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Room Temperature, Palladium-Mediated *P*–Arylation of Secondary Phosphine Oxides

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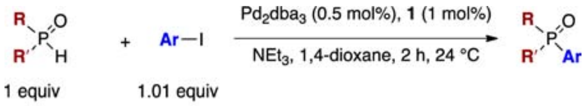
ABSTRACT



- *34 examples*
- *Broad functional group compatability*
- *Efficient access to new PCP and P-chiral phosphines*

We show that a broad range of aryl iodides are efficiently coupled with secondary phosphine oxides using 1 mol % of a catalyst formed in situ from tris(dibenzylideneacetone)dipalladium and Xantphos (1). Scalemic (*S*)-methylphenylphosphine oxide [(*S*)-2e] is shown to undergo arylation without detectable stereoerosion. The application of this method to the synthesis of novel *P*-chiral phosphines and PCP ligands is demonstrated.

The widespread use of tertiary phosphines in transition metal chemistry and catalysis continues to motivate methods for their synthesis.[1] A direct route to tertiary phosphines involves functionalization of secondary phosphines; however, the latter are unstable toward oxidation and require rigorously oxygen-free conditions in their synthesis and manipulation. An approach that minimizes the handling of oxygen-sensitive intermediates comprises the functionalization of secondary phosphine oxides (SPOs) to form tertiary phosphine oxides (TPOs), followed by reduction.[2]

We recently described a practical single-step synthesis of SPOs of wide structural variability.[3] Here we describe a highly useful method for the synthesis of TPOs by the direct *P*-arylation of SPOs. We show that a catalyst formed in situ from tris(dibenzylideneacetone)dipalladium (Pd$_2$dba$_3$) and Xantphos (**1**)[4] is broadly active for the arylation of SPOs with a range of aryl and heteroaryl iodides. In most cases, the arylations proceed to completion within 2 h at 24 °C, employ equimolar amounts of coupling partners, and require only 1 mol % of palladium. These arylations occur with retention of stereochemical integrity at phosphorus, and by employing enantiomerically enriched SPO starting materials and a stereoselective reduction,[2e] *P*-chiral tertiary phosphines of high stereochemical purity may be obtained. Although palladium[5] and copper-mediated[6] SPO arylations have been reported, these typically employ high catalyst loadings (10–20 mol %) and reaction temperatures (90–120 °C) or require extended

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[1] Börner, A., Ed. *Phosphorus Ligands in Asymmetric Catalysis*; Wiley-VCH: Weinheim, 2008; Vol. 3.

[2] Selected methods for the reduction of TPOs: (a) Horner, L.; Balzer, W. D. *Tetrahedron Lett.* **1965**, *6*, 1157. (b) Naumann, K.; Zon, G.; Mislow, K. *J. Am. Chem. Soc.* **1969**, *91*, 7012. (c) Marsi, K. L. *J. Org. Chem.* **1974**, *39*, 265. (d) Coumbe, T.; Lawrence, N. J.; Muhammad, F. *Tetrahedron Lett.* **1994**, *35*, 625. (e) Imamoto, T.; Kikuchi, S.-i.; Miura, T.; Wada, Y. *Org. Lett.* **2001**, *3*, 87. (f) Berthod, M.; Favre-Reguillon, A.; Mohamad, J.; Mignani, G.; Docherty, G.; Lemaire, M. *Synlett* **2007**, 1545. (g) Busacca, C. A.; Raju, R.; Grinberg, N.; Haddad, N.; James-Jones, P.; Lee, H.; Lorenz, J. C.; Saha, A.; Senanayake, C. H. *J. Org. Chem.* **2008**, *73*, 1524.

[3] Bloomfield, A. J.; Qian, J. M.; Herzon, S. B. *Organometallics* **2010**, *29*, 4193.

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[5] (a) Xu, Y.; Xia, J.; Guo, H. *Synthesis* **1986**, 691. (b) Xu, Y.; Wei, H.; Xia, J. *Liebigs Ann. Chem.* **1988**, 1139. (c) Uozumi, Y.; Tanahashi, A.; Lee, S. Y.; Hayashi, T. *J. Org. Chem.* **1993**, *58*, 1945. (d) Toffano, M.; Dobrota, C.; Fiaud, J.-C. *Eur. J. Org. Chem.* **2006**, *2006*, 650.

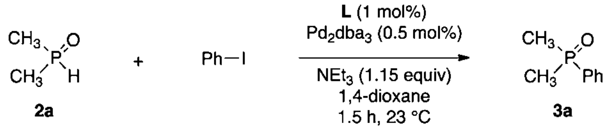
[6] (a) Huang, C.; Tang, X.; Fu, H.; Jiang, Y.; Zhao, Y. *J. Org. Chem.* **2006**, *71*, 5020. (b) Rao, H.; Jin, Y.; Fu, H.; Jiang, Y.; Zhao, Y. *Chem.—Eur. J.* **2006**, *12*, 3636. (d) Matano, Y.; Matsumoto, K.; Terasaka, Y.; Hotta, H.; Araki, Y.; Ito, O.; Shiro, M.; Sasamori, T.; Tokitoh, N.; Imahori, H. *Chem.—Eur. J.* **2007**, *13*, 891. (e) McDougal, N. T.; Streuff, J.; Mukherjee, H.; Virgil, S. C.; Stoltz, B. M. *Tetrahedron Lett.* **2010**, *51*, 5550. For a review, see: (f) Tappe, F. M. J.; Trepohl, V. T.; Oestreich, M. *Synthesis* **2010**, 3037.

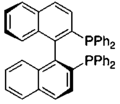
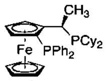
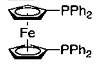
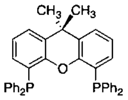
10.1021/ol301831k

times (24−58 h).[5,6] The high temperature required for an earlier palladium-catalyzed SPO arylation[5a] leads to racemization of scalemic SPO starting materials (vide infra). While the tertiary phosphines formed in this process are of the greatest utility, TPOs themselves also find applications as Lewis bases[7] and ligands in catalysis,[8] as well as ligands in the industrial-scale extraction of rare earth and precious metal ions.[9]

In preliminary studies[10] we evaluated the palladium-catalyzed *P*-arylation of a series of dialkyl, alkylaryl, and diaryl SPOs with iodobenzene. These experiments established that the arylation of dialkylphosphine oxides was significantly less efficient than alkylaryl- or diarylphosphine oxides. Accordingly, the coupling of dimethylphosphine oxide (**2a**) and iodobenzene was selected for catalyst optimization (Table 1). A panel of bidentate phosphine ligands in combination with Pd_2dba_3 as the catalyst precursor and triethylamine as the base were evaluated.

Table 1. Evaluation of Bisphosphines of Varying Bite Angle



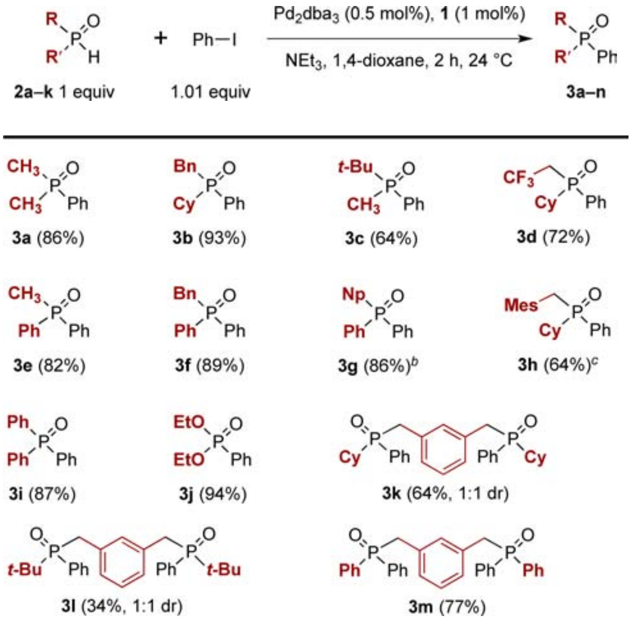
entry	L		bite angle (°)	yield **3a**[a]
1		(*S*)-BINAP	93[11]	2%
2		(*R*)-(*S*)-Josiphos	95[12]	0%
3		dppf	99[11]	85%
4		Xantphos (**1**)	108[11]	97%
5	none		—	0.5%

[a] Yield calculated by ^{31}P NMR analysis using triphenylphosphine oxide as an internal standard.

The efficiencies of these transformations increased with increasing ligand bite angle (entries 1−4). The ligand with the largest bite angle, Xantphos (**1**, bite angle = 108°), provided a 97% yield of dimethylphenylphosphine oxide (**3a**) after 1.5 h at 24 °C (entry 4). The enhanced efficiencies of larger bite angle ligands may relate to their ability to displace dba from the palladium precursor and promote the oxidative addition of iodobenzene.[13] In the absence of ligand, less than 1% of product was formed (entry 5). The success of Xantphos (**1**) in this coupling reaction prompted us to employ this ligand in subsequent experiments.

A large number of sterically and electronically diverse SPOs undergo arylation with iodobenzene in high yield at ambient temperature using this catalyst system (Table 2). Reaction times for each substrate are unoptimized[14] but are uniformly complete within 2 h using 1 mol % of palladium. A range of dialkyl phosphine oxides couple in high yield (**3a**−**3d**, **3h**, 64−93%), including *tert*-butylmethylphosphine oxide (**3c**). Alkylaryl phosphine oxides, including methyl, benzyl, and neopentylphosphine oxides, were also shown to couple in high yield (**3e**−**3g**, 82−89%).

Table 2. Scope of the SPO Component[a]



[a] Isolated yield after purification by flash-column chromatography. [b] Np = neopentyl. [c] Mes = 2,4,6-trimethylphenyl.

The trifluoromethyl-substituted phosphine oxide **3d** was obtained in 72% yield using this catalyst system. Triarylphosphine oxides (**3i**, 87%) and arylphosphite esters (**3j**, 94%) are also accessible by this method. In addition, diphosphine oxides couple in synthetically useful

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(7) Denmark, S. E.; Beutner, G. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 1560.

(8) Grushin, V. V. *Chem. Rev.* **2004**, *104*, 1629.

(9) Pailloux, S.; Shirima, C. E.; Ray, A. D.; Duesler, E. N.; Paine, R. T.; Klaehn, J. R.; McIlwain, M. E.; Hay, B. P. *Inorg. Chem.* **2009**, *48*, 3104.

(10) See Supporting Information for details of preliminary experiments.

(11) Birkholz, M.-N.; Freixa, Z.; van Leeuwen, P. W. N. M. *Chem. Soc. Rev.* **2009**, *38*, 1099.

(12) Blaser, H.-U.; Pugin, B.; Spindler, F.; Mejia, E.; Togni, A. Josiphos Ligands: From Discovery to Technical Applications. In *Privileged Chiral Ligands and Catalysts*; Zhou, Q.-L., Ed.; Wiley-VCH: Weinheim, 2011; pp 93.

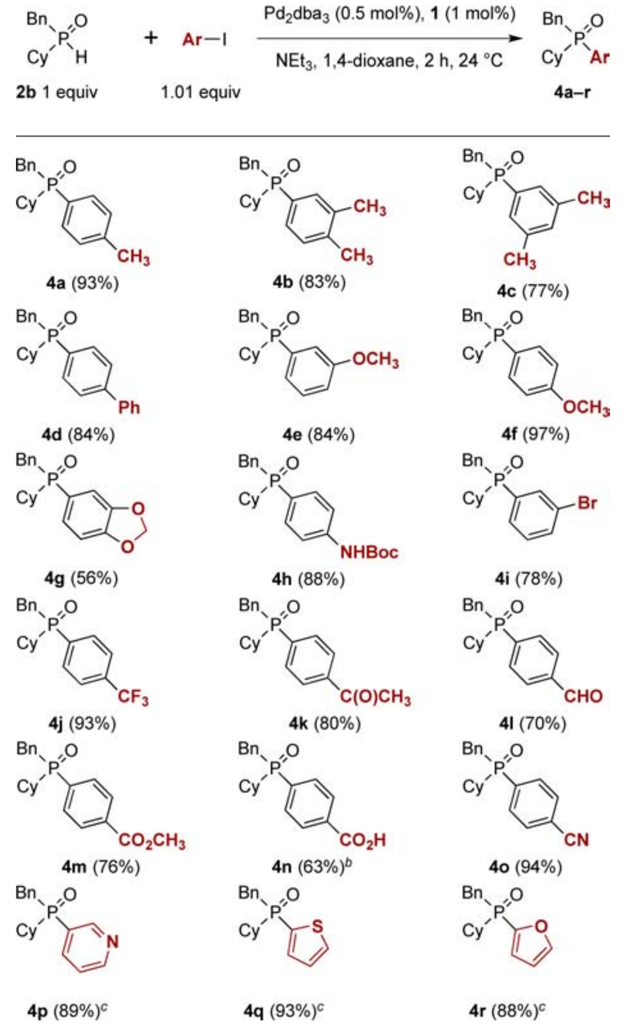
(13) Selected relevant mechanistic studies: Displacement of dba from palladium: (a) Amatore, C.; Broeker, G.; Jutand, A.; Khalil, F. *J. Am. Chem. Soc.* **1997**, *119*, 5176. P−C reductive elimination: (b) Kohler, M. C.; Grimes, T. V.; Wang, X.; Cundari, T. R.; Stockland, R. A. *Organometallics* **2009**, *28*, 1193. Effects of dba on metal reactivity: (c) Jarvis, A. G.; Fairlamb, I. J. S. *Curr. Org. Chem.* **2011**, *15*, 3175.

(14) Using 0.16 mol % palladium, the coupling of benzylcyclohexylphosphine oxide (**2b**) with iodobenzene at 26 °C shows a high initial TOF (> 3800 h^{-1}). The coupling of **2b** with iododbenzene using 5 mol % palladium proceeded at 0 °C over 12 h to afford a 93% isolated yield of **3b**.

yields (64%, 34%, and 77% for **3k**–**3m**, respectively). These data show that the electronic properties of the SPO do not significantly influence the efficiency of the arylation reaction. Steric effects appear to be important, as *tert*-butylmethylphosphine oxide reacted in reduced yield (**3c**, 64%) while the more hindered *tert*-butylphenylphosphine oxide did not afford any coupling product (^{31}P NMR analysis). These coupling reactions could be set up on a benchtop using standard air-free laboratory techniques with only a moderate decrease in yield (**3b**, 75%).

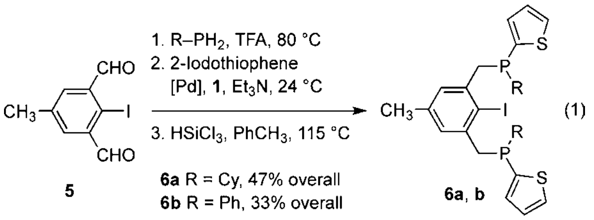
A survey of aryl iodide coupling partners revealed broad functional group compatibility (Table 3). For a series of electron-poor, -neutral, and -rich aryl iodides, high yields of product were generally obtained when benzylcyclohexylphosphine oxide (**2b**) was used as the coupling partner (**4a**–**r**, 56–97%). Thus, alkyl- and aryl-substituted aryl iodides couple in high yield (**4a**–**d**, 77–93%). Electron-rich aryl iodides also couple efficiently (**4e**, **f**, 84, 97%, respectively). 3-Bromo-iodobenzene (**4i**, 78%) and 4-(trifluoromethyl)-iodobenzene (**4j**, 93%) both couple in high yield. Additionally, a broad range of carbonyl-substituted arenes all underwent efficient coupling. Thus, ketones (**4k**, 80%), aldehydes (**4l**, 70%), esters (**4m**, 76%), carboxylic acids (**4n**, 63%), and nitriles (**4o**, 94%) are all compatible under these coupling conditions. Finally, hetereocyclic iodides, such as 3-iodopyridine (**4p**, 89%), 2-iodothiophene (**4q**, 93%), and 2-iodofuran (**4r**, 88%), underwent coupling in useful yields, although in these cases 5 mol % palladium was required to obtain full conversion of the SPO. At present, the system appears to be limited to aryl iodide coupling partners: attempted coupling of bromobenzene or phenyl triflate with benzylcyclohexylphosphine oxide (**2b**) did not lead to detectable levels of product, even after extended heating (^{31}P NMR analysis).

Table 3. Scope of the Aryl Iodide Component[a]



[a] Isolated yield after purification by flash-column chromatography. [b] 2.2 equiv of triethylamine employed. [c] 2.5 mol % Pd$_2$dba$_3$, 5 mol % **1** employed.

When coupled with our recently reported SPO synthesis,[3] this chemistry provides efficient allows access to novel PCP ligands.[15] For example, the thiopheneyl-subtituted PCP ligands **6a** and **6b** were prepared in 47% and 33% overall yield by a three-step sequence comprising SPO formation,[3] arylation, and reduction[2a] (eq 1).



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6a, **b**

As many of the TPO products in Tables 2 and 3 are *P*-chiral, it was of interest to determine the stereochemical fidelity of this coupling reaction. Stereoretention has previously been demonstrated for the palladium-catalyzed coupling of H-phosphonate diesters with benzyl bromide,[16] and isopropyl methylphosphinate with bromobenzene.[17] However, there has not yet been a similar stereochemical analysis for palladium-mediated SPO arylations. A nickel-catalyzed SPO arylation was shown to proceed with stereoerosion.[18]

To probe the stereochemical outcome, enantiomerically enriched (94% ee) (*S*)-methylphenylphosphine oxide [**(*S*)-2e**] was prepared by a modification of the method of Han and co-workers.[19] The optically active SPO **(*S*)-2e** was coupled with 2-iodothiophene to afford (*S*)-methylphenyl-(2-thiopheneyl)phosphine oxide **7** in 90% yield and 94% ee (Scheme 1, chiral stationary phase HPLC analysis). Single crystal X-ray analysis revealed that the reaction proceeded with retention of stereochemistry.

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(15) Singleton, J. T. *Tetrahedron* **2003**, *59*, 1837.

(16) Laven, G.; Stawinski, J. *Synlett* **2009**, 225.

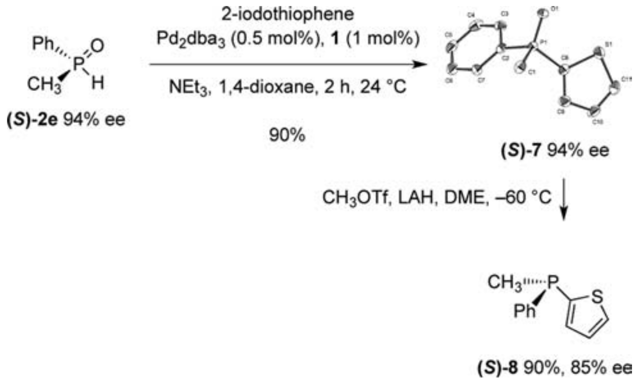
(17) Xu, Y.; Zhang, J. *J. Chem. Soc., Chem. Commun.* **1986**, 1606.

(18) Sun, M.; Zhang, H.-Y.; Han, Q.; Yang, K.; Yang, S.-D. *Chem.—Eur. J.* **2011**, *17*, 9566.

(19) Xu, Q.; Zhao, C.-Q.; Han, L.-B. *J. Am. Chem. Soc.* **2008**, *130*, 12648.

By comparison, the analogous coupling employing 2-bromothiophene and **(*S*)-2e** proceeded slowly at 100 °C with 10 mol% tetrakis(triphenylphosphine)palladium as catalyst.[5a] After 3 h, **7** was formed in only *ca.* 4% yield and 24% ee. Stereoinvertive reduction[2e] of **(*S*)-7** provided the tertiary phosphine product **(*S*)-8** in 90% yield and 85% ee.

Scheme 1. Synthesis of (*S*)-Methylphenyl-2-(thiopheneyl)phosphine



In summary, we have developed a mild, broad spectrum, room temperature *P*-arylation of SPOs. The reaction is shown to be amenable to diaryl, dialkyl, and alkylaryl SPOs as well as dialkylphosphites. Although the reaction, in its current form, is limited to aryl iodides, the scope of the aryl iodide component is broad, encompassing a range of electron-rich and -deficient aryl iodides, heterocycles, and aryl iodides bearing carbonyl derivatives and acidic functional groups. The reaction is amenable to pincer ligand synthesis and is shown to proceed with retention of stereochemistry at phosphorus. The latter result suggests its application toward the synthesis of novel *P*-chiral phosphines for applications in transition metal chemistry and catalysis.

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Supporting Information Available. Experimental procedures and spectral data (^{1}H, ^{13}C, ^{31}P NMR, IR, and HRMS) for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.