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LETTERS

Pd(0)-Cu(I) Cocatalyzed Coupling of Methylphenylphosphine-Borane with Aryl Halides and Aryl Nonaflates

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Abstract: The reaction of Ph(Me)PH·BH$_3$ with aryl halides in the presence of catalytic Pd(OAc)$_2$/Ph$_2$PMe and CuI using ^{i}Pr$_2$NEt as a base in THF at 0 °C furnished the corresponding coupling products in moderate to high yields. A (2-iodophenyl)oxazoline derivative furnished 70% phosphorylated coupling product. Phenyl nonaflate underwent coupling with LiCl as an additive.

Phosphines are undoubtedly the most important class of controller ligands for organometallic transformations.[1] Over the last few years, and largely a result of the pioneering studies of Imamoto,[2] the utility of phosphine-borane complexes as intermediates for the synthesis of specialized phosphines has become widely recognized. Recently, several accounts have appeared concerning the use of 2°-phosphine-boranes as pronucleophiles in Pd(0) catalyzed arene phosphorylation.[3] Our interest in using this reaction as a general route to aryl bearing *P*-chiral phosphines via asymmetric synthesis prompted us to investigate several of the parameters that govern the coupling process. In this letter we report an exceedingly mild procedure for arene phosphorylation using a mixed Pd(0)/Cu(I) catalyst system that permits efficient P-C bond formation at temperatures of ≤ 0 °C. The beneficial effect of Cu(I) derivatives as cocatalyst in several Pd(0) mediated coupling reactions has been recorded previously.[4] A preliminary study to ascertain the accelerating effect, if any, that a Cu(I) source could exert on Pd(0) catalyzed arene phosphorylation was carried out by way of the following two experiments. Treatment of methylphenylphosphine-borane **1** with Ph-I **2a** (1.5 equiv) in the presence of ^{i}Pr$_2$NEt (1.2 equiv) and (Ph$_3$P)$_4$Pd (5 mol %) in THF at rt led to the formation of the expected product **4a** with low efficiency (23% conversion after 5 days). By way of contrast, the inclusion of CuI (10 mol %) as a cocatalyst using conditions that were otherwise identical led to a marked improvement in coupling efficiency (82% conversion to **4a** in 48 h). After surveying a large number of supporting phosphines for Pd(0), solvent systems as well as several Pd(0) sources, it was determined that the use of "[(Ph)$_2$MeP]$_2$Pd"[5] (7.5 mol %) and CuI (20-30 mol %) in THF-Me$_2$S (4:1) with ^{i}Pr$_2$NEt (1.2 equiv) provided the optimum coupling conditions. Significantly, representative arene phosphorylations under these conditions could be achieved at temperatures as low as -10 °C to 0 °C.

The following procedure is representative: To a solution of Pd(OAc)$_2$ (7.5 mol %, 8.5 mg) in dry THF (0.5 ml) under argon atmosphere was added diphenylmethylphosphine (22 mol %, 0.022 ml) and the resulting mixture was allowed to stir for 10 min at room temperature. Iodobenzene (**2a**) (1.5 equiv, 0.08 ml) was then

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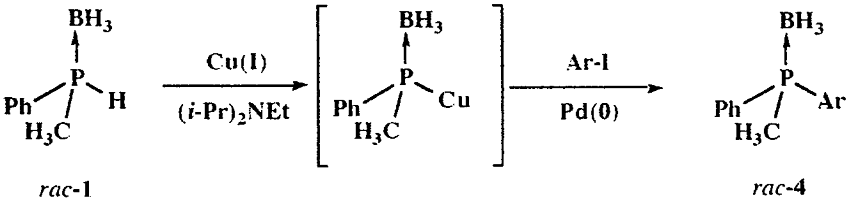
added and stirring was continued at room temperature. In another flask, CuI (30 mol %, 30 mg) was dissolved in THF (0.25 ml) and Me_2S (0.2 ml) under argon and then $^{i}Pr_2NEt$ (1.2 equiv, 0.1 ml) and methylphenylphosphine-borane **1** (0.5 mmol, 0.078 ml) were sequentially added at 0 °C. The solution of the palladium complex was then added to the phosphine-borane solution by cannula and the resulting mixture was stirred for 3 days at 0 °C. The reaction mixture was quenched by adding water, extracted with CH_2Cl_2 and the organic layer was dried over anhydrous Na_2SO_4. After removal of the solvent in vacuo, the crude product was subjected to silica gel chromatography using hexane then hexane/CH_2Cl_2 (5/1) as the eluents. The pure product **4a**[6] was isolated as an amorphous solid in 93% yield (Entry 1).

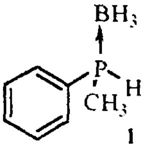
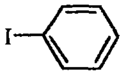
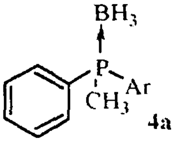
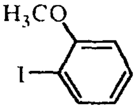
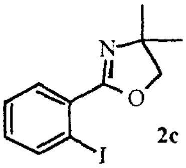
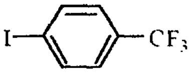
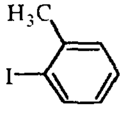
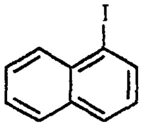
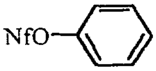
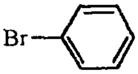
The results obtained for a series of arene phosphorylations are assembled in **Table 1**. The Pd(0)/Cu(I) catalyzed coupling of iodobenzene (**2a**) and 2-iodoanisole (**2b**) with **1** proceed in excellent yield (Entries 1-3). It is also significant that the oxazoline bearing aryl iodide **2c** participitates in efficient P-C bond formation at 0 °C (Entry 4), although unsatisfactory results were obtained for this substrate at rt.[7] Arene phosphorylation of 4-iodobenzotrifluoride (**2d**), 2-iodotoluene (**2e**), 1-iodonaphthalene (**2f**) proceeded in moderate yield (Entries 5-7). It is of additional interest that phenyl nonaflate (**3**), and even bromobenzene (**2g**), undergo coupling with reasonable efficiency (Entries 8 and 9). In the case of **3**, the use of LiCl (3.0 equiv) as a coadditive was found necessary.[8] A possible reaction path for Pd(0)/Cu(I) catalyzed coupling is shown in **Scheme 1**.

Scheme 1



In summary, we have demonstrated that Pd(0)-Cu(I) cocatalyzed arene phosphorylation is a useful procedure for the synthesis of phosphine-boranes, which are precursors to the corresponding free phosphines. The variety of substrates that react with methylphenylphosphine-borane accentuates the generality and versatility of this method. The utilization of this procedure for the asymmetric synthesis of arylphosphine-boranes will be reported in a separate account from these laboratories.

Table 1. Phosphorylation of Methylphenylphosphine-Borane (**1**) with Arylhalides **2** and Phenyl Nonaflate (**3**)[a]

Entry	Phosphine-Borane *rac*-**1**	I-Ar / NfO-Ph **2** **3**	Coupling product *rac*-**4**	Yield (%)
1	 **1**	 **2a**	 **4a**	93[b]
2	**1**	 **2b**	**4b**	97[b]
3	**1**	**2b**	**4b**	84[c]
4	**1**	 **2c**	**4c**	70[b,d]
5	**1**	 **2d**	**4d**	65[b]
6	**1**	 **2e**	**4e**	57[b,d]
7	**1**	 **2f**	**4f**	50[b]
8	**1**	 **3**	**4a**	66(8)[c,e]
9	**1**	 **2g**	**4a**	49[c]

[a] All yields are of pure product isolated by silica gel or alumina column chromatography. ^{1}H-NMR and HRMS (M^+- BH_3) data are satisfactory. [b] The reaction was performed at 0 °C. [c] The reaction was performed at rt. [d] 10 mol % $Pd(OAc)_2$ / 30 mol % Ph_2PMe was used . [e] 3.0 equiv of LiCl was used as coadditive. Yield in parenthesis is the starting 2 °-phosphine-borane.

References and Notes

1. For representative recent work in connection with phosphine-boranes, see: a) Wolfe, B.; Livinghouse, T. *J. Am. Chem. Soc.* **1998**, *120*, 5116. b) Bayston, D. J.; Fraser, J. L.; Ashton, M. R.; Baxter, A. D.; Polywka, M. E. C.; Moses, E. *J. Org. Chem.* **1998**, *63*, 3137. c) Liu, A. M.; Mok, K. F.; Leung, P. H. *J. Chem. Soc., Chem. Commun.* **1997**, 2379. d) Villemin, D.; Jaffres, P.; Nechab, B.; Chourivaud, F. *Tetrahedron Lett.* **1997**, *38*, 6581. e) Trost, B. M.; Bunt, R. C. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 99. f) Gilbertson, S. R.; Starkey, G. W. *J. Org. Chem.* **1996**, *61*, 2922. g) Longeau, A.; Langer, F.; Knochel, P. *Tetrahedron Lett.* **1996**, *37*, 2209. h) Muci, A. R.; Campos, K. R.; Evans, D. A. *J. Am. Chem. Soc.* **1995**, *117*, 9075. i) Imamoto, T.; Matsuo, M.; Nonomura, T.; Kishikawa, K.; Yanagawa, M. *Heteroatom. Chem.* **1993**, *4*, 475. j) Juaristi, E.; Aguilar, M. A. *J. Org. Chem.* **1991**, *56*, 5919. k) Sood, A.; Shaw, B. R.; Spielvogel, B. F. *J. Am. Chem. Soc.* **1990**, *112*, 9000.

2. a) Oshiki, T.; Imamoto, T. *J. Am. Chem. Soc.* **1992**, *114*, 3975. b) Imamoto, T. *Pure & Appl. Chem.* **1993**, *65*, 655-660, and references cited therein.

3. a) Lipshutz, B. H.; Buzard, D. H.; Yun, C. S. *Tetrahedron Lett.* **1999**, *40*, 201. b) Gaumont, A. C.; Hursthouse, M. B.; Coles, S. J.; Brown, J. M. *J. Chem. Soc., Chem. Commun.* **1999**, 63.

4. The authors wish to acknowledge the contributions of Dr. G. Kumaraswamy of these laboratories for initially discovering the accelerating effect of Cu(I) on arene phosphorylations. For additional references concerning Cu(I) cocatalysis, see: a) Liebeskind, L. S.; Riesinger, S. W. *J. Org. Chem.* **1993**, *58*, 408-413. b) Myers, A. G.; Dragovich, P. S. in *Organic Syntheses, Vol. 72* (Ed.: Coffen, D. L.), Organic Syntheses Inc., USA, **1993**, pp. 104 - 111. c) Arcadi, A.; Cacchi, S.; Marinelli, F. *Tetrahedron Lett.* **1989**, *30*, 2581. Other related work has been reported by Piers, E.; Romero, M. A. *J. Am. Chem. Soc.* **1996**, *118*, 1215.

5. The Pd(0) catalyst was prepared *in situ* by treating $Pd(OAc)_2$ with Ph_2PMe (3 equiv) in THF: Kulasegaram, S.; Kulawiec, R. J. *J. Org. Chem.* **1994**, *59*, 7195.

6. Spectral data for compound **4a:** ^1H NMR ($CDCl_3$, 300 MHz): δ 7.67-7.39 (m, 10H, 2X $-C_6H_5$), 1.85 (d, J = 10.2 Hz, 3H, $-CH_3$), 1.53-0.44 (br m, 3H, BH_3). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 131.7, 131.1, 130.8, 128.8, 12.1.; ^{31}P NMR ($CDCl_3$, 121 MHz): δ 10.56. HRMS: Calc'd for $C_{13}H_{13}P$ (M^+ - BH_3); 200.0761. Found: 200.0754. For compound **4c:** ^1H NMR ($CDCl_3$, 300 MHz): δ 8.15-7.34 (m, 9H, $-C_6H_5$, $-C_6H_4-$), 3.56 (m, 2H, $-CH_2$) 2.00 (d, J = 10.2 Hz, 3H, $-CH_3$), 1.03 (s, 3H, CH_3), 0.97 (s, 3H, CH_3), 1.18-0.30 (br m, 3H, BH_3). ^{13}C NMR ($CDCl_3$, 75.5 MHz): 161.5, 135.8, 132.3, 131.5, 130.6, 129.0, 78.6, 27.8, 13.8.; ^{31}P NMR ($CDCl_3$, 121 MHz): δ 18.16. HRMS: Calc'd for $C_{18}H_{23}BNOP$ (M - H^+); 309.1558. Found: 309.1568. (M^+ - BH_3); 297.1285. Found: 297.1282.

7. In an earlier paper, limitations of phosphorylation were noted when amine bearing nonaflates were used as arylating agents.[3a]

8. a) The beneficial effect of LiCl as a coadditive in the Stille coupling has been noted previously.[8b] b) For a review, see: Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508. Also see: Farina, V.; Krishnan, B.; Marshall, D. R.; Roth, G. P. *J. Org. Chem.* **1993**, *58*, 5434.