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Sulfinamides

Hydroxylamine-Derived Reagent as a Dual Oxidant and Amino Group Donor for the Iron-Catalyzed Preparation of Unprotected Sulfinamides from Thiols

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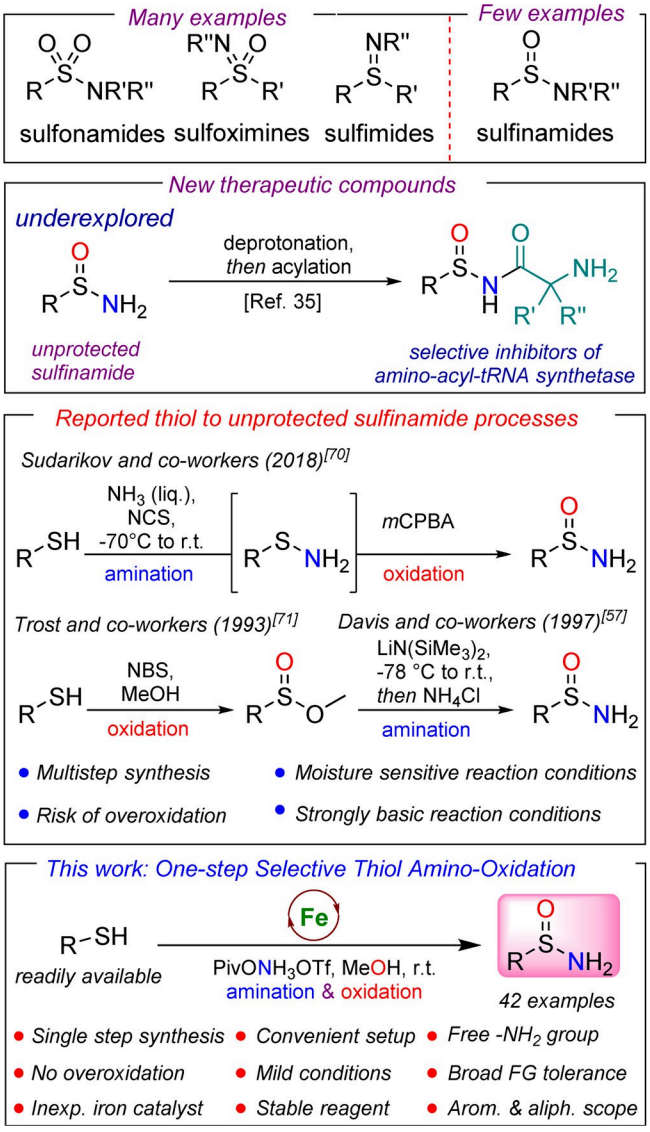
Abstract: *An iron catalyzed reaction for the selective transformation of thiols (-SH) to sulfinamides (-SONH$_2$) by a direct transfer of -O and free -NH$_2$ groups has been developed. The reaction operates under mild conditions using a bench stable hydroxylamine derived reagent, exhibits broad functional group tolerance, is scalable and proceeds without the use of any precious metal catalyst or additional oxidant. This novel, practical reaction leads to the formation of two distinct new bonds (S=O and S–N) in a single step to chemoselectively form valuable, unprotected sulfinamide products. Preliminary mechanistic studies implicate the role of the alcoholic solvent as an oxygen atom donor.*

Introduction

Sulfur-containing molecules are widespread in organic synthesis, as they are often found in pharmaceuticals, agrochemicals, materials, and fragrances.[1–5] The ability of sulfur to adopt several different oxidation states has led to countless applications of sulfur chemistry in organic synthesis. Thus, the construction of a diverse array of sulfur-containing molecules is of strategic importance, and frequently involves the formation of S–O and S–N bonds.[6] Sulfonamides, sulfoximines and sulfimides (Scheme 1) are highly relevant for medicinal chemistry and crop protection because they exhibit interesting bioactivities.[1,7–10] These exciting applications have been enabled by the development of efficient strategies for their synthesis.[7,8,11–19]

In contrast, sulfinamides, which are lower oxidation-state analogs of sulfonamides, remain relatively underexplored in medicinal and agrochemistry despite their potential for the exploration of new chemical space.[20–22] Among the few studies performed thus far, sulfinamides have been employed as amide bond isosteres, transition state analogues and in peptidomimetics.[23–26] Additionally, in the study of antiviral drugs against the hepatitis C virus (HCV), the substitution of carboxylic acids by sulfinamide group increased their potency.[27] These results showcase the potential of sulfinamides in the design of bioactive molecules and new pharmaceuticals.[28–33] Moreover, sulfinamides are also found in nature.[34]



Scheme 1. Context of the work.

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Recently, there has been a report of a new class of potential therapeutic and selective inhibitor of bacterial aminoacyl-*t*RNA synthetase with an acylated sulfinamide core structure (2-amino-*N*-(arylsulfinyl)-acetamide) (Scheme 1) whose synthesis required multiple steps to access the free, unprotected sulfinamide intermediate.[35] In biological systems, free sulfinamides are involved in metabolic pathways and are considered to contribute to oxidative stress in cells.[36,37] However, their reactivity has not been investigated in detail, presumably due to a lack of methodologies to access free sulfinamides.[34]

Sulfinamides possess a chiral sulfinyl group, which is configurationally stable,[38] making them important tools for various strategies in asymmetric synthesis.[39] For example, the popular Ellman's *tert*-butanesulfinamide[40] is employed as a versatile auxiliary to access, both in academia and industry, important chiral amine building blocks which are key intermediates in the synthesis of biologically active compounds and natural products,[39,41–46] like the anti-HIV drug maraviroc[47] and natural product (−)-vindoline.[48] Furthermore, several groups have recently reported the use of unprotected mesitylene sulfinamides as synthetic units to access unnatural amino acid residues in radical coupling reactions.[43,49,50] The potential of sulfinamides thus seem to be far reaching and highlights the critical demand for the development of novel, practical methods to access them to facilitate their application in the various fields of medicinal chemistry, biology, and organic synthesis. However, such reactions clearly lag behind the development of countless methods to access other sulfur analogues such as sulfoximines, sulfonamides, sulfoxides, and sulfones.[8,17,18,51,52] Common procedures for synthesis of sulfinamides usually involve harsh multistep processes and start from less easily accessible starting materials,[53–68] whereas methods starting from commercially available thiols remain poorly developed.[44,61,69,70] An early example of sulfinamide synthesis from thiols, reported the use of chloramine (NH_2Cl) which resulted in very low conversion to sulfinamide.[69] More recently, Sudarikov and co-workers reported a method to form sulfinamides from thiols using liquid ammonia and *N*-chlorosuccinimide (NCS) followed by oxidation of the in situ formed sulfenamide using *meta*-chloroperbenzoic acid (*m*CPBA) (Scheme 1).[44,70] Another strategy combines the process of thiol oxidation to sulfinates developed by Trost and coworkers[71] followed by amination of the resulting sulfinate using Davis' methodology to access unprotected sulfinamides (Scheme 1).[57]

Thus, so far, the traditional methods available for sulfinamide synthesis from thiols require two or more synthetic steps and harsh reaction conditions, with significant limitations in the substrate scope.[44,61,69,70,72,73] Besides these limitations, most of the methodologies for sulfinamide preparation, independently of the type of starting materials used, lead to the synthesis of *N*-functionalized sulfinamides, which often need to be subsequently deprotected[35,74] to reveal the free -NH_2 group. Therefore, the development of a method to directly transform thiols into unprotected sulfinamides is in high demand.

Widely studied iron-based enzymes have recently inspired a renewed interest in developing simple, homogeneous iron complexes for the oxidation and amination of organic substrates.[75] Toward this endeavour our group and others have been working on iron catalyzed aminofunctionalization of alkenes[76–82] using hydroxylamine derived reagents. Additionally, we and others reported aromatic C−H amination reactions[83–87] through the use of similar reagents. The versatile reactivity of these iron catalyzed reactions of hydroxylamine derivatives in hydrocarbon functionalization reactions prompted us to investigate their reactivity in heteroatom amination reactions. Notably, the Bolm group has elegantly harnessed our previously reported iron-based amination system in a sulfoxide imidation reaction to form unprotected sulfoximines.[16] However, the reactivity of the lower oxidation sulfur analogue like thiols[88] has remained unexplored.

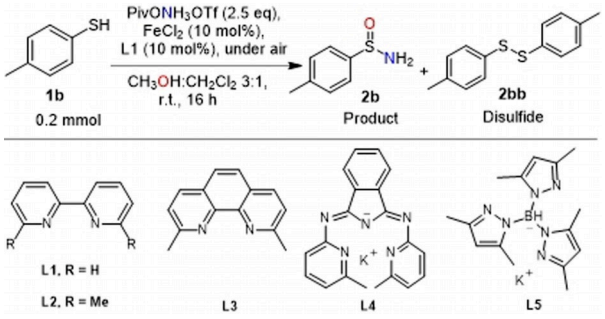
We reasoned that the oxidizing ability of the hydroxylamine derivative along with its ability to donate a -NH_2 group could potentially provide a direct route to unprotected sulfinamides through two subsequent and chemoselective oxidation events. Due to their high nucleophilicity, we expected thiols to readily engage with electrophilic aminating intermediates generated from the reaction between an iron catalyst and the N-O reagent to access sulfinamides. However, a key challenge to overcome was the possibility that the desired sulfinamide product could undergo further oxidation to an undesired S(VI) product.[61] As an additional challenge, several other sulfur species (sulfinic ester, sulfenamide, sulfoxide, sulfonic acids, sulfoximine) could possibly be formed as side-products under these reaction conditions.

Herein, we report an iron-catalyzed, direct synthesis of unprotected sulfinamides from thiols using a bench stable hydroxylamine derived triflic acid ammonium salt PivONH_3OTf (*O*-pivaloyl hydroxylamine triflic acid, Scheme 1) as the nitrogen source and oxidant. The new reaction involves the direct installation of an S−N and S=O bond (thiol aminooxidation) under mild condition, without the need for any external oxidant. The methodology is applicable to a wide range of thiols, including aromatic, benzylic and aliphatic substrates, and can be employed in late stage functionalization.

Reaction Optimization

We initiated our investigation using 4-methylbenzenethiol as a model substrate along with PivONH_3OTf as the aminating reagent to obtain unprotected sulfinamides (Table 1). Testing various first row transition metals (see Supporting Information) revealed simple iron(II) salts as promising candidates to catalyze this reaction (Table 1 and also SI). $Fe(acac)_2$ provided the desired product 4-methylbenzenesulfinamide (**2b**), also known as Davis' sulfinamide,[55] in 54% yield (Entry 2, Table 1). Interestingly, $Fe^{II}Pc$ (Iron(II) Phthalocyanine) increased the yield of product formation (60%, Table 1, entry 4), which prompted us to further investigate the ligand effect on the iron catalyzed reaction (Table 1). Simple 2,2′-bipyridine (L1) in combination with $FeCl_2$ and 2.5 equiv

Table 1: Selected examples for optimization.[a]



Entry	Deviation from standard conditions	Product **2b**[b]	Disulfide **2bb**[b]
1	No deviation from standard condition	95%	<5%
2	$Fe(acac)_2$, no L1	54%	46%
3	$FeCl_2$, no L1	45%	40%
4	FePc, no L1	60%	40%
5	L2 instead of L1	67%	21%
6	L3 instead of L1	60%	n.d.
7	L4 instead of L1	80%	15%
8	L5 instead of L1	70%	30%
9	$FeCl_3$, no L1	22%	18%
10	$RuCl_3$, no L1	<5%	98%
11	CH_3OH	80%	19%
12	CH_2Cl_2	n.d	99%
13	$FeCl_2$ (99.99% trace metal basis), no L1	46%	38%
14	1 equiv of $PivONH_3OTf$	27%	75%
15	No catalyst	<5%	50%
16	Under Argon	92%	<5%

[a] See SI for further information. [b] ^1H NMR yield. Disulfide yields are reported w.r.t the equivalents of thiol needed for their formation (actual disulfide yields are half of the given values).

of $PivONH_3OTf$ resulted in almost quantitative (95%) conversion of 4-methylbenzenethiol (**1a**) to 4-methylbenzenesulfinamide (**2b**) (95%) (Table 1, entry 1) Only traces of disulfide byproduct were observed. Other bidentate as well as tridentate ligands were screened but turned out to be less efficient (Table 1, entry 5–8 and also SI). Iron (III) salts showed reduced activity compared to iron(II) salts (Table 1, entry 9). Moving down to the second row of the periodic table, ruthenium (III) mostly catalyzed disulfide formation of thiol, without any sulfinamide formation (Table 1, entry 10).

Screening of different solvents revealed that the reaction operates most efficiently in a methanol:dichloromethane solvent mixture (3:1) (Table 1, entry 1 and entry 11) and is completely suppressed in the absence of alcoholic solvents (Table 1, entry 12 and also see SI for further information). Various other iron (II) catalysts, including an iron(II) catalyst of high purity (trace element analysis grade), (Table 1, entry 13 and SI) were found to catalyze the thiol amino-oxidation reaction efficiently, ruling out the possibility that the catalytic activity is due to trace metal impurities,[89] and implicating the key role of iron in the process. With lower amounts of aminating agent, more disulfide formation was observed with a lower yield of sulfinamide product (Table 1, entry 14 and also see SI). Increasing the equivalence of aminating agent led to higher conversion of thiol to sulfinamide. With 2.5 equiv of aminating agent, maximum sulfinamide formation was observed (Table 1, entry 1 and also SI). Remarkably, under the optimized reaction conditions, no overoxidized sulfonamide product was detected and the thiol was chemoselectively converted to its respective sulfinamide. The reaction can be run open to air, using technical grade methanol and dichloromethane, without the need for any pretreatment or precaution.

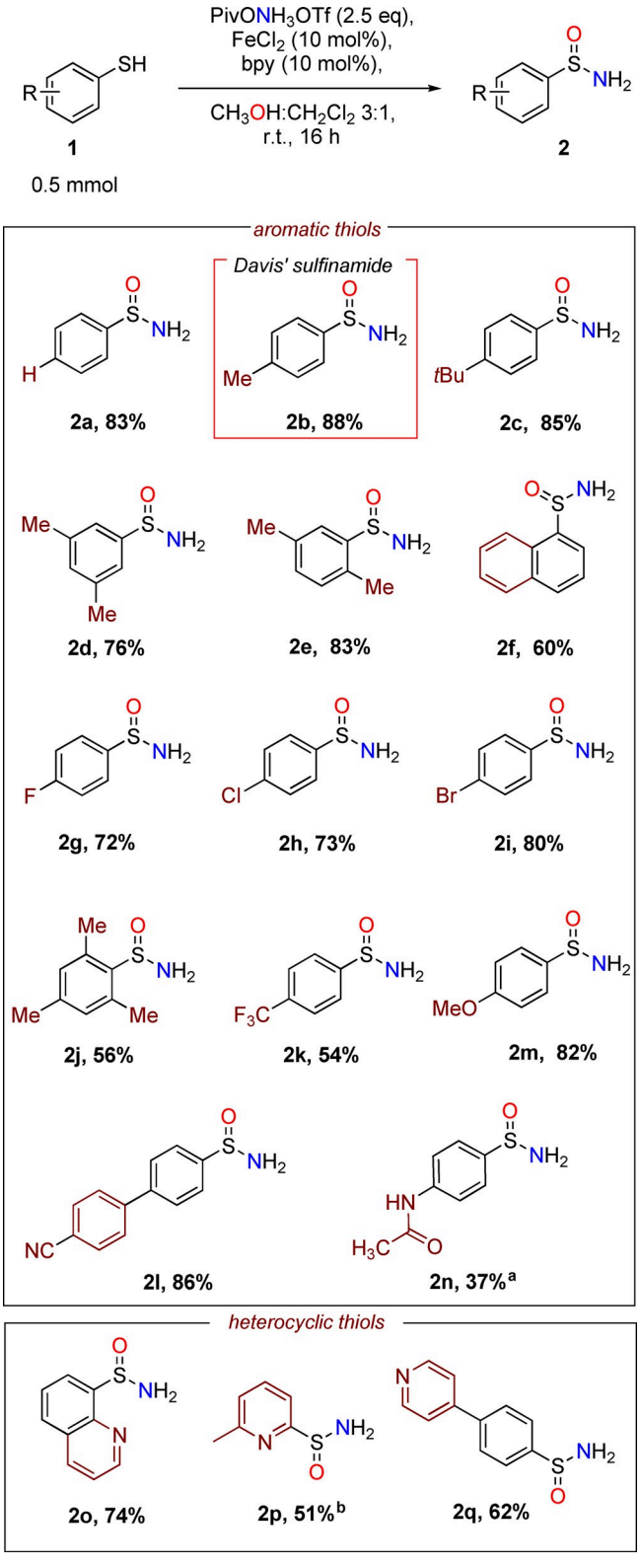
Substrate Scope

With the optimized conditions in hand, we next explored the substrate scope. Starting from both aromatic and aliphatic thiols, a wide range of starting materials were selectively converted to their corresponding sulfinamides in high yields (Scheme 2–4).

Hydrocarbon derived thiophenols with different substitution patterns (**1a–1f, 1j**) were efficiently transformed, regardless of steric bulk or substitution at the *ortho*-position, to their corresponding sulfinamides (**2a–2f, 2j**). The sterically hindered mesitylene sulfinamide (**2j**), which is used as building block for the synthesis of amino acids,[43,49,50] can be conveniently accessed by this method. Considering electronic effects, aromatic and benzylic thiols with halogen substituents (**1g–1i, 3b**) and other electron poor substrates with varied functional groups such as pseudohalides (-CN), $-NO_2$, $-CF_3$, $-OCF_3$ (**1k–1l**, **3c–3d**), were tolerated, as well as electron rich arenes (**1b–1c, 1j, 1m**). Electron-rich substrates generally gave slightly higher yields when compared to electron-poor substrates, a result consistent with the electrophilic nature of the postulated reactive iron intermediate. The reaction scope could also be successfully extended to biarylic systems (**2l and 2q**) and an aromatic amide functionality (**2n**). The broad scope of the reaction was further demonstrated by the successful application of this synthetic procedure to heterocyclic molecules, such as 8-quinolinethiol (**1o**), 6-methylpyridine-2-thiol (**1p**) and 4-(pyridin-4-yl)benzenethiol (**1q**) which all afforded the corresponding sulfinamides (**2o–2q**) in good yield.

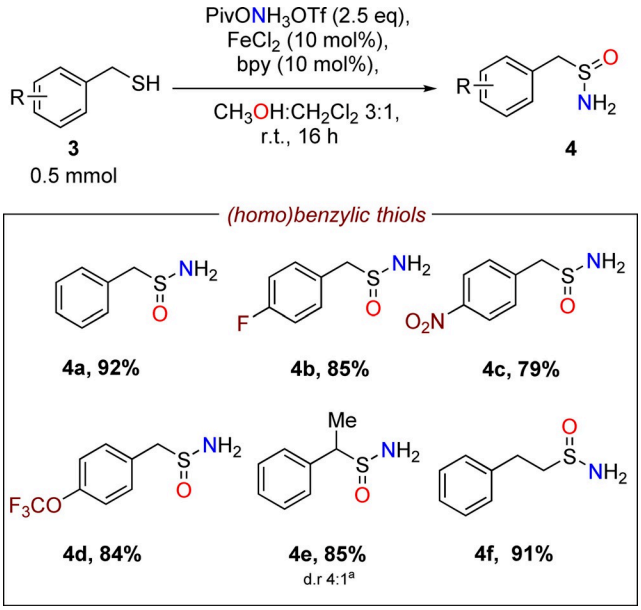
With regards to aliphatic thiols, we first investigated benzylic thiols which were transformed in excellent yields (Scheme 3). Thus, activated benzylic C–H bonds remain unaffected under the mild conditions of this selective amino-oxidation of thiols.[90,91] Secondary benzylic thiols, such as α-methyl benzylthiol, resulted in very high and selective conversion to sulfinamide **4e** with a *d.r.* of 4:1, as confirmed by NMR and HPLC analyses. Furthermore, a variety of unactivated, aliphatic primary (**3g–3q**), secondary (**3r–3u**) and tertiary thiols (**3v–3x**) could be transformed in high yields, showing the high efficiency of this protocol and tolerance towards various functional groups (Scheme 4). Ellman's sulfinamide **4w**, was obtained racemically with our methodology in a single step from *tert*-butylthiol.

The reaction tolerated several functional groups such as protected aliphatic amines (**3q**), amides (**3p**), nitriles (**3o**) and even halogen functionalities on the aliphatic chain (**3j**) to selectively form sulfinamide products. Encouraged by these results, we evaluated more complex substrates with our methodology. Thiols derived from natural products like 2-



Scheme 2. Scope of amino-oxidation of aromatic thiols. Yields are of isolated products. [a] FePc catalyst was used. [b] ligand L4 was used, see SI for further information.

pinanol (mango thiol) and cholesterol were transformed with high selectivity into their respective sulfinamide **4x** and **4y**.



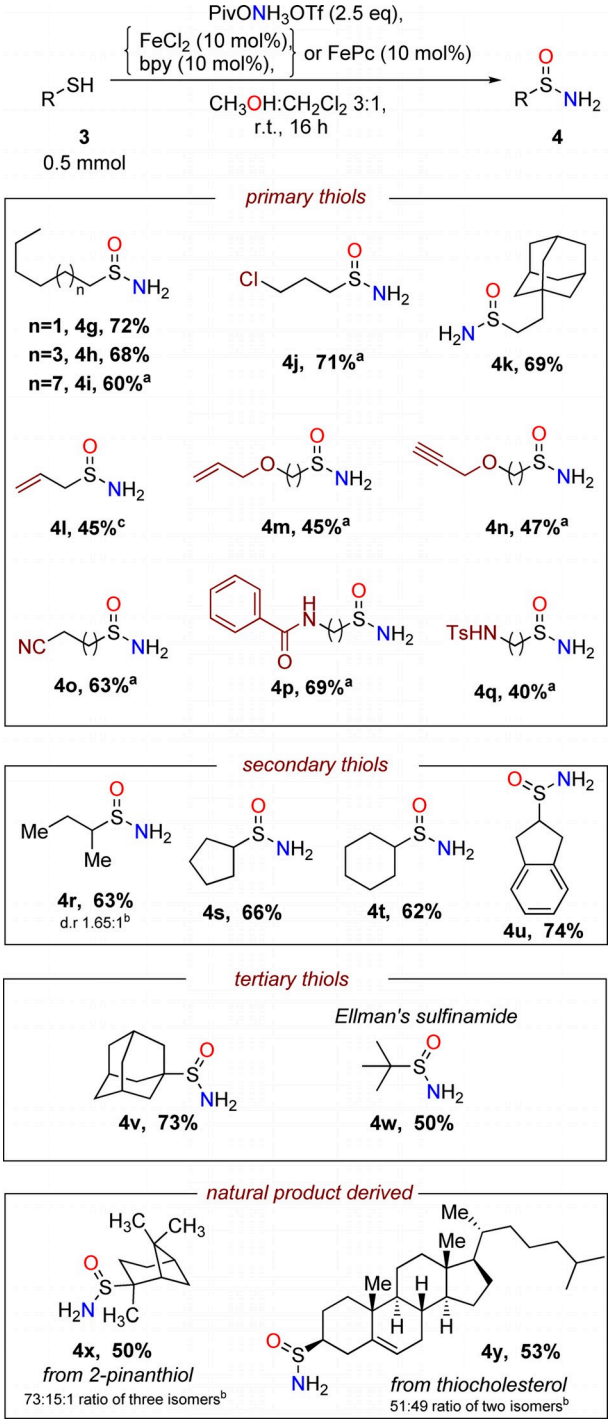
Scheme 3. Scope of amino-oxidation of benzylic thiols. Yields are of isolated products. [a] *d.r.* of isomers by ^{1}H NMR and HPLC.

Allyl mercaptan and allyl ethers preferentially underwent thiol activation to form the corresponding sulfinamide (**4l–4m)** while keeping the double bond untouched. Remarkably, even terminal alkyne-ethers were left intact forming sulfinamide (**4n**). The chemoselective transformation of the -SH group into a sulfinamide shows the method's potential as a new platform for the synthesis of structurally and functionally complex sulfinamides.

However, from our study on the substrate scope, it was evident that this methodology has limitations with regards to certain functional groups (e.g.-COOH, free amines) as well as some heterocyclic molecules (See Scheme S10, SI). Moreover, using *N*-substituted aminating agents,[82] the reaction failed to generate the desired *N*-substituted sulfinamide products (See Scheme S11, Table S7, SI).

We also performed two gram-scale experiments to test the robustness and applicability of this synthetic procedure (see SI for details). The potential of this reported methodology for synthesis of free -NH_2 sulfinamides could be exploited for the synthesis of the therapeutic compounds 2-amino-*N*-(Arylsulfinyl)-acetamide[35] by simple *N*-substitution of the sulfinamide -NH_2 group, bypassing the traditional multistep process and harsh reaction conditions previously reported.[35,57,70,71,92]

Knowing about the importance of enantioenriched sulfinamides, we tested chiral ligands on our model substrate 4-methylbenzenethiol. Unfortunately, no enantiomeric excess could be obtained with a range of chiral ligands (see SI for further information). However, this lack of stereo control in the transformation can be addressed by combining our methodology with a biocatalytic racemate resolution developed by Kazlauskas and co-workers[93] or a kinetic resolution through cross-coupling reaction with aryl iodides developed by Cai and co-workers.[94]

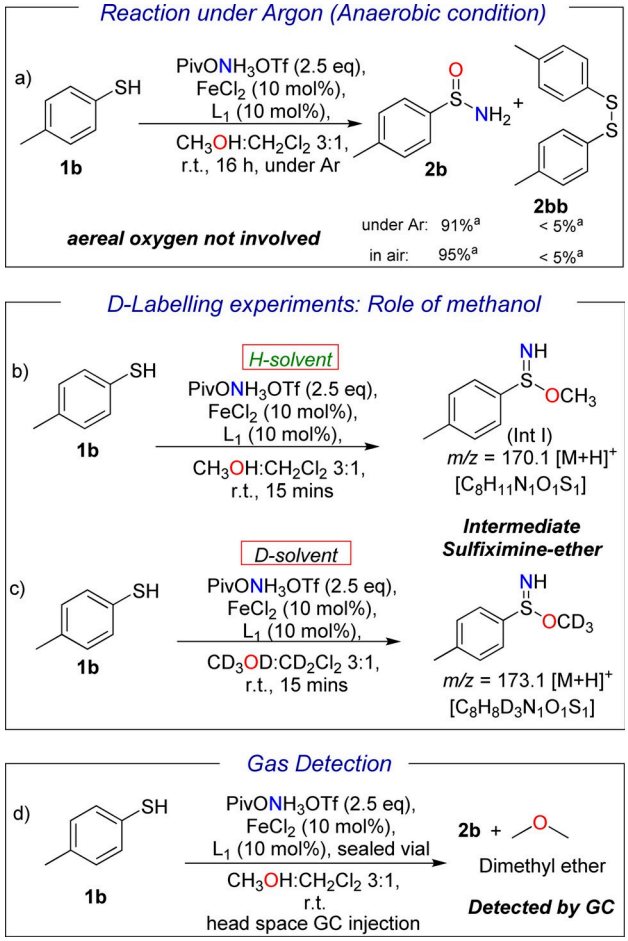


Scheme 4. Scope of amino-oxidation of aliphatic thiols.Yields are of isolated products. [a] FePc catalyst was used. [b] *d.r.* of isomers determined by ^{1}H NMR and HPLC analysis. [c] isolated along with the dimerised macrocyclic product in 2:1 ratio with an overall yield of 68%. See SI for details.

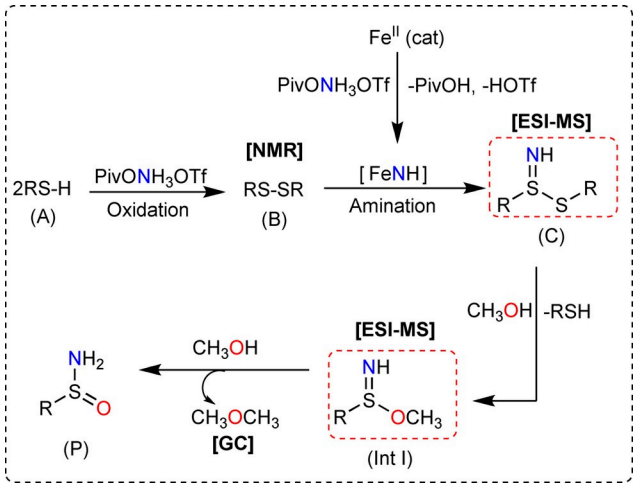
Mechanistic Experiments

The methodology involves the simultaneous formation of two new bonds (S=O and S–N) in a single reaction, directly starting from simple -SH bonds, raising questions about the mechanism of this intriguing process. In the absence of iron catalyst, under standard reaction conditions, no product formation was observed, highlighting the important role of iron in the reaction pathway (Table 1, entry 15). Under oxygen-free conditions, the reaction proceeds with nearly equal efficiency, ruling out the involvement of molecular oxygen as the source of oxygen atom or oxidant (Table 1, entry 16 and Scheme 5a). However, disulfide formation was observed, both under air and under oxygen-free conditions, in the presence of aminating agent and the thiol without the iron catalyst. (See SI for details). X-Band EPR measurements at 100 K of a freeze-quenched reaction mixture containing *N tert* Butyl-α-phenyl nitrone as a radical spin trap shows an EPR signal at $g = 2.006$, typical of a radical feature (See SI for details).[95,96] Combined with the observation that disulfides can be employed as starting materials instead of thiols (see SI), and the requirement for >2 equiv of the hydroxylamine reagent (See SI), we suggest that the first step in our reaction is rapid formation of the disulfide through oxidation with the hydroxylamine-derived reagent (Scheme 6).

Based on literature precedent, $PivONH_3OTf$ likely further acts as the source of nitrogen in a subsequent Fe-catalyzed nitrene transfer[16] to generate a transient sulfimide C type intermediate (Scheme 6). While the origin of the N



Scheme 5. Experiments to assess the source of oxygen in product sulfinamide. [a] ^{1}H NMR yield.



Scheme 6. Proposed mechanism for iron catalysed thiol amino-oxidation.

atom can be confidently assigned to the aminating reagent, the installation of the oxygen atom in the final product raises additional questions regarding the subsequent mechanistic steps. Since the reaction performed well in the absence of air/oxygen, we believe that the methanol co-solvent, which is essential to observe product formation, subsequently attacks species C to generate a sulfiximine-ether (Int I, Scheme 6).

ESI-MS-analyses of the reaction mixture during the course of reaction indeed led us to observe the proposed intermediate species C, at $m/z = 262.1$ ($M + H^+$) and also a peak at $m/z = 170.1$ ($M + H^+$) matching with the isotope distribution pattern for $C_8H_{11}N_1O_1S_1$ (Int I, Scheme 5b). Performing the same reaction in a deuterated solvent mixture shifts the m/z-value of Int I in accordance with the expected isotope distribution pattern for $C_8H_8D_3N_1O_1S_1$ ($m/z = 173.1$) (Scheme 5c). Interestingly, this species (sulfiximine-ether) decays over the course of the reaction while sulfinamide product **2b** is building up, confirming its possible role as a reaction intermediate. Such sulfiximine-ether species have been proposed in the literature to be extremely reactive, and, in presence of excess methanol as solvent, might rearrange to form an S=O bond, along with liberation of dimethyl ether.[15,97] In fact, a GC head space analysis of the reaction mixture unambiguously detected formation of dimethyl ether as a by-product (Scheme 5d and see SI for details). Additionally, experiments with $H_2{}^{18}O$ labelled water ruled out the possibility of any oxygen incorporation from water during the reaction or during aqueous work up procedures (see SI). Taken altogether, these results suggest that methanol acts as the source of oxygen in the sulfinamide product (Scheme 6).

Conclusion

In summary we have designed a practical catalytic method for the selective amino-oxidation of thiols to unprotected sulfinamides in a one step process, under mild reaction conditions, with a broad substrate scope. The subtle cooperation between an electrophilic intermediate (generated from the reaction between an iron catalyst and the N-O reagent) and the alcoholic solvent plays the key role to selectively transform readily available thiols to valuable unprotected sulfinamides, without the use of any external oxidant or precious metal catalyst. The hydroxylamine-derived reagent itself acts as a dual oxidant and amino group donor for the synthesis of structurally and functionally complex sulfinamides, showing the method's potential as a platform to explore new chemical space. Further spectroscopic characterization of iron-aminating species involved in the amination reactions[16,76,77] is currently in progress in our laboratory.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: amino oxidation · iron · sulfinamides · sustainable catalysis · thiols

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