USE OF SULFONIUM SALTS IN THE SYNTHESIS OF OXYGEN HETEROCYCLES

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Abstract. *The fundamentals and recent developments of sulfonium salts applied to the synthesis of oxygen heterocycles are reviewed. The chapter is divided into five sections, starting with the presentation of sulfonium salts and the methods to prepare them; then, application of Pummerer reactions (chemistry of the thionium ion generated from sulfoniums) is discussed. The cyclization of other sulfur species, such as sulfur ylides, is also described. Finally, the use of sulfoniums as sources of electrophiles to induce cyclization and to functionalize oxygen heterocycles is described.*

Contents

1. Introduction

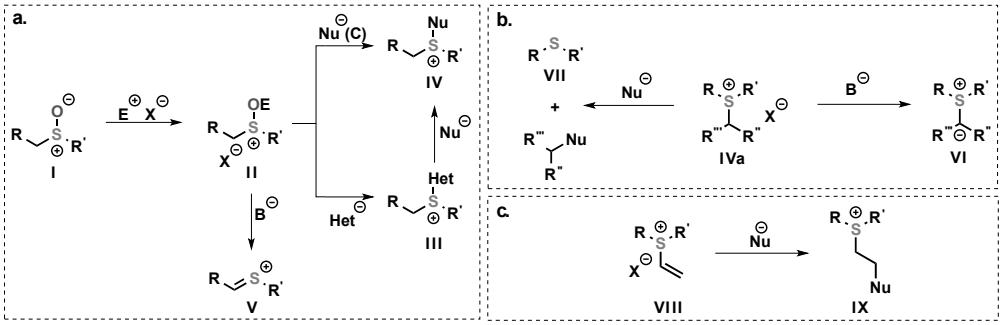
Sulfur is widely known in organic reactions; it is commonly used as the nucleophile in the production of thiols, sulfides and thioesters, among other functional groups. Further transformations of those functional groups have led to a considerable number of sulfur derivatives with well-established reactivity. In this context, the chemistry of sulfur IV species has recently been reviewed,[1] and several previous discussions and reviews on organosulfur chemistry can be found in the literature.[2]

Among the essential organosulfur derivatives or intermediates are sulfonium salts;[3] these are compounds with three substituents on a charged sulfur atom, and the substituents are most commonly two carbon atoms and one heteroatom (O, Cl, I, and F, among others). However, salts with three carbon substituents are also common and widely applied in organic synthesis.

The identity of the substituents governs the reactivity of the sulfonium salts. For example, heterosulfonium salts **II** are typically produced by the activation of sulfoxides **I** with electrophiles. In turn, **II** react with nucleophiles at the most electrophilic sulfur atom, yielding new sulfonium salts, **III** and **IV** (Scheme 1a). The reaction of **II** with bases will produce thionium ions **V** (Pummerer-type reactions). However, the reaction of carbon sulfonium salts **IVa** may provide ylides **VI** or sulfides **VII** depending on the reacting species (Scheme 1b). Finally, if one of the substituents is an unsaturated functional group, the reaction will proceed *via* conjugate addition, the equivalent of an allylic cation, generating ylides **IX** (Scheme 1c).

The present chapter is devoted to the presentation and discussion of the applications of sulfonium salts in the synthesis of oxygen heterocycles by the direct cyclization of sulfonium or by the generation of thionium ions or other intermediates. The chapter is divided into five sections starting with the summary of

the methods for the preparation of sulfonium salts. Then, we describe some Pummerer-type cyclizations (intramolecular reaction of thionium ions) and the direct cyclization of sulfonium salts, followed by a description of the cyclizations induced by sulfonium salts as sources of electrophiles. Finally, the use of sulfonium salts in the functionalization of oxygen heterocycles is described. It is noteworthy that the review is not comprehensive, and the examples shown have been selected according to their significance and potential applications.



Scheme 1. General reactivity of sulfonium salts.

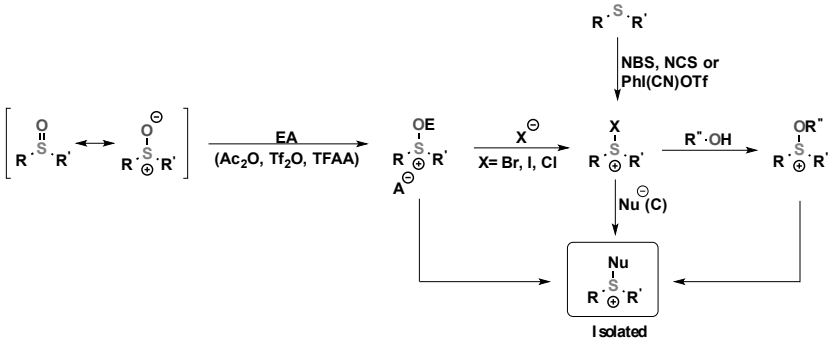
2. Preparation of sulfonium salts

We previously mentioned two different types of sulfonium salts: heterosulfonium salts and carbon-sulfonium salts. Sulfoniums with one substituent different from carbon compose the first group; sulfoniums with oxygen, chlorine, fluorine and iodine, among others, are common species in the literature. However, not all of them have been applied to the synthesis of oxygen heterocycles. On the other hand, those heterosulfoniums serve as templates or precursors in the preparation of carbon sulfonium salts.

Oxygen sulfonium salts are among the most used sulfoniums. Oxygen sulfonium salts are prepared by the *in situ* activation of a sulfoxide with an electrophilic reagent. The most commonly used are acetic anhydride, Ac_2O, triflic anhydride, Tf_2O, and trifluoroacetic anhydride, TFAA; the activation proceeds with the concomitant release of a negative counterpart, which serves as the counterion to the positive sulfonium.

Halogen sulfoniums are prepared *via* substitution of the oxygen with halogens or directly from sulfides with halogenated electrophilic reagents.

The reaction of any of those species (oxygen or halogen sulfoniums) with carbon nucleophiles will produce carbon-sulfoniums, which may be isolated; some of them are bench stable and easy to handle. Scheme 2 summarizes the methods for the preparation of sulfoniums.

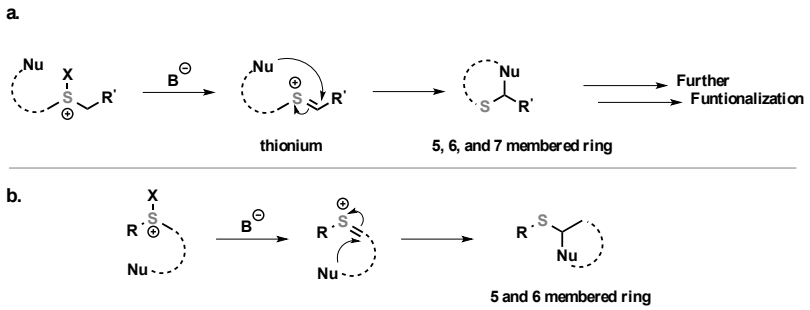


Scheme 2. Preparation of sulfonium salts.

3. Pummerer-type cyclizations

The reaction of a sulfonium with a base produces a highly reactive electrophilic intermediate called a thionium. Reactions of thionium ions with nucleophiles are called Pummerer-type reactions, and they have been extensively reviewed in the literature.[4]

The intramolecular reaction of a thionium with a nucleophile affords a cyclic compound, which can be the intermediate in a subsequent process or the final product. Most commonly, the product is an intermediate in reactions that produce sulfur-containing heterocycles (Scheme 3a). While, compounds with an exocyclic sulfur are commonly used in further transformations to yield desulfurized final products (Scheme 3b).

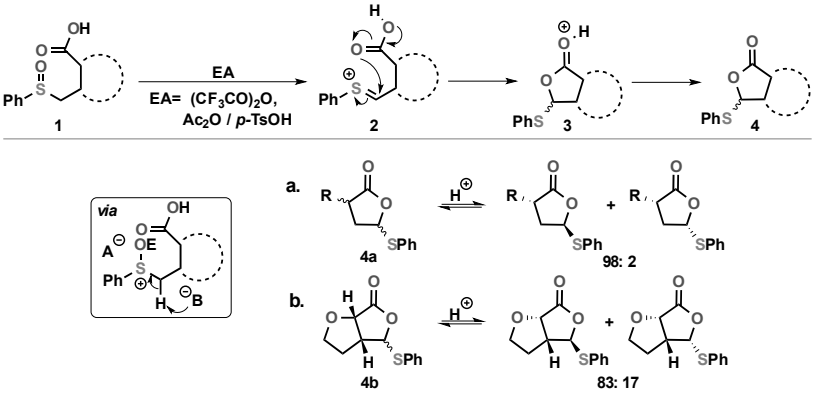


Scheme 3. Traditional Pummerer cyclizations.

3.1. Intramolecular cyclizations with oxygen nucleophiles

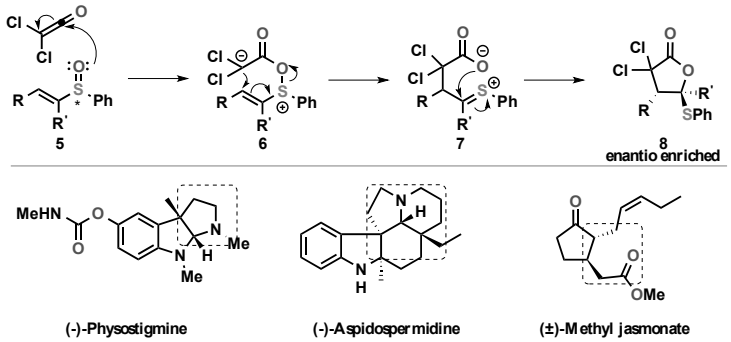
The reaction of oxygen nucleophiles (alcohols or phenols) with sulfonium salts mainly occurs at the more electrophilic sulfur atom; however, the reaction with basic species will generate a thionium intermediate. This new electrophile reacts intramolecularly with nucleophiles, producing cyclic compounds. Applications of that reactivity in the synthesis of heterocycles were reviewed some years ago.[5]

Carbonyl groups have served as nucleophiles, producing saturated, unsaturated and aromatic heterocycles. Works by Kumamoto and coworkers,[6] and Bruke and coworkers[7] describe the use of carboxylic acids as nucleophiles. The sulfoxide **1** is activated by acetic or trifluoroacetic anhydride, generating the sulfonium intermediate. Then, the thionium **2** is formed by the action of the acetate and then reacts with the nucleophilic acid, forming the five-membered ring lactone **4**. Equilibration in acidic medium produces the thermodynamically favored 3,5-*trans* product, regardless of the substitution pattern (Scheme 4).



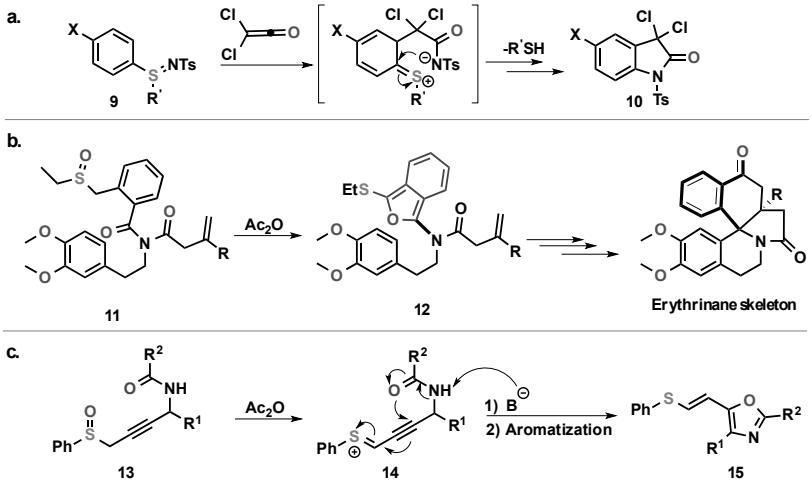
Scheme 4. Synthesis of bicyclic lactones *via* Pummerer cyclization.

In the same way, carboxylates produce lactones, as demonstrated by Marino *et al.*[8] In this case, the formation of the thionium is quite different (additive Pummerer reaction). The vinyl sulfoxide **5** reacts with dichloroketene forming a sulfonium **6**. In turn, **6** undergoes a [3,3]-sigmatropic rearrangement, generating the thionium **7**, which has the nucleophilic oxygen in suitable place to produce the lactone **8**. This reaction has been performed with enantiopure sulfoxides, yielding enantioenriched lactones. In that context, the same transformation was applied in the total synthesis of (-)-physostigmine,[8c] (+)-aspidospermine,[8d] and (-)-methyl jasmonate (Scheme 5).[9]



Scheme 5. Additive Pummerer reaction in the synthesis of lactones applied to natural products.

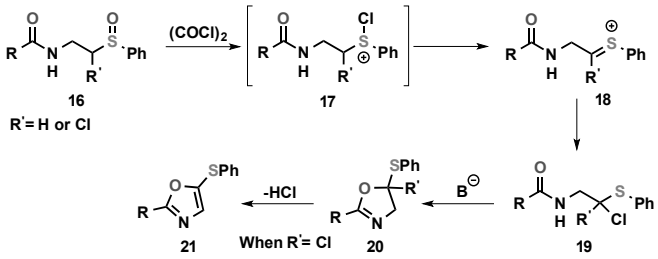
Padwa *et al.* used the same principle in the synthesis of lactams by using sulfilimides **9** instead of sulfoxides (Scheme 6a).[10] Interestingly, the carboxylate ion reacts *via* the nitrogen atom and not *via* the oxygen, which is more usual, as shown by Padwa *et al.* (Scheme 6b)[11] in the synthesis of the Erythrinane skeleton and by Zhou and coworkers in the synthesis of oxazoles (Scheme 6c).[12] In Padwa's work, the sulfoxide **11** is activated with acetic anhydride, and the thionium reacts with the nucleophilic oxygen yielding the isobezofuran **12**, that is the intermediate in the construction of more complex skeletons. On the other hand, a similar approach was described by Zhou using conjugated thioniums **14** to afford oxazoles **15**.



Scheme 6. Pummerer cyclization of amides.

Gamba-Sánchez and coworkers used oxygen nucleophiles in the synthesis of oxazolines and oxazoles (Scheme 7).[13] This time, however, the mechanism is slightly different. The authors showed the activation of

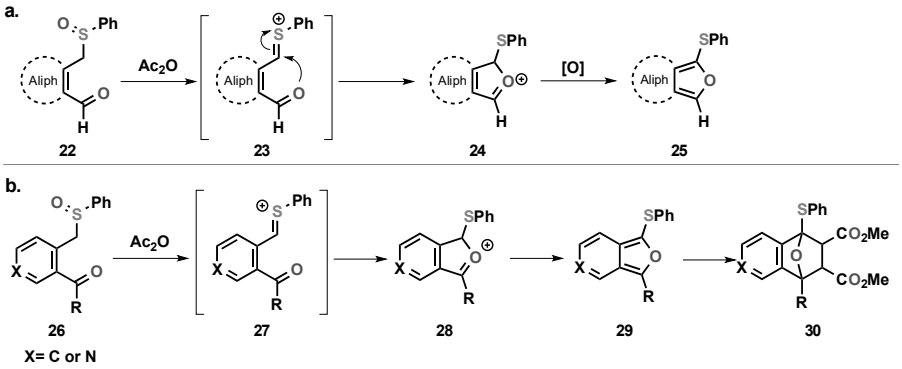
sulfoxides **16** using oxalyl chloride, thus generating a chlorosulfonium salt **17**. Then, **17** produces the intermediate thionium **18**, which is spontaneously trapped by chlorine, yielding the α-chlorosulfide **19**. Subsequently, **19** cyclizes by the action of the base, providing oxazolines **20**. When the substituent is chlorine, it may be eliminated, generating the oxazole **21**. Similar approaches using the activation of sulfides with *N*-chlorosuccinimide (NCS) have been previously described.[14]



Scheme 7. Activation of sulfoxides with $(COCl)_2$, and their application to the synthesis of oxazoles and oxazolines.

The participation of chlorine as the nucleophile and its subsequent substitution by oxygen nucleophiles is not rare. Several examples are discussed in this chapter.

Aldehydes and ketones can also serve as nucleophiles, and similar achievements may be reached. The pioneering work reported by de Groot *et al.*[15] is based on the same principle described in Scheme 4. That means that the allyl sulfoxide **22** is activated to form the thionium **23**. Next, **23** is attacked by the oxygen nucleophile, producing the unstable cyclic intermediate **24**, which undergoes spontaneous aromatization to the give thio-substituted furan **25** (Scheme 8a). Remarkably, when aromatic ketones **26** are used, the reaction produces the isobenzofuran **29**. These intermediates have been extensively used in a tandem process with Diels-Alder reactions and have been successfully applied with aromatic[16] or heteroaromatic[17] substrates (Scheme 8b).

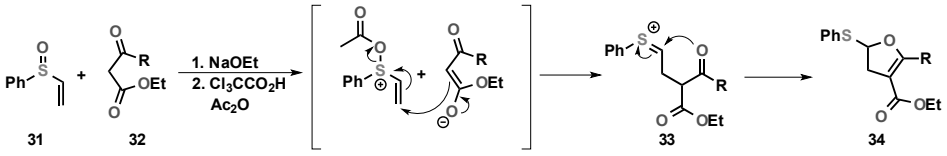


Scheme 8. Use of aldehydes and ketones in Pummerer cyclizations.

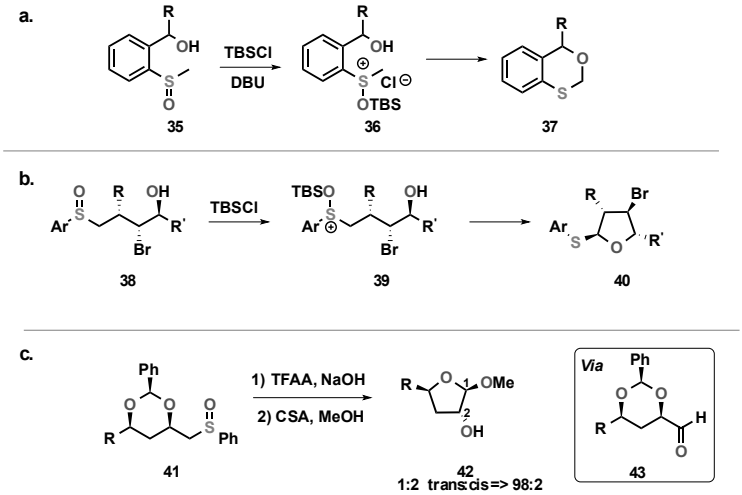
Chan *et al.*[18] described a Michael-Pummerer sequence. In this case, simultaneously, the vinyl sulfoxide **31** is activated and the 1,3-dicarbonyl **32** is deprotonated. Then, the Michael reaction affords the thionium intermediate **33**, which cyclizes to give the dihydrofuran **34** (Scheme 9).

Continuing with our description of Pummerer cyclizations using oxygen nucleophiles, we must mention the use of alcohols. Soft activation of sulfoxides with silyl chlorides is used when nucleophilic functional groups are present in the substrate. Consequently, the use of strong electrophiles becomes inconvenient. Scheme 10 shows three different approaches to construct oxygen heterocycles using alcohols as nucleophiles. However, each of these examples has its particularities. The work published by Kersey *et*

al.[19] shows the formation of the 1,3-benzoxathiine **37**. The activation of sulfoxide **35** is accomplished by TBSCl, generating the sulfonium salt **36**. It is still unclear if the next step is the formation of a thionium ion, an α-chloro-sulfide or another sulfonium salt. Any of those intermediates will produce the cyclized product by reacting with the nucleophilic alcohol (Scheme 10a). A similar approach was described by Raghavan and coworkers[20] They used the acyclic substrate **38**, which is activated by TBSCl, to form the sulfonium salt **39**. A comparable cyclization should occur since the tetrahydrofuran **40** is obtained in good yield. It should be noted that the reaction proceeds with high stereoselectivity for the new chiral center (Scheme 10b). Gamba-Sánchez and Prunet (Scheme 10c) used a slightly different approach.[21] They used a benzylidene acetal, 1,3-dioxane **41**, to mask the active oxygen, thus enabling the activation with a highly electrophilic reagent; acidic treatment produced the desired tetrahydrofuran **43** with excellent stereoselectivity (Scheme 10c). The product is obtained without the sulfur moiety since the reaction passes through the formation of an intermediate aldehyde **43**.



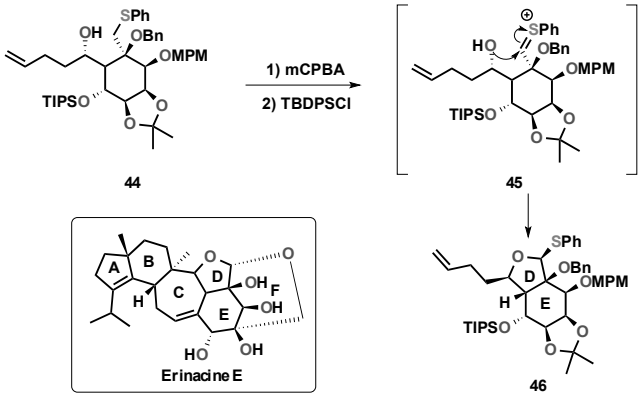
Scheme 9. Michael-Pummerer reaction.



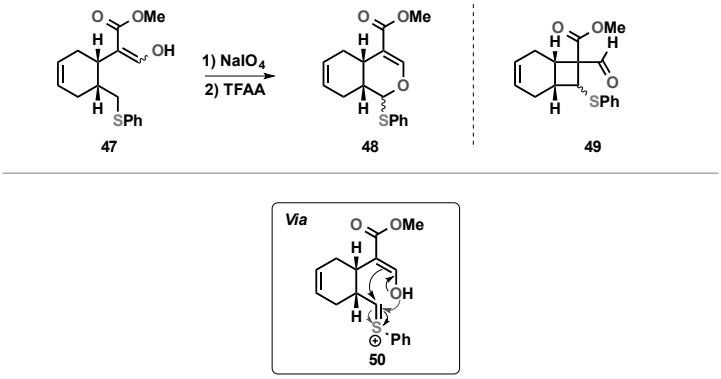
Scheme 10. Cyclizations using OH nucleophiles.

Nucleophilic alcohols have been applied in the total synthesis of complex natural products or advanced intermediates. A representative example was published by Kobayashi and coworkers[22] in the synthesis of the tricyclic core of Erinacine E. Scheme 11 shows the oxidation and subsequent activation of **44**, yielding the thionium intermediate **45**, which cyclizes spontaneously, producing the D-E bicyclic system of the natural product.

By far, enols are less common substrates in cyclizations. Nevertheless, we can mention one work published by Ikeda and Hutchinson.[23] They used the 1,3-dicarbonyl sulfide **47**, and its oxidation to the corresponding sulfoxide and its subsequent activation with TFAA generates the cyclic compound **48**. In this case, the reaction proceeds through a thionium producing **50** (Scheme 12). Since the 1,3-dicarbonyl compound is in equilibrium between its keto and enol forms, the TFAA cannot acylate the enol. Additionally, the high tension of the four-membered ring **49** avoids its formation, even if the Pummerer-Aldol reaction is feasible in other contexts.[24]



Scheme 11. Application in the synthesis of the D-E bicyclic system of Erinacine E.



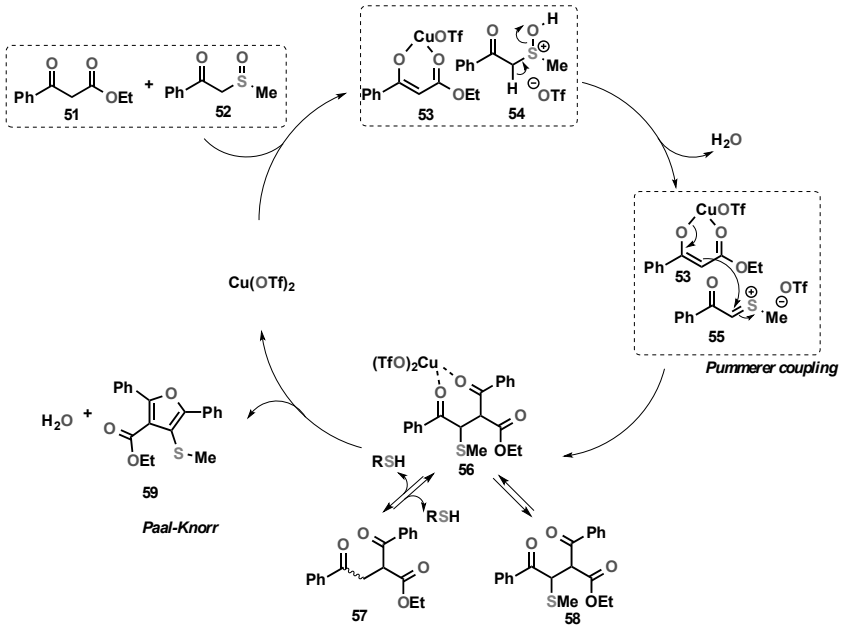
Scheme 12. Enols as nucleophiles in Pummerer cyclizations.

To the best of our knowledge, there are no descriptions of intramolecular Pummerer-Aldol reactions in the synthesis of oxygen heterocycles. However, Pappo and coworkers[25] successfully applied this sequence to obtain intermediates that readily cyclize. The reaction starts with the simultaneous activation of the sulfoxide and generation of the enolate, as presented in Scheme 9, but using $Cu(OTf)_2$ and TfOH as the activators. The thionium **55** reacts with the enolate **53** in an aldol-type reaction that the author calls Pummerer coupling. Then, the intermediate **56** generates the corresponding furan **59**. It should be noted that **56** may also produce the sulfide **58** or alkene **57** (Scheme 13).

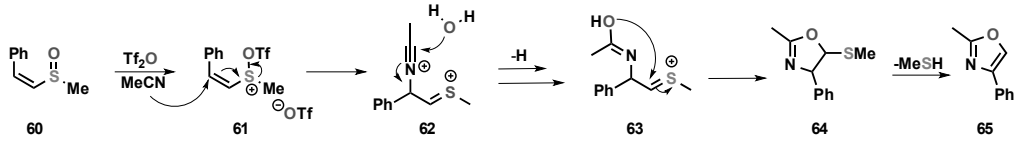
Water was recently used by Yorimitsu and coworkers in a special kind of cyclization.[26] Activation of the vinyl sulfoxide **60** with Tf_2O in the absence of external or internal nucleophiles will produce the sulfonium salt **61** that reacts with acetonitrile, generating the thionium **62** (Scheme 14). This species has two strong electrophilic sites, and its reaction with water occurs at the nitrilium ion, thus producing the intermediate **63**, which is the equivalent of previously described amide nucleophiles (Schemes 6 and 7). Consequently, the oxazoline **64** was formed and the corresponding oxazole **65** was isolated after elimination.

Phenols have been widely used in the synthesis of heterocycles by reacting with sulfonium intermediates. However, they do not always react in the same way. We will start our discussion by presenting a variant of the so-called aromatic Pummerer reaction described in Scheme 15. In this case, the heterocycle is an intermediate, and the reaction finished with the isolation of aryl sulfides or ethers.

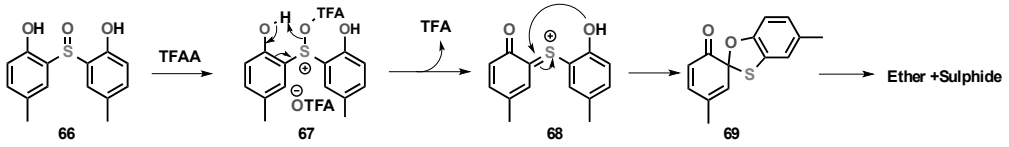
Jung *et al.*[27] described the activation of aryl-aryl sulfoxide **66** with TFAA. The sulfonium **67** is formed, and a sigmatropic rearrangement produces the thionium **68**, which cyclizes *via* the reaction of the hydroxyl group with the electrophilic carbon, yielding the spirocycle **69**.



Scheme 13. A successful Pummerer-Aldol-type reaction.



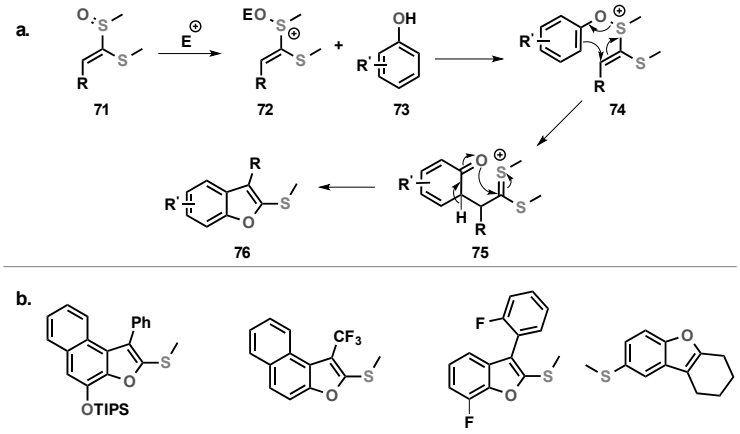
Scheme 14. Use of water as a source of nucleophilic oxygen.



Scheme 15. Phenols as nucleophiles in the aromatic Pummerer reaction.

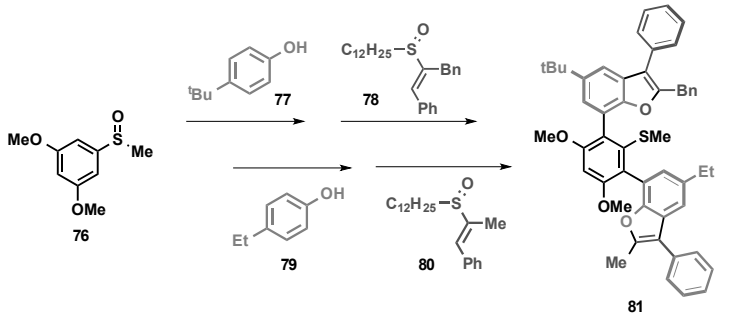
The most common use of phenols with sulfonium salts is in the tandem addition-sigmatropic rearrangement-cyclization. During the last decade, works by Yorimitsu, Procter and Maulide have shown the usefulness of the combination of phenols and sulfonium salts in organic chemistry, principally showing an interrupted Pummerer reaction, followed by a sigmatropic rearrangement. We describe some of those works, which have led to the formation of oxygen heterocycles. An excellent review focused on the use of sulfonium species in [3,3]-sigmatropic rearrangements should be consulted for more details.[28]

The general mechanism is presented in Scheme 16. The reaction starts with the activation of the sulfoxide **70**, producing the sulfonium **71**. As we mentioned before, the typical reactivity of a sulfonium with an oxygen nucleophile occurs at the most electrophilic sulfur atom, and thus, the reaction of **71** with phenols **72** will produce a new sulfonium **73** (interrupted Pummerer). That rearranges forming the thionium **74**, which may cyclize generating the benzofuran **75**. Scheme 16a shows the general mechanism, and Scheme 16b illustrates some of the structures that might be obtained using the same methodology and changing the vinyl sulfoxide.[29]



Scheme 16. Tandem interrupted Pummerer-sigmatropic rearrangement.

An iterative protocol allowed Yorimitsu *et al.*[30] to obtain the oligoarenes **81** using the same principle described before. The sequential reaction of sulfoxides **76**, **78** and **80** with phenols **77** and **79** permitted the authors to obtain a significant variety of structures, including intermediates and final products (Scheme 17).

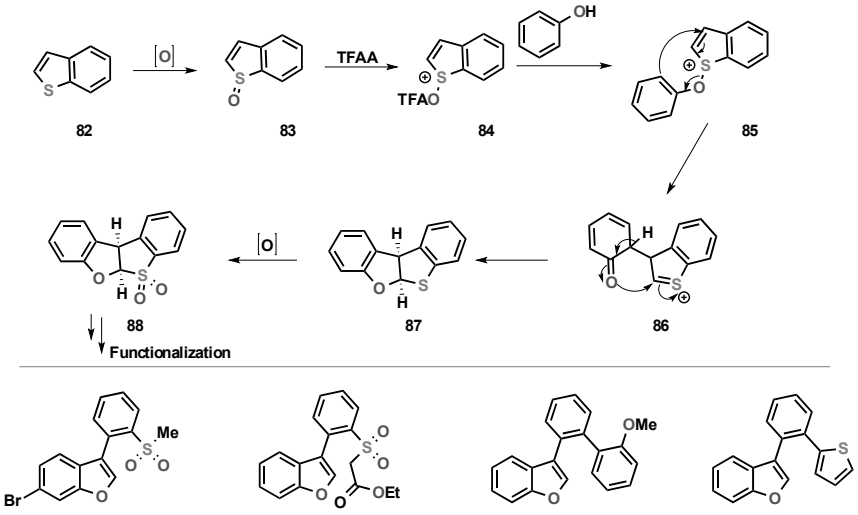


Scheme 17. Iterative synthesis of oligoarenes.

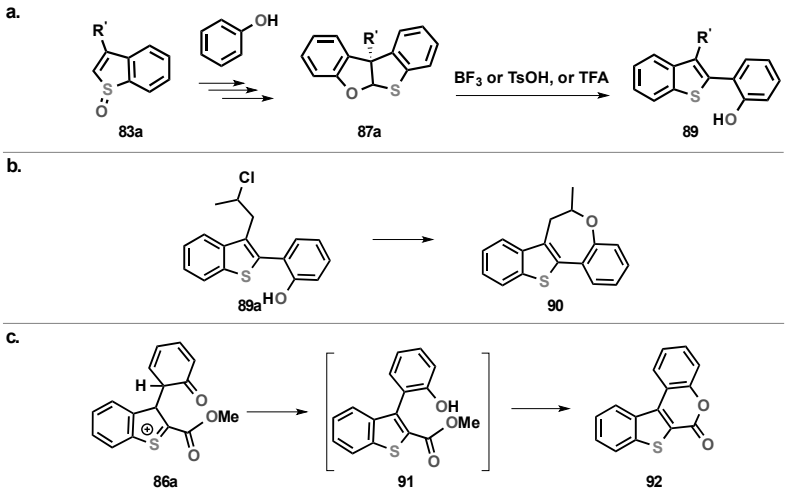
Procter and coworkers recently described the use of benzothiophenes instead of acyclic sulfoxides.[31] They started with the benzothiophene **82**, which is oxidized to the corresponding sulfoxide **83**. Then, **83** reacts with TFAA, generating the sulfonium **84**, which follows the same process previously described (interrupted Pummerer to the sulfonium **85**, sigmatropic rearrangement to the thionium **86** and cyclization). In this case, the benzofuran is replaced by the bicyclic system (thioacetal) **87**, which is then oxidized to **88**, which can undergo different functionalizations. Scheme 18 shows the general process and some of the structures obtained by using this method.

An extension of this work is the use of 3-substituted benzothiophenes.[32] The authors asked themselves if the presence of a substituent at position 3 may affect the sigmatropic rearrangement. Fortunately, an intermediate thioacetal **87a** was isolated and characterized, thus showing that the rearrangement is still possible and that substituted thiophenes followed the same reaction pathway. Scheme 19a summarizes those observations. The benzothiophene oxide **83a** undergoes activation and reaction with phenol, just as shown in Scheme 17, to produce **87a**. This product can be treated with Lewis or Brønsted acids, determining ring-opening and 1,2-migration of the aryl group, to give the 2-substituted benzothiophenes **89**. Appropriate substitution on the starting materials may produce other oxygen heterocycles, such as benzoxepine **90**, as shown in Scheme 19b. On the other hand, when the substituent of benzothiophene is in position 2, the

product is a 2,3-disubstituted benzothiophene **91** with the phenol moiety in position 3. Depending on the group in position 2, lactones (*e.g.* compound **92**) can be obtained.[33]



Scheme 18. Use of benzothiophene instead of acyclic vinyl sulfides.



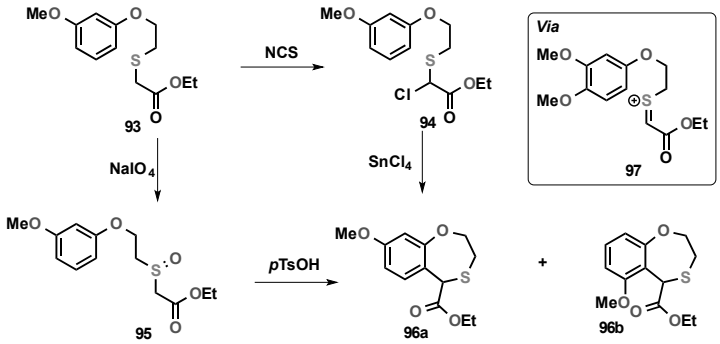
Scheme 19. Other oxygen heterocycles from substituted benzothiophenes.

3.2. Intramolecular cyclizations with carbon nucleophiles

Cyclizations of sulfoniums or thioniums with carbon nucleophiles are less common than with heteroatomic nucleophiles. The nucleophilicity of activated aromatics usually promotes those cyclizations. To the best of our knowledge, there is only one successful example of cyclization with aromatic nucleophiles bearing strongly deactivating groups. However, the molecule also has activating groups at the same time. We will discuss that in detail in this section.

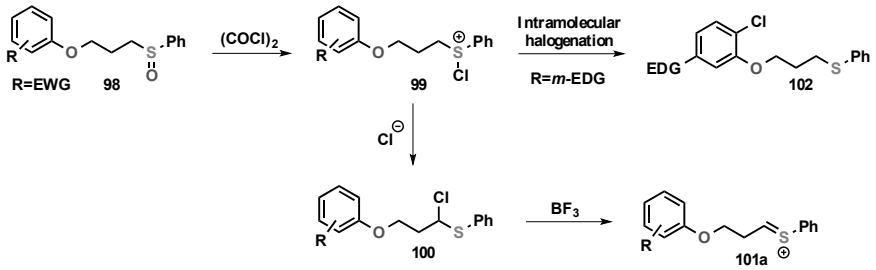
It is noteworthy to mention that some examples of cyclizations of thioniums with aromatics leading to the formation of carbocycles and nitrogen heterocycles have been described; nevertheless, those are out of the scope of this chapter.

We start our discussion with the work reported by Ikeda and coworkers.[34] They used a particular sulfoxide **95**, which can be seen as a 1,3-dicarbonyl compound with singular features, for example, the enolate form should exist in solution, thus making the α position nucleophilic, which may also stabilize a thionium ion. As a consequence, its formation should be more favoured, and less electrophilic activators should be used. The authors demonstrated that the cyclization might occur by activation of the sulfoxide with *p*-TsOH. Unfortunately, a mixture of regioisomers **96a** and **96b** was obtained due to the nucleophilic positions on the aromatic nucleophile. The same result was obtained when the α-chlorosulfide **94** was treated with $SnCl_4$, thus suggesting that both reactions proceed by the formation of the intermediate thionium **97**. This thionium is also formed by the action of the electrophilic NCS on the sulfide **93**. In other words, the first step is the formation of a chlorosulfonium salt from **93** or the formation of an oxygen sulfonium salt from **95**. Both readily undergo elimination to produce the thionium intermediate **97**, which is trapped by the nucleophilic chloride when NCS is used or by the nucleophilic aromatic ring in the absence of other nucleophiles (Scheme 20). The yield of the cyclization is approximately 50%.



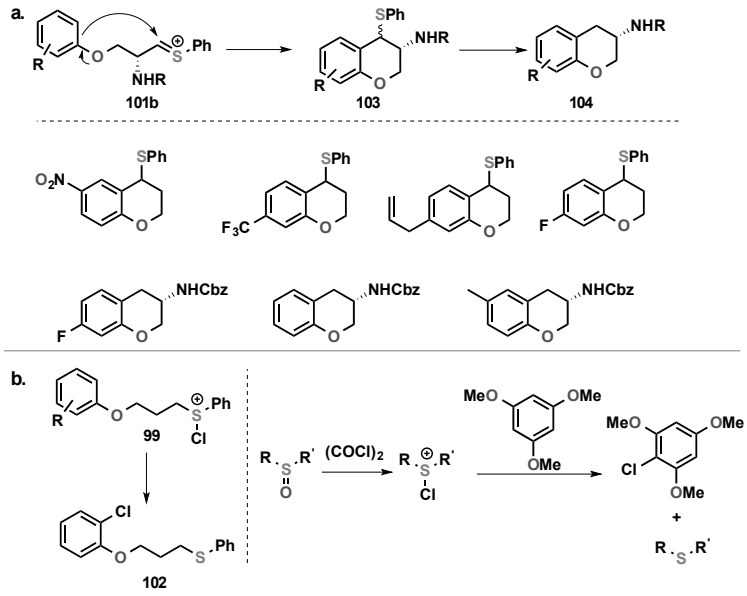
Scheme 20. Carbon nucleophiles in the cyclization of thioniums.

Recently, Gamba-Sánchez and coworkers studied this type of cyclization in more detail.[35] They unveiled a new sort of reactivity of chlorosulfonium salts. As we showed earlier in this chapter, the typical reactivity of chlorosulfonium with oxygen nucleophiles is on the more electrophilic sulfur atom. In this case, however, the oxygen nucleophile reacts on the chlorine atom or does not react, which is dependent on the nucleophilic species in the reaction mixture. Scheme 21 exemplifies the mentioned reactivity. The sulfoxide **98** is activated with oxalyl chloride $(COCl)_2$, forming the chlorosulfonium **99**. When strong nucleophiles are used as substrates (*e.g.* *m*-MeO groups on the aromatic), the reaction proceeds by intramolecular chlorination, yielding chlorosulfides **102**. However, if the aromatic is less nucleophilic, the reaction will produce the α-chlorosulfide **100**, which eventually allows the formation of a thionium, **101a**, and subsequent cyclization. Both reactions are competitive and highly dependent on the substrate.



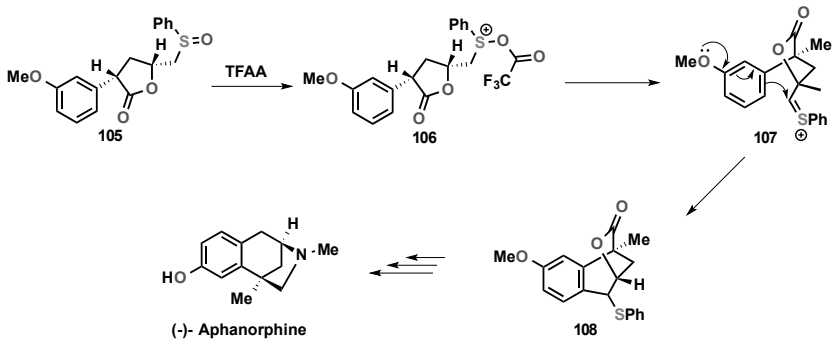
Scheme 21. Reaction of chlorosulfonium with nucleophilic aromatics.

The authors were able to apply the cyclization to a significant number of substrates, including some with chiral centers near the sulfur **101b**. The thioniums produced chromanes and the aminochromane **103**, which may be reduced to yield compounds without the sulfur moiety **104**. Scheme 22a shows some examples that illustrate the structural diversity reached, including the cyclization with substrates wearing strongly deactivating groups. Intramolecular chlorination was recently extended to the reduction of highly functionalized sulfoxides[36] following the same principle. The general features of this reaction are presented in Scheme 22b.



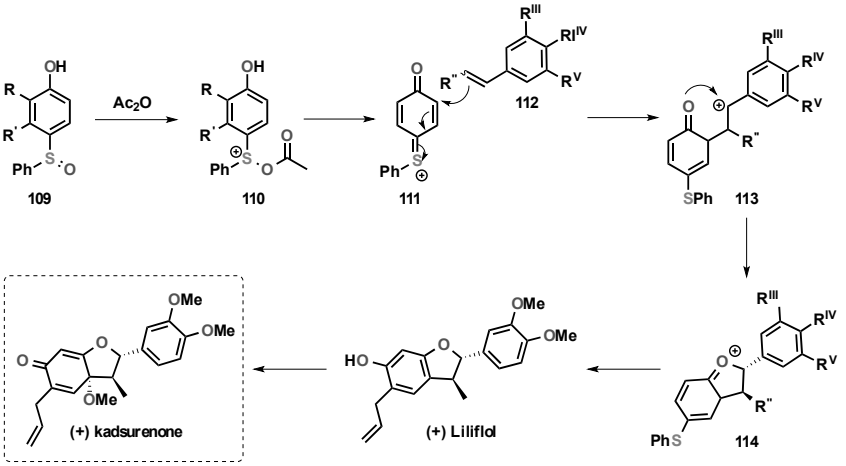
Scheme 22. Cyclization with carbon nucleophiles and the reduction of sulfoxides.

A similar approach was used by Takano *et al.* in the total synthesis of (-)-Aphanorphine. Scheme 23 shows the cyclization process starting with sulfoxide **105** activated with TFAA leading to the formation of the sulfonium **106**, which readily eliminates to form the thionium **107**. The cyclization to **108** is promoted by the high nucleophilicity of the aromatic ring; as we mentioned previously, deactivated aromatics are less reactive, and consequently, it is hard to achieve cyclizations. Further transformation leads to the synthesis of (-)-aphanorphine.



Scheme 23. Application in the synthesis of Aphanorphine.

Kita and coworkers[37] used an aromatic Pummerer reaction in the synthesis of neolignanes and applied the methodology to the synthesis of liliflol and kadsurenone. Scheme 24 summarizes the reaction mechanism and explains the aromatic Pummerer reaction. The phenol sulfoxide **109** was activated without acylation using acetic anhydride. The formation of thioniums usually requires providing protons α to the sulfur. In this case, conjugate elimination on **110** produced the quinone thionium **111**, which undergoes nucleophilic addition of the akene **112** (a pericyclic mechanism is a plausible alternative), leading to the formation of a cationic intermediate **113** that cyclizes to **114**. Aromatization and, in some cases, further functionalization let the authors obtain several natural products.



Scheme 24. Aromatic Pummerer reaction with carbon nucleophiles.

To this point, we have shown the cyclization of thionium ions generated by the elimination of sulfonium salts. However, there are several cyclizations with the participation of sulfonium salts themselves. We present some selected examples in the next section.

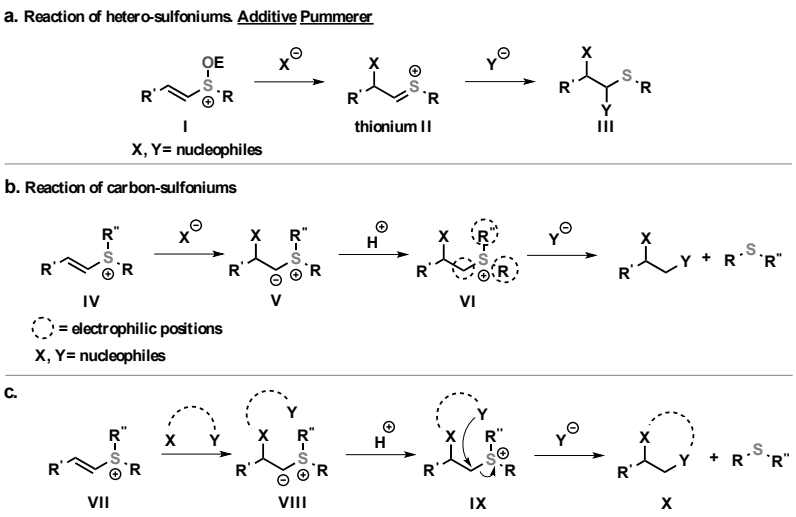
4. Cyclizations with sulfonium salts

In the previous section, we showed some examples of cyclizations where the starting material is a vinyl sulfoxide (Schemes 5, 9, 14, 16, and 18 and related discussion). In those cases, the α,β-unsaturated heterosulfonium **I** reacts with a nucleophile at the β position (a S_N2'-type reaction), generating a thionium ion **II**, which may react with a second nucleophile to yield **III**, which is called an additive Pummerer reaction. We would like to emphasize the remarkable difference in the reactivity of unsaturated heterosulfoniums compared with unsaturated carbon-sulfoniums. Scheme 25 shows the difference mentioned above. The carbon-sulfonium **IV** generates a sulfur ylide **V** and then a new sulfonium **VI** instead of a thionium. The new salt may also react with a second nucleophile, but it has three different reactive positions. If the two nucleophiles are on the substrate, the second attack is intramolecular, and a cyclic product **X** is obtained.

In this section, we will discuss some selected examples that allowed the synthesis of oxygen heterocycles following the sequence showed in Scheme 25c.

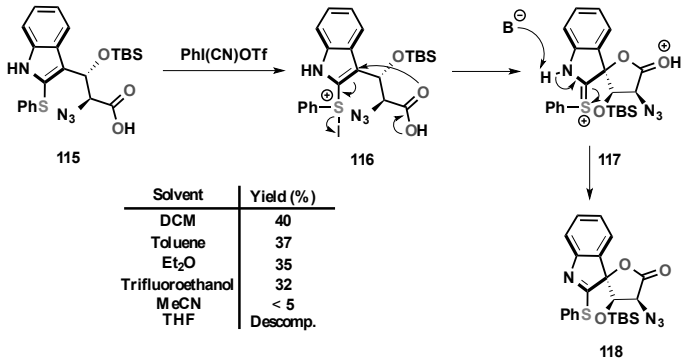
4.1. Additive Pummerer cyclizations

It is worth mentioning that very few examples of direct cyclizations with additive Pummerer reactions are found in the literature. However, we would like to show the work of Feldman and coworkers.[38] Even if they obtained a low yield and the reaction showed competition with other cyclizations, it is an excellent example to illustrate the direct cyclization of sulfonium salts *via* additive Pummerer pathways.



Scheme 25. General reaction of vinyl sulfoniums.

Scheme 26 shows Feldman's approach to the synthesis of spirocycles. The indole sulfide **115** is activated with PhI(CN)OTf, producing the iodo-sulfonium **116**. The same salt may be obtained from the corresponding sulfoxide. However, the activation of the sulfoxide proceeded with more difficulty, and consequently, lower yields were obtained. Then, the iodo-sulfonium **116** spontaneously cyclizes producing the thionium **117**, which leads to the spirocycle **118** by the action of a base. The authors studied the effects of several solvents. Unfortunately, the yield could not increase over 40%. Therefore, when carbamates (*e.g.* NHBoc) were used instead of the N_3 group, the cyclization occurred with the carbamate moiety.



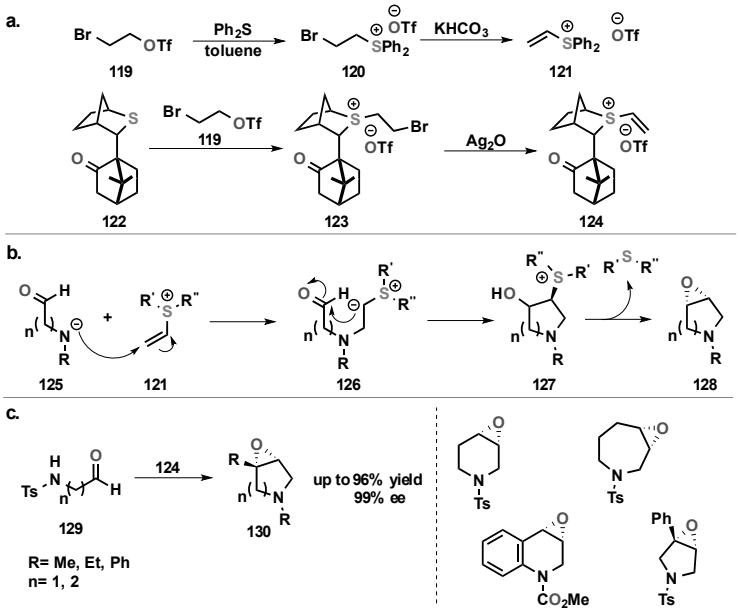
Solvent	Yield (%)
DCM	40
Toluene	37
Et_2O	35
Trifluoroethanol	32
MeCN	< 5
THF	Descomp.

Scheme 26. Feldman's approach to spirocycles.

4.2. Epoxidations

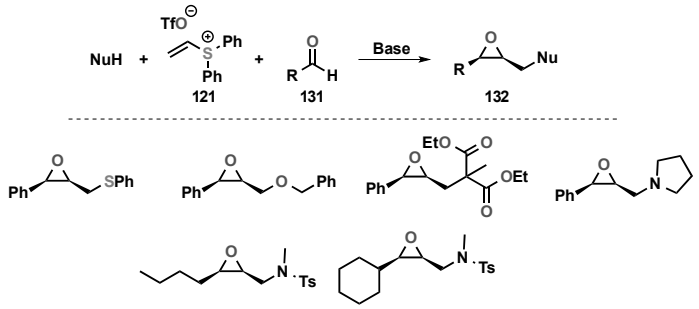
As we mentioned earlier (Scheme 25), the cyclizations we discuss require vinyl sulfonium and two nucleophiles. In most cases, the vinyl sulfonium is produced *in situ* from commercially available products. Pioneering work by Aggarwal and coworkers showed the way to achieve epoxidations and to prepare the vinyl sulfoniums.[39] Scheme 27a describes the synthesis of two vinyl sulfonium salts, **121** and **124** (chiral); both processes follow the same sequence: the nucleophilic substitution of the triflate in the compound **119** with a sulfide, followed by the elimination of bromine in **120** or **123**. The general concept is illustrated with amino-aldehyde **125** and its reaction with **121** (Scheme 27b). The nucleophilic conjugate addition of the nitrogen to the sulfonium generates the sulfur ylide **126**, which cyclizes by the reaction of the nucleophile

with the electrophilic aldehyde. The epoxidation of **127** by a S_N2 mechanism with the liberation of the sulfide produces the heterocycle **128**. Scheme 27c illustrates the variety of substrates that can be used. Additionally, this Scheme shows that an excellent enantiomeric excess can be achieved when using the nonracemic salt **124**. The effects of substrates and salts were studied by the same group, providing in-depth insights into the reaction pathway.[40]



Scheme 27. Epoxidations with sulfoniums described by Aggarwal.

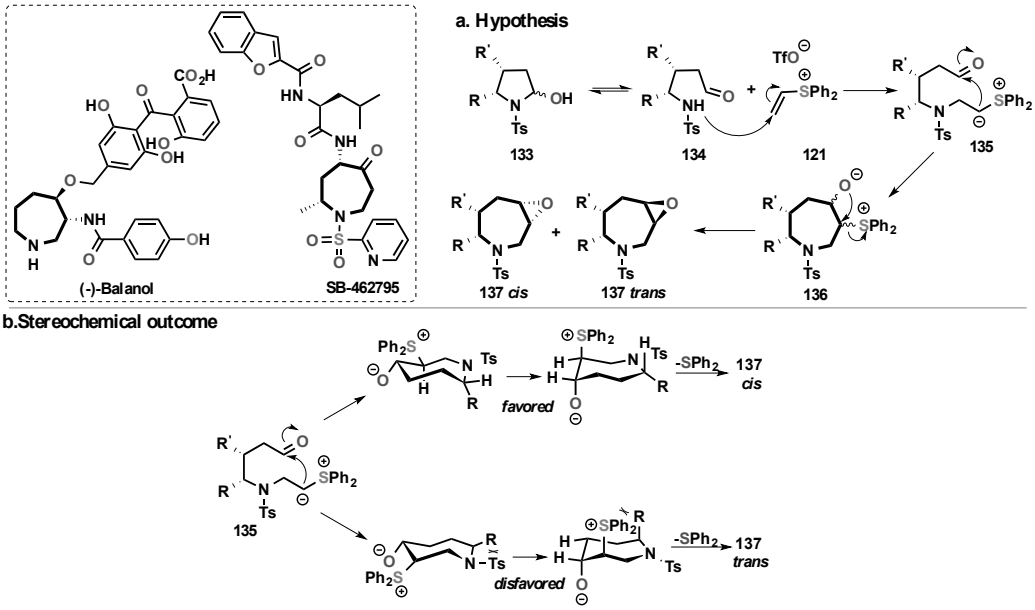
A remarkable extension of the previously shown work is sulfur ylide-mediated three-component epoxidation.[41] In this case, the reaction mixture is composed of the sulfonium salt **121**, the nucleophile and the aldehyde **131**. Thus, the first addition (nucleophile to the sulfonium) will generate the ylide, which may add to the carbonyl compound and then promote cyclization to the epoxide **132** (Scheme 28 for the structures of products that can be obtained using this methodology).



Scheme 28. Three-component epoxidation *via* sulfur ylides.

In an attempt to apply that methodology to the synthesis of the heterocyclic core of balanol and SB-462795, the same team investigated the stereochemical influence of chiral groups during the cyclization to obtain epoxy-fused azepines.[42] Scheme 29 summarizes the most significant results of this attempt. The

hemiaminal **133** is in equilibrium with its open isomer **134**. The latter may react with the vinyl sulfonium **121**, producing the ylide **135**. As usual, the ylide cyclizes to yield the sulfonium **136**, which reacts in an intramolecular nucleophilic substitution, leading to the formation of the epoxiazepine **137** (Scheme 29a). The primary hypothesis was that the chiral centers at positions 2 and 3 to the nitrogen should induce some stereochemistry on the oxygen and sulfur substituents on the azepine **136**, thus making the formation of the epoxide completely stereoselective. A careful analysis of products allowed the authors to propose the stereochemical outcome (Scheme 29b); the group at position 2 should induce the formation of the *cis* epoxide **137** since the transition state is favorable in energy. On the other hand, the experimental results showed a prevalence for the *cis* product, which unfortunately led to the 2,5-*trans* product **139** after epoxide opening (Scheme 29c). This product has the wrong stereochemistry for natural products. Consequently, further investigations are needed to apply this methodology to their synthesis.



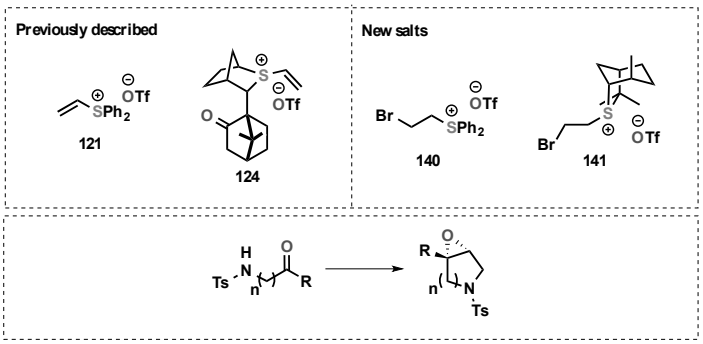
Entry		R	R'	*cis*:*trans*	Yield [%][a]
1	b	$MeCO_2$	H	4:1	62
2	c	$tBuCO_2$	H	>19:1	61
3	d	$TBDPSOCH_2$	H	>19:1	69[b]
4	e	H	H	4:1	70[b]

[a] Isolated yields after column chromatography. [b] 3 equiv of DBU and 4 equiv of 121 were used. TBDPS= *tert-butyldiphenylsilyl*.

Scheme 29. Synthesis of epoxy-azepines.

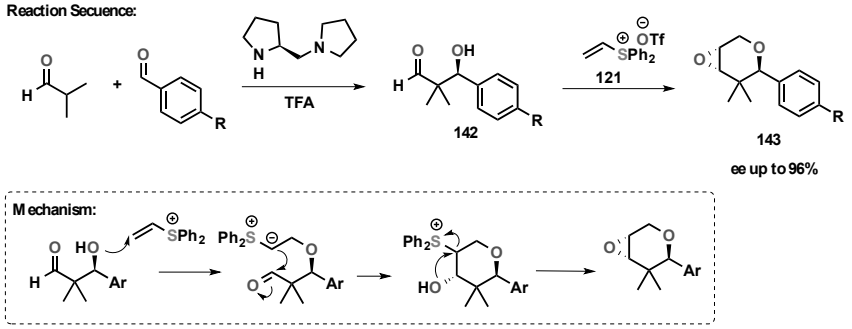
Continuing with the presentation of the work of Aggarwal's team, they tried to use other salts instead of those previously described. The main advantages are as follows: the sulfonium salt **140** is commercially available, bench stable and easy to handle. The sulfonium **141** can be obtained in a single step from the corresponding sulfide which is commercially available. They used those salts in the reaction shown in

Scheme 30.[43] Unfortunately, in all cases, the yields dropped compared with the use of vinyl sulfoniums. The same happened with the diastereoselectivity as well as the enantiomeric excess.



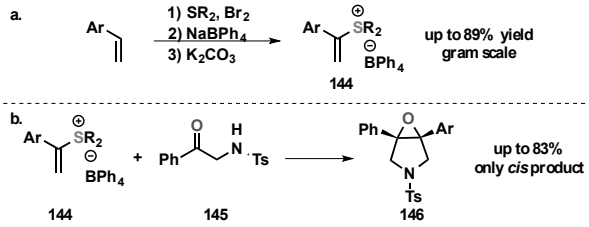
Scheme 30. Other sulfoniums that induce epoxidations.

In 2010, Ley and coworkers[44] published the use of enantioenriched 3-hydroxy aldehydes **142** as nucleophiles. The aldehydes were obtained by an aldol reaction between *iso*-butyraldehyde and aromatic aldehydes catalyzed by a chiral pyrrolidine. The hydroxy aldehyde follows the typical reaction pathway, producing the fused epoxy tetrahydropyrans **143**. The enantiomeric excesses were remarkable, and the reaction was utterly diastereoselective (Scheme 31), thus showing that many combinations of nucleophiles can be used with this reaction and, more importantly, that the stereo-induction in the epoxide formation might be successful depending on the positions of the substituents on the formed ring.



Scheme 31. Synthesis of epoxy-pyrans.

The reader should have observed by now that the investigations that we have described were mainly focused on the study of cyclization with unsubstituted sulfoniums. Thus, the stereochemistry of the product is entirely dependent on the substitution pattern of the substrate. Therefore, Aggarwal[45] studied the cyclization using aminoketones **145** and substituted salts **144**. Scheme 32 shows the principal results of this approach, displaying that the formation of sulfonium salts may follow the same principle described before and that they can be obtained at gram scale from commercially available styrenes (Scheme 32a). Additionally, the authors also showed that the reaction of substituted sulfoniums **144** is more complicated than that with unsubstituted ones. Nevertheless, they were able to achieve excellent selectivities in epoxy-fused pyrrolidines **146** (Scheme 32b). In all of the reactions presented in this section, the second nucleophile is generated *in situ* after the addition of the ylide to a carbonyl group, typically an aldehyde or ketone. The reaction of carbon-thionium salts with substrates with two nucleophilic groups has not been discussed. Consequently, we focus on that type of transformation in the next section.

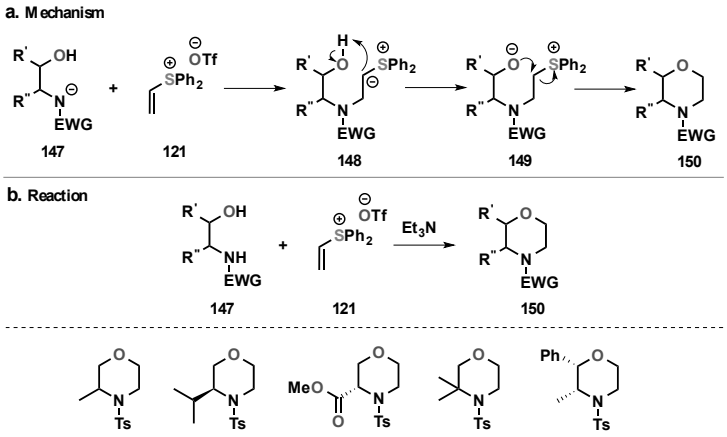


Scheme 32. Use of substituted sulfoniums in the synthesis of epoxy-pyrrolidines.

4.3. Formation of five-, six- and seven-membered rings

In this section, we present the reaction of vinyl sulfoniums with bis-nucleophilic substrates. In principle, these substrates should be more challenging since the competition between nucleophiles is a severe issue that needs to be overcome. Additionally, we showed that the fist nucleophilic addition generated a sulfur ylide, which is also nucleophilic, and therefore, after the first addition, a new competition between nucleophiles exists. Fortunately, the teams that studied this transformation have succeeded with solutions to those problems.

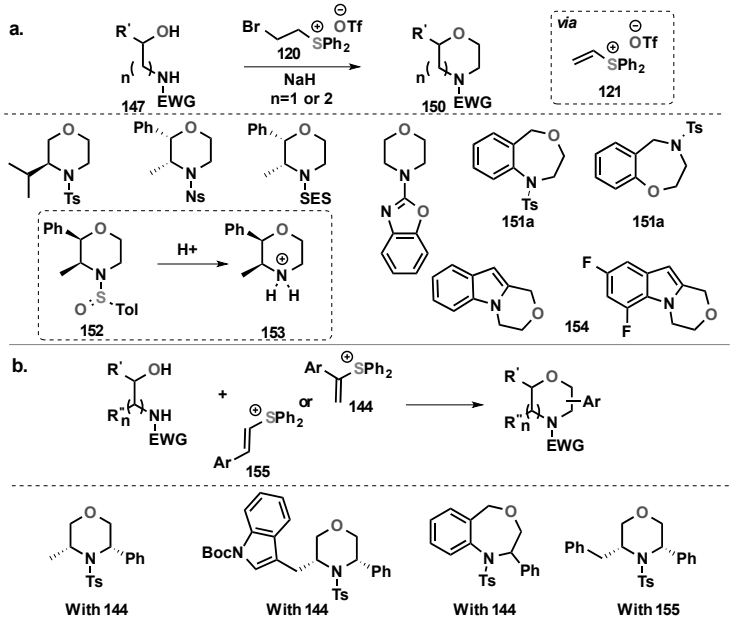
We will start our discussion with the pioneering work by Aggarwal and coworkers.[46] This work serves as a model for the reaction mechanism applied in other transformations and the synthesis of five-, six- and seven-membered oxygen heterocycles. Scheme 33a describes the reaction mechanism. First, the amino alcohol **147** adds to the vinyl sulfonium **121**. It is noteworthy to mention that the amino group has an electron-withdrawing group (EWG) to favor its deprotonation to make it more nucleophilic. The ylide **148** reacts intramolecularly, generating the new sulfonium **149**, which directly cyclizes producing the substituted morpholine **150**. Scheme 33b shows the general reaction and some of the structures obtained by Aggarwal and coworkers.



Scheme 33. Synthesis of morpholines with vinyl sulfoniums.

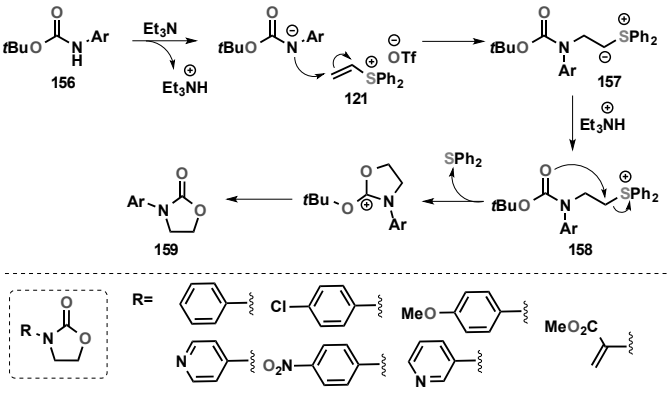
Extensions of this work were published later, showing the *in situ* formation of the vinyl sulfonium **121** from the corresponding bromide **120**. Additionally, the authors also extended the methodology to the synthesis of oxazepines **151** (Scheme 34a).[47] This methodology has a very good substrate scope and illustrates the use of other EWGs on the nitrogen atom. On the other hand, the same authors reported the use of sulfinamides to obtain protected morpholines **152**, which upon acidic treatment yield morpholine salts **153**.[48] Cheng, Xiao and coworkers[49] described the use of (1*H*-indol-2-yl)methanols as substrates, yielding compounds **154** in good to excellent yields. As a natural extension, the use of substituted sulfoniums **144** and **155** was later described.[50] Scheme 34b shows the diversity of structures that can be obtained. The use of **144**

affords excellent regio- and stereoselectivity for morpholines. Unfortunately, the use of **155** showed poor regioselectivity and an entire lack of stereoselectivity.



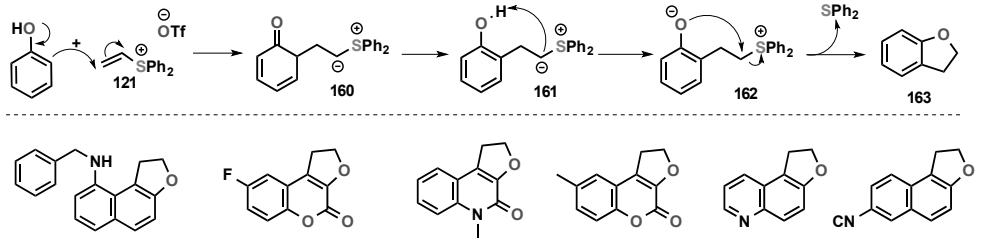
Scheme 34. Synthesis of other oxygen heterocycles by using vinyl sulfoniums.

In 2009 Liu and coworkers[51] published the use of aromatic carbamates **156**. They were able to obtain cyclic carbamates **159** by using the vinyl sulfonium **121**. The reaction starts, as usual, by the addition of the nitrogen nucleophile to produce the ylide **157**. Then, **157** is protonated to form the new sulfonium **158**, which cyclizes with the concomitant loss of isoprene to afford the cyclic carbamate **159**. Using this method, the authors obtained a significant variety of carbamates with aromatic, heteroaromatics and alkenyl groups as substituents (Scheme 35). The use of amides instead of carbamates only afforded minimum quantities of lactones.[52]



Scheme 35. Synthesis of cyclic carbamates with from vinyl sulfoniums.

Thus far, we have discussed the use of *N,O*-bis nucleophiles. Even though the use of *X,O*-bis nucleophiles is rare, Yan, Mao and coworkers[53] described a remarkable example. They showed the construction of oxygen heterocycles (coumarins and hydrofurans) by using naphthols and enols as *C,O*-bis nucleophiles. Scheme 36 summarizes Yan and Mao's results and provides a plausible reaction mechanism. The reaction of phenols, naphthols or hydroxycoumarins with **121** will produce ylides **160**, and then, as usual, the formation of a second sulfonium **162** is promoted by the presence of an acidic proton. The intermediate **162** will afford the hydrobenzofuran **163**.



Scheme 36. Use of *C,O*-bis nucleophiles with vinyl sulfoniums.

The reactions of vinyl sulfoniums to produce oxygen heterocycles have been covered in this section. However, it is clear that carbon-sulfoniums have three reactive (electrophilic) positions, and their reaction with nucleophiles depends on the stability of the sulfide formed. In the next section, we discuss a couple of works where the sulfoniums induce the cyclizations by the donation of an electrophile.

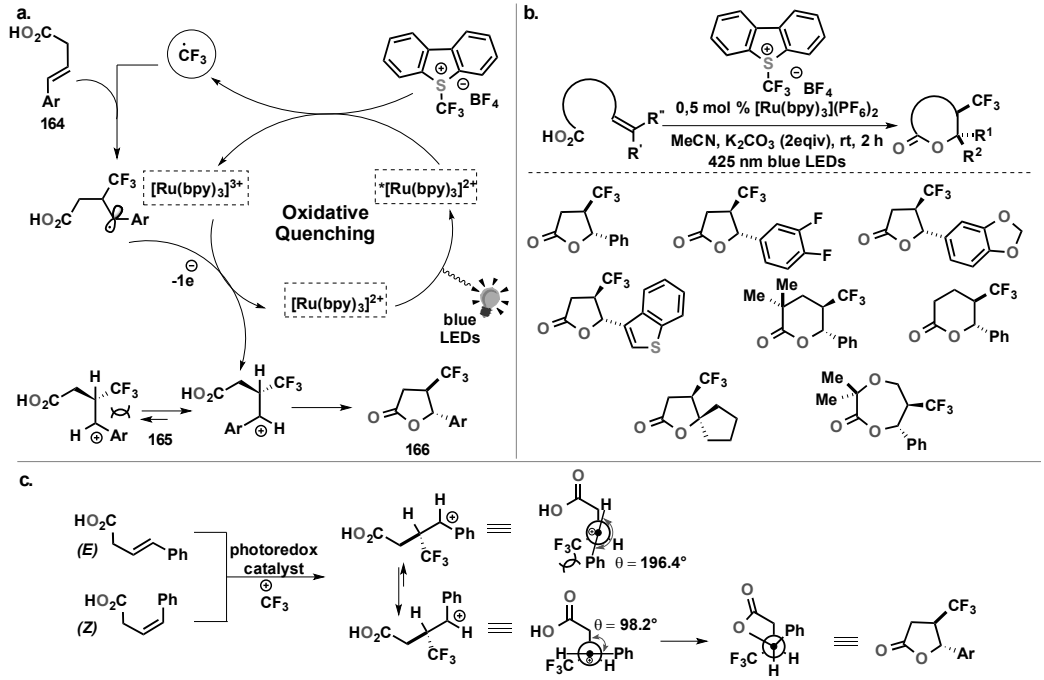
5. Sulfonium salts as electrophile sources: induction of cyclization

Sulfonium salts are known to be electrophile sources, and the typical example is Umemoto's trifluoromethylation reagent(s).[54] These reagents are trifluoromethyl sulfonium salts, and their preparation and application has been recently reviewed in the literature.[55] In this context, sulfonium salts may be used to transfer an electrophile to a second molecule, thus generating a reactive species that might cyclize. The classic preparations of sulfoniums were discussed in the first section of this chapter and may be reviewed in Scheme 2. Additional ways to prepare carbon-sulfonium salts include the treatment of sulfides with iodonium salts[56] or the direct reaction of sulfoxides with Grignard reagents,[57] among others. The examples discussed in this section may use an isolated sulfonium salt or a sulfonium formed *in situ*. When appropriate, we will show the method of synthesis or explain the way the authors obtained the sulfonium.

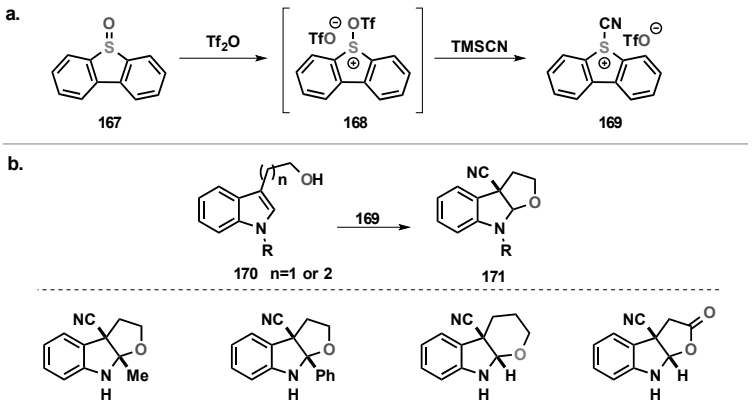
In 2014 Akita, Koike and coworkers[58] described a diastereoselective tandem trifluoromethylation-lactonization of alkenyl carboxylic acids using Umemoto's reagents. The reaction proceeds by the donation of the trifluoromethyl group to the nucleophilic double bond of reagent **164**, producing a cationic intermediate, **165**, that directly reacts with the carboxylic acid forming the lactam **166** (Scheme 37a). The reaction is performed in the presence of $[Ru(bpy)_3](PF_6)_2$ as a photocatalyst and visible blue light. The authors demonstrated that the reaction did not proceed in darkness or without the catalyst, thus suggesting a SET transfer mechanism, which provides the cationic species in a more complex procedure, which means the trifluoromethyl radical adds to the alkene and the formed radical donates an electron to regenerate the catalyst and produce the intermediate cation. It is noteworthy to mention that all of the substrates have at least one aromatic group (or a tertiary carbon) to stabilize the cation. Scheme 37b shows the variety of products obtained and that the reaction may be extended to the synthesis of six and seven-membered rings. Additionally, the authors proposed an energetic differentiation between transition states that explains the isolation of exclusively *endo* products with excellent *trans* selectivity (Scheme 37c).

It has to be highlighted that despite the strong electrophilicity of the trifluoromethyl group in Umemoto's reagent, it did not add to the alkene without the action of the catalyst. Fortunately, this is not always the case. Recently, Alcarazo and coworkers[59] described a cyanocyclization of unsaturated functions with pendant nucleophiles. They synthesized a cyanation reagent, **169** (analogue to Umemoto's reagent); the reagent was synthesized from the corresponding sulfoxide **167** through a sulfonium intermediate, **168** (Scheme 38a). As expected the reaction proceeds by addition of the more nucleophilic carbon 3 on the

pyrrole, thus generating a cationic intermediate, which, upon reaction with the free OH, affords the cyclic compound **171**. The authors were able to obtain hydrofurans, lactones and hydropyrans (Scheme 38).



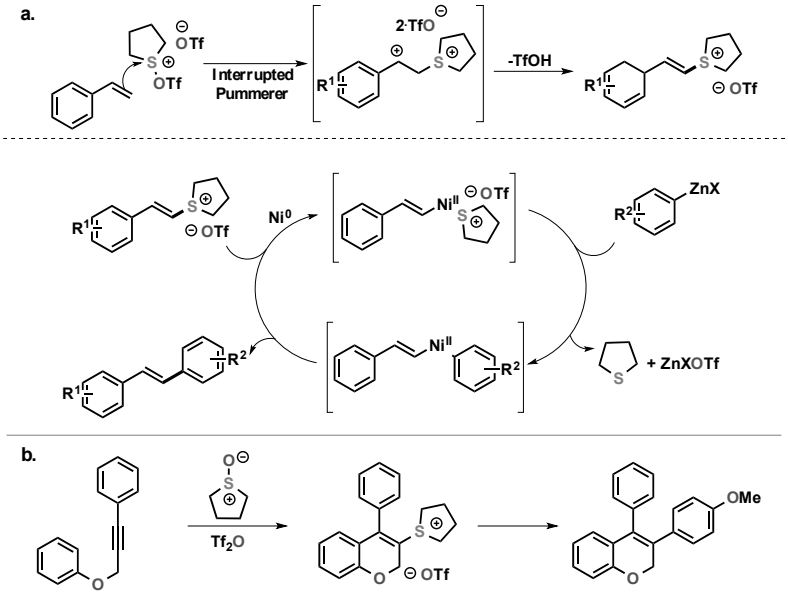
Scheme 37. Trifluoromethylation-cyclization using Umemoto's reagent.



Scheme 38. Alcarazo's cyanation-cyclization.

The two methods described before have an unsaturated functional group plus a pendant nucleophile. Thus, the addition of the electrophile to the unsaturated functional group produces a cationic intermediate, which will react with the nucleophile. However, even if the concept is simple, to the best of our knowledge, there are no further examples of this reactivity. Fortunately, other groups have studied the chemistry of sulfonium salts. Notably, Procter's group discovered a new reaction of the unsaturated functional group with

the electrophilic sulfur instead of with the electrophilic substituent;[60] therefore, the new sulfonium underwent a Negishi-type cross coupling. When the second step is intramolecular, oxygen heterocycles are obtained. A formal evaluation of this reaction let us understand the entire process as the umpolung of unsaturated functional groups. Scheme 39 shows the simplified reaction mechanism and the oxygen heterocycle obtained. It has to be noted that this is one of the infrequent examples in which a sulfoxide is used as a catalyst. We discuss this reaction with more detail in the next section.



Scheme 39. Interrupted Pummerer reaction with alkenes as nucleophiles.

The umpolung of the unsaturated functional group was also achieved by Procter using the phenol **172** and biphenyls **174**.[61] In both cases, the reaction with 1,3-dicarbonyl compounds produces a sulfonium intermediate (through an interrupted Pummerer reaction, Scheme 40a). The new sulfonium reacts with a second nucleophile, which means the natural reactivity of the phenol or phenol derivative changed and the *ortho* position is now electrophilic, allowing the reaction with other aromatics or with a dicarbonyl (enolates), thus, yielding the cycle precursor that forms *in situ* (Schemes 40b and 40c).

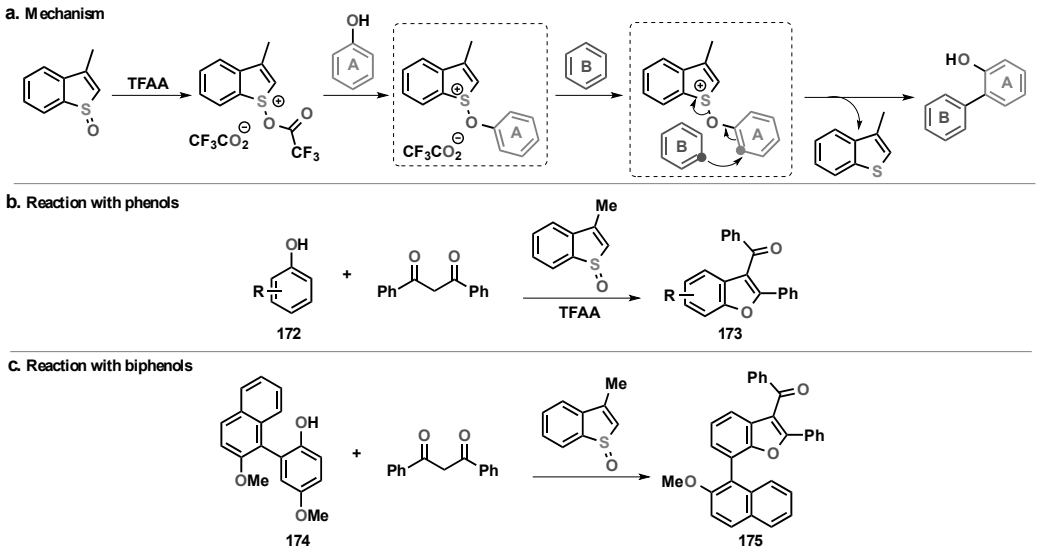
6. Sulfonium salts in the functionalization of oxygen heterocycles

Sulfonium salts are versatile reagents. Depending on their substituents, sulfonium salts may have three to four reactive sites; most commonly, they react on the sulfur atom to produce another sulfoniums. Nevertheless, sulfoniums are also electrophilic on their substituents. Consequently, as we showed in the last sections, sulfoniums have been used as sources of electrophiles. Very recently, sulfoniums have been used in the functionalization of aromatics and, in some particular cases, in the functionalization of oxygen heterocycles. In this section, we discuss the most recent and representative examples of this reactivity of sulfonium salts, dividing our presentation into methods that use photocatalysis and those without photocatalysis.

6.1. Functionalization using photocatalysis

Photocatalysis has become one of the most useful strategies to achieve late-stage transformations in organic chemistry. One of the most significant issues in organic reactions is functional group tolerance. Not in vain, some decades ago, organic chemists developed the concept and application of protecting groups, a technique that is still widely used worldwide. In that context the development of new reactions that allow the

functionalization of complex molecules is continuously growing, and among them, photocatalysis has demonstrated excellent results.



Scheme 40. Phenol umpolung induced by sulfoniums.

Sulfonium salts have been used as sources of electrophiles as well as radical precursors, usually promoted by photocatalysis. The radicals might be stabilized, and their reaction allows the late-stage functionalization of natural products, commercial drugs, and materials, among others.

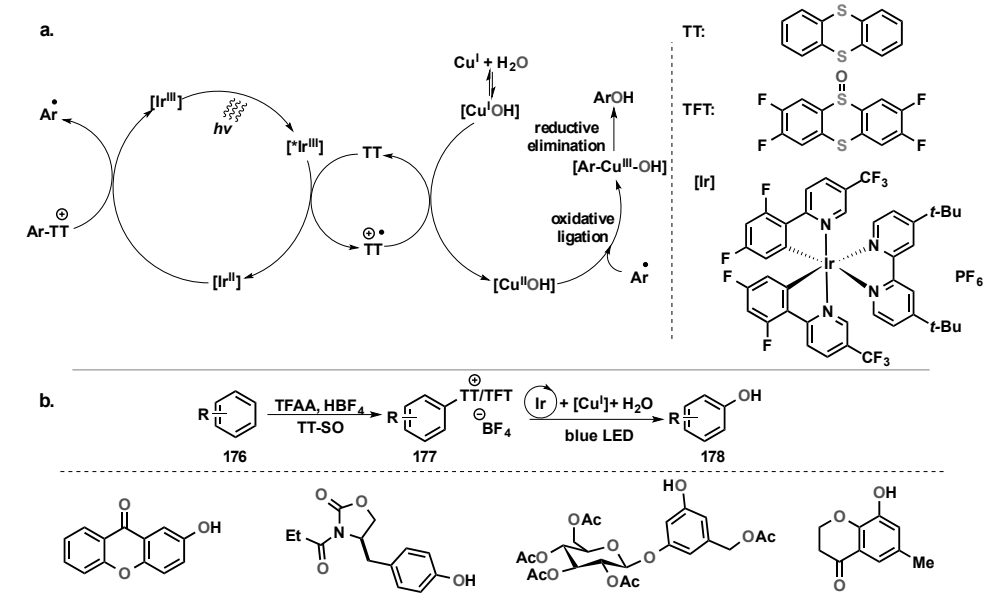
We will start our discussion with the method of oxygenation of aromatics described by Ritter and coworkers in 2019.[62] They used the activation of thianthrene *S*-oxide to generate the sulfonium, and as usual, the sulfonium reacts with a nucleophile. In this case, the nucleophilic arene **176** produces the arene-TT or arene-TFT (depending on the salt used) **177**, and this transformation can be seen as the arene umpolung discussed in the previous section. Then, the arene-TT/TFT interacts with the Ir catalysts, producing the arene radical. This radical enters into a second catalytic cycle, where it reacts with Cu, specifically a complex formed by CuTC and water. The traditional insertion of the aromatic followed by the hydroxylation led to the final hydroxy-arene **178**. Scheme 41a shows the general mechanistic proposal, and it is possible to see the two coupled catalytic cycles that show the generation of the hydroxylating species and the regeneration of the catalysts. Scheme 41b shows the global reaction and examples of hydroxylated oxygen heterocycles, including sugars, carbamates and pyranones.

The same authors used a similar approach for a site-selective trifluoromethylation.[63] The entire process works very similar to the previously described process. In this case, the photocatalyst is a ruthenium complex, which is the main difference with the previously described process. Additionally, the $CuCF_3$ is generated *in situ* and acts as the trifluoromethyl source (Scheme 42).

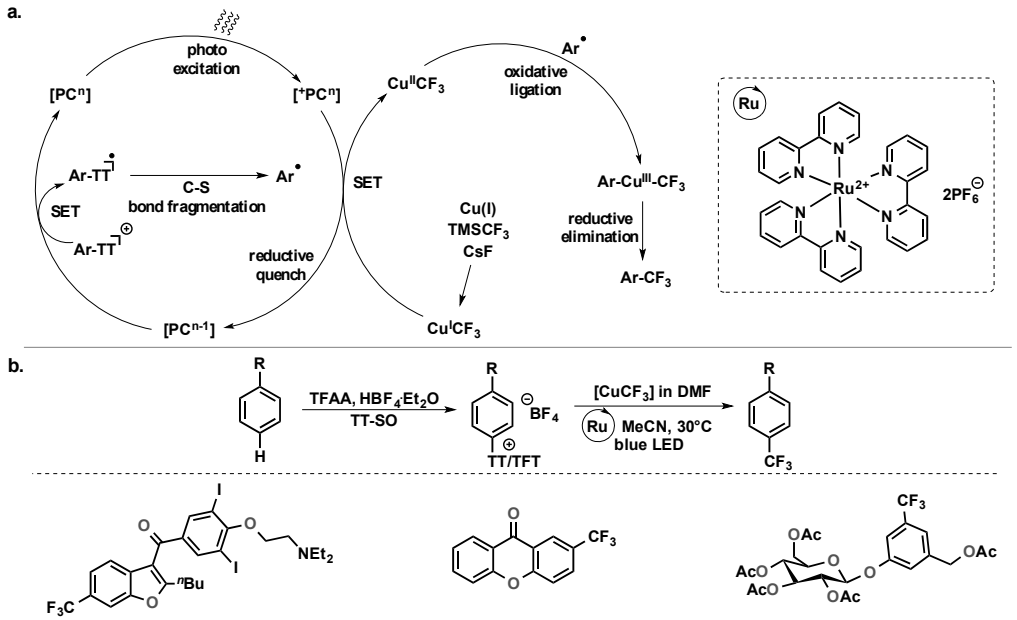
The examples described in Schemes 41 and 42 show the utility of thianthrene TT and tetrafluoro thianthrene TFT in photocatalytic reactions, which is particularly important since the use of other leaving groups has shown serious limitations in the photoredox processes, and thus, the use of the sulfonium as a reagent, particularly the TT and TFT molecules as leaving groups, has allowed excellent functional group tolerance and late-stage functionalizations.

In the last two examples, oxygenations and trifluoromethylations were achieved with excellent yields and selectivities. Ritter has focused on the development of late-stage transformations, predominantly for the introduction of functional groups or atoms with biological or pharmaceutical interest. It is well known that fluorine changes the electronic properties of active molecules without affecting its steric characteristics,

which is important since fluorinated molecules are usually more biocompatible (good balance between lipo- and hydro-solubility). Additionally, if the fluorine is at the correct position, those molecules are more stable for metabolic transformations.



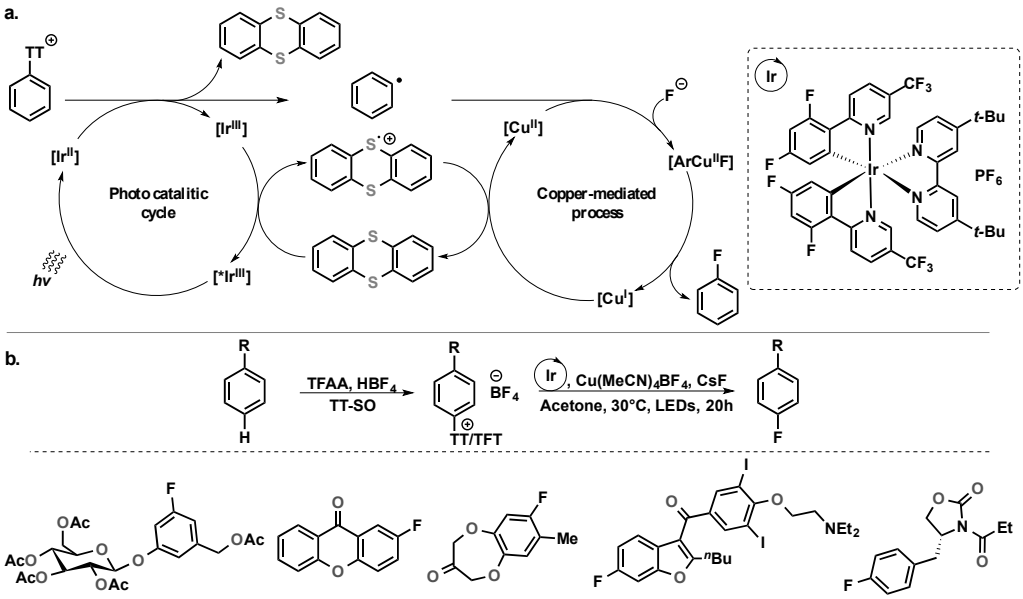
Scheme 41. Photocatalytic oxygenation of sulfoniums.



Scheme 42. Photocatalytic trifluoromethylation of sulfoniums.

In this context Ritter and coworkers[64] developed a late-stage fluorination method that allowed the regioselective functionalization of aromatics with an excellent functional group tolerance and a wide substrate scope.

The concept of the reaction was presented in the previous paragraphs. The main difference with the previously described methods for oxygenation or trifluoromethylation is the use of a copper species. Scheme 43 shows the particular features of this reaction and the oxygen heterocycles that were effectively fluorinated.



Scheme 43. Photocatalytic fluorination of sulfoniums.

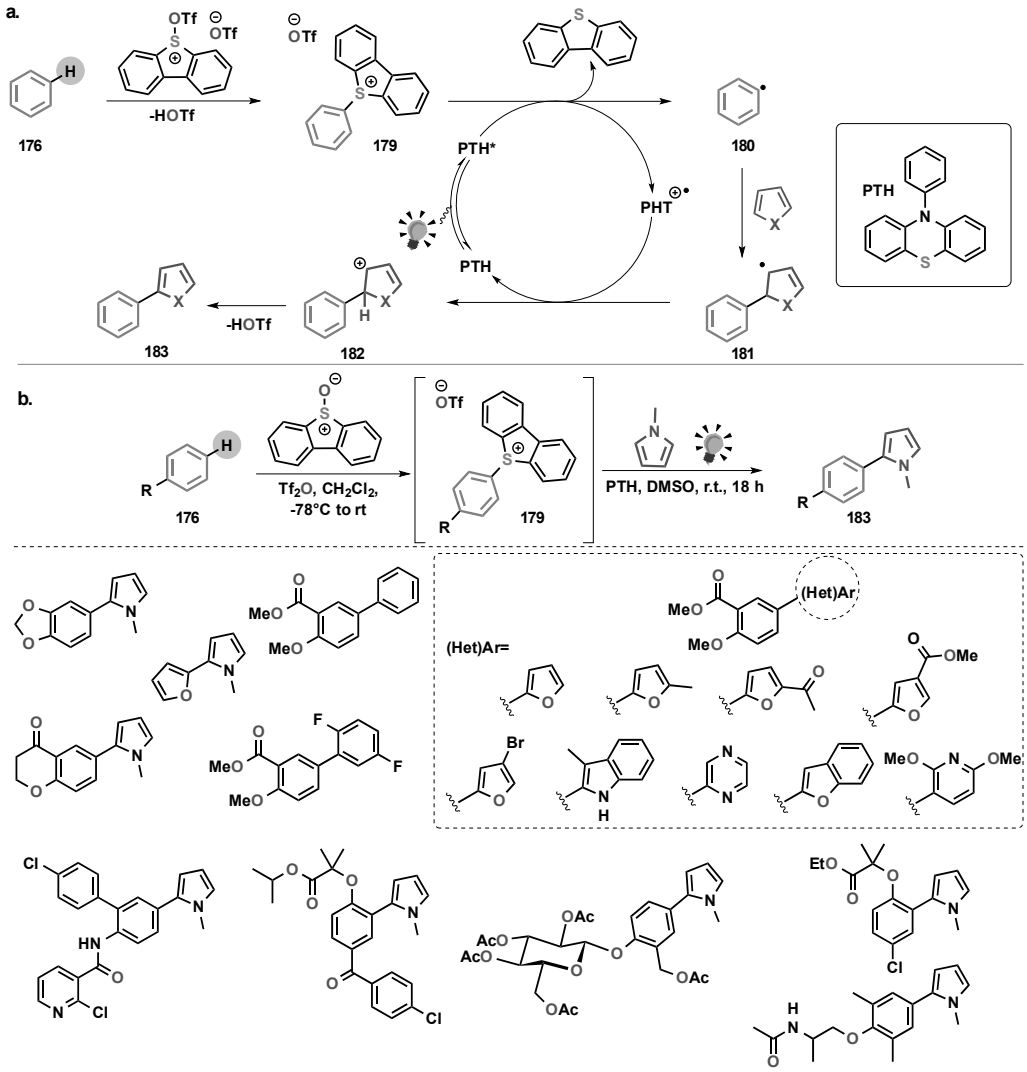
An outstanding achievement was recently described by the group of Procter,[65] as they developed a metal-free cross-coupling reaction of arenes using sulfoniums as the reagents and sulfides as the leaving groups; however the main advantage and difference with Ritter's developments is that, in this case, the authors used an organic molecule as the photocatalyst. The mechanism as well as the oxygen heterocycles obtained are shown in Scheme 44. The aromatic **176** reacts with the sulfonium to produce a new sulfonium salt **179**, as discussed in several previous examples. The sulfonium salt **179** suffers fragmentation by action of the exited photocatalyst, thus producing the radical **180**, which couples with an aromatic to produce the new radical **181** that transforms into **183** through the cationic intermediate **182**.

6.2. Functionalizations by electrophilic activation or direct coupling

In Scheme 39, we showed a reaction in which a sulfonium salt produced by the activation of a sulfoxide reacts with a nucleophilic alkene, and this sulfonium interacts with a metal catalyst to produce an organometallic species that participates in cross-coupling reactions. The ArTT and ArTFT **177** that we showed in the last section might participate in the same type of reactions.[66] Therefore, these salts will interact with a metallic species inducing cross-coupling. The use of morpholine and other nitrogen nucleophiles allows the synthesis of substituted oxygen heterocycles **184** (Scheme 45). TT has also been used in the functionalization of alkenes, including functionalized oxygen heterocycles.[67]

The formation of new sulfonium salts by the interaction of a sulfonium with aromatic nucleophiles was studied by Alcarazo and coworkers[68] They showed the use of dibenzothiophene (DBT) in the synthesis of several sulfonium salts, and this transformation can be seen as the functionalization but also as the activation of a specific position in the aromatic for further reactions with electrophiles. The reaction of sulfoniums as

electrophiles was discussed during this chapter, mostly in cyclization reactions; nevertheless, the reactions with cyclic compounds as nucleophiles are also known, and functionalizations of oxygen heterocycles have been achieved.

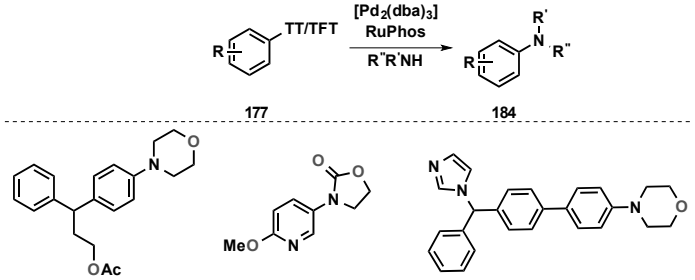


Scheme 44. Photocatalytic cross-coupling using sulfoniums.

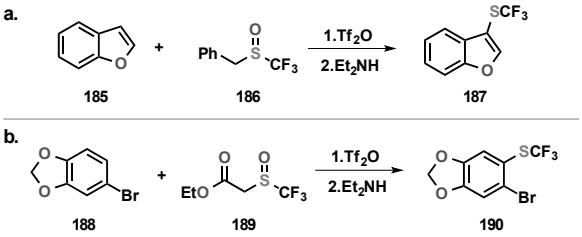
Very recently Ritter and coworkers[69] also used DBT in the formation of sulfonium salts and subsequent fluorination with ^{18}F. Unfortunately, this transformation was not applied to oxygen heterocycles.

It should be clear by now that sulfoniums have two different applications; they might act as sources of small electrophiles (*e.g.* CN, CF_3) or as activators of specific aromatic positions for the reaction with nucleophiles. In that context, Procter and coworkers[70] achieved a trifluoromethylthiolation of aromatics with excellent results and showed a great substrate scope. Scheme 46 shows the general reaction exemplified with two oxygen heterocycles, **185** and **188**. The authors used the sulfoxides **186** and **189** to generate the

sulfoniums *in situ*, and the aromatics acted as nucleophiles substituting the triflate group. The role of the diethylamine is to react as a nucleophile with one of the substituents to produce the trifluoromethyl sulfides. The choice of sulfoxides **185** and **188** is made to generate more reactive (electrophilic) positions, thus increasing the chemoselectivity in the reaction with the amine.

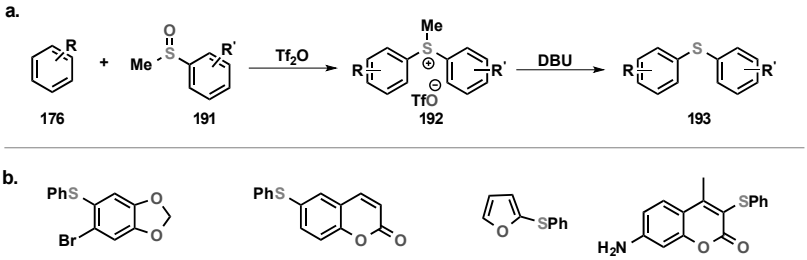


Scheme 45. Metal catalyzed amination of sulfoniums.



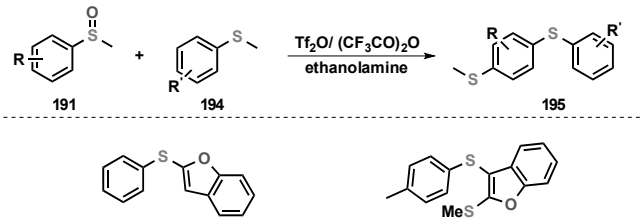
Scheme 46. Trifluormethylthiolation mediated by sulfonium salts.

When one of the sulfonium substituents is an aromatic, it may have conjugate additions, as we discussed previously (aromatic Pummerer reaction). However, reactions on the electrophilic sulfur are also possible. The final reactivity is dependent of the sulfonium substituents and the used nucleophile. Two examples are presented. The first one was reported by Procter and coworkers[71] in 2016, and it is based on the reactivity on the sulfur atom with aromatics **176** as nucleophiles. The activation of the sulfoxide **191** with triflic anhydride will generate a sulfonium, which reacts with the aromatic to yield sulfonium **192**. This sulfonium, upon treatment with DBU, produces sulfide **193** (Scheme 47).



Scheme 47. Synthesis of sulfides mediated by sulfonium salts.

Finally, we want to present the work of Yorimitsu and coworkers[72] since they used an aromatic Pummerer reaction in order to obtain sulfides. The sulfoxides **191** are activated by a mixture of triflic and trifluoroacetic anhydride; the sulfonium reacts with the sulfide **194**, which acts as the nucleophile. The steric hindrance exclusively produces the *para*-substituted aromatic, and presumably, the ethanol amine serves to trap the electrophilic methyl group (Scheme 48).



Scheme 48. Reductive metal-free coupling of sulfur derivatives.

7. Conclusion

In summary, we have presented and discussed the major uses of sulfoniums salts in the synthesis and functionalization of oxygen heterocyclic compounds. We hope that the readers will find this chapter useful in connection with the variety of chemistry that can be performed with sulfonium salts. Likely, the near future will provide the scientific community with new developments and applications of sulfoniums, compounds that are very versatile and their chemistry is continuously growing.

Acknowledgements

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