

# Scavenging and Reclaiming Phosphines Associated with Group 10 Metal-Mediated Couplings

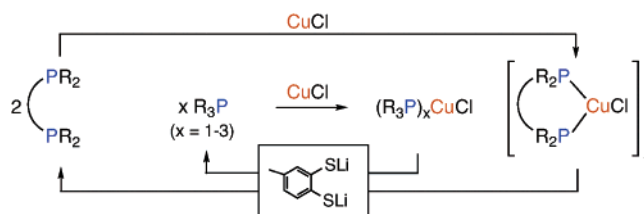
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## ABSTRACT



Exposure of any of several mono- or bidentate phosphines to CuCl leads to quick removal of unwanted ligands from solution. Most phosphines, if desired, can be easily recovered.

Many of the most popular group 10 transition-metal-catalyzed coupling reactions (e.g., Suzuki, Negishi, Stille, Sonogashira, etc.) routinely rely on phosphine ligands.<sup>1</sup> Their removal from crude reaction mixtures can oftentimes be nontrivial, in some cases forcing additional chemistry to be done solely for this purpose (e.g., oxidation with peroxides).<sup>2</sup> Although a report from our laboratories in 2001 suggested that Merrifield resin could serve to effectively remove  $\text{Ph}_3\text{P}$ ,<sup>3</sup> ideally an inexpensive method that applies to a wide range of phosphines both mono- and bidentate in nature would be welcomed. Moreover, ligands far more precious than  $\text{Ph}_3\text{P}$  are often essential for a given transformation, in particular when such species are the source of reagent chirality. The option for their recovery and hence reuse, especially in industrial-scale situations, constitutes yet another worthy goal.<sup>4</sup> We now describe a very straightforward, inexpensive,

and general method for both sequestering and subsequently recovering phosphines from a variety of metal-catalyzed bond-forming reactions.

Development of this protocol was an outgrowth of the fundamental studies by several groups on the role of CuI in Pd-catalyzed Stille couplings. Contributions by Farina,<sup>5</sup> Liebeskind,<sup>5</sup> Espinet,<sup>6</sup> Corey,<sup>7</sup> and others<sup>8</sup> have provided strong evidence that Cu(I) withdraws  $\text{Ph}_3\text{P}$  (and to a far lesser extent  $\text{Ph}_3\text{As}$ ) from the coordination sphere of a Pd(II) intermediate, thereby accelerating transmetalation. On this basis, we surmised that CuCl might be very capable of sequestering phosphines. This was readily tested by dissolving  $\text{Ph}_3\text{P}$  in  $\text{CH}_2\text{Cl}_2$  or THF followed by addition of 0.33–0.50 equiv of CuCl at ambient temperatures. Within 10 min, TLC indicated that all of the phosphine had precipitated from solution in the form of its CuCl complex. Similar observations were made for  $\text{Ph}_3\text{P}$  in  $\text{Et}_2\text{O}$  and toluene. The stoichiometry of the adduct follows from that of known

<sup>†</sup> Solved the X-ray structure of  $(R)$ -SEGPPOS-CuCl.

(1) (a) Agrofoglio, L. A.; Gillaizeau, I.; Saito, Y. *Chem. Rev.* **2003**, *103*, 1875. (b) Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029.

(2) Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 6054.

(3) Lipshutz, B. H.; Blomgren, P. *Org. Lett.* **2001**, *3*, 1869.

(4) (a) *Asymmetric Catalysis on Industrial Scale*; Blaser, H. U., Schmidt, E., Eds.; Wiley-VCH: Weinheim, 2004. (b) *Heterogeneous Catalysis and Fine Chemicals IV*; Blaser, H. U., Baiker, A., Prins, R., Eds.; Elsevier: Amsterdam, 1997.

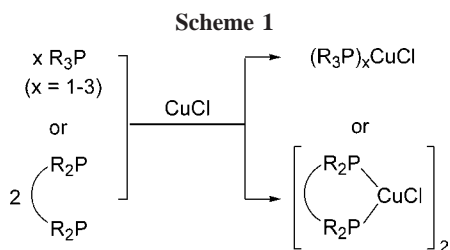
(5) Farina, V.; Kapadia, S.; Krishnan, B.; Wang, C.; Liebeskind, L. S. *J. Org. Chem.* **1994**, *59*, 5905.

(6) Casado, A. L.; Espinet, P. *Organometallics* **2003**, *22*, 1305.

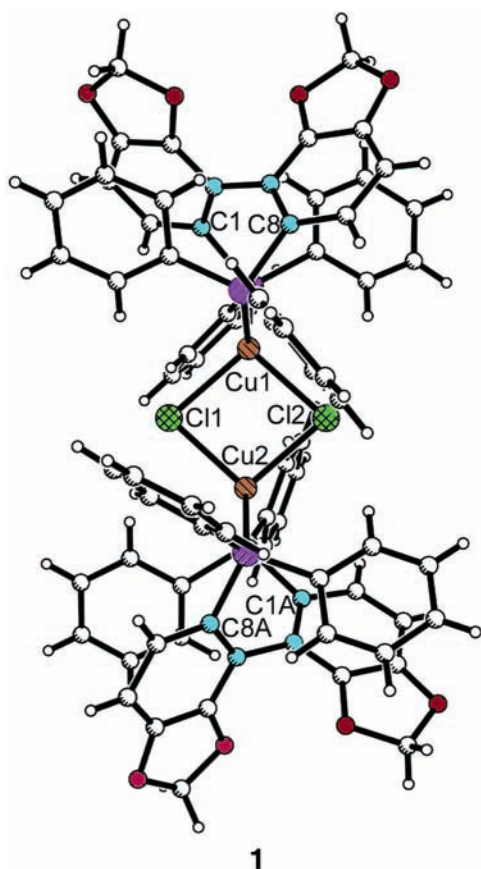
(7) Han, X.; Stoltz, B. M.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 7600.

(8) For example, cf.: Piers, E.; McEachern, E. J.; Romero, M. A. *Tetrahedron Lett.* **1996**, *37*, 1173.

complex  $(\text{Ph}_3\text{P})_3\text{CuCl}$ .<sup>9</sup> Isolation of the precipitate and comparison with authentic material confirmed the role of this copper salt. Thus, ratios of CuCl to  $\text{Ph}_3\text{P}$  as low as 1:3 are equally effective (Scheme 1).

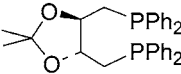
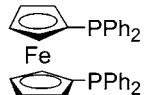
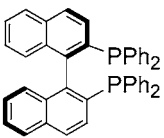
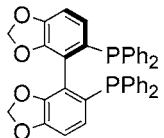
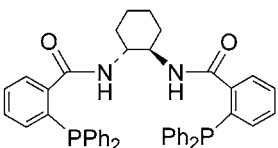
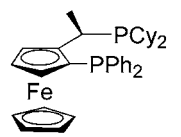
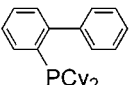


For all of the bidentate phosphines studied (with the exception of dppe and *(R,R)*-DIOP),<sup>10</sup> 1 equiv of CuCl relative to phosphorus appears to be essential. Table 1 illustrates the ligands that could be quickly (<10 min) scavenged by stirring in undistilled solvent while open to air in the presence of CuCl at room temperature. In the case of Takasago's recently introduced biaryl ligand *(R)*-SEGPHOS,<sup>11</sup> an X-ray analysis of its CuCl complex, dimeric species **1**, confirmed the 1:1 nature of the experimentally observed stoichiometry (Figure 1).

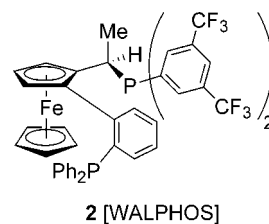


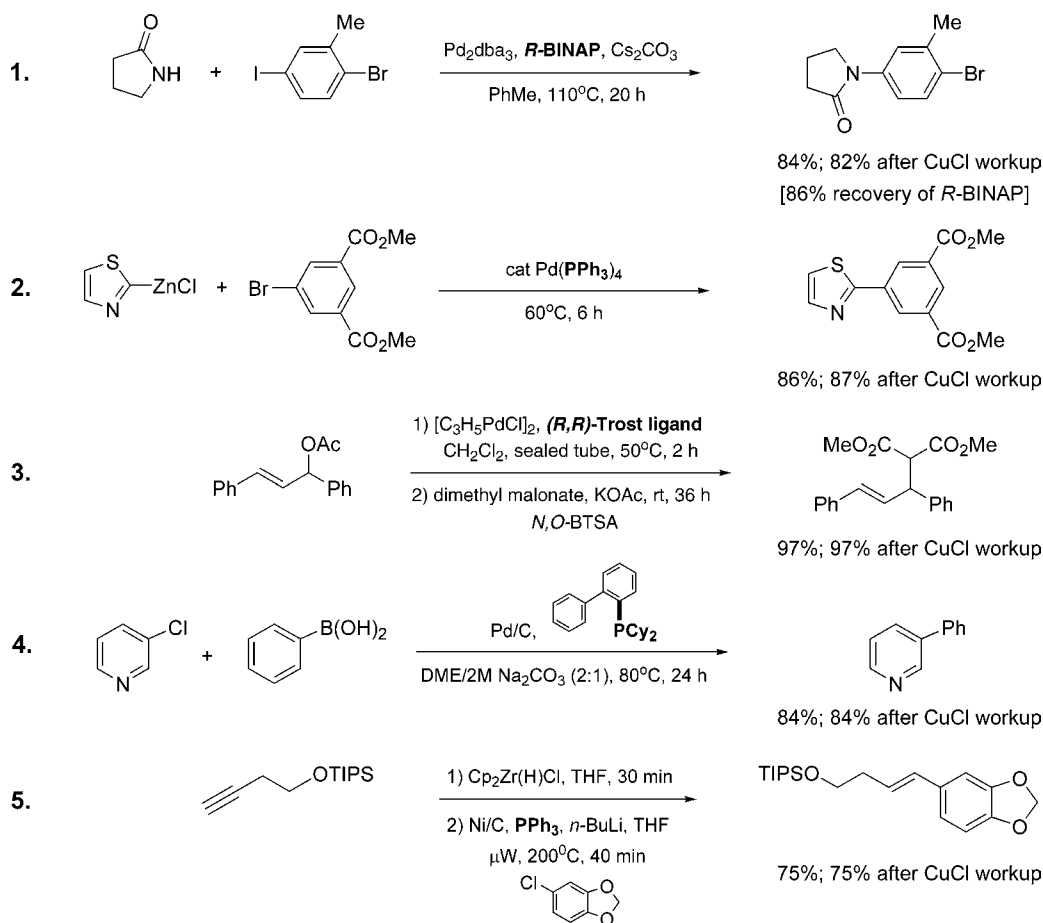
**Figure 1.**  $[\text{Cu}_2(\mu\text{-Cl})_2(\kappa^2\text{-P,P-}(R)\text{-SEGPHOS})_2]\cdot\text{CDCl}_3$ .

**Table 1.** Sequestering Phosphine Ligands with CuCl

ligand	CuCl : ligand	solvent
$\text{Ph}_3\text{P}$	1 : 3	$\text{CH}_2\text{Cl}_2$
$\text{Ph}_2\text{P}-\text{CH}_2-\text{CH}_2-\text{PPh}_2$ [dppe]	1 : 2	THF
 [ <i>R,R</i> -DIOP]	1 : 2	THF
 [dppf]	1 : 1	THF $\text{Et}_2\text{O}$
 [ <i>R</i> -BINAP]	1 : 1	THF toluene
 [ <i>R</i> -SEGPHOS]	1 : 1	toluene
 [Trost ligand]	1 : 1	THF
 [JOSIPHOS]	1 : 1	$\text{EtOAc}$ $\text{CH}_2\text{Cl}_2$
 $\text{PCy}_2$	1 : 1	THF

In line with literature observations,<sup>5,6</sup> CuCl was noticeably ineffective at removing  $\text{Ph}_3\text{As}$  (1 h, rt). Unexpectedly, the specially modified bidentate phosphine WALPHOS (**2**)<sup>12</sup> was





**Figure 2.** Reactions run with and without CuCl as a phosphine scavenger.

only partially consumed using otherwise identical conditions (i.e., 1 equiv of CuCl/ligand in toluene).

To apply these model studies under “real” reaction situations, several standard cross-couplings were carried out, initially without adding CuCl after work up, and then in a second reaction with CuCl being introduced after filtration or aqueous extraction to document that there is no impact on yield. As illustrated in Figure 2, these reactions included an amidation (reaction 1)<sup>13</sup> and a Negishi cross-coupling (reaction 2).<sup>14</sup> Trost allylic alkylation (reaction 3)<sup>15</sup> was also performed. These three feature Pd(0) catalysts being used under homogeneous conditions. A Suzuki coupling run under heterogeneous conditions employing Pd/C (reaction 4)<sup>16</sup> and a Ni(0)-catalyzed cross-coupling mediated by Ni/C under

microwave conditions (reaction 5)<sup>17</sup> likewise underwent treatment with CuCl for removal of phosphine present in each reaction mixture.

Pure phosphines could be recovered free from metal quickly and in good yields from their precipitated complexes upon exposure to a slight excess of a commercially available dithiocatechol, as its preformed dilithio salt **3** (with 2 *n*-BuLi),<sup>18</sup> under mild aqueous basic conditions (3 M NaOH; Scheme 2). In this fashion, several relatively expensive and/or nonracemic bidentate phosphines were isolated in good yields documenting the potential for ligand recycling (Figure 3).<sup>19</sup>

As foreshadowed by these initial control experiments, treatment of a crude, worked-up amidation reaction mixture with CuCl completely removed the (*R*)-BINAP present. Treatment of this CuCl complex as described above followed by purification afforded an 86% recovery of (*R*)-BINAP (cf. reaction 1, Figure 2), which could be reused without incident to afford similar results (ca. 85% yield; cf. Supporting Information).

(17) Lipshutz, B. H.; Frieman, B. *Tetrahedron* **2004**, *60*, 1309.

(18) Used for convenience in weighing; also significantly decreases odor of compound.

(19) Unfortunately, ferrocenyl-based ligands (e.g., dppf, JOSIPHOS) could not be recovered using this protocol.

(9) Folting, K.; Huffman, J.; Mahoney, W.; Stryker, J.; Caulton, K. *Acta Crystallogr.* **1987**, *C43*, 1490.

(10) Only 0.5 equiv of CuCl is needed in these cases.

(11) Saito, T.; Yokozawa, T.; Ishizaki, T.; Moroi, T.; Sayo, N.; Miura, T.; Kumobayashi, H. *Adv. Synth. Catal.* **2001**, *343*, 264.

(12) Sturm, T.; Weissensteiner, W.; Spindler, F. *Adv. Synth. Catal.* **2003**, *345*, 160.

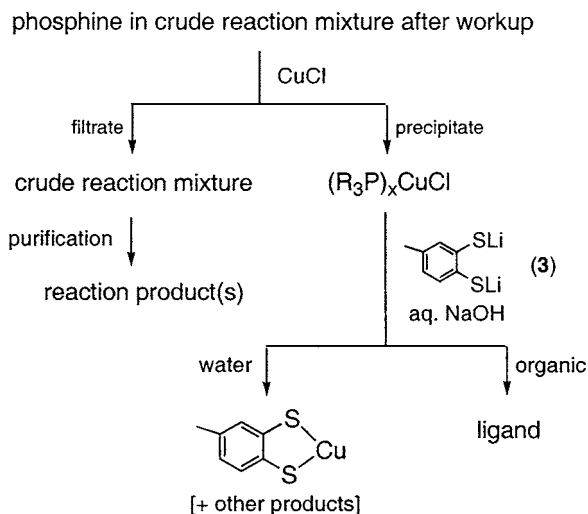
(13) Ennis, D. S.; McManus, J.; Wood-Kaczman, W.; Richardson, J.; Smith, G.; Carstairs, A. *Org. Process Res. Dev.* **1999**, *3*, 248.

(14) Reeder, M. R.; Gleaves, H.; Hoover, S.; Imbordini, R.; Pangborn, J. *Org. Process Res. Dev.* **2003**, *7*, 696.

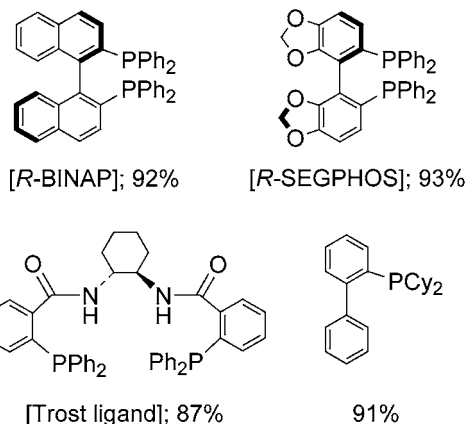
(15) Trost, B. M.; Bunt, R. C. *J. Am. Chem. Soc.* **1996**, *118*, 235.

(16) Tagata, T.; Nishida, M. *J. Org. Chem.* **2003**, *68*, 9412.

Scheme 2



In summary, an expedient protocol has been developed for the rapid removal of unwanted phosphines from crude reaction mixtures after workup. The  $\text{CuCl}$  (rather than  $\text{CuBr}$  or  $\text{CuI}$ ) used in this process is commercially available and inexpensive and requires no special handling. The derived  $\text{CuCl}$ -phosphine complexes are usually separable by simple filtration, and upon exposure to a trivial dithiol, the ligands may be isolated and reused. It is perhaps of special merit that while this method is of a "low tech" nature, it may prove to be especially useful in reactions where vestiges of phosphines tend to otherwise persist or where the economics



**Figure 3.** Recovery of phosphine ligands from their  $\text{CuCl}$  complexes.

of scale involving nontrivial phosphines might now be all the more favorable given the option for ligand recovery.

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**Supporting Information Available:** Procedures and spectral data for all new  $\text{CuCl}$  complexes. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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