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Sulfinate derivatives: dual and versatile partners in organic synthesis

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Sulfinic acids and their salts have recently emerged as versatile coupling partners to efficiently access a wide variety of hetero- and carbocyclic compounds, under relatively mild conditions. Their growing importance is attributable to their dual capacity for acting as nucleophilic or electrophilic reagents. This report summarizes recent advances in the preparation and use of sulfinites in organic synthesis.

I. Introduction

Designing molecular structures, tailored to the needs of diverse areas, organic synthesis, medical research and materials science, is an imposing challenge for chemists in order to improve the general well-being of society. For this purpose, optimizing functional structures requires the ability to access them in a time-efficient manner. Therefore, chemists are continually searching for starting materials that enable simple and convergent synthetic routes. Sulfinites represent a class of organic compounds that were rediscovered very recently. Their reactivity has been investigated since the early 1900s.¹ However, they have started to be extensively developed over the last decade. For chemists, they have two essential criteria: easily accessible starting materials and versatile reactivity.

Sulfinites are commercially or readily available, bench-stable, non-hygroscopic and easy to handle. Their growing importance in organic synthesis is due to their dual capacity for being nucleophilic or electrophilic reagents, depending on the reaction conditions (Scheme 1).

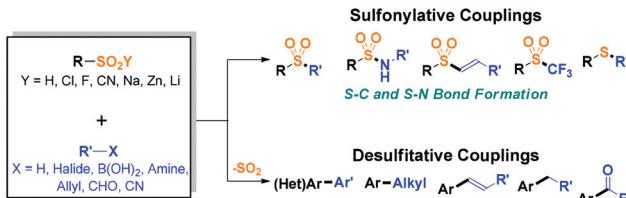
Indeed, sulfinites generate sulfone and sulfonamide derivatives, important building-blocks in medicinal chemistry (*via* sulfonylative S–C and S–N bond formation). In addition, under transition-metal catalysis, these sulfinites are employed as electrophilic or nucleophilic partners in desulfitative/cross-coupling reactions (Mizoroki–Heck, Suzuki–Miyaura, Stille couplings, C–H functionalization...) for C–C bond formation. These new sulfone and arene sources allow a better functional group tolerance along with operational ease, enabling widespread applications. For these reasons, sulfinites represent a useful tool for both organic and medicinal chemists. Moreover, these reagents can be used in academic research (safe and easy to handle compounds) as well as in industry (large scale preparations).

This review highlights recent advances in the preparation of sulfinate derivatives, emphasizing their use in sulfonylative and desulfitative reactions, making them valuable synthetic intermediates.

A. Synthesis of sulfinate derivatives

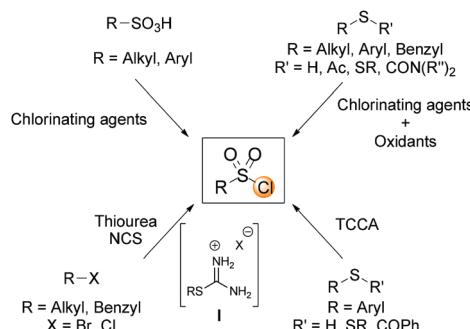
In the literature, many synthetic routes can be found for the preparation of sulfinate derivatives (sulfonyl chlorides, sulfinate salts and sulfinic acids). The most commonly used methods are depicted herein.

1. Sulfonyl chlorides (RSO_2Cl). Sulfonyl chlorides are not only used in sulfonylating and desulfitative reactions but they can also lead to other sulfinate derivatives. Alkyl and aryl sulfonyl chlorides are the most commercially available sulfinate derivatives. Otherwise, they are readily prepared from commercial sources. Chlorination of sulfonic acids and oxidative chlorination of sulfur substrates represent the main approaches to sulfonyl chlorides (Scheme 2). Chlorinating agents generally used with sulfonic acids are thionyl chloride (SOCl_2),² phosphorus chlorides (PCl_5 ,³ PCl_3 ,⁴ POCl_3 ,⁵) cyanuric chloride (NCCl_3 ,⁶ and PPh_3Cl_2).⁷ The inconvenience of using toxic chlorinating reagents in excess, as well as the formation



Scheme 1 Sulfinites, versatile coupling partners.

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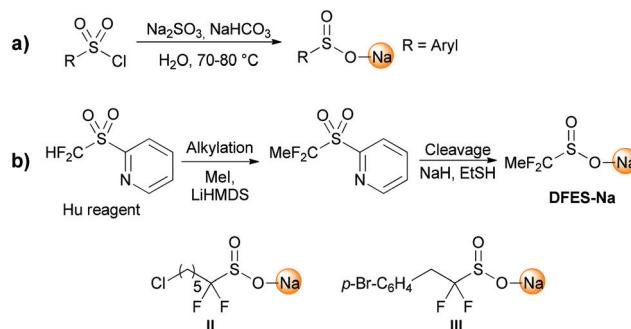


Scheme 2 Preparation of sulfonyl chlorides (NCS = *N*-chlorosuccinimide, TCCA = trichloroisocyanuric acid).

of side products, led to the development of a powerful alternative method using mild oxidative and chlorinating agents: the oxidative chlorination of thiols and their derivatives (disulfides, thioacetates, thiocarbamates) (Scheme 2). For example, *N*-chlorosuccinimide (NCS)/tetrabutylammonium chloride (Bu_4NCl) was employed for the chlorination of thiols and disulfides to obtain the corresponding arenesulfonyl chlorides.⁸ NCS/hydrochloric acid was also used with thioacetates and thiocarbamates to synthesize alkyl and aryl sulfonyl chlorides.⁹ Likewise, a mixture of nitrate salt (KNO_3)-chlorotrimethylsilane (TMSCl)¹⁰ was employed for the direct oxidative conversion of thiols and disulfides to sulfonyl chlorides. Due to the environmental toxicity and the repulsive odour of thiol derivatives, Xu and co-workers¹¹ recently developed a more eco-friendly method to synthesize benzyl and alkylsulfonyl chlorides using benzyl and alkyl halides and inexpensive thiourea. This protocol generates *in situ* *S*-alkylisothiourea salts (**I**), which will subsequently undergo an oxidative chlorosulfonation in the presence of NCS (Scheme 2). It should be noted that these conditions were applicable on a large scale. To overcome the instability of some sulfonyl chlorides (especially heteroaryl derivatives), they are prepared *in situ* from thienzoates,¹² thiols or disulfides¹³ via trichloroisocyanuric acid (TCCA) and directly converted, without isolation, into sulfonamides in the presence of amines. These conditions are more compatible with acid labile functionalities. Besides sulfonyl chlorides, fewer reports describe the use of sulfonyl fluorides and cyanides as coupling partners. They are usually formed from the electrophilic attack of fluorinating or cyanating agents on sulfonyl chlorides.

2. Sulfinate salts (RSO_2M). Sulfinate salts represent the most used sulfinate derivatives in organic reactions. This part focuses on recent advances in the synthesis of new sulfinate reagents. The advantages and the applications of these new synthetic tools will be detailed in the relative sections.

(a) *Sodium sulfinate (RSO_2Na)*. Compared to sulfonyl chlorides, sodium sulfinate derivatives are more stable and moisture-insensitive. There are only a few commercially available substrates, but they can be easily prepared by the reduction of the corresponding sulfonyl chlorides. The most common method employs a mixture of sodium sulfite and sodium bicarbonate in water (Scheme 3a).¹⁴

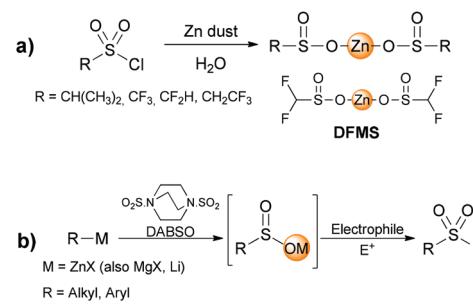


Scheme 3 Preparation of sodium sulfinate salts (EtSH = ethyl mercaptan).

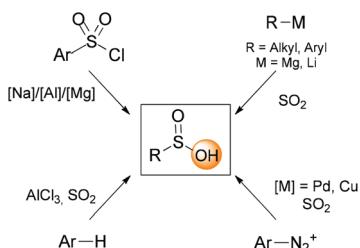
Recently, Baran's group¹⁵ synthesized sodium 1,1-difluoroethanesulfinate (DFES-Na), starting from Hu's reagent (Scheme 3b).¹⁶ This latter is alkylated with methyl iodide followed by the cleavage and liberation of sodium sulfinate salt in the presence of sodium hydride and ethyl mercaptan (EtSH). This air and water stable reagent enabled the introduction of the difluoroethyl group ($-\text{CF}_2\text{Me}$), the metabolically stable bioisostere of methoxide, to a wide variety of structures. Following the same approach, one alkyl and one benzyl difluorinated sodium sulfinate were synthesized ((**II**) and (**III**), respectively).

(b) *Zinc sulfinate (RSO_2Zn)*. The use of sulfinate zinc salts is very limited, although remarkable developments in their synthesis, purification and applications have been made, particularly by Baran's and Willis's groups. Organozinc reagents have lower reactivity than other organometallic compounds, resulting in a reduction in side reactions and better tolerance of functional groups. Even though a toolkit with several zinc bis(alkanesulfinate) reagents is commercially available from Sigma Aldrich, Baran and co-workers elaborated a simple synthesis from the ready-available sulfonyl chlorides in the presence of zinc dust and water (Scheme 4a).¹⁷

The same group invented zinc difluoromethanesulfinate (DFMS) ($\text{Zn}(\text{SO}_2\text{CF}_2\text{H})_2$) for the direct and selective difluoromethylation of heterocyclic compounds.¹⁸ This new reagent is prepared, on a large scale, from difluoromethanesulfonyl chloride ($\text{HCF}_2\text{SO}_2\text{Cl}$). It should be noted that these substrates are very stable and allow reactions in an open flask. Independently, Willis's work focused on the *in situ* formation of



Scheme 4 Preparation of zinc sulfinate salts (DABSO = 1,4-diazabicyclo[2.2.2]octane-bis-(sulfur dioxide)).



Scheme 5 Preparation of sulfinic acids.

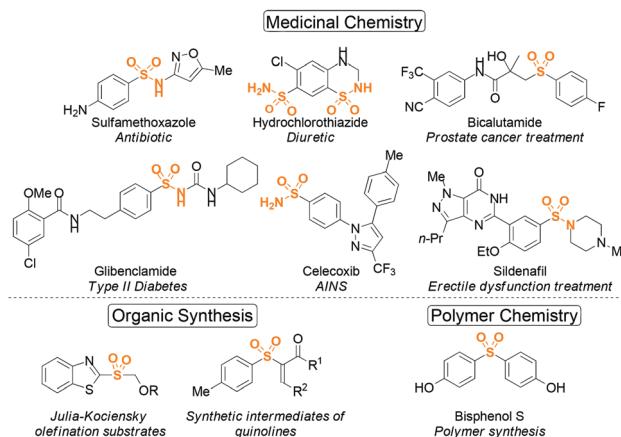
nucleophilic metal sulfinate using organometallic reagents (Grignard and organolithium reagents) and DABSO as the SO_2 source (Scheme 4b).¹⁹ DABSO is an air-stable and easy to handle white solid formed by condensing SO_2 over freshly sublimed DABCO. Using DABSO as a SO_2 source as well, Rocke and co-workers managed to synthesize sulfones using organo-zinc reagents instead of Grignard and lithiated compounds.²⁰ Mild conditions and better functional group tolerance were achieved.

(c) *Sulfinic acids (RSO_2H)*. Compared to the other sulfinate derivatives, sulfinic acids are the least stable. In fact, aliphatic sulfinic acids undergo disproportionation reactions that will lead to the corresponding thiosulfonates (RSO_2SR) and sulfonic acids (RSO_3H).²¹ However, aromatic acids are more stable and continue to be used in organic chemistry.²² Sulfinic acids are prepared by reduction of the commercially available sulfonyl chlorides.²³ Among the reducing agents, sodium sulfite,²⁴ sodium borohydride,²⁵ magnesium²⁶ and lithium aluminium hydride²⁷ are frequently used (Scheme 5).

Sulfination of organometallic compounds represents another way to access sulfinic acids. Grignard reagents are often employed specially for aliphatic substrates,²⁸ as are organolithium reagents.²⁹ Friedel–Crafts sulfination of aromatic compounds also leads to sulfinic acids.³⁰ Diazonium salts react with sulfur dioxide (SO_2) to give the corresponding sulfinic acids *via* a radical mechanism (Scheme 5). This type of reactivity was first introduced by Gattermann in 1890 where greater than stoichiometric amounts of copper were used.³¹ A century later, Keim and co-workers developed an alternative reaction with aryl diazonium tetrafluoroborates with only 10% mol palladium on activated charcoal to obtain the desired aryl sulfinic acids.³² However, for the last three methods, careful measures should be taken since an excess of sulfur dioxide (SO_2), a toxic and corrosive gas, is used. It should be handled in a well-ventilated fume-hood and the removal of excess SO_2 should be controlled carefully.

B. Sulfinate derivatives in S–C and S–N bond formation

Exploring sulfone and sulfonamide chemistry goes back to the previous century, since they cover wide applications in a diverse number of fields (Scheme 6). In medicinal chemistry,³³ a large number of bioactive molecules contain sulfone scaffolds: (i) sulfonamides, one of the first antibiotics used (*e.g.* sulfamethoxazole);³⁴ (ii) diuretics (*e.g.* hydrochlorothiazide);³⁵ (iii) anticancer drugs (*e.g.* bicalutamide for the treatment

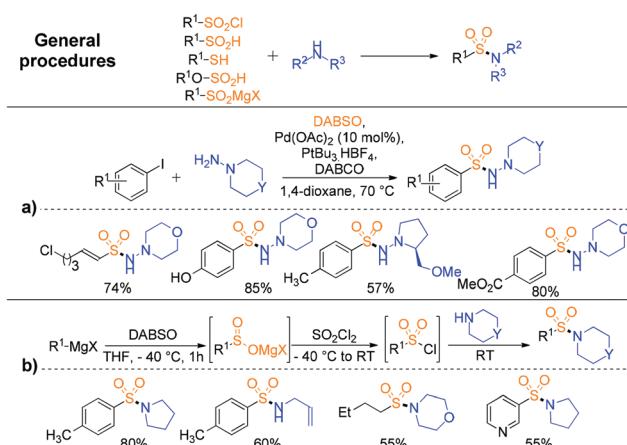


Scheme 6 Applications of sulfones and derivatives.

of prostate cancer);³⁶ (iv) sulfonylureas (*e.g.* glibenclamide),³⁷ frequently used for the treatment of type II diabetes; (v) celecoxib, a non-steroidal anti-inflammatory drug (AINS) that selectively inhibits cyclooxygenase isoform 2 (COX-2)³⁸ and (vi) sildenafil for the treatment of erectile dysfunction.³⁹ In organic synthesis, they are used as essential synthetic intermediates, for example α -halosulfones in the Ramberg–Bäcklund reaction,⁴⁰ sulfonylbenzothiazoles in Julia–Kocienski olefinations⁴¹ and β -ketosulfones for the construction of quinolines⁴² and 4*H*-pyrans.⁴³ In polymer chemistry, Bisphenol S is used as a plasticizing agent instead of Bisphenol A and as a reactant.⁴⁴

With this variety of applications, practical synthetic methods needed to be established. In fact, in medicinal chemistry, rapid structure–activity relationship (SAR) studies along with easy purification are the main issues. In addition, scalable, economic and mild conditions are required in industry. The use of sulfinate derivatives to obtain sulfone and sulfonamide derivatives was installed a long time ago (early 1900s). However, this field started to be extensively exploited only a few years ago, leading to more eco-friendly reaction conditions, functional group tolerance and efficient accessibility to useful building blocks in medicinal and organic chemistry. In the following, these recent advances will be evoked.

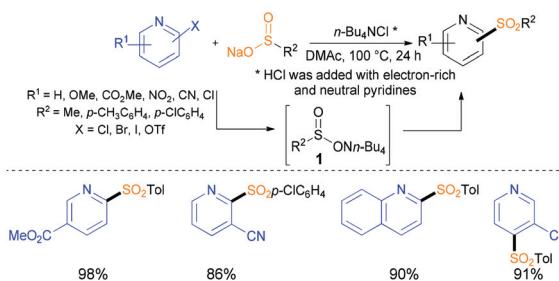
1. Sulfonylation of nucleophilic nitrogen: synthesis of sulfonamides. As seen in Scheme 6, the sulfonamide scaffold is widespread in medicinal agents. The most used procedure for the synthesis of sulfonamides is a straightforward reaction of an amine with a substituted sulfonyl chloride in the presence of a base.⁴⁵ However, sulfonyl chloride synthesis along with side reactions, due to the basic conditions and the release of a chloride ion acting as a nucleophile, limit the reaction scope. As a consequence, considerable efforts have been recently devoted to the development of milder conditions (Scheme 7). *In situ* preparation of sulfonyl chlorides by chlorination of the corresponding sulfinic acids or by a sequence of oxidation/chlorination of thiol derivatives represent more convenient approaches.⁴⁶ Metal-catalyzed sulfonylations of amine derivatives were also reported.⁴⁷ For instance, Willis's group reported



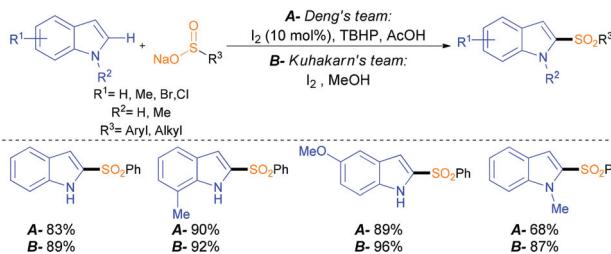
Scheme 7 Synthesis of sulfonamides.

a first synthesis of sulfonamides *via* a palladium-catalyzed three-component coupling between aryl iodides, hydrazines and DABSO (Scheme 7a).^{19b} This method is characterised by a good functional-group tolerance: hydroxyl, ester and trifluoromethane were successively coupled. Sulfonamides can also be synthesized starting from organomagnesium reagents (Scheme 7b).^{47d} Alkyl and aryl Grignard reagents afforded, under mild conditions, a variety of sulfonamides. Sulfamide compounds were also obtained from reacting electron-enriched or deficient and even sterically hindered anilines with DABSO and iodine.

2. Sulfonylation of (hetero)aryls. As previously mentioned, the sulfone scaffold is ubiquitous in medicinal and organic chemistry. The traditional procedure for the synthesis of (hetero)aryl sulfones consisted of coupling aryl halides with thiol derivatives followed by oxidation. Nevertheless, the odorous starting materials, harsh oxidative conditions and hazardous waste led to the development of alternative synthetic routes, providing the desired products more efficiently. Among them, Friedel-Crafts sulfonylation of arenes with sulfonyl chlorides used strong acid catalysts.⁴⁸ More recently, metal-catalyzed couplings between sulfinates and aryl halides were developed.⁴⁹ Nevertheless, few reports review the preparation of heterocyclic sulfones from sulfinate derivatives due to the lack of reactivity of the starting heterocycles and regioselective issues. In 2001, the first metal-free sulfonylation of pyridines was developed by Maloney and co-workers (Scheme 8).⁵⁰ For



Scheme 8 Metal-free sulfonylation of halopyridines.



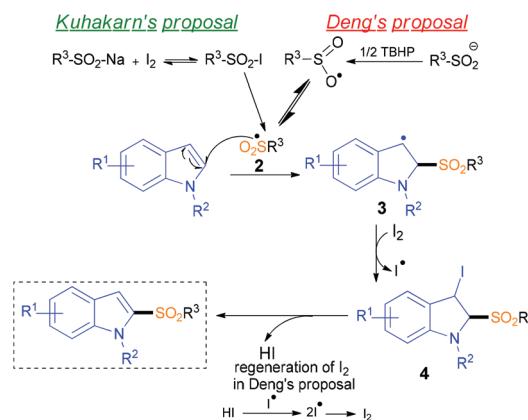
Scheme 9 2-Sulfonylation of indoles.

this purpose, sodium sulfinic salts and multi-substituted pyridine halides were used. The presence of metal (copper, palladium) had no effect on the outcome of the reaction. However, a catalytic amount of the phase-transfer agent, tetrabutylammonium chloride (TBACl) was necessary. The authors postulated the formation of $n\text{-Bu}_4\text{NSO}_2\text{R}^2$ species (**1**) from the sulfinic derivative (RSO_2Na) and TBACl. In consequence, an increase in the reaction rate led to full conversion in a shorter period of time. A nucleophilic heteroaromatic substitution (SNHetAr) mechanism was proposed based on the high reactivity of positions C2 and C4 of the pyridines and a lack of reactivity at position C3.

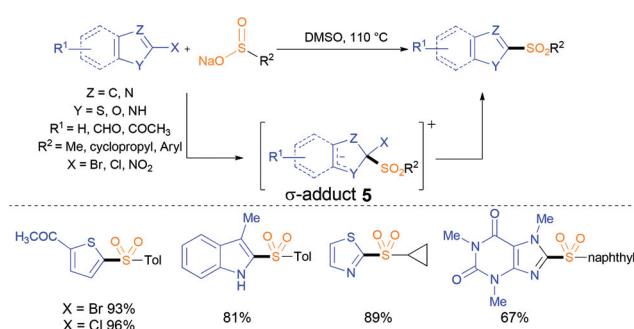
Direct sulfonylations, *via* C–H functionalization leading to sulfones, are gaining more attention. For example, an indole moiety was subjected to direct sulfonylation at the C2 position using sulfinates. This transformation was particularly challenging since the C2 position of the indole moiety is less active than the C3 position and since the existing methods were not straightforward and required sensitive reagents. Deng and Kuhakarn's groups reported separately the iodine-based regioselective 2-sulfonylation of indoles (Scheme 9).

Conditions developed by Deng's group used a catalytic amount of iodine in the presence of an oxidant: *tert*-butyl hydroperoxide (TBHP) and acetic acid as the solvent.⁵¹ Meanwhile, Kuhakarn and co-workers found the same regioselectivity with stoichiometric amounts of iodine but without the need for any oxidant.⁵² In both cases, a wide variety of substituted indoles and sodium sulfinates reacted to give the desired 2-sulfonylindoles (Scheme 9). A radical process was proposed based on experimental and previous related works (Scheme 10). Under Deng's oxidative conditions, the sulfonyl radical (**2**) is obtained by oxidation of the sulfinates by TBHP.⁵³ When stoichiometric iodine is used under Kuhakarn's conditions, radical (**2**) is generated from the homolytic cleavage of sulfonyl iodide ($\text{R}^3\text{-SO}_2\text{-I}$) formed *via* the reaction between sulfinates and iodine.⁵⁴ Then, addition of (**2**) to the indole moiety gives intermediate (**3**), which reacts with iodine to form intermediate (**4**). The desired substituted indoles are obtained upon HI elimination. When the catalytic system (Deng's conditions) is used,⁵¹ TBHP reoxidizes HI into an iodine atom. This latter, with the other iodine atom, formed during the transformation of (**3**) into (**4**), regenerates the iodine molecule.

Whereas previous examples managed to sulfonylate nitrogen-containing heterocycles, Yu's group put in place metal-free



Scheme 10 Proposed mechanisms for the iodine-based 2-sulfonylation of indoles.

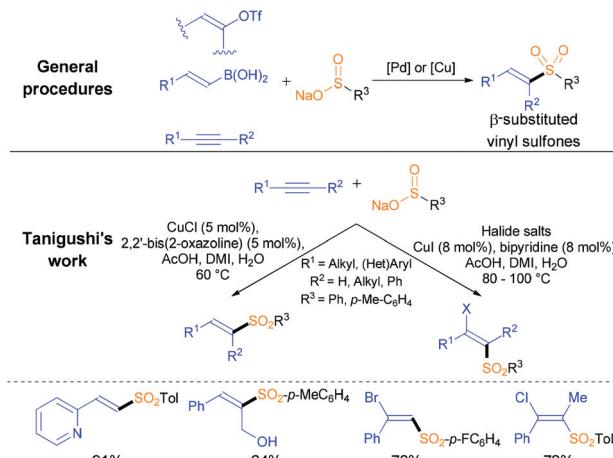


Scheme 11 Metal-free sulfonylation of heterocycles.

conditions to sulfonylate a range of five-membered heterocycles: thiophenes, furans, indoles, imidazoles, thiazoles and oxazoles, bearing leaving groups (Br, Cl, NO₂) at the C2 position (Scheme 11).⁵⁵ The difficulty of this type of coupling is due to the poor reactivity of these substrates towards nucleophilic additions because of their π -excessive character.

Nevertheless, the authors managed to develop metal-free conditions in the presence of a wide range of sodium sulfinate salts. It was interesting to notice that the chlorine and nitro groups were as active leaving groups as bromine. Furthermore, more nucleophilic electron-enriched sodium sulfinate salts were more active than electron-poor ones. A nucleophilic aromatic substitution (SNHetAr) mechanism was proposed *via* the formation of σ -adduct (5) upon the addition of the sulfinate anion to the electrophilic heterocycle.

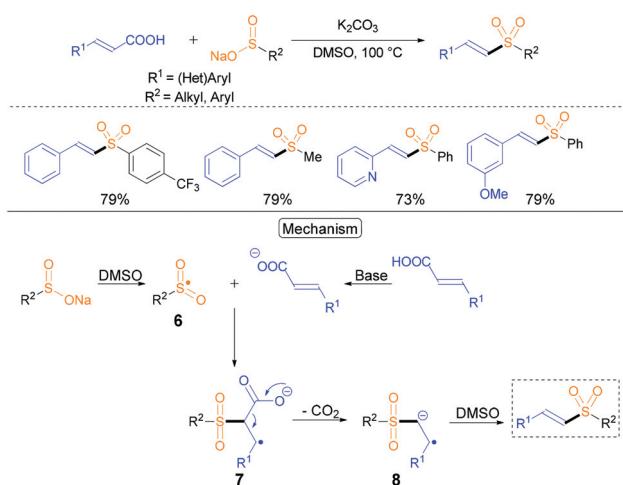
3. Sulfonylation of alkenes and alkynes. Vinyl sulfones are valuable intermediates in medicinal chemistry and in organic synthesis.^{33b,56} They are usually synthesized by Michael additions and Horner-Emmons reactions from scarcely available starting materials. Palladium or copper-catalyzed cross-coupling reactions of sulfinate derivatives with vinyl halides, alkenes, boronic acids and alkynes represent interesting alternative synthetic methods (Scheme 12).^{49b,57} In most cases, *trans*-configurated β -substituted vinyl sulfones are obtained. For example, Tanigushi's group developed copper-catalyzed



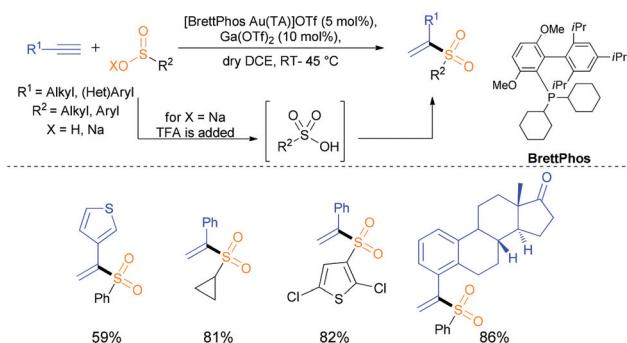
Scheme 12 Synthesis of vinyl sulfones (DMI = 1,3-dimethyl-2-imidazolidinone).

hydro- and halo-sulfonylations of terminal and di-substituted alkynes.⁵⁸ On one hand, in the presence of CuCl under aerobic conditions, *trans*-vinyl sulfones are formed stereoselectively (Scheme 12). On the other hand, adding halide salts (KBr, LiCl, KI) to a mixture of sodium sulfinate and alkynes under CuI-catalysis led to *trans*- β -halo-vinyl sulfones, which were subjected to further functionalizations *via* Suzuki-Miyaura coupling.

Decarboxylative sulfonylations represent another approach to *trans* vinyl sulfones.⁵⁹ Jiang's team developed an eco-friendly and metal-free β -substituted vinyl sulfone synthesis (Scheme 13).^{59a} The synthesis is achieved by a metal free tandem decarboxylative/cross-coupling reaction between two readily available starting materials: sodium sulfinate and cinnamic acids. DMSO was used as oxidant and solvent at the same time. These mild conditions allowed easy access to a wide variety of vinyl sulfones regardless of the electronic effects of the substituents, along with good functional group tolerance. A radical mechanism is proposed as well



Scheme 13 Metal-free vinyl sulfone synthesis.



Scheme 14 Gold-catalyzed sulfinic acid addition to alkynes: synthesis of α -substituted vinyl sulfones (DCE = 1,2-dichloroethene).

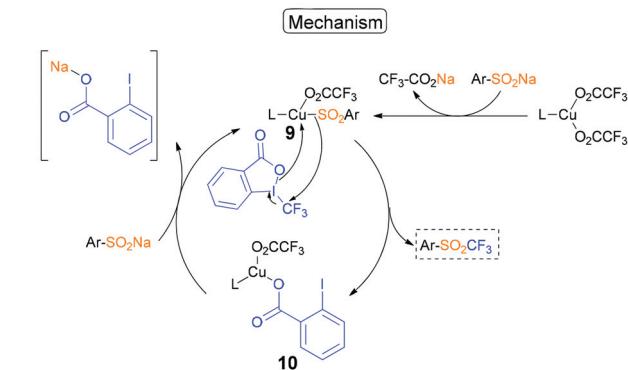
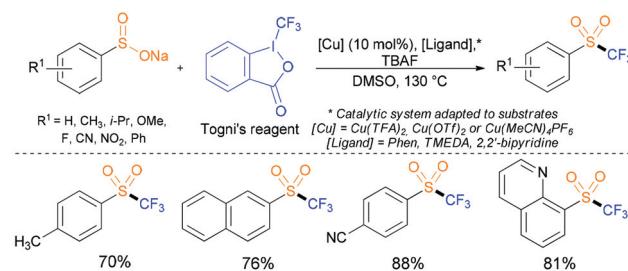
(Scheme 13). Oxidation of the sodium sulfinate by DMSO generates sulfonyl radical (**6**). Radical addition of (**6**) to the deprotonated cinnamic acid forms intermediate (**7**). Then, decarboxylation of (**7**) to intermediate (**8**) is followed by the formation of the desired vinyl sulfones.

α -Substituted vinyl sulfones are also of interest in organic synthesis.⁶⁰ Shi and co-workers established a Markovnikov addition of sulfinic acids to terminal alkynes, leading exclusively to α -substituted vinyl sulfones.⁶¹ This transformation was catalyzed by a triazole gold complex that remained active in the presence of sulfinic acids and activated the alkyne, favouring a Markovnikov addition. Due to stability issues, *in situ* formation of sulfinic acids was also proposed starting from commercially available sodium sulfinites (Scheme 14). By this means, the authors synthesized a variety of alkyl and aryl α -substituted vinyl sulfones with electron-deficient and enriched alkynes and/or sulfinites.

4. Sulfenylation of other coupling partners. Besides the typically used halides and amines as coupling partners with sulfinites to access sulfonyl derivatives, there are other substrates allowing greater diversity in sulfur-containing products.

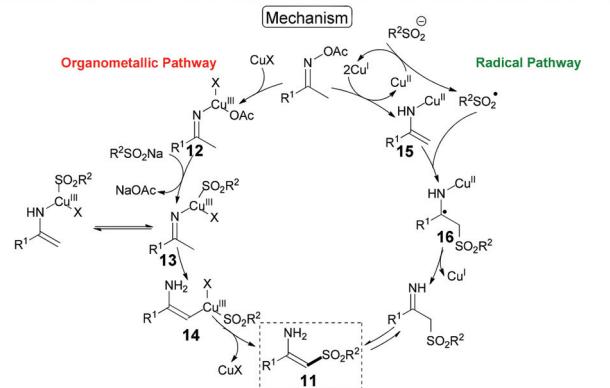
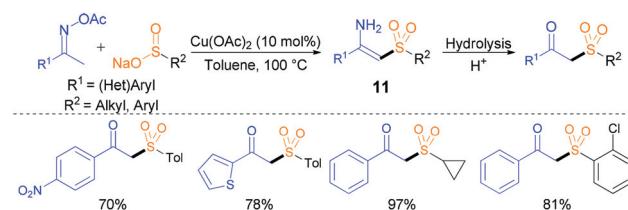
(a) *Fluorinating agents.* Introduction of fluorine-containing substituents can lead to profound modifications in physical and biological properties of organic molecules. In particular, trifluoromethylsulfone substrates represent promising biological activities.⁶² One of the few approaches available for their synthesis is the oxidation of the corresponding sulfides, which suffers from limited availability of trifluoromethyl sulfides and lack of functional group tolerance. In 2013, Weng and co-workers established a convenient copper-catalyzed trifluoromethylation of aryl sulfinites in the presence of Togni's reagent as a source of electrophilic CF_3 (Scheme 15).⁶³ Several aryl sodium sulfinites were successively trifluoromethylated with moderate to very good yields. The optimal conditions were compatible with methoxy, nitrile and nitro groups.

The proposed mechanism (Scheme 15) started with the transmetalation of the ligated-copper species with sodium sulfinate to give intermediate (**9**). Nucleophilic attack to Togni's reagent gives the desired trifluoromethylated product and the copper-benzoate intermediate (**10**). Then intermediate (**10**) reacts with sodium sulfinate to regenerate (**9**).



Scheme 15 Copper-catalyzed aryl trifluoromethyl sulfone synthesis (TBAF = tetrabutylammonium fluoride).

(b) *Oxime acetates.* β -Ketosulfones, important synthetic intermediates,^{42,43} are mainly prepared by alkylation of sulfinites with alkyl or phenacyl halides. However, these methods needed tedious conditions (long reaction times, high temperatures, expensive reagents). Jiang and co-workers⁶⁴ introduced oxime acetates as readily available coupling partners for the preparation of β -ketosulfones. The reaction consisted of a copper-catalyzed oxidative coupling in which oximes played a double role: reactant and oxidant (Scheme 16). The first step



Scheme 16 Oxidative coupling between oxime acetates and sodium sulfinites.

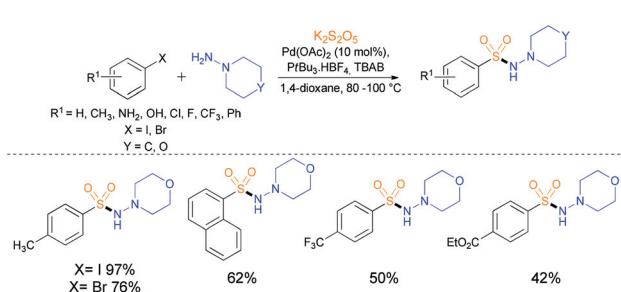
of the reaction leads to (*Z*)-sulfonylvinylamine derivatives (**11**) that give the corresponding β -ketosulfones after hydrolysis (under acidic conditions). The optimized conditions allowed coupling between alkyl and aryl sodium sulfinate with aryl and heteroaryl oximes (Scheme 16). Oximes with electron-withdrawing groups and alkyloximes were not active under these conditions. Organometallic and radical pathways were envisioned as possible mechanisms (Scheme 16). In the organometallic pathway, the first step consists of an additive oxidation of the N–O bond of the oximes to Cu^I. Then, coordination of the sulfinate to the organo-copper^{III} intermediate (**12**) gives species (**13**). After tautomerization and activation of the vinylic C–H bond by Cu^{III}, intermediate (**14**) is formed. A final reductive elimination step forms vinylamine (**11**). In the radical pathway, copper enamide (**15**) reacts with the sulfonyl radical to form intermediate (**16**). Then, single electron transfer (SET) and tautomerization afford sulfonylvinylamine (**11**).

5. In situ generation of sulfinate anions. The development of one-pot processes has rapidly progressed in recent literature. The main objectives of such transformations are time and energy savings and waste reduction. With this goal, many groups tried to synthesize sulfonyl compounds from broadly available halides and boronic acids without isolating the sulfinate intermediates. Meanwhile, in order to respect the environmentally friendly aspects of these processes, alternative sources of the gaseous and toxic SO₂ reagent needed to be discovered.

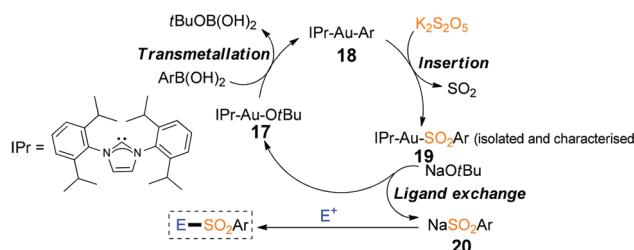
(a) K₂S₂O₅. In 2012, Wu and co-workers introduced for the first time potassium metabisulfite (K₂S₂O₅) as a commercially available and safe equivalent to SO₂ (Scheme 17).^{47a} With this reactant, a palladium-catalyzed coupling between aryl halides and hydrazines to access *N*-aminosulfonamides was established.

Recently, Toste's group reported the first sulfonyl compound synthesis *via* a gold-catalyzed coupling between aryl boronic acids and an electrophile with potassium metabisulfite as the SO₂ source.⁶⁵ First of all, this work illustrates a method for the preparation of gold sulfinate (Au–SO₂–Ar), which were fully characterized. Then, the authors proposed the transformation of this stoichiometric reaction into a catalytic sulfinate preparation system, leading to a direct synthesis of sulfones and sulfonamides (Scheme 18).

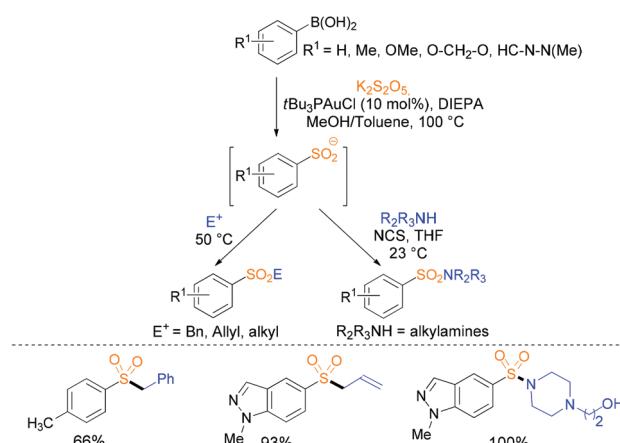
The gold catalyst (**17**) forms intermediate (**18**) after transmetallation with the boronic acid. Then, SO₂ insertion gives



Scheme 17 K₂S₂O₅, a new SO₂ equivalent.



Scheme 18 Proposed mechanism for the gold-catalyzed sulfonylation.

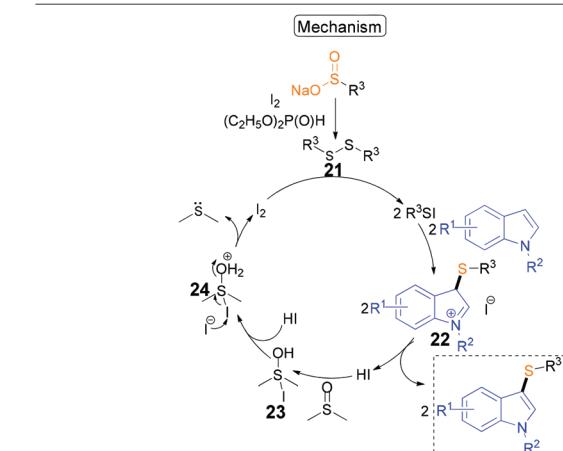
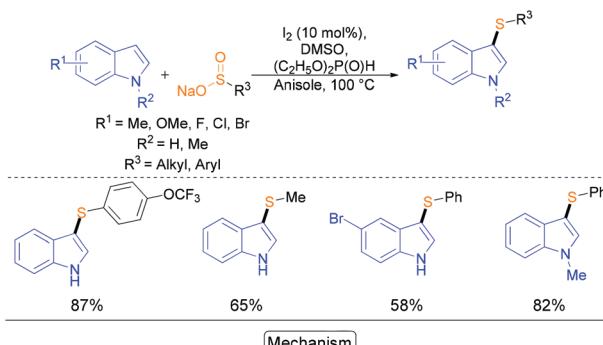
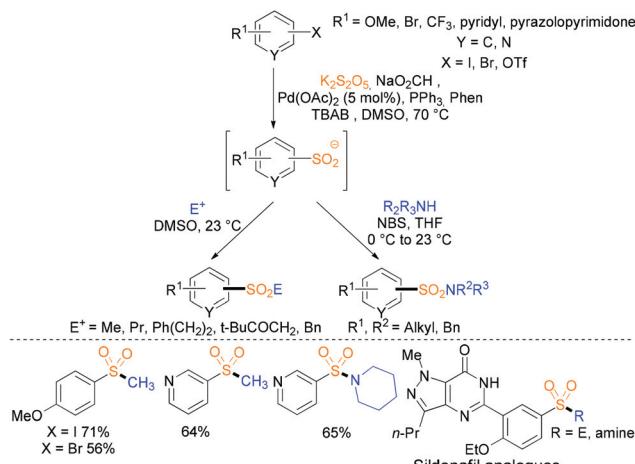


Scheme 19 Gold-catalyzed sulfonylation (DIEPA = diisopropylethylamine).

the gold sulfinate (**19**). A ligand exchange under basic conditions leads to sulfinate salt (**20**), which will be ready for an electrophilic trapping and subsequent formation of sulfones. Following this path, different aryl and *N*-methylindazole boronic acids were coupled (Scheme 19). However, electron-deficient acids were inactive due to the lack of reactivity towards SO₂ insertion.

In 2013, a Pfizer research group developed a palladium-catalyzed one-pot synthesis of sulfones and sulfonamides from aryl halides.⁶⁶ Once again, K₂S₂O₅ was used as a safe SO₂ source in order to form *in situ* the sulfinate anions, which will be subsequently trapped with an electrophile or an amine (Scheme 20). Aryl and heteroaryl iodides and bromides successfully reacted with alkyl and benzylic electrophiles to give sulfones in moderate to good yields. Sulfonamide derivatives were obtained after adding aliphatic amines to the *in situ* generated sulfonyl bromides, formed from sulfinate anions and *N*-bromosuccinimide (NBS) (Scheme 20). This method enabled a convergent and easy access to sulfone and sulfonamide analogues of sildenafil, containing a pyrazolopyrimidone backbone. This one-pot protocol offers new possible applications of sulfinites in medicinal chemistry where rapid synthesis of sulfone derivatives is needed.

(b) DABSO. As mentioned above, DABSO (DABCO·2SO₂) was used for the first time by Willis's group as an alternative to gaseous SO₂ for the sulfonylation of different types of



electrophiles *via* *in situ* formation of nucleophilic metal sulfonates.^{19,47d,67} The synthesis of sulfonamide derivatives using this reagent is presented in Scheme 7. Willis's group pursued his investigations into the possible applications of DABSO reagent with organometallic substrates (Scheme 21).

Metal sulfonates, formed *in situ*, from Grignard or organolithium reagents and DABSO, were trapped with a large variety of electrophiles: benzyl, allyl and alkyl halides, iodonium salts and epoxides (Scheme 21a).^{19a} As a consequence, sulfone derivatives were broadly accessed under mild and metal-free conditions. Very recently, Willis *et al.* reported the formation of ammonium sulfonates using aryl halides, DABSO and triethylamine. These sulfonates can be converted *in situ* into a wide variety of organosulfur derivatives (sulfonyl chlorides, sulfones, sulfonamides and 1,2-disulfides).⁶⁸

Rocke's team accomplished direct sulfonylation of alkyl halides using organozinc reagents and DABSO (Scheme 21b).²⁰ As mentioned above, the main advantage of organozinc reagents is their lower reactivity, resulting in reduced side reactions, higher functional group tolerance (esters, nitrile and alkyls) and room temperature reactions.

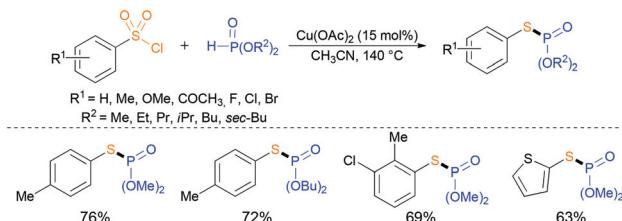
6. Sulfinate for the synthesis of other organosulfur compounds. Preparation of 3-arylthioindole building blocks is generally achieved *via* transition-metal catalyzed direct sulfenylation of the corresponding indoles using disulfides, sulfenyl halides and thiols. To overcome the use of metal catalysts, Deng's group used sulfonates as sulfenylating agents.⁶⁹ In fact, they developed the first direct 3-sulfenylation of indoles with sodium sulfonates.⁷⁰ The sulfenylation is catalyzed by iodine in the presence of stoichiometric amounts of diethyl phosphite ($(C_2H_5O)_2P(O)H$) and DMSO as oxidant (Scheme 22).

These metal-free conditions were found to be compatible with alkyl and aryl sodium sulfonates as well as various substitutions on the indole moiety (electron-donating and withdrawing). The proposed mechanism is depicted in Scheme 22: iodine and diethyl phosphite transform the sulfonate into 1,2-disulfide (21), which interacts with iodine to give electrophilic R^3SI . This latter reacts with indole to give intermediate (22). Once (22) is deprotonated, 3-sulfenylindole is released with HI. Then, some of the HI reacts with DMSO to give intermediate (23), which will be protonated into intermediate (24). The other portion of HI attacks the iodide atom of (24) to regenerate iodine.

Very recently, Wu *et al.* reported the first synthesis of *S*-aryl phosphorothioates *via* a copper-catalyzed reductive coupling between sulfonyl chlorides and H-phosphonates (Scheme 23).⁷¹

C. Sulfinate derivatives: C–S bond cleavage and C–C bond formation

Metal-catalyzed cross-coupling reactions have gained tremendous utility in organic synthesis. Continuous developments

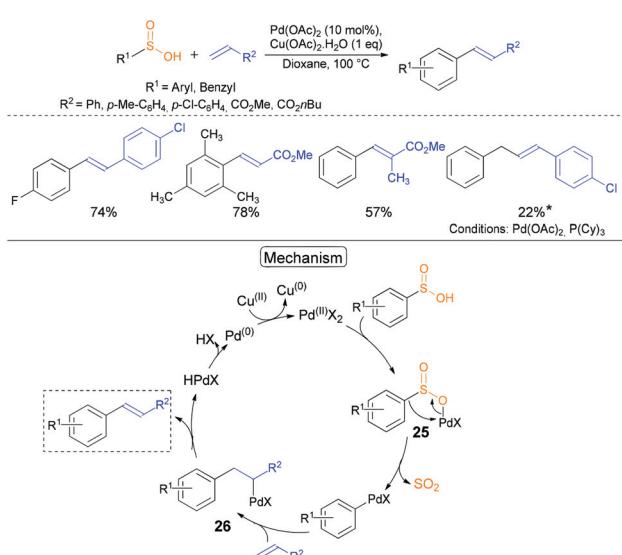


Scheme 23 Copper-mediated coupling between sulfonyl chlorides and H-phosphonates.

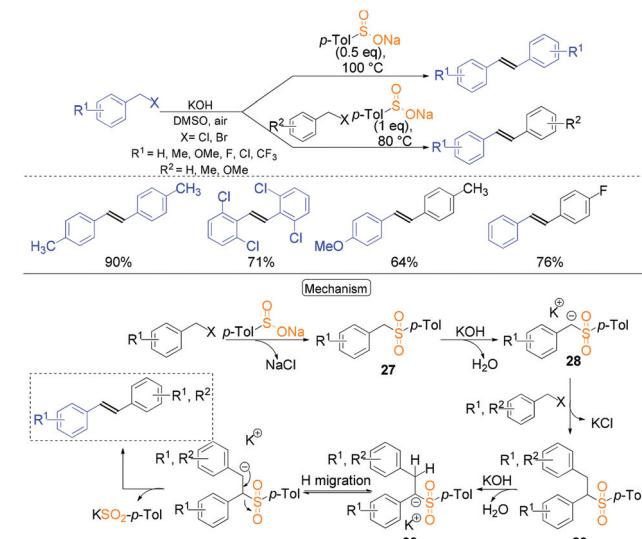
are being made in this field in order to efficiently synthesize complex carbo- and heterocyclic structures, under mild and more eco-friendly conditions. Desulfitative/cross-coupling reactions using sulfinate derivatives as coupling partners go back to 1966.⁷² Collman and Roper prepared iridium sulfinate complexes and noticed SO_2 elimination upon heating at 110 °C. In fact, energies for C–I, C–S, C–Br and C–Cl bonds are 213, 272, 285 and 327 kJ mol⁻¹, respectively.⁷³ Therefore, the reactivity of sulfinate derivatives towards metallic additions is somehow located between the reactivities of iodine and bromine derivatives. In the last years, an extensive number of desulfitative cross-coupling reactions was developed:⁷⁴ Mizoroki–Heck, Suzuki–Miyaura, Stille and Hiyama couplings, C–H arylations... Recent advances in this area will be presented.

1. $\text{Csp}^2\text{–Csp}^2$ bond formation reactions

(a) *Mizoroki–Heck-type reactions.* Aryl halides and carboxylic acids are the most used arene sources in the Mizoroki–Heck coupling. Replacing these arylating agents by sulfinites led to milder reaction conditions (no ligand and no base) and broader substrate scope.⁷⁵ In 2011, Wang and co-workers developed a palladium-catalyzed Mizoroki–Heck-type reaction in the presence of $\text{Cu}(\text{OAc})_2$ as an oxidant.^{75c} The conditions turned out to be very efficient for coupling various aryl sulfinites with acrylic esters and electron-rich and electron-deficient styrenes (Scheme 24).



Scheme 24 Sulfinic acids, arene sources in Mizoroki–Heck-type reaction.



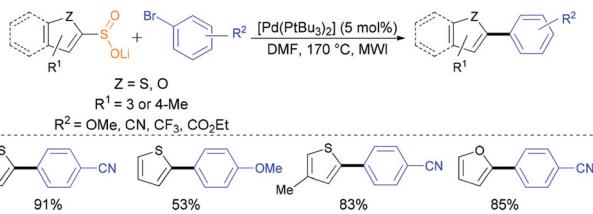
Scheme 25 Sodium sulfinate-mediated *trans*-stilbene synthesis.

Exclusive *trans*-stilbenes were obtained regioselectively. It was even possible to couple benzylsulfinic acid with alkenes. Despite the low yields obtained, these results are very promising since no such coupling is obtained with alkyl halides. The authors proposed the following mechanism: complex (25) is formed after a ligand exchange between $\text{Pd}(\text{OAc})_2$ and the aryl sulfinitic acid. SO_2 extrusion followed by insertion into the olefin gives intermediate (26). The desired *trans*-stilbenes are formed by the β -H elimination of (26). Finally, the Pd^0 species is oxidized by $\text{Cu}(\text{OAc})_2$ and the active Pd^{II} species is regenerated. Similar transformation can be achieved with sodium sulfinate and vinyl substrates (acrylate esters, acrylonitrile and styrene).^{75b}

(b) *Sodium sulfinate-mediated stilbene synthesis.* Sodium *p*-toluenesulfinate was used by Deng's team as a transitional reagent to access symmetrical and unsymmetrical *trans*-stilbenes from benzylic halides (Scheme 25).⁷⁶

This conversion, which took place under basic and metal-free conditions, is an attractive alternative to the common and multi-step Wittig–Horner reaction for stilbene synthesis. Electron-donating and withdrawing groups on the benzylic halides were compatible with the reaction conditions and selectively produced *trans*-stilbenes in moderate to good yields. The *in situ* formation of benzylic sulfones (27) (from benzylic halides and sodium *p*-toluenesulfinate) is the driving force of this transformation. Based on control experiments, the following mechanism was suggested by the authors (Scheme 25): benzyl *p*-tolyl sulfone (27), obtained by the reaction of benzyl halide with sulfinate, is deprotonated into intermediate (28). In the presence of another equivalent of benzyl halide, (28) generates benzyl sulfones (29) that will be deprotonated into (30). Finally, H-migration and subsequent reductive elimination affords *trans*-stilbenes.

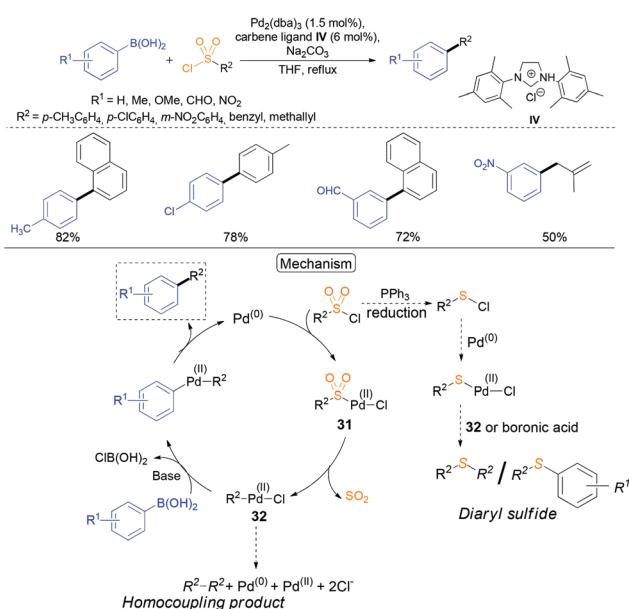
2. Desulfitative versus decarboxylative arylations. In 2013, Forgione and co-workers developed a base- and additive-free



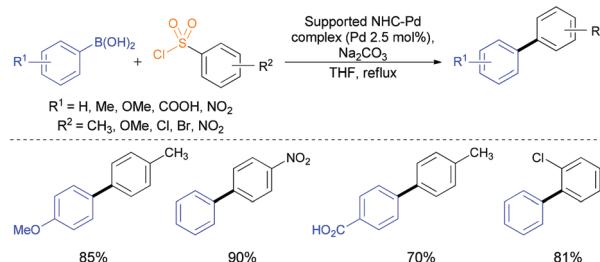
Scheme 26 Desulfitative C2 arylation.

desulfitative cross-coupling between lithiated heteroaromatic sulfinates and aryl bromides (Scheme 26).⁷⁷ In this work, the authors claimed the potential of sulfinic acids in desulfitative C–C arylations as an alternative to carboxylic acids in decarboxylative cross-couplings, particularly towards regioselective C2 arylations of azoles. In fact, the increased π -nucleophilicity and the out-of-plan position of the OH group in sulfinic acids may be responsible for a better selectivity towards C2 activation of heteroaryls. Furthermore, previous computational study demonstrated that SO₂ extrusion is easier than CO₂.⁷⁸ Various 2-sulfinylated heteroaryls (thiophene, furan and benzofuran) were regioselectively coupled with aryl bromides. Electron-deficient and neutral bromides were more active than electron-donating ones (Scheme 26).

3. Suzuki–Miyaura coupling reactions. Organoboronic acids are sometimes used with sulfinates as coupling partners for the synthesis of sulfone derivatives.^{57a,65} Under different conditions (catalyst, bulky ligands, high temperatures), SO₂ elimination can take place, leading to the corresponding cross-coupling products.⁷⁹ Vogel and co-workers^{79a} developed a Suzuki–Miyaura cross-coupling reaction between diverse electronically-substituted arene-, benzyl and methallylsulfonyl chlorides and aryl boronic acids (Scheme 27). A reactivity order



Scheme 27 Suzuki–Miyaura cross-coupling: reaction scope and mechanism.



Scheme 28 Recyclable catalytic system for the desulfitative Suzuki–Miyaura coupling (NHC = N-heterocyclic carbene).

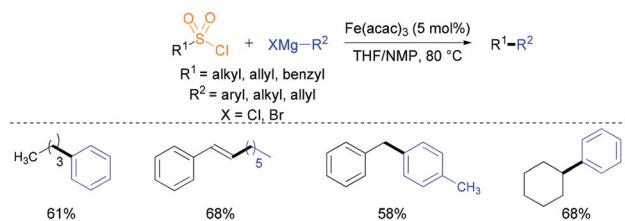
towards boronic acids was issued: ArI > ArSO₂Cl > ArBr ≫ ArCl. As a consequence, readily available sulfinates can replace organic halides in this coupling. The authors clearly stated the importance of the base (Na₂CO₃) and the ligand (bulky carbene ligand) in increasing the formation of the desired coupling products and reducing the by-products (homocoupling and diaryl sulfide products) (Scheme 27). The following mechanism is suggested: oxidative addition of the Pd complex onto the C–S bond of the sulfonyl chloride generates intermediate (31) which, under heating, loses SO₂ and the Pd complex (32) is obtained. Then, transmetalation followed by reductive elimination gives the desired coupling biaryl.

Two years later, Luo's group established for the first time a recyclable catalytic system for the desulfitative Suzuki–Miyaura coupling (Scheme 28).^{79b} The catalytic system is composed of a polymer-supported N-heterocyclic carbene (NHC)-palladium complex. Immobilization of catalysts on insoluble supports has become an attractive tool enabling catalyst and ligand recovery.

To be efficient, ligand systems have to stabilize all species involved in the catalytic cycle. Among those systems, NHC ligands are capable of remaining strongly bonded to the metal center throughout many catalytic cycles.⁸⁰ With 2.5 mol% catalyst loading, several aryl sulfonyl chlorides were coupled with aryl boronic acids, giving biaryls in very good yields and with excellent compatibility with functional groups: halides, carboxylic acid and nitro groups (Scheme 28). The catalytic system was able to be recycled up to 5 times.

4. Corriu–Kumada coupling reactions. It is well known that reactions using alkyl halides as coupling partners are generally sluggish and accompanied by many decomposition products. Corriu–Kumada's coupling of Grignard reagents with alkyl sulfonyl chlorides was attempted for the first time by Vogel and co-workers.⁸¹ Since under palladium and nickel catalysis, alkyl sulfonyl chlorides produced β -H elimination products along with the desired coupling product, it was found that the iron catalyst was more suitable for this desulfitative coupling (Scheme 29). By this means, the authors expanded the reaction's scope: aryl, alkyl and alkenyl magnesium halides were efficiently coupled with various alkyl sulfinates.

5. C–H functionalizations. Nowadays, the development of methods for the direct conversion of unreactive C–H bonds of (hetero)arenes or alkyl chains into C–C and C–heteroatom new



Scheme 29 Alkyl sulfonyl chlorides: effective coupling partners with Grignard reagents (NMP = *N*-methylpyrrolidone).

bonds is one of the main challenges in organic synthesis. This type of transformation responds exactly to the actual demands: low catalytic amounts of the organometallic species, no need for pre-functionalization of the starting materials and atom-economy.

(a) *Fluorination of nitrogen-containing heterocycles.* Fluorine substitutions have gained interest in medicinal chemistry, improving drug potencies and ensuring metabolic stabilization. To this end, Baran's team developed sulfinate reagents for the direct fluorination of electron-rich and nitrogen-containing heterocycles (xanthines, pyridines, indoles and imidazoles derivatives) (Scheme 30).⁸² These sulfinate represented valuable alternatives to traditional toxic and corrosive reagents (especially trifluoromethylating agents) under relatively harsh conditions (strong acidic or basic media). In 2011, commercially available sodium trifluoromethanesulfinate ($\text{CF}_3\text{SO}_2\text{Na}$, Langlois reagent)⁸³ was used for the trifluoromethylation of heterocycles.⁸² This room temperature transformation allowed the introduction of the metabolically stable $-\text{CF}_3$ group on several bioactive compounds and the synthesis of an antiviral drug, trifluridine (Scheme 30). A radical mechanism was suggested for this transformation: *tert*-butyl hydroperoxide (TBHP) generates the corresponding radical species in the presence of metal traces or another radical initiator. The *tert*-butoxy radical interacts with the sulfinate anion to give radical (33), which decomposes into SO_2 and the trifluoromethyl radical. In the presence of an innate activated heterocyclic



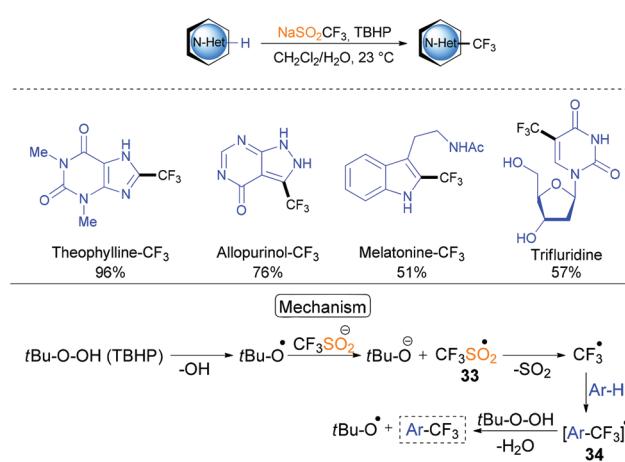
Scheme 31 C-H functionalization using zinc sulfinate (TBHP: *tert*-butyl hydroperoxide).

position, radical (34) will be formed and then oxidized into the desired fluorinated product, generating another *tert*-butoxy radical.

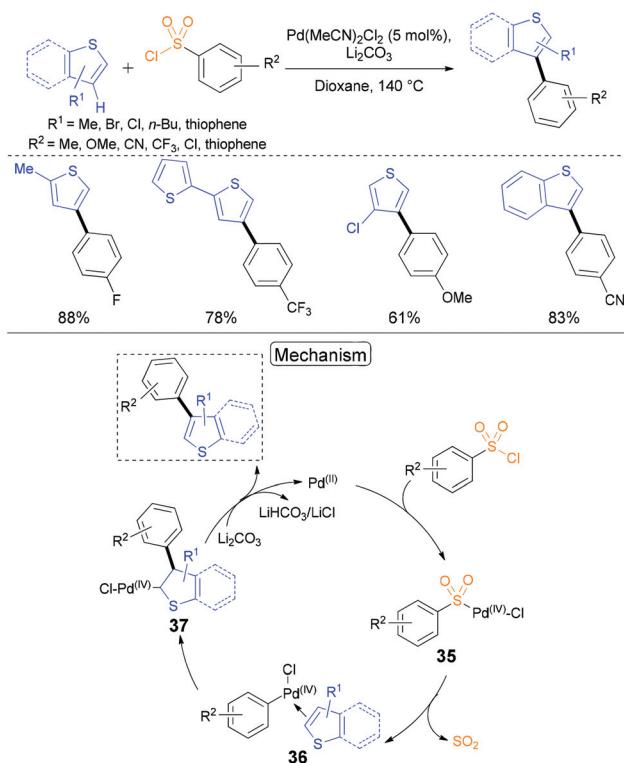
Pursuing their interest in fluorinating agents, the same team made two new alkylating agents: sodium 1,1-difluoroethanesulfinate (DFES-Na)¹⁵ and zinc difluoromethanesulfinate (DFMS).¹⁸ They presented afterwards the synthesis and applications of zinc sulfinate salts.¹⁷ As mentioned at the beginning of this report, a zinc bis(alkanesulfinate) toolkit is commercially available at Sigma Aldrich. Nevertheless, they can be easily prepared^{17a} and they allowed the highly regioselective introduction of fluoroalkyl, alkyl and alkylalkoxy groups into nitrogen-containing heterocyclic frameworks (xanthines, pyridines, quinoxalines, pyrimidines, pyridazines and pyrroles), always using TBHP as a radical initiator and in an open flask (Scheme 31). Regioselectivity issues can be avoided by a fine tuning of solvents on pH.

(b) *Regioselective C-H arylations.* Regioselectivity remains challenging in C-H functionalization reactions in the presence of similarly active C-H bonds. Very recently, Doucet and co-workers employed aryl sulfonyl chlorides to selectively introduce arenes at position C3 of various substituted thiophene derivatives.⁸⁴ It should be noticed that the C2 position is generally more reactive. Compared to the direct arylation of thiophenes using aryl halides or organometallic species (boronic acids,⁸⁵ trimethyl silanes⁸⁶), this coupling took place in the absence of an oxidant, a ligand and a directing group on the heteroaryls (Scheme 32). The authors showed that electron-deficient sulfonyl chlorides were more reactive under the optimized conditions. Halide substitutions on the sulfinate or the thiophene were preserved, leading to further functionalizations. Other functionalities were also tolerated: acetyl, nitro, nitrile and ester groups. The authors proposed the following mechanism: oxidative addition of the sulfinate to Pd^{II} gave Pd^{IV} species (35). SO_2 extrusion and subsequent coordination of thiophene afforded (36). Complex (37) obtained by aryl migration to position C3 of the thiophene is then subjected to β -H elimination under basic conditions.

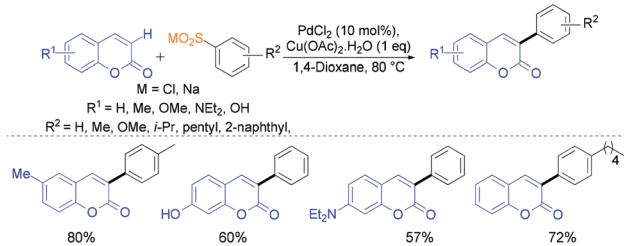
Moreover, under oxidative conditions, sulfonyl chlorides lead to exclusively 3-aryl coumarins without any prior functionalization. In fact, Jafarpour's team developed a palladium-catalyzed C-H activation of coumarins *via* desulfitative coupling with aryl sulfonyl chlorides and aryl sodium sulfonates



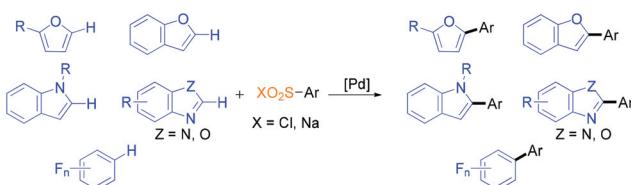
Scheme 30 C-H trifluoromethylation: applications and mechanism (TBHP: *tert*-butyl hydroperoxide).



Scheme 32 Selective C3 arylation of thiophenes.



Scheme 33 Synthesis of 3-aryl coumarins.

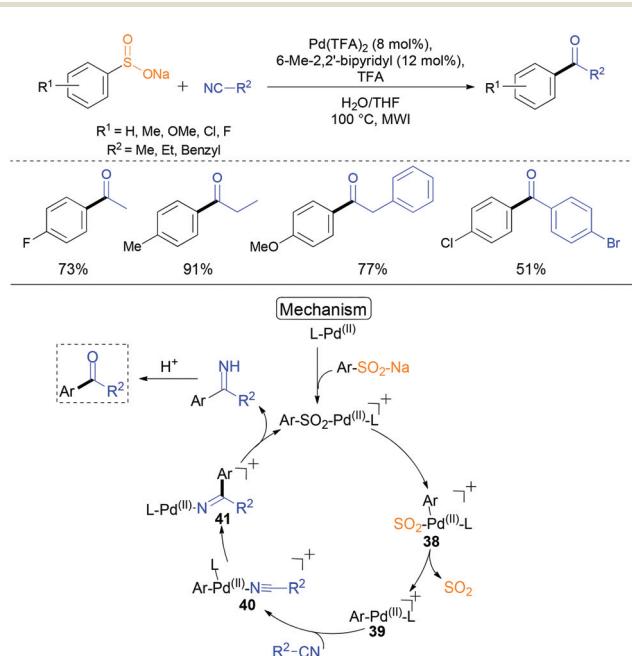


Scheme 34 Regioselective C–H arylations using sulfinates.

(Scheme 33).⁸⁷ It is noteworthy that the reaction took place under base-free and external ligand-free conditions. The coupling was limited to electron-rich coumarins and to aryl sulfinates.

Other regioselective direct C–H arylations of several heteroaromatics (furans, azoles, indoles and polyfluoroarenes) using sulfinates as coupling partners were also reported (Scheme 34).⁸⁸

6. Carbonylative reactions. The ketone moiety is ubiquitous in bioactive molecules, functional materials and as a functional group in organic chemistry. For these reasons, many synthetic methods were reported over the years, in particular the insertion of an aryl palladium complex into nitrile. The traditional arene sources used were aryl boronic acids and carboxylic acids. The former were limited by their cost and their availability; while the latter required the presence of *ortho* activating substituents. In 2011, several groups introduced sulfinic acid salts as aryl palladium precursors for a wider application of the carbonylative reactions.⁸⁹ Larhed *et al.* managed to determine conditions for the nitrile insertion using sodium sulfinates under microwave irradiations, leading to better yields along with a notable decrease in reaction time (Scheme 35).^{89a} Aliphatic, aromatic and benzylic nitriles were successfully coupled with diversely substituted aryl sodium sulfinates. The authors investigated the reaction mechanism by using electrospray ionization mass spectrometry (ESI-MS) and they suggested the mechanism depicted in Scheme 35. A first step of coordination of the sulfinic acid to palladium^{II} affords complex (38). SO₂ extrusion generates aryl palladium species (39) followed by coordination of the nitrile group to form complex (40) and subsequent 1,2-insertion of nitrile to generate ketimine (41) (most likely rate-determining step). Then, protonation to get free ketimine followed by acidic hydrolysis yields the desired ketone. Instead of the nitriles, insertion can take place into another type of polar multiple bond, the aldehydes. A rhodium-catalyzed coupling between aryl sodium sulfinates and benzaldehydes was described by Li and co-workers.^{89d} [RhCl(COD)]₂ appeared to be the best catalyst under O₂ (1 atm) and without any additive. The conditions were compatible only with arenesulfinic acids and with

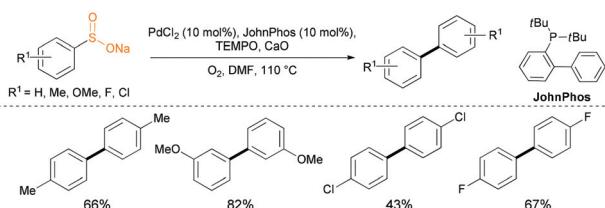


Scheme 35 Microwave-assisted carbonylative reaction using sulfinic acid salts and mechanism elucidation by ESI-MS (TFA = trifluoroacetate).

variously substituted benzaldehydes (OMe, Br, Cl, CN and CF_3 groups).

7. Conjugate 1,4-addition reactions. Conjugate addition of organometallic species (boron and silicon containing substrates, carboxylic acids) to α,β -unsaturated carbonyl compounds suffer from stability and availability issues of the starting materials as well as the necessity of electron-poor substituents at the *ortho*-position. As a consequence, organic chemists began getting interested in readily available sulfinic acid derivatives.⁹⁰ Duan's group studied sulfinic acid addition to α,β -unsaturated carbonyls *via* an aerobic palladium-catalyzed desulfitative coupling (Scheme 36).^{90a} An optimisation study was necessary to identify the best conditions: $\text{Pd}(\text{OAc})_2$ gave better results with pyridine-type ligands than with phosphine ligands. Various cyclic and acyclic α,β -unsaturated carbonyl compounds reacted efficiently with aryl sulfinic acids. In this case also, ESI-MS interpretation helped to elucidate the mechanism (Scheme 36). Coordination of sulfinic acid and SO_2 elimination lead to nucleophilic aryl Pd^{II} (42). Coordination of the ketone forms C=O-Pd enolate (43), which is subjected to migratory insertion on the C=C with the aryl Pd^{II} to obtain intermediate (44), substituted on the β -position. Tautomerization and protonolysis give the desired ketone and regenerate the Pd^{II} species. For this reason, the acidity of the medium is crucial for reducing the formation of Mizoroki-Heck by-products by β -H elimination.

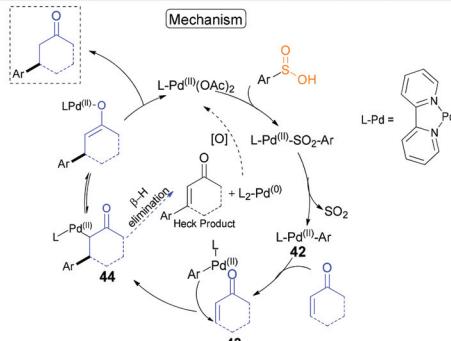
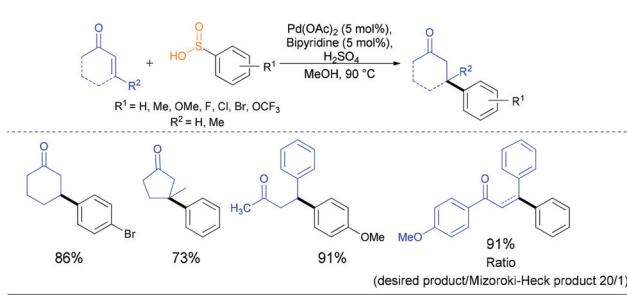
8. Homocoupling reactions. Sulfinic acid derivatives are also reported for the synthesis of symmetrical biaryls by homocoupling reactions.⁹¹ They represent a convenient alternative to carboxylic acids, which require an *ortho* substitution, or to boronic acids, which generate many side products. For example, Forgione *et al.* succeeded in employing catalytic amounts of TEMPO with molecular oxygen as oxidants in



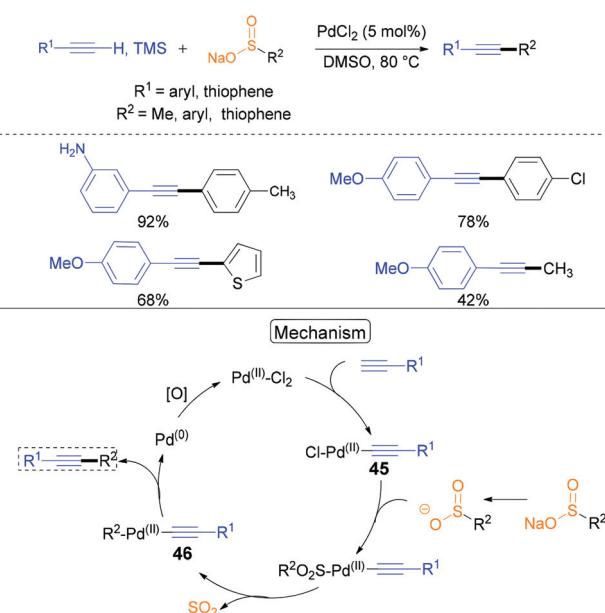
Scheme 37 Homocoupling of sulfinate co-catalyzed by palladium and TEMPO (TEMPO = 2,2,6,6-tetramethylpiperidin-1-oxyl).

the homocoupling reaction of various sodium sulfinites (Scheme 37).^{91a} Moderate to good yields were observed when applying these conditions to electron-rich or electron-poor sulfinites.

9. Sonogashira-type couplings. In most cases, sulfinate derivatives react with alkynes affording vinyl sulfones.^{57b,58,61,92} However, in 2014, Jiang *et al.* described the synthesis of unsymmetrical alkynes *via* a ligand-free and palladium-catalyzed cross-coupling reaction of sodium sulfinites and alkynes (Scheme 38).⁹³ Compared with conventional Sonogashira couplings with aryl halides, neither copper co-catalysis nor bases were needed. The optimized conditions (PdCl_2 in DMSO under air atmosphere) furnished a variety of internal alkynes in moderate to good yields. Diverse aryl sodium sulfinites were coupled with electron-rich (alkoxy, amine and hydroxyl substituents) and mildly electron-deficient (ester and F substituents) aryl alkynes (Scheme 38). Unprotected hydroxyl and amine substrates were efficiently coupled. In the presence of strongly electron-withdrawing groups (NO_2 , CN) on the alkynes, the authors noticed, under the same conditions, the exclusive formation of vinyl sulfones (this part will not be developed here). The mechanism proposed by the authors



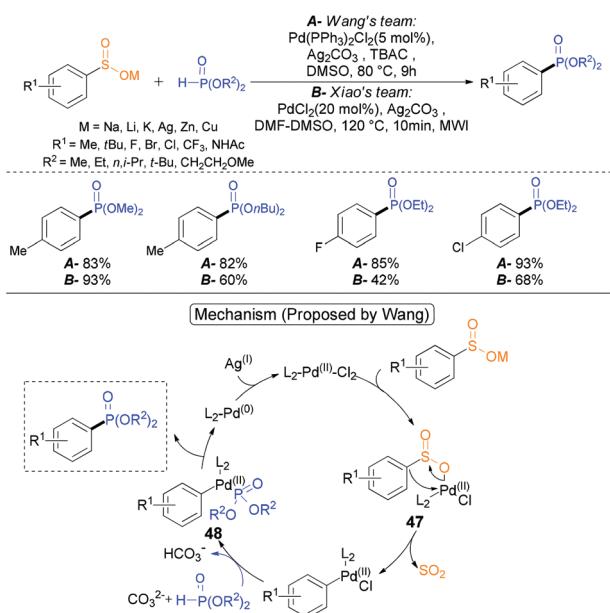
Scheme 36 Desulfitative conjugate addition of aryl sulfinic acids.



Scheme 38 Unsymmetrical alkyne synthesis with sodium sulfinites as coupling partners.

(Scheme 38) starts with coordination of alkynes to Pd^{II} affording alkynylpalladium complex (45). Nucleophilic displacement of chlorine followed by SO_2 extrusion generates intermediate (46). At the end, the desired alkynes are obtained by reductive elimination of Pd^0 , which is reoxidized into Pd^{II} .

10. Sulfinates for the creation of C-P bonds. The formation of C-P bonds usually takes place under cross-coupling reactions between phosphorus compounds and highly reactive aryl halides (iodides, triflates) catalyzed by metal complexes. More practical and efficient methods needed to be established. Wang and Xiao's groups developed separately very similar operating conditions for the synthesis of aryl phosphonates *via* unprecedented palladium-catalyzed desulfitative/C-P coupling of sodium sulfinate and H-phosphonates (Scheme 39).⁹⁴ In both cases, the presence of silver carbonate (Ag_2CO_3) as an oxidant was essential. Tetrabutylammonium chloride (TBAC) helped improve the reaction yield under conventional heating in the first case.^{94b} However, microwave irradiation allowed Xiao's team to efficiently create the C-P bond using palladium and Ag_2CO_3 in just 10 minutes.^{94a} In the two examples, electron-rich and deficient substituted aryl sulfinate salts were successfully coupled; the reaction's conditions were compatible with halides (Cl, Br), acetamide and *t*Bu substitutions. Likewise, several H-phosphonates were also tested. Under microwave irradiations, Li, K, Ag, Zn and Cu sulfinate salts were also coupled. According to the mechanism proposed by Wang, the transformation starts by the reaction of the Pd species with the sulfinate affording complex (47) (Scheme 39). SO_2 elimination followed by nucleophilic coordination of the phosphonate to the Pd complex formed affords intermediate (48). Reductive elimination of (48) gives the desired aryl phosphonate and Pd^0 , which will be reoxidized into Pd^{II} by silver salts.



Scheme 39 First C-P bond formation with sulfinate salts (TBAC = tetrabutylammonium chloride).

D. Outlook

Sulfinate derivatives represent the intermediates of choice for the synthesis of sulfone and sulfonamide building blocks in drug discovery. However, late-stage functionalization of molecules of pharmaceutical interest is barely exploited and further developments need to be performed. In this area, advances should be made in direct sulfonylation of hetero(aryls) *via* C-H activation, improving the reactivity of the starting hetero(aryls) and allowing better regioselectivity. Moreover, there remains a need to develop new sulfinate derivatives (as has been done with fluorinated sulfinites, *e.g.* DFES-Na and DFMS) to access complex structures in practical and efficient synthesis. The development of safe sources of SO_2 ($\text{K}_2\text{S}_2\text{O}_5$, DABSO) will open the way to more industrial applications of this chemistry.

In traditional cross-coupling reactions, sulfinites are used as alternatives to arylating agents: organic halides, benzoic acids and boronic acids. Despite the tremendous work undergone for the creation of Csp^2 - Csp^2 bonds, formation of Csp^3 - Csp^2 bonds is still largely unexploited. For example, the use of alkyl sulfinites in coupling reactions or direct C-H activation of Csp^3 -H bonds (*e.g.* alkylations, α -arylations) using sulfinites could be envisioned. In addition to C-C and C-P bond formation, sulfinites should be investigated in the creation C-heteroatom bonds, *e.g.* C-O, C-N, C-F.

II. Conclusion

In summary, the application of sulfinic acids and their derivatives has witnessed a remarkable expansion over the past few years. They are bench-stable, readily available and non-hygroscopic reagents used as efficient alternatives to traditional coupling substrates. They were first explored in sulfonylative reactions for the synthesis of sulfones and derivatives. These compounds are important backbones in bioactive molecules as well as in synthetic intermediates. However, these same starting materials can undergo desulfitative/cross-coupling reactions and act as arene sources in C-C bond formation. This reactivity enabled synthetic chemists to overcome the limits of the well-known cross-coupling reactions. In both applications (sulfonylation or desulfonylation), more eco-friendly conditions were developed, leading sometimes to catalyst, base and ligand-free approaches. Moreover, mild operating conditions led to broadening of the reaction scope, along with a better functional group tolerance. For all these reasons, sulfinites represent a versatile tool in organic synthesis that is not yet fully discovered.

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