RESEARCH ARTICLE

Check for updates

Synthesis of *N*-trifluoromethylsulfilimines *via* trifluoromethyl nitrene and their synthetic potential†

Norbert Baris,[a,b] Martin Dračínský, [ID] [a] Luca Julianna Tóth,[a,b] Blanka Klepetářová[a] and Petr Beier [ID] *[a]

Trifluoromethyl nitrene generated photocatalytically from azidotrifluoromethane was added to sulfides to afford new *N*-trifluoromethylsulfilimines. Their methylation yielded *N*-methyl-*N* trifluoromethyl sulfonium salts and oxidation provided *N*-trifluoromethyl sulfoximines.
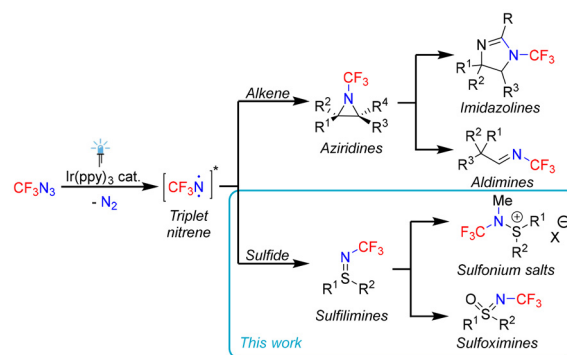
Introduction

Fluorinated compounds are essential across various disciplines, including materials science, agrochemistry, and pharmaceuticals. Notably, over 20% of approved drugs feature at least one fluorine atom,[1–7] underscoring the critical need for advanced synthetic strategies that enable the precise and selective incorporation of fluorine atoms and fluorine-containing moieties into molecular frameworks. Recent studies have shown that the substitution of an azole by the trifluoromethyl group might enhance its medicinal properties such as cell membrane permeability, lipophilicity, and metabolic stability.[8] Regardless of their high demand, *N*-fluoroalkylated compounds are still much less explored in comparison to their *O*-, *S*-, and *C*-fluoroalkylated counterparts, which is partly due to their underdeveloped synthetic approaches. Despite the extensive literature on fluoroalkylation, direct fluoroalkylation is challenging due to the selectivity issues, particularly in the late-stage modification of complex substrates.[9,10] For instance, rather than introducing a fluoroalkyl group onto a heteroatom such as nitrogen, it may be more efficient to incorporate the heteroatom-fluoroalkyl unit into the molecule in a single step.

The incorporation of N–R into a molecular framework with R being alkyl, acyl, or aryl might be envisioned *via* nitrenes. Nitrenes have been utilized in synthetic organic chemistry for several decades for the modification of various structures.[11] Nowadays, there are numerous methods known for the generation of these highly reactive species *in situ* under mild and well-controlled conditions.[12] The most atom-economical way starts from the corresponding azides by photolysis, heating, or microwave-assisted methods, by which a molecule of nitrogen is eliminated to form the electrophilic nitrene.[13,14] The application of these uncharged species might be favoured as they can be utilized in the late-stage modification or skeletal editing of molecules.[15]

Previously, fluoroalkylated nitrenes were not known to partake in intermolecular reactions as they were formed under harsh conditions that promoted their quick rearrangement and decomposition.[16,17] Last year, we published a method that enabled the generation of triplet trifluoromethyl nitrene (CF₃N) by mild, photochemical conditions and showcased the utilization of the nitrene in alkene aziridination (Scheme 1).[18]

Apart from aziridination and C–H amination reactions, nitrenes are known to transfer to electron-rich heteroatoms such as sulfur.[19,20] The resulting products are sulfilimines, featuring an S=N double bond, with electrophilic character at the sulfur atom and nucleophilic character at the nitrogen

[a]Institute of Organic Chemistry and Biochemistry of the Czech Academy of Sciences, Flemingovo náměstí 2, 166 00 Prague, Czechia. E-mail: beier@uochb.cas.cz
[b]Department of Organic Chemistry, Faculty of Science, Charles University, Hlavova 2030/8, 128 43 Prague, Czechia

Scheme 1 Synthetic application of triplet trifluoromethyl nitrene. Our previous study and the present work.

atom, which opens the possibility for further modifications.[21] Different sulfilimines are known in the literature having various substituents on the nitrogen atom such as alkyl, aryl,[22] or electron-acceptor moieties such as acyl[23] or tosyl.[24] Sulfilimines are good substrates for the preparation of biologically relevant sulfoximines by simple oxidation. The significance of these molecules is demonstrated by their diverse applications,[25,26] including their use as a pest control agent (sulfoxaflor)[27] and as an ATR inhibitor (ceralasertib).[28]

In the present study, we aimed at harvesting further the reactivity of *in situ* generated triplet trifluoromethyl nitrene by the preparation of novel *N*-trifluoromethyl sulfilimines from sulfides. The synthetic application of these novel structures was shown through the preparation of their derivatives: *N*-methyl-*N*-trifluoromethyl sulfonium salts and *N*-trifluoromethyl sulfoximines (Scheme 1).
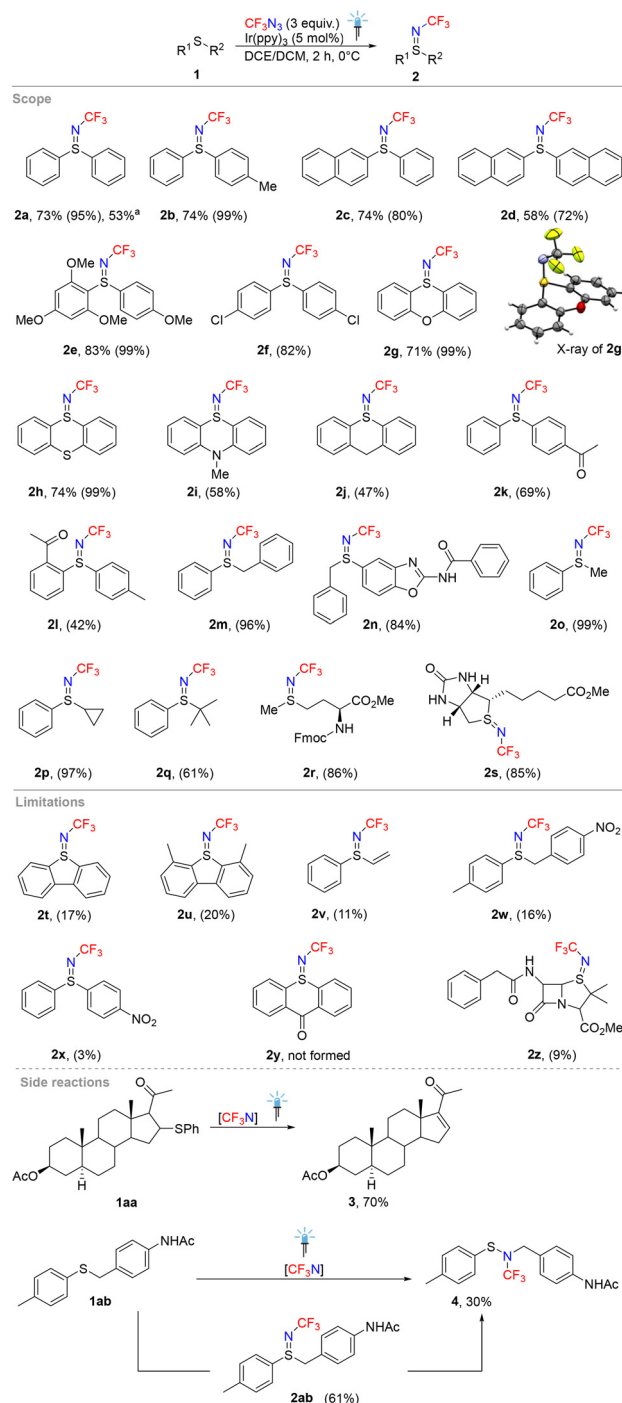
Results and discussion

Azidotrifluoromethane was prepared according to our previously published procedure.[18] We described the generation of trifluoromethyl nitrene using $Ir(ppy)_3$ as a photocatalyst through energy transfer. Then we optimized the conditions for the formation of previously unknown *N*-trifluoromethyl sulfilimines **2** (Table 1). First, the catalyst load was examined by irradiating the reaction mixture for 30 min with different equivalents of the photocatalyst (entries 1–4). It showed that increasing the amount of $Ir(ppy)_3$ resulted in a higher ^{19}F NMR yield. Next, the procedure was conducted separately, without a photocatalyst and light, which ensured that both were necessary for the reaction to occur (entries 5 and 6). Finally, the reaction time was optimized (entries 7–9). From the comparison of entries 8 and 9, it is evident that the reaction reached almost full conversion in 90 minutes, but to make sure that quantitative yield is achieved a two-hour irradiation was used.

Table 1 Optimization of photocatalytic sulfilimination[a]

Entry	$Ir(ppy)_3$ (mol%)	Time (min)	Yield of **2a**[b] (%)
1	1.0	30	37
2	2.0	30	55
3	3.5	30	62
4	5.0	30	71
5[c]	5.0	30	0
6	—	30	0
7	5.0	60	88
8	5.0	90	98
9	5.0	120	>98

[a] **1a** (0.1 mmol), CF_3N_3 (3 equiv.), $Ir(ppy)_3$, 3 Å molecular sieves, DCE/DCM under Ar atmosphere, irradiated with visible light LED (λ_{max} = 400 nm, 3 W). [b] ^{19}F NMR yields using $PhCF_3$ as an internal standard. [c] No light.

The scope of the photochemical sulfilimination reaction, including the major limitations, is summarized in Scheme 2. The optimized conditions were applicable to a broad range of sulfides; however, electron-rich diaryl sulfides showed the highest reactivity. Compounds **2a–h** formed in high yields and
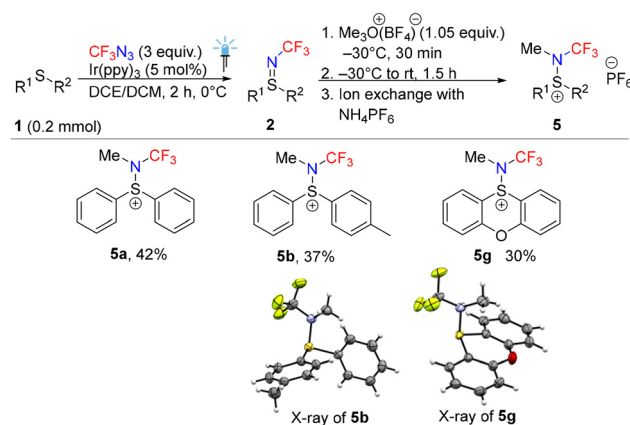

Scheme 2 Sulfilimination scope. Sulfide (0.1–0.2 mmol), $Ir(ppy)_3$ (5 mol%), CF_3N_3 (3 equiv.) and 3 Å molecular sieves sealed under argon at 0 °C irradiated for 2 h with LED light (400 nm, 3 W); isolated yields; ^{19}F NMR yields using $PhCF_3$ as an internal standard in parentheses. [a] 1 mmol scale and 6 h reaction time.

This journal is © the Partner Organisations 2025

Org. Chem. Front., 2025, **12**, 5610–5615 | **5611**

in most cases, quantitative ^{19}F NMR yields were achieved. Scale-up from 0.1 mol to 1 mmol scale of **2a** required the extension of reaction time from 2 hours to 6 hours. Compounds **2g** and **2h** were obtained in excellent yields and exhibited high stabilities. Additionally, the structure of **2g** was confirmed by single-crystal X-ray diffraction analysis. Notably, in the case of **2h**, only one of the sulfur atoms participated in the reaction, and no trace of a double sulfiliminated product was detected. Compounds **2i** and **2j** gave less favorable results: in the case of **2i**, an unidentified side product formed, while the yield of **2j** was lower due to possible C–H amination at the activated benzylic position. The electron-acceptor acyl group was tolerated on the aromatic ring of the sulfide; however, in the *ortho* position the steric hindrance further reduced product yield (**2l**). Generally, diaryl sulfilimines showed sufficient stability for purification by crystallization. The unreacted substrate was washed off with an apolar solvent, and the product dissolved in diethyl ether which efficiently removed the residual catalyst and any decomposed material. Aryl–benzyl and aryl–alkyl sulfides took part in the sulfilimination reaction efficiently; however, product stabilities were reduced. Compounds **2m** and **2n** can be handled at room temperature, but during the lengthy process of crystallization, both slowly decomposed. Products **2o** and **2p** formed almost quantitatively, but **2o** was unstable even at −20 °C in solution or neat. In product **2q** the *t*-Bu group was partially cleaved with the applied irradiation conditions. The formation of products **2r** and **2s** showed that the reaction efficiently proceeds with dialkyl substrates. Together with **2n**, they show that the procedure can be applied in late-stage introduction of the *N*-CF$_3$ moiety into complex sulfides. The major limitation of the scope were electron-deficient substrates. Thiophene derivatives and electron-poor sulfides afforded products only in low to moderate yields. Vinyl sulfide reacted partially on the alkene moiety in alkene aziridination fashion. Other electron-poor sulfides were mostly unreactive. Side reactions were not observed which showed that the process is generally selective to the electron-rich sulfur atom. Exceptions were compounds **1aa**, which gave **3** in good yield by thiol elimination, and **1ab**, which underwent a rearrangement after initial sulfimination at low temperature.

Next, we explored the reactivity novel *N*-CF$_3$ sulfilimines **2**. Some *N*-substituted sulfilimines were shown to undergo methylation on nitrogen to form sulfonium salts. This area has been relatively unresearched in recent decades as most of the relevant literature is from the 1970s and 1980s. Strong methylating reagents, such as FSO$_3$Me,[29] CF$_3$SO$_3$Me[30] and (Me$_3$O)BF$_4$[31] were used for methylation of electron-poor sulfilimines. Several examples of the exotic *N*-methyl-*N*-trifluoromethyl sulfonium salts **5** were prepared and isolated as hexafluorophosphate salts by reacting sulfilimines **2** with the Meerwein salt, followed by ion exchange (Scheme 3).

Sulfilimines are known to be oxidized to sulfoximines by various oxidants. Several conditions were tested: KO$_2$[32] or KMnO$_4$[33] in the presence of crown ether, Davis reagent, *m*CPBA with K$_2$CO$_3$,[34] TPAP with NMO[35] and RuCl$_3$ in the pres-

Scheme 3 Preparation of *N*-methylated sulfonium salts **5** in one pot from **1**.

ence of periodate for the *in situ* formation of ruthenium tetroxide.[36] In the case of sulfilimines **2**, the modified methods utilizing *m*CPBA or the RuCl$_3$/NaIO$_4$ systems resulted in oxidation. However, with *m*CPBA only a maximum of 30% conversion could be reached. Reaction optimization with Ru(III) was conducted on compound **2a** (Table 2). The process gave a mixture of products; apart from the anticipated sulfoximine (**6a**), diphenyl sulfone (**7a**) was formed.
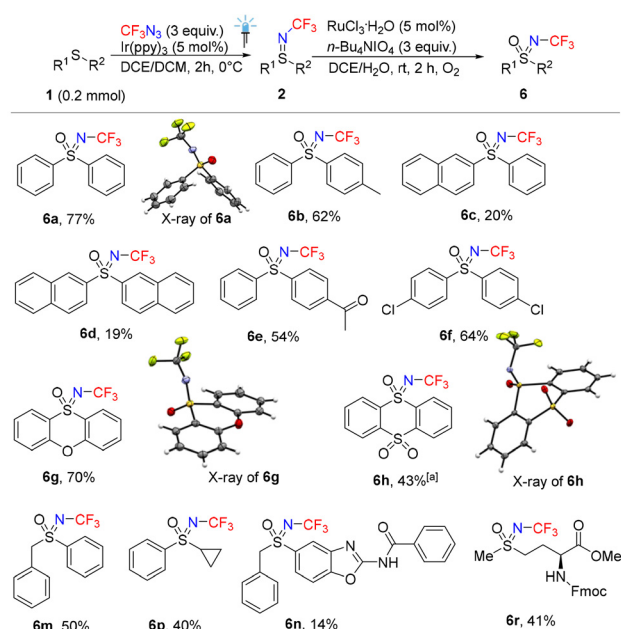
First, NaIO$_4$ was tested with a higher Ru(III) load under an inert and oxygenated atmosphere (entries 1 and 2). In both cases, full conversion was achieved within the two-hour reaction time; however, the absence of oxygen negatively impacted the **6a**/**7a** ratio. The catalyst load was reduced to 5 mol% which resulted in approximately the same product ratio (entry 3). Periodate with a lipophilic tetrabutylammonium cation was tested in different solvents (entries 4–9) revealing that this oxidant was superior to NaIO$_4$. The reaction was best conducted in DCE/water mixture as in the absence of water only sulfone **7a** was formed.

Table 2 Optimization of the sulfoximination process to **6a**

Entry	Oxidant	MeCN/DCE/H$_2$O	6a/7a
1^{a,b}	NaIO$_4$	1:1:2	48:52
2^a	NaIO$_4$	1:1:2	82:18
3	NaIO$_4$	1:1:2	83:17
4	*n*-Bu$_4$NIO$_4$	1:1:1	31:69
5	*n*-Bu$_4$NIO$_4$	2:0:1	10:90
6	*n*-Bu$_4$NIO$_4$	10:10:1	1:99
7	*n*-Bu$_4$NIO$_4$	1:1:0	1:99
8	*n*-Bu$_4$NIO$_4$	1:1:2	86:14
9	*n*-Bu$_4$NIO$_4$	0:1:1	**91:9**
10	NaIO$_4$	0:1:2	58:42
11	*n*-Bu$_4$NIO$_4$	0:1:2	75:25
12	NaIO$_4$	0:1:1	73:27

^{a} RuCl$_3$·H$_2$O (20 mol%). ^{b} Under N$_2$ atmosphere.

5612 | *Org. Chem. Front.*, 2025, **12**, 5610–5615

This journal is © the Partner Organisations 2025

Organic Chemistry Frontiers

Scheme 4 Scope of the sulfoximines **6** prepared in two steps from sulfides **1**. [a] n-Bu$_4$NIO$_4$ (5 equiv.).

Applying the optimized conditions (entry 9), a range of N-trifluoromethyl sulfoximines **6** was prepared and isolated successfully in moderate to good yields (Scheme 4). The oxidative procedure worked efficiently with various substrates including diaryl, aryl–alkyl and even dialkyl substituted sulfilimines. Good yields were obtained mainly with the diaryl-substituted sulfilimines. In the case of **6h** the free sulfur atom was also oxidized during the reaction upon using a higher excess of the oxidant. Additionally, structures **6a**, **6g** and **6h** were confirmed by single-crystal X-ray analysis. Moderate yields of sulfoximines **6m**, **6p** and **6r** were obtained from rather unstable, non-isolable sulfilimines. In the case of **6r** a mixture of diastereomers in 1 : 1 ratio was isolated. The procedure was extended to more complex structures such as **6n** and **6r**. The scope clearly demonstrated that even poorly stable N-CF$_3$-sulfilimines can be oxidized using this procedure, yielding products stable in aqueous media. This paves the way for further exploration of the properties of these rare trifluoromethyl-containing sulfoximine moieties.

Conclusions

In conclusion, we demonstrated a new reactivity of the *in situ* formed trifluoromethyl nitrene under mild photocatalytic conditions. This highly reactive nitrene species selectively added to electron-rich sulfides, leading to previously unreported N-CF$_3$ sulfilimines. They were further functionalized through nitrogen methylation and sulfur oxidation giving N-methyl-N-trifluoromethyl sulfonium salts and N-trifluoromethyl sulfoximines, respectively. Access to these structures significantly enhances the diversity of N-CF$_3$-containing molecular library,

offering promising opportunities for applications in synthetic and medicinal chemistry.

Author contributions

N. B. conceived the idea, performed experiments, and partially wrote the manuscript, M. D. performed NMR experiments, L. J. T. synthesized and characterized **1n**, B. K. performed X-ray crystallography. P. B. conceived the idea, acquired funding, administered and supervised the project, and partially wrote the manuscript.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included as part of the ESI.† Crystallographic data has been deposited at the CCDC under the following accession numbers: **2g** (2457295), **5b** (2457296), **5g** (2457297), **6a** (2457298), **6g** (2457299), **6h** (2457300).†

References

1   A. A. Abbas, T. A. Farghaly and K. M. Dawood, Recent progress in therapeutic applications of fluorinated five-membered heterocycles and their benzo-fused systems, *RSC Adv.*, 2024, **14**, 33864–33905.

2   V. Prakash Reddy, *Organofluorine compounds in biology and medicine*, Elsevier, 2015.

3   M. Inoue, Y. Sumii and N. Shibata, Contribution of organofluorine compounds to pharmaceuticals, *ACS Omega*, 2020, **5**, 10633–10640.

4   H.-J. Böhm, D. Banner, S. Bendels, M. Kansy, B. Kuhn, K. Müller, U. Obst-Sander and M. Stahl, Fluorine in medicinal chemistry, *ChemBioChem*, 2004, **5**, 637–643.

5   N. Sheikhi, M. Bahraminejad, M. Saeedi and S. S. Mirfazli, A review: FDA-approved fluorine-containing small molecules from 2015 to 2022, *Eur. J. Med. Chem.*, 2023, **260**, 115758.

This journal is © the Partner Organisations 2025

Org. Chem. Front., 2025, **12**, 5610–5615 | **5613**

6 S. Purser, P. R. Moore, S. Swallow and V. Gouverneur, Fluorine in medicinal chemistry, *Chem. Soc. Rev.*, 2008, **37**, 320–330.

7 N. A. Meanwell, Fluorine and fluorinated motifs in the design and application of bioisosteres for drug design, *J. Med. Chem.*, 2018, **61**, 5822–5880.

8 S. Schiesser, H. Chepliaka, J. Kollback, T. Quennesson, W. Czechtizky and R. J. Cox, N-Trifluoromethyl Amines and Azoles: An Underexplored Functional Group in the Medicinal Chemist's Toolbox, *J. Med. Chem.*, 2020, **63**, 13076–13089.

9 R. Britton, V. Gouverneur, J.-H. Lin, M. Meanwell, C. Ni, G. Pupo, J.-C. Xiao and J. Hu, Contemporary synthetic strategies in organofluorine chemistry, *Nat. Rev. Methods Primers*, 2021, **1**, 47.

10 D. Lin, M. Coe, V. Krishnamurti, X. Ispizua-Rodriguez and G. K. S. Prakash, Recent Advances in Visible Light–Mediated Radical Fluoro–alkylation,–alkoxylation,–alkylthiolation,–alkylselenolation, and–alkylamination, *Chem. Rec.*, 2023, **23**, e202300104.

11 W. Lwowski, Nitrenes and the decomposition of carbonylazides, *Angew. Chem., Int. Ed. Engl.*, 1967, **6**, 897–906.

12 Y. C. Wang, X. J. Lai, K. Huang, S. Yadav, G. Qiu, L. Zhang and H. Zhou, Unravelling nitrene chemistry from acyclic precursors: recent advances and challenges, *Org. Chem. Front.*, 2021, **8**, 1677–1693.

13 K. Shin, H. Kim and S. Chang, Transition-metal-catalyzed C–N bond forming reactions using organic azides as the nitrogen source: a journey for the mild and versatile C–H amination, *Acc. Chem. Res.*, 2015, **48**, 1040–1052.

14 T. Uchida and T. Katsuki, Asymmetric nitrene transfer reactions: sulfimidation, aziridination and C–H amination using azide compounds as nitrene precursors, *Chem. Rec.*, 2014, **14**, 117–129.

15 P. Bhatti, A. Gupta, S. B. Chaudhari, R. K. Valmiki, J. K. Laha and S. Manna, Skeletal Editing via Transition–Metal–Catalyzed Nitrene Insertion, *Chem. Rec.*, 2024, **24**, e202400184.

16 C. J. Schack and K. O. Christe, Reactions of azidotrifluoromethane with halogen-containing oxidizers, *Inorg. Chem.*, 1983, **22**, 22–25.

17 C. G. Krespan, Fluoroalkyl azide chemistry, *J. Org. Chem.*, 1986, **51**, 332–337.

18 N. Baris, M. Dračínský, J. Tarábek, J. Filgas, P. Slavíček, L. Ludvíková, S. Boháčová, T. Slanina, B. Klepetářová and P. Beier, Photocatalytic generation of trifluoromethyl nitrene for alkene aziridination, *Angew. Chem., Int. Ed.*, 2024, **63**, e202315162.

19 V. Bizet, L. Buglioni and C. Bolm, Light–Induced Ruthenium–Catalyzed Nitrene Transfer Reactions: A Photochemical Approach towards N–Acyl Sulfimides and Sulfoximines, *Angew. Chem., Int. Ed.*, 2014, **53**, 5639–5642.

20 Z. Liu, H. Wu, H. Zhang, F. Wang, X. Liu, S. Dong, X. Hong and X. Feng, Iron-catalyzed asymmetric imidation of sulfides via sterically biased nitrene transfer, *J. Am. Chem. Soc.*, 2024, **146**, 18050–18060.

21 T. L. Gilchrist and C. J. Moody, The chemistry of sulfilimines, *Chem. Rev.*, 1977, **77**, 409–435.

22 T. Meng, L. A. Wells, T. Wang, J. Wang, S. Zhang, J. Wang, M. C. Kozlowski and T. Jia, Biomolecule-compatible dehydrogenative Chan–Lam coupling of free sulfilimines, *J. Am. Chem. Soc.*, 2022, **144**, 12476–12487.

23 Q. Liang, L. A. Wells, K. Han, S. Chen, M. C. Kozlowski and T. Jia, Synthesis of Sulfilimines Enabled by Copper-Catalyzed S-Arylation of Sulfenamides, *J. Am. Chem. Soc.*, 2023, **145**, 6310–6318.

24 M. Han, Z. Tang, G. Li and Q. Wang, Electrochemical oxidation chemoselective sulfimidation of thioether with sulfonamide via catalytic iodobenzene, *Tetrahedron Lett.*, 2022, **102**, 153925.

25 M. Frings, C. Bolm, A. Blum and C. Gnamm, Sulfoximines from a medicinal chemist's perspective: physicochemical and in vitro parameters relevant for drug discovery, *Eur. J. Med. Chem.*, 2017, **126**, 225–245.

26 P. Mäder and L. Kattner, Sulfoximines as rising stars in modern drug discovery? Current status and perspective on an emerging functional group in medicinal chemistry, *J. Med. Chem.*, 2020, **63**, 14243–14275.

27 J. M. Babcock, C. B. Gerwick, J. X. Huang, M. R. Loso, G. Nakamura, S. P. Nolting, R. B. Rogers, T. C. Sparks, J. Thomas, G. B. Watson and Y. Zhu, Biological characterization of sulfoxaflor, a novel insecticide, *Pest Manage. Sci.*, 2011, **67**, 328–334.

28 M. Kwon, G. Kim, R. Kim, K.-T. Kim, S. T. Kim, S. Smith, P. G. S. Mortimer, J. Y. Hong, A.-B. Loembé, I. Irurzun-Arana, L. Koulai, K.-M. Kim, W. K. Kang, E. Dean, W.-Y. Park and J. Lee, Phase II study of ceralasertib (AZD6738) in combination with durvalumab in patients with advanced gastric cancer, *J. Immunotherap. Cancer*, 2022, **10**, e005041.

29 E. Vilsmaier, M. Huber and J. Schütz, Umlagerung von (Tosylamino) sulfoniumsalzen, *Liebigs Ann. Chem.*, 1980, **1980**, 1055–1063.

30 D. Darwish and S. K. Datta, The racemization of an optically active sulfilimine and optically active aminosulfonium salts, *Tetrahedron*, 1974, **30**, 1155–1160.

31 C. R. Johnson, J. J. Rigau, M. Haake, D. McCants, J. E. Keiser and A. Gertsema, N-alkylation of sulfilimines and sulfoximines, *Tetrahedron Lett.*, 1968, **9**, 3719–3722.

32 K. Akutagawa, N. Furukawa and S. Oae, Oxidation of S, S-diaryl-N-(p-tolylsulfonyl) sulfilimines and N-unsubstituted S, S-diaryl-sulfilimines with potassium hyperoxide anion radical (O_2^-) in the presence of 1-bromopropane, benzoyl chloride, para-tolylsulfonyl chloride, carbon-tetrachloride, chloroform, or dichloromethane in aprotic media, *Bull. Chem. Soc. Jpn.*, 1984, **57**, 1104–1107.

33 C. A. Dannenberg, V. Bizet and C. Bolm, Direct access to n-alkylsulfoximines from sulfides by a sequential imidation/oxidation procedure, *Synthesis*, 2015, 1951–1959.

34 J. Wang, M. Frings and C. Bolm, Enantioselective nitrene transfer to sulfides catalyzed by a chiral iron complex, *Angew. Chem., Int. Ed.*, 2013, **52**, 8661–8665.

5614 | *Org. Chem. Front.*, 2025, **12**, 5610–5615

This journal is © the Partner Organisations 2025

35 Z.-X. Zhang, T. Q. Davies and M. C. Willis, Modular sulfon-diimine synthesis using a stable sulfinylamine reagent, *J. Am. Chem. Soc.*, 2019, **141**, 13022–13027.

36 P. Wu, J. Demaerel, B. J. Statham and C. Bolm, Azasulfur(IV) derivatives of sulfite and sulfinate esters by formal S–S bond insertion of dichloramines, *Chem. Sci.*, 2024, **15**, 5333–5339.

This journal is © the Partner Organisations 2025

Org. Chem. Front., 2025, **12**, 5610–5615 | **5615**