J|A|C|S
COMMUNICATIONS

Palladium-Catalyzed Amination of Aromatic C−H Bonds with Oxime Esters

Yichen Tan and John F. Hartwig*

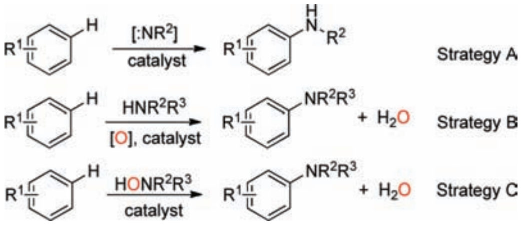
Department of Chemistry, University of Illinois at Urbana-Champaign, 600 South Mathews Avenue,
Urbana, Illinois 61801

Received January 25, 2010; E-mail: jhartwig@illinois.edu

Aromatic amines and their derivatives are common in pharmaceuticals, agrochemicals, dyes, herbicides, and conducting polymers.[1] Therefore, intense effort has been focused on the development of methods for the synthesis of the C−N bonds in aromatic amines. Traditional routes to aromatic amines by nitration, reduction, and alkylation have been largely displaced by catalytic amination of aryl halides and pseudohalides.[2] However, the direct amination of C−H bonds[3] would provide a complementary approach to the synthesis of arylamines by eliminating the need to prepare the aryl halides or pseudohalides. Two general strategies for the direct amination of C−H bonds have been followed: formal insertion of a nitrene into an aromatic C−H bond (strategy A in Scheme 1)[4] and oxidative amination of arenes with amine derivatives (strategy B in Scheme 1).[5] In the former, a highly active nitrene intermediate is involved, and in the latter, an external oxidant is required; both processes typically require high catalyst loadings (5−20%).

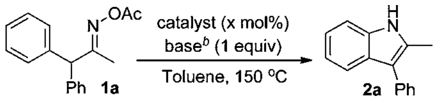
We envisioned an alternative approach to the direct amination of C−H bonds based on reactions of hydroxylamine derivatives[6] as the nitrogen source (strategy C in Scheme 1). Such reactions would be an umpolung of the amination of aryl halides, operate under overall redox-neutral conditions, and occur by a manifold outside of that with nitrene intermediates. Thus, a range of complexes could catalyze this process, and conditions with low catalyst loadings could ultimately be achieved. Herein, we describe our initial results on a Pd-catalyzed amination of aromatic C−H bonds with oxime esters, in this case to form indole products. Our data support a mechanism operating by an unusual initial oxidative addition of a N−O bond to Pd(0), the product of which has been isolated for the first time.

Scheme 1. General Strategies for Direct Amination



We began our study by investigating the cyclization of the oxime acetate **1a** derived from 1,1-diphenylacetone to form 2-methyl-3-phenylindole (**2a**) from a combination of C−H amination and tautomerization (Table 1, entry 1). The oxidative addition of the N−O bond in an oxime ester to Pd(0) was proposed but not directly observed in previous studies of amino-Heck reactions,[7] and the resulting Pd(II) species would be similar to the Pd(II) carboxylate intermediates proposed to cleave aromatic C−H bonds during reactions catalyzed by Pd(OAc)$_2$.[3c,5] After a survey of reaction variables, we found that oxime acetate **1a** formed indole **2a** after 4 h in toluene at 150 °C in good yield when a stoichiometric amount of Pd(dba)$_2$ was used. Reactions conducted with other Pd complexes formed **2a** in lower yields under the same conditions.[8]

Table 1. Selected Conditions for C−H Bond Amination[a]



entry	catalyst	base	time (h)	yield (%)[c]
1	Pd(dba)$_2$ (100 mol %)	−	4	70
2	Pd(dba)$_2$ (10 mol %)	K_3PO_4	24	74
3	Pd(dba)$_2$ (1 mol %)	Cs_2CO_3	24	72
4	Pd(PCy$_3$)$_2$ (1 mol %)	Cs_2CO_3	24	56

[a] The reactions were conducted on 0.05 mmol scale in 1 mL of toluene. [b] Dried in a furnace at 500 °C. [c] GC yields.

We hypothesized that stoichiometric amounts of palladium were needed because the acetic acid side product was consuming the potential catalyst. Thus, further reactions with catalytic amounts of Pd(dba)$_2$ were conducted in the presence of bases, and these experiments (see the Supporting Information) showed that reactions conducted with K_3PO_4 or Cs_2CO_3 as the base (Table 1, entries 2 and 3) formed the cyclized product **2a** in good yield. Moreover, reactions with just 1 mol % Pd(dba)$_2$ as the catalyst and Cs_2CO_3 as the base occurred in the same yields as reactions with stoichiometric amounts of Pd(dba)$_2$. Reactions conducted with phosphine-ligated Pd(0) catalysts resulted in lower yields of **2a** than those catalyzed by Pd(dba)$_2$. Nevertheless, the reaction catalyzed by 1 mol % Pd(PCy$_3$)$_2$ formed the indole product in 56% yield after 24 h.

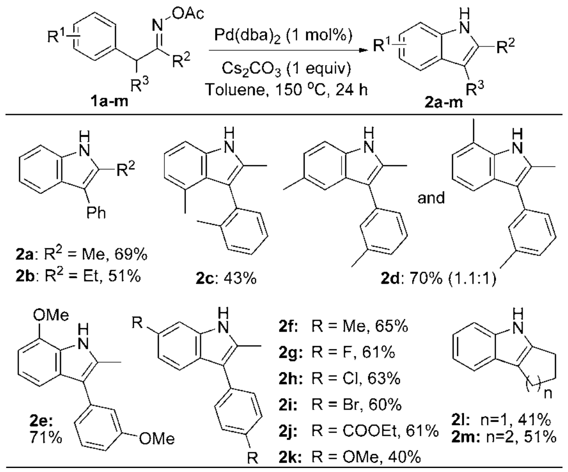
Having developed conditions for the catalytic amination of aromatic C−H bonds with oxime esters, we conducted reactions with substrates that would test the effect of steric and electronic influences on the functionalization process and the potential of this approach to provide indoles with substitution patterns that are less accessible by traditional routes (Table 2). Reactions of substrates containing meta substituents (**1d** and **1e**) to test the regioselectivity of this cyclization revealed a strong dependence on the substituents. A 1:1.1 mixture of isomers (**2d**) was isolated from the reaction of a substrate containing *m*-methyl groups. However, a single isomer (**2e**) was isolated from the reaction of a substrate containing *m*-methoxy groups, and for reasons we do not fully understand, this isomer was formed by reaction at the *more* sterically hindered position ortho to this group.

To study the effects of the electronic properties of substituents on the C−H amination process, cyclizations of a series of substrates containing groups in the para position (**1f**−**k**) were studied. These results showed that electron-withdrawing substituents had little effect on the yield of the C−H amination. Greater than 60% yields of the indole products **2g**−**j** were obtained. However, reaction of substrate **1k** containing electron-donating groups occurred in lower yield. Aryl chlorides and bromides were inert under these reaction conditions, implying that the Pd(0) catalyst preferentially reacts with the N−O bond of the oxime acetate over the carbon−halogen bonds. Finally, substrates **1l** and **1m** also underwent cyclization in moderate yields, indicating that the *gem*-diaryl substructure was not required for the C−H amination process to occur, although the monocyclic substrate

10.1021/ja100676r

1b containing an ethyl group as R^2 reacted in lower yield than the substrates containing a methyl group as R^2.[9]

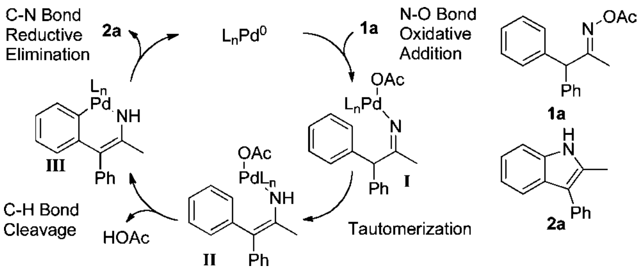
Table 2. Pd-Catalyzed Cyclization of Oxime Acetates[a,b]



[a] Reactions were conducted on 0.1 mmol scales in 10 mL of toluene. [b] Isolated yields.

On the basis of previous studies of amino-Heck reactions[7] and C−H amination conducted with $Pd(OAc)_2$,[3c,5] we envisioned that the cyclization of **1a** could occur by oxidative addition of the N−O bond to Pd(0) followed by tautomerization to generate complex **II** (Scheme 2). Subsequent C−H bond cleavage would form palladacyclic complex **III**. C−N bond-forming reductive elimination from **III** would afford the indole product **2a** and regenerate the active Pd(0) catalyst. Alternatively, the C−H bond-cleavage step could occur prior to the tautomerization.

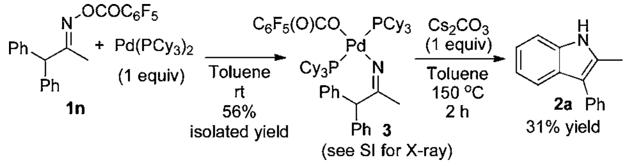
Scheme 2. Proposed Catalytic Cycle



To assess whether N−O bond oxidative addition could be the first step of the catalytic cycle, we sought to isolate a complex generated from N−O bond oxidative addition. Because of the difficulty of isolating Pd(II) products with dba as the sole ancillary ligand, we conducted mechanistic studies with complexes ligated by PCy_3, which were shown to catalyze the cyclization process (see above). Indeed, the reaction of an oxime ester containing a pentafluorobenzoyl group (**1n**) with a stoichiometric amount of $Pd(PCy_3)_2$ provided Pd(II) complex **3** in high yield (Scheme 3). The structure of **3** was determined by X-ray diffraction.[8] Complex **3** is the first isolated complex formed by oxidative addition of an N−X bond (X = N, O, halide) to Pd(0).[10]

The reaction of oxime ester **1a** catalyzed by 1 mol % of isolated complex **3** formed indole **2a** in a yield (58%) similar to that for the reaction of **1a** catalyzed by 1 mol % $Pd(PCy_3)_2$ (56%, see above). In addition, heating complex **3** at 150 °C in toluene with added Cs_2CO_3 provided **2a** in 31% yield (Scheme 3). Although the yields do not exactly match those for the reactions of oxime acetates because the pentafluorobenzoate complex **3** is not the precise intermediate **I** in the proposed catalytic cycle for reaction of these substrates, the reaction of complex **3** to form indole **2a** suggests that an acetate analogue of **3** would form the indole product under the conditions of the catalytic process. Thus, our data are consistent with the mechanism proposed in Scheme 2.

Scheme 3. Isolation and Reaction of the Product of Oxime Addition



In summary, we have demonstrated a novel approach to the direct amination of aromatic C−H bonds using oxime esters under redox-neutral conditions. These reactions occur with relatively low catalyst loadings through a Pd(II) complex generated from N−O bond oxidative addition. Such a complex has been isolated for the first time, and evidence for its intermediacy in the catalytic reaction has been gained. Further investigations of the mechanism and an expansion of this methodology to intermolecular amination of aromatic C−H bonds are ongoing in our laboratory.

Acknowledgment. This work is dedicated to the memory of Keith Fagnou. We thank the NSF for financial support through the Center for Enabling New Technologies through Catalysis (CENTC), CHE-0650456, and Profs. William D. Jones and Wes T. Borden for helpful suggestions.

Supporting Information Available: Experimental procedures, spectra for all compounds, and crystallographic data for **3** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Cheng, J.; Kamiya, K.; Kodama, I. *Cardiovasc. Drug Rev.* **2001**, *19*, 152. (b) Sànchez, C.; Mèndez, C.; Salas, J. A. *Nat. Prod. Rep.* **2006**, *23*, 1007.
(2) For reviews, see: (a) Hartwig, J. F. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley-Interscience: New York, 2002; p 1051. (b) Jiang, L.; Buchwald, S. L. *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; Wiley-VCH: Weinheim, Germany, 2004; Vol. 2, p 699.
(3) For reviews of C−H amination, see: (a) Mueller, P.; Fruit, C. *Chem. Rev.* **2003**, *103*, 2905. (b) Davies, H. M. L.; Long, M. S. *Angew. Chem., Int. Ed.* **2005**, *44*, 3518. (c) Dick, A. R.; Sanford, M. S. *Tetrahedron* **2006**, *62*, 2439. (d) Davies, H. M. L.; Manning, J. R. *Nature* **2008**, *451*, 417.
(4) (a) Díaz-Requejo, M. M.; Belderrain, T. R.; Nicasio, M. C.; Trofimenko, S.; Pérez, P. J. *J. Am. Chem. Soc.* **2003**, *125*, 12078. (b) Thu, H.-Y.; Yu, W.-Y.; Che, C.-M. *J. Am. Chem. Soc.* **2006**, *128*, 9048. (c) Li, Z.; Capretto, D. A.; Rahaman, R. O.; He, C. *J. Am. Chem. Soc.* **2007**, *129*, 12058. (d) Stokes, B. J.; Dong, H.; Leslie, B. E.; Pumphrey, A. L.; Driver, T. G. *J. Am. Chem. Soc.* **2007**, *129*, 7500. (e) Chiba, S.; Hattori, G.; Narasaka, K. *Chem. Lett.* **2007**, *36*, 52.
(5) (a) Tsang, W. C. P.; Zheng, N.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 14560. (b) Chen, X.; Hao, X.-S.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 6790. (c) Inamoto, K.; Saito, T.; Katsuno, M.; Sakamoto, T.; Hiroya, K. *Org. Lett.* **2007**, *9*, 2931. (d) Yamamoto, M.; Matsubara, S. *Chem. Lett.* **2007**, *36*, 172. (e) Jordan-Hore, J. A.; Johansson, C. C. C.; Gulias, M.; Beck, E. M.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 16184. (f) Tsang, W. C. P.; Munday, R. H.; Brasche, G.; Zheng, N.; Buchwald, S. L. *J. Org. Chem.* **2008**, *73*, 7603. (g) Brasche, G.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 1932. (h) Mei, T.-S.; Wang, X.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 10806.
(6) For a recent example, see: Zhu, L. F.; Guo, B.; Tang, D. Y.; Hu, X. K.; Li, G. Y.; Hu, C. W. *J. Catal.* **2007**, *245*, 446.
(7) (a) Kitamura, M.; Narasaka, K. *Chem. Rec.* **2002**, *2*, 268. (b) Narasaka, K.; Kitamura, M. *Eur. J. Org. Chem.* **2005**, 4505.
(8) See the Supporting Information for details.
(9) All of the amination reactions we report occurred to full conversion. Diarylmethane was the major side product, and the ratio of major to minor products was not significantly affected by the catalyst loading.
(10) For examples of the isolation of oxidative addition products of oximes to low-valent rhenium and titanium complexes, see: (a) Ferreira, C. M. P.; Guedes da Silva, M. F. C.; Kukushkin, V. Y.; Fraústo da Silva, J. J. R.; Pombeiro, A. J. L. *J. Chem. Soc., Dalton Trans.* **1998**, 325. (b) Kukushkin, V. Y.; Pombeiro, A. J. L. *Coord. Chem. Rev.* **1999**, *181*, 147. (c) Tillack, A.; Arndt, P.; Spannenberg, A.; Kempe, R.; Rosenthal, U. *Z. Anorg. Allg. Chem.* **1998**, *624*, 737.

JA100676R