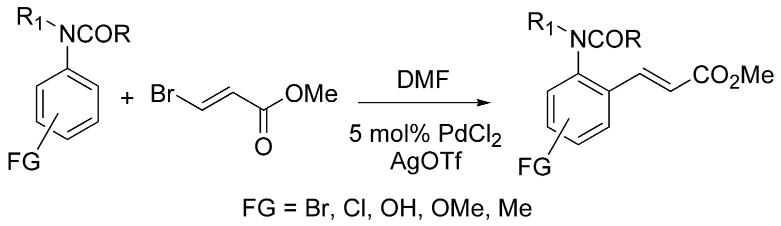
Communication

Catalytic Coupling of Haloolefins with Anilides

Vladimir G. Zaitsev, and Olafs Daugulis

J. Am. Chem. Soc., **2005**, 127 (12), 4156-4157• DOI: 10.1021/ja050366h • Publication Date (Web): 03 March 2005



Journal of the American Chemical Society is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

J|A|C|S
COMMUNICATIONS

Catalytic Coupling of Haloolefins with Anilides

Vladimir G. Zaitsev and Olafs Daugulis*

Department of Chemistry, University of Houston, Houston, Texas 77204-5003

Received January 19, 2005; E-mail: olafs@uh.edu

Extensive synthetic methodology has been developed based on oxidative addition reactions of C−X bonds (X = halogen, heteroatom).[1] Catalytic C−C bond-forming reactions arising from C−H bond activations are less common despite the wider availability, price, and environmental advantages of the starting hydrocarbons compared to functionalized compounds.[2] The focus of many recent studies has moved from investigations of the C−H bond activation step to the application of these findings in catalytic processes.

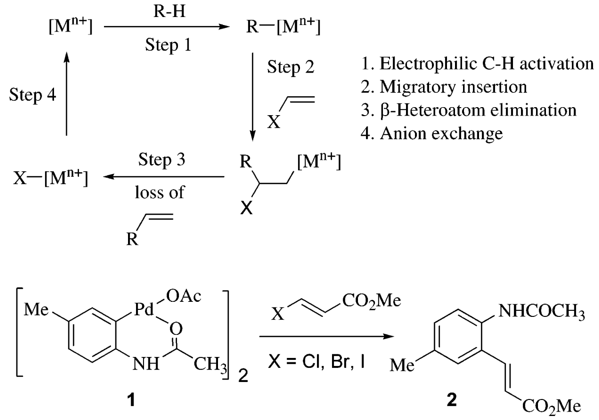
An example illustrating the catalytic C−C bond-forming reaction is palladium-catalyzed oxidative coupling of benzene derivatives with alkenes bearing electron-withdrawing groups.[3] This process requires a stoichiometric reoxidant, usually oxygen, peroxides, or Cu(II) since in the functionalization step, Pd^{2+} is reduced to Pd^0. The reoxidation step quite often is inefficient or turnover limiting, and there are relatively few examples where high catalyst turnovers have been demonstrated.[3] Presence of Pd^0 in the reaction mixture may bring about side reactions if the arene contains halogen substituents thus limiting the synthetic potential of this reaction.[3a] Additionally, use of high pressures of the cheapest reoxidant (oxygen) is unsafe in combination with flammable organic compounds and elevated temperatures requiring special equipment.

We report here a strategy in which C−H activation reactions promoted by Pd(II) have been combined with β-heteroatom elimination to create a catalytic cycle (Scheme 1) and achieve the arylation of haloolefins. The catalytic cycle can be subdivided into four parts: (1) C−H activation; (2) the functionalization step, migratory insertion of the olefin into a metal−carbon bond; (3) β-heteroatom elimination; and (4) exchange of metal halide (if X = halogen) for a less coordinating anion. In these processes, the oxidation state of the metal does not change in the catalytic cycle, and an oxidant is not required. A few Pd(II)-catalyzed reactions employ β-acetate or β-halide eliminations as the terminating step.[4] These examples demonstrate the viability of β-heteroatom elimination as a method to regenerate the catalytic species. This process may be called a "reverse" Heck reaction with the heteroatom−carbon bond breaking being the terminating and not the initiating step.[1a]

The initial experiments were carried out with acetanilide derivatives since these compounds are easily ortho-palladated, and the palladated anilides readily react with acrylates (Scheme 1).[5] 3-Haloacrylates were chosen as the olefin components. The reaction of ortho-palladated anilides with 3-chloroacrylate esters is very fast in trifluoroacetic acid. However, the precipitated palladium halide is virtually insoluble in the reaction medium, and thus the reaction could not be rendered catalytic. Reaction in acetic acid produced 3-acetoxyacrylate ester in competition with the desired C−C coupling process. Use of trifluoroethanol or methanol resulted in production of Pd black. Efficient and relatively fast reaction was observed in DMF, which was chosen as a solvent for further investigations.

Next, reaction of preformed palladated anilide **1** with several haloacrylates was investigated. The observed order of reactivity was as follows: *cis*-chloro < *trans*-chloro ∼ *cis*-iodo < *cis*-bromo < *trans*-bromo.[6] As a consequence, all following reactions were performed using *trans*-bromo ester.

Scheme 1. Proposed Mechanistic Scheme



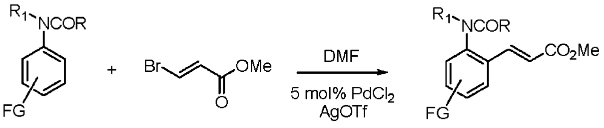
A number of N-acylated anilines were found to be good substrates for this reaction (Table 1). In some cases, better results were obtained using pivaloylated substrates instead of acetanilides. The yields and conversions are good for anilides possessing substituents that are more electron donating than hydrogen. An *m*-chloro substituent is compatible with the reaction conditions; in this case, however, reduction of yield is observed. Even bromo substituents are tolerated (entry 6), which would be problematic if the reaction involved a Pd(0)−Pd(II) couple.[3a] Free phenolic hydroxyl is also tolerated, and the coupling product was obtained in 65% yield (entry 7). Interestingly, the N-methylated derivatives were also found to be reactive, and the coupling products were isolated in 40 (entry 8) and 98% (activated 3-methoxy substrate, entry 9) yield. N-Alkylated anilides have been reported to be unreactive if methyl acrylate is used as the olefin component.[3b] No reaction was observed with 2-trifluoromethylacetanilide. With more active substrates, it was possible to use *cis*-1-phenyl-3-bromo-2-propenone as the olefinic component (entry 10). *cis*-3-Bromoacrylonitrile produced no desired coupling product under our conditions.

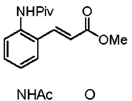
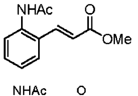
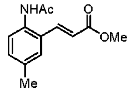
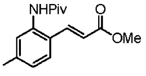
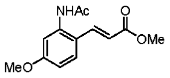
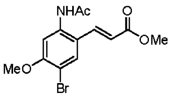
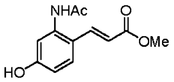
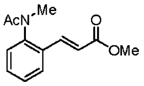
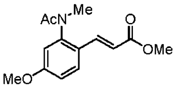
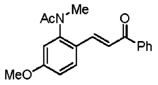
We have carried out preliminary mechanistic investigations of this coupling process. There are other mechanistic possibilities besides the suggested one. First, elimination of HHal from the haloalkene may produce the alkyne which may react with the palladated anilide similar to the method of Fujiwara.[7] A control experiment was carried out by substituting the bromoalkene by methyl propiolate. Under the usual reaction conditions, no product was observed.

Second, simple Lewis acid-catalyzed electrophilic aromatic substitution may be excluded based on the regioselectivity (exclusive ortho-substitution) of the reaction.[9] A reaction mechanism proposed by Tremont for Pd-promoted alkylation of anilides and *N*-benzilidene imines is unlikely.[10] The intermediate palladated

10.1021/ja050366h CCC: $30.25 © 2005 American Chemical Society

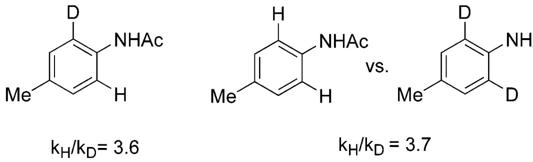
Table 1. Coupling of Haloolefins with Anilides[a]



Entry	Anilide	Time Temp	Product	Yield
1	R = tBu R_1 = H FG = H	1 h 90 °C		85%
2	R = Me R_1 = H FG = H	2 h 90 °C		56%
3	R = Me R_1 = H FG = 4-Me	2 h 80 °C		80%
4	R = tBu R_1 = H FG = 3-Cl	1.5 h 110 °C		33%[b]
5	R = Me R_1 = H FG = 3-MeO	1.5 h 90 °C		85%
6	R = tBu R_1 = H FG = 3-MeO- 4-Br	3 h 90 °C		61%
7	R = Me R_1 = H FG = OH	1 h 90 °C		65%
8	R = Me R_1 = Me FG = H	3 h 110 °C		40%
9	R = Me R_1 = Me FG = 3-MeO	2 h 90 °C		98%
10[c]	R = Me R_1 = Me FG = 3-MeO	3 h 100 °C		43%

[a] Substrate (1 equiv), olefin (1−1.5 equiv), AgOTf (1 equiv), Pd(OAc)$_2$ (5 mol %). Piv = pivaloyl. Yields are isolated yields. Silver was recovered almost quantitatively as AgBr.[8] See the Supporting Information for details. [b] The starting anilide partially recovered after the reaction. [c] *cis*-1-Phenyl-3-bromo-2-propenone was used as the olefin component.

Scheme 2. Kinetic Isotope Effects



anilides react with haloacrylate esters at room temperature, producing the coupling products. This all points to an alkene coordination−insertion mechanism as opposed to other possible pathways. The reaction is inhibited by the coupling products. If 1 equiv of **2** was added to the reaction mixture, only 15% conversion to the product was observed. Under similar conditions, 50% conversion was observed with no starting material added. This may be the reason for lower conversion in the case of less reactive substrates (entries 4 and 8). Both inter- and intramolecular deuterium isotope effects were obtained for the reaction of *p*-toluanilide with methyl bromoacrylate (Scheme 2). The intramolecular isotope effect is almost the same as that in the intermolecular (3.6 vs 3.7) and is within the expected range for a C−H activation process.[11] These data suggest that C−H bond cleavage occurs in the turnover-limiting step.

In conclusion, we have developed a new alkene arylation process based on C−H activation. The method is more functional group tolerant compared with the existing alkene−arene coupling methods based on electrophilic C−H activation. Efforts are underway to extend this methodology to other classes of arenes and alkenes.

Acknowledgment. We thank the Welch Foundation (Grant No. E-1571) and the University of Houston Small Grants Program for supporting this research. We also thank Prof. Maurice Brookhart for helpful comments.

Supporting Information Available: Detailed experimental procedures and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Heck, R. F. *Acc. Chem. Res.* **1979**, *12*, 146. (b) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009.
(2) Reviews: (a) Shilov, A. E.; Shul'pin, G. B. *Chem. Rev.* **1997**, *97*, 2879. (b) Kakiuchi, F.; Chatani, N. *Adv. Synth. Catal.* **2003**, *345*, 1077. (c) Labinger, J. A.; Bercaw, J. E. *Nature* **2002**, *417*, 507. (d) Dyker, G. *Angew. Chem., Int. Ed.* **1999**, *38*, 1698.
(3) (a) Tani, M.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* **2004**, *69*, 1221. (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. (c) Dams, M.; De Vos, D. E.; Celen, S.; Jacobs, P. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 3512. Other recent examples of Pd-catalyzed C−H activations: (d) Sezen, B.; Sames, D. *J. Am. Chem. Soc.* **2004**, *126*, 13244. (e) Desai, L. V.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 9542.
(4) (a) Zhang, Z.; Lu, X.; Xu, Z.; Zhang, Q.; Han, X. *Organometallics* **2001**, *20*, 3724. (b) Wang, Z.; Zhang, Z.; Lu, X. *Organometallics* **2000**, *19*, 775. (c) Shen, H.; Jordan, R. F. *Organometallics* **2003**, *22*, 1878. Catalysis by GaCl$_3$: (d) Kobayashi, K.; Arisawa, M.; Yamaguchi, M. *J. Am. Chem. Soc.* **2002**, *124*, 8528.
(5) (a) Ryabov, A. D.; Sakodinskaya, I. K.; Yatsimirsky, A. K. *J. Organomet. Chem.* **1991**, *406*, 309. (b) Horino, H.; Inoue, N. *J. Org. Chem.* **1981**, *46*, 4416.
(6) Comparative haloacrylate reaction rates are provided as Supporting Information.
(7) (a) Jia, C.; Piao, D.; Oyamada, J.; Lu, W.; Kitamura, T.; Fujiwara, Y. *Science* **2000**, *287*, 1992. (b) Fujiwara, Y.; Jia, C. *Pure Appl. Chem.* **2001**, *73*, 319. (c) Jia, C.; Lu, W.; Oyamada, J.; Kitamura, T.; Matsuda, K.; Irie, M.; Fujiwara, Y. *J. Am. Chem. Soc.* **2000**, *122*, 7252.
(8) Halide exchange was unsuccessful when NaOTf or NaOCOCF$_3$ was used instead of AgOTf (about 1.5 turnovers observed). The use of AgOAc leads to the production of acetoxyacrylate.
(9) For a recent example of the metallocene catalyzed reaction of a chloroalkene with arenes, see: Dash, A. K.; Jensen, T. R.; Stern, C. L.; Marks, T. J. *J. Am. Chem. Soc.* **2004**, *126*, 12528.
(10) Either an electrophilic attack on the Pd−C bond or a mechanism involving a Pd(IV) intermediate has been proposed. In our case, the observed order of reactivity (RBr > RI ∼ RCl) is inconsistent with either of these possibilities. (a) Tremont, S. J.; Rahman, H. U. *J. Am. Chem. Soc.* **1984**, *106*, 5759. (b) McCallum, J. S.; Gasdaska, J. R.; Liebeskind, L. S.; Tremont, S. J. *Tetrahedron Lett.* **1989**, 4085.
(11) (a) Jones, W. D. *Acc. Chem. Res.* **2003**, *36*, 140. (b) Hennessy, E. J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 12084.

JA050366H