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Rh Catalyzed C−H Activation and Oxidative Olefination without Chelate Assistance: On the Reactivity of Bromoarenes

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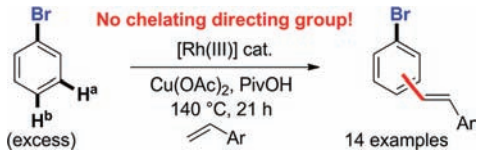
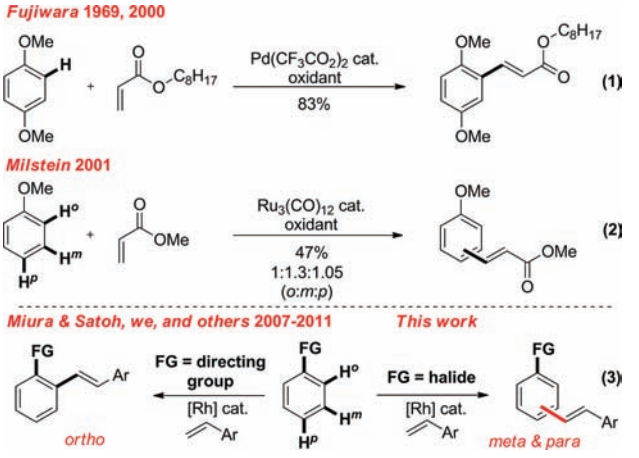
ABSTRACT



A Rh catalyzed, no-chelate-assisted C−H activation/oxidative olefination reaction of bromoarenes has been discovered, in which the latter ones seem to act as a substrate, terminal oxidant, *and* catalyst modifier.

Since its first introduction in 1969 by Fujiwara and Moritani,[1] the Pd catalyzed C−H oxidative olefination of arenes has received little attention compared to the more established Mizoroki−Heck reaction.[2] However in the past decade or so, the field of C−H activation mediated cross-coupling chemistry has considerably expanded.[3] These reactions are highly useful because they obviate the else wise required preactivation steps, leading to generally cheaper and greener synthetic methods. Mostly Pd,[4] Ru,[5] and lately Rh[6] are found to be efficient catalysts in these C−H activation processes. However, the use of a proximal chelate-assisting directing group is almost always required for activity and selectivity, a serious limitation of their synthetic utility. In this respect, the topography of the substrate is crucial, as the proximal directing group must possess the proper bonding strength and alignment toward the targeted C−H bond.



We and others have recently found that a number of functional/directing groups were efficient for the Rh catalyzed oxidative *ortho* olefination reaction, including phenylpyrazoles,[6b] acetanilides,[6d] benzamides, and phenones.[6e]

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[‡] The presented research was carried out at the WWU Münster; current address of F.P.: TU Kaiserslautern.

(1) (a) Fujiwara, Y.; Moritani, I.; Danno, S.; Asano, R.; Teranishi, S. *J. Am. Chem. Soc.* **1969**, *91*, 7166. For other selected references, see: (b) Jia, C.; Piao, D.; Oyamada, J.; Lu, W.; Kitamura, T.; Fujiwara, Y. *Science* **2000**, *287*, 1992. (c) Jia, C.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res.* **2001**, *34*, 633.

(2) For recent reviews on the Mizoroki−Heck reaction: (a) Bräse, S.; de Meijere, A. In *Metal-Catalyzed Cross-Coupling Reactions*; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: New York, 2004; p 217. (b) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4442.

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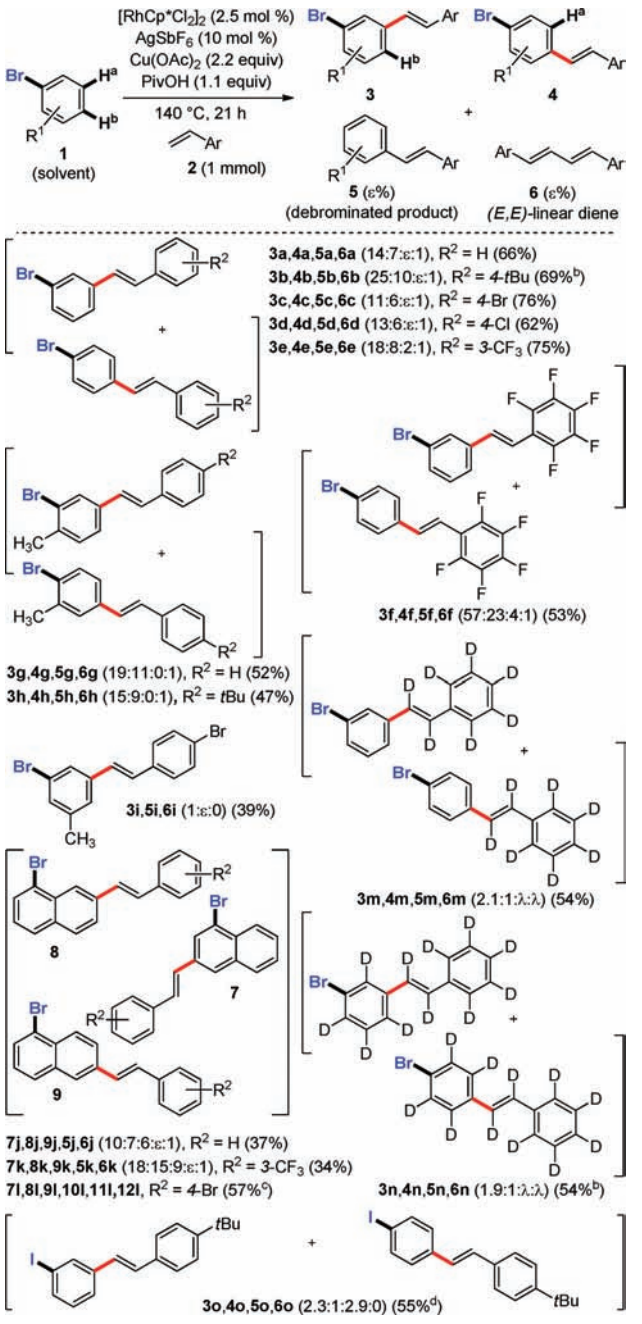
In contrast, only a few no-chelate assisted cases exist, and these are limited to activated C−H positions of some specific heterocyclic structures.[7]

The pioneering work of Fujiwara (eq 1),[1] Milstein (eq 2),[8] and others[9] offer promising leads for these challenges, although so far they are typically limited to electron-rich arenes and usually activated acrylate derivatives. Herein we wish to report the particular reactivity of bromoarenes for the no-chelate assisted C−H activation and oxidative olefination with styrenes (eq 3 and Scheme 1).

Scheme 1. Oxidative Olefination of Bromoarenes[a]



[a] Isolated yields, run on a 1 mmol scale; the bromoarene (5 mL) is engaged neat. $\varepsilon < 5\%$. λ: not determined. *Ortho*-regioisomers typically account for less than 1%; in the cases of **3i** and **7j**,**k**, they account for less than 5%. [b]Reaction time: 48 h. [c]In the case of **7l**, at least six of the seven possible regioisomers were found. [d]55% isolated yield, which is a mixture of 0.29 mmol of **3o**/**4o** and 0.26 mmol of **5o**.

While originally investigating the prospective potential of Rh catalysts for the C(sp^3)−H bond activation of some pivalic derivatives, we were surprised to discover that the

(3) For recent reviews on C−H activation, see: (a) Wencel-Delord, J.; Dröge, T.; Liu, F.; Glorius, F. *Chem. Soc. Rev.* **2011**, *40*, 4740. (b) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215. (c) Satoh, T.; Miura, M. *Chem.—Eur. J.* **2010**, *16*, 11212. (d) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (e) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624. (f) Xu, L.-M.; Yang, Z.; Shi, Z.-J. *Chem. Soc. Rev.* **2010**, *39*, 712. (g) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Commun.* **2010**, *46*, 677. (h) Li, C.-J. *Acc. Chem. Res.* **2009**, *42*, 335. (i) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 9792. (j) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094. (k) Giri, R.; Shi, B.-F.; Engle, K. M.; Maugel, N.; Yu, J.-Q. *Chem. Soc. Rev.* **2009**, *38*, 3242. (l) Li, B.-J.; Yang, S.-D.; Shi, Z.-J. *Synlett* **2008**, 949. (m) Kakiuchi, F.; Kochi, T. *Synthesis* **2008**, 3013. (n) Satoh, T.; Miura, M. *Top. Organomet. Chem.* **2008**, *24*, 61. (o) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174.

(4) For selected (chelate assisted) Pd catalyzed examples, see: (a) Cai, G.; Fu, Y.; Li, Y.; Wan, X.; Shi, Z. *J. Am. Chem. Soc.* **2007**, *129*, 7666. (b) Cho, S. H.; Hwang, S. J.; Chang, S. *J. Am. Chem. Soc.* **2008**, *130*, 9254. (c) Garcia-Rubia, A.; Arrayas, R. G.; Carretero, J. C. *Angew. Chem., Int. Ed.* **2009**, *48*, 6511. (d) Zhang, H.; Ferreira, E. M.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 6144. (e) Würtz, S.; Rakshit, S.; Neumann, J. J.; Dröge, T.; Glorius, F. *Angew. Chem., Int. Ed.* **2008**, *47*, 7230. (f) 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. See also: (g) Li, J.-J.; Mei, T.-S.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2008**, *47*, 6452. (h) Wang, D.-H.; Engle, K. M.; Shi, B.-F.; Yu, J.-Q. *Science* **2010**, *327*, 315. (i) Shi, B.-F.; Zhang, Y.-H.; Lam, J. K.; Wang, D.-H.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 460. (j) Nishikata, T.; Lipshutz, B. H. *Org. Lett.* **2010**, *12*, 1972. (k) Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2010**, *49*, 6169. (l) Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 14137. (m) Lu, Y.; Wang, D.-H.; Engle, K. M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 5916. (n) Garcia-Rubia, A.; Fernandez-Ibanez, M. A.; Arrayas, R. G.; Carretero, J. C. *Chem.—Eur. J.* **2011**, *17*, 3567. (o) Dai, H.-X.; Stepan, A. F.; Plummer, M. S.; Zhang, Y.-H.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 7222.

(5) Arguably, there are very few *oxidative* examples based on Ru catalysts; see for example: (a) Ueyama, T.; Mochida, S.; Fukutani, T.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2011**, *13*, 706. (b) Ackermann, L.; Pospech, J. *Org. Lett.* **2011**, *13*, 4153. (c) Kwon, K.-H.; Lee, D. W.; Yi, C. S. *Organometallics* **2010**, *29*, 5748. (d) Padala, K.; Jeganmohan, M. *Org. Lett.* **2011**, *13*, 10.1021/ol202580e. (e) Hashimoto, Y.; Ueyama, T.; Fukutani, T.; Hirano, K.; Satoh, T.; Miura, M. *Chem. Lett.* **2011**, *40*, 1165. However, a number of interesting (chelate assisted) C−H activation processes that couple arenes with olefins exist. For selected examples, see: (f) Murai, S.; Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N. *Nature* **1993**, *366*, 529. (g) Martinez, R.; Chevalier, R.; Darses, S.; Genet, J.-P. *Angew. Chem., Int. Ed.* **2006**, *45*, 8232. (h) Simon, M.-O.; Genet, J.-P.; Darses, S. *Org. Lett.* **2010**, *12*, 3038. (i) Watson, A. J. A.; Maxwell, A. C.; Williams, J. M. J. *Org. Lett.* **2010**, *12*, 3856.

(6) For selected (chelate assisted) Rh catalyzed examples, see: (a) Lenges, C. P.; Brookhart, M. *J. Am. Chem. Soc.* **1999**, *121*, 6616. (b) Umeda, N.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2009**, *74*, 7094. (c) Ueura, K.; Satoh, T.; Miura, M. *Org. Lett.* **2007**, *9*, 1407. (d) Patureau, F. W.; Glorius, F. *J. Am. Chem. Soc.* **2010**, *132*, 9982. (e) Patureau, F. W.; Besset, T.; Glorius, F. *Angew. Chem., Int. Ed.* **2011**, *50*, 1064. (f) Rakshit, S.; Grohmann, C.; Besset, T.; Glorius, F. *J. Am. Chem. Soc.* **2011**, *133*, 2350. (g) Tsai, A. S.; Brasse, M.; Bergman, R. G.; Ellman, J. A. *Org. Lett.* **2011**, *13*, 540. (h) Wang, F.; Song, G.; Du, Z.; Li, X. *J. Org. Chem.* **2011**, *76*, 2926. (i) Gong, T.-J.; Xiao, B.; Liu, Z.-J.; Wan, J.; Xu, J.; Luo, D.-F.; Fu, Y.; Liu, L. *Org. Lett.* **2011**, *13*, 3235. (j) Mochida, S.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2011**, *76*, 3024. (k) Park, S. H.; Kim, J. Y.; Chang, S. *Org. Lett.* **2011**, *13*, 2372. (l) Chen, J.; Song, G.; Pan, C.-L.; Li, X. *Org. Lett.* **2010**, *12*, 5426. (m) Wang, F.; Song, G.; Li, X. *Org. Lett.* **2010**, *12*, 5430. (n) Willwacher, J.; Rakshit, S.; Glorius, F. *Org. Biomol. Chem.* **2011**, *9*, 4736. (o) Besset, T.; Kuhl, N.; Patureau, F. W.; Glorius, F. *Chem.—Eur. J.* **2011**, *17*, 7167.

(7) For no-chelate assisted C−H oxidative olefination of some specific heterocyclic structures, see for example: (a) Grimster, N. P.; Gauntlett, C.; Godfrey, C. R. A.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 3125. For reviews, see: (b) Beck, E. M.; Gaunt, M. J. *Top. Curr. Chem.* **2010**, *292*, 85. (c) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173 and references cited therein.

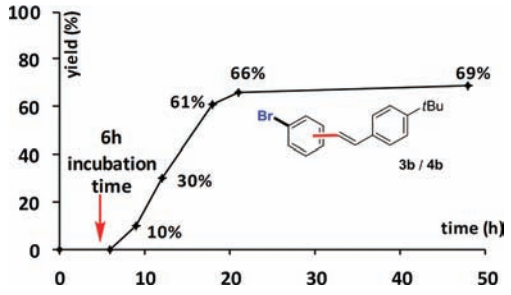


Figure 1. Formation of **3b**/**4b** as a function of time. The 9 and 12 h yields were determined by ^{1}H NMR integration; the later ones were isolated.

C−H activation and subsequent oxidative olefination of bromobenzene (5 mL, 48 mmol) with styrene (1 mmol) is possible at 140 °C, using Cp*Rh$(SbF_6)_2$ as the catalyst, $Cu(OAc)_2$, and pivalic acid. Bromostilbene **3a**/**4a** was obtained in 66% yield as a 2:1 *meta*/*para* mixture (Scheme 1).[10] Interestingly, the *ortho* bromostilbene is almost not detected (< 1%),[10] while debrominated stilbene and linear 1,4-diene (**5** and **6**, respectively) are inseparable side products, albeit usually in small quantities (Scheme 1). Omission of pivalic acid leads to low conversion and omission of $Cu(OAc)_2$ shuts down the reactivity, demonstrating the importance of these two components.[11] Chlorobenzene affords only traces of the desired product, and fluorobenzene does not react at all (neither does toluene). Iodobenzene showed good reactivity, but unacceptably large amounts of deiodinated product was typically observed in the mixture (**3o**/**4o**/**5o**, Scheme 1). In general, the regioisomeric ratios obtained are found "quasi-statistical"; that is all (nonsterically shielded) C−H positions have an almost equal chance of reacting. In other words bromobenzene tends to afford a 2:1 *meta*/*para* mixture of products, 1,2-disubstituted bromoarenes tend toward 1:1 *meta*/*para* mixtures (1,2,4 and 1,2,5), and 1,3-disubstituted arenes tend toward the single *meta* regioisomer (1,3,5), although this steric effect typically comes at the cost of lower reactivity and conversion.[12] Intriguingly, the reaction displays a very long and arguably unusual incubation time, presumably linked to the formation of the "true" active species (Figure 1). The fact that only halogenated arenes are suitable substrates (reactivity: F < Cl ≪ Br), tends to indicate that cleavage of the halide−carbon bond may be important. To probe this hypothesis, a 1:1 mixture of bromobenzene and toluene was engaged in the reaction with 4-*t*Bu-styrene, leading to low conversion of the expected olefinated bromoarene as well as olefinated toluene, approximately in a 1:1 ratio.[13] This clearly indicates that the intrinsic halogenated character of the substrate is essential for catalyst reactivity. We propose that the excess amount of bromoarene serves as a terminal oxidant by C−Br bond cleavage.[14] In order to probe the postulated reversibility of the C−H activation event, an H/D scrambling experiment was carried out by engaging bromobenzene and bromobenzene-d_5 (1:1) under identical reaction conditions, but without the olefin coupling partner (eq 4). Considering the large excess of bromobenzene (used as solvent), the detection of low levels of H/D scrambling is difficult. The small amounts of H/D scrambled products observed were within the margin of error[10] (linked to the initial isotopic purity and distribution of the commercial starting materials), at least indicating that the C−H activation/back reaction sequence is not rapidly entertained. In addition, a strong H/D kinetic isotope effect (KIE: k_H/k_D = 3.4, eq 5) was observed, leaving little doubt that the C−H activation event is also the rate-limiting step of the catalytic cycle.[15−17] The initial TOF (measured between 9 and 12 h, Figure 1) amounts to ∼1.3 h^{-1}, a very modest rate compared to chelate assisted C−H activation.[18] On the basis of these experiments, we propose that the C−H activation is the result of a "random collision" between the active Rh species and the most accessible C−H positions, followed by classical olefin insertion and β-hydride elimination. We propose that the

(8) Weissman, H.; Song, X.; Milstein, D. *J. Am. Chem. Soc.* **2001**, *123*, 337.

(9) For other pioneering examples of no-chelate assisted C−H oxidative olefinations, see: (a) Matsumoto, T.; Yoshida, H. *Chem. Lett.* **2000**, 1064. (b) Dams, M.; De Vos, D. E.; Celen, S.; Jacobs, P. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 3512. (c) Yokota, T.; Tani, M.; Sakaguchi, S.; Ishii, Y. *J. Am. Chem. Soc.* **2003**, *125*, 1476. (d) Tani, M.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* **2004**, *69*, 1221. (e) Yamada, T.; Sakakura, A.; Sakaguchi, S.; Obora, Y.; Ishii, Y. *New J. Chem.* **2008**, *32*, 738. (f) Zhang, Y.-H.; Shi, B.-F.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 5072. (g) Ye, M.; Gao, G.-L.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 6964. (h) Hickman, A. J.; Sanford, M. S. *ACS Catal.* **2011**, *1*, 170.

(10) See experimental details in the Supporting Information.

(11) Using only a catalytic loading of $Cu(OAc)_2$, e.g., 20 mol%, is not sufficient to effect reactivity (no conversion).

(12) 1,4-Disubstituted bromoarenes (like 4-bromotoluene), do not react at all. 1,3-Dibromobenzene, 1,3-bromo-chlorobenzene, and 1,3-bromo-fluorobenzene afford only low to very low conversions; 1,2-dibromobenzene or 2-bromoanisole do not react at all. Activated olefins, such as *n*-butylacrylate and styrenes that are functionalized with polar substitutents (4-MeO-, 4-*t*BuO-), do not lead to any product formation, maybe due to rapid olefin decay.

(13) We are very interested in this reactivity transfer phenomenon, but our initial attempts in this direction remain unsatisfactory. For instance, engaging a 1:1 mixture of 1,3,5-bromoxylene (sterically shielded oxidant) and toluene (as the C-H activation substrate) with 4-*t*Bu-styrene only led to traces of products (isomeric mixture of (*t*Bu-styryl)-toluene), even with an extended 48 h reaction time.

(14) The usage of bromobenzene as reoxidant in Rh catalysis was previously postulated; for example see: (a) Barrett, A. G. M.; Itoh, T.; Wallace, E. M. *Tetrahedron Lett.* **1993**, *34*, 2233. See also: (b) Bouffard, J.; Itami, K. *Top. Curr. Chem.* **2010**, *292*, 231.

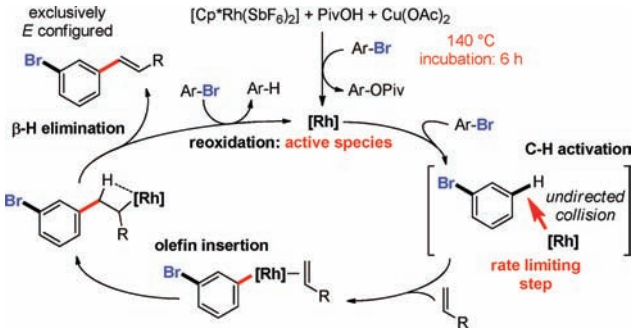
(15) It is interesting to note that a detectable H/D scrambling did occur in the products of the experiment of eq 5. In particular, the D_3-product represents 7% of the total amount of **3p/4p** (expected as a D_4-product), probably due to PivOH being an important proton source; see experimental details in the Supporting Information.

(16) During the preparation of this manuscript, an insightful report appeared describing the Pd catalyzed arylation on monosubstituted arenes: (a) Wang, X.; Leow, D.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 13864. In comparison with our work, their transformation is more regioselective (up to 99% *para* selectivity), but their kinetic isotopic data tend to indicate an electrophilic attack mechanism (k_H/k_D = 1). An early work describing the carbonylation of arenes by Rh C−H activation reports a more related k_H/k_D = 3; see: (b) Grushin, V. V.; Marshall, W. J.; Thorn, D. L. *Adv. Synth. Catal.* **2001**, *343*, 161.

(17) The reaction tolerates 1 equiv of TEMPO (2,2,6,6-tetramethylpiperidinooxy), although the conversion is then typically lower.

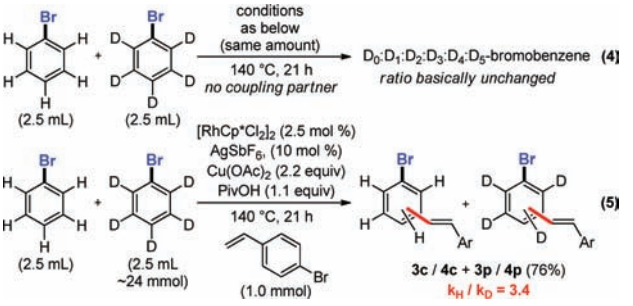
(18) In the Rh catalyzed oxidative olefination of acetanilides with *n*Bu-acrylate, a kinetic measurement situated the initial average TOF at around 1080 h^{-1}; see ref 6d.

Scheme 2. Proposed Mechanism



reoxidation through C−Br bond cleavage is responsible for the formation of the active Rh intermediate, possibly containing a bromide ligand, although the reason why this might be important remains unclear. The very slow activation of the $Cp^*Rh(AgSbF_6)_2$ precatalyst toward the active species is not clear either. The traces of Ar-OPiv usually found in the crude mixtures may be connected with this event (Scheme 2).

In conclusion, we have discovered a unique type of Rh-catalyzed C−H activation reactivity, which does not require a chelate-assisting directing group. We have demonstrated that bromoarenes are an essential component of this reactivity (we assume as both a terminal oxidant and catalyst modifier). This sheds light on new Rh catalyzed C−H activation processes and will serve as the basis for future investigations.



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