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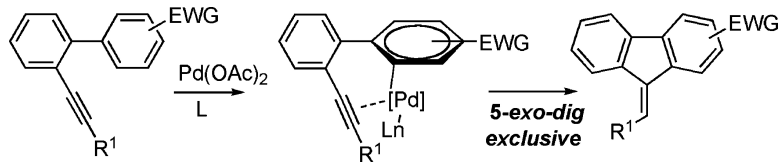

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Exclusive 5-*exo-dig* Hydroarylation of *o*-Alkynyl Biaryls Proceeding via C−H Activation Pathway

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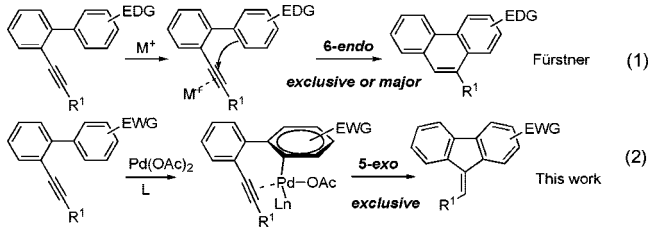
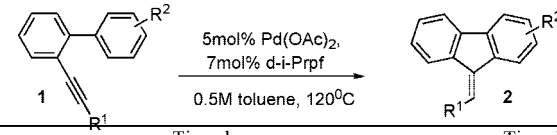
Intramolecular palladium-catalyzed hydroarylation of alkynes was first reported by Fujiwara in 2000.[1a−c] Shortly after, other transition-metal-[2,3] and Lewis acid-catalyzed[4] versions of this transformation emerged, and the method quickly became a powerful tool for the construction of carbo- and heterocycles. This transformation is most efficient with electron-rich aromatic rings, hence, not surprisingly, a Friedel–Crafts-type electrophilic aromatic substitution path has been generally accepted as the most probable mechanism for this reaction.[3,5] Thus, one of the representative examples reported by Fürstner[3b] shows that *o*-alkynyl biaryls possessing an electron-rich aryl ring in the presence of transition metals undergo a facile intramolecular hydroarylation reaction. Reaction proceeds via electrophilic activation of the triple bond followed by exclusive or predominant 6-*endo-dig*[6] carbocyclization, leading to the phenanthrene frameworks (eq 1). Herein, we wish to report the first example of the Pd-catalyzed exclusive 5-*exo-dig* hydroarylation of electron-neutral and electron-deficient *o*-alkynyl biaryls proceeding via a C−H activation path (eq 2).

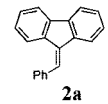
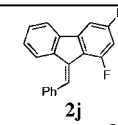
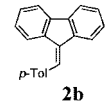
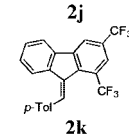
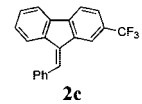
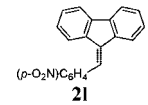
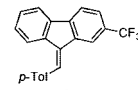
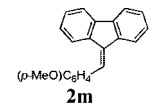
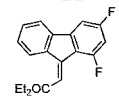
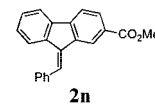
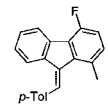
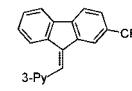
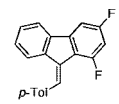
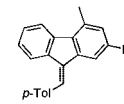
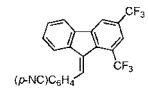
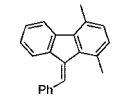
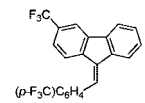
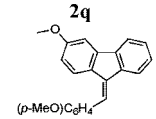


We turned our attention to the palladium-catalyzed intramolecular hydroarylation of alkynes, which proceeds under ligand-free acidic conditions and produces the 6-*endo-dig* cyclization products.[1,2] Although a C−H activation motif was initially proposed,[1] an electrophilic aromatic substitution path has been suggested later as the most probable path for this transformation.[3,5] We hypothesized that switching from acidic to neutral reaction conditions may affect the reaction mechanism. To this end, cyclization of *o*-alkynyl biaryls **1** in the presence of a palladium catalyst/phosphine ligand combination has been investigated. We were pleased to find that 2-(phenylethynyl)biphenyl (**1a**) in the presence of the $Pd(OAc)_2$/dppf system in toluene at 120 °C underwent smooth 5-*exo-dig* carbocyclization to produce fluorene **2a** in 70% GC yield! Moreover, switching to bulkier 1,1′-bis(diisopropylphosphino)ferrocene allowed us to obtain **2a** in nearly quantitative yield (Table 1, entry 1).

With these conditions in hand, the generality of the cyclization has been studied. It was found that a variety of *o*-alkynyl biaryls bearing electron-neutral, and even more surprisingly electron-deficient aryl rings, underwent highly effective 5-*exo-dig* carbocyclization to give 9-benzylidene-9*H*-fluorene derivatives **2a**−**2j** in good to excellent yields (Table 1). Various groups, such as F, NO_2, CO_2Me, and OMe, were perfectly tolerated under these reaction conditions. Importantly, in contrast to the previously reported intramolecular hydroarylation of alkynes,[1−5] *o*-alkynyl biaryls, possessing electron-deficient substituents (R^2 = F, CF_3, CO_2Me), underwent substantially faster cyclization compared to that for the *o*-alkynyl biaryls bearing electron-

Table 1. Pd-Catalyzed Hydroarylation of *o*-Alkynyl Biaryls[a]

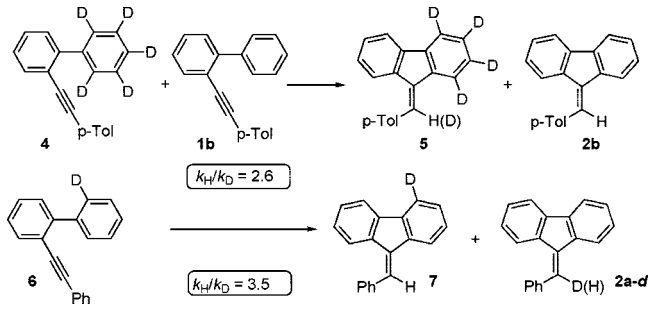


#	Product	Time, h Yield, %[b]	#	Product	Time, h Yield, %[b]
1	 **2a**	2.5 98	10	 **2j**	3.0 93
2	 **2b**	3.0 95	11	 **2k**	3.0 94
3	 **2c**	1.5 96	12	 **2l**	4.0 89
4	 **2d**	2.0 96	13	 **2m**	5.0 87
5	 **2e**	0.5 79	14	 **2n**	1.0 85
6	 **2f**	3.0 92	15	 **2o**	1.5 77
7	 **2g**	4.0 95	16	 **2p**	24 47
8	 **2h**	1.0 93	17	 **2q**	48 30
9	 **2i**	0.5 98	18	 **2r**	6.0 86

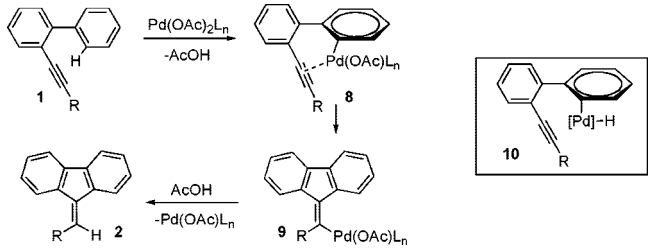
[a] Reaction conditions: 0.5 mmol of **1**, 0.025 mmol of $Pd(OAc)_2$, 0.035 mmol of 1,1′-bis(diisopropylphosphino)ferrocene, 1 mL of toluene, 120 °C. [b] Isolated yields.

10.1021/ja8006534 CCC: $40.75

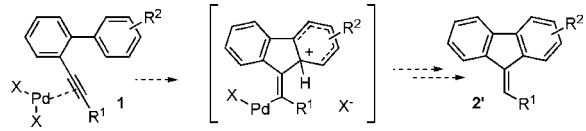
Scheme 1. Kinetic Isotope Effect Studies



Scheme 2. Proposed Mechanism



Scheme 3. Electrophilic Path for Cyclization of **1**



neutral aryl rings. Substrates with electron-deficient groups at the alkyne moiety (R^1) reacted slightly faster, though no significant effect of the nature of R^1 on the reaction yield has been observed (Table 1, entries 5, 7, 8, and 11). Remarkably, cyclizations of all compounds **1a**−**r** proceeded with high *cis*-selectivity, providing geometrically pure fluorenes **2a**−**r** (Table 1).[7]

In order to better understand this transformation, we performed kinetic isotope effect studies. Experiment demonstrated that this cyclization exhibits significant intermolecular (k_H/k_D = 2.6) and intramolecular (k_H/k_D = 3.5) hydrogen/deuterium kinetic isotope effect (Scheme 1).[8] These data are in a range of the isotope effects observed for the reactions proceeding via the Pd-catalyzed aromatic C−H activation pathways.[9,10] Accordingly, we envision that this reaction proceeds via *ortho*-palladation of intermediate **1** to give **8** (Scheme 2), which, upon migratory insertion to a triple bond, gives vinylpalladium species **9**. Protiodepalladation of **9** produces **2** and regenerates the catalyst. An alternative path may involve palladium hydride species **10**, which, via consecutive carbopalladation of the triple bond and reductive elimination, would furnish the reaction product. However, on the basis of the substantial loss of deuterium observed in the cyclization of **4**,[11] this pathway was considered to be less likely. Possible involvement of the Friedel–Crafts mechanism (Scheme 3) was ruled out based on the higher propensity of the electron-deficient alkynes toward this hydroarylation reaction, as well as on the high values of the kinetic isotope effects (Scheme 1).[12] The stereochemistry of the obtained products **2** also contradicts with the electrophilic pathway. Indeed, based on the literature reports,[1–5] Friedel–Crafts cyclization of **1** is expected to proceed in the *trans*-fashion to produce (*Z*)-fluorene **2′** (Scheme 3). In contrast, the Pd-catalyzed hydroarylation, described herein, produces fluorene **2**[13] with alternative geometry of the double bond apparently, via a *cis*-cyclization path (Table 1, Scheme 2).

In conclusion, we have demonstrated the first example of the palladium-catalyzed exclusive 5-*exo*-*dig* hydroarylation. This method allows for efficient cyclization of a variety of *o*-alkynyl biaryls possessing electron-neutral and electron-deficient aryl rings into the corresponding fluorenes. On the basis of the high efficiency of the cyclization of substrates bearing electron-deficient aryl rings, the observed high values of kinetic isotope effects, as well as on the exclusive *cis*-selectivity of cyclization, a mechanism involving the C−H activation motif has been proposed for this transformation.

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Note Added after ASAP Publication. Errors in the Supporting Information have been corrected on April 5, 2008.

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

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(6) In the single reported example, the Pt-catalyzed cyclization of *o*-biaryl alkynes, possessing an ester group at the triple bond, proceeds via 5-*exo*-*dig* mode. The geometry of the double bond of the obtained fluorene was not specified. See ref 3b.

(7) It was assumed that the geometry of all geometrically pure products was the same as that for **2e**,**f**, the geometry of which was confirmed by NOESY experiments. See Supporting Information for details.

(8) See Supporting Information for details.

(9) For a discussion on kinetic isotope effects in Pd-catalyzed C−H activation processes, see: (a) García-Cuadrado, D.; de Mendoza, P.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2007**, *129*, 6880. (b) Cárdenas, D. J.; Martín-Matute, B.; Echavarren, A. M. *J. Am. Chem. Soc.* **2006**, *128*, 5033. (c) Campeau, L.-C.; Parisien, M.; Jean, A.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 581. (d) Campeau, L.-C.; Parisien, M.; Leblanc, M.; Fagnou, K. *J. Am. Chem. Soc.* **2004**, *126*, 9186. (e) García-Cuadrado, D.; Braga, A. A.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2006**, *128*, 1066. (f) Xia, J.-B.; You, S.-L. *Organometallics* **2007**, *26*, 4869.

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(11) Cyclization of **4** produced **5** in 85% yield with 60% deuterium incorporated at the vinylic position.

(12) The inverse kinetic isotope effect (k_H/k_D = 0.64) was reported for the electrophilic cyclization mechanism. See ref 5b.

(13) Careful analysis of the reaction at the early stages indicated that the obtained stereoisomers of fluorenes **2** are the kinetic products of this cyclization.

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