Available online at www.sciencedirect.com

ScienceDirect

Tetrahedron Letters

Tetrahedron Letters 48 (2007) 7472–7475

# Synthesis of diarylmethane derivatives from Stille cross-coupling reactions of benzylic halides

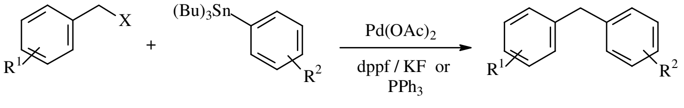
Tatiana Z. Nichele and Adriano L. Monteiro*

*Laboratory of Molecular Catalysis, Instituto de Química, UFRGS, Av. Bento Gonçalves, 9500 Porto Alegre 91501-970, CP 15003, RS, Brazil*

Received 21 May 2007; accepted 20 August 2007
Available online 24 August 2007

**Abstract**—A catalyst precursor prepared in situ from palladium acetate and a phosphine ligand was used for the Stille cross-coupling reaction of benzylic bromides and chlorides with aryltributyltin analogues. The reactions were performed at 80 °C using dppf as ligand in the presence of KF, or more conveniently using $PPh_3$ in the absence of base, furnishing diarylmethane derivatives in high yields (86–99%). Using $Pd(OAc)_2/PPh_3$ as catalyst precursor competitive Stille and Suzuki cross-coupling reactions with benzyl chloride showed that in the absence of base or in the presence of KF the Stille product is the majority product, and only the Suzuki product was obtained in the presence of KOH as base.

Transition metal-catalyzed cross-couplings have emerged as a powerful method for the construction of carbon–carbon bonds.[1] Among transition metals, palladium is the most frequently applied and has found widespread use in organic and polymer synthesis.[2] Diarylmethane derivatives, which are important building blocks in organic synthesis, can be obtained by a cross-coupling reaction of benzylic halides with an arylmetallic coupling partner. However, compared with aryl halides, benzylic halide couplings have been studied to a lesser extent, and most of the reactions involve a Pd-catalyzed Suzuki coupling.[3–13] Alternatively, Pd-catalyzed cross-coupling with indium organometallics[14] and Cu(I)-catalyzed cross-coupling reactions between Grignard reagents and benzylic halides[15] or phosphates[16] have also been reported. Suzuki reactions employing a benzyl halide have been exploited to produce a macrobicycle and antagonists of the human EP3 receptor[17] and polybenzyls.[18] A Stille coupling between a chiral stannane and a benzyl bromide was used as the key step for stereoselective production of a macrolactone.[19] Although the toxicity of organotin compounds can present problems on an industrial scale, the Stille coupling reaction presents similar advantages to the Suzuki reaction (accessibility of organostannanes, air and moisture stability, tolerance toward most functional groups) and is usually superior for the synthesis of complex molecules, displaying high selectivity and a broad synthetic scope.[2,20] Few Stille couplings of benzyl halides have been reported,[21–26] and despite the very good activity of some palladium complexes for this reaction the development of simple protocols using common palladium sources is always worthwhile. In this context, we have successfully demonstrated that a simple catalyst precursor prepared in situ from palladium acetate and triphenylphosphine displays high activity for the Suzuki cross-coupling reaction of benzylic bromides and chlorides with arylboronic acids at low catalyst loadings and under mild conditions.[7] In this paper, we wish to report that a simple system composed of palladium



**Scheme 1.**

---

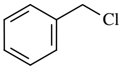
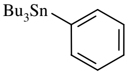
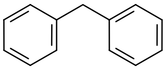
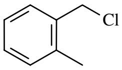
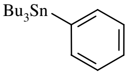
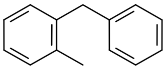
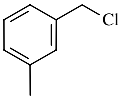
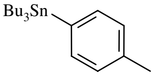
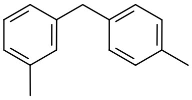
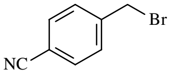
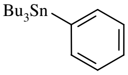
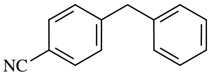
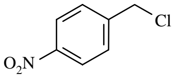
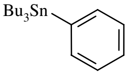
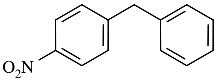
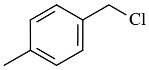
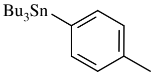
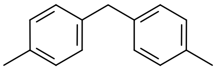
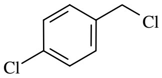
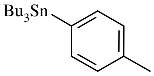
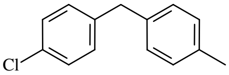
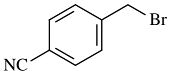
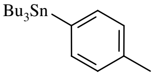
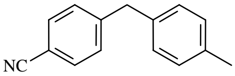
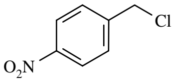
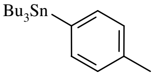
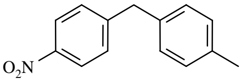
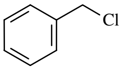
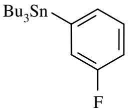
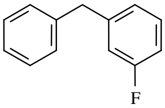
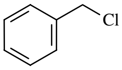
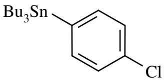
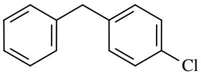
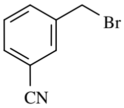
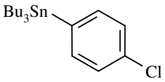
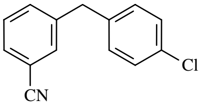
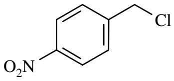
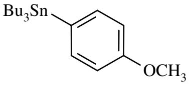
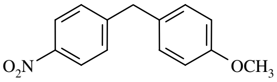
* Corresponding author. Tel.: +55 51 33086303; fax: +55 51 33087304; e-mail: almonte@iq.ufrgs.br

0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.08.072

acetate and triphenylphosphine or dppf is able to effect the Stille cross-coupling reaction of benzylic bromides and chlorides under mild conditions.

In our initial study, we investigated the coupling of benzyl chloride with phenyltributyltin using $Pd(OAc)_2$ as catalyst precursor in the presence of phosphine ligand, base, and dioxane as solvent (Scheme 1). Initially, the reaction was carried out in the absence of base giving low yield (17%: 2 mol % Pd, $Pd/PPh_3 = 2$, 80 °C, 3 h). Both CsF and KF improve the yield (38% yield for CsF and 40% yield for KF) and since KF is a cheaper source of fluoride ions we decided to follow the optimization using KF. No reaction was observed without the

**Table 1.** Pd-Catalyzed Stille cross-coupling reaction of benzyl bromide and chloride with aryltributyltins[a]

| Entry | ArX | $ArSnBu_3$ | Ligand | Base | Diarylmethane | Yield[b] (%) |
|---|---|---|---|---|---|---|
| 1 |  |  | dppf | KF |  | 94 |
| 2 |  |  | dppf | KF |  | 90 |
| 3 |  |  | dppf | KF |  | 99 |
| 4 |  |  | dppf | KF |  | 98 |
| 5 |  |  | dppf | KF |  | 93 |
| 6 |  |  | dppf | KF |  | 89 |
| 7 |  |  | dppf | KF |  | 74 |
| 8 |  |  | dppf | KF |  | 96 |
| 9 |  |  | dppf | KF |  | 92 |
| 10[c] |  |  | $PPh_3$ | — |  | 99 |
| 11[c] |  |  | $PPh_3$ | — |  | 98 |
| 12[c] |  |  | $PPh_3$ | — |  | 98 |
| 13[c] |  |  | $PPh_3$ | — |  | 94 |

[a] Reaction conditions: benzylic halide (1 mmol), aryltributyltin (1.5 mmol), KF (4 mmol), $Pd(OAc)_2$ (0.04 mmol), dppf (0.08 mmol), 1,4-dioxane (6 mL), 80 °C, 3 h.

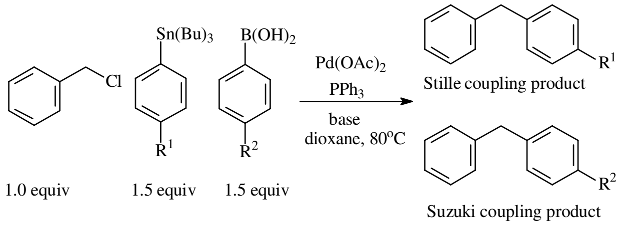
[b] Isolated yields.

[c] Reaction conditions: benzylic halide (1 mmol), aryltributyltin (1.5 mmol), $Pd(OAc)_2$ (0.04 mmol), $PPh_3$ (0.08 mmol), 1,4-dioxane (6 mL), 80 °C, 20 h.

$PPh_3$ ligand and the increment of the ratio of $PPh_3$/Pd over 2 equiv had a negative effect on the yield (only 12% with 8 equiv). The effects of different phosphines were also investigated and among the phosphines evaluated ($PCy_3$, P*o*$Tol_3$, dppe, dppp, dppb, xantphos, binap, dppf) dppf gave the best results. The coupling of benzyl halides with aryltributyltin was evaluated using 4 mol % of $Pd(OAc)_2$, dppf as ligand and KF as base under optimized reaction conditions (Table 1, entries 1–9).[27] Therefore benzyl chlorides and bromides were coupled under mild conditions furnishing the diarylmethanes in high yields (74–99%). No significant effect was observed by changing the position of a methyl group in the ring or the substituent group on the aromatic ring of benzyl chloride and arylboronic acid. After having established a successful protocol for the coupling of benzyl halides we decided to investigate the alternative of a free-base protocol. Although long reaction times were necessary (20 h instead of 3 h), we have found that $PPh_3$ was the best ligand under free-base conditions that gave the coupling products in high yields (94–99%; Table 1, entries 10–13).

The accepted catalytic cycle for cross-coupling reactions, which employs Pd(0) as the catalyst, centers around a standard oxidative addition/transmetallation/reductive elimination sequence. In both Stille[28] and Suzuki[29,30] coupling reactions, bases are used to increase the reactivity of organometallic species, via hypercoordinate intermediates, which enhances the polarization of the organic ligand, and facilitates transmetallation step.[31–33] We have found protocols for Stille and Suzuki[7] couplings of benzyl chlorides having in common the use of $Pd(OAc)_2/PPh_3$ as catalyst precursor. Therefore, we decided to run competitive Stille and Suzuki cross-coupling reactions with benzyl chloride in the absence of base and the presence of base (Table 2). Only the Suzuki product was obtained when the reaction was carried out in the presence of KOH (Table 2, entries 3 and 6). Hydroxide ions gave rise to an important rate enhancement for the Stille coupling of aryl halides in aqueous solution.[34,35] However, determination of initial rates for the Stille reaction showed that in dioxane media, KOH gave a detrimental effect and the reaction was two times slower compared with those carried out in the absence of base (Table 3). On the other hand, the Suzuki reaction between benzyl chloride and phenylboronic acid was 92 times faster in the presence of KOH (Table 3). We have recently described the synthesis of tri- and tetrasubstituted olefins via a Suzuki coupling where the base of choice was KOH (MeOH/THF as solvent, room temperature and low loading of Pd).[36] No reaction was observed in the absence of base and electrospray ionization mass spectrometry analysis indicated that the base initially reacts with the arylboronic acid to form trihydroxyarylborate anions,[37] which was the species involved in the transmetallation process with the palladium catalyst.[38] In the presence of KF both coupling products are formed with a slight selectivity for the Stille product since the reactional conditions were optimized for this coupling (Table 2, entries 3 and 6). Despite some examples of free-base Suzuki reactions,[37,39–47] in general, the Suzuki protocol needs a stoichiometric or excess amount of base for efficient conversion. Therefore, we were expecting to obtain only the Stille product in the absence of base. The Stille product was the major product although we also observed some Suzuki product (Table 2, entries 1 and 4). We reinvestigated the coupling of benzyl chloride with phenylboronic acid and using the palladium loading as we have described for the Suzuki reaction (0.002–1 mmol %) and no reaction was observed in the absence of base. We have only observed coupling product in the absence of base using a higher loading of palladium (10–20% conversion with 4 mol % of Pd after 24 h). The observation of intramolecular transmetallation from boron to rhodium without the participation of added activators was recently described and this process should be considered as a possible pathway also for palladium.[48]

**Table 2.** Competitive Pd-catalyzed Stille and Suzuki cross-coupling reactions with benzyl chloride[a]



| Entry | $R^1$ | $R^2$ | Base | Stille product | Suzuki product |
|---|---|---|---|---|---|
| 1 | $CH_3$ | $CH_3O$ | — | 79 | 21 |
| 2 | $CH_3$ | $CH_3O$ | KF | 60 | 40 |
| 3 | $CH_3$ | $CH_3O$ | KOH | 0 | 100 |
| 4 | $CH_3O$ | $CH_3$ | — | 68 | 32 |
| 5 | $CH_3O$ | $CH_3$ | KF | 52 | 49 |
| 6 | $CH_3O$ | $CH_3$ | KOH | 0 | 100 |

[a] Reactions conditions: benzyl chloride (0.25 mmol), arylboronic acid (0.375 mmol), aryltributyltin (0.375 mmol), base (1 mmol), $Pd(OAc)_2$ (0.01 mmol), $PPh_3$ (0.02 mmol), 1,4-dioxane (6 mL), overnight.

In summary, we have found that a simple catalyst precursor prepared in situ from palladium acetate and a phosphine ligand can be used for the Suzuki cross-coupling reaction of benzylic bromides and chlorides with aryltributyltins. The reactions were performed at 80 °C using dppf as ligand in the presence of KF or more conveniently using $PPh_3$ in the absence of base furnishing diarylmethane derivatives in high yields (74–99%). From a synthetic point of view this protocol is a cheap and easy alternative for the synthesis of diarylmethanes from benzylic halides.

**Table 3.** Relative reactivity for the Pd-catalyzed Stille and Suzuki cross-coupling reactions with benzyl chloride[a]

| Ph-M | Without base | KF | KOH |
|---|---|---|---|
| $PhSnBu_3$ | 1 | 2 | 0.5 |
| $PhB(OH)_2$ | 1 | 5 | 92 |

[a] Reactions conditions: benzyl chloride (0.25 mmol), phenylboronic acid or phenyltributyltin (0.375 mmol), base (1 mmol), $Pd(OAc)_2$ (0.01 mmol), $PPh_3$ (0.02 mmol), 1,4-dioxane (6 mL), 10–50 min (conversion < 10%).

## Acknowledgments

We thank FAPERGS, PRONEX, and CNPq for partial financial support. We also thank CAPES (T.Z.N.) for scholarship.

## References and notes

1. Diederich, F.; Stang, P. J. *Metal-Catalyzed Cross-coupling Reactions*; VCH: Weinheim, 1998.
2. Corbet, J. P.; Mignani, G. *Chem. Rev.* **2006**, *106*, 2651.
3. Miyaura, N.; Yano, T.; Suzuki, A. *Tetrahedron Lett.* **1980**, *21*, 2865.
4. Chowdhury, S.; Georghiou, P. E. *Tetrahedron Lett.* **1999**, *40*, 7599.
5. Chahen, L.; Doucet, H.; Santelli, M. *Synlett* **2003**, 1668.
6. Langle, S.; Abarbri, M.; Duchene, A. *Tetrahedron Lett.* **2003**, *44*, 9255.
7. Nobre, S. M.; Monteiro, A. L. *Tetrahedron Lett.* **2004**, *45*, 8225.
8. Kuwano, R.; Yokogi, M. *Chem. Commun.* **2005**, 5899.
9. Kuwano, R.; Yokogi, M. *Org. Lett.* **2005**, *7*, 945.
10. McLaughlin, M. *Org. Lett.* **2005**, *7*, 4875.
11. Molander, G. A.; Elia, M. D. *J. Org. Chem.* **2006**, *71*, 9198.
12. Bandgar, B. P.; Bettigeri, S. V.; Phopase, J. *Tetrahedron Lett.* **2004**, *45*, 6959.
13. Singh, R.; Viciu, M. S.; Kramareva, N.; Navarro, O.; Nolan, S. P. *Org. Lett.* **2005**, *7*, 1829.
14. Perez, I.; Sestelo, J. P.; Sarandeses, L. A. *J. Am. Chem. Soc.* **2001**, *123*, 4155.
15. Dohle, W.; Lindsay, D. M.; Knochel, P. *Org. Lett.* **2001**, *3*, 2871.
16. Kofink, C. C.; Knochel, P. *Org. Lett.* **2006**, *8*, 4121.
17. Juteau, H. N.; Gareau, Y.; Labelle, M.; Sturino, C. F.; Sawyer, N.; Tremblay, N.; Lamontagne, S.; Carriere, M. C.; Denis, D.; Metters, K. M. *Bioorg. Med. Chem.* **2001**, *9*, 1977.
18. Klarner, C.; Greiner, A. *Macromol. Rapid Commun.* **1998**, *19*, 605.
19. Holloway, G. A.; Hugel, H. M.; Rizzacasa, M. A. *J. Org. Chem.* **2003**, *68*, 2200.
20. Derdau, V.; Oekonomopulos, R.; Schubert, G. *J. Org. Chem.* **2003**, *68*, 5168.
21. Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1979**, *101*, 4992.
22. Kamlage, S.; Sefkow, M.; Peter, M. G. *J. Org. Chem.* **1999**, *64*, 2938.
23. Crawforth, C. M.; Fairlamb, I. J. S.; Taylor, R. J. K. *Tetrahedron Lett.* **2004**, *45*, 461.
24. Crawforth, C. M.; Burling, S.; Fairlamb, I. J. S.; Kapdi, A. R.; Taylor, R. J. K.; Whitwood, A. C. *Tetrahedron* **2005**, *61*, 9736.
25. Crawforth, C. M.; Fairlamb, I. J. S.; Kapdi, A. R.; Serrano, J. L.; Taylor, R. J. K.; Sanchez, G. *Adv. Synth. Catal.* **2006**, *348*, 405.
26. Appukkuttan, P.; Husain, M.; Gupta, R. K.; Parmar, V. S.; Van der Eycken, E. *Synlett* **2006**, 1491.
27. In a typical experiment an oven-dried resealable Schlenk flask was evacuated and back-filled with argon and charged with $Pd(OAc)_2$ (0.04 mmol), dppf (0.08 mmol), and KF (4 mmol). The flask was evacuated and back-filled with argon and then the benzyl halide (1 mmol), aryltributyltin (1.5 mmol), and 1,4-dioxane (6 mL) were added. The reaction mixture was stirred at the desired temperature until complete conversion as judged by GC (3–20 h). After purification by flash-chromatography the diarylmethane product was characterized by $^{1}H$ and $^{13}C$ NMR and GC-MS.
28. Espinet, P.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 4704.
29. Bellina, F.; Carpita, A.; Rossi, R. *Synthesis* **2004**, 2419.
30. Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147.
31. Smith, P. J. *Chemistry of Tin*; Blackie: New York, 1998.
32. Miyaura, N. *J. Organomet. Chem.* **2002**, *653*, 54.
33. Molander, G. A.; Figueroa, R. *Aldrichim. Acta* **2005**, *38*, 49.
34. Roshchin, A. I.; Bumagin, N. A.; Beletskaya, I. P. *Tetrahedron Lett.* **1995**, *36*, 125.
35. Rai, R.; Aubrecht, K. B.; Collum, D. B. *Tetrahedron Lett.* **1995**, *36*, 3111.
36. Nunes, C. M.; Steffens, D.; Monteiro, A. L. *Synlett* **2007**, 103.
37. Cammidge, A. N.; Goddard, V. H. M.; Gopee, H.; Harrison, N. L.; Hughes, D. L.; Schubert, C. J.; Sutton, B. M.; Watts, G. L.; Whitehead, A. J. *Org. Lett.* **2006**, *8*, 4071.
38. Nunes, C. M.; Monteiro, A. L. *J. Braz. Chem. Soc.* **2007**, *18*, in press.
39. Savarin, C.; Liebeskind, L. S. *Org. Lett.* **2001**, *3*, 2149.
40. Yasuike, S.; Qin, W. W.; Sugawara, Y.; Kurita, J. *Tetrahedron Lett.* **2007**, *48*, 721.
41. Yan, J.; Zhu, M.; Zhou, Z. *Eur. J. Org. Chem.* **2006**, 2060.
42. Darses, S.; Jeffery, T.; Genet, J. P.; Brayer, J. L.; Demoute, J. P. *Tetrahedron Lett.* **1996**, *37*, 3857.
43. Andrus, M. B.; Song, C. *Org. Lett.* **2001**, *3*, 3761.
44. Sengupta, S.; Bhattacharyya, S. *J. Org. Chem.* **1997**, *62*, 3405.
45. Yan, J.; Zhou, Z. S.; Zhu, M. *Tetrahedron Lett.* **2005**, *46*, 8173.
46. Tsukamoto, H.; Sato, M.; Kondo, Y. *Chem. Commun.* **2004**, 1200.
47. Dai, M. J.; Liang, B.; Wang, C. H.; Chen, J. H.; Yang, Z. *Org. Lett.* **2004**, *6*, 221.
48. Zhao, P. J.; Incarvito, C. D.; Hartwig, J. F. *J. Am. Chem. Soc.* **2007**, *129*, 1876.