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# Novel Class of Tertiary Phosphine Ligands Based on a Phospha-adamantane Framework and Use in the Suzuki Cross-Coupling Reactions of Aryl Halides under Mild Conditions

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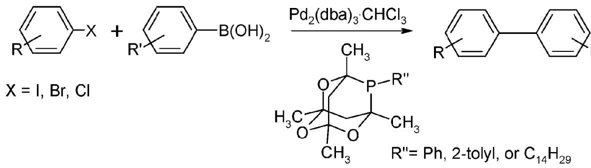
## ABSTRACT



**A new class of sterically hindered phosphines based on a phospha-adamantane framework is described. Arylation or alkylation of the 1,3,5,7-tetramethyl-2,4,8-trioxa-6-phospha-adamantane system allows for the preparation of tertiary phosphines suitable for use in palladium-catalyzed cross-coupling reactions. For example, use of a catalytic system incorporating Pd$_2$(dba)$_3$ and 1,3,5,7-tetramethyl-2,4,8-trioxa-6-phenyl-6-phospha-adamantane is shown to promote the Suzuki cross-coupling of aryl iodides, bromides, and activated chlorides with a variety of aryl boronic acids at room temperature in a few hours with high yields.**

The family of reactions incorporating palladium-catalyzed cross-coupling chemistry[1] to form carbon−carbon bonds is among the most useful in organic synthesis. Mechanistically, these reactions begin with the oxidative addition of an aryl, alkenyl, or alkynyl halide or triflate to Pd(0) to form an organopalladium(II) halide or triflate.[2] Coupling can then occur with a variety of partners including alkenes (Heck reaction[3]), organoboron compounds (Suzuki−Miyaura reaction[4]), amines (palladium-catalyzed amination[5]), or organotin compounds (Stille coupling[6]). Reductive elimination regenerates the palladium catalyst, which can initiate another cycle. Most procedures commonly used for these processes employ palladium−triarylphosphine-based catalyst systems and require elevated reaction temperatures to function efficiently

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[1] *Metal-Catalyzed Cross Coupling Reactions*; Diederich, F., Stang, P., Eds.; Wiley-VCH: New York, 1998.

[2] Recent work has allowed for the use of alkyl bromides possessing $\beta$-hydrogens: Netherton, M. R.; Dai, C.; Neuschutz, K.; Fu, G. C. *J. Am. Chem Soc.* **2001**, *123*, 10099.

[3] Heck, R. F. *Palladium Reagents in Organic Synthesis*; Academic Press: London, 1985.

[4] Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147.

[5] Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805.

[6] Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508.

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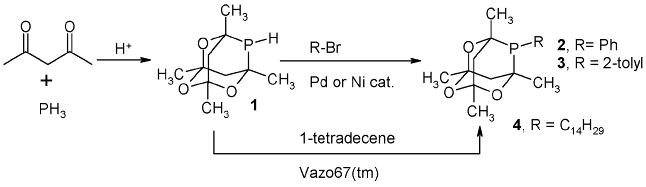
in some cases. Furthermore, these catalyst systems tend to be unreactive toward the more readily available and less-expensive aryl chloride substrates (generally attributed to the lower rate of oxidative addition to Pd(0)).[7]

Recent work has established that certain palladium-catalyzed coupling reactions of the more demanding electron-deficient aryl halides can be accomplished efficiently in the presence of sterically hindered, electron-rich phosphines.[8] The addition of $P(tBu)_3$, for example, results in a marked improvement of the Suzuki,[9] Heck,[10] and Stille[11] couplings of aryl halides including aryl chlorides. Using bulky, electron-rich ligands such as $PCy_3$ or $P(iPr)_3$ allowed for palladium-catalyzed amination of various aryl chlorides in excellent yields.[12] While others[13,14] have shown similar benefits exhibited by bulky alkylphosphines, work to determine their exact role and mode of action is ongoing.[15]

**Scheme 1.** Synthesis of the Phospha-adamantanes



In an effort to develop new, sterically hindered ligands for use in transition-metal catalysis, a reexamination of the 1,3,5,7-tetramethyl-2,4,8-trioxa-6-phospha-adamantane system (**1**, Figure 1) has been undertaken. First described by Epstein and Buckler,[16] the phospha-adamantane **1** is a white crystalline solid readily prepared via the condensation of $PH_3$ with 2,4-pentanedione under acidic conditions. The reaction has since seen a number of variations including the use of fluorine-containing diones[17] and the synthesis of bis(phospha-adamantyl)alkanes from diprimary phosphines.[18] While phosphines incorporating an adamantane motif have been used previously in organopalladium chemistry (adamantyl-di-*tert*-butylphosphine, for example[19]), systems such as **1** have the phosphorus entrenched within the adamantane framework and the inherent steric crowding about the P atom makes **1** an ideal architecture for further derivitization to bulky trisubstituted phosphines suitable for use as ligands.

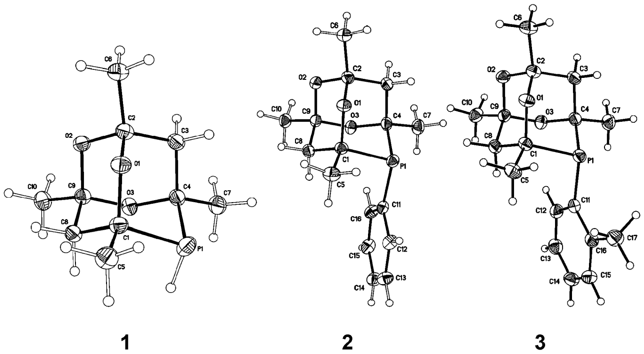


**Figure 1.** Structures of the phospha-adamantanes.

We have synthetically elaborated **1** to introduce both aryl and alkyl groups. Arylation of **1** to give **2** or **3**, for example, can be carried out by treating the secondary phosphine with either bromobenzene or *o*-bromotoluene in refluxing xylene in the presence of either di($\mu$-acetato)bis[*o*-(di-*o*-tolylphosphino)benzyl] dipalladium(II) or nickel acetate, respectively, as the catalyst. Purified specimens of **2** or **3** were obtained by recrystallization of the crude products from 95% ethanol. Alternatively, alkylation at the phosphorus can be affected via a phosphinyl radical addition protocol described previously.[20] Using this procedure, **1** was reacted with 1-tetradecene in the presence of a radical initiator to afford **4**. Unlike the other phospha-adamantanes, **4** is an oily white solid that oxidizes slowly when exposed to air.[21] Crystal structures for compounds **1**, **2**, and **3** appear in Figure 1.

Attention was then turned to the application of the phospha-adamantanes to palladium-catalyzed cross-coupling chemistry. While our initial screening revealed that each of **2**, **3**, and **4** affected Suzuki coupling, our studies focused on the development of a general, robust methodology involving phosphine **2**. Preliminary studies determined that $Pd_2(dba)_3$ was the best palladium source for the reaction and that optimum conditions were achieved when using Pd(0) and **2** in a 1:1 ratio (although slightly higher ligand loadings were used for the aryl chlorides). While the reactions proceed with various bases ($Et_3N$, $iPr_2NEt$, etc.) or solvents (THF, dioxane), the best results were obtained with either potassium phosphate or cesium carbonate as the base and toluene as the solvent.

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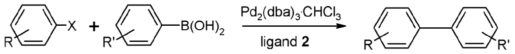
[20] Robertson, A.; Bradaric, C.; Frampton, C. S.; McNulty, J.; Capretta, A. *Tetrahedron Lett.* **2001**, *42*, 2609.

[21] Treatment of **4** with an aqueous solution of $HBF_4$ allowed for the production of the corresponding, air-stable phosphonium salt. Netherton, M. R.; Fu, G. C. *Org. Lett.* **2001**, *3*, 4295.

**Table 1.** Suzuki Cross-Coupling of Aryl Halides



| entry | aryl halide | boronic acid | product | yield[a] |
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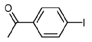
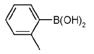
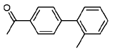
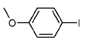
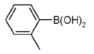
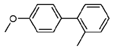
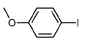
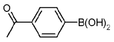
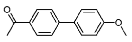
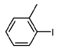
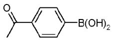
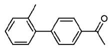
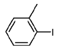
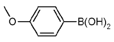
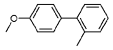
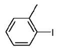
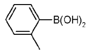
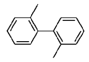
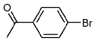
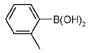
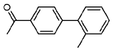
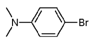
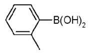
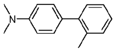
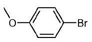
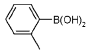
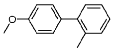
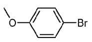
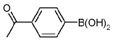
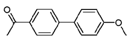
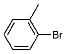
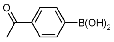
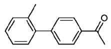
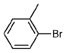
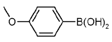
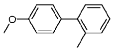
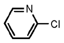
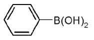
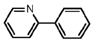
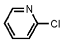
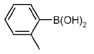
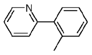
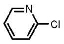
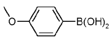
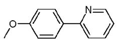
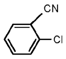
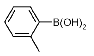
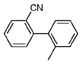
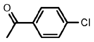
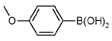
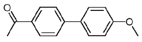
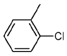
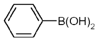
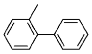
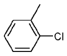
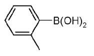
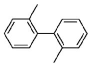
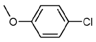
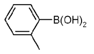
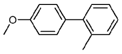
| 1 |  |  |  | 95[b] |
| 2 |  |  |  | 90[b] |
| 3 |  |  |  | 94[b] |
| 4 |  |  |  | 96[b] |
| 5 |  |  |  | 94[b] |
| 6 |  |  |  | 98[b] |
| 7 |  |  |  | 97[c] |
| 8 |  |  |  | 97[c] |
| 9 |  |  |  | 95[c] |
| 10 |  |  |  | 94[c] |
| 11 |  |  |  | 96[c] |
| 12 |  |  |  | 98[c] |
| 13 |  |  |  | 92[d] |
| 14 |  |  |  | 90[d] |
| 15 |  |  |  | 89[d] |
| 16 |  |  |  | 70[d] |
| 17 |  |  |  | 92[d] |
| 18 |  |  |  | 88[e] |
| 19 |  |  |  | 93[e] |
| 20 |  |  |  | 96[f] |

[a] Based on the average isolated yield of two runs. [b] 1% Pd$_2$(dba)$_3$, 2% **2**, 2.4 equiv of K$_3$PO$_4$, toluene, rt, 1 h. [c] 1% Pd$_2$(dba)$_3$, 2% **2**, 2.4 equiv of K$_3$PO$_4$, toluene, rt, 6 h. [d] 2% Pd$_2$(dba)$_3$, 5% **2**, 2 equiv of Cs$_2$CO$_3$, toluene, rt, 24 h. [e] 2% Pd$_2$(dba)$_3$, 5% **2**, 2 equiv of Cs$_2$CO$_3$, toluene, 60 °C, 24 h. [f] 2% Pd$_2$(dba)$_3$, 5% **2**, 2 equiv of Cs$_2$CO$_3$, toluene, 70 °C, 24 h.

Application of the general conditions developed allowed for smooth couplings of aryl iodides, bromides, and activated chlorides with a variety of aryl boronic acids at room temperature in a few hours with high yields. As can be seen from Table 1 (entries 1−6), the cross-coupling reactions of variously substituted iodobenzenes (including electron-rich derivatives, entries 2 and 3) with a variety of aryl boronic acids proceeded efficiently and were all complete within 1 h at room temperature. The corresponding aryl bromides (entries 7−12) also reacted under these conditions but generally required between 3 and 6 h for completion. Complete conversion and high isolated yields for the electron-rich substrates such as 4-bromo-*N*,*N*-dimethylaniline and 4-bromoanisole (entries 8−10) were observed. As expected, reactions involving aryl chlorides were considerably slower requiring 12 to 24 h for completion. However, high conversions of the activated aryl chlorides (entries 13−17) were achieved at room temperature. The electron-rich and sterically demanding chlorides were slow to react (entries 18−20) and required mild heating.

As the results in Table 1 demonstrate, palladium complexes derived from ligand **2** are very active in the Suzuki cross-coupling of aryl halides including difficult aryl chlorides. The ligands reported here based on the phospha-adamantane framework are advantageous in comparison to the other phosphines currently employed in palladium-mediated cross-coupling chemistry.[8−11] Many of the best ligands, such as P(*t*Bu)$_3$, for example, are generally expensive and prone to rapid oxidation often requiring special conditions for their handling. In contrast, the aryl-substituted phospha-adamantanes are crystalline, air stable, and relatively inexpensive to manufacture. Ligand **2** matches P(*t*Bu)$_3$[9] with respect to coupling conditions and yields in the Suzuki reaction.[22] The ligand can be recovered by chromatography on silica gel and reused. In addition, the syntheses of new ligands based on **1** allow for incorporation of substituted aryl or alkyl groups onto phosphorus allowing for steric and electronic fine-tuning of the ligand. Applications involving this new family of substituted phospha-adamantane ligands in other metal-promoted cross-coupling reactions are currently under investigation.

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**Supporting Information Available:** Crystallographic data, experimental procedures, and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(22) Although the biphenyl phosphine ligands described by Wolfe et al. (Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 1162) are more active.