Mechanistic Studies of Fujiwara Hydroarylation. C−H Activation versus Electrophilic Aromatic Substitution

Jon A. Tunge* and Lindsay N. Foresee

Department of Chemistry, University of Kansas, Lawrence, Kansas 66045

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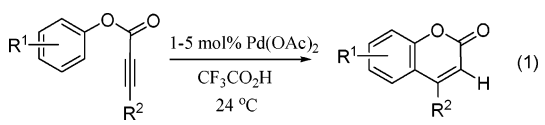
The addition of the C−H bonds of arenes across alkynes is catalyzed by $Pd(OAc)_2$ in CF_3CO_2H (Fujiwara hydroarylation). Previously it has been suggested that this transformation proceeds by C−H activation of the arene followed by *trans*-addition of a palladium−arene bond across an alkyne. We have investigated the kinetic isotope effects of intramolecular hydroarylation with deuterated arene substrates and found that catalytic hydroarylation exhibits an inverse KIE. The observed inverse isotope effect is not consistent with known KIEs for C−H activation by electrophilic palladium; thus it suggests that the reaction proceeds by electrophilic aromatic substitution.

Introduction

Over the past decade great strides have been made toward the identification of mechanisms for the activation of C−H bonds at transition metal centers.[1] In recent years, well-defined platinum complexes have been used in elegant studies of the mechanism of stoichiometric addition and elimination of C−H bonds at electrophilic metal centers.[2,3] In contrast, similar mechanistic studies on systems that result in catalytic C−H functionalization by electrophilic palladium or platinum complexes are rare.[4,5]

In 2000, Fujiwara reported the catalytic hydroarylation of alkenes and alkynes using $M(OAc)_2$ [M = Pd, Pt] in trifluoroacetic acid (eq 1).[6−8] Alkyne hydroarylation by $M(OAc)_2$ is characterized by *trans*-addition of aryl−hydrogen bonds to the alkyne, which gives rise to less stable *cis*-olefins in intermolecular hydroarylation. Moreover, the reactions occur at room temperature and functional groups on the arene such as halides, esters, and alcohols are tolerated. Thus, we thought that Fujiwara hydroarylation would provide an interesting system with which to study the mechanism of catalytic functionalization of C−H bonds by electrophilic palladium and platinum complexes. Although a cursory mechanistic study was done by the authors,[6b] a detailed understanding of the mechanism is important not only to understanding this system but also for the development of new C−H functionalization reactions. Herein we report that the observed isotope effects for catalytic alkyne hydroarylation are not consistent with a "C−H activation" mechanism; rather they suggest that hydroarylation occurs by electrophilic aromatic substitution.[9]



(1)

The proposed mechanism for hydroarylation involves four transformations: (i) alkyne coordination to Pd(II), (ii) activation of a C−H bond to form σ-arylpalladium intermediate **B**, (iii) *trans*-insertion of an alkyne into a

* Corresponding author. E-mail: tunge@ku.edu.

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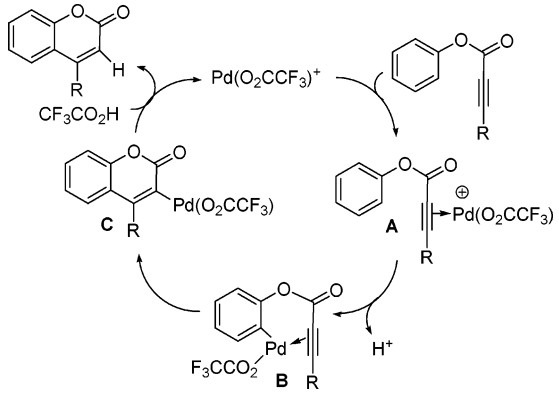
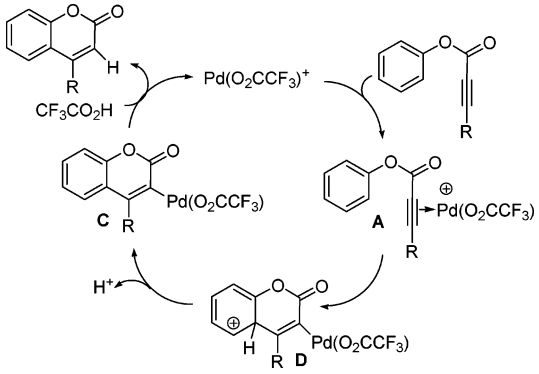
Scheme 1. Hydroarylation by C−H Activation



Scheme 2. Hydroarylation by EAS



Pd−aryl bond giving intermediate **C**, and (iv) protonolysis of the resulting Pd−vinyl complex (Scheme 1). However, the proposed mechanism was suggested on the basis of few experimental results.[6a]

In addition to the C−H activation mechanism, another mechanism is consistent with the current experimental results, including the observed regio- and stereochemistry (Scheme 2).[6c,e] The electrophilic palladium catalyst could initiate the reaction by coordination to the alkyne.[10] The resulting activated alkyne could undergo nucleophilic attack by an arene to form Wheland intermediate **D**, which would provide vinylpalladium complex **C** upon proton transfer. Finally, protic cleavage of the vinyl−palladium bond could liberate product and regenerate the catalyst. Such electrophilic activation of an alkyne toward aromatic substitution has precedent.[7,11,12]

The study of the mechanism of Fujiwara hydroarylation under the actual reaction conditions presents several difficulties. Primarily, the isolation and study of intermediates in the reaction is prohibitively difficult since catalysis occurs in the absence of stabilizing ligands.[13] Despite this difficulty, strong indirect evidence for the intermediacy of vinyl palladium intermediate **C** was provided by product studies of Fujiwara;[6a−c] thus both mechanisms focus on formation of this intermediate. We reasoned that the two mechanisms for the formation of **C** are distinguished by their expected kinetic isotope effects resulting from deuteration of the *ortho*-arene positions. Simply, if the C−H activation mechanism applies, one would expect a normal primary isotope effect for breaking the C−X (X = H, D) bond.[14,15] However, if electrophilic aromatic substitution is involved, then formation of the Wheland intermediate **D** will exhibit, at most, a secondary isotope effect.[16] Moreover, one would expect the steric crowding at the labeled carbon in the transition state for C−C bond formation to result in an inverse isotope effect.[17]

Fujiwara reported that attempts to measure the isotope effect of the hydroarylation were thwarted by rapid H/D exchange of mesitylene with trifluoroacetic acid solvent.[6b] We reasoned that the observed H/D exchange could be attributed to an uncatalyzed protonation−deprotonation since electron-rich arenes undergo rapid H/D exchange with CF_3CO_2H.[18] Thus, a less electron-rich aromatic could allow measurement of the kinetic isotope effect. Furthermore, intramolecular hydroarylation was chosen for investigation to increase the likelihood that hydroarylation is faster than H/D exchange of the arene hydrogens with solvent.

Experimental Results

H/D Exchange Is Slow. 4-*tert*-Butylphenyl-3-phenylpropiolate (**1**) was chosen as a substrate for mechanistic studies because its cyclization proceeds with minimal byproducts and it has several spectroscopic handles. To gauge the rate of H/D exchange with solvent, we prepared 4-*tert*-butylphenyl acetate (**3**) as an electronically similar model compound that cannot undergo cyclization. Dissolving **3** (0.19 M) in CF_3CO_2D containing 25 mol % $Pd(OAc)_2$ resulted in <10% H/D exchange over a period of 24 h (eq 3). Similarly, treatment of **3** with 1 equiv of $Pd(OAc)_2$ in CF_3CO_2D did not result in any appreciable reaction (by ^1H NMR spectroscopy) until the mixture was

(8) Transformations of C−H bonds with Pt/Pd in CF_3CO_2H: (a) Clark, F. R. S.; Norman, R. O. C.; Thomas, C. B. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1289−1294. (b) Sen, A.; Gretz, E.; Oliver, T. F.; Jiang, Z. *New J. Chem*. **1989**, *13*, 755−760. (c) Kao, L.-C.; Hutson, A. C.; Sen, A. *J. Am. Chem. Soc*. **1991**, *113*, 700−701. (d) White, S.; Bennett, B. L.; Roddick, D. M. *Organometallics* **1999**, *18*, 2536−2542. Muehlhofer, M.; Strassner, T.; Herrmann, W. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1745−1747.

(9) We use the term C−H activation as a generic term encompassing all mechanisms by which a C−H bond is transformed into a C−M bond.

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(14) (a) Jones, W. D. *Acc. Chem. Res*. **2003**, *36*, 140−146. (b) Churchill, D. G.; Janak, K. E.; Wittenberg, J. S.; Parkin, G. *J. Am. Chem. Soc*. **2003**, *125*, 1403−1420.

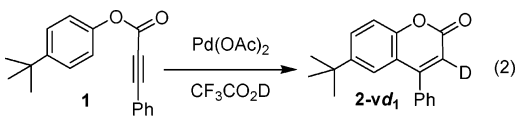
(15) For examples of palladation of arenes by $Pd(OAc)_2$ see: (a) Gretz, E.; Oliver, T. F.; Sen, A. *J. Am. Chem. Soc.* **1987**, *109*, 8109−8112 [k_H/k_D = 5.0(5)]. (b) Boele, M. D. K.; van Strijdonck, G. P. F.; de Vries, A. H. M.; Kamer, P. C. J.; de Vries, J. G.; van Leeuwen, P. W. N. M. *J. Am. Chem. Soc*. **2002**, *124*, 1586−1587 [k_H/k_D = 3]. (c) Shue, R. S. *J. Am. Chem. Soc*. **1971**, *93*, 7116−7117 [k_H/k_D = 5.0(4)]. (d) Stock, L. M.; Tse, K.; Vorvick, L. J.; Walstrum, S. A. *J. Org. Chem*. **1981**, *46*, 1759−1760 [k_H/k_D = 3.5]. (e) Hennessey, E. J.; Buchwald, S. L. *J. Am. Chem. Soc*. **2003**, *125*, 1586−1587 [k_H/k_D = 4]. (f) Peters, R. G.; White, S.; Roddick, D. M. *Organometallics* **1998**, *17*, 4493−4499 [k_H/k_D = 3.3-(2)].

(16) Electrophilic aromatic substitution by carbon electrophiles does not generally exhibit a primary isotope effect because proton transfer from the Wheland intermediate **D** is fast. Taylor, R. *Electrophilic Aromatic Substitution*; John Wiley & Sons: New York, 1990.

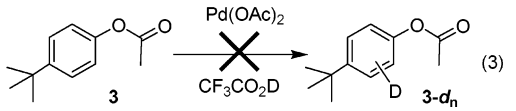
(17) For a more complete analysis of the factors that effect secondary isotope effects in electrophilic aromatic substitution see: Olah, G. A.; Kuhn, S. J.; Flood, S. H. *J. Am. Chem. Soc*. **1962**, *84*, 1688−1695.

(18) Mesitylene is protonated >10^7 times faster than benzene. (a) Lauer, W. M.; Watson, G. W.; Stedman, G. *J. Am. Chem. Soc.* **1958**, *80*, 6433−6438. (b) Lauer, W. M.; Stedman, G. *J. Am. Chem. Soc*. **1958**, *80*, 6439−6441.

heated to 50 °C. Heating this mixture overnight resulted in significant decomposition and the formation of a Pd^0 mirror. The remaining starting material, which made up approximately 50% of the mixture, was only ca. 20% deuterated. The absence of an observable metalation product or appreciable deuterium incorporation into **3** under the conditions for catalysis indicates that it is unlikely that **3** undergoes C−H activation at 25 °C.



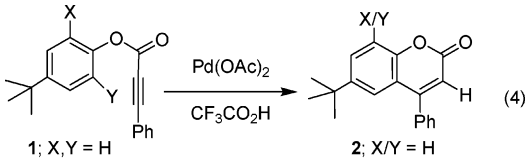
(2)



(3)

Encouraged by the lack of H/D exchange in **3**, we prepared aryl alkynoate **1** and performed its cyclization over 1 h at 25 °C using 5 mol % $Pd(OAc)_2$ in CF_3CO_2D. Consistent with Fujiwara's demonstration that the vinyl proton/deuteron originates from the solvent,[6b] ^1H NMR spectroscopy showed that the vinyl position was 94% deuterated (eq 2). There was no deuterium incorporation into any other site in the product. Thus, if formation of an arylpalladium complex is occurring, it is irreversible. In addition, careful scrutiny of the reaction by ^1H NMR spectroscopy did not reveal the buildup of any reaction intermediates. The cyclization is kinetically well-behaved, and clean first-order decay of the substrate is observed to $>3t_{1/2}$. Furthermore, reactions conducted at different $Pd(OAc)_2$ concentrations indicate that the reaction is first-order in $Pd(OAc)_2$.[19]

Next, we designed three experiments to investigate the kinetic isotope effect of *o*-deuteration of **1** (eq 4). Specific investigations include the direct rate comparison of the catalytic cyclization of isotopomers (**1** vs **1-*d*$_2$**), intermolecular competition between cyclization of isotopomers (**1** vs **1-*d*$_2$**), and intramolecular competition between the isotopically differentiated sites in **1-*d*$_1$**.



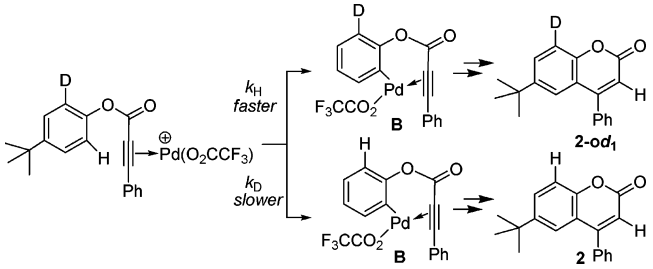
(4)

Intermolecular Isotope Effects. The rate of a reaction will be affected by isotopic substitution of D for H if C−H/C−D bond breaking is involved in the rate-limiting step. Thus, the rates of cyclization of **1** versus **1-*d*$_2$** were compared to determine if C−H/C−D bond breaking is involved in the rate-limiting step of hydroarylation. Specifically, the observed first-order rate constants for disappearance of **1** and **1-*d*$_2$** with 1.82 mM $Pd(OAc)_2$ (3 mol %) were determined by monitoring the decay of starting material and growth of product by ^1H NMR spectroscopy in CF_3CO_2D at 25 °C. The rate constants for cyclization were found to be $1.3(1) \times 10^{-3}$ s^{-1} for **1** and $1.4(1) \times 10^{-3}$ s^{-1} for **1-*d*$_2$**.

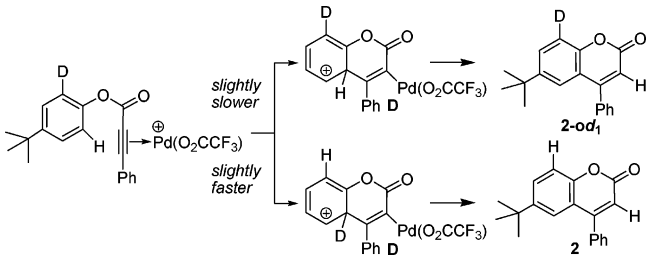
Similarly, when a 1:1 mixture of **1** and **1-*d*$_2$** was treated with catalytic $Pd(OAc)_2$ in CF_3CO_2D, the ratio of **1**:**1-*d*$_2$** remained constant throughout the reaction, indicating that the two isotopomers are converted to product at the same rate.[19] The lack of primary isotope effect in these intermolecular isotope effect experiments clearly indicates that the C−H/C−D bond breaking is not involved in the rate-limiting step of hydroarylation.

(19) See Supporting Information for details.

Scheme 3



Scheme 4



Intramolecular Isotope Effects. Since C−H bond breaking is not involved in the rate-limiting step for catalytic hydroarylation, the preference for reaction with a C−H versus a C−D bond cannot be determined by rate measurements. However, if the arene is selectively *ortho*-monodeuterated, then the substrate will be able to partition between reaction at the C−D bond and reaction at the C−H bond (Scheme 3). In such a case, the isotope effect will be evident from the level of deuterium incorporation in the product. Thus, if hydroarylation occurs by a C−H activation mechanism, the cyclization of **1-*d*$_1$** will reveal a primary isotope effect and the product is expected to have <33% *ortho*-hydrogen incorporation (**2-o*d*$_1$**:**2** > 2).[20]

Alternatively, if hydroarylation follows an electrophilic aromatic substitution pathway, then the C−H/C−D bond is not broken in the product-determining cyclization step (Scheme 4). Therefore, such a mechanism will not show a primary isotope effect and the level of deuterium incorporation in the product should be near 50% (neglecting a secondary isotope effect). In analogy with other reactions that transform an isotopically labeled sp^2-hybridized carbon to an sp^3-hybridized center, a secondary isotope effect will slightly favor C−C bond formation at the deuterated carbon (inverse isotope effect; **2-o*d*$_1$**:**2** ≤ 1).[17,21]

Subjecting **1-*d*$_1$** to the conditions of the Fujiwara cyclization in CF_3CO_2H resulted in a product that was partially deuterated at C8 (δ 7.35 ppm, Figure 1). Using the C5 proton (δ 7.52 ppm) as an internal standard, the C8 position was determined to be 55% protio, indicating a small *inverse* isotope effect of 0.82(9). The deuterated compound is also evidenced by the new doublet for the C7 proton at δ 7.73 ppm that results from loss of ^3J coupling with the adjacent deuterated center. To alleviate concern that the C8−H/D ratio might be artificially high due to H/D exchange with solvent, the same reaction was run in CF_3CO_2D. The C8 position of the product obtained from this reaction was 61% protio, indicating a k_H/k_D of 0.64(8).[22] This

(20) Zhong, H. A.; Labinger, J. A.; Bercaw, J. E. *J. Am. Chem. Soc.* **2002**, *124*, 1378−1399.

(21) For examples of electrophilic aromatic substitutions that exhibit inverse KIEs see: (a) Nakane, R.; Kurihara, O.; Takematsu, A. *J. Org. Chem.* **1971**, *19*, 2753−2756. (b) Olah, G. A.; Kuhn, S. J.; Flood, S. H. *J. Am. Chem. Soc.* **1961**, *83*, 4571−4580. (c) Szele, I. *Helv. Chim. Acta* **1981**, *64*, 2733−2737. (d) Lewandowicz, A.; Jemielity, J.; Kanska, M.; Zon, J.; Paneth, P. *Arch. Biochem. Biophys.* **1999**, *370*, 216−221.

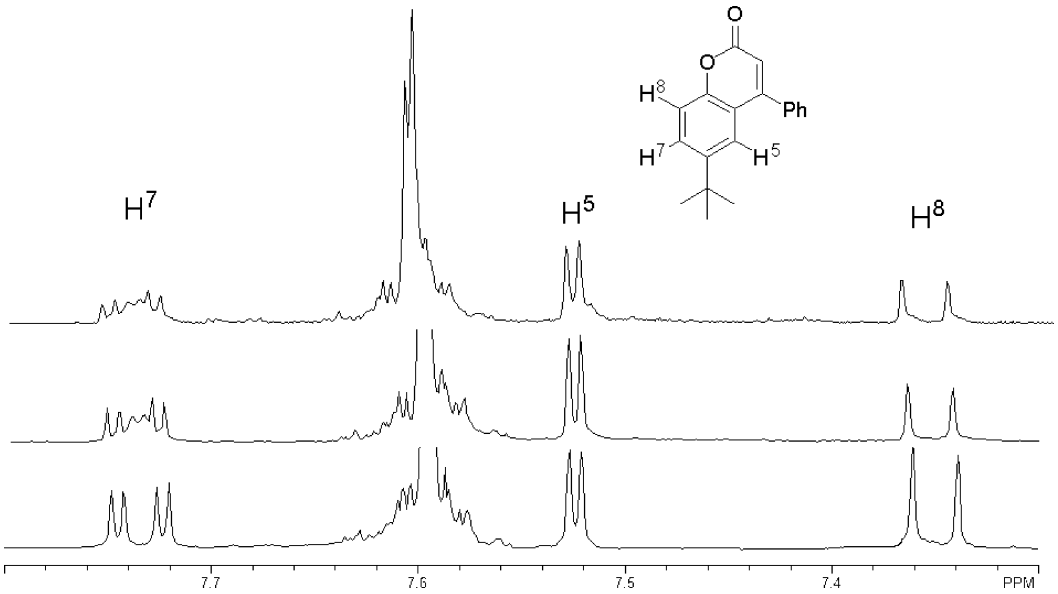


Figure 1. ^{1}H NMR spectra of **2** prepared from cyclization of **1** with $Pd(OAc)_2$ (bottom), **1-*d*$_1$** with $Pd(OAc)_2$ (middle), and **1-*d*$_1$** with $(BBBPy)Pt(O_2CCF_3)_2$ (top).

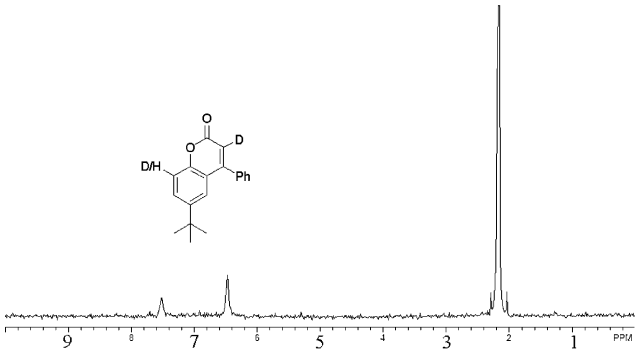


Figure 2. ^{2}H NMR spectrum of **2** prepared from **1-*d*$_1$** in CF_3CO_2D (referenced to acetone-d_6).

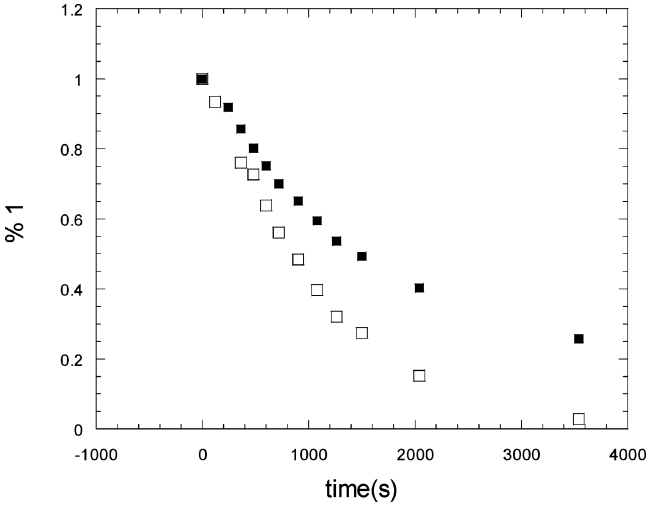


Figure 3. Normalized decay of **1** in CF_3CO_2H (□) and CF_3CO_2D (■).

experiment confirms earlier results that suggested that exchange of solvent protons with the arene hydrogens is slow. In addition to deuterium incorporation at the C8 position, the vinyl position (C3) was 90−94% deuterated when reactions were run in CF_3CO_2D. ^{2}H NMR spectroscopy confirmed that the two positions contained deuterium and the ratio measured by ^{2}H NMR was the same as that expected on the basis of the ^{1}H NMR spectrum (Figure 2).

Next, the cyclization of **1** was conducted with (4,4′-di-*tert*-butyl-2,2′-bipyridyl)$PtMe_2$ [$(BBBPy)PtMe_2$], which should form $(BBBPy)Pt(O_2CCF_3)_2$ in situ.[23] Importantly, monitoring the progress of the $(BBBPy)PtMe_2$-catalyzed cyclization of **1** by ^{1}H NMR spectroscopy shows that the bipyridyl ligand remains bound throughout the reaction.[24] Inverse isotope effects of 0.64(8) and 0.75(8) were observed for the cyclizations of **1-*d*$_1$** in CF_3CO_2D and CF_3CO_2H, respectively. Thus, palladium and platinum complexes provide similar isotope effects, suggesting they catalyze the hydroarylation by similar mechanisms.

Solvent Isotope Effect. Finally, it has been proposed that protic cleavage of the palladium vinyl intermediate (**C**) is rate-limiting.[6b] To assess this possibility, the cyclization of **1** was run in both CF_3CO_2H and CF_3CO_2D, and the rates of the reaction were directly compared. Time-dependent data were gathered by rapidly quenching aliquots of the two reaction mixtures with K_2CO_3/CH_2Cl_2 at set time intervals. These mixtures were filtered and analyzed by GC (Figure 3). The fact that the $t = 0$ aliquot showed no reaction confirmed that the quench procedure was effective. Importantly, no peaks other than **1** and product **2** are observed, and the GC data fit well to a first-order decay, with the reaction in CF_3CO_2H proceeding 1.7(2) times faster than the reaction in CF_3CO_2D. This result is consistent with rate-limiting protonolysis of the palladium−carbon bond present in intermediate **C**.

Discussion

Although catalyst speciation was not directly addressed by our experiments, it is known that $Pd(OAc)_2$ reacts rapidly with CF_3CO_2H to form $(CF_3CO_2)_2Pd(HO_2CCF_3)_2$.[25] In analogy with Chen's observation of $(diimine)Pt(O_2CCH_3)(HO_2CCH_3)^+$ in acetic acid,[5] the much stronger acid CF_3CO_2H might be expected to activate $(CF_3CO_2)_2Pd(HO_2CCF_3)_2$ by protonation, resulting in a

(22) The higher proton content in reactions run in CF_3CO_2D was reproduced three times.

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(24) In reactions run with $(BBBPy)Pd(OAc)_2$, $BBBPyH^+$ is observed to form at a rate similar to the rate of cyclization.

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Table 1. Comparison of Isotope Effects for Arene Metalation and Electrophilic Substitution

reaction	conditions	KIE	ref
Fujiwara hydroarylation	$Pd(OAc)_2$ CF_3CO_2H	0.82−0.64	this work
Fujiwara hydroarylation	(bipyridyl)$PtMe_2$ CF_3CO_2H	0.75−0.64	this work
trifluoroacetoxylation of toluene	$Pd(OAc)_2$ CF_3CO_2H	5.0(5)	15a
olefin arylation	$Pd(OAc)_2$ CH_3CO_2H	3, 5.0(4)	15b, 15c
C−H activation of benzene	(diimine)$PdMe^+$ CF_3CH_2OH	1.8−5.9	2h, 30
enolate arylation	RPdCl in toluene	4	15e
Friedel−Crafts alkylation	C_6H_6 + *i*-PrF/BF_3 hexane	0.92	21a
arene nitration	toluene + NO_2^+	0.85	21b
arene protonation	$C_6H_5SiMe_3$ + $HClO_4$	0.79(19)	21c

cationic complex $(CF_3CO_2)Pd(HO_2CCF_3)_3^+$.[26] Regardless of the nature of the active catalyst, the reaction kinetics allow us to write the empirical rate law for catalysis as $-d[\mathbf{1}]/dt = +d[\mathbf{2}]/dt = k_{obs}[Pd(OAc)_2][\mathbf{1}]$, where k_{obs} = 1.1(3) M^{-1} s^{-1}. While we could not vary the acid concentration at a constant solvent polarity, the presence of the acid in the rate law is required if protic cleavage of the palladium−vinyl bond is rate-limiting.

The major issue that this article addresses is whether the mechanism of the intramolecular hydroarylation is "C−H activation" or electrophilic aromatic substitution. The experimental facts are as follows: (1) *trans*-addition to the alkyne is observed even in intermolecular hydroarylation, (2) a simple aryl acetate does not undergo significant C−H activation over 24 h at room temperature, and (3) Fujiwara hydroarylation is characterized by an inverse KIE of 0.64−0.82.

The proposed C−H activation mechanism is intriguing since it requires an unusual *trans*-addition of a Pd−Ar bond across an alkyne. While there are a select few examples of net *trans*-addition of M−X bonds to alkynes,[27] Pd−Ar and Pt−Ar complexes are known to prefer *cis*-addition to alkynes.[28] On the other hand, electrophilic activation of alkynes toward nucleophilic attack occurs with a preference for *trans*-addition.[10,29] Thus, the stereochemistry of hydroarylation is more consistent with an electrophilic aromatic substitution mechanism.

Importantly, the isotope effects observed in the cyclization of **1** are not in agreement with the isotope effects observed for C−H activations by similar palladium and platinum compounds, which fall in the range of 2−5 (Table 1).[15] For example, the intermolecular isotope effect for trifluoroacetoxylation of toluene by $Pd(OAc)_2$ in CF_3CO_2H is 5.0(5), and directed C−H activation of *p*-methyl acetanilide by $Pd(OAc)_2$ in CH_3CO_2H has an isotope effect of 3.[15a,b] Likewise, rate-limiting C−H activation of benzene by a cationic (diimine)$Pd(H_2O)CH_3^+$ complex has an isotope effect of 4.1(5).[30] It is also known that electrophilic mercuration of chlorobenzene by $Hg(O_2CCF_3)_2$ shows a primary isotope effect of 3.9(1).[31] Thus it appears that, regardless of mechanism, electrophilic metalation reactions are characterized by significant primary isotope effects.[32] While we are unaware of any electrophilic palladation or platination reactions that have a KIE of <1.6, there remain several stringent conditions where C−H activation might not show a primary isotope effect. Nevertheless, the failure to observe C−H activation in a model aryl ester, the exclusive observation of primary isotope effects in related electrophilic palladations and platinations, and the preference for *cis*-aryl palladation of alkynes argue against a C−H activation mechanism.

If, on the other hand, the mechanism involves electrophilic aromatic substitution by a carbon electrophile, then formation of the Wheland intermediate **D** is slower than deprotonation of **D**,[16] and the expected intermolecular isotope effect (ca. 1) is in agreement with those observed experimentally for Fujiwara hydroarylation (Table 1). In cases where electrophilic aromatic substitutions exhibit inverse isotope effects, the KIE is readily explained in terms of increasing steric crowding at the labeled carbon in the transition state for C−C bond formation. Such "tight" transition states favor reaction at the deuterated carbon.[17,33]

In conclusion, Fujiwara hydroarylation provides a unique system to study the mechanism of C−H bond functionalization since the C−H functionalization (dependent on arene deuteration) and protic cleavage steps (dependent on solvent deuteration) are isotopically isolated events. Ultimately, application of Occam's razor to the available data leaves electrophilic aromatic substitution as the simplest plausible mechanism.

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

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