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SHORT COMMUNICATION

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Highly Enantioselective Biginelli Reaction Catalyzed by Double Axially Chiral Bisphosphorylimides

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Double axially chiral bisphosphorylimides have been used as catalysts in enantioselective Biginelli reactions. The three-component reaction of aromatic aldehydes, thiourea, and ethyl acetoacetate took place by using 5 mol-% catalyst in ethyl acetate at 50 °C. A series of chiral dihydropyrimidinethiones (DHPMs) were obtained in high yields (up to 97 %) with good to high enantioselectivities (up to 96 % *ee*) in only 12 hours.

Introduction

Chiral Brønsted acids that are derived from axially chiral backbones such as BINOL and VAPOL have aroused increasing interest since BINOL-phosphoric acids were initially used in an enantioselective Mannich type reaction in 2004.[1] The work of modifying the structure of BINOL-derived Brønsted acids has been carried out by many groups. In 2006, Yamamoto and co-workers developed a new chiral *N*-triflyl phosphoramide that was successfully used in enantioselective Diels–Alder reactions.[2] Before long, *N*-phosphinyl phosphoramides[3] and *N*-pyridinyl phosphoramides[4] were designed by the group of List. Recently, BINOL-derived double axially chiral bisphosphorylimides have also been recognized as a novel type of Brønsted acid catalyst. In 2012, List and co-workers reported the application of double axially chiral bisphosphorylimides in asymmetric spiroacetalization,[5] sulfoxidation,[6] and acetalization.[7] In the same year, our group also reported the results of our work on double axially chiral bisphosphorylimides catalyzing asymmetric Mannich reaction[8] and Friedel–Crafts reaction.[9]

As one of the most available multicomponent reactions, the Biginelli reaction[10] has attracted considerable attention.[11] It provides an important method for the straightforward synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones and -thiones (DHPMs), which are important components of a range of drugs[12] and natural alkaloids.[13] Accordingly, asymmetric catalytic Biginelli reactions have been the subject of extensive research over the last decades. In 2005, Zhu's group developed a new chiral Ytterbium catalyst and successfully used the catalyst in enantioselective Biginelli reaction for the first time.[14] Not long after, H_8-BINOL-phosphoric acids were first applied in organocatalytic Biginelli reaction by Gong and co-workers.[15] Since then, various organocatalytic enantioselective Biginelli reactions have been reported,[16] including those catalyzed by using primary amines,[16b–16f] proline derivatives,[16g,16h] pyrrolidinyl tetrazole,[16i] and ionic liquids.[16j] However, long reaction times (from two days to a week) are necessary in most of these reported methods. In addition, only a few examples of chiral Brønsted acid catalysts have been reported for the Biginelli reaction.[16k,16l] Herein, we wish to disclose the results of our research on the first double axially chiral bisphosphorylimides catalyzing the enantioselective Biginelli reaction in the asymmetric synthesis of DHPMs.

Results and Discussion

As shown in Scheme 1, catalysts **1a**–**d** were synthesized according to our previous work[8] and screened in the three-component Biginelli reaction of 4-nitrobenzaldehyde (**2a**), thiourea (**3**), and ethyl acetoacetate (**4**; Table 1). The reaction was performed at 25 °C in the presence of 5 mol-% catalyst in toluene. We found that **1a**, with small substituent groups, afforded relative low yield and enantioselectivity (Table 1, entry 1). Moreover, compared with catalysts **1b**–**d**, which afforded *S*-configured product, **1a** provided *R*-configured product in 17 % *ee*.[16k] Upon increasing the size of the substituents on one side of the catalyst (Table 1, entry 2), both the yield and enantioselectivity were significantly improved. Encouraged by this result, catalyst **1c** and **1d**, with 3,3′-1-naphthyl and 3,3′-2-naphthyl substituents, respectively, were subsequently used for the reaction

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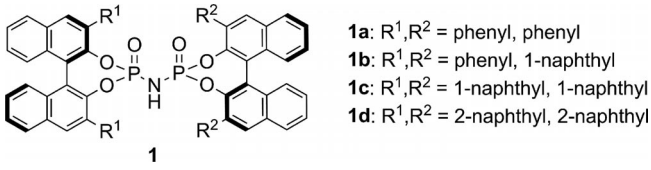
(Table 1, entries 3 and 4). Among the catalysts examined, catalyst **1d** was found to be most effective for the reaction, affording 73% yield and 93%*ee*. Interestingly, in previous work reported by Gong,[15] BINOL-derived phosphoric acids with 3,3′-phenyl substituents turned out to be highly enantioselective. In contrast, phosphoric acids with 3,3′-2-naphthyl substituents proved to have poor catalytic activity. These differences between double axially chiral bisphosphorylimides and phosphoric acids suggest that different reaction mechanisms and steric effects are in operation with the two types of catalysts. The Brønsted acidic site and Brønsted basic site of BINOL-phosphoric acids are linked with the only phosphorus atom, which requires that the two sites are close to each other. Two 3,3′-substituents are far from the active site and give a relatively loose chiral environment. On the other hand, double axially chiral bisphosphorylimides have two phosphorus atoms that link with the Brønsted acidic site and Brønsted basic site separately. The two sites stay away from each other and approach the 3,3′-substituents on each side of catalyst. Moreover, the sur-



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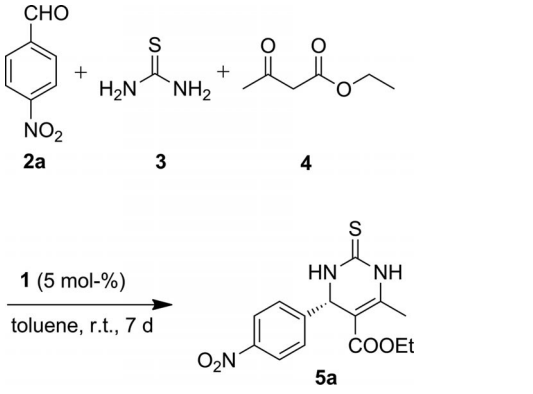
Scheme 1. BINOL- and H_8-BINOL-based chiral bisphosphorylimides.

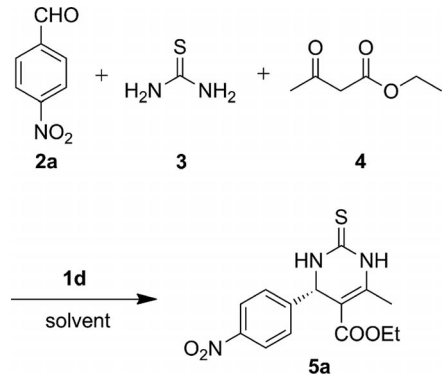
Table 1. Screening of double axially chiral bisphosphorylimides.[a]



Entry	Catalyst	Yield [%][b]	*ee* [%][c]
1	**1a**	19	–17[d]
2	**1b**	62	83
3	**1c**	66	87
4	**1d**	73	93

[a] Reaction conditions: 4-nitrobenzaldehyde (**2a**; 0.1 mmol, 1.0 equiv.), thiourea (**3**; 0.12 mmol, 1.2 equiv.), ethyl acetoacetate (**4**; 0.3 mmol, 3 equiv.), catalyst (**1**; 5 mol-%), toluene (1 mL), 25 °C, 7 d. [b] Isolated yield after flash chromatography. [c] Determined by HPLC analysis by using a chiral column. [d] The *R*-configured product was produced in 17%*ee*. The absolute configuration of **5a** was determined by comparing the retention time of products by HPLC with the published data.[16k]

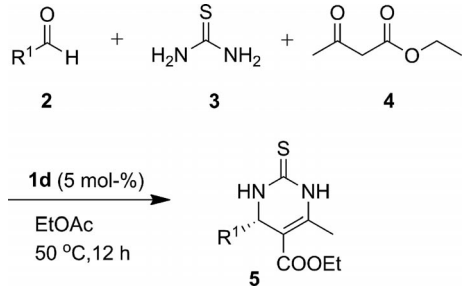
Table 2. Optimization of the reaction conditions with catalyst **1d**.[a]



Entry	**1d** [mol-%]	Solvent	*T* [°C]	*t* [d]	Yield [%][b]	*ee* [%][c]
1	5	toluene	25	7	73	93
2	5	CH_2Cl_2	25	4	75	91
3	5	THF	25	7	–	–
4	5	CH_3CN	25	4	64	73
5	5	EtOAc	25	4	75	95
6	5	$Cl(CH_2)_2Cl$	25	7	57	72
7	5	EtOAc	40	1	82	95
8	5	EtOAc	50	0.5	93	95
9	2	EtOAc	50	1	73	94
10	8	EtOAc	50	0.25	96	95

[a] Reaction conditions: 4-nitrobenzaldehyde (**2a**; 0.1 mmol, 1.0 equiv.), thiourea (**3**; 0.12 mmol, 1.2 equiv.), ethyl acetoacetate (**4**; 0.3 mmol, 3 equiv.), catalyst (**1d**; 5 mol-%), solvent (1 mL). [b] Isolated yield after flash chromatography. [c] Determined by HPLC analysis by using a chiral column.

Table 3. Scope of the enantioselective Biginelli reaction.[a]



Entry	R^1 (**2**)		Product	Yield [%][b]	*ee* [%][c]
1	4-$NO_2C_6H_4$	**2a**	**5a**	93	95
2	2-$NO_2C_6H_4$	**2b**	**5b**	90	95
3	3-BrC_6H_4	**2c**	**5c**	87	93
4	3-FC_6H_4	**2d**	**5d**	94	92
5	2-ClC_6H_4	**2e**	**5e**	89	93
6	3-ClC_6H_4	**2f**	**5f**	93	91
7	2-BrC_6H_4	**2g**	**5g**	83	93
8	4-BrC_6H_4	**2h**	**5h**	92	90
9	2-MeC_6H_4	**2i**	**5i**	88	90
10	2-FC_6H_4	**2j**	**5j**	94	90
11	4-CNC_6H_4	**2k**	**5k**	97	93
12	4-$CF_3C_6H_4$	**2l**	**5l**	92	93
13	2,4-$Cl_2C_6H_3$	**2m**	**5m**	95	96

[a] Reaction conditions: benzaldehyde derivative (**2**; 0.1 mmol, 1.0 equiv.), thiourea (**3**; 0.12 mmol, 1.2 equiv.), ethyl acetoacetate (**4**; 0.3 mmol, 3 equiv.), catalyst (**1d**; 5 mol-%), ethyl acetate (1 mL), 50 °C, 12 h. [b] Isolated yield after flash chromatography. [c] Determined by HPLC analysis by using a chiral column.

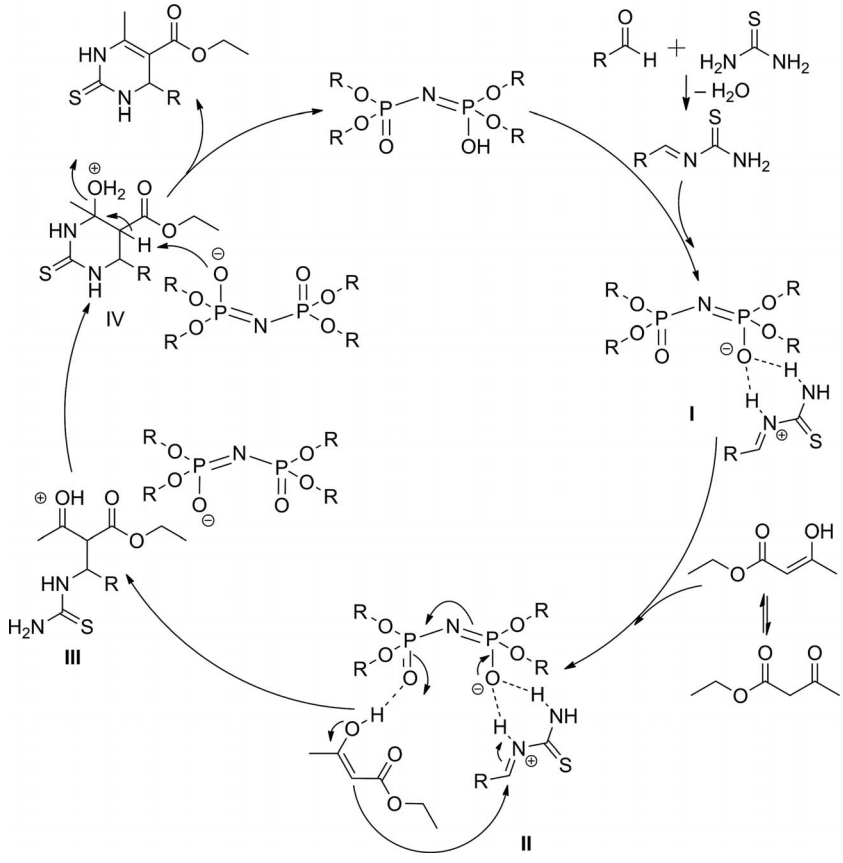
rounding two pairs of 3,3′-substituents further define the chiral environment and create an interlocking system.

Having identified **1d** as the optimal catalyst, we studied the solvent effects on this reaction. As summarized in Table 2, good to high *ee* values of 72 to 95% were obtained in all solvents except tetrahydrofuran (Table 2, entries 1–6). As the best solvent, ethyl acetate afforded 75% yield and 95% enantiomeric excess (Table 2, entry 5). In addition, temperature and catalyst loading were also surveyed (Table 2, entries 7–10). To our surprise, performing the reaction at 50 °C with 5 mol-% **1d** led to complete conversion in just 12 hours (Table 2, entry 8). Furthermore, the yield improved to 93% and the enantioselectivity hardly changed despite the temperature increase from 25 to 50 °C. We then reduced the catalyst loading of **1d** to 2 mol-% (Table 2, entry 9), but found a drop in both the yield and enantioselectivity. Increasing the catalyst loading did not show a clear improvement in the catalytic performance (Table 2, entry 10). By screening a series of reaction conditions, operating with 5 mol-% **1d** in ethyl acetate at 50 °C was found to be the most favorable.

With the optimal conditions established, the Biginelli reactions of a variety of aromatic aldehydes with thiourea and ethyl acetoacetate were investigated with catalyst **1d**. As can be seen in Table 3, the reaction afforded DHPMs in high yields (83–97%) with excellent enantioselectivities (90–96%*ee*). Substrates with *ortho*-, *meta*- or *para*-substituents on the phenyl ring gave products with similar yields. However, the electronic nature of the substituents of the phenyl ring played an important role in controlling the enantioselectivity. Most aromatic aldehydes with electron-withdrawing groups on the phenyl ring led to reactions with higher enantioselectivities. For example, the use of *ortho*- and *para*-nitro-substituted benzaldehydes **2a** and **2b** resulted in excellent enantioselectivities (95%*ee*; Table 3, entries 1 and 2). Other electron-withdrawing aromatic aldehydes also underwent the reaction with 90–93%*ee* (Table 3, entries 3–8 and 10–12). Furthermore, substrate **2m**, with two electron-withdrawing groups, afforded the highest enantioselectivity (96%*ee*; Table 3, entry 12). In contrast, electron-rich 2-methylbenzaldehyde (**2i**) underwent the reaction with relatively low enantioselectivity (90%ee; Table 3, entry 9).

Biginelli reactions of urea with aromatic aldehydes and ethyl acetoacetate were also tested on the basis of the optimal conditions and with adjusted reaction conditions (solvent, temperature and feed ratio), but the corresponding products were not obtained.

Base on relevant reports,[5,11d,16k] a plausible reaction mechanism is shown in Scheme 2. Initially, the dehydration condensation of aldehyde with thiourea produces the corresponding imine, which interacts with chiral bisphosphorylimide through a dual H-bond to the imine to give intermediate **I**. Subsequently, the enol form of ethyl acetoacetate is



Scheme 2. A plausible reaction mechanism for the Biginelli reaction catalyzed by double axially chiral bisphosphorylimides.

activated by a second P=O bond to form intermediate **II**. The ethyl acetoacetate then attacked the imine to give chiral intermediate **III**. Intramolecular cyclization takes place through attack of the amino group on the C=O bond close to the methyl group. Finally, intermediate **IV** is converted into the product through dehydration, which also releases the chiral bisphosphorylimide.

Conclusions

Double axially chiral bisphosphorylimides have been shown to be effective for the enantioselective Biginelli reaction. Under the optimal reaction conditions, a variety of chiral DHPMs were obtained in good yields (up to 97%) with excellent enantioselectivities (up to 96%) in only 12 hours. Further exploration of the catalytic mechanism and applications of the novel bisphosphorylimides in asymmetric catalysis are in progress in our laboratory.

Experimental Section

General Remarks: All reagents were used without purification. All solvents were purified and dried according to standard methods. The reaction products were purified by flash column chromatography on 200–300 mesh silica gel. Optical rotations were measured with a Jasco-P-2000 digital polarimeter at 25 °C and concentrations (c) are given in g×(100 mL)$^{-1}$. ^{1}H and ^{13}C NMR spectra were recorded with Bruker 300 MHz spectrometers (300 MHz for ^{1}H NMR, 75 MHz for ^{13}C NMR); chemical shifts (δ) are given in ppm. Enantiomeric excess values were measured by analytical HPLC with Daicel ChiralPak AD-H, Daicel ChiralPak AS-H or Daicel Chiralcel OD-H columns.

Synthesis of Catalyst 1d: The catalyst **1d** was prepared according to our previous work.[8]

Compound (*R*,*R*)-1d: White solid; m.p. 252–253 °C; $[\alpha]_D^{25}$ = –416.0 (c = 0.5, THF). ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 8.28 (d, J = 5.4 Hz, 4 H), 8.17–8.15 (m, 2 H), 8.02–8.00 (d, J = 7.8 Hz, 2 H), 7.86–7.75 (m, 7 H), 7.65–7.30 (m, 26 H), 7.21–7.14 (m, 4 H), 7.07–7.04 (d, J = 8.7 Hz, 2 H), 7.00–6.95 (t, J = 7.5 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 145.34, 145.20, 134.61, 134.29, 134.10, 133.63, 132.97, 132.64, 132.31, 131.84, 131.39, 131.30, 130.65, 130.30, 128.76, 128.62, 128.38, 128.15, 127.97, 127.70, 127.08, 126.85, 126.55, 126.31, 125.76, 125.54, 123.45, 122.59 ppm. HRMS (ESI): calcd. for $C_{80}H_{50}NO_6P_2^+$ [M + H]$^+$ 1182.3108; found 1182.3108.

General Procedure for the Organocatalytic Biginelli Reaction: A solution of aldehyde (0.1 mmol), thiourea (0.12 mmol), and catalyst (5 mol-%, 0.005 mmol) in EtOAc (1 mL) was stirred at 25 °C for 2 h, then ethyl acetoacetate (0.3 mmol) was added. The reaction mixture was stirred at 50 °C for 12 h (reaction progress monitored by TLC). EtOAc and silica gel were added and, after removal of the solvent, the residue was purified by flash column chromatography on silica gel (ethyl acetate/petroleum ether, 1:5 to 1:2) to afford the pure products.

(*S*)-Ethyl 6-Methyl-4-(4-nitrophenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (5a): Yield 0.0298 g (93%); 95%*ee* [HPLC with a Daicel Chiralpak AS-H; *n*-hexane/2-propanol, 70:30; flow rate: 1.0 mL/min; λ = 254 nm; t_R = 18.08 (minor), 22.48 (major) min]; $[\alpha]_D^{25}$ = +202.1 (c = 0.5, EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.20 (d, J = 9.0 Hz, 2 H), 8.02 (s, 1 H), 7.59 (s, 1 H), 7.48 (d, J = 8.7 Hz, 2 H), 5.52 (d, J = 3.0 Hz, 1 H), 4.13 (q, J = 6.8 Hz, 2 H), 2.39 (s, 3 H), 1.21 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 174.9, 165.3, 150.9, 147.4, 146.4, 128.3, 124.5, 100.2, 60.2, 54.2, 17.7, 14.5 ppm.

(*S*)-Ethyl 6-Methyl-4-(2-nitrophenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (5b): Yield 0.0288 g (90%); 95%*ee* [HPLC with a Daicel Chiralpak AD-H; *n*-hexane/2-propanol, 90:10; flow rate: 1.0 mL/min; λ = 254 nm; t_R = 19.58 (major), 29.68 (minor) min]; $[\alpha]_D^{25}$ = +242.1 (c = 0.5, EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.12 (s, 1 H), 7.93 (d, J = 8.1 Hz, 1 H), 7.65 (t, J = 7.1 Hz, 1 H), 7.52 (s, 1 H), 7.48 (t, J = 8.4 Hz, 2 H), 5.85 (d, J = 2.7 Hz, 1 H), 3.99–3.91 (m, 2 H), 2.49 (s, 3 H), 0.96 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 174.6, 165.0, 147.8, 146.3, 138.6, 134.7, 130.0, 129.6, 124.7, 100.3, 60.0, 49.7, 17.6, 14.2 ppm.

(*S*)-Ethyl 6-Methyl-4-(3-bromophenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (5c): Yield 0.0307 g (87%); 93%*ee* [HPLC with a Daicel Chiralpak AS-H; *n*-hexane/2-propanol, 70:30; flow rate: 1.0 mL/min; λ = 254 nm; t_R = 9.60 (minor), 12.42 (major) min]; $[\alpha]_D^{25}$ = +87.3 (c = 0.5, EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.91 (s, 1 H), 7.44–7.41 (m, 2 H), 7.39 (s, 1 H), 7.23 (t, J = 7.4 Hz, 2 H), 5.38 (s, 1 H), 4.16–4.07 (m, 2 H), 2.38 (s, 3 H), 1.20 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 174.8, 165.4, 146.5, 146.1, 131.5, 131.1, 129.8, 125.9, 122.2, 100.6, 60.2, 54.1, 17.7, 14.5 ppm.

(*S*)-Ethyl 6-Methyl-4-(3-fluorophenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (5d): Yield 0.0277 g (94%); 92%*ee*; [HPLC with a Daicel Chiralpak AD-H; *n*-hexane/2-propanol, 80:20; flow rate: 1.0 mL/min; λ = 254 nm; t_R = 9.23 (major), 10.23 (minor) min]; $[\alpha]_D^{25}$ = +61.7 (c = 0.5, EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.87 (s, 1 H), 7.34–7.27 (m, 2 H), 7.09 (d, J = 8.1 Hz, 1 H), 6.99 (t, J = 8.0 Hz, 2 H), 5.41 (d, J = 2.7 Hz, 1 H), 4.17–4.06 (m, 2 H), 2.38 (s, 3 H), 1.19 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 174.9, 165.5, 161.0, 146.7, 146.0, 131.2, 122.9, 115.1, 113.7, 100.7, 60.2, 54.0, 17.7, 14.5 ppm.

(*R*)-Ethyl 6-Methyl-4-(2-chlorophenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (5e): Yield 0.0276 g (89%); 93%*ee* [HPLC with a Daicel Chiralpak AS-H; *n*-hexane/2-propanol, 80:20; flow rate: 1.0 mL/min; λ = 254 nm; t_R = 12.97 (minor), 17.83 (major) min]; $[\alpha]_D^{25}$ = +52.9 (c = 0.5, EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.98 (s, 1 H), 7.40–7.37 (m, 1 H), 7.26–7.22 (m, 4 H), 5.90 (d, J = 2.4 Hz, 1 H), 4.03 (q, J = 7.0 Hz, 2 H), 2.46 (s, 3 H), 1.06 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.0, 164.8, 144.6, 138.5, 132.5, 129.8, 129.6, 128.5, 127.6, 100.7, 60.3, 52.6, 17.8, 13.8 ppm.

(*S*)-Ethyl 6-Methyl-4-(3-chlorophenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (5f): Yield 0.0289 g (93%); 91%*ee* [HPLC with a Daicel Chiralpak AS-H; *n*-hexane/2-propanol, 70:30; flow rate: 1.0 mL/min; λ = 254 nm; t_R = 10.38 (minor), 13.53 (major) min; $[\alpha]_D^{25}$ = +82.5 (c = 0.5, EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.08 (s, 1 H), 7.53 (s, 1 H), 7.28–7.26 (m, 3 H), 7.21–7.16 (m, 1 H), 5.38 (d, J = 3.0 Hz, 1 H), 4.16–4.07 (m, 2 H), 2.38 (s, 3 H), 1.19 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.3, 165.0, 144.2, 143.4, 134.6, 130.2, 128.5, 127.0, 125.0, 102.3, 60.6, 55.6, 18.3, 14.1 ppm.

(*R*)-Ethyl 6-Methyl-4-(2-bromophenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (5g): Yield 0.0294 g (83%); 93%*ee* [HPLC with a Daicel Chiralpak AD-H; *n*-hexane/2-propanol, 80:20; flow rate: 1.0 mL/min; λ = 254 nm,; t_R = 7.50 (major), 9.38 (minor) min]; $[\alpha]_D^{25}$ = +21.7 (c = 0.5, EtOAc). ^{1}H NMR (300 MHz,

$CDCl_3$): δ = 7.89 (s, 1 H), 7.57 (d, J = 7.8 Hz, 1 H), 7.33–7.28 (m, 1 H), 7.24–7.14 (m, 3 H), 5.88 (s, 1 H), 4.02 (q, J = 7.1 Hz, 2 H), 2.46 (s, 3 H), 1.06 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 174.3, 165.2, 146.1, 142.9, 133.2, 130.2, 129.9, 129.0, 122.8, 100.6, 59.9, 54.6, 17.5, 14.5 ppm.

(*S*)-Ethyl 6-Methyl-4-(4-bromophenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (5h): Yield 0.0326 g (92%); 90%*ee* [HPLC with a Daicel Chiralpak AD-H; *n*-hexane/2-propanol, 80:20; flow rate: 1.0 mL/min; λ = 254 nm; t_R = 8.57 (minor), 11.27 (major) min]; $[\alpha]_D^{25}$ = +126.3 (c = 0.5, EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.00 (s, 1 H), 7.52 (s, 1 H), 7.45 (d, J = 8.4 Hz, 2 H), 7.17 (d, J = 8.4 Hz, 2 H), 5.36 (d, J = 2.4 Hz, 1 H), 4.10 (q, J = 7.1 Hz, 2 H), 2.36 (s, 3 H), 1.18 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 175.0, 165.9, 146.2, 143.5, 132.3, 129.5, 121.7, 101.2, 60.6, 54.4, 18.0, 14.8 ppm.

(*S*)-Ethyl 6-Methyl-2-thioxo-4-(*o*-tolyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (5i): Yield 0.0256 g (88%); 90%*ee* [HPLC with a Daicel Chiralpak AD-H; *n*-hexane/2-propanol, 90:10; flow rate: 1.0 mL/min; λ = 254 nm; t_R = 12.90 (major), 18.28 (minor) min]; $[\alpha]_D^{25}$ = +146.9 (c = 0.5, EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.05 (s, 1 H), 7.21–7.11 (m, 5 H), 5.64 (s, 1 H), 4.00 (q, J = 7.1 Hz, 2 H), 2.44 (s, 3 H), 2.40 (s, 3 H), 1.06 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.0, 165.1, 143.1, 140.4, 134.8, 130.5, 128.0, 127.6, 126.8, 102.4, 60.1, 52.3, 19.1, 17.8, 13.9 ppm.

(*R*)-Ethyl 4-(2-Fluorophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (5j): Yield 0.0277 g (94%); 90%*ee* [HPLC with a Daicel Chiralpak AS-H; *n*-hexane/2-propanol, 70:30; flow rate: 1.0 mL/min; λ = 254 nm; t_R = 9.31 (minor), 11.10 (major) min]; $[\alpha]_D^{25}$ = +114.4 (c = 0.5, EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.01 (s, 1 H), 7.32–7.27 (m, 1 H), 7.24–7.18 (m, 2 H), 7.13–7.03 (m, 2 H), 5.74 (s, 1 H), 4.06 (q, J = 7.2 Hz, 2 H), 2.42 (s, 3 H), 1.11 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, [D_6]-DMSO): δ = 174.6, 165.3, 145.8, 130.4, 130.3, 129.7, 125.1, 116.2, 115.9, 99.8, 60.0, 49.2, 17.5, 14.3 ppm.

(*S*)-Ethyl 4-(4-Cyanophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (5k): Yield 0.0291 g (97%); 93%*ee* [HPLC with a Daicel Chiralpak AD-H; *n*-hexane/2-propanol, 80:20; flow rate: 1.0 mL/min; λ = 254 nm; t_R = 12.77 (minor), 16.52 (major) min]; $[\alpha]_D^{25}$ = +87.7 (c = 0.5, EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.09 (s, 1 H), 7.68–7.62 (m, 3 H), 7.42 (d, J = 8.4 Hz, 2 H), 5.47 (d, J = 3.0 Hz, 1 H), 4.17–4.07 (m, 2 H), 2.37 (s, 3 H), 1.19 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 175.0, 165.4, 149.0, 146.3, 133.2, 127.9, 119.1, 111.0, 100.3, 60.2, 54.3, 17.7, 14.5 ppm.

(*S*)-Ethyl 6-Methyl-2-thioxo-4-[4-(trifluoromethyl)phenyl]-1,2,3,4-tetrahydropyrimidine-5-carboxylate (5l): Yield 0.0317 g (92%); 93%*ee* [HPLC with a Daicel Chiralpak AD-H; *n*-hexane/2-propanol, 80:20; flow rate: 1.0 mL/min; λ = 254 nm; t_R = 6.10 (minor), 7.30 (major) min; $[\alpha]_D^{25}$ = +109.9 (c = 0.5, EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.83 (m, 1 H), 7.60 (d, J = 8.4 Hz, 2 H), 7.42 (d, J = 8.1 Hz, 2 H), 7.33 (m, 1 H), 5.48 (d, J = 3.0 Hz, 1 H), 4.16–4.08 (m, 2 H), 2.37 (s, 3 H), 1.19 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 175.0, 165.4, 148.3, 146.2, 127.8, 126.1, 100.5, 60.2, 54.2, 17.7, 14.4 ppm.

(*R*)-Ethyl 4-(2,4-Dichlorophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (5m): Yield 0.0327 g (95%); 96%*ee* [HPLC with a Daicel Chiralpak OD-H; *n*-hexane/2-propanol, 90:10; flow rate: 1.0 mL/min; λ = 254 nm; t_R = 8.02 (major), 10.27 (minor) min]; $[\alpha]_D^{25}$ = +105.5 (c = 0.5, EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.35 (s, 1 H), 7.43 (s, 1 H), 7.40 (d, J = 2.1 Hz, 1 H), 7.25–7.15 (m, 2 H), 5.84 (s, 1 H), 4.03 (q, J = 7.1 Hz, 2 H), 2.44 (s, 3 H), 1.09 (t, J = 7.1 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.2, 164.7, 144.7, 137.2, 134.8, 133.3, 129.7, 129.5, 128.0, 100.6, 60.5, 52.2, 17.9, 13.9 ppm.

Supporting Information (see footnote on the first page of this article): ^{1}H and ^{13}C NMR spectra and HPLC chromatograms.

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