JOC The Journal of Organic Chemistry

Featured Article

pubs.acs.org/joc

Enantioselective Hydrogenation of β-Ketophosphonates with Chiral Ru(II) Catalysts

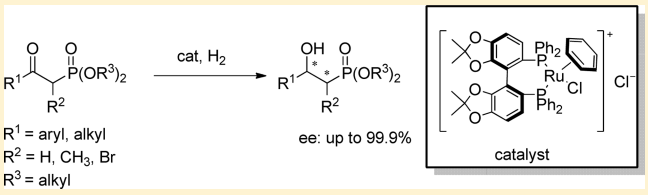
Xiaoming Tao,[†] Wanfang Li,[†] Xin Ma,[†] Xiaoming Li,[†] Weizheng Fan,[†] Lvfeng Zhu,[†] Xiaomin Xie,[†] and Zhaoguo Zhang*[,†,§]

[†]School of Chemistry and Chemical Engineering, Shanghai Jiao Tong University, 800 Dongchuan Road, Shanghai 200240, China

[§]State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, 345 Lingling Road, Shanghai 200032, China

Supporting Information

ABSTRACT: Highly effective asymmetric hydrogenation of β-ketophosphonates in the presence of Ru−(*S*)-SunPhos as catalyst was realized; good to excellent enantioselectivities (up to 99.9% ee) and excellent diastereoselectivities (96:4) were obtained.



INTRODUCTION

Chiral β-hydroxyphosphonates have attracted considerable attention in recent years because of their wide biological applications as well as their ability to mimic the corresponding hydroxyl carboxylic acids or amino acids.[1] They are also intermediates in the syntheses of potentially significant antibacterial agents, enzyme inhibitors, peptide analogues, and phosphonic acid-based antibiotics (Figure 1).[2] Chiral β-hydroxyphosphonates have been previously produced by either enzymatic, nonenzymatic kinetic resolution of the racemates or oxazaborolidine-catalyzed reduction of ketones.[3] However, these synthetic routes suffered from either low enantioselectivity or poor efficiency. Accordingly, the need for the development of versatile and efficient methods for the preparation of enantiopure β-hydroxyphosphonates is of great significance.

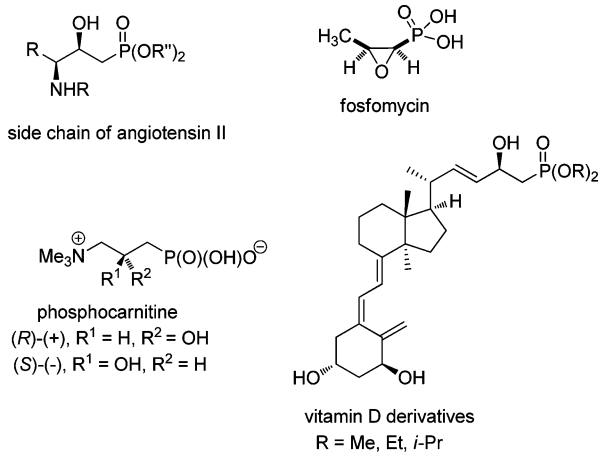


Figure 1. Chiral β-hydroxyphosphonates in pharmaceuticals.

Investigation of catalytic procedures mainly focused on the hydrogenation reactions using chiral ruthenium catalysts. In the 1990s, Noyori and co-workers first reported the asymmetric hydrogenation of several β-ketophosphonates with Ru−BINAP systems and applied this method to furnish a facile synthesis of fosfomycin.[4] Genêt et al. also hydrogenated several β-ketophophonates including a β-(3-thienyl) derivative with Ru−MeO-Biphep systems.[5] Recently, Pizzano et al. reported the highly enantioselective hydrogenation of enol phosphonates to give masked (or protected) chiral β-hydroxyphosphonates.[6] This feature is of much practical interest because the separation of geometric isomers is avoided and it confers a challenging aspect to the hydrogenation of these olefins, since structurally related *Z* isomers usually undergo slower and less enantioselective reactions than their *E* counterparts.[7] In addition, steric effects, resulting from the size of the phosphonate group, can further reduce the reactivity of these alkenes.[8] Therefore, further study of β-ketophosphonates hydrogenation is still of considerable interest.

In the past few years, our group has studied asymmetric hydrogenation of various functionalized ketones and applied the Ru−(*S*)-SunPhos catalytic system in the synthesis of some useful chiral blocks.[9] In this paper, we will disclose a general and highly enantioselective hydrogenation reaction of β-ketophosphonates.

RESULTS AND DISCUSSION

It has been well-known that subtle changes in geometric, steric, and/or electronic properties of chiral ligands can lead to dramatic variations of reactivity and enantioselectivity,[10] thus the ligands (**L1**−**L10**, Figure 2) effects were examined initially with dimethyl (2-oxo-2-phenylethyl)phosphonate (**1a**) as the

Received: July 24, 2012
Published: September 7, 2012

 © 2012 American Chemical Society

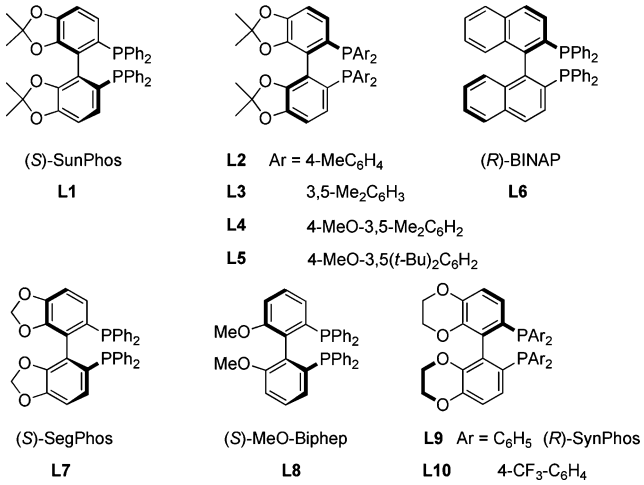
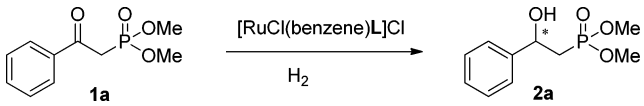


Figure 2. Structures of chiral bidentate ligands.

standard substrate. The catalyst was prepared from $[RuCl_2(benzene)]_2$ and a diphosphine ligand by refluxing them in degassed dichloromethane/ethanol (v/v = 1:1) for 1.5 h and then dried under reduced pressure.[9a] The reaction was carried out with an S/C = 200:1 under 10 bar of hydrogen pressure at 50 °C in MeOH for 19 h. All of the tested ligands show similar activity, but the enantioselectivity varied to some extent. As illustrated in Table 1, (*R*)-BINAP, (*S*)-SegPhos, (*S*)-MeO-Biphep, and (*R*)-SynPhos were workable ligands; however, they are inferior to (*S*)-SunPhos (Table 1, entries 1, 6−9, 94.1−96.5% ee vs 99.7% ee). (*R*)-4-CF_3-SynPhos, a less electron-rich ligand, resulted in only a 20.9% ee of **2a**. When **L2**−**L5** were used as ligands, corresponding ee values of 97.7%, 92.3%, 91.8%, and 49.7% were achieved (Table 1, entries 2−5), revealing that the modifications of SunPhos on P atom did impose remarkable changes in enantioselectivity of the asymmetric hydrogenation of *β*-ketophosphonates (**1a**): substituents on the phenyl appendages of the ligands had an adverse effect on the ee's, which might have resulted from the steric effect. On the basis of the above results, (*S*)-SunPhos was the ligand of choice.

Table 1. Screening of Ligands in Asymmetric Hydrogenation of 1a[a]

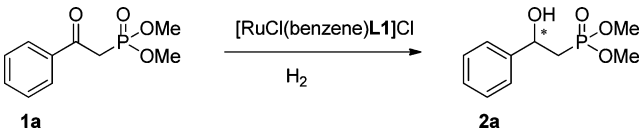


entry	ligand	ee[b] (%)	config[b]
1	**L1**	99.7	*S*
2	**L2**	97.7	*R*
3	**L3**	92.3	*R*
4	**L4**	91.8	*R*
5	**L5**	49.7	*R*
6	**L6**	94.5	*R*
7	**L7**	94.9	*S*
8	**L8**	94.1	*S*
9	**L9**	96.5	*R*
10	**L10**	20.9	*R*

[a]All reactions were carried out with a substrate (1 mmol) concentration of 0.5 M in MeOH under 10 bar of H_2 at 50 °C for 19 h, S/C = 200:1. Conversion: >99%. [b]ee values were determined by HPLC on a Chiralpak OB-H column; absolute configuration was assigned on the basis of its optical rotation or HPLC.

Optimization of solvents, hydrogen pressure, and reaction temperatures are summarized in Table 2. Enantioselectivity in MeOH (entry 1, 99.7% ee) was superior to that in EtOH (entry 2, 97.5% ee) or *i*-PrOH (entry 3, 97.9% ee). The results depicted in Table 2 showed that the stereochemical outcome of the hydrogenation was dependent on the hydrogen pressure (entries 5 and 6, 97.3% at 30 bar vs 95.4% at 50 bar), higher hydrogen pressure decreased the enantioselectivity. Temperatures also influenced the enantioselectivities (entry 1 vs 7, 8). Lower reaction temperature remarkably decreased the enantioselectivity and reaction rate while higher reaction temperature increased the reaction rate with slightly decreased enantioselectivity.[11] Reaction time remarkably influenced the conversion and enantiomeric excesses (Table 5, see the Supporting Information). Lower conversion and enantioselectivity were obtained when the reaction time was shortened (entries 1 and 2), and the enantioselectivity remained unchanged when longer reaction times were tested (entry 4).

Table 2. Optimization of Solvent, Pressure, and Temperature[a]



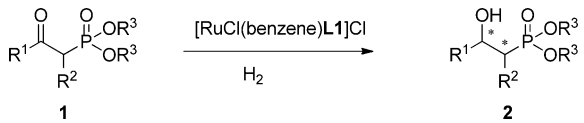
entry	solvent	*P* (bar)	*T* (°C)	ee[b] (%)
1	MeOH	10	50	99.7
2	EtOH	10	50	97.5
3	*i*-PrOH	10	50	97.9
4	*n*-PrOH	10	50	99.1
5	MeOH	30	50	97.3
6	MeOH	50	50	95.4
7	MeOH	10	30	89.5
8	MeOH	10	70	99.1

[a]All reactions were carried out with a substrate (1 mmol) concentration of 0.5 M in solvent for 19 h. S/C = 200:1. Conversion: > 99%. [b]ee values were determined by HPLC on a ChiralPak OB-H column.

On the basis of these results, the optimized reaction conditions were therefore set as follows: 0.5 mol % of [RuCl(benzene)(*S*)-SunPhos]Cl as the catalyst, MeOH as the solvent with a substrate concentration of 0.5 M, and 10 bar of H_2 at 50 °C.

Under the optimized reaction conditions, a variety of *β*-ketophosphonates were hydrogenated, and the results are presented in Table 3. When a series of alkyl (2-oxo-2-phenylethyl)phosphonates were hydrogenated at the optimized reaction conditions, methyl, ethyl, and isopropyl (2-oxo-2-phenylethyl)phosphonates afforded the corresponding alcohols, **2a**, **2b**, and **2c** in 99.7, 95.5, and 90.0% ee, respectively. Obviously, the bulkiness of the alcohol plays an important role in achieving good enantioselectivity. Because methyl phosphonate is superior to ethyl or isopropyl phosphonate (Table 3, entry 1 vs 3 or 4), methyl phosphates were chosen in the following investigation. Most methyl (2-oxo-2-phenylethyl)-phosphonates gave excellent enantioselectivities (entries 1−12). Furthermore, the reaction proceeded smoothly on multigrams scale with excellent enantiofacial discrimination, up to 99.3% ee under 15 bar of hydrogen pressure and 50 °C

Table 3. Asymmetric Hydrogenation of β-Ketophosphonates[a]



entry	1	R^1	R^2	R^3	2 ee[b] (%)	2 config[b]
1	**1a**	C_6H_5	H	Me	99.7	*S*
2[d]	**1a**	C_6H_5	H	Me	99.3	*S*
3	**1b**	C_6H_5	H	Et	95.5	*S*
4	**1c**	C_6H_5	H	*i*-Pr	90.0	*S*
5	**1d**	*o*-OMe-C_6H_4	H	Me	96.6	S
6	**1e**	*o*-Me-C_6H_4	H	Me	85.5	*S*
7	**1f**	*m*-Me-C_6H_4	H	Me	99.8	*S*
8	**1g**	*p*-Me-C_6H_4	H	Me	99.8	*S*
9	**1h**	*p*-OMe-C_6H_4	H	Me	99.6	*S*
10	**1i**	*p*-F-C_6H_4	H	Me	88.7	*S*
11	**1j**	*p*-Cl-C_6H_4	H	Me	98.7	*S*
12	**1k**	*p*-Br-C_6H_4	H	Me	99.9	*S*
13	**1l**	*p*-CF_3-C_6H_4	H	Me	96.7	*S*
14	**1m**	CH_3	H	Me	97.2[c]	*S*
15	**1n**	C_2H_5	H	Me	95.3[c]	*S*
16	**1o**	$CH(CH_3)_2$	H	Me	95.7[c]	*S*
17	**1p**	C_5H_{11}	H	Me	96.3[c]	*S*
18	**1q**	$C_{11}H_{23}$	H	Me	94.1[c]	*S*
19	**1r**	Cy	H	Me	96.4[c]	*S*
20	**1s**	$BocNHCH_2$	H	Me	97.3[c]	*S*
21	**1t**	CH_3	Me	Me	98.6[c]	(1*R*, 2*S*)
22	**1u**	CH_3	Et	Me	99.8[c]	(1*R*, 2*S*)
23	**1v**	CH_3	Me	Et	99.5[c]	(1*R*, 2*S*)
24[e]	**1w**	CH_3	Br	Me	99.7[c]	(1*R*, 2*S*)

[a]Unless otherwise stated, all reactions were carried out with a substrate (1 mmol) concentration of 0.5 M in MeOH under 10 bar of H_2 at 50 °C for 19 h, S/C = 200:1. Conversion: > 99%. [b]ee values were determined by HPLC on a Chiralpak OB-H column or AD-H column; absolute configuration was assigned on the basis of its optical rotation or HPLC. [c]ee values were determined through their corresponding *p*-nitrobenzoyl derivatives **3m**−**w**. [d]Reaction using 23.0 g of **1a** at 15 bar of H_2 for 48 h at 50 °C. S/C = 10000:1. [e]An 87:13 mixture of **2u** and **2m**, *syn*/*anti* = 96:4. (The optimization of the reaction conditions is provided in the Supporting Information.)

using a low catalyst loading of 0.01 mol % of [RuCl(benzene)-(*S*)-SunPhos]Cl (entry 2) were obtained. For the phosphonates possessing an *ortho* substituent on the aromatic ring, the hydrogenation results were dependent on the nature of the substituents: for a noncoordinating *ortho*-substituent, the ee dropped dramatically (entry 5 vs 1, 85.5 vs 99.7% ee); for a coordinating *ortho*-substituted substrate, the ee dropped slightly (entry 4 vs 1, 96.6 vs 99.7% ee). A range of *para*-substituted aryl substrates were also studied, and the results showed that the electron density of the aromatic ring also had a dramatic effect on the enantioselectivity. Substrates with electron-donating groups on the aromatic rings usually gave higher ee values (entries 7−11, 98.7−99.9% ee), while substrates with an electron-withdrawing substitution group, such as the fluoro in **1i**, the ee of hydrogenation product **2i** (88.7% ee), which is an important intermediate of the synthesis of cholesterol inhibitor, was drastically decreased.[2g] Enantioselective hydrogenation of dimethyl 2-(*p*-trifuoromethylphenyl)-2-oxoethylphosphonate (**1l**) afforded the corresponding alcohol (**2l**) in 96.7% ee (entry 12). Electronic influences of the *para* substituents were presumed to affect the coplanarity of the benzene rings with C═O in the transition state,[12] thereby generating an asymmetric bias. Simple *meta*-substituted substrates gave excellent enantiomeric excesses up to 99.8% (entry 6).

Hydrogenation of aliphatic analogues also gave excellent enatioselectivities (entry 13, 97.2% ee, R^1 = Me), even for the more hindered carbonyl groups (entry 15, 95.7% ee, R^1 = *i*-Pr and entry 18, 96.4% ee, R^1 = Cy).

Our catalyst was also fruitful in the asymmetric hydrogenation of *N*-Boc-γ-amino substituted β-ketophosphonate (**1s**), giving excellent ee values of **2s** (entry 19, 97.3% ee). When three β-ketophosphonates with a alkyl substituent at the α-position were used, *syn*/*anti* ratio *ca.* 94:6 to 96:4 were observed with the acyclic substrate (entries 21−23).[13] Asymmetric hydrogenation of dimethyl 1-bromo-2-oxopropylphosphonate (**1u**) afforded the corresponding alcohol (**2u**) in 99.7% ee and a *syn*/*anti* ratio of 96:4. Enantiopure **2u** has been applicated in the practical synthesis of fosfomycin.[14]

■ CONCLUSION

In conclusion, we have developed a convenient and general protocol for the asymmetric hydrogenation of a variety of alkyl- and aryl-substituted β-ketophosphonates with excellent enantioselectivities. SunPhos was the best chiral ligand among screened all ligands, while electron-withdrawing ligands remarkably decreased the enantiomeric excesses. An *ortho* substituent on the aromatic rings had a negative effect on the enantioselectivity of the phenyl phosphonates. Electron-donating groups on the *para*-positions of the phenyl rings usually led to higher ee values, while electron-withdrawing groups drastically decreased the enantioselectivities of the hydrogenation products. Notably, α-alkyl- or bromo-substituted β-ketophosphonates can be hydrogenated through DKR to produce the corresponding *syn* products with excellent diastereo- and enantioselectivity.

■ EXPERIMENTAL SECTION

General Methods. Commercially available reagents were used throughout without further purification other than those detailed below. The solvents used in catalyst preparation and hydrogenation reactions were pretreated by the following procedures: MeOH and EtOH were distilled over magnesium under nitrogen. *i*-PrOH was distilled over calcium hydride. All reactions were carried out under an atmosphere of nitrogen using standard Schlenk techniques or in a nitrogen-filled glovebox, unless otherwise noted. ^{1}HNMR spectra were recorded at 400 MHz, with TMS as internal standard. ^{13}CNMR spectra were obtained at 101 MHz and referenced to the central peak of 77.0 ppm for $CDCl_3$. Coupling constants (*J*) are reported in hertz and refer to apparent peak multiplications. Mass spectroscopy data were collected on an HRMS-EI instrument. Flash column chromatography was performed on silica gel (300−400 mesh).

Typical Procedure for the Preparation 1a−r.[15] A three-necked, round-bottomed flask equipped with a nitrogen inlet adapter, addition funnel, thermocouple, and mechanical stirrer was charged with the ester (1.0 equiv), dimethyl or diethyl or diisopropyl methylphosphonate (1.2 equiv), and THF. The reaction mixture was cooled at −5 °C while LDA (2.1 equiv) was added dropwise via addition funnel keeping the internal temperature below 0 °C. After complete addition, the reaction mixture was stirred at 0 °C until complete consumption of the ester as determined by TLC analysis. The reaction mixture was then carefully quenched with 6 M HCl to adjust the pH to ca. 4−5 and diluted with CH_2Cl_2. The aqueous layer was separated and extracted with CH_2Cl_2. The combined organic layers were washed with water and brine, dried over Na_2SO_4, filtered, and evaporated in vacuo. The

residue was purified by column chromatography with petroleum ether and ethyl acetate.

Dimethyl (2-Oxo-2-phenylethyl)phosphonate (1a).[15] The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/petroleum ether 1:1) to give **1a** (12.2 g, 86.7%) as a colorless liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 − 7.89 (m, 2H), 7.58−7.50 (m, 1H), 7.36−7.45 (m, 2H), 3.74 (s, 1H), 3.70 (s, 3H), 3.59 (d, J = 22.6 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.7, 136.3, 133.7, 128.9, 128.6, 53.0, 38.0, 36.7.

Diethyl (2-Oxo-2-phenylethyl)phosphonate (1b).[16] The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/petroleum ether 1:4) to give **1b** (5.7 g, 82.2%) as a colorless liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01−7.96 (m, 2H), 7.59−7.53 (m, 1H), 7.54−7.26 (m, 2H), 4.15−4.06 (m, 4H), 3.60 (d, J = 23.6 Hz, 2H), 1.27−1.22 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.9, 127.8, 126.9, 125.3, 68.2, 61.3, 61.1, 36.2, 34.8, 15.8.

Diisopropyl (2-Oxo-2-phenylethyl)phosphonate (1c).[17] The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/petroleum ether 1:2) to give **1c** (6.8 g, 83.7%) as a colorless liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95−7.99 (m, 2H), 7.58−7.51 (m, 1H), 7.47−7.40 (m, 2H), 4.75−4.64 (m, 2H), 3.54 (d, J = 26.0 Hz, 2H), 1.24 (dd, J = 6.1, 3.0 Hz, 12H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.1, 136.6, 133.5, 129.1, 128.5, 71.5, 40.3, 39.0, 24.0, 23.8.

Dimethyl [2-(*o*-Methoxyphenyl)-2-oxoethyl]phosphonate (1d).[18] The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/petroleum ether 1:1) to give **1d** (12.0 g, 88.5%) as a yellow liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (dd, J = 7.8, 1.7 Hz, 1H), 7.49 (dd, J = 7.8, 1.7 Hz, 1H), 6.99 (ddd, J = 12.0, 9.2, 4.7 Hz, 2H), 3.93 (s, 3H), 3.80 (d, J = 21.6 Hz, 2H), 3.75 (s, 3H), 3.72 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.9, 158.6, 134.4, 130.9, 127.2, 120.7, 111.5, 55.5, 52.7, 42.2, 40.9.

Dimethyl [2-(*o*-Methylphenyl)-2-oxoethyl]phosphonate (1e).[18] The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/petroleum ether 1:2) to give **1e** (6.7 g, 85.2%) as a light yellow liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, J = 7.8 Hz, 1H), 7.42−7.38 (m, 1H), 7.31−7.25 (m, 2H), 3.77 (s, 3H), 3.74 (s, 3H), 3.60 (d, J = 22.4 Hz, 2H), 2.52 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.5, 138.7, 136.7, 131.8, 129.3, 125.5, 52.7, 40.4, 21.0.

Dimethyl [2-(*m*-Methylphenyl)-2-oxoethyl]phosphonate (1f). The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/petroleum ether 1:2) to give **1f** (4.6 g, 86.7%) as a yellow liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, J = 8.3 Hz, 2H), 7.28−7.21 (m, 2H), 3.76 (s, 3H), 3.73 (s, 3H), 3.59 (d, J = 22.6 Hz, 2H), 2.39 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.5, 138.1, 136.6, 134.1, 128.9, 128.2, 125.9, 52.7, 37.6, 20.8; HRMS (collected on an UPLC and Q-TOF MS spectrometer) calcd for $C_{11}H_{15}O_4P$ $(M + Na)^+$ 265.0606, found 265.0612.

Dimethyl [2-(*p*-Methylphenyl)-2-oxoethyl]phosphonate (1g).[18] The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/petroleum ether 1:1) to give **1g** (12.2 g, 86.5%) as a light yellow liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, J = 8.0 Hz, 2H), 7.25 (d, J = 8.0 Hz, 2H), 3.76 (s, 3H), 3.73 (s, 3H), 3.59 (d, J = 22.6 Hz, 2H), 2.38 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.2, 144.8, 133.9, 129.4, 129.3, 53.1, 38.1, 21.7.

Dimethyl [2-(*p*-Methoxyphenyl)-2-oxoethyl]phosphonate (1h).[18] The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/petroleum ether 1:1) to give **1h** (10.1 g, 78.9%) as a colorless liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, J = 8.8 Hz, 2H), 6.95 (d, J = 8.8 Hz, 2H), 3.87 (s, 3H), 3.78 (s, 3H), 3.75 (s, 3H), 3.58 (d, J = 22.6 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 189.7, 163.7, 131.0, 129.1, 113.5, 55.1, 52.7, 37.4, 36.4.

Dimethyl [2-(*p*-Fluorophenyl)-2-oxoethyl]phosphonate (1i).[19] The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/petroleum ether 1:3) to give **1i** (6.3 g, 88.0%) as a light yellow liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06−8.02 (m, 2H), 7.18−7.13 (m, 2H), 3.80 (s, 3H), 3.77 (s, 3H), 3.60 (d, J = 22.8 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.0, 167.2, 132.7, 131.6, 115.5, 52.9, 38.0, 36.7.

Dimethyl [2-(*p*-Chlorophenyl)-2-oxoethyl]phosphonate (1j).[19] The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/petroleum ether 1:2) to give **1j** (7.5 g, 88.9%) as a yellow liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, J = 8.8 Hz, 2H), 7.46 (d, J = 8.8 Hz, 2H), 3.79 (s, 3H), 3.76 (s, 3H), 3.60 (d, J = 22.8 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.3, 140.8, 134.8, 130.2, 128.7, 52.9, 37.9, 36.6.

Dimethyl [2-(*p*-Bromophenyl)-2-oxoethyl]phosphonate (1k).[17] The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/petroleum ether 1:1) to give **1k** (10.8 g, 86.3%) as a yellow liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, J = 8.6 Hz, 2H), 7.63 (d, J = 8.6 Hz, 2H), 3.79 (s, 3H), 3.76 (s, 3H), 3.60 (d, J = 22.8 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.6, 134.9, 131.8, 130.4, 129.0, 53.0, 38.0, 36.7.

Dimethyl [2-(*p*-Trifluoromethylphenyl)-2-oxoethyl]-phosphonate (1l).[18] The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/petroleum ether 1:1) to give **1l** (8.2 g, 91.0%) as a yellow liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (t, J = 1.7 Hz, 1H), 7.88 (ddd, J = 8.0, 2.1, 1.1 Hz, 1H), 7.57 (ddd, J = 8.0, 2.1, 1.1 Hz, 1H), 7.44 (t, J = 1.7 Hz, 1H), 3.80 (s, 3H), 3.77 (s, 3H), 3.60 (d, J = 22.8 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.8, 138.8, 134.9, 134.6, 134.3, 133.9, 129.8, 129.1, 125.4, 121.9, 52.9, 38.2.

Dimethyl (2-oxopropyl)phosphonate (1m).[4a] The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/petroleum ether 1:5) to give **1m** (26.7 g, 56.7%) as a colorless liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.79 (s, 3H), 3.77 (s, 3H), 3.09 (d, J = 22.8 Hz, 2H), 2.32 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.2, 52.6, 42.3, 37.6, 30.9.

Dimethyl (2-Oxobutyl)phosphonate (1n).[20] The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/petroleum ether 1:5) to give **1n** (7.5 g, 67.0%) as a colorless liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.62 (s, 3H), 3.59 (s, 3H), 2.93 (d, J = 22.8 Hz, 2H), 2.47 (q, J = 7.2 Hz, 2H), 0.88 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.9, 59.8, 52.6, 41.1, 7.1.

Dimethyl (3-Methyl-2-oxobutyl)phosphonate (1o).[21] The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/petroleum ether 1:5) to give **1o** (7.9 g, 88.0%) as a colorless liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.79 (s, 3H), 3.76 (s, 3H), 3.12 (d, J = 22.4 Hz, 2H), 2.81 (dd, J = 13.8, 6.9 Hz, 1H), 1.12 (s, 3H), 1.11 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 205.7, 52.9, 41.7, 39.5, 17.7.

Dimethyl (2-Oxoheptyl)phosphonate (1p).[20] The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/petroleum ether 1:5) to give **1p** (7.9 g, 87.1%) as a colorless liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.79 (s, 3H), 3.77 (s, 3H), 3.08 (d, J = 22.5 Hz, 2H), 3.05 (s, 1H), 2.60 (t, J = 7.3 Hz, 2H), 1.62−1.54 (m, 2H), 1.34−1.22 (m, 5H), 0.88 (t, J = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.9, 52.8, 43.9, 41.7, 40.4, 30.8, 22.8, 22.2, 13.7.

Dimethyl (2-Oxotridecyl)phosphonate (1q).[22] The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/petroleum ether 1:5) to give **1q** (5.4 g, 78.1%) as a colorless liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.66 (s, 3H), 3.63 (s, 3H), 2.95 (d, J = 22.7 Hz, 2H), 2.47 (t, J = 7.3 Hz, 2H), 1.11 (s, 18H), 0.73 (t, J = 6.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.6, 52.7, 52.6, 43.8, 41.5, 40.2, 31.5, 29.3, 29.2, 29.1, 29.0, 28.6, 23.6, 22.6, 13.8.

Dimethyl (2-Cyclohexyl-2-oxoethyl)phosphonate (1r).[20] The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/petroleum ether 1:4) to give **1r** (5.6 g, 87.0%) as a yellow liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.79 (s, 3H), 3.77 (s, 3H), 3.12 (d, J = 22.2 Hz, 2H), 2.60−2.51 (m, 1H), 1.89−1.83 (m, 2H), 1.81−1.75 (m, 2H), 1.38−1.14 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.2, 52.0, 50.6, 38.9, 27.4, 25.1, 24.7.

Dimethyl [2-Oxo-3-(*N*-*tert*-butoxycarbonylamino)propyl]-phosphonate (1s).[23] The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/petroleum ether 1:1) to give **1s** (7.8 g, 89.0%) as a colorless liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.27 (s, 1H), 4.13 (d, J = 5.2 Hz, 2H), 3.80 (s, 3H),

3.77 (s, 3H), 3.73 (d, J = 10.7 Hz, 1H), 3.12 (d, J = 22.8 Hz, 2H), 1.43 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.7, 155.5, 79.9, 53.1, 51.1, 39.2, 37.9, 28.1.

Dimethyl (1-Methylacetonyl)phosphonate (1t).[24] Iodomethane (4.7 g, 33.11 mmol) was added to a mixture of potassium carbonate (5.4 g, 39.13 mmol) and dimethyl (2-oxopropyl)-phosphonate (5.0 g, 30.10 mmol) in acetone (20 mL) at 0 °C. The mixture was stirred at 0 °C for 1 h, allowed to warm to room temperature, and stirred for a further 19 h. Aqueous saturated ammonium chloride solution (15 mL) was added, the organic solvents were removed by rotary evaporation, and the aqueous phase was extracted with ethyl acetate (4 × 30 mL). The combined organic solvents were dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography with petroleum ether and ethyl acetate to afford **1t** (4.1 g, 75.2%) as a light yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.76 (d, J = 11.0 Hz, 3H), 3.74 (d, J = 11.0 Hz, 3H), 3.30−3.11 (m, 1H), 2.31 (s, 3H), 1.45−1.32 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.5, 53.2, 47.3, 30.2, 10.7.

Dimethyl (1-Ethylacetonyl)phosphonate (1u). The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/petroleum ether 2:1) to give **1u** (4.5 g, 68.2%) as a light yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.75 (d, J = 11.0 Hz, 3H), 3.72 (d, J = 11.0 Hz, 3H), 3.21−3.06 (m, 1H), 2.29 (s, 3H), 1.42−1.35 (m, 2H), 1.34−1.22 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.5, 53.0, 47.3, 30.0, 20.2, 10.7; HRMS (collected on an UPLC and Q-TOF MS spectrometer) calcd for $C_7H_{15}O_4P$ $(M + H)^+$ 195.0786, found 195.0786.

Diethyl (1-Methylacetonyl)phosphonate (1v).[25] The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/petroleum ether 1:1) to give **1v** (3.5 g, 65.2%) as a light yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.09−4.02 (m, 4H), 3.20−3.07 (m, 1H), 2.27 (d, J = 4.3 Hz, 3H), 1.31−1.23 (m, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.6, 62.4, 47.9, 46.6, 30.2, 16.2, 10.6.

Dimethyl 1-Bromo-2-oxopropylphosphonate (1w).[4a] A 500 mL, three-necked, round-bottomed flask equipped with a Teflon-coated stirring bar, two pressure-equalizing dropping funnels was charged with dimethyl 2-oxopropylphosphonate (**1m**) (20.0 g, 0.12 mol) and THF (350 mL). The funnels were filled with 30% aqueous hydrogen peroxide (13.7 mL, 0.12 mol) and 40% aqueous hydrogen bromide (12.3 mL, 0.12 mol). The two solutions were then added to the THF solution of **1m** at 25 °C during 4 h. After the mixture was stirred at 25 °C for another 2 h, the solvent was evaporated under reduced pressure. The resulting residue was partitioned between ether (80 mL) and water (50 mL). The organic layer was extracted with four portions of water (50 mL). The combined aqueous layer were washed with ether (80 mL) and then partially saturated with sodium chloride (ca. 10.0 g). After being successively washed with hexane (80 mL) and a 1:1 hexane−ether mixture (80 mL) and then saturated with sodium chloride (ca. 10.0 g), the aqueous layer was extracted with five 50-mL portions of ether. Drying of the combined organic layers over anhydrous sodium sulfate and evaporation of the solvent afforded a yellow oil. Distillation (95−100 °C/0.01 mmHg) gave **1w** (17.5 g, 59.3%) as a light yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.36 (d, J = 15.1 Hz, 1H), 3.76 (s, 3H), 3.73 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.5, 54.7, 54.5, 44.0, 27.5, 13.8.

Typical Procedure for the Asymmetric Hydrogenation. To a 20 mL Schlenk tube were added $[RuCl_2(benzene)]_2$ (5.0 mg, 0.01 mmol) and (S)-SunPhos (15.0 mg, 0.02 mmol). The tube was vacuumed and purged with nitrogen three times before addition of freshly distilled and freeze−thaw−degassed $EtOH/CH_2Cl_2$ (2 mL/2 mL). The resulting mixture was heated at 50 °C for 1.5 h and then cooled to room temperature. The solvent was removed under reduced pressure to give the catalyst as a yellow solid. The catalyst was dissolved in degassed MeOH (8 mL), and then the solution was equally divided into four vials. The β-ketophosphonates (1.00 mmol) were added to these vials, respectively, and were transferred to an autoclave. The autoclave was purged five times with H_2 and the required pressure of H_2 was set. The autoclave was stirred under specified reaction conditions. After being cooled to ambient temperature and careful release of the hydrogen, the autoclave was opened and the solvent was evaporated. The enantiomeric excess was determined by HPLC after passing the residue through a short pad of silica gel column with petroleum ether and ethyl acetate.

Dimethyl 2-Hydroxy-2-phenylethylphosphonate (2a).[25] The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/petroleum ether 2:1) to give **2a** (226.0 mg, 98.3%) as a colorless liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29−7.11 (m, 5H), 4.97 (t, J = 9.7 Hz, 1H), 4.57 (d, J = 3.6 Hz, 1H), 3.56 (s, 3H), 3.50 (s, 3H), 2.22−1.97 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.0, 128.2, 127.3, 125.4, 68.4, 52.3, 35.5; HPLC (Chiralcel OB-H column, hexane/i-PrOH 96/4, 1.0 mL min^{-1}, 220 nm): t_1 = 17.9 min (major), t_2 = 26.9 min (minor).

Diethyl 2-Hydroxy-2-phenylethylphosphonate (2b).[26] The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/petroleum ether 3:1) to give **2b** (250.0 mg, 97.0%) as a colorless liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (d, J = 7.5 Hz, 2H), 7.13 (d, J = 7.5 Hz, 2H), 7.05 (dd, J = 10.3, 4.2 Hz, 1H), 4.92−4.84 (m, 1H), 4.75 (d, J = 3.4 Hz, 1H), 3.85−3.70 (m, 4H), 2.13−1.87 (m, 2H), 1.04 (t, J = 7.1 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.9, 127.8, 126.9, 125.3, 68.2, 61.3, 36.2, 15.8; HPLC (Chiralcel AS-H column, hexane/i-PrOH 90/10, 0.6 mL min^{-1}, 220 nm) t_1 = 12.3 min (major), t_2 = 13.9 min (minor).

Diisopropyl 2-Hydroxy-2-phenylethylphosphonate (2c).[3h] The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/petroleum ether 3:1) to give **2c** (280.0 mg, 98.0%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.24 (m, 5H), 5.07 (ddd, J = 12.8, 6.3, 2.3 Hz, 1H), 4.80−4.64 (m, 2H), 4.23−4.19 (m, 1H), 2.17−2.10 (m, 2H), 1.32 (ddd, J = 23.7, 11.9, 5.1 Hz, 12H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.5, 128.4, 127.5, 125.4, 70.8, 70.7, 70.6, 68.7, 37.7, 36.4, 24.0; HPLC (Chiralcel AD-H column, hexane/i-PrOH 97/3, 0.4 mL min^{-1}, 220 nm) t_1 = 50.3 min (minor), t_2 = 54.9 min (major).

Dimethyl [2-Hydroxy-2-(2-methoxyphenyl)ethyl]-phosphonate (2d).[27] The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/petroleum ether 3:1) to give **2d** (256.0 mg, 98.5%) as a light yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (dd, J = 7.6, 1.4 Hz, 1H), 7.23 (ddd, J = 9.5, 6.8, 2.8 Hz, 1H), 6.96 (td, J = 7.5, 0.8 Hz, 1H), 6.84 (d, J = 8.2 Hz, 1H), 5.36−5.26 (m, 1H), 3.82 (s, 3H), 3.74 (s, 3H), 3.71 (s, 3H), 2.39−2.13 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.5, 128.4, 127.5, 125.4, 70.8, 70.7, 68.7, 37.7, 36.4, 24.0; HPLC (Chiralcel AD-H column, hexane/i-PrOH 97/3, 0.4 mL min^{-1}, 220 nm) t_1 = 27.7 min (minor), t_2 = 35.2 min (major).

Dimethyl [2-Hydroxy-2-(2-methylphenyl)ethyl]-phosphonate (2e).[3h] The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/petroleum ether 2:1) to give **2e** (240.0 mg, 98.4%) as a light yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, J = 7.6 Hz, 1H), 7.14−6.97 (m, 3H), 5.24−5.15 (m, 1H), 4.40 (d, J = 3.5 Hz, 1H), 3.59 (s, 3H), 3.54 (s, 3H), 2.23 (s, 3H), 2.12−1.90 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.3, 134.0, 130.4, 127.4, 126.4, 125.3, 65.2, 52.7, 34.7, 19.0; HPLC (Chiralcel OB-H column, hexane/i-PrOH 90/10, 1.0 mL min^{-1}, 220 nm) t_1 = 7.5 min (major), t_2 = 23.5 min (minor).

Dimethyl [2-Hydroxy-2-(3-methylphenyl)ethyl]-phosphonate (2f).[3h] The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/petroleum ether 3:1) to give **2f** (238.0 mg, 97.5%) as a light yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.91 (ddd, J = 18.9, 14.1, 7.7 Hz, 4H), 4.80 (dd, J = 44.1, 7.6 Hz, 2H), 3.46−3.18 (m, 6H), 2.04 (d, J = 14.6 Hz, 4H), 1.88−1.71 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.0, 140.9, 136.1, 128.1, 124.9, 67.5, 51.6, 35.1, 20.2; HPLC (Chiralcel OB-H column, hexane/i-PrOH 98/2, 0.4 mL min^{-1}, 220 nm) t_1 = 65.4 min (major), t_2 = 76.2 min (minor).

Dimethyl [2-Hydroxy-2-(4-methylphenyl)ethyl]-phosphonate (2g).[3h] The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/petroleum ether 2:1) to give **2g** (240.0 mg, 98.5%) as a light yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10−7.01 (m, 2H), 6.92 (d, J = 6.5 Hz, 2H), 4.91−4.69 (m, 2H), 3.45−3.36 (m, 6H), 2.12 (d, J = 2.1 Hz, 3H), 2.09−1.83 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.0, 136.3,

128.4, 125.0, 67.7, 51.9, 35.2, 20.4; HPLC (Chiralcel OB-H column, hexane/*i*-PrOH 98/2, 0.4 mL min^{-1}, 220 nm) t_1 = 66.8 min (major), t_2 = 77.6 min (minor).

Dimethyl [2-Hydroxy-2-(4-methoxyphenyl)ethyl]-phosphonate (2h).[3h] The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/petroleum ether 3:1) to give **2h** (258.0 mg, 99.2%) as a light yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33−7.27 (m, 2H), 6.90−6.84 (m, 2H), 5.07 (t, *J* = 10.2 Hz, 1H), 3.79 (d, *J* = 1.1 Hz, 3H), 3.76−3.70 (m, 6H), 2.30−2.10 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.5, 135.9, 126.4, 113.2, 67.7, 54.7, 52.0, 35.3; HPLC (Chiralcel OB-H column, hexane/*i*-PrOH 96/4, 0.3 mL min^{-1}, 220 nm) t_1 = 63.5 min (major), t_2 = 75.1 min (minor).

Dimethyl [2-hydroxy-2-(4-fluorophenyl)ethyl]phosphonate (2i).[3h] The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/petroleum ether 2:1) to give **2i** (240.0 mg, 96.8%) as a light yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33−7.27 (m, 2H), 6.96 (td, *J* = 8.7, 1.6 Hz, 2H), 5.02 (dd, *J* = 11.6, 8.0 Hz, 1H), 4.46 (s, 1H), 3.66−3.61 (m, 6H), 2.25−2.02 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.4, 160.9, 139.7, 139.6, 127.5, 127.3, 115.3, 115.1, 68.1, 68.0, 52.6, 35.8; HPLC (Chiralcel OB-H column, hexane/*i*-PrOH 96/4, 1.0 mL min^{-1}, 220 nm) t_1 = 19.8 min (major), t_2 = 32.6 min (minor).

Dimethyl [2-Hydroxy-2-(4-chlorophenyl)ethyl]phosphonate (2j).[3h] The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/petroleum ether 3:1) to give **2j** (260.0 mg, 98.5%) as a light yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (dd, *J* = 5.6, 2.9 Hz, 4H), 4.92 (d, *J* = 3.4 Hz, 1H), 4.79 (s, 1H), 3.61−3.43 (m, 6H), 2.19−1.88 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.6, 132.9, 128.2, 126.8, 67.7, 52.4, 35.4; HPLC (Chiralcel OB-H column, hexane/*i*-PrOH 96/4, 1.0 mL min^{-1}, 220 nm) t_1 = 19.5 min (major), t_2 = 25.7 min (minor).

Dimethyl [2-Hydroxy-2-(4-bromophenyl)ethyl]phosphonate (2k).[3h] The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/petroleum ether 3:1) to give **2k** (306.0 mg, 99.5%) as a light yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26−7.21 (m, 2H), 7.06 (d, *J* = 8.4 Hz, 2H), 4.99 (s, 1H), 4.82 (t, *J* = 9.2 Hz, 1H), 3.45−3.38 (m, 6H), 2.09−1.84 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.2, 131.0, 127.1, 120.8, 67.5, 52.4, 35.2; HPLC (Chiralcel OB-H column, hexane/*i*-PrOH 97/3, 1.0 mL min^{-1}, 220 nm) t_1 = 28.8 min (major), t_2 = 37.4 min (minor).

Dimethyl [2-Hydroxy-2-(4- trifuoromethylphenyl)ethyl]-phosphonate (2l). The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/petroleum ether 5:1) to give **2l** (290.0 mg, 97.3%) as a light yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.2 Hz, 2H), 7.52−7.46 (m, 2H), 5.17 (dt, *J* = 14.4, 3.4 Hz, 1H), 4.35−4.29 (m, 1H), 3.76−3.69 (m, 6H), 2.26−2.09 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.7, 130.2, 129.9, 129.5, 125.9, 125.7, 125.6, 68.3, 52.9, 35.7; HRMS (collected on an UPLC and Q-TOF MS spectrometer): calcd for $C_{11}H_{14}F_3O_4P$ (M + Na)$^+$ 321.0479, found 321.0480; HPLC (Chiralcel OD-H column, hexane/*i*-PrOH 90/10, 0.8 mL min^{-1}, 220 nm) t_1 = 19.8 min (minor), t_2 = 24.5 min (major).

Dimethyl (2-Hydroxypropyl)phosphonate (2m).[4a] The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/petroleum ether 2:1) to give **2m** (160.0 mg, 95.3%) as a light yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.20 (s, 1H), 3.82−3.69 (m, 6H), 3.36 (s, 1H), 1.99−1.89 (m, 2H), 1.32−1.25 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 62.0, 51.9, 34.4, 23.9.

Dimethyl (2-Hydroxybutyl)phosphonate (2n).[28] The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/petroleum ether 2:1) to give **2n** (178.0 mg, 97.8%) as a light yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.80 (s, 2H), 3.65 (s, 3H), 3.62 (s, 3H), 1.88−1.76 (m, 2H), 1.48−1.38 (m, 2H), 0.82 (dd, *J* = 12.3, 4.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 67.3, 52.0, 32.5, 30.9, 30.7, 9.4.

Dimethyl (2-Hydroxy-3-methylbutyl)phosphonate (2o).[4a] The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/petroleum ether 3:1) to give **2o** (190.0 mg, 97.0%) as a light yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.78−3.74 (m, 6H), 3.26 (d, *J* = 3.0 Hz, 1H), 1.99−1.80 (m, 3H), 1.73 (dd, *J* = 12.9, 6.6 Hz, 1H), 0.92 (dd, *J* = 6.7, 5.8 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 70.8, 52.4, 34.2, 29.9, 17.9, 17.3.

Dimethyl (2-Hydroxyheptyl)phosphonate (2p).[4a] The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/petroleum ether 3:1) to give **2p** (220.0 mg, 98.2%) as a light yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.10−3.90 (m, 1H), 3.78−3.74 (m, 6H), 3.26 (d, *J* = 3.2 Hz, 1H), 2.02−1.96 (m, 2H), 1.60−1.54 (m, 1H), 1.45 (dd, *J* = 9.5, 3.9 Hz, 2H), 1.36−1.28 (m, 6H), 0.90 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 66.2, 52.2, 38.2, 33.1, 31.5, 24.9, 22.4, 13.8.

Dimethyl (2-Hydroxytridecyl)phosphonate (2q).[22] The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/petroleum ether 3:1) to give **2q** (304.0 mg, 98.7%) as a light yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.99 (s, 1H), 3.77−3.74 (m, 6H), 3.29 (s, 1H), 1.99−1.84 (m, 2H), 1.66−1.38 (m, 4H), 1.25 (s, 19H), 0.87 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 66.5, 52.4, 38.3, 38.1, 33.1, 31.8, 29.6, 29.5, 29.4, 29.3, 25.3, 22.6, 14.0.

Dimethyl (2-Hydroxycyclohexyl)phosphonate (2r).[22] The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/petroleum ether 3:1) to give **2r** (230.0 mg, 97.5%) as a light yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.78 (s, 3H), 3.75 (s, 3H), 3.21 (d, *J* = 3.1 Hz, 1H), 2.02−1.88 (m, 2H), 1.87−1.73 (m, 4H), 1.44−1.35 (m, 1H), 1.26−0.98 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 69.8, 52.0, 51.9, 51.8, 51.7, 44.0, 43.8, 29.9, 28.2, 27.3, 26.0, 25.7, 25.6.

Dimethyl 2-Hydroxy-3-(*N*-*tert*-butoxycarbonylamino)-phosphonate (2s).[6b] The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/petroleum ether 3:1) to give **2s** (280.0 mg, 98.9%) as a light yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.26 (s, 1H), 4.09−4.04 (m, 1H), 3.74−3.69 (m, 6H), 3.30 (s, 1H), 3.11 (dd, *J* = 13.4, 6.4 Hz, 1H), 2.01−1.88 (m, 3H), 1.40 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.5, 79.4, 66.0, 52.5, 46.7, 30.4, 29.0, 28.2.

Dimethyl (3-Hydroxybut-2-yl)phosphonate (2t). The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/petroleum ether 4:1) to give **2t** (178.0 mg, 97.8%) as a light yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.93 (ddd, *J* = 10.6, 8.1, 4.5 Hz, 1H), 3.90−3.74 (m, 6H), 2.05−1.88 (m, 1H), 1.80 (s, 1H), 1.24 (dd, *J* = 9.1, 3.1 Hz, 3H), 1.15−1.09 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 67.7, 66.0, 52.9, 21.1, 11.0; HRMS (collected on an UPLC and Q-TOF MS spectrometer) calcd for $C_6H_{15}O_4P$ (M + Na)$^+$ 205.0606, found 205.0606.

Dimethyl (2-Hydroxypentan-3-yl)phosphonate (2u). The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/petroleum ether 4:1) to give **2u** (185.0 mg, 94.4%) as a light yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.20 (s, 1H), 4.00−3.88 (m, 1H), 3.78 (s, 3H), 3.76 (s, 3H), 1.24 (dd, *J* = 8.8, 3.2 Hz, 3H), 1.18 (d, *J* = 18.6 Hz, 3H), 1.13−1.06 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 67.4, 65.8, 52.4, 39.2, 29.6, 10.7.; HRMS (collected on an UPLC and Q-TOF MS spectrometer) calcd for $C_7H_{17}O_4P$ (M + Na)$^+$ 219.0762, found 219.0762.

Diethyl 3-Hydroxybut-2-ylphosphonate (2v).[29] The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/petroleum ether 3:1) to give **2v** (206.0 mg, 98.1%) as a light yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.13−4.05 (m, 4H), 3.90 (d, *J* = 4.7 Hz, 1H), 2.42 (s, 1H), 1.95−1.77 (m, 1H), 1.33−1.26 (m, 6H), 1.19 (dd, *J* = 9.7, 6.0 Hz, 3H), 1.12−1.02 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 67.2, 61.8, 38.2, 20.6, 16.3, 7.0.

Dimethyl 1-Bromo-2-hydroxypropylphosphonate (2w).[4a] The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/petroleum ether 3:1) to give **2w** (210.0 mg, 85.0%) as a light yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.16 (dt, *J* = 11.9, 6.2 Hz, 1H), 3.74 (t, *J* = 1.8 Hz, 1H), 3.73−3.70 (m, 6H), 1.25 (dd, *J* = 6.2, 2.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 62.1, 51.9, 34.7, 24.0.

Typical Procedure for the Preparation 3m−u. A 25 mL round flask was charged with **2m** (168.0 mg, 1.0 mmol), triethylamine (303.2 mg, 3.00 mmol), 4-nitrobenzoyl chloride (185.6 mg, 1.50 mmol), DMAP (24.4 mg, 0.20 mmol), and CH_2Cl_2 (10 mL). The mixture was

stirred at 26−30 °C for 8 h, saturated aqueous $NaHCO_3$ solution (6 mL) was added, and the organic layer was separated. The organic layer was washed with water and brine, dried over Na_2SO_4, filtered, and evaporated in vacuo. The residue was purified by column chromatography with petroleum ether and ethyl acetate to give compound 1-(dimethoxyphosphoryl)propan-2-yl 4-nitrobenzoate (**3m**, 254.0 mg, 80.1%) as a light yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29−8.24 (m, 2H), 8.23−8.16 (m, 2H), 5.45−5.42 (m, 1H), 3.73−3.68 (m, 6H), 2.36−2.10 (m, 2H), 1.52 (dd, *J* = 6.3, 0.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.7, 150.4, 135.5, 130.7, 123.4, 67.8, 52.5, 32.4, 31.0, 21.1; HRMS (collected on an UPLC and Q-TOF MS spectrometer) calcd for $C_{12}H_{16}NO_7P$ (M + H)$^+$ 318.0743, found 318.0743; HPLC (Chiralcel AD-H column, hexane/*i*-PrOH 85/15, 1.0 mL min^{-1}, 254 nm) t_1 = 14.6 min (major), t_2 = 16.1 min (minor).

1-(Dimethoxyphosphoryl)butan-2-yl 4-Nitrobenzoate (3n). The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/petroleum ether 1:8) to give **3n** (258.0 mg, 77.9%) as a light yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30−8.26 (m, 2H), 8.22 (d, *J* = 9.0 Hz, 2H), 5.42−5.31 (m, 1H), 3.73−3.67 (m, 6H), 2.35−2.13 (m, 2H), 1.88 (dd, *J* = 14.4, 7.2 Hz, 2H), 0.98 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.9, 150.4, 135.6, 130.7, 123.5, 115.8, 52.5, 30.2, 28.8, 28.0, 9.3; HRMS (collected on an UPLC and Q-TOF MS spectrometer): calcd for $C_{13}H_{18}NO_7P$ (M + Na)$^+$ 354.0719, found 354.0719; HPLC (Chiralcel AD-H column, hexane/*i*-PrOH 90/10, 1.0 mL min^{-1}, 254 nm) t_1 = 20.0 min (major), t_2 = 25.5 min (minor).

1-(Dimethoxyphosphoryl)-3-methylbutan-2-yl 4-Nitrobenzoate (3o). The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/petroleum ether 1:8) to give **3o** (260.0 mg, 74.7%) as a light yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30−8.23 (m, 2H), 8.23−8.17 (m, 2H), 5.33−5.30 (m, 1H), 3.73−3.57 (m, 6H), 2.29−2.05 (m, 3H), 0.97 (td, *J* = 7.9, 2.8 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.8, 150.1, 135.6, 130.6, 123.4, 74.2, 52.5, 32.2, 32.1, 27.6, 26.2, 18.1, 17.0; HRMS (collected on an UPLC and Q-TOF MS spectrometer): calcd for $C_{14}H_{20}NO_7P$ (M + H)$^+$ 346.1056, found 346.1056; HPLC (Chiralcel AD-H column, hexane/*i*-PrOH 85/15, 1.0 mL min^{-1}, 254 nm) t_1 = 12.3 min (major), t_2 = 13.9 min (minor).

1-(Dimethoxyphosphoryl)heptan-2-yl 4-Nitrobenzoate (3p). The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/petroleum ether 1:8) to give **3p** (250.0 mg, 67.0%) as a light yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, *J* = 9.0 Hz, 2H), 8.19 (d, *J* = 9.0 Hz, 2H), 5.43−5.33 (m, 1H), 3.70−3.64 (m, 6H), 2.26−2.16 (m, 2H), 1.87−1.74 (m, 2H), 1.40−1.24 (m, 6H), 0.86−0.80 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.9, 150.3, 135.5, 130.6, 123.4, 70.7, 52.4, 52.3, 34.9, 31.2, 30.5, 29.1, 24.6, 22.3, 13.8; HRMS (collected on an UPLC and Q-TOF MS spectrometer) calcd for $C_{16}H_{24}NO_7P$ (M + H)$^+$ 374.1369, found 374.1369; HPLC (Chiralcel AD-H column, hexane/*i*-PrOH 90/10, 0.6 mL min^{-1}, 254 nm) t_1 = 29.6 min (major), t_2 = 33.6 min (minor).

1-(Dimethoxyphosphoryl)tridecan-2-yl 4-Nitrobenzoate (3q). The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/petroleum ether 1:6) to give **3q** (289.0 mg, 63.2%) as a light yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29−8.26 (m, 2H), 8.21 (d, *J* = 8.9 Hz, 2H), 5.40 (dt, *J* = 12.2, 6.2 Hz, 1H), 3.72−3.67 (m, 6H), 2.33−2.23 (m, 2H), 1.87−1.79 (m, 2H), 1.25 (d, *J* = 18.6 Hz, 18H), 0.85 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.9, 150.5, 135.6, 130.7, 127.3, 123.5, 70.9, 52.5, 35.0, 34.9, 31.8, 30.6, 29.5, 29.4, 29.3, 29.2, 29.1, 25.0, 22.6, 14.0; HRMS (collected on an UPLC and Q-TOF MS spectrometer) calcd for $C_{22}H_{36}NO_7P$ (M + H)$^+$ 458.2308, found 458.2308; HPLC (Chiralcel AD-H column, hexane/*i*-PrOH 90/10, 0.6 mL min^{-1}, 254 nm) t_1 = 17.6 min (major), t_2 = 20.2 min (minor).

1-Cyclohexyl-2-(dimethoxyphosphoryl)ethyl 4-Nitrobenzoate (3r). The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/petroleum ether 1:6) to give **3r** (301.0 mg, 78.2%) as a light yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, *J* = 9.0 Hz, 2H), 8.19 (d, *J* = 9.0 Hz, 2H), 5.31 (ddd, *J* = 8.5, 6.5, 3.9 Hz, 1H), 3.75 (s, 3H), 3.72 (s, 3H), 2.20 (s, 2H), 1.90−1.80 (m, 4H), 1.36−1.34 (m, 1H), 1.06 (ddd, *J* = 22.5, 12.3, 3.2 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.8, 159.5, 150.3, 135.6, 130.7, 123.4, 73.7, 70.3, 52.4, 44.2, 42.1, 30.1, 28.7, 28.6, 28.5, 27.8, 27.7, 27.6, 26.3, 26.0, 25.9, 25.7; HRMS (collected on an UPLC and Q-TOF MS spectrometer) calcd for $C_{17}H_{24}NO_7P$ (M + H)$^+$ 386.1369, found 386.1369; HPLC (Chiralcel AD-H column, hexane/*i*-PrOH 90/10, 0.6 mL min^{-1}, 254 nm) t_1 = 29.6 min (minor), t_2 = 32.8 min (major).

1-[(*tert*-Butoxycarbonyl)amino]-3-(dimethoxyphosphoryl)-propan-2-yl 4-Nitrobenzoate (3s). The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/petroleum ether 1:6) to give **3s** (320.0 mg, 75.8%) as a light yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (dd, *J* = 9.7, 7.5 Hz, 4H), 5.39 (dd, *J* = 10.4, 5.4 Hz, 1H), 5.09 (s, 1H), 3.72−3.64 (m, 6H), 3.61 (dd, *J* = 9.3, 5.3 Hz, 1H), 3.51 (dd, *J* = 13.7, 7.3 Hz, 1H), 2.37−2.20 (m, 2H), 1.36 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.8, 155.8, 150.5, 135.1, 130.8, 123.4, 79.6, 70.1, 52.5, 43.5, 28.1, 26.5; HRMS (collected on an UPLC and Q-TOF MS spectrometer): calcd for $C_{17}H_{25}N_2O_9P$ (M + H)$^+$ 433.1376, found 433.1389; HPLC (Chiralcel AD-H column, hexane/*i*-PrOH 85/15, 0.5 mL min^{-1}, 254 nm) t_1 = 36.9 min (minor), t_2 = 40.8 min (major).

3-(Dimethoxyphosphoryl)butan-2-yl 4-Nitrobenzoate (3t). The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/petroleum ether 1:8) to give **3t** (310.0 mg, 93.8%) as a light yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28−8.24 (m, 2H), 8.21 (dd, *J* = 9.0, 2.0 Hz, 2H), 5.45 (ddd, *J* = 9.2, 6.5, 4.8 Hz, 1H), 3.91 (dd, *J* = 12.8, 5.8 Hz, 1H), 3.78 (d, *J* = 11.0 Hz, 3H), 3.76 (d, *J* = 11.0 Hz, 3H), 2.45 (ddd, *J* = 22.4, 7.4, 4.8 Hz, 1H), 1.27 (s, 3H), 1.15 (d, *J* = 10.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.9, 150.4, 135.6, 130.7, 123.5, 71.9, 52.5, 28.8, 17.9, 9.3; HRMS (collected on an UPLC and Q-TOF MS spectrometer) calcd for $C_{13}H_{18}NO_7P$ (M + H)$^+$ 332.0899, found 332.0899; HPLC (Chiralcel IC-3 column, hexane/*i*-PrOH 85/15, 1.0 mL min^{-1}, 254 nm): t_1 = 11.8 min (minor), t_2 = 12.9 min (minor), t_3 = 16.7 min (major), t_4 = 22.4 min (minor).

3-(Dimethoxyphosphoryl)pentan-2-yl 4-Nitrobenzoate (3u). The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/petroleum ether 1:6) to give **3u** (312.0 mg, 90.1%) as a light yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, *J* = 9.0 Hz, 2H), 8.22 (d, *J* = 9.0 Hz, 2H), 5.35 (dd, *J* = 11.5, 5.6 Hz, 1H), 3.76 (d, *J* = 7.6 Hz, 1H), 3.70 (s, 3H), 3.68 (s, 3H), 1.88 (d, *J* = 7.2 Hz, 3H), 1.33−1.00 (m, 2H), 0.98 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.9, 150.5, 135.6, 130.7, 123.5, 71.9, 52.6, 30.2, 28.8, 17.4, 9.4; HRMS (collected on an UPLC and Q-TOF MS spectrometer) calcd for $C_{14}H_{20}NO_7P$ (M + H)$^+$ 346.1056, found 346.1056; HPLC (Chiralcel IC-3 column, hexane/*i*-PrOH 85/15, 1.0 mL min^{-1}, 254 nm) t_1 = 20.6 min (minor), t_2 = 23.1 min (minor), t_3 = 33.9 min (minor), t_4 = 40.8 min (major).

3-[(Diethoxyphosphoryl)butyl]-2-nitrobenzoate (3v). The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/petroleum ether 1:8) to give **3v** (301.0 mg, 83.8%) as a light yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.8 Hz, 2H), 8.04 (d, *J* = 8.8 Hz, 2H), 4.11 (s, 1H), 3.92−3.79 (m, 6H), 1.12 (s, 6H), 1.04 (s, 3H), 0.97 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.2, 150.1, 135.4, 130.3, 123.0, 66.5, 61.3, 39.1, 20.0, 16.0, 9.5; HRMS (collected on an UPLC and Q-TOF MS spectrometer) calcd for $C_{15}H_{22}NO_7P$ (M + H)$^+$ 360.1212, found 360.1220; HPLC (Chiralcel AD-H column, hexane/*i*-PrOH 95/5, 1.0 mL min^{-1}, 254 nm) t_1 = 20.0 min (minor), t_2 = 25.4 min (minor), t_3 = 26.7 min (major), t_4 = 39.8 min (minor).

Bromo 1-[(Dimethoxyphosphoryl)propan-2-yl]-4-nitrobenzoate (3w). The crude material was purified by column chromatography on silica gel (eluting with ethyl acetate/petroleum ether 1:8) to give **3w** (321.0 mg, 81.5%) as a light yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25−8.20 (m, 2H), 8.18−8.12 (m, 2H), 5.44−5.42 (m, 1H), 3.72−3.68 (m, 6H), 2.40−2.30 (m, 1H), 2.17−2.10 (m, 1H), 1.50 (dd, *J* = 6.3, 0.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.7, 150.4, 135.5, 130.7, 123.4, 67.8, 52.5, 32.4, 31.0, 21.1; HRMS (collected on an UPLC and Q-TOF MS spectrometer): calcd for $C_{12}H_{15}BrNO_7P$ (M + H)$^+$ 395.9848, found 395.9870; HPLC

(Chiralcel AD-H column, hexane/*i*-PrOH 80/20, 0.4 mL min^{-1}, 254 nm) t_1 = 18.0 min (minor), t_2 = 20.3 min (major), t_3 = 22.5 min (minor), t_4 = 27.6 min (minor).

■ ASSOCIATED CONTENT

Supporting Information

NMR and/or HPLC data of compounds **1**−**3**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: zhaoguo@sjtu.edu.cn.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the National Natural Science Foundation of China, the Science and Technology Commission of Shanghai Municipality, and the Education Commission of Shanghai Municipality for financial support.

■ REFERENCES

(1) (a) Wynberg, H.; Smaardijk, A. A. *Tetrahedron Lett.* **1983**, *24*, 5899−5900. (b) Huber, R.; Knierzinger, A.; Obrecht, J.-P.; Vasella, A. *Helv. Chim. Acta* **1985**, *68*, 1730−1747. (c) Seebach, D.; Charczuk, R.; Gerber, C.; Renaud, P.; Berner, H.; Schneider, H. *Helv. Chim. Acta* **1989**, *72*, 401−425. (d) Sawamura, M.; Ito, Y.; Hayashi, T. *Tetrahedron Lett.* **1989**, *30*, 2247−2250. (e) Groth, U.; Richter, L.; Schöllkopf, U. *Tetrahedron* **1992**, *48*, 117−122. (f) Yokomatsu, T.; Yamagishi, T.; Shibuya, S. *Tetrahedron: Asymmetry* **1993**, *4*, 1783−1784. (g) Li, Y.-F.; Hammerschmidt, F. *Tetrahedron: Asymmetry* **1993**, *4*, 109−120. (h) Yager, K. M.; Taylor, C. M.; Smith, A. B. *J. Am. Chem. Soc.* **1994**, *116*, 9377−9378.

(2) (a) Wróblewski, A. E.; Halajewska-Wosik, A. *Tetrahedron: Asymmetry* **2004**, *15*, 3201−3205. (b) Dellaria, J. F.; Maki, R. G.; Stein, H. H.; Cohen, J.; Whittern, D.; Marsh, K.; Hoffman, D. J.; Plattner, J. J.; Perun, T. J. *J. Med. Chem.* **1990**, *33*, 534−542. (c) Cui, P.; Tomsig, J. L.; McCalmont, W. F.; Lee, S.; Becker, C. J.; Lynch, K. R.; Macdonald, T. L. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1634−1640. (d) Hashimoto, M.; Hemmi, K.; Takeno, H.; Kamiya, T. *Tetrahedron Lett.* **1980**, *21*, 99−102. (e) Dellaria, J. F., Jr; Maki, R. G. *Tetrahedron Lett.* **1986**, *27*, 2337−2340. (f) Sampson, N. S.; Bartlett, P. A. *J. Org. Chem.* **1988**, *53*, 4500−4503. (g) Wu, G.; Wong, Y.; Chen, X.; Ding, Z. *J. Org. Chem.* **1999**, *64*, 3714−3718.

(3) (a) Guanti, G.; Zannetti, M. T.; Banfi, L.; Riva, R. *Adv. Synth. Catal.* **2001**, *343*, 682−691. (b) Żurawiński, R.; Nakamura, K.; Drabowicz, J.; Kiełbasiński, P.; Mikołajczyk, M. *Tetrahedron: Asymmetry* **2001**, *12*, 3139−3145. (c) Zhang, Y.; Yuan, C.; Li, Z. *Tetrahedron* **2002**, *58*, 2973−2978. (d) Mikołajczyk, M.; Łuczak, J.; Kiełbasinski, P. *J. Org. Chem.* **2002**, *67*, 7872−7875. (e) Pàmies, O.; Bäckvall, J.-E. *J. Org. Chem.* **2003**, *68*, 4815−4818. (f) Ordóñez, M.; González-Morales, A.; Ruíz, C.; Cruz-Cordero, R. D. l.; Fernández-Zertuche, M. *Tetrahedron: Asymmetry* **2003**, *14*, 1775−1779. (g) Rojas-Cabrera, H.; Fernández-Zertuche, M.; García-Barradas, O.; Muñoz-Muñiz, O.; Ordóñez, M. *Tetrahedron: Asymmetry* **2007**, *18*, 142−148. (h) Moriyama, A.; Matsumura, S.; Kuriyama, M.; Onomura, O. *Tetrahedron: Asymmetry* **2010**, *21*, 810−824. (i) Meier, C.; Laux, W. H. G. *Tetrahedron* **1996**, *52*, 589−598. (j) Nesterov, V. V.; Kolodiazhnyi, O. I. *Tetrahedron* **2007**, *63*, 6720−6731.

(4) (a) Kitamura, M.; Tokunaga, M.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 2931−2932. (b) Kitamura, M.; Tokunaga, M.; Pham, T.; Lubell, W. D.; Noyori, R. *Tetrahedron Lett.* **1995**, *36*, 5769−5772.

(5) (a) Gautier, I.; Ratovelomanana-Vidal, V.; Savignac, P.; Genêt, J.-P. *Tetrahedron Lett.* **1996**, *37*, 7721−7724. (b) Madec, J.; Pfister, X.; Phansavath, P.; Ratovelomanana-Vidal, V.; Genêt, J.-P. *Tetrahedron* **2001**, *57*, 2563−2568.

(6) (a) Vargas, S.; Suárez, A.; Álvarez, E.; Pizzano, A. *Chem.—Eur. J.* **2008**, *14*, 9856−9859. (b) Chávez, M. Á.; Vargas, S.; Suárez, A.; Álvarez, E.; Pizzano, A. *Adv. Synth. Catal.* **2011**, *353*, 2775−2794.

(7) (a) You, J.; Drexler, H.-J.; Zhang, S.; Fischer, C.; Heller, D. *Angew. Chem., Int. Ed.* **2003**, *42*, 913−916. (b) Hu, X.-P.; Zheng, Z. *Org. Lett.* **2005**, *7*, 419−422. (c) Zhu, G.; Chen, Z.; Zhang, X. *J. Org. Chem.* **1999**, *64*, 6907−6910.

(8) Rubio, M.; Suarez, A.; Alvarez, E.; Pizzano, A. *Chem. Commun.* **2005**, 628−630.

(9) (a) Sun, Y.; Wan, X.; Guo, M.; Wang, D.; Dong, X.; Pan, Y.; Zhang, Z. *Tetrahedron: Asymmetry* **2004**, *15*, 2185−2188. (b) Wan, X.; Sun, Y.; Luo, Y.; Li, D.; Zhang, Z. *J. Org. Chem.* **2005**, *70*, 1070−1072. (c) Sun, Y.; Wan, X.; Wang, J.; Meng, Q.; Zhang, H.; Jiang, L.; Zhang, Z. *Org. Lett.* **2005**, *7*, 5425−5427. (d) Wan, X.; Meng, Q.; Zhang, H.; Sun, Y.; Fan, W.; Zhang, Z. *Org. Lett.* **2007**, *9*, 5613−5616. (e) Sun, X.; Zhou, L.; Li, W.; Zhang, X. *J. Org. Chem.* **2008**, *73*, 1143−1146. (f) Meng, Q.; Sun, Y.; Ratovelomanana-Vidal, V.; Genêt, J. P.; Zhang, Z. *J. Org. Chem.* **2008**, *73*, 3842−3847. (g) Meng, Q.; Zhu, L.; Zhang, Z. *J. Org. Chem.* **2008**, *73*, 7209−7212. (h) Zhu, L.; Meng, Q.; Fan, W.; Xie, X.; Zhang, Z. *J. Org. Chem.* **2010**, *75*, 6027−6030. (i) Yao, Y.; Fan, W.; Li, W.; Ma, X.; Zhu, L.; Xie, X.; Zhang, Z. *J. Org. Chem.* **2011**, *76*, 2807−2813. (j) Fan, W.; Li, W.; Ma, X.; Tao, X.; Li, X.; Yao, Y.; Xie, X.; Zhang, Z. *J. Org. Chem.* **2011**, *76*, 9444−9451. (k) Tao, X.; Li, W.; Ma, X.; Li, X.; Fan, W.; Xie, X.; Ayad, T.; Ratovelomanana-Vidal, V.; Zhang, Z. *J. Org. Chem.* **2012**, *77*, 612−616. (l) Fan, W.; Li, W.; Ma, X.; Tao, X.; Li, X.; Yao, Y.; Xie, X.; Zhang, Z. *Chem. Commun.* **2012**, *48*, 4247−4249. (m) Ma, X.; Li, W.; Li, X.; Tao, X.; Fan, W.; Xie, X.; Ayad, T.; Ratovelomanana-Vidal, V.; Zhang, Z. *Chem. Commun.* **2012**, *48*, 5352−5354. (n) Li, W.; Ma, X.; Fan, W.; Tao, X.; Li, X.; Xie, X.; Zhang, Z. *Org. Lett.* **2011**, *13*, 3876−3879.

(10) (a) Zhang, Z.; Qian, H.; Longmire, J.; Zhang, X. *J. Org. Chem.* **2000**, *65*, 6223−6226. (b) Saito, T.; Yokozawa, T.; Ishizaki, T.; Moroi, T.; Sayo, N.; Miura, T.; Kumobayashi, H. *Adv. Synth. Catal.* **2001**, *343*, 264−267. (c) Wu, S.; Wang, W.; Tang, W.; Lin, M.; Zhang, X. *Org. Lett.* **2002**, *4*, 4495−4497. (d) de Paule, S. D.; Jeulin, S.; Ratovelomanana-Vidal, V.; Genêt, J.-P.; Champion, N.; Dellis, P. *Eur. J. Org. Chem.* **2003**, *2003*, 1931−1941. (e) Kakei, H.; Nemoto, T.; Ohshima, T.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 317−320.

(11) Tsutsumi, K.; Katayama, T.; Utsumi, N.; Murata, K.; Arai, N.; Kurono, N.; Ohkuma, T. *Org. Process Res. Dev.* **2009**, *13*, 625−628.

(12) Casy, A. F.; Drake, A. F.; Ganellin, C. R.; Mercer, A. D.; Upton, C. *Chirality* **1992**, *4*, 356−366.

(13) The absolute configuration of **2t** was assigned as (1*R*,2*S*) on the basis of its optical rotation and NMR; see: Żymańczyk-Duda, E.; Lejczak, B.; Kafarski, P.; Grimaud, J.; Fischer, P. *Tetrahedron* **1995**, *51*, 11809−11814.

(14) Giordano, C.; Castaldi, G. *J. Org. Chem.* **1989**, *54*, 1470−1473.

(15) Maloney, K. M.; Chung, J. Y. L. *J. Org. Chem.* **2009**, *74*, 7574−7576.

(16) Kramer, S. r.; Dooleweerdt, K.; Lindhardt, A. T.; Rottlaìnder, M.; Skrydstrup, T. *Org. Lett.* **2009**, *11*, 4208−4211.

(17) Wei, W.; Ji, J.-X. *Angew. Chem., Int. Ed.* **2011**, *50*, 9097−9099.

(18) Milburn, R. R.; McRae, K.; Chan, J.; Tedrow, J.; Larsen, R.; Faul, M. *Tetrahedron Lett.* **2009**, *50*, 870−872.

(19) Friedrich, M.; Waechtler, A.; Meijere, A. d. *Synlett.* **2002**, *4*, 619−621.

(20) Grieco, P. A.; Pogonowski, C. S. *J. Am. Chem. Soc.* **1973**, *95*, 3071−3072.

(21) Gasteiger, J.; Herzig, C. *Tetrahedron Lett.* **1980**, *21*, 2687−2688.

(22) Balreddy, K.; Dong, L.; M. Simpson, D.; Titmas, R. *Tetrahedron Lett.* **1993**, *34*, 3037−3040.

(23) Chakravarty, P. K.; Combs, P.; Roth, A.; Greenlee, W. J. *Tetrahedron Lett.* **1987**, *28*, 611−612.

(24) Delarue-Cochin, S.; Panc, J.-J.; Dauteloup, A.; Hendra, F.; Pan, J.-J.; Angoh, R. G.; Joseph, D.; Stephens, P. J.; Cavé, C. *Tetrahedron: Asymmetry* **2007**, *18*, 685−691.

(25) Genov, D. G.; Tebby, J. C. *J. Org. Chem.* **1996**, *61*, 2454−2459.

(26) Wang, Z.; Wroblewski, A. E.; Verkade, J. G. *J. Org. Chem.* **1999**, *64*, 8021−8023.

(27) Zhang, Y.; Li, Z.; Yuan, C. *Tetrahedron Lett.* **2002**, *43*, 3247−3249.
(28) Pámies, O.; Bäckvall, J.-E. *J. Org. Chem.* **2003**, *68*, 4815−4818.
(29) Żymańczyk-Duda, E.; Lejczak, B.; Kafarski, P.; Grimaud, J.; Fischer, P. *Tetrahedron* **1995**, *51*, 11809−11814.