JOC Note

Proline/Pipecolinic Acid-Promoted Copper-Catalyzed *P*-Arylation

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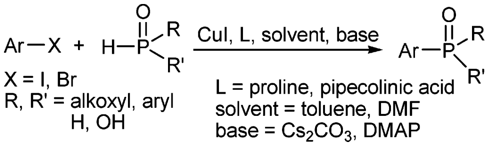

We have developed a convenient and efficient approach for *P*-arylation of organophosphorus compounds containing P−H. Using commercially available and inexpensive proline and pipecolinic acid as the ligands greatly improved the efficiency of the coupling reactions, so the method can provide an entry to arylphosphonates, arylphosphinates and arylphosphine oxides.

Copper-catalyzed Ullmann coupling reactions have recently attracted much attention, including *N*-arylation of amines/amides[1] and *O*-arylation of substituted phenol[2] or alcohol.[3] This progress relied on the utilization of some special bidentate additives, for example, aliphatic diamines,[4] 1,10-phenanthroline and its derivatives,[2f] ethylene glycol,[5a] diethylsalicylamide,[5b] amino acids,[6] oxime-type and Schiff base ligands,[7] thiophene-2-carboxylate,[8] bidentate phosphines,[9] diphosphinidenecyclobutene,[10] and diphenyl pyrrolidine-2-phosphonate[11] for *N*-arylation of amines/amides and 1-naphthoic acid,[2a] 2,2,6,6-tetramethylheptane-3,5-dione,[2b] phosphazene P_4-*t*-Bu base,[2c] *N*,*N*-dimethylglycine,[2d] 8-hydroxyquinoline,[2e] and salicylaldoxime (Salox)[2g] for *O*-arylation of substituted phenol or alcohol. Although arylphosphonates[12] and phosphane oxides[13] are of practical application, to the best of our knowledge, examples of copper-mediated C−P bond formation are rare.[14] Since proline is an efficient ligand for the copper-catalyzed Ullmann coupling reactions,[6i,15] here we report it and its analogue pipecolinic acid as efficient bidentate ligands for the formation of copper-catalyzed C−P bonds.

We initially optimized the catalysis conditions, including copper source, base, solvent, amount of catalyst, and ligand (proline or pipecolinic acid), to achieve good coupling yields of aryl halides with organophosphorus compounds containing P−H. The experimental results showed the catalyst system using CuI as the catalyst, Cs_2CO_3 or DMAP as the base, and toluene or DMF as the solvent could provide higher coupling yields (see Table 1 for experimental details). However, no *P*-arylation products were obtained when no catalyst or ligand was added to the reaction system, which indicated that CuI/L could greatly promote the reactivity of the substrates.

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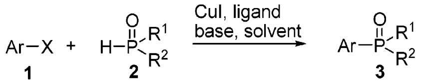
TABLE 1. Proline- or Pipecolinic Acid-Promoted Copper-Catalyzed Coupling of Aryl Halides and Organophosphorus Compounds Containing P−H[a]



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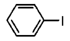
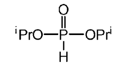
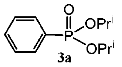
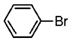
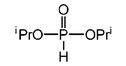
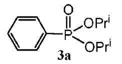
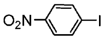
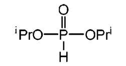
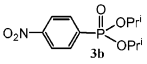
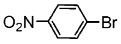
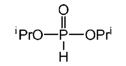
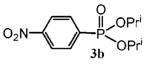
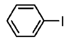
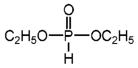
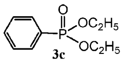
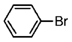
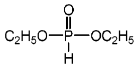
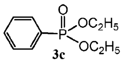
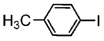
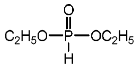
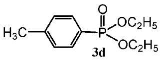
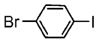
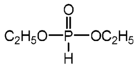
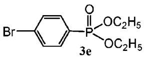
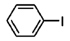
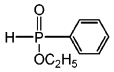
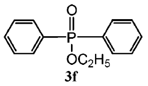
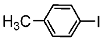
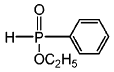
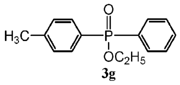
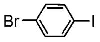
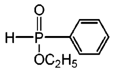
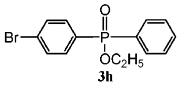
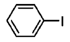
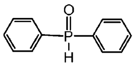
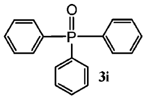
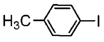
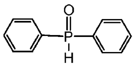
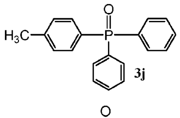
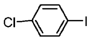
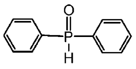
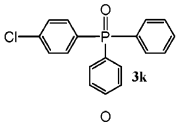
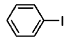
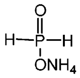
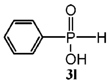
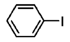
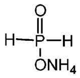
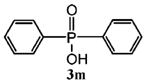
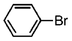
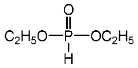
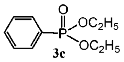
1			Cs_2CO_3	toluene	20[b] 20[c]	 **3a**	90[b] 91[c]
2			Cs_2CO_3	toluene	36[b] 72[b]	 **3a**	34[b] 36[b]
3			Cs_2CO_3	toluene	20[b]	 **3b**	68[b]
4			Cs_2CO_3	toluene	20[b]	 **3b**	47[b]
5			Cs_2CO_3	toluene	36[b] 20[c]	 **3c**	84[b] 88[c]
6			Cs_2CO_3	toluene	20[b]	 **3c**	31[b]
7			Cs_2CO_3	toluene	36[b] 20[c]	 **3d**	68[b] 66[c]
8			Cs_2CO_3	toluene	20[b] 20[c]	 **3e**	86[b] 85[c]
9			Cs_2CO_3	toluene	24[b] 36[c]	 **3f**	68[b] 67[c]
10			Cs_2CO_3	toluene	24[b] 36[c]	 **3g**	87[b] 84[c]
11			Cs_2CO_3	toluene	24[b] 36[c]	 **3h**	75[b] 78[c]
12			Cs_2CO_3	toluene	36[b] 36[c]	 **3i**	73[b] 74[c]
13			Cs_2CO_3	toluene	36[b] 36[c]	 **3j**	66[b] 67[c]
14			Cs_2CO_3	toluene	36[b] 36[c]	 **3k**	87[b] 85[c]
15			DMAP	DMF	48[b] 48[c]	 **3l**	72[b] 75[c]
16			DMAP	DMF	48[b]	 **3m**	39[b,f]
17			K_2CO_3	toluene	24 + 36[b]	 **3c**	83[b,g]

[a] Reaction conditions: **1** (1 mmol), **2** (1.1 mmol), CuI (10 mol %). [b] Proline. [c] Pipecolinic acid (40 mol %), base (2 mmol), and solvent (3 mL) at 110 °C under N_2. [d] Isolated yield (average of two runs). [e] CuI (15 mol %), ligand (40 mol %) for entries 15 and 16. [f] **1** (3 mmol), **2** (1 mmol), DMAP (*N,N*-dimethylaminopyridine) (4 mmol). [g] After reaction of **1** (1.2 mmol) with KI (1.2 mmol) for 24 h in the presence of CuI (20 mol %) and proline (40 mol %) at 110 °C, the solution was cooled to room temperature, **2** (1 mmol) was added to the solution, add the solution was warmed to 110 °C and stirred for 36 h.

Proline-promoted copper-catalyzed coupling reactions of aryl halides and organophosphorus compounds containing P−H were carried out. As shown in Table 1, aryl iodides gave the good to excellent yields. Unfortunately, aryl bromides were weak substrates, and only a low yield of product was obtained even if the reaction time was elongated (entry 2). The coupling reactions of 1-bromo-4-iodobenzene with diethyl phosphite (entry 8) and diphenylphospine oxide (entry 11) yielded the target products **3e** and **3h** containing bromine on the benzene ring, respectively, which also showed that aryl iodides were much more reactive than aryl bromides. However, reaction of aryl bromide with 2 equiv of KI for 24 h under our catalytic conditions (see Table 1) provided the corresponding aryl iodide,[16] and when diethyl phosphite was added to the resulting solution, the desired product **3c** was obtained in a good yield (entry 17), which is comparable with the yields in the reaction of iodobenzene with diethyl phosphite (entry 5). In general, the dialkyl phosphites and ethyl phenylphosphinate displayed higher reactivity than diphenylphosphine oxides and hypophosphite, and the former could provide higher yields in a short amount of time. The aryl iodides containing electron-withdrawing groups usually provided higher yields (compare entries 5, 7 and 8, 12, 13, and 14). Unexpectedly, 4-iodotoluene gave a higher yield than phenyl iodide and 1-bromo-4-iodobenzene (compare entries 9−11), and 1-iodo-4-nitrobenzene provided product **3b** in only 68% yield with some side products appearing. Reaction of phenyl iodide with 1.1 equiv of ammonium hypophosphite led to the functionalized monoarylphosphinic acid **3l** (entry 15), and disubstituted product **3m** was obtained in 39% yield when 3 equiv of phenyl iodide relative to ammonium hypophosphite was added to the reaction system (entry 16). The effect of bases was investigated, and the experimental results showed that Cs_2CO_3 was most effective in the coupling reactions.

We also attempted pipecolinic acid−copper-catalyzed coupling of aryl iodides with organophosphorus compounds containing P−H under catalysis conditions similar to those shown in Table 1, and the corresponding target products were obtained in yields similar to those for proline-promoted copper-catalyzed coupling reactions. All of the above results indicated that the coupling reactions of aryl iodides with the organophosphorus compounds provided an approach to arylphosphonates, arylphosphinates, and arylphosphine oxides.

A commercially available and inexpensive proline- or pipecolinic acid-promoted copper-catalyst system has been developed for the formation of arylphosphonates, arylphosphinates, and arylphosphine oxides through *P*-arylation of organophosphorus compounds containing P−H, and the method can be of practical application for the construction of biological molecules and catalytic ligands containing phosphorus.

Experimental Section

General Procedure for the Preparation of Compounds 3a−k. Aryl halide, organophosphorus compound containing P−H, and proline,or pipecolinic acid were added to a flask with Cs_2CO_3 or DMAP and toluene or DMP (see Table 1 for the amounts of all chemicals and solvents used), the mixture was stirred for 30 min at room temperature under nitrogen atmosphere, and CuI was added to the flask. The flask was immersed in an oil bath, and the reaction mixture was stirred at the temperature and time indicated in Table 1. The reaction mixture was then allowed to cool to room temperature, diluted with 10 mL of ethyl ether, and filtered, and the filtrate was concentrated under vacuum. Purification by column chromatography on silica gel (hexane−chloroform 4:1 to 100% chloroform) afforded the desired pure product.

General Procedure for the Preparation of Compounds 3l−m. Aryl iodide, ammonium hypophosphite, and proline or pipecolinic acid were added to a flask with DMAP in DMF (3 mL), the mixture was stirred for 30 min at room temperature under nitrogen atmosphere, and CuI was added to the flask (see Table 1 for the amounts of all chemicals used). The flask was immersed in an oil bath, and the reaction mixture was stirred at 110 °C for the time indicated in Table 1. The reaction mixture was then allowed to cool to room temperature, evaporated, diluted with 10 mL of water, washed with Et_2O, and acidified with $KHSO_4$ (1 M, saturated with NaCl). The resulting aqueous phase was extracted with acetate (3 mL × 4). The organic phase was combined, dried with $MgSO_4$, filtrated, and concentrated under vacuum to give the pure product.

Diisopropyl phenylphosphonate (3a):[17] oil; ^{31}P NMR ($CDCl_3$, 121 MHz) δ 17.07; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.83 (t, $J = 7.58$ Hz, 1H), 7.50 (d, $J = 7.89$ Hz, 2H), 7.26−7.33 (m, 2H), 3.92−3.95 (m, 2H), 1.36 (d, $J = 7.56$ Hz, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 136.3 ($J = 5.7$ Hz), 134.0 ($J = 159$ Hz), 132.1 ($J = 2.9$ Hz), 129.2 ($J = 2.2$ Hz), 71.3 ($J = 5.7$ Hz), 24.4 ($J = 7.9$ Hz); HR-EI-MS M^+ *m/z* calcd for $C_{12}H_{19}O_3P$ 242.1072, found 242.1077.

Phenylphosphinic acid (3l):[18] oil; ^{31}P NMR ($CDCl_3$, 121 MHz) δ 21.52; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 11.28 (br, s, 1H), 7.75−7.80 (m, 2H), 7.59 (d, $J = 7.56$ Hz, 2H), 7.44−7.45 (m, 1H), 6.16 (d, $J = 566$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 133.0 ($J = 3.7$ Hz), 132.0 ($J = 3.6$ Hz), 129.7 ($J = 185.7$ Hz), 128.4 ($J = 13.6$ Hz); HR-ESI-MS $[M + H]^+$ *m/z* calcd for $C_6H_8O_2P$ 143.0262, found 143.0256.

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Supporting Information Available: Gerneral experimental procedures, characterization data and ^{31}P, ^{1}H, and ^{13}C NMR spectra for compounds **3a−m**. This material is available free of charge via the Internet at http://pubs.acs.org.

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