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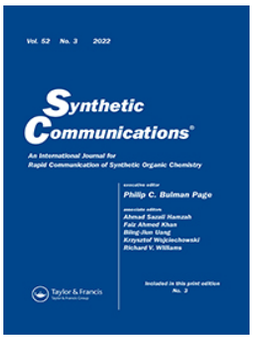

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N-tosylhydrazones as acceptors for nucleophilic alkyl radicals in photoredox catalysis: A short case study on possible side reactions

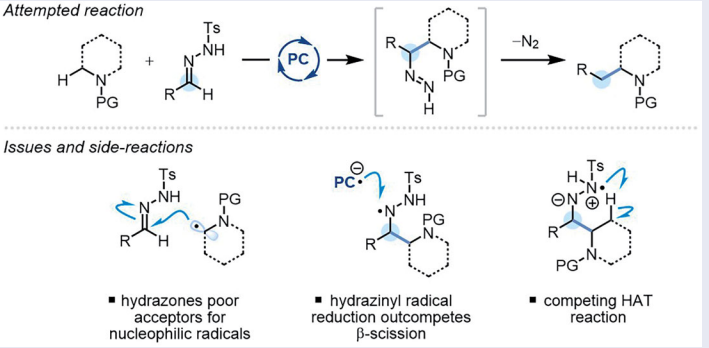
Anna G. Kinsella[a], Joshua D. Tibbetts[a], Darren Stead[b], and Alexander J. Cresswell[a]

[a]Department of Chemistry, University of Bath, Bath, UK; [b]AstraZeneca, Oncology R&D, Research & Early Development, Cambridge, UK

ABSTRACT

We report the attempted development of a photoredox-catalyzed α-C–H alkylation reaction of aliphatic amine derivatives, using *N*-tosylhydrazones as radical alkylating partners. The original intention was to intercept α-aminoalkyl radical intermediates with *N*-tosylhydrazones, followed by the expulsion of a sulfonyl radical by β-scission to generate *N*-H diazene species. Facile denitrogenation of these intermediates would remove all traces of the hydrazone moiety and provide a net C–H alkylation process. However, our plans were derailed by issues with the low reactivity of *N*-tosylhydrazones toward intermolecular capture by nucleophilic radicals, and several unexpected side reactions. Our findings, though unsuccessful, do serve to identify challenges for future researchers attempting to develop similar transformations.

GRAPHICAL ABSTRACT



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Amines; hydrazones; photoredox; radicals; side reactions

Introduction

The centrality of aliphatic amines in drug discovery[1] and the ever-increasing drive to expand chemical space in this area has spurred the design of new and creative approaches to these important building blocks.[2] As part of this effort, chemists have

CONTACT Alexander J. Cresswell a.j.cresswell@bath.ac.uk Department of Chemistry, University of Bath, Claverton Down, Bath, BA2 7AY, UK.

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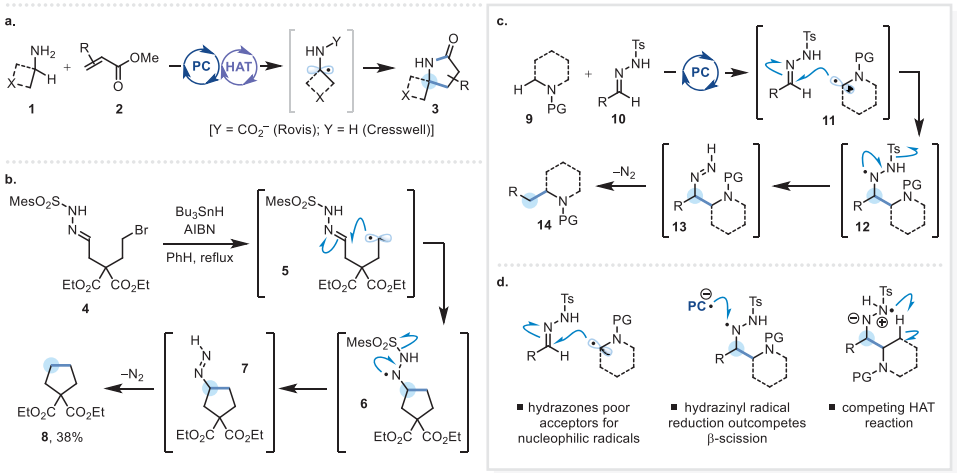
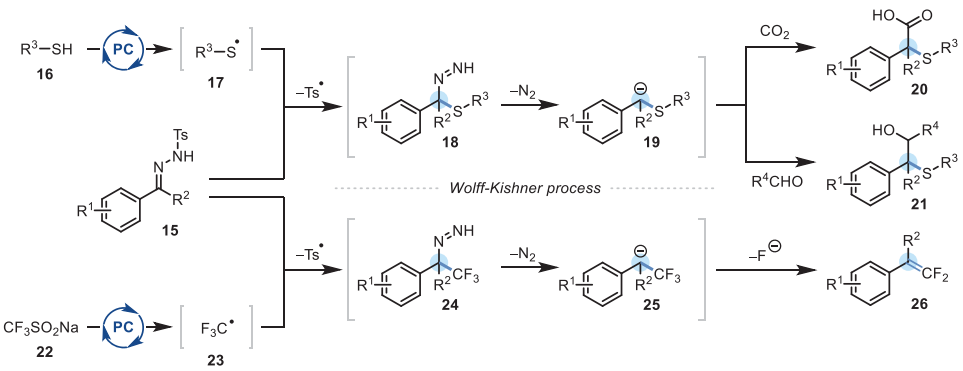


Scheme 1. (a) Prior art: Catalytic γ-lactam synthesis from unprotected 1° alkylamines; (b) Inspiration: traceless alkyl-alkyl cross-coupling using *N*-tosylhydrazones; (c) Original aim of this work: metal-free α-C–H alkylation of amines; (d) Problems and side reactions.

made significant strides in the area of C–H functionalization of aliphatic amines, addressing C–H bonds α- and β- to nitrogen, as well as more remote C–H bonds.[3] For example, we recently reported a powerful new approach for the catalytic α-C–H alkylation of primary amines **1**,[4] using photoredox catalysis[5] in conjunction with hydrogen atom transfer (HAT) catalysis[6] (e.g., **1** + **2** → **3**, Scheme 1a). Given the profound effect that the introduction of simple alkyl groups—including methyl groups[7]—can have upon the physicochemical properties of drugs, we were motivated to develop an α-C–H alkylation reaction for alkylamines that could introduce such motifs without the need for transition metal co-catalysis.[3a,b] We were inspired by reports utilizing *N*-tosylhydrazones as alkylating agents for either alkyllithium reagents[8] or alkyl radicals,[9] in each case relying upon denitrogenation of transient diazenes[10] to enable a "traceless" C–C bond-forming process (e.g., **4** → **8** from reference[9c], Scheme 1b). Our intended reaction design was to harness established photoredox protocols for the generation of α-amino radicals **11**[11] from *N*-protected aliphatic amines **9** and intercept these radicals with *N*-tosylhydrazones **10**. A subsequent β-scission[12] event from hydrazinyl radical **12** would expel a sulfonyl radical (to oxidatively turnover the photoredox catalyst) and furnish *N*–H diazenes **13**. Subsequent denitrogenative decomposition of these species would give the desired α-alkylated amines **14** (Scheme 1c). However, a number of reactivity problems and unexpected side reactions conspired to derail our ambitions, including poor radicophilicity of *N*-tosylhydrazones toward intermolecular capture by highly nucleophilic α-amino radicals, competitive SET reduction of the putative hydrazinyl radical intermediate **12**, and a suspected intramolecular HAT process possible with cyclic amine substrates (Scheme 1d).

As the studies described herein were nearing completion, König et al. reported the successful execution of a very similar concept to our intended "traceless" alkylation, albeit with electrophilic thiyl (RS•) or trifluoromethyl (F_3C•) radicals *in lieu* of nucleophilic α-amino radicals (Scheme 2).[9a] In this instance, the *N*-tosylhydrazones are

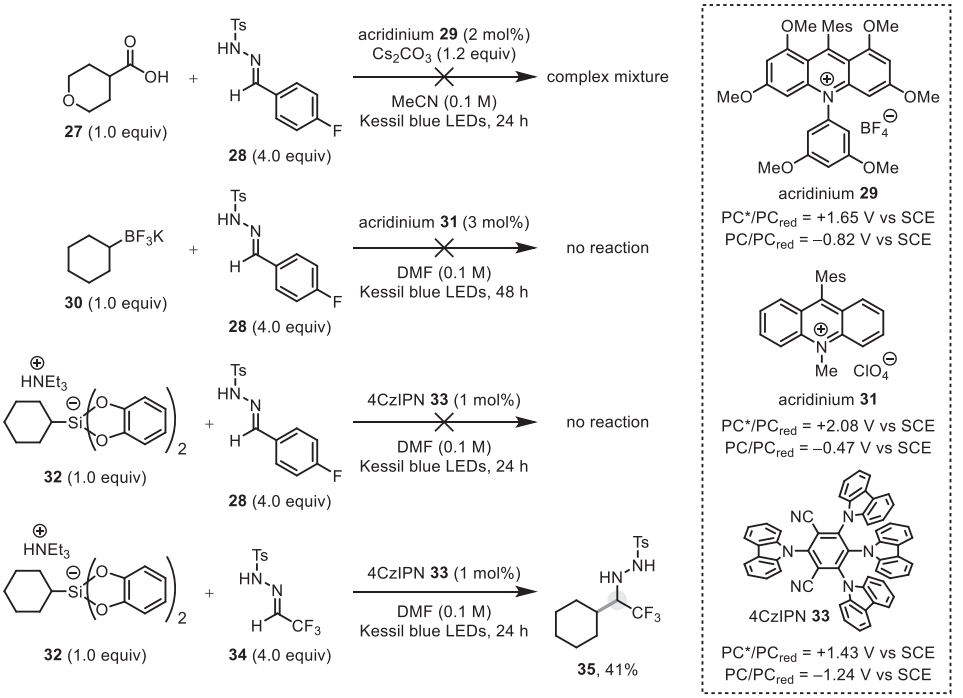


Scheme 2. König's merger of photoredox catalysis with Wolff-Kishner-type reactivity of *N*-tosylhydrazones.

displaying *nucleophilic* reactivity[10] at carbon, in contrast to the *electrophilic* behavior[8,9] we have envisioned. The successful β-scission step to expel a sulfonyl radical, leading to diazenes **18** and **24** as key intermediates, is also noteworthy, and contrasts with our own findings (*vide infra*).

Results and discussion

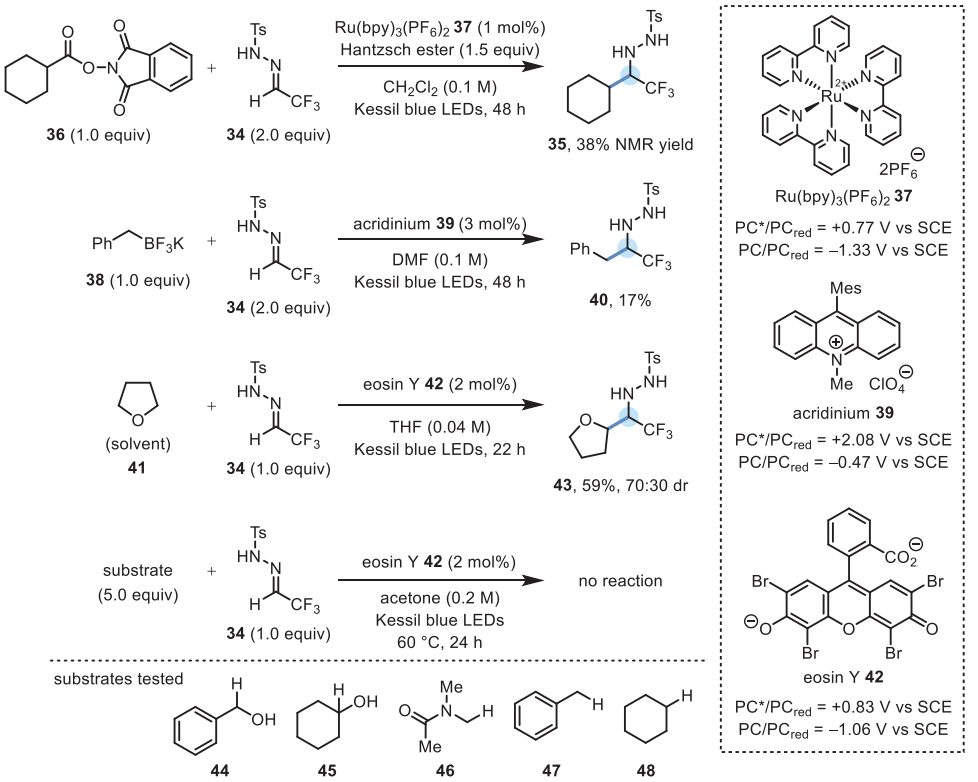
Our investigations commenced to add photogenerated simple alkyl radicals to *N*-tosylhydrazone **28** (derived from 4-fluorobenzaldehyde), using the *para*-fluoro group as a spectroscopic handle for ^{19}F NMR (Scheme 3). Initial attempts with acridinium photocatalysts employing carboxylic acids (e.g., **27**) or trifluoroborates (i.e., **30**) were unsuccessful, with only a complex mixture generated in the former case and no reaction in the latter. Control experiments verified that hydrazone **28** is sensitive to extensive decomposition on exposure to Cs_2CO_3, even in the absence of light, likely *via* generation of the corresponding diazo species. We next tested the easily oxidized bis(catecholato)silicate **32** ($E_{p/2}^{red} = +0.69$ V *vs.* SCE in DMF)[13] as an alkyl radical precursor, and 2,4,5,6-tetra(9*H*-carbazol-9-yl)isophthalonitrile (4CzIPN) **33** [$E_{1/2}$ (PC*/PC$^{\bullet-}$) = +1.43 V *vs.* SCE in MeCN][14] as the photoredox catalyst. Again, with *N*-tosylhydrazone **28**, no reactivity was observed, but with the much more activated hydrazone **34** (derived from trifluoroacetaldehyde), a successful reaction ensued to give α-CF_3 hydrazide **35** in 41% isolated yield (albeit alongside several other, unidentified minor products). This result suggests that simple aromatic *N*-tosylhydrazones like **28** are not sufficiently electrophilic to efficiently capture nucleophilic radicals,[9a] but that strong electron-withdrawing groups on the hydrazone carbon (as in **34**) can remedy this situation. Unfortunately, this result also indicated that our originally conceived β-scission[12] to expel a sulfonyl radical and generate a transient *N*-H diazene is not operative in this case and that the hydrazinyl radical generated after hydrazone addition is rapidly quenched *via* SET reduction by the reduced photocatalyst [$E_{1/2}$ (PC/PC$^{-\bullet}$) = −1.24 V *vs.* SCE in MeCN]. We also attempted to use an α-CF_3 hydrazone substituted with a 4-(trifluoromethyl)phenylsulfonyl group instead of a Ts group, but the photoredox reaction with **32** was significantly messier and lower-yielding than that with hydrazone **34**, and the product could not be isolated by chromatography without extensive decomposition.



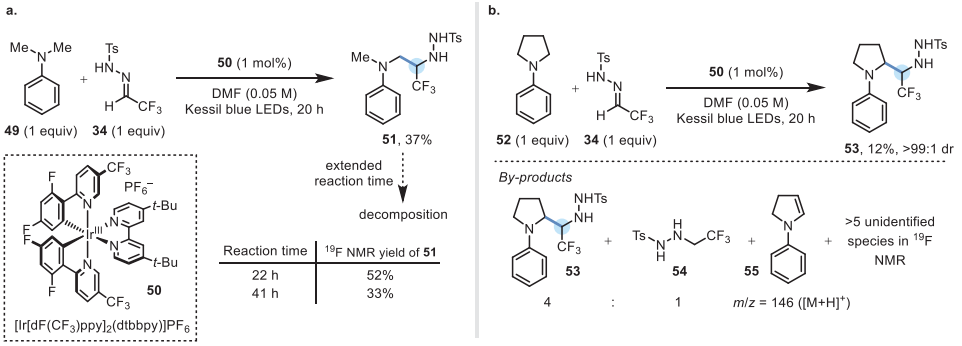
Scheme 3. Attempts at photocatalytic alkyl radical addition to *N*-tosylhydrazones.

We next investigated some other alkyl radical precursors[15] with α-CF_3 hydrazone **34** as the acceptor, in the hope that we might identify an instance in which the *β*-scission step might be competitive with reduction of the *N*-centred radical (Scheme 4). With redox-active ester **36** as the radical precursor, a set of reaction conditions previously reported for photocatalytic conjugate additions[15a] gave α-CF_3 hydrazide **35** in 38% NMR yield, but no sign of the desired alkyl-alkyl cross-coupling product (*via* a *β*-scission and denitrogenation pathway analogous to that in Scheme 1c). The outcome was similar for benzylic trifluoroborate **38**, from which the α-CF_3 hydrazide **40** was isolated in a 17% yield. In both cases, the crude product mixtures were complex and difficult to deconvolute *via* ^{19}F NMR, with several unidentified, minor fluorinated species also evident. We also attempted the reaction of tetrahydrofuran **41** (as the solvent and radical precursor) with *N*-tosylhydrazone **34**, using eosin Y **42** as a photo-HAT catalyst.[15b] In this case also, an α-CF_3 hydrazide **43** was isolated in 59% yield (70:30 dr), but again with no sign of products resulting from a putative *N*-H diazene. Unfortunately, this process did not prove to be general with other substrates (**44**–**48**), all of which gave no reaction, despite being used in a 5-fold excess, relative to **34**.[15b]

Given that there is precedent for the controlled decomposition of *N*-tosyl hydrazides by a Wolff-Kishner-type pathway,[9a,b] we reasoned that our original goal of a "traceless" α-C–H alkylation process for aliphatic amines may still be within reach, albeit as a two-step process (i.e., *via* an *N*-tosyl hydrazide intermediate). Thus, we next investigated the reactivity of *N*-tosylhydrazone **34** with *N*,*N*-dimethylaniline **49**—a known precursor to α-amino radicals *via* SET oxidation-deprotonation.[11] Using an

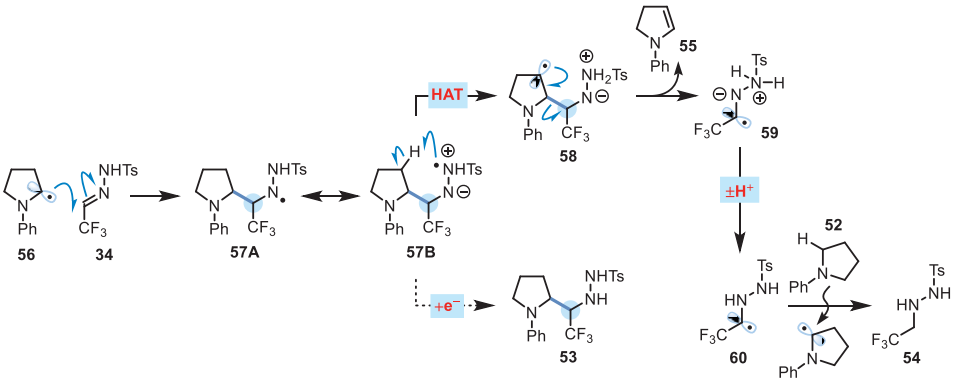


Scheme 4. Further studies using other alkyl radical precursors.



Scheme 5. (a) Photoredox coupling of *N,N*-dimethylaniline **49** with *N*-Ts hydrazone **34**. (b) Photoredox coupling of *N*-Ph pyrrolidine **52** with *N*-Ts hydrazone **34**.

iridium photocatalyst (**50**) previously employed with *N*-Ph amines,[16] the coupling of *N,N*-dimethylaniline **49** ($E_{1/2}$ = +0.74 V *vs.* SCE)[17] with *N*-tosylhydrazone **34** generated hydrazide **51** in 37% isolated yield (Scheme 5a). Minor unidentified by-products were observed by ^{19}F NMR, alongside remaining hydrazone starting material **34**. However, allowing the reaction to proceed until all of the starting hydrazone **34** had been consumed (41 h) led to a decrease in product **51** yield, suggesting that **51** may be

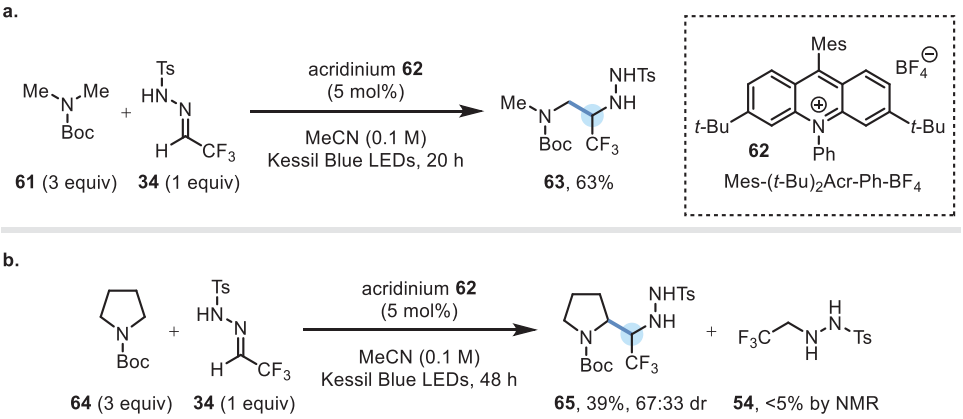


Scheme 6. Proposed mechanistic rationale for the generation of reduced hydrazone by-product **54** when using cyclic amine **52**.

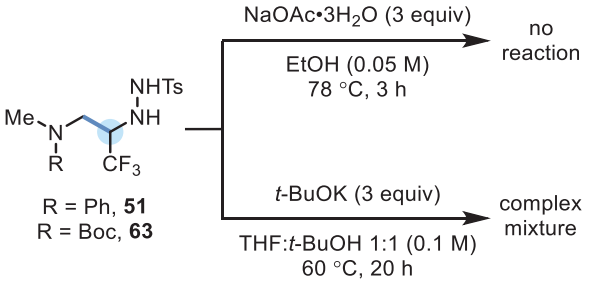
decomposing under the conditions. Moreover, on repetition of this reaction, the yield of **51** and the extent of decomposition varied considerably. Attempts to stem the decomposition by varying both the photocatalyst and the reaction solvent (i.e., MeOH, MeCN, CH_2Cl_2) were fruitless. Moreover, employing a large excess of hydrazone **34** (8.0 equiv.) conferred no benefit, providing an NMR yield of 30% of **51** after 20 h. Concurrently, the reaction of *N*-Ph pyrrolidine **52** ($E_{1/2} = +0.70$ V *vs.* SCE)[16] with *N*-tosylhydrazone **34** was also studied, and a hydrazide product **53** was isolated in 12% yield and >99:1 dr (though it is possible that a minor diastereomer was removed during chromatographic purification) (Scheme 5b). In this case, a new hydrazide species **54** (a reduction product of **34**) was detected, and mass spectroscopic evidence consistent with enamine **55** was also found (i.e., *m/z* peaks of 146 for $[M+H]^+$ and 289 for $[2M+H]^+$).[18]

Given that none of the reduced hydrazone by-product **54** was detected in the reaction of *N*,*N*-dimethylaniline **49**, this suggests that cyclic amine substrate **52** is prone to a side-reaction to afford **54** that is not possible with compound **49**. On the basis that *N*-Ph enamine **55** was also detected by MS analysis from **52** (see Scheme 5b), a speculative mechanistic rationalization to account for these findings is presented in Scheme 6. Assuming that the reaction proceeds *via* α-amino radical attack onto the C=N bond of the CF_3 hydrazone **34**, the resultant hydrazinyl radical **57** may be able to engage in a 1,5-HAT with a C–H bond on the ring of the cyclic amine. *β*-Scission of the alkyl radical would then generate enamine by-product **55**, alongside the α-CF_3 radical species **59**. Proton transfer (to give **60**) could potentially be followed by an intermolecular HAT from the amine substrate, delivering the reduced hydrazone species **54**. Concomitant generation of an α-amino radical from **52** could then feasibly lead to a chain process.

In parallel to investigations with *N*-Ph amines as radical precursors, *N*-Boc amines were also tested as substrates for a photoredox-catalyzed α-C–H functionalization with α-CF_3 hydrazone **34**. Given that carbamates possess much higher oxidation potentials than *N*-Ph amines (i.e., $E_{1/2} = +1.96$ V *vs.* SCE for *N*-Boc piperidine),[19] we opted to use the strongly oxidizing acridinium photocatalyst **62** [$E_{1/2}$ ($PC^*/PC^{\bullet-}$) = +2.15 V *vs.* SCE in MeCN] recently developed by Nicewicz and coworkers.[19] Thus, *N*-Boc dimethylamine **61** in MeCN was reacted with α-CF_3 hydrazone **34** in the presence of



Scheme 7. (a) Photoredox coupling of *N*-Boc dimethylamine **61** with *N*-Ts hydrazone **34**. (b) Photoredox coupling of *N*-Boc pyrrolidine **64** with *N*-Ts hydrazone **34**.



Scheme 8. Attempted denitrogenative decomposition of *N*-Ts hydrazides **51** and **63**.

acridinium catalyst **62** (5 mol%) with irradiation by Kessil blue LEDs for 20 h (Scheme 7a). Under these conditions, the α-CF_3 hydrazide **63** was isolated in a 63% yield. Unfortunately, attempts to reduce the stoichiometry of *N*-Boc dimethylamine **61** to 1.0 equiv. led to extensive by-product formation and a complex mixture. A similar reaction using *N*-Boc pyrrolidine **64** gave the corresponding α-CF_3 hydrazide **65** in only 39% isolated yield (67:33 dr). The reduced hydrazone by-product **54** was only observed at a trace level (<5% by NMR), suggesting that the side reaction operative for *N*-Ph pyrrolidine **52** does not make a significant contribution in this case (Scheme 7b).

At this stage, we attempted a base-induced denitrogenative decomposition of *N*-Ts hydrazide products **51** and **63**, to gauge the possibility of developing a one-pot protocol for "traceless" α-C–H alkylation (or, more specifically, trifluoroethylation if using **34**). Using literature conditions for *N*-sulfonyl hydrazide decomposition with NaOAc (*via* a radical pathway from an intermediate *N*-H diazene),[9b,20] no reaction was observed. The complete lack of reactivity is surprising, and we postulate that the strongly inductively-withdrawing CF_3 group may render the transient *N*-centered anion too thermodynamically stable to eliminate the *β*-sulfinyl group. Further attempts to induce denitrogenative decomposition of **51** and **63** using the stronger base *t*-BuOK[21] were also unsuccessful, with both compounds suffering extensive degradation to afford

complex mixtures of unidentifiable products (Scheme 8). A β-elimination of fluoride ion from a putative α-CF_3 carbanion in the latter case may be to blame.[22]

Conclusions

The reactivity of *N*-tosylhydrazones as acceptors for nucleophilic radicals generated by photoredox catalysis has been briefly explored, as part of studies directed toward a "traceless," metal-free α-C–H alkylation of aliphatic amine derivatives. The introduction of an electron-withdrawing trifluoromethyl group on the hydrazone carbon proved necessary to switch on reactivity for intermolecular capture with nucleophilic radicals, presumably by increasing the electrophilicity of what is otherwise a relatively nucleophilic site. The intended β-scission step from the hydrazinyl radical intermediates—to expel a sulfonyl radical and generate *N*-H diazenes—was outcompeted by SET reduction by the reduced form of the photocatalyst, leading to *N*-Ts hydrazide products. A side reaction involving a suspected 1,5-HAT process and subsequent fragmentation appears to operate with *N*-Ph pyrrolidine as the substrate, eroding the yield of *N*-Ts hydrazide product. Attempted denitrogenative decomposition of *N*-Ts hydrazide products was not fruitful and gave either no reaction or complex mixtures of unidentified species. Although unsuccessful, these studies do serve to identify challenges for future researchers attempting to develop similar radical-based transformations with *N*-tosylhydrazones.

Experimental

Synthesis of N-(1-cyclohexyl-2,2,2-trifluoroethyl)-4-methylbenzenesulfonylhydrazide (35)

An oven-dried, 20-mL scintillation vial equipped with a stirrer bar was charged with silicate **32** (96 mg, 0.22 mmol, 1.0 equiv.), hydrazone **34** (238 mg, 0.89 mmol, 4.0 equiv.) and 4CzIPN **33** (1.8 mg, 2.3 µmol, 1 mol%). The vial was sealed with an upturned septa and evacuated and backfilled with nitrogen three times. DMF (anhydrous, 2.5 mL) was added and the mixture was sparged with nitrogen for 15 min. The resultant solution was stirred under irradiation (Kessil H150-Blue LED lamp) for 18 h. The reaction mixture was diluted with EtOAc (15 mL) and washed with H_2O (5 × 15 mL). The organic layer was dried with a phase separating cartridge and then concentrated *in vacuo*. Purification *via* preparative HPLC (Waters CSH C_{18} OBD column, 5 µ silica, 30 mm diameter, 100 mm length) using decreasingly polar mixtures of H_2O [containing 1% by volume of NH_4OH (28–30% in H_2O)] and MeCN as eluents gave **35** as a white, crystalline solid (32 mg, 41%). mp 161 °C. ^{1}H NMR (500 MHz, chloroform-*d*) 7.71–7.91 (m, 2H, Ar*H*), 7.34 (d, $J = 7.9$ Hz, 2H, Ar*H*), 6.10 (s, 1H, N*H*), 3.71 (d, $J = 8.3$ Hz, 1H, N*H*), 2.94–3.11 (m, 1H, C(1′)*H*), 2.45 (s, 3H, C(9)H_3), 1.57–1.78 (m, 5H, *Cy*), 1.49 (s, 1H, *Cy*), 1.04–1.25 (m, 4H, *Cy*), 0.83–1.01 (m, 1H, *Cy*). ^{13}C NMR (126 MHz, DMSO-d_6) δ 143.7 (*Ar*), 137.0 (*Ar*), 130.2 (*Ar*), 128.7 (*Ar*), 127.4 (q, $J = 287$ Hz, *C*(2′)), 67.2 (q, $J = 24.4$ Hz, *C*(1′), 37.3 (*C*(1)), 29.9 (*Cy*), 29.2 (*Cy*), 26.7 (*Cy*), 26.7 (*Cy*), 26.6 (*Cy*), 21.9 (*C*(9)). ^{19}F NMR (376 MHz, chloroform-*d*) δ −73.3 (d, $J = 8.0$ Hz). IR (neat, cm^{-1}) 3297 (w), 3249 (w), 2923 (w), 2853 (w), 1601 (w), 1509 (w), 1497 (w), 1455 (w), 1354 (w), 1320 (w), 1258 (w), 1228 (w), 1189 (w), 1156 (m), 1145 (m), 1086 (w), 971 (w),

842 (w), 817 (w), 801 (w), 748 (w), 707 (w), 689 (w), 666 (w). HRMS (ESI^+) calculated for $C_{15}H_{21}F_3N_2O_2S$: $[M+H]^+$ 351.1354; found: $[M+H]^+$ 351.1363.

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