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Preface

In their analysis of experiments and in their planning of syntheses, organic chemists consciously or unconsciously tend to use the principle of least motion, the chemical equivalent of *Occam's razor*. In rearrangement reactions this principle is violated and may make rearrangements problematic reactions. At the same time, there is always fascination in the unexpected and so rearrangement reactions are also an attractive field of study. Consequently, our understanding of rearrangement reactions is now quite advanced and allows strategic uses in organic synthesis. Here, a helpful tool that may easily be overlooked is the influence of organosulfur functionalities on these rearrangements. In fact, the presence of sulfur may make rearrangements predictable and productive or allow specific transformations which would otherwise require a tedious synthetic detour. The present account is meant to spread this knowledge. In addition, an introductory chapter gives a survey of the basics of organosulfur chemistry to put the information in the individual chapters into perspective and to help readers who are less familiar with the peculiarities of sulfur in an organic environment.

The amount of material requiring coverage was so vast that the volume had to be split into two parts. We hope that readers will appreciate the comprehensive and up-to-date information on sulfur-mediated rearrangements. Fortunately, leading experts were available to write the individual chapters and provide state-of-the-art reviews of the current research on sulfur-mediated rearrangements. It was a pleasure to work with these colleagues and I appreciate their involvement in spite of many other obligations. This volume should help the chemical community in their synthetic work and so it was worth the effort.

Clausthal-Zellerfeld, October 2006 Ernst Schaumann

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Sulfur is More Than the Fat Brother of Oxygen. An Overview of Organosulfur Chemistry

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Abstract A survey of the structure and synthetic applications of organosulfur compounds is given. The emphasis is on the key features of organosulfur chemistry.

Keywords Structure · Reactivity · Chirality · Reagents

Abbreviations

LG	leaving group
LDBB	lithiated 4,4′-di-*tert*-butyl-biphenyl
LDMAN	lithiated 1-dimethylaminonaphthaline
MO	molecular orbital
TBS	*tert*-butyl(dimethyl)silyl
TOMAC	methyl(trioctyl)ammonium chloride

1 Introduction

Replacing oxygen by sulfur in a functional group does not just correspond to a small step in the periodic table, but may well lead to another world of chemistry. The differences in chemical reactivity and stability can be explained by the change in atomic radii, in electronegativity, and in polarizability between oxygen and sulfur. On the other hand, as VIA (group 16) elements oxygen and sulfur have the same number of outer-shell electrons and so there are also many similarities.

The difference in covalent radii of oxygen (70.2 pm) and sulfur (104.9 pm) clearly shows for carbon as bonding partner (covalent radius 77.2 pm) that an organosulfur compound will have a weaker σ bond and also overlap of p_z orbitals in a π bond will be less efficient in a thiocarbonyl as compared to a carbonyl group [1, 2]. In fact, the dissociation energy of the single bond of carbon with oxygen (355–380 kJ/mol) [3] and of the C – S single bond (255 kJ/mol) [4] quantitatively reflects the change in bonding efficiency. The analogous situation is seen for the dissociation energies of the double bond of carbon with oxygen (678.3 kJ/mol) and with sulfur (377 kJ/mol) [5, 6].

The electronegativities are a reflection of electron affinities, ionization potentials and bond energies. Table 1 shows the pertinent data for carbon, oxygen and sulfur. The data clearly demonstrate the familiar situation that in a carbon–oxygen bond the polarization will be with a partial electropositive charge on carbon and with a partial negative charge on oxygen. In contrast, a comparison of the data as given by different methods gives no clear picture of the polarization of the C – S bond. However, the data of the Sanderson scale of electronegativities are of particular interest as this scale is based on the "compactness" of an atom's electron cloud and so represents the polarizability of the atom [2]. This is obviously quite pronounced for sulfur and is an important feature to account for charge stabilization on adjacent centers and for leaving group abilities.

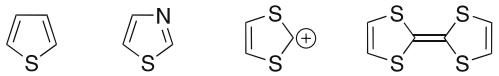
Whatever the direction of the polarization of a C – S bond may be, the polarization is not pronounced and the ionic character of organosulfur compounds is lessened as compared to their oxygen congeners. Therefore, hy-

Table 1 Electronegativities of carbon, oxygen and sulfur on different scales [2, 7]

Element	Pauling	Mulliken	Allred and Rochow	Sanderson
C	2.50	2.63	2.50	2.746
O	3.44	3.17	3.17	3.654
S	2.58	2.41	2.44	2.957

drogen bonding is much less important for sulfur compounds, for example in contrast to alcohols the sulfur in thiols is poor at hydrogen bonding. On the other hand, this makes thiocarboxylic acids and thiols stronger acids than their oxygen analogues.

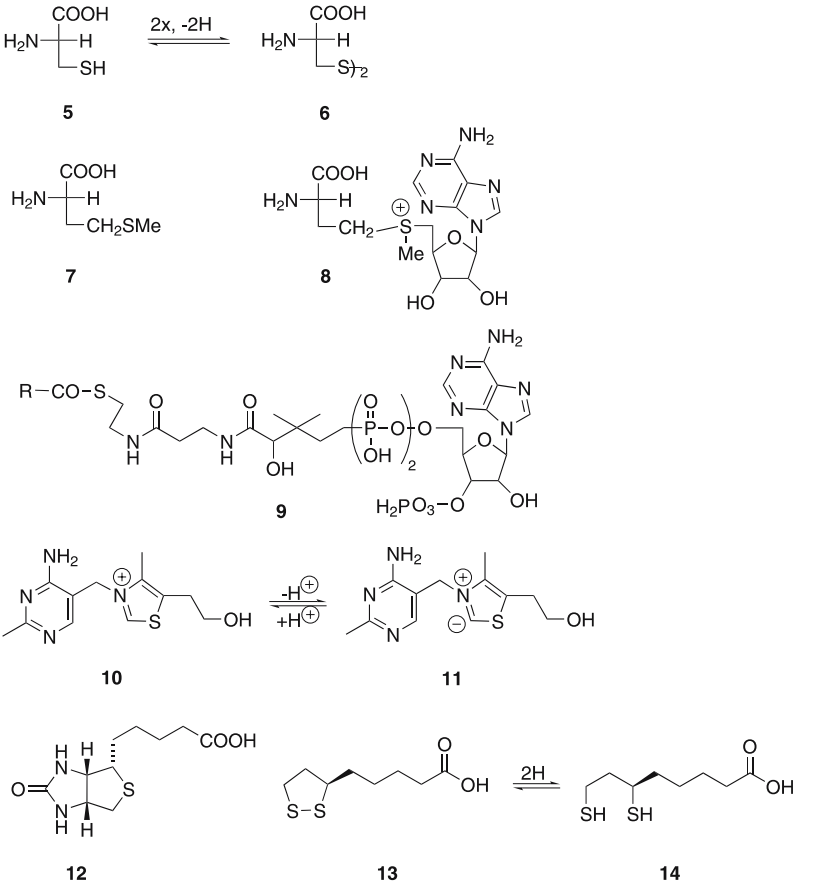
Sulfur plays an important role as a ring member in hetarenes. Actually, thiophene **1** (resonance energy 113 kJ/mol) is less aromatic than benzene, but, interestingly, more aromatic than its oxygen congener furan (resonance energy 75 kJ/mol) [8, 9]. This can be understood in terms of the low electronegativity of sulfur which allows more efficient integration of the nonbonding electron pair into the aromatic system. An explanation involving the d-orbitals of sulfur appears not to be in line with the recent experimental evidence and with MO calculations [8, 9]. Thiazole **2** is another sulfur-containing hetarene with a rich chemistry [10]. Also 1,3-dithiolium salts **3** are aromatic and are of particular interest as starting materials for tetrathiafulvalenes **4** which are superior electron-donating components for charge-transfer complexes and salts with high electrical conductivity ("organic metals") [11–13] (Scheme 1).



1 **2** **3** **4**

Scheme 1 Aromatic sulfur-containing hetarenes and the related tetrathiafulvalene system

Also the importance of organosulfur compounds for the chemistry of life should be noted. Key examples include amino acids such as cysteine **5** with its dehydrogenation product cystine **6** and methionine **7**, the thioester acetyl coenzyme A **9** (R = CH_3), thiamine (Vitamin B_1) **10**, biotin **12** (Vitamin H) or α-lipoic acid **13**. Thus, amino acid **7**, coupled to adenosine as in **8** ("*S*-adenosylmethionine"), is nature's iodomethane or diazomethane equivalent for methyl transfer reactions. Similarly, what an acyl chloride or anhydride is in an organic laboratory, is acyl coenzyme A **9** for acyl transfer reactions in nature. Thiamine **10** gives an example for the use of umpolung chemistry in nature when deprotonation on C-2 of the heteroaromatic ring converts an electrophilic into a nucleophilic center as in **11**. Lipoic acid **13** is involved in biochemical redox chemistry taking up hydrogen from an alcohol to give a carbonyl product [14–16] (Scheme 2).

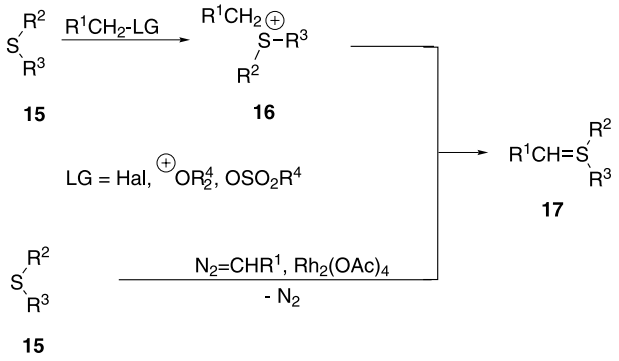


Scheme 2 Sulfur-containing biomolecules

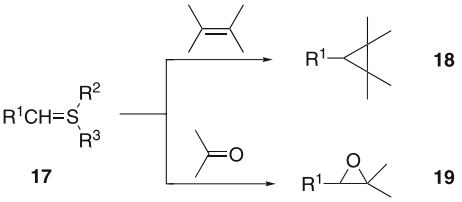
2 Sulfur Ylides

Oxonium salts are in the first place strong alkylating agents [17]. Their sulfur analogues **16** are obtained easily because of the strong nucleophilicity of the sulfide sulfur and they also act as alkyl transfer reagents [18, 19], but their most noteworthy feature is their acidity allowing ready *S*-ylide formation to **17** by base treatment; alternatively, carbene transfer to the parent sulfide **15** is a possible route to *S*-ylides **17** [20] (Scheme 3) [21].

The *S*-Ylides **17** thus formed play an important role in formal methylene transfer to alkenes giving cyclopropanes **18** or to carbonyl compounds giving epoxides **19** [22, 24, 25] (Scheme 4). Interestingly, the reaction of aryldiazomethanes, sulfides and aldehydes shows high diastereoselectivity for *trans*-1,2-disubstituted oxiranes **19** [24].

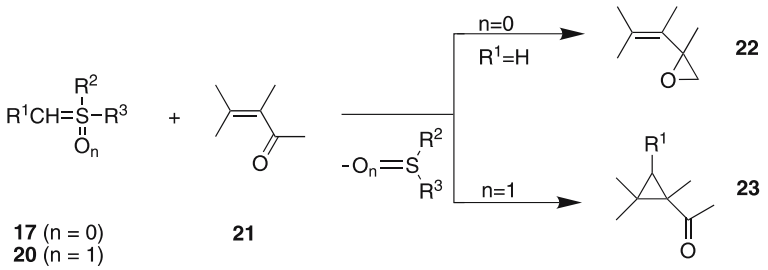


Scheme 3 *S*-Ylide formation from sulfides via sulfonium salts or via carbene transfer



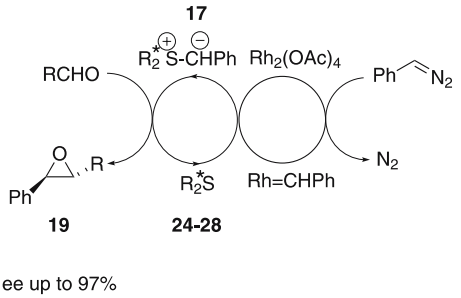
Scheme 4 Cyclopropane or oxirane formation using *S*-Ylides

An interesting dichotomy is observed for α,β-unsaturated carbonyl compounds **21** which give vinyloxiranes **22** or acylcyclopropanes **23** depending on the type of *S*-Ylide used [22] (Scheme 5). In particular, the highly reactive dimethyl-methylen-sulfurane **17** (R^1 = H, R^2 = R^3 = Me) attacks the carbonyl group to give a vinyloxirane **22** while less reactive *S*-Ylides, especially sulfoxonium ylides **20**, add to the C = C unit to give vinyloxiranes.



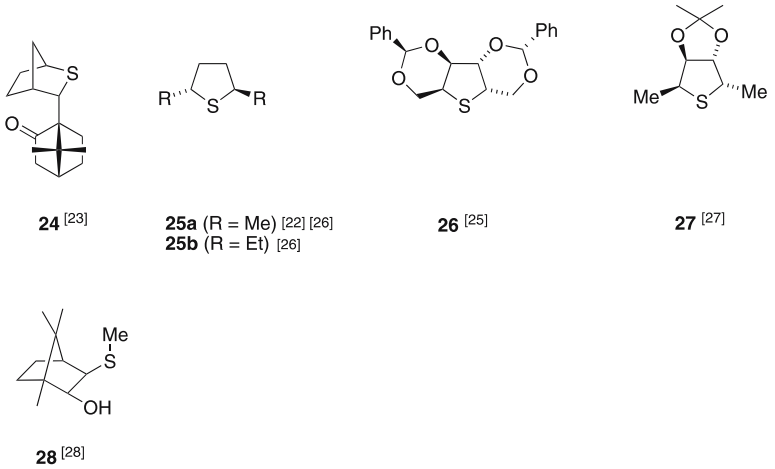
Scheme 5 Acylcyclopropanes or vinyloxiranes from α,β-unsaturated carbonyl compounds and *S*-Ylides

Recently, efficient asymmetric versions of oxirane formation via *S*-Ylides **17** and aldehydes were developed in particular by the Aggarwal [23], Goodman [26] and Metzner groups [27, 28] (Scheme 6). Here, a sulfide with



Scheme 6 Catalytic cycle for enantioselective oxirane formation from aldehydes and chiral *S*-Ylides **24–28**

a chiral carbon backbone is used and allows us to generate oxiranes with high enantioselectivity in a catalytic cycle. Scheme 7 shows sulfides **24–28** as examples of useful sources of chiral information in the enantioselective process.

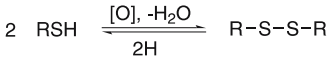


24 [23] **25a** (R = Me) [22] [26] **25b** (R = Et) [26] **26** [25] **27** [27] **28** [28]

Scheme 7 Examples of useful chiral sulfides

3 Oxidation

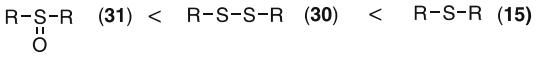
The ready oxidation of sulfur(II) compounds by appropriate reagents is a key feature of organosulfur chemistry. Thus, the reversible oxidation of a thiol **29** to a disulfide **30** is an essential structural element in many biomolecules as mentioned above of the pair cysteine **5**/cystine **6** and in redox chemistry (cf. **13/14**; Scheme 8) [30].



29 **30**

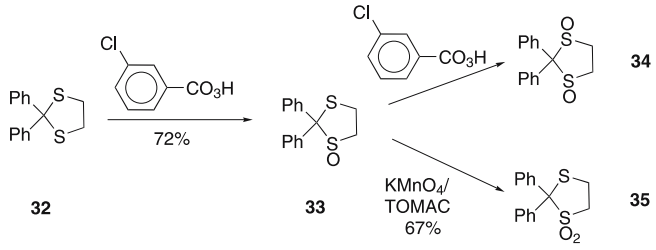
Scheme 8 Thiol/disulfide redox system

The oxidation of sulfides to sulfoxides and sulfones is now usually carried out with *m*-chloroperbenzoic acid. An approximate order of increasing ease of oxidation is given in Scheme 9 [31].



Scheme 9 Relative ease of oxidation of different substrates

This implies that in the competition experiment of sulfide **15** vs. sulfoxide **31** oxidation in a thioacetal *S*-oxide **33** the *S*,*S*′-dioxide **34** is formed preferentially. Selective oxidation of a sulfoxide unit to a sulfone is possible using hydroperoxides [32, 33], peracids in an alkaline medium [34, 35] or in particular permanganate [36, 37]. Scheme 10 shows an example where compound **35** with a sulfone unit in a thioacetal is generated; a reasonable yield is achieved using phase transfer catalysis.

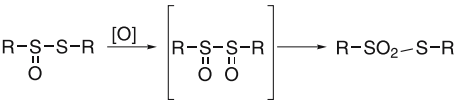


Scheme 10 Selective oxidation of a thioacetal *S*-oxide

Use of alternative oxidizing agents such as hydrogen peroxide/acetic acid may lead to preferential oxidation of disulfides over sulfides [31].

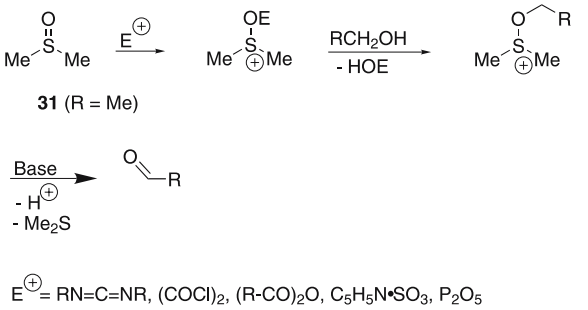
In the oxidation of disulfide *S*-monoxides **36** a possible *S*,*S*′-dioxide **37** usually rapidly rearranges to give the *S*,*S*-dioxide **38** (thiosulfonate *S*-ester; Scheme 11) [38, 39].

Among the sulfoxides, dimethyl sulfoxide (31, R = Me) has found wide application as an oxygen carrier in reagent systems for the oxidation of alcohols, particularly of primary alcohols to aldehydes [40] (Scheme 12). Sulfone chemistry is the main focus in "The Smiles Rearrangement and the Julia-Kocienski Olefination Reaction" by K. Plesniak, A. Zarecki and J. Wicha, in this volume.



36 37 38

Scheme 11 Oxidation of disulfides to thiosulfonates

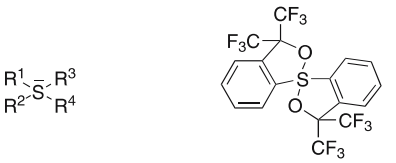


31 (R = Me)

$E^{\oplus}$ = RN=C=NR, $(COCl)_2$, $(R\text{-}CO)_2O$, $C_5H_5N{\bullet}SO_3$, P_2O_5

Scheme 12 Electrophile-assisted oxidation of primary alcohols by dimethyl sulfoxide

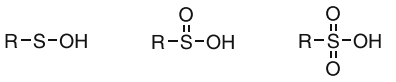
An apparent violation of the octet rule can be seen in sulfuranes **39** where the central sulfur atom shows a decet structure. Such species have been discussed for a long time as reaction intermediates, but with first reports in 1971 [41, 42] stable sulfuranes of type **40** could be prepared and their chemistry be studied in detail [43] (Scheme 13).



39 **40**

Scheme 13 Sulfuranes

Apart from disulfide formation, another formal oxidation pathway of thiols involves increasing incorporation of oxygen to give sulfenic acids **41**, sulfinic acids **42** and finally sulfonic acids **43** (Scheme 14).



41 **42** **43**

Scheme 14 Formal oxidation products of thiols

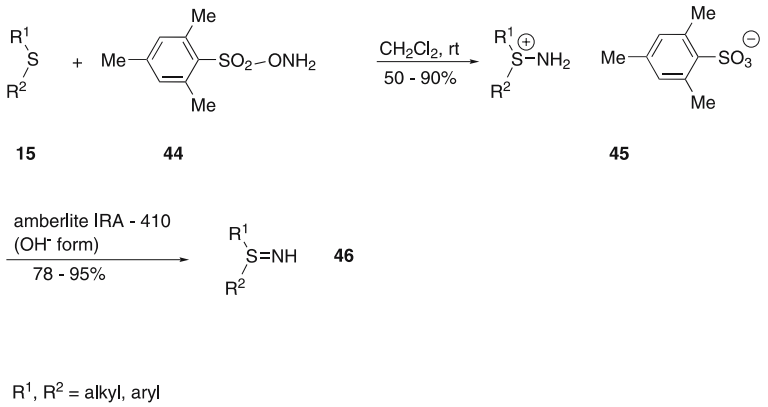
Sulfenic acids **41** are inherently unstable [44], but play a role in biochemical pathways [45, 46]. Sulfinic acids **42** [47] as well as sulfonic acids **43** and their derivatives [48] play an important role as synthetic intermediates.

4
Higher Oxidation States Involving Nitrogen

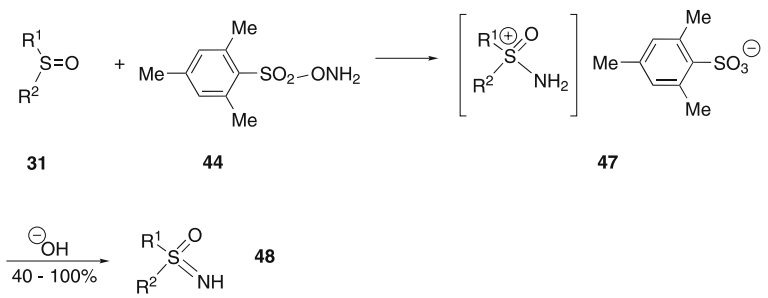
Sulfilimines (Chemical Abstracts nomenclature) or the preferred simpler name sulfimines **46** (IUPAC nomenclature) are the nitrogen analogues of sulfoxides **31** [49, 50]. The synthesis of sulfimines is usually achieved by imination of sulfides **15** using haloamines or -amides, azides or in particular *O*-mesitylenesulfonyl-hydroxylamine (**44**, MSH; Scheme 15) [51].

The MSH method is also useful to obtain sulfoximines **48** from sulfoxides **31** in usually excellent yields [52, 53] (Scheme 16).

Because of their possible chirality (vide infra), sulfoximines **48** have been recognized as an interesting class of synthetic intermediates or as chiral ligands [54].



Scheme 15 Formation of sulfimines by imination of sulfides with MSH (**44**)



Scheme 16 Formation of sulfoximines by imination of sulfoxides with MSH

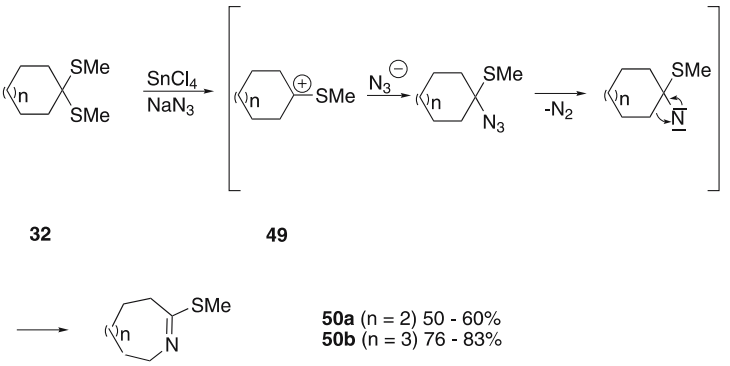
The S – N bond in sulfilimines or sulfoximines is not as strong as the S – O bond in sulfoxides or sulfones. In particular, S – N bond cleavage by reduction or by hydrolysis is a ready reaction [50, 53].

5
Sulfur May Stabilize Carbenium Ions

Even though the difference in electronegativities between carbon and sulfur is negligible, a non-bonding electron-pair in a sulfide unit will exert a stabilizing electron-donating (+ M) effect on a neighboring carbon with a positive charge; alternatively, the stabilizing effect may be ascribed to the polarizability of the sulfur atom (Scheme 17).

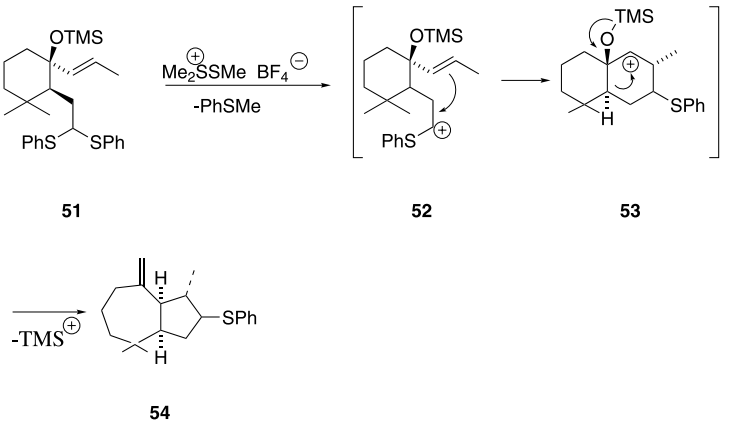
Scheme 17 Sulfur as electron donor to a carbenium ion

Trost noted that thioacetals **32** provide ready access to sulfur-stabilized carbenium ions **49** ("thionium ions") [55] and that these species display enhanced carbonyl reactivity; so they were addressed as "super carbonyl" groups. Thus, in cyclic thioacetals **32** one sulfur unit is removed by the action of tin(IV) chloride (Scheme 18).



Scheme 18 Thioacetals as super carbonyl groups: sulfur substitution by azide and Curtius-type rearrangement

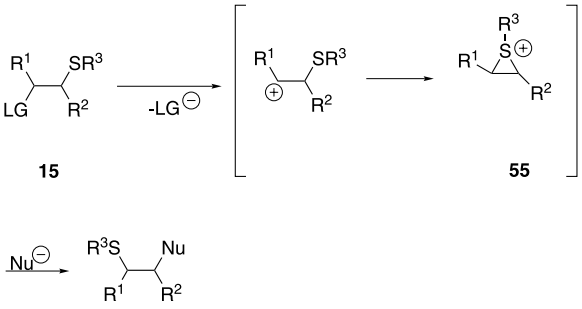
An illustrative example of the carbenium-stabilizing effect of sulfur is provided by a key reaction step in Overman's synthesis of Shahamin K [56]. Treatment of the hydroxyaldehyde derivative **51** with dimethyl(methylthio)-sulfonium tetrafluoroborate (DMTSF) leads apparently to *S*-methylation and from there to elimination of thioanisole to give an *S*-stabilized carbenium ion



Scheme 19 Sulfur-induced pinacol rearrangement in the synthesis of Shahamin K

52 which is attacked by the alkene unit to trigger a pinacol rearrangement in **53** (Scheme 19).

The electron-donating effect of sulfur is also a key feature in 1,2-sulfur shifts (cf. "1,2-Sulfur Migrations" by A. Sromek and V. Gvorgyan, in this volume) which occur via thiiranium intermediates **55** securing the stereoselective nature of the process (Scheme 20).

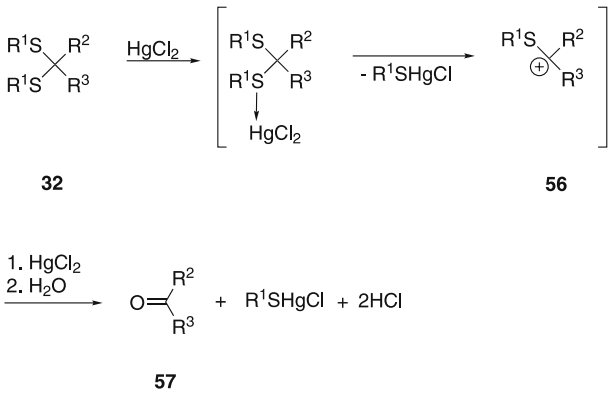


Scheme 20 1,2-Shifts of sulfide groups via thiiranium ions

6
Association with Non-Carbon Electrophiles

Because of the size of the atom, non-bonding electron-pairs on sulfur are softer (more polarizable) than those on oxygen. Consequently, electron-pairs on sulfur are better nucleophiles, but less basic. Following the HSAB principle, sulfur compounds tend to associate preferentially with soft Lewis acids rather than with the hard proton. This is, for example, significant in the for-

mal hydrolysis of thioacetals **32** which, in contrast to acetal hydrolysis, does not work with simple acid catalysis. Instead, soft Lewis acids, especially thiophilic mercury(II) salts, have to be employed. Oxidative methods based on the formation of sulfur(IV) intermediates offer an environmentally benign and often chemically more efficient alternative [57–59] (Scheme 21). As the reaction proceeds via a cationic intermediate **56**, carbenium-stabilizing groups R^2, R^3 will favor hydrolysis to give finally aldehydes or ketones **57**.

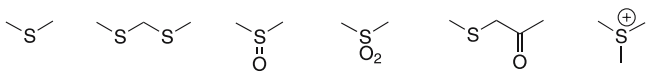


Scheme 21 Hydrolysis of a thioacetal

A specific interaction is observed between thiols **29** and gold. Actually, thiol molecules are adsorbed readily from solution onto gold creating a dense monolayer with the organic tail pointing outwards from the surface [60, 61].

7
Sulfur May Stabilize Carbanions

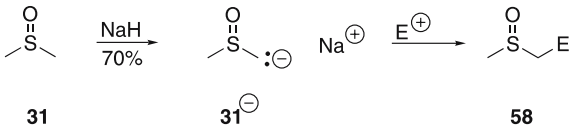
A sulfide, sulfoxide or sulfone group will acidify hydrogen on the adjacent carbon atom. This effect has been explained by resonance-stabilization of the carbanion involving d-orbitals on sulfur, but the polarizability of the sulfur group is now considered to give a better description [62] and also electronegativities have to be taken into account [63]. Actually, the stabilizing effect of a phenyl sulfonyl group is comparable to that of a cyano group, though smaller than that of a carbonyl or nitro function [64]. α-Phenylthio substitution increases the acidity of cyclohexanone by 3 pK units [65]. In Scheme 22



Scheme 22 Order of increasing acidities for some sulfur functionalities

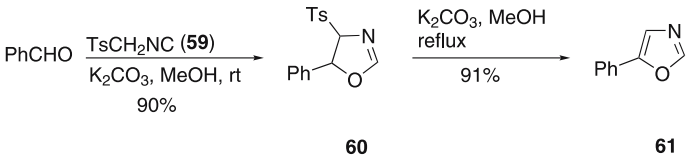
an approximate order of increasing acidities is given for some important sulfur functionalities [66–68].

The deprotonation of sulfonium salts **16** was discussed above as an entry to *S*-Ylides **17**. Sodium methylsulfinylmethylide ("dimsyl sodium") has been found to be formed easily from dimethyl sulfoxide and reacts with electrophiles to give products **58** (Scheme 23), but is also often used as a base [69].



Scheme 23 Formation of sodium methylsulfinylmethylide and reaction with electrophiles

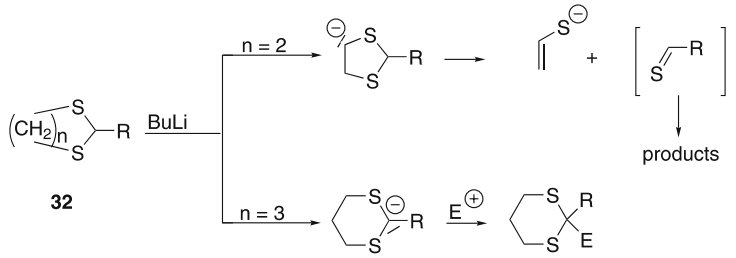
Obviously, it is an advantage for synthetic applications if an acidifying sulfur functionality is combined with another electron-withdrawing group. So there is a rich chemistry of sulfonate- or sulfonamide-stabilized carbanions [70]. Similarly, tosylmethyl isocyanide (**59**, TosMIC) [71, 72] has found a plethora of synthetic applications. Scheme 24 shows an example of oxazole **61** formation [71].



Scheme 24 Deprotonation of "TosMIC" and use in heterocyclic synthesis

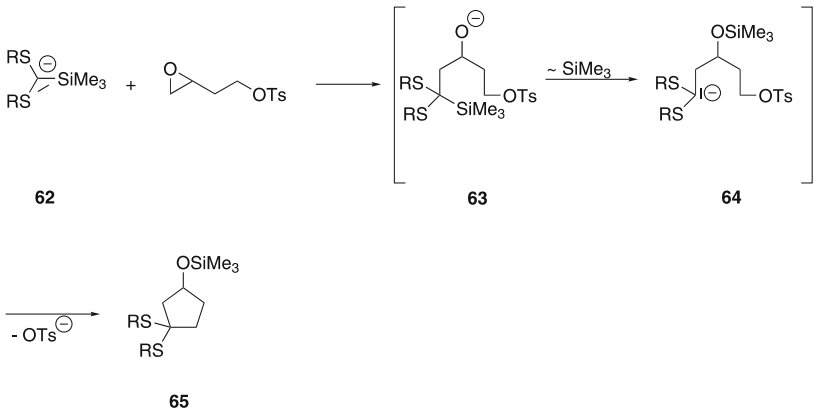
Corey and Seebach noted that, in contrast to acetals, in spite of their moderate acidity thioacetals **32** can be deprotonated and readily react with various types of electrophiles [59, 73–75]. It was emphasized that the thioacetal reaction represents an excellent example of umpolung chemistry as the normal a^1 reactivity of a carbonyl carbon is reversed into d^1 in its thioacetal anion [76, 77]. Cyclic thioacetals of the 1,3-dithiane type (**32**, $n = 3$) usually give the best results [57, 75], whereas the anions of 1,3-dithiolanes (**32**, $n = 2$) tend to give preferentially ring opening by a 1,3-anionic cycloreversion and should be avoided [36, 37, 78] (Scheme 25).

2-Silyl-thioacetals **62** are useful building blocks in a domino process involving a 1,4 silyl migration homo-Brook rearrangement [79] in **63** and giving carbo- or heterocycles; best results are obtained for synthesis of cyclopentanes **65** [80] (Scheme 26).



32

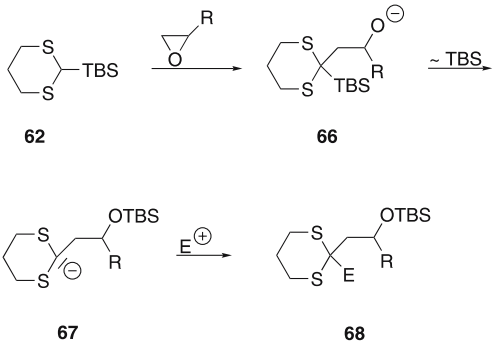
Scheme 25 1,3-Anionic cycloreversion of 1,3-dithiolanes vs. use of 1,3-dithianes in umpolung chemistry



62 63 64 65

Scheme 26 2-Silylthioacetals in a cyclopentane-forming domino process

This type of thioacetal-supported domino process has been successfully applied to secure formation of a second carbanion **67** from 1,3-dithianes **62** [81] (Scheme 27).



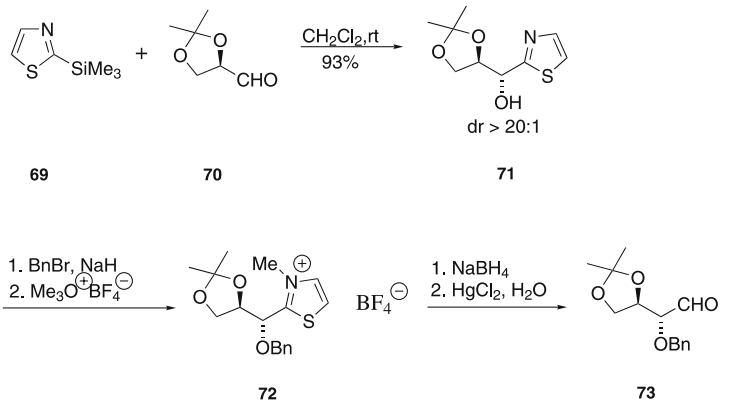
62 66 67 68

Scheme 27 "Linchpin chemistry" using a silyl migration to achieve a formal second thioacetal deprotonation

Elegant applications of this reaction principle in natural product synthesis have been published under the trademark of "linchpin chemistry" [81]. Many more applications of thioacetals in natural product synthesis have been reported [82].

In place of thioacetals, also thioacetal *S*,*S*-dioxides of type **35** have been used as d^1 synthons [83].

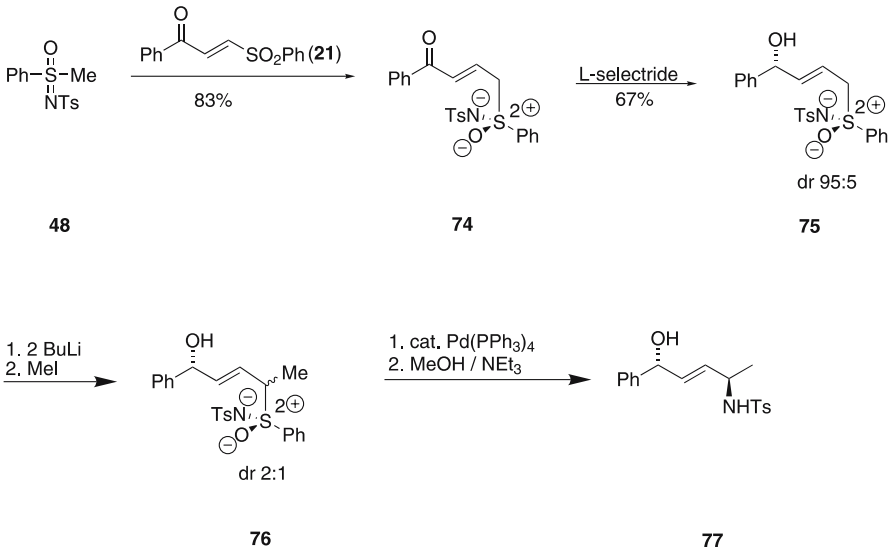
Also other heterocyclic formyl anion equivalents than thioacetals or congeners have been employed [59, 84]. Thus, Dondoni has developed use of 2-lithio-1,3-thiazole or of the corresponding trimethylsilyl derivative **69** as formyl equivalent allowing chain extension of aldehydes such as **70** (Scheme 28) [85, 86]. The heterocyclic auxiliary can be removed by alkylation with Meerwein reagent, reduction with sodium borohydride and mercury chloride-assisted hydrolysis to give aldehyde **73.**



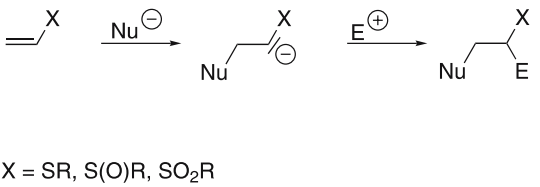
Scheme 28 Chain elongation of 2,3-O-isopropylidene-D-glyceraldehyde with a thiazole reagent

The acidity in the α position to a sulfide, sulfoxide or sulfone function is also seen for sulfoximines and has allowed quite a few synthetic applications [53, 87–89]. Even tandem diastereoselective reactions are possible as shown by the Michael-addition of deprotonated sulfoximine **48** to a sulfonyl-substituted enone **21** and subsequent highly diastereoselective reduction to hydroxyalkenyl-sulfoximine **75.** After methylation to **76,** treatment with a palladium catalyst resulted in reorganization of the *N*-tosyl-sulfoximine unit to an *N*-benzensulfinyl-tosylamide and eventually to tosylamide **77** [90] (Scheme 29).

The stabilizing effect of sulfur functionalities on carbanions is not only important in deprotonation chemistry, but also as an electronic effect in the stabilization of reactive intermediates. Thus, sulfanyl, sulfinyl or sulfonyl substituents on a C = C bond make the alkene electron deficient and encourage nucleophilic addition (Michael addition; cf. Scheme 30) [91].

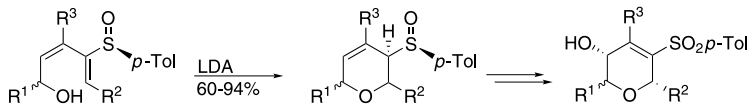


Scheme 29 Diastereoselective synthesis of 1,4-aminoalcohols via 1,4-stereochemical control using sulfoximines



Scheme 30 Michael-type addition reactions to vinyl sulfides, sulfoxides or sulfones

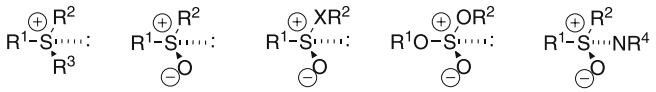
An application giving eventually functionalized dihydropyrans is shown in Scheme 31 [92].



Scheme 31 Cyclization of sulfinyl-substituted dienols to dihydropyrans

8
Chiral Sulfur

Sulfur exhibits pyramidal bonding in sulfonium salts **16**, sulfoxides **31**, sulfinic acid **42** and derivatives, sulfurous acid derivatives **78**, and sulfox-

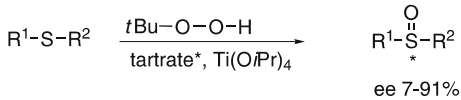


16 31 42 78 48

Scheme 32 Chiral sulfur functionalities

imines **48**. Thus, these compounds are chiral by substitution with unequal residues ($R^1 \neq R^2$, and for sulfonium salts also $\neq R^3$ Scheme 32).

Access to optically active sulfoxides **31** is mainly by oxidation of sulfides **15** in the presence of an optically active catalyst or by nucleophilic substitution on an optically active sulfinate **79** [93]. In the former route, modified Sharpless conditions are employed (Scheme 33) [94, 95]; alternatively, 1,1′-bis-2-naphthol is used [96]. However, the approach is limited to alkyl aryl sulfoxides (**31**; R^1 = alkyl, R^2 = aryl) and even here the efficiency in terms of optical yield is variable [97].



ee 7-91%

15 31

Scheme 33 Oxidation of sulfides to optically active sulfoxides in the presence of D- or L-tartrate

Because of the lack of a general asymmetric oxidation method, carbanion chemistry involving the displacement of a chiral leaving group is often chosen to obtain optically active sulfoxides **31** [93] even though the chiral auxiliary has to be applied in stoichiometric amounts and again only alkyl aryl sulfoxides are obtained with reasonable ee's. Here, the Andersen procedure where an organometallic reagent attacks menthyl *p*-toluenesulfinate **79** is the most popular as separation of sulfinate diastereomers by fractional crystallization is usually convenient [98–100] (Scheme 34).

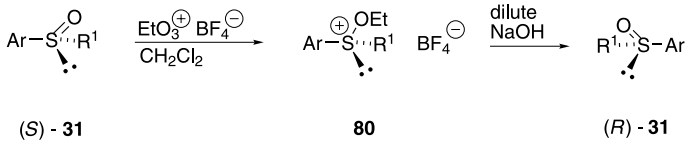
79 31

40-88%
ee 85-98%

R=Me, Et, *i*Pr, Ph, tBuOOCCH$_2$

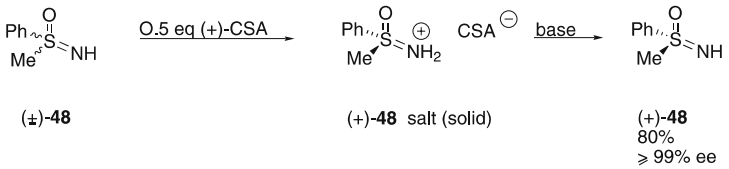
Scheme 34 Non-racemic *p*-tolyl alkyl sulfoxides from menthyl *p*-toluenesulfinate

The Andersen procedure normally provides products with sulfur in the *S* configuration. If the enantiomer is desired, the Johnson approach of alkylation to **80** and hydrolysis by aqueous base allows inversion of configuration (Scheme 35) [100, 101].



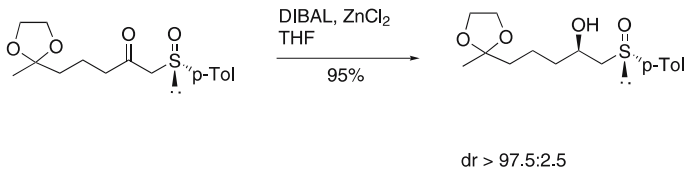
Scheme 35 Inversion of configuration in a sulfoxide

Convenient access is available to an optically pure sulfoximine **48** by fractional crystallization with (+)-camphorsulfonic acid (CSA); the (+)-enantiomer of *S*-methyl-*S*-phenylsulfoximine forms a solid salt with CSA that can be cleaved by base to give the pure (+) form while the (–) form can be isolated from the filtrate (Scheme 36) [102, 103].



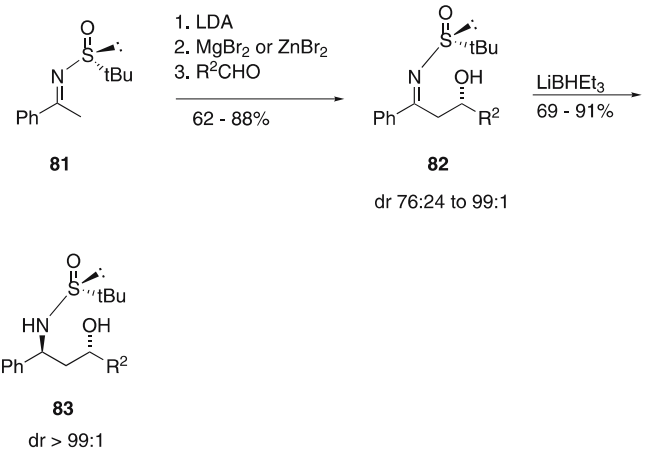
Scheme 36 (+)-*S*-Methyl-*S*-phenylsulfoximine by crystallization with CSA

There are numerous examples where chiral sulfur functionalities serve as the auxiliary in asymmetric synthesis [104]. Very often, based on the Andersen approach, non-racemic *p*-tolyl-substituted sulfoxides are applied [105, 106]. Thus, it has been shown that a sulfoxide group as a chiral sulfur auxiliary allows a diastereoselective reduction of a neighboring oxo group [107] (Scheme 37).



Scheme 37 Sulfoxide-directed diastereoselectivity in ketone reduction

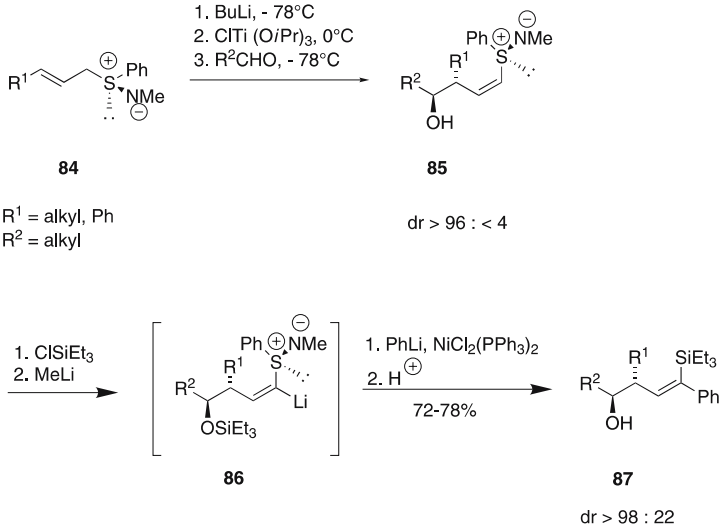
The Davis [108] and Ellman [109, 110] groups have demonstrated that chiral sulfinylimines **81** are very useful auxiliaries allowing various synthetic transformations with full control of the configuration. Thus, sulfinylimines **81** with α-hydrogen can be used as chiral aza-enolates in a modified aldol



Scheme 38 Aza-aldol reaction with diastereoselective control by a sulfinylimine group

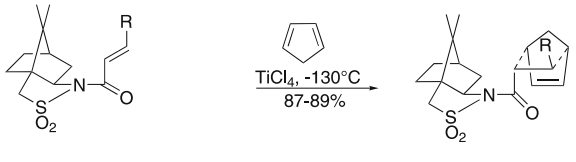
reaction to provide hydroxyalkylimines **82**; further highly diastereoselective reduction yields 1,3-aminoalcohols **83** [111] (Scheme 38).

Presently, sulfoximines **48** may be the most popular example of a sulfur-based functional group which is used in asymmetric synthesis [53]. Thus, the titanates of non-racemic *trans*-allyl sulfoximines **84** add aldehydes in a highly regio- and diastereoselective fashion to give *anti*-(*Z*)-configured homoallylic alcohols **85** [112]; subsequent silylation and deprotonation, followed by a nickel-catalyzed substitution initiates a 1,5 silicon migration and provides homoallylic alcohol **87** with a vinyl silane moiety [113] (Scheme 39).



Scheme 39 Reaction of the anions of allyl sulfoximines with aldehydes

In asymmetric versions of the Diels–Alder reaction, Oppolzer found a practical control element which at the same time activates the dienophile and is based on the presence of a sultam unit as in **88** [114] (Scheme 40). In the presence of a Lewis acid and at low temperatures excellent diastereomeric excess in [4 + 2] cycloadduct **89** (dr up to 99 : 1) could be achieved.

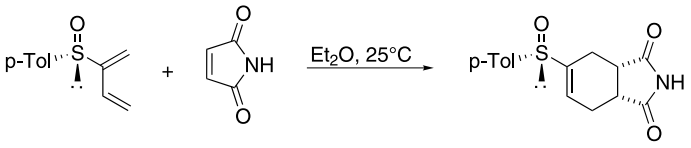


88 **89**

R=H, Me

Scheme 40 The Oppolzer sultam as a chiral auxiliary in Diels–Alder reactions

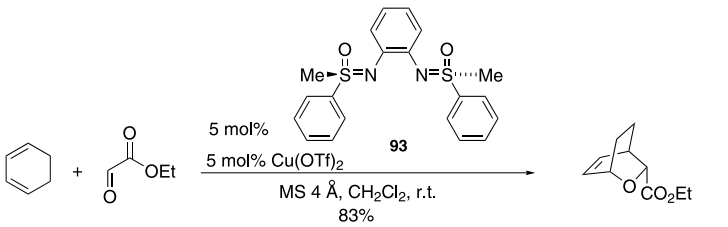
A chiral sulfoxide substituent in the 1- or 2-position of a diene gives a chiral 4π component of a Diels–Alder reaction [115]. Thus, reaction of the optically pure dienylsulfoxide **90** with maleimide **91** gives cycloadduct **92** as a single enantiomer [116] (Scheme 41).



90 **91** **92**

Scheme 41 [4 + 2] Cycloaddition of an optically pure dienylsulfoxide

A non-racemic sulfur functionality is also a useful feature in a catalyst for [4 + 2] cycloaddition; very good results were obtained with the C2-symmetric bis(sulfoximine) copper(II) complex **93** [117] (Scheme 42).



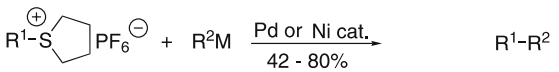
98% ee, endo:exo 99:1

Scheme 42 Enantioselective catalysis of a [4 + 2] cycloaddition by a C2-symmetric sulfoximine ligand

9
Sulfur as the Leaving Group

The main goal in doing organosulfur chemistry is usually to achieve a specific transformation with ease and elegance, but once this has been achieved there is often no more need for the presence of sulfur and the sulfur has to be removed—preferably in a way that will generate another useful functionality. The main routes to remove sulfur are substitution, elimination, oxidation and reduction.

In substitution reactions, the excellent polarizability makes thiolates and their oxygen-substituted congeners good leaving groups. A current field of application is CC bond formation by reaction of a sulfur-functionalized substrate and an organometallic compound [118, 119]. Thus, Stille-, Suzuki-, and Negishi-type cross-coupling reactions are possible between thiolane-derived sulfonium salts **94** and organotin compounds, boronic acids, or organozinc compounds in the presence of palladium or nickel catalysts [120] (Scheme 43).



94 **95**

R^1 = Ar, Hetaryl, Bn
R^2 = Alkenyl
M = Sn, B, Zn

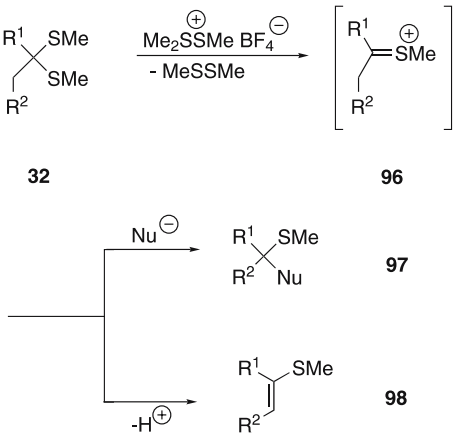
Scheme 43 Cross-coupling of sulfonium salts with organometallics

Trost found that reaction of thioacetals **32** with dimethyl(methylthio)sulfonium fluoroborate (DMTSF) offers an efficient way to substitute one alkylthio group via an intermediate thionium salt **96**; from here, substitution by nucleophiles or elimination are possible giving products **97** and **98**, respectively [121] (Scheme 44; cf. also Scheme 18).

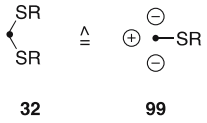
Combined with the possibility to deprotonate thioacetals and add electrophiles to the resulting carbanion (vide supra), the reaction of Scheme 44 implies that a thioacetal is the equivalent of a dianion-cation [121] (Scheme 45).

For alkene-forming elimination reactions, a study of vinyl sulfone **102** formation from a series of 2-substituted sulfones **100** has allowed to determine the relative order of sulfur-based leaving groups (Scheme 46) [122].

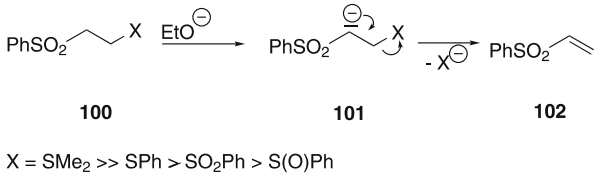
A sulfone unit may also be employed in thermal elimination reactions as shown by the pyrolysis of a dihydroisothianaphthene dioxide **103** to give the highly reactive o-quinodimethane **104** (Scheme 47) [123].



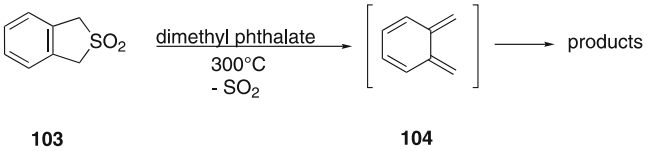
Scheme 44 Reaction of thioacetals with dimethyl(methylthio)sulfonium fluoroborate (DMTSF)



Scheme 45 Thioacetals as dianion-cation equivalent



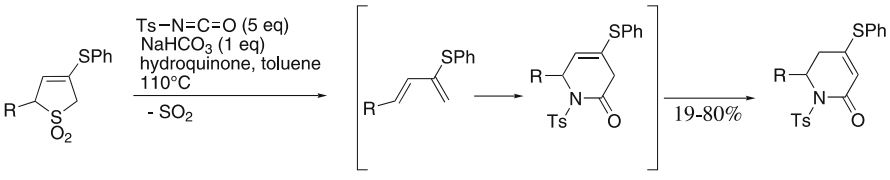
Scheme 46 Relative leaving-group abilities of sulfur-based functions in vinyl sulfone formation



Scheme 47 Elimination of sulfur dioxide from a cyclic sulfone

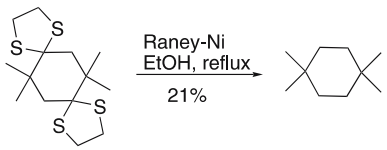
Similarly, sulfur dioxide extrusion from 3-sulfolenes **105** generates reactive dienes **106** which can, for example, be employed in aza-Diels–Alder reactions to give pyridine derivatives **108** via **107** [124] (Scheme 48).

In the reduction of carbonyl compounds to alkanes, use of thioacetals **32** sometimes shows advantages over Wolff–Kishner procedures [125]; in Scheme 49 an example of a two-fold reduction is given.



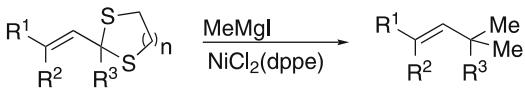
105 106 107 108

Scheme 48 Extrusion of sulfur dioxide from 3-sulfolenes as a route to aza-Diels–Alder chemistry



Scheme 49 Alkane formation by reduction of thioacetals

The classical reduction of thioacetals **32** is nicely complemented by procedures of reductive alkylation giving compounds with quaternary carbons in good yields (Scheme 50) [126, 127].

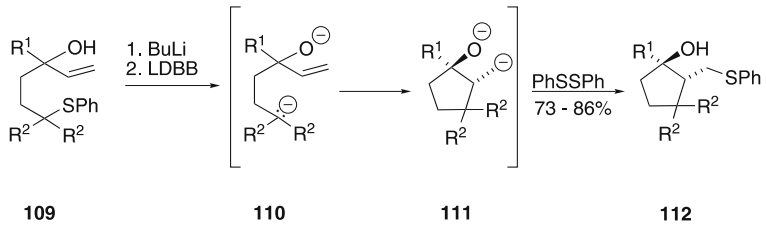


n=1,2
R^1, R^2, R^3=H, alkyl, aryl

Scheme 50 Nickel-catalyzed reductive alkylation of allylic thioacetals

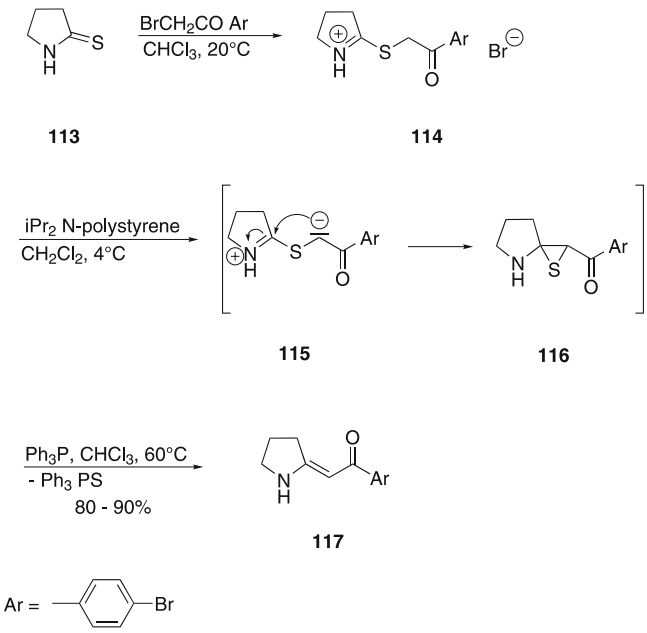
Cohen found that treatment of sulfide or thioacetal units by the radical anion of 1-dimethylamino-naphthaline (LDMAN) or 4,4′-di-*tert*-butyl-biphenyl (LDBB), each as lithium salt, gives reductive metallation yielding highly reactive carbanions [128]; Scheme 51 shows an example where the intermediate carbanion **110** undergoes ring closure to **111** and is finally intercepted by diphenyl disulfide to yield sulfide **112**.

Sometimes, a constructive way to eliminate sulfur is by way of forming a strained three-membered ring (in particular a thiirane or a thiirane *S*,*S*-dioxide) which easily eliminates sulfur or sulfur dioxide. An elegant application of the first-mentioned possibility is the Eschenmoser reaction which allows us to convert thioamides into β-aminoenones (equivalents of 1,3-dicarbonyl compounds) by way of an alkylation reaction. Thus, thiobutyrolactam **113** is alkylated with a phenacyl bromide to give a thioimidate **114** which by base-treatment easily forms an enolate **115**. This intermedi-



Scheme 51 Reductive metallation of a sulfide by lithiated 4,4′-di-*tert*-butyl-biphenyl (LDBB), ring closure and interception by diphenyl disulfide

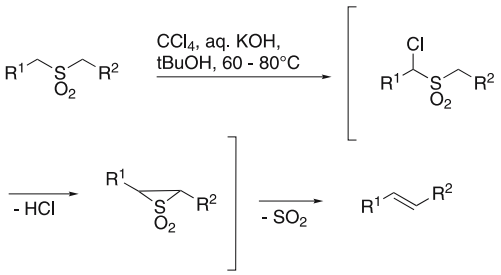
ate cyclizes to a thiirane **116** by attacking the electrophilic iminium unit. Finally, thiirane **116** is desulfurized by a phosphorus(III) reagent to give β-aminoenone **117** (Scheme 52) [129]. Additional examples are found in the recent literature [130, 131].



Scheme 52 Eschenmoser reaction of thiobutyrolactam **113** to giver a β-amino-enone **117**

Extrusion of sulfur dioxide from a thiirane *S*,*S*-dioxide intermediate is a key feature of the Ramberg–Bäcklund reaction [132, 133]. Interestingly, this reaction is sometimes addressed as a rearrangement [134–136], but a closer

look shows that no reorganization of the carbon framework takes place but formation of a C = C bond in the position of a previous sulfone unit (Scheme 53).

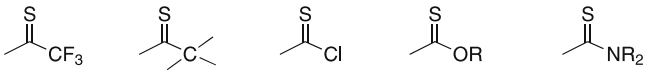


Scheme 53 The Ramberg–Bäcklund reaction

A particularly elegant way of making synthetic use of a sulfur functionality is the Mislow–Evans rearrangement which allows us to convert allyl sulfoxides into allyl alcohols (cf. "[2,3]-Sigmatropic Rearrangements of Allylic Sulfur Compounds" by M. Regglin, in this volume).

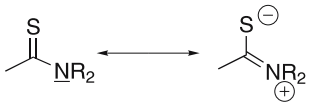
10
Carbonyl vs. Thiocarbonyl Chemistry

The carbonyl group is certainly the most important functional group as shown, for example, by the importance of aldol chemistry or of olefination reactions. So many carbonyl compounds will be among the standard repertoire of an organic laboratory. In contrast, thiocarbonyl compounds may be highly unstable, elusive species. As pointed out above, this can be explained in terms of poor overlap of orbitals in a 2p–3p π bond between carbon and sulfur. However, a closer look shows that thiocarbonyl compounds comprise a wide range of stability and reactivity depending on the substituents of the thiocarbonyl group. If thioformaldehyde is taken as a basis, substituents may lead to decreasing charge density on sulfur giving a polarization that is the inverse of the charge distribution in carbonyl compounds, or substituents may have the opposite effect. For some typical residues, the following order of increasing nucleophilicity and accordingly decreasing electrophilicity of the sulfur may be given [137] (Scheme 54):



Scheme 54 Sequence of increasing nucleophilicity (decreasing electrophilicity) of thiocarbonyl compounds

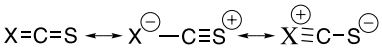
Consequently, hexafluorothioacetone is the prototype of a thiocarbonyl compound with electrophilic sulfur showing—relative to ketones—an inverse sense of addition reactions [138]. In contrast, high negative charge density is seen for the sulfur in thioamides, thionocarbamates and thioureas because of resonance interaction between the non-bonding electron pair on nitrogen and the carbon–sulfur π bond favoring resonance structure **118b** (Scheme 55):



118a **118b**

Scheme 55 Thioamide resonance

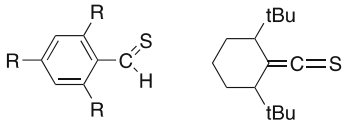
The same considerations apply to compounds with a cumulated thiocarbonyl unit. If the atom X at the other end of the cumulated system can act as an electron-donor because of available π or non-bonding electrons, resonance structure **119c** will be important giving some stability to the system whereas the reverse is true for groups X which are electron-accepting and favor resonance structure **119b** (Scheme 56).



119a **119b** **119c**

Scheme 56 Resonance in cumulated thiocarbonyl systems

So thionocarboxylic [139, 140] and thionocarbonic acid derivatives [141, 142] and also isothiocyanates (X = RN) [143] or carbon disulfide (X = S) [143, 144] are compounds with a highly nucleophilic sulfur as shown in **118b**, **119c**, but their thermal stability is quite pronounced. Even thioketenes may enjoy considerable stability if cumulated with a triphenylphosphoranylidene (X = $R_3P=C$) or an alkylidene unit (X = $R_2C=C$) [137, 145] or if the system is cumulated as in carbon subsulfide (X = S = C = C) [146]. The notorious instability of thiocarbonyl compounds is in particular seen for thioaldehydes [114, 147–150], aliphatic thioketones [114, 151–155] and thioketenes [137, 145] where an ambiphilic nature may be assigned to the C = S group giving a high tendency to dimerize, oligomerize or even polymerize. However, the thermodynamic lability of the thiocarbonyl group may be overruled by kinetic stabilization using bulky substituents. Typical examples include Okazaki's thioaldehydes **120** [156, 157] and thioketene **121** [158] (Scheme 57).



120 121

R=CH(SiMe$_3$)$_2$, tBu

Scheme 57 Examples of thiocarbonyl compounds with steric stabilization

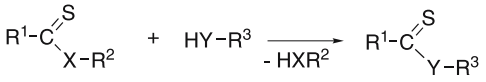
In thiocarbonyl compounds which lack electronic stabilization and which have hydrogen in the α position as in **122**, formation of the corresponding enethiol **123** is much more favored than enolization for carbonyl compounds (Scheme 58).

122 123

Scheme 58 Thione-enethiol tautomerism

So rapid formation of the enethiol is often observed on synthesizing a thioketone with α hydrogen(s).

While acylation is a standard reaction in organic chemistry, thioacylation is much more delicate. The reason is that the sulfur equivalents of the usual acylating reagents, i.e. thioacyl chlorides, thionoanhydrides or thioketenes, are unstable or even elusive species. So thioacylation chemistry is mainly based on thionoesters (**124**, X = O) or dithioesters (**124**, X = S) [140, 159] which are activated by the leaving-group efficiency of residue R^2 (Scheme 59) or by special reaction conditions [130, 160, 161].



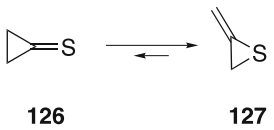
124 125

X = O, S
Y = O, S, NR^1; NNR^{4}R^5 etc.

Scheme 59 Thioacylation

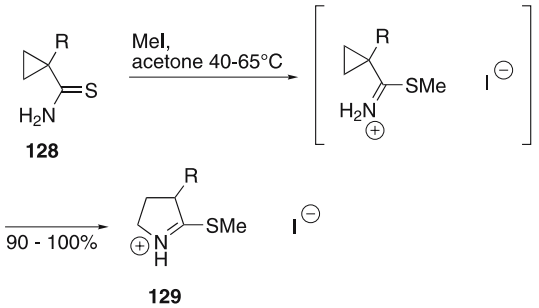
Cyclopropanethione **126** is handicapped by a non-stabilized thiocarbonyl group and by ring strain. So it is an elusive species and a formal 1,3 sig-

matropic shift will rapidly give methylenethiirane **127** [162] (Scheme 60). Similarly, ring strain probably is the main driving force in the rearrangement of cyclopropanethiocarboxamides **128** to pyrrolines **129** [163] (Scheme 61).



126 **127**

Scheme 60 Rearrangement of cyclopropanethione



128 **129**

R = Me, CF_3, COOBu, NHBz, OBn, Ph

Scheme 61 Formal 1,3-sigmatropic shift in cyclopropanethiocarboxamides

A special feature of thiocarbonyl compounds is the relatively small energy for a n,π^* transition making thioaldehydes, thioketones, thioketenes and thioquinones colored. A rich photochemistry has been reported also involving the π,π^* transition [164, 165] which quite often leads to different photoreactions.

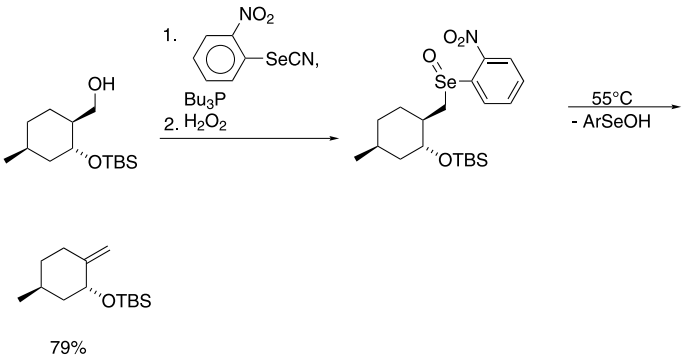
Furthermore, the relatively weak C = S π-bond makes thiocarbonyl compounds useful in cycloaddition chemistry, where the thiocarbonyl compounds normally enter as 2π systems, but 4π reactivity of α,β-unsaturated thiocarbonyl compounds is also seen [130, 160]. In particular, thiones are "superdipolarophiles" in [2 + 3] cycloaddition reactions, for example with diphenyldiazomethane [166], and have also been named "superdienophiles" in Diels–Alder reactions [167].

The inefficient p_π–p_π C = S bond is the basis for the thione-thiol (Newman–Kwart) rearrangement (see "Thione-thiol Rearrangement: Newman–Kwart Rearrangement and Others" by C. Zonta, O. de Lucci, R. Volpicelli and L. Cotarca, in this volume) and is an interesting feature in the efficiency of [3.3] sigmatropic rearrangements of allyl vinyl sulfide-type compounds (see

"Sulfur Participation in [3,3]-Sigmatropic Rearrangements" by R. Fernandez, de la Pradilla, M. Tortosa and A. Viso, in this volume).

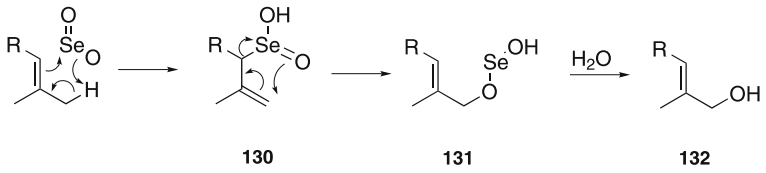
11 And Selenium?

When sulfur is so beneficial in many organic transformations, the question may be raised whether selenium isn't even more useful. In fact, some reactions of organosulfur chemistry proceed with greater ease or under milder conditions if the corresponding selenium compound is employed [168–170]. A prominent example is the alkene-forming elimination of selenoxides; Scheme 62 shows an illustrative example from a natural product synthesis [171].



Scheme 62 C = C Bond formation by thermolysis of a selenoxide

Selenium dioxide has been used for specific oxidation reactions. An important application is the hydroxylation of allylic C – H bonds [172]. The reaction proceeds with complete stereocontrol indicating a sequence of ene reaction and [2, 3]-sigmatropic rearrangement of intermediate **131** (Scheme 63).



Scheme 63 Allylic oxidation using selenium dioxide

However, concerns about the toxicity of organoselenium compounds [173] apparently hamper the broad use of these materials as reagents and as synthetic intermediates.

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References

1. Hardt HD (1987) Die periodischen Eigenschaften der chemischen Elemente, 2nd edn. Thieme, Stuttgart
2. Sanderson RT (1983) J Am Chem Soc 105:2259
3. Lovering EG, Laidler KJ (1960) Can J Chem 38:2367
4. Pitzer KS (1948) J Am Chem Soc 70:2140
5. Pauling L (1948) The Nature of the Chemical Bond. Cornell, Ithaca
6. Grelbig T, Pitter B, Seppelt K (1987) Chem Ber 120:815
7. Cotton FA, Wilkinson G (1982) Anorganische Chemie, 4th edn. Verlag Chemie, Weinheim
8. Henriksson-Enfoe A (1985) In: Gronowitz S (ed) Thiophene and its Derivatives. Wiley, New York
9. Eicher T, Hauptmann S (1994) Die Chemie der Heterocyclen. Thieme, Stuttgart
10. Kikelj D, Urleb U (2002) In: Schaumann E (ed) Science of Synthesis, vol 11. Thieme, Stuttgart, p 627
11. Schukat G, Fanghänel E (2002) In: Schaumann E (ed): Science of Synthesis, vol 11. Thieme, Stuttgart, p 191
12. Segura JL, Martín N (2001) Angew Chem 113:1416
13. Segura JL, Martín N (2001) Angew Chem Int Ed 40:1372
14. Damani LA (1988) Sulphur-containing drugs and related organic compounds. Ellis Horwood, Chichester
15. Lehninger AL (1987) Prinzipien der Biochemie. de Gruyter, Berlin
16. Tolstikov GA, Shul'ts EE, Tolstikov AG (1997) Russ Chem Rev 66:813
17. Meerwein H (1965) In: Houben–Weyl–Müller, vol VI/3. Thieme, Stuttgart, p 325
18. Nenaidenko VG, Balenkova ES (2003) Russ J Org Chem 39:391
19. Tillett J (1976) Chem Rev 76:747
20. Aggarwal V, Richardson J (2004) In: Padwa A (ed) Science of Synthesis, vol 27. Thieme, Stuttgart, p 21
21. Heydt H, Vilsmaier E (1985) In: Klamann D (ed) Houben–Weyl–Müller, vol E11. Thieme, Stuttgart, p 405
22. Claus PK (1985) In: Klamann D (ed) Houben–Weyl–Müller, vol E11. Thieme, Stuttgart, p 1344
23. Aggarwal VK, Richardson J (2003) Chem Commun 2644
24. Aggarwal VK, Aragnocillo C, Winn CL (2005) Synthesis 1378
25. Lakeev SN, Maydanova IO, Galin FZ, Tolstikov GA (2001) Russ Chem Rev 70:655
26. Winn CL, Bellenie BR, Goodman JM (2002) Tetrahedron Lett 43:5427
27. Zanardi J, Leriverend C, Aubert D, Julienne K, Metzner P (2001) J Org Chem 66:5620
28. Davoust M, Brière JF, Jaffrès PA, Metzner P (2005) J Org Chem 70:4166
29. Tang Y, Ye S, Sun XL (2005) Synlett 2720
30. Procter DJ (2000) J Chem Soc Perkin Trans 1:335
31. Weigand W, Bräutigam S, Mloston G (2003) Coord Chem Rev 245:167
32. Ogata Y, Suyama S (1971) Chem Ind 707
33. Ogata Y, Suyama S (1973) J Chem Soc, Perkin Trans 1:755
34. Curi R, Modena G (1963) Tetrahedron Lett 1749

35. Curi R, Modena G (1965) Tetrahedron Lett 863
36. Schaumann E, Wriede U, Rühter G (1983) Angew Chem 95:52
37. Schaumann E, Wriede U, Rühter G (1983) Angew Chem Int Ed Engl 22:55
38. Freeman F (1984) Chem Rev 84:117
39. Oshida H, Ishii A, Nakayama J (2002) Tetrahedron Lett 43:5033
40. Schaumann E (1984) In: Kropf H (ed) Houben–Weyl–Müller, vol VI/1b. Thieme, Stuttgart, p 879
41. Martin JC, Arhart R (1971) J Am Chem Soc 93:2339
42. Kapovits I, Kalman A (1971) Chem Commun 649
43. Furukawa N, Sato S (1999) Top Curr Chem 205:89
44. O'Donnell JS, Schwan AL (2004) J Sulfur Chem 25:183
45. Block E (1992) Angew Chem 104:1158
46. Block E (1992) Angew Chem Int Ed Engl 31:1135
47. Krauthausen E (1985) In: Klamann D (ed) Houben–Weyl–Müller, vol E11. Thieme, Stuttgart, p 618
48. Pawlenko S (1985) In: Klamann D (ed) Houben–Weyl–Müller, vol E11. Thieme, Stuttgart, p 1055
49. Oae S, Furukawa N (1983) Sulfilimines and Related Derivatives, ACS Monograph 179. ACS, Washington, DC, p 7
50. Haake M (1985) In: Klamann D (ed) Houben–Weyl–Müller, vol E11. Thieme, Stuttgart, p 887
51. Tamura Y, Minamikawa J, Ikeda M (1977) Synthesis 1
52. Haake M (1985) In: Klamann D (ed) Houben–Weyl–Müller, vol E11. Thieme, Stuttgart, p 1299
53. Reggelin M, Zur C (2000) Synthesis 1
54. Okamura H, Bolm C (2004) Chem Lett 33:482
55. Trost BM, Vaultier M, Santiago ML (1980) J Am Chem Soc 102:7929
56. Overman LE, Lebsack AD, Valentekovich RJ (2001) J Am Chem Soc 123:4851
57. Seebach D (1969) Synthesis 17
58. Burghardt TE (2005) J Sulfur Chem 26:411
59. Gröbel BT, Seebach D (1977) Synthesis 357
60. Brust M, Walker M, Bethell D, Schiffrin DJ, Whyman R (1994) J Chem Soc, Chem Commun 801
61. Templeton AC, Wuelfing WP, Murray RW (2000) Acc Chem Res 33:27
62. Lehn JM, Wipff G (1976) J Am Chem Soc 98:7498
63. Wiberg KB, Castejon H (1994) J Am Chem Soc 116:10489
64. Solladié G (1991) In: Trost BM, Fleming I, Winterfeldt E (eds) Comprehensive Organic Synthesis, vol 6. Pergamon Press, Oxford, p 133
65. Coates RM, Pigott HD, Ollinger J (1974) Tetrahedron Lett 3955
66. Bordwell FG (1988) Acc Chem Res 21:456
67. Bordwell FG, Liu WZ (1998) J Phys Org Chem 11:397
68. Cheng JP, Liu B, Zhao Y, Sun Y, Zhang XM, Lu Y (1999) J Org Chem 64:604
69. Mondal M (2005) Synlett 2697
70. Postel D, Nguyen van Nhien A, Marco JL (2003) Eur J Org Chem 3713
71. Van Leusen D, Van Leusen AM (2001) Org React 57:417
72. Tandon VK, Rai S (2003) Sulfur Rep 24:307
73. Corey EJ, Seebach D (1965) Angew Chem 77:1134–1135
74. Corey EJ, Seebach D (1965) Angew Chem Int Ed Engl 4:1075–1077
75. Corey EJ, Seebach D (1975) J Org Chem 40:231
76. Seebach D (1969) Angew Chem 81:690

77. Seebach D (1969) Angew Chem Int Ed Engl 8:639
78. Schaumann E (1986) Bull Soc Chim Belges 95:995
79. Moser WH (2001) Tetrahedron 57:2065
80. Schaumann E, Kirschning A (2007) Synlett (in press)
81. Smith AB III, Adams CM (2004) Acc Chem Res 37:378
82. Yus M, Najera C, Foubelo F (2003) Tetrahedron 59:6147
83. Ogura K, Tsuruda T, Takahashi K, Iida H (1986) Tetrahedron Lett 27:3665
84. Aitken RA, Thomas AW (2001) Adv Heterocycl Chem 79:89
85. Dondoni A (1998) Synthesis 1681
86. Dondoni A, Marra A (2004) Chem Rev 104:2557
87. Johnson CR, Barbachyn MR, Meanwell NA, Stark CJ Jr, Zeller JR (1985) Phosphorus Sulfur 24:151
88. Johnson CR (1985) Aldrim Acta 18:3
89. Pyne SG (1999) Sulfur Rep 21:281
90. Pyne SG, Dong Z (1999) Tetrahedron Lett 40:6131
91. Carretero JC, Arrayas RG, Buezo ND, Garrido JL, Alonso I, Adrio J (1999) Phosphorus Sulfur Silicon Relat Elem 153/154:259
92. de la Pradilla RF, Tortosa M (2004) Org Lett 6:2157
93. Capozzi MAM, Cardellicchio C, Naso F (2004) Eur J Org Chem 1855
94. Pitchen P, Duñach E, Deshmukh, Kagan HB (1984) J Am Chem Soc 106:8188
95. Di Furia F, Modena G, Seraglia R (1984) Synthesis 325
96. Komatsu N, Hashizume M, Sugita T, Uemura S (1993) J Org Chem 58:4529,7624
97. Bolm C (2000) Peroxide Chem 494
98. Andersen KK, Gaffield W, Papanikolaou E, Foley JW, Perkins RI (1964) J Am Chem Soc 86:5637
99. Andersen KK (1988) In: Patai S, Rappoport Z, Stirling C (eds) The chemistry of functional groups, The chemistry of sulfones and sulfoxides. Wiley, Chichester, p 55–94
100. Barbachyn MR, Johnson CR (1984) In: Morison JD, Scott JW (eds) Asymmetric Synthesis, vol 4. Academic, Orlando, p 227
101. Johnson CR, McCants D Jr (1965) J Am Chem Soc 87:5404
102. Shiner CS, Berks AH (1988) J Org Chem 53:5542
103. Brandt J, Gais HJ (1997) Tetrahedron Asymmetry 8:909
104. Gnas Y, Glorius F (2006) Synthesis 1899
105. Matsuyama H (1999) Sulfur Rep 22:85
106. Fernandez I, Khiar N (2003) Chem Rev 103:3651
107. Solladié G, Chu GH (1996) Tetrahedron Lett 37:111
108. Zhou P, Chen BC, Davis FA (2004) Tetrahedron 60:8003
109. Ellman JA, Owens TD, Tang TP (2002) Acc Chem Res 35:984
110. Ellman JA (2003) Pure Appl Chem 75:39
111. Kochi T, Tang TP, Ellman JA (2002) J Am Chem Soc 124:6518
112. Gais HJ, Hainz R, Müller H, Bruns PR, Giesen N, Raabe G, Runsink J, Nienstedt S, Decker J, Schleusner M, Hachtel J, Loo R, Woo CW, Das P (2000) Eur J Org Chem 3973
113. Gais HJ, Müller H, Decker J, Hainz R (1995) Tetrahedron Lett 36:7433
114. Okuma K (2002) Sulfur Rep 23:209
115. Garcia Ruano JL, De la Plata BC (1999) Top Curr Chem 204:1
116. Gosselin P, Bonfand E, Hayes P, Retoux R, Maignan C (1994) Tetrahedron Asymmetry 5:781
117. Bolm C, Simic O (2001) J Am Chem Soc 123:3830
118. Dubbaka SR, Vogel P (2005) Angew Chem 117:7848

119. Dubbaka SR, Vogel P (2005) Angew Chem Int Ed 44:7674
120. Srogl J, Allred GD, Liebekind LS (1997) J Am Chem Soc 119:12376
121. Trost BM, Sato T (1985) J Am Chem Soc 107:719
122. Marshall DR, Thomas PJ, Stirling CJM (1977) J Chem Soc, Perkin Trans 1 1898
123. Cava MP, Deana AA (1959) J Am Chem Soc 81:4266
124. Chou SSP, Chiu HC, Hung CC (2003) Tetrahedron Lett 44:4653
125. Asinger F, Vogel HH (1970) In: Houben–Weyl–Müller, vol V/1a. Thieme, Stuttgart, p 327
126. Luh TY (2002) J Organomet Chem 653:209
127. Luh TY, Lee CF (2005) Eur J Org Chem 3875
128. Deng K, Bensari A, Cohen T (2002) J Am Chem Soc 124:12106
129. Roth M, Dubs P, Götschi E, Eschenmoser A (1971) Helv Chim Acta 54:710
130. Metzner P (1999) Top Curr Chem 204:127
131. Bellec C, Gaurat O (2004) Can J Chem 82:1289
132. Taylor RJK (1999) Chem Commun 217
133. Taylor RJK, Casy G (2003) Org React 62:357
134. Braverman S, Zafrani Y (1998) Tetrahedron 54:1901
135. MaGee DI, Beck EJ (2000) J Org Chem 65:8367
136. Oh S, Jeong IH, Lee S (2004) J Org Chem 69:984
137. Schaumann E (1989) In: Patai S (ed) The chemistry of functional groups, Supplement A: The chemistry of double-bonded functional groups. Wiley, Chichester, p 1269
138. Middleton WJ, Sharkey WH (1965) J Org Chem 30:1384
139. Walter W, Voß J (1970) In: Zabicky J (ed) The Chemistry of Amides. Interscience, London, p 383
140. Voß J (1997) In: Patai S (ed) The Chemistry of Acid Derivatives, Suppl. B, Pt II. Interscience, London, p 1021
141. Rossi L (2005) In: Knight JG (ed) Science of Synthesis, vol 18. Thieme, Stuttgart, p 461
142. Sato S, Furukawa N (2005) In: Knight JG (ed) Science of Synthesis, vol 18. Thieme, Stuttgart, p 821
143. Braverman S, Cherinsky M, Birsa ML (2005) In: Knight JG (ed) Science of Synthesis, vol 18. Thieme, Stuttgart, p 65
144. Yokoyama M, Imamoto T (1984) Synthesis 797
145. Schaumann E (1988) Tetrahedron 44:1827
146. Stadlbauer W, Kappe T (1977) Chem Ztg 101:137
147. Voß J (1985) In: Klamann D (ed) Houben–Weyl–Müller, vol E11. Thieme, Stuttgart, p 188
148. Okazaki R (1987) Nippon Kagaku Kaishi 1142
149. Okazaki R (1988) Chem Abstr 108:74875
150. Sajiki H, Hirota K (1997) Trends Heterocycl Chem 5:91
151. Runge W (1981) Prog Phys Org Chem. 13:315
152. Paquer D (1972) Int J Sulfur Chem 7:269
153. Paquer D (1973) Int J Sulfur Chem 8:173
154. Voß J (1985) In: Klamann D (ed) Houben–Weyl–Müller, vol E11. Thieme, Stuttgart, p 195
155. Mloston G (1999) Phosphorus Sulfur Silicon Relat Elem 153/154:217
156. Okazaki R, Ishii A, Fukuda N, Oyama H, Imamoto N (1982) Chem Commun 1187
157. Tokitoh N, Takeda N, Okazaki R (1994) J Am Chem Soc 116:7907
158. Schaumann E, Harto S, Adiwidjaja G (1979) Chem Ber 112:2698

159. Castro EA (1999) Chem Rev 99:3505
160. Metzner P (1992) Synthesis 1185
161. Schaumann E (1991) In: Trost BM, Fleming I, Winterfeldt E (eds) Comprehensive Organic Synthesis, vol 6. Pergamon, Oxford, p 419
162. Block E, Penn RE, Ennis MD, Owens TA, Yu SL (1978) J Am Chem Soc 100:7436
163. Chang RK, Dipardo RM, Kuduk SD (2005) Tetrahedron Lett 46:8513
164. Sakamoto M, Nishio T (2003) Heterocycles 59:399
165. Coyle JD (1985) Tetrahedron 41:5393
166. Huisgen R, Langhals E (2006) Heteroatom Chem 17:433
167. Rohr U, Schatz J, Sauer J (1998) Eur J Org Chem 2875
168. Reich HJ, Renga JM, Reich IL (1975) J Am Chem Soc 97:5434
169. Wirth T (2000) Angew Chem 112:3890
170. Wirth T (2000) Angew Chem Int Ed 41:3740
171. Wovkulich PM, Shankaran K, Kiegiel J, Uskokovi'c MR (1993) J Org Chem 58:832
172. Woggon WD (1995) In: Helmchen G, Hoffmann RW, Mulzer J, Schaumann E (eds) Houben–Weyl–Müller, vol E21e. Thieme, Stuttgart, p 4947
173. Nogueira CW, Zeni G, Rocha JBT (2004) Chem Rev 104:6255

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Recent Advances in Pummerer Reactions

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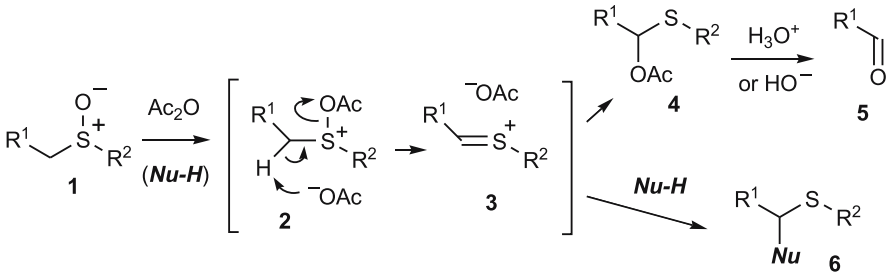
Abstract The Pummerer and Pummerer-type reactions of sulfoxides generate sulfonium ion intermediates, to which either internal or external nucleophilic species add to form carbon–carbon and carbon–heteroatom bonds at the α-position of the sulfur functional groups. Lately, various kinds of new reactions initiated by the Pummerer and Pummerer-type reactions have been developed. These reactions have received considerable attention as synthetically useful tools and have been applied to total syntheses of biologically important natural products and highly functionalized unnatural compounds. This review focuses on recent remarkable progress in these chemistries, published in 2001 and later. The main topics involve (i) optically active sulfoxides as both chiral auxiliaries and carbonyl equivalents, (ii) the domino bond-forming reactions, (iii) the asymmetric Pummerer reactions, (iv) the aromatic Pummerer-type reactions, (v) the interrupted Pummerer reactions, and (vi) the fluorination reactions.

Keywords Pummerer reaction · Asymmetric reaction · Total synthesis · Carbon–carbon bond-forming reaction

1 Introduction

The Pummerer rearrangement reaction, first reported by Pummerer in 1909 [1, 2], has been studied extensively over the past century and has received considerable attention both mechanistically and as a synthetically useful process [3, 5, 6]. The most typical protocol for the Pummerer rearrangement involves the treatment of a sulfoxide **1** with a carboxylic acid anhydride to form an acyloxysulfonium salt **2**, thereby converting this oxygen into a good leaving group. Removal of a proton from the α-carbon with elimination of the acyloxy group generates a sulfonium ion **3**, to which addition of the counter anion, the carboxylate ion, takes place immediately to give an α-acyloxy sulfide **4**. Because **4** can be readily hydrolyzed to a carbonyl compound **5**, the sulfinyl group has been employed as a useful equivalent (or a precursor) of the carbonyl group [7–13] (upper pathway in Scheme 1). On the other hand, in the presence of a nucleophilic species, the sulfonium ion **3** serves as a highly reactive electrophile to accept the addition of the nucleophile. This reaction forms a new carbon–carbon or carbon–heteroatom bond at the α-position of the sulfur functional group in inter- and intramolecular fashion and has found wide applicability as a powerful tool for constructing molecules [14–17] (lower pathway in Scheme 1).



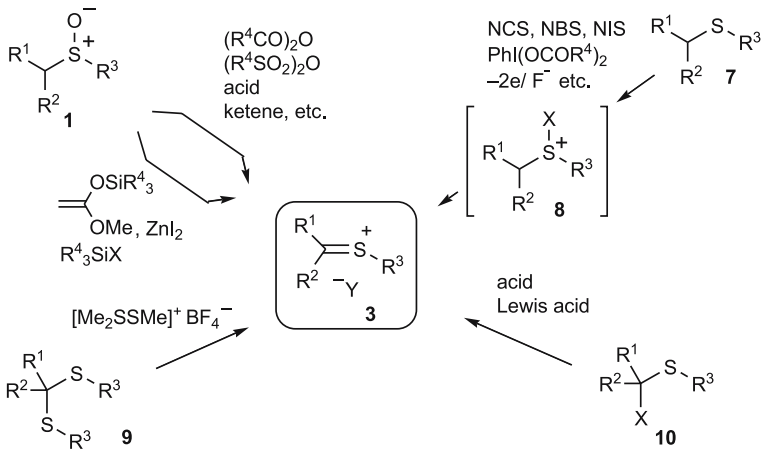
Scheme 1

In addition to the common acetylation method, the sulfonium ion intermediates **3** are available by many different methods:

1. Activation of sulfoxides **1** with various kinds of acylating reagents, sulfonylating reagents, acids, or silylating reagents [18]
2. Oxidative activation of sulfides **7** with halogenation reagents or hypervalent iodine reagents [19], and also by electrolysis in the presence of fluoride salt [16]

3. Oxidative deacetalization of thioacetals **9** with $[Me_2SSMe]^+BF_4^-$ [20, 21]
4. Cleavage of *O*,*S*-acetals **10** (X = $OCOR^4$) and α-halo sulfides **10** (X = halogen) with acids or Lewis acids [14, 15, 17, 22] (Scheme 2)

All reactions initiated by the generation of **3** followed by a bond-forming reaction are called the "Pummerer reactions" and, in analogous cases, "Pummerer-type reactions."



Scheme 2

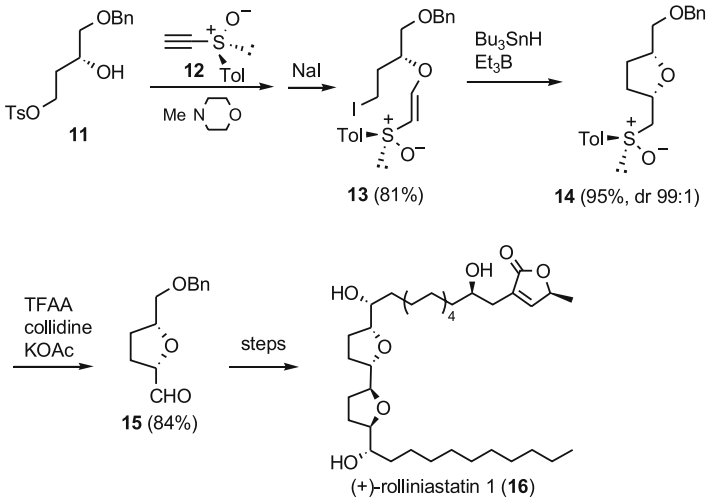
During the past two decades, this chemistry has undergone remarkable progress including the vinylogous Pummerer reactions [23], the additive Pummerer reactions [24], the domino (or cascade, tandem) reactions [25–29], the asymmetric Pummerer reactions [30–35], the aromatic Pummerer-type reactions [31–33, 36, 37], and the interrupted Pummerer reactions. Comprehensive reviews cover these chemistries up to around 2000 [25–38], hence the focus of this review centers on the recent remarkable progress of the Pummerer and the Pummerer-type reactions published in 2001 and after, along with some essential background.

2
Optically Active Sulfoxides as Both Chiral Auxiliaries and Carbonyl Equivalents

Due to ready availability of both enantiomers of optically pure sulfoxides such as methyl *p*-tolyl sulfoxides and their high ability for asymmetric induction, the optically active sulfinyl groups have served as powerful auxiliaries for the diastereoselective asymmetric reactions. Their synthetic utility is further strengthened by their subsequent conversion to carbonyl groups via the Pum-

merer rearrangement reaction. A number of examples are found in the total synthesis of biologically active natural products [38] and highly functionalized, optically active compounds.

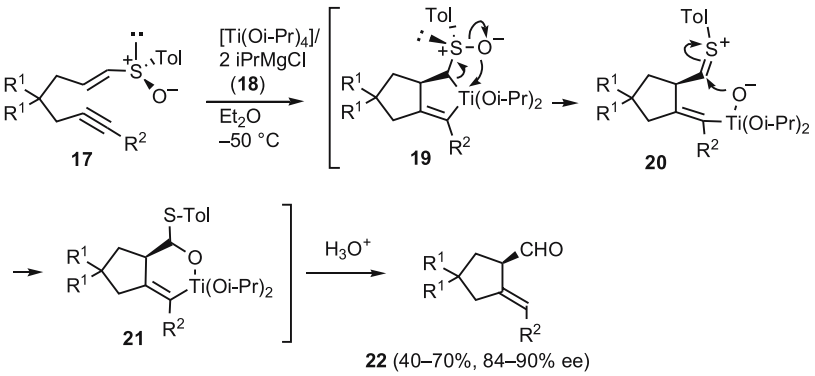
Recently Lee and colleagues installed an optically pure vinyl sulfoxide moiety on the alcohol **11** and used it as an acceptor for the highly diastereoselective radical cyclization (**13** → **14**). The product **14** was converted into the aldehyde **15** by the Pummerer reaction in 84% yield. Asymmetric total synthesis of natural *Annonaceous* acetogenin, (+)-rolliniastatin 1 (**16**) was achieved by the repetition of this protocol [39, 40] (Scheme 3).



Scheme 3

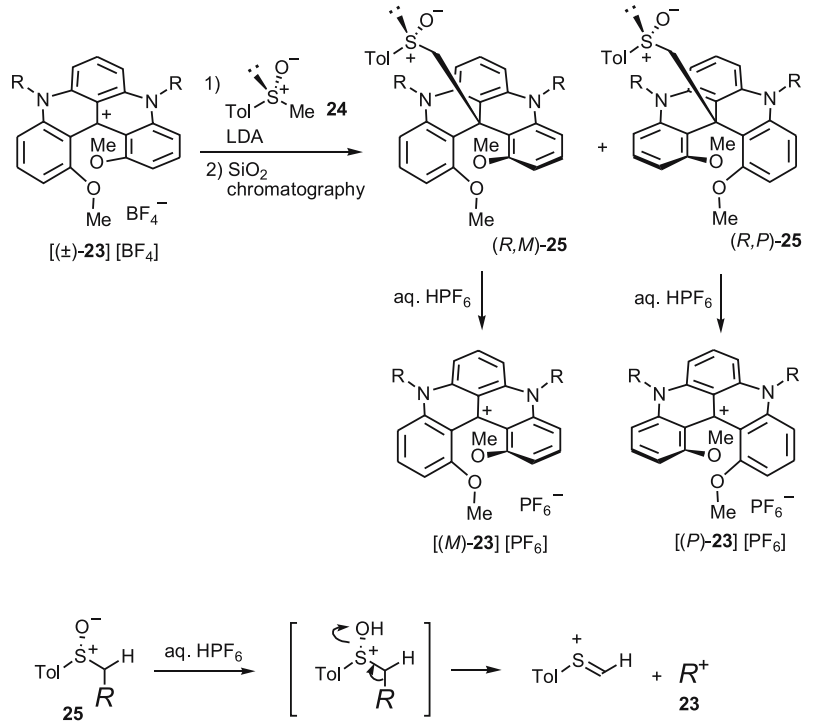
Sato and colleagues reported a novel domino asymmetric cyclization/Pummerer-type reaction of the optically pure sulfoxides **17** promoted by a titanium(II) alkoxide, in situ-generated from the reagent, $[Ti(OiPr)_4]/2iPrMgCl$ **18**, which directly afforded the cyclic aldehydes **22** in good yields and high diastereoselectivities. This reaction could be rationalized by the titanium-mediated cyclization of **17** giving the titanacycle **19**, followed by the Pummerer-type rearrangement to give **22** after hydrolytic workup, while the chiral integrity of **17** was transferred to the newly generated stereogenic carbon center of **22** [41, 42] (Scheme 4).

Lacour and colleagues utilized an optically pure sulfinyl moiety for the optical resolution of the [4]heterohelicenium dyes **23** and reported an unprecedented carbon–carbon bond fragmentation reaction initiated by the Pummerer reaction. The cationic dyes **23** adopted a twisted helical conformation and were configurationally stable at room temperature. The reaction of (±)-**23** with lithiated **24** afforded a mixture of two diastereomers **25** in good yields, which were readily separated by silica gel chromatography to give



Scheme 4

diastereomerically pure **25**. When treated with aqueous HPF_6 in acetone, **25** underwent the carbon–carbon bond cleavage at the α-position of the sulfinyl group to regenerate the cation **23** with high optical purity. This cleavage reaction is probably explained by high chemical stability ($pK_{R+} > 19$) of **23**, which functioned as a better leaving group than H^+ [43, 44] (Scheme 5).

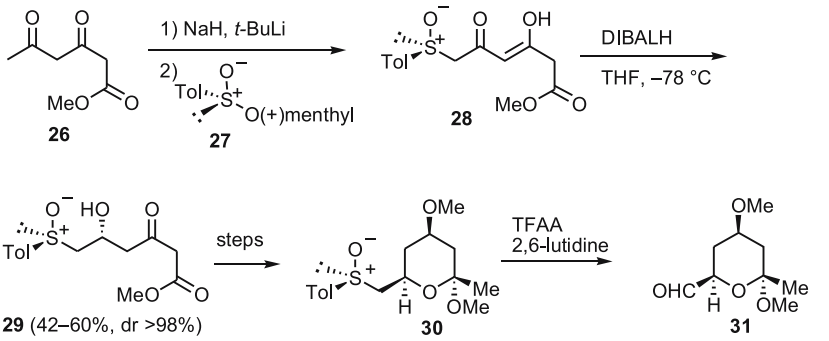


Scheme 5

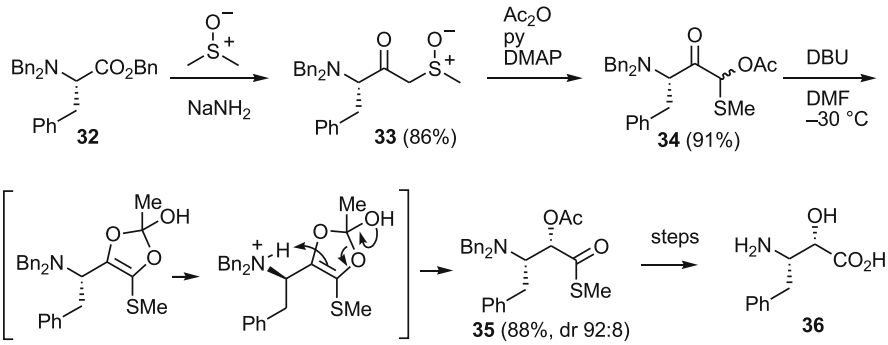
The reduction of the optically pure diketosulfoxide **28**, obtained by the coupling of the diketo ester **26** and the optically pure sulfinate **27**, with DIBALH afforded **29** in high chemo- and diastereoselective fashion, probably due to the coordination of the aluminum atom of DIBALH to the sulfinyl oxygen. Preparation of the enantiomerically pure C32–C38 fragment **31** of antitumor macrolides, phorboxazoles, was attained by Carreño and colleagues via the Pummerer reaction of thus derived cyclic sulfoxide **30** [45] (Scheme 6).

Some other diastereoselective reactions utilizing the chirality of optically pure sulfinyl group followed by the Pummerer reaction were reported, which led to asymmetric total syntheses of natural products [46, 47].

A unique synthesis of the optically active 3-amino-2-hydroxy-4-phenylbutyric acid **36**, a useful intermediate of enzyme inhibitors, was developed by Izawa and colleagues. This involves the Pummerer rearrangement reaction of the β-ketosulfoxide **33**, derived from the protected L-phenylalanine **32**, followed by the highly stereoselective acyl migration. The *N*-protective group exerted a substantial influence over the protonation step that determined the absolute stereochemistry of the newly generated stereogenic center of **35** [48] (Scheme 7).



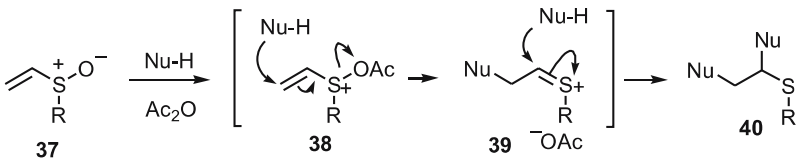
Scheme 6



Scheme 7

3
Pummerer Reaction-Initiated Bond-Forming Reactions

The addition reactions of internal or external nucleophiles to sulfonium ion intermediates, generated by the Pummerer and the Pummerer-type reactions, have found wide application in making carbon–carbon bonds and carbon–heteroatom bonds at the α-position of the sulfur functional group (lower pathway in Scheme 1). An analogous reaction of the vinyl sulfoxide **37** undergoes an S_N2'-type displacement of the initially formed *O*-acylated sulfoxide **38** with a nucleophile, followed by the trapping of the thus-generated sulfonium ion **39** with a second nucleophile. Thereby, this reaction, called the "additive Pummerer reaction", allows installation of two (different) nucleophiles at the α- and β-positions of the sulfur functional group [24] (Scheme 8).



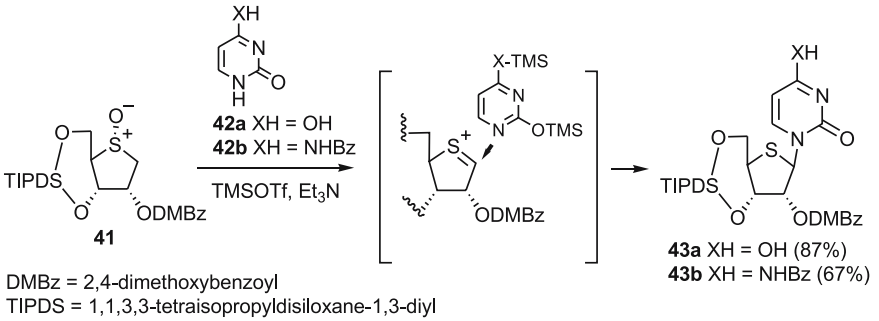
Scheme 8

3.1
Intermolecular Bond-Forming Reactions

One of the most significant applications of the Pummerer-based intermolecular bond-forming reactions during the past several years involves the glycosylation of pentacyclic sulfoxides with suitably protected nucleobases, because the products, 4′-thioribonucleosides, have been gaining increased attention as antiviral, antitumor, and anti-HIV agents [49]. Noteworthy is a method developed by Matsuda and colleagues, in which the protected β-sulfoxide **41** and the in-situ protected nucleobase derived from **42a** were treated with TMSOTf to give the β-nucleoside **43a** as a single diastereomer [50]. A similar reaction with **42b** provided **43b** in tens of grams [51] (Scheme 9).

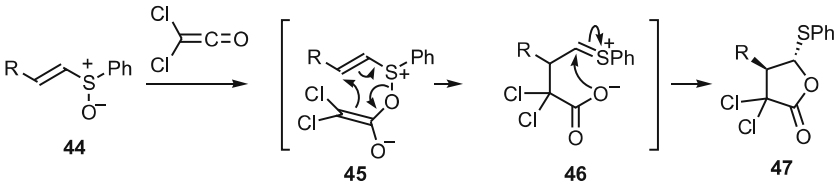
Glycosylation reactions of thioriboses having different protective groups were also investigated; however, the stereoselectivities and the chemical yields of the thioribonucleosides varied depending on the protective groups [52–55]. 1,3-Dithiolane nucleoside analogs [56] and D- and L-thietanose nucleosides [57] were prepared by similar glycosylation protocols.

Another unique example of the intermolecular carbon–carbon bond-forming reactions includes the additive Pummerer reactions using dichloroketene, developed by Marino and colleagues. The reaction starts with the add-



Scheme 9

ition of the oxygen of a vinyl sulfoxide **44** to dichloroketene to form the zwitterionic intermediate **45**, which undergoes a 3,3-sigmatropic rearrangement to give the sulfonium ion **46**. Subsequent addition of the internal carboxylate anion moiety of **46** to the sulfonium ion provides the γ-butyrolactone **47**, which retains the geometry of the olefin **44** [58] (Scheme 10). Elegant applications of this reaction are found in the total syntheses of (+)-aspidospermidine [59] and (±)-desoxyeseroline [60]. The details of these chemistries are described in the chapter on "Sulfur participation in [3.3]-sigmatropic rearrangements" in this volume.



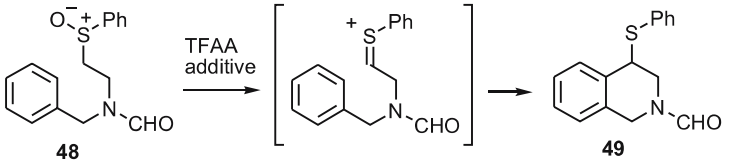
Scheme 10

3.2 Intramolecular Bond-Forming Reactions

Intramolecular versions of the Pummerer-based bond-forming reactions, in which nucleophiles are tethered to sulfoxides, provide cyclic molecules. Effective applications have been demonstrated in synthesis of heterocyclic compounds, which have been outlined in several reviews by Padwa and colleagues [25–29]. Additional recent examples mentioned below have amplified the synthetic utility of this protocol.

Sulfonium ion intermediates generated by the Pummerer reaction have been efficiently used for Friedel–Crafts reactions. Electron-sufficient aromatic compounds [61–65] and allylsilanes [66] were shown to be reactive

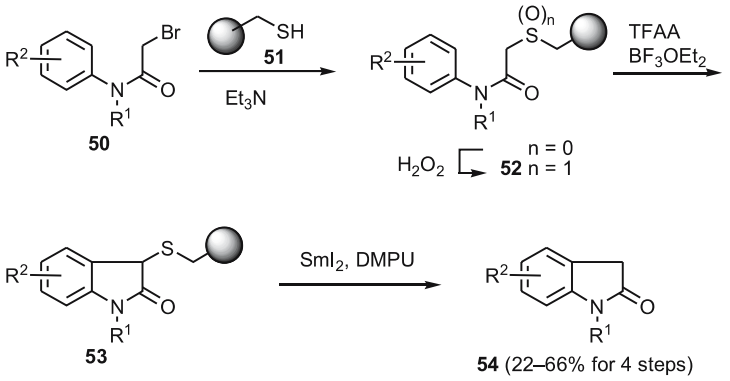
nucleophiles. In the case of less reactive substrates such as **48**, use of the combination of TFAA with either $BF_3 \cdot OEt_2$ or TfOH was shown by Sano and colleagues to accelerate the reactions dramatically, and thereby, the products were obtained in high yields in shorter time. A pair of comparative examples is shown in Scheme 11 [67–72].



additive	reaction time (h)	yield of **49**
none	20	not obtained
$BF_3.OEt_2$	2.5	99%

Scheme 11

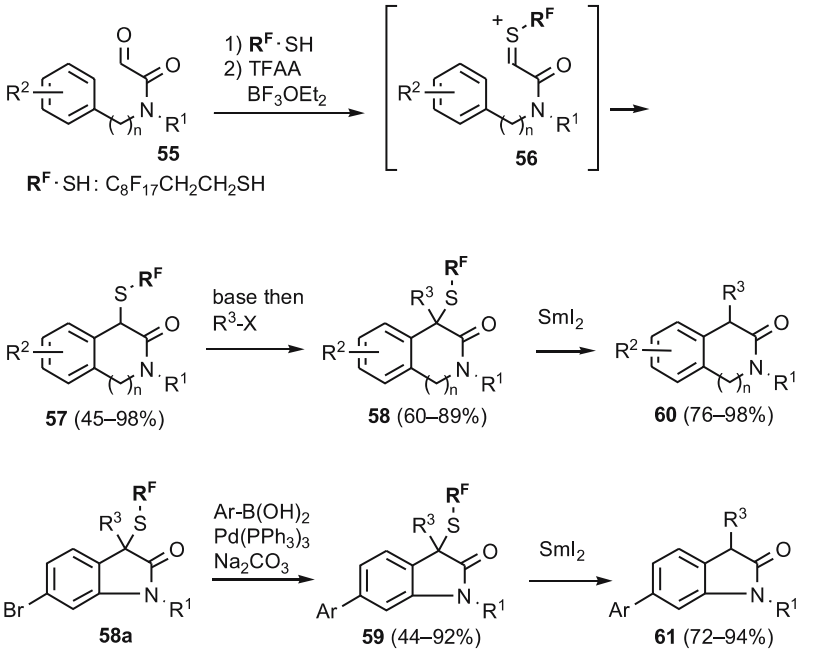
The first Pummerer cyclization in the solid phase was developed by Procter and colleagues. Immobilization of the α-bromoacetoamides **50** with a Merrifield resin **51** having a benzyl thiol moiety was carried out in good yields. The Pummerer cyclization reaction of the derived sulfoxides **52** was found to most efficiently carried out using the combination of TFAA and $BF_3 \cdot OEt_2$. The chemoselective cleavage of the sulfur-link to resin **53** was attained using SmI_2 and DMPU to release the oxindoles **54** in moderate-to-good overall yields [73] (Scheme 12).



Scheme 12

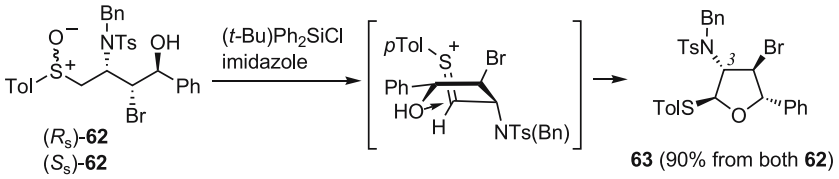
However, the above-mentioned method met difficulties in monitoring the transformation as many solid-phase processes suffer. The same authors found an alternative solution for this issue using fluorous chemistry. Thus, the treatment of the glyoxamides **55** with a fluorous-phase tag, $C_8F_{17}CH_2CH_2SH$,

resulted in rapid capture of the substrate as the hemithioacetals. The thionium ion intermediates **56** were then generated, not by the usual Pummerer process that involves the redox chemistry, but by the deacetalization with TFAA and $BF_3 \cdot OEt_2$. Subsequent intramolecular cyclization of **56** provided the nitrogen-containing heterocycles **57** after rapid purification by the fluorous solid-phase extraction. Further modifications of the products were readily available by the traditional base-mediated alkylation or acylation reactions (**57** → **58**) as well as the palladium-catalyzed carbon–carbon bond-forming reactions (**58a** → **59**). Finally, the highly functionalized heterocycles (**60, 61**) were isolated by the traceless removal of the fluorous-phase tag via reduction with SmI_2 [74, 75] (Scheme 13).



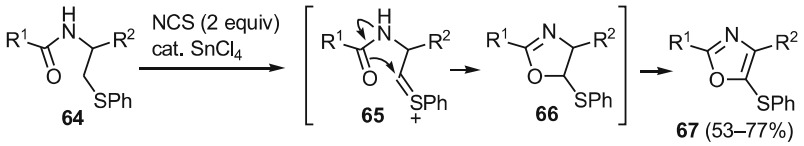
Scheme 13

The Pummerer reaction-initiated cyclization reactions were also useful for the transformation of the δ-hydroxysulfoxides **62** to the highly substituted tetrahydrofuran **63**. In this case, (*t*-Bu)Ph_2SiCl and imidazole promoted the reactions at room temperature, and **63** was isolated in high yield with exclusive stereoselectivity. The phenylthio group of **63** was disposed *anti* to the C3-substituent, which was independent of the stereochemistry of the sulfur atom of **62**. Typical examples are shown in Scheme 14 [76]. A similar cyclization was used for the synthesis of tunicaminyluracil derivatives [77].



Scheme 14

Magnus and colleagues reported a convenient preparation of the 5-(phenylthio)oxazoles **67** initiated by the Pummerer reaction. The treatment of the sulfide **64** with two equivalents of NCS in the presence of a catalytic amount of $SnCl_4$ generated the sulfonium ion **65**, followed by their cyclization to give the oxazolines **66.** These underwent further oxidation with the second equivalent of NCS to afford **67** in good yields [78] (Scheme 15). At the same time, a new method for preparing 2,3-benzo-1,3a,6a-triazapentalenes was reported by Kim and colleagues through Pummerer reaction-initiated cyclization of 3-(benzotriazol-1-yl)allyl sulfoxides [79].



Scheme 15

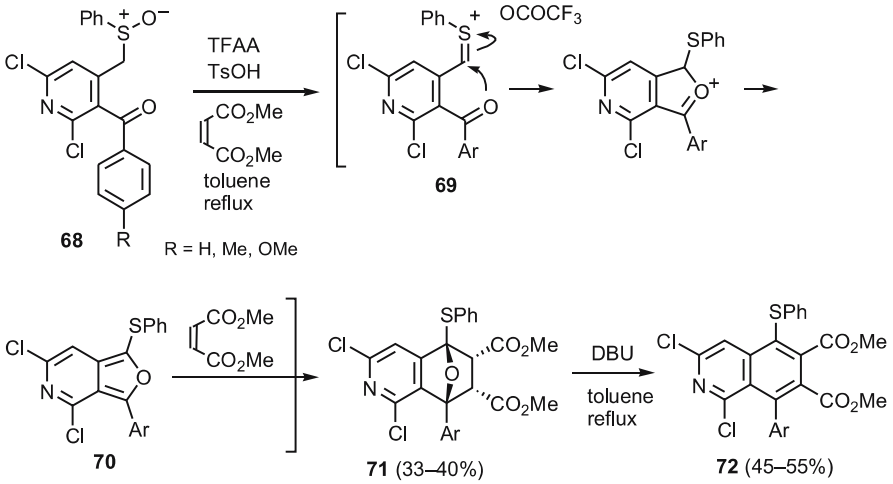
3.3 Domino Reactions

A domino reaction involves two or more bond-forming sequential transformations under the same reaction conditions without adding additional reagents and catalysts, and is of particular interest because it can provide complex polycyclic carbon skeletons with generating multiple stereogenic centers from relatively simple starting materials. The Pummerer cyclization reactions of suitably designed substrates generate reactive intermediates, which in turn cause the second (and in some cases further) carbon–carbon or carbon–heteroatom bond formation(s). Thus, they achieve the domino reaction, which is also called tandem or cascade reaction.

Padwa and colleagues have developed various kinds of domino reactions initiated by the Pummerer and the Pummerer-type reactions. Most of their pioneering work was introduced in their reviews [25–29, 80], and recently some applications thereof were presented as follows [81, 82].

Sarkar and colleagues reported domino reactions involving the generation of the furo[3,4-*c*]pyridines **70** and their intermolecular Diels–Alder reactions.

The reaction of the *o*-aroylpyridylmethyl sulfoxides **68** with TFAA and TsOH in the presence of dimethyl maleate in refluxing toluene caused the interception of the sulfonium ions **69** by an internal carbonyl group to generate **70** as transient intermediates. The subsequent Diels–Alder reaction of **70** with the maleate gave the cycloadducts **71**, which were then subjected to a base-mediated aromatization to afford the isoquinoline derivatives **72.** These products are expected to be useful as heterocyclic analogs of 1-arylnaphthalene lignans [81, 82] (Scheme 16).

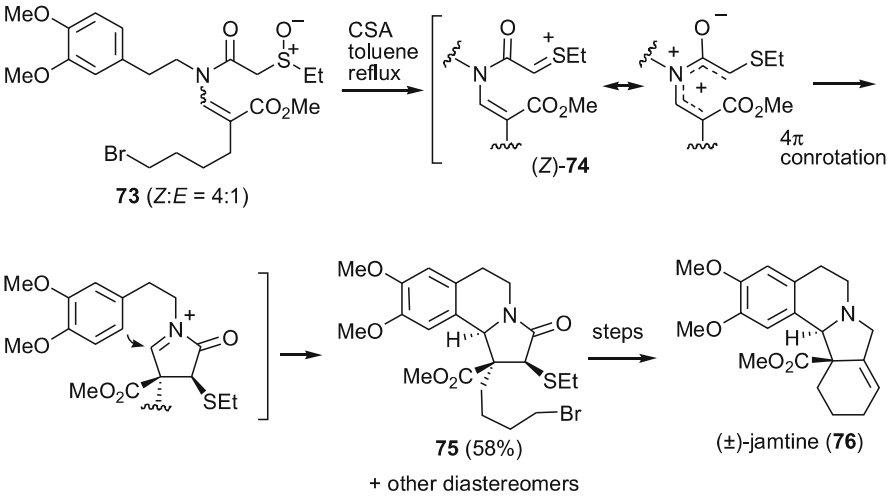


Scheme 16

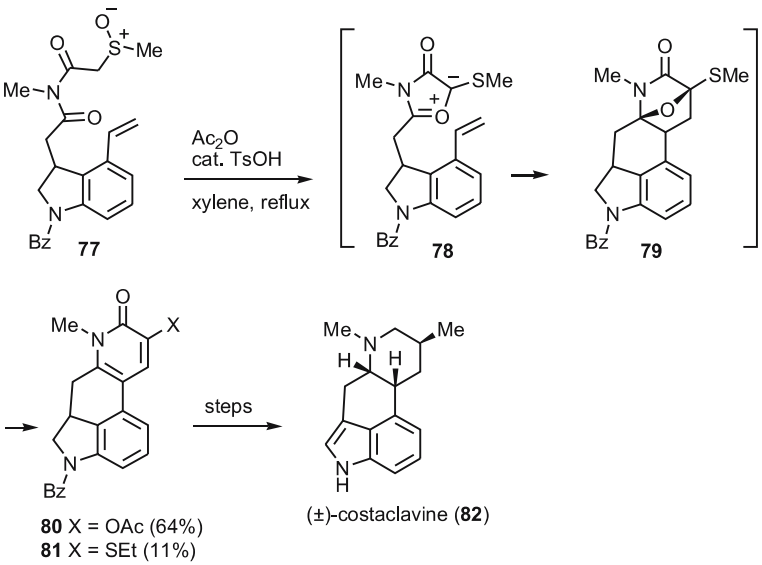
Another example, reported by Padwa and colleagues, includes the Pummerer-initiated intramolecular cyclization of the *N*-acyl enamine **73** (a 4 : 1 mixture of *Z* and *E*-isomers) followed by the ring closure of thus generated *N*-acyliminium ion intermediate **74.** This domino reaction gave the pyrrolidine-containing tricyclic compound **75** as the major product among a mixture of four possible diastereomers. The preferential formation of **75** was reported to be due to the 4π-Nazarov-type conrotation of the major (*Z*)-isomer **74** [83]. The alkaloid, jamtine **76,** was prepared from **75** [84] (Scheme 17).

The Pummerer reaction of the sulfinyl imide **77** generated the mesoionic betaine **78,** which caused the 1,3-dipolar cyclization with the internal olefin to give the pyridines (**80** and **81**) after aromatization of the initial cycloadduct **79.** The indole alkaloid, (±)-costaclavine **82,** was synthesized from **80** [85] (Scheme 18).

Padwa and colleagues also developed a consecutive sulfonium/*N*-acyliminium ion cyclization sequence starting from sulfinyl amides such as **83.** The use of the silyl ketene acetal **84** as an initiator, developed by Kita and col-

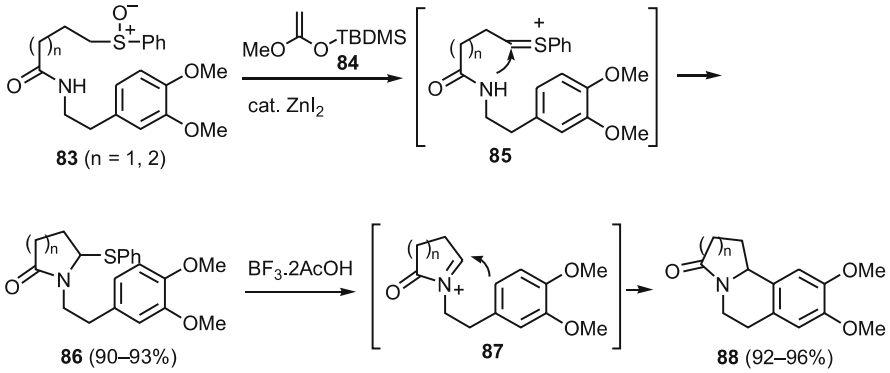


Scheme 17



Scheme 18

leagues [18], was essential to achieve this domino process, because the use of the most common initiators, acetic anhydride and TFAA, gave the corresponding α-acyloxy sulfide. Due to the absence of a carboxylate counter anion, the use of **84** allowed the internal amide moiety to attack the sulfonium ion **85** to give the lactam **86** in more than 90% yields. The reaction of **86** with



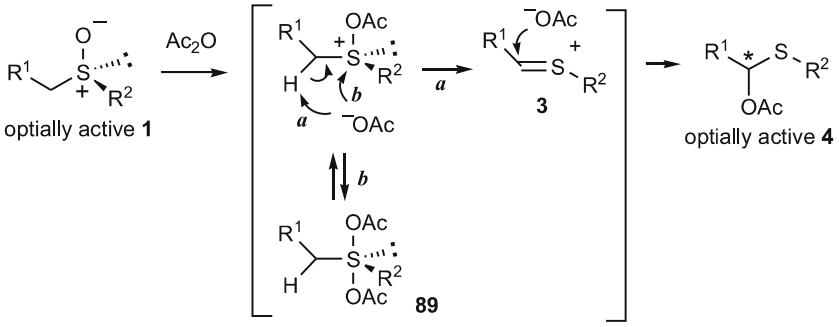
Scheme 19

$BF_3 \cdot 2AcOH$ was associated with the elimination of the phenylthio group, and the intramolecular cyclization of the resulting *N*-acyliminium ion **87** afforded the tricyclic product **88** (Scheme 19). Olefinic moieties were also applicable to this method as the second internal nucleophiles [86].

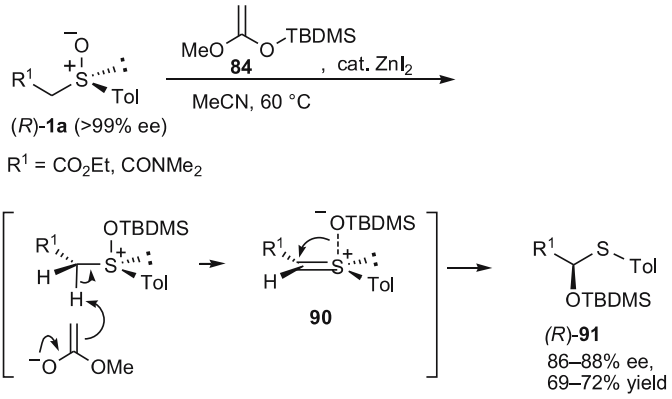
4
Asymmetric Pummerer Reactions

The stereoselective Pummerer reactions of optically active sulfoxides are of considerable interest because of their potential to provide optically active α-substituted sulfides. However, the pioneering work done by Oae and colleagues showed that reactions of the optically pure sulfoxides **1** (R^1 = CN, $PO(OMe)_2$; R^2 = Tol) with acetic anhydride resulted in formation of the α-acetoxy sulfides **4** with less than 30% ee. The racemization is probably due to the formation of the achiral sulfurane intermediates **89** caused by addition of the generated carboxylate counter anion to the sulfur atom (path *b*) [87, 88]. They added dicyclohexylcarbodiimide to the above-mentioned reaction in order to trap acetate anion and acetic acid and improved the optical purity of **4** to 70% ee; however, the chemical yield decreased to 10% (Scheme 20) [89].

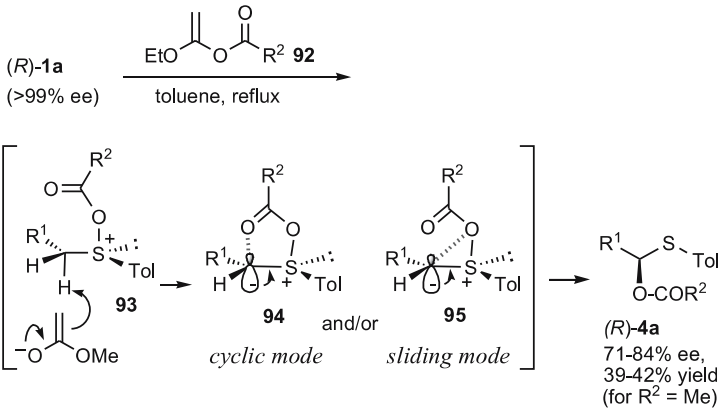
Kita and colleagues achieved the first highly asymmetric Pummerer-type rearrangement reactions using the *O*-silyl ketene acetal **84** as an initiator, which gave the α-silyl sulfides (*R*)-**91**(86–88% ee) in good chemical yields [90, 91] (Scheme 21). The same authors discovered that the similar *O*-acetyl ketene acetal **92** (R^2 = Me) also served as an effective initiator to give (*R*)-**4a** with better optical and chemical yields than those obtained using acetic anhydride [92] (Scheme 22). These successful results obtained by using both **84** and **92** are probably due to the avoidance of the formation of the achiral sulfurane intermediate **89**. The reaction probably proceeded via a five-membered



Scheme 20



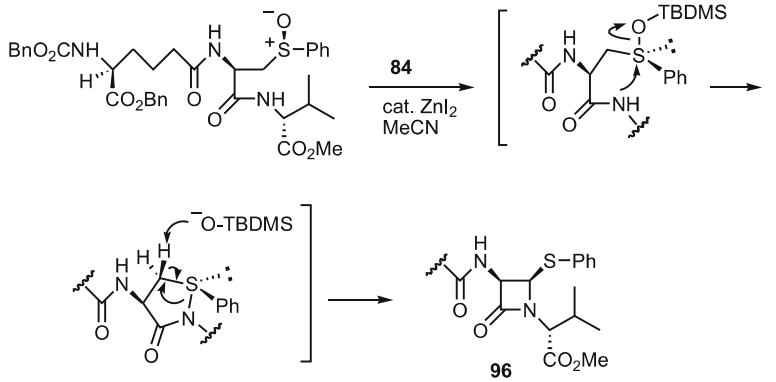
Scheme 21



Scheme 22

ring transition state **94** (cyclic mode) and/or a three-membered ring transition state (**90** and **95**) (sliding mode), while transferring the chirality of the starting sulfoxides (*R*)-**1a** to their α-carbon. Use of the ethoxyvinyl benzoate derivatives **92** [$R^2 = C_6H_2$-3,4,5-$(OMe)_3$, C_6H_4-4-OMe] increased the optical purity of (*R*)-**4a**. The electron-donating nature of the R^2 group is believed to inhibit the dissociation of the carboxylate anion from the sulfonium ion **93** and accelerate the rearrangement via the more intimate intramolecular process(es) [30–35].

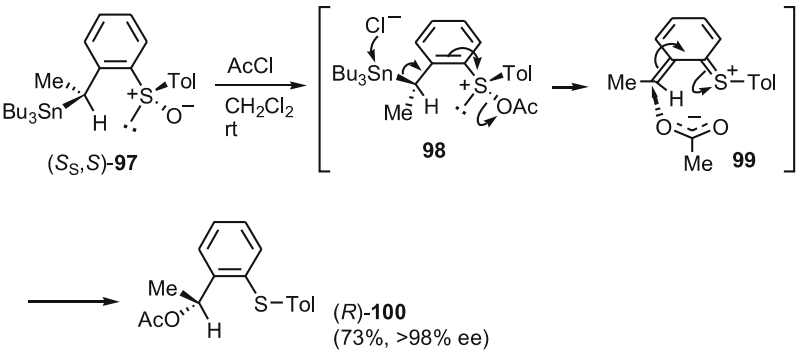
The silicon-induced asymmetric Pummerer-type reactions were applied to the asymmetric biomimetic intramolecular cyclization reactions, affording a penicillin analog, the *cis*-*β*-lactam **96** [93] (Scheme 23).



Scheme 23

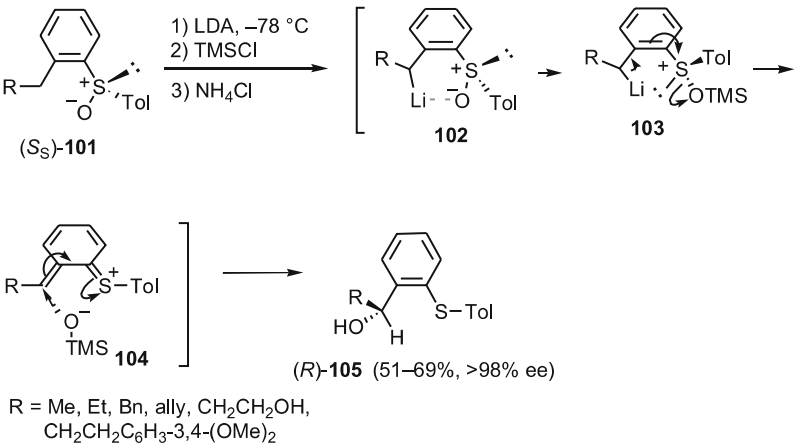
Padwa and colleagues found that treatment of the optically pure (*Ss*,*S*)-**97** with acetyl chloride in CH_2Cl_2 at room temperature afforded (*R*)-**100** with exclusive enantioselectivity. The reaction probably started with the *O*-acylation followed by the nucleophilic attack of the counter chloride anion at the tin of thus generated salt **98** to give the *ortho*-quinone methide sulfonium intermediate **99**. The nucleophilic conjugate addition of the acetate ion to the benzylic γ-carbon of **99** afforded **100**. Polar solvents, acylating reagents that generate stable carboxylate anion, and higher reaction temperature resulted in a decrease in the enantioselectivity. These results can be explained by assuming the formation of an intimate ion pair **99**, as mentioned above (Scheme 22), followed by its internal collapse with complete retention of the chiral integrity [94] (Scheme 24).

Similar enantioselective reactions of the optically pure sulfoxides (*Ss*)-**101** were also reported by the same group using TMSCl as a mediator. Thus, (*Ss*)-**101** was treated with LDA at – 78 °C, and the generated benzyl lithiated intermediate **102** was reacted with TMSCl to cause the *O*-silylation **103**. The 1,4-migration of the oxygen atom took place to give the optically pure ben-



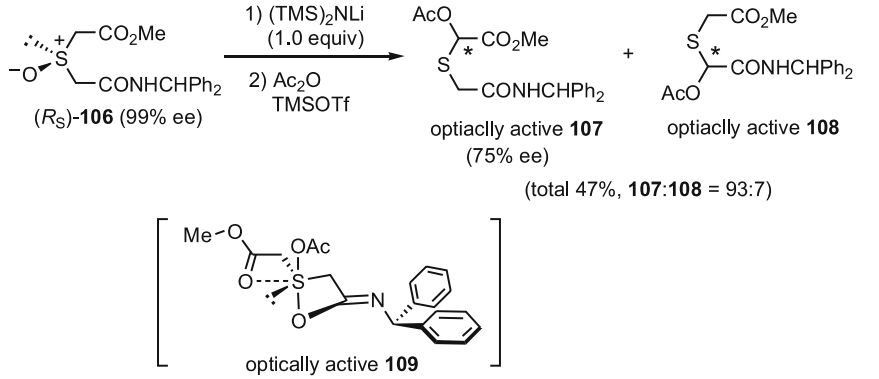
Scheme 24

zyl alcohols (*R*)-**105** in good yields. It is worth noting that the silylation of **102** occurred at the oxygen of the sulfoxide in favor of the benzylic carbanion, although a similar reaction of the *o*-methyl sulfoxide (*Ss*)-**101** (R = H) afforded the *C*-silylated product. The complete stereoselectivity of the migration process suggests the intermediacy of the intimate ion pair **104** as shown in Scheme 21 [95, 96] (Scheme 25).



Scheme 25

Nagao and colleagues disclosed that use of classical acetic anhydride, when combined with TMSOTf, initiated the enantio- and chemoselective Pummerer rearrangement reaction of optically pure sulfoxide (R_S)-**106**. Although the degrees of both chiral transfer and chemoselectivity were dependent on the reaction solvent, a satisfactory result (75% ee of **107**, **107** : **108** = 93 : 7) was obtained in CH_2Cl_2 when (R_S)-**106** was treated with $(TMS)_2NLi$ (one equivalent) before the Pummerer reaction. The high stereoselectivity is thought to



Scheme 26

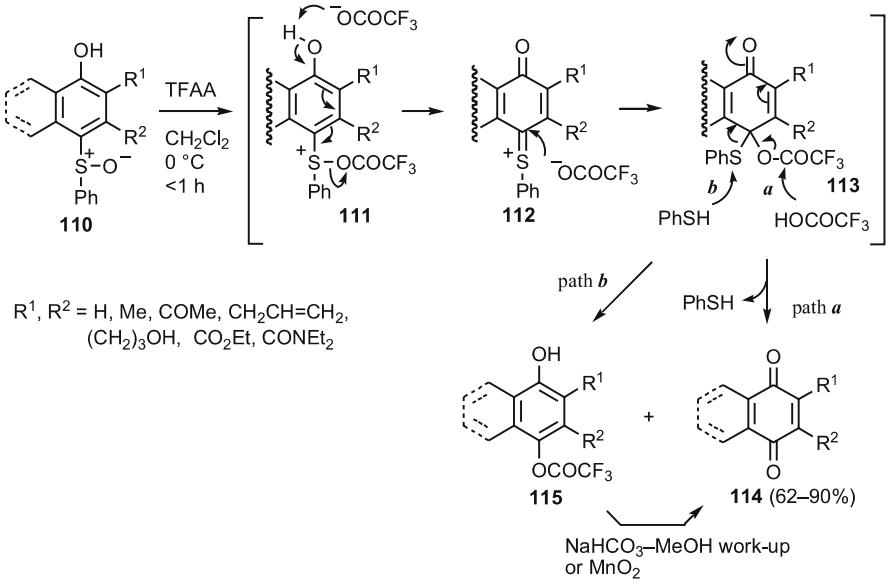
be due to the intervention of the optically active sulfurane intermediate **109**, whose conformation was fixed by the intramolecular nonbonded S · · · O interaction [97–100] (Scheme 26).

5
Aromatic Pummerer-Type Reactions

5.1
Installation of Oxygen Functional Group at the *para*-Position of Phenols and Phenol Ethers

As in the original Pummerer reactions of aliphatic sulfoxides used to convert the sulfinyl group to a carbonyl group (upper pathway in Scheme 1), Kita and colleagues reported sequential reactions of the *p*-sulfinylphenols **110** to the *p*-quinones **114**. Thus, the reaction of **110** with TFAA in CH_2Cl_2 proceeded immediately at 0 °C to give 1 : 1 mixtures of **114** and the dihydroquinone **115** almost quantitatively. The strong electron-donating hydroxyl group at the *para*-position of the sulfinyl group is believed to strongly accelerate both *O*-acetylation of **110** and subsequent S – O bond fission of **111** to give **112**. Immediate 1,2-addition of the counter acetate ion to the sulfonium group gives the quinone mono-*O*, *S*-acetal **113**. Hydrolysis of the acetoxy group of **113** gives **114** with release of thiophenol, which is thought to attack the sulfur atom of **113** to give **115**. Work-up of the crude products with $NaHCO_3$ in MeOH or treatment with MnO_2 readily converted **115** into **114**, affording high yields of **114**. This protocol is compatible with various functional groups [101, 102] (Scheme 27).

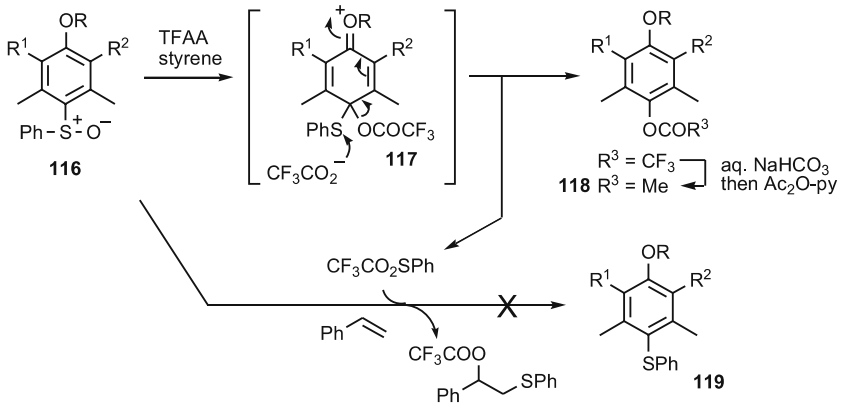
In a like manner, the reaction of the corresponding phenol ethers **116** with TFAA provided the protected *p*-dihydroquinones **118**, after conversion of the



Scheme 27

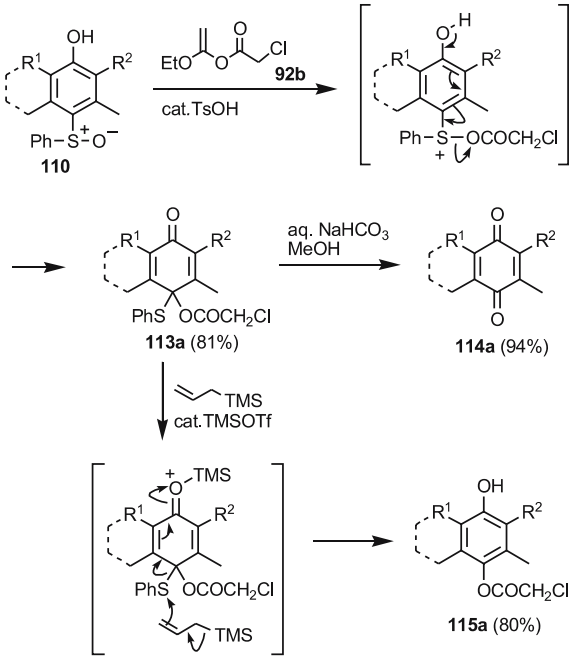
trifluoroacetyl group into the more stable acetyl group, along with the corresponding sulfide **119**. The formation of **118** is probably accountable for by the generation of the cationic intermediates **117**, to which the counter carboxylate anion selectively attacked the sulfur atom to give **118**. Kita and colleagues discovered that the addition of olefins such as styrene depressed the formation of **119** and afforded **118** quantitatively. This additive is believed to capture CF_3CO_2SPh that reduces **116** to **119**. Electron-rich phenol ethers such as TBDMS ethers **116** (R = TBDMS) and methyl ethers **116** (R = Me) are suitable substrates of this reaction, while the corresponding acetate **116** (R = COMe) was less reactive. The reaction proceeded at 0 °C to room temperature within 2 h and is compatible with various functional groups, including labile formyl groups [102] (Scheme 28).

These reactions, named aromatic Pummerer-type reactions [31–33, 36, 37], were believed to proceed through the quinone *O,S*-acetals (**113** and **117**); however, no evidence for their formation could be obtained. The difficulties were probably due to the use of acid anhydrides because the acid or the counter carboxylate anion would readily react with **113** and **117**. After intensive studies, Kita and colleagues succeeded in the isolation of **113a** in good yields using the ketene acetal **92b** as an initiator. The success is probably due to the nearly neutral reaction conditions and the release of neutral and stable ethyl acetate as a single co-product. The selective conversion of **113a** to either the *p*-quinone **114a** or the dihydroquinone **115a** was achieved almost quantitatively [103, 104] (Scheme 29).



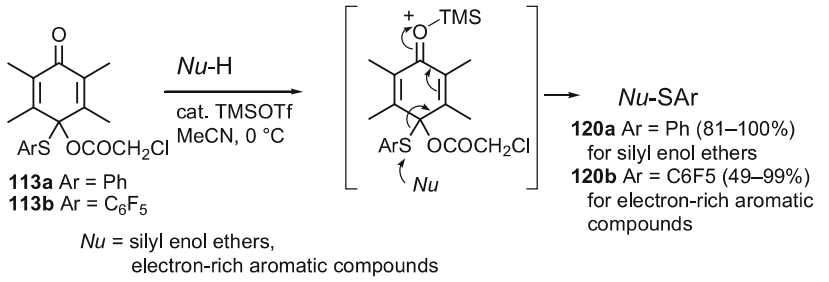
R^1, R^2 = Pr, allyl, $(CH_2)_3OTBDMS$, $(CH_2)_3OAc$, $(CH_2)_3OH$, $(CH_2)_2CHO$

Scheme 28

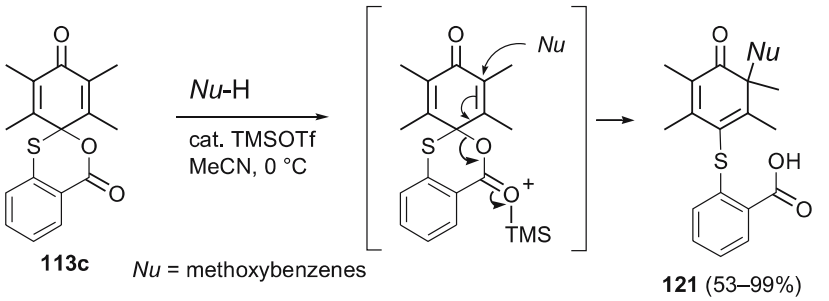


Scheme 29

The isolated **113a** was found to serve as an effective sulfenylation reagent of various silyl enol ethers and electron-rich aromatic compounds under mild conditions. The pentafluorophenyl derivative **113b** was more reactive to give the products **120b** in good-to-high yields [105, 106] (Scheme 30).



Scheme 30

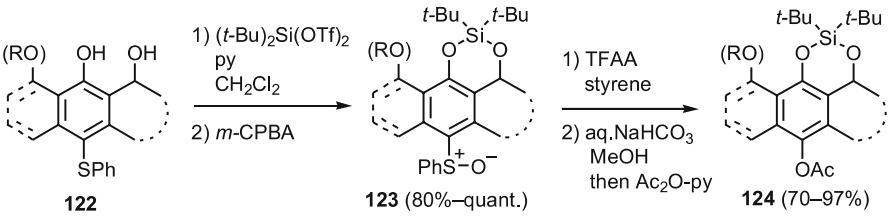


Scheme 31

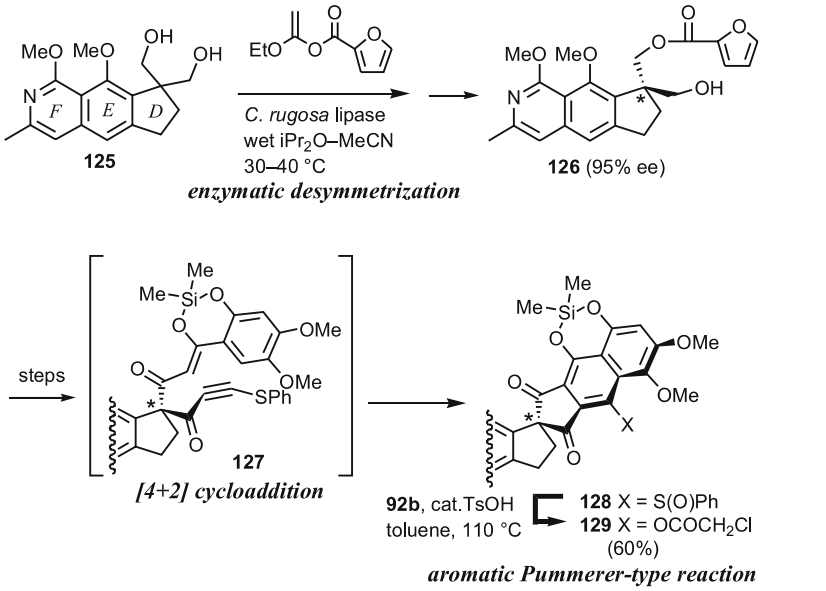
On the other hand, the cyclic *O*,*S*-acetal **113c**, similarly prepared from 2-[(4-hydroxy-2,3,5,6-tetramethylphenyl)sulfinyl]benzoic acid in a quantitative yield, accepted the regioselective nucleophilic addition of some electron-rich methoxybenzenes at the β-position of the acetal to give **121** [107] (Scheme 31).

The conversion of **116** to **118** shown in Scheme 28 provides an unprecedented method for the *ipso*-substitution of the sulfinyl group by an oxygen functional group on phenol rings. Kita and colleagues applied this method to construct *peri*-hydroxyl dihydroquinones **124**. Thus, the treatment of the sulfide **122** with $(t\text{-Bu})_2\text{Si}(\text{OTf})_2$ and subsequent oxidation gave the silylene-protected sulfoxides **123** in high yields. The following aromatic Pummerer-type reaction gave **124** in 70–97% yields. In this transformation, protection of the neighboring two *peri*-hydroxyl groups as the stable and easy-to-handle di(*t*-butyl)silylene ethers was essential, because separate protection of two *peri*-hydroxyl groups and the Pummerer-type reactions thereof resulted in forming complicated products [108] (Scheme 32).

Based on an application of this methodology, the same authors achieved the asymmetric total synthesis of the antitumor antibiotic, fredericamycin A (**130**) [109] (Scheme 33) and its analogs [110]. In this study, the installation of the second hydroxy group on the B-ring of synthetic intermediates



Scheme 32



Scheme 33

had been an intractable problem, while a combination of the intramolecular [4 + 2] cycloaddition of the optically active ω-(phenylthio)ethynyl compound (**127** → **128**) and the above-mentioned aromatic Pummerer-type reaction (**128** → **129**) provided an efficient solution to this issue. In particular, the use of the ketene acetal reagent **92b** was inevitable, because the use of ordinary TFAA resulted in formation of only an undesired product. The pivotal optically active stereogenic carbon center of **130** was generated by the lipase-

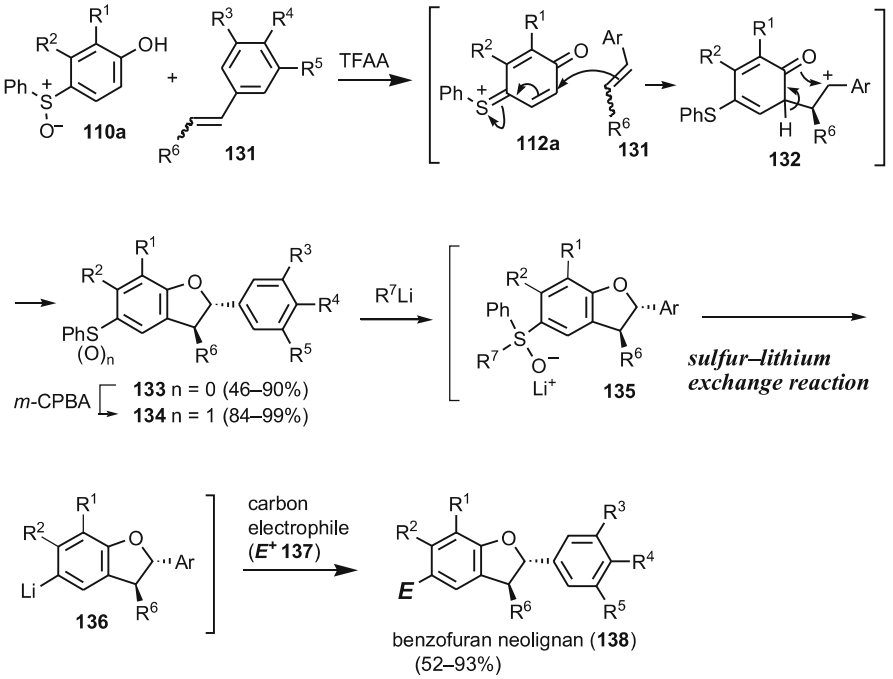
catalyzed desymmetrization of the prochiral diol (**125** → **126**) [37, 111], and the asymmetric total synthesis was accomplished with complete retention of the chiral integrity.

5.2 Nucleophilic Installation of Carbon Substituents on Phenol and Aniline Rings

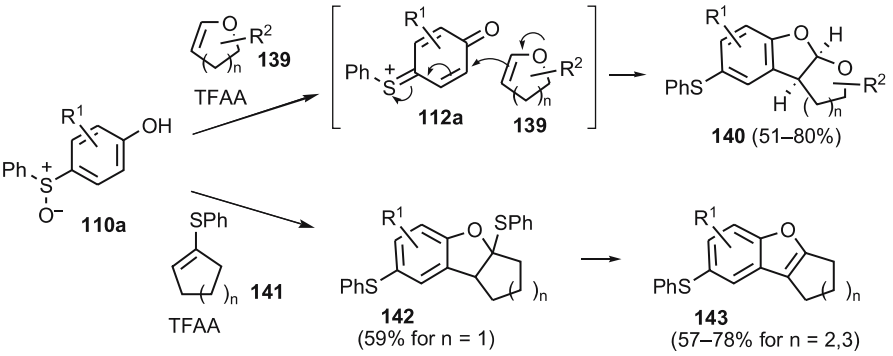
During studies on the installation of hydroxyl groups on phenol rings (Sect. 5.1), Kita and colleagues discovered that similar aromatic Pummerer-type reactions of **110a** in the presence of electron-rich styrene derivatives **131** underwent regioselective carbon–carbon bond formation in preference to the *p*-quinone formation. In this case, 1,4-addition of **131** to the conjugated $C = S^+$ system of the quinone sulfonium intermediates **112a** took place exclusively, probably due to the electron-withdrawing nature of the $C = S^+$ group being stronger than that of the C = O group. The dihydrobenzofurans **133** were obtained in good-to-high yields after the subsequent intramolecular cyclization of the intermediates **132**. A unique feature of this method is reuse of the same sulfur functional group remaining on **133** for the second carbon–carbon bond-forming reaction. Thus, treatment of the derived sulfoxides **134** with either *n*-BuLi or PhLi caused the sulfur–lithium exchange reaction via the sulfurane intermediates **135** to generate the 5-lithiobenzofurans **136**, which then reacted with carbon electrophiles **137** to install carbon substituents at the *ipso*-position of the sulfur functional group. Thereby, the overall process provides a convergent synthesis of diverse natural and unnatural benzofuran neolignans **138** by the combination of three components (**110a**, **131**, and **137**) [112] (Scheme 34).

Other electron-rich olefins such as cyclic enol ethers **139** and cycloalkenyl sulfides **141** served as good nucleophiles for the above-mentioned aromatic Pummerer-type cyclization reactions to give the ring-fused benzofurans (**140**, **142**, and **143**) with high regioselectivity (Akai et al. unpublished results) (Scheme 35).

Similarly, use of the α-methylene cyclic ethers **144** directly afforded the bisbenzannelated spiro ketals **145**, the core structure of biologically important antibiotic rubromycins and their related natural products. The product **145a** having a (methoxycarbonyl)oxy group as the R^2 group was converted to the sulfoxide **146** having a TfO group in high yield, which regioselectively generated the benzyne **149** via the sulfur–lithium exchange reaction followed by elimination of the TfO group from the lithiated intermediate **148**. In the presence of a furan **147**, the Diels–Alder reaction of **147** with **149** proceeded immediately to give the pentacyclic quinone **150** after oxidation of the Diels–Alder adduct. Thus, a new method for regioselective installation of two different kinds of aromatic rings on the phenol platform **110a** has been exemplified by using the aromatic sulfinyl group (Akai et al. unpublished results) (Scheme 36).

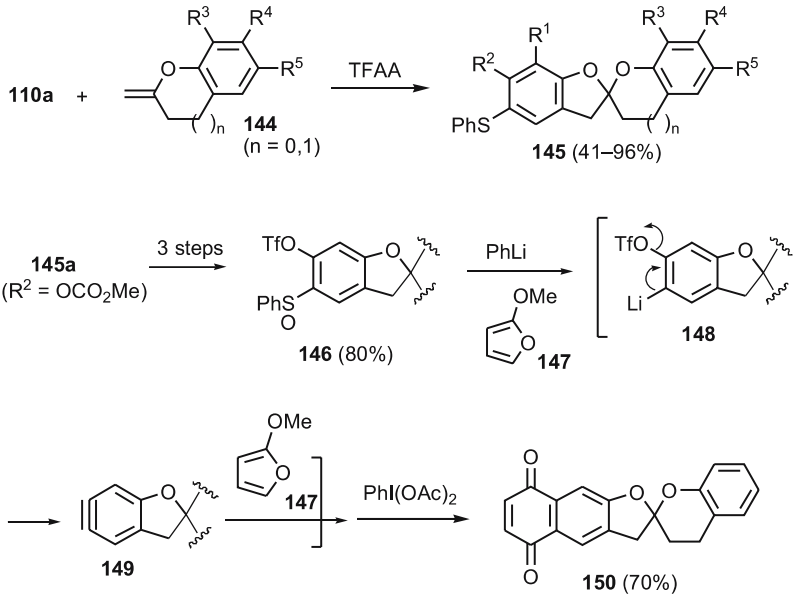


Scheme 34

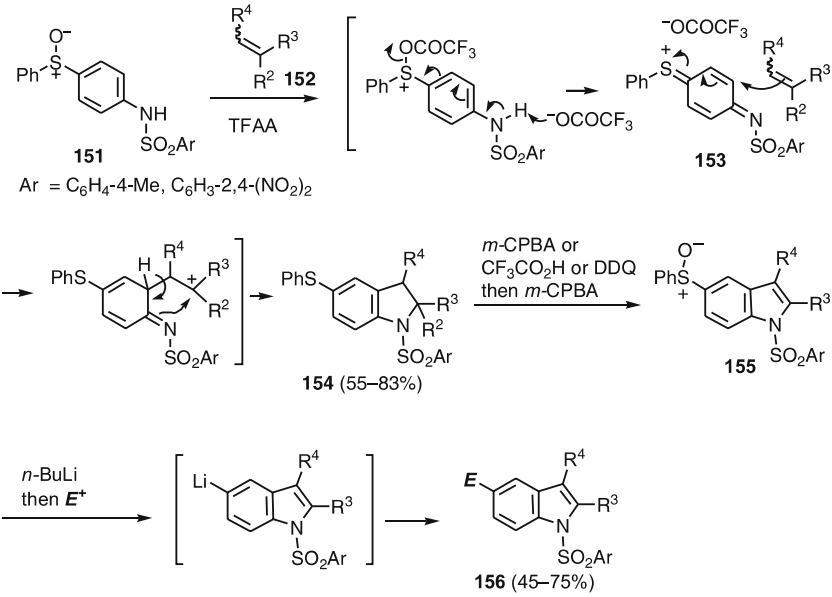


Scheme 35

The aromatic Pummerer-type cyclization methodology was applicable to the *N*-(arylsulfonyl)anilines **151**. Thus, the reactions of **151** with the electron-rich olefins **152** in the presence of TFAA afforded the indolines **154** via the iminoquinone sulfonium intermediates **153.** Oxidation of **154** to the sulfinyl indoles **155**, and similar *ipso*-substitution reactions of their sulfinyl group by the carbon electrophiles (E^+) gave the 2,3,5-trisubstituted indoles **156** [113] (Scheme 37).



Scheme 36



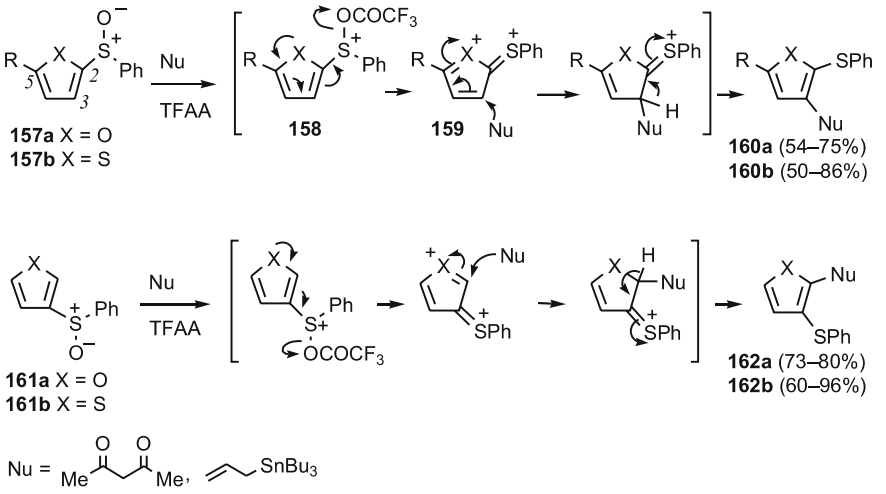
Scheme 37

5.3
Nucleophilic Installation of Carbon Substituents on Electron-Rich Heteroaromatic Compounds

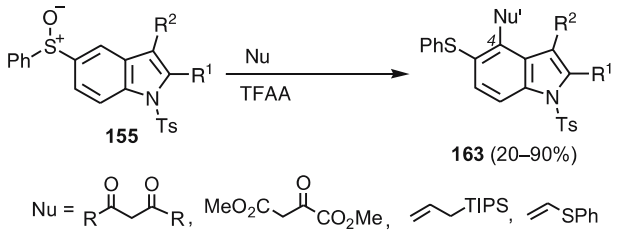
Kita and colleagues also disclosed that similar aromatic Pummerer-type reactions took place on electron-rich heteroaromatics such as furans and thiophenes to produce nucleophilic installation of carbon functional groups thereon. Thus, the treatment of the 2-phenylsulfinylfurans **157a** with TFAA in the presence of carbon nucleophiles such as allylstannane and acetylacetone afforded the 3-substituted products **160a** with complete regioselectivity. In like manner, the 2-sulfinylthiophene **157b** gave the 2-substituted products **160b**, whereas the 3-sulfinylfurans **161a** and -thiophenes **161b** provided 2-substituted products **162a,b** as single regioisomers. Based on the fact that the electronic nature of the C5-substituents of **157** significantly affected the reactivity, the most plausible reaction mechanism involves the electron donation by the aromatic heteroatom to accelerate the elimination of the acyloxy group from **158**, followed by nucleophilic addition to the sulfonium intermediates **159** [114] (Scheme 38).

The 5-sulfinylindoles **155**, prepared by the aromatic Pummerer-type reactions (Scheme 37) were found to cause the second nucleophilic carbon–carbon bond-forming reactions at the C4-position of the indole nucleus under similar Pummerer-type reaction conditions. The products **163** were isolated in moderate-to-high yields with exclusive regioselectivity [115] (Scheme 39).

Feldman and colleagues have developed regio- and stereoselective oxidative cyclization reactions of 3-(ω-nucleophile)-tethered indoles **164a,b** based



Scheme 38



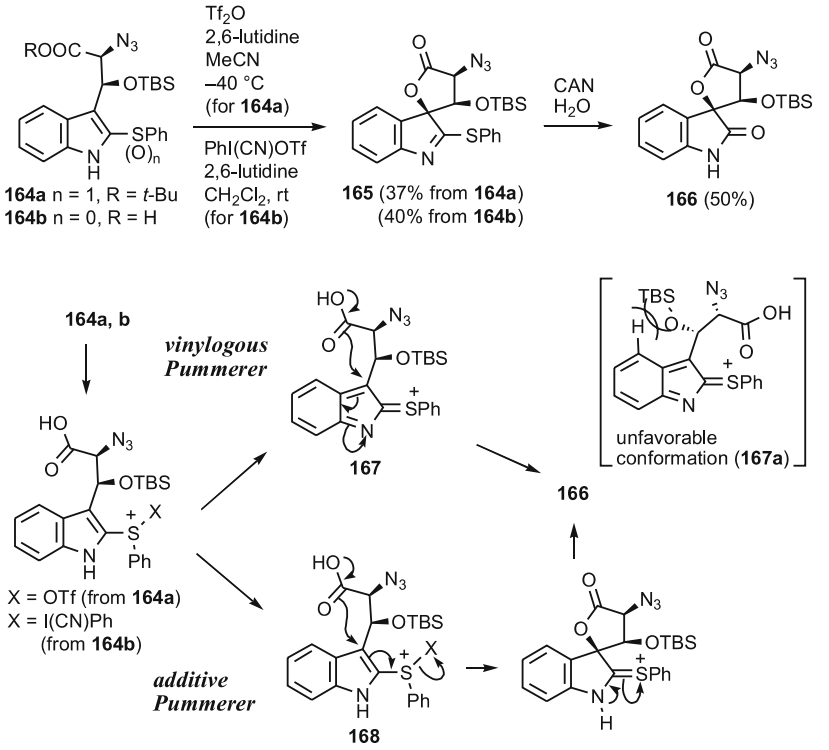
Scheme 39

on an application of the Pummerer reaction. The sulfoxides **164a** gave, when treated with Tf_2O and 2,6-lutidine, the spiro compound **165** as a single diastereomer. The same product **165** was also obtained by the reaction of the sulfide **164b** with PhI(CN)OTf and 2,6-lutidine. The CAN-mediated hydrolysis of **165** afforded the spirooxindole **166**. Both cyclization reactions are thought to proceed via the nucleophilic conjugate addition of the internal carboxylate oxygen to the sulfonium intermediate (either **167** or **168**) at the C3-position. Steric repulsion of the protected hydroxyl group with the C4 – H in the conformer **167a** probably dominated the diastereoselectivity. The authors speculate that the latter pathway seems to be more plausible, although the former course cannot be completely ruled out [116] (Scheme 40).

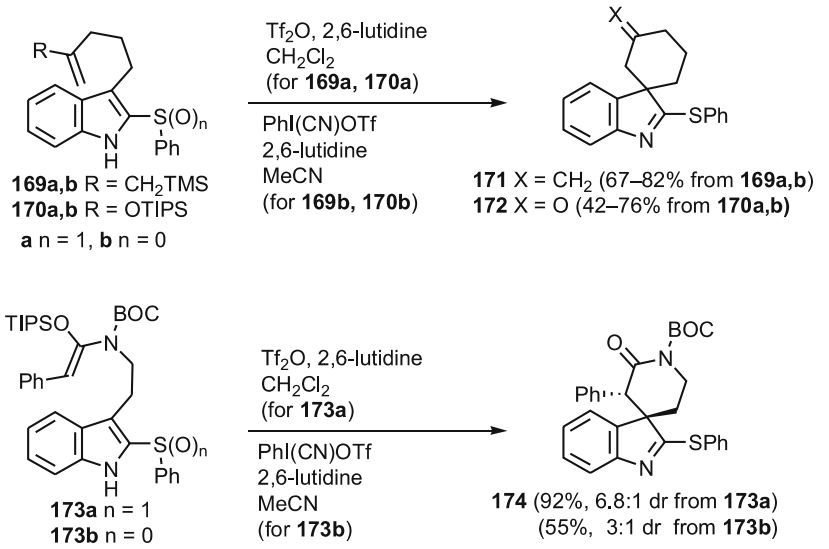
Similar cyclization reactions were also reported by the same group using the treatment of the sulfoxides (**169a**, **170a**, and **173a**) with Tf_2O and the treatment of the sulfides (**169b**, **170b**, and **173b**) with PhI(CN)OTf. Yields of the products (**171**, **172**, and **174**) varied depending on the substrates, some of which are shown in Scheme 41 [117–120].

Feldman and colleagues applied this Pummerer reaction-initiated cyclization protocol to the few-step preparation of dibromophakellstatin **177**. The 2-(phenylthio)imidazole **175**, equipped with a suitably functionalized side chain, was treated with PhI(CN)OTf with $(i\text{-}Pr)_2NEt$ to cause the stepwise double cyclization affording the *cis*-fused tetracyclic isothiourea **176** as a single product. The CAN-mediated hydrolysis furnished **177** [120] (Scheme 42).

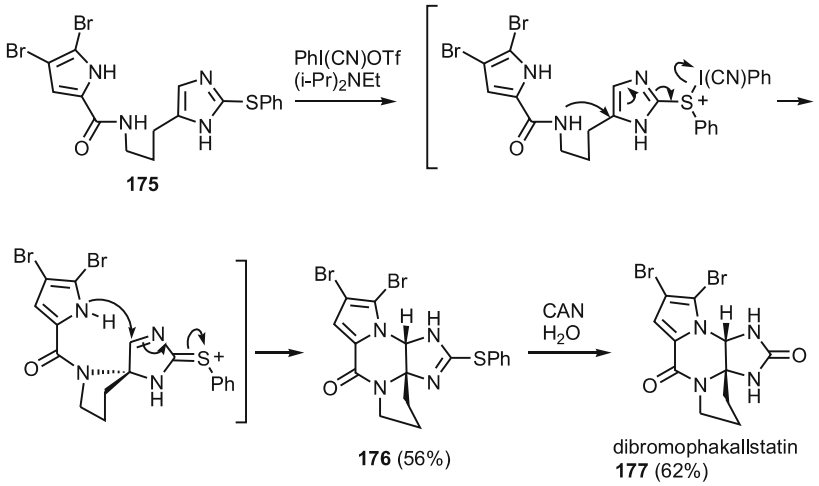
Padwa and colleagues reported the Pummerer-type reaction-initiated nucleophilic carbon–carbon bond-forming reactions of 1-naphthyl **178**, 2-furyl **180**, benzofuran-2-yl **180**, and 3-thienyl sulfilimines. They reacted with allyltributylstannane or acetylacetone in the presence of TFAA to give the products (**179** and **181**) having carbon-substituents at the adjacent position of the sulfur functional group. As some examples show in Scheme 43, the additive Pummerer reaction mechanism is probable in these cases [121].



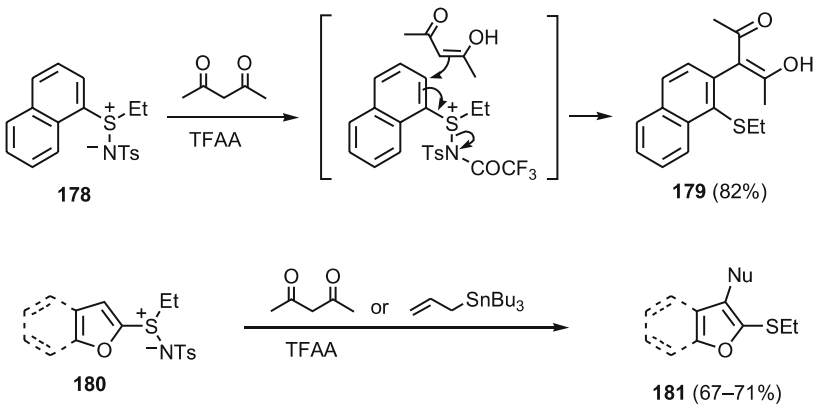
Scheme 40



Scheme 41



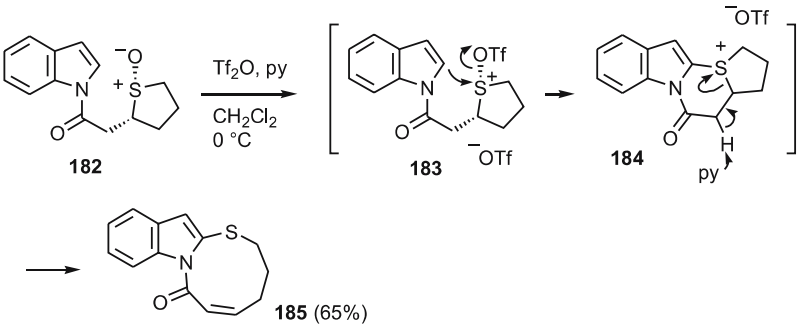
Scheme 42



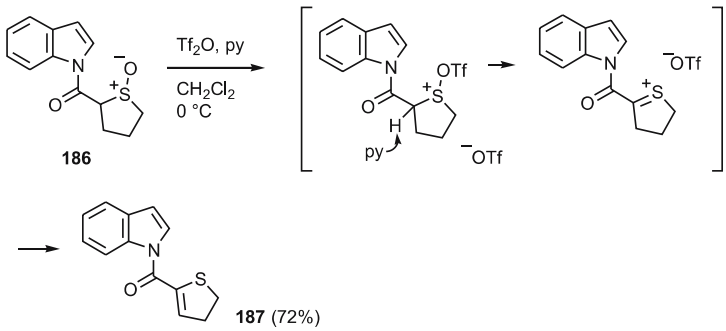
Scheme 43

6 Interrupted Pummerer Reactions

Bate and colleagues reported that the reaction of the indole sulfoxide **182** with Tf_2O and pyridine directly gave the heterocycle-fused indole **185**. This reaction is thought to take place via nucleophilic attack by the intramolecular indole ring on the sulfur of the Pummerer reaction intermediate **183**, displacing the trifluoroacetate to form the tetracyclic sulfonium ion **184**. Deprotonation at the β-position to the sulfonium ion caused fragmentation, to afford the ring expanded product **185** (Scheme 44). In contrast, a similar reaction of **186**, having a carbonyl group at the β-position to the sulfonium



Scheme 44



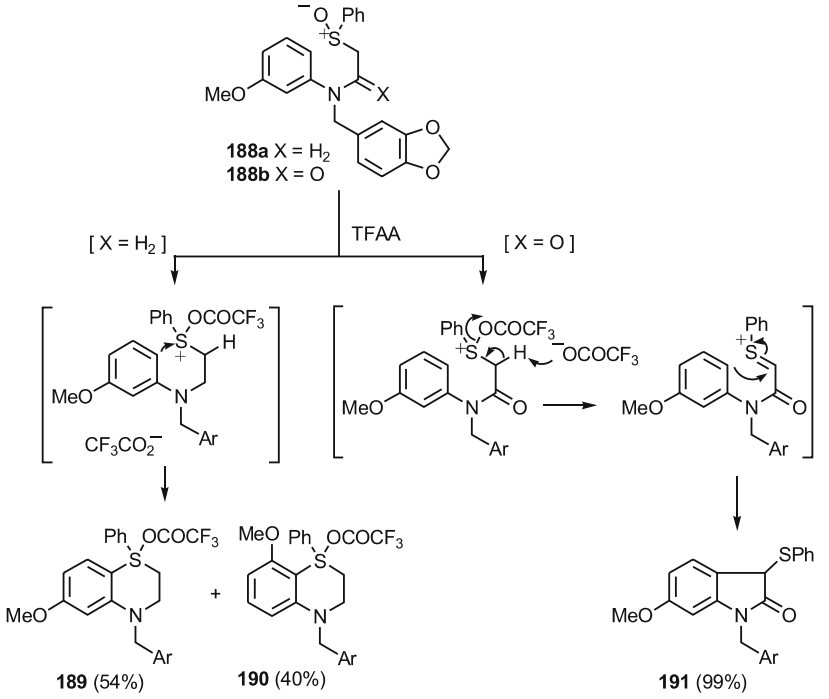
Scheme 45

ion, resulted in the formation of only the typical elimination product **187** (Scheme 45). Therefore, the acidity of the proton adjacent to the intermediate sulfonium ion was the key to switch these two types of reactions. The former reaction is called the "interrupted Pummerer reaction" or the "sulfoxide electrophilic sulfenylation process," and some examples have been reported [28, 122].

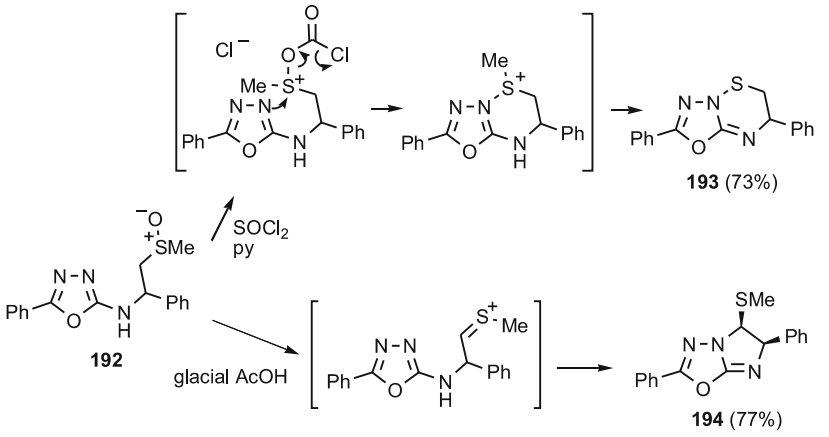
Sano and colleagues obtained similar results from the Pummerer reactions of the sulfoxides **188a,b** with TFAA. The sulfuranes (**189** and **190**) were isolated from **188a**, while a typical Pummerer-type ring closing reaction took place when **188b** was used to give the oxindole **191** exclusively. The acidity of the α-proton of the sulfinyl group again played an important role in selecting the reaction pathways [67, 123] (Scheme 46).

The activating reagents were another factor in changing these two pathways. The treatment of **192** with $SOCl_2$ and pyridine caused the interrupted Pummerer reaction to give the thiadiazines **193**, whereas the use of glacial AcOH gave the imidazolines **194** via the ordinary Pummerer reaction [124] (Scheme 47).

Treatment of the sulfides **195** with $PhI(OCOCF_3)_2$ also caused an interrupted Pummerer reaction to give the isothiazolones **196** [125] (Scheme 48).

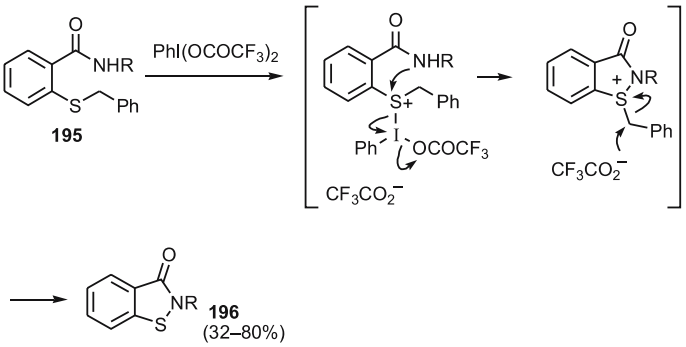


Scheme 46



Scheme 47

Zanda and colleagues developed stereoselective S_N2-displacement reactions of the sulfinyl group of the β-aminosulfoxides **197** with either a hydroxyl [126–131] or a chloro group [132, 133], which proceeded by the interrupted Pummerer reactions. The reaction of **197** with TFAA in the presence

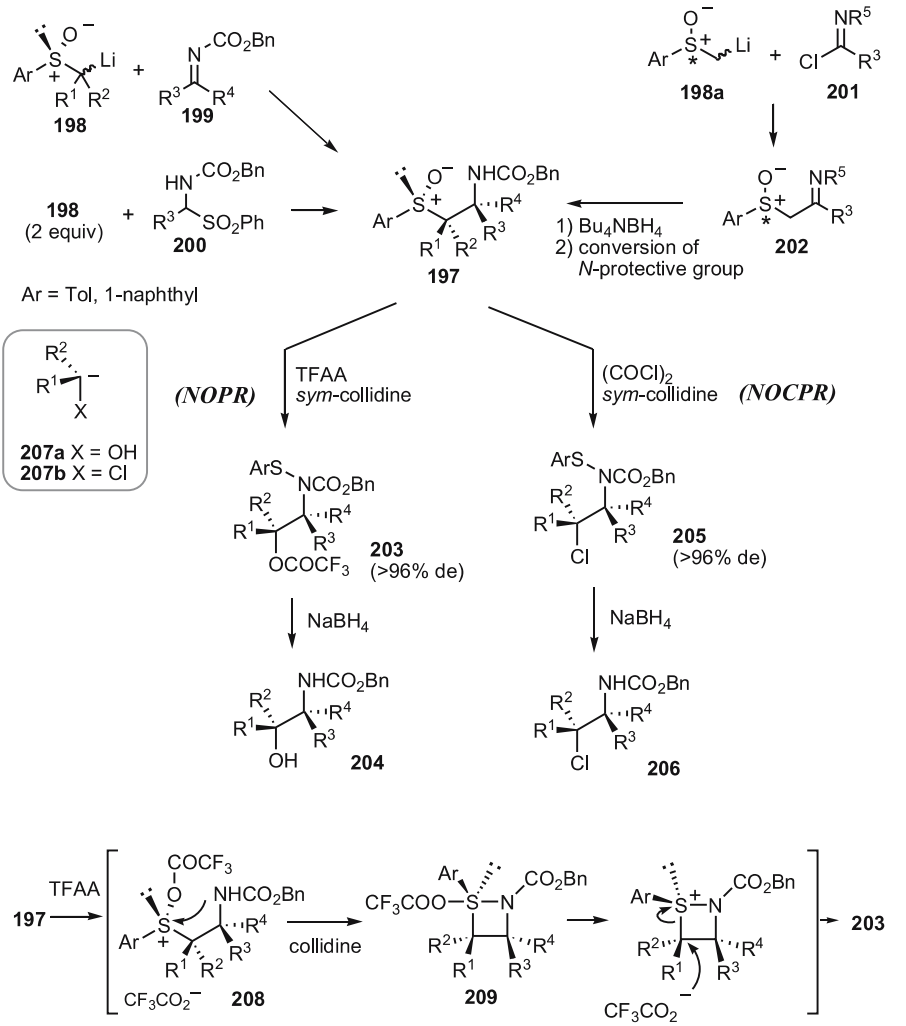


Scheme 48

of *sym*-collidine directly afforded the β-(trifluoroacetoxy)amines **203**. The reactions were exclusively stereoselective and independent of the structure of **197**. They proposed a probable mechanism of these reactions involving the formation of the sulfurane intermediates **209**, followed by a S_N2 displacement of the sulfur atom by trifluoroacetate anion. Formation of **209** was proposed based on an NMR study [128]. The reduction of **203** with $NaBH_4$ gave **204**, and thereby the sulfinyl group of **197** was replaced with a hydroxyl group with complete inversion. This type of reaction, called a "non-oxidative Pummerer reaction (NOPR)", was then applied to the chloro variant, "non-oxidative chloro-Pummerer reaction (NOCPR)". Thus, the use of oxalyl chloride instead of TFAA provided the β-chloroamines **206** in the same S_N2 displacement fashion [132, 133].

The sulfoxides **197** were available by the nucleophilic addition of the enantiomerically pure α-lithiosulfoxides **198** to the *N*-protected imines **199** [127] or to their easy-to-handle precursors **200** [130] with moderate-to-good diastereoselectivities. An alternative preparation of **197** was reported by the reaction of the optically pure **198a** with chloroimines **201** followed by the highly diastereoselective reduction of the thus generated **202** [129]. Therefore, the overall process demonstrates that the optically active α-lithiated alkylsulfoxides **198** serve as equivalents of the α-hydroxy-**207a** or the α-chloro-alkyl carbanions **207b** (Scheme 49).

Later, Ruano and colleagues reported that the reactions of lithium carbanions, derived from optically pure (*S*)-**198** with (*S*)-*N*-arylsulfinylketimines (*S*)-**210**, took place with complete stereoselectivity due to the double asymmetric induction to give the β-aminosulfoxides **211** having three consecutive stereogenic carbon centers. The NOPR of the derived **212** having a *N*-Cbz group, followed by reduction afforded the 1,2,2-trisubstituted 2-aminoethanol **213**. They also mentioned, based on their NMR study of the NOPR reaction and the reaction rate of some diastereomers of **212**, that the signals that Zanda assigned as the four-membered sulfurane **209**

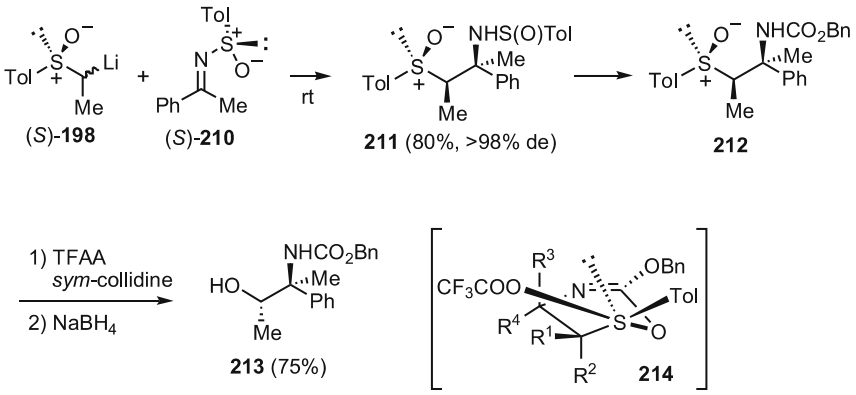


Scheme 49

were those corresponding to the sulfonium salts **208**. They instead proposed a six-membered sulfurane **214** as the most probable intermediate [134] (Scheme 50).

The NOPR chemistry was applied by Zanda and colleagues to enantioselective syntheses of amino acid analogs [128, 129], (+)- and (–)-statines [130], and an epimer of Saquinavir [131].

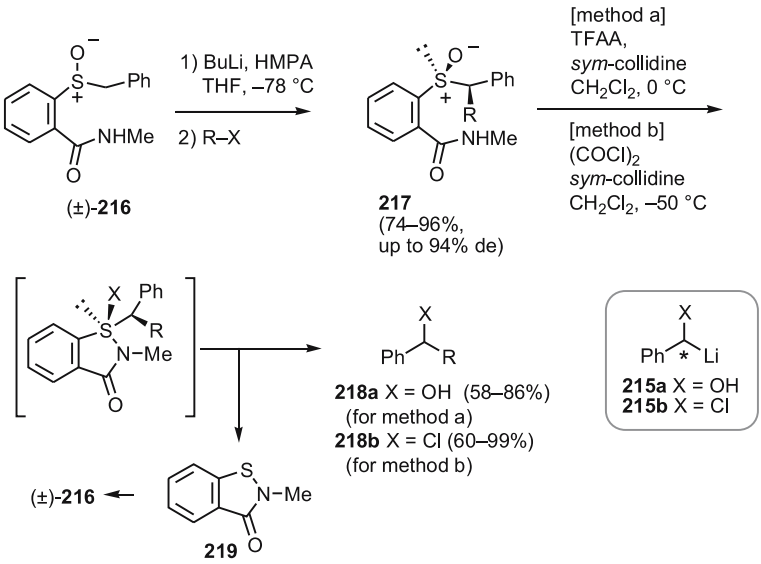
The same authors presented conceptual equivalents of the optically active α-hydroxy **215a** and α-chlorobenzyl carbanions **215b** based on the NOPR chemistry. Thus, alkylation of the bislithiated compound, derived from



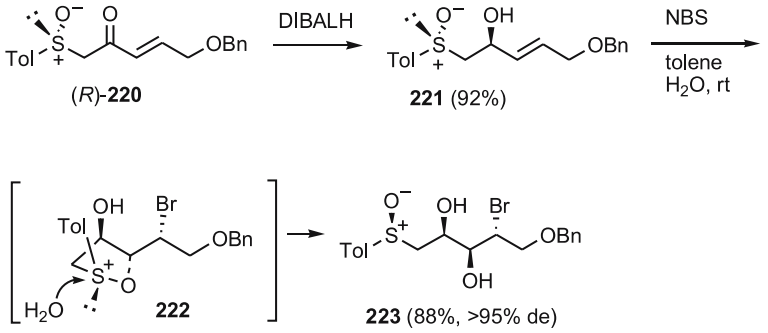
Scheme 50

(±)-**216**, with various alkyl halides, afforded **217** with high stereoselectivity. The subsequent NOPR and NOCPR of **217** gave the benzyl alcohols **218a** and the chlorides **218b** in good overall yields. Provided optically active **216** became available, this could afford a novel method for the asymmetric synthesis of **218** (Scheme 51) [135].

Raghavan and colleagues utilized optically pure sulfinyl moiety as an internal nucleophile for the enantio-, regio-, and stereoselective bromohydrin formation of olefins. Thus, the optically pure sulfoxide **221**, prepared by the diastereoselective reduction of the β-ketosulfoxide (*R*)-**220**, was treated with



Scheme 51



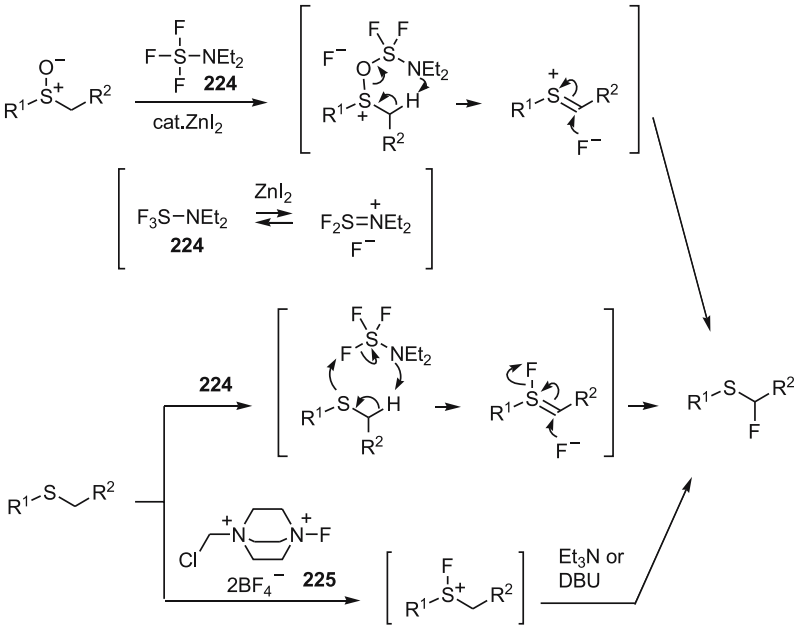
Scheme 52

NBS in a mixture of toluene and water at room temperature to give the bromohydrin **223** as a single product. Such high selectivities can be explained by the intermediacy of the sulfonium ion **222**, which, upon hydrolysis by attack of water on sulfur in a S_N2 fashion, affords **223** with inversion of the sulfur configuration [136] (Scheme 52). This methodology was applicable to the range of sulfinyl olefins having either (*E*)- or (*Z*)-geometry to give bromohydrins with > 95% diastereoselectivity [137]. It has been utilized for asymmetric total synthesis of sphingosines [136, 138] and polyoxamic acid [139].

7
Pummerer Reaction-Initiated Fluorination Reactions

Fluorination of biologically important compounds provides their isosteres with additional special biological activities [140, 141]. This is also used to prepare effective Michael acceptors that serve as enzyme inhibitors and active site affinity labels [142]. The Pummerer and the Pummerer-type reactions have found effective applications in the α-fluorination of thioethers during the past two decades. The products, α-fluorosulfides, have been proved to be valuable in modifying biologically active molecules and in serving as useful synthetic intermediates. Powerful and easy-handling reagents for the Pummerer-type α-fluorination have been developed. The combination of (diethylamino)sulfur trifluoride (DAST, **224**) and a catalytic amount of ZnI_2 is effective for sulfoxides [143, 144]. **224** with or without a catalytic amount of $SbCl_3$ is effective for both sulfoxides and sulfides [145, 146], and selectfluor **225** is useful for sulfides [147] (Scheme 53).

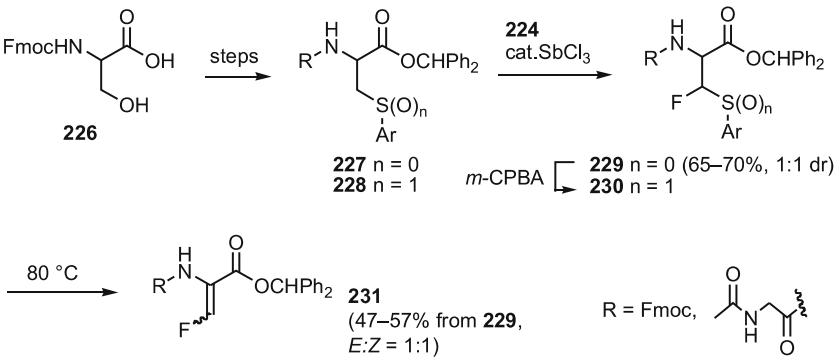
Donk and colleagues prepared the (*E*)- and (*Z*)-3-fluorodehydroalanine derivatives **231** from the protected serine **226**. In this case, the reaction of the sulfide **227** with either **224** or **225** gave the α-fluorosulfide **229** in low yields, whereas the fluorination of the sulfoxides **228** with **224** – cat.$SbCl_3$



Scheme 53

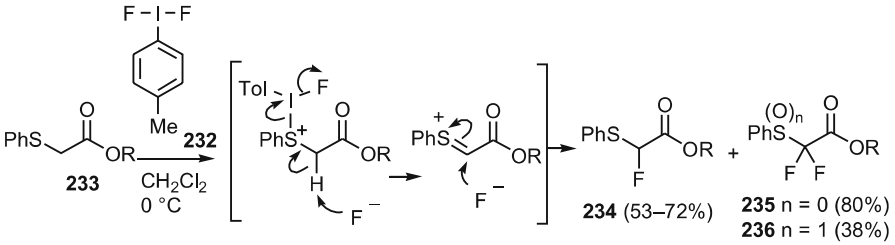
gave satisfactory yields of **229** as a 1 : 1 mixture of two diastereomers. Oxidation of **229** followed by thermal elimination afforded a 1 : 1 mixture of the (*E*)- and (*Z*)-**231** (Scheme 54). They also prepared a peptide containing the 3-fluoro-1,2-dehydroalanine moiety. These products served as effective Michael acceptors [142, 148].

Difluoroiodotoluene (DFIT) **232**, readily prepared from iodotoluene, is a crystalline and storable reagent that offers a mild method for the α-fluorination of sulfides without any other additives. Motherwell and col-

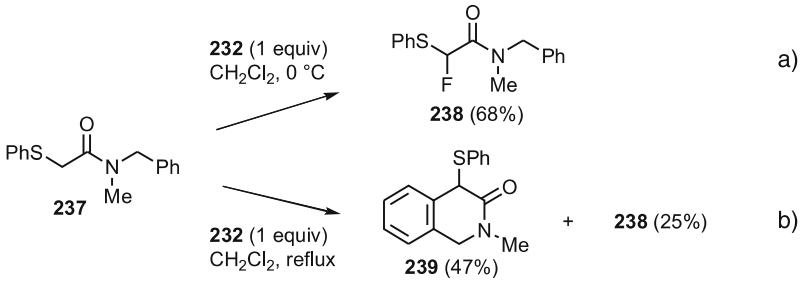


Scheme 54

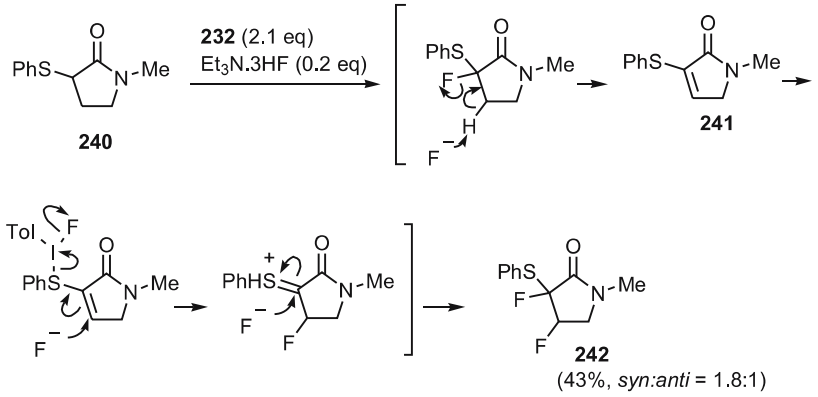
leagues reported some examples on the fluorination of the α-phenylthio esters **233** using **232**, and the control of the amount of **232** afforded different products. Thus, use of one equivalent of **232** in CH_2Cl_2 at 0 °C provided the corresponding α-fluoro ester **234** in good yields. The use of two equivalents of **232** gave the difluoro ester **235**, and that of three equivalents resulted in formation of the difluoro sulfoxide **236** as the major product [149] (Scheme 55).



Scheme 55



Scheme 56



Scheme 57

In a like manner, the reaction of the amide **237** with one equivalent of **232** in CH_2Cl_2 at 0 °C afforded the α-fluorinated amides **238** (upper pathway in Scheme 56), whereas a similar reaction in refluxing CH_2Cl_2 gave the lactam **239** as the major product along with **238** (lower pathway in Scheme 56). The preferential intermolecular reaction in the latter case can be explained by the preferred transoid conformation of the amide linkage at low temperature. However, the generality of these reactions has not been established [150].

Reaction of the lactam **240** with more than two equivalents of **232** gave the α,β-difluorinated product **242**, which was probably obtained via formation of the enone **241** followed by the additive Pummerer reaction with the second equivalent of **232** [150, 151] (Scheme 57).

8 Conclusion

The Pummerer and the Pummerer-type reactions have found a variety of applications as a powerful tool in modern synthetic organic chemistry. The sulfonium ion intermediates, generated by the Pummerer reactions, function not only as equivalents (or precursors) of the carbonyl group but also as highly reactive electrophiles, which initiate various kinds of carbon–carbon and carbon–heteroatom bond-forming reactions in both intermolecular and intramolecular fashion. The synthetic utility of these reactions has been proved by a large number of total syntheses of natural and unnatural biologically useful compounds [38].

This article has emphasized the progress of the Pummerer and Pummerer-type reactions since 2001 and revealed some noteworthy trends: The availability of optically pure sulfinyl moieties has opened wider applicability of the Pummerer reactions to asymmetric bond-forming reactions. The domino reactions initiated by the Pummerer reactions have also found increased efficacy to construct the polycyclic molecules in one-pot and will continue to draw attention as an environmentally benign synthetic methodology. The aromatic Pummerer-type reactions on various kinds of electron-sufficient aromatic rings provide new methods for the functionalization of aromatic compounds and are expected to make further progress. A combination of the Pummerer chemistry with recent technologies such as solid-phase synthesis [73, 152, 153] or fluorous chemistry [74, 75] is another area to be intensively investigated for more convenient protocols. Just after completion of this article, an excellent review written by Feldman was published, in which the modern Pummerer reactions were thoroughly described [154].

References

1. Pummerer R (1909) Ber Dtsch Chem Ges 42:2282
2. Pummerer R (1910) Ber Dtsch Chem Ges 43:1401
3. Oae S, Numata T, Yoshimura T (1981) Heterosulphonium salts. In: Stirling CJM, Patai S (eds) The chemistry of the sulphonium group. Wiley, New York, p 571
4. De Lucchi O, Miotti U, Modena G (1991) Org React 40:157
5. Grierson DS, Husson HP (1991) In: Trost BM, Fleming I (eds) Comprehensive organic synthesis, vol 6. Pergamon, Oxford, p 909
6. Kennedy M, McKervey MA (1991) In: Trost BM, Fleming I (eds) Comprehensive organic synthesis, vol 7. Pergamon, Oxford, p 193
7. Dreeßen S, Schabbert S, Schaumann E (2001) Eur J Org Chem 2001(2):245
8. Hagiwara H, Kobayashi K, Miya S, Hoshi T, Suzuki T, Ando M, Okamoto T, Kobayashi M, Yamamoto I, Ohtsubo S, Kato M, Uda H (2002) J Org Chem 67:5969
9. Perales JB, Makino NF, Van Vranken DL (2002) J Org Chem 67:6711
10. Hirai A, Tonooka T, Tanino K, Miyashita M (2003) Chirality 15:108
11. Kato I, Higashimoto M, Tamura O, Ishibashi H (2003) J Org Chem 68:7983
12. Okano T, Chokai M, Hiraishi M, Yoshizawa M, Kusukawa T, Fujita M (2004) Tetrahedron 60:4031
13. Cho BT, Shin SH (2005) Tetrahedron 61:6959
14. Ishida H, Itoh K, Ohno M (2001) Tetrahedron 57:1737
15. Bozó E, Gáti T, Demeter A, Kuszmann J (2002) Carbohydr Res 337:1351
16. Baba D, Fuchigami T (2003) Electrochimica Acta 48:755
17. Raghavan S, Kumar CN (2006) Tetrahedron Lett 47:1585
18. Kita Y, Yasuda H, Tamura O, Itoh F, Tamura Y (1984) Tetrahedron Lett 25:4681
19. Tamura Y, Yakura T, Shirouchi Y, Haruta J (1986) Chem Pharm Bull 34:1061
20. Trost BM, Murayama E (1981) J Am Chem Soc 103:6529
21. Padwa A, Waterson AG (2000) J Org Chem 65:235
22. Tamura Y, Shindo H, Uenishi J, Ishibashi H (1980) Tetrahedron Lett 21:2547
23. Padwa A, Kuethe JT (1998) J Org Chem 63:4256
24. Shibata N, Fujimori C, Fujita S, Kita Y (1996) Chem Pharm Bull 44:892
25. Padwa A (1999) Phosphorus Sulfur Silicon Relat Elem 153–154:23
26. Padwa A, Bur SK, Danca DM, Ginn JD, Lynch SM (2002) Synlett, p 851
27. Padwa A (2003) Pure Appl Chem 75:47
28. Bur SK, Padwa A (2004) Chem Rev 104:2401
29. Padwa A (2004) Pure Appl Chem 76:1933
30. Kita Y, Shibata N (1996) Synlett, p 289
31. Kita Y (1997) Phosphorus Sulfur Silicon Relat Elem 120–121:145
32. Kita Y (1997) Yakugaku Zasshi 117:282
33. Kita Y (1997) Chem Abstr 126:330218
34. Shibata N, Kita Y (1998) Chem Heterocycl Compd 1463
35. Matsugi M, Shibata N, Kita Y (2000) Advances Sulfur Chem 2:215
36. Akai S, Kita Y (1998) Org Prep Proced Int 30:603
37. Kita Y, Akai S (2004) Chem Rec 4:363
38. Prilezhaeva EN (2001) Russian Chem Rev 70:897
39. Keum G, Kang SB, Kim Y, Lee E (2004) Org Lett 6:1895
40. Keum G, Hwang CH, Kang SB, Kim Y, Lee E (2005) J Am Chem Soc 127:10396
41. Narita M, Urabe H, Sato F (2002) Angew Chem Int Ed 41:3671
42. Narita M, Urabe H, Sato F (2002) Angew Chem 114:3823

43. Laleu B, Mobian P, Herse C, Laursen BW, Hopfgartner G, Bernardinelli G, Lacour J (2005) Angew Chem Int Ed 44:1879
44. Laleu B, Mobian P, Herse C, Laursen BW, Hopfgartner G, Bernardinelli G, Lacour J (2005) Angew Chem 117:1913
45. Brinkmann Y, Carreño MC, Urbano A, Colobert F, Solladié G (2004) Org Lett 6:4335
46. Stefani HA, Menezes PH, Costa IM, Silva DO, Petragnani N (2002) Synlett, p 1335
47. Raghavan S, Rajender A (2004) Tetrahedron 60:5059
48. Suzuki T, Honda Y, Izawa K, Williams RM (2005) J Org Chem 70:7317
49. Yokoyama M (2000) Synthesis, p 1637
50. Naka T, Minakawa N, Abe H, Kaga D, Matsuda A (2000) J Am Chem Soc 122:7233
51. Minakawa N, Kaga D, Kato Y, Endo K, Tanaka M, Sasaki T, Matsuda A (2002) J Chem Soc Perkin Trans 1:2182
52. Zhang X, Qing FL (2002) J Org Chem 67:1016
53. Paquette LA, Fabris F, Gallou F, Dong S (2003) J Org Chem 68:8625
54. Paquette LA, Dong S (2005) J Org Chem 70:5655
55. Yoshimura Y, Kuze T, Ueno M, Komiya F, Haraguchi K, Tanaka H, Kano F, Yamada K, Asami K, Kaneko N, Takahata H (2006) Tetrahedron Lett 47:591
56. Caputo R, Guaragna A, Palumbo G, Pedatella S (2003) Eur J Org Chem 346
57. Choo H, Chen X, Yadav V, Wang J, Schinazi RF, Chu CK (2006) J Med Chem 49:1635
58. Marino JP, Neisser M (1981) J Am Chem Soc 103:7687
59. Marino JP, Rubio MB, Cao G, de Dios A (2002) J Am Chem Soc 124:13398
60. Padwa A, Nara S, Wang Q (2005) J Org Chem 70:8538
61. Jousse-Karinthi C, Riche C, Chiaroni A, Desmaële D (2001) Eur J Org Chem 3631
62. Montaño RG, Zhu J (2002) Chem Commun, p 2448
63. Huang HY, Wang HM, Hou RS, Chen LC (2004) J Chinese Chem Soc 51:1025
64. Boudou M, Enders D (2005) J Org Chem 70:9486
65. Bousquet T, Fleury JF, Daïch A, Netchitaïlo P (2006) Tetrahedron 62:706
66. Magnus P, Rainey T, Lynch V (2003) Tetrahedron Lett 44:2459
67. Sano T (2001) Trends Heterocyclic Chem 7:117
68. Saitoh T, Ichikawa T, Horiguchi Y, Toda J, Sano T (2001) Chem Pharm Bull 49:979
69. Horiguchi Y, Saitoh T, Terakado S, Honda K, Kimura T, Toda J, Sano T (2001) Heterocycles 54:967
70. Saitoh T, Shikiya K, Horiguchi Y, Sano T (2003) Chem Pharm Bull 51:667
71. Horiguchi Y, Ogawa K, Saitoh T, Sano T (2004) Chem Pharm Bull 52:214
72. Abe K, Saitoh T, Horiguchi Y, Utsunomiya I, Taguchi K (2005) Biol Pharm Bull 28:1355
73. McAllister LA, Brand S, de Gentile R, Procter DJ (2003) Chem Commun, p 2380
74. McAllister LA, McCormick RA, Brand S, Procter DJ (2005) Angew Chem Int Ed 44:452
75. McAllister LA, McCormick RA, Brand S, Procter DJ (2005) Angew Chem 117:456
76. Raghavan S, Rajender A, Rasheed MA, Reddy SR (2003) Tetrahedron Lett 44:8253
77. Ichikawa S, Matsuda A (2004) Nucleosides Nucleotides Nucleic Acids 23:239
78. Kreisberg JD, Magnus P, Shinde S (2002) Tetrahedron Lett 43:7393
79. Kim T, Kim K, Park YJ (2002) Eur J Org Chem 493
80. Padwa A (2005) Phosphorus Sulfur Silicon Relat Elem 180:1149
81. Sarkar TK, Basak S, Panda N (2002) Tetrahedron Lett 43:1341
82. Sarkar TK, Panda N, Basak S (2003) J Org Chem 68:6919
83. Padwa A, Heidelbaugh TM, Kuethe JT, McClure MS, Wang Q (2002) J Org Chem 67:5928

84. Padwa A, Danca MD, Hardcastle KI, McClure MS (2003) J Org Chem 68:929
85. Padwa A, Heidelbaugh TM, Kuethe JT (2000) J Org Chem 65:2368
86. Padwa A, Waterson AG (2000) Tetrahedron 56:10159
87. Numata T, Itoh O, Oae S (1977) Chem Lett, p 909
88. Mikolajczyk M, Zatorski A, Grzejsczak S, Costisella B, Midura W (1978) J Org Chem 43:2518
89. Numata T, Itoh O, Yoshimura T, Oae S (1983) Bull Chem Soc Jpn 56:257
90. Kita Y, Shibata N, Yoshida N (1993) Tetrahedron Lett 34:4063
91. Kita Y, Shibata N, Yoshida N, Fujita S (1994) J Chem Soc Perkin Trans 1:3335
92. Shibata N, Matsugi M, Kawano N, Fukui S, Fujimori C, Gotanda K, Murata K, Kita Y (1997) Tetrahedron: Asymmetry 8:303
93. Kita Y, Shibata N, Kawano N, Tohjo T, Fujimori C, Ohishi H (1994) J Am Chem Soc 116:5116
94. García Ruano JL, Alemán J, Padwa A (2004) Org Lett 6:1757
95. García Ruano JL, Alemán J, Aranda MT, Arévalo MJ, Padwa A (2005) Org Lett 7:19
96. García Ruano JL, Alemán J, Aranda MT, Arévalo MJ, Padwa A (2005) Phosphorus Sulfur Silicon Relat Elem 180:1497
97. Nagao Y, Miyamoto S, Hayashi K, Mihira A, Sano S (2002) Chem Pharm Bull 50:558
98. Nagao Y (2002) Yakugaku Zasshi 122:1
99. Nagao Y (2002) Chem Abstr 136:309438
100. Nagao Y, Miyamoto S, Hayashi K, Mihira A, Sano S (2002) Tetrahedron Lett 43:1519
101. Akai S, Takeda Y, Iio K, Yoshida Y, Kita Y (1995) J Chem Soc Chem Commun, p 1013
102. Akai S, Takeda Y, Iio K, Takahashi K, Fukuda N, Kita Y (1997) J Org Chem 62:5526
103. Kita Y, Takeda Y, Matsugi M, Iio K, Gotanda K, Murata K, Akai S (1997) Angew Chem Int Ed Engl 36:1529
104. Kita Y, Takeda Y, Matsugi M, Iio K, Gotanda K, Murata K, Akai S (1997) Angew Chem 109:1525
105. Matsugi M, Murata K, Nambu H, Kita Y (2001) Tetrahedron Lett 42:1077
106. Matsugi M, Murata K, Gotanda K, Nambu H, Anilkumar G, Matsumoto K, Kita Y (2001) J Org Chem 66:2434
107. Matsugi M, Murata K, Anilkumar G, Nambu H, Kita Y (2001) Chem Pharm Bull 49:1658
108. Kita Y, Takeda Y, Iio K, Yokogawa K, Takahashi K, Akai S (1996) Tetrahedron Lett 37:7545
109. Akai S, Tsujino T, Fukuda N, Iio K, Takeda Y, Kawaguchi K, Naka T, Higuchi K, Akiyama E, Fujioka H, Kita Y (2005) Chem Eur J 11:6286
110. Akai S, Tsujino T, Fukuda N, Iio K, Takeda Y, Kawaguchi K, Naka T, Higuchi K, Kita Y (2001) Org Lett 3:4015
111. Akai S, Naka T, Fujita T, Takebe Y, Tsujino T, Kita Y (2002) J Org Chem 67:411
112. Akai S, Morita N, Iio K, Nakamura Y, Kita Y (2000) Org Lett 2:2279
113. Akai S, Kawashita N, Morita N, Nakamura Y, Iio K, Kita Y (2002) Heterocycles 58:75
114. Akai S, Kawashita N, Satoh H, Wada Y, Kakiguchi K, Kuriwaki I, Kita Y (2004) Org Lett 6:3793
115. Akai S, Kawashita N, Wada Y, Satoh H, Alinejad AH, Kakiguchi K, Kuriwaki I, Kita Y (2006) Tetrahedron Lett 47:1881
116. Feldman KS, Vidulova DB (2004) Tetrahedron Lett 45:5035
117. Feldman KS, Vidulova DB (2004) Org Lett 6:1869
118. Feldman KS, Karatjas AG (2004) Org Lett 6:2849
119. Feldman KS, Vidulova DB, Karatjas AG (2005) J Org Chem 70:6429

120. Feldman KS, Skoumbourdis AP (2005) Org Lett 7:929
121. Padwa A, Nara S, Wang Q (2006) Tetrahedron Lett 47:595
122. Bate DK, Winters RT, Picard JA (1992) J Org Chem 57:3094
123. Horiguchi Y, Sonobe A, Saitoh T, Toda J, Sano T (2001) Chem Pharm Bull 49:1132
124. Yadav LDS, Kapoor R (2003) Synthesis, p 1079
125. Wang HM, Huang HY, Kang IJ, Chen LC (2001) Heterocycles 55:1231
126. Arnone A, Bravo P, Bruché L, Crucianelli M, Vichi L, Zanda M (1995) Tetrahedron Lett 36:7301
127. Bravo P, Guidetti M, Viani F, Zanda M, Markovsky AL, Sorochinsky AE, Soloshonok IV, Soloshonok VA (1998) Tetrahedron 54:12789
128. Crucianelli M, Bravo P, Arnone A, Corradi E, Meille SV, Zanda M (2000) J Org Chem 65:2965
129. Fustero S, Navarro A, Pina B, Soler JG, Bartolomé A, Asensio A, Simón A, Bravo P, Fronza G, Volonterio A, Zanda M (2001) Org Lett 3:2621
130. Pesenti C, Bravo P, Corradi E, Frigerio M, Meille SV, Panzeri W, Viani F, Zanda M (2001) J Org Chem 66:5637
131. Pesenti C, Arnone A, Arosio P, Frigerio M, Meille SV, Panzeri W, Viani F, Zanda M (2004) Tetrahedron Lett 45:5125
132. Volonterio A, Bravo P, Pesenti C, Zanda M (2001) Tetrahedron Lett 42:3985
133. Volonterio A, Bravo P, Panzeri W, Pesenti C, Zanda M (2002) Eur J Org Chem, p 3336
134. García Ruano JL, Alemán J, del Prado M, Fernández I (2004) J Org Chem 69:4454
135. Volonterio A, Bravo P, Zanda M (2002) Tetrahedron Lett 43:6537
136. Raghavan S, Rajender A (2003) J Org Chem 68:7094
137. Raghavan S, Reddy SR, Tony KA, Kumar CN, Varma AK, Nangia A (2002) J Org Chem 67:5838
138. Raghavan S, Rajender A, Yadav JS (2003) Tetrahedron: Asymmetry 14:2093
139. Raghavan S, Joseph SC (2003) Tetrahedron Lett 44:6713
140. Pihko PM (2006) Angew Chem Int Ed 45:544
141. Pihko PM (2006) Angew Chem 118:558
142. Zhou H, Schmidt DMZ, Gerlt JA, van der Donk WA (2003) ChemBioChem 4:1206
143. McCarthy JR, Peet NP, LeTourneau ME, Inbasekaran M (1985) J Am Chem Soc 107:735
144. Jarvi ET, McCarthy JR, Mehdi S, Matthews DP, Edwards ML, Prakash NJ, Bowlin TL, Sunkara PS, Bey P (1991) J Med Chem 34:647
145. Wnuk SF, Robins MJ (1990) J Org Chem 55:4757
146. Robins MJ, Wnuk SF (1993) J Org Chem 58:3800
147. Lal GS (1993) J Org Chem 58:2791
148. Zhou H, van der Donk WA (2001) Org Lett 3:593
149. Motherwell WB, Greaney MF, Tocher DA (2002) J Chem Soc Perkin Trans 1:2809
150. Motherwell WB, Greaney MF, Edmunds JJ, Steed JW (2002) J Chem Soc Perkin Trans 1:2816
151. Greaney MF, Motherwell WB, Tocher DA (2001) Tetrahedron Lett 42:8523
152. Rolland C, Hanquet G, Ducep JB, Solladié G (2001) Tetrahedron Lett 42:7563
153. Tai CH, Wu HC, Li WR (2004) Org Lett 6:2905
154. Feldman KS (2006) Tetrahedron 62:5003

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1,2-Sulfur Migrations

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Abstract 1,2-Thio migration has emerged as a valuable synthetic tool for organic chemists. The most common route of 1,2-thio migration proceeds through a thiiranium intermediate. The latter usually proceeds stereoselectively, since substitution of a vicinal leaving group of sulfur takes place with good stereocontrol; substitution or elimination to open the thiiranium ring also proceeds stereoselectively. This and other types of 1,2-thio migration, including 1,2-thio shifts, formal 1,2-thio migration through fragmentation-recombination, [1,5]∼thio migration in five-membered ring systems, and radical 1,2-thio migrations are discussed in this review.

Keywords Carbohydrates · Heterocycles · Morin rearrangement · Sulfur migration · Thiiranium

Abbreviations

1°	primary
2°	secondary
4A MS	four Angstrom molecular sieves
Ac	acetyl
AIBN	2,2′-azobisisobutyronitrile
Ar	aryl
Bn	benzyl
Bz	benzoyl
CDI	carbonyl diimidazole
DAST	diethylamino sulfur trifluoride
DEAD	diethyl azodicarboxylate
DMAP	*N*,*N*-dimethylaminopyridine
DMA	*N*,*N*-dimethylacetamide
DMF	*N*,*N*-dimethylformamide
DMS	dimethylsulfide
DMSO	dimethylsulfoxide
d.r.	diastereomeric ratio
E	electrophile
ee	enantiomeric excess
Et	ethyl
hν	irradiation; light
IBX	2-iodoxybenzoic acid
LA	Lewis acid
LG	leaving group
m-CPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
MOM	methoxymethyl
Ms	mesyl
naphth	naphthyl
Nu	nucleophile
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NIS	*N*-iodosuccinimide
n-Pr	*normal*-propyl
p	*para*
Ph	phenyl
Phth	phthalimido
PMB	*para*-methoxybenzyl
PMP	*para*-methoxyphenyl
PNB	*para*-nitrobenzyl
PPh_3	triphenylphosphine
Pv	pivaloyl
rt	room temperature
TBS	*tert*-butyldimethylsilyl
t-Bu	*tert*-butyl

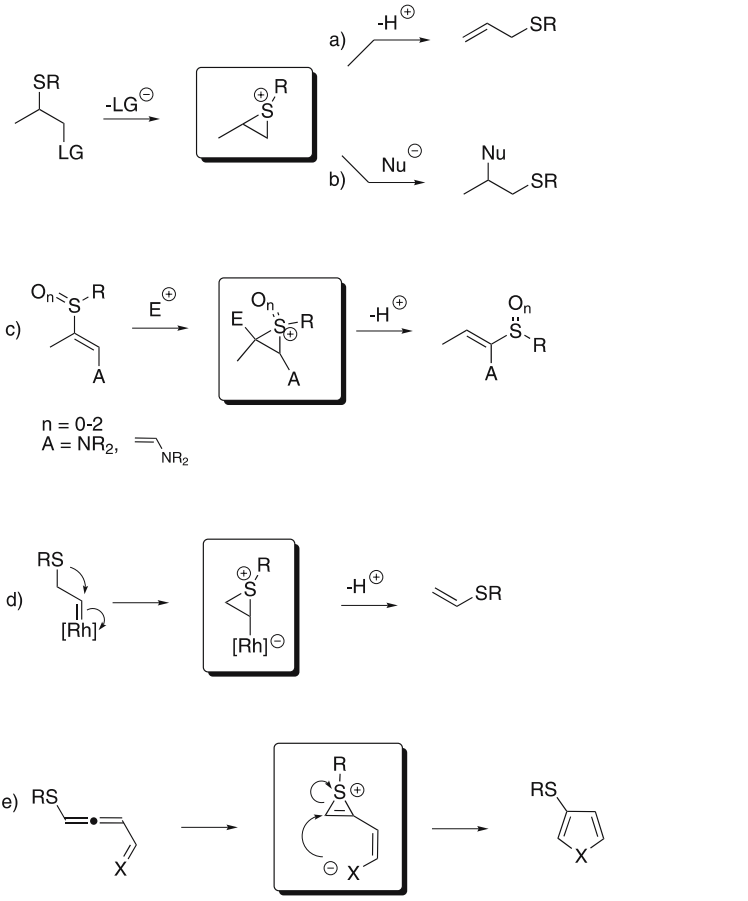
TEAB	tetraethylammonium bromide
TES	triethylsilyl
TIPS	tri*iso*-propylsilyl
Tf	trifluoromethanesulfonyl
TFAA	trifluoroacetic acid
Tr	trityl; triphenylmethyl
Ts	*para*-toluenesulfonyl
TsOH	*para*-toluenesulfonic acid

1 Introduction

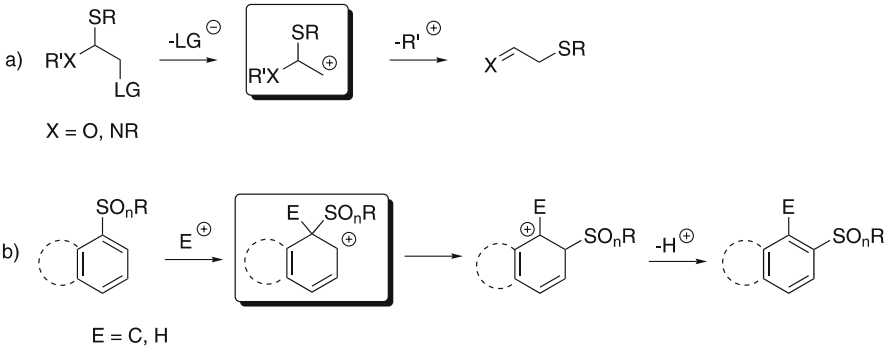
Several different manifolds of sulfur migration to a vicinal site have been observed, some of which have been developed into valuable tools for organic synthesis. A review of 1,2-thio migration is presented here, with emphasis placed on chemistry reported during the last decade. Known modes of 1,2-thio group migration may be systematized into six main categories (Schemes 1–6).

The first category involves migrations proceeding through a key thiiranium intermediate. One route involves a stereospecific vicinal nucleophilic substitution, resulting in thiiranium species depicted in the first box in Scheme 1. This intermediate can undergo either elimination, leading to allyl thioethers (a), or substitution, leading to formally transposed substitution products (b). These types of transformations have been the subject of several excellent reviews, including: Warren's review on synthesis of thio-substituted heterocycles and allyl thioethers in 2002 [1, 2] and 1999 [3]; a review on sulfur migration in carbohydrates proceeding through a thiiranium intermediate by Smoliakova in 2000 [4]; and thia-Payne rearrangement, reviewed by Rayner in 1997 [5] and Hanson in 2002 [6]. Thiiranium species can also be obtained through a vicinal nucleophilic addition to an electron-deficient center (c). This mode operates in heteroaromatic systems. Early examples were reviewed by Braverman in 1988 [7, 8]. A variation involves migration to a carbenoid center (d). The thiiranium species in the last two modes typically opens by elimination. 1,2-Thio migration can also proceed through a *thiirenium* intermediate, which is opened by an intramolecular nucleophilic substitution leading to five-membered heterocycles (e).

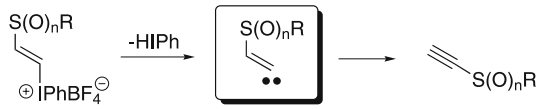
The second type of thio migration has been reported to proceed through a 1,2-shift to a cationic center (Scheme 2). This type of migration was reviewed by Braverman in 1988 [7, 8]. The third type of 1,2-thio shift occurs in neutral, electron-deficient carbenes, furnishing thioalkynes (Scheme 3). A fourth type of formal 1,2-thio migration proceeds via cleavage of the sulfur–carbon bond, followed by readdition (Scheme 4). This type of transformation is almost always used in cyclic substrates to ensure intramolecular



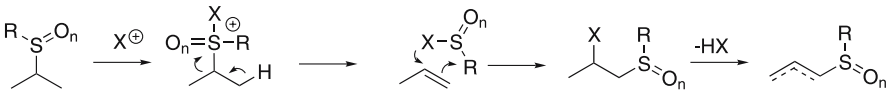
Scheme 1 1,2-Sulfur migration proceeding through a thiiranium or thiirenium intermediate



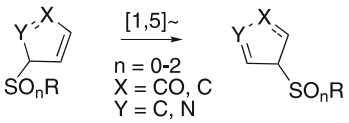
Scheme 2 1,2-Sulfur shift to a cationic center



Scheme 3 1,2-Sulfur shift to a carbene



Scheme 4 1,2-Sulfur migration through fragmentation/recombination



Scheme 5 Sigmatropic [1,5]-sulfur shift in a five-membered ring

Scheme 6 1,2-Radical sulfur migration

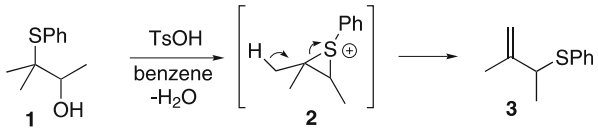
addition. A fifth type of formal 1,2-thio migration occurs during [1,5]~thio shift in five-membered ring systems (Scheme 5). Finally, the sixth type is radical 1,2-thio migration, which proceeds through a thiirane radical (Scheme 6).

2
1,2-Sulfur Migration Through a Thiiranium Intermediate

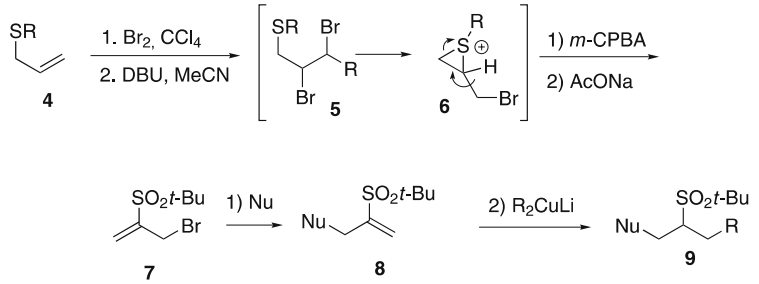
2.1
1,2-Sulfur Migration/Elimination

2.1.1
Synthesis of Allyl Thiols

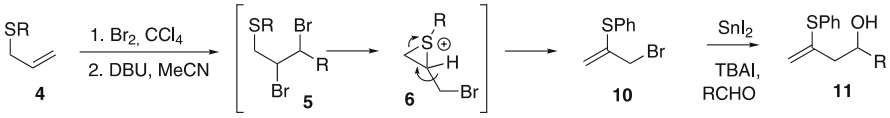
The synthesis of allyl thioethers **3** proceeding through a thiiranium intermediate **2** with 1,2-thio migration (Scheme 7) was reviewed by Warren in 2002 [1, 2] and in 1999 [3], and thus will not be discussed in this section. However, the formation of allyl thioethers **3** as side products in the synthesis of thio-substituted heterocycles will be discussed in Sect. 2.2.1.



Scheme 7 Sulfur migration followed by elimination: allyl thioethers



Scheme 8 Sulfur migration followed by elimination: vinyl thioethers



Scheme 9 1,2-Thio migration in allyl thioethers

Allyl thioethers **4** have been used as precursors to vinyl thioethers **7**. The transformation involves dibromination followed by base-assisted elimination of hydrobromic acid. Knochel and Normant first introduced this type of approach to the versatile synthon, vinyl sulfone **7**, in 1985 (Scheme 8) [9]. The intermediate dibromothiopropane **5** was oxidized prior to elimination of hydrobromic acid, furnishing vinyl sulfone **7**. The latter was shown to undergo nucleophilic substitution to produce monosubstituted vinyl sulfone **8** or substitution followed by addition of another nucleophile, leading to or disubstituted derivative **9**.

More recently, vinyl thioether **10** was used in allylation of aldehydes, serving as a more reactive allylating agent than 2-alkyl allyl bromide (Scheme 9) [10].

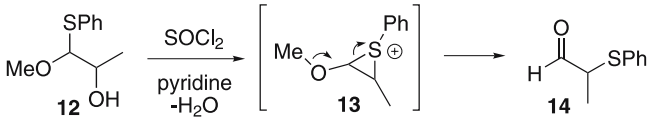
2.1.2
1,2-Sulfur Migration of Thioacetals

Analogously to thioethers **1**, which undergo rearrangement and elimination to form allyl thioethers **3** (Scheme 10), mixed thioacetals **12** also undergo 1,2-thio migration/elimination reactions. In de Groot rearrangement, dealky-

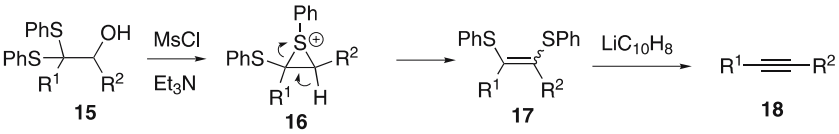
lation of the alkoxy substituent of thiiranium intermediate **13** results in the formation of α-thioaldehyde **14** (Scheme 10) [11, 12]. The requisite α-hydroxy thioacetals **12**, in turn, are routinely available by addition of di(phenylthio)- or methoxy(phenylthio) methyllithium to a carbonyl compound.

In contrast to mixed thioacetals **12**, dithioacetals **15** do not produce the analogous α-thio-thiones; they undergo migration with elimination of an α-proton to produce 1,2-dithioolefin **17** instead. Otera showed that the latter can be reduced with lithium naphthalide to give unsymmetrically substituted alkynes **18** (Scheme 11) [13].

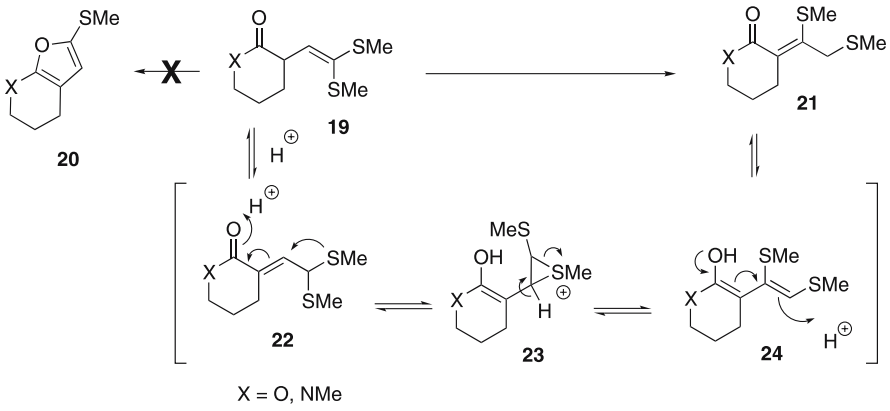
A similar transformation as a side process was reported by Padwa during attempts to cyclize nonconjugated dithioketene acetal **19** to furan derivative **20** under acidic conditions [14, 15]. Formation of the target fused furan **20** was not observed; the thio-migrated enone **21** was formed as the sole reaction product instead (Scheme 12).



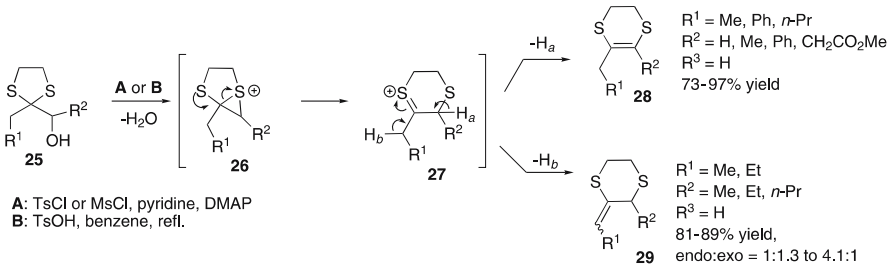
Scheme 10 de Groot rearrangement



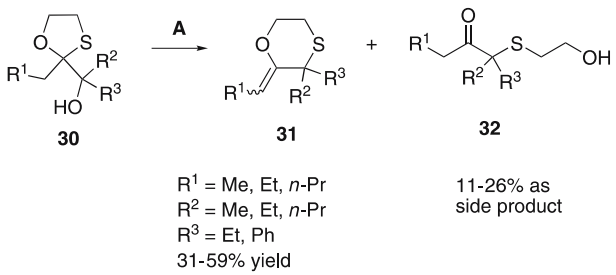
Scheme 11 Employment of sulfur migration for the synthesis of alkynes



Scheme 12 Acid-catalyzed rearrangement of nonconjugated enone to conjugated enone with 1,2-sulfur migration



Scheme 13 Dithioacetal ring expansion through a bicyclic thiiranium intermediate



Scheme 14 Oxathioacetal ring expansion with partial hydrolysis of oxathiane

Afonso and Maycock applied the thio-migration/elimination approach to cyclic dithioacetals **25**, leading to ring-expanded 2,3-dihydro-1,4-dithiines **28** and exomethylene 1,4-dithianes **29** (Scheme 13) [16, 17]. Endocyclic 2,3-dihydro-1,4-dithiines **28** were formed selectively in good yield when elimination of H_b was not possible. However, when elimination was possible from both sides, mixtures of products **28** and **29** were observed. Nevertheless, exomethylene 1,4-dithiane **29** can be converted into the more thermodynamically preferred 2,3-dihydro-1,4-dithiine **28** by treatment with a Brönsted acid catalyst (Scheme 13) [17].

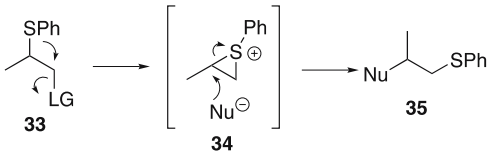
Oxathioacetals **30** also participate in analogous ring expansion; however, oxathianes **31** are more labile than the dithiane counterparts, and partially hydrolyze under reaction conditions to ketones **32** in notable amounts (Scheme 14).

2.2
1,2-Sulfur Migration with Substitution at a Thiiranium Intermediate

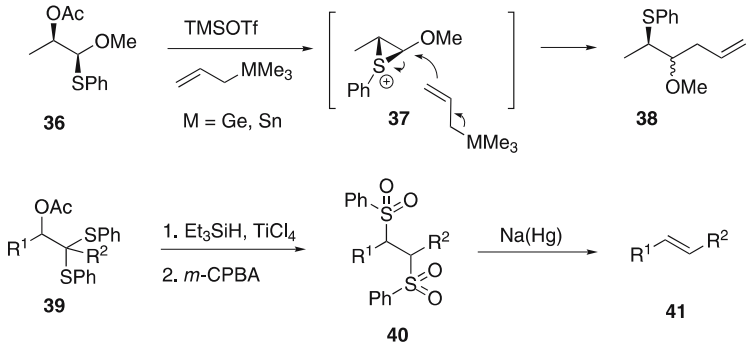
The intramolecular displacement of a neighboring leaving group by sulfur in **33** leads to formation of the reactive thiiranium species **34**, which is a useful intermediate for a variety of transformations. Besides undergoing elimination as mentioned above, this intermediate can be opened with a nucleophile to

form a rearranged substitution product **35** (Scheme 15). Nucleophilic attack takes place at the more substituted side of the thiiranium intermediate, presumably through a loose S_N2 reaction, unless other factors (directing groups, cation-stabilizing groups) influence substitution at the less hindered side.

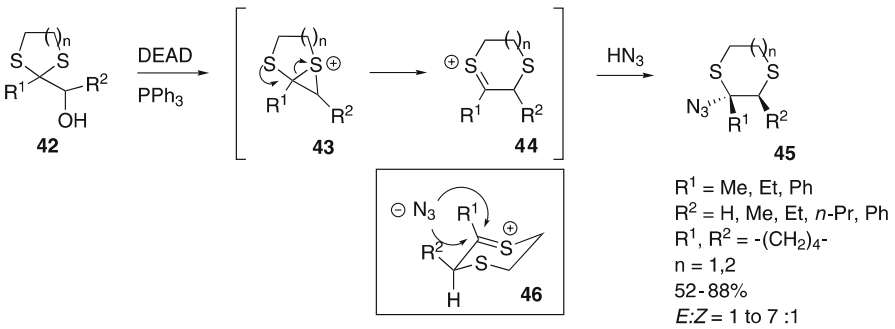
The sulfur migration/nucleophilic substitution approach was used by Otera in the Lewis acid-mediated allylation of α-acetoxy thioacetals **36** (Scheme 16) [18]. He also demonstrated that α-acetoxy dithioacetals **39** undergo 1,2-thio migration with hydride opening the thiiranium intermediate.



Scheme 15 Substitution at the thiiranium intermediate



Scheme 16 Lewis acid-assisted sulfur migration/allylation and migration/oxidation/reduction protocols



Scheme 17 Tandem ring expansion and azidation

The latter, upon oxidation and subsequent reduction, gave access to olefins **41** (Scheme 16) [13].

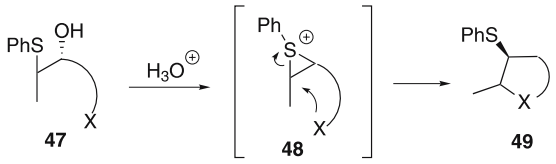
Afonso and Maycock developed a tandem dithioacetal ring expansion-azidation to produce 1,4-dithianes **45** (Scheme 17) [19]. When enantiopure dithioacetals **42** were used, enantiopure products were obtained, supporting the intermediacy of thiiranium species **43**. The *cis* product was favored in most cases, presumably due to azide attack from the less hindered side of cyclic thionium species **44** (**46**, Scheme 17). However, it should be mentioned that almost no diastereoselectivity was observed when R^2 was phenyl or CH_2CO_2Et (*cis* : *trans* ranged from about 1 : 1 to 2 : 1).

2.2.1
Addition of Tethered Nucleophiles to Thiiranium Intermediates

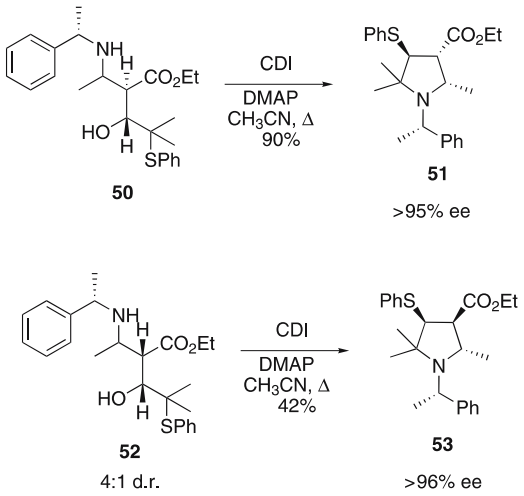
The vast majority of work published on the topic of 1,2-sulfur migration in **47** followed by intramolecular nucleophilic trapping on a thiiranium intermediate **48** en route to stereodefined heterocycles **49** was by Warren (Scheme 18); he reviewed most of this work in 2002 [1, 2] and in 1999 [3]. Accordingly, only new developments since the latest review will be discussed herein.

Reactions of α-hydroxy thioethers which bear tethered nucleophiles have been previously shown to undergo stereoselective 1,2-thio migration upon ring closure [1–3]. In 2002, Warren disclosed a rapid and high-yielding route toward highly functionalized, enantiomerically pure pyrrolidines **51** and **53** (Scheme 19) [20].

One new direction in the synthesis of heterocycles involves the recently discovered transformations of cyclic carbamates. While searching for milder conditions for the 1,2-thio migration/amine cyclization cascade, which would be compatible with a wider range of functional groups than existing methods [1–3], Warren found that carbamates undergo the reaction using silica gel as the catalyst. The reaction can proceed in three possible directions: decarboxylative ring closure to form cyclic amines; ring closure of the tethered carbamate to form cyclic carbamates; or elimination to form allyl thioethers. The course of the reaction is governed by the substitution pattern of the precursor and the size of the incipient heterocycle. Thus, when oxazinone **54** is heated with silica gel in chloroform, two thio-migrated products are formed, the spirocyclic pyrrolidine **56** (resulting from



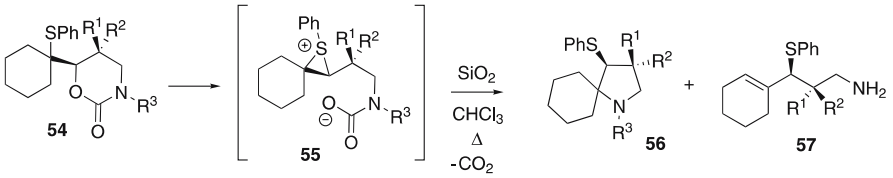
Scheme 18 Synthesis of thio-substituted heterocycles



Scheme 19 Synthesis of stereodefined pyrrolidine derivatives

intramolecular nucleophilic attack of nitrogen on the thiiranium intermediate), and the allyl thioether **57** (resulting from competing elimination of a proton, Table 1) [21, 22]. Geminally disubstituted oxazinone **54** (Table 1, Entry 2) favors formation of pyrrolidine **56** due to the Thorpe–Ingold effect. However, this tendency is overruled by the steric effect of the nitrogen substituent. As *N*-substituent R^3 increases in size, from methyl to benzyl to

Table 1 Decarboxylative pyrrolidine cyclization vs. elimination



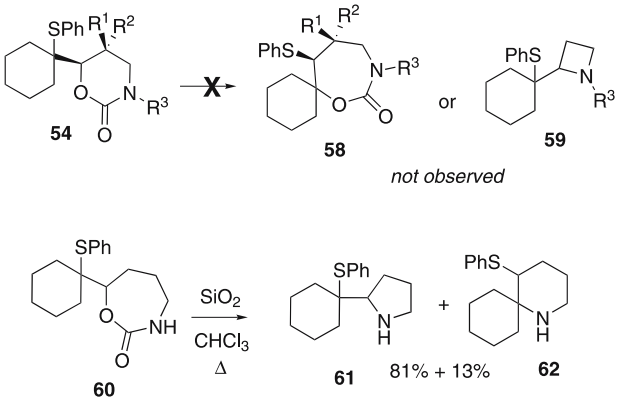
Entry	R^1	R^2	R^3	**56** : **57** (%) [a]
1	CH_3	H	H	62 : 11
2	CH_3	CH_3	H	> 95 : < 5
3	CH_3	CH_3	CH_3	77 : 14
4	CH_3	CH_3	Bn	54 : 30
5	CH_3	CH_3	*i*-Pr	1 : 88
6	H	H	H	96 : 0 [b]

[a] NMR yield. [b] Isolated yield.

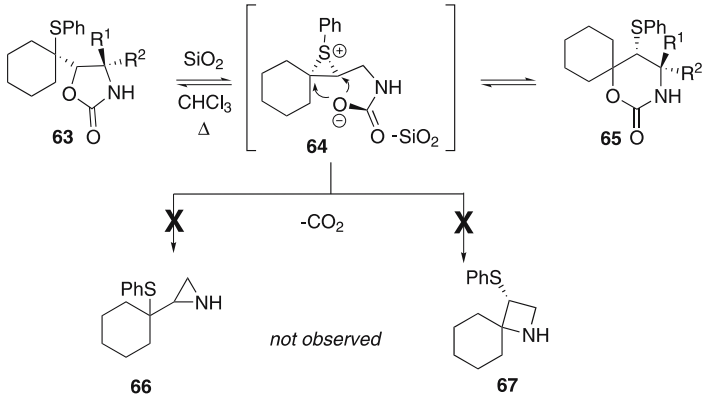
iso-propyl, formation of allyl thioether **56** becomes increasingly more favorable (Entries 2–5).

Formation of cyclic amine derivatives was reasonably explained in terms of Baldwin's rules. Oxazinone **54** did not isomerize into oxazepinone **58**, nor into decarboxylated azetidine **59** (Scheme 20). Furthermore, when unsubstituted oxazepinone **60** is heated with silica gel in chloroform, the nonmigrated pyrrolidine **61** was favored over fused piperidine **62** (Scheme 20) [21, 22].

In the case of oxazolidinone **63**, decarboxylative ring closure would lead to formation of highly strained aziridines **66** or azetidines **67** (Scheme 21) [23]. In this case, decarboxylation did not occur. In accord with Baldwin's rules, ring closure to form the more favorable 5- and 6-membered oxazolidinone **63** and oxazinone **64** occurred, in which the carboxylate acted as the tethered nucleophile (Scheme 21) [23]. The silica gel-mediated equilibration of oxa-



Scheme 20 Limits of ring size in decarboxylative cyclization



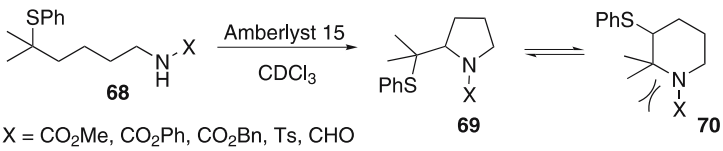
Scheme 21 Nondecarboxylative ring closure

zolidinone **63** and oxazinone **65** is governed by steric effects. For example, spirocyclic product **65** is favored over **63**, which is destabilized by *cis* methyl and (phenylthio)cyclohexyl groups at positions 4 and 5. However, when the groups are placed in a less-crowded *trans* relationship, the *trans*-substituted oxazolidinone **63** predominates.

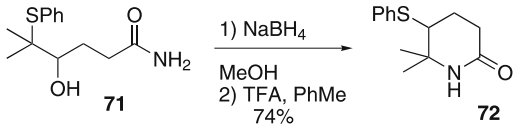
Alternatively, using more robust acyclic carbamates **68** allows for equilibration between cyclized *N*-acyl pyrrolidine and piperidine derivatives **69** and **70**, since they do not undergo decarboxylation, and thus, do not irreversibly form mixtures of cyclic amines. Indeed, it was shown that, in all cases except for the formamide, the carbamates and tosylamide **68**, under prolonged treatment with Amberlyst 15 in chloroform-*d*, slowly equilibrated from mixtures of **69** and **70** to exclusive formation of nonmigrated pyrrolidine **69** (Scheme 22) [24].

However, the 6-membered lactam **72** is obtained as the sole reaction product from amide **71** (Scheme 23). It was hypothesized that "additional restriction of the torsional angles of amide" **71** prohibit formation of the pyrrolidinone [24].

The cyclization of different triols has also been studied by Warren [25]. It was found that triols **73a–f** (Table 2, Entries 1–6), which can potentially undergo cyclization to form either tetrahydrofuran **74** or tetrahydropyran **75** derivatives, invariably formed the less-substituted tetrahydrofurans **74a–f** in generally high yields (Entries 1–6, Method **A**) [25]. Since 1,2-sulfur migration proceeds stereospecifically, the stereochemical information was relayed to the products. In contrast, attempts to synthesize tetrahydropyrans **75**, by sequentially acylating the middle hydroxyl group and then heating with tosic acid (conditions **B**), led to different products, depending on the stereochemical relationship of the three hydroxyl groups. In Entries 1, 2, and 3, the tetrahydropyran products **75a–c** predominate. However, the tetrahydropyran **75d**, the expected cyclization product of triol **73d**, was disfavored, due

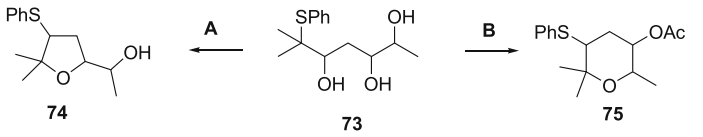


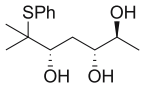
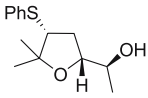
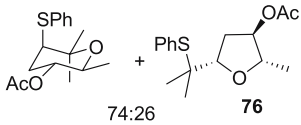
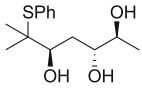
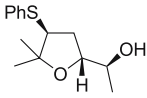
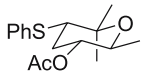
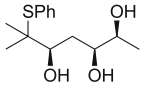
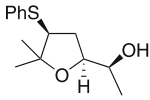
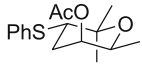
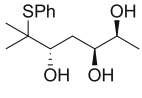
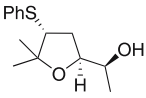
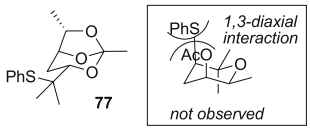
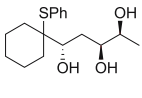
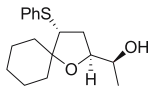
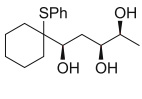
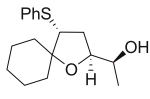
Scheme 22 Equilibration of pyrrolidine and piperidine derivatives



Scheme 23 Cyclization of amides

Table 2 1,2-Sulfur migration/cyclization of different triols

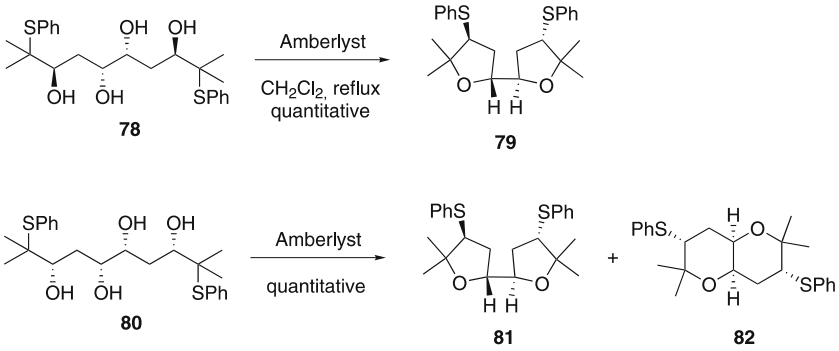


Entry	Triol **73**	Method **A** **74**	Yield %	Method **B** **75**	Yield %
1	 (a)		89	 74:26 **76**	83
2	 (b)		75		88
3	 (c)		93		85
4	 (d)		96	 **77**	96
5	 (e)		93		
6	 (f)		81		

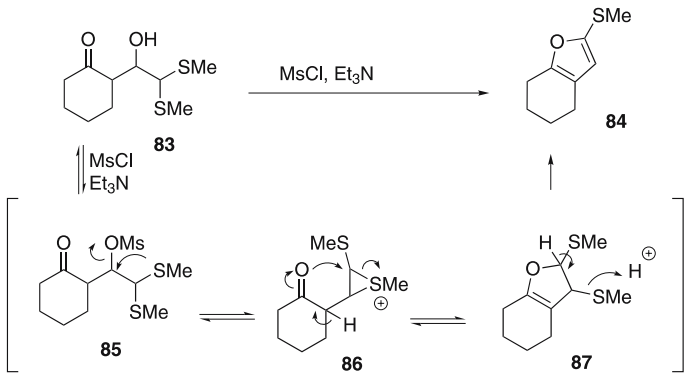
A: TsOH, CH_2Cl_2, 40 °C. **B**: (a) $(MeO)_3CMe$, PPTS, CH_2Cl_2; (b) TsOH, CH_2Cl_2, 40 °C

to 1,3-diaxial interactions; bicyclic orthoacetate **77** was obtained as the sole product instead.

Warren also investigated double-fold cyclization [26]. When *anti, syn, anti* tetrol **78** was subjected to cyclization conditions, tetrahydrofuran dimer



Scheme 24 Double-fold sulfur migration/cyclization



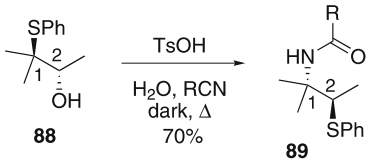
Scheme 25 Sequential sulfur migration/elimination in synthesis of 2-thiofuran

79 was smoothly formed (Scheme 24). However, *syn, syn, syn* tetrol **80** yielded mixtures of tetrahydrofuran dimer **81** and fused bitetrahydropyran **82** (Scheme 24).

Additionally, an example of 1,2-thio-migration/cyclization in dithioacetals was reported by Padwa [15]. In this case, α-hydroxydithioacetal **83** underwent reaction to form 1,2-dithiodihydrofuran **87**, which gave fused thiofuran **84** upon elimination of methanethiol (Scheme 25).

2.2.2 The Ritter Reaction with 1,2-Sulfur Migration

Warren briefly investigated the possibility of incorporating 1,2-thio migration in **88** into the Ritter reaction as a route toward stereodefined amines or amides **89** (Scheme 26) [27]. It should be mentioned that Toshimitsu also reported an analogous reaction on thiiranium species, which were formed by adding phenylthiolate to epoxides [28, 29].



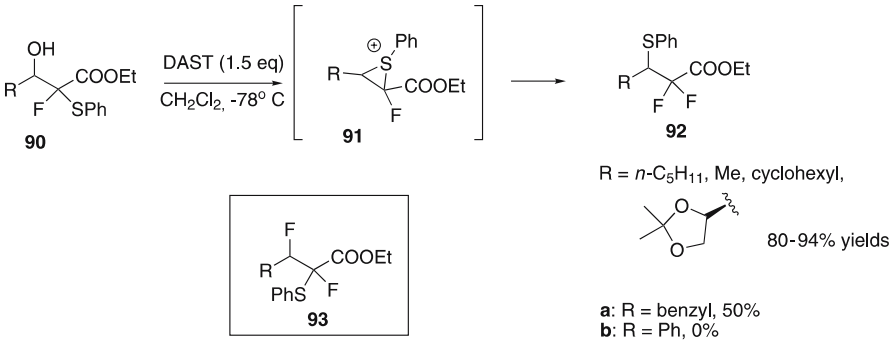
Scheme 26 The Ritter reaction with 1,2-sulfur migration

2.2.3 1,2-Sulfur Migration/Perfluorination

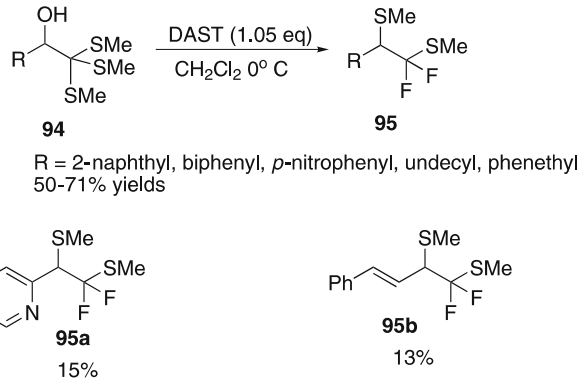
Fluorinated compounds are abundant members among valuable biologically active molecules. Accordingly, intensive attempts from the synthetic community resulted in a number of methods for the synthesis of fluorinated compounds. Among them is the development of a method for polyfluorination of an alkyl chain with concomitant 1,2-thio migration. Several reports on this type of chemistry have appeared in recent years.

Ducep reported that treatment of hydroxythioethers **90** with DAST led to formation of geminally fluorinated, thio-migrated esters **92** (Scheme 27) [30]. The reaction is mild and generally high-yielding. However, homobenzylic alcohol **90a** gives a markedly decreased yield of product **92a**, and benzylic alcohol **90b** undergoes fluorination at the benzylic position under the reaction conditions, producing vicinal difluoride **93** instead (Scheme 27) [30]. In these cases, either direct fluorination occurs to the free benzylic cation, or opening of the thiiranium intermediate **91b** is more facile from the benzylic side, leading to alternative product **93**.

An analogous transformation in tri(methylthio)orthoester **94** was reported by Kuroboshi (Scheme 28) [31, 32]. In agreement with Ducep's findings [30], pyridyl and cinnamyl alcohols **95a**,**b** gave low yields of the desired products (Scheme 28).



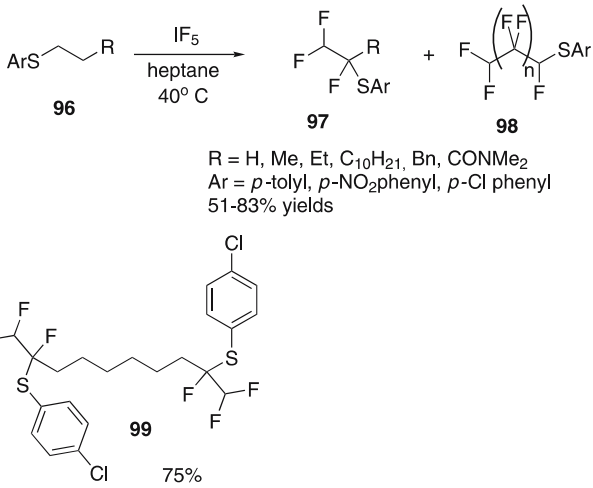
Scheme 27 Sulfur migration with monofluorination



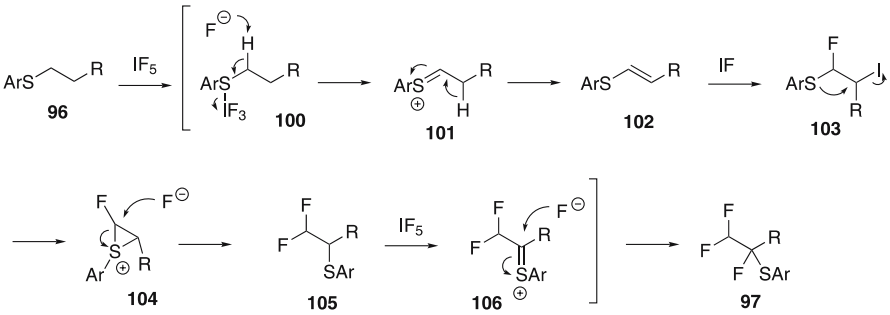
Scheme 28 Difluorination/sulfur migration of methylthio orthoester

An unusual variation of 1,2-thio migration/fluorination in alkyl thioethers was reported by Hara. 1,2-Thio migration is induced by heating the substrates **96** with hypervalent iodonium pentafluoride to give polyfluorinated thioethers **97** and **98** as products (Scheme 29) [33, 34]. Hara even demonstrated the 1,2-thio migration/fluorination of a tethered disulfide, leading to hexafluorinated product **99**. Moreover, this is an especially efficient method of perfluorinating alkyl aryl thioethers: fluorination can proceed through the entire length of the alkyl chain [34].

This reaction is quite unusual, because a vicinal hetero leaving group is not required. A plausible mechanism is depicted in Scheme 30 [33]. Sulfur is activated by the iodonium ion, and fluoride deprotonates α to sulfur,



Scheme 29 Polyfluorination of thioether



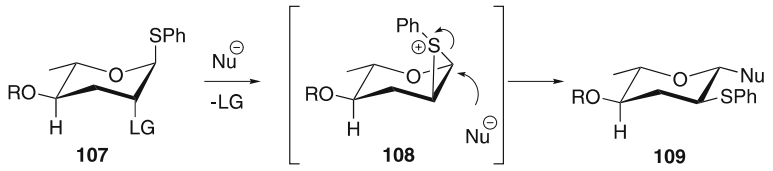
Scheme 30 Mechanism of IF_5 trifluorination of thioethers

forming thionium species **101**. The latter rearranges to vinyl thioether **102**; subsequent iodofluorination of which results in **103**. Intramolecular displacement of iodide by sulfur furnishes the requisite thiiranium species **104**, which undergoes a second fluoride addition to form difluoride **105**. A second activation of sulfur/deprotonation takes place to form thionium species **106**, which is quenched by addition of the third fluoride to produce trifluoride **97** as the reaction product. The mechanistic pathway is supported by observation of reaction intermediate **105** at the early stages of the reaction [33]. The process iteratively continues until sulfur reaches the end of the chain, producing polyfluoroalkylthioether **98** (Scheme 30) [34].

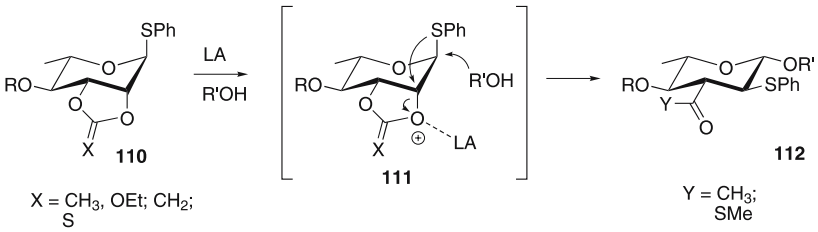
2.2.4
1,2-Sulfur Migration in Carbohydrates

Thiosaccharides are extremely valuable and versatile synthons, as a wide range of substitution is possible from carbohydrates containing the anomeric sulfur group. Indeed, 1,2-thio migration in sugars **107**, proceeding through a thiiranium intermediate **108** toward **109**, is a well-established process (Scheme 31). The subject of thiiranium intermediates in carbohydrate chemistry, including transformations through 1,2-thio migration, was recently reviewed by Smoliakova in 2000 [4]; thus, new developments since 2000 will be discussed below.

One important consideration concerning thio migration in carbohydrates is the choice of leaving group at position 2. Yu has addressed this issue



Scheme 31 General scheme of sulfur migration with substitution at the anomeric center



Scheme 32 Yu's Lewis acid-assisted domino migration

by developing an elegant strategy involving a domino cleavage-migration-substitution of 1-thio-2,3-acetal saccharides **110** toward **112** (Scheme 32) [35–38]. The product would have three different substituents with set stereochemistry at three different centers from one reaction. The main challenge to this approach was to find an appropriate acetal protecting/leaving group. The transformation is triggered by a Lewis acid, which cleaves the acetal linkage at position 3, inducing formation of a thiiranium ring between positions 1 and 2. The latter is quenched by an alcohol (glycoside acceptor). Initial work employing orthoacetates **110a–d** met with limited success, due to ethanol, a byproduct of the reaction, competing with the nucleophile (Table 3, Entries 1–4) [35, 36, 38]. One solution to this problem was to employ ketene acetal **110e**, which, upon addition of the nucleophile in the presence of TMS-OTf, would release the ketene hemiacetal, a tautomer of the acetoxy group, as a leaving group. Accordingly, cholesterol glycoside **112e** was obtained in 78% yield (Entry 6). However, this approach is not very convenient, as preparation of the ketene acetal **110e** takes five steps, and the intermediates are unstable. Thus, the best group was found to be the 1,2-*O*-thionocarbonate group (**110f**, Entry 6). It is available in only one step from the 1,2-diol by treatment with 1,1′-thiocarbonyldiimidazole. Selective methylation of the thionocarbonyl moiety, rather than the anomeric phenylthio group, triggers elimination to form the thiiranium intermediate, which is quenched by addition of different glycoside acceptors in good to high yields (**112f**, Entry 6) [37]. Additionally, the resulting 2-*O*-methylthiocarbonyl group is readily cleaved in high yield by treatment with sodium methoxide in methanol in 93% yield. However, it should be mentioned that etherified substrates are compatible with the reaction conditions but acylated carbohydrates were reported to give complex mixtures only [36]. Nevertheless, Yu employed this methodology for the synthesis of the hexasaccharide fragment of the antitumor and DNA-inhibitory Landomycin A [39].

Fluorinated carbohydrates and their derivatives are important from a biological standpoint. In 1986, Nicolaou reported stereocontrolled DAST-induced fluorination of 2-hydroxyl-1-thiophenyl carbohydrates with 1,2-thio migration [40]. He recently applied this methodology for the total synthesis of apoptolidin [41] and everninomycin 13,384-1 [42]. Likewise, Bertozzi

Table 3 Summary of sulfur migration in carbohydrates

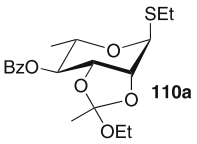
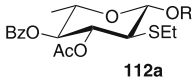
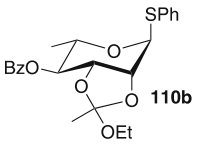
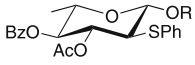
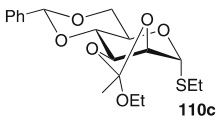
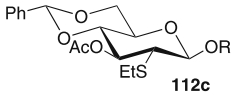
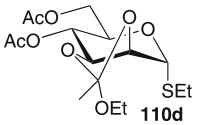
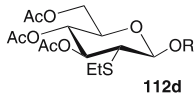
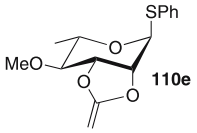
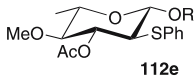
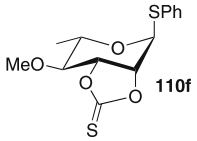
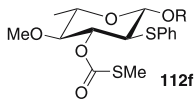
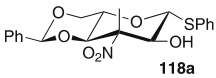
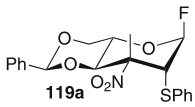
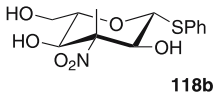
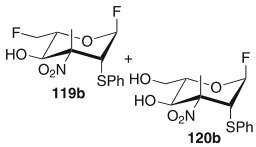
Entry	Starting material	Nu	Conditions	Product	Yield %	Refs.
1	 **110a**	1°, 2° ROH	TMSOTf (15%) CH_2Cl_2 4A MS, 0 °C	 **112a**	39–68	[36]
2	 **110b**	1°, 2° ROH		 **112b**	43–53	[35] [36]
3	 **110c**	2° ROH		 **112c**	40–70	[35] [36]
4	 **110d**	1°, 2° ROH		 **112d**	40–87	[35] [36]
5	 **110e**	cholesterol	TMSOTf (0.2 equiv), CH_2Cl_2, 4A MS, rt	 **112e**	76	[38]
6	 **110f**	1°, 2° ROH	MEOTf CH_2Cl_2, 4A MS, rt	 **112f**	64–90	[37]
7	 **118a**	$F^{\ominus}$	DAST (5 equiv), CH_2Cl_2, 0 °C	 **119a**	85	[44] [45]
8	 **118b**			 **119b** + **120b**	58 + 15	[44] [45]

Table 3 (continued)

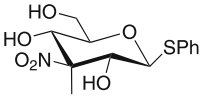
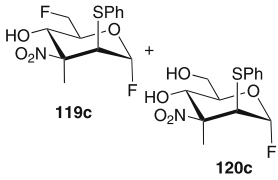
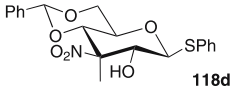
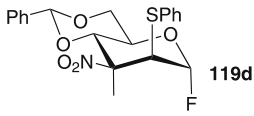
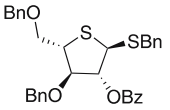
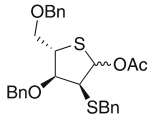
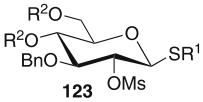
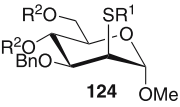
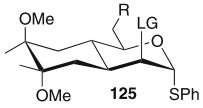
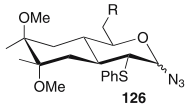
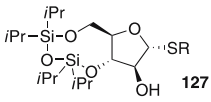
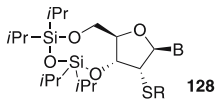
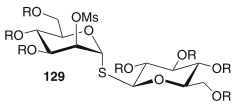
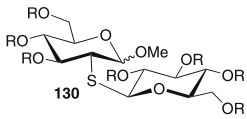
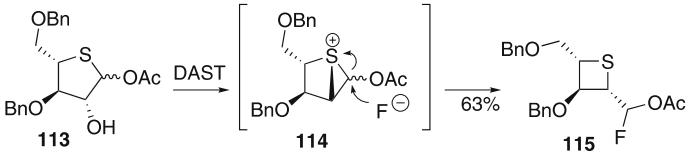
Entry	Starting material	Nu	Conditions	Product	Yield %	Refs.
9	 **118c**			 **119c** + **120c**	60 + 10	[44] [45]
10	 **118d**			 **119d**	80	[44] [45]
11	 α:β = 10:1 **121**	DAST (followed by F to OAc exchange)		 **122**	38	[46]
	 **123**	$MeO^{\ominus}$	NaOMe (5 equiv), MeOH, reflux	 **124**		[47]
	R^1	**R^2**				
12	PMB	Bn			90	
13	2′-Me-naphth	Bn			91	
14	Trityl				93	
	 **125**	$N_3^{\ominus}$	NaN_3, DMF, 130 °C	 **126**		[48]
	R	**LG**		***α* : *β***		
15	OTIPS	OTs		1 : 2.5	64	
16	OH	OTs		1 : 2	46	
17	N_3	OMs		2.5 : 1	76	
18	N_3	OTs		1.2 : 1	62	

Table 3 (continued)

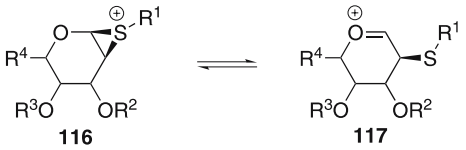
Entry	Starting material	Nu	Conditions	Product	Yield %	Refs.
	 **127**		PPh_3 (1.5 equiv), DEAD (1.5 equiv), DMF	 **128**		[49]
	R			***α* : *β***		
19	Ph	N^3-BzThy		1 : 10	71	
20	*t*-Bu	N^3-BzThy		0 : 1	52	
21	*t*-Bu	6-Cl-purine		1 : 12	50	
	 **129**			 **130**		[49]
	R			**R** ***α* : *β***		
22	Bn		MeOH buffer, reflux	Bn 1 : 3	100	
23	Bz		NaOMe, MeOH, reflux	Ac 2 : 3	88	

employed this methodology in the synthesis of a biantennary N-linked glycoform of CD52 [43]. One attractive feature of this approach is that the 2-hydroxyl group does not have to be converted into a better leaving group. This methodology continues to find application in synthesis. It was used recently by Cabrera-Escribano for the synthesis of fluorinated sugars **119a–d** as precursors to β-amino acid derivatives [44, 45] (Table 3, Entries 7–10). When completely unprotected carbohydrates **118b,c** are used in the reaction, difluorinated carbohydrates **119b,c** are obtained as major products, from additional fluoride attack at the primary hydroxyl group (Entries 8, 9). Likewise, Jeong used this transformation in the synthesis of L-SFMAU [(–)-(L)-β-1,3-oxathiolanylcytosine], a potential hepatitis B therapeutic (step shown in Entry 11) [46]. It was also unexpectedly found that thiofuranose **113** also undergoes rearrangement through an endocyclic thiiranium intermediate **114**, leading to the strained thietane **115** as a major product (Scheme 33) [46].

Other recent examples which involve thiiranium intermediates in carbohydrate chemistry involve addition of different nucleophiles and development of different reaction conditions. As an alternative to Lewis acid-induced substitution/thio migration methodologies, Liptak developed basic conditions for



Scheme 33 Ring contraction with sulfur migration



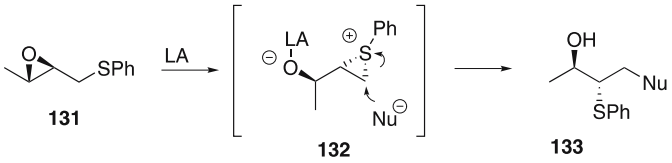
Scheme 34 Tautomeric forms thiiranium ion vs. oxacarbenium ion

thio migration/methoxylation of **123**; the products **124** can then be oxidized into the corresponding sulfonic acids (Table 3, Entries 12–14) [47].

The examples discussed above involve stereospecific transformations of 1-thio carbohydrates. However, stereospecific migrative substitutions of 1-thio carbohydrates still remain a challenge, because the intermediate thiiranium ion **116** is also a thioacetal, and can exist in equilibrium with the tautomeric oxonium ion **117** (Scheme 34). Thus, some difficulty with maintaining stereocontrol has often been encountered. For example, Maiareanu reported azidation of thiiranium species of **125**, which retains the relative configuration at the thio group but not at the anomeric carbon, giving mixtures of α and β isomers **126** (Table 3, Entries 15–18) [48]. Another approach was used by Castillon, who employed Mitsunobu conditions to effect 1,2-thio migration and addition of nucleoside bases to the anomeric center of **127** (Table 3, Entries 19–21) [49]. Conditions were carefully developed to maximize stereocontrol; it was found that using DMF as the solvent allowed for the most stereoselective reaction, and the electron-rich *tert*-butylthio group was superior to phenylthio- or phenylseleno groups (Entries 20, 21). However, not all cases are amenable. For example, Pinto reported only modest selectivities ($\alpha : \beta = 1 : 3$, 2 : 3, Entries 22, 23) while attempting to rearrange 1,1′-thio-linked glucopyranosyl α-D-mannopyranosides **129** into 1,2′-thio linked sophoroside derivatives **130** using methoxide as the nucleophile, due to addition of methoxide to the oxacarbenium tautomer rather than the thiiranium tautomer [50].

2.2.5 Thia-Payne Rearrangement

Thia-Payne rearrangement is the Lewis acid-assisted epoxide ring opening of **131**, which allows for stereospecific formation of a thiiranium interme-

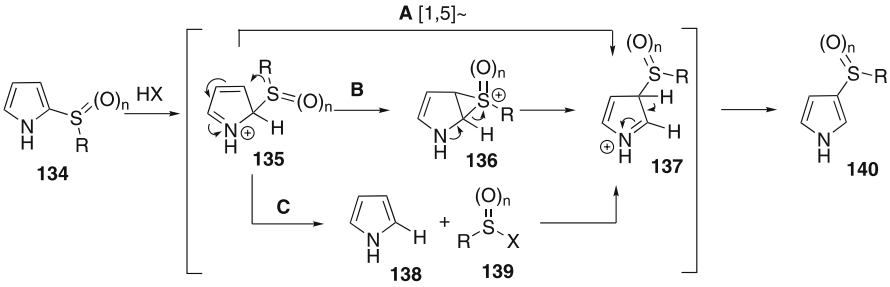


Scheme 35 Thia-Payne rearrangement

diate **132** (Scheme 35). Nucleophilic attack may take place at either side of the thiiranium species; when it occurs at the side opposite to the Lewis acid-coordinated oxygen, as shown in **132**, it allows for migration of the thio group, leading to an *anti* vicinal hydroxyl thioether **133** (Scheme 35). No new examples of Thia-Payne rearrangement with 1,2-thio migration have been reported since reviews by Rayner in 1997 [5] and Hanson in 2002 [6], and will therefore not be discussed in this section.

2.2.6 Sulfur Migration in Heterocycles

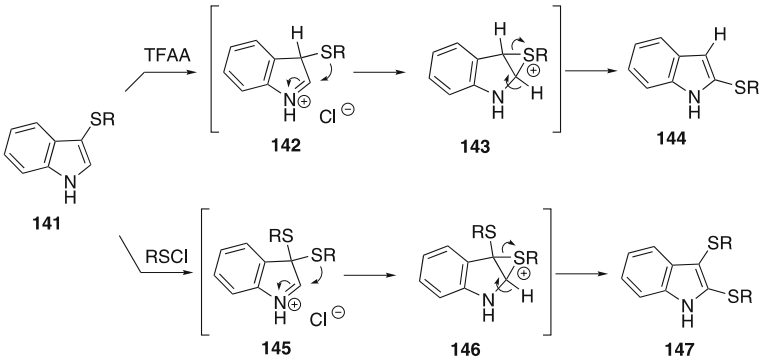
1,2-Thio group migration has been reported in heterocycles. Early examples were disclosed by Greenhouse, which involve the acid-catalyzed 1,2-migration of sulfides, sulfoxides, and sulfones in pyrroles **134** leading to their regioisomers **140** (Scheme 36) [51, 52]. These examples have been reviewed by Braverman [7, 8], and thus will be only briefly discussed herein. Functionalizing pyrroles at the β positions is difficult if the more reactive α positions are unsubstituted. Gratifyingly, the acid-catalyzed 2- to 3-thio migration in pyrroles serves as a solution to this problem. Possible mechanisms for this thio migration, depicted in Scheme 36, include either: a [1,5]~thio group shift (path **A**); an intramolecular nucleophilic attack by sulfur to the protonated 2*H*-pyrrole **135** resulting in an intermediate thiiranium species **136**, which ultimately rearranges into 3-thiopyrrole **140** (path **B**); or a dissociative mechanism (path **C**). Experimental evidence supports pathway **B** and partial involvement of pathway **C** [51, 52].



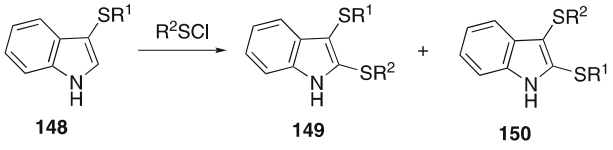
Scheme 36 Possible routes to sulfur migration in pyrroles

A similar 1,2-thio migration was reported by Ottenheijm in 1986 in the sulfenylation of indoles [53, 54]. He proposed that sulfenylation occurred at position 3, and addition of a second electrophile to position 3 is followed by a 1,2-thio migration to position 2. Analogously to Greenhouse's findings, Ottenheijm also showed that treatment of **141** with trifluoroacetic acid induces rearrangement into 2-sulfenylindole **144** (Scheme 37) [54]. More recently, Hamel undertook the mechanistic investigations of disulfenylation of indole **141**, to elucidate whether the second sulfenylation indeed takes place at position 3 and undergoes migration to position 2, or if position 2 is directly sulfenylated [55, 56]. He found that if 3-sulfenyl indole **141** was treated with a different sulfenyl chloride, 2,3-disulfenylindoles **149** or **150** bearing the more electron-rich sulfide at position 2 was the major product, regardless of whether it originally resided on the indole or was introduced during sulfenylation (Scheme 38) [55]. These results support an initial sulfenylation at position 3 followed by selective migration of the more nucleophilic thio group to an electrophilic center, position 2.

Additionally, 3,3-di(phenylthio)indole **151** undergoes rearrangement to 2,3-di(phenylthio)indole **153** upon treatment with phenylsulfenyl chloride. It



Scheme 37 Sulfur migration in dithioindole

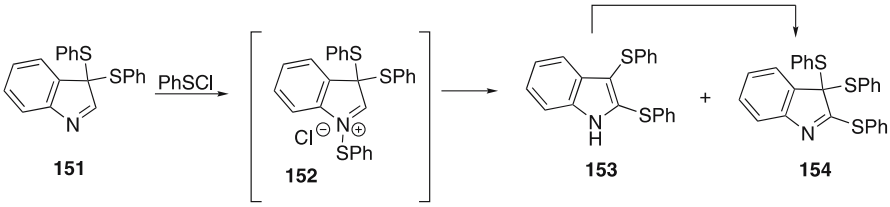


R^1	R^2	**149:150**
p-methoxyphenyl	phenyl	6:61
p-nitrophenyl	*p*-methoxyphenyl	63:0

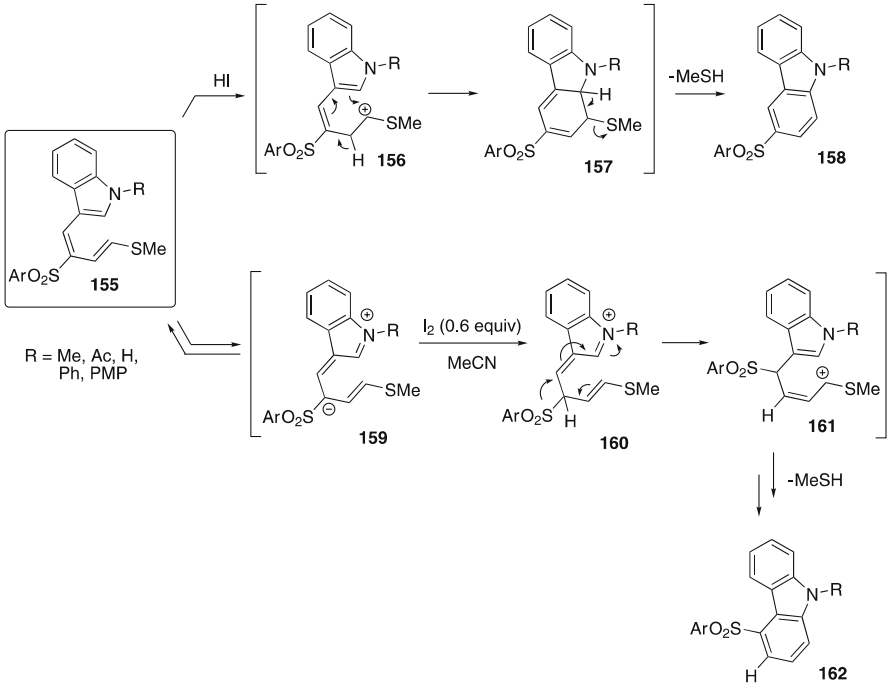
Scheme 38 Sulfenylation of indole

was found necessary to quaternize the indole nitrogen and effect 1,2-thio migration (Scheme 39). Interestingly, tris(phenylthio-3H-)indole **154** was observed in up to 19% yield as a side product. It was thought to arise from sulfenylation of 2,3-di(phenylthio)indole **134** [57]. Hamel's experiments bring support to the idea that the second sulfenylation of indole occurs at position 3 and is followed by migration of one sulfenyl group to position 2, probably through a thiiranium intermediate. However, the possibility that the rearrangement occurs intermolecularly was not disproved.

Another unusual sulfonyl migration was reported by Ogura, who demonstrated a dramatic reversal of regioselectivity of electrocyclization/elimination



Scheme 39 Further sulfenylation of 3,3-di(phenylthio)indole

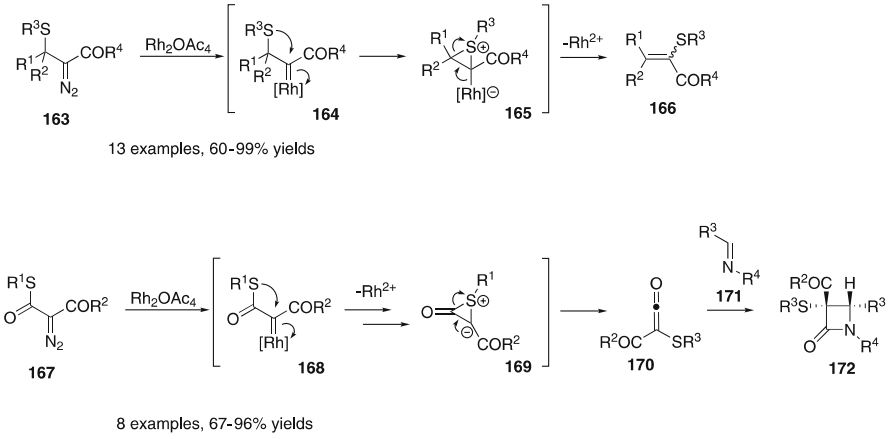


Scheme 40 Sulfone migration in indole derivatives

of indolyldiene **155** (Scheme 40) [58]. Protonation of indolyldiene **155** with hydroiodic acid β to the methylthio group leads to stabilized cationic intermediate **156**, which after ring closure produces **157**; elimination of methyl mercaptan furnishes nonmigrated product **158** (Scheme 40). In contrast, using iodine instead of hydroiodic acid follows an unexpected pathway. Presumably the reaction begins by protonation α to the sulfonyl group, followed by 1,2-sulfonyl migration to give intermediate **161** (Scheme 40). Cyclization, followed by elimination of methyl mercaptan, yields formation of alternative migrated product **162**. It is unclear at present why migrated products are obtained using iodine instead of hydroiodic acid as a reagent. Notably, indoles with more electron-rich substituents at nitrogen favor the migrative pathways (methyl and *p*-methoxyphenyl derivatives give about 15 : 85 ratios of **158** to **162**). The *N*-acetyl derivative, however, does not undergo reaction, and the *N*-phenyl derivative is comparatively less selective (about 1 : 1 ratio of products).

2.3
Sulfur Migration to a Carbenoid Center

So far it has been shown that thiiranium species can be generated when there is a leaving group at the vicinal position, or when the vicinal position is electrophilic. Wang recently reported that the thio group migration can also occur to an electron-deficient carbenoid center (Scheme 41) [59]. The transformation is analogous to 1,2-acyloxy migration to a carbenoid center [60, 61]. When thio-substituted diazo ketones and esters **163** are decomposed with dirhodium tetraacetate, the incipient metal carbenoid **164** is trapped with sulfur, leading to formation of thiiranium zwitterion **165** (Scheme 41). Elim-

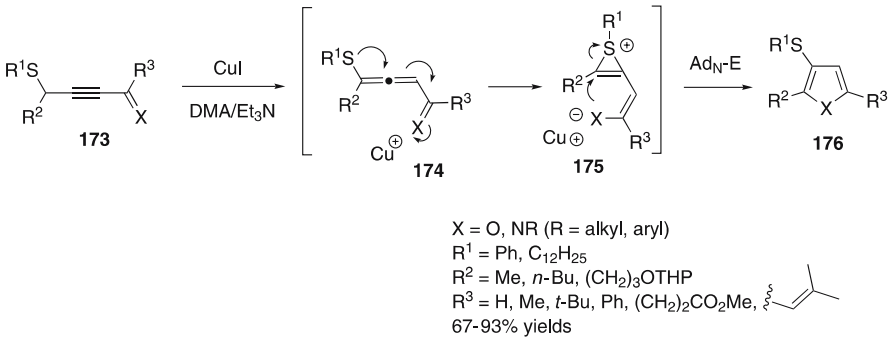


Scheme 41 1,2-Sulfur migration to carbenoid center

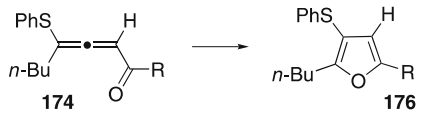
ination of rhodium leads to rearranged vinyl thioether **166** in good to high yields. Analogously, Xu showed that when diazo thioesters **167** are used, migration of sulfur to the carbenoid center in **168**, followed by elimination of rhodium, allows for formation of thiiranium ylides **169**, which collapse into thio-substituted ketenes **170** (Scheme 41) [62]. The latter were demonstrated to undergo the Staudinger reaction with various imines to give azetidinones in good to excellent yields.

2.4
1,2-Sulfur Migration Proceeding Through Thiirenium Intermediate

The majority of examples which exist on 1,2-thio migration are proposed to go through a thiiranium intermediate. However, Gevorgyan recently reported an unusual 1,2-thio migration proceeding through a *thiirenium* intermediate in the mild and efficient cycloisomerization of thio alkynyl ketones **173** into 3-thio-containing furans and pyrroles **176** (Scheme 42) [63, 64]. It was proposed that first propargylthio alkynyl ketones **173** undergo base- and copper-assisted rearrangement into thioallenyl ketones **174**. Coordination of copper to the enone moiety triggers an intramolecular Michael addition of the thio group to the allenyl *sp* carbon, producing zwitterionic thiirenium intermedi-



Scheme 42 Synthesis of heterocycles through thiirenium intermediate



R	Conditions	Yield (%)
Ph	130 °C, 2h	100
$(CH_2)_3OMOM$	CuI (5 mol %), 36h, rt	82

Scheme 43 Cycloisomerization of thioallenyl ketones into furans

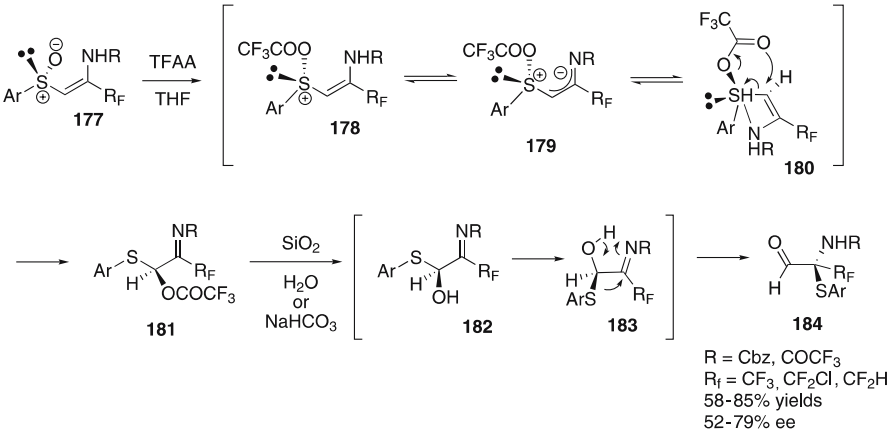
ate **175**. The latter undergoes either an intramolecular addition–elimination sequence or vinylic substitution to produce the corresponding 3-thio furans or pyrroles **176**. This approach proved to be an efficient and mild method towards functionalized 3-thio heterocycles. However, when primary propargyl sulfides are used (R^2 = H), mixtures of 2, and 3-thio heterocycles are formed, due to competing proton transfer to the allenic carbon.

Additional support for the proposed mechanism, proceeding through the allenyl intermediate, was obtained through independent synthesis of intermediate thioallenyl ketones **174a,b** and their successful cycloisomerization into their corresponding 3-thiofurans **176a,b** (Scheme 43).

3
1,2-Sulfur Shift to a Carbocation

In the previous section, thio migration proceeding through a bridged intermediate was discussed. Alternatively, thio migration has also been shown to occur through a 1,2-shift. This type of migration generally proceeds to an electron-deficient, or even cationic, center.

Zanda reported an elegant Pummerer rearrangement/1,2-thio shift cascade in his approach towards stereodefined fluoropyruvaldehyde *N*,*S*-ketals **184** (Scheme 44) [65–67]. A number of different optically active sulfinylenamines **177** undergo the reaction with moderate to good enantioselectivity and good yields. Both steps of this cascade transformation are remarkable. Zanda proposes that the stereoselective Pummerer rearrangement takes place through conformationally locked chiral azathio ylide **180** (Scheme 44) [65]. It should be mentioned that prolonged treatment with trifluoroacetic acid racemized



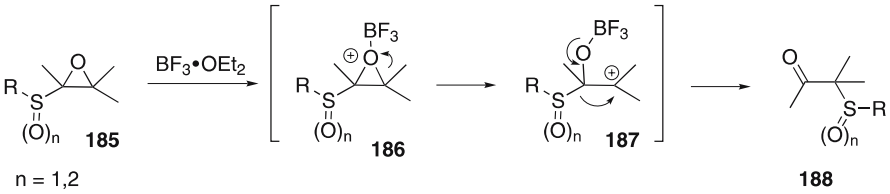
Scheme 44 Sequential Pummerer rearrangement/1,2-sulfur migration

product **181**. The second crucial step, the 1,2-thio shift, is carried out by hydrolyzing the trifluoroacetate ester. The α-hydroxy-imine to α-amino aldehyde rearrangement is initiated by hydrogen bonding between the imino nitrogen and hydroxyl proton (**183**). This locks the molecule into a five-membered transition state, and assures stereospecific thio migration [65].

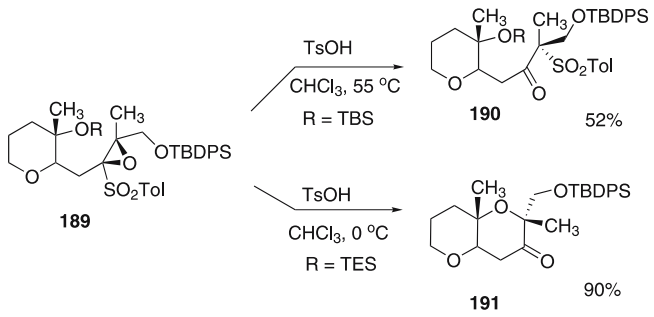
Durst's and Tavares' thermal or Lewis acid-catalyzed ring opening of epoxides **185** with concomitant 1,2-sulfonyl and sulfinyl shift to the cationic center of **187** (Scheme 45) was reviewed by Braverman, and will not be discussed in this section [7, 68, 69].

More recently, Mori employed sulfonyl oxiranes as building blocks for construction of *trans*-fused polyether structures, which are designed to undergo a tandem desilylation and alkoxide attack at the oxirane, followed by desulfonylation to give fused cyclic ethers **191** (Scheme 46) [70, 71]. When tetrasubstituted oxiranes **189** were used, rearranged product **190** was obtained unexpectedly (Scheme 46). It was found that the rearrangement could be suppressed and the desired fused diether product **191** could be obtained when the reaction was carried out at lower temperatures, although the use of a more acid-labile silyl protecting group was necessary.

Fernandez de la Pradilla and Viso investigated the use of vinyl and alkynyl epoxy sulfoxides as substrates for directed S_N2' reactions with cuprates as a route to stereodefined allylic alcohols [72]. They observed that when α-epoxide **192** was treated with MeCuCNLi, instead of the expected product,



Scheme 45 Sulfenyl and sulfonyl shift with Lewis acid-assisted epoxide opening

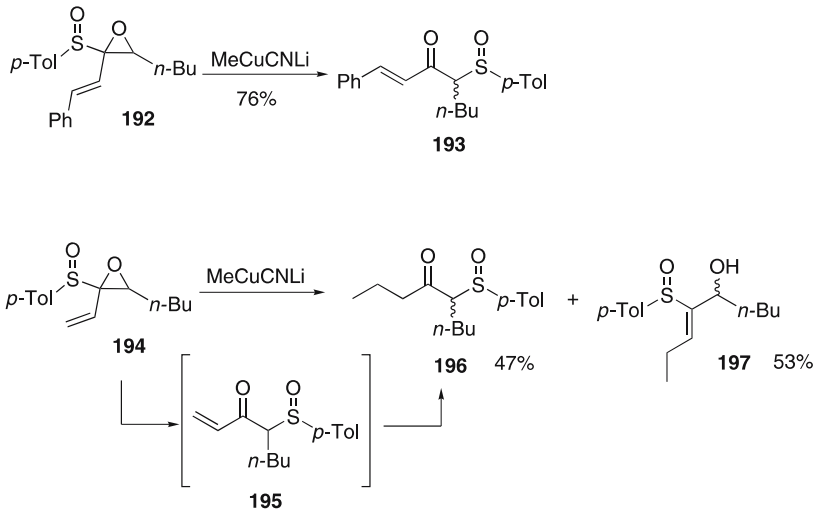


Scheme 46 Competing oxirane rearrangement and substitution

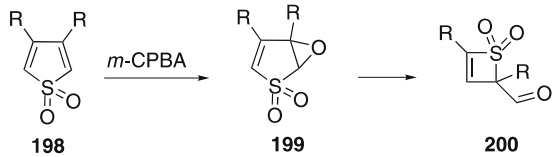
a diastereomeric mixture of enone **193** was obtained (Scheme 47). Evidently, ring opening with sulfoxide migration is more facile in this case than addition of the cuprate reagent to the hindered and deactivated olefin moiety. In the case of terminal olefin **194**, rearrangement/addition product **196** was observed along with the unrearranged allylic alcohol **197** (Scheme 47). Formation of **196** was explained by initial rearrangement of **194** to enone **195** followed by conjugate addition of the cuprate reagent.

Epoxide opening with sulfone shift is also a known process. Thus, Nakiyama reported an intramolecular 1,2-sulfonyl shift of thiophene *S*-dioxides **198** to give strained thiete dioxides **200** (Scheme 48) [73].

The acid-catalyzed sulfone migration in naphthalenes has also been documented [74–76]. The rearrangement takes place through reversible protonation of naphthalene **201** α to the sulfone (**202**, Scheme 49). A 1,2-sulfone shift followed by deprotonation affords **204** as the sole product. The relief of 1,3 allylic strain is believed to be the driving force for this rearrangement.

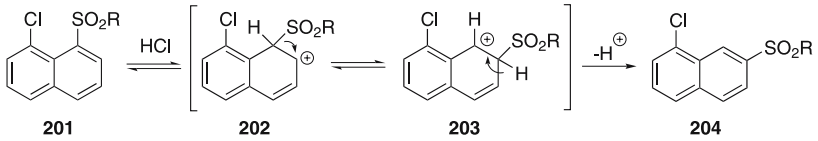


Scheme 47 Cuprate-assisted epoxide cleavage with sulfenyl migration



R = *t*-butyl, adamantyl

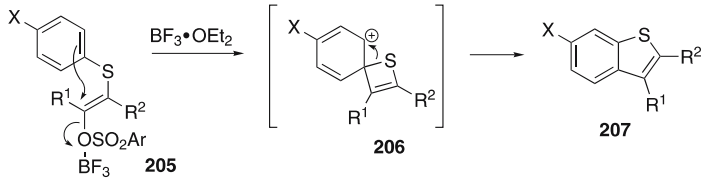
Scheme 48 Ring contraction of thiophene S-dioxide



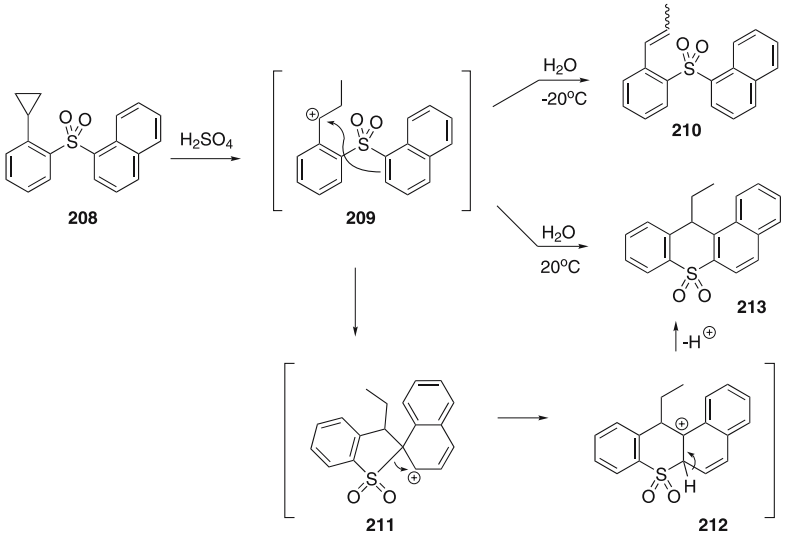
Scheme 49 Acid-catalyzed sulfonyl migration in naphthalene system

Modena investigated the cyclocondensation of aryl vinyl sulfides **205** into the corresponding benzothiophenes (Scheme 50) [77–80]. When *para*-substituted substrates **205** were used, the unexpected *meta*-substituted products **207** were obtained. They were formed by Friedel–Crafts alkenylation of the aryl ring, leading to spiro-fused thietene intermediates **206**, which undergo a 1,2-thio shift with ring expansion to afford benzothiophenes **207** (Scheme 50). The analogous transformations of aryl vinyl sulfonates was reviewed by Braverman and will not be discussed herein [7].

A similar transformation was reported by Veselovskaya in the rearrangement of sulfone **208** into **213** (Scheme 51) [81]. Protonation and ring opening



Scheme 50 Friedel–Crafts alkenylation followed by 1,2-sulfur migration

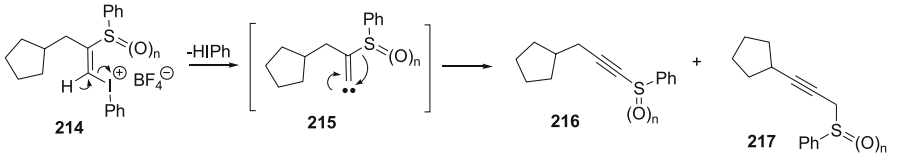


Scheme 51 Acid-catalyzed sulfonyl shift in naphthalene system

of the cyclopropyl moiety of **202** leads to benzylic cation **209**. The latter can undergo elimination at – 20 °C to form styryl sulfone **210**, or a Friedel–Crafts alkylation of the naphthalenyl moiety at 20 °C, leading to spiro cationic intermediate **211**, which undergoes a 1,2-thio shift to **212** and subsequent deprotonation to form tetracyclic sulfone **213**.

4
1,2-Sulfur Shift to a Carbene

Another type of sulfur migration involving a 1,2-thio shift to a carbene center was reported by Ochiai and Nagao (Scheme 52) [82]. Alkenyl iodonium tetrafluoroborate **214** undergoes base-induced α-elimination, resulting in the formation of alkylidene carbene **215**. The latter undergoes a 1,2-thio shift to the carbene center, affording alkynyl thioether **216a**. In the case of employment of sulfoxide as the substrate, mixtures of alkynyl and propargyl sulfoxides **216b** and **217** were formed (Scheme 52).



	n	216:217	yield (%)
a	0	1:0	72
b	1	79:21	84

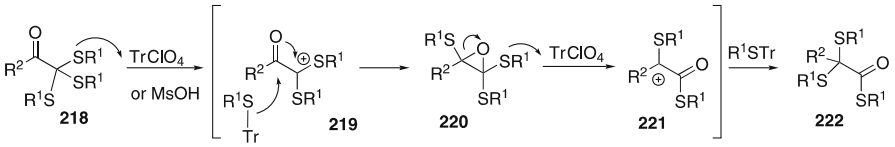
Scheme 52 1,2-Sulfur shift to carbene

5
Formal 1,2-Sulfur Migration Through Fragmentation/Recombination

1,2-Thio group migration has so far been shown to proceed through an intramolecular 1,2 migration. Alternatively, formal 1,2-thio group migration can proceed through cleavage of the carbon–sulfur bond and recombination of the sulfide and carbocation.

5.1
Rearrangement of Trithioorthocarboxylates

Degani and Fochi reported an unusual rearrangement of α,α,α-trialkylthio aryl ketones **218** in the presence of Lewis or Brönsted acids [83, 84]. A pro-



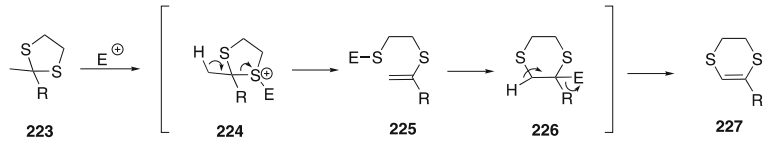
Scheme 53 Carbonyl transposition of α-ketotrithio ester

posed mechanism is depicted in Scheme 53. An alkylthio group of **218** is either protonated and leaves, or it is abstracted by the trityl cation, producing cationic species **219**. The oxygen lone pair quenches the cationic center, and the alkylthio group is added to the carbonyl carbon, to produce epoxide **220** as an intermediate. Abstraction of a second alkylthio group, followed by ring opening of the epoxide, produces cationic species **221**, which, upon addition of the alkylthio group to the thiocarbenium ion, furnishes rearranged thioester **222**. The dissociative migration pathway is supported by the detection of mixed alkylthio products when the reaction is run in the presence of trityl sulfide. The reaction is facile for different aryl and alkyl ketones, and even for the aldehyde. However, *ortho*-halophenyl ketones as well as fluoromethyl and methoxymethyl ketones do not undergo the reaction, presumably due to the inductive effect of the electron-withdrawing groups, which would destabilize the cationic intermediate **219**.

5.2 Ring Expansion of Cyclic Thioacetals

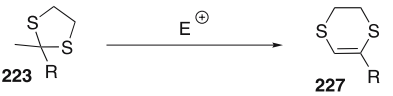
The ring expansion of cyclic dithioacetals through sulfide elimination and readdition has been extensively studied. In contrast to Afonso and Maycock's ring expansion of thioacetals, this mode does not require a vicinal leaving (hydroxyl) group. The migration is triggered by activating one of the sulfur atoms of **224** with an electrophilic reagent (such as NBS), followed by elimination to afford tethered sulfenyl intermediate **225** (Scheme 54). Addition of S – E across the resulting olefin gives expanded intermediate **226**, which undergoes elimination of H – E to give 2,3-dihydro-1,4-dithiine **227**.

Thus, a few approaches for ring expansion of thioacetals into 1,4-dithiolanes have been developed. Plumet used NBS in carbon tetrachloride to effect dithioacetal expansion of **228** and **230** into the fused naphthalene 1,4-dithiolanes **229** and **231** in good to high yields (Table 4, Entries 1–4) [85].



Scheme 54 Ring expansion

Table 4 Summary of sulfur migration in thioacetals



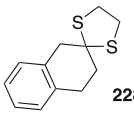
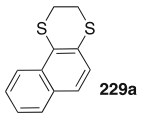
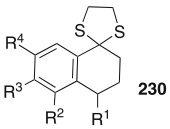
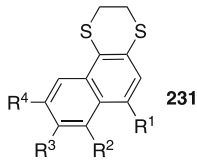
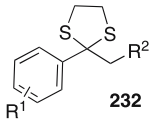
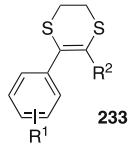
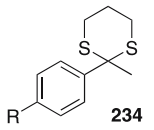
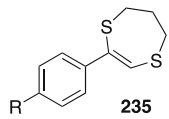
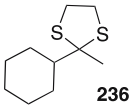
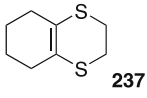
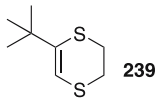
Entry	Substrate	Conditions	Product	Yield	Refs.
1	 **228a**	NBS, CCl_4	 **229a**	74	[85]
	 **230**		 **231**		[85]
	R^1 **R^2** **R^3** **R^4**				
2	Me H H H			80	
3	H OMe H H			98	
4	H Me – OCH_2O –			90	
	 **232**	IBX, TEAB, $CHCl_3$	 **233**		[87]
	R^1				
5	H			89	
6	*p*-OMe			85	
7	*p*-CO_2Ph			84	
8	*p*-Cl			85	
9	*m*-NO_2			65	
10	H			85	
	 **234**		 **235**		[87]
	R				
11	H			72	
12	Cl			69	

Table 4 (continued)

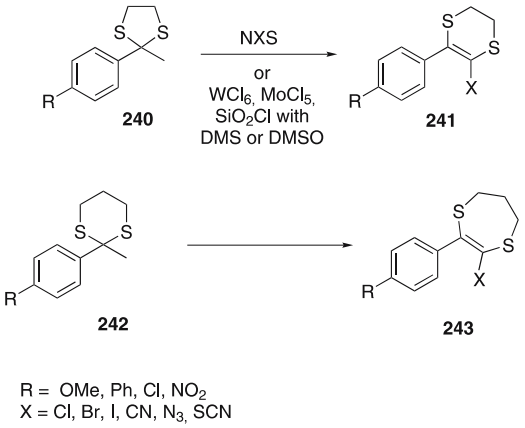
Entry	Substrate	Conditions	Product	Yield	Refs.
13	 **236**		 **237**	84	[87]
14	 **238**		 **239**	20	[87]

Plumet modified Palumbo's conditions for ring expansions of dithioacetals to avoid bromination of the aryl ring as a side reaction [86]. The initial migrated product, the fused styrene derivative, underwent a spontaneous dehydrogenation to afford an aromatic naphthalene derivative. Akamanchi used IBX and tetraethylammonium bromide complex to carry out ring expansion of dithioacetals (Entries 5–14) [87]. Differently substituted benzylic dithioacetals **232**, **234**, having both electron-donating and electron-withdrawing groups, underwent expansion in generally high yields. One exception, the *meta*-nitrobenzyl dithioacetal **232**, afforded a somewhat lower yield of **233**. The cyclohexyl analog **236** (Entry 13) also underwent expansion, although the *tert*-butyl analog **238** was reportedly unselective, leading to mixtures of products (Entry 14).

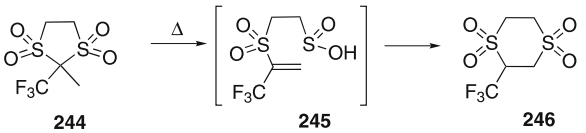
Firouzabadi and Iranpoor developed the electrophile-induced ring expansion of **240** and **242** to obtain functionalized dithiolenes **241** and dithiepines **243** (Scheme 55) [88, 89]. It was found that using *N*-halosuccinimide was most general for making halogenated derivatives **241** and **243**. Analogously, the nitrile, azide, and thiocyanate substituted products **241** and **243** could be efficiently obtained using the succinimide complex as the electrophile. Both five- and six-membered dithioacetals **240** and **242** participate in ring expansion; however, it appears that the expansion is more facile for five-membered dithioacetals **240**.

There is also a single report by Sundermeyer on flash-vacuum pyrolysis of dithioacetal tetraoxide **244** into 1,4-dithiane **246** which proceeds via formal 1,2-migration of the sulfonyl group (Scheme 56) [90].

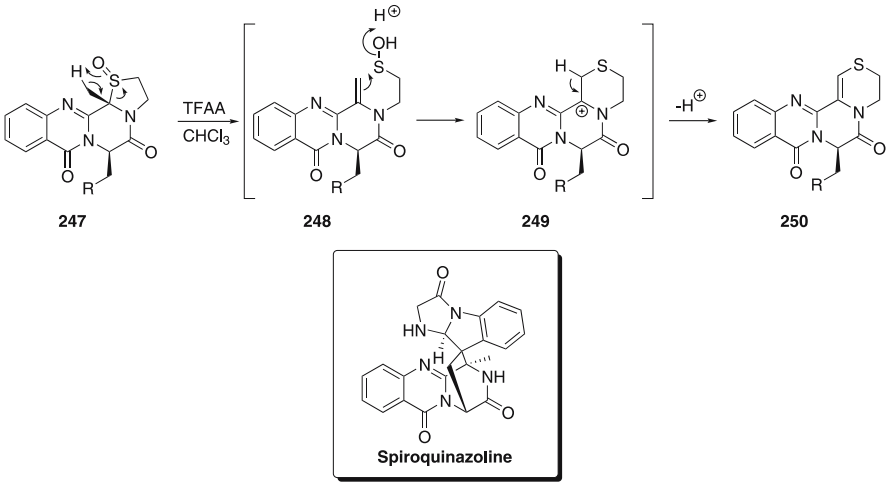
Hart explored the possibility of employing Morin ring expansion (vide infra) in azathioketals of type **247** in the total synthesis of spiroquinazoline [91, 92]. The proposed mechanistic pathway is shown in Scheme 57. Protonation of sulfoxide **247** leads to elimination of sulfanol, yielding **248**. Readdition to the less hindered side of the newly formed olefin produces thiazinium **249**, and a loss of proton from which affords **250**.



Scheme 55 Dithioacetal ring expansion/functionalization approach

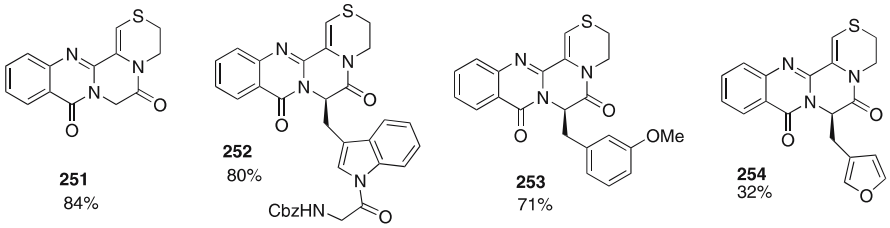


Scheme 56 Thermal expansion of disulfonate

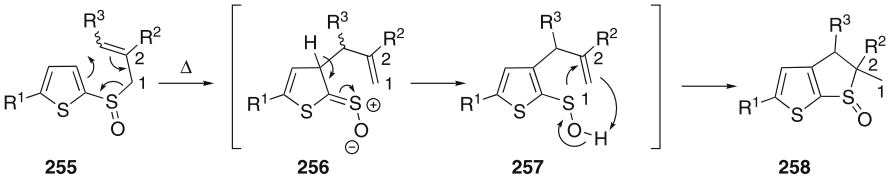


Scheme 57 Involvement of thioacetal ring expansion in synthetic studies toward spiroquinazoline

This sequence proved successful in the synthesis of four functionalized model compounds **251–252** (Scheme 58). However, the next step towards the desired bridged intermediate proved to be less selective, so the approach was abandoned.



Scheme 58 Model compounds toward synthesis of spiroquinazoline



Scheme 59 Isomerization of allyl thiophenyl sulfoxide

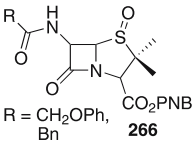
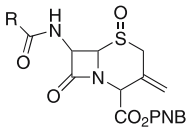
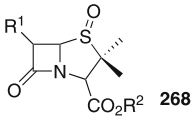
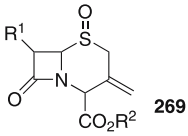
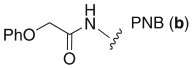
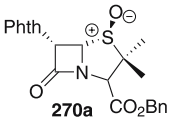
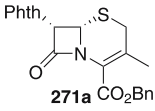
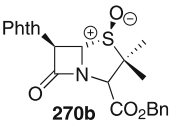
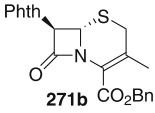
Litvinova reported a ring contraction of allyl thiophenyl sulfoxide **255** proceeding via a formal 1,2-shift of a sulfoxide group (Scheme 59) [93]. The reaction starts with a [3,3]∼sigmatropic rearrangement of **255** into isomer **256.** A 5-exo trig cyclization proceeding via nucleophilic addition of sulfur to the more substituted olefinic carbon in **257** leads to the formation of fused dithiophene derivative **258.**

5.3
Morin Rearrangement: Penicillin to Cephalosporin Transformation

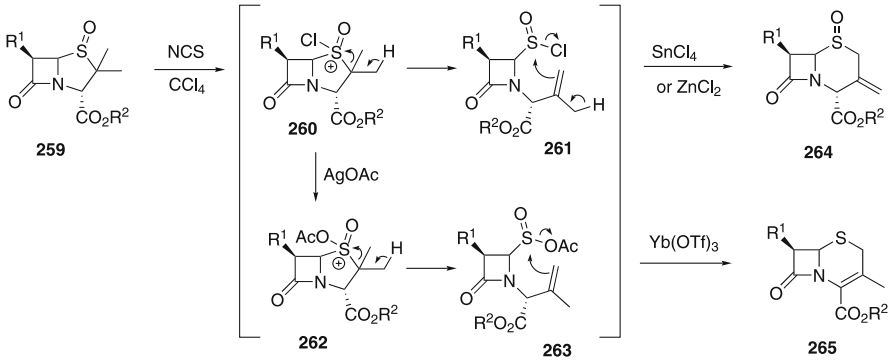
As mentioned in Sect. 5.1, the most useful and most studied class of 1,2-thio migration proceeding through fragmentation and recombination is known as the Morin rearrangement [94]. Since its discovery in 1963, it has been continuously modified as the main route toward conversion of the penicillin core into cephalosporin derivatives. A general route is depicted in Scheme 60. The reaction is triggered by an electrophilic chlorination of sulfoxide of **259** leading to **260**, which undergoes elimination to form ring-opened intermediate **261**. Lewis acid-mediated condensation of sulfinyl chloride and tethered olefin results in formation of cephalosporin derivatives **264** or **265**.

A summary of some recent developments in this important area are summarized in Table 5. Traditionally, tin tetrachoride was used stoichiometrically to effect the transformation, so alternative methods, which employ either less toxic or substoichiometric reagents, are highly desirable improvements to the process. Khanna recently demonstrated that, as an alternative, zinc chloride is an effective Lewis acid for the isomerization of penicillins **266** into cephalosporins **267** (Table 5, Entry 1) [95]. Barrett also recently investigated

Table 5 Some recent developments of the Morin rearrangement

Entry	Penicillin	Conditions	Cephalosporin	Yield (%)	Refs.
1	 R = CH_2OPh, Bn **266**	(a) N-chlorophthalimide (b) $ZnCl_2$-Et_2O (c) MeOH/IPA	 **267**	60–70	[95]
	 **268**		 **269**		[96]
2	**R^1** Phth **R^2** Me **(a)**	(a) NCS, CCl_4 (b) NaOAc, CCl_4 (c) $[Yb(OH)_2]_9(OTf)_3$, $MeNO_2$, 20 °C		54	
3		(a) NCS, CCl_4 (b) AgOBz, CCl_4 (c) $[Yb(OH)_2]_9(OTf)_3$, $MeNO_2$, 20 °C		44	
4		(a) NCS, CCl_4 (b) NaOAc, CCl_4; (c) Neat, no LA, 125 °C		25 [a]	
5		(a) NCS, CCl_4 (b) NAOPv, CCl_4		46 [a]	
6		(a) NCS, CCl_4 (b) $Yb(OTf)_3$ (10 mol %), $MeNO_2$, 20 °C (c) NAOPv, $Yb(OTf)_3$ (10 mol %), $MeNO_2$, 20 °C		53 [a]	
7	 **270a**	TsOH (cat), DMF, 100 °C, 90 min	 **271a**	50	[97]
8	 **270b**	TsOH (cat), DMF, 100 °C, 17 h	 **271b**	33	

[a] Yield reported from step 2



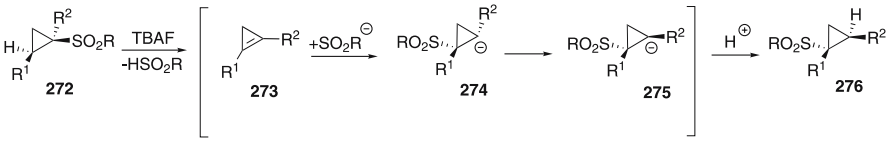
Scheme 60 General routes of penicillin to cephalosporin conversion

the possibility of using lanthanide salts as catalysts (Scheme 60, Table 5, Entries 2–6) [96]. In order to react with the oxophilic Yb triflate catalyst, the intermediate sulfinyl chloride **260** must be converted into the more reactive sulfinyl carboxylate **263.** Nevertheless, catalytic and even one-pot conditions were found to effect the reaction (Table 5, Entries 2–6). However, some drawbacks still need to be addressed, as the reaction proved to be sensitive to the lactam substituent R^1 of **268**, and sulfinyl chlorides were still required as precursors to the sulfinyl carboxylate intermediates. Another Entry in this area was made by Baldwin, in the tosic acid-catalyzed conversion of *trans*-fused penicillin derivatives **270a**,**b** into the corresponding cephalosporins **271a**,**b** (Entries 7, 8) [97]. The more highly strained penicillin **270a** undergoes faster and higher-yielding expansion at lower temperatures than **270b.**

5.4
Sulfonyl Migration in *gem*-Disulfonyl Compounds

So far all examples of 1,2-thio migration, which proceed through fragmentation and recombination, were intramolecular, as they involve migration of tethered thio groups. Two unique reports are discussed below, which involve sulfonate elimination and intermolecular addition to afford the more thermodynamically favored product.

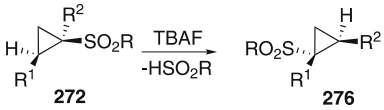
Yoshimatsu reported an unusual fluoride-induced rearrangement of geminal disulfonyl cyclopropanes **272** into vicinal disulfonyl cyclopropanes **276** (R^2 = SO_2R, Scheme 61) [98]. It is proposed that the rearrangement takes place by elimination of sulfinic acid from cyclopropane **272**, leading to intermediate cyclopropene **273.** Michael addition of sulfonate to cyclopropene generates *cis*-cyclopropyl anion **274**, and subsequent isomerization of the latter to the thermodynamically more favorable *trans*-cyclopropyl anion **275**, followed by protonation, affords **276.**

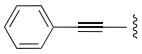
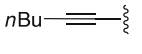
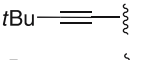
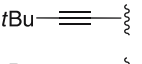
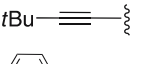
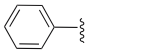
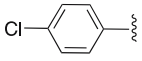
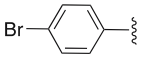


Scheme 61 Fluoride-induced formal 1,2-sulfonyl shift in cyclopropanes

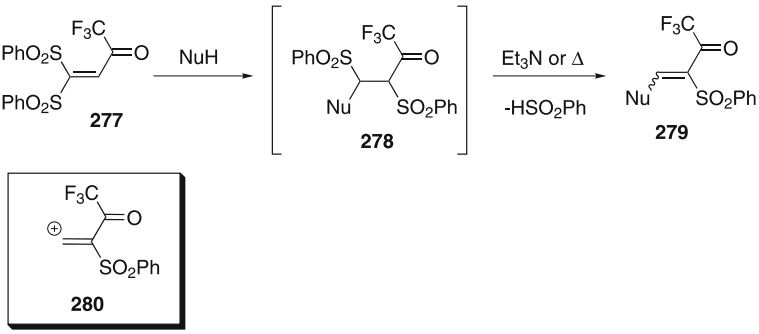
Thus, alkynyl-substituted cyclopropanes **272** undergo selective rearrangement to **276** in THF without competing ring opening (Table 6, Entries 1–3). In contrast, some ring-opened byproduct was formed from phenylcyclopropane (Entry 6). However, introduction of electron-withdrawing groups at the *para* position of the aryl substituent inhibits the ring-opening process and results in high yields of rearranged cyclopropanes (Entries 7, 8). When the cyclopropane is geminally substituted with methanesulfonyl and benzenesulfonyl groups, the more stable anion, the benzenesulfonyl anion, migrates selectively (Entry 5). However, geminal bromobenzenesulfonyl cyclopropane only undergoes the reaction in low yield (Entry 4) [98].

Table 6 Fluoride-induced sulfonate migration in cyclopropanes



Entry	R^1	R^2	Yield (%)
1		$PhSO_2$	96
2		$PhSO_2$	60
3		$PhSO_2$	89
4		Br	29
5		$MeSO_2$	86
6		$PhSO_2$	68 [a]
7		$PhSO_2$	91
8		$PhSO_2$	99

[a] Accompanied by 14% of ring-opened product.



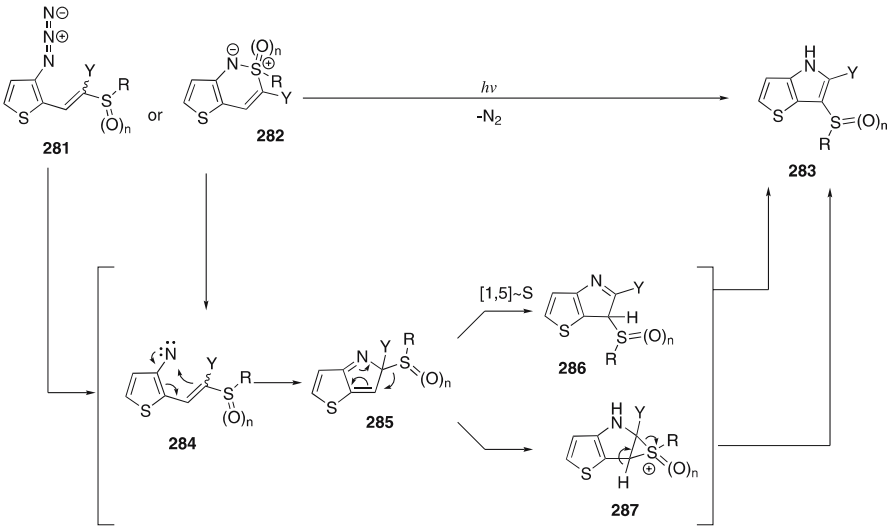
Scheme 62 Conjugate addition to disulfonyl enone followed by sulfonyl migration

Another very unusual sulfonate migration was reported by Nenajdenko in additions to β,β-disulfonyl enone **277** (Scheme 62) [99]. Enone **277** undergoes conjugate addition with a variety of mild nucleophiles, such as 2-methylthiophene or 1,3-dimethoxybenzene, to give substituted rearranged enone **279** as a product (Scheme 62). When 2-methylindole or *N*-methylpyrrole is used as the nucleophile, rearranged disulfonyl ketone **278** is obtained, which eliminates sulfinic acid upon heating or treatment with base. The authors do not propose a mechanistic pathway. However, the authors state that enone **277** acts as a "synthetic equivalent of a 1,1,1-trifluoro-3-(phenylsulfonyl)but-3-en-2-one cation" **280**, which suggests that migration of one sulfonyl group may take place *prior* to Michael addition.

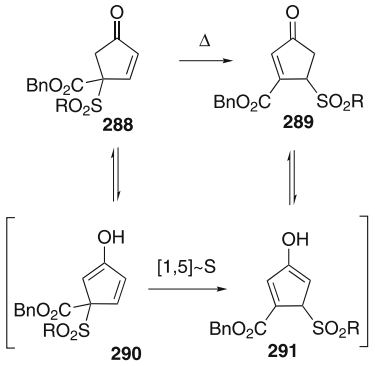
6
Sigmatropic [1,5]∼Sulfur Shift in 5-Membered Ring Systems

A special case of formal 1,2-sulfur migration occurs as a [1,5]∼sigmatropic shift of the thio group. This type of migration was briefly mentioned in Sect. 2.2.6, as a possible alternative mechanism in thio-group migration in pyrroles.

Rees reported that the photolysis of azides **281** or ylides **282** resulted in fused thienopyrroles **283** in generally high yields (Scheme 63) [100–102]. Irradiation of **281** or **282** produces a reactive nitrene intermediate **284**, which undergoes ring closure to form fused, nonaromatic 2*H*-pyrrole **285.** A photochemical [1,5]∼thio-migration followed by a [1,5]∼hydride shift affords **286.** Alternatively, a possible 1,2-thio migration, proceeding through a thiiranium intermediate **287**, was not ruled out. The relative migratory aptitude of different thio groups compared to other groups was found to be: RSO > RS∼H > RSO_2 > RCO > CO_2Et. It should be mentioned that this is in contrast to Greenhouse's findings, in which sulfenyl, sulfinyl, and sulfonyl groups all mi-



Scheme 63 Photochemical [1,5]∼thio shift



Scheme 64 Thermal [1,5]∼sulfur shift

grated preferentially to hydrogen in pyrroles (Scheme 38), which indicates that Greenhouse's and Rees's rearrangements may follow different mechanistic pathways.

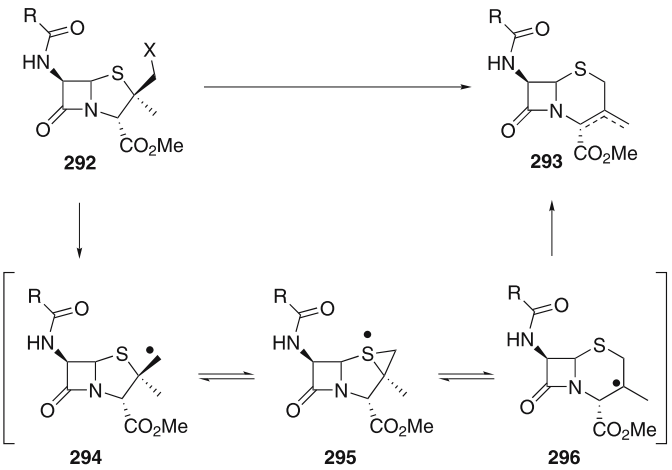
As discussed above, the thio group can undergo a photochemical [1,5] ∼shift. Alternatively, Fuchs reported a thermal [1,5]∼shift of the sulfonyl group (Scheme 64) [103]. In this case, cyclopentenone **288** undergoes thermal enol tautomerization into cyclopentadiene **290** from which a [1,5]∼sulfonyl shift, followed by tautomerization, yields **289** in nearly quantitative yield. This selective migration is in agreement with Rees's relative migratory aptitudes of sulfonyl > ester groups.

7
Radical Sulfur Migration

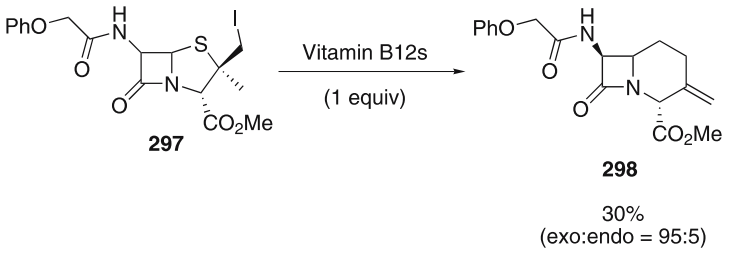
The last type of 1,2-thio migration discussed herein proceeds via radical intermediates. Efficient radical 1,2-thio migration can be carried out in properly designed substrates. Relatively few investigations have been done in this area to date. The selective few examples which were found were proposed to involve a thiirane radical intermediate. One transformation in particular, the penicillin **292** to cephalosporin **293** expansion through radical intermediates, has been briefly investigated as an alternative to the Morin rearrangement (Scheme 65) [104, 105]. In this mode, homolysis of the C – X bond of **292** leads to the formation of methyl radical **294**, which is trapped by sulfur to form the thiirane radical **295**. Homolysis of the most substituted sulfur–carbon bond leads to tertiary radical **296**, which can produce **293** by abstracting X from another molecule of **292**, thus propagating the reaction.

Baldwin employed vitamin B12s (which was made by reducing vitamin B12 with sodium borohydride) in a cobalt-mediated radical transformation of iodopenicillin derivative **297** into cephalosporin derivative **298** (Scheme 66) [104]. The rearrangement proceeded stereoselectively, although in 30% yield only.

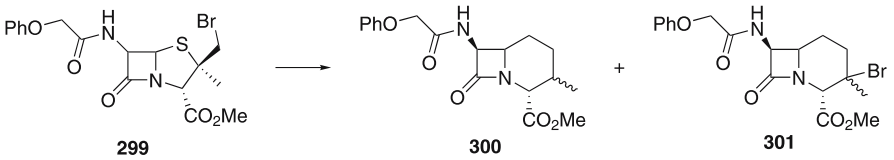
Using the analogous bromopenicillin derivative **299**, Torii effected a radical ring expansion into cephalosporin **300** in 80% yield using triphenyl tin radical, which was generated by passing a current through the reaction medium (Scheme 67) [105]. Alternatively, using AIBN as the radical initiator afforded a similar yield of product **300**, although accompanied by 8% of brominated cephalosporin **301**.



Scheme 65 Radical version of Morin transformation



Scheme 66 Cobalt-mediated conversion of penicillin to cephalosporin



(a) 0.2 F/mol electricity, Ph_3SnH (1.2 equiv), Bu_4NClO_4, THF; 80% of **a** (b) Ph_3SnH (1.3 equiv), AIBN (0.2 equiv), **300**:**301** = 80:8%.

Scheme 67 Electrical homolytic bond cleavage in radical penicillin to cephalosporin conversion

8 Conclusion

1,2-Thio migration continues to be a valuable tool for synthetic organic chemists. 1,2-Thio migration has been found to proceed efficiently through a number of different pathways. The most active investigations involve reactions of thiiranium intermediates, as exemplified by Warren's continuous studies on synthesis of thio-substituted heterocycles, its broad application in carbohydrate chemistry, and the development of thioacetal ring expansion reactions. Because of the constant need for newer, more effective antibiotics, synthesis of efficient routes toward cephalosporin derivatives, through formal 1,2-thio migration via the fragmentation/recombination approach, will be a constant focus of research. However, two attractive areas of 1,2-thio migration, namely: [1,5]∼shifts of thio groups in five-membered rings, and radical sulfur shifts remain relatively unexplored.

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References

1. Fox DJ, House D, Warren S (2002) Angew Chem Int Ed 41:2462
2. Fox DJ, House D, Warren S (2002) Angew Chem 114:2572

3. House D, Warren S (1999) Phosphorus Sulfur 153–154:59
4. Smoliakova IP (2000) Curr Org Chem 4:589
5. Rayner CM (1997) Synlett 11
6. Hanson RM (2002) Epoxide migration (Payne rearrangement) and related reactions. In: Overman LE et al. (eds) Organic reactions, vol 60. Wiley, New York, p 1
7. Braverman S (1988) Rearrangements involving sulfones. In: Patai S, Rappaport Z, Stirling C (eds) The chemistry of sulphones and sulphoxides. Wiley, New York, p 665
8. Braverman S (1988) Rearrangements involving sulfoxides. In: Patai S, Rappaport Z, Stirling C (eds) The chemistry of sulphones and sulphoxides. Wiley, New York, p 717
9. Knochel P, Normant JF (1985) Tetrahedron Lett 26:425
10. Masuyama Y, Sano T, Oshima M, Kurusu Y (2003) Bull Chem Soc Jpn 76:1679
11. Jansen BMJ, Peperzak RM, de Groot Ae (1987) Recl Trav Chim Pays-Bas 106:489
12. Jansen BMJ, Peperzak RM, de Groot Ae (1987) Recl Trav Chim Pays-Bas 106:549
13. Sato T, Tsuchiya H, Otera J (1995) Synlett 628
14. Padwa A, Ginn JD, McClure MS (1999) Org Lett 1:1559
15. Padwa A, Eidell CK, Ginn JD, McClure MS (2002) J Org Chem 67:1595
16. Barros MT, Maycock CD, Santos LS (1998) Heterocycles 48:1121
17. Afonso CAM, Barros MT, Godinho LS, Maycock CD (1991) Synthesis 575
18. Sato T, Otera J, Nozaki H (1990) J Org Chem 55:6116
19. Afonso CAM, Barros MT, Maycock CD (1999) Tetrahedron 55:801
20. Baldwin IC, Briner P, Eastgate MD, Fox DG, Warren S (2002) Org Lett 4:4381
21. Caggiano L, Davies J, Fox DJ, Moody DC, Warren S (2003) Chem Commun 1648
22. Caggiano L, Fox DJ, Warren S (2002) Chem Commun 2528
23. Caggiano L, Davies J, Fox DJ, Moody DC, Warren S (2003) Chem Commun 1650
24. Fox DJ, Morley TJ, Taylor S, Warren S (2005) Org Biomol Chem 3:1369
25. House D, Kerr F, Warren S (2002) J Chem Soc Perkin Trans 1 2652
26. Carlisle J, Fox DJ, Warren S (2003) Chem Commun 269
27. Eastgate MD, Fox DJ, Morley TJ, Warren S (2002) Synthesis 2124
28. Toshimitsu A, Hirosawa C, Tanimoto S (1991) Tetrahedron Lett 32:4317
29. Toshimitsu A, Hirosawa C, Tamao K (1994) Tetrahedron 50:8997
30. Bildstein S, Ducep J-B, Jacobi D (1996) Tetrahedron Lett 37:8759
31. Kuroboshi M, Furuta S, Hiyama T (1995) Tetrahedron Lett 36:6121
32. Furuta S, Kuroboshi M, Hiyama T (1998) Bull Chem Soc Jpn 71:2687
33. Ayuba S, Hiramatsu C, Fukuhara T, Hara S (2004) Tetrahedron 60:11445
34. Ayuba S, Fukuhara T, Hara S (2003) Org Lett 5:2873
35. Yang Z, Yu B (2001) Carbohydrate Research 333:105
36. Yu B, Yang Z (2000) Tetrahedron Lett 41:2961
37. Yu B, Yang Z (2001) Org Lett 3:377
38. Yang Z, Cao H, Hu J, Shan R, Yu B (2003) Tetrahedron 59:249
39. Yu B, Wang P (2002) Org Lett 4:1919
40. Nicolaou KC, Ladduwahetty T, Randall JL, Chucholowski A (1986) J Am Chem Soc 108:2466
41. Nicolaou KC, Fylaktakidou KC, Monenschein H, Li Y, Wetershausen B, Mitchell HJ, Wei H-x, Guntupalli P, Hepworth D, Sugita K (2003) J Am Chem Soc 125:15433
42. Nicolaou KC, Rodriguez RM, Mitchell HJ, Suzuki H, Fylaktakidou KC, Baudoin O, van Delft FL (2000) Chem Eur J 6:3095
43. Pratt MR, Bertozzi CR (2003) J Am Chem Soc 125:6149
44. Borrachero P, Cabrera-Escribano F, Carmona AT, Gomez-Guillen M (2000) Tetrahedron: Asymmetry 11:2927

45. Carmona AT, Borrachero P, Cabrera-Escribano F, Dianez MJ, Estrada MD, Lopez-Castro A, Ojeda R, Gomez-Guillen M, Perez-Garrido S (1999) Tetrahedron: Asymmetry 10:1751
46. Jeong LS, Moon HR, Yoo SJ, Lee SN, Chun MW, Lim Y-H (1998) Tetrahedron Lett 39:5201
47. Liptak A, Sajtos F, Janossy L, Gehle D, Szilagyi L (2003) Org Lett 5:3671
48. Maiareanu C, Kanai A, Wiebel J-M, Pale P (2005) J Carb Chem 24:831
49. Viso A, Poopeiko N, Castillon S (2000) Tetrahedron Lett 41:407
50. Johnston BD, Pinto BM (2000) J Org Chem 65:4607
51. Carmona O, Greenhouse R, Landeros R, Muchowski JM (1980) J Org Chem 45:5336
52. DeSales J, Greenhouse R (1982) J Org Chem 47:3668
53. Plate R, Nivard RJF, Ottenheim HCJ (1986) Tetrahedron 42:4503
54. Plate R, Ottenheijm HCJ (1986) Tetrahedron 42:4511
55. Hamel P, Preville P (1996) J Org Chem 61:1573
56. Hamel P (2002) J Org Chem 67:2854
57. Hamel P (1997) Tetrahedron Lett 38:8473
58. Matsumoto S, Kishimoto T, Ogura K (2002) Chem Lett 134
59. Xu F, Shi W, Wang J (2005) J Org Chem 70:4191
60. Ikota N, Takamura N, Young SD, Ganem B (1981) Tetrahedron Lett 22:4163
61. Lopez-Herrera FJ, Sarabia-Garcia F (1994) Tetrahedron Lett 45:4563
62. Jiao L, Zhang Q, Liang Y, Zhang S, Xu J (2006) J Org Chem 71:815
63. Kim JT, Kel'in AV, Gevorgyan V (2003) Angew Chem Int Ed 42:98
64. Kim JT, Kel'in AV, Gevorgyan V (2003) Angew Chem 115:102
65. Volonterio A, Zanda M (1997) J Org Chem 62:8031
66. Volonterio A, Bravo P, Capelli S, Meille V, Zanda M (1997) Tetrahedron Lett 38:1847
67. Bravo P, Crucianelli M, Fronza G, Zanda M (1996) Synlett 249
68. Durst T, Tin KC (1970) Tetrahedron Lett 2369
69. Tavares DF, Estep RE, Blezard M (1970) Tetrahedron Lett 2373
70. Furuta H, Takase T, Hayashi H, Noyori R, Mori Y (2003) Tetrahedron 59:9767
71. Mori Y, Furuta H, Takase T, Mitsuoka S, Furukawa H (1999) Tetrahedron Lett 40:8019
72. Fernandez de la Pradilla R, Viso A, Castro S, Fernandez J, Manzano P, Tortosa M (2004) Tetrahedron 50:8171
73. Kamiyama H, Hasemi R, Nakayama J (1993) Heteroatom Chem 4:445
74. Koptyug VA, Gerasimova TN, Vorozhtov NN (1959) Khim Nauk Promyshl 4:414
75. Koptyug VA, Gerasimova TN, Vorozhtov NN (1960) Chem Abstr 437
76. Koptyug VA, Gerasimova TN, Vorozhtov NN (1961) J Gen Chem USSR 31:3116
77. Capozzi G, Melloni G, Modena G (1970) J Chem Soc Sec C 2621
78. Capozzi G, Melloni G, Modena G, Piscitelli M (1968) Tetrahedron Lett 4039
79. Capozzi G, Melloni G, Modena G (1970) J Org Chem 35:1217
80. Capozzi G, Melloni G, Modena G (1973) J Chem Soc Perkin Trans I 2250
81. Veselovskaya SV, Saginova LG, Tafeenko VA, Shabarov YuS (1986) J Org Chem USSR 22:1939
82. Ochiai M, Takaoka Y, Nagao Y (1988) J Am Chem Soc 110:6565
83. Degani I, Dughera S, Fochi R, Gazzetto S (1997) J Org Chem 62:7228
84. Clericuzio M, Degani I, Dughera S, Fochi R (2002) Synthesis 921
85. Esteban G, Lopez G, Plumet J, del Valle A (1997) Heterocycles 45:1921
86. Caputo R, Ferreri C, Palumbo G, Russo F (1991) Tetrahedron 47:4187
87. Shukla VG, Salgaonkar PD, Akamanchi KG (2005) Synlett 1483
88. Firouzabadi H, Iranpoor N, Karimi B (1999) Synlett 413

89. Firouzabadi H, Iranpoor N, Garzan A, Shaterian HR, Ebrahimzadeh F (2005) Eur J Org Chem 416
90. Schuler B, Sundermeyer W (1990) Chem Ber 123:177
91. Hart DJ, Magomedov N (1999) J Org Chem 64:2990
92. Freed JD, Hart DJ, Magomedov NA (2001) J Org Chem 66:839
93. Litvinova VV, Anisimov AV, Viktorova EA (1991) Sulfur Lett 13:19
94. Morin RB, Jackson BG, Mueller RA, Lavagnino ER, Scanlon WB, Andrews SL (1969) J Am Chem Soc 91:1401
95. Thaper RK, Kumar Y, Khanna JM (1995) Synth Commun 25:883
96. Barrett AGM, Braddock DC, Cooper RDG, Henschke JP (2002) Tetrahedron 58:8313
97. Fekner T, Baldwin JE, Adlington RM, Jones TW, Prout CK, Schofield CJ (2000) Tetrahedron 56:605
98. Yoshimatsu M, Konishi K, Tanabe G, Muraoka O (1998) Tetrahedron Lett 39:1781
99. Krasovsky AL, Druzhinin SV, Nenajdenko VG, Balenkova ES (2004) Tetrahedron Lett 45:129
100. Gairns RS, Moody CJ, Rees CW (1986) J Chem Soc Perkin Trans I 501
101. Gairns RS, Moody CJ, Rees CW, Tsoi SC (1986) J Chem Soc Perkin Trans I 497
102. Gairns RS, Moody CJ, Rees CW (1985) J Chem Soc Chem Commun 1818
103. Nantz MH, Fuchs PL (1987) J Org Chem 52:5298
104. Baldwin JE, Adlington RM, Kang TW (1991) Tetrahedron Lett 32:7093
105. Tanaka H, Suga H, Ogawa H, Abdul Hai AKM, Torii S, Jutand A, Amatore C (1992) Tetrahedron Lett 33:6495

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1,3-Sulfur Shifts: Mechanism and Synthetic Utility

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Abstract While allylic migrations are well known, 1,3-sulfur shifts are relatively rare. These shifts occur through a variety of mechanisms depending upon the substrate type and the reaction conditions. Radical-chain, ion-pair, dipolar, and symmetry-forbidden 1,3-sigmatropic mechanisms have all been proposed. Allylic sulfur shifts have been used in the synthesis of sulfides and sulfones of higher complexity, the stereospecific synthesis of alkenes, and the construction of ketones. This comprehensive survey of 1,3-sulfur migrations pays particular attention to the reported mechanisms and synthetic application.

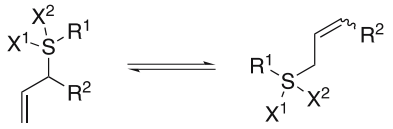
Keywords Sulfide · Sulfoxide · Sulfone · 1,3-shift · Mechanism

1 Introduction

Sulfur groups provide versatile functional handles that aid the synthesis of complex molecules [1, 2]. Groups containing sulfur, in a variety of oxidation

states, can stabilize anions, thus facilitating carbon–carbon bond formation. They can be removed by reduction or, for some oxidation states, through elimination reactions to generate alkenes. This utility can be extended, however, through rearrangements that move the sulfur atom to positions that allow it to be leveraged for further transformations.

The observation of 1,3-sulfur rearrangements, generalized by the equilibrium between **1** and **2** (Eq. 1), and the subsequent development of synthetic methods based upon these 1,3-shifts have expanded the role of sulfur-based chemistry. This mode of rearrangement, however, is much less common than 1,2- and 2,3-migrations. Thermal suprafacial/suprafacial 1,3-sigmatropic rearrangements are symmetry forbidden. Consequently, much attention has focused on the mechanism of these rearrangements. Several mechanisms have been invoked to explain these allylic shifts, depending upon substrate and reaction conditions.



1 **2**

X^1, X^2 = Lone Pair, =O

Equation 1

Braverman has reviewed 1,3-shifts of sulfoxides and sulfones [3, 4], but recent examples have further defined the scope of these reactions. Additionally, sulfides have been reported to undergo these rearrangements. This review attempts to present a more complete collection of reports, focusing on the mechanism, scope, and creative applications of 1,3-sulfur migrations. While no single organizational scheme can easily be applied to the full range of reactions reported, the examples are organized first by the oxidation states of the sulfur undergoing the migration, then by either substrate type or apparent mechanism.

2
Allyl Sulfide Rearrangements

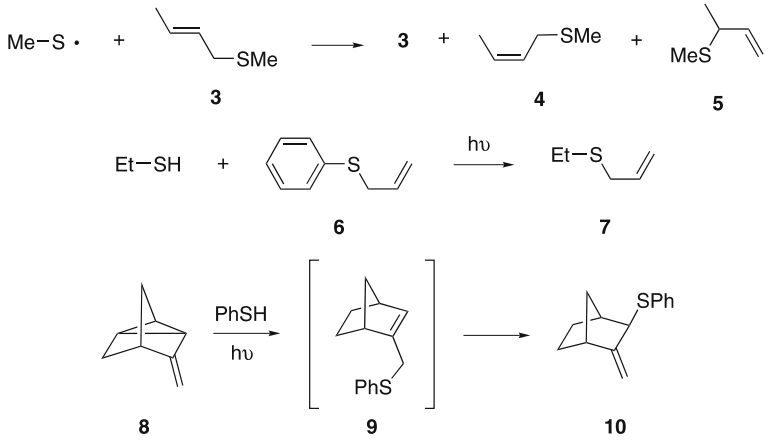
Of the various oxidation states of sulfur that participate in allylic shifts, sulfides have received the most detailed mechanistic studies. Under some conditions, it seems obvious that a radical chain-reaction mechanism is consistent with the observed product distribution. In other cases, however, no clear mechanism is easily invoked to explain the observations. This is particularly

true of thermally promoted 1,3-sulfanyl shifts. In these cases, the evidence for a proposed mechanism is provided in as much detail as is available.

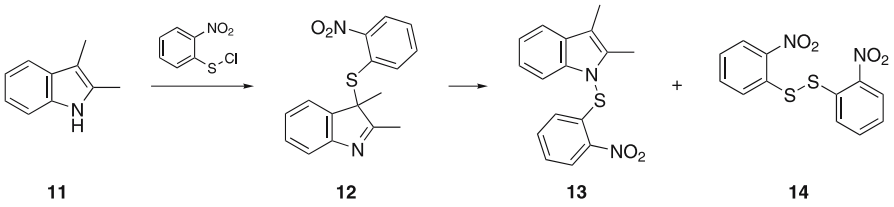
2.1 Allylic Reversal

One of the first reported examples of 1,3-"migrations" involving sulfides came from studies on the radical mediated isomerization of *trans*-crotyl methyl sulfide (**3**, Scheme 1) [5]. Reaction of methane thiyl radical with **3** produced a mixture (16.4 : 2.8 : 1) of **3**, **4**, and **5** along with products arising from the addition of methanethiol. A similar reaction, wherein the addition of ethanethiol to allyl phenyl sulfide, **6**, produced allyl ethyl sulfide, **7**, in 63% yield, was reported at the same time [6]. A radical addition/elimination mechanism seems to operate for these reactions, and the radical mediated interchange of allylic substituents was dubbed an "allylic reversal" reaction. Interestingly, when a sample of predominantly **5** was photolyzed in the absence of methanethiol, a mixture (7.7 : 1 : 4.9) of **3**, **4**, and **5** was obtained [5]. The proposed mechanism of this rearrangement follows the same radical addition/elimination pathway as the initial isomerization reactions. Cristol later invoked this allylic reversal to explain the isolation of **10**, rather than the kinetically preferred **9**, when tricyclic alkene **8** was exposed to thiophenol under irradiation conditions [7].

Dmitrienko examined the ambident nucleophilic nature of indoles in the context of preparing 3-heteroatom substituted indolenines. A series of indoles (such as **11**) was reacted with *o*-nitrophenylsulfenyl chloride to produce 3-arylsulfanylindolenines (such as **12**) in 75–98% yield (Scheme 2) [8]. Interestingly, compound **12** was particularly unstable; upon heating to 95 °C, **12**



Scheme 1 Radical addition/elimination reaction for the isomerization of allyl sulfide



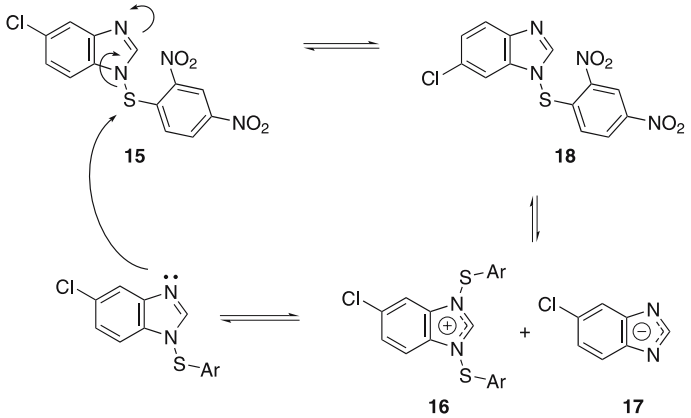
Scheme 2 Arylsulfanylindolenine to sulfenamide rearrangement

decomposed to provide sulfenamide **13** in 14% yield. It would appear, then, that indolenine **12** is the kinetic product, whereas the sulfenamide **13** is the thermodynamic product. The isolation of indole **11** (in 23% yield) and traces of disulfide **14** after the thermolysis of **12** suggests that this is a homolytic dissociation/recombination process.

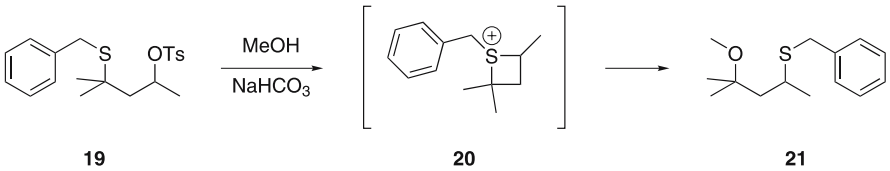
2.2 Solvolytic Conditions

While examining the barrier to rotation about N – S bonds in systems related to **13**, Raban's group examined the rearrangement of 2,4-dinitrophenylsulfanyl substituted benzimidazoles. Equilibration of **15** and **18** at 65 °C was observed to be second order in substrate, and the isomerization was catalyzed by benzimidazole (Scheme 3) [9]. To explain these observations, a mechanism involving nucleophilic displacement to afford the ion pair **16** and **17** was proposed.

Early evidence for ionic 1,3-sulfanyl migrations comes from work by Eliel and coworkers. Upon heating **19** in methanol at reflux, only the rearranged solvolysis product **21** was isolated (Scheme 4) [10]. When the carbon bearing



Scheme 3 Isomerization of *N*-sulfanylbenzimidazole derivatives

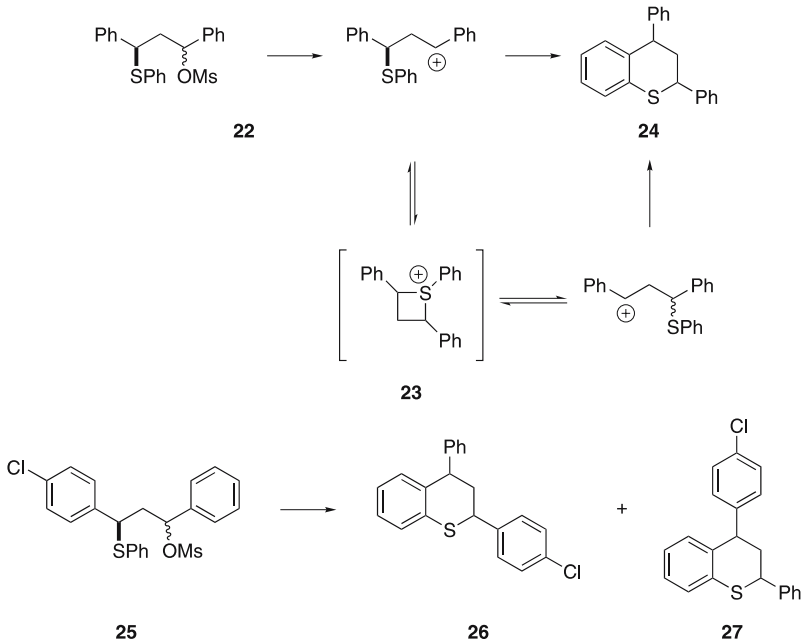


19 20 21

Scheme 4 Anchiomeric assistance leading to 1,3-migration

the sulfanyl group was primary or secondary, very little rearranged material was observed in the solvolysis product. To explain this rearrangement, a four-membered ring thionium intermediate **20**, derived by participation of the sulfur during the ionization of the tosylate, was invoked. The Thorpe-Ingold effect was used to explain the effects of substitution on the rearrangement in that sulfides with greater α-branching would more easily form the four-membered ring intermediate.

More recently, Skarzewski et al. have reported a similar rearrangement. Upon ionization of mesylate **22**, racemic **24** was isolated in 98% yield as a mixture (ca. 5 : 1) of *cis*- and *trans*-isomers (Scheme 5) [11]. The racemization was explained by a 1,3-sulfur shift involving the thionium ion intermediate **23**. As further evidence of the sulfanyl migration, mesylate **25** produced a mixture (83 : 17) of **26** and **27**.



22 24 23 25 26 27

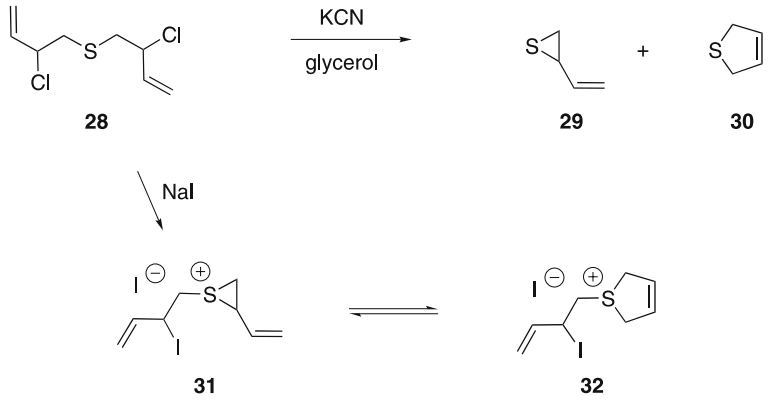
Scheme 5 Racemization via 1,3-sulfur shift before cyclization

2.3 Cyclic Sulfides

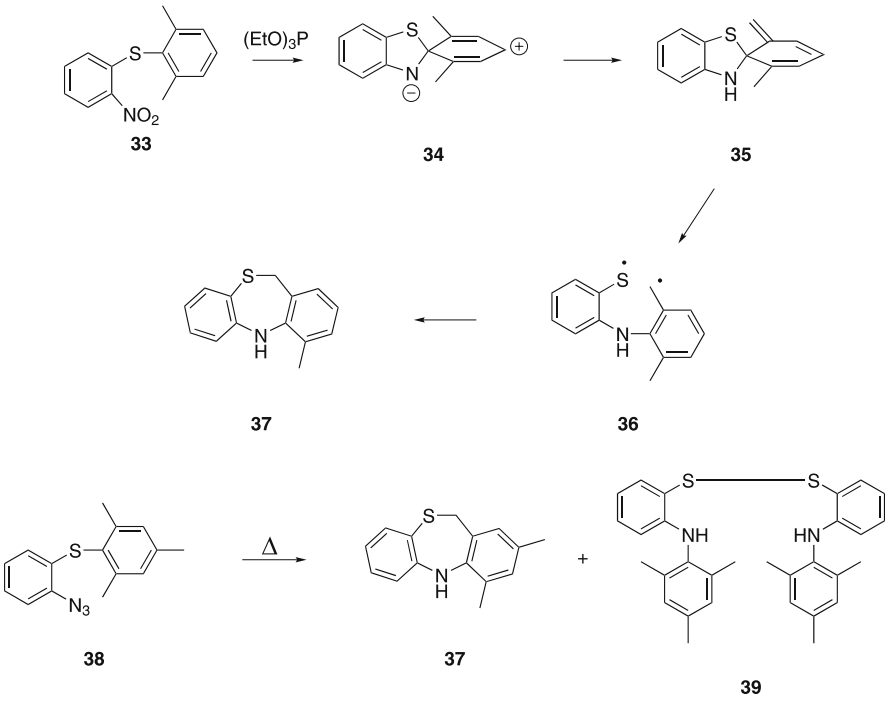
Lautenschlaeger reported that chlorosulfide products, derived from the reaction of sulfur dichloride with various dienes, underwent unusual rearrangements. In particular, it was noted that sulfide **28** rearranged to give episulfide **29** and dihydrothiophene, **30**, in < 5% yield upon dehalogenation with potassium cyanide in glycerol (Scheme 6) [12]. Attempts to facilitate the reaction by displacement of the chlorines with iodide, using sodium iodide, produced **30** in 35% yield along with butadiene (48%), iodine, and polymeric material. It was proposed that an intermediate sulfonium ion **31** could rearrange to produce **32**, and both **31** and **32** fragment to form **29** or **30**, respectively, along with 3,4-diiodobutene (which further decomposes to iodine and butadiene).

While examining the reduction of aryl nitro- and nitroso-compounds with phosphite reagents, Cadogan isolated products that resulted from 1,3-sulfur shifts [13]. Exposure of **33** to triethyl phosphite produced **37** in 11% yield, along with the *N*-phosphoramidate derived from **33** in 73% yield (Scheme 7). Presumably, the initially formed nitrene added to the pendant aromatic ring to give **34**, rather than C – H insertion. This addition product isomerized to produce intermediate **35**. Homolysis of the C – S bond to form **36** with subsequent radical recombination was proposed to account for the formation of **37**. Evidence for the intermediacy of a diradical species came from a reaction in which pyrolysis of **38** afforded **37** in 45% yield and disulfide **39** in 33% yield.

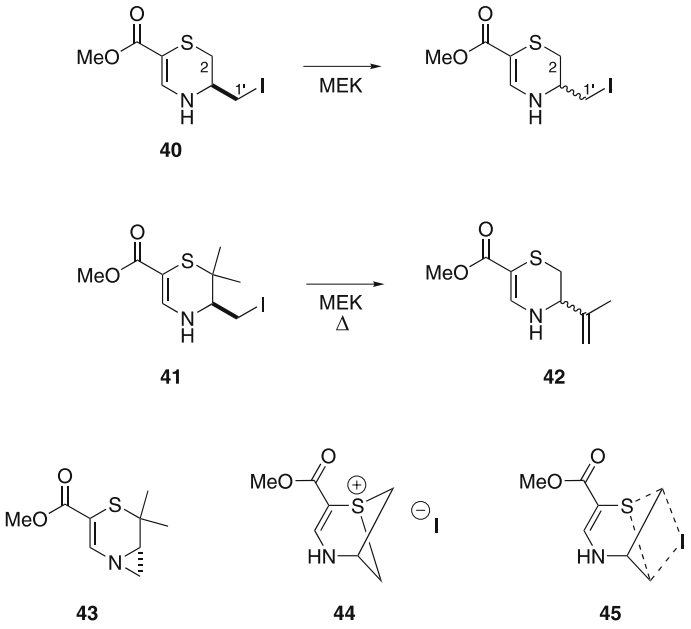
Stoodley invoked a 1,3-sulfur migration to explain the thermal racemization of compounds such as **40** (Scheme 8) [14, 15]. Heating a sample of **40**, in which C(1)′ was labeled with deuterium, in methyl ethyl ketone (MEK) for 9 days returned racemic **40** wherein the deuterium was evenly distributed between C(2) and C(1)′. Furthermore, heating the *gem*-dimethyl derivative **41**



Scheme 6 Thionium ion rearrangement



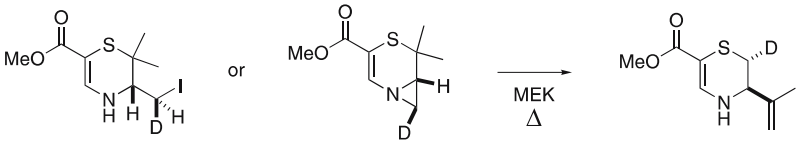
Scheme 7 Nitrene-induced rearrangement



Scheme 8 Dihydro-1,4-thiazine rearrangement

in MEK for 5 days furnished **42** in 67% yield. Interestingly, aziridine **43** also produced **42** in 53% yield after heating at 110 °C in toluene for 4 days [16].

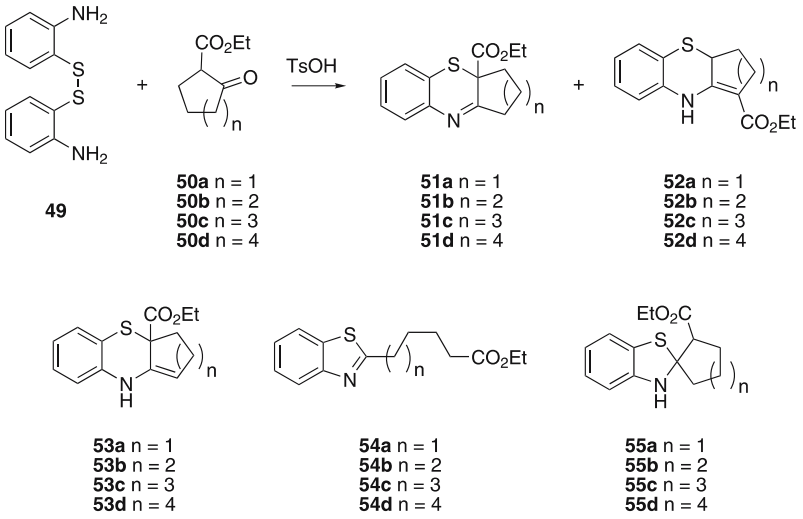
Two mechanistic paths were considered: The rearrangements could involve an ion-paired intermediate, such as **44**, or they could occur in a concerted manner involving a transition state such as **45**. An ion-paired intermediate would proceed with inversion of configuration at C(1)′, whereas the concerted mechanism requires retention of configuration at this center. Reactions in which mono-deuterated derivative **46** was heated in MEK produced **48**, indicating that the 1,3-shift proceeded with inversion of configuration (Eq. 2) [17]. Alternatively, heating mono-deuterated aziridine **47** in toluene for 4 days also provided **48**, but this signifies a 1,3-shift proceeding with retention of configuration [17, 18].



46 **47** **48**

Equation 2

Trapani and coworkers have encountered a similar 1,3-sulfur shift in other benzothiazine systems. For example, the acid-catalyzed condensation of **49** with keto esters of the form **50** was expected to provide benzothiazines **51** (Scheme 9) [19]. In the condensation with **50a,b**, however, vinylogous car-



49

50a n = 1
50b n = 2
50c n = 3
50d n = 4

51a n = 1
51b n = 2
51c n = 3
51d n = 4

52a n = 1
52b n = 2
52c n = 3
52d n = 4

53a n = 1
53b n = 2
53c n = 3
53d n = 4

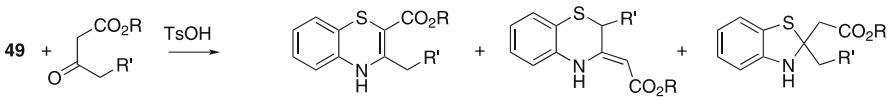
54a n = 1
54b n = 2
54c n = 3
54d n = 4

55a n = 1
55b n = 2
55c n = 3
55d n = 4

Scheme 9 Condensation of β-keto esters with bis(*o*-aminophenyl)disulfides

bamates **52a,b** were isolated in 50 and 48% yield, respectively, along with benzothiazoles **54a,b** in 50 and 52% yields respectively. Compounds **52a,b** are presumably formed through a 1,3-shift involving the enamine tautomer **53a,b**. In condensation reactions of **49** with **50c,d**, which contain a larger ring, the expected benzothiazines **51c,d** were isolated (37 and 23% yields, respectively) along with **52c,d** (15 and 29% yields, respectively) and spirocyclic benzothiazoles **54c,d** (47 and 48% yields, respectively). The dependence of product distribution on ring size is interesting, though the authors did not offer an explanation. Additionally, compounds **51c,d** could be converted into **52c,d** upon heating a benzene solution to reflux in the presence of catalytic amounts of TsOH.

This reaction was then shown to be more general in that acyclic β-keto esters also undergo the rearrangement. For example, the acid-catalyzed condensation of **49** with **56a–e** produced mixtures of products **57**, **58**, and **59** (Eq. 3) [20]. In each case, **59** was isolated in 50% yield, while the distribution of **57** and **58** varied depending upon the substitution pattern of **56**. Specifically, **56a–c** produced **58a–c** in 50% yield. Keto ester **56d** produced **57d** and **59d** in equal amounts, whereas **56e** provided **57e** in 36% yield and **58e** in 14% yield. Again, thiazines **57d,e** could be converted into **58d,e** upon heating benzene solutions of these compounds to reflux with catalytic amounts of TsOH.

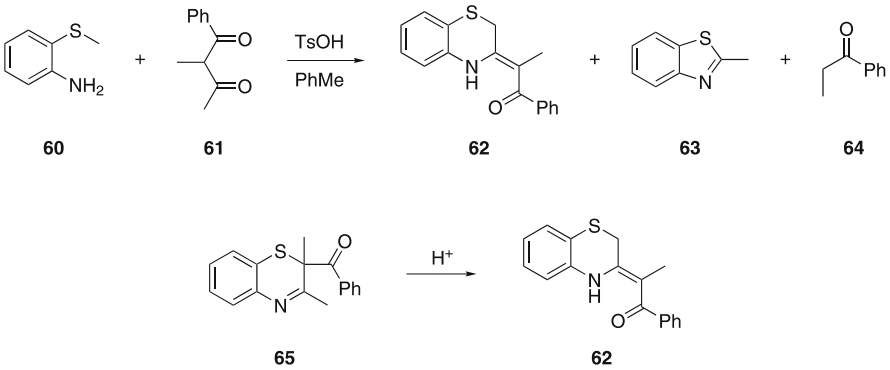


56a R = Et, R' = CO_2Et	**57a**	**58a**	**59a**
56b R = Me, R' = CO_2Me	**57b**	**58b**	**59b**
56c R = Et, R' = H	**57c**	**58c**	**59c**
56d R = Me, R' = Ph	**57d**	**58d**	**59d**
56e R = Et, R' = $(CH_2)_2CO_2Et$	**57e**	**58e**	**59e**

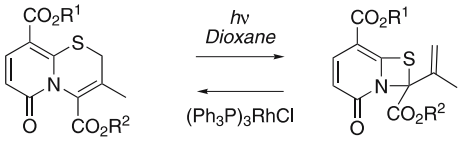
Equation 3

β-Diketones undergo similar condensations with thioanilines. Condensation of **60** with **61** produced **62, 63**, and **64** (Scheme 10) [21]. Based upon the work outlined above, the formation of **62** was explained as arising from an acid-catalyzed 1,3-sulfur shift of the initially formed **65**.

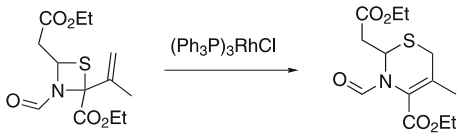
Young and coworkers discovered that 1,3-thiazines such as **66** undergo a ring contraction upon irradiation to give vinyl 1,3-thiazetidines such as **67** (Eq. 4) [22]. It was also found that exposure of **67** to $(Ph_3P)_3RhCl$ (Wilkinson's catalyst) effected isomerization to give **66** [23]. The ring expansion also occurred upon treating **68** with Wilkinson's catalyst (Eq. 5). Catalysts such as PtO_2 and Pd/C affected a 1,2-sulfur shift, rather than a 1,3-migration. In these reactions, Rh was proposed to act as a Lewis acid, though no mechanistic studies were conducted.



Scheme 10 Condensation of β-diketones with *o*-aminophenyl sulfides



Equation 4



Equation 5

Bushweller and Lemal studied the dynamic NMR spectrum of Dewar thiophene derivative **70** (Fig. 1) [24]. At 94 °C, the ^{19}F NMR spectrum of **70** showed two signals as expected. Upon heating to 190 °C, the signals coalesced, indicating a rapid equilibration that renders the CF_3 groups identical. The experimental enthalpy of activation was too low for a stepwise rearrangement mechanism ($\Delta H^{\ddagger} = 18.8\,\text{kcal mol}^{-1}$), and the entropy of ac-

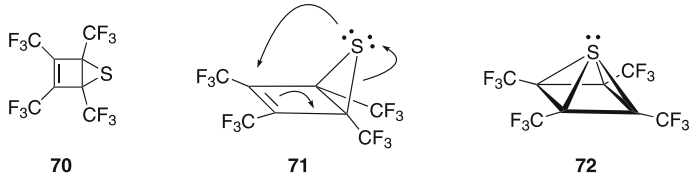


Fig. 1 Interconversion of Dewar thiophene ligands

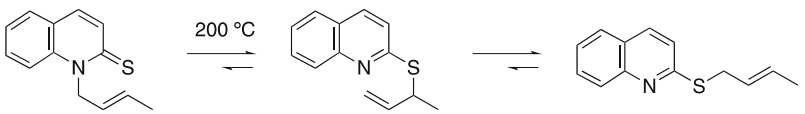
tivation was negative ($\Delta S^{\ddagger} = -7.7 \pm 0.8$). Consequently, the authors favor a pseudopericyclic-sigmatropic rearrangement (*vide infra*), as depicted in **71**, to explain the degeneracy. A transition state such as **72** could not be ruled out, however.

2.4 Thermolysis

Makisumi and Sasatani observed another 1,3-rearrangement while exploring the thia-Claisen rearrangement. In their experiment, thermolysis of compound **73** afforded the expected thia-Claisen product **74** and the 1,3-rearrangement product **75** (Scheme 11) [25]. As the reaction progressed, the appearance of compound **74** coincided with the disappearance of **73**, while **75** accumulated slowly once **74** had formed. That sulfide **75** probably results from a thermodynamic equilibration was established by heating **74** at 200 °C for 90 min to provided **74** and **75** in 4 and 80% yields, respectively. Pyrolysis of **75** under the same conditions returned 95% of **75** with only small amount of **74**.

At about the same time as Makisumi and Sasatani reported their findings, Kwart and coworkers, also investigating the thia-Claisen rearrangement, observed that crotyl aryl sulfides such as **76** rearranged to give α-methylallyl aryl sulfides (i.e., **77**) prior to giving thiacoumaran products (Eq. 6) [26].

Intrigued, they initiated a series of mechanistic investigations into the thermal behaviour of allyl sulfides [27]. It was found that allylic sulfur shifts could be promoted either photochemically or thermally. For the thermal reactions, a series of NMR experiments provided kinetic data on the rearrangement of deuterated allyl phenyl sulfides **78** and **79** (Scheme 12) [28]. In nitrobenzene, the reaction rate was independent of the initial concentration of **78**, and a slightly negative entropy of activation was determined

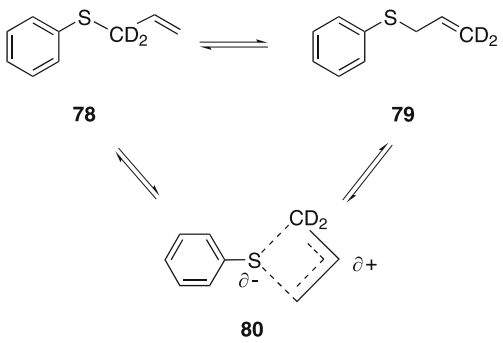


73 **74** **75**

Scheme 11 Thia-Claisen with subsequent 1,3-migration

76 **77**

Equation 6



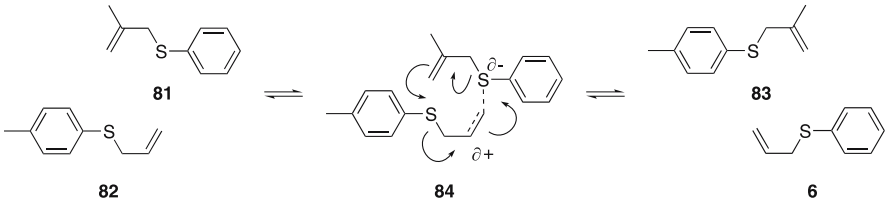
Scheme 12 Unimolecular dipolar mechanism

($\Delta S^{\ddagger} = -1.1 \pm 1.2$). In less polar solvents (e.g., decaline), however, a direct dependence on initial concentration was observed even though the apparent first-order plot was linear, and the entropy of activation was much more negative ($\Delta S^{\ddagger} = -23.2 \pm 1.8$). Because of these differences in activation parameters and the concentration dependence in polar vs. non-polar solvents, two mechanisms, unimolecular and bimolecular, were postulated.

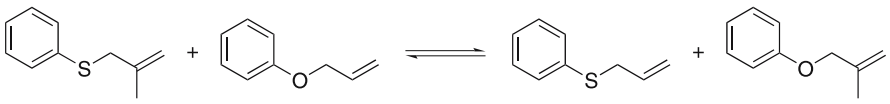
For the unimolecular mechanism, the activation parameters and solvent effects were interpreted as disfavoring either a non-polar sigmatropic rearrangement mechanism (which normally has a more negative $\Delta S^{\ddagger}$ and is insensitive to solvent polarity) or a dissociation mechanism (i.e., initial ionization of the C – S bond). A radical mechanism was considered unlikely in these thermal rearrangements because no radical recombination products (e.g., disulfide) were observed. Instead, Kwart proposed a dipolar mechanism involving a transition state complex such as **80**.

The bimolecular reaction was probed using several crossover experiments. For example, a mixture of **81** and **82** were heated to provide crossed products **6** and **83** (Scheme 13). A transition state complex such as **84** was invoked.

In both complex **80** and **84**, sulfur has an expanded valence. The ability of sulfur to expand its valence appears to be what distinguishes the thermal reactivity of allyl aryl sulfides from allyl aryl ethers. A deuterated sample of allyl phenyl ether, for example, does not undergo a 1,3-oxygen shift when heated (neat) to 160 °C. At 195 °C, the expected Claisen rearrangement is ob-



Scheme 13 Cross-over products and bimolecular mechanism



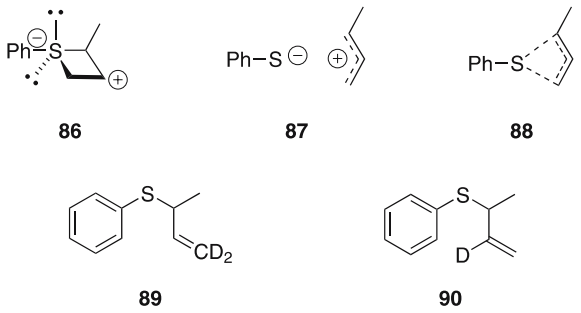
81 6 85

Equation 7

served [27]. In the presence of **81**, however, crossed products **85** and **6** are observed at 160 °C (Eq. 7) [28].

Substitution effects also support a charge separated transition state for the rate-determining step [27]. Several *p*-substituted derivatives of **78** were examined, and the *p*-nitro analogue was determined to have an enthalpy of activation nearly 5 kcal mol^{-1} lower than the *p*-methoxy compound. Also, β-methyl allyl phenyl sulfide (**81**) had an enthalpy of activation approximately 4.5 kcal mol^{-1} lower than α-methyl allyl phenyl sulfide (**77**), which is consistent with the build up of cationic character on the β-allylic carbon.

Further evidence for a dipolar (associative) transition state, such as **86**, as opposed to either a dissociative (ionic, **87**) or non-polar concerted (1,3-sigmatropic, **88**) mechanism, was presented in the form of sulfur kinetic isotope effects (Fig. 2) [29]. Theoretical isotope effects (k_{32}/k_{34}) corresponding to these three transition states were calculated: **86** = 1.004; **87** = 1.012; **88** = 1.008. High-precision measurements determined a $k_{32}/k_{34} = 1.004 \pm 0.0016$, in agreement with the associative transition state wherein the sulfur center incurs an increase in bonding. In addition, inverse secondary deuterium isotope effects were observed for both **89** ($k_H/k_D = 0.936$) and **90** ($k_H/k_D = 0.918$) [30]. These results, in conjunction with the other kinetic data given above, were interpreted to support a transition structure such as **86**. A radical addition–elimination mechanism was specifically discounted as other reports suggest that **90** should not show an isotope effect if radical addition to the terminus of the double bond were rate determining [31].



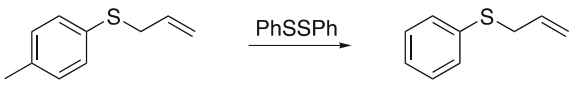
86 87 88

89 90

Fig. 2 Limiting transition states and deuterated derivatives for kinetic isotope effect studies

Several attempts of this reaction involving alkyl allyl sulfides failed to produce allylic rearrangement products, and the geometry of **86** is used to explain the dependence of the allylic rearrangement on the aryl sulfur group [27]. In a hypervalent sulfur complex with trigonal bipyramidal geometry as shown in **86**, the two colinear apical bonds (i.e., Ph – S – C) can be described as a single three-center-four-electron bond. As such, the electronegativity of the aryl group increases the electron affinity of the sulfur and lowers the energy of the hypervalent complex, while alkyl groups would not have the same stabilizing effect. In order for an allylic shift product to be observed, the apical and equatorial ligands must interchange prior to scission of the apical bond in the hypervalent complex. This pseudorotation event is postulated to be the rate-determining step of the rearrangement and is consistent with the mechanistic observations.

Singlet oxygen was found to catalyze the rearrangement without producing oxidation products, while $^3O_2$ was found to be an even more potent catalyst. Presumably, the oxygen binds to the sulfur and facilitates the formation of the hypervalent sulfur complex [32]. Diaryl disulfides also accelerated the rate of the reaction, and reactions in which the aryl group in the disulfide was not the same as in the allyl sulfide produced cross products (e.g., **82** → **6**; Eq. 8) [33]. The origin of the rate acceleration is explained by a reduced barrier to pseudorotation in the corresponding hypervalent complex.



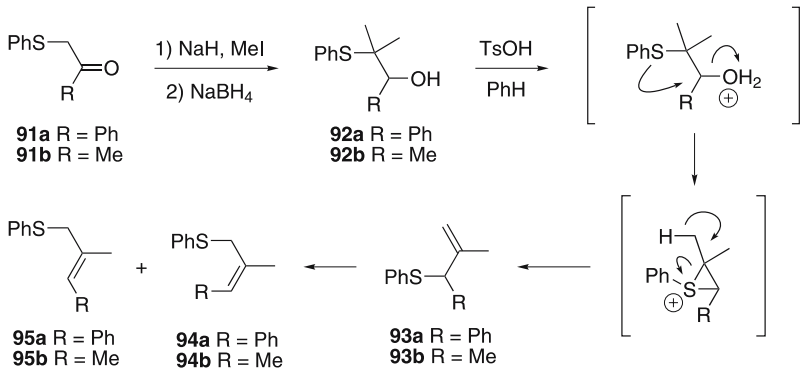
82 **6**

Equation 8

2.5 Application and Further Mechanistic Studies

Warren and coworkers have exploited the 1,3-sulfanyl shift to build complex allyl sulfides as synthons for further synthesis [34, 35]. Alkylation of phenylsulfanyl ketones **91** followed by reduction of the carbonyl group afforded sulfanyl alcohols **92** (Scheme 14) [36]. Heating **92** with an acid catalyst produced allyl sulfide **93** via the loss of water with a concomitant 1,2-sulfur migration. A subsequent 1,3-shift promoted by heat, light, or acid catalysis formed mixtures of **94a/95a** or **94b/95b**. The initial 1,2-shift is rapid compared to the subsequent 1,3-rearrangement; consequently, sulfides **93** can be isolated if light is excluded while running the 1,2-rearrangement reaction.

The rearrangement of **93a** occurred under several sets of conditions. By simply conducting the experiment in daylight, for example, **94a** and **95a** were formed in 34 and 66% yield, respectively. Heating **93a** to 100 °C without sol-



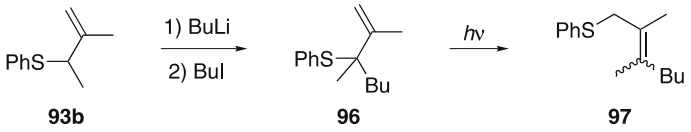
Scheme 14 Sequential 1,2- and 1,3-sulfur migrations

vent provided similar results. When the reaction was catalyzed by TsOH in benzene at reflux, however, only **95a** was observed. Interestingly, **93b** behaved similarly under both thermal and photochemical conditions, equilibrating to a mixture of **93b**, **94b** and **95b** in 5, 35 and 60% yield, respectively, whereas acid catalysis caused no rearrangement. Rather, vinyl sulfides that result from olefin migration were observed under acidic conditions.

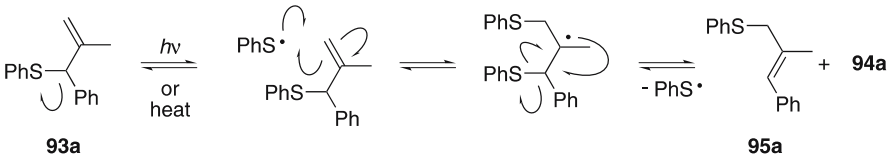
The intermediate allyl sulfides could be alkylated prior to rearrangement. The reaction of **93b** with BuLi followed by alkylation with butyl iodide, for example, provided **96** (Scheme 15). Exposure of **96** to light promoted the sulfur migration to give **97** as a mixture (4 : 1) of isomers (*E* : *Z*).

The observed product distributions of these reactions under each of the three distinct reaction conditions prompted Warren to discard Kwart's dipolar mechanism to explain these reactions [37]. In particular, the observation that the thermal rearrangement, run in the dark, occurs only at 100–110 °C and without solvent suggests that these reactions behave differently from those in Kwart's reports. That the thermal and photochemical rearrangements of **93a** give the same mixture of *E*- and *Z*-isomers (i.e., **94a** and **95a**) while the acid-catalyzed rearrangement provides a single isomer, **95a**, suggests two distinct pathways for the transformations.

The photochemical rearrangement was determined to be faster when the reaction was exposed to direct sunlight or radiation at 254 nm than when the light is diffused through the laboratory window and a Pyrex flask. The rates of the reactions were similar when the experiment was conducted either



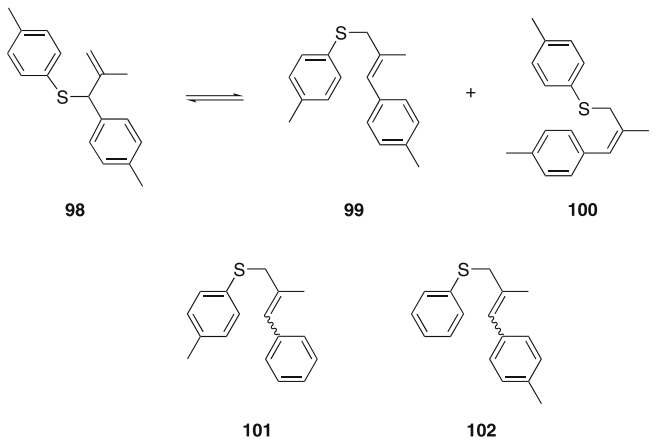
Scheme 15 Elaboration of allyl sulfide



Scheme 16 Radical chain-reaction mechanism for migration

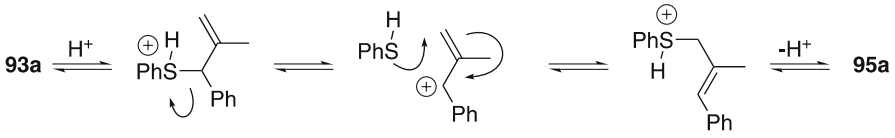
neat or in solvents that possessed a range of polarities. Accordingly, a photochemically initiated radical chain reaction, similar to that observed for the isomerization of **3** (cf. Scheme 1), was proposed (Scheme 16).

The reaction of **98** to give **99** and **100** was compared to the reactivity of **93a** to test this radical mechanism (Eq. 9). For example, thermally induced crossover experiments involving **93a** and **98** showed a statistically equilibrated mixture (1 : 1 : 2) of **94a/95a**, **99/100**, and cross products **101/102**. This result was interpreted to be consistent with a radical chain-reaction, but not a dipolar mechanism. Addition of thiophenol, under conditions known to produce phenythiyl radical, was also shown to catalyze the reaction of **93a** to give **94a** and **95a** in the same ratio as the thermal or photochemical rearrangements while a control sample did not rearrange.



Equation 9

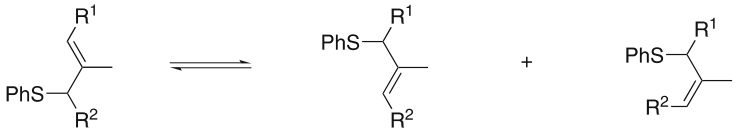
Under acid-catalyzed conditions, **98** rearranged at a faster rate than did **93a**. Crossover experiments involving **98** and **93a** conducted under acid-catalyzed conditions did not give the same product distribution as the photochemical or thermal reactions. Rather, a mixture (1 : 2 : 2) of **95a**, **99**, and **101/102** was observed. These observations were explained by invoking a heterolytic mechanism (Scheme 17). The intermediate allyl cation derived from **98**, for example, is more stable and consequently forms faster than the cation



Scheme 17 Ionic mechanism for acid-catalyzed migration

derived from **93a**. Accordingly, the differing rates should shift the product distribution. A solvent effect was also noted; the rearrangement in acetonitrile proceeded more rapidly than in benzene. The intermediacy of an allyl aryl cation is consistent with the observed selectivity for the *E*-isomers, such as **95a** and **99**, in that the planar intermediate is more sensitive to steric influences. This acid-catalyzed ionization mechanism is also consistent with the production of vinyl sulfides for alkyl substituted aryl sulfides, such **93b**, because the intermediate carbocation is more difficult to form than with aryl substituents.

These reactions, regardless of which conditions are employed, are equilibrium reactions, and the final product distribution depends upon the substitution pattern of the allyl sulfides involved. As mentioned above, the product mixture of **93b** contained 5% starting material in both the photochemically and thermally induced equilibration. In addition, allyl sulfide **103a** does not rearrange, and **103b** equilibrated to a give **103b**, **104b**, and **105b** in 7, 70, and 23% yields respectively under photolytic conditions (Eq. 10). Reactions involving **93a**, **93b**, **98**, and **103b** all produce a more highly substituted olefin, and both **93a** and **98** produce double bonds in conjugation with an aryl group. Where there is no clear enthalpic driving force, as in **103a**, the reaction appears to fail.



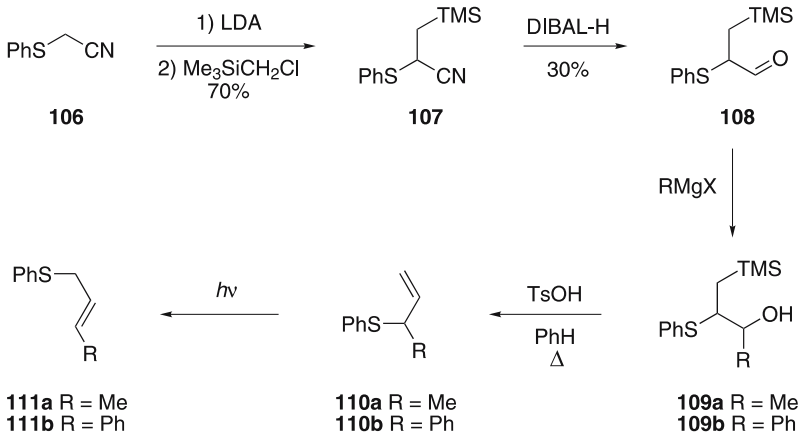
103a R^1 = ^{i}Bu, R^2 = Me
103b R^1 = H, R^2 = iso-C_5H_{11}

104a R^1 = ^{i}Bu, R^2 = Me
104b R^1 = H, R^2 = iso-C_5H_{11}

105a R^1 = ^{i}Bu, R^2 = Me
105b R^1 = H, R^2 = iso-C_5H_{11}

Equation 10

The synthesis of the 1,3-migration substrates as depicted in Scheme 14 was limited in the kinds of allyl sulfides that could be constructed. Warren later reported synthetic methods that expanded the kinds of allyl sulfides that could be formed [38]. The anion of cyano sulfide **106** could be alkylated with chlorotrimethylsilylmethane to provide **107** in 70% yield (Scheme 18). Reduction of the nitrile in **107** with DIBAL-H afforded sulfanyl aldehyde **108** in 30% yield. Addition of either methyl or phenyl Grignard reagent to the aldehyde

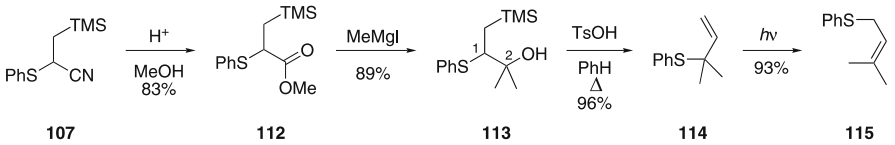


Scheme 18 Synthesis of 1,2-disubstituted alkenes

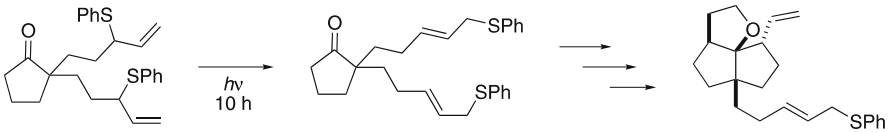
in **108** produced the requisite alcohols **109a,b** in 94 and 96% yield, respectively. As opposed to alcohols **92a,b** (cf. Scheme 14) that have tertiary sulfanyl groups, these alcohols contain secondary sulfanyl groups. Exposure of **109a,b** to catalytic amounts of acid in benzene at reflux promoted the 1,2-sulfur shift to give **110a,b** in 93 and 99% yields, respectively. Irradiation of **110a,b** caused the 1,3-sulfur shift to produce 1,2-disubstituted alkenes **111a,b** in 98 and 80% yields, respectively.

Alternatively, nitrile **107** could be hydrolized in acidic methanol to provide sulfanyl ester **112** in 83% yield (Scheme 19). Addition of excess methyl Grignard reagent furnished tertiary alcohol **113** in 89% yield. This alcohol also contains a secondary sulfanyl group. An acid-mediated 1,2-shift provided allyl sulfide **114** in 96% yield. Photochemical rearrangement of **114** provided 1,1,2-trisubstituted alkene **115** in 93% yield.

The acid-catalyzed 1,2-rearrangement of substrates wherein the sulfur group shifts from a secondary carbon center, such as C(1) in **113**, to either another secondary center or tertiary center, such as C(2), failed in substrates lacking the β-silyl group. The ability of silicon to stabilize the positive charge that builds up on C(1) during the course of the reaction provides a driving force of the sulfur shift, and the ease with which the trimethylsilyl group is removed facilitates formation of the alkene. The expansion of the 1,2-sulfur



Scheme 19 Synthesis of 1,1,2-trisubstituted alkene



116 117 118

Scheme 20 1,3-sulfanyl shift in the synthesis of diquinanes

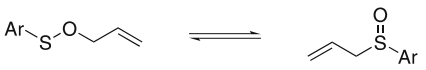
migration methodology to include a wider variety of substrate types further extends the utility of the 1,3-shift by providing access to a larger array of allyl sulfide structures.

Paquette has incorporated the photochemical 1,3-shift in a synthetic route toward the construction of functionalized diquinanes, such as **118** (Scheme 20). Irradiation of bis-sulfide **116**, using a sunlamp, for 10 h produced **117** in 70% yield [39].

With exception of the photochemically induced ring contraction of **66** to **67** (cf. Eq. 4), allylic sulfide migrations seem to be general and are thermodynamically controlled. Though there does not appear to be a single mechanism that accounts for the reactivity of various allyl sulfides, 1,3-sulfanyl shifts can be strategically employed to selectively construct substituted alkenes. The sulfide group can be leveraged for further transformations, thus extending the utility of the rearrangement reaction.

3
Allyl Sulfoxide Rearrangements

The rearrangement of allyl sulfoxides is more rare than that of the corresponding sulfides or sulfones. This is presumably due to the more facile 2,3-sigmatropic rearrangement that interconverts sulfenate esters (i.e., **119**) and sulfoxides (i.e., **120**; Eq. 11).



119 120

Equation 11

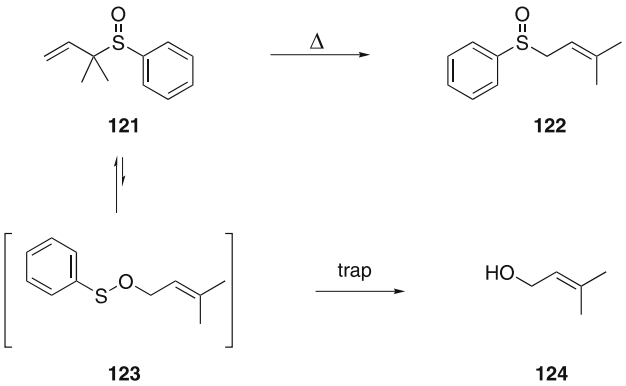
3.1
Acyclic Sulfoxides

In the context of developing new methods for the synthesis of allylic alcohols, Evans observed that heating **121** to 40 °C resulted in a clean rearrangement to the more thermodynamically stabile **122** (Scheme 20) [1]. It is interesting

to note that a deuterated sample of allyl tolyl sulfoxide showed no evidence of 1,3-rearrangement after heating at 70 °C in chlorobenzene for 45 minutes [40]. By heating **121** in the presence of a sulfenate ester trapping agent, however, the sulfenate product of the more rapid [2,3]-sigmatropic rearrangement reaction, **123**, could be converted into allyl alcohol **124**.

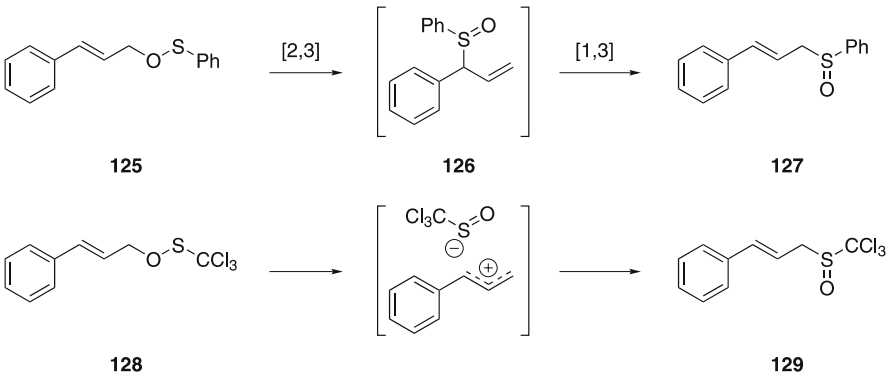
Baechler noted that cinnamyl phenylsulfenate, **125**, was slowly converted into cinnamyl phenyl sulfoxide, **127**, when allowed to stand at room temperature for several hours (Scheme 22) [41]. Although sulfoxide **126** was not observed, a 2,3-sigmatropic rearrangement followed by a 1,3-sulfoxide shift, analogous to that observed by Evans, was proposed.

Braverman has studied similar systems, and his observations support an ionization mechanism for sulfenates with increased nucleofugicity, rather than a 2,3-sigmatropic rearrangement followed by a sulfoxide shift. For example, cinnamyl trichloromethanesulfenate, **128**, rearranges to cinnamyl trichlorosulfoxide, **129**, slowly at 80 °C [42, 43].



121 122 123 124

Scheme 21 1,3-Sulfoxide shift and alternate[2,3]-shift



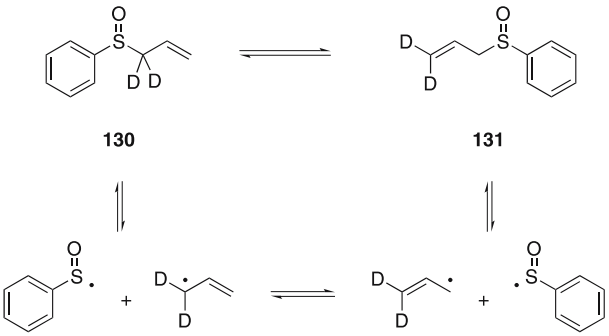
125 126 127 128 129

Scheme 22 Sequential [2,3]- and [1,3]-shift and an alternate ionization mechanism

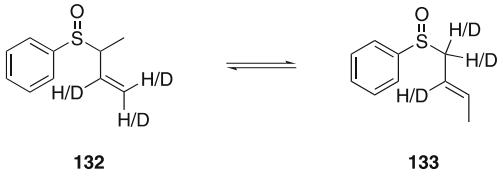
Both Kwart and Baechler have studied the mechanism by which allylic sulfoxides are interconverted. In the equilibration of **130** and **131**, Baechler and coworkers found a first-order rate with a positive entropy of activation ($\Delta S^{\ddagger} = +12.4 \pm 3.2$) in nitrobenzene (Scheme 23) [44]. In the less-polar solvent toluene, the rate was still first order and activation parameters were identical within the limits of error. By comparison, Kwart determined a first-order rate and a negative entropy of activation ($\Delta S^{\ddagger} = -13.3 \pm 2.3$) for a β-methylallyl phenyl sulfide derivative (i.e., **81**, Scheme 13) in nitrobenzene, but competition between first and second-order rates for rearrangements in nonpolar solvents [27]. Sulfoxide **130** isomerized nearly ten times faster than the corresponding sulfide **81**.

Based upon these observations, a homolytic dissociation–recombination process involving allyl and arylsulfinyl radicals, as shown in Scheme 23, was proposed. This mechanism accounts for the insensitivity of the reaction to solvent polarity, the rate acceleration for α-methylallyl substituted substrates (i.e., **121**, 40 °C) when compared with unsubstituted sulfoxides (i.e., **130**, 110 °C), and the positive entropy of activation.

Kinetic isotope effects reported by Kwart also suggest a different mechanism for the 1,3-sulfoxide shift than for the corresponding sulfide shift (*vide supra*) [45]. Using high-resolution mass spectroscopic methods for the determination of the sulfur isotope effect, a k_{32}/k_{34} of 1.0191 ± 0.0021 was determined for the interconversion of **132** and **133** (Eq. 12). A k_{32}/k_{34} value of



Scheme 23 Sulfoxide rearrangement and proposed mechanism



132 133

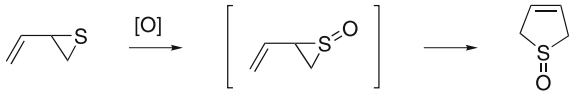
Equation 12

1.0194 was calculated for a dissociative mechanism. Additionally, secondary deuterium isotope effects for samples of **132** containing deuterium at either the β- or γ-positions showed normal isotope effects ($k_H/k_D = 1.0027 \pm 0.0017$ and 1.0285 ± 0.0021 per D, respectively). This is in contrast to the inverse isotope effects found for the corresponding sulfides (cf. Fig. 2). Rather than Baechler's proposal of a radical dissociation, however, Kwart favored a dipolar or tetrapolar transition state for the equilibration.

3.2 Cyclic Sulfoxides

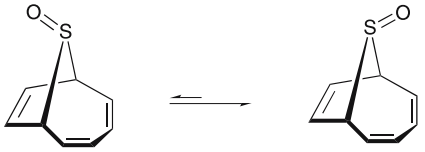
Lautenschlaeger observed a very facile 1,3-sulfoxide shift when thiirane **134** was exposed to hydrogen peroxide at room temperature. Dihydrothiophene oxide **136** was the only isolable product (25% yield; Scheme 24) [12]. Lemal and coworkers carried out the same reaction using peroxytrifluoroacetic acid and observed that the presumed intermediate **135** is short-lived, even at temperatures below – 65 °C [46].

Anastassiou reported mechanistic studies on the apparent inversion of the sulfoxide moiety in 9-thiabicyclo[4.2.1]nona-2,4,7-triene derivatives. For example, heating **137** above 100 °C in benzene produces a mixture (1 : 9) of **137** and **138** (Eq. 13). The activation energy for the processes ($\Delta G^{\ddagger} = 29.5\,\text{kcal mol}^{-1}$) is considerably less than has been ascribed to a simple inversion ($\Delta G^{\ddagger} = 42\,\text{kcal mol}^{-1}$) [47]. The entropy of activation was small and negative ($\Delta S^{\ddagger} = -4$), contrary to that expected for a dissociative process. Heating a sample of **137** in which the bridgehead hydrogens were replaced by deuterium produced mixtures of **137** and **138** wherein the deuterium distribution suggests a series of 1,3-sulfoxide shifts. The authors concluded that



134 135 136

Scheme 24 Rearrangement of vinylthiirane upon oxidation



137 138

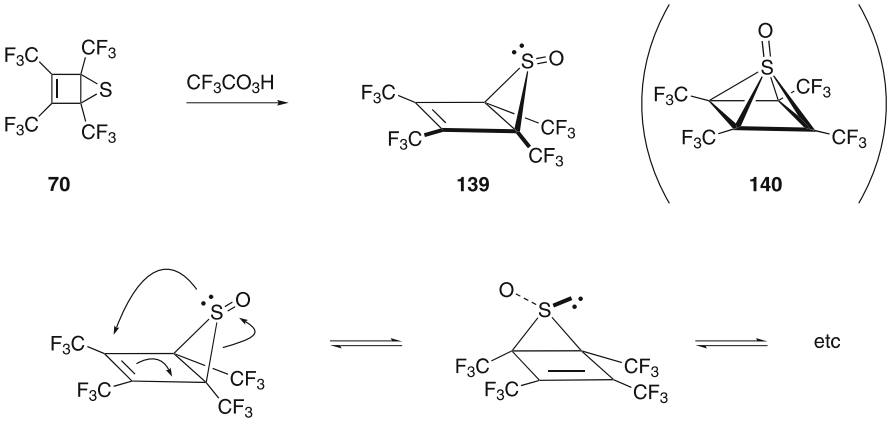
Equation 13

the evidence is consistent with a symmetry forbidden suprafacial–suprafacial 1,3-sigmatropic process.

Lemal and coworkers have examined the unusual behavior of Dewar thiophene derivative **70** upon oxidation with peroxytrifluoroacetic acid (Scheme 25) [46]. The resulting compound had a composition consistent with **139**. The ^{19}F NMR spectrum, however, contains only a single line at temperatures as low as – 95 °C, suggesting a structure such as **140**. Below – 100 °C, the signal evolves into two resonances of equal area. The enthalpy of activation for this exchange of CF_3 groups at – 124 °C was determined to be much lower than for **70** ($\Delta H^{\ddagger} = 6.6 \pm 0.2$ kcal mol^{-1}; cf. Fig. 1), though the entropy of activation was still negative ($\Delta S^{\ddagger} = -0.5 \pm 0.6$) [24].

The *exo*-orientation of the sulfoxide group in **139** was established by examining the products from a series of Diels–Alder reactions in which only products from an *exo*-sulfoxide were observed [46]. Both this observation, and the presence of only one resonance in NMR spectrum of the rapidly equilibrating system indicate that the 1,3-sulfoxide shift must occur with inversion of the sulfur stereocenter so that each rearrangement product contains an *exo*-oxide. This stereochemical outcome stands in contrast with that observed by Anastassiou (e.g., Eq. 13), indicating a different mechanism of interconversion. Since no *endo*-derived products were observed and the entropy of activation was negative, a "pseudopericyclic" mechanism was proposed to account for the degeneracy of the CF_3 groups. The authors propose that "a pseudopericyclic reaction is a concerted transformation whose primary changes in bonding compass a cyclic array of atoms, at one (or more) of which nonbonding and bonding atomic orbitals interchange roles" [46].

Specifically, the lone pair of the sulfur atom become bonding electrons, as shown in Scheme 25, and a pair of C – S bonding electrons are converted into



Scheme 25 Rapid exchange of CF_3 groups via pseudopericyclic process

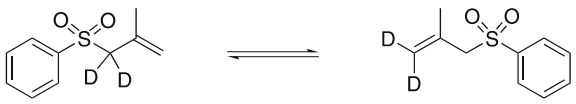
a nonbonding pair. This results in an inversion of the sulfur center, accounting for the *exo*-oriented oxide in each of the rearranged products. Snyder and Halgren, however, conducted theoretical studies of the pseudopericyclic concept using similar structures and found no evidence to support lone-pair participation [48]. Kwart's experience with the mechanisms of both sulfide and sulfoxide allylic rearrangements favors the structure **140**, containing a hypervalent sulfur for equilibration [30]. In particular, the significantly lower energy of activation for **139** ($\Delta G^{\ddagger} = 6.7 \pm 0.1$ kcal mol^{-1}) compared with that for **70** ($\Delta G^{\ddagger} = 22.1 \pm 0.1$ kcal mol^{-1}) can easily be rationalized by the electron withdrawing oxygen lowering the barrier to pseudorotation in the hypervalent complex (*vide supra*).

Overall, the 1,3-sulfoxide shift, like the corresponding sulfide shift, appears to be thermodynamically controlled, and there is not a single mechanism through which the rearrangement occurs. Although the sulfoxide shift appears to be more facile than the sulfide migration, this transformation has not been exploited for synthesis.

4
Allyl Sulfone Rearrangements

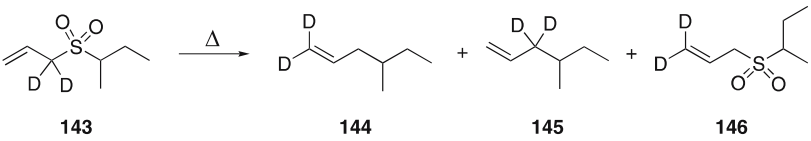
The rearrangement of allyl sulfones is much more common than the rearrangement of either sulfides or sulfoxides. While the 1,3-rearrangement of allyl sulfides has been used to synthesize allyl sulfides of higher complexity, the rearrangement of allylic sulfones has found relatively more synthetic application. As with the other 1,3-rearrangements, the mechanism by which the sulfur group migrates depends upon the nature of the substrate and the conditions under which the substrate rearranges.

Sulfones migrate relatively slowly under thermal conditions. Baechler's comparison of 1,3-allylic sulfur shifts demonstrated that under thermal conditions, sulfoxides isomerize nearly 200 times faster than sulfones, and sulfides rearrange nearly 20 times faster [44]. The kinetic data for the sulfone shift showed a marked increase in rate when **141** was heated in toluene at 150 °C compared with the reaction in nitrobenzene (Eq. 14). Furthermore, data collected at lower temperatures (130 and 140 °C) showed pronounced deviations from first-order linearity.



141 **142**

Equation 14

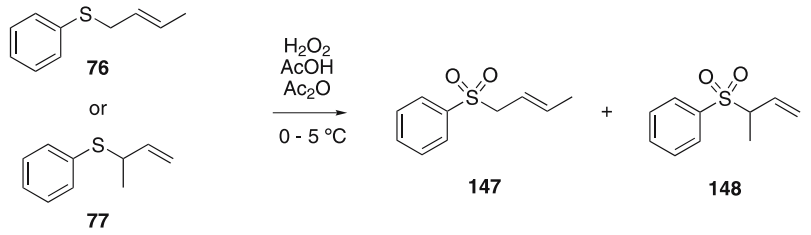


Equation 15

In the gas phase, some isomerization of sulfones has been observed, but the primary products result from extrusion of SO_2. Pyrolysis of **143** at 562 °C produced a mixture (1 : 1) of **144** and **145** (Eq. 15) [49]. At 278 °C, a 4.2 : 1 mixture was obtained. Interconversion of **144** and **145** was not observed in control experiments, and when the reaction was stopped early, small amounts (< 30%) of **146** were observed. Crossover experiments wherein a mixture of **143** and allyl isopropyl sulfone was heated to 178 °C showed some allyl *s*-butyl sulfone, though it was present in less than 3% of the mixture. Taken together, these data indicate that the mechanism is complex, but at least some of the isomerization may involve homolytic dissociation.

4.1 Oxidative/Radical Conditions

Cope reported that both **76** and **77** independently gave the same mixture (9 : 1) of compounds **147** and **148** upon oxidization (Eq. 16) [50]. Several plausible mechanisms were proposed for the isomerization of the two sulfones, but it was unclear whether or not the sulfones themselves were rapidly equilibrating under the reaction conditions. Mislow later observed, however, that sulfone **148** rearranged to give a mixture (60 : 40) of **147** and **148** upon standing (neat) for 9 days [40]. After 12 days, the mixture contained 78% **147** and 22% **148.**



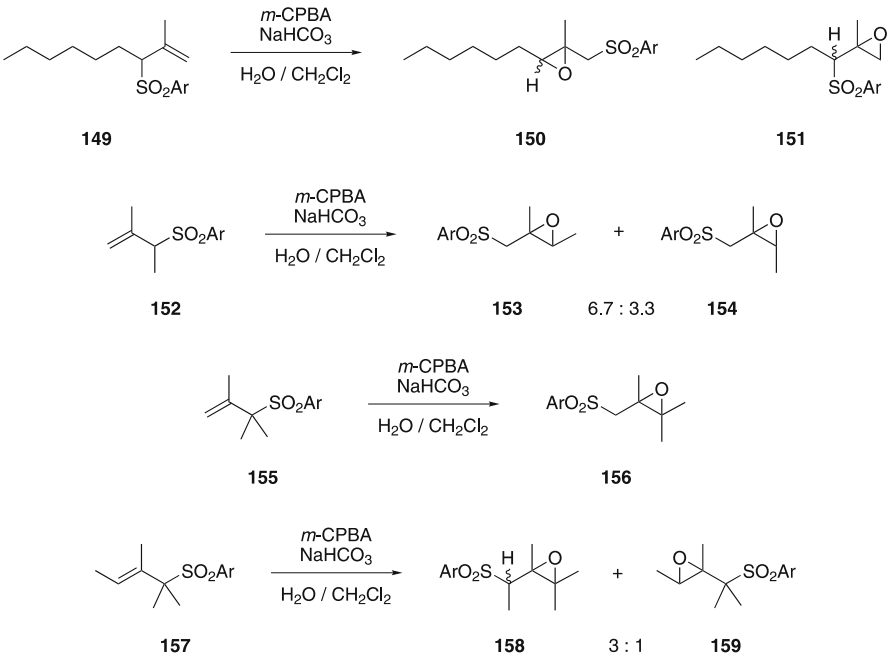
Equation 16

While examining the reductive elimination of epoxysulfones to produce allylic alcohols, Kocienski also observed a rearrangement upon oxidation of a series of allyl sulfones. Exposure of **149** to *m*-CPBA and $NaHCO_3$ in aqueous CH_2Cl_2 produced **150** in 74% yield, rather than the expected **151**

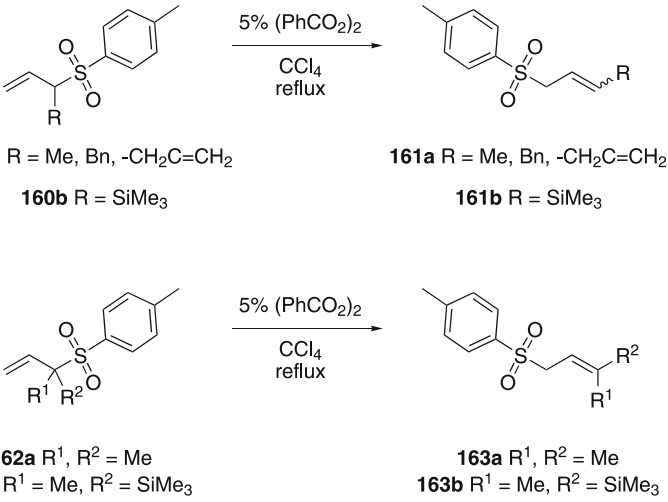
(Scheme 26) [51, 52]. Control experiments confirmed that *m*-CPBA was not acting as a catalyst for the 1,3-rearrangement *per se*, but that $NaHCO_3$ was also required; exposure of **149** to *m*-CPBA in CH_2Cl_2 produced **151**. The rearranged products were also formed in the dark if both *m*-CPBA and $NaHCO_3$ were present.

The rearrangement was found to be general but dependant upon the sulfone migrating from a more substituted carbon to a less substituted carbon. For example, **152** (a secondary sulfone) produced a mixture (6.7 : 3.3) of stereoisomers **153** and **154** (both primary sulfones) in 55% yield under aqueous $NaHCO_3$ conditions. Tertiary sulfone **155** produced rearranged **156** as the sole product in 85% yield. Rearrangement from a tertiary sulfone to a secondary sulfone was less efficient; sulfone **157** produced a mixture (3 : 1) of **158** and **159** in 90% yield. No rearrangements from less substituted sulfones to more substituted sulfones were observed, though the stereoselectivity with respect to the epoxide functionality (i.e., **153** vs. **154**) demonstrated that the starting alkene is at least partially isomerized. This combination of the experiments suggests a radical chain mechanism for the rearrangement, and addition of a radical inhibitor suppresses both the rearrangement and the alkene isomerization.

Following Kocienski's publication, Whitham reported that the 1,3-rearrangement of acyclic allylic sulfones could be promoted with catalytic



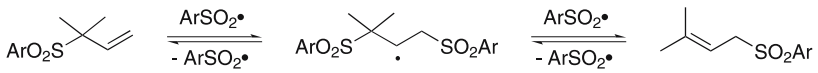
Scheme 26 Sulfone rearrangement upon oxidizing conditions



Scheme 27 Peroxide-catalyzed 1,3-sulfone shift

amounts of benzoyl peroxide [53]. Heating **160a** to reflux in CCl_4 with benzoyl peroxide (5 mol %) for 18 h produced a mixture (3 : 1) of isomeric **161a** in which the *E*-isomer predominated, whereas **160b** produced only the *E*-isomer **161b** under the same conditions (Scheme 27). Tertiary sulfones **162a,b** produced **163a,b**. As in Kocienski's work, the rearrangement favors generation of the more stable carbon–carbon double bond.

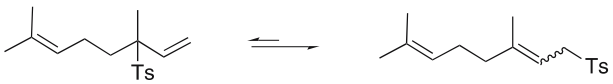
Whitham proposed a radical chain mechanism to explain the observed rearrangements, and analogy was drawn to the allylic reversal mechanism (cf. Scheme 1) [53]. Propagation of the chain reaction was postulated to involve addition of arenesulfonyl radical to the allyl sulfone (e.g., **164**) to form a disulfone radical such as **165** (Eq. 17). Elimination of sulfonyl radical could produce either the starting sulfone or the "rearranged" sulfone. Initiation of the chain could occur through either phenyl or benzoyloxyl radical.



Equation 17

Rearrangement of acyclic allyl sulfones such as **160a**, and **162a** could also be promoted by heating aqueous acetic acid solutions of these substrates to 100 °C with up to seven equivalents of sodium toluenesulfinate ($NaSO_2Tol$, NaTs) [53]. It was initially thought that a nucleophile-assisted ion-pair or an $S_{RN}1$ type mechanism was in effect, because these substrates fail to isomerize in the absence of NaTs.

At about this time, Julia examined the isomerization of **167** and **168** and found that the sulfur shift was promoted by sulfinic acids [54]. Heating **167** to 60 °C in THF for 3 h with either TsNa or H_2SO_4 produced a mixture (98 : 2) of **167** and **168** (Eq. 18). When heated in the presence of both TsNa and H_2SO_4, however, a mixture (13 : 87) in which **168** predominated was observed. As in Whitham's experiments, heating **167** with TsNa and NaOAc in acetic acid also effected the isomerization, though at higher temperatures (115 °C), to produce mixtures (3 : 97) containing predominantly **168**.

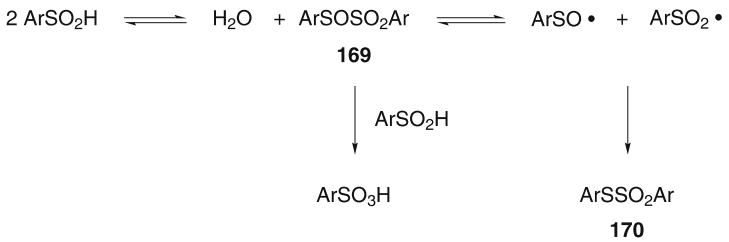


167 **168**

Equation 18

Considering the results in Julia's report along with further studies from his own group, Whitham discarded the ion-pair and $S_{RN}1$ mechanisms, and the data were interpreted as being more consistent with the radical chain mechanism outlined in Eq. 17 [55]. NaTs alone does not promote the rearrangement. In acetic acid, NaTs is only required in catalytic amounts, and in reactions involving catalytic NaTs, hydroquinone inhibited the reaction. To explain these observations, it was suggested that NaTs may be acting as a source of sulfinyl radical. Arenesulfinic acids are known to disproportionate to give thiolsulfonate (**170**) and sulfonic acid (Scheme 28). These thiolsulfonates are isolated as by-products in the NaTs promoted isomerization reactions. One of the steps of this disproportionation involves the formation and homolytic dissociation of arenesulfinyl aryl sulfone (**169**).

Alicyclic sulfones such as **171** were found to undergo radical initiated isomerization under either benzoyl peroxide or sulfinic acid conditions (Fig. 3) [55]. Sulfones such as **172**, however, did not. It was thought that, because the addition of the sulfonyl radical to the π-bond must be axial, an unfavorable diaxial sulfonyl–sulfonyl or sulfonyl–alkyl interaction must de-



Scheme 28 Disproportionation of arylsulfinic acid to produce radicals

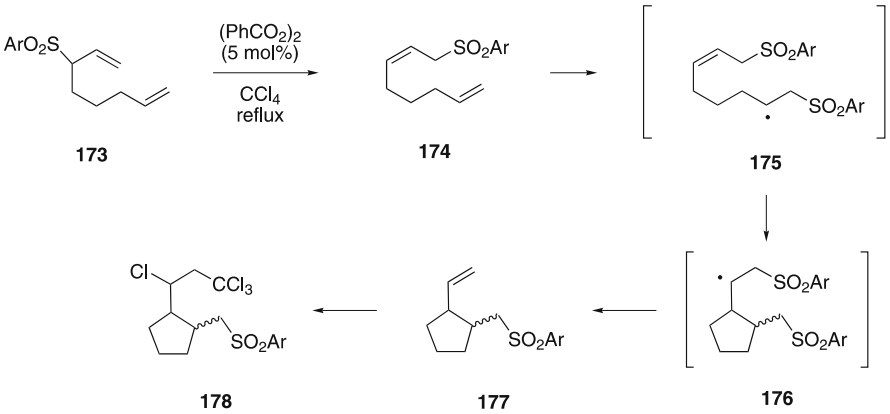
Fig. 3 Alicyclic sulfones

velop that inhibits the rearrangement in these systems. They were, however, isomerized when heated in aqueous acetic acid (*vide infra*).

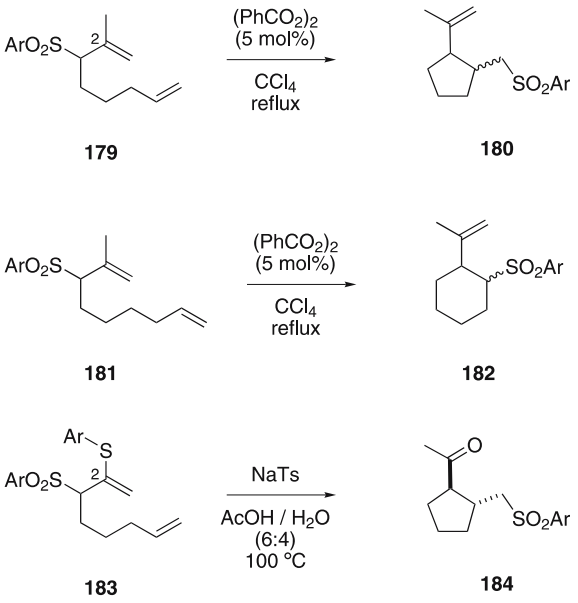
Since these reactions were believed to proceed via a radical chain mechanism, it was thought that the rearrangement could be linked with a radical cyclization to produce cyclic products that would be otherwise difficult to obtain. Thus, when sulfone **173** was heated to reflux in CCl_4 with catalytic amounts of benzoyl peroxide, sulfone **177** was isolated as a mixture (3 : 1) of diastereomers (Scheme 29) [56]. Upon prolonged reaction times, **178**, a known radical addition product from CCl_4, could be isolated [57]. Heating **173** with NaTs in aqueous acetic acid also produced **177**.

Several other examples were reported. The rates of cyclization increased when an alkyl group was introduced at C(2), as in **179** (Scheme 30) [57]. Six-membered rings could also be formed, as demonstrated by the conversion of **181** into a diastereomeric mixture (1 : 1) of **182** in 60% yield. Attempts to form an eight-membered ring were unsuccessful. The reaction of **183**, containing a sulfide substituent at C(2), with NaTs under aqueous acetic acid conditions produced ketone **184** exclusively as the *trans*-diastereomer. Quaternary centers formed easily at either cyclizing carbon. Quaternary centers adjacent to tertiary centers were also formed, though vicinal quaternary centers could not be formed under these radical cyclization conditions.

In another series of experiments, Whitham found that the 1,3-sulfone migration was unsuccessful in cases where the intermediate sulphonyl radical

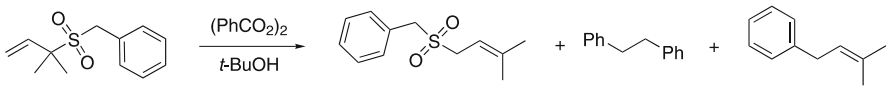


Scheme 29 Radical initiated tandem 1,3-shift-cyclization



Scheme 30 Tandem rearrangement-cyclization

could undergo decomposition by loss of SO_2 to give an alkyl stabilized radical [58]. Reaction of **185** with benzoyl peroxide in *t*-BuOH, for example, gave traces of 1,2-diphenylethane, 2-methyl-5-phenyl-2-pentene, and the expected rearrangement product **186** (Eq. 19).

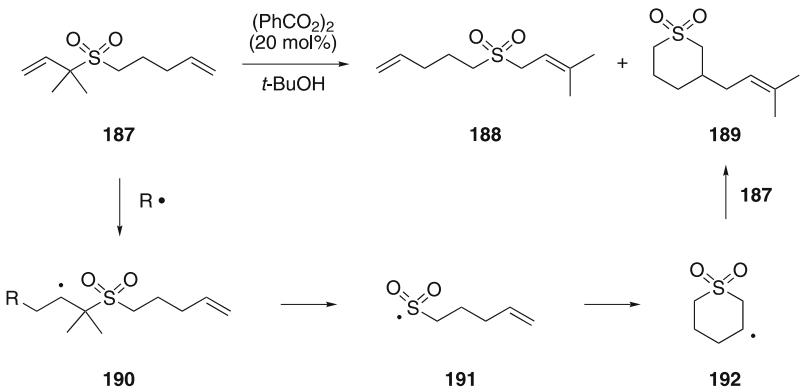


185 186

Equation 19

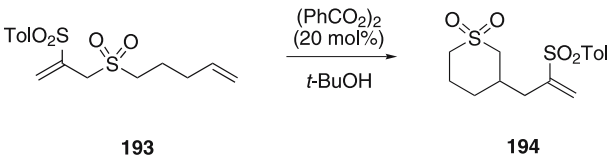
It was thought that the sulfonyl radical that propagates the chain reaction could be trapped by an internal alkene, leading to cyclic products (Scheme 31). Accordingly, when **187** was heated with benzoyl peroxide in *t*-BuOH, a mixture of starting **187** (23% yield), 1,3-rearrangement product **188** (8% yield) and cyclic sulfone **189** (14% yield) was isolated [58]. The radical chain propagation for formation of **189** is illustrated by fragmentation of intermediate **190** to produce sulfonyl radical **191**. Cyclization of **191** produces a new radical that can then react with **187** to complete the chain reaction.

Radicals such as **191** are known to be electrophilic, while those such as **192** are known to be nucleophilic. It was thought, therefore, that if an electron withdrawing substituent could be introduced in **187** such that it facilitates the



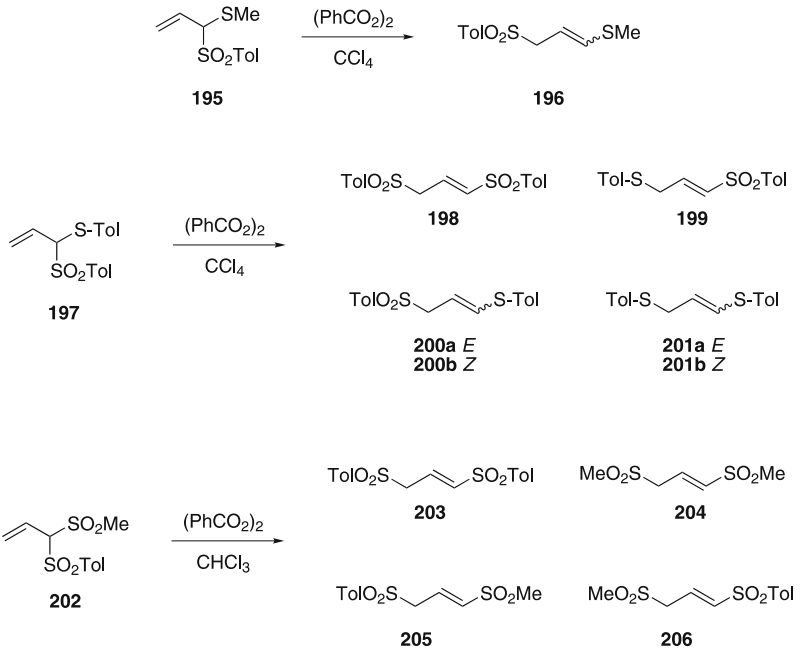
Scheme 31 Rearrangement accompanied by intermediate sulfonyl radical cyclization

addition of **192**, this pathway would become predominant. To test this hypothesis, disulfone **193** was prepared and subjected to the radical initiated rearrangement conditions (Eq. 20) [58]. Thus, heating **193** in the presence of benzoyl peroxide produced a mixture of starting **193** (25% yield) and cyclization product **194** (45% yield).



Equation 20

Baechler's comparison of the rates with which sulfides, sulfoxides, and sulfones isomerize showed that sulfones are particulary slow relative to sulfides under thermal conditions (*vide supra*). Whitham examined how systems that contain both sulfide and sulfone groups behave under radical initiated conditions [59]. When methylthio substituted sulfone **195** was heated with benzoyl peroxide, a mixture (2 : 1) of *E*- and *Z*-isomers of **196** was produced (Scheme 32). In this case, rearrangement occurs cleanly through migration of the sulfone moiety. Interestingly, when tolylthio substituted sulfone **197** was subjected to the same conditions, a mixture (4.9 : 1.9 : 7.1 : 6.3 : 1.7 : 1) of **198**–**201** was isolated. Obviously, the arylthio group migrates much more readily than the alkylthio group under radical initiated conditions. That **198** (bis-sulfone) and **201** (bis-sulfides) were isolated supports the radical chain mechanism. When bis-sulfone **202** was heated with benzoyl peroxide, a roughly equal mixture of the four possible bis-sulfones **203**–**206** were isolated. In all of these cases, vinyl sulfides were isolates as mixtures of *E*- and *Z*-isomers whereas vinyl sulfones were isolates as the *E*-isomers exclusively.

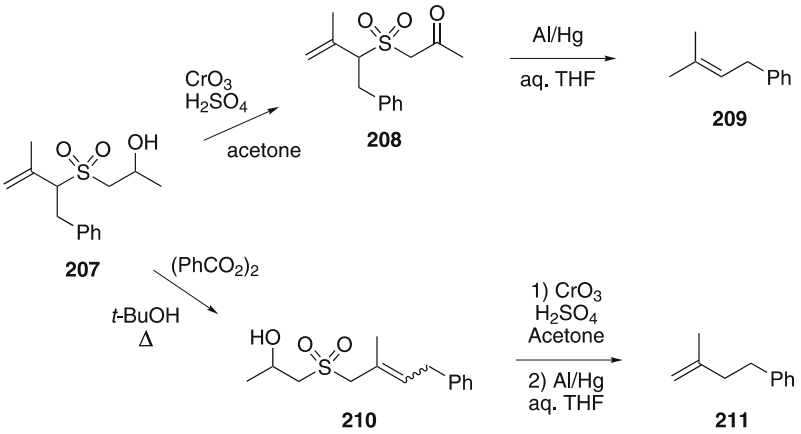


Scheme 32 Competition reactions involving alkylthio and arylthio sulfones

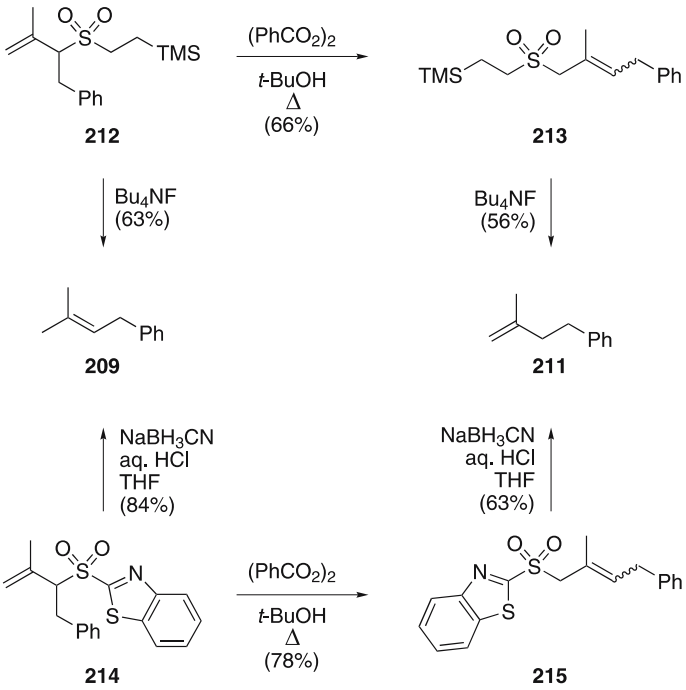
Following a report by Baldwin and co-workers [60], Whitham demonstrated the utility of the 1,3-sulfone migration to the regioselective synthesis of alkenes. Jones oxidation of sulfone **207**, for example, followed by treatment of the intermediate keto-sulfone with aluminum-amalgam produced **209** in 77% yield (Scheme 33) [61]. Alternatively, radical initiated isomerization of **207** produced isomeric sulfone **210** in 66% yield. Jones oxidation followed by exposure to aluminum-amalgam produced **211** in 82% yield from **210**.

In order to reduce the number of chemical manipulations in the sequence, other sulfonyl groups that could undergo both the 1,3-isomerization and desulfonylation were investigated. Reaction of sulfone **212**, for example, with Bu_4NF in THF produced **209** in 63% yield, while isomerization to sulfone **213** followed by exposure to Bu_4NF afforded **211** in 37% yield from **212** (Scheme 34) [61]. Alternatively, benzothiazol-2-yl sulfones were also found to undergo the 1,3-rearrangement and could be desulfonylated with $NaBH_3CN$ in acidic media. Thus, sulfone **214** was converted into **209** in 84% yield and **211** in 49% yield.

Several groups have reported photochemically induced 1,3-sulfone shifts. Ogura, for example, observed that an aqueous dioxane solution of **216** irradiated (254 nm) for short periods of time in the presence of $NaHCO_3$ produced a mixture (38 : 62) of **216** and **217** in 73% yield (Eq. 21) [62]. Treatment of this mixture with silica gel (*vide infra*) produced the thermodynamically con-



Scheme 33 Regioselective synthesis of alkenes



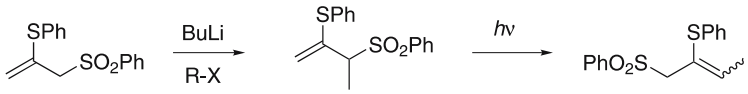
Scheme 34 Alternative sulfones for regioselective alkene synthesis

trolled equilibrium mixture (91 : 9) of **216** and **217**, and it is interesting to note that photolysis, in this case, affords predominantly the kinetic product. Again, the sulfone moiety migrates in preference to the methylthio group.

216 **217**

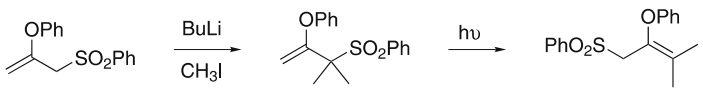
Equation 21

Padwa and coworkers demonstrated that the lithium salt of **218** could be alkylated to produce sulfone **219** (Eq. 22) [63]. It was observed that **219** isomerized to **220** upon heating at 80 °C, but the reaction failed when conducted in the dark. The reaction appears to be photochemically promoted, and even daylight, diffused through a window and the Pyrex reaction flask, promoted the reaction. Structurally similar enol **221** could also be metallated with BuLi and the resulting sulfonyl anion alkylated to afford **222** (Eq. 23). Irradiation of **222** resulted in a quantitative rearrangement to provide **223**.



218 **219** **220**

Equation 22

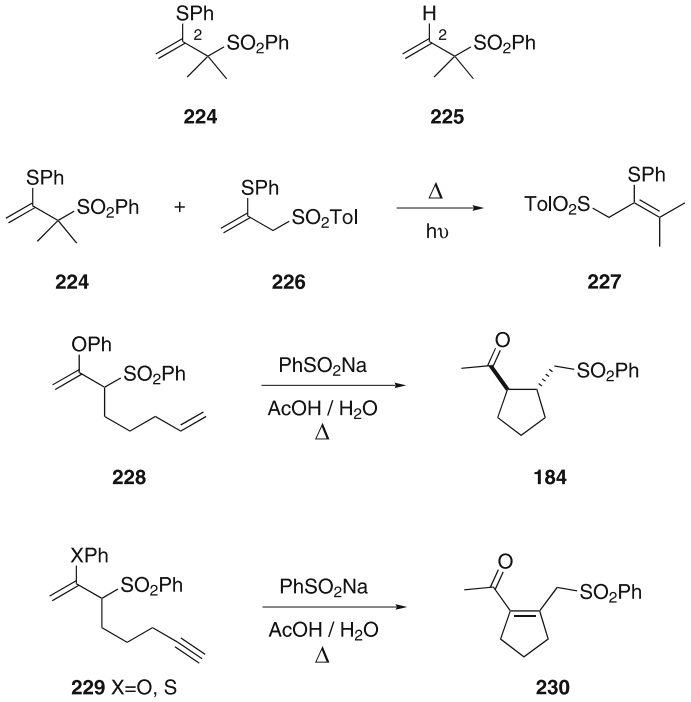


221 **222** **223**

Equation 23

The presence of a heteroatom on C(2) has a marked impact on the relative rates of isomerization. The rate of rearrangement for sulfone **224**, for example, is nearly two orders of magnitude faster than for **225** (Scheme 35) [64]. This is consistent with addition of an electrophilic sulfonyl radical to a π-bond in the rate determining step. Furthermore, heating a mixture of **224** and **226** together in benzene afforded a significant quantity of cross-over product **227**.

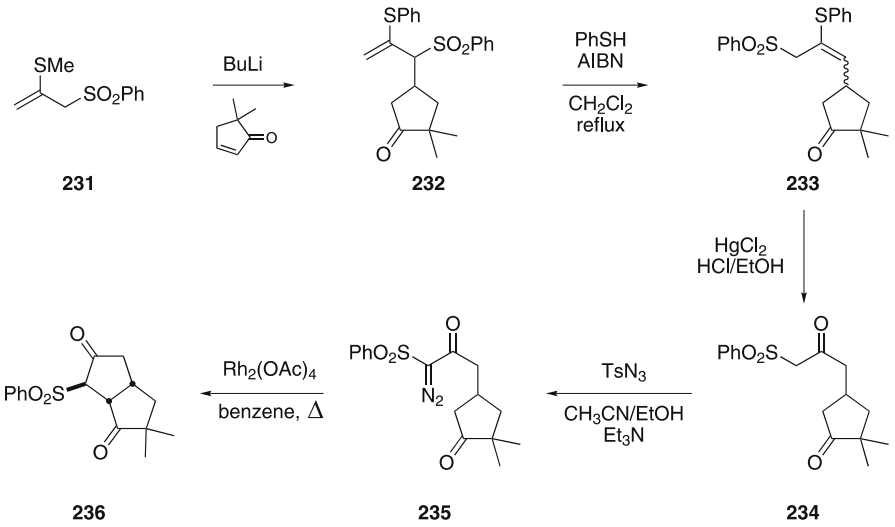
Padwa also explored the tandem isomerization–cyclization sequence reported by Whitham. In these cases, enol ethers, such as **228**, behaved similarly to vinylsulfides to produce ketones, such as **184**, under sulfinic acid-promoted conditions [64, 65]. Alkynes **229** also cyclized to give α,β-unsaturated ketone **230**. It should be noted that these cyclization reactions did not occur under the photolysis conditions that promote the 1,3-sulfone shift.



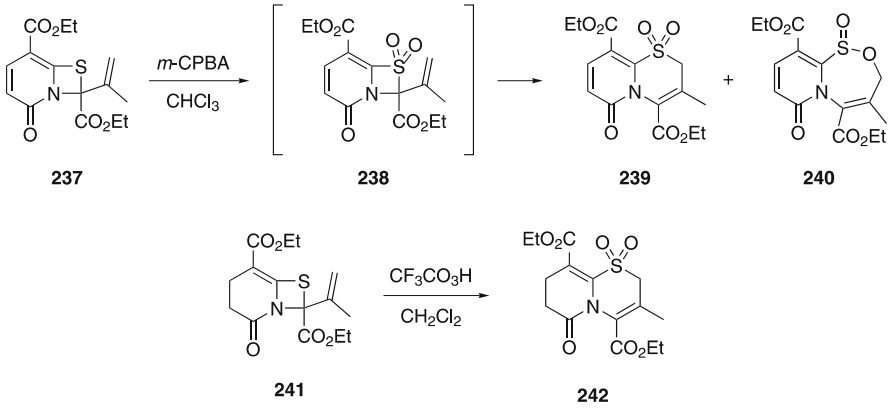
Scheme 35 Enol ethers in tandem isomerization–cyclization

Uguen reported that the lithium salt of **231** reacted with various electrophiles, including α,β-unsaturated ketones, to produce allylsulfones, such as **232** (Scheme 36) [66]. Upon heating **232** with catalytic amounts of thiophenol and AIBN, an isomeric mixture (1 : 1) of sulfones **233** was isolated in 68% yield. Heating sulfone **233** and $HgCl_2$ to reflux in ethanolic HCl hydrolized the vinylsulfide to give ketone **234.** Conversion of this α-sulfonylketone **234** into the corresponding diazoketone (**235**) followed by exposure to catalytic amounts of $Rh_2(OAc)_4$ in hot benzene afforded cyclization products **236.** Several other examples in which this methodology formed cyclization products that are difficult to obtain in other ways were presented.

More recently, Young and coworkers observed the ring expansion of vinylthiazetidines to thiazine sulfones under oxidation conditions. Exposure of **237** to *m*-CPBA in chloroform produced thiazine **239** in 66% yield along with **240** in 6% yield (Scheme 37) [67]. Likewise, **241** produced **242** in 56% yield when reacted with trifluoroperacetic acid. The isolation of **240** likely arises from a 2,3-sigmatropic rearrangement of the intermediate sulfone **238.** Unlike the experiments reported by Kocienski (cf. Scheme 24), $NaHCO_3$ is not required for these rearrangements.



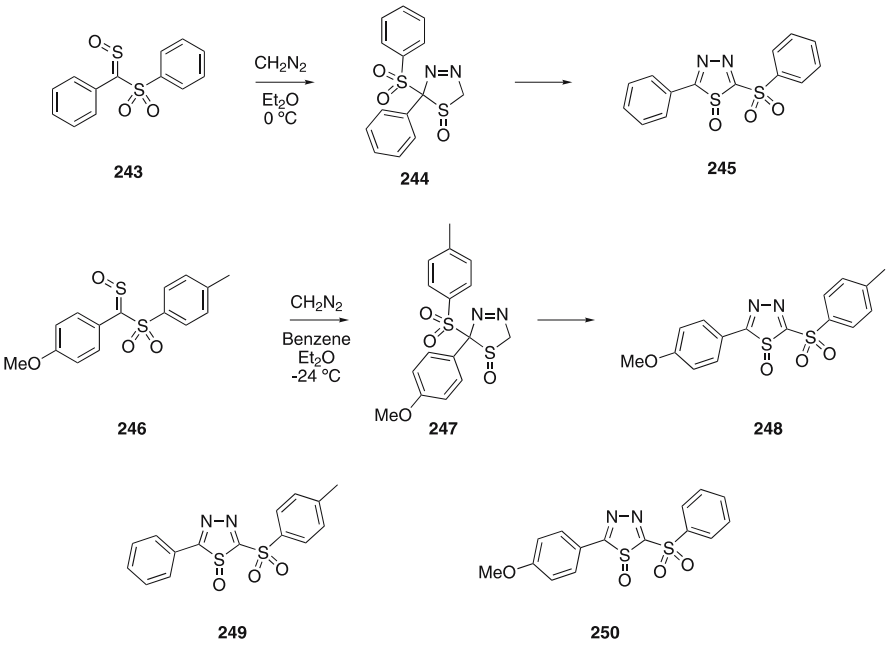
Scheme 36 Synthesis of bicyclic structures using 1,3-sulfone rearrangement



Scheme 37 Oxidative rearrangement of vinylthiazetidines

4.2 Solvolysis

Zwanenburg observed an unusual 1,3-sulfone migration during cycloaddition studies involving sulfines and diazomethane. Sulfine **243** reacted with diazomethane at 0 °C to provide thiadiazoline **244** (Scheme 38) [68]. Upon standing overnight, **244** decomposed to **245**. Sulfine **246** reacted with diazomethane under similar conditions to give **247**, which also decomposed when allowed to stand at room temperature, providing **248**. Elution of **247** through silica



243 **244** **245**

246 **247** **248**

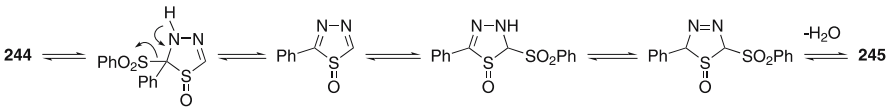
249 **250**

Scheme 38 Rearrangement and dehydration in thiadiazoline derivatives

gel also gave **248** in 85% yield. In order to understand the mechanism, a mixture (1 : 1) of **243** and **246** was treated with diazomethane, then the resulting mixture was allowed to stand at room temperature for 2 days. Along with the expected **245** and **248**, cross-over products **249** and **250** were isolated.

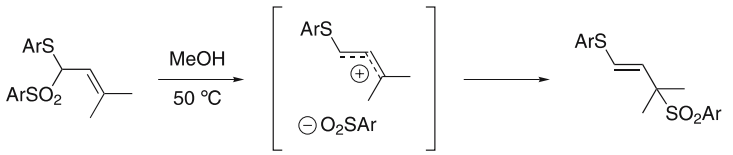
The presence of cross-over products **249** and **250** prompted the authors to suggest a mechanism that is initiated by a tautomerism of, for example, **244** to **251** (Scheme 39). Sulfinic acid is then eliminated to give thiadiazoline **252.** Addition of sulfinic acid to the least substituted carbon then gives **253.** Tautomerization of **253** produces **254,** and dehydration through a Pummerer-type aromatization provides **245.**

Studies by Bordwell and Pagani demonstrated that sulfone **255** slowly isomerized to **257** when heated to 50 °C in methanol (Scheme 40) [69]. No rearrangement was observed in benzene at 50 °C, but the addition of catalytic amounts of silica or alumina promoted the rearrangement. The 1,3-sulfone



251 **252** **253** **254**

Scheme 39 Mechanism for rearrangement of thiadiazolines



255 256 257

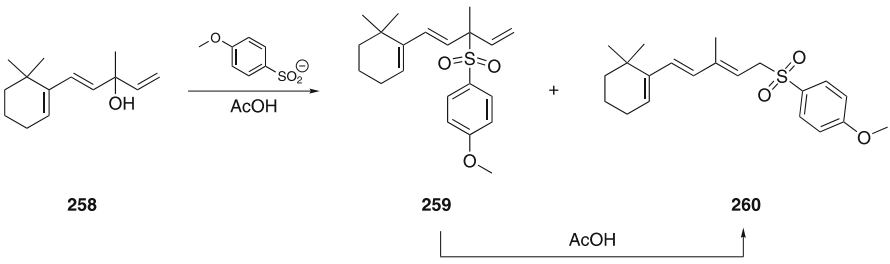
Scheme 40 Ionization/recombination mechanism for sulfone rearrangement

shift was explained by an ionization/recombination processes involving **256.** Equilibrium should favor **257** if one assumes that the carbon–carbon double bond is stabilized more by the ArS group than by the two methyl groups.

In the course of synthesizing vitamin A, researchers at Hoffmann-La Roche observed a similar sulfone migration upon exposure of vinyl-β-ionol (**258**) to sulfinate salts in acetic acid (Scheme 41) [70]. The starting material disappears rapidly, giving a complex mixture that equilibrated over time to **260** as the major product. By stopping the reaction early, sulfone **259** was isolated. It was shown that **259** isomerized to give **260** when allowed to stand in acetic acid at room temperature.

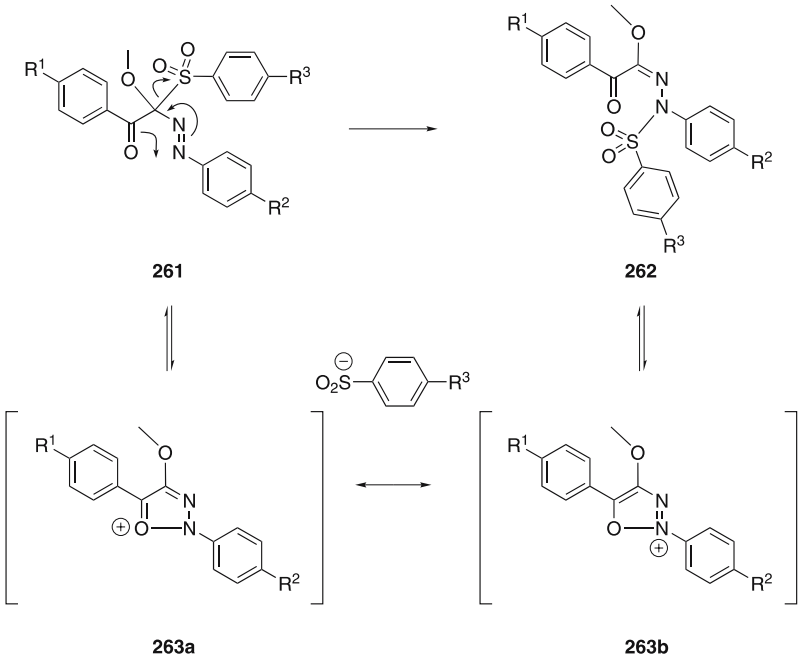
Schank and Jeblick isolated sulfonamides **262**, which result from a 1,3-sulfone migration, upon heating **261** (Scheme 42) [71]. Further studies indicated that the rate of isomerization increased with increasing solvent polarity, and when R^3 was an electron-withdrawing group; this is consistent with an ionization mechanism [72]. The rate also increased, however, when R^1 and R^2 were electron-withdrawing groups, a formal contradiction of the expected Hammett correlation for a transition state building cationic character. To account for this, a 1,2,3-oxadiazolinium ion **263** was suggested as an intermediate. In this structure, the repulsion of the vicinal heteroatoms is countered by rising positive charge due to R^1 and R^2.

Palladium has been shown to catalyze the 1,3-sulfone shift to give thermodynamically more stable products. Inomata, for example, noted that a THF/MeOH solution of linalyl acetate (**264**) reacted with NaTs in the presence of $Pd(PPh_3)_4$ to give **265** (78%) and **266** (9%, $E/Z = 81/19$) if the reaction



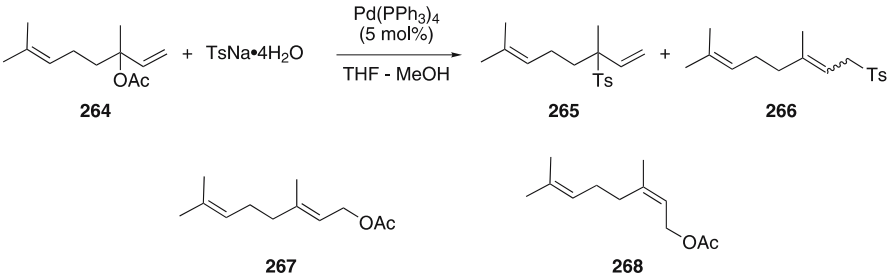
258 259 260

Scheme 41 Key reaction in the Hoffmann-La Roche synthesis of vitamin A



Scheme 42 Sulfone migration in arylazo compounds

were conducted and quenched at 0 °C (Eq. 24) [73]. If the reaction was conducted at room temperature and quenched after 1 minute, the amount of **265** isolated was reduced to 62% while the yield of **266** (E/Z = 70/30) increased to 23%. If allowed to react for prolonged periods, only **266** (E/Z = 87/13) was isolated in 84% yield.

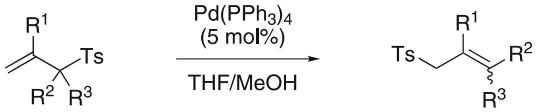


Equation 24

These experiments suggest that **265** is kinetically favored whereas **266** is formed under thermodynamic control. That the *E*-isomer of **266** predominated is also consistent with thermodynamic control. Similar reactions of geranyl acetate (**267**) indicate that short reaction times produce mixtures of

265 and **266** in which **265** predominates, and longer reaction times produce only **266** in 90% yield. Neryl acetate (**268**) gave a 57% yield of **265** and an 8% yield of **266** ($E/Z = 79/21$) after 25 minutes, but after reacting overnight, only **266** ($E/Z = 82/18$) was isolated in 87% yield.

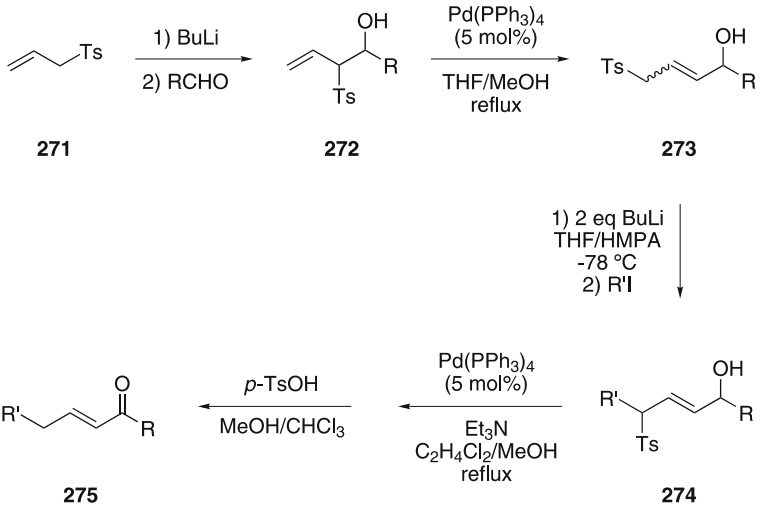
This palladium-catalyzed isomerization was found to be more general. A series of secondary and tertiary sulfones of general structure **269**, when heated at reflux in THF/MeOH, rearranged to primary sulfones **270** in the presence of 5 mol % $Pd(PPh_3)_4$ (Eq. 25) [74]. In each case, the *E*-isomer predominated.



269 **270**

Equation 25

The controlled isomerization of allyl sulfones expands the utility of these substrates. Kotake and coworkers demonstrated some of the potential of this reaction in the synthesis of α,β-unsaturated ketones. Allyl sulfone **271** was treated with BuLi followed by an aldehyde to produce homoallylic alcohols **272** (R = Ph, *n*-octyl, *n*-butyl) in 75–86% yields (Scheme 43) [74]. Heating **272** in THF/MeOH with catalytic amounts of $Pd(PPh_3)_4$ afforded mixtures of allylic alcohols **273** ($E/Z = 95/5$–$97/3$) in 87–97% yields. Alkylation of **273** with alkyl halides gave secondary sulfones **274** in moderate yields (57–76%).

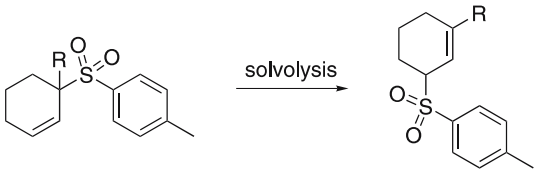


271 **272** **273** **274** **275**

Scheme 43 Synthesis of α,β-unsaturated ketones

Sulfones **274** were exposed to catalytic amounts of palladium in the presence of Et_3N to provide **275** in 59–71% yields together with small amounts of the β,γ-unsaturated ketones.

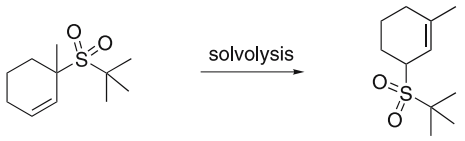
As noted previously, Whitham found that acyclic allyl sulfones rearranged under radical initiated conditions, but cyclohexenyl sulfones, such as **276**, rearranged very sluggishly under these conditions (*vide supra*). It was found, however, that some cyclohexenyl derivatives could be isomerized by heating in aqueous acetic acid. Tertiary sulfone **276a**, for example, produced **277a** after heating at 100 °C for 8 h in an AcOH – H_2O (6 : 4) solution (Eq. 26) [53]. Secondary sulfones, such as **276b**, did not rearrange under these conditions. Experiments wherein **276a** was heated in the presence of $PhSO_2Na$ led to the isolation of cross-products. This was originally interpreted as support that an ion-pair mechanism may be in operation for these rearrangements, but later work suggested a radical addition–elimination pathway (cf. Eq. 17 and Scheme 28). Interestingly, sulfone **278** could be isomerized to **279** in either aqueous THF (1 : 1) solutions at 100 °C or in AcOH – H_2O (6 : 4) solutions at 20 °C (Eq. 27).



276a R = Me
276b R = H

277a R = Me
277b R = H

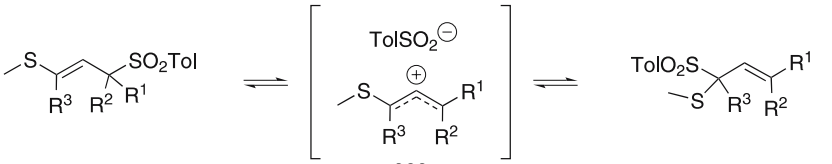
Equation 26



278 **279**

Equation 27

Work by Ogura et al. provides a little more insight into the acid-catalyzed rearrangement. Exposure of allyl sulfone **280a** to silica gel produced an equilibrium mixture (91 : 9) of **280a** and **281a** (Eq. 28) [62]. When the size of R^1 and R^2 are increased as in **280b**, the equilibrium mixture (6 : 94) favors **281b**, and exposure of **280c** to silica gel produced only **281c**. Substitution at R^3 as in **280d** shifts the equilibrium; sulfone **281d** was not observed upon exposure to silica gel. Exposure of **281d** to these conditions produced only **280d**, confirm-

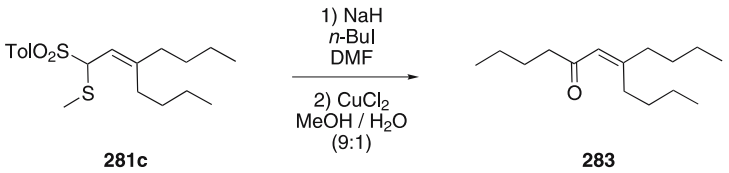


280a R^1, R^2 = Me, R^3 = H
280b R^1, R^2 = *n*-Pr, R^3 = H
280c R^1, R^2 = *n*-Bu, R^3 = H
280d R^1, R^3 = Me, R^2 = H

282

281a R^1, R^2 = Me, R^3 = H
281b R^1, R^2 = *n*-Pr, R^3 = H
281c R^1, R^2 = *n*-Bu, R^3 = H
281d R^1, R^3 = Me, R^2 = H

Equation 28



281c **283**

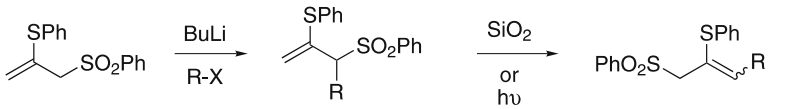
Equation 29

ing that the equilibrium favors **280d**. A heterolytic ionization mechanism (i.e., **282**) was proposed in which the sulfinate adds back to form the more stabile isomer.

The allyl sulfide products **281** could be further transformed into α,β-unsaturated ketones. The sodium salt of sulfone **281c**, for example, was alkylated with *n*-BuI. Exposure of the resulting sulfone to $CuCl_2$ in aqueous methanol afforded ketone **283** in 51% yield from **281c** (Eq. 29) [62]. The synthesis of several other ketones using this methodology was also reported.

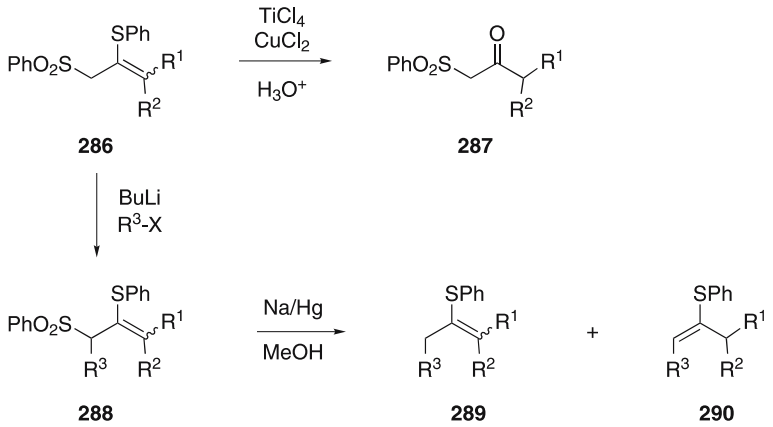
Padwa has reported methodology that uses phenylsulfanyl substituted sulfones as acetone dianion equivalents. Metallation of **218** with BuLi followed by reaction with alkyl halides produced **284** in 85–98% yields (Scheme 44) [63]. By passing **284** through a silica gel column, isomerization products **285** were isolated as mixtures (E/Z = ca. 3/1) in 98% yield. The same isomerization occurs when mixtures of **284** in benzene were heated in the presence of light (cf. Eq. 22).

Dialkylation of **218** followed by isomerization produced compounds **286** (Scheme 45) [63]. These dialkyl sulfones could be converted to α-sulfonyl ketones **287** by exposure to $TiCl_4$ and $CuCl_2$. The sulfonyl moiety in **286** could



218 **284** R = Me, Et, Bn, Allyl **285** R = Me, Et, Bn, Allyl

Scheme 44 Silica-catalyzed sulfone rearrangement



Scheme 45 Synthesis of ketones and vinyl sulfides

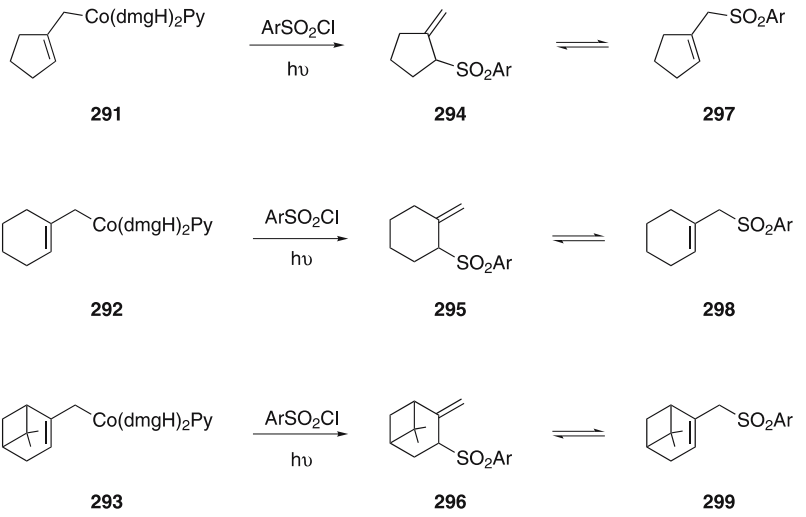
be used for further alkylation by exposure to BuLi and an alkyl halide to give **288**. Reductive desulfonylation of **288** produced a mixture (2 : 1) **289** and **290**.

4.3 Thermolysis

Roy et al. reported an interesting set of experiments involving the addition of radical sulfones to allyl metal complexes. In particular, when cobalt complexes **291–293** were irradiated in the presence of a series of arylsulfonyl chlorides, endocyclic methylene compounds **294–296** were produced (Scheme 46) [75]. Under thermal conditions, however, the product distribution was much different. When heated in the presence of TsCl at temperatures below 80 °C, **291** gave only **294**. In CCl_4 at 80 °C, however, a mixture (4 : 6) of **294** and **297** was isolated in 72% yield. Under the same conditions, **292** produced a mixture (95 : 5) of **295** and **298** in 65% yield, whereas **293** produced a mixture (5 : 95) of **296** and **299** in 62% yield.

No rearrangement of the parent cobalt complexes occurred upon heating at 80 °C. The sulfones **294–296**, however, were observed to rearrange under thermal conditions. Compound **294** required heating to 69 °C (*n*-hexane) for 10 min for complete conversion into **297**, while **295** required heating to 80 °C for several hours. Compound **296** began to slowly rearrange in CH_2Cl_2 at 40 °C, but could be completely isomerized when heated in *n*-hexane at 69 °C for 15 min. Molecular mechanics calculations show that isomers **297–299** are thermodynamically more stable.

Thermally promoted rearrangement occurred when the reactions were conducted in the dark, and the rearrangements were not inhibited by hydroquinone. Photolysis at 20 °C did not promote the rearrangement. Based upon these observations, the authors discarded a radical chain mechanism.



Scheme 46 Thermal rearrangements of exocyclic methylene substrates derived from allyl (dmgH = dimethyl glyoximato)

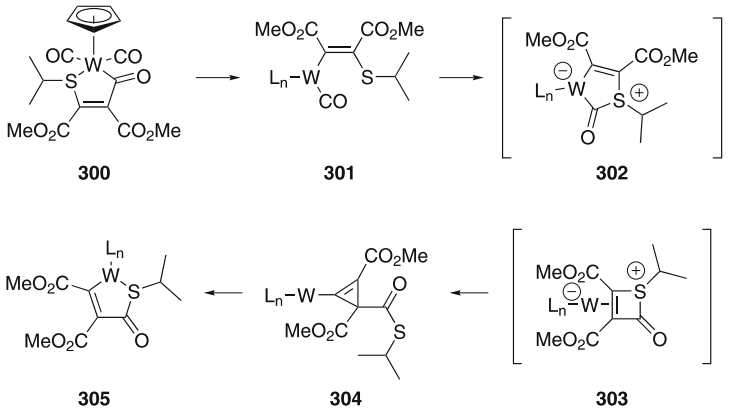
Because the reactions were run in the absence of acid, as opposed to most of the examples of non-radical mediated rearrangements given above, an ion-pair mechanism was also discarded. Instead, a concerted 1,3-sigmatropic rearrangement was favored.

5 Organometallic Substrates

Davidson and Muir encountered an interesting metal promoted 1,3-sulfur shift involving an apparent carbon monoxide insertion into a C – S bond. Complex **300** was found to undergo a thermal rearrangement to **305** via a mechanism outlined in Scheme 47 [76, 77]. Extrusion of carbon monoxide from the acyl moiety of **300** provides a vinyl complex **301**. Nucleophilic attack on the coordinated CO by the sulfur followed by ring closure gives **303**. Subsequent ring-opening gives a η^2-vinyl complex **304** that isomerizes to give **305**.

6 Conclusions

As illustrated by the examples above, significant effort has been expended to understand the mechanism of 1,3-rearrangements involving sulfur atoms. It



Scheme 47 Unusual metal promoted 1,3 sulfur rearrangement

is clear that several different mechanisms can explain the observed reactivity. Depending upon the conditions under which the reactions are conducted, radical chain mechanisms, heterolytic cleavage/recombination mechanisms, and associative mechanisms involving hypervalent sulfur have all found support. Lemal has proposed a "pseudopericyclic" mechanism, whereas Anastassiou and Roy have both observed reactivity that suggests a symmetry forbidden 1,3-sigmatropic rearrangement, though further investigations may provide alternate explanations. Baechler's comparison of the reaction kinetics for sulfur rearrangements indicates that, under thermal conditions, sulfoxides isomerize much more rapidly than sulfides with sulfones reacting most slowly [44]. Whitham found that aryl sulfones migrate more rapidly than alkyl sulfides under radical conditions, but that migration rates are competitive between aryl sulfones and aryl sulfides [59].

It is also clear that these rearrangements tend to favor thermodynamic mixtures of allylic sulfides, sulfoxides, and sulfones. The photochemical ring contraction discovered by Young et al. (cf. Eq. 4) and Ogura's observed product distribution from the irradiation of gamma-thioallyl sulfone **216** (cf. Eq. 21) stand as interesting exceptions. The rearrangement of both sulfides and sulfoxides has been strategically employed to construct synthetic intermediates of higher complexity. The rearrangement of aryl sulfones has also been an important step in the synthesis of vitamin A. The migration of sulfoxides, however, has seen little development as a synthetic tool.

Although 1,3-sulfur shifts are not as common as other rearrangements, they constitute an important synthetic tool for the selective construction of alkenes and ketones. There is still much to learn about these reactions, however. Further research will undoubtedly expand our understanding of the scope and mechanism of these reactions. Such research will also increase the synthetic utility of these reactions.

References

1. Evans DA, Andrews GC (1974) Acc Chem Res 7:147
2. Magnus PD (1977) Tetrahedron 33:2019
3. Braverman S (1988) In: Patai S, Rappoport Z, Stirling C (eds) The Chemistry of Sulfones and Sulphoxides. Wiley, New York, p 665
4. Braverman S (1988) In: Patai S, Rappoport Z, Stirling C (eds) The Chemistry of Sulfones and Sulphoxides. Wiley, New York, p 717
5. Huyser ES, Kellogg RM (1965) J Org Chem 30:2867
6. Hall DN, Oswald AA, Griesbaum K (1965) J Org Chem 30:3829
7. Cristol SJ, Kellman R (1971) J Org Chem 36:1866
8. Dmitrienko GI, Friesen RW, Carson L, Vice SF (1982) Tetrahedron Lett 23:821
9. Raban M, Chang H, Craine L, Hortelano E (1985) J Org Chem 50:2205
10. Eliel EL, Pearson WH, Jewell LH, Abatjoglou AG (1980) Tetrahedron Lett 21:331
11. Skarzewski J, Zielinska-Blajet M, Roszak S, Turowska-Tyrk I (2003) Tetrahedron 59:3621
12. Lautenschlaeger F (1969) J Org Chem 34:3998
13. Cadogan JIG, S. K (1971) J Chem Soc C, 2621
14. Dunn AR, Stoodley RJ (1969) Chem Comm 1169
15. Dunn AR, Stoodley RJ (1972) J Chem Soc C, Perkin I, 2509
16. Dunn AR, Stoodley RJ (1969) Chem Comm 1368
17. Kitchin J, Stoodley RJ (1973) J Chem Soc C, Perkin I, 2460
18. Kitchin J, Stoodley RJ (1973) J Am Chem Soc 95:3439
19. Marchini P, Trapani G, Liso L, Berardi V, Liberatore F, Moracci FM (1976) Phos Sulf 2:109
20. Marchini P, Trapani G, Liso G, Berardi V (1977) Phos Sulf 3:309
21. Trapani G, Latrofa A, Reho A, Liso G (1989) J Het Chem 26:721
22. Capps NK, Davies GM, Hitchcock PB, Loakes D, McCabe RW, Young DW (1992) J Chem Soc, Perkin I, 621
23. Capps NK, Davies GM, Loakes D, Young DW (1992) Tetrahedron 48:10149
24. Bushweller HC, Ross JA, Lemal DM (1977) J Am Chem Soc 99:629
25. Makisumi Y, Sasatani T (1969) Tetrahedron Lett 10:1975
26. Kwart H, Cohen MH (1968) Chem Comm 319
27. Kwart H, Johnson NA (1977) J Am Chem Soc 99:3441
28. Kwart H, Johnson A (1970) J Am Chem Soc 92:6064
29. Kwart H, Stanulonis J (1976) J Am Chem Soc 98:4009
30. Kwart H, George TJ (1977) J Am Chem Soc 99:5214
31. Pryor WA, Henderson RW, Patsiga RA, Carroll N (1966) J Am Chem Soc 88:1199. Although this reference determined an inverse isotope effect (0.91) for radical addition to styrene-alpha-d, the authors communicate that another group has observed no secondary isotope effect
32. Kwart H, Johnson NA, Eggerichs T, George TJ (1977) J Org Chem 42:172
33. Kwart H, Johnson NA (1977) J Org Chem 42:2855
34. Warren S (1978) Acc Chem Res 11:401
35. Fox DJ, House D, Warren S (2002) Angew Chem Int Ed 41:2462
36. Brownbridge P, Warren S (1975) J Chem Soc, Chem Comm 820
37. Brownbridge P, Warren S (1976) J Chem Soc, Perkin I, 2125
38. Brownbridge P, Fleming I, Pearce A, Warren S (1976) J Chem Soc, Chem Comm 751
39. Usui S, Paquette LA (1999) Tetrahedron Lett 40:3495
40. Bickart P, Carson FW, Jacobus J, Miller EG, Mislow K (1968) J Am Chem Soc 90:4869

41. Baechler RD, San Filippo LJ, Schroll A (1981) Tetrahedron Lett 22:5247
42. Braverman S (1971) Int J Sulf Chem C 6:149
43. Braverman S, Stabinsky Y (1967) Chem Comm 270
44. Baechler R, Bentley P, Deuring L, Fisk S (1982) Acc Chem Res 23:2269
45. Kwart H, Bencko DA (1979) J Am Chem Soc 101:1277
46. Ross JA, Seiders RP, Lemal DM (1976) J Am Chem Soc 98:4325
47. Rayner DR, Gordon AJ, Mislow K (1968) J Am Chem Soc 90:4854
48. Snyder JP, Halgren TA (1980) J Am Chem Soc 102:2861
49. Myong SO, Linder LWJ, Seike SC, Little RD (1985) J Org Chem 50:2244
50. Cope AC, Morrison DE, Field L (1950) J Am Chem Soc 72:59
51. Kocienski P (1983) J Chem Soc, Perkin I, 945
52. Kocienski P (1979) Tetrahedron Lett 20:441
53. Lin P, Whitham GH (1983) J Chem Soc, Chem Comm 1102
54. Julia M, Nel M, Righini A, Uguen D (1982) J Organomet Chem 235:113
55. Knight DJ, Lin P, Whitham GH (1987) J Chem Soc, Perkin I, 2707
56. Smith TAK, Whitham GH (1985) J Chem Soc, Chem Comm 897
57. Smith TAK, Whitham GH (1989) J Chem Soc, Perkin I, 319
58. Phillips ED, Whitham GH (1993) Tetrahedron Lett 34:2537
59. Fox JM, Morris CM, Smyth GD, Whitham GH (1994) J Chem Soc, Perkin I, 731
60. Baldwin JE, Adlington RM, Ichikawa Y, Kneale CJ (1988) J Chem Soc, Chem Comm 702
61. Phillips ED, Warren ES, Whitham GH (1997) Tetrahedron 53:307
62. Ogura K, Iihama T, Kiuchi S, Kajiki T, Koshikawa O, Takahashi K, Iida H (1986) J Org Chem 51:700
63. Padwa A, Bullock WH, Dyszlewski AD (1987) Tetrahedron Lett 28:3193
64. Padwa A, Bullock WH, Dyszlewski AD (1990) J Org Chem 55:955
65. Padwa A, Bullock WH, Dyszlewski AD (1991) J Org Chem 56:3556
66. Barre V, Uguen D (1987) Tetrahedron Lett 28:6045
67. Capps NK, Davies GM, McCabe RW, Young DW (1999) J Chem Soc, Perkin I, 3569
68. Zwanenburg B, Wagenaar A (1973) Tetrahedron Lett 14:5009
69. Bordwell FG, Pagani GA (1975) J Am Chem Soc 97:118
70. Manchand PS, Rosenberger M, Saucy G, Wherli PA, Wong H, Chambers L, Ferro MP, Jackson W (1976) Helv Chim Act 59:387
71. Jeblick W, Schank K (1976) Liebigs Ann Chem, 1727
72. Jeblick W, Schank K (1977) Liebigs Ann Chem, 1096
73. Inomata K, Yamamoto T, Kotake H (1981) Chem Lett, 1357
74. Inomata K, Murata Y, Kato H, Tsukahara Y, Kinoshita H, Kotake H (1985) Chem Lett, 931
75. Roy S, Das I, Bhanuprakash K, Gupta BD (1994) Tetrahedron 50:1847
76. Davidson JL, Carlton L (1984) J Chem Soc, Chem Comm 964
77. Davidson JL, Shiralian M, Manojlovic-Muir L, Muir KW (1979) J Chem Soc, Chem Comm 30

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