HETEROCYCLES, Vol. 96, No. 8, 2018, pp. 1383 - 1397. © 2018 The Japan Institute of Heterocyclic Chemistry
Received, 9th May, 2018, Accepted, 12th July, 2018, Published online, 20th July, 2018
DOI: 10.3987/COM-18-13918

CINCHONA ALKALOID THIOUREA-CATALYZED ONE-POT SYNTHESIS AND BIOSELECTIVE ACTIVITIES OF *β*-AMINO ACID ESTER DERIVATIVES CONTAINING A PYRIMIDINE MOIETY

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Abstract – We have studied the synthesis of enantiomerically pure optically active *β*-amino acid ester derivatives with good biological activities. Here, we report that both enantiomers of *β*-amino acid ester derivatives that contain a pyrimidine moiety can be produced in an enantioselective Mannich-type one-pot reaction with good yields and excellent enantiomeric excess (up to >99% *ee*) by chiral cinchona alkaloid thiourea catalysts. An evaluation of the antiviral activities of our reaction products against tobacco mosaic virus (TMV) was promising with high and selective biological activities. Compound **(−)-4h** showed an excellent anti-TMV activity (curative activity, 56.1%; inactivation activity, 70.7%; protection activity, 95.7%) at 500 *μ*g/mL. These values exceed those of the commercially available antiviral agent, ningnanmycin (curative activity, 52.6%; inactivation activity, 62.0%; protection activity, 90.2%). These novel chiral compounds could be used as protective agents against TMV disease.

INTRODUCTION

The catalytic asymmetric Mannich-type reaction is one of the most effective methods for the preparation of optically active *β*-amino acid ester compounds, and therefore is a very important C–C bond-forming

reaction.[1] *β*-Amino acid esters and their derivatives are a class of nitrogen-containing compounds that are distributed widely in natural products and biologically active molecules, and play an important role in organic medicinal chemistry.[2] They have shown a wide range of biological activities, including anti-tumor,[3] anti-HIV[4] anti-plant virus[5] and antileishmanial properties.[6] Therefore, the synthesis of enantiomerically enriched *β*-amino acid ester derivatives has received considerable attention, and several organocatalytic asymmetric Mannich-type reactions to prepare enantioenriched *β*-amino acid ester derivatives have been reported.[7] Although various substrates have been reported in asymmetric Mannich reactions, only a few reports exist on the utilization of heteroaromatic primary amines to synthesize chiral *β*-amino ester derivatives. Song et al. reported the use of an aldimine bearing a benzothiazole moiety in Mannich-type reaction that was catalyzed by cinchona alkaloid organocatalysts.[8] Subsequently, Du et al. also reported a cinchona-based squaramide-catalyzed enantioselective Mannich reaction of malonates with imines that bear a benzothiazole or isoxazole.[9] The pyrimidine derivatives, which belong to the N-containing heterocyclic compounds, consist of an important skeleton that are associated with several biologically active compounds, and they are used extensively to design chemical drugs.[10] In the field of antivirals, several aminopyrimidine derivatives with anti-plant virus activities have been described. For example, Yuan et al. found that *N*-(pyrimidin-5-yl)-*N*'-phenylureas displayed excellent anti-TMV activity.[11] Subsequently, Wu et al. designed and synthesized two series of aminopyrimidine derivatives that showed good to excellent antiviral activity against TMV.[12] Chiral thiourea derivatives, which can bind to the oxygen or nitrogen atom and serve as catalysts, have been identified as efficient chiral hydrogen-bond donors in several asymmetric reactions.[13] Cinchona alkaloids and derivatives that are used as chiral hydrogen-bond acceptors were found to be effective catalysts for the activation of malonates for enantioselective conjugate additions.[14] Notably, in the design of synthetic compounds, the pyrimidine moiety contains the nitrogen atom, which easily forms hydrogen bonds in the chiral cinchona alkaloid-based thiourea-catalyzed synthesis. Few studies exist on the synthesis of highly enantiomerically pure *β*-amino acid esters with pyrimidine that exhibit highly anti-plant virus activities. To exploit highly effective and environmentally safe chiral anti-plant virus agents, we would like to develop a bifunctional cinchona alkaloid-based thiourea-catalyzed, highly enantioselective Mannich-type reaction to obtain novel *β*-amino acid ester derivatives that contain aromatic heterocyclic pharmacophores. This is the first report on the enantioselective synthesis of *β*-amino acid ester derivatives that contain a pyrimidine moiety by using the catalyst. The antiviral activities against tobacco mosaic virus (TMV) of both enantiomers from our catalytic reactions were evaluated.

RESULTS AND DISCUSSION

To determine the optimal experimental conditions, we used quinine and cinchona alkaloid thioureas **A1–5**

(**Figure 1**) in the one-pot asymmetric catalytic Mannich-type reaction of 4-(dimethoxymethyl)pyrimidin-2-amine, benzaldehyde and diethyl malonate. The desired product **4a** was obtained with **A1** or **A5** as the catalyst (entries 2 and 6, **Table 1**). Quinine-derived thiourea catalyst **A2**, **A3** and **A4** could achieve the reaction with a lower enantioselectivity (entries 3, 4 and 5, **Table 1**). Quinine was a poor catalyst and indicated that the H-bonding donor group plays a major role in the catalysis (entry 1, **Table 1**). Cinchona alkaloid derivatives (**A1–A5**) that bear a hydrogen-bond donor thiourea and hydrogen-bond acceptor tertiary amine groups are superior catalysts to quinine. Catalysts **A1** and **A5** comprise strong electron-withdrawing groups, namely two CF_3 groups, that promote the asymmetric Mannich-type reaction through double-hydrogen bond activation of the substrate.

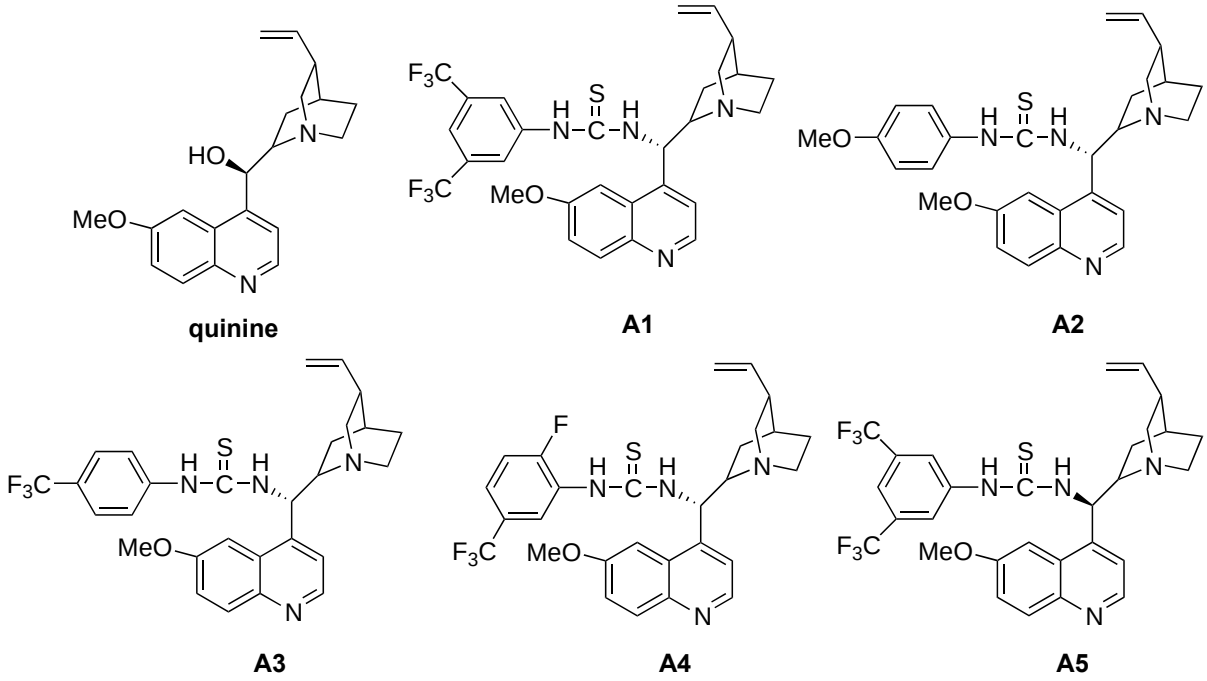
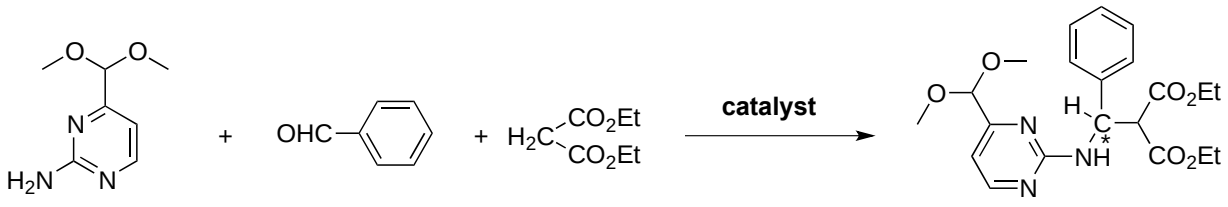


Figure 1. Structure of commercially available quinine and cinchona alkaloid thiourea catalysts **A1**–**A5**

Table 1. Screening of various catalysts for the one-pot asymmetric Mannich-type reaction[a]



1a **2a** **3a** **4a**

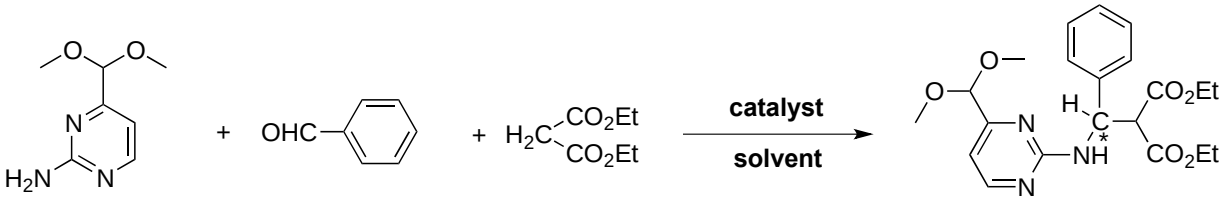
Entry	Catalyst	Yield[b] (%)	ee[c] (%)
1	quinine	23	52
2	**A1**	58	70

3	**A2**	36	43
4	**A3**	47	60
5	**A4**	43	62
6	**A5**	55	72

[a] Reactions were performed with 0.30 mmol of **1a**, 0.30 mmol of **2a**, 0.30 mmol of **3a**, 10 mol% catalyst in 3.0 mL of *p*-xylene at 40 °C for 36 h. [b] Yield of isolated product. [c] Determined by HPLC analysis (Chiralpak IA column).

The influences of reaction temperature, solvent and catalyst loading were studied by using the optimal catalysts **A1** and **A5** (**Table 2**). Because the nature of the solvent affects catalyst performance, we screened commonly used solvents for this Mannich–type reaction. Solvent *p*-xylene provided the desired products in a high enantioselectivity and yield (entries 5–9, **Table 2**), whereas in coordinating solvents, such as trichloromethane, acetone, tetrahydrofuran and ethanol, decreased activities were observed (entries 1–4, **Table 2**). Catalyst loading had a pronounced effect on the yield and enantioselectivity. A significant increase in enantioselectivity was achieved when the catalyst load was increased from 10 mol% to 20 mol% (entries 5 and 8, **Table 2**). However, a small decrease in enantioselectivity and no significant increase in reactivity were observed when the reaction temperature was increased from 50 °C to 60 °C (entries 5–6, **Table 2**). It should be noted that the other enantiomers of the reaction could be obtained by using **A5** as the catalyst (entries 9, **Table 2**). The best result was achieved at 50 °C with 20 mol% catalyst loading in *p*-xylene.

Table 2. Optimization of the one-pot asymmetric Mannich-type reaction[a]



1a **2a** **3a** **4a**

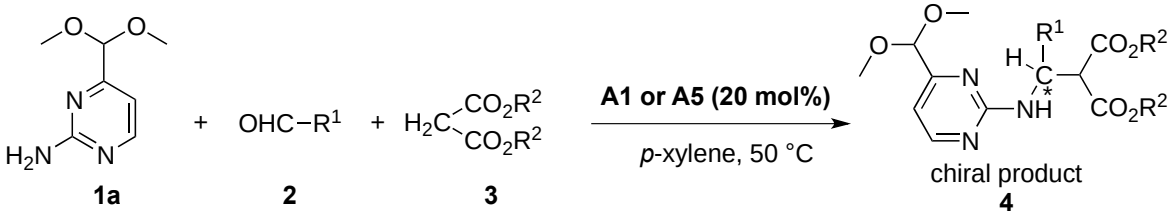
Entry	Catalyst (mol%)	Temp. (°C)	Solvent	Yield[b] (%)	ee[c] (%)
1	**A1 (10)**	40	$CHCl_3$	35	42
2	**A1 (10)**	40	acetone	54	58
3	**A1 (10)**	40	THF	62	53
4	**A1 (10)**	40	EtOH	44	66

5	**A1 (10)**	50	*p*-xylene	80	73
6	**A1 (10)**	60	*p*-xylene	86	70
7	**A1 (5)**	50	*p*-xylene	72	70
8	**A1 (20)**	50	*p*-xylene	90	89
9	**A5 (20)**	50	*p*-xylene	88	95

[a] Reactions were performed with 0.30 mmol of **1a**, 0.30 mmol of **2a**, 0.30 mmol of **3a** in 3.0 mL of solvent for 48 h. [b] Yield of isolated product. [c] Determined by HPLC analysis (Chiralpak IA column).

Once the optimal reaction conditions had been established, the reaction synthesis was examined with various aldehydes and malonates. Representative results of our studies are summarized in **Table 3**. Aromatic and aliphatic aldehydes afforded excellent enantioselectivities and yields. In general, furfural reacted with dimethyl malonate to afford the corresponding product **(−)-4h** in excellent yield (94%) with a high enantioselectivity (>99% ee) (entry 15, **Table 3**). For reactions that involved substrates with electron-donating (-Me, -OMe) or electron-withdrawing (-Cl) substituents on the 4-position of the aromatic aldehydes, the desired products were obtained in 81–94% yields with 89–97% ee. Next, we investigated the substrate generality of other amines. 6-Chloropyrimidin-4-amine (**1b**) as the substrate showed high yields and excellent enatioselectivities (>99% ee) (entries 17–18, **Table 3**). Unfortunately, the reaction of 3-nitroaniline **(1c)** failed to provide any product, which demonstrates that this reaction is critically dependent on the amine structure (entry 19, **Table 3**).

Table 3. Scope of enantioselective Mannich-type reaction[a]



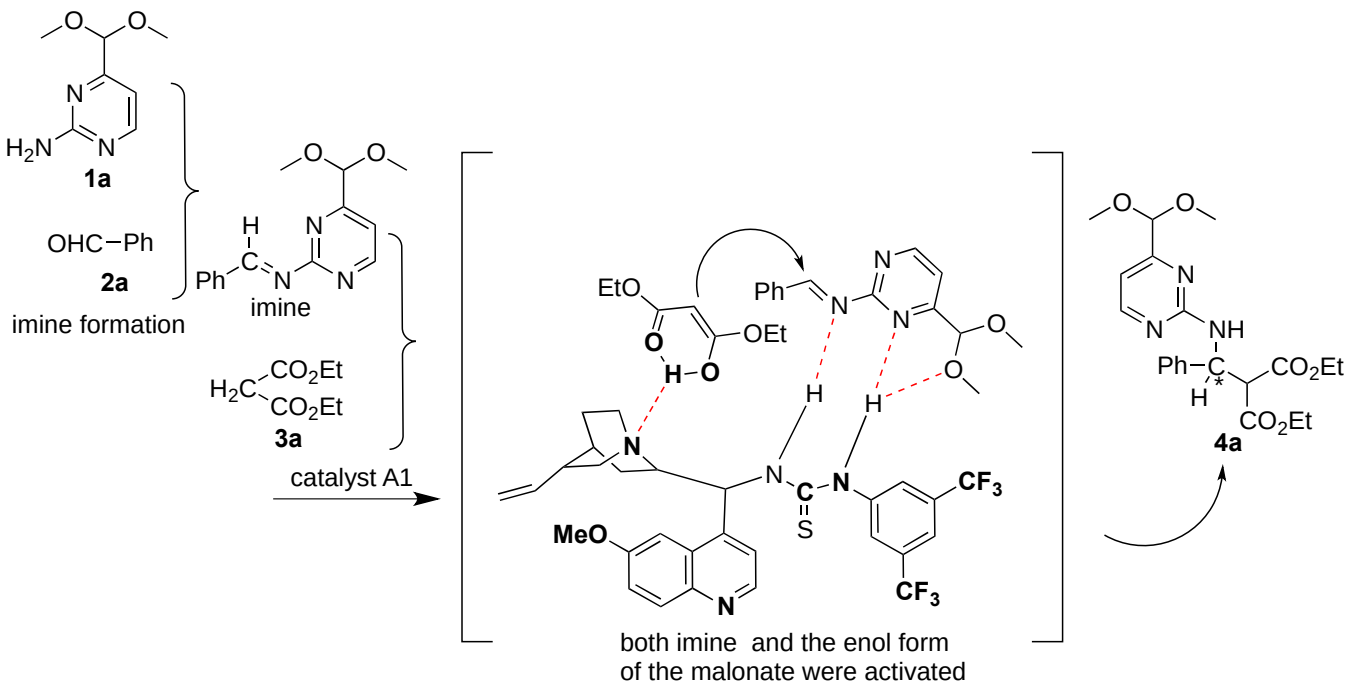
1a **2** **3** **4**

Entry	4	Catalyst	1	R^1	R^2	Time (h)	Yield[b] (%)	ee[c] (%)
1	**(−)-4a**	**A1**	**1a**	Ph	Et	48	90	89
2	**(+)-4a**	**A5**	**1a**	Ph	Et	48	88	95
3	**(−)-4b**	**A1**	**1a**	4-MeO-Ph	Et	48	93	95
4	**(+)-4b**	**A5**	**1a**	4-MeO-Ph	Et	48	88	93
5	**(−)-4c**	**A1**	**1a**	cyclohexyl	Et	60	92	93

6	**(+)-4c**	**A5**	**1a**	cyclohexyl	Et	60	93	97
7	**(−)-4d**	**A1**	**1a**	Ph	Me	48	85	93
8	**(+)-4d**	**A5**	**1a**	Ph	Me	48	90	97
9	**(−)-4e**	**A1**	**1a**	4-Cl-Ph	Me	48	82	93
10	**(+)-4e**	**A5**	**1a**	4-Cl-Ph	Me	48	89	95
11	**(−)-4f**	**A1**	**1a**	4-Me-Ph	Me	60	81	96
12	**(+)-4f**	**A5**	**1a**	4-Me-Ph	Me	60	87	95
13	**(−)-4g**	**A1**	**1a**	cyclohexyl	Me	60	80	91
14	**(+)-4g**	**A5**	**1a**	cyclohexyl	Me	60	84	94
15	**(−)-4h**	**A1**	**1a**	2-furyl	Me	60	94	>99
16	**(+)-4h**	**A5**	**1a**	2-furyl	Me	60	92	98
17	**(−)-4i**	**A1**	**1b**[d]	4-MeO-Ph	Et	60	91	>99
18	**(+)-4i**	**A5**	**1b**[d]	4-MeO-Ph	Et	60	93	>99
19	**(−)-4j**	**A1**	**1c**[d]	2-furyl	Me	60	0	n.d.

[a] Reactions were performed with 0.30 mmol of **1a**, 0.30 mmol of **2a**, 0.30 mmol of **3a** in 3.0 mL of *p*-xylene in the presence of 20 mol% catalyst **A1** or **A5** at 50 °C for 48–60 h. [b] Yield of isolated product. [c] Determined by HPLC analysis (Chiralpak IA column). [d] **1b** = 6-Chloropyrimidin-4-amine, **1c** = 3-nitroaniline.

A mixture of 4-(dimethoxymethyl)pyrimidin-2-amine (**1a**) and benzaldehyde (**2a**) was treated with diethyl malonate (**3a**) in the presence of catalyst **A1** at 50 °C for 10 h. The *in-situ* generation of imine was confirmed by thin-layer chromatography (TLC) and mass spectrometry. We believe that catalyst **A1** may act in a bifunctional fashion. The enol form of diethyl malonate (**3a**) is activated by the basic nitrogen atom in a tertiary amine, and the imine is activated by the thiourea moiety through double hydrogen bonding. Thus, nucleophilic attack of the diethyl malonate on heteroaromatic imine in the favored *Re*-face direction occurs via the transition state. These interactions in our proposed mechanism may be responsible for the observed stereochemical outcome of the reaction and the enhancement in reaction rate.



Scheme 1. Proposed Mannich-type reaction mechanism

The antiviral activities of chiral products from our reactions against TMV were tested. Commercially available antiviral agent, ningnanmycin, was used as the positive control.[15] The bioassay results *in vivo* are shown in **Table 4**. Most chiral compounds showed low to high antiviral activities against TMV at 500 μg/mL. Compound **(−)-4h** possesses remarkable curative, inactivation and protective activities at 500 μg/mL with values of 56.1%, 70.7% and 95.7%, respectiviely, which is obviously better than that of commercial agent ningnanmycin (52.6%, 62.0% and 90.2%). The phenyl substitution pattern had a great influence on the anti-TMV activity of the chiral compounds. The Cl- moieties at the 4 position of the phenyl ring also showed a good anti-TMV activity *in vivo* (compounds **(−)-4e** and **(+)-4e**). Compound **(−)-4h** could have great potential for further development as a chiral antiviral agent.

Table 4. Inhibitory effect of chiral compounds against TMV *in vivo* at 500 μg/mL

Compd.	Curative activity (%)[a]	Inactivation activity (%)[a]	Protective activity (%)[a]
(−)-4a	31.3 ± 1.6	38.2 ± 2.4	57.1 ± 1.7
(+)-4a	39.4 ± 3.1	49.4 ± 3.0	40.3 ± 2.8
(−)-4b	38.4 ± 3.2	41.4 ± 1.3	55.7 ± 3.1
(+)-4b	47.1 ± 2.0	54.4 ± 2.9	71.7 ± 2.6
(−)-4c	44.3 ± 2.7	55.1 ± 3.1	62.2 ± 3.4
(+)-4c	53.6 ± 1.3	61.6 ± 3.2	85.7 ± 3.4

(−)-4d	45.2 ± 1.5	55.4 ± 2.7	54.0 ± 2.4
(+)-4d	50.6 ± 2.1	62.5 ± 2.6	64.4 ± 3.2
(−)-4e	50.2 ± 2.4	61.5 ± 2.4	82.5 ± 2.7
(+)-4e	55.1 ± 2.2	69.7 ± 1.5	94.5 ± 1.1
(−)-4f	38.6 ± 2.1	46.4 ± 3.2	45.3 ± 1.7
(+)-4f	45.2 ± 3.9	56.6 ± 4.3	49.4 ± 3.2
(−)-4g	27.3 ± 2.8	31.4 ± 2.2	28.2 ± 2.1
(+)-4g	48.3 ± 3.7	53.3 ± 3.5	67.2 ± 1.8
(−)-4h	56.1 ± 3.5	70.7 ± 4.3	95.7 ± 3.6
(+)-4h	48.6 ± 2.5	56.7 ± 3.4	78.3 ± 4.9
ningnanmycin[b]	52.6 ± 2.2	62.0 ± 3.0	90.2 ± 2.4

[a] Average of three replicates. [b] The commercial, agricultural and antiviral product ningnanmycin was used to compare the activity.

In conclusion, we have developed a highly efficient and enantioselective one-pot method for the synthesis of novel *β*-amino ester derivatives that contain a pyrimidine moiety. The desired compounds were obtained in high yields with an excellent enantiomeric excess (up to >99% ee). Some chiral products from our reaction showed moderate to excellent antiviral activities against TMV. Given the promising bioactivity of this class of molecules and the simplicity of the catalysts and substrates, based on antiviral studies on the antiviral mechanisms, tests on the crop safety, field tests and the acute toxicities of these compounds, they can be considered for further development as a new class of chiral anti-plant-virus agents. Further studies aimed at product antivirus spectra and antiviral mechanisms are ongoing in our laboratory.

EXPERIMENTAL

Infrared (IR) spectra were recorded on a Bruker VECTOR 22 spectrometer (Bruker, Karlsruhe, Germany) with KBr disks. NMR spectra were recorded on a Bruker 400 NMR (Bruker, Karlsruhe, Germany). HRMS data were measured on a Shimadzu Scientific LCMS-IT-TOF (Shimadzu, Kyoto, Japan). Elemental analysis was performed on an Elementar Vario-III CHN analyzer (Elementar, Frankfurt, Germany). HPLC analysis was conducted by using a Fuli Analytical Technologies LC5090 series system (Fuli analytical instrument Co., China), Chiralpak IA column (Daicel, Shanghai, China). Optical rotation values were measured by a Wzz-2s polarimeter (Shanghai Yue Feng Instrument and Meter Co., China). All reactions were carried out in oven-dried glassware with magnetic stirring. Unless otherwise stated, the reagents were from Aladdin Chemicals Co. (Aladdin, Shanghai, China) and Daicel Chiral Technologies

China Co., (Daicel, Shanghai, China). Catalysts A**1**, **A2**, **A3**, **A4** and **A5** were prepared according to procedures previously reported, and their data were identical to those reported in the literature.[8,16]

General experimental procedure to prepare 4. Reactions were performed with 0.30 mmol of 4-(dimethoxymethyl)pyrimidin-2-amine (**1a**), 0.30 mmol of aldehyde **2**, 0.30 mmol of malonate **3** in 3.0 mL of *p*-xylene in the presence of 20 mol% catalyst **A1** or **A5** at 50 °C and stirred for 48–60 h. After completion of the reaction (as observed by TLC), the crude product was purified by preparative TLC (GF254 silica gel: hexane/EtOAc = 5/1), which yielded the target product.

Diethyl 2-(((4-(dimethoxymethyl)pyrimidin-2-yl)amino)(phenyl)methyl)malonate (4a): light-yellow oil; yield 78%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, *J* = 4.9 Hz, 1H), 7.41 (d, *J* = 7.7 Hz, 2H), 7.29 (t, *J* = 7.8 Hz, 2H), 7.22 (t, *J* = 7.2 Hz, 1H), 6.75 (d, *J* = 4.9 Hz, 1H), 6.68 (d, *J* = 9.6 Hz, 1H), 6.06 (dd, *J* = 9.5, 5.9 Hz, 1H), 5.06 (s, 1H), 4.15-4.09 (m, 4H), 3.99 (d, *J* = 5.7 Hz, 1H), 3.39 (s, 3H), 3.32 (s, 3H), 1.14 (t, *J* = 8.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.81, 167.09, 166.05, 161.52, 158.70, 139.83, 128.44, 127.47, 126.72, 108.17, 103.00, 61.74, 61.52, 60.39, 57.38, 53.79, 53.64, 14.20, 13.88; IR (KBr): *ν*3220, 3011, 2951, 2923, 1654, 1582, 1525, 1498, 1369, 1244, 1027, 757 cm^{-1}; Anal. Calcd for $C_{21}H_{27}N_3O_6$: C, 60.42; H, 6.52; N, 10.07. Found: C, 60.35; H, 6.59; N, 10.00. HR-MS (ESI$^+$) *m*/*z* Calcd for $C_{21}H_{27}N_3O_6$ [M + H]$^+$418.1973; found 418.1983.

(−)-Diethyl 2-(((4-(dimethoxymethyl)pyrimidin-2-yl)amino)(phenyl)methyl)malonate (−)-(4a): This product was obtained as a light-yellow oil from a reaction catalyzed by **A1** (20 mol%) at 50 °C for 48 h; yield 90% by preparative TLC (GF254 silica gel: hexane/Et_2O = 5/1); 89% ee as determined by HPLC [Daicel Chiralpak IA, hexane/IPA = 90/10, 1.0 mL·min^{-1}, λ = 220 nm, tr (major) = 13.87 min, tr (minor) = 9.35 min]; $[\alpha]_D^{25}$ −41.2 (c 0.52, $CHCl_3$).

(+)-Diethyl 2-(((4-(dimethoxymethyl)pyrimidin-2-yl)amino)(phenyl)methyl)malonate (+)-(4a): This product was obtained as a light-yellow oil from a reaction catalyzed by **A5** (20 mol%) at 50 °C for 48 h; yield 88% by preparative TLC (GF254 silica gel: hexane/Et_2O = 5/1); 95% ee as determined by HPLC [Daicel Chiralpak IA, hexane/IPA = 90/10, 1.0 mL·min^{-1}, λ = 220 nm, tr (major) = 9.19 min, tr (minor) = 13.89 min]; $[\alpha]_D^{25}$ +80.2 (c 0.85, $CHCl_3$).

Diethyl 2-(((4-(dimethoxymethyl)pyrimidin-2-yl)amino)(4-methoxyphenyl)methyl)malonate (4b): light-yellow oil; yield 74%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, *J* = 4.9 Hz, 1H), 7.33 (d, *J* = 8.1 Hz, 2H), 6.83 (d, *J* = 8.0 Hz, 2H), 6.75 (d, *J* = 4.9 Hz, 1H), 6.57 (d, *J* = 9.5 Hz, 1H), 6.01-5.97 (m, 1H), 5.06 (s, 1H), 4.15-4.08 (m, 4H), 3.95 (d, *J* = 5.9 Hz, 1H), 3.76 (s, 3H), 3.38 (s, 3H), 3.33 (s, 3H), 1.16-1.10 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.90, 167.14, 166.02, 161.52, 158.90, 158.74, 131.91, 127.91, 113.82, 108.14, 61.72, 61.52, 57.54, 55.24, 53.68, 53.31, 14.21, 13.93, 13.89; IR (KBr): *ν*3225, 3005, 2953, 2923, 1621, 1586, 1497, 1451, 1363, 1234, 1031, 760 cm^{-1}; Anal. Calcd for $C_{22}H_{29}N_3O_7$: C, 59.05; H, 6.53; N, 9.39. Found: C, 59.11; H, 6.47; N, 9.42. HR-MS (ESI$^+$) *m*/*z* Calcd for $C_{22}H_{29}N_3O_7$ [M +

H]$^+$448.2087; found 448.2078.

(−)-Diethyl 2-(((4-(dimethoxymethyl)pyrimidin-2-yl)amino)(4-methoxyphenyl)methyl)malonate (−)-(4b): This product was obtained as a light-yellow oil from a reaction catalyzed by **A1** (20 mol%) at 50 °C for 48 h; yield 93% by preparative TLC (GF254 silica gel: hexane/Et_2O = 5/1); 95% ee as determined by HPLC [Daicel Chiralpak IA, hexane/IPA = 90/10, 1.0 mL·min^{-1}, λ = 220 nm, tr (major) = 14.78 min, tr (minor) = 9.45 min]; $[\alpha]_D^{25}$ −77.6 (c 1.10, $CHCl_3$).

(+)-Diethyl 2-(((4-(dimethoxymethyl)pyrimidin-2-yl)amino)(4-methoxyphenyl)methyl)malonate (+)-(4b): This product was obtained as a light-yellow oil from a reaction catalyzed by **A5** (20 mol%) at 50 °C for 48 h; yield 88% by preparative TLC (GF254 silica gel: hexane/Et_2O = 5/1); 93% ee as determined by HPLC [Daicel Chiralpak IA, hexane/IPA = 90/10, 1.0 mL·min^{-1}, λ = 220 nm, tr (major) = 9.49 min, tr (minor) = 14.85 min]; $[\alpha]_D^{25}$ +81.6 (c 0.99, $CHCl_3$).

Diethyl 2-(cyclohexyl((4-(dimethoxymethyl)pyrimidin-2-yl)amino)methyl)malonate (4c): light-yellow oil; yield 72%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (s, 1H), 6.70 (d, *J* = 4.8 Hz, 1H), 6.06 (s, 1H), 5.06 (s, 1H), 4.76 (s, 1H), 4.24-4.21 (m, 2H), 4.05 (d, *J* = 10.4 Hz, 2H), 3.78 (d, *J* = 4.6 Hz, 1H), 3.38 (d, *J* = 5.2 Hz, 6H), 2.05 (s, 1H), 1.85-1.56 (m, 6H), 1.24 (s, 4H), 1.10-1.06(m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.47, 168.28, 165.89, 162.51, 158.28, 107.40, 102.85, 61.45, 61.29, 54.72, 53.63, 53.25, 41.65, 30.19, 29.35, 26.11, 26.02, 25.92, 14.02, 13.80. IR (KBr): *v*3203, 3003, 2983, 2912, 1651, 1544, 1493, 1251, 1230, 1172, 1094, 826 cm^{-1}; Anal. Calcd for $C_{21}H_{33}N_3O_6$: C, 59.56; H, 7.85; N, 9.92. Found: C, 59.50; H, 7.89; N, 9.96. HR-MS (ESI$^+$) *m/z* Calcd for $C_{21}H_{33}N_3O_6$ [M + H]$^+$ 424.2442; found 424.2441.

(−)-Diethyl 2-(cyclohexyl((4-(dimethoxymethyl)pyrimidin-2-yl)amino)methyl)malonate (−)-(4c): This product was obtained as a light-yellow oil from a reaction catalyzed by **A1** (20 mol%) at 50 °C for 60 h; yield 92% by preparative TLC (GF254 silica gel: hexane/Et_2O = 5/1); 93% ee as determined by HPLC [Daicel Chiralpak IA, hexane/IPA = 90/10, 1.0 mL·min^{-1}, λ = 220 nm, tr (major) = 9.78 min, tr (minor) = 7.04 min]; $[\alpha]_D^{25}$ −103.1 (c 0.81, $CHCl_3$).

(+)-Diethyl 2-(cyclohexyl((4-(dimethoxymethyl)pyrimidin-2-yl)amino)methyl)malonate (+)-(4c): This product was obtained as a light-yellow oil from a reaction catalyzed by **A5** (20 mol%) at 50 °C for 60 h; yield 93% by preparative TLC (GF254 silica gel: hexane/Et_2O = 5/1); 97% ee as determined by HPLC [Daicel Chiralpak IA, hexane/IPA = 90/10, 1.0 mL·min^{-1}, λ = 220 nm, tr (major) = 6.91 min, tr (minor) = 9.84 min]; $[\alpha]_D^{25}$ +52.6 (c 0.43, $CHCl_3$).

Dimethyl 2-(((4-(dimethoxymethyl)pyrimidin-2-yl)amino)(phenyl)methyl)malonate (4d): light-yellow oil; yield 75%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, *J* = 5.0 Hz, 1H), 7.40 (d, *J* = 7.7 Hz, 2H), 7.30 (t, *J* = 7.4 Hz, 2H), 7.22 (t, *J* = 7.2 Hz, 1H), 6.76 (d, *J* = 5.0 Hz, 1H), 6.69 (d, *J* = 9.5 Hz, 1H), 6.06 (dd, *J* = 9.5, 5.9 Hz, 1H), 5.06 (s, 1H), 4.01 (d, *J* = 5.8 Hz, 1H), 3.65 (s, 6H), 3.32 (d, *J* = 26.5 Hz,

6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.18, 167.45, 166.10, 161.45, 158.69, 139.71, 128.52, 127.59, 126.65, 108.29, 102.98, 57.14, 53.90, 53.69, 52.73, 52.53; IR (KBr): *v*3226, 3002, 2953, 2927, 1654, 1581, 1527, 1494, 1365, 1243, 1026, 750 cm^{-1}; Anal. Calcd for $C_{19}H_{23}N_3O_6$: C, 58.60; H, 5.95; N, 10.79. Found: C, 58.65; H, 5.91; N, 10.74. HR-MS (ESI^+) *m*/*z* Calcd for $C_{19}H_{23}N_3O_6$ $[M + H]^+$390.1660; found 390.1671.

(−)-Dimethyl 2-(((4-(dimethoxymethyl)pyrimidin-2-yl)amino)(phenyl)methyl)malonate (−)-(4d): This product was obtained as a light-yellow oil from a reaction catalyzed by **A1** (20 mol%) at 50 °C for 48 h; yield 85% by preparative TLC (GF254 silica gel: hexane/Et_2O = 5/1); 93% ee as determined by HPLC [Daicel Chiralpak IA, hexane/IPA = 90/10, 1.0 mL·min^{-1}, λ = 220 nm, tr (major) = 14.39 min, tr (minor) = 10.71 min]; $[\alpha]_D^{25}$ −35.6 (c 0.69, $CHCl_3$).

(+)-Dimethyl 2-(((4-(dimethoxymethyl)pyrimidin-2-yl)amino)(phenyl)methyl)malonate (+)-(4d): This product was obtained as a light-yellow oil from a reaction catalyzed by **A5** (20 mol%) at 50 °C for 48 h; yield 90% by preparative TLC (GF254 silica gel: hexane/Et_2O = 5/1); 97% ee as determined by HPLC [Daicel Chiralpak IA, hexane/IPA = 90/10, 1.0 mL·min^{-1}, λ = 220 nm, tr (major) = 10.59 min, tr (minor) = 14.36 min]; $[\alpha]_D^{25}$ +52.6 (c 0.82, $CHCl_3$).

Dimethyl 2-((4-chlorophenyl)((4-(dimethoxymethyl)pyrimidin-2-yl)amino)methyl)malonate (4e): light-yellow oil; yield 71%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, *J* = 5.0 Hz, 1H), 7.35 (d, *J* = 8.3 Hz, 2H), 7.28 (d, *J* = 8.1 Hz, 2H), 6.78 (d, *J* = 5.0 Hz, 1H), 6.68 (d, *J* = 9.3 Hz, 1H), 5.99 (dd, *J* = 9.3, 5.8 Hz, 1H), 5.06 (s, 1H), 3.97 (d, *J* = 5.6 Hz, 1H), 3.66 (s, 6H), 3.39 (d, *J* = 23.8 Hz, 6H).^{13}C NMR (100 MHz, $CDCl_3$) δ 168.03, 167.24, 166.17, 161.26, 158.69, 138.34, 133.41, 128.69, 128.17, 108.55, 102.87, 56.88, 53.67, 53.44, 52.85, 52.66. IR (KBr): *v* 3223, 3006, 2952, 2929, 1623, 1587, 1494, 1455, 1360, 1235, 1035, 768 cm^{-1}; Anal. Calcd for $C_{19}H_{22}ClN_3O_6$: C, 53.84; H, 5.23; N, 9.91. Found: C, 53.80; H, 5.19; N, 9.86. HR-MS (ESI^+) *m*/*z* Calcd for $C_{19}H_{22}ClN_3O_6$ $[M + H]^+$ 424.1270; found 424.1270.

(−)-Dimethyl 2-((4-chlorophenyl)((4-(dimethoxymethyl)pyrimidin-2-yl)amino)methyl)malonate (−)-(4e): This product was obtained as a light-yellow oil from a reaction catalyzed by **A1** (20 mol%) at 50 °C for 48 h; yield 82% by preparative TLC (GF254 silica gel: hexane/Et_2O = 5/1); 93% ee as determined by HPLC [Daicel Chiralpak IA, hexane/IPA = 90/10, 1.0 mL·min^{-1}, λ = 220 nm, tr (major) = 11.85 min, tr (minor) = 8.48 min]; $[\alpha]_D^{25}$ −80.1 (c 0.62, $CHCl_3$).

(+)-Dimethyl 2-((4-Chlorophenyl)((4-(dimethoxymethyl)pyrimidin-2-yl)amino)methyl)malonate (+)-(4e): This product was obtained as a light-yellow oil from a reaction catalyzed by **A5** (20 mol%) at 50 °C for 48 h; yield 89% by preparative TLC (GF254 silica gel: hexane/Et_2O = 5/1); 95% ee as determined by HPLC [Daicel Chiralpak IA, hexane/IPA = 90/10, 1.0 mL·min^{-1}, λ = 220 nm, tr (major) = 8.42 min, tr (minor) = 11.87 min]; $[\alpha]_D^{25}$ +91.5 (c 0.75, $CHCl_3$).

Dimethyl 2-(((4-(dimethoxymethyl)pyrimidin-2-yl)amino)(*p*-tolyl)methyl)malonate (4f): light-yellow

oil; yield 77%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, *J* = 4.9 Hz, 1H), 7.28 (d, *J* = 7.6 Hz, 2H), 7.11 (d, *J* = 7.7 Hz, 2H), 6.75 (d, *J* = 5.0 Hz, 1H), 6.65 (d, *J* = 9.6 Hz, 1H), 6.01 (dd, *J* = 9.5, 5.9 Hz, 1H), 5.06 (s, 1H), 3.99 (d, *J* = 5.8 Hz, 1H), 3.65 (s, 6H), 3.38 (d, *J* = 19.8 Hz, 6H), 2.29 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.23, 167.50, 166.08, 161.45, 158.66, 137.23, 136.68, 129.22, 126.54, 108.21, 57.20, 53.73, 53.65, 52.70, 52.51, 21.05. IR (KBr): *ν*3205, 3001, 2982, 2915, 1657, 1548, 1499, 1255, 1233, 1171, 1090, 825 cm^{-1}; Anal. Calcd for $C_{20}H_{25}N_3O_6$: C, 59.54; H, 6.25; N, 10.42. Found: C, 59.50; H, 6.21; N, 10.46. HR-MS (ESI$^+$) *m*/*z* Calcd for $C_{20}H_{25}N_3O_6$ $[M + H]^+$ 404.1816; found 404.1817.

(−)-Dimethyl 2-(((4-(dimethoxymethyl)pyrimidin-2-yl)amino)(p-tolyl)methyl)malonate (−)-(4f): This product was obtained as light-yellow oil from a reaction catalyzed by A1 (20 mol%) at 50 °C for 60 h; yield 81% by preparative TLC (GF254 silica gel: hexane/Et_2O = 5/1); 96% ee as determined by HPLC [Daicel Chiralpak IA, hexane/IPA = 90/10, 1.0 mL·min^{-1}, λ = 220 nm, tr (major) = 11.02 min, tr (minor) = 7.72 min]; $[\alpha]_D^{25}$ −78.3 (c 1.05, $CHCl_3$).

(+)-Dimethyl 2-(((4-(dimethoxymethyl)pyrimidin-2-yl)amino)(p-tolyl)methyl)malonate (+)-(4f): This product was obtained as a light-yellow oil from a reaction catalyzed by A5 (20 mol%) at 50 °C for 60 h; yield 87% by preparative TLC (GF254 silica gel: hexane/Et_2O = 5/1); 95% ee as determined by HPLC [Daicel Chiralpak IA, hexane/IPA = 90/10, 1.0 mL·min^{-1}, λ = 220 nm, tr (major) = 7.63 min, tr (minor) = 10.93 min]; $[\alpha]_D^{25}$ +41.8 (c 0.56, $CHCl_3$).

Dimethyl 2-(cyclohexyl((4-(dimethoxymethyl)pyrimidin-2-yl)amino)methyl)malonate (4g): light-yellow oil; yield 76%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (s, 1H), 6.71 (d, *J* = 4.3 Hz, 1H), 6.03 (s, 1H), 5.07 (s, 1H), 4.76 (s, 1H), 3.82 (d, *J* = 3.7 Hz, 1H), 3.75 (s, 3H), 3.58 (s, 3H), 3.40 (s, 6H), 2.05 (s, 1H), 1.85-1.55 (m, 6H), 1.20-1.01(m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.60, 165.92, 162.47, 158.33, 107.50, 102.77, 54.81, 53.69, 52.86, 52.37, 52.35, 41.47, 30.16, 29.32, 26.07, 25.97, 25.86; IR (KBr): *ν*3223, 3002, 2958, 2921, 1658, 1584, 1529, 1491, 1364, 1243, 1023, 753cm^{-1}; Anal. Calcd for $C_{19}H_{29}N_3O_6$: C, 57.71; H, 7.39; N, 10.63. Found: C, 57.76; H, 7.35; N, 10.61; HR-MS (ESI$^+$) *m*/*z* Calcd for $C_{19}H_{29}N_3O_6$ $[M + H]^+$ 396.2129; found 396.2131.

(−)-Dimethyl 2-(cyclohexyl((4-(dimethoxymethyl)pyrimidin-2-yl)amino)methyl)malonate (−)-(4g): This product was obtained as light-yellow oil from a reaction catalyzed by A1 (20 mol%) at 50 °C for 60 h; yield 80% by preparative TLC (GF254 silica gel: hexane/Et_2O = 5/1); 91% ee as determined by HPLC [Daicel Chiralpak IA, hexane/IPA = 90/10, 1.0 mL·min^{-1}, λ = 220 nm, tr (major) = 10.92 min, tr (minor) = 7.27 min]; $[\alpha]_D^{25}$ −41.7 (c 0.77, $CHCl_3$).

(+)-Dimethyl 2-(cyclohexyl((4-(dimethoxymethyl)pyrimidin-2-yl)amino)methyl)malonate (+)-(4g): This product was obtained as a light-yellow oil from a reaction catalyzed by A5 (20 mol%) at 50 °C for 60 h; yield 84% by preparative TLC (GF254 silica gel: hexane/Et_2O = 5/1); 94% ee as determined by HPLC [Daicel Chiralpak IA, hexane/IPA = 90/10, 1.0 mL·min^{-1}, λ = 220 nm, tr (major) = 7.40 min, tr

(minor) = 10.98 min]; $[\alpha]_D^{25}$ −63.5 (c 0.96, $CHCl_3$).

Dimethyl 2-(((4-(dimethoxymethyl)pyrimidin-2-yl)amino)(furan-2-yl)methyl)malonate (4h): light-yellow oil; yield 79%; ^{1}H NMR (400 MHz, CDCl3) δ 8.35 (d, *J* = 4.8 Hz, 1H), 7.27 (d, *J* = 18.1 Hz, 1H), 6.82 (d, *J* = 4.9 Hz, 1H), 6.40 (d, *J* = 9.7 Hz, 1H), 6.27 (d, *J* = 6.3 Hz, 2H), 6.16 (d, *J* = 9.9 Hz, 1H), 5.09 (s, 1H), 4.15 (d, *J* = 5.4 Hz, 1H), 3.67 (d, *J* = 18.0 Hz, 6H), 3.39 (d, *J* = 6.6 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.00, 167.25, 166.25, 161.31, 158.70, 152.42, 142.06, 110.42, 108.62, 106.99, 54.52, 53.80, 52.77, 52.65, 48.56. IR (KBr): *v*3228, 3002, 2953, 2924, 1622, 1587, 1495, 1458, 1362, 1232, 1030, 765 cm^{-1}; Anal. Calcd for $C_{17}H_{21}N_3O_7$: C, 53.82; H, 5.58; N, 11.08. Found: C, 53.85; H, 5.57; N, 11.11. HR-MS (ESI^+) *m*/*z* Calcd for $C_{17}H_{21}N_3O_7$ $[M + H]^+$ 380.1452; found 380.1451.

(−)-Dimethyl 2-(((4-(dimethoxymethyl)pyrimidin-2-yl)amino)(furan-2-yl)methyl)malonate (−)-(4h): This product was obtained as a light-yellow oil from a reaction catalyzed by A1 (20 mol%) at 50 °C for 60 h; yield 94% by preparative TLC (GF254 silica gel: hexane/Et_2O = 5/1); >99% ee as determined by HPLC [Daicel Chiralpak IA, hexane/IPA = 90/10, 1.0 mL·min^{-1}, λ = 220 nm, tr (major) = 15.00 min, tr (minor) = 9.54 min]; $[\alpha]_D^{25}$ −80.1 (c 0.60, $CHCl_3$).

(+)-Dimethyl 2-(((4-(dimethoxymethyl)pyrimidin-2-yl)amino)(furan-2-yl)methyl)malonate (+)-(4h): This product was obtained as a light-yellow oil from a reaction catalyzed by A5 (20 mol%) at 50 °C for 60 h; yield 92% by preparative TLC (GF254 silica gel: hexane/Et_2O = 5/1); 98% ee as determined by HPLC [Daicel Chiralpak IA, hexane/IPA = 90/10, 1.0 mL·min^{-1}, λ = 220 nm, tr (major) = 9.54 min, tr (minor) = 15.01 min]; $[\alpha]_D^{25}$ +107.2 (c 0.89, $CHCl_3$).

Diethyl 2-(((6-chloropyrimidin-4-yl)amino)(4-methoxyphenyl)methyl)malonate (4i): light-yellow oil; yield 78%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (s, 1H), 7.25 (d, *J* = 8.7 Hz, 2H), 6.84 (s, 2H), 6.41 (s, 1H), 4.14 (ddtd, *J* = 14.3, 10.8, 7.3, 3.5 Hz, 4H), 3.91 (d, *J* = 4.9 Hz, 1H), 3.78 (s, 3H), 1.17 (td, *J* = 7.1, 5.3 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.78, 162.58, 159.31, 158.46, 127.57, 114.21, 62.13, 61.90, 56.95, 55.26, 13.90; IR (KBr): *v*3210, 2998, 2924, 2901, 1647, 1572, 1481, 1443, 1357, 1240, 1022, 794 cm^{-1}; Anal. Calcd for $C_{19}H_{22}ClN_3O_5$: C, 55.95; H, 5.44; N, 10.30. Found: C, 55.93; H, 5.42; N, 10.31. MS(ESI): *m*/*z* = 408 ($[M+H]^+$), 430 ($[M+Na]^+$).

(−)-Diethyl 2-(((6-chloropyrimidin-4-yl)amino)(4-methoxyphenyl)methyl)malonate (−)-(4i): This product was obtained as a light-yellow oil from a reaction catalyzed by A1 (20 mol%) at 50 °C for 48 h; yield 91% by preparative TLC (GF254 silica gel: hexane/Et_2O = 5/1); 99% ee as determined by HPLC [Daicel Chiralpak IA, hexane/IPA = 90/10, 1.0 mL·min^{-1}, λ = 220 nm, tr (major) = 15.67 min, tr (minor) = 9.57 min]; $[\alpha]_D^{25}$ −36.2 (c 0.55, $CHCl_3$).

(+)-Diethyl 2-(((6-chloropyrimidin-4-yl)amino)(4-methoxyphenyl)methyl)malonate (+)-(4i): This product was obtained as a light-yellow oil from a reaction catalyzed by A5 (20 mol%) at 50 °C for 48 h; yield 93% by preparative TLC (GF254 silica gel: hexane/Et_2O = 5/1); 99% ee as determined by HPLC

[Daicel Chiralpak IA, hexane/IPA = 90/10, 1.0 mL · min^{-1}, λ = 220 nm, tr (major) = 9.55 min, tr (minor) = 15.77 min]; $[\alpha]_D^{25}$ +40.3 (c 0.48, $CHCl_3$).

ACKNOWLEDGEMENTS

We are grateful for financial support from the National Natural Science Foundation of China (Gran No. 21602039), the Natural Science Foundation of Guizhou Province (Gran No. Qian Ke He Ji Chu[2017]1066), the Opening Foundation of the Key Laboratory of Green Pesticide and Agricultural Bioengineering, the Ministry of Education, Guizhou University (Grant No. 2016GDGP0103), The Research Center for Microreaction Engineering of Guizhou Colleges and Universities (Grant No. Qian Jiao He KY Zi[2015]339), and the Academic Sprout Cultivation and Exploring Innovation Project of Guizhou Institute of Technology (Grant No. Qian Ke He Ping Tai Ren Cai [2017]5789-06).

REFERENCES AND NOTES

1. For reviews on asymmetric Mannich reactions, see: (a) A. Ting and S. E. Schaus, *Eur. J. Org. Chem.*, 2007, 5797; (b) J. M. M. Verkade, L. J. C. van Hemert, P. J. L. M. Quaedflieg, and F. P. J. T. Rutjes, *Chem. Soc. Rev.*, 2008, **37**, 29.
2. For reviews on synthesis of *β*-amino acids, see: (a) J.-A. Ma, *Angew. Chem. Int. Ed.*, 2003, **42**, 4290; (b) B. Weiner, W. Szymański, D. B. Janssen, A. J. Minnaard, and B. L. Feringa, *Chem. Soc. Rev.*, 2010, **39**, 1656; (c) S. M. Kim and J. W. Yang, *Org. Biomol. Chem.*, 2013, **11**, 4737.
3. Y. Jing, G. Wang, Y. Ge, M. Xu, and Z. Gong, *Molecules*, 2015, **20**, 7309.
4. D. Sriram, P. Yogeeswari, N. Srichakravarthy, and T. R. Bal, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 1085.
5. H. Xiao, P. Li, D. Y. Hu, and B.-A. Song, *Bioorg. Med. Chem. Lett.*, 2014, **24**, 3452.
6. I. P. Singh, S. K. Jain, A. Kaur, S. Singh, R. Kumar, P. Garg, S. S. Sharma, and S. K. Arora, *Eur. J. Med. Chem.*, 2010, **45**, 3439.
7. (a) Y. You, L. Zhang, L. Cui, X. Mi, and S. Luo, *Angew. Chem. Int. Ed.*, 2017, **56**, 13814; (b) P. Chauhan, S. Mahajan, U. Kaya, A. Peuronen, K. Rissanen, and D. Enders, *J. Org. Chem.*, 2017, **82**, 7050; (c) C.-M. Jia, H.-X. Zhang, J. Nie, and J.-A. Ma, *J. Org. Chem.*, 2016, **81**, 8561; (d) B.-A. Song, S. Yang, and P. S. Bhadury, *Curr. Org. Synth.*, 2012, **9**, 695; (e) R. D. Momo, F. Fini, L. Bernardi, and A. Ricci, *Adv. Synth. Catal.*, 2009, **351**, 2283; (f) D. Uraguchi and M. Terada, *J. Am. Chem. Soc.*, 2004, **126**, 5356; (g) A. G. Wenzel and E. N. Jacobsen, *J. Am. Chem. Soc.*, 2002, **124**, 12964; (h) B. List, P. Pojarliev, W. T. Biller, and H. J. Martin, *J. Am. Chem. Soc.*, 2002, **124**, 827.
8. (a) L. Li, B. A. Song, P. S. Bhadury, Y. P. Zhang, D. Y. Hu, and S. Yang, *Eur. J. Org. Chem.*, 2011, 4743; (b) W. H. Li, B. A. Song, P. S. Bhadury, L. Li, Z. Wang, X. Zhang, D. Y. Hu, Z. Chen, Y.

Zhang, S. Bai, J. Wu, and S. Yang, *Chirality*, 2012, **24**, 223.

9. H.-X. He and D.-M. Du, *RSC Adv.*, 2013, **3**, 16349.
10. F. Buron, J. Y. Mérour, M. Akssira, G. Guillaumet, and S. Routier, *Eur. J. Med. Chem.*, 2015, **95**, 76.
11. D. K. Yuan, D. Q. Zhang, R. X. Li, D. Q. Wang, and X. L. Yang, *Chin. Chem. Lett.*, 2011, **22**, 18.
12. (a) W. N. Wu, A. Q. Tai, Q. Chen, and G. P. Ouyang, *J. Heterocycl. Chem.*, 2015, **53**, 2243; (b) W. N. Wu, Q. Chen, A. Q. Tai, G. Q. Jiang, and G. P. Ouyang, *Bioorg. Med. Chem. Lett.*, 2015, **25**, 2243.
13. (a) A. G. Wenzel, M. P. Lalonde, and E. N. Jacobsen, *Synlett*, 2003, 1919; (b) Y. Zhang, Y.-K. Liu, T.-R. Kang, Z.-K. Hu, and Y.-C. Chen, *J. Am. Chem. Soc.*, 2008, **130**, 2456; (c) H. Zhang, Y. Chuan, Z. Li, and Y. Peng, *Adv. Synth. Catal.*, 2010, **351**, 2288; (d) H. Kim, Y. Kim, and S.-G. Kim, *J. Org. Chem.*, 2017, **82**, 8179.
14. (a) J. Song, Y. Wang, and L. Deng, *J. Am. Chem. Soc.*, 2006, **37**, 6048; (b) M. Amere, M. Lasne, and J. Rouden, *Org. Lett.*, 2007, **9**, 2621; (c) F. Li, Y.-Z. Li, Z.-S. Jia, M.-H. Xu, P. Tian, and G.-Q. Lin, *Tetrahedron*, 2011, **67**, 10186; (d) M. Chiarucci, M. Lombardo, C. Trombini, and A. Quintavalla, *Adv. Synth. Catal.*, 2012, **354**, 364; (e) H.-X. He and D.-M. Du, *RSC Adv.*, 2013, **3**, 16349; (f) S. Konda and J. C.-G. Zhao, *Tetrahedron Lett.*, 2014, **55**, 5216; (g) V. Ashokkumar and A. Siva, *Org. Biomol. Chem.*, 2015, **13**, 10216.
15. (a) G. V. Gooding, Jr. and T. T. Hebert, *Phytopathology*, 1967, **57**, 1285; (b) Z. Fan, Z. Shi, H. Zhang, X. Liu, L. Bao, L. Ma, X. Zuo, Q. Zheng, and N. Mi, *J. Agric. Food Chem.*, 2009, **57**, 4279; (c) B. Song, H. Zhang, H. Wang, S. Yang, L. Jin, D. Hu, L. Pang, and W. Xue, *J. Agric. Food Chem.*, 2005, **53**, 7886.
16. (a) B. Vakulya, S. Varga, A. Csámpai, and T. Soós, *Org. Lett.*, 2005, **7**, 1967; (b) S. Bai, X. Liang, B. A. Song, P. S. Bhadury, D. Hu, and S. Yang, *Tetrahedron: Asymmetry*, 2011, **22**, 518.