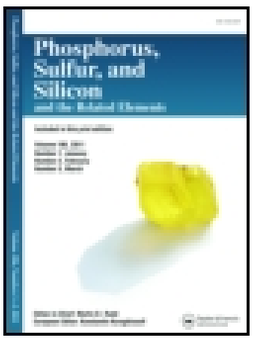

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Convenient Synthesis of α-Diarylmethylphosphonates by HOTf Catalyzed Friedel-Crafts Arylation of α-Aryl α-hydroxyphosphonates

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Convenient Synthesis of α-Diarylmethylphosphonates by HOTf Catalyzed Friedel-Crafts Arylation of α-Aryl α-hydroxyphosphonates

We report a convenient catalytic Friedel-Crafts arylation of α-aryl α-hydroxyphosphonates with various (hetero)aromatic compounds. HOTf (trifluoromethanesulfonic acid) is identified to be the best Brønsted acid catalyst, and the desired α-diarylmethylphosphonates were obtained in up to 41-95% yield.

Keywords: alcohols; Friedel-Crafts arylation; α-Diarylmethylphosphonates; homogeneous catalysis; α-hydroxyphosphonates

Introduction

Organophosphonates and their derivatives are one of the most important families of heteroatom-containing compounds, which not only have wide applications in the area of agricultural,[1] pharmaceutical[2] and material chemistry,[3] but also have been regarded as ligands[4] and reagents[5] in organic synthesis. Among them, α-diarylmethylphosphonates often show particularly interesting

properties in the field of drug chemistry[6] and chemiluminescence materials (Figure 1).[7] Besides, they are essential precursors for introducing diarylethene moiety through the Horner-Wadsworth-Emmons (HWE) reaction.

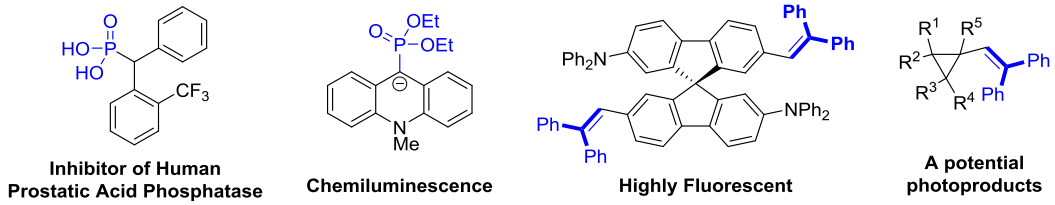
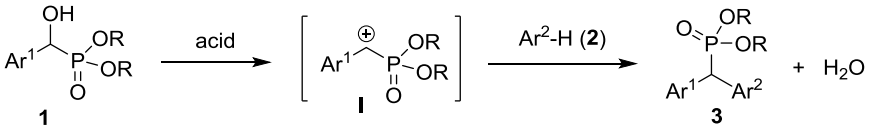


Figure 1. Important interesting molecules obtained from α-diarylmethylphosphonates

Despite the ubiquitous application of α-diarylmethylphosphonates, synthetic methods for their preparation are limited. Classical methods involve Michaelis-Arbuzov or Michaelis-Becker reactions,[8] which often suffer from harsh reaction conditions and the unavailability of the starting materials. As an alternative, the Walsh group developed an attractive method for accessing these compounds via Pd-catalyzed α-arylation of benzylic phosphonates.[9] And recently, Anand and co-workers[10a] reported a NHC catalyzed 1,6-hydrophosphonylation of *p*-quinone methides for their synthesis.[10] In spite of these achievements, it is necessary to develop other alternative and cost-effective process to construct these compounds.

The Friedel-Crafts reaction[11] of α-aryl α-hydroxyphosphonates and aromatic compounds, possibly via a carbocationic intermediate (Scheme 1),[12] would be an atom-economical procedure[13] for the synthesis of α-diarylmethylphosphonates, as it only produces water as by-product. The major advantages of this reaction include the easily available α-aryl α-hydroxyphosphonates **1**[14] and the rich diversity of product **3** by using various aromatic compounds and varying the Ar^1 and R group of **1**. The Chakravarty group reported this reaction

by using 1.0 equivalent of $FeCl_3$ as an acid promoter.[15] However, the substrate scope with respect to both α-aryl α-hydroxyphosphonates and aromatic compounds was very limited. And to date, no catalytic version of this reaction has been reported. To develop a catalytic version, the main challenge consists in the difficulty in the formation of carbocationic intermediate I (Scheme 1) for the Friedel-Crafts reaction step, which resulted from the net destabilizing effect of the strong electron-withdrawing phosphoryl group of **1**. Despite several achievements in the catalytic Friedel-Crafts arylation of alcohols with an α-electron-withdrawing substitutent[16] have been made, all of them needed to use special alcohols that could generate reactive oxonium[16e] or vinylogous iminium intermediate.[17] Even so, Zhou and co-workers recently developed a highly efficient catalytic Friedel-Crafts arylation of α-hydroxyesters or α-hydroxyketones that could not form oxonium or vinylogous iminium intermediate.[18a] Inspired by this positive result, we envisaged this reaction might be achieved by using suitable Lewis or Brønsted acids as catalyst and adjusting reaction parameters such as solvent and reaction temperature. Herein, we are pleased to find this arylation could proceed smoothly by using HOTf as Brønsted acid catalyst and CH_3NO_2 as solvent, affording α-diarylmethylphosphonates in good yields and regioselectivities.



Chakravarty's work: $FeCl_3$ (**1.0 equiv**), Ar^2-H (**3-20.0** equivs), 7 examples, 82-92% yields

This work: HOTf (**20 mol%**), Ar^2-H (2.0 equivs), 28 examples, 41-95% yields

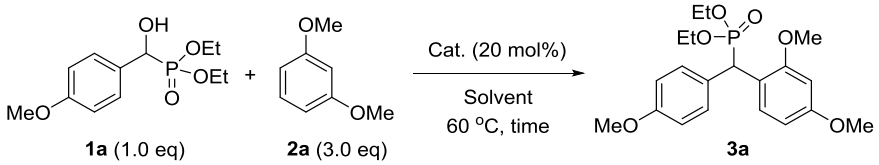
Scheme 1. Friedel-Crafts arylation of α-aryl α-hydroxyphosphonates

Results and Discussion

To circumvent the destabilizing effect of phosphoryl group, we assumed introducing *para*-methoxyphenyl, a carbocation stabilizing group, at the adjacent position of the generated carbocation **I**. Therefore, the reaction of α-hydroxyphosphonate **1a** and 1,3-dimethoxybenzene **2a** was selected as the model reaction for condition optimization, and typical results were presented in Table 1.

Inspired by the work of Chakravarty, we first examined $FeCl_3$ as Lewis acid catalyst, and found that the desired product **3a** could be obtained only in 45% yield after 72 h when 20 mol% of $FeCl_3$ was used (Table 1, entry 1). Then, the inexpensive and easily to handle metal perchlorate hydrates,[19] known as powerful Lewis acids were screened. Fe^{III}-, Cu^{II}- and Ag^{I}-derived perchlorate hydrates all could catalyze the reaction smoothly, and giving product **3a** in moderate yields (Table 1, entries 2-4). And we found that metal triflates[20] could also mediate the reaction. For example, under the catalysis of $Fe(OTf)_3$ and AgOTf, product **3a** was obtained in 75% and 24% yield, respectively (entries 5-6). Finally, different Brønsted acids[21] were investigated, and only $HClO_4$[18] and HOTf could catalyze the Friedel-Crafts reaction well, furnishing the corresponding product **3a** in 75% and 82% yields, respectively (entries 7-8).

Table 1. Condition optimization



Entry[a]	Cat.	Solvent	Time (h)	Yield (%)[b]
1	$FeCl_3$	$ClCH_2CH_2Cl$	72	45
2	$Fe(ClO_4)_3 \cdot 6H_2O$	$ClCH_2CH_2Cl$	24	70
3	$Cu(ClO_4)_2 \cdot 6H_2O$	$ClCH_2CH_2Cl$	72	69
4	$AgClO_4 \cdot H_2O$	$ClCH_2CH_2Cl$	7	78
5	$Fe(OTf)_3$	$ClCH_2CH_2Cl$	24	75
6	AgOTf	$ClCH_2CH_2Cl$	96	24
7	$HClO_4$	$ClCH_2CH_2Cl$	10	75
8	HOTf	$ClCH_2CH_2Cl$	3	82
9	HOTf	THF	24	29
10	HOTf	Ethyl acetate	16	53
11	HOTf	Acetone	24	50
12	HOTf	CH_3CN	2.5	95
13	HOTf	CH_3NO_2	0.5	99
14[c]	**HOTf**	**CH_3NO_2**	**1.0**	**95**
15[c,d]	HOTf	CH_3NO_2	10	88
16[c,e]	HOTf	CH_3NO_2	24	57

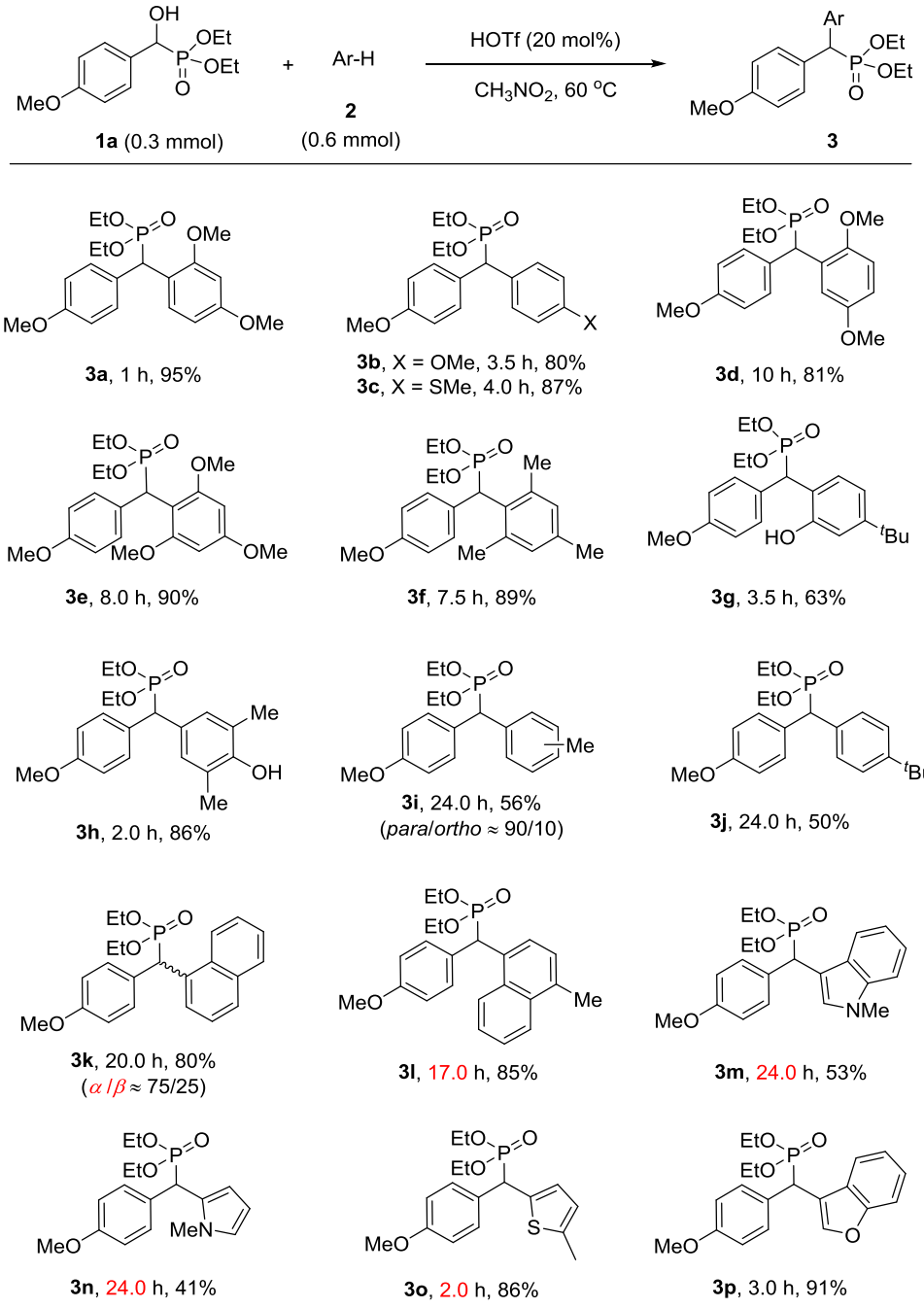
[a] On a 0.20 mmol scale. [b] Isolated yield. [c] 0.20 mmol of **1a** and 0.40 mmol of **2a**. [d] 10 mol% of HOTf. [e] 40 ^oC.

Next, solvent effects were evaluated in the presence of 20 mol% HOTf. We found that the solvent had a great effect on reaction outcome. For instance, the use of tetrahydrofuran (THF) as solvent led to deep decrease in reaction yield (entry 9), and only moderate yields were obtained in ethyl acetate and acetone. To our delight, excellent yields could be achieved when CH_3CN and CH_3NO_2 were used (entries 12-13). And CH_3NO_2 was found to be the best solvent in terms of reaction yield and time, which gave **3a** in 99% yield within 0.5 h (entry 13). It should be noted

that **3a** could still be achieved in 95% yield even if reducing the amount of **2a** to from 3.0 to 2.0 equivalents (entry 14).

Finally, we attempted to decrease the catalyst loading to 10 mol%, and found lower yields (88%) along with longer period (10 h) was observed (entry 15). In addition, only 57% yield was obtained when reducing the reaction temperature to 40 ^{o}C, as the reaction could not proceed completely even if extending the reaction time to 24 h (entry 16). The evaluation of substrate scope was then carried out in CH_3NO_2 at 60 °C, using 20 mol % of HOTf as the catalyst.

Firstly, we examined a variety of (hetero)aromatic compounds (Scheme 2), and found activated arenes such as 1,3-dimethoxybenzene, anisole, methyl(phenyl)sulfane and 1,4-dimethoxybenzene all could work well to afford the corresponding products **3a**-**3d** in good to high yields. It was worth mentioning that excellent regioselectivities were achieved for **3b**-**3c**, as only one isomer was observed from the crude ^{1}H and ^{31}P NMR spectrum of **3b**-**3c**. Mesitylene, 1,3,5-trimethoxybenzene, 4-(*tert*-butyl)phenol and 2,6-dimethylphenol were also effective, and the desired products **3e**-**3h** could be obtained in moderate to good yields. Noticeably, unactivated arenes such as toluene, *tert*-butylbenzene, naphthalene and 1-methylnaphthalene could be also compatible,[22] but 50 mol% of HOTf should be used. When *tert*-butylbenzene and 1-methylnaphthalene were used, the corresponding products **3j** and **3l** were isolated in 50% and 85% yield with only one regioisomer detected. However, as anticipated, the reaction of **1a** with toluene and naphthalene gave products **3i** and **3k** with a mixture of two regioisomers (probably *para*/*ortho* 90:10 and α/β 75/25, respectively) as confirmed by ^{1}H and ^{31}P NMR spectrum of **3i** and **3k**.



Scheme 2. The substrate scope of different (hetero)aromatics

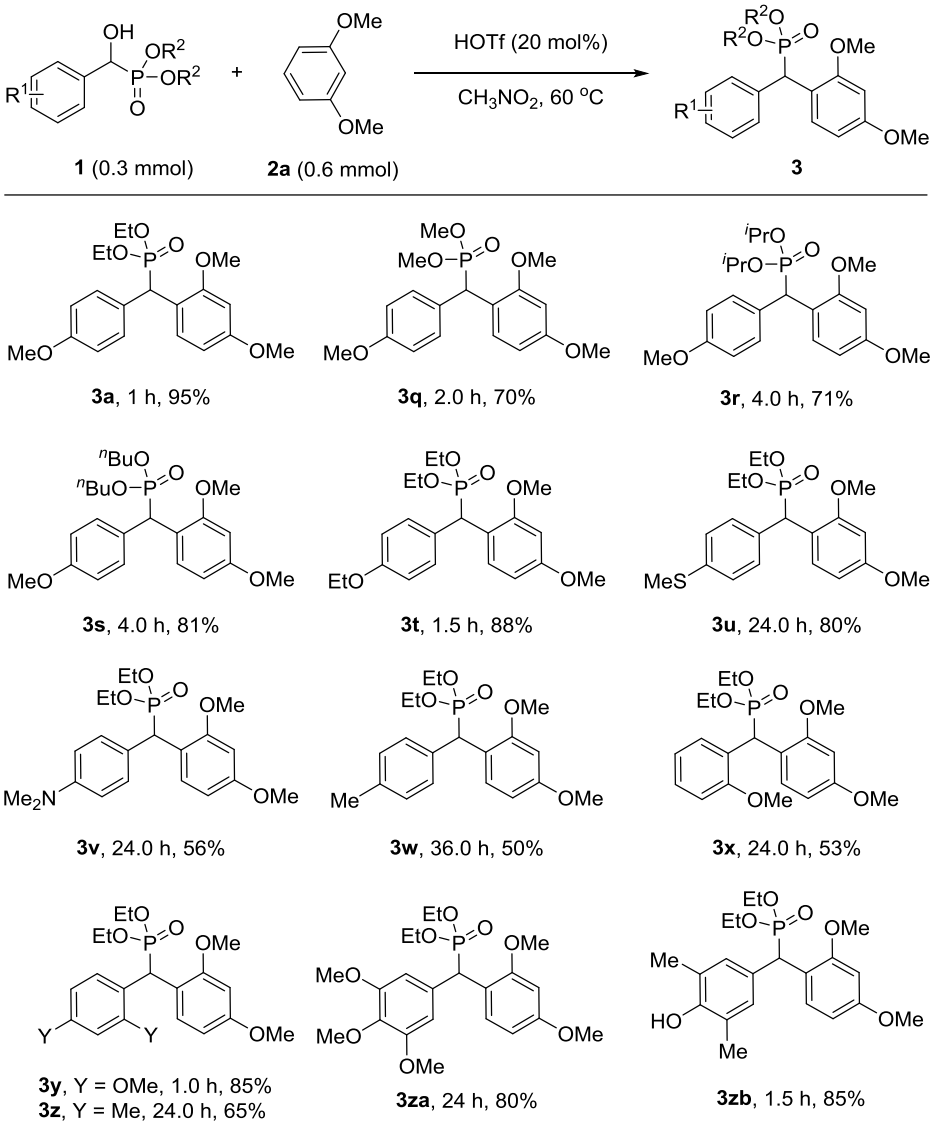
In addition to arenes, (hetero)aromatic compounds were also suitable substrates for this Friedel-Crafts arylation. For examples, *N*-methyl indole, *N*-methyl pyrrole, 2-

methylthiophene and benzofuran all performed well, furnishing the expected products **3m-3p** in reasonable yields. Generally, 2-methylthiophene and benzofuran showed higher reactivity than *N*-methyl indole and *N*-methyl pyrrole as much higher yields and shorter reaction time were observed for **3o-3p** than that of **3m-3n**. In case of *N*-methyl indole and *N*-methyl pyrrole, undesired reactions occurred along with some side-products detected, which finally resulted in lower yields for **3m-3n**. Other (hetero)arenes such as furan, *N*-unprotected indole and indoline were also tried, but no desired product was detected.

The 1,3-dimethoxybenzene was then selected to evaluate the scope of α-aryl α-hydroxyphosphonates (Scheme 3). α-Hydroxyphosphonates with methyl, isopropyl and *n*-butyl as the ester functionality could also give the corresponding products **3q-3s** in good yields. As expected, the electronic and steric effects of substituents on α-hydroxyphosphonates **1** had a great effect on reaction outcome. For example, α-hydroxyphosphonates bearing ethoxy and methylthio at the *para*-position of the phenyl ring afforded the desired products **3t-3u** in good yields (80-88%), while α-hydroxyphosphonate with a simple methyl at the *para*-position of the phenyl ring was much less reactive and only 50% yield was obtained for **3w**. And almost no reaction occurred when phenyl substituted α-hydroxyphosphonate was used, even increasing the reaction temperature or the catalyst loading.

The steric effect lied in the fact that the methoxy group at the *ortho*-position of the phenyl ring slowed down the reaction rate significantly, and the corresponding product **3x** was obtained in only 53% yield after 24 h. α-Hydroxyphosphonates with 2,4-dimethoxyphenyl or 2,4-dimethylphenyl worked well to afford the desired products **3y** and

3z in good yields. Moreover, α-hydroxyphosphonates with 3,4,5-trimethoxyphenyl or 3,5-dimethyl-4-hydroxylphenyl were also viable substrates for the reaction, furnishing products **3za** and **3zb** in 80% and 85% yield, respectively.



Scheme 3. The substrate scope of α-aryl α-hydroxyphosphonates

Conclusions

In summary, we have developed a metal-free catalytic Friedel-Crafts arylation of α-aryl α-hydroxyphosphonates with various (hetero)aromatic compounds, which provides a facile method for the synthesis of α-diarylmethylphosphonates. The cheap and easily available Brønsted acid HOTf was identified as a powerful acid catalyst to promote the reaction, affording the desired α-diarylmethylphosphonates in good to excellent yields. The exploration of potential applications of the obtained α-diarylmethylphosphonates and the development of new efficient acid catalysts to enlarge the substrate scope is under investigation in our laboratory.

Experimental

General information: Reactions were monitored by thin layer chromatography using UV light to visualize the reaction course. Purification of reaction products was carried out by flash chromatography on silica gel. Chemical yields refer to pure isolated substances. ^{1}H and ^{13}C NMR spectra were obtained using a Bruker DPX-400 spectrometer. The ^{31}P NMR spectra were recorded at 162 MHz with 85% H_3PO_4 as external standard. All reactions were run under an atmosphere of air. Anhydrous CH_3NO_2 was prepared by first drying with anhydrous Na_2SO_4 and then distilling under reduced pressure. Commercially available HOTf (trifluoromethanesulfonic acid) was used as received. α-Hydroxyphosphonates **1** were prepared according to the literature report.[14] Compounds **3b**[6], **3f**[15], **3k**[15] are known products.

The Supplemental Materials contains ^{1}H, ^{13}C and ^{31}P NMR spectra of the products 3 (Figures S 1 – S 83).

General procedure for the Friedel-Crafts arylation of α-aryl α-hydroxyphosphonates

The reaction was carried out under an air atmosphere. To a 5 mL vial were added α-hydroxyphosphontes **1** (0.3 mmol), (hetero)arenes **2** (0.6 mmol, 2.0 equivs) and anhydrous CH_3NO_2 (1 mL). After adding HOTf (9.0 mg, 20 mol%) which was prepared as a solution in CH_3NO_2, the reaction mixture was stirred at 60 ^{o}C till almost full conversion of **1** by TLC analysis. The reaction mixture was then directly subjected to column chromatography using methylene dichloride/ethyl acetate (v/v) as the eluent to afford the desired product **3**.

Diethyl ((2,4-dimethoxyphenyl)(4-methoxyphenyl)methyl)phosphonate (3a): 112 mg, 95% yield, white solid; Mp: 50-52 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.82 (dd, *J* = 8.6 Hz, 1.2 Hz, 1H), 7.43-7.41 (m, 2H), 6.82-6.79 (m, 2H), 6.50 (dd, *J* = 8.4 Hz, 2.4 Hz, 1H), 6.41 (s, 1H), 4.94 (d, *J* = 25.2 Hz, 1H), 4.00-3.93 (m, 2H), 3.88-3.79 (m, 2H), 3.78 (s, 3H), 3.77 (s, 3H), 3.75 (s, 3H), 1.13 (t, *J* = 7.2 Hz, 3H), 1.12 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.6 (d, *J* = 1.0 Hz), 158.2 (d, *J* = 2.0 Hz), 157.4 (d, *J* = 11.0 Hz), 130.4 (d, *J* = 5.0 Hz), 130.3 (d, *J* = 2.0 Hz), 129.2 (d, *J* = 4.0 Hz), 118.1 (d, *J* = 3.0 Hz), 113.6, 104.1, 98.5, 62.3 (d, *J* = 7.0 Hz), 62.2 (d, *J* = 7.0 Hz), 55.5 (d, *J* = 2.0 Hz), 55.1 (d, *J* = 2.0 Hz), 55.0 (d, *J* = 2.0 Hz), 40.1 (d, *J* = 140.0 Hz), 16.13, 16.07; ^{31}P NMR (162 MHz, $CDCl_3$): δ = 26.8; IR (neat): 3060, 2923, 2838, 1607, 1503, 1206, 1023, 962, 608 cm^{-1}; HRMS (ESI): Exact mass calcd for $C_{20}H_{28}O_6P$ $[M+H]^+$: 395.1618, Found: 395.1617.

Diethyl (bis(4-methoxyphenyl)methyl)phosphonate (3b)[6]: 87 mg, 80% yield, white solid; Mp: 53-55 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42-7.40 (m, 4H), 6.84-6.82 (m,

4H), 4.32 (d, *J* = 25.2 Hz, 1H), 4.01-3.93 (m, 2H), 3.85-3.78 (m, 2H), 3.75 (s, 6H), 1.12 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.5 (d, *J* = 2.0 Hz), 130.3 (d, *J* = 8.0 Hz), 129.1 (d, *J* = 5.0 Hz), 113.8, 62.5, 62.4, 55.09, 55.07, 49.3 (d, *J* = 139.0 Hz), 16.2, 16.2; ^{31}P NMR (162 MHz, $CDCl_3$): *δ* = 25.7.

Diethyl ((4-methoxyphenyl)(4-(methylthio)phenyl)methyl)phosphonate (3c): 99 mg, 87% yield, white solid; Mp: 46-48 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42-7.38 (m, 4H), 7.17-7.15 (m, 2H), 6.82-6.80 (m, 2H), 4.36 (d, *J* = 25.2 Hz, 1H), 4.00-3.90 (m, 2H), 3.87-3.75 (m, 2H), 3.72 (s, 3H), 2.39 (s, 3H), 1.10 (dt, *J* = 4.8 Hz, 2.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.5 (d, *J* = 2.0 Hz), 136.9 (d, *J* = 3.0 Hz), 133.8 (d, *J* = 5.0 Hz), 130.2 (d, *J* = 8.0 Hz), 129.6 (d, *J* = 8.0 Hz), 128.6 (d, *J* = 5.0 Hz), 126.4, 113.8, 62.4 (d, *J* = 7.0 Hz), 62.3 (d, *J* = 8.0 Hz), 54.96, 54.95, 49.5 (d, *J* = 138.0 Hz), 16.1 (d, *J* = 6.0 Hz), 15.5; ^{31}P NMR (162 MHz, $CDCl_3$): *δ* = 25.2; IR (neat): 2981, 2957, 1510, 1242, 1024, 960, 741 cm^{-1}; HRMS (ESI): Exact mass calcd for $C_{19}H_{26}O_4PS$ $[M+H]^+$: 381.1284, Found: 381.1283.

Diethyl ((2,5-dimethoxyphenyl)(4-methoxyphenyl)methyl)phosphonate (3d): 96 mg, 81% yield, colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53-7.52 (m, 1H), 7.45-7.43 (m, 2H), 6.81-6.70 (m, 4H), 5.02 (d, *J* = 24.8 Hz, 1H), 4.01-3.90 (m, 2H), 3.88-3.80 (m, 2H), 3.76 (s, 3H), 3.73 (s, 3H), 3.72 (s, 3H), 1.12 (td, *J* = 6.8 Hz, 1.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.4 (d, *J* = 2.0 Hz), 153.4 (d, *J* = 2.0 Hz), 150.9 (d, *J* = 10.0 Hz), 130.6 (d, *J* = 7.0 Hz), 128.8 (d, *J* = 5.0 Hz), 126.9 (d, *J* = 3.0 Hz), 115.9 (d, *J* = 5.0 Hz), 113.7, 112.9, 112.0, 62.4 (d, *J* = 2.0 Hz), 62.3 (d, *J* = 3.0 Hz), 56.4 (d, *J* = 2.0 Hz), 55.6 (d, *J* = 3.0 Hz), 55.1 (d, *J* = 3.0 Hz), 40.9 (d, *J* = 141.0 Hz), 16.23, 16.19; ^{31}P NMR (162 MHz, $CDCl_3$):

δ = 26.3; IR (neat): 3468, 2986, 2835, 1609, 1498, 1234, 1097, 956, 794 cm^{-1}; HRMS (ESI): Exact mass calcd for $C_{20}H_{28}O_6P$ $[M+H]^+$: 395.1618, Found: 395.1615.

Diethyl ((4-methoxyphenyl)(2,4,6-trimethoxyphenyl)methyl)phosphonate (3e): 114 mg, 90% yield, colorless oil; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.40 (dd, *J* = 8.8 Hz, 2.0 Hz, 2H), 6.75 (d, *J* = 8.8 Hz, 2H), 6.11 (s, 2H), 5.13 (d, *J* = 28.0 Hz, 1H), 4.00-3.83 (m, 4H), 3.76 (s, 6H), 3.75 (s, 3H), 3.71 (s, 3H), 1.18-1.11 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.3 (d, *J* = 1.0 Hz), 158.8, 157.9 (d, *J* = 2.0 Hz), 130.5 (d, *J* = 8.0 Hz), 129.3 (d, *J* = 8.0 Hz), 113.2, 107.6 (d, *J* = 4.0 Hz), 90.9, 61.7 (d, *J* = 7.0 Hz), 61.6 (d, *J* = 7.0 Hz), 55.6, 55.1 (d, *J* = 2.0 Hz), 55.0 (d, *J* = 2.0 Hz), 39.0 (d, *J* = 143.0 Hz), 16.3, 16.2 (d, *J* = 7.0 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ = 27.5; IR (neat): 3450, 2978, 2935, 2838, 1605, 1510, 1245, 1026, 950, 748, 633 cm^{-1}; HRMS (ESI): Exact mass calcd for $C_{21}H_{30}O_7P$ $[M+H]^+$: 425.1724, Found: 425.1723.

Diethyl (mesityl(4-methoxyphenyl)methyl)phosphonate (3f)[15]: 100 mg, 89% yield, white solid; Mp: 90-92 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.33 (d, *J* = 8.8 Hz, 2H), 6.89 (s, 1H), 6.79 (d, *J* = 8.8 Hz, 2H), 6.75 (s, 1H), 5.02 (d, *J* = 30.8 Hz, 1H), 4.26-4.08 (m, 2H), 3.90-3.80 (m, 1H), 3.76 (s, 3H), 3.48-3.38 (m, 1H), 2.46 (s, 3H), 2.24 (s, 3H), 2.06 (s, 3H), 1.33 (t, *J* = 7.2 Hz, 3H), 1.01 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.7, 139.3 (d, *J* = 4.0 Hz), 137.6 (d, *J* = 7.0 Hz), 136.4 (d, *J* = 4.0 Hz), 131.0, 131.0, 129.7 (d, *J* = 11.0 Hz), 129.3 (d, *J* = 1.0 Hz), 128.8, 113.4, 62.7 (d, *J* = 7.0 Hz), 61.3 (d, *J* = 7.0 Hz), 55.1, 43.8 (d, *J* = 140.0 Hz), 21.4 (d, *J* = 25.0 Hz), 20.7, 16.3 (d, *J* = 6.0 Hz), 16.1 (d, *J* = 6.0 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ = 26.5.

Diethyl ((4-(tert-butyl)-2-hydroxyphenyl)(4-methoxyphenyl)methyl)phosphonate (3g): 77 mg, 63% yield, white solid; Mp: 148-150 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.86 (brs 1H), 7.44-7.42 (m, 2H), 7.19-7.17 (m, 1H), 7.07 (s, 1H), 6.93-6.91 (m, 1H), 6.88-6.86 (m, 2H), 4.59 (d, *J* = 26.8 Hz, 1H), 4.06-3.97 (m, 2H), 3.92-3.81 (m, 2H), 3.79 (s, 3H), 1.21 (s, 9H), 1.17 (t, *J* = 7.2 Hz, 3H), 1.10 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.6 (d, *J* = 2.0 Hz), 152.6 (d, *J* = 6.0 Hz), 143.4, 130.7 (d, *J* = 8.0 Hz), 128.0 (d, *J* = 8.0 Hz), 127.4 (d, *J* = 5.0 Hz), 125.8 (d, *J* = 3.0 Hz), 122.5 (d, *J* = 6.0 Hz), 118.7 (d, *J* = 2.0 Hz), 113.9, 63.6 (d, *J* = 8.0 Hz), 63.2 (d, *J* = 7.0 Hz), 55.2 (d, *J* = 2.0 Hz), 47.1 (d, *J* = 136.0 Hz), 34.0, 31.4, 16.2 (d, *J* = 5.0 Hz), 16.0 (d, *J* = 6.0 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): *δ* = 28.8; IR (neat): 3330, 3111, 2963, 2860, 1549, 1248, 1186, 1018, 959, 826, 749 cm^{-1}; HRMS (ESI): Exact mass calcd for $C_{22}H_{32}O_5P$ $[M+H]^+$: 407.1982, Found: 407.1979.

Diethyl ((4-hydroxy-3,5-dimethylphenyl)(4-methoxyphenyl)methyl)phosphonate (3h): 98 mg, 86% yield, colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41 (dd, *J* = 6.8 Hz, 1.6 Hz, 2H), 7.06 (s, 2H), 6.82 (d, *J* = 8.8 Hz, 2H), 6.20 (brs, 1H), 4.26 (d, *J* = 25.2 Hz, 1H), 4.03-3.92 (m, 2H), 3.89-3.77 (m, 2H), 3.74 (s, 3H), 2.17 (s, 6H), 1.16-1.11 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.4 (d, *J* = 2.0 Hz), 151.8 (d, *J* = 2.0 Hz), 130.3 (d, *J* 8.0 Hz), 129.2 (d, *J* = 5.0 Hz), 129.2 (d, *J* = 2.0 Hz), 127.7 (d, *J* = 5.0 Hz), 123.8, 113.8, 62.54, 62.47, 55.1 (d, *J* = 2.0 Hz), 49.3 (d, *J* = 138.0 Hz), 16.1; ^{31}P NMR (162 MHz, $CDCl_3$): *δ* = 26.0; IR (neat): 3243, 2984, 2911, 1608, 1390, 1249, 1022, 960, 746 cm^{-1}; HRMS (ESI): Exact mass calcd for $C_{20}H_{28}O_5P$ $[M+H]^+$: 379.1669, Found: 379.1670.

Diethyl ((4-methoxyphenyl)(p-tolyl)methyl)phosphonate (3i): a regioisomer mixture with a ratio of 9:1. 58 mg, 56% yield, colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44-

7.37 (m, 4H), 7.12-7.10 (m, 2H), 6.85-6.83 (m, 2H), 4.34 (d, *J* = 25.2 Hz, 1H), 4.02-3.92 (m, 2H), 3.87-3.79 (m, 2H), 3.77 (s, 3H), 2.30 (s, 3H), 1.13 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.5 (d, *J* = 2.0 Hz), 136.6 (d, *J* = 2.0 Hz), 134.1 (d, *J* = 4.0 Hz), 130.4 (d, *J* = 8.0 Hz), 129.2, 129.1 (d, *J* = 12.0 Hz), 129.0, 113.9 (d, *J* = 1.0 Hz), 62.6 (d, *J* = 1.0 Hz), 62.5 (d, *J* = 2.0 Hz), 55.2, 49.8 (d, *J* = 138.0 Hz), 21.0, 16.3 (d, *J* = 2.0 Hz), 16.2 (d, *J* = 1.0 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): *δ* = 25.6; IR (neat): 3060, 2921, 2854, 1500, 1250, 1040, 965, 709 cm^{-1}; HRMS (ESI): Exact mass calcd for $C_{19}H_{26}O_4P$ $[M+H]^+$: 349.1563, Found: 349.1561.

Diethyl ((4-(tert-butyl)phenyl)(4-methoxyphenyl)methyl)phosphonate (3j): 59 mg, 50% yield, colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46-7.40 (m, 4H), 7.32-7.30 (m, 2H), 6.86-6.84 (m, 2H), 4.35 (d, *J* = 25.2 Hz, 1H), 4.02-3.92 (m, 2H), 3.86-3.79 (m, 2H), 3.77 (s, 3H), 1.28 (s, 9H), 1.14-1.09 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.6 (d, *J* = 2.0 Hz), 149.8 (d, *J* = 3.0 Hz), 133.9 (d, *J* = 5.0 Hz), 130.5 (d, *J* = 8.0 Hz), 129.1 (d, *J* = 5.0 Hz), 128.9 (d, *J* = 8.0 Hz), 125.4 (d, *J* = 1.0 Hz), 113.9, 62.6, 62.5 (d, *J* = 7.0 Hz), 55.2, 49.9 (d, *J* = 138.0 Hz), 34.4, 31.3, 16.3, 16.2 (d, *J* = 7.0 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): *δ* = 25.7; IR (neat): 3100, 2921, 2854, 1440, 1250, 1052, 960, 751 cm^{-1}; HRMS (ESI): Exact mass calcd for $C_{22}H_{32}O_4P$ $[M+H]^+$: 391.232, Found: 391.2027.

Diethyl ((4-methoxyphenyl)(naphthalen-1-yl)methyl)phosphonate (3k)[15]: a regioisomer mixture with a ratio of 3:1. 92 mg, 80% yield, colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.25-8.23 (m, 1H), 8.08-8.06 (m, 1H), 7.84-7.77 (m, 3H), 7.54-7.50 (m, 1H) (belonging to the major isomer), 7.48-7.43 (m, 4H), 6.82 (d, *J* = 8.4 Hz, 2H), 5.24 (d, *J* = 26.4 Hz, 1H), 4.60-3.94 (m, 2H), 3.88-3.80 (m, 2H), 3.77 (s, 1H) (belonging to the minor

isomer), 3.73 (s, 3H) (belonging to the major isomer), 1.18 (t, *J* = 7.2 Hz, 3H) (belonging to the major isomer), 1.14 (t, *J* = 7.2 Hz, 1H) (belonging to the minor isomer), 1.11 (t, *J* = 6.8 Hz, 3H) (belonging to the minor isomer), 1.04 (t, *J* = 7.2 Hz, 3H) (belonging to the major isomer).

Diethyl ((4-methoxyphenyl)(4-methylnaphthalen-1-yl)methyl)phosphonate (3l): 101 mg, 85% yield, colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.18-8.16 (m, 1H), 8.09-8.07 (m, 1H), 8.02-7.99 (m, 1H), 7.50-7.45 (m, 4H), 7.38 (d, *J* = 7.6 Hz, 1H), 6.82 (d, *J* = 8.8 Hz, 2H), 5.23 (d, *J* = 26.4 Hz, 1H), 4.04-3.95 (m, 2H), 3.88-3.80 (m, 2H), 3.72 (s, 3H), 2.68 (s, 3H), 1.18 (t, *J* = 7.2 Hz, 3H), 1.07 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.5 (d, *J* = 2.0 Hz), 133.8 (d, *J* = 1.0 Hz), 133.2, 131.5 (d, *J* = 12.0 Hz), 131.0 (d, *J* = 2.0 Hz), 130.5 (d, *J* = 8.0 Hz), 128.6 (d, *J* = 7.0 Hz), 127.0 (d, *J* = 7.0 Hz), 126.1 (d, *J* = 1.0 Hz), 125.8, 125.2, 124.9, 123.6, 113.8 (d, *J* = 2.0 Hz), 62.54, 62.47, 55.0, 44.9 (d, *J* = 139.0 Hz), 19. 4, 16.3 (d, *J* = 6.0 Hz), 16.1 (d, *J* = 6.0 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): *δ* = 26.3; IR (neat): 3474, 2980, 2837, 1462, 1247, 1051, 751, 610 cm^{-1}; HRMS (ESI): Exact mass calcd for $C_{23}H_{28}O_4P$ $[M+H]^+$: 399.1720, Found: 399.1719.

Diethyl ((4-methoxyphenyl)(1-methyl-1H-indol-3-yl)methyl)phosphonate (3m): 62 mg, 53% yield, brown oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50 (s, 1H), 7.49-7.41 (m, 3H), 7.28-7.25 (m, 1H), 7.19-7.16 (m, 1H), 7.05-7.02 (m, 1H), 6.83-6.80 (m, 2H), 4.67 (d, *J* = 24.0 Hz, 1H), 4.04-3.86 (m, 3H), 3.78 (s, 3H), 3.76-3.72 (m, 1H), 3.74 (s, 3H), 1.16-1.10 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.5 (d, *J* = 3.0 Hz), 136.6, 130.3 (d, *J* = 7.0 Hz), 129.1 (d, *J* = 6.0 Hz), 128.3 (d, *J* = 5.0 Hz), 127.5 (d, *J* = 12.0 Hz), 121.6, 118.9, (d, *J* = 21.0 Hz), 113.7 (d, *J* = 2.0 Hz), 109.6 (d, *J* = 7.0 Hz), 109.1, 62.7 (d, *J* = 7.0 Hz), 62.4 (d, *J* = 7.0

Hz), 55.1 (d, *J* = 2.0 Hz), 40.8 (d, *J* = 139.0 Hz), 32.8 (d, *J* = 2.0 Hz), 16.3; ^{31}P NMR (162 MHz, $CDCl_3$): δ = 26.3; IR (neat): 3250, 2960, 2854, 1600, 1240, 1025, 960, 790 cm^{-1}; HRMS (ESI): Exact mass calcd for $C_{21}H_{27}NO_4P$ $[M+H]^+$: 388.1672, Found: 388.1670.

Diethyl ((4-methoxyphenyl)(1-methyl-1H-pyrrol-2-yl)methyl)phosphonate (3n): 41 mg, 41% yield, brown oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29-7.26 (m, 2H), 6.84-6.82 (m, 2H), 6.58-6.57 (m, 1H), 6.53 (t, *J* = 6.0 Hz, 1H), 6.09 (t, *J* = 8.0 Hz, 1H), 4.38 (d, *J* = 28.0 Hz, 1H), 4.08-4.02 (m, 1H), 4.00-3.89 (m, 2H), 3.82-3.80 (m, 1H), 3.77 (s, 3H), 3.38 (s, 3H), 1.20-1.14 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.6 (d, *J* = 3.0 Hz), 130.4 (d, *J* = 6.0 Hz), 127.3 (d, *J* = 6.0 Hz), 126.6, 122.2, 113.8 (d, *J* = 2.0 Hz), 109.5 (d, *J* = 4.0 Hz), 106.7, 62.9 (d, *J* = 7.0 Hz), 62.6 (d, *J* = 7.0 Hz), 55.2, 42.1 (d, *J* = 142.0 Hz), 33.7, 16.3, 16.2 (d, *J* = 4.0 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ = 24.2; IR (neat): 3200, 2850, 1510, 1253, 1095, 755, 697, 650 cm^{-1}; HRMS (ESI): Exact mass calcd for $C_{17}H_{25}NO_4P$ $[M+H]^+$: 338.1516, Found: 338.1511.

Diethyl ((4-methoxyphenyl)(5-methylthiophen-2-yl)methyl)phosphonate (3o): 91 mg, 86% yield, brown oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42-7.40 (m, 2H), 6.97-6.96 (m, 1H), 6.86-6.84 (m, 2H), 6.59-6.58 (m, 1H), 4.51 (d, *J* = 24.0 Hz, 1H), 4.08-3.93 (m, 3H), 3.82-3.74 (m, 1H), 3.77 (s, 3H), 2.40 (s, 3H), 1.21 (t, *J* = 8.0 Hz, 3H), 1.11 (t, *J* = 8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.8 (d, *J* = 3.0 Hz), 139.3 (d, *J* = 3.0 Hz), 136.7 (d, *J* = 4.0 Hz), 130.3 (d, *J* = 7.0 Hz), 128.55 (d, *J* = 3.0 Hz), 126.64 (d, *J* = 8.0 Hz), 124.9 (d, *J* = 2.0 Hz), 113.9 (d, *J* = 1.0 Hz), 62.9 (d, *J* = 8.0 Hz), 62.7 (d, *J* = 8.0 Hz), 55.2, 45.5 (d, *J* = 140.0 Hz), 16.3, 16.2 (d, *J* = 6.0 Hz), 15.2; ^{31}P NMR (162 MHz, $CDCl_3$): δ = 23.6; IR (neat):

2928, 1713, 1475, 1253, 878, 739, 696 cm^{-1}; HRMS (ESI): Exact mass calcd for $C_{17}H_{24}O_4PS$ $[M+H]^+$: 355.1127, Found: 355.1125.

Diethyl (benzofuran-3-yl(4-methoxyphenyl)methyl)phosphonate (3p): 102 mg, 91% yield, colorless oil; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.54-7.52 (m, 1H), 7.45-7.40 (m, 3H), 7.24-7.16 (m, 2H), 6.93-6.92 (m, 1H), 6.89-6.87 (m, 2H), 4.62 (d, *J* = 25.6 Hz, 1H), 4.14-3.95 (m, 3H), 3.86-3.79 (m, 1H), 3.76 (s, 3H), 1.23 (t, *J* = 7.2 Hz, 3H), 1.14 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.0 (d, *J* = 3.0 Hz), 154.5, 153.1, 130.4 (d, *J* = 6.0 Hz), 128.3 (d, *J* = 2.0 Hz), 125.6 (d, *J* = 6.0 Hz), 123.8, 122.6, 120.7, 113.9 (d, *J* = 2.0 Hz), 110.8, 105.3 (d, *J* = 5.0 Hz), 63.0 (d, *J* = 7.0 Hz), 62.8 (d, *J* = 7.0 Hz), 55.0, 44.6 (d, *J* = 140.0 Hz), 16.2, 16.1 (d, *J* = 7.0 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): *δ* = 21.8; IR (neat): 3200, 2950, 1513, 1480, 1253, 1095, 755 cm^{-1}; HRMS (ESI): Exact mass calcd for $C_{20}H_{24}O_5P$ $[M+H]^+$: 375.1356, Found: 375.1354.

Dimethyl ((2,4-dimethoxyphenyl)(4-methoxyphenyl)methyl)phosphonate (3q): 77 mg, 70% yield, white solid; Mp: 98-100 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.80 (dd, *J* = 8.4 Hz, 1.6 Hz, 1H), 7.42-7.41 (m, 2H), 6.83-6.81 (m, 2H), 6.51 (dd, *J* = 7.2 Hz, 2.4 Hz, 1H), 6.42 (s, 1H), 4.97 (d, *J* = 25.6 Hz, 1H), 3.78 (s, 6H), 3.76 (s, 3H), 3.56 (dd, *J* = 10.4 Hz, 7.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.8, 158.4 (d, *J* = 3.0 Hz), 157.4 (d, *J* = 11.0 Hz), 130.5 (d, *J* = 2.0 Hz), 130.4, 129.0 (d, *J* = 5.0 Hz), 117.9 (d, *J* = 3.0 Hz), 113.8, 104.3, 98.7, 55.6 (d, *J* = 2.0 Hz), 55.2 (d, *J* = 2.0 Hz), 55.1 (d, *J* = 2.0 Hz), 53.2, 39.8 (d, *J* = 140.0 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): *δ* = 29.1; IR (neat): 2949, 2922, 2847, 1608, 1457, 1246, 1022, 797, 608 cm^{-1}; HRMS (ESI): Exact mass calcd for $C_{18}H_{24}O_6P$ $[M+H]^+$: 367.1305, Found: 367.1302.

Diisopropyl ((2,4-dimethoxyphenyl)(4-methoxyphenyl)methyl)phosphonate (3r): 90 mg, 71% yield, colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85 (dd, *J* = 8.6 Hz, 1.6 Hz, 1H), 7.44-7.41 (m, 2H), 6.79-6.77 (m, 2H), 6.48 (dd, *J* = 8.4 Hz, 2.4 Hz, 1H), 6.39 (s, 1H), 4.87 (d, *J* = 25.6 Hz, 1H), 4.53-4.44 (m, 2H), 3.75 (s, 3H), 3.74 (s, 3H), 3.72 (s, 3H), 1.22-1.19 (m, 6H), 0.93-0.91 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.6 (d, *J* = 2.0 Hz), 158.2 (d, *J* = 2.0 Hz), 157.5 (d, *J* = 11.0 Hz), 130.5 (d, *J* = 8.0 Hz), 130.4 (d, *J* = 6.0 Hz), 129.7 (d, *J* = 5.0 Hz), 118.6 (d, *J* = 3.0 Hz), 113.5 (d, *J* = 1.0 Hz), 104.0, 98.5, 70.7 (d, *J* = 8.0 Hz), 70.6 (d, *J* = 7.0 Hz), 55.5, 55.1 (d, *J* = 11.0 Hz), 40.5 (d, *J* = 142.0 Hz), 24.1 (d, *J* = 3.0 Hz), 23.3, 23.2 (d, *J* = 6.0 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): *δ* = 25.1; IR (neat): 2980, 2922, 2847, 1600, 1436, 1250, 1022, 797, 608 cm^{-1}; HRMS (ESI): Exact mass calcd for $C_{22}H_{32}O_6P$ $[M+H]^+$: 423.1931, Found: 423.1929.

Dibutyl ((2,4-dimethoxyphenyl)(4-methoxyphenyl)methyl)phosphonate (3s): 109 mg, 81% yield, white solid; Mp: 58-60 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.82 (dd, *J* = 8.6 Hz, 1.6 Hz, 1H), 7.42-7.40 (m, 2H), 6.79-6.77 (m, 2H), 6.48 (dd, *J* = 8.4 Hz, 2.4 Hz, 1H), 6.39 (s, 1H), 4.94 (d, *J* = 25.2 Hz, 1H), 3.92-3.84 (m, 2H), 3.81-3.77 (m, 2H), 3.74 (s, 3H), 3.73 (s, 3H), 3.71 (s, 3H), 1.46-1.38 (m, 4H), 1.26-1.16 (m, 4H), 0.80 (td, *J* = 8.0 Hz, 2.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.6 (d, *J* = 2.0 Hz), 158.2 (d, *J* = 2.0 Hz), 157.4 (d, *J* = 10.0 Hz), 130.39, 130.38 (d, *J* = 8.0 Hz), 129.3 (d, *J* = 5.0 Hz), 118.2 (d, *J* = 3.0 Hz), 113.5, 104.1, 98.5, 65.9 (d, *J* = 7.0 Hz), 65.8 (d, *J* = 7.0 Hz), 55.4, 55.1 (d, *J* = 2.0 Hz), 55.0 (d, *J* = 1.0 Hz), 40.0 (d, *J* = 140.0 Hz), 32.3 (d, *J* = 2.0 Hz), 32.2 (d, *J* = 2.0 Hz), 18.4 (d, *J* = 3.0 Hz), 13.4; ^{31}P NMR (162 MHz, $CDCl_3$): *δ* = 26.7; IR (neat): 2956, 2905,

2870, 1583, 1239, 1025, 976, 609 cm^{-1}; HRMS (ESI): Exact mass calcd for $C_{24}H_{36}O_6P$ $[M+H]^+$: 451.2244, Found: 451.2242.

Diethyl ((2,4-dimethoxyphenyl)(4-ethoxyphenyl)methyl)phosphonate (3t): 108 mg, 88% yield, colorless oil; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.80 (dd, *J* = 8.6 Hz, 1.6 Hz, 1H), 7.39 (dd, *J* = 11.0 Hz, 5.0 Hz, 2H), 6.77 (d, *J* = 8.4 Hz, 2H), 6.48 (dd, *J* = 8.4 Hz, 2.4 Hz, 1H), 6.40-6.39 (m, 1H), 4.92 (d, *J* = 25.2 Hz, 1H), 3.98-3.91 (m, 4H), 3.86-3.77 (m, 2H), 3.74 (s, 3H), 3.73 (s, 3H), 1.34 (t, *J* = 7.2 Hz, 3H), 1.10 (td, *J* = 7.2 Hz, 2.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.6 (d, *J* = 2.0 Hz), 157.6 (d, *J* = 2.0 Hz), 157.4 (d, *J* = 11.0 Hz), 130.39, 130.38 (d, *J* = 8.0 Hz), 129.0 (d, *J* = 5.0 Hz), 118.1 (d, *J* = 3.0 Hz), 114.1, 104.1 (d, *J* = 1.0 Hz), 98.5, 63.1, 62.3, 62.2 (d, *J* = 7.0 Hz), 55.5 (d, *J* = 2.0 Hz), 55.1 (d, *J* = 2.0 Hz), 40.1 (d, *J* = 140.0 Hz), 16.13, 16.08, 14.7; ^{31}P NMR (162 MHz, $CDCl_3$): *δ* = 26.8; IR (neat): 2960, 2900, 2874, 1600, 1240, 1025, 976, 609 cm^{-1}; HRMS (ESI): Exact mass calcd for $C_{21}H_{30}O_6P$ $[M+H]^+$: 409.1774, Found: 409.1773.

Diethyl ((2,4-dimethoxyphenyl)(4-(methylthio)phenyl)methyl)phosphonate (3u): 98 mg, 80% yield, white solid; Mp: 80-82 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.81 (dd, *J* = 8.8 Hz, 2.0 Hz, 1H), 7.43-7.40 (m, 2H), 7.16-7.14 (m, 2H), 6.49 (dd, *J* = 8.4 Hz, 2.4 Hz, 1H), 6.41-6.40 (m, 1H), 4.94 (d, *J* = 25.6 Hz, 1H), 4.00-3.94 (m, 2H), 3.88-3.81 (m, 2H), 3.76 (s, 3H), 3.75 (s, 3H), 2.41 (s, 3H), 1.15-1.10 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.7 (d, *J* = 1.0 Hz), 157.4 (d, *J* = 11.0 Hz), 136.5 (d, *J* = 3.0 Hz), 134.2 (d, *J* = 4.0 Hz), 130.4 (d, *J* = 5.0 Hz), 129.8 (d, *J* = 8.0 Hz), 126.4 (d, *J* = 1.0 Hz), 117.7 (d, *J* = 4.0 Hz), 104.1 (d, *J* = 1.0 Hz), 98.5, 62.4 (d, *J* = 7.0 Hz), 62.2 (d, *J* = 7.0 Hz), 55.5 (d, *J* = 2.0 Hz), 55.1 (d, *J* = 2.0 Hz), 40.5 (d, *J* = 140.0 Hz), 16.1 (d, *J* = 6.0 Hz), 15.7; ^{31}P NMR (162 MHz,

$CDCl_3$): δ = 26.3; IR (neat): 2962, 2921, 2851, 1610, 1584, 1408, 1236, 1045, 965, 633 cm^{-1}; HRMS (ESI): Exact mass calcd for $C_{20}H_{28}O_5PS$ $[M+H]^+$: 411.1390, Found: 411.1388.

Diethyl ((2,4-dimethoxyphenyl)(4-(dimethylamino)phenyl)methyl)phosphonate (3v): 68 mg, 56% yield, brown oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.82 (dd, *J* = 8.6 Hz, 2.0 Hz, 1H), 7.36 (dd, *J* = 8.8 Hz, 2.0 Hz, 2H), 6.65 (d, *J* = 8.8 Hz, 2H), 6.49 (dd, *J* = 8.8 Hz, 2.4 Hz, 1H), 6.40 (s, 1H), 4.91 (d, *J* = 25.2 Hz, 1H), 4.01-3.92 (m, 2H), 3.89-3.78 (m, 2H), 3.76 (s, 6H), 2.88 (s, 6H), 1.15-1.10 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.5 (d, *J* = 1.0 Hz), 157.5 (d, *J* = 10.0 Hz), 149.3, 130.5 (d, *J* = 5.0 Hz), 130.0 (d, *J* = 8.0 Hz), 125.0, 118.6 (d, *J* = 3.0 Hz), 112.5, 104.1, 98.6, 62.24, 62.17, 55.6, 55.2, 40.5, 40.0 (d, *J* = 140.0 Hz), 16.23 (d, *J* = 2.0 Hz), 16.18 (d, *J* = 3.0 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): δ = 27.2; IR (neat): 3301, 2920, 2854, 1585, 1408, 1240, 1045, 965, 609 cm^{-1}; HRMS (ESI): Exact mass calcd for $C_{21}H_{31}NO_5P$ $[M+H]^+$: 408.1934, Found: 408.1931.

Diethyl ((2,4-dimethoxyphenyl)(p-tolyl)methyl)phosphonate (3w): 57 mg, 50% yield, colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.83-7.81 (m, 1H), 7.40-7.38 (m, 2H), 7.08-7.06 (m, 2H), 6.51-6.48 (m, 1H), 6.41-6.40 (m, 1H), 5.00-4.94 (d, *J* = 25.6 Hz, 1H), 4.01-3.92 (m, 2H), 3.88-3.80 (m, 2H), 3.77 (s, 3H), 3.76 (s, 3H), 2.28 (s, 3H), 1.15-1.10 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.7, 157.5 (d, *J* = 11.0 Hz), 136.2 (d, *J* = 2.0 Hz), 134.2 (d, *J* = 5.0 Hz), 130.6 (d, *J* = 5.0 Hz), 129.3 (d, *J* = 7.0 Hz), 128.9, 118.0 (d, *J* = 3.0 Hz), 104.2, 98.6, 62.4 (d, *J* = 7.0 Hz), 62.2 (d, *J* = 7.0 Hz), 55.5, 55.2, 40.6 (d, *J* = 140.0 Hz), 20.9, 16.2, 16.1; ^{31}P NMR (162 MHz, $CDCl_3$): δ = 27.3; IR (neat): 3440, 3030, 2965, 2850, 1506, 1450, 1232, 1049, 938, 614 cm^{-1}; HRMS (ESI): Exact mass calcd for $C_{20}H_{28}O_5P$ $[M+H]^+$: 379.1669, Found: 379.1664.

Diethyl ((2,4-dimethoxyphenyl)(2-methoxyphenyl)methyl)phosphonate (3x): 63 mg, 53% yield, white solid; Mp: 66-68 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.79 (dt, *J* = 7.6 Hz, 2.0 Hz, 1H), 7.72 (dd, *J* = 8.6 Hz, 2.0 Hz, 1H), 7.19-7.15 (m, 1H), 6.93-6.89 (m, 1H), 6.83-6.81 (m, 1H), 6.46 (dd, *J* = 8.6 Hz, 2.4 Hz, 1H), 6.41-6.40 (m, 1H), 5.62 (d, *J* = 24.8 Hz, 1H), 4.00-3.89 (m, 2H), 3.88-3.82 (m, 2H), 3.80 (s, 3H), 3.78 (s, 3H), 3.75 (s, 3H), 1.15-1.09 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.6 (d, *J* = 2.0 Hz), 158.0 (d, *J* = 10.0 Hz), 157.0 (d, *J* = 9.0 Hz), 131.0 (d, *J* = 5.0 Hz), 130.5 (d, *J* = 5.0 Hz), 127.8 (d, *J* = 2.0 Hz), 126.1 (d, *J* = 4.0 Hz), 120.5 (d, *J* = 2.0 Hz), 118.2 (d, *J* = 4.0 Hz), 110.9, 104.2 (d, *J* = 1.0 Hz), 98.8, 62.3, 62.2 (d, *J* = 7.0 Hz), 55.84 (d, *J* = 2.0 Hz), 55.77 (d, *J* = 2.0 Hz), 55.2 (d, *J* = 2.0 Hz), 32.8 (d, *J* = 141.0 Hz), 16.2, 16.1 (d, *J* = 6.0 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): *δ* 27.1; IR (neat): 3831, 2924, 2852, 1607, 1438, 1241, 1020, 955, 751, 622 cm^{-1}; HRMS (ESI): Exact mass calcd for $C_{20}H_{28}O_6P$ $[M+H]^+$: 395.1618, Found: 395.1615.

Diethyl (bis(2,4-dimethoxyphenyl)methyl)phosphonate (3y): 108 mg, 85% yield, colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.68 (dd, *J* = 8.6 Hz, 2.0 Hz, 2H), 6.43 (dd, *J* = 8.4 Hz, 2.4 Hz, 2H), 6.38 (s, 2H), 5.49 (d, *J* = 25.2 Hz, 1H), 4.00-3.89 (m, 2H), 3.87-3.78 (m, 2H), 3.75 (s, 6H), 3.73 (s, 6H), 1.11 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.4 (d, *J* = 2.0 Hz), 157.8 (d, *J* = 10.0 Hz), 130.8 (d, *J* = 5.0 Hz), 118.3 (d, *J* = 3.0 Hz), 104.0 (d, *J* = 1.0 Hz), 98.6, 62.1, 62.0, 55.7, 55.1, 32.1 (d, *J* = 142.0 Hz), 16.13, 16.07; ^{31}P NMR (162 MHz, $CDCl_3$): *δ* = 27.4; IR (neat): 3830, 2924, 2854, 1607, 1440, 1260, 1045, 955, 761, 649 cm^{-1}; HRMS (ESI): Exact mass calcd for $C_{21}H_{30}O_7P$ $[M+H]^+$: 425.1724, Found: 425.1722.

Diethyl ((2,4-dimethoxyphenyl)(2,4-dimethylphenyl)methyl)phosphonate (3z): 76 mg, 65% yield, brown oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.79-7.77 (m, 1H), 7.67-7.64 (m, 1H), 6.97-6.95 (m, 1H), 6.93 (s, 1H), 6.49-6.46 (m, 1H), 6.40-6.39 (m, 1H), 5.12 (d, *J* = 25.6 Hz, 1H), 4.01-3.91 (m, 2H), 3.89-3.80 (m, 2H), 3.78 (s, 3H), 3.76 (s, 3H), 2.36 (s, 3H), 2.24 (s, 3H), 1.14 (t, *J* = 7.2 Hz, 3H), 1.11 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.6 (d, *J* = 2.0 Hz), 157.5 (d, *J* = 10.0 Hz), 136.6 (d, *J* = 11.0 Hz), 136.1 (d, *J* = 2.0 Hz), 132.6 (d, *J* = 5.0 Hz), 130.9 (d, *J* = 5.0 Hz), 129.4 (d, *J* = 5.0 Hz), 126.6 (d, *J* = 2.0 Hz), 118.1 (d, *J* = 3.0 Hz), 104.2 (d, *J* = 2.0 Hz), 98.4, 62.4, 63.2 (d, *J* = 8.0 Hz), 55.4, 55.2, 36.8 (d, *J* = 141.0 Hz), 20.9, 19.6, 16.3, 16.2 (d, *J* = 7.0 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): *δ* = 27.5; IR (neat): 3500, 3029, 2960, 2850, 1500, 1450, 1240, 1051, 940, 621 cm^{-1}; HRMS (ESI): Exact mass calcd for $C_{21}H_{30}O_5P$ $[M+H]^+$: 393.1825, Found: 393.1820.

Diethyl ((2,4-dimethoxyphenyl)(3,4,5-trimethoxyphenyl)methyl)phosphonate (3za): 94 mg, 80% yield, white solid; Mp: 74-76 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75 (dd, *J* = 8.4 Hz, 2.0 Hz, 1H), 6.74-6.73 (m, 2H), 6.44 (dd, *J* = 8.6 Hz, 2.4 Hz, 1H), 6.40-6.39 (m, 1H), 4.89 (d, *J* = 25.6 Hz, 1H), 3.99-3.82 (m, 4H), 3.78 (s, 6H), 3.75 (s, 3H), 3.74 (s, 3H), 3.73 (s, 3H), 1.11 (t, *J* = 7.2 Hz, 3H), 1.07 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.7 (d, *J* = 1.0 Hz), 157.4 (d, *J* = 10.0 Hz), 152.6 (d, *J* = 1.0 Hz), 136.6 (d, *J* = 2.0 Hz), 132.7 (d, *J* = 4.0 Hz), 130.3 (d, *J* = 5.0 Hz), 117.4 (d, *J* = 43.0 Hz), 106.5 (d, *J* = 8.0 Hz), 104.2, 98.5, 62.4 (d, *J* = 7.0 Hz), 62.2 (d, *J* = 7.0 Hz), 60.5, 55.8 (d, *J* = 1.0 Hz), 55.5 (d, *J* = 2.0 Hz), 55.0 (d, *J* = 2.0 Hz), 40.8 (d, *J* = 140.0 Hz), 16.11, 16.07; ^{31}P NMR (162 MHz, $CDCl_3$): *δ* = 26.3; IR (neat): 3436, 3029, 2965, 2852, 1606, 1454, 1232, 1051, 938, 614 cm^{-1}; HRMS (ESI): Exact mass calcd for $C_{22}H_{32}O_8P$ $[M+H]^+$: 455.1829, Found: 455.1827.

Diethyl ((2,4-dimethoxyphenyl)(4-hydroxy-3,5-dimethylphenyl)methyl)phosphonate (3zb): 116 mg, 85% yield, brown oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.79-7.76 (m, 1H), 7.06 (s, 2H), 6.50-6.47 (m, 1H), 6.41-6.40 (m, 1H), 5.73 (brs, 1H), 4.89 (d, *J* = 25.2 Hz, 1H), 4.00-3.93 (m, 2H), 3.88-3.81 (m, 2H), 3.76 (s, 6H), 2.14 (s, 6H), 1.14 (t, *J* = 7.2 Hz, 3H), 1.11 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.6 (d, *J* = 1.0 Hz), 157.4 (d, *J* = 10.0 Hz), 151.6 (d, *J* = 2.0 Hz), 130.6 (d, *J* = 5.0 Hz), 129.4 (d, *J* = 8.0 Hz), 127.7 (d, *J* = 5.0 Hz), 123.4 (d, *J* = 2.0 Hz), 118.1 (d, *J* = 3.0 Hz), 104.2 (d, *J* = 2.0 Hz), 98.6, 62.4 (d, *J* = 7.0 Hz), 62.3 (d, *J* = 7.0 Hz), 55.18, 55.17, 40.0 (d, *J* = 140.0 Hz), 16.1; ^{31}P NMR (162 MHz, $CDCl_3$): *δ* = 27.0; IR (neat): 3600, 3030, 2950, 2850, 1600, 1420, 1250, 1049, 940, 621 cm^{-1}; HRMS (ESI): Exact mass calcd for $C_{21}H_{30}O_6P$ $[M+H]^+$: 409.1775, Found: 409.1772.

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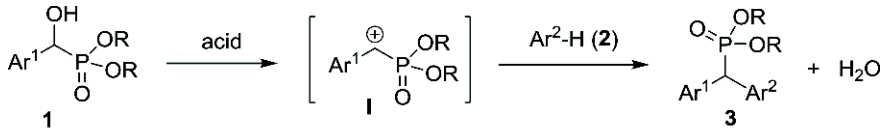
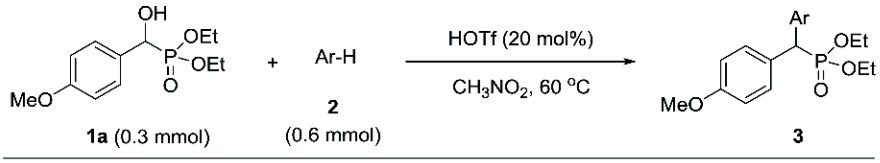
22. We also tried arenes with electronic-withdrawing group such as bromobenzene, chlorobenzene and the simple benzene and found most of α-hydroxyphosphonate **1a** underwent the retro-Pudovik reaction under the strong acid conditions. Meanwhile, due to

the low nucleophilicity of these arenes, the Friedel-Crafts arylation between **1a** and these arenes could hardly proceed, which resulted in no desired arylated product detected.

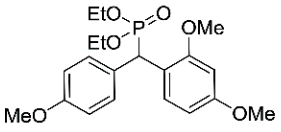


Chakravarty's work: $FeCl_3$ (**1.0 equiv**), Ar^2-H (**3-20.0** equivs), 7 examples, 82-92% yields

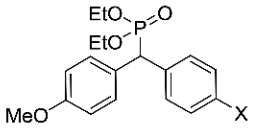
This work: HOTf (**20 mol%**), Ar^2-H (2.0 equivs), 28 examples, 41-95% yields



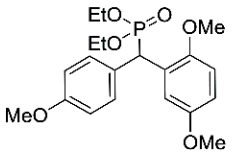
1a (0.3 mmol) **3**



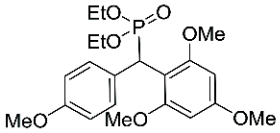
3a, 1 h, 95%



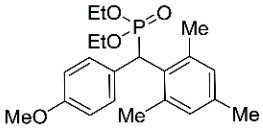
3b, X = OMe, 3.5 h, 80%
3c, X = SMe, 4.0 h, 87%



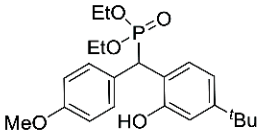
3d, 10 h, 81%



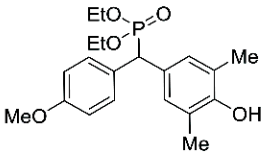
3e, 8.0 h, 90%



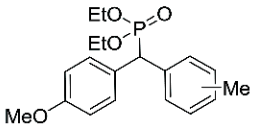
3f, 7.5 h, 89%



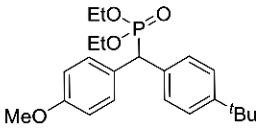
3g, 3.5 h, 63%



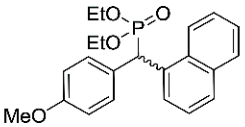
3h, 2.0 h, 86%



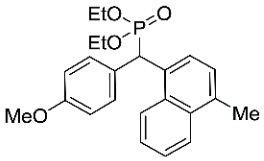
3i, 24.0 h, 56%
(*para*/*ortho* ≈ 90/10)



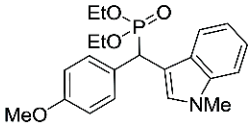
3j, 24.0 h, 50%



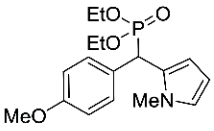
3k, 20.0 h, 80%
(α /β ≈ 75/25)



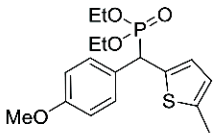
3l, 17.0 h, 85%



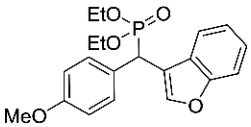
3m, 24.0 h, 53%



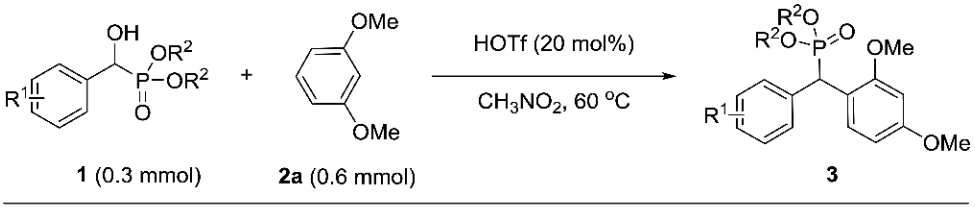
3n, 24.0 h, 41%



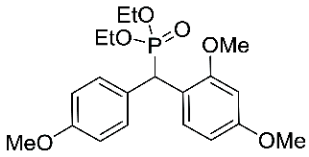
3o, 2.0 h, 86%



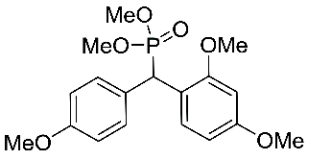
3p, 3.0 h, 91%



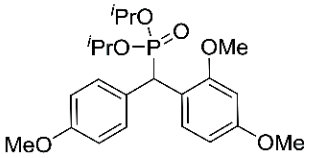
1 (0.3 mmol) **2a** (0.6 mmol) **3**



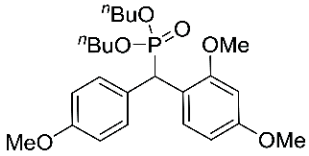
3a, 1 h, 95%



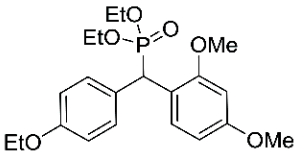
3q, 2.0 h, 70%



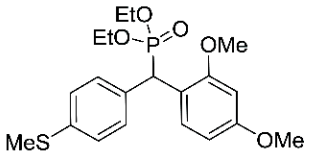
3r, 4.0 h, 71%



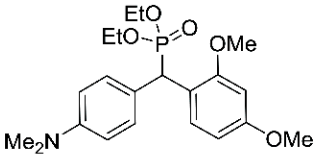
3s, 4.0 h, 81%



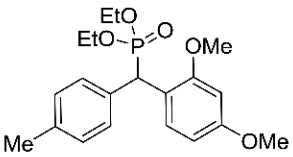
3t, 1.5 h, 88%



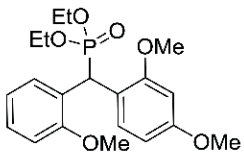
3u, 24.0 h, 80%



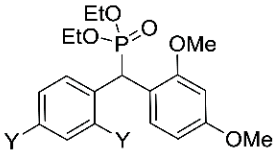
3v, 24.0 h, 56%



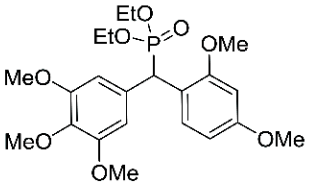
3w, 36.0 h, 50%



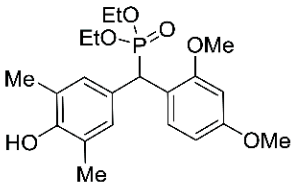
3x, 24.0 h, 53%



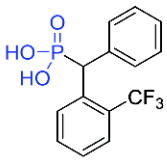
3y, Y = OMe, 1.0 h, 85%
3z, Y = Me, 24.0 h, 65%



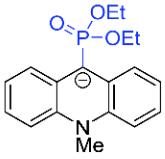
3za, 24 h, 80%



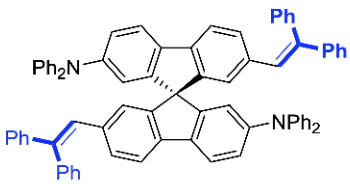
3zb, 1.5 h, 85%



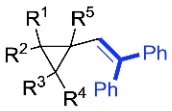
Inhibitor of Human Prostatic Acid Phosphatase



Chemiluminescence



Highly Fluorescent



A potential photoproducts