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Palladium-Catalyzed Reactions of Cyclohexadienones: Regioselective Cyclizations Triggered by Alkyne Acetoxylation

Rodolfo Tello-Aburto and Andrew M. Harned*

Department of Chemistry, University of Minnesota, Minneapolis, Minnesota 55455

harned@umn.edu

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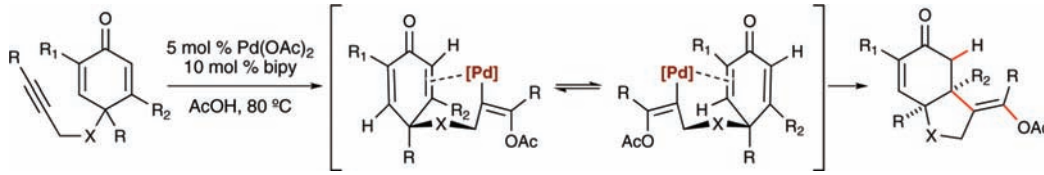
ABSTRACT



Regioselective cyclizations of alkyne-tethered cyclohexadienones can be accomplished under palladium catalysis. The cyclization involves an initial Pd-mediated acetoxylation of the alkyne, followed by migratory insertion and protonolysis of the resulting palladium enolate. The predictable regioselectivity of these atom-economical and stereoselective reactions is influenced by developing steric interactions during migratory insertion of a vinyl palladium intermediate.

As a class, cyclohexa-2,5-dienones have proven to be excellent motifs for natural product synthesis.[1,2] While several methodology studies have examined the reactivity of these compounds,[3] little work has been done exploring the use of these substrates in catalytic transformations other than hydrogenations.[4−7] There are several aspects of cyclohexadienones that make them particularly attractive substrates for catalytic processes. First, they can be synthesized in a modular fashion allowing for the facile tethering of various "reactive" partners (e.g., olefins, alkynes, aryl halides). Second, the electronics of the dienones allow for predictable outcomes of the reactions of interest. Third, by judicious substitution around the ring, one should be able to direct the reaction to a particular olefin based on either electronics or sterics. Finally, by tethering the reactive partner to the fully substituted carbon atom, stereoselective reactions can be realized through either substrate or reagent control. We

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(2) Recent examples: (a) Baxendale, I. R.; Ley, S. V.; Piutti, C. *Angew. Chem., Int. Ed.* **2002**, *41*, 2194–2197. (b) Lei, X.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2006**, *128*, 14790–14791. (c) Mejorado, L. H.; Pettus, T. R. R. *J. Am. Chem. Soc.* **2006**, *128*, 15625–15631. (d) You, Z.; Hoveyda, A. H.; Snapper, M. L. *Angew. Chem., Int. Ed.* **2009**, *48*, 547–550. (e) Wenderski, T. A.; Huang, S.; Pettus, T. R. R. *J. Org. Chem.* **2009**, *74*, 4104–4109.

(3) Selected examples: (a) Fringuelli, F.; Minuti, L.; Pizzo, F.; Taticchi, A.; Halls, T. D. J.; Wenkert, E. *J. Org. Chem.* **1983**, *48*, 1810–1813. (b) Wipf, P.; Kim, Y. *J. Am. Chem. Soc.* **1994**, *116*, 11678–11688. (c) Wang, J.; Pettus, L. H.; Pettus, T. R. R. *Tetrahedron Lett.* **2004**, *45*, 1793–1796. (d) Hoarau, C.; Pettus, T. R. R. *Org. Lett.* **2006**, *8*, 2843–2846. (e) Varin, M.; Chiaroni, A.; Lallemand, J.-Y.; Iorga, B.; Guillou, C. *J. Org. Chem.* **2007**, *72*, 6421–6426. (f) Clive, D. L. J.; Sunasee, R.; Chen, Z. *Org. Biomol. Chem.* **2008**, *6*, 2434–2441. (g) Merino, E.; Melo, R. P. A.; Ortega-Guerra, M.; Ribagorda, M.; Carreño, M. C. *J. Org. Chem.* **2009**, *74*, 2824–2831.

(4) For a hydrogenation example, see: Mejorado, L. H.; Hoarau, C.; Pettus, T. R. R. *Org. Lett.* **2004**, *6*, 1535–1538.

(5) Copper-catalyzed conjugate additions: (a) Takemoto, Y.; Kuraoka, S.; Hamaue, N.; Iwata, C. *Tetrahedron: Asymmetry* **1996**, *7*, 993–996. (b) Takemoto, Y.; Kuraoka, S.; Hamaue, N.; Aoe, K.; Hiramatsu, H.; Iwata, C. *Tetrahedron* **1996**, *52*, 14177–14188. (c) Imbos, R.; Brilman, M. H. G.; Pineschi, M.; Feringa, B. L. *Org. Lett.* **1999**, *1*, 623–625. (d) Imbos, R.; Minnaard, A. J.; Feringa, B. L. *Tetrahedron* **2001**, *57*, 2485–2489.

(6) Symmetry-breaking intramolecular Heck reaction: Imbos, R.; Minnaard, A. J.; Feringa, B. L. *J. Am. Chem. Soc.* **2002**, *124*, 184–185.

(7) Symmetry-breaking organocatalytic reactions: (a) Hayashi, Y.; Gotoh, H.; Tamura, T.; Yamaguchi, H.; Masui, R.; Shoji, M. *J. Am. Chem. Soc.* **2005**, *127*, 16028–16029. (b) Liu, Q.; Rovis, T. *J. Am. Chem. Soc.* **2006**, *128*, 2552–2553. (c) Vo, N. T.; Pace, R. D. M.; O'Hara, F.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 404–405.

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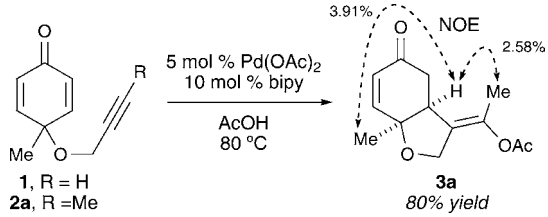
herein report our initial foray into the area of transition metal-catalyzed transformations of cyclohexadienones and that the regioselectivity of these reactions proceeds in a predictable manner.

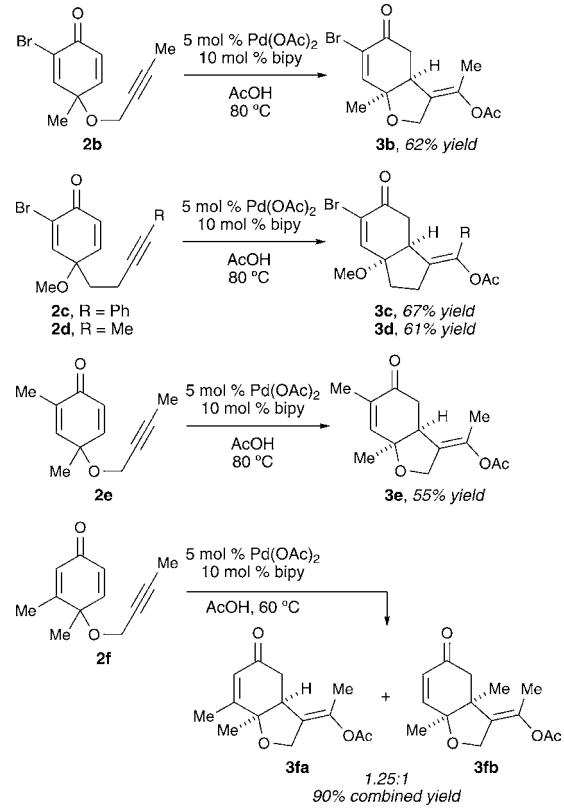
We hypothesized that cyclohexadienones with tethered alkynes would serve as excellent substrates for Pd-catalyzed cyclizations.[8] We began our investigation by heating **1** with 5 mol % $Pd(OAc)_2$ in AcOH, both with and without bipy as a ligand (Scheme 1). While these experiments resulted in complete consumption of starting material, low yields of unidentifiable reaction products were obtained. Believing that the terminal alkyne was responsible for the untoward reactivity, we constructed substrate **2a**. When this alkyne was treated with 5 mol % $Pd(OAc)_2$ in AcOH at 80 °C, the NMR and TLC were very messy. To our delight, when 10 mol % of bipy was used as a ligand, a remarkably clean NMR was obtained on the crude reaction mixture and compound **3a** was isolated in 80% yield.[9] Attempting to promote the reaction with Pd(dppb)$(OTf)_2$ only resulted in decomposition.[10]

Scheme 1. Initial Cyclization Attempts



Because the previously reported catalytic transformations all involved a symmetry-breaking event,[5−7] we felt it would be important for future reaction development to determine how the regioselectivity of the cyclization is affected by nonsymmetric substitution around the cyclohexadienone (Scheme 2). We were pleased to find that bromosubstituted dienone **2b** could be cyclized to give **3b** as a single regioisomer. This result could also be extended to the formation of carbocyclic products **3c** and **3d**. We were curious as to whether the regioselectivity observed with **2b**−**d** was due to electronics or sterics, so methyl-substituted substrates were examined. Interestingly, the product distribution appeared to be dependent on the position of the methyl group. In the case of an "*ortho*" methyl group,[11] only one cyclized product was observed. However, a "*meta*" methyl group resulted in a 1.25:1 mixture of regioisomeric products.

Scheme 2. Investigating Ring Substitution



Unfortunately, substrates with acetylenic esters or ketones could not be persuaded to cyclize. This was surprising considering other literature reports of Pd-catalyzed cyclative acetoxylations of propiolates.[8a,b,12] We were also unable to cyclize substrates containing an extra methylene unit in the tether. In both cases only products arising from addition of AcOH across the alkyne were observed.

We believe that these reactions proceed through a mechanism similar to that proposed by Lu and co-workers for the cyclization of enynes (Scheme 3).[8] Coordination of the Pd(II) catalyst to **2** will activate the alkyne for *trans*-acetoxypalladation, as shown in **4**. Vinyl palladium intermediate **5** then undergoes *syn*-migratory insertion into the less-substituted olefin of the cyclohexadienone, forming palladium enolate **6**.[13] Protonolysis affords **3** and regenerates the catalyst. The tolerance of the reaction to brominated substrates provides evidence that the palladium remains in the +2 oxidation state throughout the reaction.

(8) (a) Zhang, Q.; Lu, X. *J. Am. Chem. Soc.* **2000**, *122*, 7604–7605. (b) Zhang, Q.; Lu, X.; Han, X. *J. Org. Chem.* **2001**, *66*, 7676–7684. (c) Zhao, L.; Lu, X.; Xu, W. *J. Org. Chem.* **2005**, *70*, 4059–4063.

(9) Along with the isolated products, some reactions also yielded small amounts of an uncyclized product arising from Pd-catalyzed addition of AcOH across the alkyne as well as what appears to be the product of six membered ring formation. See Supporting Information for details.

(10) When **2a** was heated in the absence of $Pd(OAc)_2$, only starting material (TLC) was present after 12 h.

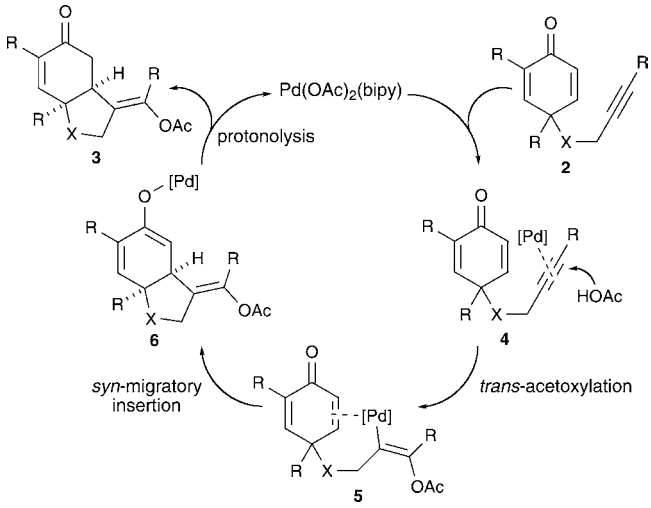
(11) We choose to refer to the substitution around the cyclohexadienone in the same manner as the phenolic precursor.

(12) (a) Welbes, L. L.; Lyons, T. W.; Cychosz, K. A.; Sanford, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 5836–5837. (b) Tong, X.; Beller, M.; Tse, M. K. *J. Am. Chem. Soc.* **2007**, *129*, 4906–4907. (c) Liu, H.; Yu, J.; Wang, L.; Tong, X. *Tetrahedron Lett.* **2008**, *49*, 6924–6928. (d) Tsujihara, T.; Takenaka, K.; Onitsuka, K.; Hatanaka, M.; Sasai, H. *J. Am. Chem. Soc.* **2009**, *131*, 3452–3453.

(13) Though it is still too early to come to a conclusion, at this time we prefer an O-bound Pd enolate, rather than a C-bound enolate. See: Keith, J. A.; Behenna, D. C.; Mohr, J. T.; Ma, S.; Marinescu, S. C.; Oxgaard, J.; Stoltz, B. M.; Goddard, W. A., III. *J. Am. Chem. Soc.* **2007**, *129*, 11876–11877.

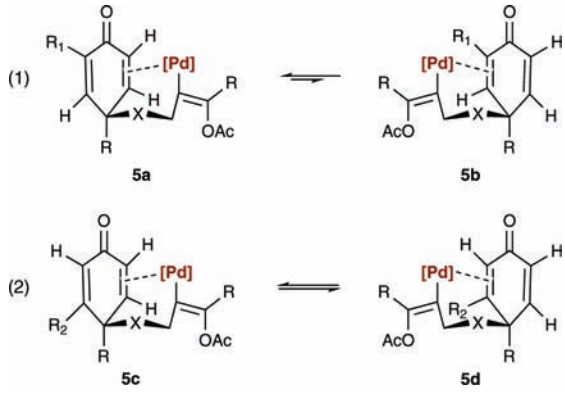
(14) While NOE analysis established the stereochemistry of the allylic alcohol contained in **7**, the unambiguous determination of the methyl ketone stereochemistry was not possible. Molecular modelling indicates that the diastereomer shown is the more stable one.

Scheme 3. Proposed Mechanism



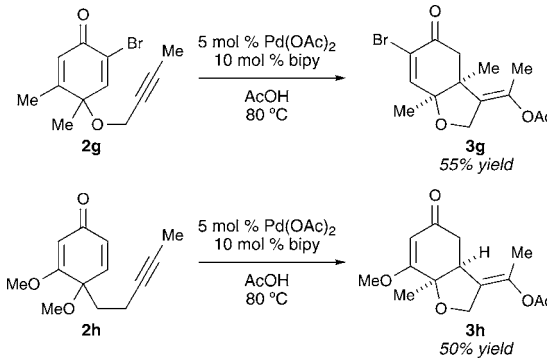
The product distributions observed with substrates **2e** and **2f** can be rationalized if one considers the possible reactive conformations of intermediate **5** (Scheme 4). In the case of cyclohexadienones with *ortho* substituents (eq 1) the vinyl Pd intermediate can sample conformations **5a** and **5b**, but will prefer to react via **5a** in order to avoid the developing steric interactions between R^1 and Pd. This allows for the selective formation of one regioisomeric product. On the other hand, meta-substituted cyclohexadienones (eq 2) will sample conformations **5c** and **5d**. In this case, the Pd center is less apt to feel the steric crowding afforded by R^2, thereby giving rise to a mixture of two regioisomeric products.

Scheme 4. Proposed Regioselectivity Model



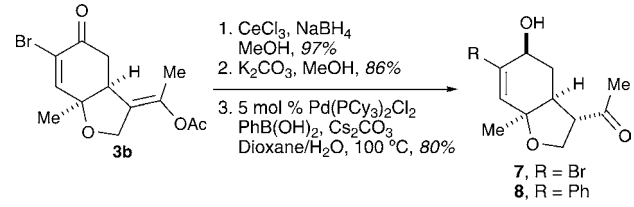
To further test this model we attempted the cyclizations of cyclohexadienones **2g** and **2h** (Scheme 5). Gratifyingly, the reactions proceeded to give compounds **3g** and **3h** as the only cyclization products. These examples show that a single substituent at the *ortho* position of a cyclohexadienone or an electron-donating substituent at the *meta* position is sufficient to shift the **5c**/**5d** equilibrium and generate a single regioisomer.

Scheme 5. Testing the Regioselectivity Model



Recognizing that the vinyl acetate generated in these reactions can function as a latent ketone, we designed a short sequence to further elaborate the bicyclic products (Scheme 6). Thus enone **3b** was cleanly reduced under Luche conditions and the methyl ketone was revealed to afford **7** as a single diastereomer.[14] The vinyl bromide was then converted to **8** via Suzuki coupling.

Scheme 6. Product Elaboration



In conclusion, we have shown that alkyne-tethered cyclohexadienones are competent substrates for Pd(II)-catalyzed cyclization reactions. While the regioselectivity of these reactions appears to be governed primarily by developing steric interactions between the enone and a vinyl Pd intermediate, electronic effects are very important as well. The knowledge gained about the regioselectivity of this atom-economical transformation will be quite useful for designing other transition metal-catalyzed reactions with cyclohexadienones. We are currently working to expand the scope of these Pd-catalyzed reactions and will report these results in due course.

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

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