Synthesis of Monosubstituted Phosphinic Acids: Palladium-Catalyzed Cross-Coupling Reactions of Anilinium Hypophosphite

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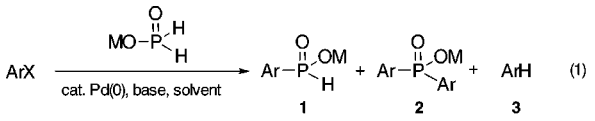
Functionalized monoarylphosphinic acids are valuable intermediates for the preparation of medicinal compounds and synthetic intermediates, but methods to access them are currently limited.[1] During studies aimed at the preparation of biologically active phosphinic acids, we required new methods for phosphorus−carbon bond formation under mild conditions. Despite recent advances in the palladium-catalyzed formation of carbon−heteroatom bonds,[2] the direct preparation of monosubstituted phosphinic acids via palladium-catalyzed cross-coupling has not been described previously. Herein, we report the novel palladium-catalyzed cross-coupling reaction of hypophosphite salts with aromatic halides, which addresses the following factors: (1) selective formation of monosubstituted products, (2) wide applicability, (3) functional group tolerance, (4) convenient reaction conditions, and (5) avoidance of hazardous anhydrous hypophosphorous acid. In principle, such preparation of monosubstituted phosphinic acids **1** is most atom-efficient because it uses the direct alkylation of environmentally benign H_3PO_2 or its salts (eq 1).

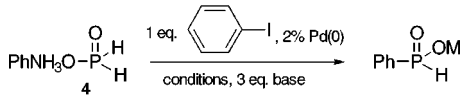


(1)

The preparation of phosphonate diesters and disubstituted phosphinate esters via cross-coupling was reported relatively early on, but is limited to nucleophiles which contain only one P−H bond.[3] In contrast, hypophosphorus derivatives are powerful reducing agents with two reactive P−H bonds, leading to the potential for unwanted disubstitution and reduction products (**2** and **3**, respectively, eq 1). Indeed, a number of substrates have been reduced with sodium hypophosphite or H_3PO_2, in the presence of transition metals such as palladium.[4] At the outset, we expected the competing catalytic transfer hydrogenation pathway to be the most difficult problem.

Inspection of the literature revealed only three publications dealing with the cross-coupling of hypophosphorus compounds, but these provided little or no discussion of the possible reductive pathways.[5,6] Holt reported a single example of cross-coupling between anhydrous H_3PO_2 and a steroidal dienyl triflate.[5] Schwabacher has developed an elegant cross-coupling of aryl iodides with methyl- or *tert*-butylhypophosphites prepared in situ.[6] However, these reactions were limited to using reactive iodides under strickly anaerobic and anhydrous conditions, because alkyl hypophosphites rapidly decompose thermally or in the presence of moisture or air.[6]

Table 1. Influence of Conditions on the Yield of Phenylphosphinate



entry	equiv of **4**	solvent[a]	base	catalyst[b]	yield[c]
1	1.5	CH_3CN	Et_3N	i	91
2	1.5	benzene	Et_3N	i	68
3	1.5	dioxane	Et_3N	i	53
4	1.5	THF	Et_3N	i	85
5	1.1	dry DMF	Et_3N	i	96
6	1.1	reagent DMF	Et_3N	i	87
7	2.0	reagent DMF, in air	Et_3N	i	86
8	2	CH_3CN	Et_3N	i	97
9	2	CH_3CN	Et_3N	ii	92
10	2	CH_3CN	Et_3N	iii	96
11	2	CH_3CN	Et_3N	i + 10% BHT	96
12	2	CH_3CN, in air	Et_3N	i	86
13	1.1	CH_3CN	Et_3N	i	81
14	1.1	CH_3CN	pyr.	i	78
15	1.2	CH_3CN	none	i	38

[a] Reactions in DMF were conducted at 85 °C, all others were at the reflux temperature. Reaction times: entries 1−7, 12−24 h; entries 8−11, 8 h; entries 12−15, 3−6 h. HPLC grade CH_3CN was used. PhI concentration was 0.2 M. [b] Catalyst: i, $Pd(PPh_3)_4$; ii, $Cl_2Pd(PPh_3)_2$; iii, $Pd(OAc)_2 + 4\ PPh_3$. BHT = 2,6-di-*tert*-butyl-4-methylphenol. [c] Yields were determined by ^{31}P NMR analysis of the crude reaction mixtures.

To avoid the problems associated with handling anhydrous H_3PO_2, we developed a safer reagent. Anilinium hypophosphite **4**, a cheap, highly crystalline, high-melting, and nonhygroscopic salt, was found to be most convenient.[7,8] Initial investigations focused on the reaction of **4** with iodobenzene using $Pd(PPh_3)_4$ (2 mol %) as the catalyst (Table 1). Several solvents are satisfactory, but acetonitrile and anhydrous DMF are the most suitable. Remarkably, no special precautions are necessary, and phenylphosphinic acid is still obtained in good yield using reagent grade DMF (entry 6), even in the presence of air (entry 7). Various palladium catalysts delivered consistently high yields, and the presence of a radical inhibitor had no effect (Table 1, entries 8−11), while no product was observed without catalyst. Finally, the influence of the base was briefly probed, and pyridine was found to be equivalent to triethylamine (Table 1, entry 14 vs 13), while in the absence of added base (Table 1, entry 15), the yield was lowered but a significant amount of product was still produced.

The reaction displays a remarkably broad scope for a single set of conditions, and these results are summarized in Table 2. Aryl iodides, bromides, and triflates, as well as benzylic chlorides, all undergo cross-coupling in moderate to excellent yields. The monophosphinic acid product could be obtained conveniently, and

(1) Typically, monoaryl phosphinic acids are prepared from the corresponding dichlorophosphines. For a discussion, see: Bennett, S. N. L.; Hall, R. G. *J. Chem. Soc. Trans. 1* **1995**, 1145. The Ciba Geigy group reported an alternative two-step synthesis of phosphinic acids, based on the masking of a P−H bond and cross-coupling with 10% $Pd(PPh_3)_4$.

(2) Reviews: (a) Hartwig, J. F. *Acc. Chem. Res.* **1998**, *31*, 852. (b) Barañano, D.; Mann, G.; Hartwig, J. F. *Curr. Org. Chem.* **1997**, *1*, 287. See also references cited in: (c) Harris, M. C.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 5327. (d) Huang, J.; Grasa, G.; Nolan, S. P. *Org. Lett.* **1999**, *1*, 1307. (e) Al-Masum, M.; Kumaraswamy, G.; Livinghouse, T. *J. Org. Chem.* **2000**, *65*, 4776. (f) Oshidi, T.; Imamoto, T. *J. Am. Chem. Soc.* **1992**, *114*, 3975.

(3) (a) Hirao, T.; Masunaga, T.; Ohshiro, Y.; Agawa, T. *Tetrahedron Lett.* **1980**, *21*, 3595. (b) Hirao, T.; Masunaga, T.; Yamada, N. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 909. (c) Xu, Y.; Zhang, J. *Synthesis* **1984**, 778. (d) Xu, Y.; Li, Z.; Xia, J.; Guo, H.; Huang, Y. *Synthesis* **1983**, 377. (e) Xu, Y.; Li, Z.; Xia, J.; Guo, H.; Huang, Y. *Synthesis* **1984**, 781.

(4) (a) Johnstone, R. A. W.; Wilby, A. H. *Chem. Rev.* **1985**, *85*, 129. (b) Boyer, S. K.; Bach, J.; McKenna, J.; Jagdmann, E., Jr. *J. Org. Chem.* **1985**, *50*, 3408.

(5) Holt, D. A.; Erb, J. M. *Tetrahedron Lett.* **1989**, *30*, 5393.

(6) (a) Lei, H.; Stoakes, M. S.; Schwabacher, A. W. *Synthesis* **1992**, 1255. (b) Schwabacher, A. W.; Stefanescu, A. D. *Tetrahedron Lett.* **1996**, *37*, 425.

(7) See Supporting Information for details. This salt has been reported in the literature: Schmidt, H. *Chem. Ber.* **1948**, *81*, 477.

(8) Other reagents can be used: Montchamp, J.-L.; Dumond, Y. R. Unpublished results. (a) Triethylammonium and *N*-ethylpiperidinium hypophosphites give slightly lower yields than **4**, and are less convenient to handle. Ammonium and sodium hypophosphites can also react but require experimental modifications. (b) In situ generated $(TMSO)_2PH$ also undergoes the reaction.

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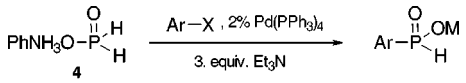
Table 2. Cross-Coupling Reactions of Anilinium Hypophosphite[a]



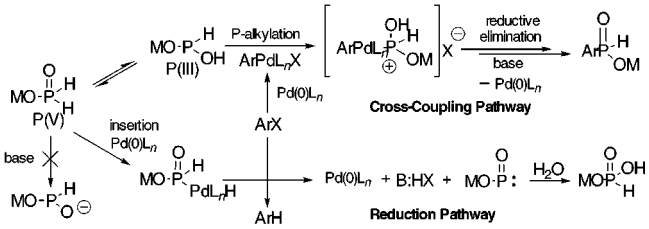
entry	Ar−X	solvent	^{31}P NMR yield, %[b] (isolated yield, %)
1	C_6H_5−I	CH_3CN	97
2	C_6H_5−I	DMF	96 (89)
3	2-MeC_6H_4−I	CH_3CN	96 (91)
4	4-$CH_3COC_6H_4$−I	CH_3CN	93 (74)
5	3-MeC_6H_4−I	CH_3CN	98 (87)
6	4-$O_2NC_6H_4$−I	CH_3CN	92
7	4-$MeOC_6H_4$−I	CH_3CN	48
8	4-$MeOC_6H_4$−I	CH_3CN	91 (85)[c]
9	2-BrC_6H_4−I	CH_3CN	65
10	3-ClC_6H_4−I	CH_3CN	95 (94)
11	C_6H_5−Br	DMF	81
12	4-$MeOC_6H_4$−Br	DMF	51
13	4-$MeOC_6H_4$−Br	DMF	85[c]
14	4-ClC_6H_4−Br	DMF	75
15	4-$HOOCC_6H_4$−Br	DMF	quant.
16	naphthyl-2-Br	DMF	74 (71)[d]
17	C_6H_5−OTf	DMF	81
18	4-$MeO_2CC_6H_4$−OTf	DMF	65
19	naphthyl-1-OTf	DMF	74
21	$C_6H_5CH_2Cl$	CH_3CN	81 (66)
22	4-$MeOC_6H_4CH_2Cl$	CH_3CN	60 (46)
23	4-CH_2=$CHC_6H_4CH_2Cl$	CH_3CN	55 (34)
24	4-NCC_6H_4−Cl	DMF	0
25	4-NCC_6H_4−Cl	DMF	71[c]
26	2,6-$(Me)_2C_6H_3$−Br	DMF	<2
27	C_6H_5−I	CH_3CN	quant.[e]

[a] All reactions were conducted at 80−85°C and reaction times were not optimized: entries 1, 2, 4, 5, 6, 10, and 15, 2−6 h; entries 21−23, 7−9 h; all other entries, 18−24 h. 2 equiv of **4** was used in CH_3CN, 1.2 equiv of **4** was used in DMF. [b] Reduction products constitute the mass balance. In all instances, yield of $Ar_2P(O)OM$ was <2%. [c] 2 mol % $Pd(OAc)_2$ + 2.2 mol % $Ph_2P(CH_2)_3PPh_2$ (dppp) was used as the catalyst. [d] Isolated as the butyl ester (see ref 9). [e] 0.2 mol % $Pd(PPh_3)_4$ was employed.

in better than 95% purity after solvent removal, acidification, and extraction.[9] Several generalizations can be made about this novel cross-coupling. Excellent selectivity is observed for the formation of monosubstituted over disubstituted phosphinates. The reaction does not require the use of strictly anhydrous, degassed, solvents and proceeds well even in the presence of small amounts of moisture.

Even functionalities which can be reduced easily under phase-transfer hydrogenation[4] are tolerated, although the reaction time becomes important to avoid reduction of the product when an excess of **4** is employed. The best results are obtained when the reaction is conducted in DMF at 85 °C with a slight molar excess of **4** (1.1−1.2 equiv), but refluxing CH_3CN and 2 equiv of **4** is more convenient when oxidative addition into the C−X bond is facile. The amount of reduction through transfer hydrogenation becomes much more significant when the rate of oxidative addition in the C−X bond is slow. For example, substrates undergoing oxidative addition readily gave high yields of cross-coupled product, while in the case of the deactivating electron-donating methoxy substituent, reduction competed to produce anisole in 49% yield (Table 2, entry 2 vs 11 vs 12). As little as 0.2 mol % $Pd(PPh_3)_4$ gave a quantitative yield of $PhPO_2H_2$ (Table 2, entry 27). On the other hand, ortho substitution considerably slows down, or even suppresses, the reaction (Table 2, entry 26).

Scheme 1. Postulated Mechanism



A possible mechanism is presented in Scheme 1. Oxidative additions into the C−X and P−H bonds are two competitive processes. When oxidative addition into C−X is facile, little reduction is observed, but when it is slow, reduction becomes dominant. Since the base has little influence, and formation of a hypophosphite dianion is unlikely, the P(III) form of **4** is presumably the reactive species,[8b] and the reaction proceeds through a phosphonium intermediate.[10]

The influence of the phosphine ligand was briefly investigated, with the hope of controlling the partitioning between transfer hydrogenation and cross-coupling. Using $Pd(OAc)_2$/dppp (2 and 2.2 mol %, respectively) in place of $Pd(PPh_3)_4$ was a superior alternative and decreased the competing reduction (Table 2, entries 7 vs 8, 12 vs 13, and 24 vs 25). With this catalyst system, even the activated 4-chlorobenzonitrile reacted in 71% yield, while no product formed with $Pd(PPh_3)_4$. Further studies will be conducted along these promising leads.

In conclusion, a straightforward synthesis of monosubstituted phosphinic acids has been developed, based on the Pd-catalyzed reaction between anilinium hypophosphite and various aromatic electrophiles. Efforts to optimize the catalyst and to broaden the scope of this novel reaction to unactivated chlorides and alkenyl or allylic partners are currently underway in our laboratory.

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Supporting Information Available: Experimental procedures, representative spectral data, and crystallographic data for **4** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) In a typical experiment (Table 2, entry 2), iodobenzene (2 mmol), hypophosphite **4** (2.2 mmol), and Et_3N (6 mmol) were dissolved in anhydrous DMF (10 mL). $Pd(PPh_3)_4$ (0.04 mmol) was added, and the solution was heated to 85 °C under N_2. The reaction mixture was then concentrated in vacuo, acidified with aqueous $KHSO_4$ (1 M, saturated with NaCl), and extracted with EtOAc. Drying over $MgSO_4$ and concentration gave phenyl phosphinic acid in 89% yield and >98% purity. The crude acid can also be esterified; see: Dumond, Y. R.; Baker, R. L.; Montchamp, J. L. *Org. Lett.* **2000**, *2*, 3341.

(10) Intermediacy of phosphonium ions during cross-coupling has been observed previously: (a)Martorell, G.; Garcías, X.; Janura, M.; Saá, J. M. *J. Org. Chem.* **1998**, *63*, 3463. (b) Hinkle, R. J.; Stang, P. J.; Kowalski, M. H. *J. Org. Chem.* **1990**, *55*, 5033. (c) Tunney, S. E.; Stille, J. K. *J. Org. Chem.* **1987**, *52*, 748.