C–C Bond Formation via Double C–H Functionalization: Aerobic Oxidative Coupling as a Method for Synthesizing Heterocoupled Biaryls
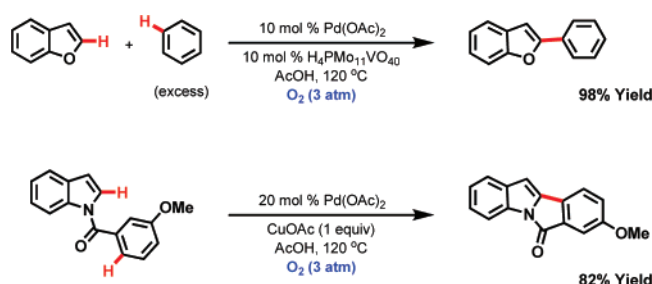
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ABSTRACT

The aerobic oxidative coupling of arenes such as benzofuran and *N*-substituted indoles with benzene and derivatives thereof is described. The reaction is shown to take place in both inter- and intramolecular scenarios.

Biaryls are common substructures in high value molecules such as organic dyes, conducting polymers, asymmetric ligands, and pharmaceuticals.[1] These substances are often synthesized by the Suzuki reaction, which is usually mild and high yielding.[2] However, the overall process, including the prefunctionalization of the substrates with boronic acids and halides, is neither atom economic nor green. Recently, several procedures have been used to synthesize biaryls by formally coupling C–H bonds with C–halogen and C–metal/metalloid bonds.[3] These processes represent significant progress toward the stated goals of Green Chemistry.[4]

However, the ideal process would form the biaryl C–C bond via simultaneous C–H bond functionalization of two unfunctionalized arene substrates (Scheme 1). Such oxidative

Scheme 1. Atom Economy of Oxidative Coupling
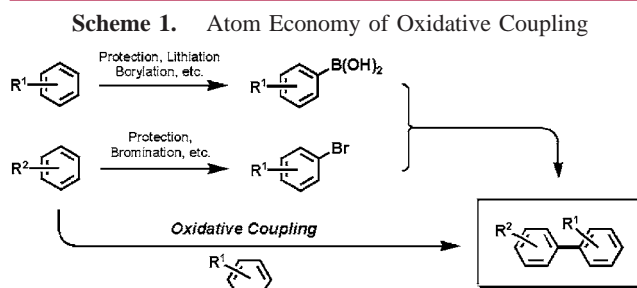
couplings have been employed to form homocoupled biaryls and to synthesize styrenes and derivatives thereof.[5] Several

(1) For a revew, see: Cepanec, I. *Synthesis of Biaryls*; Elsevier: New York, 2004.

(2) For reviews, see: (a) Zapf, A. Coupling of Aryl and Alkyl Halides with Organoboron Reagents (Suzuki Reaction). In *Transition Metals for Organic Synthesis*, 2nd ed.; Beller, M., Bolm, C., Eds.; Wiley-VCH: New York, 2004; Chapter 2.10. (b) Suzuki, A. The Suzuki Reaction with Arylboron Compounds in Arene Chemistry. In *Modern Arene Chemistry*; Astruc, D., Ed.; Wiley-VCH: New York, 2002; Chapter 4.

(3) (a) Lane, B. S.; Brown, M. A.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 8050 and refs. therein. (b) Park, C.-H.; Ryabova, V.; Seregin, I. V.; Sromek, A. W.; Gevorgyan, V. *Org. Lett.* **2004**, *6*, 1159. (c) Deprez, N. R.; Kalyani, D.; Andrew Krause, A.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 4972.

(4) Anastas, P. T.; Warner, J. C. *Green Chemistry: Theory and Practice*; Oxford University Press: New York, 1998.

of these processes even use molecular oxygen as the terminal oxidant, but aerobic oxidative coupling has not been applied to the synthesis of nondimeric biaryl molecules.[6] Presumably, previous researchers in this field assumed that these reactions would be plagued by homocouplings. Our initial investigations have demonstrated the opposite scenario: *dissimilar arenes may be heterocoupled by oxidative processes and molecular oxygen can often be used as a suitable oxidant for these reactions* (Table 1).
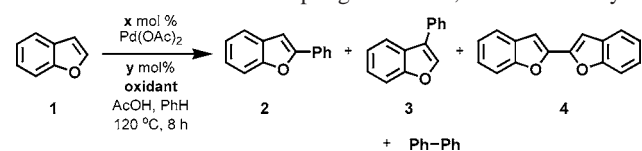
entry	Pd(OAc)$_2$ (mol %)	oxidant	yield (%)[b]			
			2	**3**	**4**	Ph−Ph
1	100	none	73	trace	0	trace
2	25	Cu(OAc)$_2$ (4 equiv)	44	trace	0	0
3	25	AgOAc (4 equiv)	44	40	0	trace
4	25	PhI(OAc)$_2$ (2 equiv)	42	trace	0	trace
5	25	benzoquinone (2 equiv)	2	0	0	0
6	25	Cu(OAc)$_2$ (1 equiv) + O$_2$[c]	55	20	0	10
7	25	AgOAc (1 equiv) + O$_2$[c]	16	23	0	0
8	10	HPMV (10 mol %) + O$_2$[d]	98	0	0	trace

[a] All reactions: AcOH/PhH = 3/2 (v/v), catalyst and oxidant equivalents are relative to substrate. [b] GC yield. [c] 1 atm. [d] 3 atm, 1.5 h.

Our initial investigations with stoichiometric amounts of palladium salts demonstrated that Pd(OAc)$_2$ in a mixed solvent system of acetic acid and benzene (3/2, v/v) successfully coupled benzofuran and benzene to produce 2-phenylbenzofuran **2** in a 73% yield (Table 1, entry 1).[7] Other salts such as PdCl$_2$, Pd(acac)$_2$, and Pd(TFA)$_2$ produced minimal coupled products. Reducing the palladium loading and introducing oxidants also proved fruitful. Catalytic amounts of Pd(OAc)$_2$ and excess Cu(OAc)$_2$ or AgOAc produced **2** but with lower yields (entries 2 and 3). PhI(OAc)$_2$

(5) For examples, see: (a) Hull, K. L.; Lanni, E. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 14047. (b) Beck, E. M.; Grimster, N. P.; Hatley, R.; Gaunt, M. J. *J. Am. Chem. Soc.* **2006**, *128*, 2528. (c) Yamada, T.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* **2005**, *70*, 5471. (d) Takahashi, M.; Masui, K.; Sekiguchi, H.; Kobayashi, N.; Mori, A.; Funahashi, M.; Tamaoki, N. *J. Am. Chem. Soc.* **2006**, *128*, 10930. (e) Jia, C.; Lu, W.; Kitamura, T.; Fujiwara, Y. *Org. Lett.* **1999**, *1*, 2097.

(6) Previous heterocoupling attempts: (a) Li, R.; Jiang, L.; Lu, W. *Organometallics* **2006**, *25*, 5973. (b) Itahara, T. *Heterocycles* **1986**, *24*, 2557. (c) Itahara, T. *J. Org. Chem.* **1985**, *50*, 5546. (d) Itahara, T. *J. Org. Chem.* **1985**, *50*, 5272. (e) Itahara, T.; Kawasaki, K.; Ouseto, F. *Bull. Chem. Soc. Japan* **1984**, *57*, 3488. (f) Itahara, T. *Synthesis* **1979**, 151.

(7) DeBoef, B. Aerobic Oxidative Coupling for the Formation of Bis-Arenes. U.S. Patent Application 60/867,641, Nov 29, 2006.

also produced **2** in modest yield, but this reaction was plagued by oxidized byproducts (entry 4). Interestingly, excess benzoquinone inhibited the reaction in that one turnover was not observed (entry 5).

Gratifyingly, we discovered that oxygen could be used as the terminal oxidant. Substoichiometric Cu(OAc)$_2$ loading (assuming that Cu(II) is a one-electron oxidant), coupled with 1 atm of O$_2$, provided a 55% yield of **2**, but this was accompanied by a partial loss of selectivity (entry 6). Finally, the heteropolymolybdovanadic acid H$_4$PMo$_{11}$VO$_{40}$ (HPMV) increased the rate of the oxidative coupling and allowed for exclusive formation of **2** in a 98% yield (entry 8).[8] In general, biphenyl formation was only observed after complete consumption of the benzofuran substrate.

The oxidative arylation of indole substrates proved to be somewhat more challenging. When subjected to the optimized conditions described in entry 8 of Table 1 (method **A**), both *N*-acetylindole and *N*-methylindole decomposed, but aerobic conditions using the milder oxidant Cu(OAc)$_2$ were effective for the arylation of *N*-acetylindole (Table 2, entry 2). The more electron-rich substrate, *N*-methylindole,

Table 2. Examples of Intermolecular Oxidative Coupling

entry	substrates	method[a]	time	yield[b]	product
1		A	1.5	84%	
2		B	3	45%	5:1
3		C	3	69%	1:1
4		A	15	32%	
5		A	15	20%[c]	
6		A	15	0%	Not Observed
7		A	2	49%	
8		A	24 min.	56%	mixture of isomers (5:3:2)

[a] Explanation of reaction conditions: (**A**) 10 mol % of Pd(OAc)$_2$, 10 mol % of HPMV, 3 atm of O$_2$, AcOH/PhH (or other arene) = 3/2 (v/v), 120 °C, 1.5 h; (**B**) 20 mol % of Pd(OAc)$_2$, 1 equiv of Cu(OAc)$_2$, 3 atm of O$_2$, AcOH/PhH = 3/2 (v/v), 120 °C, 3 h; (**C**) 15 mol % of Pd(OAc)$_2$, 4 equiv of Cu(OAc)$_2$, AcOH/PhH = 3/2 (v/v), 1 atm of argon, 3 h. [b] Isolated yield. [c] GC yield.

could only be arylated using anaerobic conditions. While the yield for this reaction was good, the selectivity for the arylation was poor (entry 3).[9] The oxidative coupling of (N-H) indole was attempted, but a complex mixture of products was observed.

When benzofuran was used as the substrate, it was observed that extended reaction times caused the formation of the 2,3-diarylated product, albeit in low yields (entry 4). Significant amounts of biphenyl were also observed in these reactions. When 2-phenylbenzofuran was subjected to the reaction conditions, arylation at the 3-position was observed (entry 5). The mass balance for this reaction was very poor, indicating that decomposition of the substrate is a competitive process. Subjecting 3-methylbenzofuran to the reaction conditions resulted in the recovery of the starting material (entry 6). Thus, we concluded that arylation at the 2-position is preferred to arylation at the more nucleophilic 3-position. However, palladation most likely occurs first on the nucleophilic 3-position, followed by migration to the 2-position and C−C bond formation.[3a]

As a general rule, the oxidative coupling yields were directly correlated to the reaction time, which, in turn, was dependent on the choice of oxidant. Judicious monitoring via GCMS was required to obtain reliable and reproducible yields. For reactions containing HPMV (method **A**), the monoarylated product was obtained in 1.5 h, and the diphenyl product was obtained at longer reaction times. For reactions containing Cu(OAc)$_2$ (methods **B** and **C**), the monoarylated product was obtained in 3 h. Reactions containing p-xylene proceeded at a slightly slower rate, but this can be attributed to steric hindrance (entry 7). Reactions using anisole proceeded at markedly quicker rates, but they resulted in a regiomeric mixture of 2-arylated products (entry 8). Reactions using electron-poor and more acidic arenes such as nitrobenzene, p-difluorobenzene, and 1,4-bis(trifluoromethyl)-benzene failed.

In addition to the intermolecular reactions shown in Table 2, the aerobic oxidative coupling was used for intramolecular cyclizations (Scheme 2). The oxidative cyclization of N-benzoylindole **5** produced a low yield of **6**. However, when an electron-donating group was added to the tethered arene, the yield nearly tripled (**7** → **8**).

We propose that the oxidative coupling proceeds via two independent palladation steps. One of these steps is analogous to the electrophilic mechanisms previously described for indole-type substrates.[3a,9] Based on the rate enhancement observed with anisole, it is tempting to postulate that the palladation of the second arene also proceeds via an electrophilic pathway. However, a competition experiment using an equimolar mixture of benzene and anisole showed that the presence of the anisole enhanced the rate of benzene

Scheme 2. Intramolecular Aerobic Oxidative Coupling
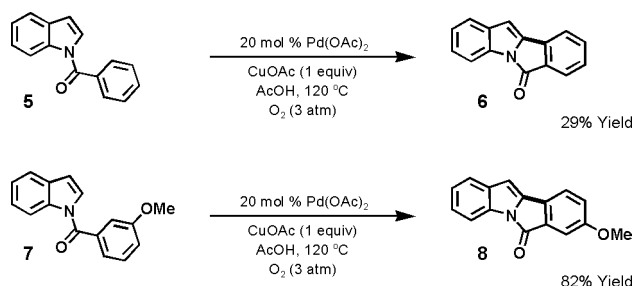
coupling, as well.[10] We postulate that anisole ligates the palladium species to create a more active catalyst. Proton abstraction is a possible mechanism for the second palladation, but this would predict that more acidic arenes, such as p-difluorobenzene, would readily react.[11] Conseqently, the reason for the selectivity of the two palladations that gives rise to heterocoupled products is still uncertain, and merits further mechanistic study.

In conclusion, we have discovered a novel method for synthesizing heterocoupled biaryls via oxidative coupling.[12] This method represents a practical advance in the synthesis of these molecules, but it introduces new mechanistic questions about the origin of the selectivity. Future work in our laboratory will be dedicated to the resolution of this issue as well as the application of this reaction to the synthesis of complex targets.

Note Added after ASAP Publication: This paper was published ASAP on July 7, 2007. The graphic in Table 1 and Scheme 2 were corrected and the acknowledgment was changed in the version published July 13, 2007.

Supporting Information Available: Experimental procedures as well as characterization of previously unknown compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) (a) Okamoto, M.; Watanabe, M.; Yamaji, T. *J. Organomet. Chem.* **2002**, *664*, 59. (b) Tarabanko, V. E.; Kozhevnikov, I. V.; Matveev, K. I. *React. Kinet. Catal. Lett.* **1978**, *8*, 77.

(9) Cu(OAc)$_2$ has been shown to produce the enhanced alkenylation of indoles at the 3-position: Grimster, N. P.; Gauntlett, C.; Godfrey, C. R. A.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 3125−3129.

(10) See the Supporting Information.

(11) (a) Lafrance, M.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 16496. (b) Lafrance, M.; Shore, D.; Fagnou, K. *Org. Lett.* **2006**, *8*, 5097. (c) Lafrance, M.; Rowley, C. N.; Woo, T. K.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 8754. (d) Davies, D. L.; Donald, S. M. A.; Macgregor, S. M. *J. Am. Chem. Soc.* **2005**, *125*, 13754.

(12) During preparation of this manuscript, Stuart and Fagnou reported the oxidative coupling of *N*-acetylindoles with arenes to selectively form 3-arylated products: Stuart, D. R.; Fagnou, K. *Science* **2007**, *316*, 1172.