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Chiral Thiourea-Catalyzed Asymmetric Michael Addition of β-Oxo Phosphonate to Nitro Olefins: Convenient Synthesis of Optically Active β-Oxo Phosphonates

Kuang Hu,[a] Tao Liu,[a] A. D. Lu,[a] Yunfeng Liu,[a] Youming Wang,*[a] Guiping Wu,[a] Zhenghong Zhou,*[a] and Chuchi Tang[a]

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β-Oxo phosphonates have been proven to be alternative Michael donors in Michael addition reactions to nitro olefins in the presence of cinchonine-based bifunctional thiourea, affording a direct and atom-economic approach to the efficient construction of synthetically and biologically valuable chiral acyclic α-substituted β-oxo phosphonates with high levels of enantioselectivity (up to 98 % *ee*).

Introduction

Michael addition is one of the most fundamental carbon–carbon bond-forming reactions. Ever since their discovery, Michael addition reactions have been very popular among organic chemists.[1] When nitro olefins are used as the Michael acceptor, the reaction provides rapid access to synthetically valuable chiral nitroalkanes. Because of the multiple reactivity of the nitro functionality, the resulting adducts can be readily converted into versatile building blocks for the synthesis of important nitrogen-containing bioactive agrochemical and pharmaceutical compounds.[2] As a result, considerable effort has been devoted to the development of catalytic enantioselective versions of the process. In particular, intensive research aimed at achieving asymmetric Michael addition to nitro olefins by employing environmentally friendly organocatalysts has been carried out in recent years.[3] In these efforts, the Michael donors used were mainly limited to aldehydes,[4] ketones,[5] and 1,3-dicarbonyl compounds,[6] such as malonates, 1,3-diketones, and β-oxo esters. In contrast, until now, organocatalytic conjugate addition reactions using β-oxo phosphonates as Michael donors, which represent a direct approach to the efficient construction of chiral acyclic α-substituted β-oxo phosphonates, have rarely been studied. It is well known that β-oxo phosphonates are of great interest not only as precursors of β-amino and β-hydroxy phosphonates[7] but also as molecules of biological importance.[8] However, only two examples of an asymmetric synthesis of α-substituted β-oxo phosphonates have been reported. By using (*S*)-1-phenylethylamine as a chiral auxiliary, Delarue-Cochin et al. realized the diastereoselective Michael addition of chiral β-enamino phosphonate to various activated alkenes, which afforded α,α-disubstituted β-oxo phosphonates after removal of the chiral auxiliary.[9] Recently, Jørgensen and coworkers developed an alternative approach to the synthesis of enantiomerically enriched β-oxo phosphonates by a chiral diarylprolinol ether organocatalyzed domino Michael–Knoevenagel reaction of ethyl 4-(diethoxyphosphoryl)-3-oxobutanoate and α,β-unsaturated aldehydes.[10] Therefore, the development of a new convenient and atom-economic approach to optically active α-substituted β-oxo phosphonates is highly desirable. Herein we report the first organocatalyzed asymmetric Michael addition of simple β-oxo phosphonates to nitro olefins, which afforded valuable α-substituted β-oxo phosphonates in satisfactory yields with good to excellent enantioselectivities.

Results and Discussion

Similarly to 1,3-dicarbonyl compounds, the hydrogen atoms situated on the carbon atom between the carbonyl and phosphoryl groups in simple β-oxo phosphonates are unusually acidic and can be readily removed by base to form a nucleophilic enolate anion. We anticipated that bifunctional thioureas[11] should be particularly well suited as catalysts to the challenging Michael addition of simple β-oxo phosphonates to nitro olefins by simultaneous activation of the β-oxo phosphonate and nitro olefin through hydrogen-bonding interactions, because their general catalytic activity has been confirmed in numerous Michael additions of 1,3-dicarbonyl compounds to nitro olefins.[6] Thus, bifunctional amine–thioureas **1**–**5** with different chiral backbones were chosen as potential catalysts (Figure 1).

[a] State Key Laboratory of Elemento-Organic Chemistry, Institute of Elemento-Organic Chemistry, Nankai University, Tianjin 300071, P. R. China
Fax: +86-22-23508939
E-mail: z.h.zhou@nankai.edu.cn

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Their catalytic activity was evaluated in the reaction of β-nitrostyrene with diethyl (2-oxo-2-phenylethyl)phosphonate in the presence of 20 mol-% catalyst in toluene at 20 °C, and the results are collected in Table 1.

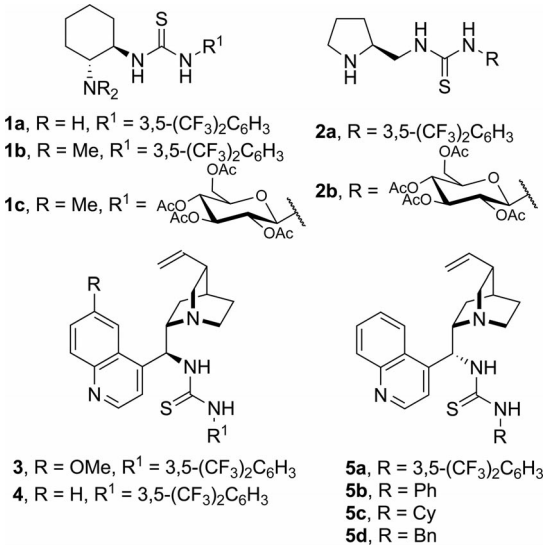
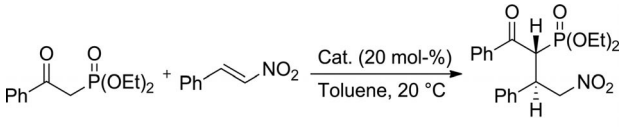


Figure 1. Different amine–thiourea organocatalysts.

Table 1. Catalyst evaluation in the β-oxo phosphonate addition to β-nitrostyrene.[a]



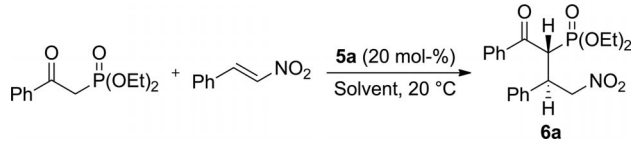
6a

Entry	Catalyst	Time [d]	Yield [%][b]	*dr*[c]	*ee* [%][d,e]
1	**1a**	5	81	1.1:1	19 (21)
2	**1b**	4.5	85	1.2:1	55 (78)
3	**1c**	5.5	83	1.2:1	67 (72)
4	**2a**	4.5	83	1.8:1	3 (3)
5	**2b**	5.5	82	2.5:1	11 (21)
6	**3**	4.5	83	1.5:1	48 (85)
7	**4**	4.5	85	1.6:1	65 (64)
8	**5a**	4.5	86	1.2:1	68 (69)
9	**5b**	5	83	1.6;1	60 (60)
10	**5c**	5	80	1.3:1	36 (41)
11	**5d**	5	82	1.4:1	57 (58)

[a] Reaction conditions: Nitro olefin (0.2 mmol), β-oxo phosphonate (0.4 mmol), toluene (0.6 mL). [b] Isolated yield. [c] Determined by ^{1}H and/or ^{31}P NMR spectroscopy. [d] Determined by chiral HPLC analysis. [e] Data in parentheses are the *ee* values of the minor diastereomer.

As shown in Table 1, all of the thioureas tested exhibited good catalytic activity in the model reaction. The corresponding Michael addition product, diethyl (4-nitro-1-oxo-1,3-diphenylbut-2-yl)phosphonate (**6a**), was obtained in good chemical yield (80–86%) in an acceptable reaction time. However, the type of thiourea catalyst used had an important influence on the enantioselectivity of the reaction. In general, tertiary amine–thioureas demonstrated much higher chiral induction ability than both primary and secondary amine–thiourea catalysts (Table 1, Entries 2, 3, 6–11 vs. Entries 1, 4, 5). In terms of enantioselectivity, (1*R*,2*R*)-cyclohexane-1,2-diamine-derived thiourea **1c**, cinchonidine-derived thiourea **4**, and cinchonine-based thiourea **5a** gave the best results (Table 1, Entries 3, 7, and 8; 67, 65, and 68% *ee* for the major diastereomer, respectively), with catalyst **5a** affording adduct **6a** in a shorter time. (1*R*,2*R*)-Cyclohexane-1,2-diamine-derived thiourea **1b** and quinine-based thiourea **3** were less effective (Table 1, Entries 2 and 6; 55 and 48% *ee*, respectively). Attempts to further improve the enantioselectivity of the reaction by changing the electronic characteristics of the *N*-substituent of catalyst **5a** failed (Table 1, Entry 8 vs. Entries 9–11). Thus, we chose thiourea **5a** as the catalyst for optimization of the reaction conditions, and the results are listed in Table 2.

Table 2. Optimization of the reaction conditions for the β-oxo phosphonate addition to β-nitrostyrene.[a]



6a

Entry	Solvent	Time [d]	Yield [%][b]	*dr*[c]	*ee* [%][d,e]
1	EtOH	2.5	82	3.3:1	–14 (64)
2	MeCN	3	83	1.8:1	73 (72)
3	EtOAc	4	81	1.7:1	74 (73)
4	THF	2.5	87	1.6:1	73 (71)
5	$CHCl_3$	3	84	1.6:1	72 (71)
6	$PhCH_3$	4.5	86	1.6:1	68 (69)
7	THF[f]	4	82	1.6:1	73 (74)
8	THF[g]	2	86	2.2:1	62 (55)
9	THF[h]	3.5	84	1.5:1	72 (70)

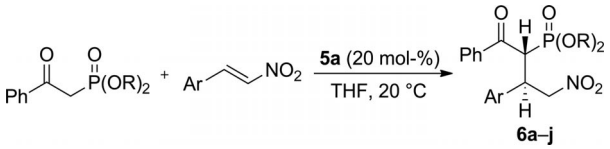
[a] Reaction conditions: Nitro olefin (0.2 mmol), β-oxo phosphonate (0.4 mmol), solvent (0.6 mL) at 20 °C. [b] Isolated yield. [c] Determined by ^{1}H and/or ^{31}P NMR spectroscopy. [d] Determined by chiral HPLC analysis. [e] Data in parentheses are the *ee* values of the minor diastereomer. [f] The reaction was carried out at 10 °C. [g] The reaction was carried out at 30 °C. [h] 15 mol-% of **5a** was used.

A survey of solvents revealed that all the reactions proceeded smoothly to provide the desired adduct with satisfactory results. With the exception of ethanol, in which the product **6a** was obtained with a much lower *ee* and reversed stereochemistry (Table 2, Entry 1), comparable enantioselectivities were observed for the major diastereomer in all the solvents tested (Table 2, Entries 2–6). With respect to both enantioselectivity and reaction time, THF is the optimal reaction solvent. Moreover, the reaction temperature was found to have a significant influence on the enantioselectivity of this reaction. Although the same *ee* was attained for the major diastereomer when lowering the reaction temperature to 10 °C, the reaction was much slower (Table 2, Entry 4 vs. Entry 7), increasing the reaction temperature to 30 °C resulted in an obvious erosion of the enantioselectivity of the reaction (Table 2, Entry 8). In ad-

dition, the use of smaller amounts of thiourea **5a** (15 mol-%) led to a marked decrease in the reaction rate (Table 1, Entry 4 vs. Entry 9).

Encouraged by these results, we next probed the scope of the reaction with a variety of nitro olefins and different β-oxo phosphonates under the optimal reaction conditions (20 mol-% of thiourea **5a** as the catalyst in THF at 20 °C). The results are summarized in Table 3.

Table 3. Substrate scope of **5a**-catalyzed asymmetric Michael addition of β-oxo phosphonates to nitro olefins.[a]



Entry	R, Ar	Time [d]	Yield [%][b]	*dr*[c]	*ee* [%][d,e]
1	Et, Ph (**a**)	2.5	87	1.5:1	73 (70)
2	Me, Ph (**b**)	4.5	85	1.6:1	37 (81)
3	Et, 2-ClC_6H_4 (**c**)	2.5	86	1.1:1	86 (87)
4	Et, 4-ClC_6H_4 (**d**)	3	85	1.7:1	74 (72)
5	Et, 2-BrC_6H_4 (**e**)	2.5	86	1.3:1	86 (86)
6	Et, 4-BrC_6H_4(**f**)	3	83	1.7:1	68 (68)
7	Et, 3-$F_3C$$C_6H_4$ (**g**)	2.5	85	1.3:1	61 (61)
8	Et, 2-MeOC_6H_4 (**h**)	3	84	1.6:1	92 (92)
9	Et, 1-naphthyl (**i**)	4	81	1.3:1	98 (67)
10	Et, 2-furyl (**j**)	4	84	1:1	50 (94)
11	Et, Et (**k**)	7	n.r.[f]	–	–

[a] Reaction conditions: Nitro olefin (0.2 mmol), β-oxo phosphonate (0.4 mmol), THF (0.6 mL). [b] Isolated yield of the two inseparable diastereomers. [c] Determined by ^{1}H and/or ^{31}P NMR spectroscopy. [d] Determined by chiral HPLC analysis. [e] Data in parentheses are the *ee* values of the minor diastereomer. [f] No reaction occurred.

As illustrated in Table 3, the ester moieties in the β-oxo phosphonate seems to have a significant influence on the reaction. The replacement of the diethyl ester with the dimethyl ester resulted in a sharp erosion of stereocontrol (Table 3, Entry 1 vs. Entry 2). More surprising, the bulky diisopropyl ester was completely inactive in this transformation and failed to give the desired conjugate addition product. Moreover, the reaction has broad applicability with respect to nitro olefins. Not only phenyl, but also electron-rich and -poor aryl groups and heteroaromatic substituents can be present in the nitro olefin. Note that the position of the substituent on the benzene ring has a significant influence on the stereochemical outcome of the reaction. In general, the enantioselectivities of the *ortho*-substituted substrates are better than those of the corresponding *para*-substituted ones (Table 3, Entries 3, 5 vs. Entries 4, 6). This indicates that steric effects are a key factor in the stereocontrol of the reaction, and a sterically more demanding substrate gives higher *ee* values. To confirm these hypotheses, the more bulky *o*-methoxy-substituted β-nitrostyrene and 1-naphthyl-substituted nitro olefin were examined. As anticipated, with an increase in steric hindrance, the enantioselectivity of the major diastereomer increased markedly to afford adducts **6h** and **6i** with 92 and 98% *ee*, respectively (Table 3, Entries 8 and 9). Further investigation revealed that the substrate scope is limited to aromatic nitro olefins; no reaction occurred even after a prolonged reaction time when the aliphatic nitro olefin (*E*)-1-nitrobut-1-ene was employed (Table 3, Entry 11).

To determine the stereochemistry of the reaction, the two diastereomers of the conjugate addition product **6a** were separated by chiral preparative HPLC. The absolute configuration of the major diastereomer of product **6a** was unequivocally established to be (*R*,*R*) by X-ray diffraction (Figure 2).[12] The remaining relative and absolute configurations were assumed by analogy.

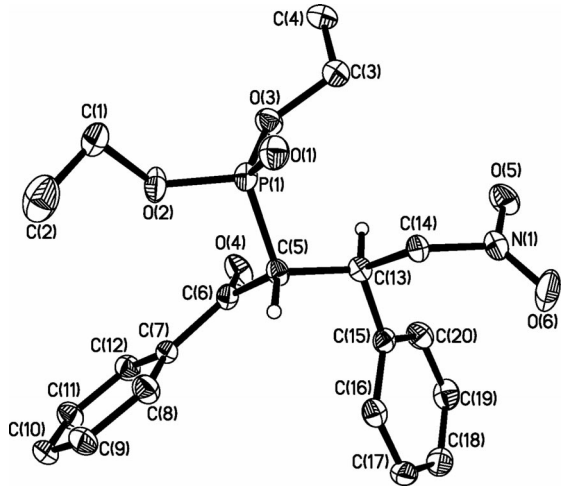


Figure 2. X-ray crystal structure of the major diastereomer of compound **6a**. Most of the hydrogen atoms have been omitted for clarity.

On the basis of the experimental results of the described reactions, we propose that the reaction proceeds by dual activation.[13] As shown in the possible transition state for this reaction in Figure 3, the tertiary amine moiety in **5a** functions as a Lewis base to deprotonate the β-oxo phosphonate to form a nucleophilic enolate anion. At the same time, the nitro olefin is activated by two hydrogen-bonding interactions between the thiourea subunit and the nitro group. Nucleophilic attack of the enolate anion at the *Re* face of the nitro olefin then results in the formation of the desired Michael addition product.

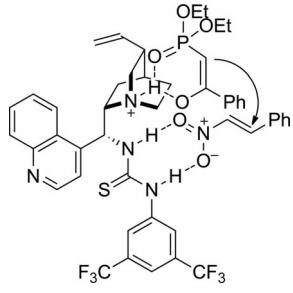


Figure 3. Proposed dual activation in the Michael addition reaction.

Conclusions

The first organocatalytic asymmetric Michael addition of β-oxo phosphonates to nitro olefins has been developed by employing cinchonine-based thiourea **5a** as the catalyst. The corresponding adducts were obtained in good yields with good to excellent enantioselectivities (up to 98% *ee*), albeit with poor diastereoselectivities due to the easily enolizable stereocenter at the α position with respect to the two electron-withdrawing groups. This protocol facilitates access to various enantioenriched α-substituted β-oxo phosphonate derivatives, potentially biologically active molecules and valuable synthetic intermediates, starting from readily available starting materials.

Experimental Section

General Methods: All reagents and solvents were commercial grade and purified prior to use when necessary. NMR spectra were acquired with a Bruker 400 MHz instrument. Chemical shifts were measured relative to residual solvent peaks of $CDCl_3$ as internal standards (^1H: δ = 7.26 ppm; ^{13}C: δ = 77.0 ppm). Specific rotations were measured with a Perkin–Elmer 341MC polarimeter. Enantiomeric excesses were determined with an HP1-100 instrument (chiral column; mobile phase: hexane/*i*PrOH). HRMS data were recorded with a Varian QFT-ESI instrument. Melting points were determined with a Taike X-4 melting-point apparatus. Thioureas **1a**,[14] **1b**,[15] **1c**,[16] **2a**,[17] **2b**,[5n] and **3**–**5a**–**d**[18] were prepared according to literature procedures.

General Procedure for the Asymmetric Michael Addition of β-Oxo Phosphonates to Nitro Olefins Catalyzed by Thiourea 5a: A solution of thiourea **5a** (22.6 mg, 0.04 mmol), β-oxo phosphonate (0.4 mmol), and nitro olefin (0.2 mmol) in anhydrous THF (0.6 mL) was stirred at 20 °C. After the reaction was complete (as monitored by TLC), the mixture was purified by column chromatography on silica gel (200–300 mesh; CH_2Cl_2/EtOAc, 30:1–10:1) to afford the desired conjugate addition products **6**.

Diethyl [(3*R*)-4-Nitro-1-oxo-1,3-diphenylbut-2-yl]phosphonate (6a): White solid, 71 mg, 87% yield, m.p. 114–116 °C, $[\alpha]_D^{20}$ = +33.8 (*c* = 1.0, $CHCl_3$), 1.5:1 *dr*, 73% *ee* for the (*R*,*R*) diastereomer, 70% *ee* for the (*R*,*S*) diastereomer. ^1H NMR (400 MHz, $CDCl_3$): diastereomeric mixture: δ = 1.01 (t, *J* = 6.8 Hz, 1.19 H, CH_3, minor isomer), 1.07–1.13 (m, 3 H, CH_3), 1.26 (t, *J* = 6.8 Hz, 1.76 H, CH_3, major isomer), 3.76–4.17 (m, 4 H, 2 OCH_2), 4.27–4.40 (m, 1 H, CH), 4.52–4.63 (m, 1 H, CH), 4.83–5.26 (m, 2 H, NCH_2), 7.00–7.19 (m, 5 H, aromatic), 7.26–7.50 (m, 3 H, aromatic), 7.62 (d, *J* = 7.6 Hz, 1.16 H, aromatic, major isomer), 7.73 (d, *J* = 7.6 Hz, 0.76 H, aromatic, minor isomer) ppm; (*R*,*R*) diastereomer: δ = 1.14 (t, *J* = 6.8 Hz, 3 H, CH_3), 1.31 (t, *J* = 6.8 Hz, 3 H, CH_3), 4.02–4.22 (m, 4 H, 2 OCH_2), 4.39–4.46 (m, 1 H, CH), 4.66 (dd, *J* = 11.2 and 20.4 Hz, 1 H, CH), 4.93 (dd, *J* = 11.2 and 12.4 Hz, 1 H), 5.31 (dd, *J* = 3.6 and 12.8 Hz, 1 H), 7.05–7.19 (m, 5 H, aromatic), 7.33 (t, *J* = 7.6 Hz, 2 H, aromatic), 7.46 (t, *J* = 7.6 Hz, 1 H, aromatic), 7.68 (d, *J* = 7.6 Hz, 2 H, aromatic) ppm; (*R*,*S*) diastereomer: δ = 0.99 (t, *J* = 6.8 Hz, 3 H, CH_3), 1.09 (t, *J* = 6.8 Hz, 3 H, CH_3), 3.79–3.93 (m, 4 H, 2 OCH_2), 4.28–4.31 (m, 1 H, CH), 4.54 (dd, *J* = 6.4 and 20.0 Hz, 1 H, CH), 5.01 (dd, *J* = 10.0 and 13.2 Hz, 1 H), 5.09 (dd, *J* = 2.8 and 13.2 Hz, 1 H), 7.16 (br. s, 5 H, aromatic), 7.32 (t, *J* = 7.6 Hz, 2 H, aromatic), 7.46 (t, *J* = 7.2 Hz, 1 H, aromatic), 7.71 (d, *J* = 7.6 Hz, 2 H, aromatic) ppm. ^{31}P NMR (161.7 MHz, $CDCl_3$): diastereomeric mixture: δ = 19.20 (minor isomer), 19.32 (major isomer) ppm; (*R*,*R*) diastereomer: δ = 19.32 ppm; (*R*,*S*) diastereomer: δ = 19.20 ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): diastereomeric mixture: δ = 16.0 (d, *J* = 6.1 Hz), 16.1 (d, *J* = 6.1 Hz), 16.2 (t, *J* = 6.0 Hz), 30.5, 42.8 (d, *J* = 3.1 Hz), 43.2 (d, *J* = 3.6 Hz), 49.7 (d, *J* = 125.4 Hz), 50.6 (d, *J* = 127.6 Hz), 62.9 (d, *J* = 7.0 Hz), 63.2 (t, *J* = 7.3 Hz), 63.5 (d, *J* = 7.1 Hz), 77.4 (d, *J* = 7.2 Hz), 78.8, 127.8, 128.0, 128.2, 128.5, 128.6, 128.8, 128.9, 130.9, 133.3, 133.7, 137.0, 137.1, 137.3, 137.4, 137.5, 137.6, 194.2 (d, *J* = 5.8 Hz), 195.6 (d, *J* = 4.9 Hz) ppm; (*R*,*R*) diastereomer: δ = 16.0 (d, *J* = 6.1 Hz), 16.2 (d, *J* = 5.9 Hz), 43.1 (d, *J* = 3.8 Hz), 49.7 (d, *J* = 125.4 Hz), 63.2 (d, *J* = 6.9 Hz), 63.5 (d, *J* = 7.1 Hz), 78.7, 127.8, 127.9, 128.1, 128.4, 128.7, 133.3, 137.0, 137.1, 137.3, 194.1 (d, *J* = 5.7 Hz) ppm; (*R*,*S*) diastereomer: δ = 15.9 (d, *J* = 6.0 Hz), 16.1 (d, *J* = 5.9 Hz), 42.8 (d, *J* = 3.2 Hz), 50.6 (d, *J* = 127.7 Hz), 62.9 (d, *J* = 7.0 Hz), 63.1 (d, *J* = 6.7 Hz), 77.4, 127.8, 128.1, 128.6, 128.9, 133.7, 137.4, 137.6, 137.7, 195.6 (d, *J* = 4.7 Hz) ppm. HRMS (ESI): calcd. for $C_{20}H_{24}NO_6P$ $[M + Na]^+$ 428.1234; found 428.1234. HPLC analysis (Chiralpak OD-H column; hexane/2-propanol, 95:5; flow rate 1.0 mL/min; wavelength 220 nm): t_r = 23.40 (minor,major isomer), 26.25 (major,major isomer), 33.56 (minor,minor isomer) and 60.84 (major,minor isomer) min.

Dimethyl [(3*R*)-4-Nitro-1-oxo-1,3-diphenylbut-2-yl]phosphonate (6b): White solid, 64 mg, 85% yield, m.p. 105–106 °C, $[\alpha]_D^{20}$ = +28.0 (*c* = 1.0, $CHCl_3$), 1.6:1 *dr*, 37% *ee* for major diastereomer, 81% *ee* for minor diastereomer. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.49 (t, *J* = 10.4 Hz, 2.30 H, CH_3, major isomer), 3.64 (d, *J* = 11.2 Hz, 1.84 H, CH_3, minor isomer), 3.74 (d, *J* = 10.8 Hz, 1.84 H, CH_3, minor isomer), 4.26–4.38 (m, 1 H, CH), 4.53–4.65 (m, 1 H, CH), 4.86 (dd, *J* = 10.8 and 13.2 Hz, 0.62 H, major isomer), 4.98 (dd, *J* = 10.0 and 13.2 Hz, 0.38 H, minor isomer), 5.06 (dd, *J* = 4.0 and 13.2 Hz, 0.38 H, minor isomer), 5.18 (dd, *J* = 4.0 and 13.2 Hz, 0.61 H, major isomer), 7.07–7.09 (m, 3 H, aromatic), 7.15–7.21 (m, 2 H, aromatic), 7.28–7.50 (m, 3 H, aromatic), 7.60 (d, *J* = 7.6 Hz, 1.23 H, aromatic, major isomer), 7.72 (d, *J* = 7.6 Hz, 0.77 H, aromatic, minor isomer) ppm. ^{31}P NMR (161.7 MHz, $CDCl_3$): δ = 21.85, 22.04 ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 42.8 (d, *J* = 3.2 Hz), 43.2 (d, *J* = 3.8 Hz), 49.3 (d, *J* = 126.1 Hz), 50.2 (d, *J* = 128.4 Hz), 53.3 (d, *J* = 7.0 Hz), 53.4, 53.5 (d, *J* = 6.7 Hz), 53.6 (d, *J* = 6.5 Hz), 53.8 (d, *J* = 6.9 Hz), 77.2, 78.7, 127.8, 128.1, 128.2, 128.3, 128.5, 128.6, 128.7, 128.8, 129.0, 133.5, 133.9, 136.7, 136.9, 137.1, 137.2, 137.3, 137.4, 194.1 (d, *J* = 5.8 Hz), 195.4 (d, *J* = 5.0 Hz) ppm. HRMS (ESI): calcd. for $C_{18}H_{20}NO_6P$ $[M + Na]^+$ 400.0920; found 400.0919. HPLC analysis (Chiralpak AS-H column; hexane/2-propanol, 95:5; flow rate 1.0 mL/min; wavelength 220 nm): t_r = 39.64 (major,major isomer), 44.69 (minor,major isomer), 50.06 (major,minor isomer), 77.57 (minor,minor isomer) min.

Diethyl [(3*R*)-3-(2-Chlorophenyl)-4-nitro-1-oxo-1-phenylbut-2-yl]-phosphonate (6c): Colorless liquid, 76 mg, 86% yield, $[\alpha]_D^{20}$ = +46.0 (*c* = 1.0, $CHCl_3$), 1.1:1 *dr*, 86% *ee* for major diastereomer, 87% *ee* for minor diastereomer. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.03 (t, *J* = 6.8 Hz, 1.50 H, CH_3, major isomer), 1.08 (t, *J* = 6.8 Hz, 1.36 H, CH_3, minor isomer), 1.19 (t, *J* = 6.0 Hz, 3 H, CH_3), 3.86–4.11 (m, 4 H, 2 OCH_2), 4.75–5.04 (m, 2 H, 2 CH), 5.24–5.38 (m, 2 H, NCH_2), 7.00–7.20 (m, 4 H, aromatic), 7.30–7.35 (m, 2 H, aromatic), 7.44 (s, 1 H, aromatic), 7.67 (d, *J* = 7.6 Hz, 0.99 H, aromatic, major isomer), 7.75 (d, *J* = 6.8 Hz, 0.92 H, aromatic, minor isomer) ppm. ^{31}P NMR (161.7 MHz, $CDCl_3$): δ = 18.80 (major isomer), 19.36 (minor isomer) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 15.9 (t, *J* = 5.0 Hz), 16.2 (t, *J* = 6.5 Hz), 38.9, 47.6 (d,

J = 126.3 Hz), 47.9 (d, *J* = 126.9 Hz), 63.0 (d, *J* = 7.0 Hz), 63.1 (d, *J* = 6.7 Hz), 63.3 (d, *J* = 6.8 Hz), 63.5 (d, *J* = 7.0 Hz), 75.3 (d, *J* = 6.0 Hz), 76.3, 127.0, 127.2, 128.3, 128.4, 128.5, 129.2, 130.4, 133.5, 133.6, 133.7, 134.4, 134.5, 194.1 (d, *J* = 5.6 Hz), 195.3 (d, *J* = 4.3 Hz) ppm. HRMS (ESI): calcd. for $C_{20}H_{23}ClNO_6P$ [M + Na]$^+$ 462.0844; found 462.0841. HPLC analysis (Chiralpak AD-H column; hexane/2-propanol, 95:5; flow rate 1.0 mL/min; wavelength 220 nm): t_r = 40.11 (minor,minor isomer), 46.09 (major,minor isomer), 49.92 (minor,major isomer), 61.72 (major,major isomer) min.

Diethyl [(3*R*)-3-(4-Chlorophenyl)-4-nitro-1-oxo-1-phenylbut-2-yl]-phosphonate (6d): White solid, 75 mg, 85% yield, m.p. 119–121 °C, $[\alpha]_D^{20}$ = +47.2 (*c* = 1.0, $CHCl_3$), 1.7:1 *dr*, 74% *ee* for major diastereomer, 72% *ee* for minor diastereomer. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* = 1.01 (t, *J* = 6.8 Hz, 1.15 H, CH_3, minor isomer), 1.07–1.13 (m, 3 H, CH_3), 1.26 (t, *J* = 6.8 Hz, 1.95 H, CH_3, major isomer), 3.80–4.14 (m, 4 H, 2 OCH_2), 4.29–4.40 (m, H, CH), 4.49–4.61 (m, 1 H, CH), 4.79–5.25 (m, 2 H, NCH_2), 7.07 (s, 2 H, aromatic), 7.13–7.20 (m, 2 H, aromatic), 7.30–7.39 (m, 2 H, aromatic), 7.44–7.53 (m, 1 H, aromatic), 7.65 (d, *J* = 8.0 Hz, 1.19 H, aromatic, major isomer), 7.77 (d, *J* = 8.0 Hz, 0.72 H, aromatic, minor isomer) ppm. ^{31}P NMR (161.7 MHz, $CDCl_3$): *δ* = 18.78 (major isomer), 18.87 (minor isomer) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): *δ* = 16.0 (t, *J* = 6.5 Hz), 16.2 (d, *J* = 5.9 Hz), 16.3 (d, *J* = 5.8 Hz), 29.6, 30.2, 42.3 (d, *J* = 3.2 Hz), 42.5 (d, *J* = 3.5 Hz), 49.5 (d, *J* = 125.4 Hz), 50.4 (d, *J* = 127.4 Hz), 63.0 (d, *J* = 7.0 Hz), 63.2 (d, *J* = 6.9 Hz), 63.3 (d, *J* = 6.8 Hz), 63.7 (d, *J* = 7.1 Hz), 78.6 (d, *J* = 4.8 Hz), 125.5, 128.2, 128.6, 128.7, 129.0, 129.1, 129.2, 129.3, 133.6, 133.8, 134.0, 134.1, 135.6, 135.8, 136.0, 136.1, 137.2, 193.8 (d, *J* = 5.8 Hz), 195.3 (d, *J* = 4.8 Hz) ppm. HRMS (ESI): calcd. for $C_{20}H_{23}ClNO_6P$ [M + Na]$^+$ 462.0844; found 462.0841. HPLC analysis (Chiralpak AS-H column; hexane/2-propanol, 90:10; flow rate 1.0 mL/min; wavelength 220 nm): t_r = 11.58 (minor,major isomer), 16.02 (minor,minor isomer), 21.73 (major,minor isomer), 42.73 (major,major isomer).

Diethyl [(3*R*)-3-(2-Bromophenyl)-4-nitro-1-oxo-1-phenylbut-2-yl]-phosphonate (6e): Pale-yellow liquid, 83 mg, 86% yield, $[\alpha]_D^{20}$ = +57.2 (*c* = 1.0, $CHCl_3$), 1.4:1 *dr*, 86% *ee* for major diastereomer, 86% *ee* for minor diastereomer. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* = 1.10 (t, *J* = 6.8 Hz, 1.73 H, CH_3, major isomer), 1.15 (t, *J* = 6.8 Hz, 1.27 H, CH_3, minor isomer), 1.27 (t, *J* = 6.8 Hz, 3 H, CH_3), 3.90–4.15 (m, 4 H, 2 OCH_2), 4.81–5.04 (m, 2 H, 2 CH), 5.24–5.48 (m, 2 H, NCH_2), 6.96–7.12 (m, 2 H, aromatic), 7.20–7.25 (m, 1 H, aromatic), 7.33–7.56 (m, 4 H, aromatic), 7.70 (d, *J* = 7.6 Hz, 1.18 H, aromatic, major isomer), 7.84 (d, *J* = 6.0 Hz, 0.84 H, aromatic, minor isomer) ppm. ^{31}P NMR (161.7 MHz, $CDCl_3$): *δ* = 18.76 (major isomer), 19.25 (minor isomer) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): *δ* = 15.9 (d, *J* = 6.1 Hz), 16.1 (d, *J* = 5.9 Hz), 16.2 (d, *J* = 5.9 Hz), 30.2, 41.1, 47.9 (d, *J* = 126.8 Hz), 63.0 (d, *J* = 7.0 Hz), 63.1, 63.4 (d, *J* = 6.8 Hz), 63.5 (d, *J* = 6.9 Hz), 75.3 (d, *J* = 4.8 Hz), 127.6, 127.8, 128.4, 128.5, 129.4, 133.4, 133.5, 133.5, 136.0, 136.4, 137.2, 194.1 (d, *J* = 5.6 Hz), 195.3 (d, *J* = 4.1 Hz) ppm. HRMS (ESI): calcd. for $C_{20}H_{23}BrNO_6P$ [M + Na]$^+$ 506.0339; found 506.0332. HPLC analysis (Chiralpak AS-H column; hexane/2-propanol, 93:7; flow rate 1.0 mL/min; wavelength 220 nm): t_r = 29.40 (minor,minor isomer), 31.08 (major,minor isomer), 37.26 (minor,major isomer), 41.48 (major,major isomer) min.

Diethyl [(3*R*)-3-(4-Bromophenyl)-4-nitro-1-oxo-1-phenylbut-2-yl]-phosphonate (6f): White solid, 80 mg, 83% yield, m.p. 128–130 °C, $[\alpha]_D^{20}$ = +37.0 (*c* = 1.0, $CHCl_3$), 1.7:1 *dr*, 68% *ee* for major diastereomer, 68% *ee* for minor diastereomer. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* = 1.07 (t, *J* = 6.8 Hz, 1.26 H, CH_3, minor isomer), 1.13–1.19 (m, 3 H, CH_3), 1.31 (t, *J* = 6.8 Hz, 2.17 H, CH_3, major isomer), 3.83–4.22 (m, 4 H, 2 OCH_2), 4.31–4.45 (m, H, CH), 4.55–4.67 (m, 1 H, CH), 4.85–5.30 (m, 2 H, NCH_2), 7.07–7.27 (m, 3 H, aromatic), 7.36–7.57 (m, 4 H, aromatic), 7.71 (d, *J* = 7.6 Hz, 1.20 H, aromatic, major isomer), 7.83 (d, *J* = 7.6 Hz, 0.71 H, aromatic, minor isomer) ppm. ^{31}P NMR (161.7 MHz, $CDCl_3$): *δ* = 18.75 (minor isomer), 18.83 ppm (major isomer) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): *δ* = 16.0 (t, *J* = 6.5 Hz), 16.1 (d, *J* = 6.1 Hz), 16.2 (d, *J* = 5.9 Hz), 29.6, 42.4 (d, *J* = 3.1 Hz), 42.5 (d, *J* = 3.5 Hz), 49.4 (d, *J* = 125.4 Hz), 50.3 (d, *J* = 127.4 Hz), 63.1 (d, *J* = 7.1 Hz), 63.2 (d, *J* = 7.2 Hz), 63.3 (d, *J* = 6.8 Hz), 63.6 (d, *J* = 7.1 Hz), 77.2, 78.5, 122.0, 122.2, 128.2, 128.6, 128.7, 129.5, 129.7, 131.9, 132.0, 133.6, 134.0, 136.2, 136.3, 136.5, 136.6, 137.0, 137.1, 193.7 (d, *J* = 5.7 Hz), 195.2 (d, *J* = 4.9 Hz) ppm. HRMS (ESI): calcd. for $C_{20}H_{23}BrNO_6P$ [M + Na]$^+$ 506.0339; found 506.0334. HPLC analysis (Chiralpak AS-H column; hexane/2-propanol, 90:10; flow rate 1.0 mL/min; wavelength 220 nm): t_r = 12.02 (minor,major isomer), 17.05 (minor,minor isomer), 23.29 (major,minor isomer), 45.44 (major,major isomer) min.

Diethyl [(3*R*)-4-Nitro-1-oxo-1-phenyl-3-[3-(trifluoromethyl)phenyl]but-2-yl]phosphonate (6g): Colorless liquid, 80 mg, 85% yield, $[\alpha]_D^{20}$ = +22.4 (*c* = 1.0, $CHCl_3$), 1.3:1 *dr*, 61% *ee* for major isomer, 61% *ee* for minor isomer. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* = 0.96 (t, *J* = 6.8 Hz, 1.32 H, CH_3, minor isomer), 1.06–1.11 (m, 3 H, CH_3), 1.24 (t, *J* = 6.8 Hz, 1.77 H, CH_3, major isomer), 3.74–4.16 (m, 4 H, 2 OCH_2), 4.36–4.47 (m, H, CH), 4.53–4.66 (m, 1 H, CH), 4.85–5.29 (m, 2 H, NCH_2), 7.18–7.51 (m, 7 H, aromatic), 7.62 (d, *J* = 7.6 Hz, 1.12 H, aromatic, major isomer), 7.79 (d, *J* = 7.6 Hz, 0.85 H, aromatic, minor isomer) ppm. ^{31}P NMR (161.7 MHz, $CDCl_3$): *δ* = 18.55 (minor isomer), 18.82 (major isomer) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): *δ* = 15.8 (d, *J* = 6.2 Hz), 16.0 (t, *J* = 5.6 Hz), 16.2 (d, *J* = 5.7 Hz), 29.6, 42.7 (d, *J* = 2.9 Hz), 42.9 (d, *J* = 3.6 Hz), 49.3 (d, *J* = 126.5 Hz), 50.1 (d, *J* = 128.3 Hz), 63.0 (d, *J* = 7.1 Hz), 63.2 (d, *J* = 6.7 Hz), 63.3 (d, *J* = 6.7 Hz), 63.7 (d, *J* = 7.1 Hz), 77.1, 77.2, 78.3, 122.2, 122.3, 124.5 (q, *J* = 3.6 Hz), 124.8 (q, *J* = 3.7 Hz), 125.0 (t, *J* = 3.8 Hz), 128.1, 128.5, 128.6, 128.7, 129.3, 129.4, 130.8, 130.9, 131.1, 131.2, 131.5, 131.7, 133.4, 134.0, 137.0, 138.2, 138.3, 138.4, 138.5, 193.9 (d, *J* = 5.9 Hz), 195.1 (d, *J* = 4.9 Hz) ppm. HRMS (ESI): calcd. for $C_{21}H_{23}F_3NO_6P$ [M + Na]$^+$ 496.1107; found 496.1104. HPLC analysis (Chiralpak AD-H column; hexane/2-propanol, 95:5; flow rate 1.0 mL/min; wavelength 220 nm): t_r = 17.85 (minor,major isomer), 23.22 (minor,major isomer), 31.53 (minor,minor isomer), 61.14 (major,minor isomer) min.

Diethyl [(3*R*)-3-(2-Methoxyphenyl)-4-nitro-1-oxo-1-phenylbut-2-yl]-phosphonate (6h): Colorless liquid, 73 mg, 84% yield, $[\alpha]_D^{20}$ = +54.8 (*c* = 1.0, $CHCl_3$), 1.6:1 *dr*, 92% *ee* for major diastereomer, 92% *ee* for minor diastereomer. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* = 1.06 (t, *J* = 7.2 Hz, 1.15 H, CH_3, minor isomer), 1.13–1.19 (m, 3 H, CH_3), 1.34 (t, *J* = 7.2 Hz, 1.84 H, CH_3, major isomer), 3.71 (s, 1.76 H, OCH_3, major isomer), 3.76 (s, 1.07 H, OCH_3, minor isomer), 3.84–4.25 (m, 4 H, 2 OCH_2), 4.39–4.48 (m, 0.61 H, CH, major isomer), 4.54–4.63 (m, 0.38 H, CH, minor isomer), 4.86–5.27 (m, 3 H, CH and NCH_2), 6.61–6.86 (m, 2 H, aromatic), 7.05–7.09 (m, 1 H, aromatic), 7.20–7.56 (m, 4 H, aromatic), 7.69 (d, *J* = 7.6 Hz, 1.14 H, aromatic, major isomer), 7.83 (d, *J* = 7.2 Hz, 0.70 H, aromatic, minor isomer) ppm. ^{31}P NMR (161.7 MHz, $CDCl_3$): *δ* = 20.10 (minor isomer), 20.53 (major isomer) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): *δ* = 15.9 (d, *J* = 6.4 Hz), 16.0 (d, *J* = 6.2 Hz), 16.2 (d, *J* = 6.0 Hz), 16.3 (d, *J* = 5.6 Hz), 30.2, 39.7, 41.9, 47.1 (d, *J* = 127.0 Hz), 47.4 (d, *J* = 128.4 Hz), 55.0, 55.1, 62.6 (d, *J* = 6.9 Hz), 62.9 (d, *J* = 6.7 Hz), 63.3 (d, *J* = 7.0 Hz), 75.9, 76.0, 110.8, 120.8, 123.7, 123.8, 124.8, 124.9, 125.4, 128.0, 128.3, 128.4, 128.6, 129.3, 129.4, 130.4, 132.2, 133.1, 133.5, 137.5, 137.6, 156.7, 157.1, 194.7

(d, J = 6.0 Hz), 195.4 (d, J = 5.0 Hz) ppm. HRMS (ESI): calcd. for $C_{21}H_{26}NO_7P$ [M + Na]$^+$ 458.1339; found 458.1340. HPLC analysis (Chiralpak AD-H column; hexane/2-propanol, 95:5; flow rate 1.0 mL/min; wavelength 220 nm): t_r = 39.77 (major,major isomer), 44.94 (minor,major isomer), 63.72 (minor,minor isomer), 159.88 (major,minor isomer) min.

Diethyl [(3*R*)-3-(Naphthalen-1-yl)-4-nitro-1-oxo-1-phenylbut-2-yl]-phosphonate (6i): Colorless liquid, 74 mg, 81% yield, $[\alpha]_D^{20}$ = +85.2 (c = 1.0, $CHCl_3$), 1.3:1 *dr*, 98% *ee* for major diastereomer, 67% *ee* for minor diastereomer. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.04 (t, J = 6.8 Hz, 1.91 H, CH_3, major isomer), 1.12 (t, J = 6.8 Hz, 1.49 H, CH_3, minor isomer), 1.18–1.23 (m, 3 H, CH_3), 3.82–4.16 (m, 4 H, 2 OCH_2), 4.69 (dd, J = 4.4 and 24.0 Hz, 0.52 H, CH, major isomer), 4.91 (dd, J = 10.4 and 21.6 Hz, 0.41 H, CH, minor isomer), 5.12–5.54 (m, 3 H, CH and NCH_2), 7.13–7.27 (m, 4 H, aromatic), 7.32–7.40 (m, 3 H, aromatic), 7.45–7.80 (m, 4 H, aromatic), 8.15–8.22 (m, 1 H, aromatic) ppm. ^{31}P NMR (161.7 MHz, $CDCl_3$): δ = 19.71 ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 16.0 (t, J = 6.4 Hz), 16.3 (t, J = 5.4 Hz), 29.6, 36.5, 49.4 (d, J = 127.8 Hz), 49.7 (d, J = 125.5 Hz), 63.1 (d, J = 6.9 Hz), 63.2, 63.3 (d, J = 6.8 Hz), 63.6 (d, J = 7.1 Hz), 76.1 (d, J = 3.9 Hz), 77.2, 78.5, 122.7, 123.7, 123.9, 124.8, 125.0, 126.0, 126.8, 127.1, 128.2, 128.3, 128.4, 128.7, 129.3, 130.6, 131.4, 133.2, 133.3, 133.6, 133.9, 134.2, 137.1, 137.4, 194.1 (d, J = 5.4 Hz), 195.8 (d, J = 4.0 Hz) ppm. HRMS (ESI): calcd. for $C_{24}H_{26}NO_6P$ [M + Na]$^+$ 478.1390; found 478.1395. HPLC analysis (Chiralpak AS-H column; hexane/2-propanol, 90:10; flow rate 1.0 mL/min; wavelength 220 nm): t_r = 12.97 (minor,minor isomer), 19.78 (major,minor isomer), 31.45 (minor,major isomer), 53.30 (major,major isomer) min.

Diethyl [(3*S*)-3-(Furan-2-yl)-4-nitro-1-oxo-1-phenylbut-2-yl]phosphonate (6j): Colorless liquid, 66 mg, 84% yield, $[\alpha]_D^{20}$ = +21.6 (c = 1.0, $CHCl_3$), 1:1 *dr*, 50% *ee* for major diastereomer, 94% *ee* for minor diastereomer. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.21–1.41 (m, 6 H, 2 CH_3), 4.02–4.27 (m, 4 H, 2 CH_2), 4.57–4.66 (m, 1 H, CH), 4.83–4.93 (m, 1 H, CH), 5.04–5.14 (m, 1 H), 5.27 (dd, J = 3.2 and 13.6 Hz, 0.5 H), 5.34 (dd, J = 3.6 and 13.6 Hz, 0.48 H), 6.18–6.20 (m, 1 H, aromatic), 6.29–6.32 (m, 1 H, aromatic), 7.33 (s, 1 H, aromatic), 7.52 (d, J = 7.6 Hz, 1 H, aromatic), 7.56 (d, J = 8.0 Hz, 1 H, aromatic), 7.63–7.69 (m, 1 H, aromatic), 7.93 (d, J = 8.0 Hz, 1 H, aromatic), 7.97 (d, J = 8.0 Hz, 1 H, aromatic) ppm. ^{31}P NMR (161.7 MHz, $CDCl_3$): δ = 18.77, 18.92 ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 16.0 (d, J = 3.4 Hz), 16.1 (d, J = 3.7 Hz), 36.6 (d, J = 3.7 Hz), 37.2 (d, J = 3.3 Hz), 47.2 (d, J = 70.5 Hz), 48.4 (d, J = 71.7 Hz), 63.1 (d, J = 6.9 Hz), 63.3 (d, J = 6.7 Hz), 63.5 (d, J = 7.0 Hz), 75.9 (d, J = 7.2 Hz), 76.3, 128.4, 128.5, 128.6, 133.5, 133.8, 136.9, 137.1, 142.3, 142.5, 149.7 (d, J = 16.8 Hz), 150.5 (d, J = 12.2 Hz), 194.2 (d, J = 5.7 Hz), 194.9 (d, J = 4.5 Hz) ppm. HRMS (ESI): calcd. for $C_{18}H_{22}NO_7P$ [M + Na]$^+$ 418.1062; found 418.1028. HPLC analysis (Chiralpak AD-H column; hexane/2-propanol, 95:5; flow rate 1.0 mL/min; wavelength 220 nm): t_r = 45.02 (minor,minor isomer), 47.19 (major,minor isomer), 51.44 (minor,major isomer), 102.98 (major,major isomer) min.

Supporting Information (see footnote on the first page of this article): NMR, HRMS, and chiral HPLC data of the prepared optically active acyclic α-substituted β-oxo phosphonates.

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