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Merging Photochemistry with Electrochemistry: Functional Group Tolerant Electrochemical Amination of sp^3 C–H Bonds

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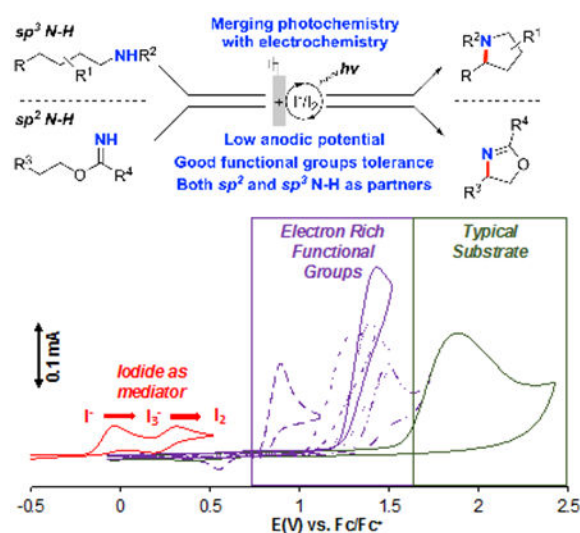
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Abstract

Direct amination of sp^3 C–H bonds is of broad interest in the realm of C–H functionalization because of the prevalence of nitrogen heterocycles and amines in pharmaceuticals and natural products. Here, we report a combined electrochemical/photochemical method for dehydrogenative C(sp^3)–H/N–H coupling that exhibits good reactivity with both sp^2 and sp^3 N–H bonds. The results show how use of iodide as an electrochemical mediator, in combination with light-induced cleavage of intermediate N–I bonds, enables the electrochemical process to proceed at low electrode potentials. This approach significantly improves the functional-group compatibility of electrochemical C–H amination, for example, tolerating electron-rich aromatic groups that undergo deleterious side reactions in the presence of high electrode potentials.

Graphical Abstract

Synergistic benefits: Visible-light irradiation is combined with an electrochemical reaction that uses iodide as a redox mediator to enable efficient intramolecular C–H amination. The combined photo/electrochemical approach allows the reactions to proceed with low anode potentials, which tolerate a wide range of functional groups.



Conflict of interest:
The authors declare no conflict of interest.

Keywords

C-H Functionalization; Amination; Iodine; Electrolysis; Photochemistry

Synthetic methods for electrochemical oxidation of organic molecules are the focus of rapidly increasing interest.^[1,2] Such reactions are appealing because protons are often effective as the terminal oxidant, resulting in the generation of H₂ as the sole stoichiometric byproduct. Important challenges, however, must be overcome to expand the utility of these methods. For example, high electrode potentials required to initiate electron transfer from an organic molecule can lead to decomposition or oxidative side reactions of ancillary functional groups in the molecule. We have been exploring strategies to enable electrochemical oxidation reactions to proceed at lower electrode potentials.^[3] Use of an electron-proton transfer mediator, such as an aminoxyl or imidoxyl species, represents one appealing strategy, as these mediators enable oxidations to proceed at electrode potentials >1 V lower than analogous non-mediated processes.^[3b,c] In spite of this progress, however, additional strategies are needed. Hydrogen-atom transfer (HAT) mediators still require high electrode potentials that constrain the functional group compatibility,^[3b,4] and we initiated the present study to explore possible methods to address this challenge. Herein, we show that use of iodide mediators in combination with visible-light illumination provides the basis for sp³ C–H amination at low electrode potentials.

Selective formation of C(sp³)–N bonds via C–H/N–H coupling is a transformation of longstanding interest.^[5] The Hofmann–Löffler–Freitag (HLF) reaction is a pioneering example of such reactivity,^[6,7] and numerous variations of the HLF reaction have emerged for C–H halogenation and nitrogen-heterocycle synthesis.^[8,9,10,11] Electrochemical methods, summarized in Figure 1, have been explored as a means to bypass the use of undesirable stoichiometric oxidants or pre-generation of N–X compounds, both of which compromise the atom-economy and other appealing features of these methods. Several distinct mechanistic approaches have been investigated in these electrochemical HLF-type reactions: (i) stepwise ET-PT-ET to generate a benzyl cation, which reacts with an appended nitrogen nucleophile,^[12] (ii) proton-coupled electron transfer (PCET) to generate a nitrogen-centered radical that promotes 1,5-HAT, similar to the key C–H activation step in the HLF reaction,^[13] and (iii) bromide-mediated formation of an *N*-bromo intermediate that undergoes thermal N–Br homolysis to achieve the key 1,5-HAT step.^[14,15] Each of these examples exhibits limited functional group compatibility, owing to the requirement for high anode potentials (Figure 1B). These issues could be addressed by using a mediator that undergoes regeneration at lower potentials. A number of modified-HLF reactions have been reported with stoichiometric chemical oxidants, catalytic I₂, and visible light illumination,^[11] raising the possibility that iodide could be used as an electrochemical mediator (Figure 1A, approach *iv*).^[16] The I[–]/I₃[–]/I₂ redox couples are ~0.4 V lower than those for bromide^[17] and 1–1.5 V lower than the electrode potentials required for the electrochemical PCET and ET-PT-ET reactions (Figure 1B).

Our efforts were initiated by testing the three previously reported electrochemical reaction conditions with two *N*-alkyl sulfonamide derivatives, **1a** and **1b**, which differ by the

presence of the electron-rich methoxynaphthyl substituent in **1b** (Scheme 1). Good reactivity and product yields were observed with **1a** under each of the three reported conditions. In contrast, negligible C–N bond formation was observed for **1b**, and nearly complete consumption of the starting material led to a complex mixture of products in each case. With these benchmarks established, we turned our attention to electrochemical conditions with iodide as a mediator. Shono's original report on bromide-mediated C–H amination included one example of iodide-mediated reactivity;^[14] however, the *N*-iodo intermediates tend to undergo beta-elimination of HI to afford imine-derived products under thermal conditions. This insight, together with the use of visible-light promoted homolysis of the N–I bond in $\text{PhI}(\text{OAc})_2/\text{I}_2$ -promoted HLF-type reactions, prompted us to consider iodide-mediated electrochemical conditions illuminated by a compact fluorescent light (CFL) bulb.

Representative data with **1b** are shown in Table 1. The reactions were conducted in an undivided glass electrolysis cell with CFL illumination, using 10% tetrabutylammonium iodide (TBAI) as the mediator, 0.1 M KPF_6 as supporting electrolyte, a graphite rod anode, a Pt wire cathode, and TFE as a co-solvent in CH_3CN (see Supporting Information for details). An applied potential of 0.3 V vs. Fc/Fc^+ , which is above the I^-/I_3^- redox wave and near the I_3^-/I_2 mid-point potential (see Figure S1), led to only small amounts of product **2b** (4%), with most of the starting material recovered unreacted (81%) (entry 1). Improved yields were observed at a higher applied potential, with a 75% yield obtained at 0.5 V (Table 1, entry 2-3). No product was generated in the absence of mediator, and much lower product yield (19%) was observed in the dark (entries 4-5).

These promising results with a tosylamide substrate prompted us to consider C–H/N–H coupling with a substrate bearing an imidate nucleophile. HLF-type reactivity with this substrate class was recently demonstrated by the groups of Nagib and Chen with stoichiometric chemical oxidants ($\text{PhI}(\text{OAc})_2/\text{I}_3^-$ and *N*-iodo-succinimide/ Ag_2O , respectively),^[18,19] but no electrochemical precedent has been reported. The experiments were initiated with **3a**, bearing an electron-rich anisole substituent. Using the conditions optimized for **1b**, the desired product **4a** was obtained in 54% yield with 18% recovered starting material (Table 2, entry 1). A comparable yield was obtained at lower applied potential (0.3 V vs Fc/Fc^+ , entry 2), while an improved result was obtained at higher potential (0.7 V; entry 3).^[20] Inclusion of 1 equivalent of pyridine in the reaction mixture led to further improvement in the yield (82%, entry 4; similar beneficial effects of pyridine were not observed with **1a** and **1b** – see Supporting Information for details). Control experiments again revealed that no product was observed in the absence of mediator or in the dark (entries 5 and 6).

A number of different *N*-alkyl sulfonamide and imidate substrates were then evaluated under the optimized iodine-mediated photo/electrochemical conditions to assess their ability to undergo dehydrogenative cyclization (Scheme 2). Scheme 2A shows the results with *N*-alkyl sulfonamide derivatives, while Scheme 2B illustrates the scope of imidates compatible with the reaction conditions. Substrates of both classes with electron-rich arenes were effectively converted to the corresponding pyrrolidine and oxazoline products under the optimized conditions (**2b-2e**, **2i** and **4a**, **4h**, **4n**, **4o**, **4t**, respectively). The oxazoline products derived

from the imidate cyclization are appealing precursors to 1,2-aminoalcohol derivatives (Scheme 2C).^[18a,19]

The majority of products arise from functionalization of activated C–H bonds (e.g., benzylic or adjacent to a heteroatom), but successful reactivity was also observed with unactivated aliphatic C–H bonds (**2g**, **2h**, **2i**, **4v**). The generation of **2h** reveals the expected preference of secondary over primary C–H functionalization.^[10f] Effective substrates feature an array of aromatic substituents, including electron-rich and electron-deficient substituted arenes, in addition to thiophene and pyridine. The good functional group tolerance enabled by merging photochemistry with a low-potential mediator was further demonstrated with an intermolecular additive screening experiment for the reaction of **1a** (see Table S5 in the Supporting Information for details).^[21] Functional groups shown to be compatible with the reaction conditions include carbazole, (benzo)thiophene, benzofuran, benzothiazole, pyridine, and carbamate derivatives, while partial decomposition and lower yields of **2a** were observed with indole, furan and aniline derivatives.

The observed reactivity is readily rationalized by an electrochemical circuit consisting of generation of I₂ at the anode and hydrogen evolution at the cathode (Scheme 3A). The latter reaction contributes to the overall catalytic process by generating a Brønsted base that promotes iodination of the N–H substrate, which then initiates the non-electrochemical C–H functionalization sequence that takes place in bulk solution (Scheme 3B).^[22] Photolysis contributes to homolysis of the N–I bond and enables formation of the *N*-centered radical that undergoes 1,5-hydrogen atom transfer (HAT) to generate an alkyl radical. Subsequent trapping of the radical with iodine generates an alkyl iodide intermediate that can undergo Brønsted base-promoted nucleophilic displacement by the appended nitrogen nucleophile.

Functional group tolerance is achieved by the combined use of a low-potential mediator (I[−]/I₂) with photochemical activation of the *N*-iodo intermediate generated under the reaction conditions.^[23] The anodic potential needed to (re)generate I₂ at the anode (0.3–0.7 V vs. Fc/Fc⁺) is well below the redox potential of electron-rich arenes and other substituents. This feature is illustrated in Scheme 4, which shows cyclic voltammograms (CVs) of the iodide mediator, including both the I[−]/I₃[−] and I₃[−]/I₂ redox couples, and several representative substrates. Comparison of the CVs for **1a** and the substrates with electron-rich aromatic substituents highlights the functional-group compatibility challenges that will be encountered in reactions initiated by direct electrochemical oxidation of substrate or proton-coupled oxidation of the nitrogen nucleophile (cf. ET-PT-ET and PCET processes in Scheme 1). The ET and PCET steps associated with these reactions often require applied potentials well above that of many valuable functional groups and will initiate substrate decomposition or undesirable side reactions. For example, ET from the arene ring in **1a** exhibits a peak potential of 1.9 V (Scheme 4), and the PCET-initiated reactions proceed with anodic potentials of >2 V.^[24,25] While the ET-PT-ET and PCET processes will have utility for substrates that tolerate high anode potentials, the magnitude of the applied potential will intrinsically limit the scope.

Overall, the results outlined herein demonstrate a novel photochemical/electrochemical strategy to enable C–H amination reactions to be conducted at lower applied potentials. In

addition to the above comparisons with ET-PT-ET and PCET-based reactions, the results may be compared to other electrochemical C–H oxidation reactions that proceed via HAT mechanisms. Phthalimido-*N*-oxyl (PINO) is perhaps the most widely used HAT reagent in electrochemical C–H oxidation reactions.^[2k,3b,4a-d] The I₃⁻/I₂ redox potential is ~0.2–0.6 V lower than the potentials needed to generate PINO from *N*-hydroxyphthalimide (NHPI).^[26] This difference is amplified when one considers that the *N*-centered radicals generated in the present reactions are much stronger H-atom acceptors than PINO (estimated BDEs: NHPI(O–H) ~ 88 kcal/mol, sulfonamide and imidate (N–H) > 100 kcal/mol^[27]). Thus, the combination of electrochemical and photochemical energy inputs allows more potent oxidants to be generated at lower electrode potentials, thereby enabling the C–H/N–H dehydrogenative coupling reaction to proceed with broad functional group tolerance. We anticipate that many other electrochemical redox processes will benefit from application of principles similar to those described here.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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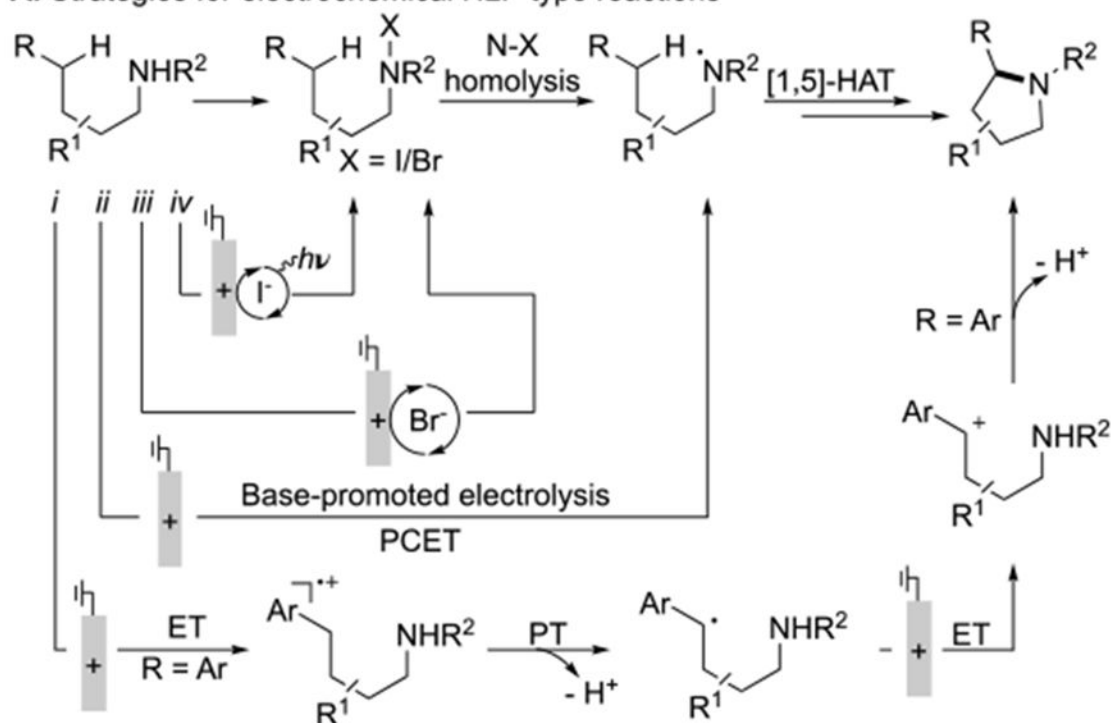
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- [25]. See Supporting Information for CV studies of TsNHMe with different bases.
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A. Strategies for electrochemical HLF-type reactions



B. Anodic potentials

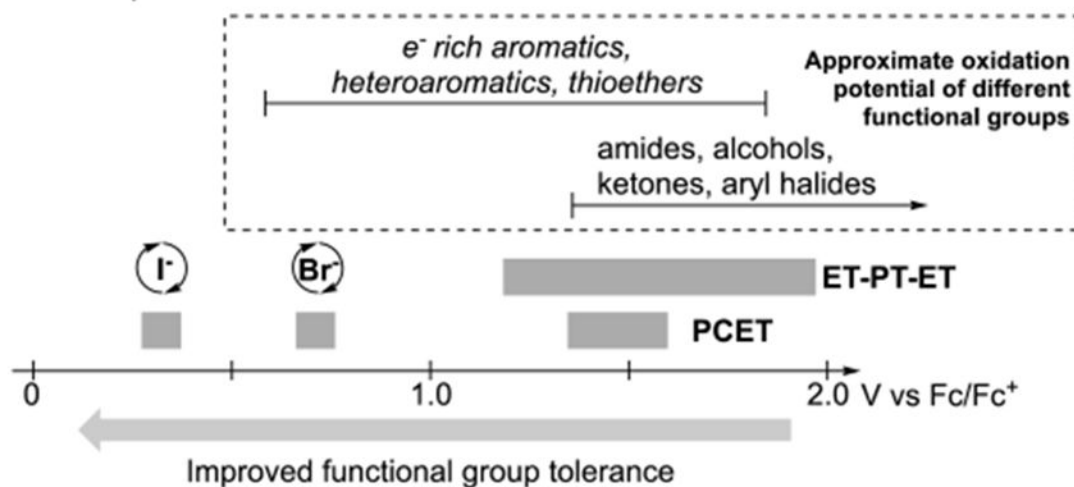
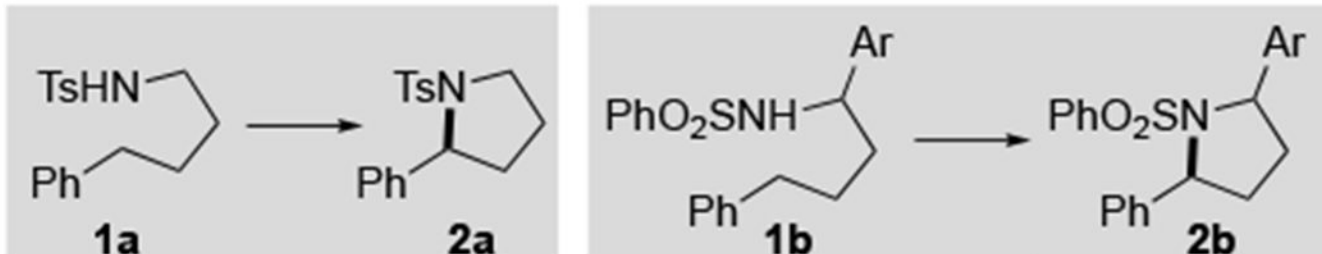
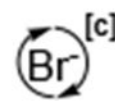
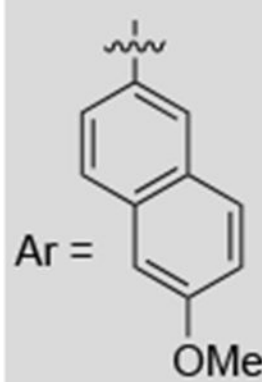


Figure 1.

Electrochemical strategies for dehydrogenative amination of sp^3 C–H bonds (A) and the associated anodic potentials required for each approach (B). ET = electron transfer, PT = proton transfer, PCET = proton-coupled electron transfer.



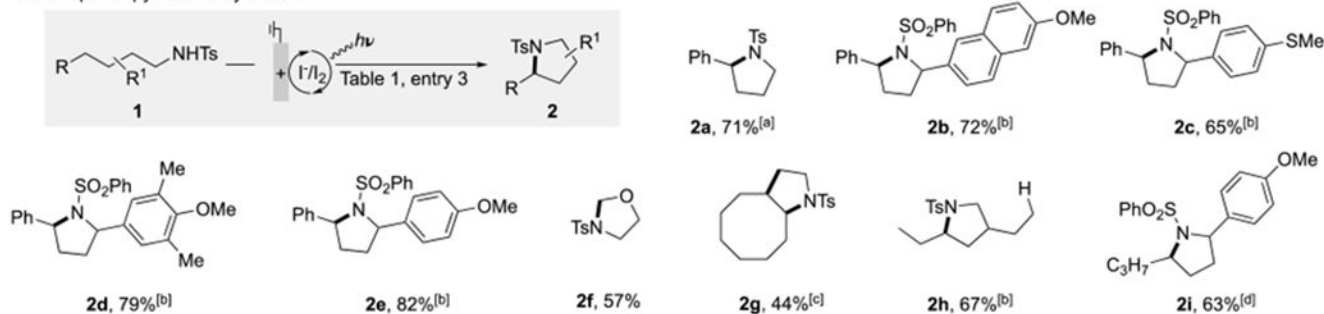
Electrochemical Method	Yield (conversion)	
	2a	2b
ET-PT-ET ^[a]	52% (84%)	n.d. (100%)
PCET ^[b]	86% (100%)	< 10% (100%)
 ^[c]	71% (85%)	< 10% (100%)

Ar = 

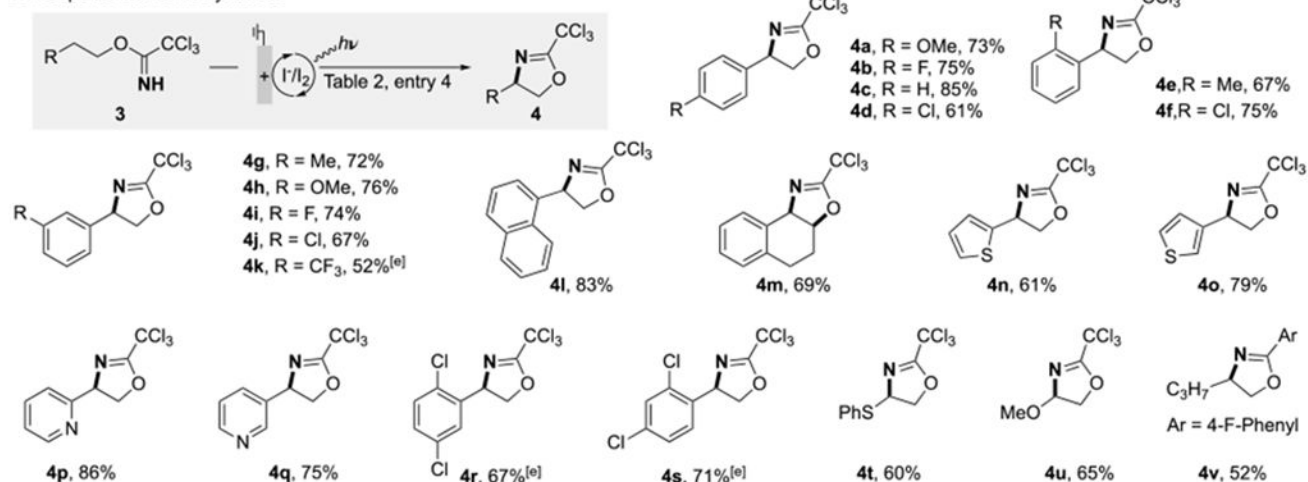
Scheme 1.

Comparison of previous electrochemical methods for sp^3 C–H amination. For detail procedures, see refs. 12–14 and Supporting Information. Yields were determined by ^1H NMR with *m*-xylene as internal standard, conversion is shown in parenthesis. [a] Conditions: **1a** or **1b** (0.2 mmol) and $^n\text{Bu}_4\text{NPF}_6$ (0.1 M) in HFIP (10 mL), 2.5 mA, RT. [b] Conditions: **1a** or **1b** (0.2 mmol), NaOAc (0.2 mmol) and $^n\text{Bu}_4\text{NBF}_4$ (0.2 mmol) in DCE/HFIP (6 mL, 2:1), 7.5 mA, RT. [c] **1a** or **1b** (0.4 mmol), NaOMe (0.2 mmol) and KBr (0.2 mmol) in methanol (6 mL) at 65 °C, 100 mA, DCE = 1,2-dichloroethane. HFIP = 1,1,1,3,3,3-hexafluoro-2-propanol. n.d. = not detected.

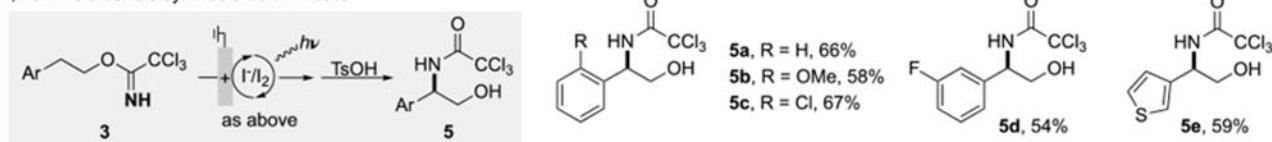
A. Scope for pyrrolidine synthesis



B. Scope for oxazoline synthesis



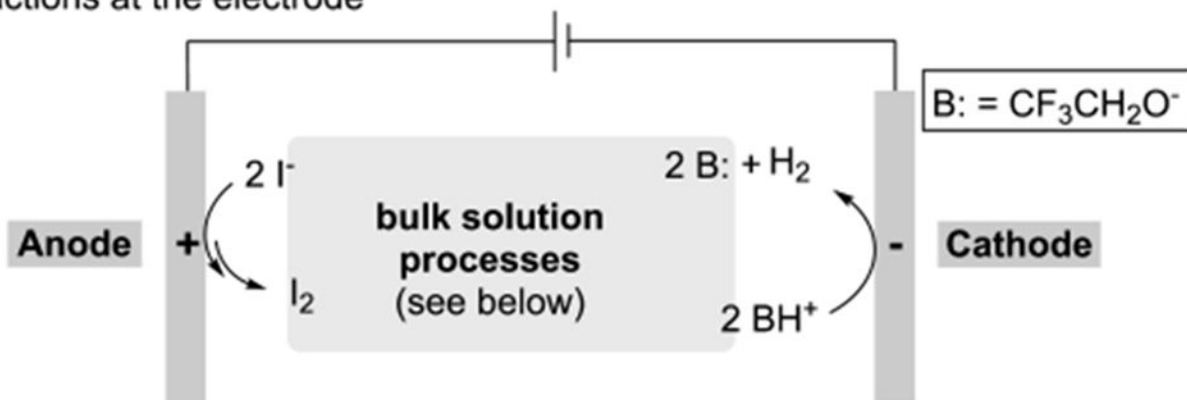
C. 1,2-amino alcohols synthesis from imidate



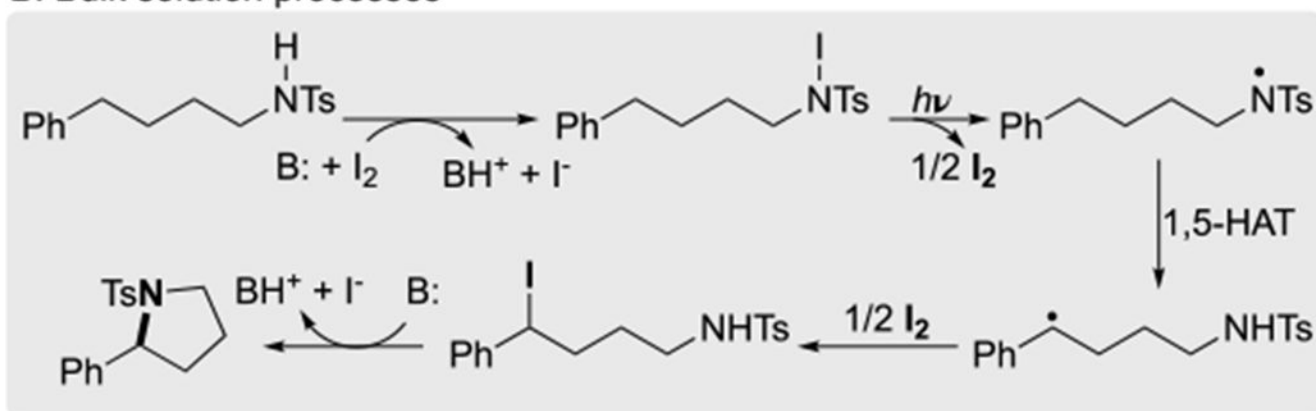
Scheme 2.

Substrate scope of iodide-mediated dehydrogenative amination. The reaction was conducted on a 0.5 mmol scale, see Supporting Information for details. All yields are isolated yield. [a] **2a** has also been produced under conditions with stoichiometric chemical oxidants: $\text{PhI}(\text{OAc})_2/\text{cat. I}_2$, 90%;^{11a} $\text{PhI}(\text{OAc})_2/\text{I}_3^-$, 93%;^{10g} $\text{mCPBA}/\text{cat. I}_2$, 54%;^{11c} [b] dr = 1:1. [c] dr = 1.8:1. [d] dr = 1.2:1. [e] With 2,6-lutidine instead of pyridine as additive. TsOH = *p*-toluenesulfonic acid.

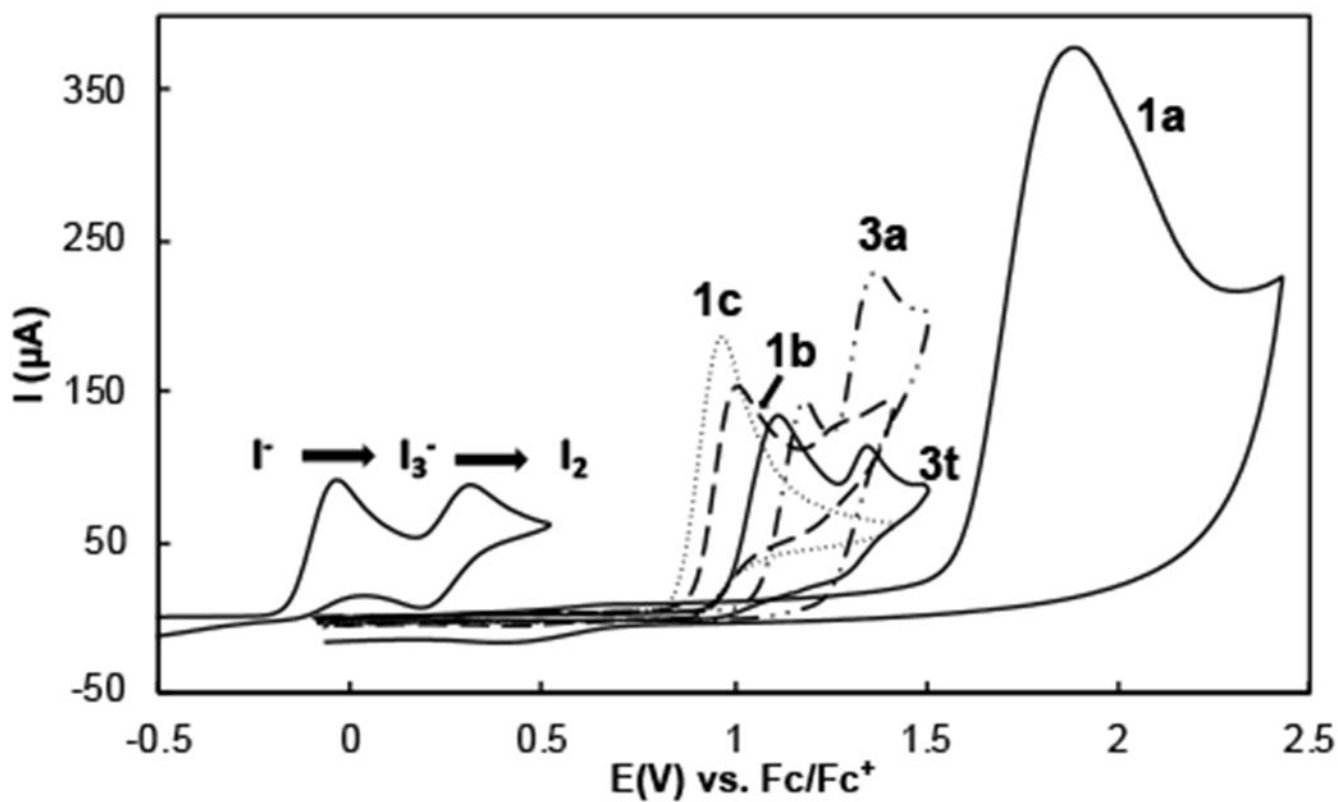
A. Reactions at the electrode



B. Bulk solution processes

**Scheme 3.**

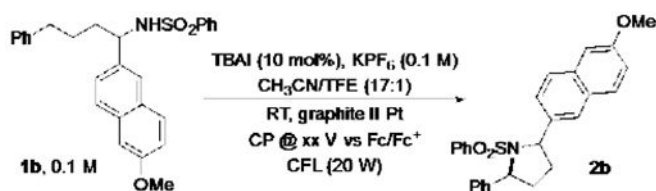
Simplified mechanism for photo/electrochemical iodide-mediated dehydrogenative C–H/N–H coupling.

**Scheme 4.**

CVs of iodide and representative substrates. Conditions: 5 mM substrate in acetonitrile with KPF_6 (0.1 M) as supporting electrolyte, glassy carbon as working electrode ($\sim 7.0 \text{ mm}^2$) and a platinum wire counter electrode, scan rate = 100 mV/s.

Table 1.

Combined electrochemical/photochemical iodide-mediated process for C–H amination.^[a]



Entry	Potential/V vs Fc/Fc ⁺	TBAI	Yield/%
1	0.3	10 mol%	4%
2	0.4	10 mol%	70%
3	0.5	10 mol%	75% (72%)
4	0.5	-	n.d.
5 ^[b]	0.5	10 mol%	19%

^[a]The reaction was performed on a 0.5 mmol scale under constant potential (CP) conditions, yields were determined by ¹H NMR with *m*-xylene as an internal standard; isolated yield shown in parenthesis.

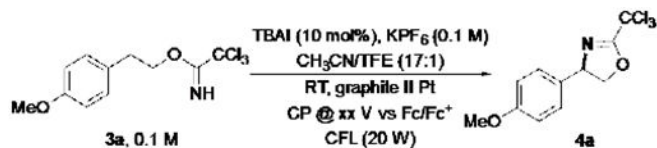
^[b]Without irradiation.

TFE = 2,2,2-Trifluoroethanol. n.d. = not detected.

Table 2.

Combined electrochemical/photochemical iodide-mediated process for dehydrogenative amination of imidate.

[^a]



Entry	Potential/V vs Fc/Fc ⁺	TBAI	Yield/%
1	0.5	10 mol%	54%
2	0.3	10 mol%	47%
3	0.7	10 mol%	71%
4 ^[b]	0.7	10 mol%	82% (73%)
5 ^[b]	0.7	-	n.d.
6 ^[b,c]	0.7	10 mol%	2%

[^a] The reaction was performed on a 0.5 mmol scale under constant potential (CP) conditions, yields were determined by ¹H NMR with *m*-xylene as an internal standard; isolated yield shown in parenthesis.

[^b] With 1 equiv of pyridine.

[^c] Without irradiation.

TFE = 2,2,2-Trifluoroethanol. n.d. = not detected.