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Palladacycle-catalyzed phosphonation of aryl halides in neat water†

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An efficient and generally applicable protocol for the palladacycle-catalyzed arylation of diisopropyl H-phosphonate in water was developed. The remarkable features of this C–P bond-forming reaction include wide substrate scope including the inactive electron-rich and electron-neutral aryl chlorides, the weak inorganic base KF instead of strong bases such as KO^tBu or NaO^tBu for the activation of C–Cl bond, and the addition of isopropanol to avoid the decomposition of diisopropyl H-phosphonate.

Introduction

Transition metal-catalyzed C–P bond-forming reactions are powerful and reliable tools for the preparation of aryl phosphonates, phosphine oxides and phosphines, many of which are versatile ligands in catalytic reactions, compounds with biological activity or building blocks in polymer sciences and material science applications.^{1,2}

After the pioneering work of palladium-catalyzed phosphonation of aryl iodides or bromides by Hirao et al. in 1980, significant progress has been achieved on the improvements and modification of the reaction conditions.^{2a,b} Typically, the reactions were performed using the transition metal (e.g., Pd, 2 Cu, 3 and Ni⁴) and phosphine ligands (e.g., dppp, dppb, dppf and Xantphos) as the catalyst system in organic solvent (e.g., DMF, DMA, THF, toluene, and CH₃CN). However, the substrate scope is mainly limited to aryl iodides and bromides, and phosphonations using more commercially available aryl chlorides as the starting materials are still relatively few. The only examples of phosphonation of electron-neutral or electrondeficient aryl chlorides have been successfully developed by Montchamp^{2j} and Han's groups^{4b} in CH₃CN and dioxane, respectively. Just recently, our group reported the first examples of phosphonation for inactive electron-rich or electron-neutral aryl chlorides using palladacycle (1 mol%) and X-Phos (4 mol%) as the catalyst system in DMA.^{2t}

On the other hand, the ideology of green chemistry calls for energy efficiency, operational simplicity, and environmental safety. From this point of view, phosphonation performed in

neat water would be an ideal and fascinating choice. To the best of our knowledge, there are only two successful examples of phosphonation in water.⁵ The first phosphonation of aryl iodides and bromides with diphenylphosphine oxide in water was reported by Tang's group^{5a} using NiCl₂·6H₂O (10 mol %)/zinc powder (0.50 mmol) as the catalyst in 2011 (Scheme 1a). Very recently, Bokhoven's group^{5b} also described cross-coupling of halogenated benzoic acids with diphenylphosphine oxide using Pd/C as the catalyst in water under microwave irradiation (Scheme 1b). However, these two works mainly realized the phosphonation of more active substrates of aryl iodides and bromides with diphenylphosphine oxides. Compared to diphenylphosphine oxides, dialkyl H-phosphonates are unstable and active phosphonating reagents, because their decomposition reaction of dialkyl H-phosphonates tends to occur in water, generating phosphorous acid and isopropanol as the byproducts. And thus phosphonation of aryl halides with dialkyl H-phosphonates in water would be a research area rich in challenges (Scheme 1c).

In recent years, research interests in our group have focused on the application of a family of efficient palladacycles, cyclopalladated ferrocenylimines, as the catalysts for catalytic reactions (Fig. 1).⁶ Based on the above-mentioned and



Scheme 1 Phosphonation of aryl halides in water.

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Fig. 1 Cyclopalladated ferrocenylimines.

our own reports,² in this work we attempt to explore the possibility of the phosphonation of aryl halides in neat water, including the more challenging reaction of aryl chlorides with dialkyl phosphonates. As we know, the decomposition of dialkyl phosphonates to phosphorous acid and isopropanol in water is a reversible reaction. To avoid this side reaction, the effect of the addition of isopropanol as one hydrolysis product to the catalytic system will also be discussed.

Results and discussion

1. The palladacycle-catalyzed phosphonation of aryl iodides and bromides in water

Initially, the cross-coupling of 4-bromoanisole with diisopropyl H-phosphonate was performed as a model reaction. In the

 Table 1
 Optimizing conditions of the reaction of 4-bromoanisole with diisopropyl H-phosphonate in water^a

<u>`</u> 0	Br 0 + H ⁻ R ⁻ O'Pr - O'Pr -	Catalyst, Ado Base, H ₂ O, Re	flux, 16 h, N ₂	O P-O'Pr O'Pr
Entry	Catalyst	Base	Additive	Yield ^b (%)
1	Palladacycle (II)	K_2CO_3	TBAB	<5
2	Palladacycle (II)	KOAc	TBAB	<5
3	Palladacycle (II)	KO ^t Bu	TBAB	<5
4	Palladacycle (II)	K_3PO_4	TBAB	<5
5	Palladacycle (II)	Cs_2CO_3	TBAB	8
6	Palladacycle (II)	KF	TBAB	69
7	Palladacycle (II)	KF	TBAB/ ⁱ PrOH	95 (93)
8	Palladacycle (II)	KF	ⁱ PrOH	15
9	Palladacycle (II)	KF	SDS/ ⁱ PrOH	31
10^{c}	Palladacycle (II)	KF	Tween-80/ ⁱ PrOH	43
11^d	Palladacycle (II)	KF	PVA-124/ ⁱ PrOH	65
12^e	Palladacycle (II)	KF	_	30
13^{f}	Palladacycle (II)	KF	TBAB/ ⁱ PrOH	<5
14^g	Palladacycle (I)/PPh3	KF	TBAB/ ⁱ PrOH	78
15^h	$Pd[P(C_6H_{11})_3]_2Cl_2$	KF	TBAB/ ⁱ PrOH	69
16 ^{<i>i</i>}	$Pd(OAc)_2/PPh_3$	KF	TBAB/ ⁱ PrOH	77
17 ^j	NiCl ₂ /PPh ₃	KF	TBAB/ ⁱ PrOH	<5
18^k	NiCl ₂ (dppe)	KF	TBAB/ ⁱ PrOH	<5

^{*a*} Reaction conditions: 4-bromoanisole (0.4 mmol), diisopropyl H-phosphonate (0.6 mmol), base (1.2 mmol), additives (0.4 mmol), ⁱPrOH (1.2 mmol) and 1 mol% of the palladacycle (II) in H₂O (2 mL) at refluxing temperature under nitrogen atmosphere for 16 h. ^{*b*} GC yield (isolated yield) based on the amount of 4-bromoanisole. ^{*c*} With 100 mg of tween-80. ^{*d*} With 100 mg of polyvinyl alcohol (PVA-124). ^{*e*} Using 4-bromoanisole (2.0 mmol), KF (6.0 mmol), and diisopropyl H-phosphonate (3.0 mmol) at 100 °C under nitrogen atmosphere for 16 h. ^{*f*} Under air. ^{*g*} Palladacycle (I) (0.5 mol%), PPh₃ (1 mol%). ^{*h*} Pd[P(C₆H₁₁₎₃]₂Cl₂ (1 mol%). ^{*i*} Pd(OAc)₂ (1 mol%). (1 mol%). ^{*j*} NiCl₂ (1 mol%), PPh₃ (1 mol%). ^{*k*} NiCl₂(dppe) (1 mol%).

presence of TBAB as the additive, various bases were screened in water under nitrogen atmosphere, and KF gave the best result with a moderate GC yield of 69% (Table 1, entries 1-6). Then, the effect of isopropanol as the other additive was also checked, and gratifyingly it could indeed prevent the decomposition of diisopropyl H-phosphonate in neat water, affording the phosphonated product with a 95% GC and 93% isolated yield (Table 1, entry 7). However, when the reaction was performed in the absence of TBAB or using other additives (e.g., SDS, tween-80 or PVA-124) instead of TBAB, the reaction only gave low to moderate GC yields (Table 1, entries 8-11). Some control experiments were also explored (Table 1, entries 12 and 13). For example, the reaction gave a low GC yield of 30% under solvent-free condition, and the desired products were not detected under air. Finally, several other palladium or nickel catalysts were also evaluated, and palladium catalyst (e.g., palladacycle (I)/PPh₃, Pd[P(C₆H₁₁)₃]₂Cl₂ and Pd(OAc)₂/PPh₃) gave moderate yields; nickel catalysts (e.g., NiCl₂(dppe) and NiCl₂/PPh₃) did not exhibit any catalytic activity at all (Table 1, entries 14-18).

With the optimized reaction conditions in hand, the substrate scope of the reaction was then investigated, as shown in Table 2. Generally, the electronic effect had no evident influence on the phosphonation of aryl iodides and bromides, and the desired products were afforded in moderate to good yields. However, the aryl halides possessing a sterically hindered *ortho* substituent would result in the relatively lower yields of the corresponding products (Table 2, entries 2 and 5). It is worth noting that the reaction of aryl bromides containing a vinyl, methoxycarbonyl or heterocyclic group could also generate the phosphonated products in moderate yields (Table 2, entries 11–13).

2. The palladacycle-catalyzed phosphonation of aryl chlorides in water

Encouraged by the above results, we first performed phosphonation of 4-chloroanisole in water using palladacycle (II) or palladacycle (I)/PPh3 as the catalyst system under the optimized conditions, but the desired product could not observed at all (Table 3, entries 1 and 2). Then, the bulky alkylphosphine ligands such as 1,2-bis(diphenylphosphino)ethane (dppe), 1,1'-bis(diphenylphosphino)ferrocene (dppf), 2-dicyclohexylphosphino-2'-(N,N-dimethylamino)biphenyl (Davephos) 2-(dicyclohexylphosphino)-2',4',6'-triisopropyl-1,1'-bipheand nyl (X-Phos) were evaluated, and X-Phos showed as the best ligand and gave the product in isolated yields 76% (Table 3, entries 3-6). These results indicate that the phosphine ligand plays an important role for the successful reactions. Finally, some control experiments were also carried out, and it was found that the reaction in air or taking other commercially available metal catalysts (e.g., Pd(OAc)₂, Pd[P(C₆H₁₁)₃]₂Cl₂ and NiCl₂) instead of palladacycle (I) led to lower or even undetected yields (Table 3, entries 7-10).

With the conditions in Table 3, entry 6, fortunately, the catalytic system could be applicable to electron-rich, electronneutral, even weakly electron-poor aryl chlorides and the

 $\mbox{Table 2}$ Cross-coupling of aryl iodides or bromides with diisopropyl H-phosphonate in water^a

		Palladacycle II, TBAB, ⁱ PrOH	0 H air
ArX X=l or E	+ H ^{ar} \'O'Pr O'Pr Br	KF, H_2O , Reflux, 16 h, N_2	Ar ^{-P-O'Pr} O'Pr
1	2a		3
Enty	ArX	Product	$\operatorname{Yield}^{b}(\%)$
1	المراجع العام ا	PO(O'Pr) ₂ 3b	94
2	Ic Ic	PO(O'Pr) ₂	58
3		PO(O'Pr) ₂	84
4		PO(O [/] Pr) ₂	88
5		PO(O ['] Pr) ₂	62
6	l 1g	PO(O ['] Pr) ₂	99
7	Br 1h	PO(O ['] Pr) ₂ 3b	60
8	O- Br 1i	0- 3g PO(0/Pr)2	86
9	Br 1j	PO(O'Pr) ₂	68
10	Br 1k	PO(O ⁱ Pr) ₂ 3h	89
11	Br 11	PO(O'Pr) ₂	53
12	OMe Im	PO(O [/] Pr) ₂ OMe	85
13	Br S	PO(O ⁱ Pr) ₂	73

^{*a*} Reaction conditions: aryl iodide or bromide (0.4 mmol), diisopropyl H-phosphonate (0.6 mmol), KF (1.2 mmol), TBAB (0.4 mmol), ¹PrOH (1.2 mmol) and 1 mol% of the palladacycle (II) in H₂O (2 mL) at refluxing temperature under nitrogen atmosphere for 16 h. ^{*b*} Isolated yield based on the amount of the aryl iodide or bromide.

desired products were obtained in moderate to good yields (Table 4). The reaction could also tolerate various functional groups such as MeO, Me₂N and Cl. Especially, phosphonation of the *ortho* sterically hindered aryl chloride could also give a moderate yield (Table 4, entry 3).

In addition, we conducted the reaction of aryl halides with diphenylphosphine oxide under the above optimized reaction conditions, and the results are summarized as Table 5. Generally, the cross-coupling of aryl iodides or bromides with diphenylphosphine oxide proceeded smoothly, and could afford the corresponding products in excellent yields (Table 5, entries

Table 3Effects of catalyst and ligands on the reaction of 4-chloroanisole withdiisopropyl H-phosphonate in water 2

0	,∽CI O + H [−] R∼O′Pr O′Pr KF, H₂O, Re 2a	I, TBAB, ⁱ PrOH flux, 16 h, N ₂	O P-O'Pr O'Pr 3a
Entry	Catalyst	Ligand	$\operatorname{Yield}^{b}(\%)$
1^{c} 2 3 4 5 6 7^{d} 8 ^e 9 ^f 10 ^e	Palladacycle (II) Palladacycle (I) Palladacycle (I) Palladacycle (I) Palladacycle (I) Palladacycle (I) Palladacycle (I) Pd(OAc) ₂ Pd[P(C ₆ H ₁₁) ₃] ₂ Cl ₂	PPh ₃ dppe dppf DavePhos X-Phos X-Phos X-Phos 	<5 <5 <5 42 76 <5 30 <5

^{*a*} Reaction conditions: 4-chloroanisole (0.4 mmol), diisopropyl H-phosphonate (0.6 mmol), KF (1.7 mmol), TBAB (0.4 mmol), ¹PrOH (1.2 mmol), 1 mol% of the palladacycle (I) and 4 mol% of the ligand in H₂O (2 mL) at refluxing temperature under nitrogen atmosphere for 16 h. ^{*b*} Isolated yield based on the amount of 4-chloroanisole. ^{*c*} 2 mol% of the palladacycle (II). ^{*d*} Under air. ^{*e*} Pd(OAc)₂ (2 mol%). ^{*f*} Pd[P-(C₆H₁₁)₃]₂Cl₂ (2 mol%). ^{*g*} NiCl₂ (2 mol%).

1–4). However, the reaction of chlorobenzene (1x) only gave a relatively low yield of 35% (Table 5, entry 5). It is worth noting that aryl iodides could couple with diphenylphosphine oxide in neat water in the absence of TBAB/ⁱPrOH, generating the phosphonated product in excellent yields (Table 5, entries 1 and 2).

Conclusion

In summary, a general and efficient catalytic system for palladium-catalyzed phosphonation of aryl halides with dialkyl H-phosphonate in water was developed, affording the phosphonated products in moderate to excellent yields. With the assist of the bulky phosphine ligands of X-Phos, cyclopalladated ferrocenylimines as a kind of palladacycles could catalyze the cross-coupling of inactive aryl chlorides with dialkyl H-phosphonates in water. Remarkably, the decomposition of dialkyl H-phosphonates was effectively suppressed by the addition of isopropanol in this reaction. Moreover, a weak base KF instead of the traditionally strong bases such as KO^tBu or NaO^tBu was used for the successful phosphonation of aryl chloride, which would enhance the potential industrial application and conform to the ideas of green chemistry. Further exploration of the substrate scope and synthetic applications of these methodologies are currently under way in our laboratory.

Experimental section

General

 1 H, 13 C and 31 P NMR spectra were recorded on a Bruker DPX-400 spectrometer with CDCl₃ as the solvent and TMS as



^{*a*} Reaction conditions: aryl chloride (0.4 mmol), diisopropyl H-phosphonate (0.6 mmol), KF (1.7 mmol), TBAB (0.4 mmol), ¹PrOH (1.2 mmol), 1 mol% of the palladacycle (I) and 4 mol% of X-Phos in H_2O (2 mL) at refluxing temperature under nitrogen atmosphere for 16 h. ^{*b*} Isolated yield based on the amount of the aryl chloride.

an internal standard. Melting points were measured using a WC-1 microscopic apparatus and were uncorrected. GC analysis was performed on Agilent 4890D gas chromatograph. Mass spectra were measured on an LC-MSD-Trap-XCT instrument. High-resolution mass spectra were measured on a MAL-DI-FTMS. Ethyl acetate and hexane (analytical grade) were used for column chromatography without purification. The palladacycles of cyclopalladated ferrocenylimines were synthesized according to the reported literature.⁷ Other chemicals were bought from commercial sources and used as-received unless otherwise noted.

The palladacycle-catalyzed the cross-coupling of aryl iodides and bromides with diisopropyl H-phosphonate in water

Aryl iodide or bromide (0.4 mmol), diisopropyl H-phosphonates (0.6 mmol), KF (1.2 mmol), TBAB (0.4 mmol), ⁱPrOH (1.2 mmol),

 Table 5
 Cross-coupling of aryl halides with diphenylphosphine oxide in water^a

ArX + $H^{-} \overset{Palladacycle II, TBAB, POH}{Ph} \xrightarrow{Palladacycle II, TBAB, POH} \overset{H}{}_{KF, H_2O, Reflux, 16 h, N_2} \overset{H}{}_{Ar^{-}} \overset{H}{\overset{P}{}_{Ph}} \overset{H}{}_{Ph}$			
Entry	1 4a ArX	Product	5 Yield ^b (%)
1 ^c	1b	O Ph P Ph 5a	97
2 ^{<i>c</i>}	الروم المراجع ا المراجع المراجع	P Ph P Ph 5b	94
3	Br	O P Ph 5a	99
4	Br 1j	O Ph Ph 5b	92
5 ^{<i>d</i>}		O Ph Ph Ph 5b	35

^{*a*} Reaction conditions: aryl halides (0.4 mmol), diphenylphosphine oxide (0.6 mmol), KF (1.2 mmol), TBAB (0.4 mmol), ⁱPrOH (1.2 mmol), 1 mol % of the palladacycle (**II**) in H₂O (2 mL) at refluxing temperature under nitrogen atmosphere for 16 h. ^{*b*} Isolated yield based on the amount of aryl halide. ^{*c*} In the absence of TBAB and ⁱPrOH. ^{*d*} Using palladacycle (**I**) (1 mol%)/X-Phos (4 mol%) instead of the palladacycle (**II**).

and palladacycle (II) (1 mol%) were dissolved in H_2O (2 mL) in a 10 mL vial under nitrogen atmosphere. After the reaction was refluxed for 16 h, the mixture was filtered through a pad of Celite and washed with ethyl acetate. The mixture was added into H_2O (25 mL) and extracted with ethyl acetate (10 mL) three times. The combined organic layer was dried over anhydrous Na_2SO_4 and filtered. After removal of the solvent in vacuum, the residue was purified by flash chromatography on silica gel (ethyl acetate/hexane) to give the pure product.

The palladacycle-catalyzed the cross-coupling of aryl chlorides with diisopropyl H-phosphonate in water

The mixture of aryl chloride (0.4 mmol), diisopropyl H-phosphonate (0.6 mmol), KF (1.7 mmol), TBAB (0.4 mmol), ⁱPrOH (1.2 mmol), and palladacycle (I) (1 mol%)/X-Phos (4 mol%) were dissolved in H_2O (2 mL) in a 10 mL vial under nitrogen atmosphere. After the reaction was under refluxing for 16 h, the mixture was filtered through a pad of Celite, and washed with ethyl acetate. And the mixture was added into H_2O (25 mL) and extracted with ethyl acetate (10 mL) for three times. The combined organic layer was dried over anhydrous Na_2SO_4 and filtered. After removal of the solvent in vacuum, the residue was purified by flash chromatography on silica gel (ethyl acetate/hexane) to give the pure product.

The palladacycle-catalyzed the cross-coupling of aryl halides with diphenylphosphine oxide in water

The mixture of aryl halide (0.4 mmol), diphenylphosphine oxide (0.6 mmol), KF (1.2 mmol), TBAB (0.4 mmol), ⁱPrOH

(1.2 mmol), and palladacycle II (1 mol%) was dissolved in H₂O (2 mL) in a 10 mL vial under nitrogen atmosphere. The mixture then refluxed for 16 h. After the reaction was complete, the mixture was filtered through a pad of Celite, and washed with dichloromethane. And the mixture was added into H₂O (25 mL) and extracted with dichloromethane (10 mL) for three times. The combined organic layer was dried over anhydrous Na₂SO₄ and filtered. After removal of the solvent in vacuum, the residue was purified by flash chromatography on silica gel (dichloromethane/methanol) to give the pure product.

Diisopropyl (2-acetamidophenyl)phosphonate (3e). Oil, yield: 62%; ¹H NMR (400 MHz, CDCl₃) δ 10.69 (s, 1H), 8.58 (t, *J* = 7.2 Hz, 1H), 7.61–7.48 (m, 2H), 7.11 (t, *J* = 5.6 Hz, 1H), 4.69–4.61 (m, 2H), 2.21 (s, 3H), 1.39 (d, *J* = 6.0 Hz, 6H), 1.23 (d, *J* = 6.0 Hz, 6H); ¹³C NMR (CDCl₃, 100 MHz) δ 169.0, 142.4 (d, *J* = 7.5 Hz), 133.7 (d, *J* = 2.2 Hz), 132.6 (d, *J* = 5.7 Hz), 122.8 (d, *J* = 13.6 Hz), 120.6 (d, *J* = 11.4 Hz), 115.1 (d, *J* = 179.1 Hz), 71.6 (d, *J* = 5.4 Hz), 25.2, 24.0 (d, *J* = 3.8 Hz), 23.7 (d, *J* = 5.0 Hz); ³¹P NMR (CDCl₃, 163 MHz) δ 17.9; HRMS: *m*/z 300.1365 ([M + H]⁺, C₁₄H₂₃NO₄P⁺ calcd 300.1365).

Diisopropyl (3-methoxyphenyl)phosphonate (3g). Oil, yield: 86%; ¹H NMR (400 MHz, CDCl₃) δ 7.42–7.32 (m, 3H), 7.08–7.05 (m, 1H), 4.73–4.64 (m, 2H), 3.85 (s, 3H), 1.38 (d, *J* = 6.4 Hz, 6H), 1.23 (d, *J* = 6.0 Hz, 6H); ¹³C NMR (CDCl₃, 100 MHz) δ 159.1 (d, *J* = 18.7 Hz), 131.0 (d, *J* = 186.1 Hz), 129.5 (d, *J* = 17.4 Hz), 123.9 (d, *J* = 9.1 Hz), 118.3 (d, *J* = 2.6 Hz), 116.2 (d, *J* = 10.2 Hz), 70.7 (d, *J* = 5.3 Hz), 55.3, 24.0 (d, *J* = 3.6 Hz), 23.8 (d, *J* = 4.7 Hz); ³¹P NMR (CDCl₃, 163 MHz) δ 17.0; HRMS: *m/z* 273.1254 ([M + H]⁺, C₁₃H₂₂O₄P⁺ calcd 273.125).

Diisopropyl (4-vinylphenyl)phosphonate (3i). Oil, yield: 58%; ¹H NMR (400 MHz, CDCl₃): δ 7.78 (dd, J = 13.2 Hz and 8.0 Hz, 2H), 7.48 (dd, J = 7.6 Hz and 3.6 Hz, 2H), 6.73 (dd, J = 17.6 Hz and 10.8 Hz, 1H), 5.85 (d, J = 17.6 Hz, 1H), 5.37 (d, J = 10.8 Hz, 1H), 4.73–4.64 (m, 2H), 1.37 (d, J = 6.4 Hz, 6H), 1.22 (d, J = 6.4 Hz, 6H); ¹³C NMR (CDCl₃, 100 MHz) δ 141.1 (d, J = 3.3 Hz), 136.0 (d, J = 1.3 Hz), 132.0 (d, J = 10.0 Hz), 128.8 (d, J = 189.0 Hz), 126.0 (d, J = 15.3 Hz), 116.3, 70.7 (d, J = 5.4 Hz), 24.0 (d, J = 3.9 Hz), 23.8 (d, J = 4.8 Hz); ³¹P NMR (CDCl₃, 163 MHz) δ 17.1; HRMS: m/z 269.1310 ([M + H]⁺, C₁₄H₂₂O₃P⁺ calcd 269.1307).

Diisopropyl (4-methoxycarbonylphenyl)phosphonate (3j). Oil, yield: 85%; ¹H NMR (400 MHz, CDCl₃) δ 8.11 (dd, J = 7.8 Hz and 3.8 Hz, 2H), 7.90 (dd, J = 12.8 and 8.0 Hz, 2H), 4.76–4.67 (m, 2H), 3.95 (s, 3H), 1.38 (d, J = 6.0 Hz, 6H), 1.23 (d, J = 6.4 Hz, 6H); ¹³C NMR (CDCl₃, 100 MHz) δ 166.4, 134.9 (d, J = 185.9 Hz), 133.2 (d, J = 3.3 Hz), 131.8 (d, J = 9.9 Hz), 129.3 (d, J = 14.9 Hz), 71.2 (d, J = 5.6 Hz), 52.5, 24.1 (d, J = 3.9 Hz), 23.8 (d, J = 4.7 Hz); ³¹P NMR (CDCl₃, 163 MHz) δ 15.3; HRMS: m/z 301.1206 ([M + H]⁺, C₁₄H₂₂O₅P⁺ calcd 301.1199).

Diisopropyl (benzo[*b***]thiophen-5-yl)phosphonate (3k).** Pale yellow solid, mp 104–105 °C; yield: 73%; ¹H NMR (400 MHz, CDCl₃) δ 8.36 (d, *J* = 14.4 Hz, 1H), 7.96 (dd, *J* = 8.4 Hz and 3.6

Hz, 1H), 7.75–7.69 (m, 1H), 7.53 (d, *J* = 5.6 Hz, 1H), 7.42 (d, *J* = 5.2 Hz, 1H), 4.75–4.66 (m, 2H), 1.40 (d, *J* = 6.4 Hz, 6H), 1.22 (d, *J* = 6.0 Hz, 6H); ¹³C NMR (CDCl₃, 100 MHz) δ 143.3 (d, *J* = 3.3 Hz), 139.1 (d, *J* = 17.0 Hz), 128.1 (d, *J* = 10.9 Hz), 127.6, 126.3 (d, *J* = 11.0 Hz), 125.5 (d, *J* = 188.5 Hz), 124.2 (d, *J* = 1.3 Hz), 122.6 (d, *J* = 15.8 Hz), 70.7 (d, *J* = 5.3 Hz), 24.1 (d, *J* = 3.9 Hz), 23.9 (d, *J* = 4.8 Hz); ³¹P NMR (CDCl₃, 163 MHz) δ 18.1; HRMS: m/z 299.0871 ($[M + H]^+$, C₁₄H₂₀O₃PS⁺ calcd 299.0871).

Diisopropyl (4-butylphenyl)phosphonate (3n). Oil, yield: 65%; ¹H NMR (400 MHz, CDCl₃) δ 7.71 (dd, J = 13.2 Hz and 8.0 Hz, 2H), 7.26 (dd, J = 8.0 Hz and 4.0 Hz, 2H), 4.71–4.62 (m, 2H), 2.65 (t, J = 7.6 Hz, 2H), 1.65–1.57 (m, 2H), 1.41–1.32 (m, 8H), 1.22 (d, J = 6.4 Hz, 6H), 0.93 (t, J = 7.4 Hz, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ 147.3 (d, J = 3.0 Hz), 131.7 (d, J = 10.2 Hz), 128.3 (d, J = 15.2 Hz), 126.6 (d, J = 189.6 Hz), 70.4 (d, J = 5.4 Hz), 35.6, 33.1, 24.0 (d, J = 3.8 Hz), 23.7 (d, J = 4.8 Hz), 22.2, 13.8; ³¹P NMR (CDCl₃, 163 MHz) δ 17.9; HRMS: m/z 299.1771 ([M + H]⁺, C₁₆H₂₈O₃P⁺ calcd 299.1775).

Diisopropyl (4-methoxy-3-methylphenyl)phosphonate (3o). Oil, yield: 90%; ¹H NMR (400 MHz, CDCl₃) δ 7.64 (dd, J =12.4 Hz and 9.0 Hz, 1H), 7.57 (d, J = 12.4 Hz, 1H), 6.87 (dd, J =8.2 Hz and 3.4 Hz, 1H), 4.69–4.60 (m, 2H), 3.86 (s, 3H), 3.09 (s, 3H), 1.37 (d, J = 6.4 Hz, 6H), 1.22 (d, J = 6.4 Hz, 6H); ¹³C NMR (CDCl₃, 100 MHz) δ 160.7 (d, J = 3.4 Hz), 133.8 (d, J = 11.1 Hz), 131.4 (d, J = 10.9 Hz), 126.6 (d, J = 15.4 Hz), 120.3 (d, J = 207.3Hz), 109.3 (d, J = 16.8 Hz), 70.2 (d, J = 5.3 Hz), 55.2, 23.9 (d, J =3.8 Hz), 23.7 (d, J = 4.8 Hz); ³¹P NMR (CDCl₃, 163 MHz) δ 18.6; HRMS: m/z 287.1407 ([M + H]⁺, C₁₄H₂₄O₄P⁺ calcd 287.1409).

Diisopropyl [3-(dimethylamino)phenyl]phosphonate (3p). Oil, yield: 90%; ¹H NMR (400 MHz, CDCl₃) δ 7.33–7.28 (m, 2H), 7.19–7.07 (m, 2H), 6.85 (dd, *J* = 8.4 Hz and 2.0 Hz, 1H), 4.71–4.62 (m, 2H), 2.98 (s, 6H), 1.37 (d, *J* = 6.4 Hz, 6H), 1.23 (d, *J* = 6.4 Hz, 6H); ¹³C NMR (CDCl₃, 100 MHz) δ 150.0 (d, *J* = 16.8 Hz), 130.0 (d, *J* = 184.3 Hz), 129.0 (d, *J* = 17.2 Hz), 119.2 (d, *J* = 9.0 Hz), 115.6 (d, *J* = 3.0 Hz), 115.2 (d, *J* = 12.5 Hz), 70.4 (d, *J* = 5.2 Hz), 40.3, 24.0 (d, *J* = 3.7 Hz), 23.7 (d, *J* = 4.9 Hz); ³¹P NMR (CDCl₃, 163 MHz) δ 18.7; HRMS: *m*/*z* 286.1567 ([M + H]⁺, C₁₄H₂₅NO₃P⁺ calcd 286.1570).

Diisopropyl (2-chlorophenyl)phosphonate (3s). Oil, yield: 69%; ¹H NMR (400 MHz, CDCl₃) δ 8.05 (dd, J = 14.4 Hz and 7.2 Hz, 1H), 7.47–7.44 (m, 2H), 7.38–7.27 (m, 1H), 4.78–4.69 (m, 2H), 1.40 (d, J = 6.0 Hz, 6H), 1.26 (d, J = 6.4 Hz, 6H); ¹³C NMR (CDCl₃, 100 MHz) δ 136.8 (d, J = 2.8 Hz), 136.0 (d, J = 8.0 Hz), 133.3 (d, J = 2.5 Hz), 130.7 (d, J = 10.1 Hz), 128.5 (d, J = 189.1 Hz), 126.3 (d, J = 13.7 Hz), 71.4 (d, J = 5.6 Hz), 24.1 (d, J = 4.1 Hz), 23.7 (d, J = 4.8 Hz); ³¹P NMR (CDCl₃, 163 MHz) δ 12.5; HRMS: m/z 277.0762 ([M + H]⁺, C₁₂H₁₉ClO₃P⁺ calcd 277.0760).

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