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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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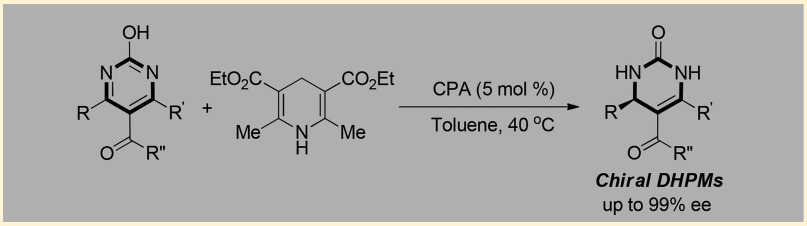
Supporting Information




**ABSTRACT:** Chiral phosphoric acid-catalyzed transfer hydrogenation of 2-hydroxypyrimidines has been successfully realized using Hantzsch ester or dihydrophenanthridine as the hydrogen source, furnishing the chiral 3,4-dihydropyrimidin-2(1*H*)-ones (DHPMs) with excellent yields and enantioselectivities of ≤99%. 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] possess a wide range of pharmacological properties, including anticancer activity, calcium channel inhibition, anti-inflammatory activity, antibacterial activity, etc.[2] Intensive research has suggested that both enantioisomers of DHPMs often show very different or even opposite biological activies. For example, the (*S*)-enantiomer of Monastrol is a more potent inhibitor of Eg5 ATPase activity than the (*R*)-enantiomer,[3] and (*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.

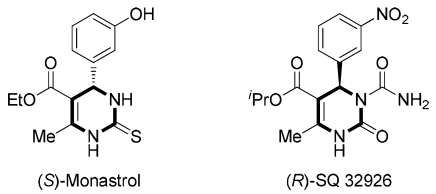
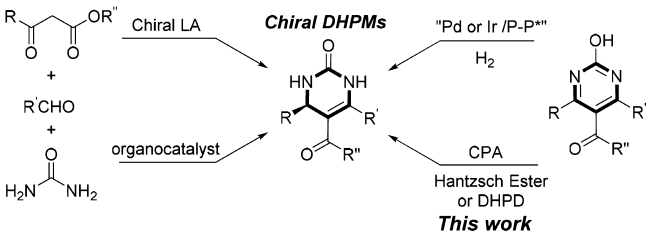



**Figure 1.** Chiral DHPMs with pharmacological activities.

Conceptually, asymmetric catalytic Biginelli reaction is the most straightforward approach to chiral DHPMs (Scheme 1).[5] However, the preparation of this kind of important compound always relied on the resolution of a racemic mixture[4,6] and chiral auxiliary-assisted synthesis[7] until a breakthrough was made in the asymmetric catalytic Biginelli reaction. In 2005, a new chiral ytterbium complex was designed and synthesized in Zhu's lab; they were able to catalyze the asymmetric Biginelli reaction with unprecedented enantioselectivity (80−99% ee).[8] Shortly afterward, Gong and co-workers reported the first organocatalytic enantioselective Biginelli reaction using a BINOL-derived chiral phosphoric acid as a catalyst, giving structurally diverse DHPMs with high ee's.[9] Feng described an enantioselective Biginelli reaction catalyzed by a chiral simple secondary amine combined with an achiral Brønsted acid in a dual activation mode.[10] Since then, a variety of catalysts have been successfully developed to promote this useful transformation, such as chiral Brønsted acids,[11] proline derivatives,[12] prime amines,[13] etc. Despite achievements with respect to the asymmetric Biginelli reaction, new approaches to chiral

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

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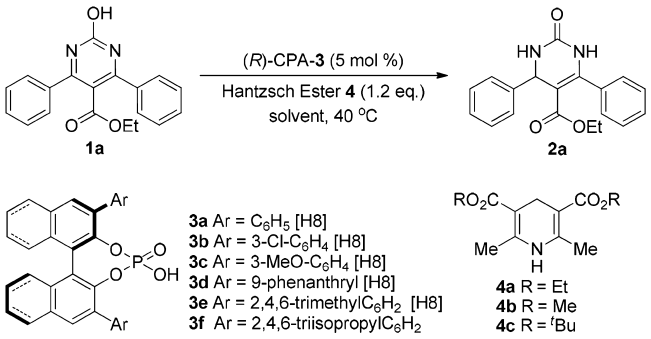
DHPMs are still of great value. In fact, asymmetric hydrogenation of aromatic compounds has been proven to be highly effective for preparing chiral cyclic molecules.[14] Partial reduction of pyrimidin-2-one may also directly produce the Beginelli-type DHPMs based on retrosynthetic analysis.

Very recently, our group realized an asymmetric hydrogenation of 2-hydroxypyrimidines using a chiral Pd or Ir catalyst to produce chiral cyclic ureas or DHPMs with high ee's, which presents a new facile method for synthesizing these kinds of important compounds.[15a,b] Herein, we disclose the first asymmetric biomimetic transfer hydrogenation of pyrimidines catalyzed by chiral phosphoric acid with Hantzsch ester or dihydrophenanthridine (DHPD) as a hydride donor, furnishing chiral DHPMs with excellent enantioselectivity and chemoselectivity.

With ethyl 2-hydroxy-4,6-diphenylpyrimidine-5-carboxylate (**1a**) as the model substrate, we began the pursuit of the enantioselective transfer hydrogenation for the 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 solvents, this transformation

**Table 1. Evaluation of Reaction Parameters**[a]



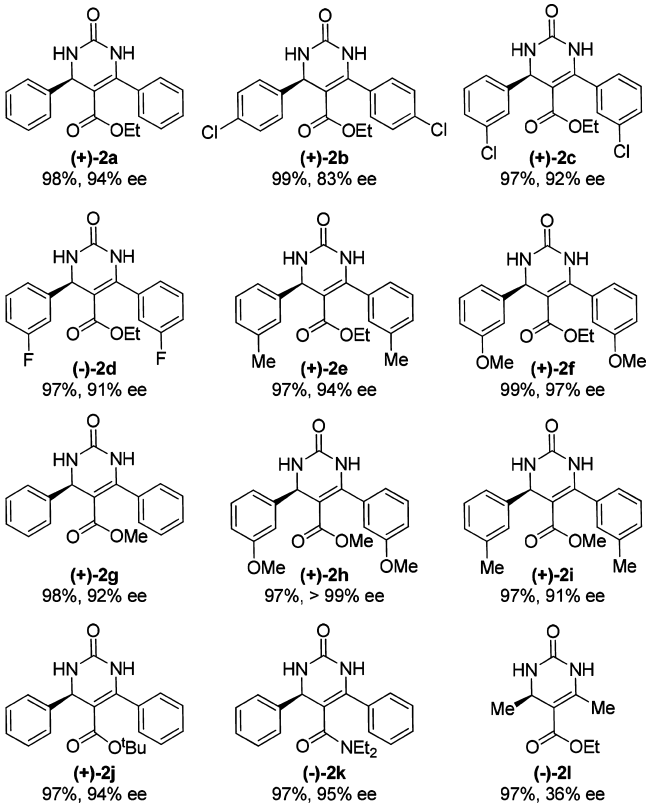

| entry | solvent | CPA | HEH (R) | yield[b] (%) | ee[c] (%) |
|---|---|---|---|---|---|
| 1 | THF | **3a** | **4a** (Et) | 97 | 40 |
| 2 | $CH_2Cl_2$ | **3a** | **4a** (Et) | 94 | 58 |
| 3 | EtOAc | **3a** | **4a** (Et) | 99 | 47 |
| 4 | 1,4-dioxane | **3a** | **4a** (Et) | 94 | 38 |
| 5 | toluene | **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 equiv), solvent (2.0 mL), 24 h, 40 °C. [b]Isolated yields. [c]Determined by chiral HPLC analysis.

could smoothly occur in the presence of CPA **3a** and Hantzsch ester **4a**, giving the desired chiral DHPMs **2a** in a good isolated yield, but toluene gave the best in terms of both yield and enantioselectivity (entry 5). When HEH **4c** with a bulky *tert*-butyl group was used as the hydride donor, the yield dramatically decreased to only 63% (entry 8). Next, different CPAs were screened with **4a** in toluene (entries 9−13). The results showed that the catalysts bearing a bulky substituent at C3 exhibit more prominent enantioselectivities. To our delight, CPA **3f** was selected as the best because of the 99% yield and 94% ee (entry 13).

Having defined an optimal reaction protocol, we explored the substrate scope to test the generality (Scheme 2). In

**Scheme 2. Substrate Scope**[a]




[a]Reaction conditions: **1** (0.2 mmol), CPA **3f** (5.0 mol %), HEH **4a** (1.2 equiv), toluene (4.0 mL), 24 h, 40 °C.

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 the yield and the enantioselectivity are very sensitive to the position of the substituents on the phenyl ring. The substrates with a *para*-substituted phenyl group (**2b**) underwent the reaction to afford the reduced product with moderate enantioselectivities (83% ee). With a *meta*-substituted phenyl group (**2c**−**2f**), DHPMs were furnished with enantioselectivities (≤97% ee) much higher than those seen for the substrates bearing a phenyl substituent at position 4. An *ortho* substituent group at the phenyl ring would suppress this reduction process completely due to steric hindrance. Replacement of the ethyl ester with methyl (**2g**−**2i**), *tert*-butyl ester (**2j**), or amide (**2k**) in the parent substrate maintained high enantioselectivities (from 92% to 99% ee) and yields. Ethyl 2-hydroxy-4,6-dimethylpyrimidine-5-carboxylate also was tested, and only a low ee obtained, albeit with a 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 the condition, excellent chemoselectivity can be achieved with DHPD used as an alternative hydride



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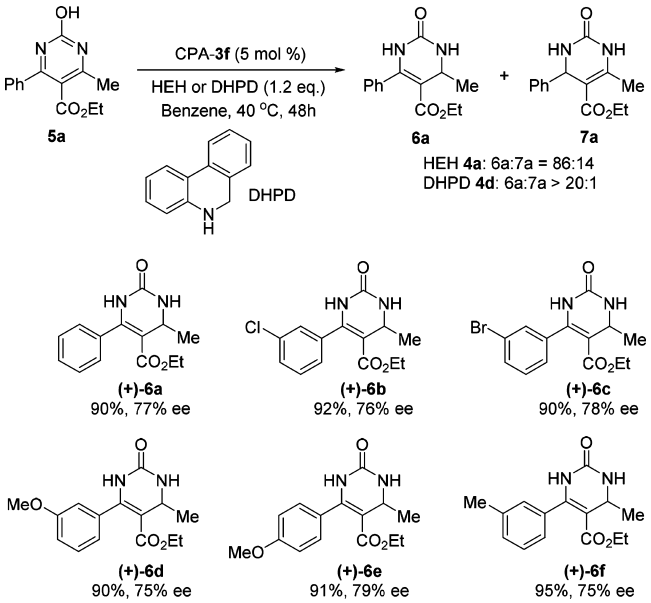
donor.[16] This improvement in chemoselectivity is possibly attributed to the discrepancy between the hydride transfer abilities of Hantzsch ester and dihydrophenanthridine. With a hydride donor that was weaker than Hantzsch ester, DHPD could be a proper reductant in accessing selective hydrogenation 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 a methyl-substituted chiral carbon atom at position 4 were prepared with good yields and moderate ee's (Scheme 3). Unfortunately, this kind of reduction failed to occur upon further study of the scope of other alkyl-substituted substrates.

**Scheme 3. Enantioselective Transfer Hydrogenation of Unsymmetrical Multisubstituted 2-Hydroxypyrimidines**[a]

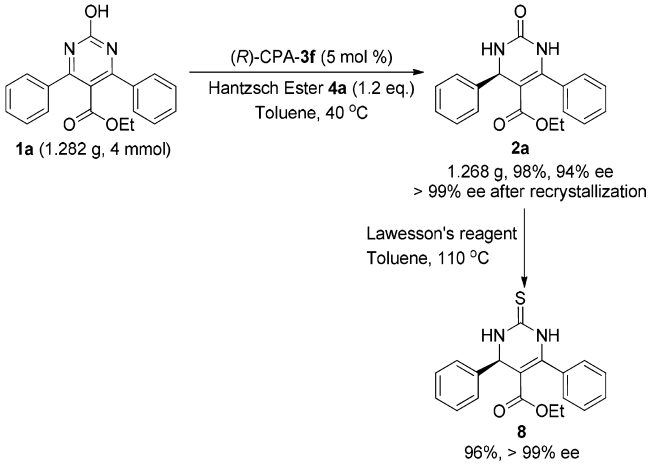



[a]Reaction conditions: **5** (0.2 mmol), CPA **3f** (5.0 mol %), DHPD (1.2 equiv), benzene (4.0 mL), 48 h, 40 °C. DHPD, dihydrophenanthridine.

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

On the basis of the experimental results presented above and the related research,[14h] a plausible stepwise hydrogenation process was proposed (Scheme 5). First, the chiral phosphoric acid facilitated the reversible isomerization to form the active tautomer **9**. Second, the C═N bond of **9** was 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 interactions and the effect of steric hindrance build up the "three-point contact

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




model" via *re* face attachment that determines the stereoselectivity.

In conclusion, we reported the first asymmetric biomimetic transfer hydrogenation of pyrimidines catalyzed by chiral phosphoric acid, successfully furnishing chiral DHPMs with excellent yields and enantioselectivities (≤99% ee). In particular, novel chiral DHPMs with an alkyl stereogenic center can be prepared through highly chemoselective transfer hydrogenation, which has seldom been previously described. The detailed investigation of the potential bioactivity of this new kind of chiral DHPM 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 a 400 MHz instrument with tetramethylsilane (TMS) as the internal standard. The enantiomeric excess was determined by HPLC analysis, using the chiral column described below in detail. Optical rotations were measured with a 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, compounds **1a**,[15a] **1d**,[15a] **1e**,[15a] **1j**,[15a] **5a** and **5b**,[17a] **5c**,[17b] and **5d**−**5f**[17c] are known (see Scheme S1).

Copper(II) trifluoromethanesulfonate (0.271 g, 5.0 mol %) was added to 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 of ethanol. After being heated at 80 °C under nitrogen for 24 h in an oil bath, the reaction mixture was cooled to 0 °C, and the precipitate 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 (*S*-)**1** or (*S*-)**5** (3.0 mmol), $CuCl_2{\cdot}2H_2O$ (5.0 mg, 1.0 mol %), and potassium carbonate (41 mg, 10 mol %) in dichloromethane (6.0 mL) was heated at 40 °C for 30 min in an oil bath, and then 65 wt % *tert*-butyl hydroperoxide (0.832 g, 6.0 mmol) was added dropwise over a period of 10 min. The resulting mixture was stirred at 35 °C for 24 h in an oil bath. Saturated aqueous sodium thiosulfate (10 mL) was added to quench the excess *tert*-butyl hydroperoxide. After being stirred for 20 min, the mixture was extracted with dichloromethane (3 × 40 mL). The combined organic layer was dried over anhydrous sodium sulfate and concentrated in vacuo. The crude product was purified by flash column chromatog-



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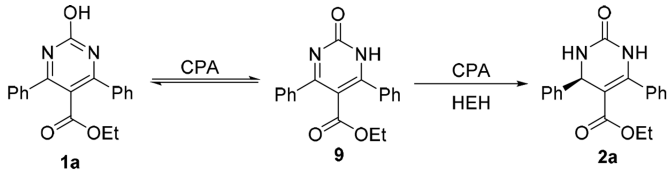
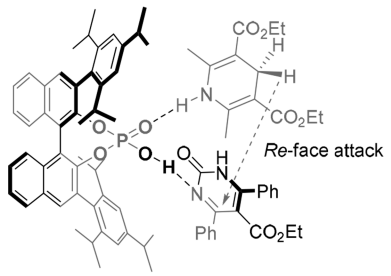
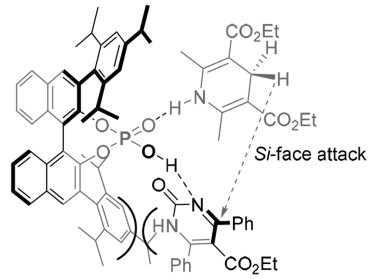
**Scheme 5. Proposed Reaction Pathway and Transition State**




transition state A: favored




transition state B: disfavored

raphy using hexanes and ethyl acetate as the eluent to give the desired products.

*Ethyl 4,6-Bis(4-chlorophenyl)-2-hydroxypyrimidine-5-carboxylate (**1b**).* 0.553 g, 36% yield (two steps), new compound, white solid; mp 95−96 °C; $R_f$ = 0.45 (10/1 dichloromethane/methanol); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 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, $CDCl_3$) $\delta$ 165.9, 157.9, 137.8, 129.6, 129.1, 111.9, 62.1, 13.4.; HRMS (ESI) $m/z$ calcd 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 (two steps), new compound, white solid; mp 160−161 °C; $R_f$ = 0.30 (1/1 hexanes/ethyl acetate); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 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, $CDCl_3$) $\delta$ 165.5, 157.6, 135.6, 134.8, 131.4, 130.2, 128.3, 126.3, 112.2, 62.2, 13.5; HRMS (ESI) $m/z$ calcd 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 (two steps), new compound, white solid; mp 184−185 °C; $R_f$ = 0.30 (1/1 hexanes/ethyl acetate); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 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, $CDCl_3$) $\delta$ 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, $CDCl_3$) $\delta$ −111.16; HRMS calcd 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 (two steps), new compound, white solid; mp 190−191 °C; $R_f$ = 0.51 (20/1 dichloromethane/methanol); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 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{$^1$H} NMR (100 MHz, $CDCl_3$) $\delta$ 165.9, 157.2, 137.9, 131.4, 128.2, 128.1, 124.6, 111.4, 61.2, 20.9, 12.9; HRMS (ESI) $m/z$ calcd 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 (two steps), new compound, white solid; mp 215−216 °C; $R_f$ = 0.35 (20/1 dichloromethane/methanol); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 13.14 (s, 1H), 7.63−7.61 (m, 4H), 7.52−7.48 (m, 6H), 3.46 (s, 3H); $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) $\delta$ 166.9, 157.9, 131.3, 128.8, 128.7, 128.1, 128.0, 111.6, 52.5; HRMS (ESI) $m/z$ calcd 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 (two steps), new compound, white solid; mp 168−169 °C; $R_f$ = 0.30 (1/1 hexanes/ethyl acetate); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 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{$^1$H} NMR (100 MHz, $CDCl_3$) $\delta$ 166.9, 159.7, 157.7, 135.3, 129.9, 120.2, 117.7, 113.0, 111.7, 55.5, 52.6; HRMS (ESI) $m/z$ calcd 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 (two steps), new compound, white solid; mp 252−253 °C; $R_f$ = 0.30 (1/1 hexanes/ethyl acetate); $^1$H NMR (400 MHz, DMSO) $\delta$ 12.53 (s, 1H), 7.39−7.30 (m, 8H), 3.39 (s, 3H), 2.37 (s, 6H); $^{13}$C{$^1$H} NMR (100 MHz, DMSO) $\delta$ 167.6, 138.3, 131.7, 128.9, 128.8, 125.3, 100.0, 52.7, 21.4; HRMS (ESI) $m/z$ calcd 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 (two steps), new compound, white solid; mp 209−210 °C; $R_f$ = 0.45 (ethyl acetate); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.65−7.63 (m, 4H), 7.52−7.47 (m, 6H), 1.15 (s, 9H); $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) $\delta$ 164.9, 157.7, 130.9, 128.6, 128.2, 83.0, 27.3; HRMS (ESI) $m/z$ calcd 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 (two steps), new compound, white solid; mp 225−226 °C; $R_f$ = 0.25 (ethyl acetate); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 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{$^1$H} NMR (100 MHz, $CDCl_3$) $\delta$ 164.9, 157.8, 130.7, 128.4, 128.1, 113.5, 42.4, 38.3, 12.4, 10.9; HRMS (ESI) $m/z$ calcd for $C_{21}H_{22}N_3O_2$ $[M + H]^+$ 348.1707, found 348.1710.

**General Procedure 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 an oil bath. After the reaction had reached completion (determined by TLC), the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel using a dichloromethane/methanol 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 (20/1 dichloromethane/methanol); 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, $CDCl_3$) $\delta$ 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, $CDCl_3$) $\delta$ 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, 80/



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20 hexane/isopropanol, flow rate of 0.7 mL/min, retention times of 13.8 min (major) 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 (30/1 dichloromethane/methanol); 83% ee; $[\alpha]^{20}_D$ = +26.02 (*c* 0.88, MeOH); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 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, $CDCl_3$) $\delta$ 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, 80/20 hexane/isopropanol, flow rate of 0.7 mL/min, retention times of 13.2 min (major) and 15.7 min; HRMS (ESI) *m*/*z* calcd 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 (1/1 hexanes/ethyl acetate); 92% ee; $[\alpha]^{20}_D$ = +8.15 (*c* 0.54, MeOH); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 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, $CDCl_3$) $\delta$ 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, 80/20 hexane/isopropanol, flow rate of 0.7 mL/min, retention times of 14.3 min (major) and 16.2 min; HRMS (ESI) *m*/*z* calcd 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 (1/1 hexanes/ethyl acetate); 91% ee; $[\alpha]^{20}_D$ = −3.87 (*c* 0.80, MeOH); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 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, $CDCl_3$) $\delta$ 164.9, 163.0 (d, $J_{C-F}$ = 246.8 Hz), 162.2 (d, $J_{C-F}$ = 247.1 Hz), 153.3, 146.2 (d, $J_{C-F}$ = 2.0 Hz), 145.8 (d, $J_{C-F}$ = 6.1 Hz), 136.5 (d, $J_{C-F}$ = 8.1 Hz), 130.4 (d, $J_{C-F}$ = 8.1 Hz), 129.8 (d, $J_{C-F}$ = 8.2 Hz), 124.0 (d, $J_{C-F}$ = 3.0 Hz), 122.1 (d, $J_{C-F}$ = 2.8 Hz), 116.5 (d, $J_{C-F}$ = 21.0 Hz), 115.6 (d, $J_{C-F}$ = 22.9 Hz), 115.1 (d, $J_{C-F}$ = 21.2 Hz), 113.5 (d, $J_{C-F}$ = 22.0 Hz), 102.2, 60.3, 54.9, 13.5; $^{19}$F NMR (376 MHz, $CDCl_3$) $\delta$ −112.01, −112.49; HPLC Chiracel AD-H column, 254 nm, 30 °C, 85/15 hexane/isopropanol, flow rate of 0.9 mL/min, retention times of 13.3 min (major) and 15.0 min; HRMS (ESI) *m*/*z* calcd 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 (30/1 dichloromethane/methanol); 94% ee; $[\alpha]^{20}_D$ = +25.18 (*c* 0.81, MeOH); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 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{$^1$H} NMR (100 MHz, $CDCl_3$) $\delta$ 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, 80/20 hexane/isopropanol, flow rate of 0.8 mL/min, retention times of 10.1 min (major) and 12.9 min; HRMS (ESI) *m*/*z* calcd 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 (20/1 dichloromethane/methanol); 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, $CDCl_3$) $\delta$ 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{$^1$H} NMR (100 MHz, $CDCl_3$) $\delta$ 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, 70/30 hexane/isopropanol, flow rate of 0.8 mL/min, retention times of 14.8 min (major) 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 (30/1 dichloromethane/methanol); 92% ee; $[\alpha]^{20}_D$ = +10.33 (*c* 1.22, MeOH); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.44−7.31 (m, 10H), 7.02 (brs, 1H), 5.90 (brs, 1H), 5.52 (s, 1H), 3.41 (s, 3H); $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) $\delta$ 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, 80/20 hexane/isopropanol, flow rate of 0.8 mL/min, retention times of 11.1 min (major) and 14.5 min; HRMS (ESI) *m*/*z* calcd 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 (30/1 dichloromethane/methanol); >99% ee; $[\alpha]^{20}_D$ = +26.61 (*c* 1.30, MeOH); $^1$H NMR (400 MHz, DMSO) $\delta$ 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{$^1$H} NMR (100 MHz, DMSO) $\delta$ 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, 70/30 hexane/isopropanol, flow rate of 0.8 mL/min, retention times of 14.0 min (major) and 17.0 min; HRMS (ESI) *m*/*z* calcd 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 (30/1 dichloromethane/methanol); 91% ee; $[\alpha]^{20}_D$ = +24.68 (*c* 0.62, MeOH); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 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{$^1$H} NMR (100 MHz, $CDCl_3$) $\delta$ 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, 80/20 hexane/isopropanol, flow rate of 0.7 mL/min, retention times of 11.5 min (major) and 15.8 min; HRMS (ESI) *m*/*z* calcd 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 (4/1 dichloromethane/ethyl acetate); 94% ee; $[\alpha]^{20}_D$ = +32.50 (*c* 0.68, MeOH); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.43−7.21 (m, 11H), 6.10 (s, 1H), 5.42 (s, 1H), 1.04 (s, 9H); $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) $\delta$ 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, 80/20 hexane/isopropanol, flow rate of 0.7 mL/min, retention times of 9.6 min (major) and 11.6 min; HRMS (ESI) *m*/*z* calcd 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, $CDCl_3$) $\delta$ 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{$^1$H} NMR (100 MHz, $CDCl_3$) $\delta$ 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, 80/20 hexane/isopropanol, flow rate of 0.8 mL/min, retention times of 13.9 and 16.1 min (major); HRMS (ESI) *m*/*z* calcd 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) $\delta$ 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{$^1$H} NMR (100 MHz, DMSO) $\delta$ 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, 80/20 hexane/isopropanol, flow rate of 0.7 mL/min, retention times of 7.8 min (major) and 8.6 min.

**General Procedure 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



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mL) was stirred at 40 °C under nitrogen for 24 h. The mixture was then cooled to room temperature, and DHPD **4d** (36 mg, 0.20 mmol, 1 equiv) was added again under the nitrogen atmosphere. The reaction mixture was placed in an oil bath at 40 °C under nitrogen for an additional 24 h. After the reaction had reached completion (determined by TLC), the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel to yield the desired 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 (1/2 hexanes/ethyl acetate); 77% ee; $[\alpha]^{20}_D$ = +102.90 (*c* 0.62, MeOH); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 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); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 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, 90/10 hexane/isopropanol, flow rate of 0.7 mL/min, retention times of 13.5 and 14.8 min (major).

*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 (1/2 hexanes/ethyl acetate); 76% ee; $[\alpha]^{20}_D$ = +84.55 (*c* 0.68, MeOH); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 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); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 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, 90/10 hexane/isopropanol, flow rate of 0.9 mL/min, retention times of 9.6 and 10.6 min (major); HRMS (ESI) *m*/*z* calcd 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 (1/2 hexanes/ethyl acetate); 78% ee; $[\alpha]^{20}_D$ = +73.93 (*c* 1.22, MeOH); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 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); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 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, 90/10 hexane/isopropanol, flow rate of 0.9 mL/min, retention times of 10.1 and 10.8 min (major); HRMS (ESI) *m*/*z* calcd 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 (1/2 hexanes/ethyl acetate); 75% ee; $[\alpha]^{20}_D$ = +102.71 (*c* 0.70, MeOH); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 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, $CDCl_3$) $\delta$ 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, 90/10 hexane/isopropanol, flow rate of 0.7 mL/min, retention times of 22.2 and 24.6 min (major); HRMS (ESI) *m*/*z* calcd 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 (1/2 hexanes/ethyl acetate); 79% ee; $[\alpha]^{20}_D$ = +81.92 (*c* 0.78, MeOH); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 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, $CDCl_3$) $\delta$ 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, 90/10 hexane/isopropanol, flow rate of 0.9 mL/min, retention times of 14.7 and 17.0 min (major); HRMS (ESI) *m*/*z* calcd 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 (1/2 hexanes/ethyl acetate); 75% ee; $[\alpha]^{20}_D$ = +90.22 (*c* 0.90, MeOH); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 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, $CDCl_3$) $\delta$ 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, 90/10 hexane/isopropanol, flow rate of 0.9 mL/min, retention times of 9.8 and 11.0 min (major); HRMS (ESI) *m*/*z* calcd 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 had reached completion (determined by TLC), the resulting mixture was concentrated in vacuo and further purification was performed by a silica gel column eluted with the ethyl acetate/methanol eluent to give the hydrogenation product (*R*)-(+)-**2a** (1.268 g, 98% yield, 94% ee).

**Synthesis of the Chiral Cyclic Thiourea.** According to a 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 a 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 (3 × 15 mL). The combined organic layer was washed twice with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure to give a viscous oil. The crude product was purified by flash column chromatography using a dichloromethane/methanol 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 (1/2 hexanes/ethyl acetate); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 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); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 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, 90/10 hexane/isopropanol, flow rate of 0.9 mL/min, retention times of 16.6 min (major) and 18.3 min.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.8b03128.

NMR spectra of products and HPLC data for racemic and chiral products of all compounds (PDF)

Crystallographic data (CIF)

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### Notes

The authors declare no competing financial interest.

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