Note

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Enantioselective Synthesis of 3,4-Dihydropyrimidin-2(1*H*)-ones through Organocatalytic Transfer Hydrogenation of 2-Hydroxypyrimidines

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ABSTRACT

Chiral phosphoric acid-catalyzed transfer hydrogenation of 2-hydroxypyrimindines has been successfully realized using Hantzsch ester or dihydrophenanthridine as hydrogen sources, furnishing the chiral 3,4-dihydropyrimidin-2(1*H*)-ones (DHPMs) with excellent yields and up to 99% ee of enantioselectivities. Notably, a novel kind of chiral DHPMs with an alkyl stereogenic center can be prepared through highly chemoselective transfer hydrogenation.

Functionalized 3,4-dihydropyrimidin-2(1*H*)-ones (DHPMs), the products of the well-known Biginelli three-component condensation reaction,[1] posses a wide range of pharmacological properties, including anticancer activity, calcium channel inhibition, anti-inflammatory activity, antibacterial activity, etc.[2] Intensive researches suggested that both enantioisomers of DHPMs often show very different or even opposite biological activies. For example, (*S*)-enantiomer of Monastrol is a more potent inhibitor of Eg5 ATPase activity than the (*R*)-enantiomer[3] and the (*R*)-SQ 32926 presents >400 fold more antihypertensive activity as a calcium channel

blocker than its (*S*)-enantiomer[4] (Figure 1). Therefore, highly enantioselective synthesis of optically pure DHPMs is undoubtedly a desirable objective.

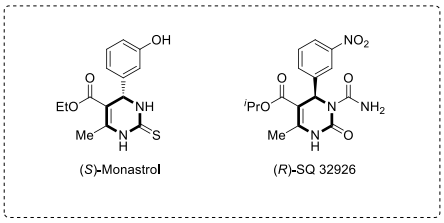
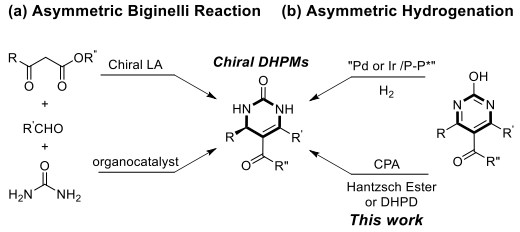


Figure 1. Chiral DHPMs with pharmacological activities.

Conceptually, asymmetric catalytic Biginelli reaction is the most straightforward approach to chiral DHPMs.[5] However, the preparation of this kind of important compound always relied on the resolution of racemic mixture[4, 6] and chiral auxiliary-assisted synthesis[7] until a breakthrough has been made on the asymmetric catalytic Biginelli reaction. In 2005, a new chiral ytterbium complex was designed and synthesized in Zhu's lab, which is able to catalyze asymmetric Biginelli reaction with unprecedented enantioselectivity (80-99% ee).[8] Shortly afterwards, Gong and coworkers reported the first organocatalytic enantioselective Biginelli reaction using a BINOL-derived chiral phosphoric acid as catalyst, giving structurally diverse DHPMs with high ees.[9] Feng described an enantioselective Biginelli reaction catalyzed by a chiral simple secondary amine combined with achiral Brønsted acid in a dual activation mode.[10] Since then, a variety of catalysts has been successfully developed to promote this useful transformation, such as chiral Brønsted acids,[11] proline derivatives,[12] prime amines[13] and etc. Despite achievements obtained in asymmetric Biginelli reaction, new approaches to chiral DHPMs is still of great value. In facts, asymmetric hydrogenation of aromatic compounds has been proved highly effective for preparing chiral cyclic molecules.[14] Partial reduction of pyrimidin-2-one may also directly construct the Beginelli-type DHPMs based on retrosynthetic analysis.

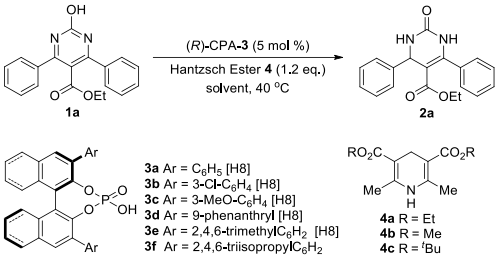
Scheme 1. Enantioselective Catalytic Synthesis of Chiral 3,4-dihydropyrimidin-2-ones.



Very recently, our group realized an asymmetric hydrogenation of 2-hydroxypyrimindines using chiral Pd or Ir catalyst to offer chiral cyclic ureas or DHPMs with high ees, which presents a new facile method to synthesize this kind of important compounds.[15a, 15b] Herein, we disclosed the first asymmetric biomimetic transfer hydrogenation of pyrimindines catalyzed by chiral phosphoric acid with Hantzsch ester or dihydrophenanthridine (DHPD) as a hydride donor, furnishing chiral DHPMs with excellent enantioselectivity

and chemoselectivity.

Table 1. The Evaluation of Reaction Parameters[a]

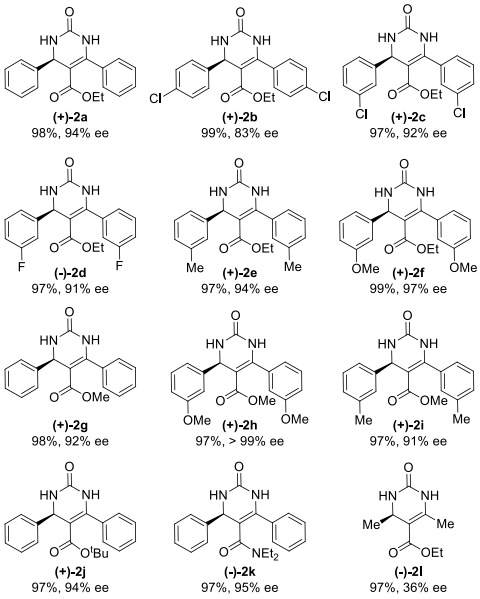


Entry	Solvent	**CPA**	**HEH (R)**	Yield [b](%)	Ee[c](%)
1	THF	**3a**	**4a (Et)**	97	40
2	CH_2Cl_2	**3a**	**4a (Et)**	94	58
3	EtOAc	**3a**	**4a (Et)**	99	47
4	1,4-dioxane	**3a**	**4a (Et)**	94	38
5	Toluene	**3a**	**4a (Et)**	99	69
6	Benzene	**3a**	**4a (Et)**	97	66
7	Toluene	**3a**	**4b (Me)**	94	65
8	Toluene	**3a**	**4c (^{t}Bu)**	63	69
9	Toluene	**3b**	**4a (Et)**	88	74
10	Toluene	**3c**	**4a (Et)**	97	70
11	Toluene	**3d**	**4a (Et)**	66	91
12	Toluene	**3e**	**4a (Et)**	78	92
13	Toluene	**3f**	**4a (Et)**	99	94

[a] Reaction condition: **1a** (0.1 mmol), CPA-**3** (5.0 mol%), HEH (1.2 eq.), solvent (2.0 mL), 24 h, 40 °C. [b] Isolated yields. [c] Determined by chiral HPLC analysis.

With ethyl 2-hydroxy-4,6-diphenylpyrimidine-5-carboxy-late (**1a**) as the model substrate, we began the pursuit of the enantioselective transfer hydrogenation for synthesis of chiral DHPMs. Initially, solvent effects were evaluated with one representative set of reaction conditions exemplified in Table 1 (entries 1-6). In most solvent, this transformation could smoothly occur in presence of CPA **3a** and Hantzsch ester **4a**, giving the desired chiral DHPMs **2a** with good isolated yield. But toluene gave the best in term of both yield and enantioselectivity (entry 5). When the HEH **4c** with bulky t-butyl group used as hydride donor, the yield dramatically dropped down to only 63% (entry 8). Next, different CPAs were screened with 4a in toluene (entries 9-13). The results showed that the catalysts bearing bulky substituent at C3 position exhibit more prominent enantioselectivities. To our delight, CPA **3f** was selected as the best one for 99% yield and 94% ee obtained (entry 13).

Scheme 2. Substrate Scope



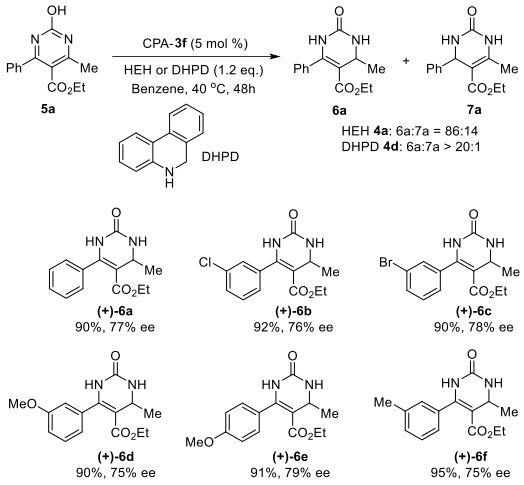
Reaction condition: **1** (0.2 mmol), CPA-**3f** (5.0 mol%), HEH **4a** (1.2 eq.), toluene (4.0 mL), 24 h, 40 ºC

Having defined an optimal reaction protocol, exploration of substrate scope was carried out to test the generality (Scheme 2). In general, a variety of 2-hydroxy-4,6-diarylpyrimidine-5-carboxylate derivatives **1** were converted into chiral DHPMs **2** with good enantioselectivities and yields. It appears that both yield and enantioselectivity are very sensitive for the position of substitutes on the phenyl ring. The substrates with para-substituented phenyl group (**2b**) underwent the reaction to afford the reduced product with moderate enantioselectivities (83% ee). When bearing meta-substituented phenyl group (**2c**, **2d**, **2e**, **2f**), DHPMs were furnished with much higher enantioselectivities (up to 97% ee) than the substrates bearing 4-substituent phenyl. And an ortho-substituent group at phenyl ring would suppress this reduction process completely due to a steric hindrance. Replacement of the ethyl ester with methyl (**2g, 2h, 2i**), tert-butyl ester (**2j**) or amide (**2k**) in the parent substrate kept a high level of enantioselectivities (92~> 99% ee) and yields. Ethyl 2-hydroxy-4,6-dimethyl pyrimidine-5-carboxylate also was tested and only a low ee obtained, albeit 97% yield (**2l**).

Next, we turned our attention to multisubstituted 2-hydroxypyrimidines **5** with an unsymmetrical structure, which may lead to the more classic Biginelli products. In the initial investigation, an inseparable mixture of **6a** and **7a** was obtained under the standard reaction condition. After careful reoptimization of condition, excellent chemoselectivity can be achieved with DHPD used as alternative hydride donor.[16] This improvement of chemoselectivity is possibly attributed to the discrepancy of hydride-transfer ability of hantzsch ester and dihydrophenanthridine. With weaker hydride donor than hantzsch ester, DHPD could be a proper reductant in accessing selective hydrogenation of molecules containing more than one unsaturated bond. [16b] It is interesting that compound **6a** was detected exclusively in the crude reaction mixture in moderate enantioselectivity (77%

ee). To the best of our knowledge, effective synthesis of DHPMs with an alkyl substituted chiral center is still rare. Some novel chiral DHPMs with methyl substituted chiral carbon atom at C-4 position were prepared with good yields and moderate values of ee (Scheme 3). Unfortunately, this kind of reduction failed to undergo in further study on scope of other alkyl substituted substrates.

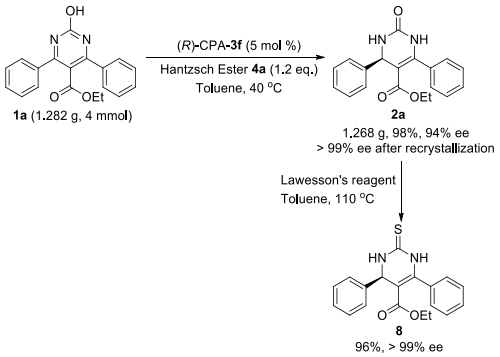
Scheme 3. Enantioselective Transfer Hydrogenation of Unsymmetrical Multisubstituted 2-Hydroxy-pyrimidines



Reaction condition: **5** (0.2 mmol), CPA-**3f** (5.0 mol %), DHPD (1.2 eq.), benzene (4.0 mL), 48 h, 40 °C. DHPD: dihydrophenanthridine.

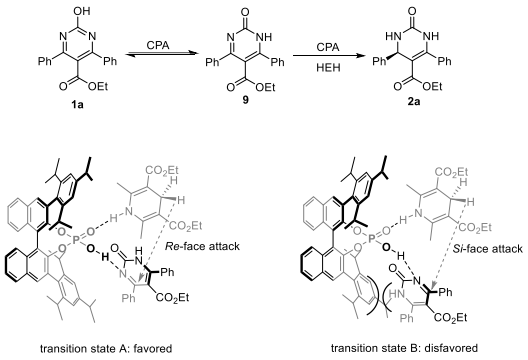
To demonstrate the practical utility of this method, chiral DHPM **2a** was prepared on a gram scale with 98% yield and 94% ee under the optimal conditions. After recrystallization once, the ee was rised up to >99%. Treating **2a** with Lawesson's reagent gave the corresponding 3,4-dihydro-pyrimidin-2(1*H*)-thione **8** in nearly quantitative yield without any loss of value of ee (Scheme 4). This procedure provides new accesses to a wide spectrum of structurally diverse dihydropyrimidinethiones and their pharmaceutically relevant derivatives with high enantiomeric purity.[9]

Scheme 4. Gram Scale Experiment and Synthesis of Chiral 3,4-dihydropyrimidin-2(1*H*)-thione



Based on the above experimental results and the relative researches[14h], a plausible stepwise hydrogenation process was proposed (Scheme 5). Firstly, the chiral phosphoric acid facilitated the reversible isomerization to form the active tautomer **9**. Secondly, C=N double bond of **9** is hydrogenated to give the final chiral product. The origin of enantioselectivity can be explained by the stereochemical model as illustrated in Scheme 5. These two hydrogen bonding interaction and the effect of steric hindrance build up "three-point contact model" *via* re-face attach that determines the stereoselectivity.

Scheme 5. Proposed Reaction Pathway and Transition State



In conclusion, we reported the first asymmetric biomimetic transfer hydrogenation of pyrimindines catalyzed by chiral phosphoric acid, successfully furnishing a chiral DHPMs with excellent yields and enantioselectivities (up to 99% ee). In partically, a novel chiral DHPMs with an alkyl stereogenic center can be prepared through highly chemoselective tranfer hydrogenation, which is seldom descrided before. The detailed investigation on potential bioactivity of this new kind of chiral DHPMs is ongoing in our cooperative lab.

EXPERIMENTAL SECTION

Commercially available reagents were used without further purification. Solvents were treated prior to use according to the standard methods. ^{1}H NMR, ^{13}C{^{1}H} NMR and ^{19}F NMR spectra were recorded at room temperature in $CDCl_3$on 400 MHz instrument with tetramethylsilane (TMS) as internal standard. Enantiomeric excess was determined by HPLC analysis, using chiral column described below in detail. Optical rotations were measured by polarimeter. Flash column chromatography was performed on silica gel (200-300 mesh).

General Procedure for Trisubstituted 2-Hydroxypyrimidines: Trisubstituted 2-hydroxypyrimidine derivatives **1** can be conveniently prepared according to the known literature procedure with some minor modifications.[1] Among them, the compounds **1a**,[15a] **1d**,[15a] **1e**,[15a] **1j**,[15a] **5a-5b**,[17a] **5c**,[17b] 5**d-5f**,[17c] are known (see

Scheme S1).

Copper(II) trifluoromethanesulfonate (0.271 g, 5.0 mol %) was added into a solution of aldehyde (15.0 mmol), urea (1.08 g, 18.0 mmol), and ethyl 3-oxo-3-arylpropanoate (15.0 mmol) in 40 mL ethanol. After heated at 80 °C under nitrogen for 24 h in oil bath, the reaction mixture was cooled to 0 °C, the precipitation was collected by filtration and dried. The resulting white powder was triturated with cooled ethanol to afford S-**1** or S-**5** as a pale yellow powder.

A solution of above S-**1** or S-**5** (3.0 mmol), $CuCl_2$•$2H_2O$ (5.0 mg, 1.0 mol %), potassium carbonate (41 mg, 10 mol %) in dichloromethane (6.0 mL) was heated at 40 °C for 30 min in oil bath, and then 65 wt% tert-butyl hydroperoxide (0.832 g, 6.0 mmol) was added dropwise over a period of 10 minutes. The resulting mixture was stirred at 35 ℃ for 24 h in oil bath. The saturated aqueous sodium thiosulfate (10 mL) was added to quench the excess tert-butyl hydroperoxide. After stirred for 20 minutes, the mixture was extracted with dichloromethane (40 mL×3). The combined organic layer was dried over anhydrous sodium sulfate, concentrated in vacuo. The crude product was purified by flash column chromatography using the hexanes and ethyl acetate as eluent to give the desired products.

*Ethyl 4,6-bis(4-chlorophenyl)-2-hydroxypyrimidine-5-carboxylate (**1b**)*: 0.553 g, 36% yield (2 steps), new compound, white solid, mp: 95-96 °C, R_f = 0.45(dichloromethane/methanol = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 13.43 (s, 1H), 7.57 (d, *J* = 8.6 Hz, 4H), 7.45 (d, *J* = 8.6 Hz, 4H), 3.95 (q, *J* = 7.1 Hz, 2H), 0.91 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ (ppm) 165.9, 157.9, 137.8, 129.6, 129.1, 111.9, 62.1, 13.4. HRMS (ESI) m/z Calculated for $C_{19}H_{15}Cl_2N_2O_3$ $[M+H]^+$ 389.0454, found 389.0459.

*Ethyl 4,6-bis(3-chlorophenyl)-2-hydroxypyrimidine-5-carboxylate (**1c**):* 2.942 g, 52% yield (2 steps), new compound, white solid, mp: 160-161 °C, R_f = 0.30 (hexanes/ethyl acetate = 1/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.61 (s, 2H), 7.58-7.48 (m, 4H), 7.44-7.42 (m, 2H), 4.01 (q, *J* = 7.1 Hz, 2H), 0.97 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ (ppm) 165.5, 157.6, 135.6, 134.8, 131.4, 130.2, 128.3, 126.3, 112.2, 62.2, 13.5. HRMS (ESI) m/z Calculated for $C_{19}H_{15}Cl_2N_2O_3$ $[M+H]^+$ 389.0454, found 389.0452.

*Ethyl 4,6-bis(3-fluorophenyl)-2-hydroxypyrimidine-5-carboxylate (**1d**)*: 2.549 g, 52% yield (2 steps), new compound, white solid, mp: 184-185 °C, R_f = 0.30 (hexanes/ethyl acetate = 1/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.37-7.22(m, 8H), 3.99 (q, *J* = 7.1 Hz, 2H), 0.93 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ (ppm) δ 165.6, 162.5 (d, J_{C-F} = 248.4 Hz), 157.7, 136.0, 130.6 (d, J_{C-F} = 8.1 Hz), 123.9 (d, J_{C-F} = 3.1 Hz), 118.4 (d, J_{C-F} = 21.1 Hz), 115.5, 115.3, 112.1, 62.1, 13.4. ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) -111.16. HRMS Calculated for $C_{19}H_{15}F_2N_2O_3$ $[M+H]^+$ 357.1045, found 357.1049.

*Ethyl 2-hydroxy-4,6-di-m-tolylpyrimidine-5-carboxylate (**1e**):* 1.104 g, 55% yield (2 steps), new compound, white solid, mp: 190-191 °C, R_f = 0.51 (dichloromethane/methanol = 20/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ

(ppm) 13.04 (s, 1H), 7.42-7.29 (m, 8H), 3.93 (q, *J* = 6.7 Hz, 2H), 2.38 (s, 6H), 0.88 (t, *J* = 6.9 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm) 165.9, 157.2, 137.9, 131.4, 128.2, 128.1, 124.6, 111.4, 61.2, 20.9, 12.9. HRMS (ESI) m/z Calculated for $C_{21}H_{21}N_2O_3$ $[M+H]^+$ 349.1547, found 349.1553.

*Methyl 2-hydroxy-4,6-diphenylpyrimidine-5-carboxylate (**1g**):* 0.969 g, 57% yield (2 steps), new compound, white solid, mp: 215-216 °C, R_f = 0.35 (dichloromethane/methanol = 20/1); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 13.14 (s, 1H), 7.63-7.61 (m, 4H), 7.52-7.48 (m, 6H), 3.46 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm) 166.9, 157.9, 131.3, 128.8, 128.7, 128.1, 128.0, 111.6, 52.5. HRMS (ESI) m/z Calculated for $C_{18}H_{15}N_2O_3$ $[M+H]^+$ 307.1077, found 307.1075.

*Methyl 2-hydroxy-4,6-bis(3-methoxyphenyl)pyrimidine-5-carboxylate (**1h**):* 2.356 g, 42% yield (2 steps), new compound, white solid, mp: 168-169 °C, R_f = 0.30 (hexanes/ethyl acetate = 1/1); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.39-7.35 (m, 2H), 7.19-7.16 (m, 4H), 7.07-7.04 (m, 2H), 3.86 (s, 6H), 3.50 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm) 166.9, 159.7, 157.7, 135.3, 129.9, 120.2, 117.7, 113.0, 111.7, 55.5, 52.6. HRMS (ESI) m/z Calculated for $C_{20}H_{19}N_2O_5$ $[M+H]^+$ 367.1288, found 367.1290.

*Methyl 2-hydroxy-4,6-di-m-tolylpyrimidine-5-carboxylate (**1i**):* 2.195 g, 40% yield (2 steps), new compound, white solid, mp: 252-253 °C, R_f = 0.30 (hexanes/ethyl acetate = 1/1); ^1H NMR (400 MHz, DMSO) δ (ppm) 12.53 (s, 1H), 7.39-7.30 (m, 8H), 3.39 (s, 3H), 2.37 (s, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, DMSO) δ (ppm) 167.6, 138.3, 131.7, 128.9, 128.8, 125.3, 100.0, 52.7, 21.4. HRMS (ESI) m/z Calculated for $C_{20}H_{19}N_2O_3$ $[M+H]^+$ 335.1390, found 335.1392.

*tert-Butyl 2-hydroxy-4,6-diphenylpyrimidine-5-carboxylate (**1j**):* 1.697 g, 67% yield (2 steps), new compound, white solid, mp: 209-210 °C, R_f = 0.45 (ethyl acetate); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.65-7.63 (m, 4H), 7.52-7.47 (m, 6H), 1.15 (s, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm) 164.9, 157.7, 130.9, 128.6, 128.2, 83.0, 27.3. HRMS (ESI) m/z Calculated for $C_{21}H_{21}N_2O_3$ $[M+H]^+$ 349.1547, found 349.1548.

*N, N-diethyl-2-hydroxy-4,6-diphenylpyrimidine-5-carboxamide (**1k**):* 1.358 g, 56% yield (2 steps), new compound, white solid, mp: 225-226 °C, R_f = 0.25 (ethyl acetate); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.80-7.78 (m, 4H), 7.49-7.43 (m, 6H), 3.19-3.18 (m, 2H), 2.85-2.83 (m, 2H), 0.79 (t, *J* = 7.1 Hz, 3H), 0.49 (t, *J* = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm) 164.9, 157.8, 130.7, 128.4, 128.1, 113.5, 42.4, 38.3, 12.4, 10.9. HRMS (ESI) m/z Calculated for $C_{21}H_{22}N_3O_2$ $[M+H]^+$ 348.1707, found 348.1710.

GeneralProcedure for Hydrogenation of 2-Hydroxypyrimidines: A mixture of 2-hydroxypyrimidines**1** (0.20 mmol), Hantzsch ester **4a** (61 mg, 0.24 mmol, 1.2 equiv), and chiral phosphoric acid (*R*)-**3f** (7.5 mg, 0.01 mmol, 5 mol %) in toluene (4 mL) was stirred at 40 °C under nitrogen for 24 h in oil bath. After the reaction was completed (determined by TLC), the solvent was removed under the reduced pressure. The residue was purified by flash chroma- tography on silica gel using the dichloromethane/methanol as eluent to

give the desired product **2**. The enantiomeric excesses were determined by chiral HPLC.

*Ethyl (R)-(+)-2-oxo-4,6-diphenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**2a**)*: 63 mg, 98% yield, known compound,[15] white solid, R_f = 0.45 (dichloromethane/methanol = 20/1), 94% ee, $[\alpha]^{20}_D$ = +27.43 (*c* 0.74, MeOH). [lit.[15]: $[\alpha]^{20}_D$= -31.1 (*c* 0.44, MeOH) for 97% ee (*S*)], ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.43-7.25 (m, 10H), 7.09 (s, 1H), 5.98 (s, 1H), 5.48 (s, 1H), 3.84-3.80 (m, 2H), 0.80 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ (ppm) 165.5, 153.7, 147.6, 143.7, 134.8, 129.4, 128.8, 128.3, 128.0, 127.9, 126.6, 102.0, 60.0, 55.3, 13.6. HPLC: Chiracel AD-H column, 254 nm, 30 °C, hexane/*i*-propanol = 80/20, flow = 0.7 mL/min, retention time 13.8 min(maj) and 17.3 min.

*Ethyl (R)-4,6-bis(4-chlorophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**2b**):* 77 mg, 99% yield, new compound, white solid, mp: 190-191°C, R_f = 0.45 (dichloromethane/methanol = 30/1), 83% ee, $[\alpha]^{20}_D$ = +26.02 (*c* 0.88, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.90 (s, 1H), 7.36-7.24 (m, 8H), 6.50 (s, 1H), 5.37 (d, *J* = 3.0 Hz, 1H), 3.88 -3.83 (m, 2H), 0.87 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ (ppm) 164.9, 153.1, 146.2, 141.8, 135.8, 134.0, 133.1, 129.6, 129.1, 128.5, 127.9, 102.4, 60.3, 55.1, 13.6. HPLC: Chiracel AD-H column, 254 nm, 30 °C, hexane/*i*-propanol = 80/20, flow = 0.7 mL/min, retention time 13.2 min(maj) and 15.7 min. HRMS (ESI) m/z Calculated for $C_{19}H_{17}Cl_2N_2O_3$ $[M+H]^+$ 391.0611, found 391.0606.

*Ethyl (R)-4,6-bis(3-chlorophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**2c**):* 76 mg, 97% yield, new compound, white solid, mp: 208-209 °C, R_f = 0.60 (hexanes/ethyl acetate = 1/1), 92% ee, $[\alpha]^{20}_D$ = +8.15 (*c* 0.54, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.59 (s, 1H), 7.42-7.21 (m, 9H), 6.20 (s, 1H), 5.47 (s, 1H), 3.91-3.86 (m, 2H), 0.89 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ (ppm) 164.1, 152.1, 145.3, 144.6, 135.8, 134.2, 133.6, 129.7, 129.2, 129.1, 128.0, 127.9, 126.4, 125.7, 124.2, 102.0, 59.8, 54.9, 13.0. HPLC: Chiracel AD-H column, 254 nm, 30 °C, hexane/*i*-propanol = 80/20, flow = 0.7 mL/min, retention time 14.3 min(maj) and 16.2 min. HRMS (ESI) m/z Calculated for $C_{19}H_{17}Cl_2N_2O_3$ $[M+H]^+$ 391.0611, found 391.0615.

*Ethyl (R)-4,6-bis(3-fluorophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**2d**):* 70 mg, 97% yield, new compound, white solid, mp: 184-185 °C, R_f = 0.60 (hexanes/ethyl acetate = 1/1), 91% ee, $[\alpha]^{20}_D$ = -3.87 (*c* 0.80, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.19 (s, 1H), 7.35-7.02 (m, 8H), 6.79 (s, 1H), 5.40 (d, *J* = 3.2 Hz, 1H), 3.92-3.86 (m, 2H), 0.88 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ (ppm) 164.9, 163.0 (d, $J_{C\text{-}F}$ = 246.8 Hz), 162.2 (d, $J_{C\text{-}F}$ = 247.1 Hz), 153.3, 146.2 (d, $J_{C\text{-}F}$ = 2.0 Hz), 145.8 (d, $J_{C\text{-}F}$ = 6.1 Hz), 136.5 (d, $J_{C\text{-}F}$ = 8.1 Hz), 130.4 (d, $J_{C\text{-}F}$ = 8.1 Hz), 129.8 (d, $J_{C\text{-}F}$ = 8.2 Hz), 124.0 (d, $J_{C\text{-}F}$ = 3.0 Hz), 122.1 (d, $J_{C\text{-}F}$ = 2.8 Hz), 116.5 (d, $J_{C\text{-}F}$ = 21.0 Hz), 115.6 (d, $J_{C\text{-}F}$ = 22.9 Hz), 115.1 (d, $J_{C\text{-}F}$ = 21.2 Hz), 113.5 (d, $J_{C\text{-}F}$ = 22.0 Hz), 102.2, 60.3, 54.9, 13.5. ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) -112.01 ,

-112.49. HPLC: Chiracel AD-H column, 254 nm, 30 °C, hexane/*i*-propanol = 85/15, flow = 0.9 mL/min, retention time 13.3 min(maj) and 15.0 min. HRMS (ESI) m/z Calculated for $C_{19}H_{17}F_2N_2O_3$ $[M+H]^+$ 359.1202, found 359.1204.

*Ethyl (R)-2-oxo-4,6-di-m-tolyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**2e**):* 68 mg, 97% yield, new compound, white solid, mp: 196-197 °C, R_f = 0.35 (dichloromethane/methanol = 30/1), 94% ee, $[\alpha]^{20}_D$ = +25.18 (*c* 0.81, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.42 (s, 1H), 7.24-7.09 (m, 8H), 6.27 (s, 1H), 5.39 (d, *J* = 2.7 Hz, 1H), 3.86-3.81 (m, 2H), 2.33 (d, *J* = 4.8 Hz, 6H), 0.83 (t, *J* = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm) 165.4, 153.0, 147.1, 143.5, 138.4, 137.8, 135.0, 130.2, 128.8, 128.7, 128.6, 128.1, 127.4, 125.2, 123.7, 102.2, 59.9, 55.8, 21.6, 21.3, 13.6. HPLC: Chiracel AD-H column, 254 nm, 30 °C, hexane/*i*-propanol = 80/20, flow = 0.8 mL/min, retention time 10.1 min(maj) and 12.9 min. HRMS (ESI) m/z Calculated for $C_{21}H_{23}N_2O_3$ $[M+H]^+$ 351.1703, found 351.1700.

*Ethyl (R)-4,6-bis(3-methoxyphenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**2f**):* 75 mg, 99% yield, known compound,[15] white solid, R_f = 0.45 (dichloromethane/methanol = 20/1), 97% ee, $[\alpha]^{20}_D$ = +23.78 (*c* 0.74, MeOH). [lit.[15]: $[\alpha]^{20}_D$= -22.4 (*c* 0.58, MeOH) for 99% ee (*S*)], ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.69 (s, 1H), 7.27-7.22 (m, 2H), 6.99-6.98 (m, 2H), 6.96-6.80 (m, 4H), 6.50 (s, 1H), 5.37 (d, *J* = 2.4 Hz, 1H), 3.87-3.82 (m, 2H), 3.76 (d, *J* = 6.7 Hz, 6H), 0.85 (t, *J* = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm) 165.3, 159.9, 159.3, 153.1, 147.0, 145.0, 136.1, 129.9, 129.2, 120.6, 118.8, 115.3, 113.5, 113.2, 112.5, 102.0, 60.0, 55.6, 55.3, 55.2, 13.6. HPLC: Chiracel AD-H column, 254 nm, 30 °C, hexane/*i*-propanol = 70/30, flow = 0.8 mL/min, retention time 14.8 min(maj) and 16.4 min.

*Methyl (R)-2-oxo-4,6-diphenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**2g**):* 61 mg, 98% yield, new compound, white solid, mp: 211-212 °C, R_f = 0.45 (dichloromethane/methanol = 30/1), 92% ee, $[\alpha]^{20}_D$ = +10.33 (*c* 1.22, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.44 -7.31 (m, 10H), 7.02 (brs, 1H), 5.90 (brs, 1H), 5.52 (s, 1H), 3.41 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm) 165.2, 152.6, 147.0, 142.9, 134.3, 129.1, 128.4, 127.7, 127.5, 126.1, 126.0, 101.4, 55.1, 50.6. HPLC: Chiracel IA column, 254 nm, 30 °C, hexane/*i*-propanol = 80/20, flow = 0.8 mL/min, retention time 11.1 min(maj) and 14.5 min. HRMS (ESI) m/z Calculated for $C_{18}H_{17}N_2O_3$ $[M+H]^+$ 309.1234, found 309.1237.

*Methyl (R)-4,6-bis(3-methoxyphenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**2h**):* 72 mg, 97% yield, new compound, white solid, mp: 209-210 °C, R_f = 0.60 (dichlorome- thane/methanol = 30/1), > 99% ee, $[\alpha]^{20}_D$ = +26.61 (*c* 1.30, MeOH). ^{1}H NMR (400 MHz, DMSO) δ (ppm) 9.28 (s, 1H), 7.86 (s, 1H), 7.30 (t, *J* = 7.8 Hz, 2H), 6.99-6.86 (m, 6H), 5.22 (d, *J* = 3.2 Hz, 1H), 3.76 (d, *J* = 9.8 Hz, 6H), 3.30 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, DMSO) δ (ppm) 165.9, 159.8, 159.1, 152.6, 149.4, 146.2, 136.5, 130.2, 129.4, 121.3, 118.8, 115.3, 114.1, 112.9, 112.8, 100.3, 55.6, 55.5, 54.4, 51.2. HPLC: Chiracel AD-H column, 254 nm, 30 °C, hexane/*i*-

propanol = 70/30, flow = 0.8 mL/min, retention time 14.0 min(maj) and 17.0 min. HRMS (ESI) m/z Calculated for $C_{20}H_{21}N_2O_5$ $[M+H]^+$ 369.1445, found 369.1443.

*Methyl (R)-2-oxo-4,6-di-m-tolyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**2i**):* 65 mg, 97% yield, new compound, white solid, mp: 227-228 °C, R_f = 0.60 (dichloromethane/methanol = 30/1), 91% ee, $[\alpha]^{20}_D$ = +24.68 (*c* 0.62, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.30-7.09 (m, 10H), 6.15 (s, 1H), 5.40 (d, *J* = 2.9 Hz, 1H), 3.39 (s, 3H), 2.35 (s, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm) 165.2, 152.3, 146.9, 142.8, 138.0, 137.5, 134.3, 129.9, 128.4, 128.2, 127.9, 127.6, 126.7, 124.7, 123.1, 101.3, 55.3, 50.6, 21.1, 20.8. HPLC: Chiracel AD-H column, 254 nm, 30 °C, hexane/*i*-propanol = 80/20, flow = 0.7 mL/min, retention time 11.5 min(maj) and 15.8 min. HRMS (ESI) m/z Calculated for $C_{20}H_{21}N_2O_3$ $[M+H]^+$ 337.1547, found 337.1551.

*tert-Butyl (R)-2-oxo-4,6-diphenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**2j**):* 68 mg, 97% yield, new compound, white solid, mp: 166-167 °C, R_f = 0.50 (dichloromethane/ethyl acetate = 4/1), 94% ee, $[\alpha]^{20}_D$ = +32.50 (*c* 0.68, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.43-7.21 (m, 11H), 6.10 (s, 1H), 5.42 (s, 1H), 1.04 (s, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm) 164.7, 153.0, 145.6, 143.4, 135.5, 129.3, 128.8, 128.2, 128.1, 127.9, 126.6, 104.0, 80.4, 56.1, 27.6. HPLC: Chiracel AD-H column, 254 nm, 30 °C, hexane/*i*-propanol = 80/20, flow = 0.7 mL/min, retention time 9.6 min(maj) and 11.6 min. HRMS (ESI) m/z Calculated for $C_{20}H_{23}N_2O_3$ $[M+H]^+$ 351.1703, found 351.1704.

*(R)-N,N-diethyl-2-oxo-4,6-diphenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (**2k**):* 68 mg, 97% yield, new compound, white solid, mp: 266-267 °C, R_f = 0.35 (ethyl acetate), 95% ee, $[\alpha]^{20}_D$ = -46.23 (*c* 1.22, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.38-7.21 (m, 12H), 5.74 (s, 1H), 5.62 (s, 1H), 3.90-2.94 (m, 2H), 2.37 (d, *J* = 55.5 Hz, 2H), 0.69 (t, *J* = 6.9 Hz, 3H), -0.07 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm) 167.3, 154.0, 141.9, 133.5, 131.5, 129.6, 128.7, 128.5, 128.1, 127.5, 126.8, 106.5, 59.0, 41.6, 37.5, 11.9, 11.5. HPLC: Chiracel AD-H column, 254 nm, 30 °C, hexane/*i*-propanol = 80/20, flow = 0.8 mL/min, retention time 13.9 min and 16.1 min(maj). HRMS (ESI) m/z Calculated for $C_{21}H_{24}N_3O_2$ $[M+H]^+$ 350.1863, found 350.1859.

*Ethyl (R)-4,6-dimethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**2l**):* 39 mg, 97% yield, known compound,[18] white solid, R_f = 0.45 (ethyl acetate), 36% ee, $[\alpha]^{20}_D$ = -54.51 (*c* 0.62, MeOH). ^{1}H NMR (400 MHz, DMSO) δ (ppm) 4.13-4.06 (m, 3H), 2.16 (s, 3H), 1.19 (t, *J* = 7.1 Hz, 3H), 1.10 (d, *J* = 6.2 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, DMSO) δ (ppm) 165.8, 152.9, 148.1, 100.9, 59.5, 46.7, 23.8, 18.1, 14.7. HPLC: Chiracel AD-H column, 254 nm, 30 °C, hexane/*i*-propanol = 80/20, flow = 0.7 mL/min, retention time 7.8 min(maj) and 8.6 min.

GeneralProcedure for Hydrogenation of Pyrimidin-2-ols 5:

A mixture of 2-hydroxypyrimidine **1** (0.20 mmol), dihydrophenanthridine (DHPD) **4d** (36 mg, 0.20 mmol, 1 equiv), and chiral phosphoric acid (*R*)-**3f** (7.5 mg, 0.01 mmol, 5 mol %) in Benzene (4 mL) was stirred at 40

°C under nitrogen for 24 h. The mixture was then cooled to room temperature, DHPD **4d** (36 mg, 0.20 mmol, 1 equiv) was added again under the nitrogen atomsphere. The reaction mixture was replaced into the oil bath at 40 °C under nitrogen for another 24 h.After the reaction was completed (determined by TLC), the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel to yield desire product. The enantiomeric excesses were determined by chiral HPLC. Racemates of **6** were prepared by the reduction of **5** using the racemic catalyst.

*Ethyl 4-methyl-2-oxo-6-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate **(6a)**:* 47 mg, 90% yield, known compound,[18]white solid, R_f = 0.40 (hexanes/ethyl acetate = 1/2), 77% ee, $[\alpha]^{20}_D$ = +102.90 (*c* 0.62, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.43-7.28 (m, 5H), 6.67 (s, 1H), 5.55 (s, 1H), 4.56-4.55 (m, 1H), 3.95 (q, *J* = 7.1 Hz, 2H), 1.45 (d, *J* = 6.3 Hz, 3H), 0.93 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ (ppm) 165.4, 153.3, 146.7, 135.3, 129.5, 128.3, 127.9, 103.7, 60.0, 48.2, 23.6, 13.6. HPLC: Chiracel OD-H column, 254 nm, 30 °C, *hexane*/*i*-propanol = 90/10, flow = 0.7 mL/min, retention time 13.5 min and 14.8 min (maj).

*Ethyl 6-(3-chlorophenyl)-4-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate **(6b)**:* 54 mg, 92% yield, new compound, white solid, mp: 205-206 °C, R_f = 0.40 (hexanes/ethyl acetate = 1/2), 76% ee, $[\alpha]^{20}_D$ = +84.55 (*c* 0.68, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.42-7.12 (m, 5H), 5.92 (s, 1H), 4.42-4.40 (m, 1H), 3.92-3.85 (m, 2H), 1.33 (d, *J* = 6.4 Hz, 3H), 0.87 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ (ppm) 164.6, 153.5, 144.9, 136.1, 133.3, 128.9, 128.1, 125.9, 103.5, 59.6, 47.4, 23.0, 13.1. HPLC: Chiracel OD-3 column, 254 nm, 30 °C, *hexane*/*i*-propanol = 90/10, flow = 0.9 mL/min, retention time 9.6 min and 10.6 min (maj). HRMS (ESI) m/z Calculated for $C_{14}H_{16}ClN_2O_3$ $[M+H]^+$ 295.0844, found 295.0848.

*Ethyl 6-(3-bromophenyl)-4-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate **(6c)**:* 61 mg, 90% yield, new compound, white solid, mp: 199-200 °C, R_f = 0.35 (hexanes/ethyl acetate = 1/2), 78% ee, $[\alpha]^{20}_D$ = +73.93 (*c* 1.22, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.83 (s, 1H), 7.54-7.52 (m, 1H), 7.45 (s, 1H), 7.28-7.25 (m, 2H), 6.23 (s, 1H), 4.45 (d, *J* = 5.3 Hz, 1H), 3.99-3.91 (m, 2H), 1.41 (d, *J* = 6.3 Hz, 3H), 0.95 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ (ppm) 164.6, 153.3, 144.7, 136.3, 131.8, 130.9, 129.1, 126.3, 121.4, 103.6, 59.6, 47.4, 23.1, 13.2. HPLC: Chiracel OD-3 column, 254 nm, 30 °C, *hexane*/*i*-propanol = 90/10, flow = 0.9 mL/min, retention time 10.1 min and 10.8 min (maj). HRMS (ESI) m/z Calculated for $C_{14}H_{16}BrN_2O_3$ $[M+H]^+$ 339.0339, found 339.0342.

*Ethyl 6-(3-methoxyphenyl)-4-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate **(6d)**:* 52 mg, 90% yield, new compound, white solid, mp: 232-233 °C, R_f = 0.40 (hexanes/ethyl acetate = 1/2), 75% ee, $[\alpha]^{20}_D$ = +102.71 (*c* 0.70, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.60 (s, 1H), 7.29-7.25 (m, 1H), 6.94-6.83 (m, 3H), 6.41 (s, 1H), 4.44-4.41 (m, 1H), 3.97-3.91 (m, 2H), 3.80 (s, 3H), 1.41 (d, *J* = 6.3 Hz, 3H), 0.95 (t, *J* = 7.1

Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm) 165.5, 159.3, 153.9, 146.6, 136.3, 129.2, 120.5, 115.2, 113.4, 103.5, 59.9, 55.3, 47.9, 23.5, 13.7. HPLC: Chiracel AD-H column, 254 nm, 30 °C, *hexane*/*i*-propanol = 90/10, flow = 0.7 mL/min, retention time 22.2 min and 24.6 min (maj). HRMS (ESI) m/z Calculated for $C_{15}H_{19}N_2O_4$ $[M+H]^+$ 291.1339, found 291.1341.

Ethyl 6-(4-methoxyphenyl)-4-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate ***(6e)****:* 53 mg, 91% yield, new compound, white solid, mp: 214-215 °C, R_f = 0.40 (hexanes/ethyl acetate = 1/2), 79% ee, $[\alpha]^{20}_D$ = +81.92 (*c* 0.78, MeOH). ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.60 (brs, 1H), 7.28-7.25 (m, 2H), 6.91-6.89 (m, 2H), 6.18 (brs, 1H), 4.45 (s, 1H), 4.00-3.96 (m, 2H), 3.80 (s, 3H), 1.39 (d, *J* = 6.3 Hz, 3H), 0.94 (t, *J* = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm) 165.6, 160.6, 153.8, 146.8, 129.6, 127.1, 113.5, 103.0, 59.9, 55.3, 48.0, 23.5, 13.9. HPLC: Chiracel OD-3 column, 254 nm, 30 °C, *hexane*/*i*-propanol = 90/10, flow = 0.9 mL/min, retention time 14.7 min and 17.0 min (maj). HRMS (ESI) m/z Calculated for $C_{15}H_{19}N_2O_4$ $[M+H]^+$ 291.1339, found 291.1334.

Ethyl 4-methyl-2-oxo-6-(m-tolyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate ***(6f)****:* 52 mg, 95% yield, new compound, white solid, mp: 240-241 °C, R_f = 0.40 (hexanes/ethyl acetate = 1/2), 75% ee, $[\alpha]^{20}_D$ = +90.22 (*c* 0.90, MeOH). ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.20-7.01 (m, 5H), 6.03 (brs, 1H), 4.40 (s, 1H), 3.89-3.83 (m, 2H), 2.28 (s, 3H), 1.33 (d, *J* = 4.8 Hz, 3H), 0.84 (t, *J* = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ (ppm) 165.5, 153.5, 147.0, 137.9, 135.1, 130.2, 128.6, 128.1, 125.1, 103.4, 59.9, 48.0, 23.6, 21.3, 13.7. HPLC: Chiracel OD-3 column, 254 nm, 30 °C, *hexane*/*i*-propanol = 90/10, flow = 0.9 mL/min, retention time 9.8 min and 11.0 min (maj). HRMS (ESI) m/z Calculated for $C_{15}H_{19}N_2O_4$ $[M+H]^+$ 275.1390, found 275.1387.

Hydrogenation of Pyrimidin-2-ols at Gram Scale: A mixture of Pyrimidin-2-ols **1a** (1.282 g, 4.0 mmol), Hantzsch ester **4a** (1.216 g, 4.8 mmol, 1.2 equiv), and chiral phosphoric acid (*R*)-**3f** (151 mg, 0.2 mmol, 5 mol %) in Toluene (40 mL) was stirred at 40 °C under nitrogen for 24 h. After the reaction was completed (determined by TLC). The resulting mixture was concentrated in *vacuo* and further purification was performed by a silica gel column eluted with ethyl acetate/methanol to give thehydrogenation product (*R*)-(+)-**2a** 1.268 g in 98% yield and 94% ee.

Synthesis of the Chiral Cyclic Thiourea: According to the known report:[19] To a solution of cyclic urea (*R*)-(+)-**2a** (> 99% ee after recrystallization, 65 mg, 0.20 mmol) in anhydrous toluene (4.0 mL) was added Lawesson's reagent (97 mg, 0.24 mmol) under nitrogen atmosphere. The resulting solution was refluxed overnight. Toluene was removed in *vacuo* and the residue was diluted with water. The aqueous mixture was extracted with dichloromethane (15 mL×3). The combined organic layer was washed twice with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to give viscous oil. The crude product

was purified by flash column chromatography using dichloromethane/methanol as eluent to give the chiral thiourea 65 mg.

*Ethyl (R)-4,6-diphenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**8a**):* 65 mg, 96% yield, known compound,[20] white solid, > 99% ee, $[\alpha]^{20}_{D}$ = -7.98 (*c* 0.94, MeOH), R_f = 0.40 (hexanes/ethyl acetate = 1/2). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.82 (brs, 1H), 7.45-7.33 (m, 10H), 5.58 (s, 1H), 3.94-3.84 (m, 2H), 0.86-0.83 (m, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ (ppm) 174.5, 164.8, 143.9, 142.1, 134.0, 129.9, 129.0, 128.5, 128.4, 128.1, 126.9, 103.7, 60.4, 56.4, 13.5. HPLC: Chiracel AD-H column, 254 nm, 30 °C, *hexane*/*i*-propanol = 90/10, flow = 0.9 mL/min, retention time 16.6 min (maj) and 18.3 min.

ASSOCIATED CONTENT

Supporting information

NMR spectra of products, and HPLC for racemic and chiral products of all compounds. This material is available free of charge *via* the internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) (a) Biginelli, P. Aldehyde-urea derivatives of aceto-and oxaloacetic acids. *Gazz. Chim. Ital.* **1893**, *23*, 360. (b) Kappe, C. O. Recent Advances in the Biginelli Dihydropyrimidine Synthesis. New Tricks from an Old Dog. *Acc. Chem. Res.* **2000**, *33*, 879. (c) Kappe, C. O. The Generation of

Dihydropyrimidine Libraries Utilizing Biginelli Multicomponent Chemistry. *QSAR Comb. Sci.* **2003**, *22*, 630.

(2) (a) Fátima, Â.; Braga, T. C.; Neto, L. S.; Terra, B. S.; Oliveira, B. G. F.; Silva, D. L.; Modolo, L. V. A mini-review on Biginelli adducts with notable pharmacological properties. *J. Adv. Res.* **2015**, *6*, 363. (b) Kappe, C. O. Biologically active dihydropyrimidones of the Biginelli-type-a literature survey. *Eur. J. Med. Chem.* **2000**, *35*, 1043. (c) Stemper, J.; Isaac, K.; Pastor, J.; Frison, G.; Retailleau, P.; Voituriez, A.; Betzer, J.-F.; Marinetti, A. *Adv. Synth. Catal.* **2013**, *355*, 3613.

(3) Debonis, S.; Simorre, J. P.; Crevel, I.; Lebeau, L.; Skoufias, D. A.; Blangy, A.; Ebel, C.; Gans, P.; Cross, R.; Hackney, D. D.; Wade, R. H.; Kozielski, F. Interaction of the Mitotic Inhibitor Monastrol with Human Kinesin Eg5. *Biochemistry* **2003**, *42*, 338.

(4) Atwal, K. S.; Swanson, B. N.; Unger, S. E.; Floyd, D. M.; Moreland, S.; Hedberg, A.; O'Reilly, B. C. Dihydropyrimidine calcium channel blockers.3.3-Carbamoyl-4-aryl-1,2,3,4-tetrahydro-6-methyl-5-pyrimidinecarboxylic acid esters as orally effective antihypertensive agents. *J. Med. Chem.* **1991**, *34*, 806.

(5) For reviews on asymmetric catalytic Biginelli reaction: (a) Gong, L.-Z.; Chen, X.-H.; Xu, X.-Y. Asymmetric Organocatalytic Biginelli Reactions: A New Approach To Quickly Access Optically Active 3,4-Dihydropyrimidin-2-(1*H*)-ones. *Chem. Eur. J.* **2007**, *13*, 8920. (b) Heravi, M. M.; Asadi, S.; Lashkariani, B. M. Recent progress in asymmetric Biginelli reaction. *Mol Divers* **2013**, *17*, 389. (c) Rao, H.; Quan, Z.; Bai, L.; Ye, H. Progress on the Synthesis of Enantiomerically Pure 3,4-Dihydropyrimidin-2-one Derivatives. *Chin. J. Org. Chem.* **2016**, *36*, 283. (d) Yu, J.; Shi, F.; Gong, L.-Z. Brønsted-Acid-Catalyzed Asymmetric Multicomponent Reactions for the Facile Synthesis of Highly Enantioenriched Structurally Diverse Nitrogenous Heterocycles. *Acc. Chem. Res.* **2011**, *44*, 1156.

(6) (a) Sidler, D. R.; Barta, N.; Li, W.; Hu, E.; Matty, L.; Ikemoto, N.; Campbell, J. S.; Chartrain, M.; Gbewonyo, K.; Boyd, R.; Corley, E. G.; Ball, R. G.; Larsen, R. D.; Reider, P. Efficient synthesis of the optically active dihydropyrimidinone of a potent α1A- selective adrenoceptor antagonist. *J. Can. J. Chem.* **2002**, *80*, 646. (b) Schnell, B.; Strauss, U. T.; Verdino, P.; Faber, K.; Kappe, C. O. Synthesis of enantiomerically pure 4-aryl-3,4-dihydropyrimidin-2(1*H*)-ones via enzymatic resolution: preparation of the antihypertensive agent (*R*)-SQ 32926. *Tetrahedron: Asymmetry* **2000**, *11*, 1449.

(7) (a) Dondoni, A.; Massi, A. Design and Synthesis of New Classes of Heterocyclic C-Glycoconjugates and Carbon-Linked Sugar and Heterocyclic Amino Acids by Asymmetric

Multicomponent Reactions (AMCRs). *Acc. Chem. Res.* **2006**, *39*, 451. (b) Kappe, C. O.; Uray, G.; Roschger, P.; Lindner, W.; Kratky, C.; Keller, W.Synthesis and reactions of biginelli compounds-5. Facile preparation and resolution of a stable 5-dihydropyrimidinecarboxylic acid. *Tetrahedron* **1992**, *48*, 5473.

(8) Huang, Y.; Yang, F.; Zhu, C. Highly Enantioseletive Biginelli Reaction Using a New Chiral Ytterbium Catalyst: Asymmetric Synthesis of Dihydropyrimidines. *J. Am. Chem. Soc.* **2005**, *127*, 16386.

(9) (a) Chen, X.-H.; Xu, X.-Y.; Liu, H.; Cun, L.-F.; Gong, L.-Z. Highly Enantioselective Organocatalytic Biginelli Reaction. *J. Am. Chem. Soc.* **2006**, *128*, 14802. (b) Li, N.; Chen, X.-H.; Song, J.; Luo, S.-W.; Fan, W.; Gong, L.-Z. Highly Enantioselective Organocatalytic Biginelli and Biginelli-Like Condensations: Reversal of the Stereochemistry by Tuning the 3,3'-Disubstituents of Phosphoric Acids. *J. Am. Chem. Soc.* **2009**, *131*, 15301.

(10) Xin, J.; Chang, L.; Hou, Z.; Shang, D.; Liu, X.; Feng, X. An Enantioselective Biginelli Reaction Catalyzed by a Simple Chiral Secondary Amine and Achiral Brønsted Acid by a Dual-Activation Route. *Chem. Eur. J.* **2008**, *14*, 3177.

(11) (a) Xu, F.; Huang, D.; Lin, X.; Wang, Y. Highly enantioselective Biginelli reaction catalyzed by SPINOL-phosphoric acids. *Org. Biomol. Chem.* **2012**, *10*, 4467. (b) An, D.; Fan, Y.-S.; Gao, Y.; Zhu, Z.-Q.; Zheng, L.-Y.; Zhang, S.-Q. Highly Enantioselective Biginelli Reaction Catalyzed by Double Axially Chiral Bisphosphorylimides. *Eur. J. Org. Chem.* **2014**, 301. (c) Stucchi, M.; Lesma, G.; Meneghetti, F.; Rainoldi, G.; Sacchetti,A.; Silvani, A. Organocatalytic Asymmetric Biginelli-like Reaction Involving Isatin. *J. Org. Chem.* **2016**, *81*, 1877. (d) Hu, X.; Zhang, R.; Xie, J.; Zhou, Z.; Shan, Z. Synthesis of a novel sterically hindered chiral cyclic phosphoric acid derived from L-tartaric acid and application to the asymmetric catalytic Biginelli reaction. *Tetrahedron: Asymmetry* **2017**, *28*, 69. (e) Barbero, M.; Cadamuro, S.; Dughera, S. A Brønsted acid catalysed enantioselective Biginelli reaction. *Green Chem.* **2017**, *19*, 1529.

(12) (a) Wu, Y.-Y.; Chai, Z.; Liu, X.-Y.; Zhao, G.; Wang, S.-W. Synthesis of Substituted 5-(Pyrrolidin-2-yl)tetrazoles and Their Application in the Asymmetric Biginelli Reaction. *Eur. J. Org. Chem.* **2009**, 904. (b) Sohn, J.-H.; Choi, H.-M.; Lee, S.; Joung, S.; Lee, H.-Y. Probing the Mode of Asymmetric Induction of Biginelli Reaction Using Proline Ester Salts. *Eur. J. Org. Chem.* **2009**, 3858. (c) Saha, S.; Moorthy, J. N. Enantioselective Organocatalytic Biginelli Reaction: Dependence of the Catalyst on Sterics, Hydrogen Bonding, and Reinforced Chirality. *J. Org. Chem.* **2011**, *76*, 396. (d) Li, Z.-Y.; Chen, J.-W.; Liu, Y.; Xia, W.; Wang, L. The Use of Calixarenes in

Asymmetric Catalysis. *Curr. Org. Chem.* **2011**, *15*, 39. (e) Fedorova, O. V.; Titova, Y. A.; Vigorov, A. Y.; Toporova, M. S.; Alisienok, O. A.; Murashkevich, A. N.; Krasnov, V. P.; Rusinov, G. L.; Charushin, V. N. Asymmetric Biginelli Reaction Catalyzed by Silicon, Titanium and Aluminum Oxides. *Catal. Lett.* **2016**, *146*, 493. (f) Hang, Z.; Zhu, J.; Lian, X.; Xu, P.; Yu, H.; Han, S. A highly enantioselective Biginelli reaction using self-assembled methanoproline–thiourea organocatalysts: asymmetric synthesis of 6-isopropyl-3,4-dihydropyrimidines. *Chem. Commun.* **2016**, *52*, 80. (g) Yu, H.; Xu, P.; He, H.; Zhu, J.; Lin, H.; Han, S. Highly enantioselective Biginelli reactions using methanopyroline/thiourea-based dual organocatalyst systems: asymmetric synthesis of 4-substituted unsaturated aryl dihydropyrimidines. *Tetrahedron: Asymmetry* **2017**, *28*, 257.

(13) (a) Wang, Y.; Yang, H.; Yu, J.; Miao, Z.; Chen, R. Highly Enantioselective Biginelli Reaction Promoted by Chiral Bifunctional Primary Amine-Thiourea Catalysts: Asymmetric Synthesis of Dihydropyrimidines. *Adv. Synth. Catal.* **2009**, *351*, 3057. (b) Cai, Y.-F.; Yang, H.-M.; Li, L.; Jiang, K.-Z.; Lai, G.-Q.; Jiang, J.-X.; Xu, L.-W. Cooperative and Enantioselective NbCl5/Primary Amine Catalyzed Biginelli Reaction. *Eur. J. Org. Chem.* **2010**, 4986. (c) Ding, D.; Zhao, C.-G.Primary Amine Catalyzed Biginelli Reaction for the Enantioselective Synthesis of 3,4-Dihydropyrimidin-2(1*H*)-ones. *Eur. J. Org. Chem.* **2010**, 3802. (d) Xu, D.-Z.; Li, H.; Wang, Y. Highly enantioselective Biginelli reaction catalyzed by a simple chiral primary amine catalyst: asymmetric synthesis of dihydropyrimidines. *Tetrahedron* **2012**, *68*, 7867.

(14) For reviews on asymmetric hydrogenation of heteroarenes, see: (a) Glorius, F. Asymmetric hydrogenation of aromatic compounds. *Org. Biomol. Chem.* **2005**, *3*, 4171. (b) Zhou, Y.-G. Asymmetric hydrogenation of aromatic compounds. *Acc. Chem. Res.* **2007**, *40*, 1357. (c) Kuwano, R. Catalytic Asymmetric Hydrogenation of 5-Membered Heteroaromatics. *Heterocycles* **2008**, *76*, 909. (d) Wang, D.-S.; Chen, Q.-A.; Lu, S.-M.; Zhou, Y.-G. Asymmetric Hydrogenation of Heteroarenes and Arenes.*Chem. Rev.* **2012**, *112*, 2557. (e) He, Y.-M.; Song, F.-T.; Fan, Q.-H. Advances in Transition Metal-Catalyzed Asymmetric Hydrogenation of Heteroaromati. *Top. Curr. Chem.* **2014**, *343*, 145. (f) Nagano, T.; Iimuro,A.; Yamaji, K.; Kita, Y.; Mashima, K. Additive Effects on Asymmetric Hydrogenation of N-Heteroaromatics. *Heterocycles* **2014**, *88*, 103. (g) Zhao, D.; Candish, L.; Paul, D.; Glorius, F. N-Heterocyclic Carbenes in Asymmetric Hydrogenation. *ACS Catal.* **2016**, *6*, 5978. (h) Parmar, D.; Sugiono, E.; Raja, S.; Rueping, M. Complete Field Guide to Asymmetric BINOL-Phosphate Derived Brønsted Acid and Metal Catalysis: History and Classification by Mode of Activation; Brønsted Acidity, Hydrogen Bonding, Ion Pairing, and Metal Phosphates. *Chem. Rev.* **2014**, *114*, 9047.

(15) (a) Feng, G.-S.; Chen, M.-W.; Shi, L.; Zhou, Y.-G. Facile Synthesis of Chiral Cyclic Ureas through Hydrogenation of 2-Hydroxypyrimidine/Pyrimidin-2(1*H*)-one Tautomers. *Angew. Chem. Int. Ed.* **2018**, *57*, 5853. (b) Feng, G.-S.; Shi, L.; Meng, F.-J.; Chen, M.-W.; Zhou, Y.-G. Iridium-Catalyzed Asymmetric Hydrogenation of 4,6-Disubstituted 2-Hydroxypyrimidines. *Org. Lett.* **2018**, *20*, 6415.

(16) (a)Chen, Q.-A.; Gao, K.; Duan, Y.; Ye, Z.-S.; Shi, L.; Yang, Y.; Zhou, Y.-G. Dihydrophenanthridine: A New and Easily Regenerable NAD(P)H Model for Biomimetic Asymmetric Hydrogenation. *J. Am. Chem. Soc.* **2012**, *134*, 2442. (b) Chen, Z.-P.; Chen, M.-W.; Guo, R.-N.; Zhou, Y.-G. 4,5-Dihydropyrrolo [1,2-a]quinoxalines: A Tunable and Regenerable Biomimetic Hydrogen Source. *Org. Lett.* **2014**, *16*, 1406.

(17) (a) Memarian, H. R.; Farhadi, A. Light-induced dehydrogenation of 3,4-dihydropyrimidin-2(1*H*)-ones. *Monatsh. Chem.* **2009**, *140*, 1217. (b) Gorjizadeh, M.; Afshari, M. 4-Bis(triphenyl-phosphonium)-2-butene peroxodisulfate as an efficient oxidizing agent for one-pot synthesis of ethyl pyrimidin-2(1*H*)-one-5-carboxylates. *Russ. J. Gen. Chem.* **2017**, *87*, 842. (c) Karade, H. N.; Acharya, J.; Kaushik, M. P. An efficient and rapid dehydrogenation of 4-aryl-3,4-dihydropyrimidin-2(1*H*)-ones (DHPMs) using CAN/HCl. *Tetrahedron Lett.* **2012**, *53*, 5541.

(18) Singh, K.; Singh, K. Magnesium/methanol: an effective reducing agent for chemoselective reduction of pyrimidine-2(1*H*)-ones. *Tetrahedron Lett.* **2009**, *50*, 2219.

(19) Thanigaimalai, P.; Lee, K.-C.; Bang, S.-C.; Lee, J.-H.; Yun, C.-Y.; Roh, E.; Hwang, B.-Y.; Kim, Y.; Jung, S.-H. Inhibitory effect of novel tetrahydropyrimidine-2(1*H*)-thiones on melanogenesis. *Bioorg. Med. Chem.* **2010**, *18*, 1135.

(20) Sari, O.; Roy, V.; Métifiot, M.; Marchand, C.; Pommier, Y.; Bourg, S.; Bonnet, P.; Schinazi, R. F.; Agrofoglio, L. A.Synthesis of dihydropyrimidine α,γ-diketobutanoic acid derivatives targeting HIV integrase. *Eur. J. Med. Chem.* **2015**, *104*, 127.