Synthesis of Sulfinamidines and Sulfinimidate Esters by Transfer of Nitrogen to Sulfenamides

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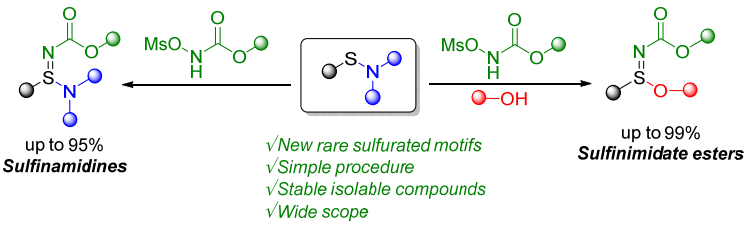
Supporting Information Placeholder



ABSTRACT: In this work we report a new synthetic tactic for the straightforward preparation of hardly accessible sulfinamidines and sulfinamide esters, by using a simple metal-free protocol. The process is robust and uses readily available sulfenamides as the S-donor and sulfonyloxycarbamates as N-source. Scope and mechanism have also been investigated.

The development of novel synthetic strategies for the installation of sulfur-bearing functional groups has great impact in drug discovery, since these motifs can be found in several biologically active molecules and natural products, and their preparation allows the assessment of interesting bioisosteres. [1] Tetravalent sulfur motifs as sulfones and sulfonamides are well established in pharmaceutics, and recently there has been a growing interest in the development of synthetic methodologies for the preparation of their aza analogues such as sulfoximines and sulfonamidamides. [2] In particular, the replacement of the oxygen atom with nitrogen is crucial to the efficient modulation of physicochemical properties and to the introduction of molecular diversity. In striking contrast, the landscape of trivalent sulfur motifs is dominated by sulfoxides, sulfinate esters and sulfinamides while the preparation of other potentially important trivalent sulfur aza-analogues such as sulfinimidate esters and sulfinamidines, remains a very poorly explored topic (Figure 1). In fact, synthesis of either sulfinimidate esters or sulfinamidines represents a challenge, and the very few methods available for their preparation have several limitations. Sulfinamidines have been prepared by reaction of sulfurdiimide with conjugated dienes or alkenes (Scheme 1, a), [3,4] or by using sodium arylsulfonylchloroamide and disulfides (Scheme 1, b). [5] Other strategies with limited scope and versatility have been reported. [6,7,8]

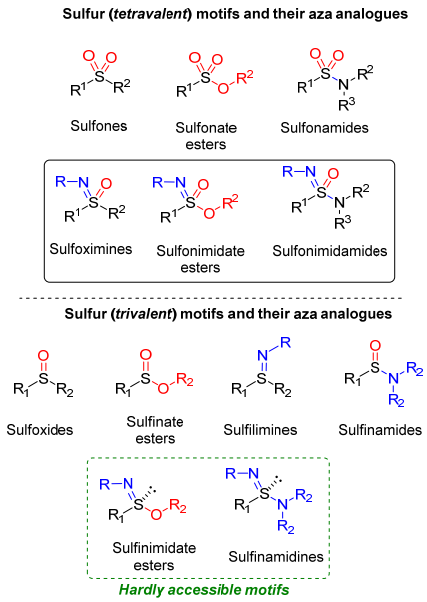
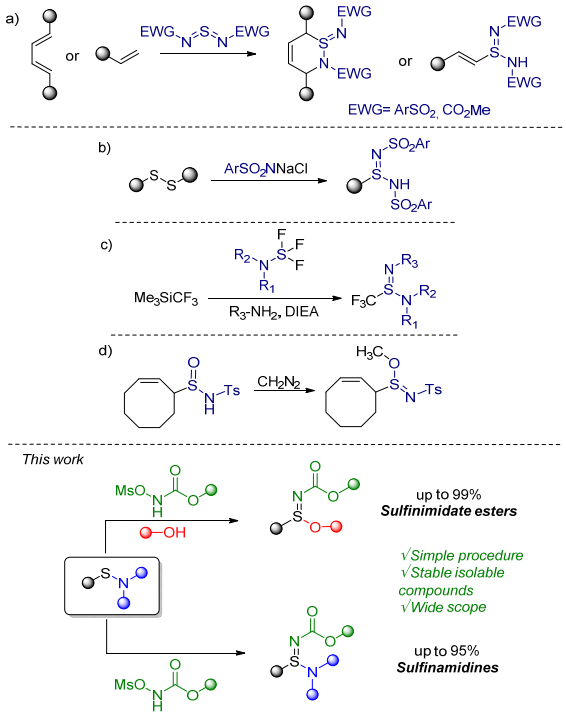


Figure 1. Sulfur-bearing functional groups and their aza analogues

Ferry reported the use of dialkylaminosulfur trifluorides, amines and trifluoromethyltrimethylsilane for a specific

synthesis of trifluoromethyl-substituted sulfinamidines (Scheme 1, c). [9] In spite of their application as ligands, synthetic intermediates, and additives for lithium power sources,[5,6,10] no relevant advances have been reported during the last decades for a general synthesis of sulfinamidines. Furthermore, the preparation and chemistry of sulfinimidate esters remains still severely underdeveloped. Interestingly, only a single case of *N*-tosylmethyloxysulfinimidate, relying on the reaction of *N*-tosyl sulfinamide with diazomethane, has been reported (Scheme 1, d). [11] Sulfinimidate esters have been reported as byproducts or as sulfonium salts.[12,13]

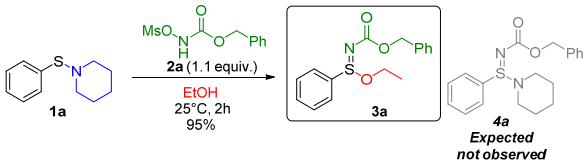
Scheme 1. Strategies to access sulfinamidines and sulfinimidate esters



Regarding the synthesis of aza analogues of sulfurated compounds, the direct imination of the sulfur atom represents an interesting transformation, and important advances have been achieved during the past few years by several research groups. [14] Most of the reported strategies for the imination of thioethers and sulfoxides involve the use of electrophilic aminating reagents, with or without metal catalysis.[14a, 15] Moreover, several imination strategies have been developed for the nitrogen transfer on other sulfurated compounds such as sulfenamides, sulfinamides and thiols.[14g-f,16] In continuation of our interest in the development of strategies for the electrophilic *N*-transfer to sulfur atom, we became interested in the development of an efficient strategy for accessing extremely rare sulfinamidines and sulfinimidate esters. Herein, we present a robust synthetic methodology to streamline the preparation of such sulfurated motifs offering, for the first time, a widely applicable tactic, overcoming concerns related to the old procedures. Inspired by recent contributes by Lebel and Amstrong, on the use of sulfonyloxycarbamates as nitrene sources for the imination of thioethers, we wanted to explore the reaction of such *N*-donor species with sulfenamides en route to the corresponding sulfinamidines.[15e,17]

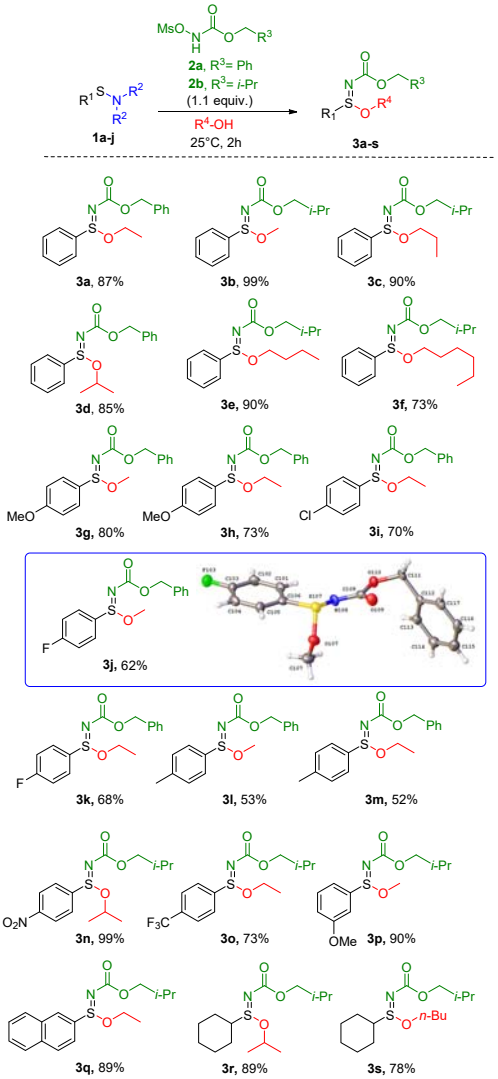
Our investigation started with the reaction of methylsulfonyloxycarbamate **2a** with sulfenamide **1a** in EtOH (Scheme 2). With our surprise, we observed a quantitative conversion of **2a** into the corresponding ethyl *N*–((benzyloxy)carbonyl)phenylsulfinimidate **3a** as confirmed by NMR and MS analysis (see SI), without evidence for the expected sulfinamidine **4a**.

Scheme 2. Preparation of *N*–[(benzyloxy)carbonyl]phenylsulfinimidate 3a



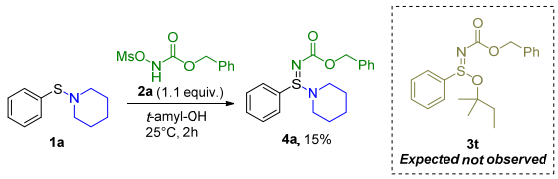
However, we considered this result remarkable in its own. In fact, this simple procedure would have allowed the preparation of not easily accessible sulfinimidate esters. With the aim to further explore the reaction and validate the method, sulfenamides **1a-j** were reacted with *N*-mesyloxycarbamates **2a** and **2b** in various alcoholic solvents (Scheme 3). With our delight sulfinimidate esters **3a-3s** where isolated with good to excellent yields. These results suggest that both **2a** and **2b** act as suitable electrophilic nitrogen sources in the reaction with sulfenamides.

Scheme 3. Scope for sulfinimidate esters 3.



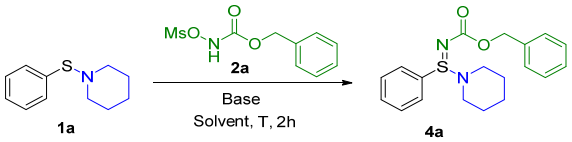
Moreover, the method tolerated different substituents on the aromatic ring of the sulfenamide such as *p*-Cl (**3i**), *p*-F (**3j** and **3k**), *p*-NO_2 (**3n**) and *p*-CF_3 (**3o**). Similarly, the presence of electron-donating groups such as *p*-OMe (**3g** and **3h**), *p*-Me (**3l** and **3m**) and *m*-OMe (**3p**) allowed the preparation of the products in good yields. The method was also compatible with different aromatic and aliphatic S-substituents. The reaction proceeds efficiently with naphthyl-substituted sulfenamide **1j**, giving sulfinimidate ester **3q** in 89% isolated yield, and with aliphatic sulfenamide **1j**, leading to derivatives **3r** and **3s** in good yields (Scheme 3). It should be noted that the reaction proceeds with piperidine-, pyrrolidine- and morpholine-substituted sulfenamides, and several primary and secondary alcohols can participate towards the formation of the corresponding sulfinimidate esters. The structure of these unusual sulfur derivatives was assigned on the basis of NMR and HMRS analysis and in the case of **3j** confirmed by X-ray analysis. Interestingly, the crystal structure of sulfinimidate ester **3j** revealed an almost pyramidal sulfur atom, with bond angles in the range 99° – 111°, and bond lengths of 1.78 Å (C-S), 1.62 Å (S-O) and 1.59 Å (S=N) respectively.[18] However, the reaction must comply with steric requirements, since the use of *tert*-amyl alcohol did not allow for the preparation of the corresponding sulfinimidate ester **3t** from sulfenamide **1a** even in traces (Scheme 4). Much to our surprise, we were able to isolate the benzyl–(phenyl(piperidin–1–yl)–λ^4–sulfanylidene)carbamate **4a** in 15% yield. The structure of **4a** was initially assessed based on NMR, IR and HRMS analysis.

Scheme 4. First evidence for sulfinamidine.



Encouraged by this preliminary result, we persevered in our search for an efficient synthetic strategy for the preparation of sulfinamidines. Firstly, we ran an optimization study for the reaction of sulfenamide **1a** with **2a** as the nitrogen source (Table 1).

Table 1. Optimization study for the preparation of 4a.

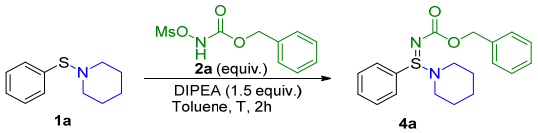


Entry	Solvent	T (°C)	Base (equiv.)	**2a** (equiv.)	**4a** yield [a]
1	toluene	25	-	1.0	20%
2	toluene	60	-	1.0	-
3	toluene	25	K_2CO_3 (1.5)[b]	1.0	35%
4	toluene	25	DIPEA (1.5)	1.0	38%
5	toluene	50	DIPEA (1.5)	1.2	53%
6	CH_2Cl_2	0	K_2CO_3 (1.5) [b]	1.0	21%
7	CH_2Cl_2	25	K_2CO_3 (1.5) [b]	1.0	35%
8	CH_2Cl_2	0	K_2CO_3 (1.5) [b]	1.3	29%
9	CH_2Cl_2	25	K_2CO_3 (1.5) [b]	1.3	43%
10	2-MeTHF	25	K_2CO_3 (1.5) [b]	1.0	-
11	MeOH	25	K_2CO_3 (1.5) [b]	1.0	traces

[a] Yields calculated by ^{1}H NMR analysis of the crude reaction mixture in the presence of internal standard. [b] An aqueous solution of K_2CO_3 was employed.

Sulfinamidine **4a** was obtained in 20% of yield when an equimolar quantity of **1a** and **2a** were stirred in toluene at room temperature for 2 h (Table 1, entry 1). However, raising the temperature up to 60°C, resulted in decomposition of the reactants (Table 1, entry 2). Assuming that a base would have been required in this process, we ran the reaction in the presence of 1.5 equivalents of aqueous K_2CO_3 or DIPEA (diisopropylethylamine). Under these conditions (Table 1, entries 3-4) **4a** was obtained in 35% and 38% yield respectively. The yield of **4a** improved up to 53%, using 1.2 equivalents of **2a** at 50°C in toluene (Table 1, entry 5). Similar results were obtained running the reaction in CH_2Cl_2 (Table 1, entries 6-9), while complex mixtures were observed in polar solvents such as 2-MeTHF or MeOH (Table 1, entries 10-11). With the aim to improve yields of **4a** and speed up the optimization study, a Design of Experiment (DoE) approach was applied to this process. The equivalents of **2a**, and the temperature were selected as main variables, since such factors appeared to be critical for the reaction. Therefore, a full factorial 2^2 design (see S.I. for details) was selected, and the reactions were performed in toluene in the presence of 1.5 equivalents of DIPEA (Table 2).

Table 2. DoE optimization study for the preparation of 4a.



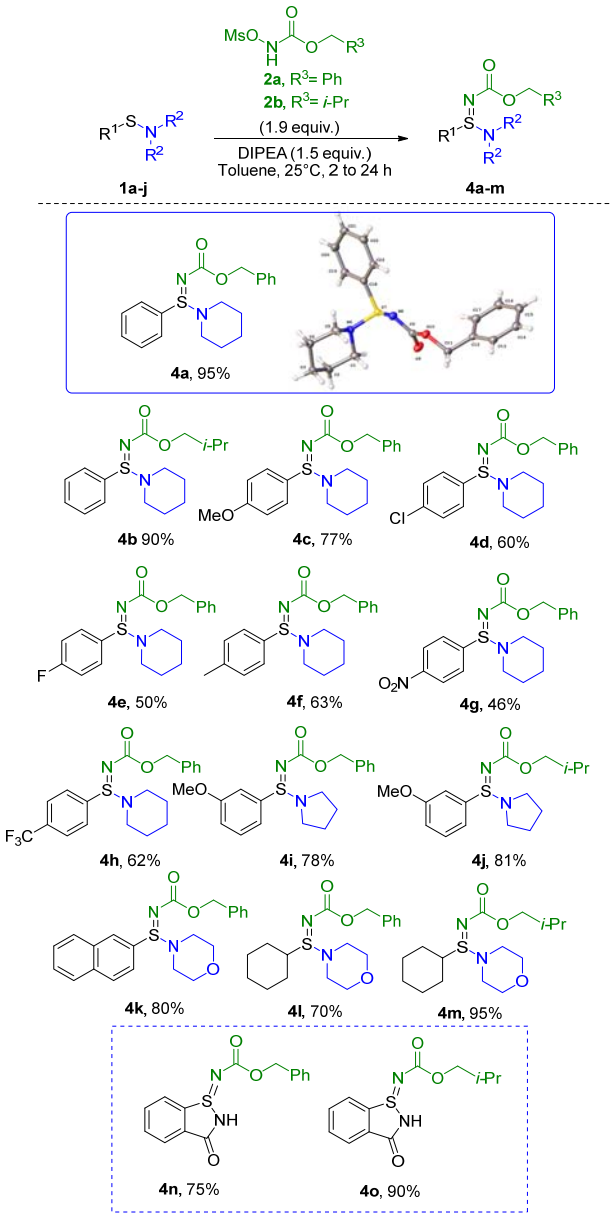
Entry	**2a** (Equiv.)	T (°C)	**4a** yield[a]
1	1.6	0	45%
2	1.9	0	53%
3	1.6	25	73%
4	**1.9**	**25**	**95%**

[a] Yields calculated by ^{1}H NMR analysis of the crude reaction mixture in the presence of internal standard.

Remarkably, sulfinamidine **4a** could be obtained in 95% yield carrying out the reaction at 25 °C, and with the use of 1.9 equivalents of **2a**. With the optimal conditions in hand, the scope of the reaction was explored (Scheme 5). Sulfenamides **1a-k** were reacted with N-sources **2a** and **2b** under the optimized conditions observing the formation of the corresponding sulfinamidines **4a-m** in good to excellent yields. The reaction leading to **4a** was scaled to 2 mmol and the corresponding sulfinamidine crystallized. With our delight, X-ray analysis confirmed the structure of **4a** and revealed a pyramidal sulfur atom with angles in the range 99° - 111° and bond lengths of 1.62 and 1.68 Å for S-N double and single bonds respectively, and 1.78 Å for C-S bond.[19] The reaction tolerated both electron-withdrawing (i.e. **4d**,**f**, **4g**,**h**) and electron-donating groups (i.e. **4c**, **4i**,**j**) as well as naphthyl group (**4k**) and aliphatic S-substituents (**4l**,**m**). However, the transformation of ((cyclohexyl)thio)morpholine **1j** required longer reaction times (24h), affording the products in excellent yields. Similarly, when 1–((4–nitrophenyl)thio)piperidine **1f** was reacted, the reaction mixture was stirred during 24h before observing the total consumption of sufenamide. Remarkably, the use of commercially available NH-sulfenamide **1k** returned the corresponding sulfinamidines

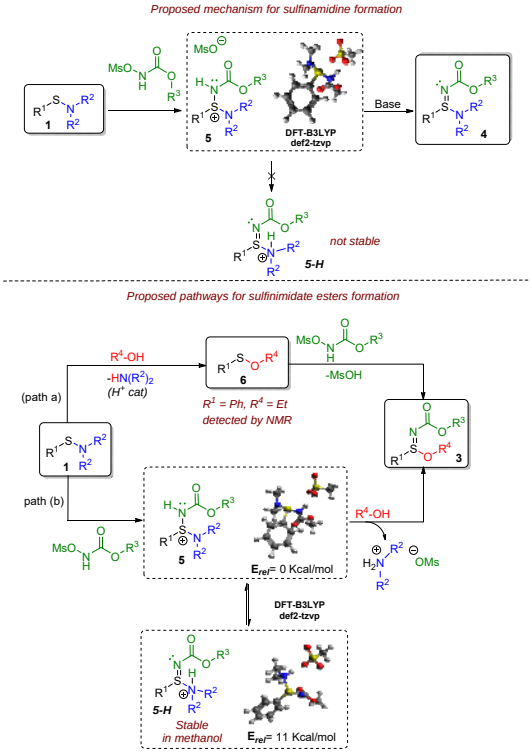
4n and **4o** in good yields. However, the preparation of this kind of scaffold would require multistep synthesis.[20]

Scheme 5. Scope for synthesis of sulfinamidines 4.



After assessing the methods for the preparation of either sulfinimidate esters **3** and sulfinamidines **4**, we turned our attention to the mechanism of the reaction. To this end, we performed a NMR investigation conducting the reaction in a NMR tube (see SI). Firstly, we studied the formation of sulfinamidine **4a** by monitoring the reaction with sequential ^{1}H NMR analysis. This study revealed a quick reaction between **2a** and **1a** with an almost instantaneous formation of an intermediate species, likely the salt **5** (Scheme 6). Subsequently, the addition of DIPEA to the solution cleanly afforded sulfinamidine **4a**. A slightly different situation was observed in the case of sulfinimidate ester **3a**. In fact, the outcome of the experiments depended on the adopted reaction conditions. The NMR investigation revealed a competition in the formation either of **4a** or **3a**, and that the presence of the alcohol was crucial for speed up the reaction and selectivity. It was observed that in the presence of the alcohol and traces of acid, sulfenamide **1a** was partially converted into a sulfenate ester (**6**, Scheme 6). Upon addition of the N-source **2a**, conversion of ester **6** into the sulfinamidate ester **3** occurred. Based on our mechanistic investigation, we proposed the pathways depicted in Scheme 6 to justify the formation of derivatives **3** and **4**. To further support our hypotheses, the reaction was investigated computationally *in silico* on a model system using DFT-B3LYP method with def2-tzvp basis set (see SI).

Scheme 6. Proposed mechanisms.



Computational results suggested that the substitution reaction leading to intermediate **5** (Scheme 6) is an exothermic process, with a calculated enthalpy $\Delta H = -94.9\ kJ/mol$ (see SI). In addition, a proton transfer forming **5H** was ruled out by calculations. It is reasonable that adducts of the kind of **5** give sulfinamidines **4** when reacted under basic conditions. Our attention was subsequently focused on the elucidation of the mechanisms for the formation of sulfinimidate esters **3**. The NMR study suggested that the reaction can follow different pathways. Sulfinimidate esters may arise by direct immination of sulfenate ester **6** (path a, Scheme 6) or from a solvent-induced (R^4OH) displacement of the aminic portion on intermediate **5** or **5-H**, after proton exchange between the carbammic and aminic nitrogen, followed by the final deprotonation (path b, Scheme 6). On the other hand, the proton exchange may be promoted by the solvent proximity in a concerted transformation. Such hypotheses are supported by calculations that revealed a minimum for **5-H** in methanol, although this is less stable than **5**, while intermediacy of a tetrahedral intermediate was ruled out by calculations. In conclusion, in this work we reported a new synthetic route for the straightforward preparation of hardly accessible sulfinamidines and sulfinamide esters using a simple metal-free procedure. The mechanism has been investigated spectroscopically and computationally, and a mechanism proposed. The

process is robust and provide stable trivalent sulfur derivatives that could be used as precursors of other interesting sulfur derivatives such as sulfonimidates, sulfoximines and sulfonimidamides.[21] Further investigations are ongoing in our lab and will be reported in due course.

ASSOCIATED CONTENT

Supporting Information.

The Supporting Information is available free of charge on the ACS Publications website. Characterization data for the prepared molecules, list of sulfenamides, optimization study by DoE, mechanistic study, DFT-calculations, Ortep views of crystal structures.

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Author Contributions

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

‡M.A. and M.S. contributed equally to this work

Notes

The authors declare no competing financial interests.

Dedication

Dedicated to Prof. Saverio Florio on the occasion of his 80th birthday.

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REFERENCES

(1) (a) Feng, M.; Tang, B.; H. Liang, S.; Jiang, X. Sulfur Containing Scaffolds in Drugs: Synthesis and Application in Medicinal Chemistry. *Curr. Top. Med. Chem.* **2016**, 16 (11), 1200–1216; (b) Zhao, C.; Rakesh, K. P.; Ravidar, L.; Fang, W.-Y.; Qin, H.-L. Pharmaceutical and Medicinal Significance of Sulfur (SVI)-Containing Motifs for Drug Discovery: A Critical Review. *Eur. J. Med. Chem.* **2019**, 162, 679–734.

(2) a) Lücking, U. Neglected Sulfur(VI) Pharmacophores in Drug Discovery: Exploration of Novel Chemical Space by the Interplay of Drug Design and Method Development. *Org. Chem. Front.* **2019**, 6 (8), 1319–1324. b) Nandi, G. C.; Arvidsson, P. I. Sulfonimidamides: Synthesis and Applications in Preparative Organic Chemistry. *Adv. Synt. Cat.* **2018**, 360, 2976 – 3001.

(3) Natsugari, H.; Whittle, R. R.; Weinreb, S. M. Stereocontrolled Synthesis of Unsaturated Vicinal Diamines from Diels-Alder Adducts of Sulfur Dioxide Bis(imides*). J. Am. Chem. Soc.* **1984**, 106 (25), 7867–7872.

(4) (a) Bussas, R.; Kresze, G. Zur Chemie der Schwefeldiimide, 8. En-Reaktionen mit Schwefeldiimiden — Struktur der En-Komponente und Reaktivität bei der Umsetzung mit Ditosylschwefeldiimid. *Liebigs Annalen der Chemie* **1980**, 1980 (4), 629–649; (b) Bao, H.; Bayeh, L.; Tambar, U. K. Allylic Functionalization of Unactivated Olefins with Grignard Reagents. *Angew. Chem. Int. Ed.* **2014**, 53 (6), 1664–1668; (c) Bao, H.; Tambar, U. K. Catalytic Enantioselective Allylic Amination of Unactivated Terminal Olefins via an Ene Reaction/[2,3]-Rearrangement. *J. Am. Chem. Soc.* **2012**, 134 (45), 18495–18498; (d) Qin, L.; Sharique, M.; Tambar, U. K. Controllable, Sequential, and Stereoselective C–H Allylic Alkylation of Alkenes. *J. Am. Chem. Soc.* **2019**, 141 (43), 17305–17313.

(5) Koval, I. V. Imination of Sulfur-containing Compounds: XXXV. New Preparation Method and Oxidative Benzenesulfonylimination of Unsymmetrical Disulfides *Russ. J. Org. Chem.* **2002**, 38 (2), 232–234.

(6) (a) Haake, M.; Jürgler, W.; Spreemann, R. C-S Bond Cleavage Reactions of Sulfonediimines. *Phosphorus, Sulfur Relat. Elem.* **1994**, 95 (1–4), 315–316; (b) Diederich, W. E.; Haake, M. Synthesis and Structure of Novel $1\lambda^{4,2,6}$-Thiadiazines. *J. Org. Chem.* **2003**, 68 (10), 3817–3830.

(7) Barrett, A. G. M.; Gray, A. A.; Hill, M. S.; Hitchcock, P. B.; Procopiou, P. A.; White, A. J. P. Imino Sulfinamidines: Synthesis and Coordination Chemistry of a Novel Class of Chiral Bidentate Ligands. *Inorg. Chem.* **2006**, 45 (8), 3352–3358.

(8) (a) Minato, H.; Okuma, K.; Kobayashi, M. Syntheses of Diaza-, Azaoxa-, Diazaoxa-, and Triazasulfonium Ions. *J. Org. Chem.* **1978**, 43 (4), 652–658; (b) Celentano, G.; Colonna, S. Highly Enantioselective Synthesis of Dialkyl and Alkyl Aryl N-Tosylsulfimides. *Chem. Commun.* **1998**, No. 6, 701–702.

(9) Ferry, A.; Billard, T.; Langlois, B. R.; Bacqué, E. Synthesis of Trifluoromethanesulfinamidines and -Sulfanylamides. *J. Org. Chem.* **2008**, 73 (23), 9362–9365.

(10) Koval', I. V.; Shembel', E. M.; Chervakov, O. V.; Oleinik, T. G.; Globa, N. I. Lithium Salts of N,N'-Disubstituted Pentanesulfinamidines as Promising Additives for Lithium Power Sources. *Russ. J. Appl. Chem.* **2003**, 76 (10), 1611–1614.

(11) Ruminy, A. J.; Kresze, G. Reaktionen Vonn-Sulfinylverbindungen, XVI Neue Wege Zu Sulfinsäurederivaten Über En-addukte Vonn-Sulfinyl-Nonafluorbutansulfonamid. *Phosphorus, Sulfur Relat. Elem.* **1987**, 29 (1), 49–56.

(12) Dell'erba, C.; Corallo, G. P.; Novi, M.; Leandri, G. On the Reaction of Disulfides with Chloroamine-T in Alcoholic Solvents. A Reexamination. *Phosphorus, Sulfur Relat. Elem.* **1981**, 12 (1), 123–125.

(13) Kitagawa, H.; Matsuo, J.; Iida, D.; Mukaiyama, T. Oxidation of Primary Alkyl Triflates to the Corresponding Aldehydes via Alkoxy(N-Tert-Butylamino)(methyl)sulfonium Triflates. *Chem. Lett.* **2001**, 30 (6), 580–581

(14) (a) Zenzola, M.; Doran, R.; Luisi, R.; Bull, J. A. Synthesis of Sulfoximine Carbamates by Rhodium-Catalyzed Nitrene Transfer of Carbamates to Sulfoxides. *J. Org. Chem.* **2015**, 80 (12), 6391–6399; (b) Tota, A.; Zenzola, M.; Chawner, S. J.; John-Campbell, S. S.; Carlucci, C.; Romanazzi, G.; Degennaro, L.; Bull, J. A.; Luisi, R. Synthesis of NH-Sulfoximines from Sulfides by Chemoselective One-Pot N- and O-Transfers. *Chem. Commun.* **2017**, 53 (2), 348–351. (c) Lohier, J.-F.; Glachet, T.; Marzag, H.; Gaumont, A.-C.; Reboul, V. Mechanistic Investigation of the NH-Sulfoximination of Sulfide. Evidence for λ^6-Sulfanenitrile Intermediates. *Chem. Commun.* **2017**, 53 (12), 2064–2067; (d) Chaabouni, S.; Lohier, J.; Barthelemy, A.; Glachet, T.; Anselmi, E.;

Dagousset, G.; Diter, P.; Pégot, B.; Magnier, E.; Reboul, V. One-Pot Synthesis of Aryl- and Alkyl S -Perfluoroalkylated NH -Sulfoximines from Sulfides. *Chem. Eur. J.* **2018**, 24 (64), 17006–17010; (e) Tota, A.; St John-Campbell, S.; Briggs, E. L.; Estévez, G. O.; Afonso, M.; Degennaro, L.; Luisi, R.; Bull, J. A. Highly Chemoselective NH- and O-Transfer to Thiols Using Hypervalent Iodine Reagents: Synthesis of Sulfonimidates and Sulfonamides. *Org. Lett.* **2018**, 20 (9), 2599–2602; (f) Izzo, F.; Schäfer, M.; Stockman, R.; Lücking, U. A New, Practical One-Pot Synthesis of Unprotected Sulfonimidamides by Transfer of Electrophilic NH to Sulfinamides. *Chem. Eur. J.* **2017**, 23 (60), 15189–15193; (g) Briggs, E. L.; Tota, A.; Colella, M.; Degennaro, L.; Luisi, R.; Bull, J. A. Synthesis of Sulfonimidamides from Sulfenamides via an Alkoxy-amino-λ^6-sulfanenitrile Intermediate. *Angew. Chem. Int. Ed.* **2019**, 58 (40), 14303–14310; (h) Izzo, F.; Schäfer, M.; Lienau, P.; Ganzer, U.; Stockman, R.; Lücking, U. Exploration of Novel Chemical Space: Synthesis and in Vitro Evaluation of N-Functionalized Tertiary Sulfonimidamides. *Chem. Eur. J.* **2018**, 24 (37), 9295–9304; (i) Bizet, V.; Hendriks, C. M. M.; Bolm, C. Sulfur imidations: access to sulfimides and sulfoximines *Chem. Soc. Rev*. **2015**, *44*, 3378–3390.

(15) (a) Okamura, H.; Bolm, C. Rhodium-Catalyzed Imination of Sulfoxides and Sulfides: Efficient Preparation of N-Unsubstituted Sulfoximines and Sulfilimines. *Org. Lett.* **2004**, 6 (8), 1305–1307; (b) Lai, C.; Mathieu, G.; Gabrielli Tabarez, L. P.; Lebel, H. Batch and Continuous-Flow Iron(II)-Catalyzed Synthesis of Sulfilimines and Sulfoximines Using N -Mesyloxycarbamates. *Chem. Eur. J.* **2019**, 25 (40), 9423–9426; (c) Lebel, H.; Piras, H.; Borduy, M. Iron-Catalyzed Amination of Sulfides and Sulfoxides with Azides in Photochemical Continuous Flow Synthesis. *ACS Catal.* **2016**, 6 (2), 1109–1112; (d) Lebel, H.; Piras, H. Stereoselective Synthesis of Chiral Sulfilimines from N-Mesyloxycarbamates: Metal-Nitrenes versus Metal-Nitrenoids Species. *J. Org. Chem.* **2015**, 80 (7), 3572–3585; (e) Lebel, H.; Piras, H.; Bartholoméüs, J. Rhodium-Catalyzed Stereoselective Amination of Thioethers with N-Mesyloxycarbamates: DMAP and Bis(DMAP)CH_2Cl_2 as Key Additives. *Angew. Chem.* **2014**, 126 (28), 7428–7432; (f) Yu, H.; Li, Z.; Bolm, C. Iron(II)-Catalyzed Direct Synthesis of NH Sulfoximines from Sulfoxides. *Angew. Chem.* **2017**, 130 (1), 330–333.

(16) (a) Yu, H.; Li, Z.; Bolm, C. Copper-Catalyzed Transsulfinamidation of Sulfinamides as a Key Step in the Preparation of Sulfonamides and Sulfonimidamides. *Angew. Chem. Int. Ed.* **2018**, 57 (47), 15602–15605; (b) Davies, T. Q.; Hall, A.; Willis, M. C. One-Pot, Three-Component Sulfonimidamide Synthesis Exploiting the Sulfinylamine Reagent N -Sulfinyltritylamine, TrNSO. *Angew. Chem. Int. Ed.* **2017**, 56 (47), 14937–14941.

(17) (a) Armstrong, A.; Emmerson, D. P. G. Enantioselective Synthesis of Allenamides via Sulfimide [2,3]-Sigmatropic Rearrangement. *Org. Lett.* **2009**, 11 (7), 1547–1550; (b) Azek, E.; Khalifa, M.; Bartholoméüs, J.; Ernzerhof, M.; Lebel, H. Rhodium(II)-Catalyzed C–H Aminations Using N-Mesyloxycarbamates: Reaction Pathway and by-Product Formation. *Chem. Sci.* **2019**, 10 (3), 718–729.

(18) CCDC Deposition Number 2016493.

(19) CCDC Deposition Number 2016492.

(20) Patent application WO2020/102100 A1. Applicant: Novartis Inflammasome Research Inc. 2020.

(21) a) Mendonça Matos, P.; Lewis, W.; Argent, S. P.; Moore, J. C.; Stockman, R. A. General Method for the Asymmetric Synthesis of N–H Sulfoximines via C–S Bond Formation *Org. Lett.* **2020**, 22, 2776-2780. b) Zhang, Z. X.; Davies, T. Q.; Willis, M. C., Modular Sulfondiimine Synthesis Using a Stable Sulfinylamine Reagent. *J. Am. Chem. Soc.* **2019**, 141, 13022-13027. c) Wojaczyńska, E.; Wojaczyński, J. Modern Stereoselective Synthesis of Chiral Sulfinyl Compounds *Chem. Rev*. **2020**, 120, 4578–4611