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H_8-BINOL chiral imidodiphosphoric acids catalyzed cyclization reactions of β,γ-unsaturated α-ketoesters, arylamines and 1,3-dicarbonyl compounds: enantioselective synthesis of 1,4-dihydropyridines

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ABSTRACT

Penta-substituted 1,4-dihydropyridines were synthesized via catalytic enantioselective cyclization reactions of β,γ-unsaturated α-ketoesters, arylamines and acetylacetone for the first time. H_8-BINOL-type chiral imidodiphosphoric acid **4c** was a suitable catalyst and exhibited high catalytic and stereocontrolling abilities in these enone-type reactions. Under the optimized conditions, these 1,4-dihydropyridines were obtained with excellent enantioselectivities (up to 97% ee). In addition, the typical product **8ba** was converted into the corresponding substituted piperidine with high yield (87%) and excellent enantioselectivity (95% ee) in a single-step reduction.

1. Introduction

Over the last five decades, 1,4-dihydropyridines have been extensively researched due to their significant pharmacological and biological activities. As a class of calcium channel blockers, drugs containing 4-aryl-1,4-dihydropyridines, such as nicardipine, nimodipine, nilvadipine and amlodipine (Fig. 1, A), are widely used in the treatment of hypertension and other cardiovascular diseases.[1] Further research on 1,4-dihydropyridines has revealed their bioactivities including anticancer, antioxidant, antidiabetic and antitumour activities (Fig. 1, B).[2] With the increasingly widespread biological applications, chiral 1,4-dihydropyridines have received much attention and have been shown to have a significant effect on the biochemical properties.[3] For example, the (−)-isomer of mebudipine exhibited more than 1000 times higher activity than the (+)-isomer in the L-type Ca^{2+} channel assay (Fig. 1, C).[3e] The best-known (*R*)-(+)-Bay K 8644 even showed an opposite biological effect compared with its enantiomer (Fig. 1, D).[3a] Chiral 1,4-dihydropyridines also act as important building blocks in the synthesis of many natural products and alkaloids, and as NADH models in asymmetric reductions.[4]

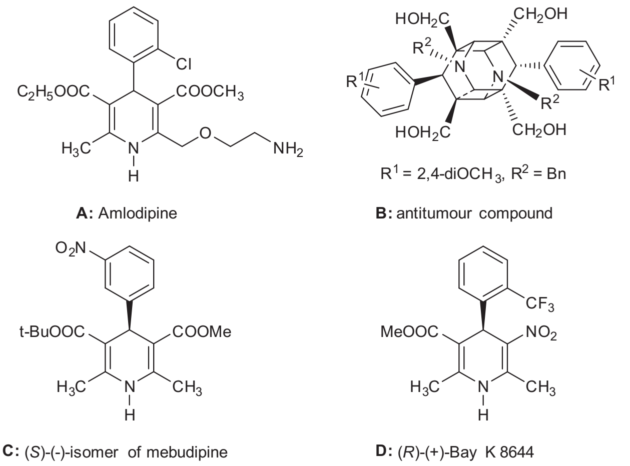

Figure 1. 4-Aryl-1,4-dihydropyridines and their derivatives with biological activities.

Despite plenty of reports for the preparation of symmetrical or racemic 1,4-dihydropyridines,[5] methods to obtain chiral 1,4-dihydropyridines were not enough. Compared with most reports for chiral auxiliaries and resolutions,[3,6] few examples of catalytic

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enantioselective syntheses are currently available.[7–11] Besides chiral phosphoric acids catalytic enantioselective Hantzsch reactions[7] and YCl$_3$ together with chiral silver phosphate catalytic asymmetric aza-Diels–Alder reactions,[8] enantioselective cyclization reactions of α,β-unsaturated aldehydes, primary amines and 1,3-dicarbonyl compounds could effectively produce chiral 1,4-dihydropyridines. In 2008, Jørgensen et al. successfully used the pyrrolidine catalyst in this reaction and obtained chiral 1,4-dihydropyridines with moderate yields and high enantioselectivities.[9] At the same time, chiral phosphoric acids were applied in this reaction by Gong et al. and moderate to good yields and high enantioselectivities were obtained.[10] Not long after, chiral thiourea–ammonium salts and pyrrolidine were used in cyclization reactions of α,β-unsaturated aldehydes and β-enamino esters.[11] These enantioselective cyclization reactions are limited to α,β-unsaturated aldehyde and only give 1,2,3,4-tetra-substituted 1,4-dihydropyridines (Fig. 2).[9–11]

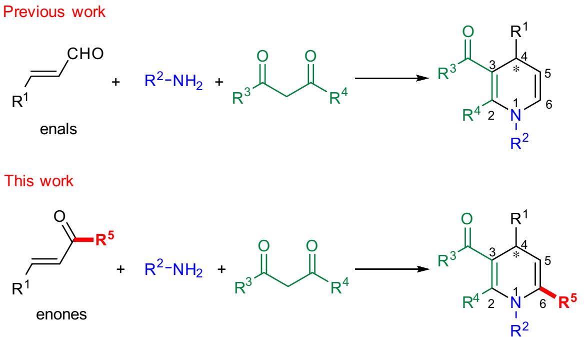


Figure 2. Comparison of enals and enones in the cyclization reactions.

The substituents at the C-2 and C-6 positions of 1,4-dihydropyridines make a crucial contribution to their conformation and are very important for their biological activities.[1a,c] Enones could introduce a substituent at C-6 position directly and afford 1,2,3,4,6-penta-substituted chiral 1,4-dihydropyridines. Nevertheless, because of the sterically hindered effect and electronic effect, the enone might exhibit relatively low activity and difficult to stereocontrol by chiral catalysts. To the best of our knowledge, enones have never been used in these enantioselective cyclization reactions.

Chiral imidodiphosphoric acids have proven to be particularly powerful in several enantioselective reactions since their first report in 2012.[12] In order to further expand upon the structural diversity and application scope of this new type of catalysts, we developed H$_8$-BINOL derived chiral imidodi-phosphoric acids not long ago.[13] Herein, we report the first organocatalytic enantioselective cyclization of β,γ-unsaturated α-ketoesters, arylamines and acetylacetone to obtain 1,2,3,4,6-five-substituted chiral 1,4-dihydropyridines.

2. Results and discussion

As shown in Figure 3, BINOL- and H$_8$-BINOL-based chiral phosphoric acids and imidodiphosphoric acids were screened in the cyclization of β,γ-unsaturated α-ketoester **5a**, *m*-methoxyaniline **6a** and acetylacetone **7** (Table 1). The reaction was performed in the presence of 5 mol % catalyst in toluene at 50 °C. The BINOL-phosphoric acids **1a**–**c** were tested and afforded low yields and enantioselectivities (Table 1, entries 1–3). H$_8$-BINOL phosphoric **2a**–**b** gave slightly improved yields and enantioselectivities (Table 1, entries 4 and 5); this could be inferred from the comparison that the H$_8$-BINOL scaffold might be more effective for this reaction. The screening of BINOL-based imidodiphosphoric acids **3a**–**b** revealed low yields but enantioselectivities were increased to 61–65% ee (Table 1, entries 6 and 7). Varying the BINOL scaffold to H$_8$-BINOL provided better yields and enantioselectivities (Table 1, entries 8–10). Among the H$_8$-BINOL-based imidodiphosphoric acids, **4c** with phenyl substituents was found to be the best catalyst for the reaction, affording 54% yield and 88% ee (Table 1, entry 10).

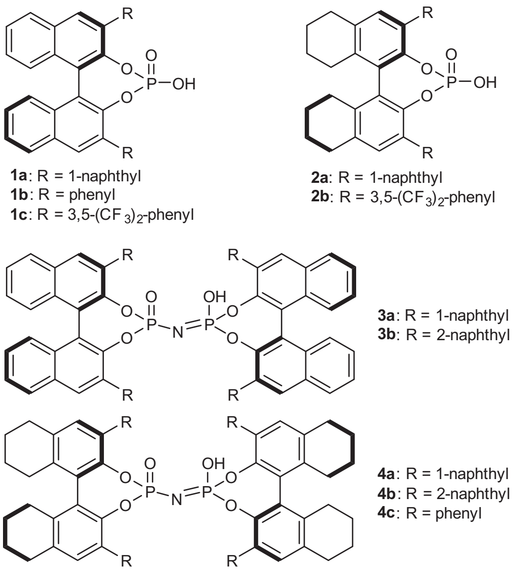
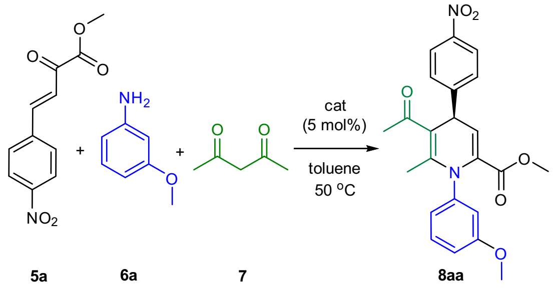


Figure 3. BINOL- and H$_8$-BINOL-based chiral phosphoric acids and imidodiphosphoric acids.

Table 1
Screening of BINOL- and H$_8$-BINOL-based chiral phosphoric acids and imidodiphosphoric acids[a]

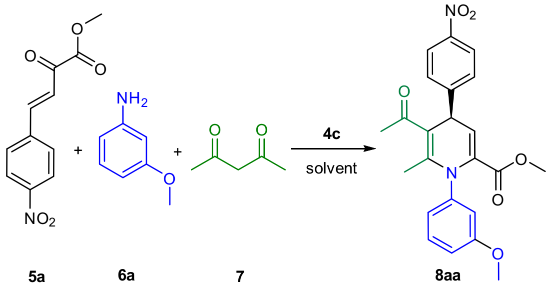


Entry	Catalyst	*t* (d)	Yield[b] (%)	ee[c] (%)
1	**1a**	4	32	29
2	**1b**	4	39	40
3	**1c**	4	19	16
4	**2a**	3	43	51
5	**2b**	3	46	34
6	**3a**	3	22	65
7	**3b**	2	36	61
8	**4a**	2	44	38
9	**4b**	2	43	86
10	**4c**	2	54	88

[a] Reaction conditions: **5a** (0.1 mmol, 1.0 equiv), **6a** (0.12 mmol, 1.2 equiv), **7** (0.2 mmol, 2 equiv), catalyst (5 mol %), toluene (1 mL), 50 °C.
[b] Isolated yield after flash chromatography.
[c] Determined by HPLC analysis with Daicel ChiralPak AD-H column.

Further screening of solvents showed that benzene afforded approximately the same yield and enantioselectivity with a long

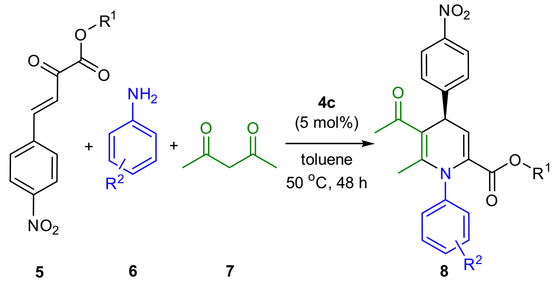
Table 2
Optimization of the reaction conditions with catalyst **4c**[a]



Entry	Solvent	**4c** (mol %)	*T* (°C)	*t* (d)	Yield[b] (%)	ee[c] (%)
1	Toluene	5	50	2	54	88
2	Benzene	5	50	3	53	87
3	Trimethyl-benzene	5	50	2	48	80
4	Cyclo-hexane	5	50	3	49	82
5	CH_2Cl_2	5	50	2	28	77
6	Isopropyl ester	5	50	3	43	88
7	Dioxane	5	50	2	50	71
8	THF	5	50	4	—	—
9	Ethanol	5	50	4	—	—
10	Toluene	5	25	7	24	90
11	Toluene	5	40	4	46	89
12	Toluene	5	60	1	55	83
13	Toluene	2	50	3	38	83
14	Toluene	8	50	2	47	86

[a] Reaction conditions: **5a** (0.1 mmol, 1.0 equiv), **6a** (0.12 mmol, 1.2 equiv), **7** (0.2 mmol, 2 equiv), solvent (1 mL).
[b] Isolated yield after flash chromatography.
[c] Determined by HPLC analysis with Daicel ChiralPak AD-H column.

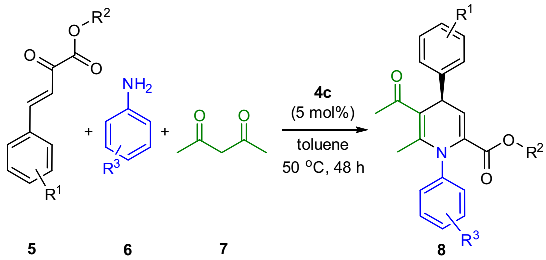
Table 3
Scope of ester groups of β,γ-unsaturated α-ketoesters and arylamines[a]



Entry	R^1	R^2	**8**	Yield[b] (%)	ee[c] (%)
1	Methyl	3-OCH_3	**8aa**	54	88
2	Ethyl	3-OCH_3	**8ab**	61	85
3	Isopropyl	3-OCH_3	**8ac**	54	90
4	Benzyl	3-OCH_3	**8ad**	51	89
5	Isopropyl	3-Cl	**8ae**	53	91
6	Isopropyl	4-Cl	**8af**	52	89
7	Isopropyl	3-Br	**8ag**	54	88
8	Isopropyl	3-F	**8ah**	58	94
9	Isopropyl	4-F	**8ai**	53	87
10	Isopropyl	3-CH_3	**8aj**	55	83
11	Isopropyl	4-CH_3	**8ak**	58	75

[a] Reaction conditions: **5** (0.1 mmol, 1.0 equiv), **6** (0.12 mmol, 1.2 equiv), **7** (0.2 mmol, 2 equiv), catalyst **4c** (5 mol %), toluene (1 mL), 50 °C, 48 h.
[b] Isolated yield after flash chromatography.
[c] Determined by HPLC analysis with Daicel ChiralPak AD-H column.

Table 4
Scope of β,γ-unsaturated α-ketoesters[a]



Entry	R^1	R^2	R^3	**8**	Yield[b] (%)	ee[c] (%)
1	4-NO_2	Benzyl	3-Cl	**8ba**	54	94
2	4-NO_2	Benzyl	3-Br	**8bb**	56	94
3	4-Br	Isopropyl	3-Cl	**8bc**	54	92
4	4-Br	Isopropyl	3-Br	**8bd**	58	91
5	3-Br	Methyl	3-Cl	**8be**	41	93
6	4-CN	Isopropyl	3-Cl	**8bf**	56	95
7	4-CN	Isopropyl	3-Br	**8bg**	51	94
8	4-F	Ethyl	3-Br	**8bh**	55	91
9	4-CF_3	Ethyl	3-Cl	**8bi**	53	91
10	3,4-2-Cl	Methyl	3-Cl	**8bj**	55	95
11	3,4-2-Cl	Isopropyl	3-Cl	**8bk**	55	93
12	3,4-2-Cl	Methyl	3-Br	**8bl**	54	94
13	3,4-2-Cl	Ethyl	3-Br	**8bm**	55	92
14	4-CH_3	Isopropyl	3-Br	**8bn**	48	90
15	3-NO_2	Methyl	3-Br	**8bo**	43	94
16[d]	4-NO_2	Benzyl	3-F	**8bp**	34	97
17[d]	4-CN	Isopropyl	3-Cl	**8bq**	46	96
18[d]	3,4-2-Cl	Methyl	3-Cl	**8br**	52	96

[a] Reaction conditions: **5** (0.1 mmol, 1.0 equiv), **6** (0.12 mmol, 1.2 equiv), **7** (0.2 mmol, 2 equiv), catalyst **4c** (5 mol %), toluene (1 mL), 50 °C, 48 h.
[b] Isolated yield after flash chromatography.
[c] Determined by HPLC analysis with Daicel ChiralPak AD-H column.
[d] The reaction was carried out at 40 °C for 4 d.

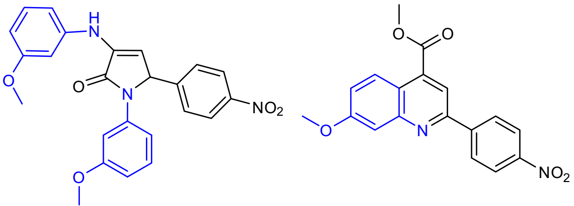
reaction time (Table 2, entry 2). The isopropyl ester also gave 88% ee value but the yield decreased to 43% (Table 2, entry 6). We then tested the temperature and catalyst loading. The best 90% ee was achieved when performing the reaction at 25 °C, however the yield and reaction rate decreased dramatically (Table 2, entry 10). In addition, reducing the catalyst loading to 2 mol % led to a decrease in both the yield and enantioselectivity, while increasing the catalyst loading did not improve the catalytic performance (Table 2, entries 13 and 14). Taking all these factors into consideration, 5 mol % **4c** in toluene at 50 °C were selected as the reaction conditions for further studies. It should be mentioned that high catalyst loadings (from 10 to 20 mol %) were required in previous reports for the enantioselective synthesis of 1,4-dihydropyridines.[7–11]

Under the optimized conditions, β,γ-unsaturated α-ketoesters with different ester groups were examined (Table 3, entries 1–4). An enone with an ethyl ester group slightly decreased the enantioselectivity, but afforded the best yield (61%; Table 3, entry 2). Replacing the ester group with isopropyl and benzyl gave products with higher enantioselectivities (89–90% ee; Table 3, entries 3 and 4). We next investigated arylamines with different substituents. The *meta*- and *para*-substituted arylamines bearing either electron-donating or electron-withdrawing groups smoothly underwent the reaction with moderate yields and high enantioselectivities. However *ortho*-substituted arylamines were found to have very low reactivity and did not generate the products. The *meta*-substituted arylamines afforded higher enantioselectivities than the *para*-substituted arylamines. The *p*-nitroaniline and 1-naphthylamine were also tested, but the corresponding products were not obtained.

The scope of β,γ-unsaturated α-ketoesters was subsequently investigated. High enantioselectivities were achieved when enones with electron-withdrawing groups on the aromatic ring were used in the reaction. Notably, *para*-NO_2 and *para*-CN substituted enones formed 1,4-dihydropyridines with excellent enantioselectivities (94–95% ee; Table 4, entries 1, 2, 6 and 7). Enones with *meta*-

substituents were also tested, giving slightly lower yields with high enantioselectivities (Table 4, entries 5 and 15). However the reaction of enones with *ortho*-substituents progressed very slowly and hardly generated the products. The reaction of 3,4-2-Cl substituted enones with different ester groups gave 1,4-dihydropyridines with 92–95% ee (Table 4, entries 10–13). We also examined enones with electron-rich substituents, obtaining 48% yield and 90% ee (Table 4, entry 14). The enantioselectivities could be further improved (96–97% ee) upon when the reaction temperature was decreased to 40 °C, but with a slight reduction in the yield (Table 4, entries 16–18). The reaction of α,β-unsaturated ketone was also tested, but it did not occur under the same conditions.

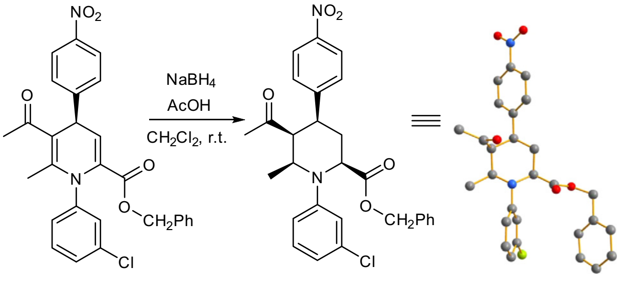
In the cyclization reaction of β,γ-unsaturated α-ketoester **5a**, *m*-methoxyaniline **6a** and acetylacetone **7** (Table 2, entry 1), two by-products, 3-arylaminopyrroline-2-one **9** with 29% yield and 2-arylquinoline-4-carboxylate **10** with 11% yield, were observed (Fig. 4). Compound **9** might be produced through aza-Michael addition of arylamine **6a** and β,γ-unsaturated α-iminoester, which was formed by β,γ-unsaturated α-ketoester **5a** and another arylamine. The intramolecular cyclization of the intermediate gave compound **9**.[14] The formation of compound **10** was via Michael addition and intramolecular cyclization of β,γ-unsaturated α-ketoester **5a** and arylamine **6a**. The generation of these by-products is a reason for the moderate yields of 1,4-dihydropyridines.



9 **10**

Figure 4. By-products of the cyclization reaction.

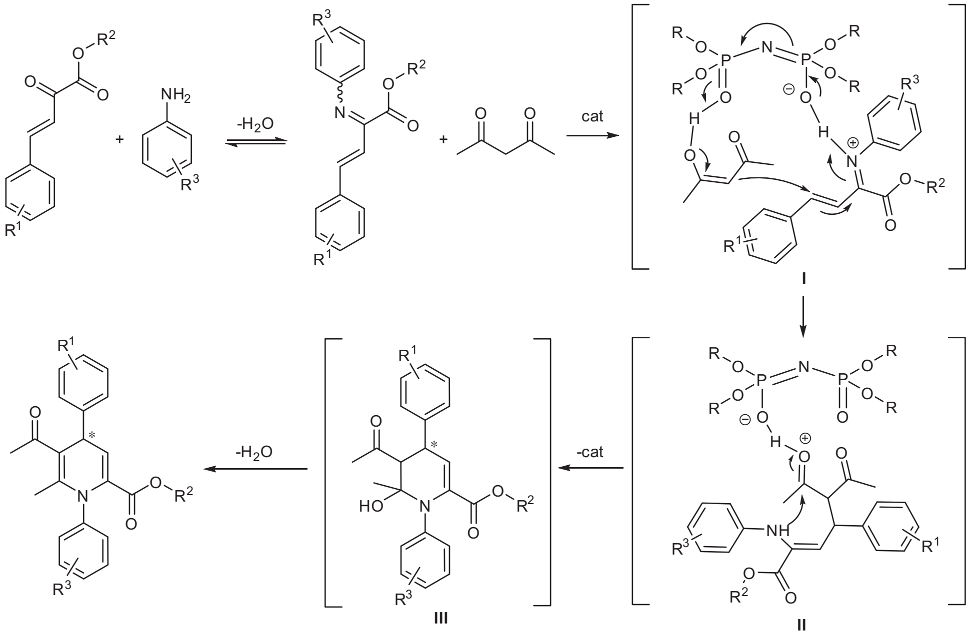
Chiral multisubstituted 1,4-dihydropyridines can be transformed into chiral piperidines and tetrahydropyridines, which are important components of some drugs and natural products.[4a,c] For example, a single-step reduction of the cyclization product **8ba** produced chiral multisubstituted piperidine **11** in 87% yield and with 95% ee in the presence of $NaBH_4$ and acetic acid (Scheme 1). The absolute configuration of **11** was established by X-ray crystallography. Accordingly, the stereogenic center at the C-4 position in **8ba** was not affected by the reduction, thus **8ba** was determined to have an (*R*)-configuration.



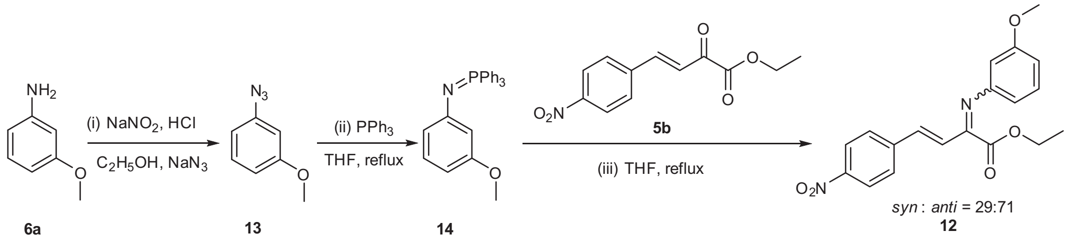
8ba **11**

Scheme 1. Reduction of product **8ba** and the absolute configuration of **11**.

A plausible mechanism for the cyclization reaction of β,γ-unsaturated α-ketoester, arylamine and acetylacetone is shown in Scheme 2. At the beginning, dehydration condensation of β,γ-unsaturated α-ketoester and arylamine produces β,γ-unsaturated α-iminoester. The *anti*-isomer of the iminoester is activated by forming a hydrogen bond with imidodiphosphoric acid. Meanwhile, the enol form of acetylacetone interacts with imidodiphosphoric acid by forming another hydrogen bond with P=O bond to give transition state **I**. The Michael addition then takes place to form intermediate **II**. Subsequently, the amino group attacked the activated C=O bond of acetylacetone to give cyclization intermediate **III**. Finally, chiral 1,4-dihydropyridines are generated via dehydration of intermediate **III**.



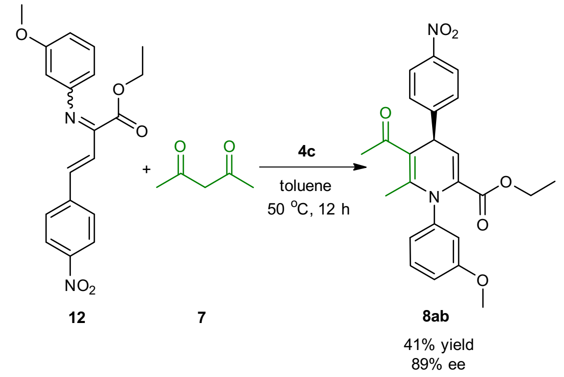
Scheme 2. A plausible mechanism for the cyclization reaction in the presence of imidodiphosphoric acids.



Scheme 3. Synthesis of β,γ-unsaturated α-iminoester **12**.

Next, β,γ-unsaturated α-iminoester **12** was synthesized to confirm the plausible mechanism (Scheme 3). The 1-azido-3-methoxybenzene **13** could be easily achieved by azidation of 3- methoxyaniline **6a**.[15] The arylazides **13** then interacted with triphenylphosphine to give *N*-aryl triphenylphoshazenes **14**. Subsequently, Wittig-type condensation of *N*-aryl triphenyl-phoshazenes **14** with β,γ-unsaturated α-ketoester **5b** afforded the β,γ-unsaturated α-iminoester **12** as an *syn*/*anti* mixture (29:71).[16]

On the basis of the plausible mechanism, β,γ-unsaturated α-iminoester **12** was used in the cyclization reaction with acetylacetone **7** (Scheme 4). Initially, under a nitrogen atmosphere, 0.1 mmol β,γ-unsaturated α-iminoester **12** and 5 mol % catalyst **4c** were dissolved in 1 mL of toluene and stirred at 25 °C for 10 min, after which 0.2 mmol acetylacetone was added, and the reaction mixture was stirred at 50 °C. After 12 h, product **8ab** was obtained with 41% yield and 89% ee. We also tried to recover the iminoester **12** after the reaction was carried out for 8 h and found that the recovered iminoester was mainly the *syn*-isomer, while the *anti*-isomer had almost disappeared. The *syn*-isomer was independently used in the reaction, but this did not give product **8ab**, which is another reason for the moderate yields of 1,4-dihydropyridines. These results strongly support the existence of β,γ-unsaturated α-iminoester intermediate in the three-component cyclization reaction and the formation of the iminoester intermediate is most probably the rate-determining step. This also indicated that the *anti*-isomer of β,γ-unsaturated α-iminoester **12** was more suitable for generating 1,4-dihydropyridines.



Scheme 4. Cyclization reaction of β,γ-unsaturated α-iminoester **12** and acetylacetone **7**.

3. Conclusions

In conclusion, the enantioselective cyclization of β,γ-unsaturated α-ketoesters, arylamines and acetylacetone enabled the highly enantioselective synthesis of penta-substituted chiral 4-aryl-1,4-dihydropyridines. In these enone-type reactions, H_8-BINOL type chiral imidodiphosphoric acids showed high catalytic and stereocontrolling abilities in comparison to chiral phosphoric acids. By using enones, 1,4-dihydropyridines substituted at the C-6 position were obtained with excellent enantioselectivities. The reduction of these products then gave the chiral multisubstituted piperidine in a single-step reaction. Further applications of the H_8-BINOL type chiral imidodiphosphoric acids are currently in progress in our laboratory.

4. Experimental

4.1. General methods

All reagents were used without purification. All solvents were purified and dried according to standard methods. The reaction products were purified by flash column chromatography on 200–300 mesh silica gel. The melting point was recorded on a melting point apparatus (MPA100, Stanford Research Systems, Inc.). Optical rotations were measured with a Jasco-P-2000 digital polarimeter at 25 °C and concentrations (*c*) are given in $g \times (100\,mL)^{-1}$. ^1H and ^{13}C NMR spectra were recorded with Bruker 400 MHz spectrometers (400 MHz for ^1H NMR, 101 MHz for ^{13}C NMR) and Bruker 300 MHz spectrometers (300 MHz for ^1H NMR, 75 MHz for ^{13}C NMR); chemical shifts (δ) are given in ppm. High-resolution mass spectrometry analysis (HRMS) data were measured on a Bruker ApexII mass spectrometer by means of the ESI technique. Analytical HPLC was recorded on a HPLC machine equipped with Agilent 1100 series or Ichrom 5100 series quaternary pump with a UV diode array detector. Enantiomeric excess values were measured by analytical HPLC with Daicel ChiralPak AD-H or Daicel Chiralcel OD-H column.

4.2. Synthesis of catalyst 4c

Catalyst **4c** was prepared according to our previous work.[13] NaH (80% in oil, 2 mmol) was added to a stirred solution of H_8-BINOL-type phosphoryl chloride (1.3 mmol) in dry DMF (10 ml) under a nitrogen atmosphere at room temperature. After stirring for 5 min, H_8-BINOL-type phosphoramide (1 mmol) was added and the mixture was stirred for another 1 h. After the reaction was completed, 30 ml of CH_2Cl_2 was added to the flask and the mixture was washed with saturated brine (50 ml × 5). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified with silica gel column chromatography. The product was dissolved in CH_2Cl_2, acidified with 4 M HCl (10 ml), washed with brine (20 ml × 2), dried over Na_2SO_4 and concentrated in vacuo to give catalyst **4c**.

4.2.1. H_8-BINOL-type chiral imidodiphosphoric acid catalyst 4c

White solid; 82% yield; mp 343–345 °C; $[\alpha]_D^{20} = -334.8$ (*c* 1, $CHCl_3$); ^1H NMR (300 MHz, CDCl3) δ 7.37–7.35 (m, 4H), 7.29–7.24 (m, 5H), 7.22–7.19 (m, 2H), 7.16 (s, 2H), 7.05–6.98 (m, 11H), 3.00–2.97 (m, 4H), 2.87–2.65 (m, 8H), 2.57–2.51 (m, 2H), 2.38–2.33 (m, 2H), 2.00–1.97 (m, 4H), 1.91–1.78 (m, 10H), 1.67–1.60 (m, 2H); ^{13}C NMR (75 MHz, CDCl3) δ 143.8, 143.3, 137.2, 136.6, 134.4, 134.3, 132.2, 131.5, 130.6, 130.4, 129.6, 128.2, 127.7, 127.3, 126.8, 126.7, 29.5, 29.2, 27.9, 22.9, 22.8, 22.7, 22.6; ^{31}P NMR (162 MHz, DMSO-d_6) δ 7.66; HRMS (ESI) *m*/*z* calcd for $C_{64}H_{58}NO_6P_2$ ($[M+H]^+$): 998.3734, found: 998.3725.

4.3. General procedure for the enantioselective three-component cyclization reaction

A solution of β,γ-unsaturated α-ketoester (0.1 mmol), arylamine (0.12 mmol), and catalyst **4c** (5 mol %, 0.005 mmol) in toluene (1 mL) was stirred at 25 °C for 10 min, then acetylacetone (0.2 mmol) was added. The reaction mixture was stirred at 50 °C for 48 h (reaction progress monitored by TLC). Next, EtOAc and silica gel were added and, after removal of the solvent, the residue was purified by flash column chromatography on silica gel (ethyl acetate/petroleum ether, 1:5 to 1:2) to afford the pure products.

4.3.1. (*R*)-Methyl-5-acetyl-1-(3-methoxyphenyl)-6-methyl-4-(4-nitrophenyl)-1,4-dihydropyridine-2-carboxylate 8aa

Colorless oil, 54% yield, 88% ee [Daicel Chiralcel AD-H column, *n*-hexane/*i*-PrOH = 70:30, 1.0 ml/min, λ = 254 nm, *t* (minor) = 16.05 min, *t* (major) = 19.88 min]; $[\alpha]_D^{20}$ = +143.4 (*c* 0.456, EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, *J* = 8.4 Hz, 2H), 7.50 (d, *J* = 8.8 Hz, 2H), 7.28 (t, *J* = 8.4 Hz, 1H), 6.89 (dd, *J* = 2.4, 8.4 Hz, 1H), 6.77 (dd, *J* = 1.2, 8.0 Hz, 1H), 6.70 (t, *J* = 2.4 Hz, 1H), 6.07 (d, *J* = 6.8 Hz, 1H), 4.84 (d, *J* = 6.4 Hz, 1H), 3.79 (s, 3H), 3.50 (s, 3H), 2.18 (s, 3H), 2.17 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.38, 163.17, 159.89, 152.57, 150.04, 146.82, 142.07, 133.50, 129.48, 128.07, 124.25, 121.74, 117.14, 115.56, 113.61, 110.73, 55.37, 52.11, 40.18, 30.42, 19.34. HRMS(ESI) *m*/*z* calcd for $C_{23}H_{23}N_2O_6$ ($[M+H]^+$): 423.1551, found: 423.1544.

4.3.2. (*R*)-Ethyl-5-acetyl-1-(3-methoxyphenyl)-6-methyl-4-(4-nitrophenyl)-1,4-dihydropyridine-2-carboxylate 8ab

Colorless oil, 61% yield, 85% ee [Daicel Chiralcel AD-H column, *n*-hexane/*i*-PrOH = 70:30, 1.0 ml/min, λ = 254 nm, *t* (minor) = 13.75 min, *t* (major) = 20.48 min]; $[\alpha]_D^{25}$ = +145.2 (*c* 0.566, EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23 (d, *J* = 8.7 Hz, 2H), 7.50 (d, *J* = 9.0 Hz, 2H), 7.28 (t, *J* = 7.8 Hz, 1H), 6.89 (dd, *J* = 2.4, 8.4 Hz, 1H), 6.78 (dd, *J* = 2.1, 7.5 Hz, 1H), 6.71 (t, *J* = 2.1 Hz, 1H), 6.04 (d, *J* = 6.6 Hz, 1H), 4.84 (d, *J* = 6.6 Hz, 1H), 3.96–3.79 (m, 2H), 3.79 (s, 3H), 2.19 (s, 3H), 2.17 (s, 3H), 1.01 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.47, 162.93, 159.92, 152.66, 149.83, 146.85, 142.23, 133.89, 129.49, 128.12, 124.26, 121.72, 116.69, 115.61, 113.60, 110.77, 61.28, 55.39, 40.32, 30.39, 19.35, 13.69. HRMS(ESI) *m*/*z* calcd for $C_{24}H_{25}N_2O_6$ ($[M+H]^+$): 437.1707, found: 437.1707.

4.3.3. (*R*)-Isopropyl-5-acetyl-1-(3-methoxyphenyl)-6-methyl-4-(4-nitrophenyl)-1,4-dihydropyridine-2-carboxylate 8ac

Colorless oil, 54% yield, 90% ee [Daicel Chiralcel AD-H column, *n*-hexane/*i*-PrOH = 70:30, 1.0 ml/min, λ = 254 nm, *t* (minor) = 9.45 min, *t* (major) = 15.42 min]; $[\alpha]_D^{25}$ = +238.0 (*c* 0.484, EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, *J* = 8.8 Hz, 2H), 7.50 (d, *J* = 8.8 Hz, 2H), 7.28 (t, *J* = 8.0 Hz, 1H), 6.88 (dd, *J* = 2.4, 8.4 Hz, 1H), 6.77 (dd, *J* = 1.2, 8.0 Hz, 1H), 6.71 (t, *J* = 2.0 Hz, 1H), 5.99 (d, *J* = 6.8 Hz, 1H), 4.83 (d, *J* = 6.4 Hz, 1H), 4.79–4.73 (m, 1H), 3.79 (s, 3H), 2.20 (s, 3H), 2.16 (s, 3H), 1.01 (d, *J* = 6.4 Hz, 3H), 0.92 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.52, 162.62, 159.92, 152.72, 149.69, 146.83, 142.33, 134.21, 129.49, 128.13, 124.26, 121.66, 116.37, 115.61, 113.57, 110.75, 69.10, 55.40, 40.41, 30.37, 21.29, 21.10, 19.37. HRMS(ESI) *m*/*z* calcd for $C_{25}H_{27}N_2O_6$ ($[M+H]^+$): 451.1864, found: 451.1862.

4.3.4. (*R*)-Benzyl-5-acetyl-1-(3-methoxyphenyl)-6-methyl-4-(4-nitrophenyl)-1,4-dihydropyridine-2-carboxylate 8ad

Colorless oil, 51% yield, 89% ee [Daicel Chiralcel AD-H column, *n*-hexane/*i*-PrOH = 70:30, 1.0 ml/min, λ = 254 nm, *t* (minor) = 32.33 min, *t* (major) = 34.95 min]; $[\alpha]_D^{25}$ = +179.8 (*c* 0.502, EtOAc). ^{1}H NMR (400 MHz, DMSO) δ 8.26 (d, *J* = 8.4 Hz, 2H), 7.60 (d, *J* = 8.8 Hz, 2H), 7.32–7.28 (m, 4H), 7.09–7.07 (m, 2H), 6.96 (dd, *J* = 2.4, 8.4 Hz, 1H), 6.76–6.74 (m, 2H), 6.11 (d, *J* = 6.8 Hz, 1H), 4.89 (s, 2H), 4.88 (d, *J* = 6.8 Hz, 1H), 3.70 (s, 3H), 2.14 (s, 3H), 2.11 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 198.18, 162.87, 159.88, 153.43, 149.85, 146.78, 142.25, 135.68, 133.52, 130.22, 128.82, 128.79, 128.63, 128.49, 124.72, 121.68, 117.92, 115.91, 114.31, 110.62, 66.90, 55.72, 39.67, 30.72, 19.26. HRMS(ESI) *m*/*z* calcd for $C_{29}H_{27}N_2O_6$ ($[M+H]^+$): 499.1864, found: 499.1865.

4.3.5. (*R*)-Isopropyl-5-acetyl-1-(3-chlorophenyl)-6-methyl-4-(4-nitrophenyl)-1,4-dihydropyridine-2-carboxylate 8ae

Colorless oil, 53% yield, 91% ee [Daicel Chiralcel AD-H column, *n*-hexane/*i*-PrOH = 70:30, 1.0 ml/min, λ = 254 nm, *t* (minor) = 7.27 min, *t* (major) = 11.03 min]; $[\alpha]_D^{25}$ = +226.7 (*c* 0.486, EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, *J* = 8.8 Hz, 2H), 7.49 (d, *J* = 8.4 Hz, 2H), 7.38–7.32 (m, 2H), 7.22 (t, *J* = 2.0 Hz, 1H), 7.07 (dt, *J* = 1.6, 7.2 Hz, 1H), 6.05 (d, *J* = 6.4 Hz, 1H), 4.84 (d, *J* = 6.8 Hz, 1H), 4.83–4.77 (m, 1H), 2.16 (s, 3H), 2.15 (s, 3H), 1.03 (d, *J* = 6.0 Hz, 3H), 0.94 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.68, 162.29, 152.27, 148.81, 146.93, 142.60, 134.46, 133.78, 130.14, 129.86, 128.49, 128.12, 127.70, 124.37, 117.25, 111.27, 69.34, 40.48, 30.33, 21.31, 21.14, 19.26. HRMS(ESI) *m*/*z* calcd for $C_{24}H_{24}ClN_2O_5$ ($[M+H]^+$): 455.1368, found: 455.1360.

4.3.6. (*R*)-Isopropyl-5-acetyl-1-(4-chlorophenyl)-6-methyl-4-(4-nitrophenyl)-1,4-dihydropyridine-2-carboxylate 8af

Colorless oil, 52% yield, 89% ee [Daicel Chiralcel AD-H column, *n*-hexane/*i*-PrOH = 80:20, 1.0 ml/min, λ = 254 nm, *t* (minor) = 14.95 min, *t* (major) = 22.19 min]; $[\alpha]_D^{25}$ = +226.5 (*c* 0.476, EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, *J* = 8.8 Hz, 2H), 7.48 (d, *J* = 8.4 Hz, 2H), 7.36 (d, *J* = 8.8 Hz, 2H), 7.12 (d, *J* = 8.8 Hz, 2H), 6.05 (d, *J* = 6.4 Hz, 1H), 4.83 (d, *J* = 6.4 Hz, 1H), 4.81–4.75 (m, 1H), 2.15 (s, 6H), 1.03 (d, *J* = 6.4 Hz, 3H), 0.97 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.57, 162.27, 152.32, 149.23, 146.90, 139.86, 134.12, 133.80, 130.84, 129.11, 128.08, 124.35, 117.19, 111.05, 69.34, 40.39, 30.31, 21.33, 21.19, 19.25. HRMS(ESI) *m*/*z* calcd for $C_{24}H_{24}ClN_2O_5$ ($[M+H]^+$): 455.1368, found: 455.1363.

4.3.7. (*R*)-Isopropyl-5-acetyl-1-(3-bromophenyl)-6-methyl-4-(4-nitrophenyl)-1,4-dihydropyridine-2-carboxylate 8ag

Colorless oil, 54% yield, 88% ee [Daicel Chiralcel AD-H column, *n*-hexane/*i*-PrOH = 80:20, 1.0 ml/min, λ = 254 nm, *t* (minor) = 10.97 min, *t* (major) = 18.21 min]; $[\alpha]_D^{25}$ = +240.6 (*c* 0.271, EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, *J* = 8.8 Hz, 2H), 7.51–7.47 (m, 3H), 7.37 (t, *J* = 1.6 Hz, 1H), 7.28–7.24 (m, 1H), 7.13–7.11 (m, 1H), 6.05 (d, *J* = 6.4 Hz, 1H), 4.84 (d, *J* = 6.4 Hz, 1H), 4.81–4.73 (m, 1H), 2.16 (s, 3H), 2.15 (s, 3H), 1.03 (d, *J* = 6.4 Hz, 3H), 0.94 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.67, 162.28, 152.26, 148.78, 146.92, 142.74, 133.79, 132.97, 131.38, 130.12, 128.20, 128.13, 124.36, 122.21, 117.25, 111.30, 69.35, 40.47, 30.32, 21.31, 21.15, 19.26. HRMS(ESI) *m*/*z* calcd for $C_{24}H_{24}BrN_2O_5$ ($[M+H]^+$): 499.0863, found: 499.0846.

4.3.8. (*R*)-Isopropyl-5-acetyl-1-(3-fluorophenyl)-6-methyl-4-(4-nitrophenyl)-1,4-dihydropyridine-2-carboxylate 8ah

Colorless oil, 58% yield, 94% ee [Daicel Chiralcel AD-H column, *n*-hexane/*i*-PrOH = 80:20, 1.0 ml/min, λ = 254 nm, *t* (minor) = 11.54 min, *t* (major) = 22.66 min]; $[\alpha]_D^{25}$ = +248.0 (*c* 0.508, EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, *J* = 8.8 Hz, 2H), 7.49 (d, *J* = 8.8 Hz, 2H), 7.38–7.32 (m, 1H), 7.10–7.06 (m, 1H), 6.97–6.95 (m, 2H), 6.05 (d, *J* = 6.4 Hz, 1H), 4.83 (d, *J* = 6.4 Hz, 1H), 4.81–4.73 (m, 1H), 2.18 (s, 3H), 2.15 (s, 3H), 1.02 (d, *J* = 6.4 Hz, 3H), 0.95 (d, *J* = 6.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.67, 163.67, 162.31, 161.19, 152.30, 148.91, 146.90, 142.91, 133.80, 130.05, 128.10, 125.16, 124.35, 117.24, 115.31, 111.21, 69.28, 40.44, 30.34, 21.29, 21.13, 19.23. HRMS(ESI) *m*/*z* calcd for $C_{24}H_{24}FN_2O_5$ ($[M+H]^+$): 439.1664, found: 439.1658.

4.3.9. (*R*)-Isopropyl-5-acetyl-1-(4-fluorophenyl)-6-methyl-4-(4-nitrophenyl)-1,4-dihydropyridine-2-carboxylate 8ai

Colorless oil, 53% yield, 87% ee [Daicel Chiralcel AD-H column, *n*-hexane/*i*-PrOH = 80:20, 1.0 ml/min, λ = 254 nm, *t* (minor) = 12.97 min, *t* (major) = 22.22 min]; $[\alpha]_D^{25}$ = +303.4 (*c* 0.470, EtOAc). ^1H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, *J* = 8.4 Hz, 2H), 7.49 (d, *J* = 8.4 Hz, 2H), 7.18–7.15 (m, 2H), 7.09–7.05 (m, 2H), 6.03 (d, *J* = 6.8 Hz, 1H), 4.83 (d, *J* = 6.4 Hz, 1H), 4.81–4.73 (m, 1H), 2.15 (s, 3H), 2.15 (s, 3H), 1.03 (d, *J* = 6.4 Hz, 3H), 0.97 (d, *J* = 6.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.53, 163.19, 162.39, 160.71, 152.44, 149.58, 146.86, 137.13, 134.00, 131.36, 128.07, 124.34, 116.77, 115.94, 115.71, 110.90, 69.28, 40.34, 30.32, 21.33, 21.20, 19.24. HRMS(ESI) *m*/*z* calcd for $C_{24}H_{24}FN_2O_5$ ($[M+H]^+$): 439.1664, found: 439.1669.

4.3.10. (*R*)-Isopropyl-5-acetyl-6-methyl-4-(3-nitrophenyl)-1-(*m*-tolyl)-1,4-dihydropyridine-2-carboxylate 8aj

Colorless oil, 55% yield, 83% ee [Daicel Chiralcel AD-H column, *n*-hexane/*i*-PrOH = 80:20, 1.0 ml/min, λ = 254 nm, *t* (minor) = 9.41 min, *t* (major) = 14.22 min]; $[\alpha]_D^{25}$ = +117.4 (*c* 0.301, EtOAc). ^1H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, *J* = 8.4 Hz, 2H), 7.43 (d, *J* = 8.4 Hz, 2H), 7.23–7.13 (m, 1H), 7.07 (d, *J* = 7.1 Hz, 1H), 6.91 (s, 2H), 5.90 (d, *J* = 6.4 Hz, 1H), 4.76 (d, *J* = 6.4 Hz, 1H), 4.72–4.57 (m, 1H), 2.28 (s, 3H), 2.10 (s, 3H), 2.08 (s, 3H), 0.92 (d, *J* = 6.4 Hz, 3H), 0.88 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.12, 162.39, 152.47, 149.61, 146.50, 140.82, 138.59, 133.99, 129.67, 128.60, 128.34, 127.82, 126.13, 123.94, 115.83, 110.18, 68.74, 40.12, 30.04, 29.34, 20.93, 20.72, 19.13. HRMS(ESI) *m*/*z* calcd for $C_{25}H_{27}N_2O_5$ ($[M+H]^+$): 435.1914, found: 435.1921.

4.3.11. (*R*)-Isopropyl-5-acetyl-6-methyl-4-(3-nitrophenyl)-1-(*p*-tolyl)-1,4-dihydropyridine-2-carboxylate 8ak

Colorless oil, 58% yield, 75% ee [Daicel Chiralcel AD-H column, *n*-hexane/*i*-PrOH = 80:20, 1.0 ml/min, λ = 254 nm, *t* (minor) = 11.39 min, *t* (major) = 16.75 min]; $[\alpha]_D^{25}$ = +102.2 (*c* 0.256, EtOAc). ^1H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, *J* = 8.5 Hz, 2H), 7.52 (d, *J* = 8.5 Hz, 2H), 7.19 (d, *J* = 8.0 Hz, 2H), 7.07 (d, *J* = 8.0 Hz, 2H), 6.00 (d, *J* = 6.6 Hz, 1H), 4.84 (d, *J* = 6.6 Hz, 1H), 4.77 (dt, *J* = 12.3, 6.2 Hz, 1H), 2.39 (s, 3H), 2.19 (s, 3H), 2.18 (s, 3H), 1.02 (d, *J* = 6.2 Hz, 3H), 0.94 (d, *J* = 6.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.39, 162.67, 152.81, 150.30, 146.84, 138.55, 138.25, 134.33, 129.51, 129.22, 128.14, 124.29, 116.27, 110.50, 69.13, 40.38, 30.40, 29.70, 21.33, 21.13, 19.43. HRMS(ESI) *m*/*z* calcd for $C_{25}H_{27}N_2O_5$ ($[M+H]^+$): 435.1914, found: 435.1928.

4.3.12. (*R*)-Benzyl-5-acetyl-1-(3-chlorophenyl)-6-methyl-4-(4-nitrophenyl)-1,4-dihydropyridine-2-carboxylate 8ba

Colorless oil, 54% yield, 94% ee [Daicel Chiralcel AD-H column, *n*-hexane/*i*-PrOH = 90:10, 1.0 ml/min, λ = 254 nm, *t* (minor) = 53.96 min, *t* (major) = 66.14 min]; $[\alpha]_D^{25}$ = +189.2 (*c* 0.446, EtOAc). ^1H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, *J* = 8.8 Hz, 2H), 7.47 (d, *J* = 8.8 Hz, 2H), 7.32–7.29 (m, 3H), 7.28–7.27 (m, 1H), 7.23 (t, *J* = 8.0 Hz, 1H), 7.15 (t, *J* = 1.6 Hz, 1H), 7.13–7.10 (m, 2H), 7.05–7.03 (m, 1H), 6.14 (d, *J* = 6.8 Hz, 1H), 4.64 (d, *J* = 12.0 Hz, 1H), 4.87 (d, *J* = 12.0 Hz, 1H), 4.83 (d, *J* = 6.4 Hz, 1H), 2.15 (s, 3H), 2.13 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.57, 162.44, 152.08, 148.97, 146.95, 142.27, 134.72, 134.50, 133.21, 129.81, 128.61, 128.55, 128.51, 128.45, 128.11, 127.82, 124.36, 118.13, 111.35, 67.23, 40.38, 30.34, 19.23. HRMS(ESI) *m*/*z* calcd for $C_{28}H_{24}ClN_2O_5$ ($[M+H]^+$): 503.1368, found: 503.1364.

4.3.13. (*R*)-Benzyl-5-acetyl-1-(3-bromophenyl)-6-methyl-4-(4-nitrophenyl)-1,4-dihydropyridine-2-carboxylate 8bb

Colorless oil, 56% yield, 94% ee [Daicel Chiralcel AD-H column, *n*-hexane/*i*-PrOH = 80:20, 1.0 ml/min, λ = 254 nm, *t* (minor) = 25.74 min, *t* (major) = 31.56 min]; $[\alpha]_D^{25}$ = +193.5 (*c* 0.307, EtOAc). ^1H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, *J* = 8.8 Hz, 2H), 7.47 (d, *J* = 8.4 Hz, 2H), 7.43 (d, *J* = 8.0 Hz, 1H), 7.32–7.30 (m, 4H), 7.17 (t, *J* = 8.0 Hz, 1H), 7.12–7.09 (m, 3H), 6.14 (d, *J* = 8.4 Hz, 1H), 4.97 (d, *J* = 12.0 Hz, 1H), 4.88 (d, *J* = 12.0 Hz, 1H), 4.83 (d, *J* = 6.8 Hz, 1H), 2.15 (s, 3H), 2.13 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.58, 162.44, 152.07, 148.97, 146.95, 142.41, 134.72, 133.22, 132.60, 131.51, 130.06, 128.57, 128.52, 128.45, 128.37, 128.12, 124.37, 122.29, 118.16, 111.40, 67.24, 40.38, 30.35, 19.25. HRMS(ESI) *m*/*z* calcd for $C_{28}H_{24}BrN_2O_5$ ($[M+H]^+$): 547.0863, found: 547.0838.

4.3.14. (*R*)-Isopropyl-5-acetyl-4-(4-bromophenyl)-1-(3-chlorophenyl)-6-methyl-1,4-dihydropyridine-2-carboxylate 8bc

Colorless oil, 54% yield, 92% ee [Daicel Chiralcel AD-H column, *n*-hexane/*i*-PrOH = 90:10, 1.0 ml/min, λ = 254 nm, *t* (minor) = 10.03 min, *t* (major) = 17.29 min]; $[\alpha]_D^{25}$ = +417.2 (*c* 0.494, EtOAc). ^1H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.4 Hz, 2H), 7.34–7.28 (m, 2H), 7.22–7.18 (m, 3H), 7.08 (dt, *J* = 2.0, 6.8 Hz, 1H), 6.07 (d, *J* = 6.4 Hz, 1H), 4.81–4.72 (m, 1H), 4.66 (d, *J* = 6.4 Hz, 1H), 2.13 (s, 3H), 2.08 (s, 3H), 1.02 (d, *J* = 6.4 Hz, 3H), 0.94 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.44, 162.47, 148.36, 144.12, 143.01, 134.32, 132.99, 132.17, 130.13, 129.73, 129.04, 128.25, 127.81, 120.95, 118.71, 111.34, 69.08, 40.27, 29.92, 21.32, 21.16, 19.00. HRMS(ESI) *m*/*z* calcd for $C_{24}H_{24}BrClNO_3$ ($[M+H]^+$): 488.0623, found: 488.0636.

4.3.15. (*R*)-Isopropyl-5-acetyl-1-(3-bromophenyl)-4-(4-bromophenyl)-6-methyl-1,4-dihydropyridine-2-carboxylate 8bd

Colorless oil, 58% yield, 91% ee [Daicel Chiralcel AD-H column, *n*-hexane/*i*-PrOH = 90:10, 1.0 ml/min, λ = 254 nm, *t* (minor) = 10.13 min, *t* (major) = 16.63 min]; $[\alpha]_D^{25}$ = +160.9 (*c* 0.307, EtOAc). ^1H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 8.4 Hz, 2H), 7.49–7.46 (m, 1H), 7.37 (t, *J* = 1.6 Hz, 1H), 7.24–7.22 (m, 1H), 7.19 (d, *J* = 8.4 Hz, 2H), 7.14–7.12 (m, 1H), 6.06 (d, *J* = 6.4 Hz, 1H), 4.81–4.72 (m, 1H), 4.66 (d, *J* = 6.4 Hz, 1H), 2.12 (s, 3H), 2.08 (s, 3H), 1.02 (d, *J* = 6.0 Hz, 3H), 0.94 (d, *J* = 6.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.45, 162.48, 148.21, 144.13, 143.17, 133.00, 132.97, 132.16, 131.13, 129.99, 129.05, 128.31, 122.09, 120.94, 118.67, 111.41, 69.09, 40.27, 29.94, 21.33, 21.17, 18.97. HRMS(ESI) *m*/*z* calcd for $C_{24}H_{24}Br_2NO_3$ ($[M+H]^+$): 532.0117, found: 532.0128.

4.3.16. (*R*)-Methyl-5-acetyl-4-(3-bromophenyl)-1-(3-chlorophenyl)-6-methyl-1,4-dihydropyridine-2-carboxylate 8be

Colorless oil, 41% yield, 93% ee [Daicel Chiralcel AD-H column, *n*-hexane/*i*-PrOH = 90:10, 1.0 ml/min, λ = 254 nm, *t* (minor) = 11.59 min, *t* (major) = 17.78 min]; $[\alpha]_D^{25}$ = +217 (*c* 0.203, EtOAc). ^1H NMR (400 MHz, $CDCl_3$) δ 7.45 (s, 1H), 7.40 (dt, *J* = 2.4, 6.8 Hz, 1H), 7.34–7.31 (m, 2H), 7.24–7.21 (m, 2H), 7.21 (s, 1H), 7.15–7.12 (m, 1H), 6.17 (d, *J* = 6.4 Hz, 1H), 4.68 (d, *J* = 6.4 Hz, 1H), 3.51 (s, 3H), 2.13 (s, 3H), 2.12 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.12, 163.00, 147.20, 142.63, 134.40, 132.31, 130.69, 130.34, 130.25, 130.13, 129.88, 129.66, 128.48, 128.18, 125.86, 123.32, 119.55, 111.11, 52.12, 40.32, 30.09, 19.04. HRMS(ESI) *m*/*z* calcd for $C_{22}H_{20}BrClNO_3$ ($[M+H]^+$): 460.0310, found: 460.0310.

4.3.17. (*R*)-Isopropyl-5-acetyl-1-(3-chlorophenyl)-4-(4-cyanophenyl)-6-methyl-1,4-dihydropyridine-2-carboxylate 8bf

Colorless oil, 56% yield, 95% ee [Daicel Chiralcel AD-H column, *n*-hexane/*i*-PrOH = 80:20, 1.0 ml/min, λ = 254 nm, *t* (minor) = 10.82 min, *t* (major) = 17.16 min]; $[\alpha]_D^{25}$ = +704 (*c* 0.486, EtOAc). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.68 (d, J = 8.4 Hz, 2H), 7.43 (d, J = 8.0 Hz, 2H), 7.36–7.31 (m, 2H), 7.20 (t, J = 1.6 Hz, 1H), 7.06 (dt, J = 1.6, 7.2 Hz, 1H), 6.05 (d, J = 6.4 Hz, 1H), 4.81–4.74 (m, 2H), 2.15 (s, 3H), 2.13 (s, 3H), 1.03 (d, J = 6.4 Hz, 3H), 0.94 (d, J = 6.4 Hz, 3H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 198.80, 162.31, 150.29, 148.72, 142.65, 134.40, 133.61, 132.90, 130.09, 129.81, 128.42, 128.08, 127.72, 118.74, 117.52, 111.15, 110.85, 69.28, 40.67, 30.24, 21.30, 21.12, 19.19. HRMS(ESI) *m/z* calcd for $C_{25}H_{24}ClN_2O_3$ ([M+H]$^+$): 435.1470, found: 435.1464.

4.3.18. (*R*)-Isopropyl-5-acetyl-4-(4-cyanophenyl)-1-(3-fluorophenyl)-6-methyl-1,4-dihydropyridine-2-carboxylate 8bg

Colorless oil, 51% yield, 94% ee [Daicel Chiralcel AD-H column, *n*-hexane/*i*-PrOH = 80:20, 1.0 ml/min, λ = 254 nm, *t* (minor) = 11.39 min, *t* (major) = 19.98 min]; $[\alpha]_D^{25}$ = +249.9 (*c* 0.214, EtOAc). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.68 (d, J = 8.4 Hz, 2H), 7.43 (d, J = 8.0 Hz, 2H), 7.37–7.32 (m, 1H), 7.10–7.05 (m, 1H), 6.97–6.93 (m, 2H), 6.04 (d, J = 6.8 Hz, 1H), 4.82–4.73 (m, 2H), 2.16 (s, 3H), 2.13 (s, 3H), 1.02 (d, J = 6.0 Hz, 3H), 0.94 (d, J = 6.0 Hz, 3H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 198.81, 162.35, 150.34, 148.80, 142.98, 133.66, 132.90, 130.00, 128.07, 125.14, 118.74, 117.46, 117.22, 115.46, 115.25, 111.12, 110.83, 69.24, 40.66, 30.25, 21.29, 21.12, 19.16. HRMS(ESI) *m/z* calcd for $C_{25}H_{24}FN_2O_3$ ([M+H]$^+$): 419.1765, found: 419.1767.

4.3.19. (*R*)-Ethyl-5-acetyl-1-(3-bromophenyl)-4-(4-fluorophenyl)-6-methyl-1,4-dihydropyridine-2-carboxylate 8bh

Colorless oil, 55% yield, 91% ee [Daicel Chiralcel AD-H column, *n*-hexane/*i*-PrOH = 80:20, 1.0 ml/min, λ = 254 nm, *t* (minor) = 7.98 min, *t* (major) = 14.21 min]; $[\alpha]_D^{25}$ = +213.1 (*c* 0.502, EtOAc). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.47 (d, J = 8.0 Hz, 1H), 7.36 (t, J = 2.0 Hz, 1H), 7.29–7.23 (m, 3H), 7.16 (d, J = 8.0 Hz, 1H), 7.07 (t, J = 8.4 Hz, 2H), 6.13 (d, J = 6.4 Hz, 1H), 4.69 (d, J = 6.4 Hz, 1H), 4.00–3.86 (m, 2H), 2.11 (s, 3H), 2.09 (s, 3H), 1.05 (t, J = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 199.65, 162.89, 160.64, 148.04, 143.14, 140.89, 132.83, 132.44, 131.18, 129.92, 128.87, 128.79, 128.51, 122.09, 119.44, 116.01, 115.80, 111.79, 61.23, 40.00, 29.89, 18.93, 13.73. HRMS(ESI) *m/z* calcd for $C_{23}H_{22}BrFNO_3$ ([M+H]$^+$): 458.0762, found: 458.0767.

4.3.20. (*R*)-Ethyl-5-acetyl-1-(3-chlorophenyl)-6-methyl-4-(4-(trifluoromethyl)phenyl)-1,4-dihydropyridine-2-carboxylate 8bi

Colorless oil, 53% yield, 91% ee [Daicel Chiralcel AD-H column, *n*-hexane/*i*-PrOH = 90:10, 1.0 ml/min, λ = 254 nm, *t* (minor) = 8.80 min, *t* (major) = 15.17 min]; $[\alpha]_D^{25}$ = +205.7 (*c* 0.244, EtOAc). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.64 (d, J = 8.0 Hz, 2H), 7.44 (d, J = 8.4 Hz, 2H), 7.35–7.29 (m, 2H), 7.21 (s, 1H), 7.10 (dt, J = 2.0, 6.8 Hz, 1H), 6.12 (d, J = 6.4 Hz, 1H), 4.79 (d, J = 6.4 Hz, 1H), 4.00–3.87 (m, 2H), 2.14 (s, 3H), 2.11 (s, 3H), 1.03 (t, J = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 199.13, 162.75, 148.97, 148.59, 142.77, 134.39, 132.97, 130.05, 129.74, 128.43, 127.94, 127.66, 126.10, 126.06, 118.51, 111.32, 61.33, 40.56, 30.12, 19.06, 13.72. HRMS(ESI) *m/z* calcd for $C_{24}H_{22}ClF_3NO_3$ ([M+H]$^+$): 464.1235, found: 464.1254.

4.3.21. (*R*)-Methyl-5-acetyl-1-(3-chlorophenyl)-4-(3,4-dichlorophenyl)-6-methyl-1,4-dihydropyridine-2-carboxylate 8bj

Colorless oil, 55% yield, 95% ee [Daicel Chiralcel AD-H column, *n*-hexane/*i*-PrOH = 80:20, 1.0 ml/min, λ = 254 nm, *t* (minor) = 7.78 min, *t* (major) = 11.01 min]; $[\alpha]_D^{25}$ = +240.0 (*c* 0.490, EtOAc). ^{1}H NMR (400 MHz, DMSO) δ 7.66 (d, J = 8.4 Hz, 1H), 7.55 (d, J = 2.0 Hz, 1H), 7.47–7.42 (m, 2H), 7.32–7.28 (m, 2H), 7.16–7.13 (m, 1H), 6.16 (d, J = 6.8 Hz, 1H), 4.77 (d, J = 6.8 Hz, 1H), 3.42 (s, 3H), 2.09 (s, 3H), 2.08 (s, 3H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 198.83, 162.92, 148.95, 145.22, 142.46, 134.43, 133.15, 132.54, 131.11, 130.99, 129.87, 129.71, 129.19, 128.56, 128.07, 126.55, 118.78, 111.15, 52.16, 39.71, 30.23, 19.12. HRMS(ESI) *m/z* calcd for $C_{22}H_{19}Cl_3NO_3$ ([M+H]$^+$): 450.0425, found: 450.0418.

4.3.22. (*R*)-Isopropyl-5-acetyl-1-(3-chlorophenyl)-4-(3,4-dichlorophenyl)-6-methyl-1,4-dihydropyridine-2-carboxylate 8bk

Colorless oil, 55% yield, 93% ee [Daicel Chiralcel AD-H column, *n*-hexane/*i*-PrOH = 90:10, 1.0 ml/min, λ = 254 nm, *t* (minor) = 8.13 min, *t* (major) = 11.54 min]; $[\alpha]_D^{25}$ = +191.6 (*c* 0.262, EtOAc). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.45 (d, J = 8.0 Hz, 1H), 7.38 (d, J = 2.0 Hz, 1H), 7.35–7.29 (m, 2H), 7.23 (s, 1H), 7.15 (dd, J = 2.0, 6.4 Hz, 1H), 7.09 (dt, J = 2.0, 6.8 Hz, 1H), 6.04 (d, J = 6.8 Hz, 1H), 4.82–4.73 (m, 1H), 4.67 (d, J = 6.4 Hz, 1H), 2.14 (s, 3H), 2.12 (s, 3H), 1.03 (d, J = 6.4 Hz, 3H), 0.95 (d, J = 6.4 Hz, 3H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 198.97, 162.36, 148.63, 145.37, 142.77, 134.40, 133.33, 133.12, 131.06, 130.98, 130.16, 129.79, 129.27, 128.37, 127.78, 126.63, 118.02, 111.19, 69.22, 39.91, 30.17, 21.33, 21.16, 19.11. HRMS(ESI) *m/z* calcd for $C_{24}H_{23}Cl_3NO_3$ ([M+H]$^+$): 478.0738, found: 478.0747.

4.3.23. (*R*)-Methyl-5-acetyl-1-(3-bromophenyl)-4-(3,4-dichlorophenyl)-6-methyl-1,4-dihydropyridine-2-carboxylate 8bl

Colorless oil, 54% yield, 94% ee [Daicel Chiralcel AD-H column, *n*-hexane/*i*-PrOH = 80:20, 1.0 ml/min, λ = 254 nm, *t* (minor) = 8.01 min, *t* (major) = 10.94 min]; $[\alpha]_D^{25}$ = +201.5 (*c* 0.271, EtOAc). ^{1}H NMR (400 MHz, DMSO) δ 7.66 (d, J = 8.4 Hz, 1H), 7.59 (d, J = 8.0 Hz, 1H), 7.55 (d, J = 1.6 Hz, 1H), 7.42 (s, 1H), 7.39 (t, J = 8.0 Hz, 1H), 7.30 (dd, J = 1.6, 8.0 Hz, 1H), 7.21 (d, J = 8.0 Hz, 1H), 6.17 (d, J = 6.8 Hz, 1H), 4.77 (d, J = 6.8 Hz, 1H), 3.43 (s, 3H), 2.10 (s, 3H), 2.08 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 198.60, 163.07, 148.91, 146.81, 142.92, 132.85, 132.61, 131.94, 131.72, 131.66, 131.26, 129.87, 129.48, 129.00, 127.93, 121.68, 119.16, 111.10, 52.60, 38.89, 30.62, 19.07. HRMS(ESI) *m/z* calcd for $C_{22}H_{19}BrCl_2NO_3$ ([M+H]$^+$): 493.9920, found: 493.9920.

4.3.24. (*R*)-Ethyl-5-acetyl-1-(3-bromophenyl)-4-(3,4-dichlorophenyl)-6-methyl-1,4-dihydropyridine-2-carboxylate 8bm

Colorless oil, 55% yield, 92% ee [Daicel Chiralcel AD-H column, *n*-hexane/*i*-PrOH = 90:10, 1.0 ml/min, λ = 254 nm, *t* (minor) = 10.06 min, *t* (major) = 16.03 min]; $[\alpha]_D^{25}$ = +179.5 (*c* 0.507, EtOAc). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.49 (d, J = 8.0 Hz, 1H), 7.45 (d, J = 8.0 Hz, 1H), 7.38 (d, J = 8.8 Hz, 2H), 7.28–7.24 (m, 1H), 7.15 (d, J = 8.0 Hz, 2H), 6.09 (d, J = 6.4 Hz, 1H), 4.68 (d, J = 6.8 Hz, 1H), 4.01–3.88 (m, 2H), 2.13 (s, 6H), 1.05 (t, J = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 198.88, 162.66, 148.73, 145.29, 142.76, 133.14, 132.96, 132.84, 131.36, 131.10, 130.98, 130.00, 129.24, 128.46, 126.61, 122.17, 118.36, 111.25, 61.37, 39.83, 30.20, 19.13, 13.74. HRMS(ESI) *m/z* calcd for $C_{23}H_{21}BrCl_2NO_3$ ([M+H]$^+$): 508.0076, found: 508.0076.

4.3.25. (*R*)-Isopropyl-5-acetyl-1-(3-bromophenyl)-6-methyl-4-(*p*-tolyl)-1,4-dihydropyridine-2-carboxylate 8bn

Colorless oil, 48% yield, 90% ee [Daicel Chiralcel AD-H column, *n*-hexane/*i*-PrOH = 90:10, 1.0 ml/min, λ = 254 nm, *t* (minor) = 8.53 min, *t* (major) = 12.93 min]; $[\alpha]_D^{25}$ = +195.6 (*c* 0.226, EtOAc). ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.45 (d, J = 8.0 Hz, 1H), 7.38 (t, J = 1.6 Hz, 1H), 7.25–7.16 (m, 6H), 6.12 (d, J = 6.4 Hz, 1H), 4.80–4.71 (m, 1H), 4.64 (d, J = 6.4 Hz, 1H), 2.35 (s, 3H), 2.12 (s, 3H), 2.05 (s, 3H), 1.01 (d, J = 6.4 Hz, 3H), 0.93 (d, J = 6.4 Hz, 3H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 200.04, 162.65, 147.76, 143.55, 142.18, 136.72, 133.00, 132.50, 130.92, 129.87, 129.79, 128.48, 127.28, 122.01, 119.91, 111.78, 68.86, 40.57, 29.82, 21.35, 21.20, 21.04, 18.81. HRMS(ESI) *m/z* calcd for $C_{25}H_{27}BrNO_3$ ([M+H]$^+$): 468.1169, found: 468.1175.

4.3.26. (*R*)-Methyl-5-acetyl-1-(3-bromophenyl)-6-methyl-4-(3-nitrophenyl)-1,4-dihydropyridine-2-carboxylate 8bo

Colorless oil, 43% yield, 94% ee [Daicel Chiralcel AD-H column, *n*-hexane/*i*-PrOH = 90:10, 1.0 ml/min, λ = 254 nm, *t* (minor) = 10.78 min, *t* (major) = 12.21 min]; $[\alpha]_D^{25}$ = +273.4 (*c* 0.237, EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (s, 1H), 8.13 (d, *J* = 8 Hz, 1H), 7.69–7.67 (m, 1H), 7.57–7.49 (m, 2H), 7.40 (s, 1H), 7.30–7.23 (m, 2H), 6.18 (d, *J* = 4.0 Hz, 1H), 4.83 (d, *J* = 4.0 Hz, 1H), 3.53 (s, 3H), 2.19 (s, 3H), 2.15 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.44, 162.88, 149.32, 147.26, 145.14, 142.37, 133.46, 132.93, 132.82, 131.62, 130.07, 129.90, 128.62, 125.63, 122.23, 122.13, 118.45, 111.57, 52.23, 40.02, 30.51, 19.38. HRMS(ESI) *m*/*z* calcd for $C_{22}H_{20}BrN_2O_5$ ($[M+H]^+$): 471.0550, found: 471.0540.

4.3.27. (*R*)-Benzyl-5-acetyl-1-(3-fluorophenyl)-6-methyl-4-(4-nitrophenyl)-1,4-dihydropyridine-2-carboxylate 8bp

Colorless oil, 34% yield, 97% ee [Daicel Chiralcel AD-H column, *n*-hexane/*i*-PrOH = 70:30, 1.0 ml/min, λ = 254 nm, *t* (minor) = 23.64 min, *t* (major) = 26.25 min]; $[\alpha]_D^{25}$ = +251.5 (*c* 0.334, EtOAc). ^{1}H NMR (400 MHz, DMSO) δ 8.25 (d, *J* = 8.8 Hz, 2H), 7.60 (d, *J* = 8.4 Hz, 2H), 7.44–7.38 (m, 1H), 7.29–7.28 (m, 3H), 7.23–7.15 (m, 2H), 7.11–7.09 (m, 2H), 7.00 (d, *J* = 8.0 Hz, 1H), 6.17 (d, *J* = 6.8 Hz, 1H), 4.94–4.87 (m, 3H), 2.11 (s, 3H), 2.10 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 198.38, 162.61, 153.13, 149.09, 146.81, 142.71, 135.62, 133.05, 130.96, 128.86, 128.82, 128.66, 128.52, 125.72, 124.73, 118.61, 117.68, 115.91, 110.99, 66.95, 40.32, 30.68, 19.12. HRMS(ESI) *m*/*z* calcd for $C_{28}H_{24}FN_2O_5$ ($[M+H]^+$): 487.1664, found: 487.1651.

4.3.28. 1-(3-Methoxyphenyl)-3-((3-methoxyphenyl)amino)-5-(4-nitrophenyl)-1*H*-pyrrol-2(5H)-one 9

White solid, 29% yield, mp 135.5–136.4 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15 (d, *J* = 11.6 Hz, 2H), 7.35 (d, *J* = 11.6 Hz, 2H), 7.24–7.16 (m, 3H), 7.00 (dd, *J* = 2.8, 10.8 Hz, 1H), 6.68–6.64 (m, 3H), 6.61 (t, *J* = 2.8 Hz, 1H), 6.53 (dd, *J* = 2.8, 10.8 Hz, 1H), 6.03 (d, *J* = 3.6 Hz, 1H), 5.77 (d, *J* = 3.2 Hz, 1H), 3.79 (s, 3H), 3.76 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.92, 160.64, 160.14, 147.72, 145.19, 142.08, 137.83, 132.68, 130.26, 129.84, 127.48, 124.39, 113.30, 110.68, 109.63, 107.65, 106.59, 103.31, 63.40, 55.28, 29.69. HRMS(ESI) *m*/*z* calcd for $C_{24}H_{22}N_3O_5$ ($[M+H]^+$): 432.1554, found: 432.1542.

4.3.29. Methyl-7-methoxy-2-(4-nitrophenyl)quinoline-4-carboxylate 10

White solid, 11% yield, mp 197.6–198.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (d, *J* = 8.4 Hz, 2H), 8.05 (s, 1H), 7.83 (s, 1H), 7.74–7.70 (m, 3H), 7.32 (dd, *J* = 2.4, 9.2 Hz, 1H), 4.12 (s, 3H), 4.01 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.65, 161.50, 149.95, 148.12, 147.49, 147.18, 144.09, 130.51, 125.85, 123.95, 123.07, 122.36, 119.25, 108.65, 55.88, 53.36. HRMS(ESI) *m*/*z* calcd for $C_{18}H_{15}N_2O_5$ ($[M+H]^+$): 339.0975, found: 339.0989.

4.4. General procedure for chiral multisubstituted piperidine 11

Glacial acid (0.2 ml) was added to a stirred solution of 4-aryl-1,4-dihydropyridine **8ba** (0.0177 g, 0.035 mmol) in dry CH_2Cl_2 (1 ml) at room temperature. Next, a solution of $NaBH_4$ (0.0067 g, 0.177 mmol) in dry CH_2Cl_2 (0.5 mL) was added gradually over 30 min after which the mixture was stirred for 12 h at room temperature. After the reaction was completed, 10 ml of CH_2Cl_2 were added and the mixture was washed with 10 ml of saturated aqueous sodium hydrogen carbonate. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified with silica gel column chromatography to give chiral multisubstituted piperidine **11** in 87% yield.

4.4.1. (2*S*,4*S*,5*S*,6*S*)-Benzyl-5-acetyl-1-(3-chlorophenyl)-6-methyl-4-(4-nitrophenyl)piperidine-2-carboxylate 11

White solid, 87% yield, 95% ee [Daicel Chiralcel OD-H column, *n*-hexane/*i*-PrOH = 70:30, 1.0 ml/min, λ = 254 nm, *t* (major) = 30.16 min, *t* (minor) = 38.10 min]; mp 157.3–158.1 °C; $[\alpha]_D^{25}$ = +83.2 (*c* 0.149, EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, *J* = 8.8 Hz, 2H), 7.39 (d, *J* = 8.8 Hz, 2H), 7.31–7.28 (m, 3H), 7.21 (s, 1H), 7.19–7.13 (m, 2H), 7.11–7.07 (m, 3H), 4.95 (d, *J* = 12.0 Hz, 1H), 4.90 (d, *J* = 12.0 Hz, 1H), 3.95 (dd, *J* = 2.8, 11.2 Hz, 1H), 3.31–3.27 (m, 2H), 3.18 (t, *J* = 4.0 Hz, 1H), 3.02 (dd, *J* = 12.8, 24.4 Hz, 1H), 2.14–2.10 (m, 1H), 2.09 (s, 3H), 0.87 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.95, 171.25, 149.70, 148.70, 146.92, 135.17, 134.40, 129.85, 128.48, 128.23, 128.15, 128.03, 127.14, 126.74, 125.46, 123.84, 67.19, 66.70, 59.09, 58.57, 43.03, 34.75, 29.51, 19.28. HRMS(ESI) *m*/*z* calcd for $C_{28}H_{28}ClN_2O_5$ ($[M+H]^+$): 507.1681, found: 507.1688. CCDC 1045862 for compound **11** contains the supplementary crystallographic data for this paper. These data can be obtained from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

4.5. General procedure for β,γ-unsaturated α-iminoester 12

3-Methoxyaniline (1 g, 8.13 mmol) was suspended in 50 mL of hydrochloric acid (17%) at room temperature. The solution was cooled to 0 °C and $NaNO_2$ (0.8415 g, 12.20 mmol) was added in small portions. After stirring at 0 °C for 15–30 min, NaN_3 (0.7930 g, 12.20 mmol) was slowly added and the mixture was stirred for an additional 2 h at room temperature. The reaction mixture was extracted with diethyl ether (40 mL × 3) and the combined organic fractions were washed with saturated $NaHCO_3$ solution (30 mL × 3) and with brine (30 mL). After drying over $MgSO_4$, the ether was removed under reduced pressure and the desired 1-azido-3-methoxybenzene was obtained without further purification. A solution of triphenylphosphine (0.6295 g, 2.40 mmol) in dry THF (7 mL) was added dropwise to a solution of the 1-azido-3-methoxybenzene (0.3590 g, 2.40 mmol) in dry THF (5 mL) under argon over 30 min. The reaction mixture was stirred at room temperature for 2 h and then heated at reflux for 30 min then the reaction mixture was allowed to cool to room temperature, whereupon (*E*)-ethyl 4-(4-nitrophenyl)-2-oxobut-3-enoate (0.2988 g, 1.20 mm ol) was added. The mixture was heated at reflux for 4 h and cooled to room temperature. The solvent was removed in vacuo. The crude product was purified by silica gel column chromatography to afford β,γ-unsaturated α-iminoester **12** as a yellow oil in 84% yield.

4.5.1. (3*E*)-Ethyl 2-((3-methoxyphenyl)imino)-4-(4-nitro-phenyl)but-3-enoate 12

Yellow oil, 84% yield, *syn*:*anti* = 29:71; ^{1}H NMR (400 MHz, DMSO) δ 8.26 and 8.21 (d, *J* = 8.8 Hz, and d, *J* = 8.8 Hz, 2H), 8.03 and 7.77 (d, *J* = 8.8 Hz, and d, *J* = 8.8 Hz, 2H), 7.49–7.30 (m, 2H), 7.29 and 7.04 (t, *J* = 8.4 Hz, and t, *J* = 8.4 Hz, 1H), 6.84–6.75 (m, 1H), 6.49–6.31 (m, 2H), 4.42 and 4.16 (q, *J* = 6.8 Hz, and q, *J* = 6.8 Hz, 2H), 3.76 and 3.75 (s, 3H), 1.36 and 1.00 (t, *J* = 6.8 Hz, and t, *J* = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, DMSO) δ (major + minor) ^{13}C NMR (101 MHz, DMSO) δ 164.85, 164.02, 160.96, 160.85, 160.49, 160.21, 151.19, 149.84, 148.32, 148.24, 141.73, 141.64, 140.27, 139.57, 130.62, 130.37, 130.28, 129.69, 129.50, 129.41, 124.56, 124.47, 112.27, 111.96, 111.59, 111.43, 105.80, 105.59, 62.43, 62.01, 55.63, 55.28, 14.54, 14.02. HRMS(ESI) *m*/*z* calcd for $C_{19}H_{19}N_2O_5$ ($[M+H]^+$): 355.1288, found: 355.1289.

4.6. General procedure for the enantioselective cyclization of β,γ-unsaturated α-iminoester 12 and acetyl-acetone

A solution of β,γ-unsaturated α-iminoester **12** (0.1 mmol) and catalyst **4c** (5 mol %, 0.005 mmol) in toluene (1 mL) under a nitrogen atmosphere was stirred at 25 °C for 10 min, then acetylacetone (0.2 mmol) was added. The reaction mixture was stirred at 50 °C for 12 h (reaction progress monitored by TLC). EtOAc and silica gel were added and, after removal of the solvent, the residue was purified by flash column chromatography on silica gel (ethyl acetate/petroleum ether, 1:5 to 1:2) to afford the pure products.

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