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Copper-Catalyzed C–P Bond Construction via Direct Coupling of Secondary Phosphines and Phosphites with Aryl and Vinyl Halides

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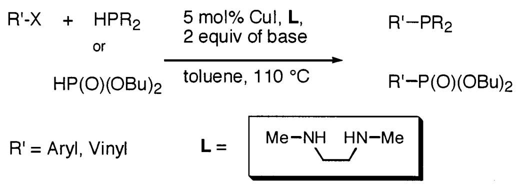
ABSTRACT



A general method for the coupling of aryl and vinyl halides with diaryl and dialkyl phosphines, as well as with dibutyl phosphite, is reported. This highly efficient transformation is realized through the use of copper(I) iodide as a catalyst, *N,N'*-dimethylethylenediamine as a ligand, and Cs_2CO_3 as a base. A variety of sterically hindered and/or functionalized substrates were found to react under these reaction conditions to provide products in good to excellent yields.

The formation of carbon−heteroatom bonds by transition-metal-catalyzed cross-coupling methodology has been the subject of intensive investigation in recent years.[1] Although the majority of efforts have been focused on the formation of carbon−nitrogen,[2] −oxygen,[3] and −sulfur bonds,[4] limited protocols for direct coupling of aryl halides with secondary phosphines have been published.[5] Recent reinvestigation of Ullmann-type chemistry showed that many of the above-mentioned cross-coupling processes may be performed using a catalytic quantity of a copper complex.[6] However, examples of copper-mediated carbon−phosphorus bond formation are rare.[7] In this communication, we wish to report a general

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(1) For reviews, see: (a) Hartwig, J. F. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley-Interscience: New York, 2002; p 1051. (b) Muci, A. R.; Buchwald, S. L. *Top. Curr. Chem.* **2002**, *219*, 131.

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(4) For a review, see: (a) Kondo, T.; Mitsudo, T. *Chem. Rev.* **2000**, *100*, 3205. For copper-catalyzed C−S bond formation, see: (b) Kwong, F. Y.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 3517. (c) Bates, C. G.; Gujadhur, R. K.; Venkataraman, D. *Org. Lett.* **2002**, *4*, 2803.

(5) (a) Brauer, D. J.; Hingst, M.; Kottsieper, K. W.; Liek, C.; Nickel, T.; Tepper, M.; Stelzer, O.; Sheldrick, W. S. *J. Organomet. Chem.* **2002**, *645*, 14. (b) Stadler, A.; Kappe, C. O. *Org. Lett.* **2002**, *4*, 3541. (c) Kraatz, H.-B.; Pletsch, A. *Tetrahedron: Asymmetry* **2000**, *11*, 1617. (d) Bergbreiter, D. E.; Liu, Y.-S.; Furyk, S.; Case, B. L. *Tetrahedron Lett.* **1998**, *39*, 8799. (e) Machnitzki, P.; Nickel, T.; Stelzer, O.; Landgrafe, C. *Eur. J. Inorg. Chem.* **1998**, 1029. (f) Herd, O.; Hessler, A.; Hingst, M.; Trepper, M.; Stelzer, O. *J. Organomet. Chem.* **1996**, *522*, 69. (g) Cai, D.; Payack, J. F.; Bender, D. R.; Hughes, D. L.; Verhoeven, T. R.; Reider, P. J. *J. Org. Chem.* **1994**, *59*, 7180.

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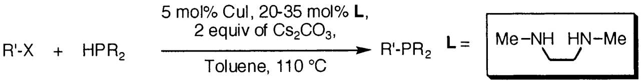
Table 1. Copper-Catalyzed Phosphination of Aryl and Vinyl Halides



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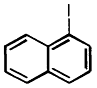
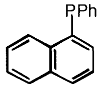
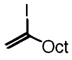
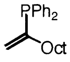
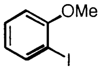
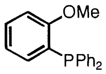
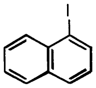
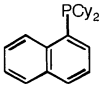
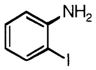
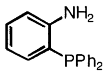
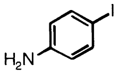
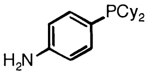
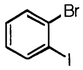
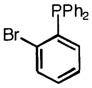
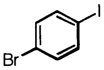
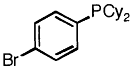
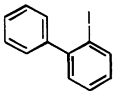
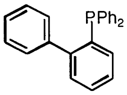
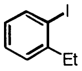
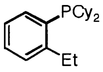
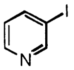
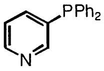
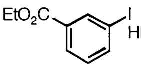
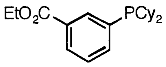
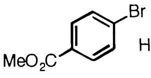
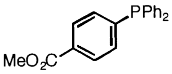
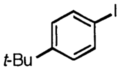
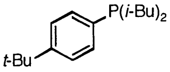
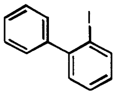
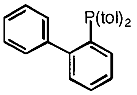
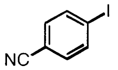
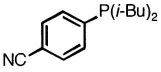
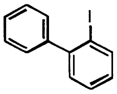
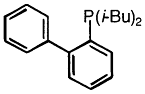
1		$HPPh_2$	A		20	89	9[d]		$HPPh_2$	B		9	83
2		$HPPh_2$	B		20	91	10		$HPCy_2$	C		16	79
3		$HPPh_2$	B		20	86	11		$HPCy_2$	D		13	72
4		$HPPh_2$	A		24	84	12		$HPCy_2$	D		14	72
5		$HPPh_2$	B		20	81	13		$HPCy_2$	C		12	86
6		$HPPh_2$	B		14	60	14		$HPCy_2$	B		9	85
7		$HPPh_2$	B		20	70	15		$HP(i\text{-Bu})_2$	B		19	88
8		$HP(tol)_2$	B		14	79	16		$HP(i\text{-Bu})_2$	C		14	79
							17		$HP(i\text{-Bu})_2$	B		15	73

[a] Conditions A: R-I (1 mmol), R_2PH (1.1 mmol), CuI (5 mol %), Cs_2CO_3 (2 mmol) in toluene at 110 °C. Conditions B: R-X (1 mmol), R_2PH (1 mmol), CuI (5 mol %), ligand (35 mol %), Cs_2CO_3 (2 mmol) in toluene at 110 °C. Conditions C: R-X (1 mmol), R_2PH (0.9 mmol), CuI (5 mol %), ligand (35 mol %), Cs_2CO_3 (2 mmol) in toluene at 110 °C. Conditions D: R-X (1 mmol), R_2PH (1.1 mmol), CuI (5 mol %), ligand (20 mol %), Cs_2CO_3 (2 mmol) in toluene at 110 °C. [b] Isolated yield (average of two runs). [c] All dialkylarylphosphines were isolated as borane complexes to aid in isolation. [d] 1.5 equiv of base was used.

protocol for copper-*catalyzed* synthesis of tertiary phosphines and phosphonates from aryl or vinyl halides and secondary phosphines or phosphites. Both classes of products are of great importance in organic synthesis: tertiary phosphines are widely used as ligands for transition-metal-catalyzed reactions, and alkenylphosphonates are common precursors for preparation of biologically active molecules,[8] flame retardants,[9] and polymer additives.[10]

1-Iodonaphthalene and diphenylphosphine were selected as prototypical reaction partners for ligand-free copper-catalyzed coupling reactions. Initial examination, which was aimed at the discovery of the optimum reaction conditions, revealed that 5 mol % of CuI can effect the transformation of 1-iodonaphthalene to 1-diphenylphosphinonaphthalene. This reaction was performed using 1.1 equiv of diphenylphosphine and 2 equiv of Cs_2CO_3 as a base with 1 equiv of the aryl iodide in toluene at 110 °C (Table 1, entry 1). Reduction of the starting aryl iodide was the only side reaction (up to 7%). Applying these conditions to cross-coupling reactions between a variety of aryl halides and different phosphines immediately revealed several problems. For instance, the reaction was sensitive to the steric bulk of the aryl iodide when dialkylphosphines were used as coupling partners; this was reflected in the formation of a large amount of the reduced arene.[11] In addition, aryl bromides did not react under these reaction conditions. Furthermore, using a 1:1 ratio of phosphine/aryl iodide, the reaction did not go to completion. The use of excess phosphines to obtain complete

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(8) (a) Raboisson, P.; Baurand, A.; Cazenave, J.-P.; Gachet, C.; Schultz, D.; Spiess, B.; Bourguigon, J.-J. *J. Org. Chem.* **2002**, *67*, 8063. (b) Holstein, S. A.; Cermak, D. M.; Wiemer, D. F.; Lewis, K.; Hohl, R. J. *Bioorg. Med. Chem.* **1998**, *6*, 687. (c) Lazrek, H. B.; Rochdi, A.; Khaider, H.; Barascut, J. L.; Imbach, J. L.; Balzarini, J.; Witvrouw, M.; Pannecouque, C.; De Clercq, E. *Tetrahedron* **1998**, *54*, 3807. (d) Smith, P. W.; Chamiec, A. J.; Cobley, K. N.; Duncan, K.; Howes, P. D.; Whittington, A. R.; Wood, M. R. *J. Antibiot. Tokyo* **1995**, *48*, 73.

(9) Welch, C. M.; Gonzales, E. J.; Guthrie, J. D. *J. Org. Chem.* **1961**, *26*, 3270.

(10) Jin, J. I. U.S. Patent 74-496233; *Chem. Abstr.* **1979**, *90*, 153010m.

(11) Up to 70% of conversion to the reduced products were found in all reactions using *ortho*-substituted aryl iodides.

conversion complicated the isolation procedure. Thus, we sought an alternative set of reaction conditions that would be capable of overcoming the above-listed problems.

Recently, we reported that chelating diamine ligands could be employed to enhance the efficiency of copper-catalyzed reactions.[6,12] Therefore, we decided to test commercially available *N*,*N*′-dimethylethylenediamine as a ligand for the copper-catalyzed phosphination of aryl halides. To our delight, when 35 mol % of this ligand was used in combination with 5 mol % of CuI, a dialkylphosphine (Cy_2PH) could be successfully coupled with 1-iodonaphthalene. Further examination revealed that various aryl iodides reacted with diaryl- and dialkylphosphines even when a 1:1 ratio of aryl iodide/phosphine was used. In this case the separation and the purification of the product were greatly simplified, and for some runs a sample of ~95% pure compound could be obtained simply by filtering the crude reaction mixture through a short pad of silica gel, followed by concentrating the filtrate.

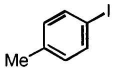
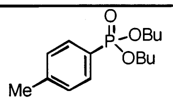
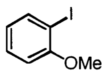
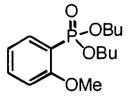
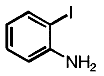
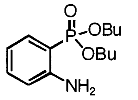
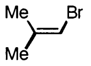
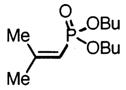
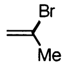
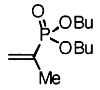
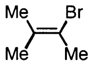
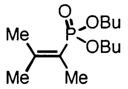
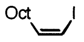
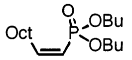
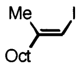
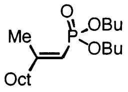
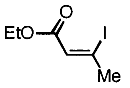
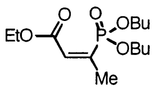
The reaction is tolerant to the steric bulk of the starting aryl iodide. Thus, using this technique, we were able to prepare *o*-diphenyl-biphenyl phosphine ligands[2d,13] in good yields (Table 1, entries 5, 8, and 17). We also found that in some instances aryl bromides could be successfully converted to the desired products under these new reaction conditions. For instance, electron-poor methyl 4-bromo-benzoate could be coupled with diphenylphosphine in 70% isolated yield (Table 1, entry 7). Unfortunately, chemoselective phosphination of bromoiodoarenes was problematic because of the formation of a complex mixture of mono- and disubstituted products, as well as reduced byproducts. In this case, applying ligand-free conditions is recommended in order to prepare halosubstituted tertiary phosphines (Table 1, entry 4). Interestingly, these mild reaction conditions also allow the presence of a number of functional groups (e.g., amino, cyano, esters) as listed in Table 1 (entries 3, 7, 11, 14, and 16).

The electronic and steric properties of phosphines are important for the success of the reaction. Diarylphosphines are typically more reactive than their dialkyl analogues in this process. For example, aryl bromides failed to couple with dialkylphosphines even in the presence of ligand. It seems that the steric demand of the phosphine rather than of the aryl halide determines the rate and the efficiency of the transformation. Thus, for example, no reaction was observed with bulky *t*-Bu_2PH. In contrast, relatively fast reactions took place when *i*-Bu_2PH or Cy_2PH were used as the coupling partners. In addition, an excess of dialkylphosphine (1.1 equiv) was required in some cases in order to reach complete conversion (Table 1, entries 11 and 12). *i*-Bu_2PH exhibited reactivity higher than that of Cy_2PH and reacted with the excess of aryl iodide, leading to comparable yields of the tertiary phosphines (Table 1, entries 11, 14, and 17). However, an increased amount of reduction product (up to 15%) was observed in several reactions of Cy_2PH (Table 1, entries 12 and 13). We also discovered that vinyl phosphine can be accessed from the corresponding iodide in satisfactory yields (Table 1, entry 10) under the same conditions.

We have also found that the described copper-catalyzed cross-coupling protocol can be extended to the preparation of aryl and vinyl phosphonates. Despite the variety of recently published protocols, regio- and stereoselective approaches are still lacking.[7,14] We found that various aryl iodides could be successfully coupled with dibutyl phosphite, employing this newly developed chemistry to afford the desired aryl phosphonates in good to excellent yields (Table 2, entries 1−3). The coupling of vinyl iodides with dibutyl phosphite using the same protocol proceeded even under milder reaction conditions (Table 2, entries 7−9). Thus, a variety of vinyl iodides as well as vinyl bromides were coupled to phosphite in high yield. We also demonstrated that the

Table 2. Copper-Catalyzed Coupling of Aryl and Vinyl Halides with $HP(O)(OBu)_2$

$$\text{R-X} + HP(O)(OBu)_2 \xrightarrow[\text{Toluene, 110 °C}]{\text{5 mol\% CuI, 20 mol\% } \mathbf{L}\text{, 2 equiv of } Cs_2CO_3\text{,}} \text{R-}P(O)(OBu)_2$$

entry	R-X	product	yield (%)[a]
1[b]			88
2[b]			85
3[b]			86
4[b]			92
5[b]			91
6[b]			88
7[c]			81
8[c]			86
9[c]			64

[a] Isolated yield (average of two runs). [b] Reaction was conducted at 110 °C. [c] Reaction was conducted at 70 °C;

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reaction of vinyl halides with dibutyl phosphite proceeds stereoselectively and with retention of the original stereochemistry. For instance, only a negligible amount of the *E* stereoisomer was detected when *Z* vinyl iodides were used (Table 2, entries 7−9) under the suggested reaction conditions. Such high stereoselectivity is of great value due to easy access of starting materials with well-defined stereochemistry.[15]

In conclusion, we have developed a general and efficient copper-catalyzed carbon−phosphorus bond-forming protocol for both aromatic and vinylic halides under relatively mild conditions. This method is of particular value given its experimental simplicity, functional group compatibility, and the low cost of the catalytic system.

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Supporting Information Available: Experimental procedure and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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