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Facile C–S Bond Cleavage of Aryl Sulfoxides Promoted by Brønsted Acid

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Dedicated with respect and admiration to Prof. Barry M. Trost, a founding member of Science of Synthesis, on the occasion of the 20th anniversary of Science of Synthesis.

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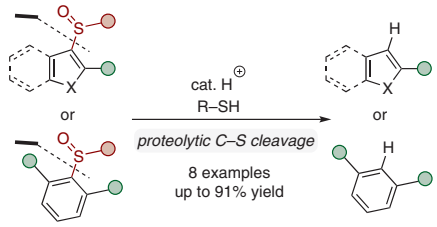

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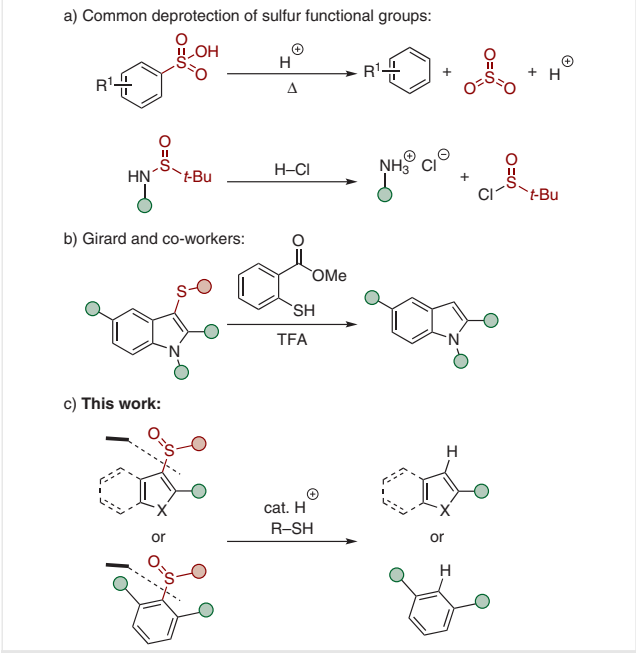
Abstract A method for the Brønsted acid promoted desulfination of aryl sulfoxides is presented. In the presence of a thiol, electron-rich sulfoxides undergo C–S bond cleavage to give the corresponding protodesulfinated arenes and disulfides.

Key words sulfoxides, protodesulfination, deprotection, acid

Sulfoxides are versatile reagents in organic synthesis. Besides their widespread use as ligands[1] and chiral auxiliaries,[2] sulfoxides have found application as directing groups.[3] In particular, we and others have shown that aromatic sulfoxides are especially useful for functionalization at the *ortho*-position.[4] More recently, the functionalization of *meta*-[5] and *para*-positions[6] in aromatic sulfoxides has also been achieved. Importantly, the chiral information encoded on the tetrahedral sulfur can be harnessed to control new stereocenters on carbon through chirality transfer.[7a,b]

While cross-coupling and other methods enable the post-reaction conversion of sulfur residues,[8] their substitution by a simple hydrogen atom is a commonly performed reaction. Amongst the different sulfur-based functional groups, several undergo facile C–S or heteroatom–S bond cleavage under acidic conditions. Examples include the desulfonylation of aromatic sulfonic acids[9] in strongly acidic media or the removal of Ellman's auxiliary with hydrochloric acid (Scheme 1, a).[10] Interestingly, indolylsulfides can also be cleaved when dissolved in TFA in the presence of a thiol, as has been shown by Girard and co-workers (Scheme 1, b).[11] The removal of *sulfoxides*, however, commonly requires hydrogenation with the pyrophoric Raney-nickel[12] or sulfoxide–lithium exchange with organolithium reagents such as *t*-BuLi.[13]

We have recently discovered that certain sulfoxides can be cleaved under mildly acidic conditions. Herein, we present the preliminary results of our investigations towards an acid-catalyzed desulfination reaction (Scheme 1, c).



Scheme 1 (a) Deprotection of aryl sulfonic acids and sulfonamides under acidic conditions. (b) Desulfenylation reported by Girard. (c) This work: Sulfoxide C–S bond cleavage in acidic media.

We started our investigations using sulfoxide **1a** as our standard substrate and employing triflic acid as the protic catalyst (Table 1). Dichloromethane proved to be the best solvent at a concentration of 0.2 M and a catalyst loading of 50 mol% was required to achieve full conversion after 12 hours.

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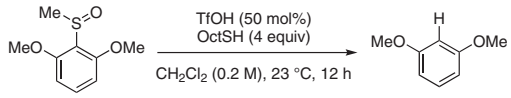
Triflimide showed comparable results. Importantly, an external nucleophilic thiol was found to promote the process in agreement with the previous results of Girard.[11]

Table 1 Optimization of the Desulfination Reaction Conditions



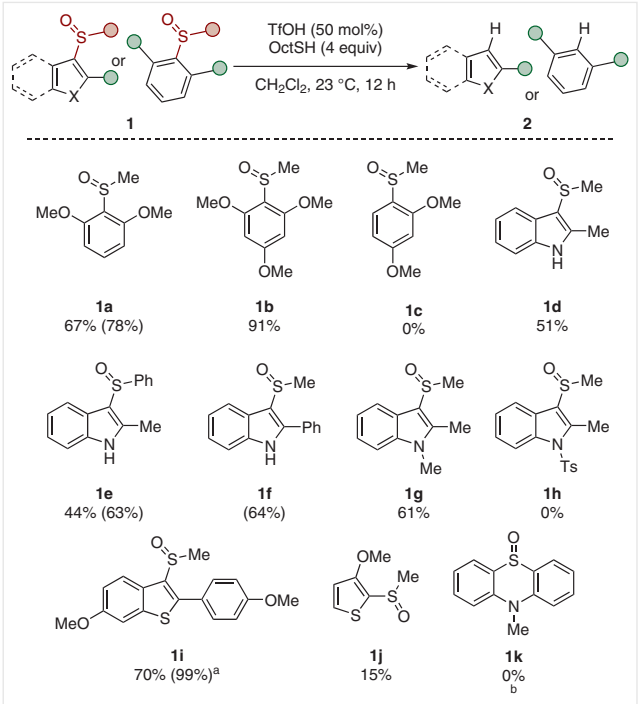
1a **2a**

Entry	Deviation from general conditions	Conversion
1	MeOH	0%
2	acetone	0%
3	Et_2O	0%
4	HFIP	traces
5	CH_2Cl_2 (0.5 M)	traces
6	Tf_2NH (80 mol%), 20 h	100%
7	standard conditions	100% (67%)[a]

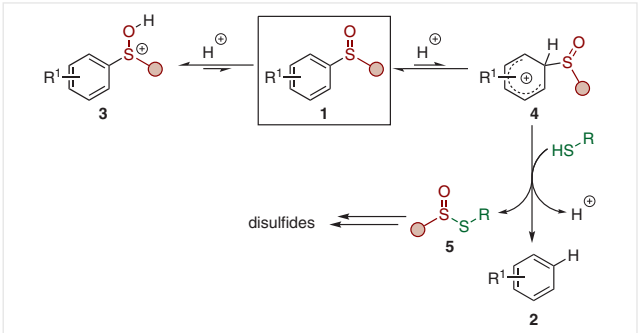
[a] Isolated yield in parentheses.

We then went on to explore the generality of this protocol with a range of sulfoxides (Scheme 2). *o*,*o*-Disubstituted derivatives were readily cleaved under the optimized reaction conditions, while less hindered sulfoxide **1c** showed no conversion. This indicates that steric hindrance greatly facilitates the reaction. Heteroaromatic sulfoxides **1d–g** also underwent the reaction smoothly, whereas less electron-rich derivative **1h** bearing a Ts-protecting group was fully recovered after the reaction. Benzothiophene **1i** required an elevated temperature, showing only traces of the desulfinated product at room temperature. In the case of methoxythiophene derivative **1j**, the product was found to be unstable under the reaction conditions, with only a small amount of isolated protodesulfinated material being obtained. The reaction with cyclic sulfoxide **1k** led to quantitative formation of a sulfide, the product of reduction.

Our mechanistic proposal is outlined in Scheme 3. Addition of a Brønsted acid to a sulfoxide presumably leads to association with the highly polarized sulfoxide oxygen.[14] Alternatively, protonation on the electron-rich arene would generate a short-lived intermediate **4**, which would rapidly be intercepted by the nucleophilic thiol generating the product **2** and one equivalent of thiosulfinate **5**. The thiosulfinate formed in this process is not stable under the reaction conditions and further reacts to give a mixture of symmetrical and unsymmetrical disulfides as the only detectable byproducts.[15]



Scheme 2 Substrate scope for the desulfination of sulfoxides; the yields given are those of the corresponding deprotected products **2**. NMR yields are reported in parentheses. [a] The reaction was heated to 40 °C. [b] Full conversion into the reduced sulfide was observed.



Scheme 3 Proposed mechanism for the acid-catalyzed sulfoxide cleavage

In summary, we have developed a convenient method for the desulfination of electron-rich aryl sulfoxides promoted by a Brønsted acid.[16,17]

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1707109.

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(16) **Protodesulfination; General Procedure**
To a solution of the sulfoxide (0.2 mmol, 1.0 equiv) and 1-octanethiol (0.8 mmol, 4.0 equiv) in CH_2Cl_2 (0.2 M) in a vial, trifluoromethanesulfonic acid (0.1 mmol, 0.5 equiv) was added and the mixture was stirred for 12 h at 23 °C. The reaction was quenched by the addition of solid $NaHCO_3$, stirred at 23 °C for 10 min, filtered and extracted with CH_2Cl_2. The resulting organic phase was dried over $MgSO_4$ and concentrated under reduced pressure to give a crude product that was purified by column chromatography (heptane/ethyl acetate).

(17) **1,3,5-Trimethoxy-2-(methylsulfinyl)benzene (1b)**
IR (neat): 2943, 1582, 1465, 1458, 1436, 1412, 1340, 1230, 1208, 1187, 1162, 1125, 1086, 1026 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ = 6.12 (s, 2 H), 3.88 (s, 6 H), 3.84 (s, 3 H), 3.04 (s, 3 H). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 164.7, 161.3, 111.5, 91.3, 56.3, 55.7, 38.0. HRMS (ESI+): *m*/*z* $[M + Na]^+$ calcd for $C_{10}H_{14}O_4SNa$: 253.0505; found: 253.0512.