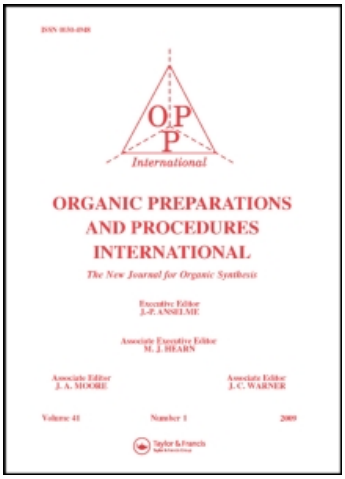

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SYNTHESIS AND REACTIONS OF SULFINYL CHLORIDES. AN UPDATE

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SYNTHESIS AND REACTIONS OF SULFINYL CHLORIDES. AN UPDATE

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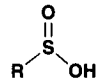
SCOPE AND INTRODUCTION

The sulfinyl chloride functionality is the acid chloride of a sulfinic acid. Over the last four decades, since the pioneering synthetic work of Douglass,[1] sulfinyl chlorides have clearly advertised their usefulness in a variety of synthetic situations. Perhaps the most important is their role in the evolution of homochiral sulfinate ester chemistry targeted toward the generation of optically enriched sulfoxides.

sulfinyl chloride



sulfinic acid

This review will encompass newer aspects of sulfinyl chloride chemistry emphasizing accomplishments of the late 1980's and the 1990's. Some of the noteworthy chemistry unearthed during this time period includes the use of sulfinyl chlorides in the construction of sulfinamide- and sulfonamide-containing peptidomimetics,[2] the exploitation of kinetic diastereoselectivity for efficient sulfinate formation by way of alcohol substitution reactions[3] and the first synthesis of α,β-unsaturated sulfinyl chlorides.[4,5] Two older reviews have been published, the most recent being by Tillett[6] in a monograph pertaining to sulfinic acids and derivatives. The review of Douglass[1] addresses only synthetic aspects of sulfinyl chlorides.

This review will not emphasize the reactions and utility of homochiral sulfinate esters, although there is a large body of asymmetric chemistry that results from optically pure menthyl *p*-toluenesulfinates, which in turn are prepared from sulfinyl chlorides. A recent noteworthy adaptation of this homochiral sulfinate chemistry is the use of *N*-(*p*-toluenesulfinyl)sulfinimines for asymmetric synthesis.[7,8] The review will not address the chemistry of chlorosulfinates except where direct inclusion of that material is required to provide a more complete story of sulfinyl chlorides.

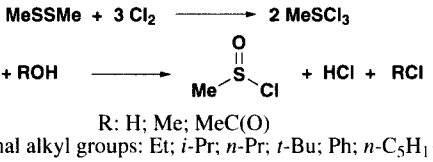
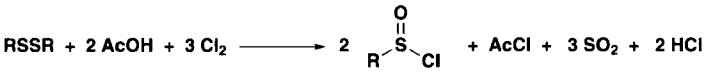
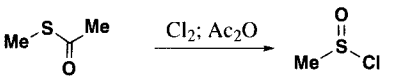
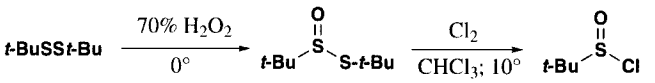
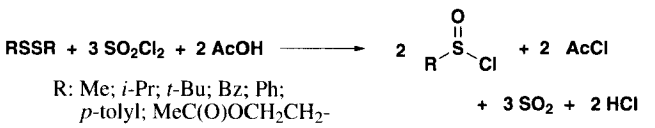
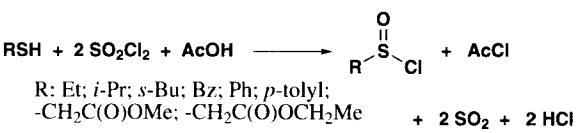
This review is structured with an update of synthetic approaches to sulfinyl chlorides. Following that, the reactivity sections are subdivided mostly on the basis of *immediate* products formed. The reader should be aware that in many instances diverse chemistry often is observed after the first reaction of the sulfinyl chloride. Section II.A.1.c) is particularly indicative in this regard in that all initial reactions outlined yield sulfinic acid derivatives, which in turn succumb to various rearrangements.

Finally, in keeping with the synthetic mandate of this *Journal*, the review will not necessarily be biased toward the synthetic value of sulfinyl chlorides, but will on occasion inform the reader of preferred or comparable alternatives for achieving particular synthetic targets.

I. SYNTHESES OF SULFINYL CHLORIDES

A number of methods have been developed for the preparation of a variety of sulfinyl chlorides (Table 1).[1,9-14] The lower molecular weight sulfinyl chlorides, such as the alkanesulfinyl chlorides and simple arenesulfinyl chlorides are liquids, and many of these have been purified via vacuum distillation. Care must be taken, however, as a number of explosions have been reported.[11] Substituted arenesulfinyl chlorides are typically solids.[11] A tabulation of some novel sulfinyl chlorides prepared by established and recent protocols is found later in this section.

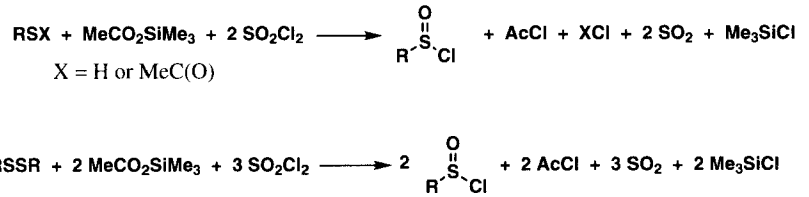
Table 1. Preparative Methods for Sulfinyl Chlorides

Synthetic Method	Reference
	9
	10
	11
	1
	12
	13
	14

The preparation of sulfinyl chlorides from thiolacetates has been previously reported (Table 1).[1,10-14] A suggested modification to this method involves replacing gaseous chlorine with sulfuryl chloride (*Scheme 1*).[15] This procedure was originally proposed in 1978[16] but only in the paper's experimental section, and went unnoticed[17] for several years before being rediscovered. Using this procedure alkyl and aryl thiolacetates have been converted to the corresponding sulfinyl chlorides in high yields (86-97%). The advantages of this modification are that the formation of large amounts of gaseous HCl does not occur and only the volatile reaction by-products SO_2 and acetyl chloride are formed. This protocol also avoids the use of thiols since the alkyl or aryl thiolacetates can be prepared from the corresponding alcohol.

Scheme 1

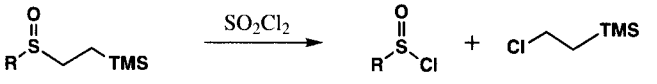
Another modification to this procedure makes use of trimethylsilyl acetate as an alternative to acetic anhydride.[17] This reagent simultaneously serves as both the oxygen donor and the chloride ion acceptor. The reaction can be used for the preparation of alkane- and arenesulfinyl chlorides from either thiols, thiolacetates, or disulfides in 80-100% yield (*Scheme 2*). Again the process is advantageous in that only relatively mild reaction by-products are generated. These preparations also occur rapidly; compared to alternative procedures which may take as long as 16 hours, the aliphatic sulfinyl chlorides are formed in minutes and the arenesulfinyl chlorides are created in less than five hours. The method is not ideal for benzyl sulfinyl chloride (50% yield) and *t*-butyl sulfinyl chloride does not form at all.



Scheme 2

Schwan and coworkers have also used sulfuryl chloride to prepare a variety of aliphatic and aromatic sulfinyl chlorides[18,19] via an oxidative fragmentation of aliphatic and aryl 2-trimethylsilylethyl sulfoxides (**1**), respectively. The key to this chemistry is that in most cases the normally observed α-oxidation of the sulfoxides is precluded by the presence of the 2-trimethylsilylethyl functionality which promotes oxidative fragmentation and sulfinyl chloride generation (*Scheme 3*). For aliphatic sulfinyl chlorides, the method is most effective when by-product **2** can be removed under reduced pressure prior to distillation of the sulfinyl chlorides; this is not a problem for the aromatic congeners.[18] Starting from sulfoxides **3** or **4**, this methodology could also be applied for the preparation of 2-(trimethylsilyl)ethanesulfinyl chloride (**5**) (*Scheme 4*). Interestingly, the oxidative fragmenta-

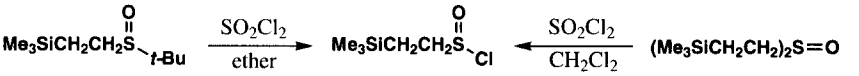
tion mode of **3** has a notable solvent dependence: *t*-butanesulfinyl chloride becomes a significant product if the reaction is performed in CH_2Cl_2.[19] Similar fragmentation routes to sulfinyl chlorides using phthalimidomethyl sulfoxides have been reported.[20,21]



1 2

R: Ph; *p*-MeC_6H_4; *p*-ClC_6H_4; 2-naphthyl; *n*-Pr; $PhCH_2$; $TMS(CH_2)_2$; $CH_2{=}CHCH_2$; *c*-C_6H_{11}; *n*-$C_{12}H_{23}$

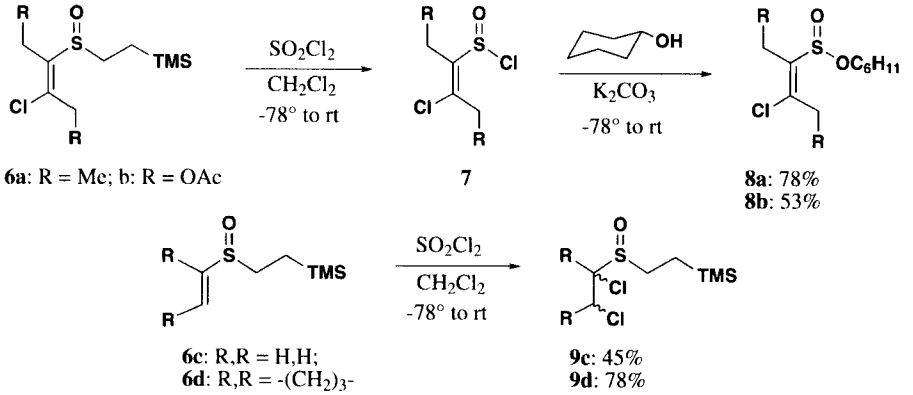
Scheme 3



3 5 4

Scheme 4

The oxidative fragmentation method was viewed as a possible method for the first preparation of 1-alkenesulfinyl chlorides. The concept was that the conjugated double bond of a *sulfoxide* starting substrate should have reduced nucleophilic character and would be less reactive toward electrophilic chlorine reagents. As a continuation of this thinking, 1-alkenyl 2-(trimethylsilyl)ethyl sulfoxides (**6a-d**) were prepared and subjected to the oxidative fragmentation conditions (*Scheme 5*). In the case of **6a** and **6b** the corresponding sulfinyl chlorides (**7a/b**) were observed via TLC and IR spectroscopy, and were isolated as their cyclohexyl 1-alkenesulfinate esters (**8a/b**)[4] as a means to complete characterization. When compounds **6c** and **6d** were treated under identical reaction conditions, formation of the corresponding sulfinyl chlorides was not observed. Instead, α,β-dichlorination products **9c** and **9d** were isolated. Products **9c/d** are presumed to be formed as a result of an additive Pummerer reaction.[22]



6a: R = Me; b: R = OAc

7

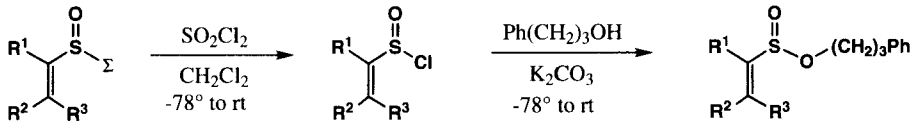
8a: 78%
8b: 53%

6c: R,R = H,H;
6d: R,R = -$(CH_2)_3$-

9c: 45%
9d: 78%

Scheme 5

Prompted by the partial success of the 2-(trimethylsilyl)ethyl group, Schwan and coworkers investigated other groups and found the diphenylmethyl (DPM) and a *p*-methoxybenzyl (PMB) units to be most useful. Several 1-alkenyl sulfoxides bearing these groups were prepared and treated under similar reaction conditions (*Scheme 6*).[4,5] In each case the presence of 1-alkenesulfinyl chlorides could be observed through TLC and solution cell IR analysis (sulfinyl stretching frequency ~ 1140-1150 cm^{-1}) of the reaction mixture. Again, owing to their inherent instability, the sulfinyl chlorides were isolated as 1-alkenesulfinate esters. Lower molecular weight sulfinyl chlorides **10** and **11**, prepared from the corresponding DPM sulfoxide were isolated (90% purity) when subjected to flash distillation conditions.[5]



Σ = diphenylmethyl (DPM); *p*-methoxybenzyl (PMB)
R: various alkyl, aryl and ester groups

Scheme 6

10 11

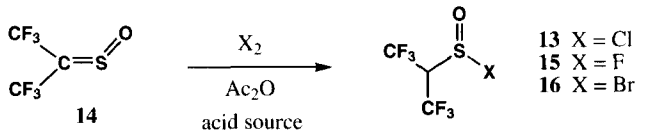
The oxidative fragmentation procedure suggested by Schwan and coworkers is advantageous in that it can be used to prepare a variety of aliphatic, aryl and now vinylic sulfinyl chlorides without any of the acidic by-products such as HCl, acetic acid or acetyl chlorides which are normally found with some of the earlier procedures.

Haloalkanesulfinyl chlorides (**12**) have been prepared from the corresponding sulfinic acid upon treatment with thionyl chloride (*Scheme 7*).[23] As in many cases the sulfinyl chlorides were not directly characterized, but instead were confirmed through analysis of their sulfinate ester derivative. It was found that these sulfinyl chlorides are relatively stable, hydrolyzing slowly in water. Other groups have shown that the method can also accommodate unique alkyl groups not involving halogens and in those cases the sulfinic acid was accessed through MCPBA oxidation of the corresponding thiol.[24,25] The method of *Scheme 7* is directly comparable to the chemistry of carboxylic acids and is a slight variation of the familiar sulfinyl chloride preparation using sulfinate salts and $SOCl_2$.[26]

12 R: CCl_3; $CFCl_2$; CF_3CCl_2
CF_2Cl; CF_3CBrCl

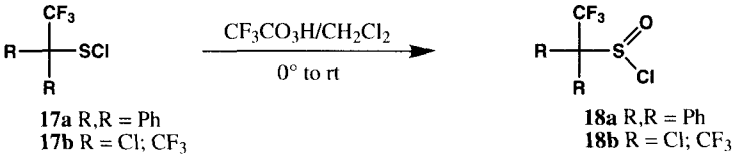
Scheme 7

In a series of papers Sundermeyer and coworkers report the preparation of haloalkanesulfinyl chlorides **13** from the corresponding sulfine (**14**) (*Scheme 8*).[27-30] This is accomplished through treatment of the sulfine with Cl_2 and either acetic anhydride or HCl.[27,28,30] On an interesting note, when F_2 or Br_2 are used as the halogenating agent the corresponding sulfinyl fluoride (**15**) or sulfinyl bromide (**16**) can be prepared.[28-30] The preparation of sulfines from sulfinyl chlorides will be discussed in Section IIB of this review.



Scheme 8

There are also examples for the preparation of sulfinyl chlorides from the oxidation of the corresponding sulfenyl chloride (*Scheme 9*).[31,32] Oxidation of sulfenyl chlorides **17** with trifluoroperacetic acid affords sulfinyl chlorides **18**. Preparation of sulfenyl chlorides is typically achieved by treating the corresponding thiol with SO_2Cl_2.[31,32]



Scheme 9

Methanesulfinyl chloride can be prepared containing an ^{18}O label by treating the disulfide with SO_2Cl_2 in the presence of hexamethyldisiloxane, which serves as the ^{18}O carrier.[33]

Table 2. New Sulfinyl Chlorides using Established Procedures

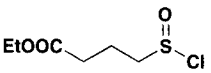
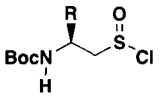
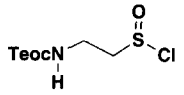
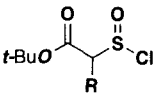
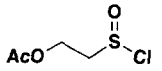
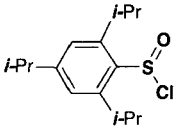
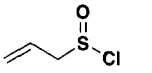
Sulfinyl Chloride	Starting Substrate	Reagents[a]	Synthetic Reference
	thiolacetate	Cl_2/Ac_2O[1]	34
 R = TMS	sulfinic acid	$SOCl_2$[24]	25
R = H	disulfide	Cl_2/Ac_2O[11]	35
	thiolacetate	SO_2Cl_2/Ac_2O[15]	35

Table 2. New Sulfinyl Chlorides using Established Procedures

Sulfinyl Chloride		Starting Substrate	Reagents[a]	Synthetic Reference
	**19**, R = H	thiolacetate	Cl_2; Ac_2O[1]	36
			SO_2Cl_2; Ac_2O[15]	37
	20, R = Me **21** R = Bn	thiolacetate	Cl_2; Ac_2O[1]	38
	**22**	disulfide	Cl_2; Ac_2O[11]	37
	R = H, Me	thiolacetate	Cl_2; Ac_2O[1]	39
	**23**	thiolacetate	SO_2Cl_2; Ac_2O[15]	40, 41
		sodium sulfinate	$SOCl_2$[26]	42
		magnesium sulfinate	$SOCl_2$[26]	43

a Original or usual protocol for sulfinyl chloride generation, with the corresponding reference.

As a means to indicate the sustained usefulness of some of the synthetic routes to sulfinyl chlorides as described above, a compilation of novel sulfinyl chlorides is presented in Table 2.[25, 34-43] The compounds in this Table are indicative of the types of sulfinyl chlorides required for modern synthetic and structural pursuits.

II. REACTIONS

Sulfinyl chlorides have limited uses themselves and their practical role is as intermediates in the synthesis of other compounds. The high electrophilicity of the sulfinyl functionality coupled with the good leaving capability of chloride makes sulfinyl chlorides willing partners in substitution reactions. Moreover, the electron withdrawing power of the S, O and Cl atoms permits chemistry initiated by α-deprotonation, which in most cases leads to sulfine formation.

A. Substitutions

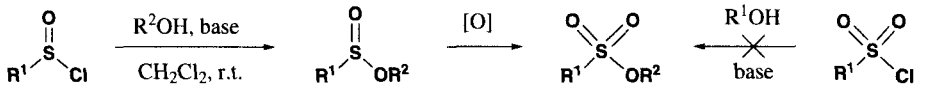
In the manifold of substitution reactions, simple conversion to other sulfinic acid derivatives is well established and recent applications are documented below. Some novel approaches to effecting successful substitution reactions involve the use of atoms other than hydrogen on the nucleophilic

partner[44] or groups other than chlorine on the sulfinyl unit. Nevertheless, the major focus of subsequent sections will be on newer discoveries pertaining to the substitution reactions for the preparation of optically enriched sulfinic derivatives and the application of sulfinamides to peptide synthesis.

1. Conversion to Sulfinic Acid Derivatives

Reactions with oxygen or nitrogen nucleophiles tend to be the more common substitution reactions observed. Indeed, sulfinate ester formation via alcohol substitution was performed by the Schwan group as a means to obtain full characterization of 1-alkenesulfinyl chlorides produced in an oxidative fragmentation reaction.[4,5] The increased stability of the sulfinates over their sulfinyl chloride precursors allows comparatively facile isolation and full spectroscopic analysis.

As part of a study of sterically crowded sulfonate acid derivatives, Netscher and Prinzbach[31] required a series of *t*-butane- and 2,2,2-trifluoro-1,1-diphenylethanesulfonate esters (**23**). A direct synthesis of these targets by substitution on the sulfonyl chloride proved unsuccessful, perhaps due to steric hindrance of the large groups. The problem was solved through esterification of the sulfinyl chloride and oxidation of the sulfinate to the sulfonate (*Scheme 10*). A number of sulfinates bearing a variety of alkoxy groups could be oxidized with $CF_3CO_3H/NaHPO_4/CH_2Cl_2$ (65-100%) to finalize the synthesis of the sulfonates.



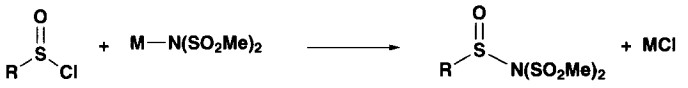
23

R^1 = *t*-Bu, base = Et_3N, 76-95%
R^1 = $Ph_2(CF_3)C$, base = Me-Im, 58-82%

Scheme 10

In a related report, Wienreb and co-workers introduced the *t*-butyl sulfonyl group as a protecting group for amines.[45] Again, due to the lack of reactivity of the sulfonyl chloride, the authors attached *t*-butanesulfinyl chloride to a series of primary and secondary amines and called upon an oxidation procedure to access the sulfonamide-protected amine. Sulfinamide formation and oxidation (MCPBA or $RuCl_3/NaIO_4$) proceeded in good to excellent yield. For the deprotection step, TfOH is slightly preferred over TFA. A comparable substitution/oxidation sequence was also employed in the construction of sulfonylimidazole derivatives, prepared for evaluation as inhibitors of farnesyl-protein transferase.[46] Regarding intramolecular substitution reactions, the mechanism of the diastereoselective formation of a cyclic sulfinamide is discussed in terms of rates of reactions of diastereomeric sulfinyl chlorides.[47]

A recent report describes the preparation of the first sulfinic acid amides with two sulfonyl groups on the nitrogen (*Scheme 11*).[48] Exchange reactions could be achieved when bis(methanesulfonyl)amine was derivatized with either a TMS unit or a Ag^+ counterion.

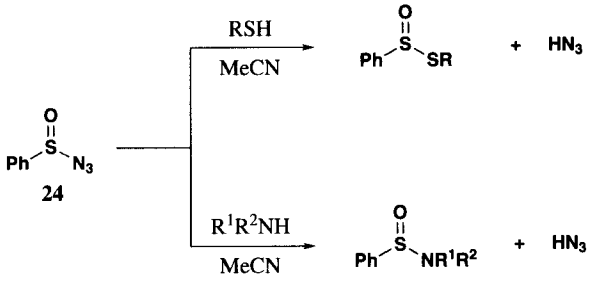


Scheme 11

Although efficient conditions exist for the direct preparation of thiosulfinates from sulfinyl chlorides and a thiol,[34] thiosulfinates can also be prepared through the reaction of sulfinyl chlorides with organotin mercaptides, as depicted in *Scheme 12*.[49] The reaction is complete in only 10 minutes at r.t. or lower affording thiosulfinates bearing alkyl, aryl or aralkyl groups in >89% yield. Methyl or *n*-butyl groups on the tin serve the role of R^2.

Scheme 12

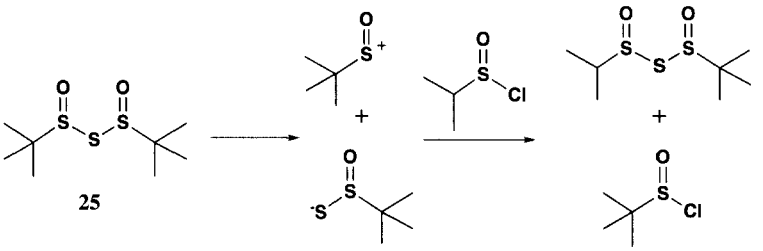
A less direct approach to thiosulfinates and sulfinamides advertises the intermediacy of a sulfinyl azide.[50] Benzenesulfinyl azide (**24**),[51] prepared from the corresponding sulfinyl chloride undergoes reactions with thiols to form thiosulfinates in 41-93% yield (*Scheme 13*). Similarly, the azide group can be displaced by primary or secondary amines to afford the sulfinamide (48-78%). Hydrazoic acid, HN_3, is a by-product in both reactions. As an advantage, the reaction is tolerant of hydroxyl groups on both the thiol and the amine. One disadvantage of this approach is that the sulfinyl azide is explosive above 0°. The thermal breakdown of *t*-butyl sulfinyl azide has been utilized to prepare *t*-butanesulfonamide.[52]



Scheme 13

Another sulfur substitution was demonstrated as part of a study concerning the interconversion of oxides of organic trisulfides. In this example, a unique substitution reaction was applied to secure evidence concerning the behavior of *t*-butyl sulfinic thioanhydride (**25**).[53] Thioanhydride **25** was thought to decompose by ionic scission of the S-S(O) bond and to gain evidence for this theory, **25** was exposed to isopropyl sulfinyl chloride. In that reaction mixture, *t*-butyl sulfinyl chloride was

observed and the authors proposed a scheme beginning with the proposed unimolecular fragmentation to account for the findings. Although it appeared that the reaction may not have gone to completion, the observations were sufficient to gain information about the reactivity of **25** (*Scheme 14*).[53]



Scheme 14

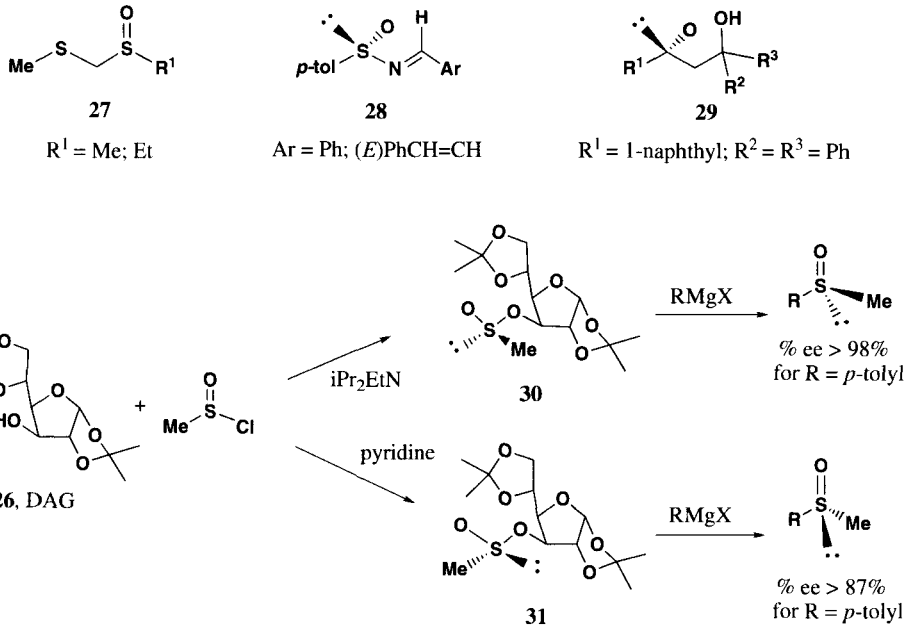
a. Optically Enriched Sulfinic Acid Derivatives for Asymmetric Synthesis

i. Sulfinic Ester Derivatives

The general method for preparing a sulfinate ester involves reacting the sulfinyl chloride with an aliphatic or aromatic alcohol in the presence of base (i.e., K_2CO_3; pyridine). This reaction once thought to proceed via an S_N2 mechanism[54] is now generally theorized to involve a sulfurane intermediate.[3] This new mechanistic understanding has allowed researchers to advance the original Andersen strategy[55,56] for the preparation of optically enriched sulfinate esters which in turn have proved to be a vital source of optically pure sulfoxides. The role of homochiral sulfoxides in the synthesis of optically enriched carbon compounds is well established.[57]

The original Andersen chemistry involves the reaction of a sulfinyl chloride with menthol.[55,56] Separation of menthyl sulfinate diastereomers requires several recrystallizations. Access to the optically pure sulfoxide is achieved by treating the optically pure form of the sulfinate ester with an organometallic reagent. This substitution reaction has been shown to proceed with inversion of configuration at the sulfur centre.[56,58] While the original Andersen strategy is useful for the preparation of diaryl and alkyl aryl sulfoxides, it has limited applications for the preparation of dialkyl sulfoxides as the required menthyl alkanesulfinates are typically found as oils and are difficult to isolate as a single diastereomer. To overcome this difficulty chiral alcohols other than menthol have been examined.[3,59] The Tillett review[6] addresses this chemistry through the late 1980's.

One of the most synthetically useful adaptations to the Andersen strategy has been the use of di-acetone D-glucose (DAG, **26**) as the chiral alcohol.[3,60-62] Since the method was first introduced the resulting optically pure DAG sulfinates have been used to prepare a number of compounds including alkyl methylthiomethyl sulfoxides (**27**),[63] chiral *N*-sulfinyl imines (**28**)[64] and enantiomerically pure hydroxy sulfoxides (**29**).[65] Many of these compounds were then used to generate other chiral species.[63-65]



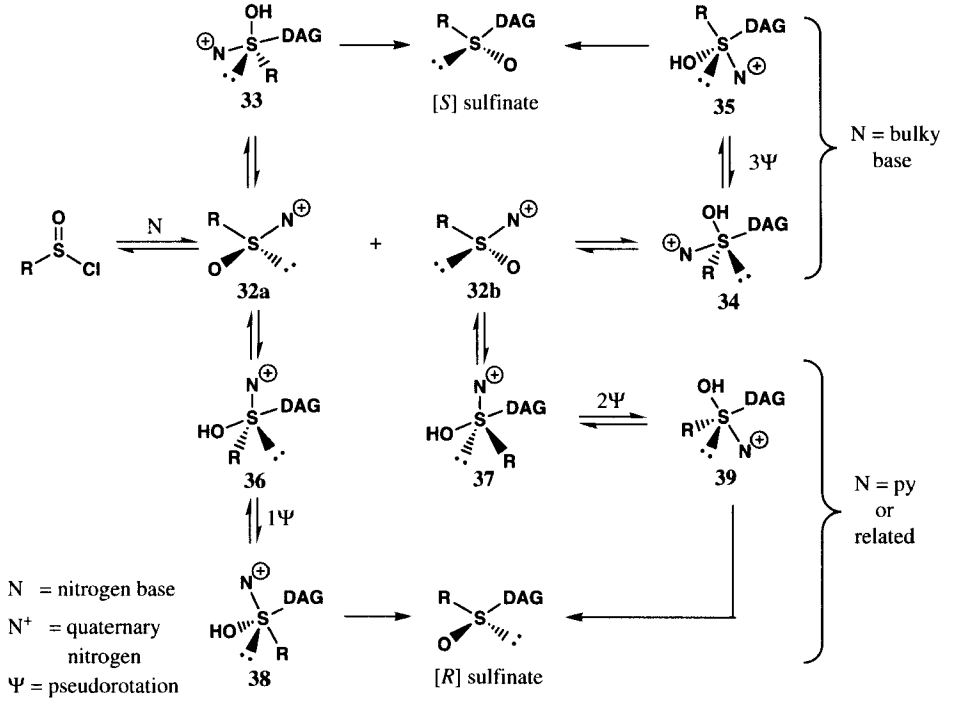
Scheme 15

The unique facet of this chemistry is that either configuration of sulfinate is available simply by choosing the correct base and solvent combination. For instance, the researchers found that addition of racemic methanesulfinyl chloride in toluene to a solution of DAG in the presence of $i\text{Pr}_2\text{EtN}$, showed only a single diastereomer (de ≥ 95 %) by ^{1}H NMR analysis of the crude reaction mixture. Purification by recrystallization afforded the (*S*)-DAG methanesulfinate **30**. When the base was changed from $i\text{Pr}_2\text{EtN}$ to pyridine under the same reaction conditions, (*R*)-DAG methanesulfinate **31** was isolated (*Scheme 15*). Conversion to substituted optically enriched sulfoxides is readily accomplished through treatment with various alkyl and aryl Grignard reagents.[3,60]

Upon closer examination of the reaction conditions (i.e., base and solvent) Alcudia and coworkers were able to demonstrate a relationship between the base and solvent used and the stereoselectivity of the reaction.[3] Pyridine-like bases, including DMAP and imidazole, afford the (*R*)-sulfinate (de's 56-86%). The (*S*)-sulfinates (de's = 16-95%) can be prepared using $i\text{Pr}_2\text{EtN}$ or comparable bulky bases such as Et_3N, collidine and dimethylaniline (DMA). Choice of solvent is also important with the highest de's obtained using THF for pyridine-like bases and toluene for $i\text{Pr}_2\text{EtN}$ like bases. The sulfinates are isolated using column chromatography or recrystallization.

More recent work has been done to examine whether this base/solvent effect is due to the nature of the chiral alcohol or if it is applicable to all chiral secondary alcohols.[62] Several different chiral secondary alcohols were examined such as dicyclohexylidine-D-glucose (DCG), menthol, cholesterol and base/solvent effect was again observed. However, except for DCG which is structurally similar to DAG the de's were significantly lower.

The mechanism proposed to account for the diastereoselectivity has as its basis the geometry of the substituents in various sulfurane intermediates. The mechanism requires that reaction does not proceed through a sulfine intermediate and that it is kinetically controlled.[3] Another assumption is that the alcohol reacts with both sulfinyl chloride enantiomers. In the first step of the proposed mechanism (*Scheme 16*), an equilibrium reaction occurs between the sulfinyl chloride and the base affording a racemic pair of sulfinyl ammonium (or pyridinium) enantiomers **32**. Intermediate **32** then reacts with the chiral alcohol to generate diastereomeric sulfurane intermediates. When a bulky $i\text{Pr}_2\text{EtN}$-type base is used the approaching alcohol and the base assume apical positions, generating sulfuranes **33** and **34**. The (*S*)-sulfinate can be directly formed from **33**, while sulfurane **34** requires a series of pseudorotations to form sulfurane **35** and eventually the (*S*)-sulfinate. The formation of **34** may be less favorable due to a destabilizing interaction between the R group and the C-5 of the sugar ring.



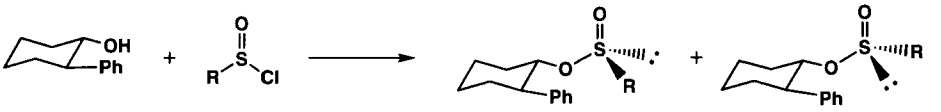
Scheme 16

When the smaller pyridine-type bases are used the base occupies the equatorial position while the alcohol takes on an apical position generating sulfuranes **36** and **37**. Both sulfuranes **36** and **37** undergo 1 or 2 pseudorotations forming sulfuranes **38** and **39**, respectively, which then form the (*R*)-sulfinate. It is possible that the formation of sulfurane **37** is preferred with sulfurane **36** being less stable because of an unfavorable interaction between the R group and the C-5 of the sugar.

Conversion of the DAG sulfinates to optically pure sulfoxides was accomplished using a variety of alkyl and aryl Grignard reagents.[3,42,60-62] The purification difficulties that sometimes arise during the preparation of the optically pure sulfoxides on a larger scale can be overcome by treating

the DAG/sulfoxide mixture with a TFA/water solution. This solution serves to selectively hydrolyze one of the two acetal groups in the DAG molecule. The hydrolyzed DAG is water soluble and can be easily separated from the sulfoxide.[66]

Whitesell and Wong have investigated the use of chiral alcohol *trans*-2-phenylcyclohexanol (**40**) as a chiral auxiliary (*Scheme 17*).[67] The diastereomeric sulfinate esters **41** are prepared in good yield with better selectivity [(4-10):1] than observed with menthol [(2-3):1].[68] More importantly, the diastereomers can be separated via chromatography and/or recrystallization. The latter is possible as the major diastereomers are crystalline in the cases examined.[67] Each of these sulfinates reacts cleanly with Grignard reagents to afford the corresponding optically pure sulfoxide.

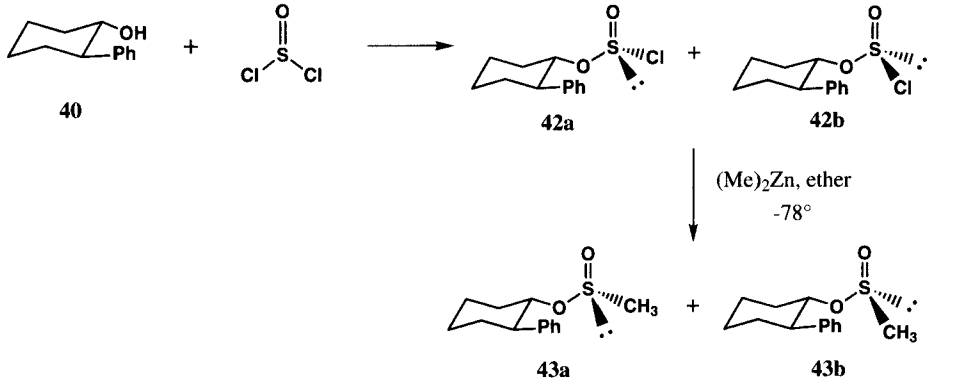


40 **41a** **41b**

R = *p*-tolyl, 2-naphthyl, Me, *i*-Pr

Scheme 17

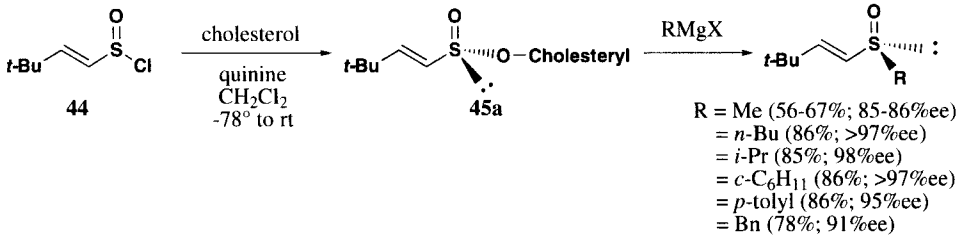
In a related study, Whitesell and Wong have also used chiral alcohol **40** in an alternative preparation of optical pure sulfinates not involving a sulfinyl chloride (*Scheme 18*).[69] When chiral alcohol **40** was reacted with thionyl chloride the resulting diastereomeric (1:1 at rt and 2:1 at -78°) chlorosulfinate esters **42** were sufficiently stable such that full characterization could be obtained. When chlorosulfinates **42** were treated with Grignard and organolithium reagents the diastereomeric ratio observed for the resulting sulfinate esters (**43**) mirrored that observed for the chlorosulfinates. When treated with 0.9 eq of dimethylzinc the sulfinate esters were generated in a diastereomeric mixture of 98:2 in good chemical yield.



40 **42a** **42b** **43a** **43b**

Scheme 18

Schwan and Strickler have reported the first synthesis of an optically pure vinylic sulfinate ester, which was prepared by treating 1-alkenesulfinyl chloride **44** with cholesterol and base.[70] Access to either diastereomer **45** can be achieved using either quinine (for access to the [*R*]-sulfinate, **45a**) or quinidine ([*S*]-sulfinate, **45b**, not shown) as the base. Following one to two recrystallizations the [*R*]-sulfinate can be isolated in an optically pure form (100% de), while the [*S*]-sulfinate can be isolated in an optically enriched form (≤75% de). The diastereomeric purity of the sulfinates was established through ^{1}H NMR analysis in C_6D_6 while the absolute configuration was assigned using [*R*]-(-)-2,2,2-trifluoro-1-(9-anthryl)ethanol as a chiral solvating agent. Subsequent preparation of 1-alkenyl sulfoxides was accomplished through treatment with a variety of Grignard reagents (*Scheme 19*).[70]



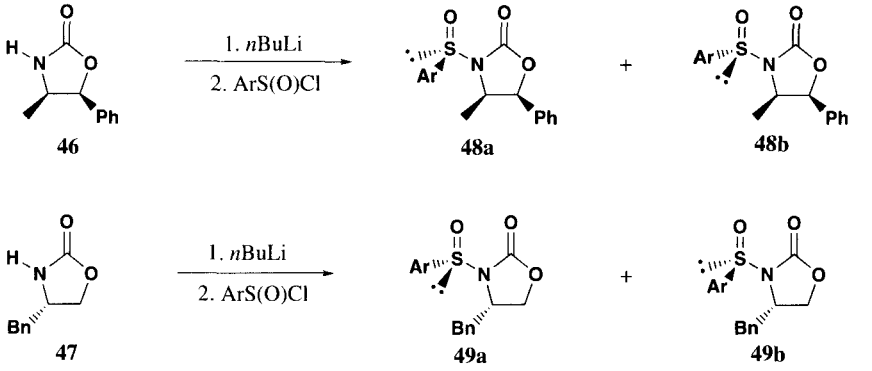
Scheme 19

ii. Sulfinic Amide Derivatives

Complementary and sometimes improved access to homochiral sulfinic acid derivatives and hence sulfoxides can be achieved through the use of several sulfinamides. Analagous to sulfinate esters, optically pure sulfinamides are prepared through a substitution reaction with an optically pure nitrogen compound. Also in keeping with the chemistry of sulfinate esters, the reaction between an optically active sulfinamide and an organometallic reagent proceeds with inversion of configuration at the sulfur centre to generate optically active sulfoxides. For a number of years the oxazolidinone class of chiral auxiliaries has garnered considerable attention and two members of the oxazolidinone family (**46** and **47**) have been used by Evans and coworkers as auxiliaries to generate a new class of chiral sulfinyl transfer reagents.[71]

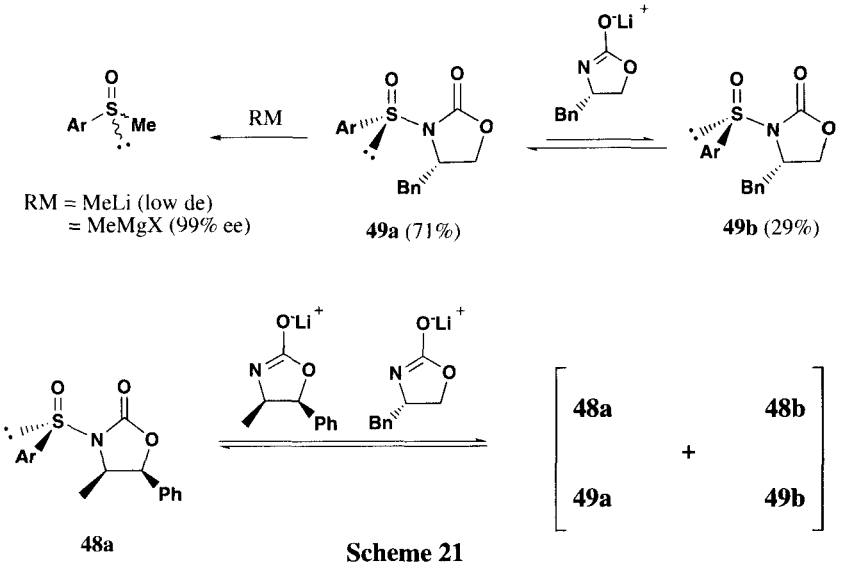
When lithiated oxazolidinones **46** and **47** are reacted with a sulfinyl chloride two diastereomers are formed, with de's of 4.6:1 (**48**) and 2:1 (**49**), respectively (*Scheme 20*). The major diastereomer is isolated after a single recrystallization in excellent optically purity (**48a/49a**; each > 99% de by HPLC). Depending upon the choice of the chiral oxazolidinone, access to both epimers at sulfur can be achieved. The [*R*]-sulfinamide can be prepared using **46** while the [*S*]-sulfinamide arises through the use of **47**.

Experimental evidence has shown that an equilibrium is established between the diastereomeric products (*Scheme 21*) and it is this equilibrium which accounts for the observed diastereoselectivity. This was tested in a control experiment with each of the sulfinamide diastereomers **49**. When [*S*]-**49a** was treated with 1.0 or 0.1 eq of lithiated **47** at -78°, a 71:29 mixture of **49a** and **b** was obtained after less than 1 minute. The same ratio was observed when the reaction started with [*R*]-**49b**. In an additional experiment when [*R*]-**48** was treated with a mixture of lithiated **46** and **47** a

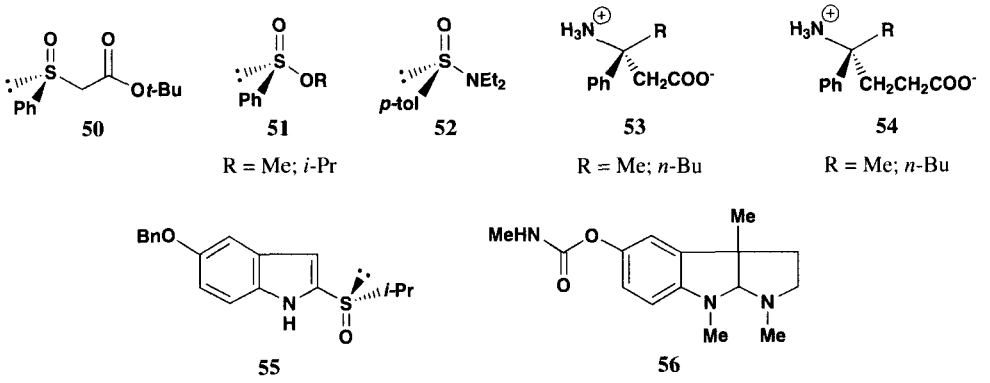


Scheme 20

randomized set of sulfinamide diastereomers was obtained. The rate at which the equilibrium is established is dependent on the nature of the metal ion present. Equilibrium is established quickly with lithiated oxazolidinones (1 minute at -78°), but takes more time with magnesium conjugates. This has important consequences during nucleophilic substitutions at sulfur as the nature of the metal counterion could influence the sulfinyl stereochemistry. For example, when sulfinamide [*S*]-**49a** was treated with methyllithium the optical purity of the isolated sulfoxide was significantly reduced, while reaction with a methyl Grignard yielded the same sulfoxide in high optical purity (99% ee) (*Scheme 21*). As such using [*S*]-**49a**, Evans and coworkers have been able to prepare several alkyl aryl sulfoxides (82-87% yield; 90-91% ee) and dialkyl sulfoxides (78-92% yield; 93-≥97% ee). As well, the *N*-sulfinyloxazolidinones have been shown to be at least two orders of magnitude more reactive than sulfinate esters.[71]



Scheme 21



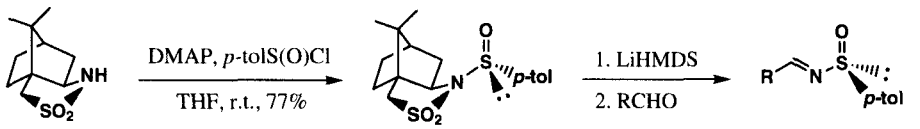
50 51 52 53 54

R = Me; *i*-Pr R = Me; *n*-Bu R = Me; *n*-Bu

55 56

In addition to being used to prepare optically pure sulfoxides, the *N*-sulfinyl oxazolidinones can also be used to prepare other organosulfur compounds including alkyl α-(alkylsulfinate) acetates **50**, sulfinate esters **51**, sulfinamide **52**[71] and β– and γ–amino acids **53** and **54**.[72] They have also been used to prepare indolyl sulfoxide **55** which in turn was elaborated further for the preparation of naturally occurring (-)-physostigmine (**56**).[73]

The Oppolzer group has subsequently shown the use of bornane-10, 2-sultam (**57**, Oppolzer's sultam) as a new chiral sulfiny transfer agent.[74] When sultam **57** is reacted with a sulfinyl chloride, gram scale amounts of sulfinylsultam **58** result as a 6.2:1 mixture of diastereomers (*Scheme 22*). Subsequent recrystallization from hexanes/ether provided access to the [*R*]-sulfinylsultam in good yield (72%).[74] Unlike the Evans chiral auxiliaries, however, both sulfur epimers are not accessible.

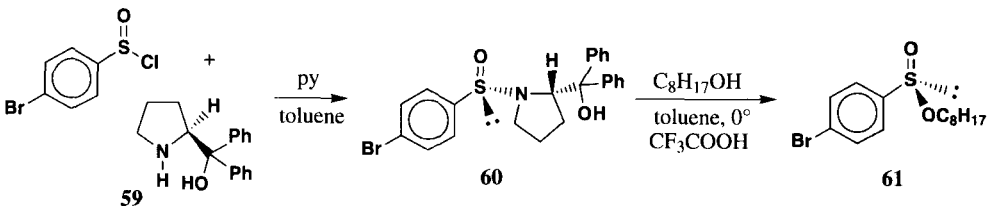


57 58

Scheme 22

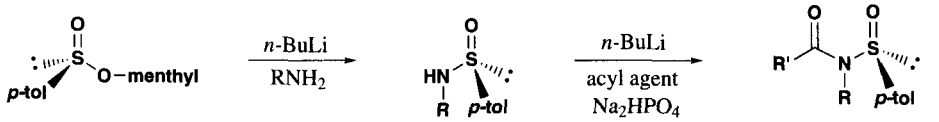
Subsequent reaction of the Oppolzer sulfinylsultam **58** with a variety of Grignard or Reformatsky reagents proceeds with inversion of configuration at the sulfur centre affording the corresponding sulfoxide in high yield (79-97%) and optical purity (96-≥99% ee). In addition, the chiral auxiliary can be recovered in 91 to 98% yield. Sulfinylsultam **58** can also react with enolizable and non-enolizable aldehydes to afford enantiopure sulfinimines,[74] a class of compounds with broad synthetic utility (*Scheme 22*).[7,8]

Optically pure sulfinamides can also be used to prepare optically active *n*-alkyl arenesulfinate esters. When chiral pyrrolidine derivative **59** was treated with a bromobenzenesulfinyl chloride, sulfinamide **60** was obtained in optically pure form in good yield (71-91%, *Scheme 23*).[75] Acidic alcoholysis in the presence of TFA provided sulfinate ester **61** in good yield and high enantiomeric excess (>95%).



Scheme 23

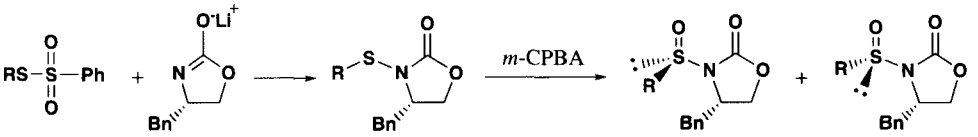
An alternative preparation of enantiomerically pure sulfinamides indirectly avoids the use of sulfinyl chlorides by using an optically pure sulfinate ester as the chiral transfer agent. Thus, treatment of menthyl sulfinate **62** (which is commercially available in both enantiomeric forms) with a lithium amide affords the optically active sulfinamide **63** (*Scheme 24*).[76] As in similar reactions, this transformation occurs with inversion of configuration at the sulfur centre. Chiral sulfinamide **63** can be converted to acylated sulfinamide **64**, which in turn is a source of optically pure sulfoxides via organometallic substitution. This latter reaction is advantageous as it occurs at a faster rate than the corresponding reaction with **62**.



R = Bn; *t*-Bu; R' = Et; Me; (E)-MeCH=CH; CF_3

Scheme 24

In some cases, progression to chiral sulfinic acids is achieved through sulfenic acid derivatives. For instance, Evans and coworkers were able to show that the preparation of sulfinamide **49** could be achieved through an oxidation of the sulfur, avoiding the use of any sulfinyl chlorides.[71] To pursue this strategy, the reaction of arenethiosulfonate **65** and lithiated **47** leads to sulfenamide **66** (*Scheme 25*). Unfortunately, the oxidation of **66** evolved with low diastereoselectivity (2.5:1) and the resulting sulfinamides (**49**) had to be separated by chromatography.

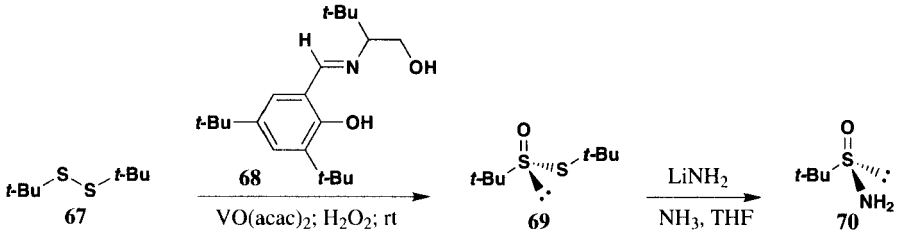


R = Ph; Me; *t*-Bu

Scheme 25

Access to chiral sulfinamides and sulfoxides has been achieved through an asymmetric oxidation reaction, circumventing use of stoichiometric chiral auxiliaries such as **46** or **57**. The oxidation of disulfide **67** with H_2O_2, $VO(acac)_2$ and Schiff base ligand **68** afforded optically enriched thio-

sulfinate **69** in excellent yield (92%) and good enantioselectivity (91% ee) (*Scheme 26*).[77] To demonstrate the value of **69**, its treatment with $LiNH_2$ leads to *t*-butanesulfinamide (**70**) in high yield and selectivity (91% yield; 91% ee). Other sulfinamides and sulfoxides evolve from similar chemistry of **69**. This alternative method allows for large scale preparations with inexpensive reagents and avoids the use of high molecular weight chiral auxiliaries. The method also avoids chromatographic separations in that the sulfinamides can be purified using recrystallization.



Legend: $VO(acac)_2$ = vanadyl acetylacetonate

Scheme 26

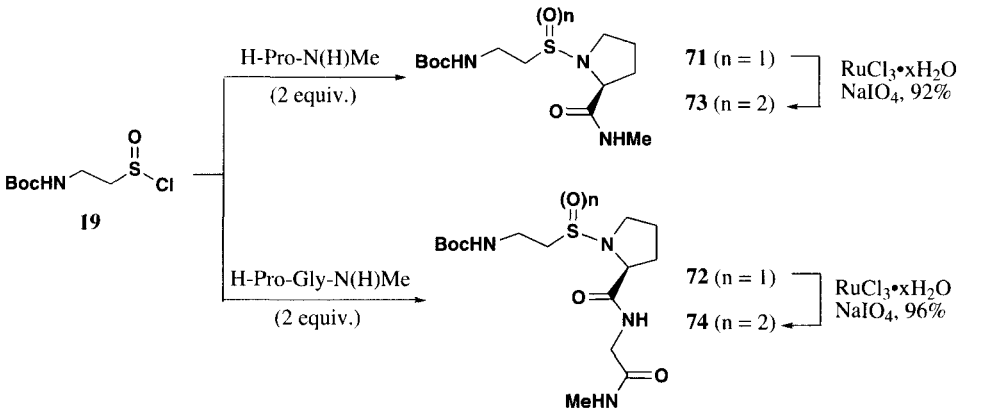
b. Placement in Peptidomimetic Isosteres

A number of groups have probed transition state analogues as a means to uncover the mode of activity of enzyme inhibitors.[78] Such peptidomimetics are often called transition state isosteres since they are designed with functionality that are sterically comparable to the tetrahedral intermediate involved in the hydrolysis of the amide bond of proteins and peptides.[78,79] Among the functionalities employed as transition state isosteres are the sulfonamide group and to a lesser extent the sulfinamide group. This area of research is important in the context of this review since one contributing laboratory, the Liskamp group of Utrecht University in The Netherlands, has elected to prepare a number of sulfonamide and sulfinamide containing peptidomimetics by way of sulfinyl chloride chemistry.

As an entry into this area, the Liskamp group addressed the synthesis and some reactions of sulfinyl chloride **19**.[36] Thus, **19** was treated with H-Pro-N(H)Me and H-Pro-Gly-N(H)Me to provide the corresponding sulfinamides **71** (72%) and **72** (70%), respectively. These yields are the best obtainable and are achieved when a second equivalent of the nucleophile was employed to act as a base. Even though yields were attenuated by 10% when *N*-methylmorpholine was the base, the latter procedure is preferred since it only consumes one equivalent of amino acid derived amine.[37] Sulfinamides **71** and **72** were oxidized to their corresponding sulfonamides in high yield (*Scheme 27*). The direct formation of **73** and **74** via amine reaction with a sulfonyl chloride was not viable due to difficulties with the sulfonyl chloride synthesis.[36]

Other sulfinyl chlorides have also been employed as part of the Liskamp work. Sulfinyl chlorides **20-22** were treated with various amines and Table 3 shows some of the additional peptidomimetic sulfinamides and sulfonamides that have been prepared, either directly or through functionalization of a more simple precursor.[38]

Several reactions leading to the products in Table 3 are of note. For instance, the conversion to **75** is possible by deprotection of **74** and introduction of Boc-Ala-OH using the mixed anhydride



Scheme 27

method. Application of the same procedure to sulfinamide **72**, however gave a low yield due to high reactivity of the sulfinamide linkage during the TFA treatment required for the Boc removal. As an alternative, the 2-(trimethylsilyl)ethyloxycarbonyl (Teoc) group of sulfinamide **76** is removable with F^- and the deprotected form of **76** could be converted to **77** using the DCC/HOBT method.[37] Diastereomeric sulfonamides **78** could be obtained by removal of an α-proton (4.4 eq. of LDA) and addition of $PhCH_2Br$. The Boc group of **73** could be removed and replaced with an acetyl unit.[80]

In another study,[2] optically pure amino acids were employed to prepare sulfinyl chlorides **20**, **21**, and **79a/b** with configurationally fixed α and β alkyl groups. In combination with diastereomeric sulfinyl chlorides **79c**, a number of other sulfonamides were prepared. For instance, sulfonamides **80-82** were prepared as potential HIV protease inhibitors, based on their similarity to Ro 31-8959(*R*) (**83**). Compounds **80-82** failed to meet expectations in an HIV protease assay despite Austin Method 1 (AMPAC) predictions that suggested the sulfonamide functionality has steric and electronic properties comparable to the phosphonamidate group and to the transition state of the hydrolysis of the amide bond. Higher level calculations (RHF/6-31+G*)[81] indicate the sulfonamide linkage lacks the charge and electrostatic potential of the other groups, accounting for its reduced activity.

Table 3. Sulfonamide and Sulfinamide Containing Peptidomimetic Isosteres

Starting Sulfinyl Chloride	Sulfinamide/Sulfonamide Products

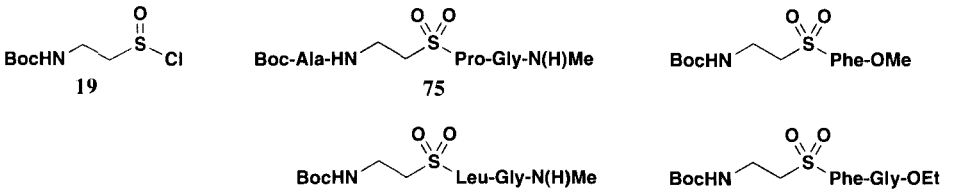
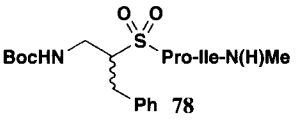


Table 3. Continued...

Starting Sulfinyl Chloride	Sulfinamide/Sulfonamide Products



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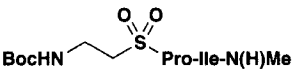

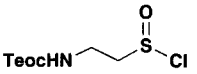

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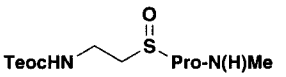

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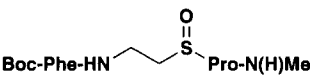
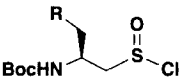
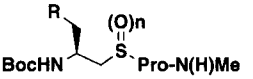


77



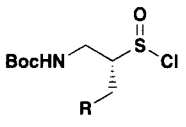
20, R=H; 21, R=Ph



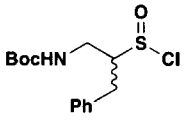
R = H, Ph; n = 1,2

As depicted by compound **84**, several different sulfinyl chlorides can be incorporated into a single peptide. The procedure requires several iterations of a sulfinamide formation, oxidation and deprotection sequence.[2]

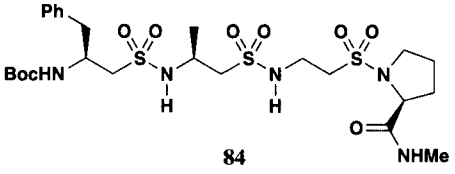
Attempts have been made to adapt the solution chemistry presented in this section for solid phase synthesis and entry to libraries of sulfur containing peptidomimetics.[82] Attachment of the glycine residue to the Merrifield resin was followed by introduction of sulfinyl chloride **19**. Difficulties with the subsequent oxidation procedure led to experiments with the Tentagel® resin which could be readily adapted with the Fmoc-Gly unit. Following removal of the Fmoc group the sulfinyl chloride unit (**19**, **21**, **85**) could be attached to the resin (*Scheme 28*). Each resin-bound sulfinamide was oxidized with OsO_4/NMMO or nBu$_4$N/oxone and a subsequent transesterification reaction with MeOH released the peptide from the resin.[82]



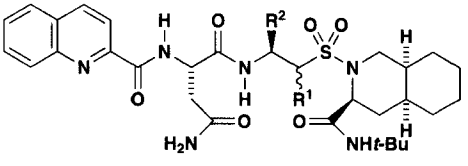
79a R = H
79b R = Ph



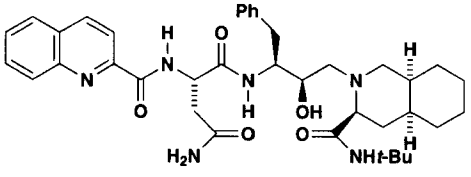
79c



84

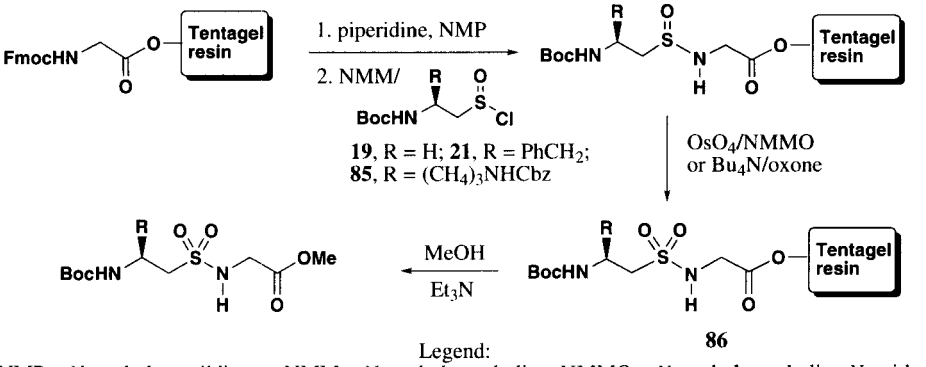


80, 81 R^1 = Bn, R^2 = H; **82** R^1 = H, R^2 = Bn



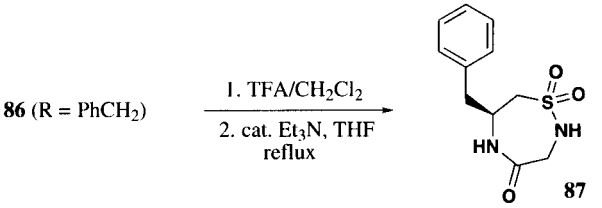
83

The utility of the solid support methodology is also demonstrated by the preparation of cyclic peptidosulfonamide **87** via cleavage from the resin (**86**) and *in situ* cyclization (*Scheme 29*).[82] A number of peptidosulfonamides were also prepared directly using solid phase methodology involving attachment of the sulfur from the sulfonyl chloride rather than the sulfinyl chloride.[83] The Liskamp group has also prepared a number of sulfonamide-containing synthetic receptors that resemble molecular tweezers. These compounds, exemplified by peptidomimetic **88**, could be prepared by multiple attachments of either sulfinyl chloride[84] or sulfonyl chloride[85] to a functionalized diol or diamine.

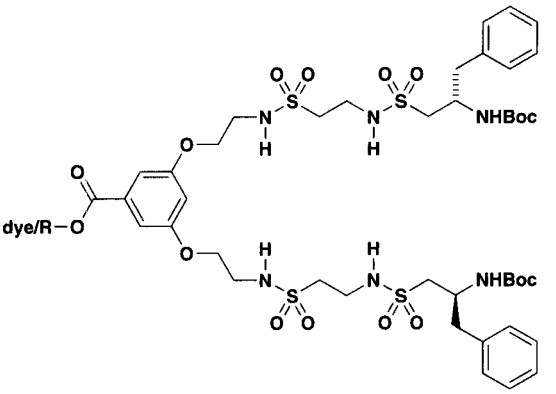


Legend:
NMP = *N*-methylpyrrolidinone; NMM = *N*-methylmorpholine; NMMO = *N*-methylmorpholine *N*-oxide

Scheme 28



Scheme 29



88

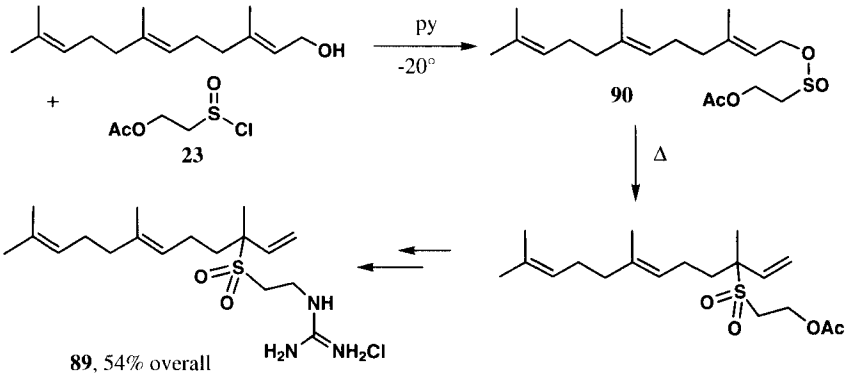
Other groups have made valuable contributions toward the preparation and evaluation of sulfinamide-[79,86] and sulfonamide-containing[79,87-90] peptide isosteres, but their preparative procedures did not incorporate sulfinyl chloride chemistry.

c. Rearrangement or Conversion of Sulfinic Acid Derivatives to Sulfonyl Compounds

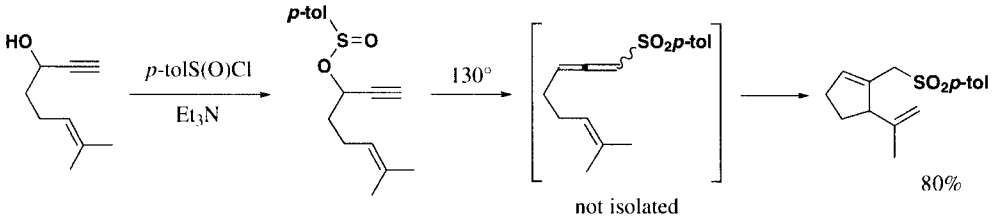
Due to thermal lability, some sulfinic acid esters are readily converted to their thermodynamically more stable valence isomer, a sulfone. The modes for this transformation usually entail either a dissociation/re-association mechanism or a 2,3-sigmatropic rearrangement and all such reactions of sulfinates have been thoroughly reviewed.[91] Some rearrangements of thiosulfinic esters, which may or may not have been prepared via sulfinyl chlorides, are covered in the Block review on the organosulfur chemistry of garlic and onions.[92] Only recent applications of sulfinate rearrangements in synthesis will be noted here.

One form of the 2,3-sigmatropic rearrangement occurs when a sulfinate with oxygen attachment to an allyl unit rearranges to a sulfone with sulfur attachment at the opposite allyl carbon. The rearrangement has found utility in a biomimetic synthesis of Agelasidine A (**89**).[41] Thermal activation of sulfinate **90** derived from farnesol and sulfinyl chloride **23** creates the requisite sulfone and a quaternary center in a single step. The synthesis was completed in 54% overall yield (*Scheme 30*).

The 2,3-sigmatropic sulfone formation is not limited to allylic systems. Thus, the Uguen group has demonstrated that the established 2,3-rearrangement of propargyl sulfinates can be immediately followed by an intramolecular ene reaction, as shown for the simple example in *Scheme 31*.[93] The chemical yields for four examples were in the 75-90% range. Some cyclic analogs are also prone to the consecutive pericyclic conversions: spirocycle **91** was prepared and was modified to **92**, a known precursor of pentalenic acid.[94]

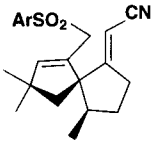


Scheme 30

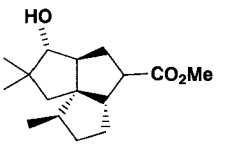


Scheme 31

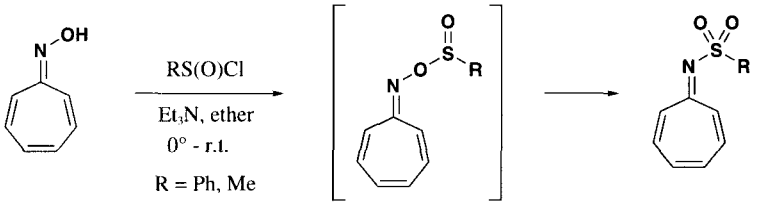
The capture of sulfinyl chlorides with hydroxyl amines or oximes affords sulfinate esters with the additional reactivity of the N-O bond. Thus as shown in *Scheme 32*, the conversion of sulfinate to sulfonyl isomer proceeds readily at room temperature.[95] The isomerization reaction of the tropone oxime-derived sulfinates **93** affords compounds **94** which serve as novel starting materials in the preparation of 1-azaazulene derivatives. Regarding the mechanism of sulfonamide formation, it has been shown that for the related reaction of *N,N*-dialkylhydroxylamines with sulfinyl chlorides, the eventual formation of sulfonamides proceeds with the intermediacy of an aminyl radical.[96] This chemistry has been utilized as a synthetic source of iminyl radicals.[97]



91



92



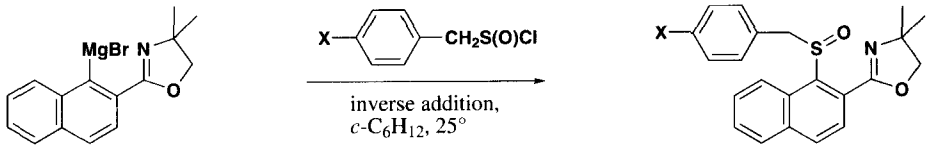
93 94

Scheme 32

2. Direct Syntheses of Sulfoxides

The direct organometallic attack of sulfinyl chlorides, though not particularly common is more viable than organometallic attack of carboxylic acid chlorides. The over-reaction that commonly occurs with carboxyl chlorides is much less common with sulfinyl chlorides although one should be wary of further reaction via ligand exchange chemistry which may be significant with some attached groups.[98] Some examples of sulfoxide formation through the reaction of an organometal with a sulfinyl chloride are shown below, although in many instances, the more conservative approach is to first convert the sulfinyl chloride to an ester or amide before substitution.

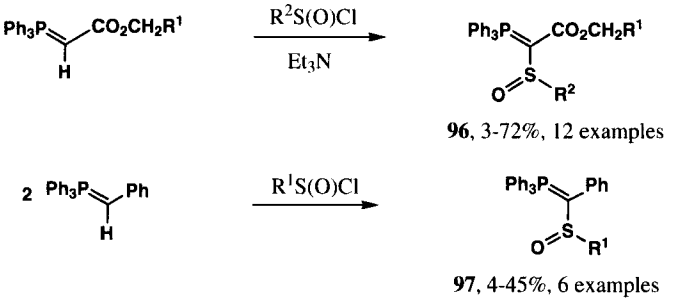
In the early stages of a study toward the preparation of binaphthyl-derived ligand, Baker and Sargent[99-101] prepared two 1-sulfinyl naphthalenes bearing an oxazoline unit at the adjoining position (*Scheme 33*). Compounds **95** served as model compounds to gain information regarding the viability of replacing the sulfinyl unit with naphthyl and related units.



95 X = H, 43%
X = Cl, 53%

Scheme 33

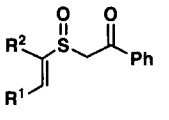
A series of sulfinyl substituted, stabilized phosphorus ylides were subjected to flash vacuum pyrolysis (FVP) conditions to generate alkoxycarbonyl(sulfenyl)carbenes[102,103] or alkoxycarbonyl(sulfinyl)carbenes.[104] Sulfinyl ylides **96**, the precursors of alkoxycarbonyl(sulfenyl)carbenes, were prepared through a direct substitution reaction on a sulfinyl chloride in low to moderate yields as shown in *Scheme 34*. The major products upon pyrolysis of ylides **96** were vinyl sulfides, proposed as breakdown products of sulfenyl β-lactones.[102,103]



Scheme 34

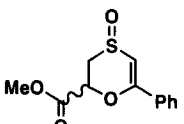
A slightly different approach was employed for the preparation of phenyl substituted ylides. Compounds **97**, the precursors of alkoxycarbonyl(sulfinyl)carbenes among other intermediates, were generated in low yield using two equivalents of ylide instead of a tertiary amine (*Scheme 34*).[104] Thioesters are the major products when alkoxycarbonyl(sulfinyl)carbenes are generated from **97** through FVP exposure.

β-Keto sulfoxides can be prepared by the Lewis acid induced reaction of sulfinyl chlorides with trimethylsilyl enol ethers.[105] The application of this chemistry to 1-alkenesulfinyl chlorides using $TiCl_4$ as a catalyst met with mixed success.[5] The highest yields of keto sulfoxides **98** were obtained using α-styryl trimethylsilyl ether (41-72%, 3 examples), while other TMS enol ethers gave lower yields. One problem may have been the tendency of the keto sulfoxides to enolize. Evidence for this behavior was obtained through isolation of 1,4-oxathiin *S*-oxide **99** when the 1-alkenesulfinyl chloride held a 2-carbomethoxy group in its 2 position. Formation of this heterocycle is most likely explained by internal Michael addition of the keto oxygen after conversion to an enol or enolate.



98

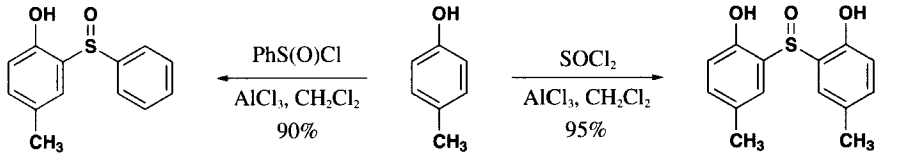
R^1, R^2 = H, H: 59%
R^1, R^2 = *t*-Bu,H: 72%
R^1, R^2 = -$(CH_2)_4$-, 41%



99

Lewis acids can also induce electrophilic aromatic substitutions under specific circumstances. The usual conditions of PhS(O)Cl/$AlCl_3$/CH_2Cl_2/0° effect benzenesulfinylation at the para position of phenols when the *ortho* positions are blocked.[106] Similarly it has been shown by Jung that

p-cresol can be functionalized at one of its ortho positions when the para position is occupied (*Scheme 35*).[107] The Jung group has extended this chemistry to create a diaryl sulfoxide with more functionality. Utilizing an established protocol, they prepared sulfoxide **100** by employing thionyl chloride as a di-functional sulfinyl chloride.[108] The overall reaction inevitably entails a two step sequence that requires the intermediacy of a hydroxyarenesulfinyl chloride. Other symmetric aryl sulfoxides can be prepared using $SOCl_2$ with trifluoromethanesulfonic acid catalysis.[109]



100

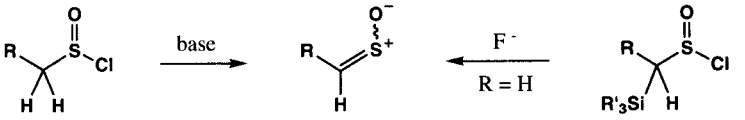
Scheme 35

As an access to *p*-quinones and protected *p*-dihydroquinones, Kita and coworkers used the electrophilic aromatic substitution conditions in selected cases (10-89%) for the para arenesulfinylation of selected phenols.[110] For phenolic substrates bearing ortho hydrogens or electron-withdrawing groups the synthetic approach was unsuccessful. To achieve the equivalent of arenesulfinylation in those circumstances, a multi-step procedure was developed commencing with an electrophilic thiocyanation to introduce the sulfur.[110,111]

B. Sulfine Formation

The use of sulfinyl chlorides as a source of sulfines (thial *S*-oxides) was not addressed in the Tillett review.[6] Although several other more general reviews of sulfines are known,[112, 113] these reviews do not focus solely on sulfinyl chlorides as a source of sulfines.

Sulfine formation from sulfinyl chlorides involves either the base-mediated dehydrochlorination of α-hydrogen bearing sulfinyl chlorides or the fluoride induced elimination of R_3Si-Cl from α-silylated sulfinyl chlorides (*Scheme 36*).



101

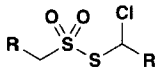
Scheme 36

The dehydrochlorination reaction was first reported in 1964 by two groups[114,115] and has since been shown to be a valuable reaction on a number of occasions. In many instances the sulfine is isolable after formation[39,116] and such chemistry has been particularly beneficial for the synthetic preparation of the onion lachrymator (**101,** R = Et, *Scheme 36*) from *n*-propanesulfinyl chloride. For a series of R groups (*Scheme 36*, R = Me, Et, *i*-Pr, *t*-Bu, Me_3Si), the dehydrochlorination reaction (conditions = $Et_3N/CFCl_3/< 0°$) gives a mixture of geometric isomers favoring the (*Z*)-configuration,

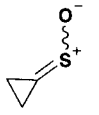
although increasing the size of the R group induces a reduction of the (*Z*):(*E*) ratio of the products. The sulfines were fully characterized by ^{1}H, ^{13}C and natural abundance ^{17}O NMR spectroscopies. Access to **101** (R = Et) by this method allowed Block and coworkers to definitively assign the structure of the onion lachrymatory factor.[116]

A noteworthy reaction has been found when sulfinyl chlorides are treated with less than one equivalent of tertiary base.[117] In those situations, the sulfine that is produced reacts with the remaining sulfinyl chloride to eventually yield α-chloroalkyl alkanethiosulfonate esters (e.g., **102**). Under these conditions it has been found that 0.65 equiv. of Et_3N gives the highest yield.[117] The reaction has also been achieved in DMF which acts as both solvent and base[118] and a mechanism for thiosulfonate formation has been offered in a number of papers.[19,35,119]

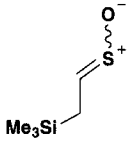
When a sulfine cannot be isolated, researchers often generate the sulfine with its immediate sulfinyl chloride precursor still actively present in order to obtain the corresponding α-chloroalkyl alkanethiosulfonate. Such a result is readily construed as evidence for the existence of the sulfine in solution.[19,35,120] The Et_3N induced reaction has been employed as a tool to establish the existence of cyclopropanethial *S*-oxide (**103**)[35] and 2-trimethylsilylethanethial *S*-oxide (**104**)[19] while the DMF method generated methanethial *S*-oxide, the parent sulfine.[120]



102



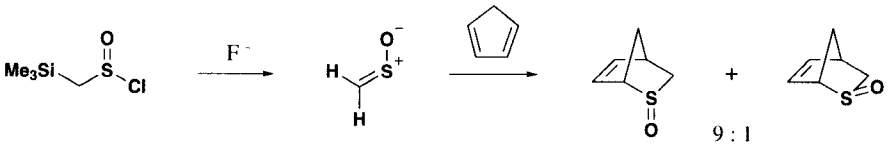
103



104

Sulfine formation from sulfinyl chlorides is sometimes hindered by the presence of the tertiary amine and its salt. For this reason Block and Wall[121,122] developed the fluorodesilylative approach to methanethial *S*-oxide by the reaction trimethylsilylmethanesulfinyl chloride with F^- (*Scheme 37*). The overall approach has only been applied to the α-silylmethanesulfinyl chloride since other α-silylalkanesulfinyl chlorides could not be successfully prepared. It is believed that stray chloride ions associated with established synthetic approaches induce unwanted Si-C scission during sulfinyl chloride preparation. The use of silyl groups with larger substituents may impart greater stability during the sulfinyl chloride preparation and would still demonstrate the desired responsiveness to F^-.

Finally, Braverman and coworkers have shown that 1,1,1-trichloromethyl sulfoxides bearing α-hydrogens behave like sulfinyl chlorides in that they undergo base-induced sulfine formation.[123,124] Similarly, selected heteroaryl sulfoxides also serve as sulfine precursors.[125]



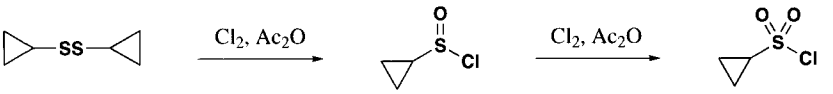
Scheme 37

C. Redox Chemistry

Sulfinyl chloride behavior is dominated by substitution and elimination reaction motifs so any other reactions are often conspicuous. This section describes a few examples of redox chemistry where the sulfur is oxidized while the S-Cl bond remains intact or where the -S(O)Cl group is reduced.

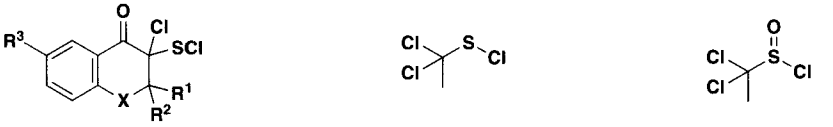
The method of chlorination of a thiolacetate[1] or disulfide[11] in the presence of Ac_2O for the preparation of sulfinyl chlorides also serves as an approach to sulfonyl chlorides. It has been demonstrated that the reaction affords sulfinyl chloride initially and prolonged exposure to the reaction conditions eventually leads to the sulfonyl chloride.[11,35] The second step of the reaction corresponds to a monooxygenation of sulfinyl chloride. *Scheme 38* represents an example where such chemistry was observed.[35]

Similar chemistry is observed in the oxidation of sulfenyl chlorides **105**[126] and **106**[127] to sulfonyl chlorides with excess H_2O_2/HOAc and perphthalic acid, respectively. Evidence that these oxidations most likely proceed through the sulfinyl chloride oxidation state was found when **107** was directly oxidized to the sulfonyl chloride.[127]



may be isolated

Scheme 38

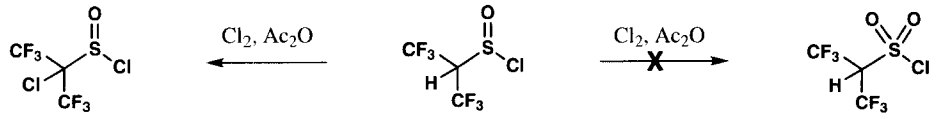


105, R's = alkyl, aryl
X = O, SO_2

106

107

An exception to this general mode of reactivity has been noted. In an attempt to convert sulfinyl chloride **108** to sulfonyl derivative **109,** oxygenation of sulfur did not occur and α-oxidized sulfinyl chloride **110** was obtained instead (*Scheme 39*).



110

108

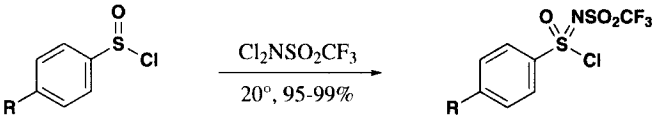
109

Scheme 39

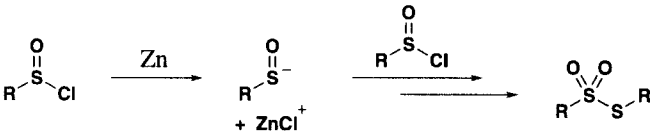
Conversion of sulfinyl chlorides to a higher oxidation state can also proceed via an imination reaction. Thus, selected arenesulfinyl chlorides were treated with *N,N*-dichlorotrifluoromethane-

sulfonamide at 20° to provide arenesulfonimidoyl chlorides **111** in nearly quantitative yield (*Scheme 40*).[128] Compounds **111** were targeted to determine the σ_p value of the *N*-mesylated sulfonimidoyl chloride group. Experimental measurements resulted in a rather large value of 1.49.

In an example of a reduction of sulfinyl chlorides, their reaction with zinc affords thiosulfonates (*Scheme 41*).[129] One mechanistic theory is that the zinc removes the equivalent of Cl^+ from the sulfinyl chloride leaving an opportunity for attack by a second molecule of sulfinyl chloride. Rearrangement then affords the thiosulfonate in fair to moderate yield. Only alkanesulfinyl chlorides were employed.[129]



Scheme 40



Scheme 41

III. CONCLUSIONS

Recent work in the area of sulfinyl chloride chemistry has clearly demonstrated the synthetic utility of these sulfur acid derivatives. One of the noteworthy recurring themes in this review was the use of sulfinyl chloride chemistry for access to *sulfonyl* compounds. In many instances, when sulfonyl derivatives were needed and the logical precursor was either unavailable or did not demonstrate accommodating chemistry, sulfinyl chemistry and an oxidation step delivered the requisite material.

The noteworthy discoveries in the 1990's include applications of sulfinyl chlorides to peptidomimetics and the use of DAG as the preferred chiral auxiliary for the efficient conversion of chiral sulfinates to sulfoxides. The development of complementary chemistry with sulfinamides using chiral oxazolidinones, for example, has made chiral sulfoxides substantially more accessible. Finally, the first preparation of 1-alkenesulfinyl chlorides opens a new realm of reactive species possessing not only the electrophilic sulfur, but also a double bond available for manipulation either before or after chemistry at the sulfinyl group.

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