

A General Photocatalytic Strategy for Nucleophilic Amination of Primary and Secondary Benzylic C–H Bonds

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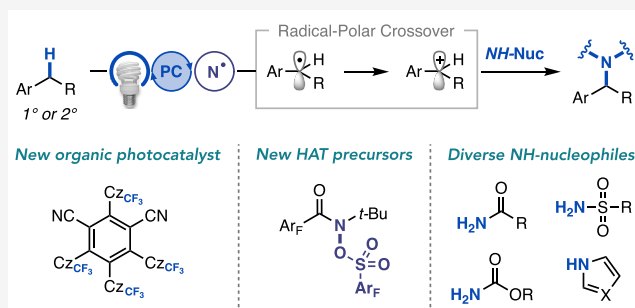


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ABSTRACT: We report a visible-light photoredox-catalyzed method that enables nucleophilic amination of primary and secondary benzylic C(sp³)–H bonds. A novel amidyl radical precursor and organic photocatalyst operate in tandem to transform primary and secondary benzylic C(sp³)–H bonds into carbocations via sequential hydrogen atom transfer (HAT) and oxidative radical-polar crossover. The resulting carbocation can be intercepted by a variety of N-centered nucleophiles, including nitriles (Ritter reaction), amides, carbamates, sulfonamides, and azoles, for the construction of pharmaceutically relevant C(sp³)–N bonds under unified reaction conditions. Mechanistic studies indicate that HAT is amidyl radical-mediated and that the photocatalyst operates via a reductive quenching pathway. These findings establish a mild, metal-free, and modular protocol for the rapid diversification of C(sp³)–H bonds to a library of aminated products.



INTRODUCTION

The merger of hydrogen atom transfer (HAT) with transition-metal-catalyzed oxidative radical relay (ORR) or oxidative radical-polar crossover (ORPC) has recently emerged as a promising strategy to enable mild C(sp³)–H functionalization reactions with nucleophilic coupling partners.¹ Due to the prevalence of nitrogen functionality in bioactive compounds, this strategy is of particular interest as an approach to C(sp³)–H amination for feedstock chemical conversion and late-stage derivatization (Figure 1A).² C(sp³)–H amidations proceeding via HAT-ORPC (Ritter-type reactions) have been reported under a variety of oxidative conditions using solvent quantities of nitrile as the nucleophile.³ Of note, Lambert and co-workers have reported a mild method for Ritter-type C–H amidation via electrophotocatalysis, the only example to date that does not require stoichiometric oxidant.⁴ Whereas most Ritter reactions target secondary and tertiary benzylic or unactivated tertiary C(sp³)–H bonds, recently König and co-workers have disclosed a unique strategy for Ritter amidation, utilizing visible light excitation of *in situ*-generated iodine(III)–BF₃ complexes to amidate primary benzylic C–H bonds.⁵

Despite these important advances, expansion of N-nucleophile identity beyond nitriles in solvent quantity has been comparatively less explored. Copper-catalyzed platforms, including variants of the original Karasch–Sosnocky reaction⁶ as well as more recent developments by Stahl, Liu, and others, have proven most versatile, enabling C–H (sulfonyl)-amidation,^{7–13} azolation,¹⁴ and azidation.^{15,16} Alternatively, transition-metal-free platforms for C(sp³)–H (sulfonyl)-amidation^{17–19} and C(sp³)–H azolation^{20–23} exist, but each

method and set of reaction conditions is confined to a single nucleophile class (amides, sulfonamides, or azoles, but never all three within one protocol) (Figure 1B). Moreover, many still require stoichiometric oxidants such as Selectfluor, NFSI, or DDQ. Thus, identification of reagents and catalysts that can enable selective activation of a wider array of C(sp³)–H partners, under more practical and functional-group-tolerant conditions and with greater generality with respect to NH-nucleophile identity, would be of broad value.

With this in mind, we questioned whether recent work in our lab,²⁴ reported concurrently with the Musacchio lab,²⁵ combining HAT with ORPC might be suited to the development of a general and mild C(sp³)–H amination. Our prior reaction platform included Ir(*p*-F-ppy)₃ as a photocatalyst and *N*-acyloxypthalimide as the HAT precursor, and we demonstrated that this platform enabled fluorination of secondary and tertiary benzylic and allylic C(sp³)–H bonds (Figure 1C). Whereas other nucleophiles such as chloride, alcohols, thiols, and water were also tolerated, nitrogen-based nucleophiles were unreactive, aside from a single report of C(sp³)–H azidation. Likewise, Musacchio and co-workers reported only a single example of C–N bond formation using a

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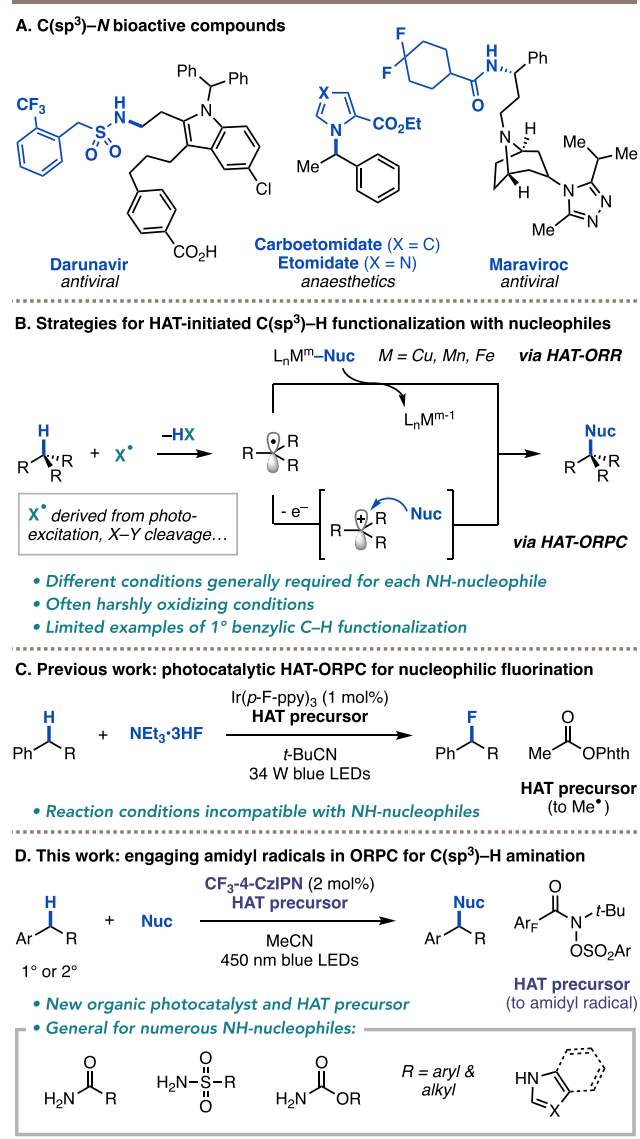


Figure 1. Prior art in C(sp³)-H functionalization with N-nucleophiles and an overview of this work.

pyrazole derivative;²⁵ they have since expanded this catalyst platform to include secondary benzylic and tertiary benzylic and aliphatic C(sp³)-H azolations.²³

In our original report, inclusion of NEt₃·3HF was necessary in order to obtain high yields of C(sp³)-H functionalization (even for non-fluoride nucleophiles), likely because this additive accelerated single-electron reduction and decarboxylation of *N*-acyloxyphthalimide with excited-state Ir(*p*-F-ppy)₃, affording higher concentrations of the HAT reagent (methyl radical). However, we found that NH-nucleophiles, such as sulfonamides and amides, were deactivated by competitive hydrogen bonding with the NEt₃·3HF additive. Hydrogen bonding to the NH-nucleophile also inhibited methyl radical generation from *N*-acyloxyphthalimide, NEt₃·3HF, and Ir(*p*-F-ppy)₃. We hypothesized that identification of novel HAT precursors that deliver polarity-matched HAT agents under less reducing conditions and/or a photoredox catalyst with an expanded redox window for reductive generation of the HAT reagent and radical oxidation could address this limitation.

We describe below the application of a novel amidyl radical HAT precursor and new organic photoredox catalyst to a mild, Ritter-type C(sp³)-H amidation with acetonitrile and water and amination with a range of exogenous *N*-nucleophiles such as amides, sulfonamides, carbamates, and azoles (Figure 1D). Moreover, we establish the versatility of this platform to achieve C(sp³)-H halogenation, esterification, etherification, and hydroxylation. Data-science-informed evaluation of the C(sp³)-H substrate scope reveals the breadth and limitations of this method for secondary benzylic C(sp³)-H substrates. Notably, primary benzylic C(sp³)-H sites of abundant toluene-derived feedstocks also undergo amidation. Finally, in-depth mechanistic studies are presented which show that reductive quenching of the photocatalyst by the HAT reagent enables the HAT-ORPC catalytic cycle to take place.

RESULTS AND DISCUSSION

Our optimization studies began with the preparation and evaluation of a series of new HAT precursors. Amidyl radicals containing 3,5-bis(trifluoromethyl) substitution on the benzamide moiety, along with *tert*-butyl substitution on nitrogen, were targeted as HAT agents on the basis of precedent from the Alexanian group, who demonstrated that this motif is highly effective in engaging in rapid and selective intermolecular hydrogen atom abstraction.²⁶ Photocatalytic reductive generation of amidyl radicals has been previously achieved using *O*-aryl,²⁷ *O*-benzoyl,²⁸ and very recently *O*-alkenyl^{29,30} hydroxamic acid derivatives. Nevertheless, the implementation of these reagents in an ORPC platform is currently unknown and presents multiple challenges. In particular, the propensity for charge recombination after single-electron reduction could result in extremely small concentrations of all downstream species, rendering HAT and radical oxidation kinetically slow.^{31,32} We reasoned that installation of a sulfonate ester leaving group on the nitrogen center would address this requirement and a few others:³³ it would (1) provide a strong thermodynamic driving force for single-electron reduction, (2) facilitate selective mesolytic fragmentation, (3) produce a sulfonate anion that would not interfere with nucleophilic trapping, and (4) confer stability under blue light irradiation. Similar *N*-sulfonate (sulfon)amides have been previously reported as precursors to sulfonamidyl radicals that undergo addition into electron-rich heterocycles.^{34,35} HAT reagents A-C were prepared in two steps without chromatography, giving bench-stable solids (Figure 2).

We interrogated these HAT reagents in a Ritter-type C(sp³)-H amidation of ethylbenzene (**1a**) to afford acetamide **1b** using acetonitrile as the solvent and H₂O (2 equiv) as the nucleophile (Figure 2). Employing HAT reagent A (1 equiv) afforded product **1b** in 69% yield using Ir(*p*-F-ppy)₃ as a photocatalyst (entry 1). Analysis of the ¹⁹F NMR spectrum of the crude reaction mixture revealed decomposition of the iridium photocatalyst and incomplete conversion of the HAT reagent. We thus turned our attention to the use of organic photocatalysts, in particular cyanoarene-based 4-CzIPN derivatives, which have demonstrated improved stability relative to transition-metal photocatalysts in various transformations and represent more sustainable and cost-effective options.^{36,37} Additionally, the modular features of organic CzIPN derivatives enable the systematic fine-tuning of both the donor substituents and the acceptor core of the catalyst structure, which can expand the “redox window” of the photocatalysts. This makes them a more attractive platform for

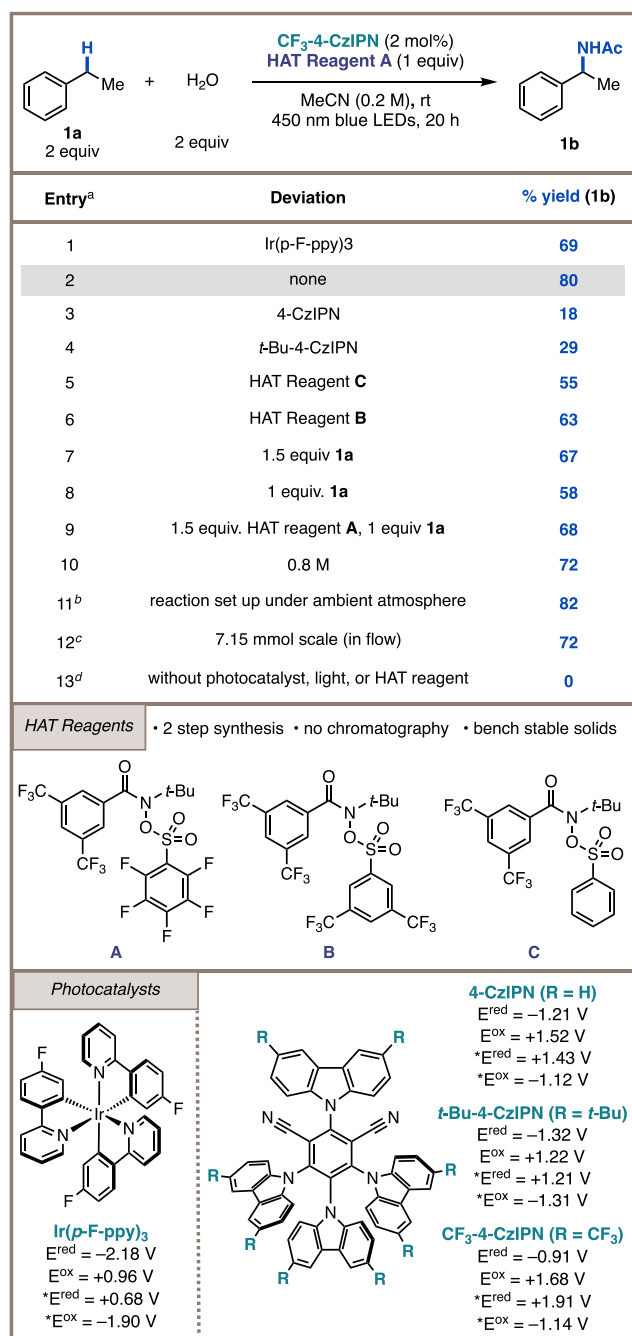


Figure 2. Optimization of reaction conditions. ^aReactions run on a 0.1 mmol scale. Yields determined by ¹H NMR spectroscopy with 1,3,5-trimethoxybenzene as an external standard. Redox potentials are reported in volts vs SCE in MeCN. ^bVial sealed with parafilm after reaction setup. ^cFor the exact reaction setup, see the Supporting Information. ^dReaction performed independently without blue LEDs, without photocatalyst, and without HAT reagent A.

the development of radical-polar crossover reactions.³⁶ To our surprise, preliminary photocatalyst screening using high-throughput experimentation demonstrated that many organic photocatalyst scaffolds were competent in the reaction (see the Supporting Information (SI)). Although yields were lower when using 4-CzIPN and *t*-Bu-4-CzIPN (entries 3 and 4) than Ir, no decomposition of the organic photocatalysts was observed at the end of the reaction.

When using the more oxidizing CF₃-4-CzIPN as a catalyst, a marked improvement in reactivity was observed, giving product **1b** in 80% yield (entry 2). Such an improvement in yield may reflect CF₃-4-CzIPN's enhanced photophysical properties relative to 4-CzIPN, including a higher photoluminescence quantum yield (PLQY), longer excited-state lifetimes, and higher excited-state energies.³⁸ While CF₃-4-CzIPN has been previously used in the development of thermally activated delayed fluorescence organic light-emitting diodes (TADF OLEDs),³⁸ to the best of our knowledge, this photocatalyst scaffold has not been used in a synthetic organic transformation.³⁹

Using CF₃-4-CzIPN as photocatalyst, Ritter amidation proceeds with poorer efficiency with HAT reagents C and B as compared to A (entries 5 and 6). The highly electron-withdrawing perfluoroarene on A likely leads to acceleration of both single-electron reduction by the photocatalyst and fragmentation to the amidyl radical. While 2 equiv of C–H partner delivers optimal yields, using 1.5 or 1 equiv of C–H partner instead still yields **1b** in 67% and 58% yield, respectively (entries 7 and 8). Additionally, using 1 equiv of **1a** with a slight excess of HAT reagent A leads to formation of acetamide **1b** in 68% yield (entry 9). Repeating the reaction at higher concentrations (0.8 M) gives the desired product in a slightly lower yield, likely due to the sparing solubility of the photocatalyst in acetonitrile (entry 10). Gratifyingly, setting up the reaction on the benchtop under ambient atmosphere delivers product **1b** in 82% yield (entry 11), demonstrating the unique redox stability of CF₃-4-CzIPN against traditional air-mediated photocatalyst deactivation pathways.⁴⁰ To highlight the practical utility of the conditions, the transformation was also conducted on a 7.15 mmol scale using an R-Series Vapourtec photoflow reactor setup, which afforded the desired product in 72% yield (entry 12; see SI for details on experimental setup). Finally, control experiments revealed that all components of the reaction are necessary to generate the product (entry 13). Additional details of further optimization experiments, including those for reactions with other nucleophiles and Ritter-type amidation of primary benzylic C–H substrates, are provided in the SI. These conditions represent an exceptionally mild method for performing Ritter-type amidation on benzylic C–H bonds relative to classical methods, which previously have relied on strong stoichiometric oxidants, high temperatures, and extended reaction times.

With the optimized conditions in hand, we next turned our attention to the generality of the method. In an effort to systematically select a diverse collection of C–H substrates, we applied a data-science-driven approach previously published by our group.⁴¹ First, we searched the Reaxys database for compounds containing a secondary benzylic C–H site, which provided >3,000,000 compounds. This library was subsequently filtered based on molecular weight, commercial availability, available spectral data, and functional group compatibility (see SI for full details). Filtering in this manner provided a dataset of ~2500 substrates. To visualize this dataset, we next pursued molecular featurization using DFT to extract global (such as dipole, highest occupied molecular orbital energy, and electronegativity) and atomic features (such as buried volume and NMR shift) of the substrates. This was performed using Auto-QChem, a tool previously built by our group which automates the generation and storage of

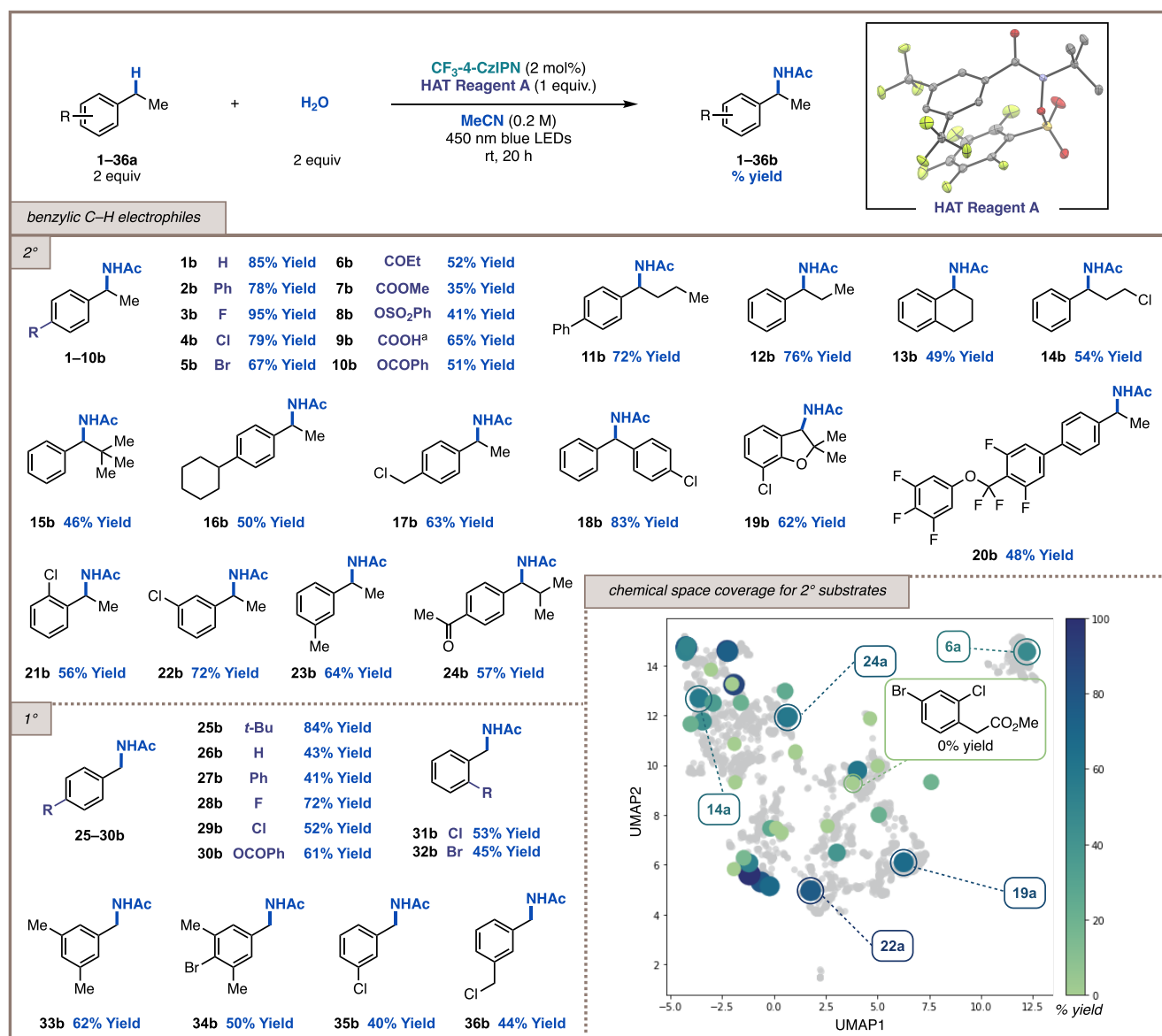


Figure 3. Substrate scope of benzylic C–H partners for photocatalytic Ritter amidation (0.3 mmol scale, isolated yields). For chemical space coverage, reactions were run on a 0.1 mmol scale, and yields were determined by ¹H NMR spectroscopy with 1,3,5-trimethoxybenzene as an external standard. ^aReaction performed on a 0.1 mmol scale with 1,3,5-trimethoxybenzene added as an external standard (¹H NMR yield is reported).

chemical descriptors for organic molecules in a web-accessible database.^{42,43}

With the molecular featurization completed, we used Uniform Manifold Approximation and Projection (UMAP) to reduce the featurization to two dimensions for chemical space visualization.⁴⁴ To cover the chemical space, we selected 45 molecules to evaluate under the optimized C(sp³)–H amidation conditions. The Ritter amidation yields, as determined by ¹H NMR of the crude reaction mixture and their distribution over the substrate chemical space, are illustrated in Figure 3. Given the observed distribution of yields, we note that the method is relatively high yielding with a variety of compounds, particularly substrates in the upper left, right, and lower boundaries of the map (Figure 3). Further reaction development will likely be required to identify conditions that enable C–H functionalization of substrates in the middle of the map, which performed poorly. Many of

these substrates possess benzylic C–H bonds adjacent to a carbonyl derivative, making them less likely to engage in HAT with the electrophilic amidyl radical based on a polarity mismatch. Additionally, these substrates tend to contain nitro groups *para* to the benzylic C–H bond, which presumably leads to strong deactivation toward HAT. The structures and associated ¹H NMR yields for all examples shown in Figure 3 can be found in the SI.

The substrates that delivered ¹H NMR yields >30% were subjected to the Ritter conditions on a 0.3 mmol scale to obtain isolated yields, as shown in Figure 3. We were pleased to find that ethylbenzenes bearing a range of electronically diverse substituents were tolerated in the reaction, affording good to high yields of benzylic acetamide products (1b–10b). Potentially reactive functional groups such as esters (7b), carboxylic acids (9b), phenol derivatives (8b, 10b), benzylic halides (17b), and aryl halides (3b–5b, 19b–22b) were all

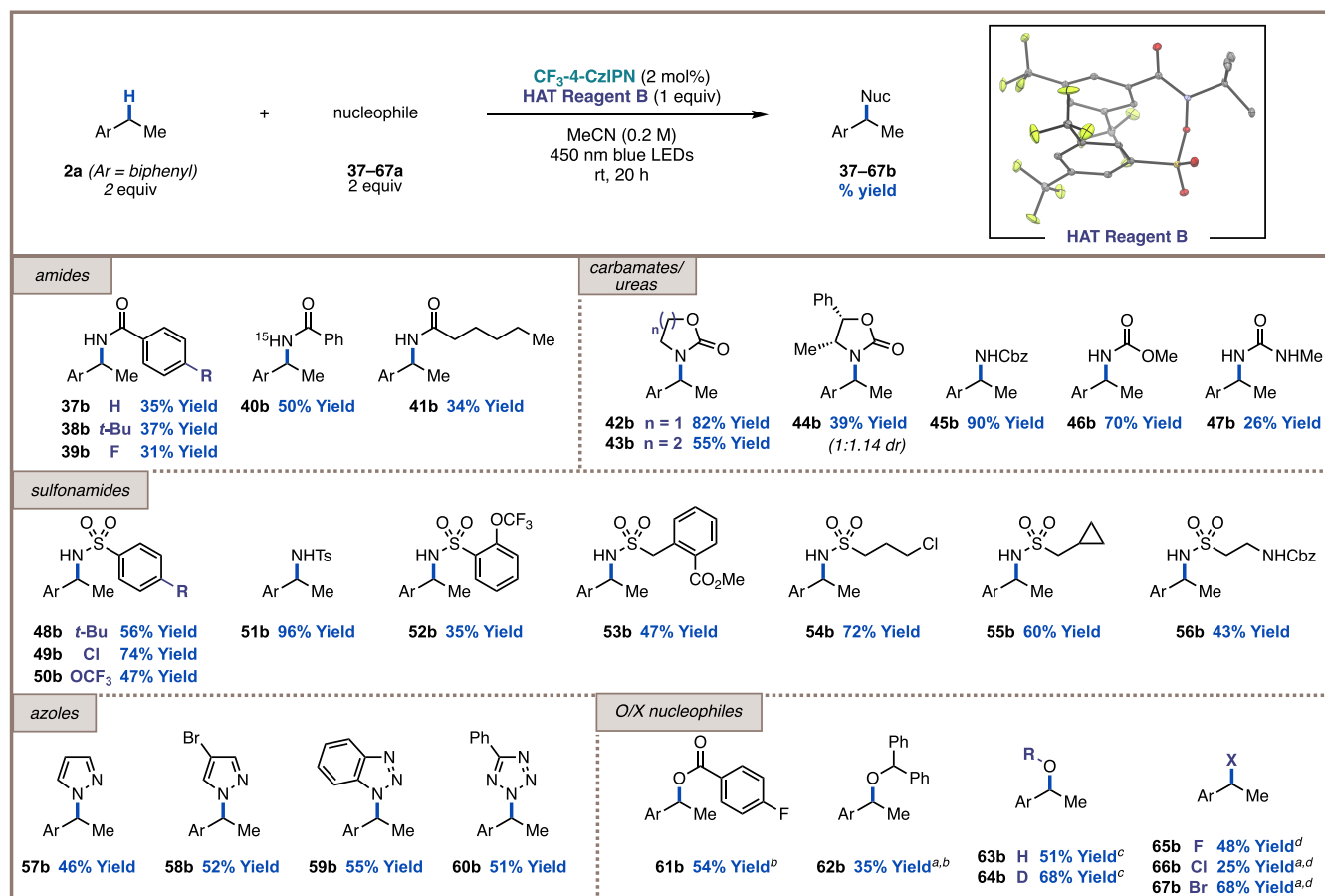


Figure 4. Substrate scope of nucleophiles for photocatalytic C(sp³)–H functionalizations (0.3 mmol scale, isolated yields). ^aReactions performed on a 0.1 mmol scale with 1,3,5-trimethoxybenzene added as an external standard (¹H NMR yield is reported, average of 2 runs) ^bReactions performed with 1.5 equiv of 2,4,6-tri-*tert*-butylpyridine. ^cReactions performed with 2 mol% of *t*-Bu-4-CzIPN as photocatalyst, 28 equiv of nucleophile, and 1 equiv of K₃PO₄. ^dReactions performed with 6 equiv of nucleophile (65b: NEt₃·3HF; 66b: TBACl; 67b: TBABr).

tolerated in the reaction. Various cyclic and acyclic *n*-alkyl benzenes (11b–15b) underwent selective amidation at the benzylic site. For substrates that contained multiple benzylic C–H bonds (16b–18b, 23b), we observed exclusive regioselectivity for functionalization at the secondary benzylic C–H site. Of note, despite two secondary benzylic C–H sites in substrate 17a, we observe complete selectivity for abstraction of the more hydridic C–H bond. Finally, substrates with greater structural complexity (19b, 20b) were suitable coupling partners. Moreover, additive screening experiments developed by Glorius and co-workers demonstrated a number of additional functional groups were tolerant to the standard reaction conditions beyond those shown in Figure 3 (see SI for details).⁴⁵ These additional functionalities include nitriles, internal alkynes, aliphatic alcohols and ethers, aliphatic protected amines, and amine HCl salts, as well as boronic acids and Bpin esters. Notably, additional optimization will be necessary to make this method tolerant of heterocyclic C–H substrates, which were observed in the additive screening to be incompatible (see SI for a full list of functional groups).

The abundance and affordability of toluenes led us to examine their use as substrates for photocatalytic amidation. We found that a variety of *para*-substituted toluene derivatives, 25a–30a, underwent reaction in 41–84% yield when the photocatalyst loading was increased to 5 mol%. Additionally, *meta*- and *ortho*-substituted toluenes 31a–36a were successful

in the reaction. Noteworthy among these examples, benzylic halide 36a gives the corresponding acetamide product with exclusive selectivity for the primary C–H position while leaving the benzylic chloride and 2° C–H bonds intact. Moreover, no difunctionalization is observed for both primary and secondary C–H substrates, a testament to the mildness of the reaction conditions and selectivity via polarity matching with the amidyl radical HAT reagent. Overall, these results represent a relatively rare example of Ritter C(sp³)–H amidation that operates on primary benzylic substrates, serving as a complement to alternative protocols that operate on tertiary and secondary substrates exclusively.

We next sought to evaluate whether this strategy could serve as a more general blueprint for C(sp³)–H amination with amides, carbamates, ureas, sulfonamides, and azoles, all of which are important motifs in pharmaceutically relevant bioactive compounds. Indeed, replacing water with 2 equiv of an *N*-nucleophile under the optimized Ritter conditions and switching to HAT reagent B afforded C(sp³)–H (sulfonyl)-amidation with both aliphatic and aromatic primary amides (Figure 4, 37b–41b) and sulfonamides (48b–56b) in 31–96% yield. Of particular importance, installing aliphatic amides and sulfonamides proceeds efficiently, with yields up to 72%. Functionalization with [¹⁵N]-benzamide afforded product 40b in 50% yield, providing a simple route for the generation of ¹⁵N-labeled compounds in two steps starting from inexpensive

and commercially available [^{15}N]- NH_4Cl . Cyclic and acyclic carbamates were readily coupled (**42b**–**46b**), offering a potentially valuable avenue to introduce protected amine functionality in a synthetic sequence. Using a chiral oxazolidinone as a nucleophile delivered product **44b** in 39% yield as a 1:1.14 diastereomeric ratio at the newly formed stereocenter. Additionally, we found that C–N bond construction was possible from a variety of electron-rich nitrogen heterocycles. Couplings with pyrazole (**57b**, **58b**, 46–52% yield), triazole (**59b**, 55% yield), and tetrazole (**60b**, 51% yield) motifs all resulted in good yields of the desired product.

Although not the main focus of our study, these conditions also translated to the incorporation of alternative nucleophiles such as halides (**65b**–**67b**), including bromination and fluorination in 68% and 48% yield, respectively. Additionally, ureas (**47b**), carboxylic acids (**61b**), alcohols (**62b**), and water (**63b**, **64b**) are all compatible nucleophiles, highlighting the generality of this platform for $\text{C}(\text{sp}^3)\text{--H}$ functionalization beyond simply Ritter-type amidation. By selecting various combinations of C–H partners and exogenous nucleophiles from Figures 3 and 4, more complex reaction products can also be assembled in one step from commercially available starting materials (as shown in Figure 5, **68b**–**71b**). This approach is

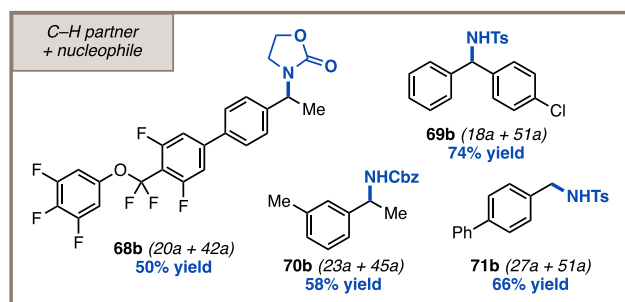


Figure 5. Substrate scope of additional products constructed from various C–H partners and nucleophiles (0.3 mmol scale, isolated yields). For full details on the experimental setup, see the Supporting Information.

potentially attractive from a medicinal chemistry perspective, where a single set of reaction conditions can rapidly generate a diverse library of C–H functionalized products.

The breadth of compatible nucleophiles for this transformation, along with the effectiveness of the new trifluoromethylated photocatalyst, prompted us to interrogate the mechanistic features of this reaction. Our initial hypothesis was that an amidyl radical was being generated *in situ* from HAT reagent **A** via an oxidative photocatalytic quenching cycle, similar to the mechanism proposed in our prior work on HAT-ORPC fluorination.²⁴ In this cycle, excited-state $\text{CF}_3\text{--4--CzIPN}$ performs a single-electron reduction of the HAT reagent, inducing mesolytic cleavage. From there, the oxidized photocatalyst would be responsible for oxidizing the benzylic radical formed after HAT, completing the ORPC.

Based on this mechanistic rationale, we first sought to confirm the generation of *N-tert*-butyl radicals in the reaction. Indeed, *N-tert*-butylamide **72** was isolated from a typical reaction mixture in a high yield (Figure 6A). Furthermore, when the benzylic $\text{C}(\text{sp}^3)\text{--H}$ partner and nucleophile were replaced by 1,1-diphenylethylene, the enamide **73** was obtained, arising from addition of the nitrogen-centered radical into the alkene, followed by oxidation and base-mediated

elimination (Figure 6B). With evidence that HAT reagent **A** affords an amidyl radical under the reaction conditions, we next sought to probe the mechanism by which the amidyl radical is generated. First, we carried out a series of Stern–Volmer luminescence quenching experiments (Figure 6C).

To our surprise, HAT reagent **A** does not quench the luminescence of $\text{CF}_3\text{--4--CzIPN}$, indicating that the reaction is unlikely to proceed via oxidative quenching with this photocatalyst. Additional experiments revealed that none of the reaction components quenched the excited-state $\text{CF}_3\text{--4--CzIPN}$ photocatalyst (see SI), including ethylbenzene, ruling out direct oxidation of the $\text{C}(\text{sp}^3)\text{--H}$ substrate. UV–vis spectroscopy experiments demonstrated that an electron-donor–acceptor (EDA) complex between HAT reagent **A** and $\text{CF}_3\text{--4--CzIPN}$ is also unlikely to facilitate single-electron redox chemistry (see SI). However, Stern–Volmer experiments do indicate that **A** efficiently quenches the excited state of $\text{Ir}(p\text{-F-ppy})_3$ (Figure 6C). This suggests divergent mechanisms, indicative that product formation with more reducing photocatalysts such as $\text{Ir}(p\text{-F-ppy})_3$ is occurring via an oxidative quenching pathway, while the more oxidizing $\text{CF}_3\text{--4--CzIPN}$ is not sufficiently reducing in the excited state to enable HAT reagent activation in this way.

From these data, we considered alternative potential mechanisms. The quantum yield of this transformation was measured to be 0.002, indicating that a radical chain process is unlikely or inefficient, and that the reaction is most likely unimolecular with respect to the photocatalyst.⁴⁶ Instead, we questioned whether a reductive quenching cycle could be operative, wherein the radical anion of $\text{CF}_3\text{--4--CzIPN}$ is responsible for single-electron reduction of the HAT reagent. Cyclic voltammograms revealed that the reduction potential of HAT reagent **A** is -1.36 V vs SCE, making reduction of **A** by the $\text{CF}_3\text{--4--CzIPN}$ radical anion thermodynamically uphill by $\sim 9\text{ kcal/mol}$. Nonetheless, given the slightly elevated reaction temperature in the photoreactors and subsequent irreversible exergonic steps following single-electron reduction, this step could be feasible. To determine whether this elementary step was operable, we carried out voltammetry on solutions containing $\text{CF}_3\text{--4--CzIPN}$ and HAT reagent **A** (Figure 6D). While voltammograms of the photocatalyst alone were reversible, when both species were present an increased current response and lack of reversibility for the PC/PC $^{\bullet-}$ couple were observed.⁴⁷ These results suggest that reduction of HAT reagent **A** likely occurs via an SET mechanism mediated by the radical anion of $\text{CF}_3\text{--4--CzIPN}$, consistent with our earlier results from Stern–Volmer luminescence quenching experiments.

To gain more insight into this mechanistic possibility, various spectroscopic studies and control experiments were performed. First, upon irradiation of a solution of $\text{CF}_3\text{--4--CzIPN}$ and DIPEA with blue LEDs, a color change from light yellow to dark yellow/orange was observed. UV–vis spectroscopy demonstrated a blue-shift of the maximum absorption peak (Figure 6F, left). Upon irradiation of these two species, normalized emission spectra revealed a hypsochromic shift (from 486 to 428 nm), indicating the formation of a new species, analogous to previously published results for other cyanoarene-based photocatalysts (Figure 6F, right).^{48,49} To verify that this new species is indeed the radical anion $\text{CF}_3\text{--4--CzIPN}^{\bullet-}$, electron paramagnetic resonance (EPR) spectroscopy was performed (Figure 6E). The experimental and simulated EPR spectra for $\text{CF}_3\text{--4--CzIPN}^{\bullet-}$ are in agreement,

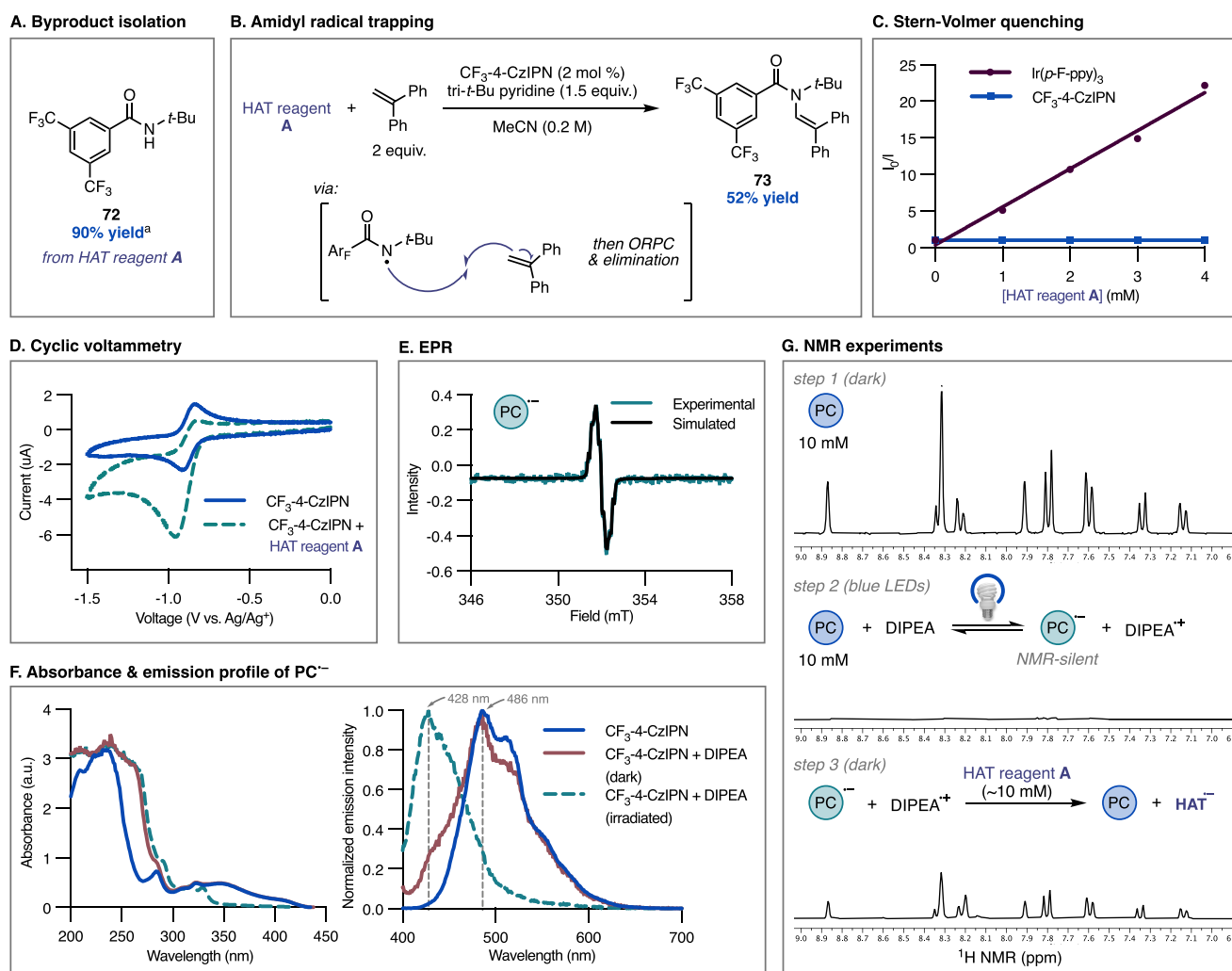


Figure 6. Mechanistic experiments supporting the proposed mechanism. (A) Isolation of HAT reagent A byproduct under the standard reaction conditions shown in Figure 3. (B) Amidyl radical trapping experiment with HAT reagent A. (C) Stern–Volmer luminescence quenching experiments (excitation at 395 nm). (D) Cyclic voltammograms of CF₃-4-CzIPN with and without added HAT reagent A. (E) Experimental and simulated EPR spectra supporting the presence of CF₃-4-CzIPN^{•-}. (F) Absorbance and emission profiles for CF₃-4-CzIPN and CF₃-4-CzIPN^{•-} (1.0 mM, 1.0 cm path length, and excitation at 390 nm). (G) NMR spectroscopic evidence supporting the proposed reductive quenching cycle.

lending support for the formation of this reduced photocatalytic intermediate.

To obtain direct evidence of the ability of PC^{•-} to reduce HAT reagent A, we turned to ¹H NMR experimentation. The characteristic NMR signals of CF₃-4-CzIPN were detected from a mixture of the photocatalyst and DIPEA in CD₃CN in a J. Young NMR tube (Figure 6G, step 1). Upon direct exposure of the solution within the NMR tube to 450 nm blue LEDs for 5 min (Figure 6G, step 2), we observed line broadening and significant signal reduction, most likely due to the generation of a paramagnetic CF₃-4-CzIPN^{•-} species, which has a strong influence on NMR resonance relaxation rates due to the presence of an unpaired electron. Under nitrogen, this species was stable for at least 2 h and could be quenched by exposure of the NMR tube to air to convert the photocatalyst back to the ground state. Upon addition of HAT reagent A to the radical anion species in the absence of light, a similar quenching effect was observed. We observed NMR signals consistent with reformation of the ground-state CF₃-4-CzIPN

photocatalyst (Figure 6G, step 3). Additionally, when HAT reagent A is added to an EPR sample of CF₃-4-CzIPN^{•-}, a loss of signal is observed, indicative that the paramagnetic radical anionic species no longer exists (see SI). This is consistent with a proposal that the radical anion CF₃-4-CzIPN^{•-} reduces the HAT reagent, prompting fragmentation to its reactive amidyl radical species, which then subsequently engages in HAT.

While the NMR experiments described suggest that the ground-state PC^{•-} is reducing the HAT reagent, under the standard reaction conditions, which include constant irradiation with blue LEDs, we cannot necessarily rule out a consecutive photoinduced electron transfer (ConPET) process wherein the photocatalyst radical anion is excited by a second photon to generate the excited-state radical anion ^{*}CF₃-4-CzIPN^{•-}.^{49–52}

Taken together, these results are consistent with the proposed catalytic cycle in Figure 7. The reaction is initiated by an off-cycle reductive quenching of ^{*}CF₃-4-CzIPN to

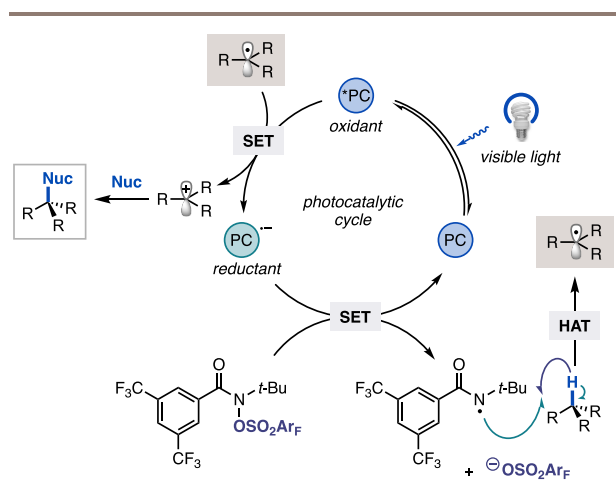


Figure 7. Proposed mechanism for HAT-ORPC amination through a reductive photocatalytic quenching cycle.

generate its ground-state radical anion, which subsequently reduces the HAT reagent, followed by mesolytic fragmentation to generate the active amidyl radical species. Alternatively, under the standard reaction conditions, we observe minimal (~2%) formation of a HAT reagent byproduct, indicative of homolytic N–O bond cleavage (see SI for details of experiments characterizing this byproduct), which could also initiate the catalytic cycle upon HAT of the C–H substrate. Experiments are currently ongoing to distinguish between these two possibilities. In subsequent turns of the catalytic cycle, the excited-state photocatalyst oxidizes the benzylic radical intermediate, turning over the cycle to PC^{•+} and furnishing a carbocation. Finally, this carbocation is trapped by a nucleophile to afford the desired product.

CONCLUSION

We have developed a mild, photocatalytic method for site-selective C(sp³)–H (sulfonyl)amidation, azolation, hydroxylation, esterification, etherification, and halogenation. The method employs readily available, low-cost nucleophiles as coupling partners, an amidyl radical HAT reagent, and a novel organic photocatalyst for HAT-ORPC. Mapping of the secondary benzylic C(sp³)–H substrate chemical space demonstrates the broad scope of the method. Moreover, we show that this HAT-ORPC platform is capable of functionalizing primary benzylic C(sp³)–H substrates, offering complementary reactivity compared to previous C(sp³)–H amination methods. Mechanistic studies including stoichiometric reactions, Stern–Volmer luminescence experiments, and paramagnetic NMR and EPR studies are consistent with amidyl radical-mediated HAT and suggest that reductive quenching of the CF₃-4-CzIPN photocatalyst is operative. These studies highlight the synthetic opportunities that can accompany further reagent and photocatalyst design in the field.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/jacs.3c04912>.

Experimental procedures, experimental data, C–H substrate chemical space construction, characterization, and spectral data (PDF)

List of SMILES for chemical space (TXT)

Accession Codes

CCDC 2258612–2258614 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

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ABBREVIATIONS

NFSI, *N*-fluorobenzenesulfonimide; DDQ, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone

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