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Asymmetric synthesis of 2-alkyl-3-phosphonopropanoic acid derivatives via Rh-catalyzed asymmetric hydrogenation

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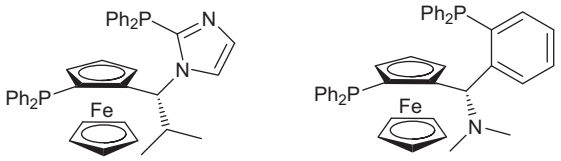
ABSTRACT

The commercially available ferrocene-based diphosphine ligand (S_c,S_{Fc})-TaniaPhos was found to be highly effective in the Rh-catalyzed asymmetric hydrogenation of 3-aryl-2-(phosphonomethyl)propenates. Excellent enantioselectivity (90–98% ee) and high catalytic activity (S/C up to 1000) have been achieved, which represents the best results reported so far.

1. Introduction

Chiral 2-alkyl-3-phosphonopropanoic acid derivatives have received considerable attention over the past few years in bioorganic and medicinal chemistry because of their important biological activities as phosphonate and phosphinate enzyme inhibitors.[1] The present synthesis of enantioenriched 2-alkyl-3-phosphonopropanoic acid derivatives mainly focuses on asymmetric induction using a chiral auxiliary.[2] However, these methods are not catalytic, requiring stoichiometric chiral materials, and in many cases the diastereoselectivity obtained is unsatisfactory. The need for the development of an efficient and catalytic method for the enantioselective synthesis of chiral 2-alkyl-3-phosphonopropanoic acid derivatives is therefore apparent. Over past few decades, optically active succinates have been prepared efficiently via the catalytic asymmetric hydrogenation of itaconate derivatives with a variety of chiral P-ligand/Rh complexes.[3] Due to their structural similarity, we therefore envisioned that the catalytic asymmetric hydrogenation of 2-(phosphonomethyl)propenoates (phosphono analogues of itaconates) should be an ideal approach for the preparation of optically active 2-alkyl-3-phosphonopropanoic acid derivatives. In 2007 Spilling and co-workers reported the first example of the enantioselective synthesis of chiral 2-alkyl-3-phosphonopropanoic acids or esters via catalytic asymmetric hydrogenation of the corresponding 2-(phosphonomethyl)propenoate derivatives.[4] However, the level of asymmetric induction with Rh/diphosphine (e.g., DIPAMP, DuPHOS, ferrotane, Tangphos) complexes were found to be very low (0–52% ee). Although up to 91% ee was observed in the hydrogenation of 2-(phosphonomethyl) propenoic acids with a (*R*)-Cl-MeO-BIPHEP/Ru catalyst, for most substrates the enantioselectivities were less satisfactory. In 2009, we reported a new ferrocene-based 1,5-diphosphine ligand, (R_c,S_{Fc})-ImiFerroPhos **1**, which displayed high enantioselectivities in the Rh-catalyzed asymmetric hydrogenation of various 3-aryl-2-(phosphonomethyl)propenoates.[5] However, the synthesis of this ligand is very difficult. The search of a new catalytic system, one that would be commercially available, for the enantioselective hydrogenation of a wider range of 2-(phosphonomethyl)propenoate derivatives is still desirable. Due to the structural similarity, we surmised that the commercially available ferrocenyl 1,5-diphosphine ligand, (S_c,S_{Fc})-TaniaPhos **2** (Fig. 1), might be an ideal alternative. As a result, we herein report our detailed studies on the Rh-catalyzed asymmetric hydrogenation of 3-substituted 2-(phosphonomethyl)propenoates with (S_c,S_{Fc})-TaniaPhos **2**.



(R_c,S_{Fc})-ImiFerroPhos **1** (S_c,S_{Fc})-TaniaPhos **2**

Figure 1. The structure of (R_c,S_{Fc})-ImiFerroPhos **1** and (S_c,S_{Fc})-TaniaPhos **2**.

2. Results and discussion

2.1. Synthesis of 3-substituted 2-(phosphonomethyl) propenoates

3-Substituted 2-(phosphonomethyl)propenoates **7** are prepared from various aldehydes via a two-step transformation as outlined

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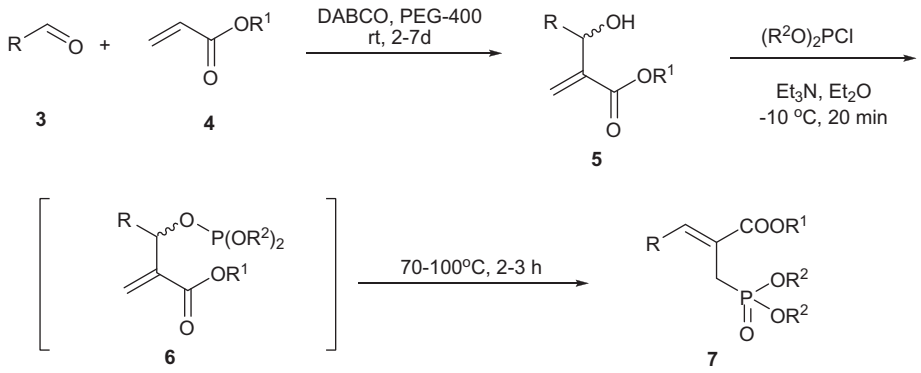


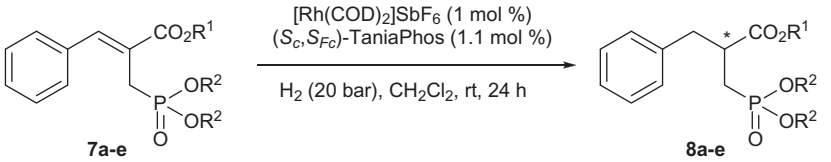
Scheme 1. Synthesis of 3-substituted 2-(phosphonomethyl)propenoates **7**.

in Scheme 1. Initially, the Baylis–Hillman reaction of aldehydes with acrylates gave intermediate allylic alcohols **5**. The treatment of Baylis–Hillman adducts **5** with dialkyl phosphorchloridite in the presence of triethylamine followed by heating the crude intermediates **6** for 2–3 h at 70–100 °C formed the desired 2-(phosphonomethyl)propenoates **7**, which can be isolated from the reaction mixture by column chromatography in moderate to good yields. The Arbuzov rearrangement of the dialkyl allyl phosphites **6** to the corresponding 2-(phosphonomethyl)propenoates **7** is a highly stereoselective process, giving exclusively the corresponding 2-(phosphonomethyl)propenoates **7** with the *Z*-configuration.[6]

2.2. The Rh-catalyzed asymmetric hydrogenation of 3-substituted 2-(phosphonomethyl)propenoates with (S_c,S_{Fc})-TaniaPhos

Initially, the hydrogenation of ethyl 2-[(dimethoxyphosphoryl)methyl]-3-phenyl-2-propenoate **7a** with (S_c,S_{Fc})-TaniaPhos **2** was performed in CH_2Cl_2 at room temperature under 20 bar of H_2 pressure for 24 h and with an Rh/ligand ratio of 1:1.1; the results are listed in Table 1. This ligand showed excellent enantioselectivity (up to 96% ee) (entry 1), and was higher than that obtained with (R_c,S_{Fc})-ImiFerroPhos **1** (93% ee) under the same hydrogenation conditions (entry 2). This result suggested the potential of this commercially available diphosphine, (S_c,S_{Fc})-TaniaPhos **2**, in this hydrogenation. We next investigated the effect of the ester functional group of 2-(phosphonomethyl)propenoates on this hydrogenation. Replacing an ethyl ester **7a** with a methyl ester **7b** had less effect on the reactivity and enantioselectivity, and methyl 2-[(dimethoxyphosphoryl)methyl]-3-phenyl-2-propenoate **7b** was hydrogenated in >95% conversion and with 95% ee (entry 3). However, the hydrogenation of substrate **7c** with a bulky *t*-Bu ester group resulted in a significant decrease in reactivity and enantioselectivity (entry 4). The introduction of the bulkier ester functional group onto the phosphoryl moiety also lowered both the conversion and enantioselectivity (entries 5 and 6). These

Table 1
Rh-catalyzed asymmetric hydrogenation of 3-phenyl-2-(phosphonomethyl)propenoates[a]



Entry	Ligand	Substrate (R^1, R^2)	Solvent	H_2 (bar)	Conversion[b] (%)	ee[c] (%)
1	TaniaPhos **2**	**7a** (Et, Me)	CH_2Cl_2	20	>95	96
2	ImiFerroPhos **1**	**7a** (Et, Me)	CH_2Cl_2	20	>95	93
3	TaniaPhos **2**	**7b** (Me, Me)	CH_2Cl_2	20	>95	95
4	TaniaPhos **2**	**7c** (*t*-Bu, Me)	CH_2Cl_2	20	77	82
5	TaniaPhos **2**	**7d** (Et, *i*-Pr)	CH_2Cl_2	20	77	79
6	TaniaPhos **2**	**7e** (Et, Ph)	CH_2Cl_2	20	68	83
7	TaniaPhos **2**	**7a** (Et, Me)	MeOH	20	>95	70
8	TaniaPhos **2**	**7a** (Et, Me)	THF	20	>95	88
9	TaniaPhos **2**	**7a** (Et, Me)	Toluene	20	87	83
10	TaniaPhos **2**	**7a** (Et, Me)	CH_2Cl_2	50	>95	95
11	TaniaPhos **2**	**7a** (Et, Me)	CH_2Cl_2	10	>95	96
12	TaniaPhos **2**	**7a** (Et, Me)	CH_2Cl_2	50	>95	88[d]
13	ImiFerroPhos **1**	**7a** (Et, Me)	CH_2Cl_2	10	>95	94
14	ImiFerroPhos **1**	**7a** (Et, Me)	CH_2Cl_2	50	<10	—[d,e]

[a] Reagents and conditions: 1 mL of solvent, 0.25 mmol of substrate **7a**–**e**, 1 mol % of catalyst prepared in situ from $[Rh(COD)_2]SbF_6$ and 1.1 equiv of TaniaPhos, 20 bar of H_2 pressure, room temperature for 24 h, unless otherwise noted.
[b] Conversions were determined by ^1H NMR.
[c] Enantiomeric excesses were determined by HPLC, using a chiral AD-H, or OD-H column.
[d] Catalyst loading, 0.1 mol %.
[e] Not determined.

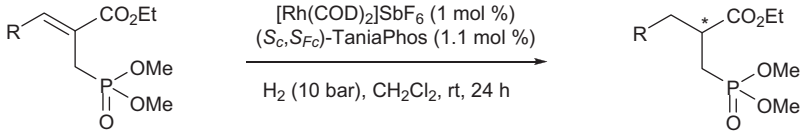
results suggested that the ester functional group of 2-(phosphonomethyl)propenoates had a significant influence on the reactivity and enantioselectivity, and the substrate with the less sterically hindered ester functional group is favorable for this hydrogenation. The hydrogenation is also sensitive to the solvent used. Protic solvents, such as MeOH, tended to give lower enantioselectivity (entry 7). The reaction proceeded smoothly in THF, giving slightly lower enantioselectivity (entry 8). Toluene proved to be an inferior solvent, in which low conversion was observed (entry 9). The pressure of H_2 had less influence on the reactivity and enantioselectivity at a catalyst loading of 1 mol % (entries 10 and 11). Lowering the catalyst loading to 0.1 mol %, however, required a higher H_2 pressure of 50 bar in order to complete the hydrogenation with reduced enantioselectivity (88% ee) (entry 12). In a contrast, (R_c,S_{Fc})-ImiFerroPhos only showed low conversion under the same catalyst loadings (0.1 mol %) and hydrogenation conditions (entry 14). This result demonstrated the high efficiency of (S_c,S_{Fc})-TaniaPhos in the Rh-catalyzed asymmetric hydrogenation of 2-(phosphonomethyl)propenoates.

Having established the optimal ester functional group of the 2-(phosphonomethyl)propenoates and the hydrogenation conditions, we next examined the Rh-catalyzed asymmetric hydrogenation of a variety of 3-substituted 2-[(dimethoxyphosphoryl)methyl]-2-propenoates **7f–q** with (S_c,S_{Fc})-TaniaPhos, and the results are summarized in Table 2. Initially, the hydrogenation of 3-aryl substituted substrates **7f–o** was investigated. The electronic nature of the *para*-substituents on the phenyl ring of these substrates had no significant effect on the enantioselectivity. All substrates with a *para*-substituent gave high enantioselectivities (entries 2–5). The positions of the substituent on the phenyl ring had some effect on the enantioselectivities. All of the substrates with a methoxy group on the different position of the phenyl ring were hydrogenated with high enantioselectivity (entries 5–7); the substrate with a 2-methoxy group gave the best enantioselectivity (97% ee, entry 7). However, the substrates with a Cl-substitutent showed entirely different reactivities towards this hydrogenation (entries 3, 8 and 9). The substrates bearing a 3-Cl and 4-Cl group were hydrogenated in high yields and enantioselectivities (entries 3 and 8), while the 2-Cl substituted substrate only gave low conversion (entry 9). The hydrogenation of the substrates with a heteroaromatic substituent also led to good enantioselectivities (entries 10 and 11). The hydrogenation of 2-thienyl substituted substrate **7o** provided the best enantioselectivity of up to 98% ee (entry 11). In comparison with those obtained with (R_c,S_{Fc})-ImiFerroPhos **1** (as shown in parentheses in Table 2), the present catalytic system normally induced higher enantioselectivity. In particular, the present catalytic system displayed excellent enantioselectivity (92% ee) and high yields (99%) in the hydrogenation of ethyl 3-(3-chlorophenyl)-2-[(dimethoxyphosphoryl)methyl]-2-propenoate **7l** (entry 8), while the corresponding Rh/(R_c,S_{Fc})-ImiFerroPhos complex gave only very low conversion (entry 8). These results demonstrated the high efficiency of the present catalytic system in the Rh-catalyzed asymmetric hydrogenation of 3-aryl-2-(phosphonomethyl)propenoates. The shortcoming of the present catalytic system lies in its inferior performance in the hydrogenation of 3-alkyl substituted substrates. Thus, the hydrogenation of ethyl 2-[(dimethoxyphosphoryl)methyl]-2-propenoate **7p** gave full conversion but with very low enantioselectivity (entry 12); while the hydrogenation of ethyl 2-[(dimethoxyphosphoryl)methyl]-4-methyl-2-pentenoate **7q** only showed very low conversion (entry 13).

3. Conclusion

In conclusion, we have found that a commerically available ferrocene-based diphosphine ligand (S_c,S_{Fc})-TaniaPhos is highly effective in the Rh-catalyzed asymmetric hydrogenation of 2-(phosphonomethyl)propenoates. In comparison with reactivities obtained with (R_c,S_{Fc})-ImiFerroPhos, the present catalytic system shows higher reactivities (S/C up to 1000/1) and generally better

Table 2
Rh-catalyzed asymmetric hydrogenation of 3-substituted 2-(phosphonomethyl)propenoates[a]



7a, 7f-q **8a, 8f-q**

Entry	Substrate	R	Yield[b] (%)	ee[c] (%)
1	**7a**	Ph	99	96 (94)
2	**7f**	4-FC_6H_4	99	91 (91)
3	**7g**	4-ClC_6H_4	97	96 (92)
4	**7h**	4-$NO_2C_6H_4$	98	95 (89)
5	**7i**	4-$MeOC_6H_4$	97	95 (95)
6	**7j**	3-$MeOC_6H_4$	98	95 (92)
7	**7k**	2-$MeOC_6H_4$	95	97 (93)
8	**7l**	3-ClC_6H_4	99	92 (−)
9	**7m**	2-ClC_6H_4	35	−[d]
10	**7n**	2-Furyl	97	90 (90)
11	**7o**	2-Thienyl	98	98 (98)
12	**7p**	H	98	<10
13	**7q**	*i*-Pr	<10	−[d]

[a] Reagents and conditions: 2 mL of CH_2Cl_2, 0.5 mmol of substrate, 1 mol % of catalyst prepared in situ from $[Rh(COD)_2]SbF_6$ and 1.1 equiv of TaniaPhos, 10 bar of H_2 pressure, room temperature for 24 h.
[b] Isolated yields.
[c] Enantiomeric excesses were determined by HPLC using a chiral AD-H, OD-H or OJ-H column. Enantiomeric excesses of **8p–q** were determined by GC using a γ-DEX-225 capillary. Those in parentheses were obtained with (R_c,S_{Fc})-ImiFerroPhos.
[d] Not determined due to low conversions.

enantioselectivities. With (S_c,S_{Fc})-TaniaPhos, various 3-aryl-2-(phosphonomethyl)-propenoates were hydrogenated in 90–98% ee, which represents the best results reported to date.

4. Experimental

4.1. General

All reactions were conducted under either a nitrogen or argon atmosphere unless otherwise noted. Anhydrous procedures were conducted using oven dried or flame dried glassware and standard syringe and cannula transfer techniques. Hydrogenation was performed in a stainless steel autoclave. Solvents were of reagent grade, dried and distilled before use following standard procedures. ^{1}H NMR spectra were recorded on a 400 MHz spectrometer. Chemical shifts were reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$, δ = 7.26). Data are reported as follows: chemical shift (ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (Hz), integration, and assignment. ^{13}C NMR data were collected on a 100 MHz spectrometer with complete proton decoupling. Chemical shifts are reported in ppm from the tetramethylsilane with the solvent resonance as an internal standard ($CDCl_3$, δ = 77.0). ^{31}P NMR spectra were recorded on a 162 MHz spectrometer. The enantiomeric excesses were determined by chiral HPLC. Optical rotations were reported as follows: $[\alpha]_D^{25}$ (*c* g/100 mL, in solvent).

4.2. General procedure for preparation of 3-substituted 2-(phosphonomethyl)-propenoates

To a stirred solution of aldehyde (50 mmol) and acrylate (75 mmol) in 30 mL of PEG (400), was added DABCO (50 mmol). The solution was stirred for 2–7 days, then it was diluted with Et_2O, washed with 1 N HCl and water, dried over Na_2SO_4, filtered and evaporated in vacuo to give the crude adduct. The crude mixture was purified by column chromatography (SiO_2, hexane/ethyl acetate, 5:1) to give the pure product.

To a stirred solution of the Baylis–Hillman adduct (20 mmol) and Et_3N (2.02 g, 20 mmol) in Et_2O (50 mL), dimethyl phosphorochloridite (2.57 g, 20 mmol) was added dropwise at −10 °C under argon, and stirring was continued for 20 min at −10 °C. The precipitate was filtered off and washed with Et_2O (2 × 10 mL). The filtrate was evaporated and the residue was heated at 70–100 °C under argon for 2–3 h. The resultant product was purified by column chromatography (SiO_2, hexane/ethyl acetate, 2:1).

4.2.1. Ethyl 2-[(dimethoxyphosphoryl)methyl]-3-phenyl-2-propenoate 7a[7]

Yield: 54%. Oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.37 (t, *J* = 7.1 Hz, 3H), 3.24 (d, *J* = 22.6 Hz, 2H), 3.70 (dd, *J* = 10.9, 2.8 Hz, 6H), 4.32 (q, *J* = 7.2 Hz, 2H), 7.35 (m, 1H), 7.42 (m, 2H), 7.56 (d, *J* = 7.5 Hz, 1H), 7.82 (d, *J* = 5.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.3, 25.2 (d, *J* = 140 Hz), 52.7 (d, *J* = 6 Hz), 61.3, 123.8 (d, *J* = 11 Hz), 128.6, 129.0, 129.3, 134.8, 141.6 (d, *J* = 11 Hz), 167.4; ^{31}P NMR (162 MHz, $CDCl_3$): δ 28.9.

4.2.2. Methyl 2-[(dimethoxyphosphoryl)methyl]-3-phenyl-2-propenoate 7b[4,8]

Yield: 49%. Oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.23 (d, *J* = 22.5 Hz, 2H), 3.70 (d, *J* = 10.8 Hz, 6H), 3.85 (s, 3H), 7.35 (d, *J* = 7.2 Hz, 1H), 7.41 (t, *J* = 7.2 Hz, 2H), 7.56 (d, *J* = 7.2 Hz, 2H), 7.82 (d, *J* = 5.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.2 (d, *J* = 140 Hz), 52.3, 52.6 (d, *J* = 6 Hz), 123.4 (d, *J* = 12 Hz), 128.6, 129.0, 129.2, 134.6, 141.7 (d, *J* = 10 Hz), 167.7; ^{31}P NMR (162 MHz, $CDCl_3$): δ 28.8.

4.2.3. *t*-Butyl 2-[(dimethoxyphosphoryl)methyl]-3-phenyl-2-propenoate 7c[4]

Yield: 71%. Oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.56 (s, 9H), 3.20 (d, *J* = 22.6 Hz, 2H), 3.70 (d, *J* = 10.8 Hz, 6H), 7.34 (t, *J* = 7.4 Hz, 1H), 7.41 (t, *J* = 7.3 Hz, 2H), 7.55 (d, *J* = 7.5 Hz, 2H), 7.72 (d, *J* = 5.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.3 (d, *J* = 139 Hz), 28.0, 52.7 (d, *J* = 7 Hz), 81.3, 125.2 (d, *J* = 12 Hz), 128.6, 128.7, 129.2, 135.1, 140.6 (d, *J* = 11 Hz), 166.5; ^{31}P NMR (162 MHz, $CDCl_3$): δ 29.3.

4.2.4. Ethyl 2-[(diisopropoxyphosphoryl)methyl]-3-phenyl-2-propenoate 7d

Yield: 32%. Oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.26 (d, *J* = 6.2 Hz, 6H), 1.30 (d, *J* = 6.2 Hz, 2H), 1.37 (t, *J* = 7.1 Hz, 3H), 3.21 (d, *J* = 22.6 Hz, 2H), 4.30 (q, *J* = 7.1 Hz, 2H), 4.71 (m, 2H), 7.34 (t, *J* = 7.2 Hz, 1H), 7.40 (t, *J* = 7.4 Hz, 2H), 7.64 (d, *J* = 7.6 Hz, 2H), 7.77 (d, *J* = 5.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2, 23.8 (d, *J* = 5 Hz), 24.0 (d, *J* = 2 Hz), 27.5 (d, *J* = 141 Hz), 61.1, 70.6 (d, *J* = 6 Hz), 124.6 (d, *J* = 11 Hz), 128.4, 128.8, 129.5, 135.0, 140.7 (d, *J* = 11 Hz), 167.6; ^{31}P NMR (162 MHz, $CDCl_3$): δ 24.4. HRMS (ESI): calcd for $C_{18}H_{27}O_5P$ $[M+Na]^+$: 377.1494, found: 377.1498.

4.2.5. Ethyl 2-[(diphenoxyphosphoryl)methyl]-3-phenyl-2-propenoate 7e

Yield: 57%. Viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.29 (t, *J* = 7.1 Hz, 3H), 3.59 (d, *J* = 22.6 Hz, 2H), 4.26 (q, *J* = 7.1 Hz, 2H), 7.10–7.15 (m, 6H), 7.28 (m, 4H), 7.35–7.40 (m, 3H), 7.59 (d, *J* = 7.3 Hz, 2H), 7.94 (d, *J* = 5.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2, 26.9 (d, *J* = 142 Hz), 61.5, 120.5 (d, *J* = 4 Hz), 123.2 (d, *J* = 12 Hz), 125.2 (d, *J* = 14 Hz), 128.8, 129.1, 129.4, 129.7, 134.7, 142.5 (d, *J* = 12 Hz), 150.5 (d, *J* = 9 Hz), 167.2; ^{31}P NMR (162 MHz, $CDCl_3$): δ 19.3. HRMS (ESI): calcd for $C_{24}H_{23}O_5P$ $[M+Na]^+$: 445.1181, found: 445.1193.

4.2.6. Ethyl 2-[(dimethoxyphosphoryl)methyl]-3-(4-fluorophenyl)-2-propenoate 7f

Yield: 59%. Oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.37 (t, *J* = 7.1 Hz, 3H), 3.20 (dd, *J* = 22.6, 4.6 Hz, 2H), 3.74 (dd, *J* = 10.9, 4.8 Hz, 6H), 4.31 (q, *J* = 7.2 Hz, 2H), 7.10 (m, 2H), 7.60 (m, 2H), 7.77 (d, *J* = 5.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2, 25.2 (d, *J* = 140 Hz), 52.7 (d, *J* = 6 Hz), 61.3, 115.6 (d, *J* = 22 Hz), 123.4 (d, *J* = 12 Hz), 130.8, 131.3 (d, *J* = 8 Hz), 140.4 (d, *J* = 11 Hz), 161.6, 164.1, 167.1; ^{31}P NMR (162 MHz, $CDCl_3$): δ 28.7. HRMS (ESI): calcd for $C_{14}H_{18}FO_5P$ $[M+Na]^+$: 339.0774, found: 339.0782.

4.2.7. Ethyl 2-[(dimethoxyphosphoryl)methyl]-3-(4-chlorophenyl)-2-propenoate 7g

Yield: 59%. Oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.37 (t, *J* = 7.1 Hz, 3H), 3.20 (d, *J* = 22.6 Hz, 2H), 3.74 (dd, *J* = 10.9, 4.8 Hz, 6H), 4.31 (q, *J* = 7.1 Hz, 2H), 7.38 (d, *J* = 8.5 Hz, 2H), 7.55 (d, *J* = 8.4 Hz, 2H), 7.76 (d, *J* = 5.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2, 25.2 (d, *J* = 139 Hz), 52.7 (d, *J* = 6 Hz), 61.3, 124.2 (d, *J* = 12 Hz), 128.8, 130.6, 133.1 (d, *J* = 3 Hz), 134.8, 140.1 (d, *J* = 11 Hz), 167.0; ^{31}P NMR (162 MHz, $CDCl_3$): δ 28.5. HRMS (ESI): calcd for $C_{14}H_{18}ClO_5P$ $[M+Na]^+$: 355.0478, found: 355.0480.

4.2.8. Ethyl 2-[(dimethoxyphosphoryl)methyl]-3-(4-nitrophenyl)-2-propenoate 7h

Yield: 51%. White crystals, mp: 78–80 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.38 (t, *J* = 7.2 Hz, 3H), 3.17 (d, *J* = 23.2 Hz, 2H), 3.75 (d, *J* = 10.8 Hz, 6H), 4.34 (q, *J* = 7.2 Hz, 2H), 7.77 (d, *J* = 8.4 Hz, 2H), 7.82 (d, *J* = 5.6 Hz, 1H), 8.28 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2, 25.5 (d, *J* = 139 Hz), 52.9 (d, *J* = 6 Hz), 61.8, 123.8, 127.1 (d, *J* = 12 Hz), 138.9 (d, *J* = 11 Hz), 141.3, 147.6, 166.6; ^{31}P NMR (162 MHz, $CDCl_3$): δ 27.9. HRMS (ESI): calcd for $C_{14}H_{18}NO_7P$ $[M+Na]^+$: 366.0719, found: 366.0728.

4.2.9. Ethyl 2-[(dimethoxyphosphoryl)methyl]-3-(4-methoxyphenyl)-2-propenoate 7i

Yield: 56%. Oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.36 (t, J = 7.1 Hz, 3H), 3.26 (d, J = 22.3 Hz, 2H), 3.73 (d, J = 10.8 Hz, 6H), 3.82 (s, 3H), 4.30 (q, J = 7.0 Hz, 2H), 6.95 (d, J = 8.6 Hz, 2H), 7.58 (d, J = 8.4 Hz, 2H), 7.78 (d, J = 5.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.3, 25.4 (d, J = 140 Hz), 52.8 (d, J = 5 Hz), 55.3, 61.2, 114.1, 121.2 (d, J = 11 Hz), 127.2, 131.4, 141.4 (d, J = 11 Hz), 160.3, 167.7; ^{31}P NMR (162 MHz, $CDCl_3$): δ 29.2. HRMS (ESI): calcd for $C_{15}H_{21}O_6P$ $[M+Na]^+$: 351.0973, found: 351.0987.

4.2.10. Ethyl 2-[(dimethoxyphosphoryl)methyl]-3-(3-methoxyphenyl)-2-propenoate 7j

Yield: 62%. Oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.37 (t, J = 7.1 Hz, 3H), 3.24 (d, J = 22.6 Hz, 2H), 3.73 (d, J = 10.8 Hz, 6H), 3.84 (s, 3H), 4.31 (q, J = 7.1 Hz, 2H), 6.91 (dd, J = 8.1, 1.6 Hz, 1H), 7.10 (d, J = 7.5 Hz, 1H), 7.20 (s, 1H), 7.32 (t, J = 7.9 Hz, 1H), 7.80 (d, J = 5.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2, 25.4 (d, J = 140 Hz), 52.7 (d, J = 7 Hz), 55.4, 61.3, 114.0, 115.2, 121.7, 123.9 (d, J = 11 Hz), 129.6, 136.1, 141.6 (d, J = 11 Hz), 159.7, 167.3; ^{31}P NMR (162 MHz, $CDCl_3$): δ 29.0. HRMS (ESI): calcd for $C_{15}H_{21}O_6P$ $[M+Na]^+$: 351.0973, found: 351.0979.

4.2.11. Ethyl 2-[(dimethoxyphosphoryl)methyl]-3-(2-methoxyphenyl)-2-propenoate 7k

Yield: 49%. White crystal, mp: 95–96 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.37 (t, J = 7.2 Hz, 3H), 3.18 (d, J = 22.4 Hz, 2H), 3.69 (dd, J = 10.8, 2.0 Hz, 6H), 3.85 (s, 3H), 4.31 (q, J = 7.2 Hz, 2H), 6.91 (d, J = 8.4 Hz, 1H), 7.01 (t, J = 7.6 Hz, 1H), 7.34 (t, J = 7.6 Hz, 1H), 7.66 (d, J = 7.6 Hz, 1H), 7.94 (d, J = 5.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.3, 25.4 (d, J = 140 Hz), 52.7 (d, J = 7 Hz), 55.5, 61.2, 110.5, 120.6, 123.8 (d, J = 11 Hz), 129.9, 130.5, 137.9 (d, J = 12 Hz), 157.4, 167.4; ^{31}P NMR (162 MHz, $CDCl_3$): δ 29.4. HRMS (ESI): calcd for $C_{15}H_{21}O_6P$ $[M+Na]^+$: 351.0973, found: 351.0979.

4.2.12. Ethyl 2-[(dimethoxyphosphoryl)methyl]-3-(3-chlorophenyl)-2-propenoate 7l

Yield: 59%. Oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.37 (t, J = 7.1 Hz, 3H), 3.19 (d, J = 22.6 Hz, 2H), 3.74 (dd, J = 11.0, 6H), 4.32 (q, J = 7.1 Hz, 2H), 7.34 (m, 2H), 7.47 (d, J = 7.1 Hz, 1H), 7.57 (s, 1H), 7.74 (d, J = 5.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2, 25.2 (d, J = 140 Hz), 52.7 (d, J = 7 Hz), 61.4, 125.2 (d, J = 11 Hz), 127.2, 128.8, 129.0, 129.9, 134.4, 136.5 (d, J = 2 Hz), 139.8 (d, J = 11 Hz), 166.8; ^{31}P NMR (162 MHz, $CDCl_3$): δ 28.4. HRMS (ESI): calcd for $C_{14}H_{18}ClO_5P$ $[M+Na]^+$: 355.0478, found: 355.0492.

4.2.13. Ethyl 2-[(dimethoxyphosphoryl)methyl]-3-(2-chlorophenyl)-2-propenoate 7m

Yield: 63%. Oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.38 (t, J = 7.2 Hz, 3H), 3.11 (d, J = 22.8 Hz, 2H), 3.69 (d, J = 10.8, 6H), 4.33 (q, J = 7.2 Hz, 2H), 7.32 (m, 2H), 7.43 (d, J = 7.2 Hz, 1H), 7.68 (dd, J = 7.2 Hz, 2.0 Hz, 1H), 7.874 (d, J = 5.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2, 25.02 (d, J = 139 Hz), 52.6 (d, J = 6 Hz), 61.4, 125.8 (d, J = 11 Hz), 126.9, 129.5, 129.9, 130.1, 133.4 (d, J = 3 Hz), 133.8, 138.6 (d, J = 11 Hz), 166.7; ^{31}P NMR (162 MHz, $CDCl_3$): δ 28.6. HRMS (ESI): calcd for $C_{14}H_{18}ClO_5P$ $[M+Na]^+$: 355.0478, found: 355.0480.

4.2.14. Ethyl 2-[(dimethoxyphosphoryl)methyl]-3-(2-furyl)-2-propenoate 7n

Yield: 63%. Oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.35 (t, J = 7.2 Hz, 3H), 3.54 (d, J = 23.6 Hz, 2H), 3.69 (d, J = 10.9 Hz, 6H), 4.28 (q, J = 7.2 Hz, 2H), 6.51 (dd, J = 3.6, 2.0 Hz, 1H), 6.75 (d, J = 1.6 Hz, 1H), 7.51 (d, J = 6.0 Hz, 1H), 7.58 (d, J = 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2, 25.4 (d, J = 138 Hz), 52.6 (d, J = 7 Hz), 61.2, 112.1, 116.7, 119.0 (d, J = 13 Hz), 127.2 (d, J = 11 Hz), 144.8, 150.8 (d, J = 4 Hz), 167.0; ^{31}P NMR (162 MHz, $CDCl_3$): δ 28.9. HRMS (ESI): calcd for $C_{12}H_{17}O_6P$ $[M+Na]^+$: 311.0660, found: 311.0664.

4.2.15. Ethyl 2-[(dimethoxyphosphoryl)methyl]-3-(2-thienyl)-2-propenoate 7o

Yield: 48%. Oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.36 (t, J = 7.1 Hz, 3H), 3.39 (d, J = 22.5 Hz, 2H), 3.72 (d, J = 11.0 Hz, 6H), 4.29 (q, J = 7.1 Hz, 2H), 7.11 (t, J = 4.4 Hz, 1H), 7.45 (s, 1H), 7.52 (d, J = 4.9 Hz, 1H), 7.92 (d, J = 5.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.3, 26.2 (d, J = 140 Hz), 52.8 (d, J = 6 Hz), 61.3, 119.7 (d, J = 13 Hz), 127.6, 129.6, 132,6, 133.6 (d, J = 11 Hz), 137.7 (d, J = 4 Hz), 167.1; ^{31}P NMR (162 MHz, $CDCl_3$): δ 28.2. HRMS (ESI): calcd for $C_{12}H_{17}O_5PS$ $[M+Na]^+$: 327.0432, found: 327.0438.

4.2.16. Ethyl 2-[(dimethoxyphosphoryl)methyl]-2-propenoate 7p[9]

Yield: 30%. Oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.32 (t, J = 7.1 Hz, 3H), 2.97 (d, J = 22.1 Hz, 2H), 3.75 (d, J = 10.9 Hz, 6H), 4.25 (q, J = 7.1 Hz, 2H), 5.87 (d, J = 5.4 Hz, 1H), 6.37 (d, J = 5.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 27.6 (d, J = 139 Hz), 52.8 (d, J = 7 Hz), 61.3, 128.8 (d, J = 9 Hz), 131.2 (d, J = 11 Hz), 166.0 (d, J = 5 Hz), 167.4; ^{31}P NMR (162 MHz, $CDCl_3$): δ 28.8.

4.2.17. Ethyl 2-[(dimethoxyphosphoryl)methyl]-4-methyl-2-pentenoate 7q

Yield: 63%. Oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.06 (d, J = 6.6 Hz, 6H), 1.32 (t, J = 7.1 Hz, 3H), 2.71 (m, 1H), 3.00 (d, J = 22.1 Hz, 2H), 3.73 (d, J = 10.9 Hz, 6H), 4.23 (q, J = 7.1 Hz, 2H), 6.72 (d, J = 10.5 Hz, 5.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2, 21.6, 23.8 (d, J = 139 Hz), 28.6, 52.6 (d, J = 6 Hz), 60.9, 120.3 (d, J = 9 Hz), 152.1 (d, J = 10 Hz), 166.9; ^{31}P NMR (162 MHz, $CDCl_3$): δ 29.2. HRMS (ESI): calcd for $C_{11}H_{21}O_5P$ $[M+Na]^+$: 287.1024, found: 287.1026.

4.3. General hydrogenation procedure

To a solution of $[Rh(COD)_2]SbF_6$ (2.8 mg, 0.005 mmol) in anhydrous and degassed CH_2Cl_2 (1 mL), which was placed in a nitrogen-filled glovebox, was added TaniaPhos (0.0055 mmol). The reaction mixture was stirred at room temperature for 30 min, and then a solution of the unsaturated ester (0.5 mmol) in 1 mL of CH_2Cl_2 was added. The mixture was transferred to a Par stainless autoclave. The autoclave was purged three times with hydrogen, and a hydrogen pressure of 10 bar maintained. The hydrogenation was performed at room temperature for 24 h. After carefully releasing the hydrogen gas, the solvent was removed. Conversion was directly determined by ^{1}H NMR spectroscopy. The enantiomeric excess was determined by HPLC after purification on silica gel.

4.3.1. Ethyl 2-[(dimethoxyphosphoryl)methyl]-3-phenyl-2-propionate 8a

96% ee. HPLC conditions: chiralcel OD-H, 40 °C, 215 nm, *n*-hexane/*i*-propanol = 94/6, flow rate = 1.0 mL/min; $[\alpha]_D^{20} = +16.8$ (c 1.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.15 (t, J = 7.1 Hz, 3H), 1.83–1.92 (m, 1H), 2.23 (m, 1H), 2.86 (m, 1H), 2.98 (m, 2H), 3.68 (m, 6H), 4.08 (q, J = 7.1 Hz, 2H), 7.16 (d, J = 7.4 Hz, 2H), 7.22 (d, J = 6.8 Hz, 1H), 7.28 (t, J = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 26.0 (d, J = 141 Hz), 39.5 (d, J = 14 Hz), 41.8 (d, J = 3 Hz), 52.3 (d, J = 7 Hz), 52.4 (d, J = 6 Hz), 60.8, 126.8, 128.5, 129.0, 137.8, 174.0 (d, J = 7 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ 32.0. HRMS (ESI): calcd for $C_{14}H_{21}O_5P$ $[M+Na]^+$: 323.1024, found: 323.1019.

4.3.2. Ethyl 2-[(dimethoxyphosphoryl)methyl]-3-(4-fluorophenyl)-2-propionate 8f

91% ee. HPLC conditions: chiralcel OD-H, 40 °C, 215 nm, *n*-hexane/*i*-propanol = 94/6, flow rate = 1.0 mL/min; $[\alpha]_D^{20} = +17.9$ (*c* 1.4, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 1.16 (t, *J* = 7.1 Hz, 3H), 1.82–1.92 (m, 1H), 2.22 (m, 1H), 2.88 (m, 1H), 2.98 (m, 2H), 3.70 (dd, *J* = 10.9, 2.6 Hz, 6H), 4.07 (q, *J* = 7.1 Hz, 2H), 6.97 (m, 2H), 7.13 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 26.1 (d, *J* = 142 Hz), 38.6 (d, *J* = 13 Hz), 41.8, 52.3 (d, *J* = 7 Hz), 52.5, 60.8, 115.1, 115.4, 130.5 (d, *J* = 7 Hz), 133.5, 160.5, 163.0, 173.8 (d, *J* = 7 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ 31.8. HRMS (ESI): calcd for $C_{14}H_{20}FO_5P$ $[M+Na]^+$: 341.0930, found: 341.0923.

4.3.3. Ethyl 2-[(dimethoxyphosphoryl)methyl]-3-(4-chlorophenyl)-2-propionate 8g

96% ee. HPLC conditions: chiralcel OD-H, 40 °C, 215 nm, *n*-hexane/*i*-propanol = 95/5, flow rate = 1.0 mL/min; $[\alpha]_D^{20} = +21.1$ (*c* 1.2, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 1.16 (t, *J* = 7.1 Hz, 3H), 1.82–1.91 (m, 1H), 2.17–2.28 (m, 1H), 2.85–2.98 (m, 3H), 3.71 (d, *J* = 10.7 Hz, 6H), 3.78 (s, 3H), 4.08 (q, *J* = 7.0 Hz, 2H), 7.10 (d, *J* = 8.1 Hz, 2H), 7.25 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 26.2 (d, *J* = 142 Hz), 38.7 (d, *J* = 13 Hz), 41.7, 52.4, 52.5 (d, *J* = 7 Hz), 60.9, 128.6, 130.4, 132.6, 136.3, 173.7 (d, *J* = 7 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ 31.8. HRMS (ESI): calcd for $C_{14}H_{20}ClO_5P$ $[M+Na]^+$: 357.0635, found: 357.0621.

4.3.4. Ethyl 2-[(dimethoxyphosphoryl)methyl]-3-(4-nitrophenyl)-2-propionate 8h

95% ee. HPLC conditions: chiralcel OJ-H, 40 °C, 215 nm, *n*-hexane/*i*-propanol = 90/10, flow rate = 1.0 mL/min; $[\alpha]_D^{20} = +23.7$ (*c* 1.1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 1.16 (t, *J* = 7.2 Hz, 3H), 1.87–1.96 (m, 1H), 2.21–2.32 (m, 1H), 3.07 (m, 3H), 3.74 (d, *J* = 10.9 Hz, 6H), 3.78 (s, 3H), 4.08 (dq, *J* = 7.1, 3.7 Hz, 2H), 7.38 (d, *J* = 8.5 Hz, 2H), 8.16 (d, *J* = 8.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 26.5 (d, *J* = 142 Hz), 38.7 (d, *J* = 11 Hz), 41.4 (d, *J* = 2 Hz), 52.5, 52.6 (d, *J* = 7 Hz), 61.1, 123.7, 130.3, 145.8, 146.9, 173.2 (d, *J* = 9 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ 31.1. HRMS (ESI): calcd for $C_{14}H_{20}NO_7P$ $[M+Na]^+$: 368.0875, found: 368.0871.

4.3.5. Ethyl 2-[(dimethoxyphosphoryl)methyl]-3-(4-methoxyphenyl)-2-propionate 8i

95% ee. HPLC conditions: chiralcel OJ-H, 40 °C, 215 nm, *n*-hexane/*i*-propanol = 95/5, flow rate = 1.0 mL/min; $[\alpha]_D^{20}$: 21.5 (*c* 1.2, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 1.17 (t, *J* = 7.1 Hz, 3H), 1.82–1.91 (m, 1H), 2.19 (m, 1H), 2.80 (m, 1H), 2.92 (m, 2H), 3.70 (dd, *J* = 10.9, 2.6 Hz, 6H), 3.77 (s, 3H), 4.09 (q, *J* = 7.1 Hz, 2H), 6.82 (d, *J* = 8.2 Hz, 2H), 7.07 (*J* = 8.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 25.9 (d, *J* = 141 Hz), 38.6 (d, *J* = 14 Hz), 41.9 (d, *J* = 3 Hz), 52.3 (d, *J* = 7 Hz), 52.4 (d, *J* = 7 Hz), 55.2, 60.7, 113.8, 129.7, 130.0, 158.4, 174.0 (d, *J* = 6 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ 32.2. HRMS (ESI): calcd for $C_{15}H_{23}O_6P$ $[M+Na]^+$: 353.1130, found: 353.1115.

4.3.6. Ethyl 2-[(dimethoxyphosphoryl)methyl]-3-(3-methoxyphenyl)-2-propionate 8j

95% ee. HPLC conditions: chiralpak AD-H, 40 °C, 215 nm, *n*-hexane/*i*-propanol = 90/10, flow rate = 1.0 mL/min; $[\alpha]_D^{20} = +18.8$ (*c* 1.2, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 1.18 (t, *J* = 7.2 Hz, 3H), 1.84–1.93 (m, 1H), 2.18–2.24 (m, 1H), 2.81–2.86 (m, 1H), 2.95–3.00 (m, 2H), 3.69 (dd, *J* = 10.8, 6.4 Hz, 6H), 3.78 (s, 3H), 4.10 (q, *J* = 6.8 Hz, 2H), 6.71 (s, 1H), 7.76 (m, 2H), 7.20 (t, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 26.0 (d, *J* = 141 Hz), 39.5 (d, *J* = 14 Hz), 41.7, 52.3 (d, *J* = 6 Hz), 52.4 (d, *J* = 6 Hz), 55.2, 60.8, 112.2, 114.7, 121.4, 129.5, 139.3, 159.7, 174.0 (d, *J* = 6 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ 32.1. HRMS (ESI): calcd for $C_{15}H_{23}O_6P$ $[M+Na]^+$: 353.1130, found: 353.1121.

4.3.7. Ethyl 2-[(dimethoxyphosphoryl)methyl]-3-(2-methoxyphenyl)-2-propionate 8k

97% ee. HPLC conditions: chiralcel OJ-H, 40 °C, 215 nm, *n*-hexane/*i*-propanol = 95/5, flow rate = 1.0 mL/min; $[\alpha]_D^{20} = +27.9$ (*c* 1.1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 1.14 (t, *J* = 7.2 Hz, 3H), 1.87 (m, 1H), 2.24 (m, 1H), 2.91 (m, 2H), 3.11 (m, 1H), 3.66 (dd, *J* = 10.6, 9.0 Hz, 6H), 3.82 (s, 3H), 4.06 (dq, *J* = 7.1, 2.4 Hz, 2H), 6.85 (m, 2H), 7.06 (d, *J* = 7.1 Hz, 1H), 7.20 (t, *J* = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 26.3 (d, *J* = 140 Hz), 34.9 (d, *J* = 15 Hz), 40.0, 52.2 (d, *J* = 6 Hz), 52.4 (d, *J* = 6 Hz), 55.2, 60.6, 110.3, 120.3, 126.1, 128.2, 130.9, 157.6, 174.4 (d, *J* = 4 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ 32.5. HRMS (ESI): calcd for $C_{15}H_{23}O_6P$ $[M+Na]^+$: 353.1130, found: 353.1122.

4.3.8. Ethyl 2-[(dimethoxyphosphoryl)methyl]-3-(3-chlorophenyl)-2-propionate 8l

92% ee. HPLC conditions: chiralcel OD-H, 40 °C, 215 nm, *n*-hexane/*i*-propanol = 95/5, flow rate = 1.0 mL/min; $[\alpha]_D^{20} = +17.1$ (*c* 1.2, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 1.16 (t, *J* = 7.1 Hz, 3H), 1.82–1.92 (m, 1H), 2.18–2.25 (m, 1H), 2.87–3.00 (m, 3H), 3.71 (dd, *J* = 10.9 Hz, 3.2 Hz, 6H), 3.78 (s, 3H), 4.09 (q, *J* = 7.0 Hz, 2H), 7.06 (m, 1H),7.17 (s, 1H), 7.21 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 26.2 (d, *J* = 141 Hz), 39.0 (d, *J* = 13 Hz), 41.6 (d, *J* = 2 Hz), 52.3, 52.5 (d, *J* = 7 Hz), 60.9, 127.0, 127.3, 129.2, 129.7, 134.2, 139.9, 173.6 (d, *J* = 8 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ 31.6. HRMS (ESI): calcd for $C_{14}H_{20}ClO_5P$ $[M+Na]^+$: 357.0635, found: 357.0619.

4.3.9. Ethyl 2-[(dimethoxyphosphoryl)methyl]-3-(2-furyl)-2-propionate 8n

90% ee. HPLC conditions: chiralpak AD-H, 40 °C, 215 nm, *n*-hexane/*i*-propanol = 95/5, flow rate = 1.0 mL/min; $[\alpha]_D^{20} = +10.6$ (*c* 1.1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 1.23 (t, *J* = 7.1 Hz, 3H), 1.87–1.97 (m, 1H), 2.21–2.31 (m, 1H), 2.95–3.11 (m, 3H), 3.71 (d, *J* = 10.9 Hz, 6H), 3.82 (s, 3H), 4.14 (q, *J* = 7.0 Hz, 2H), 6.07 (s, 1H), 6.27 (s, 1H), 7.31 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 25.8 (d, *J* = 142 Hz), 31.5 (d, *J* = 13 Hz), 39.3, 52.3 (d, *J* = 7 Hz), 52.4 (d, *J* = 7 Hz), 61.0, 107.4, 110.2, 141.8, 151.7, 173.6 (d, *J* = 8 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ 31.9. HRMS (ESI): calcd for $C_{12}H_{19}O_6P$ $[M+Na]^+$: 313.0841, found: 313.0827.

4.3.10. Ethyl 2-[(dimethoxyphosphoryl)methyl]-3-(2-thienyl)-2-propionate 8o

98% ee. HPLC conditions: chiralcel OD-H, 40 °C, 215 nm, *n*-hexane/*i*-propanol = 94/6, flow rate = 1.0 mL/min; $[\alpha]_D^{20} = +13.1$ (*c* 1.2, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 1.23 (t, *J* = 7.1 Hz, 3H), 1.94 (m, 1H), 2.19–2.26 (m, 1H), 3.03 (m, 1H), 3.12–3.26 (m, 2H), 3.71 (dd, *J* = 10.7, 1.9 Hz, 6H), 4.14 (q, *J* = 7.2 Hz, 2H), 6.83 (d, *J* = 3.2 Hz, 1H), 6.91 (dd, *J* = 5.0, 3.5 Hz, 1H), 7.15 (d, *J* = 5.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 25.7 (d, *J* = 142 Hz), 33.1 (d, *J* = 12 Hz), 42.0, 52.5, 61.1, 124.4, 126.4, 126.9, 139.7, 173.5 (d, *J* = 7 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ 32.0. HRMS (ESI): calcd for $C_{12}H_{19}O_5PS$ $[M+Na]^+$: 329.0589, found: 329.0584.

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