EurJOC
European Journal of Organic Chemistry

Minireview
doi.org/10.1002/ejoc.202000403

Chemistry Europe
European Chemical Societies Publishing

Synthetic Methods

Recent Advances in the Synthesis and Direct Application of Sulfinate Salts

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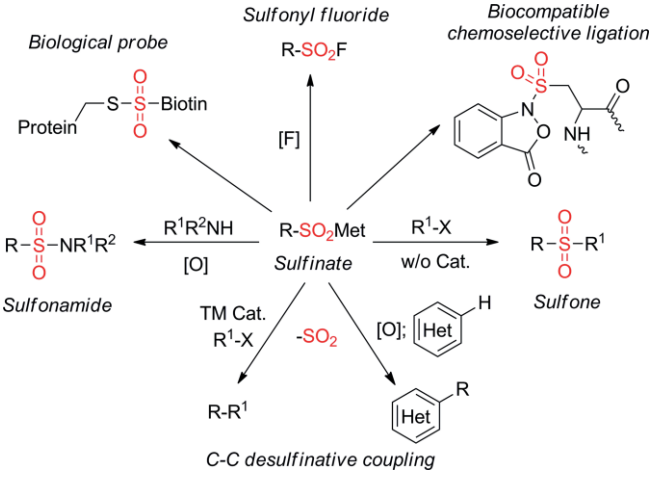
Abstract: Sulfinate salts have attracted considerable attentions due to their versatile reactivity. They have emerged as highly useful building blocks for the construction of all kinds of sulfonyl-group containing molecules, such as sulfones or sulfonamides, and for the construction of various carbon–carbon- and carbon–heteroatom-bonds via sulfur dioxide (SO_2) extrusion. Herein, we want to summarize the latest developments in the synthesis of sulfinate salts. Both improvement of classical methods and the development of various novel protocols will be discussed. Also selected one-pot methods directly utilizing in situ generated sulfinate salts as intermediates will be covered in this review article.

1. Introduction

Sulfinate salts, also named sulfinic acid salts, were reported in the chemical literature as early as 1861.[1] They have been recognized as useful building blocks for organic synthesis and haven been studied extensively.[2] Generally, sulfinate salts are colorless, odorless, non-corrosive solids. Most sulfinates are hygroscopic and exist in their hydrated forms. Compared to the parent free sulfinic acids, which are often unstable,[3] sulfinic acid salts are in general bench-stable and can be stored for prolonged time without decomposition. Therefore, sulfinate salts are often used as precursors for the free sulfinic acids, which can be liberated by a simple acidification process.

Sulfinate salts (RSO_2Met) have received wide attention among organic chemists in recent years due to their stability and versatile reactivity.[2c] As a more convenient and easy-to-handle substitute of traditional sulfonylating reagents, such as sulfonyl chlorides, sulfinate salts can be used to introduce the -SO_2- moiety into a variety of different sulfonyl-group-containing molecules, such as sulfones,[4a] sulfonamides[4b] or sulfonyl fluorides.[4c] These type of compounds are widely applied in different fields ranging from pharmaceuticals and agrochemicals to material science. In addition, sulfinate salts can also be converted into various other sulfur-containing organic molecules, e.g. sulfonyl nitrites,[5a] sulfonyl cyanides,[5b] disulfides[5c] or sulfoxides.[5d] On the other hand, sulfinic acid salts have been utilized as building blocks for the construction of carbon–carbon-bonds via a sulfur dioxide (SO_2) extrusion process.[6] The Baran group has pioneered the use of alkyl sulfinate salts as an efficient alternative to classical carboxylic acids in the Minisci reaction.[7a] Interestingly, sulfinic acid zinc salts display a remarkably enhanced reactivity compared to commonly used sodium sulfinates.[7] Aromatic and heteroaromatic sulfinate salts have been employed as replacement of organometallic reagents in transition-metal-catalyzed desulfinative coupling reactions for the formation of carbon–carbon- and carbon–heteroatom-bonds.[8] Interestingly, applications of sulfinic acid salts in chemical biology, for instance in biocompatible chemoselective ligations or as biological probes, have been reported as well (Scheme 1).[9]



Scheme 1. Applications of sulfinate salts.

In order to fully harness the complete synthetic potential of sulfinic acid salts, efficient and reliable methods for their synthesis are essential. So far there is no single, generally applicable protocol for the preparation of sulfinates. The still most

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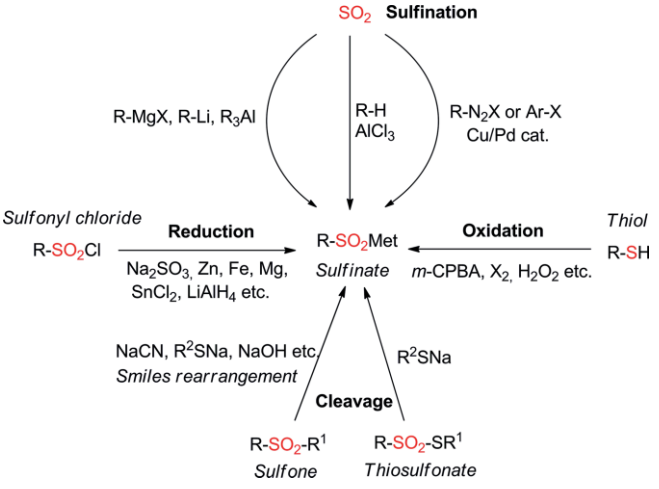
Supporting information and ORCID(s) from the author(s) for this article are available on the WWW under https://doi.org/10.1002/ejoc.202000403.

Minireview
doi.org/10.1002/ejoc.202000403

common synthetic approach is the reduction of sulfonyl chlorides, typically with sodium sulfite. Other traditional methods include the oxidation of thiols or bond cleavage processes starting from sulfones or sulfinic derivatives.[2a,2b] More recently, a variety of procedures based on the insertion of SO_2 have been developed (Scheme 2).[10] In general, the classical approaches, such as the reduction of sulfonyl chlorides, are of limited synthetic utility due to major drawbacks associated with the use of highly toxic reagents, harsh reaction conditions and low functional group tolerance. However, the development of novel synthetic methodologies in last two decades has opened new opportunities for a more efficient and sustainable synthesis of sulfinate salts.

Herein, we want to summarize recent progress in the synthesis of sulfinate salts focusing on new developments in the last twenty years.[11] In certain cases, traditional synthetic procedures from before 2000 will be presented for a direct comparison of advantages and disadvantages. In this review, both new methods for the synthesis of sulfinate salts as final product as well one-pot processes based on the formation of sulfinates as non-isolated intermediates, will be covered. The direct applications of in situ generated sulfinate salts in the construction of other sulfonyl-group containing molecules, will be discussed as well.



Scheme 2. Classical synthetic methods of sulfinate salts.

2. Reduction of Sulfonyl Chlorides

A still very popular method for the preparation of sulfinate salts is the reduction of widely available sulfonyl chlorides with different reducing agents. This protocol is mainly applicable for the preparation of aryl sulfinate salts. Alkyl sulfinic acids are in general less stable and can undergo facile disproportiona-

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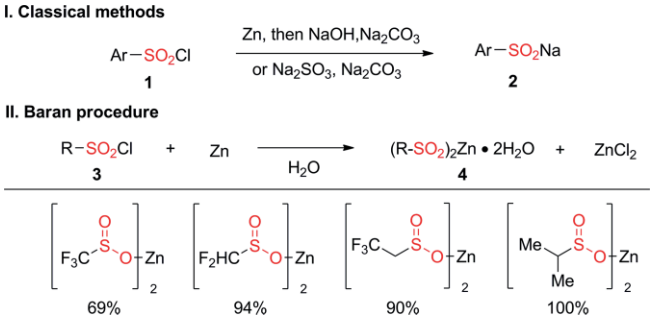
Georg Manolikakes *studied chemistry at the Ludwig-Maximilians University (LMU) Munich. At the LMU he joined the group of Prof. Paul Knochel and received his PhD in 2009 in the field of organometallic chemistry. After a postdoctoral stay with Prof. Phil S. Baran at the Scripps Research Institute, he started his independent career at the Goethe-University Frankfurt in 2010. In 2017, he was appointed as associate professor at the Technical University Kaiserslautern. His research interests cover multi-component and one-pot reactions, the synthesis of sulfonyl-containing molecules, asymmetric synthesis and medicinal chemistry.*

tion.[12] The two most common reducing agents are zinc powder[13a] and Na_2SO_3[13b] (Scheme 3 **I**).

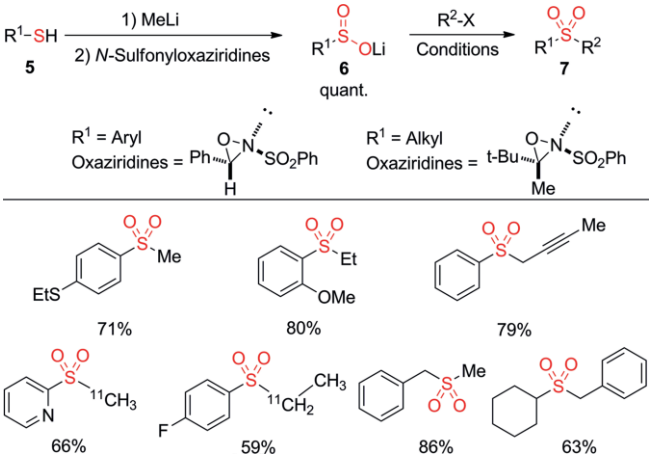


Scheme 3. Reduction of sulfonyl chlorides.

In 2006, Chumachenko and Sampson reported a general method to prepare zinc sulfinate salts, which were rarely described before, and their subsequent application in the synthesis of β-hydroxy sulfones.[14a] A complementary method for the preparation of zinc bis(alkanesulfinate)s **4** has been described by the Baran group in 2013 (Scheme 3 **II**).[14b] Various zinc alkane sulfinates, such as fluorinated alkane sulfinate salts, can be prepared in a single reduction step from the parent alkane sulfonyl chlorides and zinc powder in aqueous media. The authors found, that the crude material obtained via this method may contain up to one equivalent of $ZnCl_2$ and can be used directly in their reported further transformations without any problems.[7c]

3. Oxidation of Thiols and Thiolates

The oxidation of thiols or thiolates is a well-established method for the preparation of sulfinate salts.[15] Recent developments were focused on improving reaction conditions and decreasing the formation of side-products. Perrio and co-workers developed a general method to directly convert aryl or aliphatic lithium thiolates into the corresponding sulfinate salts.[16] Oxidation with Davis-type reagents proceeded with high chemoselectivity. In all cases, the desired sulfinate salts were isolated in quantitative yields and subsequently alkylated with different organic halides. The utility of this method was further demonstrated in the construction of ^{11}C-labled sulfones for biological studies (Scheme 4).[16c]



Scheme 4. Oxidation of lithium thiolates.

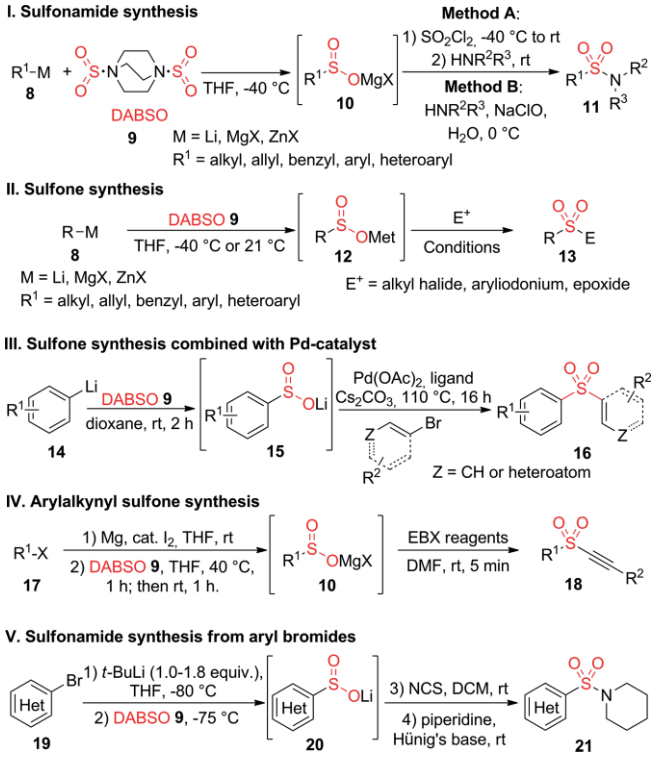
4. Trapping of Organometallic Compounds with SO_2

The direct trapping of organometallic compounds with SO_2 represents one of the most straightforward methods to prepare sulfinate salts. It has been demonstrated, that various sulfinate salts can be prepared by the reaction of SO_2 with organolithium, -magnesium or -aluminum compounds.[2] Recent studies have been focused on the extension of these classical protocols to one-pot conversion of the generated sulfinate salts into sulfones[17a,17b] or sulfonamides.[17c]

However, SO_2 itself is a toxic and corrosive gas at room temperature and its handling requires appropriate equipment, careful handling and safety procedures. Although SO_2 can be handled conveniently in its liquid form below the boiling point of –10 °C,[18] bench-stable, solid and easy-to-handle SO_2 surrogates offer an highly attractive alternative for small-scale laboratory manipulations. The arguably most versatile SO_2 surrogate is a charge-transfer complex between SO_2 and 1,4-diazabicyclo[2.2.2]octane (DABCO). This 1,4-diazabicyclo[2.2.2]octane bis(sulfur dioxide) adduct, often abbreviated as DABSO,[19a] was reported by Santos in 1988[19b] and introduced into organic synthesis by Willis in 2010[19c] for the first time. Since then, it has been widely used as an efficient and easy-to-handle replacement of gaseous SO_2.[20]

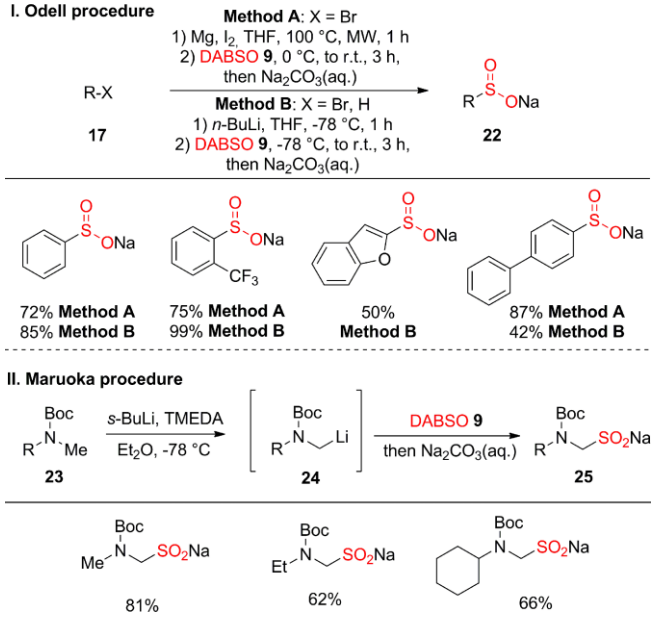
Willis and co-workers demonstrated that DABSO undergoes a smooth reaction with different organometallic reagents. The formed sulfinate salts were directly used for the preparation of sulfones or sulfonamides (Scheme 5 **I**, Scheme 5 **II**).[21a,21b] Based on this strategy, a robust array synthesis of drug-like sulfonamides was achieved.[21c] Rocke and co-workers extended the use of DABSO to the one-pot preparation of sulfones via zinc sulfinate salts. Better functional group tolerance and milder reaction conditions can be achieved due to the decreased reactivity of organozinc reagents vs. organolithium and Grignard reagents.[21d] The Willis group also reported a palladium-catalyzed cross coupling of lithium sulfinates, obtained from the corresponding organolithium reagents and DABSO, in a two-step, one-pot sequence (Scheme 5 **III**).[21e] Waser and co-worker described a one-pot, three-component synthesis of alkynyl sulfones using their ethynyl benziodoxolone (EBX) reagents as terminal electrophiles (Scheme 5 **IV**).[21f] Haufe et al. reported, that various (hetero)aryl sulfonamides can be prepared directly from the corresponding aryl bromides via a one-pot, four-step synthetic sequence, based on an initial bromine-lithium exchange (Scheme 5 **V**).[21g]

Most DABSO-based protocols are focusing solely on the one-pot synthesis of sulfones or sulfonamide. Usually the formed sulfinate salts are not isolated in their pure forms, but rather directly employed in a second transformation. In 2016, Odell et al. reported a convenient method for the preparation and isolation of sodium arylsulfinate salts from aryl halides and DABSO. Treatment of the crude products with aqueous Na_2CO_3 and pu-



Scheme 5. DABSO-based, one-pot synthesis of sulfones or sulfonamide.

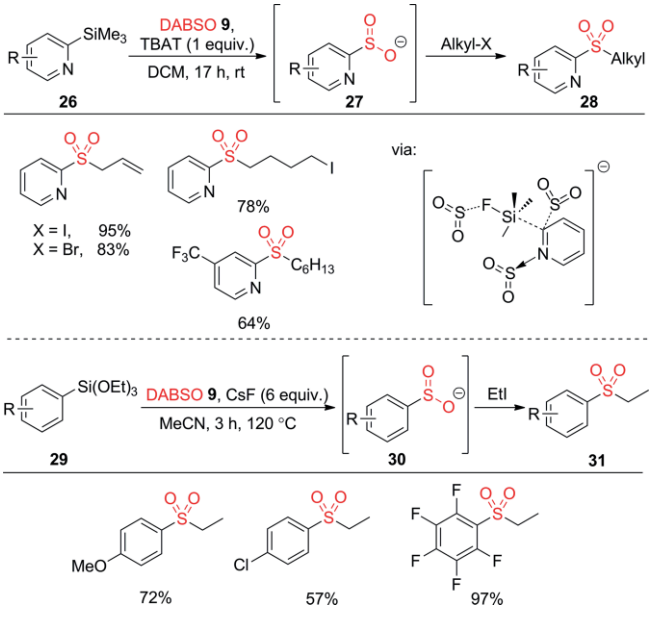
rifying by liquid–liquid and solid–liquid extraction can effectively avoid the problem of over-oxidation to sulfonic acids (Scheme 6 **I**).[22]



Scheme 6. Synthesis of sodium sulfinates via DABSO.

In 2018, Maruoka and co-workers described a novel synthetic route to prepare sodium α-aminoalkanesulfinate salts **25**, which were utilized as sources of α-aminoalkyl radicals. A two-step reaction based on a lithiation and trapping with SO_2 successfully afforded the desired sodium sulfinate salts, after aqueous work-up with sodium bicarbonate. It is worth mentioning, that in this case the chlorination of sulfonic acids followed by reduction of the parent sulfonyl chlorides failed to afford the desired sulfinates (Scheme 6 **II**).[23]

An intriguing synthesis of aromatic sulfinate salts via SO_2 insertion into organosilanes was reported by Cantat and co-workers.[24] Various pyridyl sulfones were successfully prepared in a very mild one-pot procedure via in situ generated sulfinic acid salts **27**. In stark contrast, the reaction with simple arylsilanes required considerably more forcing reaction conditions. Experimental and density functional theory (DFT) calculation results indicate, that SO_2 also plays an important role in the C-Si bond cleavage step (Scheme 7).

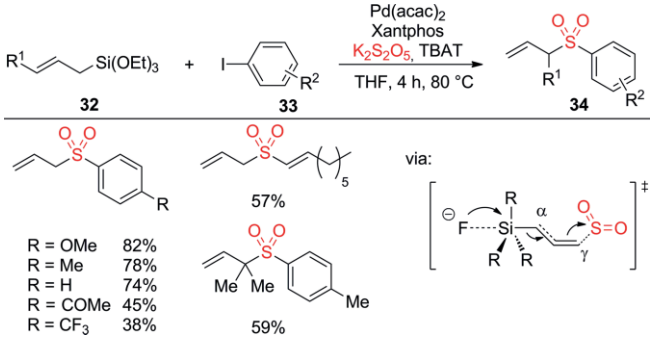


Scheme 7. SO2 insertion into organosilanes.

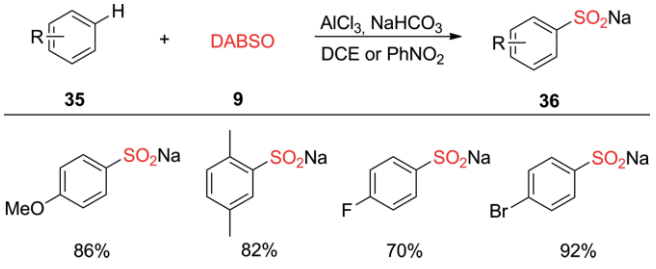
The same group further applied a similar strategy for a Pd-catalyzed sulfonylative Hiyama cross-coupling reaction. Sulfinates generated in situ via SO_2 insertion were found to be the key intermediate. This is in stark contrast to classical carbonylative cross-coupling reactions, where the insertion of CO occurs after the oxidative addition to the aryl halide. The author proposed, that the high regioselectivity of this method is attributed to the selective SO_2 insertion at the γ-position of allylsilanes **32**, which was also demonstrated by DFT calculations (Scheme 8).[25]

Wang and Zhang reported a simple preparation of aryl sulfinate salts from arenes and DABSO in the presence of $AlCl_3$. The addition of excessive $AlCl_3$ was necessary to afford desired products in good to high yields. Mechanistic studies indicate an electrophilic aromatic substitution pathway (Scheme 9).[26]

The Vogel group has shown, that SO_2 can undergo reversible cycloadditions with various dienes. Based on these pericyclic reactions, a variety of useful transformations have been developed.[27] For instance the sulfone **40** was prepared via an initial hetero-Diels-Alder reaction between the dien **37** and SO_2 and methylation of an in situ generated sulfinate **39** (Scheme 10 **I**).

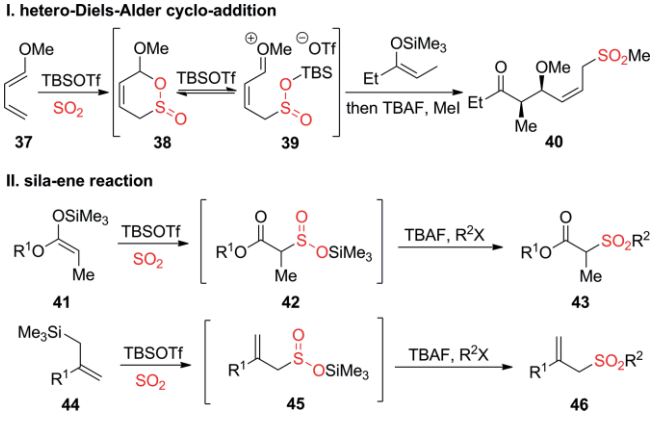


Scheme 8. SO2 insertion into allysilanes.



Scheme 9. Friedel-Crafts sulfination with DABSO.

Sila-ene reactions with SO_2 could be utilized for the synthesis of various sulfones via the corresponding silyl sulfinate intermediates (Scheme 10 **II**).

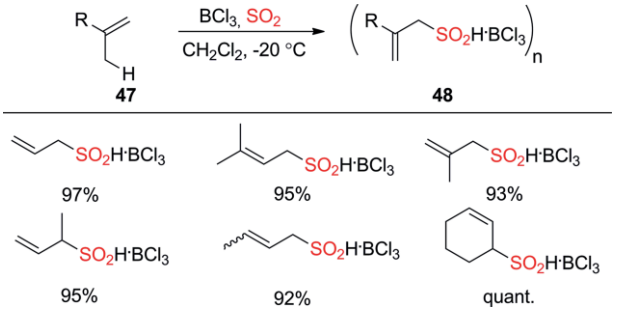


Scheme 10. Sulfone synthesis via pericyclic reactions.

In 2010, Vogel and co-workers developed a more general synthetic route to β,γ-unsaturated sulfinate salts via a BCl_3-mediated ene-reaction between SO_2 and unfunctionalized alkenes. The formed, stable sulfinic acid·BCl_3 complexes **48** seem to be crucial for suppressing desulfinylation and polymerization processes. These complexes can be converted into different sulfonyl-containing derivatives in one-pot procedures (Scheme 11).[28]

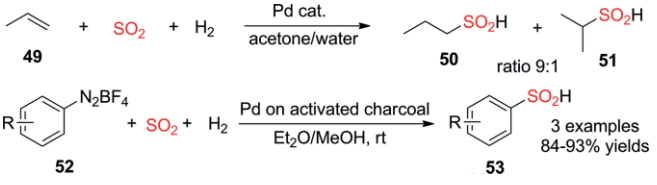
5. Transition-Metal-Catalyzed SO_2 Insertion

Both the reactivity of transition metal complexes towards SO_2 and the insertion of SO_2 into carbon–metal bonds of such complexes have been studied extensively on isolated, defined metal complexes.[29] Building upon these pioneering studies and the



Scheme 11. Sulfinic acid complex synthesis via BCl_3-medieated ene reaction.

introduction of easy-to-handle SO_2 surrogates, various catalytic processes for the insertion of SO_2 have been developed in the last ten years.[30] The first report of a transition-metal mediated synthesis of sulfinic acids, using over-stoichiometric amounts of copper powder, dates back to late 1890s.[31] Around 100 years later, Keim and co-workers reported a series of palladium-catalyzed hydrosulfination reactions for the construction of sulfinic acids using SO_2 gas.[32] For instance, aromatic sulfinic acids **53** could be prepared from aryldiazonium tetrafluoroborates, SO_2 and hydrogen gas. Interestingly, the authors could demonstrate, that the addition of methanol or water was efficient to suppress the disproportionation of the generated sulfinic acids (Scheme 12).

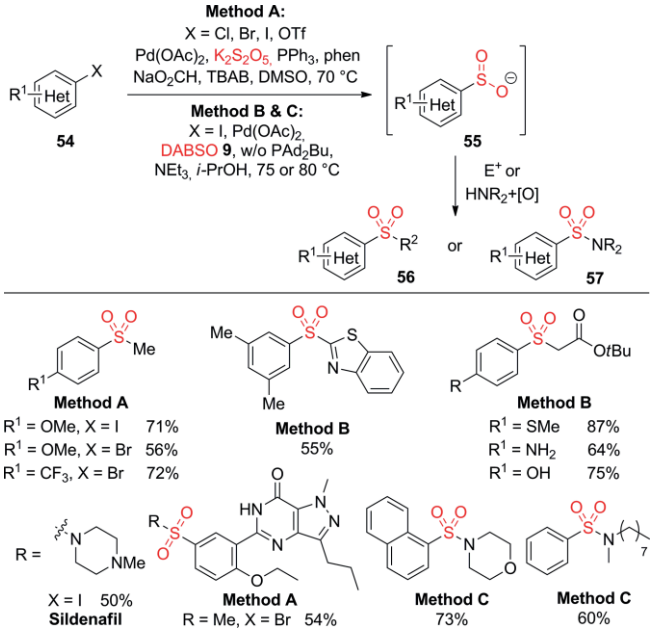


Scheme 12. Pd-catalyzed hydrosulfination.

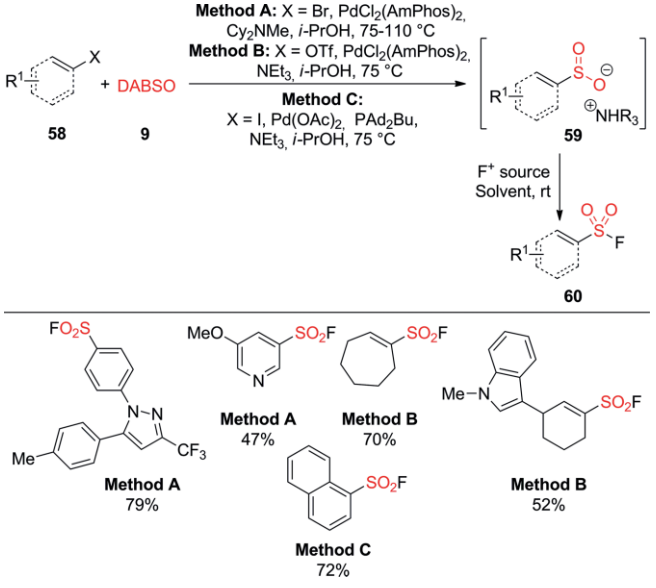
Later a team from Pfizer and the group of Willis independently reported the palladium-catalyzed sulfination of aryl and heteroaryl halides, using the SO_2 surrogates $K_2S_2O_5$[33a] and DABSO.[33b] Either sodium formate or 2-propanol serve as terminal reducing agents in these reactions. The generated sulfinates were directly converted into sulfones, sulfonamides (Scheme 13)[33] or sulfonyl fluorides (Scheme 14)[34] in a one-pot operation. The utility of these two-step protocols was demonstrated by the late-stage functionalization of drug-like scaffolds. Later on, Waser and co-workers could implement a Pd-catalyzed, one-pot, three-component arylalkynyl sulfone synthesis.[21f] Jiang et al. have realized a Pd-catalyzed construction of arylalkyl sulfones via a fleeting alkyl sulfinate as the key intermediate.[35]

(Hetero)aryl boronic acids also undergo efficient reactions with SO_2 in the presence of different Pd-catalysts. The generated sulfinates were directly used in the construction of various sulfones (Scheme 15)[36] and sulfonamides (Scheme 16)[36b,37] in one-pot, two-step protocols.

Interestingly, also gold(I)-based catalysts can efficiently promote the insertion of SO_2 into carbon-boron bonds. In the presence of an alkyl halide[38a,38b] or a diaryliodonium salt,[38c] the



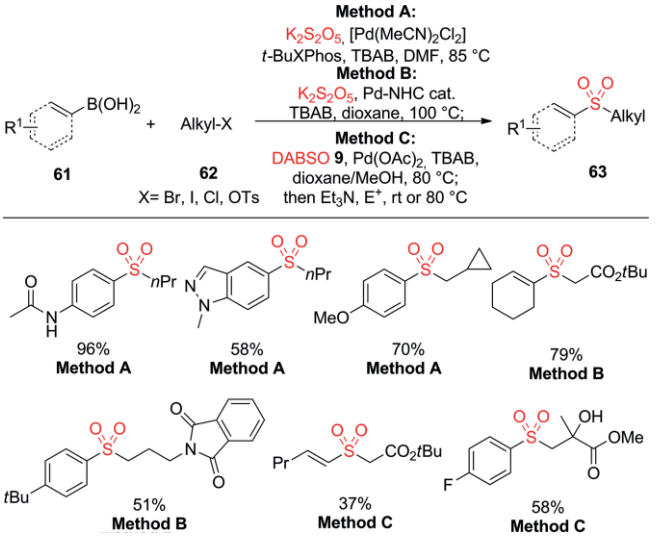
Scheme 13. Pd-catalyzed sulfination of aryl and heteroaryl halides.



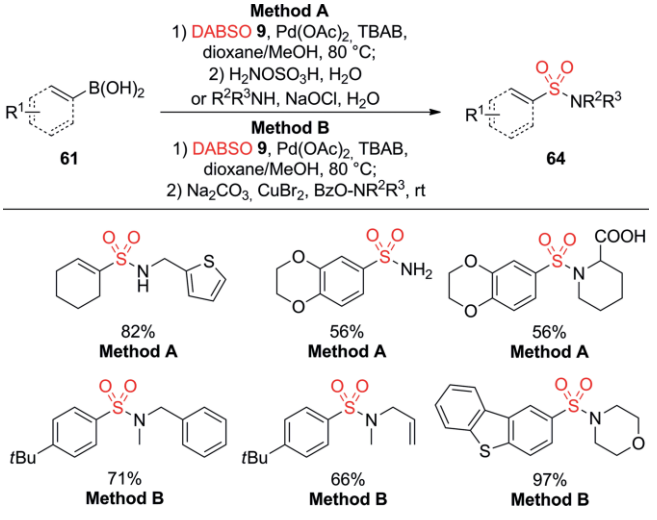
Scheme 14. Pd-catalyzed sulfination to construct sulfonyl fluorides.

direct formation of various sulfones takes place in a one-step, three-component reaction (Scheme 17).

In addition to gold- and palladium-based systems also first row-transition metals, such as cobalt, copper or nickel are capable of mediating the fixation of SO_2. For instance, the cobalt-catalyzed reaction of arylsilanes with DABSO and alkyl halides affords sulfones in good yields, presumably via a sulfinate intermediate (Scheme 18 **I**).[39a] Copper(I) salts can catalyze this transformation in a similar manner (Scheme 18 **II**).[39b] Willis et al. reported both a copper and a nickel-catalyzed sulfination of arylboronic acids. The generated sulfinates could be transformed directly into various sulfones and sulfonamides in sequential one-pot operations (Scheme 18 **III**).[39c,39d]



Scheme 15. Pd-catalyzed sulfination of (hetero)aryl boronic acids.

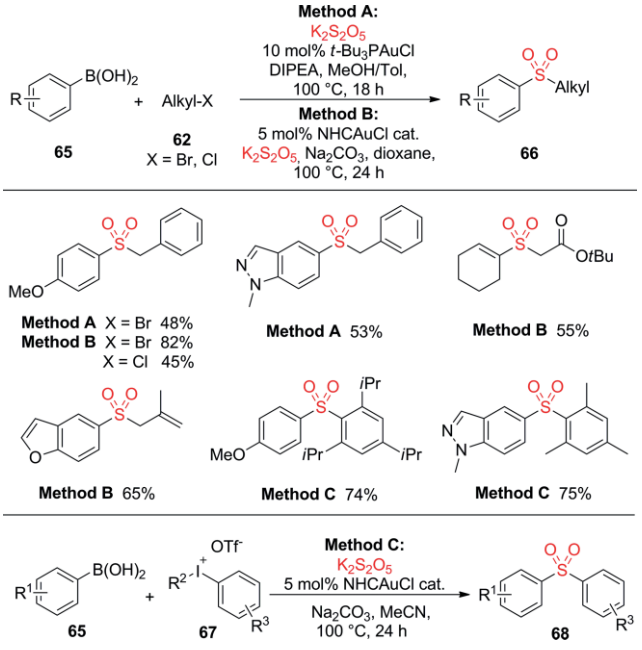


Scheme 16. Pd-catalyzed sulfination to construct sulfonamide.

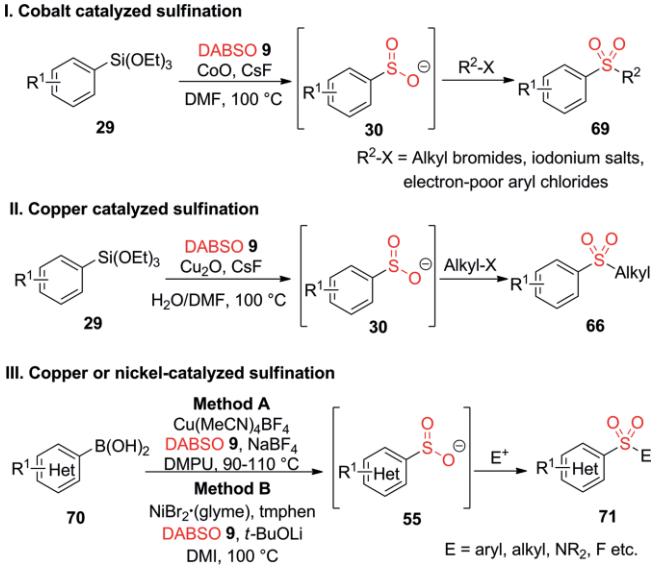
One has to mention, that these transition-metal catalyzed processes provide an interesting alternative to the use of pre-formed organometallic reagents. However, the parent sulfinic acid salts were rarely isolated as final products.

6. Nucleophilic Cleavage of Sulfonyl-Containing Compounds

The strategy to prepare alkane and aryl sulfinate salts via base induced cleavage of sulfones and other sulfonyl derivatives has been extensively explored for many years. Generally, the desired sulfinate salts can be obtained from different precursors via the displacement of a suitable leaving group.[2a,2b] A couple of selected classical examples are presented here (Scheme 19). Recent developments are mainly focusing on identifying milder reaction conditions and more sustainable procedures.



Scheme 17. Au-catalyzed sulfination of (hetero)aryl boronic acids.

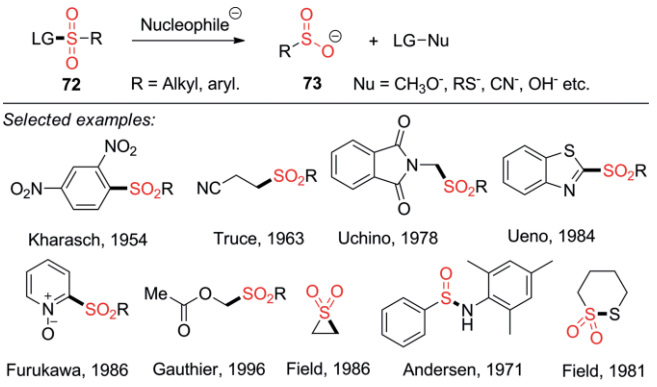


Scheme 18. First row transition metal-catalyzed sulfination.

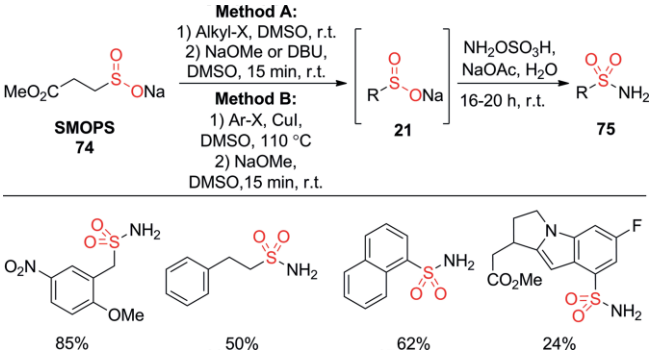
6.1. Fragmentation of Alkyl Sulfones

In 2002 Wang et al. reported sodium 3-methoxy-3-oxopropane-1-sulfinate (SMOPS) **74** as a novel 'SO_2^{2-}' reagent, which allows an efficient introduction of a masked sulfinate moiety either via S_N2-type chemistry or a copper-catalyzed coupling with aryl iodides. In this report, the free sulfinates can be released smoothly under basic conditions. They were converted directly into the corresponding primary sulfonamides using hydroxylamine-*O*-sulfonic acid. The use of harsh reaction conditions such as strongly oxidizing or organometallic reagents can be avoided (Scheme 20).[40]

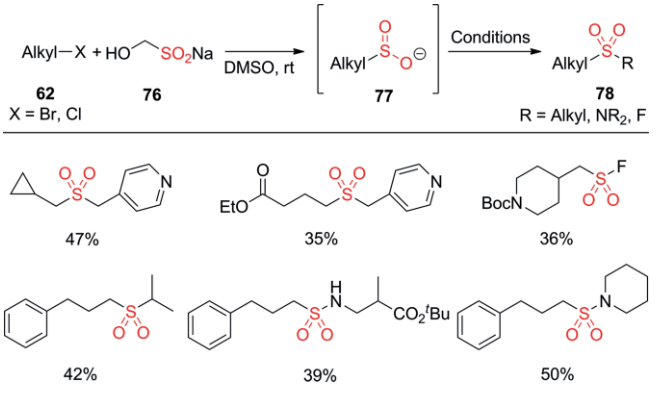
In 2016, Shavnya and co-workers reported an expeditious preparation of alkane sulfinate salts and their direct derivatization by using commercially available Rongalite **76** as the synthetic equivalent for the 'SO_2^{2-}' anion.[41] Compared to the SMOPS reagent, Rongalite is considerably cheaper and available in greater quantities. Under mild basic conditions, various aliphatic sulfones, sulfonamides, and sulfonyl fluorides can be smoothly prepared via a one-pot, two-step process (Scheme 21).



Scheme 19. Selected, established precursors for the synthesis of sulfinates via nucleophilic cleavage.



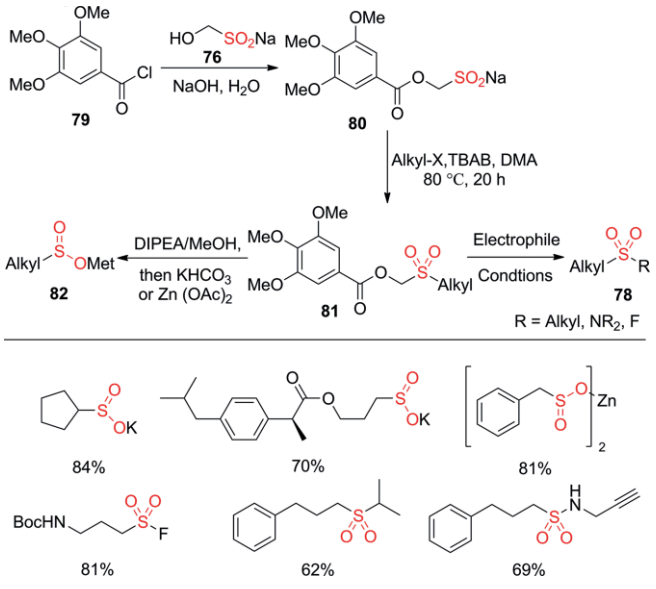
Scheme 20. Sulfinate salts synthesis from SMOPS reagent.



Scheme 21. Sulfinate salts synthesis from Rongalite.

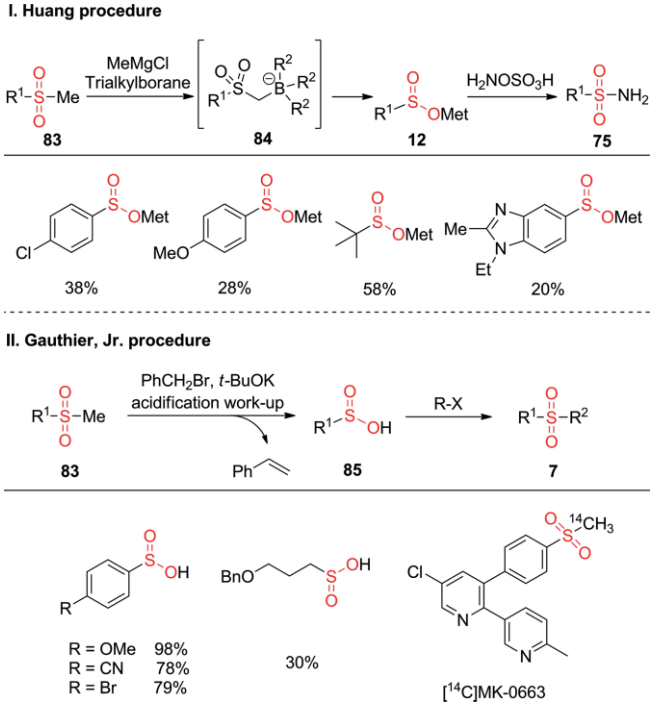
However, due to the inherent instability of Rongalite and the formed hydroxymethyl sulfone intermediate, the reaction scope is rather narrow and yields are in general not satisfying. Thus, in 2018 the same group reported an improvement method utilizing an *O*-protected derivative of Rongalite **80**.[42] In contrast to the previous method, higher yields and better functional

group compatibility were observed. More importantly, different alkane sulfinate salts can be isolated in pure form in this protocol (Scheme 22).



Scheme 22. Sulfinate salts synthesis from Rongalite derivative.

In 1994, Huang and co-workers reported a one-pot conversion of methyl sulfones to sulfinate salts and sulfonamides.[43a] The use of trialkyl boranes along with methylmagnesium chloride afforded the sulfinic acid salts in moderate yields (Scheme 23 **I**). Gauthier and co-workers improved this protocol to a convenient late stage functionalization method via an alkylation-elimination sequence.[43b] In their process, potassium *tert*-butoxide (*t*BuOK) was sufficient to promote the reaction.

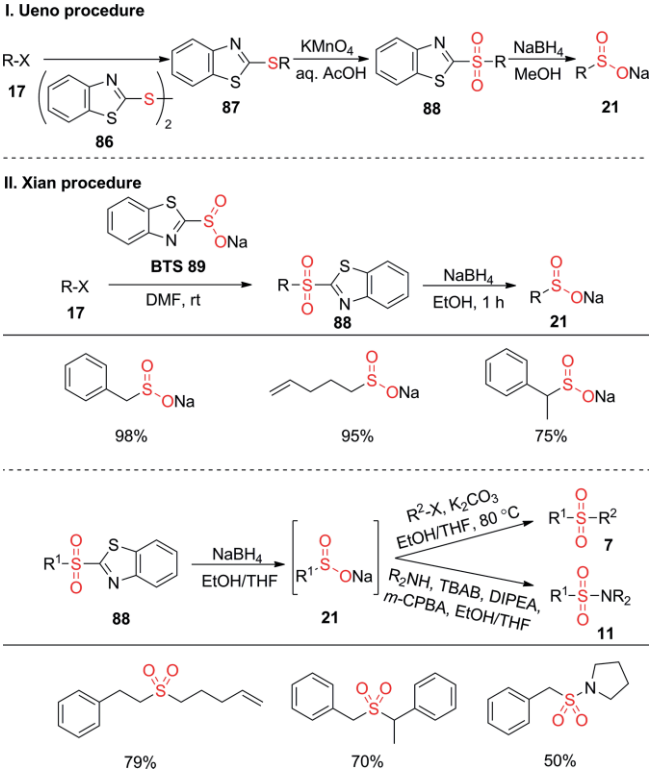


Scheme 23. Sulfinate salts synthesis from methyl sulfones.

The utility of this method was further demonstrated by introducing ^{14}C-labeled tracers into selected bioactive molecules (Scheme 23 **II**).

6.2. Base-Induced Cleavage of Heterocyclic Sulfones

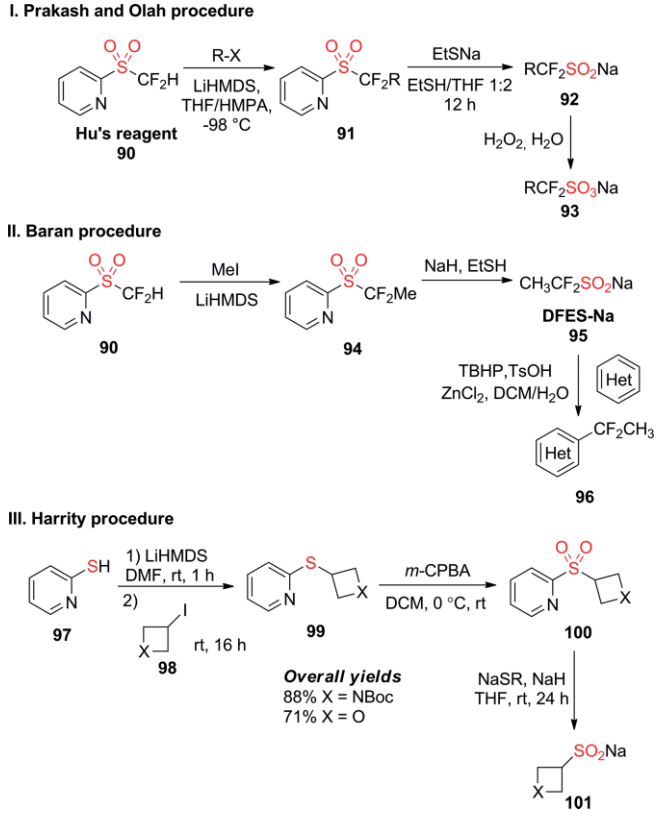
The cleavage of C–S bonds in electron-poor aromatic sulfones via an *ipso*-substitution process with suitable nucleophiles represents another useful strategy for the synthesis of sulfinate salts.[44] Based on this reactivity, several research groups have successfully designed and utilized various activated heterocyclic sulfones as key intermediates to prepare sulfinates. An early example was reported by Ueno and co-workers in 1984. 2-(Alkylsulfonyl)benzothiazoles **88** can be reductively cleaved with sodium borohydride ($NaBH_4$) to release alkane sulfinate sodium salts under mild condition in good yields (Scheme 24 **I**).[45a] In 2017, Xian and co-workers reported an improved approach to obtain the required 2-(alkylsulfonyl)benzothiazoles **88** using 2-sulfinyl benzothiazole (BTS) **89** as the starting material.[45b] A two-step reaction including benzothiazolation and $NaBH_4$ reduction was employed to transfer the sulfinate moiety from BTS to alkyl halides. In addition, the corresponding sulfones or sulfonamides can be prepared in a one-pot transformation (Scheme 24 **II**).



Scheme 24. Base-induced reductive cleavage of benzothiazole sulfones.

In a similar manner, the pyridine moiety in 2-sulfonyl pyridines can serve as a good leaving group. Prakash and Olah successfully synthesized a series of alkyl α,α-difluorinated sulfinate **92** and sulfonate **93** sodium salts from the corresponding difluoromethyl 2-pyridyl sulfones (Hu's reagent) **90** (Scheme 25 **I**).[46a] This procedure was adapted and improved by Baran and

co-workers for the scalable preparation of sodium difluoroethylsulfinate (DFES–Na) **95**. DFES–Na was successfully employed in the difluoroalkylation of various heterocycles (Scheme 25 **II**).[46b] On the other hand, the group of Harrity reported the synthesis of azetidine and oxetane sulfinate salts **101** from commercially available 3-iodoheterocycle precursors **98** (Scheme 25 **III**).[46c]



Scheme 25. Base-induced reductive cleavage of pyridyl sulfones.

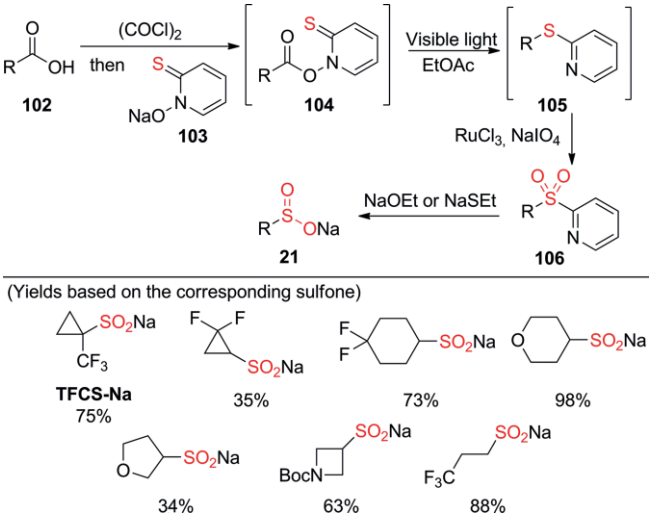
Using an interrupted Barton decarboxylation reaction to incorporate the cleavable pyridine moiety, the group of Baran was able to prepare a variety of different alkane sulfinate salts.[47] The reactivity of these salts was evaluated in a Minisci-type alkylation of four classes of heterocycles (Scheme 26).

The synthesis of stereochemically defined sulfinate salts is of particular interest for the construction of chiral sulfones or sulfonamides. However, the traditional reduction approach starting from sulfonyl chlorides is associated with partial racemization of adjacent stereocenters, due to the generation of an achiral sulfene intermediates. The group of Paras described an improved method for the synthesis of chiral sulfinate salts via pyrimidine thioethers **107**.[48] Oxidation to the sulfone **108** and based-induced cleavage with NaOMe provides a series of secondary alkyl sulfinate **109** with complete retention of the adjacent stereogenic carbon center. The formed sulfinate salts could be converted into a variety of α-chiral sulfonamides and sulfones in good yields (Scheme 27).

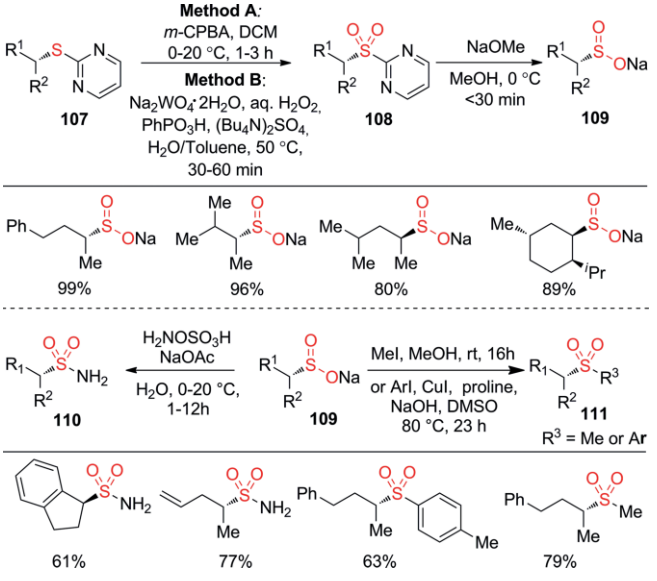
6.3. Degradation of Other Sulfonyl Derivatives

The thiosulfonate group can serve as a masked sulfinate functionality. Free sulfinates can be liberated via nucleophilic cleavage of the S–S bonds.[49] In 2017, Jang and co-workers revisited the utility of these sulfinate anion equivalents in the one-pot construction of sulfones and sulfonamides.[50a] Since thiosulfonates **113** can be easily prepared by copper-catalyzed aerobic dimerization of thiols,[50b] this procedure provides an alternate synthetic route to sulfinate salts (Scheme 28).

In a similar manner, *N*-aminosulfonamides can serve as sulfinate precursors.[51] In 2014, the Willis group reported a one-pot, three-step synthesis of sulfones from aryl or alkenyl halides.[51c] Based on their previous palladium-catalyzed aminosulfonylation reaction,[19c] trialkyl aminosulfonamide intermediates **117** can be generated in situ via the alkylation with benzyl bromide. Subsequent base-mediated degradation of these intermediates furnishes the free sulfinate salt, which can be transformed into various sulfonyl-group containing molecules (Scheme 29). Similar strategies were further applied into the

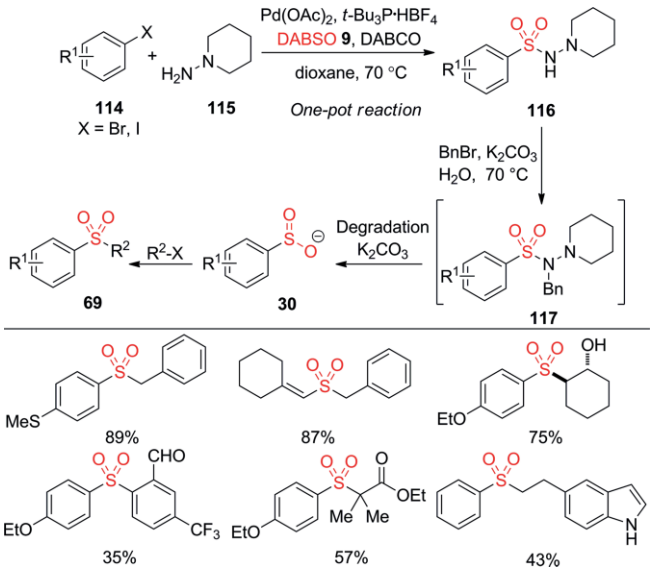


Scheme 26. Sulfinate salts synthesis from carboxylic acids.



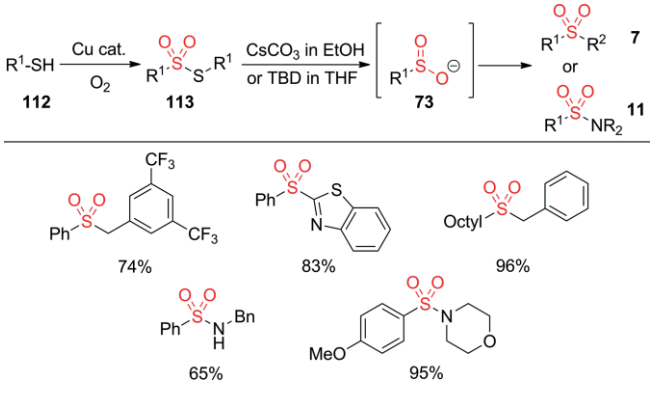
Scheme 27. Synthesis of chiral secondary alkyl sulfinate salts.

construction of other related sulfonyl-containing products via sulfinate salts as key intermediates.[52]

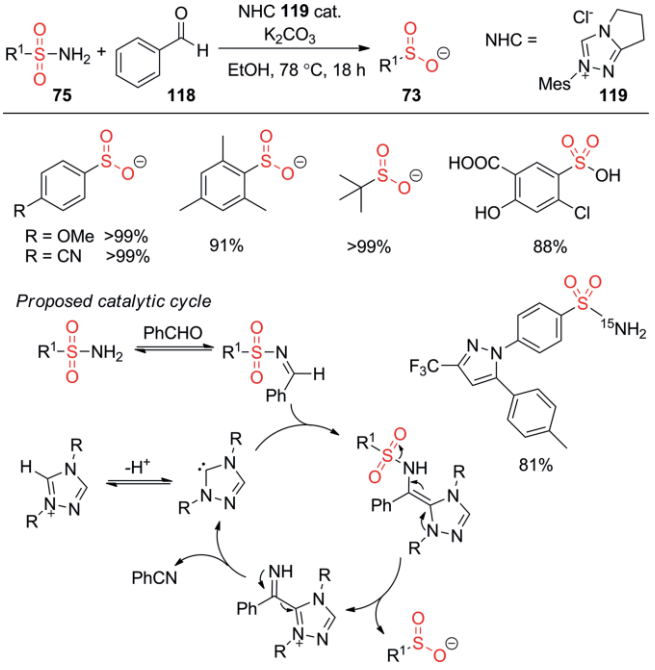


Scheme 29. Degradation of *N*-aminosulfonamides.

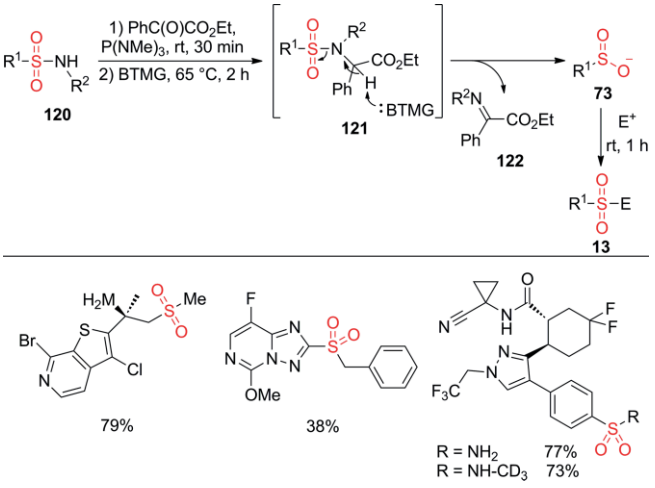
Recently, Fier and Maloney reported a novel method for the conversion of primary sulfonamides, traditionally considered as synthetic dead-ends, into sulfinic acid salts.[53a] The key step of this process is a *N*-heterocyclic carbene (NHC)-catalyzed fragmentation of an in situ generated *N*-sulfonylimine to a nitrile and a sulfinate salt. Various functional groups were well tolerated in this process and the formed crude sulfinates can be used for the synthesis of different sulfonyl derivatives in one-pot process (Scheme 30). Shortly after, the same group described a general platform for the degradation of secondary sulfonamides to the corresponding sulfinic acid salts. The reductive cleavage of the selective N–S-bond is driven by the combination of ethyl benzoylformate and tris(dimethylamino)phosphine (Scheme 31).[53b] It should be mentioned, that these methods provide a highly useful way for the late-stage manipulation of primary and secondary sulfonamide functionalities in complex molecular scaffolds.



Scheme 28. Cleavage of thiosulfonates.



Scheme 30. NHC-catalyzed deamination of primary sulfonamides.



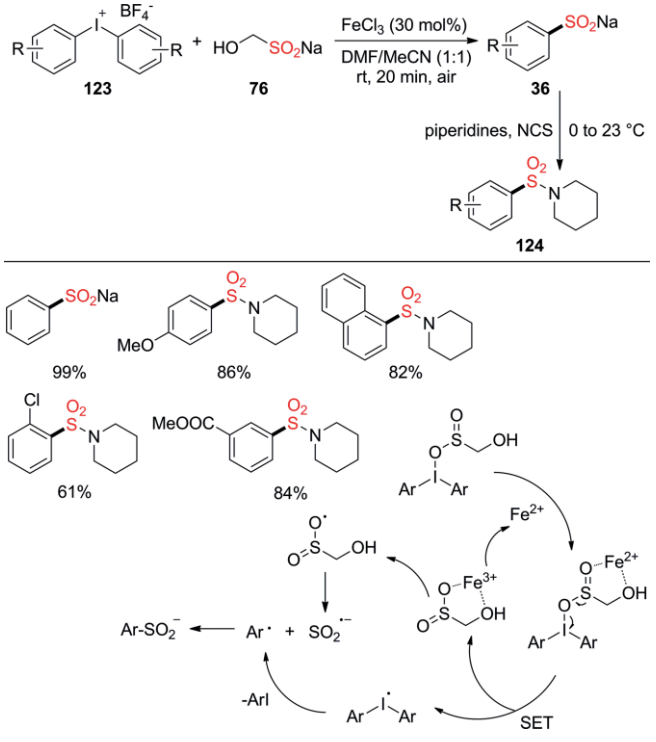
Scheme 31. Reductive cleavage of secondary sulfonamides.

7. Radical Combination with Sulfur Dioxide Radical Anion ($SO_2^{\bullet-}$)

SO_2 and related SO_2 surrogates are good radical traps. The synthesis of sulfones and sulfonamides via in situ generated sulfonyl radicals has been reviewed recently.[54] Similar transformations for preparation of sulfinic acids or their salts have been of limited use so far.[55] However, the generation and utilization of the sulfur dioxide radical anion ($SO_2^{\bullet-}$) provides an analogous avenue for the efficient synthesis of sulfinates.

In 2016, Luo and co-workers reported a facile synthesis of sulfinate salts via an iron-catalyzed radical coupling between diaryliodonium salts **123** and Rongalite.[56] The desired sulfinates can be prepared under very mild conditions in good yields and were directly converted into different sulfonamides. The authors proposed that an initial interaction between diaryl-

iodonium and Rongalite was crucial for this radical coupling reaction, and the iron catalyst greatly facilitates this process (Scheme 32).

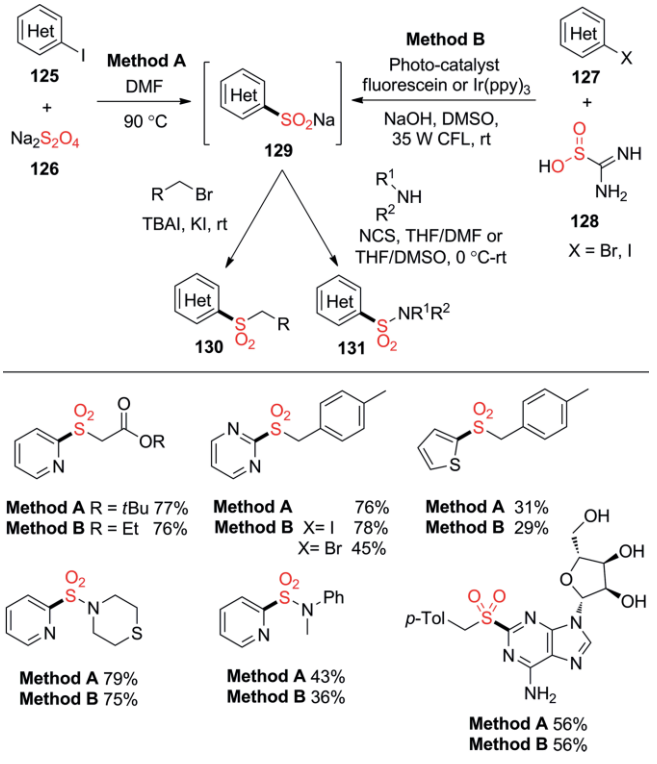


Scheme 32. Iron-catalyzed radical coupling.

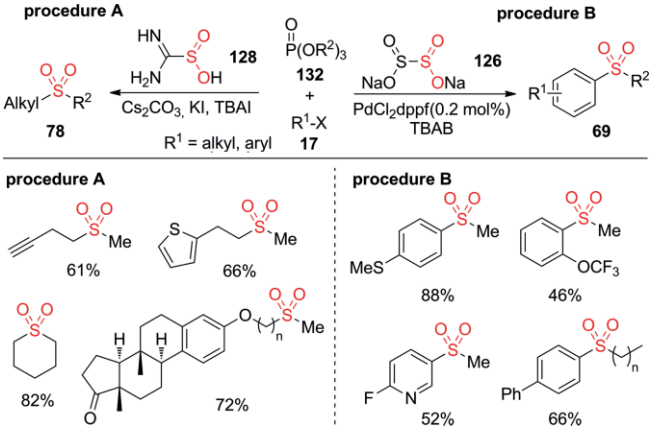
In 2018, Wu and co-workers developed a catalyst-free sulfonylation of (hetero)aryl iodides with sodium dithionite **126**.[57a] Various electron-deficient (hetero)aryl iodides were suitable reaction partners, whereas electron-neutral or -rich (heteroaryl) iodides did not react in a satisfactorily manner **(**Scheme 33. **Method A)**. Later on, the same group reported a photoredox-catalyzed process using thiourea dioxide **128** as the SO_2 surrogate.[57b] Under visible light irradiation, the reaction proceeded smoothly through a radical combination of aryl radicals and sulfur dioxide radical anions **(**Scheme 33. **Method B)**. The authors demonstrated, that in both cases the corresponding sulfinate salts were formed as key intermediates. Starting from the in situ generated sulfinic acid salt, various heteroaryl sulfones and sulfonamides were prepared successfully.

Similarly, Jiang et al. reported a general construction of sulfones with different SO_2 surrogates. By employing a phosphate ester **132** as the stable alkyl source, alkyl-alkyl sulfones could be prepared from alkyl halides and thiourea dioxide **128**; while aryl-alkyl sulfones could be afforded from aryl halides and sodium dithionite **126**, combined with a palladium catalyst. In both cases, the generation of alkane or aryl sulfinates was postulated as key intermediates (Scheme 34).[58]

Chen and Liu reported the preparation of fluoroalkyl-containing sulfinate salts **134** via a zinc-mediated, intermolecular fluoroalkyl-sulfination of unsaturated C–C-bonds.[59] In this reaction DABSO was used as the SO_2-source and the in situ generated sulfinate salts could be subsequently converted into various sulfonyl-containing compounds. Mechanistic studies demonstrated, that the sulfur dioxide radical anions were involved in the reaction process (Scheme 35).



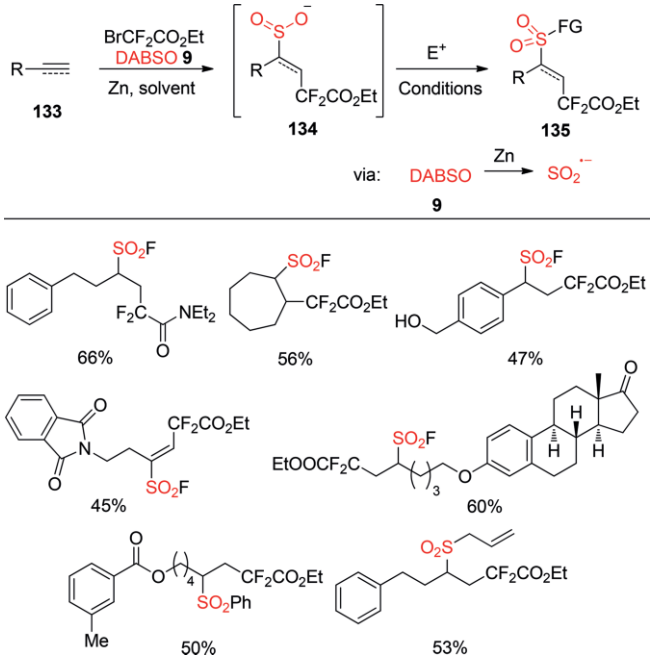
Scheme 33. Radical coupling with sodium dithionite or thiourea dioxide.



Scheme 34. Sulfone synthesis controlled by SO_2 surrogates.

8. Conclusion and Perspective

In conclusion, tremendous advances have been achieved in the preparation of sulfinate salts in last two decades. Besides the improvement of classical methods, such as the reduction of sulfonyl chlorides or the oxidation of thiols, a plethora of novel, more efficient and sustainable approaches have been developed. Among these novel methods four developments have emerged as particularly useful:



Scheme 35. Zinc-mediated reductive fluoroalkylsulfination.

1) utilization of solid, and easy-to-handle SO_2 surrogate, especially DABSO, which lead to a renaissance of organic chemistry with SO_2;

2) transition-metal-catalyzed reactions enabling the fixation of SO_2 under milder reaction conditions;

3) development of novel reagents for the facile introduction of masked sulfinates as well as for the chemoselective liberation of the desired sulfinate under very mild reaction conditions;

4) reassessment of radical reactions with SO_2 and the utility of the sulfur dioxide radical anion in organic synthesis.

Despite all these advances, the synthesis of sulfinate salts is far from being a solved problem in organic synthesis. Some of the current problems and future challenges are:

1) preparation and isolation of sulfinate salts in their pure form (rather than the nowadays still common direct trapping);

2) general applicable, more efficient and sustainable methods for the synthesis of sulfinic acids and their salts;

3) construction of sulfinates via the selective, direct functionalization of C–H-bonds.

Based on the recent developments, we are confident, that novel, exciting approaches for the synthesis of sulfinate salts will be reported in the near future.

Acknowledgments

The authors greatfully acknowledge financial support from the Qingdao University (start-up grant for S. Liang), the German Research Foundation (DFG), and the research unit NanoKat at the TU Kaiserslautern. Open access funding enabled and organized by Projekt DEAL.

Keywords: Sulfinate Salts · Sulfinic Acid Salts · Sulfur Dioxide · Sulfones · Sulfonamides

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Received: March 26, 2020