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Catalyst-Free Cross-Dehydrogenative Coupling Strategy Using Air as an Oxidant: Synthesis of α-Aminophosphonates

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Supporting Information

ABSTRACT: α-Aminophosphonates are synthesized by employing unfunctionalized starting materials using cross-dehydrogenative coupling strategy. This method does not require any catalyst and proceeds in the presence of open air as the only oxidant. Mechanistic studies revealed that the reaction is nucleophile dependent and specific to dialkyl phosphite and *N*-aryl tetrahydroisoquinoline derivatives.

INTRODUCTION

Among the traditional C−C bond-forming reactions, cross-dehydrogenative coupling (CDC) reactions have received great importance in synthetic chemistry as they provide excellent tool for forming C−C bonds between two different C−H bonds without using prefunctionalized starting materials.[1] Activation of C−H bonds via CDC reactions can be achieved by various transition-metal catalysts, such as Cu,[2] Ru,[3] Fe,[4] V,[5] Au,[6] Pt,[7] and Ir,[8] in the presence of suitable oxidants, whereas nonmetal catalysts, such as iodine,[17a−c] 2,3-dichloro-5,6-dicyano-1,4-benzoquinone,[9g] phenyliodonium diacetate,[9] Rose Bengal,[10] and Eosin Y,[10] have also shown good prospects. Oxidants used in these reactions generally accept hydrogen and/or maintain the redox catalytic cycle. Commonly used oxidants under CDC conditions are O_2, *tert*-butyl hydroperoxide (TBHP), and H_2O_2.[11] CDC reactions have been used to activate sp^3 C−H bonds of benzylic and allylic compounds and alkanes, and α-C−H bonds of heteroatoms, such as nitrogen or oxygen.[2−11] As nitrogen-containing molecules are common structural motifs in a variety of biologically active compounds, a great deal of effort has been put forward for the α-C−H activation of tertiary amines and coupling them with a variety of nucleophiles.[12] α-Aminophosphonates are one such biologically important frameworks that are isoelectronic analogues of α-amino acids (Figure 1; glyphosate, alafosfalin, etc.).[13] They find wide applications in medicinal chemistry and pharmaceutical and agricultural industries.[13] The bioactivity of these molecules as antitumor, anti-inflammatory, enzyme inhibitor, and antifungal agents is one of the reasons for them to be attractive synthetic targets.[14] Glyphosphate is one of the most used herbicides in agricultural sector,[14] whereas medicinally important compound alafosfalin has a basic α-aminophosphonate moiety.[14]

Generally, α-amino phosphoric acids are not soluble in water as well as in most of the organic solvents.[15] α-Aminophosphonates are used as intermediates in multistep synthesis.[15]

Li and co-workers were the first to report Cu-catalyzed α-phosphorylation of *N*-phenyl tetrahydroisoquinolines to produce sp^3 C−P bonds.[16a] Visible-light-mediated phosphorylation of *N*-aryl tetrahydroisoquinolines, with the help of expensive Ru(II)- and Ir(III)-based catalysts and Eosin Y, has also been reported in 2011 (Scheme 1).[16b,c,f−j] More recently, nanoporous gold skeleton catalyst has been used[16] to form C−P bonds. In this direction, others[17a−c] and our group are actively involved in functionalization of *N*-aryl tetrahydroisoquinolines.[17d−j]

Oxidation reactions are very important in organic synthesis, which are subject of exploration since time immemorial. There is a continuous urge to develop mild and selective oxidation methods for synthesizing a variety of organic molecules. In continuation of our work on CDC reactions,[17d,e] we found, serendipitously, that the reaction of *N*-phenyl tertrahydroisoquinoline (**1a**) with diethyl phosphite (**2a**) in open air (as the only oxidant) in the absence of any catalysts can lead to the formation of corresponding α-aminophosphonate (**3a**) (Scheme 1).

RESULTS AND DISCUSSION

The screening studies were carried out using *N*-phenyl tetrahydroisoquinoline (THIQ) (**1a**) and diethyl phosphite (**2a**) as nucleophile (Table 1). Thereby, *N*-phenyl tetrahydroisoquinoline (**1a**) and diethyl phosphite (**2a**) were dissolved in MeOH and stirred at room temperature (rt) for 24 h in open air. Then (the reaction was monitored by thin-layer chromatography (TLC)), a trace amount of product was observed (entry 1). When the same reaction was refluxed at 60 °C for 24 h, it was observed that the significant amount of starting material was consumed. Then, the reaction was left for additional 24 h in open air and it was surprising to find the formation of the product **3a** in 64% (entry 2, Table 1). Encouraged by this result, different solvents were screened to optimize the reaction conditions to enhance the yield. The reaction was facile in most of the solvents, except toluene and water (entries 3 and 4, respectively). The reaction of **1a** with **2a**

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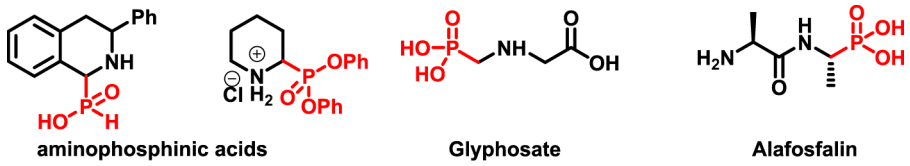


Figure 1. Biologically important compounds.

Scheme 1. The Outlook

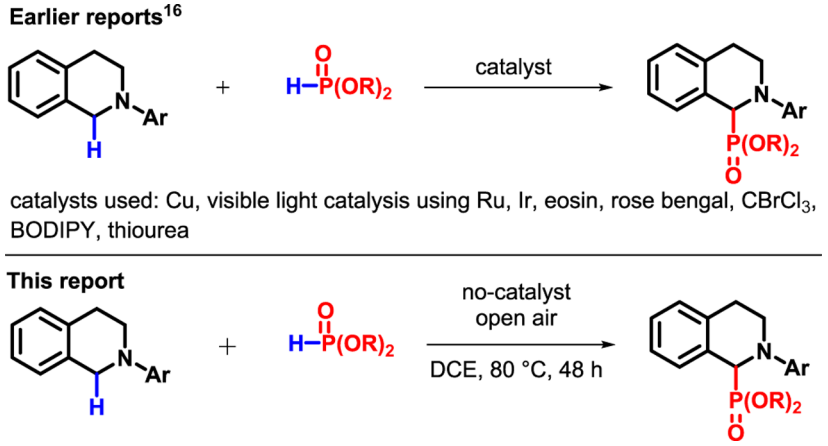
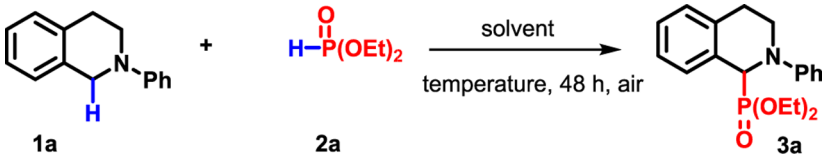


Table 1. Screening Studies for Optimization[a]



entry	solvent	temperature	NMR yield (%)[b]
1	MeOH	rt	trace
2	MeOH	60	64
3	toluene	110	nd[c]
4	H_2O	100	nd
5	CHCN	80	58
6	DMF	100	47
7	CF_3CH_2OH	60	66
8	1,4-dioxane	80	74
9	DCE	80	80[d]
10	DCE + 1,4-dioxane (1:1)	80	65
11	DCE	80	82[e]
12	DCE	80	33[f]
13	DCE	80	5[g]

[a]Reaction conditions: **1a** (0.25 mmol) and **2a** (0.5 mmol) in 2 mL of solvent. [b]1H NMR yield was calculated using terephthalaldehyde as an internal standard. [c]nd = not detected. [d]1.2 equiv of **2a** was used. [e]2 equiv of **2a** was used. [f]Reaction in argon atmosphere. [g]Reaction in degassed solvent, DCE in argon atmosphere.

in solvents such as CH_3CN, dimethylformamide, and trifluoroethanol furnished the expected product **3a** in moderate yields (58, 47, and 66%, respectively, entries 5−7, Table 1). In 1,4-dioxane, the expected product **3a** was obtained in 74% yield (entry 8), whereas in dichloroethane (DCE), the product **3a** was obtained in 80% yield (NMR yield, entry 9). When a mixture of solvents such as dichloroethane and 1,4-dioxane in 1:1 ratio was used, the reaction furnished **3a** in only 65% yield (entry 10). Increasing the amount of phosphite (**2a**) to 2 equiv furnished **3a** in 82% (entry 11). To gain more insight into the oxidation process, the reaction was carried out under argon atmosphere (entry 12). In this reaction, the yield of the expected product **3a** dropped to 33% (NMR yield, entry 12). This reaction clearly indicates that the molecular oxygen present in the open air is playing a crucial role. And, 33% yield of the expected product may be attributed to the presence of dissolved oxygen in the solvent. To corroborate our understanding, the reaction was carried out under argon atmosphere using degassed solvent (DCE) to obtain the expected product **3a** in 5% yield (entry 13).

After finding the optimal reaction conditions (entry 11, Table 1), the substrate scope and generality of the reaction were explored using a variety of tetrahydroisoquinoline derivatives and dialkyl phosphites (Scheme 2). Reaction of

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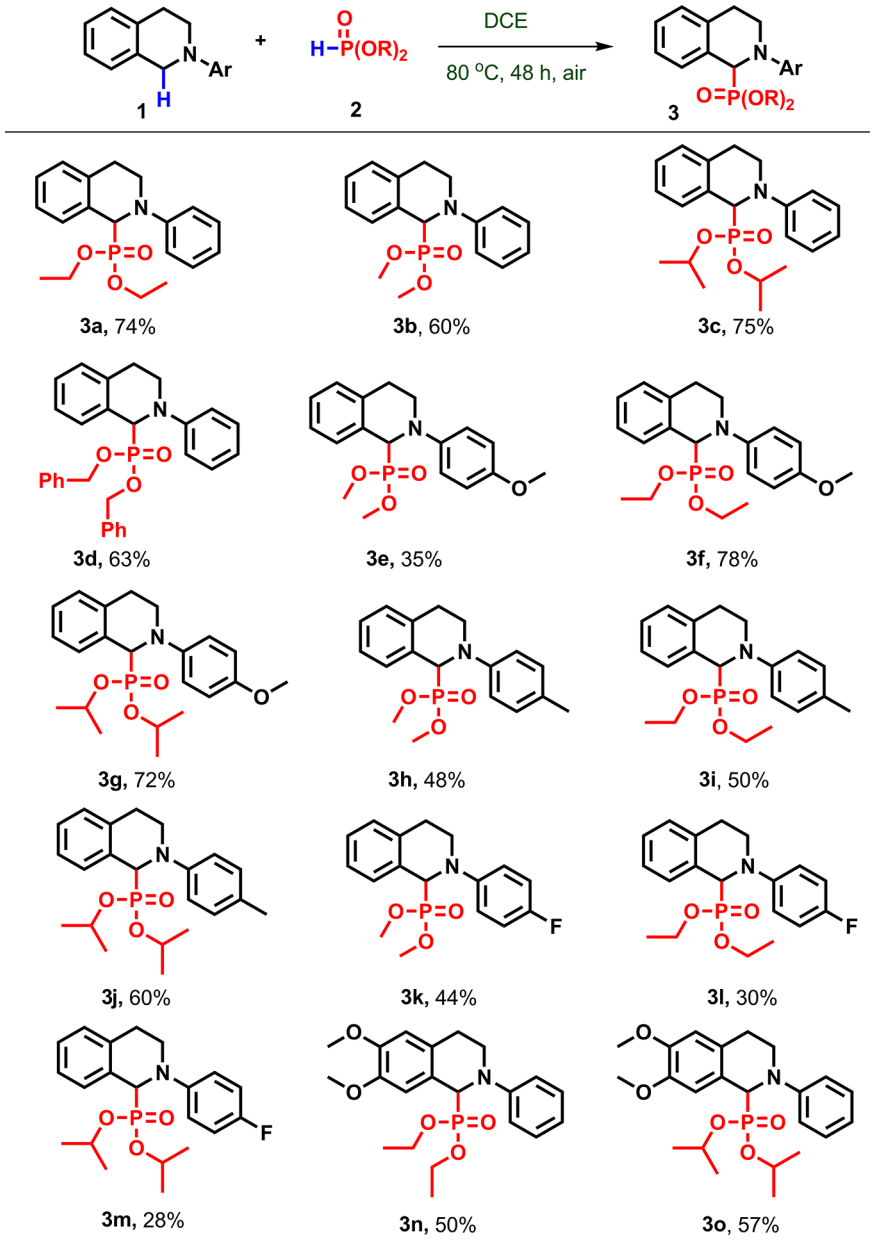
Scheme 2. Substrate Scope for C−P Bond Formation[a]



[a]Reaction conditions: **1** (0.25 mmol), **2** (0.5 mmol), DCE (2 mL), 80 °C, 48 h.

N-phenyl THIQ (**1a**) and diethyl phosphite (**2a**) under the optimal reaction conditions furnished the expected α-aminophosphonate **3a** in 74% isolated yield (Scheme 2). Other dialkyl phosphites, such as dimethyl phosphite, diisopropyl phosphite, and dibenzyl phosphite, underwent a smooth reaction with *N*-phenyl tetrahydroisoquinoline (**1a**), furnishing the coupled products **3b−d** in good to moderate yields (60, 75, and 63% yields, respectively, Scheme 2). THIQ derivatives that contain electron-releasing group on *N*-phenyl moiety, such as 2-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline, reacted well with dimethyl phosphite, diethyl phosphate, and diisopropyl phosphite, furnishing the corresponding α-aminophosphonates **3e−g** in moderate to good yields (35, 78, and 72% yields, respectively). Similarly, 2-(*p*-tolyl)-1,2,3,4-tetrahydroisoquinoline reacted with dimethyl phosphite, diethyl phosphate, and diisopropyl phosphite, furnishing the corresponding α-aminophosphonates **3h−j** in good to moderate yields (48, 50, and 60%, respectively). 2-(4-Fluorophenyl)-1,2,3,4-tetrahydroisoquinoline, in which electron-withdrawing group, such as fluorine, is attached to *N*-phenyl moiety, reacted with dimethyl phosphite, diethyl phosphite, and diisopropyl phosphite affording the cross-dehydrogenative coupled products **3k−m** in poor yields (44, 30, and 28%, respectively). The poor yields obtained in these reactions may be due to the instability of intermediate iminium-ion formed in situ in the reaction mixture. The reactions of veratrole-derived 6,7-dimethoxy-2-phenyl-1,2,3,4-tetrahydroisoquinoline with diethyl and diisopropyl phosphites were examined under the standard reaction conditions, which furnished the expected products **3n** and **3o** in moderate yields (50 and 57%, respectively).

It was disappointing to note that the reaction of diphenyl phosphite with *N*-phenyl tetrahydroisoquinoline was unsuccessful (Scheme 3). This reaction indicates that the reaction conditions are very specific for dialkyl phosphite derivatives.

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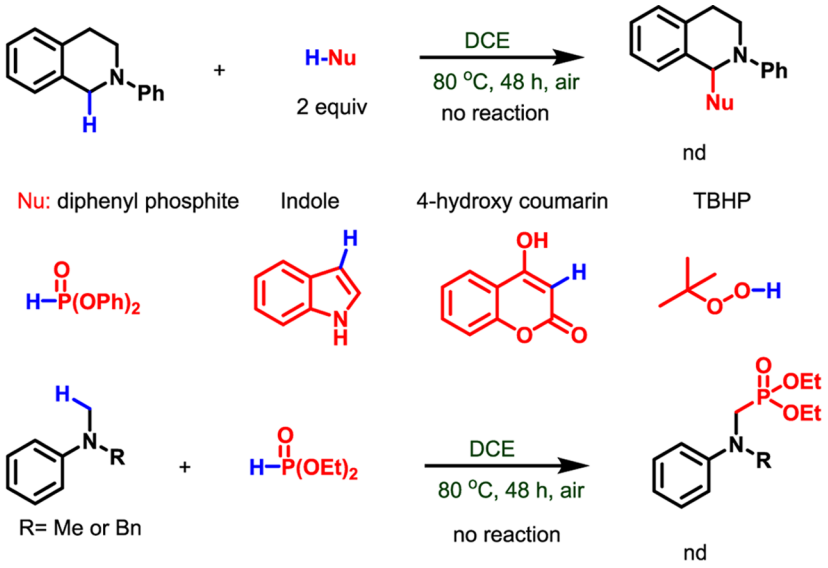
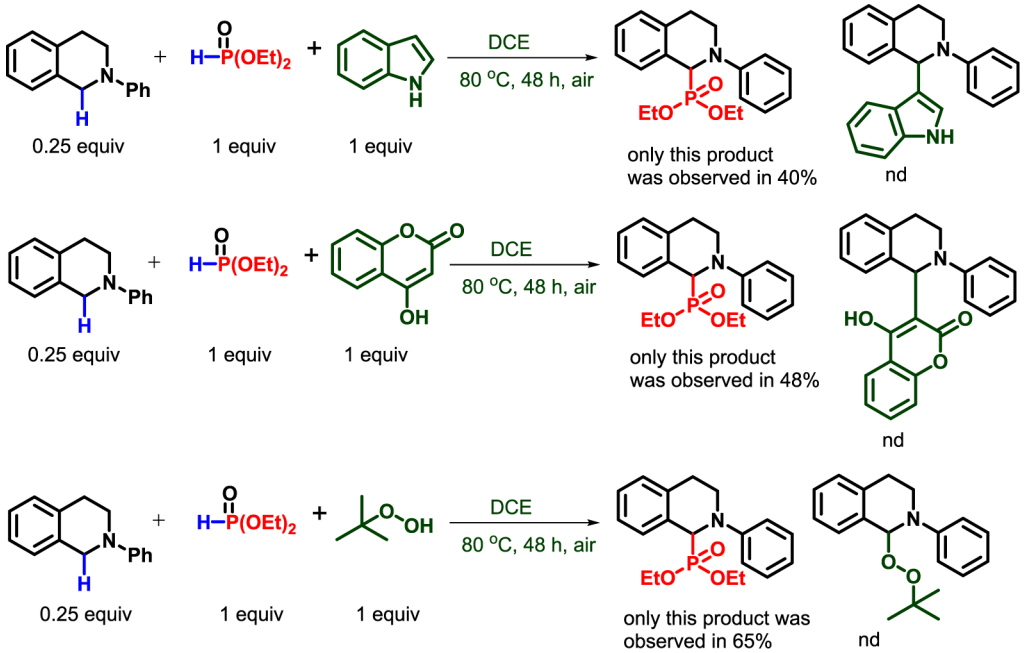
Scheme 3. Control Experiments[a]

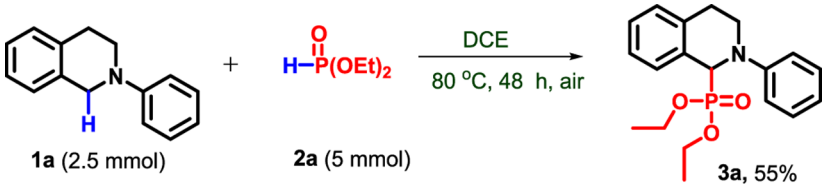


[a]Reaction conditions: amine (0.25 mmol), nucleophile (0.5 mmol), DCE (2 mL), 80 °C, 48 h.

Scheme 4. Competitive Experiments



Scheme 5. Gram-Scale Synthesis



The reactions of other nucleophiles, such as indole, 4-hydroxycoumarin, and TBHP, with *N*-phenyl tetrahydroisoquinoline did not afford the coupled products under the optimal reaction conditions (Scheme 3). Reaction of acyclic tertiary amines, such as *N*,*N*-dimethyl aniline and *N*-benzyl-*N*-methyl amine, under the standard reaction conditions, did not furnish the expected cross-dehydrogenative coupled products (Scheme 3).

Presuming that dialkyl phosphite may play a crucial role in the oxidation of tertiary amines, a reaction of *N*-phenyl THIQ and different nucleophiles (indole or 4-hydroxycoumarin or TBHP) in the presence of dialkyl phosphite was carried out

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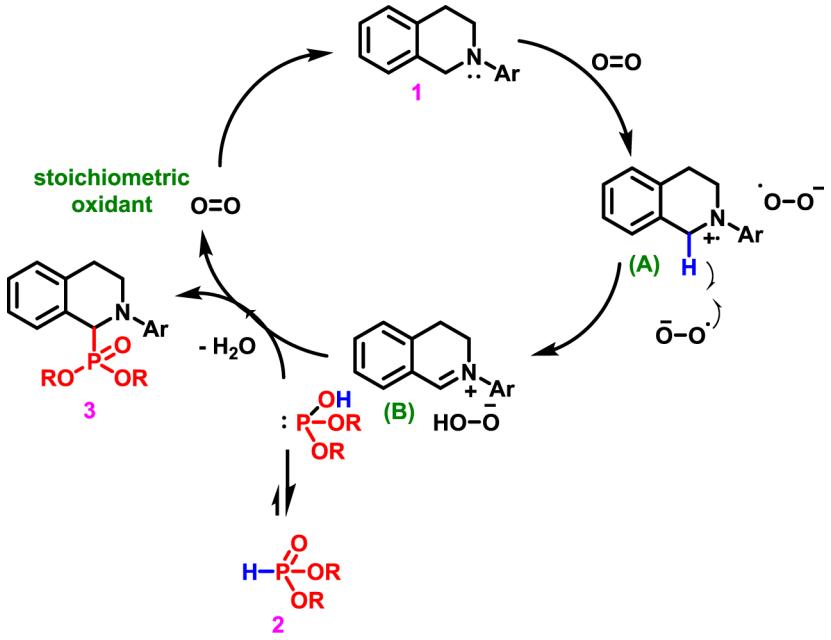
Scheme 6. Tentative Mechanism



(Scheme 4). However, in this reaction, only the phosphite-coupled product was observed (40−65%, NMR yield).

A gram-scale experiment has also been performed to explore the efficiency of the reaction. Hence, the reaction of *N*-phenyl THIQ (**1a**, 2.5 mmol) and diethyl phosphite (**2a**, 5 mmol) under the standard reaction conditions furnished the CDC product **3a** in 55% yield (Scheme 5).

On the basis of the literature precedence[1,2] as well as from our earlier studies,[17e] a tentative mechanism has been proposed (Scheme 6). *N*-Aryl THIQ (**1**) reacts with molecular oxygen, which is present in air, to form the intermediate **A**. The intermediate **A** further undergoes a radical cleavage of proton to form the iminium-ion intermediate **B**. This iminium-ion intermediate (**B**) is then captured by the active nucleophile, such as dialkyl phosphite (**2**), to afford the CDC product (**3**).

In summary, an efficient CDC reaction has been developed for the synthesis of α-aminophosphonate using open air as the only oxidant. A variety of THIQ-derived aminophosphonates were synthesized using these mild reaction conditions. Control studies revealed that the reaction occurs only when dialkyl phosphite acts as a nucleophile. Dialkyl phosphite plays a crucial role in the oxidative coupling, and the reaction is nucleophile dependent. The reaction holds good for gram-scale synthesis also.

EXPERIMENTAL SECTION

General Information. All reactions were carried out using distilled solvents. Reactions were monitored using precoated silica TLC plates. Mass spectra were recorded on electron ionization and electrospray ionization (ESI) (time-of-flight) modes. NMR spectra were recorded on 400 MHz spectrometers in $CDCl_3$, dimethyl sulfoxide (DMSO)-d_6, tetramethylsilane (δ = 0.00 ppm), which served as an internal standard for ^{1}H NMR. The corresponding residual nondeuterated solvent signal ($CDCl_3$; δ = 77.00 ppm; DMSO-d_6, δ = 39.52 ppm) was used as an internal standard for ^{13}C NMR. Column chromatography was carried out on silica gel 230−400 mesh or 100−200 mesh (Merck), and thin-layer chromatography was carried out using silica gel GF-254. Chemicals obtained from commercial suppliers were used without further purification. Tetrahydroisoquinoline derivatives were synthesized using known procedures.[17d]

Typical Experimental Procedure for the Synthesis of α-Aminophosphonates. To the mixture of *N*-phenyl tetrahydroisoquinoline **1a** (0.25 mmol) in DCE (2 mL), diethyl phosphite **2a** (0.5 mmol) was added dropwise using a syringe. The reaction mixture was heated to reflux at 80 °C for 48 h. The completion of the reaction was monitored by TLC, and reaction mixture was directly taken for purification through column chromatography using petroleum ether/ethyl acetate (EtOAc) solvent system to afford the products.

*Characterization Data for 1-Aminophosphonates. Diethyl(2-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)-phosphonate (**3a**).*[17e] Brown oily liquid; yield, 74%; Rf (30% EtOAc/hexane) 0.2; prepared as shown in general experimental procedure. IR (neat, cm^{-1}): 3465, 2981, 2264, 1500, 1244, 1024, 750; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.15−7.38 (m, 6H), 6.97 (d, J = 8.4 Hz, 2H), 6.79 (t, J = 7.2 Hz, 1H), 5.18 (d, J = 20 Hz, 1H), 3.90−4.10 (m, 5H), 3.62−3.65 (m, 1H), 2.98−3.07 (m, 2H), 1.23 (t, J = 7.2 Hz, 3H), 1.13 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.3 (d, J = 6 Hz), 136.4 (d, J = 5.3 Hz), 130.6, 129.1, 128.7, 128.6, 128.1, 127.4, 127.3, 125.8, 125.7, 118.4, 114.7, 63.3 (d, J = 7.1 Hz), 62.3 (d, J = 7.6 Hz), 58.7 (d, J = 158.3 Hz), 43.4, 26.7, 16.4 (d, J = 5.5 Hz), 16.3 (d, J = 6.1 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ 22.2; high-resolution ESI-mass spectrometry (HRESI-MS) (m/z): calcd for $C_{19}H_{24}NO_3P$ (M + Na): 368.1392, found (M + Na): 368.1392.

*Dimethyl(2-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)-phosphonate (**3b**).*[17d] Red oily liquid; yield, 60%; Rf (30% EtOAc/hexane) 0.3; prepared as shown in general experimental procedure. IR (neat, cm^{-1}): 3449, 3059, 2992, 2950 1597, 1247, 1057, 946; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 (d, J = 6.4, 1H), 7.16−7.28 (m, 5H), 6.97 (d, 2H, J = 8.4 Hz), 6.81 (t, 1H, J = 7.2 Hz), 5.20 (d, 1H, J = 20 Hz), 3.98−4.04 (m, 1H), 3.62−3.67 (m, 7H) 2.99−3.07 (m, 2H). ^{13}C NMR (100 MHz,

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$CDCl_3$): δ 149.2 (d, *J* = 5.9 Hz), 136.4 (d, *J* = 5.7 Hz), 130.38, 129.22, 128.8 (d, *J* = 2.6 Hz), 127.9 (d, *J* = 4.5 Hz), 127.5 (d, *J* = 3.4 Hz), 126.0, (d, *J* = 2.7 Hz), 118.6, 114.7, 58.7 (d, *J* = 160 Hz), 53.9 (d, *J* = 7.2 Hz), 52.9 (d, *J* = 7.7 Hz), 43.5, 26.6. ^{31}P NMR (162 MHz, $CDCl_3$): δ 24.4; HRESI-MS (*m*/*z*): calcd for $C_{17}H_{26}NO_3P$ (M + Na): 340.1079, found (M + Na): 340.1082.

*Diisopropyl(2-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)-phosphonate (**3c**).*[17e] White oily liquid; yield, 75%; Rf (20% EtOAc/hexane) 0.2; prepared as shown in general experimental procedure. IR (neat, cm^{-1}): 2978, 1598, 1499, 1240, 982, 749; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (d, *J* = 8 Hz, 1H), 7.11−7.25 (m, 5H), 6.95 (d, *J* = 8 Hz, 2H), 6.77 (t, *J* = 6.8 Hz, 1H), 5.14 (d, *J* = 21.2 Hz, 1H), 4.60−4.64 (m, 2H), 4.01−4.05 (m, 1H), 3.63−3.67 (m, 1H), 2.98−3.01 (m, 2H), 1.27−1.30 (m, 6H), 1.14 (d, *J* = 6 Hz, 3H), 0.94 (d, *J* = 6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.5 (d, *J* = 6.8 Hz), 136.4 (d, *J* = 5.6 Hz), 130.9, 130.8, 128.9, 128.7, 128.4, 128.3, 127.2, 127.2, 125.6, 125.5, 118.2, 115, 72.2 (d, *J* = 7.7 Hz), 70.8 (d, *J* = 8.1 Hz), 58.6 (d, *J* = 160.0 Hz), 43.4, 26.5, 24.5 (d, *J* = 2.6 Hz), 24.1 (d, *J* = 3 Hz), 23.7 (d, *J* = 5.6 Hz), 23.3 (d, *J* = 5.6 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ 20.9; HRESI-MS (*m*/*z*): calcd for $C_{21}H_{28}NO_3P$ (M + Na): 396.1705, found (M + Na): 396.1705.

*Dibenzyl(2-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)-phosphonate (**3d**).*[17e] Pale yellow solid; yield, 63%; mp: 98−100 °C; Rf (30% EtOAc/hexane) 0.6; prepared as shown in general experimental procedure. IR (KBr, cm^{-1}): 3034, 2892, 1593, 1497, 1230, 1008, 771, 547; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.10−7.32 (m, 16H), 6.96 (d, *J* = 8 Hz, 2H), 6.78 (t, *J* = 8.8 Hz, 1H), 5.28 (d, *J* = 20.0 Hz, 1H), 4.83−5.1 (m, 3H), 4.73−4.76 (m, 1H), 3.98−4.0 (m, 1H), 3.58−3.64 (m, 1H), 2.97−3.04 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.1, 136.1−136.5 (m), 130.3, 129.1, 128.8, 128.7, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.5, 127.4, 125.9, 118.6, 114.8, 68.6 (d, *J* = 7.2 Hz), 67.7 (d, *J* = 7.8 Hz), 58.9 (d, *J* = 157.0 Hz), 43.4, 26.7; ^{31}P NMR (162 MHz, $CDCl_3$): δ 22.9; HRESI-MS (*m*/*z*): calcd for $C_{29}H_{28}NO_3P$ (M + Na): 492.1705, found (M + Na): 492.1708.

*Dimethyl(2-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)phosphonate (**3e**).*[17e] Brown oily liquid; yield, 35%; Rf (30% EtOAc/hexane) 0.1; prepared as shown in general experimental procedure. IR (neat, cm^{-1}): 3425, 2952, 1648, 1511, 1457, 1363, 1247, 1182,1031, 827, 742; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35−7.38 (m, 1H), 7.13−7.20 (m, 5H), 6.92 (d, *J* = 9.2 Hz, 2H), 6.82 (d, *J* = 9.2 Hz, 2H), 5.04 (d, *J* = 21.5 Hz, 1H), 3.98−4.05 (m, 1H), 3.75 (s, 3H), 3.64−3.68 (m, 6H) 3.51−3.57 (m, 1H), 2.91−2.93 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.3, 144 (d, *J* = 8.5 Hz), 136.3 (d, *J* = 6.0 Hz), 130.2, 129 (d, *J* = 2.6 Hz), 127.9 (d, *J* = 4.3 Hz), 127.3 (d, *J* = 3.4 Hz), 125.9, (d, *J* = 2.9 Hz), 117.7, 114.6, 59.4 (d, *J* = 159 Hz), 55.6, 54.0 (d, *J* = 7.2 Hz), 52.8 (d, *J* = 7.5 Hz), 44.7, 26; ^{31}P NMR (162 MHz, $CDCl_3$): δ 24.4; HRESI-MS (*m*/*z*): calcd for $C_{18}H_{22}NO_4P$ (M + Na): 370.1184, found (M + Na): 370.1183.

*Diethyl(2-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)phosphonate (**3f**).*[17e] Red oily liquid; yield, 78%; Rf (30% EtOAc/hexane) 0.2; prepared as shown in general experimental procedure. IR (neat, cm^{-1}): 2925, 1509, 1243, 1025, 746; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 (d, *J* = 5.6 Hz, 1H), 7.26−7.17 (m, 3H), 6.92 (d, *J* = 9.2 Hz, 2H), 6.81 (d, *J* = 8.2 Hz, 2H), 5.02 (d, *J* = 21.2 Hz, 1H), 4.13−3.97 (m, 5H), 3.74 (s, 3H), 3.56−3.50 (m, 1H), 2.94−2.92 (m, 2H), 1.25 (t, *J* = 6.8 Hz, 3H), 1.15 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.0, 144.1 (d, *J* = 8.2 Hz), 136.3 (d, *J* = 5.9 Hz), 130.4, 128.9 (d, *J* = 2.3 Hz), 128.2 (d, *J* = 4.2 Hz), 127.2 (d, *J* = 3.3 Hz), 126.6, 125.7, 117.5, 114.5, 114.2, 63.3 (d, *J* = 7.2 Hz), 62.2 (d, *J* = 7.8 Hz), 59.3 (d, *J* = 157.9 Hz), 55.6, 44.6, 26.1, 16.4 (d, *J* = 5.5 Hz) 16.3 (d, *J* = 5.9 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ 22.2; HRESI-MS (*m*/*z*): calcd for $C_{20}H_{26}NO_4P$ (M + Na): 398.1497, found (M + Na): 398.1497.

*Diisopropyl(2-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)phosphonate (**3g**).*[17e] Dark brown solid; yield, 72%; mp: 63−65 °C; Rf (30% EtOAc/hexane) 0.3; prepared as shown in general experimental procedure. IR (KBr, cm^{-1}): 2977, 1509, 1242, 980, 730; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.4 (d, *J* = 5.6 Hz, 1H), 7.17−7.1 (m, 3H), 6.9 (d, *J* = 8.8 Hz, 2H), 6.8 (d, *J* = 8.2 Hz, 2H), 4.9 (d, *J* = 23.2 Hz, 1H), 4.72−4.58 (m, 2H), 4.1−4.03 (m, 1H), 3.73 (s, 3H), 3.73−3.53 (m, 1H), 2.93−2.82 (m, 2H), 1.31−1.28 (dd, *J*1 = 6.4 Hz, *J*2 = 12.8 Hz, 6H), 1.18 (d, *J* = 6 Hz, 3H), 1.0 (d, *J* = 6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.9, 144.3 (d, *J* = 9.5 Hz), 136.4 (d, *J* = 5.8 Hz), 130.7, 128.8, 128.5 (d, *J* = 5.7 Hz), 127.1, 125.5, 117.8, 114.3, 72.2 (d, *J* = 7.6 Hz), 70.7 (d, *J* = 8.1 Hz), 59.3 (d, *J* = 160.0 Hz), 55.58, 44.7, 25.8, 24.6−23.3 (m); ^{31}P NMR (162 MHz, $CDCl_3$): δ 20.81; HRESI-MS (*m*/*z*): calcd for $C_{22}H_{30}NO_4P$ (M + Na): 426.1810, found (M + Na): 426.1809.

*Dimethyl(2-(p-tolyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)-phosphonate (**3h**).*[17e] Pale pink liquid; yield, 48%; Rf (30% EtOAc/hexane) 0.2; prepared as shown in general experimental procedure. IR (neat, cm^{-1}): 3519, 3308, 2619, 2221, 1616, 1515, 1249, 1029, 825, 592; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 (d, *J* = 8 Hz, 1H), 7.12−7.19 (m, 3H), 7.05 (d, *J* = 8 Hz, 2H), 6.87 (d, *J* = 8.0 Hz, 2H), 5.13 (d, *J* = 20.8 Hz, 1H), 3.97−4.03 (m, 1H), 3.6−3.7 (m, 7H), 2.97−2.98 (m, 2H), 2.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.2 (d, *J* = 7 Hz), 136.4 (d, *J* = 6.6 Hz), 130.3, 129.7, 128.8, 128.2, 127.9, 127.8, 127.4, 127.3, 125.9, 115.3, 58.9 (d, *J* = 158.5 Hz), 53.98 (d, *J* = 7.0 Hz), 52.8 (d, *J* = 7.5 Hz), 43.8, 26.3, 20.2; ^{31}P NMR (162 MHz, $CDCl_3$): δ 24.4; HRESI-MS (*m*/*z*): calcd for $C_{18}H_{22}NO_3P$ (M + Na): 354.1235, found (M + Na): 354.1235.

*Diethyl(2-(p-tolyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)-phosphonate (**3i**).*[17e] Yellow oily liquid; yield, 50%; Rf (20% EtOAc/hexane) 0.2; prepared as shown in general experimental procedure. IR (neat, cm^{-1}): 3451, 2922, 1614, 1515, 1245, 800; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 (d, *J* = 4.0 Hz, 1H), 7.15−7.25 (m, 3H), 7.04 (d, *J* = 8 Hz, 2H), 6.87 (d, *J* = 8.0 Hz, 2H), 5.11 (d, *J* = 20.8 Hz, 1H), 3.8−4.1 (m, 5H), 3.56−3.62 (m, 1H), 2.97 (m, 2H), 2.24 (s, 3H), 1.25 (t, *J* = 8 Hz, 3H), 1.13 (t, *J* = 8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.3 (d, *J* = 7.0 Hz), 136.4 (d, *J* = 5.6 Hz), 130.5, 129.6, 128.7 (d, *J* = 2.0 Hz), 128.1 (d, *J* = 4.0 Hz), 127.9, 127.2, 125.7, 115.2, 63.3 (d, *J* = 7.1 Hz), 62.2 (d, *J* = 7.6 Hz), 58.9 (d, *J* = 158.0 Hz), 43.7, 26.3, 20.2, 16.4 (d, *J* = 5.3 Hz), 16.3 (d, *J* = 5.8 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ 22.2; HRESI-MS (*m*/*z*): calcd for $C_{20}H_{26}NO_3P$ (M + Na): 382.1548, found (M + Na): 382.1542.

*Diisopropyl(2-(p-tolyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)-phosphonate (**3j**).* Yellow oily liquid; yield, 60%; Rf (30% EtOAc/hexane) 0.4; prepared as shown in general experimental procedure. IR (neat, cm^{-1}): 3439, 2977, 2924, 1614, 1515, 1379, 1241, 1105, 1006; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38−7.40 (m, 1H), 7.09−7.16 (m, 3H), 7.01 (d, *J* = 8.5 Hz, 2H), 6.85 (d, *J* = 8.6 Hz, 2H), 5.05 (d, *J* = 22.2 Hz, 1H), 4.61−4.64 (m, 2H), 4.02−4.09 (m, 1H), 3.60−3.64 (m, 1H), 2.91−2.94 (m, 2H), 2.2 (s, 3H), 1.27−1.31 (m, 6H), 1.16 (d, *J* = 6.1 Hz), 0.97 (d, *J* = 6.1, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.6, 136.4 (d, *J* = 5.9 Hz), 130.8 (d, *J* = 1.5 Hz), 129.5, 128.7, 128.4 (d, *J* = 4.4 Hz), 127.8, 127.1 (d, *J* = 3.7), 125.5 (d, *J* = 3 Hz),

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115.6, 72.18 (d, J = 7.4), 70.74 (d, J = 8 Hz), 58.9 (d, J = 160 Hz), 43.8, 26.1, 24.58 (d, J = 3 Hz), 24.12 (d, J = 3 Hz), 23.77 (d, J = 5.9 Hz), 23.34 (d, J = 5.9 Hz), 20.3; ^{31}P NMR (162 MHz, $CDCl_3$): δ 20.9; HRESI-MS (m/z): calcd for $C_{22}H_{30}NO_3P$ (M + Na): 410.1861, found (M + Na): 410.1861.

*Dimethyl(2-(4-fluorophenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)phosphonate (**3k**).* Viscous liquid; yield, 44%; Rf (50% EtOAc/hexane) 0.2; prepared as shown in general experimental procedure. IR (neat, cm^{-1}): 3450, 2900, 1510, 1290, 1190, 1140; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34−7.36 (m, 1H), 7.15−7.22 (m, 3H), 6.88−6.97 (m, 4H), 5.06 (d, J = 20.2 Hz, 1H), 3.99−4.03 (m, 1H), 3.64 (d, J = 10.4 Hz, 6H), 3.51−3.57 (m, 1H), 2.95−2.97 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.4 (d, J = 238 Hz), 146 (dd, J = 2.2, 2.2 Hz), 136.2 (d, J = 5.8 Hz), 130.1, 128.9 (d, J = 2.3 Hz), 127.95 (d, J = 4.8 Hz), 127.57 (d, J = 3.7 Hz), 126.1 (d, J = 2.9 Hz), 116.68 (d, J = 7.3 Hz), 115.5 (d, J = 22 Hz), 59.2 (d, J = 160 Hz), 53.85 (d, J = 6.7 Hz), 52.9 (d, J = 7.3 Hz), 44.4, 26.4; ^{31}P NMR (162 MHz, $CDCl_3$): δ 24.2; HRESI-MS (m/z): calcd for $C_{17}H_{19}FNO_3P$ (M + Na): 358.0984, found (M + Na): 358.0982.

*Diethyl(2-(4-fluorophenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)phosphonate (**3l**).*[16e] Pale yellow oil; yield, 30%; Rf (50% EtOAc/hexane) 0.4; prepared as shown in general experimental procedure. IR (neat, cm^{-1}): 3422, 2920, 1510, 1238, 1160; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36−7.38 (m, 1H), 7.16−7.21 (m, 3H), 6.90−6.93 (m, 4H), 5.05 (d, J = 20.3 Hz, 1H), 3.9−4.11 (m, 5H), 3.50−3.56 (m, 1H), 2.9−3.0 (m, 2H), 1.23 (t, J = 7.1 Hz, 3H), 1.14 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.4 (d, J = 238.0 Hz), 146.1 (dd, J = 1.9, 6.6 Hz), 136.3 (d, J = 5.6 Hz), 130.3, 128.7 (d, J = 2.5 Hz), 128.1 (d, J = 4.5 Hz), 127.4 (d, J = 3.4 Hz), 125.9 (d, J = 2.9 Hz), 116.5 (d, J = 7.4 Hz), 115.4 (d, J =22.1 Hz), 63.2 (d, J = 7.2 Hz), 62.3 (d, J = 7.6 Hz), 59.3 (d, J = 159.0 Hz), 44.2, 26.5, 16.4 (d, J = 5.6 Hz), 16.3 (d, J = 5.9 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ 22.04; HRESI-MS (m/z): calcd for $C_{19}H_{23}FNO_3P$ (M + Na): 386.1297, found (M + Na): 386.1298.

*Diisopropyl(2-(4-fluorophenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)phosphonate (**3m**).* Pale yellow oil; yield, 28%; Rf (50% EtOAc/hexane) 0.3; prepared as shown in general experimental procedure. IR (neat, cm^{-1}): 3403, 2977, 1510, 1106, 890; ^{1}H NMR (400 MHz, $CDCl_3$): 7.39−740 (m, 1H), 7.1−7.2 (m, 3H), 6.8−6.9 (m, 4H), 4.99 (d, J = 21.4 Hz, 1H), 4.58−4.64 (m, 2H), 4−4.07 (m, 1H), 3.53−3.57 (m, 1H), 2.92−2.98 (m, 2H), 1.2−1.3 (m, 6H), 1.15 (d, J = 6.2 Hz, 3H), 0.95 (d, J = 6.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 156.2 (d, J = 237 Hz), 146.3 (dd, J = 2.2, 2.2 Hz), 136.2 (d, J = 5.6 Hz), 130.6, 128.7 (d, J = 2.4 Hz), 128.4 (d, J = 4.5 Hz), 127.3 (d, J = 3.7 Hz), 125.6 (d, J = 2.6 Hz), 116.74 (d, J = 7.3 Hz), 115.3 (d, J = 22 Hz), 72.17 (d, J = 7.9 Hz), 70.85 (d, J = 8.3 Hz), 59.3 (d, J = 160 Hz), 44.3, 26.3, 24.5 (d, J = 2.9 Hz), 24.1 (d, J = 3.6 Hz), 23.7 (d, J = 5.8 Hz), 23.3 (d, J = 5.8 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): 20.65; HRESI-MS (m/z): calcd for $C_{21}H_{27}FNO_3P$ (M + Na): 414.1610, found (M + Na): 414.1612.

*Diethyl(6,7-dimethoxy-2-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)phosphonate (**3n**).*[17d] Pale yellow liquid; yield, 50%; Rf (50% EtOAc/hexane) 0.5; prepared as shown in general experimental procedure. IR (neat, cm^{-1}): 3414, 1597, 1518, 1384, 1271, 1253, 1110, 1025, 963, 862, 749; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26−7.24 (2H, m), 6.98−6.93 (3H, m), 6.80−6.77 (1H, m), 6.62 (1H, s), 5.09 (1H, d, J = 20.1 Hz), 4.12−3.99 (4H, m), 3.86 (3H, s), 3.84 (3H, s), 3.68−3.64 (2H, m), 2.92−2.87 (2H, m), 1.27 (3H, t, J = 7.0 Hz), 1.15 (3H, t, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.4 (d, J = 7.1 Hz), 148.3 (d, J = 3.3 Hz), 147.0 (d, J = 2.8 Hz), 129.1, 128.5 (d, J = 6.4 Hz), 121.9, 118.6, 115.2, 111.5 (d, J = 2.5 Hz), 111.0 (d, J = 3.7 Hz), 63.4 (d, J = 7.2 Hz), 62.0 (d, J = 7.6 Hz), 59.1, 57.5, 55.8 (d, J = 10.2 Hz), 43.4, 25.9, 16.4, 16.4 (d, J = 8.6 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ 22.2; HRESI-MS (m/z): calcd for $C_{21}H_{28}NO_5P$ (M + K): 444.1342, found (M + K): 444.1339.

*Diisopropyl(6,7-dimethoxy-2-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)phosphonate (**3o**).*[17d] Pale yellow liquid; yield, 57%; Rf (50% EtOAc/hexane) 0.5; prepared as shown in general experimental procedure. IR (neat, cm^{-1}): 3393, 2927, 1726, 1256, 1113, 1031, 981, 742; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26−7.20 (2H, m), 6.97−6.93 (3H, m), 6.77 (1H, t, J = 7.2 Hz), 6.60 (1H, s), 5.04 (1H, d, J = 21.4 Hz), 4.71−4.60 (2H, m), 4.09−4.02 (1H, m), 3.87 (3H, s), 3.84 (3H, s), 3.71−3.63 (1H, m), 2.93−2.77 (2H, m), 1.30 (6H, dd, $J1$ = 6.1 Hz, $J2$ = 10.1 Hz) 1.21 (3H, d, J = 6.1 Hz), 0.97 (3H, d, J = 6.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.7 (d, J = 7.9 Hz), 148.1, 146.8, 128.9, 128.5 (d, J = 6.3 Hz), 122.2, 118.5, 115.5, 111.4 (d, J = 14.8 Hz), 72.3 (d, J = 7.7 Hz), 70.5 (d, J = 7.9 Hz), 58.3 (d, J = 161.1 Hz), 55.8 (d, J = 8.3 Hz), 43.4, 25.6, 24.6 (d, J = 2.4 Hz), 24.1 (d, J = 3.4 Hz), 24.0, 23.3 (d, J = 5.6 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ 21.0; HRESI-MS (m/z): calcd for $C_{23}H_{32}NO_5P$ (M + Na): 456.1916, found (M + Na): 456.1917.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsomega.7b00881.

Optimization data; ^{1}H and ^{13}C NMR spectral data of all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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