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Pd-Catalyzed Intermolecular C−H Amination with Alkylamines

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Supporting Information

ABSTRACT: C−H amination of *N*-aryl benzamides with *O*-benzoyl hydroxylamines has been achieved with either Pd(II) or Pd(0) catalysts. Furthermore, we demonstrate that secondary amines can be directly used with benzoyl peroxide in a one-pot procedure that proceeds via the in situ generation of the appropriate *O*-benzoyl hydroxylamines. This catalytic reaction provides a new disconnection for the convergent synthesis of tertiary and secondary arylalkyl amines starting from benzoic acids.

The development of Pd-catalyzed C−H activation reactions toward synthetic applications continue to face three major interwoven challenges: (1) discovering general modes of catalysis for a diverse range of carbon−carbon and carbon−heteroatom bond-forming reactions, (2) improving the reactivity with broadly useful substrates, and (3) controlling the stereoselectivity and positional selectivity.[1] Recently, a number of catalytic systems have been established for Pd-catalyzed C−H activation/C−C bond−forming reactions that are compatible with synthetically useful substrates.[1a] In contrast, achieving the Pd-catalyzed C−H amination reaction represents a distinct challenge and has been met with a number of difficulties, as can be anticipated from the many tremendous hurdles encountered in the development of the Buchwald−Hartwig amination reaction.[2]

To date, the four modes of Pd-catalysis represented in eq 1−4 are only in their infancy in terms of scope and practicality.[3−7] At the present time, for instance, Pd-catalyzed intermolecular C−H activation/C−N bond formation is only possible with amide coupling partners.[4] Since Buchwald−Hartwig amination reactions that employ alkylamines and anilines are the most powerful tool for enabling the convergent synthesis of arylamines in both industrial and academic laboratories, complementary methods involving catalytic C−H amination with alkylamines and anilines would be highly desirable.

Herein, we report an *ortho*-C−H amination reaction of *N*-aryl benzamides electrophilic *O*-benzoyl hydroxylamines catalyzed by either Pd(II) or Pd(0) catalysts (eq 5). We also demonstrate that a one-pot procedure of using secondary amines directly in the presence of benzoyl peroxide is also possible. This finding not only represents a complementary disconnection for the synthesis of an important class of biologically active arylamines (Figure 1),[8] but it also provides insights for further work in intermolecular C−H amination with alkylamines.

Encouraged by previous success in coupling C−H bonds with organometallic reagents via a Pd(II)/Pd(0) catalytic manifold,[9] we began to investigate the possibility of achieving C−H amination with amine nucleophiles through analogous Pd redox

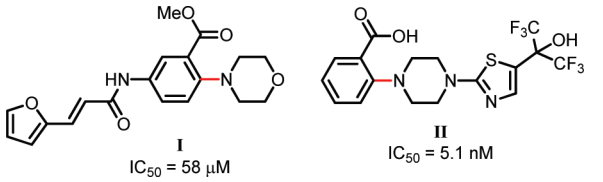
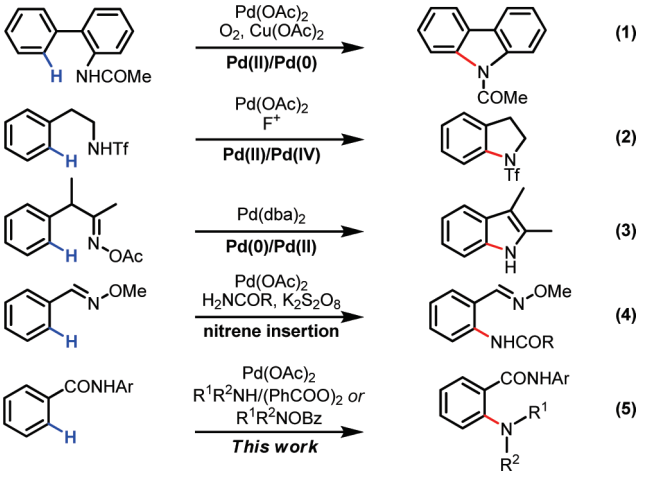


Figure 1. Biologically active amines.

chemistry. We are aware that C−N bond forming reactions represent a distinct challenge in comparison to C−C coupling processes. Although Buchwald's pioneering report established the viability of intramolecular C−H amidation/carbazole formation *via* Pd(II)/Pd(0) catalysis (eq 1),[3a] we have been largely unsuccessful in our attempts to develop an intermolecular version, even after exploring the wide range of C−H functionalization substrates previously reported in our laboratory. Recently, intramolecular C−H amidation *via* Pd(II)/Pd(IV) catalysis using bystanding F^+ oxidants (eq 2)[3f,10] and its intermolecular version have been developed with acetamide and sulfonamide partners.[4c,d] However, to date this approach has not been extended to either generally useful substrates or amine coupling partners.



In our continuing effort to search for an Evans auxiliary-like directing group for versatile C−H activation reactions, we have recently identified CONHAr (Ar = $(4\text{-}CF_3)C_6F_4$) as an exceptionally capable auxiliary for assisting a diverse range of C−H activation reactions that are elusive otherwise.[11] We therefore decided to revisit C−H amination using *N*-aryl

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Scheme 1. C−H Amination with an Alkylamine

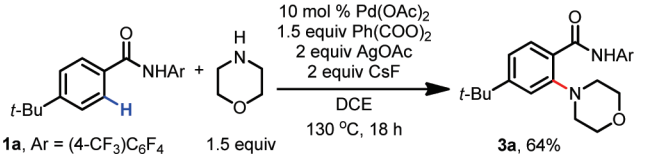
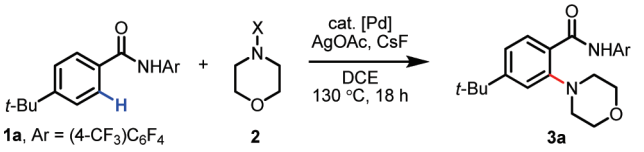


Table 1. Discovery and Evaluation of Reaction Conditions[a]



Entry	[Pd]	X	Yield (%)[b]
1	$Pd(OAc)_2$	Cl	<2
2	$Pd(OAc)_2$	OAc	90 (58[c])
3	$Pd(OAc)_2$	OBz	98 (74[c])
4	$Pd(dba)_2$	OBz	96 (70[c])
5	$Pd(OAc)_2/P^tBuMe\cdot HBF_4$	OBz	32

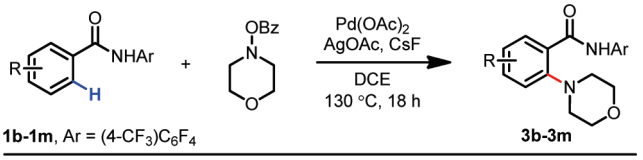
[a] Reaction conditions: **1a** (0.1 mmol), *N*-substituted morpholine (**2**, 0.2 mmol), Pd catalyst (10 mol %), AgOAc (0.1 mmol), CsF (0.2 mmol), DCE (1 mL), 130 °C, 18 h. [b] The yield was determined by ^{1}H NMR analysis of the crude product using dibromomethane as an internal standard. [c] The yields in the parentheses are obtained without AgOAc (0.1 mmol).

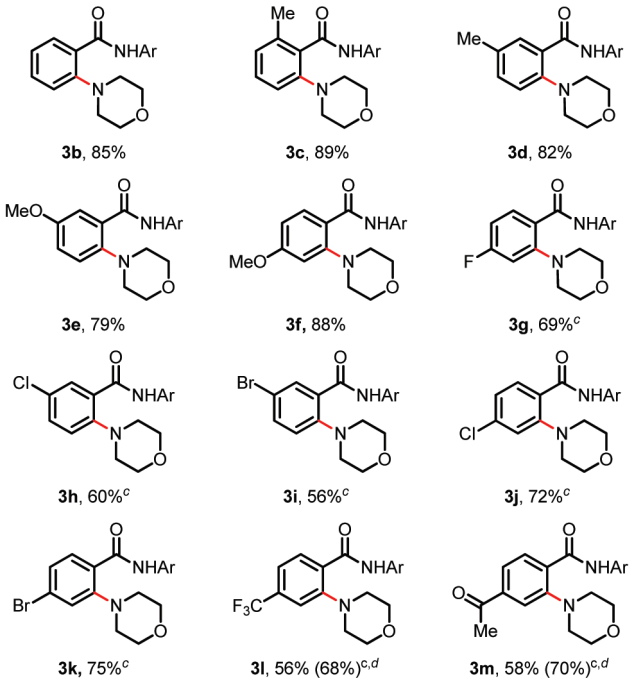
benzamide substrate **1a** by performing extensive screening of amine partners, oxidants, solvents, and other reaction parameters (see Supporting Information). We found C−H amination of **1a** with morpholine occurred in the presence of 10 mol % $Pd(OAc)_2$, 1.5 equiv of benzoyl peroxide, and 2 equiv of CsF in DCE to give the desired amination product **3a** in 53% yield. Addition of 2 equiv of AgOAc to the reaction increased the yield to 64% (Scheme 1).

Monitoring this new reaction by ^{1}H NMR, we found that morpholine reacted with benzoyl peroxide to form *O*-benzoyl hydroxylmorpholine within the first 30 min before amination products were observed. This observation suggests that the C−H activation intermediate $ArPd(II)L_n$ reacts with the *in situ* generated electrophilic amine partner (*O*-benzoyl hydroxylamine, a reagent initially developed by Johnson)[12,13] to give the desired amination product. In terms of catalysis, *O*-benzoyl hydroxylamine could react with the $ArPd(II)L_n$ intermediate through electrophilic cleavage or could oxidize Pd(II) to Pd(IV) to promote C−N reductive elimination.[3e,f]

With this insight in hand, we used substrate **1a** to test a few common electrophilic amine sources (**2**), which were prepared beforehand (Table 1). While *N*-chloroamine was unsuitable for this reaction (entry 1), both *O*-acetyl and *O*-benzoyl hydroxylamines were found to be effective aminating reagents (entries 2 and 3). *O*-Benzoyl hydroxylamines were used for further optimization due to their ease of preparation.[12c] CsF and KF were observed to be the best bases while other bases gave significantly lower yields (see Supporting Information). Although both of these reaction pathways do not require external oxidants, the addition of 1 equiv of AgOAc increased the yield from 74% to 98% (entry 3).

Table 2. Pd-Catalyzed Amination Reaction of *N*-Aryl Benzamides[a,b]





[a] Reaction conditions: benzamide substrate **1** (0.2 mmol), *O*-benzoyl hydroxylmorpholine (0.4 mmol), $Pd(OAc)_2$ (10 mol %), AgOAc (0.2 mmol), CsF (0.4 mmol), DCE (1 mL), 130 °C, 18 h. [b] Isolated yield. [c] α,α,α-Trifluorotoluene was used as a solvent. [d] The yields in the parentheses are obtained under the following conditions: $Pd(OAc)_2$ (20 mol %) and 48 h.

Ag_2CO_3 was found to be equally effective (see Supporting Information). The observed improvement by Ag oxidants remains unclear at this stage. Interestingly, $Pd(dba)_2$ was equally effective (entry 4), which points to the possibility of C−H amination *via* Pd(0)/Pd(II) catalysis, as demonstrated by an early intramolecular example.[3h] The presence of phosphine ligands, however, was found to be detrimental to this reaction (entry 5).

With this newly developed intermolecular C−H amination reaction in hand, we examined the reactivity of representative substrates containing synthetically useful functional groups. Amination of electron-neutral or -rich substrates in DCE afforded the desired products in 79−89% isolated yields (Table 2, **3b**−**3f**). The use of α,α,α-trifluorotoluene as the solvent was necessary to obtain acceptable yields with electron-deficient substrates (**3g**−**3m**). Although the yields decreased noticeably with electron-deficient substrates (**3g**−**3m**), the substrate scope of this reaction is significantly broader than that of previous intermolecular amidation reactions in terms of tolerance to strongly electron-withdrawing substituents on the aryl ring.[4c,d] Importantly, exclusive monoselectivity was observed in all cases. The tolerance of bromo groups (**3i** and **3k**) is especially useful, as subsequent Pd(0)-catalyzed cross-coupling and

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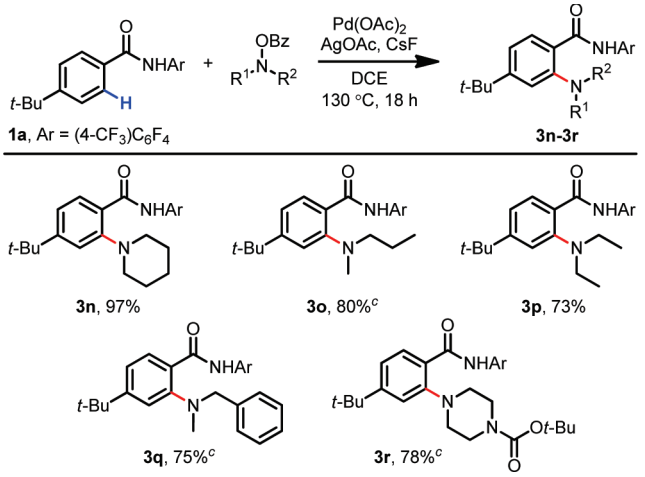
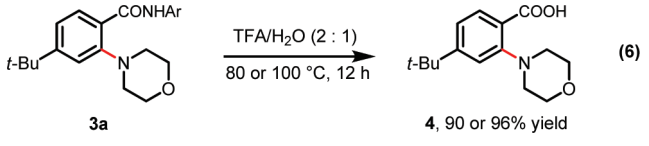
Table 3. Scope of *O*-Benzoyl Hydroxylamine Substrates[a,b]



[a] Reaction conditions: **1a** (0.2 mmol), *O*-benzoyl hydroxylamine (0.4 mmol), $Pd(OAc)_2$ (10 mol %), AgOAc (0.2 mmol), CsF (0.4 mmol), DCE (1 mL), 130 °C, 18 h. [b] Isolated yield. [c] α,α,α-Trifluorotoluene was used as a solvent.

Buchwald−Hartwig amination are possible. For instance, Pd(0)-catalyzed amination of product **3i** is an attractive route for the preparation of drug candidate **I** (Figure 1).

The ability to incorporate alkylamine moieties other than just morpholine into the *O*-benzoyl hydroxylamine scaffold is crucial for broad utility. We were thus pleased to find that **1a** reacted with several *O*-benzoyl hydroxylamines derived from simple dialkylamines in good to excellent yields (73−97%), thus allowing for the introduction of a variety of alkylamino groups (Table 3).[14] Notably, the benzyl group in **3q** can be cleaved to afford a secondary amine. These results demonstrate that a wide range of arylamines can be accessed from readily available benzoic acids using this method. To showcase the potential synthetic applications, we also performed the amination of **1a** with *O*-benzoyl hydroxylpiperazine, of which the product (**3r**) is an analogue of drug molecule **II** (Figure 1).[7] Finally, we demonstrated that this directing group can be readily removed from the amination products by treatment with TFA/H_2O to afford the corresponding carboxylic acids (eq 6).



(6)

While the detailed mechanism of this C−H amination reaction with Pd(II) or Pd(0) catalysts remains to be elucidated, possible reaction pathways can be postulated with Pd(II) catalysts based on previous studies (Figure 2).[3] First, deprotonation of the acidic amide with either CsF or KF can occur to give the corresponding salt. The weak coordination of Pd(II) with the carbonyl moiety of the benzamide salt could trigger C−H activation in a similar manner to that of benzoic acid substrates.[15] The arylpalladium(II) intermediate (**A**) could be oxidized to the Pd(IV) species (**B**)[3d−f] or react with the aminating reagent (R^1R^2NOBz) through a known electrophilic amination pathway.[7,12] The catalytic activity observed with the Pd(0) catalyst can be attributed to a pathway where oxidative addition of the aminating reagent to the Pd(0) catalyst

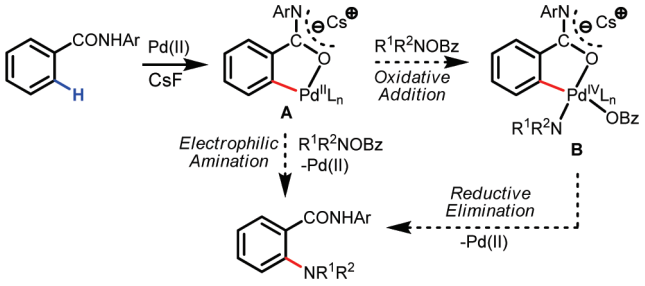


Figure 2. Possible reaction pathways with Pd(II) catalyst.

generates an active Pd(II) species that can then cleave a C−H bond.[3h]

In summary, we have developed a novel protocol to effect C−H amination on a broad range of synthetically useful benzamide substrates with electrophilic *O*-benzoyl hydroxylamines using either Pd(II) or Pd(0) catalysts. Additionally, a one-pot procedure of using secondary amines directly in the presence of benzoyl peroxide is also possible. The compatibility of this amination reaction with several different *O*-benzoyl hydroxylamine reagents derived from simple dialkylamines allows for the convergent synthesis of an important class of tertiary and secondary arylalkyl amines starting from benzoic acids.

■ ASSOCIATED CONTENT

Supporting Information. Complete ref 8b. Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ACKNOWLEDGMENT

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