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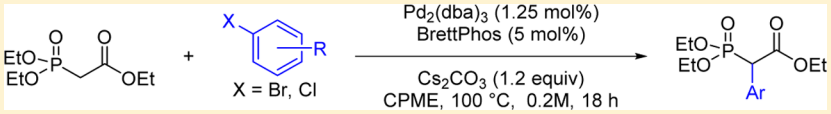
Route to α-Aryl Phosphonoacetates: Useful Synthetic Precursors in the Horner−Wadsworth−Emmons Olefination

Kelsey F. VanGelder, Melinda Wang, and Marisa C. Kozlowski*

Department of Chemistry, Roy and Diana Vagelos Laboratories, University of Pennsylvania, Philadelphia, Pennsylvania 19104-6323, United States

Supporting Information



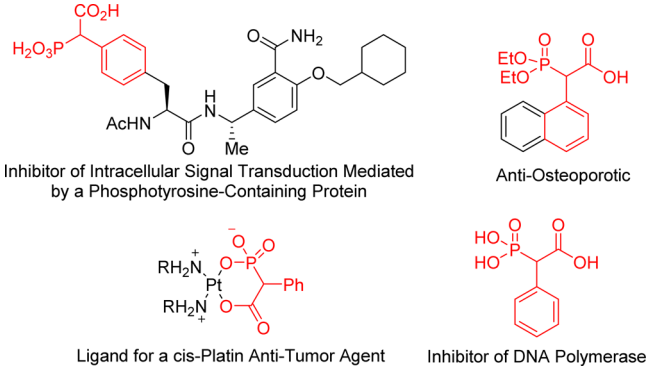
ABSTRACT: A versatile and general catalytic strategy has been developed for the α-arylation of phosphonoacetates utilizing parallel microscale experimentation. These α-substituted phosphonoacetates are widely useful, notably as substrates in the Horner−Wadsworth−Emmons-type olefinations. However, the current routes to these products involve harsh conditions, limiting the variety of functionality. The reported method can be used with a variety of aryl chlorides and aryl bromides, including several heterocyclic examples.

INTRODUCTION

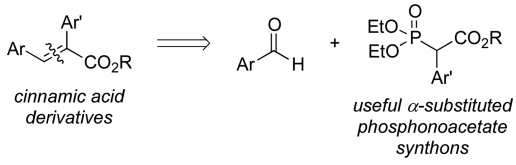
Phosphonates are biologically ubiquitous compounds, with applications in biology and medicine.[1−6] Several such compounds are shown in Scheme 1. Phosphonates and the corresponding phosphonoacetamides can also be useful as peptidomimetics.[7] Phosphonoacetates are also useful synthetic precursors, such as in Horner−Wadsworth−Emmons-type olefinations.[8] Incorporating α-substitution in a stereodefined α,β-unsaturated ester has been a significant limitation to date for this method.[8c,9] There are several valuable natural product cores that can be elaborated using the described α-arylated phosphonoacetates, especially the cinnamic acid core, shown in Scheme 2.[8c] The 2-arylcinnamic acid derivatives have been studied for their antimitotic activity,[10] as well as their activity as endothelin A receptor antagonists.[11] Unfortunately, derivatization has been limited due to an inability to broadly functionalize the α-arene.[8c]

Despite their clear utility, there are few reported methods to synthesize any variety of α-arylated phosphonoacetates.

Scheme 1. Examples of α-Aryl Phosphonoacetates

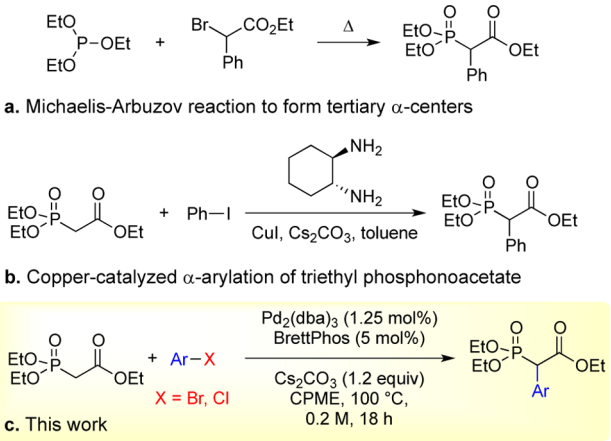


Scheme 2. Elaboration of Biologically Relevant Cinnamic Acids Using α-Aryl Phosphonoacetates



Primarily, these compounds are generated via the Michaelis−Arbuzov reaction, which requires high temperatures and has limited tolerance for sterically hindered substrates (Scheme 3a).[12] This method is also limited by the availability of the α-

Scheme 3. Literature Precedent To Form α-Arylated Phosphonates



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halo-α-aryl acetate starting materials, and the electrophilic functional group tolerance is particularly limited. This approach has been the primary route to elaborated cinnamic acids. The analogous Michaelis–Becker reaction, which uses the corresponding phosphonic acids, proceeds in poor yield, especially for sterically hindered tertiary phosphonoacetates.[12a,b] In addition, strong bases are required to deprotonate the phosphonic acids, which are incompatible with many desirable functional groups. The starting phosphonic acids are also not readily available, which further limits the utility of the method.

An alternative bond disconnection to this structural class utilizes an aryl halide and phosphonoacetate (Scheme 3b,c). There is extensive literature precedent for the α-arylation of acidic substrates to form tertiary centers, using activating functional groups such as esters, ketones, nitro groups, and amides.[13] However, in the literature to date, only the α-arylation of phosphonoacetates using aryl iodides has been reported, and the substrate scope was not thoroughly explored (Scheme 3b).[14−17] Iodobenzene works well in this transformation, but aryl bromides do not couple effectively under the reaction conditions. Since fewer aryl iodides are available relative to the bromo and chloro arenes, we targeted this transformation for study. Notably, Walsh and co-workers recently published the α-arylation of benzyl phosphonates,[18] but we have found that the addition of an acetate coordinating group greatly alters the optimal reaction conditions; such acidic substrates readily form stable chelated adducts with the metal catalyst which are not productive reaction intermediates.[19] In this report, we describe the first intermolecular α-arylation of phosphonoacetates with readily available aryl bromides and chlorides (Scheme 3c).

RESULTS AND DISCUSSION

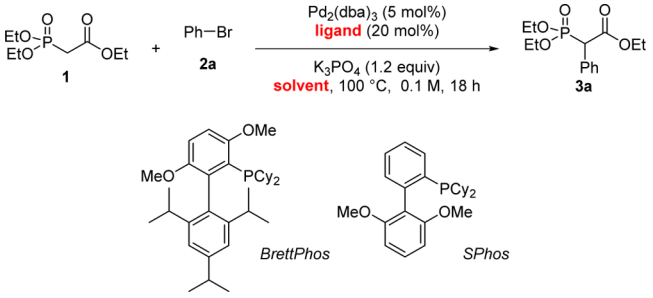
An initial survey of cross-coupling conditions from related acidic substrates[18,19] failed to cause α-arylation of phosphonoacetates. Thus, reaction conditions were investigated utilizing high-throughput parallel microscale experimentation.[20] Using bromobenzene, 12 ligands and eight solvents were evaluated using $Pd_2(dba)_3$ as a palladium source and 1.2 equiv of K_3PO_4. As shown in Table 1, cyclopentyl methyl ether (CPME) was quickly identified as the best solvent for this arylation, and both BrettPhos and SPhos afforded the product in good isolated yield upon 0.2 mmol scale validation of the microscale leads.

Most reactions still had trace starting material remaining at the end of the reaction time. Therefore, different bases were investigated with the goal of increasing conversion. With CPME as a solvent, 12 different bases and the top two ligands were again assessed via parallel microscale experimentation. The top results of that screen were validated on a 0.2 mmol scale and are shown in Table 2.

Overall, reactions using BrettPhos as the ligand had a cleaner reaction profile, and Cs_2CO_3 was the most effective base for the transformation. A further concentration study showed that moving from 0.1 to 0.2 M caused an 11% improvement in the isolated yield of the arylated product **3a**. Proceeding at a 0.2 M reaction concentration, the reactivity of aryl bromides was compared to aryl chlorides. As shown in Table 3, both aryl bromides and aryl chlorides perform well at 2.5 mol % of $Pd_2(dba)_3$. The reactivity of chlorobenzene dropped off at 1.25 mol % of $Pd_2(dba)_3$, but that of bromobenzene was well maintained.

With these conditions in hand, the substrate scope of the reaction was investigated, as shown in Schemes 4 and 5. Both electron-poor and electron-rich substrates are well-tolerated, as are several heterocyclic substrates. Nitrogenous heterocycles (**3j,n−o,q−r**) generally did not perform well in the reaction unless the nitrogen basicity was moderated, as with substrates **3n** and **3o**. Aryl halides with *ortho*-substituents did not perform well in the coupling (**3e**); presumably, the steric bulk of the *ortho*-group upon coordination to the palladium center hinders transmetalation or reductive elimination. Notably, substrates with electrophilic functional groups (**3g**) are coupled in high yield. This arylated product was previously unattainable via reported methods. Additionally, only **3a**, **3k**, and **3l** in Schemes 4 and 5 can be synthesized via the Arbuzov reaction from commercially available starting materials.[21] Both aryl chlorides

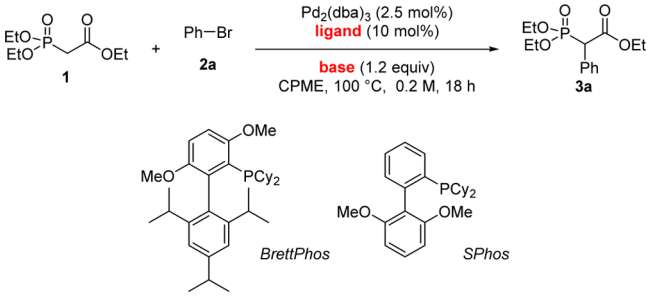
Table 1. High-Throughput Screen Validation of Ligand and Solvent



entry[a]	ligand	solvent	product/IS[b]	isolated yield (%)
1	BrettPhos	CPME	2.004	84
2	SPhos	CPME	2.013	83
3	BrettPhos	trifluorotoluene	2.031	78
4	BrettPhos	toluene	2.435	75
5	CataCXium POMetB	toluene	1.940	74
6	CataCXium POMetB	CPME	2.025	39

[a]Reactions were conducted at 100 °C and 0.1 M in solvent, with 5 mol % of $Pd_2(dba)_3$, 20 mol % of ligand, 1.2 equiv f base, and 1.1 equiv of bromobenzene. [b]Product to internal standard ratio from HTE screening.

Table 2. Ligand and Base Screening for the α-Arylation of Triethyl Phosphonoacetate with Bromobenzene



entry[a]	ligand	base	product/IS[b]	isolated yield (%)
1	BrettPhos	Cs_2CO_3	2.716	80
2	BrettPhos	K_3PO_4	2.361	75
3	SPhos	Cs_2CO_3	3.149	74
4	SPhos	K_3PO_4	3.325	70

[a]Reactions were conducted at 100 °C and 0.2 M in CPME, with 2.5 mol % of $Pd_2(dba)_3$, 10 mol % of ligand, 1.2 equiv of base, and 1.1 equiv of bromobenzene. [b]Product to internal standard ratio from HTE screening.

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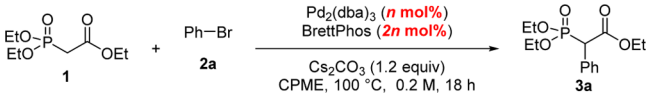
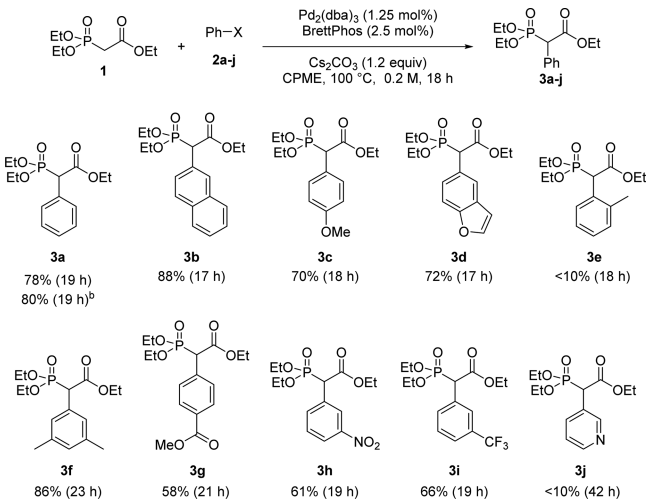
Table 3. Comparison of Chlorobenzene and Bromobenzene at Lower Catalyst Loadings



entry[a]	Ar−X	$Pd_2(dba)_3$ (mol %)	time (h)	isolated yield (%)
1	Ph−Br	2.5	19	80
2	Ph−Br	1.25	19	78
3	Ph−Cl	2.5	17	83
4	Ph−Cl	1.25	17	55

[a]Reactions were conducted at 100 °C in CPME, in a 2:1 ligand:metal ratio, with 1.2 equiv Cs_2CO_3, and 1.1 equiv aryl halide.

Scheme 4. Substrate Scope of the α-Arylation of Triethyl Phosphonoacetate with Aryl Bromides[a]



[a]Reactions were conducted at 100 °C in CPME with 1.25 mol % of $Pd_2(dba)_3$, 5 mol % of BrettPhos, 1.2 equiv of Cs_2CO_3, and 1.1 equiv of aryl bromide. [b]Reactions were conducted at 100 °C in CPME with 2.5 mol % of $Pd_2(dba)_3$, 10 mol % of BrettPhos, 1.2 equiv of Cs_2CO_3, and 1.1 equiv of aryl bromide.

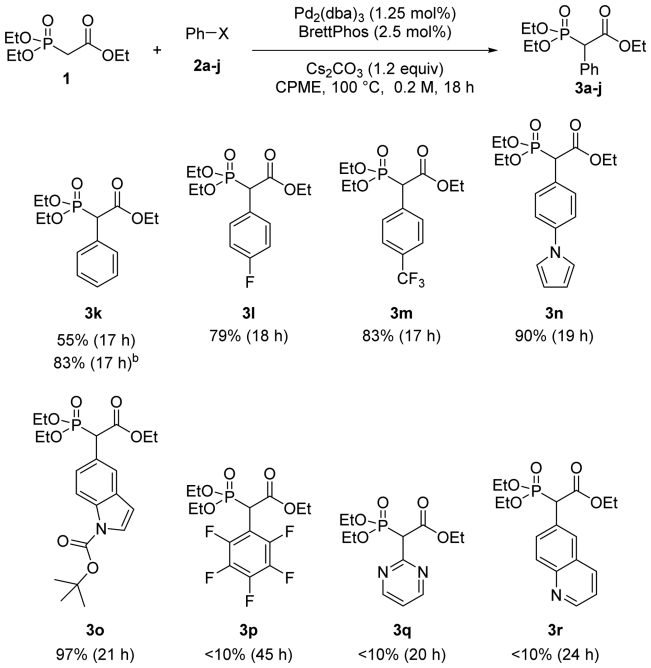
and aryl bromides are well-tolerated for a diverse array of functional groups.

We next set out to test the scalability of the reaction. As shown in Scheme 6, on a 5.0 mmol scale, this previously unreport α-arylated phosphonoacetate was able to be isolated in 80% yield.

We propose a mechanism for this transformation similar to those proposed for the α-arylations of other enolic substrates. In this case, however, the palladium can chelate to the phosphonate or the ester, as shown in Scheme 7. The different chelation modes are shown in structures **C**, **D**, and **E**. As proposed by Culkin and Hartwig, reductive elimination likely occurs from the κ^1-C-bound structure (**C**), which is accessible only in the presence of bulky ligands on the transition metal.[13a,22] The increased stability of the chelated form **D** presents the key challenge to this method, causing the reductive elimination step to be comparatively slow.

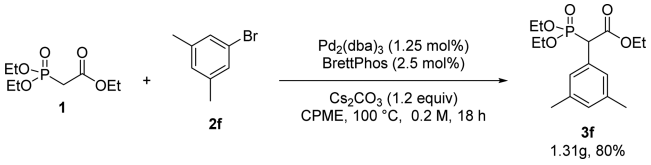
We have also begun to investigate whether this reaction can be applied to quaternary centers, a much more challenging C−C bond construction. As shown in Scheme 8, a quaternary α-arylated product, **5**, could be achieved in an unoptimized 50% yield.

Scheme 5. Substrate Scope of the α-Arylation of Triethyl Phosphonoacetate with Aryl Chlorides[a]

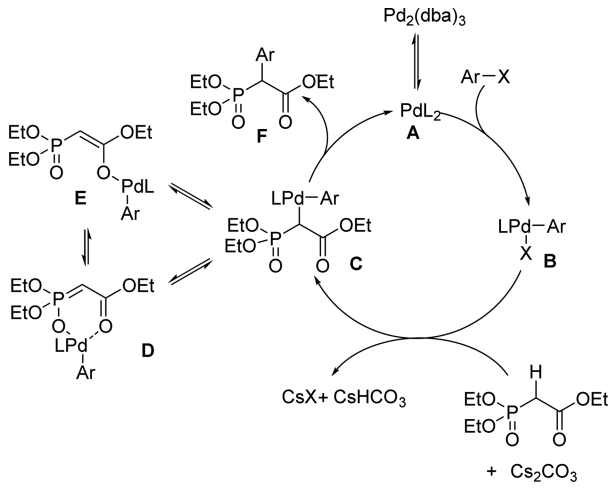


[a]Reactions were conducted at 100 °C in CPME, with 1.25 mol % of $Pd_2(dba)_3$, 5 mol % of BrettPhos, 1.2 equiv of Cs_2CO_3, and 1.1 equiv of aryl chloride. [b]Reactions were conducted at 100 °C in CPME, with 2.5 mol % of $Pd_2(dba)_3$, 10 mol % of BrettPhos, 1.2 equiv of Cs_2CO_3, and 1.1 equiv of aryl chloride.

Scheme 6. Large Scale Cross-Coupling



Scheme 7. Proposed Mechanism for the α-Arylation of Phosphonoacetates



In conclusion, a robust method for the α-arylation of phosphonoacetates has been developed. The method provides an efficient route to complex arylated products that are not

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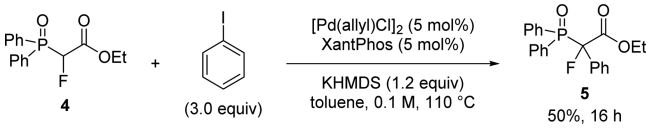
Scheme 8. Unoptimized Conditions for the α-Arylation of Phosphine Oxides to Form Quaternary Centers



otherwise accessible. This process can be utilized for a variety of functionalized aryl bromides and aryl chlorides to afford these highly useful compounds in good to excellent yields.

EXPERIMENTAL SECTION

I. General Information. Unless otherwise noted, all reagents were reagent grade and used without further purification. Cyclopentyl methyl ether (CPME) and toluene were distilled over CaH_2 and stored under argon. Flash column chromatography was performed using silica gel 60 (230−400). Analytical thin-layer chromatography (TLC) was performed using 0.25 mm silica gel 254-F plates. Visualization was accomplished with UV light and/or potassium permanganate stain. ^{1}H NMR and ^{13}C NMR spectra were recorded at 25 °C on 300, 360, or 500 MHz spectrometers. ^{31}P NMR spectra were recorded at 25 °C on 300 or 360 MHz spectrometers and are proton decoupled. Chemical shifts are reported relative to the solvent resonance peak δ 7.27 ($CDCl_3$) for ^{1}H and δ 77.23 ($CDCl_3$) for ^{13}C. For ^{19}F spectra, chemical shifts are reported relative to a capillary internal standard of δ −76.55 (trifluoroacetic acid). For ^{31}P spectra, chemical shifts are reported relative to a capillary internal standard δ 0 (H_3PO_4). Peaks are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, bs = broad singlet, m = multiplet), coupling constants, and number of protons. High-resolution mass spectra were obtained using a TOF mass analyzer in ESI ionization mode. All yields refer to isolated yields, and product purity was determined by ^{1}H NMR spectroscopy.

II. General Procedure for the Synthesis of α-Aryl Phosphonoacetates 3. In a glovebox, a flame-dried microwave vial containing a magnetic stir bar was charged with Cs_2CO_3 (78 mg, 0.24 mmol), $Pd_2(dba)_3$ (2.3 mg, 0.0025 mmol), BrettPhos (5.8 mg, 0.01 mmol), and the aryl halide (**2**) (if a solid) (0.22 mmol). The vial was capped and brought out of the glovebox. CPME was added via syringe, followed by the aryl halide (**2**) (if a liquid) (0.22 mmol) and triethyl phosphonoacetate (**1**) (40 μL, 0.20 mmol). The vial was sparged with dry argon and then heated to 100 °C in an oil bath with vigorous stirring. Upon consumption of the triethyl phosphonoacetate, as monitored by TLC, ^{1}H, or ^{31}P NMR, the reaction mixture was allowed to cool to room temperature and then quenched with 1.0 mL of 1.0 M HCl. This mixture was diluted with H_2O and extracted with EtOAc (3 × 15 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The resulting residue was purified by flash column chromatography to afford the pure α-arylated phosphonoacetates.

*Ethyl 2-(Diethoxyphosphoryl)-2-phenylacetate (Aryl Bromide) (**3a**).* The general method was followed with a reaction time of 19 h. Purification by chromatography (50% EtOAc/hexanes) provided the title compound as a pale yellow oil (47 mg, 78%). All spectra were in agreement with the published literature values.[8c,23]

*Ethyl 2-(Diethoxyphosphoryl)-2-(naphthalen-2-yl)acetate (Aryl Bromide) (**3b**).* The general method was followed with a reaction time of 17 h. Purification by chromatography (60% EtOAc/hexanes) provided the title compound as a yellow solid (62 mg, 88%): mp 65−67 °C; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.99 (m, 1H), 7.86−7.82 (m, 3H), 7.68 (ddd, J = 8.6 Hz, 1.6 Hz, 1.4 Hz, 1H), 7.50−7.47 (m, 2H), 4.43 (d, J_{H-P} = 23.4 Hz, 1H), 4.31−3.97 (m, 6H), 1.29 (t, J = 6.8 Hz, 3H), 1.28 (t, J = 6.7 Hz, 3H), 1.20 (t, J = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (125.7 MHz, $CDCl_3$) δ 167.7 (d, J = 1.5 Hz), 133.2 (d, J = 1.5 Hz), 133.8, 128.81, 128.75, 128.5 (d, J = 5.3 Hz), 128.1 (d, J = 0.9 Hz), 128.0, 127.6, 127.3 (d, J = 5.0 Hz), 126.2 (d, J = 3.8 Hz), 63.4 (d, J = 6.3 Hz), 63.1 (d, J = 7.5 Hz), 61.8, 52.4 (d, J = 134.6 Hz), 16.3 (d, J = 6.3 Hz), 16.2 (d, J = 6.3 Hz), 14.1; ^{31}P{^{1}H} NMR (145.8 MHz, $CDCl_3$) δ 19.10 (s); IR (neat) 3058, 2988, 2940, 1733, 1300, 1253, 1050, 1026 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{23}O_5PNa$ $[M + Na]^+$ m/z = 373.1181, found 373.1189.

*Ethyl 2-(Diethoxyphosphoryl)-2-(4-methoxyphenyl)acetate (Aryl Bromide) (**3c**).* The general method was followed with a reaction time of 18 h. Purification by chromatography (60% EtOAc/hexanes) provided the title compound as a yellow oil (46 mg, 70%). All spectra were in agreement with published literature values.[8c,23]

*Ethyl 2-(Benzofuran-5-yl)-2-(diethoxyphosphoryl)acetate (Aryl Bromide) (**3d**).* The general method was followed with a reaction time of 17 h. Purification by chromatography (60% EtOAc/hexanes) provided the title compound as a yellow oil (49 mg, 72%): ^{1}H NMR (300.1 MHz, $CDCl_3$) δ 7.81 (m, 1H), 7.62 (d, J = 2.2 Hz, 1H), 7.49−7.42 (m, 2H), 6.77−6.76 (m, 1H), 4.34 (d, J_{H-P} = 23.5 Hz, 1H), 4.32−3.89 (m, 6H), 1.283 (t, J = 7.1 Hz, 3H), 1.276 (t, J = 7.1 Hz, 3H), 1.19 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (90.6 MHz, $CDCl_3$) δ 168.2, 154.8, 145.7, 127.9, 126.1 (d, J = 6.3 Hz), 125.6 (d, J = 8.1 Hz), 122.6 (d, J = 6.7 Hz), 111.5, 106.9, 63.5 (d, J = 6.8 Hz), 63.3 (d, J = 7.1 Hz), 62.0, 52.2 (d, J = 135.8 Hz), 16.5 (d, J = 5.8 Hz), 16.4 (d, J = 5.8 Hz), 14.2; ^{31}P{^{1}H} NMR (121.5 MHz, $CDCl_3$) δ 18.04 (s); IR (neat) 2985, 2930, 1733, 1468, 1446, 1256, 1050, 1026 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{21}O_6PNa$ $[M + Na]^+$ m/z = 363.0973, found 363.0975.

*Ethyl 2-(Diethoxyphosphoryl)-2-(3,5-dimethylphenyl)acetate (Aryl Bromide) (**3f**).* The general method was followed with a reaction time of 23 h. Purification by chromatography (40% EtOAc/hexanes) provided the title compound as a pale oil (56.3 mg, 86%): ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.12 (s, 2H), 6.94 (s, 1H), 4.30−3.97 (m, 7H), 2.31 (s, 6H), 1.28 (t, J = 7.2 Hz, 6H), 1.22 (t, J = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (90.6 MHz, $CDCl_3$) δ 167.8, 138.0 (d, J = 1.8 Hz), 130.6 (d, J = 8.1 Hz), 129.6 (d, J = 3.6 Hz), 127.3 (d, J = 6.3 Hz), 63.3 (d, J = 7.2 Hz), 63.1 (d, J = 7.2 Hz), 61.7, 52.1 (d, J = 134.9 Hz), 21.3, 16.3 (d, J = 5.9 Hz), 16.2 (d, J = 5.9 Hz), 14.0; ^{31}P{^{1}H} NMR (145.8 MHz, $CDCl_3$) δ 19.47 (s); IR (neat) 2985, 2928, 1735, 1602, 1256, 1051, 1024, 733 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{26}O_5P$ $[M + H]^+$ m/z = 329.1518, found 329.1516.

*Methyl 4-(1-(Diethoxyphosphoryl)-2-ethoxy-2-oxoethyl)-benzoate (Aryl Bromide) (**3g**).* The general method was followed with a reaction time of 21 h. Purification by chromatography (50% EtOAc/hexanes) provided the title compound as a pale yellow oil (41.6 mg, 58%): ^{1}H NMR (360 MHz, $CDCl_3$) δ 8.01 (d, J = 8.3 Hz, 2H), 7.60 (dd, J = 8.6 Hz, 2.2 Hz, 2H), 4.31 (d, J_{H-P} = 23.8 Hz, 1H), 4.28−3.96 (m, 6H), 3.91 (s, 3H), 1.27 (t, J = 7.0 Hz, 3H), 1.26 (t, J = 7.0 Hz, 3H), 1.20 (t, J = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (90.6 MHz, $CDCl_3$) δ 167.1 (d, J = 3.6 Hz), 166.7, 136.2, 136.1, 129.73, 129.66, 63.5 (d, J = 7.2 Hz), 63.3 (d, J = 7.2 Hz), 62.0, 52.4 (d, J = 133.1 Hz), 52.1, 16.3 (d, J = 4.8 Hz), 16.2 (d, J = 4.8 Hz), 14.0; ^{31}P{^{1}H} NMR (145.8 MHz, $CDCl_3$) δ 18.44 (s); IR (neat) 2984, 2910, 1724, 1279, 1257, 1021, 734 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{23}O_7P$ $[M + Na]^+$ m/z = 381.1079, found 381.1085

*Ethyl 2-(Diethoxyphosphoryl)-2-(3-nitrophenyl)acetate (Aryl Bromide) (**3h**).* The general method was followed with a reaction time of 19 h. Purification by chromatography (60% EtOAc/hexanes) provided the title compound as a pale oil (42.3 mg, 61%). All reported spectra were in agreement with published literature values:[24] IR (neat) 2984, 2940, 1735, 1532, 1025, 735 cm^{-1}.

*Ethyl 2-(Diethoxyphosphoryl)-2-(3-(trifluoromethyl)phenyl)-acetate (Aryl Bromide) (**3i**).* The general method was followed with a reaction time of 19 h. Purification by chromatography (40% EtOAc/hexanes) provided the title compound as a pale oil (48.5 mg, 66%): ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.78 (m, 1H), 7.75−7.73 (m, 1H), 7.59−7.57 (m, 1H), 7.47 (dd, J = 7.8 Hz, 7.8 Hz, 1H), 4.32−4.00 (m, 6H), 4.30 (d, J_{H-P} = 24.1 Hz, 1H), 1.29 (t, J = 7.2 Hz, 3H), 1.27 (t, J = 7.2 Hz, 3H), 1.21 (t, J = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (125.8 MHz, $CDCl_3$) δ 167.3 (d, J = 5.0 Hz), 133.3 (d, J = 6.3 Hz), 132.4 (d, J = 8.8 Hz), 131.0 (dq, J = 32.1 Hz, 1.9 Hz), 129.1 (d, J = 2.5 Hz), 126.8−126.6 (m), 125.0−124.9 (m), 124.1 (q, J_{C-F} = 272.1 Hz), 63.8 (d, J = 6.3 Hz), 63.5 (d, J = 7.5 Hz), 62.3, 52.2 (d, J = 134.6 Hz), 16.4 (d, J = 6.3 Hz), 16.3 (d, J = 6.3 Hz), 14.2; ^{31}P{^{1}H} NMR (145.8 MHz, $CDCl_3$) δ 18.30 (s); IR (neat) 2987, 2938, 1736, 1330, 1026, 736

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cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{20}F_3O_5P$ $[M + H]^+$ m/z = 369.1079, found 369.1080.

*Ethyl 2-(Diethoxyphosphoryl)-2-phenylacetate (Aryl Chloride) (**3k**).* In a glovebox, a flame-dried microwave vial containing a magnetic stir bar was charged with Cs_2CO_3 (78 mg, 0.24 mmol), $Pd_2(dba)_3$ (4.6 mg, 0.005 mmol), and BrettPhos (11.6 mg, 0.02 mmol). The vial was capped and brought out of the glovebox. CPME was added via syringe followed by chlorobenzene (**2k**) (22 μL, 0.22 mmol) and triethyl phosphonoacetate (**1**) (40 μL, 0.20 mmol). The vial was sparged with dry argon and then heated to 100 °C in an oil bath with vigorous stirring. Upon consumption of the triethyl phosphonoacetate, as monitored by TLC, ^1H, or ^{31}P NMR, the reaction mixture was allowed to cool to room temperature and then quenched with 1.0 mL of 1.0 M HCl. The resultant mixture was diluted with H_2O and extracted with EtOAc (3 × 15 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. Purification by chromatography (50% EtOAc/hexanes) provided the title compound as a pale yellow oil (49.8 mg, 83%). All spectra were in agreement with the published literature values.[8c,23]

*Ethyl 2-(Diethoxyphosphoryl)-2-(4-fluorophenyl)acetate (Aryl Chloride) (**3l**).* The general method was followed with a reaction time of 18 h. Purification by chromatography (60% EtOAc/hexanes) provided the title compound as a pale yellow oil (50.1 mg, 79%). All reported spectra were in agreement with the published literature values:[25] $^{31}P\{^1H\}$ NMR (145.8 MHz, $CDCl_3$) δ 18.85 (d, J = 12.6 Hz); IR (neat) 2985, 2936, 1735, 1509, 1050, 1026, 735 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{20}FO_5PNa$ $[M + Na]^+$ m/z = 341.0930, found 341.0923.

*Ethyl 2-(Diethoxyphosphoryl)-2-(4-(trifluoromethyl)phenyl)-acetate (Aryl Chloride) (**3m**).* The general method was followed with a reaction time of 17 h. Purification by chromatography (60% EtOAc/hexanes) provided the title compound as a pale yellow oil (61.1 mg, 83%): ^1H NMR (300 MHz, $CDCl_3$) δ 7.68−7.60 (m, 4H), 4.33−3.96 (m, 6H), 4.31 (d, J_{H-P} = 23.7 Hz, 1H), 1.29 (t, J = 7.1 Hz, 3H), 1.28 (t, J = 7.1 Hz, 3H), 1.22 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (125.8 MHz, $CDCl_3$) δ 167.2 (d, J = 3.8 Hz), 135.4 (d, J = 8.8 Hz), 130.4 (dq, J = 32.7 Hz, J_{C-F} = 2.5 Hz), 130.2 (d, J = 6.3 Hz), 125.6−125.5 (m), 124.2 (q, J_{C-F} = 272.5 Hz), 63.8 (d, J = 7.5 Hz), 63.5 (d, J = 6.3 Hz), 62.3, 52.3 (d, J = 133.3 Hz), 16.5 (d, J = 6.9 Hz), 16.4 (d, J = 6.9 Hz), 14.2; $^{31}P\{^1H\}$ NMR (145.8 MHz, $CDCl_3$) δ 18.03 (s); IR (neat) 2985, 2936, 1736, 1325, 1020, 736 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{21}F_3O_5P$ $[M + H]^+$ m/z = 369.1079, found 369.1071.

*Ethyl 2-(4-(1H-Pyrrol-1-yl)phenyl)-2-(diethoxyphosphoryl)acetate (Aryl Chloride) (**3n**).* The general method was followed with a reaction time of 19 h. Purification by chromatography (60% EtOAc/hexanes) provided the title compound as a pale yellow oil (65.6 mg, 90%): ^1H NMR (300.1 MHz, $CDCl_3$) δ 7.59 (dd, J = 8.7 Hz, 2.3 Hz, 2H), 7.39 (d, J = 8.3 Hz, 2H), 7.10 (dd, J = 2.2 Hz, 2.2 Hz, 2H), 6.35 (dd, J = 2.1 Hz, 2.1 Hz, 2H), 4.34−3.96 (m, 6H), 4.27 (d, J_{H-F} = 23.8 Hz, 1H), 1.304 (t, J = 7.1 Hz, 3H), 1.295 (t, J = 7.1 Hz, 3H), 1.23 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (125.8 MHz, $CDCl_3$) δ 167.5 (d, J = 3.8 Hz), 140.4, 130.8 (d, J = 6.3 Hz), 128.2 (d, J = 7.5 Hz), 120.3 (d, J = 2.5 Hz), 119.1, 110.6, 63.4 (d, J = 6.3 Hz), 63.2 (d, J = 6.3 Hz), 51.6 (d, J = 133.3 Hz), 16.31 (d, J = 6.3 Hz), 16.26 (d, J = 6.3 Hz), 14.03; $^{31}P\{^1H\}$ NMR (121.5 MHz, $CDCl_3$) δ 18.79 (s); IR (neat) 3054, 2984, 2930, 1733, 1521, 1265, 735 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{25}NO_5P$ $[M + H]^+$ m/z = 366.1470, found 366.1472.

*tert-Butyl-5-(1-(Diethoxyphosphoryl)-2-ethoxy-2-oxoethyl)-1H-indole-1-carboxylate (Aryl Chloride) (**3o**).* The general method was followed with a reaction time of 21 h. Purification by chromatography (40% EtOAc/hexanes) provided the title compound as a pale yellow oil (85.6 mg, 97%): ^1H NMR (500 MHz, $CDCl_3$) δ 8.10 (d, J = 8.0 Hz, 1H), 7.75 (dd, J = 2.0 Hz, 2.0 Hz, 1H), 7.59 (d, J = 3.5 Hz, 1H), 7.44 (ddd, J = 8.6 Hz, 1.9 Hz, 1.9 Hz, 1H), 6.56 (d, J = 3.5 Hz, 1H), 4.33 (d, J_{H-P} = 23.0 Hz, 1H), 4.28−3.91 (m, 6H), 1.67 (s, 9H), 1.270 (t, J = 7.0 Hz, 3H), 1.268 (t, J = 7.0 Hz, 3H), 1.19 (t, J = 7.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (125.8 MHz, $CDCl_3$) δ 168.2 (d, J = 1.8 Hz), 149.8, 135.0, 130.9, 126.6, 125.9 (d, J = 4.3 Hz), 125.3 (d, J = 6.1 Hz), 122.3 (d, J = 5.0 Hz), 115.3, 107.5, 84.0, 63.6 (d, J = 4.5 Hz), 63.2 (d, J = 4.5 Hz), 61.9, 52.2 (d, J = 97.8 Hz), 28.3, 16.52 (d, J = 5.7 Hz), 16.48 (d, J = 5.7 Hz), 14.2; $^{31}P\{^1H\}$ NMR (145.8 MHz, $CDCl_3$) δ 19.58 (s); IR (neat) 2981, 2934, 1733, 1024, 731 cm^{-1}; HRMS (ESI) calcd for $C_{21}H_{31}NO_7P$ $[M + H]^+$ m/z = 440.1838, found 440.1823.

Large-Scale Reaction: Ethyl 2-(Diethoxyphosphoryl)-2-(3,5-dimethylphenyl)acetate (Aryl Bromide) (3f). In a glovebox, a flame-dried Schlenk flask containing a magnetic stir bar was charged with Cs_2CO_3 (1.95 g, 6.0 mmol), $Pd_2(dba)_3$ (57.2 mg, 0.0625 mmol), and BrettPhos (134.2 mg, 0.25 mmol. The flask was sealed and brought out of the glovebox. CPME (25 mL) was added, followed by 3,5-dimethylbromobenzene (657 μL, 5.5 mmol) and triethyl phosphonoacetate (**1**) (992 μL, 5.0 mmol). The flask was heated to 85 °C in an oil bath with vigorous stirring. Upon consumption of the triethyl phosphonoacetate, as monitored by TLC, the reaction mixture was allowed to cool to room temperature and then quenched with 25 mL of 1.0 M HCl. This mixture was diluted with H_2O and extracted with EtOAc (3 × 15 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The resulting residue was purified by flash column chromatography (40% EtOAc/hexanes) to provide the title compound as a pale oil (1.31g, 80%).

*Ethyl 2-(Diphenylphosphoryl)-2-fluoroacetate (**4**).* Under an argon atmosphere, a round-bottom flask containing a magnetic stir bar and equipped with a reflux condenser was charged with ethoxydiphenylphosphane.[26] Ethyl 2-bromo-2-fluoroacetate was charged, and the reaction was heated to reflux. After 4.5 h, the reaction was cooled. The resulting residue was purified by flash column chromatography (50% EtOAc/hexanes) to afford the title compound as a white powder (10.28 g, 38%, unoptimized): mp 146−147 °C; ^1H NMR (499.7 MHz, $CDCl_3$) δ 7.92−7.84 (m, 4H), 7.65−7.60 (m, 2H), 7.56−7.52 (m, 4H), 5.70 (dd, J_{H-P} = 8.0 Hz, J_{H-F} = 47.0 Hz, 1H), 4.91 (q, J = 7.2 Hz, 2H), 1.11 (t, J = 7.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (125.7 MHz, $CDCl_3$) δ 165.2 (d, J = 22.0 Hz), 133.3 (d, J = 2.8 Hz), 133.1 (d, J = 2.9 Hz), 132.1 (d, J = 2.0 Hz), 132.04 (d, J = 2.9 Hz), 131.96 (d, J = 2.9 Hz), 131.88 (d, J = 1.8 Hz), 129.0 (d, J = 14.8 Hz), 128.9 (d, J = 14.8 Hz), 88.5 (dd, J_{C-P} = 70.5 Hz, J_{C-F} = 203.6 Hz), 62.6, 14.1; $^{19}F\{^1H\}$ NMR (282.4 MHz, $CDCl_3$) δ −202.2 (d, J_{F-P} = 59.3 Hz); $^{31}P\{^1H\}$ NMR (145.8 MHz, $CDCl_3$) δ 26.3 (d, J_{P-F} = 57.7 MHz); IR (neat) 3058, 2924, 1756, 1246, 1190, 1071, 698 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{17}O_3FP$ $[M + H]^+$ m/z = 307.0899, found 307.0902.

*Ethyl 2-(Diphenylphosphoryl)-2-fluoro-2-phenylacetate (**5**).* In a glovebox, a flame-dried microwave vial containing a magnetic stir bar was charged with KHMDS (47.9 mg, 0.24 mmol), $[Pd(allyl)Cl]_2$ (3.7 mg, 0.01 mmol), XantPhos (5.8 mg, 0.01 mmol), and ethyl 2-(diphenylphosphoryl)-2-fluoroacetate (**4**) (61.3 mg, 0.2 mmol). The vial was capped and brought out of the glovebox. Toluene was added via syringe followed by iodobenzene (0.6 mmol). The vial was then heated to 110 °C in an oil bath with vigorous stirring. After 16 h, the reaction mixture was allowed to cool to room temperature and then quenched with 1.0 mL of pH = 7 phosphate buffer. This mixture was diluted with H_2O and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The resulting residue was purified by flash column chromatography (50% EtOAc/hexanes) to afford the title compound as a pale yellow oil (38.3 mg, 50%): ^1H NMR (500 MHz, $CDCl_3$) δ 8.14−8.1 (m, 2H), 7.7−7.63 (m, 3H), 7.59−7.56 (m, 2H), 7.50−7.46 (m, 3H), 7.37−7.3 (m, 5H), 4.1 (q, J = 7.0 Hz, 2H), 1.0 (t, J = 7.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (125.8 MHz, $CDCl_3$) δ 166.5 (dd, J = 4.6 Hz, 23.8 Hz), 133.0 (d, J = 2.8 Hz), 132.7 (d, J = 1.9 Hz), 132.6 (d, J = 2.1 Hz), 132.4 (dd, J = 3.3 Hz, 8.8 Hz), 131.7 (d, J = 20.7 Hz), 131.1, 129.1, 129.0, 128.9 (d, J = 12.1 Hz), 128.3, 128.2, 128.1, 125.8 (dd, J = 2.9 Hz, 10.2 Hz), 62.9, 13.9; $^{19}F\{^1H\}$ NMR (338.9 MHz, $CDCl_3$) δ −169.4 (d, J_{F-P} = 74.5 Hz); $^{31}P\{^1H\}$ NMR (145.8 MHz, $CDCl_3$) δ 27.5 (d, J_{P-F} = 74.4 MHz); IR (neat) 3057, 1750, 1591, 1265, 1246, 1206, 1116 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{20}O_3FPNa$ $[M + Na]^+$ m/z = 405.1032, found 405.1050.

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■ ASSOCIATED CONTENT

Supporting Information

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Experimental procedures and tabulated results of high-throughput experiments; ^{1}H, ^{13}C, ^{19}F, and ^{31}P NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: marisa@sas.upenn.edu.

Notes

The authors declare no competing financial interest.

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