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Synthesis of Aryl and Arylmethyl Phosphonates by Cross-Coupling of Aryl or Arylmethyl Halides (X = I, Br and Cl) with Diisopropyl H-Phosphonate

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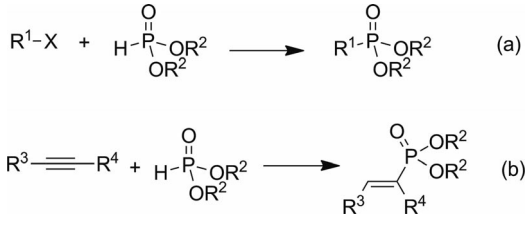
An efficient and generally applicable protocol for the palladacycle-catalysed arylation or K_2CO_3-promoted arylmethylation of diisopropyl H-phosphonate has been developed. The remarkable features of the palladacycle-catalysed arylation reaction include wide substrate scope (aryl iodides, bromides and chlorides), significant shortening of the reaction time (2 or 3 h) and a low catalyst loading of 1 mol-%. Note that with the base K_2CO_3 as promoter, arylmethylation could be achieved without any palladium catalyst. Moreover, the first example of a palladium-catalysed phosphonation of inactive electron-rich aryl chlorides with *t*BuOK as the base has been realized. This result could be considered an important improvement and complement to earlier work of Montchamp and Han, whose catalytic systems are typically compatible with electron-deficient and electron-neutral aryl chlorides.

Introduction

Aryl and arylmethyl phosphonates have wide applications as valuable building blocks in organic synthetic, biological, pharmaceutical and materials sciences.[1] There are two efficient synthetic protocols for the formation of the C–P bond (Scheme 1). The first powerful approach to C–P bond formation involves the direct cross-coupling of aryl or alkyl halides with dialkyl H-phosphonates or trialkyl phosphites.[2,3] The second method involves the addition of H-phosphonate to the triple bond of alkynes.[4]



Scheme 1. Typical C–P bond-forming protocols.

The pioneering work on palladium-catalysed phosphonation of aryl iodides or bromides belongs to Hirao and co-workers, who introduced a dialkyl phosphonate moiety at an sp^2-hybridized carbon by using the $[Pd(PPh_3)_4]/NEt_3$ catalytic system in the beginning of the 1980s.[2a,2b] Since then, much research interest has been devoted to improving the reaction conditions used by Gooßen,[2d] Stawinski[2f–2h,2j,2l] and others,[2c,2e,2i,2k,2m–2p] for example, by varying the phosphane ligands (e.g., dppp, dppb, dppf and Xantphos), organic (e.g., Et_3N, Cy_2NMe and iPr_2NEt) or inorganic (e.g., Cs_2CO_3, K_2CO_3 and K_3PO_4) bases, microwave heating and palladium sources [e.g., $Pd(PPh_3)_4$, $Pd(OAc)_2$ and Pd/C]. In addition to the palladium catalyst, other transition metals such as Cu[5] and Ni[6] could also provide efficient access to phosphonated products from aryl iodides or bromides. Nevertheless, all the above-mentioned work was focused on the phosphonation of aryl iodides and bromides. From the viewpoint of synthetic cost, phosphonation of the more commercially available aryl chlorides would be a fascinating choice. In 2008, the first phosphonation of aryl chlorides was reported by Montchamp and co-workers, albeit this catalytic system was effective for electron-deficient aryl chlorides using 1 mol-% of $Pd(OAc)_2$/dppf as the catalyst.[2i] Just recently, Han and co-workers also successfully carried out the cross-coupling reactions of electron-neutral and -deficient aryl chlorides with dimethyl H-phosphonate using 10 mol-% $[NiCl_2(dppp)]$ as the catalyst.[6b]

On the other hand, the most common and versatile pathway for the formation of sp^3 C–P bonds is the reaction of trialkyl phosphites (the Michaelis–Arbuzov reaction) or dialkyl phosphonates (the Michaelis–Becker reaction) with alkyl halides,[3a–3m] which can proceed without any transition-metal catalyst and exhibit quite general substrate scope. These reactions were performed at a higher temperature or with a base (e.g., NaH, Cs_2CO_3 and KHMDS), respectively. Another type of approach is the transition-metal-catalysed cross-coupling of alkyl halides with dialkyl

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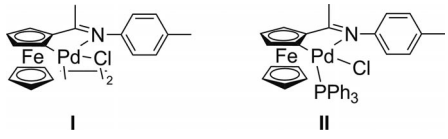
H-phosphonates.[3n–3q] In the development of these two types of phosphonations of arylmethyl halides, significant progress has been achieved by Rousseau,[3e] Salvatore,[3c] Zografos[3h] and Stawinski[3p] and their co-workers.

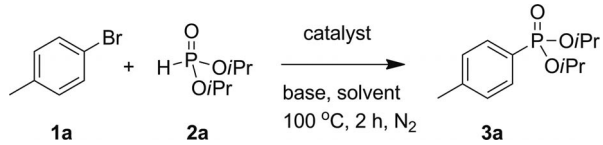
Cyclopalladated ferrocenylimines as a family of versatile palladacyclic catalysts (Figure 1), which were discovered and developed by our research group, have been successfully applied to various catalytic reactions.[7] Inspired by the above promising reports and our own work, we have focused our research interest on the possible palladacycle-catalysed cross-coupling of aryl halides or arylmethyl halides with diisopropyl H-phosphonate, especially for the reaction of inactive electron-rich and -neutral aryl chlorides. In addition, the need for a metal catalyst will also be discussed in the cross-coupling of arylmethyl halides with diisopropyl H-phosphonate.



I II

Figure 1. Cyclopalladated ferrocenylimines.

Table 1. Effects of bases and solvents on the reaction of 4-bromotoluene with diisopropyl H-phosphonate.[a]



1a 2a 3a

Entry	Catalyst	Base	Solvent	Yield [%][b]
1	Palladacycle **II**	Na_2CO_3	DMF	48
2	Palladacycle **II**	K_3PO_4	DMF	40
3	Palladacycle **II**	Cs_2CO_3	DMF	24
4	Palladacycle **II**	K_2CO_3	DMF	95 (91)
5	Palladacycle **II**	K_2CO_3	DMA	90 (85)
6	Palladacycle **II**	K_2CO_3	THF	12
7[c]	Palladacycle **II**	K_2CO_3	DMF	35
8[d]	Palladacycle **II**	K_2CO_3	DMF	73
9	–	K_2CO_3	DMF	<5
10[e]	Palladacycle **II**	K_2CO_3	DMF	31
11[f]	Palladacycle **I**/PPh_3	K_2CO_3	DMF	92
12[g]	$Pd(OAc)_2$/PPh_3	K_2CO_3	DMF	81
13[h]	$NiCl_2$/PPh_3	K_2CO_3	DMF	<5

[a] Reagents and conditions: 4-bromotoluene (0.4 mmol), diisopropyl H-phosphonate (0.6 mmol), base (1.2 mmol) and the palladacycle **II** (1 mol-%) in solvent (2 mL) at 100 °C under nitrogen for 2 h. [b] GC yield (isolated yield) based on the amount of 4-bromotoluene. [c] Using 0.5 mol-% of the palladacycle **II**. [d] Under air. [e] At 80 °C. [f] Palladacycle **I** (0.5 mol-%), PPh_3 (1 mol-%). [g] $Pd(OAc)_2$ (2 mol-%), PPh_3 (2 mol-%). [h] $NiCl_2$ (2 mol-%), PPh_3 (2 mol-%).

Results and Discussion

Palladacycle-Catalysed Phosphonation of Aryl Iodides and Bromides

In our initial study, we examined the effects of bases and solvents on the reaction of 4-bromotoluene with diisopropyl H-phosphonate (Table 1). The reaction was first performed with Na_2CO_3 as the base in DMF under nitrogen, and a relatively low yield of 48% was observed by GC (Table 1, entry 1). Other bases were employed in this reaction and K_2CO_3 was found to give the best result with a GC yield of 95% and an isolated yield of 91% (Table 1, entries 2–4). Then the effect of aprotic polar solvents was also explored (Table 1, entries 5 and 6). For example, *N*,*N*-dimethylacetamide (DMA) as solvent also afforded the coupling product in a GC yield of 90% (Table 1, entry 5) but THF did not exhibit a comparably favourable result (Table 1, entry 6). However, a decrease in the catalyst loading or temperature, the absence of catalyst or performing the reaction in air in place of nitrogen resulted in a lower or even no yield at all (Table 1, entries 7–10). Note that the combination of palladacycle **I** and PPh_3 gave the phosphonated product in a yield of 92%, which is a similar yield to that obtained with palladacycle **II** (Table 1, entry 11). Some commercially available metal catalysts were also evaluated; $Pd(OAc)_2$ gave a satisfactory yield of 81%, whereas $NiCl_2$ did not show any catalytic activity at all (Table 1, entries 12 and 13).

The substrate scope for the reaction was then investigated under the optimized reaction conditions (Table 2). In general, electronic effects had no significant influence on the phosphonation of aryl iodides and bromides, affording the desired products in moderate-to-good yields (Table 2, entries 1–13). Note that the reactions of heteroaryl bromides such as 5-bromobenzothiophene (**1g**) and 3-bromopyridine (**1n**) also gave the phosphonated products in 97 and 77% isolated yields, respectively (Table 2, entries 6 and 13). Moreover, the reaction could also tolerate aryl halides bearing a sterically hindered *ortho* substituent except for 1-bromo-2-methylnaphthalene (**1f**; Table 2, entries 1, 3 and 5).

Palladacycle-Catalysed Phosphonation of Aryl Chlorides

Subsequently we performed a similar optimization process for the palladacycle **I** catalysed phosphonation of aryl chlorides, and the effects of ligands and bases were screened (Table 3). The use of commercially available phosphane ligands (Figure 2) such as 1,2-bis(diphenylphosphanyl)ethane (dppe), 1,1′-bis(diphenylphosphanyl)ferrocene (dppf), 2-dicyclohexylphosphanyl-2′-(dimethylamino)biphenyl (Davephos) and 2-(dicyclohexylphosphanyl)-2′,4′,6′-triisopropyl-1,1′-biphenyl (X-phos) were first examined in the presence of the strong base *t*BuOK in DMA; X-phos was found to be the best ligand and gave the product in nearly quantitative yield (Table 3, entries 1–4). Other bases (e.g., *t*BuONa, Cs_2CO_3 and CsF) did not exhibit satisfactory activity (Table 3, entries 5–7). Commercially available Pd or

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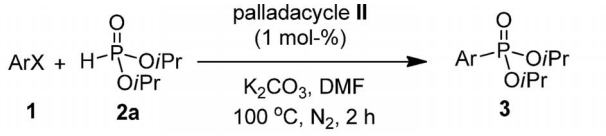
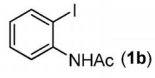
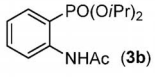
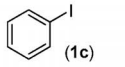
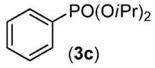
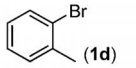
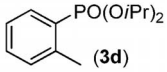
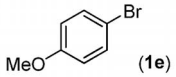
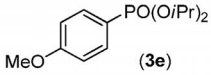
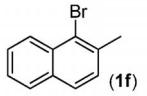
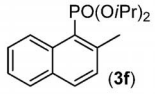
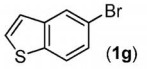
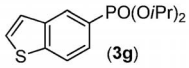
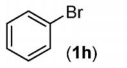
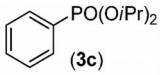
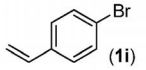
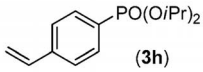
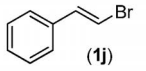
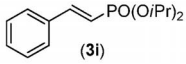
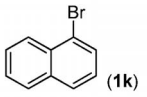
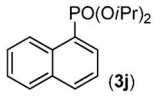
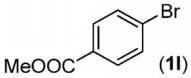
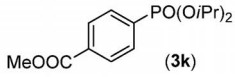
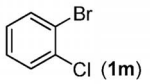
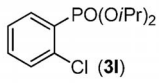
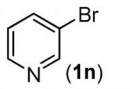
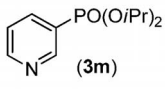
Table 2. Cross-coupling reactions of aryl iodides and bromides with diisopropyl H-phosphonate.[a]

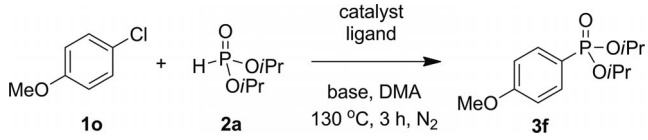


Entry	ArX	Product	Yield (%)[b]
1	 (1b)	 (3b)	88
2	 (1c)	 (3c)	90
3	 (1d)	 (3d)	86
4	 (1e)	 (3e)	99
5	 (1f)	 (3f)	40
6	 (1g)	 (3g)	97
7	 (1h)	 (3c)	86
8	 (1i)	 (3h)	99
9	 (1j)	 (3i)	93
10	 (1k)	 (3j)	94
11	 (1l)	 (3k)	95
12[c]	 (1m)	 (3l)	66
13	 (1n)	 (3m)	77

[a] Reagents and conditions: aryl halide (0.4 mmol), diisopropyl H-phosphonate (0.6 mmol), K_2CO_3 (1.2 mmol) and the palladacycle **II** (1 mol-%) in DMF (2 mL) at 100 °C under nitrogen for 2 h. [b] Isolated yield based on the amount of aryl halide. [c] After 24 h.

Ni catalysts {e.g., $Pd(OAc)_2$, $[Pd\{P(C_6H_{11})_3\}_2Cl_2]$, $[Pd_2(Pda)_3]$, $NiCl_2$ and $[NiCl_2(dppe)]$} did not give satisfactory results, which demonstrates that the palladacycle indeed has an advantage over simple metal salts (Table 3, entries 8–12).

Table 3. Effects of ligands and bases on the reaction of 4-chloroanisole with diisopropyl H-phosphonate.[a]



Entry	Catalyst	Ligand	Base	Yield [%][b]
1	Palladacycle **I**	Davephos	*t*BuOK	57
2	Palladacycle **I**	dppf	*t*BuOK	37
3	Palladacycle **I**	dppe	*t*BuOK	29
4	Palladacycle **I**	X-phos	*t*BuOK	99 (99)
5	Palladacycle **I**	X-phos	*t*BuONa	57
6	Palladacycle **I**	X-phos	Cs_2CO_3	15
7	Palladacycle **I**	X-phos	CsF	NR
8[c]	$Pd(OAc)_2$	X-phos	*t*BuOK	23
9[d]	$[Pd\{P(C_6H_{11})_3\}_2Cl_2]$	–	*t*BuOK	77
10[e]	$[Pd_2(dba)_3]$	X-phos	*t*BuOK	85
11[f]	$NiCl_2$	X-phos	*t*BuOK	<5
12[g]	$[NiCl_2(dppe)]$	–	*t*BuOK	<5

[a] Reagents and conditions: 4-chloroanisole (0.4 mmol), diisopropyl H-phosphonate (0.6 mmol), base (1.2 mmol), palladacycle **I** (1 mol-%) and phosphane ligand (4 mol-%) in DMA (2 mL) at 130 °C under nitrogen for 3 h. [b] GC yield (isolated yield) based on the amount of 4-chloroanisole. [c] Using 2 mol-% of $Pd(OAc)_2$ and 4 mol-% of X-phos as the catalyst. [d] Using 2 mol-% of $[Pd\{P(C_6H_{11})_3\}_2Cl_2]$ as the catalyst. [e] Using 2 mol-% of $[Pd_2(dba)_3]$ and 4 mol-% of X-phos as the catalyst. [f] Using 2 mol-% of $NiCl_2$ and 4 mol-% of X-phos as the catalyst. [g] Using 2 mol-% of $[NiCl_2(dppe)]$ as the catalyst.

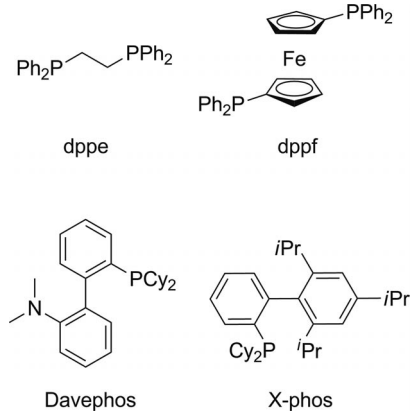


Figure 2. Phosphane ligands used in the screening of the palladacycle **I** catalysed phosphonation of aryl chlorides.

With the optimized conditions in hand, the scope of the aryl chlorides was investigated and selected results are summarized in Table 4. In general, the catalytic system was applicable to electron-rich and -neutral aryl chlorides, and the desired products were obtained in moderate-to-good yields (Table 4, entries 1–5). Notably, the reaction of 3-chlorotoluene (**1q**) with diisopropyl H-phosphonate (**2a**) afforded the product in a yield of 99% (Table 4, entry 2). However, the electron-deficient heterocyclic chloride (**1u**) was phosphonated in a low yield of only 26% (Table 4, entry 6).

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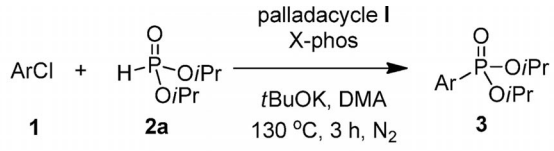
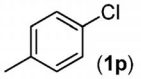
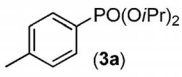
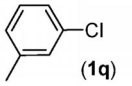
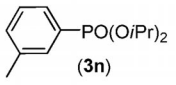
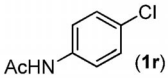
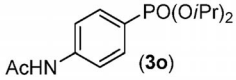
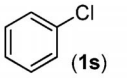
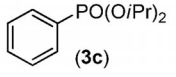
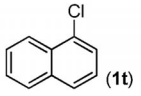
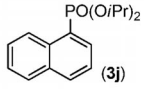
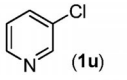
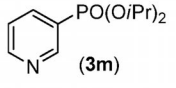
Table 4. Cross-coupling reactions of aryl chlorides with diisopropyl H-phosphonate.[a]



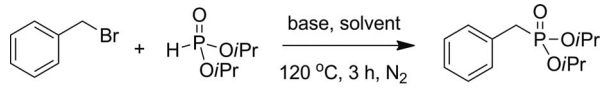
Entry	ArCl	Product	Yield (%)[b]
1	 (1p)	 (3a)	91
2	 (1q)	 (3n)	99
3	 (1r)	 (3o)	54
4	 (1s)	 (3c)	78
5	 (1t)	 (3j)	74
6	 (1u)	 (3m)	26

[a] Reagents and conditions: aryl chloride (0.4 mmol), diisopropyl H-phosphonate (0.6 mmol), *t*BuOK (1.2 mmol), palladacycle **I** (1 mol-%) and X-phos (4 mol-%) in DMA (2 mL) at 130 °C under nitrogen for 3 h. [b] Isolated yield based on the amount of aryl chloride.

Base-Promoted Arylmethylation of H-Phosphonate

We performed a similar optimization process for the palladacycle-catalysed phosphonation of arylmethyl halides and found that palladacycle **II** gave a high yield of 99% with Cs_2CO_3 as the base in DMA (Table 5, entry 1). However, in the absence of the palladacycle, the reaction also proceeded smoothly, giving the same yield of 99% (Table 5, entry 2). This suggests that the metal is not indispensable in this reaction and it prompted us to explore the arylmethylation of H-phosphonate under metal-free conditions. After extensive screening of a variety of bases and solvent, the optimal reaction conditions were found to be as follows: K_2CO_3 (1.5 equiv.) in DMA (2.0 mL) at 120 °C under nitrogen (Table 5, entry 7). Under these conditions, the reactions of electron-neutral and -rich benzyl bromides (**4a** and **4b**) proceeded smoothly, affording the corresponding products in nearly quantitative yields (Table 6, entries 1 and 2). Moreover, the reaction protocol was also tolerant of electron-deficient 4-bromobenzyl bromide (**4c**), naphthylmethyl bromide (**4d**) and benzyl chloride (**4e**), affording the phosphonated products in good yields (Table 6, entries 3–5).

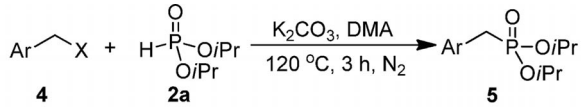
Table 5. Effect of base on the reaction of benzyl bromide with diisopropyl H-phosphonate.[a]

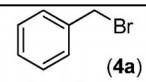
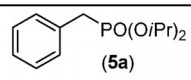
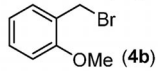
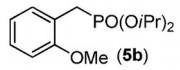
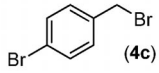
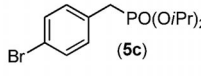
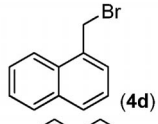
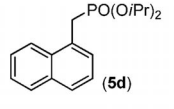
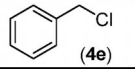
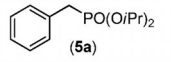


Entry	Base	Solvent	Yield [%][b]
1[c]	Cs_2CO_3	DMA	99
2	Cs_2CO_3	DMA	99
3	Na_2CO_3	DMA	<5
4	$KHCO_3$	DMA	56
5	K_3PO_4	DMA	92
6	$KF{\cdot}2H_2O$	DMA	<5
7	K_2CO_3	DMA	97
8[d]	K_2CO_3	DMA	68
9	K_2CO_3	DMF	30
10	K_2CO_3	DMF	<5
11	K_2CO_3	dioxane	25
12	K_2CO_3	toluene	17

[a] Reagents and conditions: benzyl bromide (0.4 mmol), diisopropyl H-phosphonate (0.6 mmol) and base (0.6 mmol) in DMA (2 mL) at 120 °C under nitrogen for 3 h. [b] GC yield (isolated yield) based on the amount of benzyl bromide. [c] Using 1 mol-% palladacycle **II**. [d] Under air.

Table 6. Cross-coupling reactions of arylmethyl halides with diisopropyl H-phosphonate.[a]



Entry	$ArCH_2X$	Product	Yield (%)[b]
1	 (4a)	 (5a)	97
2	 (4b)	 (5b)	94
3	 (4c)	 (5c)	87
4	 (4d)	 (5d)	86
5	 (4e)	 (5a)	92

[a] Reagents and conditions: arylmethyl halide (0.4 mmol), diisopropyl H-phosphonate (0.6 mmol) and K_2CO_3 (0.6 mmol) in DMA (2 mL) under nitrogen for 3 h. [b] Isolated yield based on the amount of arylmethyl halide.

Chemoselective Phosphonation of the sp^2 or sp^3 C–X Bond

Finally, the chemoselective phosphonation of the sp^2 or sp^3 C–X bond was investigated by using 4-chlorobenzyl bromide as the starting material (Scheme 2). We found that the reaction of the sp^3 C–X bond proceeded smoothly and chemoselectively to generate the corresponding product in

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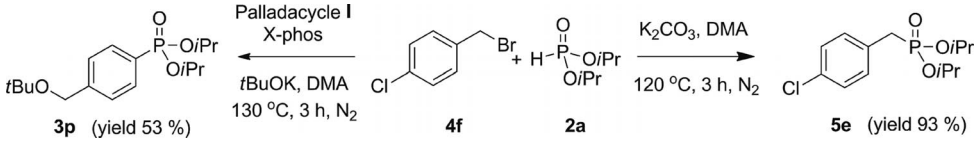

Scheme 2. Chemoselective phosphonation of the 4-chlorobenzyl bromide.

a yield of 93%; reaction of the sp^2 C–X bond afforded the product in 53% yield, albeit accompanied by alkoxylation of the sp^3 C–X bond.

Conclusions

We have developed efficient catalytic systems for the palladacycle (cyclopalladated ferrocenylimines) catalysed phosphonation of aryl iodides, bromides and chlorides. In these reactions, the palladacycles have shown higher catalytic activity than commercially available palladium or nickel salts. The phosphonation of aryl chlorides provides the first successful examples of the cross-coupling of inactive electron-donating aryl chlorides with diisopropyl H-phosphonates. In addition, the phosphonation of arylmethyl bromides and chlorides was also realized by using the cheaper base K_2CO_3 as the promoter. Current studies are focused on further exploration of the substrate scope and synthetic applications of these methodologies.

Experimental Section

General: ^{1}H, ^{13}C and ^{31}P NMR spectra were recorded with a Bruker DPX-400 spectrometer with $CDCl_3$ as the solvent and TMS as the internal standard. Melting points were measured with a WC-1 microscopic apparatus. GC analysis was performed with an Agilent 4890D gas chromatograph. Mass spectra were recorded with an LC-MSD-Trap-XCT instrument. HRMS were recorded with a MALDI-FTMS spectrometer. Ethyl acetate and hexane (analytical grade) were used as eluents for column chromatography without purification. Other solvents were purified according to the standard methods. The cyclopalladated ferrocenylimines were synthesized according to the literature.[8] Other chemicals were bought from commercial sources and used as received unless otherwise noted.

Palladacycle-Catalysed Phosphonation of Aryl Iodides and Bromides: Aryl iodide or bromide (0.4 mmol), diisopropyl H-phosphonate (0.6 mmol), K_2CO_3 (1.2 mmol) and palladacycle **II** (1 mol-%) were dissolved in DMF (2 mL) in a 10 mL vial under nitrogen. The reaction was carried out at 100 °C for 2 h. After completion of the reaction, the mixture was filtered through a pad of Celite and washed with ethyl acetate. The mixture was added to H_2O (25 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic layer was dried with anhydrous Na_2SO_4 and filtered. After removal of the solvent in vacuo, the residue was purified by flash chromatography on silica gel (ethyl acetate/hexane) to give the pure product.

Palladacycle-Catalysed Phosphonation of Aryl Chlorides: A mixture of aryl chloride (0.4 mmol), diisopropyl H-phosphonate (0.6 mmol), KO*t*Bu (1.2 mmol) and palladacycle **I** (1 mol-%)/X-phos (4 mol-%) was dissolved in DMA (2 mL) in a 10 mL vial under nitrogen. The reaction was carried out at 130 °C for 3 h. After completion of the reaction, the mixture was filtered through a pad of Celite and washed with ethyl acetate. The mixture was added to H_2O (25 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried with anhydrous Na_2SO_4 and filtered. After removal of the solvent in vacuo, the residue was purified by flash chromatography on silica gel (ethyl acetate/hexane) to give the pure product.

Phosphonation of Arylmethyl Halides: Arylmethyl halide (0.4 mmol), diisopropyl H-phosphonate (0.6 mmol) and K_2CO_3 (0.6 mmol) were dissolved in DMA (2 mL) in a 10 mL vial under nitrogen. The reaction was carried out at 120 °C for 3 h. After completion of the reaction, the mixture was filtered through a pad of Celite and washed with ethyl acetate. The mixture was added to H_2O (25 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried with anhydrous Na_2SO_4 and filtered. After removal of the solvent in vacuo, the residue was purified by flash chromatography on silica gel (ethyl acetate/hexane) to give the pure product.

Diisopropyl (2-Acetamidophenyl)phosphonate (3b): Yield 88%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.69 (s, 1 H), 8.58 (t, J = 7.2 Hz, 1 H), 7.61–7.48 (m, 2 H), 7.11 (t, J = 5.6 Hz, 1 H), 4.69–4.61 (m, 2 H), 2.21 (s, 3 H), 1.39 (d, J = 6.0 Hz, 6 H), 1.23 (d, J = 6.0 Hz, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 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) ppm. ^{31}P NMR ($CDCl_3$, 163 MHz): δ = 17.9 ppm. HRMS: calcd. for $C_{14}H_{23}NO_4P^+$ $[M + H]^+$ 300.1365; found 300.1365.

Diisopropyl (2-Methylnaphthalen-1-yl)phosphonate (3f): Yield 40%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.07 (d, J = 8.8 Hz, 1 H), 7.86 (d, J = 8.4 Hz, 1 H), 7.78 (d, J = 8.0 Hz, 1 H), 7.53 (t, J = 7.8 Hz, 1 H), 7.44 (t, J = 7.4 Hz, 1 H), 7.35–7.31 (m, 1 H), 4.78–4.69 (m, 2 H), 2.89 (s, 3 H), 1.42 (d, J = 6.4 Hz, 6 H), 1.11 (d, J = 6.0 Hz, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 143.4 (d, J = 10.5 Hz), 133.5 (d, J = 12.7 Hz), 131.6 (d, J = 3.3 Hz), 131.0 (d, J = 12.9 Hz), 129.1 (d, J = 17.3 Hz), 127.2, 126.5 (d, J = 2.9 Hz), 125.8, 124.1, 122.1 (d, J = 177.8 Hz), 69.5 (d, J = 5.2 Hz), 23.1 (d, J = 3.9 Hz), 22.9 (d, J = 3.2 Hz), 22.7 (d, J = 4.8 Hz) ppm. ^{31}P NMR ($CDCl_3$, 163 MHz): δ = 17.5 ppm. HRMS: calcd. for $C_{14}H_{24}O_3P^+$ $[M + H]^+$ 307.1463; found 307.1464.

Diisopropyl (Benzo[*b*]thiophen-5-yl)phosphonate (3g): Yield 97%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.37 (d, J = 14.5 Hz, 1 H), 7.97 (dd, J = 8.3, 3.4 Hz, 1 H), 7.74 (dd, J = 12.0, 8.4 Hz, 1 H), 7.54 (d, J = 5.2 Hz, 1 H), 7.43 (d, J = 5.6 Hz, 1 H), 4.79–4.67 (m, 2 H), 1.41 (d, J = 6.0 Hz, 6 H), 1.24 (d, J = 6.0 Hz, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 143.3 (d, J = 3.0 Hz), 139.1 (d, J = 17.1 Hz), 128.1 (d, J = 10.8 Hz), 127.6, 126.3 (d, J = 10.9 Hz), 125.6 (d, J = 188.7 Hz), 124.2, 122.6 (d, J = 15.8 Hz), 70.7 (d, J = 5.4 Hz), 24.1 (d, J = 3.8 Hz), 23.9 (d, J = 4.8 Hz) ppm. ^{31}P NMR ($CDCl_3$, 163 MHz): δ = 18.0 ppm. HRMS: calcd. for $C_{14}H_{20}O_3PS^+$ $[M + H]^+$ 299.0871; found 299.0871.

Diisopropyl (4-Vinylphenyl)phosphonate (3h): Yield 99%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.77 (dd, J = 13.2, 8.0 Hz, 2 H), 7.47 (dd, J = 8.1, 3.8 Hz, 2 H), 6.73 (dd, J = 17.6, 10.8 Hz, 1 H), 5.85 (d, J = 17.6 Hz, 1 H), 5.36 (d, J = 10.8 Hz, 1 H), 4.73–4.63 (m, 2 H),

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1.37 (d, J = 6.0 Hz, 6 H), 1.22 (d, J = 6.4 Hz, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 141.1 (d, J = 3.1 Hz), 136.0, 132.0 (d, J = 10.1 Hz), 129.0 (d, J = 189.1 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) ppm. ^{31}P NMR ($CDCl_3$, 163 MHz): δ = 17.0 ppm. HRMS: calcd. for $C_{14}H_{22}O_3P^+$ $[M + H]^+$ 269.1307; found 269.1310.

Diisopropyl (4-Methoxycarbonylphenyl)phosphonate (3k): Yield 95%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.11 (dd, J = 8.0, 3.6 Hz, 2 H), 7.90 (dd, J = 13.0, 8.2 Hz, 2 H), 4.77–4.67 (m, 2 H), 3.95 (s, 3 H), 1.38 (d, J = 6.0 Hz, 6 H), 1.23 (d, J = 6.0 Hz, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 166.3, 134.9 (d, J = 186.1 Hz), 133.2 (d, J = 3.2 Hz), 131.7 (d, J = 9.9 Hz), 129.3 (d, J = 14.9 Hz), 71.2 (d, J = 5.6 Hz), 52.4, 24.0 (d, J = 4.0 Hz), 23.8 (d, J = 4.7 Hz) ppm. ^{31}P NMR ($CDCl_3$, 163 MHz): δ = 15.1 ppm. HRMS: calcd. for $C_{14}H_{22}O_5P^+$ $[M + H]^+$ 301.1199; found 301.1206.

Diisopropyl (2-Chlorophenyl)phosphonate (3l): Yield 66%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.05 (dd, J = 14.4, 7.2 Hz, 1 H), 7.47–7.44 (m, 2 H), 7.38–7.27 (m, 1 H), 4.78–4.69 (m, 2 H), 1.40 (d, J = 6.0 Hz, 6 H), 1.26 (d, J = 6.4 Hz, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 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) ppm. ^{31}P NMR ($CDCl_3$, 163 MHz): δ = 12.5 ppm. HRMS: calcd. for $C_{14}H_{22}O_5P^+$ $[M + H]^+$ 277.0760; found 277.0762.

Diisopropyl (4-Acetamidophenyl)phosphonate (3o): Yield 54%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.26 (s, 1 H), 7.74–7.70 (m, 4 H), 4.68–4.59 (m, 2 H), 2.19 (s, 3 H), 1.35 (d, J = 6.4 Hz, 6 H), 1.22 (d, J = 6.0 Hz, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 169.4, 142.5 (d, J = 3.4 Hz), 132.7 (d, J = 10.7 Hz), 123.7 (d, J = 192.2 Hz), 119.0 (d, J = 15.2 Hz), 70.8 (d, J = 5.4 Hz), 24.5, 24.0 (d, J = 3.9 Hz), 23.8 (d, J = 4.8 Hz) ppm. ^{31}P NMR ($CDCl_3$, 163 MHz): δ = 17.2 ppm. ^{31}P NMR ($CDCl_3$, 163 MHz): δ = 17.2 ppm. HRMS: calcd. for $C_{14}H_{23}NO_4P^+$ $[M + H]^+$ 300.1365; found 300.1365.

Diisopropyl [4-(*tert*-Butoxymethyl)phenyl]phosphonate (3p): Yield 53%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.77 (dd, J = 13.2, 8.0 Hz, 2 H), 7.42 (dd, J = 7.6, 4.0 Hz, 2 H), 4.69–4.58 (m, 2 H), 4.49 (s, 2 H), 1.35 (d, J = 6.4 Hz, 6 H), 1.29 (s, 9 H), 1.20 (d, J = 6.4 Hz, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 144.4 (d, J = 3.2 Hz), 131.8 (d, J = 10.1 Hz), 128.3 (d, J = 188.5 Hz), 126.9 (d, J = 15.2 Hz), 73.7, 70.6 (d, J = 5.4 Hz), 63.6, 27.6, 24.0 (d, J = 3.9 Hz), 23.8 (d, J = 4.9 Hz) ppm. ^{31}P NMR ($CDCl_3$, 163 MHz): δ = 20.4 ppm. HRMS: calcd. for $C_{13}H_{21}ClO_3P^+$ $[M + H]^+$ 329.1882; found 329.1883.

Diisopropyl (2-Methoxybenzyl)phosphonate (5b): Yield 94%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.34 (m, 1 H), 7.24–7.18 (m, 1 H), 6.93–6.83 (m, 2 H), 4.65–4.56 (m, 2 H), 3.82 (s, 3 H), 3.21 (d, J = 21.6 Hz, 2 H), 1.27 (d, J = 6.0 Hz, 6 H), 1.17 (d, J = 6.0 Hz, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 157.2 (d, J = 7.0 Hz), 131.2 (d, J = 5.5 Hz), 127.9 (d, J = 3.6 Hz), 120.5 (d, J = 9.1 Hz), 120.3 (d, J = 5.4 Hz), 110.4 (d, J = 2.9 Hz), 70.3 (d, J = 6.9 Hz), 55.4, 27.5 (d, J = 140.4 Hz), 24.1 (d, J = 3.7 Hz), 23.7 (d, J = 5.1 Hz) ppm. ^{31}P NMR ($CDCl_3$, 163 MHz): δ = 25.9 ppm. ^{31}P NMR ($CDCl_3$, 163 MHz): δ = 25.9 ppm. HRMS: calcd. for $C_{14}H_{24}O_4P^+$ $[M + H]^+$ 287.1412; found 287.1411.

Diisopropyl (4-Bromobenzyl)phosphonate (5c): Yield 87%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42 (d, J = 8.4 Hz, 2 H), 7.18 (dd, J = 8.4, 2.4 Hz, 2 H), 4.66–4.56 (m, 2 H), 3.05 (d, J = 21.6 Hz, 2 H), 1.27 (d, J = 6.4 Hz, 6 H), 1.18 (d, J = 6.4 Hz, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 130.5 (d, J = 6.6 Hz), 130.4 (d, J = 3.0 Hz), 130.1 (d, J = 9.0 Hz), 119.7 (d, J = 4.6 Hz), 69.7 (d, J = 6.9 Hz), 33.3 (d, J = 139.2 Hz), 23.0 (d, J = 3.8 Hz), 22.8 (d, J = 5.0 Hz) ppm. ^{31}P NMR ($CDCl_3$, 163 MHz): δ = 24.0 ppm. HRMS: calcd. for $C_{13}H_{21}ClO_3P^+$ $[M + H]^+$ 335.0412; found 335.0412.

Diisopropyl (Naphthalen-1-ylmethyl)phosphonate (5d): Yield 86%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.14 (d, J = 8.4 Hz, 1 H), 7.84 (d, J = 8.0 Hz, 1 H), 7.77 (dd, J = 7.8, 0.6 Hz, 1 H), 7.57–7.41 (m, 4 H), 4.62–4.53 (m, 2 H), 3.61 (d, J = 22.0 Hz, 2 H), 1.25 (d, J = 6.0 Hz, 6 H), 1.04 (d, J = 6.0 Hz, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 133.8 (d, J = 2.6 Hz), 132.1 (d, J = 5.2 Hz), 128.5, 128.5, 128.4, 127.5 (d, J = 4.2 Hz), 125.9, 125.7, 125.3 (d, J = 4.1 Hz), 124.7 (d, J = 1.6 Hz), 70.7 (d, J = 7.1 Hz), 31.7 (d, J = 139.9 Hz), 24.1 (d, J = 3.6 Hz), 23.7 (d, J = 5.2 Hz) ppm. ^{31}P NMR ($CDCl_3$, 163 MHz): δ = 25.0 ppm. HRMS: calcd. for $C_{17}H_{24}O_3P^+$ $[M + H]^+$ 307.1464; found 307.1464.

Diisopropyl (4-Chlorobenzyl)phosphonate (5e): Yield 93%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29–7.21 (m, 4 H), 4.65–4.56 (m, 2 H), 3.06 (d, J = 21.6 Hz, 2 H), 1.27 (d, J = 6.0 Hz, 6 H), 1.17 (d, J = 6.4 Hz, 6 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 132.6 (d, J = 4.3 Hz), 131.2 (d, J = 6.6 Hz), 130.6 (d, J = 9.1 Hz), 128.5 (d, J = 3.0 Hz), 70.7 (d, J = 6.9 Hz), 34.1 (d, J = 139.2 Hz), 24.0 (d, J = 3.7 Hz), 23.8 (d, J = 4.9 Hz) ppm. ^{31}P NMR ($CDCl_3$, 163 MHz): δ = 24.3 ppm. HRMS: calcd. for $C_{13}H_{21}ClO_3P^+$ $[M + H]^+$ 291.0917; found 291.0917.

Supporting Information (see footnote on the first page of this article): Experimental procedures, characterization data, and ^{1}H, ^{13}C and ^{31}P NMR spectra for all products.

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