

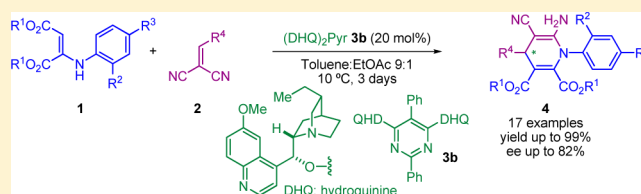
# Asymmetric Organocatalytic Synthesis of Substituted Chiral 1,4-Dihydropyridine Derivatives

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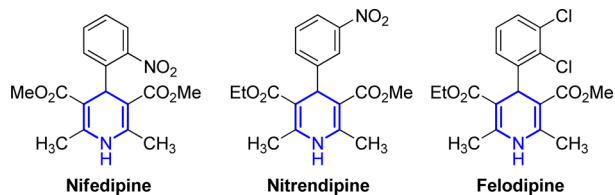
## Supporting Information

**ABSTRACT:** The first cinchona-alkaloid-organocatalyzed enantioselective synthesis of chiral 1,4-dihydropyridine derivatives is described. Bis-cinchona catalyst **3b** activates the Michael addition reaction between malononitrile derivatives **2** and enamines **1**, affording the appealing and highly substituted 1,4-dihydropyridines **4** with very good results in most cases. This is one of very few examples of the synthesis of chiral 1,4-dihydropyridines by an enantioselective catalytic procedure. The highly substituted final compounds are of interest for their potential biological activity. This efficient protocol opens the door to a new area of research for the asymmetric construction of these skeletons for which enantioselective syntheses are still very limited.



## INTRODUCTION

1,4-Dihydropyridine derivatives (1,4-DHPs) are a significant class of pharmacophore compounds frequently found in natural products and, more recently, as biomimetic reducing agents.<sup>1</sup> Their biological properties have allowed them to find medicinal application in the treatments of different diseases.<sup>2</sup> In particular, their biological importance has been demonstrated by their use as vasodilators, antihypertensive, anti-inflammatory, antihypoxic, anti-ischemic, and antitubercular agents, and above all as calcium channel modulators (Figure 1).<sup>2</sup> As with other drug



**Figure 1.** Representative structures of 1,4-dihydropyridine-based drugs.

molecules, the role of the stereochemistry at C-4 can exhibit both qualitative and quantitative differences in the biological activity of these compounds. Thus, the control of the stereoselectivity of these chiral centers becomes an inspiring task in the field of enantioselective organocatalysis.<sup>3</sup>

1,4-DHPs are generally synthesized following the classical four-component Hantzsch reaction,<sup>4</sup> which involves the condensation of an aldehyde, two equivalents of a  $\beta$ -ketoester, and ammonia or a synthetic equivalent in a multicomponent approach.<sup>5</sup> The synthesis of racemic 1,4-DHPs is an active task in organic chemistry,<sup>6</sup> and chiral analogues have mainly been

obtained either by the use of chiral auxiliaries<sup>3</sup> or by chiral resolution.<sup>7</sup> However, very few enantioselective organocatalytic methods are known.<sup>8</sup> This fact together with the biological interest of these molecules and the search for new analogues with novel binding properties, encouraged us to develop a new approach for their asymmetric synthesis via chiral organocatalysis.<sup>9</sup> We envisioned that chiral organic bases such as cinchona derivatives could promote the enantioselective version of this reaction, because  $\text{Et}_3\text{N}$  is able to promote the racemic formation of 1,4-DHPs.<sup>10</sup> Herein, we report our results concerning the synthesis of the highly functionalized 1,4-DHPs **4** via reaction of enamines **1** and malononitriles **2** in the presence of chiral basic organocatalysts **3** (Scheme 1).

## Scheme 1. Model Reaction for the Synthesis of Chiral 1,4-DHPs 4



## RESULTS AND DISCUSSION

To explore the feasibility of this approach, we studied the capacity of different chiral basic organocatalysts **3a–i** to promote the reaction (Figure 2).

We examined the reactivity and enantioselectivity provided by these catalysts in a model reaction between enamines **1a–b**

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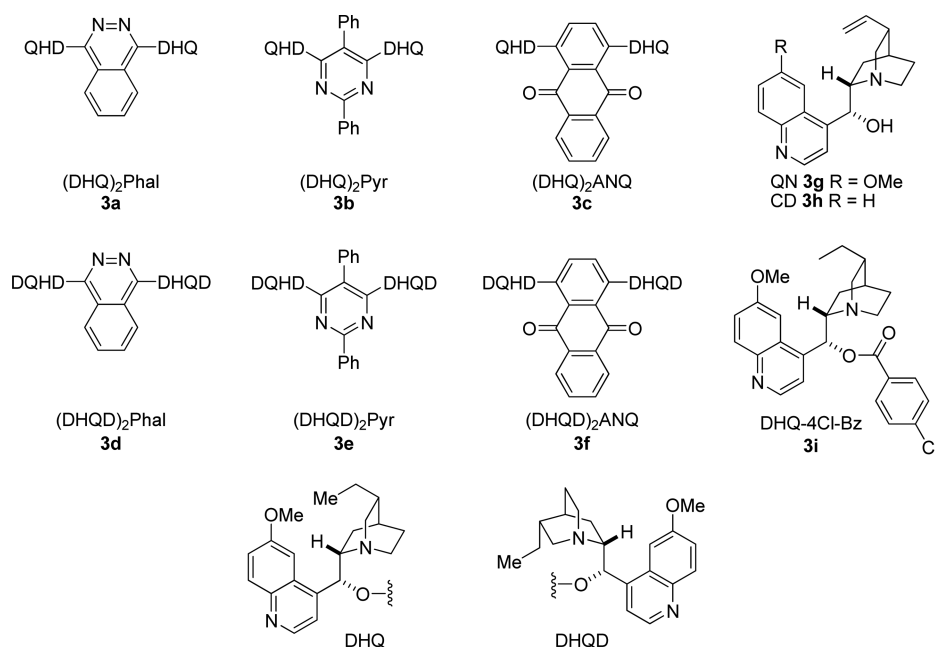
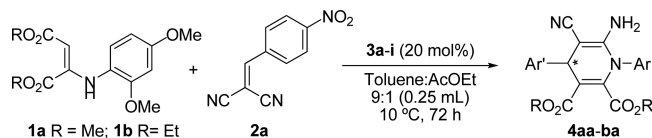


Figure 2. Cinchona alkaloids 3a–i tested as catalysts.

and malononitrile **2a**. A selection of these results is reported in Table 1.

Table 1. Screening of the Reaction Conditions for the Synthesis of Chiral 1,4-DHPs 4aa–ba<sup>a</sup>

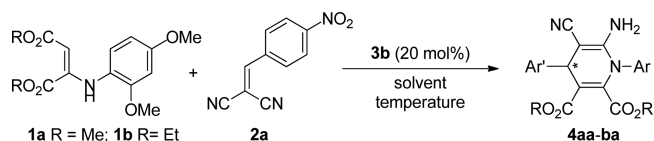


entry	catalyst	R	yield (%) <sup>b</sup>	ee (%) <sup>c</sup>
1	3a	Me	91	66
2	3b	Me	81	80
3	3b	Et	97	74
4	3c	Me	22	54
5	3d	Me	47	64
6	3e	Me	13	54
7	3f	Me	23	68
8	3g	Me	15	17
9	3h	Me	30	8
10	3i	Me	10	32

<sup>a</sup>Alkylidenmalononitrile **2** (0.1 mmol) was added to a mixture of catalyst **3a–i** (20 mol%) and enamine **1** (0.3 mmol) in toluene:AcOEt 9:1 (0.25 mL). <sup>b</sup>Isolated yield after column chromatography (SiO<sub>2</sub>, *n*-hexane:AcOEt 7:3). <sup>c</sup>Determined by chiral HPLC analysis (Daicel Chiralpak IB, *n*-hexane/*i*-PrOH 70:30, 1 mL/min).

Although promising enantioselectivity results were obtained with catalysts **3a–f**, the best results in terms of both reactivity and enantioselectivity were achieved using bis-cinchona **3b** (Table 1, entry 2). In addition, slight differences were observed between enamines **1a** and **1b**, which contained either a methyl or an ethyl ester group, respectively (entries 2 and 3). Enamine **1a** provided higher enantioselectivity (entry 2), whereas enamine **1b** resulted in a better yield (entry 3). These results encouraged us to continue with both enamines **1a,b** in the subsequent study, where different key parameters of this model reaction using catalyst **3b** were tested (Table 2).

Table 2. Screening of the Reaction Conditions for the Synthesis of Chiral 1,4-DHPs 4aa–ba<sup>a</sup>

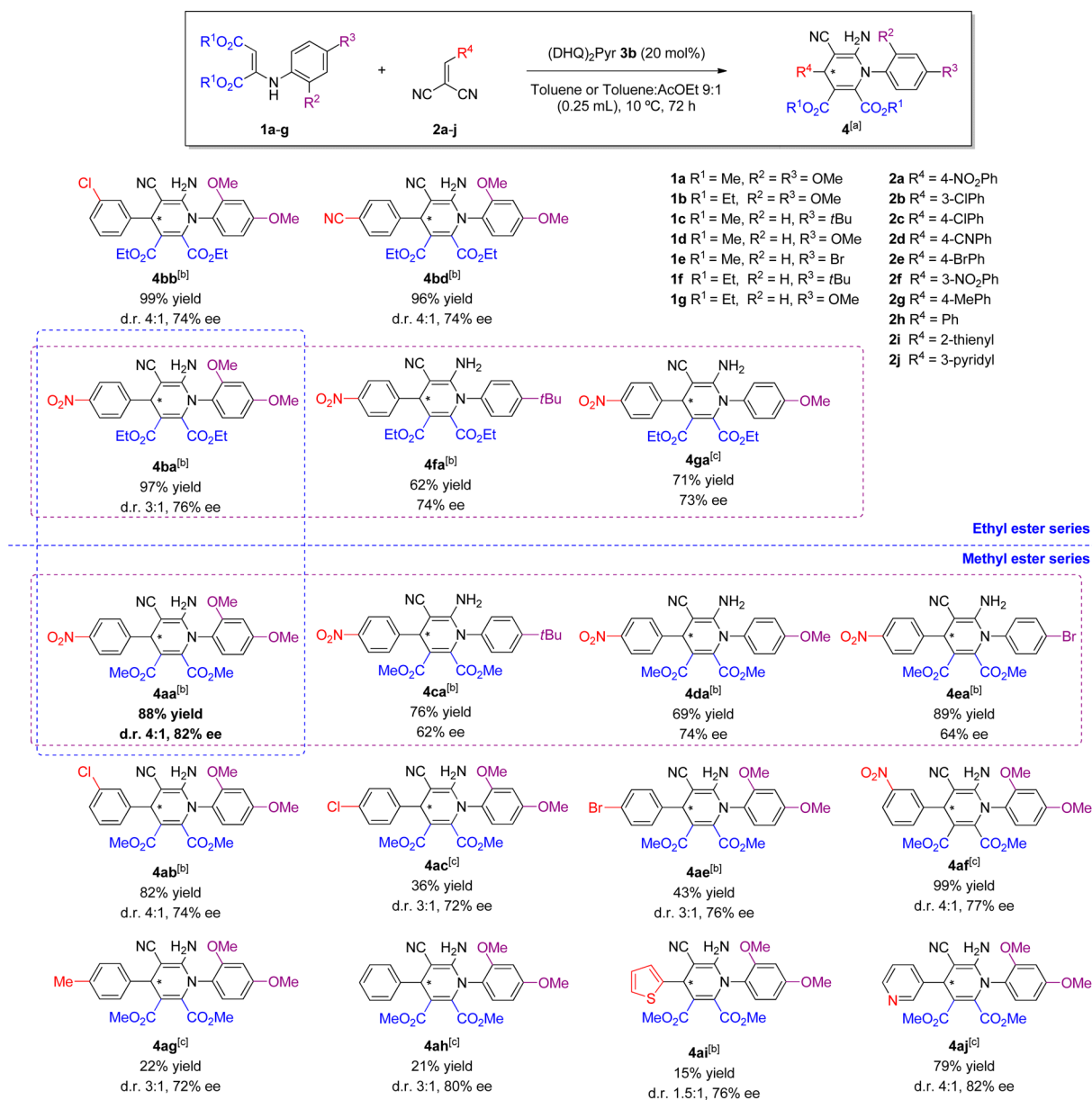


entry	solvent (mL)	enamine (equiv)	T (°C)	time (h)	yield (%) <sup>b</sup>	ee (%) <sup>c</sup>
1	AcOEt (0.25)	1a (3)	10	72	89	64
2	toluene/AcOEt 9:1 (0.25)	1a (3)	10	72	81	80
3	toluene/AcOEt 95:5 (0.25)	1a (3)	10	72	70	80
4	toluene (0.25)	1a (3)	10	72	88	82
5	toluene/AcOEt 9:1 (0.25)	1a (3)	0	72	32	80
6	toluene/AcOEt 9:1 (0.25)	1a (3)	-18	120	<5	85
7	toluene/AcOEt 9:1 (0.5)	1b (2)	10	120	49	68
8	toluene/AcOEt 9:1 (0.5)	1b (3)	10	72	93	76
9	toluene/AcOEt 9:1 (0.5)	1b (4)	10	72	93	76
10	toluene/AcOEt 9:1 (0.5)	1b (5)	10	72	95	76
11	toluene/AcOEt 9:1 (0.25)	1b (3)	10	72	97	76
12	toluene/AcOEt 9:1 (0.25)	1b (3)	-18	72	<5	90

<sup>a</sup>Alkylidenmalononitrile **2** (0.1 mmol) was added to a mixture of catalyst **3b** (20 mol%, 18.17 mg) and enamine **1** (0.3–0.5 mmol) in the corresponding solvent (0.25–0.5 mL). <sup>b</sup>Isolated yield after column chromatography (SiO<sub>2</sub>, *n*-hexane/AcOEt 7:3). <sup>c</sup>Determined by chiral HPLC analysis (Daicel Chiralpak IB, *n*-hexane/*i*-PrOH 70:30, 1 mL/min).

The ratio of toluene/AcOEt was examined to find the best polarity for the process (Table 2, entries 1–4). Although toluene was the best solvent in this case, in further experiments

Scheme 2. Scope of the Organocatalytic Synthesis of Enantiomerically Enriched 1,4-DHPs 4



<sup>[a]</sup>Reactions purified by column chromatography. <sup>[b]</sup>Reactions performed in toluene (0.25 mL). <sup>[c]</sup>Reactions performed in toluene:AcOEt 9:1 (0.25 mL).

the use of 10% of AcOEt was crucial to obtain good yields without compromising the enantioselectivity. Consequently, both media, 9:1 toluene/AcOEt and only toluene, were used to develop the final scope because depending on the substrate, better results were observed in one option or the other. (Scheme 2). Decreasing the temperature to  $-18$  °C led to a slightly improved enantioselectivity but a very low reactivity (entries 5, 6 and 12). The ratio of enamine/malononitrile was also explored, but no remarkable differences were found when using more than 3 equiv of **1b** (compare entries 8–10). In contrast, a slower reaction rate and poorer enantioselectivity were found when only 2 equiv of **1b** were used (entry 7). The concentration of the reaction had no significant effect on the enantioselectivity or the reactivity of the process (compare entries 8 and 11). Therefore, the best reaction conditions were found to be 0.25 mL of 9:1 toluene/AcOEt or only toluene, 20

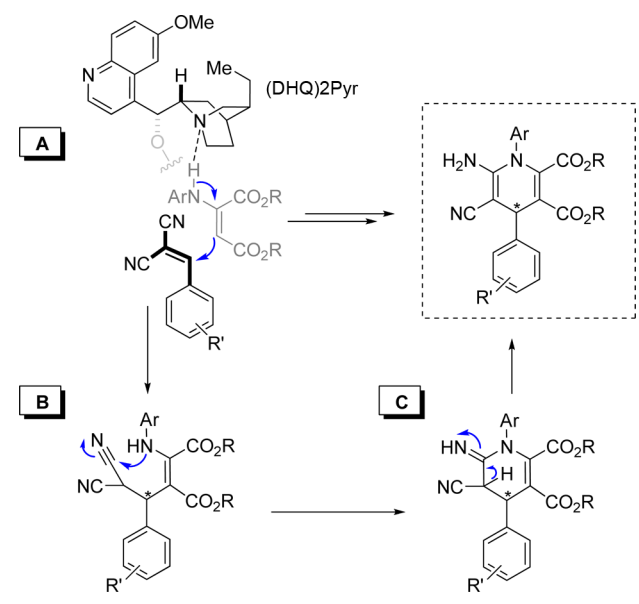
mol% of catalyst **3b** and three equiv of enamine **1**, at 10 °C. In order to develop the methodology, the efficiency of these conditions was further explored for a variety of enamines **1a–g** and alkylidene malononitriles **2a–j** (Scheme 2).

In general, the resulting chiral 1,4-DHPs **4** were achieved with good enantioselectivities (up to 82%) and moderate to very good yield (up to 99%). The correlation between the electronic environment of the enamines **1** and the reactivity and the enantioselectivity of the process remains unclear, but it seems that better results were obtained with enamines possessing two MeO groups in the aniline ring (i.e., **1a** and **1b**), in comparison with the differently substituted *p*-*t*Bu-, *p*-OMe-, *p*-Br-enamines [see: **4aa** vs **4ca-ea** (methyl ester enamine series); and **4ba** vs **4fa-ga** (ethyl ester enamine series)]. As previously shown in Tables 1 and 2 for enamines **1a-b**, slight differences were observed for methyl ester- and

ethyl ester-substituted enamines (see: **4aa** vs **4ba**; **4ca** vs **4fa**; **4da** vs **4ga**; **4ab** vs **4bb**). Although the results regarding the malononitriles **2** do not suggest a clear dependence of the reactivity of the process on the electronic properties of the starting malononitriles, those synthesized from deactivated aldehydes showed a clear reduced reactivity (see **4ag–ai**). Moreover, it seems that *meta*-substitution of the aromatic ring of the starting aldehyde provides better yields in comparison with the analogous *para*-substituted substrates (see **4af** vs **4aa** and **4ab** vs **4ac**). The structural complexity and the high functionalization of the final products of this protocol have been confirmed by the single-crystal analysis of compounds **4aa** and **4ae** (Figures S53–S55).

On the basis of the literature data for the nonasymmetric version of this reaction,<sup>10</sup> and our previous work,<sup>8f</sup> we propose the mechanism depicted in Scheme 3.

Scheme 3. Plausible Reaction Mechanism



We think that the catalyst mainly participates in the first step of the reaction (Scheme 3, A), since  $\text{Et}_3\text{N}$  is able to promote this reaction in the racemic version.<sup>10</sup> Thus, the Michael reaction between the enamine and the malononitrile would be promoted by the basic catalyst, driving the addition of the enamine to the Michael acceptor in an enantioselective manner. The ring is then formed through an intramolecular nucleophilic addition of the NH to a nitrile group, followed by an imine-enamine tautomerization (Scheme 3, B and C, respectively). A plausible proposal about the absolute configuration of the final products **4** has been provided in the Supporting Information (Figure S56).

## CONCLUSIONS

In summary, we have reported an unprecedented approach for the enantioselective formation of 1,4-dihydropyridine derivatives **4** under mild conditions and with operational simplicity. Using bis-cinchona **3b** as a catalyst, the final adducts were reached with very good results. A broad structural variety of 1,4-dihydropyridine derivatives was successfully achieved with our developed procedure. This work is one of the scarce asymmetric catalytic examples reported for the synthesis of enantiomerically enriched 1,4-dihydropyridines. Better understanding

of the mechanism and studies into the applicability of the final compounds are ongoing in our laboratories.

## EXPERIMENTAL SECTION

### General Experimental Methods and Instrumentation.

Purification of reaction products was carried out by flash chromatography using silica gel (0.063–0.200 mm). Analytical thin-layer chromatography was performed on 0.25 mm silica gel 60-F plates. ESI and MicroTof-Q mass analyzer were used for HRMS measurements.  $^1\text{H}$  NMR spectra were recorded at 300 and 400 MHz;  $^{13}\text{C}$ -APT NMR spectra were recorded at 75 MHz;  $\text{CDCl}_3$  and  $\text{DMSO}-d_6$  as the solvents. Chemical shifts were reported in the  $\delta$  scale relative to residual  $\text{CHCl}_3$  (7.26 ppm) and  $\text{DMSO}$  (2.50 ppm) for  $^1\text{H}$  NMR and to the central line of  $\text{CDCl}_3$  (77 ppm) and  $\text{DMSO}-d_6$  (39.43 ppm) for  $^{13}\text{C}$ -APT NMR.

All commercially available solvents and reagents were used as received.

**Materials.** Spectral data for enamines **1b**,<sup>8f</sup> **1c**,<sup>11</sup> **1d**,<sup>12</sup> **1e**,<sup>12</sup> **1f**,<sup>8f</sup> **1g**,<sup>8f</sup> and malononitriles **2a**,<sup>13</sup> **2b**,<sup>14</sup> **2c**,<sup>13</sup> **2d**,<sup>15</sup> **2e**,<sup>16</sup> **2f**,<sup>14</sup> **2g**,<sup>14</sup> **2h**,<sup>13</sup> **2i**,<sup>14</sup> **2j**,<sup>17</sup> are consistent with values previously reported in the literature. For the spectra and HPLC chromatograms of products **4**, see Supporting Information.

**Dimethyl 2-(2,4-dimethoxyphenylamino)maleate (1a).** Following our previous developed procedure,<sup>8f</sup> compound **1a** was obtained as a yellow oil in a 55% yield.  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  3.69 (s, 3H), 3.72 (s, 3H), 3.77 (s, 3H), 3.79 (s, 3H), 5.30 (s, 1H), 6.38 (dd,  $J = 8.6$  Hz,  $J = 2.6$  Hz, 1H), 6.46 (d,  $J = 2.6$  Hz, 1H), 6.76 (d,  $J = 8.7$  Hz, 1H), 9.52 (br s, 1H).  $^{13}\text{C}$ -APT NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  50.9 (1C), 52.4 (1C), 55.3 (1C), 55.4 (1C), 90.5 (1C), 99.1 (1C), 103.7 (1C), 121.8 (1C), 122.6 (1C), 148.6 (1C), 152.1 (1C), 157.4 (1C), 164.5 (1C), 170.0 (1C). IR (neat)  $\nu$  3294, 3007, 2983, 2951, 2930, 2832, 1741, 1673, 1604, 1588, 1518, 1463, 1450, 1435, 1413, 1392, 1331, 1278, 1203, 1147, 1121, 1036, 1027, 977, 828, 798, 775, 635. HRMS (ESI+) calcd for  $\text{C}_{14}\text{H}_{17}\text{NNaO}_6$  318.0948, found, 318.0947 [M + Na].

**General Procedure for the Synthesis of 1,4-Dihydropyridines 4.** To a mixture of catalyst **3b** (20 mol%, 18.17 mg) and enamine **1** (0.3 mmol), in 9:1 toluene:AcOEt or only toluene (0.25 mL), alkylidenmalononitrile **2** (0.1 mmol) was added. The reaction mixture was stirred for 3 days at 10 °C. Then the solvent was evaporated under vacuum, and the reaction crude was purified by column chromatography ( $\text{SiO}_2$ , *n*-hexane/AcOEt 7:3 to 1:1), giving rise to the corresponding final chiral adduct **4** (Scheme 2).

**Dimethyl 6-Amino-5-cyano-1-(2,4-dimethoxyphenyl)-4-(4-nitrophenyl)-1,4-dihydropyridine-2,3-dicarboxylate (4aa).** Following the general procedure, compound **4aa** was obtained after 72 h of reaction at 10 °C and was purified by column chromatography (*n*-hexane/AcOEt 7:3 to 1:1), as a yellow solid in 88% yield (43.5 mg). mp > 98 °C decomp. The ee of the product was determined to be 82% by HPLC, using a Daicel Chiralpak IB column (*n*-hexane/*i*-PrOH = 70:30, flow rate 1 mL  $\text{min}^{-1}$ ,  $\lambda = 254.0$  nm):  $\tau_{\text{major}} = 24.0$  min;  $\tau_{\text{minor}} = 13.1$  min;  $[\alpha]_{\text{D}}^{23} = +55.4$  ( $c = 0.27$ ,  $\text{CHCl}_3$ , 82% ee);  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ )  $\delta$  3.33 (s, 0.6H), 3.37 (s, 2.4H), 3.48 (s, 0.6H), 3.49 (s, 2.4H), 3.82 (s, 3.6H), 3.90 (s, 2.4H), 4.62 (s, 0.8H), 4.65 (s, 0.2H), 5.70 (br s, 2H), 6.54–6.57 (m, 0.8H), 6.57–6.59 (m, 0.2H), 6.69 (d,  $J = 2.6$  Hz, 0.2H), 6.72 (d,  $J = 2.6$  Hz, 0.8H), 7.14 (d,  $J = 8.7$  Hz, 0.8H), 7.24 (d,  $J = 8.7$  Hz, 0.2H), 7.53–7.59 (m, 0.4H), 7.64–7.70 (m, 1.6H), 8.25–8.30 (m, 0.4H), 8.29–8.34 (m, 1.6H);  $^{13}\text{C}$ -APT NMR (75 MHz,  $\text{DMSO}-d_6$ )  $\delta$  39.0 (1C), 51.8 (1C), 52.3 (1C), 55.5 (1C), 56.2 (1C), 58.1 (1C), 99.1 (1C), 102.7 (1C), 105.0 (1C), 115.7 (1C), 120.6 (1C), 123.8 (2C), 128.2 (2C), 132.2 (1C), 143.4 (1C), 146.4 (1C), 151.2 (1C), 153.1 (1C), 157.7 (1C), 161.8 (1C), 162.6 (1C), 164.6 (1C); IR (neat)  $\nu$  3452, 3345, 3000, 2948, 2841, 2180, 1743, 1705, 1646, 1610, 1568, 1508, 1486, 1454, 1435, 1415, 1354, 1335, 1312, 1285, 1261, 1208, 1163, 1110, 1054, 1027, 1009, 973, 933, 865, 834, 804, 778, 764, 730; HRMS (ESI+) calcd for  $\text{C}_{24}\text{H}_{22}\text{N}_4\text{NaO}_8$  517.1330, found, 517.1302 [M + Na].

**Diethyl 6-Amino-5-cyano-1-(2,4-dimethoxyphenyl)-4-(4-nitrophenyl)-1,4-dihydropyridine-2,3-dicarboxylate (4ba).** Following the general procedure, compound **4ba** was obtained after 72 h of reaction

at 10 °C and was purified by column chromatography (*n*-hexane/AcOEt 7:3 to 1:1), as a yellow solid in 97% yield (50.7 mg). mp 124–126 °C. The ee of the product was determined to be 76% by HPLC using a Daicel Chiralpak IB column (*n*-hexane/*i*-PrOH = 80:20, flow rate 1 mL min<sup>-1</sup>, λ = 276.0 nm): τ<sub>major</sub> = 27.2 min; τ<sub>minor</sub> = 16.5 min; [α]<sub>D</sub><sup>22</sup> = + 52.5 (*c* = 0.26, CHCl<sub>3</sub>, 76% ee); <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 0.88 (t, *J* = 7.2 Hz, 0.75H), 0.89 (t, *J* = 7.2 Hz, 2.25H), 1.02 (t, *J* = 7.1 Hz, 0.75H), 1.03 (t, *J* = 7.1 Hz, 2.25H), 3.81 (s, 3.75H), 3.72–3.97 (m, 4H), 3.91 (s, 2.25H), 4.62 (s, 0.75H), 4.65 (s, 0.25H), 5.68 (br s, 2H), 6.54–6.58 (m, 0.75H), 6.58–6.62 (m, 0.25H), 6.68 (d, *J* = 2.5 Hz, 0.25H), 6.71 (d, *J* = 2.1 Hz, 0.75H), 7.14 (d, *J* = 8.7 Hz, 0.75H), 7.25 (d, *J* = 8.7 Hz, 0.25H), 7.55–7.60 (m, 0.5H), 7.65–7.72 (m, 1.5H), 8.24–8.30 (m, 0.5H), 8.29–8.35 (m, 1.5H); <sup>13</sup>C-APT NMR (75 MHz, DMSO-*d*<sub>6</sub>) δ 13.2 (1C), 13.6 (1C), 39.1 (1C), 55.6 (1C), 56.2 (1C), 58.0 (1C), 60.3 (1C), 61.2 (1C), 99.1 (1C), 102.7 (1C), 105.0 (1C), 115.7 (1C), 120.7 (1C), 123.7 (2C), 128.4 (2C), 132.5 (1C), 143.2 (1C), 146.4 (1C), 151.3 (1C), 153.3 (1C), 157.8 (1C), 161.9 (1C), 162.0 (1C), 164.1 (1C); IR (neat) (cm<sup>-1</sup>) ν 3461, 3346, 3185, 2983, 2937, 2842, 2181, 1738, 1700, 1646, 1605, 1568, 1508, 1463, 1418, 1391, 1369, 1343, 1309, 1285, 1260, 1206, 1162, 1105, 1054, 1024, 935, 922, 858, 821, 729, 708; HRMS (ESI+) calcd for C<sub>26</sub>H<sub>25</sub>N<sub>4</sub>O<sub>8</sub> 521.1667, found, 521.1645 [M - H].

**Dimethyl 6-Amino-1-(4-tert-butylphenyl)-5-cyano-4-(4-nitrophenyl)-1,4-dihydropyridine-2,3-dicarboxylate (4ca).** Following the general procedure, compound 4ca was obtained after 72 h of reaction at 10 °C and was purified by column chromatography (*n*-hexane/AcOEt 7:3 to 1:1), as a yellow solid in 76% yield (37.3 mg). mp > 104 °C decomp. The ee of the product was determined to be 62% by HPLC using a Daicel Chiralpak IB column (*n*-hexane/*i*-PrOH = 70:30, flow rate 1 mL min<sup>-1</sup>, λ = 238.0 nm): τ<sub>major</sub> = 10.0 min; τ<sub>minor</sub> = 7.7 min; [α]<sub>D</sub><sup>27</sup> = + 75.3 (*c* = 0.24, CHCl<sub>3</sub>, 62% ee); <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 1.31 (s, 9H), 3.31 (s, 3H), 3.52 (s, 3H), 4.67 (s, 1H), 5.75 (br s, 2H), 7.26 (d, *J* = 8.6 Hz, 2H), 7.52 (d, *J* = 8.6 Hz, 2H), 7.58 (d, *J* = 8.8 Hz, 2H), 8.30 (d, *J* = 8.8 Hz, 2H); <sup>13</sup>C-APT NMR (75 MHz, DMSO-*d*<sub>6</sub>) δ 30.8 (3C), 34.5 (1C), 38.6 (1C), 51.9 (1C), 52.2 (1C), 58.5 (1C), 103.2 (1C), 109.4 (1C), 120.5 (1C), 124.2 (2C), 126.2 (2C), 127.8 (2C), 129.6 (2C), 132.3 (1C), 142.7 (1C), 146.4 (1C), 151.1 (1C), 152.5 (1C), 162.6 (1C), 164.6 (1C); IR (neat) (cm<sup>-1</sup>) ν 3471, 3357, 2953, 2850, 2183, 1746, 1708, 1648, 1605, 1569, 1519, 1461, 1417, 1344, 1222, 1108, 1054, 1014, 973, 931, 875, 860, 819, 728; HRMS (ESI+) calcd for C<sub>26</sub>H<sub>27</sub>N<sub>4</sub>O<sub>6</sub> 491.1925, found, 491.1898 [M + H].

**Dimethyl 6-Amino-5-cyano-1-(4-methoxyphenyl)-4-(4-nitrophenyl)-1,4-dihydropyridine-2,3-dicarboxylate (4da).** Following the general procedure, compound 4da was obtained after 72 h of reaction at 10 °C and was purified by column chromatography (*n*-hexane/AcOEt 7:3 to 1:1), as a yellow solid in 69% yield (32 mg). mp 153–155 °C. The ee of the product was determined to be 74% by HPLC using a Daicel Chiralpak IB column (*n*-hexane/*i*-PrOH = 70:30, flow rate 1 mL min<sup>-1</sup>, λ = 238.0 nm): τ<sub>major</sub> = 20.1 min; τ<sub>minor</sub> = 14.3 min; [α]<sub>D</sub><sup>26</sup> = + 34.5 (*c* = 0.26, CHCl<sub>3</sub>, 74% ee); <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 3.38 (s, 3H), 3.52 (s, 3H), 3.81 (s, 3H), 4.66 (s, 1H), 5.76 (br s, 2H), 7.03 (d, *J* = 9.0 Hz, 2H), 7.28 (d, *J* = 8.9 Hz, 2H), 7.58 (d, *J* = 8.8 Hz, 2H), 8.29 (d, *J* = 8.8 Hz, 2H); <sup>13</sup>C-APT NMR (75 MHz, DMSO-*d*<sub>6</sub>) δ 38.6 (1C), 51.9 (1C), 52.3 (1C), 55.4 (1C), 58.1 (1C), 102.8 (1C), 114.6 (2C), 120.5 (1C), 124.1 (2C), 127.1 (1C), 127.9 (2C), 131.4 (2C), 142.9 (1C), 146.4 (1C), 151.3 (1C), 152.7 (1C), 159.9 (1C), 162.6 (1C), 164.6 (1C); IR (neat) (cm<sup>-1</sup>) ν 3458, 3354, 3215, 2954, 2841, 2181, 2120, 1742, 1707, 1648, 1605, 1567, 1508, 1457, 1432, 1414, 1345, 1302, 1246, 1221, 1181, 1106, 1056, 1024, 972, 930, 874, 860, 820, 806, 747, 728, 713; HRMS (ESI+) calcd for C<sub>23</sub>H<sub>21</sub>N<sub>4</sub>O<sub>7</sub> 465.1405, found 465.1391 [M + H].

**Dimethyl 6-Amino-1-(4-bromophenyl)-5-cyano-4-(4-nitrophenyl)-1,4-dihydropyridine-2,3-dicarboxylate (4ea).** Following the general procedure, compound 4ea was obtained after 72 h of reaction at 10 °C and was purified by column chromatography (*n*-hexane/AcOEt 7:3 to 1:1), as a yellow solid in 89% yield (45.7 mg). mp > 80 °C decomp. The ee of the product was determined to be 64% by HPLC using a Daicel Chiralpak IB column (*n*-hexane/*i*-PrOH = 70:30, flow

rate 1 mL min<sup>-1</sup>, λ = 238.0 nm): τ<sub>major</sub> = 17.0 min; τ<sub>minor</sub> = 13.4 min; [α]<sub>D</sub><sup>27</sup> = - 4.3 (*c* = 0.20, CHCl<sub>3</sub>, 64% ee); <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 3.40 (s, 3H), 3.52 (s, 3H), 4.67 (s, 1H), 5.94 (br s, 2H), 7.32 (d, *J* = 8.7 Hz, 2H), 7.58 (d, *J* = 8.8 Hz, 2H), 7.71 (d, *J* = 8.7 Hz, 2H), 8.29 (d, *J* = 8.8 Hz, 2H); <sup>13</sup>C-APT NMR (75 MHz, DMSO-*d*<sub>6</sub>) δ 38.7 (1C), 52.0 (1C), 52.5 (1C), 58.4 (1C), 103.5 (1C), 120.4 (1C), 123.5 (1C), 124.2 (2C), 128.0 (2C), 132.4 (2C), 132.6 (2C), 134.4 (1C), 142.2 (1C), 146.5 (1C), 150.8 (1C), 152.5 (1C), 162.6 (1C), 164.6 (1C); IR (neat) (cm<sup>-1</sup>) ν 3336, 3110, 2955, 2918, 2849, 2217, 1731, 1592, 1560, 1521, 1488, 1436, 1398, 1346, 1240, 1160, 1106, 1071, 1010, 975, 851, 823, 785, 741, 720; HRMS (ESI+) calcd for C<sub>22</sub>H<sub>18</sub>BrN<sub>4</sub>O<sub>6</sub> 513.0404, found, 513.0364 [M + H].

**Diethyl 6-Amino-1-(4-tert-butylphenyl)-5-cyano-4-(4-nitrophenyl)-1,4-dihydropyridine-2,3-dicarboxylate (4fa).** Following the general procedure, compound 4fa was obtained after 72 h of reaction at 10 °C and was purified by column chromatography (*n*-hexane/AcOEt 7:3 to 1:1), as a yellow solid in 62% yield (32.2 mg). mp 137–140 °C. The ee of the product was determined to be 74% by HPLC using a Daicel Chiralpak IB column (*n*-hexane/*i*-PrOH = 80:20, flow rate 1 mL min<sup>-1</sup>, λ = 254.0 nm): τ<sub>major</sub> = 11.1 min; τ<sub>minor</sub> = 8.1 min; [α]<sub>D</sub><sup>27</sup> = + 64.5 (*c* = 0.24, CHCl<sub>3</sub>, 74% ee); <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 0.72 (t, *J* = 7.1 Hz, 3H), 1.03 (t, *J* = 7.1, 3H), 1.3 (s, 9H), 3.67–3.88 (m, 2H), 3.96 (q, *J* = 7.1 Hz, 2H), 4.68 (s, 1H), 5.73 (br s, 2H), 7.28 (d, *J* = 8.6 Hz, 2H), 7.52 (d, *J* = 8.7 Hz, 2H), 7.59 (d, *J* = 8.8 Hz, 2H), 8.30 (d, *J* = 8.8 Hz, 2H); <sup>13</sup>C-APT NMR (75 MHz, DMSO-*d*<sub>6</sub>) δ 12.9 (1C), 13.6 (1C), 30.8 (3C), 34.5 (1C), 38.8 (1C), 58.3 (1C), 60.5 (1C), 61.3 (1C), 103.2 (1C), 120.5 (1C), 124.1 (2C), 126.2 (2C), 128.1 (2C), 129.9 (2C), 132.3 (1C), 142.5 (1C), 146.4 (1C), 151.1 (1C), 152.6 (1C), 152.7 (1C), 162.0 (1C), 164.1 (1C); IR (neat) (cm<sup>-1</sup>) ν 3476, 3313, 3213, 2961, 2937, 2905, 2866, 2185, 1741, 1699, 1650, 1595, 1569, 1520, 1504, 1477, 1464, 1447, 1392, 1369, 1344, 1269, 1244, 1217, 1200, 1173, 1149, 1103, 1057, 1034, 1011, 956, 905, 855, 843, 818, 743, 728; HRMS (ESI+) calcd for C<sub>28</sub>H<sub>31</sub>N<sub>4</sub>O<sub>6</sub> 519.2238, found 519.2235 [M + H].

**Diethyl 6-Amino-5-cyano-1-(4-methoxyphenyl)-4-(4-nitrophenyl)-1,4-dihydropyridine-2,3-dicarboxylate (4ga).** Following the general procedure, compound 4ga was obtained after 72 h of reaction at 10 °C and was purified by column chromatography (*n*-hexane/AcOEt 7:3 to 1:1), as a yellow solid in 71% yield (35.0 mg). mp 138–141 °C. The ee of the product was determined to be 73% by HPLC using a Daicel Chiralpak IB column (*n*-hexane/*i*-PrOH = 80:20, flow rate 1 mL min<sup>-1</sup>, λ = 236.4 nm): τ<sub>major</sub> = 29.4 min; τ<sub>minor</sub> = 20.2 min; [α]<sub>D</sub><sup>22</sup> = + 43.0 (*c* = 0.26, CHCl<sub>3</sub>, 60% ee); <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 0.89 (t, *J* = 7.1 Hz, 3H), 1.03 (t, *J* = 7.1 Hz, 3H), 3.74–3.99 (m, 4H), 3.80 (s, 3H), 4.67 (s, 1H), 5.74 (br s, 2H), 7.03 (d, *J* = 9.0 Hz, 2H), 7.29 (d, *J* = 8.9 Hz, 2H), 7.58 (d, *J* = 8.8 Hz, 2H), 8.29 (d, *J* = 8.8 Hz, 2H); <sup>13</sup>C-APT NMR (75 MHz, DMSO-*d*<sub>6</sub>) δ 13.1 (1C), 13.6 (1C), 38.8 (1C), 55.5 (1C), 58.0 (1C), 60.5 (1C), 61.4 (1C), 102.9 (1C), 114.6 (2C), 120.6 (1C), 124.1 (2C), 127.2 (1C), 128.1 (2C), 131.7 (2C), 142.7 (1C), 146.4 (1C), 151.3 (1C), 152.9 (1C), 160.1 (1C), 162.0 (1C), 164.1 (1C); IR (neat) (cm<sup>-1</sup>) ν 3452, 3314, 3214, 3076, 2958, 2919, 2850, 2178, 1741, 1706, 1693, 1648, 1596, 1568, 1522, 1506, 1462, 1424, 1390, 1370, 1345, 1298, 1253, 1217, 1200, 1170, 1151, 1104, 1058, 1011, 963, 907, 852, 821, 784, 763, 746, 728; HRMS (ESI+) calcd for C<sub>25</sub>H<sub>25</sub>N<sub>4</sub>O<sub>7</sub> 493.1718, found, 493.1703 [M + H].

**Dimethyl 6-Amino-4-(3-chlorophenyl)-5-cyano-1-(2,4-dimethoxyphenyl)-1,4-dihydropyridine-2,3-dicarboxylate (4ab).** Following the general procedure, compound 4ab was obtained after 72 h of reaction at 10 °C and was purified by column chromatography (*n*-hexane/AcOEt 7:3 to 1:1), as a yellow solid in 82% yield (39.7 mg). mp 102–106 °C. The ee of the product was determined to be 74% by HPLC using a Daicel Chiralpak IB column (*n*-hexane/*i*-PrOH = 70:30, flow rate 1 mL min<sup>-1</sup>, λ = 238.0 nm): τ<sub>major</sub> = 19.0 min; τ<sub>minor</sub> = 9.3 min; [α]<sub>D</sub><sup>22</sup> = - 4.7 (*c* = 0.21, CHCl<sub>3</sub>, 74% ee); <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>) δ 3.32 (s, 0.6H), 3.36 (s, 2.4H), 3.50 (s, 0.6H), 3.51 (s, 2.4H), 3.80 (s, 0.6H), 3.81 (s, 3H), 3.89 (s, 2.4 H), 4.46 (s, 0.8H), 4.50 (s, 0.2H), 5.62 (br s, 2H), 6.55–6.59 (m, 0.8H), 6.57–6.62 (m, 0.2H), 6.68 (d, *J* = 2.6 Hz, 0.2H), 6.71 (d, *J* = 2.6 Hz, 0.8H), 7.11 (d, *J* = 8.6 Hz, 0.2H), 7.12 (d, *J* = 8.7 Hz, 0.8H), 7.23–7.47 (m, 4H); <sup>13</sup>C-APT NMR (75 MHz, DMSO-*d*<sub>6</sub>) δ 38.8 (1C), 51.7 (1C), 52.2 (1C),

55.5 (1C), 56.0 (1C), 58.7 (1C), 99.2 (1C), 103.0 (1C), 105.0 (1C), 115.7 (1C), 120.8 (1C), 126.0 (1C), 126.8 (1C), 127.0 (1C), 130.1 (1C), 132.2 (1C), 133.1 (1C), 142.9 (1C), 148.4 (1C), 151.0 (1C), 157.7 (1C), 161.7 (1C), 162.7 (1C), 164.8 (1C); IR (neat) ( $\text{cm}^{-1}$ )  $\nu$  3465, 3346, 3221, 3004, 2950, 2842, 2180, 1743, 1705, 1645, 1609, 1568, 1508, 1468, 1432, 1414, 1355, 1335, 1310, 1285, 1260, 1208, 1162, 1112, 1078, 1055, 1026, 972, 934, 829, 806, 777, 767, 730, 709; HRMS (ESI+) calcd for  $\text{C}_{24}\text{H}_{21}\text{ClN}_3\text{O}_6$  482.1113, found, 482.1100 [M - H].

**Diethyl 6-Amino-4-(3-chlorophenyl)-5-cyano-1-(2,4-dimethoxyphenyl)-1,4-dihydropyridine-2,3-dicarboxylate (4bb).** Following the general procedure, compound **4bb** was obtained after 72 h of reaction at 10 °C and was purified by column chromatography (*n*-hexane/AcOEt 7:3 to 1:1), as a yellow solid in 98% yield (50.2 mg). mp 75–78 °C. The ee of the product was determined to be 74% by HPLC using a Daicel Chiralpak IB column (*n*-hexane/*i*-PrOH = 80:20, flow rate 1 mL  $\text{min}^{-1}$ ,  $\lambda$  = 254.0 nm):  $\tau_{\text{major}}$  = 24.8 min;  $\tau_{\text{minor}}$  = 11.5 min;  $[\alpha]_{\text{D}}^{27}$  = - 8.5 (*c* = 0.29,  $\text{CHCl}_3$ , 74% ee);  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ )  $\delta$  0.88 (t, *J* = 7.1 Hz, 0.6H), 0.89 (t, *J* = 7.1 Hz, 2.4H), 1.03 (t, *J* = 7.0 Hz, 0.6H), 1.05 (t, *J* = 7.1 Hz, 2.4H), 3.81 (s, 3.6H), 3.71–4.02 (m, 4H), 3.91 (s, 2.4H), 4.47 (s, 0.8H), 4.51 (s, 0.2H), 5.60 (br s, 2H), 6.55–6.59 (m, 0.8H), 6.57–6.62 (m, 0.2H), 6.68 (d, *J* = 2.6 Hz, 0.2H), 6.72 (d, *J* = 2.6 Hz, 0.8H), 7.12 (d, *J* = 8.6 Hz, 0.2H), 7.13 (d, *J* = 8.7 Hz, 0.8H), 7.27–7.47 (m, 4H);  $^{13}\text{C}$ -APT NMR (75 MHz,  $\text{DMSO}-d_6$ )  $\delta$  13.2 (1C), 13.6 (1C), 38.9 (1C), 55.6 (1C), 56.0 (1C), 58.6 (1C), 60.3 (1C), 61.1 (1C), 99.2 (1C), 103.1 (1C), 104.9 (1C), 115.7 (1C), 120.9 (1C), 126.2 (1C), 126.8 (1C), 127.2 (1C), 130.1 (1C), 132.5 (1C), 133.0 (1C), 142.7 (1C), 148.6 (1C), 151.1 (1C), 157.9 (1C), 161.8 (1C), 162.2 (1C), 164.3 (1C); IR (neat) ( $\text{cm}^{-1}$ )  $\nu$  3461, 3345, 2983, 2937, 2181, 1738, 1699, 1647, 1609, 1567, 1508, 1470, 1415, 1391, 1369, 1344, 1332, 1309, 1285, 1260, 1239, 1205, 1163, 1106, 1078, 1055, 1017, 937, 922, 888, 861, 828, 796, 777, 730, 716; HRMS (ESI+) calcd for  $\text{C}_{26}\text{H}_{25}\text{ClN}_3\text{O}_6$  510.1426, found, 510.1416 [M - H].

**Dimethyl 6-Amino-4-(4-chlorophenyl)-5-cyano-1-(2,4-dimethoxyphenyl)-1,4-dihydropyridine-2,3-dicarboxylate (4ac).** Following the general procedure, compound **4ac** was obtained after 72 h of reaction at 10 °C and was purified by column chromatography (*n*-hexane/AcOEt 7:3 to 1:1), as a yellow solid in 36% yield (17.4 mg). mp 158–163 °C. The ee of the product was determined to be 72% by HPLC using a Daicel Chiralpak IB column (*n*-hexane/*i*-PrOH = 70:30, flow rate 1 mL  $\text{min}^{-1}$ ,  $\lambda$  = 238.0 nm):  $\tau_{\text{major}}$  = 17.6 min;  $\tau_{\text{minor}}$  = 9.1 min;  $[\alpha]_{\text{D}}^{25}$  = + 10.1 (*c* = 0.20,  $\text{CHCl}_3$ , 72% ee);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  3.47 (s, 0.75H), 3.50 (s, 2.25H), 3.59 (s, 0.75H), 3.59 (s, 2.25H), 3.85 (s, 3H), 3.89 (s, 0.75H), 3.90 (s, 2.25H), 4.16 (br s, 1.5H), 4.19 (br s, 0.5H), 4.59 (s, 0.75H), 4.66 (s, 0.25H), 6.50 (dd, *J* = 8.6 Hz, 2.6 Hz, 0.75H), 6.53–6.55 (m, 1.25H), 7.16 (d, *J* = 8.0 Hz, 0.25H), 7.19 (d, *J* = 8.6 Hz, 0.75H), 7.29–7.36 (m, 2.5H), 7.43–7.47 (m, 1.5H);  $^{13}\text{C}$ -APT NMR (75 MHz,  $\text{DMSO}-d_6$ )  $\delta$  38.4 (1C), 51.7 (1C), 52.2 (1C), 55.5 (1C), 56.01 (1C), 58.9 (1C), 99.1 (1C), 103.3 (1C), 104.9 (1C), 115.8 (1C), 120.9 (1C), 128.3 (2C), 129.0 (2C), 131.4 (1C), 132.2 (1C), 142.8 (1C), 144.9 (1C), 151.0 (1C), 157.7 (1C), 161.7 (1C), 162.8 (1C), 164.9 (1C); IR (neat) ( $\text{cm}^{-1}$ )  $\nu$  3313, 3216, 2947, 2923, 2852, 2175, 1752, 1707, 1649, 1610, 1568, 1508, 1492, 1417, 1357, 1312, 1285, 1265, 1243, 1207, 1160, 1115, 1089, 1024, 1016, 978, 934, 918, 840, 822, 804, 777, 754, 730; HRMS (ESI+) calcd for  $\text{C}_{24}\text{H}_{21}\text{ClN}_3\text{O}_6$  482.1113, found, 482.1100 [M - H].

**Diethyl 6-Amino-5-cyano-4-(4-cyanophenyl)-1-(2,4-dimethoxyphenyl)-1,4-dihydropyridine-2,3-dicarboxylate (4bd).** Following the general procedure, compound **4bd** was obtained after 72 h of reaction at 10 °C and was purified by column chromatography (*n*-hexane/AcOEt 7:3 to 1:1), as a yellow solid in 96% yield (48.2 mg). mp > 110 °C decomp. The ee of the product was determined to be 74% by HPLC using a Daicel Chiralpak IB column (*n*-hexane/*i*-PrOH = 80:20, flow rate 1 mL  $\text{min}^{-1}$ ,  $\lambda$  = 254.0 nm):  $\tau_{\text{major}}$  = 31.3 min;  $\tau_{\text{minor}}$  = 17.3 min;  $[\alpha]_{\text{D}}^{22}$  = + 26.3 (*c* = 0.20,  $\text{CHCl}_3$ , 74% ee);  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ )  $\delta$  0.88 (t, *J* = 7.1 Hz, 0.6H), 0.89 (t, *J* = 7.1 Hz, 2.4H), 1.00 (t, *J* = 7.0 Hz, 0.6H), 1.02 (t, *J* = 7.1 Hz, 2.4H), 3.81 (s, 3.6H), 3.71–3.97 (m, 4H), 3.89 (s, 2.4H), 4.54 (s, 0.8H), 4.59 (s, 0.2H), 5.64 (br s, 2H), 6.57 (dd, *J* = 8.7 Hz, *J* = 2.7 Hz, 0.8H), 6.59 (dd, *J* = 8.7

Hz, *J* = 2.7 Hz, 0.2H), 6.67 (d, *J* = 2.6 Hz, 0.2H), 6.72 (d, *J* = 2.6 Hz, 0.8H), 7.13 (d, *J* = 8.7 Hz, 0.8H), 7.20 (d, *J* = 8.7 Hz, 0.2H), 7.48 (d, *J* = 8.3 Hz, 0.4H), 7.62 (d, *J* = 8.3 Hz, 1.6H), 7.87 (d, *J* = 8.3 Hz, 0.4H), 7.93 (d, *J* = 8.3 Hz, 1.6H);  $^{13}\text{C}$ -APT NMR (75 MHz,  $\text{DMSO}-d_6$ )  $\delta$  13.2 (1C), 13.6 (1C), 39.2 (1C), 55.6 (1C), 56.0 (1C), 58.2 (1C), 60.3 (1C), 61.1 (1C), 99.1 (1C), 102.9 (1C), 104.9 (1C), 109.5 (1C), 115.7 (1C), 118.8 (1C), 120.7 (1C), 128.2 (2C), 132.4 (2C), 132.5 (1C), 143.1 (1C), 151.2 (1C), 151.3 (1C), 157.8 (1C), 161.9 (1C), 162.1 (1C), 164.1 (1C); IR (neat) ( $\text{cm}^{-1}$ )  $\nu$  3458, 3341, 3219, 2980, 2936, 2227, 2181, 1739, 1704, 1645, 1606, 1508, 1463, 1454, 1440, 1416, 1392, 1369, 1327, 1309, 1286, 1261, 1207, 1162, 1105, 1054, 1025, 936, 922, 900, 856, 828, 803, 786, 770; HRMS (ESI+) calcd for  $\text{C}_{27}\text{H}_{25}\text{N}_4\text{O}_6$  501.1769, found, 501.1744 [M - H].

**Dimethyl 6-Amino-4-(4-bromophenyl)-5-cyano-1-(2,4-dimethoxyphenyl)-1,4-dihydropyridine-2,3-dicarboxylate (4ae).** Following the general procedure, compound **4ae** was obtained after 72 h of reaction at 10 °C and was purified by column chromatography (*n*-hexane/AcOEt 7:3 to 1:1), as a yellow solid in 43% yield (22.7 mg). mp > 95 °C decomp. The ee of the product was determined to be 76% by HPLC using a Daicel Chiralpak IB column (*n*-hexane/*i*-PrOH = 70:30, flow rate 1 mL  $\text{min}^{-1}$ ,  $\lambda$  = 237.0 nm):  $\tau_{\text{major}}$  = 18.6 min;  $\tau_{\text{minor}}$  = 9.4 min;  $[\alpha]_{\text{D}}^{25}$  = + 8.7 (*c* = 0.20,  $\text{CHCl}_3$ , 76% ee);  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ )  $\delta$  3.32 (s, 0.75H), 3.36 (s, 2.25H), 3.50 (s, 3H), 3.80 (s, 0.75H), 3.81 (s, 3H), 3.86 (s, 2.25H), 4.42 (s, 0.75H), 4.47 (s, 2.25H), 5.57 (br s, 2H), 6.56 (dd, *J* = 8.7 Hz, *J* = 2.7 Hz, 0.75H), 6.60 (dd, *J* = 8.6 Hz, *J* = 2.6 Hz, 0.25H), 6.67 (d, *J* = 2.6 Hz, 0.25H), 6.71 (d, *J* = 2.6 Hz, 0.75H), 7.12 (d, *J* = 8.7 Hz, 0.75H), 7.17 (d, *J* = 8.7 Hz, 0.25H), 7.23–7.26 (m, 0.5H), 7.36–7.39 (m, 1.5H), 7.57–7.59 (m, 0.5H), 7.61–7.64 (m, 1.5H);  $^{13}\text{C}$ -APT NMR (75 MHz,  $\text{DMSO}-d_6$ )  $\delta$  38.5 (1C), 51.7 (1C), 52.2 (1C), 55.5 (1C), 56.1 (1C), 58.9 (1C), 99.2 (1C), 103.3 (1C), 104.9 (1C), 115.8 (1C), 119.9 (1C), 121.0 (1C), 129.4 (2C), 131.2 (2C), 132.2 (1C), 142.8 (1C), 145.3 (1C), 151.0 (1C), 157.7 (1C), 161.7 (1C), 162.8 (1C), 164.9 (1C); IR (neat) ( $\text{cm}^{-1}$ )  $\nu$  3451, 3353, 3219, 2950, 2920, 2849, 2180, 1744, 1706, 1646, 1605, 1568, 1508, 1455, 1416, 1344, 1313, 1285, 1261, 1208, 1163, 1108, 1053, 1026, 972, 934, 875, 860, 821, 730, 711; HRMS (ESI+) calcd for  $\text{C}_{24}\text{H}_{21}\text{BrN}_3\text{O}_6$  526.0608, found, 526.0596 [M - H].

**Dimethyl 6-Amino-5-cyano-1-(2,4-dimethoxyphenyl)-4-(3-nitrophenyl)-1,4-dihydropyridine-2,3-dicarboxylate (4af).** Following the general procedure, compound **4af** was obtained after 72 h of reaction at 10 °C and was purified by column chromatography (*n*-hexane/AcOEt 7:3 to 1:1), as a yellow solid in 99% yield (48.9 mg). mp > 106 °C decomp. The ee of the product was determined to be 77% by HPLC using a Daicel Chiralpak IB column (*n*-hexane/*i*-PrOH = 70:30, flow rate 1 mL  $\text{min}^{-1}$ ,  $\lambda$  = 238.0 nm):  $\tau_{\text{major}}$  = 23.9 min;  $\tau_{\text{minor}}$  = 12.4 min;  $[\alpha]_{\text{D}}^{24}$  = - 3.0 (*c* = 0.21,  $\text{CHCl}_3$ , 77% ee);  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ )  $\delta$  3.33 (s, 0.6H), 3.37 (s, 2.4H), 3.50 (s, 3H), 3.82 (s, 3.6H), 3.85 (s, 2.4H), 4.67 (s, 0.8H), 4.68 (s, 0.2H), 5.70 (br s, 2H), 6.54–6.59 (m, 0.8H), 6.58–6.63 (m, 0.2H), 6.69 (d, *J* = 2.6 Hz, 0.2H), 6.72 (d, *J* = 2.6 Hz, 0.8H), 7.14 (d, *J* = 8.6 Hz, 0.8H), 7.16 (d, *J* = 8.7 Hz, 0.2H), 7.75 (t, *J* = 7.9 Hz, 1H), 7.75–7.80 (m, 0.2H), 7.85–7.90 (m, Hz, 0.8H), 8.10–8.23 (m, 2H);  $^{13}\text{C}$ -APT NMR (75 MHz,  $\text{DMSO}-d_6$ )  $\delta$  38.8 (1C), 51.8 (1C), 52.3 (1C), 55.5 (1C), 56.1 (1C), 58.2 (1C), 99.2 (1C), 102.6 (1C), 105.0 (1C), 115.6 (1C), 120.7 (1C), 121.5 (1C), 121.9 (1C), 130.0 (1C), 132.2 (1C), 134.1 (1C), 143.3 (1C), 148.0 (1C), 148.1 (1C), 151.2 (1C), 157.7 (1C), 161.8 (1C), 162.6 (1C), 164.7 (1C); IR (neat) ( $\text{cm}^{-1}$ )  $\nu$  3461, 3361, 3094, 2947, 2180, 1744, 1704, 1649, 1608, 1567, 1527, 1506, 1470, 1415, 1348, 1314, 1284, 1262, 1206, 1164, 1112, 1057, 1022, 971, 934, 922, 906, 821, 805, 782, 766, 743, 730, 711; HRMS (ESI+) calcd for  $\text{C}_{24}\text{H}_{21}\text{N}_4\text{O}_8$  493.1354, found, 493.1351 [M - H].

**Dimethyl 6-Amino-5-cyano-1-(2,4-dimethoxyphenyl)-4-*p*-tolyl-1,4-dihydropyridine-2,3-dicarboxylate (4ag).** Following the general procedure, compound **4ag** was obtained after 72 h of reaction at 10 °C and was purified by column chromatography (*n*-hexane/AcOEt 7:3 to 1:1), as a yellow solid in 22% yield (10.2 mg). mp 123–126 °C. The ee of the product was determined to be 72% by HPLC using a Daicel Chiralpak IB column (*n*-hexane/*i*-PrOH = 70:30, flow rate 1 mL  $\text{min}^{-1}$ ,  $\lambda$  = 240.2 nm):  $\tau_{\text{major}}$  = 15.1 min;  $\tau_{\text{minor}}$  = 8.5 min;  $[\alpha]_{\text{D}}^{26}$  = + 7.6 (*c* = 0.20,  $\text{CHCl}_3$ , 72% ee);  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ )  $\delta$

2.30 (s, 3H), 3.32 (s, 0.9H), 3.36 (s, 2.1H), 3.50 (s, 3H), 3.82 (s, 3.9H), 3.86 (s, 2.1H), 4.38 (s, 0.7H), 4.42 (s, 0.3H), 5.38 (br s, 2H), 6.53–6.58 (m, 0.7H), 6.56–6.61 (m, 0.3H), 6.68 (d,  $J = 2.5$  Hz, 0.3H), 6.70 (d,  $J = 2.6$  Hz, 0.7H), 7.12 (d,  $J = 8.7$  Hz, 1H), 7.19 (d,  $J = 8.2$  Hz, 2.6H), 7.32 (d,  $J = 8.0$  Hz, 1.4H);  $^{13}\text{C}$ -APT NMR (75 MHz, DMSO- $d_6$ )  $\delta$  20.4 (1C), 38.4 (1C), 51.4 (1C), 52.0 (1C), 55.4 (1C), 55.8 (1C), 59.6 (1C), 99.1 (1C), 103.8 (1C), 104.9 (1C), 116.0 (1C), 120.9 (1C), 127.0 (2C), 128.7 (2C), 132.0 (1C), 135.6 (1C), 142.3 (1C), 142.8 (1C), 150.7 (1C), 157.7 (1C), 161.6 (1C), 162.8 (1C), 164.9 (1C); IR (neat) ( $\text{cm}^{-1}$ )  $\nu$  3445, 3343, 2947, 2840, 2180, 1743, 1705, 1646, 1609, 1569, 1508, 1459, 1435, 1415, 1389, 1353, 1329, 1314, 1285, 1261, 1208, 1163, 1110, 1054, 1024, 973, 933, 864, 835, 804, 788, 772, 735; HRMS (ESI+) calcd for  $\text{C}_{25}\text{H}_{24}\text{N}_3\text{O}_6$  462.1660, found, 462.1662 [M – H].

**Dimethyl 6-Amino-5-cyano-1-(2,4-dimethoxyphenyl)-4-phenyl-1,4-dihydropyridine-2,3-dicarboxylate (4ah).** Following the general procedure, compound 4ah was obtained after 72 h of reaction at 10 °C and was purified by column chromatography (*n*-hexane/AcOEt 7:3 to 1:1), as a yellow solid in 21% yield (9.4 mg). mp 90–94 °C. The ee of the product was determined to be 80% by HPLC using a Daicel Chiralpak IB column (*n*-hexane/*i*-PrOH = 70:30, flow rate 1 mL  $\text{min}^{-1}$ ,  $\lambda = 238.0$  nm):  $\tau_{\text{major}} = 17.7$  min;  $\tau_{\text{minor}} = 9.4$  min;  $[\alpha]_{\text{D}}^{28} = -13.6$  ( $c = 0.17$ ,  $\text{CHCl}_3$ , 80% ee);  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ )  $\delta$  3.32 (s, 0.75H), 3.36 (s, 2.25H), 3.50 (s, 3H), 3.81 (s, 3.75H), 3.86 (s, 2.25H), 4.41 (s, 0.75H), 4.45 (s, 0.25H), 5.50 (br s, 2H), 6.53–6.59 (m, 0.75H), 6.55–6.60 (m, 0.25H), 6.68 (d,  $J = 2.6$  Hz, 0.25H), 6.70 (d,  $J = 2.6$  Hz, 0.75H), 7.12 (d,  $J = 8.7$  Hz, 0.75H), 7.14 (d,  $J = 8.7$  Hz, 0.25H), 7.22–7.29 (m, 1.25H), 7.36–7.45 (m, 3.75H);  $^{13}\text{C}$ -APT NMR (75 MHz, DMSO- $d_6$ )  $\delta$  38.9 (1C), 51.7 (1C), 52.2 (1C), 55.5 (1C), 56.0 (1C), 59.4 (1C), 99.2 (1C), 103.7 (1C), 104.9 (1C), 116.0 (1C), 121.1 (1C), 126.7 (1C), 127.2 (2C), 128.3 (2C), 132.2 (1C), 142.7 (1C), 145.9 (1C), 150.9 (1C), 157.7 (1C), 161.7 (1C), 162.9 (1C), 165.0 (1C); IR (neat) ( $\text{cm}^{-1}$ )  $\nu$  3300, 3203, 3005, 2952, 2919, 2849, 2181, 1739, 1707, 1642, 1609, 1508, 1454, 1435, 1419, 1360, 1286, 1208, 1160, 1115, 1076, 1058, 1025, 974, 933, 861, 835, 793, 756, 728, 699; HRMS (ESI+) calcd for  $\text{C}_{24}\text{H}_{22}\text{N}_3\text{O}_6$  448.1503, found, 448.1513 [M – H].

**Dimethyl 6-Amino-5-cyano-1-(2,4-dimethoxyphenyl)-4-(thiophen-2-yl)-1,4-dihydropyridine-2,3-dicarboxylate (4ai).** Following the general procedure, compound 4ai was obtained after 72 h of reaction at 10 °C and was purified by column chromatography (*n*-hexane/AcOEt 7:3 to 1:1), as a yellow solid in 15% yield (6.8 mg). mp 139–141 °C. The ee of the product was determined to be 76% by HPLC using a Daicel Chiralpak IB column (*n*-hexane/*i*-PrOH = 70:30, flow rate 1 mL  $\text{min}^{-1}$ ,  $\lambda = 242.6$  nm):  $\tau_{\text{major}} = 14.2$  min;  $\tau_{\text{minor}} = 9.7$  min;  $[\alpha]_{\text{D}}^{26} = -3.5$  ( $c = 0.17$ ,  $\text{CHCl}_3$ , 76% ee);  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ )  $\delta$  3.32 (s, 1.2H), 3.36 (s, 1.8H), 3.59 (s, 1.8H), 3.60 (s, 1.2H), 3.76 (s, 1.8H), 3.81 (s, 4.2H), 4.73 (s, 0.6H), 4.77 (s, 0.4H), 5.55 (br s, 1.2H), 5.58 (br s, 0.8H), 6.56 (td,  $J = 8.6$  Hz,  $J = 2.6$  Hz, 1H), 6.64–6.70 (m, 1H), 6.92 (d,  $J = 2.9$  Hz, 0.4H), 6.97–7.04 (m, 2H), 7.11 (d,  $J = 8.7$  Hz, 0.6H), 7.37–7.41 (m, 1H);  $^{13}\text{C}$ -APT NMR (75 MHz, DMSO- $d_6$ )  $\delta$  33.8 (1C), 51.5 (1C), 52.0 (1C), 55.4 (1C), 55.6 (1C), 58.9 (1C), 99.1 (1C), 103.6 (1C), 104.8 (1C), 115.9 (1C), 120.8 (1C), 123.1 (1C), 124.0 (1C), 126.6 (1C), 131.8 (1C), 142.0 (1C), 149.5 (1C), 151.2 (1C), 157.6 (1C), 161.6 (1C), 162.6 (1C), 164.7 (1C); IR (neat) ( $\text{cm}^{-1}$ )  $\nu$  3433, 3330, 3000, 2947, 2842, 2182, 1745, 1710, 1647, 1609, 1574, 1508, 1462, 1434, 1413, 1351, 1332, 1313, 1284, 1210, 1163, 1105, 1054, 1029, 971, 933, 852, 825, 803, 791, 773, 752, 730, 704; HRMS (ESI+) calcd for  $\text{C}_{22}\text{H}_{20}\text{N}_3\text{O}_6\text{S}$  454.1067, found, 454.1075 [M – H].

**Dimethyl 6-Amino-5-cyano-1-(2,4-dimethoxyphenyl)-4-(pyridin-3-yl)-1,4-dihydropyridine-2,3-dicarboxylate (4aj).** Following the general procedure, compound 4aj was obtained after 72 h of reaction at 10 °C and was purified by column chromatography (*n*-hexane/AcOEt 7:3 to 1:1), as a yellow solid in 79% yield (35.6 mg). mp > 185 °C decomp. The ee of the product was determined to be 82% by HPLC using a Daicel Chiralpak IB column (*n*-hexane/*i*-PrOH = 70:30, flow rate 1 mL  $\text{min}^{-1}$ ,  $\lambda = 238.7$  nm):  $\tau_{\text{major}} = 28.1$  min;  $\tau_{\text{minor}} = 20.6$  min;  $[\alpha]_{\text{D}}^{22} = -6.9$  ( $c = 0.22$ ,  $\text{CHCl}_3$ , 82% ee);  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ )  $\delta$  3.32 (s, 0.6H), 3.36 (s, 2.4H), 3.49 (s, 0.6H), 3.51 (s,

2.4H), 3.81 (s, 3.6H), 3.87 (s, 2.4H), 4.47 (s, 0.8H), 4.53 (s, 0.2H), 5.67 (br s, 2H), 6.53–6.59 (m, 0.8H), 6.55–6.60 (m, 0.2H), 6.67 (d,  $J = 2.6$  Hz, 0.2H), 6.71 (d,  $J = 2.6$  Hz, 0.8H), 7.14 (d,  $J = 8.7$  Hz, 0.8H), 7.20 (d,  $J = 8.7$  Hz, 0.2H), 7.41–7.46 (m, 0.2H), 7.45–7.50 (m, 0.8H), 7.61 (dt,  $J = 8.0$  Hz,  $J = 2.0$  Hz, 0.2H), 7.82 (dt,  $J = 8.0$  Hz,  $J = 2.0$  Hz, 0.8H), 8.48 (dd,  $J = 4.8$  Hz,  $J = 1.6$  Hz, 1H), 8.48–8.50 (m, 0.2H), 8.62–8.65 (m, 0.8H);  $^{13}\text{C}$ -APT NMR (75 MHz, DMSO- $d_6$ )  $\delta$  36.7 (1C), 51.8 (1C), 52.3 (1C), 55.6 (1C), 56.0 (1C), 58.4 (1C), 99.2 (1C), 103.1 (1C), 105.0 (1C), 115.8 (1C), 120.9 (1C), 123.8 (1C), 132.3 (1C), 134.7 (1C), 141.1 (1C), 143.1 (1C), 148.0 (1C), 148.6 (1C), 151.3 (1C), 157.6 (1C), 161.8 (1C), 162.8 (1C), 164.8 (1C); IR (neat) ( $\text{cm}^{-1}$ )  $\nu$  3454, 3346, 3095, 2947, 2838, 2178, 1743, 1698, 1652, 1611, 1568, 1529, 1507, 1478, 1469, 1452, 1423, 1353, 1335, 1314, 1289, 1261, 1244, 1219, 1208, 1163, 1108, 1052, 1041, 1026, 971, 921, 862, 844, 826, 824, 802, 795, 781, 728, 714; HRMS (ESI+) calcd for  $\text{C}_{23}\text{H}_{23}\text{N}_4\text{O}_6$  451.1612, found, 451.1625 [M + H].

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b00176.

$^1\text{H}$  and  $^{13}\text{C}$ -APT NMR spectra of all new products. HPLC chromatograms for products 4 are also provided. (PDF)

X-ray data for 4aa (CIF)

X-ray data for 4ae (CIF)

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### Notes

The authors declare no competing financial interest.

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