*)-(3-(Furan-3-yl)acryloyl)-2-fluorobenzamide** (**7e**): Colorless solids, mp 113-114 °C (hexane-EtOAc); ^{1}H NMR δ 8.89 (d, J_{C-F} = 13.4 Hz, 1H), 8.09 (td, *J* = 8.0, 1.7 Hz, 1H), 7.83 (d, *J* = 15.4 Hz, 1H), 7.73 (s, 1H), 7.63-7.56 (m, 1H), 7.46 (d, *J* = 15.4 Hz, 1H), 7.46 (s, 1H), 7.34 (t, *J* = 8.0 Hz, 1H), 7.21 (dd, *J* = 12.2, 8.9 Hz, 1H), 6.73 (d, *J* = 1.2 Hz, 1H); ^{13}C NMR δ 166.8, 162.1, 161.5, 159.5, 144.2, 136.8, 135.0, 132.2, 125.2, 123.1, 120.4, 119.3, 116.5, 107.7; IR (KBr) ν 3123, 1678 cm^{-1}; FABMS *m/z* 262 (M-H$^+$, 100); Anal. Calcd for $C_{14}H_{10}FNO_3$: C, 64.86; H, 3.89; N, 5.40; Found: C, 64.91; H, 3.90; N, 5.35.

***N*-(*E*)-(3-(Furan-3-yl)acryloyl)-2,6-difluorobenzamide** (**7f**): Colorless solids, mp 152-153 °C (hexane-EtOAc); ^{1}H NMR δ 8.35 (s, 1H), 7.80 (d, *J* = 15.5 Hz, 1H), 7.72 (s, 1H), 7.50-7.44 (m, 2H), 7.19 (d, *J* = 15.5 Hz, 1H), 7.01 (dd, *J* = 8.6, 8.1 Hz, 2H), 6.70 (d, *J* = 1.7 Hz, 1H); ^{13}C NMR δ 165.6, 160.9, 159.9, 145.7, 144.6, 137.3, 133.1, 133.0, 122.9, 118.6, 112.2, 107.7; IR (KBr) ν 1682 cm^{-1}; FABMS *m/z* 278 (M-H$^+$, 100); Anal. Calcd for $C_{14}H_9F_2NO_3$: C, 60.66; H, 3.27; N, 5.05; Found: C, 60.50; H, 3.25; N, 4.95.

General procedure for the catalytic enantioselective Michael reaction.

A mixture of **7**, malononitrile (2 equiv.) and thiourea **1** (10 mol%) in toluene (0.1 M) was stirred at ambient temperature. After concentration *in vacuo*, the reaction mixture was purified with silica gel column chromatography (hexane-EtOAc = 4 : 1) to afford **8**.

(*R*)-*N*-(4,4-Dicyano-3-(furan-3-yl)butanoyl)-2-methoxybenzamide (**8a**): colorless solids, mp 141-145 ^{o}C (hexane-EtOAc); $[\alpha]^{23}_{D}$ −8.5 (*c* 1.2, $CHCl_3$, 92% ee); ^{1}H NMR δ 10.42 (s, 1H), 8.15 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.60 (s, 1H), 7.58 (td, *J* = 7.8, 1.8 Hz, 1H), 7.47 (t, *J* = 1.5 Hz, 1H), 7.13 (t, *J* = 7.8 Hz, 1H), 7.04 (d, *J* = 7.8 Hz, 1H), 6.60 (s, 1H), 4.63 (d, *J* = 4.9 Hz, 1H), 4.03 (s, 3H), 3.87 (ddd, *J* = 8.5, 5.5, 4.9 Hz, 1H), 3.62 (dd, *J* = 18.6, 5.5 Hz, 1H), 3.57 (dd, *J* = 18.6, 8.5 Hz, 1H); ^{13}C NMR δ 172.9, 164.0, 157.8, 144.0, 140.8, 135.3, 132.9, 121.9, 121.1, 119.4, 112.2, 111.8, 111.6, 109.4, 56.2, 40.1, 33.4, 28.5; IR (KBr) ν 3331, 1748, 1679 cm^{-1}; FABMS *m/z* 338 (M-H^{+}, 97), 135 (100); Anal. Calcd for $C_{18}H_{15}N_3O_4$: C, 64.09; H, 4.48; N, 12.46; Found: C, 64.10; H, 4.43; N, 12.48; HPLC analysis (DAICELL CIRALPAK AS-H, Hexane:2-Propanol = 70:30, flow rate = 0.5 mL/min, 254 nm) retension time; major: 59.7 min and minor: 73.9 min.

(*R*)-*N*-(4,4-Dicyano-3-(furan-3-yl)butanoyl)benzamide (**8b**): colorless solids, mp 138-139 ^{o}C (hexane-EtOAc); $[\alpha]^{23}_{D}$ −8.9 (*c* 2.4, $CHCl_3$, 90% ee); ^{1}H NMR δ 8.62 (s, 1H), 7.84 (dd, *J* = 8.3, 1.0 Hz, 2H), 7.66 (t, *J* = 8.3 Hz, 1H), 7.61 (s, 1H), 7.54 (t, *J* = 8.3 Hz, 2H), 7.49 (t, *J* = 1.5 Hz, 1H), 6.59 (s, 1H), 4.50 (d, *J* = 4.9 Hz, 1H), 3.88 (ddd, *J* = 8.9, 5.2, 4.9 Hz, 1H), 3.67 (dd, *J* = 18.9, 5.2 Hz, 1H), 3.61 (dd, *J* = 18.9, 4.9 Hz, 1H); ^{13}C NMR δ 173.2, 165.7, 144.2, 140.9, 133.9, 131.9, 129.2, 127.8, 121.0, 112.0, 111.5, 109.3, 39.5, 33.4, 28.6; IR (KBr) ν 3244, 1724, 1673 cm^{-1}; FABMS *m/z* 308 (M-H^{+}, 100); Anal. Calcd for $C_{17}H_{13}N_3O_3$: C, 66.44; H, 4.26; N, 13.67; Found: C, 66.36; H, 4.49; N, 13.54; HPLC analysis (DAICELL CHIRALPAK AD-H, Hexane:2-Propanol = 50:50, flow rate = 0.5 mL/min, 254 nm) retension time; major: 23.8 min and minor: 17.2 min.

(*R*)-2-(1-(Furan-3-yl)-3-oxo-3-phenylpropyl)malononitrile (**8c**): colorless oil; $[\alpha]^{32}_{D}$ −4.4 (*c* 1.0, $CHCl_3$, 70% ee); ^{1}H NMR δ 7.90 (d, J = 7.5 Hz, 2H), 7.57 (t, J = 7.5 Hz, 1H), 7.52 (s, 1H), 7.43 (dd, J = 14.3, 7.5 Hz, 3H), 6.51 (s, 1H), 4.55 (d, J = 4.3 Hz, 1H), 3.88 (dt, J = 8.0, 5.2 Hz, 1H), 3.49 (dd, J = 7.7, 5.2 Hz, 2H); ^{13}C NMR δ 196.6, 144.2, 140.7, 135.7, 134.3, 129.0, 128.1, 121.3, 112.0, 111.7, 109.2, 40.1, 33.3, 28.5; IR (KBr) ν 3749, 2360, 1683 cm^{-1}; FABMS *m/z* 265 (M-H^{+}, 22), 73 (100); HRMS (FAB+): Calcd for $C_{16}H_{14}N_2O_2$ (M-H^{+}) 265.0977, Found: 265.0930; HPLC analysis (DAICELL CHIRALCEL OD-H, Hexane:2-Propanol = 90:10, flow rate = 1.0 mL/min, 254 nm) retension time; major: 42.3 min and minor: 55.5 min.

(*R*)-2-(1-(Furan-3-yl)-3-(1-methyl-1H-imidazol-2-yl)-3-oxopropyl)malononitrile (**8d**): colorless oil; $[\alpha]^{30}_{D}$ −7.5 (*c* 1.0, $CHCl_3$, 64% ee); ^{1}H NMR δ 7.57 (s, 1H), 7.45 (s, 1H), 7.17 (s, 1H), 7.08 (s, 1H), 6.56 (s, 1H), 4.47 (d, *J* = 4.6 Hz, 1H), 3.99 (s, 3H), 3.91 (dt, *J* = 8.0, 6.3 Hz, 1H), 3.85 (dd, *J* = 17.8, 6.3 Hz, 1H), 3.64 (dd, *J* = 17.8, 8.0 Hz, 1H); ^{13}C NMR δ 188.5, 144.0, 142.1, 140.8, 129.9, 127.9, 121.2, 112.0, 111.5, 109.3, 40.4, 36.1, 33.5, 28.9; IR (KBr) ν 3749, 2361, 1676 cm^{-1}; FABMS *m/z* 269 ($M\text{-}H^+$, 100); HRMS (FAB+): Calcd for $C_{14}H_{13}N_4O_2$ ($M\text{-}H^+$) 269.1039, Found: 269.1039; HPLC analysis (DAICELL CHIRALCEL OD-H, Hexane:2-Propanol = 70:30, flow rate = 0.5 mL/min, 254 nm) retension time; major: 19.6 min and minor: 25.9 min.

(*R*)-*N*-(4,4-Dicyano-3-(furan-3-yl)butanoyl)-2-fluorobenzamide (**8e**): colorless solids, mp 105-106 °C (hexane-EtOAc); $[\alpha]^{23}_{D}$ −7.5 (*c* 1.0, $CHCl_3$, 95% ee); ^{1}H NMR δ 9,09 (d, *J* = 13.8 Hz, 1H), 8.06 (t, *J* = 7.5 Hz, 1H), 7.62 (t, *J* = 6.9 Hz, 1H), 7.60 (s, 1H), 7.48 (s, 1H), 7.35 (t, *J* = 7.5 Hz, 1H), 7.21 (dd, *J* = 8.6, 8.0 Hz, 1H), 6.58 (s, 1H), 4.58 (d, *J* = 5.2 Hz, 1H), 3.87 (ddd, *J* = 8.6, 5.2, 5.2 Hz, 1H), 3.63 (dd, *J* = 15.5, 5.2 Hz, 1H), 3.58 (dd, *J* = 15.5, 8.6 Hz, 1H); ^{13}C NMR δ 172.3, 162.0, 161.6, 159.6, 144.1, 140.8, 135.8, 132.4, 125.5, 120.9, 119.2, 116.6, 112.0, 111.5, 109.3, 40.1, 33.4, 28.6; IR (KBr) ν 2361, 1697 cm^{-1}; FABMS *m/z* 326 ($M\text{-}H^+$, 100); HRMS (FAB+): Calcd for $C_{17}H_{13}FN_3O_3$ ($M\text{-}H^+$) 326.0941, Found: 326.1003; HPLC analysis (DAICELL CHIRALCEL OD-H, Hexane:2-Propanol = 80:20, flow rate = 0.5 mL/min, 254 nm) retension time; major: 71.8 min and minor: 88.7 min.

(*R*)-*N*-(4,4-Dicyano-3-(furan-3-yl)butanoyl)-2,6-difluorobenzamide (**8f**): colorless amorphous; $[\alpha]^{31}_{D}$ −4.4 (*c* 1.4, $CHCl_3$,63% ee); ^{1}H NMR δ 8.61 (s, 1H), 7.59 (s, 1H), 7.53 (td, *J* = 8.5, 2.3 Hz, 2H), 7.49 (t, *J* = 1.8 Hz, 1H), 7.05 (t, *J* = 8.5 Hz, 2H), 4,54 (d, *J* = 4.6 z 1H), 3.84 (ddd, *J* = 8.6, 5.2, 5.2 Hz, 1H), 3.58 (dd, *J* = 18.9, 5.2 Hz, 1H), 3.53 (dd, *J* = 18.9, 8.6 Hz, 1H); ^{13}C NMR δ 171.7, 161.1, 159.3, 159.1, 144.2, 140.9, 134.0, 120.7, 112.7, 112.5, 111.9, 111.4, 109.2, 39.8, 33.5, 30.9, 28.6; IR (KBr) ν 3289, 2258, 1624 cm^{-1}; FABMS *m/z* 344 ($M\text{-}H^+$, 2), 45 (100); HRMS (FAB+): Calcd for $C_{17}H_{12}F_2N_3O_3$ ($M\text{-}H^+$) 344.0847, Found: 344.0876; HPLC analysis (DAICELL CHIRALPAK AS-H, Hexane:2-Propanol = 90:10, flow rate = 0.5 mL/min, 254 nm) retension time; major: 62.6 min and minor: 85.2 min.

(*R*)-*N*-Benzyl-4,4-dicyano-3-(furan-3-yl)butanamide (**9**): A mixture of **8e** (252 mg, 0.775 mmol) and benzylamine (110 μL, 1.01 mmol) in toluene (4.0 mL) was stirred at rt for 21 h. After concentrated *in vacuo*, the reaction mixture was purified by silica gel column chromatography (hexane-EtOAc = 3 : 1) to afford **9** (107 mg, 63%) as a brownish oil: $[\alpha]^{32}_{D}$ +14.6 (*c* 1.1, $CHCl_3$); ^{1}H NMR δ 7.51 (s, 1H), 7.46 (t, *J* = 1.3 Hz, 1H), 7.38-7.29 (m, 3H), 7.21 (d, *J* = 7.0 Hz, 2H), 6.49 (s, 1H), 5.90 (brs, 1H), 4,75 (d, *J* = 4.9 Hz, 1H), 4.46 (dd, *J* = 14.7, 5.8 Hz, 1H), 4.39 (dd, *J* = 14.7, 5.5 Hz, 1H), 3.77 (ddd, *J* = 8.9, 5.2, 4.9 Hz,

1H), 2.78 (dd, *J* = 16.2, 8.9 Hz, 1H), 2.71 (dd, *J* = 16.2, 5.2 Hz, 1H); ^{13}C NMR δ 168.8, 144.2, 140.7, 137.3, 128.9, 127.8, 121.0, 112.1, 111.7, 109.1, 43.8, 37.7, 34.4, 28.4; IR (neat) ν 3301, 1640 cm^{-1}; FABMS *m/z* 294 (M-H$^+$, 100); HRMS (FAB+): Calcd for $C_{17}H_{16}N_3O_2$ (M-H$^+$) 294.1243, Found: 294.1243.

(*R*)-1-Benzyl-4-(furan-3-yl)-2,6-dioxopiperidine-3-carbonitrile (**10**): To a stirred solution of **9** (105 mg, 0.359 mmol) in THF (3.6 mL) at rt, *t*-BuOK (40.2 mg, 0.359 mmol) was added and stirred at 50 ℃ for 3 h. After the reaction mixture was diluted with H_2O and acidified with 1N HCl, the resulting mixture was extracted with EtOAc, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Resulting crude enamine product was directly used for the next reaction. A suspension of the crude enamine in 1N HCl (1.71 mL, 1.71 mmol) was stirred at reflux for 3 h. After the reaction mixture was diluted with H_2O, the resulting mixture was extracted with EtOAc, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane-EtOAc = 7 : 2) to afford **10** (46.1 mg, 60% from **9**) as brownish oil: $[\alpha]^{32}_D$ +2.6 (*c* 2.5, $CHCl_3$); ^{1}H NMR (3 : 1 mixture of diastereomers, with signals corresponding to the major indicated by) δ 7.44-7.26 (m, 7H), 6.33-6.30 (m, 1H), 5.02 (dd, *J* = 13.9, 2.7 Hz, 1H), 4.96 (dd, *J* = 13.9, 5.1 Hz, 1H), 4.71 (dd, *J* = 17.6, 8.8 Hz, 1H), 4.05 (dd, *J* = 4.4, 1.0 Hz, 1H), 3.17 (dd, *J* = 17.6, 4.4 Hz, 1H), 3.05 (dd, *J* = 5.1, 1.0 Hz, 1H), 2.84 (dd, *J* = 10.5, 7.6 Hz, 1H); ^{13}C NMR δ 169.1, 168.8, 163.9, 163.8, 144.5, 144.3, 143.9, 139.8, 139.7, 135.8, 135.7, 135.6, 129.1, 129.0, 128.8, 128.7, 128.58, 128.57, 128.02, 128.00, 122.0, 120.8, 114.4, 114.0, 109.1, 108.8, 44.0, 43.9, 43.0, 42.7, 42.1, 37.6, 36.9, 36.8, 35.8, 30.3, 29.3; IR (neat) ν 3136, 2259, 1705, 1677 cm^{-1}; FABMS *m/z* 295 (M-H$^+$, 51), 73 (100); HRMS (FAB+): Calcd for $C_{17}H_{15}N_2O_3$ (M-H$^+$) 295.1083, Found: 295.1039.

ACKNOWLEDGEMENTS

This work was supported in part by a Grant-in-Aid for Scientific Research (B) (Y.T.) and Scientific Research on Priority Areas: Advanced Molecular Transformations of Carbon Resources (Y.T. and K.T.), "Targeted Proteins Research Program" from Ministry of Education, Culture, Sports, Science and Technology of Japan, and JSPS KAKENHI (3316). T. I thanks the JSPS for a Fellowship.

REFERENCES

1. For a review, see: M. Shibasaki and N. Yoshikawa, *Chem. Rev.*, 2002, **102**, 2187.
2. For recent reviews, *see*: (a) Y. Takemoto and H. Miyabe, *Chimia*, 2007, **61**, 269. (b) H. Miyabe and Y. Takemoto, *Bull. Chem. Soc. Jpn.*, 2008, **81**, 785.
3. (a) Y. Hoashi, T. Okino, and Y. Takemoto, *Angew. Chem. Int. Ed.*, 2005, **44**, 4032. (b) T. Inokuma, Y. Hoashi, and Y. Takemoto, *J. Am. Chem. Soc.*, 2006, **128**, 9413.

4. M. S. Taylor and E. N. Jacobsen, *J. Am. Chem. Soc*., 2003, **125**, 11204.
5. J. Kobayashi, D. Watanabe, N. Kawasaki, and M. Tsuda, *J. Org. Chem.*, 1997, **62**, 9236.
6. K. L. Dechant and S. P. Clissold, *Drugs*, 1991, **41**, 225.
7. For the examples of organocatalytic asymmetric Michael addition of other α,β-unsaturated ketones, see: (a) C. Gu, L. Liu, Y. Sui, J. Zhao, D. Wang, and Y. Cheng, *Tetrahedron: Asymmetry*, 2007, **18**, 455. (b) J. Wang, H. Li, L. Zu, W. Jiang, H. Xie, W. Duan, and W. Wang, *J. Am. Chem. Soc*., 2006, **128**, 12652. (c) B. Vakulya, S. Varga, A. Csampai, and T. Soos, *Org. Lett.*, 2005, **7**, 1967. (d) X. Li, L. Cun, C. Lian, L. Zhong, Y. Chen, J. Liao, J. Zhu, and J. Deng, *Org. Biomol. Chem.*, 2008, **6**, 349.
8. For the examples of organocatalytic asymmetric Michael addition of other α,β-unsaturated ester derivatives, see: (a) B. Vakulya, S. Varga, and T. Soos, *J. Org. Chem.*, 2008, **73**, 3475. (b) S. B. Tsogoeva, *Eur. J. Org. Chem.*, 2007, 1701.
9. Coupling constants ($J_{H\text{-}F}$) of a hydrogen-fluorine non-bonding interaction is generally observed at a value within 9.5-15.0 Hz in ^{1}H NMR. However, the chemical shift of the imide proton is generally observed at the similar area as that of compounds having no H-F hydrogen bond. For an example, *see*: X Zhao, X. Wang, X. Jiang, Y. Chen, Z. Liand, and G. Chen, *J. Am. Chem. Soc*., 2003, **125**, 15128.
10. Recently, a detailed simulative study of the hydrogen bond network in the transition state of α,β-unsaturated imides with malononitrile activated by thiourea is reported, see: D. Zhang, G. Wang, and R. Zhu, *Tetrahedron: Asymmetry*, 2008, **19**, 568.
11. N. S. Goodman and E. N. Jacobsen, *Adv. Synth. Catal*., 2002, **344**, 9.