

Carbon–Carbon Bond Formation via Palladium-Catalyzed Reductive Coupling in Air

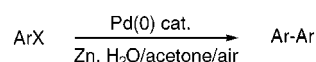
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ABSTRACT



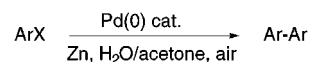
Palladium-catalyzed reactions in general are known to be carried out under an inert atmosphere because the palladium intermediates in the catalytic cycle are often known to be sensitive to oxygen. Herein we report a novel palladium-catalyzed Ullmann-type reductive coupling of aryl halides under an air atmosphere and in aqueous acetone.

Palladium-catalyzed reductive couplings are among the most important carbon–carbon bond-forming reactions in modern synthetic organic chemistry.¹ Such reactions include the π -allyl chemistry (also asymmetric),² the Stille coupling,³ the Heck reaction,⁴ the Suzuki reactions,⁵ the Sonogashira coupling,⁶ and many others. These reactions are generally air sensitive. In addition to the requirement of an inert gas atmosphere, these reactions are often carried out in the presence of a phosphine compound (which serves as the coordinating ligand to stabilize the reactive palladium intermediate). In the course of our quest for novel methodologies in aqueous media,⁷ we came across this unusual

condition wherein the palladium catalyst seemed to be stable in air.⁸ The validity of the reaction was further confirmed when carried out under an oxygen atmosphere.

As the first step, we wish to report the palladium-catalyzed zinc-mediated aryl halide coupling in air at an ambient temperature (Scheme 1). Conventionally, reductive aryl

Scheme 1



halide couplings⁹ are carried out by using the Ullmann conditions,¹⁰ where copper is used in stoichiometric quantities.¹¹ Generally, the Ullmann coupling is also carried out at a high temperature, often above 200 °C.¹²

(1) For representative reviews, see: Trost, B. M. *Tetrahedron* **1977**, *33*, 2615. Tsuji, J. *Top. Curr. Chem.* **1980**, *91*, 29. Kumada, M. *Pure Appl. Chem.* **1980**, *52*, 669. Negishi, E. I. *Acc. Chem. Res.* **1982**, *15*, 340. Tsuji, J. *Organic Synthesis with Palladium Compounds*; Springer-Verlag: Berlin, 1980; Baekvall, J. E. *Pure Appl. Chem.* **1983**, *55*, 1669. Heck, R. H. *Palladium Reagents for Organic Synthesis*; Academic Press: New York, 1985. Oppolzer, W. *Angew. Chem.* **1989**, *101*, 39. Trost, B. M. *Acc. Chem. Res.* **1990**, *23*, 34. Larock, R. C. *Adv. Met.-Org. Chem.* **1994**, *3*, 97.

(2) For representative reviews, see: Trost, B. M. *Acc. Chem. Res.* **1980**, *13*, 385.

(3) For representative reviews, see: Stille, J. F. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508.

(4) For representative reviews, see: Heck, R. H. *Acc. Chem. Res.* **1979**, *12*, 146. Overman, L. E. *Pure Appl. Chem.* **1994**, *66*, 1423.

(5) For a representative review, see: Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.

(6) For a representative review, see: Sonogashira, K. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, 1991.

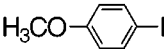
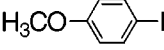
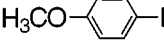
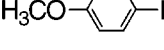
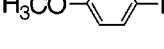
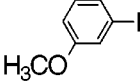
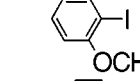
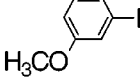
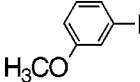
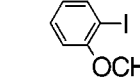
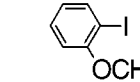
(7) Li, C. J. *Chem. Rev.* **1992**, *92*, 2023. Li, C. J.; Chan, T. H. *Organic Reaction in Aqueous Media*; John Wiley & Sons: New York, 1997. See also: *Organic Synthesis in Water*; Grieco, P. A., Ed.; Thomson Science: Glasgow, 1998.

(8) After initial submission this work, an air-stable and polymer-supported palladium-catalyzed Suzuki reaction was reported, see: Zhang, T. Y.; Allen, M. J. *Tetrahedron Lett.* **1999**, *40*, 5813. For a Heck-type reaction with arenediazonium salts, see: Brunner, H.; Le Cousturier de Courcy, N.; Genet, J.-P. *Tetrahedron Lett.* **1999**, *40*, 4815.

(9) For representative reviews, see: Bringmann, G.; Walter, R.; Weirich, R. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 977. Sainsbury, M. *Tetrahedron* **1980**, *36*, 3327.

(10) For representative reviews, see: Fanta, P. E. *Chem. Rev.* **1946**, *38*, 139; **1964**, *64*, 613; *Synthesis* **1974**, *9*. Goshav, M.; Otroshchenko, O. S.; Sadykov, A. S. *Russ. Chem. Soc. Rev.* **1972**, *41*, 1046. See also: Posner, G. H. *An Introduction to Synthesis Using Organocopper Reagents*; John Wiley: New York, 1980. Nelson, T. D.; Meyers, A. I. *J. Org. Chem.* **1994**, *59*, 2655.

Table 1. Reductive Coupling of Aryl Halides under a Variety of Conditions^a

entry	substrate (1)	conditions	coupling/ dehalogenation
1		Zn/Pd(OAc) ₂ /acetone-H ₂ O (1:1)	48 50
2		Zn/Pd-C/acetone-H ₂ O (1:1)	80 20
3		Zn/Pd(OAc) ₂ /acetone	7 0
4		Zn/Pd(OAc) ₂ /acetone/H ₂ O (9:1)	30 30
5		Sn/Pd(OAc) ₂ /acetone-H ₂ O (1:1)	5 0
6		In/Pd(OAc) ₂ /acetone-H ₂ O (1:1)	26 0
7		Zn/Pd(OAc) ₂ /CH ₃ CN	8 little
8		Zn/Ni/acetone-H ₂ O (1:1)	N.R.
9		Zn/Pt ₂ O/acetone-H ₂ O (1:1)	N.R.
10		Zn/Pd(OAc) ₂ /DMSO-H ₂ O (1:1)	19 80
11		Zn/Pd(OAc) ₂ /DMF-H ₂ O (1:1)	20 40


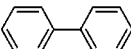

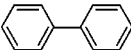

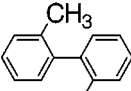
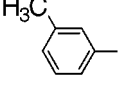
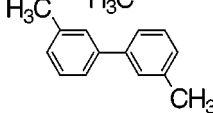
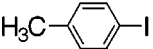
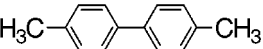

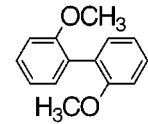
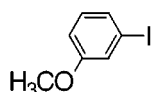
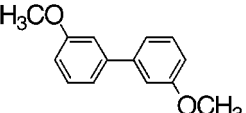
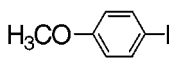
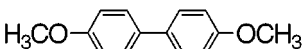

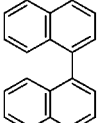
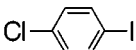
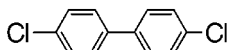
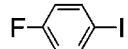
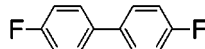

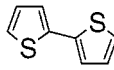
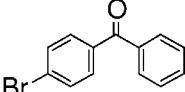
^a All reactions were carried out at room temperature under an air atmosphere on a 100 mg scale of aryl halides with aryl halide/M (1:3) and 8 mmol % of the catalyst. Yields were based on GC/MS analysis of ether extract of the reaction mixtures.

The results of the reaction are summarized in Table 1. When *p*-iodoanisole was stirred with zinc in a mixture of water/acetone (1:1) in the presence of a catalytic amount of palladium acetate (8 mol %) for 12 h under an air atmosphere, GC/MS analysis of the reaction mixture revealed the complete disappearance of the starting material, and the corresponding homo-coupled product was obtained in 48% yield together with dehalogenated anisole. It appears that the use of a mixture of water/acetone is essential in the success of the reaction. The use of acetone alone resulted in very low conversion of the starting material whereas in water alone no reaction was observed. It appears that a 40% of acetone in water is required to obtain the C–C bond formation with satisfactory results. Interestingly, the presence of triphenylphosphine inhibits rather than facilitates the

(11) For Ni-catalyzed Ullman-type couplings, see: Takagi, Hayama, Sasaki. *Bull. Chem. Soc. Jpn* **1984**, *57*, 1887. Meyer, Rollin, Perchon. *J. Organomet. Chem.* **1987**, *333*, 263.

(12) Recently, Liebeskind reported an ambient temperature Ullmann-type coupling, see: Zhang, S.; Zhang, D.; Liebeskind, L. S. *J. Org. Chem.* **1997**, *62*, 2312 and references cited therein.

Table 2. Reductive Coupling of Aryl Halides Catalyzed by Pd/C under Air Atmosphere^a

entry	substrate (1)	product (2)	yield (%)
1			94
2			92
3			84
4			89
5			92
6			73
7			79
8			92
9			70
10			94
11			96
12			64
13		reduced	0

^a All reactions were carried out at room temperature under an air atmosphere on a 100 mg scale of aryl halides with aryl halide/Zn (1:3) and 8 mmol % of Pd/C. Yields were based on GC/MS analysis of ether extract of the reaction mixtures.

reaction. DMSO or DMF can also serve as the cosolvent, but they are much less effective (entries 10 and 11). When the catalyst was changed from Pd(OAc)₂ to Pd/C,¹³ the efficiency of the coupling was significantly increased (from 48% to 80%) where the dehalogenated product has been

diminished. The use of other metals (such as tin and indium) as the reducing agent resulted in a low reactivity (entries 5 and 6). The yield of the homo-coupled product can be optimized when the reaction temperature was controlled at 0–10 °C. This might suggest that the coupling reaction is kinetically favored. Attempts to reduce the dehalogenated product by further lowering the temperature resulted in low conversion of the starting material. However, reduced reactivity was observed at 0–10 °C with Pd/C as the catalyst. Subsequently, a variety of aromatic iodides were coupled in high yields at ambient temperature under the Pd/C–Zn conditions (Table 2).¹⁴ Bromobenzene is similarly coupled in generating the carbon–carbon bond formation product (compare entries 1 and 2). An iodothiophene was also efficiently coupled in generating the thiophene dimer (entry 12), which illustrates its potential in synthesizing advanced electronic materials.¹⁵ Chloro and fluoro groups are inert under the reactions conditions, which imparts chemoselectivity (entries 10 and 11). On the other hand, only dehalogenation was observed with an electron-deficient aryl halide (entry 13).

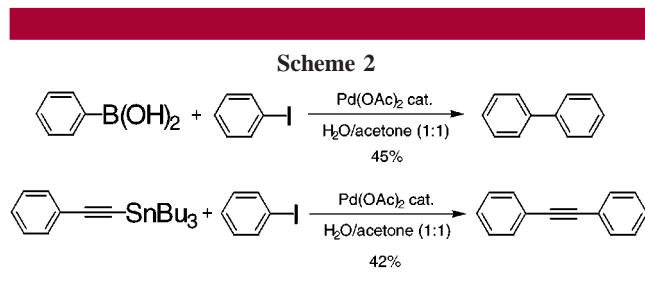
To validate the air-stability nature of this palladium catalytic system, the reductive coupling was examined and found to be successful even under an oxygen atmosphere. Comparative experiments were carried out (with iodoanisole,

(13) Previously, Pd/C was used as the catalyst for Ullmann-type coupling with moderate yields under phase-transfer conditions by refluxing at 100 °C, see: Bamfield, P.; Quan, P. M. *Synthesis* **1978**, 537.

(14) **Representative Experimental Procedure:** A mixture of Pd/C (80 mg, 10%) and zinc powder (80 mg, 1.2 mmol) in 4 mL of water/acetone (1:1) was stirred at ambient temperature under an atmosphere of air for 30 min. To the mixture was added *p*-iodoanisole (100 mg, 0.4 mmol), and the stirring was continued overnight under this same reaction conditions. The reaction mixture was extracted with ether. GC/MS analysis of the reaction mixture revealed two components with 4,4'-dimethoxybiphenyl (92%) and anisole (8%).

(15) For representative examples, see: Tour, J. *Chem. Rev.* **1996**, 96, 537. Brase, S.; De Meijere, A. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH Verlag: Weinheim, 1998; Baughman, R. H.; Bredas, J. L.; Chance, R. R.; Elsenbaumer, R. L.; Shacklette, L. W. *Chem. Rev.* **1982**, 82, 209.

zinc, and Pd/C in aqueous acetone) under nitrogen, oxygen, and air atmospheres; virtually identical results were obtained in all cases. As an indication of the promise of the air-stable palladium catalytic system, both Suzuki and Stille couplings were briefly examined (Scheme 2). Both reactions generated



the desired coupling products when Pd(OAc)₂ was used as the catalyst in aqueous acetone and under an air atmosphere, albeit with a low conversion of the starting materials. These results suggest that there might be a larger scope for air-stable palladium-catalyzed reactions. Interestingly, no reaction was observed when Pd/C was used as the catalyst in these cases.

The mechanism of the present catalytic reactions seems intriguing as it is well known that palladium intermediates in the course of catalytic reductive couplings are highly sensitive toward air. It is likely that the intermediate is somehow coordinated with the carbonyl group, which stabilizes the intermediate and facilitates the reaction, as no reaction was observed in the absence of acetone. This air-stable palladium catalytic system provides an operational convenience for synthesis. Further studies on the scope and mechanism of this intriguing catalytic system are in progress.

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