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

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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 chemistry2 and catalytic N-heterocyclic carbene (NHC) chemistry.3 Synthetically important alkyl carbanion intermediates can be obtained from carbonyl groups using the Wolf–Kishner (WK) reduction. The polarity inversion is accomplished by sequential hydrazone formation, tautomerization, and N₂-extrusion to generate a nucleophilic allylic carbanionic species (Scheme 1A). With elegant modifications from Huang Minlon4 and others,5 the WK process has evolved over the past century into a powerful carbonyl deoxygenation reaction with electrophiles including CO₂ and aldehydes, whereas CF₃ radical addition furnishes a wide range of gem-difluoroalkenes through β-fluoride elimination of the generated α-CF₃ 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.

Heck-type coupling,12 Tsuji-Trost alkylation,13 and olefination reactions14 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 nucelophilic 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 carbonyls from carbons,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-sulfonylhydrazones,7 thus installing the first functional group. Subsequently, the diazene intermediate, resulting from radical fragmentation,17 enters a similar reaction sequence as involved in the WK reduction to give functionalized derivative.

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Scheme 1. Umpolung Generation of Alkyl Carbanions from Carboxylic Acids

2. RESULTS AND DISCUSSION

2.1. Generation of α-Sulfonyl 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. 18 We postulate that photogenerated thyl radicals 20 can undergo β-deprotonation of sulfides with strong bases such as BuLi and NaNH2. 21 Building on the facile carbanion trapping by CO2 22 and our continued interest in utilization of CO2 as the C1 feedstock for photocatalytic carboxylation reactions, 22,23 we selected N-tosylhydrazone as the radical acceptor in the anticipated sequence based on the following considerations: (1) they can be easily prepared from various thiols; (2) after radical addition to carbonyl compounds with sulfonyl radical which should undergo single-electron transfer with the photocatalyst. 17,24 We commenced our study by utilizing aldehyde hydrazone 1a, thiophenol 2a, and CO2 as model substrates for the optimization of the reaction conditions.

Table 1. Screening of Reaction Conditions for Thiocarboxylation of N-Tosylhydrazone

| entry | change from standard conditions | yield (%) |
|-------|---------------------------------|-----------|
| 1     | none                            | 81%       |
| 2     | one-pot process                  | 80%       |
| 3     | MeCN instead of DMSO             | n.d.      |
| 4     | THF instead of DMSO              | n.d.      |
| 5     | 4CzIPN instead of Ir–F            | n.d.      |
| 6     | without Cs2CO3                    | n.d.      |
| 7     | without PC                       | n.d.      |
| 8     | in the dark                      | n.d.      |

*Yields were determined by 1H NMR analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene as the internal standard. 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. 1r–F = [Ir(dFCF3ppy)2dtbbpy]PF6; 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, 3i, 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-tosylhydrazine derived from 4-.
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-sulfenly 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-thiophenol 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

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**Table 2. Scope of N-Tosylhydrazones for Thiocarboxylation**

| R1 | R2 | R3 | Isolated Yield (%) |
|----|----|----|--------------------|
| 3a | 3a | 3a | 43%                |
| 3b | 3b | 3b | 58%                |
| 3c | 3c | 3c | 57%                |
| 3d | 3d | 3d | 45%                |
| 3e | 3e | 3e | 36%                |
| 3f | 3f | 3f | 59%                |
| 3g | 3g | 3g | 62%                |
| 3h | 3h | 3h | 63%                |
| 3i | 3i | 3i | 65%                |
| 3j | 3j | 3j | 66%                |
| 3k | 3k | 3k | 67%                |
| 3l | 3l | 3l | 68%                |
| 3m | 3m | 3m | 69%                |
| 3n | 3n | 3n | 70%                |
| 3o | 3o | 3o | 71%                |
| 3p | 3p | 3p | 72%                |
| 3q | 3q | 3q | 73%                |
| 3r | 3r | 3r | 74%                |
| 3s | 3s | 3s | 75%                |
| 3t | 3t | 3t | 76%                |
| 3u | 3u | 3u | 77%                |
| 3v | 3v | 3v | 78%                |

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**Table 3. Scope of the Thiols for Thiocarboxylation**

| R1 | R2 | R3 | Isolated Yield (%) |
|----|----|----|--------------------|
| 4a | 4a | 4a | 75%                |
| 4b | 4b | 4b | 50%                |
| 4c | 4c | 4c | 57%                |
| 4d | 4d | 4d | 55%                |
| 4e | 4e | 4e | 77%                |
| 4f | 4f | 4f | 71%                |
| 4g | 4g | 4g | 60%                |
| 4h | 4h | 4h | 65%                |
| 4i | 4i | 4i | 60%                |
| 4j | 4j | 4j | 60%                |
| 4k | 4k | 4k | 65%                |
| 4l | 4l | 4l | 65%                |
| 4m | 4m | 4m | 60%                |
| 4n | 4n | 4n | 60%                |
| 4o | 4o | 4o | 60%                |
| 4p | 4p | 4p | 60%                |
| 4q | 4q | 4q | 60%                |
| 4r | 4r | 4r | 60%                |
| 4s | 4s | 4s | 60%                |
| 4t | 4t | 4t | 60%                |
| 4u | 4u | 4u | 60%                |
| 4v | 4v | 4v | 60%                |

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**Table 4. Scope of the Aldehydes for Thiohydroxyalkylation**

| R1 | R2 | R3 | Isolated Yield (%) |
|----|----|----|--------------------|
| 6a | 6a | 6a | 78%                |
| 6b | 6b | 6b | 78%                |
| 6c | 6c | 6c | 66%                |
| 6d | 6d | 6d | 56%                |
| 6e | 6e | 6e | 62%                |
| 6f | 6f | 6f | 59%                |
| 6g | 6g | 6g | 60%                |
| 6h | 6h | 6h | 60%                |
| 6i | 6i | 6i | 60%                |
| 6j | 6j | 6j | 60%                |
| 6k | 6k | 6k | 60%                |
| 6l | 6l | 6l | 60%                |
| 6m | 6m | 6m | 60%                |
| 6n | 6n | 6n | 60%                |
| 6o | 6o | 6o | 60%                |
| 6p | 6p | 6p | 60%                |
| 6q | 6q | 6q | 60%                |
| 6r | 6r | 6r | 60%                |
| 6s | 6s | 6s | 60%                |
| 6t | 6t | 6t | 60%                |
| 6u | 6u | 6u | 60%                |
| 6v | 6v | 6v | 60%                |

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"Reaction conditions: unless otherwise noted, all reactions were carried out with 1 (0.2 mmol), 2a (0.3 mmol), Cs2CO3 (0.6 mmol), [Ir(dFCF3ppy)2dtbbpy]PF6 (1 mol %), and 3 atm of CO2 in 2 mL of DMSO, irradiation with blue LED (455 nm) at 25 °C for 24 h, and isolated yields were shown. 6 mmol scale, CO2 was bubbled into the reaction continuously. Reaction was conducted at 0 °C in DMF (2 mL)."
aldehydes, aliphatic aldehydes bearing short or long chains were suitable electrophiles in our system, giving the desired products in moderate yields (6g–6o). 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.

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. An important privileged fluorocontaining group is the gem-difluoroethylene moiety based on their unique property in medicinal chemistry. Moreover, gem-difluoroalkenes are versatile building blocks for the synthesis of other fluorine-containing molecules. Traditional methods such as Wittig and Julia reactions for the synthesis of 1,1-difluoroalkenes generally suffer from limited scope, modest efficiency, or harsh conditions. Another efficient pathway is the gem-difluorination of diazo compounds under metal catalytic or metal-free reaction conditions. This strategy is generally restricted to aromatic diazo compounds or diazo esters. Recently, several elegant defluorination strategies starting from α-trifluormethyl alkenes based on metal catalysis or photoredox catalysis have been developed for the synthesis of gem-difluoroalkenes. Nevertheless, this route requires the presence of trifluormethyl groups on the alkene moieties, and the product scope is limited by the accessibility of such trifluormethylated alkenes.

Following the proposal shown in Scheme 1C and encouraged by the success in the generation of α-sulfonyl 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. We used sodium trifluoracetate (Langlois reagent, CF3SO2Na), a bench-stable and commercially available trifluormethylthiation reagent, as the CF3 radical precursor and N-tosylhydrazone 7a as the model substrate. 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/acetonitrile = 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 trifluoracetate with cycloketone-derived N-tosylhydrazones led to the corresponding products 9a–9e in 75–87% yield. The yield further increased in the case of electron-rich substrates when the reaction was carried out with 10% light intensity and a longer UV light source (9f).

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38−73% yields. Interestingly, a strained substrate like azetidinone-derivatized N-tosylhydrazone could be successfully functionalized yielding difluoroalkane 9e in modest yield.46 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 phenylacetonitrile, 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-difluoroalkane. 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 

Scheme 2. Mechanistic Studies

(A) Radical inhibiting experiments

(B) Using sodium thiophenolate in place of thiophenolate

(C) Control experiments in the absence of CO2

(D) Decarboxylation incorporation experiments

(E) E1cb elimination

centered radical could interact with N-tosylhydrazone 1a irrespective of the existence of CO2. The result is in accordance with the hypothesis that a transient α-sulfonyl carbanion might occur in the reaction process. On this basis, we conducted isotope-labeling experiments. Indeed, when D2O was added in the absence of CO2 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.44 Therefore, N-tosylhydrazones bearing a methoxyl group at the vicinal carbon were prepared and subjected to the standard reaction conditions in the absence of CO2 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 [IrIII(dFCF3ppy)2dtbbpy]+ (E1/2 [4IrII/I+/] = +1.21 V vs SCE)42 is reductively quenched by sodium trflate (Eox = +1.05 V vs SCE)22a or thiophenolate (Eox = +0.75 V vs SCE),33 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-tosylhydrazine generates the aminal radical species A.44 Fragmentation of the arenosulfonyl radical from intermediate A leads to a function-alized 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-sulfonyl carbanion, subsequent nucleophilic attack to CO2 or aliphatic aldehydes give carboxylic acids or alcohols. When α-CF3 carbanions were produced, β-fluoride elimination...
occurred to furnish the gem-difluoroalkenes. Finally, single-electron transfer (SET) from the reduced photoredox catalyst IrII (E_{1/2}[IrIII/I] = -1.37 V vs SCE)24b to the aresenousyl radical (E_{red} = +0.50 V vs SCE)35 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 reaction 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 CO₂ and aldehydes or fragmentation results in thio carbocarboxylation, thiohydroxalkylation, 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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