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Palladium-Catalyzed Cross-Coupling of *H*-Phosphinate Esters with Chloroarenes

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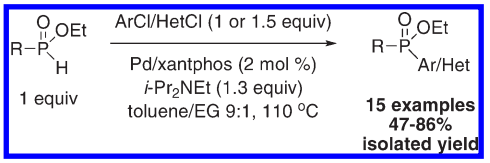
ABSTRACT



The palladium-catalyzed cross-coupling reaction between *H*-phosphinate esters and chloroarenes or chloroheteroarenes is described. This reaction is the first general metal-catalyzed phosphorus−carbon bond-forming reaction between a phosphorus nucleophile and chloroarenes.

Disubstituted phosphinic acid esters are of paramount importance in a variety of fields, especially as intermediates for the synthesis of phosphine ligands, and in the preparation of biologically active compounds.[1] A variety of metal-catalyzed cross-coupling reactions have been developed for the formation of P−C bonds.[2] However, only a few of these have been applied to chloroarene partners, and none have been reported for unactivated cases.[3]

In terms of *H*-phosphinate esters specifically, only isolated examples of cross-coupling with aryl halides have been documented, most often with phenyl-*H*-phosphinates, and/or using high palladium catalyst loadings (5−10 mol %), typically delivering moderate yields.[4] As a part of our laboratory's efforts at developing new methodologies for the formation of P−C bonds, we decided to tackle this problem and are now reporting the

(1) (a) Engel, R. *Handbook of Organophosphorus Chemistry*; Marcel Dekker: New York, 1992. (b) *The Chemistry of Organophosphorus Compounds*, Hartley, F. R., Ed.; Wiley: New York, 1996; Vol. 4. (c) Corbridge, D. E. C. *Phosphorus: An Outline of Its Chemistry, Biochemistry and Uses*, 5th ed.; Elsevier: Amsterdam, 1995. (d) *Aminophosphonic and Aminophosphinic Acids: Chemistry and Biological Activity*; Kukhar, V. P., Hudson, H. R., Eds.; Wiley: Chichester, 2000. (e) Kalir, A.; Kalir, H. H. *Chem. Organophosphorus Compd* **1996**, 767. (f) Quin, L. D. *A Guide to Organophosphorus Chemistry*; Wiley: New York, 2000. (g) Soulier, E.; Clement, J.-C.; Yaouanc, J.-J.; des Abbayes, H. *Tetrahedron Lett.* **1998**, *39*, 4291. (h) Alexandre, F.-R.; Amador, A.; Bot, S.; Caillet, C.; Convard, T.; Jakubik, J.; Musiu, C.; Poddesu, B.; Vargiu, L.; Liuzzi, M.; Roland, A.; Seifer, M.; Standring, D.; Storer, R.; Dousson, C. B. *J. Med. Chem.* **2011**, *54*, 392. (i) Devel, L.; Rogakos, V.; David, A.; Makaritis, A.; Beau, F.; Cuniasse, P.; Yiotakis, A.; Dive, V. *J. Biol. Chem.* **2006**, *281*, 11152.

(2) (a) Tappe, F. M. J.; Trepohl, V. T.; Oestreich, M. *Synthesis* **2010**, 3037. (b) Glueck, D. S. *Top. Organomet. Chem.* **2010**, *31*, 65. (c) Schwan, A. L. *Chem. Soc. Rev.* **2004**, *33*, 218. (d) Baillie, C.; Xiao, J. *Curr. Org. Chem.* **2003**, *7*, 477. (e) Engel, R.; Cohen, J. I. *Synthesis of Carbon-Phosphorus Bonds*, 2nd ed.; CRC Press: Boca Raton, FL, 2003. (f) Beletskaya, I. P.; Kazankova, M. A. *Russ. J. Org. Chem.* **2002**, *38*, 1391.

(3) (a) Belabassi, Y.; Alzghari, S.; Montchamp, J.-L. *J. Organomet. Chem.* **2008**, *693*, 3171. (b) Montchamp, J.-L.; Dumond, Y. R. *J. Am. Chem. Soc.* **2001**, *123*, 510. (c) Heinicke, J.; Gupta, N.; Surana, A.; Peulecke, N.; Witt, B.; Steinhauser, K.; Bansal, R. K.; Jones, P. G. *Tetrahedron* **2001**, *57*, 9963. (d) Maier, L.; Duerr, D.; Rempfler, H. *Phosphorus Sulfur* **1987**, *32*, 19. (e) Bard, R. R.; Bunnett, J. F.; Traber, R. P. *J. Org. Chem.* **1979**, *44*, 4918. See also:(f) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176. (g) *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, Germany, 1998.

(4) (a) Volle, J.-N.; Filippini, D.; Krawczy, B.; Kaloyanov, N.; Van der Lee, A.; Maurice, T.; Pirat, J.-L.; Virieux, D. *Org. Biomol. Chem.* **2010**, *8*, 1438. (b) Kalek, M.; Stawinski, J. *Tetrahedron* **2009**, *65*, 10406. (c) Kumar, R. J.; Chebib, M.; Hibbs, D. E.; Kim, H.-L.; Johnston, G. A. R.; Salam, N. K.; Hanrahan, J. R. *J. Med. Chem.* **2008**, *51*, 3825. (d) Beletskaya, I. P.; Karlstedt, N. B.; Nifant'ev, E. E.; Khodarev, D. V.; Kukhareva, T. S.; Nikolaev, A. V.; Ross, A. J. *Russ. J. Org. Chem.* **2006**, *42*, 1780. (e) Jiang, W.; Allan, G.; Fiordeliso, J. J.; Linton, O.; Tannenbaum, P.; Xu, J.; Zhu, P.; Gunnet, J.; Demarest, K.; Lundeen, S.; Sui, Z. *Bioorg. Med. Chem.* **2006**, *14*, 6726. (f) Huang, C.; Tang, X.; Fu, H.; Jiang, Y.; Zhao, Y. *J. Org. Chem.* **2006**, *71*, 5020. (g) Pirat, J.-L.; Monbrun, J.; Virieux, D.; Cristau, H.-J. *Tetrahedron* **2005**, *61*, 7029. (h) Beletskaya, I. P.; Negamova, E. G.; Veits, Y. A. *Russ. J. Org. Chem.* **2004**, *40*, 1782. (i) Cristau, H.-J.; Hervé, A.; Loiseau, F.; Virieux, D. *Synthesis* **2003**, 2216. (j) Luke, G. P.; Shakespeare, W. C. *Synth. Commun.* **2002**, *32*, 2951. (k) Schuman, M.; Lopez, Z.; Karplus, M.; Gouverneur, V. *Tetrahedron* **2001**, *57*, 10299. (l) Schwabacher, A. W.; Stefanescu, A. D.; Rehman, A. u. *J. Org. Chem.* **1999**, *64*, 1784. (m) Edlin, C. S.; Parker, D. *Tetrahedron Lett.* **1998**, *39*, 2797. (n) Murata, Y.; Woodward, R. M.; Miledi, R.; Overman, L. E. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2073. (o) Bennett, S. N. L.; Hall, R. G. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1145. (p) Lei, H.; Stoakes, M. S.; Schwabacher, A. W. *Synthesis* **1992**, 1255. (q) Xu, Y.; Wej, H.; Zhang, J.; Huang, G. *Tetrahedron Lett.* **1989**, *30*, 949. (r) Xu, Y.; Li, Z. *Tetrahedron Lett.* **1986**, *27*, 3017. (s) Xu, Y.; Li, Z.; Xia, J.; Guo, H.; Huang, Y. *Synthesis* **1983**, 377.

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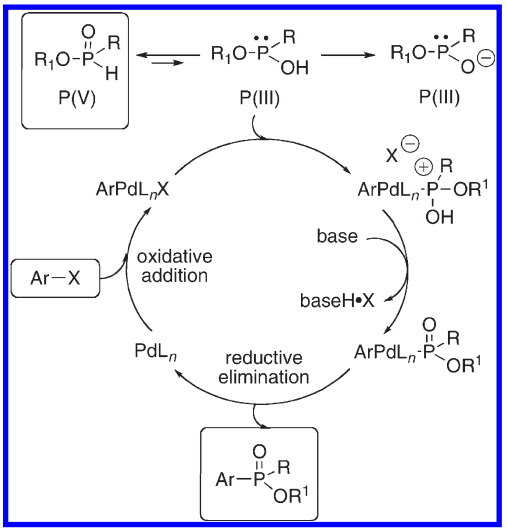
first general cross-coupling of *H*-phosphinate esters with aryl halides in general and chloroarenes in particular.

A possible mechanism for *H*-phosphinate coupling is shown in Scheme 1. Key to the reaction is the availability of the P(III) nucleophile through tautomerization of the P(V) phosphinylidene. While strong bases (like alkoxides) can form the readily oxidized P(III) anion, this is not a likely intermediate with the weak bases typically employed in these reactions, and the advantage of increasing the concentration of a P(III) form can be offset by this anion's sensitivity to oxidation.

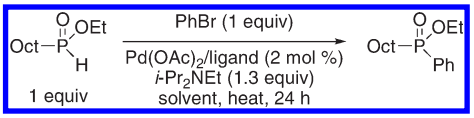
Scheme 1. Postulated Mechanism



During an investigation of the hydrophosphinylation of *H*-phosphinates, we discovered the usefulness of ethylene glycol (EG) as an additive to promote the tautomerization of P(V) *H*-phosphinates into the reactive P(III) form.[5] We therefore attempted cross-coupling reactions using EG as an additive anticipating it could also play a beneficial role. The results of this investigation are reported below.

Ethyl octyl-*H*-phosphinate was chosen as a representative model compound (unlike aryl-*H*-phosphinate esters which are special benzylic-like and activated, more easily tautomerized substrates since electron-withdrawing groups stabilize the P(III) form).[6] Bromobenzene was also selected as a more stringent test than reactive iodobenzene. Various reaction parameters, such as solvents, bases, and ligands, were explored.[7] Table 1 summarizes some of these results using 2 mol % Pd. Three ligands gave good results: dppf, xantphos, and polymer-supported nixantphos.[8] The

Table 1. Reaction Parameters with Bromobenzene[a]



entry	solvent	cosolvent additive	ligand	^{31}P NMR yield (%)[b]
1	EG	none	dppf	59
2	CH_3CN	none	dppf	0
3	CH_3CN	EG	dppf	63 (16)
4	EtOH	none	dppf	30
5	EtOH	EG	dppf	69 (7)
6	*t*-AmOH	none	dppf	30
7	*t*-AmOH	EG	dppf	72 (7)
8a	DMF	none	dppf	5
8b			xantphos	40
9	DMF	EG	dppf	71 (1)
10	toluene	none	dppf	7
11a	toluene	EG	none	70 (5)
11b			dppf	80 (7)[c]
11c			xantphos	90 (1)[c]
12	toluene	PG[d]	dppf	72 (5)
13	toluene	DME[e]	dppf	78 (7)
14a	toluene	EG	polymer	84 (4)
14b			nixantphos[f]	74 (17)[g]

[a] Conditions: the reactions were conducted at reflux using solvent or solvent/additive (9:1 v/v), or at 110 °C with DMF or neat EG. [b] Determined after addition of EtOH to obtain a homogeneous mixture. In a few cases, some 2-hydroxyethyl ester also formed and the yield is indicated in parentheses. [c] Run with 1 mol % Pd/ligand. [d] PG = propylene glycol. [e] DME = 1,2-dimethoxyethane. [f] Polystyrene-supported Pd-nixantphos, 2 mol %. [g] Using catalyst from entry 14a.

xantphos-like ligands are superior, whereas other ligands tested were significantly poorer. Of the bases tried, *i*-Pr$_2$NEt and Et$_3$N gave the best yields, but the former was ultimately selected in order to reduce the potential for dealkylation of the *H*-phosphinate starting material. Ethylene glycol consistently gave remarkable improvements in yields when added to other solvents. For example, with EtOH the yield more than doubled (entry 5 versus 4).

It was found that the toluene/EG mixture gave the best results even with only 1 mol % of catalyst (entries 11b and 11c). With toluene/EG (unlike other solvent mixtures) the medium is heterogeneous, and the temperature is also higher than that for entries 2−7.

At this time, we can only speculate about EG's mode of action in this reaction. The fact that little transesterification to the 2-hydroxyethyl ester is observed rules out the intramolecular P−H activation process we proposed for hydrophosphinylation.[5] We surmise that intermolecular hydrogen bonding might still help in the tautomerization of the P(V) *H*-phosphinate P(O)H into the active phosphonous P(III) form P−OH (Scheme 1), but this will need to be investigated in future work. Ethylene glycol (entry 1) is clearly superior to even other protic solvents, such as EtOH and *t*-AmOH (entries 4 and 6). Another role for EG

(5) Petit, C.; Fécourt, F.; Montchamp, J.-L., submitted to *Adv. Synth. Catal.*

(6) Coudray, L.; Montchamp, J.-L. *Eur. J. Org. Chem.* **2008**, 3601.

(7) Some ligands tested include PPh_3, dppe, dppp, 2-(di-*tert*-butylphosphino)biphenyl, as well as the catalysts chloro(di-2-norbornylphosphino)(2′-dimethylamino-1,1′-biphenyl-2-yl) palladium(II). Bases tested include Na_2CO_3, K_2CO_3, Cs_2CO_3, K_3PO_4, DBU, DABCO, and 1,1,3,3-tetramethylguanidine.

(8) Deprèle, S.; Montchamp, J.-L. *Org. Lett.* **2004**, *6*, 3805.

might be to stabilize the palladium catalyst and slow down its decomposition. For example, entry 11a still gave a significant yield of product, even though it is conducted in the absence of ligand. This might also explain why our reaction can employ significantly less catalyst than in the previously reported *H*-phosphinate Pd-catalyzed cross-couplings.[4] Interestingly, nontoxic propylene glycol (PG) and DME are also good additives for this reaction (entries 12 and 13) even if EG is slightly superior. Another important result is the success of our readily available polystyrene Pd/nixantphos catalyst which delivered a yield comparable to that of Pd/xantphos (entry 14a). Perhaps more importantly, this catalyst could be used in a second run without loss in P−C bond formation (91% total, entry 14b), although more 2-hydroxylethyl ester formed, which is a hallmark of a slower reaction (see also entries 3, 5, and 7).

With the promising results described above, we then turned our attention to a study of the scope of the cross-coupling between aryl halides and several *H*-phosphinate esters. Using the conditions identified in Table 1 (2 mol % Pd/xantphos, 1.3 equiv of *i*-Pr_2NEt, toluene/EG (9:1, v/v), 110 °C), various combinations of RP(O)(OEt)H and ArX/HetX were tried. These results are shown in Table 2.

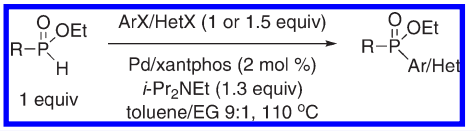
Unsurprisingly, iodobenzene gave the cross-coupling product in high yield (entry 1), as did phenyl triflate (entry 2). More challenging bromobenzene also gave an excellent result (entry 3), as expected from Table 1. Most notably, even unactivated chlorobenzene still reacted to deliver the disubstituted phosphinate in an acceptable yield (entry 4a). The use of 1.5 equiv instead of the usual equimolar ratio gave a clearly better outcome (entry 4b). A reaction under microwave irradiation gave essentially the same yield as the thermal reaction (entry 5b versus 5a).

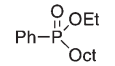
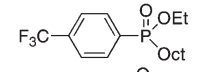
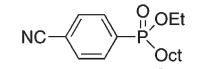
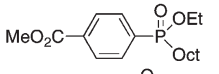
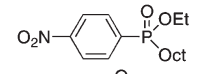
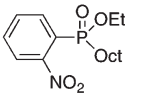
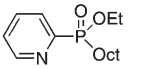
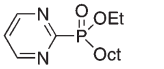
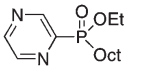
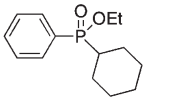
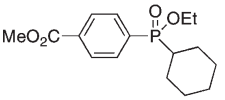
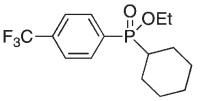
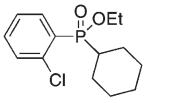
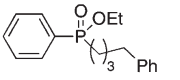
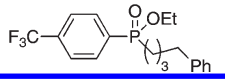
Chloro(hetero)arenes cross-coupled with several representative *H*-phosphinates. The more activated electron-deficient aromatics gave higher yields, but a variety of aryl and heteroaryl chlorides still reacted in moderate to good yields (Table 2). For example, heterocyclic phosphinates were obtained easily (entries 10−12). While *H*-phosphinate esters are clearly weaker reducing agents than hypophosphites, the formation of cross-coupled disubstituted phosphinates remains a major breakthrough. *This appears to be the first general P−C bond formation via metal-catalyzed cross-coupling employing chlorides.*[3]

Unfortunately, deactivated chloroanisole (1.5 equiv) only gave a low yield of cross-coupling with ethyl octyl-*H*-phosphinate (29% NMR yield). Nonetheless, the present work provides a very general entry into disubstituted phosphinates. More reactive aryl halides (X = I, Br, OTf) give high yields of cross-coupling, and these studies will be included in the full account. While *H*-phosphinate esters are much less reducing than the hypophosphorous derivatives, their cross-coupling reactions have nonetheless been more challenging than with *H*-phosphonates or secondary phosphine oxides. Our reaction thus solves a long-standing problem.

Because xantphos, polystyrene-supported nixantphos, and dppf were the best ligands we tested in this reaction, and because they are also the preferred choice for a variety of reactions we have developed (such as hydrophosphinylation or coupling with hypophosphorous derivatives),[6,9]

Table 2. Preliminary Scope of the Pd-Catalyzed Cross-Coupling of Ethyl *H*-Phosphinate Esters with Aryl Halides[a]



entry	ArX	product	NMR yield[b] (%)	isolated yield[c] (%)
1	PhI		90	81
2	PhOTf		88	79
3	PhBr		91	78
4a	PhCl		44	-
4b	PhCl[d]		62	50
5a	4-$F_3CC_6H_4Cl$		79	65
5b			74	58[e]
6	4-NCC_6H_4Cl		68	58
7	4-$MeO_2CC_6H_4Cl$		74	67
8	4-$O_2NC_6H_4Cl$[d]		66	64
9	2-$O_2NC_6H_4Cl$[d]		66	57
10	2-chloropyridine		86	80
11	2-chloro pyrimidine		70	52
12	chloropyrazine		87	79
13	PhCl[d]		75	69
14	4-$MeO_2CC_6H_4Cl$		94	86
15	4-$F_3CC_6H_4Cl$		90	66
16	2-ClC_6H_4Cl		57	47
17	PhCl[d]		67	53
18	4-$F_3CC_6H_4Cl$		90	82

[a] See Supporting Information for experimental details. Unless otherwise noted, equimolar amounts of *H*-phosphinate and aryl halide were employed. [b] Determined after addition of EtOH to obtain a homogeneous mixture. [c] Isolated after chromatography over silica gel. [d] 1.5 equiv. [e] Conducted with microwave heating: constant temperature mode at 130 °C.

this opens up the way for the investigation of various tandem processes. Such sequences are important because they would allow the synthesis of a variety of organophosphorus compounds starting from hypophosphorous acid and its derivatives, instead of the traditional but environmentally problematic phosphorus trichloride (PCl_3) and related P−Cl intermediates.[10]

In conclusion, a novel and general palladium-catalyzed cross-coupling between *H*-phosphinates and aryl halides was developed. Future work will aim at delineating the exact role of ethylene glycol (and other additives), as well as applications to the synthesis of important organophosphorus compounds. Whatever the detailed molecular mechanism for the additive, the present reaction provides a highly general access to disubstituted phosphinates and constitutes an exceptional example of catalytic P−C bond formation with chloro(hetero)arenes. Further detailed investigations and applications will be disclosed in due course.

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Supporting Information Available. Detailed experimental procedures, spectral data, and copies of the NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

(9) (a) Deprèle, S.; Montchamp, J.-L. *J. Am. Chem. Soc.* **2002**, *124*, 9386. (b) Bravo-Altamirano, K.; Abrunhosa-Thomas, I.; Montchamp, J.-L. *J. Org. Chem.* **2008**, *73*, 2292. (c) Coudray, L.; Montchamp, J.-L. *Eur. J. Org. Chem.* **2008**, 4101. (d) Belabassi, Y.; Bravo-Altamirano, K.; Montchamp, J.-L. *J. Organomet. Chem.* **2011**, *696*, 106.

(10) For example, see: (a) Cossairt, B. M.; Piro, N. A.; Cummins, C. C. *Chem. Rev.* **2010**, *110*, 4164. (b) Caporali, M.; Gonsalvi, L.; Rossin, A.; Peruzzini, M. *Chem. Rev.* **2010**, *110*, 4178. (c) Scheer, M.; Balázs, G.; Seitz, A. *Chem. Rev.* **2010**, *110*, 4236. (d) Trofimov, B. A.; Gusarova, N. K. *Mendeleev Commun.* **2009**, *19*, 295. (e) Milyukov, V. A.; Budnikova, Y. H.; Sinyashin, O. G. *Russ. Chem. Rev.* **2005**, *74*, 781. (f) Peruzzini, M.; de los Rios, I.; Romerosa, A.; Vizza, F. *Eur. J. Inorg. Chem.* **2001**, 593.