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THE INTERRUPTED PUMMERER REACTION: DESIGN OF SULFOXIDES AND THEIR UTILITY IN ORGANIC SYNTHESIS

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Abstract – Acid anhydride-activated sulfoxides can undergo a variety of cascade reactions after reacting with nucleophiles on its sulfur atom. Originally regarded as an abnormal phenomenon that occurs under Pummerer reaction conditions, the reports of the reaction increased gradually, and research regarding sulfoxide reactivity has advanced. In recent years, the term 'interrupted Pummerer reaction' has been introduced, and the transformation has been actively incorporated into the development of new research areas. Such studies have yielded numerous valuable sulfoxides, which contribute to the precise reaction control and to the generation of practical products. Notably, the outcome of the interrupted Pummerer reaction is characteristic for each nucleophile.

CONTENTS

1. INTRODUCTION

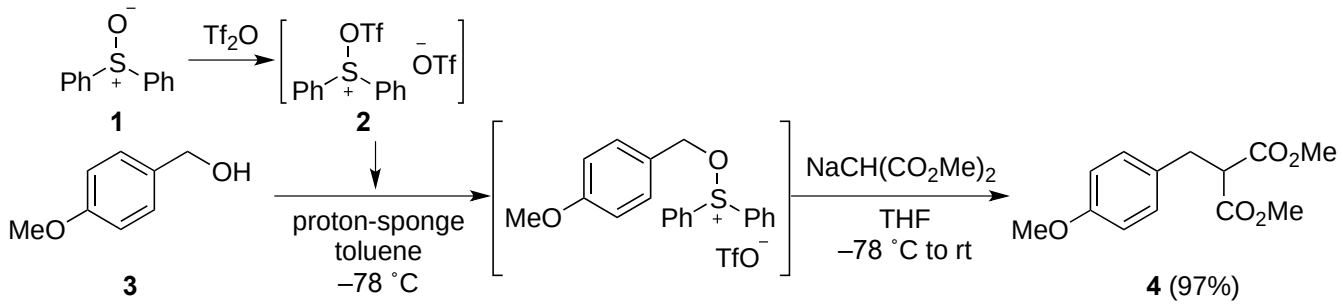
Sulfur atoms exhibit several possible valences and can exist in several forms, such as sulfanes (sulfides), sulfoxides, sulfonium salts, sulfur ylides, and sulfuranes. Therefore, detailed studies have been conducted on the physical properties and chemical reactivity of sulfur atoms, and numerous intriguing studies have been reported.[1] In addition, sulfur-containing products have attracted considerable attention as functional

materials, and have been utilized in various fields, such as polymer materials, electronic materials, pharmaceuticals, and agricultural chemicals. Sulfoxides are comprised of polarized S-O bonds and the sulfur atom is an asymmetric center, therefore, the features have elicited numerous studies.[2] In addition, sulfoxides undergo various reaction processes following activation by acid anhydrides such as TFAA and Tf_2O.[3] A particularly interesting example, namely the interrupted Pummerer reaction, involves a nucleophilic attack on the sulfur atom of the activated sulfoxide, which can be followed by various cascade reactions. Recently, vigorous research has been conducted regarding the utilization of this reaction for carbon-carbon bond formation and concise syntheses of natural products.[4] Along with those reports, excellent reviews on C-H functionalization[4c] and [3,3]-sigmatropic transition[4b,g] via interrupted Pummerer reaction, and reactivity of sulfur (IV) species[4h] have emerged, recently. Based on our unexpected findings from an interrupted Pummerer reaction in 1997, our group has been conducting research on the reaction, with the aim of expanding its generality and developing new applications.[5] In the process of the research, we realized that the type of nucleophiles is the most important factor for the determination of the reaction sequence and products.

In this review, we have classified the functionalization induced by interrupted Pummerer reaction according to the types of the nucleophile and the successive reactions.

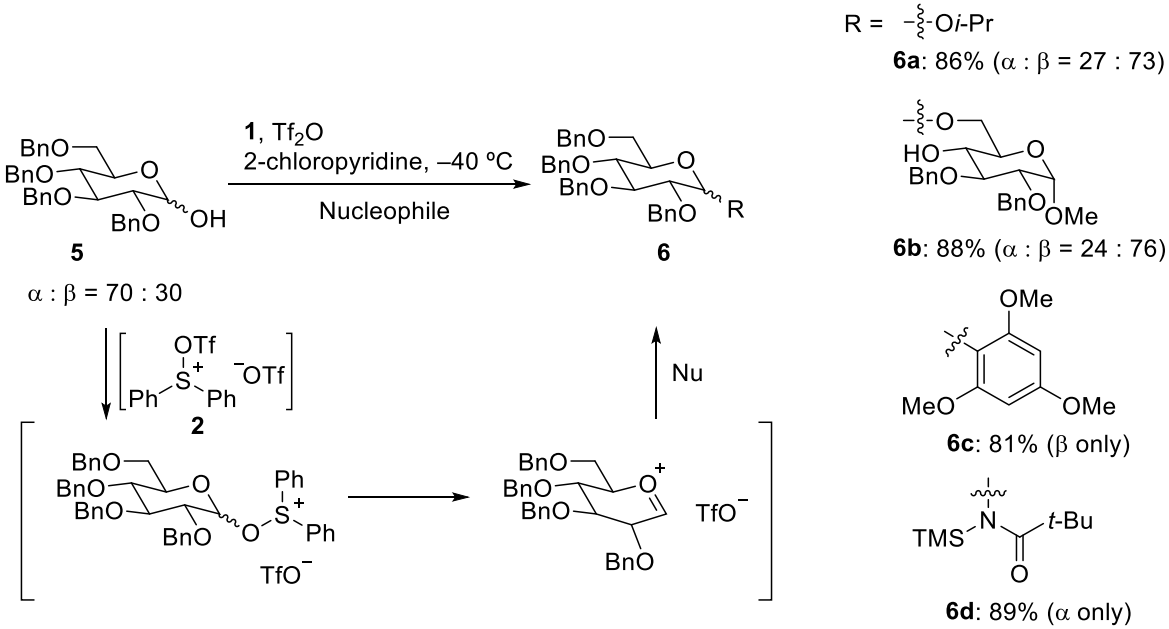
2. REACTIONS OF ALCOHOLS

The most well-known reaction of activated sulfoxide and alcohol is the Swern oxidation.[6] A hydroxy group is activated by a sulfonium salt, which is followed by elimination to afford carbonyl compounds. In Swern-type oxidations, sulfide was used as the leaving group to form the carbonyl compound. In contrast, sulfoxide moiety, generated by interrupted Pummerer reaction with sulfonium and alcohol, was used as the leaving group to install nucleophiles. Mukaiyama and coworkers developed the one-pot *C*-benzylation of sodium enolate using diphenyl sulfoxide (**1**) and Tf_2O system (Scheme 1). Benzyl alcohol **3** was activated by sulfonium species **2** in the presence of a base, and subsequent nucleophilic substitution by a sodium enolate, a soft nucleophile, delivers **4** with leaving sulfoxide moiety. Under these conditions, benzaldehyde derivatives were not obtained. The predominant formation of the *C*-alkylated product was explained by the fact that diphenyl sulfoxide is a soft leaving group.[7]



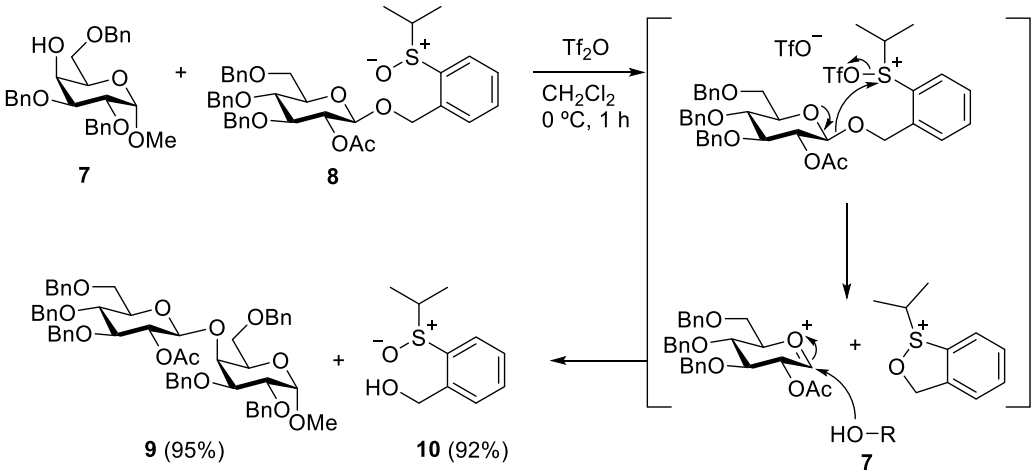
Scheme 1. Benzylation of sodium enolate mediated by sulfonium salt **2**

As a similar concept as Mukaiyama, direct glycosylation with 1-hydroxy glycosyl donor **5** using the Ph_2SO-Tf_2O system accompanying the elimination of diphenyl sulfoxide (**1**) was demonstrated by Gin (Scheme 2). This dehydrative glycosylation method involves *in situ* activation of the anomeric hydroxy group by the sulfonium salt **2**. This procedure allows for the direct preparation of a wide variety of anomeric-substituted products **6**.[8]



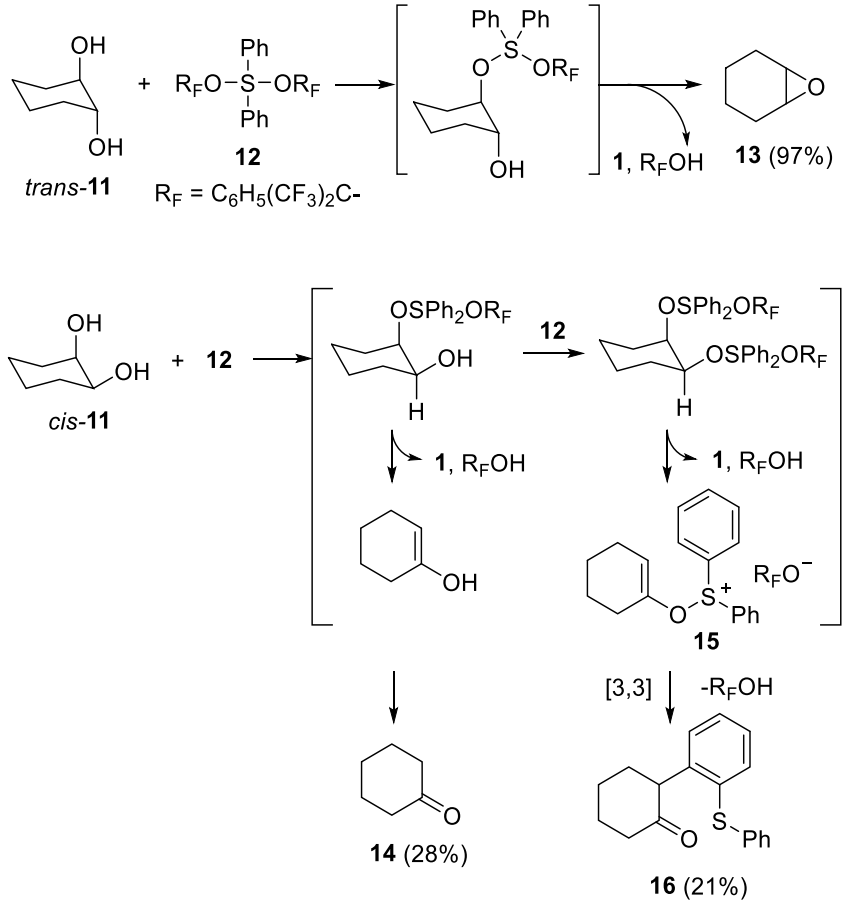
Scheme 2. Direct glycosylation with a 1-hydroxy glycosyl donor **5** using sulfonium salt **2**

As a related glycosylating method, Wan's group developed a glycosylation reaction with a novel glycosyl donor **8** bearing a 2-(2-propylsulfinyl)benzyl group as a recyclable leaving group (Scheme 3). Sulfoxide **8** was activated by Tf_2O and left from saccharide moiety. The following coupling with **7** gave disaccharide **9** and sulfoxide **10** in excellent yields.[9]



Scheme 3. Glycosylation utilizing recyclable sulfoxide moiety linked donor **8**

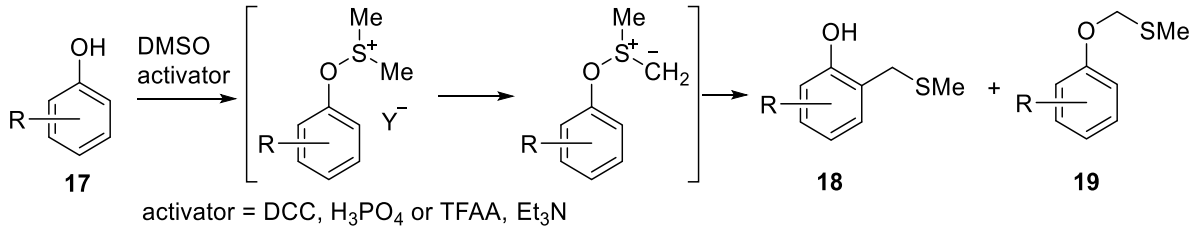
In 1974, Martin reported the reaction of diaryldialkoxysulfurane **12** towards cyclohexane-1,2-diols **11** (Scheme 4). The diol *trans*-**11** gave cyclohexene oxide (**13**) in 97% yield by the intramolecular nucleophilic substitution of alcohol with eliminating diphenyl sulfoxide (**1**). However, the diol *cis*-**11** produced cyclohexanone (**14**) by the elimination of **1** and 2-(2-thiophenyl)cyclohexanone (**16**) via the sigmatropic rearrangement of intermediate **15**.[10]



Scheme 4. Reactions of diaryldialkoxysulfurane (Martin's sulfurane: **12**) and diols **11**

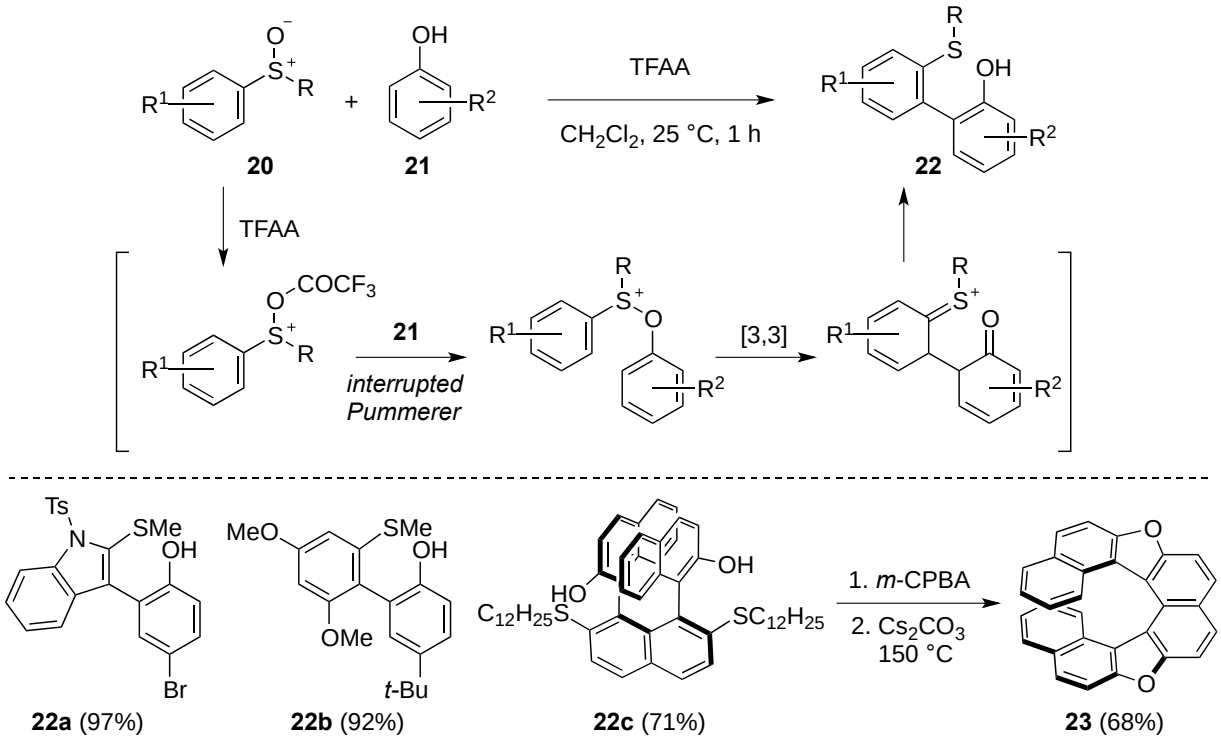
3. REACTIONS OF PHENOLS

In the reaction with phenols, sulfonium was used to functionalize the *ortho*-position of phenol through aryloxysulfonium species by combination with continuous reactions such as sigmatropic rearrangement or nucleophilic substitution. The reaction of activated DMSO with substituted phenols **17** produced *o*-methylthiomethylated products **18** by Sommlet-Hauser-type rearrangement, along with hemithioacetals **19** (Scheme 5).[11]



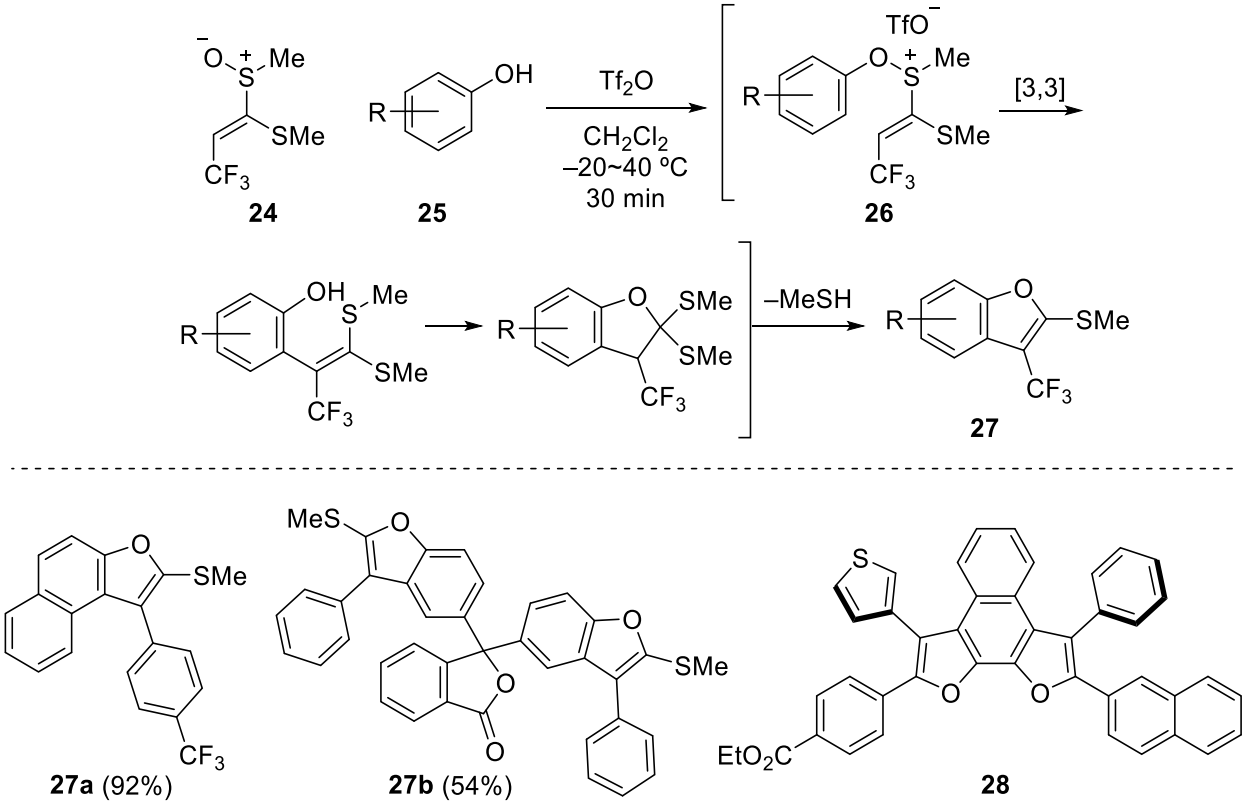
Scheme 5. *ortho*-Methylthiomethylation of phenols **17** reported by Moffatt

As the sequence of interrupted Pummerer reaction-[3,3]-sigmatropic rearrangement, the biaryl coupling of aryl sulfoxides **20** and phenols **21** has been reported by Yorimitsu and Osuka (Scheme 6).[12] By the activation of aryl sulfoxides **20** with TFAA, interrupted Pummerer reaction and [3,3]-sigmatropic rearrangement were proceeded to give biaryls **22**. Coupling reactions between heteroaromatic sulfoxides and substituted phenols or naphthols proceeded in high yields. The coupling product **22c** was transformed into a helicene derivative **23**.



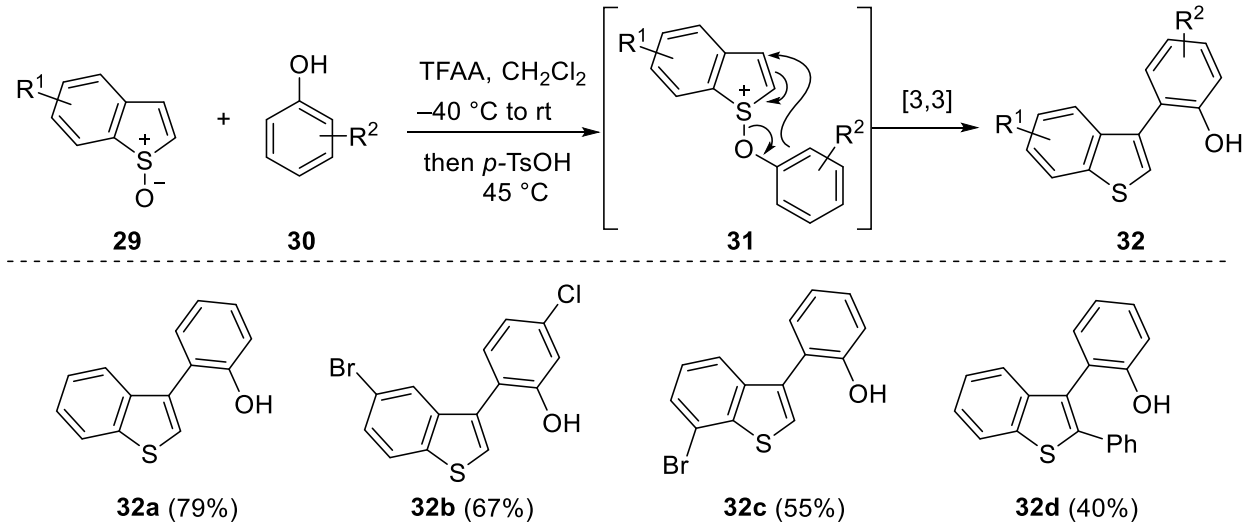
Scheme 6. Biaryl coupling via interrupted Pummerer-sigmatropic rearrangement reactions sequence

They also reported that the treatment of CF_3-substituted ketene dithioacetal monoxide (CF_3-KDM) **24** with Tf_2O and phenols **25** afforded benzofurans **27** through *ortho*-functionalized phenol, involving the sequential [3,3]-sigmatropic rearrangement of sulfonium salts **26** (Scheme 7). With the addition of TFAA as a mild activator at ambient temperature, a variety of KDMs provided a practical and diversity-oriented route to multi-substituted benzofurans. They additionally reported that the 2-methylthio moiety in benzofurans could be applied to Pd- or Ni-catalyzed cross-coupling reactions with aryl magnesium or zinc reagents to give multi-substituted benzofurans **28**.[13] Repeating their sequential strategy after oxidizing sulfide moiety of the product realized the synthesis of oligoarenes.[14] In addition, this strategy was applied to C-F arylation of polyfluorophenols.[15]



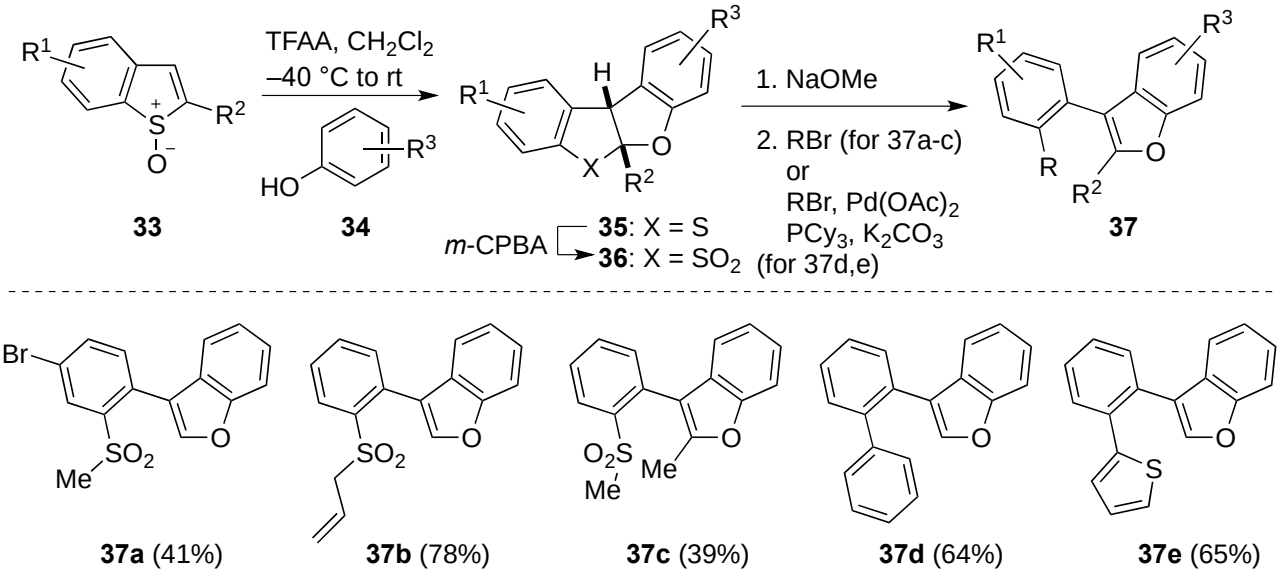
Scheme 7. Benzofuran formation from ketene dithioacetal monoxide **24** and phenols **25**

Procter reported that the reaction of benzothiophene *S*-oxides **29** with TFAA triggered an interrupted Pummerer reaction with phenols **30** to provide the corresponding intermediates **31** (Scheme 8). Consequent charge accelerated [3,3]-sigmatropic rearrangement of **31** placed the phenols at the C3-position of benzothiophenes to deliver **32** with complete regioselectivity.[16]



Scheme 8. Construction of C3 aryl-benzothiophene from benzothiophene *S*-oxides **29** with phenols **30**

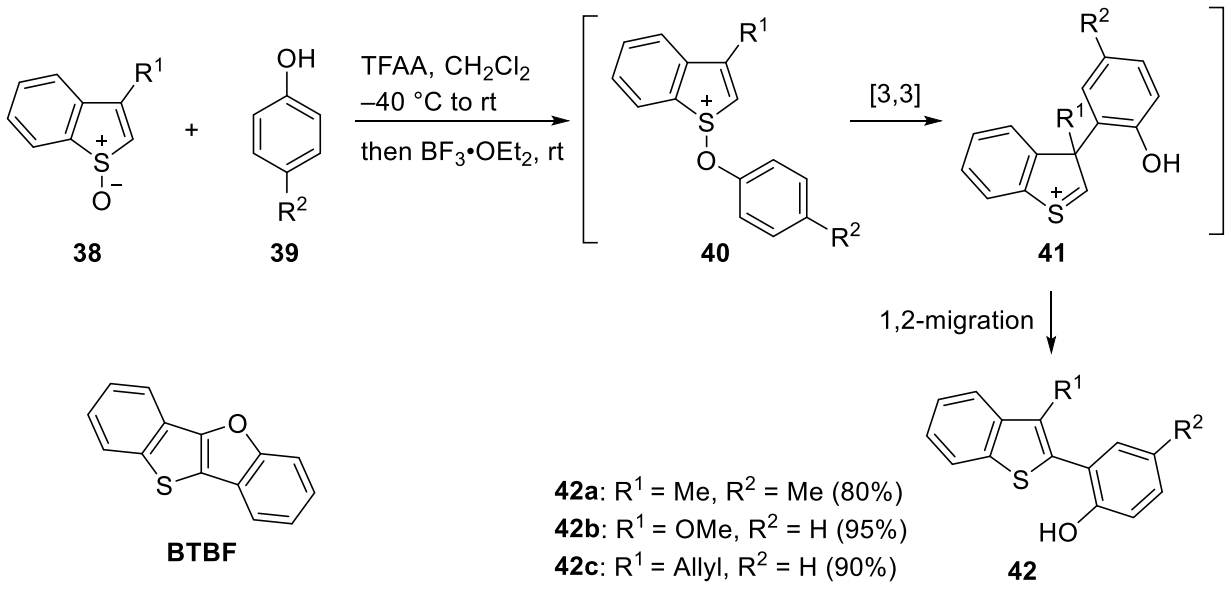
In the case of 2-substituted benzothiophene *S*-oxides **33**, the reaction of activated **33** and phenols **34** proceeded by the combination with [3,3]-sigmatropic rearrangement and subsequent cyclization of *ortho*-substituted phenols to form *S,O*-acetals **35** (Scheme 9). The successive oxidation of **35** provided the corresponding sulfones **36**, which were cleaved with the treatment of base to rearomatize to a benzofuran scaffolds. Thus, the generated sulfinate motif was transformed with alkyl halides, or by Pd-catalyzed desulfinative coupling with aryl bromides, to produce various C3-arylated benzofurans **37**.[17]



Scheme 9. Transformation from 2-substituted benzothiophene *S*-oxides **33** to 3-aryl-benzofurans **37**

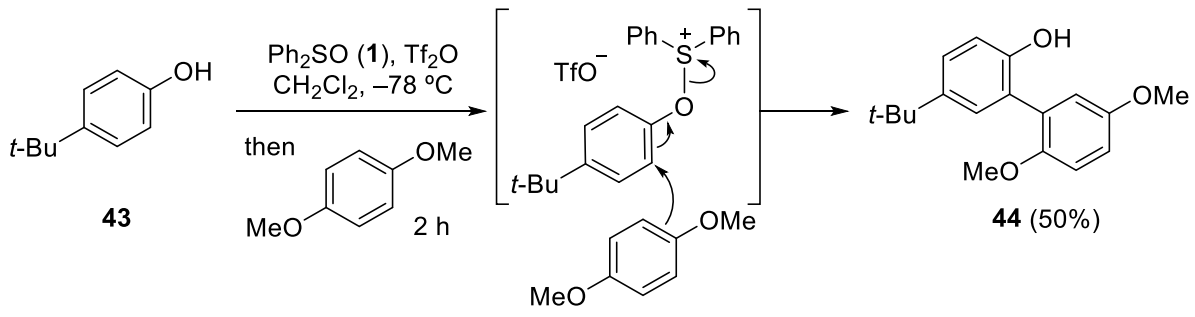
When 3-substituted benzothiophene *S*-oxides **38** was used, the cascade reaction, contains three reactions, occurred as follows (Scheme 10). As the first step, the activation of 3-substituted benzothiophene

S-oxides **38** caused an interrupted Pummerer reaction with the phenol derivatives **39** to yield sulfonium intermediates **40**. With a lack of aromaticity, [3,3]-sigmatropic rearrangement proceeded as the second step, placing the phenols at the C3 position. As the third step [1,2]-migration of the generated benzothiophenium intermediates **41** was assisted by $BF_3 \cdot OEt_2$ afforded *ortho*-substituted phenols **42**. They additionally synthesized BTBF upon heating **42b** under acidic conditions, which is the oxygen derivative of BTBT, a key component of OLEDs.[18]



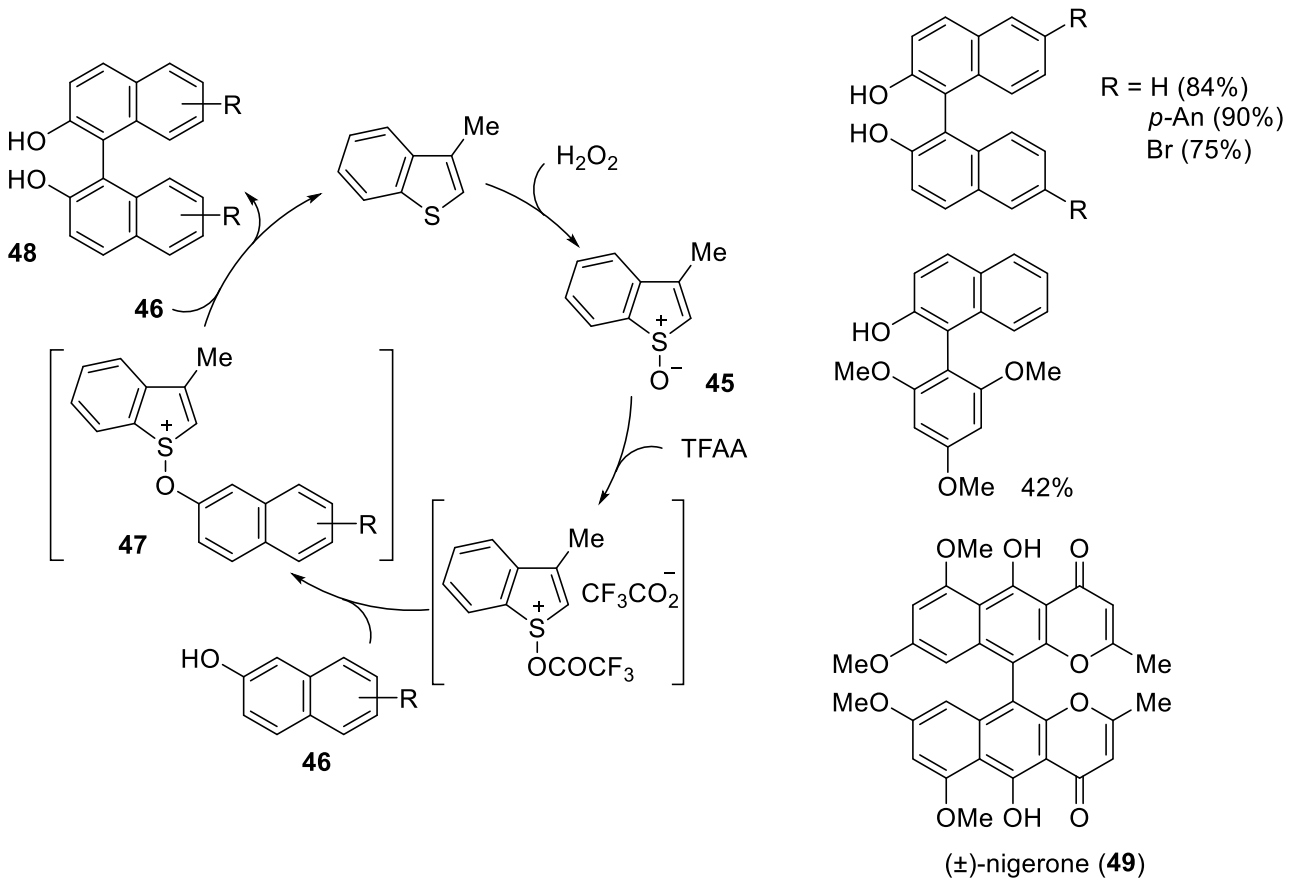
Scheme 10. Interrupted Pummerer/sigmatropic rearrangement/migration cascade

The sulfonium mediated coupling reaction utilized the elimination of sulfide was achieved by the interrupted Pummerer reaction-nucleophilic substitution sequence. The intermolecular coupling reaction of phenols or electron-rich arenes was studied using **1** and Tf_2O system. The reaction of 4-*tert*-butylphenol (**43**) with the electron-rich nucleophile such as dimethoxybenzene afforded the cross-coupled biaryl **44**, involving the elimination of diphenyl sulfide as the leaving group (Scheme 11).[19]



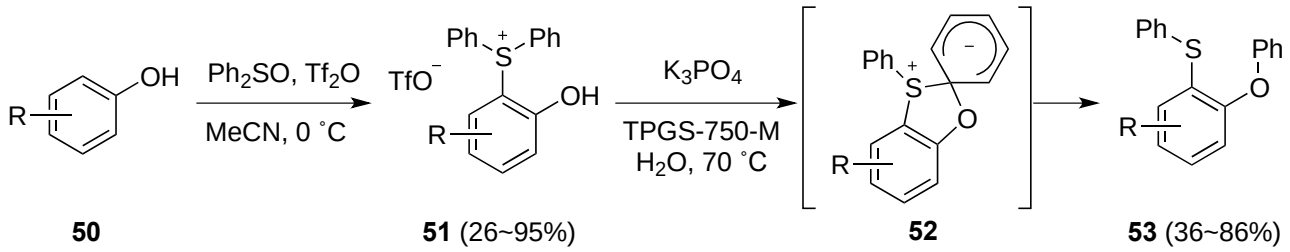
Scheme 11. Biaryl coupling reaction of phenol **43** and electron-rich arene

The catalytic system by re-oxidation of generated sulfide has been developed. 3-Methylbenzothiophene *S*-oxide (**45**) catalyzed the oxidative coupling of 2-naphthols **46** (Scheme 12). Naphthoxysulfonium intermediates **47** was formed by an interrupted Pummerer reaction. Thus, another equivalent of naphthols **46** engaged with **47** to produce BINOLs **48** and eliminate 3-methylbenzothiophene, which was re-oxidized with H_2O_2-TFA. This method was applied to the synthesis of (±)-nigerone (**49**), a compound exhibiting antitumor and antibacterial activities.[20] Utilizing this concept, oxidative cross-coupling of phenols and various nucleophilic partners, including phenols, 1,3-diketones, and arenes has been reported through phenoxysulfonium intermediates with non-catalytic system.[21]



Scheme 12. Sulfoxide-catalyzed oxidative coupling of 2-naphthols **46**

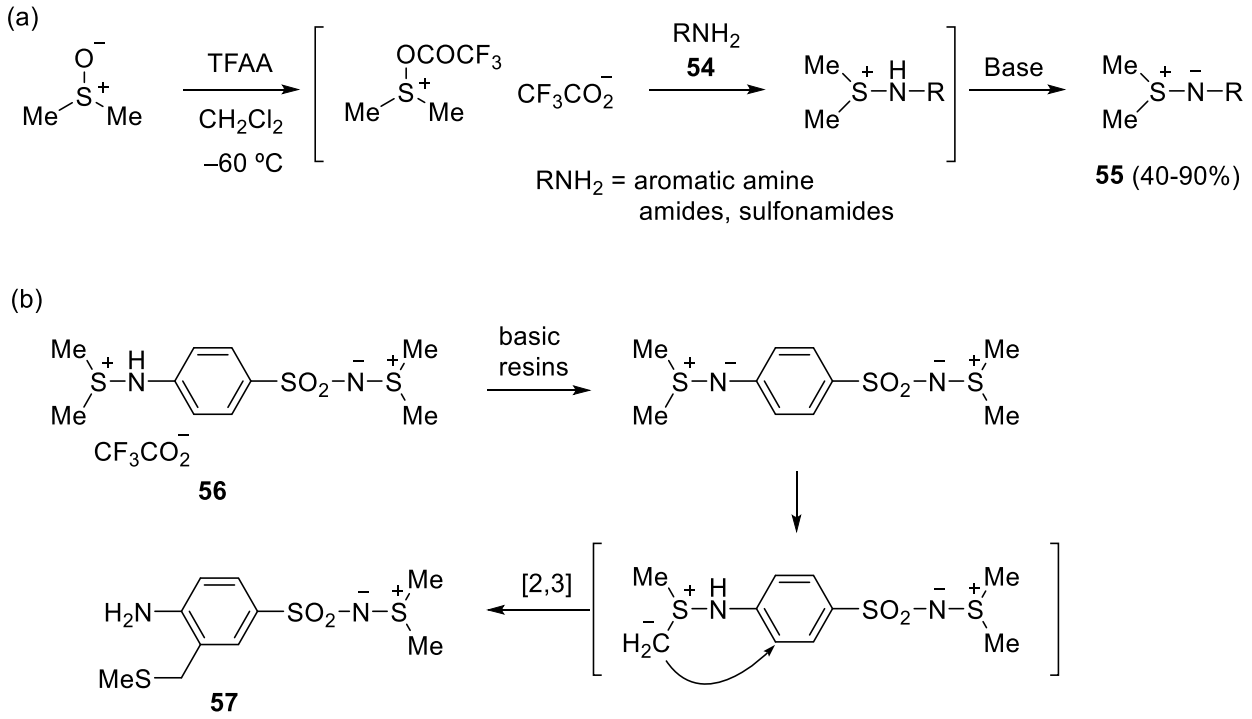
Another example of the phenol functionalization is reported by Huang et al. They identified that the reaction between activated sulfonium salts and phenols **50** in acetonitrile produced *o*-hydroxyarylsulfonium salts **51** (Scheme 13). Treatment of **51** with the base under aqueous micellar conditions containing a surfactant, produced **53** by Smiles rearrangement of **52**.[22]



Scheme 13. Difunctionalization of phenols **50** via *ortho*-sulfonium salt **51**

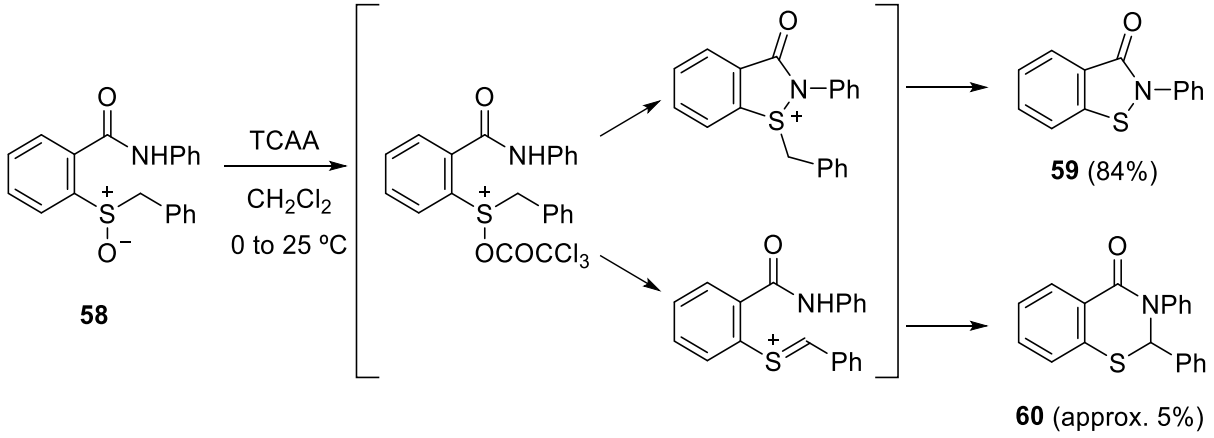
4. REACTIONS OF AMINES AND NITRILES

In the reactions with amines and nitriles, various reactions triggered by N-S bond formation have been reported. In 1975, Swern reported that activated DMSO reacted with amines **54** to give iminosulfuranes **55** (Scheme 14a). Moreover, compound **56**, prepared from a sulfanilamide, was partially transformed to aniline **57** by successive Sommlet-Hauser rearrangement, following treatment with basic resins (Scheme 14b).[23]



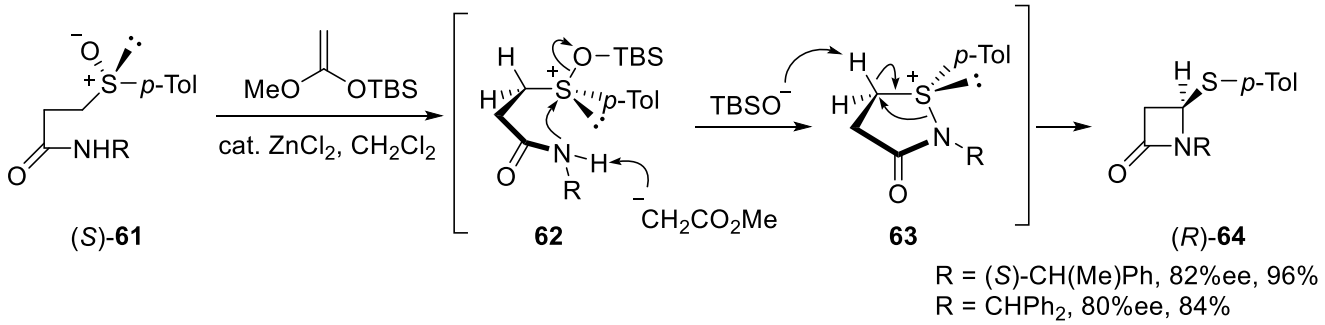
Scheme 14. (a) Conversion of DMSO to iminosulfurane **55**; (b) transformation of iminosulfurane to *ortho*-functionalized aniline **57**

Wright reported that the treatment of 2-(benzylsulfinyl)benzanilide **58** with trichloroacetic anhydride (TCAA) afforded *N*-phenylbenzisothiazolone **59** in 84% yield along with benzyl trichloroacetate. In this reaction, the Pummerer cyclized product **60** was isolated in trace amounts (Scheme 15).[24]



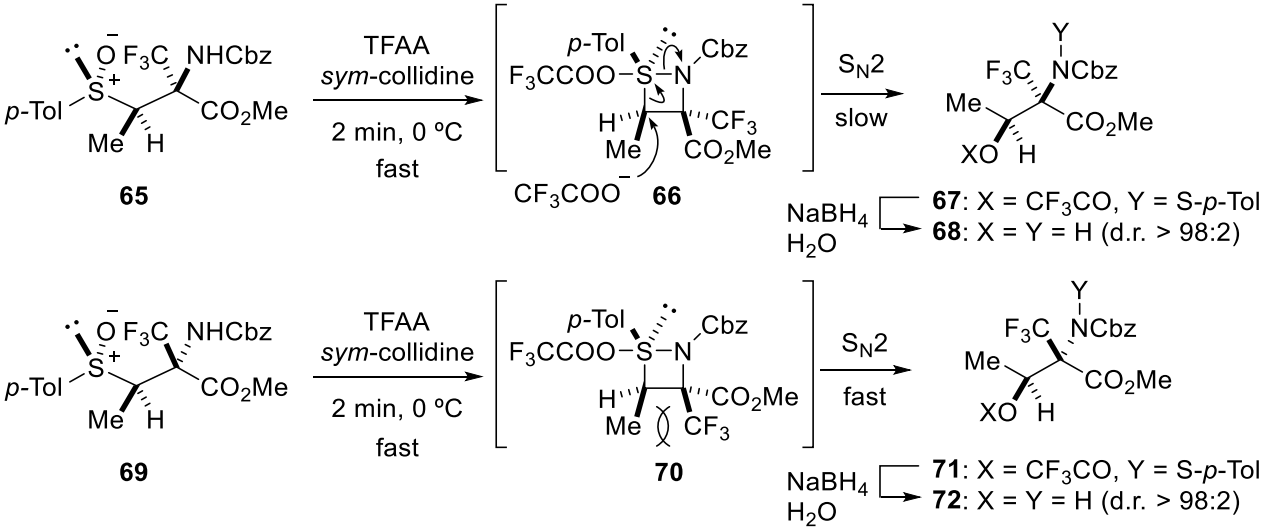
Scheme 15. Construction of benzisothiazolone **59** by intramolecular N-S bond formation

Kita reported that chiral sulfoxides, bearing an achiral amide group, gave β-lactams with high ee's under silicon-induced Pummerer conditions (Scheme 16).[25a] Sulfoxides (*S*)-**61** were transformed into intermediates **62**, which yielded chiral pseudo-isothiazolones **63**[25b] via axial attack by the amide anion. Successively, the rearrangement of amide moiety driven by N-S bond cleavage gave the β-lactams (*R*)-**64**.



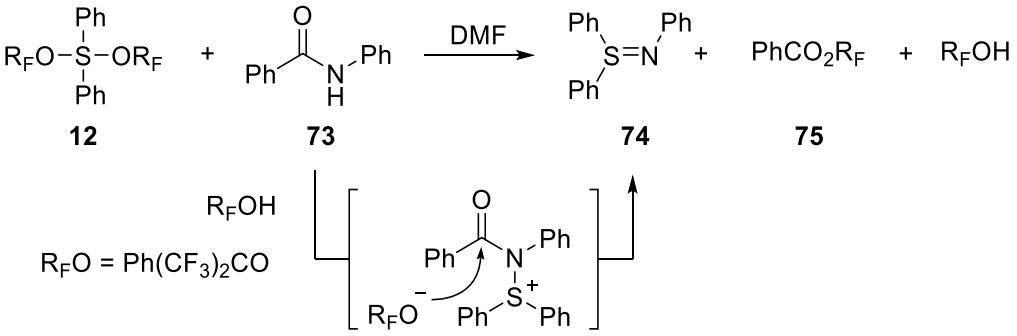
Scheme 16. β-Lactam formation by rearrangement of pseudo-isothiazolone **63** by asymmetric Pummerer reaction

The reactions of β-sulfinyl amine diastereomers **65** and **69** with TFAA were studied briefly by Zanda and coworkers (Scheme 17). X-Ray analyses of the products suggested that the S_N2 reaction of the trifluoroacetate anion occurred at the α-position of the sulfur atom in sulfurane intermediates **66** and **70**. In addition, the presence of the four-membered cyclic σ-sulfurane **66** was detected by NMR spectroscopy in the reaction of diastereomer **65**. The reaction rate of the other diastereomer **69** was faster than that of **65** owing to increased steric repulsion occurring in sulfurane intermediate **70**.[26]



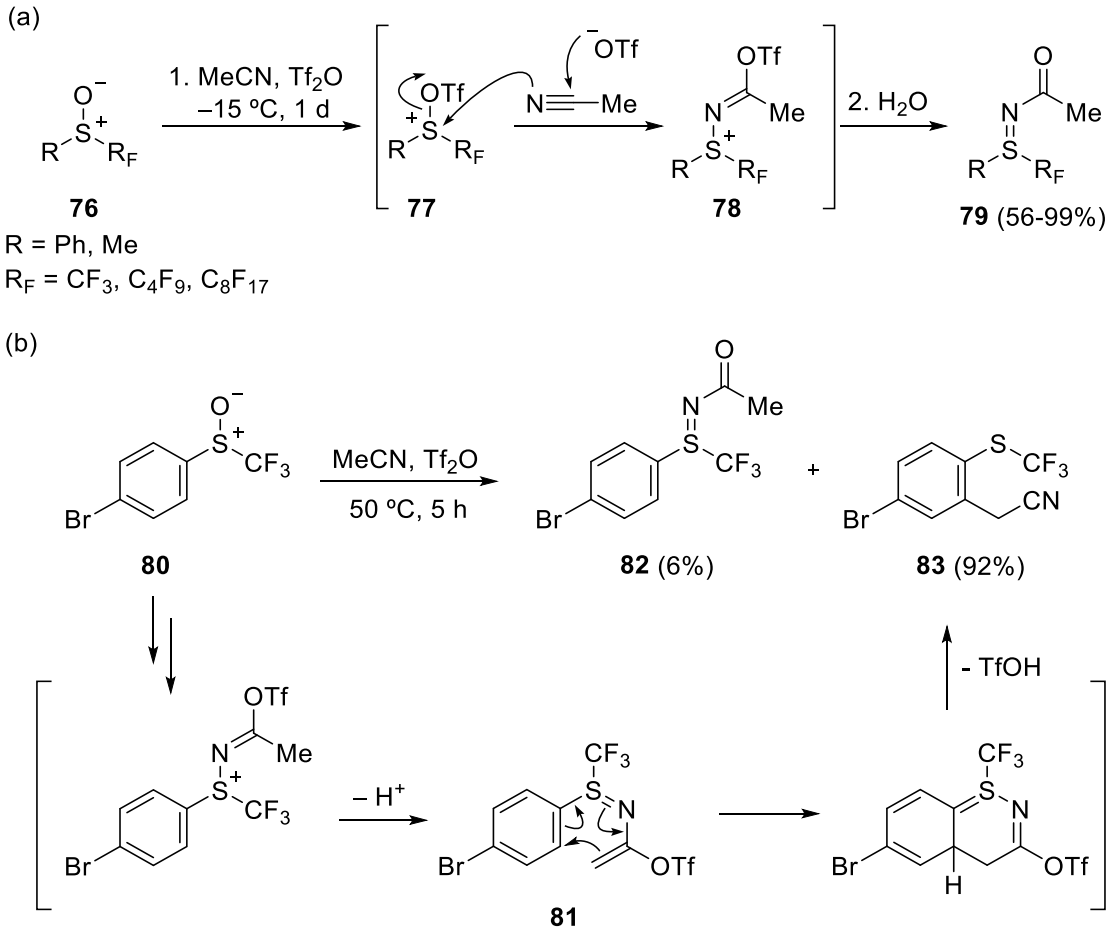
Scheme 17. Competition of reactivity between β-amino sulfoxide diastereomers under Pummerer reaction conditions

The reaction of diphenyldialkoxysulfurane **12** with secondary amide **73** resulted in cleavage of the amide moiety at room temperature to give sulfilimine **74** and benzoate **75** (Scheme 18). In the reaction of **12** with a tertiary amide, DMF, used as the solvent, remained intact.[27]



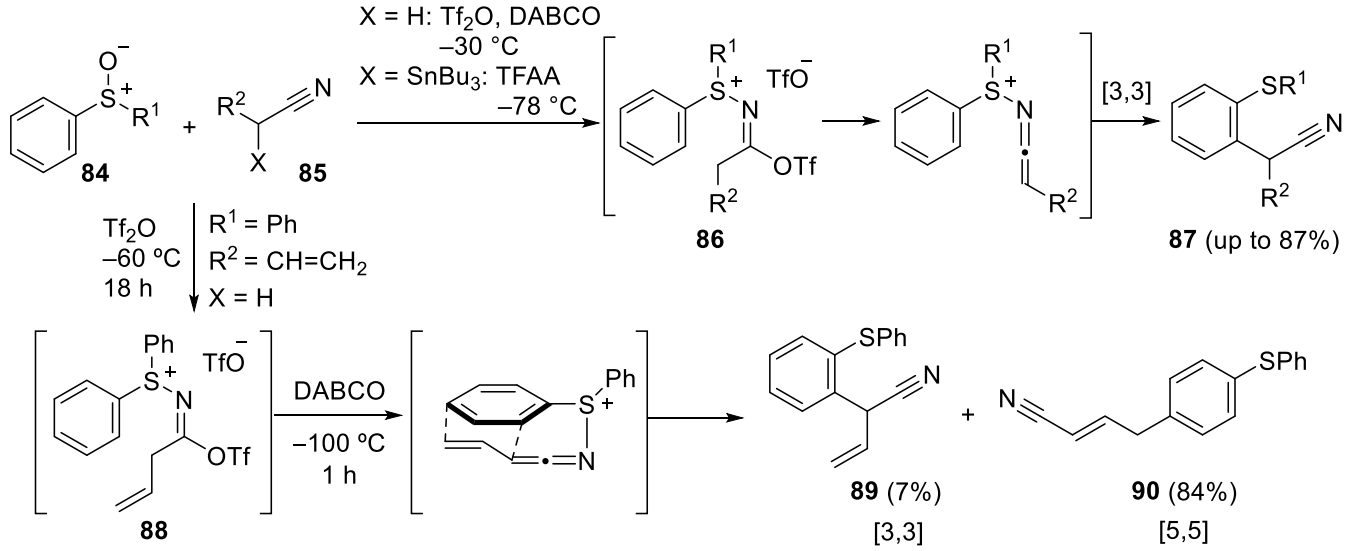
Scheme 18. Cleavage of secondary amide **73** into sulfilimine **74** and benzoate **75**

Magnier developed the preparation of perfluoroalkylated sulfilimines **79** from activated perfluoroalkylated sulfoxides **76** and nitriles (Scheme 19a). The nitrogen atom of nitrile attacks the sulfur of sulfonium **77** to form the triflic imide intermediate **78**. Consequently, the hydrolysis produced sulfilimines **79** in good yields.[28] Additionally, they discovered that the use of aryl sulfoxide **80** at higher temperatures resulted in the electrocyclization of sulfilimino keteneacetal **81** to generate (perfluoroalkylsulfanyl)phenylacetonitrile **83** in good yields with a small amount of sulfilimine **82** (Scheme 19b).[29]



Scheme 19. Sulfilimine formation from nitriles and reactions thereof

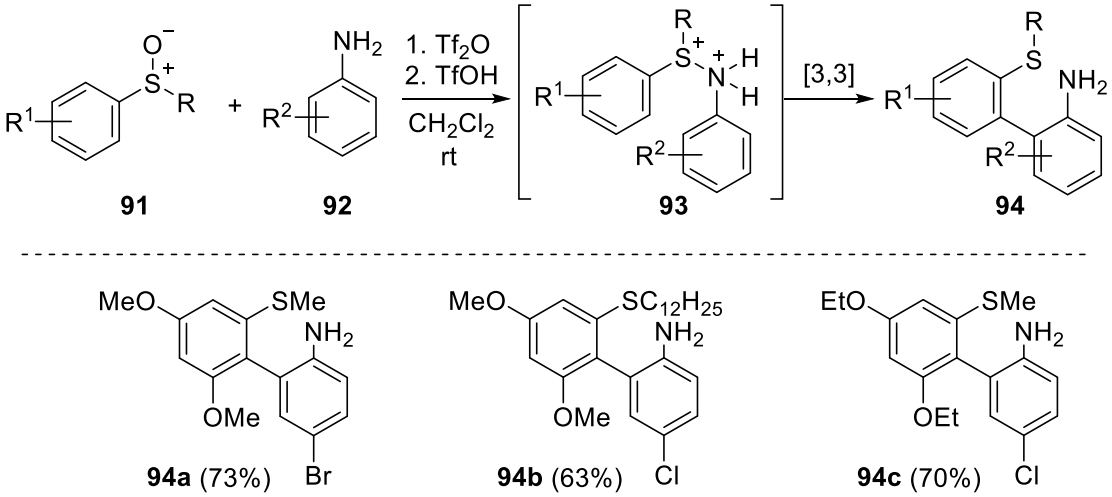
Peng and Wang reported the α-arylation of alkyl nitriles **85** with aryl sulfoxides **84** (Scheme 20). ^{1}H-NMR spectroscopy and DFT calculations revealed that the reaction pathway involved E1cB elimination from



Scheme 20. [3,3]- and [5,5]-sigmatropic rearrangements of ketenimine sulfonium intermediate

intermediate **86** and [3,3]-sigmatropic rearrangement.[30a,c] When α-stannyl nitrile (X = $SnBu_3$) was employed, the reaction proceeded under the milder reaction conditions with TFAA.[30b] On using allyl nitrile (R^2 = vinyl), γ-arylation of allyl nitrile was occurred by [5,5]-sigmatropic rearrangement of **88** to deliver sulfide **90**.[31]

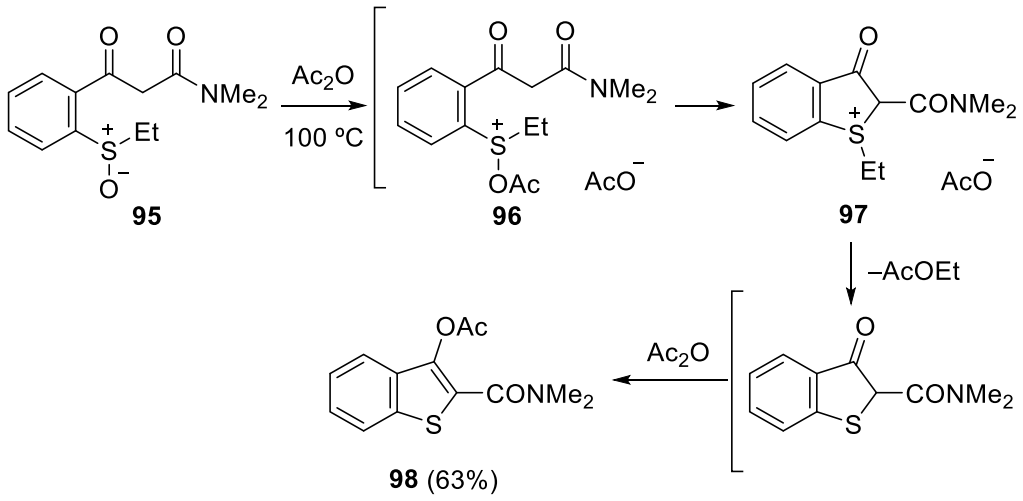
Yorimitsu reported dehydrogenative coupling of aryl sulfoxides **91** with anilines **92** by their cascade strategy of interrupted Pummerer reaction-sigmatropic rearrangement through dication intermediates **93** to provide biaryls **94** (Scheme 21).[32]



Scheme 21. Functionalization of *ortho* position of anilines **92** by cascade process

5. REACTIONS OF ENOLIZABLE KETONES

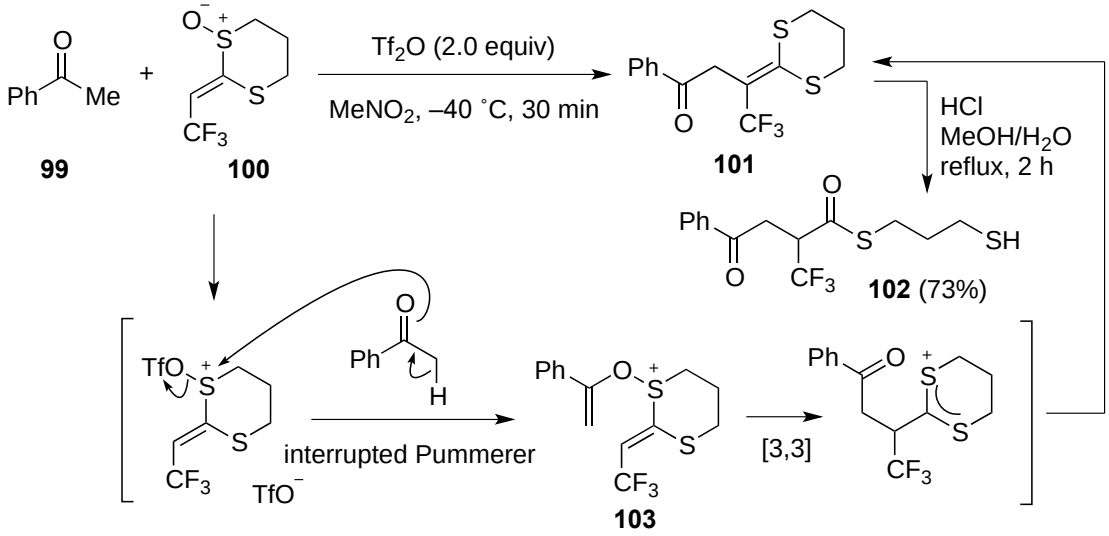
In the reaction with ketones, the attack of ketone on the sulfur atom triggered the successive reaction such as dealkylation or sigmatropic rearrangement. 3-Acetoxy-*N*,*N*-dialkylbenzo[*b*]thiophene-2-carboxamie **98** was readily obtained from sulfoxide **95** under heating in Ac_2O (Scheme 22). A plausible reaction



Scheme 22. Formation of benzo[*b*]thiophene-2-carboxamide **98** by intramolecular reaction

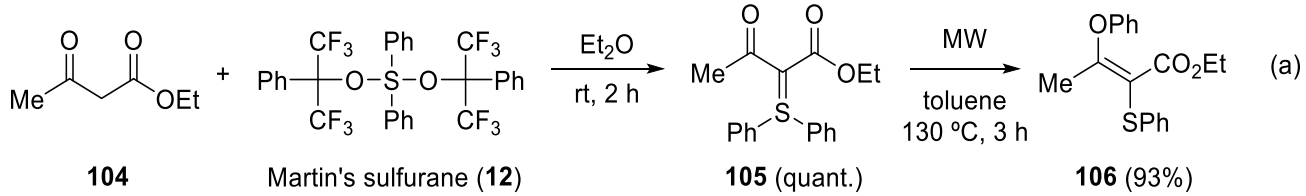
mechanism entails the interrupted Pummerer reaction of **96** and the cleavage of C_{sp3}-S bond to remove ethyl acetate from the sulfonium salt **97**.[33]

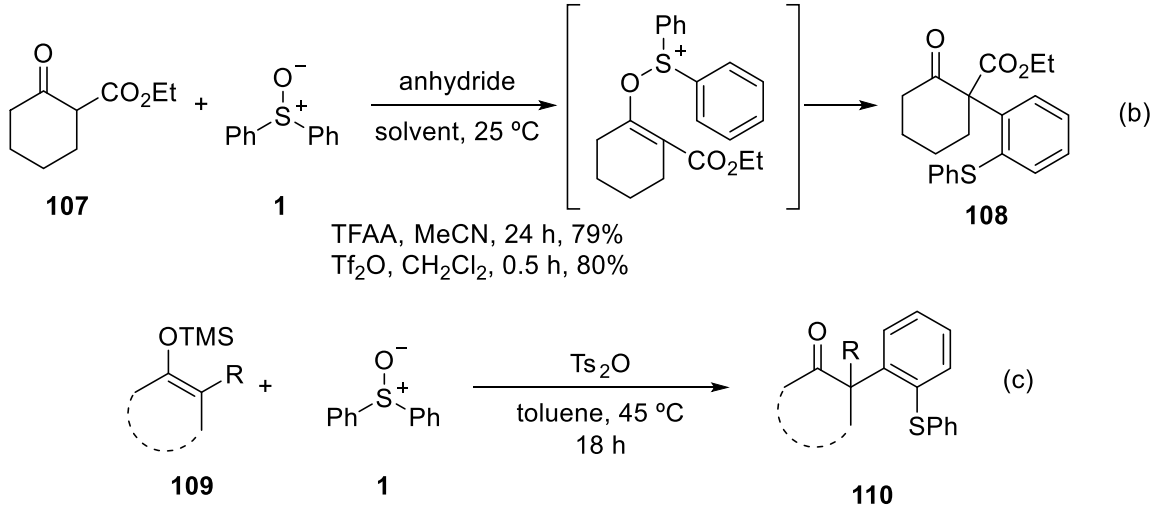
Yorimitsu and Oshima group has investigated the reaction of 2-(2,2,2-trifluoromethylidene)-1,3-dithiane monoxide (**100**) with ketone (Scheme 23). The sulfoxide **100** was activated by Tf_2O and the oxygen atom of acetophenone (**99**) executed a nucleophilic attack at the cationic sulfur atom. The resulting vinyloxysulfonium species **103** underwent [3,3]-sigmatropic rearrangement to form **101**, which upon the acidic treatment, produced thioester **102** in 73% yield. Product **102** was further transformed into 3-trifluoromethylated furan, thiophene, and pyrrole.[34]



Scheme 23. Reaction of ketene dithioacetal monoxide **100** with acetophenone (**99**)

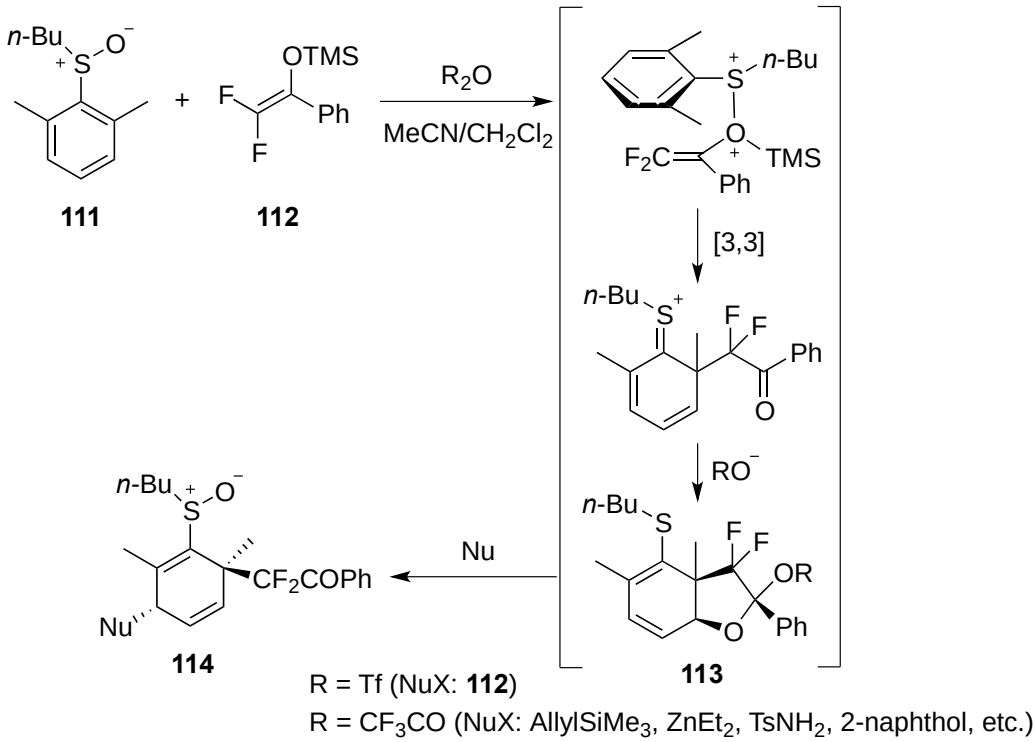
Maulide disclosed that the reaction of Martin's sulfurane (**12**) with active methylene compounds, such as **104**, provided sulfur ylide **105** in high yields. Phenyl migration from sulfur to oxygen in ylide **105** led to the formation of **106** under thermolysis conditions (Scheme 24a).[35] His group additionally developed the α-arylation of β-ketoester **107** using diphenyl sulfoxide (**1**). The complete *ortho*-selectivity of **108** arises from the nucleophilic attack of **107** at the sulfur atom and sequential [3,3]-sigmatropic rearrangement (Scheme 24b).[36] In the case of the simple carbonyl compounds, its silyl enol forms **109** proceeded the reaction with sulfoxide **1** and *p*-toluenesulfonic anhydride to generate α-arylated products **110** in moderate yields (Scheme 24c).[37]





Scheme 24. Reactions of sulfurane and active sulfonium species with carbonyl compound

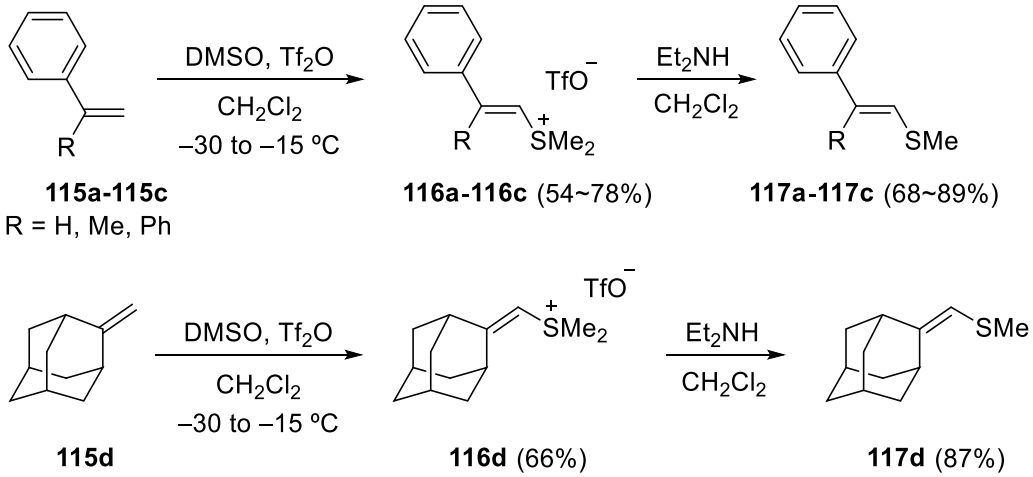
Peng reported the dearomatization of aryl sulfoxide **111** with silyl enol ether **112** by interrupted Pummerer/[3,3]-sigmatropic rearrangement/nucleophilic substitution cascade (Scheme 25).[38] The activation of **111** with acid anhydride (R_2O) induced interrupted Pummerer reaction by the attack of the oxygen atom of **112**. The following [3,3]-sigmatropic rearrangement and cyclization gave acetal **113**. When **111** was treated with Tf_2O, intermediate **113** was highly reactive to be captured by another **112** to provide **114**. On using TFAA as R_2O, the addition of external nucleophile was feasible to give **115** due to the intermediate **113** was less reactive than in the case of Tf_2O.



Scheme 25. Dearomatization and functionalization of aryl sulfoxide **111** with **112**

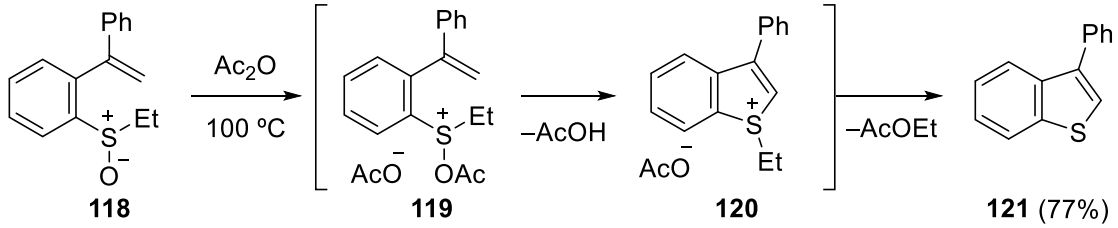
6. REACTIONS OF ALKENES AND ALKYNES

In the reactions with alkene and alkyne, sulfonium generates vinyl or allylsulfonium intermediate, which induces continuous reaction. During their studies on dimethyl sulfide ditriflate (DMSD), generated from DMSO and Tf_2O, Nenajdenko and Balenkova revealed that the reaction between DMSD and alkenes **115a-115d** produced corresponding sulfonium salts **116a-116d**. The consequent demethylation of the sulfonium salts with diethylamine delivered vinyl sulfides **117a-117d** (Scheme 26).[39]



Scheme 26. C(sp^2)-H Thiomethylations by DMSD via vinylsulfonium intermediate **116**

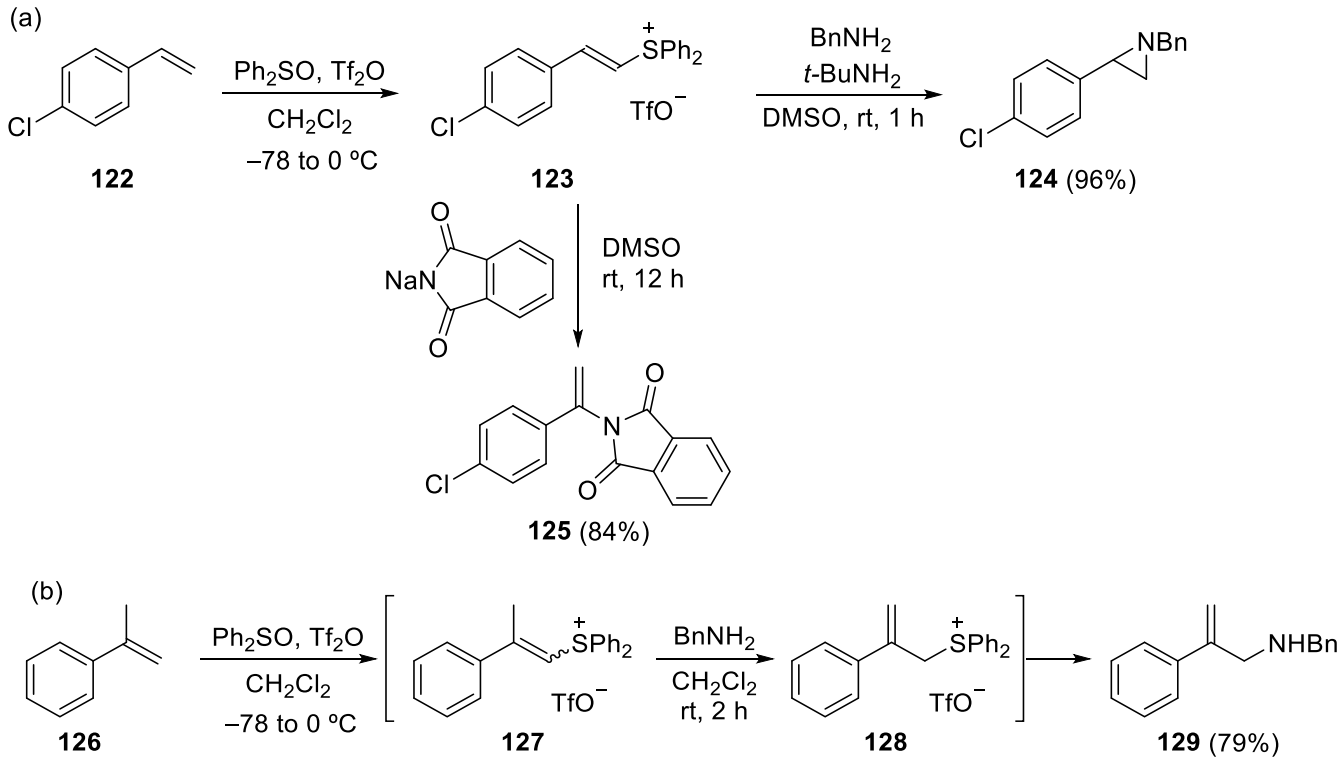
3-Arylbenzo[*b*]thiophene **121** was readily prepared from **118** under heating in Ac_2O (Scheme 27). A plausible reaction mechanism entails the interrupted Pummerer reaction of activated sulfonium intermediate **119** and the intramolecular attack of alkene moiety generated sulfonium intermediate **120**. The sequential removal of the ethyl group afforded benzothiophene **121**.[40]



Scheme 27. Formation of 3-arylbenzo[*b*]thiophene **121** by attack of alkene moiety

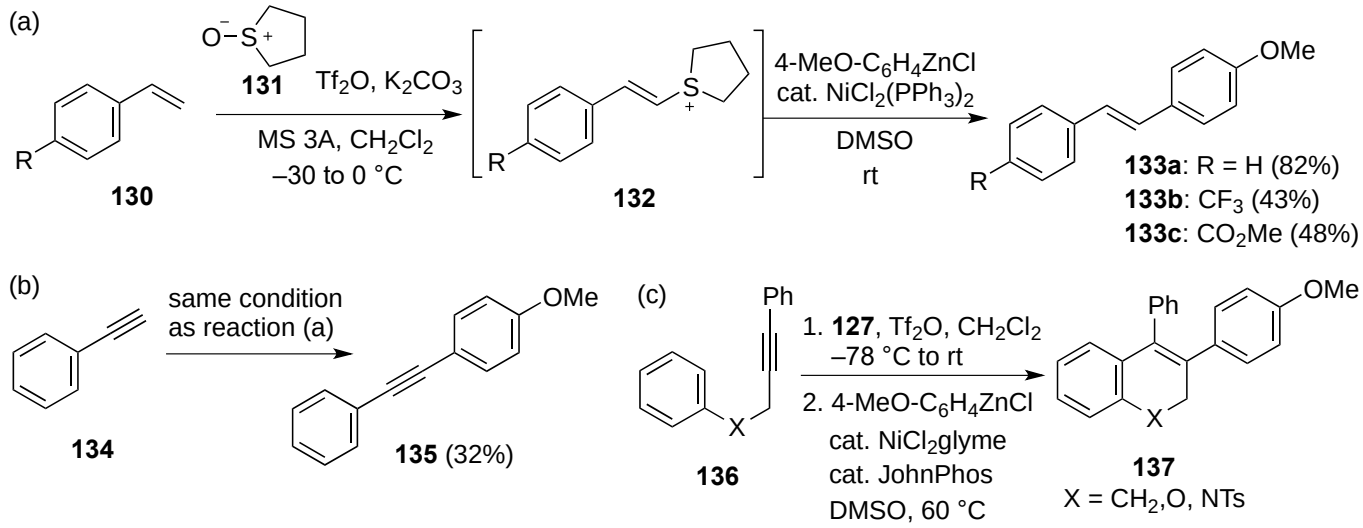
As the combination of interrupted Pummerer reaction and nucleophilic substitution, Mukaiyama et al. developed the reaction of styrene derivative **122** with diphenylsulfonium to isolate 2-arylethenyl(diphenyl)sulfonium salt **123**. The reaction of **123** with primary amine and base afforded the corresponding 2-arylaziridine **124** in high yields, while that of sodium or potassium salt of cyclic imide provided α-imidostyrene **125** (Scheme 28a). The above reaction was applied to 1,1-disubstituted alkene **126** to obtain the corresponding allyl amine **129** (Scheme 28b). The reaction mechanism involved the

formation of vinylsulfonium intermediate **127**, followed by double bond migration to allylsulfonium intermediate **128**, and nucleophilic substitution with amine.[41]



Scheme 28. Formations of vinylsulfonium salt from styrene and their transformations

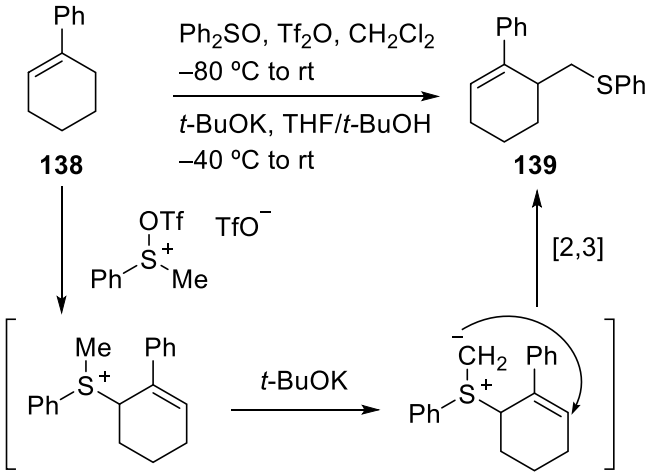
Procter revealed that C–H functionalization of alkenes **130** has been achieved by the combination of the interrupted Pummerer reaction and Negishi cross-coupling in a one-pot procedure (Scheme 29). In this reaction, sulfonium species **132**, generated from readily available sulfoxide **131** and Tf_2O, was employed as the precursor for the cross-coupling reaction (Scheme 29a). In the case of alkyne **134**, the same cascade



Scheme 29. C-H Functionalizations via sulfonium species as precursor of Ni-catalyzed coupling

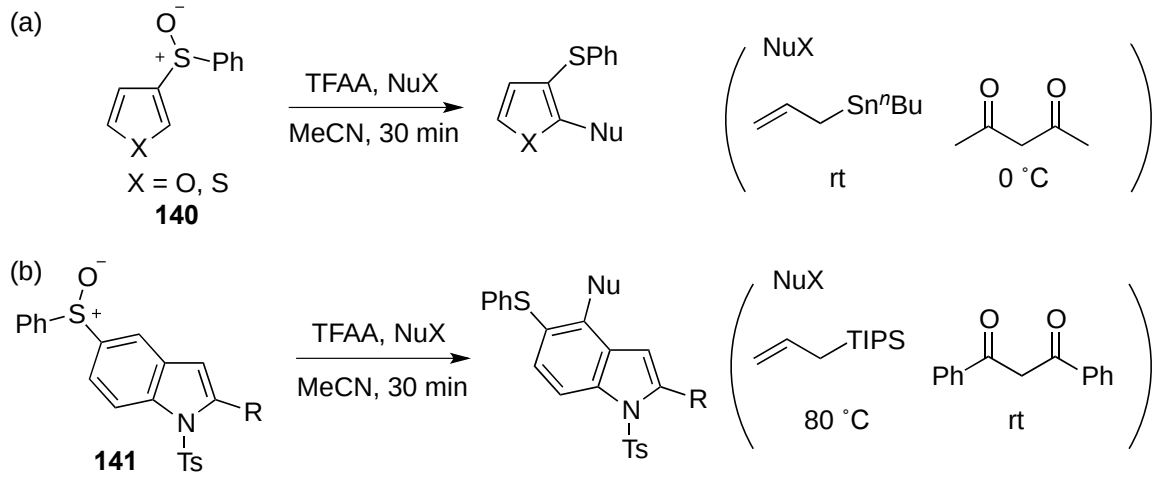
sequence proceeded on sp carbons to form internal alkyne **135** (Scheme 29b). Remarkably, the tetra-substituted alkenes **137** were achieved by incorporating the cyclization of substrates **136** into the cascade sequence (Scheme 29c).[42]

As the reaction induced by the combination with sigmatropic rearrangement, Xu and Li reported the allylic C–H alkylation of alkene **138** (Scheme 30). In this reaction process, the formation of sulfonium salt by interrupted Pummerer reaction occurred successive [2,3]-sigmatropic rearrangement in the presence of a base to give **139**. The reaction was applicable to trisubstituted and *gem*- and *vic*-disubstituted olefins.[43]



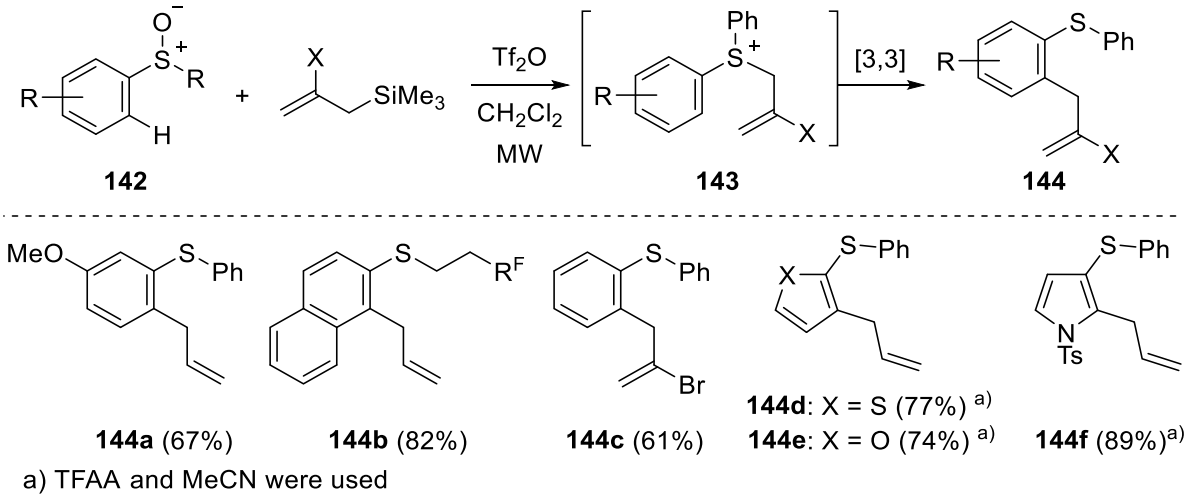
Scheme 30. C-H Thioalkylation of allylic position of cyclohexene **138**

Among their pioneering works on the aromatic Pummerer reaction, in 2004, Kita and Akai disclosed the regioselective alkylation of electron-rich heteroaryl sulfoxides **140** and **141**, such as furans, thiophenes, and indoles under Pummerer reaction condition (Scheme 31).[44]



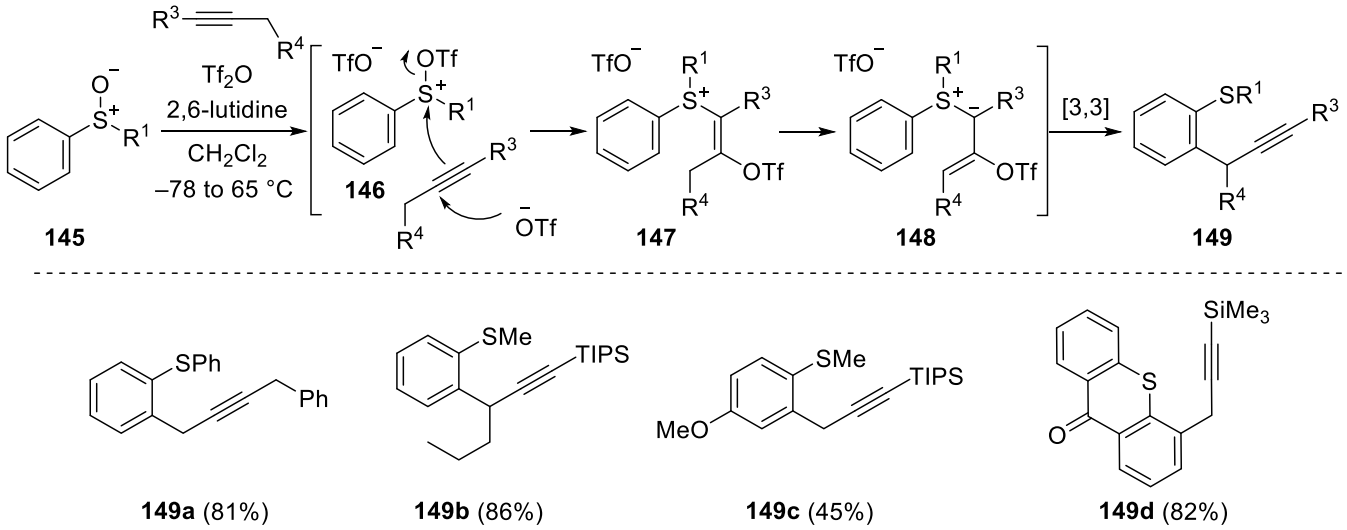
Scheme 31. Regioselective C-C bond formation using aryl sulfoxides **140** and **141**

In 2011, Procter's group reported the sulfoxide-directed *ortho*-allylation of aryl and heteroaryl sulfoxides **142** upon treatment with allylsilanes, exploiting the interrupted Pummerer-sigmatropic rearrangement cascade approach to functionalize aromatic rings (Scheme 32). Following the activation of sulfoxides **142** with Tf_2O, the reaction with allylsilanes generated the allylsulfonium intermediates **143** by an interrupted Pummerer reaction. Consecutive thio-Claisen rearrangement formed a C–C bond by transferring the allyl group to the *ortho*-position to afford allylated products **144** with complete regioselectivity.[45]



Scheme 32. Thio-Claisen rearrangement of allylsulfonium salts **143**

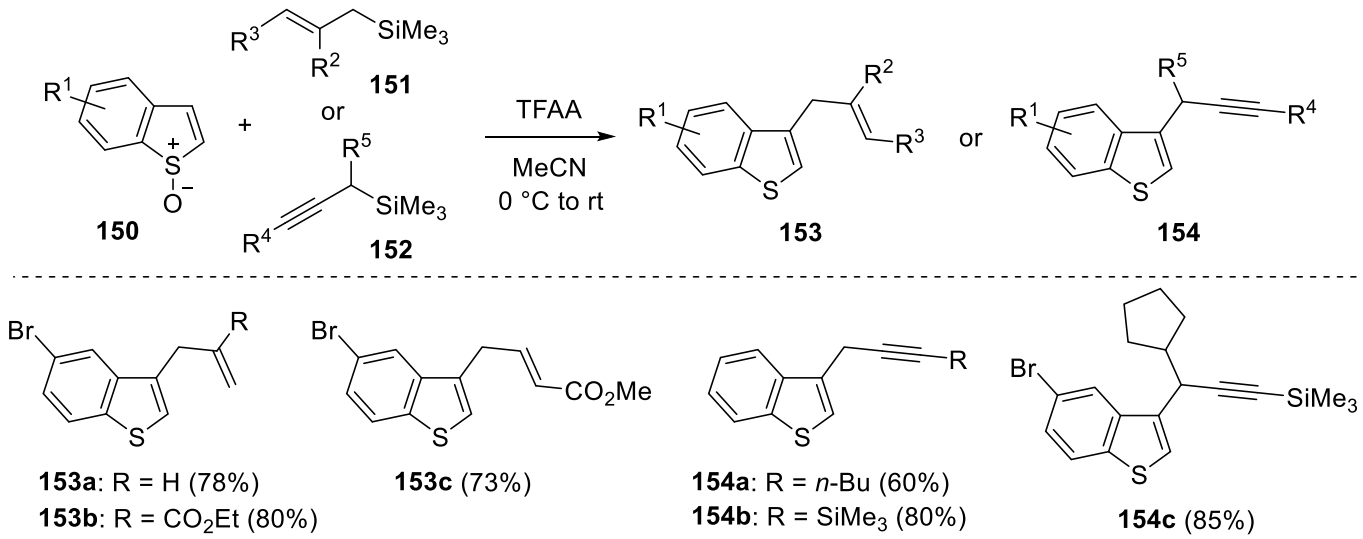
They additionally expanded the regioselective C–H propargylation of aryl sulfoxides **145** to yield **149**, employing propargyltrimethylsilanes in the interrupted Pummerer reaction-triggered cascade sequence (Scheme 33).[46] Furthermore, when non-prefuctionalized alkynes were used for the propargylation of aryl sulfoxides **145**, the reaction occurred regioselectively.[47] Alkyne was reacted with activated sulfoxides to



Scheme 33. *ortho*-Propargylation using aryl sulfoxides **145**

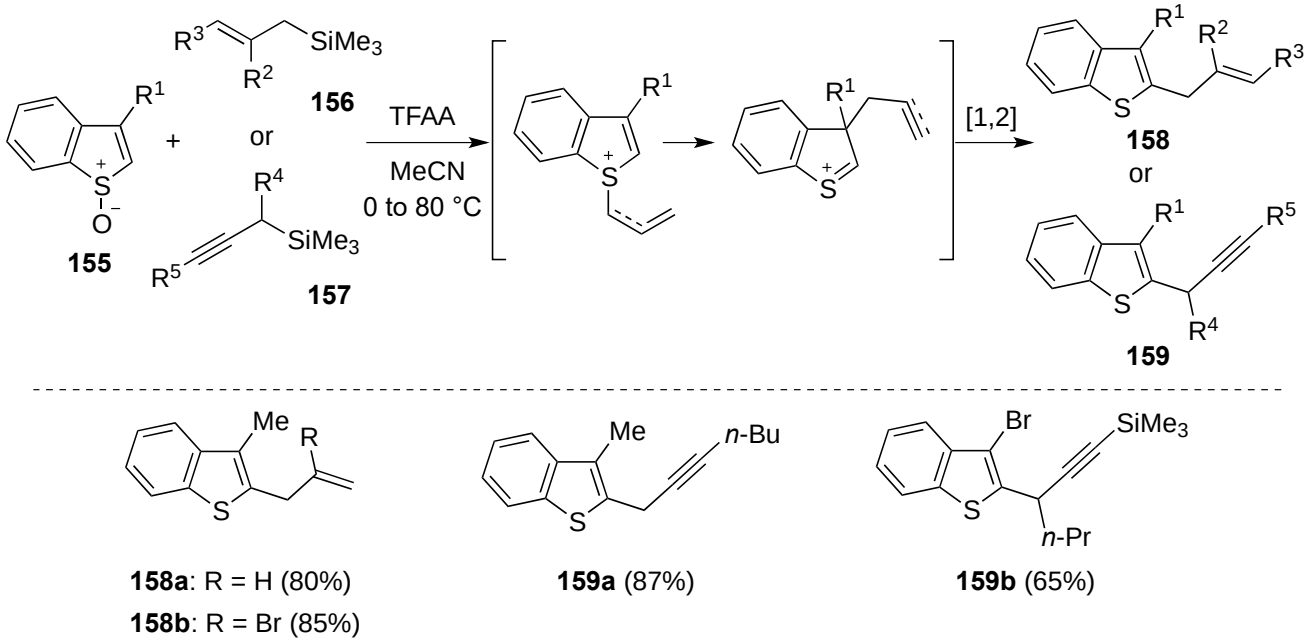
generate vinyltriflates **147**. Consequently, sulfonium ylides **148** induced [3,3]-sigmatropic rearrangement to realize C–C bond formation and produced the desired compounds **149**.

Benzothiophene *S*-oxides **150** were used as instead of aryl sulfoxide in an interrupted Pummerer reaction with allyl- or propargyl-silanes **151** or **152** yielded C3 functionalized benzothiophenes **153** or **154**, respectively, by sequential [3,3]-sigmatropic rearrangement (Scheme 34).[16]



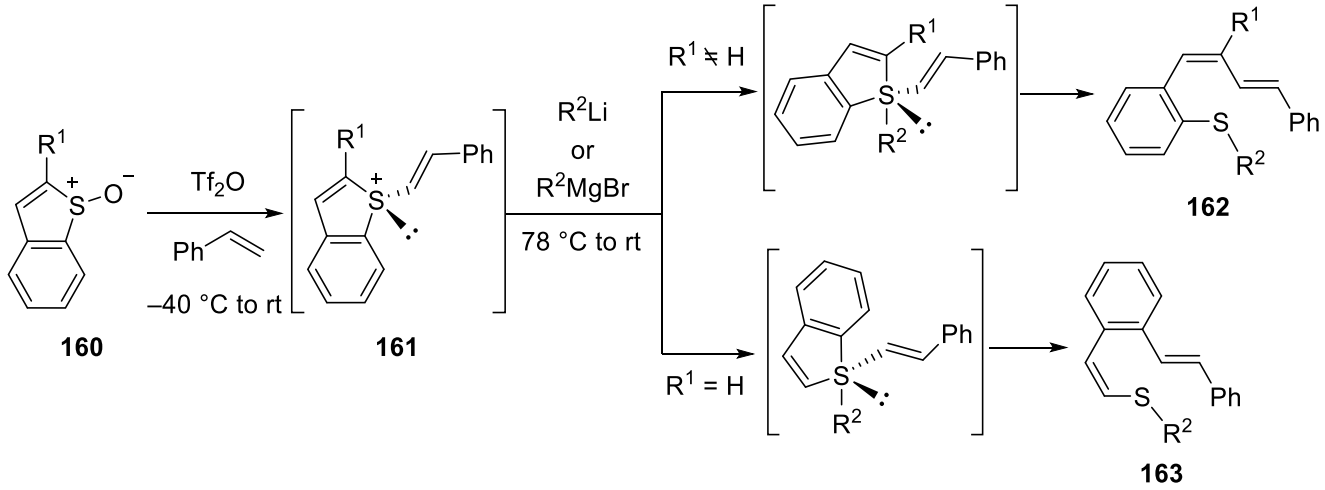
Scheme 34. C3−Alkylations using benzothiophene *S*-oxides **150**

In the case of 3-substituted benzothiophene *S*-oxides **155**, C2 functionalized benzothiophenes **158** or **159** were generated by consecutive [3,3]-sigmatropic rearrangement and additional [1,2]-migration due to the occupation of C3 position (Scheme 35).[18]



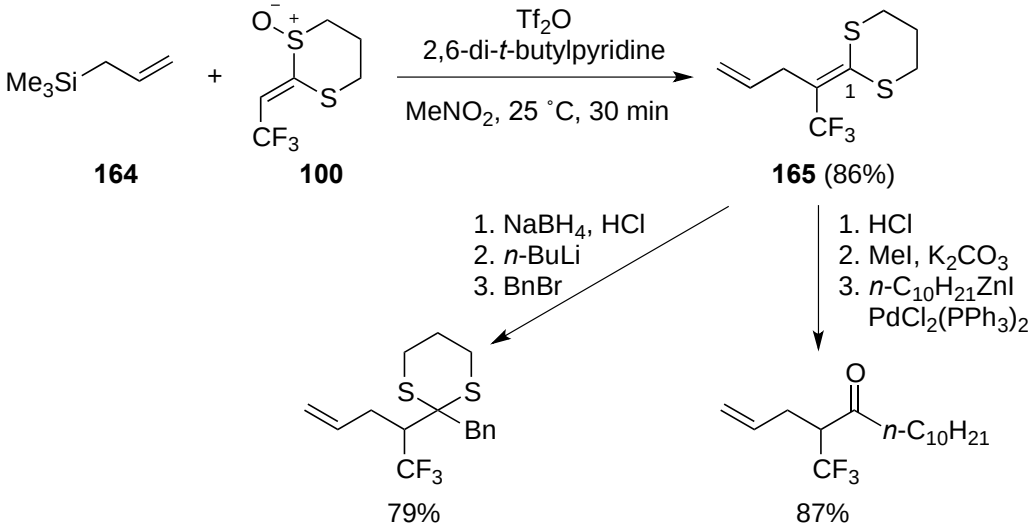
Scheme 35. C2-Alkylations of 3-substituted benzothiophene *S*-oxides **155**

2-Substituted benzothiophene *S*-oxides **160** underwent the interrupted Pummerer reaction with styrene to form sulfonium intermediates **161** (Scheme 36). The continuous nucleophilic attack by alkyllithium-magnesium reagents on **161** proceeded opposite to the bulkiest sulfur ligand for the stereoselective ligand coupled products **162** or **163**, respectively.[48]



Scheme 36. Cleavage of thiophene ring triggered by interrupted Pummerer reaction

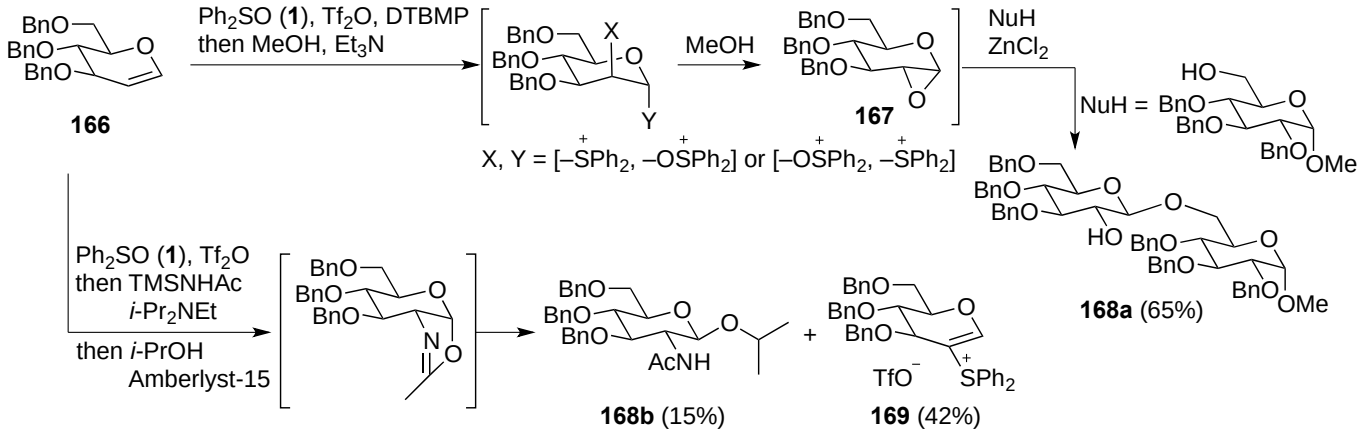
The reaction of allyltrimethylsilane **164** and 2-(2,2,2-trifluoromethylidene)-1,3-dithiane monoxide (**100**) produced C2-allylated derivatives by the interrupted Pummerer reaction and successive [3,3]-sigmatropic rearrangement (Scheme 37). The C1-position of **165** can participate as a nucleophile in C–C bond formation via the thiol ester, as well as an electrophile, via dithiane chemistry.[49]



Scheme 37. Allylation of CF_3-ketene dithioacetal monoxide **100**

Gin and coworkers explored oxidative glycosylation with glycal **166** employing the combination of **1** and Tf_2O (Scheme 38). An ^{18}O-labeling study indicated the formation of an oxirane intermediate **167** from

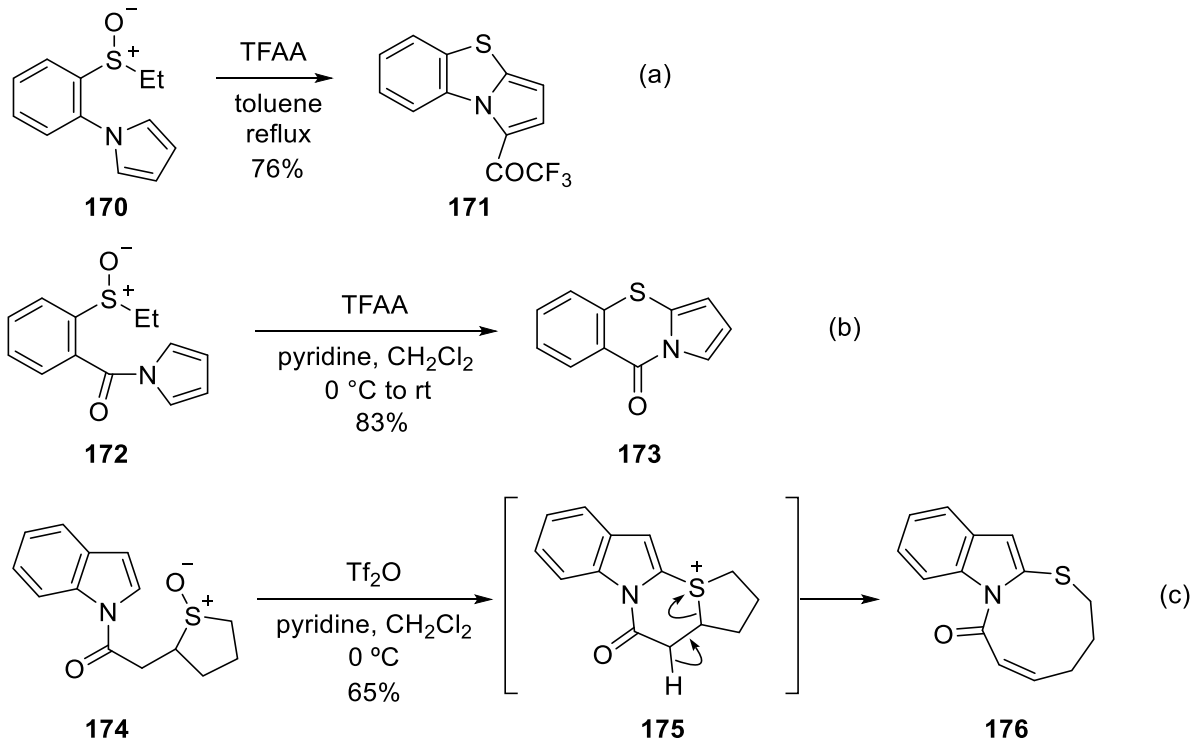
disulfonium intermediate, which was followed by the addition of glycosyl acceptors (NuH) to afford *C*2-hydroxy-β-D-glucopyranoside **168a**. When *N*-(TMS)acetamide was employed as the nitrogen transfer reagent, and 2-propanol as a glycosyl acceptor, the reaction regioselectively afforded *C*2-acetamidoglycoside **168b**, along with sulfonium salt **169**.[50]



Scheme 38. Oxidative glycosylations with glycal **166**

7. REACTIONS WITH ARENES AND HETEROARENES

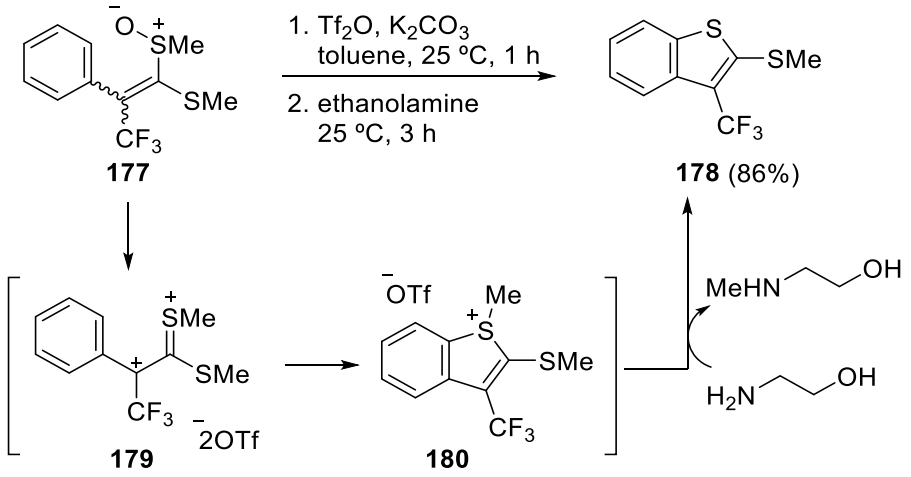
In the reactions with arene, various C–H functionalization were developed through arylsulfonium species by the combination with various continuous reaction. In 1992, Bates reported the ring closure of



Scheme 39. C-H Sulfenylation of heteroarenes by interrupted Pummerer reaction

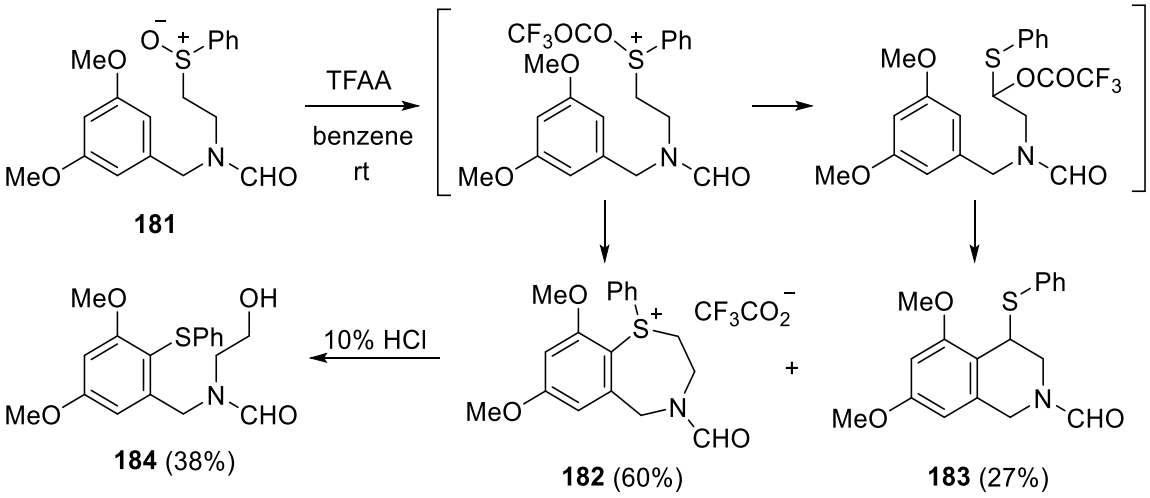
2-(ethylsulfinyl)phenylpyrrole (**170**) and 2-(ethylsulfinyl)benzoylpyrrole (**172**), proceeding by sequential dealkylation to provide **171** and **173** (Schemes 39a and 39b). Furthermore, they found that the treatment of **174** with Tf_2O-pyridine produced the 9-membered heterocycle **176** by β-elimination of the sulfonium intermediate **175** (Scheme 39c).[51]

In 2007, Yorimitsu and Oshima detailed the transformation of arylketene dithioacetal monoxide **177** into benzo[*b*]thiophene **178** by the combination of interrupted Pummerer reaction-dealkylation process (Scheme 40). Both *E*- and *Z*-stereoisomers of the substrate **177** underwent cyclization upon generation of the highly stabilized dication intermediate, followed by the removal of methyl group from **180**.[52]



Scheme 40. Formation of benzothiophene from ketene dithioacetal monoxide **177**

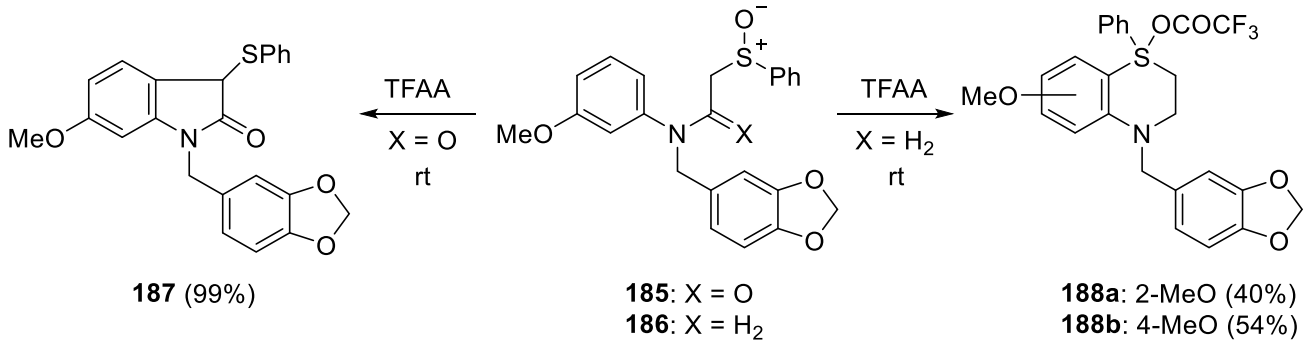
In their synthesis of tetrahydroisoquinolines, Sano et al. established that subjecting **181** to Pummerer reaction conditions produced benzothiazepine salt **182** in 60% yield along with the desired product **183** (Scheme 41). The sulfonium salt **182** was hydrolyzed under acidic conditions by the cleavage of C_{sp3}-S



Scheme 41. Competition between interrupted and standard Pummerer reactions

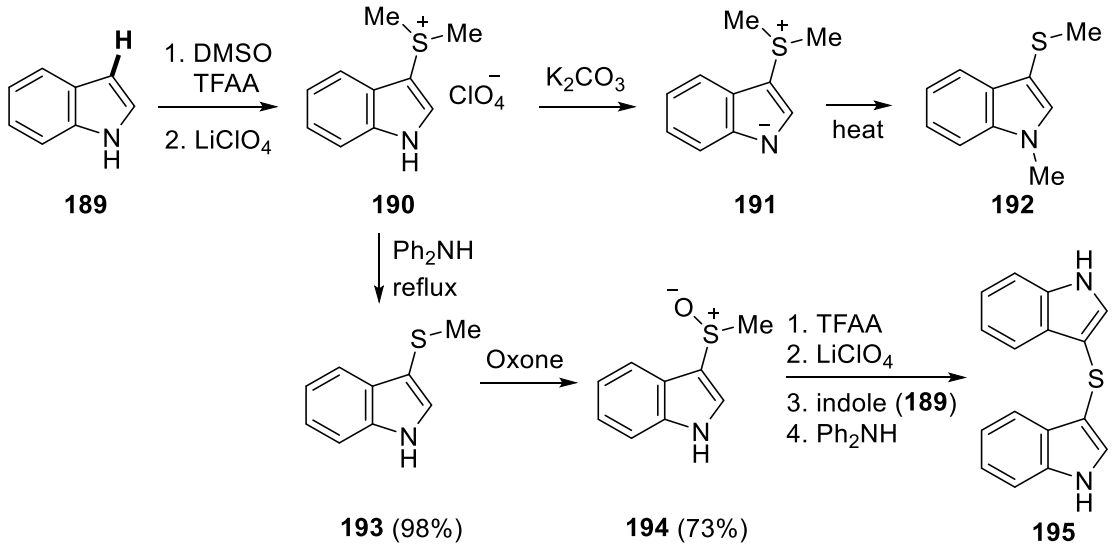
bond to afford alcohol **184**.[53]

In their further research, the Pummerer cyclization of **185** and **186** was studied and revealed that the acidity of the α-proton on the α-acyl sulfoxide was pivotal in determining the reaction pathway (Scheme 42). Specifically, the reaction of α-acyl sulfoxide **185** with TFAA gave rise to a ylide, which upon Pummerer cyclization generated oxindole **187**. In the case of alkyl sulfoxide **186**, the electron-rich aryl moiety attacked the activated sulfur atom to give sulfuranes **188a** and **188b**.[54]



Scheme 42. Distinct pathways governed by the acidity of the α-proton adjacent to the sulfinyl group

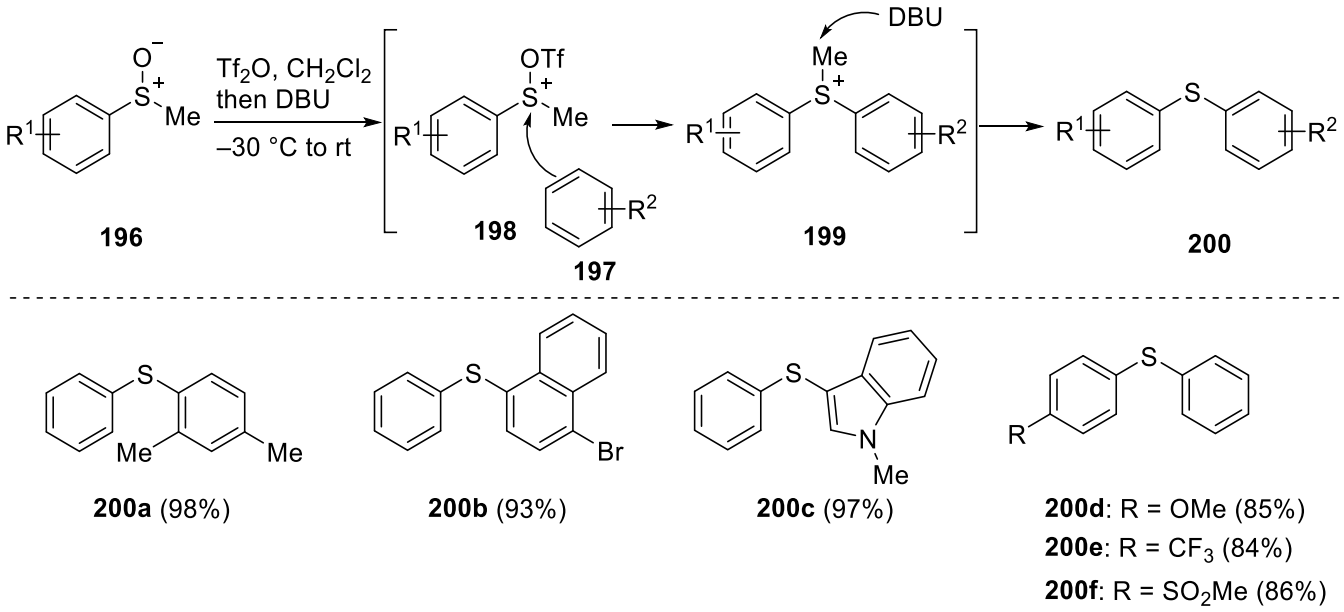
Hartke discovered that the reaction between indole (**189**) and the activated DMSO with TFAA produced the isolable sulfonium salt **190**. The treatment of the salt with K_2CO_3 afforded **191**, which was transformed to *N*-methyl-3-methylsulfanylindole **192** with heat by methyl migration (Scheme 43).[55]



Scheme 43. Methysulfanylation of indole and synthesis of bis(indol-3-yl)sulfide **195** by the combination with demethylation

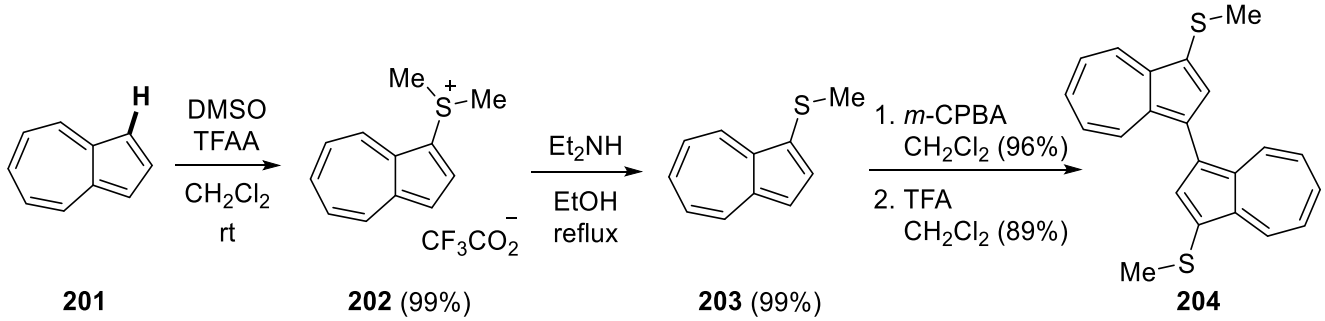
Based on this study, Suzuki's group found that the treatment of **190** with secondary amine afforded 3-methylsulfanylindole (**193**) by demethylation. The sulfanylindole was oxidized to sulfoxide **194**, which underwent the same reaction sequence as above to deliver diaryl sulfide **195**.[56]

Procter achieved the C–H thio-arylation of aromatics **197** utilizing arylmethyl sulfoxides **196** for the synthesis of valuable diaryl sulfides **200**. The method was operationally simple and employed readily available materials (Scheme 44). The interrupted Pummerer reaction was induced by the nucleophilic attack of **197** onto **198**, generated *in situ* from aryl sulfoxide **196** and Tf_2O, to form diarylmethylsulfonium intermediate **199**. Thus, the treatment of **199** with DBU afforded diaryl sulfide **200** by removal of the methyl group.[57]



Scheme 44. C-H Thio-arylation of arenes **196**

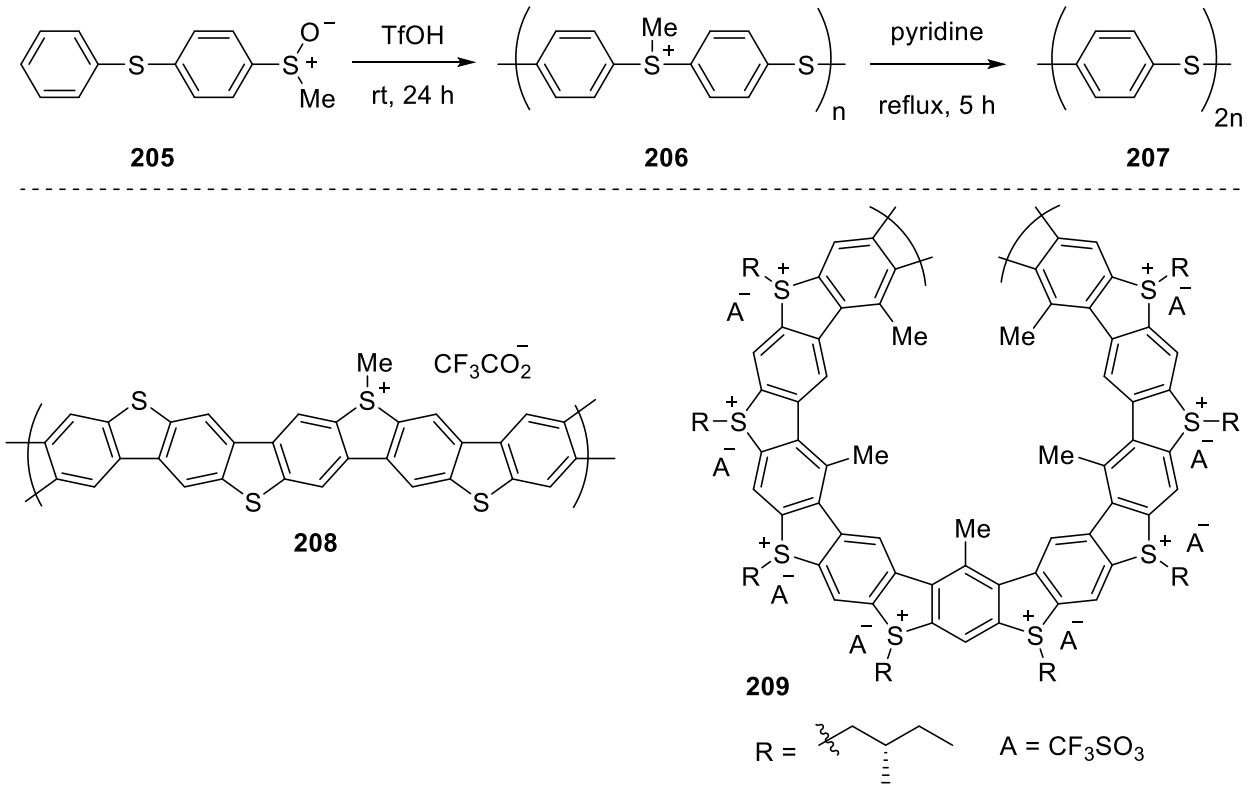
Shoji and Morita developed the reaction between an activated sulfoxide and azulene (**201**) to give azulene-sulfonium salt **202**. Treatment of **202** with a secondary amine produced1-azulenyl sulfide **203** by methyl



Scheme 45. Formation of azulenesulfonium salts **202** and its reactions

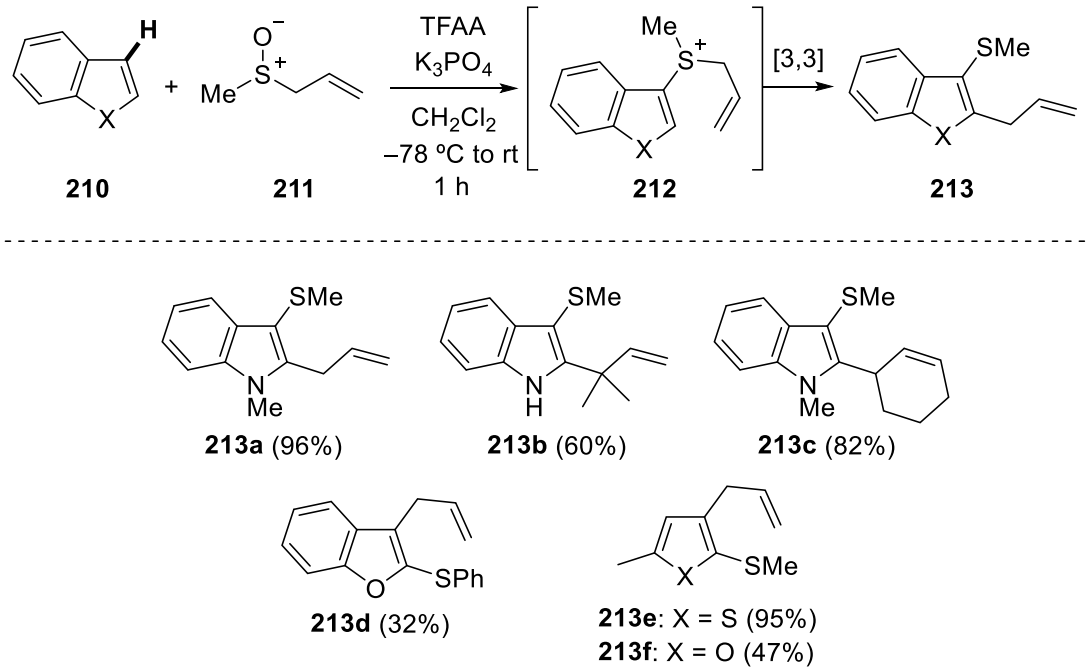
group elimination. The sulfide **203** was oxidized to the sulfoxide, which upon treatment with TFA delivered 1,1'-biazulene **204** (Scheme 45).[58]

The C-H functionalization by interrupted Pummerer reaction-dealkylation sequence was applied to the synthesis of polymer.[59] Poly(*p*-phenylene sulfide) (PPS) **207** was synthesized by the self-condensation of methyl(*p*-thiophenoxy)phenyl sulfoxide **205** in TfOH (Scheme 46). The demethylation of **206** was conducted in refluxing pyridine to give polymer **207**. The average of the molecular weight was determined to be above $M_W = 2 \times 10^5$ by GPC analysis.[59a] The methodology was utilized for the synthesis of oligo(*p*-phenylene)ladder **208**[59b] and poly(thiaheterohelicene) **209**.[59c]



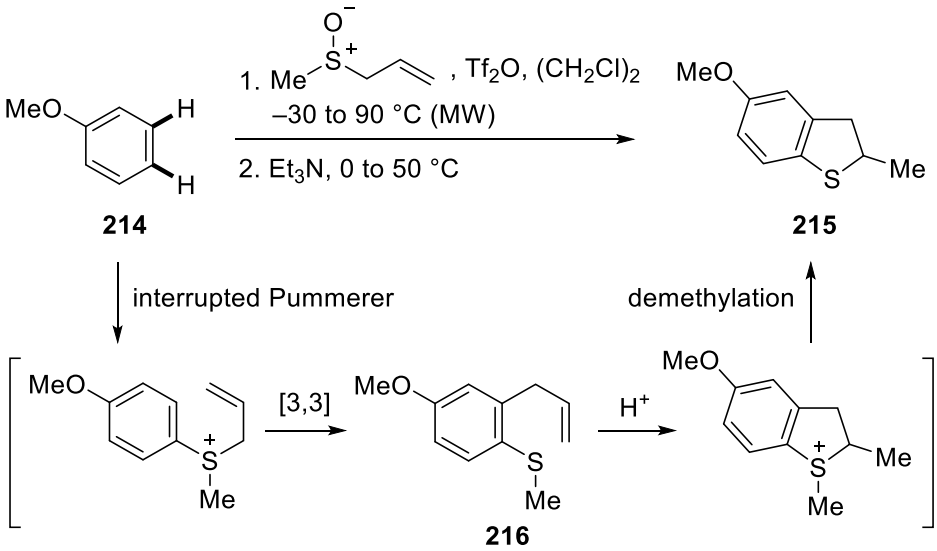
Scheme 46. Synthesis of poly(*p*-phenylene sulfide) and functional polymers

As the sequence of interrupted Pummerer reaction-sigmatropic rearrangement, Procter developed a cascade reaction with allyl sulfoxide **211** to achieve regioselective C-H allylation of heteroarenes **210** (Scheme 47). Allyl sulfoxide **211** was treated with TFAA and the resulting interrupted Pummerer reaction with aromatics **210** formed allylarylsulfonium intermediates **212**. The consecutive charge-accelerated [3,3]-sigmatropic rearrangement produced dual vicinal functionalized heteroarenes **213**.[60]



Scheme 47. Dual vicinal functionalization of heteroarenes **210** using allyl sulfoxide **211**

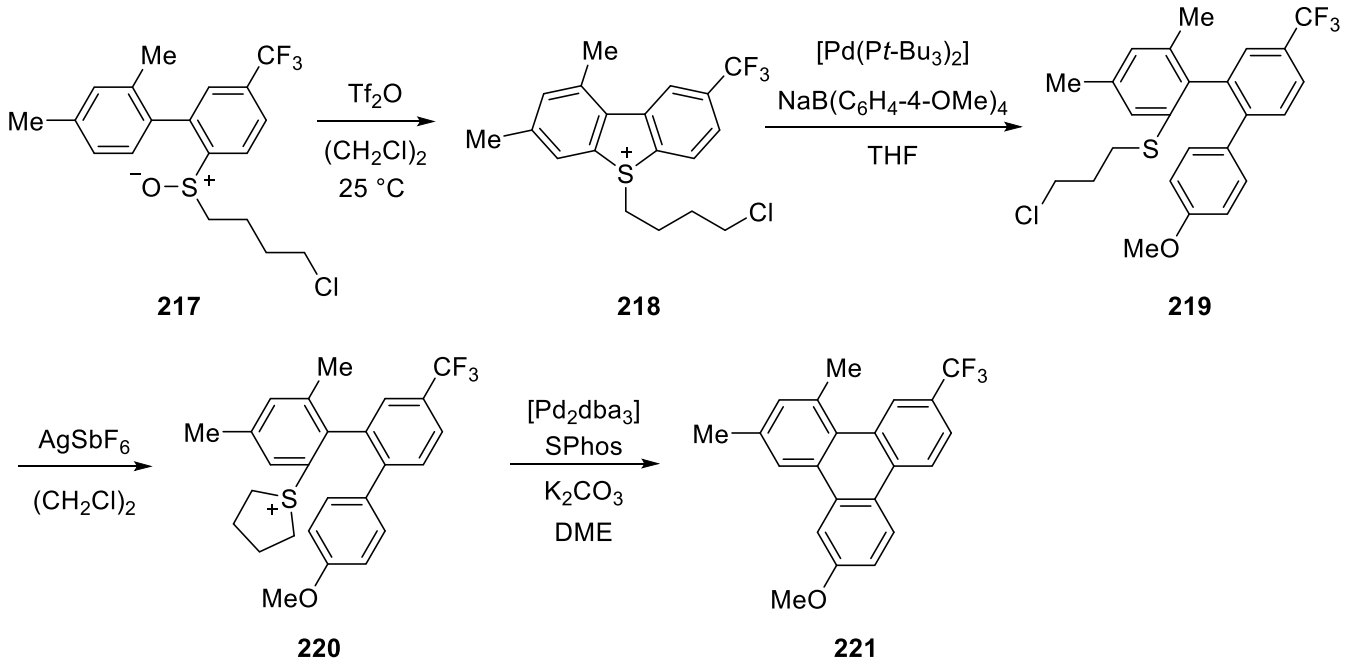
The cascade sequence was applied for the synthesis of dihydrobenzothiophene. Interrupted Pummerer reaction-sigmatropic rearrangement generated allylsulfenylarene **216** from arene **214** (Scheme 48). And then, the cyclization of **216** and removal of the methyl group afforded dihydrobenzothiophene **215**.[61]



Scheme 48. Construction of dihydrobenzothiophene scaffold **215** by combination with sigmatropic rearrangement and demethylation

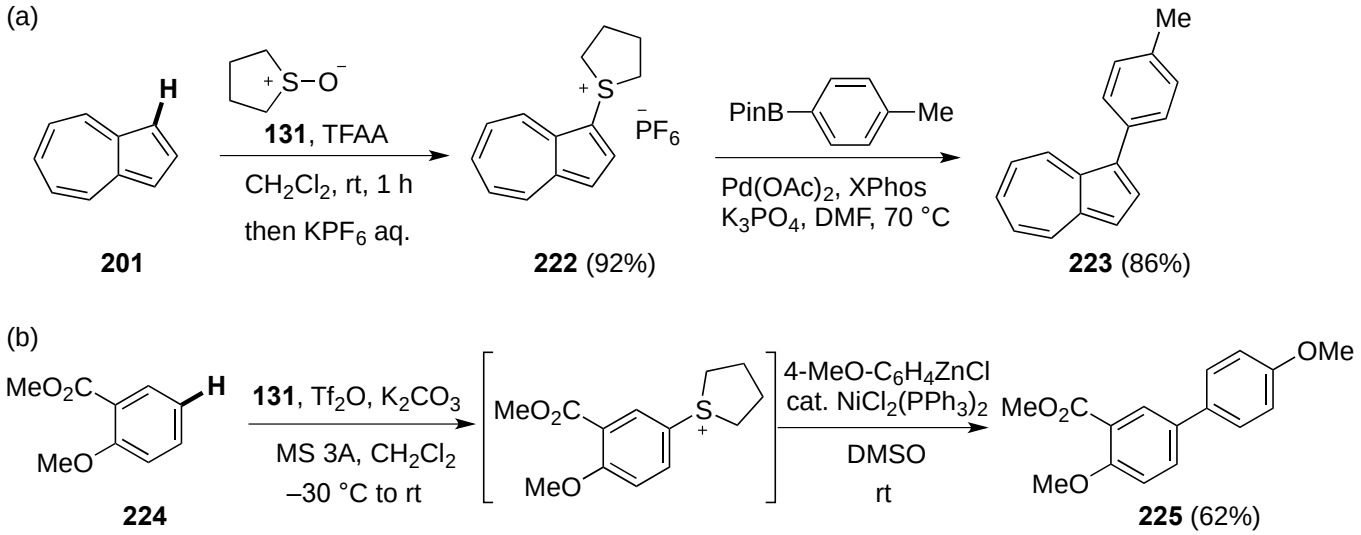
In the reaction of the interrupted Pummerer reaction-intermolecular coupling reaction system, sulfonium species was utilized as the precursor of transition metal-catalyzed coupling reaction. Yorimitsu developed the sequence of interrupted Pummerer and metal-catalyzed coupling reactions for the formation of

triphenylenes **221** (Scheme 49). In their report, sulfonium salts were utilized as the substrate of palladium-catalyzed coupling reaction. The sulfonium **218** was coupled with an aromatic group to produce biaryl **219**. The formation of thiophenium salt **220** was followed by intramolecular coupling to give triphenylene **221**.[62]



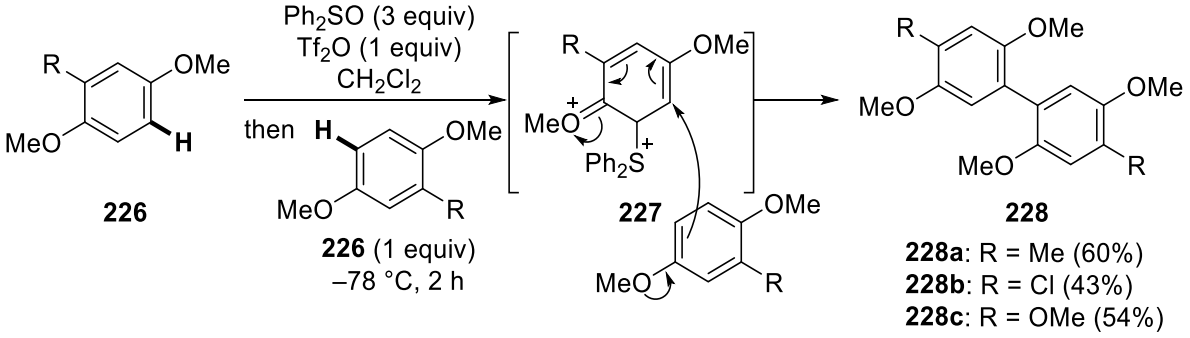
Scheme 49. Synthesis of triphenylene **221** utilizing palladium-catalyzed coupling with sulfonium salts

Cowper and Lewis used arylsulfonium salt **222** from azulene (**201**) as the precursor of Suzuki-Miyaura coupling reaction with aryl boronates to generate biaryl product **223** in good yields (Scheme 50a).[63] Instead of continuous Suzuki-Miyaura coupling, the combination with Negishi coupling in a one-pot procedure was reported by Procter to obtain biaryl **225** from non-prefunctionalized arene **224** (Scheme 50b).[42]



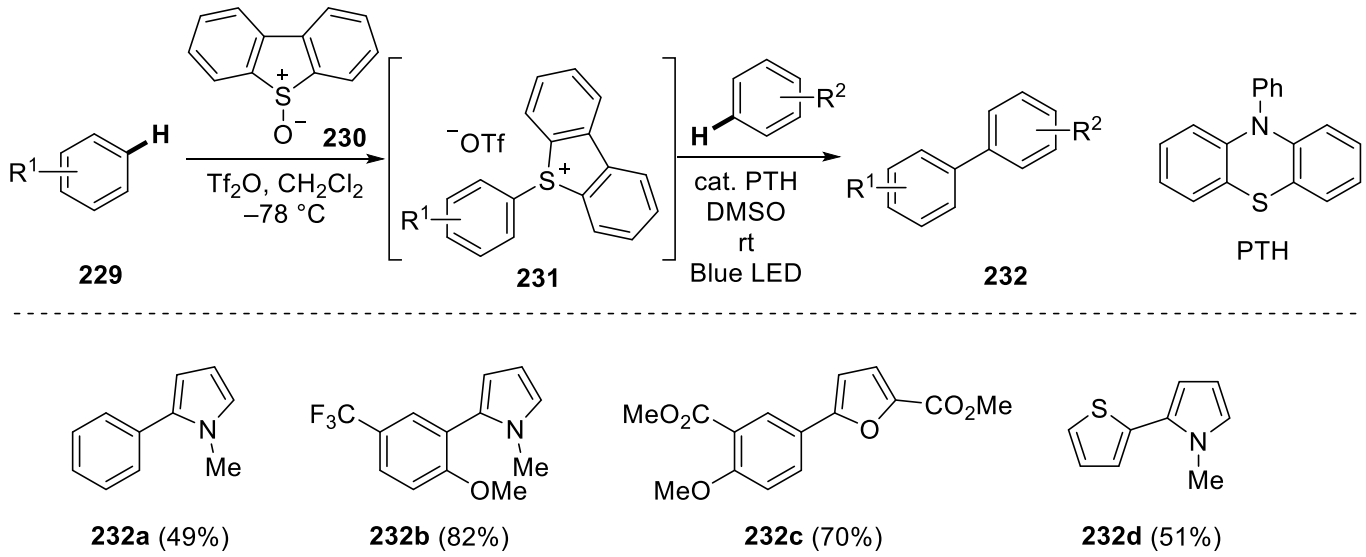
Scheme 50. Sequential systems of interrupted Pummerer and metal-catalyzed coupling reaction

As the application of sulfonium mediated coupling reaction, a metal-free method was developed. The reaction with electron-rich arenes **226** as substrate and the coupling partner produced homo-coupled biaryls **228** in moderate yield via sulfonium intermediates **227** (Scheme 51).[19]



Scheme 51. Transition metal-free coupling of arenes **226** via sulfonium species

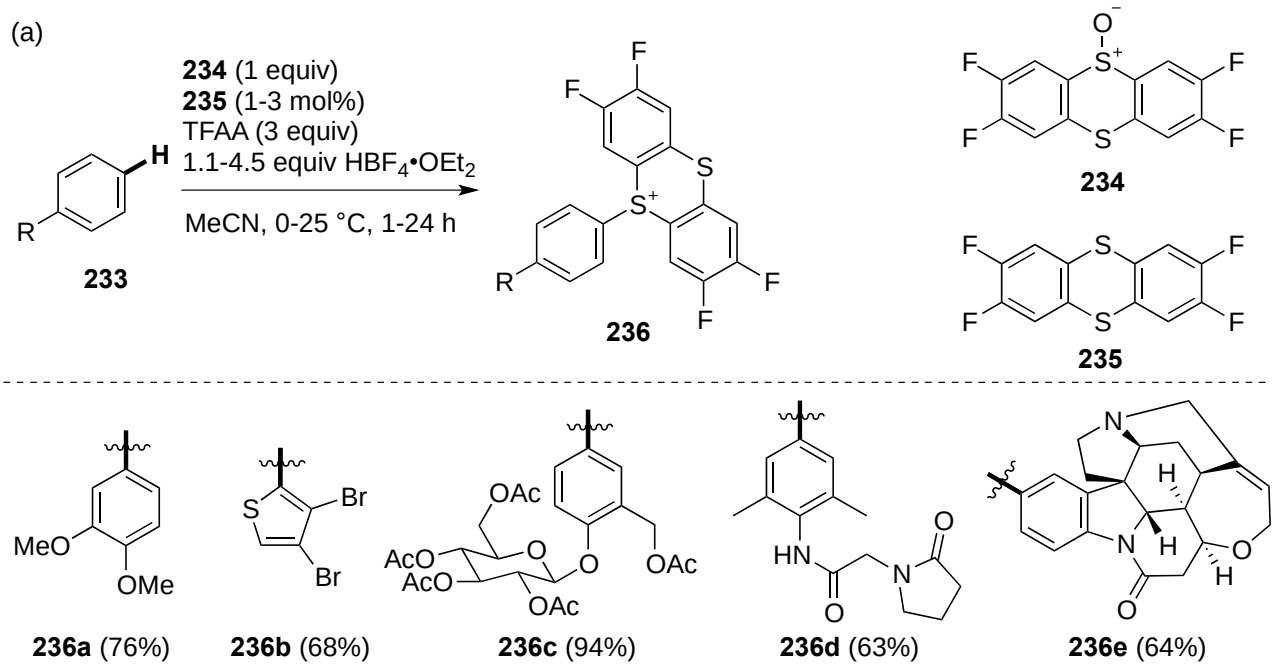
Recently, the novel C-H functionalization system was reported consisting of interrupted Pummerer and photoredox catalyzed coupling reactions. The treatment of arenes **229** with dibenzothiophene *S*-oxide (**230**) and Tf_2O generated thiophenium intermediates **231**, the key intermediate of the following photoredox catalyzed radical coupling to obtain biaryls **232** (Scheme 52).[64]

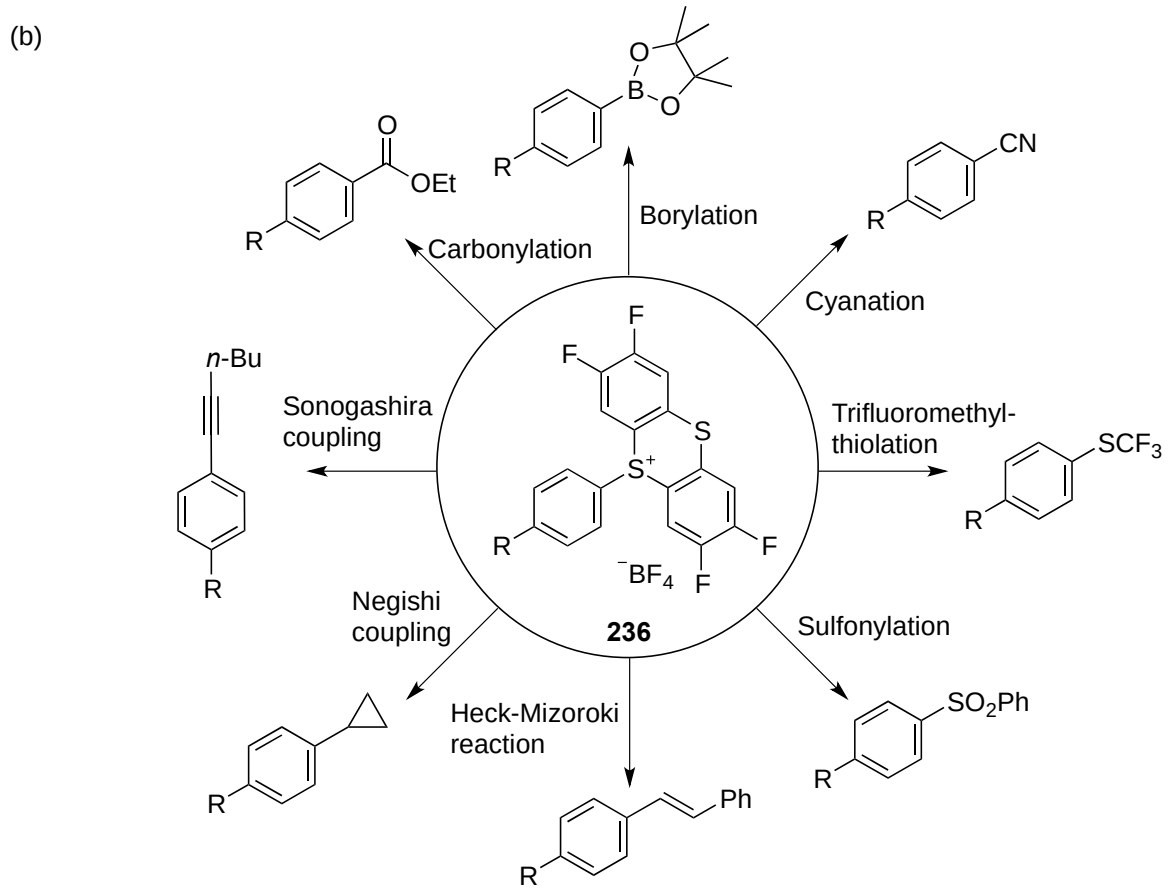


Scheme 52. Heterocoupling of arenes by interrupted Pummerer and photoredox reactions

Versatile C_{Ar}-H functionalizations induced by interrupted Pummerer reaction have been reported by Ritter's group.[65] This strategy realized to functionalize complex arenes **233** utilized thianthrenium salts **236** (Scheme 53a) that are ready to engage in a various transformation as shown by Scheme 53b, via both

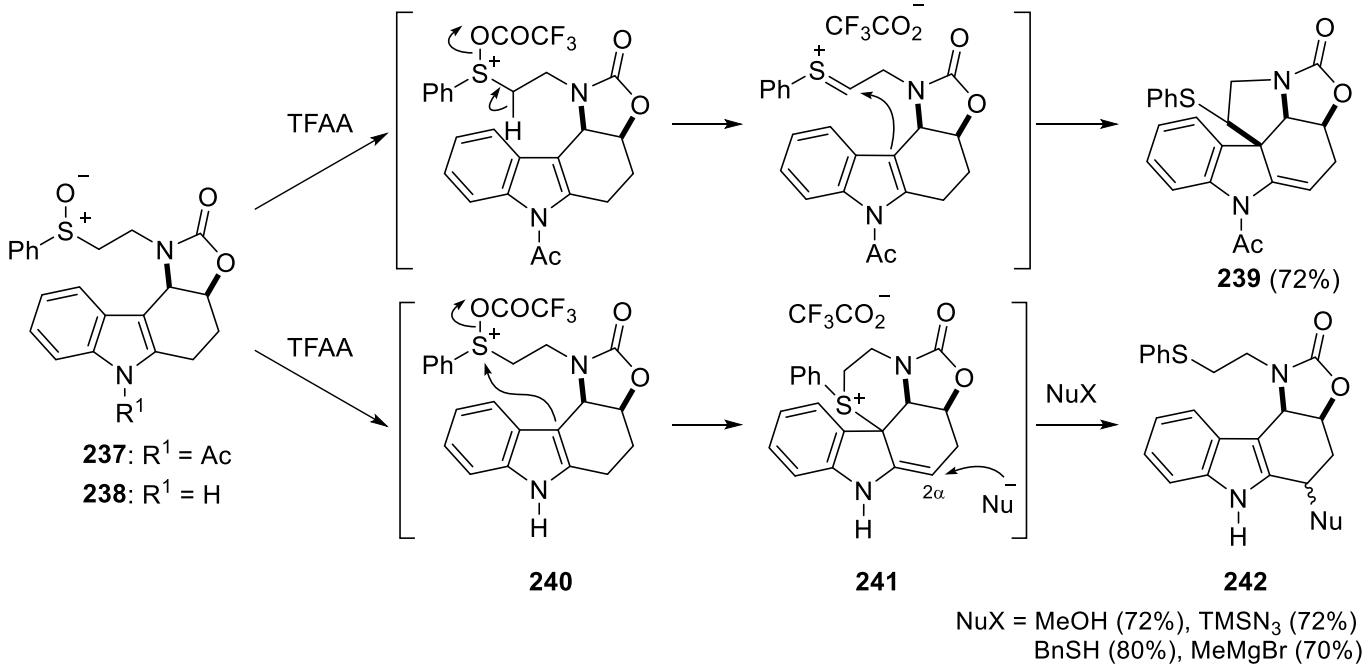
transition metal and photoredox catalysis (Scheme 53a). This transformation provides access to a large number of derivatives of complex small molecules (Scheme 53b).





Scheme 53. Synthesis of thianthrenium salts **236** and versatile functionalizations thereof

While pursuing novel synthetic strategies for indole alkaloids, Kawasaki found that the products obtained under Pummerer reaction conditions varied depending on the substituent group R^1 on the indole nitrogen of tetrahydrocarbazoles (Scheme 54). In the case of **237**, where R^1 is acetyl, elimination of the α-proton, followed by cyclization proceeded to give the Pummerer cyclized product **239**. When R^1 is hydrogen, as in **238**, substitution at the sulfur atom forms the sulfonium intermediate **240**. Subsequently, intermediate **240** isomerizes to enamine **241**, which engages in an S_N2' reaction at the 2α-position to provide product **242** utilizing high leaving group ability of sulfide moiety.[66]

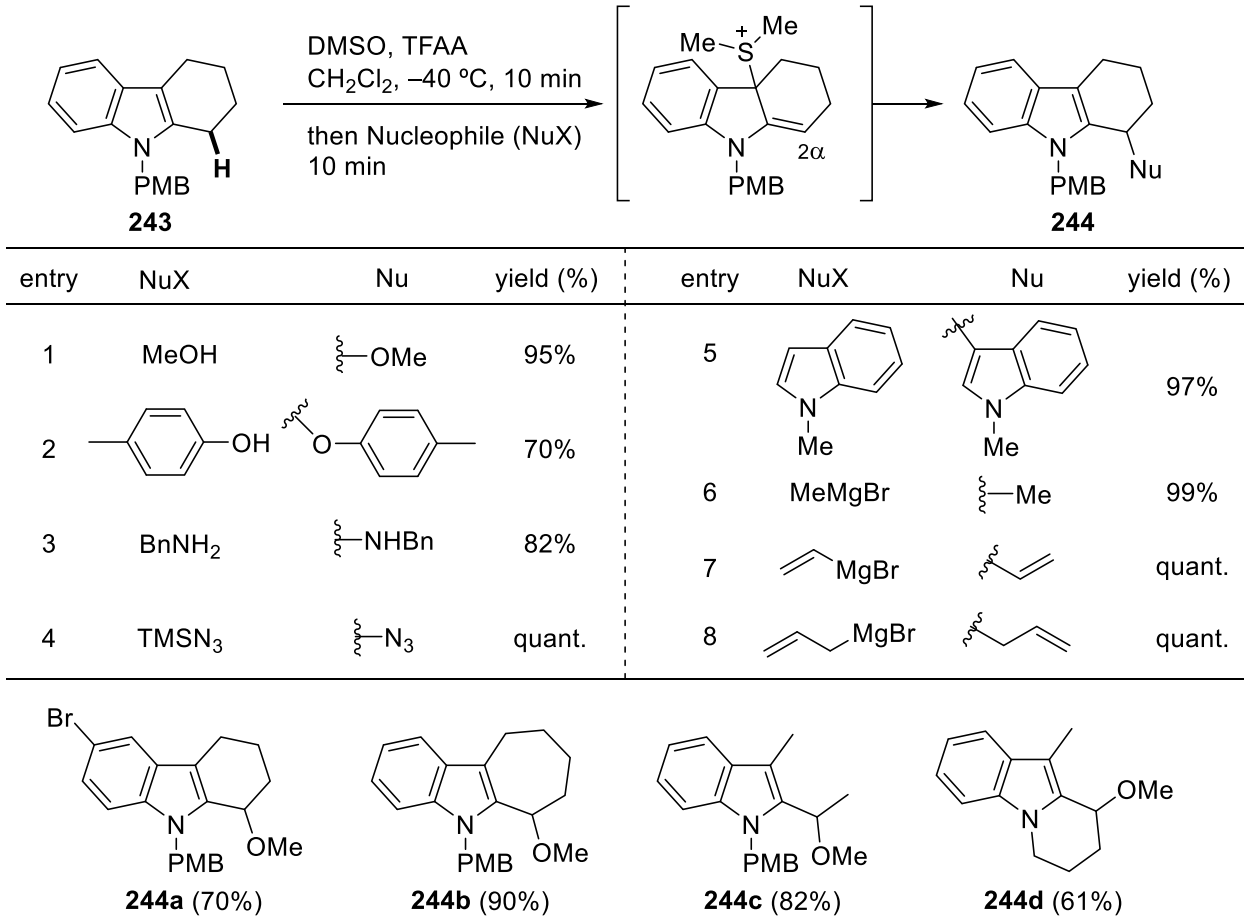


Scheme 54. Reaction pathways controlled by the nucleophilicity of the indole core

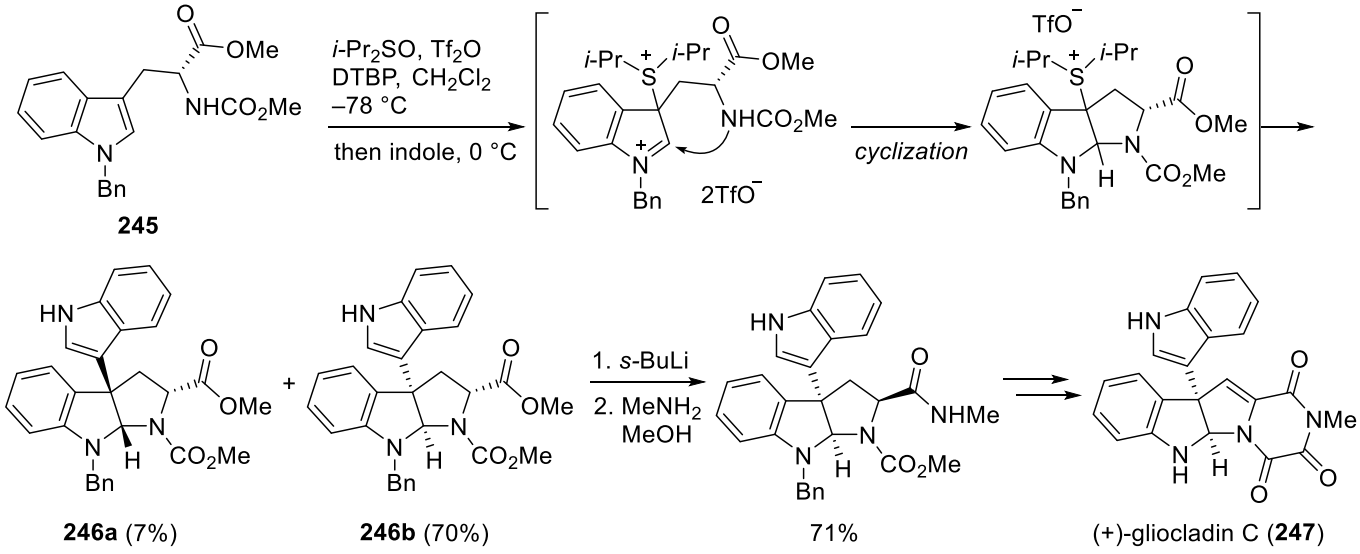
With the objective of developing an intermolecular version of the above-mentioned reaction, we investigated the reaction of activated sulfonium species with tetrahydrocarbazoles **243** (Scheme 55). Consequently, the DMSO-TFAA system effectively afforded indole derivatives functionalized at the 2α-position such as **244**. Carbon and heteroatom nucleophiles were directly introduced by a one-pot procedure in excellent yields.[67]

Under the mediation of the active sulfonium species, the tryptophan analog **245** and an indole nucleophile assembled 3a-(3-indolyl)pyrroloindolines as a mixture of diastereomers (Scheme 56). The addition of 2,6-di-*tert*-butylpyridine (DTBP) was essential to avoid the coupling of indole at the C2 position of the tryptophan. The cascade reaction, encompassing the substitution of dialkylsulfonium, cyclization to the

pyrroindoline structure, and installation of a nucleophile, produced 3a-(3-indolyl)pyrroloindolines **246a** and **246b** as a mixture of diastereomers. Then, **246b** was induced to (+)-gliocladin C (**247**).[68]

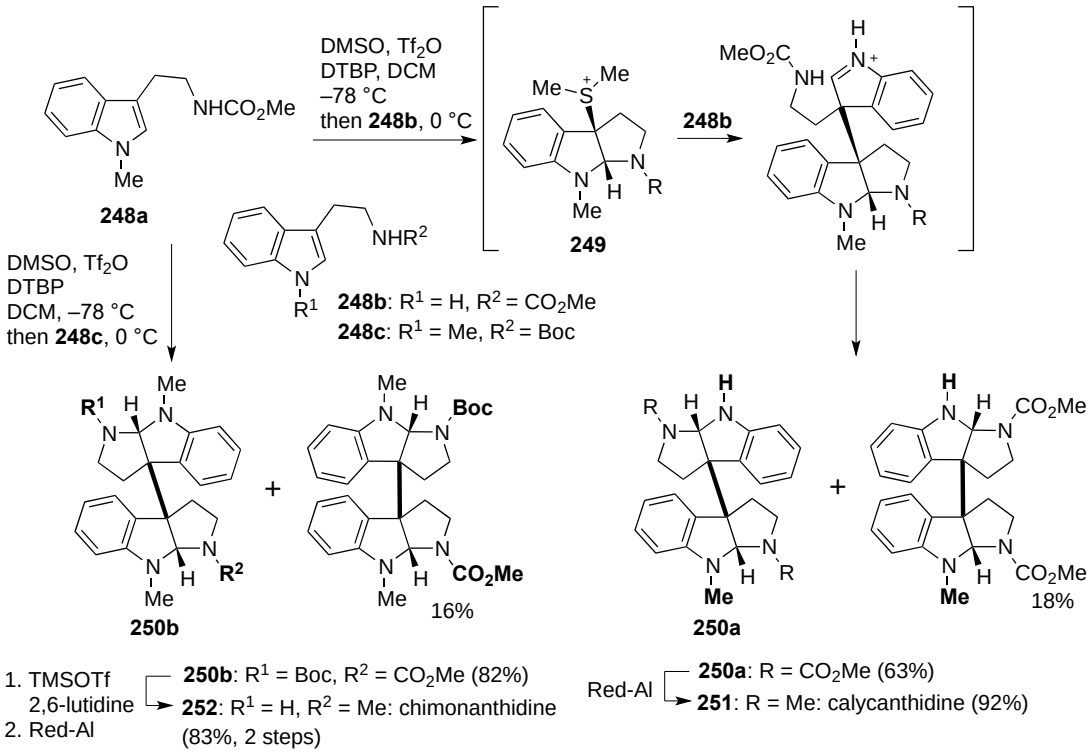


Scheme 55. Traceless functionalization of indoles **243** using sulfonium salt



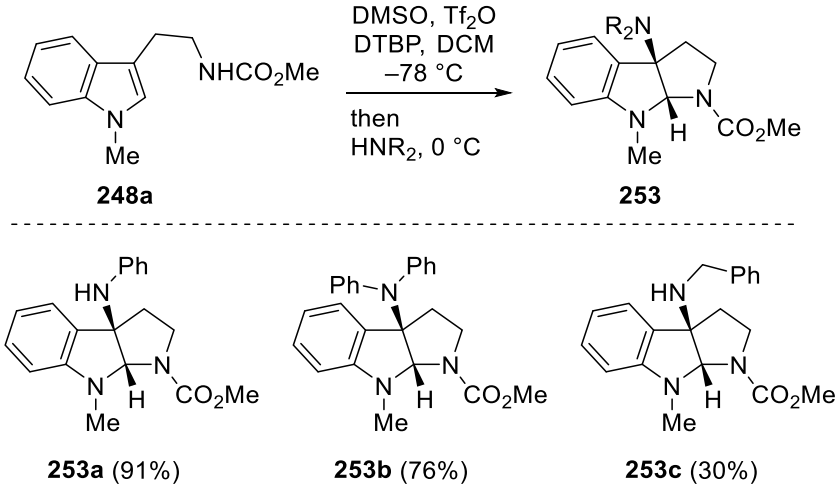
Scheme 56. Formation of 3a-substituted pyrroloindole **246** mediated with sulfonium salt

The reaction between a sulfonium species and tryptamine **248a** generated a pyrroloindoline intermediate **249**, which was reacted with another tryptamine, **248b** or **248c**, to give hetero-coupled bispyrroloindoline structures **250a** and **250b** by a one-pot procedure (Scheme 57). This method enables rapid access to heterodimeric bispyrroloindoline alkaloids, such as calycanthidine (**251**), and chimonanthidine (**252**).[69]



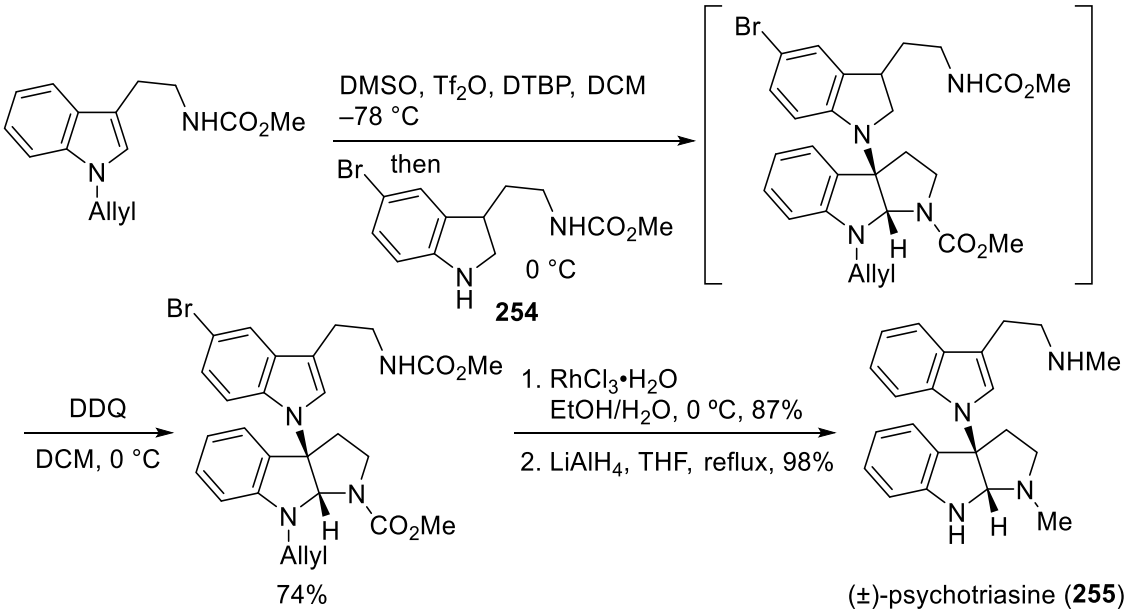
Scheme 57. One-pot synthesis of bispyrroloindole structures **250**

For the synthesis of 3a-nitrogen-substituted pyrroloindoline alkaloids, we explored the use of *N*-nucleophiles (Scheme 58). Tryptamine **248a** was treated with DMSO, Tf_2O, DTBP, and aniline to give



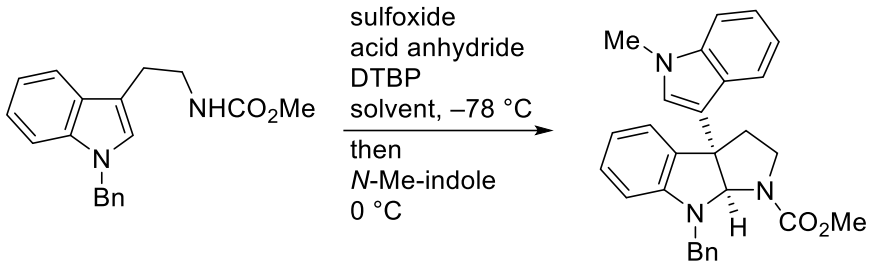
Scheme 58. Synthesis of 3a-aminopyrroindoles **253**

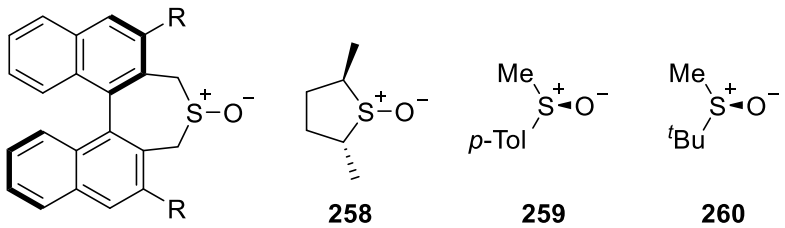
the desired 3a-anilinopyrroloindoline **253a** in 91% yield. The use of diphenylamine as a nucleophile produced **253b** in 76% yield. However, the reaction with alkylamines such as benzylamine provided the corresponding amino product **253c** in low yield. The utility of this reaction was demonstrated by accessing C3a-N1'-linked bistryptamines, including (±)-psychotriasine (**255**), which were successfully synthesized by the use of 5-bromo-2,3-dihydrotryptamine **254**, and consecutive DDQ oxidation (Scheme 59).[70]



Scheme 59. Application to the synthesis of (±)-psychotriasine (**255**)

Our group extended the above-discussed intermolecular interrupted Pummerer reaction to an asymmetric version (Scheme 60).[71] Oae reported that the chiral sulfonium center was partially racemized by the formation of sulfurane under Pummerer reaction conditions.[72] Kita improved enantioselectivity of intermolecular Pummerer reaction using *O*-silylated ketene acetal[73a,b] and ethoxy vinyl ester.[73c] Thus, we assumed that the chiral center exists around the sulfoxide moiety. The reaction using binaphthyl sulfoxides **256** and **257** resulted in moderate yields and ees. Sulfoxide **258**, activated with TFAA in EtCN, provided the highest enantioselectivity (entry 7). The synthetic utility of this reaction was demonstrated by the total synthesis of (+)-psychotriasine in 91% ee.

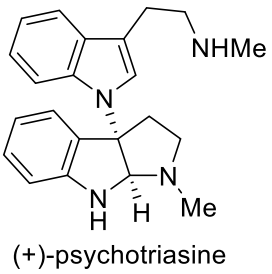




256: R = H
257: R = Ph

258 **259** **260**

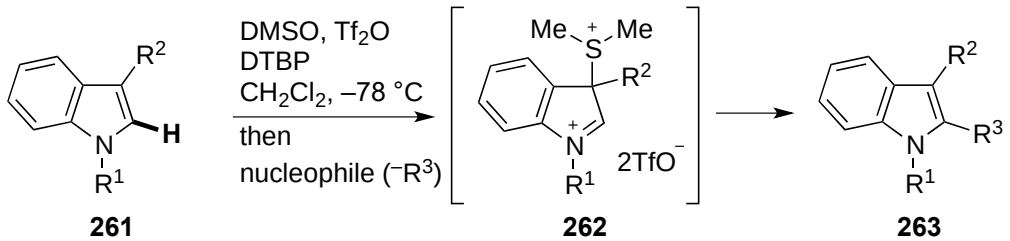
entry	sulfoxide	acid anhydride	solvent	yield (%)	ee (%)
1	**256**	Tf_2O	DCM	41	61
2	**257**	Tf_2O	DCM	40	58
3	**258**	Tf_2O	DCM	94	35
4	**259**	Tf_2O	DCM	35	2
5	**260**	Tf_2O	DCM	trace	0
6	**258**	Tf_2O	EtCN	91	45
7	**258**	TFAA	EtCN	73	93



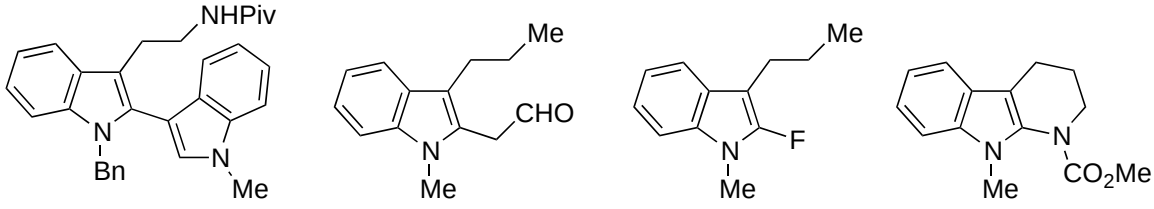
(+)-psychotriasine

91%ee

Scheme 60. Enantioselective pyrroloindoline synthesis by asymmetric interrupted Pummerer reaction



261 **262** **263**



263a (69%) **263b** (58%) **263c** (42%) **263d** (62%)

Scheme 61. C2-Functionalization of indole derivatives **261** via iminium intermediate **262**

During the formation of the C3a-substituted pyrroloindoline structure, we discovered that the nucleophilic addition competed between C3a at pyrroloindoline and C2 at indole. When C3-substituted indoles **261** reacted with sulfonium species derived from DMSO and Tf_2O, iminium intermediates **262** was formed. Nucleophiles added to intermediates **262**, and the ensuing rearomatization, afforded C2,C3-disubstituted indoles **263** in good yields (Scheme 61).[74]

In conclusion, a large amount of studies has been conducted exploiting the reactivity of active sulfonium species, and useful reactions in synthetic organic chemistry, such as the Swern oxidation and the Pummerer reaction, have been developed. Initially, the interrupted Pummerer reaction was regarded as a side reaction occurring under Pummerer reaction conditions. However, research focused on this reaction is currently expanding dramatically, owing to the unexpected formation of valuable products, a variety of reaction modes, ease of sulfoxide synthesis, and mild reaction conditions. In the future, the development of novel sulfoxides and the elegant reaction design will further advance this research field.

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