CHEMICAL REVIEWS

Review

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Bond-Forming and -Breaking Reactions at Sulfur(IV): Sulfoxides, Sulfonium Salts, Sulfur Ylides, and Sulfinate Salts

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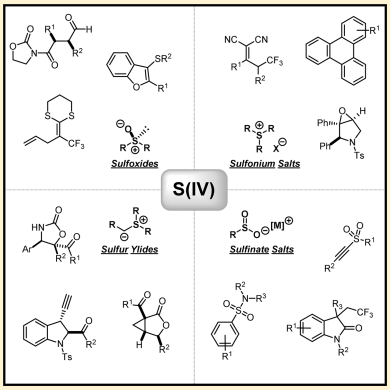
ABSTRACT: Organosulfur compounds have long played a vital role in organic chemistry and in the development of novel chemical structures and architectures. Prominent among these organosulfur compounds are those involving a sulfur(IV) center, which have been the subject of countless investigations over more than a hundred years. In addition to a long list of textbook sulfur-based reactions, there has been a sustained interest in the chemistry of organosulfur(IV) compounds in recent years. Of particular interest within organosulfur chemistry is the ease with which the synthetic chemist can effect a wide range of transformations through either bond formation or bond cleavage at sulfur. This review aims to cover the developments of the past decade in the chemistry of organic sulfur(IV) molecules and provide insight into both the wide range of reactions which critically rely on this versatile element and the diverse scaffolds that can thereby be synthesized.



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1. INTRODUCTION

Since the early days of synthetic organic chemistry, organosulfur reactivity has occupied a prominent role. Its impact on the discipline can be highlighted by the sheer number of named reactions based on the rich chemistry of this element. Apart from the range of sulfide- and sulfone-based reactions (not covered in this review article), the chemistry of sulfur at the oxidation state +IV has been extensively studied. This research has led to the development of a variety of highly useful transformations, including (but not limited to) venerable reactions such as the Pummerer rearrangement,[1−5] the Mislow−Braverman−Evans rearrangement,[6,7] the suite of Swern- and Kornblum-type oxidation reactions,[8−11] the Johnson−Corey−Chaykovsky epoxidation and cyclopropanation,[12−14] the Stevens rearrangement,[15] and the Gassman indole synthesis.[16]

Focusing on the four major groups of organosulfur(IV) compounds carrying S−C and S−O bonds, namely sulfoxides, sulfonium salts, sulfur ylides, and sulfinate salts, this review article aims to provide an overview of a decade of research up to October 2018 that has led to the development of novel reactions and the enhancement of pre-existing protocols and textbook transformations. We center our attention on reactions that involve either bond formation or bond cleavage at sulfur, thereby excluding sulfoxide-based ligands and auxiliaries (both previously reviewed: refs 17, 18, and 19 as well as 20 and 21, respectively). Additional classes of sulfur species carrying bonds to other elements (such as the S−N of sulfylimines) are not covered.

The presentation chosen focuses on new reactivity and highlights methods for the formation of C−C and C−S bonds, the synthesis of a wide range of heterocycles and, where applicable, research that has led to the development of stereoselective processes and their application in natural product synthesis.

Owing to the diverse nature of the functional groups discussed within this review, each section is accompanied by an individual brief introduction, providing context and setting the scene for the modern organosulfur(IV) chemistry presented therein.

2. SULFOXIDES

2.1. Pummerer Reactions

The venerable Pummerer rearrangement is perhaps the most well-known reaction of sulfoxides and has been the subject of several reviews in the past.[1−5] Since its discovery, it has inspired and intrigued many chemists and led to the development of numerous extensions, applications, and different modifications. Depending on the substrate substitution, different pathways are available upon activation of the sulfoxide with a suitable electrophile; these are summarized in Scheme 1. In the classical Pummerer reaction, a proton α- to the sulfur of sulfonium species **1** is abstracted and nucleophilic attack leads to α-substituted sulfides. As the nucleophile attacks a position which was previously nucleophilic in the sulfoxide starting material, this can also be considered an Umpolung process. If instead nucleophilic attack on **1** occurs directly on sulfur, an interrupted Pummerer reaction is observed and numerous applications have emerged from the resulting intermediate. Similarly, attack on the adjacent carbon in S_N1 or S_N2 fashion leads to the Pummerer fragmentation pathway.

Aromatic sulfoxides can be further substituted by means of the aromatic Pummerer reaction. With an acidic hydrogen on a substituent, nucleophilic attack will occur in *meta*-position to the sulfoxide, whereas otherwise *ortho*- or *para*-substitution is observed.

As is the case for alkyl sulfoxides, activated vinyl sulfoxides offer several pathways for attack of a nucleophile. Deprotonation of the γ-position and consequent nucleophilic addition to the same carbon is referred to as the vinylogous Pummerer reaction. Alternatively, direct nucleophilic attack on the double bond leads to the pathway of the extended Pummerer reaction. If a second nucleophilic addition occurs at the α-position of this intermediate (often with the same nucleophile), the reaction is also called additive Pummerer reaction.

The following sections will discuss the more recent applications and developments of the Pummerer reaction.

2.1.1. Classical Pummerer and Pummerer Fragmentation Reactions. Sulfoxides display tetrahedral geometry with one lone pair located on sulfur, and, providing that the two moieties on sulfur are different, are chiral compounds. In the classical Pummerer reaction, the activation of chiral sulfoxides with acetic anhydride (acetate thereby serving as the subsequent nucleophile) usually affords racemic α-acetoxysulfides. However, work by Nagao and co-workers showed that modification of the reaction conditions allowed for the reaction to be performed in a stereoselective fashion (Scheme 2).[22] Key to obtaining products in high enantioselectivities was the use of an electrophilic activator such as TMSOTf as well as an amide as additive or solvent. To gain additional insight into the origin of stereoselectivity, the mechanism was later investigated by Thiel et al., employing computational studies.[23] The electrophilic activator was found to have great influence by lowering the energy barrier for the acylation of the sulfoxide in the rate determining step. Equally as important is its role in trapping the forming acetate, thus preventing the formation of achiral sulfurane **6**. Deprotonation of the sulfonium intermediate leads to sulfonium ylide **7**, still

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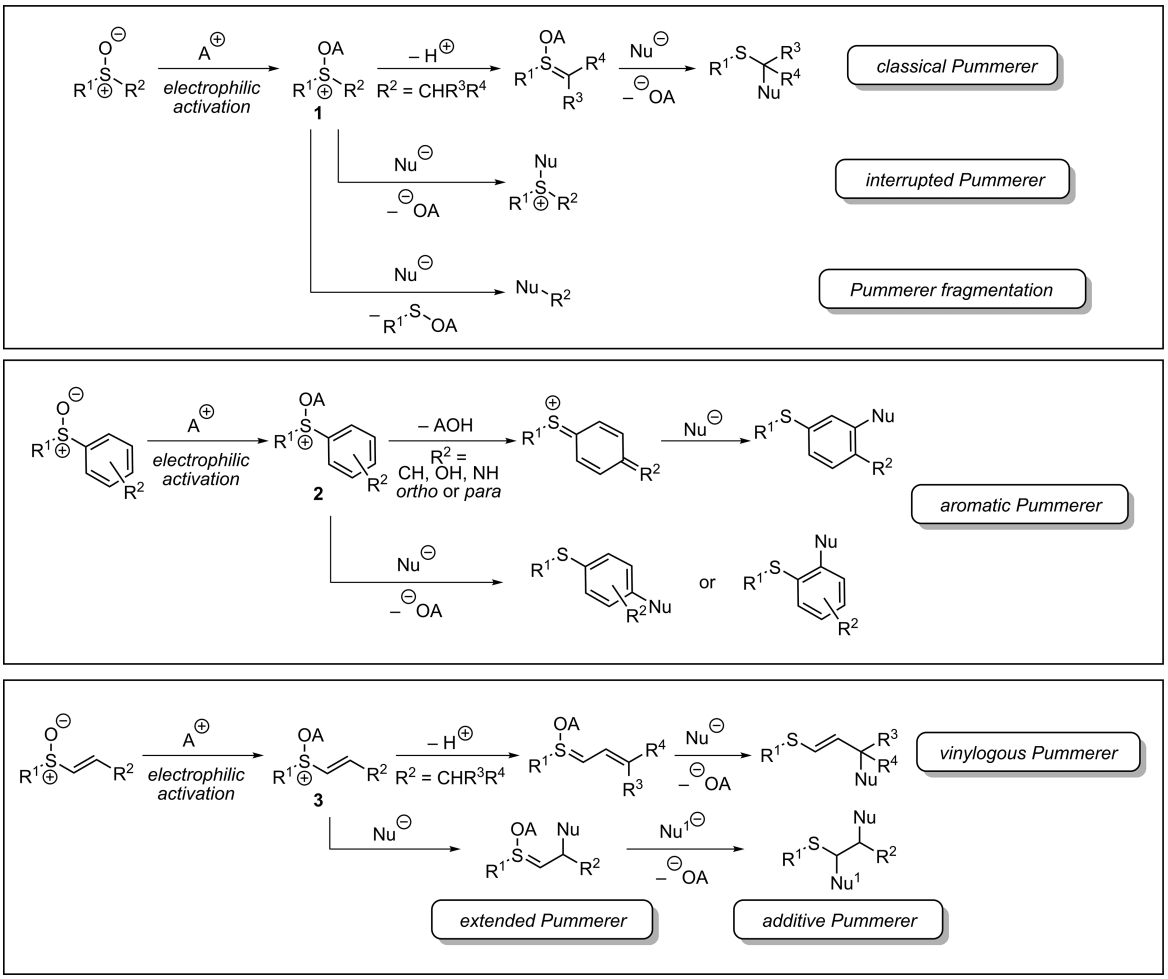
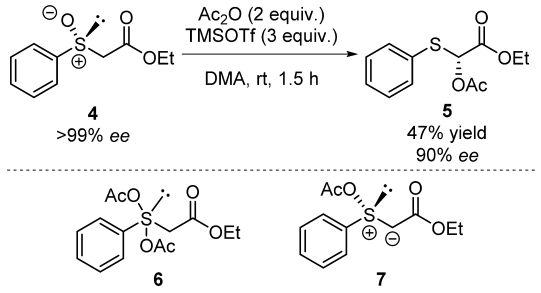
Scheme 1. Pummerer Reaction Types Depending on the Sulfoxide Substituent



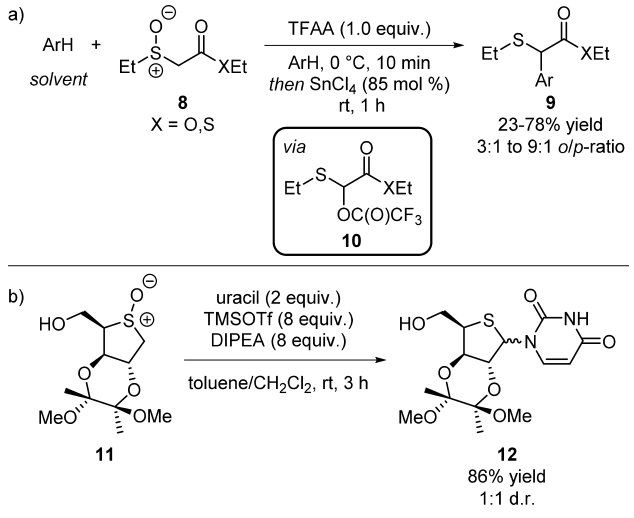
Scheme 2. Stereoselective Pummerer Reaction Studied Computationally by Thiel and Co-workers[23]



preserving the chirality on sulfur. A concerted cyclic acetate transfer is responsible for the observed chirality preservation and yields the α-acetoxysulfides **5**. It was suggested that the amide additive modulates the Lewis acidity of TMSOTf and prevents extensive racemization of the products rather than being involved in the rate-determining step itself.

Marzorati and co-workers compared the use of thioesters and sulfones to commonly used esters, as adjacent electron-withdrawing substituents, in the intermolecular Pummerer-mediated arylation with arenes (Scheme 3a).[24] Consistent with literature precendent, the reaction rate was found to be much higher for thioesters. However, the yields and ratios obtained remain similar to those observed when esters are employed. In

Scheme 3. Introduction of Arenes and Bases through a Classical Pummerer Reaction



the first reaction step, **10** is formed rapidly upon exposure of **8** to trifluoroacetic anhydride. Addition of a Lewis acid then facilitates the formation of the thionium ion prior to electrophilic aromatic substitution (S_EAr) to afford **9**.

In their synthesis of albomycin derivatives, aiming at the development of novel potent antimicrobial agents, He and co-

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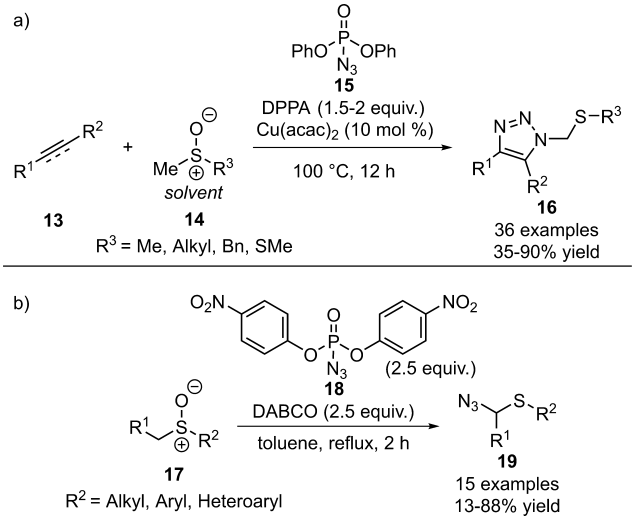
workers recently used the classical Pummerer reaction to introduce the DNA-base uracil into the thioribose structure. (Scheme 3b).[25] In this case, the silylating agent TMSOTf was used for electrophilic activation of the sulfoxide, conditions commonly used in combination with nucleobases.[26,27] Competitive nucleophilic addition of triethylamine was observed, motivating the use of the more hindered Hünig's base (DIPEA).

The use of azides as nucleophiles in the Pummerer reaction was established in a direct fashion by the group of Jiao (Scheme 4a).[28] The authors employed diphenylphosphoryl

Scheme 4. Pummerer Reaction with Azides

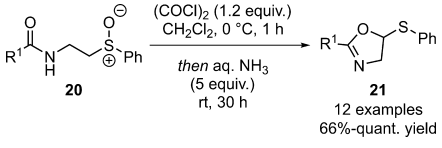


azide (DPPA, **15**) as a single reagent serving both as the electrophilic activator of the sulfoxide and as the azide source. In a one-pot procedure, the transiently formed α-azidosulfides were subjected to a 1,3-dipolar cycloaddition with alkynes (under inert conditions) or alkenes (under an oxidative atmosphere), leading to triazole products (**16**). Later, Matsugi et al. used a more electrophilic DPPA derivate (**18**) to broaden the scope of sulfoxides that could be employed (Scheme 4b).[29] A number of azidomethylsulfides (**19**) were successfully formed, while a range of unsuccessful substrates provided deeper understanding of the limitations of the method.

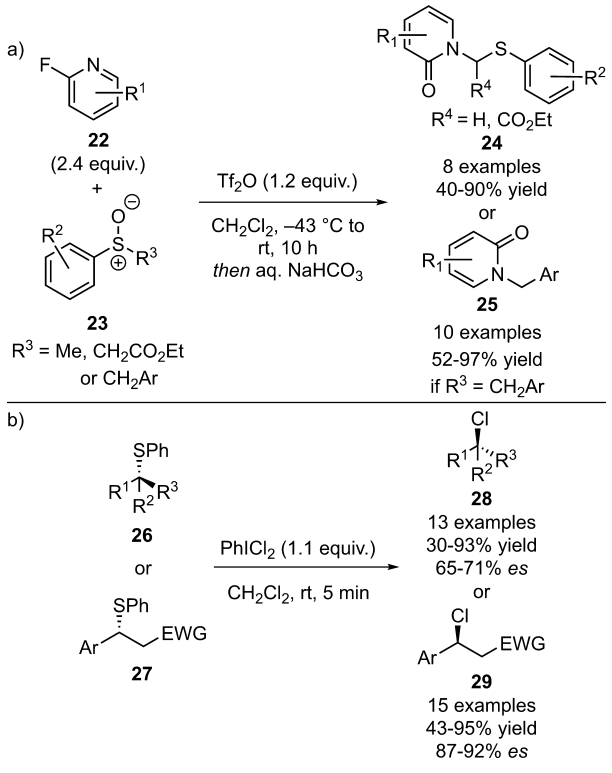
Another application of the Pummerer reaction was presented by the group of Gamba-Sánchez, accessing heterocycles.[30] They reported the synthesis of oxazolines (**21**) from β-amidosulfoxides (**20**), using oxalyl chloride (Scheme 5). In this reaction, the initially formed α-chlorosulfides readily undergo cyclization upon addition of aqueous ammonia to afford oxazolines in good to excellent yields.

The addition of 2-fluoropyridine to an *S*-methylthionium intermediate has been shown to yield 2-pyridones (**24**) (Scheme 6a).[31] Interestingly, upon changing the alkyl substituent of the sulfoxide to a benzyl moiety, the Pummerer

Scheme 5. Synthesis of Oxazolines via Pummerer Reaction



Scheme 6. Classical Pummerer Reaction and Pummerer Fragmentations That Lead to C−S Bond Cleavage



fragmentation became more favorable and direct nucleophilic displacement after activation led to desulfurated alkylation products (**25**). With 2-chloropyridines, the respective pyridinium salts could be isolated (not shown). A similar Pummerer fragmentation of a sulfonium species was reported by Adamo and co-workers.[32] In their work, a sulfur(IV) species was displaced by chloride after the treatment of phenyl sulfides with (dichloroiodo)benzene (Scheme 6b). A broad number of secondary and tertiary sulfides underwent nucleophilic substitution and the chloride products (**28** and **29**) could be isolated in good yields, even in instances where different electron-withdrawing groups would otherwise threaten elimination.

Another example of displacement of the sulfoxide group was described by Yorimitsu and co-workers during their work with 1,3-dithiane 1-oxide deriviatives (Scheme 7).[33] When **30** was treated with TFAA at 0 °C, clean cyclization of the carbamate onto the thionium intermediate **32** and subsequent elimination of cyclic disulfide **33** led to the protected indole product **31** in 92% yield.

2.1.2. Alternative Activation Strategies. Over the last decades, many different reaction conditions have been developed for the suite of Pummerer reactions, relying on a broad range of activating agents. Most commonly, acid anhydrides such as TFAA are used for electrophilic activation, but many other electrophiles, such as Brønsted or Lewis acids or even silylating agents[26,27] can be used to initiate the reaction. In some cases, the reaction conditions can be crucial for the success of the reaction, as was shown by Kuhakarn and co-workers in their synthesis of indolizidines (Scheme 8a).[34] On the basis of conditions developed in Kita's pioneering work on the synthesis on lactams,[35] *O*-silyated ketene acetals and catalytic amounts of zinc diiodide proved superior to other

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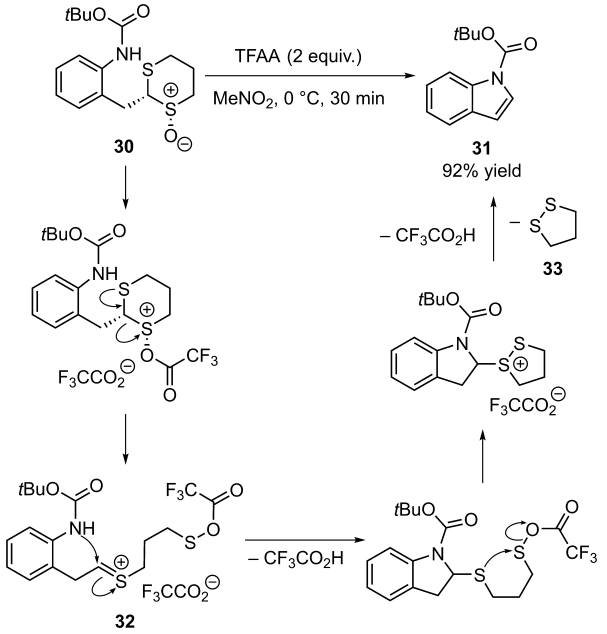
Scheme 7. Yorimitsu's Double Pummerer Fragmentation Sequence



Pummerer conditions to form the cyclized product. An example that a slight change of the conditions can lead to different regioselectivity was presented by Aucagne and co-workers.[36] In their work on sulfinylmethyl *C*-glycosides **37**, they were able to show that, by using either TFAA or the ketene acetal, opposite regioselectivities were observed, favoring attack on the methylene or methyl moieties of the sulfoxide, respectively (Scheme 8b).

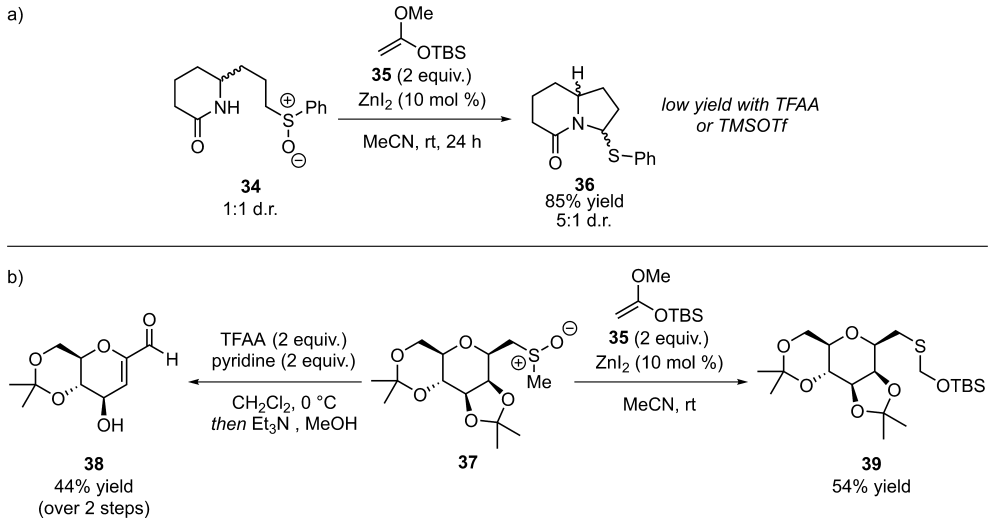
Arguably, one limitation of Pummerer-type reactions is the requirement for strong electrophilic activators to generate the electrophilic thionium intermediate, which in turn limits the scope of tolerated nucleophiles. Mendoza and co-workers recently developed a base-promoted Pummerer reaction which is even compatible with Grignard reagents as nucleophiles.[37] On the basis of seminal work by Kobayashi et al.,[38] magnesium amides **41** were found to be ideal bases for the conversion of sulfoxides **40** into Pummerer-derived products with only small amounts of dimerization and essentially no sulfoxide–magnesium exchange (for more detail on this process, see section 2.4) as the competing side reaction (Scheme 9a).

The nature of the amide base as well as the ratio of Mg to Li were found to be crucial. Deuterium-labeling studies revealed that the base does not deprotonate the sulfoxide in the absence of the Grignard reagent (Scheme 9b). A large variety of aryl, alkenyl, alkynyl, or alkyl nucleophiles including bulky teriary alkyl substituents were successfully introduced to the α-position (Scheme 9c). Interestingly, when an optically enriched chiral sulfoxide (**44**) was used, the product **46** was obtained with 40% enantiomeric excess, suggesting the intermediacy of a closed ion pair as well as hinting at possible future more enantioselective processes (Scheme 9d). Later, the same group developed a one-pot oxidation-base promoted Pummerer reaction protocol (Scheme 10).[39] The authors were able to demonstrate that simple evaporation was perfectly suited as the workup for the first step, and as little as 1.05 equiv of the respective Grignard reagent sufficed to obtain yields of **48** comparable with those of a two-step protocol. Although the yields were only moderate, a conceptually intriguing iterative process that progressively builds up the alkyl substituent of a given sulfide of interest was expounded.

In an alternative approach, Pappo et al. demonstrated that the Pummerer reaction of β-ketosulfoxides **49** can be promoted by catalytic amounts of $Cu(OTf)_2$.[40] In nitromethane at elevated temperatures, the formed thionium intermediate could be condensed with β-ketoesters (**50**) and phenol derivatives or reacted with tetraallylsilane (Scheme 11). The proposed mechanism involves the formation of triflic acid to activate the sulfoxide, and the elimination of water, forming the key thionium ion intermediate.

2.1.3. Nonsulfoxide Thionium Chemistry. A pivotal intermediate in several Pummerer-type reactions is the thionium ion, which is usually formed upon deprotonation of the α-carbon of the activated sulfoxide. The consideration of alternative means to access that thionium intermediate broadens the scope of Pummerer-type reactions considerably. Examples involve the condensation of an aldehyde and a thiol (Scheme 12, pathway A), ionization of dithioketals (pathway B) or oxidative pathways including hydride-abstraction from sulfides or oxidation and elimination (pathway C). Even

Scheme 8. *O*-Silylated Ketene Acetal Initiated Pummerer Reactions



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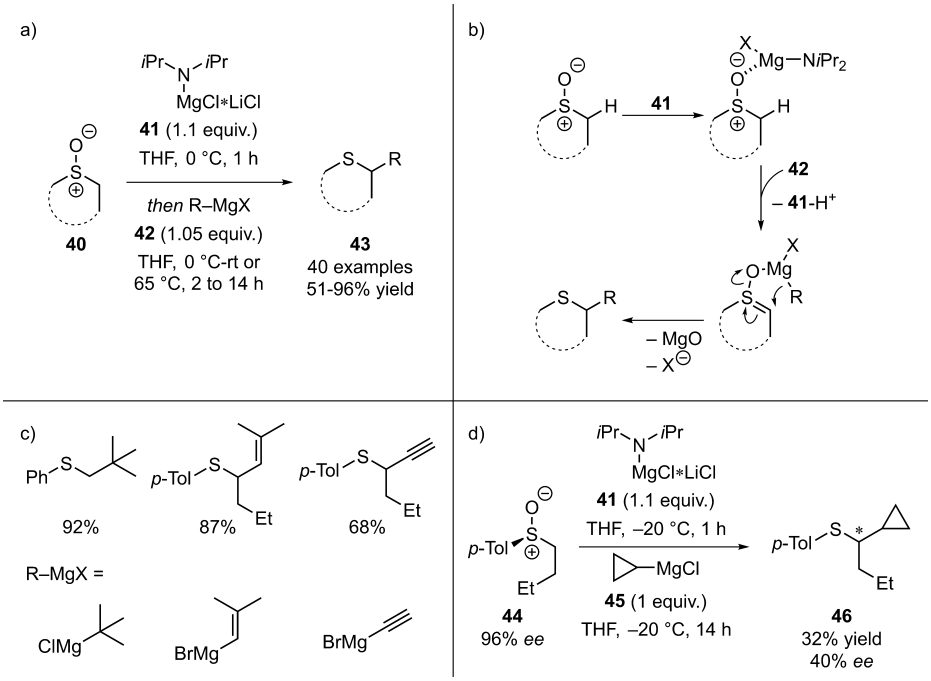
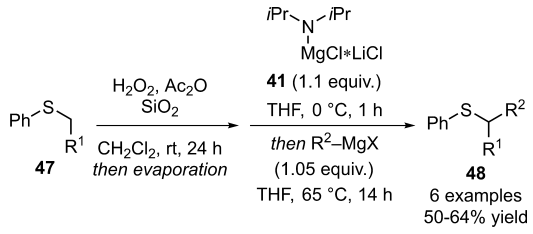
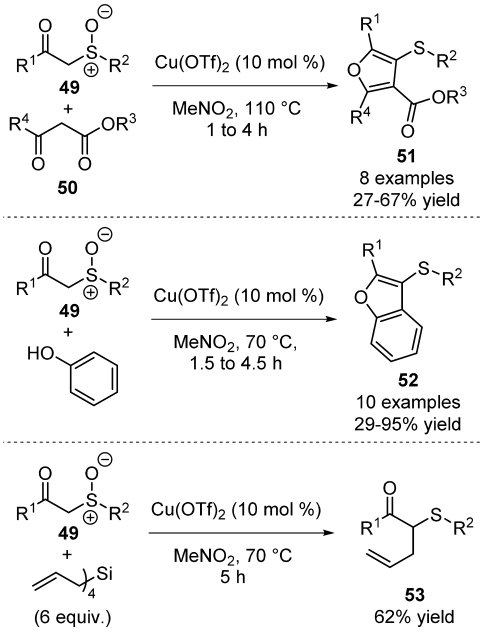
Scheme 9. Mendoza's Base-Promoted Pummerer Reaction



Scheme 10. One-Pot Procedure for Oxidation and Base-Promoted Pummerer Reaction

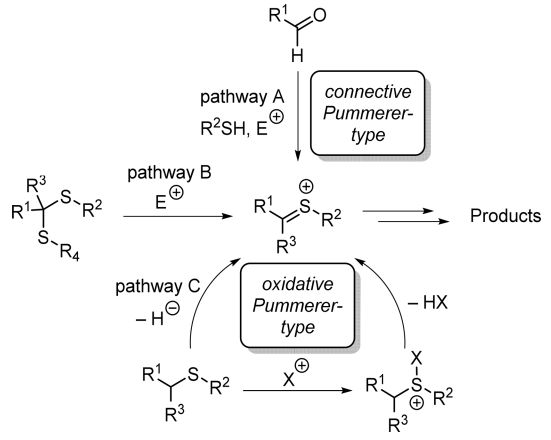


Scheme 11. Catalytic Pummerer Reaction by Pappo et al.



though these reactions do not strictly include the involvement of sulfur(IV) species, they are closely related to the Pummerer

Scheme 12. Recent Pummerer-Type Transformations Not Employing a Sulfoxide Precursor



chemistries presented herein and will be briefly discussed in the following section.

In cases where the thionium ion is accessed from an aldehyde, the process is often referred to as connective Pummerer reaction, by virtue of it forming two new bonds at the expense of a carbonyl group. Procter et al. have played a crucial role in developing this approach, using particularly electrophilic aldehydes such as **54** to afford cyclized products bearing a new sulfide moiety (Scheme 13).[41] The authors found that superstoichiometric amounts of both anhydride and Lewis acid were necessary to obtain significant product yields. Later, the protocol could be improved by the use of either catalytic amounts of $Sc(OTf)_3$ or 1.5 equiv of zinc chloride to promote dehydration of the hemithioacetal.[42]

Another example of the connective Pummerer reaction was developed by Pappo and co-workers, employing $Cu(OTf)_2$ as the catalyst (Scheme 14a).[43] Addition of three equivalents of ethanethiol to a mixture of a ketone (**60**) and an aldehyde (**61**) in highly polar solvents effected a Pummerer-aldol

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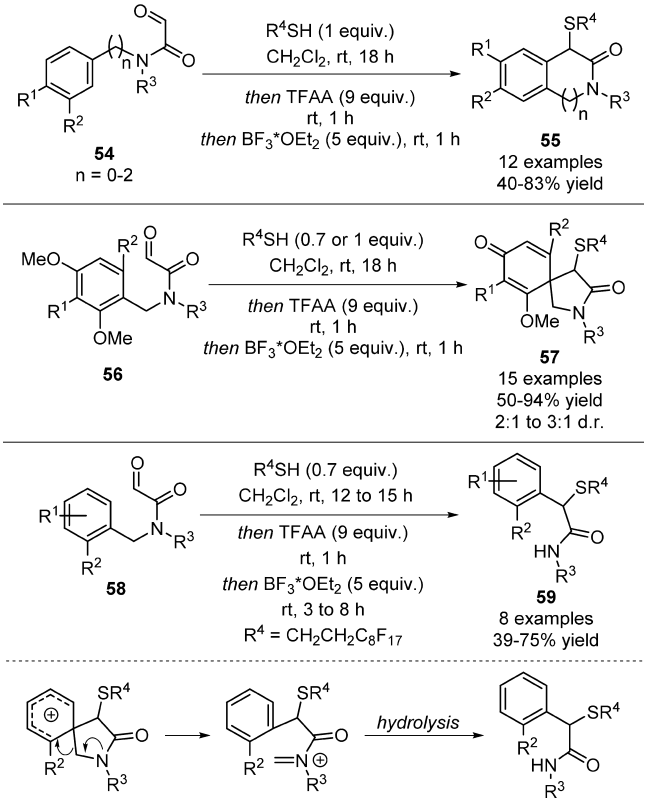
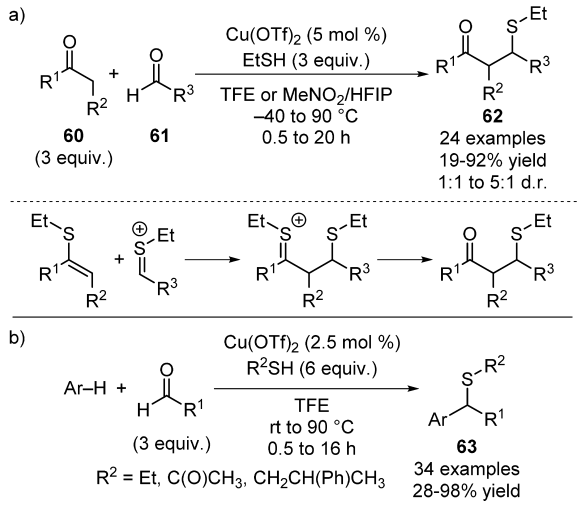
Scheme 13. Procter's Connective Pummerer-Type Cyclization



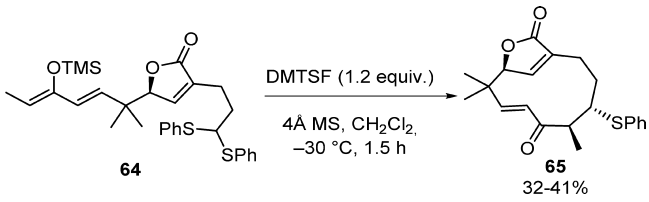
Scheme 14. Pappo's Copper-Catalyzed Thionium Chemistry



reaction. The proposed mechanism involves simultaneous vinyl sulfide/thionium ion formation and combination, followed by hydrolysis, proceeding successfully for a number of aliphatic and aromatic aldehydes. Later, this reaction was extended toward arenes as the corresponding nuclephiles, affording either the α-aryl sulfides **63** (Scheme 14b) or, if a silane was added after the reaction in one-pot fashion, desulfurated Friedel–Crafts alkylation products (not shown).[44]

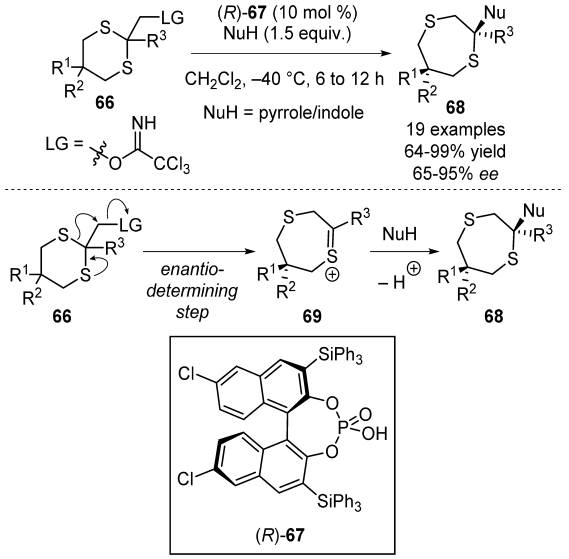
Alternatively, the thionium intermediate can be accessed by treating a dithioketal with a soft electrophilic activator. This strategy has been successfully used as the key C–C bond forming event for Trost's total synthesis of asteriscunolide D,[45] as well as an approach to the core of nakadomarin A.[46] In the former account, an effective 11-membered ring macrocyclization with very high levels of diastereoselectivity was realized, affording moderate yields of **65** (Scheme 15). In both of the mentioned reports, dimethyl(methylthio)sulfonium tetrafluoroborate (DMTSF) was used to ionize the dithioketal at low temperatures.

Scheme 15. Trost's Key Step in the Total Synthesis of Asteriscunolide D



In an interesting study on the ring expansion of cyclic dithioketals, Terada and co-workers uncovered surprising enantioselectivity using chiral phosphoric acid derivatives (**67**) (Scheme 16).[47] In contrast to the intuitive assumption

Scheme 16. Terada's Enantioselective Ring Expansion of Dithianes



that the addition of a nucleophile to the thionium intermediate is the enantiodetermining step, it was demonstrated that enantioselectivity is actually induced during the concerted 1,2-sulfur migration (**66** → **69**). Diastereospecific nucleophilic addition to the contact ion pair then furnishes the ring expanded products **68** with moderate to high levels of enantiomeric excess.

Reactions that start from a sulfide to directly access the thionium species are referred to as oxidative Pummerer-type reactions. Common reagents used for oxidative Pummerer reactions are hypervalent iodine reagents that act as both the oxidant and the leaving group. Following seminal work by Tamura et al.,[48] the reaction was applied to a number of sulfides, often bearing acidic hydrogens (such as α-ketosulfides). Recently, the groups of Wang and Chen showed that the use of ionic liquids allowed the oxidative Pummerer

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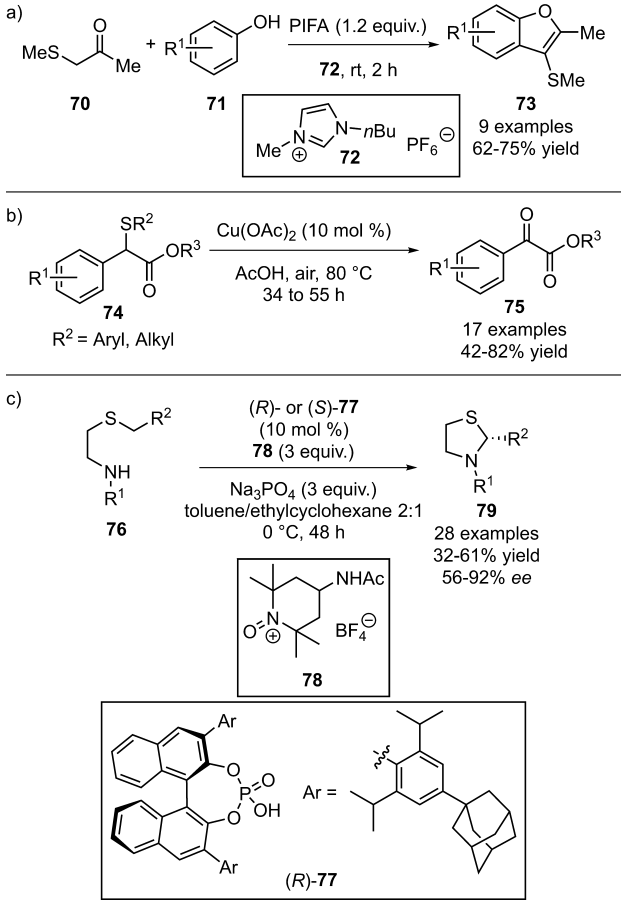
reaction to proceed at lower temperatures and with higher yields (Scheme 17a).[49] Other examples include Oda and co-

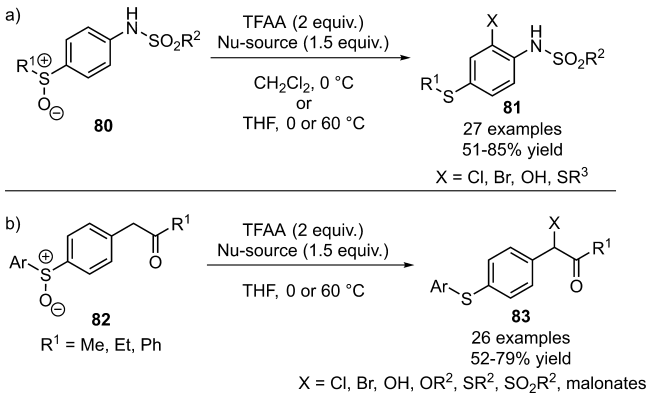
Scheme 17. Oxidative Pummerer-Type Reactions



workers' oxidative Pummerer rearrangement utilizing Koser's reagent to prepare thio-nucleosides[50] as well as reactions shown in Schemes 6b, 22b, and 28b. Alternatively, Singh and co-workers have developed a copper-catalyzed process, shown in Scheme 17b.[51] Under an atmosphere of air, the sulfides **74** were sequentially oxidized to the corresponding thionium species and hydrolyzed to deliver α-ketoester products (**75**). Recently, Toste et al. developed the first catalytic, asymmetric Pummerer-type reaction using a chiral-anion phase-transfer catalyst **77** (Scheme 17c).[52] Therein, the insoluble oxidant **78** is brought into solution by anion exchange with catalytic amounts of **77**. This highly electrophilic species can achieve hydride abstraction adjacent to sulfur, triggering an intramolecular cyclization to form *N*,*S*-acetal products (**79**). The stereoselectivity is governed by the chiral environment provided by the anion. An alternative mechanism via sulfide oxidation was ruled out by mechanistic studies.

2.1.4. Aromatic Pummerer Reactions. With an aromatic system adjacent to the activated sulfoxide, nucleophiles can attack the aromatic ring to lead to substituted aryl sulfides. Alternatively, similarly to the classical Pummerer reaction in which activated sulfoxides undergo α-deprotonation on the alkyl moiety, aryl sulfoxides carrying substituents with acidic hydrogen atoms can undergo (remote) deprotonation, leading to quinone-type intermediates. These reactions allow for the nucleophilic functionalization of the aromatic ring in a manner that is conceptually opposite to the more common *electrophilic* aromatic substitution. Such transformations are commonly referred to as aromatic Pummerer reactions, which were pioneered by Kita and co-workers at the beginning of this century.[53−56] Recently, Zhou and co-workers have employed *p*-aniline sulfoxide derivatives (**80**) as substrates for the aromatic Pummerer reaction (Scheme 18a).[57] Using ammo-

Scheme 18. Zhao's Aromatic Pummerer Reactions

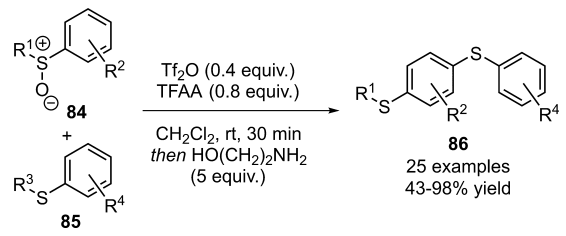


nium halide (Cl/Br) salts as the corresponding nucleophiles, addition selectively took place *meta*- to the sulfur substituent. Additionally, aqueous sodium bicarbonate and thiols were also employed and led to facile introduction of hydroxyl- or thio-substituents, respectively. Importantly, alkyl aryl sulfoxides also afforded moderate to good yields of the products of aromatic Pummerer reaction with only low amounts of classical Pummerer-type products being detected.

Aromatic sulfoxides carrying C−H acidic substituents are also viable substrates for this process, as shown by the same group shortly after their first report (Scheme 18b).[58] The reaction allowed the introduction of a broad range of nucleophiles in remote positions. However, this variant of the transformation was limited to diaryl sulfoxides (**82**).

In 2017, the group of Yorimitsu reported an aromatic additive Pummerer-type reaction relying on sulfoxide activation in the presence of sulfides (Scheme 19).[59] Following

Scheme 19. Yorimitsu's Aromatic Additive Pummerer-Type Sulfanylation



nucleophilic addition (preferentially in *para*-relationship to the sulfoxide), the resulting sulfonium salts could either be directly dealkylated by the addition of ethanolamine or isolated and used for a sequential cross-coupling (for a description of the latter process, see section 3.2).

2.1.5. Vinylogous and Extended Pummerer Reactions. As in the case of aryl sulfoxides, if vinyl sulfoxides are subjected to Pummerer reaction conditions, new reaction pathways become feasible due to influence of the conjugated

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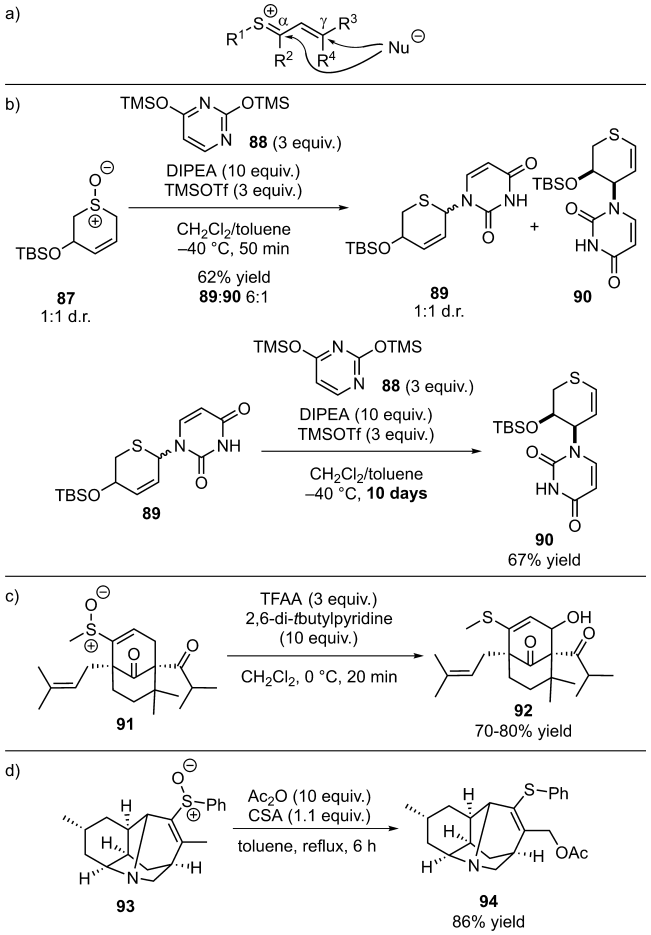
system. After activation of the sulfoxide, nucleophilic addition at the β-position leads to what is referred to as an extended Pummerer reaction pathway, whereas deprotonation and functionalization in the γ-position leads to reactions of the vinylogous Pummerer type. Predicting the regioselectivity of the nucleophilic attack between α- and γ-addition can be difficult and highly dependent on the reaction conditions (Scheme 20a). Yoshimura and co-workers studied this

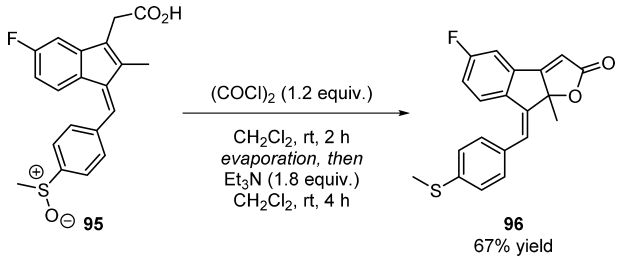
Scheme 20. General Mode and Specific Applications of the Vinylogous Pummerer Reaction



selectivity for their thioglycosylation reaction and found that nucleophilic attack can be reversible and that the kinetic α-addition product was converted to the thermodynamically more favorable γ-addition product under the reaction conditions (Scheme 20b).[60] The vinylogous Pummerer reaction has also found application in several natural product syntheses. In their route toward hyperforin, reported in 2010, Kanai, Shibasaki, and co-workers turned to a vinylogous Pummerer reaction to install a hydroxyl group in the γ-position, forming **92** (Scheme 20c).[61] In the model studies, the ratio of classic and vinylogous Pummerer products was found to be highly dependent on the base, with bulky pyridines such as 2,6-di-*t*-butylpyridine, giving the best results with yields between 70 and 80% for the vinylogous product (the *real* substrate yielded 65% of the desired product with an inconsequential dr > 33:1). One year later, Fukuyama et al. made use of a complex vinyl sulfoxide (**93**) in their total synthesis of (+)-lyconadin A (Scheme 20d).[62] With an excess of acetic anhydride and stoichiometric amounts of camphorsulfonic acid to protonate the basic nitrogen, the vinylogous Pummerer reaction afforded the desired product **94** in a high yield.

An unexpected remote functionalization was reported by Satyam and co-workers during their attempted esterification of carboxylic acid **95** with oxalyl chloride (Scheme 21).[63] In that

Scheme 21. "Long-Distance" Vinylogous Pummerer Reaction



event, the authors were surprised to obtain a lactone with a reduced sulfide substitutent (**96**). The formation of **96** can be explained by activation of the sulfoxide with oxalyl chloride, deprotonation in α-position to the carboxylic acid group, and cyclization of the carboxylate onto the ring. Thus, the reaction is best described as a "long-distance" vinylogous Pummerer type reaction.

Vinyl sulfoxides have also found use in the synthesis of thioribonucleosides by Haraguchi et al.[64] Additive Pummerer reaction of the dihydrothiophene oxide derivative **97** led to the stereoselective introduction of two new acetoxy substituents (Scheme 22a). When TMSOTf was employed instead of TMSOAc, substantial amounts of the β-triflated product were observed. After optimization, a higher stoichiometry of reagents afforded the desired product **98** in 62% yield.

Extending the Pummerer chemistry, the group of Feldman reported several studies on additive and vinylogous Pummerer-type reactions during their synthetic efforts toward dibromoagelaspongin and dibromopalau'amine.[65−68] A representative example of an oxidative vinylogous Pummerer type cyclization is shown in Scheme 22b.[69] Treatment of sulfide **99** with an oxidant such as the Stang reagent leads to activated species **101**, which undergoes deprotonation and attack by the tethered amide, followed by a second cyclization of the pyrrole unit to yield the polycycle **100** in 55% yield and as a single diasteromer.

Important work further extending the chemistry of the extended Pummerer reaction was reported by Yorimitsu et al. in 2008.[70] Therein, direct arylation of vinyl sulfoxides **104** in the β-position was reported to occur after treatment with triflic anhydride (Scheme 23). The aryl substituent R^1 played an important role in directing the electrophilic aromatic substitution to the β-position, leading to the 1,1-diaryl motif. Additional substitution on the aryl moieties led to lower yields, and strongly electron-withdrawing groups (such as *p*-CF_3) led to complex mixtures and no product formation. With an intramolecular aryl tether **108**, the only product obtained was phenanthrene **109**, being formed after an additional 1,2-carbon shift in intermediate **110**.

In 2013, the same group reported this reaction with thioalkynes and ynamides as nucleophiles (Scheme 24).[71] Interestingly, copper bromide was used as the activating agent

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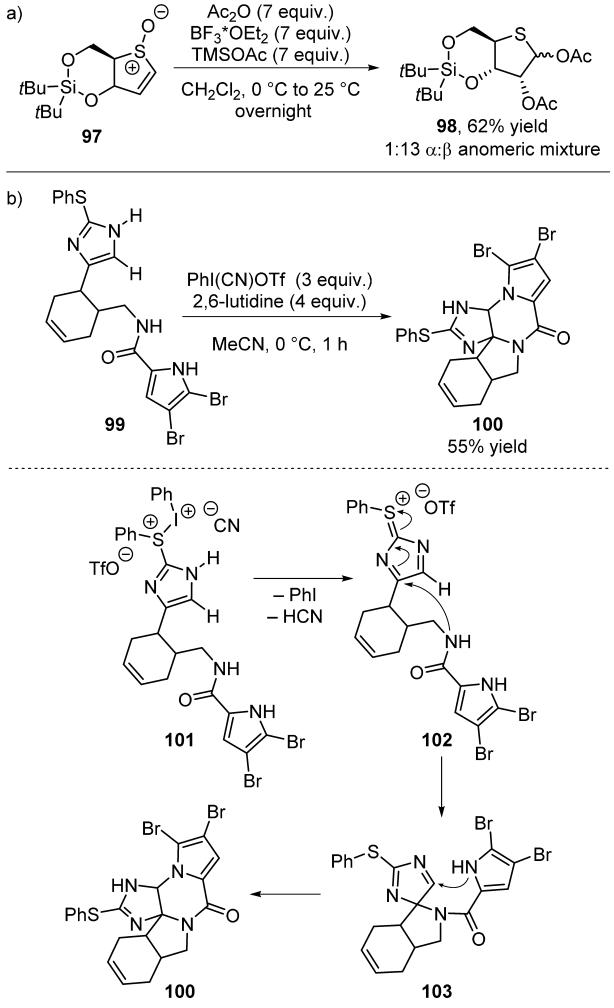
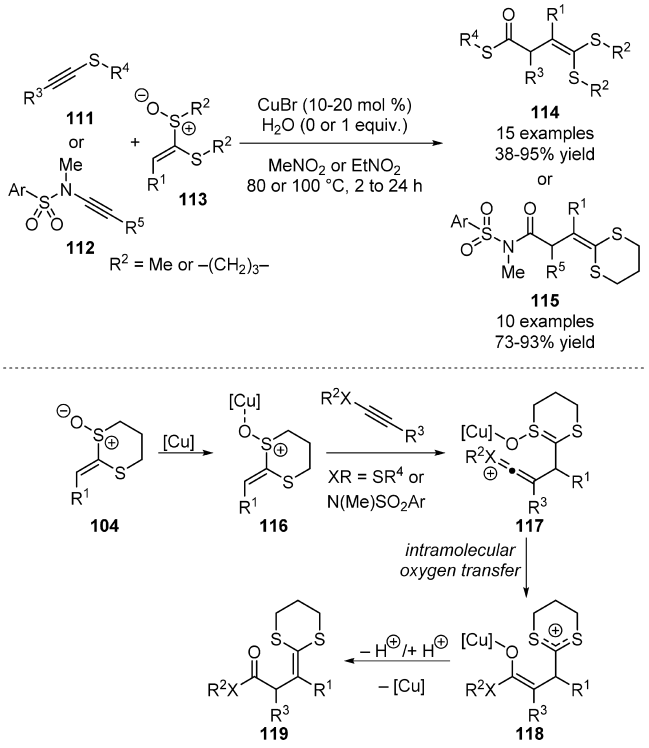
Scheme 22. Applications of Additive/Vinylogous Pummerer-Type Reactions



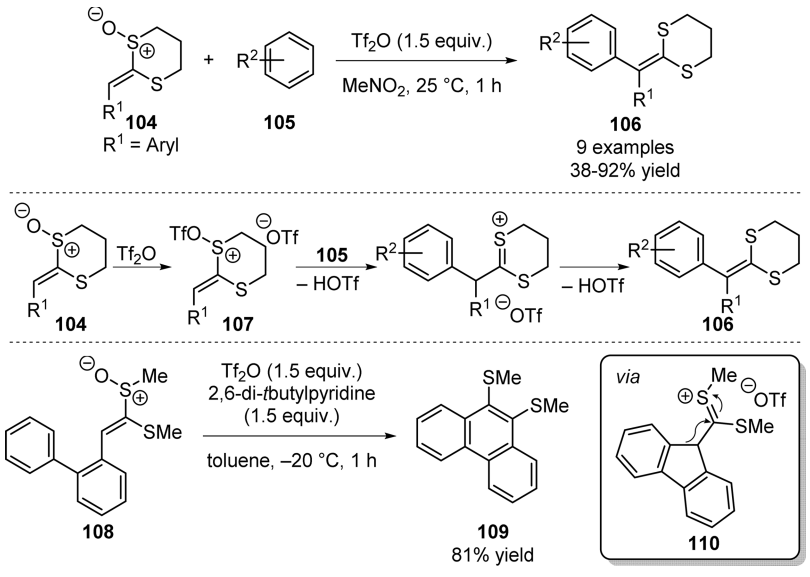
to enhance the electrophilicity of the vinyl sulfoxide toward nucleophilic attack. An intramolecular sulfur-to-carbon oxygen transfer was proposed to lead to copper enolate **118**, which affords the ketene dithioacetals **119** after proton transfer. One equivalent of water proved beneficial when thioalkynes were used as nucleophiles, increasing the yield substantially. The reaction was successful for both methyl- and aryl-substituted vinyl sulfoxide, however, more bulky groups such as cyclohexyl shut down the reaction completely. This reaction is mechanistically related to the family of reactions discussed in section 2.2.1, which involve [3,3]-sigmatropic rearrangements.

Scheme 24. Yorimitsu's Copper Catalyzed Extended Pummerer Reaction with Oxygen Transfer



2.1.6. Interrupted Pummerer Reactions. The interrupted Pummerer reaction, perhaps the most versatile of the

Scheme 23. Yorimitsu's Extended Pummerer Reaction



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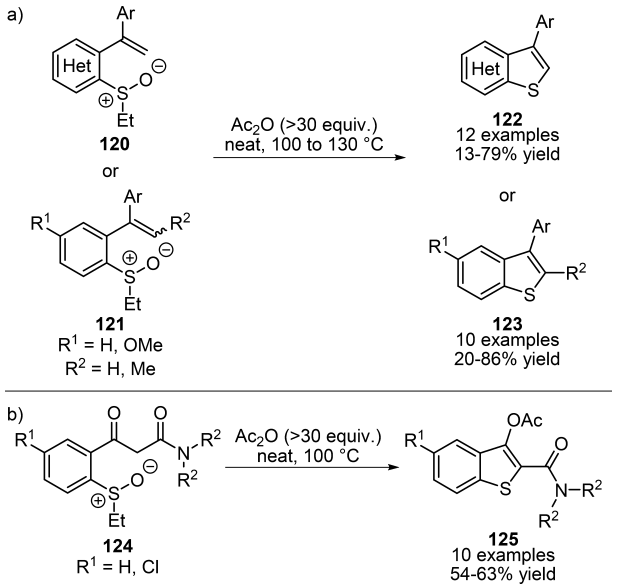
Pummerer-type reactions, is initiated when a nucleophile directly attacks the activated sulfoxide intermediate at sulfur. This reaction has been used in a variety of contexts, and the following segment will cover the most recent applications and developments. Interrupted Pummerer-initiated rearrangements and alkene functionalizations will be described in the subsequent section.

In 2009, Kobayashi et al. utilized interrupted Pummerer reactions to access a range of substituted benzothiophene derivatives from the corresponding sulfoxide precursors (Scheme 25a).[72,73]

Scheme 25. Interrupted, Dealkylative Pummerer Reaction for the Synthesis of Benzothiophenes

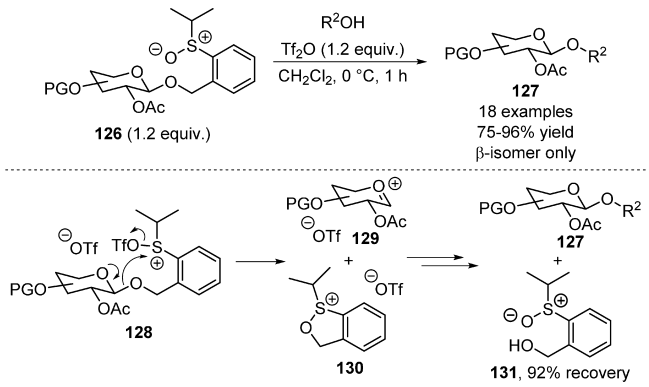


Herein, activation of the sulfoxide leads to an attack of the olefin on sulfur followed by deprotonation, with subsequent dealkylation affording the heterocycles. Shortly after, the same group reported the use of an intramolecular 1,3-dicarbonyl tethered sulfoxide **124** in which cyclization through the enol form leads to benzothiophenes (**125**) after subsequent acylation at oxygen under the reaction conditions (Scheme 25b).[74]

In 2015, Wan et al. reported the use of an interrupted Pummerer reaction in the context of carbohydrate chemistry (Scheme 26).[75] Therein, sugar derivative **126** was introduced as a bench-stable glycosyl acceptor bearing a carefully disposed sulfoxide as a "remote silent activator", that could be switched on by the use of triflic anhydride (Scheme 26, bottom). The activated sulfoxide triggers the expulsion of sulfonium species **130** and forms the active electrophile **129** which can be attacked by a variety of alcohols, most importantly diverse sugar derivatives in glycosyl transfer reactions. Importantly, hydroxysulfoxide **131** can be recovered after the reaction in 92% yield and can thereafter be recycled. Later, a detailed optimization of the sulfoxide unit and more applications of this reaction were reported,[76,77] and recently the use of sulfoxides in carbohydrate synthesis has been reviewed.[78,79]

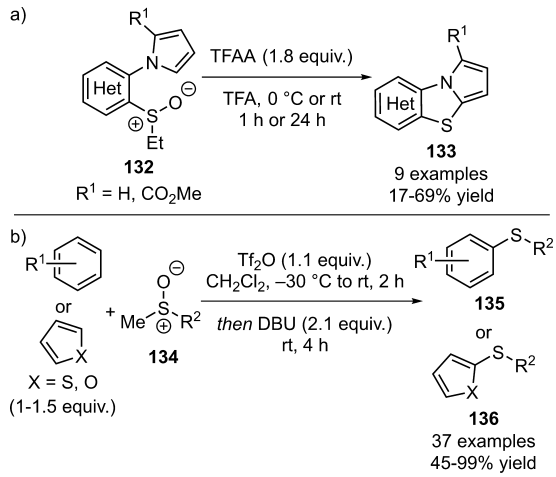
Several groups have used the interrupted Pummerer reaction for the sulfanylation of arenes. In 2015, Groombridge et al. reported the formation of novel tricyclic structures by intramolecular sulfanylation of pyrrole derivatives based on

Scheme 26. Wan's Glycosylation Using an Interrupted Pummerer Reaction



reports by Bates and co-workers (Scheme 27a).[80,81] Both pyridine- and pyrimidine-derived sulfoxides were annulated under strongly acidic conditions (TFA as the solvent) to afford a variety of heterocycles.

Scheme 27. Sulfanylation of Arenes by an Interrupted Pummerer Reaction



In an intermolecular sense, Procter and co-workers demonstrated the conversion of methyl sulfoxides **93** into aryl sulfides through activation, electrophilic aromatic substitution and, finally, a demethylation step effected by addition of an amine such as DBU (Scheme 27b).[82] A broad range of sulfoxides was employed in combination with either electron-neutral or -rich arenes in a regioselective manner. With phenolic substrates, the reaction leads to the concomitant formation of new C−S and C−O bonds, as was reported by Huang et al. in 2017 (Scheme 28a).[83] Initially, the interrupted Pummerer reaction leads to the formation of the corresponding sulfonium salts **139**. By heating the reaction in water in the presence of micellar macromolecules, an intramolecular transfer of the R^1 substituent from sulfur to oxygen is triggered, likely occurring via a Smiles-like rearrangement.

The reaction could be performed directly using sulfide starting materials **141**, as was also shown by Huang and co-workers (Scheme 28b).[84] Using $ZnCl_2$ as the Lewis acid and PIFA as the stoichiometric oxidant, a variety of electron-rich arenes could thereby be sulfanylated. The reaction mechanism was proposed to proceed via single-electron transfer (SET) of

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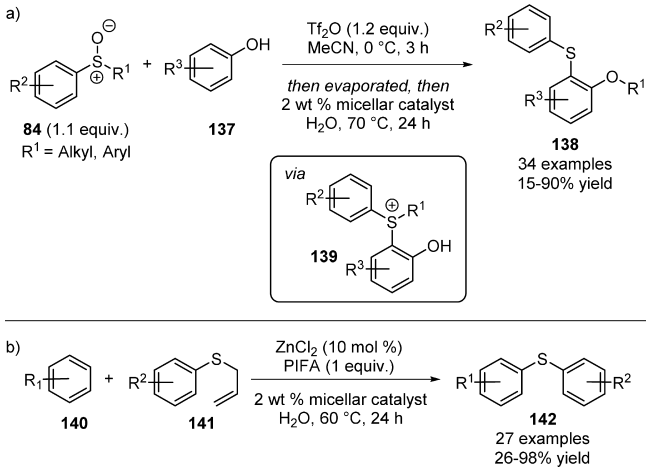
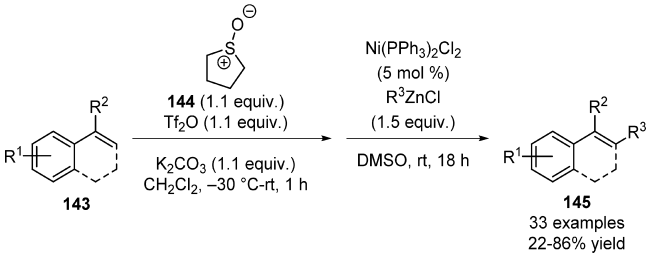
Scheme 28. Interrupted Pummerer Reaction to Form Diaryl Sulfides



the arene partner, however, oxidative activation of the sulfide in an interrupted Pummerer fashion could not be ruled out.

Recently, the Procter group utilized the intermediary sulfonium salts that are obtained via interrupted Pummerer reactions as transient leaving groups for an in situ nickel-catalyzed Negishi-type cross coupling in a one-pot manner (Scheme 29, for more information on the cross coupling of

Scheme 29. One-Pot Interrupted Pummerer/Cross Coupling Protocol



sulfonium salts, see section 3.2).[85] A broad scope of organozinc reagents was employed, and the reaction could be expanded to aryl- and alkynylsulfonium salts as well as to domino C−C bond formation employing suitable tethers.

2.2. Sigmatropic Rearrangements of Activated Sulfoxides

The activation of aryl and alkenyl sulfoxides with electrophilic reagents can lead to intermediates diverging in reactivity from classical Pummerer chemistry, undergoing structural reorganization through charge-accelerated sigmatropic rearrangements.[3,86−91] In this context, [3,3]- and [2,3]-sigmatropic rearrangements can be instigated by the formation of either unsaturated sulfonium intermediates or allylic sulfoxides and sulfur ylides.[6,7,92−94]

2.2.1. [3,3]-Sigmatropic Rearrangements of Activated Sulfoxides. In 2009, Yorimitsu, Oshima, and Yoshida reported the reaction of allyl silanes with a reactive electrophilic intermediate derived from 1,3-dithiane monoxide (**146**) to afford the allylated ketene dithioacetal **149** (Scheme 30a).[95] The authors postulated the transformation to proceed via a [3,3]-sigmatropic thio-Claisen rearrangement involving the sulfonium intermediate **148**. Identical reactivities were observed for the interactions of similar activated dithiane monoxides with both ketones[96] and phenols,[97,98] the latter leading to the formation of benzofurans (**154**) through subsequent condensation. While the reaction of aryl sulfoxides that have been activated by addition of strong electrophiles with electron-rich aromatics is also known to proceed via carbon attack on sulfur, ultimately forming aryl ethers or thioethers,[59,99] Yorimitsu and co-workers were able to show that O-nucleophilic attack of phenols onto activated aryl sulfoxides can be followed by [3,3]-sigmatropic rearrangement to elegantly afford biaryls (**157**) after rearomatization (Scheme 30b).[100]

The treatment of aryl sulfoxides with electrophilic activators such as triflic anhydride (Tf_2O) or trifluoroacetic anhydride (TFAA) has also featured prominently in recent *ortho*-arene and -heteroarene C−H functionalization chemistry (Scheme 31). In resemblance to the mechanism of sulfoxide activation in Yorimitsu et al.'s early work,[96] in 2011, Maulide and co-workers were able to show that the initial O-nucleophilic addition of β-ketoesters to activated aryl sulfoxides can lead to intermediates of type **160** (Scheme 31a), prone to charge-accelerated [3,3]-sigmatropic rearrangement, affording α-arylated ketones (**161**) as the reaction products.[101,102]

Shortly thereafter, Procter and co-workers demonstrated that the reaction of activated aryl sulfoxides with allylsilanes also leads to the formation of sulfonium intermediates poised for thio-Claisen rearrangement involving the arene, ultimately affording *ortho*-allylated aryl sulfides (**163**) (Scheme 31b).[103] The following years saw elaboration of this protocol to the allylation of various heterocycles[104] as well as the use of propargyl silanes to afford propargylated arenes via the intermediacy of allenyl aryl sulfonium ions **164** and a corresponding allenyl thio-Claisen rearrangement (Scheme 31c).[105−107] Recently, heteroaromatic *S*-oxides have been employed in C−H functionalization reactions, leading to C2- or C3-arylated, -allylated, and -propargylated benzothiophenes (**168**−**173**, Scheme 31c).[108,109] Utilizing allyl sulfoxides, Procter and co-workers have also achieved the dual vicinal functionalization of related indoles (and other heteroaromatics) via a remarkable sequence of S_EAr/[3,3]-sigmatropic rearrangement (Scheme 31d).[110]

In 2016, Procter and co-workers were able to exploit the nucleophilicity of unactivated alkynes for a formal C−H addition to aryl sulfoxides activated with triflic anhydride (Scheme 32).[111] In this mechanistically elegant transformation, an intermediate enol trilate (**179**) undergoes base-promoted isomerization to afford sulfur-ylide **180**, which rearranges to form the desired propargyl arene products **181** after [3,3]-sigmatropic rearrangement, rearomatization, and triflate elimination. One year later, expanding the reactivity to the incorporation of nitriles, Peng and co-workers were able to provide detailed mechanistic insight into this family of reactions,[112] Magnier et al. having reported a similar transformation of aryl perfluoroalkyl sulfoxides some years earlier.[113] The group of Peng was further able to extend the scope of sulfoxides by employing α-stannyl nitriles, thereby allowing for far milder reaction conditions.[114]

While the methods detailed above hinge on the treatment of a sulfoxide-oxygen with an electrophilic activator, an alternative approach engages the sulfoxide in the trapping of a second, activated reaction partner (Scheme 33). In this context, the use of aryl sulfoxides as nucleophilic reagents for the capture of activated π-systems, followed by sigmatropic rearrangement affords α-arylated carbonyl compounds in a redox-neutral

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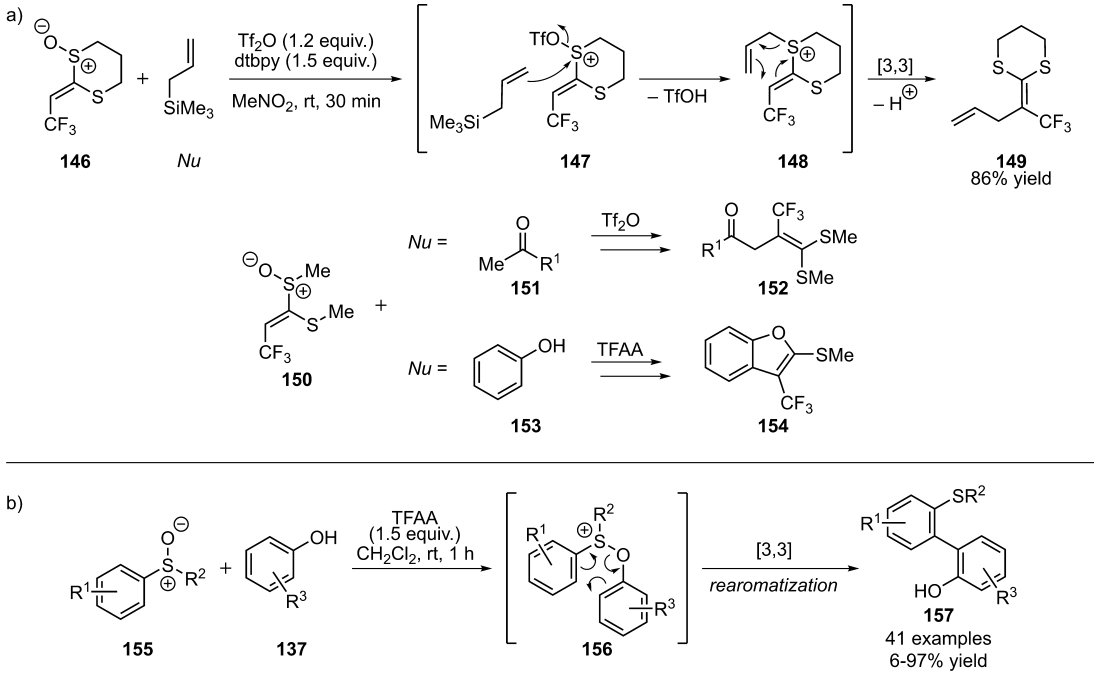
Scheme 30. Yorimitsu's Early Work and Development of the [3,3]-Sigmatropic Thio-Claisen Rearrangement Enabled by Sulfoxide Activation



manner, whereby the carbonyl oxygen of the final products originates from the sulfoxide reagent itself. The earliest reports of this type of reactivity by the groups of Zhang, Toste, and Grainger focused on the gold-mediated activation of alkynes, followed by intramolecular sulfoxide capture (Scheme 33a),[115−117] and were only shown several years later to in fact proceed via sigmatropic rearrangement.[118] The first intermolecular variants of this transformation were reported by the Liu and Asensio groups, providing access to acyclic α-aryl ketones (**187**) (Scheme 33b).[119,120]

In lieu of catalytic activation using gold, alkyne derivatives can also be competently activated by simple Brønsted acids to afford electrophilic intermediates suited for sulfoxide attack (Scheme 34). In 2014, Maulide and co-workers reported the formation of arylated amide derivatives (**191**) through transient formation of keteniminium ions (**190**) from ynamides (Scheme 34a).[121] In analogy to this transformation, proceeding via addition of an aryl sulfoxide to the electrophilic position at the center of the keteniminium ion and subsequent [3,3]-sigmatropic rearrangement, the group also reported the α-arylation of amides.[122] Pivotal to this chemistry was the electrophilic activation of the amide substrate prior to sulfoxide addition, ensuring keteniminium ion formation over more readily occurring sulfoxide activation (Scheme 34a). The breadth of application of these redox-neutral arylations was further extended by the groups of Zhu and Maulide, employing ynol ethers, thioalkynes, unactivated alkynes, and propargyl alcohols (the latter leading to the formation of α-arylated α,β-unsaturated carbonyl compounds (**194**) in an interrupted Meyer−Schuster rearrangement) as the substrates (Scheme 34b).[123−125] Notably, recent studies have shown divergence in terms of regioselectivity. With increasing electron-donating ability of substituents *ortho*- to sulfur, or additional bias in the arene substitution pattern, rearrangement into the *meta*-position becomes more favored with ratios of up to 10:1. Computational analysis revealed the new product to arise from an initial [3,3]-sigmatropic rearrangement onto the substituted *ortho*-carbon atom and a subsequent 1,2-alkyl shift, followed by rearomatization (Scheme 34c).[126]

Owing to the chirality (stereogenic sulfur) of unsymmetrically substituted sulfoxides and their facile preparation, great interest has been placed in the use of such enantiopure reagents for enantioselective carbon−carbon bond formation.[127,128] In 2017, Maulide and co-workers were able to report an asymmetric variant of the sulfoxide-mediated arylation of ynamides and thioalkynes employing enantioenriched sulfoxides (Scheme 35a).[129] Herein, careful adjustments of the transition state by choice of the counteranion enabled the synthesis of a wide array of enantioenriched α-arylated carbonyl derivatives resulting from 1,4-chirality transfer from sulfur to carbon during the key [3,3]-sigmatropic rearrangement. Importantly, similar chirality transfer using enantioenriched sulfoxides in the sulfoxide-activation mode was shown to be less efficient, leading to racemic products. Chirality transfer was high but not perfect (on average 88% for ynamides and 85% for thioalkynes), a fact that can be ascribed to the competition between dearomatizing [3,3]-sigmatropic rearrangement and potential racemization of the intermediate itself. Most recently, this chirality transfer phenomenon was considerably enhanced for *vinyl* sulfoxides in the synthesis of 1,4-dicarbonyl compounds (**203**) by Maulide and co-workers (Scheme 35b).[130] All four possible stereoisomers could be obtained selectively by fine-tuning the chiral center at sulfur (responsible for absolute stereocontrol) and double-bond geometry (responsible for relative stereocontrol). In this intriguing transformation, a chairlike transition state reminiscent of those proposed for the allylboration of aldehydes was postulated to account for the stereochemical outcome. The reaction is further amenable to the construction of quaternary centers with high stereoselectivity. It is noteworthy that the presumably lower barrier for a [3,3]-sigmatropic rearrangement event not paying the energetic penalty of dearomatiza-

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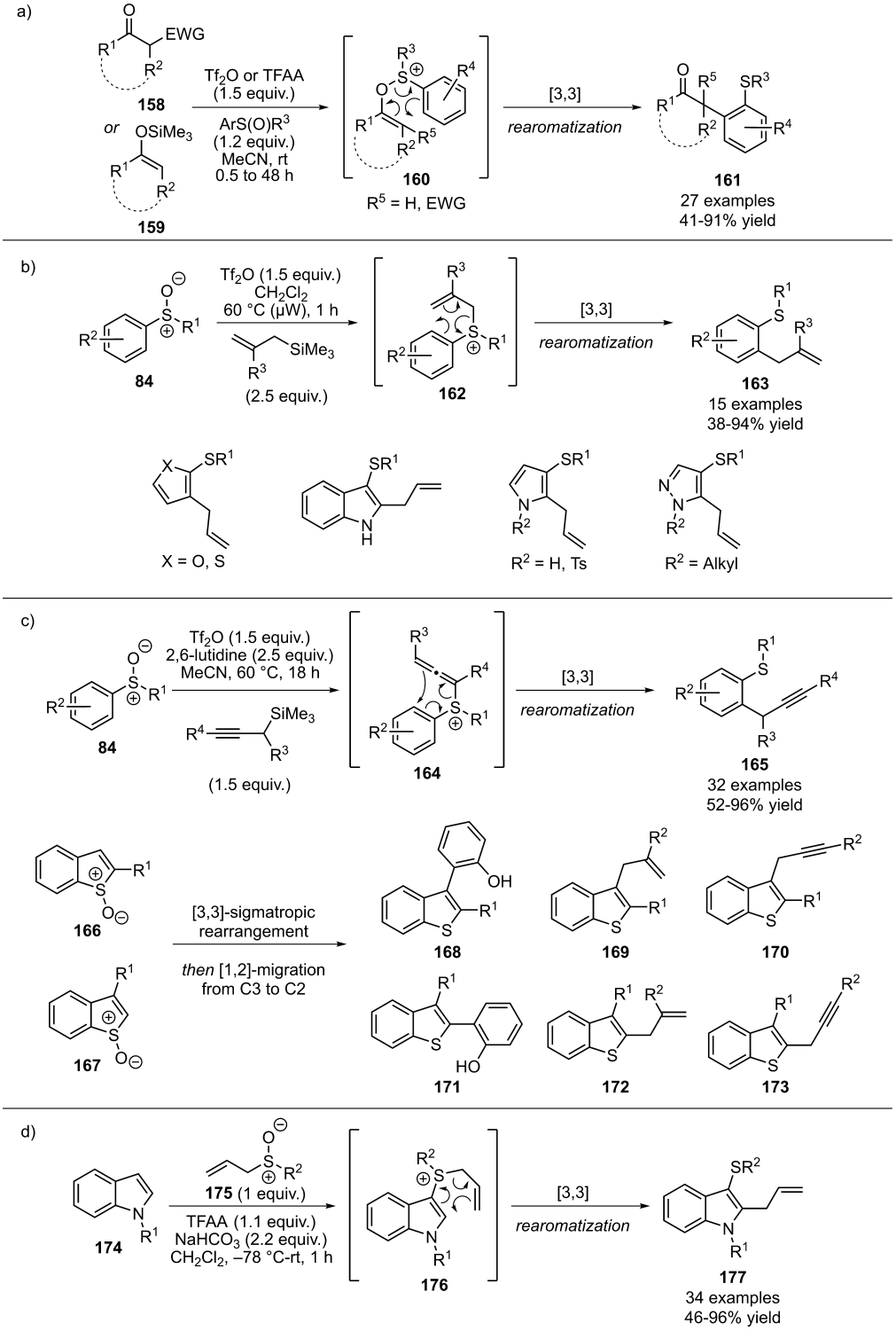
Scheme 31. Maulide's α-Arylation of Ketones and Procter's Allylation, Propargylation, and Arylation Reactions of Heterocycles with Activated Sulfoxides



tion allows complete chirality transfer without loss of enantiopurity from the reagents to the products.

2.2.2. [2,3]-Sigmatropic Rearrangements of Activated Sulfoxides. Sulfoxides are also associated with a family of [2,3]-sigmatropic rearrangements, the archetypical example being the venerable Mislow–Braverman–Evans (sometimes Mislow–Evans) rearrangement (Scheme 36). This thermal, reorganization of allylic sulfoxides (**207**) to allylic sulfenates (**208**) has found widespread application in organic methodology and synthesis,[6] and only the most recent advances shall be covered herein.

De la Pradilla and co-workers have exploited the suprafacial nature of this reaction in their syntheses of pseudoconhydrine (**212**) as well as the core-structures of *ent*-dysiherbaine and deoxymalayamicin A (**213**) (Scheme 37a).[131,132] The Chida group reported a racemic application of the Mislow–

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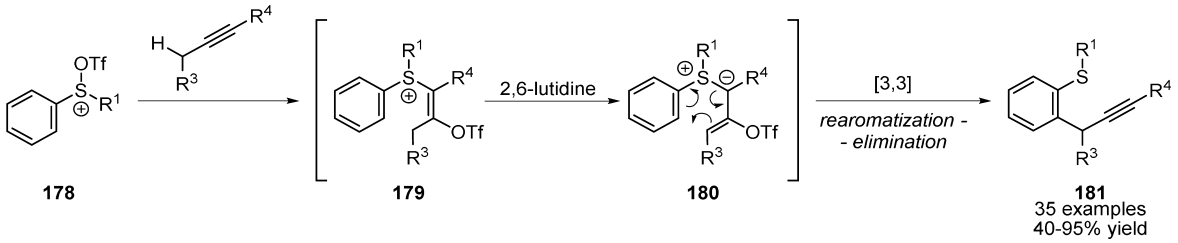
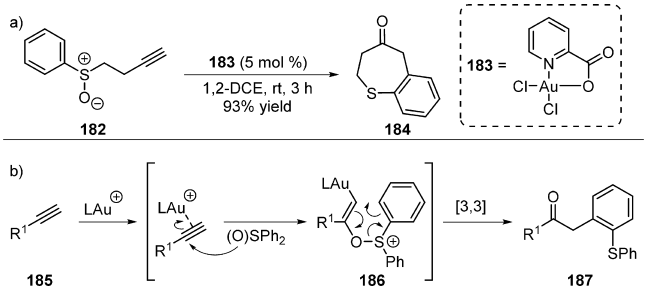
Scheme 32. Propargylation of Activated Aryl Sulfoxides with Unactivated π-Systems



Scheme 33. Trapping of π-Activated Alkynes with Sulfoxides, Followed by Arylation via Sigmatropic Rearrangement



Braverman−Evans rearrangement in their total synthesis of angelastatin.[133] In contrast to these applications, Manthorpe and co-workers observed an unwanted degradative [2,3]-sigmatropic rearrangement of vinyl bissulfoxide intermediates **216** en route to (9*R*,10*S*)-dihydrosterulic acid (Scheme 37b).[134] In addition, the groups of Fukuyama,[135] in the synthesis of stemofoline cores, and Raghavan, in their approach to brefeldin A,[136] and phoslactomycin B (applying a propargyl Mislow−Evans rearrangement, Scheme 37c),[137] have shown the synthetic utility of this textbook transformation.

De la Pradilla and co-workers have furthermore exploited the stereoretentive nature of [2,3]-sigmatropic rearrangements for the construction of allylic stereocenters following conjugate addition to enantiopure vinyl sulfoxide derivatives (Scheme 38).[138,139] A related approach (not shown) was chosen by Zard and co-workers for the synthesis of α-keto vinyl carbinols.[140]

At the beginning of this decade, the groups of Poli and Norrby investigated the synthesis of diaryl sulfoxides from allyl aryl sulfoxides (Scheme 39).[141,142] This transformation also hinges on an allylic sulfoxide−allyl sulfenate rearrangement. The resulting sulfenate ester **231** can, when attacked by a palladium catalyst, undergo oxidative addition to form a Pd−π-allyl complex (**233**) and an aryl sulfenate anion (**232**). **232**, in turn, can subsequently undergo palladium-catalyzed cross couplings with additional aryl iodides to afford unsymmetrical diaryl sulfoxides **235**.

The addition of thioethers to metal carbenes leads to the formation of sulfur ylides (Scheme 40). When allyl sulfides are employed in this addition, the resulting intermediate **238** is prone to [2,3]-sigmatropic rearrangement in what is known as the Doyle−Kirmse reaction. Recent developments in sigmatropic rearrangements of sulfur ylides not derived from sulfoxides are covered in section 4.4.1.

Li and co-workers have reported a series of metal-free [2,3]-sigmatropic rearrangements of related sulfur ylides, resulting in elegant allylic and propargylic C−H functionalization reactions (Scheme 41).[143,144] Mechanistically resembling Procter's arene-propargylation discussed in the previous section,[111] these transformations hinge on the nucleophilicity of the π-system, furnishing intermediate allyl (**242**) and allenyl (**244**) sulfonium ylides. Their respective formations set the stage for the pivotal [2,3]-sigmatropic rearrangements to afford the products of C−H alkylation.

Scheme 42 shows a brief summary of sigmatropic rearrangements based on the reactivity of sulfoxides. [3,3]-Sigmatropic rearrangements can occur after formation of intermediate **249**, which can be formed either by addition of a nucleophilic moiety (**248**) to an activated sulfoxide or by trapping an activated species such as **252** with a sulfoxide (Scheme 42a). In contrast, [2,3]-sigmatropic rearrangements as shown in Scheme 42b generally do not require activating agents and rely on thermal activation of allylic sulfoxides alone. The allyl sulfenates (**208**) formed thereby can either undergo S−O bond cleavage, affording allylic alcohols, or can be attacked by a suitable nucleophile to extrude the sulfenate, as shown by the formation of **233**.

2.3. Sulfoxide-Mediated Oxidative Functionalization Reactions

The following chapters aim to provide an overview of recent developments in oxidative functionalization based on the use of a sulfoxide as either the reactant or the oxidant. The use of the simplest sulfoxide, DMSO, as a synthon and reagent in organic chemistry has been previously expertly reviewed by the groups of Magolan[145] and Wu,[146] and these works should be sought out for additional detail on historic transformations and developments preceding the scope of this review.

2.3.1. Allylic and Benzylic Functionalization. In contrast to the transformations depicted in Scheme 41, the treatment of allyl benzenes (**251**) with activated diphenyl sulfoxide in the presence of alkylamines was shown by Li and co-workers to afford the rearranged products of allylic functionalization (**256** and **257**) (Scheme 43).[147] A variety of cationic and dicationic intermediates were proposed to account for the divergence of the reaction, hinting at the versatility of sulfur(IV)-intermediates in the functionalization of allylic or benzylic positions, as well as alkenes, alkynes, and arenes (vide infra).

A recent addition to allylic functionalization using activated DMSO was reported by Zografos and co-workers,[148] providing a direct path to allylic chlorides (Scheme 44a). This transformation is based on an ene-type allylic chlorination of electron-rich alkenes, critically attacking the chlorosulfonium ion **259** at chlorine rather than sulfur. Interestingly, the converse unusual attack of a benzylic enolate on the sulfur atom of DMSO enables a base-mediated benzylic oxidation, as disclosed by Ravikumar and co-workers (Scheme 44b).[149] Intermediate **262**, formed after this initial attack, undergoes [1,2]-sigmatropic rearrangement to afford an alkoxide, which

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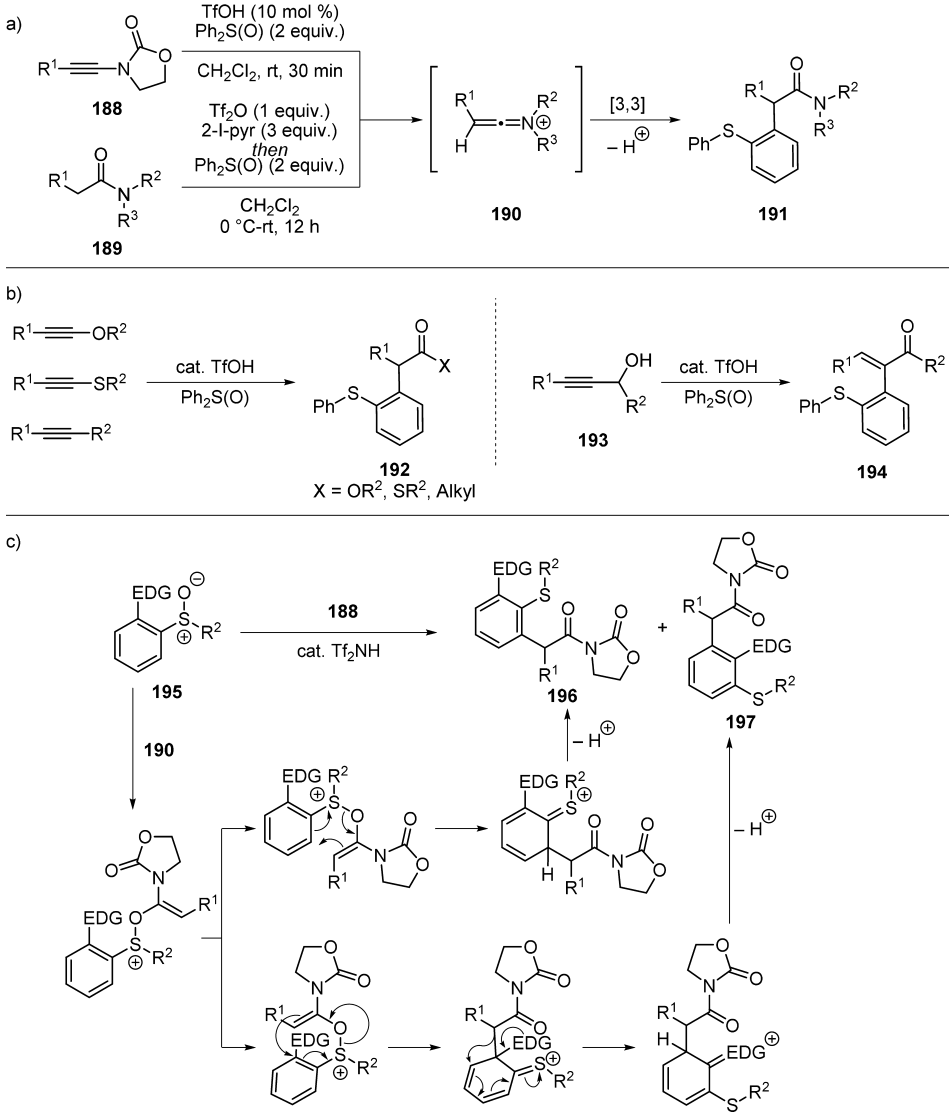
Scheme 34. Interception of Keteniminium Ions (190) and Other sp-Hybridized Cations with Aryl Sulfoxides, Followed by [3,3]-Sigmatropic Rearrangement



in turn is further oxidized following a second attack on DMSO and E1cb-elimination.

Employing sulfoxides for the oxidative functionalization of tetrahydrocarbazoles (and other 2-substituted indole derivatives), Kawasaki and co-workers have reported a range of nucleophilic additions to sulfonium-activated intermediates (Scheme 45).[150−152] The mechanistic proposal for this transformation involves nucleophilic attack of the indole on the electrophilic sulfur of activated DMSO to afford intermediate **267**. This species readily undergoes tautomerization (generating **268**) and subsequent nucleophilic allylic displacement of the sulfide to yield the products of benzylic functionalization (**269**) (Scheme 45a). A wide range of nucleophiles competently add to the activated intermediate **268**, including diphenyl sulfoxide (Scheme 45b).[151] Intermediate **270**, formed upon the second sulfoxide addition, can easily undergo Kornblum-type oxidation to form the corresponding benzylic ketone **271**.

A similar strategy was employed by the same group in the oxidative dimerization of trypatime, affording homo- or heterodimeric pyrroloindolines at will.[152]

2.3.2. Arene Functionalization. Moving away from electronically privileged allylic and benzylic positions, sulfoxide-mediated arene functionalization has also seen considerable synthetic efforts in the past decade. Recent additions to this class of transformation have focused predominantly on methyl- and alkylthiolation reactions, both in the absence and presence of transition metal catalysts (Scheme 46). In the context of metal-free methylthiolations, Roychowdhury and co-workers have reported the conversion of indoles, imidazopyridines, and other imidazo-fused heterocyclic compounds using a combination of DMSO and $POCl_3$ for the formation of chlorodimethylsulfonium ion **259** (Scheme 46a).[153] Notably, trace amounts of the corresponding chlorinated heterocycles were detected, reflecting the presence of a second electrophilic site in **259**. Disulfides[154] and other dichalcogenides[155] have been employed for the functionalization of indoles and arylboronic acids, using DMSO as the stoichiometric oxidant for the regeneration of molecular iodine (Scheme 46b). Magolan and co-workers have, in turn, employed DMSO in the methylthiolation of electron-deficient

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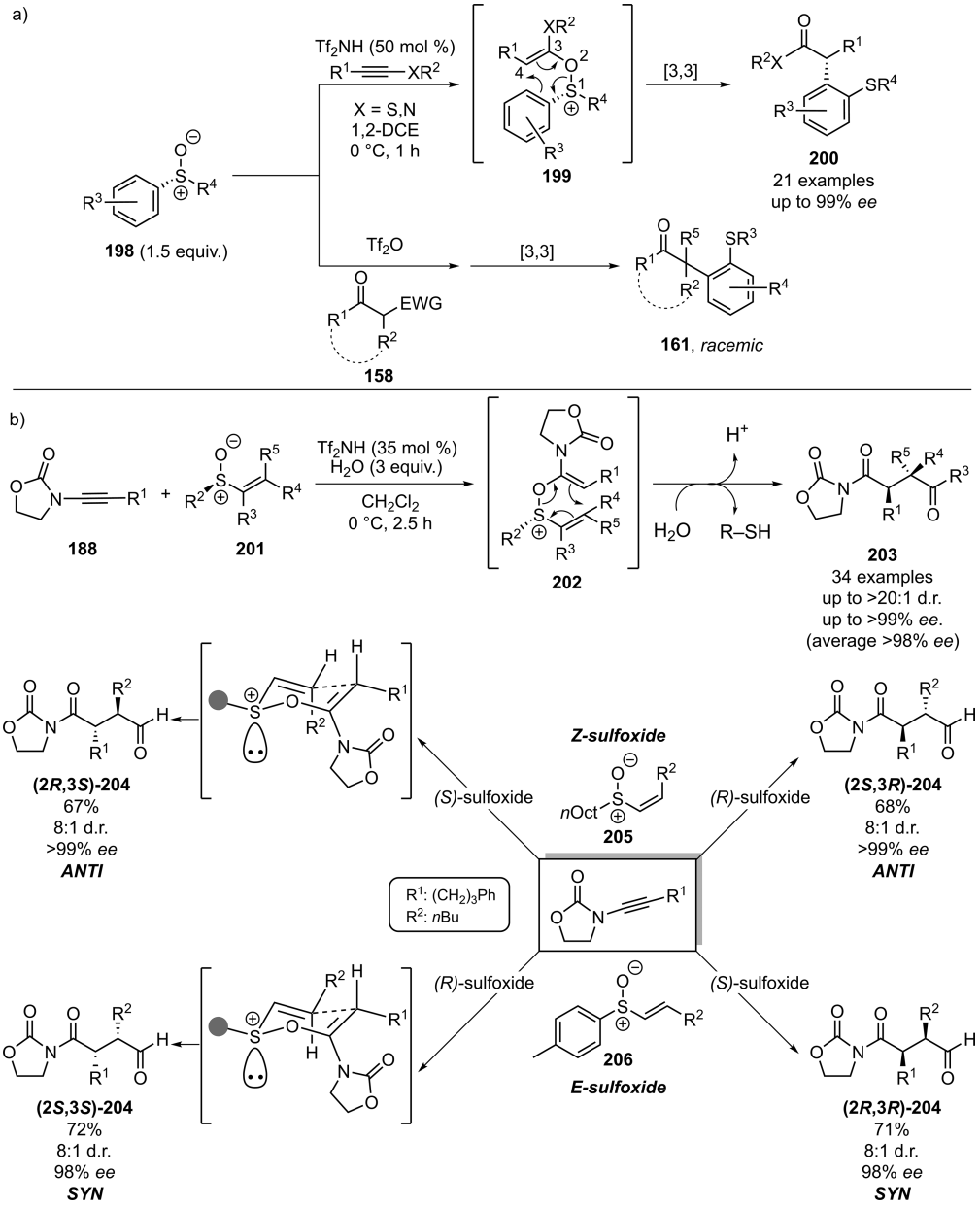
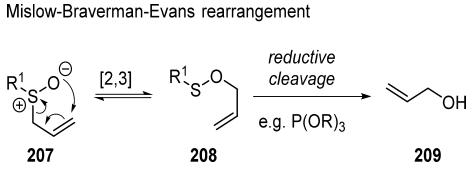
Scheme 35. (a) Enantiopure Aryl Sulfoxides Enable the Induction of Chirality at Carbon via 1,4-Chirality Transfer; (b) Enantiopure Vinyl Sulfoxides Allow a Fully Stereodivergent Synthesis of 1,4-Dicarbonyl Compounds



Scheme 36. Generalized Representation of the Mislow–Braverman–Evans Rearrangement



aryl fluorides via S_NAr with dimethyl sulfide formed in situ (Scheme 46c).[156]

A number of alternative, copper-based approaches to the methylthiolation of arenes have been reported in recent years, ranging from *ortho*-directed methylthiolation of arylpyridines proceeding via concerted metalation–deprotonation (CMD)[157,158] to the methylthiolation of aryl halides (Scheme 46d)[159−161] and heterocycles.[162] Similarly, Pan and co-workers reported the formation of 2-(phenylthiol)phenols (**279**) by tandem C–S coupling/C–H functionalization of aryl halides, aryl sulfides, and DMSO, via the proposed intermediate **280** (Scheme 46e).[163]

Combining DMSO and hydrogen halides, Jiao and co-workers have developed a scalable procedure for the halogenation of arenes (Scheme 47).[164] This process, performed on up to kilogram scale, proceeds via the in situ formation of X_2, the slow release of which is crucial for the regioselectivity of the process.

The inherent charge separation of DMSO (and indeed sulfoxides in general), rendering it both nucleophilic (at oxygen) and electrophilic (at sulfur) has led to its deployment in the functionalization of arynes (Scheme 48a). The groups of Xiao and Wang have shown that the addition of DMSO to aryne moieties can afford oxathietane intermediates **287**, prone to undergo ring-opening to cyclohexadienone–sulfur ylides

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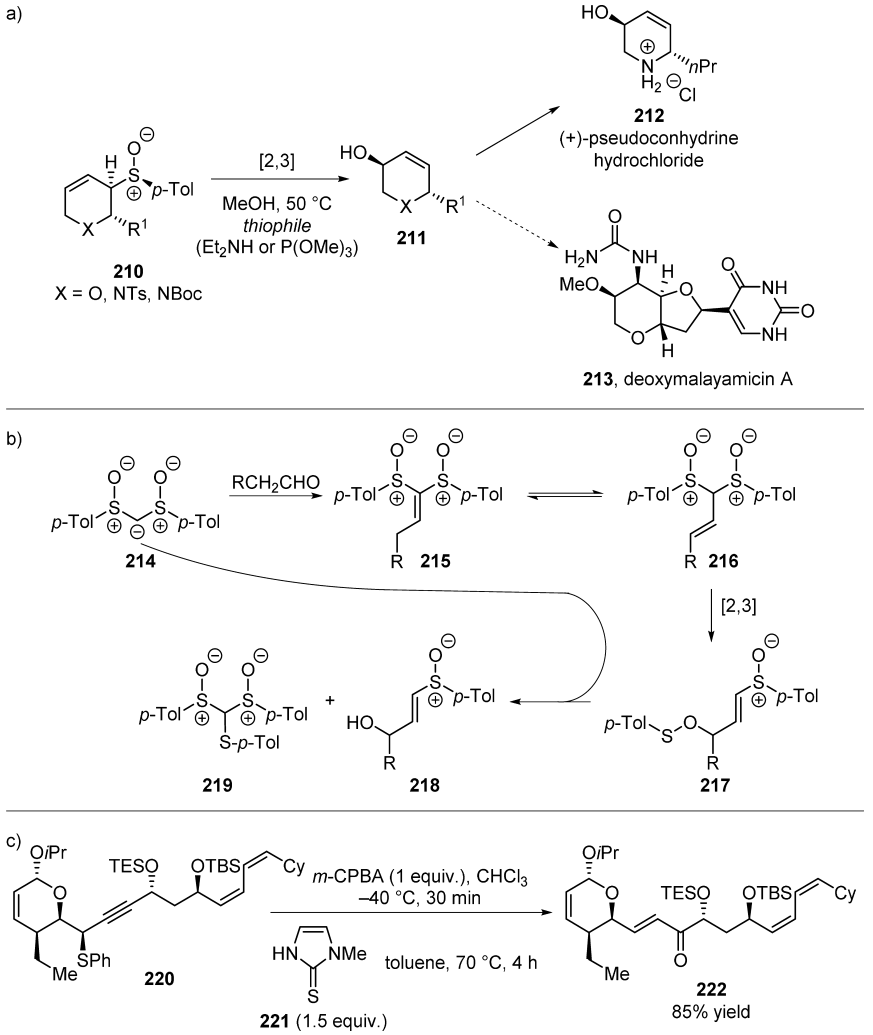
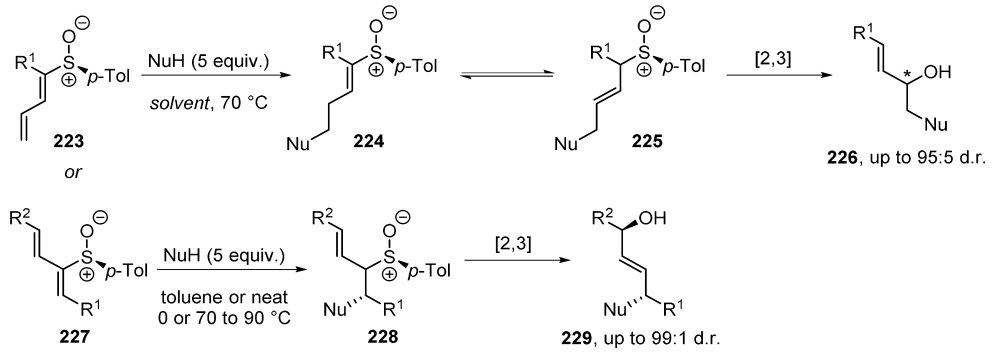
Scheme 37. Recent Applications of the Mislow–Braverman–Evans Rearrangement in Natural Product Synthesis



Scheme 38. [2,3]-Sigmatropic Rearrangements Following Conjugate Addition to Vinyl Sulfoxide Derivatives



(**288**), themselves amenable to further in situ functionalization with electrophiles.[165,166] A range of further developments has shown that arynes,[167] electron-deficient arenes,[168] or tethered enoates[169] can engage in reactions with **288**, functionalizing the intermediate phenolate. Also utilizing the reaction of arynes with sulfoxides, Li and co-workers developed a trifunctionalization reaction (Scheme 48b).[170] Herein, the use of an allyl sulfoxide leads to the formation of an oxathietane capable of undergoing an S-to-O allyl migration, followed by an oxonium Claisen rearrangement, affording a new carbon–carbon bond. A single intriguing example of aryne formation with subsequent capture with a sulfoxide was reported by the same group shortly thereafter (Scheme 48c).[171] Employing 3-triflyloxyarynes in [2 + 2]-cycloadditions, the authors were able to form benzocyclobutanes **294**, which were readily opened via Grob fragmentation to afford new arynes. Apart from several other nucleophiles, the reaction with a sulfoxide was also reported, affording **296** as a single regioisomer.

When alkyl aryl sulfoxides are employed to capture arynes, deprotonation α to sulfur leads to the formation of an ylide

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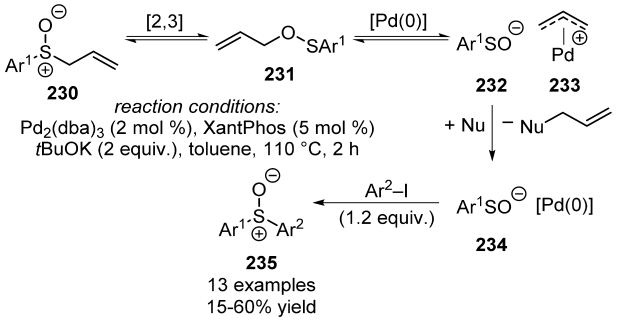
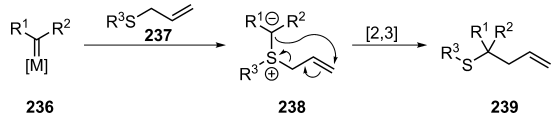
Scheme 39. Mislow–Evans Rearrangement Enables Deallylative Arylation of Allyl Sulfoxides



Scheme 40. Addition of Allyl Sulfides to Metal Carbenes Enables the Doyle–Kirmse Reaction



that can be engaged in a range of Corey–Chaykovsky-type epoxidations (Scheme 49).[13,172]

2.3.3. Alkene and Alkyne Functionalization. The combination of DMSO and a hydrogen halide, in this case HBr, enabled Magolan and co-workers to achieve the Br_2-free dibromination of olefins (Scheme 50a, left).[173] The authors propose bromodimethylsulfonium ion **303** as the active reagent, leading to intermediate bromonium ion formation, followed by opening with a further equivalent of bromide. In contrast to Magolan's method, Jiao and co-workers have reported the formation of bromohydrins **304** (observed only in some cases by Magolan) from styrene derivatives/benzylic bromides under similar reaction conditions, employing DMSO both as the oxidant and the nucleophile for the opening of the intermediate bromonium ion (Scheme 50a, right).[174] Notably, rather than undergoing Kornblum-type oxidation to form the α-bromo ketone, intermediate **305** is presumably attacked at sulfur by bromide, furnishing the alcohol and reforming **303**.

While for all intents and purposes relying on a similar combination of reagents, work by Li, Yuan and co-workers reporting the oxysulfenylation of styrenes is presumed to proceed via a radical mechanism instead (Scheme 50b).[175] There, the thermal homolytic cleavage of molecular iodine leads to the formation of both thiyl (**308**) and alkoxy (**309**) radicals that add across the reactive double bond.

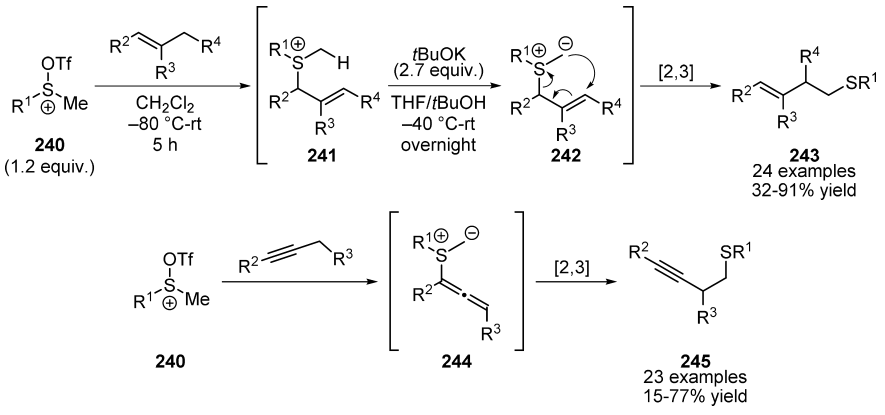
In 2012, Maulide and co-workers disclosed the sulfoxide-mediated umpolung of alkali halide salts, enabling halogenation of alkenes (through halolactonization) and enols (Scheme 50c).[176] Herein, Lewis acid activation of a sulfoxide enables the addition of a halide, forming tetrahedral intermediate **311**. This electrophilic species undergoes attack by the alkene in a halonium-type fashion.

Apart from halonium equivalents, other electrophilic reagents have also found application in the sulfoxide-mediated functionalization of alkenes (Scheme 51). In 2010, Danishefsky and co-workers described an intriguing process of epoxidation mediated by a tethered sulfoxide.[177] Herein, treatment of sulfoxide **314** with trifluoroacetic anhydride led to the formation of an electrophilic intermediate **315** (Scheme 51a). Subsequent attack of the tetrasubstituted double bond on the positively charged sulfur atom and interception of the resulting carbenium ion by the trifluoroacetate counteranion was shown to afford the stable salt **316**. Final hydrolytic cleavage of the trifluoroacetate ester and 3-*exo-tet* epoxide formation concluded the highly diastereoselective oxidation sequence.

Akita and co-workers have reported the use of electrophilic Togni's reagent as a precursor for the photoredox-catalytic formation of a CF_3-radical (Scheme 51b).[178] Following addition of said radical to a suitable olefinic coupling partner, single-electron oxidation by virtue of the photocatalyst was proposed to afford a cation (**318**), the interception of which with DMSO afforded an alkoxysulfonium intermediate (**319**). Structures of type **319** have been well-known for several decades, as they represent crucial intermediates in all DMSO-mediated carbonyl formations (vide supra). Recently, Ye and co-workers have extended this approach to the oxo-alkylation of styrenes with alkyl radicals derived from redox-active esters using photoredox-catalysis.[179]

Anodic oxidation was employed by Yoshida and co-workers for the functionalization and oxidation of both alkenes and benzylic positions (Scheme 52). Initially focusing on the direct oxidation of the substrate followed by interception of the resulting carbenium ion with DMSO (Scheme 52a),[180,181] the group later showed the potential of forming electrophilic halogens (**325**) and chalcogens through anodic oxidation (Scheme 52b).[182] Nucleophilic attack of an olefin onto **325**, followed by interception of the resulting carbocation with DMSO once more led to the formation of intermediate **326**,

Scheme 41. Li's Use of [2,3]-Sigmatropic Rearrangements of Sulfur Ylides for Allylic and Propargylic C–H Functionalization



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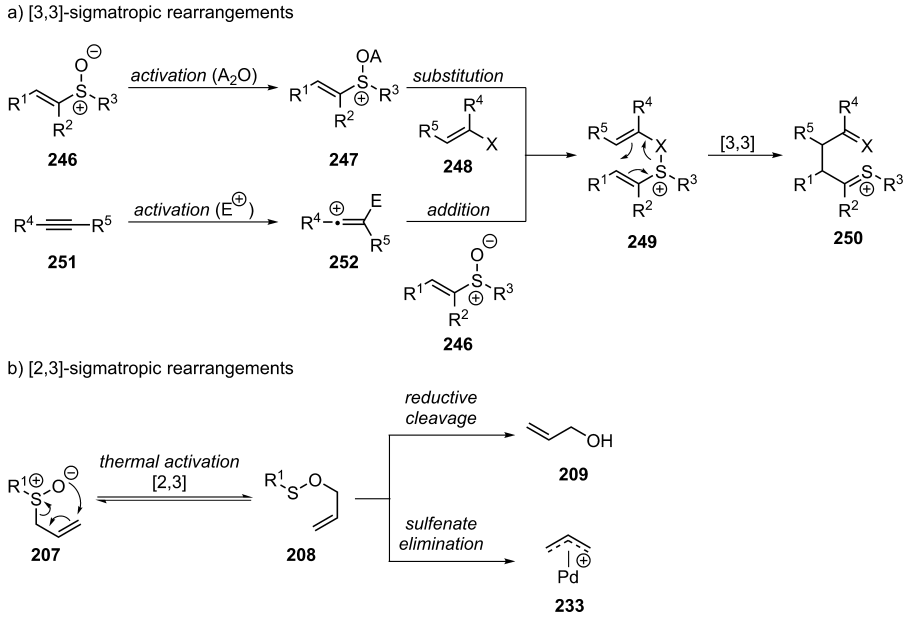
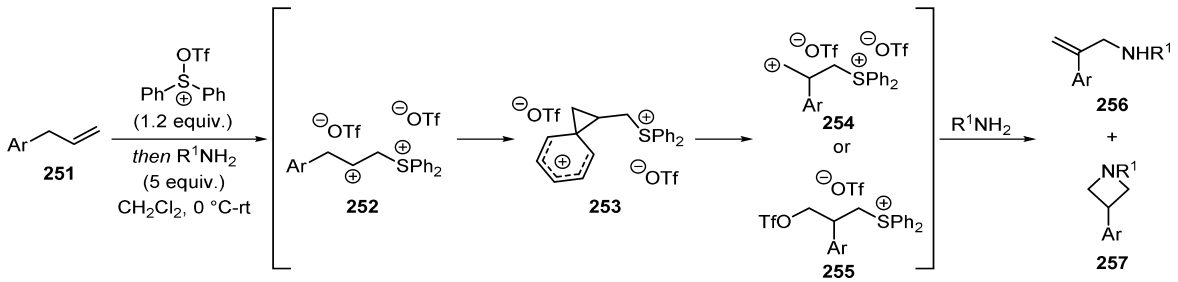
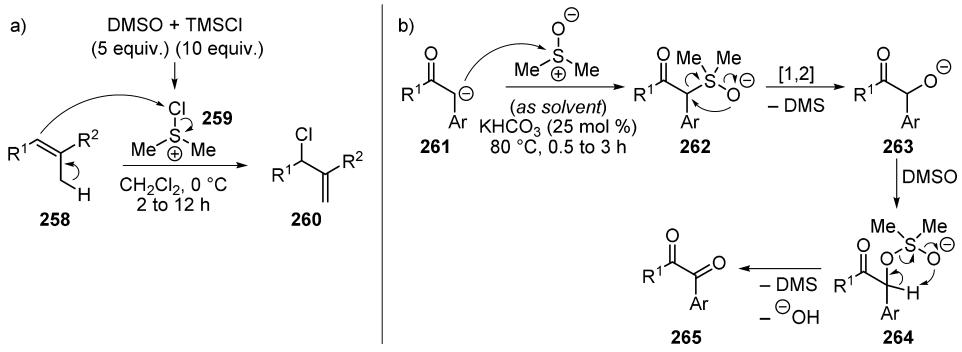
Scheme 42. Reactivity Trends of Sulfoxides in the Context of Sigmatropic Rearrangements



Scheme 43. Application of Activated Sulfoxides in the Functionalization of Allyl Benzenes



Scheme 44. Oxidative (a) Allylic and (b) Benzylic Functionalization via Unusual Attacks On Sulfur



prone to Kornblum-type oxidation and resulting in formation of α-halogenated carbonyls (**327**).

An alternative pathway for the formation of cationic species susceptible to interception with sulfoxides was described previously (section 2.2.1). In addition to the transformations presented there, which incorporate the sulfenyl moiety through sigmatropic rearrangement, the groups of Liu,[120] as well as Maulide and Niggemann,[183] have shown differing reactivity in specialized cases (Scheme 53). While Liu's work on the gold-catalyzed addition of diphenyl sulfoxide to cyclobutylalkyne **328** was shown to instigate the [3,3]-sigmatropic rearrangement pathway described previously (Scheme 53a), direct fragmentation of intermediate **331** (resulting from addition of diphenyl sulfoxide to activated cyclopropylalkyne **330**), accompanied by loss of diphenyl sulfide, was reported to lead to the formation of cyclobutenyl ketone **332** through ring-expansion. A related oxidative rearrangement, hinging on suppression of the sigmatropic shift through steric crowding of the reactive center, was recently disclosed jointly by the groups of Niggemann and Maulide (Scheme 53b).[183] Following capture of vinyl cation **334** with diphenyl sulfoxide, cleavage of the S−O bond leads to the formation of an α-carbonyl cation which readily undergoes a 1,2-hydride- or Wagner−Meerwein-type carbon shift to afford **337** after terminating deprotonation.

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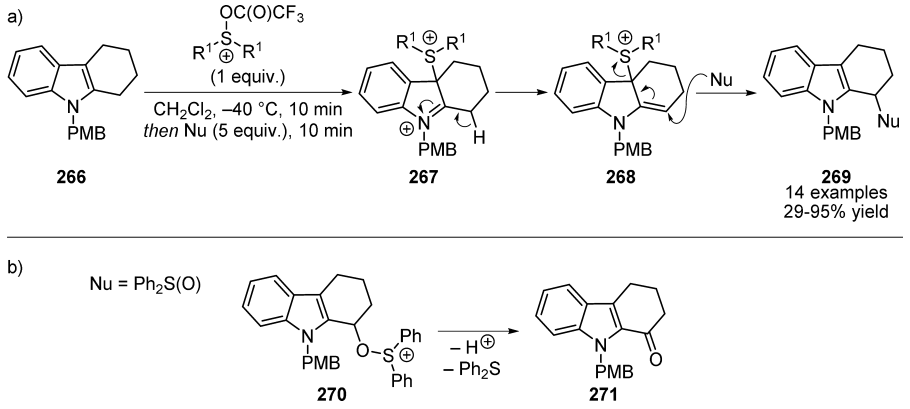
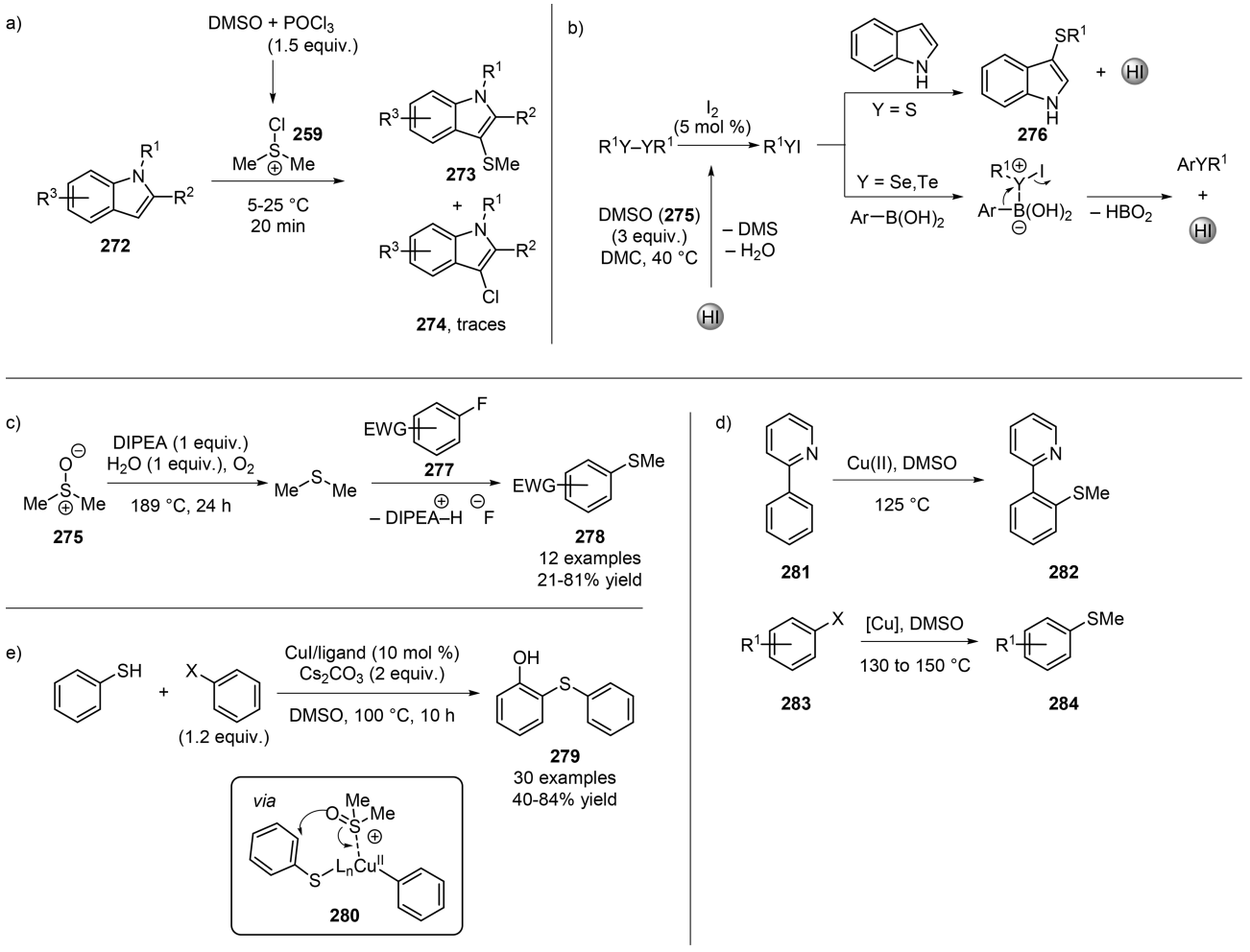
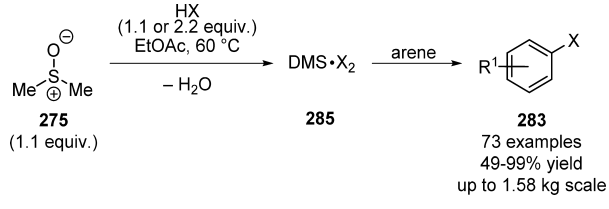
Scheme 45. Kawasaki's Benzylic Functionalization of Indole Derivatives



Scheme 46. Metal-Free and Copper-Catalyzed Methylthiolations of Arenes with DMSO



Scheme 47. Kilogram-Scale Halogenation of Arenes Enabled through DMSO-Mediated Slow Release of X_2



The use of Kornblum- or Swern-type processes for the formation of carbonyl compounds from π-unsaturated compounds, alluded to in the descriptions of several of the above transformations, has, in recent years, found application predominantly in the synthesis of α-ketoamides (Scheme 54). Starting from either styrenes (Scheme 54a, left) or phenylacetylenes (Scheme 54a, right), Shah and co-workers have shown that a combination of iodine and DMSO can lead to the formation of α-iodo ketones (**342**),[184,185] which are directly formed from ketones in works reported by the groups of

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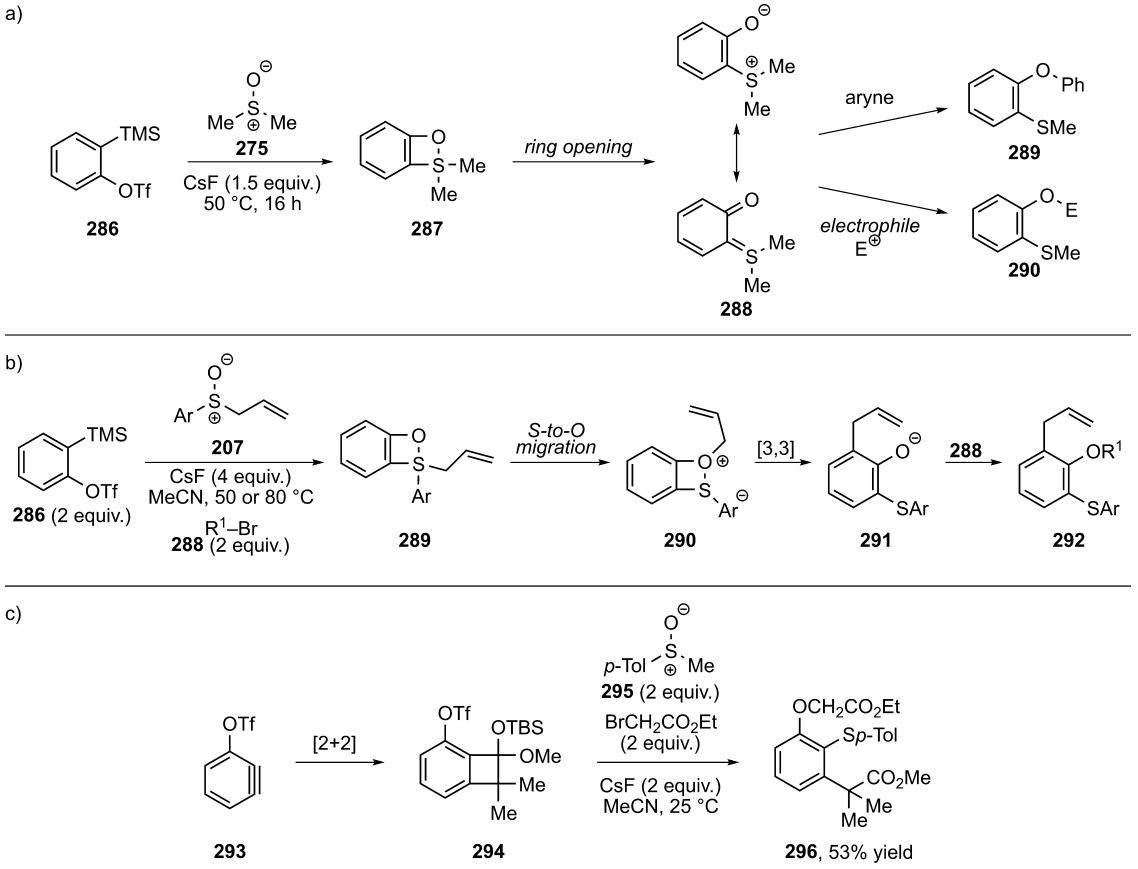
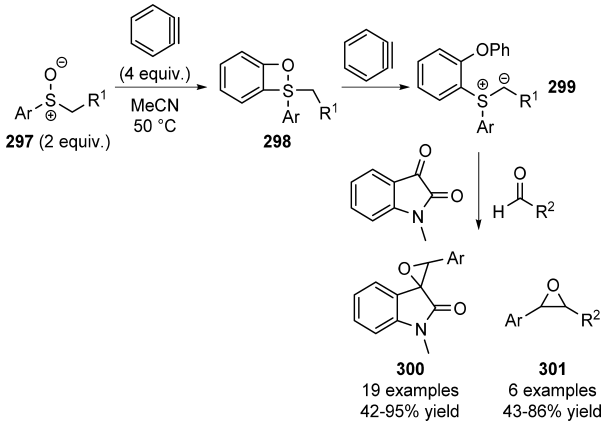
Scheme 48. Sulfoxides as Nucleophiles for the Capture of Arynes



Scheme 49. Use of Sulfoxide–Aryne Adducts for Epoxidation



Ahmed and Vishwakarma (Scheme 54b).[186,187] The formation of α-carbonyliminium ion **343** from **342** is common to all processes depicted in Scheme 54 and is followed by nucleophilic addition of DMSO and subsequent Kornblum-type oxidation to furnish the amide carbonyl.

2.3.4. Kornblum-Type Oxidations. Among the most common oxidation reactions in organic chemistry, the suite of Kornblum- and Swern-type oxidation reactions developed to date is countless, and much of recent research has focused on rendering known processes more economical and environmentally friendly. Owing to these circumstances, we urge the interested reader to turn to refs 8–11 for further and in-depth information.

As described above, the α-halogenation of ketones mediated by the combination of DMSO and a halide has been a prime source for recent developments in the area of Kornblum-type oxidations (Scheme 55). In this regard, and in addition to the previously mentioned examples, the groups of Cao and Deng have developed further protocols for the α-oxidation of ketones with DMSO and HBr.[188,189] Similar results were obtained by Jiao and co-workers, achieving selective α-hydroxylation of linear and α-branched ketones (**347**), using substoichiometric amounts of iodine and a large excess of DMSO (Scheme 55a).[190] In situ 1,2-dicarbonyl formation was additionally exploited in Wu and co-workers' oxazole synthesis, as shown in Scheme 55b.[191]

2.4. Metal–Sulfoxide Exchange

Organometallic reagents have long been employed as strong bases and highly reactive nucleophiles in organic synthesis. They are classically generated through the addition of a suitable metal (most often lithium or magnesium) to a halogenated precursor, often forming a metal salt as a byproduct. While this remains the method of choice in the generation of simple organometallic reagents, access to more complex structures usually requires a more subtle approach. The halogen–metal exchange, popularized by Gilman and Wittig in the late 1930s,[192–195] represents such an option. The formal metathesis reaction between an organolithium and an organic halide operates under thermodynamic control, affording the more stable organometallic reagent. A prime example of this control would be the reaction of an alkyl lithium species with a haloarene to generate an aryl lithium species.

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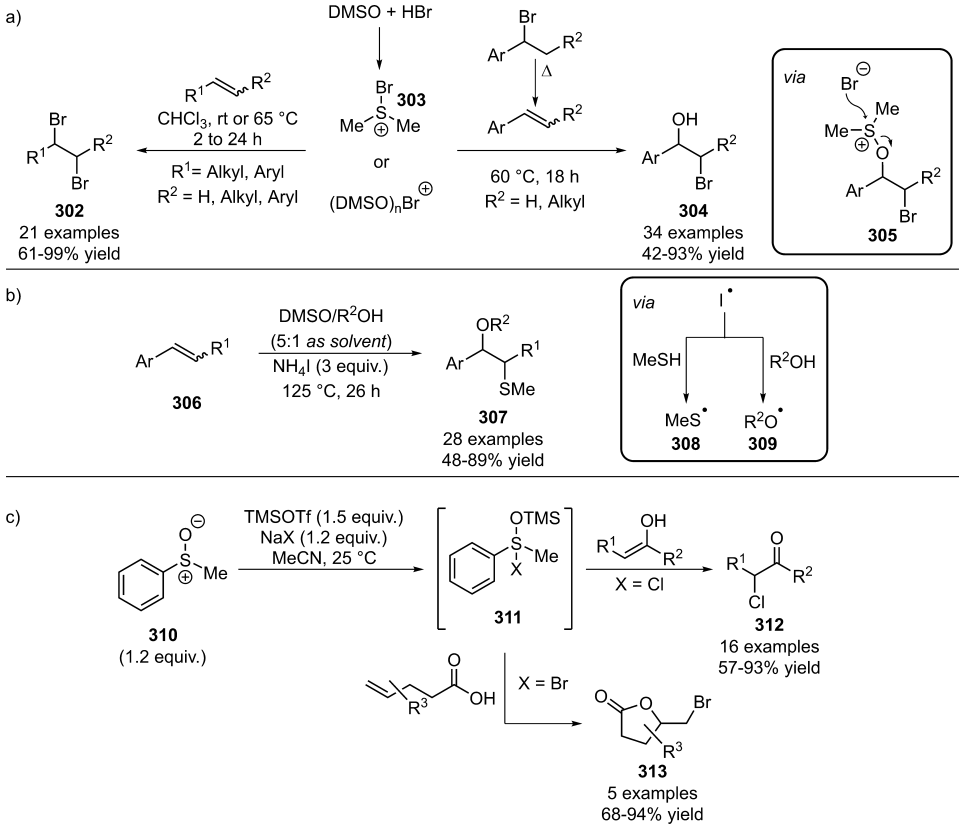
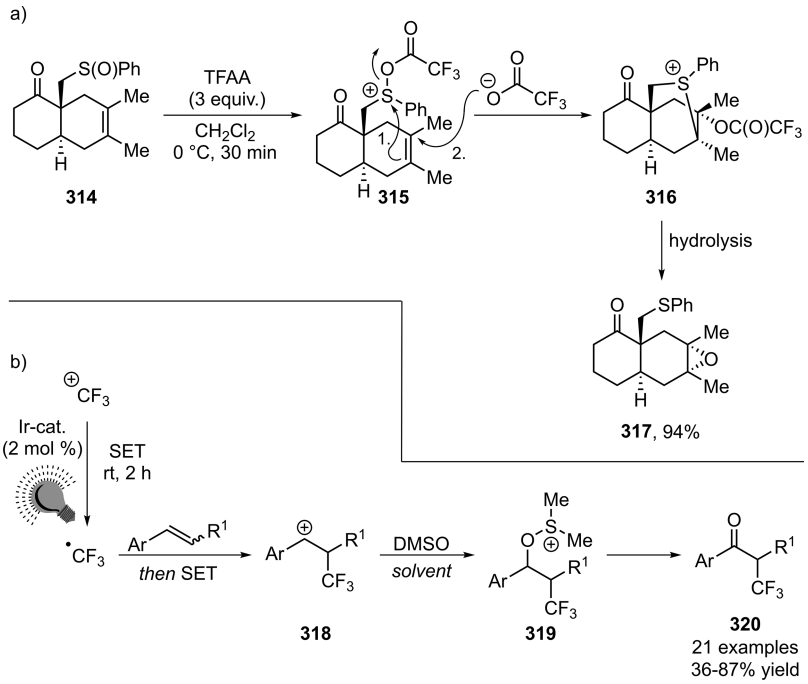
Scheme 50. (a) Polar, DMSO-Mediated Dibromination, and Bromohydrin Formation, (b) Oxysulfenylation of Alkenes via Radical Addition, and (c) Umpolung Halogenation/Halolactonization of Alkenes



Scheme 51. Application of Sulfoxides as (a) Electrophiles and (b) Nucleophiles in Alkene Functionalization



Analogous reactivity has since been demonstrated whereby, instead of halide-containing precursors, sulfoxides are the substrates of choice. As demonstrated in Scheme 56, an organometallic reagent is thought to have the ability to add reversibly to the electrophilic sulfur center, forming what is known as an σ-sulfurane (**354**). This metastable, hypervalent intermediate could then expel one ligand to generate the most stable organometallic reagent, and a sulfoxide that represents the formal product of nucleophilic substitution at the sulfur center (**355**). The precise mechanism of this process is

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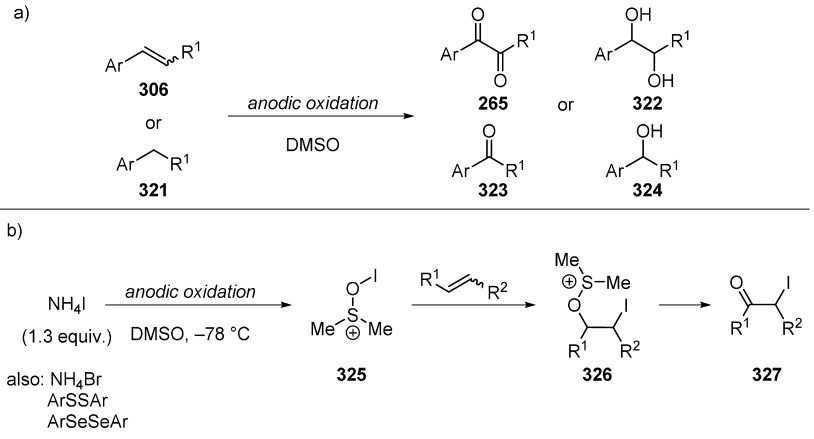
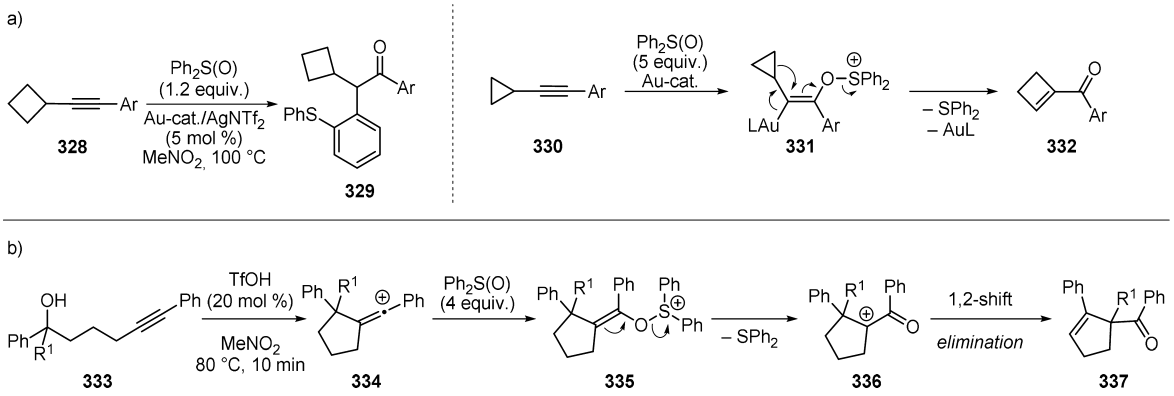
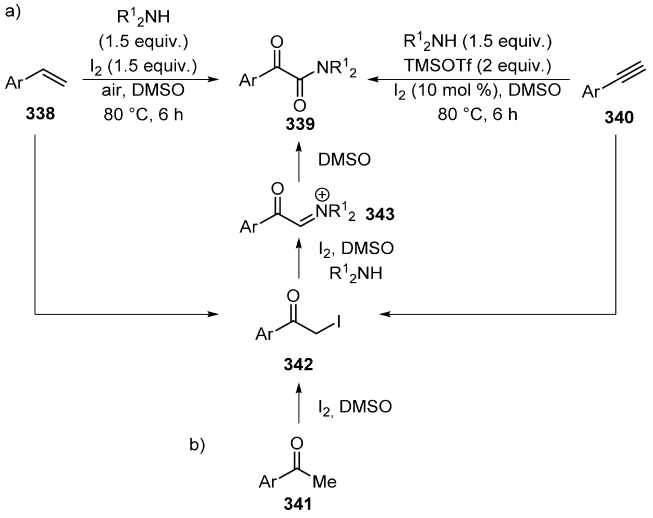
Scheme 52. Yoshida's Electrochemical Olefinic and Benzylic Oxidation Mediated by DMSO



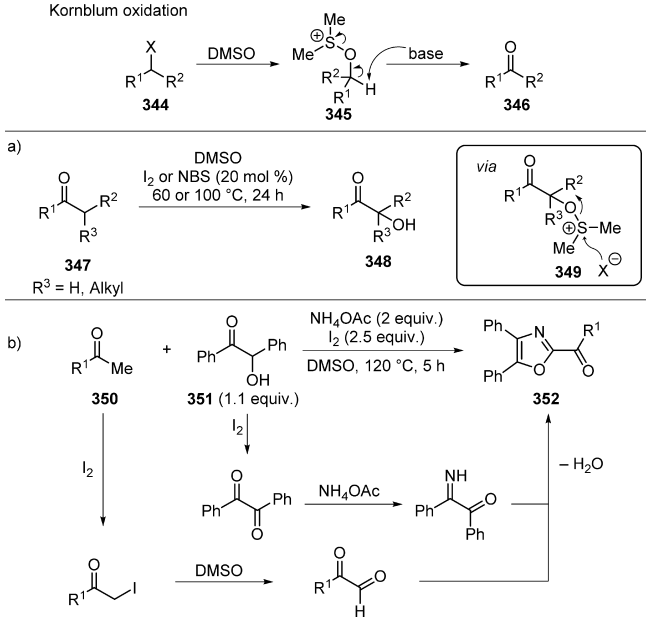
Scheme 53. Formation of Unusual Cationic Species through Elimination of Diphenyl Sulfide



Scheme 54. α-Ketoamide Formation by I_2-DMSO-Mediated Oxidation of Alkenes, Alkynes, and Ketones



Scheme 55. Recent Approaches to the Venerable Kornblum Oxidation



however unclear, with many researchers favoring an ill-defined radical pathway.

Regardless of the mechanism, this method can be used for either for the stereospecific synthesis of chiral sulfoxides (section 2.4.1) or for the selective preparation of complex organometallic reagents (as will be discussed in section 2.4.2).

2.4.1. Metal–Sulfoxide Exchange for Sulfoxide Synthesis. The synthesis of chiral alkyl aryl sulfoxides has long been reliably achieved through the use of Andersen's reagent (**356**), a menthol-derived sulfonate ester, pioneered in 1962 (Scheme 57a).[196] Reaction of the aryl sulfinate ester with an alkyl organometallic reagent forms a sulfoxide (**357**) and metal mentholate salt. The reaction is generally stereospecific, the

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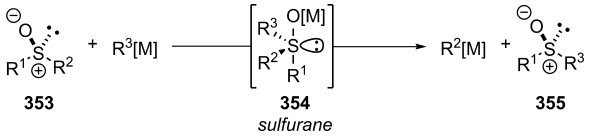
Scheme 56. Purported Intermediate in Metal−Sulfoxide Exchange



configuration of the generated sulfoxide resulting from inversion at the sulfur center.

While this stereospecificity has been observed over a wide range of aryl-derived sulfinate esters, the reliability tails off notably for alkyl sulfinate esters. As a result, alternative methods for the synthesis of dialkyl sulfoxides have been sought. Indeed, one of the very first synthetic methodologies to employ metal−sulfoxide exchange involved a lithium−sulfoxide exchange between an alkyl aryl sulfoxide and an alkyllithium species, generating a dialkyl sulfoxide with inversion of configuration.[197] More recently, Friedel−Crafts-type reactivity has been shown with racemic sulfinate salts to achieve the sulfinylation of electron-rich arenes.[198]

A recent development in this field was reported by the group of Brückner in 2015, involving the desymmetrization of symmetric diaryl sulfoxides by a chiral organometallic reagent, generated through the combination of a dialkylmagnesium with a Li_2-(*S*)-BINOLate salt (**360**) (Scheme 57b).[199] High selectivities were observed over a broad range of substrates in what represents the first example of an enantioselective metal−sulfoxide exchange. Because symmetrical aryl sulfoxides are easily synthesized, this methodology has the potential for practical applications.

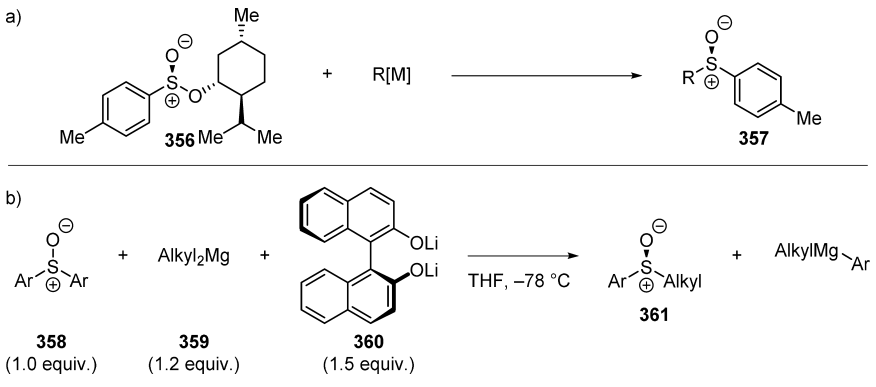
2.4.2. Metal−Sulfoxide Exchange for the Generation of Organometallic Species. While the above developments have contributed to the synthesis of enantioenriched sulfoxides, the major applications in recent years have predominantly been in the field of sulfoxides as organometallic precursors. When compared with halogen−metal exchange, the advantages of metal−sulfoxide exchange are not limited to selectivity and functional group tolerance. The chiral nature of sulfoxides allows for the facile synthesis of diastereomerically pure substrates, which can then easily be converted into enantiopure organometallic reagents, useful for asymmetric synthesis.

Remaining for the present outside the arena of asymmetric synthesis, metal−sulfoxide exchange reactions have been shown in recent years to be of use in the preparation of high-energy intermediates such as benzynes and cycloalkynes. Benzyne in particular has long been employed in organic synthesis, allowing for the rapid multifunctionalization of aromatic rings, either through a difunctionalization approach or cycloaddition chemistry.[200] The use of Grignard reagents to generate arynes through metal−sulfoxide exchange followed by β-elimination is orthogonal and complementary to the use of the classical Kobayashi precursors, relying on the fluoride-promoted elimination from an *ortho*-silyl aryl triflate (as briefly shown in section 2.3.2). Originally reported in 1987,[201] employing halide-based precursors, the methodology has recently been improved upon by the group of Hosoya by exchanging the halide leaving group for a triflate.[202] Shortly afterward the same laboratory demonstrated that a similar approach could be employed for the in situ synthesis of strained cycloalkynes.[203] The authors detail the preparation of seven- and eight-membered cycloalkynes, the latter being stable enough to isolate but the former requiring in situ preparation. These cycloalkynes generate a wide range of interesting products through either (3 + 2)- or [4 + 2]-cycloaddition reactions at 0 °C in short reaction times (Scheme 58).

In a series of publications, Knochel et al. combined a sulfoxide-directed *ortho*-metalation/functionalization reaction with a magnesium−sulfoxide exchange for the difunctionalization of arenes.[204−207] In these reports, they employ a "*Turbo*-Hauser base" (**370**) for selective *ortho*-metalation, and a "*Turbo*-Grignard reagent" for the magnesium−sulfoxide exchange (Scheme 59a), with each generated intermediate able to react with a range of electrophiles. The high functional group tolerance allows for the generation of a wide range of 1,2,4-trisubstituted arenes in addition to 1,2-disubstituted heterocycles.

In addition to simple capture with electrophiles, intermediates generated through metal−sulfoxide exchange can also be functionalized through catalytic cross-coupling reactions. A prime example of this is the synthesis of highly substituted aziridines (**375**) through a magnesium−sulfoxide exchange/cross-coupling sequence reported by Bull et al. in 2013 (Scheme 59b).[208] A range of highly functionalized sulfinyl aziridines **373**, easily accessed through a Darzens-type process between an α-halosulfoxide and PMP-imine underwent the reaction efficiently in a stereoretentive manner. The stability of the generated aziridinyl Grignard reagent **374** (and subsequent aziridinyl zinc) was a key point of interest in the investigation, with reaction yields seen to diminish when delays were introduced prior to the addition of the catalyst mixture due to degradation of the intermediate.

Scheme 57. Metal−Sulfoxide Exchange for the Synthesis of Chiral Sulfoxides



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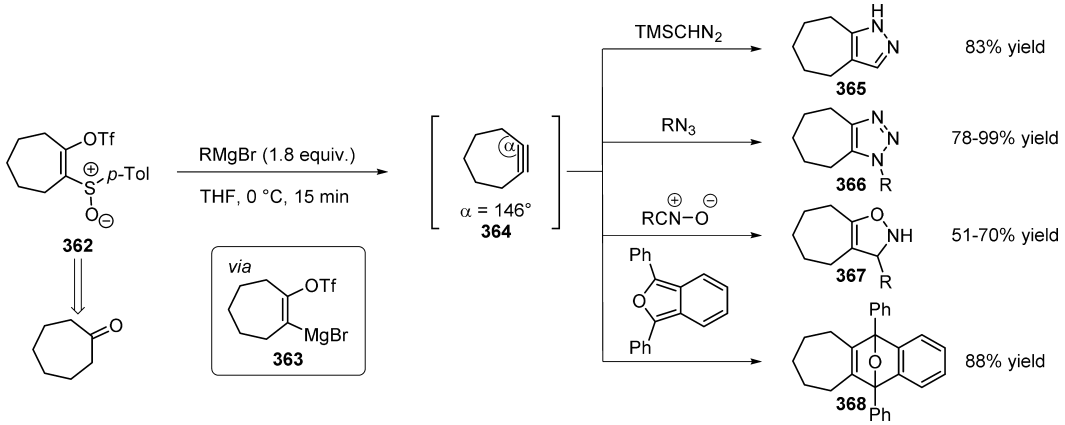
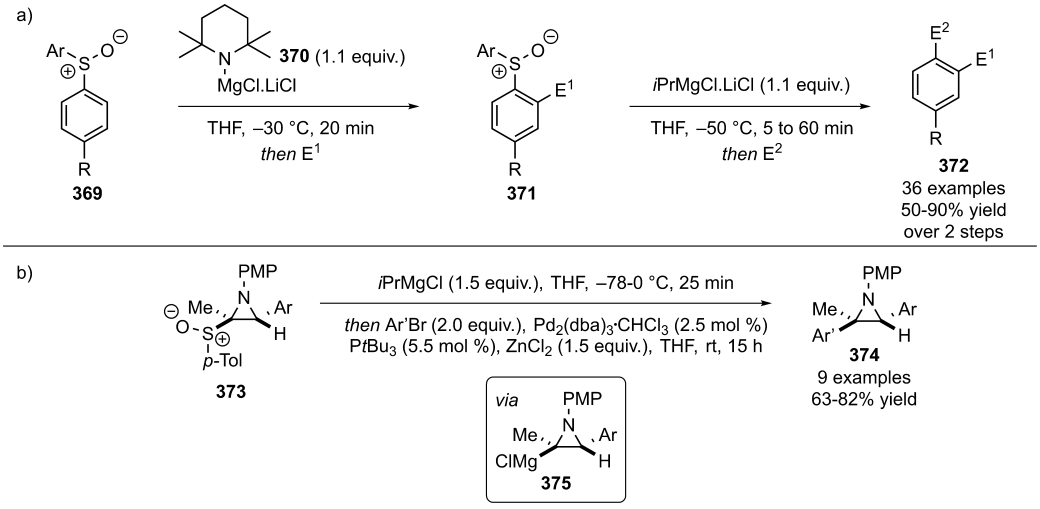
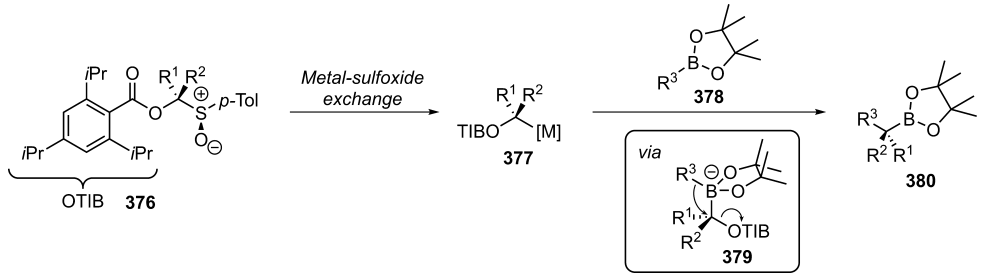
Scheme 58. Accessing Highly Strained Cycloalkynes through a Metal−Sulfoxide Exchange/Elimination Pathway



Scheme 59. Metal−Sulfoxide Exchange in the Synthesis of Highly Functionalized Targets



Scheme 60. Employing Metal-Exchange for the Generation of Chiral Metal Carbenoid Equivalents



As previously discussed, the chiral nature of sulfoxides allows for metal−sulfoxide exchange processes to be used in asymmetric synthesis. In what is by far the most common use of metal−sulfoxide exchange in the academic literature of the past decade, chiral sulfoxides can readily serve as precursors to lithium/magnesium carbenoids, typically used for the homologation of boronic esters (Scheme 60). A slew of papers detailing the use of α-halo sulfoxides have been released from the group of Blakemore over the past 10 years.[209−215] A number of deleterious side reactions were sometimes observed when these precursors are employed and, as a result, investigations by O'Brien[216] and Aggarwal[217] focused on the use of α-sulfinyl carbonates and benzoates, respectively. O'Brien's synthesis relied on a double induction strategy involving a chiral base and Andersen's sulfinate to generate the key sulfoxides. In contrast, Aggarwal and co-workers preferred to use an achiral base and separate the two diastereomers formed, allowing access to either carbenoid epimer. It was additionally possible to diastereoselectively alkylate these chiral α-sulfinyl benzoates, allowing for the generation of quaternary centers.

Once generated, these diastereomeric α-sulfinyl benzoates (**376**) readily undergo lithium−sulfoxide exchange to generate a chiral lithium carbenoid **377** (the stereochemistry at sulfur makes no difference to this step), which can react with boronic esters to generate a boronate **379** (Scheme 60). The presence of the benzoate leaving group enables a 1,2-shift (termed 1,2-metalate rearrangement), effecting a single carbon homologa-

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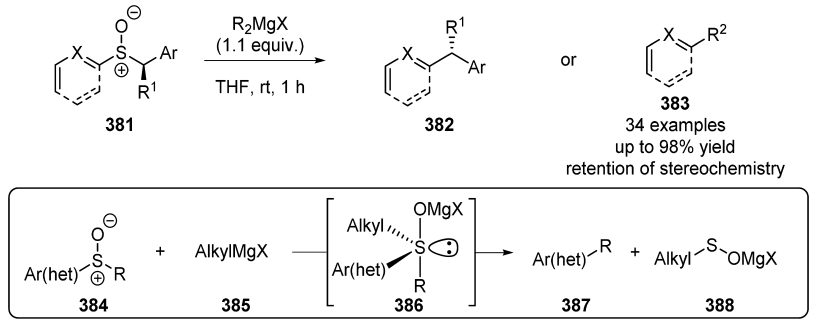
Scheme 61. Stockman's Exploration of Oae's Ligand-Coupling Reaction



tion, a process which can be performed iteratively to build a longer chain.

2.4.3. Ligand Coupling: A Mechanistic Curiosity. Despite the rich breadth of metal−sulfoxide exchange chemistry, there are of course potential difficulties when it comes to controlling the reaction outcome. Not only can the organometallic reagents potentially react with other more reactive centers, but even in the event of interaction with the sulfoxide, the reaction path can be unpredictable. Often the identities of the sulfoxide substituents are the key to this selectivity. For instance, in Knochel's arene difunctionalization chemistry,[207] the formation of the more electron-poor Grignard reagent (Ar is either *p*-anisyl or *p*-dimethylaminophenyl) is key to the method.

Despite several years of study, not much is known of the precise mechanism, with various theories propounded. In addition to an ill-defined radical pathway, an interesting proposal (as detailed in the introduction of this section 2.4) involves a reversible addition of the organometallic reagent to the sulfur center forming a metastable σ-sulfurane **386** (Scheme 61). The latter, in addition to expelling a leaving group as a new Grignard reagent, can also theoretically undergo a reductive elimination-type pathway to generate a magnesium sulfenate **388** in addition to a C−C cross coupling product. This process, first observed by Oae in the late 1980s[218] (see also Oae and Trost's ligand coupling reactions involving sulfonium salts),[219,220] was studied in great detail to try to ascertain the mechanism. However, synthetic applications have remained limited. The scope of the reaction, and the potential for accessing chiral Csp^2−Csp^3 coupled products (without resort to transition metal catalysis) was assessed in a 2016 publication by the laboratory of Stockman (Scheme 61).[221]

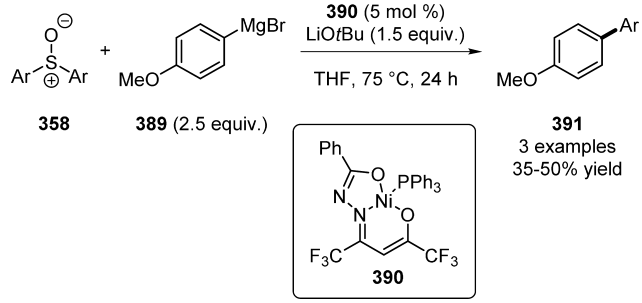
Among other results, Stockman showed that the ligand-coupling reaction could occur with faithful retention of stereochemistry at any carbon-based stereogenic centers, which can (as has been seen above) be generated by the diastereoselective functionalization of a chiral sulfoxide. While the scope of C−C coupling products is largely limited to 1,1-diarylalkanes, the reaction remains intriguing for its insight into the potential mechanism of metal−sulfoxide exchange.

2.5. Cross Coupling of Sulfoxides

Recently, the cross-coupling of organosulfur compounds as electrophiles has seen increased interest. These reactions focus mainly on the coupling of sulfonium salts, unactivated sulfides, and sulfones.[222] In stark contrast, cross-coupling reactions with sulfoxides have been far less investigated. Conceptually, two distinct approaches are known: desulfurylation reactions, proceeding under extrusion of a sulfenate as the byproduct, and sulfoxide syntheses, in which the sulfenate is engaged in metal-catalyzed coupling reactions and incorporated into the desired product. The recent advances on the cross-coupling of sulfoxides will be discussed in this section.

2.5.1. Desulfurylation Reactions. Seminal work by Wenkert and co-workers revealed the possibility of palladium-catalyzed coupling of aryl sulfoxides with methyl- and arylmagnesium reagents to obtain the corresponding desulfurized cross-coupling products.[223] In 2013, Enthaler reported a similar transformation, using nickel catalyst **390** (Scheme 62).[224] However, only three examples were reported with moderate yields.

Scheme 62. Enthaler's Cross-Coupling of Aryl Sulfoxides with Grignard Reagents



In 2017, the group of Yorimitsu developed a Sonogashira−Hagihara-type coupling of diaryl sulfoxides with terminal alkynes using palladium−PEPPSI as a precatalyst,[225] and more recently, the same group reported a palladium−NHC-catalyzed Buchwald−Hartwig-type coupling with a variety of amines, affording aniline derivatives (Scheme 63).[226]

In contrast to these palladium-catalyzed reactions of diaryl sulfoxides, in the case of nickel-catalyzed cross-coupling of the more readily accessible alkyl aryl sulfoxides with diarylzinc nucleophiles, the alkanesulfenate anions generated as leaving groups during the course of the reaction inhibit catalytic turnover. Oxidative homocoupling of the diarylzinc reagent (with concomitant reduction of the sulfenate anion to a thiolate) readily consumed the former species, resulting in an efficient catalytic reaction (Scheme 64).[227] The cross-coupling reactions afford biaryls **398** in good to excellent yields, albeit accompanied by an equimolar amount of the homocoupling byproduct, which can result in difficult purifications.

Carbon−heteroatom bond formations such as borylation[228,229] and phosphinylation[230] using aryl sulfoxides have also been reported, are, however, often low-yielding and limited in scope.

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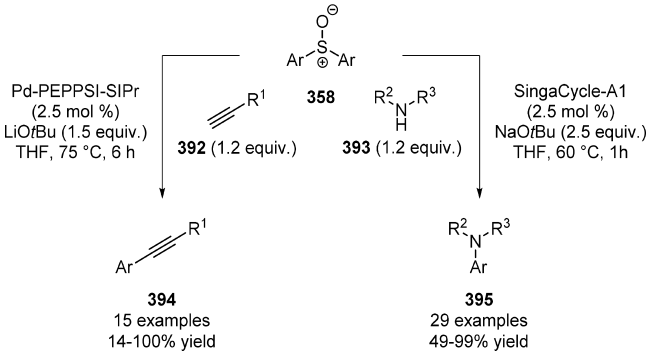
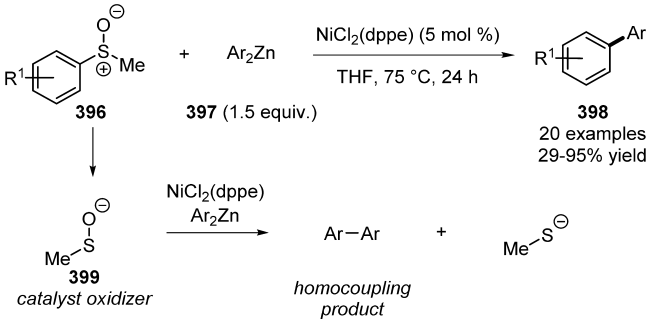
Scheme 63. Yorimitsu's Palladium-Catalyzed Cross-Coupling Reactions of Diaryl Sulfoxides with Alkynes (left) and Amines (right)



Scheme 64. Yorimitsu's Cross-Coupling of Aryl Sulfoxides with Diarylzinc Reagents



2.5.2. Sulfoxide Synthesis. Madec, Poli, and co-workers reported that sulfenate anions could also be employed as nucleophiles in palladium-catalyzed cross-coupling with aryl halides to yield diaryl sulfoxide products. β-Sulfinyl esters (**400**) could be used for the in situ generation of sulfenate anions through retro-Michael reaction (Scheme 65a). Subsequent arylation with aryl iodides afforded diaryl sulfoxides **195** in good yields but with only moderate substrate scope.[231]

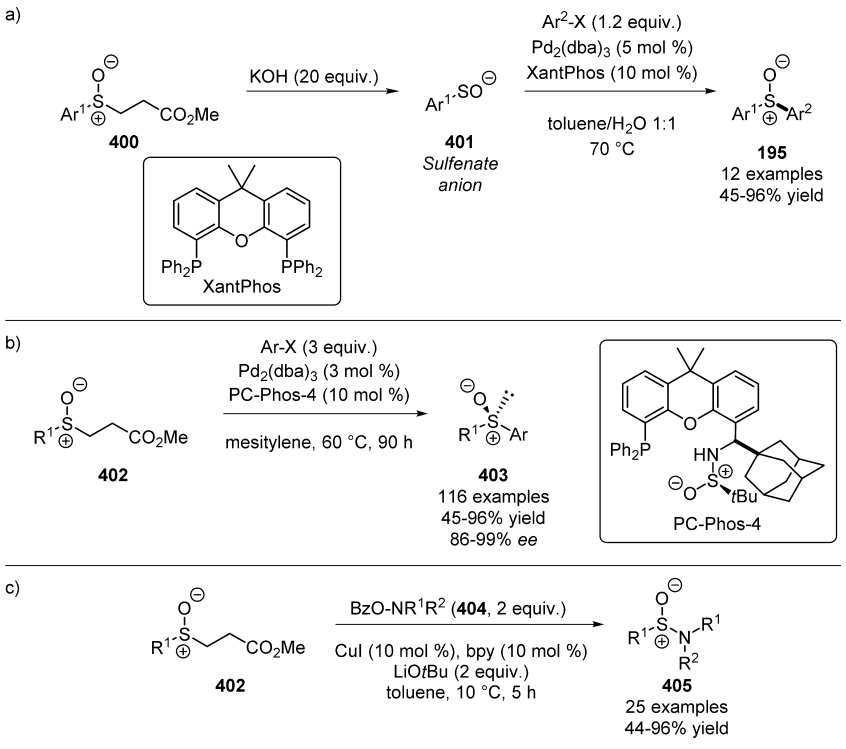
The reaction was also rendered enantioselective by replacing XantPhos with a chiral ligand. Josiphos was found to be the best ligand, affording the diaryl sulfoxides in good yields and moderate *ee* (not shown).[232] A more general and robust approach for the enantioselective arylation of general sulfenate anions was recently reported by Zhang and co-workers, using a XantPhos-derived PC-Phos ligand (Scheme 65b).[233] Additionally, Tan and co-workers disclosed an organocatalytic approach for the enantioselective alkylation of sulfenate anions generated from sulfoxides, using halogenated pentanidium salts as phase-transfer catalysts.[234]

Other strategies to generate sulfenate anions in situ through Mislow−Evans rearrangement have been previously discussed (section 2.2.2, Scheme 39) and should be complemented at this point, although not involving sulfoxide formation, by Zhang's sulfinamide synthesis (Scheme 65c).[235] Herein, the sulfenate anion is engaged in a copper-catalyzed coupling with benzoylhydroxylamines (**404**) to afford the desired products **405** in moderate to excellent yields.

The group of Walsh reported that sulfenate anions can also be generated from aryl benzyl sulfoxides (**406**) (Scheme 66).[236] The process involves sulfoxide α-arylation, C−S bond cleavage to form the sulfenate anion and finally arylation. The diarylmethyl *tert*-butyl ether byproduct **408** of C−S bond cleavage could be isolated from the reaction mixture, corroborating the proposed mechanism.

This process was found to allow for the coupling of a wide variety of readily available aryl benzyl sulfoxides with several (hetero)aryl bromides in good to excellent yields. A catalytic

Scheme 65. (a,b) Palladium-Catalyzed Arylations of Sulfenate Anions and (c) Sulfonamide Synthesis



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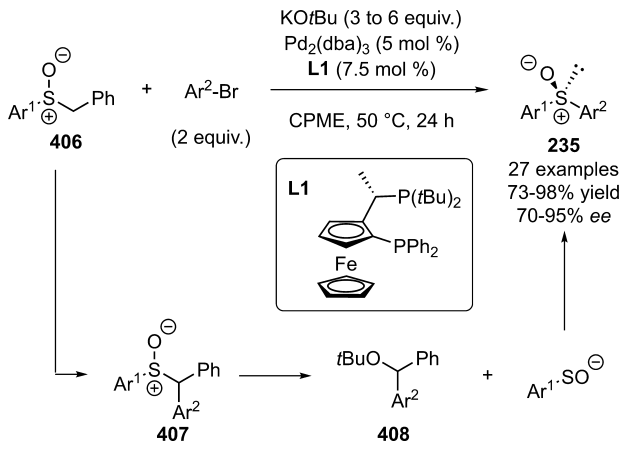
Scheme 66. Walsh's Palladium-Catalyzed Arylation of Sulfenate Anions



asymmetric coupling was achieved with a JosiPhos derivative as the ligand, affording a wide range of diaryl sulfoxides that would be difficult to synthesize using classical enantioselective sulfide oxidation protocols with good to excellent enantioselectivities.[237]

While not involving bond formation or cleavage at sulfur, the possibility of dynamic kinetic resolution of allyl[238] or vinyl sulfoxides[239] should be mentioned as an elegant means for obtaining enantioenriched sulfoxides.

3. SULFONIUM SALTS

Sulfonium ions are positively charged sulfur ions with three organic substituents and as such have been employed in a wide range of reaction types, exploiting their inherent electron deficiency. Compared to their oxygen analogues, the oxonium salts, they show increased stability and most sulfonium salts are easy to handle, bench-stable compounds. In general, the chemistry of sulfonium salts is dominated by their tendency to form an uncharged sulfide (Scheme 67). In this regard, they resemble organohalides displaying excellent nucleofugal properties, facile one-electron reduction and a propensity to undergo oxidative addition with transition metal catalysts. Sulfonium salts have thus shown to be highly versatile reagents in C−C and other bond-forming reactions and have seen a wide range of applications.

If combined with simple nucleophiles, sulfonium ions will undergo classical nucleophilic substitution reactions and have even been used as excellent leaving groups in S_NAr processes, where they display the added advantage of enabling reactivity on only moderately electron-poor aromatics due to their innate positive charge (Scheme 67a). In this context, arylsulfonium salts have found widespread application in the radiolabeling of medicinally relevant compounds with fluorine-18.[240−244] The addition of a single electron to a sulfonium ion leads to its fragmentation, forming a carbon-centered radical (Scheme 67b). This type of process has been of great interest in recent years, especially for the introduction of fluoroalkyl groups into organic substrates, the prototypical reagent for this application being Umemoto's reagent.

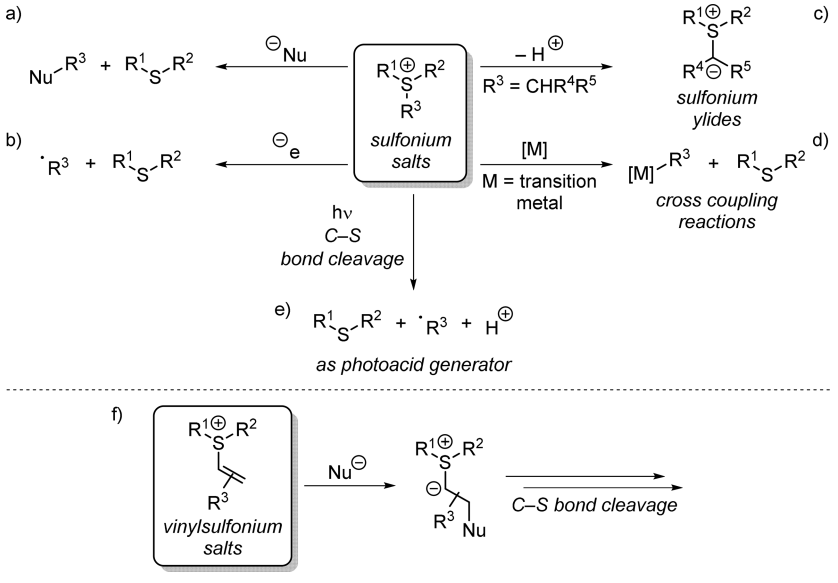
The abstraction of a proton α to the sulfonium moiety leads to the formation of sulfur ylides (Scheme 67c), a class of compounds displaying a rich and versatile chemistry which will be discussed in chapter 4.

Owing to the ease with which oxidative addition into the C−S bond of sulfonium ions can take place, these compounds have found application in transition metal-catalyzed cross-coupling reactions, mainly employing palladium and nickel catalysts (Scheme 67d).

Interestingly, the irradiation of sulfonium salts with UV light can also effect C−S bond cleavage affording radicals, the recombination of which is known to lead to the release of a proton (Scheme 67e).[245] This property has led to the use of sulfonium salts as photoacid generators, an application that has found widespread implementation in the synthesis of photoresponsive materials. Notably, recent developments have led to the synthesis of visible-light responsive sulfonium-based photoacid generators.[246]

Vinylsulfonium salts constitute a privileged class of sulfonium ions, able undergo bond formation with nucleophiles at their β-position, forming sulfur ylides which themselves can form up to two new bonds (Scheme 67f).

Scheme 67. Outline of the Reactions of Sulfonium Salts and Vinylsulfonium Salts



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Just as the wide variety of possible reactions of sulfonium ions mentioned above, the multifaceted reactivity of vinylsulfonium salts will be presented in this chapter, highlighting the most recent and compelling transformations.

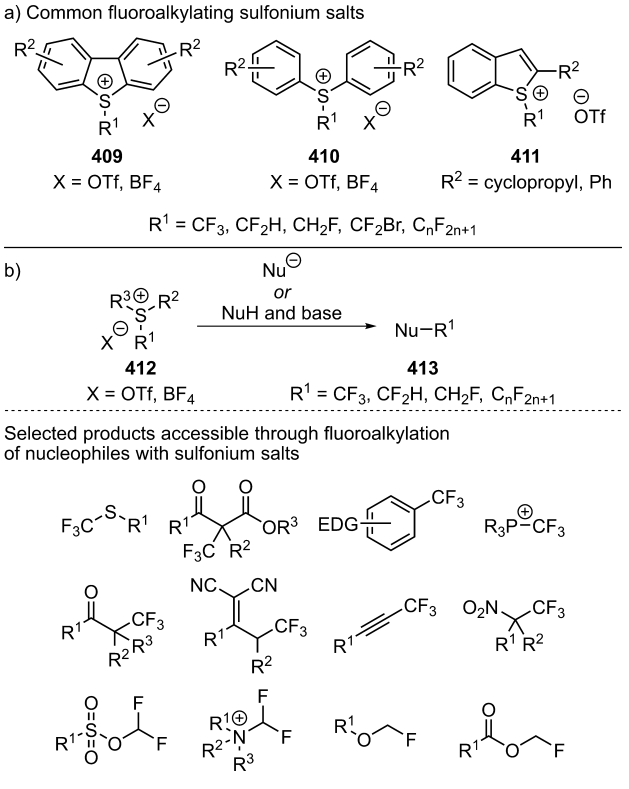
3.1. Sulfonium Salts As Fluoroalkylating Agents

Increased interest in fluorinated organic molecules by medicinal chemists has led to the development of a myriad of approaches for the introduction of fluorine or fluorinated moieties.[247,248] In this context, many sulfur-based reagents that enable a wide range of approaches for the introduction of fluorine have been developed and heavily studied. Owing to the immense impact of organofluorine compounds in recent decades and the interconnected interest in methodological development, a number of excellent reviews on the topic of fluoroalkylation have been published and should be consulted for information complementing the survey presented below.[249−262] In this section, we aim to present a short overview of their reactivity and their most commonly found transformations: reaction with nucleophiles, photoredox-catalyzed processes, and transition metal-catalyzed reactions that proceed through trifluoromethylated metal species.

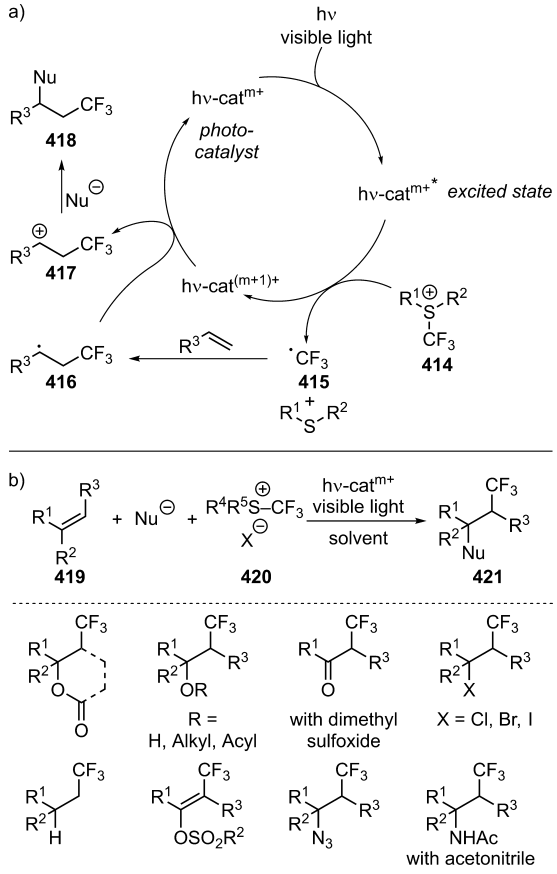
Since their emergence toward the end of the last century, several fluoroalkylated sulfonium salts have been developed as electrophilic fluoroalkylating agents, the groups of Umemoto,[263] Shreeve,[264] Shibata,[265] Prakash, and Olah[266] and others making many contributions to the advancement of the field (Scheme 68a). All of these sulfonium-based reagents possess a similar aromatic core structure. In the process of studying derivatives of **409**, it was found that the reactivity can be further enhanced by the introduction of electron-withdrawing groups;[260] moreover, sulfonate groups have been used to increase the reagents' solubility in water and thus simplify purification.[267] As shown in Scheme 68b, nucleophiles can be directly engaged in fluoroalkylation reactions in polar solvents and under mild conditions. However, the scope of suitable nucleophiles can vary immensely. This discrepancy in reactivity and generality has been attributed to a change of mechanism (that can vary between an ionic (CF_3^+) and a radical ($CF_3^\bullet$) pathway) depending on the nature of the nucleophile, the properties of the fluoroalkylating agent and the reaction conditions.[268] For example, mechanistic investigations have suggested a radical pathway in the reaction with silyl enol ethers,[269] and in rare cases, a mechanism involving carbene formation is also observed.[270] With some nucleophiles, such as amines, sulfonium salts can form donor−acceptor complexes (EDA complexes), able to generate CF_3-radicals which can be used for the trifluoromethylation of arenes.[271]

More commonly, trifluoromethyl radical transformations with sulfonium salts can be performed using photoredox catalysis (Scheme 69).[261] A representative catalytic cycle is shown in Scheme 69a: upon photoexcitation, a range of common photoredox catalysts are able to reduce trifluoromethyl sulfonium salts (**414**) via single-electron reduction, leading to fragmentation with the formation of a trifluoromethyl radical (**415**). Addition of this radical to an alkene or an alkyne forms a new carbon-centered radical (**416**) which, in turn, can be oxidized to the corresponding carbocation (**417**), thereby regenerating the photocatalyst. Alternatively, a chain-

Scheme 68. (a) Generic Structures of Fluoroalkylating Sulfonium Salts; (b) Reaction of Fluoroalkylated Sulfonium Salts with Nucleophiles



Scheme 69. (a) Representative Catalytic Cycle of Trifluoromethylation with Sulfonium Salts under Photoredox Catalysis; (b) Examples of Alkene Functionalizations



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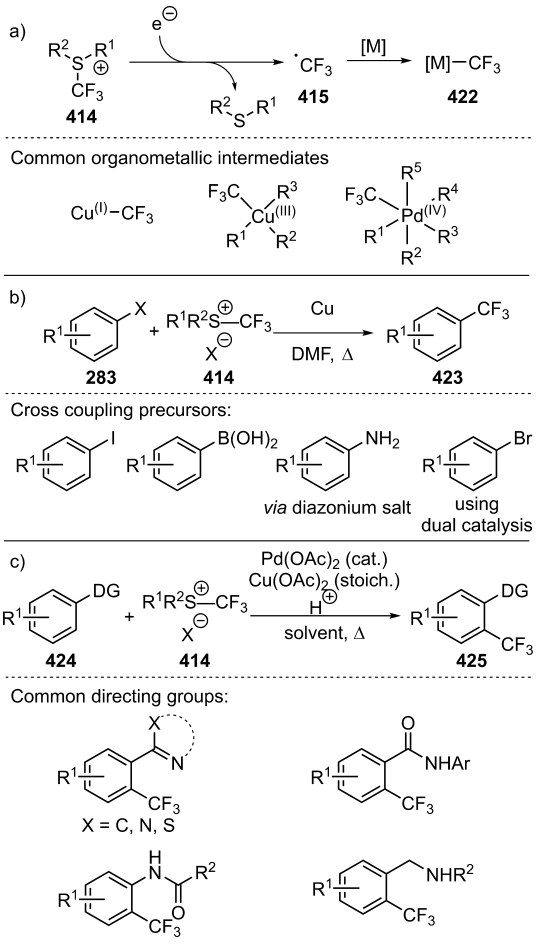
propargation mechanism involving single-electron transfer (SET) to the sulfonium salt is also feasible (not shown). **417** can be trapped by a number of nucleophiles, such as water, alcohols, carboxylates, nitriles, or halides, affording a wide range of products (Scheme 69b). As shown in Scheme 51b, using dimethyl sulfoxide as the solvent, α-trifluoromethyl ketones are obtained after Kornblum-type oxidation.[178] Direct hydrotrifluoromethylation has also been achieved using methanol as the terminal reducing agent.[272]

Under similar conditions, internal alkynes can be functionalized with sulfonate nucleophiles to afford sulfonyloxy trifluoromethylated alkenes.[273] These vinyl triflate products can be subjected to palladium-catalyzed cross coupling, allowing stereoselective access to a range of tetrasubstituted alkenes bearing a trifluoromethyl group.

The combination of transition metals (such as copper or palladium) with Umemoto's and related reagents, leading to the formation of trifluoromethylated metal species, is another extremely versatile group of transformations for the incorporation of fluoroalkyl group in organic compounds.[252,253] Most commonly, these reactions involve the intermediacy of Cu^{I}, Cu^{III}, or Pd^{IV} species (Scheme 70a). With elemental copper, trifluoromethyl sulfonium salts are readily reduced to form the highly versatile $CuCF_3$ species (after a second SET) under mild conditions. This facile process was applied to the cross coupling of aryl iodides, aryl boronic acids, and aniline derivatives, the latter reaction involving the in situ formation of the corresponding diazonium salt to form trifluoromethylted arenes (Scheme 70b). More recently, MacMillan and co-workers have been able to cross couple previously challenging aryl bromides and convert them into their trifluoromethylated-derivatives by employing a combination of photocatalysis and copper catalysis.[274]

Moreover, the trifluoromethyl group can be directly be installed with the use of directing groups.[275,276] A combination of catalytic $Pd(OAc)_2$ and stoichiometric $Cu(OAc)_2$ can be used to introduce the trifluoromethyl group at the *ortho*-posititon of a range of directing groups (Scheme 70c). This reaction is not limited to the trifluoromethyl group, also lending itself to a range of different alkyl groups that can be introduced, using the respective sulfonium salts.[277]

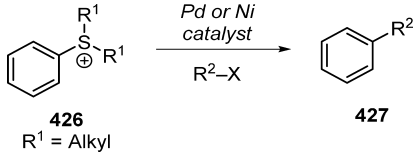
Scheme 70. Transition Metal-Catalyzed Trifluoromethylations: (a) Formation of Trifluoromethylated Organometallic Intermediates; (b) Cross Coupling of Arenes with Trifluoromethylsulfonium Salts; (c) Introduction of a Trifluoromethyl Group Using Directing Groups



3.2. Cross Coupling of Sulfonium Salts

While the cross coupling of sulfides and thioesters (both S(II) compounds and therefore not within the scope of this review) is well developed and has found many applications,[222,278,279] the use of sulfonium salts as coupling partners, pioneered by Liebeskind and co-workers toward the end of the last millennium,[280,281] offers significant advantages (Scheme 71).[90,222] Most notably, (hetero)aryl (as well as alkenyl or benzyl) sulfonium salts (**426**) promise to exhibit considerably increased tendency to undergo oxidative addition, owing to their inherent electron deficiency, and additionally, catalyst poisoning by the corresponding leaving group in sulfonium cross coupling (a thioether) is less likely than in the case of a thiolate leaving group. For these reasons, while laying dormant for several years, recent reports have highlighted the utility of transition metal-catalyzed cross-coupling reactions of sulfonium ions.

Scheme 71. Arylsulfonium Salts Allow for Transition Metal-Catalyzed Cross-Coupling Reactions



While the aforementioned traditional sulfonium cross-coupling reactions rely on activation of the $S-C_{aryl}$ bond, Lu, Shen, Lu, and co-workers reported the interesting selective cleavage of the $S-C_{vinyl}$ bond of **428** to afford styrenes (**429**) after Suzuki-type cross coupling (Scheme 72a).[282] Additional experiments highlighted the importance of the vinylogous trifluoromethyl group to ensure both the reactivity and the desired chemoselectivity. Apart from this report, all cross-coupling reactions of sulfonium ions rely on the activation and cleavage of the $S-C_{aryl}$ bond, affording a functionalized arene as the product.

In this context, in 2015, Yorimitsu and co-workers disclosed the facile transformation of dibenzothiophene (**430**) into triphenylenes (**434**), which relied on sequential double alkylation and cross coupling via alkylsulfonium salts **431** and **433** (Scheme 72b).[283,284] Following this transformation,

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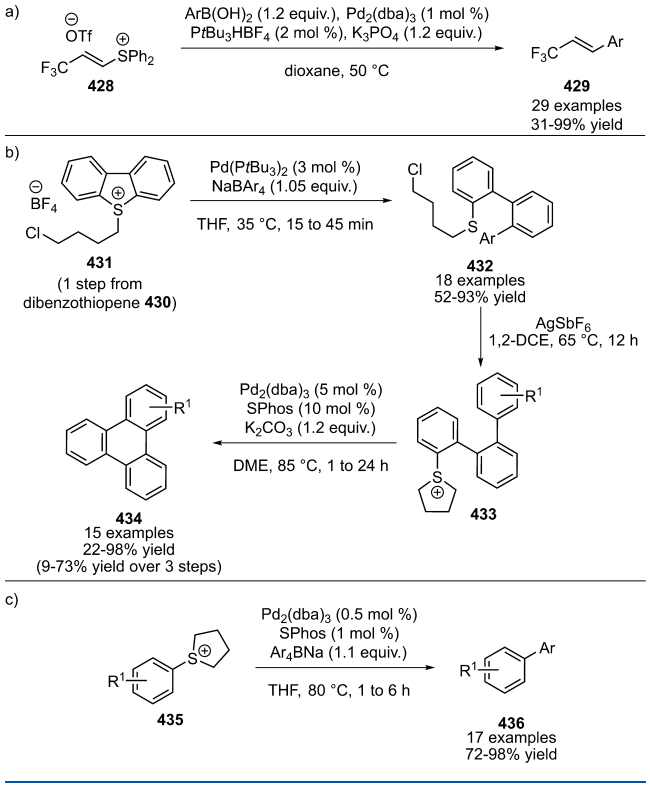
Scheme 72. Palladium-Catalyzed Cross-Coupling Reactions of (a) Vinyl- and (b,c) Arylsulfonium Salts

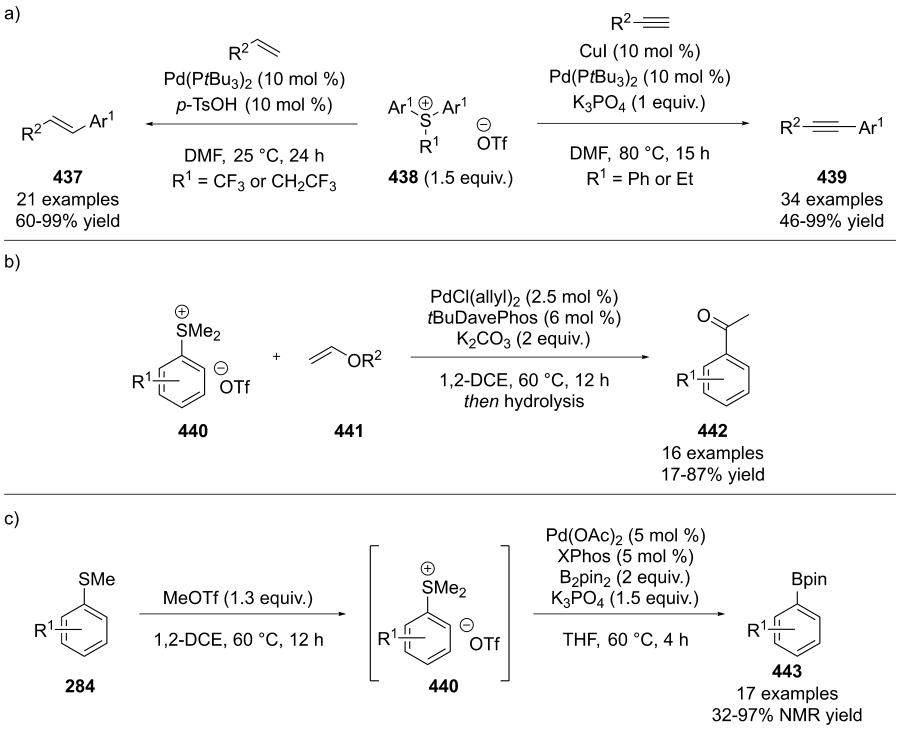


the same group was able to develop a general palladium-catalyzed cross coupling of arylsulfonium salts with sodium tetraarylborates (Scheme 72c),[285] a similar transformation, albeit on specialized substrates, having been reported in a metal-free variant a year prior by Huang and co-workers.[286]

In 2016, Zhang and co-workers, as well as the groups of Cowper and Lewis reported Suzuki-type cross-coupling reactions of arylsulfonium salts with arylboronic acids and esters, enabling the syntheses of biphenyls, stilbenes,[287] and arylated azulene derivatives, respectively.[288] Moreover, the Zhang group also developed Mizoroki–Heck and Sonogashira-type coupling reactions of diarylsulfonium salts (Scheme 73a).[289,290] A similar approach was utilized by the Yorimitsu group, coupling monoaryldialkylsulfonium salts with enol ethers, affording the corresponding aryl ketones after hydrolysis (Scheme 73b).[291] Yorimitsu and co-workers were also able to show that arylsulfonium ions readily undergo cross-coupling with diboron reagents, affording arylboronic esters (Scheme 73c).[292] Notably, the authors established that this transformation can be carried out in a one-pot process starting from the aryl sulfide that is methylated in a first step, prior to cross coupling.

More intricate methods for the two-step conversion of sulfides into sulfonium ions, followed by transition metal-catalyzed cross couplings, have also been reported. While the Yorimitsu group showed that the reation of **84** with **85** and electrophilic activators could afford the sulfanylated coupling product **86** through aromatic additive Pummerer reaction (as previously seen in section 2.1.6, Scheme 19),[59] the same publication also highlighted that the intermediate sulfonium salt **445** (isolated by facile precipitation) could be employed in cross-coupling reactions with tetraarylborates (Scheme 74). The authors encountered low chemoselectivity in the case of acyclic diarylsulfonium salts but were able to overcome this challenge by employing cyclic sulfides (**444**), favoring subsequent cleavage of the exocyclic C–S bond.

Scheme 73. (a,b) Heck- and Sonogashira-Type Reactions of Sulfonium Salts, as well as (c) a One-Pot Sulfonium Salt Formation/Borylation Reaction



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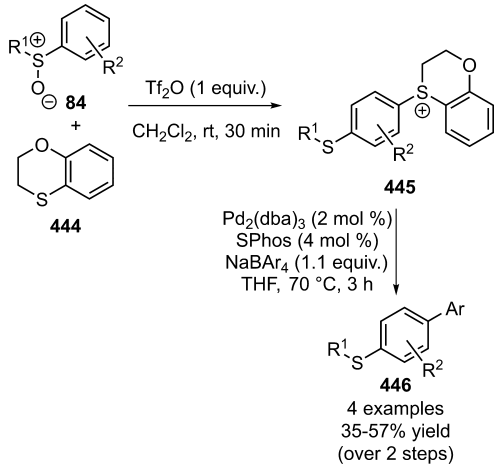
Chem. Rev. 2019, 119, 8701–8780

Scheme 74. An Aromatic Additive Pummerer Reaction Enables the Synthesis of Sulfonium Ions That Can Be Engaged in Palladium-Catalyzed Cross-Coupling Reactions

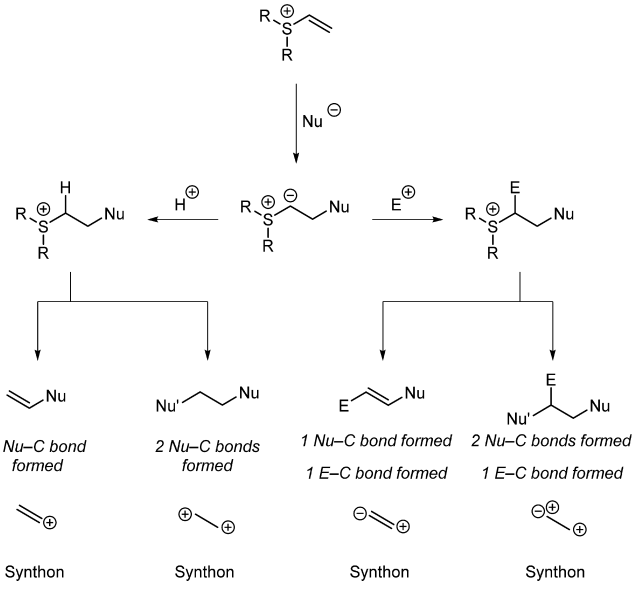


Moreover, Procter and co-workers have also established nickel-catalyzed Negishi-type cross-coupling reactions of vinylsulfonium salts as a facile means of carbon−carbon bond formation (see Scheme 29), thereby complementing the methods discussed above.[85]

3.3. Vinylsulfonium Salts

Vinylsulfonium salts are versatile reagents in organic synthesis. Their reactivity mostly relies on the transient formation of a sulfonium ylide upon conjugate addition. Depending on the further reaction pathways adopted by this ylide, a wide range of synthetic processes are available (Scheme 75), rendering these

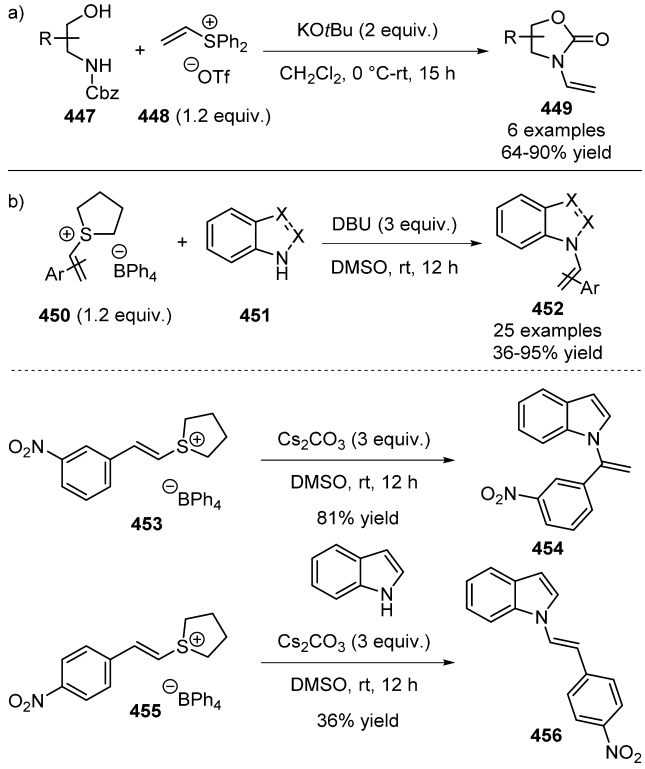
Scheme 75. Different Reaction Pathways for Reactions with Vinylsulfonium Salts



species very appealing as building blocks for synthesis. A recently published review by Kerrigan and co-workers offers a comprehensive overview of products that can be obtained from vinylsulfonium and vinylsulfoxonium salts.[293]

3.3.1. Forming One New Bond. In the simplest reaction pathway, the vinylsulfonium species acts as a vinyl cation synthon. Addition of a nucleophile with subsequent protonation and elimination of the corresponding sulfide leads overall to a vinyl transfer from sulfur to a heteroatom. This reaction is usually observed as a competing pathway in reactions with vinylsulfonium salts when a projected second nucleophile acts as a base instead, triggering elimination. In 2011, Aggarwal et al. studied the influence of the electron withdrawing substituent carried by a nitrogen nucleophile on the reaction pathway, specifically comparing sulfonamides and carbamates.[294] The latter led, after intramolecular cyclization, to the formation of vinyl carbamates (**449**) rather than morpholine derivatives by attack on the carbonyl carbon (Scheme 76a).

Scheme 76. *N*-Vinylation Reactions with Vinylsulfonium Salts



More recently, Qian and co-workers used vinylsulfonium salts for the *N*-vinylation of indoles (Scheme 76b).[295] Several *α*- and *β*-arylvinylsulfonium salts (**450**) could be transferred to heterocyclic nitrogen atoms in high yields. Interestingly, *p*-nitrophenyl and pyrimidine substituted vinylsulfonium salts reversed the regioselectivity of the vinylation and led to the *E*-double bond isomer (**456**) instead of the expected 1,1-disubstituted vinylation product akin to **454**. The authors reasoned that the strong electron withdrawing ability overrides the directing effect of the sulfonium group, leading to initial nucleophilic addition to the sulfonium-substituted carbon.

The reactivity of vinylsulfonium salts was also exploited for transformations in biological systems. In a study by Zhou and co-workers on the enzyme thiopurine methyltransferase, *S*-vinyl adenosylvinthionine **458** was synthesized which, instead of the natural *S*-methylsulfonium, bears a vinyl substituent. With suitable thiol substrates, sulfonium sulfide adducts **459** are formed which are strong inhibitors of the enzyme and thus allow only a single turnover (Scheme 77).[296] By this means,

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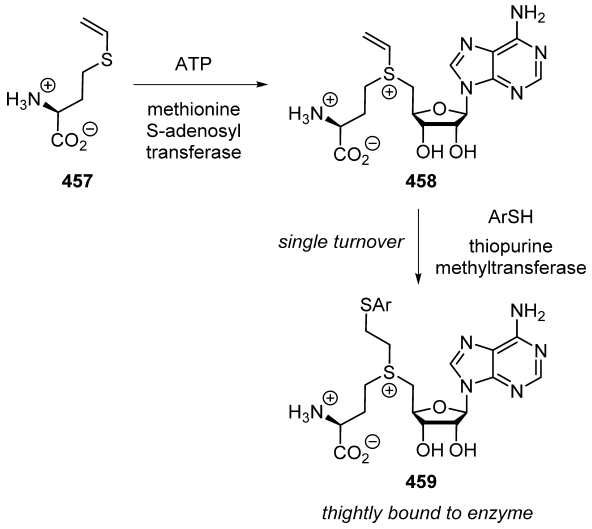
the authors could identify potential enzyme substrates and develop strong specific inhibitors.

Scheme 77. Vinylsulfonium Salts in Biological Systems



3.3.2. Forming Two New Bonds. Vinylsulfonium reagents can be used to link two nucleophiles together via a two-carbon unit, enabling annulation reactions to form cyclic products of various ring sizes.

During the past decade, several contributions have greatly advanced this chemistry. In 2008, the Aggarwal group recognized the potential of using vinylsulfonium salts (**448**) with substrates bearing two heteroatom nucleophiles, leading to a number of valuable building blocks from the morpholine, thiomorpholine, and piperazine family (Scheme 78a).[297] Excellent yields were generally obtained with sulfonamides as well as free amines.

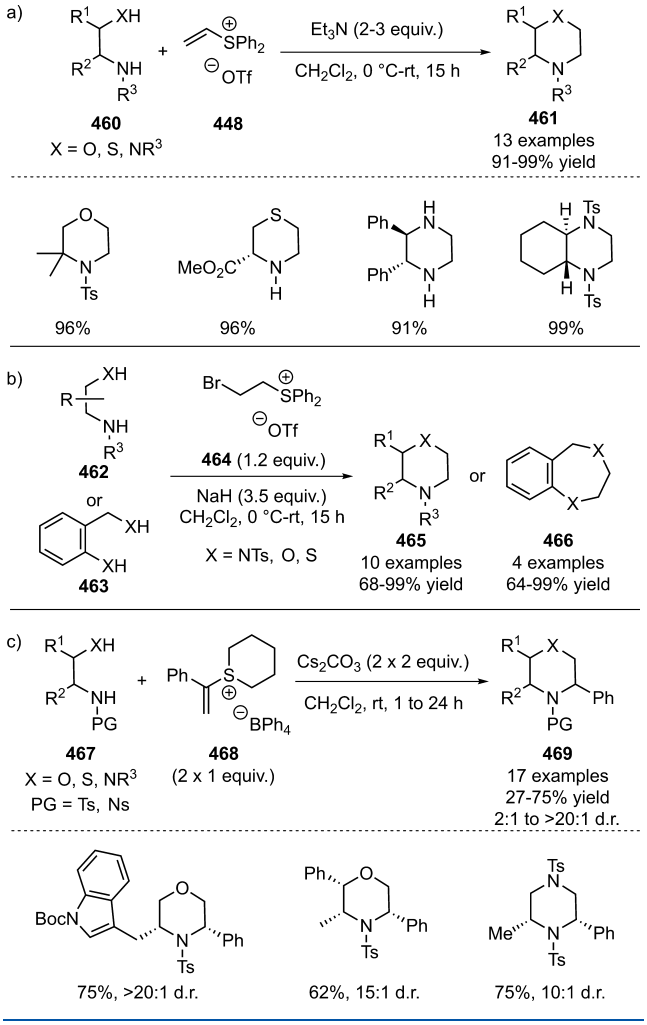
Shortly thereafter, the same group demonstrated the feasibility of using bromoethylsulfonium salt **464** as an easy-to-handle, bench-stable alternative to the oily vinylsulfonium salts (Scheme 78b).[298] Under the basic reaction conditions, the vinylsulfonium salt is generated in situ and reacts directly to afford the functionalized products. Among other six-membered rings, this enabled the synthesis of pharmacologically relevant seven-membered 1,4-benzoxazepines and 1,4-benzodiazepines (**466**).

In an attempt to access heterocycles with more substituents, an investigation into phenyl-substituted vinylsulfonium salts was also undertaken (Scheme 78c).[299] Using β-arylvinylsulfonium salts, however, only poor stereoselectivities and moderate yields were observed. Fortunately, switching to the geminally substituted isomer α-phenyl vinylsulfonium (**468**), high stereocontrol and regioselectivity were observed for a range of aminoalcohols and protected diamines.

In 2011, Xiao et al. employed the standard vinylsulfonium salt to provide access to a library of fused indole heterocycles (**472** and **473**) (Scheme 79a).[300] Interestingly, the use of the β-phenyl vinysulfonium salt led exclusively to *N*-vinylation.

Shortly thereafter, the group of Aggarwal investigated the sulfinyl moiety as a possible nitrogen protecting group alternative to the commonly used tosylamides, which are not always easy to remove.[301] To this end, the *p*-tolylsulfinyl *p*-tolyl sulfone **475** was used to install the sulfinamide group, which proved competent in the subsequent annulation (Scheme 79b). Facile removal under acidic conditions was demonstrated in high yields, using hydrogen chloride in ether. Inconveniently, sulfinamides generate diastereomeric mixtures due to the additional stereocenter at sulfur, leading to a more complex analysis (especially when other isomeric compounds can be expected to coexist in the reaction/crude mixtures).

Scheme 78. Annulation Reactions of Vinylsulfonium Salts with Dinucleophiles



Various heterocycles can also be obtained by using carboxylic acid derivatives in combination with vinylsulfonium salts. Recent additions include work by Xie and co-workers, who used simple carbamates to obtain various *N*-substituted oxazolidinones (**480**) (Scheme 80a).[302] In a similar fashion, Aggarwal et al. used formamidines (**481**) for the synthesis of imidazolinium ions (**482**) (Scheme 80b),[303] providing access to a range of symmetrical and unsymmetrical potential NHC precursors.

Extending possible modes of cyclization, Xie and co-workers used secondary amides to form γ-lactams (**485**) (Scheme 81a).[304] The reaction appears to be rather limited as the authors demonstrated that without the R^1-substituent cyclopropanation is observed and without an additional electron-withdrawing group *N*,*O*-alkylation and subsequent hydrolysis leads to linear amino esters. In the case of *N*-alkyl malonyl amides the corresponding γ-lactones are formed due to preferred *O*-alkylation and hydrolysis (Scheme 81a).

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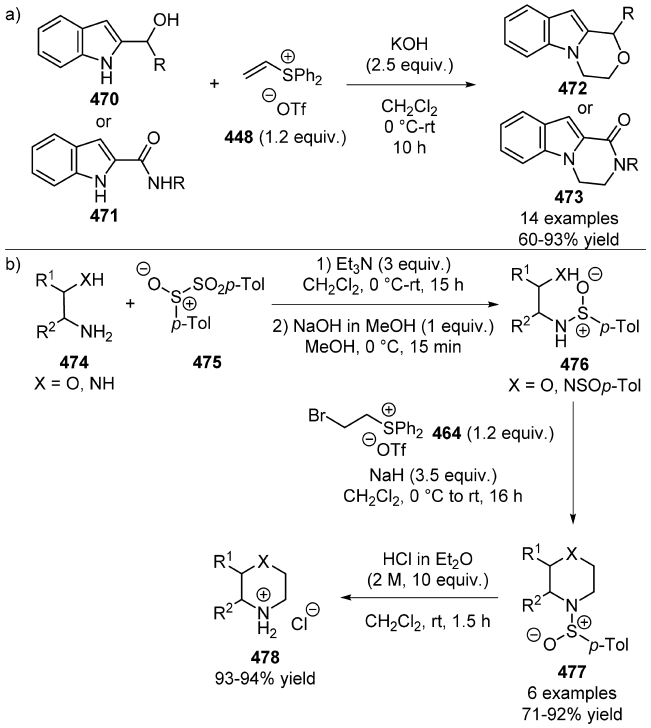
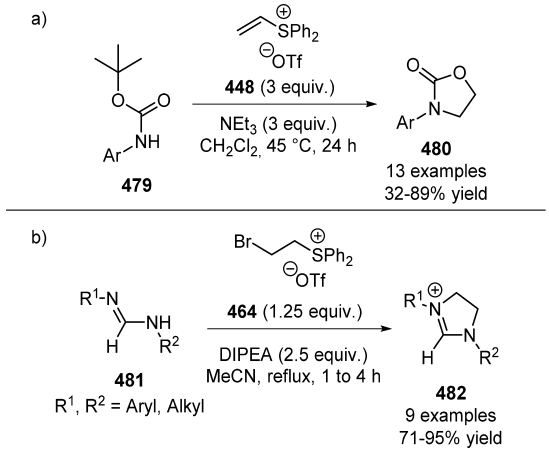
Scheme 79. Annulation Reactions of Vinylsulfonium Salts with Indole Derivatives and Sulfinamides



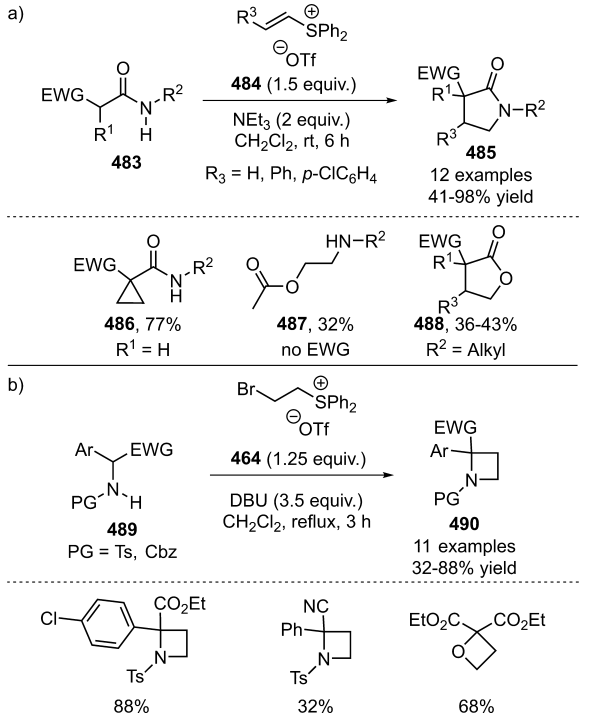
Scheme 80. Heterocycle Formations from Carboxylic Acid Derivatives



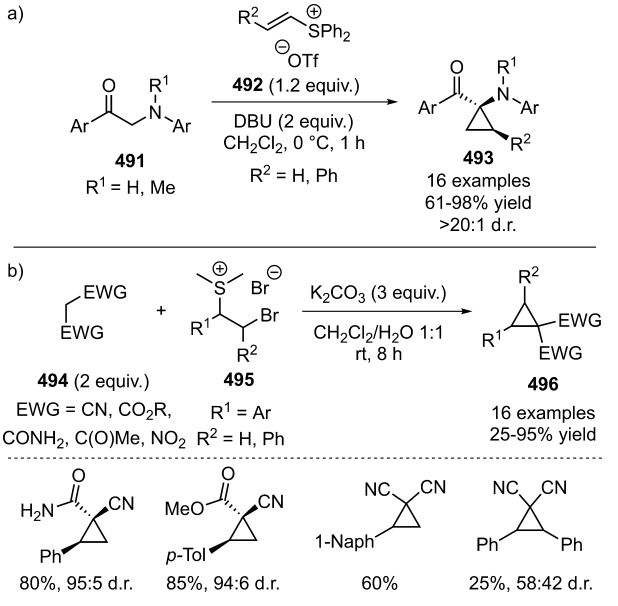
The synthesis of challenging substituted azetidines (**490**) was accomplished by Aggarwal and co-workers via the deployment of N-protected α-amino esters (Scheme 81b).[305] When malonates were employed, the process could also be extended to the synthesis of oxetanes in good yields.

The group of Lin investigated the cyclopropanation of aminoketones using substituted vinylsulfonium salts **492**, with high *cis*-selectivity observed for β-phenyl-substituted vinyl moieties (Scheme 82a).[306] In a related study, Chandrasekaran et al. investigated the scope of cyclopropanation using substituted 2-bromosulfonium salts (**395**) (Scheme 82b).[307] The use of unsymmetrical active methylene nucleophiles led to very good diastereomeric ratios, however, with higher substituted homologues, both reactivity and diastereoselectivty decreased significantly.

Scheme 81. Lactam and Azetidine/Oxetane Formation by Virtue of Vinylsulfonium Electrophilicity



Scheme 82. Cyclopropanation of (a) α-Aminoketones and (b) Malonate Derivatives with Vinylsulfonium Salts



To assess how rhodium-catalyzed cyclopropanation using diazonium salts compares to the cyclopropanation of malonates with aryl substituted sulfonium salts, Yakura and co-workers set out to study both reactions on the same substrates (Scheme 83a).[308] In all cases studied, the yield of the sulfonium salt-mediated cyclopropanation was almost 2-fold higher than the rhodium-catalyzed alternative. Recently, Qian and co-workers investigated the cyclopropanation of oxindoles (**502**) (Scheme 83b).[309] These are classically challenging substrates, as with unprotected oxindoles competitive *N*-vinylation, is commonly observed. In the event, the

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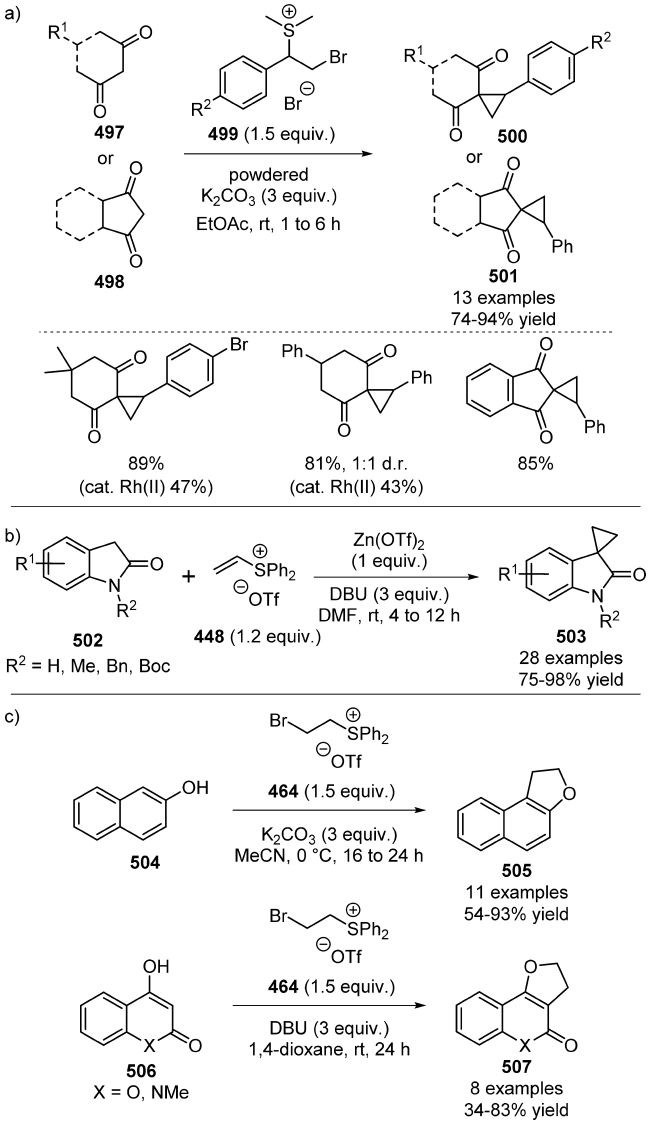
Scheme 83. Cyclopropanation of (a) Diketones and (b) Oxindoles as well as (c) Formation of Annulated Dihydrofurans with Vinylsulfonium Ions

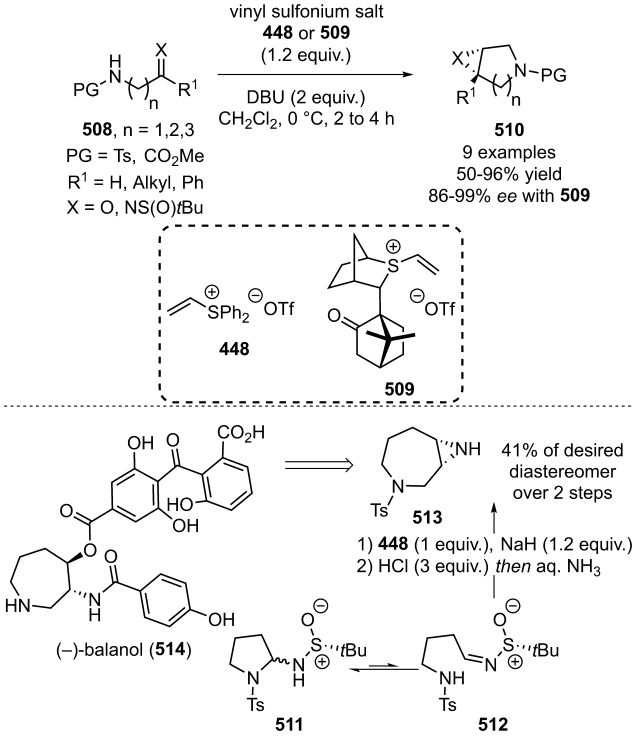


authors were able to show that the use of zinc triflate as an additive improves both reactivity and selectivity.

Another recent example of an annulation with carbon nucleophiles was published in 2018 by Yan et al. (Scheme 83c).[310] Therein, the annulation of naphthols and 4-hydroxycoumarins to form a range of dihydrofurans was accomplished in good yields. In this case, the authors propose an electrophilic aromatic substitution as the first step; subsequent cyclization affords dihydrofurans, which can be oxidized by DDQ to the respective furan derivatives.

3.3.3. Forming Three New Bonds. If, after nucleophilic attack onto the vinylsulfonium species, the transiently formed sulfonium ylide engages in a Johnson–Corey–Chaykovsky-type reaction, up to three new bonds can be formed in a single domino reaction. After Jimenez et al. showed the use of a vinylsulfonium salt in their synthesis of the mitomycin skeleton,[311,312] Aggarwal and co-workers generalized the reaction toward a number of fused nucleophiles bearing a carbonyl derivative (Scheme 84).[313] A number of epoxides fused to nitrogen heterocycles could be prepared with the use

Scheme 84. Aggarwal's Enantioselective Formation of Fused Heterocycles Using Vinylsulfonium Salt 509 and Synthesis of (−)-Balanol



of achiral vinylsulfonium salts **448** in good yield yields. Furthermore, through the use of a chiral vinylsulfonium salt **509**, the products could be obtained in high enantiomeric purity and the reaction was successfully applied in the formal synthesis of (−)-balanol (**514**).

The reaction can also be carried out in an intermolecular fashion, leading to epoxides or aziridines, respectively, as was shown shortly after by the same group (Scheme 85a).[314] A number of nucleophiles were used in the three-component reaction, albeit with modest diastereoselectivity in some cases. Interestingly, several specific substrates displayed a particular preference for either the *cis*- or *trans*-aziridine.

In an interesting extension, Aggarwal and co-workers took a closer look at substrates bearing chiral centers in combination with achiral and chiral vinylsulfonium salts (Scheme 85b).[315] Strong matched and mismatched effects were observed in the case of the chiral sulfonium salt **509**. With a slight change of conditions, from using sodium hydride to employing DBU as a base, potentially epimerizable substrates such as **516** could also be used with no observable racemization.

During these investigations, formation of seven-membered rings (**519**) from γ-aminoaldehydes (**518**) was generally challenging as they preferentially exist in the cyclic aminal form, leading to a low concentration of nucleophile in solution (Scheme 86a).[316] Stereocontrol in the reaction leading to azepines was studied in more detail by Aggarwal et al. For substrates bearing a stereogenic center, a high dependency on the solvent was observed.

In 2012, Aggarwal and co-workers investigated the use of a more accessible chiral vinylsulfonium equivalent in the form of salt **521** (Scheme 86b).[317] In most cases however, lower enantiomeric ratios were observed when compared to previously studied derivative **509**.

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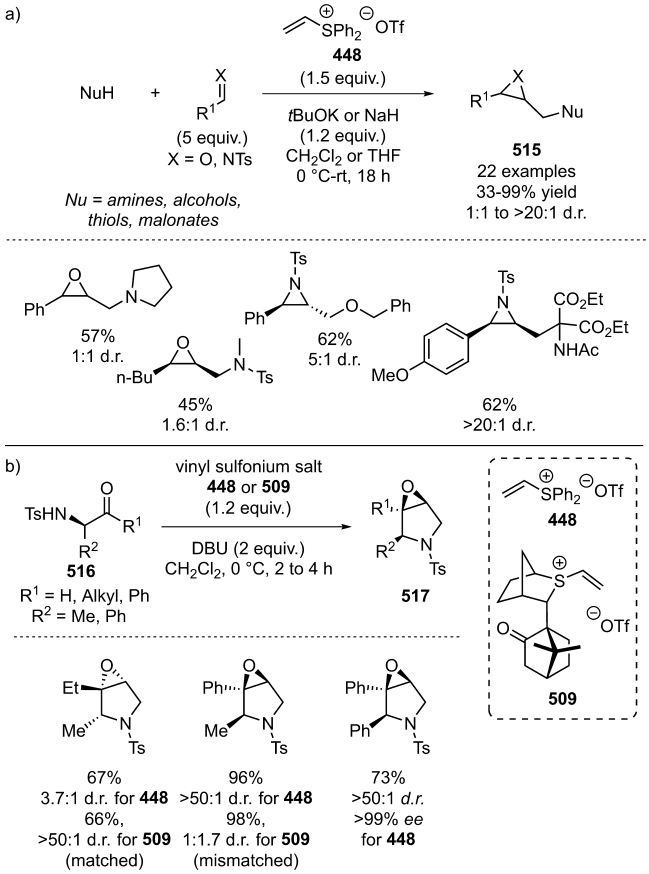
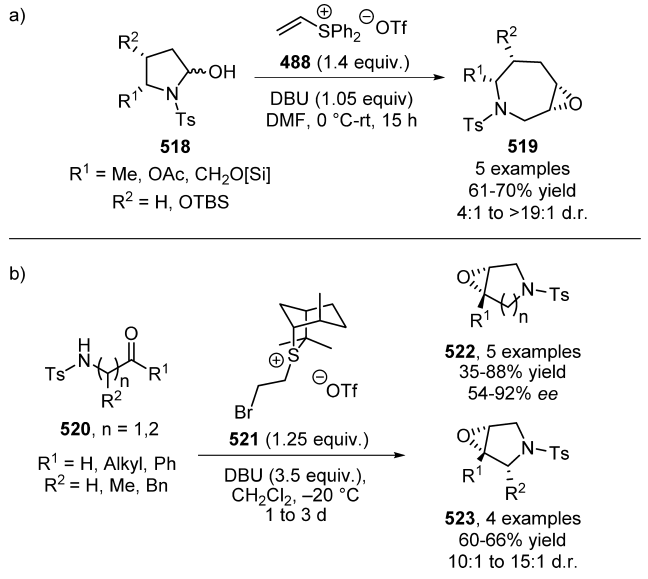
Scheme 85. Intermolecular Version of a Domino Epoxide/Aziridine Synthesis and α-Chiral Substrates

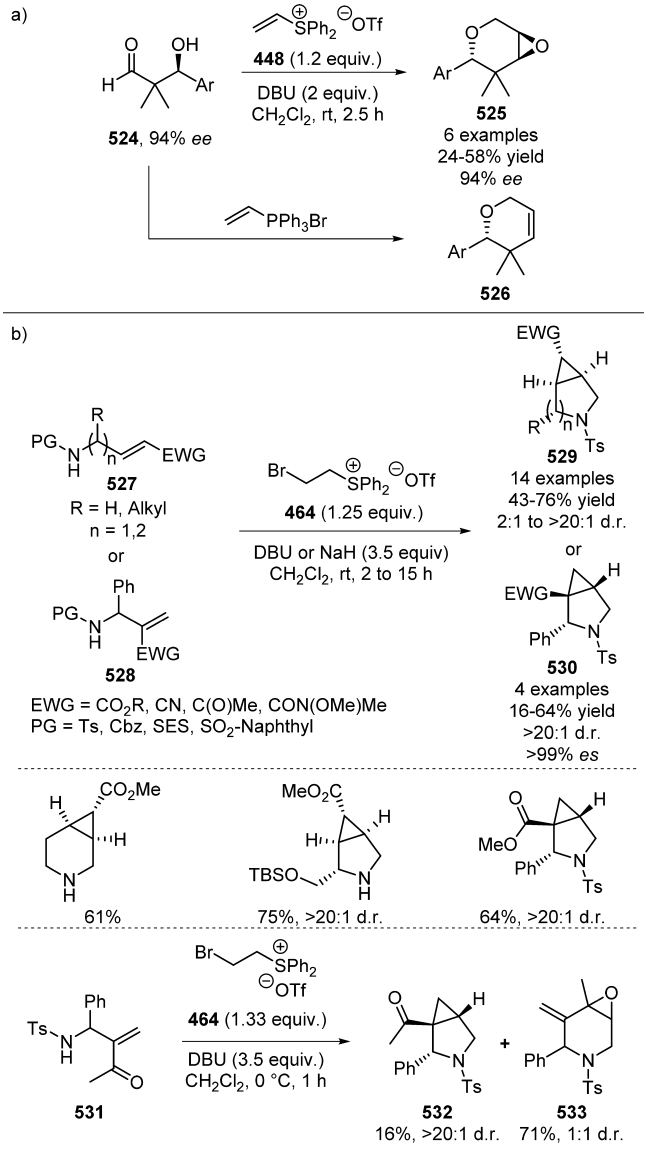


Scheme 86. Diastereoselective Synthesis of Azepins and Use of a Novel Chiral Sulfonium Salt



Ley and co-workers compared vinylsulfonium and vinylphosphonium salts in their reaction with chiral β-hydroxyaldehydes (**524**) (Scheme 87a).[318] As expected, the two reagents both behave as conjugate electrophiles in a first step, eventually diverging toward epoxidation and olefination, respectively.

Scheme 87. (a) Diverging Reactivity of Vinylsulfonium and -Phosphonium Salts; (b) Cyclopropanation of Michael Acceptors with Vinylsulfonium Salts



While tethered carbonyls afford three-membered epoxides, tethered Michael acceptors lead to cyclopropane derivatives. The group of Aggarwal employed ω-amino-unsaturated carbonyls, extending the applicability of vinylsulfonium salts to the synthesis of fused cyclopropyl pyrrolidines in a 2013 study (Scheme 87b).[319] With unsaturated ketone **531**, epoxidation outcompeted cyclopropanation, while small amounts of the Michel addition product were also observed.

To access additional substitution on the fused heterocyclic systems, Aggarwal et al. studied aryl-substituted vinylsulfonium salts **536** in combination with α-aminoketones (Scheme 88).[320] Several tetrasubstituted epoxides were thus formed in good yields and, with Michael acceptors, high diasteromeric ratios were observed in favor of the *exo*-product.

Recently, Wu and co-workers used acceptor-substituted vinylsulfonium salts in a formal (3 + 2)-cycloaddition with sodium azide (Scheme 89a).[321] Interestingly, the vinylsulfonium salt could be generated in situ by nucleophilic substitution followed by aldol condensation with an aldehyde

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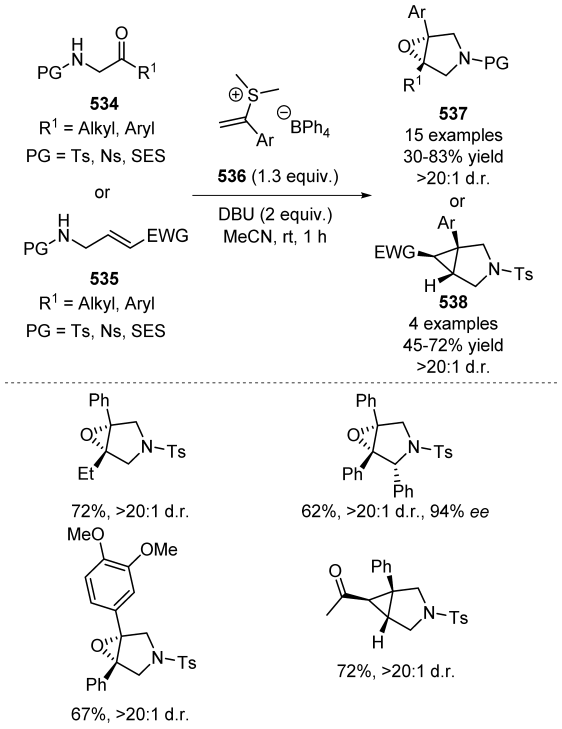
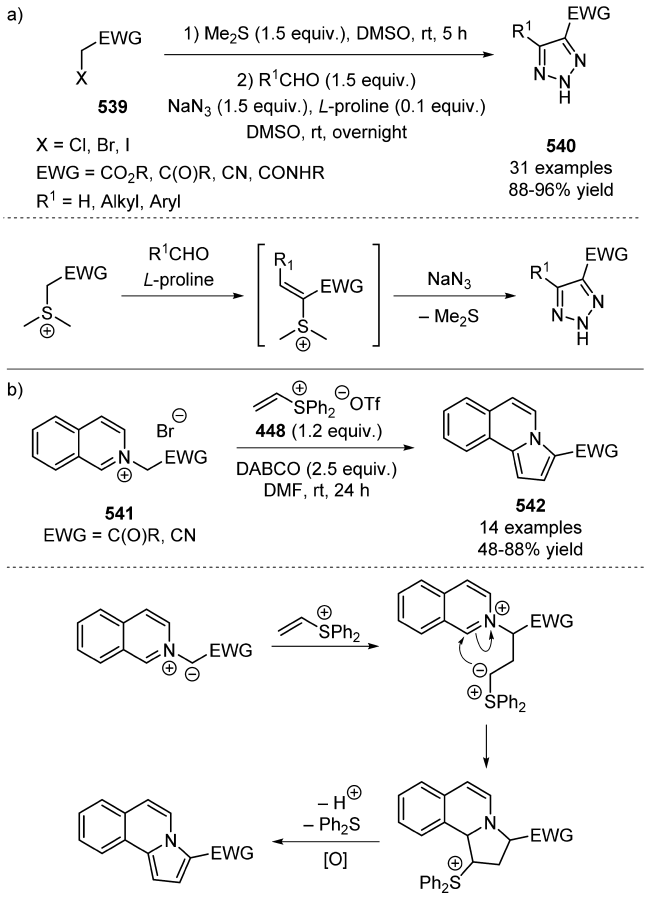
Scheme 88. Aryl Substituted Vinylsulfonium Salts in the Synthesis of Fused Heterocycles



Scheme 89. Formal Cycloaddition Reactions of Vinylsulfonium Salts

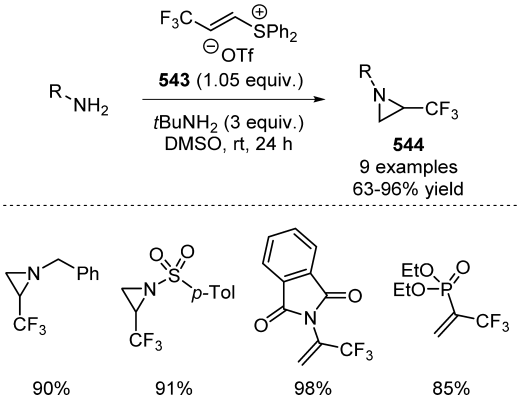


using catalytic L-proline. These acceptor-substituted vinylsulfonium species then engage the azide anion, leading to a range of triazoles (**540**). A large substrate scope and high yields add to the appeal of this method.

Another example of a formal cycloaddition of vinyl sulfonium salts was reported by Xiao et al., using stabilized isoquinolinium *N*-ylides (Scheme 89b).[322] In this case, the isoquinolinium salt (**541**) is deprotonated in situ and subsequently adds to the vinylsulfonium salt. The intermediate ylide cyclizes, followed by extrusion of diphenylsulfide, initially leading to a pyrroline derivative. Terminal oxidation delivers the fused pyrrole systems (**542**) in moderate to good yields.

3.3.4. Fluorinated Vinylsulfonium Salts. Fluorinated organic compounds play an increasingly important role in pharmaceutical chemistry. Because of its small steric, yet large electronic influence on the properties of molecules, as well as its contribution to increased metabolic stability, fluorine has gained a prevalent role in the structure of a large number of pharmaceuticals. With their wide applicability to form variously substituted heterocycles, vinylsulfonium salts have great potential to introduce fluorine atoms into readily available building blocks. Trifluoromethylated vinylsulfonium salt **543** was first prepared in 2010 by Hanamoto et al., who could show its use for the formation of trifluoromethylated aziridines (**544**) from primary amines, and as an *N*- and *P*-vinylation agent (Scheme 90).[323]

Scheme 90. Application of a Trifluoromethylated Vinylsulfonium Salt



Lu and co-workers developed the cyclopropanation of malonate derivatives with trifluoromethyl-substituted vinylsulfonium salts (Scheme 91).[324] Interestingly, three different products could be obtained simply by varying the reaction conditions. The expected cyclopropanation readily took place using DBU as the base, leading to a number of trifluoromethyl substituted cyclopropanes with good to excellent diastereomeric ratios (Scheme 91a). When sodium hydride was used, an isomeric product was formed which was shown to be cyclopropane **547** (Scheme 91b). The authors reasoned that the nucleophilic adduct would readily form a cyclobutene intermediate in the presence of sodium as the counterion. Retro-Aldol opening and subsequent displacement of diphenyl sulfide led to a new cyclopropane featuring both electron withdrawing substituents on adjacent carbons. Pleasingly, moderate to high yields and high diastereoselectivities were observed. Performing the reaction at low temperature, and using sodium hydride as the base, *O*-nucleophilic attack of the

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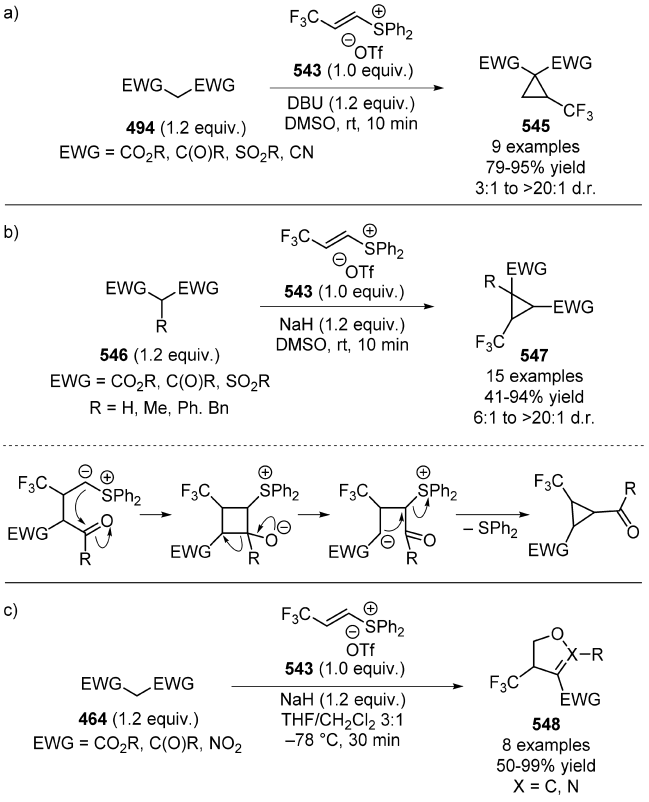
Scheme 91. Dependent on the Reaction Conditions, Trifluoromethylated Vinylsulfonium Salts Lead to Diverse Classes of Products



respective enolate species led to the formation of heterocycles **548** as the major products in good to excellent yields (Scheme 91c).

Shortly thereafter, an improved protocol by Hanamoto expanded the scope of cyclopropanation, again affording high yields and diastereoselectivities (Scheme 92a).[325] Importantly, amino alcohols only underwent vinylation of one of the heteroatoms, a challenge that could be partially circumvented by using a nonfluorinated vinylsulfonium salt for the formation of heterocycles with fluorinated substates (Scheme 92b).[326] Starting from fluorinated aziridine, trifluoromethylated piperazine (**550**) derivatives were obtained in a two-step one-pot manner.

In 2012, Aggarwal et al. successfully applied the trifluoromethylated vinylsulfonium salt **543** to make fused heterobicyclic systems (Scheme 92c).[327] It is important to note that the CF_3 group implemented a strong conformational fixation during the reaction, leading to virtually all substrates being formed as single diastereomers.

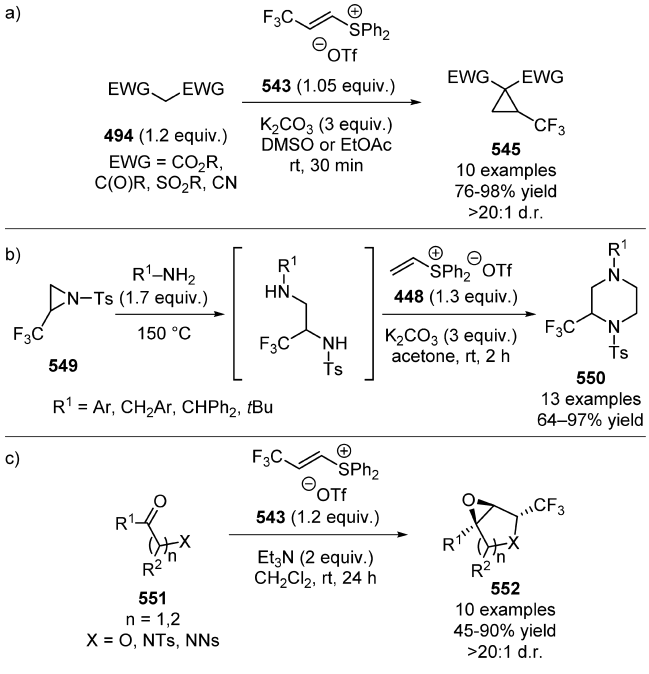
In 2015, Hanamoto and co-workers also demonstrated the synthesis and use of difluoromethyl vinylsulfonium salt **554** as a reagent for the synthesis of fluorinated building blocks (Scheme 93).[328,329] Aziridination (Scheme 93a) as well as cyclopropanation (Scheme 93b) could be carried out in very high yields using only a slight excess of the sulfonium reagent.

Similarly, cyclopropanation was also demonstrated using the α-fluorinated vinylsulfonium salt **557** (Scheme 94).[330]

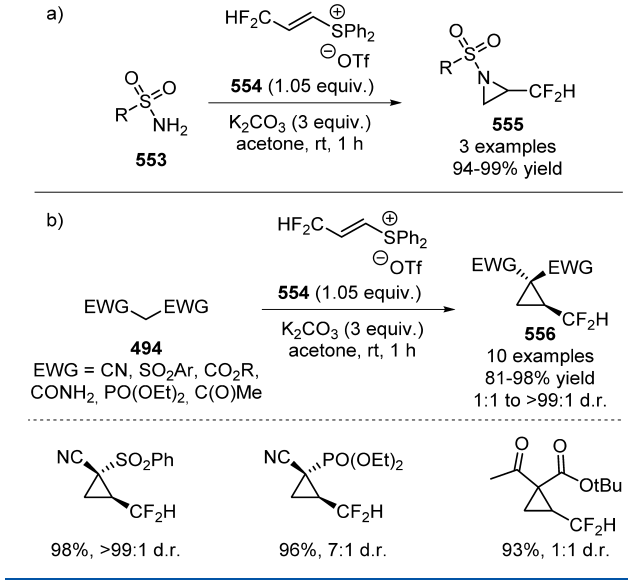
3.4. Propargylsulfonium Salts

Key to the reactivity of propargylsulfonium salts (**559**) is their facile isomerization to allenylsulfonium salts (**560**) under basic conditions (Scheme 95). These highly electrophilic intermediates can react in various, not always productive, manners, which explains the fact that their use in organic synthesis remained scarce for a long time.

Scheme 92. Further Examples of the Formation of Trifluoromethyl-Containing Cyclic Structures



Scheme 93. Difluoromethylated Vinylsulfonium Salts in the Synthesis of Aziridines and Cyclopropanes



Recently, the group of Huang has found several new domino reactions using propargylsulfonium salts, developing a synthesis of hydroindol-5-ones (**563**) in 2017 (Scheme 96).[331] After 5-*exo*-*trig* cyclization of the sulfonium ylide intermediate, double-bond migration and demethylation by attack of the bromide led to the methylthio substituted products in good yields. The authors demonstrated the dealkylation event using the cyclic sulfonium salt **565** (Scheme 96, bottom).

Later that year, the same group developed a route to hexahydropyrrolo[3,2-*b*]indoles (**569**) by utilizing the potential of vinylsulfonium salts to form three new bonds (Scheme

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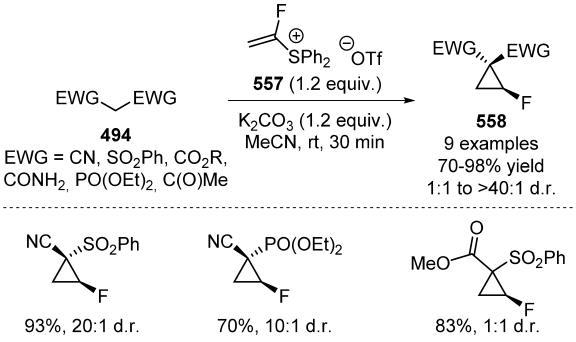
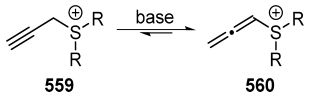
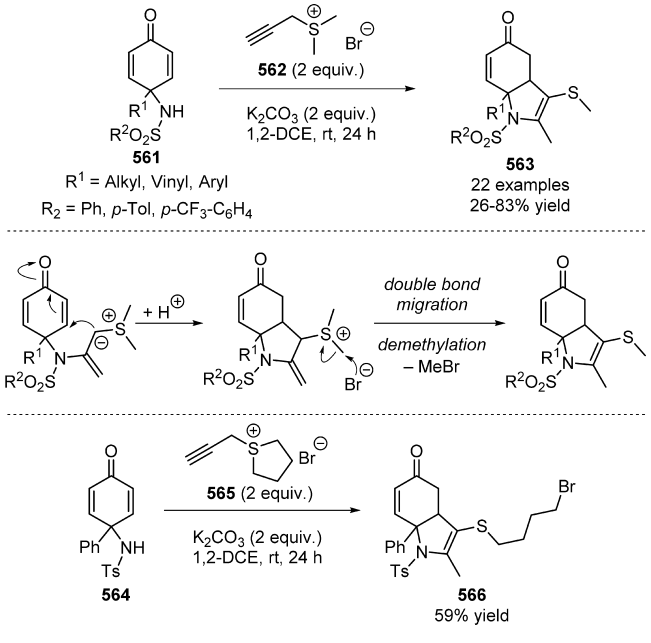
Scheme 94. Fluorinated Cyclopropanes from α-Fluorovinylsulfonium Salts



Scheme 95. Base-Promoted Isomerization of Propargyl Sulfonium Salts



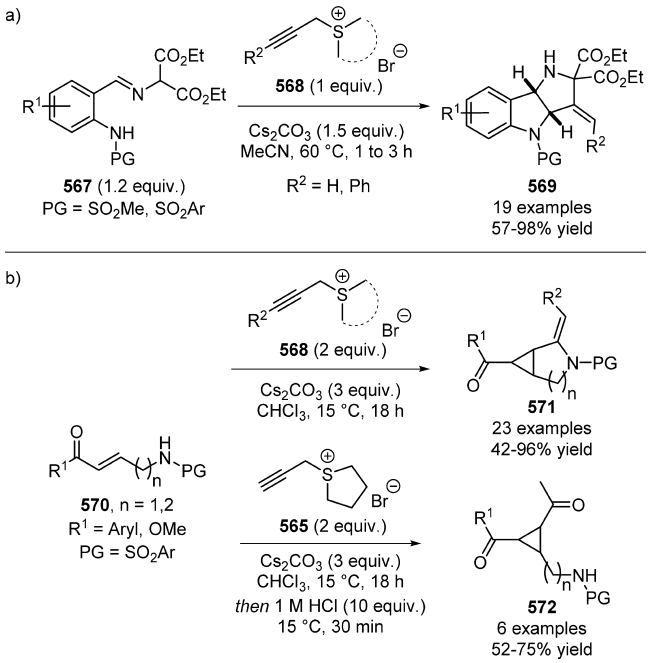
Scheme 96. Access to Hydroindol-5-ones from Propargylsulfonium Salts



97a).[332] Through a sequence of nucleophilic attack, cyclization, and displacement by a second nucleophile, the products are formed in good to excellent yields. This domino reaction leads to two new five-membered cycles and an exocyclic double bond that can serve as a reactive handle for further derivatization.

Propargylsulfonium salts were also successfully used in combination with sulfonyl amides tethered to a Michael acceptor, leading to bicylic enamides possessing a fused cyclopropane ring (**571**) (Scheme 97b).[333] The proposed mechanism is analogous to the case previously discussed for vinylsulfonium salts (see Scheme 87b). The products were found to hydrolyze over time or under acidic conditions to afford monocyclic aminoketones (**572**), a process that could be accelerated by simple addition of hydrochloric acid to the crude reaction mixture.

Scheme 97. (a) Hexahydropyrrolo[3,2-*b*]indoles Formed with Propargylsulfonium Salts and (b) Domino Reaction with Michael Acceptors Affording Annulated or Trisubstituted Cyclopropanes



Most recently, Huang and co-workers reported the reaction of propargylsulfonium salts with indolo-phenolic substrates (**573**) (Scheme 98).[334] After isomerization to the allenylsulfonium salt, 2-fold nucleophilic addition with consequent protonation led to key intermediate **576**, which afforded the sulfide **577** as a product of (5 + 1) annulation after final demethylation.

4. SULFUR YLIDES

Sulfur ylides are zwitterionic compounds defined by a carbanion and a neighboring, positively charged sulfur atom. They are known as a family of versatile reagents and have been widely applied as one-carbon synthons in a number of classical transformations, many of which have become textbook knowledge. The addition of sulfur ylides to electron-poor π-systems with subsequent elimination of the sulfonium moiety (generally in the context of epoxidation, aziridination and cyclopropanation reactions), as well as several rearrangement reactions, are the most representative examples (Scheme 99).

While reactions with unstabilized sulfonium ylides are known, most modern processes utilize stabilized versions, in which the negative charge is delocalized into one or more electron withdrawing groups. This added stability means that sulfur ylides can be used as practical, bench-stable reagents, and enables the development of reactions with increased complexity. Several classical reviews have been written to summarize the advances achieved during different periods.[335−339] Our discussion will focus on reactions of stabilized sulfur ylides in recent developments over the last 10 years.

4.1. Transition-Metal Catalysis

4.1.1. Formal (*n* + 1)-Cycloadditions. The formal (4 + 1)-cycloaddition of sulfur ylides is a powerful tool to construct highly functionalized five-membered carbo- and heterocycles. However, tradititionally, enantioselective variants typically

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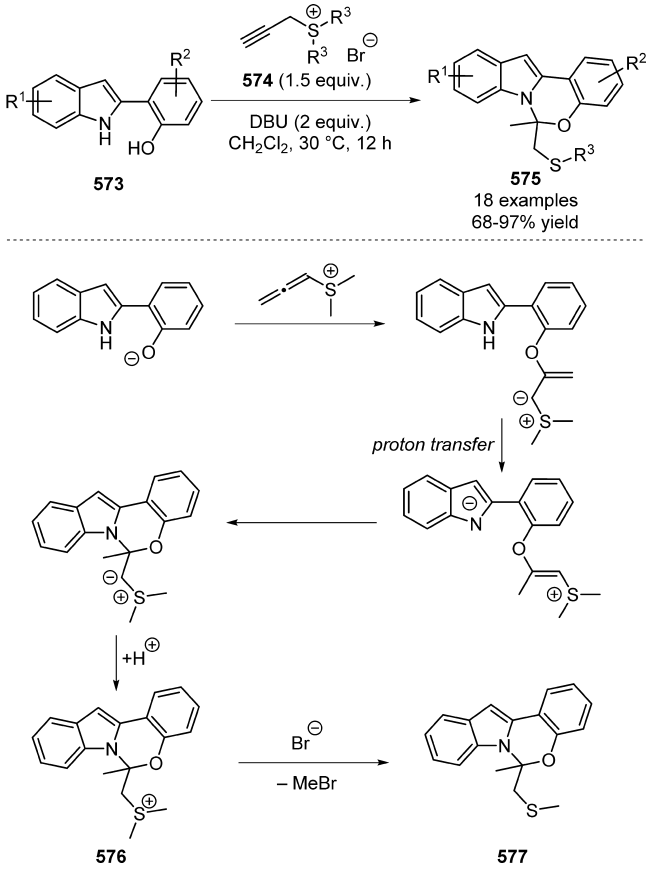
Scheme 98. Formal (5 + 1) Annulation of Bidentate Nucleophiles with in Situ-Generated Allenylsulfonium Ions



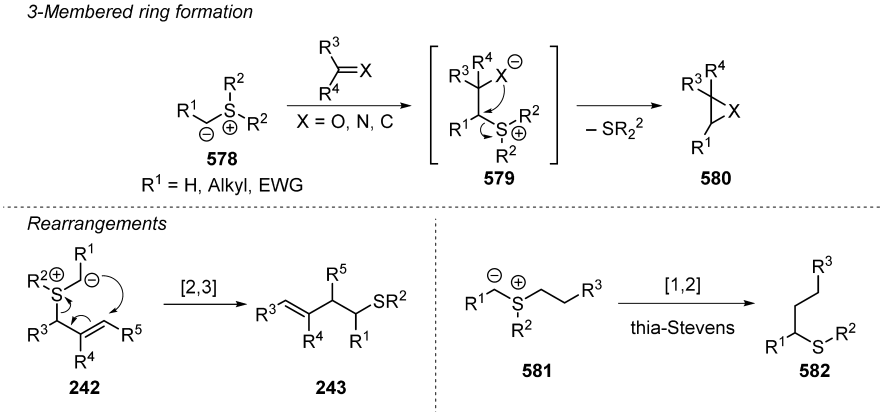
relied on the use of stoichiometric chiral sulfur ylides. In 2012, Bolm and co-workers reported a metal-triggered formal (4 + 1)-cycloaddition of sulfur ylides, which allowed for a remarkable catalytic and enantioselective version of this transformation.[340] By deprotonation of α-halo hydrazones (**583**) by action of Na_2CO_3, highly reactive azoalkene **586** was generated in situ (Scheme 100). This intermediate, further activated by coordination to a chiral BINAP−copper complex, can undergo subsequent enantioselective addition of a stabilized sulfur ylide (**584**) to afford a variety of enantioenriched dihydropyrazoles (**585**) in good yields with moderate to good enantioselectivities. Interestingly, stabilized sulfur ylides proved to be the best substrates for this reaction. While for many classical ylide transformations these compounds are usually considered as somewhat unreactive, this precise feature renders them easier to control in metal-mediated processes.

The following years would usher in major developments in the generation of 1,4-dipoles from readily available starting materials. In 2014, the group of Xiao reported a palladium-catalyzed decarboxylation/cycloaddition sequence with vinyl carbamates **587** as 1,4-dipole precursors.[341] This transformation allows the synthesis of a wide range of *trans*-2-acyl-3-vinylindolines (**590**) with excellent diastereo- and enantioselectivity (Scheme 101). This was the first time the enantioselective capture of Pd-stabilized allylic zwitterionic intermediates by sulfur ylides was achieved. Both the aromatic moiety and the ylide-stabilizing group can be modified without significant loss of enantioselectivity. The optically active indoline products constitute valuable building blocks and offer straightforward access to complex chiral targets.

In 2016, the same reaction was reported with an Fe catalyst,[342] the group of Xiao showing that nucleophilic iron complexes provide similar reactivity with a reduced ecological footprint (Scheme 102). This was the first iron-catalyzed cycloaddition reaction of sulfur ylides. Although the reaction was not performed in an enantioselective manner, *anti*-disubstituted indolines (**592**) were obtained with good yields and excellent diastereoselectivities.

Thereafter, the same group further applied asymmetric copper catalysis to a decarboxylative formal (4 + 1)-cycloaddition reaction, changing the vinyl benzoxazinanone functionality to a propargyl benzoxazinanone (**593**) (Scheme 103).[343] Copper−allenylidene intermediates were proposed as reactive 1,4-dipoles, with initial studies identifying chiral PyBOX ligands (**L3**) as the most efficient in delivering the products in good yields with moderate enantiomeric excess. However, the enantioselectivity was drastically improved when the ylide was generated in situ by deprotonation of the corresponding sulfonium salt with an excess of DIPEA. Observed nonlinear effects strongly suggest the participation of a multinuclear complex in the enantio-determining step of the reaction. Other, related allenylidene-based reactions indicate that the presence of DIPEA could help the formation of such multinuclear species.[344] This could explain the remarkable enhancement of enantioselectivity observed when the reaction was performed with an excess of base.

Scheme 99. Examples of General Sulfur Ylide Reactivity



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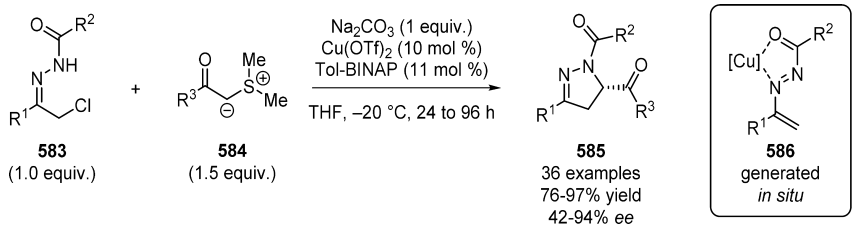
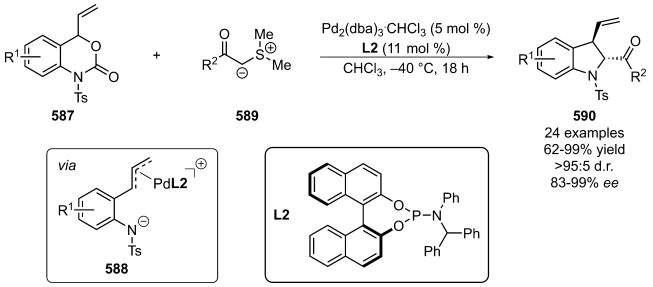
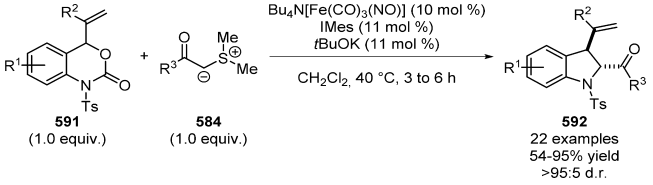
Scheme 100. Copper-Catalyzed Asymmetric Formal (4 + 1)-Cycloaddition of Azoalkenes with Sulfur Ylides



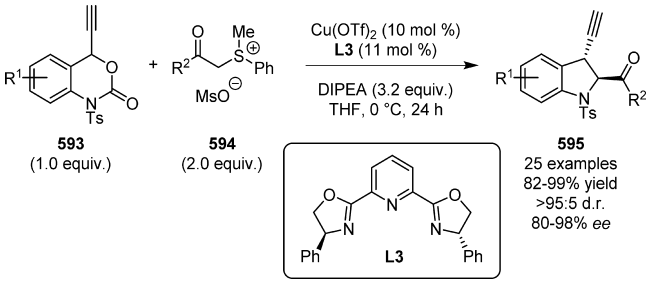
Scheme 101. Palladium-Catalyzed Decarboxylative (4 + 1)-Cycloaddition for the Asymmetric Synthesis of Indoles



Scheme 102. Iron-Catalyzed Decarboxylative Formal (4 + 1)-Cycloadditions



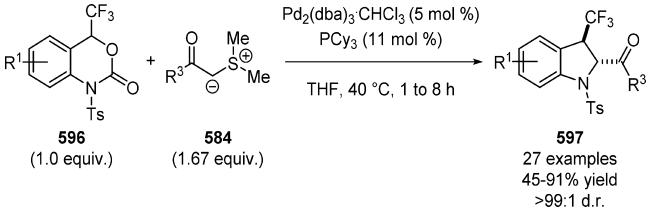
Scheme 103. Cu-Catalyzed Decarboxylative Formal (4 + 1)-Cycloaddition



Despite the significant potential of these decarboxylative formal (4 + 1)-cycloadditions, the diversity of benzoxazinanones is strongly limited to vinyl or alkynyl substituted compounds. Very recently, the groups of Gouverneur and Shibata showed in a collaborative paper that this could be extended to CF_3-substituted benzoxazinanones (**597**) (Scheme 104).[345] The CF_3 group is responsible for a strongly electron-deficient benzylic carbon, resulting in a highly electrophilic palladium-π-benzyl zwitterionic intermediate by oxidative addition to Pd(0) and enabling access to CF_3-indolines, albeit in racemic fashion.

In 2017, Doyle and co-workers reported an elegant enantioselective copper-catalyzed synthesis of cyclobutenes (Scheme 105).[346] The reported strategy relies on a formal (3 + 1)-cycloaddition between sulfonium ylides and enoldiazo compounds as 1,3-dipole precursors. A wide range of

Scheme 104. Pd-Catalyzed Decarboxylative Formal (4 + 1)-Cycloadditions of CF_3-Benzoxazinanones



cyclobutenes containing one or two stereogenic centers (**600**) were obtained in diastereoselective manner, with a bulky bisoxazoline ligand ensuring good to excellent levels of enantioselectivity.

The proposed mechanism is depicted in Scheme 105. In the first step, metal carbenoid **601** is formed by decomposition of the enoldiazo compound (**598**) in the presence of the copper catalyst. This intermediate **601** is assumed to be in equilibrium with donor–acceptor cyclopropene **602**. This assumption was supported by the finding that independently prepared **602** also afforded the cyclobutene product in similar yield and selectivity when exposed to the reaction conditions. Sulfur ylides can add to **601** in nucleophilic fashion, followed by cyclization and decomplexation to afford the desired cyclobutenes, releasing the catalyst.

Recently, the group of Doyle reported a catalytic formal (4 + 2)-cycloaddition of enoldiazoimides **605** (Scheme 106)[347] with sulfur ylides, delivering a novel approach to multifunctionalized indolizidinones **607**.

4.1.2. Transition Metal-Catalytic Activation of Alkenes and Alkynes. The tremendous development of π-acid catalysis has enabled the activation of previously unreactive π-systems toward nucleophilic attack from a wide range of nucleophiles. This has inspired several groups to envisage transition metal-catalyzed cycloadditions of such π-electrophiles with sulfur ylides. In 2012, the groups of Maulide[348] and Skrydstrup[349] independently reported syntheses of furans based on this strategy. In both cases, a cationic gold complex allowed the activation of an alkyne and promoted a formal (3 + 2)-cycloaddition with a stabilized sulfur ylide. Maulide focused on intramolecular cyclizations of doubly stabilized sulfonium ylides (**608**), prepared via direct ylide transfer,[350,351] to afford bicyclic furans (**609**) (Scheme 107a). On the other hand, an intermolecular approach developed by Skrydstrup and co-workers led to a range of 2,4-disubstituted furans (**611**) in good yields (Scheme 107b). Analogously to the Skrydstrup procedure, the group of Maulide also reported the reaction of doubly stabilized sulfur ylides in an intermolecular context. Because of the lower reactivity of the starting materials, higher temperatures and a bulkier, electron-rich ligand were needed to ensure efficient formation of 2,3,4-trisubstituted furans (**613**) (Scheme 107c).[348]

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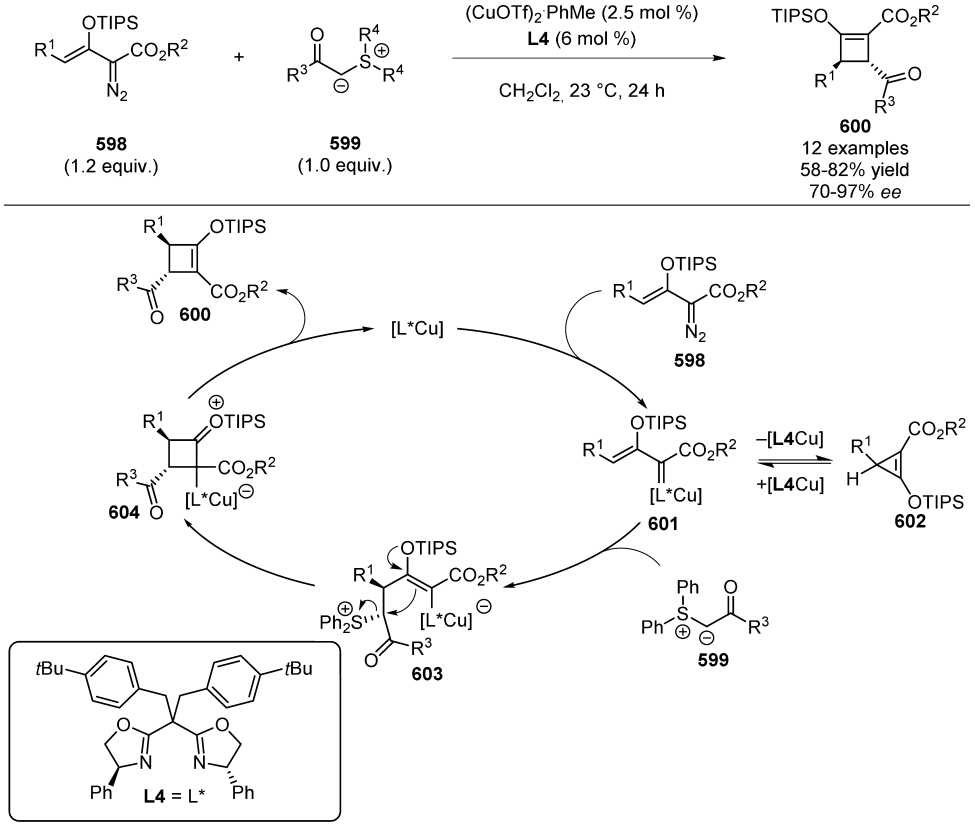
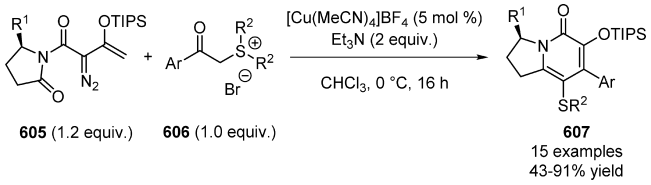
Scheme 105. Cu-Catalyzed Asymmetric Formal (3 + 1)-Cycloaddition

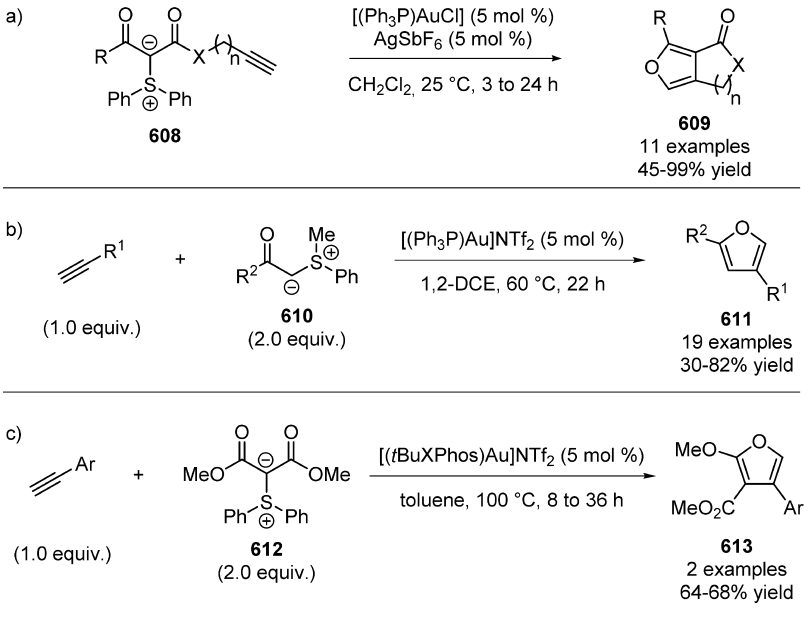


Scheme 106. Cu-Catalyzed Formal (4 + 2)-Cycloaddition of Enoldiazoimides and Sulfur Ylides



These transformations are based on similar systems, which might be expected to react in an identical fashion. Indeed, the first step leading to a vinyl−gold complex (Scheme 108, **614** and **617**, respectively) through the addition of the nucleophile onto the activated alkyne was suggested in both reports. At this point, however, both groups postulated a different cyclization step. Skrydstrup and co-workers proposed the participation of a gold−carbenoid intermediate (**615**), generated by extrusion

Scheme 107. Intermolecular and Intramolecular Au-Catalyzed Furan Synthesis



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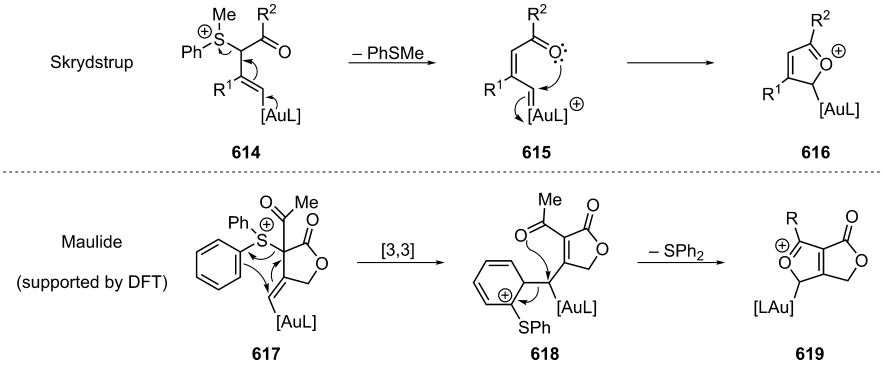
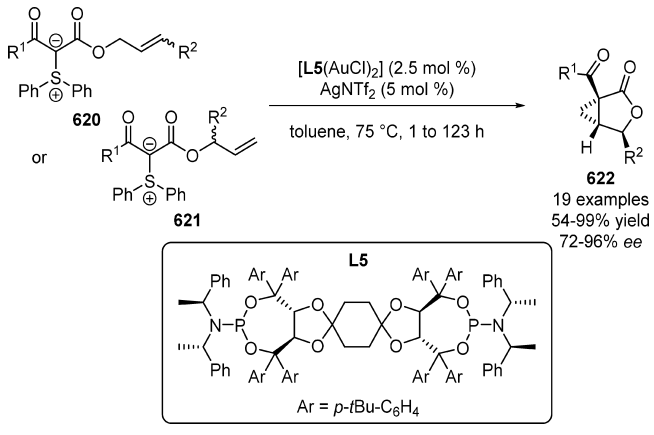
Scheme 108. Proposed Mechanisms for Furan Formation with Sulfur Ylides



of phenylmethylsulfide. Intramolecular attack of oxygen to this electrophilic carbenoid should then afford the cyclic oxocarbenium ion **616**. On the other hand, the group of Maulide proposed a [3,3]-sigmatropic rearrangement from **617**, leading to intermediate **618**. The cyclization step was then thought to proceed concomitantly with the extrusion of diphenylsulfide, delivering oxocarbenium ion **619**, which is analogous to **616**. Neither route has been conclusively disproven; nevertheless, the computational studies performed by Maulide and colleagues could not locate an energy minimum corresponding to a carbene or carbenoid intermediate.

During the development of the intermolecular furan synthesis with allyl ester substrates, the group of Maulide recognized a side product that did not incorporate the alkyne partner. Removal of the alkyne from the reaction mixture revealed that allyl ester-derived sulfur ylides are directly converted into cyclopropanes under gold catalysis. This intramolecular gold-catalyzed cyclopropanation proved to be remarkably efficient, proceeding in good yields, with excellent diastereoselectivity and tolerating a broad range of functional groups.[352] An interesting feature of the process was observed when investigating substituted substrates. Starting from either the "linear" or "branched" isomer of the starting material (**620** and **621**, respectively), the position of substituent R^2 in the cyclopropane products is identical (Scheme 109). This unexpected result suggested a complex underlying mechanism and motivated further mechanistic investigations,[353] which ultimately led to the development of an enantioselective

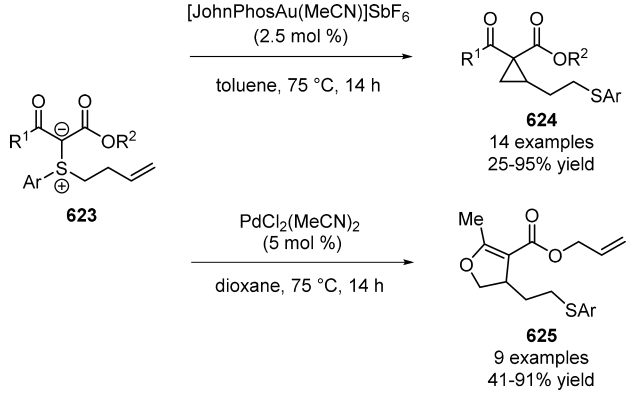
Scheme 109. Au-Promoted Intramolecular Cyclopropanation of Sulfur Ylides with Allyl Esters



version of this reaction.[354] A cationic gold complex supported by a dimeric TADDOL-based phosphoramidite ligand (**L5**) promoted asymmetric cyclopropanation with high degrees of enantioselectivity and diastereoselectivity. Strikingly, "branched" and "linear" isomers of the starting materials led to the same lactone-fused cyclopropanes (**622**) with high yields and optical purities.

Recently, the group of Maulide also reported the cyclopropanation of sulfur ylides with S-tethered olefins.[355] The cyclopropanation of sulfur ylide **623**, carrying two olefins, showed high selectivity for the S-tethered olefin, affording product **624** in 75% yield (Scheme 110). Interestingly, the

Scheme 110. Catalyst-Dependent Selectivity in Sulfur Ylide Cycloisomerization Reactions



authors describe a catalyst-dependent cyclization, where other π-acidic catalysts such as Pd(II) and Pt(II) salts selectively afforded dihydrofuran **625** in moderate to excellent yields. Mechanistic experiments and computational studies have shown that palladium unlocks an oxidative addition/reductive elimination catalytic cycle that is not accessible with gold.

Interestingly, this novel approach for synthesizing three-membered rings (Scheme 110, top) allows new opportunities for diazo-free cyclopropanations. The process, however, proved difficult to extend to an intermolecular variant. Only the cyclopropanation of electron rich allenamide derivatives **627** turned out to be feasible thus far.[356] In the presence of doubly stabilized ylides and a cationic gold complex, smooth conversion to the methylenecyclopropane (**628**) was observed at room temperature (Scheme 111). Computational studies provided mechanistic insight, helping to explain both the regio- and stereoselectivity of the reaction: The most electron rich double bond coordinates to the gold catalyst, while

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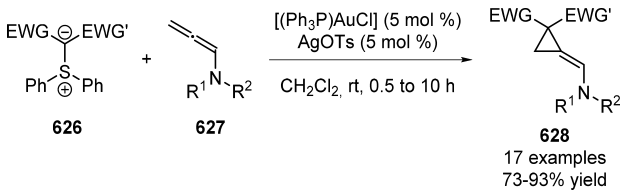
Scheme 111. Intermolecular Cyclopropanation of Allenamides with Stabilized Sulfur Ylides



nucleophilic attack occurs onto the less sterically demanding terminal position.

In most cases, variations of the substituents on the sulfonium group are of little interest because the corresponding sulfide is eliminated. In 2016, however, the Maulide group disclosed the results of their investigations into vinyl-substituted sulfur ylides **629**. When treated with a gold(I) catalyst, these compounds were shown to efficiently undergo S-to-O vinyl transfers (Scheme 112).[357] The reaction resembles a Smiles rearrangement and was proposed to occur in two steps. An initial 5-*exo*-*trig* cyclization through the attack of the carbonyl oxygen atom onto the activated vinyl substituent, followed by elimination to generate the final product. Alternative mechanistic pathways were ruled out through isotope labeling experiments. The products were in turn used as substrates for photocatalytic transformations.

4.1.3. Metal−Carbene Precursors. In the previous section it was shown how sulfur-based ylides have been used as one-carbon synthons in a number of examples. One of the most ubiquitous methods of introducing such synthons is through metal carbene intermediates (also known as metal alkylidenes), generated from diazocompounds and metal complexes. Typical reactions include cyclopropanation and insertion into C−H and X−H (X = N, O, S, P, Se) bonds.[358−362] While diazocompounds are highly efficient and often used, their large-scale applications have significant drawbacks due to concerns of both safety and operational simplicity. The use of sulfur ylides as alternative reagents has therefore been actively investigated.[337,363]

Intriguingly, the results of these investigations have shown a huge divergence in reactivity between sulfonium ylides, demonstrated as suitable substrates for cyclopropanation reactions, and sulfoxonium ylides (sulfur(VI), and therefore beyond the scope of this review), which are most suitable for X−H insertion reactions.[364−367] Neither examples of X−H insertion reactions employing sulfonium ylides, nor cyclopropanations with sulfoxonium ylides have been reported to date.

The use of sulfonium ylides for catalytic cyclopropanation dates back to a publication of 1966 by Trost,[365] however, the process remains underdeveloped. Recent advances include the use of an iron porphyrin catalyst to decompose sulfonium ylides. Gu and co-workers reported the cyclopropanation of styrenes using the fluorinated ylide generated from sulfonium salt **631** (Scheme 113).[368] Good *trans*-selectivity was observed across a broad range of styrenes, although no alkyl-substituted or 1,2-disubstituted alkenes were tolerated. Key to this novel cyclopropanation was the use of the (TPP)FeCl catalyst (**632**), which significantly outperformed other catalyst systems, with $Cu(acac)_2$ able to achieve only 16% yield, and copper sulfate and rhodium diacetate completely inactive.

In 2017, the same group reported the synthesis of difluoromethyl cyclopropanes using the same catalyst system.[369] In this case, 20 mol % of Zn dust was added to assist the reduction of Fe(III) to Fe(II), which is believed to be the active catalyst in solution.

C−H functionalizations,[370] either ylide-directed[371−374] or ylide annulation reactions,[375−377] are known, but only with sulfoxonium ions, beyond the scope of this review.

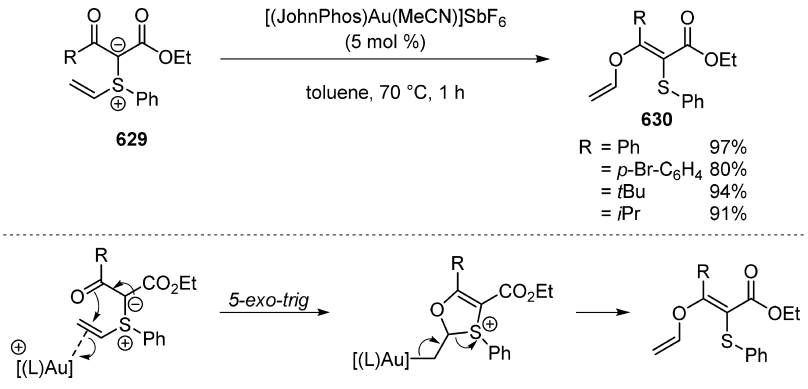
As shown in this section, transition-metal catalysis can be employed for a wide range of transformations of sulfur ylides, hinging on their reactivity as one-carbon synthons. In this context, the reaction with activated extended π-systems has enabled the efficient development of asymmetric (4 + 1)-cycloaddition reactions, as well as some examples affording ring sizes other than five. Activation of alkenes and alkynes with transition metal catalysts has shown sulfur ylides to also be versatile reagents for formal (3 + 2)- or (2 + 1)-cycloadditions, depending either on the choice of substrate or catalyst. A different approach toward the formation of cyclopropanes lies in the use of sulfur ylides as carbene precursors.

4.2. Asymmetric (Organocatalytic) Reactions

Organocatalysis has gained considerable notoriety over the past 20 years.[378] In this context, the deployment of sulfur-based ylides in organocatalytic annulation reactions based on various activation modes shall be presented in the following subsection.

4.2.1. Asymmetric Aminocatalysis. The Johnson−Corey−Chaykovsky cyclopropanation of α,β-unsaturated aldehydes or ketones can be performed enantioselectively using a chiral secondary amine as catalyst. The in situ

Scheme 112. Au-Catalyzed [1,4]-Vinyl Migration from Sulfur to Oxygen



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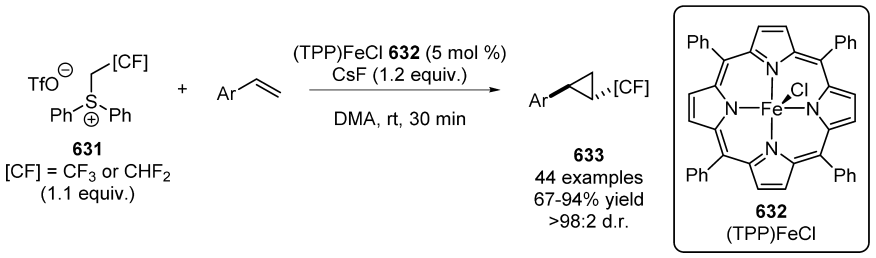
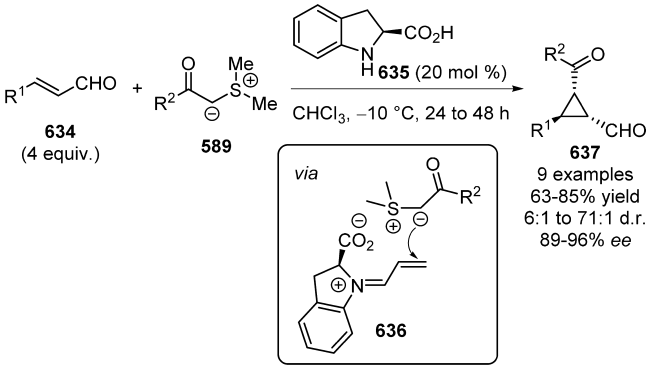
Scheme 113. Iron-Catalyzed Cyclopropanation Using Sulfur Ylides



generated iminium ions (**636**) are activated through LUMO-lowering, a strategy successfully applied by Kunz and MacMillan in 2005 to prepare highly functionalized cyclopropanes (**637**) in good yields and very good diastereo- and enantioselectivities (Scheme 114).[379]

Scheme 114. Enantioselective Cyclopropanation of α,β-Unsaturated Aldehydes with Sulfur Ylides and Aminoacids



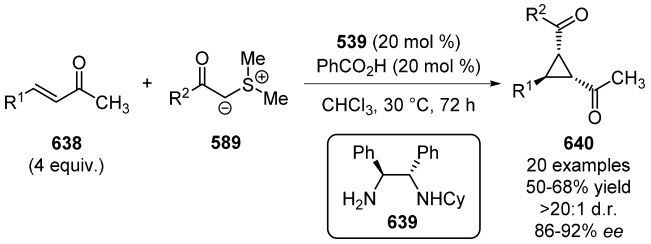
When organocatalysts without a carboxylic acid moiety were used, no product formation was observed. Attractive electrostatic interactions between the sulfonium cation and the carboxylate in the iminium complex were postulated, which could increase the nucleophilicity of the ylide and direct the nucleophilic attack. The reaction with L-proline as the organocatalyst afforded the product in a similar yield, but lower enantioselectivity due to the lack of *E*/*Z* control of the iminium configuration.

Inspired by this work, Arvidsson and co-workers developed two new organocatalysts (leading to slightly improved selectivities) by replacing the carboxylic acid functionality with either a tetrazole or aryl sulfonamide group.[380,381]

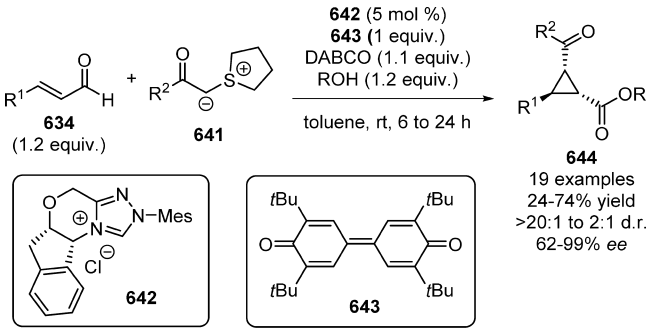
The cyclopropanation of α,β-unsaturated ketones with sulfur ylides was first reported in 2013 by Feng and co-workers.[382] In the presence of chiral diamine **639**, the reaction provided trisubstituted cyclopropanes (**640**) in moderate yields but with good enantioselectivities (Scheme 115).

4.2.2. Asymmetric Nucleophilic Catalysis. Organocatalysis with *N*-heterocyclic carbenes (NHCs) is recognized as a powerful tool in modern organic chemistry. In 2005, Studer and co-workers reported a classical example of asymmetric nucleophilic catalysis for the cyclopropanation of α,β-unsaturated aldehydes with sulfonium ylides, employing catalytic amounts of **642** (Scheme 116).[383] The reaction provided a wide range of trisubstituted cyclopropanes in moderate yields but with good diastereo- and enantioselectivities.

Scheme 115. Enantioselective Cyclopropanation of α,β-Unsaturated Ketones with Sulfur Ylides and Diamines

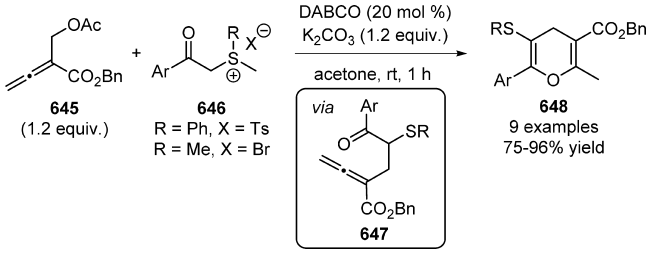


Scheme 116. Enantioselective NHC-Catalyzed Oxidative Cyclopropanation of Aldehydes with Sulfur Ylides



In 2012, Tong et al. developed a DABCO-catalyzed formal (3 + 3) annulation of 2,3-dienoate **645** with sulfur ylides (Scheme 117).[384] The reaction provides 4*H*-pyran products (**648**) with sulfide functionality under mild conditions and in good yields.

Scheme 117. DABCO-Catalyzed (3 + 3) Annulation of Allenoates with Sulfur Ylides to Deliver Achiral 4*H*-Pyrans



4.2.3. Asymmetric H-Bonding Catalysis. Cheng and Xiao reported the cyclopropanation of β,γ-unsaturated α-ketoesters with sulfur ylides, catalyzed by an H-bonding urea catalyst (**650**) (Scheme 118). A range of cyclopropanes could be synthesized in moderate to good yields with enantioselectivities up to 80% *ee*.[385]

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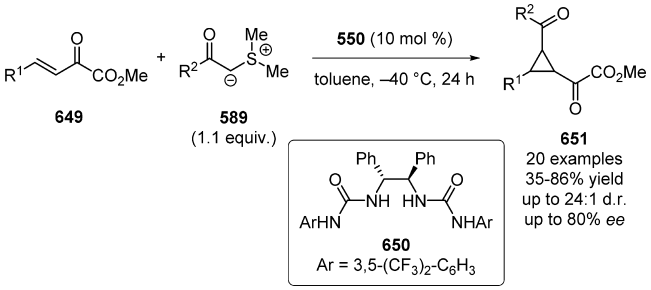
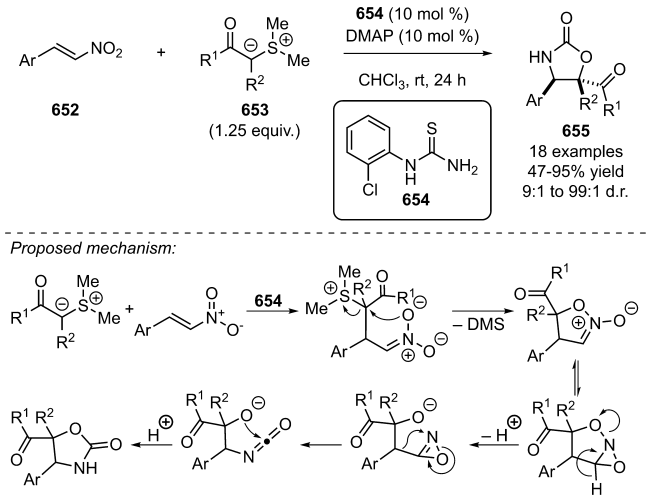
Scheme 118. Catalytic Asymmetric Cyclopropanation of *β,γ*-Unsaturated *α*-Ketoesters with Sulfur Ylides



In 2008, the group of Xiao developed a formal (4 + 1)-cycloaddition of nitrostyrenes with sulfur ylides, followed by a DMAP-catalyzed rearrangement reaction (Scheme 119).[386]

Scheme 119. Sequential (4 + 1)-Cycloaddition/ Rearrangement of Nitrostyrenes with Sulfur Ylides

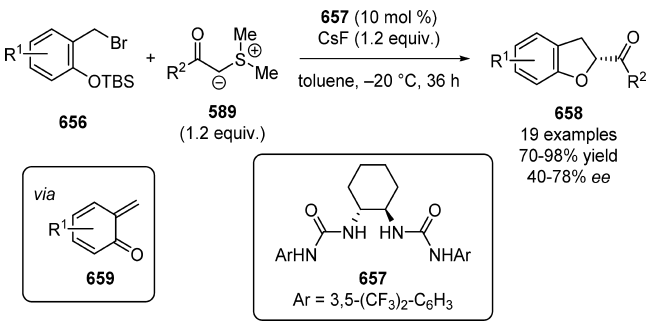


This transformation affords a range of oxazolidinones (**655**) in moderate to good yields with good to excellent diastereoselectivities. The same group also reported an enantioselective variant of this reaction, using the same chiral urea catalyst **650** as shown before (cf Scheme 118). Despite the high enantioselectivities, the high catalyst loading (50 mol %) required to achieve good yields was a slight drawback of this process.[387]

Recently, the same group disclosed an asymmetric formal (4 + 1)-cycloaddition of TBS-protected phenols with sulfur ylides (Scheme 120). The reaction proceeds through in situ generated *ortho*-quinone methides **659** and affords enantioenriched 2,3-dihydrobenzofurans (**658**) in good yields, but with moderate *ee*'s.[388]

4.2.4. Use of Enantioenriched Sulfur Ylides. In 2013, Aggarwal, McGarrigle and co-workers reported in-depth studies of sulfur ylide-mediated asymmetric epoxidations and aziridinations using a chiral sulfide **662** (Scheme 121).[389] This compound, later shown to be readily available on 25 gram scale,[390] was easily converted into the corresponding bench stable sulfonium salt **663** through alkylation (Scheme 121a). Subsequent in situ ylide formation was shown to enable diastereo- and enantioselective epoxidations and aziridinations on a wide range of substrates (Scheme 121b), with high amounts of the chiral reagent being easily recovered. In addition to exploring the scope of the transformation, extensive efforts were undertaken to determine the limitations of the reagent as well as rationalizations for the observed selectivities.

Scheme 120. Asymmetric (4 + 1)-Cycloaddition of Sulfur Ylides with in Situ-Generated *ortho*-Quinone Methides



Another type of chiral sulfonium salt, reminiscent of **521** (cf Scheme 86), was applied to the Aggarwal group's synthesis of the cyclopiazonic acid family, employing **667** (Scheme 122).[391] Herein, the bromoisoxazole ensures semistabilization of the ylide generated in situ, rendering betaine formation the enantiodetermining step and leading to high levels of enantiomeric excess and good diastereocontrol. The resulting aziridine **668** was subsequently converted into cyclopiazonic acids **669** and **670** in only four further steps.

This section has shown that, in the absence of chiral metal complexes, asymmetry can be induced in a wide range of different manners. Many of the approaches for enantioselective cyclization reactions of sulfur ylides rely on classical organocatalytic approaches, such as the condensation of chiral amines with carbonyl moieties or the transient addition of nucleophiles such as *N*-heterocyclic carbenes. Moreover, the use of (thio)urea catalysts for hydrogen-bonding catalysis and the use of chiral, enantioenriched sulfur ylides themselves has enabled a plethora of enantioselective transformations.

4.3. Photocatalytic Reactions of Sulfur Ylides

Radical reactions offer a complementary approach to ionic chemistry,[392−394] as reactive intermediates with an unpaired valence electron typically display reactivity inaccessible to two-electron manifolds. The recent years have seen a revival of radical chemistry in organic synthesis due to the advent of photoredox catalysis. These reactions rely on the ability of an appropriate catalyst to trigger single electron transfer (SET) processes upon visible light irradiation.[395,396] In 2016, Xiao et al. reported a photocatalytic reaction in which doubly stabilized sulfur ylides (**671**) underwent a SET process, thus initiating a formal C−H insertion (Scheme 123).[397]

The reaction occurs in the presence of 2 mol % of a cationic Ir(III) complex that can be excited by blue light irradiation. The resulting excited complex is a strong oxidant, capable of removing an electron from the sulfur ylide to form radical cation **673**. Formation of five-membered intermediate **674** occurs more rapidly than decomposition of the ylide to form the free carbene.[365,398] Termination through either pathway a or b affords oxindoles in moderate to good yields.

Recently, the group of Xiao also reported a photoinduced formal (4 + 1) cyclization of sulfur ylides with *N*-tosyl vinylaniline **675** and a radical precursor (Scheme 124). The reaction is promoted by blue light and the use of $Ru(phen)_3Cl_2$ as a photocatalyst to generate 2,3-disubstituted indoles in

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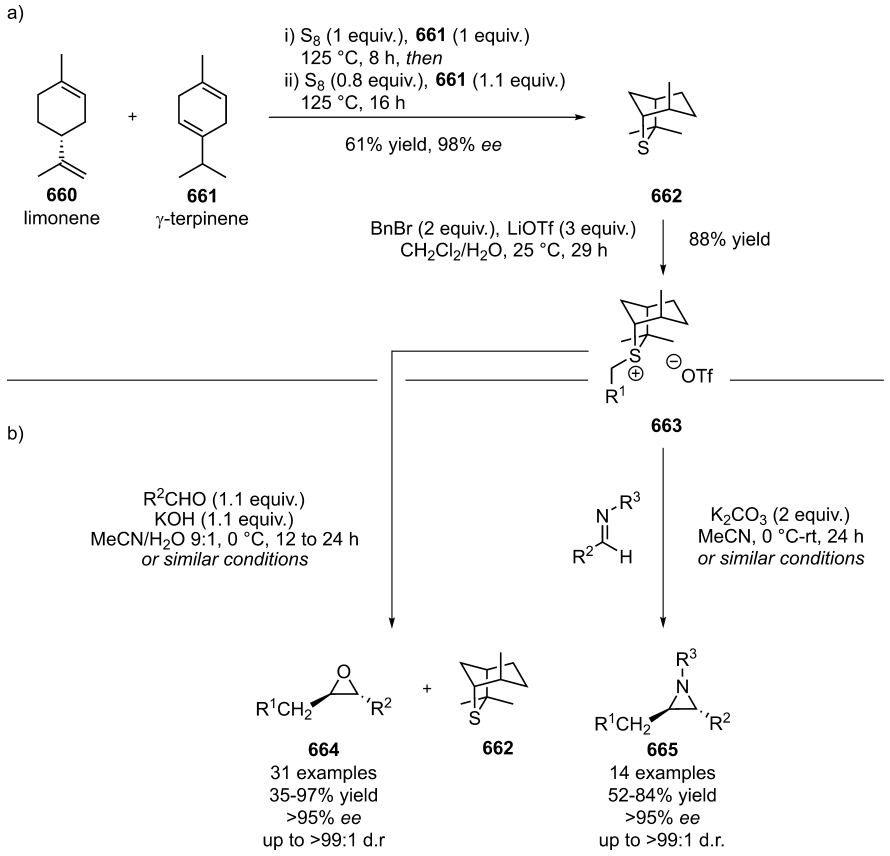
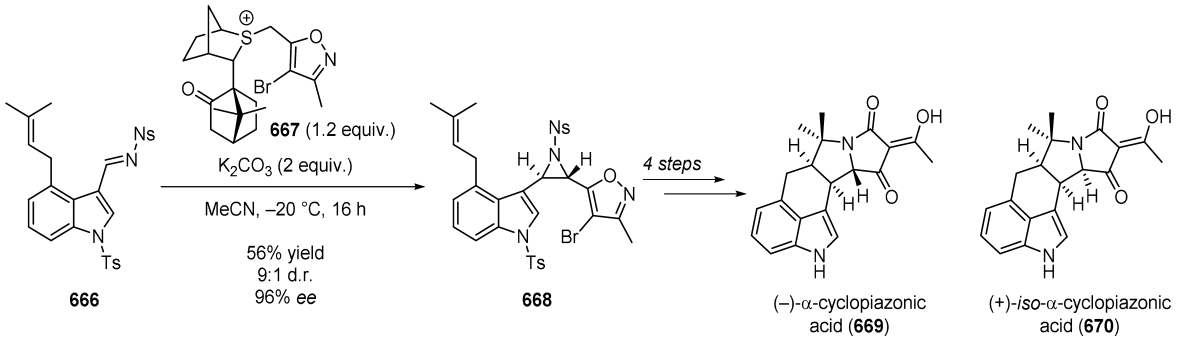
Scheme 121. Aggarwal's Chiral Sulfonium Salt for Asymmetric Epoxidations and Aziridinations



Scheme 122. Aggarwal's Synthesis of the Cyclopiazonic Acid Family Using a Chiral Sulfur Ylide



moderate to excellent yields. Interestingly, using Umemoto's reagent resulted in a remarkable catalyst-free procedure.[399]

In contrast to the previous example in this section, the sulfur ylide is not directly involved in the SET process. The proposed mechanism (Scheme 124, bottom) involves addition of the initially formed radical R• to the styrene moiety of **675**, followed by oxidation to the benzylic carbocation. The resulting *ortho*-quinone methide **678** is then captured by the sulfur ylide in a classical cycloaddition process.

4.4. Domino Reactions Involving Sulfur Ylide Formation

4.4.1. [2,3]-Sigmatropic Rearrangements. Sigmatropic rearrangements are a powerful tool for the efficient formation of C–C bonds, and [2,3]-sigmatropic rearrangements are no exception. Significant accelerations are observed when one or more bonds in the system are polarized; the fastest rearrangements take place when an atom bears a formal charge. In this context, it is not surprising that sulfur ylides are useful substrates for such transformations. The in situ formation of sulfur ylides through metal-catalyzed decomposition of diazo compounds followed by rearrangement has emerged as a synthetically appealing approach. The reaction of allyl or propargyl sulfides with metal carbenoids, followed by spontaneous [2,3]-sigmatropic rearrangement of the zwitterionic intermediate **680** is known as the Doyle–Kirmse reaction (Scheme 125, as alluded to in section 2.2.2.). This transformation has been studied extensively and offers a unique approach for the construction of S-substituted quaternary centers.[400,401]

As for many classical diazo decomposition reactions, the Doyle–Kirmse reaction has been extensively studied with copper and rhodium catalysts, as they do not require complex ligand architectures. Nonetheless, the reaction has also been studied with catalysts based on other metals such as Co,[402] Ag,[403] Pd,[404] Ru,[405–407] and Fe.[408–411]

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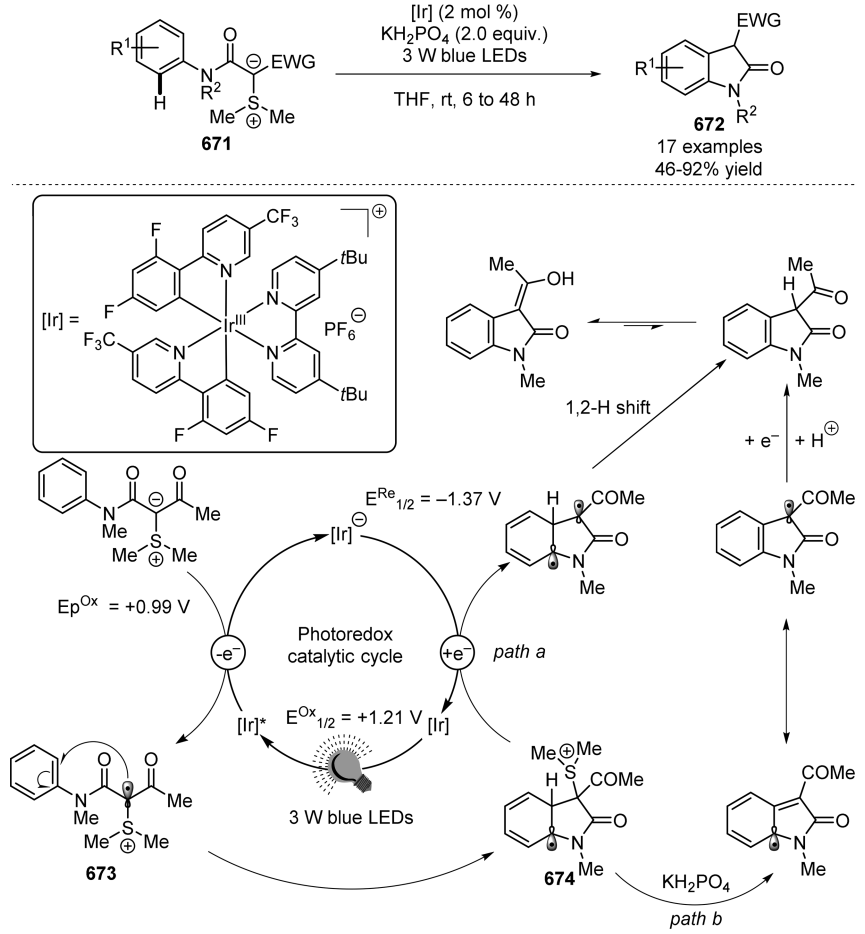
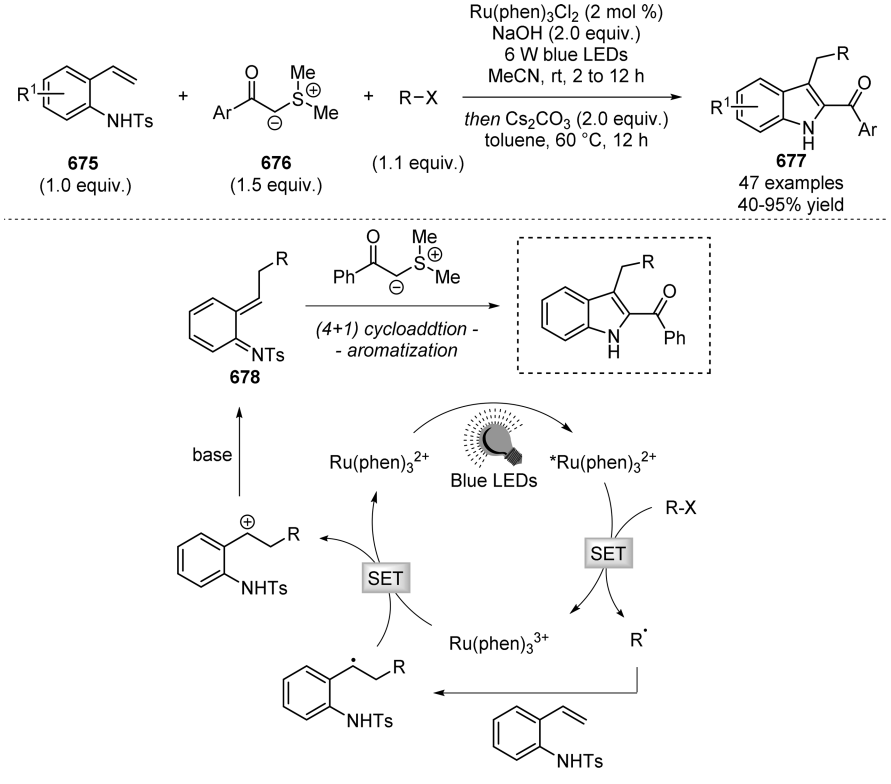
Scheme 123. Xiao's Photocatalytic Insertion of Sulfonium Ylides into Aryl-C−H Bonds for Oxindole Synthesis



Scheme 124. Photocatalytic Synthesis of 2,3-Disubstituted Indoles Employing Stabilized Sulfur Ylides



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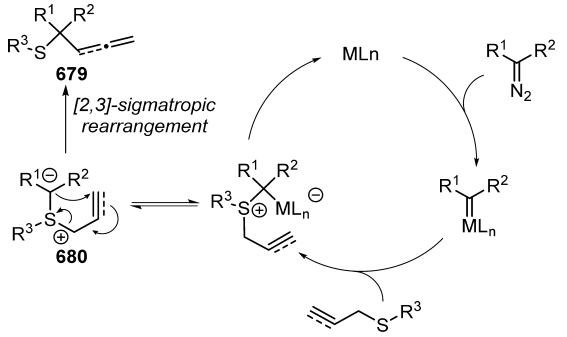
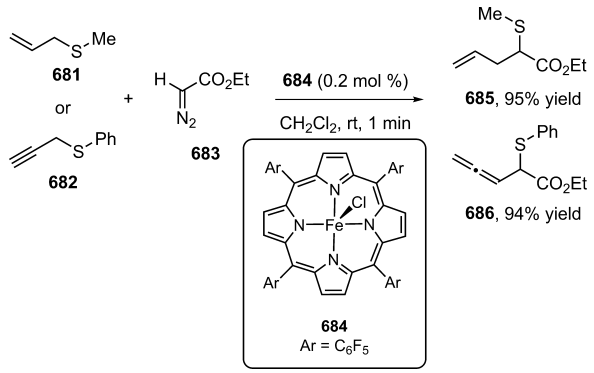
Scheme 125. General Proposed Mechanism for the Doyle–Kirmse Reaction



The exploration of iron catalysts has led to the identification of highly efficient catalyst **684** that can be used in loadings as low as 0.2 mol % (Scheme 126).[412,413] Typically, allyl sulfides

Scheme 126. Iron-Catalyzed Doyle–Kirmse Reaction of Allyl and Propargyl Sulfides

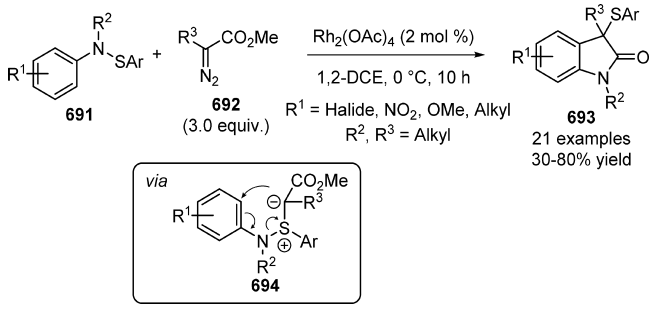


and propargyl sulfides are converted to homoallyl (**685**) and homoallenyl (**686**) sulfides, respectively, at room temperature in very short reaction times. Another compelling aspect of the Doyle–Kirmse reaction is its high functional group tolerance. Reactions can be chemoselectively performed in the presence of allyl ethers, boronates, disulfides, secondary anilines, and even free alcohols.[414]

The [2,3]-sigmatropic rearrangement can also occur with an aromatic ring as the π-component and is then known as the Sommelet–Hauser rearrangement. The first example of a thia-Sommelet–Hauser reaction was described by Wang et al. in 2008 and relies on the in situ formation of sulfur ylides from diazo(aryl)acetates (**687**) and aryl sulfides under rhodium catalysis (Scheme 127). Despite the required dearomatization step, the reactions proceed smoothly at ambient temperature and deliver a range of di- and trisubstituted arenes in moderate to good yields. Interestingly, the mechanism involves an unusual ylide transposition (to form **689**) prior to [2,3]-sigmatropic rearrangement.[415]

The group of Wang, employing a modified Gassman indole synthesis, applied this strategy for the synthesis of oxindoles (Scheme 128). Rhodium-catalyzed decomposition of diazo

Scheme 128. Wang's Modified Gassman Oxindole Synthesis

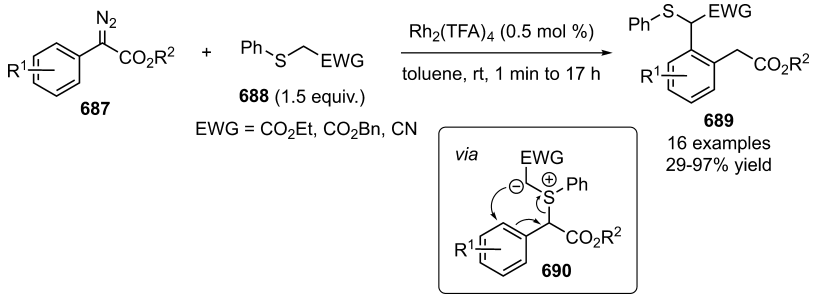


compounds in the presence of sulfenamides, followed by [2,3]-sigmatropic rearrangement allowed for a one-step preparation of oxindoles bearing quarternary centers.[416]

The development of an enantioselective variant of the Doyle–Kirmse reaction would be highly appealing, as it would enable the simultaneous stereocontrolled formation of a C–S and a C–C bond to the same carbon atom. This endeavor has been a major topic in the last two decades, and research has mainly focused on the use of chiral metal catalysts. For a long time, the best enantioselectivities were obtained through the use of both a chiral metal complex and Oppolzer's chiral auxiliary in an approach developed by Wang.[417] Only recently it has become possible to achieve good enantioselectivities in purely catalyst-controlled systems.[418]

In 2017, the Wang group was the first to report high levels of enantioselectivity for the Doyle–Kirmse reaction without the need for a chiral auxiliary (Scheme 129). The combination of a new set of ligands (**L6**) and highly electron-poor trifluoromethyl sulfides (**695** and **696**) allowed for high enantiocontrol over a wide range of alkenyl-, aryl-, and heteroaryl-substituted diazoacetate derivatives. Despite this success, low diastereoselectivities were obtained when internal olefins were used. Notably, these catalysts led to the formation of nearly racemic products when diallyl sulfide was employed. These observations support previous proposals of ligand decoordination from the metal complex prior to the [2,3]-sigmatropic event.[419]

Scheme 127. Rhodium-Catalyzed thia-Sommelet–Hauser Rearrangement of Aryl Sulfides



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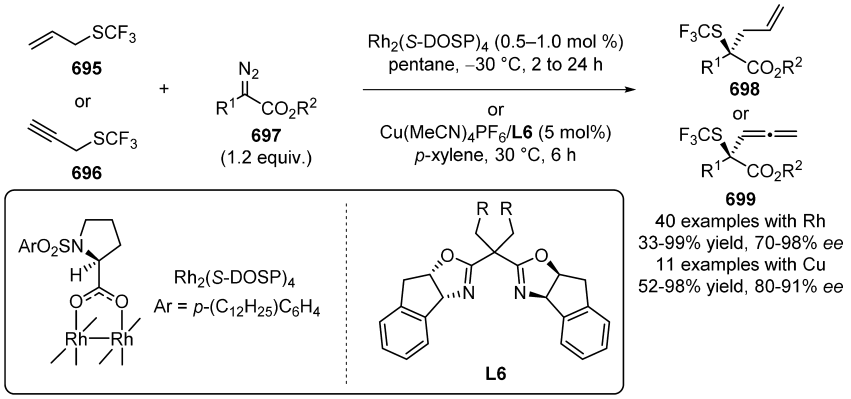
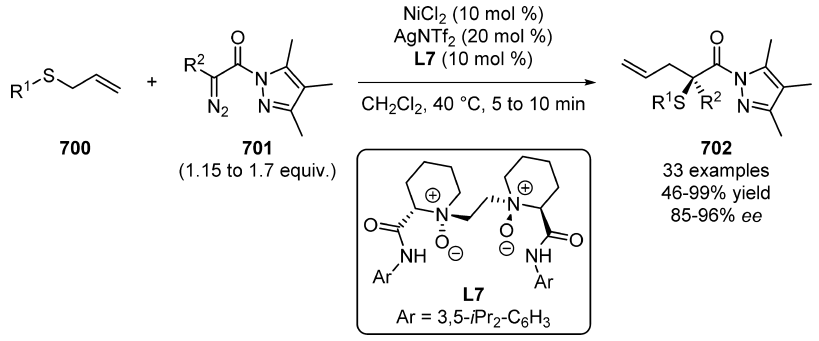
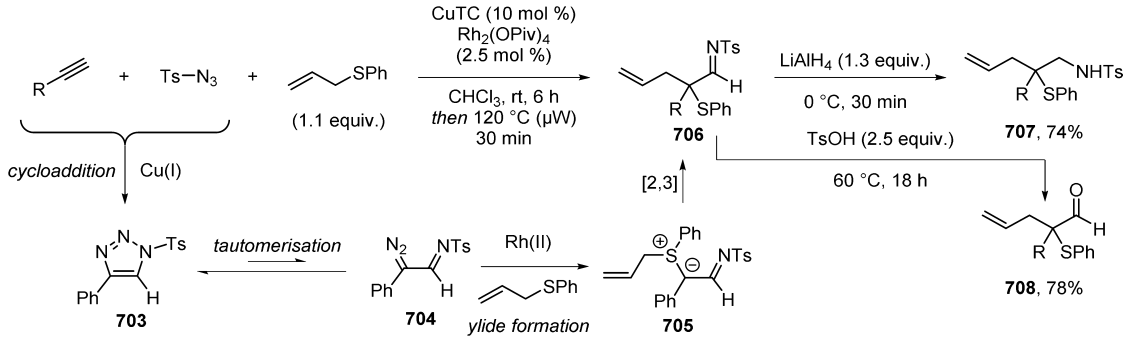
Scheme 129. Enantioselective Doyle−Kirmse Reaction with Chiral Rhodium or Copper Complexes



Scheme 130. Enantioselective Ni-Catalyzed Doyle−Kirmse Reaction with Pyrazoleamide Diazo Compounds



Scheme 131. In Situ Generation of Diazo Compounds in the Doyle−Kirmse Synthesis of Thioether Imines



In 2018, the group of Feng reported another breakthrough in asymmetric Doyle−Kirmse reactions, using a chiral nickel(II) catalyst and pyrazoleamide-derived diazocompounds (Scheme 130). The introduction of a pyrazole unit to the diazo reactant (**701**) allows the chiral catalyst to remain bound to the sulfur ylide intermediate, affording excellent yields and high enantioselectivities. Control experiments using diazo compounds that did not include the pyrazole afforded nearly racemic products under otherwise similar reaction conditions. The reaction with the pyrazole moiety and diallyl sulfide affords enantioenriched products up to 92% *ee*, proving that the catalyst remains bound to the substrate during the [2,3]-shift.[420]

Despite the fact that diazo compounds are often excellent metal carbene precursors and can react under mild conditions with good chemoselectivity, major drawbacks arise from their hazardous and potentially explosive nature, which limit their applicability for large-scale reactions. Therefore, several alternatives have been developed that avoid the direct use of diazo compounds, including the generation of diazo intermediates in situ and the access to metal carbenoids from unsaturated C−C bonds in the presence of π-acid catalysts.

In this framework, tosylhydrazones are valuable precursors of unstabilized diazo compounds through the Bamford−Stevens reaction. In the presence of base, allyl sulfides, and catalytic $Rh_2(OAc)_4$, tosylhydrazones smoothly undergo the Doyle−Kirmse reaction.[421] This approach also obviates the requirement for an electron-withdrawing group, which is usually necessary to stabilize the diazo starting material.

Another method for the in situ generation of diazo compounds is the slow addition of sodium nitrite to a primary amine. In 2017, Koenigs and co-workers applied this approach in an iron-catalyzed Doyle−Kirmse reaction.[422] Despite improvement in safety and scalability, these procedures do not yet offer as wide a scope as the Bamford−Stevens reaction.

Murakami and co-workers were the first to report the use of 1-sulfonyl-1,2,3-triazoles (**703**) as masked diazoimines in combination with the [2,3]-rearrangement of allylsulfonium

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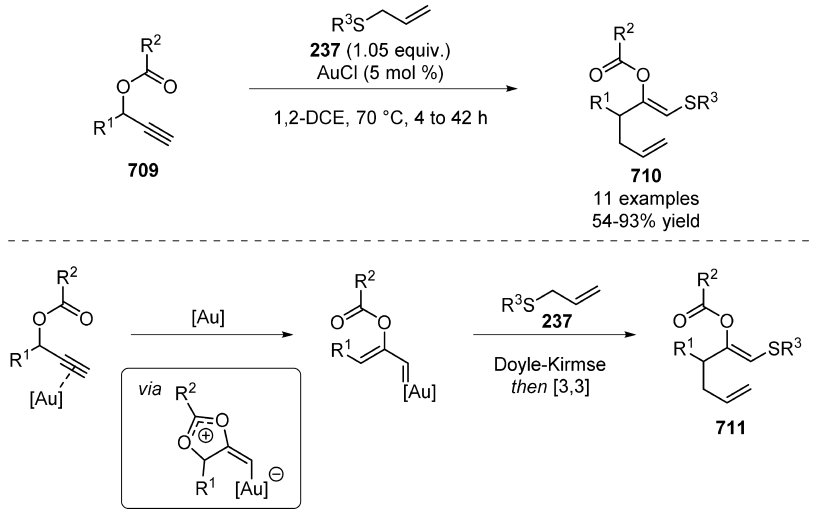
Scheme 132. Alkynes as Masked Ylides in Doyle−Kirmse Chemistry

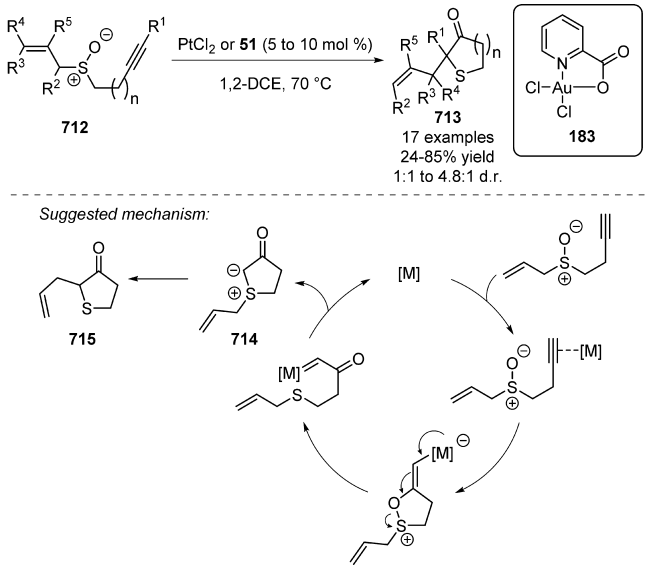


ylides.[423] The authors propose a domino process, starting with a copper-catalyzed (3 + 2)-cycloaddition between alkynes and tosylazides to form a triazole intermediate (Scheme 131). Rhodium-catalyzed decomposition of the diazoimine tautomer **704** affords an electrophilic metal carbene complex that can react with the allyl sulfide, followed by [2,3]-sigmatropic rearrangement. The resulting α-sulfenylated imines (**706**) can be either hydrolyzed to the corresponding aldehydes or reduced with $LiAlH_4$ to afford tosylamines. Especially considering the complexity of this sequence, remarkably high yields and chemoselectivities were observed. The group of Anbarasan reported a similar strategy on the rhodium-catalyzed denitrogenative synthesis of α-sulfenylated imines.[424]

While the in situ generation of diazo compounds represents an improvement from the perspective of safety and operational simplicity, other developments have been made in the generation of metal carbenoids without the need for nitrogen gas extrusion. Propargyl carbonates can also function as carbenoid precursors through migration of the acyl unit under π-acid catalysis. In 2008, Davies and co-workers used this approach in a Doyle−Kirmse reaction using gold catalysis. Notably, the expected homoallyl sulfides were not obtained, but the isolated products bore structure **710** (Scheme 132).[425] The precise mechanism of this transformation remains unclear, but [3,3]-sigmatropic rearrangement of the expected Doyle−Kirmse products would provide a plausible explanation.

In 2009, the same authors proposed a similar strategy using sulfoxides.[426] On the basis of the works of Toste[427] and Zhang,[428] alkyne oxidation was achieved through the intramolecular addition of a sulfoxide moiety, promoted by the π-acidic catalyst (Scheme 133). Following S−O bond cleavage, the resulting carbenoid and sulfide were proposed to react intramolecularly, forming ylide **714**. A final [2,3]-sigmatropic rearrangement afforded the heterocyclic products. Optimization of the reaction conditions revealed $PtCl_2$ to be the optimal catalyst for the reaction with terminal alkynes, whereas internal alkynes required dichloro(pyridine-2-carboxylato)gold(III) **183** for the efficient synthesis of cyclic sulfides bearing a quaternary stereocenter. Ester- and aryl-substituted internal alkynes were well tolerated, while highly substituted allyl sulfoxides afforded the desired product but only with low levels of diastereoselectivity.

Scheme 133. Synthesis of Sulfur Heterocycles from Alkynyl Sulfoxides through Doyle−Kirmse Reaction



More recent methodologies using the intermolecular oxidation of alkynes that employ stoichiometric amounts of *N*-oxides have also been reported. These procedures have the advantage of not having to use highly specialized substrates. As regioselectivity presents an added problem in intermolecular processes, polarized alkynes (e.g., ynamides) were used to control the reaction outcome.[429]

In 2014, the group of Zhang addressed this issue efficiently by employing syringe pump addition of the oxidizing reagent (8-methylquinoline-*N*-oxide) and, more importantly, *P*,*S*-bidentate supporting ligands (**L8**) in order to decrease the electrophilicity of the α-oxo gold carbene intermediate (Scheme 134). Starting from terminal alkynes, a three-component synthesis of α-aryl(alkyl)thio-γ,δ-unsaturated ketones (**717**) was achieved in good yields, but low diastereoselectivities were obtained with substituted allyl sulfides.[430]

Recent developments employ the release of the ring-strain of cyclopropenes for the generation of carbenoids. Treatment of cyclopropene **718** with catalytic amounts of $Rh_2(OAc)_4$

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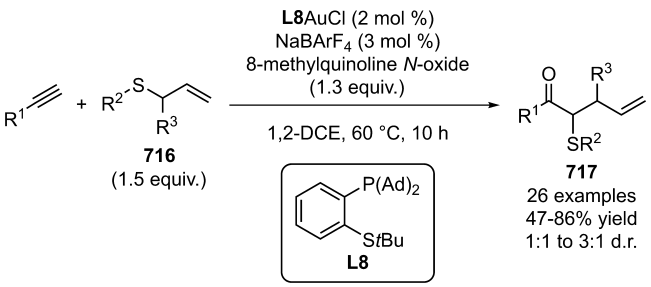
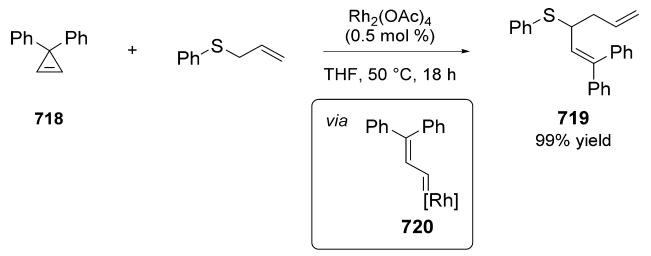
Scheme 134. Doyle−Kirmse Reaction with Terminal Alkynes as Carbenoid Precursors



resulted in spontaneous ring opening to form the corresponding rhodium carbene **720**, which could undergo Doyle−Kirmse reaction in the presence of an allyl sulfide (Scheme 135). This

Scheme 135. Doyle−Kirmse Reaction from Cyclopropenes



general transformation allowed the synthesis of sulfur-containing alkenes and allenes in good yields. Attempts to develop an asymmetric version resulted only in low enantioselectivities.[431]

This section has so far detailed that sulfur ylides containing a pendant π-system (in form of either an alkene, an alkyne or an arene) readily undergo [2,3]-sigmatropic rearrangement reactions. The metal-catalyzed Doyle−Kirmse reaction of sulfides with diazo compounds stands out in terms of the number of reports. However, the central metal−carbenoids can also be elegantly generated in situ using π-acid catalysis or the decomposition of cyclopropenes.

Metal-free sulfur ylide formation followed by [2,3]-sigmatropic rearrangement was reported independently by the groups of Biju[432] and Tan.[433] Both groups showed that allyl and propargyl thioethers can react with arynes to form sulfur ylides in situ (Scheme 136). These intermediates can then quickly undergo [2,3]-sigmatropic rearrangement to afford homoallyl sulfides (**723**). While the work of Tan and co-workers mainly focuses on symmetrical thioethers, the group of Biju incorporated an electron-withdrawing group in the R^1-position, thereby enabling the reactions to proceed at considerably lower temperatures (typically room temperature). Moreover, the formation of quatenary carbon centers was shown, increasing the procedure's synthetic value. However, in contrast to transition-metal catalyzed processes, monosubstituted benzyne derivatives were shown to afford mixtures of regioisomeric products.

4.4.2. [1,2]-Rearrangements. Direct 1,2-migration of alkyl substituents from the cationic to the anionic center of an ylide are collectively known as the Stevens rearrangement. These reactions have been extensively studied in systems based on oxonium and ammonium ylides, but the sulfur-equivalent, i.e., thia-Stevens rearrangement, has not received nearly as much attention. Despite being underdeveloped, the reaction has still proven to be a powerful tool for C−C (and C−N[434]) bond formation and the synthesis of quaternary centers. Mechanistically, the (thia-)Stevens rearrangement displays retention of configuration; this is in disagreement with a concerted reaction, which would require an antarafacial shift. Therefore, a homolytic cleavage within the solvent cage and subsequent recombination seem highly likely (Scheme 137).[335]

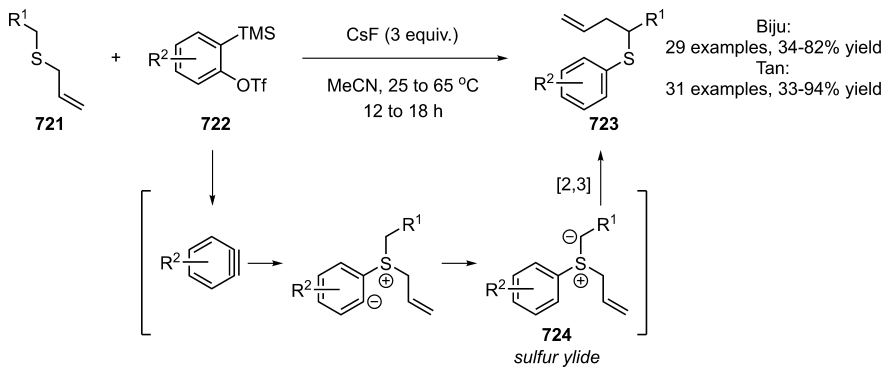
When combined with the power of in situ transition metal-catalyzed ylide formation, the synthetic potential of this strategy is greatly improved. In particular, such processes have most commonly been used for the synthesis of sulfur containing heterocycles through ring-expanding 1,2-shifts.

In this context, such a process was reported by Zakarian et al. for the synthesis of tetrahydrothiophenes from thietanes (**727**),[435] which was applied to the synthesis of a complex structure akin to the nuphar thioalkaloids' thiolane core (**731**) (Scheme 138).[436]

Further application of this strategy in natural product synthesis can be found in a report by West and co-workers, who used the thia-Stevens rearrangement of a monothioacetal-derived ylide as a key step in their formal synthesis of (+)-laurencin (**734**).[437] Medium-sized cyclic thioether **733** was obtained in 60% yield from this copper-catalyzed step (Scheme 139). Importantly, the α-stereogenic center was perfectly conserved during the 1,2-migration with stereochemical fidelity comparable to the ammonium ylide variants.

In 2009, Tang and co-workers reported a catalytic enantioselective Stevens rearrangement through the action of a chiral bisoxazoline (**737**/**738**)/copper complex (Scheme 140).[438] They were able to synthesize a number of six-membered 1,4-oxathianes (**739**) from diazomalonates and

Scheme 136. Metal-Free [2,3]-Sigmatropic Rearrangement of Sulfur Ylides Generated in Situ from Benzyne Intermediates



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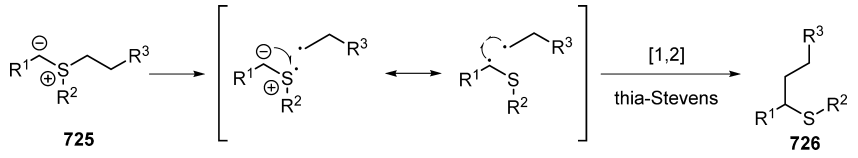
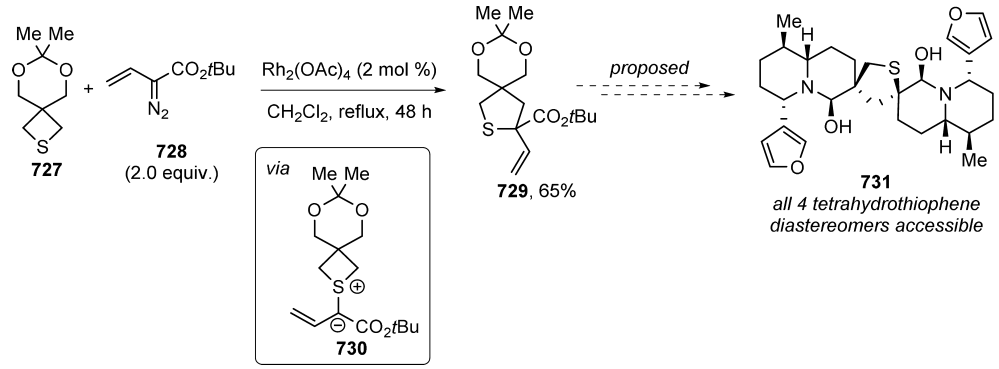
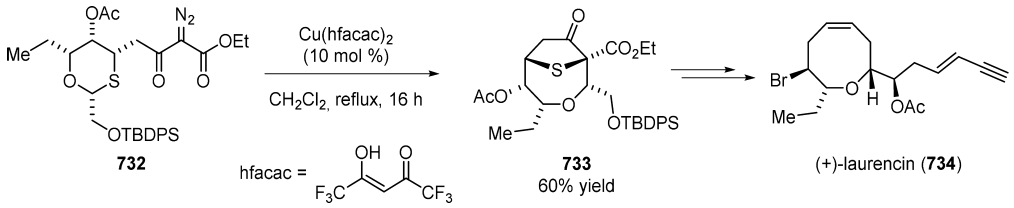
Scheme 137. General Mechanism of the thia-Stevens Rearrangement



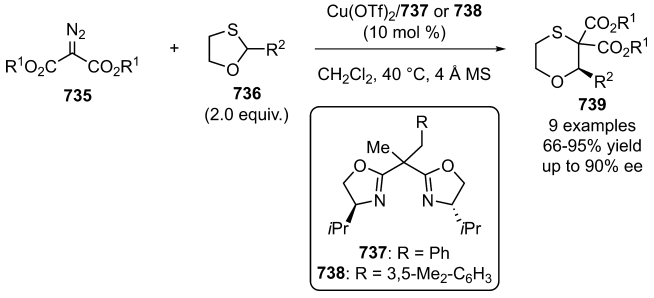
Scheme 138. Proposed Synthesis of the Nuphar Thioalkaloids Core through Ring Expansion of Thietanes



Scheme 139. A thia-Stevens Rearrangement as a Key Step in the Formal Synthesis of (+)-Laurencin



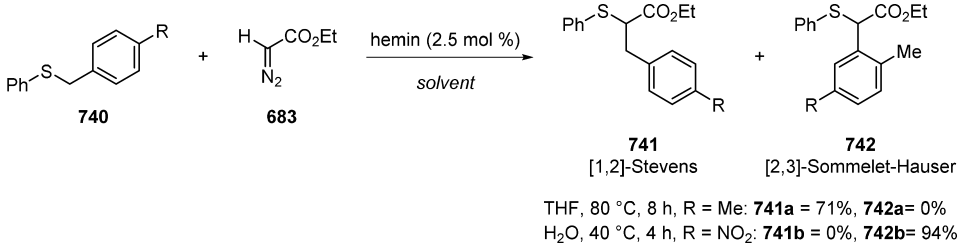
Scheme 140. Copper-Catalyzed Enantioselective 1,2-Migration of 1,3-Oxadithiolanes for the Formation of 1,4-Oxathianes



achiral 1,3-oxathiolanes in good yields and promising enantioselectivities. More electron-rich substrates required the use of the sterically more demanding ligand **738**. Interestingly, sulfur ylides with allylic functionality, shown to be good substrates for 2,3-sigmatropic shifts in section 4.4.1, exclusively underwent the 1,2-shift in this system.

Competition studies undertaken by Pan and co-workers to probe the selectivity for either 1,2- or 2,3-shift showed that the preferred pathway strongly depends on the reaction conditions and the electronic properties of the substrate.[439] Hemin-catalyzed formation and rearrangement of benzyl sulfonium ylides led to the formation of different products, dependent on both the nature of the solvent and the electronics of the substrate's aromatic ring (Scheme 141). The authors established that electron-withdrawing substituents on the benzyl unit significantly enhance the [2,3]-Sommelet–Hauser rearrangement (leading to **742**), whereas electron-rich aromatics exclusively lead to [1,2]-Stevens rearrangement (leading to **741**). Protic solvents were also found to favor the Sommelet–Hauser rearrangement.

Scheme 141. Study of Preferred Reaction Pathways (Stevens vs Sommelet–Hauser) in Dependence of Solvent and Electronic Properties



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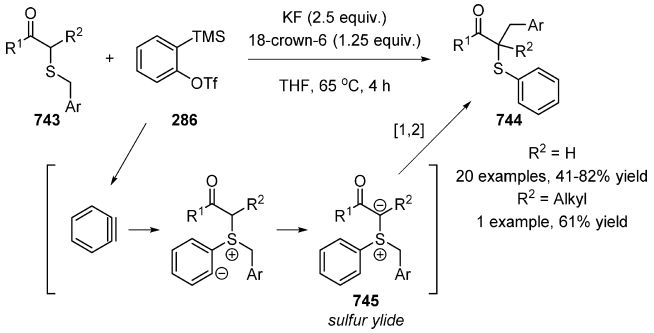
Metal-free ylide formation followed by Stevens rearrangement was achieved by employing benzyne intermediates (Scheme 142).[440] He and co-workers showed that simple

Scheme 142. Metal-Free Stevens Rearrangement of Sulfur Ylides Generated in Situ from Benzyne Intermediates



monosubstituted β-keto thioethers can add to benzynes generated in situ, forming sulfur ylides. These intermediates (**745**) undergo smooth [1,2]-rearrangement to afford substituted β-keto thioethers. The methodology could be advantageous to make quaternary carbons. However, in this paper, only one successful example was described with moderate yield.

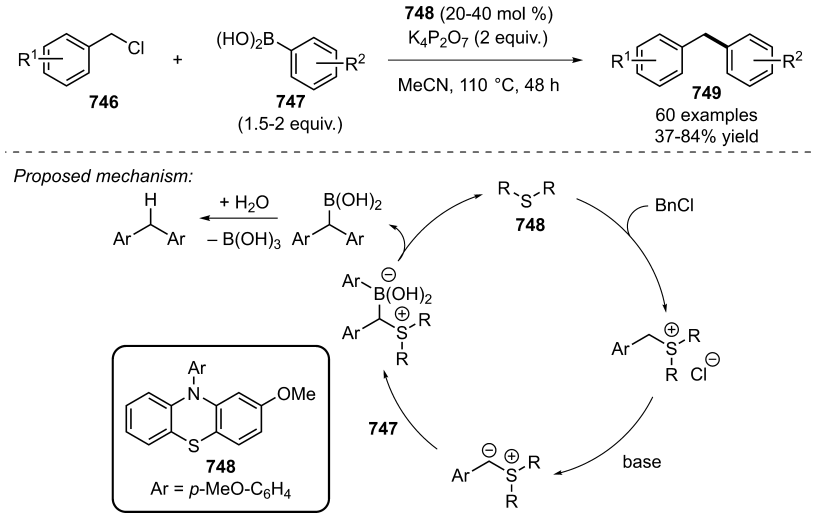
4.4.3. In Situ Generated Sulfur Ylides through Nucleophilic Substitution/Deprotonation. In addition to their versatile use in transition metal-catalyzed in situ ylide formation, sulfides are competent S_N2 nucleophiles toward activated halides. Recently, the group of Huang used this reactivity to generate sulfur ylides in situ in a base-mediated process, without the need for transition metal catalysis.[441] The corresponding ylides were employed in a coupling reaction with arylboronic acids (**747**) to generate diarylmethanes using catalytic amounts of the sulfide **748** (Scheme 143). The proposed mechanism involves ylide formation and reaction with **747** to generate a boronate complex, followed by 1,2-metalate shift and protodeboronation. The reaction represents a complementary approach to Suzuki cross couplings due to its high selectivity for benzyl chlorides over aryl halides.

4.4.4. (3 + 2)-Cycloaddition Reactions of Thiocarbonyl Ylides. Most of the ylide reactions discussed so far involve the anionic functionality of the ylide acting as a nucleophile, followed by expulsion of a sulfide, and alternative ylide structures can lead to alternative reactivity. One example of such alternative reactivity is the 1,3-dipolar behavior of thiocarbonyl ylides. While azomethine ylides,[442,443] and indeed carbonyl ylides,[444] have been extensively studied, the corresponding thiocarbonyl ylides are mostly known for being transient intermediates in the Barton–Kellogg olefination.[445] Once formed, the ylide undergoes a rapid electrocyclization, forming a thiirane (**751**), which proceeds to extrude sulfur, affording a tetrasubstituted olefin (Scheme 144a). Attempts to access 1,3-dipolar functionality have mostly focused on the use of a narrow range of ylides, normally under cryogenic conditions.[446] In 2018, the Maulide group demonstrated that by using thiouronium ylides, in which the cationic functionality is stabilized, it was possible to achieve (3 + 2)-cycloadditions at room temperature under very mild conditions, generating dihydrothiophenes (**755**) following elimination of an amine (Scheme 144b).[447] Alternative approaches have been employed in natural product syntheses by Trauner (Scheme 144c)[448] and Magauer (Scheme 144d),[449] as a strategy for *syn*-dialkylation of alkenes, because the generated tetrahydrothiophenes can be desulfurized through the use of Raney Ni. The latter example makes use of high pressure conditions to promote productive reactivity, and both examples employ highly polar solvents.

4.4.5. Formation of Sulfur Ylides through Reaction of Sulfides with Arynes. As seen in the previous sections, sulfides can add to arynes to afford sulfur ylides in situ. The general mechanism for this process can be seen in Scheme 145. The reaction of benzyne with an alkyl sulfide leads to the formation of zwitterionic intermediate **766**, and the following intramolecular 1,4-proton shift leads to the formation of a sulfur ylide (**767**).

This chemistry was mainly studied between 1960 and 1990[450,451] but has seen increased interest lately due to a 2014 report by Xu and co-workers.[452] Therein, the group reported a one-pot sulfur ylide formation, followed by epoxidation of isatins (Scheme 146). The reaction involves trapping of two

Scheme 143. A Sulfide Catalyst Enables the Sulfur Ylide-Mediated Cross-Coupling Reaction of Benzyl Halides with Arylboronic Acids



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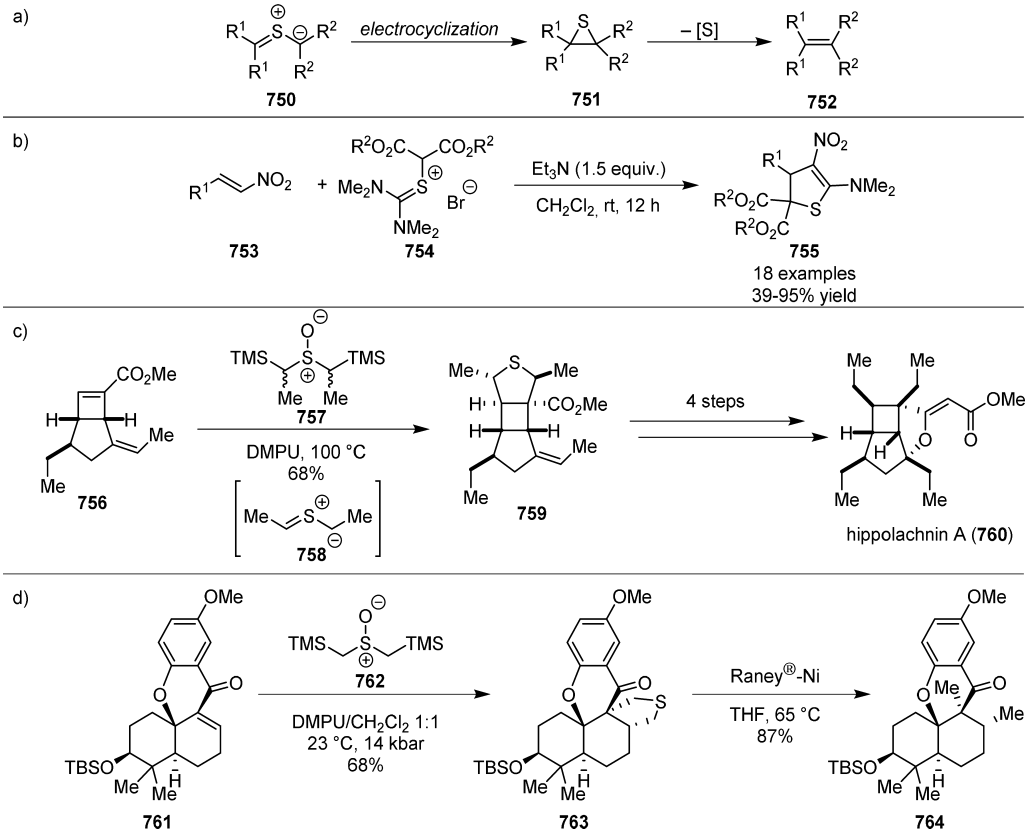
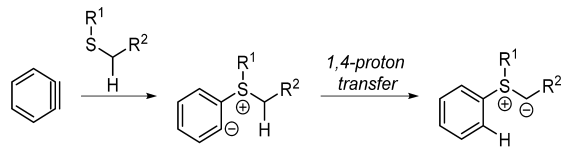
Chem. Rev. 2019, 119, 8701–8780

Scheme 144. Reactivity of Thiocarbonyl Ylides and Their Application in (3 + 2)-Cycloaddition Reactions



Scheme 145. General Mechanism of Sulfur Ylide Formation from Aryne and Sulfide



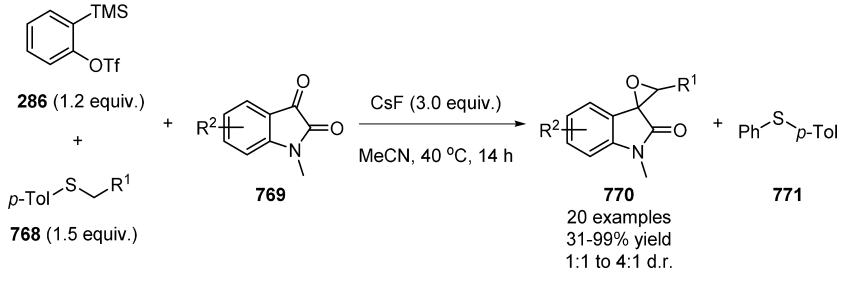
reactive intermediates under mild conditions and the corresponding products could be isolated in moderate to good yields, albeit with low diastereoselecitivty.

The group of Hoye showed an interesting three-component coupling of arynes with cyclic sulfides and protic nucleophiles (Scheme 147).[453] Notably, these reactions do not proceed through sulfur ylide formation, but the indermediate **775** is protonated by the protic nucleophile. Arynes were not generated through classical methods, but rather by thermal cycloisomerization of tethered triynes. Interesting selectivity is observed in these reactions, where the addition of sulfides to arynes outcompetes the direct addition of the protic nucleophile to the aryne. However, the regioselectivity of this addition is not always perfect, leading to a mixture of constitutional isomers.

In 2016, the group of Studer showed that the trapping of arynes with vinyl sulfides leads to the formation of benzanullated sulfur ylides via (3 + 2) cycloaddition (Scheme 148).[454] Quenching of this intermediate with water led to protonation and subsequent *β*-elimination of the sulfonium salt to afford a wide range of di- and trisubstituted alkenes, however, in moderate yield.

In 2018, the group of Mhaske reported the direct reaction of arynes with sulfur ylides (Scheme 149).[455] The proposed mechanism proceeds through a [2 + 2]-cycloaddion, followed by nucleophilic opening of the resulting four-membered ring. The reaction affords difunctionalized arenes, however, the yields are only moderate in most cases. Reagent **779** has also

Scheme 146. Epoxidation of Isatins with Sulfur Ylides Formed in Situ



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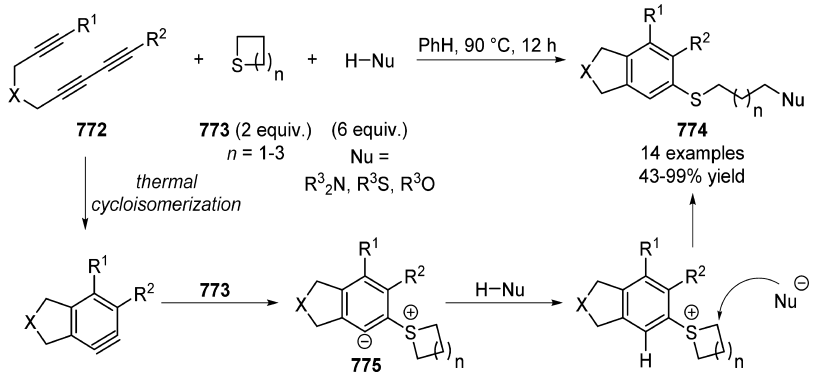
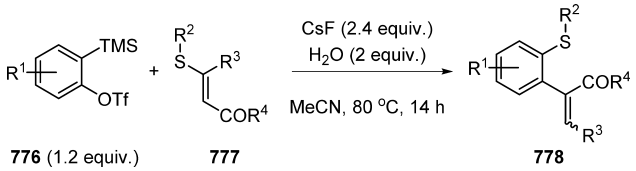
Scheme 147. Hoye's Sulfide Addition to Arynes, Followed by Nucleophilic Ring Opening



Scheme 148. Addition of Vinyl Sulfides to Arynes Leads to the Formation of *o*-Thio Styrenes

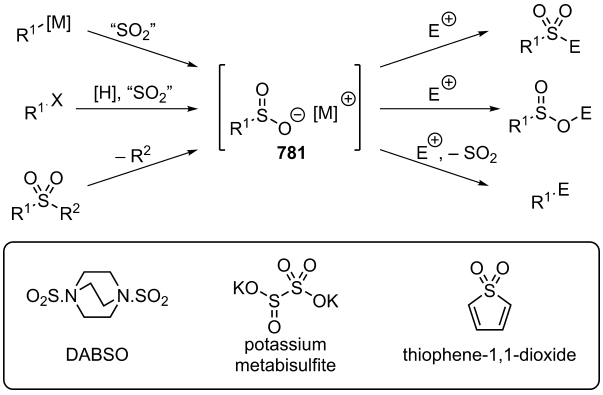


been employed in the synthesis of benzofurans from arynes, incorporating the oxygen from the solvent DMF.[456]

5. SULFINATE SALTS AND DERIVATIVES

No discussion of sulfur(IV) compounds would be complete without acknowledging the importance of sulfinate salts. Historically synthesized through the addition of organometallic reagents to SO_2 gas, or by a controlled oxidation of thiols, sulfinate salts (**781**) have long been utilized in a number of roles, both as synthetic intermediates (Scheme 150) and as protecting groups (e.g., for highly reactive imines). Despite, or perhaps as a result of this rich history, the chemistry of sulfinate salts has enjoyed a renaissance in the past 10 years, predominantly as a result of the development of SO_2 surrogates: bench stable, crystalline compounds that can either release SO_2 in situ or react directly as SO_2 equivalents (Scheme 150).[457,458] Predominant among these new reagents are DABSO[459,460] (a charge transfer complex between DABCO and two molecules of SO_2) and inorganic sulfur containing salts (e.g., potassium metabisulfite[461] and sodium sulfite[462]). As this field is so broad, with new developments reported with an astonishing regularity, it is beyond the scope of this section to conduct an exhaustive review. Readers are directed to the excellent review by Hamze.[463]

Scheme 150. Sulfinate Salts as Intermediates in Organic Synthesis



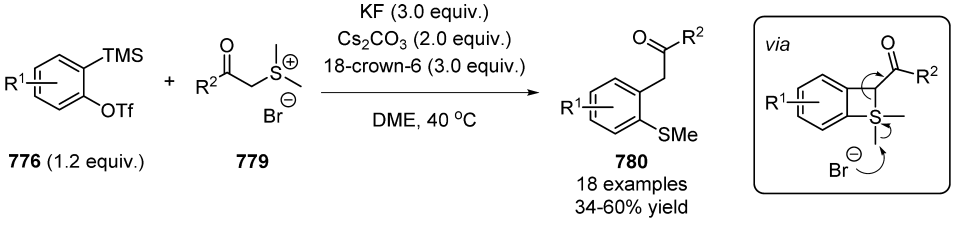
As depicted in Scheme 150, there are a number of routes for the synthesis of sulfinate salts, including catalytic methods as well as derivatizations. Their rich reactivity includes direct addition to electrophiles as well as desulfinative processes and shall be discussed below.

5.1. Sulfinate Salt Formation

One of the classical syntheses of metal sulfinate salts is the addition of organometallic reagents to SO_2 gas. However, while an efficient process, the use of SO_2 gas has a number of significant disadvantages. First, and most obviously, the gaseous nature of SO_2 means that reactions need to be designed in such a way as to disperse the gas in solution. More problematically, SO_2 is highly toxic and the large-scale application of a toxic, gaseous reagent poses technical problems of its own.

The addition of organometallic reagents to SO_2 surrogates is a straightforward solution to these problems, enabling simpler and safer protocols. Crucially, it also offers a more accurate control of stoichiometry, a potentially key issue for transition

Scheme 149. Difunctionalization of Arenes with Sulfur Ylides via a [2 + 2]-Cycloaddition



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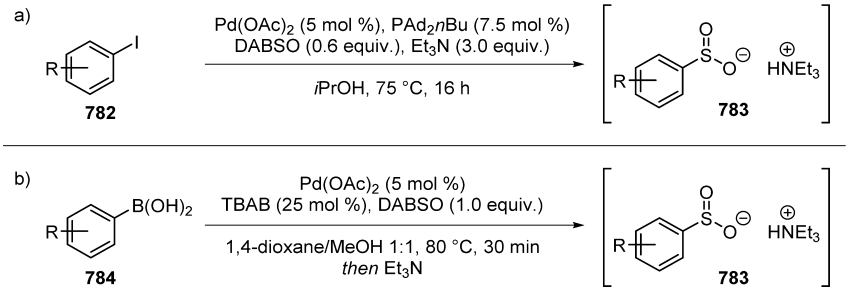
Scheme 151. Metal-Catalyzed Aryl Sulfinate Formation



metal-catalyzed processes. The addition of organometallic reagents to DABSO (usually followed by further derivatization) has been demonstrated for the synthesis of lithium,[464] magnesium,[460] zinc,[465] and sodium[466] sulfinate salts.

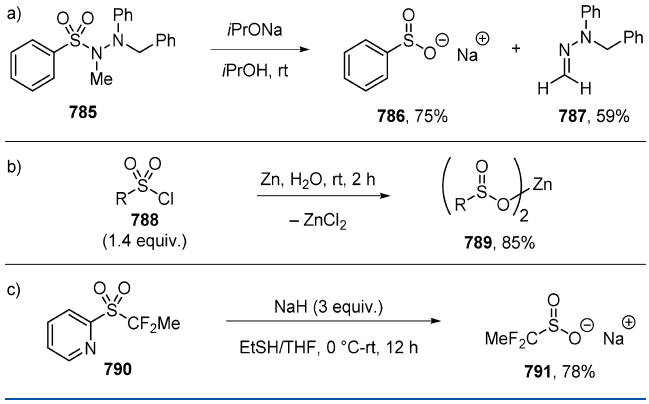
While the use of SO_2 surrogates to develop safer alternatives to classical transformations is certainly a worthy goal, the true potential of these developments can be seen in the arena of transition metal catalysis. The ability to generate sulfinate salts without the use of highly reactive organometallic species has clear operational advantages. Such a process was demonstrated in two independent reports in late 2013/early 2014 describing the palladium-catalyzed synthesis of metal sulfinates from aryl halides using $K_2S_2O_5$[467] and the palladium-catalyzed synthesis of ammonium sulfinates from iodoarenes employing DABSO[468] (Scheme 151a) (bromoarenes were successfully converted using a modified system reported more recently).[469] The former method utilized sodium formate as a stoichiometric reductant, whereas the latter was able to rely on the reductive properties of the *i*PrOH solvent. In both publications, the sulfinates thus generated were subjected to a range of derivatizations.

As well as the above reductive processes, redox-neutral methods involving the metal-catalyzed sulfinylation of boronic acids (**782**) have been achieved. A DABSO-based phosphine-free palladium-catalyzed process was developed in 2016, in which the generated sulfinic acids were subsequently deprotonated to the desired salt prior to derivatization (Scheme 151b).[470] As well as palladium(II) catalysis, similar reactivity has been demonstrated when combining boronic acids with either copper(I)[471] or gold(I)[472] complexes, as well as processes that combine aryl silanes with either copper(I)[473] or cobalt(II).[474] $K_2S_2O_5$ was used as the SO_2 surrogate for both of the examples of gold(I) catalysis, whereas DABSO could be used in each of the other cases.

Besides transition metal-catalyzed sulfinylation, Lewis acids have been used to activate DABSO in order to unlock simple S_EAr reactivity, resulting in a formal C−H sulfinylation, affording sodium sulfinates (following the addition of a sodium base).[475]

While each of the above examples builds up sulfinate salts from an SO_2 source and a nucleophilic/electrophilic reactant, a number of methods have also been developed that rely on the degradation of larger momlecular entities. One such example is the base-promoted elimination of sodium sulfinate salts from fully substituted *N*-aminosulfonamides (**785**) (Scheme 152a),[476] themselves easily synthesized through a palladium catalyzed reaction (see section 5.2.3).[459,477] This method was used to prepare a number of sulfone derivatives. When treated with base, thiosulfonates can similarly degrade to sulfinate salts.[478]

Scheme 152. Sulfinate Formation through Degradation Pathways



The Baran laboratory has demonstrated that sulfinates are ideal precursors for radical based C−H functionalization reactions (see section 5.2.2) and have developed a number of routes for their synthesis. As depicted, the reduction of commercially available sulfonyl chlorides (**788**) with dissolving zinc metal affords the corresponding zinc sulfinate (Scheme 52b),[479] while S_NAr-type processes can be used to synthesize fluorinated sodium sulfinates (**791**) (Scheme 152c).[480]

5.2. Sulfinate Salt Derivatization

5.2.1. Sulfone Synthesis. In general, the broadest synthetic use of sulfinates is the synthesis of sulfones. While organic chemists may tend to represent sulfinates analogously to a carboxylate, with oxygen-centered anionic character, in reality both the sulfur and oxygen centers are strongly nucleophilic. This ambident nature of sulfinates theoretically introduces selectivity problems as well as opportunities. In practice, however, most carbon-based electrophiles selectively undergo *S*-alkylation, resulting in the formation of sulfones, as opposed to the sulfinate esters that would result from *O*-alkylation. Thus, it is unsurprising that the majority of publications on sulfinate preparation demonstrates their use in sulfone synthesis as the archetypical application.[464−468,470−474,476,481] Common electrophiles include activated alkyl halides, such as α-halo carbonyl compounds or benzyl halides, although simple primary alkyl iodides have been used successfully, as have epoxides (Scheme 153a, left). Additionally, it has recently been demonstrated that aryl iodonium salts can be used for the direct, transition metal-free arylation of sulfinate salts.[481−483] Alkynyl benziodoxolones were subsequently shown to be valuable reagents for the synthesis of aryl alkynyl sulfones (**794**) (Scheme 153a, top right).[484]

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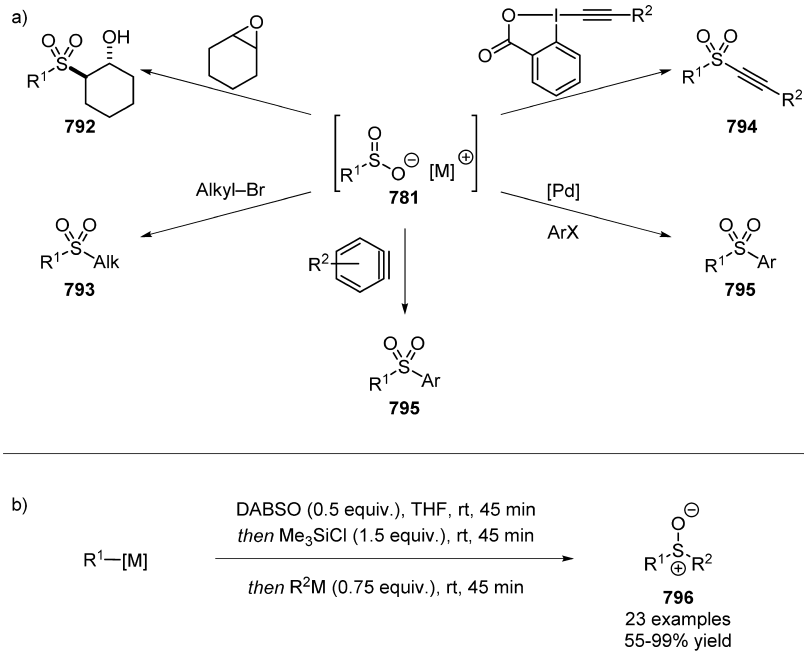
Scheme 153. Sulfone and Sulfoxide Syntheses from Sulfinate Salts



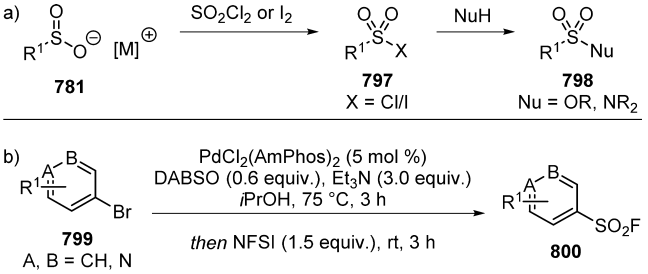
The vast majority of the above sulfone syntheses rely on sulfinate alkylation, and even the iodonium-promoted arylation is restricted by the availability of aryl iodonium salts. As a result, the arylation of metal sulfinates (e.g., for the synthesis of diaryl sulfones) represents a separate challenge for which the solution can be found in the realm of transition metal-catalyzed cross-coupling chemistry. Employing metal or ammonium sulfinates, Pd-catalyzed coupling with aryl halides has been shown to furnish diaryl sulfones in excellent yields (Scheme 153a, bottom right).[464] Furthermore, the addition of sulfinate salts to arynes has also proven a viable pathway for the synthesis of aryl sulfones (Scheme 153a, bottom middle).[485−487]

In keeping with recent trends, it has also been demonstrated that photoredox catalysis can be suitable for the coupling of metal sulfinates with arenes.[488,489]

While the majority of alkylating agents are selective for *S*-alkylation, *O*-alkylation would generate sulfinate esters, long known to be useful reagents for the synthesis of sulfoxides through the addition of organometallic reagents (see the use of Andersen's sulfinate, section 2.4.1). The Willis laboratory has reported that silylating agents are O-selective due to the large Si−O bond energy and have exploited this for a DABSO-based sulfoxide synthesis, in which DABSO formally acts as a sulfinyl dication (Scheme 153b).[490]

5.2.2. Sulfinate Halogenation. Another highly flexible method for sulfinate derivatization relies on their conversion into sulfonyl halides. These highly reactive species can be reacted with a variety of nucleophiles to form a range of sulfur(VI) species, most commonly sulfonic esters and sulfonamides. Sulfuryl chloride (SO_2Cl_2) has for many years been used for the in situ formation of sulfonyl chlorides from classically generated sulfinates (Scheme 154a). This chemistry works equally well with DABSO-derived sulfinates and has been applied to sulfonamide and sulfamide synthesis.[460] Halogenation using molecular iodine has similarly been used for the formation of sulfonic esters via the sulfonyl iodide.[491]

Scheme 154. Sulfinate Halogenation Protocols



In addition to the highly reactive sulfonyl chlorides and iodides, interest has recently increased in the synthesis of the more stable sulfonyl fluorides (such as **800**). The fine balance between reactivity and stability allows molecules containing the $-SO_2F$ moiety to be used for applications ranging from biological probes to deoxyfluorination. Treatment of ammonium sulfinates with either NFSI[469] or SelectFluor[492] has been demonstrated to be an effective protocol for their synthesis (Scheme 154b).

5.2.3. Sulfonamide Synthesis. As mentioned above, the in situ formation of sulfonyl chlorides from sulfinates has long been used as a key step in sulfonamide synthesis (see Scheme 154a). While efficient and achievable in a one-pot manner, such a process necessarily represents a three-step synthesis, which leaves room for improvement in terms of operational ease. Although the two steps required from sulfinate to sulfonamide cannot be combined, a single-step reaction between sulfinate salts and an electrophilic nitrogen source has been demonstrated to be an effective method. *N*-Chloroamines, generated in situ by the combination of bleach with the appropriate amines, have been used for the one-pot, two-step synthesis of sulfonamides (**801**), through the intermediacy of either metal[493] or ammonium[494] sulfinates (Scheme 155). Alternatively, preformed reagents such as *O*-benzoyl hydroxylamines can be used in combination with copper catalysis to achieve similar transformations.[495−497]

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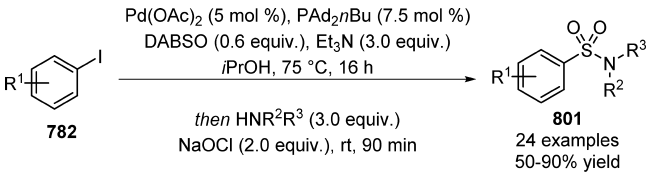
Scheme 155. Bleach-Mediated Amination of Sulfonates Affording Sulfonamides



In addition to the methods mentioned above, several further protocols for sulfonamide formation from sodium sulfinates have been reported in recent years. Common to these approaches, relying either on molecular iodine,[498−501] or the oxidation of iodide,[502−504] is the putative formation of a sulfonyl iodide intermediate.

5.2.4. Desulfinylative Methods. The use of sulfinate salts as nucleophilic coupling partners in cross-coupling reactions has been presented above in the synthesis of sulfones and/or sulfonamides. In addition to being used to afford these key sulfonyl-incorporating substrates, sulfinate salts have long been used in *desulfinylative* coupling reactions. While boronic acids are perhaps the archetypical stable organometallic reagent, stability to moisture and aerobic conditions is actually notoriously better for sulfinate salts. Often this increased stability makes little difference, which is why sulfinate salts have not supplanted boronic acids. However, there are key substrate areas where this additional stability becomes a distinct advantage. A range of desulfinylative couplings have been reported using simple aryl sulfinate salts,[505] including Suzuki−Miyaura[506] and (oxidative) Mizoroki−Heck couplings.[507] It is however in the coupling of heterocyclic fragments where the use of sulfinate salts comes into its own. In particular, reactions employing pyridyl boronic acids have long been plagued with difficulties, mostly stemming from the extreme instability of the pyridyl−boron bond to, among other things, protodeboronation. Only in recent years has the development of 2-pyridyl MIDA-boronates by Burke and coworkers begun to alleviate this problem.[508] The Willis laboratory has demonstrated that a wide range of 2-, 3-, and 4-pyridyl sulfinate salts can be coupled to aryl bromides and chlorides in excellent yields through the use of a simple palladium catalyst (Scheme 156a).[509] Further work expanded this concept to an extensive, functional group-tolerant scope of five- and six-membered heteroaryl sulfinates.[510]

In addition to transition metal-catalyzed desulfinylative couplings, a number of uncatalyzed reactions warrant discussion. As alluded to at the end of section 5.1, the Baran laboratory have in recent years reported desulfinylative Minisci-type reactions, in which a radical formed under oxidative conditions is trapped through reaction with an electron-poor heterocycle (Scheme 156b).[479,480,511−513] This desulfinylative Minisci reaction was first demonstrated by Langlois in 1991[514] and extensively probed and further developed by Baran et al. for use in direct heterocycle functionalization. The reactions are extremely robust and can be conducted in an open flask. Radicals reported in this process are usually electrophilic fluoroalkyl radicals, although recent publications have included several nucleophilic alkyl radicals which naturally exhibit different regioselectivity.[512]

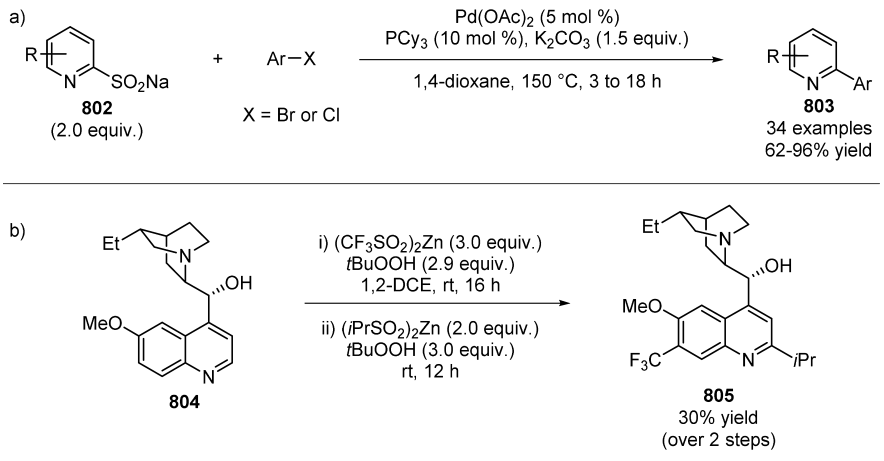
5.3. Langlois' Reagent

When talking about fluoroalkyl radicals generated from sulfinate salts, discussion of the Langlois reagent (sodium triflinate, **806**)[514] is inevitable; for a discussion of other sulfur-based trifluoromethylating reagents such as Umemoto's reagent, see section 3.1. Owing to the myriad of reports on the reactivity of Langlois' reagent published in the past decade, and the publication of expert reviews in recent years,[515−519] our aim is it provide an overview of general reactivity trends, illustrated by appropriate seminal examples.

The one-electron oxidation of the inexpensive and bench-stable solid sodium triflinate, for which several approaches are known, leads to the initial formation of a sulfonyl radical (**807**), which readily decomposes to the trifluoromethyl radical **415** under loss of SO_2 (Scheme 157a). The formation and use of **415** has experienced a resurgence in recent years and has found application in a wide range of transformations that shall be exemplified below.

Owing to the electrophilicity of **415**, several protocols for the radical trifluoromethylation of alkenes have been developed, such as the oxytrifluoromethylation and hydrotrifluoromethylation of simple alkenes. In 2013, the Maiti group's oxytrifluoromethylation of alkenes was shown to proceed through silver-catalyzed oxidative decomposition of the triflinate anion, affording **807**, which was confirmed by X-ray photoelectron spectroscopy (Scheme 157b).[520] Subsequent addition to the alkene was proposed to afford an alkyl radical, trapping of which with dioxygen was shown to lead to formation of **809**, as shown by isotopic labeling with $^{18}O_2$. A

Scheme 156. Desulfinylative Transformations



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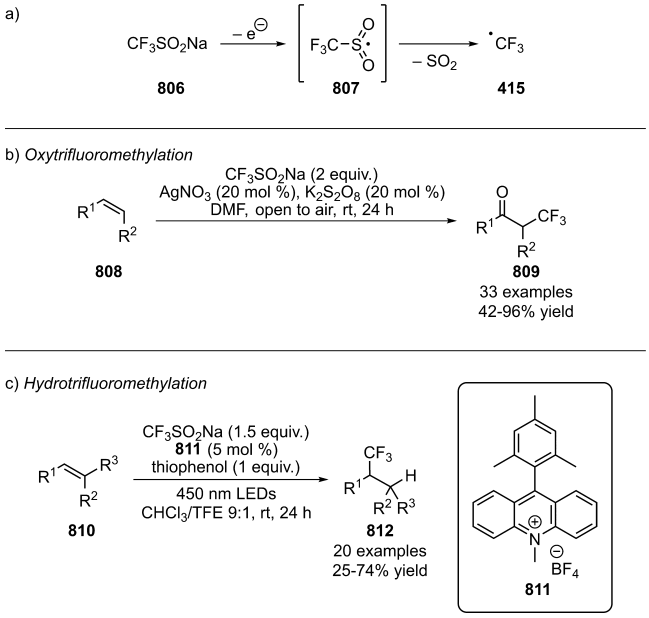
Scheme 157. One-Electron Oxidation of Langlois' Reagent to 415 and Its Application in Alkene Functionalization Reactions



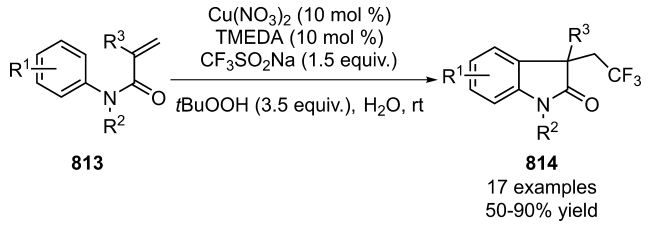
range of related procedures were reported in addition to this method.

Following an early, but low-yielding electrochemical report of hydrotrifluoromethylation of alkenes by Langlois,[521] in 2013, Nicewicz and co-workers reported this reaction in the context of photoredox catalysis (Scheme 157c).[522] Herein, *N*-methyl-9-mesitylacridinium tetrafluoroborate (**812**) serves to both oxidize the triflinate and reduce the thiyl radical generated during hydrogen-atom transfer to the intermediate alkyl radical.

Apart from oxytrifluoromethylation,[523−532] and hydrotrifluoromethylation,[533−535] procedures for the amino-,[536−538] carbo-,[539−544] and halotrifluoromethylation,[545−547] as well as the trifluoromethylation of enols and enamines,[548−551] and the decarboxylative trifluoromethylation of cinnamic acid derivatives[552−556] have also been extensively studied and reported.

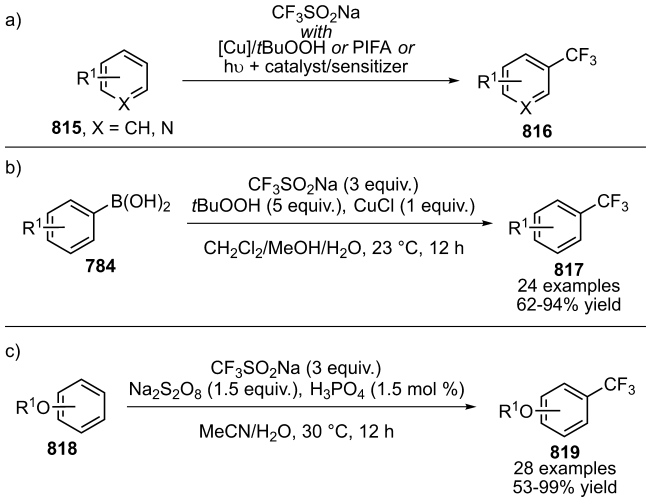
In the context of carbotrifluoromethylation, a suite of cyclization reactions has also been reported using Langlois' reagent. Most prominent among these transformations is the trifluoromethylative cyclization of an aryl moiety onto a double bond, as shown by the reaction of *N*-aryl acrylamides to form oxindoles (Scheme 158).[557−559] In addition to these templates, products of radical additions of **415** to ynamides and isonitriles are also known to be trapped by arenes,[560−562] as are cyclizations of alkynes onto the intermittent radicals.[563−565]

Scheme 158. Trifluoromethylation/Cyclization Reactions Using Langlois' Reagent



In addition to the reaction with alkenes, sodium triflinate has also been used extensively for the trifluoromethylation of arenes and heteroarenes (Scheme 159a). Following Baran's

Scheme 159. Overview of Methods for the Trifluoromethylation of (Hetero)arenes with Langlois' Reagent



early reports on the trifluoromethylation of heterocycles (see Scheme 156b),[511−513] a plethora of further protocols for the sodium triflinate-mediated protocols were developed, enabling the trifluoromethylations of a wide range of functionalized (hetero)arenes. Initial work exploited the reactivity of arylboronic acids (Scheme 159b),[566,567] whereas later work showed the tendency of electron-rich aromatics to undergo addition of trifluoromethyl radicals (Scheme 159c).[568−571]

Other examples of arene−trifluoromethylation rely on metal-catalysis in combination with directing groups,[572−574] light-mediated transformations,[575,576] or the addition of **415** to heteroarenes.[577−580]

Further applications of Langlois' reagent in recent years have included the trifluoromethylation of imines,[581,582] as well as applications in the ring opening of cyclopropanols[583] and the trifluoromethylations of nitrosoarenes[584] as well as alkynyltrifluoroborates.[585]

5.4. One-Step Sulfonylative Multicomponent Reactions (MCRs)

Although most of the sulfinate syntheses described at the beginning of this chapter are often compatible with derivatization conditions allowing for a multistep, one-pot protocol, the development of single-step processes has clear advantages from the viewpoint of operational simplicity, especially when working on scale or for combinatorial chemistry. A number of such transformations have been discussed in earlier sections, namely those involving transition metal-catalyzed sulfinate formation in the presence of an electrophile and many reactions involving Langlois' reagent. The electrophiles required for sulfone synthesis (typically activated alkyl bromides) do not tend to interfere with the initial steps and capture the transition metal-sulfinate to close the catalytic cycle. Generally, these processes are redox-neutral, employing arylsilanes or boronic acids as nucleophilic components.[471−474]

While it has been demonstrated that sulfonamide synthesis can be achieved in either a one-pot three-step protocol

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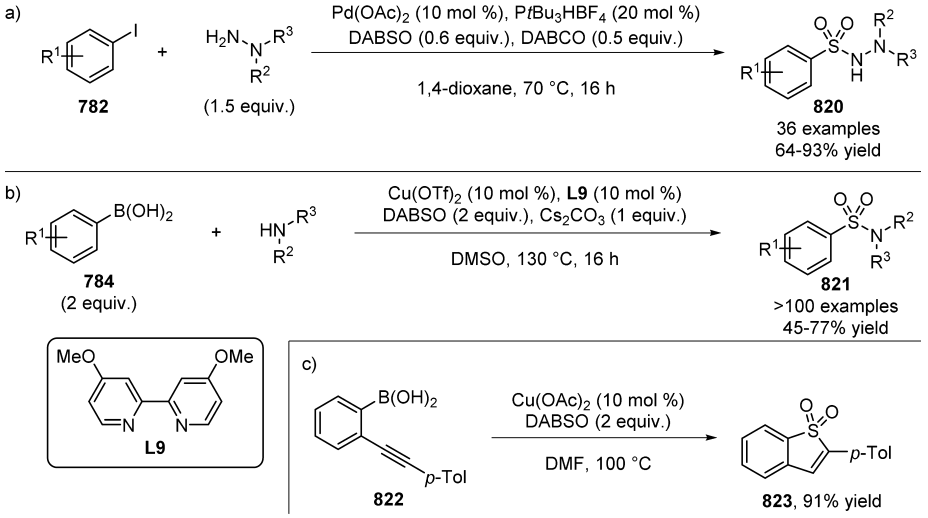
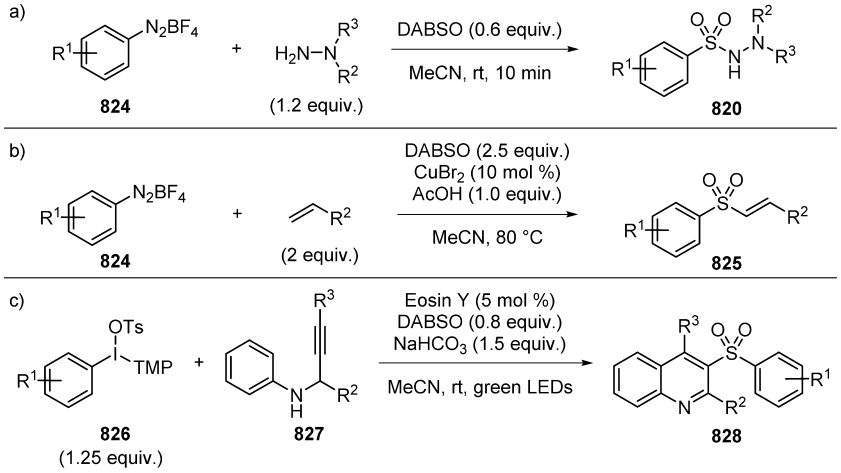
Scheme 160. Metal-Catalyzed Sulfonylative Multicomponent Reactions (MCRs)



Scheme 161. Radical-Based Sulfonylative MCRs



(sulfinate formation, chlorination, and then addition of amine) or a one-pot two-step protocol (sulfinate formation, then oxidative amination), simple one-step processes have remained elusive until recently. A far easier transformation is *N*-aminosulfonylation (Scheme 160a). The very first transformation to utilize DABSO as an SO_2 surrogate in 2010, as well as the first transition metal-catalyzed sulfonylative coupling,[459] relies on the high nucleophilicity of the hydrazine coupling partners, as simple amines are not competent substrates under the developed conditions.[477] Alternative conditions employing other SO_2 surrogates,[459] starting materials,[586] and metals[587] have been developed. A handful of sulfonamide syntheses involving radical mechanisms (see below) have been reported, however, it was not until 2018 that a direct one-step aminosulfonylation reaction employing amines and readily available carbon synthons was developed by the Willis group (Scheme 160b).[588] The exact mechanism of the transformation is yet to be elucidated, however, mechanistic experiments ruled out the intermediacy of a sulfinate salt.

Intramolecular reactions forming sultams[589] and benzothiophene dioxides (**823**)[590] are other examples of transition metal-catalyzed one-step sulfonylative processes (Scheme 160c). Interested readers are directed to more focused reviews for further examples.[591]

As mentioned previously, the major alternatives to purely transition metal-catalyzed sulfonylative MCRs are those that invoke radical mechanisms. A comprehensive review of this field has recently been published[592] and covers the area in great detail. While in discussing the combination of DABSO and transition metal catalysts the work of the Willis laboratory dominates, the lion's share of publications employing radical mechanisms have been reported by the Wu laboratory. The very first such process was an *N*-aminosulfonamide synthesis (Scheme 161a), with products analogous to the previously described Pd-catalyzed process (see Scheme 160a), employing diazonium salts (**824**) in the absence of a metal catalyst.[593] The authors propose that the release of nitrogen from the diazonium salt is mediated by a SO_2–hydrazine complex. However, the Maulide group have demonstrated subsequently that hydrazines are competent catalysts for the degradation of diazonium salts for Meerwein-type processes without the need for SO_2.[594]

Generation of the key radical species (that is rapidly sulfonylated to afford a sulfinate radical) in this way is conceptually very attractive. Nevertheless, other methods include transition metal-catalyzed radical generation (as seen

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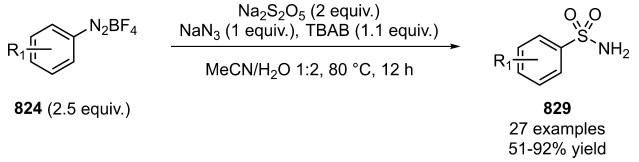
with the Mizoroki−Heck-type functionalization of styrenes in Scheme 161b),[595] and light-promoted processes, be they direct irradiation with UV light[596] or through photoredox catalysis (Scheme 161c).[597]

Recently, Jiang and co-workers have added to the suite of metal-free sulfonylative MCRs by employing sodium metabisulfite as the reducing agent (Scheme 162).[598] Herein, triphenylphosphine and sodium azide serve as the oxidant and nitrogen source, respectively, affording sulfonamides with impressive functional group tolerance.

Scheme 162. Formation of Sulfonamides from Diazonium Salts Using Sodium Metabisulfite



824 (2.5 equiv.)

829
27 examples
51-92% yield

A multitude of publications over the past five years have exploited the ease at which radicals can be sulfonylated,[592] and the rate of novel developments shows no signs of abating.

6. SUMMARY AND CONCLUSIONS

This review article has shown the wide range of chemical transformations of organic sulfur(IV) compounds that involve either bond formation or bond cleavage at sulfur. Focusing on transformations pioneered or developed over the past decade, novel reactions as well as further developments of textbook organic transformations have been presented. The breadth of reactivity exhibited by organic compounds bearing sulfur(IV) moieties spreads over several classes of functional groups. Specifically, sulfoxides, diverse types of sulfonium salts, and sulfur ylides as well as sulfinate salts and their derivatives have been at the forefront of organosulfur research and have therefore formed the core of this article.

Sulfoxides have been shown to be amenable to a broad range of Pummerer-type reactions, enabling carbon−carbon and carbon−heteroatom bond formation in the α-position of the sulfoxide starting materials, often through sigmatropic rearrangements. Importantly, several protocols for arylation or the functionalization of arenes have also been developed using sulfoxide-activation chemistry. In addition to this, following in the footsteps of the ubiquitous Swern oxidation, activated sulfoxides have continued to show great versatility in a variety of oxidation reactions of alkenes, arenes, and alcohols alike. Furthermore, metal−sulfoxide exchange has been demonstrated to be a practical alternative to the metalation of halide-containing precursors and has thus found application in the selective synthesis of organometallic reagents.

Sulfonium salts have shown remarkable reactions in the arenas of fluoroalkylation and transition metal-catalyzed cross-coupling reactions. Among this general class, vinyl- and propargylsulfonium salts stand out in terms of versatility, allowing for the formation of up to three new bonds across a simple C_2 unit. Specifically, in this context, the number of heterocycles and strained rings synthesized by virtue of the multiple reactive sites of sulfonium salts seems to know no bounds and has been shown to proceed with high levels of diastereo- and even enantioselectivity.

Sulfur ylides are arguably the most versatile class of organosulfur(IV) compounds, finding widespread application as one-carbon synthons, ranging from simple nucleophilic epoxidation, aziridination, and cyclopropanation to a wide variety of more complex $(n + 1)$-cycloadditions and transition metal-catalyzed reactions with π-systems, both of which have led to the development of a large number of novel protocols for the formation of heterocycles. Additionally, sulfur ylides have been shown to engage in a series of asymmetric transformations, either promoted by organocatalysts or by virtue of a chiral sulfur ylide itself. Furthermore, with the emergence of photoredox catalysis, sulfur ylides have recently started being employed in photocatalytic transformations. Sulfur ylides are also highly useful substrates for sigmatropic rearrangements, as the inherent charge leads to significant acceleration of the pericyclic reaction. In this regard, the further development of the Doyle−Kirmse reaction has provided several intriguing transformations, forming new carbon−sulfur bonds through the decomposition of diazo compounds in the presence of simple sulfides.

Sulfinate salts boast a long history in the context of organic chemistry. Recent developments have allowed for more facile protocols for the formation of sulfinates by utilizing bench-stable SO_2 equivalents in lieu of the notoriously toxic gas. The facilitated access to this structural motif has inspired a variety of sulfone syntheses through coupling reactions, as well as desulfinylative couplings and one-step sulfinylative multi-component reactions, affording structurally diverse and valuable products.

Although sulfur(IV) compounds enjoy a rich and fruitful history in the context of organic synthesis, this review has aimed to show that their chemical reactivity and potential utility for synthetic chemists is far from being exhausted and the various sulfur(IV) functional groups promise to provide chemical research with many more exciting discoveries and developments.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

Biographies

Daniel Kaiser completed his undergraduate degree at the University of Vienna in 2013, having worked on his master's thesis in the lab of Prof. Thomas Magauer (then LMU Munich). In 2014, he commenced his doctoral studies at the University of Vienna under the supervision of Prof. Nuno Maulide, where the majority of his work focused on electrophilic amide activation and sulfoxide-mediated sigmatropic rearrangements. After graduating from the doctoral program in 2018, he took up his current position as a postdoctoral fellow at the University of Bristol, working with Prof. Varinder K. Aggarwal.

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Immo Klose studied chemistry at the University of Vienna, where he completed his Master's thesis on sulfur ylide reactivity in the group of Prof. Maulide in 2016. After a research stay with Prof. Takemoto at the University of Kyoto, where he worked on organocatalytic transformations, he returned to Vienna, where he is currently working towards his Ph.D. His research interests focus on the stereoselective formation of carbon−carbon bonds through rearrangements utilizing chirality transfer from enantioenriched sulfoxides.

Rik Oost studied chemistry at the University of Groningen, where he obtained his M.Sc. in 2014 under supervision of Prof. Syuzanna Harutyunyan. He then moved to the University of Vienna for a Ph.D. position in the group of Prof. Nuno Maulide, focusing on asymmetric catalysis and sulfur ylide cycloisomerization reactions. After completing his Ph.D. at the end of 2018, he joined the department for process development at Janssen Pharmaceutica in Belgium, where he is currently working as a postdoctoral scientist.

James Neuhaus received his undergraduate degree from Merton College, University of Oxford. in 2012, having completed a Part II (Masters) project in the group of of Prof. Tim Donohoe. Staying in Oxford, he worked towards his Ph.D. under the supervision of Prof. Michael Willis. His research was directed towards the development of Rh-catalyzed hydroacylation and its application in heterocycle synthesis. In 2016, he joined the Maulide Group as a postdoctoral researcher. During his time in the group, he investigated a wide range of novel transformations, including π-acid promoted sulfur ylide cycloisomerizations, cycloadditions, and Ru-catalyzed ylide-diazo coupling reactions.

Nuno Maulide obtained his Ph.D. from the Université Catholique de Louvain in 2007, having worked under the supervision of Prof. Istvan Markó. Following a postdoctoral stay at Stanford, working with Prof. Barry M. Trost, he began his independent research career as a Max-Planck Group Leader at the MPI für Kohlenforschung in Mülheim before assuming his current position as Full Professor for Organic Synthesis at the University of Vienna and Adjunct PI at the Center for Molecular Medicine (CeMM) as an ERC StG, CoG, and PoC grantee. His research interests are broadly defined around the area of highly reactive intermediates and rearrangements.

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ABBREVIATIONS USED

A	activator
Ac	acetyl
acac	acetylacetonate
Ad	adamantyl
aq	aqueous
Ar	aryl
ATP	adenosine triphosphate
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
bpy	2,2′-bipyridine
*n*Bu	*n*-butyl
*t*Bu	*tert*-butyl
Bz	benzoyl
cat.	catalyst or catalytic
CBz	benzyloxycarbonyl
m-CPBA	*meta*-chloroperoxybenzoic acid
CPME	cyclopentyl methyl ether
CSA	camphorsulfonic acid
Cy	cyclohexyl
dr	diastereomeric ratio
DABCO	1,4-diazabicyclo[2.2.2]octane
DABSO	1,4-diazabicyclo[2.2.2]octane bis(sulfur dioxide) adduct
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	dichloroethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DG	directing group
DIPEA	*N*,*N*-di-*iso*-propylethylamine
DMA	*N*,*N*-dimethylacetamide
DMAP	4-dimethylaminopyridine
DMC	dimethyl carbonate
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMPU	*N*,*N*′-dimethylpropylurea
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
DMTSF	dimethyl(methylthio)sulfonium tetrafluoroborate
DPPA	diphenylphosphoryl azide
dtbpy	4,4′-di-*tert*-butyl-2,2′-dipyridyl
E/E^+	neutral/cationic electrophile
ee	enantiomeric excess
EDG	electron-donating group
equiv	equivalents
es	enantiospecificity
Et	ethyl
EWG	electron-withdrawing group
h	hours
Het	hetero(atom)
hfacac	hexafluoroacetylacetone
HFIP	1,1,1,3,3,3-hexafluoro-2-propanol
kbar	kilobar
L	ligand
LEDs	light-emitting diodes
LG	leaving group
M	metal
Me	methyl
Mes	mesityl
min	minutes
MS	molecular sieves
Ms	methanesulfonyl (mesyl)
Naph	naphthyl
NFSI	*N*-fluorobenzenesulfonimide
Ns	*para*-nitrobenzenesulfonyl (nosyl)
Nu	nucleophile
PG	protecting group
Ph	phenyl
Phen	phenanthroline
PIFA	phenyliodine bis(trifluoroacetate)
Piv	pivaloyl
PMP	*para*-methoxyphenyl
*i*Pr	*iso*-propyl
*n*Pr	*n*-propyl
rt	room temperature
SET	single-electron transfer
SES	2-(trimethylsilyl)ethanesulfonyl
TBAB	tetra-*n*-butylammonium bromide

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TBS	*tert*-butyldimethylsilyl
TES	triethylsilyl
Tf	trifluoromethanesulfonyl (triflyl)
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
TFE	2,2,2-trifluoroethanol
THF	tetrahydrofuran
TIB	2,4,6-tri*iso*-propylbenzoyl
TIPS	tri*iso*-propylsilyl
TMEDA	tetramethylethylenediamine
TMP	2,2,6,6-tetramethylpiperidine
TMS	trimethylsilyl
p-Tol	*para*-tolyl
TPP	tetraphenylporphyrin
Ts	*para*-toluenesulfonyl (tosyl)
μW	microwave irradiation

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