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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-catalyzed⁴ 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).

(1)

(2)

We turned our attention to the palladium-catalyzed intramolecular hydroarylation of alkynes, which proceeds under ligandfree 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**

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

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, NO₂, CO₂Me, 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 (R² = F, CF₃, CO₂Me), underwent substantially faster cyclization compared to that for the *o*-alkynyl biaryls bearing electron-neutral aryl rings. Substrates with electron-deficient groups at the alkyne moiety (R¹) reacted slightly faster, though no significant effect of the nature of R¹ 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**. Protodepalladation 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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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.
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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.

Scheme 1. Kinetic Isotope Effect Studies

Scheme 2. Proposed Mechanism

Scheme 3. Electrophilic Path for Cyclization of 1

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

#	Product	Time, h	Yield, % ^b	#	Product	Time, h	Yield, % ^b
5		0.5	79	14		1.0	85
6		3.0	92	15		1.5	77
7		4.0	95	16		24	47
8		1.0	93	17		48	30

#	Product	Time, h	Yield, % ^b	#	Product	Time, h	Yield, % ^b
9		0.5	98	18		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.