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# Suzuki–Miyaura Cross-Coupling of Benzylic Phosphates with Arylboronic Acids

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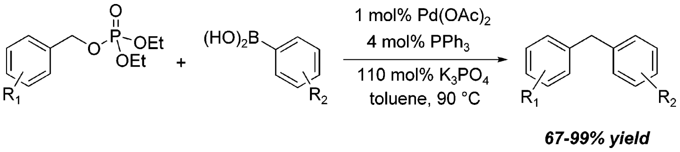
## ABSTRACT



**Suzuki–Miyaura cross-coupling of benzylic phosphates with arylboronic acids was investigated. Optimum conditions employed the simple catalytic system of palladium(II) acetate (1 mol %) and triphenylphosphine (4 mol %) with either potassium phosphate or potassium carbonate as the base and toluene as the solvent at 90 °C. Using the developed conditions, a series of structurally diverse diarylmethanes were prepared.**

Owing to its robust nature and practicality, the Suzuki−Miyaura cross-coupling reaction has become a cornerstone of organic synthesis.[1] Recent advances have significantly broadened the scope of the reaction, allowing previously unreactive substrates such as aryl chlorides[2] and sulfonates[3] to participate efficiently. Moreover, as a result of intense research into the reactivity and stability of various catalyst systems, it is now possible to conduct such reactions using low catalyst loadings and often under mild conditions.[4]

Additionally, the area of alkyl halide cross-coupling has recently witnessed important developments.[5] Traditionally, this type of reaction was problematic when applied to nonactivated alkyl substrates due to reduced rates of oxidative insertion of transition metals into alkyl halide bonds (versus aryl or vinyl systems), slow reductive elimination of the cross-coupled product from the catalyst and competing reaction pathways, such as the usually facile $\beta$-hydride elimination. On the other hand, the cross-coupling of simple benzylic substrates, still involving activation of an sp$^3$-hybridized carbon atom, is not complicated by the possibility of interfering $\beta$-hydride elimination and should, therefore, be a straightforward process. Despite this fact, the Suzuki−Miyaura cross-coupling of benzylic substrates is relatively underdeveloped and has generally been limited to the use of benzylic halides as the electrophilic component.[6]

In a recent report by Kuwano, the scope of electrophilic substrates for benzylic Suzuki−Miyaura cross-couplings was expanded to include benzylic carbonates.[7] The activation of benzylic alcohols toward nucleophilic displacement via the intermediacy of phosphate esters is well documented,[8] although cross-coupling of such phosphates with arylboronic acids has not been previously explored.[9] Hence, the Suzuki−

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[1] Reviews: (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483. (b) Suzuki, A. *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, Germany, 1998; Chapter 2. (c) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147−168. (d) Miyaura, N. *Top. Curr. Chem.* **2002**, *219*, 11−59. (e) Hassan, J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *58*, 9633−9695. (f) Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9633−9695. (g) Bellina, F.; Carpita, A.; Rossi, R. *Synthesis* **2004**, *15*, 2419−2440.

[2] For a review on Pd-catalyzed couplings of aryl chlorides, see: Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176−4211.

[3] For example, see: Baxter, J. M.; Steinhuebel, D.; Palucki, M.; Davies, I. W. *Org. Lett.* **2005**, *7*, 215−218.

[4] (a) Walker, S. D.; Barder, T.; Martinelli, J. R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 1871−1876. (b) Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685−4696.

[5] For a recent review of alkyl halide cross-couplings, see: Frisch, A. C.; Beller, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 674−688.

[6] For some recent examples of Suzuki−Miyaura cross-coupling of benzylic halides, see: (a) Chowdhury, S.; Georghiou, P. E. *Tetrahedron Lett.* **1999**, *40*, 7599−7603. (b) Langle, S.; Abarbri, M.; Duchene, A. *Tetrahedron Lett.* **2003**, *44*, 9255−9258. (c) Chahen, L.; Doucet, H.; Santelli, M. *Synlett* **2003**, 1668−1672. (d) Nobre, S. M.; Monteiro, A. L. *Tetrahedron Lett.* **2004**, *45*, 8225−8228.

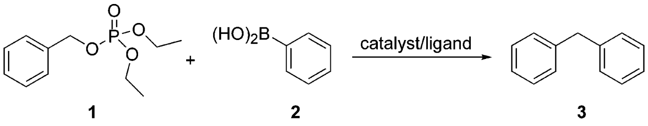
[7] Kuwano, R.; Yokogi, M. *Org. Lett.* **2005**, *7*, 945−947.

10.1021/ol0517271 CCC: $30.25

Miyaura cross-coupling of benzylic phosphates was evaluated and the results are described herein.

The benzylic phosphates required for the present study were readily prepared in high yield from the corresponding alcohols by treatment with diethyl chlorophosphate in the presence of triethylamine with catalytic DMAP.[10] Initially, the Suzuki−Miyaura cross-coupling reaction between diethyl benzyl phosphate **1** and phenylboronic acid **2** was investigated using a variety of palladium sources and ligands (Table 1).

**Table 1.** Investigation of Various Pd Sources and Ligands[a]



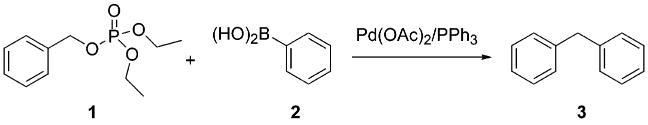
| entry | Pd source (mol %) | ligand (mol %) | assay yield % |
|---|---|---|---|
| 1 | none | none | 0 |
| 2 | Pd(OAc)$_2$ (1) | PPh$_3$ (4) | 99 |
| 3 | Pd(OAc)$_2$ (1) | P(*o*-Tol)$_3$ (4) | 6 |
| 4 | Pd(OAc)$_2$ (1) | PCy$_3$ (4) | 31 |
| 5 | Pd(OAc)$_2$ (1) | dppb (1) | 55 |
| 6 | Pd(OAc)$_2$ (1) | dppPt (1) | 99 |
| 7 | Pd(OAc)$_2$ (1) | dppf (1) | 97 |
| 8 | [PdCl(allyl)]$_2$ (1) | PPh$_3$ (4) | 99 |
| 9 | PdCl$_2$(Ph$_3$P)$_2$ (1) | none | 86 |
| 10 | Pd$_2$dba$_3$ (1) | Ph$_3$P (4) | 95 |
| 11 | Pd$_2$dba$_3$ (1) | IPrHCl (2) | 94 |
| 12 | PdCl$_2$(MeCN)$_2$ (1) | PPh$_3$ (2) | 80 |
| 13 | PdCl$_2$ (1) | PPh$_3$ (2) | 32 |

[a] Reaction conditions: 1.0 mmol of **1**, 1.5 mmol of **2** and 2.0 mmol of K$_3$PO$_4$ with the indicated quantities of catalyst/ligand in toluene (3 mL) at 90 °C for 16 h. Assay yield determined by LC versus a purified standard. (dppPt = 1,5-bis(diphenylphosphino)pentane and IPrHCl = 1,3-bis(2,6-diisopropylphenyl)imidazolium chloride).

The general conclusion from this initial screen was that the reaction appeared quite facile, affording high assay yields of diphenylmethane **3** under the influence of several catalytic systems. These results contrast with those of Kuwano for the Suzuki−Miyaura cross-coupling of benzylic carbonates, where a specific catalyst system was essential to the success of the reaction.[7] In the present work, attempted cross-coupling of diethyl benzyl phosphate **1** in the absence of any catalyst/ligand gave zero conversion of either starting material, indicating that the benzylic phosphate was otherwise stable to the reaction conditions (Table 1, entry 1). Low assay yields were obtained with the bulkier monophosphine ligands P(*o*-Tol)$_3$ and PCy$_3$ in combination with Pd(OAc)$_2$, while both starting materials suffered extensive decomposition in these instances (Table 1, entries 3 and 4). A low conversion and assay yield was also obtained with the poorly soluble PdCl$_2$ (Table 1, entry 13). These examples aside, good yields were observed using various Pd sources in conjunction with both mono- and diphosphine ligands (Table 1, entries 6−10) and also with a heterocyclic carbene ligand (Table 1, entry 11).

Although several of the intially screened catalyst systems afforded high yields of **3**, the simple and least expensive combination of Pd(OAc)$_2$/PPh$_3$ was chosen for further optimization (Table 2). The effect of the Pd/PPh$_3$ ratio was studied and clear differences between 1:2 and 1:4 ratios were observed.

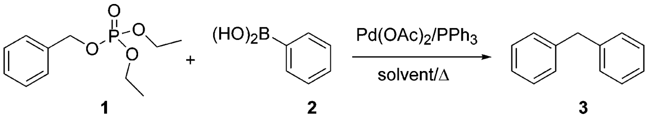
**Table 2.** Optimization of Pd(OAc)$_2$/PPh$_3$ Catalyzed Reaction[a]



| entry | mol % Pd(OAc)$_2$ | mol % PPh$_3$ | base (mol %) | mol % PhB(OH)$_2$ | assay yield % |
|---|---|---|---|---|---|
| 1 | 0.5 | 1 | K$_3$PO$_4$ (200) | 150 | 52 |
| 2 | 1 | 2 | K$_3$PO$_4$ (200) | 150 | 85 |
| 3 | 2 | 4 | K$_3$PO$_4$ (200) | 150 | 93 |
| 4 | 0.5 | 2 | K$_3$PO$_4$ (200) | 150 | 88 |
| 5 | 1 | 4 | K$_3$PO$_4$ (200) | 150 | 99 |
| 6 | 1 | 4 | K$_3$PO$_4$ (110) | 150 | 99 |
| 7 | 1 | 4 | K$_3$PO$_4$ (110) | 110 | 99 |
| 8 | 1 | 4 | K$_2$CO$_3$ (110) | 110 | 96 |
| 9 | 1 | 4 | none | 110 | 31 |

[a] Reaction conditions: 1.0 mmol of **1** with the indicated quantities of **2**, catalyst/ligand and base in toluene (3 mL) at 90 °C for 16 h. Assay yield determined by LC versus a purified standard.

**Table 3.** Solvent Compatibility[a]



| entry | solvent | temp (°C) | assay yield % |
|---|---|---|---|
| 1 | toluene | 22 | <1 |
| 2 | DMF | 90 | 99 |
| 3 | MeCN | 80 | 97 |
| 4 | *i*-PrOH | 80 | 97 |
| 5 | 1,2-DME | 80 | 97 |
| 6 | THF | 55 | 40 |
| 7 | *t*-BuOMe | 55 | 38 |

[a] Reaction conditions: 1.0 mmol of **1**, 1.1 mmol of **2** and 1.1 mmol of K$_3$PO$_4$ with 1 mol % Pd(OAc)$_2$/4 mol % PPh$_3$ using the indicated solvent/temperature for 16 h. Assay yield determined by LC versus a purified standard.

Reactions employing a 1:2 Pd/PPh$_3$ ratio consistently became black after only 15 min at 90 °C. However, despite

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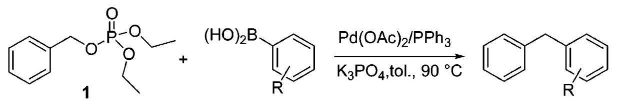
(8) For recent examples, see: (a) Chung, J. Y. L.; Cvetovich, R.; Amato, J.; McWilliams, J. C.; Reamer, R.; DiMichele, L. *J. Org. Chem.* **2005**, *70*, 3592−3601. (b) Song, Z. J.; Zhao, M.; Desmond, R.; Devine, P.; Tschaen, D. M.; Tillyer, R.; Frey, L.; Heid, R.; Xu, F.; Foster, B.; Li, J.; Reamer, R.; Volante, R.; Grabowski, E. J. J.; Dolling, U. H.; Reider, P. J.; Okada, S.; Kato, Y.; Mano, E. *J. Org. Chem.* **1999**, *64*, 9658−9667.

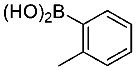
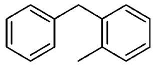
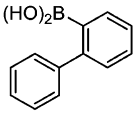
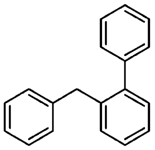
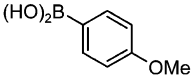
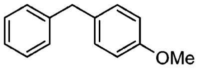
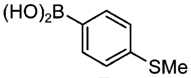
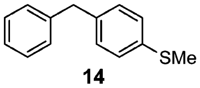
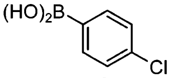
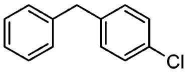
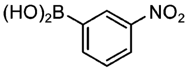
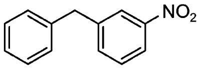
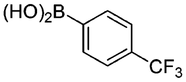
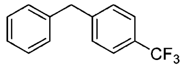
(9) The Suzuki−Miyaura cross-coupling of enol phosphates is known: (a) Huffman, M. A.; Yasuda, N. *Synlett* **1998**, 471−473. (b) Nan, Y.; Yang, Z. *Tetrahedron Lett.* **1999**, *40*, 3321−3324. (c) Lepifre, F.; Buon, C.; Rabot, R.; Bouyssou, P.; Coudert, G. *Tetrahedron Lett.* **1999**, *40*, 6373−6376.

(10) Full details of the phosphate preparations may be found in Supporting Information.

the apparent decomposition of the catalyst in these reactions, reasonably high assay yields were observed with catalyst loadings >1 mol % (Table 2, entries 2 and 3). On the other hand, reactions using a 1:4 Pd/$PPh_3$ ratio generally remained yellow throughout and provided the highest assay yields (Table 2, entries 4 and 5). In terms of catalyst loading, entry 4 indicates that as little as 0.5 mol % Pd was required for high conversion. No attempt was made to employ catalyst loadings lower than 0.5 mol %.

**Table 4.** Cross-Coupling of Diethyl Benzyl Phosphate with Various Arylboronic Acids[a]



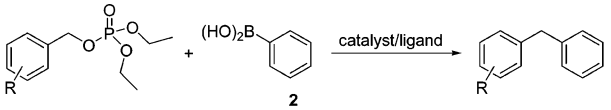
| entry | boronic acid | product | yield %[b] |
|---|---|---|---|
| 1 |  **4** |  **11** | 85 (83) |
| 2 |  **5** |  **12** | 99 (98) |
| 3 |  **6** |  **13** | 90 (88) |
| 4 |  **7** |  **14** | 91 (91) |
| 5 |  **8** |  **15** | 91 (87) |
| 6 |  **9** |  **16** | 68 (67) |
| 7 |  **10** |  **17** | 99 (94) |

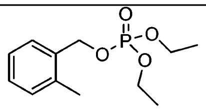
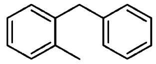
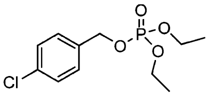
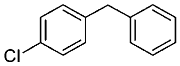
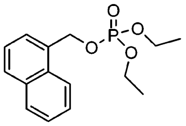
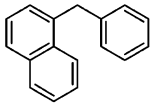
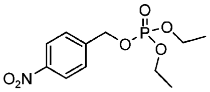
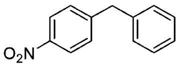
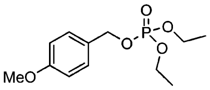
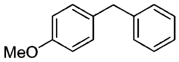
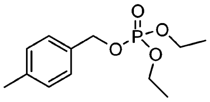
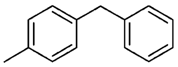
[a] Reaction conditions: 1.0 mmol of **1**, 1.1 mmol of boronic acid and 1.1 mmol of $K_3PO_4$ with 1 mol % $Pd(OAc)_2$/4 mol % $PPh_3$ in toluene at 90 °C for 16 h. Assay yield determined by LC versus a purified standard. Isolated yield determined after workup and chromatographic purification. [b] Yield in parentheses refers to isolated material.

Throughout these optimization experiments, the extent of homocoupling of phenylboronic acid was quantitatively monitored and found to be negligible (consuming <3 mol % of boronic acid). From this observation it became apparent that the cross-coupling would likely retain high conversion of the phosphate **1** with reduced quantities of phenylboronic acid **2**. Indeed, lowering the amount of **2** to 110 mol % furnished equivalent yields of **3** as when 150 mol % of **2** was used (Table 2, entries 6 and 7).

With respect to the base, $K_2CO_3$ and $K_3PO_4$ afforded similar assay yields for this reaction (Table 2, entries 7 and 8). In both cases it was determined that using 110 mol % of base maintained the reaction efficiency. The assay yield was seriously affected when the reaction was performed in the absence of added base (Table 2, entry 9).

**Table 5.** Cross-Coupling of Various Benzylic Phosphates with Phenylboronic Acid[a]



| entry | phosphate | product | yield %[b] |
|---|---|---|---|
| 1 |  **18** |  **11** | 90 (90) |
| 2 |  **19** |  **15** | 82 (80) |
| 3 |  **20** |  **24** | 91 (90) |
| 4 |  **21** |  **25** | 85 (83) |
| 5 |  **22** |  **13** | 84 (81) |
| 6 |  **23** |  **26** | 98 (98) |

[a] Reaction conditions: 1.0 mmol of benzylic phosphate, 1.1 mmol of **2** and 1.1 mmol of $K_3PO_4$ with 1 mol % $Pd(OAc)_2$/4 mol % $PPh_3$ in toluene at 90 °C for 16 h. Assay yield determined by LC versus a purified standard. Isolated yield determined after workup and chromatographic purification. [b] Yield in parentheses refers to isolated material.

After establishing the optimum catalyst system for this cross-coupling, the reaction was examined using different solvents. As shown in Table 3, using the standard catalyst system in toluene at room temperature led to zero conversion after 24 h (Table 3, entry 1).[11] At elevated temperatures (80−90 °C), the reaction proceeded smoothly in a range of solvents (Table 3, entries 2−5). The use of THF or MTBE at 55 °C led to lower conversions (Table 3, entries 6 and 7).

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[11] When this particular reaction mixture was then heated to 90 °C, a 97% assay yield was obtained.

Having optimized the cross-coupling between diethyl benzyl phosphate and phenylboronic acid, the reaction was then tested using a variety of alternative substrates. First, diethyl benzyl phosphate was reacted with a series of substituted arylboronic acids (Table 4).

As shown, the reaction was broadly successful, affording good yields with a range of electron-neutral and electron-rich arylboronic acids, including the more sterically encumbered 2-substituted arylboronic acids. With respect to electron-deficient arylboronic acids, both the 4-chloro- and 4-trifluoromethyl-substituted boronic acids performed well. However, 3-nitrobenzeneboronic acid gave a lower yield.[12]

The cross-coupling was also tested using a series of substituted benzylic phosphates (Table 5). Once again, the yield of product diarylmethanes was generally good regardless of the electronic/steric nature of the substituents.

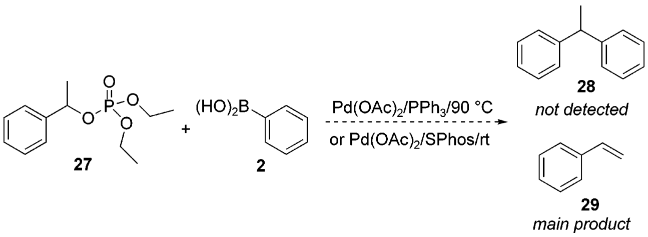

**Figure 1.** Attempted cross-coupling with phosphate **27**.

The possibility of introducing asymmetry to this process prompted investigation of a secondary phosphate substrate **27** (Figure 1). Under the developed standard conditions, both the phosphate **27** and phenylboronic acid **2** underwent significant conversion; however, no cross-coupled product **28** was observed. Not unexpectedly, $\beta$-hydride elimination was facile under these conditions and the major product was styrene **29** (identified by comparison with an authentic sample). In an attempt to suppress $\beta$-hydride elimination, the reaction using **27** was attempted using the widely applicable Buchwald Pd(OAc)$_2$/SPhos catalyst system, known to promote Suzuki–Miyaura cross-couplings at room temperature.[4] Indeed, when this catalyst system was applied to the room-temperature coupling of phenylboronic acid **2** with diethyl benzyl phosphate **1**, a 47% assay yield of diphenylmethane **3** was obtained after 24 h (vs 0% conversion using PPh$_3$ as a ligand at room temperature (Table 3, entry 1). However, application of these conditions to secondary phosphate **27** gave none of the desired cross-coupled product **28**.

In conclusion, the Suzuki–Miyaura cross-coupling reaction of benzylic phosphates and arylboronic acids was investigated. This relatively facile reaction was efficiently catalyzed by the simple combination of palladium acetate and triphenylphosphine. The generality of this cross-coupling was demonstrated using a variety of substrates and afforded high yields of the expected diarylmethanes, a substructure prevalent in numerous pharmacologically active substances.[13]

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

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(12) Electron-deficient arylboronic acids are less nucleophilic and undergo transmetalation at a slower rate than electron-neutral and electron-rich arylboronic acids. Additionally, electron-deficient arylboronic acids are prone to homocoupling. For a report, see: Wong, M. S.; Zhang, X. L. *Tetrahedron Lett.* **2001**, *42*, 4087–4089.

(13) For example, see: Long, Y.-Q.; Jiang, X.-H.; Dayam, R.; Sanchez, T.; Shoemaker, R.; Sei, S.; Neamati, N. *J. Med. Chem.* **2004**, *47*, 2561–2573.