

Electrocatalytic C–N Coupling via Anodically Generated Hypervalent Iodine Intermediates

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Abstract Development of new electrosynthetic chemistry promises to impact the efficiency and sustainability of organic synthesis. Here we demonstrate that anodically generated hypervalent iodine intermediates effectively couple interfacial electron transfer with oxidative C–H/N–H coupling chemistry. The developed hypervalent iodine electrocatalysis is applicable in both intra- and intermolecular C–N bond-forming reactions. Available mechanistic data indicates that anodic oxidation of aryl iodides generates a transient I(II) intermediate that is critically stabilized by added acetate ions. This report represents the first example of metal-free hypervalent iodine electrocatalysis for C–H functionalization and provides mechanistic insight that we anticipate will contribute to the development of hypervalent iodine mediators for synthetic electrochemistry.

Electrochemistry is an attractive approach to sustainable synthesis that obviates the need for stoichiometric redox reagents and thus, generation of the attendant waste streams.¹ Due to its inherent tunability and scalability, electrosynthesis should impact many of the enormous variety of organic transformations in which electrons are added to, or removed from, substrates. In practice, challenges such as 1) the sluggish interfacial electron transfer rates for many organic molecules, which necessitates application of substantial overpotential to achieve practical current densities,² and 2) the need to couple the single-electron events that are typical of electrochemistry with the multi-electron events required for bond-breaking and -making in organic reactions, can

limit direct electrocatalysis (Figure 1).³ Indirect electrocatalysis, in which small molecule electrocatalysts that display well-behaved electrochemistry convey applied potential from the working electrode to the bulk reaction medium, has emerged as an important strategy in selective organic electrocatalysis.⁴ Redox catalysts can both facilitate electron transfer and couple a diverse array of substrate functionalization mechanisms to the electrochemical stimulus. Important methods based on quinone-,⁵ amine-,⁶ nitroxyl radical-,⁷ and transition metal-redox catalyst⁸ have been disclosed.

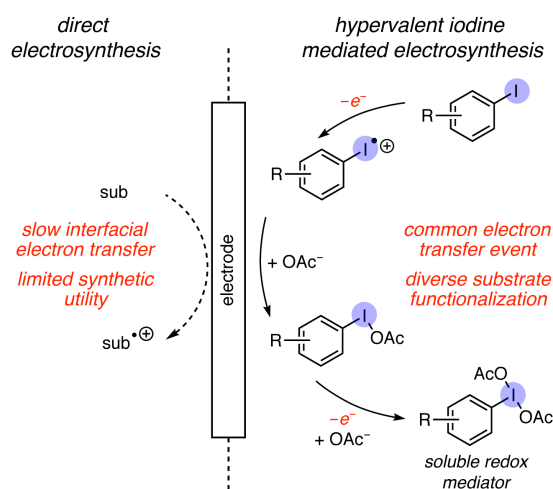


Figure 1. Strategies for electrocatalytic chemistry. The generation of soluble redox mediators, such as hypervalent iodine intermediates, provides the opportunities to couple a diverse set of substrate functionalization mechanisms to a common interfacial electron transfer event.

Hypervalent iodine reagents are a class of organic oxidants that have been deployed in a wide variety of substrate functionalization reactions.⁹ Electrochemical oxidation of aryl iodides typically requires substantial overpotential,¹⁰ thus hypervalent iodine electrochemistry has largely been limited to *ex cell* applications,¹¹ in which aryl iodides are electrolyzed in the absence of substrate and subsequently used as stoichiometric reagents, or implemented in the context of flow systems.^{12,13} During the development of aerobic hypervalent iodine catalysis,¹⁴ we discovered that the aerobic generation of hypervalent iodine compounds proceeded through the intermediacy of

acetate-stabilized iodanyl radicals (*i.e.* I(II) species; Figure 1).¹⁵ We speculated that electrolysis of aryl iodides in the presence of acetate sources may provide access to the same iodanyl radicals and thus enable hypervalent iodine electrocatalysis. Here, we report that facile acetate-dependent anodic oxidation of aryl iodides enables hypervalent iodine electrocatalysis of both intra- and intermolecular C–H / N–H coupling reactions.

We initiated our investigations of hypervalent iodine electrocatalysis by examining the intramolecular C–H/N–H coupling with *N*-([1,1'-biphenyl]-2-yl)acetamide (**1a**) to afford *N*-acetylcarbazole (**2a**) in the presence of stoichiometric amounts of aryl iodide mediators (Figure 2).¹⁶ Based on the relative onset potentials for oxidation of various substituted aryl iodides (Table S1), we selected 4-iodoanisole (**3a**) as an initial catalyst. Constant potential electrolysis (CPE) of a mixture of **1a** and **3a** in 1,1,1,3,3,3-hexafluoroisopropanol (hfip) with 0.2 M [TBA]PF₆ as supporting electrolyte resulted in no desired C–N bond forming chemistry and partial decomposition of the starting material (87% of **1a** was recovered following electrolysis; TBA = tetrabutylammonium). Based on the hypothesis that acetate ligands can stabilize initially generated iodanyl radicals,¹⁵ we examined the impact of added [TBA]OAc on the electrolysis of **3a** and found that 2.0 equivalents of [TBA]OAc, with respect to substrate, promotes electrochemical C–N coupling in 61% yield (see Table S2 for results from varying [TBA]OAc loading). No C–N coupled product was obtained in absence of aryl iodide. The loading of 4-iodoanisole can be lowered; we find the 25 mol% catalyst loading gives the best yield of 76% and that further reduction of the catalyst loading leads to attenuation of the reaction efficiency (Table S3). Examination of other solvents, *N*-protecting groups, reaction temperatures, and electrode materials did not result in substantively better reaction efficiency (Tables S3-S5). Redox balance in the

observed chemistry is achieved by proton reduction (presumably of hfip) to generate H₂, which was observed by GC analysis of the reaction headspace (Figure S1).

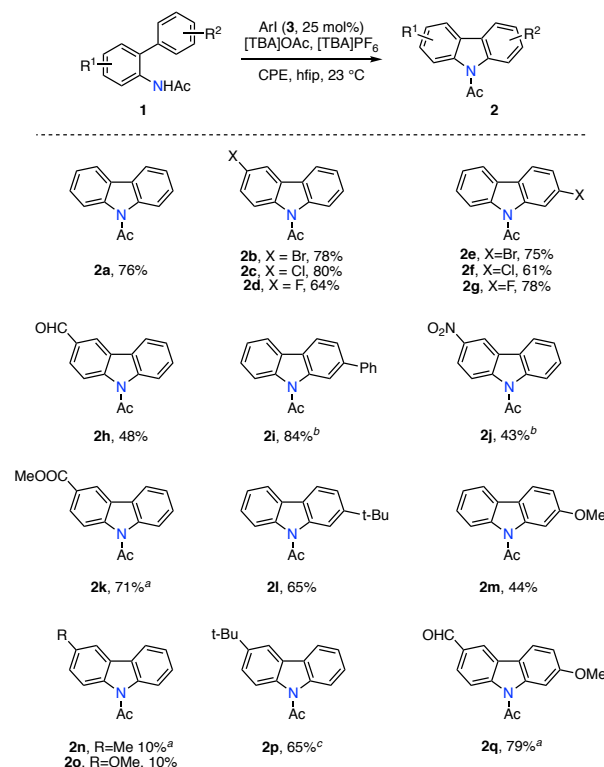


Figure 2. Intramolecular C–H/N–H coupling via hypervalent iodine electrocatalysis (yields are of isolated products). Standard conditions: catalyst **3a**, constant potential electrolysis (CPE) for 80 C, 1.5V vs. Ag/Ag⁺, undivided cell, glassy carbon anode, platinum-plated cathode, and Ag/Ag⁺ reference electrode. ^acatalyst **3b**, CPE for 80 C, 1.9V vs. Ag/Ag⁺. ^bcatalyst **3a**, constant current electrolysis (CCE) at 5 mA for 5 F/mol. ^cCPE in the absence of catalyst.

With the optimized conditions in hand, we evaluated the scope of intramolecular C–N bond-forming chemistry (Figure 2). We specifically examined the impact of substituents in the 4- and 5'-positions of the [1,1'-biphenyl]-2-acetamide scaffold (*i.e.* **1**) under constant potential conditions with **3a** as catalyst. We found that both 4- and 5'-halogenation are well tolerated (**2b-2g**), as is the introduction of weakly electron withdrawing groups like 4-aldehyde (**2h**) or 5'-phenyl (**2i**). Under these conditions, substrates with more electron-withdrawing substituents, such as nitro (**2j**) and ester (**2k**), did not afford the expected carbazole. Based on the hypothesis that these more electron-

deficient substrates may require a more oxidizing hypervalent iodine catalyst, we employed 2,2'-diiodo-4,4',6,6'-tetramethyl-1,1'-biphenyl (**3b**)¹⁷ as catalyst (onset potential for oxidation is 1.78 V vs Ag⁺/Ag for **3b** compared to the onset potential of **3a** which is 1.43 vs Ag⁺/Ag). The more oxidizing conditions allowed both **3j** and **3k** to be accessed (43% and 71% yields, respectively). Electron donating groups were tolerated in the 5'-position (*i.e.* **2l** and **2m**). In contrast, introduction of methyl and methoxy groups at the 4-position (*i.e.* **1n** and **1o**) led to trace amount of carbazole and starting material decomposition. We speculate that the presence of electron donating substituents at the 4-position decreases the onset potential for direct substrate oxidation below that of the aryl iodide catalyst and thus leads to direct substrate activation (for CV analysis, see Figure S2-S4). Consistent with this hypothesis, CPE of 4-*t*-butyl acetamide (**1p**) in the absence of aryl iodide catalyst afforded **2p** in 65% yield (none of the other substrates in Figure 2 participate in C–N coupling chemistry in the absence of **3**).¹⁸ In general, the broader tolerance for substitution in the 5'-position than the 4-position is consistent with the smaller impact of substituents in this position on the onset potential for direct substrate oxidation (Figure S2). Finally, C–N bond-formation can be accomplished in multifunctional substrates, as highlighted by the synthesis of **2p**, a precursor to anti-HIV natural product clauszoline-K.¹⁹

Hypervalent iodine electrocatalysis can also be applied to intermolecular C–N bond-forming chemistry (Figure 3). Catalyst **3b** was used as the aryl iodide mediator due to its previously reported success in furnishing intermolecular C–H amination reactions (see Table S6 for analysis of other aryl iodide catalysts).²⁰ CPE in the presence of 1 equivalent of **3b** affords 81% yield of *N*-phenylated compound **5a** and the loading can be decreased to 25 mol% without significantly depressing the yield (71% of isolated product). Similar to the above-described intramolecular C–N bond-forming chemistry, no C–N coupling products are observed in the absence of either aryl

iodide or [TBA]OAc. The intermolecular C–H amination reactions with halogenated aryl group were accomplished in 35–82% yields (**5b–f**). Electron-rich hydrocarbons like toluene, xylene, and naphthalene were not viable substrates in the intermolecular N–H arylation.

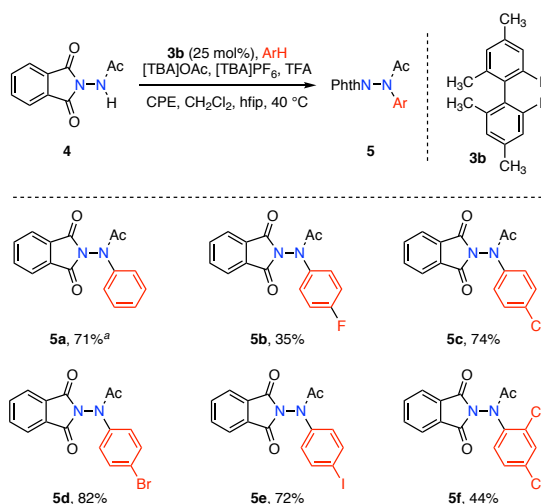
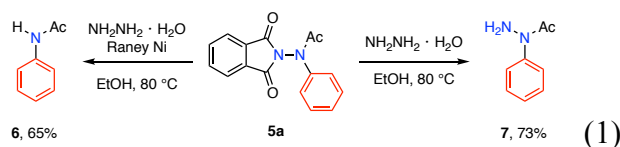


Figure 3. Intermolecular C–H / N–H coupling via hypervalent iodine electrocatalysis (yields are of isolated products). Standard conditions: catalyst **3b**, CPE for 80 C, 2.0 V vs. Ag/Ag⁺, undivided cell, glassy carbon anode, platinum-plated cathode, and Ag/Ag⁺ reference. ^aCPE at 1.8 V.

Compound **5a** can be elaborated to the corresponding arylhydrazine (**7**), which are useful precursors to various heterocyclic compounds, by treatment with hydrazine (Eq 1).²¹ Alternately, hydrogenolysis of the N–N bond leads to *N*-acyl aniline derivatives (**6**), which can be challenging to synthesize by transition-metal-catalyzed cross-coupling reactions due to the stability of ammonia adducts of many transition metals.²²



Hypervalent iodine catalyzed C–N bond forming chemistry is most often accomplished with peracid terminal oxidants.²³ While recently developed aerobic hypervalent iodine chemistry proceeds through a distinct one-electron mechanism, the autoxidation chemistry used to couple O₂ reduction to aryl iodide oxidation, produces a significant steady state concentration of peracid. For this reason, the developed aerobic oxidation conditions display substrate scope limitations similar to those displayed by peracid conditions when assayed by robustness analysis.^{15,24} We were interested in evaluating the robustness of the developed hypervalent iodine electrocatalysis to evaluate if a broader functional group tolerance may be achieved by avoiding the use or evolution of peracids. Figure 4 displays both the impact of a variety of small-molecule additives on the yield of intramolecular C–H/N–H coupling as well as the amount of recovered additive following the electrochemical reaction (see also Figure S5). The efficiency of electrocatalytic C–N coupling is superior to aerobic conditions for all additives and similar to that of peracetic acid. The electrochemical conditions display higher additive recovery, in particular when challenged against oxidatively labile functional groups, such as alkynes and olefins (96% and 92%, respectively).

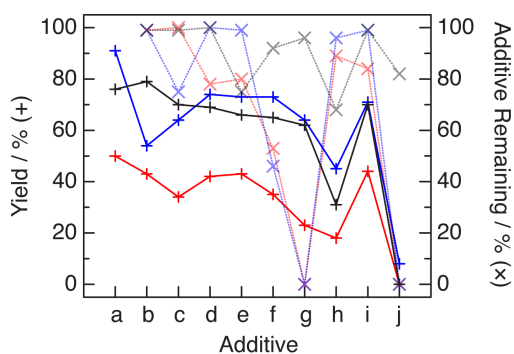


Figure 4. Summary of the results of robustness analysis. Reaction yield (solid lines) and additive recovery (dotted lines) for aerobic conditions (—,···), m-CPBA conditions (—,···), and electrochemical conditions (—,···). (a) No additive, (b) cycloheptanone, (c) benzaldehyde, (d) dimethyl terphalate, (e) 1-nonanol, (f) 1-octyne, (g) 1-octene, (h) *N*-phenylacetamide, (i) 2-chloropyridine, (j) phenol.

We envision two potential limiting mechanisms for the electrosynthesis of hypervalent iodine compounds (Figure 5). The initial interfacial electron transfer could be between the working

electrode and the aryl iodide to generate an I(II) intermediate (**8**), which would then be trapped by exogenous acetate ion to generate acetoxy iodanyl radical **9**. Subsequent oxidation chemistry would ultimately lead to I(III) (**10**). Alternatively, the observed acetate-dependent chemistry might arise from an interrupted Kolbe electrolysis²⁵ in which initially formed acetoxy radicals add to aryl iodides to generate iodanyl radical intermediates (**9**), which would subsequently undergo further oxidation to I(III) (**10**). Available evidence, summarized below, is most consistent with the former mechanistic scenario.

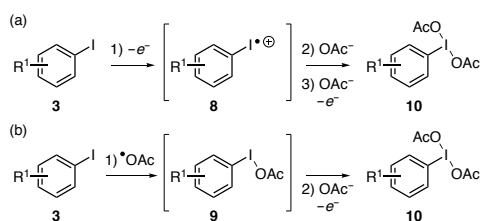


Figure 5. Potential mechanisms for the observed acetate-dependent hypervalent iodine electrocatalysis. a) Interfacial electron transfer with aryl iodide would initially generate a I(II) cation. b) Interfacial electron transfer with acetate would initially generate acetoxy radicals.

Examination of the cyclic voltammogram (CV) of iodoarenes as a function of scan rate indicate that while the oxidation is irreversible at low scan rates (*i.e.* < 100 mV/sec), chemical reversibility emerges at higher scan rates (>250 mV/sec, Figure S6-S7).²⁶ Addition of [TBA]OAc to a CV experiment of either 4-iodoanisole or 4-iodotoluene results in both the loss of reversibility and the substantial increase in the anodic current (I_{pa}), indicating that the electrochemically generated species is trapped by added acetate (Figure S8-S10). The measured peak potential is linearly correlated with the square root of scan rate, which indicates electron transfer from a solution-bound, not surface adsorbed, species (Figure S11-S12).²⁷

Regarding the potential that the reported hypervalent iodine chemistry arises from an interrupted Kolbe electrolysis, we observed that electrolysis of CH_3CN solutions containing [TBA]OAc and [TBA]PF₆ results in the products expected of Kolbe electrolysis: ethane, methane,

and CO₂ (observed by GC analysis of reaction headspace, Figure S13). In contrast, acetate oxidation is suppressed in hfip, the solvent in which the chemistry is (uniquely) effective (no volatiles are observed in headspace analysis as well as no oxidation peak in the CV (Figure S14-S15)). The suppression of Kolbe electrolysis is consistent with strong hydrogen bonding of acetate to the acidic O–H of hfip (pK_a = 9.3).²⁸ Consistent with this hypothesis, NMR analysis of solutions containing both hfip and [TBA]OAc reveals a significant downfield shift in the methine resonance (Figure S16). Job analysis indicates a 1:1 adduct is formed between these two species (Figure S17 and Table S7) and NMR analysis provides an equilibrium constant for association of 0.767 (Figure S18-S20 and Table S8).

In summary, we report the first example of hypervalent iodine electrocatalysis for C–H amination chemistry. The developed chemistry is applicable to both intra- and intermolecular C–N bond-forming reactions and demonstrates complementary functional group tolerance to both aerobic and peracid-based methods. Mechanistic experiments indicate the critical role of acetate to stabilize initially generated iodanyl radical intermediates. Given the breadth of the synthetic chemistry available to hypervalent iodine intermediates and the number of reports of hypervalent iodine electrosynthesis, demonstration of strategies to facilitate facile electrochemical generation of hypervalent iodine species promises to significantly impact the sustainable use of hypervalent iodine intermediates in synthesis.

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