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Article

Umpolung Difunctionalization of Carbonyls via Visible-Light Photoredox Catalytic Radical-Carbanion Relay

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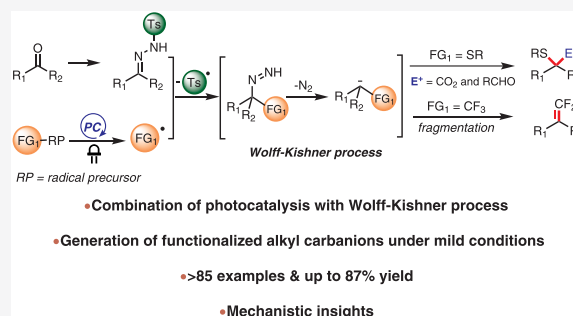
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ABSTRACT: The combination of photoredox catalysis with the Wolff–Kishner (WK) reaction allows the difunctionalization of carbonyl groups by a radical-carbanion relay sequence (photo-Wolff−Kishner reaction). Photoredox initiated radical addition to N-sulfonylhydrazones yields α-functionalized carbanions following the WK-type mechanism. With sulfur-centered radicals, the carbanions are further functionalized by reaction with electrophiles including CO_2 and aldehydes, whereas CF_3 radical addition furnishes a wide range of *gem*-difluoroalkenes through β-fluoride elimination of the generated α-CF_3 carbanions. More than 80 substrate examples demonstrate the broad applicability of this reaction sequence. A series of investigations including radical inhibition, deuterium labeling, fluorescence quenching, cyclic voltammetry, and control experiments support the proposed radical-carbanion relay mechanism.

- Combination of photocatalysis with Wolff-Kishner process
- Generation of functionalized alkyl carbanions under mild conditions
- >85 examples & up to 87% yield
- Mechanistic insights

1. INTRODUCTION

The inversion of the inherent polarity of organic functionalities, termed as *umpolung*, is a key bond-forming strategy in organic synthesis.[1] The umpolung of a carbonyl group places a negative charge on the carbon atom, making it nucleophilic and prone to attack electrophiles. Carbonyl umpolung is achieved in many ways: Acyl anion equivalents are obtained by the umpolung of electrophilic aldehydes in stoichiometric dithiane chemistry[2] and catalytic N-heterocyclic carbene (NHC) chemistry.[3] Synthetically important alkyl carbanion intermediates can be obtained from carbonyl groups using the Wolff−Kishner (WK) reduction. The polarity inversion is accomplished by sequential hydrazone formation, tautomerization, and N_2-extrusion to generate a nucleophilic alkyl carbanionic species (Scheme 1A). With elegant modifications from Huang Minlon[4] and others,[5] the WK process has evolved over the past century into a powerful carbonyl deoxygenation tool in the synthesis of complex molecules.[5] Despite being a very effective way of producing carbanions, synthetic applications of this chemistry have long been underexplored considering that the alkyl carbanion in such an umpolung can, in principle, react with many electrophiles other than a proton. Few examples based on the modified WK process have been developed for the construction of C−C bonds, wherein highly reactive alkyllithium reagents were employed to react with sulfonylhydrazones.[6] More recently, pioneering work by Li and co-workers demonstrated the direct functionalization of the carbanion in a Wolff−Kishner reaction by nucleophilic addition to carbonyl compounds,[7] imines,[8] CO_2,[9] and Michael acceptors[10] under ruthenium catalysis. The same group utilized such carbanions in metal-catalyzed Negishi-type coupling,[11]

Heck-type coupling,[12] Tsuji-Trost alkylation,[13] and olefination reactions[14] or metal-free C−C bond-forming reactions.[15] In these cases, the functional groups are installed through metal-assisted nucleophilic trapping of nonfunctionalized alkyl carbanions (Scheme 1B). Inspired by the facile generation of carbanions in the classic WK process, we questioned if functionalized carbanions can be produced catalytically for a subsequent nucleophilic reaction allowing the simultaneous installation of two functional groups at a geminal position. The scope of such a reaction sequence has remained unexplored although its realization represents a desirable synthetic tool for carbonyl group functionalization.
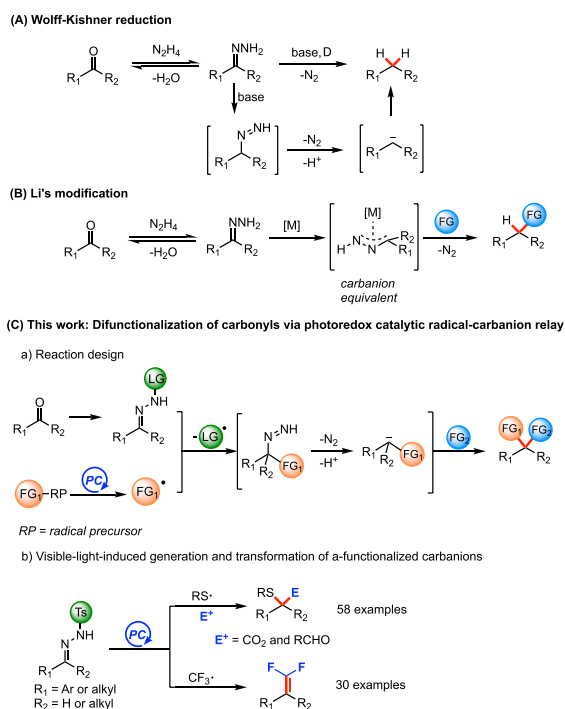
As part of our ongoing research activities in photoredox catalytic generation of functionalized carbanions from carbonyls,[16] we envisioned that a combination of a conventional WK process with photoredox catalysis might furnish functionalized alkyl carbanions for a subsequent derivatization. In the anticipated radical-carbanion relay sequence, radicals generated by the photoredox catalytic system would be captured by N-sulfonylhydrazone,[17] thus installing the first functional group. Subsequently, the diazene intermediate, resulting from radical fragmentation,[17a,c,18] enters a similar reaction sequence as involved in the WK reduction to give functionalized

Scheme 1. Umpolung Generation of Alkyl Carbanions from Carbonyls

(A) Wolff-Kishner reduction

(B) Li's modification

(C) This work: Difunctionalization of carbonyls via photoredox catalytic radical-carbanion relay

a) Reaction design

RP = radical precursor

b) Visible-light-induced generation and transformation of a-functionalized carbanions

carbanions, which offers a second opportunity for further transformations (Scheme 1C,a). Herein we report the successful implementation of this radical-carbanion relay functionalization concept. The combination of photoredox catalysis with a Wolff−Kishner process allows the facile generation of α-sulfenyl and α-CF$_3$ carbanions that undergo further nucleophilic attack or fragmentation, respectively (Scheme 1C,b).

2. RESULTS AND DISCUSSION

2.1. Generation of α-Sulfenyl Carbanions and Their Reactions with Electrophiles. Carbon−sulfur bonds are found in pharmaceuticals or natural products and are widely used in synthesis. Recent years have witnessed increasing attention to develop an efficient approach to forge C−S bonds.[19] We postulate that photogenerated thiyl radicals[20] from various thiols can engage in the radical-carbanion relay functionalization sequence. Such a process would yield synthetically useful α-sulfenyl carbanions, which are traditionally produced through deprotonation of sulfides with strong bases such as ^{n}BuLi and NaNH$_2$.[21] Building on the facile carbanion trapping by CO$_2$[22] and our continued interest in utilization of CO$_2$ as the C$_1$ feedstock for photocatalytic carboxylation reactions,[22e,23] we selected N-tosylhydrazone as the radical acceptor in the anticipated sequence based on the following considerations: (1) they can be easily prepared through condensation of carbonyl compounds with TsNHNH$_2$; (2) after radical addition to N-tosylhydrazone, rapid β-sulfone elimination was anticipated to produce a sulfinyl radical which should undergo single-electron transfer with the photocatalyst.[17,24] We commenced our study by utilizing aldehyde hydrazone **1a**, thiophenol **2a**, and CO$_2$ as model substrates for the optimization of the reaction conditions.

After systematic screening of all reaction parameters (see the SI for details), we were delighted to obtain the desired functionalized carboxylic acid **3a** in 81% yield using [Ir(dFCF$_3$ppy)$_2$dtbbpy]PF$_6$ (1 mol %) under 3 atm of CO$_2$ in DMSO (Table 1, entry 1). Polar solvents like DMSO and

## Table 1. Screening of Reaction Conditions for Thiocarboxylation of N-Tosylhydrazone[a]

entry	change from standard conditions	yield[b]
1	none	81%
2	one-pot process	80%[c]
3	MeCN instead of DMSO	n.d.
4	THF instead of DMSO	n.d.
5	4CzIPN instead of Ir−F	n.d.
6	without Cs$_2$CO$_3$	n.d.
7	without PC	n.d.
8	in the dark	n.d.

[a]Reaction conditions: compound **1a** (0.2 mmol), **2a** (0.3 mmol), Cs$_2$CO$_3$ (0.6 mmol), [Ir(dFCF$_3$ppy)$_2$dtbbpy]PF$_6$ (1 mol %), and 3 atm of CO$_2$ in 2 mL of solvent, irradiation with blue LED (455 nm) at 25 °C for 24 h. n.d. = not detected. [b]Yields were determined by ^{1}H NMR analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene as the internal standard. [c]**1a** was formed in one pot starting from p-tolualdehyde and used directly without purification. 4CzIPN = 2,4,5,6-tetra(carbazol-9-yl)isophthalonitrile. Ir−F = [Ir-(dFCF$_3$ppy)$_2$dtbbpy]PF$_6$. PC = photocatalyst.

DMF were effective for this thiocarboxylation reaction (see the SI, Table S2). Moreover, we successfully converted p-tolualdehyde into the desired product **3a** in one pot by means of a condensation and photocatalytic sequence with similar efficiency (Table 1, entry 2). Rigorous control experiments revealed that photocatalyst, base, and light were crucial for the transformation to occur (Table 1, entries 6−8).

With the optimized reaction conditions in hand, we examined the scope of the method (Table 2). The reaction gave good yields of the corresponding products with a series of aromatic aldehyde-derived N-tosylhydrazones bearing electron-neutral (**3a−3c, 3f, 3g, 3j,** and **3l**), electron-donating (**3d, 3h,** and **3o**), or electron-withdrawing (**3i, 3k,** and **3n**) groups at para-, meta-, or ortho- positions. The reaction was compatible with N-tosylhydrazones containing two substituents on the aromatic ring, affording the desired carboxylic acids (**3m−3o**) in reasonable yields (43−58%). Heterocyclic and naphthalene-containing substituents were also well tolerated by the catalytic system (**3p, 3q**).

The reaction system could also be extended to N-tosylhydrazones derived from ketones, affording a wide range of carboxylic acids with quaternary carbon-centers (**3r−3ae**). Gratifyingly, functional groups including phenyl (**3s**), halogen (**3t** and **3x**), thiophene (**3u**), benzofuran (**3v**), and methoxy (**3y**) on the aromatic rings of substrates were well tolerated. The reaction proceeded with similar efficiencies for electron-rich or electron-poor substrates. Moreover, N-tosylhydrazones bearing more sterically hindered substituents at the α-position such as ethyl (**3aa**), isopropyl (**3ab**), and cyclopropyl (**3ac**) gave the desired products in good yields, but longer reaction times were required. The reaction could be utilized for the thiocarboxylation of N-tosylhydrazone derived from 4-
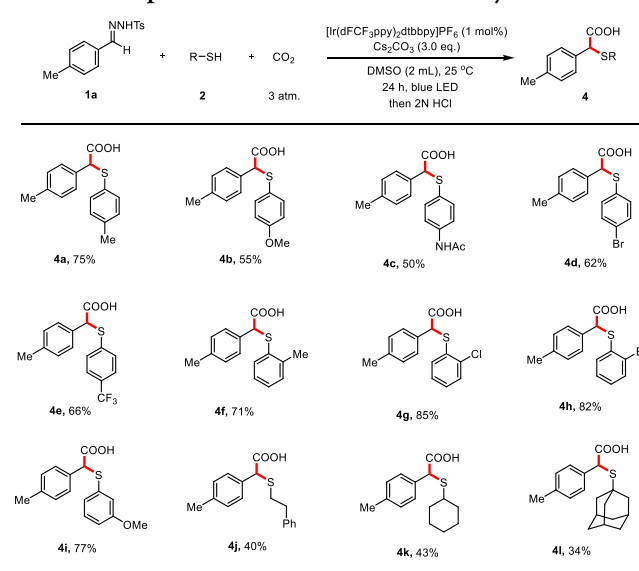
Table 2. Scope of N-Tosylhydrazones for Thiocarboxylation[a]
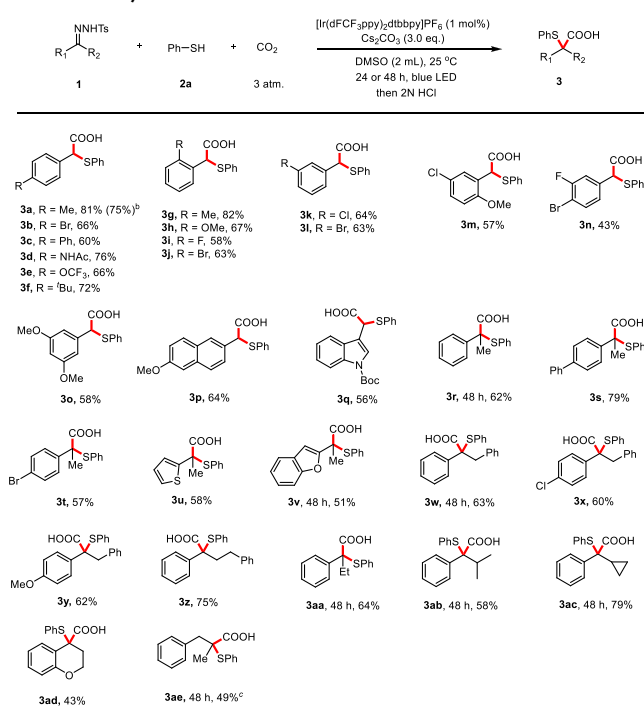
Table 3. Scope of the Thiols for Thiocarboxylation[a]

[a]Reaction conditions: unless otherwise noted, all reactions were carried out with **1a** (0.2 mmol), **2** (0.3 mmol), Cs$_2$CO$_3$ (0.6 mmol), [Ir(dFCF$_3$ppy)$_2$dtbbpy]PF$_6$ (1 mol %), and 3 atm of CO$_2$ in 2 mL of DMSO, irradiation with blue LED (455 nm) at 25 °C for 24 h, and isolated yields were shown.

[a]Reaction conditions: unless otherwise noted, all reactions were carried out with **1** (0.2 mmol), **2a** (0.3 mmol), Cs$_2$CO$_3$ (0.6 mmol), [Ir(dFCF$_3$ppy)$_2$dtbbpy]PF$_6$ (1 mol %), and 3 atm of CO$_2$ in 2 mL of DMSO, irradiation with blue LED (455 nm) at 25 °C for 24 h, and isolated yields were shown. [b]6 mmol scale, CO$_2$ was bubbled into the reaction continuously. [c]Reaction was conducted at 0 °C in DMF (2 mL)

Table 4. Scope of the Aldehydes for Thiohydroxyalkylation[a]

[a]Reaction conditions: unless otherwise noted, all reactions were carried out with **1** (0.2 mmol), **2a** (0.3 mmol), **5** (0.8 mmol), Cs$_2$CO$_3$ (0.3 mmol), [Ir(dFCF$_3$ppy)$_2$dtbbpy]PF$_6$ (1 mol %) in 2 mL of DMSO, irradiation with blue LED (455 nm) at 25 °C for 24 h, and isolated yields were shown. [b]6 mmol scale. [c]Paraformaldehyde (0.8 mmol) and DMSO (4 mL) were used.
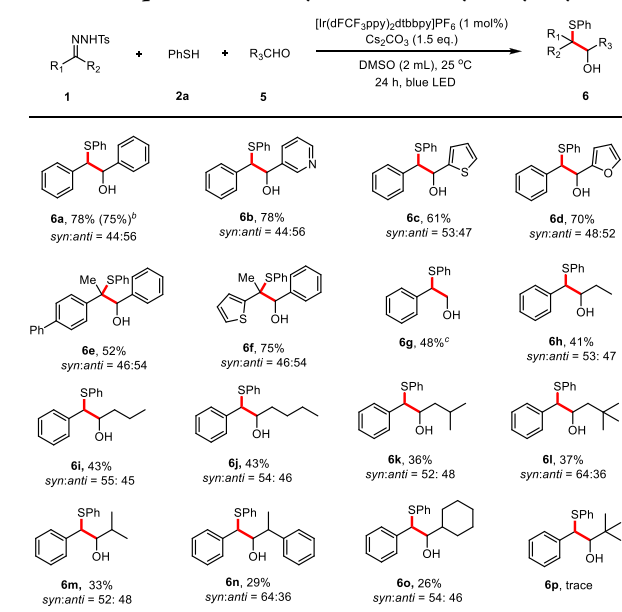
chromanone, yielding the heterocyclic product **3ad** in 43% yield. To our delight, N-tosylhydrazone derived from an aliphatic ketone reacted at 0 °C yielding product **3ae** in moderate yield. The decreased efficiency and required low reaction temperature were rationalized by the instability of the aliphatic α-sulfenyl carbanion. Importantly, this reaction is easily scalable, as demonstrated by the gram scale synthesis of **3a** in 75% yield.

Next, we explored the scope of the reaction with respect to thiols. As shown in Table 3, thiophenols bearing either electron-donating (**4a**−**4c**) or electron-withdrawing groups (**4e**) on the *para* position of the aromatic ring reacted smoothly to generate the expected products in mostly good yields. Both *ortho-* and *meta*-substituted thiophenols were suitable substrates, affording the products in high yields (71−85%). However, 4-nitro-thiolphenol failed to give the desired product. Notably, besides aromatic thiophenols, our method could be extended to primary, secondary, and tertiary aliphatic thiols (**4j**−**4l**), albeit with moderate efficiencies.

After successful application of this radical-carbanion relay sequence for carboxylation, we tested other electrophiles, like aldehydes or ketones, to realize a visible-light driven Barbier-type reaction.[22b,25] Barbier-type reactions are well-known carbon−carbon forming reactions utilizing the nucleophilic attack of organometallic species to carbonyl compounds.[26] Using slightly modified reaction conditions, we discovered that photo-Wolff−Kishner generated carbanions can be efficiently trapped with a wide range of aldehydes (Table 4).

Benzaldehyde reacted smoothly to give the desired alcohol **6a** in 78% yield. We were delighted to find that heteroaryl aldehydes readily participated in the coupling reaction to give products **6b**−**6d**. When ketone-derived N-tosylhydrazones were employed, densely functionalized sulfides (**6e**−**6f**) were constructed in synthetically useful yields. Besides aromatic

aldehydes, aliphatic aldehydes bearing short or long chains were suitable electrophiles in our system, giving the desired products in moderate yields (**6g**−**6o**).[27] Notably, solid paraformaldehyde reacted to provide the desired product (**6g**) in 48% yield. This transformation was however sensitive to steric hindrance. The presence of additional substituents at the α-carbon on the trapping aldehyde decreased the yield considerably (**6m**−**6o**), and only a trace amount of the product was detected when pivalaldehyde was employed. Moreover, ketones failed to trap the generated carbanion in the catalytic system, which may be explained by the undesired deprotonation of the α-protons to the carbonyl yielding benzyl phenyl sulfide.[28]

2.2. Generation of α-CF3 Carbanions and Their Fragmentation Reactions.

Organic molecules containing a fluorine moiety generally exhibit improved reactivity, bioactivity, and metabolic stability compared to their non-fluorinated counterparts.[29] An important privileged fluoro-containing group is the *gem*-difluoroethylene moiety based on their unique property in medicinal chemistry.[30] Moreover, *gem*-difluoroalkenes are versatile building blocks for the synthesis of other fluorine-containing molecules.[31] Traditional methods such as Wittig[32] and Julia[33] reactions for the synthesis of 1,1-difloroalkenes generally suffer from limited scope, modest efficiency, or harsh conditions. Another efficient pathway is the *gem*-difluorination of diazo compounds under metal catalytic[34] or metal-free reaction conditions.[35] This strategy is generally restricted to aromatic diazo compounds or diazo esters. Recently, several elegant defluorination strategies starting from α-trifluoromethyl alkenes based on metal catalysis[36] or photoredox catalysis[37] have been developed for the synthesis of *gem*-difluoroalkenes. Nevertheless, this route requires the presence of trifluoromethyl groups on the alkene moieties, and the product scope is limited by the accessibility of such trifluoromethylated alkenes.

Following the proposal shown in Scheme 1C and encouraged by the success in the generation of α-sulfenyl carbanions as described in section 2.1, we wondered whether difluoroalkenes could be produced involving CF3 radicals in the radical-carbanion relay sequence. The feasibility of this approach was supported by the facile E1cB elimination of α-CF3 carbanions to yield the difluoroalkenes.[37a,f,38] We used sodium triflinate (Langlois reagent, CF3SO2Na), a bench-stable and commercially available trifluoromethylation reagent, as the CF3 radical precursor and N-tosylhydrazone **7a** as the model substrate.[39] The optimized conditions (see the SI, Tables S5−S7), which include the use of [Ir-(dFCF3ppy)2dtbbpy]PF6 (2 mol %) as photocatalyst and Cs2CO3 (1.5 equiv) as the base in 1 mL of solvent (DMSO/acetone = 1/1), delivered the desired 1,1-difluoroalkene **9a** in 77% yield (Table 5, entry 2). Likewise, this transformation demonstrated retained efficiency when the reaction was carried out in a one-pot process (Table 5, entry 3). Control experiments indicated that the base, photocatalyst, and light irradiation were essential for this reaction (Table 5, entries 4−6).

Using the optimized reaction conditions for the *gem*-difluoroolefination, the scope of this methodology was evaluated. As summarized in Table 6, the reaction proceeded smoothly with a variety of N-tosylhydrazones, affording the expected *gem*-difluoroalkenes in moderate to good yields. The reactions of sodium triflinate with cycloketone-derived N-tosylhydrazones led to the corresponding products **9a**−**9e** in

Table 5. Screening of Reaction Conditions for the 1,1-Difluoroolefination of N-Tosylhydrazone[a]

entry	change from standard conditions	yield[b]
1	none	70%
2	PC (2 mol %)	77% (73%)[c]
3	one-pot, PC (2 mol %)	75%[d]
4	without Cs2CO3	n.d.
5	without PC	n.d.
6	in the dark	n.d.

[a]Reaction conditions: compound **7a** (0.2 mmol), **8** (0.3 mmol), Cs2CO3 (0.3 mmol), [Ir(dFCF3ppy)2dtbbpy]PF6 (1 mol %) in 1 mL of solvent, irradiation with blue LED (455 nm) at 25 °C for 24 h. n.d. = not detected. [b]Yields were determined by ¹⁹F NMR analysis of the crude reaction mixture using 4,4′-difluorobenzophenone as the internal standard. [c]Isolated yield. [d]**7a** was formed in one pot starting from corresponding ketone and used directly without purification. PC = photocatalyst.

Table 6. Scope of the *gem*-Difluoroolefination of N-Tosylhydrazones[a]

[a]Reaction conditions: unless otherwise noted, all reactions were carried out with **7** (0.2 mmol), **8** (0.3 mmol), Cs2CO3 (0.3 mmol), [Ir(dFCF3ppy)2dtbbpy]PF6 (2 mol %) in (DMSO/acetone = 1/1) 1 mL, irradiation with blue LED (455 nm) at 25 °C for 24 or 30 h, and isolated yields were shown. [b]8 mmol scale, reaction time: 48 h.

38−73% yields. Interestingly, a strained substrate like azetidinone-derivatized *N*-tosylhydrazone could be successfully functionalized yielding difluoroalkene **9e** in modest yield.[40] Our method could be also extended to acyclic *N*-tosylhydrazones. For instance, tosylhydrazone derived from 3-hexadecanone performed well in our reaction affording the desired product **9f** in 62% yield. Moreover, the mild reaction conditions were compatible with ketone-based tosylhydrazones bearing a wide range of functional groups including alkene (**9g**), phenol (**9h**), and amide (**9j−9l**). With *N*-tosylhydrazones derived from phenylacetones, functional groups such as phenyl, methoxy, and trifluoromethyl on the aromatic ring were well tolerated (**9m−9o**). A sterically hindered substrate **7p** participated in the reaction well to yield the *gem*-difluoroalkene. Tosylhydrazones derived from aromatic ketones were also applicable affording the desired products (**9q−9u**) in reasonable yields. The reactions proceeded smoothly with heterocycle-containing substrates (e.g., pyrazole **7i** and pyridine **7u**). Notably, ester groups on the carbon chain remained untouched (**9v**). This catalytic system was also suitable for aliphatic aldehyde-based *N*-tosylhydrazones, delivering the corresponding products in moderate to excellent yields (**9w−9aa**). The utility of this method was further demonstrated by applying it to functionalize structurally and functionally complex natural products like nabumetone, zingerone, and stanolone, providing the desired products (**9ab−9ad**) in good yields.

2.3. Reaction Mechanism. To gain insights into the reaction mechanism, a series of spectroscopic investigations and control experiments were conducted. First, no desired products were detected when the radical scavenger TEMPO (2.5 equiv) was added to the thiocarboxylation or *gem*-difluoroolefination reaction. The radical nature of this type of reaction was further confirmed by the formation of TEMPO−SPh and TEMPO−CF₃ adducts, which were detected by the HRMS (Scheme 2A and the SI). Based on our results and literature reports about the radical functionalization of *N*-sulfonylhydrazones,[17] we postulate that the sulfur-centered radical and CF₃ radical follow a similar mechanism to react with *N*-tosylhydrazones to give the carbanions. We chose the thiocarboxylation reaction as a model reaction to study the mechanism more closely.

A control experiment using sodium thiophenolate in place of the corresponding thiophenol **2a** yielded the desired carboxylic acid **3a** in 73% yield. Moreover, we found that the product could be generated in 50% yield with sodium thiophenolate even in the absence of Cs_2CO_3, suggesting that the base (Cs_2CO_3) merely serves to deprotonate the thiols (Scheme 2B). The Stern−Volmer luminescence quenching experiments revealed that sodium thiophenolate quenches the excited state of the photocatalyst much more efficiently than *N*-tosylhydrazone **1a** and thiophenol **2a** (see the SI, Figures S8−S11). Light "on−off" experiments indicated that continuous light irradiation was essential for the reaction to proceed (see the SI). Additionally, the quantum yield of this transformation was determined to be 2.1%. Hence, a radical chain process is unlikely for this reaction. The combined results suggest a transient sulfur-centered radical, generated by single-electron oxidation of thiophenolate by the excited state of photocatalyst in a reductive quenching photocatalytic cycle.

Further control experiments showed that (4-methylbenzyl)-(phenyl)sulfide could be obtained in 69% yield in the absence of CO_2 (Scheme 2C). This finding suggests that the sulfur-

Scheme 2. Mechanistic Studies
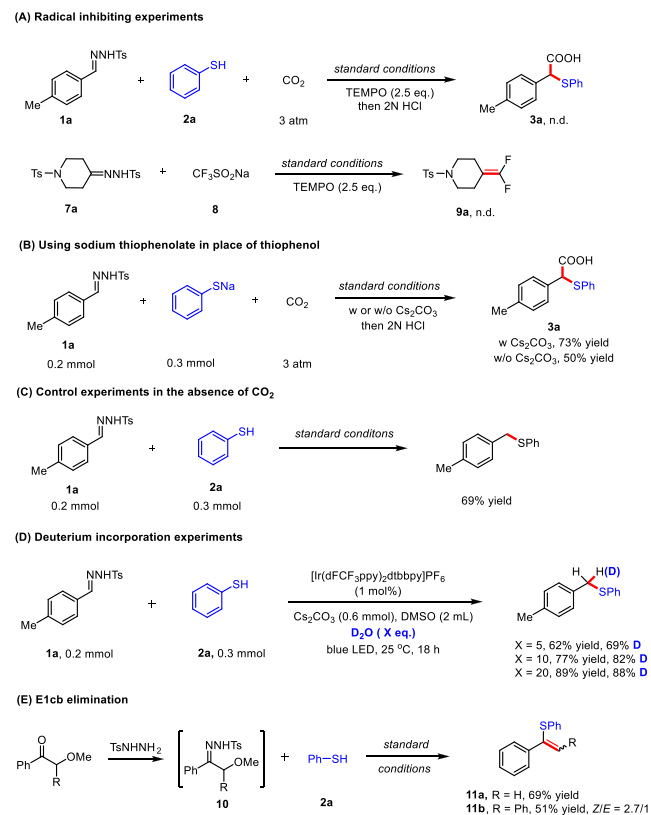
centered radical could interact with *N*-tosylhydrazone **1a** irrespective of the existence of CO_2. The result is in accordance with the hypothesis that a transient *α*-sulfenyl carbanion might occur in the reaction process. On this basis, we conducted isotope-labeling experiments. Indeed, when D_2O was added in the absence of CO_2, up to 88% deuterium incorporation into sulfide was observed (Scheme 2D). In addition, a carbanion intermediate should in principle undergo E1cB elimination when the adjacent carbon atom bears an appropriate leaving group.[41] Therefore, *N*-tosylhydrazones bearing a methoxyl group at the vicinal carbon were prepared and subjected to the standard reaction conditions in the absence of CO_2 giving the corresponding alkenes **11a** and **11b** in good yields (Scheme 2E).

Based on the above experimental evidence and mechanistic pathways reported in the literature, we propose a plausible mechanism as depicted in Scheme 3 for the reported photocatalytic generation of functionalized carbanions. Initially, the photoexcited state of $[Ir^{III}(dFCF_3ppy)_2dtbbpy]^+$ ($E_{1/2}[*Ir^{III}/^{II}]$ = +1.21 V vs SCE)[42] is reductively quenched by sodium triflinate (E_{ox} = +1.05 V vs SCE)[22a] or thiophenolate (E_{ox} = ∼0.75 V vs SCE),[43] formed through the deprotonation of thiophenol by base, affording a sulfur-centered radical and a CF₃ radical, respectively. Subsequent radical addition to the C=N bond of *N*-tosylhydrazone generates the aminyl radical species **A**.[44] Fragmentation of the arenesulfonyl radical from intermediate **A** leads to a functionalized diazene intermediate **B**,[18] and the following Wolff−Kishner type N₂ extrusion process proceeds to give *α*-CF₃ or sulfur carbanion **C** for further reactions. In the case of the *α*-sulfenyl carbanion, subsequent nucleophilic attack to CO_2 or aliphatic aldehydes give carboxylic acids or alcohols. When *α*-CF₃ carbanions were produced, *β*-fluoride elimination

Scheme 3. Proposed Mechanism of the Photo-Wolff–Kishner Carbanion Generation
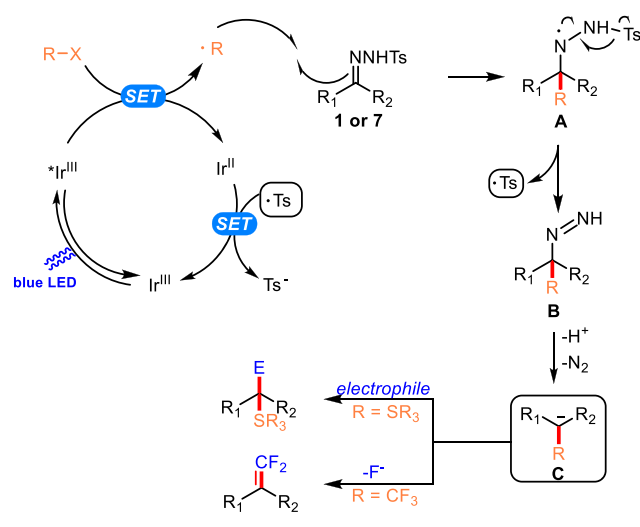
occurred to furnish the *gem*-difluoroalkenes. Finally, single-electron transfer (SET) from the reduced photoredox catalyst Ir^{II} ($E_{1/2}[\text{Ir}_{\text{III}/\text{II}}]$ = −1.37 V vs SCE)[42] to the arenesulfonyl radical (E_{red} = +0.50 V vs SCE)[24b] yields a sulfinate anion and regenerates the photocatalyst.

3. CONCLUSION

In summary, we have established a new reaction sequence for the generation of α-functionalized alkyl carbanions through the merger of photoredox catalytic radical generation with the classic Wolff–Kishner (WK) reaction. This radical-carbanion relay for carbonyl functionalization involves the radical addition to *N*-sulfonylhydrazones, which enables the formation of α-substituted carbanion intermediates. Subsequent reaction with electrophiles including CO_2 and aldehydes or fragmentation results in thiocarboxylation, thiohydroxyalkylation, and *gem*-difluoroolefination with broad substrate scope and good tolerance of many functional groups. Mechanistic studies support the hypothesis that a tandem photocatalytic radical addition/Wolff–Kishner process starting from *N*-sulfonylhydrazones facilitates the formation of the carbanion. This strategy greatly expands the synthetic potential of Wolff–Kishner reaction. Further studies aiming to generate non-stabilized carbanions by this strategy are currently under investigation.

ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.0c00629.

Experiments and spectral details for all new compounds and all reactions reported (PDF)

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Notes

The authors declare no competing financial interest.

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