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Nickel-Catalyzed Phosphorylation of Phenol Derivatives via C−O/P−H Cross-Coupling

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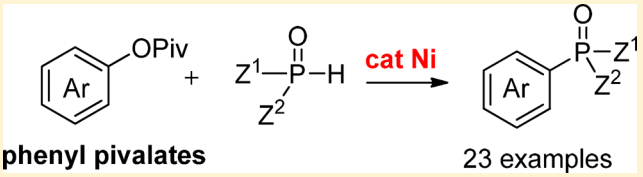
Supporting Information

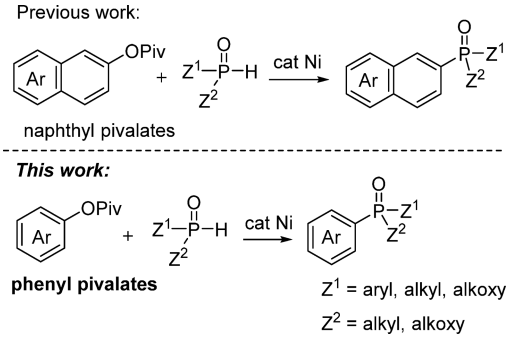
ABSTRACT: An efficient nickel-catalyzed phosphorylation of phenol derivatives with P(O)−H compounds via C−O/P−H cross-coupling is described. Under the reaction conditions, various phenyl pivalates coupled readily with hydrogen phosphoryl compounds to afford the corresponding coupling products aryl phosphonates and aryl phosphine oxides in good to high yields.



Aryl phosphonates and aryl phosphine oxides are important compounds in material chemistry, medicinal chemistry, catalysis, and organic synthesis.[1] Traditionally, those compounds were synthesized by substitutions of P(O)Cl with organolithium or Gringard reagents.[2] The Michaelis−Arbusov reactions (reactions of alkyl halides with phosphites) also were used to produce such compounds.[3] Since the pioneering work reported by Hirao and co-workers in 1980, the transition-metal-catalyzed cross-couplings of (pseudo)haloarenes with P(O)−H compounds have been extensively studied and emerged as one of the most efficient methods to access aryl phosphorus compounds.[4] Those protocols all depend on the transformation of organohalides.

Phenol derivatives are readily available and have attracted much attention as the green and efficient coupling partners replacing the organohalides in the carbon−carbon and carbon−heteroatom bonds coupling chemistry.[5−8] Recently, we reported an efficient Ni-catalyzed carbon−phosphorus bond-forming reaction via C−O/P−H cross-coupling (Scheme 1).[8] Various naphthyl pivalates coupled readily with hydrogen phosphoryl compounds to produce the corresponding organophosphorus compounds in high yields.[9] However, the phenyl pivalates did not work under the reaction conditions, which limited the application of this transformation.[10] Herein, we reported that, by tuning the reaction conditions, the phosphorylation of phenol pivalates with hydrogen phosphoryl compounds was also achieved. Various aryl phosphonates and aryl phosphine oxides were produced in good to high yields by using this nickel-catalyzed C−O/P−H cross-coupling (Scheme 1).[9]

Scheme 1. Ni-Catalyzed P−C Bond Formation via C−O Activation



We initiated the work with examining the reactivity of phenyl pivalate **1a** with diisopropyl phosphonate **2a** by using the previous Ni(COD)$_2$/dcype (1,2-bis(dicyclohexylphosphino)-ethane) catalyst, and the obtained results are compiled in Table 1. A screening on the additive showed that a suitable base was essential for the reaction (entries 1−7). At first, the yield increased as the basicity with Cs_2CO_3, giving the highest yield of the product (entries 1−4). However, the addition of stronger bases like EtONa, *t*-BuOLi, and *t*-BuONa led to a dramatic decrease of the reaction efficiency, which perhaps was due to the hydrolysis of phosphoryl groups under the reaction conditions (entries 5−7). Thus, in the presence of Ni(COD)$_2$ (10 mol %), dcype (10 mol %), and Cs_2CO_3 (1.1 equiv), phenyl pivalate **1a** reacted with **2a** in dioxane at 100 °C to produce the corresponding coupling product **3a** in 41% yield (entry 4). The yield of **3a** was further increased to 69% by using toluene as the solvent (entry 8).[11] Low yield was afforded when the reaction was performed in the apolar hexane, and no product was detected in the polar MeCN and DMF (entries 9−11). Either lowering or elevating the reaction temperature led to a decrease of the reaction efficiency (entries 12−15).[12] The phosphine ligands were also crucial for the transformation. No reaction took place with other selected ligands like PCy_3, dppp

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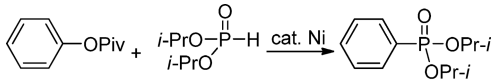
Table 1. Conditions Optimization of Ni-Catalyzed C−O/P−H Cross-Coupling of Phenyl Pivalates 1a with Diisopropyl Phosphonate 2a[a]



1a 2a 3a

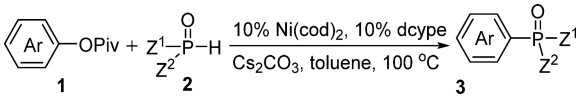
entry	ligand	base	solvent	temp (°C)	yield[b]
1	dcype	Na_2CO_3	dioxane	100	n.d.
2	dcype	K_2CO_3	dioxane	100	18%
3	dcype	K_3PO_4	dioxane	100	23%
4	dcype	Cs_2CO_3	dioxane	100	41%
5	dcype	EtONa	dioxane	100	n.d.
6	dcype	*t*-BuOLi	dioxane	100	7%
7	dcype	*t*-BuONa	dioxane	100	9%
8	dcype	Cs_2CO_3	toluene	100	69%
9	dcype	Cs_2CO_3	hexane	100	20%
10	dcype	Cs_2CO_3	CH_3CN	100	trace
11	dcype	Cs_2CO_3	DMF	100	n.d.
12	dcype	Cs_2CO_3	toluene	80	n.d.
13	dcype	Cs_2CO_3	toluene	90	28%
14	dcype	Cs_2CO_3	toluene	110	29%
15	dcype	Cs_2CO_3	toluene	120	18%
16	PCy_3	Cs_2CO_3	toluene	100	n.d.
17	dppp	Cs_2CO_3	toluene	100	n.d.
18	dppf	Cs_2CO_3	toluene	100	n.d.
19[c]	dcype	Cs_2CO_3	toluene	100	94%
20[d]	dcype	Cs_2CO_3	toluene	100	25%

[a]Reaction conditions: **1a** (0.2 mmol), $(i\text{-PrO})_2P(O)H$ (0.3 mmol), 10 mol % $Ni(COD)_2$, base (0.22 mmol), solvent (1 mL), 24 h. [b]GC yield using tridecane as an internal standard. [c]$(i\text{-PrO})_2P(O)H$ was added in two portions (0.15 mmol of **2a** was added after the reaction mixture was stirred for 12 h). [d]Phenyl dimethyl carbamate was used as a substrate.

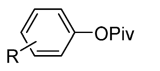
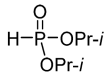
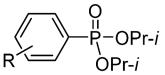
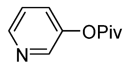
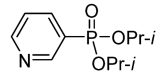
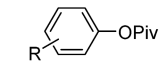
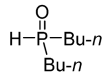
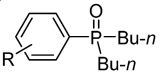
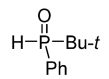
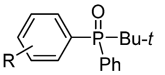
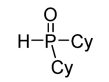
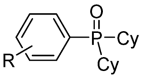
(1,3-bis(diphenylphosphino)propane), and dppf (1,1′-bis-(diphenylphosphino)ferrocene) under similar reaction conditions (entries 16−18). Worth noting is that, when **2a** was added in two portions (0.75 equiv was added at the start, and the other part was added after 12 h), an excellent yield (94% yield) of product **3a** was obtained (entry 19).[13,14] Carbamate could also be converted to the corresponding product **3a** in 25% yield under the reaction conditions (entry 20).

This transformation is applicable to other substrates. As shown in Table 2, both electron-rich and electron-deficient phenyl pivalates reacted with a variety of hydrogen phosphoryl compounds under the present reaction conditions, producing the corresponding coupling products in good to high yields. Thus, 4-methylphenyl pivalate was found as reactive as phenyl pivalate **1a** to react with diisopropyl phosphonate **2a**, giving the expected product **3b** in 93% yield (entries 1 and 2). 3-Methylphenyl pivalate also coupled with **2a** readily (entry 3). However, when 2-methylphenyl pivalate was employed as a substrate, a relatively low yield was given (entry 4). This perhaps was due to the highly steric hindrance of the substrate. Other selected derivatives of pivalates with electron-donating groups like butyl, methoxy, and amide groups on the benzene ring all served as good substrates and were converted to the corresponding aryl phosphonates in good to high yields (entries 5−7). 4-Fluorophenyl pivalate was phosphorylated successfully by diisopropyl phosphonate in the present coupling system with fluoro group intact (entry 8), whereas a chloro group did not survive. When 4-chlorophenyl pivalate was

Table 2. Ni-Catalyzed C−O/P−H Cross-Coupling of Phenyl Pivalates 1 with P(O)−H Compounds Producing Aryl Phosphonates and Aryl Phosphine Oxides 3[a]



1 2 3

entry	substrate **1**	substrate **2**	product **3** (isolated yield)
			
1	**1a**, R = 4-H	**2a**	**3a**, R = 4-H, 90%
2	**1b**, R = 4-Me		**3b**, R = 4-Me, 93%
3	**1c**, R = 3-Me		**3c**, R = 3-Me, 75%
4[b,c]	**1d**, R = 2-Me		**3d**, R = 2-Me, 36%
5	**1e**, R = 4-*n*-Bu		**3e**, R = 4-*n*-Bu, 70%
6	**1f**, R = 4-MeO		**3f**, R = 4-MeO, 92%
7[b,c]	**1g**, R = 4-NHPiv		**3g**, R = 4-NHPiv, 82%
8	**1h**, R = 4-F		**3h**, R = 4-F, 83%
9[d]	**1i**, R = 4-Cl		**3i**, R = 4-P(O)$(OPr\text{-}i)_2$, 82%
10[b,c]	**1j**, R = 4-CN		**3j**, R = 4-CN, 82%
11	**1k**, R = 4-CF_3		**3k**, R = 4-CF_3, 93%
12	**1l**, R = 4-Ac		**3l**, R = 4-Ac, 79%
13[b,e]	**1m**, R = 2-Ph		**3m**, R = 2-Ph, 52%
14[b,c]	**1n**, R = 4-Ph		**3n**, R = 4-Ph, 94%
15[b,d,f]	**1o**, R = 4-OPiv		**3i**, R = 4-P(O)$(OPr\text{-}i)_2$, 51%
			
16[b,c]	**1p**		**3o**, 71%
			
17[g]	**1a**, R = 4-H	**2b**	**3p**, R = 4-H, 95%
			
18[g]	**1a**, R = 4-H	**2c**	**3q**, R = 4-H, 93%
			
19[g]	**1a**, R = 4-H	**2d**	**3r**, R = 4-H, 97%
20[g]	**1d**, R = 4-Me		**3s**, R = 4-Me, 96%
21[g]	**1f**, R = 4-MeO		**3t**, R = 4-MeO, 94%
22[g]	**1h**, R = 4-F		**3u**, R = 4-F, 95%
23[g]	**1j**, R = 4-CN		**3v**, R = 4-CN, 98%

[a]Reaction conditions: 0.2 mmol of **1**, 0.3 mmol of **2** (added in two portions: 0.15 mmol of **2a** was added after the reaction mixture was stirred for 12 h), 10 mol % $Ni(COD)_2$, 10 mol % dcype, 0.22 mmol of Cs_2CO_3, 1 mL of toluene, 100 °C, 24 h. [b]20% mol $Ni(COD)_2$, 20 mol % dcype. [c]110 °C, 46 h. [d]0.6 mmol of **2a** was added. [e]100 °C, 46 h. [f]110 °C. [g]One-pot reaction, 0.2 mmol of **2**.

loaded, a diphosphorylated product **3i** was produced under similar reaction conditions (entry 9). Substrates with strong electron-withdrawing groups like CN, CF_3, and Ac groups on the benzene ring also coupled with diisopropyl phosphonate smoothly, furnishing the desired aryl phosphonates in high yields (entries 10−12). Phenyl pivalates bearing a phenyl group at the *ortho* or *para* position also reacted with **2a** to yield the expected products **3m** and **3n** in 52% and 94% yields, respectively (entries 13 and 14). To our delight, two phosphoryl groups were introduced into the molecule via a one-pot process by a diphosphorylation of bispivalates, as

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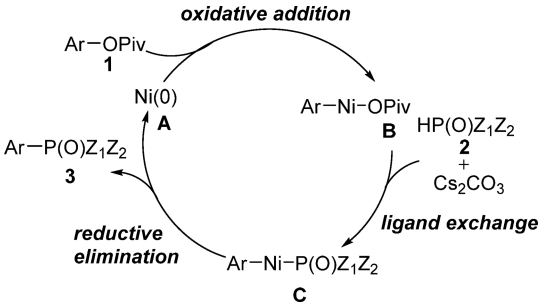
exemplified by 1,4-phenylene bispivalates (entry 15). Intriguingly, the heteroaryl phosphonate **3o** was also obtained in 71% yield from the nickel-catalyzed reaction of 3-pyrindinyl pivalate with diisopropyl phosphonate via C−O/P−H cross-coupling (entry 16).

As to the hydrogen phosphoryl compounds, comparing with H-phosphonate **2a**, secondary phosphine oxides also served well and showed higher reactivity in the current catalytic system.[15] Thus, *n*-$Bu_2P(O)H$ **2b** reacted readily with an equivalent of phenyl pivalate **1a** to produce the corresponding phenyl dibutyl phosphine oxide **3p** in 95% yield (entry 17). *t*-BuPhP(O)H **2c** also coupled with **1a** under similar reaction conditions, leading to the production of aryl phosphine oxide **3q** in 93% yield (entry 18). Even the bulky dicyclohexyl phosphine oxide **2d** was also found reactive to react with both electron-rich and electron-deficient phenyl pivalates, generating the corresponding aryl phosphine oxides in high yields (entries 19−23).

We deduce that this Ni-catalyzed cross-coupling takes place via a catalytic cycle as shown in Scheme 2.[16] The oxidative addition of $Ni(COD)_2$ with phenyl pivalates **1** at an elevated temperature took place to generate the intermediate **B**,[16a,b] followed by ligand exchange to give the intermediate **C**[16e,f] in the presence of a stronger base Cs_2CO_3. The intermediate **C** underwent reductive elimination to give the corresponding coupling product **3**.

Scheme 2. Plausible Mechanism for the Ni-Catalyzed C−O/P−H Cross-Coupling of Phenyl Pivalates with P(O)−H Compounds



In summary, an efficient Ni-catalyzed phosphorylation of phenyl pivalates with hydrogen phosphoryl compounds was developed. This Ni-catalyzed C−O/P−H cross-coupling has a broad general applicability in P−C bond formation. Various aryl phosphorus compounds were prepared successfully by using the easily available phenol derivatives as the arylating reagents via C−O activation.

EXPERIMENTAL SECTION

General Information. All reactions were carried out in oven-dried Schlenk tubes under a N_2 atmosphere. Solvents were distilled after treatment by calcium hydride. Reagents were used as received unless otherwise noted. Column chromatography was performed using Silica Gel 60 (particle size 37−54 μm). The pure products were obtained by means of column chromatography (petroleum ether and ethyl acetate were used as the gradient eluting solvents). ^1H NMR, ^{13}C NMR, and ^{31}P NMR data were acquired on a 400 spectrometer (400 MHz for ^1H, 100 MHz for ^{13}C, and 162 MHz for ^{31}P NMR spectroscopy). Chemical shifts for ^1H NMR are referred to internal Me_4Si (0 ppm) and reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz), and integration. Data for ^{31}P NMR were relative to H_3PO_4 (85% solution in D_2O, 0 ppm). The ionization method of the high-resolution mass spectrum (HRMS) is electron impact (EI). The type of the mass analyzer is quadrupole. IR data were recorded as KBr pellets on an FTIR spectrophotometer and are reported as wavenumbers (cm^{-1}).

Synthesis of Starting Materials. Aryl pivalates have been prepared via the classical reaction of the free phenol in the presence of Et_3N (1.20 equiv), PivCl (1.20 equiv) in DCM at room temperature. The products were purified by regular flash chromatography (petroleum ether/EtOAc mixtures).[7a]

Typical Procedure for the Nickel-Catalyzed C−O/P−H Cross-Coupling of P(O)−H Compounds with Alcohol Derivatives. Under a N_2 atmosphere, 0.2 mmol of phenyl pivalate **1a**, 10 mol % $Ni(COD)_2$, 10 mol % dcype, 1.1 equiv of Cs_2CO_3, and 1 mL of toluene were charged into a 10 mL Schlenk tube; then 0.15 mmol of $(i\text{-PrO})_2P(O)H$ **2a** was added to the mixture. After the reaction was processed in 100 °C for 12 h, the other 0.15 mmol of $(i\text{-PrO})_2P(O)H$ **2a** was added to the glass tube under a N_2 atmosphere. The mixture was further stirred at 100 °C for 12 h. After removal of the volatile, the residues were passed through a short silica chromatography (particle size 37−54 μm, petroleum ether/ethyl acetate as eluent) to afford analytically pure organophosphorus compounds **3**.

*Diisopropyl Phenylphosphonate (**3a**).* Purification by chromatography (petroleum ether/EtOAc = 2:1) afforded **3a** (43.6 mg, 90%) as a colorless oil. R_f = 0.59 (petroleum ether/EtOAc = 1:1); ^1H NMR (400 MHz $CDCl_3$): δ 7.85−7.79 (m, 2H), 7.54−7.42 (m, 3H), 4.75−4.64 (m, 2H), 1.37 (d, *J* = 6.4 Hz, 6H), 1.23 (d, *J* = 6.0 Hz, 6H). ^{13}C NMR (100 MHz $CDCl_3$): δ 132.0 (d, $J_{C\text{-}P}$ = 3.0 Hz), 131.6 (d, $J_{C\text{-}P}$ = 9.7 Hz), 129.9 (d, $J_{C\text{-}P}$ = 187.4 Hz), 128.2 (d, $J_{C\text{-}P}$ = 14.9 Hz), 70.6 (d, $J_{C\text{-}P}$ = 5.5 Hz), 24.0 (d, $J_{C\text{-}P}$ = 3.9 Hz), 23.8 (d, $J_{C\text{-}P}$ = 4.8 Hz). ^{31}P NMR (162 MHz $CDCl_3$): δ 16.52. This compound is known.[17]

*Diisopropyl p-Tolylphosphonate (**3b**).* Purification by chromatography (petroleum ether/EtOAc = 3:1) afforded **3b** (47.6 mg, 93%) as a colorless oil. R_f = 0.49 (petroleum ether/EtOAc = 2:1); ^1H NMR (400 MHz $CDCl_3$): δ 7.73−7.68 (m, 2H), 7.28−7.24 (m, 2H), 4.72−4.61 (m, 2H), 2.39 (s, 3H), 1.36 (d, *J* = 6.0 Hz, 6H), 1.22 (d, *J* = 6.0 Hz, 6H). ^{13}C NMR (100 MHz $CDCl_3$): δ 142.6 (d, $J_{C\text{-}P}$ = 3.1 Hz), 131.8 (d, $J_{C\text{-}P}$ = 10.2 Hz), 129.1 (d, $J_{C\text{-}P}$ = 15.3 Hz), 126.6 (d, $J_{C\text{-}P}$ = 189.7 Hz), 70.6 (d, $J_{C\text{-}P}$ = 5.4 Hz), 24.1 (d, $J_{C\text{-}P}$ = 3.9 Hz), 23.8 (d, $J_{C\text{-}P}$ = 4.8 Hz), 21.6 (d, $J_{C\text{-}P}$ = 1.1 Hz). ^{31}P NMR (162 MHz $CDCl_3$): δ 17.38. This compound is known.[17]

*Diisopropyl m-Tolylphosphonate (**3c**).* Purification by chromatography (petroleum ether/EtOAc = 2:1) afforded **3c** (38.4 mg, 75%) as a colorless oil. R_f = 0.40 (petroleum ether/EtOAc = 2:1); ^1H NMR (400 MHz $CDCl_3$): δ 7.66−7.57 (m, 2H), 7.36−7.28 (m, 2H), 4.71−4.66 (m, 2H), 2.39 (s, 3H), 1.37 (d, *J* = 6.0 Hz, 6H), 1.23 (d, *J* = 6.4 Hz, 6H). ^{13}C NMR (100 MHz $CDCl_3$): δ 138.1 (d, $J_{C\text{-}P}$ = 14.8 Hz), 132.9 (d, $J_{C\text{-}P}$ = 3.1 Hz), 132.3 (d, $J_{C\text{-}P}$ = 9.9 Hz), 129.7 (d, $J_{C\text{-}P}$ = 186.8 Hz), 128.7 (d, $J_{C\text{-}P}$ = 9.5 Hz), 128.2 (d, $J_{C\text{-}P}$ = 15.7 Hz), 70.7 (d, $J_{C\text{-}P}$ = 5.5 Hz), 24.1 (d, $J_{C\text{-}P}$ = 3.9 Hz), 23.8 (d, $J_{C\text{-}P}$ = 4.8 Hz), 21.3. ^{31}P NMR (162 MHz $CDCl_3$): δ 17.17. This compound is known.[17]

*Diisopropyl o-Tolylphosphonate (**3d**).* Purification by chromatography (petroleum ether/EtOAc = 3:1) afforded **3d** (18.4 mg, 36%) as a colorless oil. R_f = 0.51 (petroleum ether/EtOAc = 2:1); ^1H NMR (400 MHz $CDCl_3$): δ 7.97−7.92 (m, 1H), 7.41 (t, *J* = 7.6 Hz, 1H), 7.28−7.22 (m, 2H), 4.77−4.65 (m, 2H), 2.58 (s, 3H), 1.38 (d, *J* = 6.4 Hz, 6H), 1.24 (d, *J* = 6.4 Hz, 6H). ^{13}C NMR (100 MHz $CDCl_3$): δ 141.6 (d, $J_{C\text{-}P}$ = 9.7 Hz), 133.8 (d, $J_{C\text{-}P}$ = 10.4 Hz), 132.2 (d, $J_{C\text{-}P}$ = 2.9 Hz), 131.1 (d, $J_{C\text{-}P}$ = 14.7 Hz), 128.3 (d, $J_{C\text{-}P}$ = 183.8 Hz), 125.3 (d, $J_{C\text{-}P}$ = 14.9 Hz), 70.6 (d, $J_{C\text{-}P}$ = 5.7 Hz), 24.1 (d, $J_{C\text{-}P}$ = 4.1 Hz), 23.8 (d, $J_{C\text{-}P}$ = 4.6 Hz), 21.3 (d, $J_{C\text{-}P}$ = 3.4 Hz). ^{31}P NMR (162 MHz $CDCl_3$): δ 17.19. This compound is known.[17]

*Diisopropyl (4-Butylphenyl)phosphonate (**3e**).* Purification by chromatography (petroleum ether/EtOAc = 3:1) afforded **3e** (41.7 mg, 70%) as a colorless oil. R_f = 0.54 (petroleum ether/EtOAc = 2:1); ^1H NMR (400 MHz $CDCl_3$): δ 7.74−7.69 (m, 2H), 7.29−7.24 (m, 2H), 4.71−4.63 (m, 2H), 2.65 (t, *J* = 8.0 Hz, 2H), 1.65−1.57 (m, 2H), 1.40−1.31 (m, 8H), 1.22 (d, *J* = 6.4 Hz, 6H), 0.93 (d, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz $CDCl_3$): δ 147.5 (d, $J_{C\text{-}P}$ = 3.1 Hz), 131.8 (d, $J_{C\text{-}P}$ = 10.3 Hz), 128.4 (d, $J_{C\text{-}P}$ = 15.3 Hz), 126.7 (d, $J_{C\text{-}P}$ = 189.8 Hz), 70.6 (d, $J_{C\text{-}P}$ = 5.4 Hz), 35.7 (d, $J_{C\text{-}P}$ = 0.8 Hz), 33.2, 24.1 (d, $J_{C\text{-}P}$ = 4.0 Hz),

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J. Org. Chem. 2016, 81, 3911−3916

23.8 (d, J_{C-P} = 4.8 Hz), 22.3, 13.9. ^{31}P NMR (162 MHz $CDCl_3$): δ 17.44. This compound is known.[17]

*Diisopropyl (4-Methoxyphenyl)phosphonate (**3f**).* Purification by chromatography (petroleum ether/EtOAc = 2:1) afforded **3f** (50.0 mg, 92%) as a colorless oil. R_f = 0.32 (petroleum ether/EtOAc = 2:1); ^{1}H NMR (400 MHz $CDCl_3$): δ 7.77−7.72 (m, 2H), 6.96−6.94 (m, 2H), 4.71−4.59 (m, 2H), 3.85 (s, 3H), 1.36 (d, J = 6.0 Hz, 6H), 1.22 (d, J = 6.4 Hz, 6H). ^{13}C NMR (100 MHz $CDCl_3$): δ 162.6 (d, J_{C-P} = 3.3 Hz), 133.7 (d, J_{C-P} = 11.2 Hz), 121.2 (d, J_{C-P} = 194.2 Hz), 113.8 (d, J_{C-P} = 15.9 Hz), 70.4 (d, J_{C-P} = 5.4 Hz), 55.3, 24.1 (d, J_{C-P} = 3.9 Hz), 23.8 (d, J_{C-P} = 4.8 Hz). ^{31}P NMR (162 MHz $CDCl_3$): δ 17.49. This compound is known.[17]

*Diisopropyl (4-Pivalamidophenyl)phosphonate (**3g**).* Purification by chromatography (petroleum ether/EtOAc = 1:1) afforded **3g** (55.9 mg, 82%) as a white solid. R_f = 0.27 (petroleum ether/EtOAc = 1:1); ^{1}H NMR (400 MHz $CDCl_3$): δ 7.72−7.67 (m, 2H), 7.60−7.57 (m, 2H), 7.48 (s, 1H), 4.62−4.54 (m, 2H), 1.29 (d, J = 6.0 Hz, 6H), 1.26 (s, 9H), 1.14 (d, J = 6.4 Hz, 6H). ^{13}C NMR (100 MHz $CDCl_3$): δ 175.9, 140.6 (d, J_{C-P} = 3.4 Hz), 131.9 (d, J_{C-P} = 10.6 Hz), 123.8 (d, J_{C-P} = 192.0 Hz), 118.1 (d, J_{C-P} = 15.2 Hz), 69.7 (d, J_{C-P} = 5.4 Hz), 38.8, 26.5, 23.1 (d, J_{C-P} = 4.0 Hz), 22.8 (d, J_{C-P} = 4.8 Hz). ^{31}P NMR (162 MHz $CDCl_3$): δ 16.45. This compound is known.[18]

*Diisopropyl (4-Fluorophenyl)phosphonate (**3h**).* Purification by chromatography (petroleum ether/EtOAc = 3:1) afforded **3h** (43.2 mg, 83%) as a colorless oil. R_f = 0.40 (petroleum ether/EtOAc = 2:1); ^{1}H NMR (400 MHz $CDCl_3$): δ 7.86−7.79 (m, 2H), 7.14 (ddd, J = 2.8 Hz, J = 8.8 Hz, J = 8.8 Hz, 2H), 4.73−4.65 (m, 2H), 1.37 (d, J = 6.4 Hz, 6H), 1.27 (d, J = 6.0 Hz, 6H). ^{13}C NMR (100 MHz $CDCl_3$): δ 165.2 (dd, J_{C-F} = 251.4 Hz, J_{C-P} = 3.8 Hz), 134.2 (dd, J_{C-F} = 10.0 Hz, J_{C-P} = 2.4 Hz), 126.1 (dd, J_{C-F} = 3.5 Hz, J_{C-P} = 192.2 Hz), 115.6 (dd, J_{C-F} = 18.7 Hz, J_{C-P} = 5.1 Hz), 70.9 (d, J_{C-P} = 5.5 Hz), 24.0 (d, J_{C-P} = 4.0 Hz), 23.8 (d, J_{C-P} = 4.7 Hz). ^{31}P NMR (162 MHz $CDCl_3$): δ 15.59. This compound is known.[9b]

*Tetraisopropyl 1,4-Phenylenebis(phosphonate) (**3i**).* Purification by chromatography (petroleum ether/EtOAc = 1:1) afforded **3i** (pivalate **1i**, 66.6 mg, 82%; pivalate **1o**, 41.5 mg, 51%) as a white solid. R_f = 0.58 (EtOAc); m.p.: 97−98 °C; ^{1}H NMR (400 MHz $CDCl_3$): δ 7.91−7.87 (m, 4H), 4.78−4.67 (m, 4H), 1.38 (d, J = 6.0 Hz, 12H), 1.24 (d, J = 6.4 Hz, 12H). ^{13}C NMR (100 MHz $CDCl_3$): δ 134.1 (dd, J_{C-P} = 3.0 Hz, J_{C-P} = 186.5 Hz), 131.4 (dd, J_{C-P} = 12.2 Hz, J_{C-P} = 3.7 Hz), 71.2 (d, J_{C-P} = 5.7 Hz), 24.0 (d, J_{C-P} = 3.8 Hz), 23.8 (d, J_{C-P} = 4.6 Hz).^{31}P NMR (162 MHz $CDCl_3$): δ 14.79. HRMS: Cal. for $C_{18}H_{32}O_6P_2$ 406.1674. Found 406.1660. IR: 2983, 2935, 1469, 1249, 1143, 979 cm^{-1}.

*Diisopropyl (4-Cyanophenyl)phosphonate (**3j**).* Purification by chromatography (petroleum ether/EtOAc = 2:1) afforded **3j** (43.8 mg, 82%) as a colorless oil. R_f = 0.33 (petroleum ether/EtOAc = 2:1); ^{1}H NMR (400 MHz $CDCl_3$): δ 7.95−7.89 (m, 2H), 7.76−7.73 (m, 2H), 4.78−4.70 (m, 2H), 1.39 (d, J = 6.4 Hz, 6H), 1.24 (d, J = 6.0 Hz, 6H). ^{13}C NMR (100 MHz $CDCl_3$): δ 135.5 (d, J_{C-P} = 187.3 Hz), 132.2 (d, J_{C-P} = 9.7 Hz), 131.9 (d, J_{C-P} = 14.8 Hz), 117.9 (d, J_{C-P} = 1.4 Hz), 115.7 (d, J_{C-P} = 3.6 Hz), 71.6 (d, J_{C-P} = 5.8 Hz), 24.0 (d, J_{C-P} = 4.1 Hz), 23.8 (d, J_{C-P} = 4.7 Hz). ^{31}P NMR (162 MHz $CDCl_3$): δ 13.12. This compound is known.[18]

*Diisopropyl (4-(Trifluoromethyl)phenyl)phosphonate (**3k**).* Purification by chromatography (petroleum ether/EtOAc = 3:1) afforded **3k** (57.7 mg, 93%) as a colorless oil. R_f = 0.51 (petroleum ether/EtOAc = 2:1); ^{1}H NMR (400 MHz $CDCl_3$): δ 7.98−7.93 (m, 2H), 7.73−7.71 (m, 2H), 4.79−4.68 (m, 2H), 1.39 (d, J = 6.0 Hz, 6H), 1.24 (d, J = 6.4 Hz, 6H). ^{13}C NMR (100 MHz $CDCl_3$): δ 134.4 (d, J_{C-P} = 187.9 Hz), 133.7 (dd, J_{C-P} = 3.3 Hz, J_{C-F} = 32.3 Hz), 132.1 (d, J_{C-P} = 10.0 Hz), 125.2 (dq, J_{C-P} = 3.7 Hz, J_{C-F} = 15.0 Hz), 123.6 (q, J_{C-F} = 271.2 Hz), 71.3 (d, J_{C-P} = 5.7 Hz), 24.0 (d, J_{C-P} = 4.0 Hz), 23.8 (d, J_{C-P} = 4.7 Hz). ^{31}P NMR (162 MHz $CDCl_3$): δ 14.07. This compound is known.[18]

*Diisopropyl (4-Acetylphenyl)phosphonate (**3l**).* Purification by chromatography (petroleum ether/EtOAc = 3:1) afforded **3l** (45.0 mg, 79%) as a colorless oil. R_f = 0.44 (petroleum ether/EtOAc = 2:1); ^{1}H NMR (400 MHz $CDCl_3$): δ 8.04−8.01 (m, 2H), 7.95−7.90 (m, 2H), 4.77−4.69 (m, 2H), 2.65 (s, 3H), 1.39 (d, J = 6.0 Hz, 6H), 1.24 (d, J = 6.4 Hz, 6H). ^{13}C NMR (100 MHz $CDCl_3$): δ 197.6, 139.6 (d, J_{C-P} = 3.1 Hz), 134.9 (d, J_{C-P} = 186.1 Hz), 132.0 (d, J_{C-P} = 9.9 Hz), 127.9 (d, J_{C-P} = 15.0 Hz), 71.2 (d, J_{C-P} = 5.6 Hz), 26.8, 24.0 (d, J_{C-P} = 4.0 Hz), 23.8 (d, J_{C-P} = 4.7 Hz). ^{31}P NMR (162 MHz $CDCl_3$): δ 14.60. This compound is known.[19]

*Diisopropyl [1,1′-Biphenyl]-2-ylphosphonate (**3m**).* Purification by chromatography (petroleum ether/EtOAc = 3:1) afforded **3m** (33.2 mg, 52%) as a colorless oil. R_f = 0.49 (petroleum ether/EtOAc = 2:1); ^{1}H NMR (400 MHz $CDCl_3$): δ 8.11−8.05 (m, 1H), 7.53 (t, J = 7.2 Hz, 1H), 7.46−7.29 (m, 7H), 4.63−4.52 (m, 2H), 1.16 (d, J = 6.4 Hz, 6H), 1.12 (d, J = 6.4 Hz, 6H). ^{13}C NMR (100 MHz $CDCl_3$): δ 145.9 (d, J_{C-P} = 9.4 Hz), 141.7 (d, J_{C-P} = 3.9 Hz), 133.6 (d, J_{C-P} = 10.0 Hz), 131.7 (d, J_{C-P} = 2.9 Hz), 131.5 (d, J_{C-P} = 14.1 Hz), 129.7, 128.5 (d, J_{C-P} = 187.8 Hz), 127.3, 127.2 (d, J_{C-P} = 9.0 Hz), 126.7 (d, J_{C-P} = 14.6 Hz), 70.7 (d, J_{C-P} = 6.3 Hz), 23.9 (d, J_{C-P} = 4.2 Hz), 23.7 (d, J_{C-P} = 4.9 Hz). ^{31}P NMR (162 MHz $CDCl_3$): δ 16.16. This compound is known.[20]

*Diisopropyl [1,1′-Biphenyl]-4-ylphosphonate (**3n**).* Purification by chromatography (petroleum ether/EtOAc = 3:1) afforded **3n** (59.8 mg, 94%) as a colorless oil. R_f = 0.44 (petroleum ether/EtOAc = 2:1); ^{1}H NMR (400 MHz $CDCl_3$): δ 7.91−7.86 (m, 2H), 7.69−7.66 (m, 2H), 7.61 (d, J = 7.6 Hz, 2H), 7.46 (t, J = 8.0 Hz, 2H), 7.39 (t, J = 7.2 Hz, 2H), 4.76−4.68 (m, 2H), 1.39 (d, J = 6.4 Hz, 6H), 1.26 (d, J = 6.0 Hz, 6H). ^{13}C NMR (100 MHz $CDCl_3$): δ 144.8 (d, J_{C-P} = 3.2 Hz), 140.1 (d, J_{C-P} = 0.7 Hz), 132.3 (d, J_{C-P} = 10.2 Hz), 128.9, 128.5 (d, J_{C-P} = 189.3 Hz), 128.1, 127.3, 127.0 (d, J_{C-P} = 15.1 Hz), 70.8 (d, J_{C-P} = 5.5 Hz), 24.1 (d, J_{C-P} = 3.9 Hz), 23.9 (d, J_{C-P} = 4.8 Hz). ^{31}P NMR (162 MHz $CDCl_3$): δ 16.84. This compound is known.[9b]

*Diisopropylpyridin-3-ylphosphonate (**3o**).* Purification by chromatography (petroleum ether/EtOAc = 1:1) afforded **3o** (34.5 mg, 71%) as a colorless oil. R_f = 0.28 (petroleum ether/EtOAc = 1:1); ^{1}H NMR (400 MHz $CDCl_3$): δ 8.91−8.90 (m, 1H), 8.68−8.67 (m, 1H), 8.05−8.00 (m, 1H), 7.32−7.31 (m, 1H), 4.70−4.65 (m, 2H), 1.33−1.30 (m, 6H), 1.19−1.17 (m, 6H). ^{13}C NMR (100 MHz $CDCl_3$): δ 152.6 (br), 152.2 (d, J_{C-P} = 12.1 Hz), 139.3 (d, J_{C-P} = 8.2 Hz), 126.4 (d, J_{C-P} = 188.8 Hz), 123.2 (d, J_{C-P} = 11.4 Hz), 71.4 (d, J_{C-P} = 5.8 Hz), 24.0 (d, J_{C-P} = 4.1 Hz), 23.8 (d, J_{C-P} = 4.8 Hz). ^{31}P NMR (162 MHz $CDCl_3$): δ 13.49. This compound is known.[18]

*Dibutyl(phenyl)phosphine Oxide (**3p**).* Purification by chromatography (petroleum ether/EtOAc = 1:2) afforded **3p** (45.2 mg, 95%) as a white solid. R_f = 0.53 (EtOAc); ^{1}H NMR (400 MHz $CDCl_3$): δ 7.73−7.68 (m, 2H), 7.53−7.49 (m, 3H), 2.04−1.81 (m, 4H), 1.67−1.54 (m, 2H), 1.48−1.31 (m, 6H), 0.87 (t, J = 7.2 Hz, 6H). ^{13}C NMR (100 MHz $CDCl_3$): δ 132.7 (d, J_{C-P} = 91.6 Hz), 131.4 (d, J_{C-P} = 2.7 Hz), 130.4 (d, J_{C-P} = 8.6 Hz), 128.6 (d, J_{C-P} = 11.0 Hz), 29.7 (d, J_{C-P} = 68.1 Hz), 24.1 (d, J_{C-P} = 14.4 Hz), 23.5 (d, J_{C-P} = 4.1 Hz), 13.6. ^{31}P NMR (162 MHz $CDCl_3$): δ 41.91. This compound is known.[21]

*Tert-butyldiphenylphosphine Oxide (**3q**).* Purification by chromatography (petroleum ether/EtOAc = 1:2) afforded **3q** (48.0 mg, 93%) as a white solid. R_f = 0.60 (EtOAc); ^{1}H NMR (400 MHz $CDCl_3$): δ 7.96 (dd, J = 8.8 Hz, J = 8.8 Hz, 4H), 7.54−7.46 (m, 6H), 1.25 (d, J = 14.8 Hz, 9H). ^{13}C NMR (100 MHz $CDCl_3$): δ 132.2 (d, J_{C-P} = 8.0 Hz), 131.5 (d, J_{C-P} = 2.5 Hz), 131.1 (d, J_{C-P} = 89.8 Hz), 128.3 (d, J_{C-P} = 10.8 Hz), 34.0 (d, J_{C-P} = 70.4 Hz), 25.2. ^{31}P NMR (162 MHz $CDCl_3$): δ 39.22. This compound is known.[21]

*Dicyclohexyl(phenyl)phosphine Oxide (**3r**).* Purification by chromatography (petroleum ether/EtOAc = 1:2) afforded **3r** (56.4 mg, 97%) as a white solid. R_f = 0.43 (EtOAc); ^{1}H NMR (400 MHz $CDCl_3$): δ 7.67 (dd, J = 8.4 Hz, J = 8.4 Hz, 2H), 7.54−7.42 (m, 3H), 2.06 (br, 4H), 1.82−1.61 (m, 8H), 1.32−1.12 (m, 10H). ^{13}C NMR (100 MHz $CDCl_3$): δ 131.5 (d, J_{C-P} = 7.6 Hz), 131.2 (d, J_{C-P} = 2.3 Hz), 129.8 (d, J_{C-P} = 85.2 Hz), 128.2 (d, J_{C-P} = 10.3 Hz), 35.7 (d, J_{C-P} = 67.1 Hz), 26.4 (d, J_{C-P} = 12.4 Hz), 26.3 (d, J_{C-P} = 11.1 Hz), 25.8, 25.5 (d, J_{C-P} = 1.8 Hz), 24.6 (d, J_{C-P} = 3.1 Hz). ^{31}P NMR (162 MHz $CDCl_3$): δ 45.74. This compound is known.[22]

*Dicyclohexyl(p-tolyl)phosphine Oxide (**3s**).* Purification by chromatography (petroleum ether/EtOAc = 1:2) afforded **3s** (58.4 mg, 96%) as a colorless oil. R_f = 0.47 (EtOAc); ^{1}H NMR (400 MHz $CDCl_3$): δ 7.55 (dd, J = 8.8 Hz, J = 8.8 Hz, 2H), 7.29−7.28 (m, 2H), 2.40 (s, 3H), 2.03−2.00 (m, 4H), 1.81−1.60 (m, 8H), 1.34−1.12 (m,

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10H). ^{13}C NMR (100 MHz $CDCl_3$): δ 141.6 (d, J_{C-P} = 2.6 Hz), 131.5 (d, J_{C-P} = 8.0 Hz), 129.1 (d, J_{C-P} = 10.8 Hz), 126.3 (d, J_{C-P} = 87.4 Hz), 35.1 (d, J_{C-P} = 67.0 Hz), 26.4 (d, J_{C-P} = 11.1 Hz), 26.3 (d, J_{C-P} = 10.4 Hz), 25.8, 25.5 (d, J_{C-P} = 2.2 Hz), 24.6 (d, J_{C-P} = 3.3 Hz), 21.5. ^{31}P NMR (162 MHz $CDCl_3$): δ 46.08. HRMS: Cal. for $C_{19}H_{29}OP$ 304.1956. Found 304.1950. IR: 2933, 2852, 1444, 1207, 1163, 808 cm^{-1}.

*Dicyclohexyl(4-methoxyphenyl)phosphine Oxide (**3t**).* Purification by chromatography (petroleum ether/EtOAc = 1:2) afforded **3t** (60.2 mg, 94%) as a colorless oil. R_f = 0.53 (EtOAc); ^{1}H NMR (400 MHz $CDCl_3$): δ 7.59 (dd, J = 8.8 Hz, J = 8.8 Hz, 2H), 6.99 (dd, J = 8.8 Hz, J = 1.2 Hz, 2H), 3.85 (s, 3H), 2.04−1.97 (m, 4H), 1.81−1.61 (m, 8H), 1.34−1.09 (m, 10H). ^{13}C NMR (100 MHz $CDCl_3$): δ 161.9 (d, J_{C-P} = 2.7 Hz), 133.1 (d, J_{C-P} = 8.7 Hz), 120.7 (d, J_{C-P} = 90.6 Hz), 113.8 (d, J_{C-P} = 11.2 Hz), 55.2, 35.2 (d, J_{C-P} = 67.4 Hz), 26.4 (d, J_{C-P} = 12.5 Hz), 26.3 (d, J_{C-P} = 11.9 Hz), 25.8 (d, J_{C-P} = 0.6 Hz), 25.5 (d, J_{C-P} = 2.3 Hz), 24.6 (d, J_{C-P} = 3.2 Hz). ^{31}P NMR (162 MHz $CDCl_3$): δ 45.75. This compound is known.[22]

*Dicyclohexyl(4-fluorophenyl)phosphine Oxide (**3u**).* Purification by chromatography (petroleum ether/EtOAc = 2:1) afforded **3a** (58.6 mg, 95%) as a white solid. R_f = 0.55 (EtOAc); m.p.: 133−135 °C; ^{1}H NMR (400 MHz $CDCl_3$): δ 7.62−7.56 (m, 2H), 7.13−7.09 (m, 2H), 1.96−1.91 (m, 4H), 1.78−1.52 (m, 8H), 1.24−1.02 (m, 10H). ^{13}C NMR (100 MHz $CDCl_3$): δ 163.8 (dd, J_{C-P} = 3.1 Hz, J_{C-F} = 250.6 Hz), 132.7 (dd, J_{C-P} = 8.0 Hz, J_{C-F} = 8.0 Hz), 124.5 (dd, J_{C-P} = 86.4 Hz, J_{C-F} = 3.7 Hz), 114.7 (d, J_{C-P} = 9.7 Hz, J_{C-F} = 11.3 Hz), 34.2 (d, J_{C-P} = 67.2 Hz), 25.4 (d, J_{C-P} = 12.2 Hz), 25.3 (d, J_{C-P} = 11.9 Hz), 24.8 (d, J_{C-P} = 1.1 Hz), 24.5 (d, J_{C-P} = 2.5 Hz), 23.6 (d, J_{C-P} = 3.3 Hz). ^{31}P NMR (162 MHz $CDCl_3$): δ 45.32. HRMS: Cal. for $C_{18}H_{26}OFP$ 308.1705. Found 308.1693. IR: 2927, 2852, 1593, 1500, 1228, 1163 cm^{-1}.

*4-(Dicyclohexylphosphoryl)benzonitrile (**3v**).* Purification by chromatography (petroleum ether/EtOAc = 1:2) afforded **3a** (61.8 mg, 98%) as a yellow oil. R_f = 0.55 (EtOAc); ^{1}H NMR (400 MHz $CDCl_3$): δ 7.83−7.77 (m, 4H), 2.07−2.05 (m, 4H), 1.86−1.57 (m, 8H), 1.36−1.11 (m, 10H). ^{13}C NMR (100 MHz $CDCl_3$): δ 136.2 (d, J_{C-P} = 79.5 Hz), 132.1 (d, J_{C-P} = 7.6 Hz), 131.7 (d, J_{C-P} = 10.1 Hz), 118.0 (d, J_{C-P} = 0.4 Hz), 115.1 (d, J_{C-P} = 2.9 Hz), 35.2 (d, J_{C-P} = 66.7 Hz), 26.3 (d, J_{C-P} = 9.9 Hz), 26.2 (d, J_{C-P} = 9.4 Hz), 25.7 (d, J_{C-P} = 1.0 Hz), 25.5 (d, J_{C-P} = 2.6 Hz), 24.6 (d, J_{C-P} = 3.3 Hz). ^{31}P NMR (162 MHz $CDCl_3$): δ 46.39. HRMS: Cal. for $C_{19}H_{26}ONP$ 315.1752. Found 315.1742. IR: 3493, 3423, 2229, 1649, 1444, 1392, 1211, 1105 cm^{-1}.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00289.

Copies of ^{1}H, ^{13}C, and ^{31}P NMR spectra and IR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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(10) As reported for C−O activation, the phenyl-based derivatives generally showed lower reactivity than the naphthyl-based derivatives; see refs 5a and 6e. Along this line, by elevating the reaction temperature and employing a stronger base, we achieved the cross-

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J. Org. Chem. 2016, 81, 3911−3916

coupling between phenyl-based derivatives and P(O)−H compounds, producing the corresponding aryl phosphorus compounds in good to high yields. Compared with ref 8, the solvent was also changed to toluene, and the starting material H-phosphonates was added in two portions in the present catalytic system. Those measures may decrease the decomposition (hydrolysis) of H-phosphonates.

(11) The result perhaps was due to the lower solubility of base in toluene, which decreased the decomposition (hydrolysis) of H-phosphonates. The base also played an important role in the C−O activation; see: Xu, H.; Muto, K.; Yamaguchi, J.; Zhao, C.; Itami, K.; Musaev, D. G. *J. Am. Chem. Soc.* **2014**, *136*, 14834.

(12) Low temperature led to difficulty for C−O activation, whereas high temperature led to severe decomposition (hydrolysis) of H-phosphonates.

(13) The reaction with 5 mol% $Ni(COD)_2$ was also performed; however, low yield of **3a** (40% yield) was given under similar reaction conditions.

(14) We performed the reaction in 2.0 mmol scale; 82% yield of **3a** was obtained.

(15) These results perhaps were due to the slight decomposition of H-phosphonates (hydrolysis) in the presence of a base. The guess was further supported by the experiment: when the easily hydrolyzed dimethyl phosphonate was employed as the substrate under the reaction conditions, no expected product was detected.

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J. Org. Chem. 2016, 81, 3911−3916