

Photoelectrochemical Heterodifunctionalization of Olefins: Carboamidation Using Unactivated Hydrocarbons

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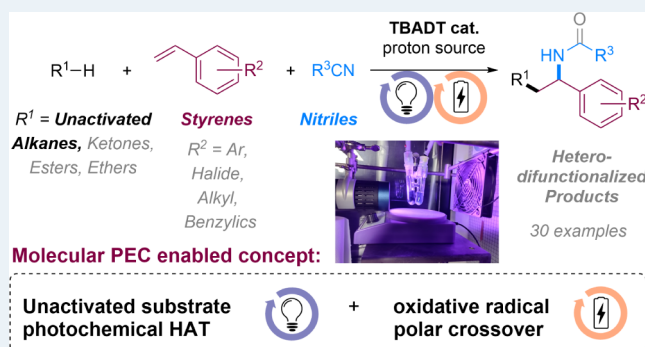
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ABSTRACT: A mild carboamidation of electronically different styrenes with diverse hydrocarbons was developed by merging photocatalysis and electrochemistry without using external oxidants. The reaction proceeds through a tandem photocatalytic hydrogen atom transfer (HAT), radical addition to styrenes, radical polar crossover, and subsequent Ritter-type amidation. Key to engaging unactivated alkanes is the use of tetrabutylammonium decatungstate (TBADT) as a HAT photocatalyst, which is regenerated from its reduced form by anodic oxidation. A diverse set of C–H precursors, including alkanes, was successfully utilized. Styrenes bearing different functionalities in their arene rings were selectively difunctionalized. Overall, we demonstrate how photoelectrochemistry forges unconventional reactivity by merging HAT with an oxidative radical polar crossover.

KEYWORDS: photoelectrochemistry, hydrogen atom transfer, Ritter reaction, carboamidation, difunctionalization



INTRODUCTION

Efficiently activating inert C(sp³)–H bonds for selective organic synthesis is a topic of great interest, especially considering the abundance of unactivated hydrocarbons in nature. Nonetheless, the elusive oxidative potential associated with unactivated alkanes renders their single electron transfer (SET) activation a highly challenging endeavor. In spite of the formidable bond dissociation energy (BDE) of unactivated C(sp³)–H bonds, direct hydrogen atom transfer (HAT) leading to the formation of alkyl radicals dominates as a widely employed strategy for the alteration of these bonds.¹ Catalytic HAT strategies are particularly appealing among the various approaches. As a green and sustainable energy source, visible light has been used to drive a wide range of catalytic organic transformations.² Photocatalysis involving HAT has emerged as a prominent area of research interest.^{3,4} In particular, reactions that employ a visible light excitable HAT catalyst represent green methods for C(sp³)–H functionalizations of alkanes, omitting stoichiometric conventional HAT agent precursors such as peroxides.⁵ The generated alkyl radicals can be intercepted by diverse radical trapping reagents, among which alkenes are highly valuable feedstocks for building molecular complexity. For example, inspired by seminal reports from Hill,^{6–8} Fagnoni, Ryu, Ravelli, and others on the HAT activation of unactivated hydrocarbons,^{9–12} TBADT was used as a HAT photocatalyst by the Noël group to abstract hydrogen atoms from “light” alkanes under photoirradiation (Figure 1a).¹³ The active species *w*O was generated by

photoexcitation and subsequent decay within the excited state. The generated alkyl radical adds to an electron-deficient alkene to afford a carbon-centered radical with an α -electron-withdrawing group, which undergoes reductive radical polar crossover (RPC) to afford a hydroalkylated product. When styrene was used the reaction failed because the benzylic radical formed by radical addition was not sufficiently electron-deficient to undergo reductive RPC.¹⁴ This, together with the local proximity of protons from the reduced TBADT, constrains the applications of the HAT/reductive radical polar crossover strategy to electron-poor olefins and monofunctionalizations.

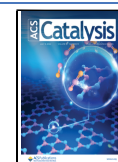
First-row transition metals offer promise for further functionalization of the benzylic radical. For example, Wu used Co(II) to capture benzyl radicals, leading to a Co(III) species that undergoes a formal β -H elimination to afford a Heck-like monofunctionalized alkene product, accompanied by H₂ evolution.¹⁵ Only very recently, the Kong group disclosed a rare example of alkene difunctionalization by the combination of TBADT photocatalysis and nickel catalysis.¹⁶ The alkyl radical was trapped by the Ni(II) species generated by the

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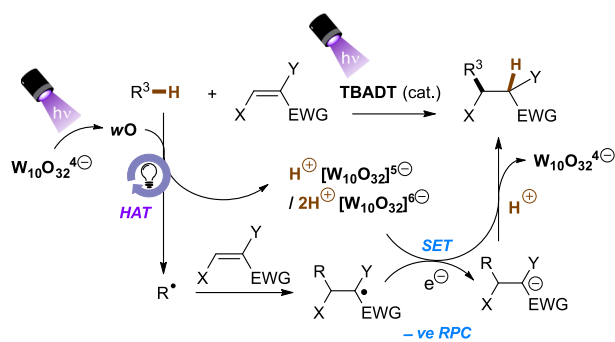
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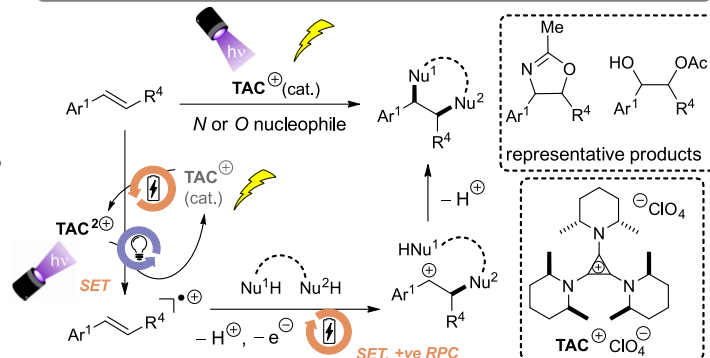
Previous strategy: HAT + reductive SET radical polar crossover

a) Hydroalkylative monofunctionalization of electron-deficient alkenes



Previous strategy: oxidative SET + oxidative SET radical polar crossover

b) electro-activated photocatalytic bis-heteroatomic styrene difunctionalizations



c) Carboamidative heterodifunctionalization of styrenes via electro-recycled TBADT photocatalysis

d) mechanistic hypothesis

This Strategy: HAT + oxidative SET radical polar crossover

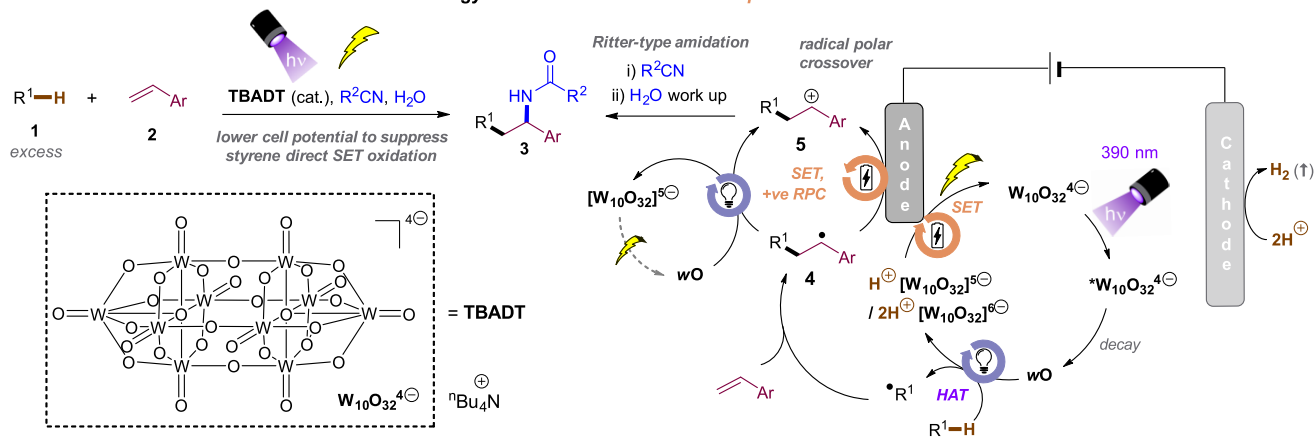


Figure 1. Previous work on: a) hydroalkylation of electron-deficient alkenes via TBADT photocatalysis; b) photoelectrochemical bis-heteroatomic functionalization of styrenes through single electron oxidation. This strategy focuses on: c) carboamidation of styrenes with unactivated hydrocarbons through tandem photoinduced HAT, radical addition, oxidative radical polar crossover, and Ritter-type amidation.

oxidative addition of Ni(0) with bromoarenes and subsequent reductive elimination to deliver C(sp³)–C(sp²) coupling products. A HAT-mediated difunctionalization of olefins using a single catalytic system is still challenging and highly desirable.

Synthetic photoelectrochemistry (PEC), the merger of photoredox catalysis (PRC) and synthetic organic electrochemistry (SOE) that first emerged in 1979,¹⁷ has rapidly gained momentum since 2019.^{18–20} This technique garnered significant interest from organic chemists due to its abilities (i) to provide a broader redox window; (ii) to allow gentler and more environmentally friendly synthetic conditions for functionalizing complex molecules; and (iii) to eliminate external redox mediators.^{21–30} Among the PEC reports, those that focus on alkene functionalizations are particularly captivating. The Lambert group developed PEC bis-heteroatomic difunctionalizations of styrenes using a trisaminocyclopropenium (TAC⁺) ion catalyst (Figure 1b).^{31,32} The reactions proceeded through PEC oxidation of styrene, followed by a nucleophilic attack with a heteroatom nucleophile, affording a benzylic radical, which underwent oxidative RPC to a benzylic cation. The generated cationic species undergoes a second nucleophilic attack inter- or intramolecularly by another heteroatomic nucleophile to yield a difunctionalized product. The potent oxidizing capability of the photoexcited radical dication (*TAC²⁺) is crucial to

engage the styrene substrate in initial SET oxidation. To date,³³ PEC functionalizations of styrenes are limited to bis-heteroatom functionalizations.

RESULTS AND DISCUSSION

Inspired by these elegant reports and as a continuation of our interest in PEC,^{34–36} we envisioned a PEC carboamidation of styrenes by merging TBADT photocatalysis with electrolysis (Figure 1c). We envisioned that controlling the cell voltage below the oxidative potential of styrene would allow its double bond to endure direct anodic SET activation. Instead, it would accept an alkyl radical generated by HAT activation of alkanes by photoexcited TBADT.^{26,27} The resulting benzylic radicals undergo an oxidative radical polar crossover at the anode (or by *w*O) and a subsequent Ritter-type amidation,³⁷ ultimately yielding a carboamidation product. Meanwhile, reduced TBADT can be turned over by anodic oxidation. We examined the viability of our hypothesis by investigating the photoelectrochemical carboamidation of styrene **2a** with cyclohexane **1a** by using TBADT as a catalyst in a divided cell. Through extensive optimizations (see Supporting Information for details), reaction conditions were identified giving product **3a** in 64% NMR yield. Specifically, trifluoroacetic acid (TFA) (10 equiv. +10 equiv.) as a proton source, LiBF₄ (0.1 M) as electrolyte, reticulated vitreous carbon (RVC) (+) and Pt (–) as electrodes, 390 nm light, +1.4 V cell potential applied until 2

Table 1. Optimization of the Reaction Conditions^a

Standard Conditions

entry	variation from standard conditions	yield of 3a ^a
1	no variation	64%
2	+1.4 V, 40 h instead of 2 F/mol	62%
3	in the dark	n.d.
4	no current	3%
5	no acid	trace
6	no electrolyte	10%
7	^t Bu ₄ N·PF ₆ (0.1 M) as electrolyte	27%
8	^t Bu ₄ N·BF ₄ (0.1 M) as electrolyte	30%
9	LiClO ₄ (0.1 M) as electrolyte	49%
10	LiClO ₄ (0.1 M) as electrolyte, Nafion membrane modular divided cell	34%
11	LiBF ₄ (0.3 M) as electrolyte	53%
12	LiBF ₄ (0.5 M) as electrolyte	53%
13	graphite plate anode	49%
14	2 mA instead of +1.4 V	46%

^aNMR yields of 3a are given.

F/mol (or 40 h) were optimal (Table 1, entries 1–2). Light and current were both indispensable for this reaction (entries 3–4), affirming the photoelectrochemical nature of this chemical process. The presence of acid is crucial for this reaction (entry 5), such that the reduced TBADT is not sufficient to provide protons for the cathodic half-reaction. The yield was lower when TFA was only added into the cathodic chamber than when added to both chambers (Tables S2 and S6). This difference was less pronounced at +1.4 V but more pronounced at +2.3 V. We assume the additional TFA helps to stabilize the cathodic potential at higher applied cell potentials. Only a 10% yield of 3a was observed in the absence of LiBF₄, showing that TFA alone is not sufficient to serve as an electrolyte (entry 6). Substituting LiBF₄ with other alternative electrolytes, such as LiClO₄, TBABF₄, or TBAPF₆, resulted in decreased yields of 3a (entries 7–9, Table S7).

Substituting the glass-frit divided cell with a Nafion membrane divided modular cell gave a lower yield (34%, entry 10).³⁸ The model reaction performed less efficiently with higher concentrations of LiBF₄ electrolyte (entries 11–12). The choice of working electrode material impacted the outcomes of the reaction.³⁹ When a graphite plate was used as the anode, the yield of 3a was 49% (entry 13). Applying a constant current of 2 mA instead of +1.4 V of constant potential led to a decrease in product yield (entry 14). A higher cell potential, such as +1.7 V or +2.0 V, had a modestly adverse impact on this reaction (Table S4). This is likely a consequence of direct SET oxidation of the styrene substrate becoming competitive at elevated cell potentials; however, its impact may be tempered by radical capture of the radical cation to give 5, the same intermediate.

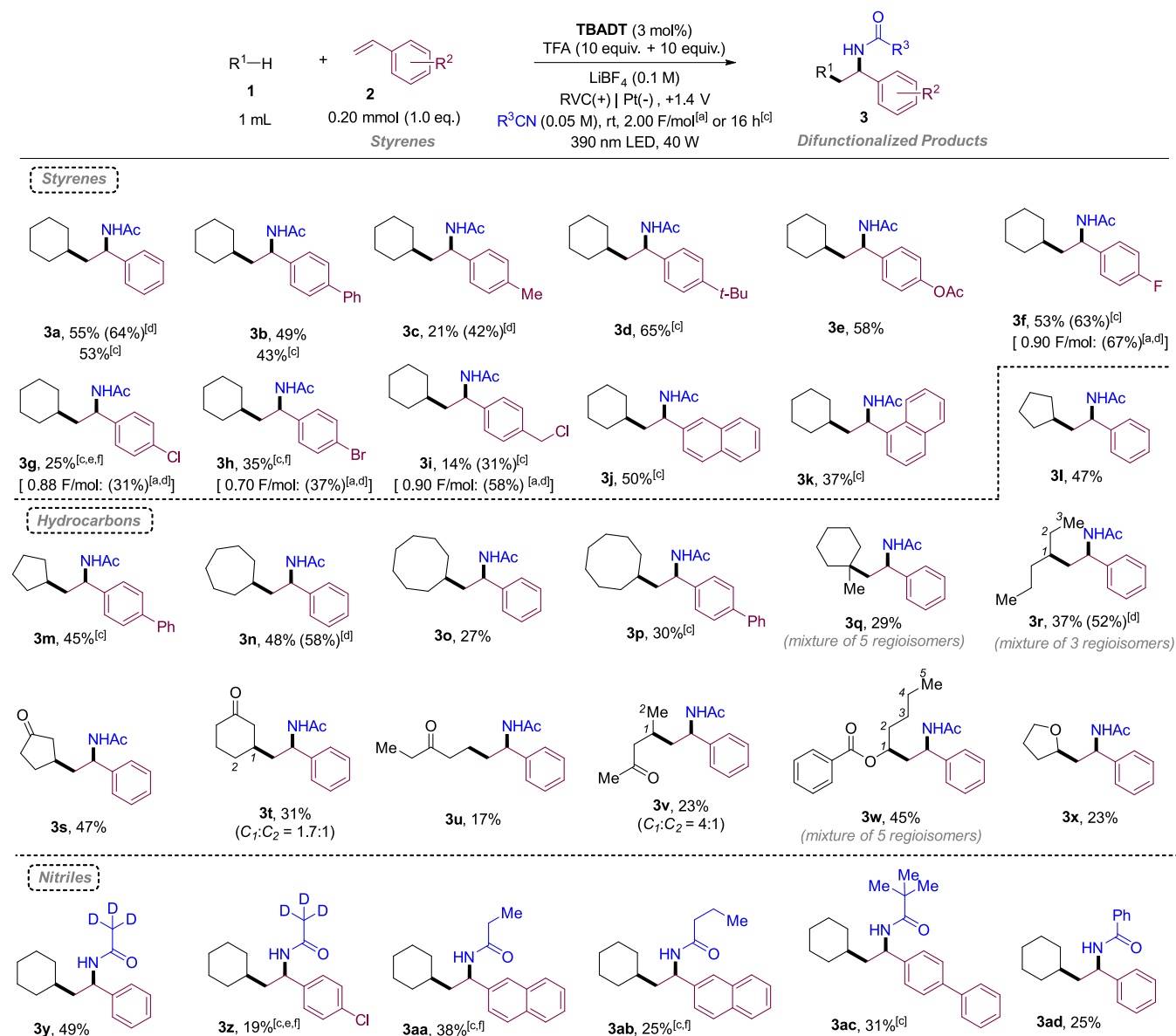
Other factors tested include an undivided cell, stoichiometry of TBADT and 2a, and the use of water and weaker acid additives (Tables S1–S8). It is also noteworthy that the weaker acid AcOH was also suitable for the reaction, albeit in a slightly lower yield than TFA (Table S2).

With the optimal conditions established, we proceeded to explore the substrate scope of this reaction (Table 2). First,

different alkene feedstocks were employed. The π -extended styrene 4-vinylbiphenyl did not participate in SET-initiated side reactions, affording product 3b in 49% isolated yield. Despite its easily abstractable H atoms, *para*-methylstyrene successfully delivered the desired product (3c) in an NMR yield of 42%, while the more electron-donating *tert*-butyl substituent with less abstractable H atoms was better tolerated (3d, 65%). Acetoxy-substituted product 3e was obtained in 58% yield, showing the tolerance of esters to hydrolysis under the PEC conditions. The reaction tolerated olefins containing aryl halides (3f–h), and no detectable dehalogenated products were observed. However, yields were lower than those of electron-rich or electron-neutral olefins, presumably due to the more challenging oxidation of the benzylic radical intermediate to its cation for the Ritter reaction step. Impressively, the highly reactive benzylic chloride moiety was untouched under the standard conditions (3i); neither dechlorination nor S_N2 side reactions were observed. Both 1- and 2-vinyl naphthalenes were tolerated, despite their π -extended systems that might encourage SET-initiated reactions.

A diverse set of hydrocarbons was then tested. Carbocycles like cyclopentane, cycloheptane, and cyclooctane readily underwent HAT as well as further downstream processes to give products 3m–p in modest to good 27–58% yields. Methylcyclohexane with five different HAT sites was engaged to furnish a mixture of five carboamidation products. Similarly, three different products were obtained in a combined NMR yield of 52% using *n*-hexane as the substrate (3r). These results highlight the challenges of using TBADT as known in the field of photocatalysis; its outstanding high reactivity in HAT that can engage unactivated hydrocarbons comes at the cost of selectivity in discriminating between the many C–H bonds within such molecules. We were further interested in employing ketones as coupling partners. Employing cyclopentanone led to difunctionalized product 3s as a single regioisomer. In contrast, cyclohexanone exhibited moderate regioselectivity, resulting in two isomers with a 1.7:1 ratio with a combined yield of 31% (3t). These inherent selectivities

Table 2. Reaction Scope



^aUnless otherwise stated, reactions under the conditions shown (Conditions A), see Supporting Information for details. ^bUnless otherwise stated, isolated yields of product **3**. ^cReactions under Conditions B: 5 mol % TBADT and LiClO₄ were used, see Supporting Information for details. ^dNMR yields are shown in parentheses. ^e7 mol % TBADT was used. ^fAverage of two runs ($\pm 3\%$).

dictated by polarity matching are exactly consistent with those reported for the TBADT-photocatalyzed HAT reactions of cyclic ketones.¹¹ Acyclic ketones also proved to be appropriate substrates. While pentan-2-one was functionalized in a less regioselective manner (**3v**), pentan-3-one was converted into **3u** as a single isomer. The success with *n*-pentyl benzoate constitutes a new method for the preparation of 1,*n*-amino alcohols (**3w**). Moreover, this catalytic system is also capable of functionalizing more activated C(sp³)-H bonds, such as those in tetrahydrofuran at its α -position (**3x**), in exclusive regioselectivity. Furthermore, we extended our exploration to include different nitriles as amidation reagents. CD₃CN was competent to intercept the *in situ* generated benzylic cations, generating *D*-incorporated products **3y–z** (again, the *p*-chlorostyrene was less efficient and **3z** was obtained in comparable yield to **3g**). Nitriles containing longer-chain aliphatic groups tended to deliver the corresponding products

in diminished yields (**3aa–ab**) compared to the model reaction providing **3a**, presumably due to competing HAT at the nitrile's C–H bonds. The reaction proceeded with sterically encumbered pivalonitrile (**3ac**) and less nucleophilic benzonitrile (**3ad**), albeit in modest yields.

The reaction mechanisms of TBADT engaging hydrocarbons in photocatalyzed reactions are already well-investigated in the literature,^{9–12} even under the conditions of photoelectrochemical Minisci reactions.²⁷ Nonetheless, we prioritized understanding the origin of the limited yields of the reaction (the model substrate giving an NMR yield of 64%). We noticed the rapid onset of a deep blue color in the reaction mixture upon light irradiation, which persisted throughout the course of the reaction (Figure 2). A slower onset was observed for unactivated hydrocarbons and a faster one for ethers. This blue color is attributed to inactive reduced TBADT species in the literature,⁴⁰ specifically to the one- and

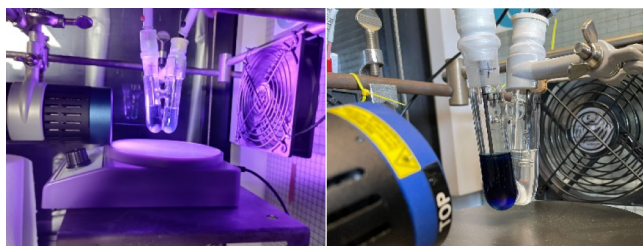


Figure 2. Pictures of the reaction setup. During (left) and after (right) potential and light irradiation were applied.

two-electron reduced species $\text{H}^+[\text{W}_{10}\text{O}_{32}^{5-}]/2\text{H}^+[\text{W}_{10}\text{O}_{32}^{6-}]$ (denoted $\text{HW}/\text{H}_2\text{W}$). Reoxidation of these species to **TBADT** in prior photoredox catalysis studies was found to be rate limiting,⁴⁰ and we assumed this to be the case for the PEC reactions herein to explain the limited yields. Therefore, we elected to probe the synthetic PEC reaction progress over time by (i) sampling the reaction for conversion of styrene to **3a** by HPLC; (ii) recirculating the reaction mixture through a UV/vis flow cell monitoring at $\lambda = 700$ nm to monitor $\text{HW}/\text{H}_2\text{W}$; and (iii) monitoring current and charge passed over time (for reactor setup, see SI file). After potential and irradiation were applied, the absorption at 700 nm immediately increased alongside the visual observation of the deep blue color, which was attributed to $\text{HW}/\text{H}_2\text{W}$ (Figure 3).

The 700 nm absorption then stabilized over the first 1.5 h, during which time the rate of starting material conversion tracked with the charge passed over time but did not track with the slow rate of product formation. This suggests a reaction induction period in which primarily styrene degradation occurs. The decomposed styrene may graft to the RVC anode, decreasing the RVC surface area and therefore decreasing the reoxidation rate of $\text{HW}/\text{H}_2\text{W}$ (and further decomposition of styrene). After 1.5 h, the induction period ended, and the product formation rate increased together with an increase in $\text{HW}/\text{H}_2\text{W}$. However, the product formation rate diverged from the charge passed, suggesting product degradation, which became obvious after ~ 15 h.⁴¹ Photo-excited **TBADT**'s high reactivity limits its ability to discriminate between different $\text{C}(\text{sp}^3)\text{-H}$ bonds, and so promiscuous HAT occurs with the product's C-H bonds.

The slow degradation of the product was accompanied by a gradual increase in $\text{HW}/\text{H}_2\text{W}$, which implied that the oxidative regeneration of active **TBADT** is inhibited by the degraded product. Overall, the kinetic profile shows (i) how conversion is limited by reoxidation of the $\text{HW}/\text{H}_2\text{W}$ and (ii) how initial degradation of styrene and later degradation of the product prohibit high yields (>65%) for this reaction. Consistent with this, running the reaction to ~ 0.9 F/mol mitigated product decomposition and either led to similar or even higher product yields,⁴² as seen with products **3f–3i**.

CONCLUSION

In summary, we report a novel photoelectrochemical carboamidation of styrenes with unactivated hydrocarbons. The use of **TBADT** as the catalyst allowed successful engagement of truly unactivated hydrocarbons, while the unique radical polar crossover reactivity accessible by PEC conditions allowed to further engage the radical intermediate in oxidation, addressing limitations in prior photocatalytic **TBADT** reports to (i) electron-poor olefin trapping partners and (ii) monofunctionalizations. The low cell potentials of our new catalytic reaction allowed us to evade direct SET oxidation of styrene and thus discourage side reactions. Kinetic studies revealed that further engagement of the product in deleterious HAT processes could be mitigated by controlling the charge that was passed. The reaction demonstrated good functional group tolerance with respect to both styrenes and alkanes, offering a green approach to pharmaceutically important cores, such as 1,*n*-amino alcohols and amino-substituted ketones without using stoichiometric chemical oxidants.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acscatal.4c02320>.

Experimental procedures, detailed information on mechanistic studies; characterization data for all compounds; and ^1H , ^{13}C , and ^{19}F spectra (PDF)

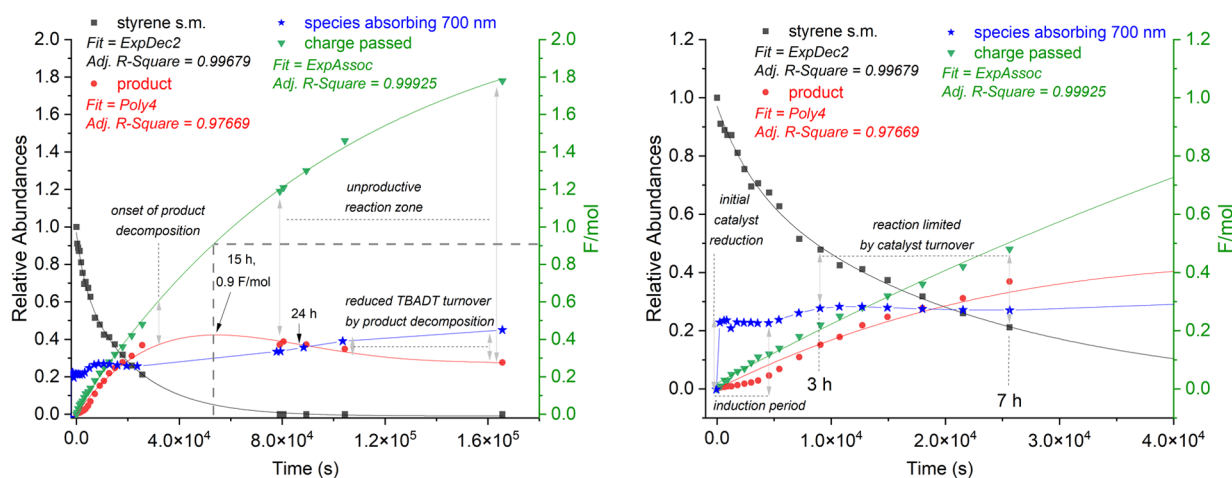


Figure 3. Kinetic profile for the reaction forming **3a** at $U_{\text{cell}} = +1.4$ V, monitoring at $\lambda_{\text{abs}} = 700$ nm. The HPLC abundances of the components were corrected based on response factors and normalized. Absorption intensity and charge passed are absolute values. Left: whole profile, 50 h. Right: expanded initial profile, 11 h.

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Author Contributions

#S.S. and S.W. contributed equally to this work. S.W. discovered the reaction and contributed to initial reaction optimizations, with supervision from J.P.B. The optimal reactor setup and reaction conditions were developed by S.S. who contributed the majority of the substrate scope. X.T., S.W., and I.D. also contributed to the substrate scope (in that order). I.D. ran reactions to ~0.9 F/mol. M.D. conducted the kinetic study. X.T. and J.P.B. co-wrote the manuscript, with minor contributions from S.W. and S.S. X.T. wrote the majority of the SI file with assistance from S.S., S.W., and J.P.B. X.T. and J.P.B. co-supervised S.S., I.D., and M.D. in their experimental contributions. J.P.B. directed the project and dealt with peer-review of the manuscript.

Notes

The authors declare no competing financial interest.

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- (41) The rest of the mass balance and the degraded products could not be conclusively identified due to complex lumpy aromatic NMR peaks (or by mass spectroscopy). We suspect that HAT occurs at the activated benzylic, α -amido position of the product which reacts further with styrene.
- (42) We speculate the benzylic radical intermediate formed during the reaction may initiate polymerization of the styrene if not oxidized fast enough. Such a rationale would explain styrenes which are particularly electron-poor (more so than 4-bromo or 4-chlorostyrene) give no product (see SI, Section 10) despite high conversion of those styrenes. However, for electron richer styrenes, the potentials of +1.7 V or +2.0 V would be sufficient to promote direct oxidation of the styrene, so we pre-emptively chose +1.4 V to avoid this. The promotion of **3i**'s yield at 0.9 F/mol may be explained by the activated benzylic position of its product undergoing promiscuous HAT as the reaction progresses further.