JOC The Journal of Organic Chemistry

Note

pubs.acs.org/joc

Silver-Catalyzed, Aldehyde-Induced α-C−H Functionalization of Tetrahydroisoquinolines with Concurrent C−P Bond Formation/N-Alkylation

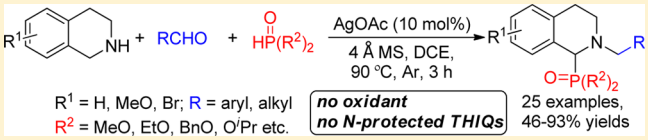
Gaobo Hu,[†,∥] Weizhu Chen,[†,§,∥] Dumei Ma,[‡] Yun Zhang,[†] Pengxiang Xu,[†] Yuxing Gao,*[,†] and Yufen Zhao[†]

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

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

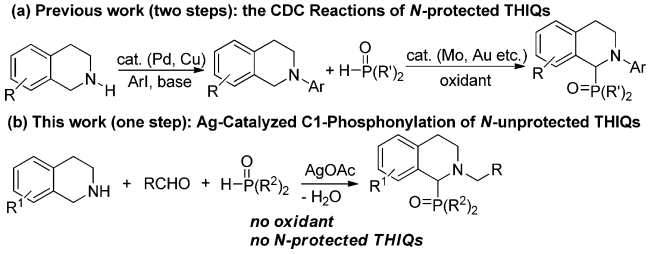
Supporting Information

ABSTRACT: The first facile and efficient silver-catalyzed, aldehyde-induced three-component reaction of N-unprotected tetrahydroisoquinolines, aldehydes, and dialkyl phosphonates has been developed, providing a general one-step approach to structurally diverse C1-phosphonylated THIQs accompanied by concurrent C−P bond formation/N-alkylation with remarkable functional group tolerance and excellent regioselectivity for endo products.



Considerable interest in organic and medicinal chemistry over the past several decades has been given to α-aminophosphonates and their derivatives because they are functional surrogates for both natural and unnatural α-amino carboxylic acids,[1] which have broad applications owing to their unusual structural features and their association with diverse biological activities in agrochemicals and medicines,[2] as herbicides,[3] plant virucides,[3a,4] antibacterial agents,[5] antifungal agents,[4,6] antiviral agents,[7] and enzyme inhibitory[2a,8] and catalytic antibody activities.[9] Among these α-aminophosphonates, C1-phosphonylated 1,2,3,4-tetrahydroisoquinolines (THIQs) as α-amino acid mimics have attracted significant attention from synthetic chemists because they are both α-aminophosphonates and alkaloids containing the potentially biologically active THIQ moiety[10] and thus probably exhibit intriguing biological properties. Not surprisingly, many efforts have been devoted to the efficient synthesis of C1-phosphonylated THIQs, and a few synthetic methods have emerged in recent years. In 2009, Li's group reported the first synthesis of C1-phosphonylated THIQs through a copper-catalyzed aerobic cross-dehydrogenative-coupling (CDC) reaction of N-protected THIQs.[11] Subsequently, this oxidative C−H functionalization of N-protected THIQs was further developed based on several methods including Mo_2O_3-,[12] Au-,[13] photo-,[14] DDQ-,[15] I_2-,[16] SO_2Cl_2-,[17] Sb/NHPI-,[18] triarylaminium salt-,[19] and CBr_4-catalyzed[20] CDC reactions (Scheme 1a). Despite the success of these procedures for the C1-phosphonylation of THIQs, almost all of these methods suffer from three fundamental drawbacks: these methods require both stoichiometric amounts of oxidants to facilitate the reaction and the previous preparation of N-protected THIQs through transition-metal-catalyzed C−N coupling of N-unprotected THIQs;[21] in addition, the substrate scope is limited to N-aromatic substituted THIQs, thus limiting the synthesis and discovery of novel α-aminophosphonates of biological importance. Therefore, it is of great value to develop a new method for direct C1-phosphonylation of N-unprotected THIQs under oxidant-free conditions, which might significantly extend the scope of the synthesis of C1-phosphonylated THIQs. In connection with our efforts to develop new methods for the synthesis of phosphorus-containing compounds,[22] we herein reveal the first example of a one-pot preparation of diverse C1-phosphonylated THIQs through a facile and efficient Ag-catalyzed three-component C1-phosphonylation of unprotected THIQs (Scheme 1b) with readily available aldehydes under oxidant-free, mild reaction conditions, with remarkable functional group tolerance, high regioselectivity, and good to excellent yields. This reaction features a combination of an oxidative α-C−H functionalization and a reductive N-alkylation, providing rapid access to various new α-aminophosphonates not easily accessible by known CDC

Scheme 1. Methods for the Synthesis of C1-Phosphonylated THIQs



Received: November 16, 2015
Published: January 12, 2016

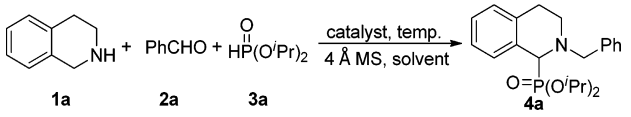
DOI: 10.1021/acs.joc.5b02625
J. Org. Chem. 2016, 81, 1704−1711

methods; to the best of our knowledge, this method has not been reported to date.

We started our studies of the C1-phosphonylation of THIQ (**1a**) in the presence of AgOAc (10 mol %) and toluene (1 mL) under an argon atmosphere at room temperature for 24 h (Table 1, entry 1). At first, without activated 4 Å molecular sieves (MS), the three-component reaction of THIQ (**1a**), benzaldehyde (**2a**), and diisopropyl phosphonate (**3a**) did not proceed (Table1, entry 1). Gratifyingly, upon adding 4 Å MS to the mixture, the reaction occurred and afforded the desired C1-phosphonylation product **4a** in 44% yield (Table 1, entry 2), revealing that 4 Å MS are essential for the transformation. Encouraged by this promising result, some commonly used solvents were investigated. It was found that 1,2-dichloroethane (DCE) was the best choice for this reaction, affording **4a** in 76% yield (Table 1, entry 5). To advance the process further, other silver salts such as $AgNO_3$ and Ag_2CO_3 were also explored, but improved results were not obtained (Table 1, entries 7 and 8). Notably, without AgOAc, the yield of **4a** dropped substantially to 26%, clearly indicating that the silver catalyst AgOAc was crucial for this reaction (Table 1, entry 9). Subsequently, the effect of temperature was evaluated. To our delight, raising the temperature to 90 °C and decreasing the reaction time to 3 h gave an increased yield up to 93% (Table 1, entry 11). Yet, further increasing the reaction temperature to 100 °C resulted in a yield reduction (Table 1, entry 12). Finally, the loading of AgOAc was also evaluated, and 5 mol % of AgOAc led to a slightly reduced yield (Table 1, entry 13). Under open air, the reaction yield decreased to 88%, probably due to the influence of moisture in air (Table 1, entry 14). It is worth noting that only endo-phosphonylation product **4a** was observed and that exo-phosphonylation product **4a′** was not produced in the above cases.

With the optimized reaction conditions in hand (footnote *a*, Table 2), we investigated the substrate scope of the AgOAc-catalyzed C1-phosphonylation of **1a** with various aldehydes. The results are summarized in Table 2. The method was found

Table 1. Optimization of Reaction Conditions[a]

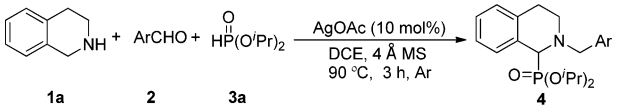


1a 2a 3a 4a

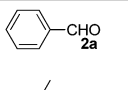
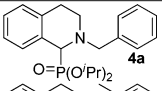
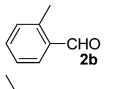
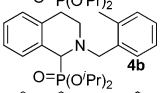
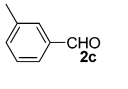
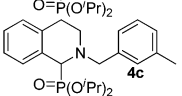
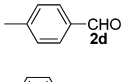
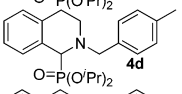
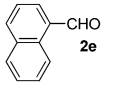
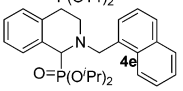
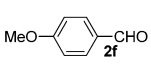
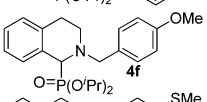
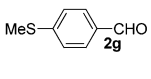
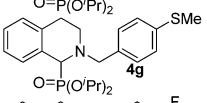
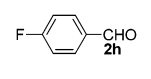
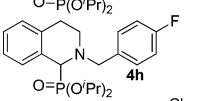
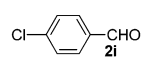
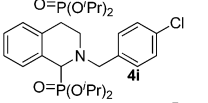
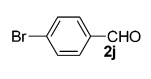
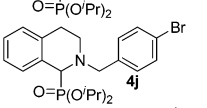
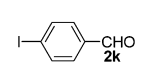
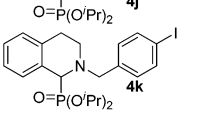
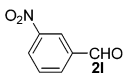
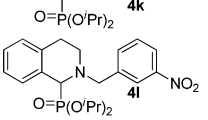
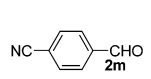
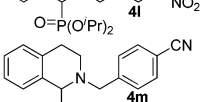
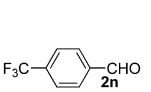
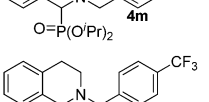
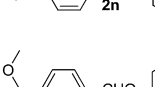
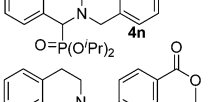
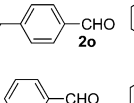
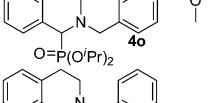
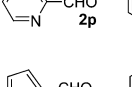
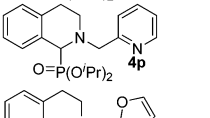
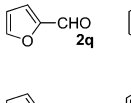
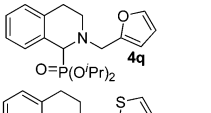
entry	catalyst	solvent	temp (°C)	time (h)	yield (%)
1	AgOAc	toluene	rt	24	0[b]
2	AgOAc	toluene	rt	24	44
3	AgOAc	THF	rt	24	21
4	AgOAc	DCM	rt	24	54
5	AgOAc	DCE	rt	24	76
6	AgOAc	dioxane	rt	24	32
7	$AgNO_3$	DCE	rt	24	30
8	Ag_2CO_3	DCE	rt	24	13
9		DCE	rt	24	26
10	AgOAc	DCE	70	12	88
11	**AgOAc**	**DCE**	**90**	**3**	**93**
12	AgOAc	DCE	100	3	87
13	AgOAc	DCE	90	3	85[c]
14	AgOAc	DCE	90	3	88[d]

[a]Ratio: **1a**/**2a**/**3a** = 1.2:1.0 (0.3 mmol):1.2 equiv; 100 mg 4 Å MS; under argon. [b]Without 4 Å MS. [c]Using 5 mol % of AgOAc. [d]Under open air.

Table 2. Reaction Scope of Aromatic Aldehydes with 3a and 1a[a]



1a 2 3a 4

Entry	2	4	Yield (%)
1			93
2			81
3			77
4			85
5			82
6			61
7			74
8			86
9			82
10			86
11			78
12			66
13			78
14			74
15			81
16			54
17			83
18			79

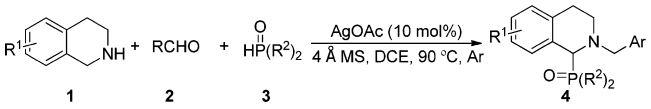
[a]Ratio: **1**/**2**/**3** = 1.2:1.0 (0.3 mmol):1.2 equiv; 100 mg 4 Å MS; DCE (1 mL); 90 °C; 3 h; under argon.

DOI: 10.1021/acs.joc.5b02625
J. Org. Chem. 2016, 81, 1704−1711

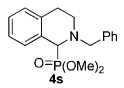
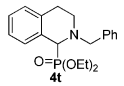
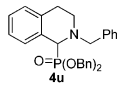
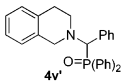
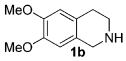
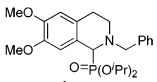
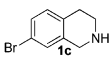
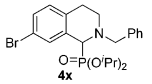
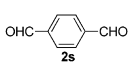
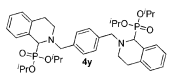
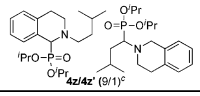
to be quite general, and a variety of aromatic aldehydes bearing electron-donating groups such as MeO and MeS (**4f** and **4g**) and electron-withdrawing groups such as F, Cl, Br, I, NO_2, CN, CF_3, and COOMe (**4h**–**4o**), as well as ortho- (**4b**), meta- (**4c**), and para- (**4d**) methyl substituted groups, were all suitable for this method, providing the corresponding endo-phosphonylated THIQs in good to excellent yields. These results revealed that the electronic effect and steric hindrance are not evident in this transformation. The conjugated aromatic aldehyde 1-naphthaldehyde **2e** was also compatible with the reaction conditions and afforded the desired product **4e** in 82% yield. In addition, some heterocyclic aromatic aldehydes such as picolinaldehyde **2p**, furan-2-carbaldehyde **2q**, and thiophene-2-carbaldehyde **2r** were all well-tolerated and produced the corresponding products **4p**, **4q**, and **4r** in 54, 83, and 79% yields, respectively. Notably, under the present catalysis system, only endo products **4a**–**4r** were observed, clearly showing that this protocol has excellent regioselectivity.

The versatility of the reaction was further demonstrated for the three-component reaction of different P(O)H substrates with benzaldehyde **2a** and THIQ **1a** (Table 3, entries 1–4). It was found that, in addition to **1a**, dimethyl phosphonate **3b**, diethyl phosphonate **3c**, and dibenzyl phosphonate **3d** were all suitable reaction partners for this C1-phosphonylation, generating desired products **4s**–**4u** in 75–84% yields. However, only exo-phosphonylated product **4v′** was obtained in 64% yield when diphenylphosphine oxide **3e** was employed in this reaction system. Apart from the model substrate **1a**, some derivatives of THIQ were also examined. For instance, 6,7-dimethoxytetrahydroisoquinoline **1b** and 7-bromo-tetrahydroisoquinoline **1c** were also suitable substrates for this reaction, providing corresponding products **4w** and **4x** in 66 and 77% yields, respectively (Table 3, entries 5 and 6). Interestingly, bifunctionalized product **4y** could be synthesized in moderate yield by doubling the amount of THIQ **1a**, diisopropyl phosphonate **3a**, and 4 Å molecular sieves as well as extending the reaction time to 6 h (Table 3, entry 7). In addition, aliphatic aldehyde 3-methylbutanal **2t** was also a suitable reaction partner and afforded the products **4z**/**4z′** (9:1) in 72% yield in spite of having a slightly reduced regioselectivity. Obviously, this protocol with broad substrate applicability could provide a facile and powerful tool for the preparation of various valuable C1-phosphonylated THIQs.

Table 3. Reaction Scope of Aldehydes with P(O)H and THIQs[a]



1 2 3 4

Entry	1	2	3	4	Yield (%)
1	**1a**	**2a**	 **3b**	 **4s**	82
2	**1a**	**2a**	 **3c**	 **4t**	84
3	**1a**	**2a**	 **3d**	 **4u**	75
4	**1a**	**2a**	 **3e**	 **4v′**	64
5	 **1b**	**2a**	**3a**	 **4w**	66
6	 **1c**	**2a**	**3a**	 **4x**	77
7	**1a**	 **2s**	**3a**	 **4y**	46[b]
8	**1a**	 **2t**	**3a**	 **4z/4z′** (9/1)[c]	72

[a]Ratio: **1**/**2**/**3** = 1.2:1.0 (0.3 mmol):1.2 equiv; 100 mg 4 Å MS; DCE (1 mL); 90 °C; 3 h; under argon. [b]Ratio: **1**/**2**/**3** = 2.4:1.0 (0.3 mmol):2.4 equiv; 200 mg 4 Å MS; DCE (2 mL); 90 °C; 6 h; under argon. [c]The ratio was determined by ^{31}P NMR analysis.

On the basis of these experimental results and previous reports on three-component Kabachnik–Fields reactions involving dialkyl phosphonates, amines, and aldehydes,[23] a plausible reaction pathway is proposed in Scheme 2. Initially, the exo-iminium **A** was generated from THIQ (**1a**) and benzaldehyde (**2a**) in the presence of AgOAc. Then, **A** easily isomerized to its thermodynamically stable isomer endo-iminium **B** with the assistance of Ag^+.[24] Finally, nucleophilic addition of **3a** to **B** (in the form of the trivalent phosphite **C**) gave the desired product **4a** and completed C1-phosphonylation of THIQs.

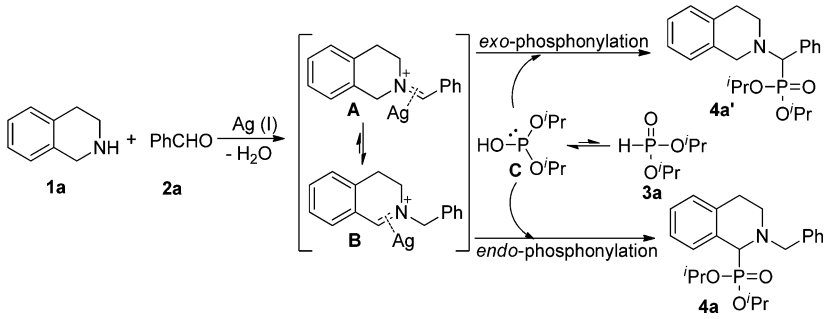
In conclusion, we have successfully developed the first facile and efficient Ag-catalyzed three-component reaction of readily available THIQs, aldehydes, and H-phosphonates, furnishing a new route to structurally diverse C1-phosphonylated THIQs along with concurrent C–P bond formation/N-alkylation. Importantly, in contrast, this reaction is performed without needing an oxidant and various valuable endo products can be conveniently obtained in a one-pot process. Furthermore, direct use of N-unprotected THIQs without the requirement of having preformed N-protected THIQs, which greatly improves the reaction efficiency, represents a prominent advantage of the method. In addition, the method also has other noticeable advantages, including operational simplicity, remarkable functional group tolerance, excellent regioselectivity, and good to excellent yields. Therefore, we believe that this method will open new avenues for the synthesis of potentially biologically active α-aminophosphonates and should find a broad application in modern synthetic chemistry and medicinal science.

EXPERIMENTAL SECTION

General Information. All reactions were carried out under dry argon. ^1H NMR and $^{13}C\{^1H\}$ NMR spectra were recorded on a 500 MHz spectrometer with TMS as internal standard (^1H NMR: TMS at 0.00 ppm, $CHCl_3$ at 7.26 ppm; $^{13}C\{^1H\}$ NMR: $CDCl_3$ at 77.16 ppm). ^{31}P NMR spectra were recorded on the same instrument with 85% H_3PO_4 as external standard. Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants in hertz (Hz), integration. All compounds were further characterized by HRMS. The products were purified by column chromatography on silica gel 300–400 mesh.

DOI: 10.1021/acs.joc.5b02625
J. Org. Chem. 2016, 81, 1704–1711

Scheme 2. Plausible Reaction Pathway



General Procedure for the Synthesis of C1-Phosponylated Tetrahydroisoquinolines. THIQ (0.36 mmol), aldehyde (0.30 mmol), P(O)H (0.36 mmol), 4 Å MS (100 mg), and AgOAc (0.03 mmol) were mixed in DCE (1 mL) and stirred at 90 °C for the indicated time under argon. The resulting mixture was directly purified by silica gel chromatography using a mixture of petroleum ether and ethyl acetate as eluent.

*Diisopropyl (2-Benzyl-1,2,3,4-tetrahydroisoquinolin-1-yl)-phosphonate (**4a**).* 93% yield, 108 mg; pale yellow oil; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.39 (d, J = 7.1 Hz, 2H), 7.34−7.29 (m, 3H), 7.27−7.23 (m, 1H), 7.20−7.10 (m, 3H), 4.69−4.51 (m, 2H), 4.14 (d, J = 21.2 Hz, 1H), 3.97 (d, J = 13.3 Hz, 1H), 3.85 (d, J = 13.3 Hz, 1H), 3.65−3.58 (m, 1H), 2.95−2.86 (m, 1H), 2.81−2.75 (m, 1H), 2.73−2.66 (m, 1H), 1.294 (d, J = 6.2 Hz, 3H, overlapped), 1.292 (d, J = 6.1 Hz, 3H, overlapped), 1.21 (d, J = 6.2 Hz, 3H), 1.10 (d, J = 6.1 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 139.0, 136.1 (d, J_{C-P} = 5.9 Hz), 130.3, 129.6 (d, J_{C-P} = 3.9 Hz), 129.1, 129.0 (d, J_{C-P} = 2.7 Hz), 128.3, 127.2, 126.9 (d, J_{C-P} = 3.6 Hz), 125.5 (d, J_{C-P} = 2.9 Hz), 71.5 (d, J_{C-P} = 7.5 Hz), 70.7 (d, J_{C-P} = 7.7 Hz), 61.0 (d, J_{C-P} = 158.5 Hz), 59.6 (d, J_{C-P} = 12.3 Hz), 45.1 (d, J_{C-P} = 2.2 Hz), 25.2, 24.6 (d, J_{C-P} = 3.2 Hz), 24.3 (d, J_{C-P} = 2.9 Hz), 24.0 (d, J_{C-P} = 5.5 Hz), 23.8 (d, J_{C-P} = 5.5 Hz); ^{31}P NMR ($CDCl_3$, 202 MHz): δ 22.04; IR (liquid film) υ_{max}: 2976, 2930, 1653, 1493, 1454, 1384, 1373, 1244, 1177, 1140, 1106, 982, 746 cm^{-1}; HRMS (ESI-TOF): [M + H]$^+$ m/z calcd for $C_{22}H_{30}NO_3PH^+$, 388.2042; found, 388.2046.

*Diisopropyl (2-(2-Methylbenzyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)phosphonate (**4b**).* 81% yield, 97 mg; pale yellow oil; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.36−7.32 (m, 2H), 7.21−7.11 (m, 6H), 4.62−4.45 (m, 2H), 4.12 (d, J = 22.2 Hz, 1H), 3.85 (s, 2H), 3.71−3.65 (m, 1H), 3.01−2.94 (m, 1H), 2.88−2.84 (m, 1H), 2.70−2.64 (m, 1H), 2.35 (s, 3H), 1.26 (d, J = 6.1 Hz, 3H), 1.25 (d, J = 6.2 Hz, 3H), 1.17 (d, J = 6.2 Hz, 3H), 1.00 (d, J = 6.2 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 137.7, 136.9, 135.9 (d, J_{C-P} = 5.9 Hz), 130.4, 120.3 (d, J_{C-P} = 4.2 Hz, overlapped), 129.8 (d, J_{C-P} = 4.5 Hz), 129.7, 129.1 (d, J_{C-P} = 2.7 Hz), 127.2, 127.0 (d, J_{C-P} = 3.5 Hz), 125.7, 125.5 (d, J_{C-P} = 3.3 Hz), 71.4 (d, J_{C-P} = 7.5 Hz), 70.6 (d, J_{C-P} = 7.9 Hz), 60.7 (d, J_{C-P} = 156.2 Hz), 57.1 (d, J_{C-P} = 13.0 Hz), 45.1, 24.7, 24.5 (d, J_{C-P} = 2.8 Hz), 24.3 (d, J_{C-P} = 3.4 Hz), 24.0 (d, J_{C-P} = 5.5 Hz), 23.6 (d, J_{C-P} = 5.4 Hz); ^{31}P NMR ($CDCl_3$, 202 MHz): δ 22.43; IR (liquid film) υ_{max}: 2976, 2931, 1491, 1452, 1384, 1373, 1245, 1177, 1140, 1106, 981, 744 cm^{-1}; HRMS (ESI-TOF): [M + H]$^+$ m/z calcd for $C_{23}H_{32}NO_3PH^+$, 402.2198; found, 402.2195.

*Diisopropyl (2-(3-Methylbenzyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)phosphonate (**4c**).* 77% yield, 93 mg; pale yellow oil; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.33 (d, J = 7.4 Hz, 1H), 7.22−7.10 (m, 6H), 7.07 (d, J = 6.6 Hz, 1H), 4.67−4.54 (m, 2H), 4.14 (d, J = 21.5 Hz, 1H), 3.92 (d, J = 13.3 Hz, 1H), 3.81 (d, J = 13.3 Hz, 1H), 3.65−3.59 (m, 1H), 2.95−2.88 (m, 1H), 2.81−2.77 (m, 1H), 2.71−2.65 (m, 1H), 2.34 (s, 3H), 1.30 (d, J = 6.1 Hz, 3H), 1.29 (d, J = 6.0 Hz, 3H), 1.22 (d, J = 6.3 Hz, 3H), 1.11 (d, J = 6.2 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 138.9, 136.1 (d, J_{C-P} = 6.1 Hz), 130.3, 129.8, 129.6 (d, J_{C-P} = 4.3 Hz), 129.0 (d, J_{C-P} = 2.7 Hz), 128.2, 127.9, 126.9 (d, J_{C-P} = 3.6 Hz), 126.2, 125.5 (d, J_{C-P} = 2.9 Hz), 71.5 (d, J_{C-P} = 7.5 Hz), 70.7 (d, J_{C-P} = 7.7 Hz), 61.0 (d, J_{C-P} = 158.2 Hz), 59.5 (d, J_{C-P} = 12.3 Hz), 45.0 (d, J_{C-P} = 1.7 Hz), 25.0, 24.6 (d, J_{C-P} = 3.0 Hz), 24.3 (d, J_{C-P} = 3.0 Hz), 24.0 (d, J_{C-P} = 5.5 Hz), 23.7 (d, J_{C-P} = 5.5 Hz), 21.5; ^{31}P NMR ($CDCl_3$, 202 MHz): δ 22.15; IR (liquid film) υ_{max}: 2976, 2930, 1455, 1383, 1372, 1244, 1177, 1140, 1106, 982, 744 cm^{-1}; HRMS (ESI-TOF): [M + H]$^+$ m/z calcd for $C_{23}H_{32}NO_3PH^+$, 402.2198; found, 402.2202.

*Diisopropyl (2-(4-Methylbenzyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)phosphonate (**4d**).* 85% yield, 102 mg; pale yellow oil; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.33 (d, J = 7.5 Hz, 1H), 7.28 (d, J = 7.9 Hz, 1H), 7.19−7.10 (m, 5H), 4.68−4.52 (m, 2H), 4.14 (d, J = 21.4 Hz, 1H), 3.92 (d, J = 13.2 Hz, 1H), 3.81 (d, J = 13.2 Hz, 1H), 3.64−3.58 (m, 1H), 2.94−2.86 (m, 1H), 2.80−2.76 (m, 1H), 2.71−2.65 (m, 1H), 2.34 (s, 3H), 1.30 (d, J = 6.2 Hz, 3H), 1.29 (d, J = 6.1 Hz, 3H), 1.22 (d, J = 6.2 Hz, 3H), 1.11 (d, J = 6.2 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 136.7, 136.1 (d, J_{C-P} = 5.7 Hz), 135.9, 130.3, 129.6 (d, J_{C-P} = 4.3 Hz), 129.1, 129.0, 128.9 (d, J_{C-P} = 2.7 Hz), 126.9 (d, J_{C-P} = 3.6 Hz), 125.5 (d, J_{C-P} = 2.9 Hz), 71.5 (d, J_{C-P} = 7.5 Hz), 70.7 (d, J_{C-P} = 8.0 Hz), 60.9 (d, J_{C-P} = 158.7 Hz), 59.3 (d, J_{C-P} = 12.3 Hz), 45.0 (d, J_{C-P} = 2.6 Hz), 25.1, 24.6 (d, J_{C-P} = 3.1 Hz), 24.3 (d, J_{C-P} = 3.2 Hz), 24.0 (d, J_{C-P} = 5.9 Hz), 23.7 (d, J_{C-P} = 5.5 Hz), 21.2; ^{31}P NMR ($CDCl_3$, 202 MHz): δ 22.09; IR (liquid film) υ_{max}: 2976, 2929, 1653, 1514, 1491, 1452, 1383, 1373, 1245, 1177, 1140, 1107, 983, 743 cm^{-1}; HRMS (ESI-TOF): [M + H]$^+$ m/z calcd for $C_{23}H_{32}NO_3PH^+$, 402.2198; found, 402.2197.

*Diisopropyl (2-(Naphthalen-1-ylmethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)phosphonate (**4e**).* 82% yield, 107 mg; pale yellow oil; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.41−8.39 (m, 1H), 7.86−7.84 (m, 1H), 7.79 (d, J = 8.1 Hz, 1H), 7.51−7.45 (m, 3H), 7.41−7.37 (m, 2H), 7.23−7.13 (m, 3H), 4.63−4.45 (m, 2H), 4.35 (d, J = 13.2 Hz, 1H), 4.26 (d, J = 13.2 Hz, 1H), 4.23 (d, J = 22.4 Hz, 1H), 3.72−3.65 (m, 1H), 3.04−2.97 (m, 1H), 2.93−2.88 (m, 1H), 2.72−2.67 (m, 1H), 1.24 (d, J = 6.2 Hz, 3H), 1.22 (d, J = 6.3 Hz, 3H), 1.11 (d, J = 6.2 Hz, 3H), 0.92 (d, J = 6.3 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 136.0 (d, J_{C-P} = 5.6 Hz), 134.5, 134.0, 130.1, 130.0 (d, J_{C-P} = 4.0 Hz), 129.0 (d, J_{C-P} = 2.6 Hz), 128.4, 128.2, 127.5, 127.0 (d, J_{C-P} = 3.6 Hz), 125.9, 125.7, 125.5 (d, J_{C-P} = 3.3 Hz), 125.2, 71.5 (d, J_{C-P} = 7.6 Hz), 70.7 (d, J_{C-P} = 7.6 Hz), 61.0 (d, J_{C-P} = 158.9 Hz), 57.6 (d, J_{C-P} = 13.6 Hz), 45.3 (d, J_{C-P} = 1.2 Hz), 24.8, 24.4 (d, J_{C-P} = 2.9 Hz), 24.3 (d, J_{C-P} = 2.9 Hz), 23.9 (d, J_{C-P} = 5.6 Hz), 23.6 (d, J_{C-P} = 5.4 Hz); ^{31}P NMR ($CDCl_3$, 202 MHz): δ 22.99; IR (liquid film) υ_{max}: 2975, 2930, 1507, 1455, 1384, 1373, 1245, 1177, 1132, 1105, 980, 791 cm^{-1}; HRMS (ESI-TOF): [M + H]$^+$ m/z calcd for $C_{26}H_{32}NO_3PH^+$, 438.2198; found, 438.2199.

*Diisopropyl (2-(4-Methoxylbenzyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)phosphonate (**4f**).* 61% yield, 76 mg; pale yellow oil; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.33−7.26 (m, 3H), 7.19−7.09 (m, 3H), 6.84 (d, J = 8.5 Hz, 2H), 4.66−4.53 (m, 2H), 4.12 (d, J = 21.5 Hz, 1H), 3.88 (d, J = 13.1 Hz, 1H), 3.80 (s, 3H), 3.77 (d, J = 13.1 Hz, 1H), 3.63−3.57 (m, 1H), 2.92−2.86 (m, 1H), 2.79−2.75 (m, 1H), 2.70−2.64 (m, 1H), 1.29 (d, J = 6.3 Hz, 3H), 1.28 (d, J = 6.1 Hz, 3H), 1.21 (d, J = 6.2 Hz, 3H), 1.10 (d, J = 6.2 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 158.9, 136.1 (d, J_{C-P} = 5.6 Hz), 131.0, 130.3, 129.6 (d, J_{C-P} = 4.3 Hz), 129.0 (d, J_{C-P} = 2.7 Hz), 126.9 (d, J_{C-P} = 3.6 Hz), 125.5 (d, J_{C-P} = 3.3 Hz), 113.7, 71.5 (d, J_{C-P} = 8.2 Hz), 70.7 (d, J_{C-P} = 7.7 Hz), 60.7 (d, J_{C-P} = 158.8 Hz), 58.9 (d, J_{C-P} = 12.5 Hz), 55.4, 44.9 (d, J_{C-P} = 1.6 Hz), 25.0, 24.6 (d, J_{C-P} = 2.8 Hz), 24.3 (d, J_{C-P} = 3.3

DOI: 10.1021/acs.joc.5b02625
J. Org. Chem. 2016, 81, 1704−1711

Hz), 24.0 (d, J_{C-P} = 5.5 Hz), 23.8 (d, J_{C-P} = 5.5 Hz); ^{31}P NMR ($CDCl_3$, 202 MHz): δ 22.11; IR (liquid film) υ_{max}: 2976, 2931, 2834, 1611, 1511, 1454, 1383, 1372, 1243, 1131, 1177, 1140, 1107, 981, 742 cm^{-1}; HRMS (ESI-TOF): $[M + H]^+$ m/z calcd for $C_{23}H_{32}NO_4PH^+$, 418.2147; found, 418.2148.

*Diisopropyl (2-(4-(Methylthio)benzyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)phosphonate (**4g**).* 74% yield, 96 mg; pale yellow oil; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.31 (d, J = 8.1 Hz, 3H), 7.21 (d, J = 8.2 Hz, 2H), 7.18−7.10 (m, 3H), 4.66−4.53 (m, 2H), 4.11 (d, J = 21.1 Hz, 1H), 3.92 (d, J = 13.3 Hz, 1H), 3.79 (d, J = 13.4 Hz, 1H), 3.62−3.56 (m, 1H), 2.92−2.85 (m, 1H), 2.78−2.73 (m, 1H), 2.71−2.66 (m, 1H), 2.48 (s, 3H), 1.29 (d, J = 6.2 Hz, 6H), 1.20 (d, J = 6.2 Hz, 3H), 1.10 (d, J = 6.2 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 137.0, 136.0 (d, J_{C-P} = 5.6 Hz), 135.9, 130.2, 129.61, 129.57 (d, J_{C-P} = 4.3 Hz), 129.0 (d, J_{C-P} = 2.7 Hz), 127.0 (d, J_{C-P} = 3.6 Hz), 126.7, 125.5 (d, J_{C-P} = 3.3 Hz), 71.5 (d, J_{C-P} = 7.8 Hz), 70.8 (d, J_{C-P} = 8.0 Hz), 60.9 (d, J_{C-P} = 158.6 Hz), 59.1 (d, J_{C-P} = 12.2 Hz), 45.1 (d, J_{C-P} = 1.9 Hz), 25.2, 24.5 (d, J_{C-P} = 3.0 Hz), 24.3 (d, J_{C-P} = 2.9 Hz), 24.0 (d, J_{C-P} = 5.6 Hz), 23.8 (d, J_{C-P} = 5.5 Hz), 21.2; ^{31}P NMR ($CDCl_3$, 202 MHz): δ 22.01; IR (liquid film) υ_{max}: 2976, 2921, 1492, 1451, 1383, 1372, 1243, 1177, 1140, 1106, 982, 744 cm^{-1}; HRMS (ESI-TOF): $[M + H]^+$ m/z calcd for $C_{23}H_{32}NO_3PSH^+$, 434.1919; found, 434.1922.

*Diisopropyl (2-(4-Fluorobenzyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)phosphonate (**4h**).* 86% yield, 104 mg; pale yellow oil; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.37−7.31 (m, 3H), 7.19−7.10 (m, 3H), 7.01−6.96 (m, 2H), 4.66−4.49 (m, 2H), 4.10 (d, J = 20.8 Hz, 1H), 3.94 (d, J = 13.2 Hz, 1H), 3.80 (d, J = 13.3 Hz, 1H), 3.60−3.54 (m, 1H), 2.93−2.84 (m, 1H), 2.76−2.67 (m, 2H), 1.28 (d, J = 6.2 Hz, 3H), 1.27 (d, J = 6.2 Hz, 3H), 1.20 (d, J = 6.2 Hz, 3H), 1.10 (d, J = 6.2 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 162.2 (d, J_{C-F} = 244.7 Hz), 136.0 (d, J_{C-P} = 5.5 Hz), 134.8 (d, J_{C-F} = 3.0 Hz), 130.5 (d, J_{C-F} = 8.0 Hz), 130.3, 129.6 (d, J_{C-P} = 4.4 Hz), 128.9 (d, J_{C-P} = 2.7 Hz), 127.0 (d, J_{C-P} = 3.6 Hz), 125.5 (d, J_{C-P} = 3.1 Hz), 115.1 (d, J_{C-F} = 21.1 Hz), 71.4 (d, J_{C-P} = 7.9 Hz), 70.8 (d, J_{C-P} = 8.0 Hz), 61.0 (d, J_{C-P} = 158.6 Hz), 59.0 (d, J_{C-P} = 11.5 Hz), 45.2 (d, J_{C-P} = 2.5 Hz), 25.5, 24.5 (d, J_{C-P} = 3.3 Hz), 24.3 (d, J_{C-P} = 3.1 Hz), 24.0 (d, J_{C-P} = 5.5 Hz), 23.8 (d, J_{C-P} = 5.4 Hz); ^{31}P NMR ($CDCl_3$, 202 MHz): δ 21.94; IR (liquid film) υ_{max}: 2977, 2933, 2837, 1653, 1602, 1508, 1452, 1384, 1373, 1243, 1221, 1154, 1177, 1140, 1106, 982, 743 cm^{-1}; HRMS (ESI-TOF): $[M + H]^+$ m/z calcd for $C_{22}H_{29}FNO_3PH^+$, 406.1947; found, 406.1950.

*Diisopropyl (2-(4-Chlorobenzyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)phosphonate (**4i**).* 82% yield, 103 mg; pale yellow oil; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.35−7.31 (m, 3H), 7.28−7.26 (m, 2H), 7.20−7.10 (m, 3H), 4.67−4.51 (m, 2H), 4.09 (d, J = 20.5 Hz, 1H), 3.95 (d, J = 13.5 Hz, 1H), 3.80 (d, J = 13.5 Hz, 1H), 3.59−3.54 (m, 1H), 2.94−2.84 (m, 1H), 2.75−2.67 (m, 2H), 1.28 (d, J = 6.2 Hz, 3H), 1.27 (d, J = 6.2 Hz, 3H), 1.20 (d, J = 6.2 Hz, 3H), 1.10 (d, J = 6.2 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 137.7, 136.0 (d, J_{C-P} = 5.6 Hz), 132.9, 130.3, 130.2, 129.5 (d, J_{C-P} = 4.3 Hz), 129.0 (d, J_{C-P} = 2.7 Hz), 128.5, 127.0 (d, J_{C-P} = 3.6 Hz), 125.6 (d, J_{C-P} = 3.3 Hz), 71.5 (d, J_{C-P} = 7.9 Hz), 70.8 (d, J_{C-P} = 8.0 Hz), 61.1 (d, J_{C-P} = 158.4 Hz), 59.1 (d, J_{C-P} = 11.4 Hz), 45.3 (d, J_{C-P} = 2.4 Hz), 25.6, 24.5 (d, J_{C-P} = 2.9 Hz), 24.3 (d, J_{C-P} = 3.1 Hz), 24.0 (d, J_{C-P} = 5.3 Hz), 23.8 (d, J_{C-P} = 5.4 Hz); ^{31}P NMR ($CDCl_3$, 202 MHz): δ 21.89; IR (liquid film) υ_{max}: 2977, 2931, 2836, 1490, 1452, 1384, 1373, 1244, 1176, 1140, 1105, 1089, 982, 744 cm^{-1}; HRMS (ESI-TOF): $[M + H]^+$ m/z calcd for $C_{22}H_{29}ClNO_3PH^+$, 422.1652; found, 422.1649.

*Diisopropyl (2-(4-Bromobenzyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)phosphonate (**4j**).* 86% yield, 120 mg; pale yellow oil; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.44−7.41 (m, 2H), 7.32−7.28 (m, 3H), 7.19−7.10 (m, 3H), 4.65−4.52 (m, 2H), 4.09 (d, J = 20.5 Hz, 1H), 3.93 (d, J = 13.6 Hz, 1H), 3.78 (d, J = 13.6 Hz, 1H), 3.59−3.53 (m, 1H), 2.93−2.81 (m, 1H), 2.74−2.67 (m, 2H), 1.28 (d, J = 6.2 Hz, 3H), 1.27 (d, J = 6.2 Hz, 3H), 1.20 (d, J = 6.2 Hz, 3H), 1.10 (d, J = 6.2 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 138.2, 136.0 (d, J_{C-P} = 5.5 Hz), 131.4, 130.7, 130.2, 129.5 (d, J_{C-P} = 4.3 Hz), 128.9 (d, J_{C-P} = 2.6 Hz), 127.0 (d, J_{C-P} = 3.6 Hz), 125.6 (d, J_{C-P} = 3.0 Hz), 71.5 (d, J_{C-P} = 7.8 Hz), 70.8 (d, J_{C-P} = 8.0 Hz), 61.1 (d, J_{C-P} = 158.6 Hz), 59.1 (d, J_{C-P} = 11.3 Hz), 45.3 (d, J_{C-P} = 2.2 Hz), 25.6, 24.5 (d, J_{C-P} = 2.9 Hz), 24.3 (d, J_{C-P} = 3.3 Hz), 24.0 (d, J_{C-P} = 5.6 Hz), 23.8 (d, J_{C-P} = 5.4 Hz); ^{31}P NMR ($CDCl_3$, 202 MHz): δ 21.88; IR (liquid film) υ_{max}: 2976, 2931, 1486, 1383, 1372, 1243, 1177, 1140, 1105, 981, 743 cm^{-1}; HRMS (ESI-TOF): $[M + H]^+$ m/z calcd for $C_{22}H_{29}BrNO_3PH^+$, 466.1147; found, 466.1143.

*Diisopropyl (2-(4-Iodobenzyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)phosphonate (**4k**).* 78% yield, 120 mg; pale yellow oil; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.63 (dt, J = 8.3, 1.8 Hz, 2H), 7.31 (d, J = 7.5 Hz, 1H), 7.19−7.10 (m, 5H), 4.65−4.52 (m, 2H), 4.09 (d, J = 20.5 Hz, 1H), 3.93 (d, J = 13.7 Hz, 1H), 3.77 (d, J = 12.8 Hz, 1H), 3.59−3.53 (m, 1H), 2.90−2.83 (m, 1H), 2.74−2.67 (m, 2H), 1.28 (d, J = 6.2 Hz, 3H), 1.27 (d, J = 6.2 Hz, 3H), 1.20 (d, J = 6.2 Hz, 3H), 1.10 (d, J = 6.2 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 138.9, 137.4, 136.0 (d, J_{C-P} = 5.6 Hz), 130.0, 130.2, 129.5 (d, J_{C-P} = 4.4 Hz), 128.9 (d, J_{C-P} = 2.9 Hz), 127.0 (d, J_{C-P} = 3.6 Hz), 125.6 (d, J_{C-P} = 3.4 Hz), 92.5, 71.5 (d, J_{C-P} = 7.6 Hz), 70.8 (d, J_{C-P} = 7.9 Hz), 61.1 (d, J_{C-P} = 158.3 Hz), 59.2 (d, J_{C-P} = 11.2 Hz), 45.3 (d, J_{C-P} = 2.4 Hz), 25.5, 24.5 (d, J_{C-P} = 3.3 Hz), 24.3 (d, J_{C-P} = 2.9 Hz), 24.0 (d, J_{C-P} = 5.7 Hz), 23.8 (d, J_{C-P} = 5.4 Hz); ^{31}P NMR ($CDCl_3$, 202 MHz): δ 21.89; IR (liquid film) υ_{max}: 2975, 2931, 2834, 1482, 1451, 1383, 1372, 1243, 1176, 1140, 1105, 1006, 982, 743 cm^{-1}; HRMS (ESI-TOF): $[M + H]^+$ m/z calcd for $C_{22}H_{29}INO_3PH^+$, 514.1008; found, 514.1009.

*Diisopropyl (2-(3-Nitrobenzyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)phosphonate (**4l**).* 66% yield, 85 mg; yellow oil; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.33 (s, 1H), 8.11 (dd, J = 8.2, 1.4 Hz, 1H), 7.74 (d, J = 7.6 Hz, 1H), 7.47 (t, J = 7.9 Hz, 1H), 7.33 (d, J = 7.5 Hz, 1H), 7.20−7.09 (m, 3H), 4.69−4.53 (m, 2H), 4.13 (d, J = 6.3 Hz, 1H), 4.10 (d, J = 11.9 Hz, 1H), 3.92 (d, J = 13.9 Hz, 1H), 3.57−3.52 (m, 1H), 2.93−2.84 (m, 1H), 2.78−2.69 (m, 2H), 1.29 (d, J = 6.2 Hz, 3H), 1.28 (d, J = 6.2 Hz, 3H), 1.21 (d, J = 6.2 Hz, 3H), 1.11 (d, J = 6.2 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 148.6, 141.8, 135.9 (d, J_{C-P} = 5.7 Hz), 134.9, 130.0, 129.5 (d, J_{C-P} = 4.3 Hz), 129.2, 129.0 (d, J_{C-P} = 2.7 Hz), 127.2 (d, J_{C-P} = 3.6 Hz), 125.7 (d, J_{C-P} = 3.3 Hz), 123.7, 122.4, 71.6 (d, J_{C-P} = 7.8 Hz), 71.0 (d, J_{C-P} = 7.8 Hz), 61.4 (d, J_{C-P} = 159.0 Hz), 59.3 (d, J_{C-P} = 10.4 Hz), 45.6 (d, J_{C-P} = 2.8 Hz), 26.0, 24.5 (d, J_{C-P} = 3.4 Hz), 24.3 (d, J_{C-P} = 3.3 Hz), 24.0 (d, J_{C-P} = 5.4 Hz), 23.7 (d, J_{C-P} = 5.3 Hz); ^{31}P NMR ($CDCl_3$, 202 MHz): δ 21.61; IR (liquid film) υ_{max}: 2977, 2932, 1529, 1453, 1384, 1373, 1348, 1242, 1177, 1140, 1105, 982, 732 cm^{-1}; HRMS (ESI-TOF): $[M + H]^+$ m/z calcd for $C_{22}H_{29}N_2O_5PH^+$, 433.1892; found, 433.1888.

*Diisopropyl (2-(4-Cyanobenzyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)phosphonate (**4m**).* 78% yield, 96 mg; colorless oil; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.60−7.58 (m, 2H), 7.54 (d, J = 8.4 Hz, 2H), 7.31 (d, J = 7.5 Hz, 1H), 7.19−7.10 (m, 3H), 4.67−4.49 (m, 2H), 4.09−4.05 (m, 2H), 3.88 (dd, J = 14.3, 1.5 Hz, 1H), 3.54−3.49 (m, 1H), 2.90−2.83 (m, 1H), 2.76−2.67 (m, 2H), 1.28 (d, J = 6.2 Hz, 3H), 1.25 (d, J = 6.2 Hz, 3H), 1.18 (d, J = 6.2 Hz, 3H), 1.09 (d, J = 6.2 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 145.1, 135.8 (d, J_{C-P} = 5.5 Hz), 132.2, 130.1, 129.4, 128.9 (d, J_{C-P} = 2.9 Hz), 127.1 (d, J_{C-P} = 3.5 Hz), 125.6 (d, J_{C-P} = 3.3 Hz), 119.1, 111.0, 71.5 (d, J_{C-P} = 7.9 Hz), 70.9 (d, J_{C-P} = 7.9 Hz), 61.4 (d, J_{C-P} = 158.2 Hz), 59.7 (d, J_{C-P} = 10.0 Hz), 45.7 (d, J_{C-P} = 2.7 Hz), 26.0, 24.5 (d, J_{C-P} = 3.3 Hz), 24.2 (d, J_{C-P} = 3.3 Hz), 24.0 (d, J_{C-P} = 5.4 Hz), 23.7 (d, J_{C-P} = 5.1 Hz); ^{31}P NMR ($CDCl_3$, 202 MHz): δ 21.63; IR (liquid film) υ_{max}: 2978, 2933, 2226, 1453, 1384, 1373, 1242, 1177, 1141, 1105, 983, 748 cm^{-1}; HRMS (ESI-TOF): $[M + H]^+$ m/z calcd for $C_{23}H_{29}N_2O_3PH^+$, 413.1994; found, 413.1997.

*Diisopropyl (2-(4-(Trifluoromethyl)benzyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)phosphonate (**4n**).* 74% yield, 101 mg; pale yellow oil; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.57−7.53 (m, 4H), 7.33 (d, J = 7.5 Hz, 1H), 7.20−7.11 (m, 3H), 7.19−7.10 (m, 3H), 4.67−4.53 (m, 2H), 4.10 (d, J = 20.1 Hz, 1H), 4.06 (d, J = 14.0 Hz, 1H), 3.89 (d, J = 14.0 Hz, 1H), 3.59−3.54 (m, 1H), 2.92−2.85 (m, 1H), 2.76−2.71 (m, 2H), 1.29 (d, J = 5.7 Hz, 3H), 1.28 (d, J = 5.9 Hz, 3H), 1.20 (d, J = 6.1 Hz, 3H), 1.10 (d, J = 6.3 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 143.5, 136.0 (d, J_{C-P} = 5.8 Hz), 130.2, 129.5 (d, J_{C-P} = 4.3 Hz), 129.4 (q, J_{C-F} = 32.2 Hz), 129.1, 129.0 (d, J_{C-P} = 2.1 Hz), 127.1 (d, J_{C-P} = 3.6 Hz), 125.6 (d, J_{C-P} = 2.9 Hz), 125.3 (q, J_{C-F} = 3.7 Hz), 124.4 (q, J_{C-F} = 272.1 Hz), 71.5 (d, J_{C-P} = 7.6 Hz), 70.9 (d, J_{C-P} = 8.0 Hz), 61.4 (d, J_{C-P} = 158.2 Hz), 59.5 (d, J_{C-P} = 10.7 Hz), 45.5 (d, J_{C-P}

DOI: 10.1021/acs.joc.5b02625
J. Org. Chem. 2016, 81, 1704−1711

= 2.5 Hz), 25.8, 24.5 (d, J_{C-P} = 3.3 Hz), 24.3 (d, J_{C-P} = 3.0 Hz), 24.0 (d, J_{C-P} = 5.5 Hz), 23.8 (d, J_{C-P} = 5.4 Hz); ^{31}P NMR ($CDCl_3$, 202 MHz): δ 21.78; IR (liquid film) υ_{max}: 2978, 2934, 1455, 1417, 1385, 1373, 1325, 1243, 1163, 1124, 1107, 1066, 983, 744 cm^{-1}; HRMS (ESI-TOF): $[M + H]^+$ m/z calcd for $C_{23}H_{29}F_3NO_3PH^+$, 456.1915; found, 456.1912.

*Methyl 4-((1-(Diisopropoxyphosphoryl)-3,4-dihydroisoquinolin-2(1H)-yl)methyl)benzoate (**4o**).* 81% yield, 108 mg; pale yellow oil; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.98 (dt, J = 8.3, 1.7 Hz, 2H), 7.48 (d, J = 8.3 Hz, 2H), 7.31 (d, J = 7.5 Hz, 1H), 7.19−7.10 (m, 3H), 4.66−4.52 (m, 2H), 4.10 (d, J = 20.3 Hz, 1H), 4.04 (d, J = 14.0 Hz, 1H), 3.90 (s, 3H, overlapped), 3.89 (d, J = 12.7 Hz, 1H, overlapped), 3.59−3.53 (m, 1H), 2.92−2.85 (m, 1H), 2.75−2.68 (m, 2H), 1.28 (d, J = 6.1 Hz, 3H), 1.27 (d, J = 6.1 Hz, 3H), 1.19 (d, J = 6.2 Hz, 3H), 1.10 (d, J = 6.2 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 167.2, 144.7, 136.0 (d, J_{C-P} = 5.6 Hz), 130.2, 129.7, 129.5 (d, J_{C-P} = 4.0 Hz), 129.1, 128.9 (d, J_{C-P} = 2.8 Hz), 128.8, 127.0 (d, J_{C-P} = 3.5 Hz), 125.6 (d, J_{C-P} = 3.3 Hz), 71.5 (d, J_{C-P} = 7.6 Hz), 70.8 (d, J_{C-P} = 7.8 Hz), 61.3 (d, J_{C-P} = 158.4 Hz), 59.6 (d, J_{C-P} = 10.9 Hz), 45.5 (d, J_{C-P} = 2.4 Hz), 25.7, 24.5 (d, J_{C-P} = 3.1 Hz), 24.3 (d, J_{C-P} = 3.0 Hz), 24.0 (d, J_{C-P} = 5.6 Hz), 23.8 (d, J_{C-P} = 5.5 Hz); ^{31}P NMR ($CDCl_3$, 202 MHz): δ 21.83; IR (liquid film) υ_{max}: 2977, 2934, 1723, 1610, 1452, 1434, 1384, 1373, 1279, 1245, 1175, 1140, 1107, 983, 757 cm^{-1}; HRMS (ESI-TOF): $[M + H]^+$ m/z calcd for $C_{24}H_{32}NO_5PH^+$, 446.2096; found, 446.2091.

*Diisopropyl (2-(Pyridin-2-ylmethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)phosphonate (**4p**).* 54% yield, 63 mg; pale yellow oil; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.49 (d, J = 4.7 Hz, 1H), 7.67−7.63 (m, 2H), 7.33 (d, J = 7.3 Hz, 1H), 7.17−7.08 (m, 4H), 4.65−4.48 (m, 2H), 4.21 (d, J = 19.8 Hz, 1H), 4.12 (d, J = 14.6 Hz, 1H), 4.01 (d, J = 14.6 Hz, 1H), 3.58−3.52 (m, 1H), 2.94−2.89 (m, 1H), 2.79−2.72 (m, 2H), 1.26 (d, J = 6.2 Hz, 6H), 1.19 (d, J = 6.2 Hz, 3H), 1.04 (d, J = 6.2 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 159.7, 148.9, 136.6, 136.1 (d, J_{C-P} = 5.7 Hz), 130.1, 129.5 (d, J_{C-P} = 4.3 Hz), 128.9 (d, J_{C-P} = 2.8 Hz), 127.0 (d, J_{C-P} = 3.6 Hz), 125.5 (d, J_{C-P} = 3.0 Hz), 123.1, 122.1, 71.5 (d, J_{C-P} = 7.6 Hz), 70.8 (d, J_{C-P} = 7.9 Hz), 61.8 (d, J_{C-P} = 10.2 Hz), 61.4 (d, J_{C-P} = 159.1 Hz), 46.0 (d, J_{C-P} = 2.7 Hz), 26.0, 24.5 (d, J_{C-P} = 3.2 Hz), 24.2 (d, J_{C-P} = 3.4 Hz), 24.0 (d, J_{C-P} = 5.5 Hz), 23.6 (d, J_{C-P} = 5.5 Hz); ^{31}P NMR ($CDCl_3$, 202 MHz): δ 22.05; IR (liquid film) υ_{max}: 2976, 2932, 1589, 1433, 1384, 1373, 1243, 1177, 1141, 1105, 982, 758 cm^{-1}; HRMS (ESI-TOF): $[M + H]^+$ m/z calcd for $C_{21}H_{29}N_2O_3PH^+$, 389.1994; found, 389.1991.

*Diisopropyl (2-(Furan-2-ylmethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)phosphonate (**4q**).* 83% yield, 94 mg; yellow oil; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.33 (s, 1H), 7.32 (d, J = 7.4 Hz, 1H), 7.16−7.07 (m, 3H), 6.29 (t, J = 2.5 Hz, 1H), 6.20 (d, J = 3.1 Hz, 1H), 4.65−4.53 (m, 2H), 4.20 (d, J = 20.6 Hz, 1H), 4.00 (d, J = 14.4 Hz, 1H), 3.86 (d, J = 14.5 Hz, 1H), 3.62−3.56 (m, 1H), 2.91−2.81 (m, 2H), 2.78−2.72 (m, 1H), 1.29 (d, J = 6.2 Hz, 3H, overlapped), 1.27 (d, J = 6.2 Hz, 3H, overlapped), 1.21 (d, J = 6.2 Hz, 3H), 1.10 (d, J = 6.2 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 152.4, 142.2, 136.1 (d, J_{C-P} = 6.1 Hz), 130.1 (d, J_{C-P} = 1.3 Hz), 129.6 (d, J_{C-P} = 4.4 Hz), 128.8 (d, J_{C-P} = 2.9 Hz), 126.9 (d, J_{C-P} = 3.6 Hz), 125.5 (d, J_{C-P} = 3.2 Hz), 71.8 (d, J_{C-P} = 7.7 Hz), 70.9 (d, J_{C-P} = 7.8 Hz), 60.0 (d, J_{C-P} = 160.6 Hz), 51.7 (d, J_{C-P} = 12.0 Hz), 45.8 (d, J_{C-P} = 2.4 Hz), 25.7, 24.6 (d, J_{C-P} = 2.8 Hz), 24.2 (d, J_{C-P} = 3.3 Hz), 23.9 (d, J_{C-P} = 5.8 Hz), 23.6 (d, J_{C-P} = 5.5 Hz); ^{31}P NMR ($CDCl_3$, 202 MHz): δ 21.72; IR (liquid film) υ_{max}: 2976, 2932, 1452, 1384, 1373, 1242, 1177, 1140, 1106, 1006, 983, 733 cm^{-1}; HRMS (ESI-TOF): $[M + H]^+$ m/z calcd for $C_{20}H_{28}NO_4PH^+$, 378.1834; found, 378.1833.

*Diisopropyl (2-(Thiophen-2-ylmethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)phosphonate (**4r**).* 79% yield, 93 mg; pale yellow oil; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.32 (d, J = 7.4 Hz, 1H), 7.23 (t, J = 3.3 Hz, 1H), 7.18−7.09 (m, 3 H), 6.93−6.92 (m, 2H), 4.69−4.56 (m, 2H), 4.21 (d, J = 20.6 Hz, 1H), 4.11 (s, 2H), 3.64−3.57 (m, 1H), 2.92−2.82 (m, 2H), 2.75−2.69 (m, 1H), 1.30 (d, J = 6.2 Hz, 3H), 1.29 (d, J = 6.1 Hz, 3H), 1.23 (d, J = 6.2 Hz, 3H), 1.14 (d, J = 6.2 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 142.4, 136.0 (d, J_{C-P} = 6.0 Hz), 130.2, 129.5 (d, J_{C-P} = 4.0 Hz), 128.9 (d, J_{C-P} = 2.8 Hz), 127.0 (d, J_{C-P} = 3.6 Hz), 126.4, 126.3, 125.5 (d, J_{C-P} = 3.0 Hz), 71.7 (d, J_{C-P} = 7.5 Hz), 70.9 (d, J_{C-P} = 7.9 Hz), 60.8 (d, J_{C-P} = 158.7 Hz), 54.1 (d, J_{C-P} = 12.2 Hz), 44.8 (d, J_{C-P} = 2.1 Hz), 25.4, 24.6 (d, J_{C-P} = 2.8 Hz), 24.3 (d, J_{C-P} = 3.3 Hz), 24.0 (d, J_{C-P} = 5.6 Hz), 23.8 (d, J_{C-P} = 5.5 Hz); ^{31}P NMR ($CDCl_3$, 202 MHz): δ 21.68; IR (liquid film) υ_{max}: 2976, 2930, 1455, 1384, 1373, 1245, 1177, 1140, 1106, 982, 698 cm^{-1}; HRMS (ESI-TOF): $[M + H]^+$ m/z calcd for $C_{20}H_{28}NO_3PSH^+$, 394.1606; found, 394.1610.

*Dimethyl (2-Benzyl-1,2,3,4-tetrahydroisoquinolin-1-yl)-phosphonate (**4s**).* 82% yield, 81 mg; colorless oil; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.37 (d, J = 7.6 Hz, 2H), 7.32 (t, J = 7.4 Hz, 2H), 7.27 (d, J = 7.1 Hz, 2H), 7.21−7.13 (m, 3H), 4.19 (d, J = 21.8 Hz, 1H), 3.91 (d, J = 13.2 Hz, 1H), 3.84 (d, J = 13.4 Hz, 1H), 3.67 (d, J = 10.5 Hz, 3H), 3.64 (d, J = 10.5 Hz, 3H), 2.97−2.91 (m, 1H), 2.87−2.83 (m, 1H), 2.72−2.68 (m, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 138.7, 136.0 (d, J_{C-P} = 6.0 Hz), 129.5, 129.22 (d, J_{C-P} = 2.8 Hz), 129.18 (d, J_{C-P} = 3.7 Hz, overlapped), 129.17, 128.4, 127.4, 127.2 (d, J_{C-P} = 3.6 Hz), 125.9 (d, J_{C-P} = 3.4 Hz), 59.6 (d, J_{C-P} = 158.1 Hz), 59.5 (d, J_{C-P} = 12.9 Hz), 53.7 (d, J_{C-P} = 7.3 Hz), 53.1 (d, J_{C-P} = 7.3 Hz), 45.6 (d, J_{C-P} = 1.5 Hz), 24.9; ^{31}P NMR ($CDCl_3$, 202 MHz): δ 25.55; IR (liquid film) υ_{max}: 3024, 2950, 2847, 1492, 1453, 1249, 1181, 1131, 1055, 1029, 882, 745 cm^{-1}; HRMS (ESI-TOF): $[M + H]^+$ m/z calcd for $C_{18}H_{22}NO_3PH^+$, 332.1416; found, 332.1404.

*Diethyl (2-Benzyl-1,2,3,4-tetrahydroisoquinolin-1-yl)-phosphonate (**4t**).* 84% yield, 90 mg; colorless oil; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.38 (d, J = 7.5 Hz, 2H), 7.33−7.25 (m, 4H), 7.21−7.12 (m, 3H), 4.17 (d, J = 22.0 Hz, 1H), 4.07−3.96 (m, 4H), 3.93 (d, J = 13.2 Hz, 1H), 3.84 (d, J = 13.3 Hz, 1H), 3.69−3.64 (m, 1H), 2.96−2.89 (m, 1H), 2.85−2.81 (m, 1H), 2.73−2.67 (m, 1H), 1.25 (d, J = 7.2 Hz, 3H, overlapped), 1.23 (d, J = 7.1 Hz, 3H, overlapped); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 138.8, 136.1 (d, J_{C-P} = 6.0 Hz), 129.8, 129.3 (d, J_{C-P} = 4.4 Hz), 129.1 (overlapped), 129.0 (d, J_{C-P} = 2.4 Hz, overlapped), 128.4, 127.3, 127.1 (d, J_{C-P} = 3.6 Hz), 125.7 (d, J_{C-P} = 3.4 Hz), 62.9 (d, J_{C-P} = 7.3 Hz), 62.3 (d, J_{C-P} = 7.5 Hz), 60.0 (d, J_{C-P} = 158.0 Hz), 59.5 (d, J_{C-P} = 12.7 Hz), 45.6 (d, J_{C-P} = 1.6 Hz), 25.0, 16.6 (d, J_{C-P} = 3.5 Hz), 16.5 (d, J_{C-P} = 3.4 Hz); ^{31}P NMR ($CDCl_3$, 202 MHz): δ 23.34; IR (liquid film) υ_{max}: 3025, 2979, 2905, 1493, 1453, 1389, 1246, 1094, 1054, 1026, 961, 746 cm^{-1}; HRMS (ESI-TOF): $[M + H]^+$ m/z calcd for $C_{20}H_{26}NO_3PH^+$, 360.1729; found, 360.1732.

*Dibenzyl (2-Benzyl-1,2,3,4-tetrahydroisoquinolin-1-yl)-phosphonate (**4u**).* 75% yield, 109 mg; colorless oil; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.31−7.29 (m, 8H), 7.25−7.19 (m, 9H), 7.14−7.10 (m, 2H), 4.99−4.86 (m, 4H), 4.27 (d, J = 21.4 Hz, 1H), 3.92 (d, J = 13.3 Hz, 1H), 3.85 (d, J = 13.3 Hz, 1H), 3.72−3.66 (m, 1H), 2.94−2.88 (m, 1H), 2.86−2.82 (m, 1H), 2.68−2.64 (m, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 138.7, 137.8 (d, J_{C-P} = 6.3 Hz), 136.6 (d, J_{C-P} = 5.9 Hz), 136.2 (d, J_{C-P} = 6.2 Hz), 129.5, 129.4 (d, J_{C-P} = 4.2 Hz), 129.2 (d, J_{C-P} = 2.7 Hz), 129.1, 128.5, 128.4, 128.3 (d, J_{C-P} = 7.5 Hz), 128.1, 127.9, 127.3, 127.2 (d, J_{C-P} = 3.6 Hz), 68.3 (d, J_{C-P} = 7.3 Hz), 67.8 (d, J_{C-P} = 7.6 Hz), 60.3 (d, J_{C-P} = 156.9 Hz), 59.5 (d, J_{C-P} = 12.8 Hz), 45.6, 25.0; ^{31}P NMR ($CDCl_3$, 202 MHz): δ 24.00; IR (liquid film) υ_{max}: 3062, 3029, 2948, 2836, 1494, 1454, 1376, 1247, 1213, 1078, 995, 736, 696 cm^{-1}; HRMS (ESI-TOF): $[M + H]^+$ m/z calcd for $C_{30}H_{30}NO_3PH^+$, 484.2042; found, 484.2038.

*((3,4-Dihydroisoquinolin-2(1H)-yl)(phenyl)methyl)-diphenylphosphine Oxide (**4v'**).* 64% yield, 81 mg; white solid; mp 166−168 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.95−7.91 (m, 2H), 7.57−7.51 (m, 4H), 7.48−7.39 (m, 3H), 7.32 (t, J = 7.3 Hz, 1H), 7.26−7.19 (m, 5H), 7.06−7.03 (m, 2H), 7.01−6.98 (m, 1H), 6.93−6.91 (m, 1H), 4.53 (d, J = 11.3 Hz, 1H), 4.01 (d, J = 14.9 Hz, 1H), 3.70−3.64 (m, 2H), 2.80−2.62 (m, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 135.2, 134.6, 132.9 (d, J_{C-P} = 99.3 Hz), 132.6 (d, J_{C-P} = 95.5 Hz), 131.8 (d, J_{C-P} = 8.6 Hz), 131.6 (d, J_{C-P} = 2.6 Hz), 131.4 (d, J_{C-P} = 7.4 Hz), 131.34 (d, J_{C-P} = 2.8 Hz), 131.3 (d, J_{C-P} = 1.8 Hz, overlapped), 131.28 (d, J_{C-P} = 8.7 Hz, overlapped), 128.6, 128.4 (d, J_{C-P} = 11.7 Hz), 128.2 (d, J_{C-P} = 11.8 Hz), 128.1 (d, J_{C-P} = 7.6 Hz, overlapped), 126.5, 125.8, 125.4, 69.3 (d, J_{C-P} = 86.2 Hz), 53.9 (d, J_{C-P} = 10.1 Hz), 48.6 (d, J_{C-P} = 5.0 Hz), 30.0; ^{31}P NMR ($CDCl_3$, 202 MHz): δ 30.98; IR (liquid film) υ_{max}: 3055, 3023, 2913, 2811, 1493, 1453, 1436, 1387, 1173, 1090, 908, 735, 718, 700 cm^{-1}; HRMS (ESI-

DOI: 10.1021/acs.joc.5b02625
J. Org. Chem. 2016, 81, 1704−1711

TOF): $[M + H]^+$ m/z calcd for $C_{28}H_{26}NOPH^+$, 424.1830; found, 424.1831.

*Diisopropyl (2-Benzyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-1-yl)phosphonate (**4w**).* 66% yield, 89 mg; colorless oil; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.38 (d, J = 7.1 Hz, 2H), 7.30 (d, J = 7.4 Hz, 2H), 7.25−7.22 (m, 1H), 6.88 (d, J = 1.8 Hz, 1H), 6.59 (s, 1H), 4.70−4.54 (m, 2H), 4.04 (d, J = 21.4 Hz, 1H), 3.91 (d, J = 13.4 Hz, 1H), 3.85 (s, 1H), 3.84 (s, 1H), 3.82 (d, J = 13.2 Hz, 1H), 3.64−3.58 (m, 1H), 2.87−2.76 (m, 2H), 2.57−2.50 (m, 1H), 1.31 (d, J = 6.2 Hz, 3H), 1.28 (d, J = 6.2 Hz, 3H), 1.23 (d, J = 6.2 Hz, 3H), 1.10 (d, J = 6.2 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 148.2 (d, J_{C-P} = 3.4 Hz), 146.9, 139.0, 129.1, 128.3, 128.1 (d, J_{C-P} = 6.4 Hz), 127.2, 121.7, 112.6 (d, J_{C-P} = 4.0 Hz), 111.6 (d, J_{C-P} = 3.5 Hz), 71.5 (d, J_{C-P} = 7.7 Hz), 70.5 (d, J_{C-P} = 7.9 Hz), 60.5 (d, J_{C-P} = 160.0 Hz), 59.3 (d, J_{C-P} = 13.4 Hz), 56.0, 55.9, 45.0, 24.6 (d, J_{C-P} = 2.7 Hz), 24.3 (d, J_{C-P} = 3.5 Hz), 24.2 (d, J_{C-P} = 5.2 Hz, overlapped), 24.18, 23.8 (d, J_{C-P} = 5.5 Hz); ^{31}P NMR ($CDCl_3$, 202 MHz): δ 22.19; IR (liquid film) υ_{max}: 2976, 2934, 2833, 1608, 1516, 1464, 1453, 1383, 1372, 1228, 1176, 1130, 1110, 981, 739 cm^{-1}; HRMS (ESI-TOF): $[M + H]^+$ m/z calcd for $C_{24}H_{32}NO_5PH^+$, 448.2253; found, 448.2258.

*Diisopropyl (2-Benzyl-7-bromo-1,2,3,4-tetrahydroisoquinolin-1-yl)phosphonate (**4x**).* 77% yield, 107 mg; colorless oil; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.45 (t, J = 2.1 Hz, 1H), 7.38−7.36 (m, 2H), 7.33−7.31 (m, 2H), 7.30−7.25 (m, 2H), 6.99 (d, J = 8.2 Hz, 1H), 4.74−4.56 (m, 2H), 4.04 (d, J = 22.8 Hz, 1H), 3.88 (d, J = 13.2 Hz, 1H), 3.81 (d, J = 13.5 Hz, 1H), 3.73−3.66 (m, 1H), 2.89−2.78 (m, 2H), 2.64−2.56 (m, 1H), 1.32 (d, J = 6.2 Hz, 3H), 1.30 (d, J = 6.2 Hz, 3H), 1.24 (d, J = 6.2 Hz, 3H), 1.20 (d, J = 6.2 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 138.5, 135.0 (d, J_{C-P} = 5.7 Hz), 132.5, 132.4 (d, J_{C-P} = 4.0 Hz), 130.7 (d, J_{C-P} = 2.7 Hz), 130.0 (d, J_{C-P} = 3.6 Hz), 129.1, 128.4, 127.4, 118.8 (d, J_{C-P} = 3.7 Hz), 71.6 (d, J_{C-P} = 7.8 Hz), 71.0 (d, J_{C-P} = 7.7 Hz), 60.4 (d, J_{C-P} = 160.7 Hz), 59.3 (d, J_{C-P} = 13.4 Hz), 44.7 (d, J_{C-P} = 1.4 Hz), 24.5 (d, J_{C-P} = 3.1 Hz), 24.3 (d, J_{C-P} = 3.0 Hz), 24.0, 23.9 (d, J_{C-P} = 5.5 Hz), 23.8 (d, J_{C-P} = 5.9 Hz); ^{31}P NMR ($CDCl_3$, 202 MHz): δ 20.72; IR (liquid film) υ_{max}: 2976, 2930, 1652, 1481, 1455, 1384, 1373, 1243, 1175, 1131, 1106, 983, 738 cm^{-1}; HRMS (ESI-TOF): $[M + H]^+$ m/z calcd for $C_{22}H_{29}BrNO_3PH^+$, 466.1147; found, 466.1140.

*Tetraisopropyl(2,2′-(1,4-phenylenebis(methylene))bis(1,2,3,4-tetrahydroisoquinoline-2,1-diyl))bis(phosphonate) (**4y**).* 46% yield, 96 mg; colorless oil; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.33−7.32 (m, 6H), 7.19−7.10 (m, 6H), 4.66−4.53 (m, 2H), 4.14 (d, J = 21.1 Hz, 2H), 3.94 (d, J = 13.3 Hz, 1H), 3.93 (d, J = 13.2 Hz, 1H), 3.83 (d, J = 13.3 Hz, 2H), 3.64−3.58 (m, 2H), 2.94−2.87 (m, 2H), 2.80−2.76 (m, 2H), 2.70−2.66 (m, 2H), 1.29 (d, J = 6.2 Hz, 3H), 1.28 (d, J = 6.1 Hz, 3H), 1.21 (d, J = 6.2 Hz, 3H), 1.09 (d, J = 6.2 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 137.8, 136.1 (d, J_{C-P} = 6.6 Hz), 130.3 (d, J_{C-P} = 1.7 Hz), 129.6 (d, J_{C-P} = 4.1 Hz), 128.9 (overlapped, 2 C), 126.9 (d, J_{C-P} = 3.5 Hz), 125.5 (d, J_{C-P} = 2.8 Hz), 71.53 (d, J_{C-P} = 7.3 Hz), 71.51 (d, J_{C-P} = 7.1 Hz), 70.7 (d, J_{C-P} = 7.8 Hz), 61.0 (d, J_{C-P} = 158.4 Hz), 60.9 (d, J_{C-P} = 158.7 Hz), 59.32 (d, J_{C-P} = 12.1 Hz), 59.30 (d, J_{C-P} = 12.2 Hz), 45.1 (d, J_{C-P} = 1.5 Hz), 45.0 (d, J_{C-P} = 1.6 Hz), 25.10, 25.06, 24.6 (d, J_{C-P} = 2.8 Hz), 24.3 (d, J_{C-P} = 3.1 Hz), 24.0 (d, J_{C-P} = 5.6 Hz), 23.7 (d, J_{C-P} = 5.5 Hz); ^{31}P NMR ($CDCl_3$, 202 MHz): δ 22.06, 22.04; IR (liquid film) υ_{max}: 2976, 2932, 2835, 1492, 1452, 1384, 1372, 1244, 1177, 1140, 1106, 982, 743 cm^{-1}; HRMS (ESI-TOF): $[M + H]^+$ m/z calcd for $C_{38}H_{54}N_2O_6P_2H^+$, 697.3535; found, 697.3530.

*Diisopropyl (2-Isopentyl-1,2,3,4-tetrahydroisoquinolin-1-yl)-phosphonate (**4z**).* 72% yield, 79 mg; colorless oil; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.32 (dt, J = 7.3, 1.6 Hz, 1H), 7.16−7.09 (m, 2H), 7.07 (d, J = 6.6 Hz, 1H), 4.66−4.56 (m, 2H), 4.04 (d, J = 22.8 Hz, 1H), 3.67−3.61 (m, 1H), 2.91−2.80 (m, 2H), 2.75−2.62 (m, 3H), 1.64−1.54 (m, 1H), 1.46−1.39 (m, 2H), 1.31 (d, J = 6.6 Hz, 3H, overlapped), 1.29 (d, J = 6.5 Hz, 3H, overlapped), 1.22 (d, J = 6.2 Hz, 3H), 1.13 (d, J = 6.2 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 136.3 (d, J_{C-P} = 5.9 Hz), 130.5, 129.6 (d, J_{C-P} = 3.9 Hz), 128.9 (d, J_{C-P} = 2.7 Hz), 126.8 (d, J_{C-P} = 3.6 Hz), 125.4 (d, J_{C-P} = 3.3 Hz), 71.7 (d, J_{C-P} = 7.5 Hz), 70.6 (d, J_{C-P} = 7.9 Hz), 61.3 (d, J_{C-P} = 159.8 Hz), 53.7 (d, J_{C-P} = 13.4 Hz), 45.3 (d, J_{C-P} = 1.3 Hz), 36.9, 26.5, 24.7, 24.6 (d, J_{C-P} = 2.7 Hz), 24.3 (d, J_{C-P} = 3.0 Hz), 24.0 (d, J_{C-P} = 5.5 Hz), 23.7 (d, J_{C-P} = 6.1 Hz), 22.9 (d, J_{C-P} = 8.3 Hz); ^{31}P NMR ($CDCl_3$, 202 MHz): δ 22.05; IR (liquid film) υ_{max}: 2955, 2929, 2869, 1466, 1455, 1383, 1372, 1245, 1177, 1107, 982, 739 cm^{-1}; HRMS (ESI-TOF): $[M + H]^+$ m/z calcd for $C_{20}H_{34}NO_3PH^+$, 368.2355; found, 368.2369.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02625.

NMR spectra of **4a**−**4z** (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: gaoxingchem@xmu.edu.cn.

Author Contributions

‖G.H. and W.C. contributed equally to this work.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the Chinese National Natural Science Foundation (nos. 21202135 and 41576081), the Natural Science Foundation of Fujian Province of China (nos. 2013J05031 and 2015N0009), and the National Basic Research Program of China (no. 2012CB821600).

■ REFERENCES

(1) Selected publications: (a) Yokomatsu, T.; Yoshida, Y.; Shibuya, S. *J. Org. Chem.* **1994**, *59*, 7930. (b) *Aminophosphonic and Aminophosphinic Acids: Chemistry and Biological Activity*, 5th ed.; Kukhkhar, V. P., Hudson, H. R., Eds.; Wiley: Chichester, 2000. (c) Ali, T. E. *ARKIVOC* **2014**, 21. (d) Das, D.; Seidel, D. *Org. Lett.* **2013**, *15*, 4358.

(2) (a) Moonen, K.; Laureyn, I.; Stevens, C. V. *Chem. Rev.* **2004**, *104*, 6177. (b) Orsini, F.; Sello, G.; Sisti, M. *Curr. Med. Chem.* **2010**, *17*, 264. (c) Mucha, A.; Kafarski, P.; Berlicki, Y. *J. Med. Chem.* **2011**, *54*, 5955.

(3) Selected publications: (a) Forlani, G.; Occhipinti, A.; Berlicki, L.; Dziedziola, G.; Wieczorek, A.; Kafarski, P. *J. Agric. Food Chem.* **2008**, *56*, 3193. (b) Occhipinti, A.; Berlicki, Ł.; Giberti, S.; Dziedziola, G.; Kafarski, P.; Forlani, G. *Pest Manage. Sci.* **2010**, *66*, 51. (c) Forlani, G.; Berlicki, L.; Duo, M.; Dziedziola, G.; Giberti, S.; Bertazzini, M.; Kafarski, P. *J. Agric. Food Chem.* **2013**, *61*, 6792.

(4) Chen, M. H.; Chen, Z.; Song, B. A.; Bhadury, P. S.; Yang, S.; Cai, X. J.; Hu, D. Y.; Xue, W.; Zeng, S. *J. Agric. Food Chem.* **2009**, *57*, 1383.

(5) For representative publications, see: (a) Pratt, R. F. *Science* **1989**, *246*, 917. (b) Krishna, A. B.; Reddy, M. V. N.; Reddy, G. C. S.; Krishna, B. S.; Nayak, S. K.; Reddy, C. S. *Int. J. Appl. Biol. Pharm. Technol.* **2010**, *1*, 873. (c) Ali, N. A. S.; Zakir, S.; Patel, M.; Farooqui, M. *Eur. J. Med. Chem.* **2012**, *50*, 39. (d) Burchacka, E.; Walczak, M. M.; Sieńczyk, M.; Dubin, G.; Zdźalik, M.; Potempa, J.; Oleksyszyn, J. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 5574.

(6) (a) Kafarski, P.; Lejczak, B. *Phosphorus, Sulfur Silicon Relat. Elem.* **1991**, *63*, 193. (b) Devineni, S. R.; Doddaga, S.; Donka, R.; Chamarthi, N. R. *Chin. Chem. Lett.* **2013**, *24*, 759.

(7) (a) Lavielle, G.; Hautefaye, P.; Schaeffer, C.; Boutin, J. A.; Cudennec, C. A.; Pierré, A. *J. Med. Chem.* **1991**, *34*, 1998. (b) Huang, J.; Chen, R. *Heteroat. Chem.* **2000**, *11*, 480.

(8) (a) Logusch, E. W.; Walker, D. M.; McDonald, J. F.; Leo, G. C.; Franz, J. E. *J. Org. Chem.* **1988**, *53*, 4069. (b) Allen, M. C.; Fuhrer, W.; Tuck, B.; Wade, R.; Wood, J. M. *J. Med. Chem.* **1989**, *32*, 1652. (c) Hiratake, J.; Oda, J. *Biosci., Biotechnol., Biochem.* **1997**, *61*, 211.

DOI: 10.1021/acs.joc.5b02625
J. Org. Chem. 2016, 81, 1704−1711

(9) Hirschmann, R.; Smith, A. B.; Taylor, C. M.; Benkovic, P. A.; Taylor, S. D.; Yager, K. M.; Sprengeler, P. A.; Benkovic, S. J. *Science* **1994**, *265*, 234.
(10) (a) Scott, J. D.; Williams, R. M. *Chem. Rev.* **2002**, *102*, 1669. (b) Chrzanowska, M.; Rozwadowska, M. D. *Chem. Rev.* **2004**, *104*, 3341.
(11) Basle, O.; Li, C.-J. *Chem. Commun.* **2009**, 4124.
(12) Alagiri, K.; Devadig, P.; Prabhu, K. R. *Tetrahedron Lett.* **2012**, *53*, 1456.
(13) Xie, J.; Li, H.; Xue, Q.; Cheng, Y.; Zhu, C. *Adv. Synth. Catal.* **2012**, *354*, 1646.
(14) Selected recent publications: (a) Hari, D. P.; König, B. *Org. Lett.* **2011**, *13*, 3852. (b) Rueping, M.; Zoller, J.; Fabry, D. C.; Poscharny, K.; Koenigs, R. M.; Weirich, T. E.; Mayer, J. *Chem. - Eur. J.* **2012**, *18*, 3478. (c) Meng, Q.-Y.; Zhong, J.-J.; Liu, Q.; Gao, X.-W.; Zhang, H.-H.; Lei, T.; Li, Z.-J.; Feng, K.; Chen, B.; Tung, C.-H.; Wu, L.-Z. *J. Am. Chem. Soc.* **2013**, *135*, 19052. (d) Rueping, M.; Vila, C.; Bootwicha, T. *ACS Catal.* **2013**, *3*, 1676. (e) Yoo, W.-J.; Kobayashi, S. *Green Chem.* **2014**, *16*, 2438.
(15) Alagiri, K.; Devadig, P.; Prabhu, K. R. *Chem. - Eur. J.* **2012**, *18*, 5160.
(16) Dhineshkumar, J.; Lamani, M.; Alagiri, K.; Prabhu, K. R. *Org. Lett.* **2013**, *15*, 1092.
(17) Tanoue, A.; Yoo, W.-J.; Kobayashi, S. *Org. Lett.* **2014**, *16*, 2346.
(18) Tanoue, A.; Yoo, W.-J.; Kobayashi, S. *Adv. Synth. Catal.* **2013**, *355*, 269.
(19) Huo, C.; Wang, C.; Wu, M.; Jia, X.; Wang, X.; Yuan, Y.; Xie, H. *Org. Biomol. Chem.* **2014**, *12*, 3123.
(20) Huo, C.; Xie, H.; Wu, M.; Jia, X.; Wang, X.; Chen, F.; Tang, J. *Chem. - Eur. J.* **2015**, *21*, 5723.
(21) (a) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2047. (b) Kwong, F. Y.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 581.
(22) (a) Gao, Y.; Wang, G.; Chen, L.; Xu, P.; Zhao, Y.; Zhou, Y.; Han, L.-B. *J. Am. Chem. Soc.* **2009**, *131*, 7956. (b) Hu, G.; Gao, Y.; Zhao, Y. *Org. Lett.* **2014**, *16*, 4464. (c) Gao, Y.; Deng, H.; Zhang, S.; Xue, W.; Wu, Y.; Qiao, H.; Xu, P.; Zhao, Y. *J. Org. Chem.* **2015**, *80*, 1192.
(23) (a) Fields, E. K. *J. Am. Chem. Soc.* **1952**, *74*, 1528. (b) Cherkasov, R. A.; Galkin, V. I. *Russ. Chem. Rev.* **1998**, *67*, 857. (c) Wu, J.; Sun, W.; Sun, X.; Xia, H.-G. *Green Chem.* **2006**, *8*, 365. (d) Bhagat, S.; Chakraborti, A. K. *J. Org. Chem.* **2008**, *73*, 6029.
(24) (a) Grigg, R.; Sarker, M. A. B. *Tetrahedron* **2006**, *62*, 10332. (b) Álvarez-Corral, M.; Muñoz-Dorado, M.; Rodríguez-García, I. *Chem. Rev.* **2008**, *108*, 3174.

DOI: 10.1021/acs.joc.5b02625
J. Org. Chem. 2016, 81, 1704−1711