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Electrophilic Fluorination of Secondary Phosphine Oxides and Its Application to P–O Bond Construction

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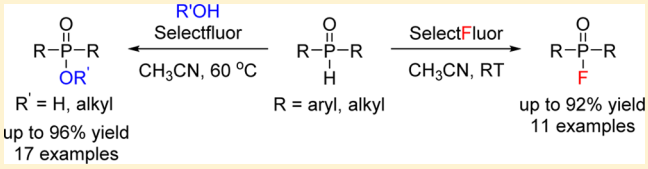
Supporting Information

ABSTRACT: A novel and efficient electrophilic fluorination of secondary phosphine oxides with Selectfluor has been achieved. This transformation provides direct access to phosphoric fluorides in up to 92% yield under mild conditions. In addition, P–O bond construction via a one-pot coupling process of secondary phosphine oxides with water or alcohols in the presence of Selectfluor leads to the formation of phosphinic acids or phosphinates in up to 96% yield.

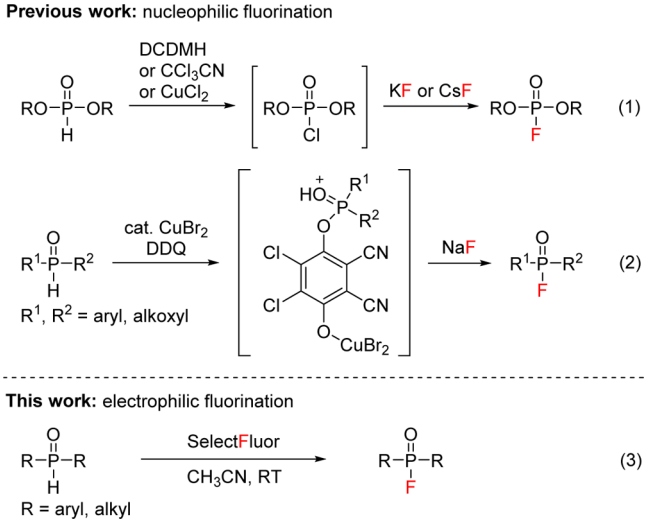


Organophosphorus compounds bearing a P–F bond have been of general interest due to their particular applications in enzymatic reactions as mechanistic probes or potent inhibitors.[1−5] A variety of methods for P–F bond construction from various phosphoric substrates using special fluorinating reagents have been reported, while harsh reaction conditions, toxic, expensive, unstable, and moisture-sensitive reagents or long reaction times are generally required.[6] The nucleophilic fluorination of P(O)–H compounds using fluoride ions as fluoride sources are popularly used for constructing P–F bonds (Scheme 1). Kaushik, Dubey, and co-workers reported a one-pot synthesis of dialkyl fluorophosphates via in situ formation of dialkyl chlorophosphates from dialkyl phosphites with dichlorodimethylhydantoin–KF, trichloroacetonitrile–KF, or $CuCl_2$–CsF as the fluorinating reagent (eq 1).[7] Recently, Yang and co-workers developed an efficient copper-promoted oxidative-fluorination of P(O)–H compounds using NaF as the fluorinating reagent and DDQ as the oxidant (eq 2).[8] However, these methods require the assistance of a source of chlorine or an additional oxidant with a copper catalyst because the weak nucleophilicity of fluoride ions limits access to P–F bonds via direct nucleophilic substitution reactions. Thus, the development of a direct protocol for the preparation of phosphoric fluorides under milder conditions is still a significant issue.

Electrophilic fluorinating reagents have attracted much attention due to their applications in fluorination reactions.[9] For example, *N*-fluorobis(benzenesulfonyl)imide (NFSI) or 1-chloromethyl-4-fluorodiazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (Selectfluor) provides a convenient entry to site-selective monofluorination.[9,10] Most recently, our group achieved an efficient oxidation protocol for triarylphosphines with Selectfluor to form triarylphosphine oxides, which were generated via hydration of unstable fluorophosphonium cation intermediates and a subsequent elimination of HF.[11] We then became interested in studying P–F bond construction through direct electrophilic substitution of P(O)–H compounds with electrophilic fluorinating reagents. We envisioned that the interaction between P(O)–H compounds and NFSI/Selectfluor might produce phosphoric fluorides via the corresponding fluorophosphonium cations. Herein, we report an efficient electrophilic fluorination of secondary phosphine oxides to afford phosphoric fluorides under mild conditions (eq 3), and a one-pot coupling process of secondary phosphine oxides with water or alcohols in the presence of Selectfluor was further investigated.

To test the hypothesis, we first examined the reaction of diphenylphosphine oxide **1a** with NFSI in CH_3CN at room temperature, while only trace amounts of the desired diphenylphosphinic fluoride **2a** were detected. When the

Scheme 1. Overview of the Fluorination of P(O)–H Compounds



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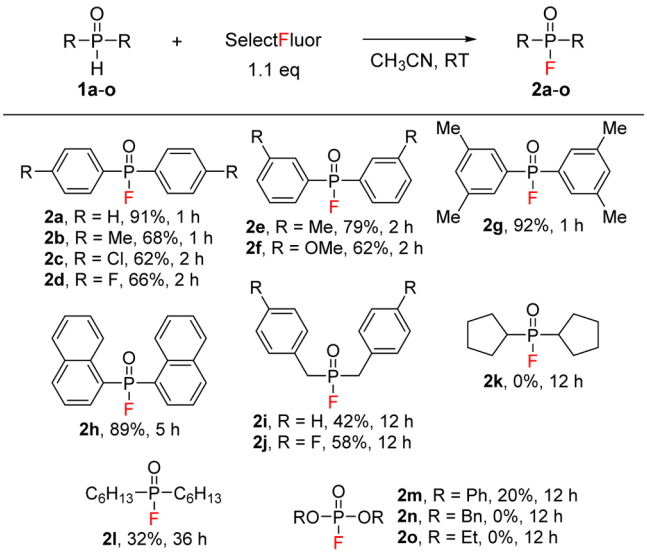
reaction temperature was raised to 60 °C, **2a** was isolated in only 14% yield. To our delight, when the fluorinating reagent was switched from NSFI to Selectfluor, the reaction proceeded smoothly at room temperature to lead to the formation of **2a** in 91% yield. We then turned to screen other solvents. The use of THF, ethanol, or DCM did not give the desired product, and the use of DME afforded **2a** in a low yield of only 25%. It is noteworthy that the fluorination reaction in aqueous CH_3CN under an air atmosphere also smoothly gave **2a** in high yield.

To investigate the scope of the fluorination protocol, we applied the reaction conditions to a variety of P(O)−H compounds, and the results are illustrated in Scheme 2. For the reaction of diarylphosphine oxides with Selectfluor, both electron-donating groups and electron-withdrawing groups on the aromatic rings were all well tolerated, and the corresponding fluorides **2a**−**g** were isolated in 62−92% yields. It is noteworthy that the reaction of sterically hindered di(naphthalen-1-yl)phosphine oxide with bulky Selectfluor also successfully afforded the desired fluoride **2h** in 89% yield, although more reaction time (5 h) was required. When dibenzylphosphine oxides were employed, **2i** and **2j** were obtained in moderate yields. Dihexylphosphine oxide gave the desired fluoride **2l** in only 32% yield, while dicyclopentylphosphine oxide failed to produce the corresponding product **2k**. We then turned to the fluorination of phosphite esters. The reaction of diphenyl phosphite with Selectfluor gave the desired fluoride **2m** in a low yield of 20%, and dibenzyl/diethyl phosphite failed to produce the corresponding products **2n** and **2o**. The difference in the fluorination between arylphosphine oxides and alkylphosphine oxides/phosphite esters might be explained by their nucleophilic abilities.

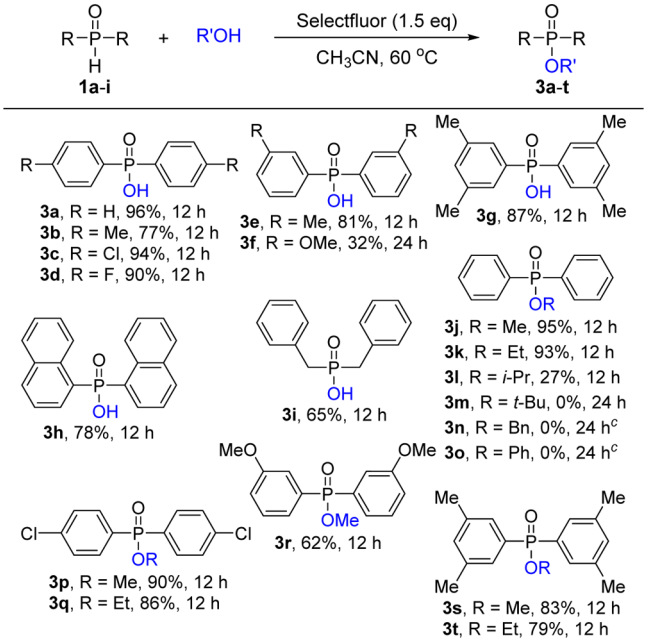
In comparison with phosphinic chlorides/bromides, phosphinic fluorides are neither air nor moisture sensitive. However, much less attention has been paid to the synthetic utility of phosphinic fluorides[12] probably due to the toxicity of fluorides. We then turned to study the reactivity of phosphoric fluorides. Diphenylphosphinic fluoride **2a** was smoothly hydrolyzed in the presence of Cs_2CO_3 in aqueous CH_3CN at 60 °C to produce diphenylphosphinic acid **3a** in 75% yield.[12] Thus, we then attempted a one-pot coupling reaction of diphenylphosphine oxide **1a** with water in the presence of Selectfluor. To our delight, the reaction gave the desired acid **3a** in 96% yield. As a comparison, the traditional protocol for the preparation of phosphinic acids and phosphinates from P(O)−H compounds mainly relies on the Atherton−Todd reaction,[13] which usually requires the use of the toxic tetrachloromethane as the halogenating reagent and solvent. Thus, this one-pot process via in situ formation of phosphoric fluorides and subsequent hydrolysis or alcoholysis might provide an alternative method for P−O bond construction. Water/alcohols and various secondary phosphine oxides were then applied in the one-pot process, and the results are illustrated in Scheme 3. When water was used as the nucleophile, electron-rich and electron-poor diarylphosphine oxides **1a**−**h** were all well tolerated for the one-pot coupling reaction to give the corresponding diarylphosphinic acids **3a**−**h** in 32−96% yields. Dibenzylphosphine oxide **1i** also efficiently produced the P−O coupling product **3i** in 65% yield. When methanol or ethanol served as the nucleophile, diarylphosphine oxides gave the corresponding methyl or ethyl diarylphosphinates in moderate to excellent yields. When 2-propanol was employed, the desired **3l** was obtained in a low yield of 27%. The reaction of **1a** with *tert*-butyl alcohol under the same conditions did not give the corresponding product **3m**, but *N*-*tert*-butylacetamide was isolated in quantitative yield (yield based on Selectfluor). This kind of byproduct was probably generated by the reaction between alcohols (tertiary or benzylic alcohols) and nitriles, which is well known by the name "Ritter reaction".[14] In this case, Selectfluor might activate the hydroxyl group of *tert*-butyl

Scheme 2. Fluorination of P(O)−H Compounds[a,b]



[a]Reaction conditions: **1** (0.2 mmol), Selectfluor (0.22 mmol) in CH_3CN (2 mL), stirring at rt. [b]Isolated yield.

Scheme 3. One-Pot Coupling Reaction of P(O)−H Compounds with Water or Alcohols[a,b]



[a]Reaction conditions: **1** (0.1 mmol), Selectfluor (0.15 mmol) in a mixed solvent of water (1 mL) or alcohols (1 mL) and CH_3CN (1 mL) stirring at 60 °C. [b]Isolated yield. [c]BnOH (5 equiv) or PhOH (5 equiv) was added.

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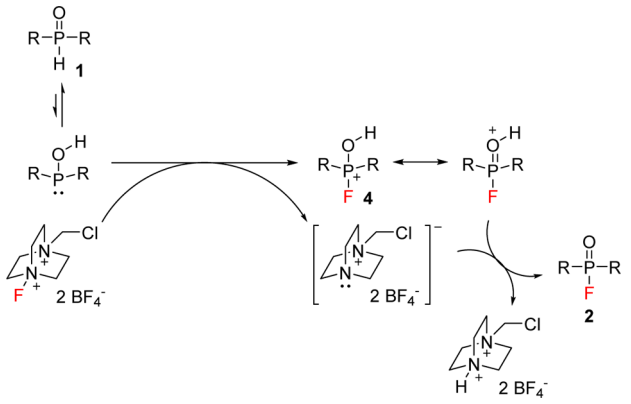
alcohol to generate *tert*-butyl cation followed by the electrophilic addition to acetonitrile. Similarly, benzyl alcohol and phenol failed to give the corresponding products probably due to the disturbance of Ritter reaction.

To gain more insight about the mechanism of the fluorination reaction, a control experiment was conducted for the fluorination of **1a**. In the presence of radical scavenger TEMPO (2 equiv), fluoride **2a** was isolated in 68% yield, while the possible TEMPO adducts were not found in the reaction mixture. This result suggests that a single-electron transfer (SET) process[15] is disfavored in this case, and the reaction involves a direct electrophilic fluorination. Thus, a plausible mechanism of the fluorination of secondary phosphine oxides with Selectfluor is proposed as shown in Scheme 4. The less

Scheme 4. Plausible Mechanism of the Fluorination Reaction



stable P(III) form, which exists with the P(V) phosphinylidene **1** through the tautomerization,[16] interacts with Selectfluor to generate the unstable fluorophosphonium cation **4**. Subsequent deprotonation gives the desired fluoride **2**. According to the proposed mechanism, it is reasonable to conclude that diarylphosphine oxides possess high reactivity in the fluorination reaction owing to the p–π conjugated system, which may enhance the nucleophilicity of the corresponding P(III) form. Dialkylphosphine oxides showed lower reactivity owing to the lack of this conjugated system, and the failure to obtain fluoride **2k** might be explained by the steric hindrance between dicyclopentylphosphine oxides and bulky Selectfluor. Dibenzyl/diethyl phosphite showed no reactivity mainly due to their low nucleophilicity, while diphenyl phosphite showed slight reactivity depending on the electron-rich aromatic rings.

In summary, we have developed a direct electrophilic fluorination of readily available secondary phosphine oxides with Selectfluor, which provides a highly efficient protocol for the synthesis of phosphoric fluorides under mild conditions. To the best of our knowledge, this finding is the first example of electrophilic fluorination of P(O)–H compounds. In addition, this fluorination has been successfully applied to the one-pot coupling process of secondary phosphine oxides with water or alcohols, which provides a simple method for P–O bond construction. This property of Selectfluor should lead to new and useful applications in organophosphorus chemistry.

EXPERIMENTAL SECTION

General Details. All reactions were carried out using oven-dried glassware and standard syringe/septa techniques. Commercial reagents were used without purification unless otherwise noted. Secondary phosphine oxides which were not commercially available were prepared according to the literature.[17] Petroleum ether refers to the petroleum fraction bp 40–60 °C. Flash chromatography was performed using the indicated solvent system on silica gel standard grade 60 (230–400 mesh). ^{1}H NMR spectra were recorded on a 400 MHz spectrometer. ^{13}C NMR spectra were recorded on a 100 MHz spectrometer. ^{31}P NMR spectra were recorded on a 162 MHz spectrometer. ^{19}F NMR spectra were recorded on a 376 MHz spectrometer. Chemical shifts are reported relative to $CDCl_3$ (δ 7.26 ppm) or DMSO-d_6 (δ 2.50 ppm) for ^{1}H NMR and $CDCl_3$ (δ 77.16 ppm) or DMSO-d_6 (δ 39.52 ppm) for ^{13}C NMR. High-resolution mass spectra (HRMS) were recorded on ESI-TOF. The known compounds **2a**,[8] **2b**,[8] **2e**,[8] **2m**,[18] **3a**,[19] **3c**,[17b] **3f**,[20] **3g**,[21] **3i**,[22] **3j**,[23] **3k**,[24] **3l**,[23] **3p**,[17b] **3r**,[20] and **3t**[25] showed characterization data in full agreement with previously reported data.

General Procedure for the Fluorination Reaction. To a solution of diphenylphosphine oxide **1a** (40 mg, 0.2 mmol) in acetonitrile (2 mL) was added Selectfluor (78 mg, 0.22 mmol). The mixture was stirred for 1 h at room temperature. After removal of the solvent, the residue was purified by flash column chromatography on silica gel with petroleum ether/ethyl acetate (2:1) to give product **2a** (40 mg, 91%).

General Procedure for the Synthesis of Phosphinic Acids. To a solution of diphenylphosphine oxide **1a** (20 mg, 0.1 mmol) in 2 mL of CH_3CN/H_2O (v/v = 1/1) was added Selectfluor (53 mg, 0.15 mmol). The mixture was stirred at 60 °C for 12 h. After removal of the solvent, the residue was isolated by precipitation in chloroform to give product **3a** (21 mg, 96%).

General Procedure for the Synthesis of Phosphinates. To a solution of diphenylphosphine oxide **1a** (20 mg, 0.1 mmol) in 2 mL of CH_3CN/MeOH (v/v = 1/1) was added Selectfluor (53 mg, 0.15 mmol). The mixture was stirred at 60 °C for 12 h. After removal of the solvent, the residue was purified by flash column chromatography on silica gel with petroleum ether/ethyl acetate (2:1) to give product **3j** (22 mg, 95%).

*Diphenylphosphinic fluoride (**2a**):* pale yellow oil (40 mg, 91%);[8] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86–7.77 (m, 4H), 7.63–7.57 (m, 2H), 7.53–7.46 (m, 4H); ^{31}P NMR (162 MHz, $CDCl_3$) δ 40.90 (d, J = 1020 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −75.15 (d, J = 1020 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.4 (d, J = 2.3 Hz), 131.4 (dd, J = 11.3, 1.9 Hz), 128.9 (d, J = 14.1 Hz), 128.8 (dd, J = 140.0, 22.3 Hz).

*Di-p-tolylphosphinic fluoride (**2b**):* pale yellow oil (34 mg, 68%);[8] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73–7.65 (m, 4H), 7.32–7.27 (m, 4H), 2.40 (s, 6H); ^{31}P NMR (162 MHz, $CDCl_3$) δ 42.02 (d, J = 1014 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −74.36 (d, J = 1014 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.0 (d, J = 2.3 Hz), 131.4 (dd, J = 11.7, 1.8 Hz), 129.5 (d, J = 14.5 Hz), 125.8 (dd, J = 143.0, 22.0 Hz), 21.7.

*Bis(4-chlorophenyl)phosphinic fluoride (**2c**):* white amorphous solid (36 mg, 62%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78–7.70 (m, 4H), 7.53–7.47 (m, 4H); ^{31}P NMR (162 MHz, $CDCl_3$) δ 38.76 (d, J = 1023 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −73.99 (d, J = 1023 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.5 (d, J = 3.8 Hz), 132.8 (dd, J = 12.3, 1.8 Hz), 129.4 (d, J = 14.9 Hz), 126.8 (dd, J = 144.0, 23.0 Hz); HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{12}H_9Cl_2FOP$ 288.9747, found 288.9749.

*Bis(4-fluorophenyl)phosphinic fluoride (**2d**):* white amorphous solid (34 mg, 66%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88–7.78 (m, 4H), 7.25–7.18 (m, 4H); ^{31}P NMR (162 MHz, $CDCl_3$) δ 38.83 (d, J = 1019 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −72.95 (d, J = 1019 Hz), −103.26; ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0 (dd, J = 254.0, 4.0 Hz), 134.2 (ddd, J = 12.8, 9.2, 2.0 Hz), 124.6 (ddd, J = 147.1, 23.7, 3.0 Hz), 116.5 (dd, J = 21.7, 15.5 Hz); HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{12}H_9F_3OP$ 257.0338, found 257.0342.

*Di-m-tolylphosphinic fluoride (**2e**):* colorless oil (39 mg, 79%);[8] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69–7.55 (m, 4H), 7.43–7.34 (m, 4H), 2.39 (s, 6H); ^{31}P NMR (162 MHz, $CDCl_3$) δ 41.63 (d, J = 1019 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −75.47 (d, J = 1019 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.8 (d, J = 14.0 Hz), 134.1 (d, J = 2.8 Hz),

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131.8 (dd, J = 11.3, 1.9 Hz), 128.8 (dd, J = 140.0, 22.0 Hz), 128.7 (d, J = 14.8 Hz), 128.5 (dd, J = 11.3, 1.9 Hz), 21.3.

*Bis(3-methoxyphenyl)phosphinic fluoride (**2f**):* colorless oil (35 mg, 62%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44−7.31 (m, 6H), 7.15−7.09 (m, 2H), 3.82 (s, 6H); ^{31}P NMR (162 MHz, $CDCl_3$) δ 40.69 (d, J = 1022 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −75.06 (d, J = 1022 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.7 (d, J = 17.7 Hz), 130.2 (d, J = 16.7 Hz), 129.9 (dd, J = 139.0, 22.0 Hz), 123.6 (dd, J = 11.1, 1.9 Hz), 119.6 (d, J = 2.8 Hz), 116.1 (dd, J = 12.7, 1.9 Hz), 55.5; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{14}H_{15}FO_3P$ 281.0737, found 281.0736.

*Bis(3,5-dimethylphenyl)phosphinic fluoride (**2g**):* white amorphous solid (51 mg, 92%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, J = 13.4 Hz, 4H), 7.22 (s, 2H), 2.35 (s, 12H); ^{31}P NMR (162 MHz, $CDCl_3$) δ 42.32 (d, J = 1018 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −75.93 (d, J = 1018 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.6 (d, J = 14.7 Hz), 135.0 (d, J = 2.6 Hz), 128.9 (dd, J = 11.3, 1.8 Hz), 128.8 (dd, J = 138.0, 22.0 Hz), 21.2; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{16}H_{19}FOP$ 277.1152, found 277.1155.

*Di(naphthalen-1-yl)phosphinic fluoride (**2h**):* white amorphous solid (57 mg, 89%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58−8.51 (m, 2H), 8.10 (d, J = 8.2 Hz, 2H), 8.03 (dd, J = 17.0, 7.1 Hz, 2H), 7.96−7.89 (m, 2H), 7.60−7.48 (m, 6H); ^{31}P NMR (162 MHz, $CDCl_3$) δ 44.48 (d, J = 1019 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −67.94 (d, J = 1019 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.6 (d, J = 3.1 Hz), 133.9 (dd, J = 12.0, 3.9 Hz), 133.6 (d, J = 11.3 Hz), 132.7 (d, J = 10.9 Hz), 129.1 (d, J = 1.5 Hz), 128.1, 126.9, 126.3 (d, J = 6.0 Hz), 125.6 (dd, J = 137.0,19.0 Hz), 124.6 (d, J = 16.2 Hz); HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{20}H_{15}FOP$ 321.0839, found 321.0836.

*Dibenzylphosphinic fluoride (**2i**):* white amorphous solid (21 mg, 42%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31−7.13 (m, 10H), 3.15 (dd, J = 16.0, 8.0 Hz, 4H); ^{31}P NMR (162 MHz, $CDCl_3$) δ 58.57 (d, J = 1041 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −76.71 (d, J = 1041 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 129.8 (d, J = 6.3 Hz), 129.2 (d, J = 7.3 Hz), 129.0 (d, J = 2.7 Hz), 127.6 (d, J = 3.3 Hz), 34.8 (dd, J = 85.9, 14.5 Hz); HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{14}H_{15}FOP$ 249.0839, found 249.0845.

*Bis(4-fluorobenzyl)phosphinic fluoride (**2j**):* white amorphous solid (33 mg, 58%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22−7.15 (m, 4H), 7.03 (t, J = 8.4 Hz, 4H), 3.20 (dd, J = 16.0, 4.0 Hz, 4H); ^{31}P NMR (162 MHz, $CDCl_3$) δ 57.67 (d, J = 1042 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −76.88 (d, J = 1042 Hz), −114.36; ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.3 (dd, J = 247.1, 3.6 Hz), 131.5−131.2 (m), 124.8−124.6 (m), 116.0 (dd, J = 21.7, 2.6 Hz), 34.0 (dd, J = 86.6, 14.8 Hz); HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{14}H_{13}F_3OP$ 285.0651, found 285.0650.

*Dihexylphosphinic fluoride (**2l**):* white amorphous solid (15 mg, 32%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.89−1.77 (m, 4H), 1.69−1.57 (m, 4H), 1.45−1.36 (m, 4H), 1.34−1.25 (m, 8H), 0.88 (t, J = 6.4 Hz, 6H); ^{31}P NMR (162 MHz, $CDCl_3$) δ 70.46 (d, J = 1016 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −78.22 (d, J = 1016 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.2, 30.2 (d, J = 14.7 Hz), 27.8 (dd, J = 87.8, 14.5 Hz), 22.3, 21.2 (d, J = 4.4 Hz), 13.9; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{12}H_{27}FOP$ 237.1778, found 237.1787.

*Diphenyl phosphorofluoridate (**2m**):* colorless oil (10 mg, 20%);[18] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42−7.36 (m, 4H), 7.29−7.21 (m, 6H); ^{31}P NMR (162 MHz, $CDCl_3$) δ −21.49 (d, J = 1002 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −77.83 (d, J = 1002 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.8 (d, J = 7.1 Hz), 130.1, 126.3, 119.8 (d, J = 4.9 Hz).

*Diphenylphosphinic acid (**3a**):* white amorphous solid (21 mg, 96%);[19] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74−7.69 (m, 4H), 7.46−7.43 (m, 2H), 7.37−7.32 (m, 4H), 7.06 (brs, 1H); ^{31}P NMR (162 MHz, $CDCl_3$) δ 32.65; ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.9 (d, J = 139.4 Hz), 131.9 (d, J = 2.7 Hz), 131.4 (d, J = 10.5 Hz), 128.4 (d, J = 13.3 Hz).

*Di-p-tolylphosphinic acid (**3b**):* white amorphous solid (19 mg, 77%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (s, 1H), 7.62−7.55(m, 4H), 7.19−7.08 (m, 4H), 2.34 (s, 6H); ^{31}P NMR (162 MHz, $CDCl_3$) δ 33.25; ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.0 (d, J = 2.7 Hz), 131.2 (d, J = 10.9 Hz), 129.8 (d, J = 142.0 Hz), 128.9 (d, J = 13.8 Hz), 21.6; HRMS (ESI-TOF) m/z $[M + 2Na - H]^+$ calcd for $C_{14}H_{14}O_2PNa_2$ 291.0521, found 291.0532.

*Bis(4-chlorophenyl)phosphinic acid (**3c**):* white amorphous solid (27 mg, 94%);[17b] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 (s, 1H), 7.58 (t, J = 9.0 Hz, 4H), 7.31 (d, J = 8.0 Hz, 4H); ^{31}P NMR (162 MHz, $CDCl_3$) δ 28.87; ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.8, 132.6 (d, J = 10.9 Hz), 130.7 (d, J = 143.0 Hz), 128.8 (d, J = 13.6 Hz).

*Bis(4-fluorophenyl)phosphinic acid (**3d**):* white amorphous solid (23 mg, 90%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.71 (s, 1H), 7.72−7.64 (m, 4H), 7.06−7.00 (m, 4H); ^{31}P NMR (162 MHz, $CDCl_3$) δ 29.38; ^{19}F NMR (376 MHz, $CDCl_3$) δ −106.48; ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.1 (d, J = 252.0 Hz), 133.8 (dd, J = 11.4, 9.1 Hz), 128.6 (d, J = 144.0 Hz), 115.7 (dd, J = 21.4, 14.4 Hz); HRMS (ESI-TOF) m/z $[M + 2Na - H]^+$ calcd for $C_{12}H_8F_2O_2PNa_2$ 299.0020, found 299.0025.

*Di-m-tolylphosphinic acid (**3e**):* white amorphous solid (20 mg, 81%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.82 (s, 1H), 7.57−7.47 (m, 4H), 7.29−7.20(m, 4H), 2.29 (s, 6H); ^{31}P NMR (162 MHz, $CDCl_3$) δ 33.58; ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.0 (d, J = 13.3 Hz), 132.6 (d, J = 2.5 Hz), 132.6 (d, J = 139.0 Hz), 131.6 (d, J = 10.5 Hz), 128.4 (d, J = 10.6 Hz), 128.2 (d, J = 14.1 Hz), 21.3; HRMS (ESI-TOF) m/z $[M + 2Na - H]^+$ calcd for $C_{14}H_{14}O_2PNa_2$ 291.0521, found 291.0532.

*Bis(3-methoxyphenyl)phosphinic acid (**3f**):* white amorphous solid (9 mg, 32%);[20] ^{1}H NMR (400 MHz, d_6-DMSO) δ 7.44−7.35 (m, 2H), 7.31−7.20 (m, 4H), 7.09 (d, J = 8.0 Hz, 2H), 5.36 (s, 1H), 3.77 (s, 6H); ^{31}P NMR (162 MHz, d_6-DMSO) δ 23.03; ^{13}C NMR (100 MHz, d_6-DMSO) δ 159.4 (d, J = 15.8 Hz), 136.8 (d, J = 133.0 Hz), 130.3 (d, J = 14.7 Hz), 123.6 (d, J = 9.6 Hz), 117.5 (d, J = 2.5 Hz), 116.5 (d, J = 11.0 Hz), 55.7.

*Bis(3,5-dimethylphenyl)phosphinic acid (**3g**):* white amorphous solid (24 mg, 87%);[21] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (s, 1H), 7.34 (d, J = 12.0 Hz, 4H), 7.06 (s, 2H), 2.27 (s, 12H); ^{31}P NMR (162 MHz, $CDCl_3$) δ 34.88; ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.8 (d, J = 14.0 Hz), 133.5, 132.6 (d, J = 137.0 Hz), 128.7 (d, J = 10.0 Hz), 21.2.

*Di(naphthalen-1-yl)phosphinic acid (**3h**):* white amorphous solid (25 mg, 78%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (d, J = 8.5 Hz, 2H), 8.16 (dd, J = 15.9, 6.9 Hz, 2H), 7.93 (d, J = 7.9 Hz, 2H), 7.81 (d, J = 7.9 Hz, 2H), 7.45−7.28 (m, 6H), 6.32 (s, 1H); ^{31}P NMR (162 MHz, $CDCl_3$) δ 36.84; ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.6 (d, J = 10.9 Hz), 133.4 (d, J = 10.3 Hz), 133.3 (d, J = 2.9 Hz), 132.7 (d, J = 11.0 Hz), 129.0 (d, J = 136.0 Hz), 128.7, 127.1, 126.6 (d, J = 5.0 Hz), 126.1, 124.5 (d, J = 15.1 Hz); HRMS (ESI-TOF) m/z $[M + 2Na - H]^+$ calcd for $C_{20}H_{14}O_2PNa_2$ 363.0521, found 363.0520.

*Dibenzylphosphinic acid (**3i**):* white amorphous solid (16 mg, 65%);[22] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30−7.15 (m, 10H), 4.74 (s, 1H), 2.86 (d, J = 16.0 Hz, 4H); ^{31}P NMR (162 MHz, $CDCl_3$) δ 50.85; ^{13}C NMR (100 MHz, $CDCl_3$) δ 131.4 (d, J = 7.3 Hz), 130.0 (d, J = 5.2 Hz), 128.5, 126.8, 36.0 (d, J = 88.0 Hz).

*Methyl diphenylphosphinate (**3j**):* colorless oil (22 mg, 95%);[23] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84−7.77 (m, 4H), 7.55−7.49 (m, 2H), 7.48−7.41 (m, 4H), 3.76 (d, J = 11.1 Hz, 3H); ^{31}P NMR (162 MHz, $CDCl_3$) δ 33.26; ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.2 (d, J = 2.8 Hz), 131.7 (d, J = 10.1 Hz), 131.1 (d, J = 136.0 Hz), 128.6 (d, J = 13.1 Hz), 51.5 (d, J = 6.0 Hz).

*Ethyl diphenylphosphinate (**3k**):* colorless oil (23 mg, 93%);[24] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84−7.77 (m, 4H), 7.53−7.47 (m, 2H), 7.46−7.40 (m, 4H), 4.14−4.05 (m, 2H), 1.36 (t, J = 7.1 Hz, 3H); ^{31}P NMR (162 MHz, $CDCl_3$) δ 31.35; ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.1 (d, J = 2.8 Hz), 131.7 (d, J = 136 Hz), 131.6 (d, J = 10.1 Hz), 128.5 (d, J = 13.1 Hz), 61.1 (d, J = 5.9 Hz), 16.5 (d, J = 6.7 Hz).

*Isopropyl diphenylphosphinate (**3l**):* white amorphous solid (7 mg, 27%);[23] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85−7.77 (m, 4H), 7.53−7.46 (m, 2H), 7.46−7.39 (m, 4H), 4.73−4.60 (m, 1H), 1.34 (d, J = 6.1 Hz, 6H); ^{31}P NMR (162 MHz, $CDCl_3$) δ 29.80; ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.4 (d, J = 136.0 Hz), 131.9 (d, J = 2.7 Hz), 131.6 (d, J = 10.1 Hz), 128.4 (d, J = 13.1 Hz), 70.2 (d, J = 6.0 Hz), 24.3 (d, J = 4.2 Hz).

*Methyl bis(4-chlorophenyl)phosphinate (**3p**):* colorless oil (27 mg, 90%);[17b] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76−7.68 (m, 4H), 7.47−

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7.40 (m, 4H), 3.76 (d, J = 11.2 Hz, 3H); ^{31}P NMR (162 MHz, $CDCl_3$) δ 31.23; ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.1 (d, J = 3.5 Hz), 133.0 (d, J = 11.0 Hz), 129.2 (d, J = 139.0 Hz), 129.1 (d, J = 13.8 Hz), 51.7 (d, J = 6.0 Hz).

*Ethyl bis(4-chlorophenyl)phosphinate (**3q**):* colorless oil (27 mg, 86%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76−7.67 (m, 4H), 7.46−7.39 (m, 4H), 4.15−4.05 (m, 2H), 1.36 (t, J = 7.0 Hz, 3H); ^{31}P NMR (162 MHz, $CDCl_3$) δ 29.31; ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.0 (d, J = 3.6 Hz), 133.0 (d, J = 11.0 Hz), 129.9 (d, J = 139.0 Hz), 129.0 (d, J = 13.8 Hz), 61.5 (d, J = 5.9 Hz), 16.5 (d, J = 6.5 Hz); HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{14}H_{14}Cl_2O_2P$ 315.0103, found 315.0105.

*Methyl bis(3-methoxyphenyl)phosphinate (**3r**):* colorless oil (18 mg, 62%);[20] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39−7.31 (m, 6H), 7.08−7.02 (m, 2H), 3.82 (s, 6H), 3.77 (d, J = 11.2 Hz, 3H); ^{31}P NMR (162 MHz, $CDCl_3$) δ 33.15; ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.6 (d, J = 16.5 Hz), 132.3 (d, J = 135.0 Hz), 129.8 (d, J = 15.5 Hz), 123.8 (d, J = 9.8 Hz), 118.5 (d, J = 2.8 Hz), 116.4 (d, J = 11.3 Hz), 55.4, 51.6 (d, J = 6.1 Hz).

*Methyl bis(3,5-dimethylphenyl)phosphinate (**3s**):* colorless oil (24 mg, 83%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, J = 12.5 Hz, 4H), 7.14 (s, 2H), 3.74 (d, J = 11.1 Hz, 3H), 2.33 (s, 12H); ^{31}P NMR (162 MHz, $CDCl_3$) δ 34.45; ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.2 (d, J = 13.8 Hz), 133.9 (d, J = 2.9 Hz), 130.9 (d, J = 135.0 Hz), 129.2 (d, J = 10.1 Hz), 51.4 (d, J = 6.0 Hz), 21.2; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{17}H_{22}O_2P$ 289.1352, found 289.1356.

*Ethyl bis(3,5-dimethylphenyl)phosphinate (**3t**):* colorless oil (24 mg, 79%);[25] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, J = 12.5 Hz, 4H), 7.13 (s, 2H), 4.13−4.03 (m, 2H), 2.33 (s, 12H), 1.37 (t, J = 7.0 Hz, 3H); ^{31}P NMR (162 MHz, $CDCl_3$) δ 32.62; ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.1 (d, J = 13.7 Hz), 133.7 (d, J = 2.8 Hz), 131.6 (d, J = 135.0 Hz), 129.2 (d, J = 10.1 Hz), 60.9 (d, J = 5.8 Hz), 21.2, 16.5 (d, J = 6.5 Hz).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01932.

^{1}H, ^{13}C, ^{19}F and ^{31}P NMR spectra for compounds **2** and **3** (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Metzler, D. E. In *Biochemistry*; Academic Press: New York, 1950; Vol. *371*; p 1013. (b) Saunders, B. C. *Some Aspects of the Chemistry and Toxic Action of Organic Compounds Containing Phosphorus and Fluorine*; Cambridge University Press: Cambridge, 1957. (c) Wilson, B. W.; Walker, C. R. *Proc. Natl. Acad. Sci. U. S. A.* **1974**, *71*, 3194. (d) Bartlett, P. A.; Lamden, L. A. *Bioorg. Chem.* **1986**, *14*, 356. (e) Majoral, J. P. *New Aspects in Phosphorus Chemistry I & II*; Springer: Berlin, 2000.

(2) (a) Kosolapoff, G. M. *Organic Phosphorus Compounds*; Wiley Interscience: New York, 1950; Vol. *6*; p 319. (b) Eto, M. *Organophosphorus Phosphorus Pesticides: Organic and Biological Chemistry*; CRC Press: Boca Raton, 1974. (c) Engel, R. *Chem. Rev.* **1977**, *77*, 349.

(3) (a) Schrader, G. *Die Entwicklung neuer Insektizide auf Grundlage Organischer Fluor- und Phosphor-Verbindungen*; Verlag Chemie: Weinheim, 1952; p 5. (b) Camps, F.; Coll, J.; Fabrias, G.; Guerrero, A. *Tetrahedron* **1984**, *40*, 2871. (c) De Frank, J. J. In *Applications of Enzyme Biotechnology*; Kelly, J. W., Baldwin, T. O., Eds.; Plenum: New York, 1991; pp 165−180.

(4) (a) Marjit, D. N.; Sharma, U. S. *Indian J. Chem.* **1989**, *28A*, 958. (b) Sikder, A. K.; Pandey, K. S.; Jaiswal, D. K.; Dube, S. N.; Kumar, D.; Husain, K.; Bhattacharya, R.; Das Gupta, S. *J. Pharm. Pharmacol.* **1992**, *44*, 1038. (c) Sikder, A. K.; Ghosh, A. K.; Jaiswal, D. K. *J. Pharm. Sci.* **1993**, *82*, 258.

(5) (a) Koelle, G. J. *J. Pharmacol. Exp. Ther.* **1946**, *88*, 232. (b) Eyer, P. *Toxicol. Rev.* **2003**, *22*, 165. (c) Kim, T. H.; Oh, K. A.; Park, N. J.; Park, N. S.; Kim, Y. J.; Yum, E. K.; Jung, Y. S. *J. Appl. Biomed.* **2006**, *4*, 67.

(6) For selected examples, see: (a) Lopusinski, A.; Michalski, J. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 294. (b) Dabkowski, W.; Michalski, J. *J. Chem. Soc., Chem. Commun.* **1987**, 755. (c) Lermontov, S. A.; Popov, A. V.; Zavorin, S. I.; Sukhojenko, I. I.; Kuryleva, N. V.; Martynov, I. V.; Zefirov, N. S.; Stang, P. *J. Fluorine Chem.* **1994**, *66*, 233. (d) Farooq, O. *J. Chem. Soc., Perkin Trans. 1* **1998**, 839. (e) Chworos, A.; Wozniak, L. A. *Tetrahedron Lett.* **1999**, *40*, 9337. (f) Gololobov, Y. G.; Krasnova, I. Y.; Matveeva, E. V.; Petrovskii, P. V. *Russ. Chem. Bull.* **2010**, *59*, 1059.

(7) (a) Gupta, A. K.; Acharya, J.; Dubey, D. K.; Kaushik, M. P. *J. Fluorine Chem.* **2008**, *129*, 226. (b) Gupta, A. K.; Acharya, J.; Pardasani, D.; Dubey, D. K. *Tetrahedron Lett.* **2008**, *49*, 2232. (c) Purohit, A. K.; Pardasani, D.; Kumar, A.; Goud, D. R.; Jain, R.; Dubey, D. *Tetrahedron Lett.* **2015**, *56*, 4593.

(8) Liu, N.; Mao, L.-L.; Yang, B.; Yang, S.-D. *Chem. Commun.* **2014**, *50*, 10879.

(9) For selected reviews, see: (a) Nyffeler, P. T.; Durón, S. G.; Burkart, M. D.; Vincent, S. P.; Wong, C.-H. *Angew. Chem., Int. Ed.* **2005**, *44*, 192. (b) Shimizu, M.; Hiyama, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 214. (c) Liang, T.; Neumann, C.; Ritter, T. *Angew. Chem., Int. Ed.* **2013**, *52*, 8214. (d) Champagne, P. A.; Desroches, J.; Hamel, J.-D.; Vandamme, M.; Paquin, J.-F. *Chem. Rev.* **2015**, *115*, 9073.

(10) For selected examples, see: (a) Hamashima, Y.; Sodeoka, M. *Synlett* **2006**, *2006*, 1467. (b) Rauniyar, V.; Lackner, A. D.; Hamilton, G. L.; Toste, F. D. *Science* **2011**, *334*, 1681. (c) Yin, F.; Wang, Z.; Li, Z.; Li, C. *J. Am. Chem. Soc.* **2012**, *134*, 10401. (d) Li, Z.; Wang, Z.; Zhu, L.; Tan, X.; Li, C. *J. Am. Chem. Soc.* **2014**, *136*, 16439.

(11) Chen, Q.; Zeng, J.; Yan, X.; Huang, Y.; Du, Z.; Zhang, K.; Wen, C. *Tetrahedron Lett.* **2016**, *57*, 3379.

(12) Babouri, R.; Rolland, M.; Sainte-Catherine, O.; Kabouche, Z.; Lecouvey, M.; Bakalara, N.; Volle, J.-N.; Virieux, D.; Pirat, J.-L. *Eur. J. Med. Chem.* **2015**, *104*, 33.

(13) (a) Atherton, F. R.; Openshaw, H. T.; Todd, A. R. *J. Chem. Soc.* **1945**, 660. (b) Atherton, F. R.; Todd, A. R. *J. Chem. Soc.* **1947**, 674. (c) Wang, G.; Shen, R.; Xu, Q.; Goto, M.; Zhao, Y.; Han, L.-B. *J. Org. Chem.* **2010**, *75*, 3890. (d) Ashmus, R. A.; Lowary, T. L. *Org. Lett.* **2014**, *16*, 2518.

(14) (a) Ritter, J. J.; Minieri, P. P. *J. Am. Chem. Soc.* **1948**, *70*, 4045. (b) Benson, F. R.; Ritter, J. J. *J. Am. Chem. Soc.* **1949**, *71*, 4128. (c) Tamaddon, F.; Khoobi, M.; Keshavarz, E. *Tetrahedron Lett.* **2007**, *48*, 3643. (d) Yaragorla, S.; Singh, G.; Saini, P. L.; Reddy, M. K. *Tetrahedron Lett.* **2014**, *55*, 4657.

(15) For selected reviews, see: (a) Marcus, R. A. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1111. (b) Rosokha, S. V.; Kochi, J. K. *Acc. Chem. Res.* **2008**, *41*, 641.

(16) (a) Deal, E. L.; Petit, C.; Montchamp, J.-L. *Org. Lett.* **2011**, *13*, 3270. (b) Janesko, B. G.; Fisher, H. C.; Bridle, M. J.; Montchamp, J.-L. *J. Org. Chem.* **2015**, *80*, 10025.

(17) (a) Hays, H. R. *J. Org. Chem.* **1968**, *33*, 3690. (b) Harger, M. J. P.; Westlake, S. *Tetrahedron* **1982**, *38*, 1511.

(18) Norlin, R.; Juhlin, L.; Lind, P.; Trogen, L. *Synthesis* **2005**, *2005*, 1765.

DOI: 10.1021/acs.joc.6b01932
J. Org. Chem. 2016, 81, 10043−10048

(19) Olszewski, T. K.; Boduszek, B. *Tetrahedron* **2010**, *66*, 8661.
(20) Cornforth, J.; Sierakowski, A. F.; Wallace, T. W. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2299.
(21) Watson, D. A.; Chiu, M.; Bergman, R. G. *Organometallics* **2006**, *25*, 4731.
(22) Majewski, P. *Phosphorus, Sulfur Silicon Relat. Elem.* **1989**, *45*, 151.
(23) Goldeman, W.; Olszewski, T. K.; Boduszek, B.; Sawka-Dobrowolska, W. *Tetrahedron* **2006**, *62*, 4506.
(24) Rao, H.; Jin, Y.; Fu, H.; Jiang, Y.; Zhao, Y. *Chem. - Eur. J.* **2006**, *12*, 3636.
(25) Park, S.; Seo, B.; Shin, S.; Son, J. Y.; Lee, P. H. *Chem. Commun.* **2013**, *49*, 8671.

DOI: 10.1021/acs.joc.6b01932
J. Org. Chem. 2016, 81, 10043−10048