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Communication

# 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 indicate 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] Because of its inherent tunability and scalability, electrosynthesis could impact 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 necessitate 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 multielectron events required for bond-breaking and -making in organic reactions, can limit direct electrosynthesis (Figure 1).[3] Indirect electrocatalysis, in which small molecule redox catalysts (i.e., electrocatalysts) convey applied potential from the working electrode to the bulk reaction medium, has emerged as an important strategy in selective organic electrocatalysis.[4] Soluble electrocatalysts facilitate interfacial electron transfer, circumvent unselective side reactions, and can couple a diverse array of substrate functionalization mechanisms to the electrochemical stimulus.[1g] Important methods based on quinone-,[5] amine-,[6] nitroxyl radical-,[7] and transition metal-redox catalysts[8] have been disclosed.

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] *Ex cell* methods require stoichiometric generation of hypervalent iodine species, which obviate many of the potential advantages of electrochemistry *vis-à-vis* sustainability, and fail to address the central challenge of hypervalent iodine electrocatalysis, which is achieving selective oxidation of aryl iodides in the presence of substrates.[4d]

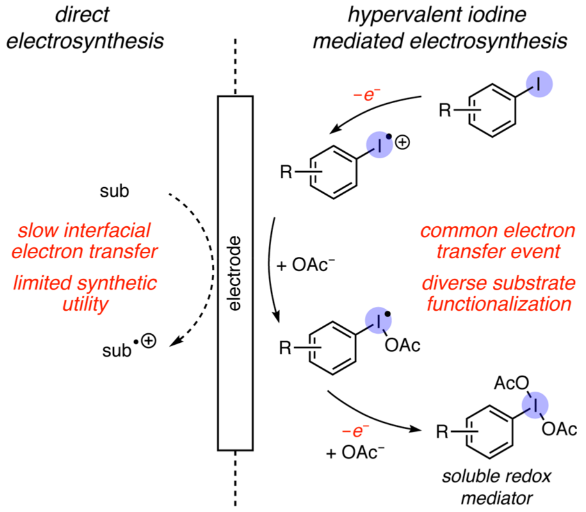

**Figure 1.** Strategies for electrosynthetic chemistry. The generation of soluble redox mediators, such as hypervalent iodine intermediates, provides the opportunities to couple a diverse set of substrate functionalization mechanisms to a common interfacial electron transfer event.

During the development of aerobic hypervalent iodine catalysis,[14] we proposed 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 hypothesized that anodic oxidation of aryl iodides in acetate-rich media could provide access to the

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same acetate-stabilized iodanyl radicals and thus enable the development of hypervalent iodine electrocatalysis. Here, we report that acetate-dependent anodic oxidation of aryl iodides enables hypervalent iodine electrocatalysis of both intra- and intermolecular C−H/N−H coupling reactions. Further, we report a series of mechanistic studies that demonstrate the importance of transient iodanyl radical intermediates in electrocatalysis.

We initiated our investigations of hypervalent iodine electrocatalysis by examining the onset potential for variously substituted iodoarenes by cyclic voltammetry (CV, Table S1) and identified 4-iodoanisole (**3a**) as an attractive initial catalyst target (onset potential ∼1.40 V vs $Ag^+/Ag$). We chose the intramolecular C−H/N−H coupling of *N*-([1,1′-biphenyl]-2-yl)acetamide (**1a**) to afford *N*-acetylcarbazole (**2a,** pictured in Figure 2) as an initial reaction target to evaluate hypervalent iodine electrochemistry because this transformation has important precedent both with stoichiometric hypervalent iodine promoters and hypervalent iodine catalysis in the presence of peracid terminal oxidants.[16]

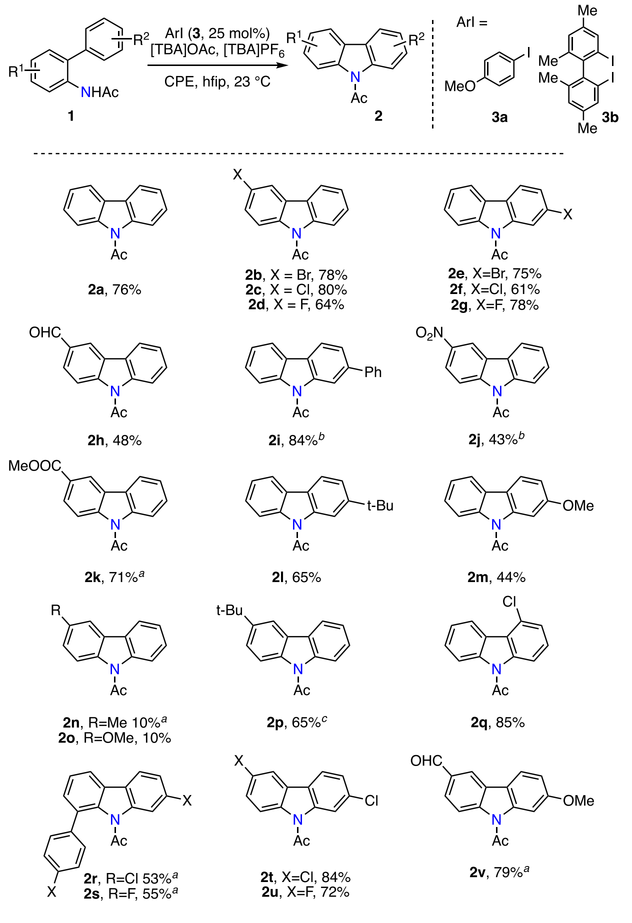

**Figure 2.** Intramolecular C−H/N−H coupling via hypervalent iodine electrocatalysis (yields are of isolated products). Standard conditions: catalyst **3a**, CPE at 1.5 V versus $Ag^+/Ag$ for 80 C, undivided cell, glassy carbon anode, platinum-plated cathode, and $Ag^+/Ag$ reference electrode. *a*,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

Constant potential electrolysis (CPE) of a 1:1 mixture of **1a** and **3a** in 1,1,1,3,3,3-hexafluoroisopropanol (hfip) with 0.2 M $[TBA]PF_6$ as supporting electrolyte resulted in no C−N bond-forming chemistry and partial decomposition of the starting material (87% of **1a** was recovered following electrolysis; TBA = tetrabutylammonium).[17] Based on the hypothesis that acetate ligands can stabilize initially generated iodanyl radicals,[15] we examined the electrolysis of a mixture of **1a** and **3a** with added [TBA]OAc and found that 2.0 equiv of [TBA]OAc, with respect to substrate, promotes electrochemical C−N coupling in 61% yield (see Table S4 for results from varying [TBA]OAc loading). No C−N coupled product was obtained in absence of aryl iodide. The loading of **3a** can be lowered; we find that 25 mol% affords 76% yield.[18] Following intramolecular C−N bond-forming chemistry, analysis of the crude reaction mixture by $^1H$ NMR indicates <5% catalyst decomposition. Examination of other solvents, reaction temperatures, *N*-protecting groups, and electrode materials did not result in substantively better reaction efficiency (Tables S5−S7). Redox balance in the observed chemistry is achieved by proton reduction (presumably of hfip) to generate $H_2$, which was observed by GC analysis of the reaction headspace (Figure S1).

With the optimized conditions in hand, we evaluated the scope of intramolecular C−N bond-forming chemistry (Figure 2). Reactions were run until 80 C of charge was passed (4.15 F/mol), which typically resulted in reaction times of 6−12 h. Using 4-iodoanisole (**3a**) as catalyst, we found that both 5- and 4′-halogenation are well tolerated (**2b**−**2g**), as is the introduction of weakly electron withdrawing groups like 5-formyl (**2h**) or 4′-phenyl (**2i**). Under these conditions, substrates with more electron-withdrawing substituents, such as 5-nitro (**2j**) and 5-methylcarboxylate (**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**)[19] as catalyst (onset potential for oxidation is 1.68 V vs $Ag^+/Ag$ for **3b** compared to the onset potential of **3a** which is 1.40 V vs $Ag^+/Ag$). The more oxidizing conditions allowed both **2j** and **2k** to be accessed (43% and 71% yields, respectively). Electron donating groups were tolerated in the 4′-position (i.e., **2l** and **2m**). In contrast, introduction of methyl and methoxy groups at the 5-position (i.e., **1n** and **1o**) led to starting material decomposition and trace amount of carbazole. We speculate that the presence of electron donating substituents at the 5-position decreases the onset potential of the substrate below that of the aryl iodide catalyst and thus leads to direct and unselective substrate activation (for CV analysis of all substrates, see Figures S2−S6 and Table S8). Consistent with this hypothesis, CPE of 5-*t*-butyl acetamide (**1p**) in the absence of aryl iodide catalyst afforded **2p** in 65% yield (background reactions of the other substrates in Figure 2 indicate that only **1p** and **1v** participate in appreciable C−N coupling chemistry in the absence of **3**, Table S9).[20] The broader tolerance for substitution in the 4′-position than the 5-position is consistent with the smaller impact of substituents in this position on the onset potential for direct substrate oxidation (Figure S6). Intramolecular cyclization is also tolerant to substitution at the 2′- (**2q**) and 3- positions (**2r** and **2s**) and can be accomplished in multifunctional substrates, as highlighted by the synthesis of **2v**, a precursor to anti-HIV natural product clauszoline-K.[21] Robustness analysis[22] for electrocatalytic intramolecular C−N bond-forming chemistry, and comparison with both aerobic and peracid−based methods, is summarized in Figure S7.

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Hypervalent iodine electrocatalysis can also be applied to intermolecular C−N bond-forming chemistry (Figure 3).

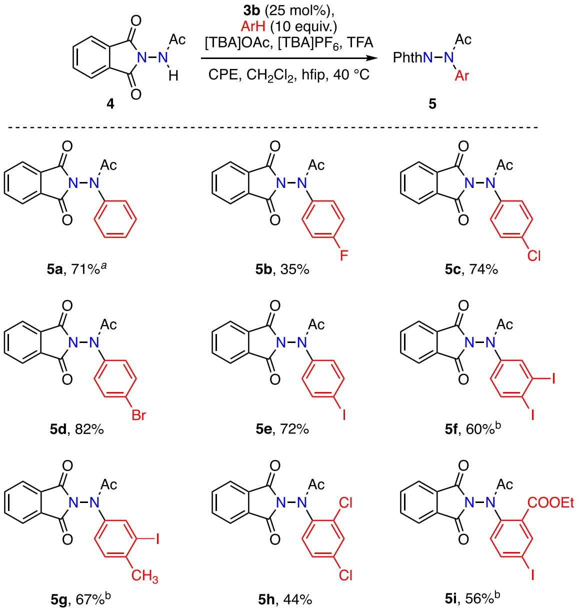
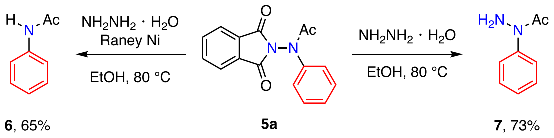


**Figure 3.** Intermolecular C−H/N−H coupling via hypervalent iodine electrocatalysis (yields are of isolated products). Standard conditions: catalyst **3b**, CPE for 80 C, 2.0 V versus $Ag^+/Ag$, undivided cell, glassy carbon anode, platinum-plated cathode, and $Ag^+/Ag$ reference. *a*, CPE at 1.8 V. *b*, 5 equiv of ArH.

Catalyst **3b** was used as the aryl iodide mediator due to its previously reported success in furnishing intermolecular C−H amination reactions (see Table S10 for analysis of other aryl iodide catalysts).[23] CPE of a $CH_2Cl_2$/hfip solution of hydrazine derivative **4** and 10 equiv of benzene in the presence of 1 equiv of **3b** affords 81% yield of *N*-phenylated compound **5a**. The catalyst loading can be decreased to 25 mol% without significantly compromising 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. Amine derivatives that feature onset potentials for direct oxidation below that of **3b** (i.e., 2.0 V vs $Ag^+/Ag$), such as TsNHOMe, TrocNHOMe, and PhNHAc, did not engage in intermolecular C−N coupling (for CV analysis of amine derivatives see Figure S8). The intermolecular C−H amination reactions with halogenated aryl group were accomplished in 35−82% yields (**5b**−**5f**). Positional selectivity for difunctionalized arenes (i.e., **5f**−**5i**) is consistent with electrophilic aromatic substitution preferences. Electron-rich hydrocarbons like toluene, xylene, and naphthalene were not viable substrates in the intermolecular N−H arylation.

Hydrogenolysis of the N−N bond in compounds **5** 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 (eq 1).[24] Alternately, compounds **5** can be elaborated to the corresponding arylhydrazines (**7**), which are useful precursors to various heterocyclic compounds, by treatment with hydrazine(eq 1).[25]

With interest in gaining deeper understanding of the observed acetate-dependent hypervalent iodine electrocatalysis, we considered two potential anodic oxidation mechanisms (Figure 4). 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** (Figure 4, path a). Subsequent oxidation chemistry would ultimately lead to I(III) (**10**). Alternatively, the observed acetate-dependent chemistry might arise from an interrupted Kolbe electrolysis[26] 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**) (Figure 4, path b). Available evidence, summarized below, is most consistent with the former mechanistic scenario.



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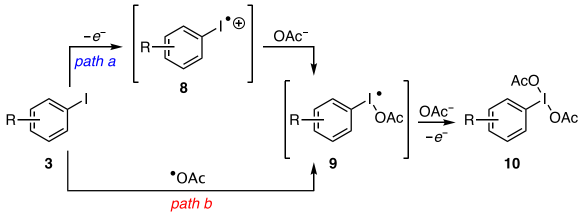

**Figure 4.** Potential mechanisms for the observed acetate-dependent hypervalent iodine electrocatalysis. (a) Interfacial electron transfer with aryl iodide would initially generate a I(II) cation. (b) Interfacial electron transfer with acetate would initially generate acetoxy radicals.

Examination of the CV of **3a** as a function of scan rate in hfip indicates that while the oxidation is irreversible at low scan rates (i.e., < 100 mV/s), electrochemical reversibility emerges at higher scan rates (>250 mV/s, Figure 5a; for corresponding data for 4-iodotoluene, see Figures S9−S11).[27] Addition of [TBA]OAc to a CV experiment of **3a** in hfip 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 5b). The measured peak potential is linearly correlated with the square root of scan rate, which indicates electron transfer from a solution-borne, not surface adsorbed, species (Figure 5a inset).[28] Trapping of electrochemically generated iodanyl radicals is not limited to acetate. A variety of common hypervalent iodine ligands including pyridine, cyanide, trifluoroacetate, and fluoride all give rise to the same enhanced current and suppressed reversibility that is diagnostic of trapping the electrochemically generated species (Figures S12−S15).

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 $[TBA]PF_6$ results in the products expected of Kolbe electrolysis: ethane, methane, and $CO_2$ (observed by GC analysis of reaction headspace, Figure S16). 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 S17 and S18). The suppression of Kolbe electrolysis is consistent with strong hydrogen bonding of acetate to the acidic O−H of hfip ($pK_a$ = 9.3).[29] Consistent with this

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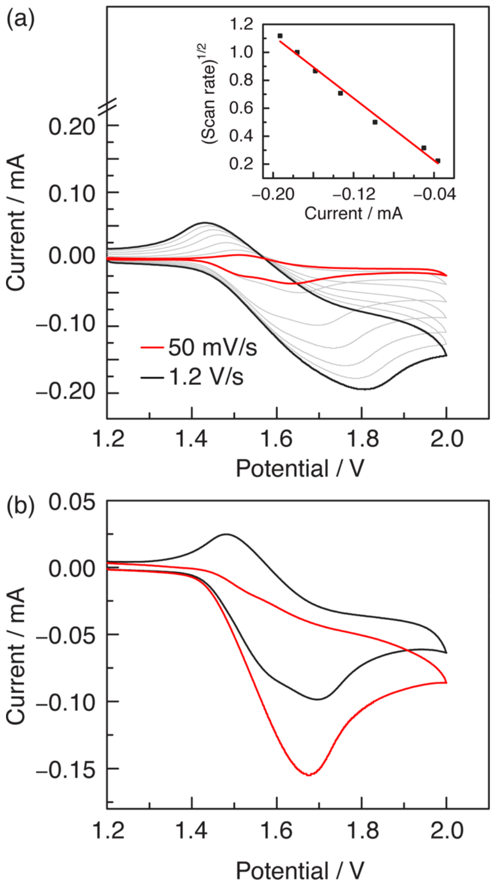

**Figure 5.** (a) Increasing reversibility of **3a** oxidation in hfip is observed in CVs collected with increasing scan rate: 0.05 (red), 0.1, 0.25, 0.50, 0.75, 1.0, and 1.2 V/s (black). Inset: Plot of peak anodic current ($I_{pa}$) of **3a** versus square root of scan rate [$R^2$ = 0.99]. (b) CVs of **3a** in a 0.2 M [TBA]$PF_6$ solution of hfip (black) and in the presence of 2.0 equiv of [TBA]OAc (red).

hypothesis, NMR analysis of solutions containing both hfip and [TBA]OAc reveals a significant downfield shift in the methine resonance (Figure S19). Job analysis indicates a 1:1 adduct is formed between these two species (Figure S20 and Table S11), and NMR analysis provides an equilibrium constant for association of 0.767 (Figures S21−S23 and Table S12).

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. 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.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications Web site. The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.9b13918.

Experimental procedures, spectroscopic and electrochemical data (PDF)

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### Notes

The authors declare no competing financial interest.

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