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Sulfinate Derivatives: Dual and Versatile Partners in Organic Synthesis

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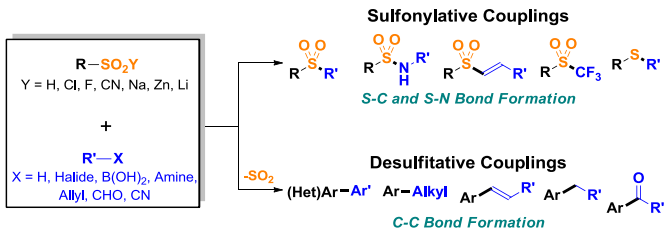
Sulfinic acids and their salts have recently emerged as versatile coupling partners to efficiently access a wide variety of hetero- and carbocyclic compounds, under relatively mild conditions. Their growing importance is attributable to their dual capacity for acting as nucleophilic or electrophilic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

Introduction

Designing molecular structures, tailored to the needs of diverse areas: organic synthesis, medical research and material science, is the imposing challenge for chemists 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 in continuous search for starting materials that enables simple and convergent synthetic routes. Sulfinates represent a class of organic compounds rediscovered very recently. Their reactivity was investigated since the early 1900's.[1] However, they started to be extensively developed during the last decade. In fact, for chemists, they have two essential criteria: easily accessible starting materials and versatile reactivity.

Sulfinates 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).



Scheme 1: Sulfinates, versatile coupling partners

Indeed, sulfinates 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 sulfinates 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 an operational ease enabling widespread applications. For these reasons, sulfinates represent a useful tool for both organic and medicinal chemists. Moreover, these reagents can be used in academic (safe and easy to handle compounds) as well as in industry (large scale preparations).

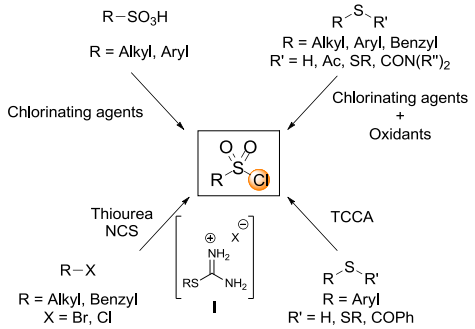
This review highlights the recent advances in the preparation of sulfinate derivatives emphasizing on their use in sulfonylative and desulfitative reactions, making them valuable synthetic intermediates.

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 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 $PPh_3.Cl_2$.[7] The inconvenience of using toxic chlorinating reagents in excess, as well as the formation of side products, led to the development of a powerful alternative method using mild oxidative and chlorinating agents: the oxidative chlorination of thiols and



Scheme 2: Preparation of sulfonyl chlorides (NCS = *N*-chlorosuccinimide, TCCA = TriChloroisoCyanuric Acid)

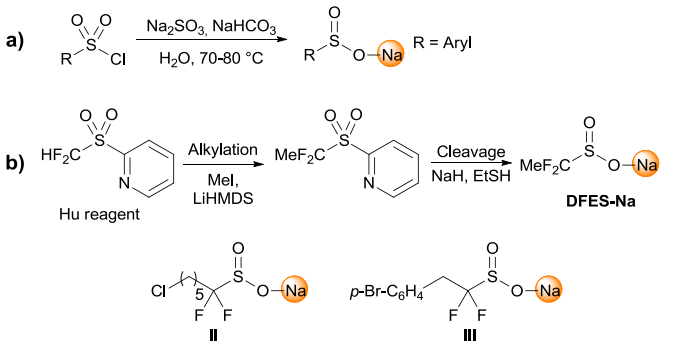
their derivatives (disulfides, thioacetates, thiocarbamates) (Scheme 2). For example, *N*-chlorosuccinimide (NCS)/tetrabutylammonium chloride (Bu_4NCl) were employed for the chlorination of thiols and disulfides to obtain the corresponding arenesulfonyl chlorides.[8] NCS/hydrochloric acid were also used 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-workers[11] developed recently 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 undertake 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 (specially heteroaryl derivatives), they are prepared *in situ* from thiobenzoates,[12] thiols or disulfides[13] *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 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 the recent advances in the synthesis of new sulfinate reagents. The advantages and the applications of these new synthetic tools will be detailed in the related sections.

a) Sodium sulfinates (RSO_2Na)

Compared to sulfonyl chlorides, sodium sulfinate derivatives are more stable and moisture-insensitive. There are only 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 3-a).[14]

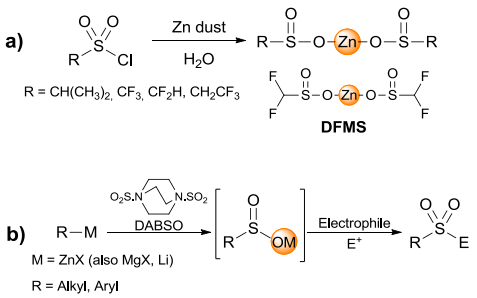


Scheme 3: Preparation of sodium sulfinic acid salts (EtSH = Ethyl Mercaptan)

Recently, Baran's group[15] synthesized sodium 1,1-difluoroethanesulfinate (DFES-Na), starting from Hu's reagent (Scheme 3-b).[16] This latter is alkylated with methyl iodide followed by the cleavage and the 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 ($-CF_2Me$), the metabolically stable and bioisostere of methoxide, to a wide variety of structures. Following the same approach, one alkyl and one benzyl difluorinated sodium sulfinates were synthesized ((**II**) and (**III**) respectively).

b) Zinc sulfinates (RSO_2Zn)

The use of sulfinate zinc salts is very limited although remarkable developments in their synthesis, purification and applications have been done, particularly by Baran's and Willis's groups. Organozinc reagents have lower reactivity than other organometallic compounds, resulting in side reaction reduction and better tolerance in 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 presence of zinc dust and water (Scheme 4-a).[17]

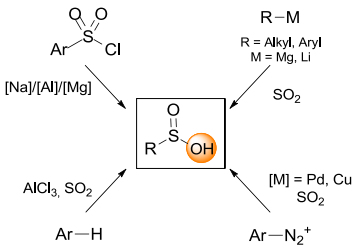


Scheme 4: Preparation of zinc sulfinic acid salts (DABSO = (1,4-diazabicyclo[2.2.2]octane-bis-(sulfur dioxide))

The same group invented zinc difluoromethanesulfinate (DFMS) ($Zn(SO_2CF_2H)_2$) for a direct and selective difluoromethylation of heterocylic compounds.[18] This new reagent is prepared, on a large scale, from difluoromethanesulfonyl chloride (HCF_2SO_2Cl). 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 nucleophilic metal sulfinates using organometallic reagents (Grignard and organolithium reagents) and DABSO as the SO_2 source (Scheme 4-b).[19] DABSO is an air-stable and easy to handle white solid formed by condensing SO_2 over freshly sublimed DABCO. Using DABSO as SO_2 source as well, Rocke and co-workers managed to synthesize sulfones using organozinc 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 reaction 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 reducing agents, sodium sulfite,[24] sodium borohydride,[25] magnesium,[26] lithium aluminium hydride [27] are frequently used (Scheme 5).

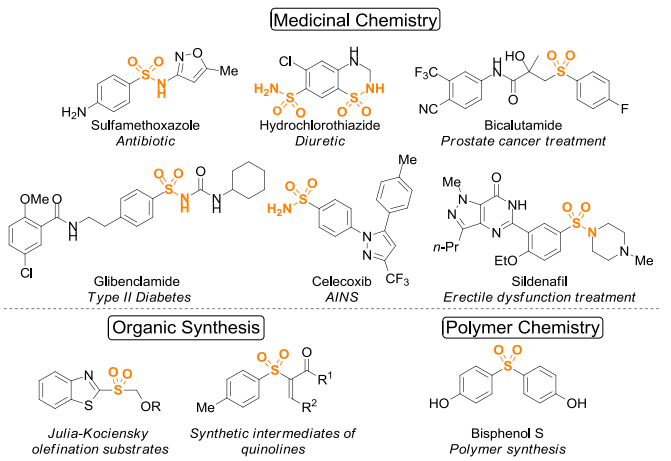


Scheme 5: Preparation of sulfinic acids

Sulfination of organometallic compounds represent another way to access sulfinic acids. Grignard reagents are often employed specially for aliphatic substrates[28] as well as 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 over-stoechiometric 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 of palladium on activated charcoal to obtain the desired aryl sulfinic acids.[32] However, for the last three methods, careful measures should be undertaken since excess of sulfur dioxide (SO_2), a toxic and corrosive gas, is employed. It should be handled in a well-ventilated fume-hood and the removal of excess SO_2 should be controlled cautiously.

B- Sulfinate derivatives in S-C and S-N Bond Formation

Exploring sulfones and sulfonamides chemistry goes back to the past century since they enclose wide applications in a diversity of fields (Scheme 6). In medicinal chemistry,[33] a large number of bioactive molecules contains sulfone scaffold: *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 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 dysfunctions.[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 olefinations[41] and β-ketosulfones for the construction of quinolines[42] 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]

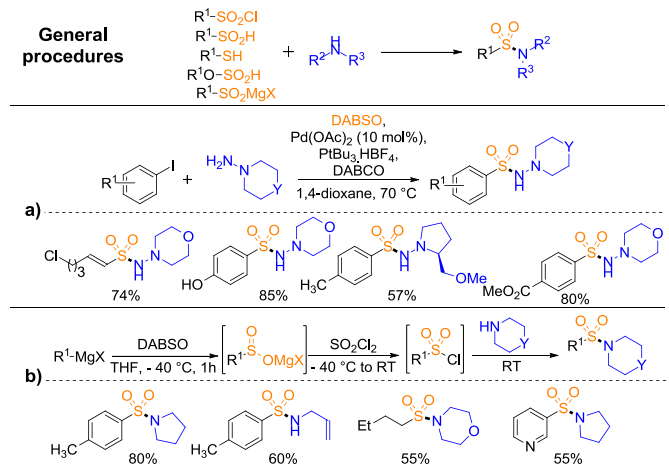


Scheme 6: Applications of sulfones and derivatives

With this variety of applications, practicable 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 sulfones and sulfonamides derivatives was installed long time ago (early 1900's). However, this field started to be extensively exploited only 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

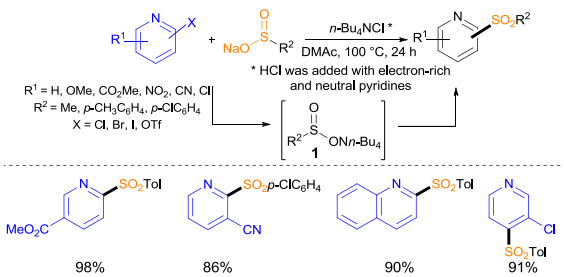
As seen in scheme 6, sulfonamide scaffold is widespread in medicinal agents.The most used procedure for the synthesis of sulfonamides is a straightforward reaction of an amine with a substituted sulfonyl chloride in the presence of a base.[45] However, sulfonyl chlorides synthesis along with side reactions, due to the basic conditions and the release of chloride ion acting as 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 a first synthesis of sulfonamides *via* a palladium-catalyzed three-component coupling between aryl iodides, hydrazines and DABSO (Scheme 7-a).[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 7-b).[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.



Scheme 7: Synthesis of sulfonamides

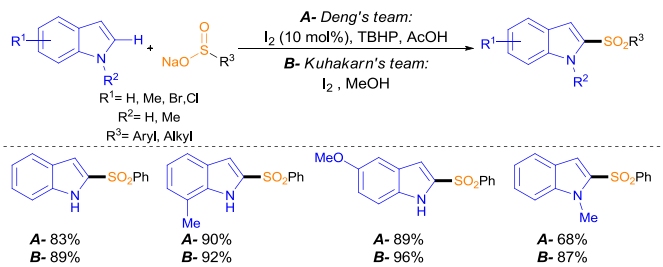
2- Sulfonylation of (hetero)aryls

Like previously mentioned, 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 this purpose, sodium sulfinate salts and multi-substituted pyridine halides were used. The presence of metal (copper, palladium) had no effect on the outcome of the reaction. However, catalytic amount of the phase-transfer agent, tetrabutylammonium chloride (TBACl) were necessary. The authors postulated the formation of *n*-$Bu_4NSO_2R^2$ species (**1**) from the sulfinate derivative (RSO_2Na) and TBACl. In consequence, an increase in the reaction rate led to full conversion in a shorter period of time. Nucleophilic heteroaromatic substitution (SNHetAr) mechanism was proposed based on the high reactivity of positions C2 and C4 of the pyridines and lack of reactivity at the position C3.



Scheme 8: Metal-free sulfonylation of halopyridines

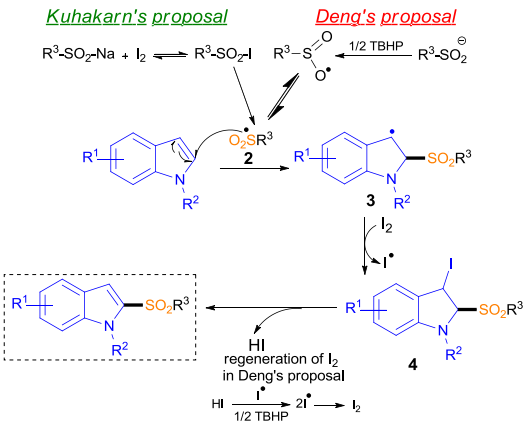
Direct sulfonylations, *via* C-H functionalization leading to sulfones, are gaining more attention. For example, indole moiety was subjected to direct sulfonylation at the C2 position using sulfinates. This transformation was particularly challenging since the C2 position of the indole moiety is the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



Scheme 9: 2-sulfonylation of indoles

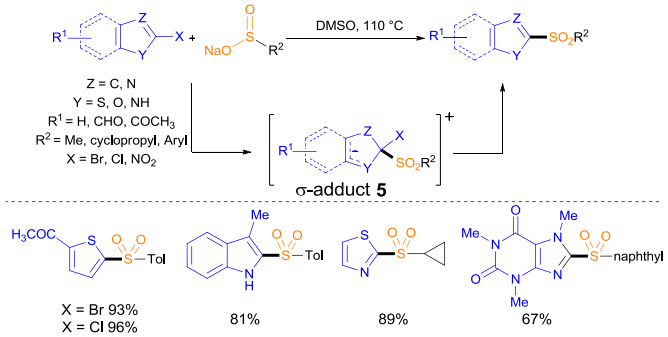
Conditions developed by Deng group used catalytic amount of iodine in the presence of an oxidant: *tert*-butyl hydroperoxide (TBHP) and acetic acid as solvent.[51] Meanwhile, Kuhakarn and co-workers found the same regioselectivity with stoichiometric

amounts of iodine but without the need of 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, 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 homolytic cleavage of sulfonyl iodide (R^3-SO_2-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**), regenerate the iodine molecule.



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

Whereas previous examples managed to sulfonylate nitrogen-containing heterocyles, Yu's group put in place metal-free conditions to sulfonylate a range of five-membered heterocycles: thiophenes, furans, indoles, imidazoles, thiazoles and oxazoles, bearing leaving groups (Br, Cl, NO_2) at 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.

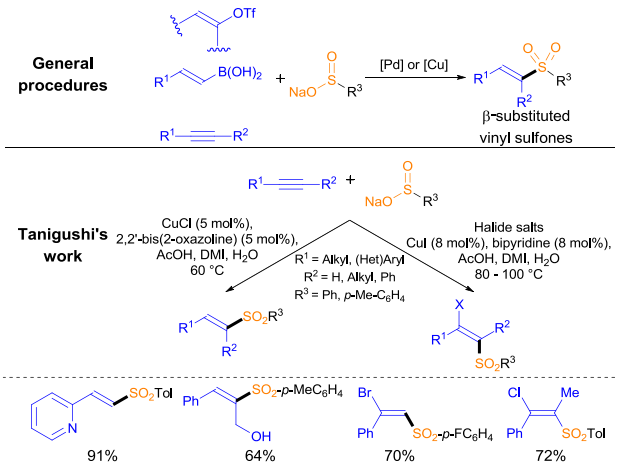


Scheme 11: Metal-free sulfonylation of heterocycles

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 chlorine and nitro groups were as active leaving groups as bromine. Furthermore, more nucleophilic electron-enriched sodium sulfinates 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

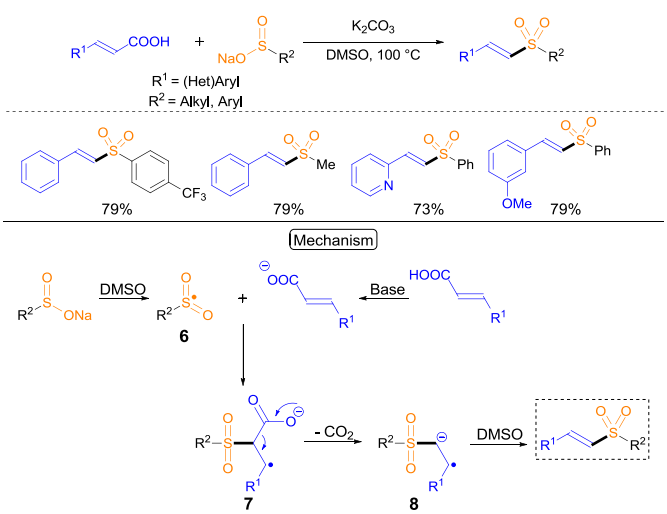
Vinyl sulfones are valuable intermediates in medicinal chemistry and in organic synthesis.[33b, 56] They are usually synthesized by Michael additions and Horner-Emmons reactions from not readily available starting materials. Palladium or copper-catalyzed cross-coupling reactions of sulfinate derivatives 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 group developed copper-catalyzed hydro- and halo-sulfonylations of terminal and di-substituted alkynes.[58] On one hand, in 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 sulfinates and alkynes under CuI-catalysis led to *trans*-β-halo-vinyl sulfones which were subjected to further functionalizations *via* Suzuki-Miyaura coupling.



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

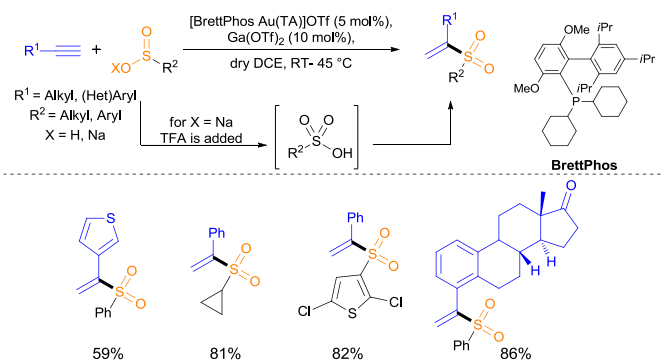
Decarboxylative sulfonylations represent another approach to *trans* vinyl sulfones.[59] Jiang's team developed an eco-friendly and metal-free β-substituted vinyl sulfones synthesis (Scheme 13).[59a] The synthesis is achieved by a metal free *tandem* decarboxylative/cross-coupling reaction between two readily available starting materials: sodium sulfinates 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

substituants along with good functional group tolerance. A radical mechanism is proposed as well (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.



Scheme 13: Metal-free vinyl sulfones synthesis

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 which remained active in presence of sulfinic acids and activated properly the alkyne favouring a Markovnikov addition. Due to stability issues, *in situ* formation of sulfinic acids was also proposed starting from commercially available sodium sulfinates (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 sulfinates.



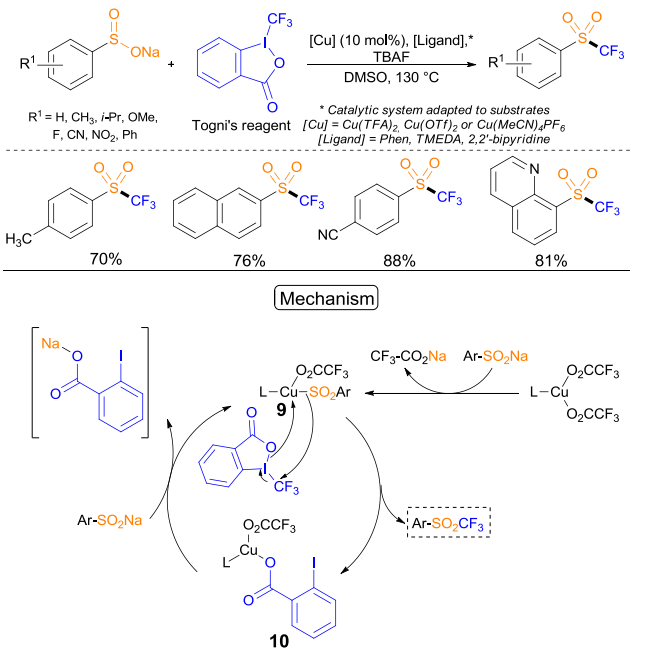
Scheme 14: Gold-catalyzed sulfinic acids addition to alkynes: synthesis of α-substituted vinyl sulfones (DCE = 1,2-DiChloroEthene)

4- Sulfonylation of other coupling partners

Besides the typically used halides and amines as coupling partners with sulfinates to access sulfonyl derivatives, there are other substrates allowing larger 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 sulfinates in the presence of Togni's reagent as a source of electrophilic CF_3 (Scheme 15).[63] Several aryl sodium sulfinates were successively trifluoromethylated with moderate to very good yields. The optimal conditions were compatible with methoxy, nitrile and nitro groups.



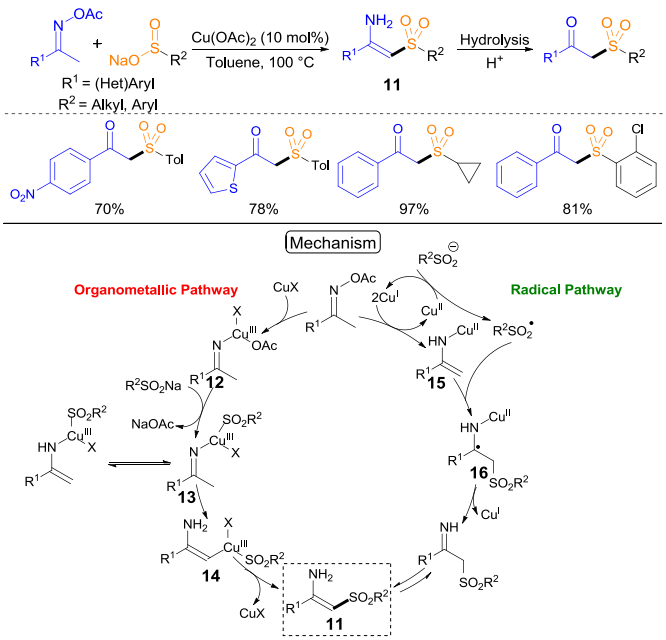
Scheme 15: Copper-catalyzed aryl trifluoromethyl sulfones synthesis (TBAF = TetraButylAmmonium Fluoride)

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

b) Oxime acetates

β-ketosulfones, important synthetic intermediates,[42-43] are mainly prepared by alkylation of sulfinates with alkyl or

phenacyl halides. However, these methods needed tedious conditions (long reaction times, high temperatures, expensive reagents). Jiang and co-workers[64] introduced oxime acetates as readily available coupling partners for the preparation of β-ketosulfones. The reaction consisted in a copper-catalyzed oxidative coupling in which oximes played a double role: reactant and oxidant (Scheme 16). The first step of the reaction leads to (*Z*)-sulfonylvinylamine derivatives (**11**) that gives the corresponding β-ketosulfones after hydrolysis (under acidic conditions). The optimized conditions allowed coupling between alkyl and aryl sodium sulfinates 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 in 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**).



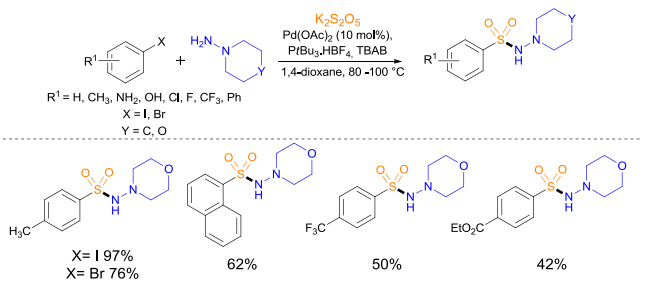
Scheme 16: Oxidative coupling between oxime acetates and sodium sulfinates

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 environmental friendly aspects of these processes, alternative sources to the gaseous and toxic SO_2 reagent needed to be discovered.

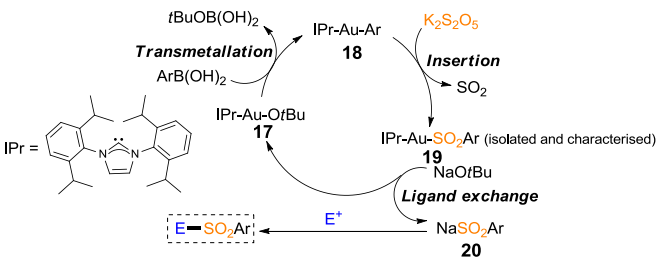
a) $K_2S_2O_5$

In 2012, Wu and co-workers introduced for the first time potassium metabisulfite ($K_2S_2O_5$) as a commercially available and safe equivalent to SO_2 (Scheme 17).[47a] With this reactant, a palladium-catalyzed coupling between aryl halides and hydrazines to access *N*-aminosulfonamides was established.



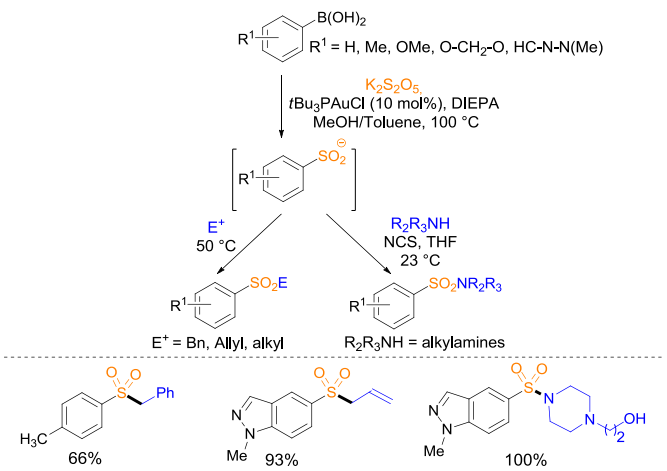
Scheme 17: $K_2S_2O_5$, a new SO_2 equivalent

Recently, Toste's group reported the first sulfonyl compounds synthesis *via* a gold-catalyzed coupling between aryl boronic acids and an electrophile with potassium metabisulfite as SO_2 source.[65] First of all, this work illustrates a method for the preparation of gold sulfinates (Au-SO_2-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).



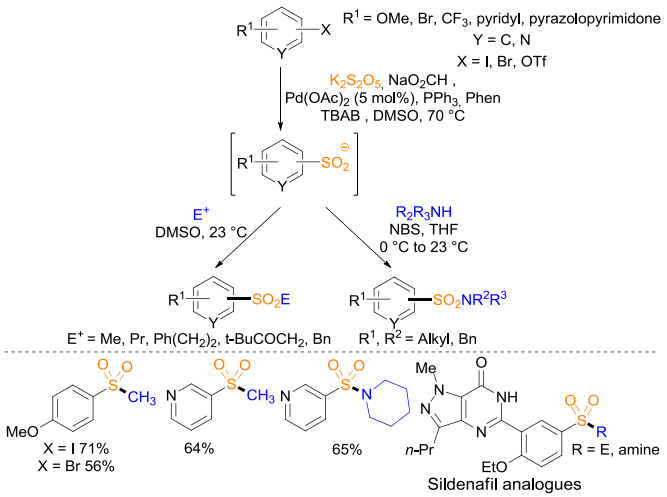
Scheme 18: Proposed mechanism for the gold-catalyzed sulfonyl formation

The gold catalyst (**17**) forms intermediate (**18**) after transmetallation with the boronic acid. Then, SO_2 insertion gives the gold sulfinate (**19**). A ligand exchange under basic conditions leads to sulfinate salt (**20**) that 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 SO_2 insertion.



Scheme 19: Gold-catalyzed sulfonylation (DIEPA = Di*Iso*PropylEthylAmine)

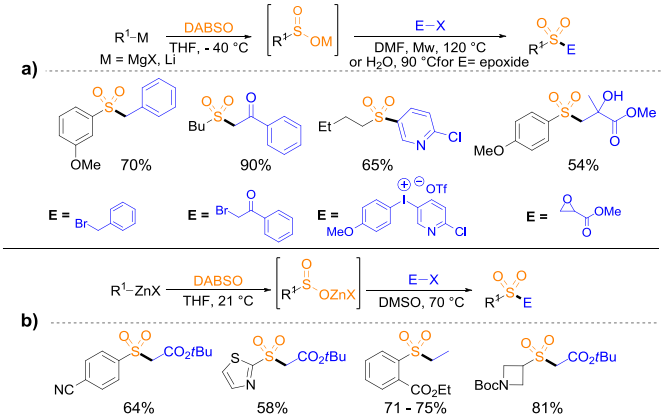
In 2013, a Pfizer research group developed a palladium-catalyzed one-pot synthesis of sulfones and sulfonamides from aryl halides.[66] Once again, $K_2S_2O_5$ was used as a safe SO_2 source in order to form *in situ* the sulfinate anions which will be subsequently trapped with an electrophile or an amine (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*-bromosuccimide (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 sulfinates in medicinal chemistry where rapid synthesis of sulfone derivatives is needed.



Scheme 20: One-pot synthesis of sulfones and sulfonamide derivatives

a) DABSO

As mentioned above, DABSO (DABCO.2SO_2) was used for the first time by Willis's group as an alternative to gaseous SO_2 for the sulfonylation of different types of electrophiles *via in situ* formation of nucleophilic metal sulfinates.[19, 47d, 67] The synthesis of sulfonamide derivatives using this reagent was presented in scheme 7. Willis's group pursued his investigations in the possible applications of DABSO reagent with organometallic substrates (Scheme 21).



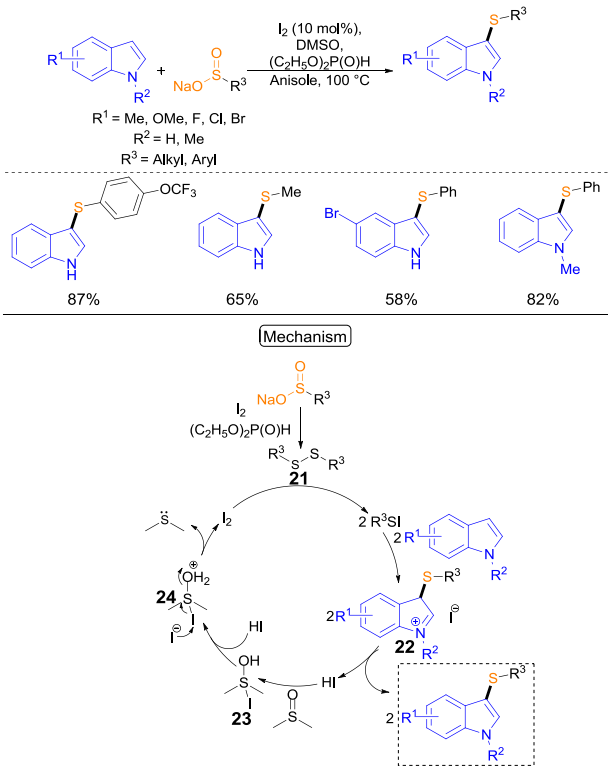
Scheme 21: DABSO for the *in situ* formation of sulfinates

Metal sulfinates, 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 21-a).[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 sulfinates using aryl halides, DABSO and triethylamine. These sulfinates 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 21-b).[20] Like 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

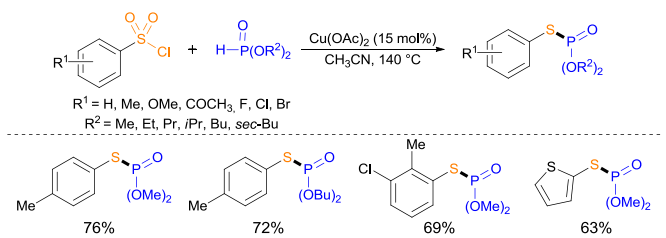
Preparation of 3-arylthioindole building blocks is generally achieved *via* transition-metal catalyzed direct sulfenylation of the corresponding indoles using disulfides, sulfenyl halides and thiols. To overcome the use of metal catalysts, Deng's group used sulfinates as sulfenylating agents.[69] In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



Scheme 22: Sodium sulfinates as sulfenylating agents

These metal-free conditions were found to be compatible with alkyl and aryl sodium sulfinates 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 sulfinate 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-sufenylindole is released with HI. Then, part of 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]



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

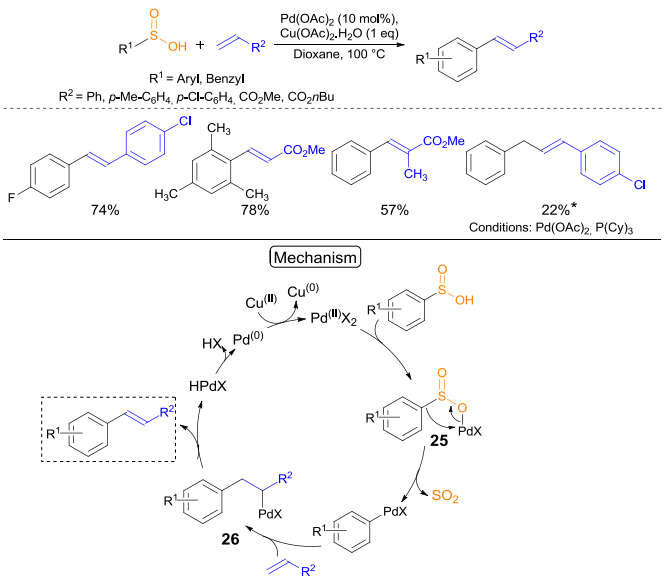
C- Sulfinate derivatives: C-S Bond Cleavage and C-C Bond Formation

Metal-catalyzed cross-coupling reactions have gained tremendous utility in organic synthesis. Continuous developments 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 goes 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 respectively.[73] Therefore, the reactivity of sulfinate derivatives towards metallic additions is somehow located between 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- Csp^2-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 sulfinates 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 presence of $Cu(OAc)_2$ as oxidant.[75c] The conditions turned out to be very efficient for coupling various aryl sulfinic acids with acrylic esters and electron-rich and –deficient styrenes (Scheme 24).

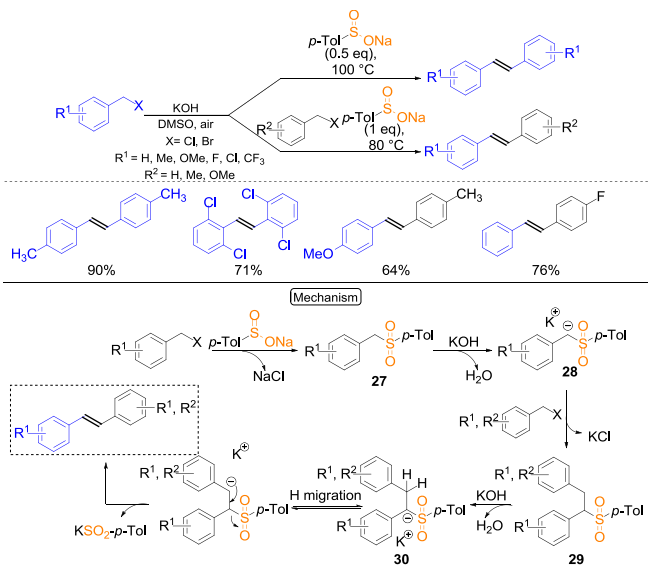


Scheme 24: Sulfinic acids, arene sources in Mizoroki-Heck-type reaction

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 $Pd(OAc)_2$ and the aryl sulfinic 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, $Pd^{(0)}$ species is oxidized by $Cu(OAc)_2$ 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 stilbenes 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]

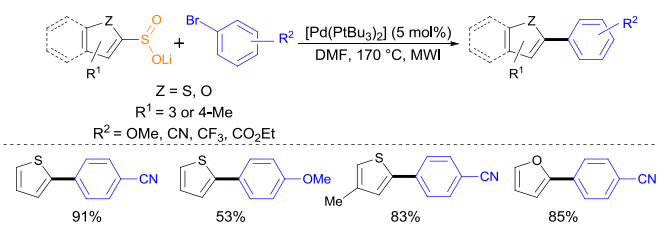


Scheme 25: Sodium sulfinate-mediated *trans*-stilbenes synthesis

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 the stilbenes synthesis. Electron-donating and withdrawing groups on the benzylic halides were compatible with the reaction conditions and selectively produced *trans*-stilbenes with 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 sulfones (**27**), obtained by the reaction of benzyl halide with sulfinate, is deprotonated into intermediate (**28**). In 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

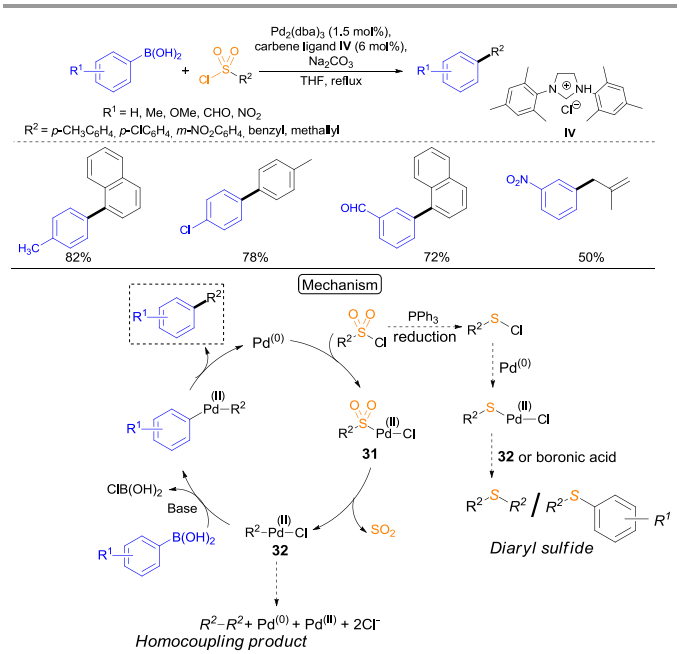
In 2013, Forgione and co-workers developed a base and additive-free desulfitative cross-coupling between lithiated heteroaromatic sulfinates and aryl bromides (Scheme 26).[77] In this work, the authors claimed the potential of sulfinic acids in desulfitative C-C arylations as alternative to carboxylic 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 SO_2 extrusion is easier than CO_2.[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).



Scheme 26: Desulfitative C2 arylation

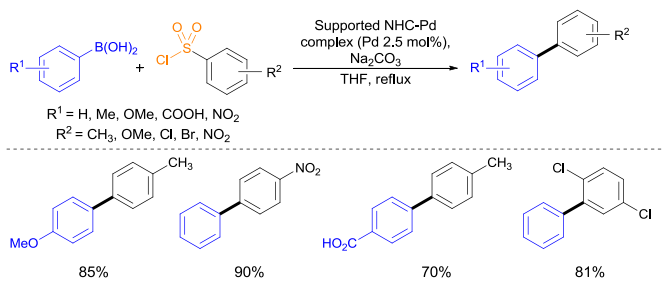
3- Suzuki-Miyaura coupling reactions

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), SO_2 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 towards boronic acids was issued: ArI > $ArSO_2Cl$ > ArBr >> ArCl. As a consequence, readily available sulfinates can replace organic halides in this coupling. The authors clearly stated the importance of the base (Na_2CO_3) 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, looses SO_2 and Pd complex (**32**) is obtained. Then, transmetallation followed by reductive elimination furnish the desired coupling biaryl.



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

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 polymer-supported *N*-heterocyclic carbene (NHC)-palladium complex. Catalysts immobilization on insoluble supports has become an attractive tool that enables catalyst and ligand recovery.

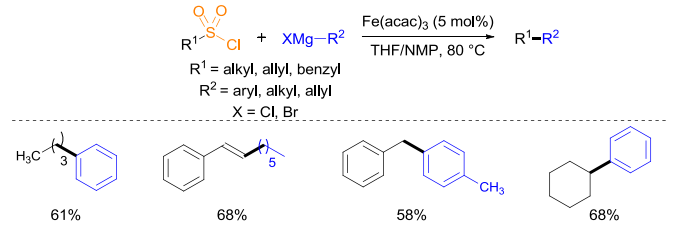


Scheme 28: Recyclable catalytic system for the desulfitative Suzuki-Miyaura coupling (NHC = *N*-Heterocyclic Carbene)

To be efficient, ligand systems have to stabilize all species involved in the catalytic cycle. Among those systems, NHC ligands are capable to remain 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 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.



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

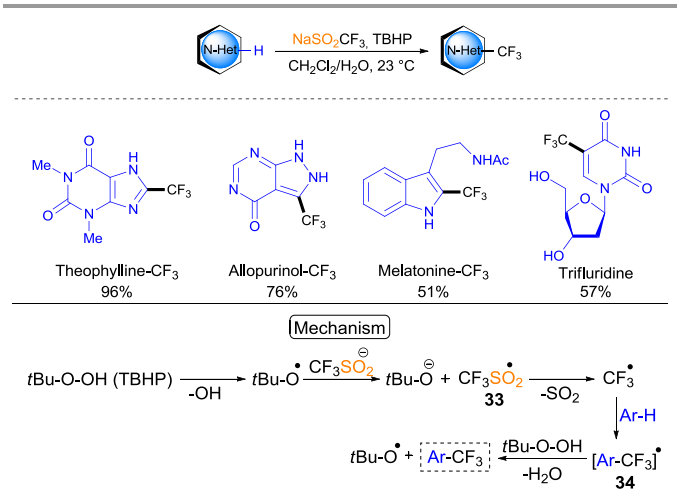
5- C-H functionalizations

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 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

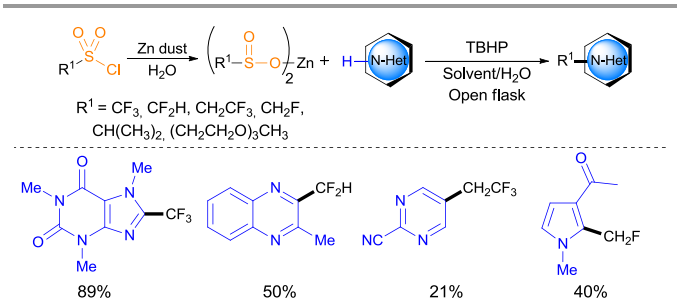
Fluorine substitutions have gained interest in medicinal chemistry improving drug potencies and insuring metabolic stabilization. To this end, Baran's team developed sulfinate reagents for the direct fluorination of electron-rich and nitrogen-containing heterocycles (xanthines, pyridines, indoles and imidazole derivatives) (Scheme 30).[82] These sulfinates 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 (CF_3SO_2Na, Langlois reagent)[83] was used for trifluoromethylating heterocycles.[82] This room temperature transformation allowed the introduction of the metabolically stable $–CF_3$ 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. *Tert*-butoxy radical interacts with

sulfinate anion to give radical (**33**), which decomposed into SO_2 and trifluoromethyl radical. In presence of an innate activated heterocyclic position, radical (**34**) will be formed and then oxidized into the desired fluorinated product with generation of another *tert*-butoxy radical.



Scheme 30: C-H trifluoromethylation: applications and mechanism (TBHP: *tert*-Butyl Hydroperoxide)

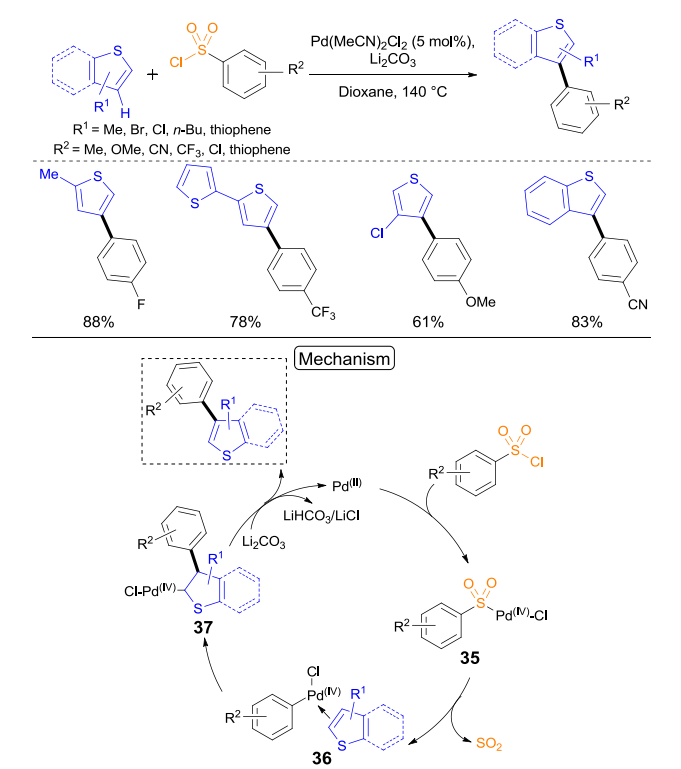
Pursuing their interest in fluorinating agents, the same team made two new alkylating agents: sodium 1,1-difluoroethanesulfinate (DFES-Na)[15] and zinc difluoromethanesulfinate (DFMS).[18] They presented afterwards the synthesis and applications of zinc sulfinate salts.[17] As mentioned at the beginning of this report, a zinc bis(alkanesulfinate) toolkit is commercially available at Sigma Aldrich. Nevertheless, they can be easily prepared[17a] and they permitted 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 radical initiator and in an open flask (Scheme 31). Regioselectivity issues can be avoided by a fine tuning of solvents on pH.



Scheme 31: C-H functionalization using zinc sulfinates (TBHP: *tert*-Butyl Hydroperoxide)

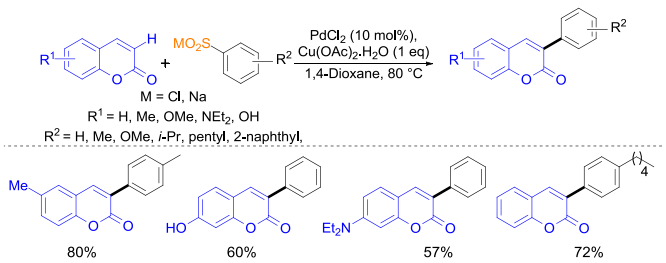
b) Regioselective C-H arylations

Regioselectivity remains challenging in C-H functionalization reactions in the presence of similar 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 silanes[86]), 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.



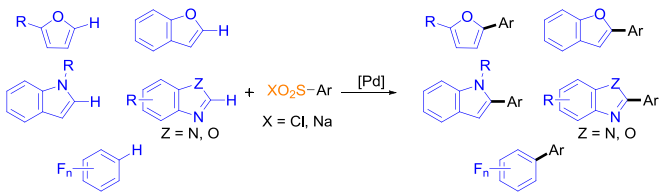
Scheme 32: Selective C3 arylation of thiophenes

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 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.



Scheme 33: Synthesis of 3-aryl coumarins

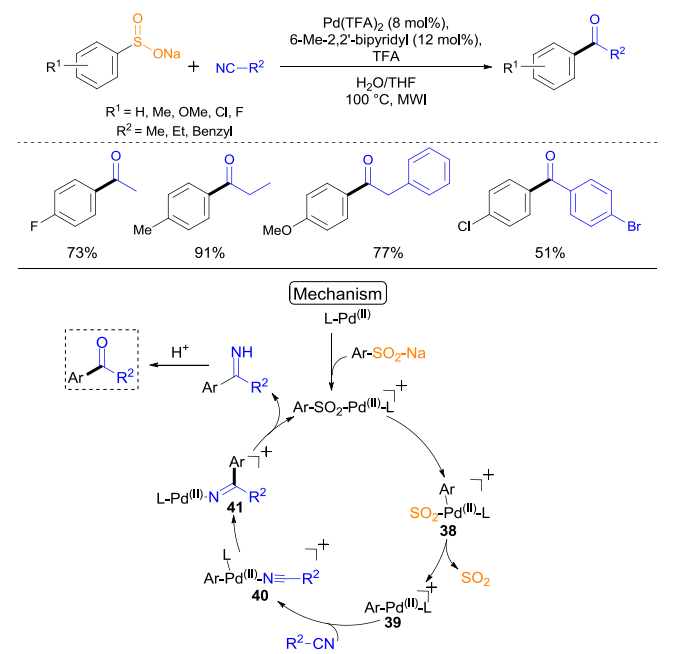
Other regioselective direct C-H arylations of several heteroaryls (furans, azoles, indoles and polyfluoroarenes) using sulfinates as coupling partners were also reported (Scheme 34).[88]



Scheme 34: Regioselective C-H arylations using sulfinates

6- Carbonylative reactions

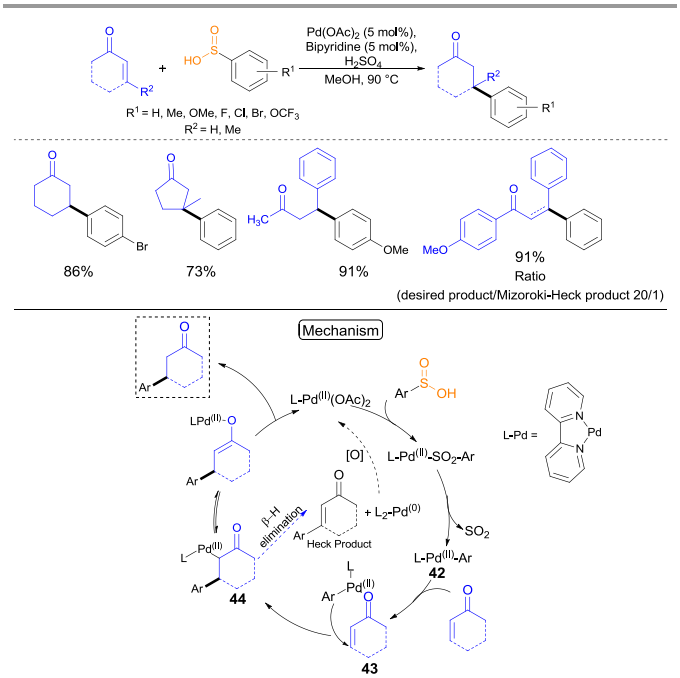
The ketone moiety has a ubiquitous presence in bioactive molecules, functional materials and as a functional group in organic chemistry. For these reasons, many synthetic methods were reported over the years, in particular insertion of an aryl palladium complex into nitrile. The traditional arene sources used were aryl boronic acids and caboxylic 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 the 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 sulfinate to palladium$^{(II)}$ affords complex (**38**). SO_2 extrusion generates aryl palladium species (**39**) followed by coordination of the nitrile group forms complex (**40**) and subsequent 1,2-insertion of nitrile generates ketimine (**41**) (most likely rate-determining step). Then, protonation to get free ketimine followed by acidic hydrolysis acquires the desired ketone. Instead of the nitriles, insertion can take place into another type of polar multiple bonds, 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 O_2 (1 atm) and without any additive. The conditions were compatible only with arenesulfinic acids and with variously substituted benzaldehydes (OMe, Br, Cl, CN and CF_3 groups).



Scheme 35: Microwave-assisted carbonylative reaction using sulfinate salts and mechanism elucidation by ESI-MS (TFA = TriFluoroAcetate)

7- Conjugate 1,4-addition reactions

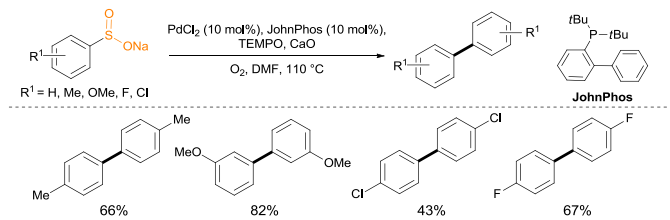
Conjugate addition of organometallic species (boron and silicon containing substrates, carboxylic acids) to α, β-unsaturated carbonyl compounds suffer from stability and availability issues of the starting materials as well as the necessity of electron-poor substituents at *ortho*-position. As a consequence, 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: $Pd(OAc)_2$ 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 elucidating 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**) that is subjected to migratory insertion on the C=C with the aryl Pd$^{(II)}$ to obtain intermediate (**44**), substituted on the ß-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.



Scheme 36: Desulfitative conjugate addition of aryl sulfinic acids

8- Homocoupling reactions

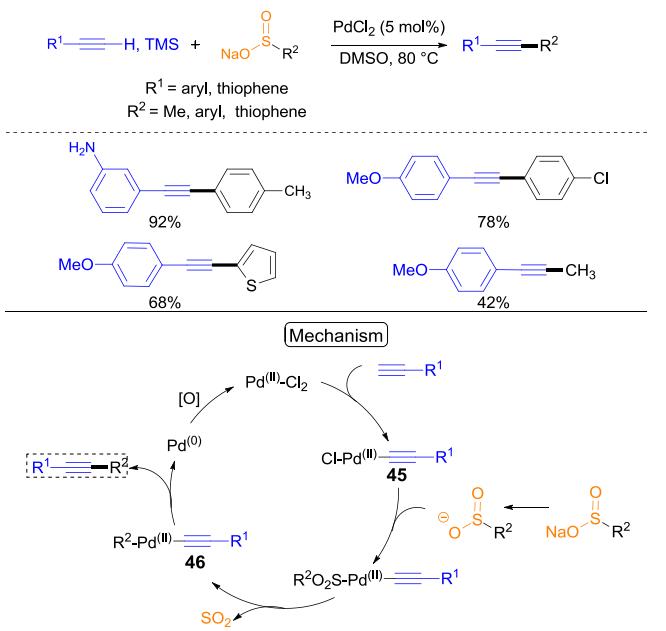
Sulfinate derivatives are also reported for the synthesis of symmetrical biaryls by homocoupling reactions.[91] They represent a convenient alternative to carboxylic acids which require an *ortho* substitution or to boronic acids which generate many side products. For example, Forgione *et al.* succeeded employing catalytic amounts of TEMPO with molecular oxygen as oxidants in the homocoupling reaction of various sodium sulfinates (Scheme 37).[91a] Moderate to good yields were observed when applying these conditions to electron-rich or electron-poor sulfinates.



Scheme 37: Homocoupling of sulfinates co-catalyzed by palladium and TEMPO (TEMPO = 2,2,6,6-TEtraMethylPiperidin-1-Oxyl)

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 sulfinates 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 sulfinates 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 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 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 $Pd^{(II)}$.

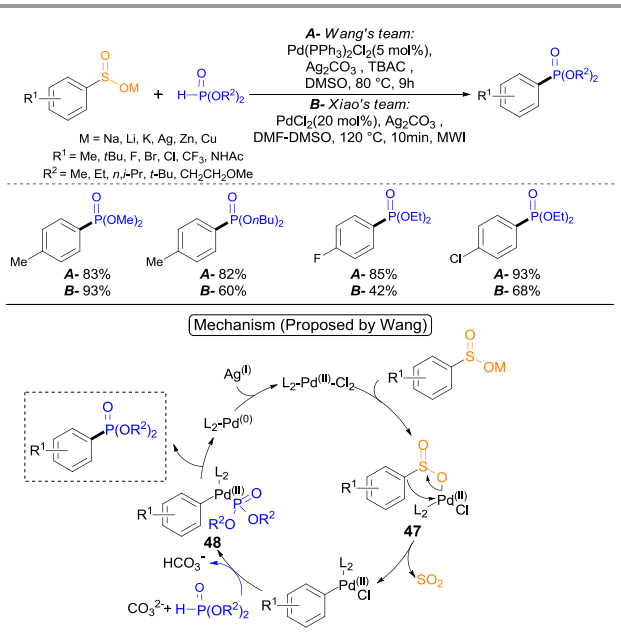


Scheme 38: Unsymmetrical alkynes synthesis with sodium sulfinates as coupling partners

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 sulfinates and H-phosphonates (Scheme 39).[94] In both cases, the presence of silver carbonate (Ag_2CO_3) as 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 C-P bond using palladium and Ag_2CO_3 in just 10 minutes.[94a] In the two examples, electron-rich and deficient

substituted aryl sulfinates 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- Outlooks

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 (like it has been done with fluorinated sulfinates, e.g DFES-Na and DFMS) to access complex structures in practical and efficient synthesis. The development of safe sources of SO_2 ($K_2S_2O_5$, DABSO) will open the way to more industrial applications of this chemistry.

In traditional cross-coupling reactions, sulfinates are used as alternatives to arylating agents: organic halides, benzoic acids and boronic acids. Despite tremendous work realized 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 sulfinates in coupling reactions or direct C-H activation of Csp^3-H bonds (e.g.: alkylations, α-arylations) using sulfinates could be envisioned. In addition to C-C and C-P bond formation, sulfinates should be investigated in the creation C-heteroatom bonds, e.g.: C-O, C-N, C-F.

Conclusion

In summary, the application of sulfinic acids and their derivatives are witnessing 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 broaden the reaction scope along with a better functional group tolerance. For all these reasons, sulfinates represent a versatile tool in organic synthesis that is not yet fully discovered.

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