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Palladium-Catalyzed Reductive *ortho*-Arylation: Evidence for the Decomposition of 1,2-Dimethoxyethane and Subsequent Arylpalladium(II) Reduction

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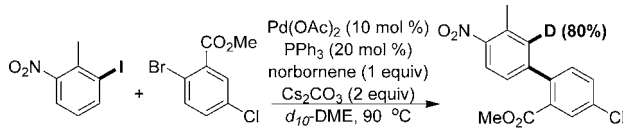
ABSTRACT



arylpalladium(II) reduction via deuteride transfer from d_{10}-DME!

A palladium-catalyzed crossed biaryl coupling/reduction sequence enables the formation of *meta*-substituted biaryls via solvent-mediated arylpalladium(II) reduction. Isotope labeling studies determined that the decomposition of 1,2-dimethoxyethane (DME) is indeed involved in the reductive process.

Reductive processes in metal-catalyzed organic synthesis are often well understood when common reducing agents such as molecular hydrogen, formates, and activated alcohols are used.[1] When reduction products are formed, often unexpectedly, in the absence of these traditional reducing agents, the reductive mechanism can be unclear. Such a process was recently discovered in our laboratories.[2] Our research into reductive *ortho*-benzylation reactions of aryl iodides found that reduction of the terminal arylpalladium(II) species occurred through hydride transfer from coupling partners in addition to an undefined process. We believed that the solvent (1,2-dimethoxyethane, DME) was the likely reductant, prompting us to develop a system where hydride transfer from DME would be the predominant pathway. Herein, we report the development and study of a highly selective palladium-catalyzed process involving crossed *ortho*-arylation of aryl iodides followed by reduction to afford *meta*-substituted biaryls (Scheme 1). Deuterium isotope labeling studies further revealed that reduction of the terminal arylpalladium(II) species involves DME.

Building upon the studies in our laboratories and that of Catellani regarding palladium-catalyzed homo and crossed *ortho*-arylation reactions of aryl iodides,[3] we chose to develop a crossed reductive *ortho*-arylation where, unlike our previous system,[2] obvious α- and/or β-elimination pathways for arylpalladium(II) reduction are absent. Beginning our studies with the reaction of methyl 2-iodobenzoate, we were pleased to obtain unsymmetrical homobiaryl **3a** in quantitative yield under our optimized conditions (Table 1, entry 1). This result confirmed our belief that *arylpalladium(II) reduction can occur without the addition of traditional reductants*.[4] Furthermore, careful control of

(1) (a) Tsuji, J. In *Palladium Reagents and Catalysts: New Perspectives for the 21st Century*; Tsuji, J., Ed.; Wiley-VCH: Weinheim, 2004. (b) Negishi, E.-I. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-I., Ed.; Wiley-VCH: Weinheim, 2002. (c) De Meijere, A.; Diederich, F. In *Metal-Catalyzed Cross-Coupling Reactions*; De Meijere, A., Diederich, F., Ed.; Wiley-VCH: Weinheim, 2004.

(2) Martins, A.; Lautens, M. *Org. Lett.* **2008**, *10*, 4351.

(3) (a) Martins, A.; Mariampillai, B.; Lautens, M. *Top. Curr. Chem.* **2010**, 1. (b) Catellani, M. *Top. Organomet. Chem.* **2005**, *14*, 21.

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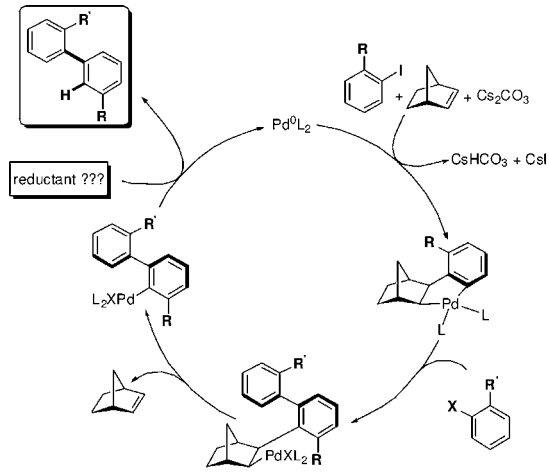
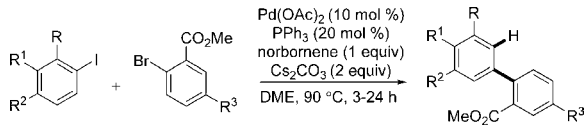
Scheme 1. Generalized Reaction Mechanism

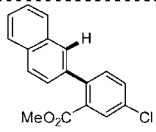
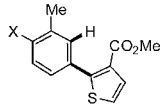
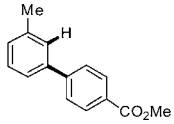


palladium ligation and temperature favors the desired *ortho*-arylation/reduction sequence over the *ortho*-arylation/C=O addition sequence that we previously reported.[5] We further extended this method to a crossed reductive arylation sequence by employing electron-deficient aryl halide coupling partners. We found that the best coupling partners for crossed reductive arylation were derivatives of methyl 2-bromobenzoate. Using functionalized *ortho*-substituted aryl iodides, and commercially available methyl 2-bromobenzoates, a variety of *meta*-substituted biaryls were synthesized in good to excellent yields (entries 2−10). We were also able to use methyl 2-bromo-3-thiophene carboxylate (entries 12 and 13) as well as methyl 4-bromobenzoate (entry 14) as reaction partners, albeit in moderate yields.

Our next focus was to seek out potential reductants and determine whether or not they contribute to the reductive arylation sequence. We quickly excluded norbornene as we found that catalytic amounts of norbornene could be used with comparable yields, implying that it is not consumed in the reductive process.[6] Next, we used deuterium labeled aryl iodide **4**[7] as a presumptive source of $CsDCO_3$ (Scheme 2) under the reaction conditions. We obtained the reduction product; however, analysis revealed no deuterium incorporation.

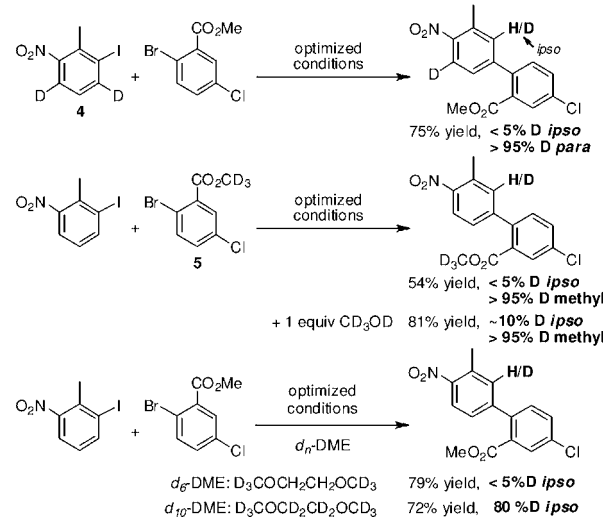
Table 1. Homo and Crossed Domino *ortho*-Arylation/Reduction



entry	R	R^1	product R^2	R^3	**3**	yield (%)[a]
1	CO_2Me	H	H	-	**3a**	100[b]
2	Me	NO_2	H	H	**3b**	68
3	Me	NO_2	H	OMe	**3c**	60
4	Me	NO_2	H	Cl	**3d**	95
5	Me	Cl	H	Cl	**3e**	74
6	Me	NHAc	H	Cl	**3f**	66
7	Me	CF_3	H	Cl	**3g**	87
8	Me	NHBoc	H	OMe	**3h**	56
9	Me	H	NO_2	Cl	**3i**	77
10	Me	H	F	Cl	**3j**	56
11					**3k**	61
			X			
12			NO_2		**3l**	38
13			F		**3m**	36
14					**3n**	33

[a] Isolated yield (%). [b] Using 2 equiv of aryl iodide with respect to norbornene, and no aryl bromide was added.

Scheme 2. Deuterium Labeling Experiments

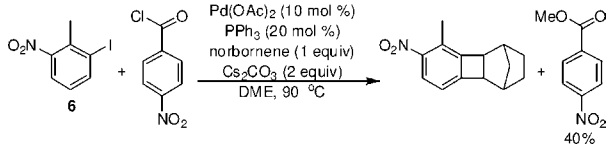


During the course of our studies, we observed the presence of methanol in ^{1}H NMR spectra of the crude reaction mixtures. The methanol formed may be derived either from decomposition of the ester or DME. We excluded decomposition of the ester by subjecting deuterated ester **5** to our reaction conditions and obtaining product with no detectable deuterium incorporation at the *ipso* position and no erosion of deuterium content in the ester. The higher concentration of this reaction (0.2 M with respect to aryl iodide) can account for the lower yield. We further determined that DME is the source of methanol through a trapping experiment. Replacing the bromobenzoate coupling partner with 4-nitrobenzoyl chloride (Scheme 3), we obtained methyl 4-nitrobenzoate in addition to a norbornene incorporation

(4) Catellani reported a homo *ortho*-arylation/reduction of aryl iodides using benzyl alcohol as a stoichiometric reductant. See: Deledda, S.; Motti, E.; Catellani, M. *Can. J. Chem.* **2005**, *83*, 741.

(5) Zhao, Y.-B.; Mariampillai, B.; Candito, D. A.; Laleu, B.; Li, M.; Lautens, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 1849.

Scheme 3. Methanol Trapping Experiment



product. Further control experiments determined that the nitrobenzoate is not formed in the absence of palladium catalyst. From these experiments, we can conclude that methanol is derived from DME under the reaction conditions.

Although our observation of methanol in crude spectra led us to believe that it is not consumed in the reductive process, a recent report of deuterium transfer by CD_3OD under palladium catalysis[8] prompted us to add it in the reaction with deuterated ester **5**. This substrate was chosen as the undeuterated ester was found to irreversibly exchange to the deuterated ester in the presence of CD_3OD under the reaction conditions. When 1 equiv of CD_3OD was added to the reaction of **5**, we obtained product with no more than 10% deuterium at the *ipso* position and believe that it is not a major contributor to the reductive pathway.

Finally, we synthesized two different isotopomers of DME: one with deuterium atoms on the methyl carbons (d_6-DME) and the other completely deuterated (d_{10}-DME). Under the optimized conditions, d_6-DME did not afford any observable *ipso* deuteration. Conversely, when d_{10}-DME was used, we observed 80% deuteration of the *ipso* carbon based upon both ^{1}H and ^{2}H NMR spectra. This result confirmed that the solvent was involved in the reduction of the terminal arylpalladium(II) species. Furthermore, it appears as though there is a preference for the metal catalyst to transfer the methylene hydrogen atoms from the solvent. Although partial hydride transfer has been previously reported using ethereal solvents such as 1,4-dioxane in the presence of palladium catalysts,[9] to the best of our knowledge, hydride transfer has not been observed with 1,2-dimethoxyethane. Furthermore, a preference for the abstraction of methylene versus methyl hydrogens in ethereal solvents under palladium catalysis has not been described.

Although we have determined the source of reducing hydrogens, the mechanism of hydride transfer and the formation of methanol remain unclear. Keay has proposed a β-hydride elimination pathway for 1,4-dioxane, which is plausible in the present system. We believe that the stoichiometry of the base is important to the reductive process, as using less than 2 equiv of Cs_2CO_3 leads to a drastic reduction in product yields. Further research is required to fully elucidate the reductive mechanism.

In summary, we have developed and studied a method for the synthesis of *meta*-substituted biaryls through a reductive *ortho*-arylation sequence. Through investigation of the reduction using deuterium-labeled reagents and solvents, we have determined that palladium-catalyzed decomposition of DME is responsible for the reduction of the terminal arylpalladium(II) species.

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Supporting Information Available: Experimental details and characterization data for compounds **3b**−**3n**, **5**, d_6-DME, and d_{10}-DME. This material is available free of charge via the Internet at http://pubs.acs.org.

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(6) Under the optimized conditions with 25 mol % norbornene, **3d** was obtained in 75% isolated yield. Norbornene was also observed in near quantitative amounts in crude ^{1}H NMR analyses.

(7) Martins, A.; Lautens, M. *Org. Lett.* **2008**, *10*, 5095.

(8) Wisily, A.; Nguyen, Y.; Fillion, E. *J. Am. Chem. Soc.* **2009**, *131*, 15606.

(9) Lau, S. Y. W.; Andersen, N. G.; Keay, B. A. *Org. Lett.* **2001**, *3*, 181. Up to 1:1 H:D ratios reported. Under our conditions, d_8-dioxane only afforded traces of product and did not incorporate deuterium.