

A Combined Zirconocene Benzyne–Palladium Cross-Coupling Route to Substituted Biphenyls and Terphenyls

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The biaryl unit is present in many natural products, pharmaceuticals, and ligands for homogeneous catalysis.¹ In addition, biphenyls and terphenyls, particularly *m*-terphenyls, are of interest as building blocks of host–guest complexes.^{2,3} Palladium-catalyzed cross-coupling has become one of the methods of choice for the synthesis of unsymmetrical biaryls.⁴ This process is primarily limited by the availability of the coupling partners, particularly if the target biaryl has a complex substitution pattern. Therefore, new methods for the efficient preparation of multi-substituted biaryls are of interest.

Zirconocene-stabilized aryne complexes,^{5,6} best described as zirconacyclopropenes, are nucleophilic in nature and display rich reaction chemistry.^{7,8} Herein we report a one-pot procedure for the synthesis of multisubstituted biaryl and *m*-terphenyl derivatives from simple, readily available precursors that combines the features of Pd-catalyzed cross-coupling methodology with the chemistry of zirconocene-stabilized benzyne complexes.

In one version of the Negishi cross-coupling process, vinyl zirconocene complexes are combined with vinyl halides to form 1,3-dienes.⁹ We reasoned that a zirconocene-stabilized benzyne complex likewise might transmetalate to a Pd(II) oxidative addition complex¹⁰ (Figure 1). Thus, reaction of **1** with **2** would produce a mixture of regioisomers **3** and **3a**, which, after reductive elimination, would give regioisomers **4** and **4a**, respectively. Our previous results indicated that insertion into the less hindered C–Zr bond to give **3** would predominate,⁵ yielding **4** as the major

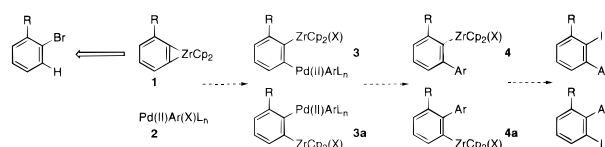
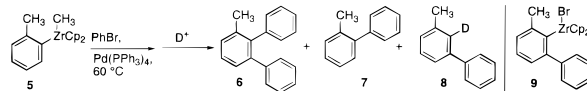
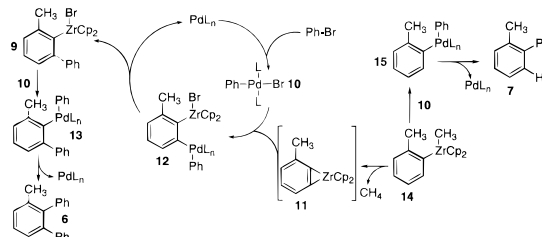


Figure 1.

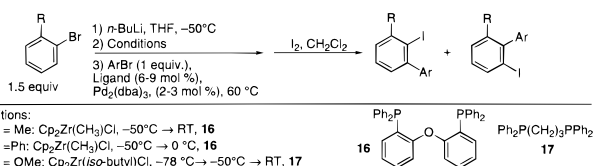
Scheme 1



Scheme 2



Scheme 3



product. The C–Zr bond could then be cleaved with iodine (or other electrophiles) to provide the synthetically versatile biaryl iodides.

In practice, heating **5**, bromobenzene, and a catalytic amount of Pd(0) at 60 °C, followed by treatment of the crude reaction mixture with a 20% DCl solution in D₂O, yielded three products, identified as **6**, **7**, and **8** (Scheme 1).¹¹ We believe that the deuterium-containing product **8** is produced from the intermediate **9**. We propose the reaction pathway shown in Scheme 2. Oxidative addition of bromobenzene to PdL_n produces **10**. Subsequent transmetalation of **11** with **10** gives **12** (and its corresponding regioisomer). Reductive elimination from **12** affords the desired product **9**. Further Pd-catalyzed reaction of **9** (or more likely its regioisomer) with **10** produces **13**, which yields the triaryl byproduct **6** by reductive elimination. The byproduct **7** is formed from the intermediate **15**, which arises by a transmetalation from aryl zirconocene **14** prior to the benzyne formation; the absence of deuterium incorporation into **7** in the deuterium quenching experiment indicates that **7** does not arise from the deuteriolysis of an intermediate which contains a C–Zr bond.

The use of 1.5 equiv (relative to Pd) of DPEphos¹² **16** or DPPP **17** yields **9** (and the corresponding products with R = Ph, OMe) in a highly regioselective fashion under conditions that suppress the formation of **6** (Scheme 3). This optimized procedure affords the biaryl iodide products in moderate to very good yield (Tables 1 and 2).¹³

(11) In a separate experiment, protonolysis of the reaction mixture yielded three products, identified as **6**, **7**, and protio-**8** based on GC/MS analysis and comparison to the literature ¹H NMR spectra.

(12) Kranenburg, M.; van der Burgt, Y. E. M.; Kamer, P. C. J.; van Leeuwen, P. W. N.; Goubitz, K.; Fraanje, J. *Organometallics* **1995**, *14*, 3081.

(13) See Supporting Information for experimental details.

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(1) MacBride, J. A. H. In *Second Supplements to the Second Edition of Rodd's Chemistry of Carbon Compound, Vol. III D/E/F (Partial)*; Sainsbury, M., Ed.; Elsevier Science B.V.: Amsterdam, 1996; p 317.

(2) Saednya, A.; Hart, H. *Synthesis* **1996**, 1455.

(3) Bringmann, G.; Walter, R.; Weirich, R. *Synthesis* **1990**, 977.

(4) Stanforth, S. P. *Tetrahedron* **1998**, *54*, 263.

(5) (a) Buchwald, S. L.; Broene, R. D. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Elsevier Science: Tarrytown, NY, 1995; Vol. 12, p 771. (b) Buchwald, S. L.; Nielsen, R. B. *Chem. Rev.* **1988**, *88*, 1047.

(6) For a review of metal-stabilized complexes of strained organic molecules, see: Bennett, M. A.; Schwemlein, H. P. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1296.

(7) (a) Erker, G.; Kropp, K. *J. Am. Chem. Soc.* **1979**, *101*, 3659. (b) Erker, G. *J. Organomet. Chem.* **1977**, *134*, 189. (c) Peat, A. J.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 1028. (d) Akai, S.; Peat, A. J.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9119. (e) Rosa, P.; Floch, P. L.; Ricard, L.; Mathey, F. *J. Am. Chem. Soc.* **1997**, *119*, 9417. (f) Binger, P.; Bienenbach, B.; Mynott, R.; Regitz, M. *Chem. Ber.* **1988**, *121*, 1455.

(8) Bimetallic complexes have been prepared by reaction of zirconocene-stabilized benzyne complexes with transition and main-group metal compounds: (a) Erker, G.; Dorf, U.; Mynott, R.; Tsay, Y.-H.; Krüger, C. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 584. (b) Albrecht, M.; Erker, G.; Krüger, C. *Synlett* **1993**, 441. (c) de Rege, F. M. G.; Davis, W. M.; Buchwald, S. L. *Organometallics* **1995**, *14*, 4799.

(9) (a) Negishi, E.-I.; Liu, F. In *Metal-catalyzed Cross-coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, Germany, 1998; Chapter 1. (b) Wipf, P.; Jahn, H. *Tetrahedron* **1996**, *52*, 12853.

(10) Widenhoefer, R. A.; Zhong, H. A.; Buchwald, S. L. *Organometallics* **1996**, *15*, 2745.

Table 1. Preparation of Biaryls for R = Me, Ph

ArBr	Product	Yield ^a	<i>meta</i> : <i>ortho</i> ratio ^b
		64	80 : 1
		77	one isomer
		80	52 : 1
		86	one isomer
		56 ^c	87 : 1
		66	27 : 1
		40 ^c	one isomer
		66	one isomer
		44	one isomer

^a Yields refer to isolated mixture of isomers which was >95% pure by ¹H NMR, GC, and elemental analysis. ^b Determined by GC analysis of the isolated product. ^c Incomplete conversion of starting material was observed. A small amount of ArBr was detected in the crude reaction mixture by GC.

The procedure tolerates several common functional groups, including oxygen-containing substrates such as ethers, dioxolanes, and *ortho*-esters. Compounds containing aromatic carbon–chloride bonds and benzophenone protected anilines can also be successfully employed.¹⁴ The reaction is highly regioselective, giving the desired:undesired regioisomer in $\geq 27:1$ ratio.

In the case of the anisole derivatives (Table 2), the use of Cp₂Zr(Me)Cl resulted in formation of *ortho*-coupled desiodobiaryl, such as **7**, as the major product. By employing Cp₂Zr(*iso*-butyl)Cl¹⁵ and DPPP as the ligand, the desired product was selectively formed. We attribute the discrepancy in reactivity between substrates with R = OMe and those with R = Me or Ph to the difference in steric bulk of the respective substituents R, which affects the rate of benzyne formation from a precursor such as **14**.¹⁶ Due to the relatively small size of the methoxy group, when the alkyl group on Zr is methyl, transmetalation to form an intermediate such as **15** predominates, regardless of the phosphine ligand used. The much larger size of the *iso*-butyl group compared

(14) Functional groups which can react with zirconocene-stabilized benzyne complexes without the agency of Pd, such as ketones, nitriles, carboxylic esters, carboxylic amides, and nitro groups, are incompatible with the reaction conditions.

(15) Barr, K. J.; Watson, B. T.; Buchwald, S. L. *Tetrahedron Lett.* **1991**, 32, 5465.

Table 2. Preparation of Biaryls for R = OMe

ArBr	Product	Yield ^a	<i>meta</i> : <i>ortho</i> ratio ^b
		83	49 : 1
		78	51 : 1
		84	43 : 1
		90	52 : 1
		84	105 : 1
		84	47 : 1
		89	38 : 1
		72	53 : 1

^a Yields refer to isolated mixture of isomers which was >95% pure by ¹H NMR, GC, and elemental analysis. ^b Determined by GC analysis of the isolated product.

to the methyl group increases the rate of β -hydride abstraction, in addition to lowering the rate of the transmetalation from **14** to form **15**.¹⁷

In summary, a one-pot method for the synthesis of 3-aryl-2-iodo-1-substituted benzene derivatives has been developed. This methodology allows for the synthesis of polysubstituted biaryls and *m*-terphenyls while increasing the level of functionalization of one of the aryl rings by one. These results provide the foundation for further investigations into cross-coupling reactions of metal-stabilized complexes of unsaturated organic molecules.

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Supporting Information Available: Experimental procedures and spectroscopic and analytical data for relevant compounds (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(16) (a) Buchwald, S. L.; Lum, R. T.; Fisher, R. A.; Davis, W. M. *J. Am. Chem. Soc.* **1989**, 111, 9113. (b) Buchwald, S. L.; King, S. M. *J. Am. Chem. Soc.* **1991**, 113, 258.

(17) Transmetalation from Zr to Pd is very sensitive to steric effects.⁹