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Accelerated Electrophotocatalytic C(sp³)-H Heteroarylation Enabled by an Efficient Continuous-Flow Reactor**

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Abstract: Electrophotocatalytic transformations are garnering attention in organic synthesis, particularly for accessing reactive intermediates under mild conditions. Moving these methodologies to continuous-flow systems, or flow ElectroPhotoCatalysis (*f*-EPC), showcases potential for scalable processes due to enhanced irradiation, increased electrode surface, and improved mixing of the reaction mixture. Traditional methods sequentially link photochemical and electrochemical reactions, using flow reactors connected in series, yet struggle to accommodate reactive transient species. In this study, we introduce a new flow reactor concept for electrophotocatalysis (EPC) that simultaneously utilizes photons and electrons. The reactor is designed with a transparent electrode and employs cost-effective materials. We used this technology to develop an efficient process for electrophotocatalytic heteroarylation of C(sp³)-H bonds. Importantly, the same setup can also facilitate purely electrochemical and photochemical transformations. This reactor represents a significant advancement in electrophotocatalysis, providing a framework for its application in flow for complex synthetic transformations.

In the past decade, the employment of photocatalytic transformations in organic synthesis has markedly increased,

a shift largely ascribed to the exceptional ability of photocatalysts to absorb light energy and exploit it to access reactive intermediates under mild reaction conditions.^[1] Similarly, electrocatalysis has ascended in prominence, recognized for its inherent selectivity, which obviates the need for high-energy oxidants or reductants, thus providing a robust and selective pathway for molecular activation.^[2]

Recently, the integration of these two activation modes has given rise to the field of electrophotocatalysis (EPC), providing new opportunities in synthetic organic chemistry.^[3] This synergistic use of light and electricity enables the in situ formation of super-oxidants,^[4] super-reductants,^[5] and can also be harnessed for the regeneration of photocatalysts in photoredox reactions, eliminating the need for sacrificial oxidants or reductants. Although catalyst and substrate often interact via single electron transfer processes,^[6] the successful execution of hydrogen atom transfer^[7] and decarboxylative methodologies^[8] has also been demonstrated. However, the union of photo- and electrochemistry in these methodologies often requires prolonged reaction times, spanning from 10 to 48 hours, which hinders productivity and poses significant challenges for scaling efforts (Scheme 1).

Transitioning these batch methodologies to continuous-flow systems, specifically flow ElectroPhotoCatalysis (*f*-EPC), holds the potential for an efficient scale-up process, subjecting the reaction mixture to more homogeneous irradiation and improved mixing. Additionally, flow reactors enhance safety and reproducibility of the reactions and pave the way toward a more approachable strategy for automation.^[9] Particularly in the realm of flow electrochemical reactors, the narrow inter-electrode distance leads to a reduced ohmic drop, thereby facilitating selective, reproducible, and scalable processes.^[10]

Despite known attempts at employing *f*-EPC, it is noteworthy that the photochemical and electrochemical steps have not been operated simultaneously in practice to date.^[11] Conventionally, starting materials traverse through a photochemical and an electrochemical reactor connected in series, likely attributed to a blend of technological and chemical challenges in balancing the rates of the two concurrent transformations.^[6,12] However, from a chemical perspective, the transient nature of species formed in electrophotocatalysis necessitates the simultaneous execution of both the photochemical and electrochemical steps for effective outcomes. Technologically, the paragon reactor must adeptly navigate practical challenges inherent to both photo- and electrochemistry, each presenting its own scalability hurdles. Thus, in a unified reactor, electrodes

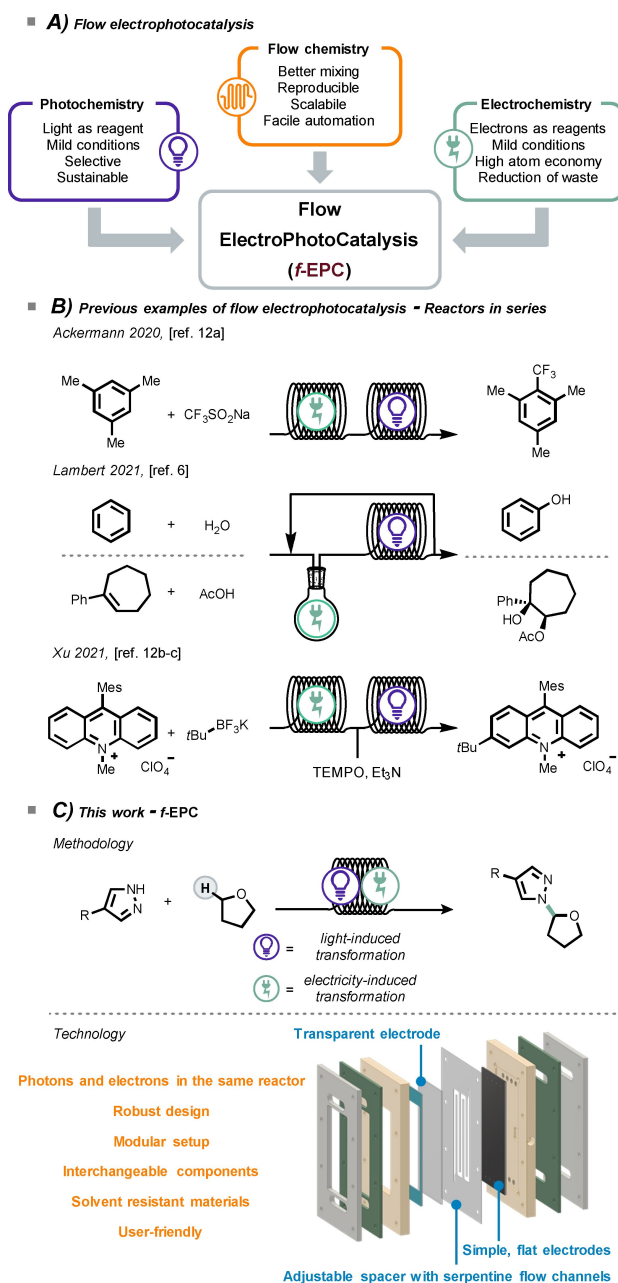
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Scheme 1. A) Flow electrophotocatalysis (*f*-EPC). B) Previous examples of flow electrophotocatalysis. C) Electrophotocatalytic C(sp³)-H heteroarylation via the merger of photocatalysis and electrocatalysis enabled by a newly fabricated *f*-EPC reactor.

must be installed while concurrently ensuring adequate illumination of the reaction medium. This implies that technological barriers, such as the Ohmic drop in electrochemistry and the attenuation effect in photochemistry, must be surmounted simultaneously to guarantee process scalability and reproducibility.

In light of the aforementioned challenges, achieving the construction of an effective *f*-EPC reactor remains a pivotal yet unfulfilled objective. Recently, the Atobe group made strides in this domain, introducing a prototype of a flow cell for synthetic electrophotocatalysis.^[13] While it intro-

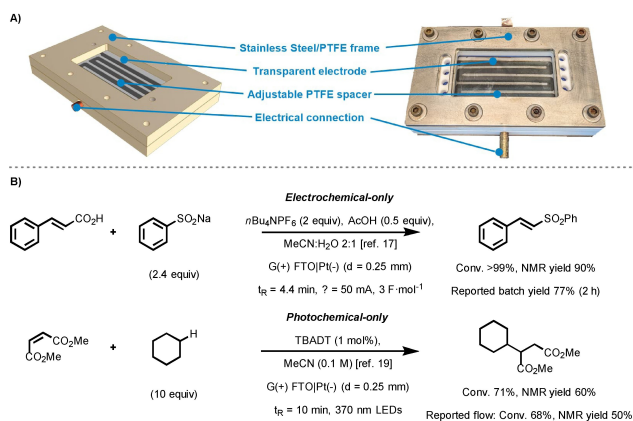
duced valuable insights and advancements, there were aspects regarding robustness and productivity that requires further refinement and exploration. The desired reactor would ideally be i) modular and robust, ii) comprised of interchangeable, solvent-resistant materials, iii) safe and user-friendly, and iv) versatile, facilitating either independent or simultaneous execution of photochemistry and electrochemistry.

Based on our experience, we posit that the challenges intrinsic to photochemistry and electrochemistry can be concurrently addressed through reaction miniaturization. Given the short-lived nature of the generated reactive species, it is plausible to suggest that all pertinent processes will occur in close proximity to the electrodes. Consequently, efficient photon delivery near the electrode surface becomes crucial. Thus, an optimal *f*-EPC reactor should feature at least one transparent electrode to ensure effective light penetration. Lastly, the reactor's volume should be adaptable to modulate productivity, such as by altering the inter-electrode gap using gaskets. Capitalizing on our experience,^[7c,14] we present herein the development of such reactor to perform an efficient electrophotocatalytic heteroarylation of C(sp³)-H bonds. The achievement of this transformation was realized through the combination of hydrogen atom transfer (HAT) via LMCT photocatalysis^[15] and an electrochemical oxidation.

In adherence to the previously outlined criteria, we constructed the *f*-EPC reactor, integrating stainless steel and PTFE (polytetrafluoroethylene) frames (160 mm × 95 mm × 10 mm) to house the electrodes within an insulating and solvent-resistant environment. This design ensures that the electrodes can be firmly compressed, and the inter-electrode distance can be finely tuned by utilizing serpentine-shaped PTFE gaskets of varying thickness (0.1 mm–0.5 mm), thereby allowing a cell volume of 0.28–1.4 mL. Liquids can be introduced directly into the reactor using Super Flangeless Nuts (PEEK, 1/4-28 Flat bottom, for 1/16"OD). Evidently, at least one of the electrodes must be transparent to ensure effective light penetration into the reactor. Thus, we implemented an FTO (fluorine-doped tin oxide) glass slab coated with a thin layer of Pt nanoparticles via a previously reported procedure^[16] to boost its catalytic activity to proton reduction.^[14b]

With this apparatus in hand, we embarked on its validation, conducting a series of transformations, encompassing electrochemical, photochemical, and electrophotocatalytic processes (Scheme 2). In verifying the reactor for electrochemistry, we opted for the synthesis of vinyl sulfones from cinnamic acids and sodium sulfonates, as detailed by Zha, Wang, and co-workers.^[17] Notably, pushing a mixture of cinnamic acid and sodium phenylsulfinate through the reactor yielded the desired product at 90%, with a residence time (*t_R*) of 4.4 minutes and a total charge of 3 F·mol⁻¹. This outcome mirrors the results presented in the original paper, underscoring the feasibility of conducting electrochemical-only reactions with our new reactor concept.

In a parallel vein, the *f*-EPC reactor was explored under photochemical-only conditions by executing a photocata-



Scheme 2. A) Design and picture of the newly constructed *f*-EPC reactor. B) Validation of the flow reactor for electrochemical- and photochemical-only reactions.

lytic Giese-type radical hydroalkylation.^[18] When a mixture of dimethyl maleate and cyclohexane was flowed through the reactor, a good performance was observed, achieving a 60% ¹H NMR yield of the anticipated product within a 10-minute residence time (further information are reported in the Supporting Information in Section S2).^[19]

While the preliminary results positively showcased the ability of the reactor to handle electrochemical and photochemical processes, achieving a successful outcome in electrophotocatalytic transformations presented a unique challenge, necessitating meticulous tuning of the kinetics within electron- and photon-driven elementary steps to increase efficiency.

We chose the azolation of C(sp³)-H bonds as a benchmark transformation to showcase the capabilities of our setup. Traditional approaches to this chemistry^[14c,20] have depended on stoichiometric oxidants, which significantly limits scalability, reaction mildness, and tolerance to various functional groups. We reasoned that our electrophotocatalytic flow technology would be the ideal solution to provide a robust and scalable strategy to replace stoichiometric oxidants with a recyclable electrode. Our initial investigations commenced by studying the coupling of ethyl pyrazole-4-carboxylate (**1a**) and tetrahydrofuran (**2a**) to afford product **3** (Table 1). This was pursued under irradiation with a purple LED ($\lambda = 390$ nm, 52 W input power) and in galvanostatic mode (77 mA, 3.2 mA·cm⁻², 6 F·mol⁻¹). By flowing an acetonitrile solution of **1a** (0.1 M), **2a** (6 equiv), and FeCl₃ (5 mol%)—employed as a photocatalyst^[15]—through the *f*-EPC reactor, in the presence of acetic acid (10 equiv) and Et₄NCl (1 equiv), we secured product **3** in excellent yield (88%) with a mere 15-minute residence time (Table 1, Entry 1). Expectedly, product formation was negligible without electricity and/or light, demonstrating the electrophotocatalytic nature of this transformation (Table 1, Entries 2–4). Removing the electrolyte, the proton source or the iron catalyst led to reduced yields (Table 1, Entries 5–7), whereas reducing the applied current to 51 mA (2.3 mA·cm⁻²) demonstrated a less pronounced impact on the reaction (Table 1, Entry 8).

Table 1: Optimization of reaction conditions and control experiments for the electrophotocatalytic C(sp³)-H heteroarylation in flow.^[a]

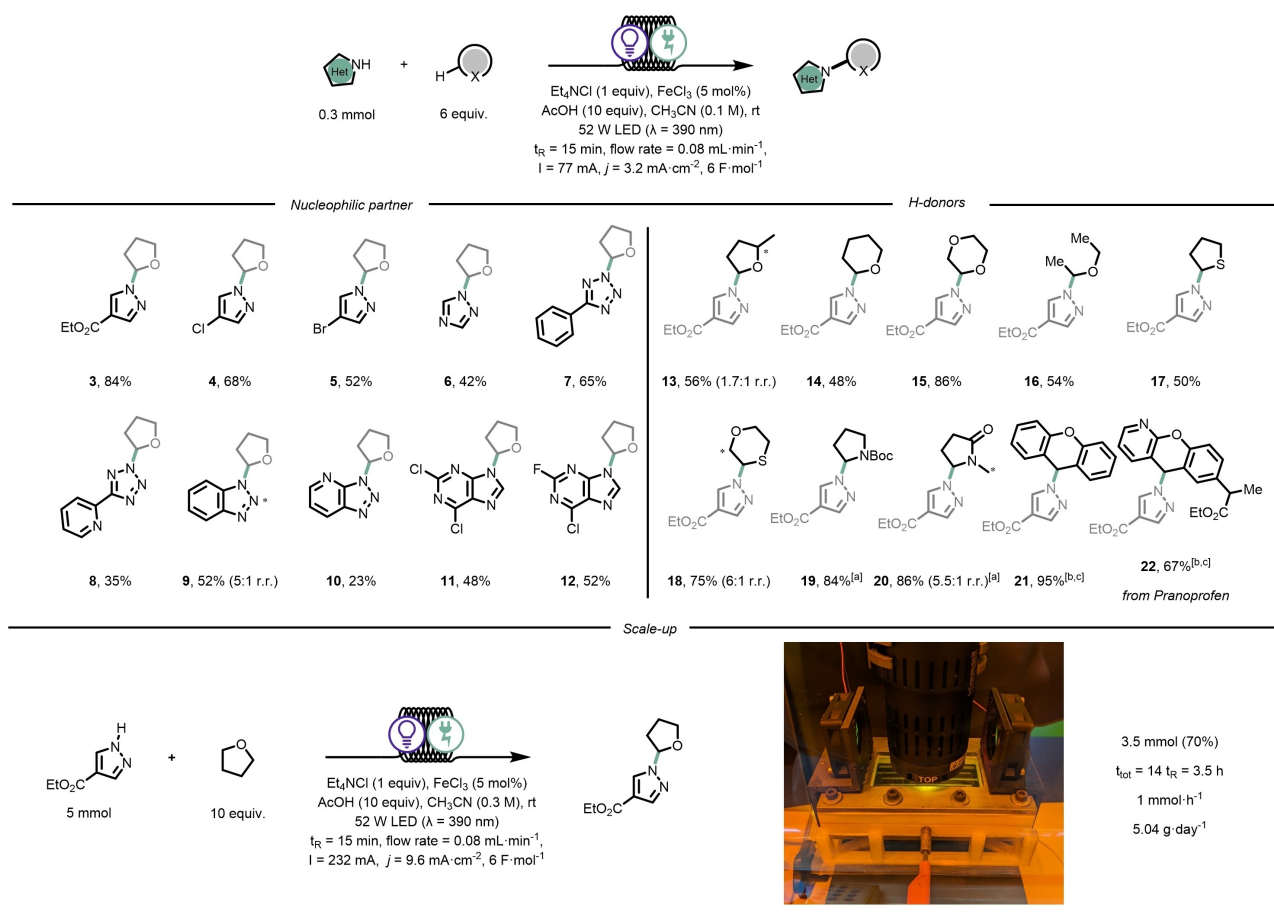
Entry	Variation from conditions	Yield ^[b]
1	None	88 (84)
2	Without electricity	< 5
3	Without light irradiation	—
4	Without electricity or light irradiation	—
5	Without AcOH	35
6	Without Et ₄ NCl	31
7	Without FeCl ₃	24
8	51 mA, 2.1 mA·cm ⁻² , 4 F·mol ⁻¹	68
9	THF (15 equiv)	84
10	2x52 W LED	82
11	Batch: 12 mA, 1 mA·cm ⁻² , 6 F·mol ⁻¹ , 4 h	80

[a] **1a** (0.3 mmol), **2a** (6 equiv), FeCl₃ (5 mol%), Et₄NCl (1 equiv), AcOH (10 equiv) in CH₃CN (0.1 M, 3 mL); solution sparged with N₂ prior to irradiation. Flow setup (see SI): V_R = 1.2 mL, flow rate = 0.08 mL·min⁻¹, $\tau = 15$ min, 52 W LED ($\lambda = 390$ nm), undivided cell: C anode/Pt|FTO cathode, $I = 77$ mA, $j = 3.2$ mA·cm⁻², 6 F·mol⁻¹. [b] Yields determined by ¹H NMR spectroscopy using CH₂Br₂ as external standard. Yield of the isolated product is given in parenthesis.

Interestingly, neither the use of additional equivalents of **2a** nor an increase in LED power affected the product yield (Table 1, Entries 9–10). Finally, conducting the reaction in batch delivered similar results after 4 hours of photoelectrolysis (Table 1, Entry 11, see Supporting Information for additional details on the batch reactor).

Having established the optimized reaction conditions, we turned our focus to examining the scope of our electrophotocatalytic transformation, as illustrated in Scheme 3. Our initial exploration revolved around the coupling of model substrate **1a** with a variety of nitrogen-containing heteroarenes. Pyrazoles, especially those featuring electron-withdrawing groups (e.g., ethyl-ester **3**, chloro **4**, and bromo **5**), yielded the anticipated cross-coupled products in satisfactory to excellent yields (52–84%). Furthermore, additional nitrogen-containing five-membered rings, like triazole (**6**, 42%), tetrazoles (**7–8**, 35–65%) and fused heteroaromatic structures (**9–10**, 23–52%) were successfully employed. We also managed to effectively functionalize halogenated purines, obtaining the respective tetrahydrofuran-adducts (**11–12**, 48–52%).

Venturing further, we subjected a diverse set of H-donor substrates to our flow-based electrophotocatalytic reaction conditions. Efficient α -to-O C(sp³)-H functionalization across various cyclic and linear ethers delivered the sought-after compounds in commendable yields (**13–16**, 48–86%). Notably, selective α -to-S and α -to-N C-H bond functionalization was observed as well (**17–20**, 50–93%), maintaining excellent selectivity over competing α -to-O C-H activation, as seen, for instance, with compound **18**. Our method also demonstrated capability in functionalizing



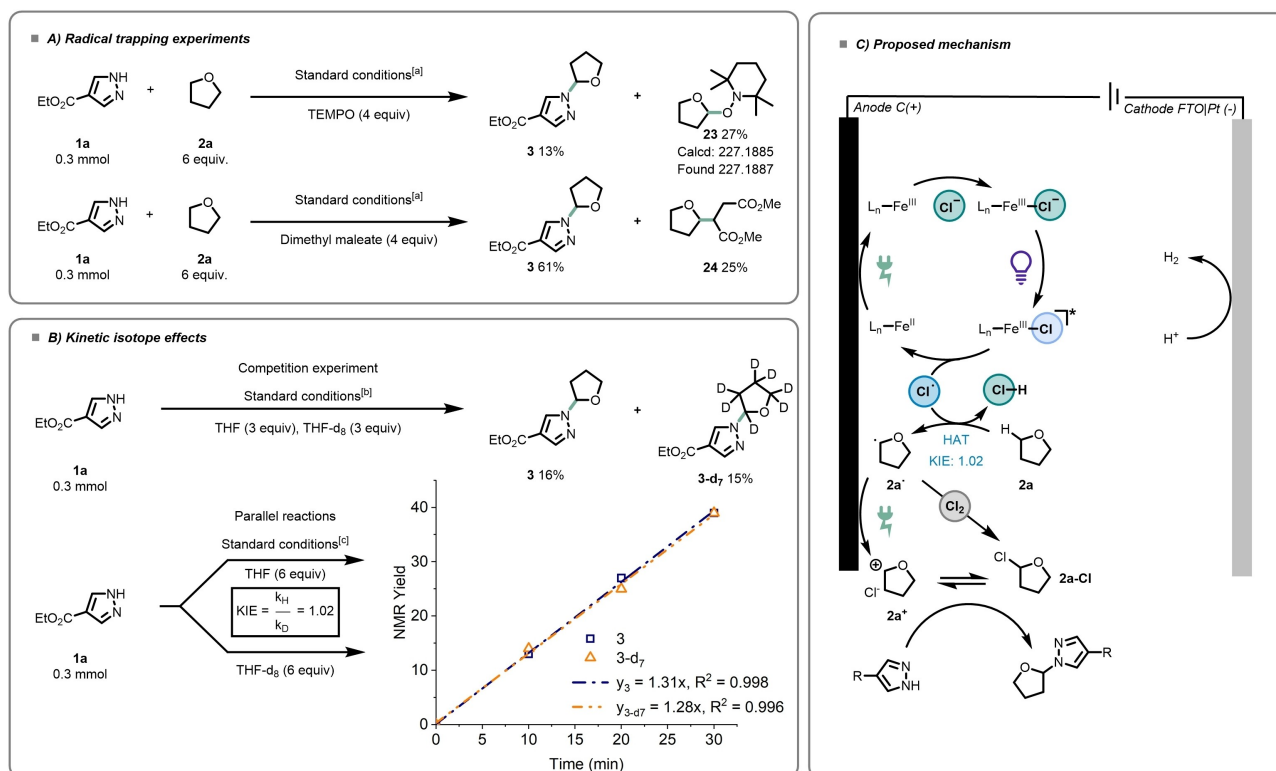
Scheme 3. Substrate scope for the electrophotocatalytic C(sp³)-H heteroarylation in flow. Heteroarene (0.3 mmol), hydrogen donor (6 equiv), FeCl₃ (5 mol%), Et₄NCl (1 equiv), AcOH (10 equiv) in CH₃CN (0.1 M, 3 mL); solution sparged with N₂ prior to irradiation. Flow setup: V_R = 1.2 mL, flow rate = 0.08 mL·min⁻¹, t_R = 15 min, 52 W LED (λ = 390 nm), undivided cell: C anode/Pt|FTO cathode, I = 77 mA, j = 3.2 mA·cm⁻², 6 F·mol⁻¹. Isolated yields are given. [a] 3 equiv. of the hydrogen donor were used. [b] 2 equiv. of the hydrogen donor were used [c] I = 32 mA, j = 1.3 mA·cm⁻², 2.5 F·mol⁻¹. Minor regioisomer is denoted with an asterisk.

benzylic positions; xanthene was functionalized yielding notably high yields (**21**, 95%). Remarkably, functionalization of the nonsteroidal anti-inflammatory drug pranoprofen was accomplished, procuring product **22** (67% yield). Finally, our benchmark reaction involving ethyl pyrazole-4-carboxylate (**1a**) and tetrahydrofuran (**2a**) was readily scaled up in flow using the standard procedure, with an enhanced concentration (0.3 M) and a larger H-donor excess (10 equiv) for extended operation times (5 mmol, 70% isolated yield, productivity: 1 mmol·h⁻¹). The reactor maintained adequate performance even after 210 minutes (corresponding to 14 residence times).

We subsequently carried out a series of experiments to unravel the intricacies of the reaction mechanism, presenting our findings in Scheme 4. Our initial step involved conducting the reaction under optimized conditions while introducing TEMPO (4 equiv), a well-known radical scavenger. Notably, the reactivity was entirely quenched, and adduct **23** was identified via HRMS, confirming the presence of radical species. Parallely, a reaction utilizing an electron-deficient olefin, namely dimethyl maleate, afforded product **24** (25% NMR yield) alongside product

3, further underlining the likely intermediacy of an α-oxyalkyl radical through a chlorine-mediated HAT step (Scheme 4A). Next, Kinetic Isotope Effect (KIE) evaluations, through both competitive and parallel approaches,^[21] consistently presented a value approximating 1. This suggests that the Hydrogen Atom Transfer (HAT) is not the rate-determining step (Scheme 4B).

A proposed reaction mechanism, illustrated in Scheme 4C, has been derived from these mechanistic observations. Initially, a chloride ligand associates with the iron center: the tetrachlorate complex absorbs purple light to yield the corresponding excited state. This is followed by the homolysis of the Fe-Cl bond, generating a chlorine radical and a reduced Fe^{II} species.^[22] The reduced catalyst is then oxidized at the anode, resulting in the formation of the Fe^{III} center, which closes the catalytic cycle. Iron plays a pivotal role in this transformation. In the absence of iron, we still observe product formation, however, it is accompanied by a substantial production of molecular chlorine, resulting in the unwanted chlorination of pyrazole substrates. Importantly, the presence of iron effectively curtailed this unintended pathway.^[23b] We hypothesize that



Scheme 4. Mechanistic investigations into the electrophotocatalytic C(sp³)-H heteroarylation. A) Radical trapping experiments. B) Kinetic isotope effects: Standard conditions: [a] **1a** (0.3 mmol), **2a** (6 equiv), FeCl₃ (5 mol%), Et₄NCl (1 equiv), AcOH (10 equiv) in CH₃CN (0.1 M, 3 mL); solution sparged with N₂ prior to irradiation. Flow setup: V_R = 1.2 mL, flow rate = 0.08 mL·min⁻¹, t_R = 15 min, 52 W LED (λ = 390 nm), undivided cell: C anode/Pt|FTO cathode, I = 77 mA, j = 3.2 mA·cm⁻², 6 F·mol⁻¹. Yields determined by ¹H NMR spectroscopy using CH₂Br₂ as external standard. [b] t_R = 4 min. [c] Reactions performed in batch: 12 mA, 6 F·mol⁻¹. C) proposed mechanism.

this inhibition occurs due to the lower redox potential of Fe(II) compared to chloride ($E_{Fe^{III}/Fe^{II}} = +0.53$ V vs SCE, $E_{Cl^+/Cl^-} = +1.12$ V vs SCE), essentially making the iron catalyst function as a safeguard against both overoxidation and chlorination of the pyrazole substrates. Meanwhile, the chlorine radical executes C-H bond cleavage adjacent to a heteroatom (i.e., O, N, or S), thus generating a nucleophilic carbon-centered α -oxyalkyl radical (**2a[•]**).^[23a] At this point, two scenarios can be envisaged. On the one hand, **2a[•]** can be electrochemically oxidized to form a stabilized, electrophilic oxocarbenium ion (**2a⁺**). The latter intermediate is subsequently trapped by the nucleophile, forming the desired C-N bond.

On the other hand, the α -oxyalkyl radical (**2a[•]**) can be trapped by minor amounts of solubilized Cl₂-formed via the anodic oxidation of chloride-resulting in a chloride intermediate (**2a-Cl**).^[23a] Although the intermediate **2a-Cl** was not observed in our experiments, it would theoretically lead to the formation of product **3** via nucleophilic substitution, aided by the anomeric effect.^[24] Despite extensive efforts, the C(sp³)-H heteroarylation method could not be extended to unactivated aliphatic C(sp³)-H bonds (see Supporting Information). The fact that these substrates are unreactive suggests that the oxidation from intermediate **2a[•]** to **2a⁺** is only realized when the latter is

adequately stabilized, as observed with an oxocarbenium ion.

In conclusion, we have successfully developed an efficient *f*-EPC reactor for electrophotocatalysis. In contrast to previous studies, our new flow reactor concept simultaneously accommodates photons and electrons in the microchannel allowing for the handling of transient species. The *f*-EPC reactor enables us to utilize this reactor in photochemical, electrochemical, and electrophotocatalytic conversions, with a specific utility in forging C(sp³)-N bonds. The new synthetic method to establish C(sp³)-N bonds in flow merges the electrochemically-induced radical-polar crossover concept with HAT photocatalysis, functioning under remarkably mild conditions. This allows the functionalization of a diverse set of organic compounds, enabling late-stage drug functionalization. The electrophotochemical heteroarylation occurs at room temperature, demands no external oxidants, and ensures short reaction times, enhancing overall productivity compared to existing protocols.^[7d,14c,20c,25] Ongoing studies in our laboratory aim to further explore the generality of the *f*-EPC reactor in advancing synthetic electrophotocatalytic applications.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Electrophotocatalysis · Flow Chemistry · Heteroarylation · Hydrogen Atom Transfer · Microreactor

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