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# α-Heteroarylation of Thioethers via Photoredox and Weak Brønsted Base Catalysis

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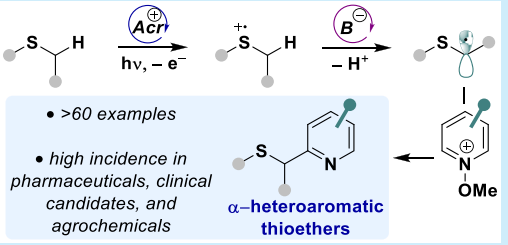
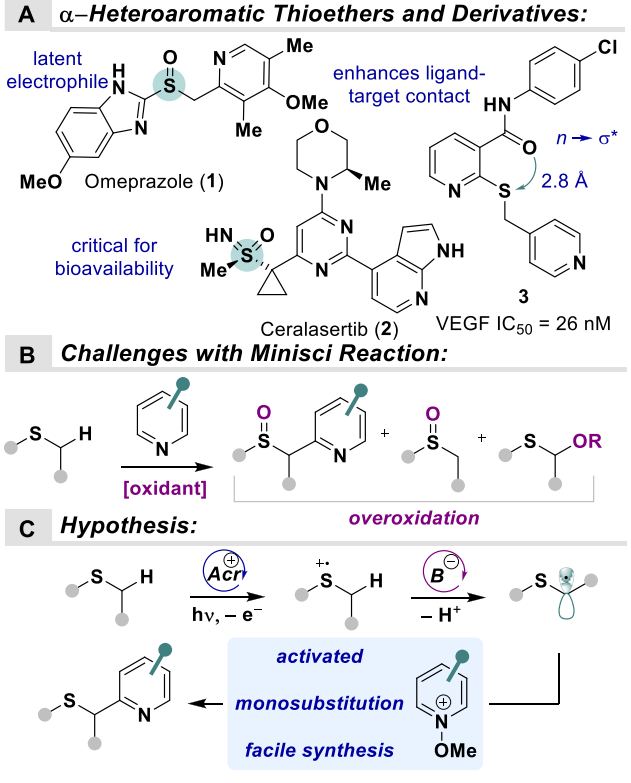
**ABSTRACT:** We report the C−H activation of thioethers to α-thio alkyl radicals and their addition to *N*-methoxyheteroarenium salts for the redox-neutral synthesis of α-heteroaromatic thioethers. Studies are consistent with a two-step activation mechanism, where oxidation of thioethers to sulfide radical cations by a photoredox catalyst is followed by α-C−H deprotonation by a weak Brønsted base catalyst to afford α-thio alkyl radicals. Further, *N*-methoxyheteroarenium salts play additional roles as a source of methoxyl radical that contributes to α-thio alkyl radical generation and a sacrificial oxidant that regenerates the photoredox catalytic cycle.






α-Heteroaromatic thioethers and their higher oxidation state congeners, typically derived from the former, are essential structures that confer function to pharmaceuticals, clinical candidates, and agrochemicals (Scheme 1A).[1,2] For instance, the sulfoxide in Omeprazole (**1**) serves as an electrophile for inhibition of gastric $H^+/K^+$-ATPase.[3] Ceralasertib (**2**), an ATR kinase inhibitor being investigated in clinical trials, has an α-heteroaromatic sulfoximine indispensable for bioavailability.[4] Compound **3** is a VEGF inhibitor leveraging an intramolecular chalcogen bond that improves ligand-target contact.[5] Despite their success and diversity of function, methods for the synthesis of these motifs are scant. Generally, entry to these has relied on displacement reactions, for example, with a thiolate and heterobenzylic electrophile. New reactions for the synthesis of α-heteroaromatic thioethers and their derivatives that can expand their accessible chemical space are desired.[6−8]

**Scheme 1. Strategy for α-Heteroarylation of Thioethers**




Given their availability and structural diversity, the Minisci reaction of thioethers is an attractive strategy for synthesizing α-heteroaromatic thioethers.[9] Hitherto, this reaction has been seldom documented and is limited to few examples.[10] This stands in stark contrast with recent developments in Minisci-type reactions, where the coupling of the isoelectronic amine and ether are much more well established.[11−17] The challenge in developing a Minisci reaction with thioethers lies in the redox activity of sulfur, making them labile to oxidation by the requisite oxidant needed in the reaction (Scheme 1B). We sought to overcome this by employing *N*-methoxyheteroarenium salts. Seminal work by Mitchell[18] and contemporary studies by Herzon,[19,20] Hong,[21−23] and Lakhdar[24,25] provide background into the capabilities and creative uses of these salts. Notably, these carry an added oxidation state, obviating the need for oxidants. Additionally, they are activated toward a single radical

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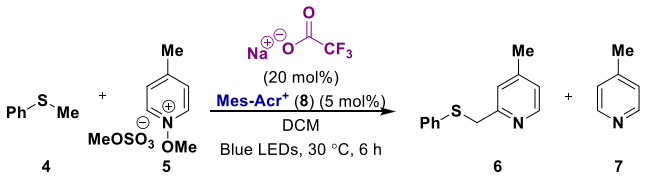
addition, precluding acid additives that limit scope and promote overalkylation. Studies by Strekowski on *N*-fluoropyridinium salts as heteroarylation reagents of sulfides provided further impetus to pursue the envisioned transformation.[26]

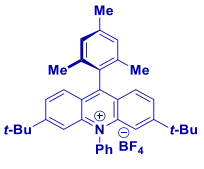
We recently established that thioethers can be activated toward $\alpha$-thio alkyl radicals via a two-step approach, where oxidation of thioethers to sulfide radical cations by a photoredox catalyst is followed by $\alpha$-C−H deprotonation by a weak Brønsted base catalyst.[27] Activating thioethers in this manner offers two advantages over previous strategies to generate $\alpha$-thio alkyl radicals: (1) site selectivity, compared to hydrogen atom transfer (HAT) methodologies in the cases where multiple hydridic C−H bonds are available,[28] and (2) entry to an abundant, yet underutilized, source of $\alpha$-thio alkyl radicals, which are more typically generated from thioethers comprising an $\alpha$-proradical group.[29−33] Here, we wed these two technologies, the dual catalytic generation of $\alpha$-thio alkyl radicals and *N*-methoxyheteroarenium salts in Minisci reactions, for the synthesis of $\alpha$-heteroaromatic thioethers (Scheme 1C).

Our studies began by evaluating thioanisole (**4**) ($E$ = +1.21 V vs SCE)[34] toward addition with 1-methoxy-4-methylpyridin-1-ium methyl sulfate (**5**) (Table 1). Similar to our previous

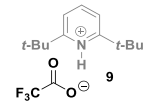
**Table 1. Control Reactions of Optimized Conditions**[a]



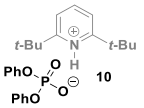

| entry | conditions | yield (%)[b] |
|---|---|---|
| 1 | as above | 66 (61) |
| 2 | weak Brønsted base **9** | 69 |
| 3 | weak Brønsted base **10** | 74 |
| 4[c] | no Mes-Acr$^+$ and $CF_3CO_2Na$ | 10 |
| 5[c] | no Mes-Acr$^+$ | 19 |
| 6[c] | no $CF_3CO_2Na$ | 49 |
| 7 | no degassing | 66 |
| 8 | no blue LEDs | 0 |




Mes-Acr$^+$ (**8**)
$E^*_{red}$ = +2.10 V vs. SCE




TFA (20 mol%)
2,6-Di-tert-butylpyridine
(20 mol%)




$(PhO)_2PO_2H$ (20 mol%)
2,6-Di-tert-butylpyridine
(20 mol%)

[a] **5** (0.5 mmol, 1 equiv), **4** (3 equiv), Mes-Acr$^+$ (5 mol %), $CF_3CO_2Na$ (20 mol %), DCM [0.2 M], blue LEDs, Ar, 30 °C. [b] $^1$H NMR yield. Yield in parentheses refer to isolated yield. [c] 24 h irradiation.

studies, an acridinium catalyst, **Mes-Acr**$^+$ (**8**) ($E^*_{red}$ = +2.10 V vs SCE in MeCN),[35] and a weak Brønsted base, sodium trifluoroacetate ($CF_3CO_2Na$), were found to cocatalyze the reaction and afford **6** in 61% isolated yield (entry 1). The remaining mass balance was attributed to 4-methylpyridine (**7**), presumed to arise through single electron transfer (SET) reduction of **5**. We posited that fully homogeneous weak Brønsted bases could increase the rate of deprotonation of sulfide radical cations and found these could be generated *in situ* from their corresponding acid and 2,6-di-*tert*-butylpyridine. Improved results were obtained using trifluoroacetate **9** and diphenyl phosphate **10** (entries 2 and 3). These conditions are relevant for scale-up procedures in flow,[36] which necessitate homogeneous conditions, but because $CF_3CO_2Na$ is inexpensive it was used to explore the scope of the reaction. Control studies showed a background reaction in the absence of **Mes-Acr**$^+$ and $CF_3CO_2Na$ (entries 4−6), though inefficient compared to the optimized conditions. This was attributed to an observed charge-transfer (CT) complex between **4** and **5** (Figure S3). The reaction is tolerant of ambient oxygen (entry 7), but we opted for degassed conditions as oxidation products were observed during prolonged irradiation. No reaction occurred in the absence of visible light (entry 8).

Pyridinium salts with substitution in the *ortho*, *meta*, and *para* positions were suitable for this reaction (Table 2A). These include methyl- (**6**), benzyloxy- (**11** and **23**), trifluoromethyl- (**12** and **24**), phenyl- (**13**), cyano-(**14**), chloro- (**15**), fluoro- (**16**), and alkyl- (**17**) substituted pyridines. Interestingly, the fluoro group in **16** appears to be *ortho*-activating the pyridinium salt, parallel to general trends of protonated pyridines.[37] Substituted quinolinium salts performed well, providing access to methoxy- (**18**), bromo- (**19**), and methyl- (**20**) substituted $\alpha$-quinoline thioethers. Pyridine (**25**), quinoline (**21**), and isoquinoline (**22**) products were also accessed. In general, when the C2 and C4 positions of *N*-methoxyheteroarenium salts are both available, C2 addition is favored in a 3:1 regioisomeric ratio (rr) or greater, except for **13**. The observed selectivity is consistent with the anticipated nucleophilicity of $\alpha$-thio alkyl radicals, which are known to add preferably to the more electrophilic C2 position.[9,12]

Aryl sulfides with substitution in the *ortho*, *meta*, and *para* positions reacted in good to excellent yields (Table 2B). These include cyano- (**26**), bromo- (**27** and **33**), chloro- (**34**), fluoro- (**28**), trifluoromethyl- (**29**), methyl- (**30**), methoxy- (**31** and **44**), acetamide- (**32**), ester- (**35**), 2-naphthyl- (**36**), and anilide- (**38**) substituted aryl sulfides. An $\alpha$-heteroaromatic sulfide containing orthogonal halogen groups (**37**) and a $\beta$-ketonitrile (**39**) were accessible using this method. Heterocycles, such as pyridine (**40** and **41**), 2-chloropyridine (**42**), and *N*-Boc-indole (**43**), were also tolerated. Secondary $\alpha$-thio alkyl radicals can be coupled to produce methyl- (**45** and **46**) and methanol- (**47**) branched $\alpha$-heteroaromatic thioethers. Cyclic sulfides reacted on average with good yields. These include five- (**48**) and six- (**50**) membered sulfides. Biotin **49** was functionalized with site selectivity, albeit affording a 1:1 diastereomeric ratio (dr). Substitution on tetrahydrothiopyran (THTP) at the four position was amenable, providing entry to ketone- (**51**), alcohol- (**52**), and methanol- (**53**) containing products. Saturated heterocycles possessing multiple heteroatoms (S, N, and O) afforded the desired product with site selectivity (**54**−**56**). In **55**, a trace amount of an undesired regioisomer was isolated, pertinent to the reaction mechanism. Lastly, aliphatic sulfides containing adamantyl- (**57**), *tert*-butyl- (**58**), ethyl- (**59**), cyclohexyl- (**60**), isopropyl- (**61**), and methyl- (**62**) substitution participated in the reaction. We observed no reaction with thioethers that could only generate tertiary $\alpha$-thio alkyl radicals, explaining the regioselectivity observed with **60** and **61**. To showcase further the use of this reaction, we engaged THTP in sequential C−H activation (Table 2C). Heteroarylation of THTP at C2 was followed by alkylation at C6, using our previously developed alkylation method, affording **63**. Additionally, we executed a two-step synthesis of potent VEGF inhibitor **3** (Table 2D).[5]

We sought to study the mechanism of this reaction. To support the involvement of sulfide radical cations, we performed



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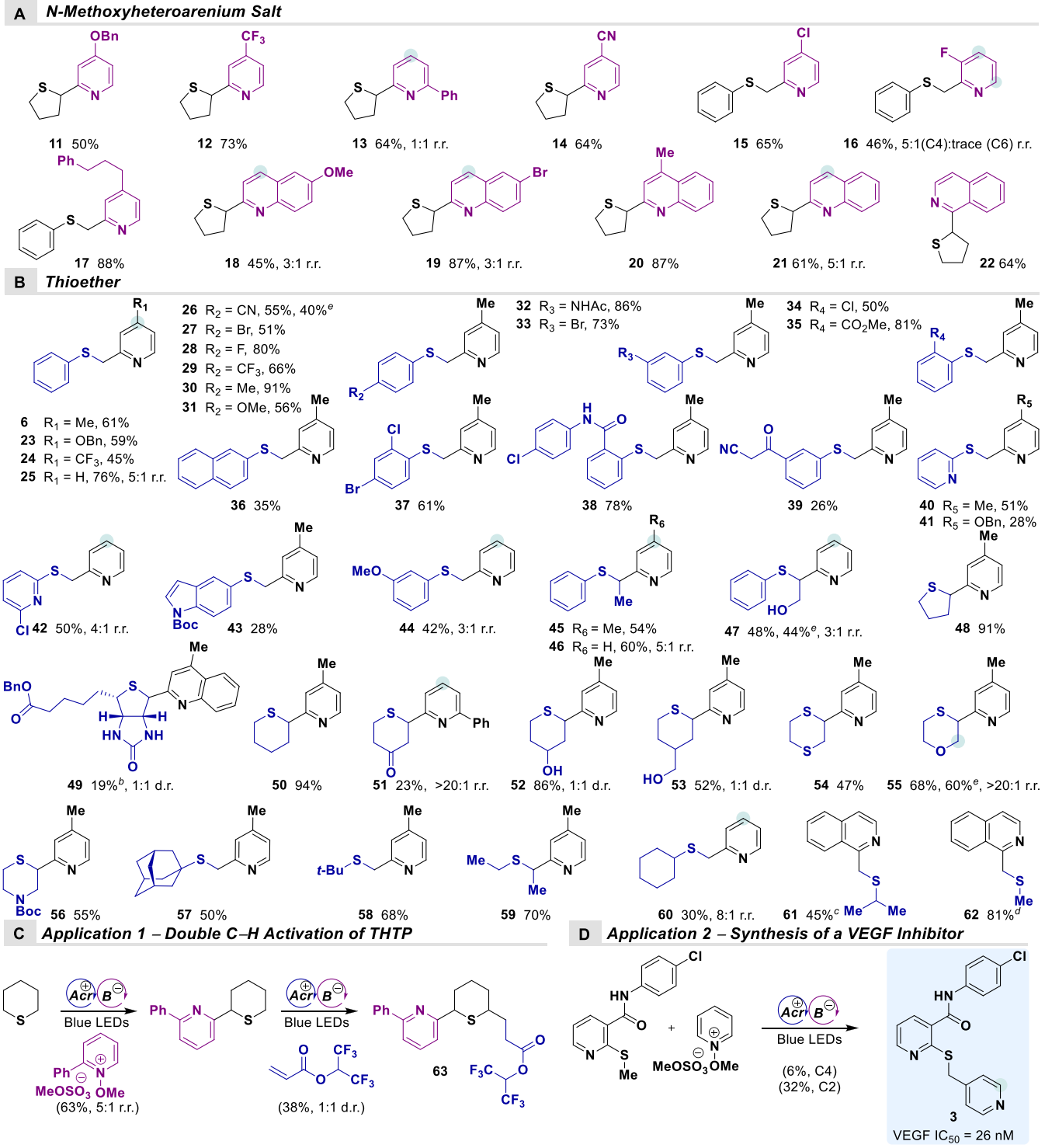
**Table 2. Scope of α-Heteroarylation of Thioethers**[a]




[a]Reaction conditions: *N*-methoxyheteroarenium salt (0.5 mmol, 1 equiv), thioether (3 equiv), Mes-Acr$^+$ (5 mol %), $CF_3CO_2Na$ (20 mol %), DCM [0.2 M], Ar, 30 °C, blue LEDs. [b]Thioether (2 equiv). [c]Thioether (5 equiv). [d]Thioether (10 equiv). [e]1-g scale.

luminescence quenching studies. Stern−Volmer (SV) analysis revealed thioanisole quenches ($K_{sv}$ = 214 $M^{-1}$) the luminescence of **Mes-Acr**$^+$ four times more efficiently than *N*-methoxypyridinium salt ($K_{sv}$ = 51 $M^{-1}$) and $CF_3CO_2Na$ ($K_{sv}$ = 47 $M^{-1}$).[38] The p$K_a$ of the α-C−H bonds in the thioanisole and dimethyl sulfide radical cations have been previously estimated to be p$K_a$ ≈ 2.1 and 0, respectively, lending credence to the hypothesized deprotonation.[27,39] Though $CF_3CO_2Na$ (p$K_a$ = 0.23 in $H_2O$)[40] is a weak base, its catalytic role was confirmed by observing that the rate of the model reaction is nearly tripled ($K_B^-/K_{w/o\ B}^-$ = 2.8) in its presence.[38] Kinetic isotope effect (KIE) experiments conducted with thioanisole and thioanisole-$d_3$ revealed C−H bond cleavage is both product- (KIE = 4.9) and rate-determining (KIE = 2.5).[38] We have



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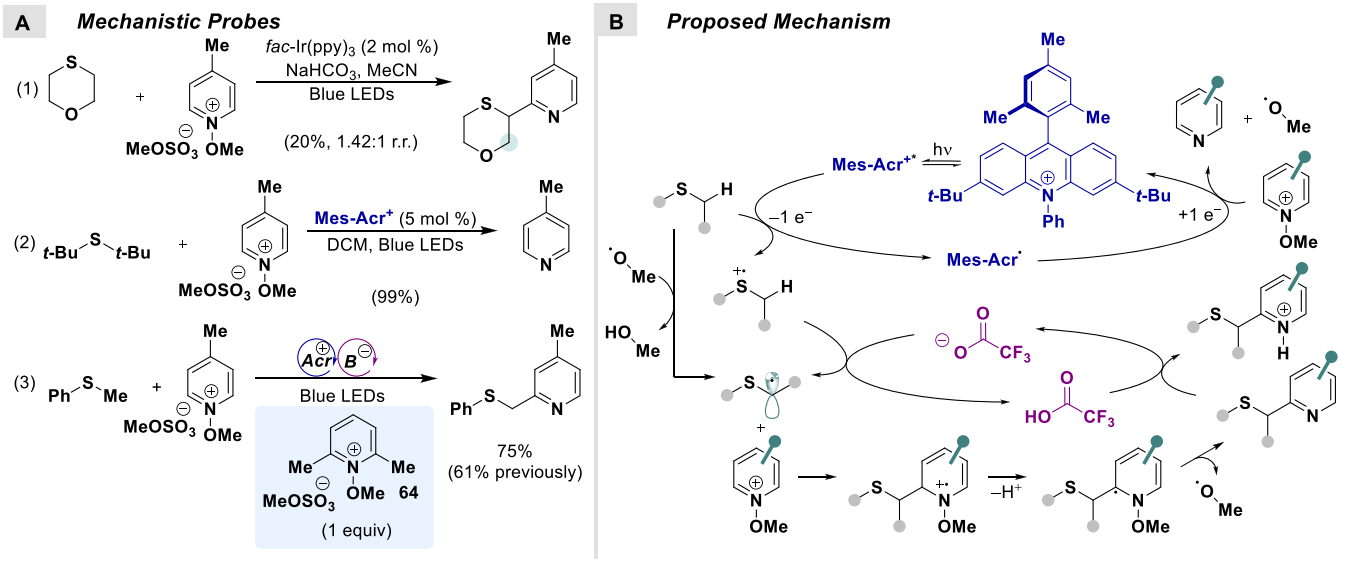


**Figure 1.** (A) Mechanistic probes. (B) Proposed mechanism.

previously demonstrated an olefin can capture a thioether radical clock in a formal (3 + 2) cycloaddition under analogous conditions, providing evidence for the intermediacy of $\alpha$-thio alkyl radicals.[27] Together, these data support oxidation and $\alpha$-C−H deprotonation of thioethers as a working mechanism for $\alpha$-thio alkyl radical formation.

We then focused on understanding how the product is generated. Studies using *N*-methoxyheteroarenium salts in Minisci-type reactions propose the following mechanism for product formation: (1) radical addition, forming an *N*-methoxy radical cation; (2) subsequent $\alpha$-C−H deprotonation to afford an *N*-methoxy $\alpha$-amino alkyl radical; and (3) homolytic fragmentation, which generates methoxyl radical (MeO$^\bullet$) and the Minisci product.[22,25] We conducted a competition experiment with 1-methoxypyridin-1-ium sulfate and 1-methoxypyridin-1-ium-$d_5$ sulfate, but a KIE was not observed, signifying $\alpha$-C−H bond cleavage of the *N*-methoxy radical cation is fast.[38] MeO$^\bullet$ can serve as a latent electrophilic HAT agent and propagate a radical chain. In our system, HAT of a hydridic $\alpha$-C−H bond from a thioether, for example, thioanisole (BDE = 93 kcal mol$^{-1}$),[41] by MeO$^\bullet$ (BDE = 104 kcal mol$^{-1}$)[42] is likely to be exergonic and kinetically favored by polar effects.[43] When measuring the quantum yield of the reaction with thioanisole, a value above unity ($\Phi$ = 1.14) was observed. In contrast, the quantum yield of the reaction with 1,4-oxathiane, the parent thioether to **55**, was below unity ($\Phi$ = 0.22). It appeared that radical chains are occurring in the reaction, but their extent is substrate dependent.

Instead, isolation of trace amounts of an undesired regioisomer of **55** provided convincing evidence for the intermediacy of MeO$^\bullet$. We wondered whether we could use 1,4-oxathiane and its observed regioselectivity (>20:1 rr) as a probe to gain insights into the extent that HAT from MeO$^\bullet$ is responsible for generating $\alpha$-thio alkyl radicals. We posited that the high selectivity observed in our system could not be recapitulated by a reaction chiefly operating through MeO$^\bullet$ HAT. To test this hypothesis, we turned to conditions recently developed by Lakhdar and co-workers for C−H alkylation of *N*-methoxyheteroarenium salts.[44] Important here is that *fac*-Ir(ppy)$_3$, a strongly reducing ($E^*_{ox}$ = −1.73 vs SCE)[45] but weakly oxidizing ($E^*_{ox}$ = +0.31 V vs SCE)[45] photoredox catalyst, was found to be optimal to promote the reaction. Under these reductive conditions (Figure 1A, eq 1), the reaction with 1,4-oxathiane afforded **55** with little selectivity (1.42:1 rr), providing evidence that, in the developed reaction, formation of $\alpha$-thio alkyl radicals via a stepwise approach is critical for the observed efficiency and selectivity.

Lastly, we wanted to understand how both catalysts turnover. It was thought that the background reduction of *N*-methoxyheteroarenium salts ($E_{p/2} \approx -0.6 - -0.7$ V vs SCE)[22,46] to their corresponding heteroarene arose from competitive SET from **Mes-Acr**$^\bullet$ ($E_{p/2}$ = −0.56 V vs SCE in MeCN), renewing the photoredox catalytic cycle.[35] To test this, we submitted di-*tert*-butyl sulfide ($E_{p/2}$ = +1.42 V vs SCE in MeCN),[47] which is excluded from generating $\alpha$-thio alkyl radicals but capable of reductively quenching excited **Mes-Acr**$^{+}$*, to the developed reaction (Figure 1A, eq 2). Indeed, quantitative reduction of the *N*-methoxyheteroarenium salt was observed. Control studies implicated **Mes-Acr**$^+$, di-*tert*-butyl sulfide, and visible light as necessary for this reaction.[38] In the case of $CF_3CO_2^-$, $^1$H NMR time course analysis demonstrated $\alpha$-heteroaromatic thioethers become protonated as they appear in solution (Figure S9). This data support deprotonation of *in situ* generated trifluoroacetic acid (TFA) by $\alpha$-heteroaromatic thioethers as the turnover step to regenerate $CF_3CO_2^-$.

The discovery that **Mes-Acr**$^+$ is regenerated by reduction of an *N*-methoxyheteroarenium salt led us to hypothesize that the reaction yield could be improved by identifying a sacrificial heteroarenium salt. In a preliminary study, we identified **64** as a candidate since it was observed to be quantitatively reduced, despite having the C4 position accessible for addition (Figure 1A, eq 3). When we probed **64** as an additive in our model reaction an improved yield of 75% (previously 61%) was observed. This preliminary study provides proof-of-concept for further refining of this reaction.

The existing experimental studies and literature precedent support the mechanism depicted in Figure 1B. Catalysis is initiated through visible light irradiation of **Mes-Acr**$^+$, which promotes it to its excited state. This species can be reductively quenched by thioethers, furnishing reduced **Mes-Acr**$^\bullet$ and sulfide radical cations. Deprotonation of the latter by $CF_3CO_2^-$ produces $\alpha$-thio alkyl radicals and TFA. Addition of $\alpha$-thio alkyl


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radicals to *N*-methoxyhetereoarenium salts affords an *N*-methoxy radical cation. Subsequent deprotonation and homolytic fragmentation of the emerging *N*-methoxy $\alpha$-amino alkyl radical lead to MeO$^\bullet$ and the desired $\alpha$-heteroaromatic thioether. TFA deprotonation by the product and reduction of a sacrificial quantity of *N*-methoxyheteroarenium salt by **Mes-Acr**$^\bullet$ regenerates the weak Brønsted base and photoredox catalytic cycles, respectively. The MeO$^\bullet$ generated throughout the reaction progress contributes to product formation through HAT of thioethers to $\alpha$-thio alkyl radicals. At present, reduction of the *N*-methoxy radical cation by **Mes-Acr**$^\bullet$ and elimination of methanol cannot be ruled out.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c02151.

Experimental procedures and data (PDF)

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### Notes

The authors declare no competing financial interest.

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## ■ REFERENCES


(1) Scott, K. A.; Njardarson, J. T. Analysis of US FDA-Approved Drugs Containing Sulfur Atoms. *Top. Curr. Chem.* **2018**, *376*, 5.

(2) Devendar, P.; Yang, G.-F. Sulfur-Containing Agrochemicals. *Top. Curr. Chem.* **2017**, *375*, 82.

(3) Howden, C. W. Clinical Pharmacology of Omeprazole. *Clin. Pharmacokinet.* **1991**, *20*, 38−49.

(4) Foote, K. M.; Nissink, J. W. M.; McGuire, T.; Turner, P.; Guichard, S.; Yates, J. W. T.; Lau, A.; Blades, K.; Heathcote, D.; Odedra, R.; Wilkinson, G.; Wilson, Z.; Wood, C. M.; Jewsbury, P. J. Discovery and Characterization of AZD6738, a Potent Inhibitor of Ataxia Telangiectasia Mutated and Rad3 Related (ATR) Kinase with Application as an Anticancer Agent. *J. Med. Chem.* **2018**, *61*, 9889−9907.

(5) Honda, T.; Tajima, H.; Kaneko, Y.; Ban, M.; Inaba, T.; Takeno, Y.; Okamoto, K.; Aono, H. Conformation−Activity Relationship on Novel 4-Pyridylmethylthio Derivatives with Antiangiogenic Activity. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2939−2943.

(6) Beno, B. R.; Yeung, K.-S.; Bartberger, M. D.; Pennington, L. D.; Meanwell, N. A. A Survey of the Role of Noncovalent Sulfur Interactions in Drug Design. *J. Med. Chem.* **2015**, *58*, 4383−4438.

(7) Meanwell, N. A. Synopsis of Some Recent Tactical Application of Bioisosteres in Drug Design. *J. Med. Chem.* **2011**, *54*, 2529−2591.

(8) Lücking, U. Sulfoximines: A Neglected Opportunity in Medicinal Chemistry. *Angew. Chem., Int. Ed.* **2013**, *52*, 9399−9408.

(9) Minisci, F.; Fontana, F.; Vismara, E. Substitutions by Nucleophilic Free Radicals: A New General Reaction of Heteroaromatic Bases. *J. Heterocycl. Chem.* **1990**, *27*, 79−96.

(10) Wu, Y.-H.; Wang, N.-X.; Zhang, T.; Zhang, L.-Y.; Gao, X.-W.; Xu, B.-C.; Xing, Y.; Chi, J.-Y. Rare-Earth Y(OTf)$_3$ Catalyzed Coupling Reaction of Ethers with Azaarenes. *Org. Lett.* **2019**, *21*, 7450−7454.

(11) Proctor, R. S. J.; Phipps, R. J. Recent Advances in Minisci-Type Reactions. *Angew. Chem., Int. Ed.* **2019**, *58*, 13666−13699.

(12) Tauber, J.; Imbri, D.; Opatz, T. Radical Addition to Iminium Ions and Cationic Heterocycles. *Molecules* **2014**, *19*, 16190−16222.

(13) Jin, J.; MacMillan, D. W. C. Direct $\alpha$-Arylation of Ethers through the Combination of Photoredox-Mediated C−H Functionalization and the Minisci Reaction. *Angew. Chem., Int. Ed.* **2015**, *54*, 1565−1569.

(14) Dong, J.; Xia, Q.; Lv, X.; Yan, C.; Song, H.; Liu, Y.; Wang, Q. Photoredox-Mediated Direct Cross-Dehydrogenative Coupling of Heteroarenes and Amines. *Org. Lett.* **2018**, *20*, 5661−5665.

(15) Bosset, C.; Beucher, H.; Bretel, G.; Pasquier, E.; Queguiner, L.; Henry, C.; Vos, A.; Edwards, J. P.; Meerpoel, L.; Berthelot, D. Minisci-Photoredox-Mediated $\alpha$-Heteroarylation of N-Protected Secondary Amines: Remarkable Selectivity of Azetidines. *Org. Lett.* **2018**, *20*, 6003−6006.

(16) Huang, C.-Y.; Li, J.; Liu, W.; Li, C.-J. Diacetyl as a "Traceless" Visible Light Photosensitizer in Metal-Free Cross-Dehydrogenative Coupling Reactions. *Chem. Sci.* **2019**, *10*, 5018−5024.

(17) Grainger, R.; Heightman, T. D.; Ley, S. V.; Lima, F.; Johnson, C. N. Enabling Synthesis in Fragment-Based Drug Discovery by Reactivity Mapping: Photoredox-Mediated Cross-Dehydrogenative Heteroarylation of Cyclic Amines. *Chem. Sci.* **2019**, *10*, 2264−2271.

(18) Katz, R. B.; Mistry, J.; Mitchell, M. B. An Improved Method for the Mono-Hydroxymethylation of Pyridines. A Modification of the Minisci Procedure. *Synth. Commun.* **1989**, *19*, 317−325.

(19) Ma, X.; Herzon, S. B. Intermolecular Hydropyridylation of Unactivated Alkenes. *J. Am. Chem. Soc.* **2016**, *138*, 8718−8721.

(20) Ma, X.; Dang, H.; Rose, J. A.; Rablen, P.; Herzon, S. B. Hydroheteroarylation of Unactivated Alkenes Using N -Methoxyheteroarenium Salts. *J. Am. Chem. Soc.* **2017**, *139*, 5998−6007.

(21) Jung, S.; Lee, H.; Moon, Y.; Jung, H.-Y.; Hong, S. Site-Selective C−H Acylation of Pyridinium Derivatives by Photoredox Catalysis. *ACS Catal.* **2019**, *9*, 9891−9896.

(22) Kim, I.; Kang, G.; Lee, K.; Park, B.; Kang, D.; Jung, H.; He, Y.-T.; Baik, M.-H.; Hong, S. Site-Selective Functionalization of Pyridinium Derivatives via Visible-Light-Driven Photocatalysis with Quinolinone. *J. Am. Chem. Soc.* **2019**, *141*, 9239−9248.

(23) Lee, W.; Jung, S.; Kim, M.; Hong, S. Site-Selective Direct C−H Pyridylation of Unactivated Alkanes by Triplet Excited Anthraquinone. *J. Am. Chem. Soc.* **2021**, *143*, 3003−3012.

(24) Quint, V.; Morlet-Savary, F.; Lohier, J.-F.; Lalevée, J.; Gaumont, A.-C.; Lakhdar, S. Metal-Free, Visible Light-Photocatalyzed Synthesis of Benzo[ b ]Phosphole Oxides: Synthetic and Mechanistic Investigations. *J. Am. Chem. Soc.* **2016**, *138*, 7436−7441.

(25) Rammal, F.; Gao, D.; Boujnah, S.; Hussein, A. A.; Lalevée, J.; Gaumont, A.-C.; Morlet-Savary, F.; Lakhdar, S. Photochemical C−H Silylation and Hydroxymethylation of Pyridines and Related Structures: Synthetic Scope and Mechanisms. *ACS Catal.* **2020**, *10*, 13710−13717.

(26) Kiselyov, A. S.; Strekowski, L.; Semenov, V. V. Facile Synthesis of 2-[1-(Alkylthio)Alkyl]Pyridines and Phenyl-Substituted Derivatives. *J. Heterocycl. Chem.* **1993**, *30*, 329−332.

(27) Alfonzo, E.; Hande, S. M. Photoredox and Weak Brønsted Base Dual Catalysis: Alkylation of $\alpha$-Thio Alkyl Radicals. *ACS Catal.* **2020**, *10*, 12590−12595.

(28) Le, C.; Liang, Y.; Evans, R. W.; Li, X.; MacMillan, D. W. C. Selective Sp3 C−H Alkylation via Polarity-Match-Based Cross-Coupling. *Nature* **2017**, *547*, 79−83.

(29) Hasegawa, E.; Brumfield, M. A.; Mariano, P. S.; Yoon, U. C. Photoadditions of Ethers, Thioethers, and Amines to 9,10-Dicyanoanthracene by Electron Transfer Pathways. *J. Org. Chem.* **1988**, *53*, 5435−5442.
(30) Li, Y.; Miyazawa, K.; Koike, T.; Akita, M. Alkyl- and Aryl-Thioalkylation of Olefins with Organotrifluoroborates by Photoredox Catalysis. *Org. Chem. Front.* **2015**, *2*, 319−323.
(31) Zhu, X.-L.; Huang, Y.; Xu, X.-H.; Qing, F.-L. Silver-Catalyzed C−H Aryloxydifluoromethylation and Arylthiodifluoromethylation of Heteroarenes. *Org. Lett.* **2020**, *22*, 5451−5455.
(32) Garza-Sanchez, R. A.; Patra, T.; Tlahuext-Aca, A.; Strieth-Kalthoff, F.; Glorius, F. DMSO as a Switchable Alkylating Agent in Heteroarene C−H Functionalization. *Chem. - Eur. J.* **2018**, *24*, 10064−10068.
(33) Graham, M. A.; Noonan, G.; Cherryman, J. H.; Douglas, J. J.; Gonzalez, M.; Jackson, L. V.; Leslie, K.; Liu, Z.; McKinney, D.; Munday, R. H.; Parsons, C. D.; Whittaker, D. T. E.; Zhang, E.; Zhang, J. Development and Proof of Concept for a Large-Scale Photoredox Additive-Free Minisci Reaction. *Org. Process Res. Dev.* **2021**, *25*, 57−67.
(34) Jonsson, M.; Lind, J.; Merényi, G.; Eriksen, T. E. Redox Properties of 4-Substituted Aryl Methyl Chalcogenides in Water. *J. Chem. Soc., Perkin Trans. 2* **1995**, *2*, 67−70.
(35) White, A.; Wang, L.; Nicewicz, D. Synthesis and Characterization of Acridinium Dyes for Photoredox Catalysis. *Synlett* **2019**, *30*, 827−832.
(36) Cambié, D.; Bottecchia, C.; Straathof, N. J. W.; Hessel, V.; Noël, T. Applications of Continuous-Flow Photochemistry in Organic Synthesis, Material Science, and Water Treatment. *Chem. Rev.* **2016**, *116*, 10276−10341.
(37) O'Hara, F.; Blackmond, D. G.; Baran, P. S. Radical-Based Regioselective C−H Functionalization of Electron-Deficient Heteroarenes: Scope, Tunability, and Predictability. *J. Am. Chem. Soc.* **2013**, *135*, 12122−12134.
(38) See Supporting Information for details.
(39) Merényi, G.; Lind, J.; Engman, L. The Dimethylhydroxysulfuranyl Radical. *J. Phys. Chem.* **1996**, *100*, 8875−8881.
(40) Serjeant, E. P.; Dempsey, B. *Ionisation Constants of Organic Acids in Aqueous Solution*; Permagon Press: Oxford, 1979.
(41) Bordwell, F. G.; Zhang, X.; Alnajjar, M. S. Effects of Adjacent Acceptors and Donors on the Stabilities of Carbon-Centered Radicals. *J. Am. Chem. Soc.* **1992**, *114*, 7623−7629.
(42) Blanksby, S. J.; Ellison, G. B. Bond Dissociation Energies of Organic Molecules. *Acc. Chem. Res.* **2003**, *36*, 255−263.
(43) Roberts, B. P. Polarity-Reversal Catalysis of Hydrogen-Atom Abstraction Reactions: Concepts and Applications in Organic Chemistry. *Chem. Soc. Rev.* **1999**, *28*, 25−35.
(44) Rammal, F.; Gao, D.; Boujnah, S.; Gaumont, A.; Hussein, A. A.; Lakhdar, S. Visible-Light-Mediated C−H Alkylation of Pyridine Derivatives. *Org. Lett.* **2020**, *22*, 7671−7675.
(45) Dixon, I. M.; Collin, J.-P.; Sauvage, J.-P.; Flamigni, L.; Encinas, S.; Barigelletti, F. A Family of Luminescent Coordination Compounds: Iridium(III) Polyimine Complexes. *Chem. Soc. Rev.* **2000**, *29*, 385−391.
(46) Schnabel, W. Cationic Photopolymerization with the Aid of Pyridinium-Type Salts. *Macromol. Rapid Commun.* **2000**, *21*, 628−642.
(47) Cottrell, P. T.; Mann, C. K. Electrochemical Oxidation of Aliphatic Sulfides under Nonaqueous Conditions. *J. Electrochem. Soc.* **1969**, *116*, 1499.


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