

Efficient Scavenging of Ph_3P and $\text{Ph}_3\text{P}=\text{O}$ with High-Loading Merrifield Resin

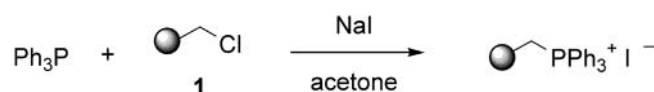
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ABSTRACT



A simple, highly effective method for removing triphenylphosphine and/or triphenylphosphine oxide from reaction mixtures is described. Commercially available high-loading chloromethylated polystyrene **1**, modified in situ with NaI, acts as a scavenger resin. Several coupling reactions catalyzed by Pd(0) or Ni(0) which require the removal of triphenylphosphine are tested.

Metal-catalyzed cross-coupling reactions are among the most highly valued methods in organic synthesis.¹ Recent advances in synthetic technology associated with group 10 metal-mediated processes have propelled Pd-, and to a lesser degree, Ni-based chemistry to the forefront of the field.² While ligandless conditions can occasionally be used to great advantage,³ most reactions rely on phosphine-ligated species throughout the sequence, with triphenylphosphine being the most heavily used and least expensive. Removal of this highly nonpolar phosphine from reaction mixtures after workup can be problematic, especially in cases where products of similar polarity are involved. One potential solution has recently been described involving a PEG-dichlorotriazine as scavenger of various nucleophiles.⁴

Alternative approaches (e.g., resin-bound phosphines)^{5a-c} and workups designed to specifically address such issues have been developed: however, these rely either on additional chemistry done in the presence of the desired product(s)^{5d,e} or expensive sulfonated phosphine ligands in solution.^{5f,g} We now describe a very simple, expedient, and

selective protocol for scavenging Ph_3P , as well as $\text{Ph}_3\text{P}=\text{O}$, which relies on commercially available Merrifield resin.

Conceptually, exposure of high-loading Merrifield resin **1** (4.38 mmol of Cl/g) to triphenylphosphine should remove the phosphine as its derived phosphonium salt. However, presumably due in part to the hindrance of the polymer backbone and poor leaving group ability, access to the benzylic site is denied and no displacement occurs at ambient temperatures in a polar medium such as acetone. Upon addition of NaI, however, stirring overnight at room temperature leads to complete disappearance of the Ph_3P in solution, as analyzed by TLC, capillary GC, and the increase in weight of the polymer. Resin loadings on the order of 3.1 mmol of Ph_3P /g could be routinely realized, although further development of this method relied on standardized conditions using 1 g of resin to remove 2 mmol of phosphine at 25 °C.

Tests of this method were conducted under “real” coupling conditions, not only to assess effectiveness but to evaluate the impact on yields of desired coupling products. With a preponderance of Pd(Ph_3P)₄-catalyzed processes,^{1c} the 4:1 ratio of phosphine to metal can lead to substantial levels of

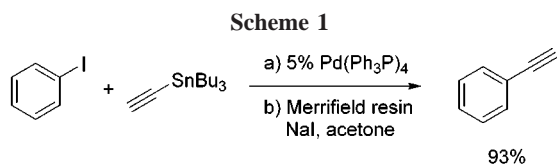
(1) (a) Schlosser, M. *Organometallics in Synthesis-A Manual*; John Wiley & Sons: New York, 1994 (b) Stang, P.; Diederich, F. *Metal-Catalyzed Cross Coupling Reactions*; VCH: Weinheim, 1998. (c) Tsuji, J. *Palladium Reagents and Catalysts-Innovations in Organic Synthesis*; John Wiley & Sons: New York, 1995.

(2) For one recent example, see: Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 2719 and references therein.

(3) Reetz, W. M.; Westermann, E. *Angew. Chem., Int. Ed.* **2000**, *39*, 165. Beletskaya, I. P.; Cheprakov A. V. *Chem. Rev.* **2000**, *100*, 3009.

(4) Falchi, A.; Taddei, M. *Org. Lett.* **2000**, *2*, 3429.

(5) (a) Amos, R. A.; Emblige, R. W.; Havens, N. *J. Org. Chem.* **1983**, *48*, 3598. (b) Gulyás, H.; Árva, P.; Bakos, J. *Chem Commun.* **1997**, 2385. (c) Tunoori, A. R.; Dinah, D.; Georg, G. I. *Tetrahedron Lett.* **1998**, *39*, 8751. (d) Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 6054. (e) Starkey, G. W.; Parlow, J. J.; Flynn, D. L. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2385. (f) Kattesh, V. K.; Hariprasad, G.; Charles, J. S.; Douglas, E. B. *Acc. Chem. Res.* **1999**, *32*, 9. (g) Cornils, B. *Org. Process Res. Dev.* **1998**, *2*, 121.



undesired Ph_3P . As illustrated in Scheme 1, the representative Stille reaction proceeds in excellent yield,⁶ while the (20 mol %) phosphine originally present in solution is quantitatively removed.

Triphenylphosphine removal from nickel(0)-catalyzed reactions, in our experience, can oftentimes present an even greater challenge than that faced using palladium(0). This can be the case whether Ni(0) is employed under homo- or heterogeneous⁷ conditions (i.e., $\text{Ni}(\text{Ph}_3\text{P})_4$ or $\text{Ni}(0)/\text{C} + 4\text{Ph}_3\text{P}$, respectively). Table 1 summarizes results from both

Table 1. Representative $\text{Ni}(\text{Ph}_3\text{P})_4$ -Catalyzed Couplings

entry	aryl chloride	organometallic	catalyst	yield (%) ^a
1			5% NiCl_2^b 20% Ph_3P	91
2			5% NiCl_2^b 20% Ph_3P	94
3			10% $\text{Ni}(0)/\text{C}$ 40% Ph_3P	88
4			10% NiCl_2^b 40% Ph_3P	92
5			6% $\text{Ni}(0)/\text{C}$ 24% Ph_3P	82
6			5% NiCl_2^b 20% Ph_3P	98 ^c

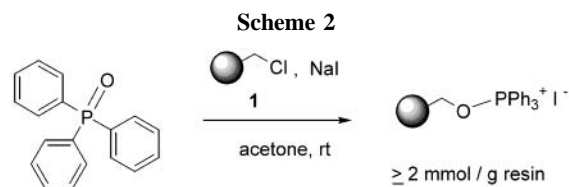
^a Isolated, chromatographically purified material. ^b Reduced to Ni(0) with 2 equiv of *n*-BuLi. ^c Determined via GC.

types of catalyzed reactions. Thus, Negishi-like couplings between an aryl chloride and functionalized alkyl (entry 1) or aryl (entry 2) zinc halide using Ni(0) in solution gave high yields of the corresponding products following treatment

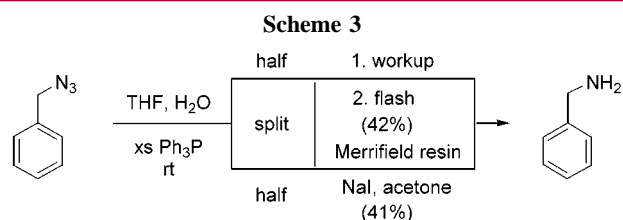
(6) Negishi, E.; Kotora, M.; Xu, C. D. *J. Org. Chem.* **1997**, *62*, 8957. (7) (a) Lipshutz, B. H.; Sclafani, J. A.; Blomgren, P. A. *Tetrahedron* **2000**, *56*, 2139. (b) Lipshutz, B. H.; Blomgren, P. A. *J. Am. Chem. Soc.* **1999**, *121*, 5819. (c) Lipshutz, B. H.; Tomioka, T.; Blomgren, P. A.; Blomgren, P. A.; Kim, S.-K. *Tetrahedron Lett.* **1999**, *40*, 197. (d) Lipshutz, B. H.; Blomgren, P. A. *Tetrahedron Lett.* **1999**, *40*, 197.

of the crude reaction mixtures with the scavenger resin. Suzuki-like biaryl formations (entries 3–5) using 5% Ni/C (along with 20 mol % of Ph_3P) showed no loss in overall reaction efficiencies. Catalyst loading levels with associated Ph_3P as high as 40 mol % (entries 3 and 4) only served to increase the isolated yield after removal of the unwanted phosphine. Kumada coupling of an aryl Grignard (entry 6) revealed a close to quantitative GC yield of the mixed biaryl, while the phosphine originally present was not detected after exposure to the resin.

In the course of workup of these “name” reactions, much of the Ph_3P may be converted to $\text{Ph}_3\text{P}=\text{O}$, which is relatively polar and can further complicate product purification. We have examined the propensity for this modified Merrifield resin to scavenge this species as well, only to find an identical level of effectiveness (Scheme 2).



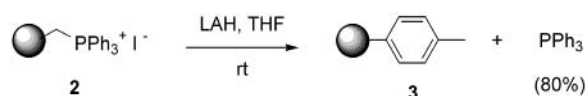
The chemoselectivity of the iodide-modified Merrifield resin for Ph_3P and $\text{Ph}_3\text{P}=\text{O}$ relative to other nucleophiles has also been investigated, most notably with respect to basic amines. As a test case, the Staudinger reaction was applied to benzyl azide, which, along with excess Ph_3P , generates byproduct $\text{Ph}_3\text{P}=\text{O}$ as well as the primary amine product (Scheme 3). Usual extractive workup of half the reaction



mixture led to a mix of three components, which upon flash chromatography afforded the pure amine (42%). Alternatively, treatment of the remaining half of the reaction mixture with the Merrifield resin/NaI combination removed both phosphorus-containing materials, allowing for isolation of benzylamine in 41% yield. Thus, under our standard conditions (acetone, rt), a free amine does not react with this scavenger resin.

Finally, removal of the phosphine from the resin can be accomplished upon exposure to LAH in THF at room temperature (80% recovered from a predetermined amount of **2**; Scheme 4). Although the resulting resin **3** can be re-

Scheme 4



converted to its original chloromethylated form,⁸ we are continuing to search for conditions that will permit direct recycling of **2**.

In summary, an operationally straightforward method for scavenging triphenylphosphine and triphenylphosphine oxide has been developed.⁹ It relies on a simple modification of the widely available Merrifield resin,¹⁰ which in its iodide form reacts in the presence of these nucleophiles under mild conditions. Reaction products bearing most functional groups,

(8) Le Carre, E.; Lewis, N.; Ribas, C.; Wells, A. *Org. Process Res. Dev.* **2000**, *4*, 606.

including free amines and alcohols (e.g., benzyl alcohol), are unaffected. Given the high loading capability of the resin, this process may find widespread use in both small- and large-scale processes which give rise to these byproducts.

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(9) **Representative procedure.** The crude reaction was filtered, and the filtrate (containing triphenylphosphine: 75 mg, 0.28 mmol) was concentrated on a rotary evaporator. Acetone (1.5 mL), sodium iodide (84 mg, 0.56 mmol), and high-loading Merrifield resin (140 mg, 4.38 mmol of Cl/g) were added, and the slurry was allowed to stir at room temperature. After 18 h the mixture was filtered and washed with THF (3×3 mL), water ($3 \text{ mL} \times 3$), acetone ($3 \text{ mL} \times 3$), and finally methanol. GC analysis of combined filtrates, and weight gain of the resin, indicated complete removal of triphenylphosphine from the reaction mixture.

(10) Merrifield's peptide resin was obtained from Aldrich, catalog number 47, 451-7; 1% cross-linked, 200–400 mesh, containing 4.38 mmol of Cl/g.