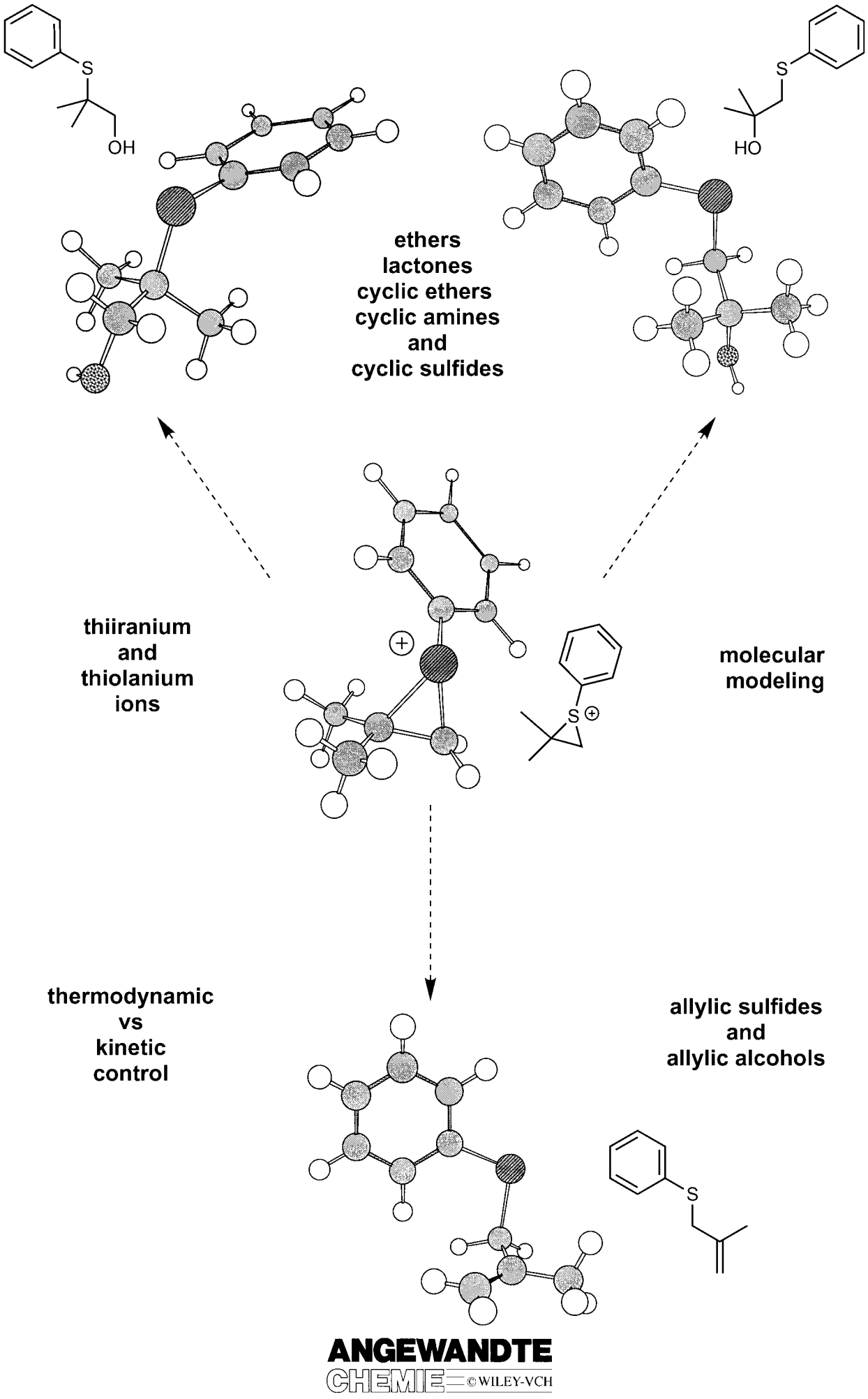

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Mechanisms of Sulfanyl (RS) Migrations: Synthesis of Heterocycles

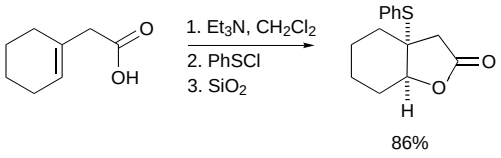
David J. Fox, David House,* and Stuart Warren*

Thiiranium (episulfonium) ions had been acknowledged as reaction intermediates for many years, but it was not until 1977 that Nicolaou demonstrated systematically that these reactive heterocyclic cations could be trapped by carboxylic acids to give lactones. In the years that followed this report, extensive research greatly extended the scope of this reaction, particularly with regard to the methods for generating thiiranium ions, the types of nucleophiles that are compatible with this reaction, and the selectivity involved in the cyclization reactions. For many years we have been using thiiranium ions for the synthesis of saturated heterocycles. Whereas Nicolaou's method relied on electrophilic sulfenylation of alkenes, we have generated thiiranium ions by displacement of a leaving group with neighboring-group participation by a sulfanyl group. Many of the examples we have reported are of cyclizations that are reversible and so where two (and in some cases more) products can result, the outcome of the reactions provides fundamental information about the relative stability of different heterocyclic ring systems. This Review will begin with a brief introduction to sulfanyl participation as a method for generating thiiranium (and thiolanium) ions, and will go on to explore the idea of using sulfanyl migrations in synthesis. Initially, emphasis will be placed on mechanisms of [1,2] sulfanyl migrations: we will look specifically at [1,2] sulfanyl migrations (usually PhS) with elimination, substitution, and cyclization. Emphasis will then shift to the factors that affect the outcome of cyclization reactions. In particular, we will cover cyclizations with hydroxy nucleophiles and examine situations in which there are more than one hydroxy nucleophile present. We will also examine cyclizations with other nucleophiles, namely amines and sulfides. After our discussion of [1,2] sulfanyl migrations, we will look very briefly at the scope of [1,4] sulfanyl participation, before finally drawing up some guidelines that (we hope) will help other organic chemists take advantage of the rearrangement reactions that the sulfanyl group has to offer.

Keywords: cyclization · heterocycles · rearrangement · sulfanyl groups · thiiranium ions

1 Introduction

In 1977 Nicolaou reported a lactonization procedure of unsaturated carboxylic acids with phenylsulfenyl chloride.[1] This "sulfenyl–lactonization" reaction is shown in Scheme 1. The reaction of phenylsulfenyl chloride with alkenes was already known to produce thiiranium ions,[2] but for the first time it was demonstrated that these useful intermediates could be trapped to produce a range of lactones. Following this report, numerous examples were published in which thiiranium ions from alkene precursors were trapped.[3]



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Scheme 1. Sulfenyl/lactonization procedure of Nicolaou and co-workers.

In 1975, we published our first results on the use of thiiranium ions for the preparation of allylic sulfides.[4] Our procedure was different to that of Nicolaou and Lysenko: the thiiranium ions were generated by treatment of 2-phenylsulfanyl alcohols with a sulfonic acid. One of our earliest observations was that these thiiranium ions generated from 2-phenylsulfanyl alcohols tended to react by [1,2] phenylsulfanyl *migration* (see Section 2). The aim of this Review is to collect, for the first time, our results of the use of sulfanyl migrations in stereoselective organic synthesis and to rationalize the products that are formed in these reactions.

[*] Dr S. Warren, Dr D. J. Fox
University Chemical Laboratory
Lensfield Road, Cambridge CB2 1EW (UK)
Fax: (+44) 1223-336-913
E-mail: sw134@cam.ac.uk
Dr D. House
Dyson Perrins Laboratory
South Parks Road, Oxford OX11 3QY (UK)
E-mail: david house@hotmail.com

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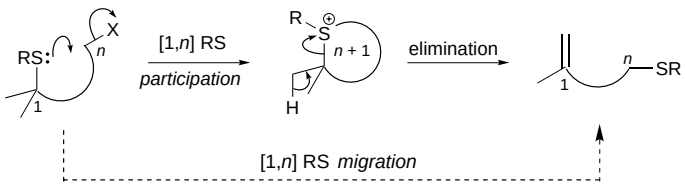
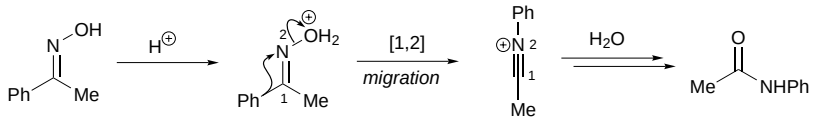
We will use the terms *participation*, *migration*, and *rearrangement* throughout the discussion to describe reactions of thiiranium ions and so at this point we need to define precisely what they mean to us:

- [1,*n*] RS *participation* refers to the nucleophilic displacement of a leaving group by a 1,*n*-related sulfanyl group (RS) to give a (1+*n*)-membered cyclic cationic intermediate. In most cases *n* will be 2 and hence thiiranium ions will be produced, although brief mention will be made of [1,4] participation from which thiolanium ions result.
- [1,*n*] RS *migration* refers to the actual movement of the sulfanyl group. Sulfanyl migrations are mechanistically different from most carbon migrations[*] (e.g. the Beckmann rearrangement[5]) since the migration occurs in two separate steps (Scheme 2): first, [1,*n*] participation to give a cyclic intermediate, and second, cleavage of the C1–S bond either by nucleophilic attack or elimination.

rearrangement of a molecule with [1,*n*] RS *migration*:
consists of [1,*n*] RS *participation* followed by elimination (or cyclization)



rearrangement of a molecule by a concerted [1,2] migration (e.g. Beckmann rearrangement)



Scheme 2. Illustration of [1,*n*] RS participation, [1,*n*] RS migration, and rearrangement.

- *Rearrangement* refers to an overall reaction in which the sulfanyl group moves from C1 to C*n*. A rearrangement will normally involve a [1,*n*] migration and either a cyclization or an elimination.

During the discussion we hope to demonstrate the effectiveness of using a sulfanyl group (RS) as a tool for constructing allylic and heterocyclic compounds with, in most

[*] Clearly, not all carbon migrations are concerted. Phenyl groups, for example, may migrate in a stepwise fashion via bridged phenonium ion intermediates.

S. Warren

D. Fox

D. House

Stuart Warren was born in Hertforshire in England in 1938 and brought up in Cheshire. He did his first degree and Ph.D. (with Dr. Malcolm Clark) at Cambridge University and postdoctoral work with Prof. Frank Westheimer at Harvard University. In 1971 he was appointed as a lecturer at Cambridge University and as a teaching fellow at Churchill College and was promoted to reader in 2000. His research is centered on asymmetric synthesis with phosphorus and sulfur, and he has a special interest in rearrangement reactions. His interest in teaching has been expressed in several text books and in courses given in industry and was recognized by the Royal Society of Chemistry and Cambridge University with teaching awards. In 2002 he was awarded the Bader prize by the Royal Society of Chemistry.

David Fox was born in 1972 in Leamington Spa, Warwickshire (UK). In 1994 he gained a degree in chemistry from the University of Oxford. He remained in Oxford to carry out research on asymmetric addition reactions of organometallic reagents to carbonyl compounds under the direction of Prof. Stephen Davies, leading to a D.Phil. in 1998. He then moved to Cambridge, to the laboratories of Dr Stuart Warren, where is working on sulfanyl migration reactions and phosphane oxide chemistry.

David House was born in 1974 in Nuneaton, Warwickshire (UK). In 1996 he gained a degree in chemistry from the University of Cambridge. He remained in Cambridge to carry out research on phenylsulfanyl migration reactions under the direction of Dr Stuart Warren, leading to a Ph.D. in 1999. He then moved to Geneva, where he spent 12 months in the laboratories of Prof. E. Peter Kündig working on the synthesis and reactions of planar chiral (arene)chromium tricarbonyl complexes. He is currently working as a research associate at the University of Oxford with Dr Timothy Donohoe on the Birch reduction of aromatic heterocycles.

cases, total control over the product stereochemistry. Generally, the phenylsulfanyl group (R = Ph) is used, as this provides molecules with a chromophore to aid in chromatographic separations, but alkyl sulfanyl groups, the pyridylsulfanyl group, and even sulfanyl (SH) behave in much the same way (see Section 5.2).

The phenylsulfanyl group is tolerant of many oxidizing agents, for example, olefins can be dihydroxylated in the presence of a PhS group,[6] diols may even be cleaved with sodium periodate without oxidation of sulfur[7] (more aggressive oxidants such as *meta*-chloroperbenzoic acid, however, rapidly effect oxidation to sulfoxide and even sulfone.[8]) Figure 1 summarizes some of the principal strategies that we have used for the construction of compounds that contain the phenylsulfanyl group. Our syntheses of sulfanyl compounds are not included in this Review: we will concern ourselves only with the outcome of the rearrangement reactions themselves.

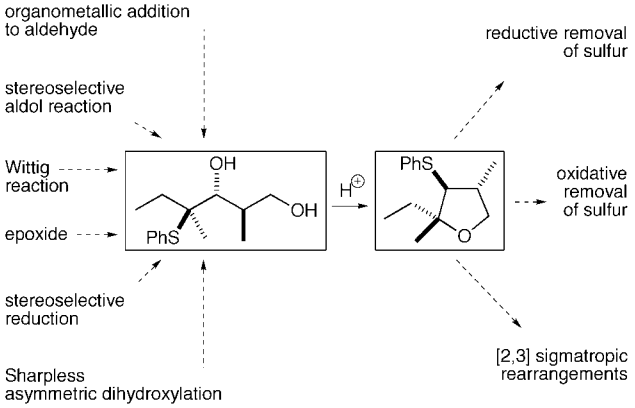


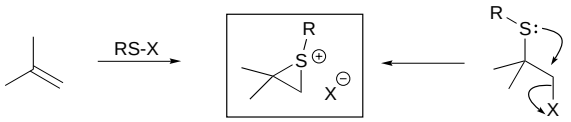
Figure 1. Strategies for the synthesis of cyclization precursors.

Once the sulfanyl group has served its purpose, it can be removed easily from the molecules (Figure 1) by reductive (e.g. Raney nickel) or oxidative methods (e.g. oxidation to sulfoxide followed by *syn* elimination) or by [2,3] sigmatropic rearrangements of the derived sulfoxides or sulfonium ylides. These are processes that may also introduce new functionality or stereochemistry into the molecule.

2 Mechanisms of Sulfanyl Migrations

2.1 Generation and Structure of Thiiranium Ions

As we have shown, thiiranium ions are normally generated in one of two ways (Scheme 3): 1) treatment of alkenes with a sulfur electrophile (usually RSCl), or 2) nucleophilic displacement of a good leaving group (often H_2O) with neighboring-group participation by sulfur. Both methods will be encountered throughout the ensuing discussion.



Scheme 3. Generation of thiiranium ions.

Thiiranium ions are reactive intermediates and are not generally isolable. However, in certain cases thiiranium ions have been isolated with non-nucleophilic counterions, especially $SbCl_6^-$ and BF_4^-, as fine crystalline powders with sharp melting points (although they decompose on melting).[9] X-ray crystallographic data have recently been collected for the thiiranium ions **1** and **2**, which bear *tert*-butyl substituents in a *cis* and *trans* arrangement, respectively.[10] The data shown in Figure 2 highlight the long C–S bond and the narrow C-S-C angle. ^{1}H And ^{13}C NMR spectra have also been recorded for thiiranium ions (in dichloromethane at 20 °C): characteristic proton resonances occur in the range 3.7 – 4.8 ppm.[9, 10]

As reactive intermediates, thiiranium ions normally decompose in one of two ways:[*] 1) loss of a β proton to form allylic sulfides, or 2) nucleophilic capture (Scheme 4). Although we will discuss allylic sulfide formation by proton loss, the majority of our article will focus on the second reaction, nucleophilic capture. Nucleophilic attack on thiiranium ions is

[*] Lucchini et al. have shown that thiiranium ions may also decompose by ring expansion to thietanium ions, although this slow reaction has only been observed for "stable" thiiranium ions and is not dealt with in this Review.[11]

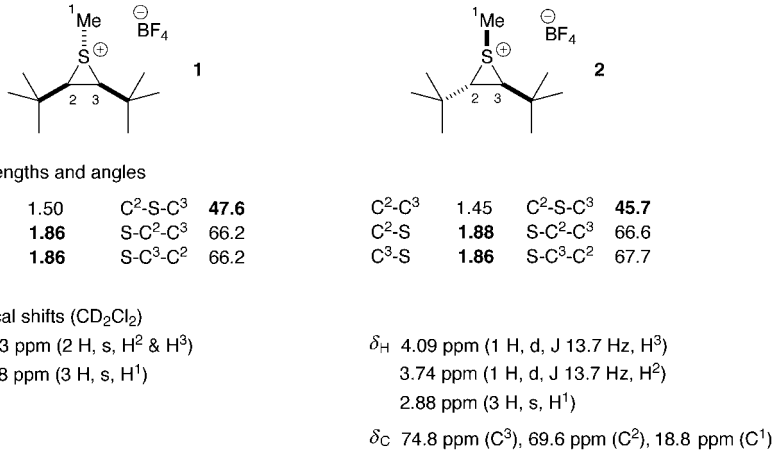
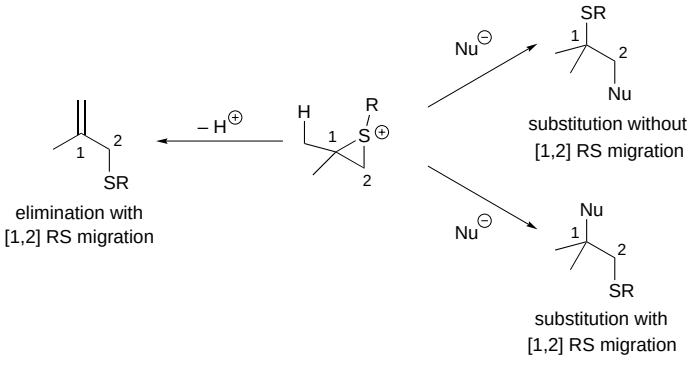


Figure 2. Selected data for thiiranium ions.



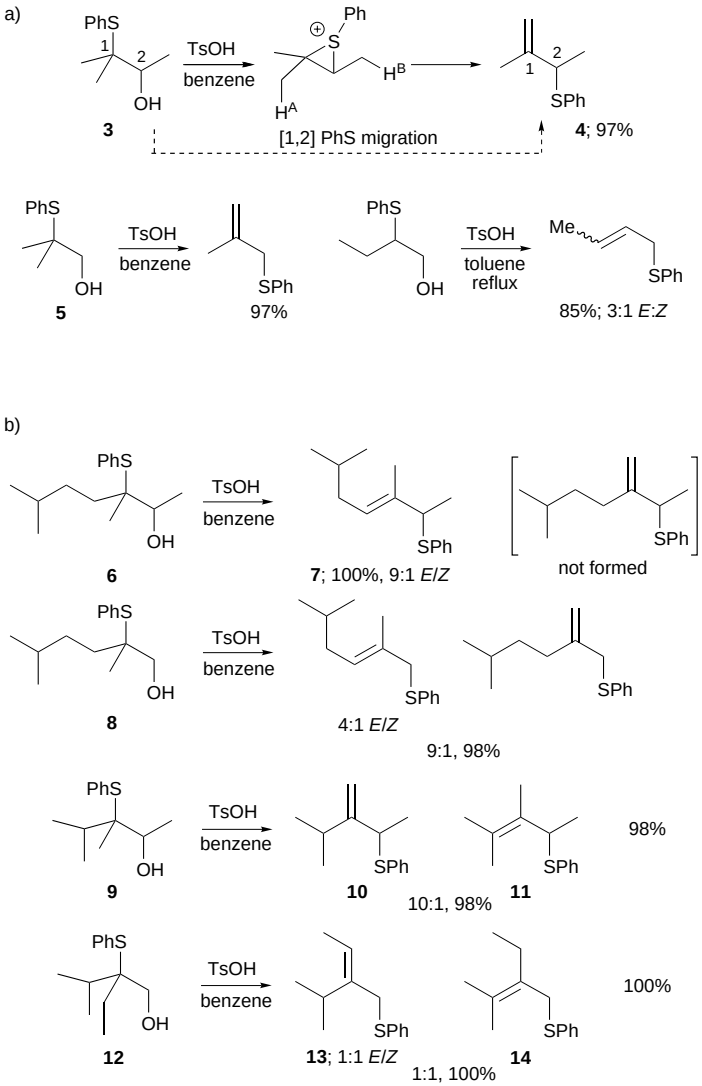
Scheme 4. Reactions of thiiranium ions.

often irreversible and two possible regioisomeric products may be formed; the product distribution will necessarily reflect the relative rates of reaction at the two electrophilic sites. In our own work however, most examples of nucleophilic attack are reversible and so the product ratios are determined by thermodynamic factors. Both the reversible and irreversible cases will be discussed in detail.

2.2 Elimination Reactions of Thiiranium Ions with [1,2] RS Migration

2.2.1 [1,2] RS Migration from 2-Phenylsulfanyl Alcohol Precursors

We begin our discussion with elimination reactions of thiiranium ions and with a simple thiiranium ion precursor, 2-phenylsulfanyl alcohol **3**. Treatment of this secondary alcohol with *p*-toluenesulfonic acid in benzene (5 min) gives a single product, the allylic sulfide **4** (Scheme 5a).[4] Proton loss occurs only from the more substituted end of the thiiranium ion (H^A) and consequently the sulfanyl group has undergone a [1,2] PhS migration. Similar behavior is observed for the primary alcohol **5**: again the sole product is that formed by [1,2] PhS migration (Scheme 5a).[12] In both cases the sulfanyl group has moved to a less substituted carbon atom and to simplify discussion we refer to this process as a "downhill" migration. Downhill migration of a sulfanyl group from a secondary to a primary center is also possible, although slightly more vigorous conditions are needed: 1 equiv TsOH, refluxing toluene, 4–6 hr (Scheme 5a).[12]



Scheme 5. a) Elimination reactions with downhill migration; b) selectivity in the formation of allylic sulfides.

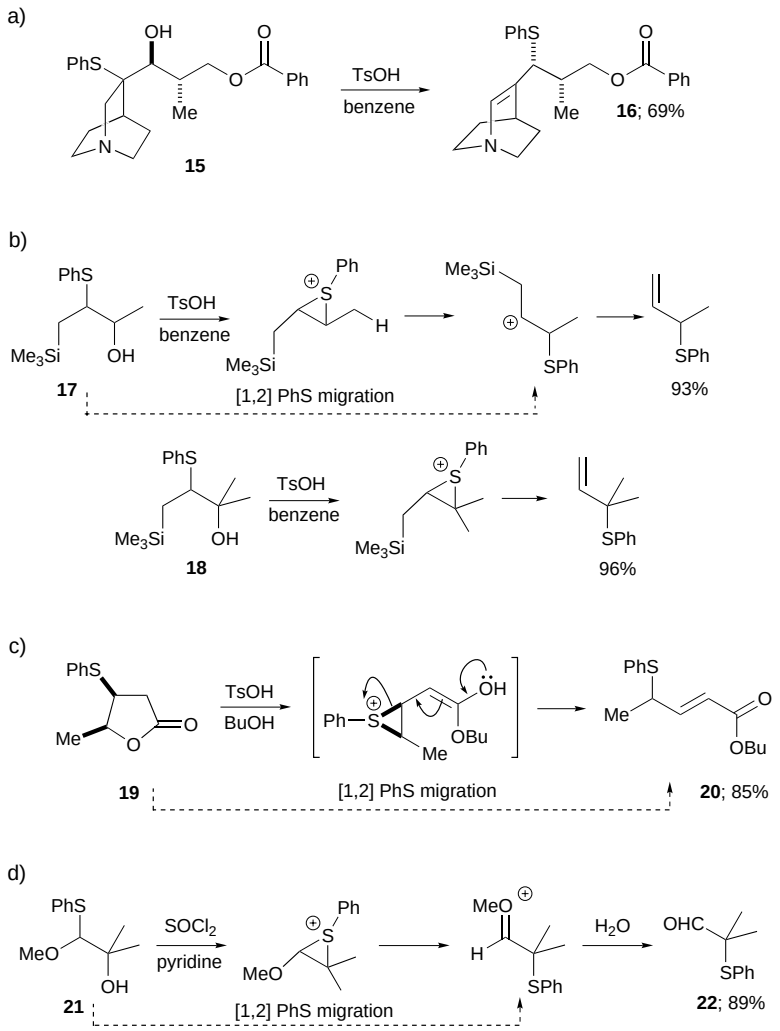
When the migration origin is unsymmetrically substituted, as in alcohol **6**, two different products of downhill migration may be formed (Scheme 5b).[12] For tertiary to secondary migrations, regioselectivity is generally excellent. Alcohol **6** gives a single regioisomer of allylic sulfide **7** (*E*/*Z* 9:1) on treatment with acid in benzene. The primary alcohol **8**, with a primary migration terminus, rearranges slightly less selectively. If the migration origin bears a secondary substituent (e.g. isopropyl) both regio- and stereocontrol are impaired (Scheme 5b). Secondary alcohol **9** rearranges to give the regioisomeric allylic sulfides **10** and **11** (10:1) and the primary alcohol **12** gives only a 1:1 mixture of regioisomers **13** and **14**. For the cases in which regioisomeric products can be formed, the mixtures are thought to be dependent on steric crowding in the transition state for allylic sulfide formation.

More highly functionalized allylic sulfides have also been generated in this way. For example, the stable enamine **16** could be prepared by rearrangement of the 2-phenylsulfanyl alcohol **15** (prepared by an *anti*-selective aldol reaction) (Scheme 6a).[13] "Flat" (secondary to secondary) and "uphill" migrations are generally not possible unless there is an extra driving force for the reaction. This driving force can be provided by a "sacrificial" silyl group; thus alcohols **17** and **18** undergo flat and uphill migrations, respectively (Scheme 6b).[14] The silyl group stabilizes the cation that results from the [1,2] migration by the β-silyl effect. "Flat" migrations can also be driven forward by unsaturated ester formation from lactones. For example, the lactone **19** was converted into the unsaturated ester **20** by treatment with *p*-toluenesulfonic acid in butanol (Scheme 6c).[15, 16]

The final example in this section is a remarkable [1,2] RS migration commonly referred to as the de Groot rearrangement.[17, 18] Treatment of tertiary alcohols such as **21** with thionyl chloride generates a chlorosulfite, which is rapidly displaced by the neighboring sulfanyl group to give a thiiranium ion substituted with an ether oxygen atom (Scheme 6d). By analogy with the β-silyl effect, the [1,2] PhS migration is completed in a second step in a formally uphill sense by π-bond formation of the ether oxygen atom. After hydrolysis of the oxenium ion, a 2-phenylsulfanyl aldehyde **22** is generally obtained in excellent yield.

2.2.2 Isomerization of Allylic Sulfides: The [1,3] RS Migration

In the preceding section, almost all the reaction products were allylic sulfides. These allylic sulfides may undergo a second sulfur-promoted rearrangement: a [1,3] RS migration in which the sulfur group will again move to a less substituted



Scheme 6. a) Formation of a "stable" enamine by [1,2] PhS migration; b) elimination reactions with flat and uphill migration; c) flat migration driven by unsaturated ester formation; d) de Groot rearrangement (an uphill [1,2] PhS migration).

carbon atom. This reaction has been shown by crossover experiments to be a radical process (Scheme 7a).[19] Generally, the [1,3] RS migration is so efficient, even in daylight, that for the isolation of the allylic sulfides formed directly from the [1,2] RS migration it is necessary to exclude light if the [1,3] RS migration is to be prevented. Unlike the acid-catalyzed formation of allylic sulfides by [1,2] RS migration, the [1,3] RS migration is reversible and so equilibrium ratios result.

Use of the tandem [1,2]/[1,3] PhS migration considerably increases the scope of the allylic sulfide synthesis, since a common precursor (e.g. alcohols **3**, **9**, **17**, and **18**) can give either of the two allylic sulfides (**4**, **10**, **25**, and **27**) or (**23**, **24**, **26**, and **28**), respectively (Scheme 7b).[20] Clearly the [1,3] PhS is not observed in some allylic sulfides because the two rearranged compounds are the same.

Paquette and co-workers have recently made use of this rearrangement for the preparation of the functionalized cyclopentanone **29** (Scheme 7c).[21] We have also used the [1,3] PhS migration to equilibrate double bond isomers of alkenes. Wittig reactions of the aldehydes **22** and **31** gave the allylic sulfides **30** and **32**, respectively, as a mixture of *E* and *Z* isomers. On prolonged exposure to daylight, solutions of both dienes were equilibrated to give (*E*)-**30** and (*E*,*E*)-**32**, respectively, as single geometrical isomers (Scheme 7d).[7]

2.2.3 Allylic Alcohol Synthesis: Coupled [1,2] RS Migrations and [2,3] Evans–Mislow Rearrangements

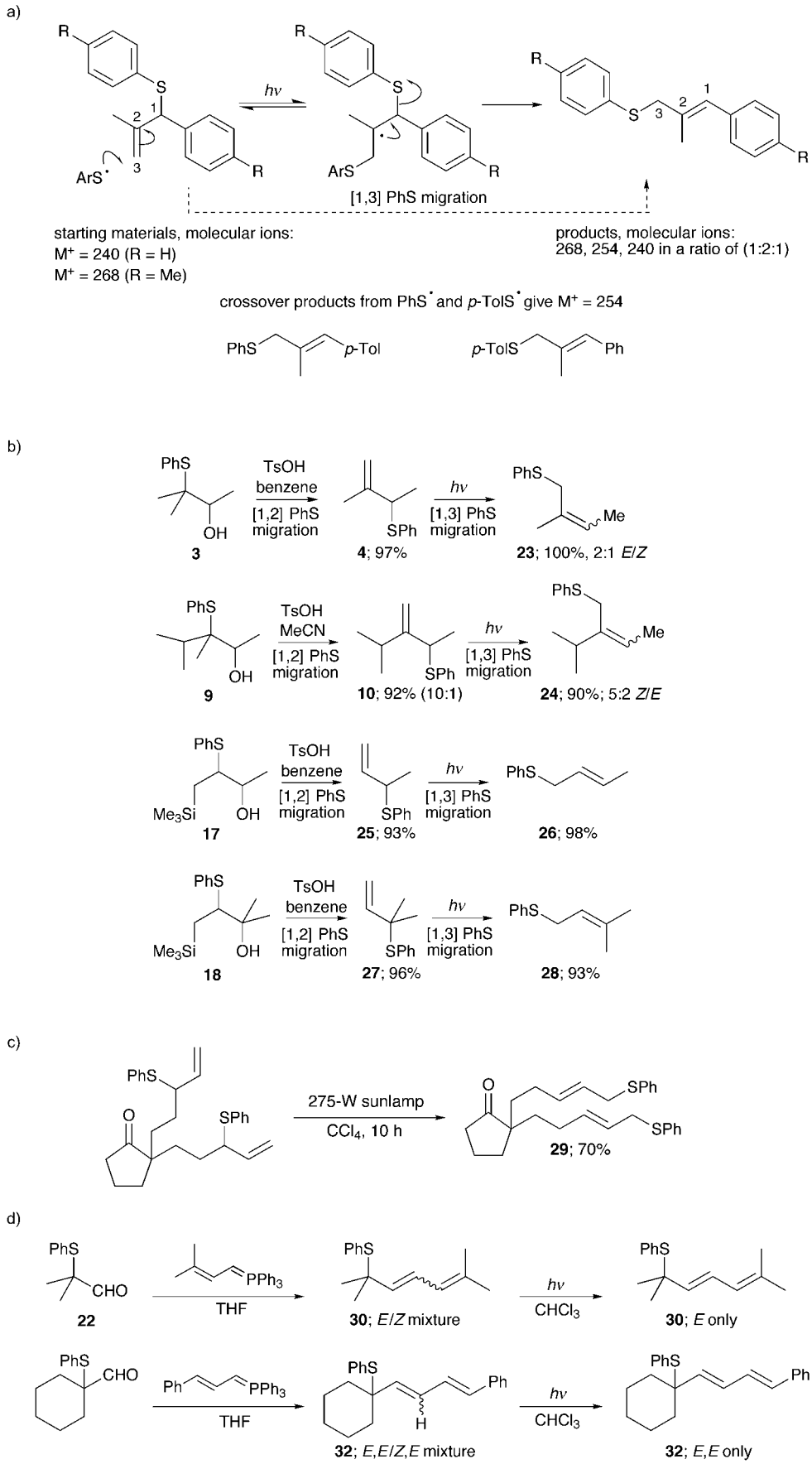
We have shown how the [1,2] PhS migration has been used to prepare allylic sulfides. Oxidation of the allylic sulfides produced in this reaction to allylic sulfoxides enables us to take advantage of yet another sulfur-promoted rearrangement: the Evans–Mislow rearrangement.[22] The combination of these two rearrangements provides an efficient route to diastereomerically pure allylic alcohols with 1,4-related stereogenic centers with control over the intervening double-bond geometry. For example, treatment of the alcohol **33** (derived from an *anti*-selective aldol reaction) with *p*-toluenesulfonic acid results in the stereospecific formation of allylic sulfide **34** (Scheme 8).[23][*] Oxidation of sulfide **34** with sodium periodate followed by treatment with a thiophile (NaSPh) leads to the *syn* allylic alcohol **35**. Complete control over the 1,4-related stereogenic centers is possible because both rearrangements are stereospecific. Similarly, the allylic sulfide **36** was oxidized with sodium borate and rearranged to give the allylic alcohol **37**.[24]

2.3 Nucleophilic Attack on Thiiranium Ions

2.3.1 Nucleophilic Attack on Thiiranium Ions Derived from Alkenes

So far we have shown thiiranium ions that are generated by using sulfur as a nucleophile. However, an alternative approach is to react an alkene with an electrophilic source of sulfur. The most common sulfur electrophiles used for this purpose are sulfenyl chlorides (RSCl). Initially, a thiiranium ion is formed, and in the absence of added nucleophiles, the chloride counterion attacks the thiiranium ion, thus producing regioisomeric mixtures of β-chlorosulfides.[25] These chlorosulfides tend to be rather unstable and are generally not isolated or separated. Despite the difficulty in handling these compounds, β-chlorosulfides may be dehydrated with good regioselectivity to give allylic sulfides. For example, geranyl benzyl ether **38** undergoes chemoselective sulfenylation to give the β-chlorosulfide regioisomers **39** and **40** (Scheme 9a).[26] Treatment of this mixture with camphorsulfonic acid (CSA) gave the allylic sulfide **41**. The high regioselectivity observed in the elimination is a consequence of the

[*] The stereochemistry of the [1,2] PhS migration is discussed in Section 3.1.1.



Scheme 7. a) Mechanistic probe of the [1,3] PhS migration; b) tandem [1,2] and [1,3] PhS migrations; c) example of a double [1,3] PhS migration; d) use of the [1,3] PhS migration to equilibrate alkene double bond geometry.

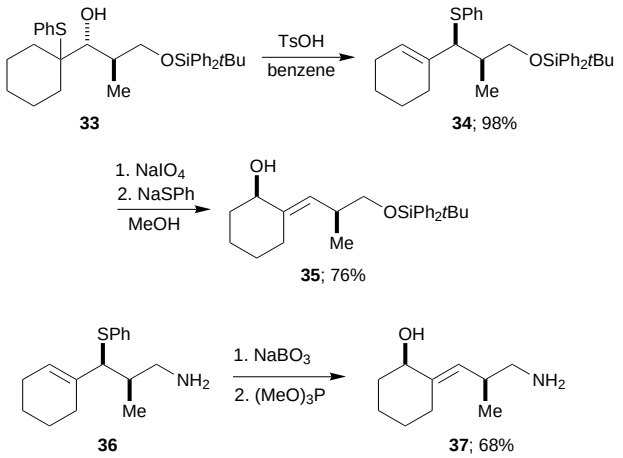
elimination, which proceeds via a thiiranium ion intermediate, as already discussed.

Besides undergoing elimination reactions, β-chlorosulfides can undergo nucleophilic substitution reactions. For example, treatment of the previous mixture of β-chlorosulfide regioisomers **39** and **40** with silica gel gives the β-hydroxysulfide **42** in which the sulfanyl group has undergone a [1,2] migration (Scheme 9b).[26] By analogy with our previous observations we note that reaction has occurred exclusively at the more substituted end of the thiiranium ion, thus promoting a downhill sulfanyl migration. Similarly, treatment of the alkene **43** with phenylsulfenyl chloride followed by sodium acetate in acetic acid gave the β-acetoxysulfide **44** as a single isomer, again the products of downhill migration (Scheme 9c).[27]

2.3.2 Nucleophilic Attack on Thiiranium Ions Derived from 2-Phenylsulfanyl Alcohols

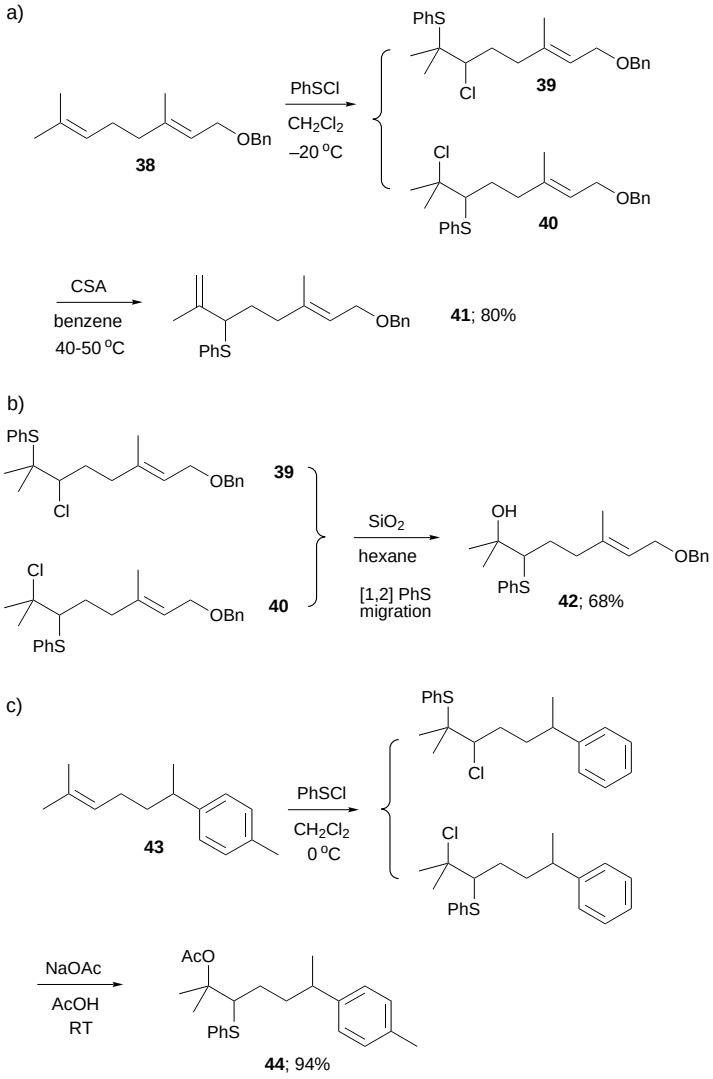
In Section 2.2.1 we discussed the dehydration of a simple 2-phenylsulfanyl alcohol **3** to give a single allylic sulfide regioisomer by treatment with *p*-toluenesulfonic acid in benzene solution. If this experiment is performed with ethanol as the solvent, none of the allylic sulfide **4** is formed; instead, ethyl ether **45** is formed by nucleophilic attack of ethanol on the intermediate thiiranium ion (Scheme 10a).[20] Isomeric ether **46** is not produced, which reflects the reversible nucleophilic trapping of the thiiranium ion: the thiiranium ion can be regenerated by protonation of the ether oxygen atom and sulfur participation.

Given that this reaction is thermodynamically control-

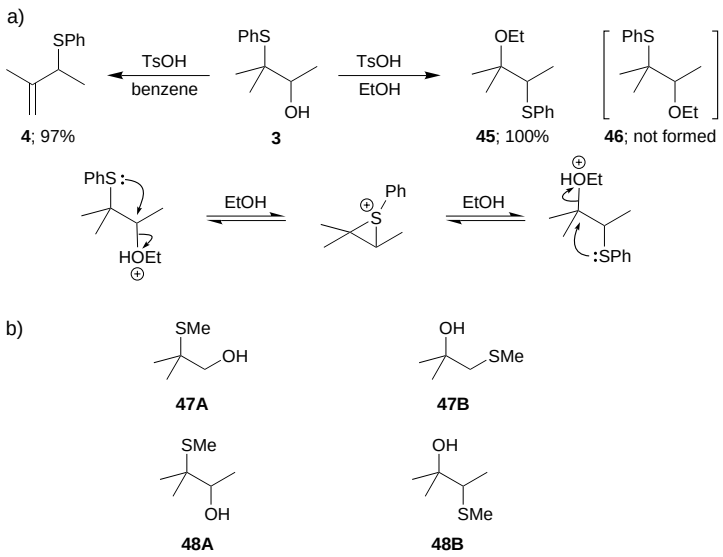


Scheme 8. Stereocontrolled allylic alcohol synthesis by tandem [1,2] PhS migration and [2,3] Evans–Mislow rearrangement.

led, we need to account for the difference in stabilities of the two ethers **45** and **46**. To this end we performed semiempirical molecular modeling calculations on some



Scheme 9. a) Dehydration of β-chlorosulfides; b) nucleophilic attack of water onto thiiranium ions; c) nucleophilic attack of acetate onto thiiranium ions.



Scheme 10. a) Nucleophilic attack under thermodynamic control; b) isomeric 2-methylsulfanyl alcohols compared by PM3 semiempirical molecular-modeling.

simple isomeric compounds, with very interesting results. The calculations involved the comparisons of the enthalpies of formation of sulfide isomers **47A** and **47B** and of **48A** and **48B** (Scheme 10b).[*] Table 1 shows the values of ΔH_f (from the elements) calculated for these molecules in the gas phase at 298 K. Although we are not comparing Gibbs free energies (ΔG_f) (no entropy term), the results are nevertheless interesting; in both cases the more stable isomer has the sulfur substituent on the less substituted carbon atom. We believe this enthalpy difference to be a fundamental driving force for sulfur to move "downhill" in our [1,2] RS migrations under thermodynamic control.

Table 1. Calculated gas phase enthalpies of formation for sulfide isomers: **47A**, **47B** and **48A**, **48B**.

Compound	ΔH_f(298 K) [kcal mol^{-1}]	No. of conformations
47A	– 62.1 to – 58.7	8
47B	– **68.8** to – **63.8**	11
48A	– 66.4 to – 61.6	22
48B	– **69.0** to – **64.3**	24

Out of interest, we calculated the enthalpies of formation for isobutyl alcohol, *tert*-butyl alcohol, isobutyl thiol, and *tert*-butyl thiol (Table 2). Whilst these calculations must be interpreted cautiously (given the lack of gas-phase thermo-

Table 2. Calculated gas-phase enthalpies of formation for alcohol and thiol isomers.

Compound	ΔH_f(298 K) [kcal mol^{-1}]
*i*BuOH	– 69.9
*t*BuOH	– **71.3**
*i*BuSH	– **20.3**
*t*BuSH	– 17.9

[*] Calculations were performed with CS MOPAC Pro version 5.0 with a PM3 basis set.

chemical data) it is interesting to see that isobutyl thiol is predicted to be the lower-energy isomer, whereas *tert*-butyl alcohol is lower in energy than isobutyl alcohol.

3 Cyclization Reactions with [1,2] RS Migration by Using Oxygen Nucleophiles

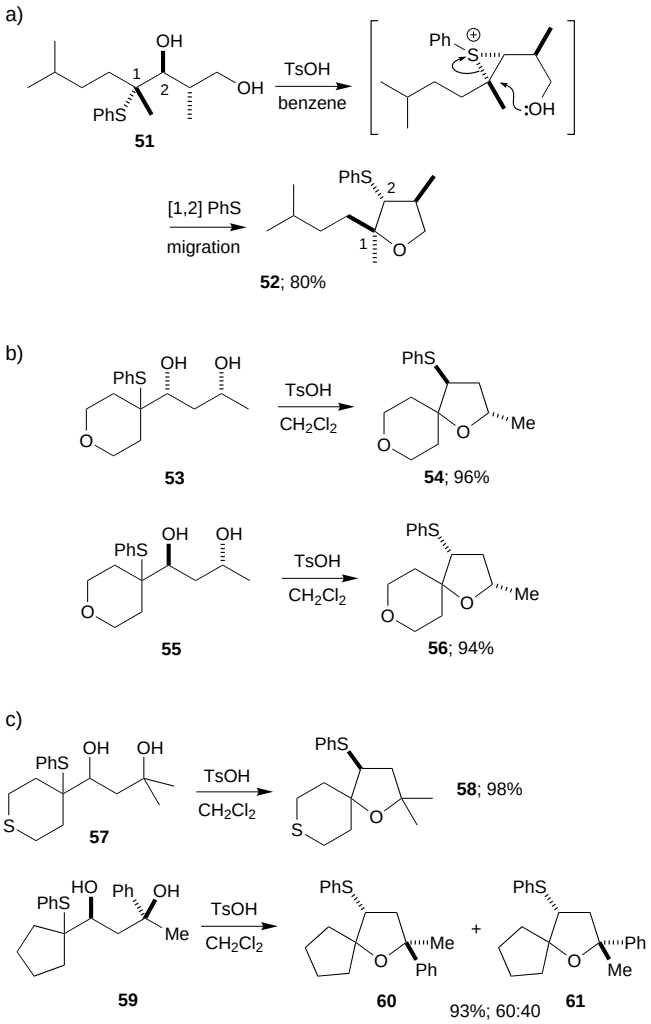
In Section 2.2.3 we discussed the preparation of allylic alcohols by using a [1,2] RS migration with elimination to give allylic sulfides, which underwent [2,3] sigmatropic rearrangement after oxidation to sulfoxides. If the diol **49**, rather than the protected diol **33**, was treated with *p*-toluenesulfonic acid, the reaction followed an altogether different course: cyclization occurred to give the tetrahydrofuran (THF) **50** as the only product of the reaction (Scheme 11).[23] The remainder of this Review will focus on the use of thiiranium ions to prepare saturated heterocycles in high yields and, in almost all cases, with complete stereocontrol.

3.1 Cyclizations of Alcohols through Intramolecular Attack of Thiiranium Ions

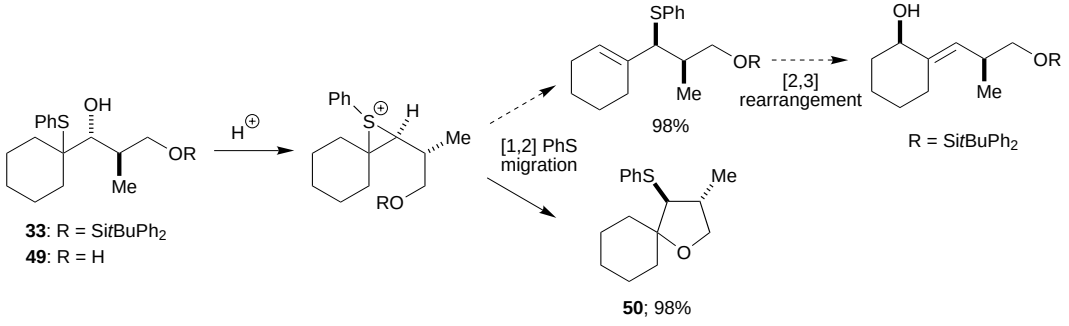
3.1.1 Stereochemistry of Cyclization Reactions

We were able to show that cyclizations through intramolecular attack onto thiiranium ions occur with complete inversion of configuration at the migration origin and terminus.[28] For example, treatment of the diol **51** with an acid catalyst gave the THF **52** with the stereochemistry indicated in Scheme 12a. Though at first this may seem to be an obvious observation, nucleophilic substitution at a tertiary carbon center would normally proceed by an S_N1 mechanism with loss of stereochemical integrity. Here the long C–S bond means that the electrophilic carbon atom can adopt a near-planar geometry and the cyclization may occur via a "loose" S_N2-type transition state. Table 3 illustrates the generality of this cyclization reaction: notably, in all cases products are formed in high yield and without loss of stereochemical integrity. Even sulfanyl (SH) groups undergo the [1,2] RS migration, albeit more slowly.[29]

By preparing compounds with a secondary hydroxy group as the nucleophile, we were able to show that no epimerization of this stereogenic center occurs during the cyclization reaction (**53** → **54** and **55** → **56**, Scheme 12b).[30] The real test, however, came when a tertiary hydroxy group was used as the nucleophile. Tertiary alcohol **57** gave **58** on treatment with acid (Scheme 12c).[30] Remarkably, dehydration is not a competing pathway in this reaction! The benzylic tertiary alcohol **59** also showed no sign of dehydration, though epimerization of this stereogenic center resulted in the formation of the THFs **60** and **61** (60:40).

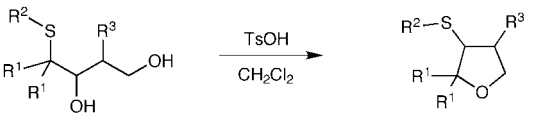


Scheme 12. Stereochemical outcome of cyclization reactions: a) inversion occurs at migration origin and terminus; b) no epimerization of nucleophilic secondary hydroxy group occurs; c) no dehydration occurs with tertiary hydroxy groups but benzylic tertiary hydroxy groups are prone to epimerization.



Scheme 11. Rearrangements with [1,2] PhS migration with subsequent elimination or cyclization.

Table 3. Examples of THF synthesis by [1,2] RS Migration.



R^1	R^2	R^3	THF	Yield
Me	H	H		96%
Me	Bn	H		96%
Me	H	*syn*-Me	*syn*	95%
Me	H	*anti*-Me	*anti*	98%
$-CH_2CH_2(NMe)CH_2CH_2-$	Ph	*anti*-Me	*anti*	85%
$-CH_2CH_2OCH_2CH_2-$	Ph	*syn*-Me	*syn*	94%
$-CH_2CH_2SCH_2CH_2-$	Ph	*anti*-Me	*anti*	99%
$-CH_2CH_2SCH_2CH_2-$	Ph	*syn*-Me	*syn*	99%
c-C_8H_{16}	Ph	*anti*-Me	*anti*	76%
c-$C_{12}H_{24}$	Ph	*anti*-Me	*anti*	100%

3.1.2 Cyclization of 1,3-Diols: Kinetic vs Thermodynamic Control

In the preceding section we discussed the cyclization onto thiiranium ions to give "rearranged" THFs. (By "rearranged" we mean a product formed by a [1,2] RS migration. Conversely, "unrearranged" products are formed without [1,2] RS migration). We have rather overlooked the possibility of the alternative cyclization onto the less substituted end of the thiiranium ion to give unrearranged oxetanes as products (e.g. **62** →**63** in contrast to **62** →**64**, Scheme 13a). Since these cyclizations are reversible, the formation of oxetanes is doubly disadvantaged on account of the strain energy of a four-membered ring and the sulfur group not having migrated downhill.

The question of the relative rates of the two cyclizations remained unanswered, however, and so non-equilibrating conditions were sought to gain further insight into the reaction mechanism. We prepared cyclic sulfites of 1,3-diols and studied their decomposition by sulfanyl participation and loss of SO_2 and subsequent cyclization of the oxyanion onto the thiiranium ion.[31] A ratio of 14:86 for **65**/**66** represents the kinetic distribution for the cyclization of oxyanion **67** (Scheme 13b). Clearly this need not be the same ratio as for cyclization in acid, but it is a good model since no equilibration can occur under basic conditions. Similarly, the cyclic sulfite prepared from diol **68** decomposed to give **69** and **70** (25:75).

We found that oxetanes could be prepared as the sole products from 1,3-diols under modified Mitsunobu conditions by using Ziram (zinc dimethyldithiocarbamate)[32] (Scheme 13c).[31] Although the role of Ziram in this reaction remains unclear, it seems likely that it prevents the sulfur group from displacing the phosphorus leaving group, thus allowing the secondary hydroxy group to act as the nucleophile in an unprecedented fashion. Brief exposure of these oxetanes to acid results in total conversion into THFs, for example, **71** →**72** (Scheme 13c).

If we make the migration origin a secondary center, the cyclization should be less beneficial because in both the starting material and product the sulfur is bound to an equally substituted carbon atom ("flat" migration). It turns out that the stereochemistry plays the deciding role in these cyclizations.[28] Diol **73** rearranges to give **74** with 2,3-*anti*, 3,4-*anti* stereochemistry (Scheme 13d). Diol **75** gives the THF **76** with 2,3-*syn*, 3,4-*anti* stereochemistry, but the diastereomeric diol **77** does not give the corresponding (2,3-*anti*,3,4-*syn*)-**78**, only decomposition products (Scheme 13d). Presumably, the eclipsing interaction that results from the development of 3,4-*syn* stereochemistry severely destabilizes the transition state for cyclization. A 1,3-diol with a primary migration origin does not result in any cyclization, regardless of the stereochemistry. In this case, THF formation would require the sulfanyl group to move to a more highly substituted carbon atom which, as we have already mentioned, is a thermodynamically unfavorable process.

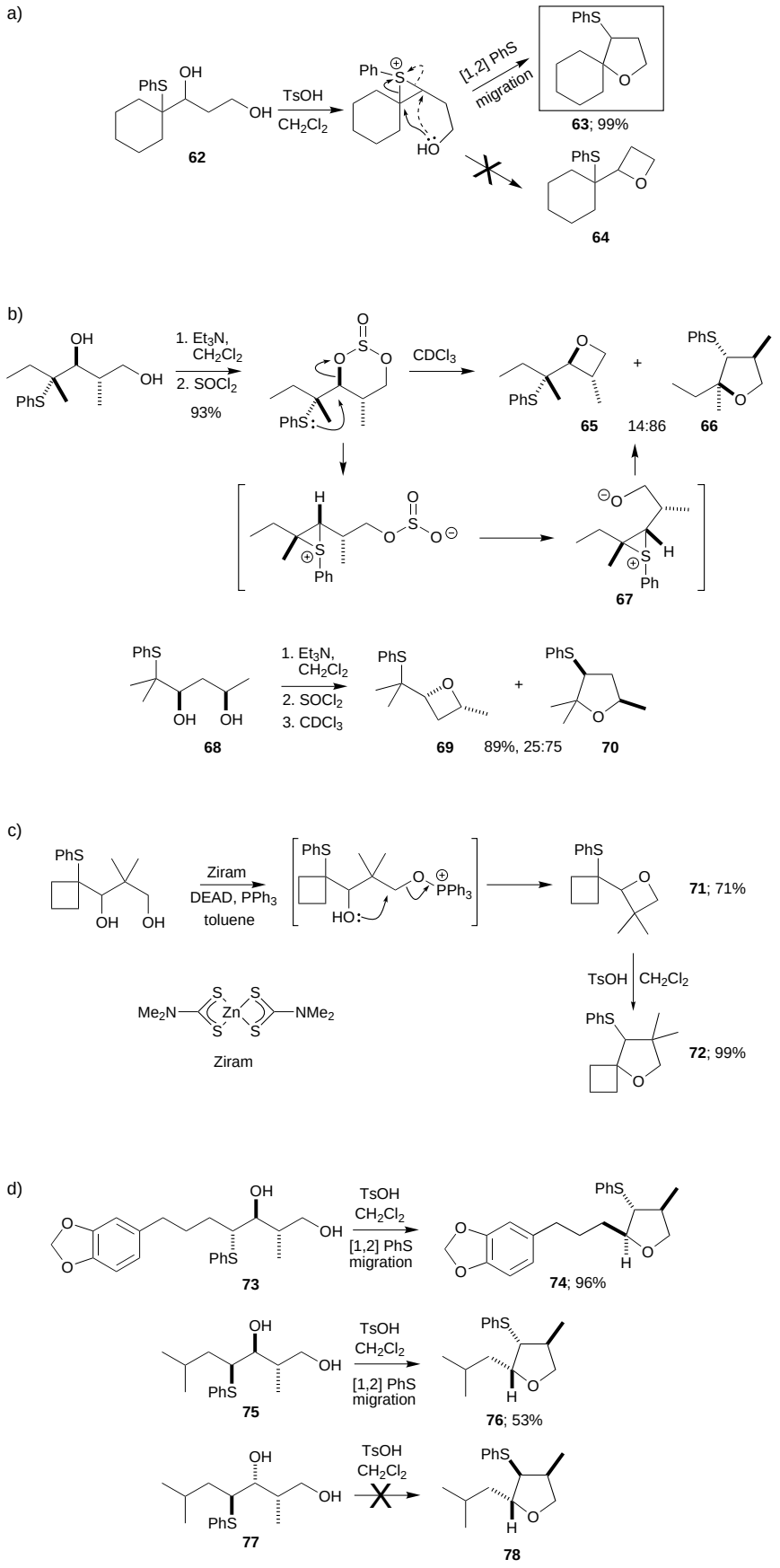
In a closely related series of experiments, Williams and Phillips prepared highly substituted THFs from diol precursors; however the alcohol and sulfanyl functionalities are transposed to give 1,4-diols with an intervening 2-phenylsulfanyl group (Scheme 14a).[33] The cyclizations (e.g. **79** →**80**) were triggered by treating these compounds with a hard methylating agent (e.g. dimethyl sulfate). In this way the same thiiranium ions are formed and in all of the cases reported THFs are obtained as the sole product, that is, no oxetane is present (Scheme 14a). The juxtaposition of the hydroxy and sulfanyl groups means that these cyclizations occur *without* [1,2] PhS migration, but with retention of configuration.

Fallis and Tuladhar prepared oxygen heterocycles by generating thiiranium ions from alkenes.[34] Interestingly, attempts to cyclize 3-buten-1-ol by treatment with phenylsulfenyl chloride and diisopropylethylamine (to neutralize HCl production and prevent equilibration) led only to the alcohol **81** in which the thiiranium ion had been captured by a chloride ion rather than by the tethered nucleophile (Scheme 14b). In light of the previous discussion, the reason for this is clear: for the sulfanyl group to migrate downhill (secondary to primary center) an oxetane must be formed and intermolecular capture by a chloride ion is clearly faster than the 4-*exo-tet* cyclization to the oxetane.

Knight and co-workers have prepared THFs by a related approach in which iodine was used as the electrophile.[35, 36] For example when the alkene **82** was treated with iodine in acetonitrile, the highly substituted THF **83** was obtained (Scheme 14c).

3.1.3 Cyclizations of 1,4 Diols: THFs and THPs

Perhaps a more interesting cyclization is that of the 1,4-diol **84**; in this case the two possible products are either an unrearranged THF **85** or a rearranged tetrahydropyran (THP) **86** (Scheme 15a). Both types of heterocycle are frequently encountered and so the factors that determine their relative stability might be expected to be more subtle than for the THF *vs* oxetane. It turns out that THP **86**, the product of downhill [1,2] PhS migration, is formed as the sole product when diol **84** is treated with acid.[37] Why should the THP **86** be more stable than THF **85**? We believe that the answer again lies in the position of the sulfanyl group: in THP **86** the sulfur group has moved downhill to a secondary center and the oxygen atom has now become bonded to a tertiary center. In the THF **85** the situation is reversed. If the 1,4-diol **84** is



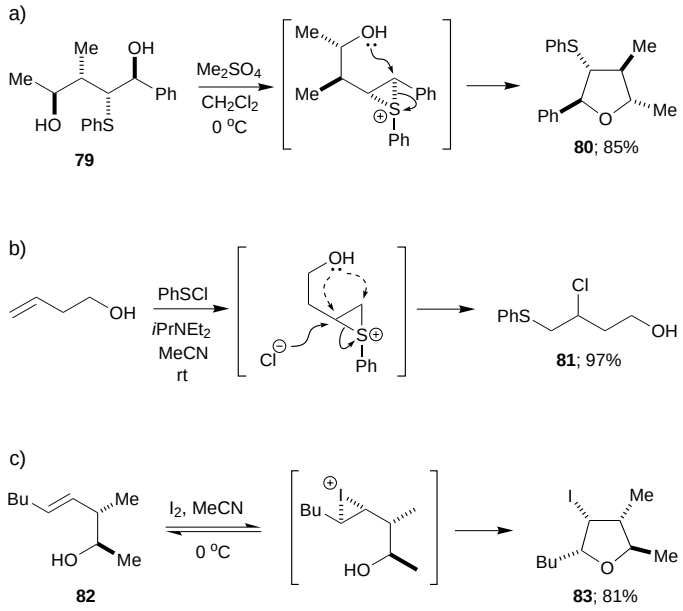
Scheme 13. a) Oxetanes are not formed in acid-catalyzed cyclization reactions; b) oxetanes may be formed under kinetic conditions; c) unusual oxetane synthesis under modified Mitsunobu conditions; d) scope and limitations of THF synthesis with flat migrations.

treated with *p*-toluenesulfonyl chloride instead of acid, the *rearranged* THP **86** is no longer formed. Instead the *unrearranged* THF **85** is formed as a result of tosylation of the primary hydroxy group and the secondary hydroxy group acting as the nucleophile (Scheme 15b).[37] We were again able to demonstrate why the unrearranged product had not been isolated from the acid-catalyzed reaction; treating this THF with acid caused equilibration to give only the product of [1,2] RS migration, THP **86**.

Together with Fallis and co-workers, we studied the sulfenyletherification of several 4-penten-1-ols.[38] The parent alkene **87** gives the THF **88** as a single product in 84% yield; in this case the sulfanyl group is bound to a primary center, in the THP alternative **89** it is bound to a secondary center (Scheme 15c). If Baldwin's rules[39] are invoked (these cyclizations are under kinetic control), then the outcome of this reaction represents a pure 5-*exo-tet* cyclization, as opposed to a hybrid 6-*exo*/7-*endo-tet* cyclization. Accordingly, the trisubstituted alkene **90** gave only THP **91**, which avoids the sulfanyl group occupying a tertiary position (Scheme 15c).[38] In a similar way, Clive et al. have studied the capture of seleniranium ions by oxygen nucleophiles, in this case phenols.[40] Interestingly, the alkene **92** cyclizes on treatment with phenylselenyl chloride to give the benzodihydrofuran **93** with the phenylselenyl group bound to a primary center (Scheme 15d). On the other hand, cyclization of the dimethyl homologue **94** gives the benzodihydropyran **95** with the phenylselenyl group occupying a secondary center (rather than a tertiary center if the alternative product was formed).

3.1.4 Cyclizations of 1,n-Diols ($n = 2$, 5, and 6): Limitations of Cyclization Reactions

To investigate further the scope of cyclization reactions of tethered alcohols onto thiiranium ions, 1,*n*-diols ($n = 2$, 5, and 6) were prepared.[37] The 1,2-diol **96** gave the allylic sulfide **97** on treatment with acid (Scheme 16a). Perhaps unsurprisingly, neither of the two possible cyclization products, epoxide **98** or oxetane **99**, were formed. The unstable epoxide **98** could be prepared by an alternative route and on treatment with



Scheme 14. a) Williams' THF synthesis occurs without [1,2] PhS migration; b) sulfenylation of 3-buten-1-ol does not produce an oxetane or THF; c) Knight's iodoetherification reaction conditions.

acid rearranged quantitatively to the allylic sulfide **97** (Scheme 16a). Clearly, ring strain in these small-ring heterocycles makes allylic sulfide **97** the most favorable product. The 1,5-diol that might be expected to cyclize with [1,2] PhS migration to give the oxepane **100**, in fact gives the unrearranged THP **101** as the major product, along with some of the allylic sulfide **102** (Scheme 16b). Ring strain in the seven-membered ring is clearly sufficient to override the inherent preference for downhill migration. Attempting to favor the cyclization by incorporation of a *Z* olefin in the side chain (diol **103**) resulted only in the formation of dihydropyran **104** (Scheme 16b). Finally, attempts to prepare oxocane **105** no longer result in cyclization; instead the thiiranium ion formed in this reaction decomposes by elimination to give allylic sulfide **106** (Scheme 16c). The chain has become too long for cyclization to be efficient.

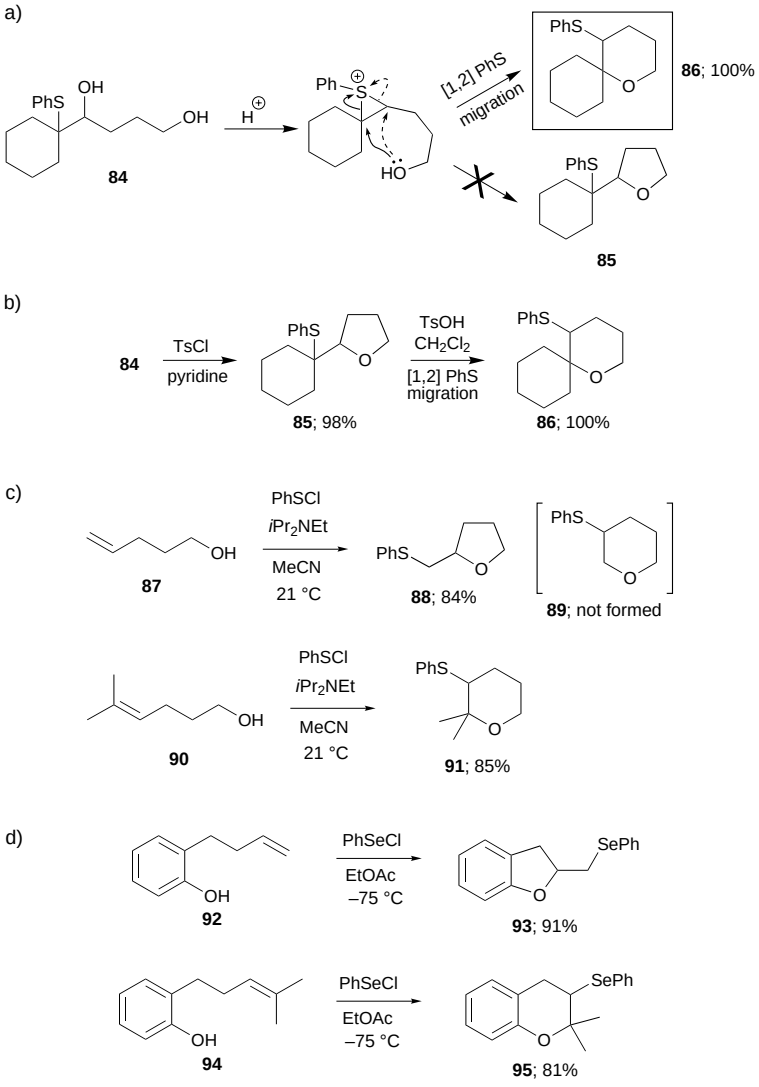
3.2 Higher Levels of Competition: Cyclization with Triol Substrates

In this section we look at more complicated cyclizations: substrates with two competing nucleophiles. In each of these reactions there will, in principle, be four possible products. Either one of the oxygen nucleophiles present could cyclize onto either end of a thiiranium ion. By studying these reactions we could investigate the subtle factors that stabilize one ring system over another.

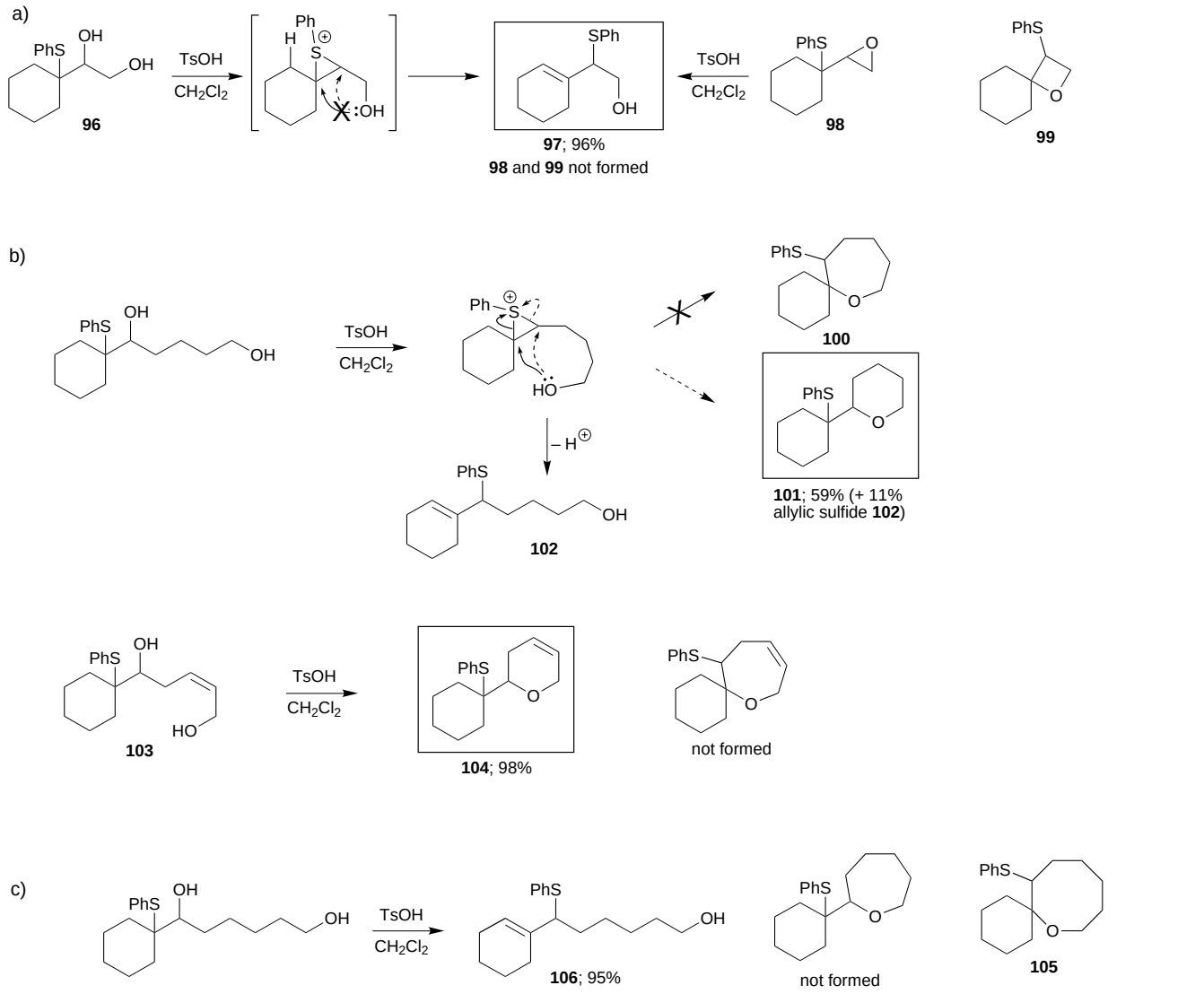
3.2.1 Competition between Primary Hydroxy End Groups of Branched Side Chains

When triol **107**, which contains two diastereotopic hydroxy groups, was cyclized, two products could result, depending on which hydroxy group was involved in the cyclization.[*] The result is that only the *anti* THF **108** is formed in quantitative yield (Scheme 17a).[41] Increasing the length of one of the side chains of triol **107** gives two diastereomeric triols: *anti*-**109** and *syn*-**111** (Scheme 17b). This time, each cyclization can give a rearranged THF or a rearranged THP, again depending on which of the two primary hydroxy groups is involved in the cyclization.[41] Treatment of *anti* triol **109** with *p*-toluenesulfonic acid gave exclusively the *anti* THP **110**. However, treatment of the *syn* diastereoisomer **111** with acid led to the formation of the *anti* THF **112**. Together, these reactions established the importance of the ring stereochemistry: 3,4-*syn* stereochemistry in THFs is unfavorable because the groups are eclipsed, and a

[*] Clearly, two diastereomeric oxetanes could also result by cyclization onto the less substituted end of the thiiranium ion, but, as we have already seen, these compounds are much less stable than the THFs.



Scheme 15. a) Competing THF and THP formation under thermodynamic control; b) evidence for [1,2] PhS migrations being under thermodynamic control; c) competing THF and THP formation under kinetic control; d) competing THF and THP formation under kinetic control with a selenium electrophile.



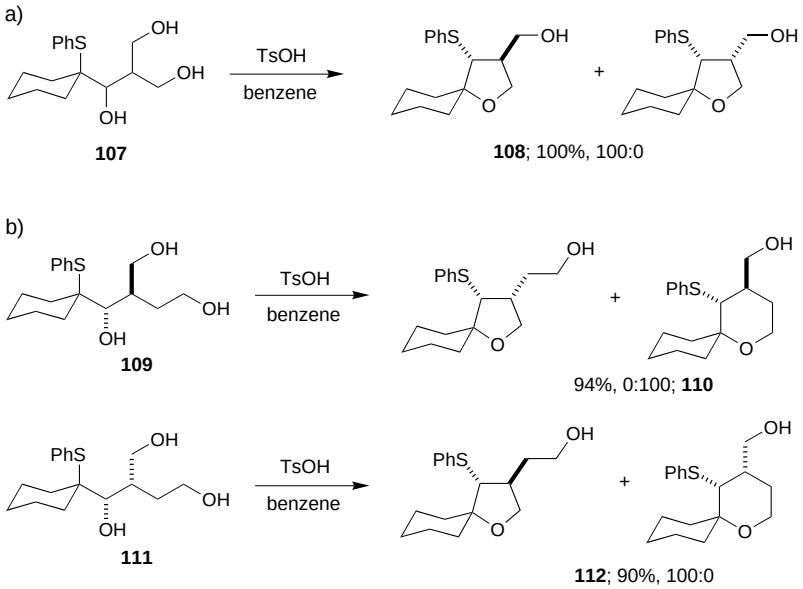
Scheme 16. Limitations of cyclization reactions: a) epoxides and oxetanes are not formed under acid catalysis; b) THPs are formed without [1,2] PhS migration instead of the oxepane alternatives; c) oxocanes and larger rings sizes are not favorable.

3,4-*syn* relationship in the THP would necessitate that one of the substituents be axial.

3.2.2 Competition between Primary Hydroxyl Endgroups of Separate Side Chains

In a series of closely related experiments, we looked at cyclizations onto thiiranium ions in which two separate side chains were terminated by a primary hydroxy group each. An orthogonal protecting group strategy was used to prepare authentic samples of the different cyclization products to establish unequivocally the structure of the products from these competitive cyclization reactions. These reactions were mostly designed to probe the importance of substitution pattern on ring stability. Triol **113** could produce either THF **114** or THF **115** by [1,2] PhS migration (Scheme 18a).[42] It was shown that the major product was the more highly substituted THF **114**. This has been attributed to a thermodynamic manifestation of the Thorpe – Ingold effect.[43, 44] By removing the methyl group from the side chain (triol **116**) it was assumed that the Thorpe – Ingold effect would be minimized and that the product balance would be altered. Indeed the balance was completely altered, and the major product was the THF **117** in which the sulfur group has migrated onto the side chain rather than onto the ring.

In a second series of experiments, competitions were set up between five- and six-membered rings. For example, triol **118** could cyclize to produce either THF **119** or THP **120** (Scheme 18b).[45] Once again the major product was shown to be the more highly substituted heterocycle **119**. The final variation made to this series of compounds was the addition of a pair of *gem* methyl groups to the left-hand side chain to give triol **121**. It was assumed that this substitution would reverse the selectivity to favor the THP **123**. This hypothesis was correct: a complete reversal in THF/THP selectivity was



Scheme 17. a) Competition between diastereotopic hydroxy nucleophiles: *anti* THF is the thermodynamic product; b) stereochemistry can be more important than ring size.

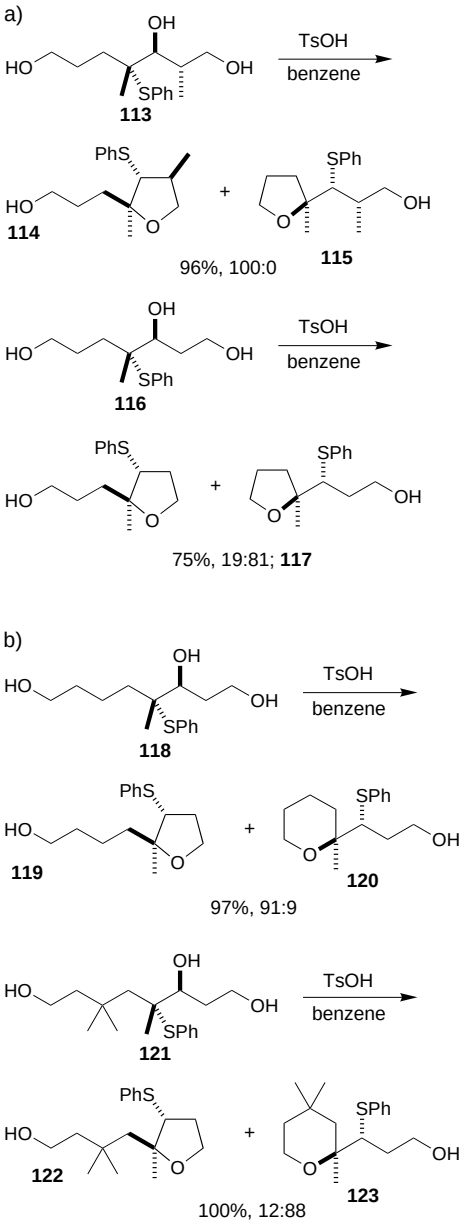
observed from 91:9 (**119**/**120**) to 12:88 (**122**/**123**).[*] The conclusion of these experiments was that ring size (five- or six-membered) is relatively unimportant in deciding the outcome of the reaction; the degree of substitution of the rings is a more important consideration.

3.2.3 Competition between Primary and Secondary Hydroxy Groups in the Same Side Chain

Recently we have studied the cyclization reactions of triols with all three hydroxy groups in the same chain. Four triols **124**, **126**, **128**, and **130** were prepared by asymmetric dihydroxylation and stereocontrolled reduction and rearranged by treatment with *p*-toluenesulfonic acid in refluxing dichloromethane. In each case the thermodynamic products were found to be the THFs **125**, **127**, **129**, and **131**, respectively (Scheme 19a).[6]

In contrast to the rearrangement of the branched triols **109** and **111** (Scheme 17b) ring size has become more important than the relative stereochemistry. Now that the two substituents are 2,4- rather than 3,4-related, a 2,4-*syn* THF is preferred to the alternative 2,4-*anti* THP (Scheme 19a), in which one of the two substituents would enter an axial environment. More interestingly though, the 2,4-*anti* THF is preferred to the 2,4-*syn* THP, in which both groups could now be equatorial. We presume in this case that the factor that governs the outcome of the cyclization (the degree of substitution being equal for both rings) is the *gem*-disubstituted migration origin. In the THP, one of the C–C bonds is forced to be axial; presumably the 1,3-diaxial interactions are too severe and the flatter THF ring is preferred.

[*] It is possible in this case that equilibrium was not reached.

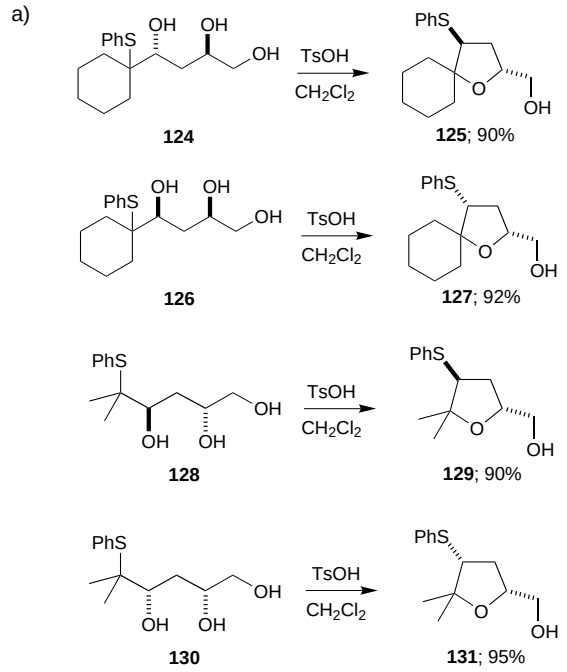


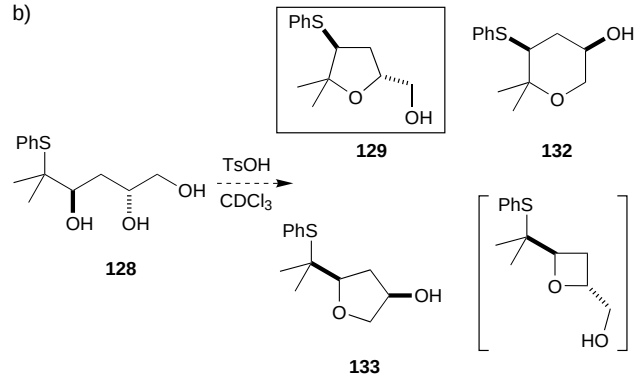
Scheme 18. a) The Thorpe–Ingold effect plays a role in determining the outcome of the cyclization; b) The Thorpe–Ingold effect can reverse the outcome of a competitive cyclization reaction.

By following these cyclizations by ^{1}H NMR spectroscopy, it could be shown that the products of the reaction were very time-dependent, that is, equilibrium was reached slowly.[6] For example, rearrangement of triol **128** in $CDCl_3$ at 40 °C gave three products (unrearranged THF **133**, rearranged THF **129**, and rearranged THP **132**) and starting material after two hours (Scheme 19b). After nine hours, the THF **129**/**132** ratio in the mixture was approximately 1:1; after 36 hours, THF **129** was present with only a trace amount of THP **132**.

3.2.4 Competition between Two Secondary Hydroxy Groups in the Same Side Chain

In the final experiments in this series, the four diastereomeric triols **134**, **136**, **139**, and **141**, which contain three



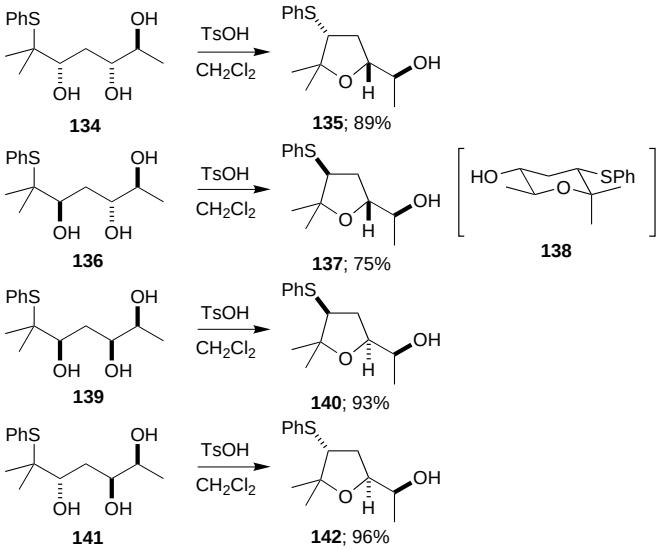


Scheme 19. a) THFs as thermodynamic products from competitive cyclization reactions; b) four possible outcomes of a competition experiment: no oxetane is observed but initially all three products may be observed by ^{1}H NMR spectroscopic analysis.

secondary hydroxy groups in the same side chain, were prepared.[46] This would prove to be the most conclusive test of the relative influence of ring size and stereochemistry. Again it was found that THFs **135**, **137**, **140**, and **142** were produced in very high yields under thermodynamic control (Scheme 20). Only in the case of triol **136** with 2,4-*anti*, 4,5-*anti* stereochemistry was any THP isolated. In this case, THP **138**, which has the maximum number of equatorial substituents, accounted for 17 % of the final product mixture. It seems sensible therefore that 1,3-diaxial interactions that result from an axial methyl group should strongly disfavor THP formation in these types of compounds.

3.2.5 Kinetic Control in Competitive Cyclizations

In Sections 3.2.3 and 3.2.4, we saw that 2,4,5-triols that bear a phenylsulfanyl group at C1 rearrange to THFs as thermodynamic products, independent of the stereochemistry of the

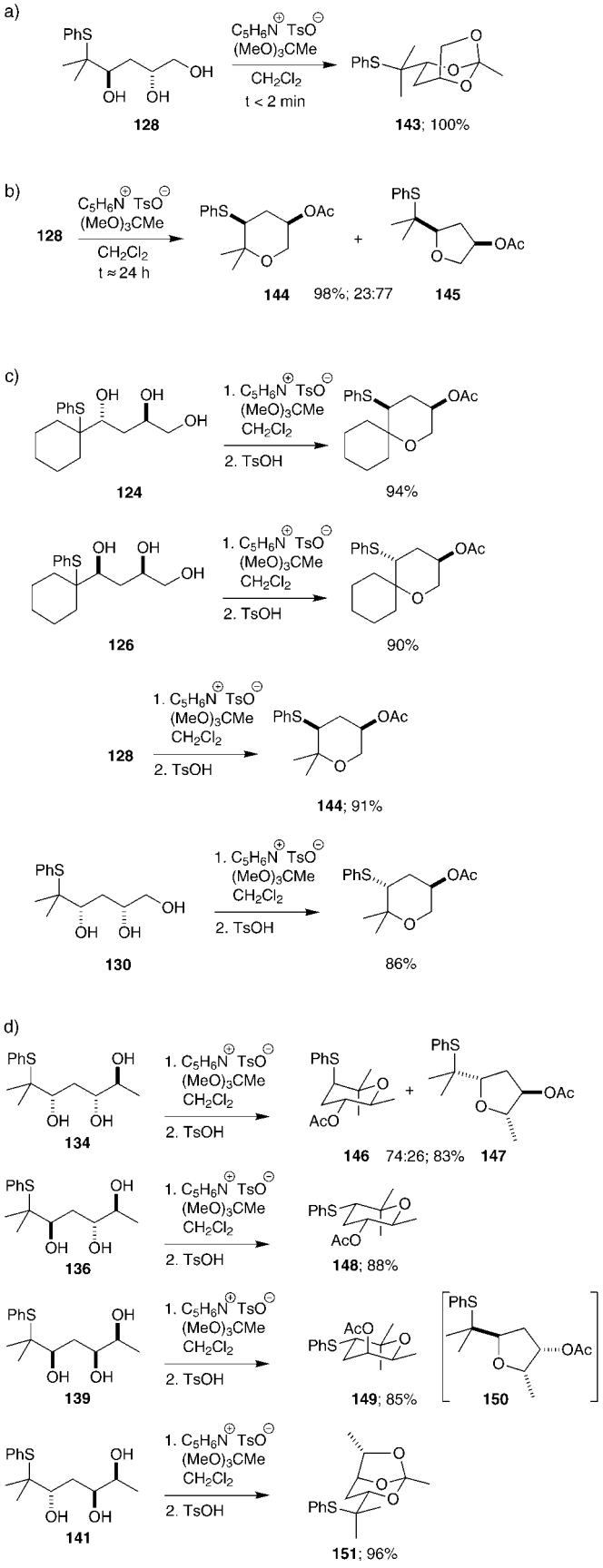


Scheme 20. Cyclization of each triol diastereoisomer gives a THF as the thermodynamic product.

triol. THFs are favored over THPs as a result of unfavorable 1,3-diaxial interactions in the THPs. The same triols were rearranged by using a reagent system specially developed to protect the secondary hydroxy nucleophile and activate the secondary hydroxy leaving group simultaneously.[47] The reagents used were trimethyl orthoacetate and pyridinium *p*-toluenesulfonate (PPTS, $pK_a \sim 5.5$). The choice of acid is very important: orthoesters are known to exchange under general acid catalysis,[48] but we believe that the acid-catalyzed rearrangement of 2-phenylsulfanyl alcohols is a specific acid-catalyzed process (the hydroxy group is protonated before displacement by the sulfanyl group). Generation of a leaving group under these mild conditions ensures that there is no competing direct rearrangement.

Treatment of the *anti* triol **128** under the conditions described gives the bicyclic orthoester **143** after a very short reaction time ($t < 2$ min) (Scheme 21 a). However, if the triol **128** is reacted for a longer period ($t \sim 24$ h), two different products are formed: rearranged THP **144** and unrearranged THF **145** (Scheme 21 b). By following this experiment by ^{1}H NMR spectroscopy and performing a series of control experiments, we could show that the two heterocycles are formed under kinetic control and that the product ratio is independent of reaction time. The results of this experiment complement our earlier studies on cyclic sulfites (Section 3.1.3) and the kinetic analysis of the competing formation of THFs and THPs. This model provides a true kinetic ratio for the acid-catalyzed cyclization, as the nucleophile is a hydroxy group rather than the oxyanion in the cyclic sulfite reactions.

This important mechanistic observation may appear to be useless for synthetic purposes because of the product mixtures that are formed. On the contrary, treatment of the product mixtures with *p*-toluenesulfonic acid leads to complete equilibration to the protected THP **144** in which the sulfanyl group has moved "downhill" (Scheme 21 c).[47] For the triols **124**, **126**, **128**, and **130** (from Section 3.2.3), which contain a primary hydroxy group, this reaction proved to be general (Scheme 21 c).



Scheme 21. a) Formation of an unusual bicyclic orthoester; b) acid-catalyzed rearrangement of a triol under kinetic control; c) two-step rearrangement of triols to give protected THPs as thermodynamic products; d) scope and limitation of the two-step rearrangement of triols.

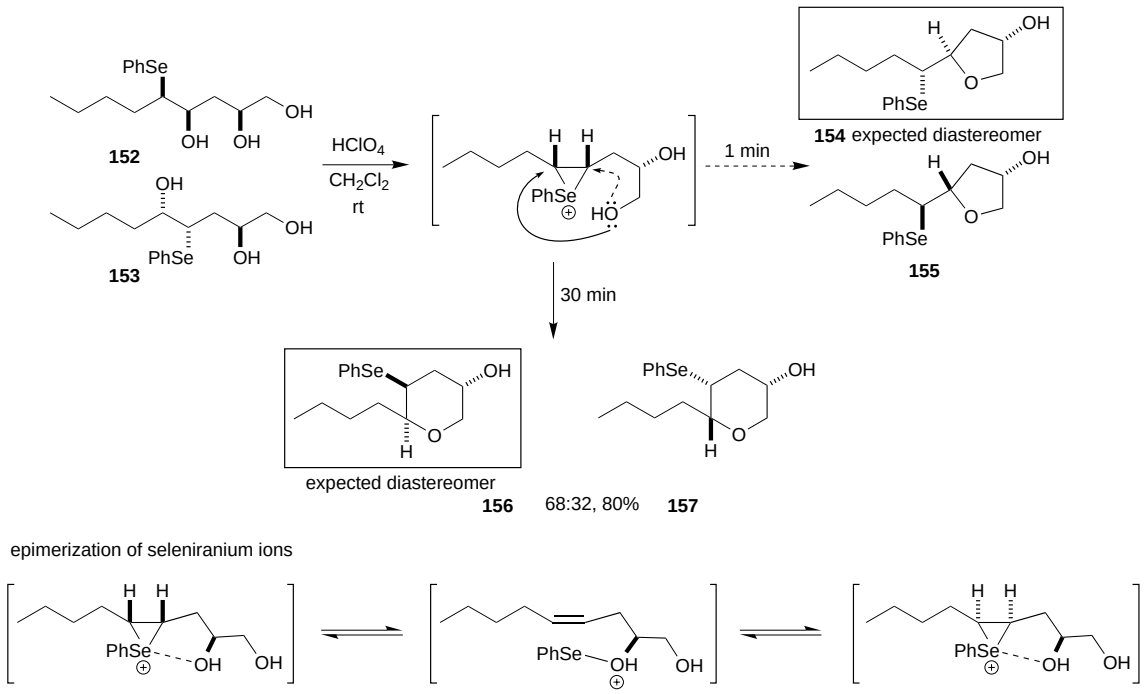
The triols **134**, **136**, **139**, and **141** (see Section 3.2.4), which contain three secondary hydroxy groups, revealed that this two-step route to protected THPs is not without limitations (Scheme 21 d).[46] Depending on the stereochemistry, different products are observed. Rearrangement and equilibration of the 2,4-*syn*, 4,5-*anti* triol **134** gave only a 74:26 mixture of the rearranged THP **146** and unrearranged THF **147**. The inference in this case could be that it is unfavorable for the sulfur group to occupy an axial position, indeed it could be sufficiently unfavorable that it can partly overcome the driving force for "downhill" migration. The 2,4-*anti*, 4,5-*anti* triol **136** behaved quite differently; after equilibration of an initial THF/THP mixture, the only product identified was the THP **148** with the methyl, acetoxy, and phenylsulfanyl groups all occupying equatorial positions (Scheme 21 d). The 2,4-*syn*, 4,5-*syn* triol **139** gave, after the two-step reaction sequence, the THP **149** with an axial acetate (the alternative THF **150** contains an unfavorable 2,3-*syn* relationship) (Scheme 21 d). Finally, the 2,4-*anti*, 4,5-*syn* diastereoisomer **141** gave only the bicyclic orthoester **151** after prolonged treatment with trimethyl orthoacetate and PPTS.

Gruttadauria et al. have examined competitive cyclizations of a series of hydroxyselenides and sulfides.[49–52] When the triols **152** and **153** (which form the same intermediate seleniranium ion) were treated with perchloric acid in dichloromethane at room temperature, the two diastereomeric THFs **154** and **155** were produced after one minute (Scheme 22).[50] These THFs are unrearranged products (i.e. products in which no [1,2] PhSe migration has occurred). However, if the reaction was run for 30 minutes, unrearranged THPs **156** and **157** were produced. Clearly the THPs are the thermodynamic products of this reaction. To explain the fact that diastereomeric products are formed, the authors proposed that one of the hydroxy groups might interact with the selenium atom of the seleniranium ion intermediate to the extent that the C–Se bonds are broken to give a transient alkene. This would allow rotation to occur and a second addition of the selenium onto the opposite face of the alkene. The equilibration of seleniranium ions represents one of main differences between cyclizations with selenium and sulfur compounds.

4 Cyclization with Sulfur and Nitrogen Nucleophiles

4.1 Synthesis of Sulfur-Containing Heterocycles

The use of thiiranium ions to promote cyclization reactions has been extended to include thiols as nucleophiles.[53, 54] The 1,*n*-hydroxythiols **158**–**160** were prepared by Mitsunobu displacement of the primary alcohol of the corresponding 1,*n*-diol by using Ziram followed by reduction with lithium aluminum hydride (Scheme 23 a). This route could not be used to prepare the 1,3-hydroxythiol; as we saw in Section 3.1.2, this reaction gives oxetanes instead (Scheme 13 c).[53] However, aldol reaction of aldehyde **31** with the lithium enolate of ethyl dithioacetate followed by reduction did give the required 1,3-hydroxythiol **161** (Scheme 23 b). On treatment with acid, the 1,3-hydroxythiol **161** gave the spirocyclic



Scheme 22. Cyclizations involving seleniranium ions.

thiolane **162**, which belongs to a class of compounds that is not well-known (Scheme 23c).[54] None of the thietane **163** was detected.

The second member of the series, 1,4-hydroxythiol **158**, rearranged to give not the expected thiane **164**, but instead the unrearranged thiolane **165** (Scheme 23d).[54] This is exactly the opposite situation to the analogous alcohol **84** cyclization in which the rearranged THP **86** is formed. Our criteria for sulfur moving "downhill" can no longer be applied in this case because two sulfur atoms are present. The primary sulfide nucleophile is necessarily moving "uphill" and so this must counteract the tendency of the tertiary sulfanyl group to move "downhill". In this seemingly subtle example, the deciding factor is likely to be the adverse 1,3-diaxial interactions that would be present in the thiane **164**. As expected the 1,5-hydroxythiol **159** does not give the thiepane **166**, instead the unrearranged thiane **167** is formed.[54] This must reflect the increased strain in the seven-membered ring (Scheme 23e). Finally, as we saw for the 1,6-diol, the 1,6-hydroxythiol **160** undergoes elimination to give the allylic sulfide **168** because the side chain has now become too long for cyclization to compete with elimination (Scheme 23f).[54]

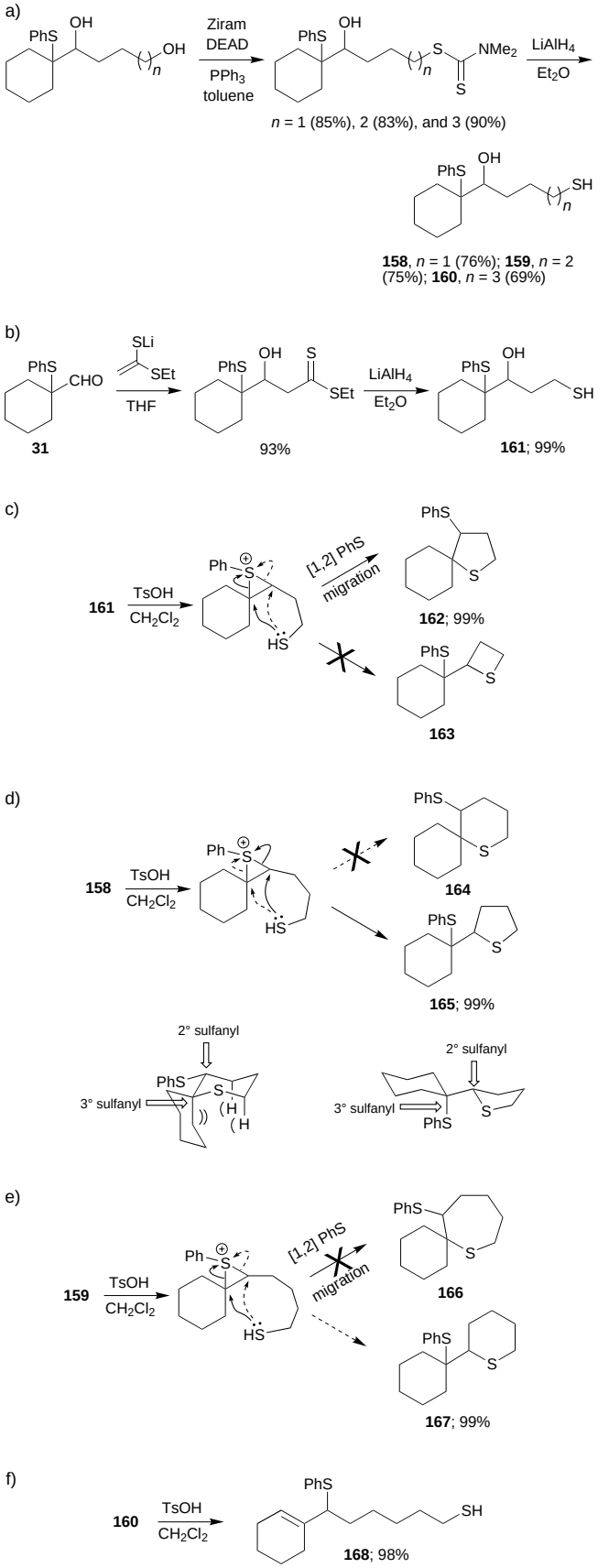
It is not yet clear whether the cyclization reactions with sulfur nucleophiles are under kinetic or thermodynamic control. Sulfides are much less basic than ethers and so once formed, the heterocycles might not be reopened. An alternative approach to thiolanes by using [1,4] participation of a benzylsulfanyl (BnS) group is discussed in Section 5.2.

4.2 Synthesis of Nitrogen-Containing Heterocycles

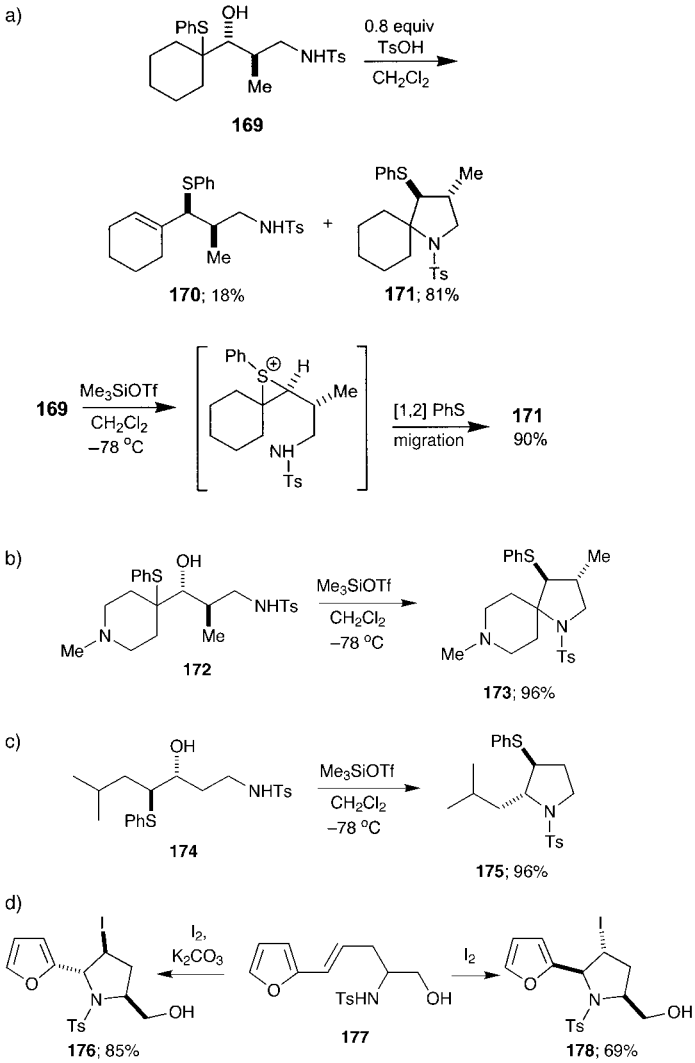
The synthesis of nitrogen heterocycles by sulfanyl migration presents a real challenge. Within the acidic reaction conditions used to generate thiiranium ions, any amine nucleophiles will be protonated and hence their nucleophilicity removed. A successful strategy would require the generation of a leaving group under non-acidic conditions (a subject of current research) or the fine-tuning of the basicity of the nitrogen atom with minimal detriment to its nucleophilicity. Sulfonamides were found to satisfy this second criterion partially.[24] Treatment of sulfonamide **169** with *p*-toluenesulfonic acid in dichloromethane gives some of the allylic sulfide **170**, together with the pyrrolidine **171**, but use of trimethylsilyl triflate gives the protected pyrrolidine **171** in satisfactory yield (Scheme 24a).

The synthesis of protected pyrrolidines with trimethylsilyl triflate is quite general, for example, amine functionality in the substrate is tolerated (e.g. **172**→**173**, Scheme 24b) and "flat" migrations are also possible (e.g. **174**→**175**, Scheme 24c), as was the case for certain cyclic ethers.[24] Table 4 shows some other examples of this reaction; enantiomerically pure starting materials could be prepared by an Evans *syn*-selective asymmetric aldol reaction[55, 56] and products with 3,4-*syn* stereochemistry are possible.

Knight et al. have published details of their iodine-induced cyclizations by using nitrogen nucleophiles.[57] A particularly interesting example was the treatment of sulfonamide **177** with iodine under basic conditions to give the 2,5-*anti* pyrrolidine **176** and under acidic conditions to give the 2,5-*syn* pyrrolidine **178** (Scheme 24d). The authors rationalized this observation by invoking the participation of the furan oxygen atom in the base-catalyzed cyclization. Our attempts to use carbon nucleophiles to trap thiiranium ions have so far met with only limited success. Edstrom and Livinghouse have reported the reaction of electron-rich arene nucleophiles with thiiranium ions in the presence of silver salts.[58]

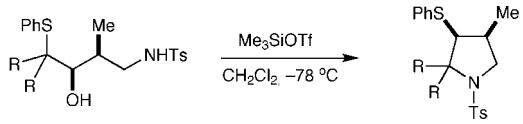


Scheme 23. a) Synthesis of 1,*n*-hydroxythiols ($n+3$); b) synthesis of 1,3-hydroxythiols; c) rearrangement of 1,3-hydroxythiols to give thiolanes; d) 1,4-hydroxythiols give thiolanes without [1,2] PhS migration; e) 1,5-hydroxythiols give thianes without [1,2] PhS migration; f) 1,*n*-hydroxythiols with $n > 5$ rearrange to allylic sulfides.



Scheme 24. a) Trimethylsilyl triflate promoted cyclization with a sulfonamide nucleophile; b) pyrrolidine formation; c) flat migrations may be tolerated in pyrrolidine formation; d) iodine-promoted pyrrolidine formation.

Table 4. Examples of Me_3SiOTf-promoted pyrrolidine synthesis with [1,2] PhS migration.



R	Yield
c-C_5H_8	96% (>98% *ee*)
c-C_6H_{10}	99%
$-CH_2CH_2(NMe)CH_2CH_2-$	89%

5 Thiolanium Ions and [1,4] RS Participation

Until now the discussion has been mostly centered around thiiranium ions formed by [1,2] sulfanyl participation, which is by far the most common example of sulfur participation. Sulfur is also known to participate to give thietanium,[59, 60] thiolanium,[61, 62] and thianium ions.[62, 63] We concern ourselves here with only thiolanium ions, as sulfur participation to give

four- and six-membered rings is kinetically less favorable and consequently less well documented.

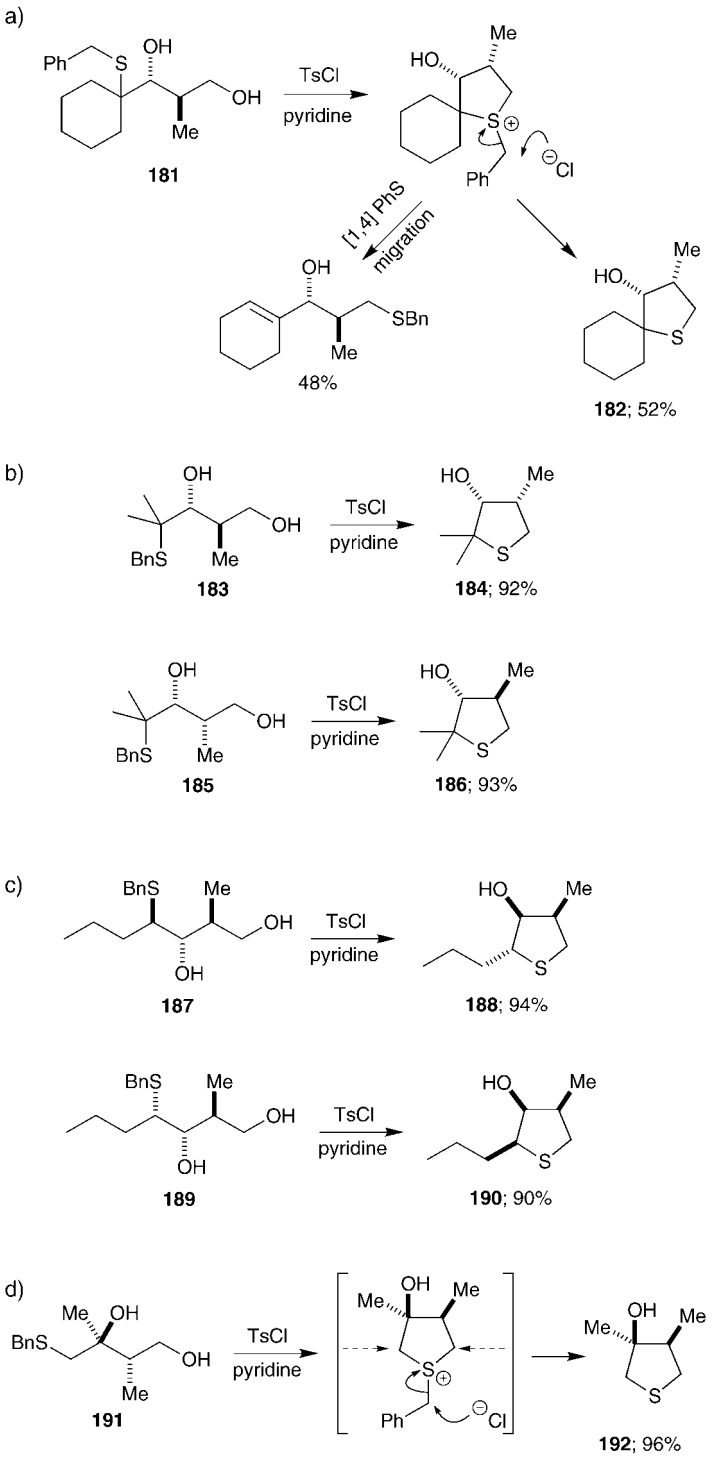
5.1 Elimination Reactions of Thiolanium Ions

In Section 3 we discussed the 1,3-diol **49** and noted that this compound provided the link between elimination and cyclization reactions of thiiranium ions: on treatment with acid, the free diol cyclizes, whereas the primary protected compound **33** undergoes elimination (Scheme 11). If diol **49** is treated with *p*-toluenesulfonyl chloride instead of acid, an altogether different pathway is followed (Scheme 25).[37] The primary hydroxy group is first tosylated; in a second step sulfur participates in a [1,4] fashion through a five-membered ring to give the thiolanium ion **179**. With no suitably placed nucleophiles, elimination occurs to give the allylic alcohol **180** in which the sulfanyl group has undergone a [1,4] migration.

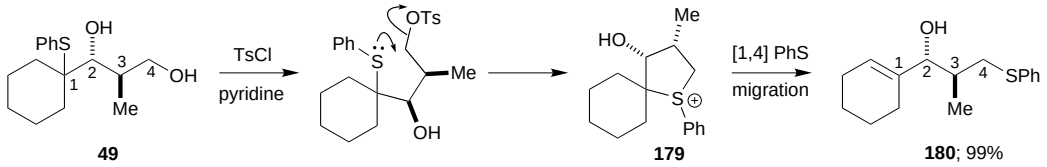
5.2 Thiolane Synthesis by Debenzylation of Thiolanium Ions

The choice of R in [1,2] RS migration reactions is largely irrelevant. Most commonly, R = Ph because it provides a chromophore to aid in chromatographic processes. Alkylsulfanyl (R = Me, Et, *t*Bu), benzylsulfanyl, and even sulfanyl (R = H) groups have also been used successfully.[29] TsCl-promoted [1,4] PhS migration of the benzylsulfanyl diol **181** opened up yet another reaction pathway. Not only does elimination occur onto the thiolanium ion, but the chloride ion released in the reaction also debenzylates the thiolanium ion to give the some of the thiolane **182** (Scheme 26a).[64] With a view to increasing the yields of thiolane formed in these reactions, acyclic sulfides were also examined (elimination of an axial proton from within the cyclohexane ring is particularly favorable). From *anti* diol **183** and *syn* diol **185** thiolanes *syn*-**184** and *anti*-**186** were formed in yields of 92% and 93%, respectively (Scheme 26b).[64] Table 5 shows that sterically crowded thiolanes may also be formed by using this reaction.

Secondary sulfides also perform well in this reaction: *anti* sulfide **187** and *syn* sulfide **189** were converted into thiolanes **188** and **190** in yields of 94% and 90% yields, respectively (Scheme 26c).[64] Amazingly, even primary sulfides are well behaved in this reaction: the sulfide *anti*-**191** gives thiolane *syn*-**192** on treatment with *p*-toluene-

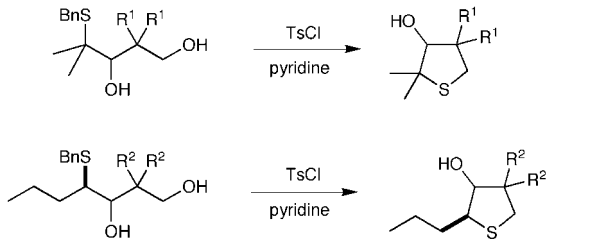


Scheme 26. a) Alternative thiolane synthesis in the presence of a benzylsulfanyl group; b) the stereochemistry is not affected in the [1,4] BnS migration; c) flat migrations are tolerated in cyclizations with [1,4] BnS migration; d) successful [1,4] BnS migration of primary sulfides.



Scheme 25. [1,4] PhS migration proceeds via a thiolanium ion intermediate.

Table 5. Examples of thiolane synthesis by [1,4] BnS participation and debenzylation.



R^1	R^2	Stereochemistry	Thiolane	Yield
H	–	n/a		93 %
Me	–	n/a		94 %
–	H	*anti*	*anti*	94 %
–	H	*syn*	*syn*	91 %
–	Me	*anti*	*anti*	96 %

sulfonyl chloride, despite there being three appealing sites for an S_N2 reaction (Scheme 26d).

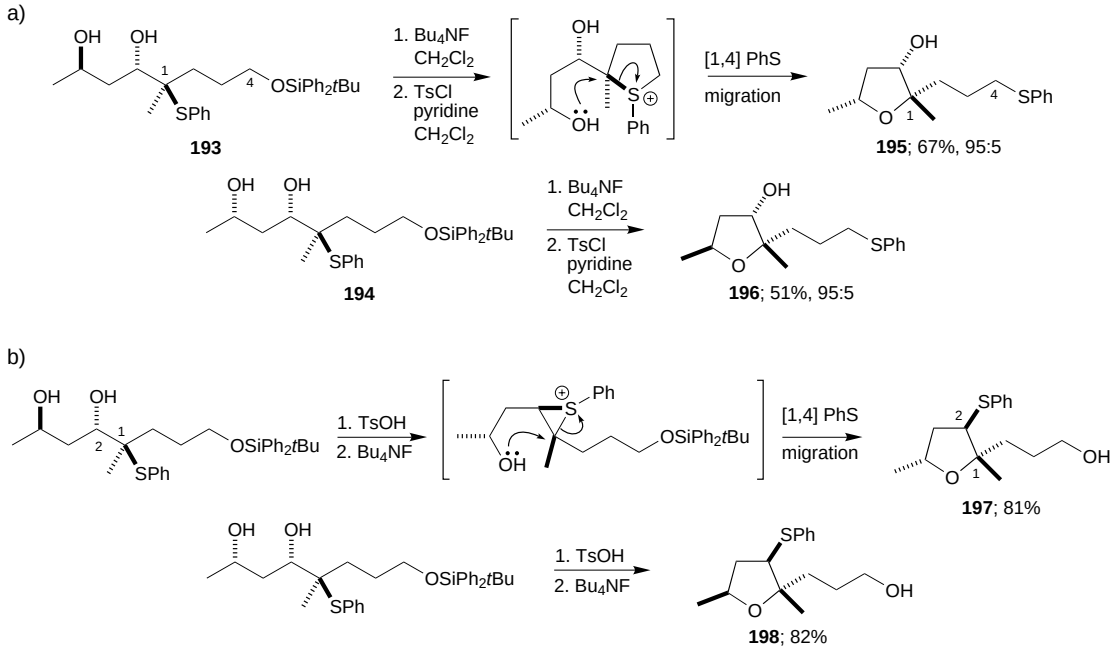
5.3 [1,4] PhS Migration as an Alternative Route to THFs

A logical extension to the [1,4] RS participation is to introduce suitably placed nucleophiles to permit cyclization by a [1,4] RS migration. Primary protected triols *anti*-**193** and *syn*-**194** could be prepared by a short sequence of reactions that included an aldol reaction and a stereocontrolled reduction. Deprotection of these triols (TBAF) and treatment with *p*-toluenesulfonyl chloride led to the highly substituted THFs **195** and **196**, albeit in rather modest yields (Scheme 27a).[65] The cyclization was shown to be stereospecific (NOESY) with inversion at the migration origin as expected. The minor isomers formed in these reactions are believed to be the C2 epimers formed by ring opening and reclosing of the thiolanium ion, a process that we have never observed for thiiranium ion mediated cyclizations. To prove that these compounds had not been formed by the normal [1,2] PhS pathway, the protected triols were rearranged with *p*-toluenesulfonic acid and deprotected to give the isomeric THFs **197** and **198** (OH-, PhS-exchanged, and different stereochemical series) (Scheme 27).

6 Summary and Outlook

The strategy of migrating functional groups represents a useful and efficient method in organic synthesis. The sulfanyl group enjoys a prominent role in rearrangement reactions; perhaps no other element in the periodic table offers as diverse a potential for rearrangement reactions. We have shown how [1,2], [1,3], and [1,4] sulfanyl migrations can bring about rearrangements in a high-yielding and stereocontrolled fashion. One of the main aims of this Review has been to highlight the kinds of molecules that can be prepared by using the strategy of sulfanyl migration: this method is particularly suited to the stereocontrolled synthesis of five- and six-membered saturated heterocycles and functionalized alkenes with 1,4-related stereogenic centers. From the examples encountered in this Review, some general guidelines for cyclizations can be drawn:

- Only THFs and THPs are formed under equilibrating conditions; epoxides, oxetanes, and saturated oxygen heterocycles with seven or more atoms have never been observed.
- THFs with 3,4-*syn* stereochemistry are thermodynamically unfavorable; if a THF or THP alternative is available, this is likely to be the major product.



Scheme 27. a) Capture of thiolanium ions by hydroxy nucleophiles—an alternative stereocontrolled THF synthesis; b) synthesis of isomeric THFs by [1,2] PhS migration.

- *gem*-Dialkyl substitution on a cyclizing side chain may stabilize a product according to the Thorpe – Ingold effect.
- In situations in which the same *gem*-dialkyl pair are present in a THF or a THP, a THF is likely to result.

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