Acyl Azolium-Photoredox Enabled Synthesis of β-Keto Sulfides

Michael J. Rourke, Charles T. Wang, Cullen R. Schull, Karl A. Scheidt*

Department of Chemistry, Northwestern University, 2145 Sheridan Road, Evanston, IL 60208 (USA)

azolium, sulfur containing compound, sulfide, photocatalysis, Pummerer, metal-free, thioether

ABSTRACT: α-Heteroatom functionalization is a key strategy for C–C bond formation in organic synthesis, as exemplified by the addition of a nucleophile to electrophilic functional groups such as iminium ions, oxocarbenium ions and their sulfur analogs, sulfenium ions. We envisioned a photoredox-enabled radical Pummerer-type reaction realized through the single-electron oxidation of a sulfide. Following this oxidative event, α-deprotonation affords α-thioradicals that participate in radical-radical coupling reactions with azolium-bound ketyl radicals, accessing a commonly proposed mechanistic intermediate en route to functionalized additive Pummerer products. This system provides a new and complementary synthetic approach to highly functionalized sulfurous products and beckons further exploration in C-C bond formations previously limited in the standard two-electron process.

The Pummerer reaction and its modifications have had significant utility in organic synthesis since their discovery.[1] These reactions transform a sulfoxide bearing an α-proton into a substituted sulfide via a sulfenium intermediate.[2] The general approach involves oxidation of a sulfide followed by electrophilic activation of the resultant sulfoxide for elimination into a sulfenium species (**Figure 1A**). These electrophilic sulfenium ions are known to accept a range of soft nucleophiles in both intra- and intermolecular addition reactions to form carbon-carbon or carbon-hetero atom bonds. These nucleophiles include enolate equivalents,[3] enol silanes,[4] ene-donors,[5] silanes,[6] electron rich arenes,[7] and turbo Grignards.[8] Traditional syntheses of these β-keto sulfides include the reaction of mercaptans with alpha-halo ketones or sulfenyl halides with enolates.[9] An alternate route could employ umpolung reactivity i.e. polarity inversion to access an acyl anion equivalent as a carbon-based nucleophile for addition into the sulfenium (**Fig. 1B**). However, this approach remains unreported to the best of our knowledge. In this work, we present an intermolecular radical coupling approach to this umpolung bond formation utilizing acyl and sulfenium radical equivalents (**Fig. 1C**).

Recently, the rapidly expanding field of single-electron chemistry has offered new applications of oxidized sulfides. In 2020, a photoredox/Brønsted base dual catalytic system was reported by Hande.[10] This method employs a photocatalyst to oxidize a sulfide to the corresponding sulfur radical cation, which is then deprotonated at the α-carbon. The resulting carbon-centered α-thio radical has been employed in conjugate addition reactions. More recently, this α-C(sp3)–H activation strategy has been employed in heteroarylation and radical coupling with isatins.[11] Previous methods of α-thio radical generation include C–H abstraction, single electron oxidation and heterolytic cleavage of silyl, trifluoroborate, or carboxyl leaving groups.[12] Inspired by this novel means of generating α-thio radicals, we envisioned a new variant of the Pummerer reaction wherein single-electron oxidation of a sulfide affords a radical sulfenium, which subsequently undergoes α-deprotonation and radical-radical coupling to afford functionalized

products. Towards this end, we present the radical-radical coupling of α-thio radicals utilizing bench stable acyl azolium reagents as acyl radical equivalents and photoredox catalysis (**Fig. 1D**).
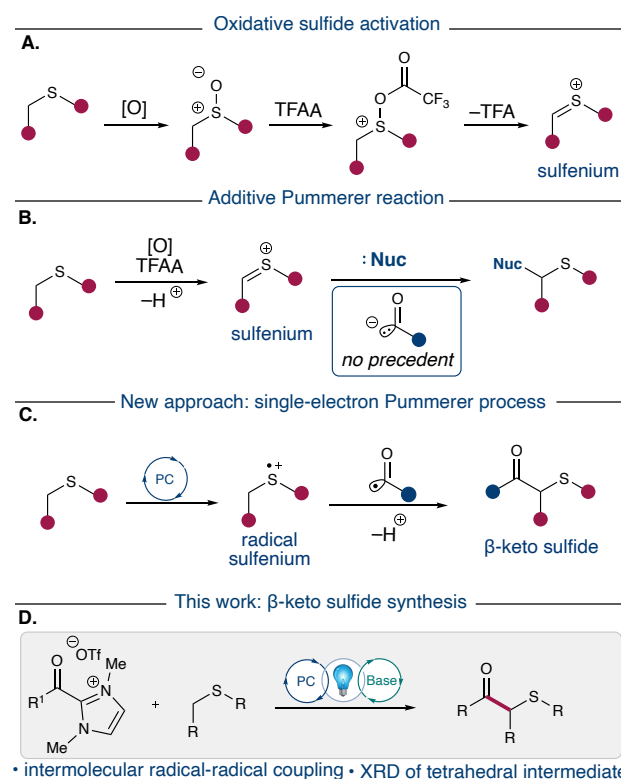
Figure 1: Reaction Plan Overview

N-heterocyclic carbenes, NHCs, are common acyl transfer catalysts in biological systems and have been employed in organocatalysis as umpolung operators to generate acyl anion equivalents.[13] Our group initially reported the redox activity of the Breslow intermediate, an NHC-aldehyde adduct. This MnO₂ enabled oxidation results in an

acyl azolium. Facile displacement of the azolium by alcohols affords the ester product.[14] Following this report, organic, catalytic transition metals, and electrochemical oxidants have been employed in the tandem oxidation process.[15] A recent development, the single-electron transformation of these NHC-acyl adducts, proceed through oxidation of the strongly reducing Breslow intermediate or reduction of an electron-deficient acyl azolium to afford ketyl radicals.[16] In 2019, Ohmiya and coworkers reported the coupling of Breslow intermediate-derived ketyl- and carbon-centered radicals in the NHC-catalyzed decarboxylative alkylation of aldehydes.[17] Our growing interest in SET via photoredox catalysis motivated the development of a complementary radical–radical coupling of a reductively generated azolium radical intermediate.[18] This unique approach involves a photocatalytic single-electron reduction of acyl azoliums to access a ketyl radical for application in radical–radical coupling reactions and later the adaptation to conjugate addition methods.[19] A unique aspect of these zwitterionic ketyl intermediates is presumably the advantageous delocalization into the aromatic azolium structure. These stabilized captodative radicals are more persistent relative to traditional acyl radicals, thus facilitating cross-coupling with transient radical coupling partners.[16h, 20]

The potential merger of an acyl azolium-photoredox system in the single-electron Pummerer process enables the synthesis of β-Keto Sulfides **3a-ab**. Thioethers in combination with the higher oxidation states S(II) (sulfoxides) and S(IV) (sulfones, sulfoximines and others) are structurally integral to pharmaceuticals, natural products, materials, and agrochemicals.[21] This system offers the coupling of alpha heteroatom carbon centered radicals with azolium-derived ketyl radicals, as well as structural confirmation of a commonly proposed mechanistic intermediate **4d**.

Our rational approach to develop a set of generalized conditions was guided by a broad screen of acyl azolium species and various reaction conditions (**Table 1**). Variables considered for optimization included acyl azoliums, sulfides, Brønsted bases, photocatalyst and solvent. As part of this work, various isolated azoliums recently developed for cross-coupling were evaluated in the reaction with thioanisole. Interestingly, while the electron rich thiazoliums (**Az-7** and **Az-8**) and the highly conjugated benzimidazoliums (**Az-5** to **6**) all failed to yield the product **3x**, the imidazolium **Az-1** was the only species that resulted in isolable product in the qualitative LC-MS screen. Also, the triflate **Az-4** provided a mass corresponding to trace product. This stands in contrast to previous work reported with **Az-3** and **Az-6** and suggests that iodide is incompatible with benzyl and aryl sulfide substrates under photocatalytic conditions or that the triflate may participate in the reaction.[19a] Further development utilized **Az-1** as the standard azolium, screening 13 photocatalysts, 6 Brønsted bases, 6 Lewis acids (figure SI). Review of preliminary screening established photocatalyst, **4CzIPN**, and a weak base, NaCO₂CF₃, as the optimal platform. Furthermore, Lewis acids were determined to be deleterious. In our initial foray into this chemistry, GC-MS yields surprisingly failed to translate to isolated yields. Further investigations by LC-MS analysis revealed a mass corresponding to two potential intermediates. We hypothesized that heating transformed the intermediates to the desired ketone product during analysis. Thus, we performed a brief screen of workup conditions following the photochemical reaction and determined that a DBU base led to disappearance of one intermediate (**see 4d**) and comparable yields to the high throughput GC-MS screen.

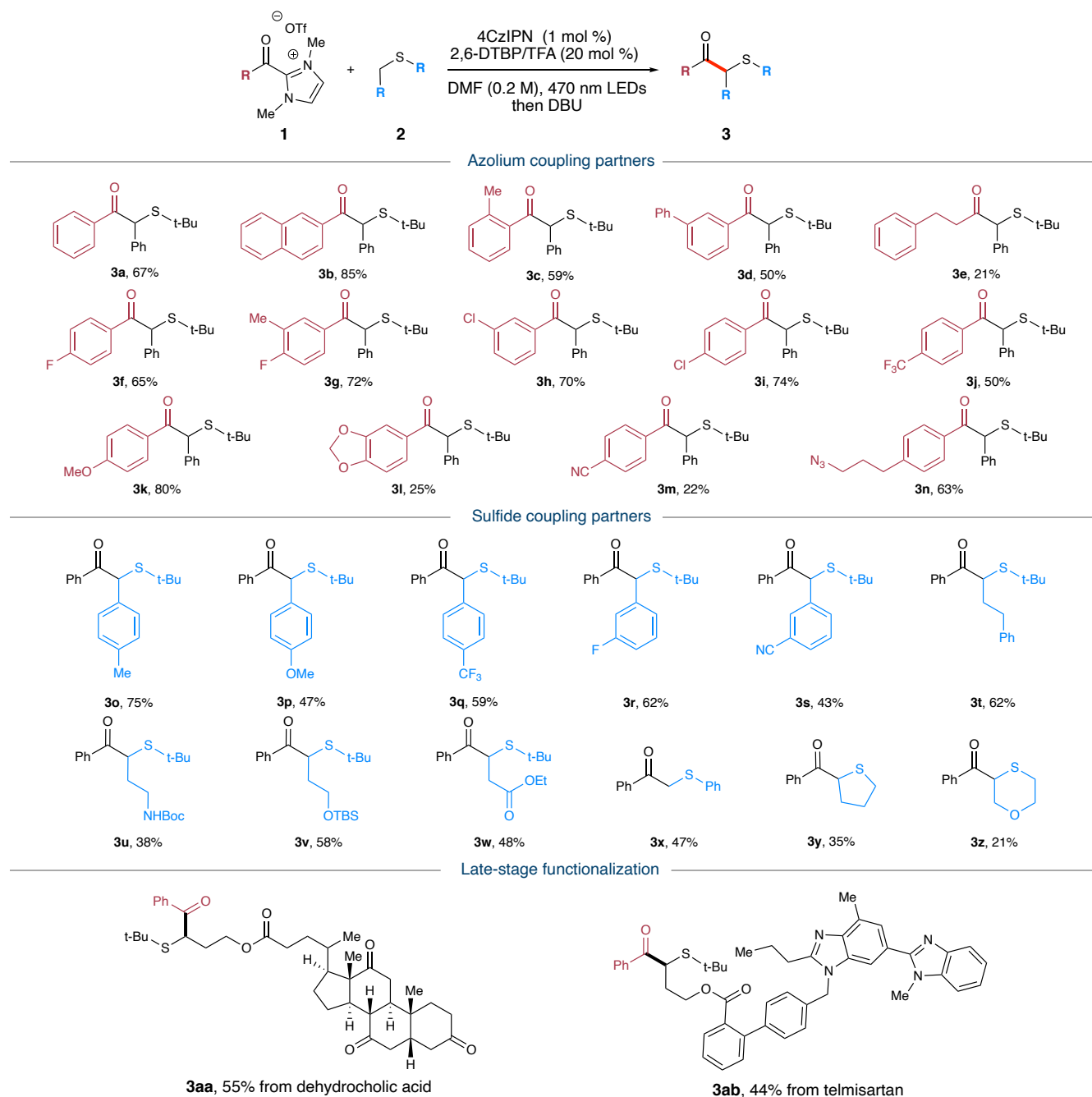**Table 1. Optimization of Reaction Conditions**

entry	deviation from standard	yield (%)
1	none	63
2	DCM instead of DMF	47
3	NaCO₂CF₃, DCM	37
4	NaCO₂CF₃,DCM, sulfide (1 equiv)	28
5	No TFA	47
6	No 2,6-Di-*tert*-butylpyridine	49
7	No 2,6-Di-*tert*-butylpyridine/TFA	32
8	No 4CzIPN	6
9	no light	0

Az-1, X = OTf   **Az-4**, X = OTf   **Az-7**   **Az-8**
Az-2, X= BF₄   **Az-5**, X= BF₄
Az-3, X= I   **Az-6**, X= I

Formal optimization of the reaction was performed with azolium **1a** and the sulfide **2a** to afford the coupled product **3a.** When the reaction was conducted with NaCO₂CF₃ a yield of 28% was observed (**Table 1, entry 4**). This improved further by increasing the equivalency of the sulfide **2a,** which achieved a 37% yield (**Table 1, entry 3**). However, undesirable byproducts persisted in the reaction mixture. The selection of base proved crucial to the success of this radical coupling process. For example, the absence of Brønsted base results in a 32% yield (**Table 1, entry 6**), illustrating its key role in generating the α-thio alkyl radical **4b** for the overall transformation. Previous KIE studies by Hande suggested that deprotonation is the rate-limiting step in the formation of the α-thio alkyl radical.[11a] Informed by this work, we hypothesized that a fully soluble Brønsted base would increase the rate of α-thioalkyl radical generation and through a proton shuttle and mitigate the formation of the undesired azolium side products. Thus, substituting NaCO₂CF₃ for TFA in combination with 2,6-di-*tert*-butylpyridine enabled *in-situ* generation of the weak base trifluoroacetate (**Table 1, entry 2**) providing a 47% yield. A brief solvent screen indeed demonstrated preference for high dielectric solvents: using DMF instead of DCM (**Table 1, entry 1**) resulting in intermediate **4d** that was transformed to the product **3a** in a satisfactory yield of 63%. Independent yields for TFA (**Table 1, entry 4**) or 2,6-di-*tert*-butylpyridine (**Table 1, entry 5**) were 46% and 49%, respectively.

With these optimized conditions, we conducted a survey of the scope of acyl azoliums amenable to radical-radical cross coupling. A range of both electron-withdrawing and electron-donating aromatic substituents were tolerated on the acyl subunit of the dimethyl imidazolium. Napthyl ketone **3b** was isolated in high yield, suggesting the importance of additional resonance stabilization in radical persistence. Sterically encumbered substrate **3c** and the biphenyl substrate **3d** also achieved good yields. Gratifyingly, the aliphatic substrate **3e** could be obtained in 21% yield, despite the challenge posed by aliphatic substrates in similar past work.[16g, 19b, 19f] Halogenated *meta*- and *para*-substituted acyl azoliums gave product in good yields, with **3f-j**. Electron rich alkoxy-substituted substrate **3k** demonstrated a slower rate of reaction but ultimately a higher overall yield after 120 h. The strongly electron donating 3,4-methylenedioxy substrate **3l** proceeded very slowly, stalling at a 25% overall yield. Also, the nitrile **3m** was successfully isolated albeit in

reduced yields. Additionally, an azido functionalized product **3n** was prepared in moderate yield offering a functional handle for application in click reactions.

Table 2: β-Keto Sulfide Scope

3a, 67%   **3b**, 85%   **3c**, 59%   **3d**, 50%   **3e**, 21%

3f, 65%   **3g**, 72%   **3h**, 70%   **3i**, 74%   **3j**, 50%

3k, 80%   **3l**, 25%   **3m**, 22%   **3n**, 63%

Sulfide coupling partners

3o, 75%   **3p**, 47%   **3q**, 59%   **3r**, 62%   **3s**, 43%   **3t**, 62%

3u, 38%   **3v**, 58%   **3w**, 48%   **3x**, 47%   **3y**, 35%   **3z**, 21%

Late-stage functionalization

3aa, 55% from dehydrocholic acid

3ab, 44% from telmisartan

A variety of benzylic sulfides were initially examined to investigate the alkyl sulfide scope in the coupling reaction. A methyl substituted sulfide was well tolerated, providing product **3o** with improved yields. However, stronger electron donating groups such as methoxy led to moderate yields (see ketone **3p**). Electron withdrawing substituents at the meta and para positions provided ketones **3q** and **3r** in yields consistent with the unsubstituted benzyl *tert*-butyl sulfide. Product **3s** bearing a meta-substituted nitrile was accessed in moderate yield, offering a functional handle for further diversification. In general, secondary sulfides with a variety of functional groups performed well in the reaction. Ketones derived

from an alkyl sulfide **3t**, carbamate protected amine **3u**, silyl protected alcohol **3v**, and ethyl ester **3w** were isolated in moderate yields. Additionally, coupling of the arene-stabilized sulfide thioanisole to yield product **3x** proceeded under these conditions. Products **3y** and **3z** containing sulfur heterocycles were isolated in reduced yields. Late-stage functionalization was performed on esterified derivatives of the pharmaceutical drugs dehydrocholic acid and telmisartan to afford **3aa** and **3ab**.

In line with our optimization, we present a mechanism dependent on the photocatalyst **4CzIPN**, $((E1/2 (PC/PC\bullet-) = -1.24$ V; E1/2

(PC*/PC•−) = +1.43 V vs SCE).[22] The significant improvement over the 6% yield in the absence of a photocatalyst (**Table 1, entry 6**) and dependence on light (**Table 1, entry 7**), led us to propose that upon excitation by visible light, the photocatalyst **4CzIPN*** oxidizes sulfide **1b** to generate the sulfur-centered radical cation **4a** and reduced photocatalyst **4CzIPN⁻** (**Table 3**). The radical cation **4a** is then deprotonated by trifluoroacetate at the α-position to afford the α-thioalkyl radical **4b**. Concurrently, the reduced photocatalyst is able to reduce an acyl azolium **1a** through SET (single-electron transfer) to access the π-stabilized azolium radical intermediate **4c**, a persistent ketyl radical species.[23]

Table 3: Proposed Mechanism of Radical-Radical Coupling
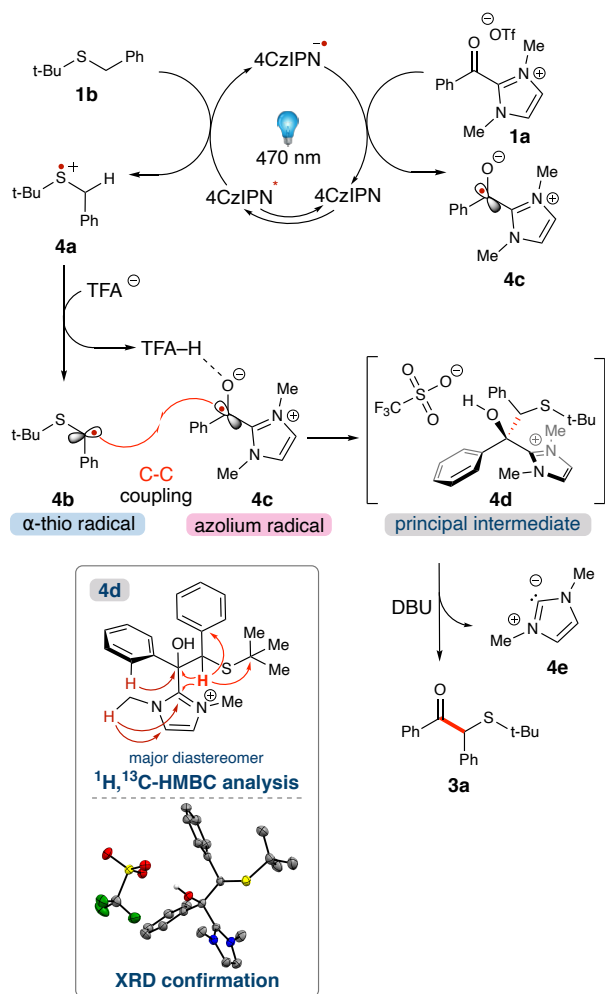
We propose that the radical-radical cross-coupling between the α-thio alkyl radical **4b** and the azolium radical **4c** proceeds via mechanism consistent with previously-reported DFT calculations.[19c, 24] The resulting product of the coupling under the mildly acidic reaction conditions results in a tetrahedral tertiary alcohol intermediate **4d** that was characterized by single-crystal X-ray diffraction. This principal intermediate was transformed to the product in the presence of DBU, liberating the neutral azolium **4e** and the desired β-keto sulfide product **3a**.

We also sought to apply our methodology to the functionalization of the amino acid methionine and related tripeptides in **Table 4**. A limited number of methods have reported site-selective modification at methionine via sulfonium and sulfinimine

intermediates.[39–41] The continued development of direct bioconjugation methods targeting methionine residues could have significant utility in chemistry and the biological sciences.[25] Motivated by these opportunities, MacMillan and other groups have applied photocatalytic α-thioalkyl radical generation to methionine in Giese-type coupling reactions, but have not engaged the corresponding radicals in radical-radical coupling reactions.[26] We were able to acylate *N*-Boc-methyl methionate in 61% yield with 2:3 (**5a** : **5b**) regioselectivity. Building upon these results, tripeptides bearing a C-terminal and internal methionine residue were successfully functionalized, providing ketones **5c** and **5d** in 53% and 57% yields, respectively.
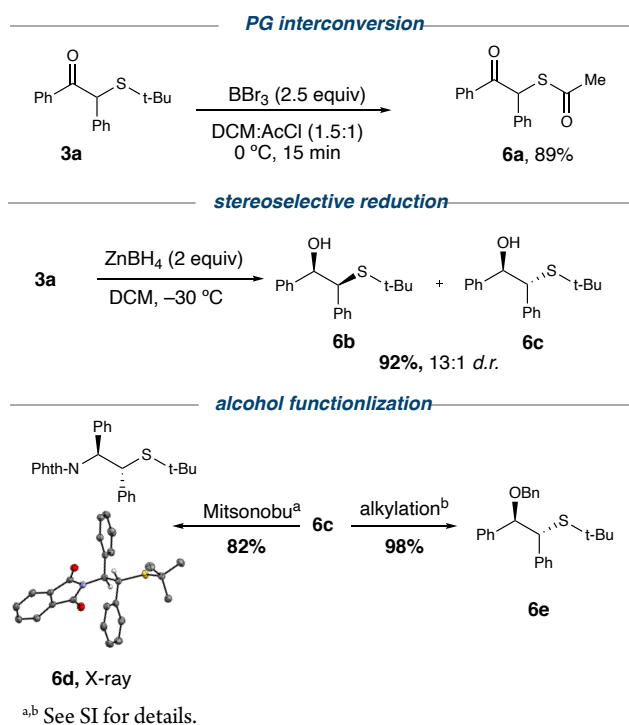
Table 4: Methionine Functionalization
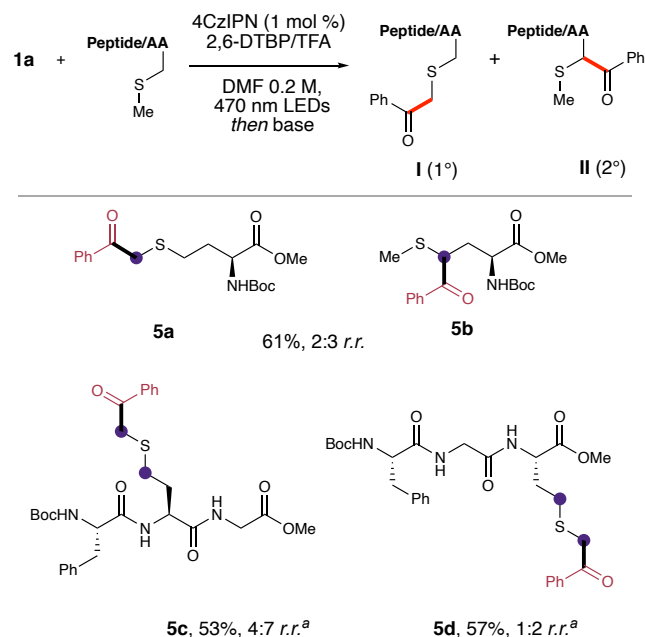
[a]Regioselectivity ratio (*r.r.*) reported as (1°:2°).

Substrates containing *tert*-butyl sulfide moieties avoid the complications of regioselectivity in this transformation and offer further utility through functional group interconversion. The *tert*-butyl sulfide undergoes a facile Lewis acid-mediated conversion to the thioester product **6a** in 89% yield. The thioester protecting group has been shown to provide the free thiol under mild conditions in the presence of various functional groups while mitigating oxidation to the undesired disulfides.[27] These β-keto sulfide products **3** are also useful precursors in the synthesis of a known class of ligands.[28] Towards this end, a zinc borohydride reduction of the standard substrate **3a** afforded the respective 1,2-thio alcohols **6b** and **6c** in 13:1 *d.r.* and excellent yield. The corresponding alcohol **6c** underwent further transformation to afford the phthalimide **6d** and the benzyl ester **6e**.

Scheme 1: Application of Standard Substrate

PG interconversion

3a + BBr₃ (2.5 equiv), DCM:AcCl (1.5:1), 0 °C, 15 min → **6a**, 89%

stereoselective reduction

3a + ZnBH₄ (2 equiv), DCM, –30 °C → **6b** + **6c**, 92%, 13:1 *d.r.*

alcohol functionlization

6c ← Mitsonobu[a], 82% — **6d**, X-ray — alkylation[b], 98% → **6e**

[a,b] See SI for details.

The work herein includes the development of a photoredox-catalyzed coupling of sulfides with acyl azoliums to synthesize β-keto sulfides. This advancement in single-electron acyl azolium chemistry offers a mild umpolung strategy for α-heteroatom functionalization. A principal characteristic is a persistent azolium bound ketyl radical that couples with a α-thio radical to access an isolable tetrahedral intermediate. This method enables access to a wide variety of β-keto sulfides with applications in small molecule synthesis, late-stage functionalization, and methionine conjugation. Ongoing investigations include the application of this technology to larger biomolecules in pursuit of an acyl azolium and photoredox-enabled bioconjugation platform.

ASSOCIATED CONTENT

SUPPORTING INFORMATION

The Supporting Information is available free of charge on the ACS Publications website.

Experimental details and characterization data, computational data, and crystallographic files (CCDC 2195732 (**4d**) and 2223444 (**6d**)).

AUTHOR INFORMATION

Corresponding Author

*Karl A. Scheidt – Department of Chemistry, Northwestern University, Evanston, Illinois 60208, United States; orcid.org/0000-0003-4856-3569; Email: scheidt@ northwestern.edu

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

ABBREVIATIONS

2,6-DTBP, 2,6-Di-tert-butylpyridine; 4CzIPN, 2,4,5,6-Tetrakis(9H-carbazol-9-yl) isophthalonitrile; SET, single-electron transfer; 1,8-Diazabicyclo(5.4.0)undec-7-ene
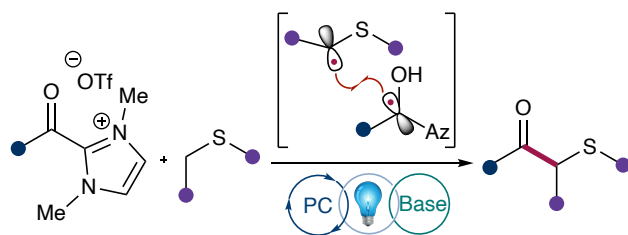
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- *umpolung reactivity*
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- *XRD mechanistic intermediate*