DABSO – A reagent to revolutionize organosulfur chemistry

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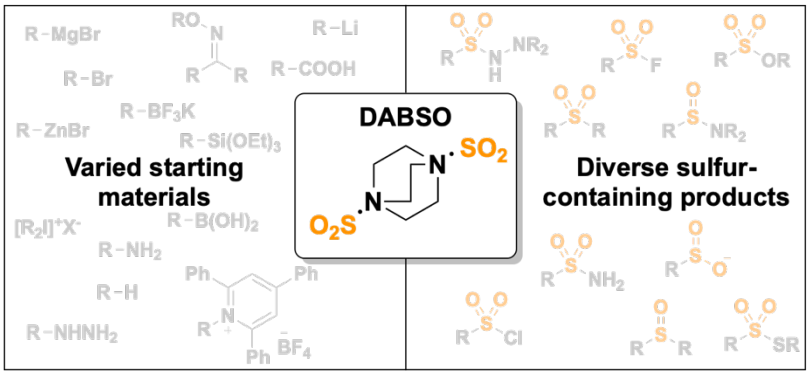

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Abstract The introduction of easy-to-handle SO_2 surrogates has transformed the field of sulfur chemistry, enabling methodologies utilising SO_2 to be carried out without specialized apparatus, and paving the way for the development of new methodologies. This review highlights some of the varied and significant developments associated with one of the most prominent SO_2 surrogates: DABSO.

Key words sulfur dioxide, sulfones, sulfinates, radical reactions, catalysis

1 Introduction

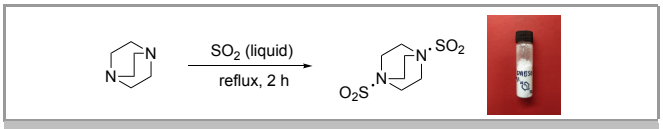
Although cheap and abundant gaseous SO_2 can be used in many interesting reactions for the synthesis of high-value compounds, the challenges associated with handling SO_2 gas, such as the use of specialised equipment, high toxicity and environmental concerns, have prevented the wide adoption of such methodologies and have hindered their further development. The requirement to use a large excess of SO_2 can also be detrimental due to overreaction, or reaction and catalyst poisoning.

The introduction of easier to handle surrogates for SO_2 means that many of these challenges can be avoided or mitigated.[1] This has resulted in a resurgence in the development of new methodologies incorporating SO_2 into high-value products.

2 DABSO

The Lewis acidity of the sulfur atom in SO_2 enables the formation of 1:1 charge-transfer complexes with Lewis bases such as amines. The interaction between ammonia and SO_2 had been noted on several occasions in the 19th century, but it wasn't until 1900 where the products of this interaction were isolated and studied.[2] A wide variety of amine-SO_2 charge-transfer complexes have since been prepared, and their structures and properties studied using a wide variety of techniques.[3] Prior to 2010, however, reports of their synthetic uses were scarce, and even fewer of those incorporated the SO_2 motif into the product to give valuable sulfinyl- or sulfonyl-containing products.[4]

The bench-stable Lewis adduct formed between 1,4-diazabicyclo[2.2.2]octane (DABCO) and two molecules of SO_2. DABCO·$(SO_2)_2$, henceforth referred to as DABSO, was first prepared by Mello and co-workers in order to study its Raman spectrum.[5] DABSO can be readily prepared by refluxing DABCO in liquid SO_2 (Scheme 1),[6] although alternative preparations have been developed using the Karl Fischer reagent[7] or using sodium sulfite as the source of SO_2.[8] It is available commercially from multiple vendors. Due to its ease of preparation, favorable physical properties, and high proportion (>50%) of its molecular weight as SO_2, DABSO was identified as an ideal choice to study the use of amine-SO_2 Lewis-adducts as SO_2 surrogates.



Scheme 1 Preparation of DABSO.

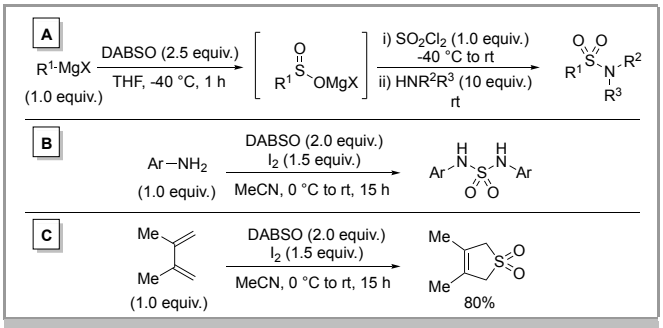
3 Reactions with Nucleophilic Reagents

In order to demonstrate the utility of DABSO in synthetic organic chemistry, Willis and co-workers reported its use as a

replacement for gaseous SO_2 in a series of reactions.[9] Organometallic reagents had previously been used in reactions with gaseous SO_2 for the synthesis of sulfinates and their derivatives.[10] Willis and co-workers demonstrated that aryl or alkyl Grignard reagents could be combined with DABSO to give a sulfinate salt intermediate (Scheme 2A). Reaction with sulfuryl chloride to give a sulfonyl chloride followed by addition of an amine gave sulfonamide products. Yields were comparable to those obtained by Barrett and co-workers following a similar synthetic sequence using the gaseous reagent, and the reactions with DABSO could be achieved without a large excess of SO_2.

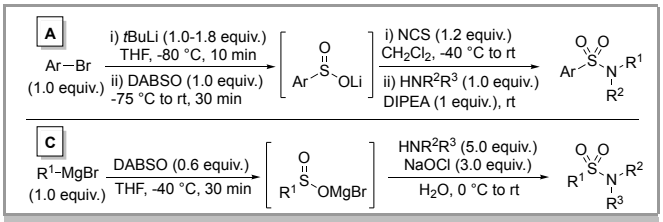
Rudkevich and co-workers previously demonstrated that sulfamides could be prepared using iodine and pyridine in combination with SO_2 gas.[11] It was proposed that these reactions involved the *in situ* formation of sulfuryl iodide (SO_2I_2), which then reacts with 2 molecules of aniline. Willis and co-workers demonstrated that DABSO can be effectively used in the same transformation with comparable yields, but only 2 equivalents of DABSO were needed, whereas previously it is estimated that ~100 equivalents of SO_2 were required (Scheme 2B).[9]

Willis and co-workers also demonstrated that cheletropic reactions are possible using DABSO instead of SO_2 gas in the synthesis of a sulfolene using 2,3-dimethylbutadiene (Scheme 2C).[9] Bischoff and Martial later showed that cheletropic additions using DABSO could be accelerated by the additon of Lewis acids such as $BF_3.OEt_2$.[12]



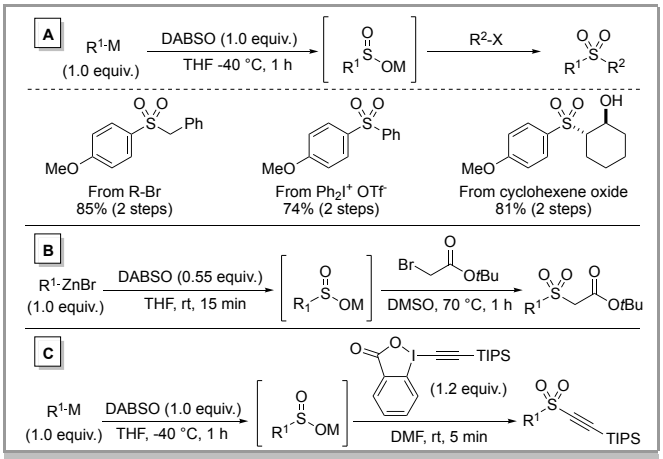
Scheme 2 A: Grignard addition to DABSO. B: Sulfamide synthesis using DABSO, C: Cheletropic addition to diene using DABSO.

Kopka and co-workers showed that *in situ* generated aryllithium reagents can be used to generate lithium sulfinates by reaction with DABSO, which can be oxidatively chlorinated using *N*-chlorosuccinimide (NCS) to generate a sulfonyl chloride that in turn reacts with an amine to give a sulfonamide product (Scheme 3A).[13] An alternative two-step procedure was developed by Willis and co-workers to prepare sulfonamides. The sulfinate intermediate is prepared from Grignard reagents, organolithium or organozinc nucleophiles and DABSO. Free amine and aqueous sodium hypochlorite are then added to form an electrophilic *N*-chloroamine intermediate, which reacts with the sulfinate to give a sulfonamide product (Scheme 3B).[14]



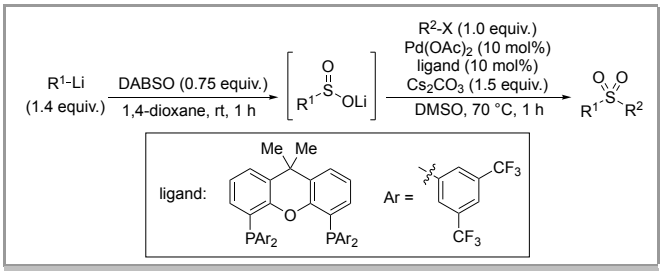
Scheme 3 A: *In situ* aryllithium generation and addition to DABSO. B: Sulfonamide synthesis using *N*-chloroamine intermediates.

Sulfone products can also be obtained from organometallic reagents by further reaction of the in situ sulfinate salts. The Willis group demonstrated this reactivity by using alkyl halides, epoxides or diaryliodonium salts to synthesize sulfones from Grignard or organolithium reagents (Scheme 4A).[15] Shavnya and co-workers also prepared sulfone products, but used organozinc reagents to prepare the intermediate sulfinate salt (Scheme 4B).[16] Waser and co-workers prepared alkynyl sulfones from Grignard reagents using ethynyl-benziodoxolone (EBX) reagents as alkynyl electrophiles (Scheme 4C).[17]



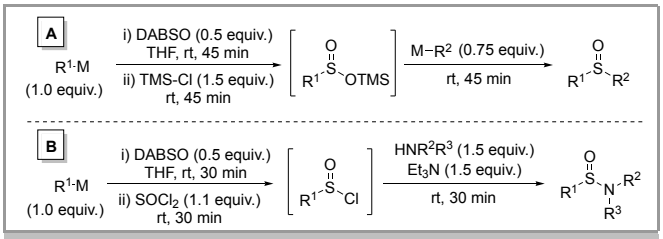
Scheme 4 A: Sulfone synthesis from sulfinates. B: Sulfone synthesis using organozinc reagents. C: Alkynyl sulfone synthesis using EBX reagents.

Sulfinates derived from aryllithium addition to DABSO have been used in a Pd-catalyzed coupling with aryl halides to give sulfones in a one-pot procedure (Scheme 5).[18] XantPhos-type ligands were found to be key for reactivity in the Pd-catalyzed step, as previously demonstrated by Bernini and co-workers,[19] but in this one-pot procedure, aryl-aryl exchange between the sulfinate and XantPhos was observed as a side-product. Electron-poor XantPhos analogues containing 3,5-*bis*(trifluoromethyl)phenyl groups were found to prevent this side-reaction, allowing the desired sulfone to be formed in good yield.



Scheme 5 Sulfone synthesis via Pd-catalyzed coupling of sulfinates.

Methods utilising organometallic reagents have also been used for the synthesis of S(IV) functional groups, including sulfoxides and sulfinamides. The Willis group generated sulfinates from organometallic addition to DABSO, and subsequent reaction with trimethylsilyl chloride (TMS-Cl) gave a sulfinate silyl ester (Scheme 6A).[20] This electrophilic intermediate then reacts with a second organometallic nucleophile to give unsymmetrical sulfoxide products in a one-pot procedure. A related procedure, also developed by the Willis group, prepares sulfinyl chlorides from sulfinates using thionyl chloride (Scheme 6B).[21] These electrophilic intermediates are then reacted with amine nucleophiles to give sulfinamide products.

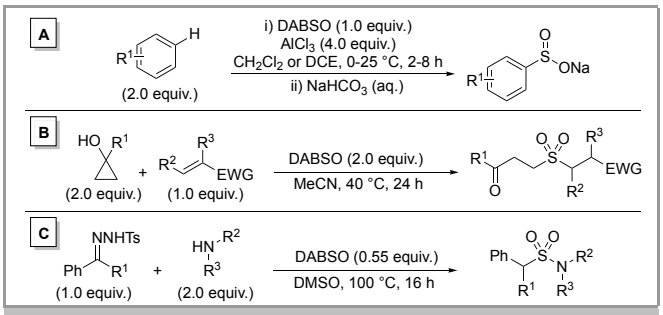


Scheme 6 A: Sulfoxide synthesis via nucleophilic addition to a sulfinate silyl ester intermediate. B: A: Sulfinamide synthesis via amine addition to a sulfinyl chloride intermediate.

Zhang and co-workers disclosed an $AlCl_3$-promoted Friedel Crafts-type reaction of arenes and DABSO to give sulfinates (Scheme 7A).[22] Formation of an SO_2-$AlCl_3$ adduct was proposed to enable nucleophilic attack from the arene to give the sulfinate product. Electron-rich arenes performed best in this transformation, with electron-poor arenes giving no reaction.

Wu and co-workers prepared γ-keto sulfones from cyclopropanols, DABSO and Michael acceptors (Scheme 7B).[23] It was observed that the reaction did not proceed via a radical process, but instead a sulfinate intermediate was observed, which undergoes a Michael addition to give a sulfone. Reaction of the sulfinate intermediate with C-electrophiles to give other γ-keto sulfones was also later demonstrated.[24]

Mascitti and co-workers showed that sulfonamide products could be prepared from *N*-tosylhydrazones (Scheme 7C).[25] The mechanism remains unclear, but was shown to proceed through a non-radical pathway. The *N*-tosylhydrazone could also be prepared *in situ* from a ketone, and the reaction was shown to be compatible with primary and secondary amines.



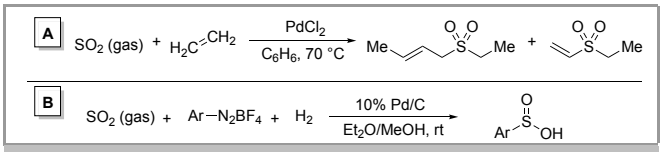
Scheme 7 A: Friedel-Crafts-type sulfination of arenes using DABSO and $AlCl_3$. B: Synthesis of γ-keto sulfones from cyclopropanols, DABSO and Michael acceptors. C: Synthesis of sulfonamides from *N*-tosylhydrazones.

4 Metal-Catalyzed Reactions

SO_2 can act as a versatile ligand for metals. Its amphoteric nature due to a high-lying HOMO capable of electron-donation as well as a low-lying LUMO enabling back-donation, results in efficient binding to soft metal centres.[26] The first transition metal-SO_2 complex was identified in 1938,[27] and structural and spectroscopic properties of these complexes have been well-studied since.[28]

The molecular orbital properties and transition metal coordination modes of SO_2 are notably similar to carbon monoxide.[26b] Metal-catalyzed carbonylations, involving migratory insertion of CO into a metal-carbon bond, are widely used methodologies.[29] However, reports of the analogous use of gaseous SO_2 are scarce.

Migratory insertion of SO_2 to metal-carbon bonds has been demonstrated previously. Klein and co-workers demonstrated the first migratory insertion to give a palladium-sulfinato complex intermediate in a hydrosulfination reaction utilising ethylene and SO_2, giving a mix of vinyl sulfone products (Scheme 8A).[30] Other examples of metal-catalyzed reaction of SO_2 and alkenes have also been reported,[31] and an example of sulfinic acid synthesis from a aryldiazonium salt was reported by Keim and co-workers (Scheme 8B).[32] These examples demonstrate the potential for the use of metal catalysis for the synthesis of valuable sulfonyl-derived products.

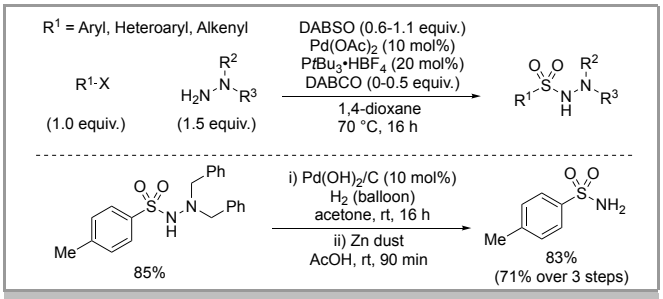


Scheme 8 A: Pd-catalyzed hydrosulfination of ethylene and SO_2 gas. B: Pd-catalyzed synthesis of sulfinic acids from aryl diazonium salts and SO_2 gas.

The relative lack of metal-catalyzed reactions using gaseous SO_2, aside from challenges associated with handling the toxic gas, may be a result of the poisoning of metal catalysts due to the use of a large excess of gaseous SO_2. Use of SO_2 surrogates allow for precise control of SO_2 loading, and consequently, following the introduction of DABSO, new metal catalyzed sulfinylation reactions were reported.

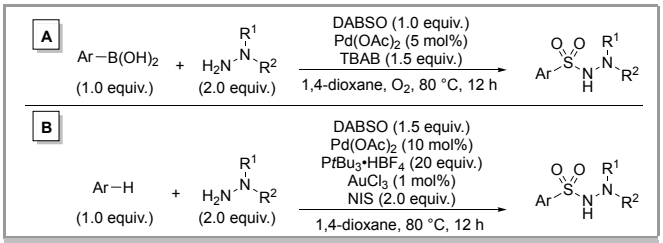
4.1 Palladium-Catalyzed Reactions

In the first reported synthetic use of DABSO, Willis and coworkers introduced a metal-catalyzed sulfonylative reaction of aryl halides (Scheme 9).[6,33] In this three-component Pd-catalyzed reaction, aryl halides, DABSO and hydrazines were coupled to give *N*-aminosulfonamides. It was noted that low DABSO loading was shown to improve the yield, supporting the hypothesis that high SO_2 loading could hamper reactivity due to catalyst poisoning. Primary sulfonamides could be prepared from a dibenzylated *N*-aminosulfonamide via a 2-step deprotection sequence, extending the utility of this transformation. The reaction was later demonstrated to work on large scale.[34] This method was subsequently extended to prepare benzosultams from 2-(2-iodoalkenyl)aryl bromides by subjecting the alkenyl *N*-aminosulfonamide to a further Pd-catalyzed cyclisation step.[35]



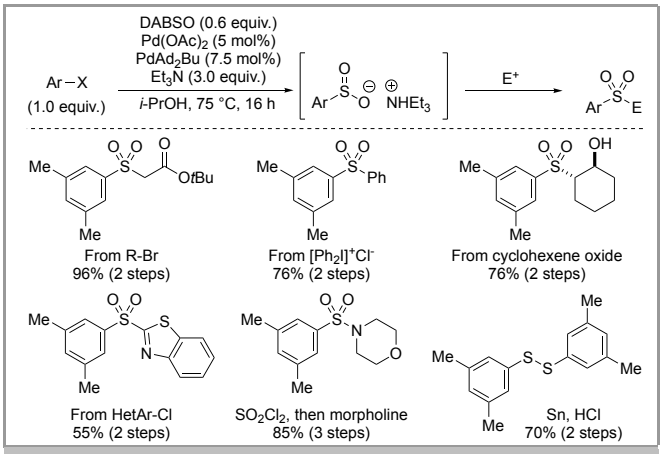
Scheme 9 Pd-catalyzed synthesis of *N*-aminosulfonamides from aryl halides.

Alternative substrates have also been used to prepare *N*-aminosulfonamide products using Pd- catalysis. Wu and co-workers used Pd-catalysis to prepare *N*-aminosulfonamides from arylboronic acids (Scheme 10A).[36] No ligand was required, and a balloon of O_2 was used to complete the catalytic cycle. The authors demonstrate good functional group compatibility. Wu and co-workers later demonstrated that aryl iodides could be generated *in situ* using gold(III) catalysis (Scheme 10B).[37] The subsequent Pd-catalyzed sulfonylation reaction proceeded effectively to give *N*-aminosulfonamide products in one-pot from unactivated arenes. The reaction was shown to perform best with electron-rich arenes, although electron-poor examples were demonstrated, albeit with low yields.



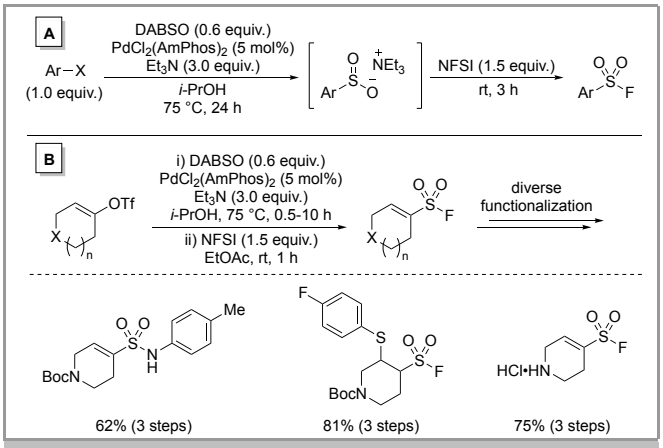
Scheme 10 A: *N*-aminosulfonamides from boronic acids. B: *N*-aminosulfonamides from arenes via *in situ* generation of aryl iodides.

In order to deliver a versatile method for the preparation of diverse sulfonyl derivatives, the Willis group and a group from Pfizer independently developed Pd-catalyzed syntheses of aryl sulfinates from aryl halides. The Willis group used DABSO (Scheme 11),[38] whereas the group from Pfizer used $K_2S_2O_5$ as an alternative SO_2 surrogate.[39] The Willis group used a $Pd(OAc)_2$/PAd_2Bu catalytic system, and it was noted that their reaction solvent, isopropanol, could also act as the reductant, removing the requirement for an additional reducing agent such as sodium formate to maintain Pd(0)/Pd(II) turnover. Both aryl iodide and bromide substrates could be used, although iodides were found to give higher yields. From the sulfinate intermediate, sulfones were prepared using various *C*-based electrophiles, and sulfonamides were prepared via the addition of amines to *in situ*-generated sulfonyl chlorides, demonstrating the versatility of the reaction. Willis later demonstrated that the *in situ* preparation of an *N*-chloroamine using sodium hypochlorite could be used to access sulfonamide products without the formation of a sulfonyl chloride intermediate.[40] Lautens and co-workers showed that cyclic sulfonated products could be prepared through a Pd-catalyzed intramolecular Heck reaction followed by a Pd-catalyzed reaction with DABSO to prepare a sulfinate, from which sulfones, sulfonamides and sulfonyl fluorides were prepared.[41]



Scheme 11 Pd-catalyzed synthesis of sulfonyl derivatives from aryl halides.

Sulfonyl fluorides are valuable products. They are hydrolytically stable, but under the correct conditions can undergo sulfur(VI) fluoride exchange (SuFEx) "click chemistry" reactions.[42] Willis and co-workers used the preparation of sulfonyl fluoride products using NFSI to showcase a new catalyst system for the synthesis of aryl sulfinates, this time focusing on improving yields for aryl bromide substrates (Scheme 12A).[43] Key to the improved system was the use of AmPhos as the ligand, which can also be used as part of a preformed Pd/AmPhos complex, giving an improved yield of sulfinate, whilst avoiding the generation of reduction side-products. Willis and co-workers later expanded upon this work in the preparation of cyclic alkenylsulfonyl fluorides from alkenyl triflate substrates (Scheme 12B).[44] The varied reactivity of these cyclic alkenylsulfonylfluoride products was demonstrated in a series of functionalizations.

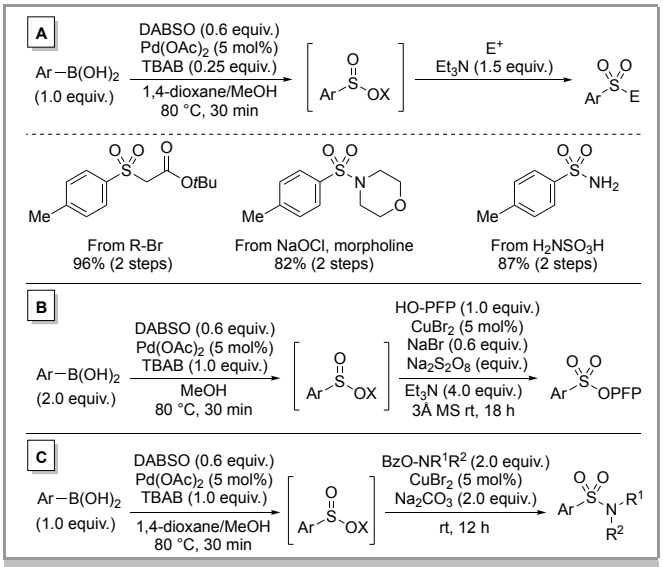


Scheme 12 A: Pd-catalyzed synthesis of sulfonyl fluorides. B: Pd-catalyzed synthesis of cyclic alkenylsulfonyl fluorides.

Willis and co-workers used arylboronic acids under ligand-free palladium catalysis to provide a new redox-neutral route to aryl sulfinates (Scheme 13A).[45] This method could be used to access a broad range of sulfonyl-containing products, including sulfones and sulfonamides in a one-pot procedure. It was noted that the sulfones could be prepared in a one-step procedure by inclusion of the electrophile in the Pd-catalyzed sulfination step. This method required a significantly reduced reaction time compared to those using aryl halides as starting materials.

Pentafluorophenyl (PFP) sulfonate esters, stable alternatives to sulfonyl chlorides, were prepared by Willis and co-workers in a

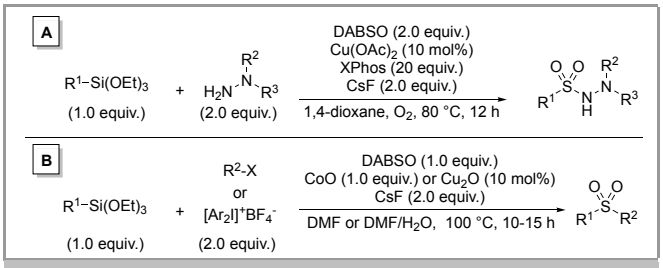
two-step procedure (Scheme 13B).[46] The intermediate sulfinate was prepared using previously optimised Pd-catalyzed conditions from arylboronic acids or aryl halides. This was followed by a copper-catalyzed oxidative step to prepare the PFP sulfonate esters using pentafluorophenol. The utility of PFP sulfonate esters as electrophiles was demonstrated by the preparation of a selection of sulfonamides, sulfonyl fluorides and sulfonate esters. In a related procedure, Tu and co-workers prepared aryl sulfonamides via the Cu-catalyzed coupling of sulfinates with *O*-benzoyl hydroxylamines (Scheme 13C).[47]



Scheme 13 A: Pd-catalyzed synthesis of sulfinates from arylboronic acids. B: Pd/Cu-catalyzed synthesis of pentafluorophenyl sulfonate esters. C: Pd/Cu-catalyzed synthesis of sulfonamides using *O*-benzoyl hydroxylamines.

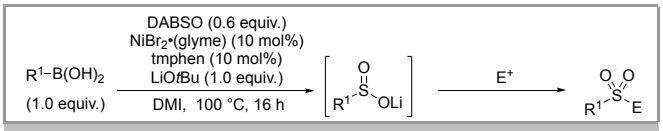
4.2 Other Transition Metal Catalysis

Due to the high cost and relatively scarcity of palladium, the development of catalytic methods using less expensive and readily available first row transition metal catalysts is important. Wu and co-workers developed an alternative procedure for the preparation of *N*-aminosulfonamides from triethoxysilane reagents using Cu-catalysis and an XPhos ligand under oxidative conditions (Scheme 14A).[48] Notably, this method is compatible with alkyl substrates, where the aforementioned Pd-catalyzed methods are only compatible with aryl or alkenyl substrates. Wu and co-workers later developed methods for the preparation of sulfones from triethoxysilanes using copper or cobalt catalysis (Scheme 14B).[49]



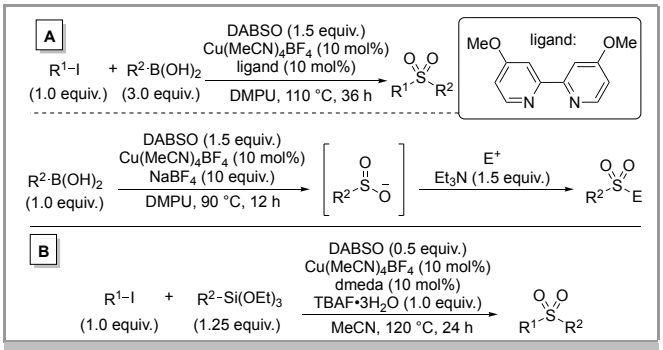
Scheme 14 A: Cu-catalyzed synthesis of *N*-aminosulfonamides from triethoxysilanes. B: Cobalt or copper-mediated synthesis of sulfones from triethoxysilanes.

Willis and co-workers showed that Ni-catalysis with a 3,4,7,8-tetramethylphenanthroline (tmphen) ligand could be used to prepare sulfinates from boronic acids (Scheme 15).[50] This methodology was compatible with a broad scope of boronic acids, and a wide variety of sulfonyl-derived products were prepared in this one-pot two-step procedure. Similarly, use of ruthenium catalysts was demonstrated by Turks and co-workers for the synthesis of aryl sulfinates and their derivatives.[51]



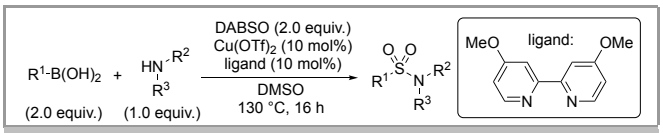
Scheme 15 Ni-catalyzed synthesis of aryl sulfinates from arylboronic acids.

Whilst the aforementioned methods provide new routes to sulfinate intermediates, multiple reaction steps are generally needed for the preparation of sulfonyl-derived products. Willis and co-workers developed an approach analogous to carbonylative Suzuki Miyaura couplings to access biaryl sulfones (Scheme 16A).[52] This copper-catalyzed sulfonylative Suzuki-Miyaura coupling requires no ligand or base to give biaryl sulfones. An electron-rich bipyridine ligand was needed in order to obtain high yields, and the authors also noted that the addition of a stoichiometric amount of $NaBF_4$ interrupted the coupling to give a sulfinate salt, providing an alternative to previous palladium-catalyzed methods. Cantat and co-workers later developed a sulfonylative Hiyama coupling from triethoxysilanes to prepare biaryl sulfone products (Scheme 16B).[53]



Scheme 16 Cu-catalyzed sulfonylative Suzuki-Miyaura cross-coupling. B: Cu-catalyzed sulfonylative Hiyama coupling.

Willis and co-workers developed a 3-component synthesis of sulfonamides from arylboronic acids, DABSO and amines in a sulfonylative Chan-Lam type coupling (Scheme 17). An electron-rich bipyridine ligand was again found to be important, and addition of base gave an improved yield. The authors demonstrated a broad scope for the boronic acid and amine components, including a selection of pharmaceutically relevant fragments.

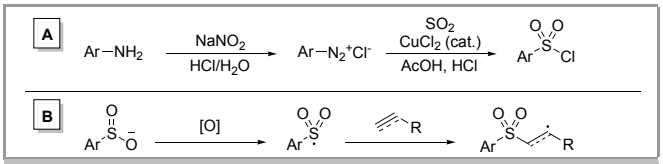


Scheme 17 Cu-catalyzed sulfonylative Chan-Lam coupling.

5 Radical Reactions

Addition of C-centered radicals to sulfur dioxide to give sulfonyl radicals is well established in synthetic chemistry, with methods from Reed and later Meerwein exploiting radical addition to gaseous SO_2 to prepare sulfonyl chlorides from alkanes and aryldiazonium salts respectively (Scheme 18A).[54]

Sulfonyl radicals derived from alternative precursors such as sulfinate salts, or sulfonyl chlorides, have also been utilized for the preparation of sulfonyl products (Scheme 18B).[55]

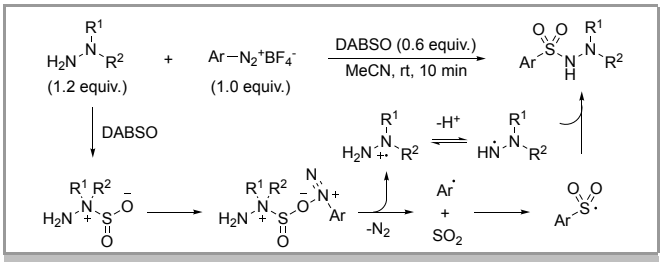


Scheme 18 A: Meerwein synthesis of sulfonyl chlorides using SO_2. B: Sulfonyl radicals from sulfinates and subsequent addition to radical traps.

The introduction of solid surrogates of SO_2, as well as modern methods for the generation of radicals from various precursors, has resulted in a rapid development of new methods for the synthesis of sulfonyl-derived products.[56]

5.1 Aryldiazonium salts

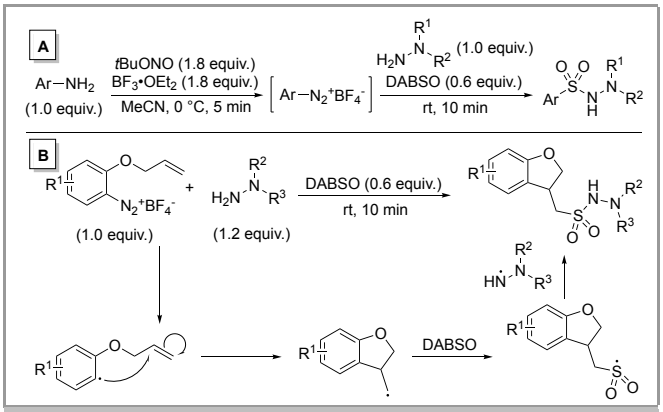
During the development of a Pd-catalyzed aminosulfonylation of aryldiazonium salts, Wu and co-workers noticed that the reaction proceeded efficiently in the absence of the catalyst. Based on experimental and computational studies, it was found to be operating via a radical pathway (Scheme 19).[57] The reaction was proposed to proceed via the initial formation of a hydrazine-SO_2 charge-transfer complex, from which electrostatic interactions between this complex and the diazonium salt are proposed to initiate the transformation by homolytic cleavage of the S-N bond, single-electron transfer (SET) and loss of N_2 to give an aryl radical and a hydrazine radical cation. The aryl radical adds to SO_2 to give a sulfonyl radical, which combines with hydrazine radical to give the *N*-aminosulfonamide product. A broad range of hydrazines and aryldiazonium salts were compatible with the methodology and subsequent methods utilising *N*-aminosulfonamides as precursors to other sulfonyl products have been developed.[58]



Scheme 19 Metal-free aminosulfonylation of aryldiazonium salts.

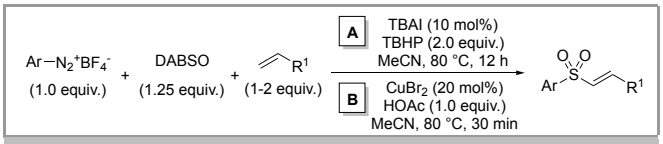
Subsequently, Wu and co-workers demonstrated that a similar reaction could also be carried out starting from anilines (Scheme 20A).[59] The *in situ* preparation of aryldiazonium salts using *tert*-butyl nitrite (*t*BuONO) and $BF_3{\cdot}OEt_2$ as a Lewis acidic additive was followed by addition of DABSO to give *N*-aminosulfonamide products. Yields were found to be comparable to those using the aryldiazonium salt starting materials.

Radical methodologies utilising SO_2 can also be used to prepare structurally complex sulfonyl-containing molecules. For example, 2-allyloxyaniline or its diazonium salt derivative can be used to prepare cyclized products via aryl radical generation, intramolecular 5-*exo*-trig cyclization and subsequent alkyl radical addition to SO_2 (Scheme 20B).[60]



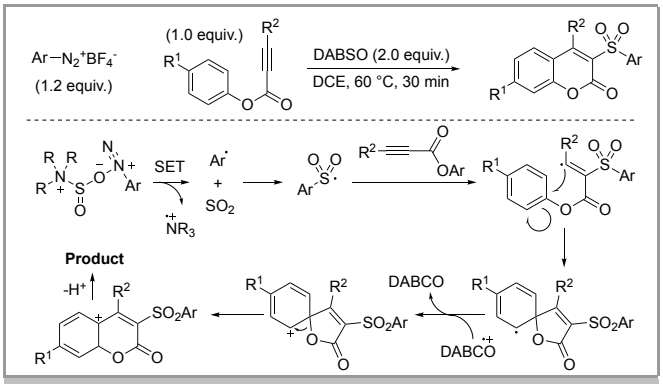
Scheme 20 A: Aminosulfonylation of anilines via *in situ* aryldiazonium salt formation. B: Cyclization and aminosulfonylation from aryldiazonium salts.

The addition of sulfonyl radicals to alkenes and alkynes has been previously used for the synthesis of sulfone products. Feng and co-workers used a combination of *tert*-butylhydroperoxide (TBHP) and tetrabutylammonium iodide (TBAI) to give aryl radicals (Scheme 21A),[61] whereas Wu and co-workers used a Cu(II) catalyst to generate aryl radicals (Scheme 21B).[62] In both methods, aryl radical addition to DABSO, and subsequent sulfonyl radical addition to an alkene followed by oxidation gives a cationic intermediate. Deprotonation of this cation, or iodide addition and elimination, gave vinyl or allyl sulfone products.



Scheme 21 Synthesis of sulfones via sulfonyl radical to alkenes.

During the development of a synthesis of 3-sulfonated coumarins, Wu and co-workers noticed in a control experiment that a copper catalyst was not necessary in the transformation (Scheme 22).[63] In their proposed mechanism the DABCO-SO_2 charge-transfer complex could undergo a homolytic cleavage of the S-N bond and SET to give an aryl radical, similar to the mechanism proposed using hydrazines. This new metal-free method proceeded to give the 3-sulfonated coumarins by sulfonyl radical addition to alkyne, spirocyclization onto an arene, oxidation, rearrangement and deprotonation to give the 3-sulfonated coumarin product.

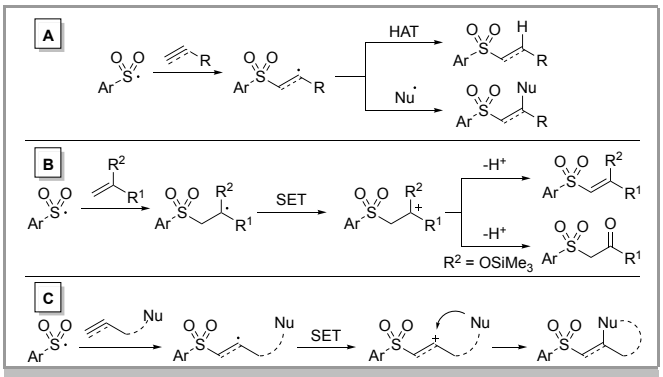


Scheme 22 Metal-free synthesis of 3-sulfonated coumarins.

Following these studies, the combination of aryldiazonium salts and DABSO has been extensively used for preparation of sulfone products. Sulfonyl radical addition to alkenes or alkynes gives a β-sulfonyl radical, which can then be quenched by hydrogen atom transfer (HAT),[64] or by reaction with *in situ* generated radicals (Scheme 23).[65]

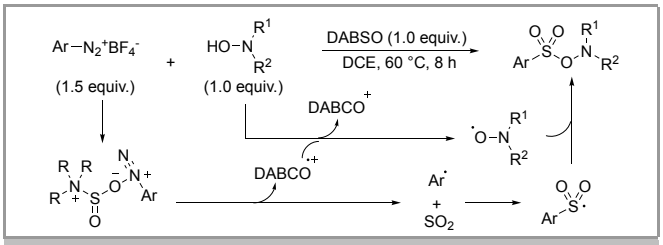
A SET step can be used to prepare a carbocation intermediate, from which deprotonation gives alkene or alkyne products (Scheme 23B). The DABCO radical cation, derived from radical generation, can be used in this SET step,[63] but copper catalysts or photocatalysts have also been employed to facilitate this.[66] Using this reaction framework, Wu and co-workers demonstrated that sulfonyl radical addition to silyl enol ethers, SET to generate a carbocation, and desilylation could be used to prepare β-keto sulfones.[67]

Several methods have also been used to prepare β-functionalized sulfones via addition of nucleophiles to cation intermediates (Scheme 23C).[68] Intramolecular nucleophile addition can also be used to prepare cyclized products,[69] and the combination of several radical addition and cyclization steps has been used to prepare complex sulfonyl-containing molecules.[70]



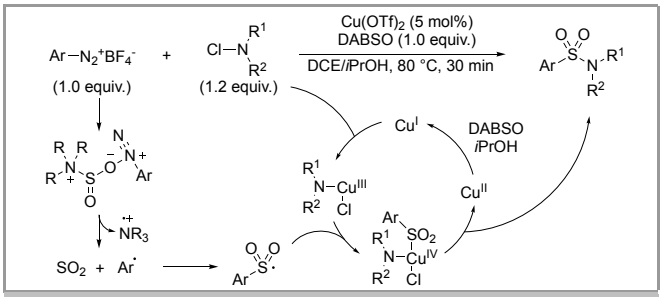
Scheme 23 A: Deprotonation or desilylation from cationic intermediates. B: Trapping of cationic intermediates using (intramolecular) nucleophiles.

Methods involving the trapping of the sulfonyl radical with other *in situ* generated radicals provides an alternative route to sulfonyl-containing products.[71] An example reported by Wu and co-workers uses *in situ* generated alkoxy radicals to prepare *O*-aminosulfonates, and further demonstrated their utility in the synthesis of sulfonamides (Scheme 24).[72]



Scheme 24 Trapping with *in situ*-generated radicals.

Metal catalysts can also be used to capture the sulfonyl radical intermediate. For example, Wu and co-workers used a copper catalyst in the synthesis of aryl sulfonamides using *N*-chloroamines (Scheme 25).[73] The proposed mechanism involves oxidative addition of the *N*-chloroamine to give a Cu(III)-intermediate. Subsequent capture of the sulfonyl radical gives a proposed Cu(IV)-intermediate, from which reductive elimination gives the sulfonamide product. This method provides the sulfonamide product in one-step, but has been shown to only be compatible with secondary chloramines. Sulfonyl radical capture by metal catalysts has also been used to prepare sulfones,[74] sulfonate esters,[75] and sulfonyl fluorides.[76]



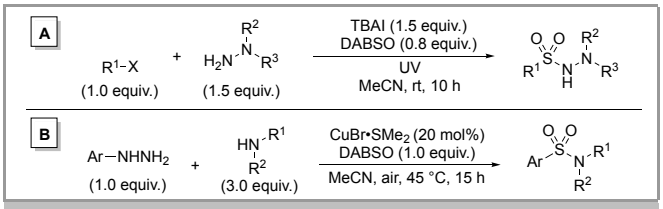
Scheme 25 Copper-catalyzed coupling of diazonium salts and *N*-chloroamines.

5.2 Other aryl radical precursors

Whilst a large body of research has been carried out using aryldiazonium salts, their relative instability and potentially explosive nature means the development of methods utilising alternative radical precursors is desirable.

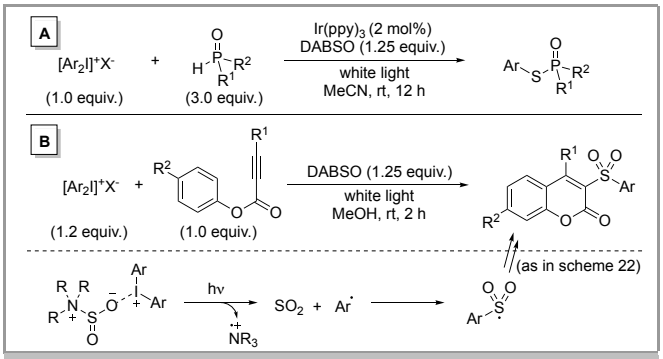
Aryl radicals can also be generated from C-X bond homolysis using UV light. Wu and co-workers demonstrated the preparation of *N*-aminosulfonamides from aryl halides, DABSO, hydrazines and TBAI (Scheme 26A).[77] Aryl chlorides, bromides and iodides were compatible with the methodology, and this chemistry was also found to be compatible with alkyl halides. A 5-*exo*-tet cyclization prior to SO_2 capture has also been used to prepare cyclized products.[778]Wu and co-workers demonstrated the use of aryl/alkyl halides in the preparation of sulfone products.[79]

In the presence of oxygen and copper, aryl radicals can be prepared from aryl hydrazines with loss of N_2. Wu and co-workers used aryl hydrazines in a preparation of aryl sulfonamides via capture of the sulfonyl radical with copper and reductive elimination with an amine (Scheme 26B).[80] The reaction was compatible with primary and secondary amines, and both electron-rich and electron-poor aryl hydrazines were tolerated. The authors later used a related radical generation to prepare β-hydroxysulfones from sulfonyl radical addition to alkenes and coupling with a peroxyl radical.[81]



Scheme 26 A: Preparation of *N*-aminosulfonamides via UV irradiation of aryl/alkyl halides. B: Cu-catalyzed preparation of aryl sulfonamides via radical generation from aryl hydrazines under aerobic conditions.

Aryl radicals can be generated from diaryliodonium salts by oxidative quenching of an excited photocatalyst. Wu and co-workers exploited this to prepare thiophosphates from diarylphosphine oxides using an Ir-photocatalyst (Scheme 27A).[82] Related methods were also developed for the preparation of sulfones.[83] Photoinduced catalyst-free methods were also developed for the generation of aryl radicals from diaryliodonium salts.[84] Manolikakes found that a photocatalyst was not required during their synthesis of sulfonylated coumarins (Scheme 27B).[84a] The authors proposed that visible light-induced SET from a charge-transfer complex that forms between DABSO and diaryliodonium salts generates aryl radicals.[84b]

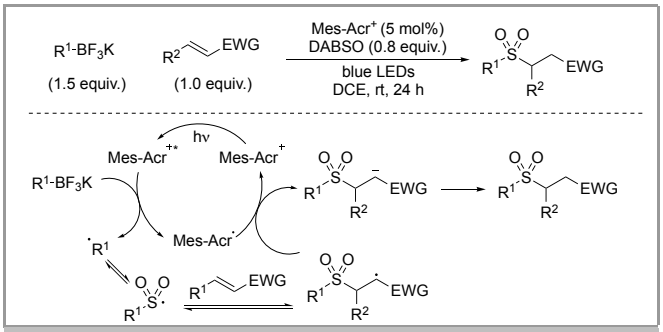


Scheme 27 A: Photocatalyzed synthesis of thiophosphates from diarylphosphine oxides, diaryliodonium salts and DABSO. B: Metal-free photoinduced synthesis of sulfonylated coumarins using diaryliodonium salts.

5.3 Alkyl radical precursors

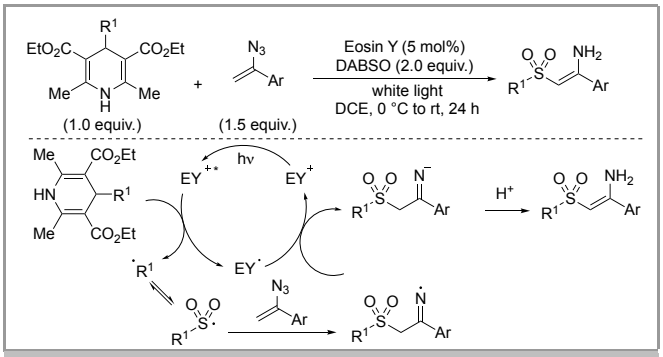
The preparation of diverse alkyl sulfonyl derivatives using the aforementioned methods is challenging due to poor reactivity or poor functional group tolerance. Recent developments in the generation of alkyl radicals under mild conditions in combination with DABSO has enabled the development of several new methodologies for the preparation of alkylsulfonyl products.

Reductive quenching of an excited photocatalyst can be used to generate radicals from potassium trifluoroborate salts. Wu and co-workers used this methodology with DABSO to form sulfonyl radicals, and addition to electron-poor alkenes followed by reduction and protonation gave alkyl sulfone products (Scheme 28).[85] Wu and co-workers later reported related procedures to prepare sulfones from trifluoroborate salts using alkynes and allyl halides.[86]



Scheme 28 Preparation of sulfones from alkyltrifluoroborates and alkenes.

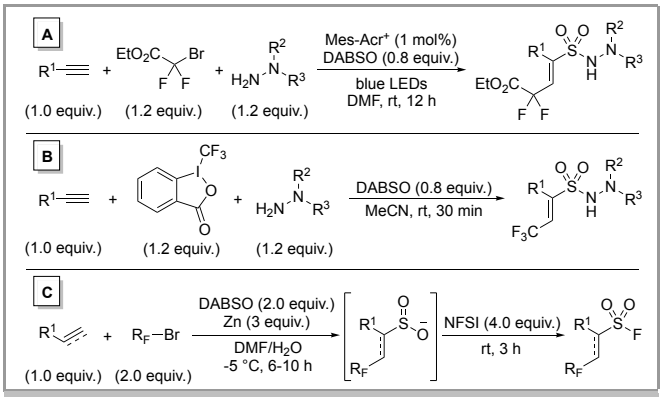
Alkyl radicals can also be generated from 4-substituted Hantzsch esters by reductive quenching of an excited photocatalyst. Wu and co-workers used this process in combination with DABSO and vinyl azides (Scheme 29).[87] Addition of a sulfonyl radical to the vinyl azide, followed by loss of N_2 and reduction gives enamine products. The transformation was shown to be compatible with both primary and secondary radicals, and variation of the aryl component of the vinyl azide was also tolerated. Sulfonyl radicals derived from 4-substituted Hantzsch esters could also be combined with electron-deficient alkenes to provide other sulfone products.[88]



Scheme 29 Preparation of sulfones from 4-substituted Hantzsch esters.

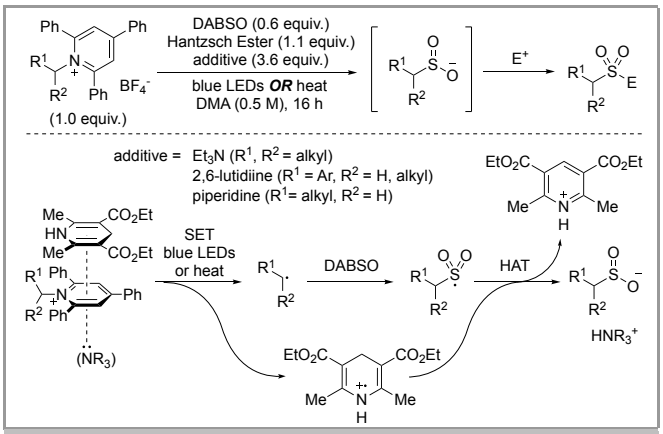
Vicinal di- or trifluoroalkylation and hydrosulfination of alkynes was explored by Wu and co-workers. For example, they developed a difluoromethylation procedure using a photocatalyst to prepare difluoroalkyl radicals from ethyl 2-bromo-2,2-difluoracetate (Scheme 30A).[89] SET from hydrazine to Togni's reagent generates trifluoromethyl radicals, which add to the alkyne and then to DABSO give a sulfonyl radical. Combination with the previously formed hydrazine radical gave an *N*-aminosulfonamide product (Scheme 30B). [90]

Liu and co-workers developed a related process using SET from zinc to generate the fluoroalkyl radicals (Scheme 30C).[91] Addition to an alkene or alkyne followed by trapping with a sulfonyl radical anion or addition to SO_2 and reduction by zinc gives a sulfinate product. The authors demonstrate compatibility with a wide variety of functional groups, using a diverse selection of fluoroalkyl bromides, and prepare a variety of sulfonyl fluorides and sulfones to demonstrated the versatility of this transformation.



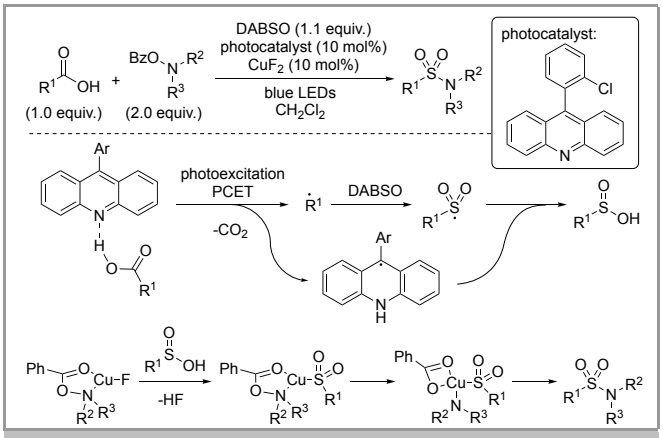
Scheme 30 A: Vicinal difluoroalkylation and aminosulfonylation of alkynes. B: Vicinal trifluoromethylation and aminosulfonylation of alkynes. C: Vicinal fluoroalkylation and fluorosulfonylation of alkenes and alkynes.

Willis and co-workers developed a method for the synthesis of alkyl sulfinates and their derivatives from Katritzky pyridinium salts (Scheme 31).[92] This method forms alkyl radicals by photo- or thermally induced SET from an EDA complex formed between a Katritzky salt, Hantzsch ester and an amine additive. This method was shown to have good functional group tolerance, and conditions were developed for use of α-secondary, α-primary and benzylic starting materials. The versatility of the procedure was demonstrated through the preparation of a variety of sulfones, sulfonamides, and sulfonyl fluorides.



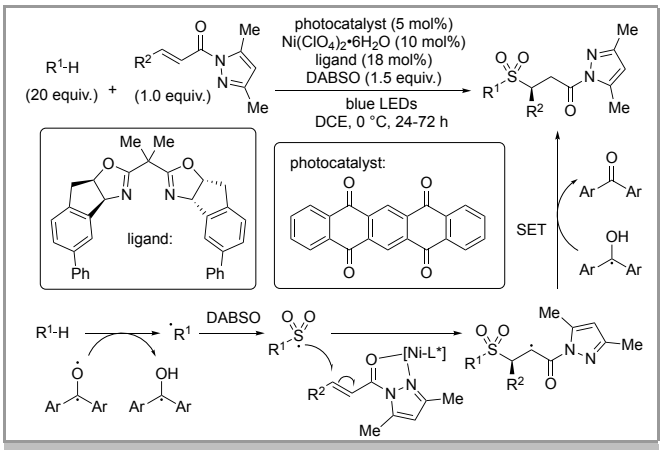
Scheme 31 Deaminative synthesis of alkyl sulfinates from Katritzky pyridinium salts via EDA complex formation.

Larionov and co-workers developed a decarboxylative route to sulfinates from carboxylic acids (Scheme 32).[93] Based on DFT computational studies, the mechanism is proposed to procced through the formation of a hydrogen-bonded complex between the carboxylic acid and an acridine photocatalyst. Photoexcitation results in a proton-coupled electron transfer (PCET), generating an alkyl radical with loss of CO_2. Alkyl radical addition and subsequent HAT from the dihydropyridine intermediate gives a sulfinic acid intermediate. Then copper-catalyzed S-N bond formation with either electrophilic N-centered coupling partners, or nucleophilic coupling partners in the presence of an oxidant, gives a sulfonamide or sulfonyl azide product. The authors demonstrated that the methodology was compatible with a broad variety of carboxylic acids and amines.



Scheme 32 Photocatalyzed decarboxylative synthesis of sulfonamides.

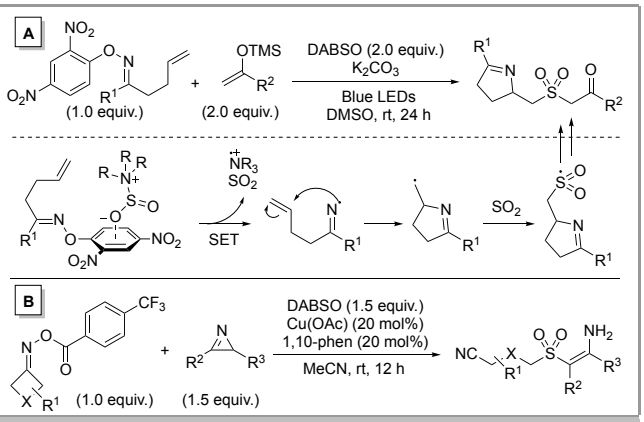
Gong and co-workers developed a photocatalyzed asymmetric C-H functionalization of alkanes (Scheme 33).[94] The photocatalyst is excited to its triplet state, and subsequent HAT from an alkane provides the alkyl radical, which is trapped by DABSO to give a sulfonyl radical. The chiral Ni complex coordinates to the α,β-unsaturated *N*-acylpyrazole, blocking one face to attack by sulfonyl radical. Sulfonyl radical addition sets the stereochemistry, and SET and proton transfer provides the enantioenriched sulfone products. The methodology was shown to be compatible benzylic, secondary and primary substrates, giving moderate to good yields, high regioselectivity, and good enantioselectivity of up to 95% ee.



Scheme 33 Photocatalytic asymmetric C-H sulfinylation of alkanes.

Formation of an EDA complex with DABSO and *O*-aryl oximes can enable generation of an *N*-centered radical by photoinduced SET and N-O bond homolysis. In a report from Wu and co-workers, a 5-*exo*-tet cyclisation followed by addition to DABSO and then to silyl enol ethers gave sulfonated 3,4-dihydro-2*H*-pyrroles (Scheme 34A).[95] Another method from Wu and co-workers uses 1,5-*H*-abstraction, followed by addition to DABSO and cyclisation to give 1*H*-benzo[*d*][1,2]thiazine 2,2-dioxide products.[96]

Metal catalyzed SET can be used to generate *N*-centered radicals from *N*-acyl oximes by N-O bond homolysis. Ring-opening results in a *C*-centered radical, and addition to SO_2 then generates a sulfonyl radical. Wu and co-workers used this method with a variety of radical traps, such as 2*H*-azirine,[97] to prepare sulfone products containing a nitrile functional group (Scheme 34B).[98]



Scheme 34 A: Photoinduced cyclization from *O*-aryl oximes. B: Metal-catalyzed cyclization from *O*-acyl oximes.

6 Conclusion

Whilst gaseous SO_2 is cheap and widely available, and the molecular orbital properties of SO_2 enable a variety of reactivity, its synthetic use has been limited. The introduction of DABSO as an SO_2 surrogate has enabled the rapid development of a broad range of new methods for the preparation of valuable pharmaceutically relevant products. These include the versatile syntheses of many diverse functional groups, or the preparation of complex sulfonyl-containing products. Whilst other SO_2 surrogates, such as inorganic metal sulfites, are also used by synthetic organic chemists, DABSO remains a popular choice, and new methods continue to be reported in the literature.

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Conflict of Interest

The authors declare no conflict of interest.

References

(1) (a) Ye, S.; Yang, M.; Wu, J. *Chem. Commun.* **2020**, *56*, 4145; (b) Patel, B. K.; Sahoo, A. K.; Dahiya, A.; Rakshit, A. *SynOpen* **2021**, *05*, 232; (c) Emmett, E. J.; Willis, M. C. *Asian. J. Org. Chem.* **2015**, *4*, 602.
(2) (a) Divers, E.; Ogawa, M. *J. Chem. Soc., Trans.* **1900**, *77*, 327; (b) Divers, E.; Ogawa, M. *J. Chem. Soc., Trans.* **1901**, *79*, 1099.
(3) (a) Burg, A. B. *J. Am. Chem. Soc.* **1943**, *65*, 1629; (b) Christian, S. D.; Grundnes, J. *Nature* **1967**, *214*, 1111; (c) Hata, T.; Kinumaki, S. *Nature* **1964**, *203*, 1378; (d) Faria, D. L. A.; Santos, P. S. *J. Raman Spectrosc.* **1988**, *19*, 471; (e) Kanamueller, J. M. *J. Inorg. Nucl. Chem.* **1971**, *33*, 4051; (f) Santos, P. S.; Lieder, R. *J. Mol. Struct.* **1986**, *144*, 39; (g) Byrd, W. E. *Inorg. Chem.* **1962**, *1*, 762; (h) Oh, J. J.; Labarge, M. S.; Matos, J.; Kampf, J. W.; Hillig, K. W.; Kuczkowski, R. L. *J. Am. Chem. Soc.* **1991**, *113*, 4732; (i) Wong, M. W.; Wiberg, K. B. *J. Am. Chem. Soc.* **1992**, *114*, 7527; (j) De Faria, D. L. A.; Santos, P. S. *Magn. Reson. Chem.* **1987**, *25*, 592.
(4) Eugene, F.; Langlois, B.; Laurent, E. *J. Org. Chem.* **1994**, *59*, 2599.
(5) Santos, P. S.; Mello, M. T. S. *J. Mol. Struct.* **1988**, *178*, 121.
(6) Nguyen, B.; Emmett, E. J.; Willis, M. C. *J. Am. Chem. Soc.* **2010**, *132*, 16372.
(7) Bischoff, L.; Martial, L. *Org. Synth.* **2013**, *90*, 301.
(8) Van Mileghem, S.; De Borggraeve, W. M. *Org Process Res Dev* . **2017**, *21*, 785.
(9) Woolven, H.; González-Rodríguez, C.; Marco, I.; Thompson, A. L.; Willis, M. C. *Org. Lett.* **2011**, *13*, 4876.
(10) (a) Hamada, T.; Yonemitsu, O. *Synthesis* **1986**, *10*, 852; (b) Pandya, R.; Murashima, T.; Tedeschi, L.; Barrett, A. G. M. *J. Org. Chem.* **2003**, *68*, 8274; (c) Wu, J.-P.; Emeigh, J.; Su, X.-P. *Org. Lett.* **2005**, *7*, 1223; (d) Truce, W. E.; Lyons, J. F. *J. Am. Chem. Soc.* **1951**, *73*, 126.
(11) Leontiev, A. V.; Rasika Dias, H. V.; Rudkevich, D. M. *Chem. Commun.* **2006**, 2887.
(12) Martial, L.; Bischoff, L. *Synlett* **2015**, *26*, 1225.
(13) Waldmann, C.; Schober, O.; Haufe, G.; Kopka, K. *Org. Lett.* **2013**, *15*, 2954.
(14) Deeming, A. S.; Russell, C. J.; Willis, M. C. *Angew. Chem. Int. Ed.* **2015**, *54*, 1168.
(15) Deeming, A. S.; Russell, C. J.; Hennessy, A. J.; Willis, M. C. *Org. Lett.* **2014**, *16*, 150.
(16) Rocke, B. N.; Bahnck, K. B.; Herr, M.; Lavergne, S.; Mascitti, V.; Perreault, C.; Polivkova, J.; Shavnya, A. *Org. Lett.* **2014**, *16*, 154.
(17) Chen, C. C.; Waser, J. *Org. Lett.* **2015**, *17*, 736.
(18) Emmett, E. J.; Hayter, B. R.; Willis, M. C. *Angew. Chem. Int. Ed.* **2013**, *52*, 12679.
(19) Cacchi, S.; Fabrizi, G.; Goggiamani, A.; Parisi, L. M.; Bernini, R. *J. Org. Chem.* **2004**, *69*, 5608.
(20) Lenstra, D. C.; Vedovato, V.; Ferrer Flegeau, E.; Maydom, J.; Willis, M. C. *Org. Lett.* **2016**, *18*, 2086.
(21) Lo, P. K. T.; Oliver, G. A.; Willis, M. C. *J. Org. Chem.* **2020**, *85*, 5753.
(22) Wang, T.; Wang, F.; Shen, J.; Pang, T.; Ren, Y.; Wu, B.; Zhang, X. *Tetrahedron Lett.* **2018**, *59*, 1183.
(23) Zhang, C.; Huang, J.; Ye, S.; Tang, J.; Wu, J. *Chem. Commun.* **2020**, *56*, 13852.
(24) Zhang, C.; Zhang, C.; Tang, J.; Ye, S.; Ma, M.; Wu, J. *Adv. Synth. Catal.* **2021**, *363*, 3109.
(25) Tsai, A. S.; Curto, J. M.; Rocke, B. N.; Dechert-Schmitt, A.-M. R.; Ingle, G. K.; Mascitti, V. *Org. Lett.* **2016**, *18*, 508.
(26) (a) Mingos, D. M. P. *Transition Met. Chem.* **1978**, *3*, 1; (b) Li, J.; Rogachev, A. Y. *Physical Chemistry Chemical Physics* **2015**, *17*, 1987.
(27) Gleu, K.; Breuel, W.; Rehm, K. *Z Anorg Allg Chem* **1938**, *235*, 201.
(28) (a) Vaska, L.; Bath, S. S. *J. Am. Chem. Soc.* **1966**, *88*, 1333; (b) Vaska, L.; Catone, D. L. *J. Am. Chem. Soc.* **1966**, *88*, 5324; (c) Levison, J. J.; Robinson, S. D. *Chem. Commun. (London)* **1967**, 198; (d) Kubas, G. J. *Acc. Chem. Res.* **1994**, *27*, 183; (e) Schenk, W. A. *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 98; (f) Kubas, G. J. *Inorg. Chem.* **1979**, *18*, 182.
(29) (a) Barnard, C. F. J. *Organometallics* **2008**, *27*, 5402; (b) Brennführer, A.; Neumann, H.; Beller, M. *Angew. Chem. Int. Ed.* **2009**, *48*, 4114.
(30) Klein, H. S. *Chem. Commun. (London)* **1968**, 377.
(31) (a) Keim, W.; Herwig, J. *J. Chem. Soc., Chem. Commun.* **1993**, 1592; (b) Herwig, J.; Keim, W. *Inorg. Chim. Acta* **1994**, *222*, 381; (c) Keim, W.; Herwig, J.; Pelzer, G. *J. Org. Chem.* **1997**, *62*, 422; (d) Wojcinski, L. M.; Boyer, M. T.; Sen, A. *Inorg. Chim. Acta* **1998**, *270*, 8; (e) Dzhemilev, U. M.; Kunakova, R. V. *J. Organomet. Chem.* **1993**, *455*, 1.
(32) Pelzer, G.; Keim, W. *J. Mol. Catal. A: Chem.* **1999**, *139*, 235.
(33) Emmett, E. J.; Richards-Taylor, C. S.; Nguyen, B.; Garcia-Rubia, A.; Hayter, B. R.; Willis, M. C. *Org. Biomol. Chem.* **2012**, *10*, 4007.
(34) Richards-Taylor, C. S.; Blakemore, D. C.; Willis, M. C. *Chem. Sci.* **2014**, *5*, 222.
(35) Richards-Taylor, C. S.; Willis, M. C. *Tetrahedron* **2021**, *83*, 131988.
(36) Ye, S.; Wu, J. *Chem. Commun.* **2012**, *48*, 7753.
(37) Ye, S.; Wang, H.; Xiao, Q.; Ding, Q.; Wu, J. *Adv. Synth. Catal.* **2014**, *356*, 3225.
(38) Emmett, E. J.; Hayter, B. R.; Willis, M. C. *Angew. Chem. Int. Ed.* **2014**, *53*, 10204.
(39) Shavnya, A.; Coffey, S. B.; Smith, A. C.; Mascitti, V. *Org. Lett.* **2013**, *15*, 6226.
(40) Willis, M.; Flegeau, E.; Harrison, J. *Synlett* **2015**, *27*, 101.
(41) Bajohr, J.; Diallo, A. G.; Whyte, A.; Gaillard, S.; Renaud, J.-L.; Lautens, M. *Org. Lett.* **2021**, *23*, 2797.
(42) (a) Dong, J.; Krasnova, L.; Finn, M. G.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2014**, *53*, 9430; (b) Barrow, A. S.; Smedley, C. J.; Zheng, Q.; Li, S.; Dong, J.; Moses, J. E. *Chem. Soc. Rev.* **2019**, *48*, 4731.
(43) Davies, A. T.; Curto, J. M.; Bagley, S. W.; Willis, M. C. *Chem. Sci.* **2017**, *8*, 1233.
(44) Lou, T. S. B.; Bagley, S. W.; Willis, M. C. *Angew. Chem. Int. Ed.* **2019**, *58*, 18859.
(45) Deeming, A. S.; Russell, C. J.; Willis, M. C. *Angew. Chem. Int. Ed.* **2016**, *55*, 747.
(46) Vedovato, V.; Talbot, E. P. A.; Willis, M. C. *Org. Lett.* **2018**, *20*, 5493.
(47) Zhu, H.; Shen, Y.; Deng, Q.; Huang, C.; Tu, T. *Chem. Asian J.* **2017**, *12*, 706.
(48) Wang, X.; Xue, L.; Wang, Z. *Org. Lett.* **2014**, *16*, 4056.
(49) (a) Zheng, D.; Chen, M.; Yao, L.; Wu, J. *Org. Chem. Front.* **2016**, *3*, 985; (b) Zheng, D.; Mao, R.; Li, Z.; Wu, J. *Org. Chem. Front.* **2016**, *3*, 359.
(50) Lo, P. K. T.; Chen, Y.; Willis, M. C. *ACS Catal.* **2019**, *9*, 10668.
(51) Gulbe, K.; Turks, M. R. *J. Org. Chem.* **2020**, *85*, 5660.

(52) Chen, Y.; Willis, M. C. *Chem. Sci.* **2017**, *8*, 3249.
(53) Adenot, A.; Anthore-Dalion, L.; Nicolas, E.; Berthet, J.-C.; Thuéry, P.; Cantat, T. *Chem. Eur. J.* **2021**, in press; DOI: 10.1002/chem.202103371.
(54) Meerwein, H.; Dittmar, G.; Göllner, R.; Hafner, K.; Mensch, F.; Steinfort, O. *Chem. Ber.* **1957**, *90*, 841.
(55) Dong, D. Q.; Han, Q. Q.; Yang, S. H.; Song, J. C.; Li, N.; Wang, Z. L.; Xu, X. M. *ChemistrySelect* **2020**, *5*, 13103.
(56) (a) Qiu, G.; Zhou, K.; Gao, L.; Wu, J. *Org. Chem. Front.* **2018**, *5*, 691; (b) Hofman, K.; Liu, N. W.; Manolikakes, G. *Chem. Eur. J.* **2018**, *24*, 11852; (c) Ye, S.; Li, X.; Xie, W.; Wu, J. *Eur. J. Org. Chem.* **2019**, 1274.
(57) Zheng, D.; An, Y.; Li, Z.; Wu, J. *Angew. Chem. Int. Ed.* **2014**, *53*, 2451.
(58) (a) Liu, X.; Li, W.; Zheng, D.; Fan, X.; Wu, J. *Tetrahedron* **2015**, *71*, 3359; (b) Zheng, D.; Kuang, Y.; Wu, J. *Org. Biomol. Chem.* **2015**, *13*, 10370; (c) Sheng, J.; Li, Y.; Qiu, G. *Org. Chem. Front.* **2017**, *4*, 95.
(59) Zheng, D.; Li, Y.; An, Y.; Wu, J. *Chem. Commun* **2014**, *50*, 8886.
(60) An, Y.; Zheng, D.; Wu, J. *Chem. Commun.* **2014**, *50*, 11746.
(61) Fan, W.; Su, J.; Shi, D.; Feng, B. *Tetrahedron* **2015**, *71*, 6740.
(62) Mao, R.; Yuan, Z.; Zhang, R.; Ding, Y.; Fan, X.; Wu, J. *Org. Chem. Front.* **2016**, *3*, 1498.
(63) Zheng, D.; Yu, J.; Wu, J. *Angew. Chem. Int. Ed.* **2016**, *55*, 11925.
(64) Das, P.; Das, S.; Varalaxmi, K.; Jana, R. *Adv. Synth. Catal.* **2021**, *363*, 575.
(65) (a) Zhang, J.; An, Y.; Wu, J. *Chem. Eur. J.* **2017**, *23*, 9477; (b) Zhou, K.; Zhang, J.; Lai, L.; Cheng, J.; Sun, J.; Wu, J. *Chem. Commun.* **2018**, *54*, 7459; (c) Kumar, M.; Ahmed, R.; Singh, M.; Sharma, S.; Thatikonda, T.; Singh, P. P. *J. Org. Chem.* **2020**, *85*, 716; (d) Jakkampudi, S.; Sakkani, N.; Zhao, J. C. G. *Tetrahedron Lett.* **2021**, *76*, 153229.
(66) (a) Herrera, F.; Luna, A.; Almendros, P. *Org. Lett.* **2020**, *22*, 9490; (b) Zhu, T.-H.; Zhang, X.-C.; Zhao, K.; Loh, T.-P. *Org. Chem. Front.* **2019**, *6*, 94; (c) Zhu, T. H.; Zhang, X. C.; Cui, X. L.; Zhang, Z. Y.; Jiang, H.; Sun, S. S.; Zhao, L. L.; Zhao, K.; Loh, T. P. *Adv. Synth. Catal.* **2019**, *361*, 3593.
(67) Liu, T.; Zheng, D.; Ding, Y.; Fan, X.; Wu, J. *Chem. Asian J.* **2017**, *12*, 465.
(68) (a) Xiang, Y.; Kuang, Y.; Wu, J. *Chem. Eur. J.* **2017**, *23*, 6996; (b) Yu, J.; Mao, R.; Wang, Q.; Wu, J. *Org. Chem. Front.* **2017**, *4*, 617; (c) He, F.-S.; Wu, Y.; Zhang, J.; Xia, H.; Wu, J. *Org. Chem. Front.* **2018**, *5*, 2940; (d) Zong, Y.; Lang, Y.; Yang, M.; Li, X.; Fan, X.; Wu, J. *Org. Lett.* **2019**, *21*, 1935.
(69) (a) Zhang, J.; Zhou, K.; Wu, J. *Org. Chem. Front.* **2018**, *5*, 813; (b) Zhou, K.; Xia, H.; Wu, J. *Org. Chem. Front.* **2017**, *4*, 1121; (c) Liu, T.; Zheng, D.; Li, Z.; Wu, J. *Adv. Synth. Catal.* **2018**, *360*, 865; (d) Zhou, K.; Zhang, J.; Qiu, G.; Wu, J. *Org. Lett.* **2019**, *21*, 275; (e) He, F. S.; Cen, X.; Yang, S.; Zhang, J.; Xia, H.; Wu, J. *Org. Chem. Front.* **2018**, *5*, 2437.
(70) (a) Wang, H.; Sun, S.; Cheng, J. *Org. Lett.* **2017**, *19*, 5844; (b) Liu, T.; Zheng, D.; Wu, J. *Org. Chem. Front.* **2017**, *4*, 1079; (c) Wang, Y.; Deng, L.; Zhou, J.; Wang, X.; Mei, H.; Han, J.; Pan, Y. *Adv. Synth. Catal.* **2018**, *360*, 1060; (d) Wang, H.; Wang, B.; Sun, S.; Cheng, J. *Org. Chem. Front.* **2018**, *5*, 2547; (e) Wang, X.; Li, Y.; Qiu, G.; Wu, J. *Org. Chem. Front.* **2018**, *5*, 2555; (f) Zhang, J.; Zhang, F.; Lai, L.; Cheng, J.; Sun, J.; Wu, J. *Chem. Commun.* **2018**, *54*, 3891; (g) Chen, H.; Liu, M.; Qiu, G.; Wu, J. *Adv. Synth. Catal.* **2019**, *361*, 146; (h) Yao, Y.; Yin, Z.; He, F.-S.; Qin, X.; Xie, W.; Wu, J. *Chem. Commun.* **2021**, *57*, 2883.
(71) (a) Zhou, K.; Chen, M.; Yao, L.; Wu, J. *Org. Chem. Front.* **2018**, *5*, 371; (b) Li, G.; Gan, Z.; Kong, K.; Dou, X.; Yang, D. *Adv. Synth. Catal.* **2019**, *361*, 1808; (c) Nair, A. M.; Kumar, S.; Halder, I.; Volla, C. M. R. *Org. Biomol. Chem.* **2019**, *17*, 5897.
(72) Liu, T.; Zheng, D.; Li, Z.; Wu, J. *Adv. Synth. Catal.* **2017**, *359*, 2653.
(73) Zhang, F.; Zheng, D.; Lai, L.; Cheng, J.; Sun, J.; Wu, J. *Org. Lett.* **2018**, *20*, 1167.
(74) (a) Liu, T.; Zhou, W.; Wu, J. *Org. Lett.* **2017**, *19*, 6638; (b) Li, G.-H.; Dong, D.-Q.; Deng, Q.; Yan, S.-Q.; Wang, Z.-L. *Synthesis* **2019**, *51*, 3313.
(75) (a) Wang, Y.; Deng, L.; Deng, Y.; Han, J. *J. Org. Chem.* **2018**, *83*, 4674; (b) Idris, M. A.; Lee, S. *Org. Lett.* **2021**, *23*, 4516.
(76) Liu, Y.; Yu, D.; Guo, Y.; Xiao, J.-C.; Chen, Q.-Y.; Liu, C. *Org. Lett.* **2020**, *22*, 2281.
(77) Li, Y.; Zheng, D.; Li, Z.; Wu, J. *Org. Chem. Front.* **2016**, *3*, 574.
(78) Zhou, K.; Xia, H.; Wu, J. *Org. Chem. Front.* **2016**, *3*, 865.
(79) (a) Gong, X.; Ding, Y.; Fan, X.; Wu, J. *Adv. Synth. Catal.* **2017**, *359*, 2999; (b) Zhou, K.; Liu, J. B.; Xie, W.; Ye, S.; Wu, J. *Chem. Commun.* **2020**, *56*, 2554; (c) Ye, S.; Zhou, K.; Rojsitthisak, P.; Wu, J. *Org. Chem. Front.* **2020**, *7*, 14.
(80) Du, B.; Wang, Y.; Sha, W.; Qian, P.; Mei, H.; Han, J.; Pan, Y. *Asian. J. Org. Chem.* **2017**, *6*, 153.
(81) Zhang, J.; Xie, W.; Ye, S.; Wu, J. *Org. Chem. Front.* **2019**, *6*, 2254.
(82) Gong, X.; Chen, J.; Liu, J.; Wu, J. *Org. Chem. Front.* **2017**, *4*, 2221.
(83) (a) Sun, D.; Yin, K.; Zhang, R. *Chem. Commun.* **2018**, *54*, 1335; (b) Breton-Patient, C.; Naud-Martin, D.; Mahuteau-Betzer, F.; Piguel, S. *Eur. J. Org. Chem.* **2020**, *2020*, 6653.
(84) (a) Chen, Z.; Liu, N.-W.; Bolte, M.; Ren, H.; Manolikakes, G. *Green Chem.* **2018**, *20*, 3059; (b) Liu, N.-W.; Chen, Z.; Herbert, A.; Ren, H.; Manolikakes, G. *Eur. J. Org. Chem.* **2018**, *2018*, 5725.
(85) Liu, T.; Li, Y.; Lai, L.; Cheng, J.; Sun, J.; Wu, J. *Org. Lett.* **2018**, *20*, 3605.
(86) (a) Liu, T.; Ding, Y.; Fan, X.; Wu, J. *Org. Chem. Front.* **2018**, *5*, 3153; (b) Ye, S.; Li, X.; Xie, W.; Wu, J. *Asian. J. Org. Chem.* **2019**, *8*, 893.
(87) Wang, X.; Li, H.; Qiu, G.; Wu, J. *Chem. Commun.* **2019**, *55*, 2062.
(88) Wang, X.; Yang, M.; Xie, W.; Fan, X.; Wu, J. *Chem. Commun.* **2019**, *55*, 6010.
(89) Xiang, Y.; Li, Y.; Kuang, Y.; Wu, J. *Chem. Eur. J.* **2017**, *23*, 1032.
(90) Li, Y.; Xiang, Y.; Li, Z.; Wu, J. *Org. Chem. Front.* **2016**, *3*, 1493.
(91) Liu, Y.; Lin, Q.; Xiao, Z.; Zheng, C.; Guo, Y.; Chen, Q.-Y.; Liu, C. *Chem. Eur. J.* **2019**, *25*, 1824.
(92) Andrews, J. A.; Pantaine, L. R. E.; Palmer, C. F.; Poole, D. L.; Willis, M. C. *Org. Lett.* **2021**, *23*, 8488.
(93) Nguyen, V. T.; Haug, G. C.; Nguyen, V. D.; Vuong, N. T. H.; Arman, H. D.; Larionov, O. V. *Chem. Sci.* **2021**, *12*, 6429.
(94) Cao, S.; Hong, W.; Ye, Z.; Gong, L. *Nat. Commun.* **2021**, *12*, 2377.
(95) Mao, R.; Yuan, Z.; Li, Y.; Wu, J. *Chem. Eur. J.* **2017**, *23*, 8176.
(96) Li, Y.; Mao, R.; Wu, J. *Org. Lett.* **2017**, *19*, 4472.
(97) Zhang, J.; Yang, M.; Liu, J.-B.; He, F.-S.; Wu, J. *Chem. Commun.* **2020**, *56*, 3225.
(98) Tu, X.; Huang, J.; Xie, W.; Zhu, T.; Wu, J. *Org. Chem. Front.* **2021**, *8*, 1789.

Biosketches

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