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Catalytic C–H Imidation of Aromatic Cores of Functional Molecules: Ligand-Accelerated Cu Catalysis and Application to Materials- and Biology-Oriented Aromatics

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Supporting Information

ABSTRACT: Versatile imidation of aromatic C–H bonds was accomplished. In the presence of copper bromide and 6,6′-dimethyl-2,2′-bipyridyl, a range of aromatics, such as polycyclic aromatic hydrocarbons, aromatic bowls, porphyrins, heteroaromatics, and natural products, can be imidated by *N*-fluorobenzenesulfonimide. A dramatic ligand-accelerated copper catalysis and an interesting kinetic profile were uncovered.

The introduction of amino groups can have dramatic effects on the properties of aromatic molecules. Amino groups can tune the optoelectronic properties of aromatic core structures by changing the highest occupied and lowest unoccupied molecular orbitals (HOMO/LUMO) and energies, introducing hydrogen-bonding sites, and adding unique three-dimensionality to otherwise flat structures. For these reasons, arylamines have long been privileged structures in materials-oriented[1] and biology-oriented aromatics[2] (Figure 1A). For example, arylamine derivatives are key components in the recently emerging perovskite-based solar cells[1c,d] and in live-cell super-resolution imaging.[2c]

The development of new amination reactions for arenes has thus made a significant impact in multidisciplinary fields of science including materials, biological, and pharmaceutical science. Conventionally, transition metal-catalyzed aminations of carbon–halogen bonds in halogenated arenes are largely regarded as reliable and versatile.[3] As an emerging synthetic route, transition metal-catalyzed aryl C–H aminations[4−9] have become an alternative to conventional amination. However, this approach is still in its infancy and has several disadvantages such as (1) the necessity for a directing group,[5] (2) the requirement for a large excess of arene,[6] and (3) limited substrate scope especially for 5-membered heterocycles.[7] Recently, Ritter reported a breakthrough in the form of a palladium-catalyzed aromatic imidation with the arene as the limiting reagent,[8a] and in 2014, Baran reported the ferrocene-catalyzed imidation.[8b] The substrate scope of these reactions was wide enough to cover benzene derivatives including bioactive molecules.[8a,b] Although arylamine materials are equally important as bioactive molecules, the synthetic chemistry community has paid less attention to the development of direct amination methods for the preparation of aromatic materials.[1,9] Since π-aromatics are expensive and the installation of directing groups is inherently difficult, methods to directly aminate 1 equiv of aromatics through a directing-group-free route is highly desirable.

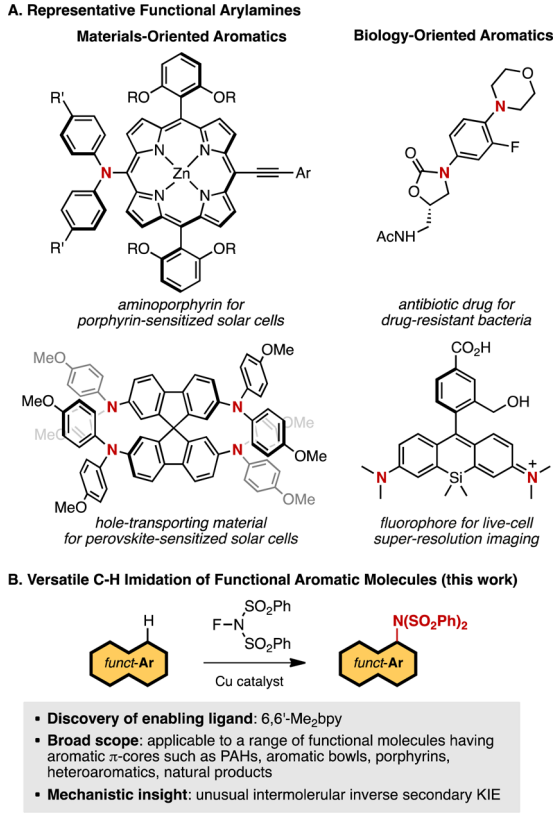

Figure 1. (A) Functional molecules having arylamine cores. (B) C–H imidation of functional aromatics.

Here, we describe a facile and versatile C–H imidation of arenes with *N*-fluorobenzenesulfonimide (NFSI) as an imide source that can be applied to a range of materials- and biology-oriented aromatics (Figure 1B).[7i,10] The combination of copper bromide (I) and 6,6′-dimethyl-2,2′-bipyridyl (6,6′-Me_2bpy) showed outstanding catalytic activity for the C–H imidation of a wide variety of substrates such as polycyclic aromatic

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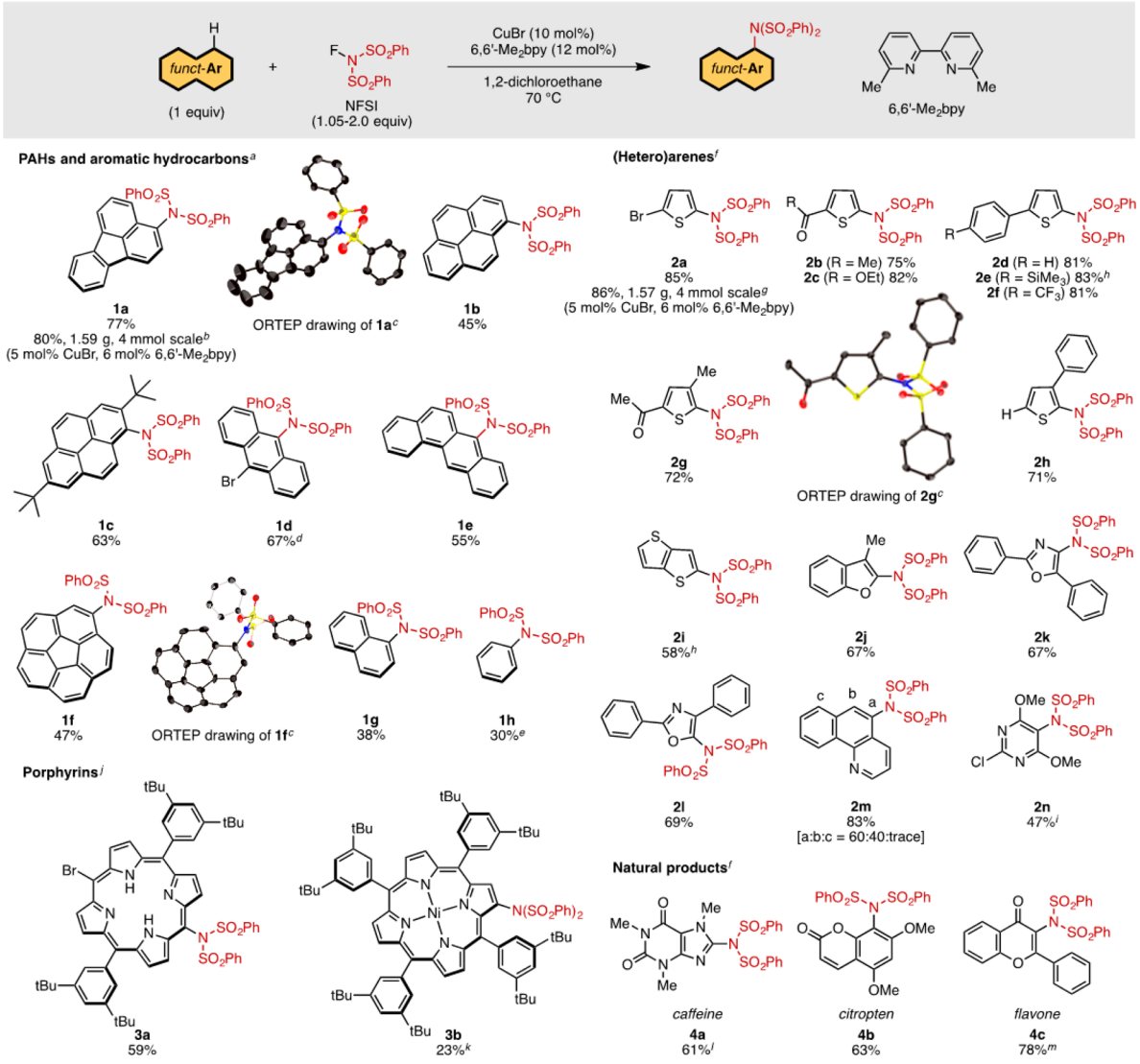

Figure 2. Scope of aromatic C−H imidation catalyzed by CuBr/6,6′-Me_2bpy. (a) Arene (0.20 mmol), NFSI (1.3 equiv), 1,2-dichloroethane (3 mL), 70 °C, 12 h. (b) Fluoranthene (4.0 mmol), NFSI (1.3 equiv), CuBr (5.0 mol %), 6,6′-Me_2bpy (6.0 mol %), 1,2-dichloroethane (20 mL), 12 h. (c) ORTEP drawing. Thermal ellipsoids are drawn at the 50% probability level and hydrogen atoms are omitted for clarity. (d) NFSI (1.05 equiv). (e) Arene (2 mmol), NFSI (0.2 mmol), CuBr (20 mol %), 6,6′-Me_2bpy (24 mol %), 1,2-dichloroethane (1 mL), 24 h. (f) Arene (0.20 mmol), NFSI (1.05 equiv), 1,2-dichloroethane (1 mL), 9 h. (g) 2-Bromothiophene (4.0 mmol), NFSI (1.3 equiv), CuBr (5.0 mol %), 6,6′-Me_2bpy (6.0 mol %), 1,2-dichloroethane (10 mL). (h) NFSI (1.3 equiv). (i) NFSI (1.5 equiv), CuBr (10 mol %), 6,6′-Me_2bpy (12 mol %), 9 h, then additional CuBr (10 mol %), 6,6′-Me_2bpy (12 mol %), 9 h. (j) Porphyrin (0.050 mmol), NFSI (1.3 equiv), CuBr (20 mol %), 6,6′-Me_2bpy (24 mol %), 1,2-dichloroethane (2 mL), 12 h. (k) NFSI (2 equiv). (l) 25 °C, 15 h. (m) NFSI (1.05 equiv), CuBr (10 mol %), 6,6′-Me_2bpy (12 mol %), 1,2-dichloroethane (1 mL), 8 h, then additional NFSI (1.05 equiv), CuBr (10 mol %), 6,6′-Me_2bpy (12 mol %), 16 h.

hydrocarbons (PAHs), aromatic bowls, porphyrins, heteroaromatics, and natural products. An interesting mechanistic insight was gained through kinetic studies on this newly developed C−H imidation catalysis.

The scope of the aromatic C−H imidation reaction is shown in Figure 2. For example, treatment of fluoranthene with 1.3 equiv of NFSI in the presence of a catalytic amount of CuBr (10 mol %) and 6,6′-Me_2bpy (12 mol %) in 1,2-dichloroethane at 70 °C for 12 h provided the corresponding imidated product **1a** in 77% yield as a single isomer. The structure of **1a** was confirmed unambiguously by X-ray crystallographic analysis. The reaction was scalable such that 4 mmol of fluoranthene could be efficiently converted to 1.59 g of **1a** in 80% yield with a reduced loading of CuBr (5 mol %) and 6,6′-Me_2bpy (6 mol %). Pyrene and 2,7-di(*tert*-butyl)pyrene were cleanly imidated to provide **1b** and **1c**, respectively, with virtually complete regioselectivity. The reaction of 9-bromoanthracene furnished **1d**, leaving the bromo group intact. Benzo[*a*]anthracene reacted regioselectively at the less hindered position to provide **1e** in 55% yield. Corannulene, a unique bowl-shaped PAH, was also imidated to afford **1f** in reasonable yield. Though not high-yielding, simple electron-neutral aromatics such as naphthalene and benzene actually can be imidated under CuBr/6,6′-Me_2bpy.

In addition to PAHs, a wide variety of 5-membered heteroarenes that are ubiquitous in organic materials and pharmaceutically relevant molecules could be regioselectively functionalized. Various substituted thiophenes underwent regioselective C−H imidation at the α-position to afford **2a**−**g** in high yields with good tolerance of functional groups (halide, ketone, ester, and silyl groups). The reaction was also scalable,

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and 4 mmol of 2-bromothiphene was smoothly converted to **2a** in 80% yield. 3-Phenylthiophene reacted regioselectively to provide **2h**. Other 5-membered heteroaromatics such as thieno[3,2-*b*]thiophene, benzofuran, and oxazole derivatives were efficiently converted into **2i**–**l**. Nitrogen atoms contained within heteroaromatic structures were not observed to play a role as directing groups in the reaction. For example, benzo[*h*]-quinolone was transformed to **2m** as a mixture of regioisomers. Electron-rich methoxy-substituted 6-membered arenes were also viable substrates (**2n**). Along with PAHs and heteroarenes, functional aromatic π-materials such as porphyrins could also be employed as substrates. 5-Bromo-10,20-diarylporphyrin was selectively imidated at the *meso*-position to produce **3a** in 59% yield. Although the yield was modest, 5,10,15,20-tetraarylporphyrin also underwent selective imidation. Natural products including caffeine, citropten, and flavone were smoothly converted into the corresponding imidated products **4a**–**c**.

During the course of our catalyst development process, we discovered a significant substituent effect of bipyridyl- and phenanthroline-based ligands that led to establishment of the CuBr/6,6′-Me_2bpy system for aromatic C–H imidation. Shown in Figure 3 are the effects of representative ligands in the copper-

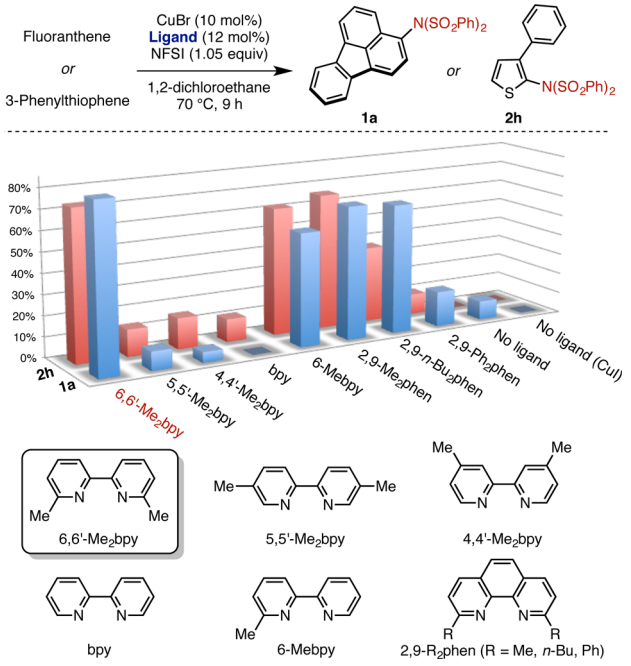
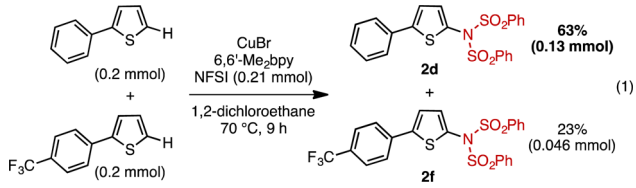


Figure 3. Dramatic ligand effect in Cu-catalyzed C–H imidation.

catalyzed imidation of fluoranthene and 3-phenylthiophene. While the C–H imidation did not occur with catalytic amounts of CuBr or CuI[7i] in the absence of ligands, we discovered a huge rate-acceleration effect upon addition of ligands where one or two methyl groups were attached at the 6-position(s) of the 2,2′-bipyridyl backbone (6-Mebpy and 6,6′-Me_2bpy). Interestingly, methyl substitution at the 4- and 5-positions (4,4′-Me_2bpy and 5,5′-Me_2bpy) had little effect on the catalytic activity, indicating that the observed rate-acceleration by 6,6′-Me_2bpy is steric in nature. The ligands having a phenanthroline backbone were slightly less active than those with a bipyridyl backbone (2,9-Me_2phen vs 6,6′-Me_2bpy). Phenanthroline having a bulkier *n*-butyl group (2,9-*n*-Bu_2phen) or phenyl group (2,9-Ph_2phen) retarded the reaction. Overall, this represents a unique, steric-accelerated ligand effect in the copper-catalyzed C–H trans-

formation that not only is counterintuitive but also reflects the unique role of *N*-bidentate ligands in the reaction mechanism.

To shed light on the reaction mechanism, we conducted several kinetic experiments. First, a mixture of 2-phenylthiophene and 2-(4-trifluoromethylphenyl)thiophene with NFSI was subjected to copper catalysis in order to elucidate the electronic preference of the reacting arenes (eq 1). Under

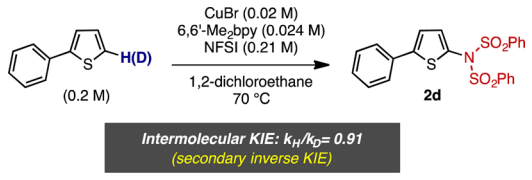


competitive conditions (equimolar amounts of the three reagents), we observed the predominant formation of **2d**, which was generated from the more electron-rich 2-phenylthiophene. Similarly, a competitive reaction between 2-phenylthiophene and 2-acetylthiophene resulted in the exclusive formation of **2d**. Furthermore, sterically congested but more electron-rich 2-acetyl-4-methylthiophene reacted faster than 2-acetylthiophene to afford **2g** as the predominant product (see the Supporting Information for details). These results clearly indicate that, in essence, the present imidation can be described as a net electrophilic substitution of a nucleophilic arene.

Although the details remain unclear at present, we assume that NFSI is the first-reacting agent with CuBr/6,6′-Me_2bpy in the productive pathway, generating an electrophilic imidyl radical as an active species for the reaction.[10c] The thus-generated imidyl radical reacts with arene to provide the corresponding product. It is also possible that an imidyl cation or a metal-aminyl species[12] is an active species.

Two independent deuterium labeling studies for the reactions of 2-phenylthiophene and 2-deuterio-5-phenylthiophene showed the intermolecular kinetic isotope effect (KIE) value as $k_H/k_D = 0.91$ (Scheme 1). Although the observation of an inverse

Scheme 1. Independent KIE Experiments



KIE value is rare in C–H functionalization chemistry, this secondary and inverse KIE provides significant information. It has been known that inverse secondary KIEs can be observed in some reactions where a C–H (C–D) bond experiences $sp^2 \rightarrow sp^3$ rehybridization in the rate-determining step such as electrophilic nitration of benzene and carbonyl addition reactions.[11] Thus, the observed inverse secondary KIE implicates the addition of the imidyl radical to the arene as the rate-determining step. Interestingly, the Ritter group recently reported quite distinct KIE values in their palladium-catalyzed aromatic C–H imidation.[8a] It was found that *intermolecular* and *intramolecular* KIE values were 1.03 and 0.8, respectively, which led them to conclude that irreversible substrate binding occurs before C–N bond formation and that the rate-determining step is the oxidation of the palladium catalyst with NFSI.

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Further studies are clearly needed to fully uncover the precise mechanism of our copper-catalyzed C−H imidation as well as the significance of the ligand effect in copper catalysis. Nevertheless, with a direct method for activating/converting otherwise difficult aromatic substrates in hand, we and others are now in a position to synthesize a range of new functional arylamine materials.[13]

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures and spectral data for all compounds, including scanned images of ^{1}H and ^{13}C NMR spectra. 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.

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(13) For the transformation of the imide group to an amine, see ref 8a.

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