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Photoredox-Catalyzed Site-Selective α-C(sp^3)–H Alkylation of Primary Amine Derivatives

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Abstract: *The synthetic utility of tertiary amines to oxidatively generate α-amino radicals is well established, however, primary amines remain challenging because of competitive side reactions. This report describes the site-selective α-functionalization of primary amine derivatives through the generation of α-amino radical intermediates. Employing visible-light photoredox catalysis, primary sulfonamides are coupled with electron-deficient alkenes to efficiently and mildly construct C–C bonds. Interestingly, a divergence between intermolecular hydrogen-atom transfer (HAT) catalysis and intramolecular [1,5] HAT was observed through precise manipulation of the protecting group. This dichotomy was leveraged to achieve excellent α/δ site-selectivity.*

The formation of α-amino radicals using visible-light photoredox catalysis has garnered significant attention as a mild method to construct C–C bonds.[1] Electron-rich tertiary amines can be oxidized to generate nitrogen radical cations, allowing facile access to α-amino radicals after deprotonation of the α-C–H bond.[2] Competitive N-alkylation events for primary and secondary amines can hinder the formation of α-amino radicals (Figure 1 a).[3] A cleavable functionality at the α-position may be pre-installed to circumvent undesired reactivity by accessing α-amino radicals (Figure 1 b).[4] Hydrogen-atom transfer (HAT) catalysts have been successfully implemented to achieve α-C–H functionalization of acylated secondary amine derivatives devoid of α-pre-functionalization.[5] Our group has recently reported the selective α-functionalization of primary aliphatic amines to afford γ-lactams under dual photoredox and HAT catalysis utilizing CO_2 as an activating group, wherein we identified an acceleration of the HAT event by an electrostatic interaction between the quinuclidinium cation and carbamate anion.[6] We recognized, however, that ring closure is not always

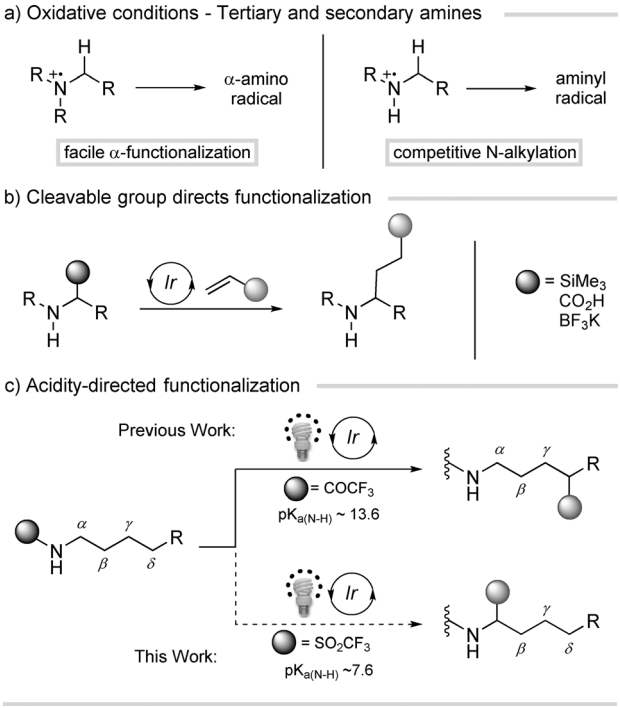

Figure 1. Photoredox functionalization: a) Tertiary versus secondary amines. b) Installation of cleavable functionality to direct α-amino radical formation. c) Acidity-controlled site-selectivity.

desired and manipulation of primary amines themselves can be challenging in multistep synthetic planning. For this reason, we further explored the impact of either different common activating or protecting groups searching for a broadly applicable α-alkylation of primary amine derivatives.

We sought to develop a protocol for amine C–H functionalization in which the site-selectivity can be achieved through the judicious choice of the directing group on nitrogen. Independently, our group and the group of Knowles demonstrated the robustness of δ-C(sp^3)–H alkylation through [1,5] HAT.[7] Utilizing trifluoroacetamides, amidyl radicals are formed under oxidative conditions to remotely activate the δ-C–H bond (Figure 1 c), an undesirable pathway for α-derivatization. We reasoned that using a more acidifying functionality could pivot reactivity towards the activation of α-C(sp^3)–H bonds by leveraging the following consequences: a change in the nature of the protecting group results in a change in the bond strength and the pK_a value of the NH.[8]

After surveying a variety of amine protecting groups, we gratifyingly observed promising reactivity and selectivity

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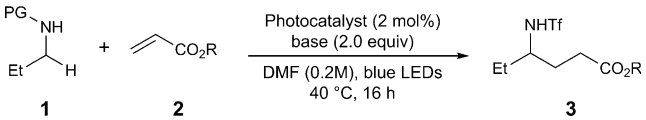
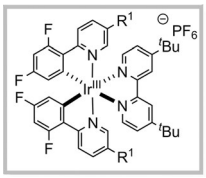
using trifluoromethanesulfonamides. We were delighted to observe α-functionalization of **1a** in 50% yield with benzyl acrylate in the presence of a carbonate base, the photocatalyst **A**, and blue light (Table 1, entry 1). A superior yield was

Table 1: Reaction optimization.



1 **2** **3**

Entry	PG	Photocatalyst	R	Base	Yield [%][b]
1	Tf	**A**	Bn	Cs_2CO_3	50
2	Tf	**A**	Bn	K_2CO_3	54
3	Tf	**A**	Bn	K_3PO_4	58
4	Tf	**B**	Bn	K_3PO_4	65
5	Tf	**A**	^{t}Bu	quinuclidine	71
6	Tf	**B**	^{t}Bu	quinuclidine	77[c]
7	$COCF_3$	**B**	^{t}Bu	quinuclidine	0
8	Ts	**B**	^{t}Bu	quinuclidine	0
9	Ac	**B**	^{t}Bu	quinuclidine	0



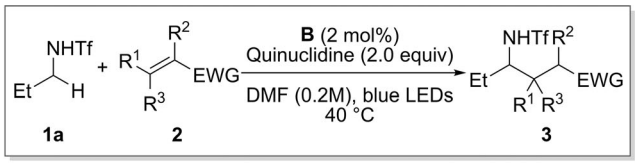
A: Ir(dF-CF_3) R^1 = CF_3
B: Ir(dF-Me) R^1 = Me

[a] **1a** (0.1 mmol), alkene (0.15 or 0.3 mmol), base (0.2 mmol), photocatalyst (2.0 mol%), DMF (0.2 M), 34 W blue LED, ca. 40°C, 16 h. [b] Yields determined by ^{1}H NMR spectroscopy using trimethoxybenzene as an internal standard. [c] Yield of isolated product. Ac = acetyl, Bn = benzyl, DMF = *N*,*N*-dimethylformamide, Et = ethyl, Me = methyl, PG = protecting group, ^{t}Bu = *tert*-butyl, Tf = triflyl, Ts = tosyl.

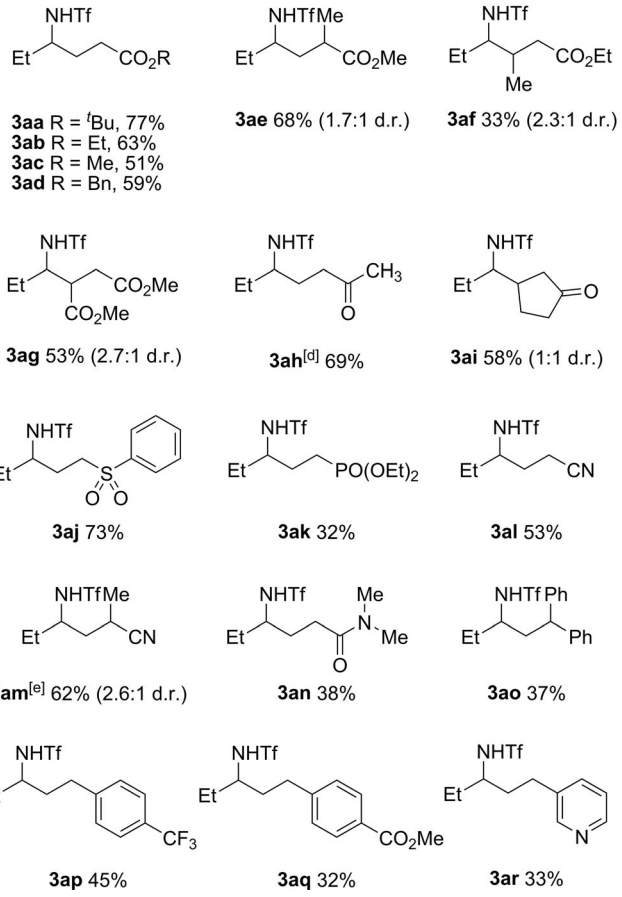
obtained when using [Ir(dF-CH_3-ppy)$_2$(dtbbpy)PF_6] (**B**)[9] as the photocatalyst, and subjecting quinuclidine to the reaction conditions (entry 6). Control experiments confirmed photocatalyst, base, and light were all essential for successful α-alkylation of **1a** (see the Supporting Information for details). Desired product formation was not obtained with weaker electron-withdrawing groups on nitrogen (entries 7–9).

With optimized reaction conditions in hand, we sought to investigate the scope with respect to the alkene with **1a** as the substrate (Scheme 1). Both acrylates devoid of α-substituents (**3aa**–**ad**), as well as methyl-methacrylate (**3ae**), give products in acceptable yields. Acrylates containing β-substituents (**3af**) lead to a moderate drop in reactivity (33%) except in the case of highly activated dimethyl fumarate (**3f**), which proceeds in moderate yield (53%). In addition to acrylates, enones provide the desired α-functionalization (**3ah**–**ai**). Additional Michael acceptors, including vinyl sulfones (**3aj**), vinyl phosphonates (**3ak**), and acrylonitrile (**3al**–**am**) are well tolerated. Dimethylacrylamide (**3an**) is incorporated with a slightly compromised yield (38%). Of note is the successful use of electron-deficient styrene derivatives as coupling partners (**3ao**–**aq**) as well as a heteroarene-substituted olefin (**3ar**).[10]

We examined the scope with respect to the amine using either *tert*-butyl acrylate (**2a**) or ethyl acrylate (**2b**) as the

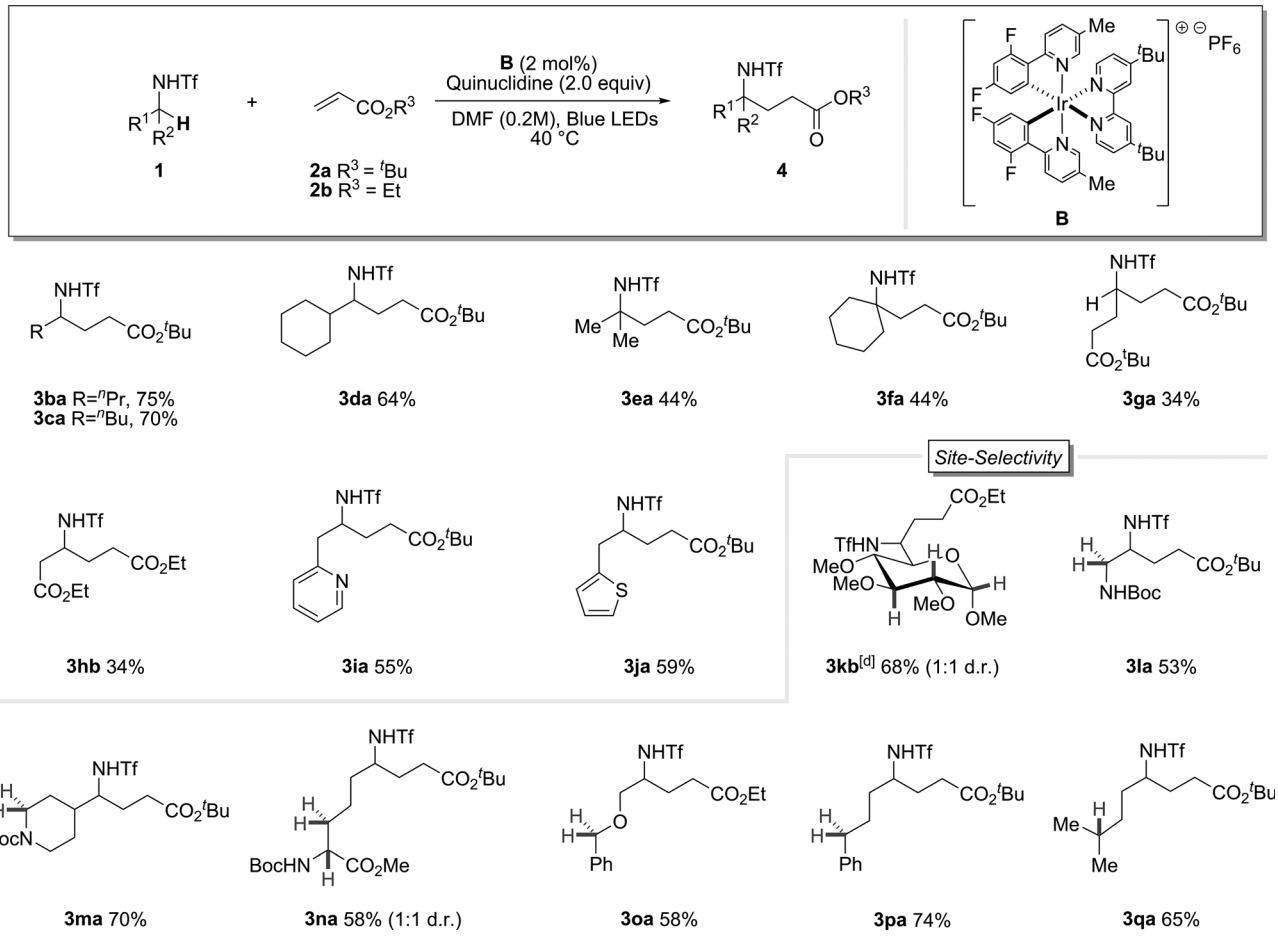


1a **2** **3**



Scheme 1. Olefin scope. [a] **1a** (0.1 mmol), alkene (0.15 or 0.3 mmol), quinuclidine (0.2 mmol), [Ir(dF-CH_3-ppy)$_2$(dtbbpy)PF_6] (2.0 mol%), DMF (0.2 M), 34 W blue LED, ca. 40°C, 16 h. [b] Yield of the isolated products. [c] The d.r. value was determined by ^{1}H NMR analysis of the isolated product. [d] Used 1.2 equiv of 3-buten-2-one. [e] 0.3 mmol scale. EWG = electron-withdrawing group.

coupling partner (Scheme 2). Substrates containing secondary α-C(sp^3)–H bonds (**3ba**–**da**) provide product in good yields, whereas tertiary (**3ea**–**fa**) α-positions show lower levels of reactivity. Interestingly, methyl-triflamide (**3ga**) as substrate leads to a 34% yield of the dialkylated product as nearly the sole product. Altering the ratio of triflamide and olefin coupling partner did not suppress dialkylation. We reasoned the second alkylation event occurs by a faster rate because of the resulting radical stability from the first (primary carbon radical) versus second hydrogen-atom abstraction event (secondary carbon radical). Nearby electron-withdrawing groups create a more difficult alkylation event (**3hb**, 34%) presumably because of the decreased hydridicity of the triflamide α-C–H bond. Absence of over-alkylation in the formation of the products **3ba** and **3ca** can be attributed to this mode of deactivation in conjunction with



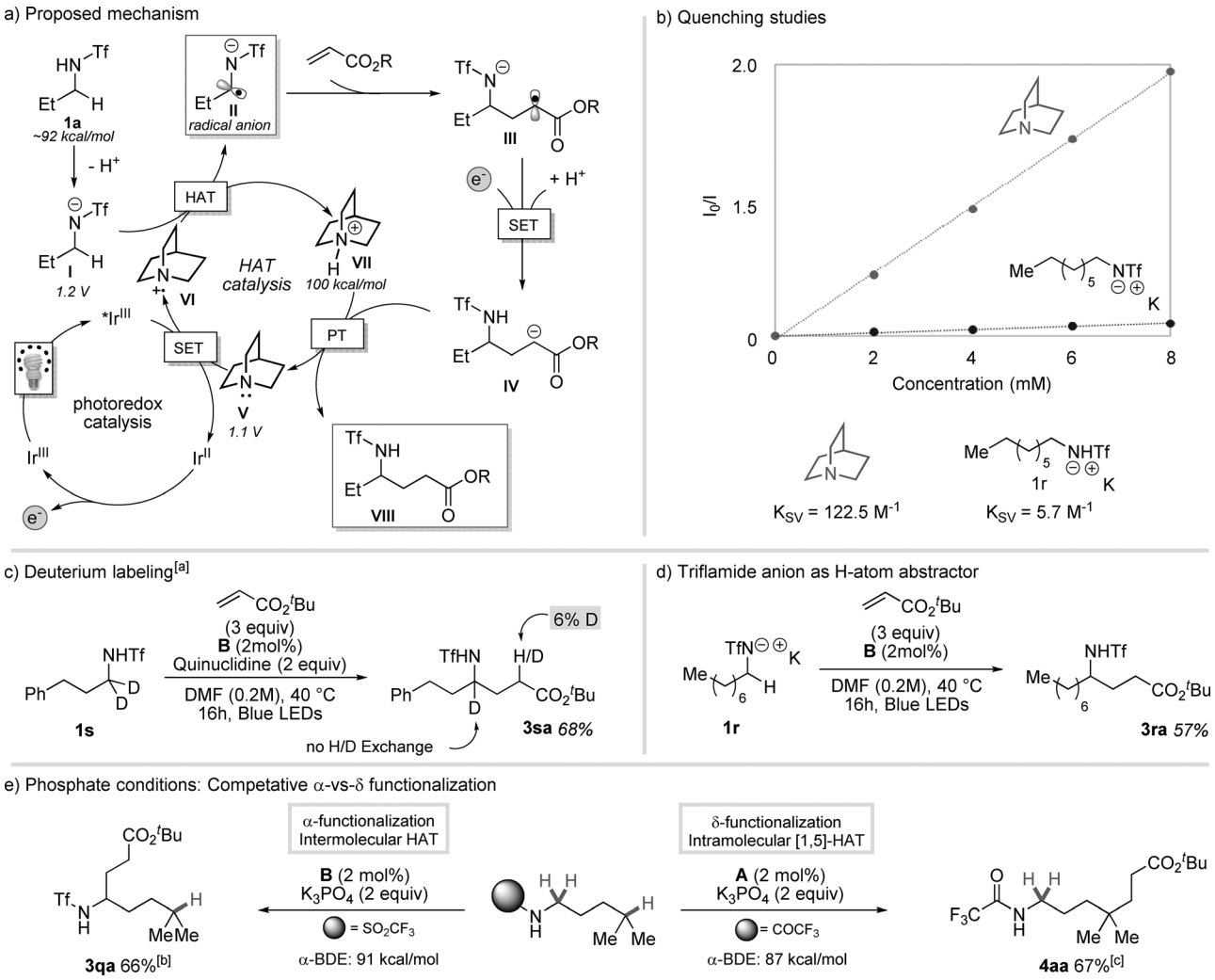
Scheme 2. Triflamide scope. [a] **1a** (0.1 mmol), alkene (0.15 or 0.3 mmol), quinuclidine (0.2 mmol), $[Ir(dF\text{-}CF_3\text{-}ppy)_2(dtbbpy)PF_6]$ (2.0 mol%), DMF (0.2 M), 34 W blue LED, ca. 40 °C, 16 h. [b] Yield of isolated products are reported. [c] The d.r. value was determined by ^1H NMR analysis of isolated product. [d] 0.3 mmol scale. Boc = *tert*-butyloxycarbonyl.

a sterically demanding environment. Furthermore, the formation of the fully branched **3ea** and **3fa** proceeds in lower yield. This methodology also proved tolerant of heterocyclic derivatives (**3ia–ja**).

To demonstrate the robustness of our site-selective α-alkylation, we sought to functionalize sulfonamides bearing additional potential sites of activation. A glucose derivative containing multiple abstractable tertiary C(sp^3)–H bonds affords the desired α-functionalization selectively to form **3kb** in 68% yield (Scheme 2). The inclusion of primary (**3la**) and secondary Boc-protected amines (**3ma**) provide a competitive site for α-functionalization. Previous work from the group of MacMillan demonstrates a quinuclidine radical cation can abstract a hydrogen atom from these sites.[5] Gratifyingly, alkylation occurs site-selectively at the α-C-(sp^3)–H triflamide site. A lysine-derived triflamide also participates, delivering **3na** as a single constitutional isomer in 58% yield. Preference for the selective formation of α-amino radicals over [1,5] HAT pathways is further demonstrated with the products **3oa–qa**. This selectivity is quite remarkable considering our previous work with trifluoroacetamide directing groups which activate the δ-C–H bond by [1,5] HAT.

Several mechanistic experiments proved enlightening. Stern–Volmer quenching studies (Scheme 3b) reveal a strong kinetic preference for the single-electron oxidation of quinuclidine ($E_{1/2}^{red} = 1.1$ V vs. SCE in DMF) over the triflamide anion ($E_{1/2}^{red} = 1.2$ V vs. SCE in DMF) by the excited state of **B**. A deuterium-labelling experiment reveals a lack of appreciable deuteration at the position α to the ester, suggesting that a chain-transfer mechanism by direct HAT from another molecule of substrate to the enoyl radical is a minor pathway at best. Taken together, we propose the following mechanism to explain these observations. Under quinuclidine conditions, a dual HAT/photoredox catalytic cycle is proposed (Scheme 3a).[11] The highly electrophilic quinuclidinium radical cation (**VI**) abstracts an activated hydridic α-hydrogen atom of the triflamide anion (**I**) to deliver an α-amino radical anion (**II**).[12] Subsequent radical trapping by an electron-deficient olefin coupling partner will furnish a carbon-centered radical (**III**). Single-electron reduction of **III** by the reduced iridium photocatalyst ($E_{1/2}^{red} = Ir^{III}/Ir^{II} = -1.42$ V vs. SCE) and a final protonation event affords the desired product **VIII**, closing the catalytic cycle.

More significant, perhaps, is the question of mechanism in the presence of phosphate as a base (entry 3 in Table 1).



Scheme 3. Mechanistic interrogation. [a] No deuterium/hydrogen scrambling was observed α to the nitrogen center. Deuterium incorporation was measured in the product. Reaction was repeated under phosphate conditions in which about 1% incorporation was observed. [b] Phosphate conditions. [c] Reaction conditions: trifluoroacetamide (0.1 mmol), alkene (0.15 or 0.3 mmol), K_3PO_4 (0.2 mmol), $[Ir(dF\text{-}CF_3\text{-}ppy)_2(dtbbpy)PF_6]$ (2.0 mol%), $PhCF_3$ (0.4 M), blue LED. [c] K_{SV} = Stervn–Volmer quenching constant.

While phosphate has been implicated as a potential HAT catalyst, [13] we believe its dominant role is to deprotonate the acidic triflamide forming the anion in high concentration. A control experiment revealed that the potassium salt of the triflamide undergoes the α-alkylation reaction in the absence of added phosphate or quinuclidine in similar yield (Scheme 3d). As mentioned above, Stern–Volmer studies support triflamide oxidation by the excited state of the photocatalyst. Thus, we suggest the N-centered triflamidyl radical undergoes intermolecular HAT from another molecule of triflamide anion, delivering the C-centered radical.

By subjecting isohexylamine derivatives to the photoredox catalyzed C–H activation reaction (Scheme 3e) we find that trifluoroacetamides site-selectively functionalize at the δ-position (**4aa**), whereas triflamides conserve α-activation (**3qa**). This divergence in reactivity can be attributed to the resulting nitrogen radical stability and extent of deprotonation of the N–H bond. Computational studies suggest the nitrogen radical from a trifluoroacetamide is less stable than that from a triflamide.[8] Under phosphate conditions, trifluoroacetamides lie toward heavily protonated, thus, α-C–H bond activation is minimized when compared to their triflamide counter partners. The trifluoroacetamide nitrogen-centered radical will experience a larger driving force for intramolecular [1,5] HAT due to nitrogen radical instability and the absence of activated α-C–H bonds in solution (trifluoroacetamides in solution lie in the protonated state). The more stable nitrogen-centered radical present on triflamide acts as an intermolecular hydrogen-atom abstractor to deprotonated triflamides in solution, which possess highly activated α-C–H bonds due to the anionic character. This pivot in reactivity allows selective functionalization of both α- and δ-C–H bonds depending on the installed nitrogen protecting group.

In summary, we have developed a site-selective, visible-light-driven photocatalyzed α-functionalization of primary amines. Key to success is the use of a trifluoromethanesulfonyl group on nitrogen as it allows full deprotonation of the N–H

bond and renders the α-C–H bond more hydridic and susceptible to intermolecular HAT. Our reaction allows the formation of a C–C bond at the α position of primary amine derivatives through coupling α-amino radicals and electron-deficient alkenes.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: amines · photochemistry · radicals · reaction mechanisms · synthetic methods

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[9] S. Ladouceur, D. Fortin, E. Zysman-Colman, *Inorg. Chem.* **2011**, *50*, 11514–11526; The photocatalyst **B** has a slightly higher reduction potential (−1.43 V vs. SCE) than the photocatalyst **A** (−1.37 V vs. SCE). A common by-product observed during optimization was a 1:2 adduct resulting from oligomerization of acrylate off the enoyl radical formed from the initial addition. **B** may allow a more facile reduction of this resulting carbon-centered radical and minimize undesired reactivity.

[10] Background styrene polymerization is somewhat competitive to desired product formation.

[11] The reaction proceeds with catalytic amounts of quinuclidine. However, byproducts that are observed include those arising from acrylate oligomerization (from **III**). Increasing the equivalents of quinuclidine ensures high reaction efficiency. As seen in Table 1, K_3PO_4 gives comparable yields.

[12] We cannot discount an electrostatic attraction between **VI** and the triflamide anion, analogous to what we observe with CO_2-derived carbamates (see Ref. [6]).

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Communications

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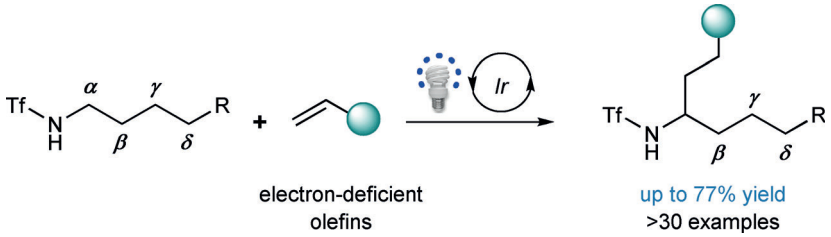

By choice: Judicious choice in nitrogen protecting group allows the site-selective functionalization α to a primary amine. Under photoredox catalysis conditions, a variety of alkene acceptors participate, leading to good yields and excellent selectivities. Tf = trifluoromethanesulfonyl.