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Palladium-Catalyzed (Ullmann-Type) Homocoupling of Aryl Halides: A Convenient and General Synthesis of Symmetrical Biaryls via Inter- and Intramolecular Coupling Reactions

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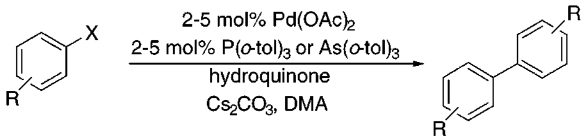
ABSTRACT



A convenient new procedure is described for both inter- and intramolecular homocoupling of aryl halides (Ullmann reaction) using catalytic palladium in the presence of hydroquinone, a homogeneous reductant. Optimal conditions for the reductive coupling include the use of a 1:1 molar ratio of $Pd(OAc)_2$ and As(*o*-tolyl)$_3$ in catalytic amounts under basic conditions.

The importance of the biaryl motif in biologically significant natural products as well as its pivotal role in unnatural systems of interest—particularly as the chiral scaffold of many asymmetric catalysts[1]—has stimulated the development of numerous methods for its construction.[2] The original and most widely used route to biaryls is via the Ullmann reaction, the copper-mediated homocoupling of aryl halides.[3] The need to avoid the harsh conditions typically required for Ullmann couplings (neat, >200 °C) has motivated the search for milder variations.[4,5] Of particular significance are methods that utilize zerovalent nickel catalysts, wherein a co-reductant such as zinc or electrochemical reduction regenerates the catalytically active species.[6] The relatively few palladium mediated homocouplings reported to date have either not been general or, as with the nickel procedures, require inconvenient reaction conditions to regenerate the active Pd^0 species.[7,8] In connection with our interest in aryl coupling reactions,[9] we have examined many different conditions for

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[1] (a) Noyori, R.; Takaya, H. *Acc. Chem. Res.* **1990**, *23*, 345−350. (b) Rosini, C.; Franzini, L.; Raffaelli, A.; Salvadori, P. *Synthesis* **1992**, 503−517.

[2] (a) Sainsbury, M. *Tetrahedron* **1980**, *36*, 3327−3359. (b) Bringmann, G.; Walter, R.; Weirich, R. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 977−991. (c) Bringmann, G.; Walter, R.; Weirich, R. In *Stereoselective Synthesis*; Houben-Weyl, 4th ed.; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Georg Thieme Verlag: Stuttgart, 1995; Vol. E21a, pp 567−586.

[3] (a) Fanta, P. E. *Synthesis* **1974**, 9−21. For recent applications, see: (b) Meyers, A. I. *J. Heterocycl. Chem.* **1998**, *35*, 991−1002. (c) Degnan, A. P.; Meyers, A. I. *J. Am. Chem. Soc.* **1999**, *121*, 2762−2769.

[4] (a) Cohen, T.; Cristea, I. *J. Org. Chem.* **1975**, *40*, 3649−3651. (b) Ziegler, F. E.; Chliwner, I.; Fowler, K. W.; Kanfer, S. J.; Kuo, S. J.; Sinha, N. D. *J. Am. Chem. Soc.* **1980**, *102*, 790−798.

[5] A remarkably mild procedure was recently reported for the Ullmann coupling. The procedure requires the use of 3 equiv of copper(I) thiophene carboxylate and necessitates the presence of a ligating functionality ortho to the aryl halide: Zhang, S.; Zhang, D.; Liebeskind, L. S. *J. Org. Chem.* **1997**, *62*, 2312−2313.

[6] (a) Semmelhack, M. F.; Helquist, P. M.; Jones, L. D. *J. Am. Chem. Soc.* **1971**, *93*, 5908−5910. (b) Jutand, A.; Mosleh, A. *Synlett* **1993**, 568−570. (c) Percec, V.; Bae, J.-Y.; Zhao, M.; Hill, D. H. *J. Org. Chem.* **1995**, *60*, 1066−1069.

[7] For an excellent overview on the use of palladium reagents in organic synthesis, see: Tsuji, J. *Palladium Reagents and Catalysts*; Wiley: New York, 1995.

[8] (a) Clark, F. R. S.; Norman, R. O. C.; Thomas, C. B. *J. Chem. Soc., Perkin Trans. 1* **1975**, 121−125. (b) Uchiyama, M.; Suzuki, T.; Yamakazi, Y. *Chem. Lett.* **1983**, 1165−1166. (c) Torii, S.; Tanaka, H.; Morisaki, K. *Tetrahedron Lett.* **1985**, *26*, 1655−1658. (d) Jutand, A.; Negri, S.; Mosleh, A. *J. Chem. Soc., Chem. Commun.* **1992**, 1729−1730.

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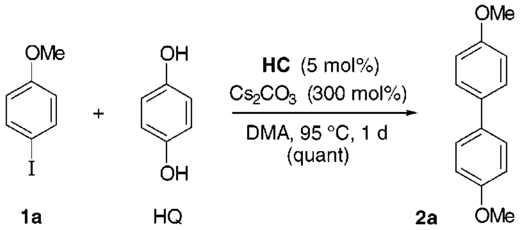
Table 1. Effect of Changing Reagents and Reaction Conditions on the Yield of **2a**

entry	$Pd(OAc)_2$ (mol%)	ligand (5 mol%)	reductant (mol%)	method[a]	temp (°C)	time (h)	**1a:2a**[b] (yield)[c]	recovd HQ (%)[d]
1	HC (2.5%)[e]	—	HQ (100)	B	50	35	0:100[f] (88)	–
2	5	P(*o*-Tol)$_3$	HQ (100)	A	50	35	0:100[f] (94)	67
3	5	As(*o*-Tol)$_3$	HQ (100)	B	50	15	0:100[f] (72)	64
4	5	As(*o*-Tol)$_3$	HQ (100)	A	50	15	0:100[f] (84)	69
5	2	As(*o*-Tol)$_3$	HQ (55)	B	75	3	0:100[f] (95)	–
6	1	As(*o*-Tol)$_3$	HQ (55)	A	75	24	0:100[f]	–
7	0.5	As(*o*-Tol)$_3$	HQ (55)	A	75	24	62:38	–

[a] The stoichiometries are with respect to the aryl iodide. Method **A**: A solution of $Pd(OAc)_2$ and a ligand was added to a mixture of *p*-iodoanisole, HQ and Cs_2CO_3 (100 mol%). Method **B**: DMA was added to a mixture of *p*-iodoanisole, $Pd(OAc)_2$, a ligand, HQ and Cs_2CO_3 (100 mol%); [b] Ratio of SM (starting material, *p*-iodoanisole):biaryl was calculated by ^1H NMR [c] Isolated yield. [d] Unless indicated, the hydroquinone present in the product mixture was not isolated. [e] Herrmann's catalyst (ref 11) was used instead of $Pd(OAc)_2$ and a ligand. [f] SM was not detected.

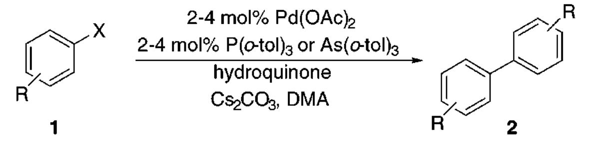
the homocoupling of aryl halides and report here a simple, general method for carrying out such couplings.[10]

The initial serendipitous discovery of the palladium catalyzed homocoupling reaction followed an attempted intermolecular arylation of hydroquinone (HQ) with 4-iodoanisole (**1a**) under our standard conditions [5 mol % of Herrmann's palladacyclic catalyst (HC),[11] Cs_2CO_3 (300 mol %), in *N*,*N*-dimethylacetamide (DMA) at 95 °C].[9] The product of this reaction was not the expected 2-arylhydroquinone, but 4,4′-dimethoxybiphenyl (**2a**), which was isolated in quantitative yield. A careful examination of the reaction conditions uncovered interesting aspects of this homocoupling reaction (Table 1). First, the HC-mediated reaction worked well even when the reaction temperature was lowered to 50 °C (entry 1). The use of a preformed palladacyclic catalyst was not essential for a successful coupling. The product was formed in comparably high yield when a solution of 1:1 $Pd(OAc)_2$−P(*o*-tol)$_3$ in DMA was added to the remaining reagents (entry 2). The order of mixing of the reagents is important, however, and the reaction proceeded more slowly when DMA was added to a mixture of all the reagents. Hydroquinone is essential for the success of the reaction; its omission or replacement with catechol or benzoquinone resulted in recovery of most of the starting material.[12] The coupling proceeded more rapidly using As(*o*-tol)$_3$ than with P(*o*-tol)$_3$ (entries 2 and 4; also Table 2, entries 5 and 7). The reaction worked almost as well with NaOH and K_2CO_3 as bases. Of the different solvents



(Eq 1)

Table 2. Palladium-Catalyzed Ullmann Coupling of Substituted Aryl Iodides and Bromides



entry	R	X	conditions[a]	time (h)	product	% yield
1	4-MeO	I	**A**	3	**2a**	95
2	4-MeO	Br	**B**	48	**2a**	54[b]
3	3-MeO	I	**A**	5.5	**2b**	96
4	2-MeO	I	**B**	48	**2c**	82
5	H	I	**A**	3	**2d**	96
6	H	I	**C**	21	**2d**	39
7	H	I	**D**	3	**2d**	37[c]
8	H	Br	**B**	24	**2d**	56
9	4-CO_2Me	I	**A**	2	**2e**	99
10	4-CO_2Me	I	**D**	2	**2e**	95
11	2-CO_2Me	I	**B**	18	**2f**	82
12	4-NO_2	I	**A**	1	**2g**	86
13	4-NO_2	I	**D**	2	**2g**	89
14	4-NO_2	Br	**B**	24	**2g**	88
15	3-NO_2	I	**A**	2.5	**2h**	86

[a] **A**: 2 mol% $Pd(OAc)_2$, 2 mol% As(*o*-tol)$_3$, 50 mol% hydroquinone, 100 mol% Cs_2CO_3, 0.4 M, 75 °C; **B**: same as **A** except 4 mol% $Pd(OAc)_2$ and As(*o*-tol)$_3$, 1 M, 100 °C; **C**: same as **A** except the reaction was carried out at room temperature (25 °C); **D**: same as **A** except 2 mol% P(*o*-tol)$_3$. [b] 11% recovered starting material. [c] Conversion yield by ^1H NMR.

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(9) (a) Rawal, V. H.; Florjancic, A. S.; Singh, S. P. *Tetrahedron Lett.* **1994**, *35*, 8985−8988. (b) Hennings, D. D.; Iwasa, S.; Rawal, V. H. *J. Org. Chem.* **1997**, *62*, 2−3. (c) Hennings, D. D.; Iwasa, S.; Rawal, V. H. *Tetrahedron Lett.* **1997**, *38*, 6379−6382.

(10) This work is taken from the Ph.D. dissertation of D.D.H., The University of Chicago, 1997. After this work had been completed and the dissertation submitted, Lemaire and co-workers reported another example of a palladium catalyzed Ullmann coupling reaction: Hassan, J.; Penalva, V.; Lavenot, L.; Gozzi, C.; Lemaire, M. *Tetrahedron* **1998**, *54*, 13793−13804 and references therein.

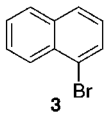
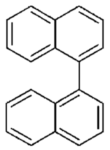
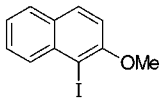
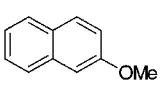
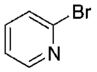
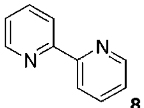
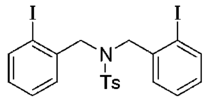
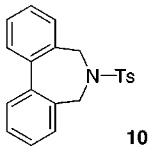
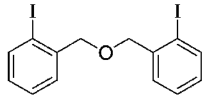
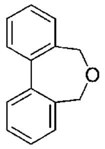
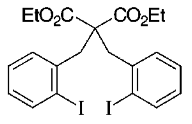
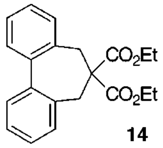
(11) (a) Herrmann, W. A.; Brossmer, C.; Ofele, K.; Reisinger, C.-P.; Priermeier, T.; Beller, M.; Fischer, H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1844−1848. (b) Beller, M.; Fischer, H.; Herrmann, W. A.; Ofele, K.; Brossmer, C. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1848−1849.

examined (DMA, DMF, DME, MeCN, PhMe), the amide solvents were the best. Intriguingly, in DMA or DMF, it was possible to use substoichiometric quantities of hydroquinone and still obtain the product in good yield (vide infra). The rate of the reaction became progressively longer with decreasing catalyst loading (entries 5−7).

The palladium-catalyzed homocoupling protocol that we have developed is applicable to a wide range of aryl halides, as evident from Table 2. The reactions were performed in DMA using 2−4 mol % of Pd(OAc)$_2$, an equal amount of As(*o*-tol)$_3$, 50 mol % of HQ, and 100 mol % of Cs$_2$CO$_3$. The coupling reaction of both electron-rich and electron-poor aryl iodides worked well. Substrates having a substituent at the meta or para positions reacted particularly well and afforded the corresponding biaryls in 86−99% yields (entries 1, 3, 5, 9, 10, 12, 13, and 15). The coupling of substrates with ortho substitution progressed more slowly under the standard conditions (conditions A, see Table 2), but proceeded well at a higher temperature and with 4 mol % of the catalyst (conditions B; entries 4, 11). The clean formation of 2,2′-dimethoxybiphenyl stands in contrast to Dyker's observed formation of triaryl products from the same starting material under similar reaction conditions.[13] As expected, aryl bromides were less reactive than aryl iodides under the standard conditions (entries 2, 8, and 14). However, the Ullmann product is produced in high yield if the substrate possesses an electron-withdrawing group (entry 14). Entry 6 is interesting in that it shows that the homocoupling proceeds even at room temperature using 2 mol % of the palladium catalyst (entry 6). Attempts to extend this coupling methodology to aryl triflates failed due to the ready hydrolysis of the triflates to phenols under the reaction conditions.

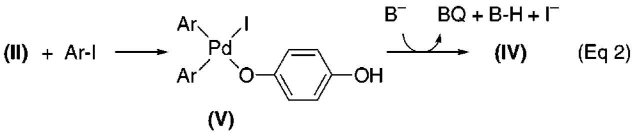
The present method promotes the Ullmann coupling of other aryl systems, as well as intramolecular couplings (Table 3). The reaction of 1-bromonaphthalene using 4 mol % catalyst loading gave 1,1′-binaphthyl in 90% yield (entry 1). However, the couplings of more hindered naphthyls, such as 1-iodo-2-methoxynaphthalene or 1-bromo-2-methylnaphthalene, were unsuccessful; the main products in these cases were the deiodinated monomers (cf. entry 2). The coupling of 2-bromopyridine afforded 2,2′-dipyridyl in good yield (entry 3). Symmetrical medium-ring biaryls can also be formed using intramolecular Ullmann couplings, although the rates of conversion were slower than expected for intramolecular processes, presumably due to the steric influence of the ortho substituents (entries 4−6). Under more vigorous conditions, however, all three cyclization reactions proceeded well and did not necessitate high dilution conditions.

Table 3. Inter- and Intramolecular Ullmann Coupling Catalyzed by Palladium

entry	substrate	conditions[a]	time (h)	product	% yield[b]
1	 **3**	**A**	48	 **4**	90
2	 **5**	**B**	48	 **6**	91
3	 **7**	**A**	24	 **8**	72
4	 **9**	**C**	48	 **10**	82
5	 **11**	**C**	24	 **12**	61 (70)
6	 **13**	**D**	48	 **14**	65 (76)

[a] **A**: 4 mol% Pd(OAc)$_2$, 4 mol% As(*o*-tol)$_3$, 50 mol% hydroquinone, 100 mol% Cs$_2$CO$_3$, 1 M, 100 °C; **B**: same as **A** except 5 mol% Pd(OAc)$_2$ and As(*o*-tol)$_3$, 125 °C; **C**: same as **A** except 5 mol% Pd(OAc)$_2$ and As(*o*-tol)$_3$, 0.4 M; **D**: same as **A** except 5 mol% cat, 0.25M. [b] The yields shown in parantheses are based on recovered starting material.

A plausible mechanism for the hydroquinone-mediated palladium-catalyzed Ullmann reaction is shown in Scheme 1. Under the basic conditions used, the intermediate Pd^{II} species (**II**) can eliminate benzoquinone (BQ) to form an anionic arylpalladium species **III**, similar to the intermediates proposed by Jutand.[14] The reaction of **III** with Ar−I with loss of I$^-$ would produce diarylpalladium species **IV**, from which reductive elimination of Pd^0 would give the Ullmann product. An alternate possibility is that species **II** reacts directly with the aryl iodide to produce a Pd^{IV} intermediate[15] (**V**, eq 2), the redox chemistry of which would generate diaryl



(Eq 2)

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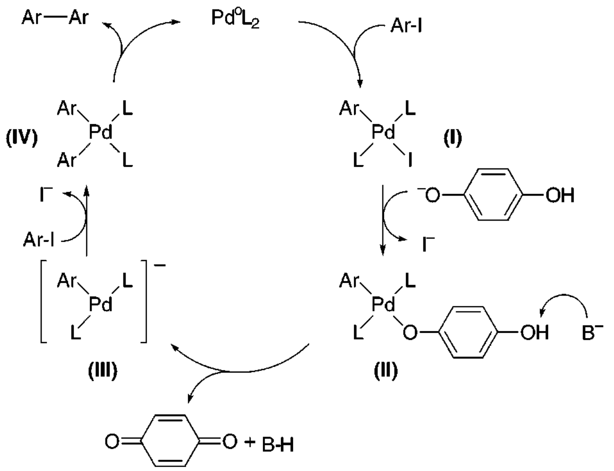
(12) Hydroquinone evidently mediates the redox chemistry at the palladium during these reductive coupling reactions. To our knowledge, the use of hydroquinone as an in situ stoichiometric reductant of oxidized forms of palladium has not previously been reported. The use of hydroquinone in this capacity complements the more widely recognized use of benzoquinone to reoxidize Pd^0 formed during a reaction. Cf.: Weider, P. R.; Hegedus, L. S.; Asada, H.; D'Andreq, S. V. *J. Org. Chem.* **1985**, *50*, 4276−4281. We thank Professor Hegedus (Colorado State University) for helpfull discussions.

(13) Dyker, G. *Angew. Chem., Ind. Ed. Engl.* **1992**, *31*, 1023−1025. The present work shows that in the presence of a reducing agent the putative palladacycle proposed by Dyker proceeds on to the Ullmann coupling stage but not further.

Scheme 1



palladium **IV** and benzoquinone. Given the probable mechanistic scenario, the complete absence of benzoquinone at the end of the reaction is at first inexplicable and raises questions as to the role of hydroquinone in the reaction.[16]

In summary, we have developed a convenient palladium-catalyzed alternative to the Ullmann coupling of aryl halides. The procedure is relatively mild and appears to have broad applicability, being useful for the coupling of both electron-deficient and electron-rich aromatic iodides and bromides. In addition, this procedure also represents, to our knowledge, the first use of hydroquinone as a stoichiometric in situ reductant of higher oxidized palladium species.

Acknowledgment. We thank The University of Chicago and Pfizer Inc. for financial support. D.D.H. thanks the Department of Education for a GAANN Fellowship.

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

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(14) Jutand, A.; Mosleh, A. *J. Org. Chem.* **1997**, *62*, 261−274.

(15) For a review of Pd^{IV} species, see: Canty, A. J. *Acc. Chem. Res.* **1992**, *25*, 83−90.

(16) Although necessary for the present coupling method, a significant percentage of the hydroquinone was recovered at the end of the coupling reactions. Factoring in the recovered HQ (see Table 1), the present method uses substoichiometric amounts of HQ. Indeed, we have found that even with 10 mol % of HQ it is possible to get the biaryl product in up to 50% yield. These observations necessitate a pathway for regeneration of the HQ from BQ during the reaction. A likely possibility is the Michael addition of a carbonate ion to BQ to yield 1,2,4-trihydroxybenzene, after loss of CO_2 and tautomerization.[17a,b] Under the basic reaction conditions, the trihydroxybenzene can then either directly reduce an oxidized form of Pd or reduce a molecule of BQ to HQ and form hydroxybenzoquinone. More highly oxidized benzenes can be formed similarly by further Michael additions of carbonate onto oxidized benzoquinones.[17c] We have extensively investigated the reaction of BQ with bases in various solvents and, consistent with literature reports,[17] have found that in DMA in the presence of Cs_2CO_3 or KOH BQ (room temperature, 4 h; or 70 °C, 2 h) is completely converted to HQ, which was isolated in 40−50% yield, along with some intractable black material.[17a] This formation of HQ from BQ under basic conditions explains the inability to recover BQ at the end of a coupling reaction as well as the feasibility of using less than a full 1 equiv of HQ and yet get good yields of the biaryl products.

(17) (a) Erdtman, H.; Granath, M. *Acta Chem. Scand.* **1954**, *8*, 811−816. (b) Eigen, M.; Matthies, P. *Chem. Ber.* **1961**, *94*, 3309−3317. (c) Fukuzumi, S.; Nakanishi, I.; Maruta, J.; Yorisue, T.; Suenobu, T.; Itoh, S.; Arakawa, R.; Kadish, K. M. *J. Am. Chem. Soc.* **1998**, *120*, 6673−6680.