

Two Reactivities for the Price of One Cycle: Sulfonamides as Dual Photoinduced Electron Transfer/Hydrogen Atom Transfer Catalysts

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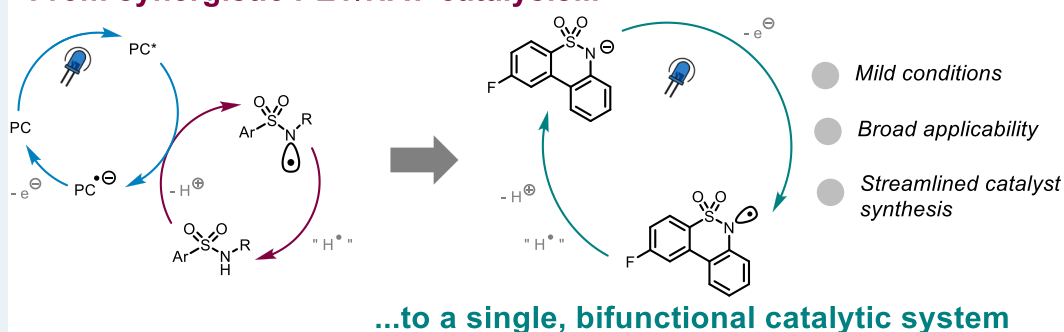


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ABSTRACT: Cyclic biaryl sulfonamides (BASNs) have emerged as a versatile and synthetically accessible class of reductive organo-photocatalysts for photoinduced electron transfer (PET) reactions. Following PET engagement of a reductively labile substrate, BASN^{•−} transforms into a nitrogen-centered radical. Leveraging this intermediate to activate C–H bonds of a second substrate via hydrogen atom transfer (HAT) would culminate in two reactivities for the price of one catalytic cycle. The bifunctional PET-HAT ability of BASN was demonstrated through the reductive activation of *gem*-difluoroalkenes and electron-deficient arenes together with selective HAT activation of α -heteroatom and allylic C(sp³)-H under visible-light irradiation. Radical ions/radicals generated from the PET- and HAT-activated substrates converge to form a single product, resulting in a high atom economy.

KEYWORDS: bifunctional catalysis, electron transfer, hydrogen atom transfer, sulfonamide, photocatalysis, fluoroalkenes

INTRODUCTION

In the last two decades, photocatalysis established itself as a versatile and sustainable tool to unlock open-shell transformation pathways, allowing the use of mild conditions involving photons as a source of energy.¹ However, the vast majority of commodity chemicals do not absorb visible light. Therefore, the development of suitable photocatalysts (PCs) capable of mediating photon absorption and transferring the resulting energy to the substrate to generate the desired open-shell reactive intermediates has become a central research focus for organic chemists.² The majority of these transformations proceed *via* single-electron transfer (SET) or hydrogen atom transfer (HAT) mechanisms.³ The latter can occur either through a direct mechanism (*d*-HAT), in which the excited PC itself serves as the HAT agent, or an indirect one (*i*-HAT), arising from photoinduced electron transfer (PET) activation of an exogenous HAT agent precursor to generate a (ground state) HAT agent *in situ*. Notable examples of *d*-HAT PCs include TBADT, benzophenone and Eosin Y.⁴ While many of these typically require higher energy UV light to access excited states resembling oxygen-centered radicals, recent developments have enabled

the use of lower energy visible light and accessed excited states resembling heteroatom-centered radicals, such as sulfur and nitrogen.⁵ On the other hand, notable examples of exogenous (ground state) HAT agent precursors for *i*-HAT include thiols, quinuclidine, and pyridine *N*-oxides.⁶

Recently, sulfonamides have gained attention as attractive scaffolds for realizing *i*-HAT transformations because they are inexpensive, readily available, tunable, and exhibit relatively high N–H bond dissociation free energies (BDFEs) (95–105 kcal·mol^{−1}).⁷ The active sulfonamidyl radical is typically generated from an exogenous (often deprotonated) sulfonamide additive by PET to, e.g., Ir(III)-based complexes, or to 4CzIPN (Scheme 1A).^{7,8} In this context, we envisaged that an (organo)photocatalytic manifold

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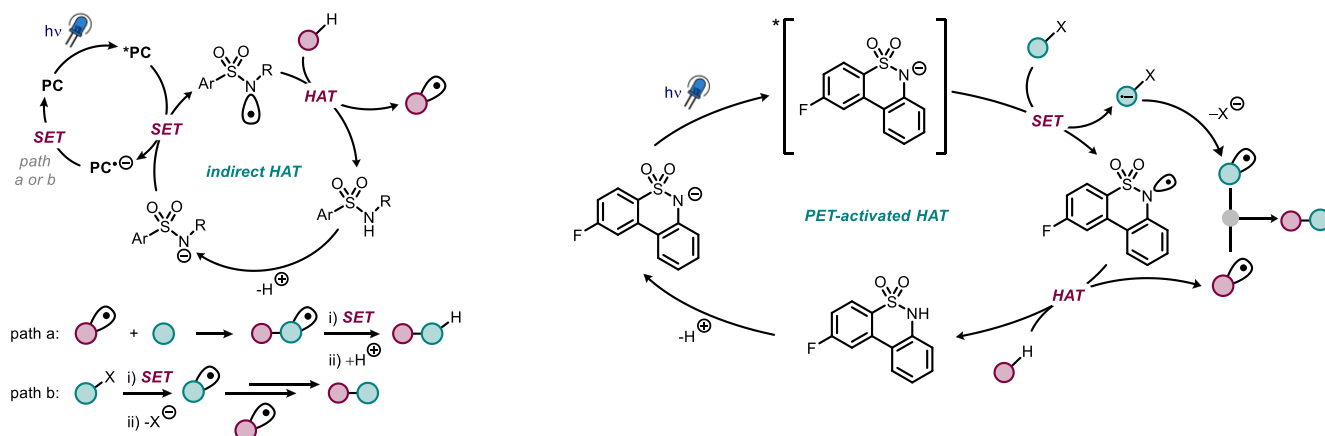
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Scheme 1. Previous Synergistic Cycles Involving Exogenous Sulfonamides and Photocatalysts (A) and the Present Work Involving a Single Unit Performing Both Roles (B)

A. State-of-the-art: sulfonamides as exogenous HAT agents precursors

B. This work: sulfonamides as bifunctional photoreductive and endogenous HAT catalysts



utilizing a deprotonated sulfonamide directly in PET—that subsequently produces an N-centered radical (NCR) for HAT—would eliminate the need for separate PET catalysts and (exogenous) HAT reagents, consolidating both reactivities within one catalytic entity. While HAT strategies thus far have been classified within the binary “boxes” of *d*-HAT or *i*-HAT—with the latter always invoking an exogenous HAT agent precursor as a *PC quencher in its mechanistic depiction³—the conceptual novelty of the envisioned strategy would lie somewhere outside said “boxes”. We therefore introduce the term “PET-activated HAT” to define this behavior because although the HAT agent is the PC itself, the active species is not formed directly upon light absorption but by a PET step with another substrate. The HAT step would then “close” the catalytic cycle and allow the turnover of the PC.⁹ In terms of synthetic utility, the bifunctional¹⁰ PET-activated HAT concept would (i) obviate the risks of any side products from exogenous HAT agent/precursor decomposition, (ii) simplify reaction design by decreasing overall catalyst loading (typically ~20% in *i*-HAT approaches with exogenous sulfonamides)^{7,8} and the associated chemical waste, and (iii) use a cheap, safe, readily accessible organophotocatalyst that is known to be recoverable in high yields after reductive PET reactions (vs IPN-type catalysts that liberate cyanide).¹¹

Last year, our group contributed to the field of photocatalyst design through the development of a novel class of organic photocatalysts, namely cyclic biaryl sulfonamides (BASNs).¹¹ These compounds are readily accessible in high yields on gram quantities from inexpensive starting materials (i.e., sulfonyl chlorides and iodoanilines) *via* a concise two-step/one-pot synthetic route. The second step was a photoredox autocatalyzed reaction where the BASN product serves as the photocatalyst for its own synthesis.¹² Since PET to the aryl iodide from *BASN^{•-} generates an NCR intermediate (BASN[•]) that is endogenous to the catalytic cycle, we questioned whether this could be used in PET-activated HAT, given the aforementioned precedence of exogenous sulfonamidyl radicals as *i*-HAT agents. Taking together the rather deep reductive redox power of *BASN^{•-} ($E_{\text{red}}^{\text{BASN}^{\bullet}/\text{*BASN}^{\bullet-}} \geq -2.47$ vs SCE),¹¹ its generality in PET reductions of various substrates, and the high BDFE values of sulfonamide N–H bonds,⁷ we anticipated that

a general applicability in PET/HAT reactions might ensue through this bifunctional catalytic manifold (Scheme 1B).

Herein, we report the realization of this bifunctional photocatalyst design, establishing BASNs as a distinct class of organophotocatalysts capable of engaging a mechanistically novel sequential PET-activated HAT process. With reactions realized in short times under exceedingly mild conditions, with an inexpensive and readily accessible/tunable sulfonamide organophotocatalyst, PET-activated HAT provides a sustainable platform for the construction of C–C bonds.

RESULTS AND DISCUSSION

We commenced our investigation by selecting a pair of PET-activated and HAT-activated substrate partners to realize the PET-activated HAT concept. Readily accessible *gem*-difluoroalkenes¹³ were chosen as electron-deficient substrates capable of undergoing rapid reductive PET activation ($E_{\text{red}}^{\text{P}} = -1.1$ V vs SCE for diaryl-substituted **1a**) from *BASN^{•-}, while trialkylamines were selected as HAT partners considering the polarity matching of their relatively hydridic $\alpha\text{-C}(\text{sp}^3)\text{-H}$ bonds to the electrophilic NCR (BASN[•]). We anticipated that cross-coupling of the radicals resulting from PET and HAT activation (Scheme 1B) would culminate in an atom-efficient access to monofluoroalkenes. Fluorinated organic compounds play a central role in pharmaceutical and agrochemical research¹⁴ and monofluoroalkenes in particular have emerged as valuable amide bioisosteres, as they closely reproduce both the geometry and electronic characteristics of the amide linkage while exhibiting resistance to enzymatic hydrolysis.¹⁵ Despite their considerable potential, the synthesis of monofluoroalkenes has long remained non-trivial, often requiring harsh thermal conditions (70–100 °C).¹⁶ In contrast, photocatalysis has profoundly enriched the synthetic chemistry toolbox to access monofluoroalkenes through radical pathways both *via* HAT¹⁷ and *via* other radical precursors.¹⁸

Initially, we examined the reaction between *gem*-difluorodiphenylethene **1a** and *N,N*-dimethylethanolamine **2a** (DMEA). After screening different reaction conditions, we found that the reaction proceeded in 75% yield using the F-BASN catalyst (5 mol %), in the presence of K₃PO₄ (1 equiv), using a slight excess of amine **2a** (1.2 equiv), and irradiating with 7 W blue LEDs for

3 h (Table 1, entry 1). Product 3 was obtained as a single regioisomer, with C–C formation occurring at the less hindered N-CH₃ group.^{17a,b,d,f} Replacing F-BASN with Me-BASN gave a considerably lower yield of only 18% (Table 1, entry 2). Interestingly, since the excited state redox potentials of *F-BASN ($E(\text{F-BASN}^+/\text{F-BASN}^-) = -2.31$ V vs SCE) and *Me-BASN (-2.45 V vs SCE) only differ by ~ 0.15 V, with both rendering a highly exergonic PET reduction of 1a (with the reduction by *Me-BASN having the higher driving force), this difference in efficiency could speak instead to electronic influences on reactivity of the BASN⁺ intermediate in the HAT step. Presumably, the inductively withdrawing F atom renders the NCR more electrophilic and hence more reactive with 2a. The ability to dramatically influence the reactivity of the NCR by altering substituents on the aromatic rings of the catalyst is an attractive salient feature of our BASN photocatalyst architecture.

Omitting K₃PO₄ led to a decreased yield (54%). This decrease in yield can be attributed to the accumulation of protons (overall formation of HF), a byproduct of the reaction, which can protonate the amine and lower its nucleophilicity. High reactivity without 1.0 equiv of K₃PO₄ could be recovered by increasing the amine loading to 2.2 equiv (Table 1, entries 3–5). Control experiments without a photocatalyst or in the dark resulted in no detectable product formation, confirming the photomediated nature of the reaction (Table 1, entry 6).

With the optimized conditions (Table 1, entry 1) in hand, the reaction scope was investigated (Scheme 2). The reaction proceeded smoothly and in good yields with a range of *N,N*-dimethylamines. In addition to free hydroxyl groups (3 and 4), an ester functionality (5) was well tolerated, and the presence of longer linear alkyl chains (6) or bulkier substituents (7–9) did not compromise the yields. Cyclic *N*-methyl trialkylamines reacted selectively on the less hindered *N*-methyl group (10–12). A dialkylaniline with a less hydridic α C–H bond likewise proved successful (13), as well as trialkylamines lacking a *N*-methyl substituent such as triethylamine (14).

To further assess the applicability of the method to more complex molecules, we examined tropine. The tropane alkaloid core

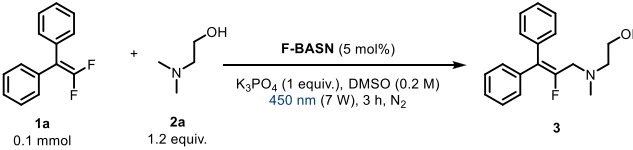
structure is present in pharmaceutically active molecules such as (–)-hyoscyamine and (–)-scopolamine, reflecting its importance and attractiveness as a target for late-stage functionalization.¹⁹ Gladly, tropine was monofluoroalkenylated to afford the desired product in 80% yield (15). The scope of *gem*-difluoroalkenes was subsequently examined using tropine as the HAT partner, resulting in moderate to excellent yields (50–84%). Both homo-substituted (16–18) and hetero-substituted *gem*-difluoroalkenes derived from diaryl ketones were successfully employed (19), with formation of both diastereoisomers in the latter case (d.r. 65:35). Yields were generally lower (44–65%) with aldehyde-derived *gem*-difluoroalkenes, and in all cases, a 1:1 diastereomeric ratio was observed (20–22). On the other hand, *gem*-difluoroalkenes derived from alkyl–aryl ketones (23–25) gave yields similar to those observed with the aryl–aryl ketone-derived substrates (52–85%), with the formation of diastereomers observed in all cases.

Finally, several bioactive molecules bearing an *N*-methyl group were successfully monofluoroalkenylated (26–30). In these cases, K₃PO₄ was deliberately added as base, to substitute for using an excess of valuable drug molecule. In all cases, complete selectivity toward the *N*-methyl amino group was observed, with no functionalization of *N*-CH₂R or *N*-CHRR' positions. This selectivity highlights the utility of our platform in rapidly derivatizing *N*-methyl alkylamines to modulate their pharmacological properties.²⁰

After establishing *gem*-difluoroalkenes and amines as competent substrates, we examined the generality of our approach in activating other PET acceptors and HAT compatible C(sp³)–H substrates. Therefore, we evaluated the PET-activated HAT platform in the arylation of HAT-compatible ethers and allylic hydrocarbons using phthalonitriles as the PET acceptors.^{8a} Following optimization of reaction conditions (see Tables S4–S8 in the Supporting Information), F-BASN·K⁺ was found to be a suitable input catalyst. Subsequent evaluation of the substrate scope revealed that ethers reacted successfully to afford products, with a high 62% yield in the case of chromane (34), while products from phthalane (35) and benzyl methyl ether (36) were formed in lower yields (39% and 29%, respectively) (Scheme 3). On the other hand, allylic hydrocarbons (five- to seven-membered rings) reacted in good to high (60–73%) yields across the board, both with terephthalonitrile (37–39) and phthalonitrile (40–42) as PET acceptors. Encouraged by these results, we sought to expand the applicability of this methodology to the coupling of an unactivated cyclic ether with *gem*-difluoroalkenes, choosing tetrahydrofuran and 1a as representative substrates. Given the lower reactivity observed with tetrahydrofuran compared to trialkylamines, a brief optimization of the reaction conditions was performed (see Table S2 in the Supporting Information). Under the optimized conditions employing a 1:1 THF:DMSO solvent mixture, the desired product was obtained in 41% yield (43).

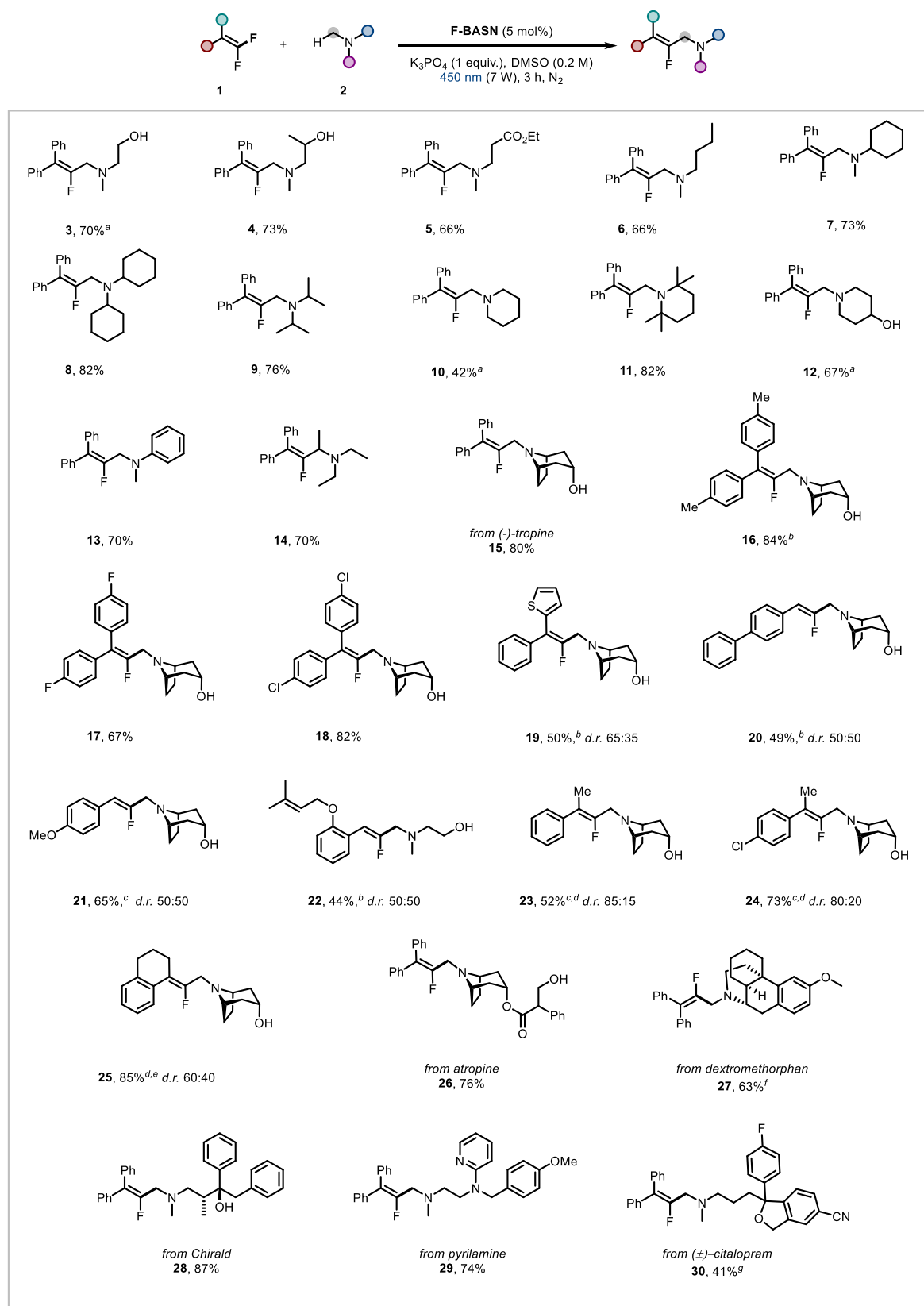
To shed light on the reaction mechanism, additional experiments and mechanistic studies were conducted. Stern–Volmer quenching experiments showed a strong quenching ($k_q = 3.8 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$) of the emission of *F-BASN⁺ by terephthalonitrile 31a (Scheme 4A) and a milder quenching ($k_q = 3.1 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$) by *gem*-difluoroalkene 1a (Figure S6 in the Supporting Information). Confirming that it was the emissive species being quenched, a decrease in the excited state lifetime of *F-BASN⁺ was observed in the presence of either 31a (by $\sim 40\%$) or 1a (by $\sim 10\%$) as quenchers (see Scheme 4B and Figure S8 in the Supporting Information). On the other hand,

Table 1. Optimization of the Reaction Conditions for the C(sp³)–H Monofluoroalkenylation of Amines^a

		
Entry	Conditions	Yield (%) ^a
1	No Deviation	72
2	Me-BASN instead of F-BASN	18
3	No K ₃ PO ₄	54
4	1.5 equiv. of amine, no K ₃ PO ₄	65
5	2.2 equiv. of amine, no K ₃ PO ₄	74
6	No light / No PC	0/0

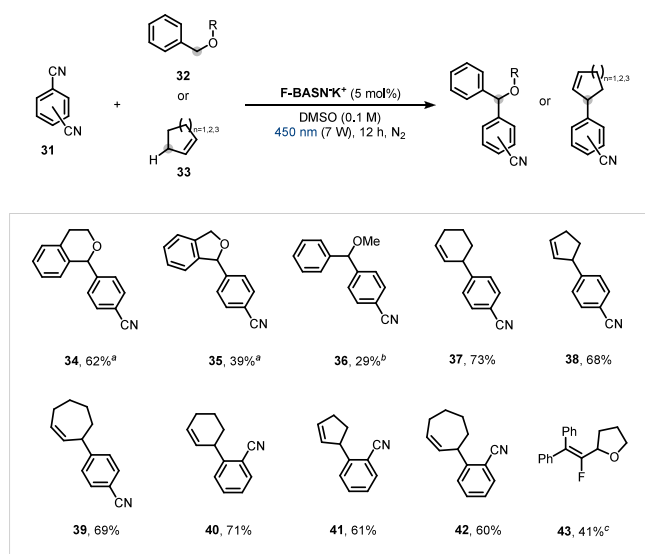
^aH-NMR yields are calculated by using dibromomethane as internal standard.

Scheme 2. Substrate Scope for the Synthesis of Monofluoroalkenes



Reaction conditions: *gem*-difluoroalkene 1 (0.1 mmol), trisubstituted amine 2 (1.2 equiv), K₃PO₄ (1 equiv), F-BASN catalyst (5 mol %), DMSO (0.2 M). Isolated yields are reported. ^aReaction time: 4 h. ^bReaction time: 5 h. ^cReaction time: 6 h. ^dF-BASN: 10 mol %. ^eReaction time: 12 h. ^fReaction time: 8 h. ^gReaction time: 2 h.

Scheme 3. Substrate Scope for Arylation of Allylic and Benzylic Position with Phthalonitriles



Reaction conditions: phthalonitrile **29** (0.1 mmol), ether **30** or allylic hydrocarbon **31** (7.5 equiv), F-BASN[•]K⁺ (5.0 mol %), and DMSO (0.1 M). Isolated yields are reported. ^a0.25 equiv of K₃PO₄. ^bReaction run for 48 h. ^cReaction run using *gem*-difluoroalkene **1a** (0.1 mmol), K₃PO₄ (1 equiv), F-BASN catalyst (10 mol %), and DMSO:THF = 1:1 (0.1 M) for 48 h.

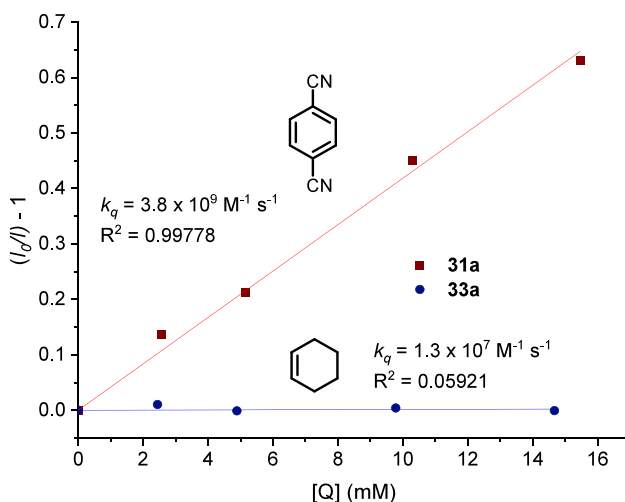
no quenching was detectable when employing cyclohexene (**33a**) and *N,N*-dimethylethanolamine **2a** as quenchers (see Figures S6–S8 in the Supporting Information).

We performed the reaction in the presence of radical inhibitors to probe if a radical mechanism was in operation. Addition of TEMPO (2 equiv) completely suppressed product formation, while addition of methyl acrylate (3 equiv) resulted in only trace amounts of the product. These results corroborate the intermediacy of radical species (Scheme 5). Measurement of the quantum yield for the reaction of terephthalonitrile **31a** with cyclohexene **33a** gave a value of $\Phi = 0.017\%$, indicating that the transformation is photocatalytic in nature and that a radical chain is either absent or extremely inefficient (see Section S8.3 in the Supporting Information for further details).²¹

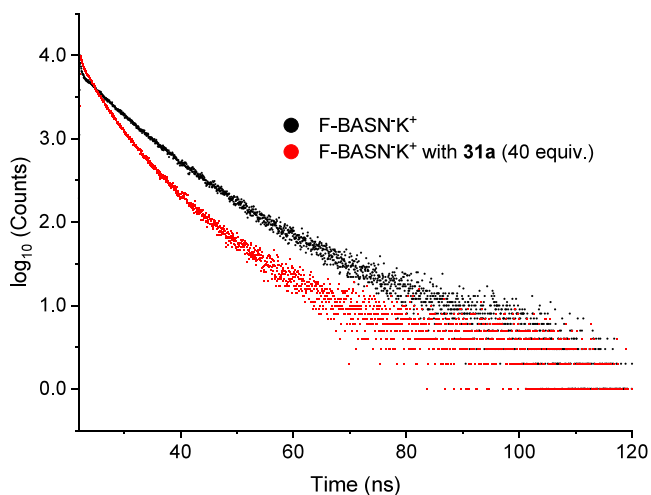
Given these results, together with the electrochemical potentials of the substrates obtained from cyclic voltammetry (see Section S8.4 in the Supporting Information), we propose the mechanism outlined in Scheme 6. In the case where a trialkylamine is present, F-BASN is first deprotonated by the amine to afford F-BASN[•], according to ¹H NMR titration studies from our previous report showing disappearance of the N–H signal.¹¹ In the absence of a trialkylamine substrate, F-BASN[•] is already present as the input catalyst in the form of its potassium salt. Upon photoexcitation, F-BASN[•] [E(F-BASN[•]/*F-BASN[•]) = −2.31 V vs SCE]¹¹ reduces *gem*-difluoroalkene **1** [E_p(**1a**/**1a**^{•−}) = −0.91 V vs SCE]^{17e} or the dicyanobenzene **31** [E_{1/2}(**31a**/**31a**^{•−}) = −1.52 V vs SCE] via a photoinduced electron transfer step. This PET step simultaneously generates the key sulfonamidyl radical intermediate F-BASN[•] for the HAT step. The N–H bond dissociation energies of sulfonamides (95–105 kcal/mol)^{8b} support the feasibility of HAT α to the heteroatom in amines (BDEs up to 93 kcal/mol),²² in tetrahydrofuran (BDE = 92 kcal/mol),²² as well as at C(sp³)-H bonds

Scheme 4. Emission (A) and Lifetime (B) Quenching Experiments

A. Stern-Volmer quenching



B. Lifetime decay

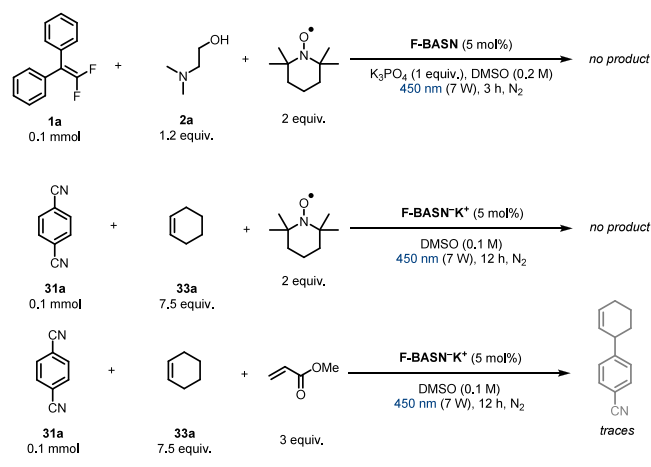


in allylic (BDEs up to 88 kcal/mol)²² and benzylic positions (BDEs up to 90 kcal/mol)²² of hydrocarbons. Following HAT, F-BASN is returned to its protonated form. Upon subsequent deprotonation, it can re-enter the catalytic cycle. Finally, the C–C bond-forming step may proceed through either (i) initial fragmentation of the radical anions **1**^{•−} and **31**^{•−} (loss of F[•] or CN[•], respectively) to generate reactive intermediates that then combine with the carbon-centered radicals generated from **2** and **32/33**^{17a,18a,b} or (ii) initial S_{RN}1 coupling of the radicals derived from **2** and **32/33** with the PET-generated corresponding radical anions from **1** or **31**, followed by elimination of F[•] or CN[•], respectively, to afford the products.^{17d}

CONCLUSIONS

In summary, while previous photocatalytic hydrogen atom transfer strategies fall into the binary definition of *d*-HAT and *i*-HAT, this work demonstrates the successful design and realization of a novel catalytic paradigm for hydrogen atom transfer in

Scheme 5. Inhibition Experiments



organophotoredox catalysis. This is accessed by PET from a deprotonated *N*-centered anionic photocatalyst to afford an *N*-centered radical. Owing to the strong *N*–H bond of their sulfonamide moiety, biarylsulfonamides represent an ideal “bifunctional” catalyst architecture for PET-activated HAT, where reactivity of the NCR can be tuned through facile modification of the aromatic ring substituents of this simple, inexpensive, and readily accessible organophotocatalyst. The “two-for-one” dual PET-activated HAT catalytic reactivity was exploited for the synthesis of monofluoroalkenes as well as the arylations of allylic hydrocarbons and ethers. These transformations proceed without the need of expensive noble metal-based photocatalysts or stoichiometric HAT agents, improving their practicality and sustainability. Mechanistic investigations support a radical pathway induced by reductive PET activation of the *gem*-difluoroolefin or dicyanobenzene substrates. Together with their previously demonstrated rapid (autophotocatalytic) library synthesis from cheap commercial materials and their high recovery compared to other organophotocatalyst families,¹¹

we envision that the disclosure of this dual PET-activated HAT reactivity furthers the establishment of BASNs as a “multipurpose” class of (organo)photocatalysts.

EXPERIMENTAL SECTION

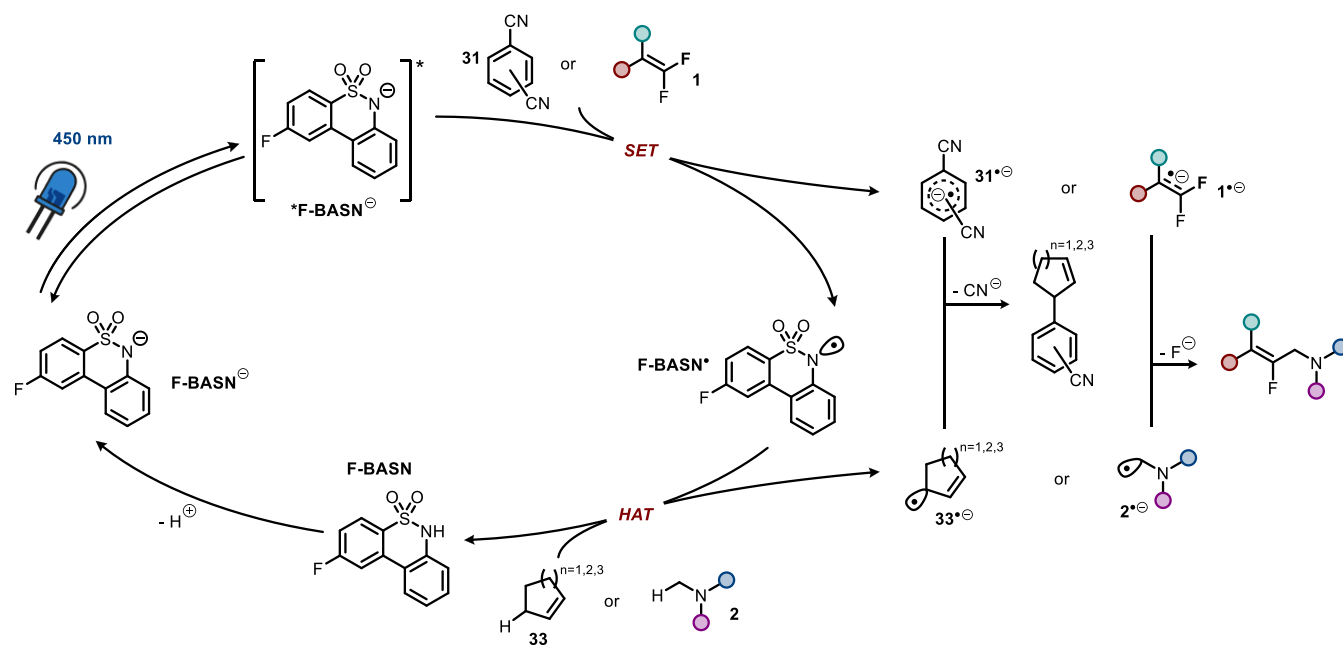
General Procedure for the Coupling of *gem*-Difluoroalkenes with Amines

A 5 mL crimp cap vial was equipped with a magnetic stir bar and charged with solid starting materials, base, and cyclic biaryl sulfonamide (F-BASN). After closing the vial, it was evacuated and back-filled with nitrogen. Afterward, 0.5 mL of anhydrous DMSO was added under nitrogen *via* a syringe and the vial was evacuated (for 4 min) and back-filled with nitrogen (for 2 min) three times. Afterward, liquid starting materials or amines were added. The reaction mixture was then stirred and irradiated through the bottom of the reaction vial using 7 W blue LEDs (450 nm) while cooling with the integrated reactor fan. The reaction mixture was then added to a separatory funnel containing sat. aq. NaCl (10 mL) and ethyl acetate (10 mL). The aqueous layer was further extracted with ethyl acetate (2×10 mL), and combined organic layers were washed with sat. aq. NaCl (10 mL) and dried over MgSO_4 . The crude product was concentrated *in vacuo* and then purified by column chromatography using silica gel and the specified solvent system to yield the corresponding product.

General Procedure for the Coupling of Dicyanobenzenes with Ethers/Alkenes

A 5 mL crimp cap vial was equipped with a magnetic stir bar and charged with solid starting materials, base, and deprotonated cyclic biaryl sulfonamide (F-BASN^{•−}). After closing the vial, it was evacuated and back-filled with nitrogen. Afterward, 1 mL of anhydrous DMSO was added under nitrogen *via* a syringe and the vial was evacuated (for 4 min) and back-filled with nitrogen (for 2 min) three times. Afterward, liquid starting materials or alkenes were added. The reaction mixture was then stirred and irradiated through the bottom of the reaction vial using 7 W blue LEDs (450 nm) while cooling with the integrated reactor fan. The reaction mixture was then added to a separatory funnel containing sat. aq. NaCl (10 mL) and ethyl acetate (10 mL). The aqueous layer was further extracted with ethyl acetate ($2 \times$

Scheme 6. Proposed Catalytic Cycle



10 mL), and combined organic layers were washed with sat. aq. NaCl (10 mL) and dried over MgSO₄. The crude product was concentrated in vacuo and then purified by column chromatography using silica gel and the specified solvent system to yield the corresponding product.

■ ASSOCIATED CONTENT

SI Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acscatal.6c02004>.

Additional experimental details, materials, methods, compound characterization data, and NMR spectra for the products discussed (PDF)

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Author Contributions

[‡]J.K. and L.D. contributed equally. The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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Notes

The authors declare no competing financial interest.

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