

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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S 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.

T he 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 hydrogenbonding sites, and adding unique three-dimensionality to otherwise flat structures. For these reasons, arylamines have long been privileged structures in materials-oriented¹ and biology-oriented aromatics² (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 aminations⁴⁻⁹ 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, (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



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

installation of directing groups is inherently difficult, methods to directly aminate 1 equiv of aromatics through a directing-groupfree route is highly desirable.

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'-Me₂bpy) showed outstanding catalytic activity for the C–H imidation of a wide variety of substrates such as polycyclic aromatic

Received: December 21, 2014



Figure 2. Scope of aromatic C–H imidation catalyzed by CuBr/6,6'-Me₂bpy. (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'-Me₂bpy (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'-Me₂bpy (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'-Me₂bpy (6.0 mol %), 1,2-dichloroethane (10 mL). (h) NFSI (1.3 equiv). (i) NFSI (1.5 equiv), CuBr (10 mol %), 6,6'-Me₂bpy (12 mol %), 9 h. (j) Porphyrin (0.050 mmol), NFSI (1.3 equiv), CuBr (20 mol %), 6,6'-Me₂bpy (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'-Me₂bpy (12 mol %), 1,2-dichloroethane (1 mL), 8 h, then additional NFSI (1.05 equiv), CuBr (10 mol %), 6,6'-Me₂bpy (12 mol %), 1,2-dichloroethane (1 mL), 8 h, then additional NFSI (1.05 equiv), CuBr (10 mol %), 6,6'-Me₂bpy (12 mol %), 1,2-dichloroethane (1 mL), 8 h, then additional NFSI (1.05 equiv). (l) 25 °C, 15 h. (m) NFSI (1.05 equiv), CuBr (10 mol %), 6,6'-Me₂bpy (12 mol %), 1,2-dichloroethane (1 mL), 8 h, then additional NFSI (1.05 equiv), CuBr (10 mol %), 6,6'-Me₂bpy (12 mol %), 1,2-dichloroethane (1 mL), 8 h, then additional NFSI (1.05 equiv), CuBr (10 mol %), 6,6'-Me₂bpy (12 mol %), 1,2-dichloroethane (1 mL), 8 h, then additional NFSI (1.05 equiv), CuBr (10 mol %), 6,6'-Me₂bpy (12 mol %), 1,2-dichloroethane (1 mL), 8 h, then additional NFSI (1.05 equiv), CuBr (10 mol %), 6,6'-Me₂bpy (12 mol %), 1,2-dichloroethane (1 mL), 8 h, then additional NFSI (1.05 equiv), CuBr (10 mol %), 6,6'-Me₂bpy (12 mol %), 1,2-dichloroethane (1 mL), 8 h, then additional NFSI (1.05 equiv), Cu

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'-Me₂bpy (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'-Me₂bpy (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'-Me₂bpy.

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,

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'-Me₂bpy 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 CuI⁷ⁱ 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′-Me₂bpy). Interestingly, methyl substitution at the 4- and 5-positions (4,4′-Me₂bpy and 5,5′-Me₂bpy) had little effect on the catalytic activity, indicating that the observed rate-acceleration by 6,6′-Me₂bpy is steric in nature. The ligands having a phenanthroline backbone were slightly less active than those with a bipyridyl backbone (2,9-Me₂phen vs 6,6′-Me₂phen) or phenyl group (2,9-Ph₂phen) 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-phenyl-thiophene. Similarly, a competitive reaction between 2-phenyl-thiophene 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 species¹² 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 $k_{\rm H}/k_{\rm D} = 0.91$ (Scheme 1). Although the observation of an inverse





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.

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

S Supporting Information

Detailed experimental procedures and spectral data for all compounds, including scanned images of ¹H and ¹³C 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.

ACKNOWLEDGMENTS

This work was supported by the ERATO program from JST (K.I.) and a Grant-in-Aid from JSPS (26888007 to K.M.). We thank Dr. Yasutomo Segawa and Mr. Takehisa Maekawa for assistance with X-ray crystallography, Dr. Keiko Kuwata with HRMS measurement, and Mr. Kei Muto with KIE experiments. Mr. Kyohei Ozaki is acknowledged for preparation of the starting materials. We thank Dr. Ayako Miyazaki and Prof. Cathleen M. Crudden for critical comments, and Prof. Jay Siegel for the generous gift of corannulene. ITbM is supported by the World Premier International Research Center (WPI) Initiative, Japan.

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