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Pd(II)-Catalyzed Amination of C−H Bonds Using Single-Electron or Two-electron Oxidants

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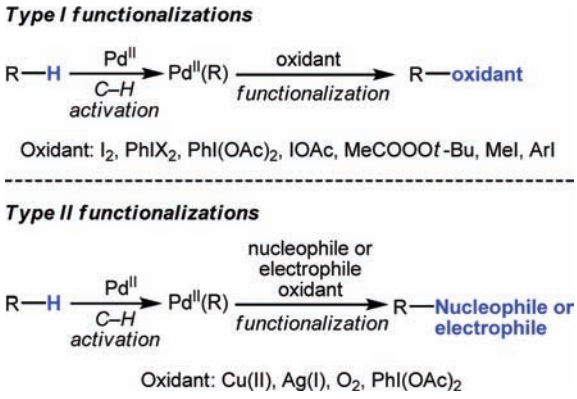
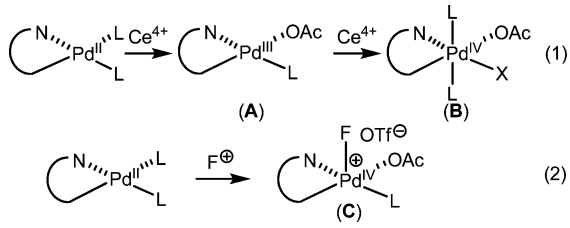
The discovery of new transformations through Pd-catalyzed C−H activation continues to attract broad interest. Despite the potential of these reactions to provide unprecedented synthetic disconnections, the need for an external oxidant in most cases represents a practical drawback. In particular, the development of C−H amination reactions with a broad substrate scope has been hampered by the lack of suitable oxidants.[1−4] Therefore, the development of new oxidation systems for Pd(II)-catalyzed C−H functionalization represents a central challenge in the field.[5] In this context, two major strategic approaches have recently been extensively studied (Scheme 1). In type I functionalizations, the oxidant is incorporated into the product. In contrast, in type II functionalizations, a broad range of nucleophiles or electrophiles can be incorporated into the product through selective reductive elimination. This latter approach, however, is often plagued by the undesired reductive elimination of the oxidant component from either Pd(II) or Pd(IV) centers (Table 1, entries 1−6).[6]

Scheme 1. Strategies for Pd(II)-Catalyzed C−H Functionalizations

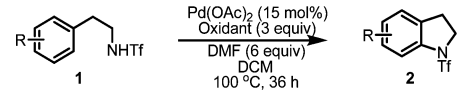


Herein we demonstrate two novel approaches to achieve highly selective reductive elimination of an amino nucleophile from oxidized Pd(III) (**A**) or Pd(IV) species (**B**, **C**) to form indolines using either a one-electron oxidant (Ce(IV)) or a two-electron oxidant (F^+). In both cases, the presence of 1−6 equiv of DMF is crucial, possibly as a labile ligand.



In our efforts to develop metal-catalyzed amination of C−H bonds, we have previously reported a method for lactamization of C−H bonds through type II catalysis using $CuCl_2$ as the oxidant.[6a] However, our attempt to achieve a broadly applicable intramolecular amination using triflamide protected alkylamines failed with a wide range of oxidants due to the nonselective reductive elimination from the Pd(IV) center giving acetoxylated or halogenated products (Table 1, entries 1−6).[7,8] We began to screen single-electron oxidants that did not contain anionic ligands capable of reductive elimination. Importantly, Pd(III) is known to exist as a dimeric octahedral[9a] or monomeric square planar complex.[9b] In the latter case, the OAc group from the catalytic amount of $Pd(OAc)_2$ could be oriented in the *trans*-position relative to the aryl group, which would prevent the undesired reductive elimination event (eq 1). Even if Pd(III) is subsequently oxidized to a Pd(IV) species, the lack of competing anions would induce the Pd(IV) complex to reductively eliminate along the desired amination pathway.

Table 1. Pd-Catalyzed Amination Using Single-Electron Oxidants

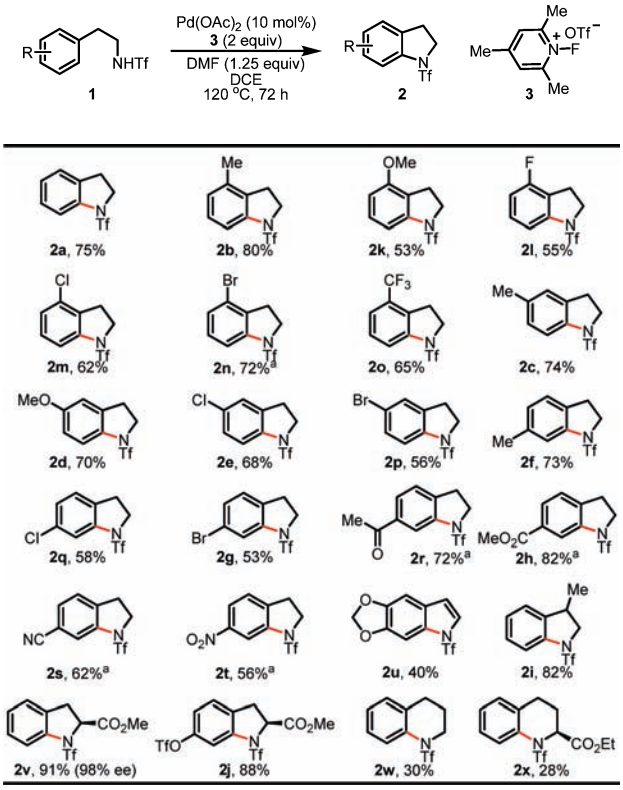


entry	substrate	oxidant	yield (%)	entry	substrate	yield (%)
1	1a	$K_2S_2O_8$	0	15	1b	73[g]
2	1a	$PhI(OAc)_2$	15[a]	16	1c	60
3	1a	IOAc	0[b]	17	1d	64
4	1a	NIS	0[c]	18	1e	52[h]
5	1a	NCS	0[d]	19	1f	61
6	1a	*tert*-butyl peroxyacetate	13[e]	20	1g	50
7	1a	$Cu(OAc)_2$	0	21	1h	40
8	1a	$FeCl_3$	0	22	1i	80[i]
9	1a	$Mn(OAc)_3{\cdot}2H_2O$	0	23	1j	61[j]
10	1a	AgOTf	0			
11	1a	V_2O_5	0			
12	1a	$(NH_4)_2Ce(NO_3)_6$	0			
13	1a	$Ce(OAc)_4$	5[f]			
14	1a	$Ce(SO_4)_2$	68			

[a] 45% acetoxylation product was isolated. [b] IOAc was generated *in situ* from $PhI(OAc)_2$ and I_2, and 40% iodination product was isolated. [c] 35% iodination product was isolated. [d] 20% chlorination product was isolated. [e] 50% acetoxylation product was isolated. [f] 35% acetoxylation product was isolated. [g] $Ce(SO_4)_2$ was used as oxidant in entry 15−23. [h] The unconverted starting materials were recovered in entry 14−23. [i] 10 mol % $Pd(OAc)_2$ was used. [j] 15 mol % $Pd(OCOCF_3)_2$ was used as Pd catalyst.

10.1021/ja904709b CCC: $40.75

Table 2. Pd-Catalyzed Amination Using F^+ As an Oxidant



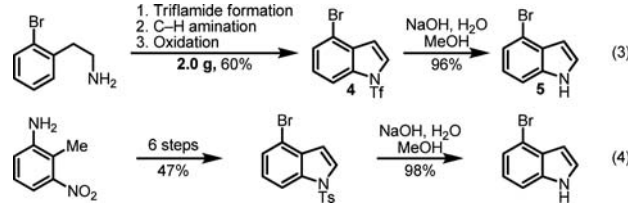
[a] 15 mol % $Pd(OAc)_2$ was used in the reactions.

Extensive screening of single-electron oxidants led us to identify anhydrous $Ce(SO_4)_2$ as a selective oxidant for amination (Table 1, entry 14). As anticipated, the use of $Ce(OAc)_4$ resulted in significant formation of the corresponding acetoxylation product (35% isolated yield). It is noteworthy that the commonly used oxidant, $(NH_4)_2Ce(NO_3)_6$, was ineffective for this reaction. Presumably, the poor solubility of $Ce(SO_4)_2$ is important as the initial oxidation of $Pd(OAc)_2$ by Ce(IV) prior to C−H activation may lead to unreactive Pd species.

With this catalytic system in hand, we examined the substrate scope. Substrates **1a**−**1d**, **1f**, **1i**, and **1j** worked well to give the corresponding indolines in 60−80% yield. Although OMe and OTf were tolerated, electron-withdrawing groups such as halides and esters lowered the yield.

We hypothesized that the presence of SO_4^{2-} anions could be detrimental to the reaction by forming unreactive $PdSO_4$ over the course of the reaction. We therefore decided to test if a previously established F^+ oxidant[10] could oxidize the same C−H insertion intermediate to Pd(IV) yet still allow selective reductive elimination to form the aminated product as a consequence of the notorious strength of the Pd−F bond. We were pleased to find that F^+ source **3** is an excellent oxidant for this amination reaction and that the substrate scope could be substantially expanded. A broad range of functional groups including several of the strongest electron-withdrawing groups (halo, acetyl, cyano, nitro, *etc.*) were tolerated. Excellent regioselectivity in the presence of *meta*-substitution was also observed (Table 2, **2c**−**2e**, **2p**). In these cases, exclusive formation of the new C−N bond at the sterically less hindered site was found. With highly electron-rich arenes, indole **2u** was formed as the major product via a subsequent dehydrogenative oxidation of the indoline. We further attempted to use phenylpropylamines as substrates. Unfortunately, the corresponding quinolines were formed in lower yields (**2w**, **2x**).

These indoline products are highly valuable building blocks for medicinal chemistry and natural product synthesis. The formation of chiral indolines from natural amino acids is of particular synthetic importance (**2j**, **2v**). The gram-scale, one-pot synthesis of 4-bromoindole (**5**), a key precursor for ergot alkaloid synthesis,[11] demonstrates the efficiency of this approach (eq 3). This new route offers a valuable alternative to the most broadly used synthesis of 4-bromoindole developed by Hegedus (eq 4).[11a]



In summary, we have developed a catalytic C−H amination reaction using either $Ce(SO_4)_2$ or a F^+ source as the oxidant. This amination reaction provides a concise route to substituted indolines.

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

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