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Pd-Catalyzed Aryl C−H Imidation with Arene as the Limiting Reagent

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Supporting Information

ABSTRACT: An amine-*N*-oxide-ligated palladium complex, in conjunction with a silver cocatalyst, catalyzes imidation of arenes by the reagent *N*-fluorobenzenesulfonimide. The reaction enables imidation of a variety of arenes at or below room temperature, requires no coordinating directing group on the substrate, and gives synthetically useful yields with only 1 equiv of arene. Mechanistic data implicate an unusual mechanism devoid of commonly invoked organometallic intermediates: oxidation of the Pd catalyst occurs as the turnover-limiting step, while C−H bond functionalization occurs subsequently at a high oxidation state of the catalyst.

Transition metal (TM) catalysis holds promise as a strategy for the direct functionalization of otherwise unreactive C−H bonds. Many reported TM-catalyzed aryl C−H functionalization approaches rely on metalation of the arene followed by functionalization of the aryl−metal σ-bond.[1] To accelerate an otherwise sluggish metalation step, coordinating directing groups are commonly employed to accelerate carbon−metal bond formation; without such directing groups, often multiple equivalents or even solvent quantities of arene are required to drive the metalation.[2] With few exceptions,[3] catalytic C−H functionalization without the aid of directing groups remains an unmet challenge. Here we report a catalytic, intermolecular C−H imidation of arenes enabled by a departure from the conventional metalation−functionalization sequence. The new palladium catalyst **1** enables group transfer without the formation of conventionally targeted organometallic intermediates. Our transformation affords synthetically useful yields *with the arene substrate as the limiting reagent*.

Historically, perhaps the most important method of introducing an amino group into arenes has been electrophilic aromatic nitration followed by reduction of the nitro group.[4] However, nitration of arenes typically requires strongly acidic or oxidizing reaction conditions, which limits its use on substrates with sensitive functional groups. Alternatively, several aniline derivatives can be reliably prepared by TM-catalyzed directed C−H amidation,[5] but the requirement for a coordinating directing group limits the potential substrate scope. Non-chelation-assisted TM-catalyzed C−H amination reactions,[6] as well as metal-free approaches involving the use of an oxidant and amine to introduce the C−N bond, have also been reported.[7] However, unless the arene has particularly acidic C−H bonds, such as in perfluoroarenes or benzoxazole derivatives,[6c,d,7b] these methods require a minimum of 1.5 equiv, and not uncommonly solvent quantities of arene substrate, and yields are often based on the amidating reagent, not the arene.

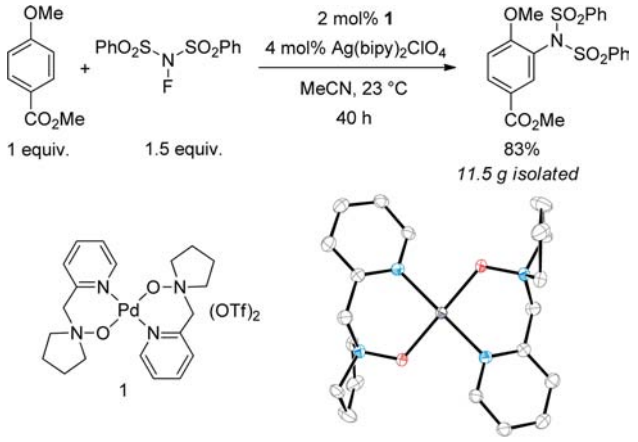

Figure 1. C−H imidation catalyzed by **1** and $Ag(bipy)_2ClO_4$, and X-ray structure of the cation of **1** (ellipsoids drawn at 50% probability).

Imidation of arenes by the reagent *N*-fluorobenzenesulfonimide (NFBS) is catalyzed by **1** and $Ag(bipy)_2ClO_4$ as shown in Figure 1. Both catalyst **1** and the Ag cocatalyst are required in the reaction; control experiments in which either is omitted gave <10% of imidated product, although the Ag cocatalyst can be replaced with $Ru(bipy)_3(PF_6)_2$ with similar results (Table 1, **2a**, **2b**). The reaction proceeds equally well in the presence or absence of light. Catalyst **1** was readily prepared from tetrakis(acetonitrile)palladium(II) triflate and the *N*-(2-pyridylmethyl)pyrrolidine-*N*-oxide ligand, which itself is available in two steps from commercial starting materials. The catalyst can also be generated in situ by mixing $Pd(NCMe)_4(OTf)_2$ and the ligand, with results nearly identical to those obtained with isolated and purified **1**. Because catalyst **1** is easily prepared and stored, we have used it directly in our investigations. The unusual pyridine-*N*-oxide ligand motif is exceptionally effective for the catalytic imidation; several other Pd-based catalysts supported by ligands such as bipyridine afforded product in at most 3% yield (Supporting Information). A rationale for the distinct ability of the amine-*N*-oxide to effect arene functionalization is presented below; we propose that the reactivity of well-defined catalyst **1** induced by the amine-*N*-oxide ligands is also responsible for the distinct reactivity when compared to other Pd-catalyzed amination reactions, such as benzylic amination with NFBS.[8]

A variety of arenes, including N- and S-heteroarenes, could be efficiently imidated (Table 1). Selectivity is substrate-intrinsic; resonance donors, such as alkoxy and halogen groups, direct imidation ortho/para, similar to electrophilic aromatic sub-

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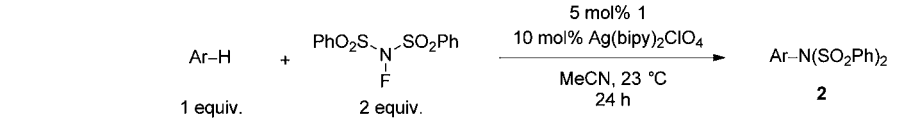
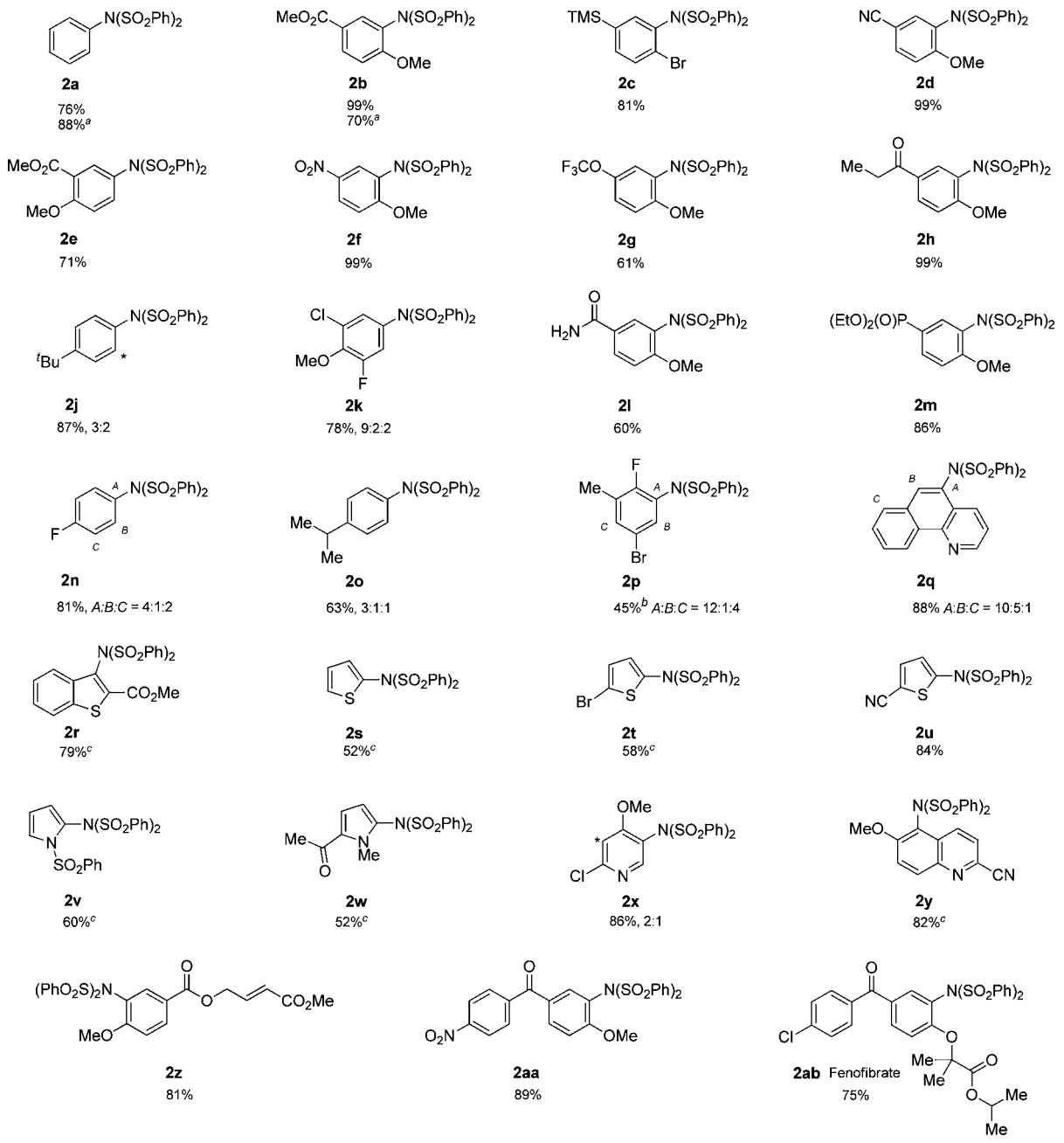
Table 1. Substrate Scope of C−H Imidation Catalyzed by 1 and $Ag(bipy)_2ClO_4$





[a]$Ru(bipy)_3(PF_6)_2$ (2.5 mol%) used in place of $Ag(bipy)_2ClO_4$, 50 °C reaction temperature, 0.2 M. [b]Along with arene imidation, 4% benzylic imidation was observed. [c]Reaction performed at 4 °C. * denotes site of amidation of other constitutional isomer.

stitution. Inductive donors do not direct as effectively (e.g., **2c**, **2j**), and substrates that lack a strong directing bias (e.g., **2n**−**2p**) afford mixtures of constitutional isomers. Functional groups that can cause problems for nitration such as esters and silanes are tolerated. Arenes more electron-poor than those shown in Table 1 show diminished reactivity and give lower yields. Competitive C−H fluorination and double imidation are significant side reactions for more electron-rich arenes, though performing the reaction at lower temperature (4 °C) can substantially reduce both side reactions for some substrates (**2r**−**2t**, **2v**, **2w**, **2y**). Potential coordinating directing groups do not influence regioselectivity as they do in directed catalytic C−H functionalization reactions[5] (**2b**, **2e**, **2l**, **2q**). The reactions for which the data are shown in Table 1 were performed rigorously dry and air-free, but similar results were obtained for reactions performed in air with reagent-quality solvents (see Supporting Information).

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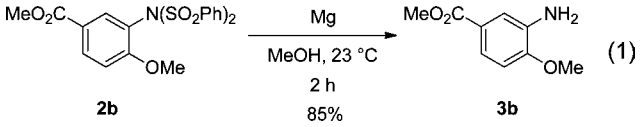
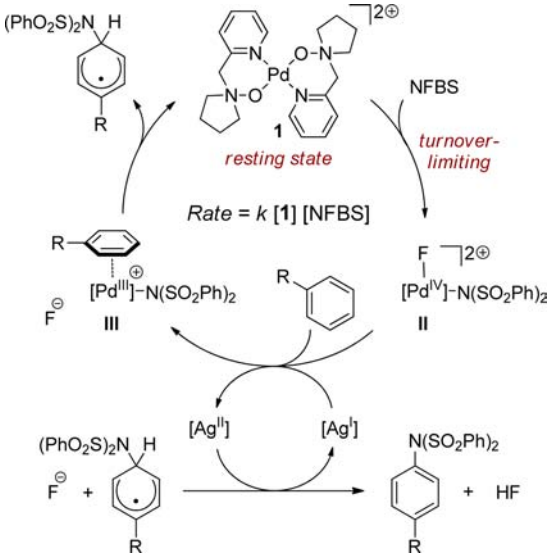
Product **2b**, synthesized on 12 g scale with this methodology, was chosen to demonstrate the removal of the sulfonyl protecting groups. Treatment of **2b** with magnesium in methanol under sonication produced aniline **3b** in 85% yield (eq 1).

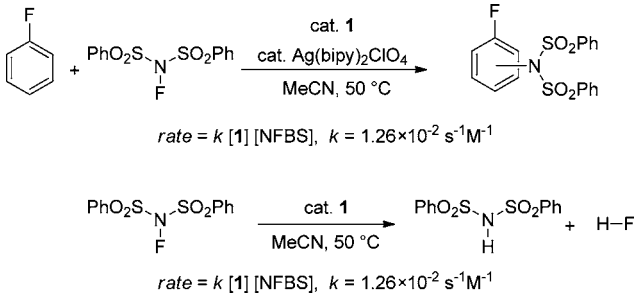


Mechanistic data, detailed below, unambiguously implicate a mechanism with the following noteworthy features: (1) oxidation of the bis-cationic Pd(II) complex **1** enabled by the amine-*N*-oxide ligands, (2) involvement of the cocatalyst in single-electron redox chemistry, (3) irreversible substrate binding prior to C−H bond functionalization, and (4) C−N bond formation occurring without C−H palladation. A plausible mechanistic proposal including these features is depicted in Scheme 1. Turnover-limiting oxidation of catalyst **1** yields Pd(IV) complex **II**. Single-electron reduction of **II** by $Ag(bipy)_2^+$ and substrate association follow to form Pd(III) intermediate **III**. Intermediate **III** formally transfers sulfonimidyl radical to the bound substrate, which expels a delocalized radical and regenerates **1**. Oxidation of the radical intermediate by $Ag(bipy)_2^{2+}$, followed by deprotonation, yields the sulfonimidated product.

Scheme 1. Proposed Catalytic Cycle



Scheme 2. Kinetic Study of Imidation and NFBS Reduction Catalyzed by 1



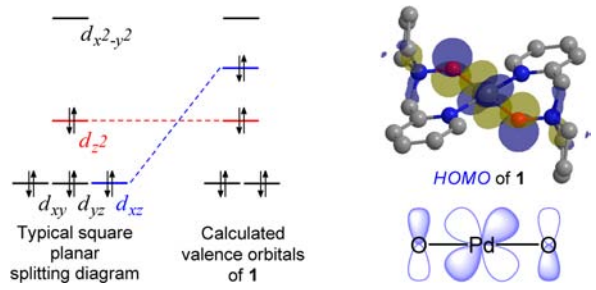


Figure 2. Valence orbital diagram of **1**.

Turnover-limiting oxidation of **1** by NFBS is supported by the measured rate law of the reaction, which is first-order with respect to both **1** and NFBS, and zero-order with respect to arene and $Ag(bipy)_2ClO_4$. When only NFBS and **1** are combined in acetonitrile, catalytic reduction of NFBS to $HN(SO_2Ph)_2$ and HF is observed, with the reducing equivalents evidently derived from the solvent. The rate of the catalytic reduction of NFBS is identical to that of NFBS consumption in the imidation reaction (Scheme 2). The rate law and the identical rate for both reactions shown in Scheme 2 establish turnover-limiting oxidation of **1** by NFBS to yield a common, short-lived high-valent Pd intermediate such as **II**.

Oxidation of Pd(II) complexes typically requires strongly σ-donating anionic ligands such as hydrocarbyl ligands, which are absent from **1**.[9] DFT calculations suggest that the HOMO of **1** is an extended M−L π-antibonding orbital of d_{xz} parentage from Pd, instead of the d_{z^2}-based orbital more typical of square-planar d^8 complexes. The oxygen lone pairs of the amine-*N*-oxide ligand interact strongly with the Pd-based d_{xz} orbital, driving it higher in energy than the d_{z^2}-based orbital (Figure 2). This interaction may explain how complex **1** can be oxidized by NFBS, despite its two formal positive charges.

We propose that the Ag cocatalyst serves to provide access to intermediate **III**, which is the putative intermediate responsible for C−N bond formation. $Ag(bipy)_2^{2+}$ was observed by EPR spectroscopy during catalysis, which implicates the cocatalyst in redox reactivity. Inner-sphere reactivity of the cocatalyst can be ruled out because coordinatively saturated $Ru(bipy)_3(PF_6)_2$ is also an effective cocatalyst. Furthermore, the oxidation of $Ru(bipy)_3^{2+}$ to $Ru(bipy)_3^{3+}$ by NFBS is substantially accelerated in the presence of **1**, consistent with oxidation of **1** to **II** by NFBS followed by single-electron oxidation of $Ru(bipy)_3^{2+}$ by **II** (see Supporting Information for details). Reduction of **II** by the cocatalyst to yield the C−N bond-forming species **III** explains why, for most arenes, substrate consumption is not observed in the absence of the cocatalyst.

Because oxidation of **1** by NFBS is turnover-limiting, the C−N bond-forming step cannot be studied kinetically. We therefore employed competition kinetic isotope effect (KIE) experiments to probe this step (Scheme 3). An inverse secondary intramolecular $k_H/k_D = 0.80 \pm 0.01$ for imidation of 1,3,5-trideuteriobenzene was measured. The measured KIE implicates rehybridization of the C−H bond from sp^2 to sp^3 in the product-determining transition state, consistent with C−N bond formation via inner-sphere addition of dibenzenesulfonimidyl radical to the bound arene in intermediate **III**. Inverse secondary KIEs are unusual for Pd-catalyzed C−H functionalization reactions; C−H palladations at Pd(II)[10] and Pd(IV)[11] typically display primary KIE values. Electrophilic addition would also be consistent with the observed intramolecular isotope effect. However, inverse secondary KIE values for electrophilic

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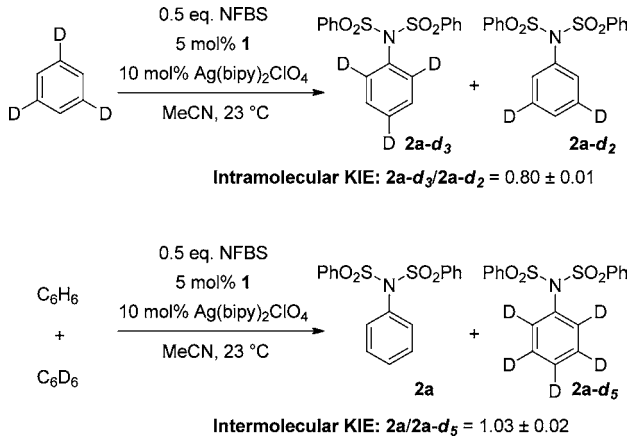
Scheme 3. Intra- and Intermolecular Kinetic Isotope Effects



substitution are rare;[12] most commonly, KIEs close to unity are observed for electrophilic processes due to the opposing effects of rehybridization and hyperconjugation on the zero-point vibrational energy of the affected C−H bond.[13] Addition of nitrogen-based radicals to arenes is well-precedented, including catalytic imidations with NFBS which are proposed to proceed through high-valent transition metal imidyl radical species.[14] Inner-sphere attack from an intermediate such as **III** to form the putative aryl radical is supported by an intermolecular competition $k_H/k_D = 1.03 \pm 0.02$. The absence of a KIE in this case is consistent with irreversible substrate binding prior to C−N bond formation.[10,11b]

We have described the first general aryl C−H imidation reaction which gives synthetically useful yields with only 1 equiv of arene and does not require coordinating directing groups. The transformation is made possible by a departure from the most common strategies: we have developed a catalyst supported by amine-*N*-oxide ligands, which enable oxidation of the doubly cationic Pd(II) complex prior to substrate activation. C−H functionalization proceeds from a high oxidation state complex without the formation of conventional organometallic intermediates. We anticipate that our distinct approach may find utility in other C−H functionalization reactions.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Detailed experimental procedures, spectroscopic characterization for all new compounds, mechanistic data, and crystallographic information files. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest. A provisional patent application on catalysts and methods presented herein has been filed through Harvard.

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