Chemoselective α-Sulfidation of Amides Using Sulfoxide Reagents

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KEYWORDS. Amide, Sulfide, Sulfidation, Sulfonium Ion.

ABSTRACT: The direct α-sulfidation of tertiary amides using sulfoxide reagents under electrophilic amide activation conditions is described. Employing readily available reagents, selective functionalization takes place to generate isolable sulfonium ions en route to α-sulfide amides. Mechanistic studies support the critical role of activated sulfoxides that promote the desired transformation. For benzylic amide substrates, a single-step protocol featuring a spontaneous dealkylation step of a sulfonium ion intermediate was developed.

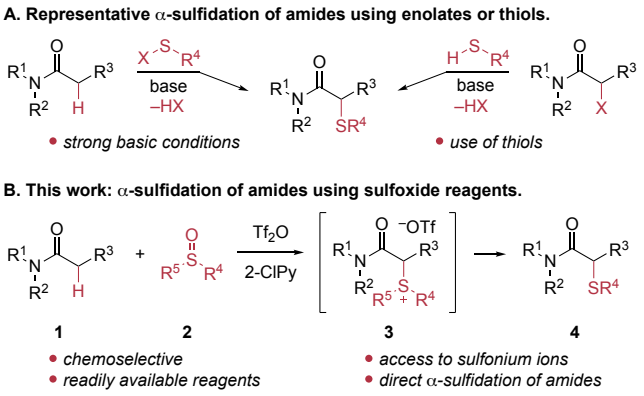
New methods for the introduction of carbon–sulfur bonds are of interest in the synthesis and diversification of bioactive compounds given the existence of hundreds of sulfur-containing structures approved by the U.S. Food and Drug Administration for the treatment of human ailments.[1-3] Existing methods for the sulfidation of amides either rely on the use of basic conditions to activate the amide for nucleophilic attack, or employ α-halo amides in combination with nucleophilic thiols (Scheme 1A).[4] As an outgrowth of our studies concerning electrophilic amide activation for practical carbon–carbon and carbon–nitrogen bond forming reactions,[5,6] we recognized an opportunity to develop an orthogonal approach compared to contemporary methods for introduction of carbon–sulfur bonds. Herein, we describe the direct α-sulfidation of amides using sulfoxide reagents (Scheme 1B). Detailed mechanistic studies are consistent with carbon–sulfur bond formation via addition to an electrophilic sulfonium ion, enabling access to α-sulfonium and α-sulfide substituted amides through judicious choice of sulfoxide reagents.

Sulfoxides can serve as ideal reagents for synthesis as they are readily available, easily derivatized, and bench stable.[7,8] We have previously reported that the reagent combination of trifluoromethanesulfonic anhydride (Tf_2O) and a substituted pyridine[5] is effective for electrophilic amide activation[9] to enable the addition of various nucleophiles. In particular, the use of 2-chloropyridine (2-ClPy)[10] as the base additive offered a range of condensative azaheterocycle syntheses[5] whereas the use of 2-fluoropyridine (2-FPy)[5e] allowed the formation of highly reactive nitrilium ions for a modified Abramovitch reaction. Innovative reports continue to demonstrate the practical nature of this approach to amide derivatization.[11,12]

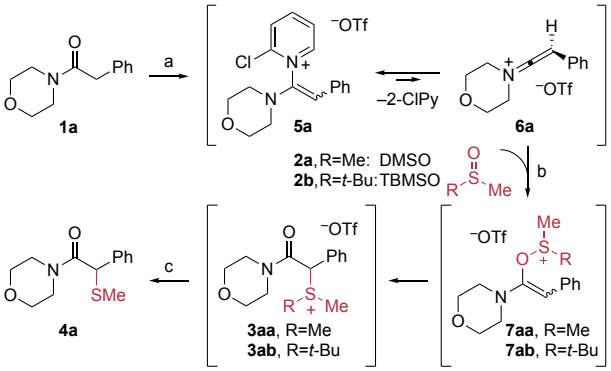
Inspired by our observations regarding the addition of pyridine *N*-oxides to nitrilium ions for carbon–nitrogen bond formation,[5e] and reports on the use of sulfoxides in carbon–carbon bond formation,[11j] we envisioned the use of sulfoxide reagents for carbon–sulfur bond formation (Scheme 2). We anticipated the addition of dimethyl sulfoxide (DMSO, **2a**) upon electrophilic activation of amide **1a** would lead to oxysulfonium ion **7aa** en route to α-sulfonium amide **3aa** and the corresponding α-sulfide amide **4a** after demethylation. Under optimal conditions[13] activation of amide **1a** with Tf_2O (1.05 equiv) and 2-ClPy (3.00 equiv) with monitoring of the reaction mixture upon addition of DMSO (**2a**, 1.20 equiv) via in situ IR-spectroscopy revealed complete sulfoxide addition and conversion to α-sulfonium amide **3aa** at –30 °C without observation of any persistent intermediates.[14] Exposure of sulfonium ion **3aa** to excess triethylamine in acetonitrile and warming to 60 °C led to quantitative demethylation[15] and afforded α-sulfide amide **4a** (67% yield, 2-steps). We further anticipated that a single-step procedure using an appropriately substituted sulfoxide reagent **2** (Scheme 1B) would enable spontaneous dealkylation of α-sulfonium amide **3** to directly afford sulfide **4**. Under optimal conditions,[13] the use of *tert*-butyl methyl sulfoxide (TBMSO, **2b**) as the sulfidation reagent led to direct conversion of amide **1a** to α-sulfide amide **4a** in 54% yield (Scheme 2).

The application of this chemistry to α-sulfidation of α-aryl amides was examined as illustrated in Table 1. Sulfide **4a** could be prepared on a 5.00-mmol scale without compromising reaction efficiency via either a two-step procedure using

Scheme 1. Methods for the α-Sulfidation of Amides



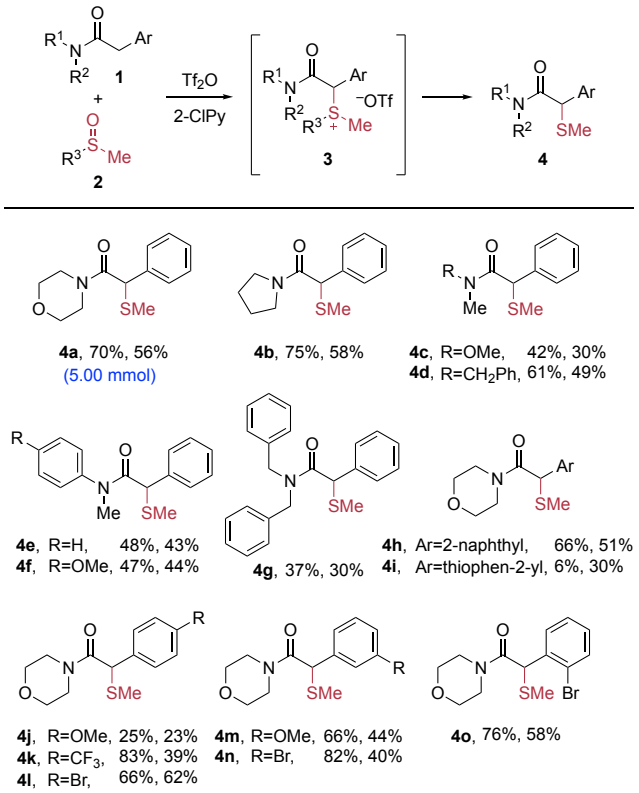
Scheme 2. α-Sulfidation of Benzylic Amide 1a



Reagents and conditions: (a) Tf_2O (1.05 equiv), 2-ClPy (3.00 equiv), CH_2Cl_2, –78 → 0 °C, 15 min; (b) Sulfoxide (**2**, 1.20 equiv), CH_2Cl_2, –78 → 22 °C, 45 min; for **3aa**: (c) Et_3N (10 equiv), MeCN, 60 °C, 15 h.

DMSO (**2a**, Method A: 70% yield, Table 1) or a single-step procedure employing TBMSO (**2b**, Method B: 56% yield, Table 1). A variety of α-aryl acetamides, including versatile morpholine-derived amides (Table 1, **4a**, and **4h–o**),[16] in addition to *N*-phenyl (Table 1, **4e–f**) and *N*-benzyl (Table 1, **4d**, and **4g**) substituted amides, served as substrates for this α-sulfidation reaction.[17,18] α-Sulfide amide **4c** was prepared from the corresponding Weinreb amide in modest yield (Table 1).[19] When the demethylation step of Method A with DMSO (**2a**) was omitted, dimethylsulfonium trifluoromethanesulfonates **3aa** and **3ba** derived from morpholine and pyrrolidine amides **1a** and **1b** could be isolated in 61% and 68% yield, respectively.[13]

Table 1. α-Sulfidation of Benzylic Amides with DMSO (2a) and TBMSO (2b)[a]

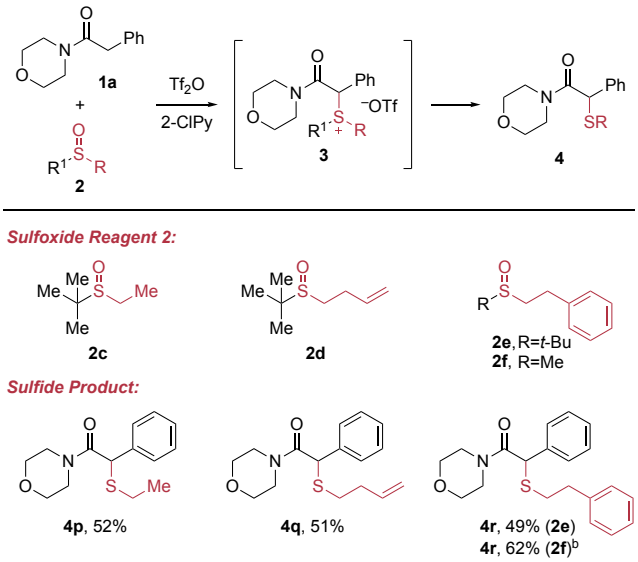


[a]Reagents and conditions: Method A (2-steps, sulfonium ion **3** isolated): Tf_2O (1.05 equiv), 2-ClPy (3.00 equiv), CH_2Cl_2, –78 → 0 °C, 15 min; DMSO (**2a**, 1.20 equiv), CH_2Cl_2, –78 → 22 °C, 45 min; Et_3N (10.0 equiv), MeCN, 60 °C, 15 h. Method B (sulfonium ion **3** not isolated): Tf_2O (1.05 equiv), 2-ClPy (3.00 equiv), CH_2Cl_2, –78 → 0 °C, 15 min; TBMSO (**2b**, 1.20 equiv), CH_2Cl_2, –78 → 22 °C, 45 min. Yields are reported: Method A, Method B.

A wide-range of substituents was tolerated on the α-aryl acetamide substrates to give the corresponding sulfide amides (Table 1, **4h–4o**). However, substituents that may compromise the stability of the α-sulfonium ion intermediate **3** (Scheme 1B) led to low isolated yields of desired product (Table 1, **4i** and **4j**). While the use of DMSO (**2a**) generally affords higher yields after one-pot demethylation, TBMSO (**2b**) forms α-thiomethyl amides more directly via spontaneous dealkylation. Additionally, the use of TBMSO (**2b**) enables the sulfidation of substrates where the α-sulfonium ion intermediate is subject to hydrolysis (e.g. sulfidation of α,α-diphenyl acetamide **S1** to α-thiomethyl amide **S4**).[13]

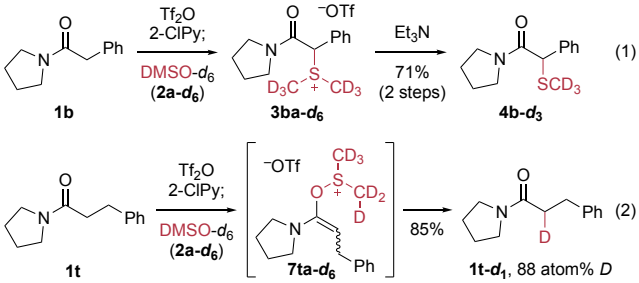
Motivated by the success of the single-step sulfidation of amides using TBMSO (**2b**; Table 1, Method B), we next examined the use of *tert*-butyl sulfoxides **2c–2e** with amide **1a** to give the corresponding α-sulfide amides **4p–4r** (Table 2).[13] In each case, the primary alkyl substituent of the *tert*-butyl sulfoxide was preserved, owing to the relative stability of the cation derived from the *tert*-butyl substituent in the spontaneous dealkylation. Complimentarily, α-sulfide amide **4r** could also be formed with methyl sulfoxide **2f** after regioselective dealkylation (62% yield), leaving the homobenzylic substituent intact.

Table 2. α-Sulfidation of Amide 1a with Sulfoxides 2c–2f[a]



[a]Reagents and conditions: Tf_2O (1.05 equiv), 2-ClPy (3.00 equiv), CH_2Cl_2, –78 → 0 °C, 15 min; sulfoxide **2c–2e** (1.20 equiv), CH_2Cl_2, –78 → 22 °C, 45 min; [b]Use of sulfoxide **2f** with Method A, Table 1.

In evaluating the scope of the transformation, we found that optimal conditions described in Table 1 were not compatible with amides other than α-aryl acetamides. With non-benzylic aliphatic amides, the addition of DMSO (**2a**) to the activated amide intermediate led to recovery of the starting amide despite successful amide activation, as evidenced by in situ reaction monitoring. We therefore pursued a series of mechanistic experiments to inform our efforts to expand the substrate scope of our amide sulfidation methodology.

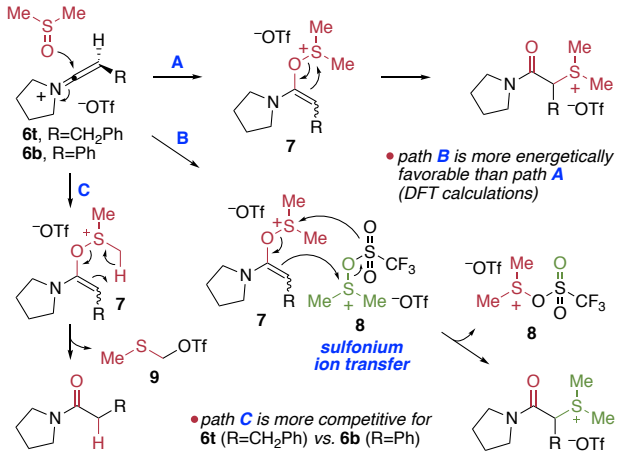


While the use of DMSO-d_6 (**2a-*d*$_6$**) for the α-sulfidation of benzylic amide **1b** led to α-sulfide amide **4b-*d*$_3$** in 71% yield (eq. 1), when DMSO-d_6 (**2a-*d*$_6$**) was used with aliphatic amide **1t**, we observed only recovery of the tertiary amide **1t-*d*$_1$** (85% yield) with 88 atom% *D*-incorporation at the α-position (eq. 2).[13] We attributed these observations to a retro-ene reaction from intermediate **7ta-*d*$_6$** that is preferred for aliphatic sub-

strates, rather than the desired α-sulfidation as seen for benzylic amides.[20,21]

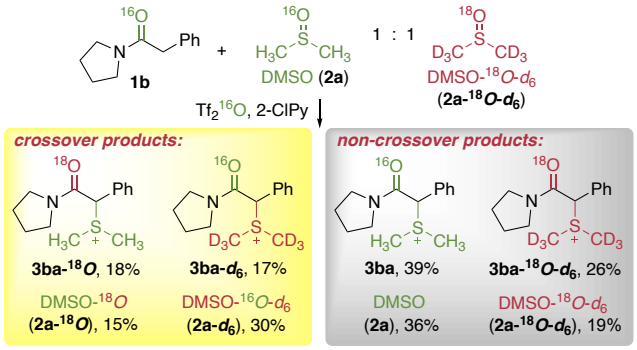
Toward our goal of mechanism-guided expansion of the scope of our α-sulfidation chemistry, it was necessary to develop a detailed understanding of the underlying reaction pathway. We envisioned that oxysulfonium ion intermediate **7**, derived from addition of sulfoxide to keteniminium **6**, could either undergo an intramolecular rearrangement as in our modified Abramovitch reaction (Scheme 3, pathway A),[5e] or intermolecular sulfidation with an electrophilically-activated sulfoxide ion **8** to give the α-sulfonium amide product (path B). Rather than undergoing productive sulfidation however, aliphatic amides (e.g. **1t**, R=CH_2Ph) react through pathway C under the conditions of Table 1, regenerating the starting amide and methylthiomethyl trifluoromethanesulfonate **9**, which could be detected in the crude reaction mixture by ^{1}H and ^{13}C NMR analysis.

Scheme 3. Possible Reaction Pathways



Distinguishing intra- and intermolecular sulfidation pathways was accomplished by means of a crossover experiment employing an equal mixture of DMSO (**2a**) and doubly labeled DMSO-^{18}O-d_6 (**2a**-^{18}***O*-d_6**).[13] When amide **1b** was subjected to standard reaction conditions using this sulfoxide mixture, we observed substantial formation of crossover sulfonium ion products **3ba**-^{18}***O*/3ba-d_6** and DMSO (**2a**-^{18}***O*/2a-d_6**), in addition to non-crossover products **3ba/3ba**-^{18}***O*-d_6** and DMSO (**2a/2a**-^{18}***O*-d_6**) by Q-TOF mass-spectrometry of the crude reaction material (Scheme 4).[22] Based on our computational studies, and the observation of all possible crossover and non-crossover products, we concluded that intermolecular sulfidation predominates over an intramolecular pathway.[23,24] An alternative intermolecular sulfidation pathway involving dimethyl sulfide addition to an α-electrophile was also considered,[25] however our DFT calculations identified a relatively high barrier for sulfur–oxygen cleavage from oxysulfonium ion **7** (ca. 18 kcal/mol vs. 3 kcal/mol for Scheme 3, pathway B). Additionally, we observed unsubstantial deuterium incorporation into the sulfonium product **3aa** upon addition of dimethyl sulfide-d_6 (1.00 equiv) to the reaction mixture at –78 °C.[13,26]

Scheme 4. Crossover Experiment with amide 1b and an equal mixture of DMSO (2a) and DMSO-^{18}O-d_6 (2a-^{18}O-d_6)[a]

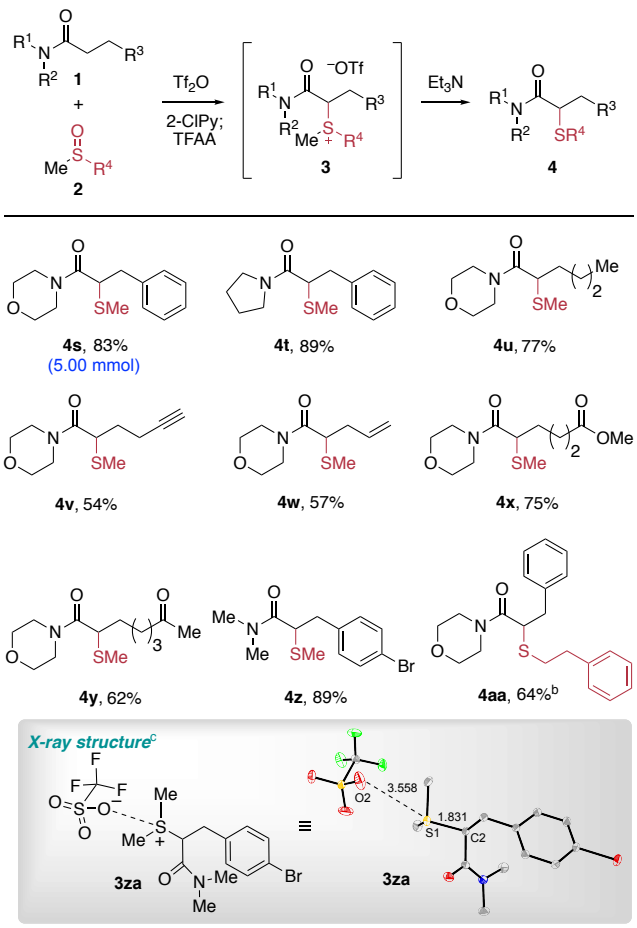


[a]Reagents and conditions: Tf_2O (1.10 equiv), 2-ClPy (2.00 equiv), $CDCl_3$, –78 → 0 °C, 15 min; DMSO (**2a**) and DMSO-^{18}O-d_6 (**2a**-^{18}***O*-d_6**) mixture (1:1, 2.00 equiv), $CDCl_3$, –78 → 22 °C, 45 min.

Based on these insights suggesting an intermolecular mechanism for the sulfidation step involving an activated sulfoxide species, we recognized that the unproductive retro-ene pathway (Scheme 3, pathway C) may be outcompeted by increasing the concentration of trifluoromethanesulfonyloxysulfonium ion **8**.[27] Indeed, α-sulfidation of aliphatic amide **1t** with DMSO (**2a**) proceeded in 79% yield by increasing the amount of sulfoxide used and adding supplemental Tf_2O after amide activation. Successful acceleration of the desired sulfidation pathway by increasing the quantity of activated sulfoxide intermediate **8** is consistent with the involvement of this species in an intermolecular sulfidation process and in turn supports the mechanistic hypothesis illustrated in Scheme 3, pathway B.[23]

Further evaluation of conditions for sulfoxide activation revealed that the addition of trifluoroacetic anhydride (TFAA) after amide activation offered the sulfidated aliphatic amides in higher yield compared to use of Tf_2O.[13,28] This modified condition, rationally identified through our mechanistic studies, provide access to a variety of α-sulfidated aliphatic amides (Table 3). Homobenzylic morpholine and pyrrolidine amides **1s** and **1t** gave the corresponding α-sulfide amides **4s** and **4t** respectively.[29,30] The α-sulfide amide **4s** could be prepared on 5.00-mmol scale without compromising reaction efficiency (83% yield, Table 3). Saturated morpholine α-sulfide amide **4u** could also be prepared with similar efficiency (77% yield). The transformation was successfully conducted with the terminal alkyne **1v** and alkene **1w**. Ester- and ketone-containing substrates **1x** and **1y** could be chemoselectively sulfidated adjacent to the amide group in the presence of other unprotected carbonyl-groups. Aliphatic amide **1aa** was sulfidated using methyl sulfoxide derivative **2f** in 64% yield after regioselective dealkylation. For amide **1z**, single crystals suitable for X-ray diffraction were obtained of intermediate **3za**[31] en route to α-sulfide product **4z**, revealing a non-covalent interaction[32] between the sulfonium-cation and trifluoromethanesulfonate anion that underlies its high solubility in organic solvents and resistance towards elimination and hydrolysis.[33]

Table 3. α-Sulfidation of Aliphatic Amides[a]



[a]Reagents and conditions, Method C: Tf_2O (1.10 equiv), 2-ClPy (3.00 equiv), CH_2Cl_2, –78 → 0 °C, 15 min; sulfoxide **2a** (2.50 equiv), TFAA (1.00 equiv), CH_2Cl_2, –78 → 22 °C, 45 min; Et_3N (10.0 equiv), MeCN, 60 °C, 15 h. [b]Sulfoxide **2f** (2.50 equiv). [c]For the ORTEP representation of **3za**, the thermal ellipsoids are shown at the 50% probability level and hydrogen atoms are omitted for clarity. Selected bond lengths and angles: S(1)–C(2) 1.831 Å, S(1)–O(2) 3.558 Å, and C(2)–S(1)–O(2) 163.79°.

In conclusion, we have identified a direct procedure for the chemoselective α-sulfidation of amides. This transformation is applicable to a wide range of tertiary amides with high functional group tolerance. The use of simple and easily accessible sulfoxides enhances the practicality of this strategy, in which benzylic amides were functionalized in single step procedures featuring a spontaneous dealkylation. Mechanistic studies supported the role of electrophilically activated sulfoxide intermediates as promoters for the sulfidation, and guided extension of the methodology to aliphatic tertiary amide substrates by rational modification of the reaction conditions. This methodology offers a valuable alternative to existing solutions for α-sulfidation of amides by introducing an orthogonal strategy under mild conditions, and provides direct access to functionalized amides for fine chemical synthesis.[1-3]

ASSOCIATED CONTENT

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.jacs.xxxxxxx.

Experimental procedures, spectroscopic data, and copies of ^{1}H, ^{13}C, and ^{19}F NMR spectra (PDF)

Sulfonium trifluoromethanesulfonate **3za** CCDC 1916405 (CIF)

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Funding Sources

We acknowledge financial support from NIH-NIGMS (GM074825). M.L. was supported by a Schrödinger Postdoctoral Fellowship, financed by the Austrian Science Fund (FWF): J3930-N34. K.A.D. acknowledges the Natural Sciences and Engineering Research Council of Canada (NSERC) for a PGS-D3 scholarship.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We thank Dr. Peter Müller for assistance with single crystal X-ray diffraction of **3za**. M.L. thanks the Graz University of Technology for access to the Zentraler Informatikdienst (ZID) computing facility and resources during manuscript refinement in the second phase of his Schrödinger Postdoctoral Fellowship in the laboratory of Prof. Dr. Rolf Breinbauer.

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13. See the Supporting Information for details.

14. A variety of substituted pyridine bases, including 2-FPy, 2-ClPy, 2-BrPy, and 2-MeOPy were examined and 2-ClPy was found to be the optimal additive consistent with our prior studies.

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17. Substrates that were found to be unsuitable for this α-sulfidation chemistry included γ-butyrolactams 1-methylindolin-2-one and 1-methyl-3-phenylpyrrolidin-2-one; diketopiperazines (3*R*,8a*S*)-2-methyl-3-phenylhexahydropyrrolo-[1,2-*a*]pyrazine-1,4-dione and (3*R*,6*S*)-1,4-dimethyl-3,6-diphenylpiperazine-2,5-dione; and secondary amides *N*-butyl-2-phenylacetamide and *N*-(4-methoxyphenyl)-3-phenylpropanamide. These observations are consistent with the inability of these substrates to form keteniminium ions under the reaction conditions. Primary amides undergo dehydration upon electrophilic activation, see Bose, D. S.; Jayalakshmi, B. A Practical Method for the Preparation of Nitriles from Primary Amides Under Non-Acidic Conditions. *Synthesis* **1999**, 64–65.

18. Side-products corresponding to oxidative C–C coupling of amides **1e**–**g** were also isolated, see the Supporting Information for details and Kaiser, D.; de la Torre, A.; Shaaban, S.; Maulide, N. Metal-Free Formal Oxidative C–C Coupling by In Situ Generation of an Enolonium Species. *Angew. Chem. Int. Ed.* **2017**, *56*, 5921–5925.

19. A similar Weinreb amide failed in a related amination reaction via electrophilic amide activation, see Tona, V.; de la Torre, A.; Padmanaban, M.; Ruider, S.; González, L.; Maulide, N. Chemo- and Stereoselective Transition-Metal-Free Amination of Amides with Azides. *J. Am. Chem. Soc.* **2016**, *138*, 8348–8351.

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21. The subambient temperature at which this retro-ene reaction takes place suggests that it may benefit from charge-acceleration. Pericyclic reactions of other sulfonium ions have been found to benefit from charge-acceleration, see Huang, X.; Klimczyk, S.; Maulide, N. Charge-Accelerated Sulfonium [3,3]-Sigmatropic Rearrangements. *Synthesis* **2012**, *44*, 175–183.

22. Complete transfer of the oxygen from the sulfoxide to the sulfidated product was verified by the reaction of amide **1b** with DMSO-^{18}O-d_6 (**2a**-^{18}***O*-*d*$_6$**). Thus, in situ formation of crossover DMSO (**2a**-^{18}***O*/2a-*d*$_6$**) via $^{16}O/^{18}O$ exchange of the sulfoxide with unlabeled Tf_2O/TfO^- does not occur prior to sulfidation.

23. When a substoichiometric quantity of Tf_2O was used in the crossover experiment (0.50 equiv), the proportion of crossover products **3ba**-^{18}***O*/3ba-*d*$_6$** observed was diminished. This is consistent with the predominance of intramolecular pathway A (Scheme 3) in the absence of trifluoromethanesulfonyloxysulfonium ion **8**, rather than an intermolecular pathway such as pathway B or dimethyl sulfide addition to an α-electrophile.

24. The use of enantiomerically enriched sulfoxide (–)-**2b** in sulfidation of amide **1a** gave racemic product **4a**.

25. Gonçalves, C. R.; Lemmerer, M.; Teskey, C. J.; Adler, P.; Kaiser, D.; Maryasin, B.; González, L.; Maulide, N. Unified Approach to the Chemoselective α-Functionalization of Amides with Heteroatom Nucleophiles. *J. Am. Chem. Soc.* **2019**, *141*, 18437–18443.

26. The distribution of sulfonium products **3ba** and **3ba-*d*$_6$** was 76% and 24%, respectively. The observation of partial formation of **3ba-*d*$_6$** is consistent with competitive reversible oxygen transfer from electrophilically activated sulfoxides to sulfides, see Tanikaga, R.; Nakayama, K.; Tanaka, K.; Kaji, A. Reversible Oxygen Transfer Reactions between Sulfoxides and Sulfides. Relative Stabilities of Acyloxysulfonium Ions. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 3089–3090.

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28. Simple organic acids such as methanesulfonic acid (MsOH) or trifluoroacetic acid (TFA) could also be added in place of additional anhydride to activate DMSO, but resulted in lower yield of the desired α-sulfidated amide. For benzylic amides such as **1b**, supplemental DMSO and anhydride were not found to be beneficial.

29. Replacing DMSO (**2a**) with TBMSO (**2b**) in Method C resulted in decreased yields of α-sulfidated amides. We hypothesize that TBMSO, upon electrophilic activation, is subject to spontaneous dealkylation of the *tert*-butyl group to give a sulfenate, see: (a) Yoshimura, T.; Tsukurimichi, E.; Yamazaki, S.; Soga, S.; Shimasaki, C.; Hasegawa, K. Synthesis of a stable sulfenic acid, *trans*-decalin-9-sulfenic acid. *J. Chem. Soc., Chem. Commun.* **1992**, 1337–1338. (b) Okuyama, T.; Fueno, T. Acid-Catalyzed Cleavage of Methoxymethyl Phenyl Sulfoxide. Solvent Effects and Mode of Bond Cleavage. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 3111–3116.

30. The starting aliphatic amides, derived from the competing retro-ene pathway, were recovered (~15%) in most cases.

31. Sulfonium trifluoromethanesulfonate **3za** can be stored at 22 °C for weeks. It can be demethylated by treatment with triethylamine according to our standard conditions to give sulfide **4z** in 92% yield.

32. The non-covalent interaction is evidenced by considerable elongation of the Me_2S^+–C bond: 1.831 Å. Additionally, the oxygen atom of the longest S–O bond in the trifluoromethanesulfonate anion is engaged in this interaction (1.444 Å vs. 1.428 Å, 1.425 Å). For a similar discussion, see Lodochnikova, O. A.; Litvinov, I. A.; Palei, R. V.; Plemenkov, V. V. Crystal structure of the sulfonium salts of natural azulenes. *J. Struct. Chem.* **2008**, *49*, 322–326.

33. Reported sulfur–carbon bond-lengths in other sulfonium trifluoromethanesulfonates: (a) (2-(2-Acetylphenyl)-1-phenylvinyl)(dimethyl)sulfonium trifluoromethanesulfonate: 1.804 Å; Hooper, J. F.; Chaplin, A. B.; González-Rodriguez, C.; Thompson, A. L.; Weller, A. S.; Willis, M. C. Aryl Methyl Sulfides as Substrates for Rhodium-Catalyzed Alkyne Carbothiolation: Arene Functionalization with Activating Group Recycling. *J. Am. Chem. Soc.* **2012**, *134*, 2906–2909. (b) (1-Diazo-2-ethoxy-2-oxoethyl)dimethylsulfonium trifluoromethanesulfonate: 1.731 Å; Schnaars, C.; Hennum, M.; Bonge-Hansen, T. Nucleophilic Halogenations of Diazo Compounds, a Complementary Principle for the Synthesis of Halodiazo Compounds: Experimental and Theoretical Studies. *J. Org. Chem.* **2013**, *78*, 7488–7497.