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Efficient Synthesis of Phosphonamidates via One-Pot Sequential Reactions of Phosphonites with Iodine and Amines

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Dedication ((optional))

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Abstract: An one-pot sequential strategy to construct phosphonamidates has been developed by generating phosphonites *in situ* from aryl magnesium bromides and triethyl phosphite followed by treatment with iodine and amines. A variety of phosphonamidates were obtained with good to excellent yields at room temperature from easily available materials.

Introduction

Phosphonamidates, as prodrugs and transition-state analogues of amide bond hydrolysis, have attracted significant attention in medicinal chemistry. They show a wide range of biological activities, such as antiviral,[1] anticancer,[2] enzyme inhibition,[3] and immune stimulant of T cell[4] (Figure 1). In particular, Tenofovir alafenamide (TAF), a phosphonoamidate prodrug of Tenofovir, has been approved by FDA to treat human immunodefificiency virus (HIV)[5] in 2015 and hepatitis B virus (HBV)[6] in 2016. Moreover, some phosphonamidates have exhibited excellent retardant efficacy and high thermal stability which makes them have good application prospects as flame retardant additives in polymer industry.[7]

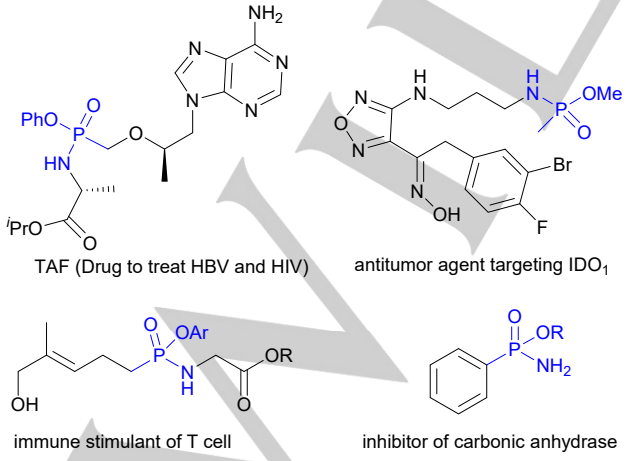
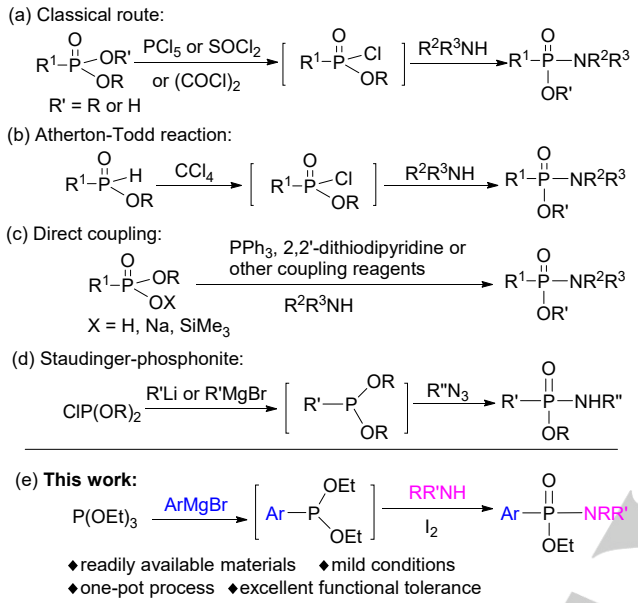


Figure 1. Examples of biologically active phosphonamidates

Several strategies have been developed for the synthesis of phosphonamidates, including (1) the classic aminolysis of phosphonochloridates from pre-generated phosphonic acid diesters or monoesters with chlorinating reagents[1b-c,2a-b,3,7a,8] (Scheme 1a); (2) Atherton-Todd reaction between amines and H-phosphinates in the presence of CCl_4 or Cl_2[7b-c,9] (Scheme 1b); (3) direct coupling of amines and phosphonic acids or salts in the presence of PPh_3 and 2,2'-dithiodipyridine or other coupling reagents[1d-h,4,10] (Scheme 1c); (4) Staudinger-phosphonite reaction of phosphonites and organic azides[11] (Scheme 1d). These methods have their own advantages as well as some major disadvantages. For example, the classic phosphonochloridate strategy is generally efficient and reliable, but it involves lengthy steps, tedious workup and is incompatible with some sensitive functional groups. The direct coupling method avoids the use of chlorinating reagents and has been successfully applied to the synthesis of phosphonamidate peptides, but some special and expensive coupling reagents and additives are needed and the yields are usually poor. Atherton-Todd reaction and Staudinger-phosphonite reaction are simple and efficient, while they both require hazardous reagents, such as CCl_4 or azides, and the starting materials are relatively expensive and not easily available. In 2018, Moduni and coworkers developed a novel approach to construct phosphonamidates from the phosphonic acid diesters and lithium amides,[12] but it needs to use expensive and moisture-sensitive triflic anhydride and the amines must be deprotonated in advance. Very recently, Tan and coworkers reported a ZnI_2-triggered oxidative cross-coupling reaction of P(O)–H compounds and amines and synthesized a series of phosphinic amides and phosphoramidates as well as two phosphonamidates.[13] The biggest obstacle to using this method for the synthesis of phosphonamidates is that the required H-phosphinates are not easily available and very limited. Therefore, it is still highly desirable to develop more practical, general, simple, green and efficient methods to prepare phosphonamidates.

The combination of phosphites and iodine is an established phosphorylation method, which has been successfully applied to synthesize phosphoramidates and mixed phospates.[14] Our group has extensively reinvestigated this kind of iodine-mediated phosphoramidation reaction[15] and found it is a very powerful and convenient way to access phosphoriamidates. We reasoned

that if we use phosphonites instead of phosphites in this reaction, phosphonoamidates with one C-P bond would be produced. However, to our surprise, such methodology has never been used to synthesize phosphonamidates thus far. Herein, we present a practical and efficient approach to synthesize phosphonamidates by an one-pot sequential procedure from triethyl phosphite, aryl magnesium bromides, amines and iodine (Scheme 1e). This strategy starts from cheap and easily available materials, needs no intermediate isolation and proceeds under mild conditions.



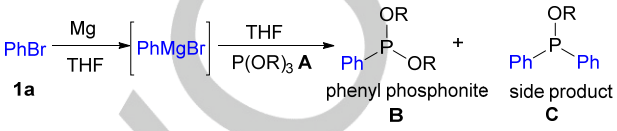
Scheme 1. Synthetic routes toward phosphonamidates

Results and Discussion

First of all, a high efficient method to generate phosphonites is required. Nucleophilic substitution of chlorophosphite, bis(dialkylamino)chlorophosphine or triethyl phosphite with organolithium reagents or Grignard reagents has been employed to prepare phosphonites.[11,16] Since trialkyl phosphite is readily available, cheap and stable, we decided to choose it as phosphorus source. In 2011, Volle et al.[16] optimized the reaction of triethyl phosphite and Grignard reagent to prepare phosphonites. However, when using their optimal conditions ($ArMgBr/P(OR)_3$ = 1.5/1, 0.2 M in THF, 70 °C, 5 h), we observed a considerable amount of byproduct diphenylphosphinite **C** except for the desired product **B** (entry 1, Table 1). Further studies showed that compounds **A**, **B** and **C** in the reaction mixture could all react with iodine and amines, which made it very difficult to purify the final product phophonamidates. A series of examinations were herein conducted to optimize the reaction. ^{31}P NMR spectroscopy and TLC were used to monitor the reaction process and some typical results were summarized in Table 1.

As shown in Table 1, when decreasing the temperature to room temperature (about 25 °C), the desired reaction could take place smoothly though at slower rate and the side reaction could be largely suppressed (entries 1–3, Table 1). For the reaction of $P(OMe)_3$ at room temperature, prolonging the reaction time and increasing the ratio of $PhMgBr/P(OMe)_3$ could improve the yield of the desired product **B**, but the side product **C** would also be gradually increased at the same time (entries 4–7). In contrast, the disubstituted side reaction was not a problem for the corresponding reaction of $P(OEt)_3$ and the yield of the desired phosphonite **B** could reach to 98% (entries 8–12, Table 1). Based on these results, we chose $P(OEt)_3$ as phosphorus source and used the optimized conditions ($ArMgBr/P(OEt)_3$ = 2.0/1, 0.2 M in THF, 25 °C, 36 h) for subsequent reactions.

Table 1 Optimization for the formation of phenyl phosphonite[a]



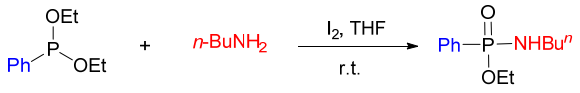
Entry	R	Ratio[b]	Temp.(°C)	Time (h)	**A**:**B**:**C**[c]
1	Me	1.5:1	70	5	5:80:15
2	Me	1.5:1	50	5	39:58:3
3	Me	1.5:1	25	5	44:55:1
4	Me	1.5:1	25	10	23:75:2
5	Me	1.6:1	25	10	18:78:4
6	Me	1.6:1	25	32	10:84:6
7	Me	2.0:1	25	10	15:80:5
8	Et	2.0:1	25	10	15:83:2
9	Et	2.0:1	25	24	7:91:2
10	Et	2.0:1	25	36	0:98:2
11	Et	1.8:1	25	24	19:79:2
12	Et	1.5:1	25	24	21:77:2

[a] Reaction conditions: $P(OR)_3$ (2 mmol), PhMgBr in anhydrous THF, under N_2, final concentration with respect to $P(OR)_3$ was 0.2 mmol/mL. [b] Molar ratio of PhMgBr to $P(OR)_3$. [c] The ratio of **A**:**B**:**C** was determined by ^{31}P NMR on the crude product (**A**: δ_P ~ 138 ppm; **B**: δ_P ~ 155 ppm; **C**: δ_P ~ 110 ppm).

Next, we turned our attention to investigate the feasibility of the iodine-mediated phosphonamidation reaction of the phosphonites. The addition order of iodine and amine was found to be crucial for the success of this reaction. When adding iodine (1 equiv) and *n*-butyl amine **2a** (2 equiv) sequentially to the above phenyl phosphonite solution (1 equiv), no desired product **3a** was detected (entry 1, Table 2). We speculated this was probably because the residual Garignard reagent in the system could react with iodine, preventing the formation of iodophosphonate and making the subsequent reaction difficult to happen (see the proposed mechanism shown in Scheme 4). Gratifyingly, when the addition order was reversed, i.e. the amine **2a** was added to the phenyl phosphonite solution first, stirred for about 5 minutes and then added iodine, the reaction proceeded smoothly and the desired product **3a** (δ_P: 22 ppm) was obtained in excellent yield within one hour (entry 2, Table 2). This was likely the presence of amine prior to addition of iodine could destroy the residual Garignard reagent and the formation of iodophosphonate could be accomplished in this reaction environment. We then examined the effect of the amount of iodine and **2a** (entries 2–5, Table 2). The results demonstrated that one equivalent of iodine and two equivalents of **2a** were necessary and sufficient. When changing the molar ratio of phosphonite **B** to **2a** from 1:2 to 1:1, one equivalent of additional

base such as Et_3N was required to scavenge the formed hydroiodic acid (entries 2, 5, Table 2). Further studies revealed that the reaction completed within 0.5 hour and the extension of the reaction time to 2 hours gave the same results (entries 2, 6, 7, Table 2).

Table 2 Synthesis of phosphonamidate **3a**[a]



phosphonite **B** **2a** **3a**

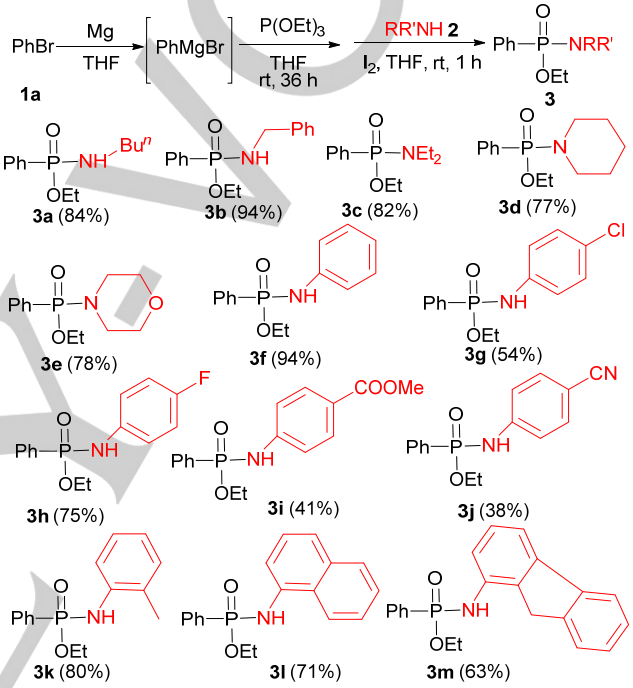
Entry	I_2 (equiv)	**2a** (equiv)	Et_3N (equiv)	Time (h)	Yield of **3a**[b]
1	1	2	0	1	0[c]
2	1	2	0	1	90
3	1.2	2	0	1	90
4	0.8	2	0	1	79
5	1	1	1	1	90
6	1	2	0	2	90
7	1	2	0	0.5	90

[a] Reaction conditions unless otherwise specified: phoshonite **B** (1.0 mmol) and **2a** in THF (2.5 mL), was added I_2 in THF (1 mL), and stirred under N_2 at rt. [b] Determined by ^{31}P NMR on the reaction mixture. [c] To the solution of phoshonite **B** was added I_2 first and then **2a**.

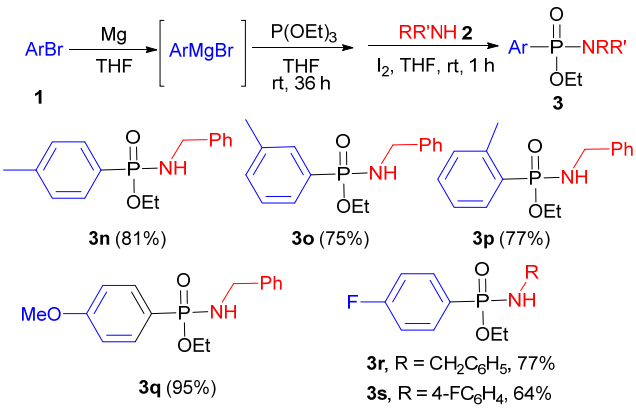
With these conditions in hand, we subsequently explored the scope and limitations of this sequential procedure with different amines and the results were summarized in Scheme 2. The reaction exhibited excellent generality and functional tolerance. The *in situ* formed phenyl phosphonite could react with various amines at room temperature, leading to a series of phosphonamidates in good to excellent yields. Both aliphatic primary amines (i.e. *n*-butylamine, benzyl amine) and secondary amines (i.e. piperidine, morpholine, diethylamine) worked well to give **3a**–**3e** in 77%–84% yields. All examined aromatic amines proceeded the reaction smoothly, while the yields of the desired products were affected by the electron nature of the substituents. For example, aniline could react with phenyl phosphonite rapidly and cleanly to afford **3f** in 94 % yield. When there is an electron-withdrawing group such as chloride and fluoride in the *para* position of aniline, the yields of the products **3g** and **3h** decreased to 75 % and 54 %, respectively. The amines bearing a 4-cyano and 4-ester group could be successfully converted into **3i** and **3j** though in relatively lower yields. The presence of a hindered methyl group in the *ortho* position of aniline had no apparent negative effect on the reaction and the target product **3k** could be obtained in 80% yield. Moreover, fused ring aromatic amines performed well, giving products **3l** and **3m** in good yields.

This method can be conveniently extended to other aryl bromides, leading to **3n**–**3s** in good to excellent yields (Scheme 3). Under the standard conditions, the aryl phosphonites from *ortho*-, *meta*-, and *para*-methyl-substituted aryl magnesium bromides and triethyl phosphite could all transformed to the target products **3n**–**3p** in good yields, indicating the reaction is not sensitive to steric hindrance. However, the electronic effect of the substituents has some impacts on the reaction. The reaction of aryl phosphonite bearing an electron-donating methoxy group produced the desired product **3q** in 95% yield, while the aryl phosphonites with one or two electron-withdrawing fluoro substituents gave the corresponding products **3r** and **3s** in only 77 % and 64 % yields.

We also made some preliminary attempts to synthesize alkyl phosphonamidates using this method. Unfortunately, under the same conditions, the reactions of ethylmagnesium bromide and ethynylmagnesium bromide with triethyl phosphite, iodine and aniline resulted in complex systems and did not lead to the desired phosphonamidates. We speculated that such results might be related to the fact that alkyl phosphonites oxidize rapidly compared to aryl phosphonites.[11f] Therefore, in order to synthesize alkyl phosphonamidates by the present strategy, the reaction conditions need to be further adjusted and explored.

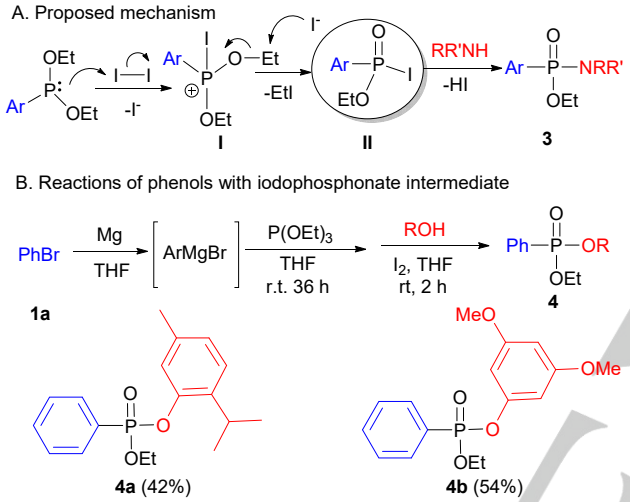


Scheme 2. Substrate scope of amines. Conditions: **1a** (4.0 mmol), Mg (4.0 mmol), $P(OEt)_3$ (2.0 mmol) in THF (10 mL) was added **2** (4.0 mmol), I_2 (2.0 mmol) in THF (2 mL). Isolated yields are given in parentheses.



Scheme 3. Substrate scope of aryl bromides. Conditions: **1** (4.0 mmol), Mg (4.0 mmol), $P(OEt)_3$ (2.0 mmol) in THF (10 mL) was added 2 (4.0 mmol), I_2 (2.0 mmol) in THF (2 mL). Isolated yields are given in parentheses.

Based on the above results and the literatures about the formation of iodophosphate from Arbuzov reaction of trialkyl phosphite with iodine,[14] a plausible mechanism was proposed in Scheme 4A. The reaction of iodine with arylphosphonite would produce intermediate **I**, which could be attacked by iodide to form iodophosphonate **II** (Arbuzov reaction). Nucleophilic attack of iodophosphonte **II** by amines, with the elimination of HI, would lead to phosphonamidates **3**. To justify this mechanism, we attempted to use oxygen nucleophiles rather than amines to catch the key intermediate **II**. When the phenyl phosphonite solution (1 equiv) was treated with substituted phenols (2 equiv), triethyl amine (1 equiv) and iodine (1 equiv), two mixed phosphonates **4a** and **4b** were obtained albeit in lower yields (Scheme 4B), indicating that the present strategy involves an iodophosphonate intermediate and has the potential to access various phosphonyl compounds.



Scheme 4. (A) Proposed mechanism. (B) Reactions of oxygen nucleophiles with iodophosphonate intermediate.

Conclusions

In conclusion, we developed a simple and efficient method for the synthesis of phosphonamidates via an one-pot sequential procedure from readily available materials. Compared with existing literature methods to phosphonamidates, the present approach demonstrates several attractive features, including cheap and easily available materials, mild conditions, high efficiency, excellent functional tolerance and simple operation. As the involving iodophosphonate intermediate has the potential to react with various nucleophiles, this method will have wide applications in the synthesis of not only phosphonamidates but also other phosphonyl compounds.

Experimental Section

General: The ^{1}H, ^{13}C, ^{31}P and ^{19}F NMR spectra were recorded on a Varian INOVA 400 NMR instrument. All melting points were measured on a WRS-3 Melting Point Meter and were uncorrected. HRMS were determined using an Agilent Technologies 6230 TOF LC/MS mass spectrometer. IR spectra were recorded using KBr pellets on a Bruker Equinox 55 FT/IR spectrometer. Column chromatography was performed on 200–300 mesh silica gel. Thin-layer chromatography was conducted on a Kieselgel 60 F254. Compounds **3a**, **3c**, **3e** and **3f** are known compounds; their identities are confirmed by ^{1}H/ ^{13}C/ ^{31}P NMR spectra which are consistent with the related literature.[17-19] Other products are new compounds; their structures are identified by their ^{1}H, ^{13}C, ^{31}P and ^{19}F NMR, HRMS and IR data.

General procedure for the synthesis of 3: A solution of aryl bromide (20 mmol) in THF (10 mL) was added dropwise to a suspension of Mg turnings (20 mmol) in THF (10 mL) under nitrogen atmosphere. The reaction mixture was stirred vigorously at reflux temperature at first until the color of the mixture became gray-black, and then cooled to room temperature with addition of the remaining aryl bromide slowly. The aryl magnesium bromide solution in THF was herein obtained when the Mg turnings disappeared and stored under nitrogen for further use. To a solution of $P(OEt)_3$ (2 mmol) in THF (6 mL) was added dropwise the above aryl magnesium bromide solution (4 mL, about 4 mmol) at room temperature over 5 to 10 min. The reaction mixture was stirred at room temperature for 36 h and then was added the solutions of amine (2 mmol) in THF (8 mL) and iodine (2 mmol) in THF (2 mL) successively. After stirring at room temperature under nitrogen atmosphere for 60 min, the reaction mixture was then evaporated in vacuo and the residue was dissolved in CH_2Cl_2 (50 mL), washed with saturated with saturated NH_4Cl, brine, and then dried over anhydrous $NaSO_4$. After removal of the solvent in vacuo, the residue was purified by column chromatography on silica gel with petroleum ether /EtOAc (10:1–1:1) as eluent to give the corresponding product **3**.

Ethyl N-butyl-P-phenylphosphonamidate (3a)[17]
Compound **3a** was isolated (405 mg, 84% yield) as pale-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (dd, J = 12.7, 7.4 Hz, 2H), 7.55–7.44 (m, 3H), 4.20–4.06 (m, 2H), 2.91–2.85 (m, 2H), 2.68 (br s, 1H), 1.51–1.41 (m, 2H), 1.37 (t, J = 7.0 Hz, 3H), 1.34–1.27 (m, 2H), 0.88 (t, J = 7.3 Hz, 3H); ^{31}P NMR (162 MHz, $CDCl_3$) δ 22.67; ^{13}C NMR (101 MHz, $CDCl_3$) δ 131.71 (d, J = 2.9 Hz), 131.40 (d, J = 9.7 Hz), 131.06 (d, J = 173.1 Hz), 128.37 (d, J = 14.2 Hz), 60.49 (d, J = 5.6 Hz), 40.61, 33.88 (d, J = 6.2 Hz), 19.75, 16.43 (d, J = 6.7 Hz), 13.67.

Ethyl N-benzyl-P-phenylphosphonamidate (3b)
Compound **3b** was isolated (518 mg, 94% yield) as pale-yellow oil. IR (KBr) 3210, 2981, 2929, 2902, 1439, 1204, 1130, 1039, 955 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89–7.78 (m, 2H), 7.56–7.51 (m, 1H), 7.49–7.44 (m, 2H), 7.33–7.24 (m, 5H), 4.16–4.04 (m, 4H), 3.20 (br s, 1H), 1.34 (td, J = 7.0, 2.8 Hz, 3H); ^{31}P NMR (162 MHz, $CDCl_3$) δ 22.32; ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.61 (d, J = 6.5 Hz), 131.86 (d, J = 2.8 Hz), 131.48 (d, J = 9.7 Hz), 130.79 (d, J = 172.8 Hz), 128.53 (d, J = 2.4 Hz), 128.37, 127.38, 127.30, 60.77 (d, J = 5.6 Hz), 44.88, 16.39 (d, J = 6.8 Hz). HRMS (ESI) m/z calculated for $C_{15}H_{18}NO_2P$ $[M+H]^+$: 276.1153, found: 276.1152.

Ethyl N,N-diethyl-P-phenylphosphonamidate(3c)[17]
Compound **3c** was isolated (396 mg, 82% yield) as pale-yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78–7.72 (m 2H), 7.54–7.35 (m, 3H), 4.22–4.11 (m, 1H), 4.1–3.99 (m, 1H), 3.30–2.81 (m, 4H), 1.38 (t, J = 7.1 Hz, 3H), 1.07 (t, J = 7.1 Hz, 6H); ^{31}P NMR (162 MHz, $CDCl_3$) δ 23.03; ^{13}C NMR (101 MHz, $CDCl_3$) δ 131.80 (d, J = 175.7 Hz), 131.31, 131.22, 128.25 (d, J = 14.1 Hz), 59.91 (d, J = 5.8 Hz), 38.86 (d, J = 4.9 Hz), 16.37 (d, J = 6.9 Hz), 14.16.

Ethyl phenyl(piperidin-1-yl)phosphinate (3d)
Compound **3d** was isolated (390 mg, 77% yield) as pale-yellow oil. IR (KBr) 3408, 2977, 2738, 2537, 2437, 1632, 1441, 1196, 1136, 1045, 946 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79–7.69 (m, 2H), 7.53–7.41 (m, 3H), 4.24–4.05 (m, 2H), 3.11–3.05 (m, 4H), 1.59–1.54 (m, 2H), 1.51–1.48 (m, 4H).1.39 (t, J = 7.1 Hz, 3H); ^{31}P NMR (162 MHz, $CDCl_3$) δ 21.69; ^{13}C NMR (101 MHz, $CDCl_3$) δ 131.41 (d, J = 2.8 Hz), 131.18 (d, J = 9.5 Hz), 130.50 (d, J = 174.5 Hz), 128.29 (d, J = 14.1 Hz), 60.15 (d, J = 6.0 Hz), 44.92 (d, J = 2.5 Hz), 26.03 (d, J = 4.7 Hz), 24.56, 16.41 (d, J = 6.7 Hz);

HRMS (ESI) m/z calculated for $C_{13}H_{20}NO_2P$ $[M+H]^+$: 254.1310, found: 254.1313.

Ethyl morpholino(phenyl)phosphinate (3e)[18]

Compound **3e** was isolated (398 mg, 78% yield) as pale-yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.76 (dd, J = 12.7, 7.3 Hz, 2H), 7.58–7.45 (m, 3H), 4.35–4.03 (m, 2H), 3.69–3.62 (m, 4H), 3.15–3.11 (m, 4H), 1.42 (t, J = 7.1 Hz, 3H); ^{31}P NMR (162 MHz, $CDCl_3$) δ 21.09; ^{13}C NMR (101 MHz, $CDCl_3$) δ 132.10 (d, J = 9.8 Hz), 131.83 (d, J = 2.9 Hz), 131.28 (d, J = 9.4 Hz), 129.99 (d, J = 173.3 Hz), 128.50 (d, J = 14.1 Hz), 67.06 (d, J = 5.8 Hz), 60.63 (d, J = 5.9 Hz), 44.15, 16.44 (d, J = 6.6 Hz).

Ethyl N,P-diphenylphosphonamidate(3f)[19]

Compound **3f** was isolated (491 mg, 94% yield) as white solid. Mp: 124–125 °C (lit. [3] 119−120 °C). ^1H NMR (400 MHz, $CDCl_3$) δ 7.88 (dd, J = 13.5, 8.0 Hz, 2H), 7.57–7.41 (m, 3H), 7.16 (t, J = 7.7 Hz, 2H), 6.95–6.87 (m, 3H), 6.50 (br s, 1H), 4.40–4.13 (m, 2H), 1.40 (t, J = 7.1 Hz, 3H); ^{31}P NMR (162 MHz, $CDCl_3$) δ 17.27; ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.20, 132.17 (d, J = 3.0 Hz), 131.53 (d, J = 104.7 Hz), 131.41 (d, J = 10.3 Hz), 129.22, 128.55 (d, J = 14.8 Hz), 121.39, 117.48 (d, J = 6.5 Hz), 60.99 (d, J = 6.2 Hz), 16.29 (d, J = 6.8 Hz).

Ethyl N-(4-chlorophenyl)-P-phenylphosphonamidate(3g)

Compound **3g** was isolated (319 mg, 54% yield) as pale-yellow oil. IR (KBr) 3150, 3057, 2946, 2867, 1598, 1495, 1438, 1218, 1130, 1025, 750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.90–7.81 (m, 2H), 7.56–7.42 (m, 3H), 7.13–7.09 (m, 2H), 6.90–6.86 (m, 2H), 6.70 (br s, 1H), 4.35–4.13 (m, 2H), 1.40 (t, J = 7.1 Hz, 3H); ^{31}P NMR (162 MHz, $CDCl_3$) δ 17.12; ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.91, 132.37 (d, J = 2.9 Hz), 131.36 (d, J = 10.3 Hz), 129.92 (d, J = 139.9 Hz), 129.17, 128.64 (d, J = 14.9 Hz), 126.47, 118.72 (d, J = 6.6 Hz), 61.13 (d, J = 6.1 Hz), 16.29 (d, J = 6.8 Hz); HRMS (ESI) m/z calculated for $C_{14}H_{15}ClNO_2P$ $[M+H]^+$: 296.0607, found: 296.0614.

Ethyl N-(4-fluorophenyl)-P-phenylphosphonamidate (3h)

Compound **3h** was isolated (419 mg, 75% yield) as white solid. Mp: 123–124 °C. IR (KBr) 3165, 3090, 2962, 2873, 1511, 1211, 1131, 1030 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.87–7.81(m, 2H), 7.56–7.51 (m, 1H), 7.47–7.42 (m, 2H), 6.92–6.82 (m, 4H), 6.21 (d, J = 5.7 Hz, 1H), 4.36–4.14 (m, 2H), 1.40 (t, J = 7.1 Hz, 3H); ^{31}P NMR (162 MHz, $CDCl_3$) δ 17.47. ^{19}F NMR (376 MHz, $CDCl_3$) δ -122.42; ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.23, 136.09, 132.29 (d, J = 3.0 Hz), 131.41 (d, J = 10.2 Hz), 129.91 (d, J = 177.2 Hz). 128.60 (d, J = 14.7 Hz), 119.08, 115.83 (d, J = 22.6 Hz), 61.10 (d, J = 5.9 Hz), 16.29 (d, J = 6.7 Hz); HRMS (ESI) m/z calculated for $C_{14}H_{15}FNO_2P$ $[M+H]^+$: 280.0903, found: 280.0907.

Methyl 4-((ethoxy(phenyl)phosphoryl)amino)benzoate (3i)

Compound **3i** was isolated (262 mg, 41% yield) as pale-yellow oil. IR (KBr) 3151, 3055, 2955, 2881, 1712, 1609, 1516, 1258, 1032 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.90–7.83 (m, 4H), 7.54–7.42 (m, 3H), 7.08 (d, J = 5.9 Hz, 1H), 6.97 (d, J = 8.8 Hz, 2H), 4.41–4.14 (m, 2H), 3.85 (s, 3H), 1.41 (t, J = 7.1 Hz, 3H); ^{31}P NMR (162 MHz, $CDCl_3$) δ 17.02; ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.78, 144.87, 132.52 (d, J = 3.0 Hz), 131.33 (d, J = 10.4 Hz), 131.16, 129.47 (d, J = 179.6 Hz), 128.71 (d, J = 14.9 Hz), 122.96, 116.66 (d, J = 6.8 Hz), 61.34 (d, J = 6.2 Hz), 51.83, 16.26 (d, J = 6.6 Hz); HRMS (ESI) m/z calculated for $C_{16}H_{18}NO_4P$ $[M+H]^+$: 320.1052, found: 320.1049.

Ethyl N-(4-cyanophenyl)-P-phenylphosphonamidate (3j)

Compound **3j** was isolated (218 mg, 38% yield) as pale-yellow oil. IR (KBr) 3132, 3034, 2935, 2870, 2218, 1725, 1608, 1513, 1294, 1037 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.85 (dd, J = 13.4, 7.6 Hz, 2H), 7.58 (t, J = 7.0 Hz, 1H), 7.53–7.40 (m, 5H), 7.01 (d, J = 7.2 Hz, 2H), 4.40–4.13 (m, 2H), 1.42 (t, J = 6.8 Hz, 3H); ^{31}P NMR (162 MHz, $CDCl_3$) δ 16.71; ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.81, 133.53, 132.79 (d, J = 2.4 Hz), 131.28 (d, J = 10.4 Hz), 129.12 (d, J = 179.4 Hz), 128.86 (d, J = 14.9 Hz), 119.17, 117.42 (d, J = 6.8 Hz), 104.22, 61.55 (d, J = 6.0 Hz), 16.27 (d, J = 6.4 Hz); HRMS (ESI) m/z calculated for $C_{15}H_{15}N_2O_2P$ $[M+H]^+$: 287.0949, found: 287.0952.

Ethyl P-phenyl-N-(o-tolyl)phosphonamidate (3k)

Compound **3k** was isolated (440 mg, 80% yield) as white solid. Mp: 143–145 °C. IR (KBr) 3154, 3080, 2984, 2897, 1583, 1501, 1217, 1131, 1026 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.87–7.81 (m, 2H), 7.55–7.41 (m, 3H), 7.11 (d, J = 7.5 Hz, 1H), 7.08–6.97 (m, 2H), 6.88–6.83 (m, 1H), 5.12 (s, 1H), 4.37–4.13 (m, 2H), 2.27 (s, 3H), 1.39 (t, J = 7.1 Hz, 3H); ^{31}P NMR (162 MHz, $CDCl_3$) δ 17.33; ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.06, 132.22 (d, J = 2.9 Hz), 131.41 (d, J = 10.2 Hz), 130.63, 130.09 (d, J = 176.7 Hz), 128.56 (d, J = 14.8 Hz), 126.98, 125.35 (d, J = 9.2 Hz), 121.82, 117.25, 61.11 (d, J = 5.9 Hz), 17.82, 16.29 (d, J = 6.8 Hz); HRMS (ESI) m/z calculated for $C_{15}H_{18}NO_2P$ $[M+H]^+$:276.1153, found: 276.1159.

Ethyl N-naphthalen-1-yl-P-phenylphosphonamidate(3l)

Compound **3l** was isolated (442 mg, 71% yield) as white solid. Mp: 138–139 °C. IR (KBr) 3151, 3056, 2980, 2929, 1576, 1518, 1469, 1210, 1131, 1037 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, J = 8.3 Hz, 1H), 7.93–7.81 (m, 3H), 7.58–7.47 (m, 4H), 7.46–7.39 (m, 2H), 7.29–7.20 (m, 2H), 5.87 (d, J = 5.1 Hz, 1H), 4.39–4.18 (m, 2H), 1.40 (t, J = 7.1 Hz, 3H); ^{31}P NMR (162 MHz, $CDCl_3$) δ 17.89; ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.85, 134.29, 132.29 (d, J = 3.0 Hz), 131.57, 131.47, 129.87 (d, J = 177.2 Hz), 128.83, 128.64, 128.50, 126.06 (d, J = 3.5 Hz), 125.84, 122.66, 120.12, 114.38 (d, J = 2.7 Hz), 61.32 (d, J = 5.9 Hz), 16.33 (d, J = 6.7 Hz); HRMS (ESI) m/z calculated for $C_{18}H_{18}NO_2P$ $[M+H]^+$: 312.1153, found: 312.1166.

Ethyl N-9H-fluoren-1-yl-P-phenylphosphonamidate(3m)

Compound **3m** was isolated (440 mg, 63% yield) as white solid. Mp: 191–193 °C. IR (KBr) 3145, 3096, 2985, 2897, 1620, 1585, 1487, 1457, 1207, 1127, 1024 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.95–7.86 (m, 2H), 7.65 (d, J = 7.6 Hz, 1H), 7.57 (d, J = 8.2 Hz, 1H), 7.53–7.43 (m, 4H), 7.35–7.17 (m, 3H), 6.96 (dd, J = 8.2, 2.0 Hz, 1H), 6.16 (d, J = 5.9 Hz, 1H), 4.39–4.19 (m, 2H), 3.79 (s, 2H), 1.42 (t, J = 7.1 Hz, 3H); ^{31}P NMR (162 MHz, $CDCl_3$) δ 17.33; ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.78, 142.60, 141.44, 139.07, 135.70, 132.24 (d, J = 3.0 Hz), 131.51, 131.41, 130.15 (d, J = 176.9 Hz), 128.59 (d, J = 14.8 Hz), 126.71, 125.83, 124.83, 120.47, 119.08, 116.47 (d, J = 6.4 Hz), 114.52 (d, J = 6.5 Hz), 61.16 (d, J = 6.1 Hz), 36.93, 16.34 (d, J = 6.8 Hz); HRMS (ESI) m/z calculated for $C_{21}H_{20}NO_2P$ $[M+H]^+$: 350.1310, found: 350.1319.

Ethyl N-benzyl-P-(p-tolyl)phosphonamidate (3n)

Compound **3n** was isolated (469 mg, 81% yield) as pale-yellow oil. IR (KBr) 3217, 3029, 2981, 2926, 1605, 1452, 1203, 1126, 1038, 958 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.74 (dd, J = 12.7, 8.0 Hz, 2H), 7.40–7.19 (m, 7H), 4.18–4.00 (m, 4H), 3.08–3.02 (m, 1H), 2.42 (s, 3H), 1.33 (t, J = 7.1 Hz, 3H); ^{31}P NMR (162 MHz, $CDCl_3$) δ 22.96; ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.37 (d, J = 2.9 Hz), 139.66 (d, J = 6.8 Hz), 131.58 (d, J = 10.2 Hz), 129.20 (d, J = 14.7 Hz), 128.54, 127.36 (d, J = 175.6 Hz), 127.34 (d, J = 8.5 Hz), 60.72 (d, J = 5.5 Hz), 44.87, 21.62, 16.39 (d, J = 6.7 Hz); HRMS (ESI) m/z calculated for $C_{16}H_{20}NO_2P$ $[M+H]^+$: 290.1310, found: 290.1304.

Ethyl N-benzyl-P-(m-tolyl)phosphonamidate (3o)

Compound **3o** was isolated (434 mg, 75% yield) as pale-yellow oil. IR (KBr) 3220, 2981, 2926, 1704, 1454, 1201, 1122, 1040, 958 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.70–7.58 (m, 2H), 7.41–7.23 (m, 7H), 4.18–4.03 (m, 4H), 3.12–3.06 (m, 1H), 2.40 (s, 3H), 1.34 (t, J = 7.1 Hz, 3H); ^{31}P NMR (162 MHz, $CDCl_3$) δ 23.03; ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.37 (d, J = 3.0 Hz), 139.67 (d, J = 6.9 Hz), 131.63, 131.53, 129.28, 129.13, 128.54, 127.38, 127.35(d, J=176.14 Hz), 127.29, 60.72 (d, J = 5.5 Hz), 44.87, 21.62, 16.39 (d, J = 6.8 Hz); HRMS (ESI) m/z calculated for $C_{16}H_{20}NO_2P$ $[M+H]^+$:290.1310, found: 290.1313.

Ethyl N-benzyl-P-(o-tolyl)phosphonamidate(3p)

Compound **3p** was isolated (446 mg, 77% yield) as pale-yellow oil. IR (KBr) 3229, 3029, 2979, 2929, 1597, 1453, 1204, 1141, 1034, 955 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.88 (dd, J = 13.8, 7.7 Hz, 1H), 7.43 (t, J =

7.5 Hz, 1H), 7.35–7.22 (m, 7H), 4.26–3.96 (m, 4H), 3.13–3.06 (m, 1H), 2.64 (s, 3H), 1.36 (t, *J* = 7.1 Hz, 3H); ^{31}P NMR (162 MHz, $CDCl_3$) *δ* 22.17; ^{13}C NMR (101 MHz, $CDCl_3$) *δ* 141.70 (d, *J* = 10.6 Hz), 139.67 (d, *J* = 6.6 Hz), 133.22 (d, *J* = 9.5 Hz), 131.96 (d, *J* = 2.6 Hz), 131.40 (d, *J* = 14.1 Hz), 128.97 (d, *J* = 170.7 Hz), 128.56, 127.44, 127.31, 125.37 (d, *J* = 13.9 Hz), 60.52 (d, *J* = 5.7 Hz), 44.92, 21.31 (d, *J* = 3.9 Hz), 16.36 (d, *J* = 6.7 Hz); HRMS (ESI) m/z calculated for $C_{16}H_{20}NO_2P$ $[M+H]^+$:290.1310, found: 290.1306.

Ethyl N-benzyl-P-(4-methoxyphenyl)phosphonamidate(3q)

Compound **3q** was isolated (580 mg, 95% yield) as white solid. Mp: 59–61 °C. IR (KBr) 3178, 2976, 2905, 2838, 1599, 1505, 1253, 1199, 1030 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.78 (dd, *J* = 12.4, 8.7 Hz, 2H), 7.35–7.25 (m, 5H), 7.01–6.94 (m, 2H), 4.19–4.01 (m, 4H), 3.87 (s, 1H), 3.02–2.95 (m, 1H), 1.33 (t, *J* = 7.1 Hz, 3H); ^{31}P NMR (162 MHz, $CDCl_3$) *δ* 23.09; ^{13}C NMR (101 MHz, $CDCl_3$) *δ* 162.49 (d, *J* = 3.3 Hz), 139.68 (d, *J* = 6.7 Hz), 133.53 (d, *J* = 11.1 Hz), 128.56, 127.34 (d, *J* = 7.7 Hz), 127.03, 121.90 (d, *J* = 179.7 Hz), 113.98 (d, *J* = 15.3 Hz), 60.71 (d, *J* = 5.5 Hz), 55.32, 44.87, 16.40 (d, *J* = 6.8 Hz); HRMS (ESI) m/z calculated for $C_{16}H_{20}NO_3P$ $[M+H]^+$: 306.1259, found: 306.1259.

Ethyl N-benzyl-P-(4-fluorophenyl)phosphonamidate (3r)

Compound **3r** was isolated (452 mg, 77% yield) as pale-yellow oil. IR (KBr) 3206, 2982, 2928, 2903, 1594, 1500, 1453, 1212, 1162, 1036, 957 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.88–7.77 (m, 2H), 7.38–7.21 (m, 5H), 7.17–7.10 (m, 2H), 4.19–3.99 (m, 4H), 3.32–3.25 (m, 1H), 1.33 (t, *J* = 7.0 Hz, 3H); ^{31}P NMR (162 MHz, $CDCl_3$) *δ* 21.36; ^{19}F NMR (376 MHz, $CDCl_3$) *δ* -107.02; ^{13}C NMR (101 MHz, $CDCl_3$) *δ* 166.25 (d, *J* = 3.7 Hz), 163.74 (d, *J* = 3.7 Hz), 139.44 (d, *J* = 6.4 Hz), 134.03 (dd, *J* = 11.1, 8.7 Hz), 128.57, 127.36 (d, *J* = 2.1 Hz), 126.92 (dd, *J* = 176.9, 3.4 Hz), 115.70 (dd, *J* = 20.7, 15.4 Hz), 60.83 (d, *J* = 5.6 Hz), 44.87, 16.37 (d, *J* = 6.7 Hz); HRMS (ESI) m/z calculated for $C_{15}H_{17}FNO_2P$ $[M+H]^+$: 294.1059, found: 294.1064.

Ethyl N,P-bis(4-fluorophenyl)phosphonamidate (3s)

Compound **3s** was isolated (380 mg, 64% yield) as white solid. Mp: 85–87 °C. IR (KBr) 3172, 2987, 2962, 2871, 1594, 1511, 1392, 1258, 1128, 1036 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.90–7.78 (m, 2H), 7.17–7.11 (m, 2H), 6.89–6.87 (m, 4H), 4.35–4.13 (m, 2H), 1.40 (t, *J* = 7.1 Hz, 3H); ^{31}P NMR (162 MHz, $CDCl_3$) *δ* 16.12; ^{19}F NMR (376 MHz, $CDCl_3$) *δ* -105.84, -121.83; ^{13}C NMR (101 MHz, $CDCl_3$) *δ* 166.47 (d, *J* = 3.9 Hz), 163.95 (d, *J* = 4.0 Hz), 159.33, 156.94, 134.02 (dd, *J* = 11.7, 8.9 Hz), 125.93 (dd, *J* = 181.2, 3.0 Hz), 119.13, 116.00 (dd, *J* = 22.0, 15.3 Hz), 61.23 (d, *J* = 5.9 Hz), 16.28 (d, *J* = 6.7 Hz); HRMS (ESI) m/z calculated for $C_{14}H_{14}F_2NO_2P$ $[M+H]^+$: 298.0808, found: 298.0811.

General procedure for the synthesis of 4: The procedure is similar to the synthesis of compounds **3** except that the starting material amine was replaced by the phenols. To a solution of the in situ prepared phenyl phosphonite (2 mmol) in THF (6 mL) was added the solutions of the corresponding substituted phenol (4 mmol) in THF (8 mL), triethyl amine (2 mmol) and iodine (2 mmol) in THF (2 mL) successively. After stirring at room temperature under nitrogen atmosphere for 2 hours, the reaction mixture was then evaporated in vacuo and the residue was dissolved in CH_2Cl_2 (50 mL), washed with saturated with saturated NH_4Cl, brine, and then dried over anhydrous $NaSO_4$. After removal of the solvent in vacuo, the residue was purified by column chromatography on silica gel with petroleum ether /EtOAc (10:1–1:1) as eluent to give the corresponding product **4**.

3,5-Dimethoxyphenyl ethyl phenylphosphonate (4a)

Compound **4a** was isolated (267 mg, 42% yield) as pale-yellow oil. IR (KBr) 3448, 2962, 2932, 2844, 1599, 1475, 1438, 1261, 1204, 1155, 1135, 1058, 1037 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.99–7.82 (m, 2H), 7.63–7.56 (m, 1H), 7.53–7.47 (m, 2H), 6.37–6.35 (m, 2H), 6.26–6.24 (m, 1H), 4.38–4.19 (m, 2H), 3.74 (s, 6H), 1.39 (t, *J* = 7.1 Hz, 3H); ^{31}P NMR (162 MHz, $CDCl_3$) *δ* 15.35; ^{13}C NMR (101 MHz, $CDCl_3$) *δ* 161.16, 152.09, 135.93 (d, *J* = 192.7 Hz), 132.79 (d, *J* = 3.0 Hz), 131.98 (d, *J* = 10.2 Hz), 128.53 (d, *J* = 15.5 Hz), 99.17 (d, *J* = 4.6 Hz), 97.32, 62.95 (d, *J* = 5.8 Hz), 55.44, 16.34 (d, *J* = 6.5 Hz); HRMS (ESI) m/z calculated for $C_{16}H_{19}O_5P$ $[M+H]^+$: 323.1048, found: 323.1052.

Ethyl (2-isopropyl-5-methylphenyl) phenylphosphonate (4b)

Compound **4b** was isolated (348 mg, 54% yield) as pale-yellow oil. IR (KBr) 3483, 2965, 2930, 2871, 1507, 1441, 1259, 1131, 1090, 1038, 967 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.97–7.84 (m, 2H), 7.60–7.45 (m, 3H), 7.19–7.11 (m, 2H), 6.93 (d, J = 7.8 Hz, 1H), 4.37–4.10 (m, 2H), 3.33–3.15 (m, 1H), 2.29 (s, 13H), 1.35 (t, *J* = 7.1 Hz, 3H), 1.19 (d, *J* = 6.9 Hz, 3H), 1.12 (d, *J* = 6.9 Hz, 3H); ^{31}P NMR (162 MHz, $CDCl_3$) *δ* 14.90; ^{13}C NMR (101 MHz, $CDCl_3$) *δ* 147.85 (d, *J* = 8.0 Hz), 136.57, 136.29 (d, *J* = 6.0 Hz), 132.64 (d, *J* = 2.9 Hz), 131.82 (d, *J* = 10.1 Hz), 128.58 (d, *J* = 13.4 Hz), 128.21 (d, *J* = 191.8 Hz), 126.38, 125.72, 120.84 (d, *J* = 2.5 Hz), 62.88 (d, *J* = 5.9 Hz), 26.55, 22.98 (d, *J* = 2.1 Hz), 20.91, 16.31 (d, J = 6.5 Hz); HRMS (ESI) m/z calculated for $C_{18}H_{23}O_3P$ $[M+H]^+$:319.1463, found: 319.1464.

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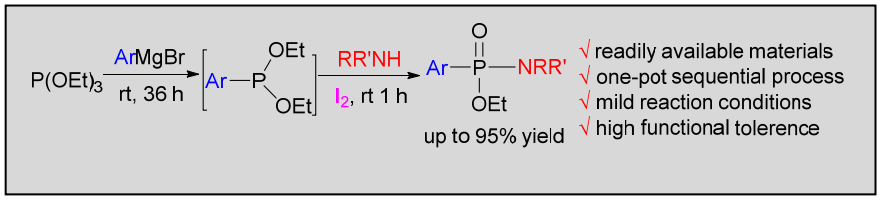

An iodine-mediated one-pot sequential phosphonoamidation of phosphonites with amines is developed. A variety of phosphonamidates were obtained from easily available starting materials with good to excellent yields under mild conditions.