JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

Copper-Catalyzed Phosphonation–Annulation Approaches to the Synthesis of β-Phosphonotetrahydrofurans Involving C–P and C–O Bonds Formation

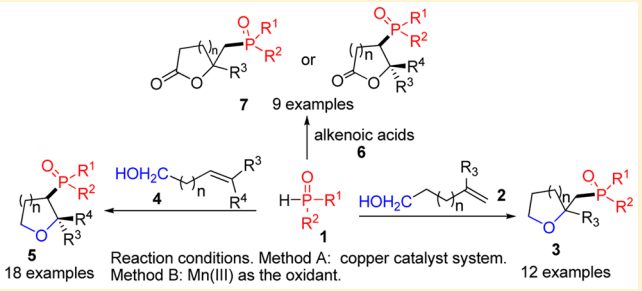
Yuzhen Gao,[†] Xueqin Li,[†] Weizhu Chen,[†,‡] Guo Tang,*[,†] and Yufen Zhao[†]

[†]Department of Chemistry, College of Chemistry and Chemical Engineering, and the Key Laboratory for Chemical Biology of Fujian Province, Xiamen University, Xiamen, Fujian 361005, China

[‡]Third Institute of Oceanography, State Oceanic Administration, Xiamen, Fujian 361005, China

Supporting Information

ABSTRACT: Substituted tetrahydrofuran derivatives play important roles as biological activities. A versatile method for the synthesis of β-phosphonotetrahydrofurans has been developed based on Cu-catalyzed difunctionalization of alkenes. This transformation would provide a new pathway for the formation of Csp^3–P and Csp^3–O bonds in one step. Furthermore, this copper catalyst system can be used in the synthesis of β-phosphonotetrahydropyrans and phosphono-γ-butyrolactones. These reactions were also performed well by using 3 equiv of $Mn(OAc)_3{\cdot}2H_2O$ as the oxidant without copper catalyst.



INTRODUCTION

Substituted tetrahydrofuran (THF) and tetrahydropyran (THP) derivatives are important scaffolds in a broad array of biologically active natural compounds, such as lignans, polyether antibiotics, and marine macrolides.[1] Some natural products are found where both THF and THP heterocycles are included, such as eribulin,[2a−c] pectenotoxins,[2d] prorocentrolide toxins,[2e,f] and the family of the antimitotic spirastrellolides.[2g,h] Over the last 20 years, more THF- and THP-containing compounds as drug candidates have increased exponentially.[2] Because of this importance, the THF moiety continues to attract the attention of organic chemists. Various methodologies have been described for the synthesis of substituted THF derivatives.[3]

As we know, organophosphorus compounds have broad applications in the fields of organic synthesis, materials, ligand chemistry, pharmaceuticals, and agrochemicals owing to their unique properties.[4] Thus, to develop a new efficient method for C–P bond construction has attracted increasing attention.[5] We speculated that, if both a phosphoryl group and a cycloether structural motif can be simultaneously introduced into organic compounds, efficient synthesis of THF- or THP-containing organophosphorus compounds might be expected, and might provide an opportunity to introduce a phosphoryl group into the original lead compounds or drugs to adjust their bioactivity. However, the efficient synthesis of THF or THP bearing a phosphoryl group is quite rare.[6]

In the past decades, reactions with the generated phosphorus radicals showed significant availability in synthesis of organophosphorus compounds.[7] We tried to synthesize α-phosphono tetrahydrofuran from THF and P(O)H compounds directly. It is a pity that the ring-opening of THF afforded α-hydroxy phosphonate in 93% yield.[8] Our continued interest in the C–P bond formation[9] and the reaction of organophosphorus radicals[10] recently prompted us to explore the possibility of using low-cost metal complexes as the catalysts for the direct formation of a C–P bond and the construction of a THF or THP ring in one reaction.

RESULTS AND DISCUSSION

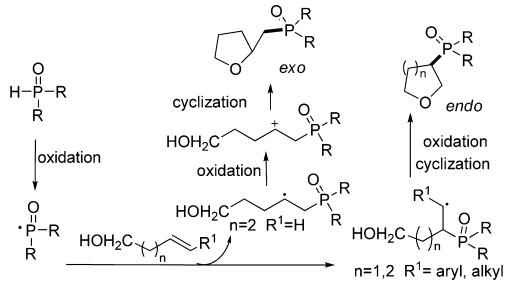
We reasoned that an appropriate metal catalyst could promote the formation of phosphorus radicals, which could add to the double bond of γ-hydroxyalkene and subsequently be oxidized to a cationic intermediate, ultimately affording an *exo*-cycloether via an intramolecular nucleophilic reaction (Scheme 1).

This idea was first examined by using diisopropyl *H*-phosphonate (**1a**) and 4-phenylpent-4-en-1-ol (**2a**) as reaction partners (Table 1). In the beginning, $AgNO_3$ was tested (entries 1 and 2),[11] but the reaction did not work well. Copper salt has been often used in organophosphorus radical reactions.[8,10a,12] When $Cu(OTf)_2$ was chosen as the catalyst and MnO_2, $K_2S_2O_8$, or $FeCl_3$ as oxidant, the product **3a** was obtained in low yield (entries 3–5). The combined use of $Cu(OTf)_2$ and TBHP (*tert*-butylhydroperoxide) gave **3a** in 64% yield (entry 6). Other Cu(II) salts were less effective (entries 7–10). The absence of $Cu(OTf)_2$ or TBHP delivered no

Received: August 31, 2015
Published: November 2, 2015

DOI: 10.1021/acs.joc.5b02026
J. Org. Chem. 2015, 80, 11398–11406

Scheme 1. Synthetic Route to β-Phosphonotetrahydrofuran

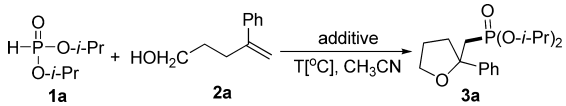


expected product (entries 11 and 12). $Mn(OAc)_3{\cdot}2H_2O$ has been considered as a prominent single-electron oxidant in the field of free-radical chemistry.[13] The reaction was performed well by using 3 equiv of $Mn(OAc)_3{\cdot}2H_2O$ as the oxidant without Cu(II) catalysts (entries 13−14). Conducting the reaction in CH_3CN, NMP, DMF, and DMSO gave the product **3a** in slightly lower yields (entries 15−19), while the reaction conducted in HOAc gave **3a** in 78% yield (entry 14). No desired product was obtained when 2.0 equiv of TEMPO was added in either Cu(II) or Mn(III) system under the optimal conditions (entries 23 and 24). This result suggests that the radical was intercepted by TEMPO and this reaction might go through a radical pathway. After optimization of the reaction conditions, we established two efficient routes to the synthesis of β-phosphonotetrahydrofuran (entries 6 and 14).

To explore the scope of this copper-catalyzed phosphonation−annulation strategy, the reactions of a variety of γ-hydroxyalkenes and P(O)-H compounds were examined. As shown in Table 2, diisopropyl, diethyl, and dibenzyl *H*-phosphonates all could be used as the substrates, generating the corresponding *exo*-selective products (**3a−3c**) in 56−64% isolated yields. It is worth noting that ethoxyphenylphosphine oxide (**1d**), diphenylphosphine oxide (**1e**), and bis(3-methylphenyl)phosphine oxide (**1f**) can be also applied in the preparation of β-phosphonotetrahydrofurans in 68, 46, and 62% yields, respectively. Racemic ethoxyphenylphosphine oxide (**1d**) gave a mixture of diastereomers of β-phosphonotetrahydrofurans. The present phosphonocycloetherification is also applicable to terminal aliphatic γ-hydroxyalkenes, giving products **3i** and **3j** in slightly lower yields. β-Phosphonotetrahydropyrans (**3k**, **3l**) were accessible under the standard reaction conditions. Furthermore, the $Mn(OAc)_3{\cdot}2H_2O$ system (method B) can also be used in the synthesis of β-phosphonotetrahydrofurans and β-phosphonotetrahydropyrans.

Table 3 summarizes the *endo*-selective phosphonocycloetherification for internal β- or γ-hydroxyalkenes **4** with different P(O)-H compounds. The reaction of (*E*)-4-phenylbut-3-en-1-ol and diisopropyl *H*-phosphonate gave the corresponding *endo*-product (**5a**) in 63% isolated yield as a single isomer. The two substituents at 2- and 3-positions are the transformation on the THF ring.[14] The alkyl group and variation of the methyl group position on the benzene ring had little influence on the

Table 1. Optimization of Reaction Conditions[a]

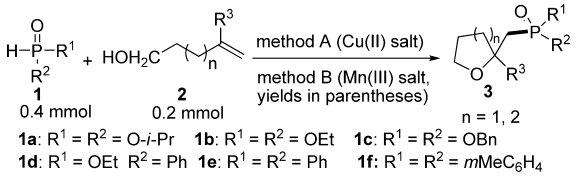


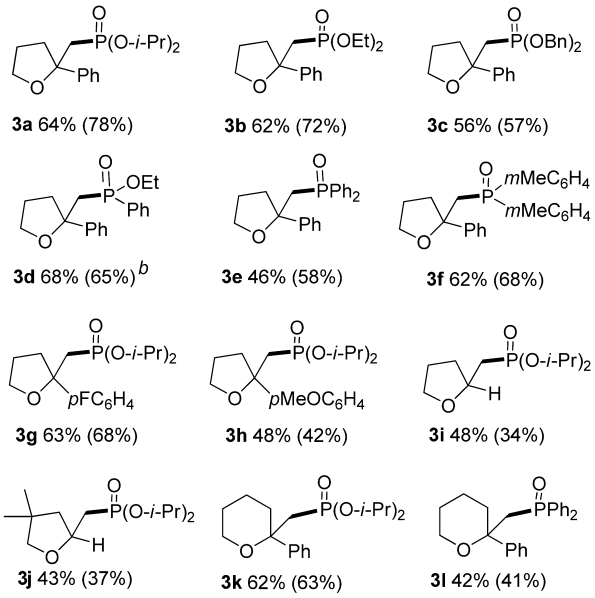
entry	additive (equiv)	solvent	*T* (°C)	yield (%)
1	$AgNO_3$ (0.1) + $K_2S_2O_8$ (2)	CH_3CN	100	trace
2	$AgNO_3$ (0.5)	CH_3CN	100	27
3	$Cu(OTf)_2$ (0.1) + MnO_2 (2)	CH_3CN	60	45
4	$Cu(OTf)_2$ (0.1) + $K_2S_2O_8$ (2)	CH_3CN	60	39
5	$Cu(OTf)_2$ (0.1) + $FeCl_3$ (2)	CH_3CN	60	trace
6	**$Cu(OTf)_2$ (0.1) + TBHP (3)**	CH_3CN	**60**	**64**
7	$CuCl_2$ (0.1) + TBHP (3)	CH_3CN	60	18
8	$Cu(acac)_2$ (0.1) + TBHP (3)	CH_3CN	60	52
9	$Cu(OAc)_2$ (0.1) + TBHP (3)	CH_3CN	60	46
10	$CuSO_4{\cdot}5H_2O$ (0.1) + TBHP (3)	CH_3CN	60	41
11	$Cu(OTf)_2$ (0.1)	CH_3CN	60	trace
12	TBHP (3)	CH_3CN	60	0
13	$Mn(OAc)_3{\cdot}2H_2O$ (3)	HOAc	60	58
14	**$Mn(OAc)_3{\cdot}2H_2O$ (3)**	**HOAc**	**80**	**78**
15	$Mn(OAc)_3{\cdot}2H_2O$ (2)	CH_3COOH	80	56
16	$Mn(OAc)_3{\cdot}2H_2O$ (3)	CH_3CN	80	74
17	$Mn(OAc)_3{\cdot}2H_2O$ (3)	NMP	80	64
18	$Mn(OAc)_3{\cdot}2H_2O$ (3)	DMF	80	28
19	$Mn(OAc)_3{\cdot}2H_2O$ (3)	DMSO	80	42
20[b]	$Mn(OAc)_3{\cdot}2H_2O$ (3)	HOAc	80	44
21[c]	$Mn(OAc)_3{\cdot}2H_2O$ (3)	HOAc	80	77
22	$Mn(OAc)_2{\cdot}4H_2O$ (0.05) + MnO_2 (2)	HOAc	80	ND
23	$Cu(OTf)_2$ (0.1) + TBHP (3) + TEMPO (2)	CH_3CN	60	0
24	$Mn(OAc)_3{\cdot}2H_2O$ (3) + TEMPO (2)	HOAc	80	0

[a]Reaction conditions: **1a** (0.4 mmol), **2a** (0.2 mmol), additive in solvent (1.5 mL) stirring under nitrogen for 4 h. Oil bath temperature. Yield of the isolated product. [b]Under air. [c]2 equiv of CH_3COONa was added.

DOI: 10.1021/acs.joc.5b02026
J. Org. Chem. 2015, 80, 11398−11406

Table 2. Reaction of P(O)-H Compounds with Terminal δ- or γ-Hydroxyalkenes[a]



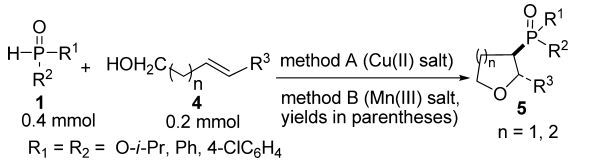


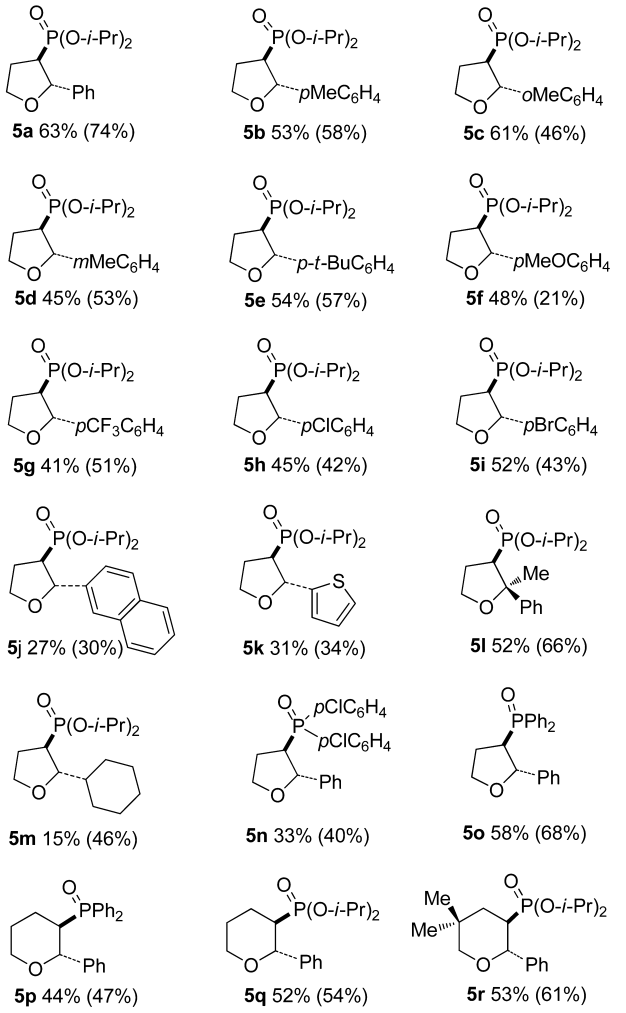
[a]Method A: **1** (0.4 mmol), **2** (0.2 mmol), $Cu(OTf)_2$ (0.02 mmol), TBHP (0.6 mmol), MeCN(1.5 mL), 60 °C, stirring under nitrogen for 4 h. Method B (yields in parentheses): **1** (0.4 mmol), **2** (0.2 mmol), $Mn(OAc)_3{\cdot}2H_2O$ (0.6 mmol), HOAc (1.5 mL), 80 °C (oil bath temperature), stirring under nitrogen for 4 h. Yield of the isolated product. [b]dr = 1:1.

reaction efficiency (**5b**−**5e**). In addition, β-hydroxyalkenes (homoallylic alcohols) having electron-rich or electron-poor substituted aryl groups were examined (**5f** and **5g**). Halogen atoms such as chloro and bromo on the aromatic ring were unaffected under the present reaction conditions to afford the corresponding products **5h** and **5i** in moderate yields, which could allow for further synthetic transformations. Moreover, homoallylic alcohols with naphthalene and thiophene were also reacted smoothly with diisopropyl *H*-phosphonate to afford products **5j** and **5k** in slightly lower yields. The phosphono-cycloetherification of (*E*)-4-phenylpent-3-en-1-ol gave *endo*-product **5l** with a quaternary carbon center. Diarylphosphine oxides were also suitable acceptors to extend the applicability of the current method and led to the formation of products (**5n**−**5p**) in moderate yields. Furthermore, the present protocol also enables the synthesis of a six-membered ether ring (**5p**−**5r**), affording β-phosphonotetrahydropyrans in 44, 52, and 53% yields, respectively. The reactions could be also conducted by using $Mn(OAc)_3{\cdot}2H_2O$ as the oxidant in HOAc at 80 °C and gave **5a**−**5r** in moderate to good yields.

Recently, we developed a $Mn(OAc)_3$-mediated radical oxidative phosphonation and lactonization of alkenoic acids with *H*-phosphonates for the synthesis of phosphono-γ-butyrolactones. In this process, $Mn(OAc)_3$ is used in excess (3 equiv), which is quite wasteful, although $Mn(OAc)_3$ is inexpensive.[14] The copper-catalyzed phosphonation−annulation work inspired us to apply this strategy in the synthesis of

Table 3. Reaction of P(O)-H Compounds with Internal β- or γ-Hydroxyalkenes[a]





[a]For reaction conditions, see footnote "*a*" in Table 2.

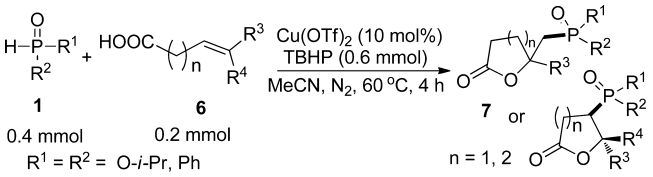
phosphono-γ-butyrolactones (Table 4). The reaction of terminal alkenoic acids **6** with different P(O)-H compounds **1** gave *exo*-selective phosphonation−lactonization products in good yields (**7a**−**7c**). The reaction of (*E*)-4-aryl-3-butenoic acids and diisopropyl *H*-phosphonate gave the corresponding *endo*-product **7d**−**7f** in moderate to good yields. Alkenoic acids without aryl groups also reacted smoothly with diisopropyl *H*-phosphonate to afford products **7h** and **7i**, respectively, in 62% and 54% yields. Comparable results were obtained in the $Mn(OAc)_3$ system, whereas the product (**7h** and **7i**) yields increased greatly in the copper catalyst system.

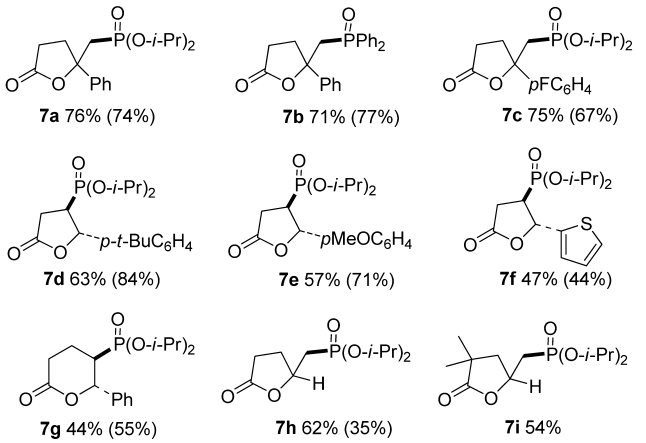
CONCLUSION

In conclusion, the combination of $Cu(OTf)_2$ and TBHP affords an efficient catalytic system for the phosphonation−annulation of alkenes to prepare β-phosphonotetrahydrofurans and β-phosphonotetrahydropyrans in moderate to good yields.

DOI: 10.1021/acs.joc.5b02026
J. Org. Chem. 2015, 80, 11398−11406

Table 4. Reaction of *H*-Phosphonates with Alkenoic Acids[a]





[a]Yields in parentheses were obtained by using $Mn(OAc)_3$ as the oxidant without copper catalyst.

Importantly, this transformation would provide a new pathway for the formation of Csp^3–P and Csp^3–O bonds in one step. This copper catalyst system can also be used in the synthesis of phosphono-γ-butyrolactones. Furthermore, the synthesis of β-phosphonotetrahydrofurans and β-phosphonotetrahydropyrans could be also conducted by using $Mn(OAc)_3{\cdot}2H_2O$ as the oxidant.

EXPERIMENTAL SECTION

General. All reactions were carried out under a nitrogen atmosphere. All reagents were purchased and used without further purification. All new compounds were further characterized by HRMS (FT-ICR-MS). The samples (**3a**–**3l** and **5a**–**5r**) whose spectra are presented were prepared by using $Mn(OAc)_3{\cdot}2H_2O$ as the oxidant. The samples (**7a**–**7i**) whose spectra are presented were prepared by using a copper catalyst system.

Experimental Procedure for the Synthesis of Terminal γ- or δ-Hydroxyalkenes.[15] To a suspension of methyltriphenylphosphonium bromide (26 mmol) in dry THF (50 mL) was added sodium *t*-butoxide (52 mmol) at 0 °C. The mixture was then stirred for 30 min. 4-Oxo-4-phenylbutanoic acid (20.0 mmol) was then added to the reaction mixture at 0 °C. The mixture was allowed to warm to room temperature, and then stirred for 16 h. After evaporation of THF, CH_2Cl_2 and 1 N NaOH were added. The aqueous layer was washed with CH_2Cl_2. 12 N HCl was then added until the pH of the aqueous layer was 2.0. The aqueous layer was then extracted with CH_2Cl_2 twice. The combined organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography using a petroleum ether/AcOEt mixture [from 10:1 to 5:1 (v/v)] as the eluent to give 4-phenylpent-4-enoic acid.

4-Phenylpent-4-enoic acid (10 mmol) was dissolved in dry THF (20 mL). Lithium aluminum hydride (20 mmol) was added portionwise at 0 °C. The reaction mixture was stirred for 30 min. The reaction was then quenched with 2 N NaOH and filtered through a pad of Celite. The organic layer was extracted with diethyl ether, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by silica gel column chromatography using a petroleum ether/AcOEt mixture (5:1, v/v) as the eluent to give **1a** (4-phenylpent-4-en-1-ol) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.40–7.38 (m, 2H), 7.32–7.28 (m, 2H), 7.26–7.22 (m, 1H), 5.28 (d, J = 1.1 Hz, 1H), 5.06 (d, J = 1.2 Hz, 1H), 3.59 (t, J = 6.5 Hz, 2H), 2.56 (t, J = 7.5 Hz, 2H), 2.22 (br, 1H), 1.71–1.64 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 148.1, 141.2, 128.4, 127.5, 126.2, 112.6, 62.3, 31.7, 31.2.

Experimental Procedure for the Synthesis of Internal Homoallylic Alcohols.[15] To a suspension of (2-caroboxyethyl)-triphenylphosphonium bromide (6 mmol) and benzaldehyde (5 mmol) in dry THF (20 mL) was slowly added potassium *t*-butoxide (12.6 mmol) at 0 °C. The mixture was stirred at 0 °C for 15 min before the solution was stirred at room temperature for overnight. The resulting reaction mixture was concentrated in vacuo, and the residue was treated with 1N NaOH. The mixture was washed with CH_2Cl_2 for three times. 12 N HCl was then added until the pH of the aqueous layer was 2.0. The aqueous layer was then extracted with CH_2Cl_2 twice. The combined organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography using a petroleum ether/AcOEt mixture (5:1, v/v) as the eluent to give (*E*)-4-phenylbut-3-enoic acid.

(*E*)-4-Phenylbut-3-enoic acid (3 mmol) was dissolved in dry THF (10 mL). Lithium aluminum hydride (6 mmol) was added portionwise at 0 °C. The reaction mixture was stirred for 30 min. The reaction was then quenched with 2 N NaOH and filtered through a pad of Celite. The organic layer was extracted with diethyl ether, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by silica gel column chromatography using a petroleum ether/AcOEt mixture (5:1, v/v) as the eluent to give **4a** ((*E*)-4-phenylbut-3-en-1-ol) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.36–7.34 (m, 2H), 7.31–7.27 (m, 2H), 7.23–7.28 (m, 1H), 6.48 (d, J = 16.1 Hz, 1H), 6.23–6.15 (m, 1H), 3.72 (t, J = 6.3 Hz, 2H), 2.49–2.44 (m, 2H), 2.00 (br, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 137.4, 132.9, 128.7, 127.4, 126.5, 126.2, 62.2, 36.5.

Experimental Procedure for the Phosphonocycloetherification of Hydroxyalkenes. *Method A.* A Schlenk tube containing $Cu(OTf)_2$ (0.02 mmol, 10%) was evacuated and purged with nitrogen three times. Hydroxyalkenes (0.20 mmol), *H*-phosphonate (0.40 mmol), TBHP (0.6 mmol), and CH_3CN (1.5 mL) were sequentially added to the system at room temperature. The reaction mixture was heated with stirring at 60 °C for 4 h. The reaction solution was concentrated in vacuo, and then 15 mL of saturated sodium bicarbonate solution was added and the resultant solution was extracted with EtOAc (3 × 10 mL). The combined organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography using a petroleum ether/AcOEt mixture [from 3:1 to 1:1 (v/v)] as the eluent to give the corresponding products.

Method B. A Schlenk tube containing $Mn(OAc)_3{\cdot}2H_2O$ (0.6 mmol) was evacuated and purged with nitrogen three times. Hydroxyalkenes (0.20 mmol), *H*-phosphonate (0.40 mmol), and CH_3COOH (1.5 mL) were sequentially added to the system at room temperature. The reaction mixture was heated with stirring at 80 °C for 4 h. The reaction solution was concentrated in vacuo, and then 15 mL of saturated sodium bicarbonate solution was added and the resultant solution was extracted with EtOAc (3 × 10 mL). The combined organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography using a petroleum ether/AcOEt mixture [from 3:1 to 1:1 (v/v)] as the eluent to give the corresponding products.

*Diisopropyl ((2-Phenyltetrahydrofuran-2-yl)methyl)phosphonate (**3a**).* Yield: 42 mg, 64% (Method A); 51 mg, 78% (Method B). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.43–7.41 (m, 2H), 7.32–7.28 (m, 2H), 7.23–7.19 (m, 1H), 4.68–4.49 (m, 2H), 4.02 (q, J = 7.5 Hz, 1H), 3.86–3.80 (m, 1H), 2.57–2.50 (m, 1H), 2.41–2.30 (m, 3H), 2.05–1.95 (m, 1H), 1.78–1.67 (m, 1H), 1.26 (d, J = 6.1 Hz, 3H), 1.20 (t, J = 5.2 Hz, 6H), 1.15 (d, J = 6.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 146.6 (d, J = 8.3 Hz), 128.1 (s), 126.8 (s), 125.4 (s), 83.9 (d, J = 2.4 Hz), 70.3 (d, J = 6.5 Hz), 69.8 (d, J = 6.9 Hz), 67.6 (s), 40.5 (d, J = 139.9 Hz), 37.7 (d, J = 4.1 Hz), 25.4 (s), 24.0 (m). ^{31}P NMR (162 MHz, $CDCl_3$) δ (ppm) 24.1. HRMS-

DOI: 10.1021/acs.joc.5b02026
J. Org. Chem. 2015, 80, 11398–11406

ESI: m/z found: 349.1541 ([M + Na]$^+$, $C_{17}H_{27}NaO_4P^+$ calcd. 349.1545).

*Diethyl ((2-Phenyltetrahydrofuran-2-yl)methyl)phosphonate (**3b**).* Yield: 40 mg, 62% (Method A); 43 mg, 72% (Method B). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.43−7.41 (m, 2H), 7.32−7.29 (m, 2H), 7.23−7.20 (m, 1H), 4.06−3.92 (m, 3H), 3.90−3.82 (m, 3H), 2.54−2.48 (m, 1H), 2.45−2.39 (m, 2H), 2.34−2.29 (m, 1H), 2.04−1.97 (m, 1H), 1.79−1.71 (m, 1H), 1.22 (t, J = 7.1 Hz, 3H), 1.15 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 146.4 (d, J = 8.0 Hz), 128.2 (s), 126.9 (s), 125.3 (s), 83.8 (d, J = 2.8 Hz), 67.8 (s), 61.7 (d, J = 6.2 Hz), 61.1 (d, J = 6.5 Hz), 39.1 (d, J = 138.5 Hz), 38.1 (d, J = 4.9 Hz), 25.4 (s), 16.4 (d, J = 6.3 Hz), 16.3 (d, J = 6.4 Hz). ^{31}P NMR (162 MHz, $CDCl_3$) δ (ppm) 26.0. HRMS-ESI: m/z found: 299.1415 ([M + H]$^+$, $C_{15}H_{24}O_4P^+$ calcd. 299.1412).

*Dibenzyl ((2-Phenyltetrahydrofuran-2-yl)methyl)phosphonate (**3c**).* Yield: 47 mg, 56% (Method A); 48 mg, 57% (Method B). Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.46−7.44 (m, 2H), 7.37−7.32 (m, 10H), 7.26−7.22 (m, 3H), 5.00−4.88 (m, 2H), 4.82 (d, J = 8.0 Hz, 2H), 4.07 (q, J = 7.5 Hz, 1H), 3.94−3.89 (m, 1H), 2.62−2.51 (m, 3H), 2.37−2.31 (m, 1H), 2.07−1.98 (m, 1H), 1.83−1.72 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 146.4 (d, J = 8.5 Hz), 136.8 (d, J = 6.5 Hz), 136.5 (d, J = 6.7 Hz), 128.5 (d, J = 1.9 Hz), 128.2 (d, J = 1.8 Hz), 128.0 (d, J = 4.7 Hz), 127.0 (s), 125.3 (s), 83.8 (d, J = 3.2 Hz), 67.9 (s), 67.3 (d, J = 6.1 Hz), 66.6 (d, J = 6.4 Hz), 39.5 (d, J = 137.9 Hz), 38.2 (d, J = 5.3 Hz), 25.4 (s). ^{31}P NMR (162 MHz, $CDCl_3$) δ (ppm) 27.2. HRMS-ESI: m/z found: 423.1731 ([M + H]$^+$, $C_{25}H_{28}O_4P^+$ calcd. 423.1725).

*Ethyl Phenyl((2-phenyltetrahydrofuran-2-yl)methyl)phosphinate (**3d**).* Yield: 45 mg, 68% (Method A); 43 mg, 65% (Method B). Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.71−7.66 (m, 2H), 7.60−7.55 (m, 2H), 7.50−7.31 (m, 10H), 7.26−7.07 (m, 6H), 4.01−3.63 (m, 8H), 2.76−2.56 (m, 6H), 2.38−2.21 (m, 2H), 2.05−1.91 (m, 2H), 1.82−1.64 (m, 2H), 1.22 (t, J = 7.0 Hz, 3H), 1.14 (t, J = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 147.2 (d, J = 7.5 Hz), 131.8 (s), 131.6 (d, J = 9.6 Hz), 131.5 (d, J = 9.0 Hz), 128.4 (s), 128.1 (s), 126.9 (s), 125.4 (s), 84.2 (s), 67.8 (s), 60.5 (d, J = 5.6 Hz), 43.33 (d, J = 38.6 Hz), 38.1 (s), 25.5 (s), 16.5 (d, J = 6.1 Hz). ^{31}P NMR (162 MHz, $CDCl_3$) δ (ppm) 39.8. HRMS-ESI: m/z found: 331.1467 ([M + H]$^+$, $C_{19}H_{24}O_3P^+$ calcd. 331.1463).

*Diphenyl((2-phenyltetrahydrofuran-2-yl)methyl)phosphine Oxide (**3e**).* Yield: 33 mg, 46% (Method A); 42 mg, 58% (Method B). White solid; mp 136−137 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.78−7.73 (m, 2H), 7.58−7.54 (m, 2H), 7.47−7.28 (m, 8H), 7.19−7.15 (m, 2H), 7.11−7.08 (m, 1H), 3.75−3.67 (m, 2H), 3.00−2.85 (m, 3H), 2.41−2.35 (m, 1H), 2.04−1.92 (m, 1H), 1.72−1.62 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 147.0 (d, J = 7.0 Hz), 135.1 (d, J = 19.0 Hz), 134.1 (d, J = 20.9 Hz), 131.2 (d, J = 2.3 Hz), 131.1 (d, J = 2.3 Hz), 130.9 (d, J = 9.4 Hz), 130.4 (d, J = 8.9 Hz), 128.5 (s), 128.4 (s), 128.2 (s), 126.9 (s), 125.2 (s), 84.9 (d, J = 4.1 Hz), 67.6 (s), 42.7 (d, J = 70.1 Hz), 37.6 (d, J = 2.5 Hz), 25.6 (s). ^{31}P NMR (162 MHz, $CDCl_3$) δ (ppm) 27.1. HRMS-ESI: m/z found: 363.1515 ([M + H]$^+$, $C_{23}H_{24}O_2P^+$ calcd. 363.1514).

*((2-Phenyltetrahydrofuran-2-yl)methyl)di-m-tolylphosphine Oxide (**3f**).* Yield: 48 mg, 62% (Method A); 53 mg, 68% (Method B). White solid; mp 122−124 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.68−7.63 (m, 2H), 7.47−7.43 (m, 2H), 7.37−7.35 (m, 2H), 7.23−7.17 (m, 4H), 7.13−7.09 (m, 3H), 3.77−3.68 (m, 2H), 3.00−2.85 (m, 3H), 2.40−2.33 (m, 4H), 2.31 (s, 3H), 2.03−1.93 (m, 1H), 1.73−1.59 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 147.3 (d, J = 7.3 Hz), 141.4 (d, J = 2.8 Hz), 141.3 (d, J = 2.6 Hz), 132.1 (d, J = 30.5 Hz), 131.1 (d, J = 31.1 Hz), 130.9 (d, J = 9.8 Hz), 130.4 (d, J = 9.5 Hz), 129.1 (d, J = 10.1 Hz), 128.9 (d, J = 11.0 Hz), 128.1 (s), 126.7 (s), 125.1 (s), 84.9 (d, J = 3.8 Hz), 67.6 (s), 42.7 (d, J = 69.5 Hz), 37.4 (d, J = 1.9 Hz), 25.6 (s), 21.6 (s), 21.5 (s). ^{31}P NMR (162 MHz, $CDCl_3$) δ (ppm) 26.7. HRMS-ESI: m/z found: 413.1649 ([M + Na]$^+$, $C_{25}H_{27}NaO_2P^+$ calcd. 413.1646).

*Diisopropyl ((2-(4-Fluorophenyl)tetrahydrofuran-2-yl)methyl)-phosphonate (**3g**).* Yield: 43 mg, 63% (Method A); 47 mg, 68% (Method B). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.43−7.39 (m, 2H), 7.01−6.97 (m, 2H), 4.68−4.50 (m, 2H), 4.01 (q, J = 7.5 Hz, 1H), 3.84−3.79 (m, 1H), 2.53−2.46 (m, 1H), 2.38−2.28 (m, 3H), 2.04−1.96 (m, 1H), 1.79−1.68 (m, 1H), 1.26 (d, J = 6.0 Hz, 3H), 1.21 (t, J = 6.3 Hz, 6H), 1.16 (d, J = 6.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 161.9 (d, J = 244.5 Hz), 142.1 (m), 127.3 (d, J = 8.0 Hz), 114.8 (d, J = 21.3 Hz), 83.6 (s), 70.3 (d, J = 6.6 Hz), 69.9 (d, J = 6.9 Hz), 67.5 (s), 40.7 (d, J = 141.3 Hz), 37.9 (d, J = 4.4 Hz), 25.4 (s), 24.0 (m). ^{31}P NMR (162 MHz, $CDCl_3$) δ (ppm) 23.7. ^{19}F NMR (377 MHz, $CDCl_3$) δ (ppm) −116.8. HRMS-ESI: m/z found: 345.1631 ([M + H]$^+$, $C_{17}H_{27}FO_4P^+$ calcd. 345.1631).

*Diisopropyl ((2-(4-Methoxyphenyl)tetrahydrofuran-2-yl)methyl)-phosphonate (**3h**).* Yield: 34 mg, 48% (Method A); 30 mg, 42% (Method B). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.36 (d, J = 8.7 Hz, 2H), 6.85 (d, J = 8.8 Hz, 2H), 4.67−4.60 (m, 1H), 4.59−4.52 (m, 1H), 4.01 (q, J = 7.7 Hz, 1H), 3.84−3.80 (m, 4H), 2.53−2.47 (m, 1H), 2.43−2.30 (m, 3H), 2.04−1.97 (m, 1H), 1.80−1.71 (m, 1H), 1.28 (d, J = 6.1 Hz, 3H), 1.22 (t, J = 6.4 Hz, 6H), 1.17 (d, J = 6.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 158.6 (s), 138.6 (d, J = 7.8 Hz), 126.8 (s), 113.5 (s), 83.8 (s), 70.2 (d, J = 6.4 Hz), 69.9 (d, J = 6.5 Hz), 67.4 (s), 55.5 (s), 40.7 (d, J = 139.4 Hz), 37.6 (d, J = 3.6 Hz), 25.5 (s), 24.1 (m). ^{31}P NMR (162 MHz, $CDCl_3$) δ (ppm) 24.1. HRMS-ESI: m/z found: 379.1650 ([M + Na]$^+$, $C_{18}H_{29}NaO_5P^+$ calcd. 379.1650).

*Diisopropyl ((Tetrahydrofuran-2-yl)methyl)phosphonate (**3i**).* Yield: 24 mg, 48% (Method A); 17 mg, 34% (Method B). Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 4.75−4.65 (m, 2H), 4.15−4.06 (m, 1H), 3.85 (q, J = 7.8 Hz, 1H), 3.70 (q, J = 7.8 Hz, 1H), 2.22−2.08 (m, 2H), 1.94−1.84 (m, 3H), 1.68−1.61 (m, 1H), 1.30 (d, J = 6.2 Hz, 12H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 74.4 (s), 70.4 (d, J = 6.7 Hz), 70.2 (d, J = 6.4 Hz), 67.7 (s), 33.9 (d, J = 139.1 Hz), 32.5 (d, J = 5.9 Hz), 25.8 (s), 24.2 (m). ^{31}P NMR (162 MHz, $CDCl_3$) δ (ppm) 25.7. HRMS-ESI: m/z found: 273.1235 ([M + Na]$^+$, $C_{11}H_{23}NaO_4P^+$ calcd. 273.1232).

*Diisopropyl ((4,4-Dimethyltetrahydrofuran-2-yl)methyl)-phosphonate (**3j**).* Yield: 24 mg, 43% (Method A); 21 mg, 37% (Method B). Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 4.74−4.64 (m, 2H), 4.31−4.23 (m, 1H), 3.50 (d, J = 8.0 Hz, 1H), 3.41 (d, J = 8.2 Hz, 1H), 2.24−2.14 (m, 1H), 1.96−1.86 (m, 2H), 1.52−1.46 (m, 1H), 1.30 (d, J = 6.2 Hz,, 12H), 1.09 (s, 3H), 1.08 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 80.0 (s), 74.4 (s), 70.4 (d, J = 6.5 Hz), 70.2 (d, J = 6.5 Hz), 48.0 (d, J = 5.2 Hz), 40.1 (s), 34.7 (d, J = 139.1 Hz), 27.0 (s), 26.6 (s), 24.2 (m). ^{31}P NMR (162 MHz, $CDCl_3$) δ (ppm) 25.4. HRMS-ESI: m/z found: 301.1541 ([M + Na]$^+$, $C_{13}H_{27}NaO_4P^+$ calcd. 301.1545).

*Diisopropyl ((2-Phenyltetrahydro-2H-pyran-2-yl)methyl)-phosphonate (**3k**).* Yield: 42 mg, 62% (Method A); 43 mg, 63% (Method B). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.46−7.45 (m, 2H), 7.37−7.34 (m, 2H), 7.27−7.23 (m, 1H), 4.68−4.58 (m, 1H), 4.46−4.35 (m, 1H), 3.71−3.66 (m, 1H), 3.42−3.36 (m, 1H), 2.70−2.67 (m, 1H), 2.30−2.10 (m, 3H), 1.70−1.60 (m, 2H), 1.54−1.46 (m, 1H), 1.38−1.33 (m, 1H), 1.26 (d, J = 6.2 Hz, 3H), 1.21 (d, J = 6.2 Hz, 3H), 1.14 (d, J = 6.2 Hz, 3H), 1.03 (d, J = 6.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 142.7 (d, J = 6.1 Hz), 128.5 (s), 127.4 (s), 127.1 (s), 76.5 (d, J = 2.4 Hz), 70.2 (d, J = 6.1 Hz), 69.7 (d, J = 6.8 Hz), 62.7 (s), 44.2 (d, J = 140.6 Hz), 32.7 (s), 26.0 (s), 24.1 (m), 20.0 (s). ^{31}P NMR (162 MHz, $CDCl_3$) δ (ppm) 23.9. HRMS-ESI: m/z found: 363.1702 ([M + Na]$^+$, $C_{18}H_{29}NaO_4P^+$ calcd. 363.1701).

*Diphenyl((2-phenyltetrahydro-2H-pyran-2-yl)methyl)phosphine Oxide (**3l**).* Yield: 32 mg, 42% (Method A); 31 mg, 41% (Method B). White solid; mp 176−179 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.73−7.68 (m, 2H), 7.45−7.36 (m, 5H), 7.33−7.31 (m, 2H), 7.28−7.26 (m, 1H), 7.20−7.17 (m, 2H), 7.13−7.09 (m, 2H), 7.03−7.00 (m, 1H), 3.75−3.67 (m, 2H), 3.00−2.85 (m, 3H), 2.41−2.35 (m, 1H), 1.67−1.60 (m, 2H), 1.58−1.43 (m, 1H), 1.37−1.24 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 142.0 (s), 135.6 (d, J = 101.5 Hz), 133.8 (d, J = 98.2 Hz), 131.2 (d, J = 2.1 Hz), 131.1 (d, J = 2.4 Hz), 130.8 (s), 130.7 (s), 130.6 (s), 128.6 (s), 128.4 (d, J = 11.7 Hz), 128.2 (d, J = 11.7 Hz), 127.2 (s), 127.1 (s), 77.8 (s), 62.7 (s), 46.2 (d, J = 70.1 Hz), 33.3 (s), 25.9 (s), 19.8 (s). ^{31}P NMR (162 MHz, $CDCl_3$) δ

DOI: 10.1021/acs.joc.5b02026
J. Org. Chem. 2015, 80, 11398−11406

(ppm) 26.2. HRMS-ESI: m/z found: 399.1490 ([M + Na]$^+$, $C_{24}H_{25}NaO_2P^+$ calcd. 399.1490).

*Diisopropyl (2-Phenyltetrahydrofuran-3-yl)phosphonate (**5a**).* Yield: 39 mg, 63% (Method A); 46 mg, 74% (Method B). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.42−7.40 (m, 2H), 7.35−7.31 (m, 2H), 7.28−7.26 (m, 1H), 5.00 (dd, J = 12.6 Hz, J = 7.3 Hz, 1H), 4.72−4.64 (m, 2H), 4.10 (dd, J = 14.9 Hz, J = 6.7 Hz, 1H), 3.98 (dd, J = 15.2 Hz, J = 7.1 Hz, 1H), 2.48−2.38 (m, 1H), 2.36−2.26 (m, 2H), 1.28 (t, J = 6.0 Hz, 6H), 1.24 (d, J = 6.2 Hz, 3H), 1.11 (d, J = 6.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 141.8 (d, J = 4.4 Hz), 128.5 (s), 127.9 (s), 126.7 (s), 81.6 (d, J = 2.2 Hz), 70.8 (d, J = 7.0 Hz), 70.5 (d, J = 7.2 Hz), 68.4 (d, J = 9.0 Hz), 45.2 (d, J = 149.2 Hz), 28.91 (d, J = 2.8 Hz), 24.1 (m). ^{31}P NMR (162 MHz, $CDCl_3$) δ (ppm) 27.3. HRMS-ESI: m/z found: 335.1388 ([M + Na]$^+$, $C_{16}H_{25}NaO_4P^+$ calcd. 335.1388).

*Diisopropyl (2-(p-Tolyl)tetrahydrofuran-3-yl)phosphonate (**5b**).* Yield: 35 mg, 53% (Method A); 38 mg, 58% (Method B). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.30−7.27 (m, 2H), 7.14−7.12 (m, 2H), 4.97 (dd, J = 12.5 Hz, J = 7.2 Hz, 1H), 4.72−4.64 (m, 2H), 4.09 (dd, J = 14.5 Hz, J = 6.7 Hz, 1H), 3.96 (dd, J = 15.2 Hz, J = 7.2 Hz, 1H), 2.44−2.37 (m, 1H), 2.33−2.28 (m, 5H), 1.28 (t, J = 5.7 Hz, 6H), 1.24 (d, J = 6.1 Hz, 3H), 1.13 (d, J = 6.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 138.8 (d, J = 4.3 Hz), 137.6 (s), 129.1 (s), 126.6 (s), 81.4 (d, J = 1.8 Hz), 70.9 (d, J = 6.7 Hz), 70.6 (d, J = 7.0 Hz), 68.3 (d, J = 8.7 Hz), 45.1 (d, J = 148.1 Hz), 28.9 (d, J = 2.4 Hz), 24.1 (m), 21.3 (s). ^{31}P NMR (162 MHz, $CDCl_3$) δ (ppm) 27.5. HRMS-ESI: m/z found: 349.1541 ([M + Na]$^+$, $C_{17}H_{27}NaO_4P^+$ calcd. 349.1545).

*Diisopropyl (2-(o-Tolyl)tetrahydrofuran-3-yl)phosphonate (**5c**).* Yield: 40 mg, 61% (Method A); 30 mg, 46% (Method B). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.24−7.20 (m, 3H), 7.08−7.07 (m, 1H), 4.97 (dd, J = 12.8 Hz, J = 7.5 Hz, 1H), 4.74−4.64 (m, 2H), 4.10 (dd, J = 14.6 Hz, J = 6.6 Hz, 1H), 3.97 (dd, J = 15.2 Hz, J = 7.2 Hz, 1H), 2.50−2.38 (m, 1H), 2.34−2.24 (m, 5H), 1.28 (dd, J = 5.9 Hz, J = 4.2 Hz, 6H), 1.24 (d, J = 6.1 Hz, 3H), 1.13 (d, J = 6.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 141.7 (d, J = 4.5 Hz), 138.0 (s), 128.6 (s), 128.3 (s), 127.3 (s), 123.8 (s), 81.6 (d, J = 2.1 Hz), 70.7 (d, J = 6.8 Hz), 70.4 (d, J = 7.0 Hz), 68.4 (d, J = 8.8 Hz), 45.1 (d, J = 148.6 Hz), 28.9 (d, J = 2.8 Hz), 24.1 (m), 21.6 (s). ^{31}P NMR (162 MHz, $CDCl_3$) δ (ppm) 27.4. HRMS-ESI: m/z found: 349.1546 ([M + Na]$^+$, $C_{17}H_{27}NaO_4P^+$ calcd. 349.1545).

*Diisopropyl (2-(m-Tolyl)tetrahydrofuran-3-yl)phosphonate (**5d**).* Yield: 29 mg, 45% (Method A); 35 mg, 53% (Method B). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.24−7.20 (m, 3H), 7.08−7.07 (m, 1H), 4.97 (dd, J = 12.8 Hz, J = 7.4 Hz, 1H), 4.74−4.63 (m, 2H), 4.10 (dd, J = 14.7 Hz, J = 6.8 Hz, 1H), 3.97 (dd, J = 15.3 Hz, J = 7.2 Hz, 1H), 2.50−2.38 (m, 1H), 2.34−2.24 (m, 5H), 1.28 (dd, J = 6.0 Hz, J = 4.2 Hz, 6H), 1.24 (d, J = 6.2 Hz, 3H), 1.13 (d, J = 6.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 141.7 (d, J = 4.2 Hz), 138.0 (s), 128.6 (s), 128.3 (s), 127.3 (s), 123.8 (s), 81.6 (d, J = 2.0 Hz), 70.7 (d, J = 6.7 Hz), 70.4 (d, J = 7.0 Hz), 68.4 (d, J = 8.8 Hz), 45.1 (d, J = 148.8 Hz), 28.9 (d, J = 2.8 Hz), 24.1 (m), 21.6 (s). ^{31}P NMR (162 MHz, $CDCl_3$) δ (ppm) 27.4. HRMS-ESI: m/z found: 349.1547 ([M + Na]$^+$, $C_{17}H_{27}NaO_4P^+$ calcd. 349.1545).

*Diisopropyl (2-(4-(tert-Butyl)phenyl)tetrahydrofuran-3-yl)-phosphonate (**5e**).* Yield: 40 mg, 54% (Method A); 42 mg, 57% (Method B). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.36−7.31 (m, 4H), 4.97 (dd, J = 12.4 Hz, J = 7.6 Hz, 1H), 4.70−4.62 (m, 2H), 4.08 (dd, J = 14.9 Hz, J = 6.9 Hz, 1H), 3.97 (dd, J = 15.0 Hz, J = 7.0 Hz, 1H), 2.49−2.39 (m, 1H), 2.35−2.25 (m, 2H), 1.30 (s, 9H), 1.27 (t, J = 6.4 Hz, 6H), 1.22 (d, J = 6.3 Hz, 3H), 1.10 (d, J = 6.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 150.9 (s), 141.6 (d, J = 4.4 Hz), 126.4 (s), 125.3 (s), 81.4 (d, J = 2.5 Hz), 70.7 (d, J = 6.9 Hz), 70.5 (d, J = 7.1 Hz), 68.2 (d, J = 9.4 Hz), 44.9 (d, J = 148.7 Hz), 34.6 (s), 31.5 (s), 28.9 (d, J = 2.7 Hz), 24.0 (m). ^{31}P NMR (162 MHz, $CDCl_3$) δ (ppm) 27.6. HRMS-ESI: m/z found: 369.2195 ([M + H]$^+$, $C_{20}H_{34}O_4P^+$ calcd. 369.2195).

*Diisopropyl (2-(4-Methoxyphenyl)tetrahydrofuran-3-yl)-phosphonate (**5f**).* Yield: 33 mg, 48% (Method A); 14 mg, 21% (Method B). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.34 (d, J = 7.8 Hz, 2H), 6.88 (d, J = 7.5 Hz, 2H), 4.95 (dd, J = 12.1 Hz, J = 7.5 Hz, 1H), 4.72−4.65 (m, 2H), 4.10 (q, J = 7.0 Hz, 1H), 3.96 (q, J = 7.2 Hz, 1H), 3.81 (s,3H), 2.45−2.28 (m, 3H), 1.29 (t, J = 5.0 Hz, 6H), 1.25 (d, J = 6.1 Hz, 3H), 1.14 (d, J = 6.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 159.5 (s), 133.9 (d, J = 3.9 Hz), 128.1 (s), 113.9 (s), 81.5 (d, J = 2.5 Hz), 70.8 (d, J = 7.0 Hz), 70.6 (d, J = 7.2 Hz), 68.3 (d, J = 9.0 Hz), 55.6 (s), 45.1 (d, J = 148.9 Hz), 29.0 (d, J = 2.5 Hz), 24.2 (m). ^{31}P NMR (162 MHz, $CDCl_3$) δ (ppm) 24.1. HRMS-ESI: m/z found: 365.1493 ([M + Na]$^+$, $C_{17}H_{27}NaO_5P^+$ calcd. 365.1494).

*Diisopropyl (2-(4-(Trifluoromethyl)phenyl)tetrahydrofuran-3-yl)-phosphonate (**5g**).* Yield: 31 mg, 41% (Method A); 39 mg, 51% (Method B). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.58 (dd, J = 18.1 Hz, J = 8.3 Hz, 4H), 5.07 (dd, J = 12.6 Hz, J = 6.8 Hz, 1H), 4.76−4.68 (m, 2H), 4.11 (dd, J = 14.7 Hz, J = 6.4 Hz, 1H), 4.01 (dd, J = 14.7 Hz, J = 7.0 Hz, 1H), 2.41−2.26 (m, 3H), 1.30 (d, J = 6.1 Hz, 6H), 1.28 (d, J = 6.2 Hz, 3H), 1.18 (d, J = 6.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 146.1 (d, J = 4.1 Hz), 130.1 (q, J = 32.5 Hz), 126.9 (s), 125.4 (q, J = 3.7 Hz), 124.3 (q, J = 271.6 Hz), 81.8 (d, J = 2.3 Hz), 71.1 (d, J = 6.9 Hz), 70.8 (d, J = 6.9 Hz), 68.6 (d, J = 9.0 Hz), 45.4 (d, J = 149.9 Hz), 29.0 (d, J = 2.8 Hz), 24.2 (m). ^{31}P NMR (162 MHz, $CDCl_3$) δ (ppm) 26.6. ^{19}P NMR (377 MHz, $CDCl_3$) δ (ppm) −62.8. HRMS-ESI: m/z found: 403.1262 ([M + Na]$^+$, $C_{17}H_{24}F_3NaO_4P^+$ calcd. 403.1262).

*Diisopropyl (2-(4-Chlorophenyl)tetrahydrofuran-3-yl)-phosphonate (**5h**).* Yield: 31 mg, 45% (Method A); 29 mg, 42% (Method B). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.36 (d, J = 8.4 Hz, 2H), 7.30 (d, J = 8.5 Hz, 2H), 4.97 (dd, J = 12.4 Hz, J = 6.7 Hz, 1H), 4.76−4.63 (m, 2H), 4.08 (dd, J = 14.6 Hz, J = 6.5 Hz, 1H), 3.97 (dd, J = 15.1 Hz, J = 7.0 Hz, 1H), 2.39−2.24 (m, 3H), 1.29 (d, J = 6.2 Hz, 6H), 1.26 (d, J = 6.1 Hz, 3H), 1.17 (d, J = 6.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 140.4 (d, J = 4.2 Hz), 133.6 (s), 128.6 (s), 128.1 (s), 80.9 (d, J = 2.2 Hz), 70.9 (d, J = 7.0 Hz), 70.6 (d, J = 7.1 Hz), 68.5 (d, J = 9.0 Hz), 45.3 (d, J = 148.9 Hz), 28.9 (d, J = 2.8 Hz), 24.2 (m). ^{31}P NMR (162 MHz, $CDCl_3$) δ (ppm) 27.0. HRMS-ESI: m/z found: 347.1180 ([M + H]$^+$, $C_{16}H_{25}ClO_4P^+$ calcd. 347.1179).

*Diisopropyl (2-(4-Bromophenyl)tetrahydrofuran-3-yl)-phosphonate (**5i**).* Yield: 41 mg, 52% (Method A); 34 mg, 43% (Method B). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.46 (d, J = 8.2 Hz, 2H), 7.30 (d, J = 8.1 Hz, 2H), 4.96 (q, J = 6.3 Hz, 1H), 4.74−4.65 (m, 2H), 4.08 (dd, J = 14.6 Hz, J = 6.7 Hz, 1H), 3.97 (dd, J = 14.2 Hz, J = 7.0 Hz, 1H), 2.42−2.22 (m, 3H), 1.29 (d, J = 6.2 Hz, 6H), 1.26 (d, J = 6.1 Hz, 3H), 1.17 (d, J = 6.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 141.0 (d, J = 4.6 Hz), 131.5 (s), 128.4 (s), 121.7 (s), 80.9 (d, J = 2.2 Hz), 70.9 (d, J = 7.0 Hz), 70.6 (d, J = 7.1 Hz), 68.5 (d, J = 8.9 Hz), 45.3 (d, J = 148.9 Hz), 28.9 (d, J = 2.9 Hz), 24.2 (m). ^{31}P NMR (162 MHz, $CDCl_3$) δ (ppm) 26.8. HRMS-ESI: m/z found: 413.0493 ([M + Na]$^+$, $C_{16}H_{24}BrNaO_4P^+$ calcd. 413.0493).

*Diisopropyl (2-(Naphthalen-2-yl)tetrahydrofuran-3-yl)-phosphonate (**5j**).* Yield: 20 mg, 27% (Method A); 22 mg, 30% (Method B). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.88−7.83 (m, 4H), 7.58−7.55 (m, 1H), 7.49−7.47 (m, 2H), 5.21 (dd, J = 13.0 Hz, J = 7.5 Hz, 1H), 4.77−4.68 (m, 2H), 4.20 (dd, J = 14.7 Hz, J = 6.8 Hz, 1H), 4.06 (dd, J = 15.3 Hz, J = 7.1 Hz, 1H), 2.58−2.48 (m, 1H), 2.42−2.32 (m, 2H), 1.30 (d, J = 5.9 Hz, 6H), 1.25 (d, J = 6.3 Hz, 3H), 1.13 (d, J = 6.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 139.3 (d, J = 4.5 Hz), 133.4 (s), 133.3 (s), 128.4 (s), 128.2 (s), 127.8 (s), 126.2 (s), 126.0 (s), 125.7 (s), 124.5 (s), 81.7 (d, J = 2.1 Hz), 70.9 (d, J = 6.9 Hz), 70.6 (d, J = 7.3 Hz), 68.6 (d, J = 8.7 Hz), 45.2 (d, J = 149.2 Hz), 29.0 (d, J = 2.8 Hz), 24.1 (m). ^{31}P NMR (162 MHz, $CDCl_3$) δ (ppm) 27.3. HRMS-ESI: m/z found: 385.1544 ([M + Na]$^+$, $C_{20}H_{27}NaO_4P^+$ calcd. 385.1545).

*Diisopropyl (2-(Thiophen-2-yl)tetrahydrofuran-3-yl)phosphonate (**5k**).* Yield: 20 mg. 31% (Method A); 22 mg, 34% (Method B). Yellow

DOI: 10.1021/acs.joc.5b02026
J. Org. Chem. 2015, 80, 11398−11406

oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.25−7.23 (m, 1H), 7.07 (d, J = 3.3 Hz, 1H), 6.94 (dd, J = 5.0 Hz, J = 3.6 Hz, 1H), 5.28 (dd, J = 12.6 Hz, J = 7.4 Hz, 1H), 4.74−4.66 (m, 2H), 4.06 (dd, J = 15.0 Hz, J = 6.9 Hz, 1H), 3.96 (dd, J = 14.0 Hz, J = 7.2 Hz, 1H), 2.59−2.49 (m, 1H), 2.40−2.24 (m, 2H), 1.30 (dd, J = 6.2 Hz, J = 2.7 Hz, 6H), 1.25 (d, J = 6.1 Hz, 3H), 1.19 (d, J = 6.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 145.4 (d, J = 5.8 Hz), 126.8 (s), 125.3 (s), 125.1 (s), 77.6 (d, J = 2.1 Hz), 70.9 (d, J = 6.8 Hz), 70.7 (d, J = 7.0 Hz), 68.2 (d, J = 9.1 Hz), 45.4 (d, J = 150.3 Hz), 28.8 (d, J = 2.8 Hz), 24.1 (m). ^{31}P NMR (162 MHz, $CDCl_3$) δ (ppm) 26.6. HRMS-ESI: m/z found: 341.0954 ($[M + Na]^+$, $C_{14}H_{23}NaO_4PS^+$ calcd. 341.0952).

*Diisopropyl (2-Methyl-2-phenyltetrahydrofuran-3-yl)-phosphonate (**5l**).* Yield: 34 mg, 52% (Method A); 43 mg, 66% (Method B). Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.58−7.56 (m, 2H), 7.32 (t, J = 7.4 Hz, 2H), 7.22 (t, J = 7.3 Hz, 1H), 4.82−4.69 (m, 2H), 4.13−4.08 (m, 1H), 3.82 (dd, J = 15.1 Hz, J = 8.1 Hz, 1H), 2.66−2.57 (m, 1H), 2.41−2.27 (m, 1H), 2.23−2.13 (m, 1H), 1.72 (s, 3H), 1.35−1.30 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 148.6 (d, J = 6.1 Hz), 128.3 (s), 126.8 (s), 125.0 (s), 85.0 (d, J = 2.9 Hz), 70.5 (t, J = 7.0 Hz), 66.4 (d, J = 11.5 Hz), 48.2 (d, J = 147.8 Hz), 29.7 (d, J = 3.1 Hz), 26.5 (d, J = 3.3 Hz), 24.3 (m). ^{31}P NMR (162 MHz, $CDCl_3$) δ (ppm) 26.1. HRMS-ESI: m/z found: 349.1541 ($[M + Na]^+$, $C_{17}H_{27}NaO_4P^+$ calcd. 349.1545).

*Diisopropyl (2-Cyclohexyltetrahydrofuran-3-yl)phosphonate (**5m**).* Yield: 10 mg, 15% (Method A); 29 mg, 46% (Method B). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 4.76−4.67 (m, 2H), 3.90−3.83 (m, 1H), 3.80−3.76 (m, 2H), 2.31−2.20 (m, 1H), 2.16−2.01 (m, 3H), 1.81−1.61 (m, 5H), 1.51−1.42 (m, 1H), 1.31 (d, J = 6.2 Hz, 12H), 1.24−1.18 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 83.6 (s), 70.5 (d, J = 7.1 Hz), 70.3 (d, J = 7.1 Hz), 67.7 (d, J = 7.2 Hz), 42.1 (d, J = 5.7 Hz), 38.6 (d, J = 149.1 Hz), 30.6 (s), 28.5 (d, J = 3.6 Hz), 27.0 (s), 26.6 (s), 26.3 (s), 24.3 (m).^{31}P NMR (162 MHz, $CDCl_3$) δ (ppm) 29.1. HRMS-ESI: m/z found: 319.2035 ($[M + H]^+$, $C_{16}H_{32}O_4P^+$ calcd. 319.2038).

*Bis(4-chlorophenyl)(2-phenyltetrahydrofuran-3-yl)phosphine Oxide (**5n**).* Yield: 27 mg, 33% (Method A); 33 mg, 40% (Method B). Paste form; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.70−7.65 (m, 2H), 7.45−7.37 (m, 4H), 7.20−7.15 (m, 3H), 7.10 (t, J = 7.7 Hz, 2H), 6.96 (d, J = 7.3 Hz, 2H), 5.03 (dd, J = 11.5 Hz, J = 8.2 Hz, 1H), 4.22−4.16 (m, 1H), 4.01 (dd, J = 15.7 Hz, J = 7.7 Hz, 1H), 2.96 (dd, J = 17.7 Hz, J = 7.9 Hz, 1H), 2.53−2.40 (m, 1H), 2.31−2.21 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 140.8 (d, J = 2.8 Hz), 138.8 (d, J = 3.4 Hz), 138.6 (d, J = 3.4 Hz), 132.4 (d, J = 10.1 Hz), 132.1 (d, J = 9.8 Hz), 131.5 (d, J = 100.1 Hz), 129.9 (d, J = 90.9 Hz), 129.4 (d, J = 12.1 Hz), 128.8 (d, J = 12.3 Hz), 128.5 (s), 128.1 (s), 126.7 (s), 80.9 (d, J = 2.9 Hz), 68.6 (d, J = 6.9 Hz), 46.4 (d, J = 74.7 Hz), 28.5 (s). ^{31}P NMR (162 MHz, $CDCl_3$) δ (ppm) 28.8. HRMS-ESI: m/z found: 417.0580 ($[M + H]^+$, $C_{22}H_{20}Cl_2O_2P^+$ calcd. 417.0578).

*Diphenyl(2-phenyltetrahydrofuran-3-yl)phosphine Oxide (**5o**).* Yield: 40 mg, 58% (Method A); 47 mg, 68% (Method B). White solid; mp 108−111 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.79−7.75 (m, 2H), 7.55−7.44 (m, 5H), 7.38−7.35 (m, 1H), 7.27−7.22 (m, 2H), 7.13−7.04 (m, 3H), 6.93 (d, J = 7.1 Hz, 2H), 5.10 (dd, J = 11.8 Hz, J = 7.9 Hz, 1H), 4.17 (dd, J = 12.4 Hz, J = 7.6 Hz, 1H), 3.99 (q, J = 7.7 Hz, 1H), 2.03 (dd, J = 16.4 Hz, J = 7.7 Hz, 1H), 2.51−2.43 (m, 1H), 2.34−2.22 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 141.4 (d, J = 3.4 Hz), 133.0 (d, J = 79.8 Hz), 132.2 (d, J = 93.4 Hz), 131.9 (d, J = 2.2 Hz), 131.7 (d, J = 2.4 Hz), 131.1 (d, J = 9.2 Hz), 130.7 (d, J = 8.9 Hz), 128.8 (d, J = 11.4 Hz), 128.5 (d, J = 11.7 Hz), 128.3 (s), 127.7 (s), 126.6 (s), 80.7 (d, J = 2.2 Hz), 68.7 (d, J = 6.1 Hz), 46.1 (d, J = 73.7 Hz), 28.6 (s). ^{31}P NMR (162 MHz, $CDCl_3$) δ (ppm) 31.2. HRMS-ESI: m/z found: 349.1360 ($[M + H]^+$, $C_{22}H_{22}O_2P^+$ calcd. 349.1357).

*Diphenyl(2-phenyltetrahydro-2H-pyran-3-yl)phosphine Oxide (**5p**).* Yield: 32 mg, 44% (Method A); 34 mg, 47% (Method B). White solid; mp 175−177 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.71−7.66 (m, 2H), 7.41−7.38 (m, 3H), 7.35−7.31 (m, 2H), 7.27−7.24 (m, 2H), 7.14−7.11 (m, 1H), 7.06−7.01 (m, 2H), 6.91−6.83 (m, 3H), 4.83 (dd, J = 9.8 Hz, J = 1.9 Hz, 1H), 4.18 (dd, J = 11.6 Hz, J = 2.0 Hz, 1H), 3.66−3.60 (m, 1H), 2.73−2.66 (m, 1H), 2.07−1.96 (m, 1H), 1.83−1.67 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 139.9 (s), 133.5 (d, J = 32.5 Hz), 132.5 (d, J = 34.2 Hz), 131.3 (d, J = 2.6 Hz), 130.7 (d, J = 8.6 Hz), 130.4 (d, J = 2.8 Hz), 130.2 (d, J = 8.8 Hz), 128.7 (d, J = 11.3 Hz), 128.2 (s), 128.1 (d, J = 1.2 Hz), 128.0 (s), 127.8 (s), 80.6 (d, J = 1.8 Hz), 68.4 (s), 41.7 (d, J = 69.9 Hz), 26.1 (d, J = 10.9 Hz), 24.4 (d, J = 1.9 Hz). ^{31}P NMR (162 MHz, $CDCl_3$) δ (ppm) 30.2. HRMS-ESI: m/z found: 385.1329 ($[M + Na]^+$, $C_{23}H_{23}NaO_2P^+$ calcd. 385.1333).

*Diisopropyl (2-Phenyltetrahydro-2H-pyran-3-yl)phosphonate (**5q**).* Yield: 34 mg, 52% (Method A); 35 mg, 54% (Method B). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.38−7.36 (m, 2H), 7.32−7.26 (m, 3H), 4.51−4.34 (m, 3H), 4.08 (dd, J = 11.3 Hz, J = 1.6 Hz, 1H), 3.60−3.54 (m, 1H), 2.33−2.28 (m, 1H), 2.22−2.11 (m, 1H), 1.87−1.72 (m, 3H), 1.16 (d, J = 6.2 Hz, 3H), 1.05−1.02 (m, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 141.1 (s), 128.19 (s), 128.17 (s), 128.11 (s), 81.4 (d, J = 2.7 Hz), 70.2 (d, J = 7.3 Hz), 69.8 (t, J = 7.4 Hz), 68.7 (s), 41.9 (d, J = 141.5 Hz), 25.8 (d, J = 13.2 Hz), 25.1 (d, J = 4.4 Hz), 23.9 (m). ^{31}P NMR (162 MHz, $CDCl_3$) δ (ppm) 25.6. HRMS-ESI: m/z found: 349.1544 ($[M + Na]^+$, $C_{17}H_{27}NaO_4P^+$ calcd. 349.1545).

*Diisopropyl (5,5-Dimethyl-2-phenyltetrahydro-2H-pyran-3-yl)-phosphonate (**5r**).* Yield: 38 mg, 53% (Method A); 43 mg, 61% (Method B). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.42−7.40 (m, 2H), 7.35−7.29 (m, 3H), 4.50−4.38 (m, 2H), 4.34 (d, J = 10.3 Hz, 1H), 3.59 (d, J = 11.2 Hz, 1H), 3.32 (d, J = 11.0 Hz, 1H), 2.44−2.33 (m, 1H), 1.99−1.96 (m, 1H), 1.70−1.63 (m, 1H), 1.2 (s, 6H), 1.06−1.04 (m, 9H), 0.9 (s 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 141.1 (s), 128.2 (s), 128.1 (s), 128.0 (s), 81.4 (d, J = 2.2 Hz), 78.3 (s), 70.2 (d, J = 7.1 Hz), 69.8 (d, J = 7.4 Hz), 38.7 (d, J = 134.2 Hz), 38.0 (s), 30.1 (d, J = 11.8 Hz), 27.1 (s), 23.9 (m), 23.5 (s). ^{31}P NMR (162 MHz, $CDCl_3$) δ (ppm) 26.1. HRMS-ESI: m/z found: 377.1858 ($[M + Na]^+$, $C_{19}H_{31}NaO_4P^+$ calcd. 377.1858).

*Diisopropyl ((5-Oxo-2-phenyltetrahydrofuran-2-yl)methyl)-phosphonate (**7a**, CAS Registry No. 1646566-97-3).* Yield: 52 mg, 76% (Method A). Yellow solid; mp 59−61 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.43−7.42 (m, 2H), 7.39−7.36 (m, 2H), 7.32−7.29 (m, 1H), 4.75−4.67 (m, 1H), 4.63−4.54 (m, 1H), 3.10−3.04 (m, 1H), 2.75−2.69 (m, 1H), 2.64−2.59 (m, 1H), 2.49 (d, J = 18.6 Hz, 2H), 2.46−2.41 (m, 1H), 1.31 (d, J = 6.2 Hz, 6H), 1.22 (d, J = 6.2 Hz, 3H), 1.18 (d, J = 6.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 176.0 (s), 143.8 (d, J = 9.4 Hz), 128.7 (s), 128.0 (s), 124.7 (s), 85.7 (s), 71.0 (d, J = 6.6 Hz), 70.6 (d, J = 6.8 Hz), 40.7 (d, J = 140.3 Hz), 33.7 (s), 28.8 (s), 23.9 (m). ^{31}P NMR (162 MHz, $CDCl_3$) δ (ppm) 21.2. MS-ESI: m/z 363.1 ($[M + Na]^+$).

*5-((Diphenylphosphoryl)methyl)-5-phenyldihydrofuran-2(3H)-one (**7b**, CAS Registry No. 1646567-10-3).* Yield: 54 mg, 71% (Method A). White solid; mp 169−171 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.75−7.71 (m, 2H), 7.54−7.44 (m, 5H), 7.40−7.27 (m, 5H), 7.20−7.13 (m, 3H), 3.41−3.35 (m, 1H), 3.10−3.01 (m, 2H), 2.75−2.68 (m, 2H), 2.42−2.35 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 175.8 (s), 143.1 (d, J = 6.0 Hz), 133.6 (d, J = 48.6 Hz), 132.7 (d, J = 48.1 Hz), 132.0 (d, J = 2.6 Hz), 131.6 (d, J = 2.6 Hz), 130.6 (d, J = 9.7 Hz), 130.3 (d, J = 9.3 Hz), 128.8 (d, J = 12.1 Hz), 128.6 (s), 128.5 (s), 128.2 (s), 124.8 (s), 86.9 (d, J = 2.5 Hz), 42.5 (d, J = 67.6 Hz), 33.6 (s), 28.7 (s). ^{31}P NMR (162 MHz, $CDCl_3$) δ (ppm) 26.0. MS-ESI: m/z 399.1 ($[M + Na]^+$).

*Diisopropyl ((2-(4-Fluorophenyl)-5-oxotetrahydrofuran-2-yl)-methyl)phosphonate (**7c**, CAS Registry No. 1646566-99-5).* Yield: 54 mg, 75% (Method A). Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.40−7.34 (m, 2H), 7.03−6.98 (m, 2H), 4.69−4.60 (m, 1H), 4.56−4.47 (m, 1H), 3.00−2.94 (m, 1H), 2.70−2.63 (m, 1H), 2.58−2.53 (m, 1H), 2.44−2.36 (m, 3H), 1.25 (d, J = 2.4 Hz, 3H), 1.24 (d, J = 2.4 Hz, 3H), 1.16 (d, J = 6.2 Hz, 3H), 1.12 (d, J = 6.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 175.8 (s), 162.4 (d, J = 247.5 Hz), 139.3 (d, J = 6.1 Hz), 126.8 (d, J = 8.2 Hz), 115.5 (d, J = 21.6 Hz), 85.5 (s), 71.1 (d, J = 6.6 Hz), 70.8 (d, J = 6.9 Hz), 40.8 (d, J = 140.3 Hz), 33.9 (s), 28.8 (s), 24.0 (m). ^{31}P NMR (162 MHz, $CDCl_3$) δ

DOI: 10.1021/acs.joc.5b02026
J. Org. Chem. 2015, 80, 11398−11406

(ppm) 20.8. ^{19}F NMR (377 MHz, $CDCl_3$) δ (ppm) −115.3. MS-ESI: m/z 381.2 ([M + Na]$^+$).

*Diisopropyl ((2S,3R)-2-(4-(tert-Butyl)phenyl)-5-oxotetrahydrofuran-3-yl)phosphonate (**7d**, CAS Registry No. 1646567-22-7).* Yield: 48 mg, 63% (Method A). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.42−7.40 (m, 2H), 7.31−7.29 (m, 2H), 5.61 (dd, J = 13.3 Hz, J = 7.1 Hz, 1H), 4.75−4.63 (m, 2H), 2.92−2.86 (m, 2H), 2.81−2.72 (m, 1H), 1.31−1.29 (m, 15H), 1.22 (d, J = 6.2 Hz, 3H), 1.15 (d, J = 6.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 174.7 (d, J = 12.2 Hz), 152.3 (s), 138.4 (d, J = 5.1 Hz), 126.0 (s), 125.8 (s), 81.2 (s), 71.8 (d, J = 7.0 Hz), 71.5 (d, J = 7.2 Hz), 41.6 (d, J = 152.7 Hz), 34.8 (s), 31.4 (s), 30.5 (d, J = 4.2 Hz), 24.0 (m). ^{31}P NMR (162 MHz, $CDCl_3$) δ (ppm) 22.5. MS-ESI: m/z 405.2 ([M + Na]$^+$).

*Diisopropyl ((2S,3R)-2-(4-Methoxyphenyl)-5-oxotetrahydrofuran-3-yl)phosphonate (**7e**, CAS Registry No. 1646567-24-9).* Yield: 41 mg, 57% (Method A). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.29 (d, J = 8.6 Hz, 2H), 6.91 (d, J = 8.7 Hz, 2H), 5.58 (dd, J = 12.9 Hz, J = 7.5 Hz, 1H), 4.74−4.65 (m, 2H), 3.81 (s, 3H), 2.92−2.87 (m, 2H), 2.81−2.73 (m, 1H), 1.30 (d, J = 2.7 Hz, 3H), 1.29 (d, J = 2.7 Hz, 3H), 1.23 (d, J = 6.2 Hz, 3H), 1.17 (d, J = 6.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 174.6 (d, J = 13.5 Hz), 160.3 (s), 130.3 (d, J = 4.7 Hz), 127.8 (s), 114.2 (s), 81.3 (s), 71.8 (d, J = 7.1 Hz), 71.5 (d, J = 7.1 Hz), 55.5 (s), 41.6 (d, J = 152.4 Hz), 34.7 (d, J = 3.9 Hz), 24.0 (m). ^{31}P NMR (162 MHz, $CDCl_3$) δ (ppm) 22.5. MS-ESI: m/z 379.1 ([M + Na]$^+$).

*Diisopropyl ((2R,3R)-5-Oxo-2-(thiophen-2-yl)tetrahydrofuran-3-yl)phosphonate (**7f**, CAS Registry No. 1646567-36-3).* Yield: 31 mg, 47% (Method A). Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.34−7.33 (m, 1H), 7.14−7.13 (m, 1H), 6.99−6.97 (m, 1H), 5.83 (dd, J = 12.8 Hz, J = 6.5 Hz, 1H), 4.78−4.62 (m, 2H), 2.95−2.87 (m, 3H), 1.29 (d, J = 3.5 Hz, 3H), 1.27 (d, J = 3.4 Hz, 3H), 1.19 (t, J = 6.0 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 173.8 (d, J = 12.5 Hz), 141.1 (d, J = 6.4 Hz), 127.1 (s), 127.0 (s), 126.8 (s), 77.3 (s), 72.0 (d, J = 6.8 Hz), 71.8 (d, J = 7.0 Hz), 41.9 (d, J = 152.4 Hz), 30.7 (d, J = 3.7 Hz), 24.0 (m). ^{31}P NMR (162 MHz, $CDCl_3$) δ (ppm) 21.8. MS-ESI: m/z 355.1 ([M + Na]$^+$).

*Diisopropyl ((2S,3R)-6-Oxo-2-phenyltetrahydro-2H-pyran-3-yl)-phosphonate (**7g**, CAS Registry No. 1646567-56-7).* Yield: 30 mg, 44% (Method A). White solid; mp 63−65 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.38−7.32 (m, 5H), 5.55 (t, J = 7.9 Hz, 1H), 4.64−4.54 (m, 2H), 2.83−2.76 (m, 1H), 2.62−2.55 (m, 1H), 2.47−2.38 (m, 1H), 2.27−2.17 (m, 2H), 1.26 (d, J = 6.1 Hz, 3H), 1.17 (d, J = 6.2 Hz, 6H), 1.09 (d, J = 6.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 170.7 (s), 138.7 (d, J = 4.6 Hz), 128.9 (s), 128.6 (s), 127.3 (s), 81.2 (s), 71.5 (d, J = 7.2 Hz), 71.1 (d, J = 7.3 Hz), 38.7 (d, J = 144.5 Hz), 28.8 (d, J = 9.2 Hz), 24.0 (m), 19.8 (d, J = 3.7 Hz). ^{31}P NMR (162 MHz, $CDCl_3$) δ (ppm) 23.8. MS-ESI: m/z 363.1 ([M + Na]$^+$).

*Disopropyl ((5-Oxotetrahydrofuran-2-yl)methyl)phosphonate (**7h**, CAS Registry No. 1646567-12-5).* Yield: 45 mg, 62% (Method A). Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 4.73−4.59 (m, 3H), 2.49−2.45 (m, 2H), 2.43−2.37 (m, 1H), 2.30−2.22 (m, 1H), 2.05−1.93 (m, 2H), 1.26−1.24 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 176.4 (s), 75.9 (s), 71.0 (d, J = 6.6 Hz), 70.8 (d, J = 6.5 Hz), 33.6 (d, J = 141.0 Hz), 28.9 (d, J = 4.8 Hz), 28.7 (s), 24.1 (m). ^{31}P NMR (162 MHz, $CDCl_3$) δ (ppm) 22.5. MS-ESI: m/z 387.1 ([M + Na]$^+$).

*Diisopropyl ((4,4-Dimethyl-5-oxotetrahydrofuran-2-yl)methyl)-phosphonate (**7i**).* Yield: 32 mg, 54% (Method A). Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 4.71−4.59 (m, 3H), 2.35−2.25 (m, 2H), 1.98−1.90 (m, 1H), 1.86−1.81 (m, 1H), 1.27−1.26 (m, 12H), 1.20 (s, 3H), 1.19 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 181.2 (s), 72.2 (s), 71.0 (d, J = 6.7 Hz), 70.8 (d, J = 6.5 Hz), 44.4 (d, J = 5.0 Hz), 40.5 (s), 33.9 (d, J = 141.4 Hz), 25.0 (s), 24.3 (s), 24.0 (m). ^{31}P NMR (162 MHz, $CDCl_3$) δ (ppm) 22.8. HRMS-ESI: m/z found: 315.1334 ([M + Na]$^+$, $C_{13}H_{25}NaO_5P^+$ calcd. 315.1337).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02026.

Copies of ^{1}H NMR and ^{13}C NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: t12g21@xmu.edu.cn. Fax: (86)592-2185780.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We acknowledge financial support from the Chinese National Natural Science Foundation (21173178, 21232005, 21375113), the National Basic Research Program of China (2012CB821600), and the Program for Changjiang Scholars and Innovative Research Team in University.

■ REFERENCES

(1) Lorente, A.; Lamariano-Merketegi, J.; Albericio, F.; Álvarez, M. *Chem. Rev.* **2013**, *113*, 4567.

(2) (a) Jackson, K. L.; Henderson, J. A.; Phillips, A. J. *Chem. Rev.* **2009**, *109*, 3044. (b) Ciminiello, P.; Dell'Aversano, C.; Forino, M.; Tartaglione, L. *Eur. J. Org. Chem.* **2014**, *2014*, 1357. (c) Ledford, H. *Nature* **2010**, *468*, 608. (d) Donohoe, T. J.; Lipiński, R. M. *Angew. Chem., Int. Ed.* **2013**, *52*, 2491. (e) Hu, T.; deFreitas, A. S. W.; Curtis, J. M.; Oshima, Y.; Walter, J. A.; Wright, J. L. C. *J. Nat. Prod.* **1996**, *59*, 1010. (f) Torigoe, K.; Murata, M.; Yasumoto, T.; Iwashita, T. *J. Am. Chem. Soc.* **1988**, *110*, 7876. (g) Suzuki, M.; Ueoka, R.; Takada, K.; Okada, S.; Ohtsuka, S.; Ise, Y.; Matsunaga, S. *J. Nat. Prod.* **2012**, *75*, 1192. (h) Paterson, I.; Dalby, S. M. *Nat. Prod. Rep.* **2009**, *26*, 865.

(3) (a) Fleming, F. F.; Gudipati, V.; Steward, O. W. *J. Org. Chem.* **2003**, *68*, 3943. (b) Ramachandran, P. V.; Nair, H. N. G.; Gagare, P. D. *J. Org. Chem.* **2012**, *77*, 5394. (c) Zhu, C.; Falck, J. R. *Angew. Chem., Int. Ed.* **2011**, *50*, 6626. (d) Makosza, M.; Judka, M. *Chem.—Eur. J.* **2002**, *8*, 4234. (e) Loh, T. P.; Hu, Q. Y.; Ma, L. T. *J. Am. Chem. Soc.* **2001**, *123*, 2450. (f) Zhu, R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2015**, *137*, 8069.

(4) (a) Baumgartner, T.; Réau, R. *Chem. Rev.* **2006**, *106*, 4681. (b) McManus, H. A.; Guiry, P. J. *Chem. Rev.* **2004**, *104*, 4151. (c) Birkholz, M.-N.; Freixa, Z.; van Leeuwen, W. N. M. *Chem. Soc. Rev.* **2009**, *38*, 1099.

(5) (a) *Phosphorus Heterocycles II*; Bansal, R. K., Ed.; *Topics in Heterocyclic Chemistry*; Springer-Verlag: Berlin, 2010; Vol. *21*. (b) *Phosphorus Chemistry II*; Montchamp, J. L., Ed.; *Topics in Current Chemistry*; Springer International Publishing AG: Cham (ZG), Switzerland, 2015.

(6) Mansueto, R.; Mallardo, V.; Perna, F. M.; Salomone, A.; Capriati, V. *Chem. Commun.* **2013**, *49*, 10160.

(7) (a) Vander Jeught, S.; Stevens, C. V. *Chem. Rev.* **2009**, *109*, 2672. (b) Mondal, M.; Bora, U. *RSC Adv.* **2013**, *3*, 18716.

(8) Zhao, Z.; Xue, W.; Gao, Y.; Tang, G.; Zhao, Y. *Chem. - Asian J.* **2013**, *8*, 713.

(9) (a) Xu, J.; Zhang, P.; Gao, Y.; Chen, Y.; Tang, G.; Zhao, Y. *J. Org. Chem.* **2013**, *78*, 8176. (b) Gao, Y.; Huang, Z.; Zhuang, R.; Xu, J.; Zhang, P.; Tang, G.; Zhao, Y. *Org. Lett.* **2013**, *15*, 4214.

(10) (a) Zhang, P.; Zhang, L.; Gao, Y.; Xu, J.; Fang, H.; Tang, G.; Zhao, Y. *Chem. Commun.* **2015**, *51*, 7839. (b) Xu, J.; Li, X.; Gao, Y.; Zhang, L.; Chen, W.; Fang, H.; Tang, G.; Zhao, Y. *Chem. Commun.* **2015**, *51*, 11240.

(11) (a) Zhou, Z. Z.; Jin, D. P.; Li, L. H.; He, Y. T.; Zhou, P. X.; Yan, X. B.; Liu, X. Y.; Liang, Y. M. *Org. Lett.* **2014**, *16*, 5616. (b) Zhang, B. C.; Daniliuc, G.; Studer, A. *Org. Lett.* **2014**, *16*, 250. (c) Chen, X.; Li, X.; Chen, X. L.; Qu, L. B.; Chen, J. Y.; Sun, K.; Liu, Z. D.; Bi, W. Z.; Xia, Y. Y.; Wu, H. T.; Zhao, Y. F. *Chem. Commun.* **2015**, *51*, 3846. (d) Li, Y. M.; Sun, M.; Wang, H. L.; Tian, Q. P.; Yang, S. D. *Angew. Chem., Int. Ed.* **2013**, *52*, 3972.

(12) (a) Xiong, B.; Feng, X.; Zhu, L.; Chen, T.; Zhou, Y.; Au, C. T.; Yin, S. F. *ACS Catal.* **2015**, *5*, 537. (b) Zhou, M.; Chen, M.; Zhou, Y.; Yang, K.; Su, J.; Du, J.; Song, Q. *Org. Lett.* **2015**, *17*, 1786. (c) Liu, N.;

Mao, L. L.; Yang, B.; Yang, S. D. *Chem. Commun.* **2014**, *50*, 10879. (d) Zhang, H. Y.; Mao, L. L.; Yang, B.; Yang, S. D. *Chem. Commun.* **2015**, *51*, 4101.

(13) (a) Snider, B. B. *Chem. Rev.* **1996**, *96*, 339. (b) Liu, W.; Zell, D.; John, M.; Ackermann, L. *Angew. Chem., Int. Ed.* **2015**, *54*, 4092. (c) Li, X.; Xu, J.; Gao, Y.; Fang, H.; Tang, G.; Zhao, Y. *J. Org. Chem.* **2015**, *80*, 2621. (d) Gao, Y.; Xu, J.; Zhang, P.; Fang, H.; Tang, G.; Zhao, Y. *RSC Adv.* **2015**, *5*, 36167. (e) Fisher, H. C.; Berger, O.; Gelat, F.; Montchamp, J. L. *Adv. Synth. Catal.* **2014**, *356*, 1199. (f) Li, D. P.; Pan, X. Q.; An, L. T.; Zou, J. P.; Zhang, W. *J. Org. Chem.* **2014**, *79*, 1850. (g) Cao, X. H.; Pan, X.; Zhou, P. J.; Zou, J. P.; Asekun, O. T. *Chem. Commun.* **2014**, *50*, 3359. (h) Zhou, S. F.; Li, D. P.; Liu, K.; Zou, J. P.; Asekun, O. T. *J. Org. Chem.* **2015**, *80*, 1214.

(14) Gao, Y.; Li, X.; Xu, J.; Wu, Y.; Chen, W.; Tang, G.; Zhao, Y. *Chem. Commun.* **2015**, *51*, 1605.

(15) (a) Huang, D.; Wang, H.; Xue, F.; Guan, H.; Li, L.; Peng, X.; Shi, Y. *Org. Lett.* **2011**, *13*, 6350. (b) Zeng, X.; Miao, C.; Wang, S.; Xia, C.; Sun, W. *Chem. Commun.* **2013**, *49*, 2418. (c) Spivey, A. C.; Laraia, L.; Bayly, A. R.; Rzepa, H. S.; White, A. J. P. *Org. Lett.* **2010**, *12*, 900.

DOI: 10.1021/acs.joc.5b02026
J. Org. Chem. 2015, 80, 11398−11406