Asymmetric organocatalytic synthesis of substituted chiral 1,4-dihydropyridine derivatives

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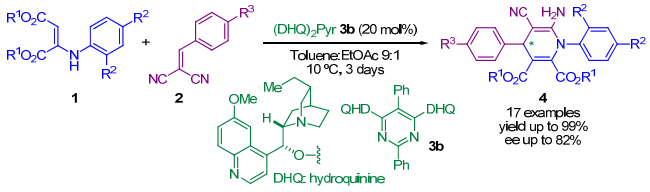
Abstract



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 a 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 interesting skeletons for which enantioselective syntheses are still very limited.

Keywords: 1,4-Dihydropyridine; Asymmetric Organocatalysis; Cinchona alkaloid; Enamine; Malononitrile

Introduction

1,4-Dihydropyridine derivatives (1,4-DHPs) are a significant class of pharmacophore compounds frequently found in natural products and, more recently, even as biomimetic reducing agents.[1] Their interesting biological properties have allowed them to find medicinal application in the treatments of different diseases.[2] 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).[2] Interestingly, as with other drug 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.[3]

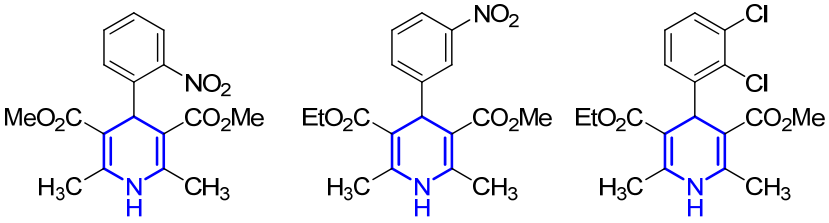
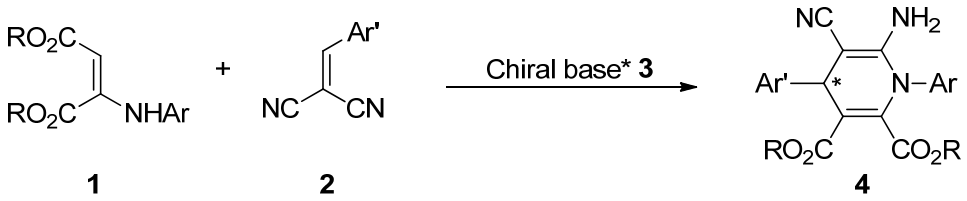


Figure 1. Representative structures of 1,4-dihydropyridine based drugs.

1,4-DHPs are generally synthesized following the classical four-component Hantzsch reaction,[4] which involves the condensation of an aldehyde, two equivalents of a β-ketoester and ammonia or a synthetic equivalent in a multicomponent approach.[5] The synthesis of racemic 1,4-DHPs is an active task in organic chemistry,[6] and chiral analogues have mainly been obtained either by the use of chiral auxiliaries[3] or by chiral resolution.[7] However, very few enantioselective organocatalytic methods are known.[8] 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.[9] We envisioned that chiral organic bases such as cinchona derivatives could promote the enantioselective version of this reaction, since Et_3N is able to promote the racemic formation of 1,4-DHPs.[10] 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).

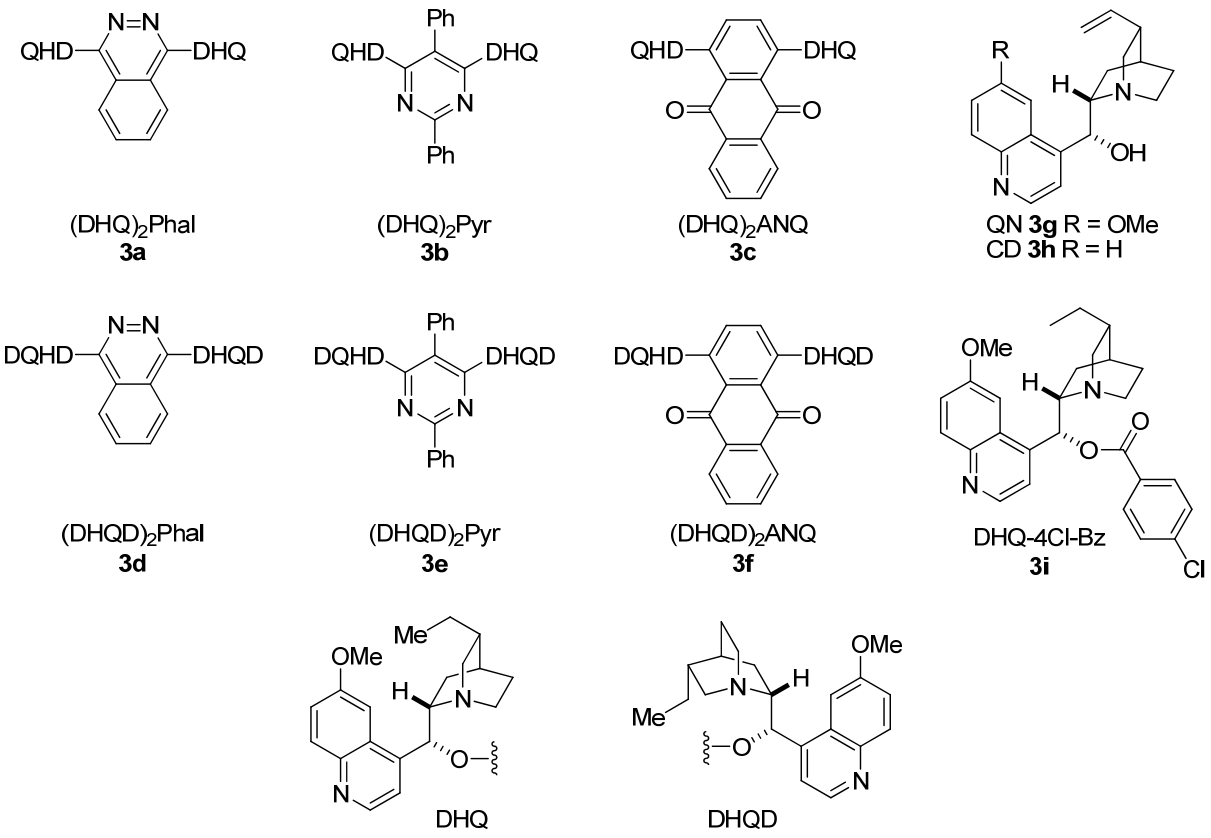
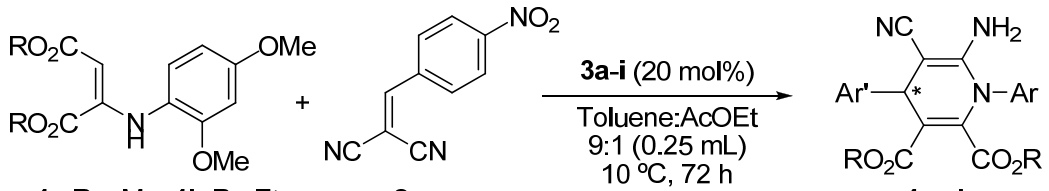


Figure 2. Cinchona alkaloids **3a-i** tested as catalysts.

We examined the reactivity and enantioselectivity provided by these catalysts in a model reaction between enamines **1a**-**b** 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**.[a]



1a R = Me; **1b** R= Et **2a** **4aa-ba**

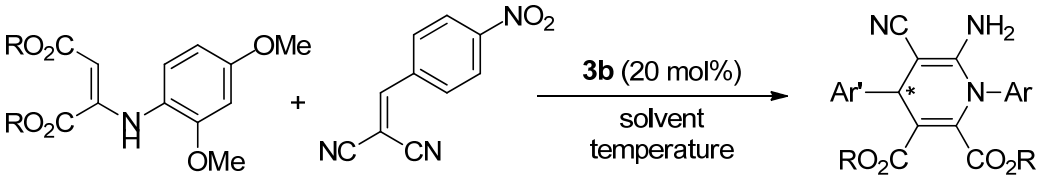
Entry	catalyst	R	yield (%)[b]	ee (%)[c]
1	**3a**	Me	91	66
2	**3b**	Me	81	80
3	**3b**	Et	97	74

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

[a] To a mixture of catalyst **3a-i** (20 mol%) and enamine **1** (0.3 mmol), in toluene:AcOEt 9:1 (0.25 mL), alkylidenmalononitrile **2** (0.1 mmol) was added. [b] Isolated yield after column chromatography (SiO_2, *n*-hexane:AcOEt 7:3). [c] Determined by chiral HPLC analysis (Daicel Chiralpak IB, *n*-hexane:*i*PrOH 70:30, 1 mL/min).

Although promising results of enantioselectivities 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 for enamines **1a**-**b**, with a methyl or an ethyl ester group, respectively (entries 2 and 3); while enamine **1a** provided higher enantioselectivity (entry 2), enamine **1b** gave 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**.[a]



1a R = Me; **1b** R= Et **2a** **4aa-ba**

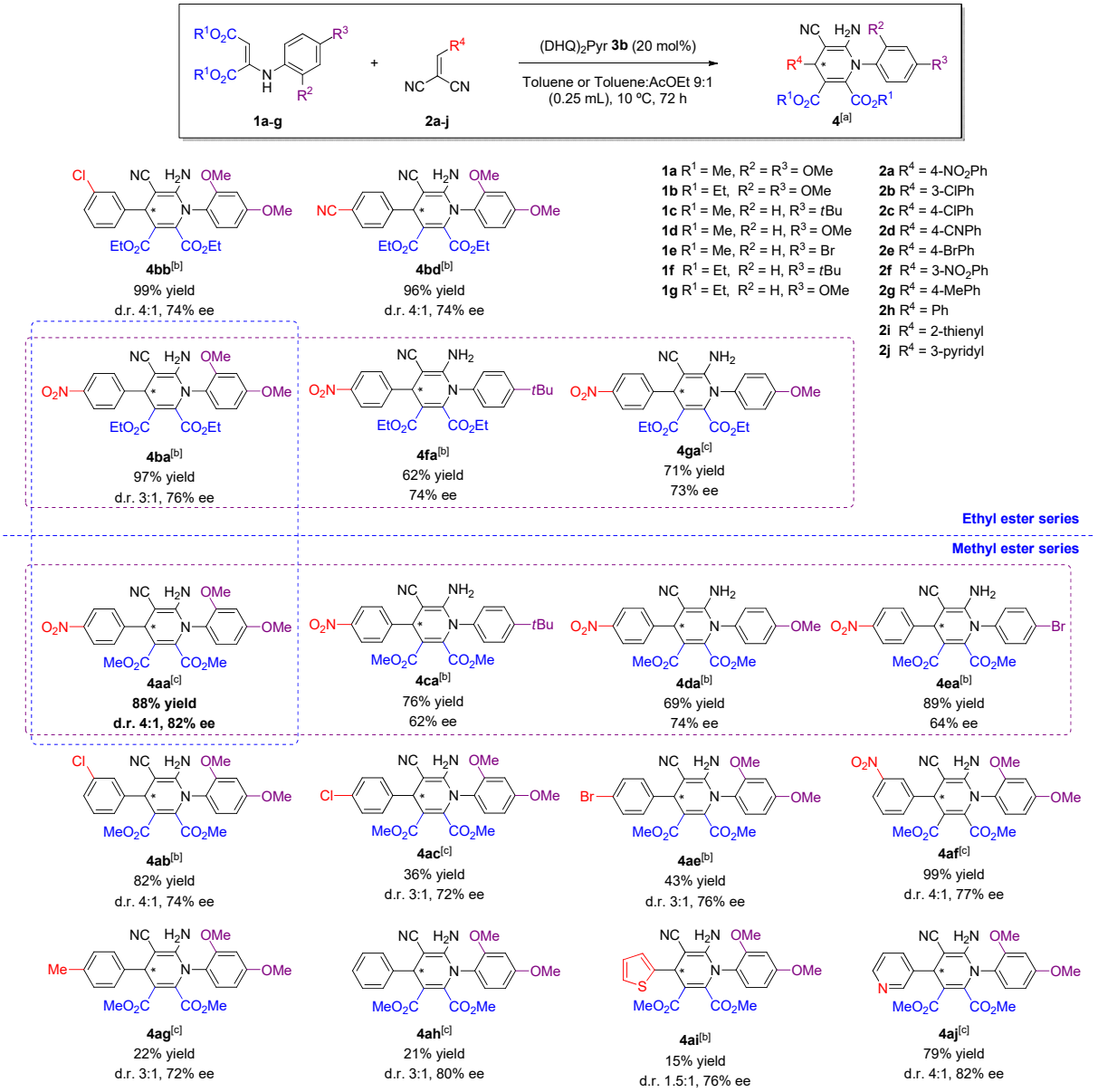
Entry	solvent (mL)	**enamine** (equiv.)	T (ºC)	time (h)	yield (%)[b]	ee (%)[c]
1	AcOEt (0.25)	**1a** (3)	10	72	89	64
2	Toluene:AcOEt 9:1 (0.25)	**1a** (3)	10	72	81	80

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

[a] 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), alkylidenmalononitrile **2** (0.1 mmol) was added. [b] Isolated yield after column chromatography (SiO_2, *n*-hexane:AcOEt 7:3). [c] Determined by chiral HPLC analysis (Daicel Chiralpak IB, *n*-hexane:*i*PrOH 70:30, 1 mL/min).

The ratio toluene:AcOEt was examined to find the best polarity for the process (Table 2, entries 1-4). Although in this case, toluene was the best solvent, in further experiments the use of 10% of AcOEt was crucial to obtain good yields without compromising the enantioselectivity. Consequently, both media, toluene:AcOEt 9:1 and only toluene, were used to develop the final scope since better results were observed in one of the options, depending on the substrates (Scheme 2). Decreasing the temperature to −18 ºC led to a slightly improved enantioselectivity but unfortunately, with a very low reactivity (entries 5, 6 and 12). The ratio of enamine:malononitrile was also explored, but no remarkable differences were found with more than three equivalents of **1** (compare entries 8-10). In contrast, slower reaction rate and poorer enantioselectivity were found when only 2 equivalents of **1b** were used (entry 7). The concentration of the reaction had no significant effect on the enantioselectivity or the

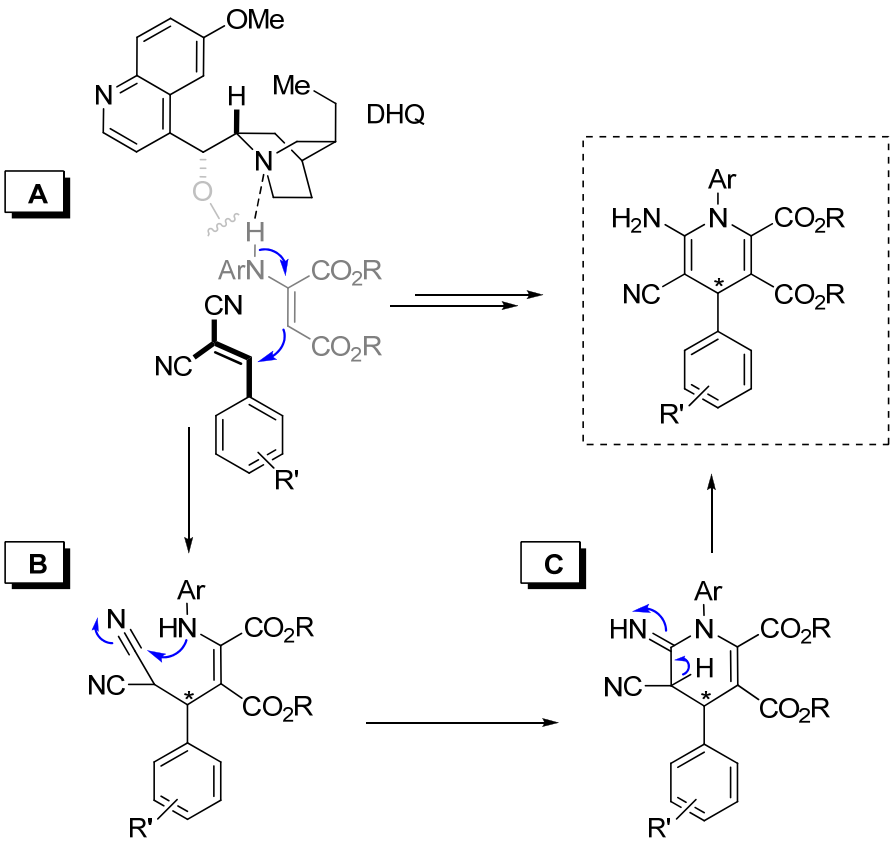
reactivity of the process (compare entries 8 and 11). Therefore, the best reaction conditions were found to be 0.25 mL of toluene:AcOEt 9:1 or only toluene, 20 mol% of catalyst **3b** and 3 equivalents of enamine **1**, at 10 ºC. In order to develop the methodology, the efficiency of these conditions was further explored for a variety of enamines **1a-g** and alkylidenmalononitriles **2a-j** (Scheme 2).



Scheme 2. Scope of the organocatalytic synthesis of enantiomerically enriched 1,4-DHPs **4**. [a] Reactions purified by column chromatography. [b] Reactions performed in toluene (0.25 mL). [c] Reactions performed in toluene:AcOEt 9:1 (0.25 mL).

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%). While the correlation between the electronic environment of the enamines **1** and the reactivity and the enantioselectivity of the process remains unclear, 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**). Regarding the malononitriles **2**, although the results 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 in general, 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** (Figure S53-S55).

Based on the literature data for the non-asymmetric version of this reaction,[10] and our previous work,[8f] 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 Et_3N is able to promote this reaction in the racemic version.[10] 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 is 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 ionization method and mass analyzer type MicroTof-Q were used for the HRMS measurements.^{1}H-NMR spectra were recorded at 300 and 400 MHz; ^{13}C-APT-NMR spectra were recorded at 75 MHz; $CDCl_3$ and DMSO-*d*$_6$ as the solvents. Chemical shifts were reported in the δ scale relative to residual $CHCl_3$ (7.26 ppm) and DMSO (2.50 ppm) for ^{1}H-NMR and to the central line of $CDCl_3$ (77 ppm) and DMSO-*d*$_6$ (39.43 ppm) for ^{13}C-APT-NMR.

All commercially available solvents and reagents were used as received.

Materials. Spectral data for enamines **1b**,[8f] **1c**,[11] **1d**,[12] **1e**,[12] **1f**,[8f] **1g**,[8f] and malononitriles **2a**,[13] **2b**,[14] **2c**,[13] **2d**,[15] **2e**,[16] **2f**,[14] **2g**,[14] **2h**,[13] **2i**,[14] **2j**,[17] 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,[8f] compound **1a** was obtained as a yellow oil in a 55% yield. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 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}C-APT-NMR (75 MHz, $CDCl_3$) δ 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) (cm^{-1}) ν 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 $C_{14}H_{17}NNaO_6$ 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 toluene:AcOEt 9:1 or toluene (0.25 mL), alkylidenmalononitrile **2** (0.1 mmol) was added. The reaction mixture was stirred 3 days at 10 ºC. Then, the solvent was evaporated under vacuum, and the reaction crude was purified by column chromatography (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 ºC and was purified by column chromatography (*n*-hexane:AcOEt 7:3 to 1:1), as a yellow solid in 88% yield (43.5 mg). M.p. >98 ºC 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 min^{-1}, λ = 254.0 nm): τ_{major} = 24.0 min; τ_{minor} = 13.1 min. $[\alpha]_D^{23}$ = +55.4 (*c* = 0.27, $CHCl_3$, 82% ee). ^{1}H-NMR (300 MHz, DMSO-*d*$_6$) *δ* 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}C-APT-NMR (75 MHz, DMSO-*d*$_6$) *δ* 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) (cm^{-1}) ν 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 $C_{24}H_{22}N_4NaO_8$ 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 ºC and was purified by column chromatography (*n*-hexane:AcOEt 7:3 to 1:1), as a yellow solid in 97% yield (50.7 mg). M.p. 124-126 ºC. 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^{-1}, λ = 276.0 nm): τ_{major} = 27.2 min; τ_{minor} = 16.5 min. $[\alpha]_D^{22}$ = +52.5 (*c* = 0.26, $CHCl_3$, 76% ee). ^{1}H-NMR (300 MHz, DMSO-*d*$_6$) 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). ^{13}C-APT-NMR (75 MHz, DMSO-*d*$_6$) 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^{-1}) 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 $C_{26}H_{25}N_4O_8$ 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 ºC and was purified by column chromatography (*n*-hexane:AcOEt 7:3 to 1:1), as a yellow solid in 76% yield (37.3 mg). M.p. >104 ºC 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^{-1}, λ = 238.0 nm): τ_{major} = 10.0 min; τ_{minor} = 7.7 min. $[\alpha]_D^{27}$ = +75.3 (*c* = 0.24, $CHCl_3$, 62% ee). ^{1}H-NMR (300 MHz, DMSO-*d*$_6$) 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). ^{13}C-APT-NMR (75 MHz, DMSO-*d*$_6$) 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^{-1}) 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 $C_{26}H_{27}N_4O_6$ 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 ºC and was purified by column chromatography (*n*-hexane:AcOEt 7:3 to 1:1), as a yellow solid in 69% yield (32 mg). M.p. 153-155 ºC. 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^{-1}, λ = 238.0 nm): τ_{major} = 20.1 min; τ_{minor} = 14.3 min. $[\alpha]_D^{26}$ = +34.5 (*c* = 0.26, $CHCl_3$, 74% ee). ^{1}H-NMR (300 MHz, DMSO-*d6*) 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). ^{13}C-APT-NMR (75 MHz, DMSO-d_6) 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^{-1}) 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 $C_{23}H_{21}N_4O_7$ 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 ºC and was purified by column chromatography (*n*-hexane:AcOEt 7:3 to 1:1), as a yellow solid in 89% yield (45.7 mg). M.p. >80 ºC 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^{-1}, λ = 238.0 nm): τ_{major} = 17.0 min; τ_{minor} = 13.4 min. $[\alpha]_D^{27}$ = −4.3 (*c* = 0.20, $CHCl_3$, 64% ee). ^{1}H-NMR (300 MHz, DMSO-*d6*) 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). ^{13}C-APT-NMR (75 MHz, DMSO-d_6) 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^{-1}) 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 $C_{22}H_{18}BrN_4O_6$ 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 ºC and was purified by column chromatography (*n*-hexane:AcOEt 7:3 to 1:1), as a yellow solid in 62% yield (32.2 mg). M.p. 137-140 ºC. 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^{-1}, λ = 254.0 nm): τ_{major} = 11.1 min; τ_{minor} = 8.1 min. $[\alpha]_D^{27}$ = +64.5 (*c* = 0.24, $CHCl_3$, 74% ee). ^{1}H-NMR (300 MHz, DMSO-*d6*) 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). ^{13}C-APT-NMR (75 MHz, DMSO-*d6*) 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^{-1}) 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 $C_{28}H_{31}N_4O_6$ 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 ºC and was purified by column chromatography (*n*-hexane:AcOEt 7:3 to 1:1), as a yellow solid in 71% yield (35.0 mg). M.p. 138-141 ºC. 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^{-1}, λ = 236.4 nm): τ_{major} = 29.4 min; τ_{minor} = 20.2 min. $[\alpha]_D^{22}$ = +43.0 (*c* = 0.26, $CHCl_3$, 60%). ^{1}H-NMR (300 MHz, DMSO-*d6*) 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). ^{13}C-APT-NMR (75 MHz, DMSO-*d6*) 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^{-1}) 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 $C_{25}H_{25}N_4O_7$ 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 ºC and was purified by column chromatography (*n*-hexane:AcOEt 7:3 to 1:1), as a yellow solid in 82% yield (39.7 mg). M.p. 102-106 ºC. 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^{-1}, λ = 238.0 nm): τ_{major} = 19.0 min; τ_{minor} = 9.3 min. $[\alpha]_D^{22}$ = −4.7 (*c* = 0.21, $CHCl_3$, 74% ee).

^{1}H-NMR (300 MHz, DMSO-*d*$_6$) 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). ^{13}C-APT-NMR (75 MHz, DMSO-*d*$_6$) 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) (cm^{-1}) ν 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 $C_{24}H_{21}ClN_3O_6$ 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 ºC and was purified by column chromatography (*n*-hexane:AcOEt 7:3 to 1:1), as a yellow solid in 98% yield (50.2 mg). M.p. 75-78 ºC. 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^{-1}, λ = 254.0 nm): τ_{major} = 24.8 min; τ_{minor} = 11.5 min. $[\alpha]_D^{27}$ = −8.5 (*c* = 0.29, $CHCl_3$, 74% ee). ^{1}H-NMR (300 MHz, DMSO-*d*$_6$) δ 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}C-APT-NMR (75 MHz, DMSO-*d*$_6$) δ 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) (cm^{-1}) ν 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 $C_{26}H_{25}ClN_3O_6$ 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 ºC and was purified by column chromatography (*n*-hexane:AcOEt 7:3 to 1:1), as a yellow solid in 36% yield (17.4 mg). M.p. 158-163 ºC. 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 min^{-1}, λ = 238.0 nm): τ_{major} = 17.6 min; τ_{minor} = 9.1 min. $[\alpha]_D^{25}$ = +10.1 (*c* = 0.20, $CHCl_3$, 72% ee). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 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}C-APT-NMR (75 MHz, DMSO-d_6) δ 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) (cm^{-1}) ν 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 $C_{24}H_{21}ClN_3O_6$ 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 ºC and was purified by column chromatography (*n*-hexane:AcOEt 7:3 to 1:1), as a yellow solid in 96% yield (48.2 mg). M.p. >110 ºC 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 min^{-1}, λ = 254.0 nm): τ_{major} = 31.3 min; τ_{minor} = 17.3 min. $[\alpha]_D^{22}$ = +26.3 (*c* = 0.20, $CHCl_3$, 74% ee). ^{1}H-NMR (300 MHz, DMSO-*d6*) δ 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}C-APT-NMR (75 MHz, DMSO-*d6*) δ 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) (cm^{-1}) ν 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 $C_{27}H_{25}N_4O_6$ 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 ºC and was purified by column chromatography (*n*-hexane:AcOEt 7:3 to 1:1), as a yellow solid

in 43% yield (22.7 mg). M.p. >95 ºC 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 min^{-1}, λ = 237.0 nm): τ_{major} = 18.6 min; τ_{minor} = 9.4 min. $[\alpha]_D^{25}$ = +8.7 (*c* = 0.20, $CHCl_3$, 76% ee). ^{1}H-NMR (300 MHz, DMSO-*d6*) δ 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, 0.25H), 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}C-APT-NMR (75 MHz, DMSO-*d6*) δ 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) (cm^{-1}) ν 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 $C_{24}H_{21}BrN_3O_6$ 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 ºC and was purified by column chromatography (*n*-hexane:AcOEt 7:3 to 1:1), as a yellow solid in 99% yield (48.9 mg). M.p. >106 ºC 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 min^{-1}, λ = 238.0 nm): τ_{major} = 23.9 min; τ_{minor} = 12.4 min. $[\alpha]_D^{24}$ = −3.0 (*c* = 0.21, $CHCl_3$, 77%). ^{1}H-NMR (300 MHz, DMSO-*d6*) δ 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, 0.2 H), 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}C-APT-NMR (75 MHz, DMSO-*d*$_6$) δ 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) (cm^{-1}) ν 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 $C_{24}H_{21}N_4O_8$ 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 ºC and was purified by column chromatography (*n*-hexane:AcOEt 7:3 to 1:1), as a yellow solid in 22% yield (10.2 mg). M.p. 123-126 ºC. 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 min^{-1}, λ = 240.2 nm): τ_{major} = 15.1 min; τ_{minor} = 8.5 min. $[\alpha]_D^{26}$ = +7.6 (*c* = 0.20, $CHCl_3$, 72% ee). ^{1}H-NMR (300 MHz, DMSO-*d*$_6$) δ 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}C-APT-NMR (75 MHz, DMSO-*d*$_6$) δ 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) (cm^{-1}) ν 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 $C_{25}H_{24}N_3O_6$ 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 ºC and was purified by column chromatography (*n*-hexane:AcOEt 7:3 to 1:1), as a yellow solid in 21% yield (9.4 mg). M.p. 90-94 ºC. 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 min^{-1}, λ = 238.0 nm): τ_{major} = 17.7 min; τ_{minor} = 9.4 min. $[\alpha]_D^{28}$ = −13.6 (*c* = 0.17, $CHCl_3$, 80% ee). ^{1}H-NMR (300 MHz, DMSO-*d*$_6$) *δ* 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}C-APT-NMR (75 MHz, DMSO-*d*$_6$) *δ* 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) (cm^{-1}) ν 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 $C_{24}H_{22}N_3O_6$ 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 ºC and was purified by column chromatography (*n*-hexane:AcOEt 7:3 to 1:1), as a yellow solid in 15% yield (6.8 mg). M.p. 139-141 ºC. 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 min^{-1}, λ = 242.6 nm): τ_{major} = 14.2 min; τ_{minor} = 9.7 min. $[\alpha]_D^{26}$ = −3.5 (*c* = 0.17, $CHCl_3$, 76% ee). ^{1}H-NMR (300 MHz, DMSO-*d*$_6$) δ 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}C-APT-NMR (75 MHz, DMSO-*d*$_6$) δ 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) (cm^{-1}) ν 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 $C_{22}H_{20}N_3O_6S$ 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 ºC and was purified by column chromatography (*n*-hexane:AcOEt 7:3 to 1:1), as a yellow solid in 79% yield (35.6 mg). M.p. >185 ºC 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 min^{-1}, λ = 238.7 nm): τ_{major} = 28.1 min; τ_{minor} = 20.6 min. $[\alpha]_D^{22}$ = −6.9 (*c* = 0.22, $CHCl_3$, 82% ee). ^{1}H-NMR (300 MHz, DMSO-*d*$_6$) δ 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}C-APT-NMR (75 MHz, DMSO-*d*$_6$) δ 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) (cm^{-1}) ν 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 $C_{23}H_{23}N_4O_6$ 451.1612; found 451.1625 [M+H].

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Notes

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Supporting Information Available: ^{1}H and ^{13}C-APT NMR spectra of all new products. HPLC chromatograms for products **4** are also provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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