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Sulfur-Mediated Rearrangements II

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In references *Topics in Current Chemistry* is abbreviated Top Curr Chem and is cited as a journal.

Visit the TCC content at springerlink.com

ISSN 0340-1022
ISBN 978-3-540-68099-4 Springer Berlin Heidelberg New York
DOI 10.1007/978-3-540-68100-7

Springer is a part of Springer Science+Business Media

springer.com

Cover design: WMXDesign GmbH, Heidelberg
Typesetting and Production: LE-TEX Jelonek, Schmidt & Vöckler GbR, Leipzig

Printed on acid-free paper 02/3100 YL – 5 4 3 2 1 0

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Preface

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

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

Clausthal-Zellerfeld, February 2007 Ernst Schaumann

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ISBN: 978-3-540-68097-0

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Top Curr Chem (2007) 275: 1–65
DOI 10.1007/128_2006_103

Published online: 13 February 2007

[2,3]-Sigmatropic Rearrangements of Allylic Sulfur Compounds

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Abstract Nine variations of [2,3]-sigmatropic rearrangements of allylic sulfur compounds are reviewed with particular emphasis on newer developments and applications in target molecule oriented research.

Keywords [2,3]-Sigmatropic rearrangements · Stereoselective synthesis · Sulfimines · Sulfinates · Sulfonium ylides

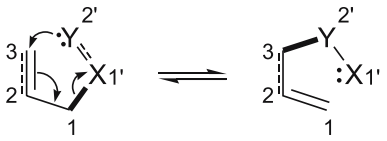
Abbreviations

Ac	Acetyl
acac	Acetylacetonate
Ar	Aryl
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
Bu	Butyl
s-Bu	*sec*-Butyl

t-Bu	*tert*-Butyl
Bz	Benzoyl
CIP	Cahn–Ingold–Prelog
Cp	Cyclopentadienyl
m-CPBA	*m*-Chloroperoxybenzoic acid
dba	Dibenzylidene acetone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DMAP	4-(Dimethylamino)pyridine
DMF	Dimethylformamide
DMP	Dess–Martin periodinane
DMSO	Dimethyl sulfoxide
ds	Diastereoselectivity
ee	Enantiomeric excess
Et	Ethyl
HMDS	Hexamethyldisilazane
LDA	Lithium diisopropylamide
Me	Methyl
ME	Mislow–Evans
MNDO	Modified neglect of differential overlap
MSH	*O*-Mesitylenesulfonyl hydroxylamine
i-Pr	Isopropyl
TBS	*t*-Butyldimethylsilyl
TMS	Trimethylsilyl
p-Tol	*p*-Tolyl
Ts	*p*-Toluenesulfonyl

1 Introduction

A [2,3]-sigmatropic rearrangement is a symmetry-allowed pericyclic reaction in the course of which the two ends of a σ-bond flanked by π-systems migrate over two and three bonds, respectively (Scheme 1).



Scheme 1 General representation of [2,3]-sigmatropic shifts

An alternative way to look at this reaction is to comprehend it as a 1,3-shift of an atom pair X–Y accompanied by a 1,2-shift of an electron pair from Y to X [1]. From that analysis it follows that X should be a heteroatom to accommodate the increasing electron density and therefore provide at least part of the driving force of the reaction.

Since their discovery in the 1950s and 1960s, virtually thousands of examples with different solutions for X and Y have appeared in the literature. This review will focus on a subset defined by the following restrictions:

1. Exactly one of the two atoms X and Y is sulfur.
2. X is a heteroatom including sulfur.
3. Y is a heteroatom or carbon.
4. The bond order between C-2 and C-3 (Scheme 1) is two.

Even within these restrictions a formidable number of possible rearrangements are thinkable (Chart 1).

To organize the material to be presented in this review, a classification based on the formal oxidation state of the sulfur atom will be used. As already discussed, in the course of the rearrangement a 1,2-shift of an electron pair from Y to X takes place entailing a formal reduction of X (the atom that the allylic moiety was bound to). If we identify X with sulfur, five rearrangements accompanied by a S(VI) to S(IV) transition can be constructed (Chart 1, top

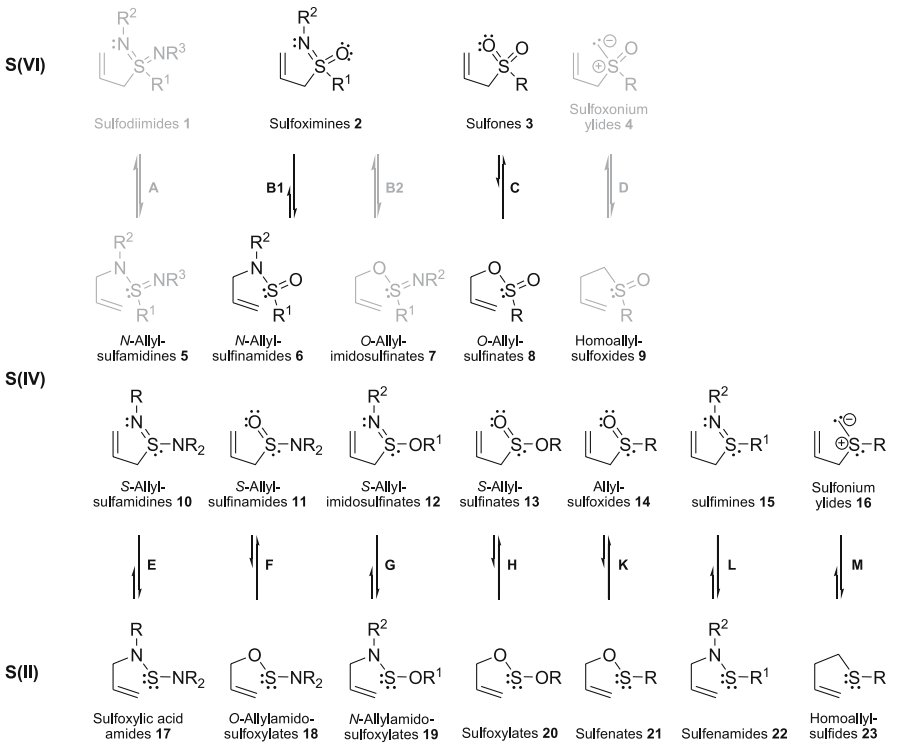


Chart 1 [2,3]-Sigmatropic rearrangements of allylic sulfur compounds and the usual equilibrium positions

row equilibria). Moreover, seven rearrangements interconvert S(IV) and S(II) species (Chart 1, bottom row equilibria).

Obviously, [2,3]-sigmatropic rearrangements of sulfur-containing systems comprise a class of reactions with a considerable constitutional scope. But the configurational consequences of the concerted suprafacial reaction mode are even more exciting, both from a stereochemical point of view and for synthetic reasons.

In a *generic* sigmatropic rearrangement substituted in such a way to achieve maximum asymmetry, a total number of four stereogenic units (entailing a maximum of 16 stereoisomers) are present: two stereogenic centers at the edges of the migrating σ-bond and the two stereogenic double bonds at the respective ends of the π-systems along which the σ-bond is shifted. A closer look at Scheme 1 and Chart 1 makes it clear that the presence of the heteroatoms X and Y changes the situation. The maximum number of four stereogenic units is reachable only if Y is a carbon atom (**D** and **M** in Chart 1). In all other cases three or only two stereogenic units are involved. Nonetheless, this analysis gives a clue to the most important stereochemical issues that are operative in a [2,3]-sigmatropic rearrangement:

1. Control of the configuration of the newly created double bond
2. Three types of "chirality transfer":
   - C-1 → C-3
   - X → C
   - X → Y

Given this constitutionally and configurationally rich chemistry offered by [2,3]-sigmatropic rearrangements in general and those containing sulfur in particular, it is not surprising that the subject has been covered in the past by numerous reviews (cited at the beginning of each section related to a particular rearrangement) and book chapters [2–5]. Excellent treatments with particular emphasis on stereochemistry are the review of Hoffmann [6] and the book chapters of Brückner (Type **K**) [1], Ritter (Types **K** [7], **L**, **E**, **G** [8]), and Kallmerten (Type **M**) [9]. For these reasons a general discussion will not be repeated here.

Moreover, most of the material covered by this review was published in 1990 or later, with a strong focus on newer developments in sulfonium ylide chemistry (Type **M**) and applications of the sulfenate–sulfoxide rearrangement (Type **K**) in the context of stereoselective, target molecule oriented synthetic work. Stressing these applications is a natural consequence of the fact that, despite the overwhelming multitude of possible processes, only very few are important from a synthetic point of view (especially Types **K**, **L**, **M**) and others have, to the best of the author's knowledge, never been described in the literature ("grayed out structures" Types **A**, **B2**, **D**). The synthetic chemist's interest in some of these transformations can be traced back mainly to their beneficial application in stereoselective transformations, or to the fas-

cinating opportunities they offer to develop catalytic asymmetric reactions (Type **M**).

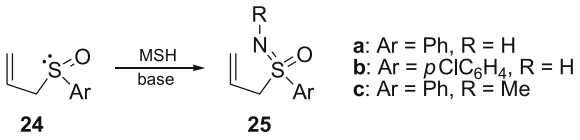
2
Sulfur(VI)–Sulfur(IV) Rearrangements

Within this class of possible rearrangements four *S*-allylic sulfur(VI) compounds have to be considered (Chart 1). Among these only the sulfoximines and especially the allylic sulfones have found some interest. Although non-allylic sulfamidines **5**/**10** are known compounds [10], nothing is known about *N*-allylic derivatives **5** and their possible rearrangement to *S*-allyl sulfodiimides **1** (Type **A** in Chart 1). The same is true for the *O*-allyl imidosulfinates **7** [10] and their relation to sulfoximines (Type **B2**). Finally, rearrangement **D** converting *S*-allyl sulfoxonium ylides **4** to homoallyl sulfoxides **9** seems to be an unknown process, too. With regard to the enormous relevance of sulfoxonium ylides as alkylidene transfer reagents, this is rather surprising.

2.1
Type B1: *S*-Allylsulfoximines ⇌ *N*-Allylsulfinamides

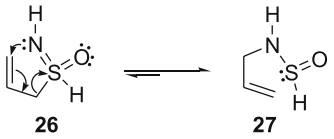
Scheme 2

In 1975 Tamura et al. reported on the synthesis of two allylic sulfoximines (**25a** and **25b**) via oxidative imination using *O*-mesitylenesulfonyl hydroxylamine (MSH) (Scheme 3) [11]. Both compounds are described as thermally stable, contrasting the behavior of the corresponding sulfimines (Sect. 3.6, Type **L**). Interestingly, 4 years later Johnson et al. pointed out that sulfoximine **25c** is readily subject to rearrangement and/or C – S bond heterolysis [12].



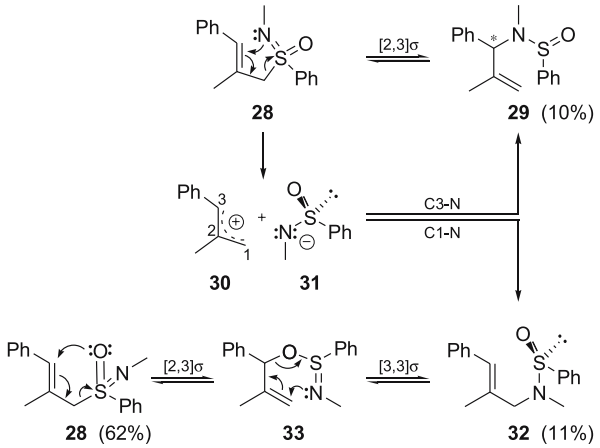
Scheme 3 *S*-Allylsulfoximines

In the time that followed allylic sulfoximines, and especially enantiomerically pure derivatives thereof, were developed to useful synthetic intermediates [13–15]. For that reason the question arose of whether these compounds are prone to rearrange to *N*-allyl sulfinamides **6** or *O*-allyl imidosulfinates **7** (Chart 1, **B1**, **B2**). Early modified neglect of differential overlap (MNDO) calculations by Harmata [16] and Pyne [17] indicated that allylic sulfinamides are thermodynamically much more stable than the corresponding sulfoximines. This was confirmed later using a much higher level of theory by Glaser and Harmata [18] (Scheme 4). On the basis of their ab initio study they estimated the conversion of **26** to **27** to be exothermic by 24.1 kcal mol^{-1} but hindered by a large kinetic barrier of ca. 28 kcal mol^{-1}. From these data it can be expected that under most synthetically relevant circumstances this rearrangement can be ignored.



Scheme 4 *S*-Allylsulfoximines in equilibrium with *N*-allylsulfinamides

Indeed, besides the work of Johnson [12], there is only one hint in the literature for such a process to take place without the intervention of a metal. In 1994 Gais et al. thermolyzed enantiomerically pure sulfoximine **28** for 112 h at 85 °C in dichloroethane (Scheme 5) [19]. As well as 62% of unchanged starting material they were able to isolate 10% of the branched and 11% of the unbranched rearrangement products **29** and **32**, respectively. Moreover, they

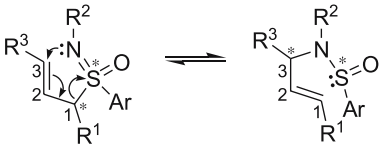


Scheme 5 Ionic vs concerted pathways in Type **B1** rearrangements

found all products as pure isomers and they assumed the rearrangement to occur with retention of the *S* configuration. A plausible explanation for these findings is either a dissociation–recombination pathway via **30** and **31** or a sequence of sigmatropic rearrangements. Most interestingly, even the linear product **32** may have formed via a combination of a [2,3]-shift of **28** involving the *O* atom of the sulfoximine, followed by a [3,3]-sigmatropic rearrangement of the intermediate imidosulfinate **33**.

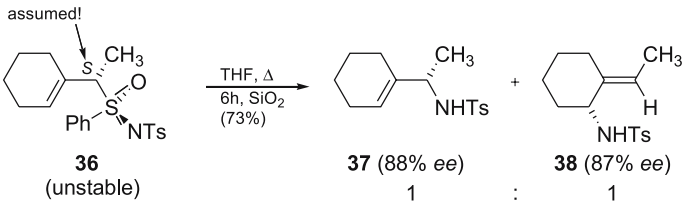
The chemistry of imidosulfinates is vastly unexplored [10] and nothing is known to date about the behavior of *O*-allyl imidosulfinates in particular. By comparison with the known process **C** (Chart 1), the sulfinate–sulfone rearrangement (Sect. 2.2), it seems rather promising to try a new sulfoximine synthesis based on that rearrangement.

As discussed above the kinetic stability of allylic sulfoximines prevents them from "going downhill" to the thermodynamically favored sulfinamides, which in turn is a precondition for their successful application as solutions for asymmetric d^3-synthons [13–15, 20–32]. On the other hand, if it would be possible to make them rearrange to allylic amines with 1,3-chirality transfer, this would be an interesting entry to this class of compounds (Scheme 6).[1]



Scheme 6 Equilibrium of sulfoximines and allylic sulfinamides

If the ion-pair mechanism discussed by Gais (Scheme 5) does play a role in the formation of the rearrangement products **32** and **29**, then stabilization of both the cation **30** and the anion **31** should increase the probability of the system to rearrange. Indeed, by replacing the *N*-Me group by an *N*-Ts group systems are available that rearrange rapidly (Scheme 7) [33].



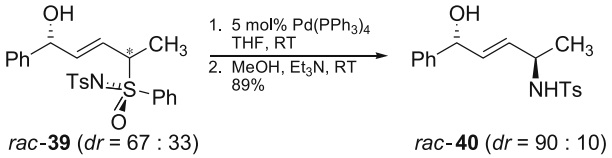
Scheme 7 Type **B1** rearrangement of secondary 2-alkenyl sulfoximines

[1] The term "chirality transfer" is somewhat misleading. Chirality is a property that applies to a molecule as a whole, which entails that it cannot be transferred from one place to another within that molecule. Chirality transfer denotes a mechanistically determined relation between two stereogenic units in the starting material and the product, respectively.

The α-methylated allylic sulfoximine **36** has been prepared by a diastereoselective methylation of the unsubstituted sulfoximine. Whether or not **38** is the product of a [2,3]-sigmatropic rearrangement or a recombination product of an ion pair is open to debate. Unfortunately, the reaction delivers **38** only as a component of an inseparable mixture with its constitutional isomer **37**.

When, on the other hand, **36** is treated with 5 mol % $Pd(PPh_3)_4$ followed by sodium hydroxide, it rearranges cleanly to **37** (88% *ee*), obviously via allylic substitution involving η^3-Pd-allyl species. This reaction has been shown to be quite general [34, 35] but most of the time it appears not to be of special synthetic value (two stereogenic centers were converted into one).

An interesting exception is a stereoconvergent process in the course of which the *S* centrochirality is destroyed but a uniformly configured stereogenic center at carbon is established (Scheme 8) [36]. As a possible explanation for the stereoconvergence, the authors discuss a rapid preequilibrium of the intermediate η^3-Pd complexes with a thermodynamic preference for the one involving a Pd–OH interaction. Despite this interesting finding, the rather elaborate synthesis of enantiomerically pure allylic sulfoximines [13], and the notorious instability of α-alkylated derivatives thereof [33], a widespread application of this methodology for the synthesis of 1,4-difunctionalized compounds of type **40** is questionable.



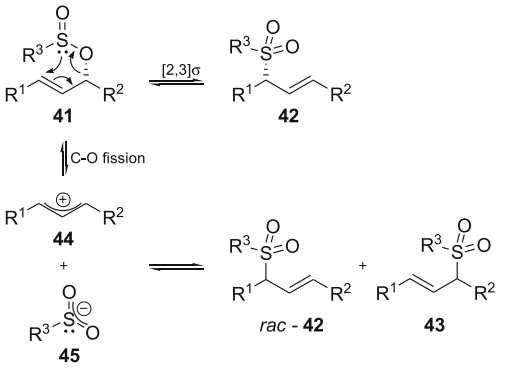
rac-**39** (*dr* = 67 : 33) *rac*-**40** (*dr* = 90 : 10)

Scheme 8 Stereoconvergent transformation of an allylic sulfoximine

2.2
Type C: *S*-Allylsulfone ⇌ Allylsulfinate Rearrangement

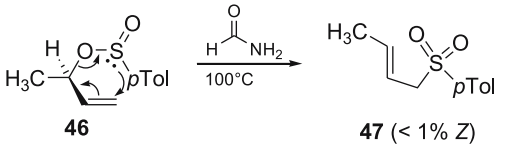
Scheme 9

Since the pioneering work of Cope [37] as early as 1950, the mechanistic and stereochemical implications of this rearrangement have been reviewed several times [4, 5, 38]). The reaction turned out to be rather sensitive to the substitution pattern and the solvent used (Scheme 10). The constitutional and stereochemical outcome of the reaction strongly depends on what position in the mechanistic spectrum the reaction takes place. For highly substituted sys-

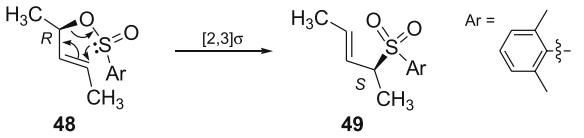


Scheme 10 Mechanistic spectrum of Type **C** rearrangements

tems without particular carbenium ion stabilizing capabilities (R^1, R^2) and/or good leaving groups (R^3), the rearrangement takes the [2,3]-sigmatropic course (Scheme 11) [39]. As a consequence complete "allylic inversion" takes place and furthermore, due to the energetically favored "transoid" transition state [6, 40], the sulfone **47** is generated with perfect *E* selectivity. Moreover, if the process really is a suprafacial sigmatropic rearrangement, "1,3-chirality transfer" should occur in suitably substituted systems. This is indeed the case, as shown by Braverman as early as 1971 [41] (Scheme 12).

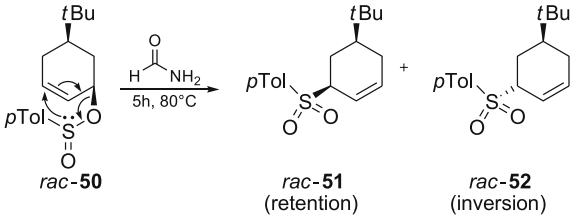


Scheme 11 *E*-selective Type **C** rearrangement



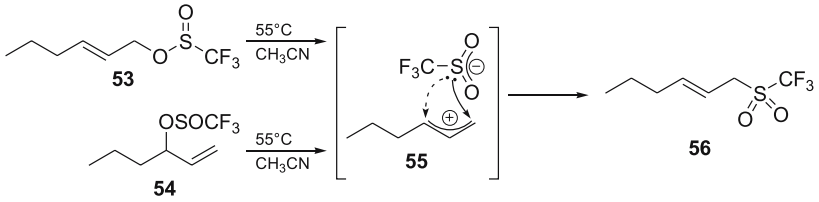
Scheme 12 1,3-chirality transfer in Type **C** rearrangements

As already pointed out in systems with increased carbocation stabilization capabilities, mixed-mode rearrangement processes with varying participation of the ion-pair extreme come into play (Scheme 13). The rearrangement of the *cis*-configured sulfinate **50** (racemic 1 : 1 mixture of *S* epimers) delivers 70% of the expected *cis*-sulfone *rac*-**51** and 30% of *rac*-**52** obviously via ion-pair recombination [39]. As expected, increasing the leaving group ability of



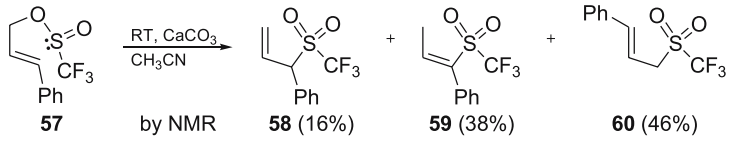
Scheme 13 Mixed-mode Type **C** rearrangement

the sulfinate (R^3, Scheme 10) also shifts the mechanism toward the ion-pair extreme, as shown by Hendrickson in 1976 (Scheme 14) [42]. In accordance with an ionic mechanism both isomeric triflinates **53** and **54** rearrange in a constitutionally convergent manner yielding sulfone **56** as the sole product.



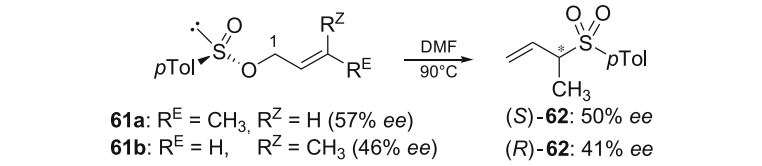
Scheme 14 Type **C** rearrangements in the ion-pair extreme

Some 30 years later Braverman showed that even under so-called buffered conditions the cinnamyl triflinate **57**, *combining* cation stabilization and leaving group quality, yields even at room temperature a mixture of three compounds from rearrangement (**58/60**) and isomerization processes (**59**) (Scheme 15) [43].



Scheme 15 Rearrangement of cinnamyl triflinates

In addition to the above-mentioned 1,3-chirality transfer, another mode of transferring centrochirality from one atom to the other is the S → C transfer. This feature of the reaction has already been discussed by Mislow in his 1968 paper [40], where he delineates all important stereochemical aspects of [2,3]-sigmatropic rearrangements using the sulfoxide–sulfenate rearrangement as an example. For the sulfinate–sulfone rearrangement under consideration here, the work of Hiroi in the early 1980s should be mentioned (Scheme 16) [44,

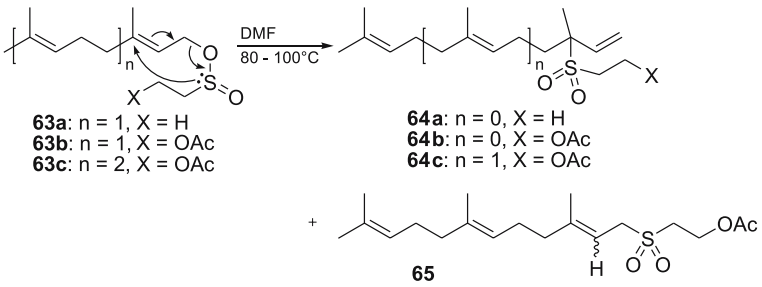


Scheme 16 Sulfur to carbon chirality transfer with enantioenriched allylic sulfinates

45]. Enantiomerically enriched, 1-unsubstituted 2-alkenylsulfinates (e.g., **61**) have been synthesized via enantioenriched sulfinamides following the work of Mikołajczyk [46] after minor modifications [47].

The examples shown in Scheme 16, which are representative for all other sulfinates studied, demonstrate a high level of stereoselectivity (around 80–90% of the original enantiomeric excess is retained after switching the stereogenic atom from sulfur to carbon). Despite these encouraging results, the somewhat tedious and stereochemically unreliable preparation of the starting sulfinates [47] may be the reason for the reluctance of the chemical community to use this chemistry as an entry to enantiomerically pure 2-alkenyl sulfones.

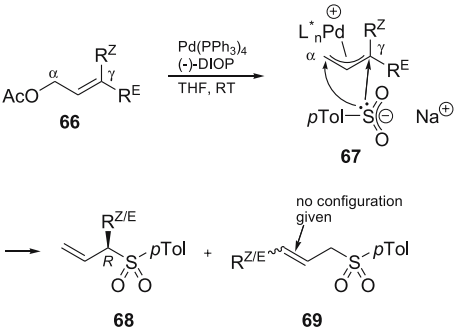
Even on the constitutional level this rearrangement has not found widespread application in synthetic, target molecule oriented work. Obviously the delicate dependence of the constitutional outcome of the reaction from parameters like substitution pattern, temperature, additives, and the solvent has hampered its application in this area. One exception is work on the synthesis of the marine natural product agelasidine A published in 1992 by Ichikawa et al. (Scheme 17) [48]. In accordance with the above discussion, the authors initially had trouble with the reaction. With the model geranyl ethyl sulfinate **63a**, only around 10% of the desired sulfone **64a** was obtained even under optimized conditions [44]. Interestingly, both the *acetates* **63b** and, more relevant to the synthesis of agelasidine A, **63c** do rearrange in the desired manner yielding between 50 and 70% of the products **64b** and **64c**. As a side product the authors observed the formal 1,3-rearrangement product **65**.



Scheme 17 Applications in natural product synthesis

Facing all the mechanism-related peculiarities of the thermally induced rearrangement it was consequential to try to shift the reaction toward one end of the mechanistic spectrum. The first steps in that direction were undertaken by Hiroi et al.; in 1984 they reported on a palladium-catalyzed variant of the reaction [49]. With enantiomerically enriched sulfinates **61** (Scheme 16) they found a much faster reaction as compared to the uncatalyzed one, allowing a reduction of the reaction temperature down to – 78 °C (!). The stereospecificity of the rearrangement depended heavily on the substitution pattern (between 28 and 92%) and was traced back to the intermediacy of a configurationally stable η^3-π-allylpalladium species whose configuration was influenced by the *S* centrochirality. Unfortunately, due to difficulties in the preparation of enantiomerically pure 2-alkenylsulfinates (see above), the *ee* values of the resulting allylic sulfones were quite low.

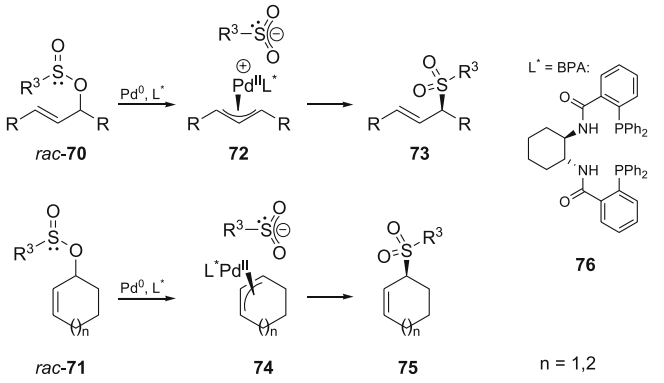
In a later paper the same author realized that the intermediate π-complex can be generated from *achiral* allylic systems and enantioselectivity may be achieved using chiral ligands on palladium [50]. Toward this end allylic acetates **66** were treated with sodium *p*-toluenesulfinate **67** in the presence of $Pd(Ph_3)_4$ and the chiral ligand [2,2-dimethyl-1,3-dioxolane-4,5-diylbis(methylene)]bis(diphenylphosphane) (DIOP) [51] (Scheme 18). With sterically undemanding substituents R^E/R^Z the desired branched product **68** is generated in a stereoconvergent manner; both double bond isomers of **66** furnished *R*-configured allylic sulfones **68** with up to 88% *ee* (R^E; $R^Z = CH_3$). Not surprisingly with increasing steric bulk in the γ-position, the amount of the linear product **69** increased, too.



Scheme 18 Palladium-catalyzed asymmetric sulfinylation of allylic acetates

In the years to follow this chemistry was developed further and it turned out that especially the Pd(0)-catalyzed alkylation of sulfinate ions with racemic allylic carbonates provides an excellent means for the asymmetric synthesis of allylic sulfones [52–55]. Despite these successes the efforts to use 2-alkenylsulfinates as precursors for enantioenriched allylic sulfones never stopped [56].

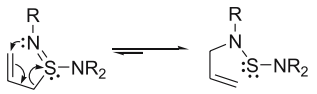
The development of this chemistry reached a preliminary climax with the work published by Gais in 2004 [57]. Herein the stereoconvergent enantioselective rearrangement of symmetrically substituted acyclic and cyclic 2-alkenylsulfinates is described (Scheme 19). With the bisphosphane BPA (**76**) [58] as chiral ligand and $Pd_2(dba)_3$ as catalyst precursor, clean conversion of the starting sulfinates *rac*-**70** (R = Me, Et; R^3 = *t*-Bu, *p*-Tol) and *rac*-**71** (mixtures of racemic diastereomers in all cases) to the target sulfones **73** and **75**, respectively, was achieved at room temperature. The enantiomeric excess of the products was found to be in the higher 90s (≥ 98% *ee* in most cases). It is worth mentioning here that the chemistry even works with the cycloalkenyl derivatives **71**, which have proven to be difficult substrates in other asymmetric allylic substitution reactions [59–61].



Scheme 19 Highly enantioselective Pd-catalyzed rearrangement of allylic sulfinates to allylic sulfones

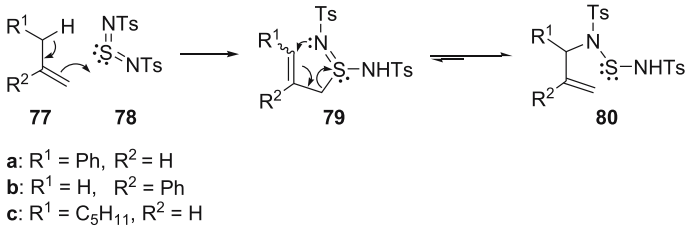
3
Sulfur(IV)–Sulfur(II) Rearrangements

3.1
Type E: *S*-Allylsulfamidines ⇌ *N*-Allylsulfoxylic Acid Amides



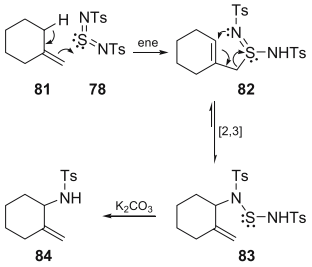
Scheme 20

In the course of a long-term study of the chemistry of *N*,*N*′-ditosyl sulfodiimide **78** [62], in 1975 Kresze discovered the high enophilicity of this compound (Scheme 21) [63]. The ene reaction of propene derivatives **77** with **78**



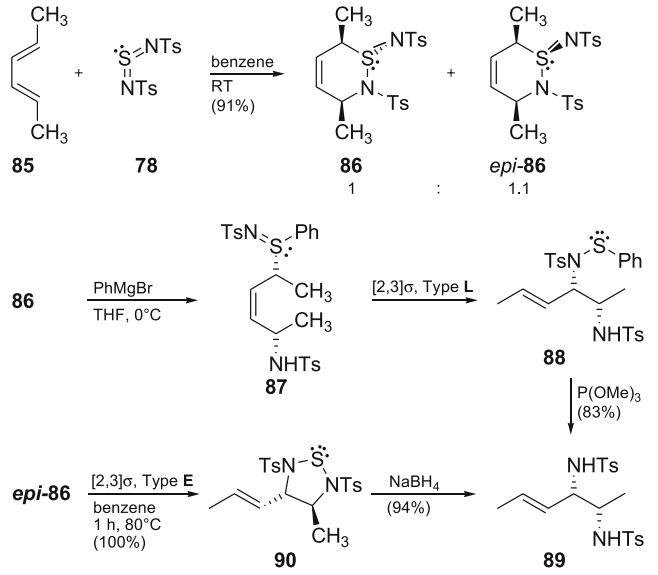
Scheme 21 Tandem ene reaction and [2,3]-sigmatropic shift

delivered the *S*-allylsulfamidines **79**, which were found to rapidly rearrange at room temperature to the *N*-tosylated sulfoxylic acid amides **80**. In a concluding remark Kresze revealed the similarity of this chemistry to that of the SeO_2-mediated oxidation of olefins [64, 65], a reaction that has been studied mechanistically these days. A year later Sharpless published work on the same chemistry including a means to cleave an S – N bond in the rearrangement products to yield *N*-tosylated allylic amines (Scheme 22) [66].



Scheme 22 Allylic amination via [2,3]-sigmatropic rearrangement of 2-alkenyl sulfamidines

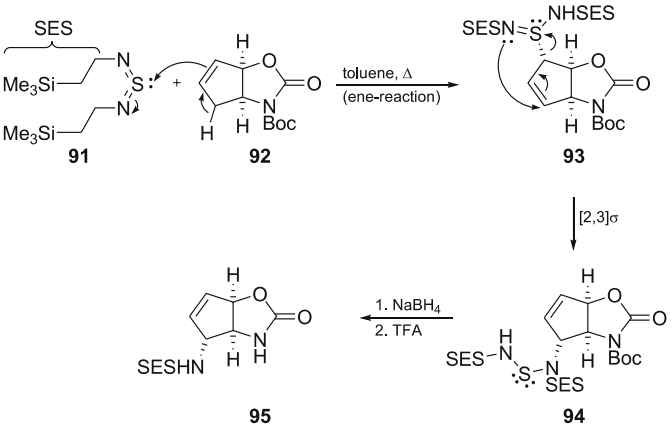
Based on these results this chemistry has been developed further to include hetero Diels–Alder reactions as an alternative means to prepare the *S*-allylsulfamidines (Scheme 23) [67–69]. The hetero Diels–Alder reaction of diene **85** with sulfur diimide **78** yields the two diastereomeric 3,6-dihydrothiazine-1,2-imines **86** and *epi*-**86** in a 1 : 1.1 ratio. Interestingly, only **86** reacts with PhMgBr to give the *S*-allylsulfimine **87** which undergoes a Type **L** (Sect. 3.6) [2,3]-sigmatropic rearrangement to tosylated sulfenamide **88**, which finally gets desulfurized by $P(OMe)_3$ to furnish the vicinal diamine **89**. Diastereomer *epi*-**86**, on the other hand, suffers a Type **E** [2,3]-sigmatropic rearrangement delivering **90** whose relative configuration is in accordance with a concerted suprafacial process. Its desulfurization with $NaBH_4$ led to the same diamine as with the other diastereomer. As expected, the influence of the absolute configuration at sulfur on the stereochemical outcome of the reaction is negligible (1,3-chirality transfer dominates [6]),



Scheme 23 Sulfamidines via hetero Diels–Alder reactions

but quite surprisingly the reactivity of the system is heavily affected by this configuration.

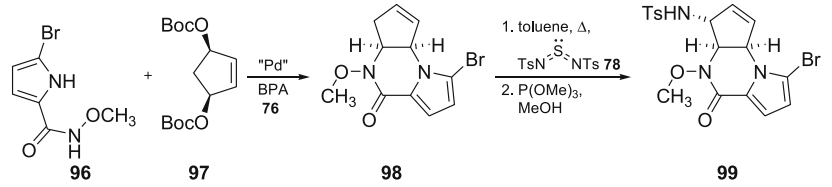
This interesting chemistry has been applied in natural product synthesis, especially in the context of the marine alkaloid agelastatin A. In 1999 the first total synthesis of racemic agelastatin A was achieved by Weinreb [70] (Scheme 24). Key intermediate **95** was synthesized via the already mentioned allylic amination sequence, this time using the new sulfodiimide **91**. As an-



Scheme 24 Application of a Type **E** rearrangement in the total synthesis of agelastatin A

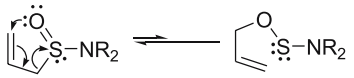
ticipated by the authors the initial ene reaction occurred from the convex face of **92**, delivering the *S*-allylsulfamidine **93** with the shown absolute configuration at the sulfurized position. This compound underwent the Type **E** [2,3]-shift with complete 1,3-chirality transfer delivering **94**, which was desulfurized to the target compound **95**.

Recently Trost et al. succeeded in the total synthesis of (+)-agelastatin A using Pd-catalyzed asymmetric allylic alkylations [71]. In the course of this study they prepared piperazinone **98** which was amenable to allylic amination via sulfodiimide **78** (Scheme 25). In the context of Weinreb's synthesis the authors claim **99** to be a suitable intermediate for the synthesis of the (–)-enantiomer of agelastatin A.



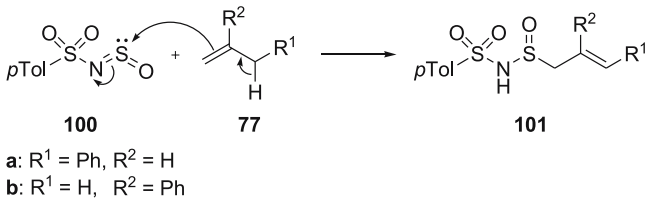
Scheme 25 Tandem Pd-catalyzed allylic alkylation–allylic amination sequence

3.2
Type F: *S*-Allylsulfinamides ⇌ *O*-Allylamidosulfoxylates



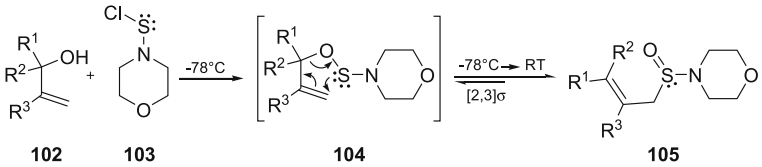
Scheme 26

In their 1975 paper on ene reactions with ditosyl sulfodiimide **78**, Kresze et al. briefly mentioned that *N*-sulfinyl sulfonamide **100** undergoes ene reactions with alkenes to yield *S*-2-alkenyl sulfinamides **101** (Scheme 27) [63]. Contrasting the behavior of the aza analogues, the *S*-allylsulfamidines (Type **E**, Sect. 3.1), the resulting 2-alkenyl sulfinamides **101** are not prone to sigmatropic rearrangement. This, on the other hand, can be taken as a hint that



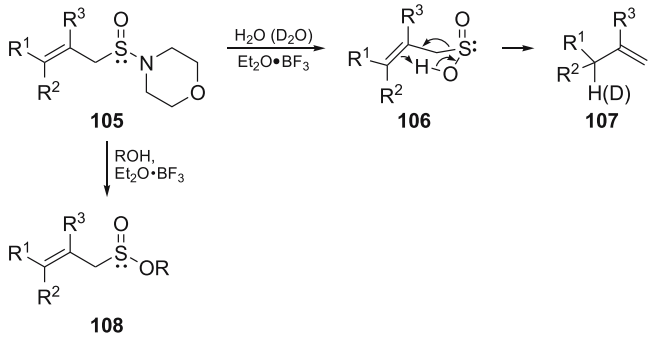
Scheme 27 Ene reactions with *N*-sulfinyl sulfonamide **100**

equilibrium **F** (Chart 1) is shifted toward the sulfinamide, which in turn raises the expectation that *O*-allylamidosulfoxylates (e.g., **104** in Scheme 28) should rearrange. This was indeed found to be the case [72] (Scheme 28).



Scheme 28 Rearrangement of *O*-allylamidosulfoxylates

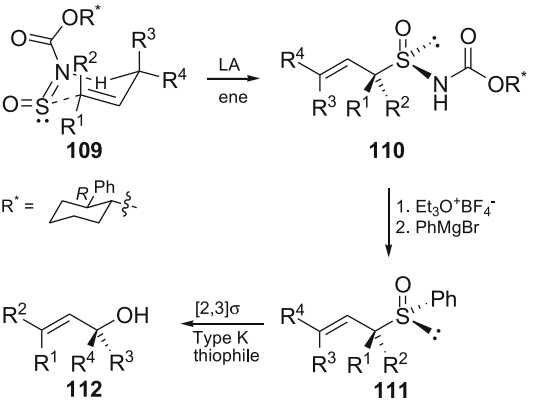
Treatment of a number of substituted allylic alcohols **102** with morpholino sulfenyl chloride **103** at low temperature led to the formation of amidosulfoxylates **104**, which rearranged readily during warm up to room temperature. In accordance with the proposed transition-state structures for [2,3]-sigmatropic rearrangements [6, 40], the double bond geometry in **105** was found to be *E* for all cases with $R^3 = H, CH_3$ (with a decreased selectivity for some functionalized substituents R^1). If R^3 was $COCH_3$ or $COOCH_3$ the double bond configuration was found to be inverted, probably due to the better delocalization in the transition state (especially if R^2 = Ph). In a 1991 study the same author reported on the diastereoselectivity of this rearrangement with respect to the relative configuration at C1 and the S atom [73]. Moreover, Baudin described some useful transformations of the allylic sulfinamides [72, 74] (Scheme 29). Following the work of Mikołaicyk [75] and Hiroi [47], Lewis acid mediated alcoholysis of **105** led to sulfinates **108** and even more interesting the hydrolysis of **105** under the same conditions produced 2-alkenyl sulfinic acids **106**, which lost SO_2 to produce alkenes **107** [4]. This process can be interpreted as a concerted retro-ene reaction, which was corroborated by the mechanistic work of Isaacs and Young in 1995 [76]. Later this chemistry and the Pd-catalyzed variants thereof [77]



Scheme 29 Transformations of *S*-allyl sulfinamides

was exploited as a means for the stereoselective synthesis of polypropionate fragments [77–79].

In 1990 an interesting, although somewhat tedious to read, paper on asymmetric induction in ene reactions of chiral sulfinylcarbamates appeared (Scheme 30) [80]. From the analysis of an assumed conformation of the chiral sulfinylcarbamate **109** the authors derived the expected topicity of attack onto the sulfinyl sulfur. This information, together with the six-membered ring transition-state model for the ene reaction, led to the prediction of sulfinamides **110** as reaction products. In accordance with that expectation the absolute configuration at sulfur was found to be *R*, irrespective of the double bond geometry in the starting olefins, and the relative configuration was as shown (> 95% *ds*). As already mentioned the position of the equilibrium interrelating the sulfinamides with their rearrangement products is shifted to the sulfinamide side. Nevertheless, the authors tried to shift it to the *O*-allylamidosulfoxylate by the addition of various thiophiles. Contrasting the behavior of *S*-allylsulfoxides (Type **K**, Sect. 3.5), no conversion to allylic alcohols was observed. Therefore, after *N*-ethylation, sulfoxides **111** (Scheme 30) were prepared by nucleophilic displacement using PhMgBr (see also [81]). These allylic sulfoxides undergo, as expected, the [2,3]-σ-shift under the influence of a thiophile, delivering allylic alcohols **112** with the double bond in the same position as in the starting alkene.

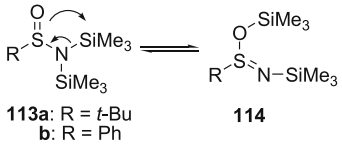


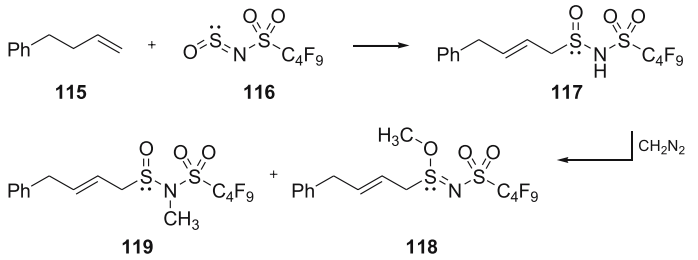
Scheme 30 Asymmetric synthesis of S-allyl sulfinamides and their conversion to enantioenriched allylic alcohols

3.3
Type G: *S*-Allylimidosulfinates ⇌ *N*-Allylamidosulfoxylates

In 1976 Marsmann et al. reported on the structures of doubly silylated sulfinamides (Scheme 31) [82]. From the analysis of ^{29}Si NMR and IR data the predominance of the imidic structure **114** was deduced. Some 10 years later,

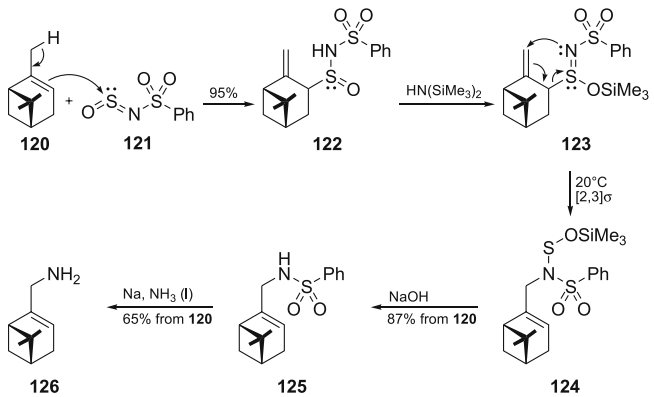
Scheme 31





Scheme 32 Early work on imidosulfinates

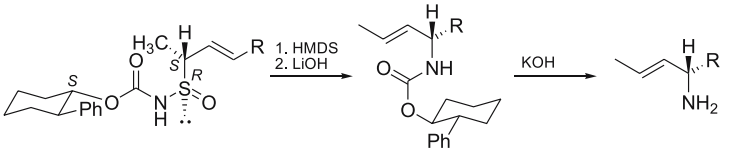
Kresze et al. found that the ene product **117**, after diazomethane treatment, formed a mixture of the *O*- and *N*-methylated compounds **118** and **119**, respectively [83] (Scheme 32). Only a year later Delerit et al. used this possibility to *O*-silylate *S*-allylsulfinamides derived from ene reactions between olefins and *N*-sulfinyl sulfonamides to develop a regioselective allylic amination sequence (Scheme 33) [84]. After the ene reaction had occurred the resulting sulfi-



Scheme 33 Regioselective allylic amination of α-pinene

namide **122** was *O*-silylated by the action of hexamethyl disilazane yielding **123** (structure made plausible by ^{29}Si NMR), whose [2,3]-sigmatropic rearrangement delivered **124** which was hydrolyzed to the protected allylic amine **125** in 87% yield from α-pinene **120**. This compound could be desulfurized by sodium in liquid ammonia furnishing free amine **126**.

An asymmetric variant of this kind of allylic amination, based on their phenylcyclohexanol-derived chiral *N*-sulfinyl carbamates, was developed by Whitesell et al. (see also Sect. 3.2) (Scheme 34) [85]. After the asymmetric ene reaction with *Z*-configured olefins (not shown) had occurred, nearly diastereomerically pure sulfinamides **127** were obtained which were found to be prone to epimerization. Their *rapid* conversion via O silylation and [2,3]-σ rearrangement delivered the carbamoylated allylic amines **128** with around 7 : 1 diastereoselectivity as crystalline compounds that can be recrystallized to enhance their isomeric purity to 95 : 5. Obviously the uniform absolute configuration at C1 in the ene products **127** was difficult to transfer completely due to the already mentioned ease of epimerization. Unlike the sulfonamides of Delerit (Scheme 33) [84], the carbonyl moiety can easily be cleaved by base treatment.



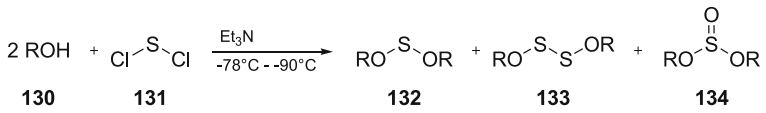
Scheme 34 Asymmetric allylic amination

3.4
Type H: *S*-Allylsulfinates ⇌ Sulfoxylates

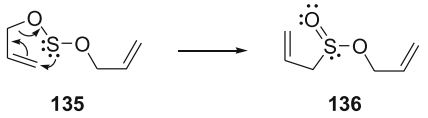
Scheme 35

In 1965 Thompson prepared a number of dialkyl sulfoxylates **132** from sulfur dichloride **131** and various alcohols (Scheme 36) [86]. Sulfoxylates **132** were steadily accompanied with impurities like **133** and **134**, but lowering the reaction temperature below – 78 °C led to formation of the desired compounds **132** with yields around 60%. With allyl alcohol he observed the formation of the rearranged sulfinate **136** (Scheme 37).

This was not only the first observation of such a Type **H** rearrangement, but also it answered the question of the position of the equilibrium. Inter-

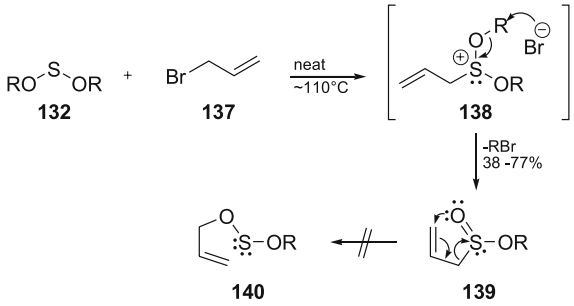


Scheme 36 Sulfoxylates by "acylation" of alcohols with sulfur dichloride

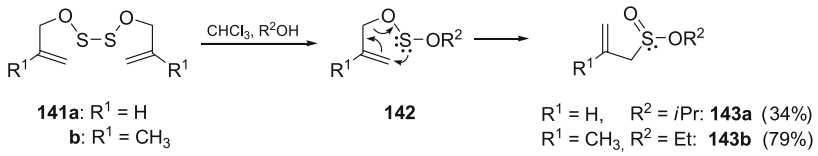


Scheme 37 First observation of a Type **H** rearrangement

estingly, this was corroborated in the mid-1970s by the independent preparation of a number of *S*-allyl sulfinates via Michaelis–Arburzov-type chemistry (Scheme 38) [87, 88]. Treatment of various dialkyl sulfoxylates with allyl bromide produced sulfinates **139** as stable compounds. Moreover, these sulfinates are "mixed allylic sulfinates", obviously difficult to prepare via the sulfur dichloride route mentioned above. In a recent paper Braverman described an alternative route to these mixed sulfinates via alcoholysis of symmetric allylic dialkoxy disulfides (Scheme 39) [89] (see also [90]).

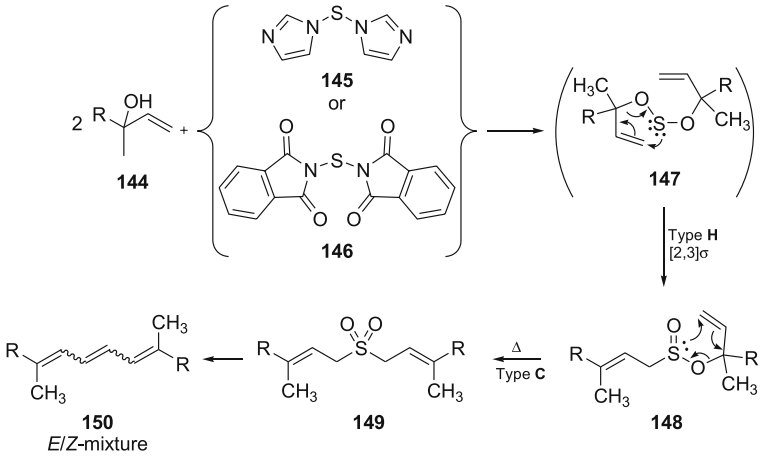


Scheme 38 Mixed allylic sulfinates via *S*-alkylation of sulfoxylates



Scheme 39 Mixed allylic sulfinates by alcoholysis of dialkoxy disulfides

Finally, it should be mentioned that as early as 1974 a combination of this rearrangement with the Type **C** rearrangement followed by a Ramberg–Bäcklund olefination [91] was used to synthesize a number of trienes



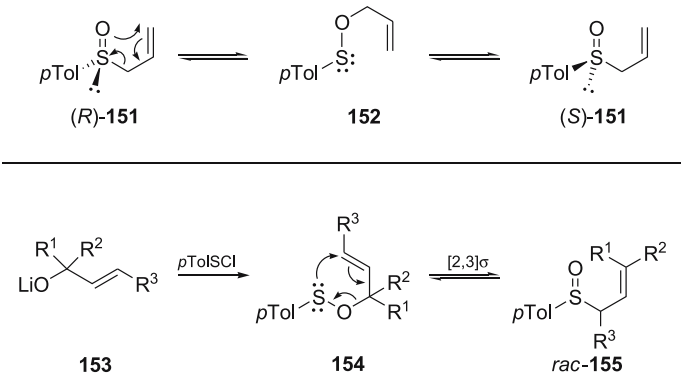
Scheme 40 Combined application of Type **H** and Type **C** rearrangements for the synthesis of trienes

(Scheme 40) [92]. For the synthesis of the sulfoxylates **147** they employed either 1,1′-thiodiimidazole **145** [93, 94] or 1,1′-thiodiphthalimide **146** [95, 96]. These sulfoxylates were never isolated, as they immediately rearranged to allylic sulfinates **148** which in turn suffered another [2,3]-sigmatropic rearrangement (Type **C**, Sect. 2.2) at elevated temperatures to give the desired sulfones **149**. These latter compounds underwent Ramberg–Bäcklund reactions [91] to furnish trienes **150** as isomeric mixtures. The sequence has been used to synthesize β-carotene [92].

3.5
Type K: Allylsulfoxides ⇌ Allylsulfenates

Scheme 41

In the mid-1960s Mislow started a research program on the mechanism of the thermal racemization of sulfoxides [97–99]. In the course of these efforts he recognized an enormous racemization rate acceleration for (*R*)-allyl-*p*-tolyl sulfoxide ((*R*)-**151**) as compared to benzyl or, even more pronounced, to alkyl sulfoxides (Scheme 42). For this compound, prepared by Andersen synthesis [100, 101], he found a racemization rate exceeding that of the phenyl-substituted sulfoxide by a factor of 560 000. Based on kinetic measurements Mislow et al. determined the activation parameters to be $\Delta H^{\ddagger} = 22$ kcal mol^{-1}



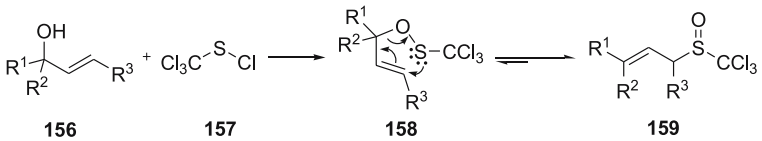
a: R^i = H
b: $R^1 = R^2$ = H; $R^3 = CH_3$
c: $R^1 = R^3$ = H; $R^2 = CH_3$

Scheme 42 Discovery of the Type **K** (Mislow–Evans) rearrangement

and $\Delta S^{\ddagger} = -9$ eu. Both values are in accordance with a concerted reaction involving synchronous bond breaking and forming in a highly ordered transition state.

In the same year (1966) these results and conclusions were corroborated by experiments with labeled allylic termini (Scheme 42) [98] using methylated allylic alkoxides **153b** and **153c**. Their reaction with *p*-toluenesulfenyl chloride led to the corresponding sulfenates **154**, which immediately rearranged with complete "allylic inversion" to *rac*-**155b** and *rac*-**155c**, respectively, thus confirming the conclusions drawn from the kinetic data discussed above.

In 1967 the work on allylic sulfenates was extended to the trichloromethyl derivatives (Scheme 43) [99, 102]. This activity was prompted by a report of Sosnovsky [103], who claimed the synthesis of the sulfenate **158a** from chloride **157** and allylic alcohol **156a** (Scheme 43). Braverman showed that **158a** was not the product of the reaction. Instead the sulfoxide **159a** was obtained, presumably via [2,3]-sigmatropic rearrangement. Positive experimental evi-



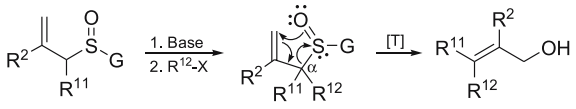
a: $R^1 = R^2 = R^3$ = H
b: $R^1 = R^2$ = D, R^3 = H
c: $R^1 = R^2$ = H, $R^3 = CH_3$
d: $R^1 = R^2$ = H, R^3 = Ph

Scheme 43 Rearrangements of allylic trichloromethyl sulfenates

dence for the concertedness of the process was presented by Mislow in the same year, again using allylic alcohols with labeled allylic termini (**156b**, **156c**) [99].

The reaction of the lithium allyl-α-d_2 alcoholate derived from **156b** with **157** gave exclusively allyl-γ-d_2 trichloromethyl sulfoxide **159b** as expected. Interestingly, the sulfenylation of crotyl alcohol **156c** delivers a mixture of the rearrangement product **159c** and unrearranged sulfenate **158c**, demonstrating the sensitivity of the equilibrium position to the substitution pattern. Moreover, it was found that cinnamyl trichloromethane sulfenate **158d** is relatively stable and rearranges under forced conditions to cinnamyl trichloromethyl sulfoxide (**159** with R^1 = Ph, R^2 = R^3 = H) *without* allylic shift, presumably via an ionic pathway [102] very much like the one discussed in Sect. 2.2. In subsequent years Mislow published excellent work on different aspects of the rearrangement including stereochemical consequences, and solvent and substituent effects [40, 104]. The discussion on the stereochemical implications [40] goes far beyond the sulfoxide–sulfenate rearrangement. These contributions were of fundamental importance for the interpretation of the stereochemical outcome of [2,3]-sigmatropic rearrangements in general (see also [105]).

In 1979 an outstanding review on the subject appeared, heavily relying on the work done by Mislow [6]. At the same time the reaction was developed more and more from a mechanistic curiosum to a synthetically useful method, a process initiated in a decisive manner by the work of Evans [106–108] (Scheme 44). As part of an effort to develop solutions for d^3-synthons, he proposed the α-alkylation of allylic sulfoxides, and forcing their rearrangement to the corresponding sulfenates by the application of thiophilic reagents [T]. In accordance with earlier findings [40, 104, 105], the configuration of the established double bond is sensitive to the substitution pattern with a distinct preference for the *E* configuration if one of the α substituents (R^{11} or R^{12}) in sulfoxide **161** is hydrogen. In the following years this chemistry was elaborated further to a general method for the synthesis of enantioenriched allylic alcohols, with special emphasis on stereochemical issues such as 1,3-chirality transfer and S → C chirality transfer [6, 109–111]). This and related work has



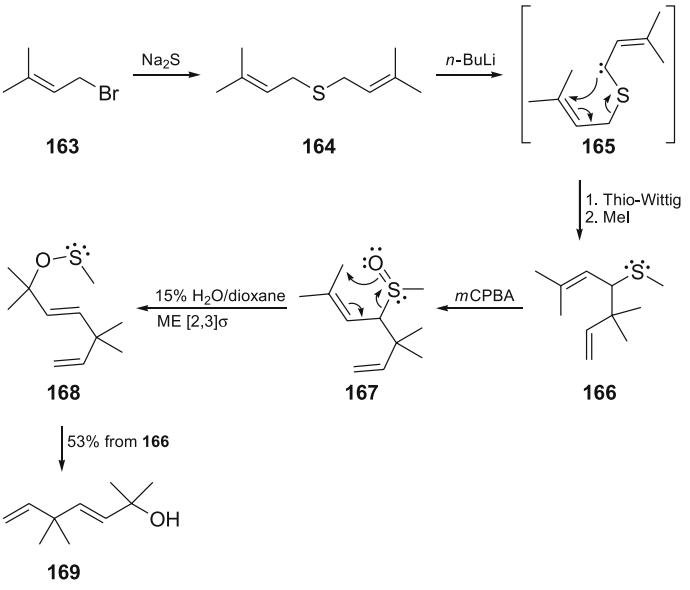
[T]: Thiophilic reagent,
$P(OMe)_3$ or various amines
G: Various aromatic and heterocyclic moieties

Scheme 44 General synthesis of allylic alcohols based on α-alkylation of allylic sulfoxides followed by [2,3]-sigmatropic rearrangement

been reviewed several times [1–3, 7, 112]. For that reason the remainder of this chapter will focus on newer applications of the Mislow–Evans (ME) rearrangement as it is called for obvious reasons. The material will be organized based on the method used to prepare the allylic sulfoxides.

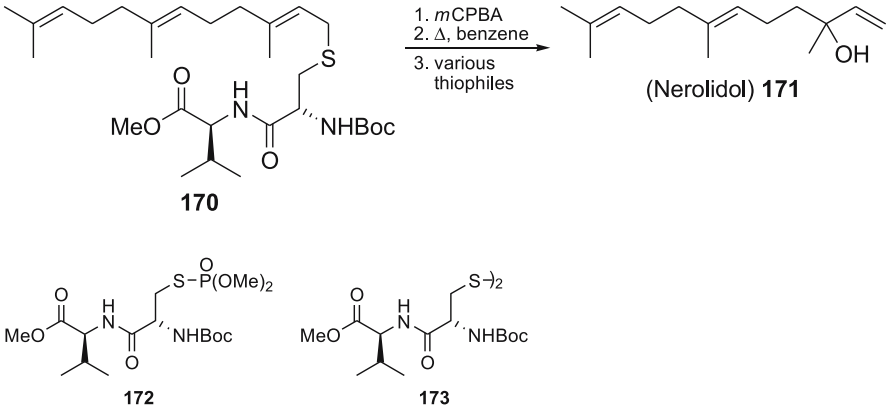
3.5.1
Sulfoxides from Substituted Allylic Systems

In a 1991 synthesis of Yomogi alcohol **169** [113], an interesting combination of two [2,3]-σ rearrangements was applied (Scheme 45) [114]. Deprotonation of diprenyl sulfide **164** obtained from prenyl bromide **163** initiated a [2,3]-sigmatropic rearrangement (the thio-analogon of the [2,3]-Wittig rearrangement) furnishing the allylic sulfide **166** after *S*-methylation. This compound was oxidized to sulfoxide **167**, which underwent an ME rearrangement upon heating in dioxane containing 15% water, finally delivering the target molecule **169** after hydrolysis of the sulfenate ester **168**. A [3,3]-sigmatropic rearrangement of **166** was not observed.



Scheme 45 Synthesis of Yomogi alcohol

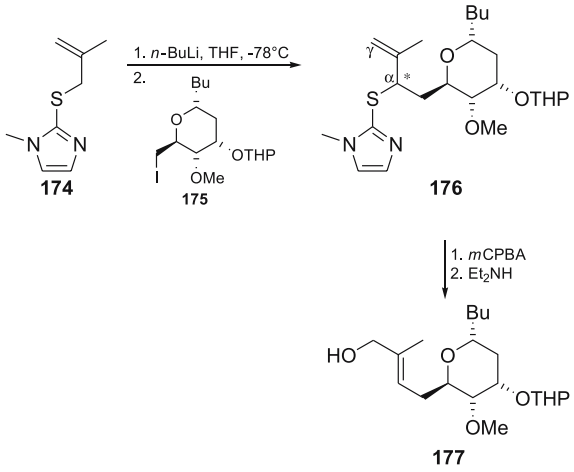
As part of an effort to find methods for the deprenylation of lipopeptides, Bristol-Myers Squibb chemists successfully applied the ME rearrangement toward this end (Scheme 46) [115]. After oxidation of the model compound **170** the resulting diastereoisomeric sulfoxides (not shown) were heated in benzene in the presence of various thiophiles. If triphenylphosphane was used for



Scheme 46 Deprenylation of lipopeptides by application of the Mislow–Evans rearrangement

that purpose, 31% of the disulfide **173** and 54% of nerolidol **171** were isolated. With trimethyl phosphite as the thiophile, 28% of **171** was isolated together with 64% of the "tagged" dipeptide **172**, thus allowing the identification of both components of the lipopeptide.

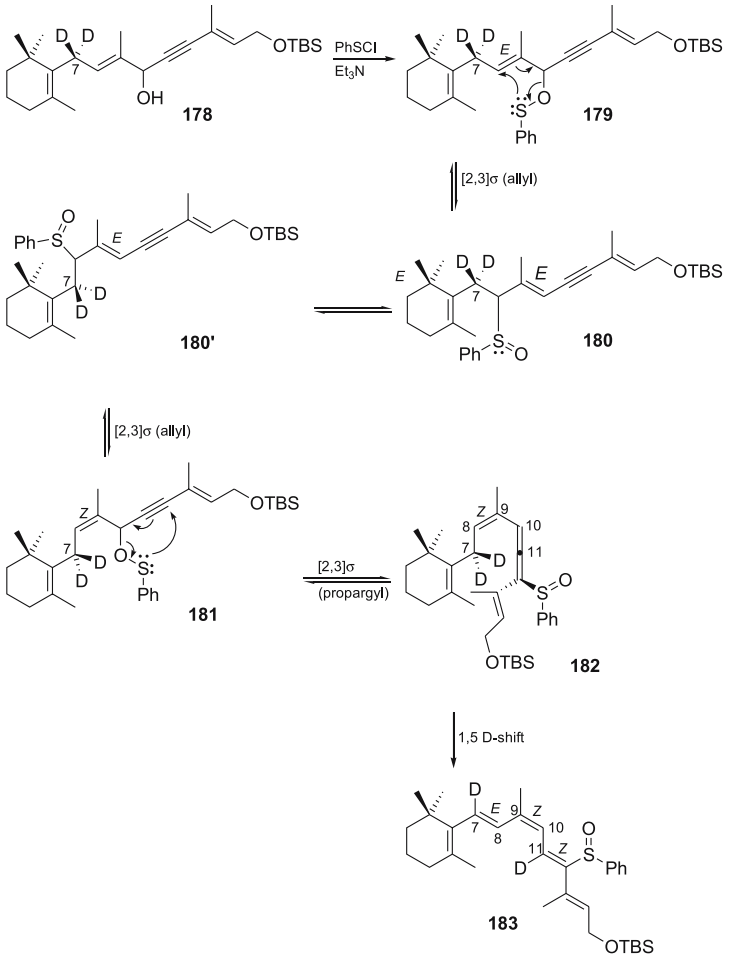
In the course of the preparation of maytansinoid model compounds Goodwin et al. [116] used the regioselective α-alkylation of an allylic sulfide attached to an imidazole unit (one member of the "G family" depicted in Scheme 44), as already proposed by Evans [106] (Scheme 47). Metalation of **174** led to an allylic lithium compound with the metal chelated by the imidazole unit. This compound readily reacted with iodide **175** delivering exclu-



Scheme 47 Allylic sulfide alkylation—ME rearrangement sequence

sively the α-alkylation product **176** as a mixture of diastereomers. Due to the fact that the allylic terminus of **176** is not prostereogenic and the α-position is heavily monosubstituted, the rearrangement product **177**, produced after oxidation and sulfenate cleavage, was formed as an *E*-allylic alcohol in a stereoconvergent manner, as expected.

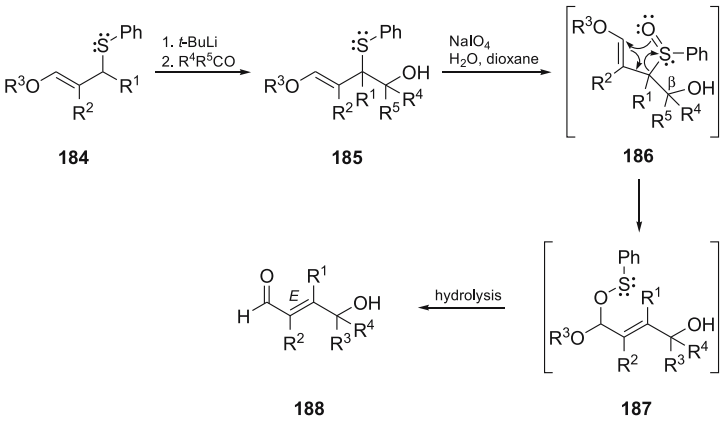
In 2000 an interesting paper on the stereocontrolled synthesis of 9-*cis*-refinoids appeared [117]. These syntheses are based on an ordered sequence of two stereoselective sigmatropic rearrangements followed by a [1,5]-sigmatropic hydrogen migration involving a sulfoxide group as stereodirector [118, 119] (Scheme 48). After considerable experimentation including model compounds and deuterium labeling, the authors came up with the



Scheme 48 9-*cis*- Retinoids by a rearrangement cascade

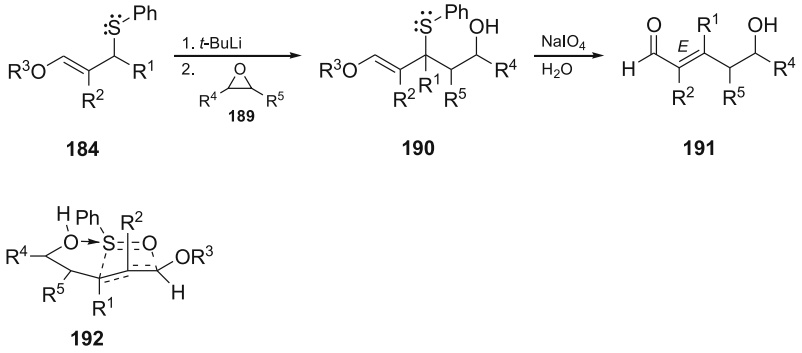
following mechanistic proposal. The *E* configured sulfenate ester **179**, prepared from alcohol **178**, suffers a double bond isomerization [6, 40, 104, 106, 120, 121] via rearranged sulfoxides **180** and its conformer **180′**. The resulting isomerized sulfenate **181** now undergoes another [2,3]-sigmatropic shift involving the triple bond furnishing the allenyl sulfoxide **182** (not isolated), which rapidly suffers a [1,5]-H-shift leading to polyene **183** with all double bonds being configured as shown and the deuterium labels in the expected positions. The rate acceleration and the enhanced stereoselectivity in the 1,5-H-shift have been attributed to a combination of the electronic effect of the sulfoxide in the postulated intermediate **182** and steric effects imparted by the bulky cyclohexenyl substituent [118].

To finish this first subchapter, [2,3]-sigmatropic rearrangements involving heteroatom-substituted allylic systems will be discussed (see also Sect. 3.5.3) (Scheme 49) [122]. The diastereomeric mixture of the α-hydroxyalkylation products **185** obtained from the starting enol ethers **184** can be oxidized to sulfoxides **186** which, in water/dioxane, undergo a rapid [2, 3]-sigmatropic shift to yield, after hydrolysis of the intermediate sulfenate esters **187**, racemic enals **188** with exclusively *E* configured double bonds [123]. The authors showed that this pronounced *E* selectivity can be traced back to the steric demand of the $R^4R^5C(OH)$ unit attached to the α-carbon [6]. Moreover, they showed that increased β-branching further enhanced the *E* selectivity irrespective of the presence of an OH or OR group at this position. Interestingly, if one moves the OH group in the γ-position with respect to the sulfinylated carbon, a pronounced effect of this OH group on the stereoselectivity is observed [124] (Scheme 50).



Scheme 49 4-Hydroxyenals from 3-alkoxylated allylic sulfides

For quite a number of compounds with different R^i, *E* selectivities of at least 90% (mostly above 95%) were achieved. If the hydroxyl group was pro-



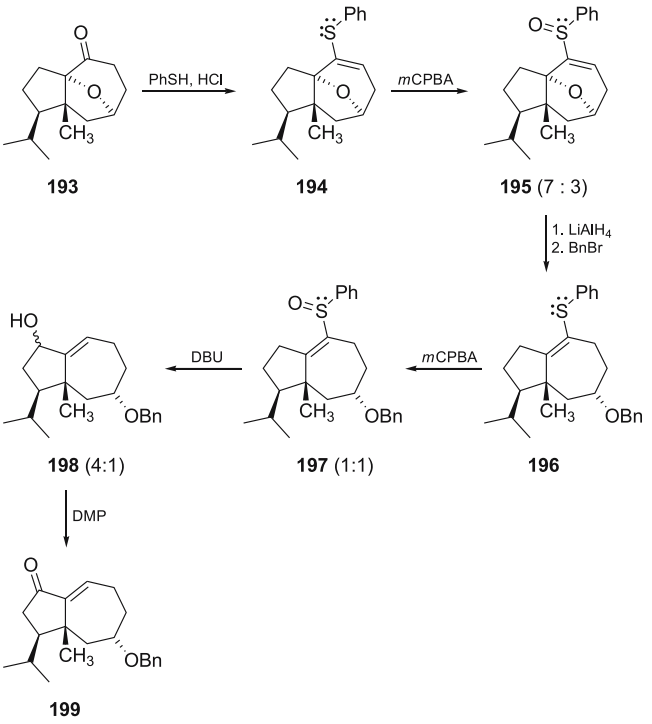
Scheme 50 Influence of a γ-hydroxy group on the stereoselectivity of the Mislow–Evans rearrangement

tected (OMe, OTBS) most of the selectivity was lost. To explain this behavior the authors propose a transition state like **192**, with an O → S interaction being responsible for the pseudo-equatorial position of the hydroxylated chain. This conformation leads to the observed *E* configuration and is disturbed after O substitution due to unfavorable interactions with the sulfur-bound phenyl group. The overall transformation is thus an interesting means for the synthesis of highly substituted δ-hydroxy enals.

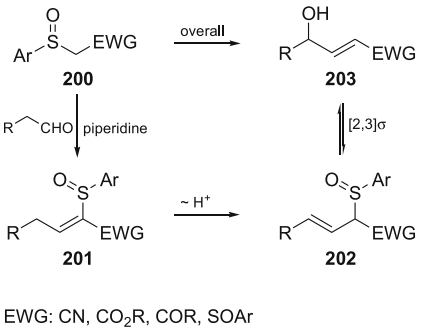
3.5.2 Allylic Sulfoxides via Isomerization of Vinylic Systems

As a means to generate allylic sulfoxides, the isomerization of vinyl sulfoxides was found to be an interesting alternative. As an example featuring this method, its application in efforts directed toward the total synthesis of guanacastepene A will be presented (Scheme 51) [125].

Ketone **193** was transformed into thioenol ether **194** by the action of thiophenol in acidic medium. The latter was oxidized to the sulfoxide **195** to prepare the system for a conjugate reduction leading to ring opening and double bond transposition. Reapplication of *m*-CPBA delivered vinylic sulfoxide **197** which, after base treatment, underwent a double bond migration to the allylic position followed by a [2,3]-σ rearrangement furnishing the allylic alcohol **198** as a 4 : 1 mixture of diastereomers. This was of no consequence for the subsequent steps, because **198** was oxidized to enone **199** which has been elaborated further as the hydroazulene portion of the target molecule. As with most contemporary applications of the ME rearrangement, the main motivation to apply it is for constitutional rather than stereochemical reasons. This is true also for a number of Knoevenagel-type chain elongation procedures based on methylene-active sulfoxides, a chemistry pioneered by Nokami et al. (Scheme 52) [126].

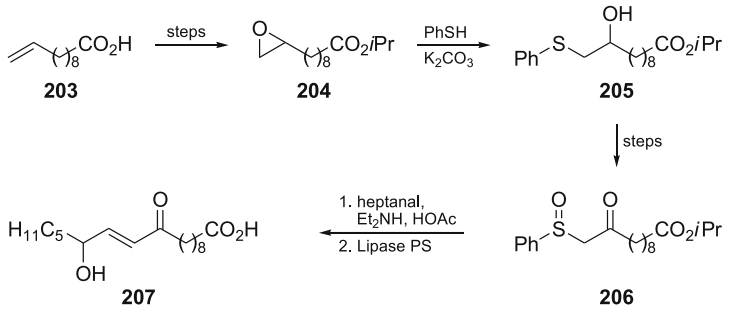


Scheme 51 Excerpt from a total synthesis of guanacastepene A featuring a simultaneous isomerization–[2,3]-sigmatropic rearrangement to yield alcohol **198** from vinyl sulfoxide **197**



Scheme 52 General scheme for the synthesis of 3-acceptor substituted allylic alcohols via Knoevenagel condensation–isomerization and ME rearrangement. EWG = electron-withdrawing group

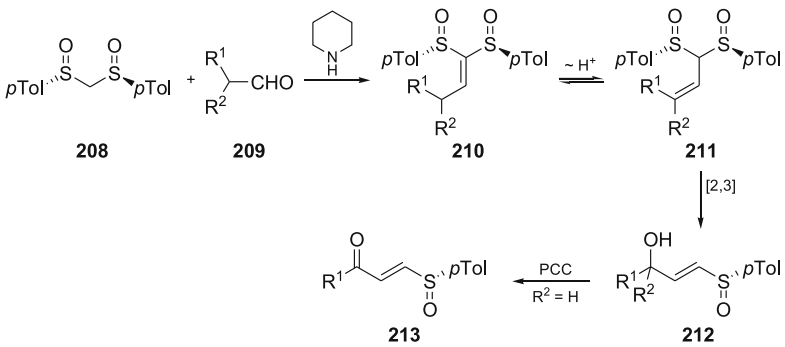
In 2001 Nokami extended his chemistry to the synthesis of 4-hydroxy-enones and applied it to the synthesis of the cytotoxic fatty acid **207** (Scheme 53) [127]. The key steps are the condensation of **206** with heptanal,



Scheme 53 Application of the Nokami sequence in target molecule oriented work

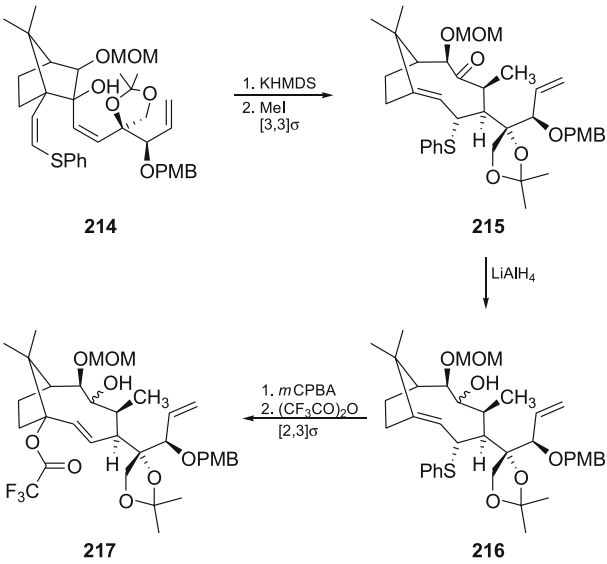
the subsequent proton shift, and the [2,3]-σ rearrangement leading to the isopropyl ester of **207** which was finally obtained by enzymatic hydrolysis.

In a recent publication the nitrile (EWG = CN) variant [126] of this chemistry was performed in water by applying *N*,*N*-diethylaminopropylated silica gel as heterogeneous catalyst [128]. Another variant of this reaction sequence, leading to chiral sulfinylated enones, has been developed by Llera [129] employing the enantiomerically pure geminal bis(sulfoxide) **208** (Scheme 54). This bis(sulfoxide) was prepared from (–)-*p*-toluenesulfinic acid menthyl ester [100], as described by Kunieda [130]. Later this procedure was improved to increase the yield from 35 to 91% [13, 131]. Treatment of **208** with enolizable aldehydes or ketones, in the presence of piperidine as a base and thiophile, initiated a reaction cascade involving a condensation step (to **210**), a proton shift to allylic sulfoxide **211**, and a [2,3]-σ-shift followed by a piperidine-mediated desulfuration delivering the alcohols **212** as isomeric mixtures. Oxidation of the latter compounds (one of the R^i = H) led to enantiomerically pure *E*-γ-oxo vinyl sulfoxides **213**.



Scheme 54 Geminal bis(sulfoxide) **208** as chiral methylene-active compound

A particularly demanding constitutional problem in the context of a bridgehead olefinic system was solved by Paquette using the ME rearrange-



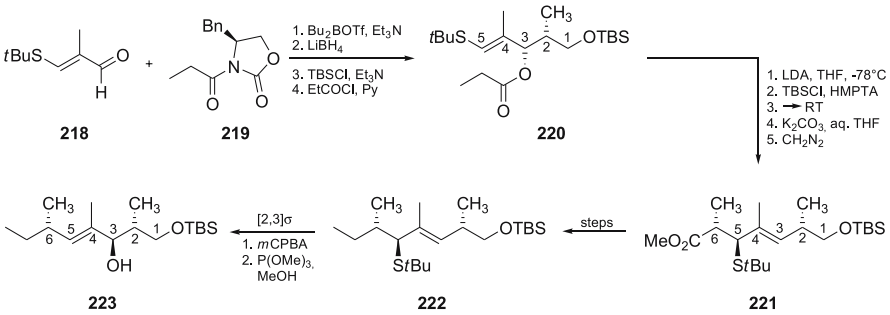
214 **215** **216** **217**

Scheme 55 Vinyl to allyl isomerization by [3,3]-sigmatropic shift

ment (Scheme 55) [132]. As part of efforts in the taxane field the advanced vinylic sulfide **214** was thought to be a suitable precursor for compounds like **217** with a bridgehead oxygen functionalization and a double bond in the allylic position. Toward this end **214** was O-deprotonated to induce an anionic oxy-Cope rearrangement, the product of which was subsequently methylated to yield *anti*-Bredt ketone **215**. Initial trials to effect a ME rearrangement with the sulfoxide derived from this ketone disappointingly led to sulfenate extrusion generating a diene which, in the presence of methanol, reacted further creating a new C – C bond across the ten-membered ring (not shown) involving the carbonyl group. To avoid this side reaction, the ketone was reduced and the resulting diastereomeric mixture of alcohols **216** was oxidized using *m*-CPBA. Even at – 78 °C the generated sulfoxide rearranged in the presence of triflic anhydride to the expected ester **217**.

A clever application of the ME rearrangement, this time including its stereochemical potential, was developed by Heathcock [133]. The concatenation of an asymmetric aldol reaction [134–136], an ester–enolate Claisen rearrangement [137, 138], and a ME reaction allow for the stereoselective generation of a 1,2,5-stereotriad.

This technology has been applied as part of the total synthesis of myxalamide A (Scheme 56) [139]. The stereoselective aldol reaction between aldehyde **218** and the propionate **219** delivered, after reduction, protection, and acylation, ester **220** as a single isomer. After *E*-silyl ketene acetal formation a [3,3]-sigmatropic rearrangement accompanied by 1,3-chirality transfer took place. This, together with the uniform prochirality at the double bonds of the

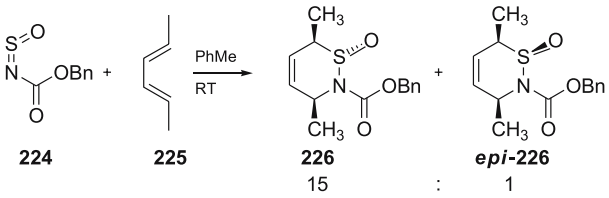


Scheme 56 ME rearrangement in the construction of 1,2,5-stereotriads

ketene acetal, set the relative and absolute configurations of the newly created stereogenic centers at carbons 5 and 6 and shifted the double bond into the allylic position. After two additional steps ester **221** was obtained and converted into allylic sulfide **222**. After *m*-CPBA oxidation the resulting sulfoxide was rearranged using $P(OMe)_3$ as a thiophile, yielding the key intermediate **223** as a single isomer with the 1,2,5-stereotriad (atom positions 2,3,6) in the correct absolute configuration.

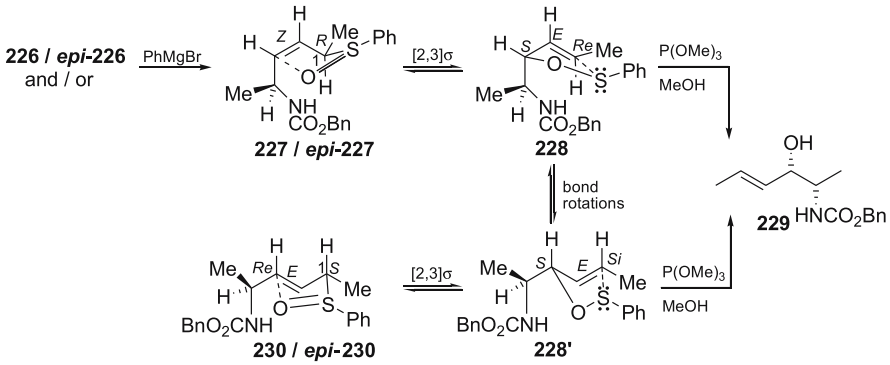
3.5.3
Allylic Sulfoxides via Cycloadditions

The reaction of *N*-sulfinyl dienophiles with 1,3-dienes yields 3,6-dihydrothiazine 1-oxides (compare the corresponding reactions with sulfur diimides, Sect. 3.1), which can be ring opened with carbon nucleophiles to yield allylic sulfoxides ready to undergo the ME rearrangement. The seminal paper on this chemistry by Weinreb appeared in 1984 (Scheme 57) [67, 140].



Scheme 57 *N*-Sulfinyl carbamates as dienophiles

When *N*-sulfinylcarbamate **224** was reacted with (*E*,*E*)-2,4-hexadiene **225** the formal [4 + 2] cycloaddition products (the reaction mechanism is a matter of debate [141–143]) **226** and *epi*-**226** were formed in a 15 : 1 ratio, respectively. Treatment of this mixture with phenylmagnesium bromide followed by refluxing the resulting mixture with trimethyl phosphite in methanol af-



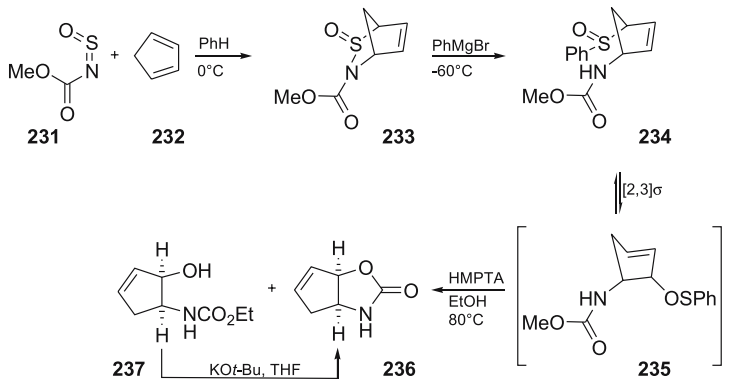
Scheme 58 Stereoconvergent amino alcohol synthesis

forded a 85% yield of the rearranged alcohol **229** as a single diastereomer (Scheme 58).

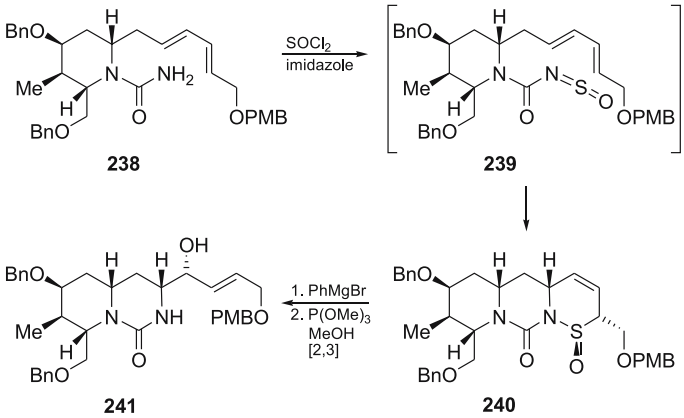
When the addition product **227** with *Z*-configured double bond (presumably with inverted absolute configuration at sulfur as compared to that in the starting material **226**) was heated in $CDCl_3$ at 50 °C an *S*-epimeric mixture of the *E*-sulfoxides **230**/*epi*-**230** was formed. This isomerization obviously takes place via sulfenate **228** which, after conformational changes, re-rearranges via **228**′ to the thermodynamically more stable *E* isomer. Due to a change in the absolute topicity of attack onto the allylic terminus in **228** vs **228**′, the absolute configuration at C1 of the sulfoxides should also be inverted (which has not been shown). Because the stereogenic character of the sulfur atom gets lost at the sulfenate stage, the same mixture of sulfoxides was obtained with the minor diastereomer *epi*-**227**, which in turn makes the stereoconvergent formation of **229** from both sulfoxides plausible.

In 1999 it was again Weinreb who used this chemistry in the context of the total synthesis of the marine sponge alkaloid agelastatin A (Scheme 59, see also Scheme 24) [70]. This time *N*-sulfinyl methylcarbamate **231** was used to yield cycloadduct **233** which was opened to allylic sulfoxide **234**. Heating in HMPTA/EtOH delivered via [2,3]-σ rearrangement a mixture of the desired cyclized carbamate **236** and the open-chain transesterification product **237**, which also cyclized under the influence of base.

In 2002 the same author demonstrated the usefulness of this method in a rather demanding context including an intramolecular cycloaddition with an *N*-sulfinyl urea as a new type of *N*-sulfinyl dienophile (Scheme 60) [144]. As key steps in the total synthesis of freshwater cyanobacterial hepatotoxins, (*E*,*E*)-diene **238** was transformed into *N*-sulfinyl urea **239** which immediately cycloadds intramolecularly yielding tricycle **240** as a single isomer in excellent yield. After reaction with phenylmagnesium bromide the intermediate allylic sulfoxide rearranges cleanly to diastereomerically pure allylic alcohol



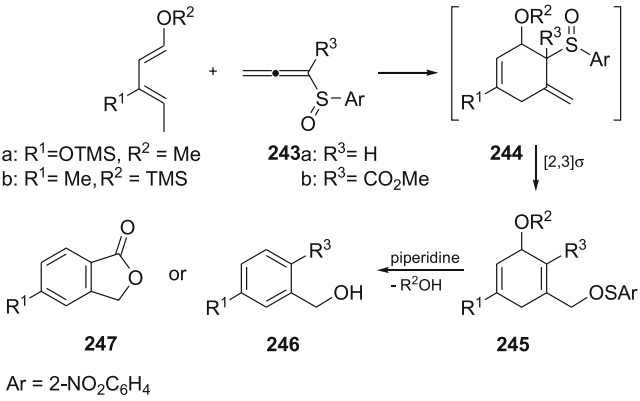
Scheme 59 Excerpt from an agelastatin A synthesis featuring the combined application of a sulfinylcarbamate cycloaddition and a ME rearrangement



Scheme 60 Intramolecular sulfinyl cycloaddition followed by ME rearrangement

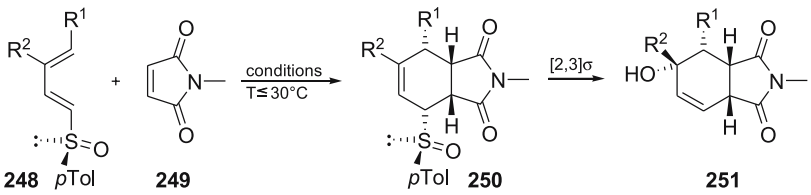
241. Similar chemistry has been applied by Hemming for the synthesis of 1,4-benzodiazepin-5-one derivatives [145].

Apart from *N*-sulfinyl dienophiles, nitroarylsulfinyl-substituted alkenes turned out to be interesting dienophiles in both Diels–Alder and 1,3-dipolar cycloaddition reactions, as exemplified by the work of Padwa et al. (Scheme 61) [146]. Allenic sulfoxides **243** are easily accessible via [2,3]-σ rearrangement of transient propargylic sulfenate esters, available by sulfenylation of the corresponding propargylic alcohols [2, 147]. Their reaction with activated dienes such as **242a** and **242b** gave rise to the formation of cycloadducts **244** which rearrange to 1,4-cyclohexdienes **245**, being derivatives of a formal cycloaddition of a propargylic alcohol and a diene. Under base treatment, these compounds aromatize via R^2OH elimination and desulfenylation to either benzylic alcohols **246** or phthalides **247** ($R^3 = CO_2Me$).



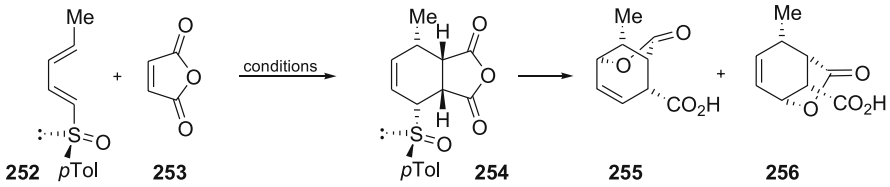
Scheme 61 Sulfinylallenes as dienophiles

This chemistry has been elaborated further to yield a number of rearranged 1,3-dipolar cycloaddition products [146]. Starting in 1994 Carreño and Ruano began research programs on the suitability of 1- and 2-*p*-tolylsulfinyl dienes for tandem cycloaddition/[2,3]-sigmatropic rearrangement reactions (Scheme 62) [148]. Various 1-sulfinylated dienes **248** (R^1 = CH_3, Ph, OEt; R^2 = H, CH_3) were obtained by condensation of the corresponding enals with enantiomerically pure methyl-*p*-tolyl sulfoxide. These dienes underwent slow Diels–Alder reactions ($\geq$ 20 days) with *N*-methylmaleimide **249** (NMM) at temperatures $\leq$ 30 °C to yield the cycloaddition products **250** and/or the rearranged alcohols **251** in moderate to good yields as single isomers. In the absence of Lewis acid catalysts rearranged alcohols **251** were generated directly when R^1 = Ph, R^2 = H or R^1 = OEt, R^2 = CH_3, obviously with NMM acting as a thiophile. When $SnCl_4$ was used as Lewis acid the reaction stopped after the cycloaddition step. Interestingly, it was found to be difficult to rearrange the isolated products **250** using $P(OMe)_3$ or other thiophilic reagents, partly due to undesired elimination reactions.



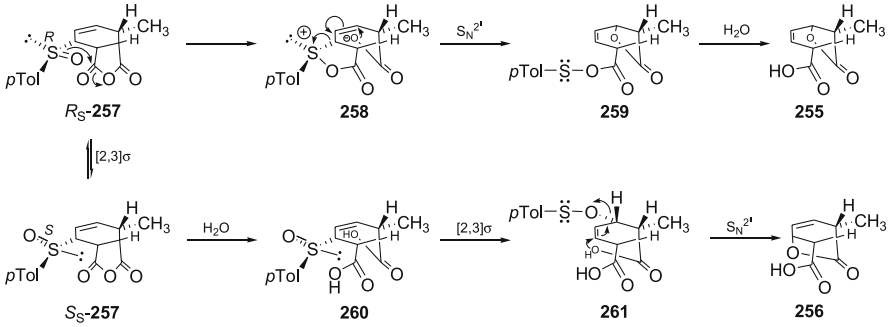
Scheme 62 Sulfinylated dienes in cycloaddition reactions

Two years later the same group extended this work using maleic anhydride as the dienophile [149]. Despite their close structural similarity, both dienophiles behave quite differently (Scheme 63). In the absence of Lewis



Scheme 63 Maleic anhydride as dienophile

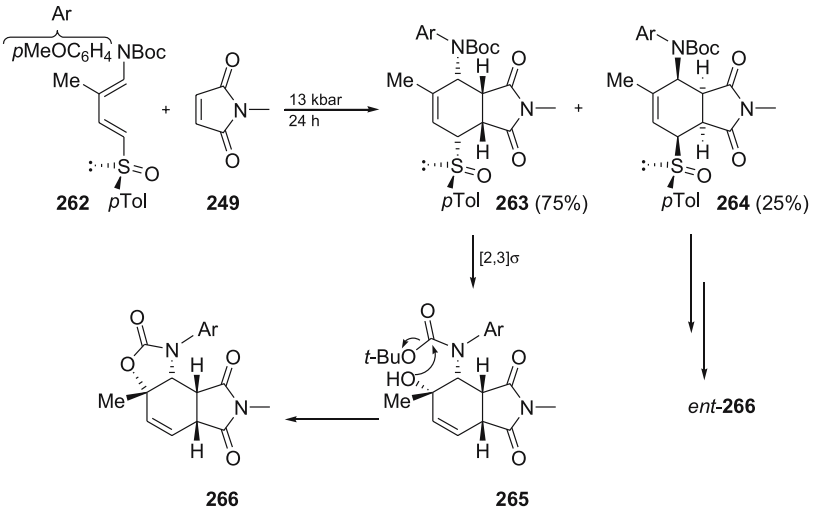
acids (their presence led to complex product mixtures!) slow reactions took place ($\geq$ 30 days, $T \leq 40\,^{\circ}C$) immediately delivering lactones **255** and **256** even without addition of thiophiles. When the temperature was increased to 70 °C in 2 days, **255** and **256** were produced in a 70 : 30 ratio (60% yield). Moreover, the *ee* of the product was 0% at room temperature and 50% at 70 °C! The primary adduct R_S–**254** was formed only after application of high-pressure conditions (70 : 30 = **254** : **255**). These rather surprising results were explained in the following way (Scheme 64).



Scheme 64 Diastereomer-dependent lactone formation from cycloadducts involving sulfinylated dienes

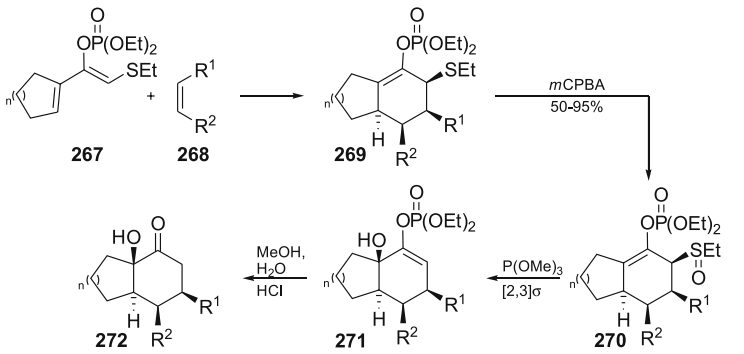
The primarily formed Diels–Alder adduct R_S–**257** rapidly epimerizes via [2,3]-σ rearrangement, setting up an equilibrium mixture between R_S–**257** and S_S–**257**. The former can adopt a conformation allowing for an intramolecular acylation of the sulfinyl oxygen, delivering the allylic acyloxysulfonium intermediate **258**. This intermediate undergoes an S_N2' reaction breaking the C – S bond and, after hydrolysis, finally yields lactone **255**. Epimer S_S-**3** hydrolyzes first, then rearranges to sulfenate **261**, which after S_N2' attack of the carboxylic acid moiety expels sulfenic acid to yield the regioisomeric lactone **256**. The surprising dependence of the enantioselectivity on the reaction conditions was explained by postulating intermolecular acylation of the sulfinyl oxygen *before* the Diels–Alder reaction. This change in the sequence of events entails an inversion in the π-facial selectivity of the cycloaddition.

In 1999 enantiomerically pure amino-substituted diene **262** was used in the Diels–Alder reaction with *N*-methylmaleimide (Scheme 65) [150]. Under high-pressure conditions a 75 : 25 mixture of *S*-epimeric *endo* products **263** and **264** was formed. Upon prolonged standing at – 20 °C (41 days) the mixture evolved to tricyclic compound **266** with 50% *ee* via [2,3]-σ rearrangement followed by intramolecular acylation.



Scheme 65 Amino-substituted dienyl sulfoxides as dienes

With 1-alkylthio-2-diethoxyphosphoryloxy-substituted 1,3-dienes an interesting route to racemic bicyclic α-hydroxycarbonyl compounds was found (Scheme 66) [122]. Dienes **267** [151] react readily with a number of dienophiles yielding *endo* products **269**. Their oxidation delivered sulfoxides

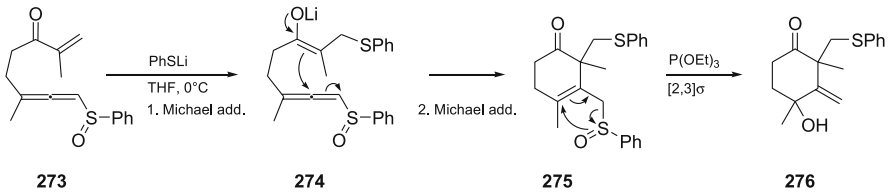


Scheme 66 α-Hydroxyketone synthesis

270 which rearranged under the influence of a thiophile to allylic alcohols **271** being masked α-hydroxyketones. Indeed, after acid treatment diastereomerically pure ketones **272** could be obtained, albeit with somewhat low yields (35–50% from **271**).

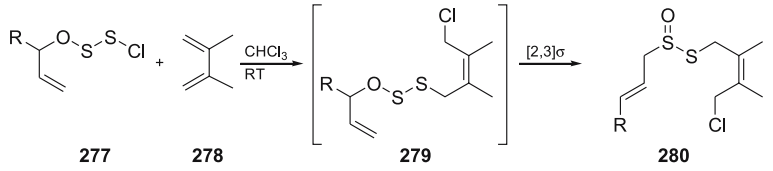
3.5.4 Miscellaneous

As part of a program to develop a new strategy for the synthesis of highly substituted cyclohexane ring systems, Parsons proposed an interesting domino double Michael addition/[2,3]-σ-shift process (Scheme 67) [152]. Treatment of allenyl sulfoxide **273**, easily prepared from dehydrolinalool via [2,3]-σ rearrangement of the corresponding propargyl sulfenate, with lithium thiophenoxide initiated a domino reaction which furnished after two consecutive Michael additions the allylic sulfoxide **275**, which in turn rearranged to the highly substituted cyclohexanone derivative **276**. Similar chemistry without the final rearrangement has been used to synthesize indol derivatives [153].



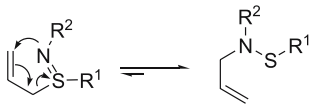
Scheme 67 Domino reaction including a ME rearrangement

In an attempt to find a new entry to unsymmetrical dialkoxydisulfides, Braverman in 2004 prepared a number of very unstable monoalkoxy chlorodisulfides **277** (Scheme 68) [154]. Although chlorides **277** turned out to be unsuitable for the initial goal, they underwent 1,4-additions to electron-rich diene **278** yielding **279** as primary adducts. These underwent [2,3]-σ-shifts producing thiosulfinates **280** as final products.



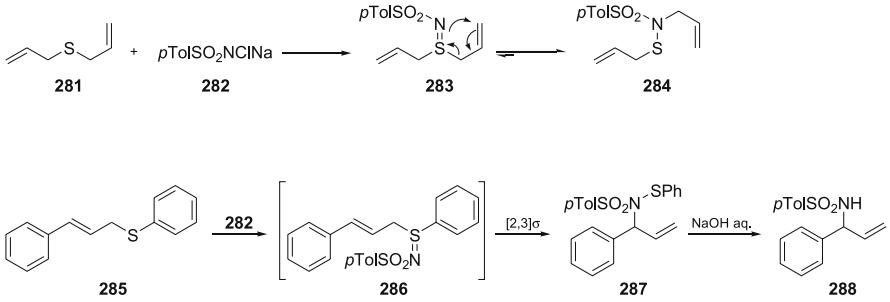
Scheme 68 1,4-Addition of monoalkoxy chlorodisulfides to electron-rich dienes

3.6
Type L: Allylsulfimines ⇌ *N*-Allylsulfenamides



Scheme 69

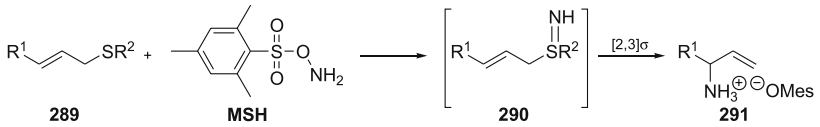
In 1951 Challenger et al. reacted diallyl sulfide **281** with chloramine T **282** and found that the reaction product, sulfimine **283**, isomerized spontaneously to *N*-allylsulfenamide **284** (Scheme 70) [155]. Some 5 years later they found that migration of the allylic group was accompanied by "allylic inversion" [156]. Cinnamyl sulfide **285** gave, via oxidative imination product **286**, the rearranged sulfenamide **287** which was hydrolyzed to branched allylic amine **288.** It is interesting to note that these results obviously were not recognized by those who, some 10 years later, worked on the oxa-analogon of this rearrangement (Type **K**; Mislow–Evans rearrangement, see Sect. 3.5).



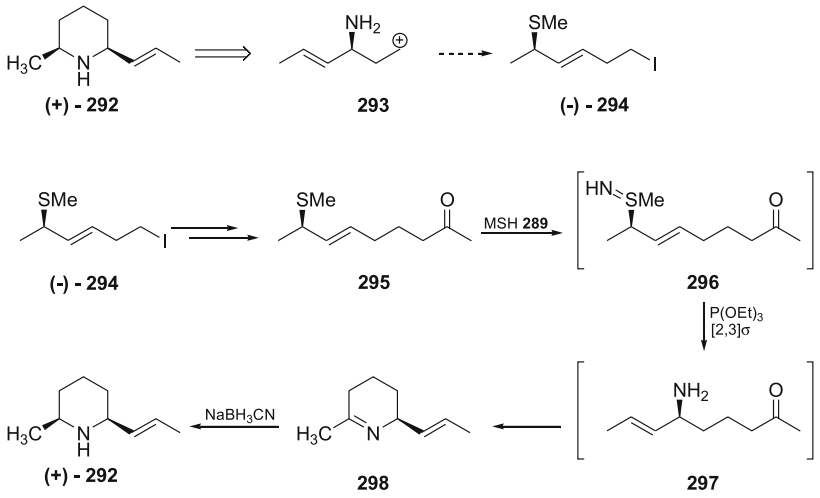
Scheme 70 First evidence for a Type **L** rearrangement

In the years to come the synthetic potential of the reaction was not really recognized by the scientific community, thus entailing its rather slow development. Things changed with the advent of mesitylenesulfonyl hydroxylamine (MSH), a powerful electrophilic amination reagent [11, 157–159]. This reagent cleanly transforms sulfides **289** including allylic sulfides via *S*-aminosulfonium salts into sulfimines **290** and, after [2,3]-σ rearrangement, into allylic amines **291** (Scheme 71) [11].

One of the first applications of this reaction in the stereoselective synthesis of natural products exploiting the mechanism-controlled 1,3-chirality transfer appeared in 1991 by Dolle et al. (Scheme 72) [160]. Their retrosynthetic analysis of alkaloid **292** ((+)-pinidine) led to a a^3-synthon **293** which



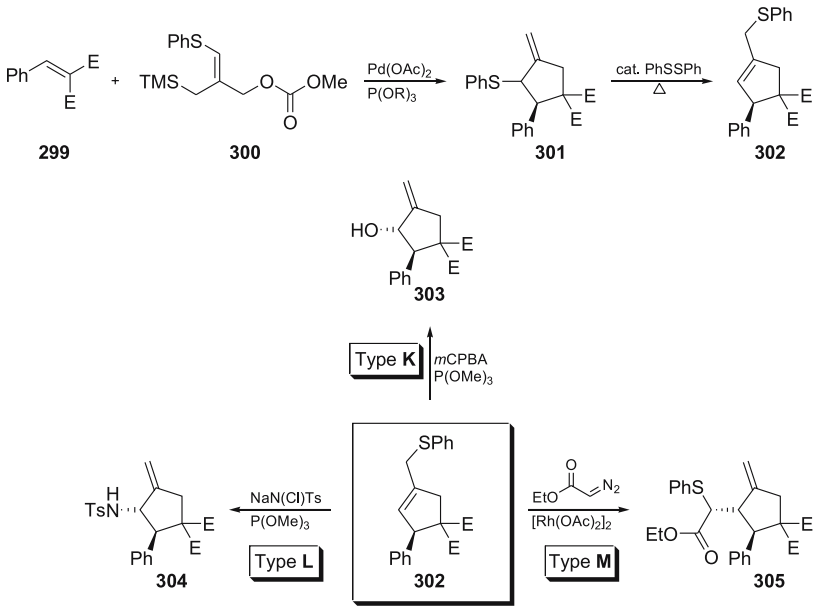
Scheme 71 Electrophilic amination with MSH



Scheme 72 Total synthesis of (+)-pinidine via a Type **L** rearrangement

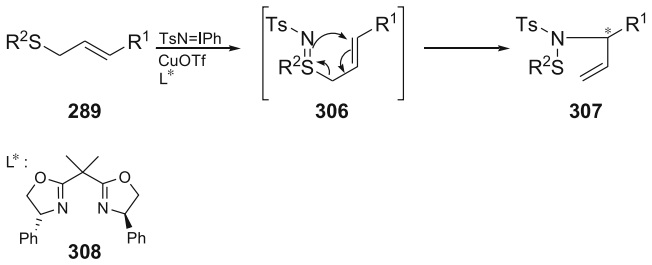
should be representable by synthetic equivalent (–)-**294**. Indeed, methyl sulfide (–)-**294** was prepared in a short sequence from (–)-ethyl lactate [161]. This compound was elaborated via methyl acetoacetate synthesis into ketone **295** which, in a one-pot procedure involving *S*-imination (to **296**), [2,3]-sigmatropic shift (to amine **297**), and a reductive amination, delivered the target molecule (+)-**292** in 70% yield. It is interesting to note that the *methyl* sulfide performed much better than aryl sulfides [161]. Another noteworthy aspect of the reaction sequence is the compatibility of the imine reduction using $NaBH_3CN$ with the reaction conditions of the preceding steps. The authors used this solution for synthon **293** a second time to prepare (–)-tabtoxinine β-lactam [161].

In Pd-catalyzed trimethylene methane [3 + 2] cycloadditions a phenylthio group was found to function as a regioselectivity control element (Scheme 73) [162]. In the presence of phosphite ligands and palladium acetate, olefin **299** and trimethylene methane (TMM) precursor **300** reacted regioselectively to give exomethylene compound **301**, which was isomerized to allylic sulfide **302**. Reactions of this latter compound with a number of reagents triggered [2,3]-sigmatropic rearrangements of types **L**, **K**, and **M**.



Scheme 73 Allylic sulfides via [3 + 2] cycloadditions as starting materials for various [2,3]-sigmatropic shifts

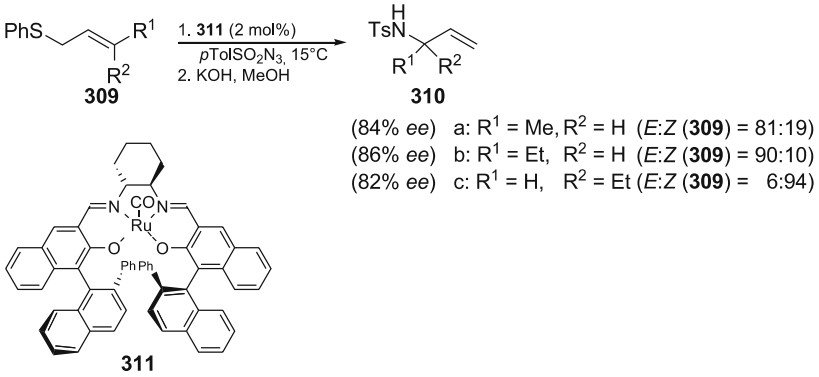
With the advent of catalytic (asymmetric) imidation reactions the interest in Type **L** rearrangements has grown considerably. Following Evans's report on [*N*-(*p*-tolylsulfonyl)imino]phenyl-iodinane (TsN = IPh) as an effective nitrene transfer reagent [163], Uemura reported on the application of this reagent in copper-catalyzed imidations of sulfides (Scheme 74) [164]. Copper-catalyzed asymmetric imination of a number of allylic sulfides **289** using bisoxazoline **308** (L*) [165, 166] as a ligand delivered rearranged allylic amines **307** with up to 58% *ee*. A little later Bach et al. showed $BocN_3$ to be an



Scheme 74 Catalytic asymmetric imination of sulfides

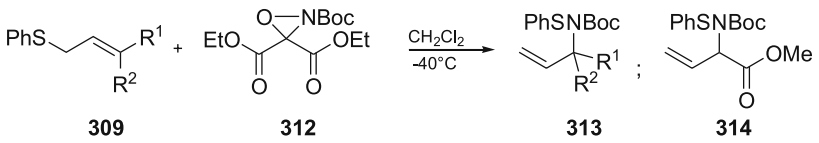
interesting imidation reagent, both from the standpoint of atom economy and ease of deprotection [167].

In 2001 Katsuki et al. found ruthenium complex **311** to be a very efficient catalyst for sulfimidations [168] of aryl allyl sulfides (up to 98% *ee*). A little later the same group investigated the coupling of this chemistry to a Type **L** rearrangement (Scheme 75) [169, 170]. Most interestingly, the sequence was not only very stereoselective but also stereoconvergent, furnishing the same enantiomer of **310** irrespective of the double bond geometry in the starting sulfide **309**.



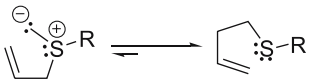
Scheme 75 Highly enantioselective imidation of allylic sulfides with chiral ruthenium complex **311**

An alternative to the Bach procedure ($BocN_3/FeCl_2$) for the synthesis of Boc-protected sulfimides was developed in 2002 (Scheme 76) [171]. Oxaziridine **312**, prepared from diethyl ketomalonate, was found to iminate allylic sulfides **309** at low temperatures. The resulting allyl sulfimide (not shown) immediately rearranged to protected amines **313** in high yields. The possibility of preparing α-amino acid derivatives like **314** is a noteworthy feature although the compounds are, of course, racemic.



Scheme 76 Oxaziridines as imination agents

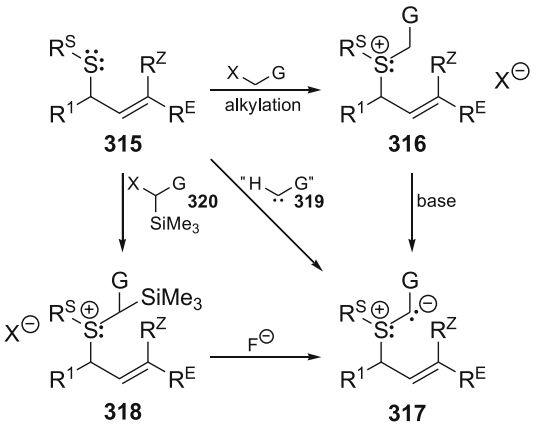
3.7
Type M: Sulfonium ylides ⇌ Homoallyl sulfides



Scheme 77

As a C – C bond-forming process, [2,3]-sigmatropic rearrangements of sulfonium ylides merit particular interest. Indeed, since their discovery in the late 1960s [172–176], this type of ylide rearrangement has become the most extensively studied and applied. This activity is well documented in a number of excellent review articles, many of them published quite recently [9, 177–179]. This demonstrates a vivid interest by the scientific community in these rearrangements which is strongly related to the advent of asymmetric and catalytic variants, as will be discussed later.

The generation of sulfonium ylides relies mostly on three strategies (Scheme 78). The classic variant uses sulfide alkylation to the sulfonium salts **316** which can be deprotonated to deliver the desired ylides **317** [180, 181]. A related method involves silane **320** as the alkylating agent to allow for regioselective ylide generation via fluoride ion induced desilylation [182]. Finally, the action of carbenes **319** or metal-bound carbenoids offers a direct means for ylide generation [183, 184].



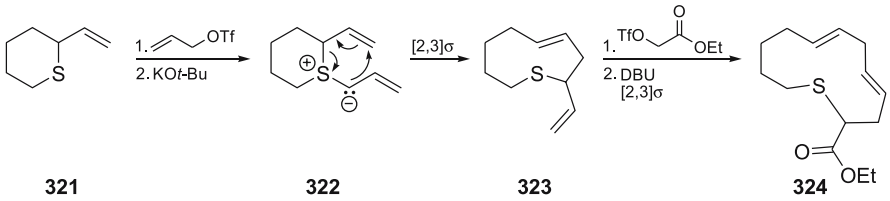
Scheme 78 Synthetic routes to sulfonium ylides

As with the rearrangements already discussed, sulfonium ylide rearrangements have been used to solve constitutional problems and as intermediates in stereoselective reactions. Therefore, the remainder of the chapter will be

subdivided into smaller sections dealing with constitutional aspects as well as with various aspects of configurational control.

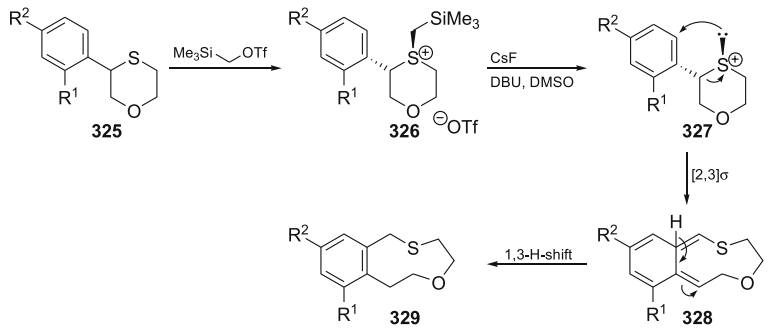
3.7.1 Constitutional Aspects

One of the first applications in this area was the three-carbon ring expansion protocol developed by Vedejs and others (Scheme 79) [185–188]. As expected from the stereochemical analysis of [2,3]-sigmatropic rearrangements [6, 40, 189, 190], the newly created double bonds are *E* configured although, for obvious reasons, in systems yielding eight-membered rings the *Z* configuration prevails. A notable feature of this chemistry is its repeatability which allows for sequential three-carbon ring enlargements (**321**$^{(6C)}$ → **323**$^{(9C)}$ → **324**$^{(12C)}$).



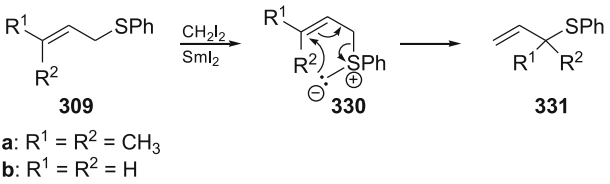
Scheme 79 Three-carbon ring expansion by Type **M** rearrangements

A variant of this ring enlargement reaction is the Sommelet–Hauser rearrangement of α-aryl cyclosulfonium ylides **327** generated by desilylation of trimethylsilyl methylated sulfonium salts **326** (Scheme 80) [191]. The yields attained for the target compounds **329** depended strongly on the nature of the substituents R^1 and R^2. Best results were found for the parent compound ($R^1 = R^2 = H$: 80%) and acceptor substituents ($R^1 = H$, $R^2 = CF_3$: 96%). As already mentioned, carbenoid addition to allylic sulfides can be used to generate al-



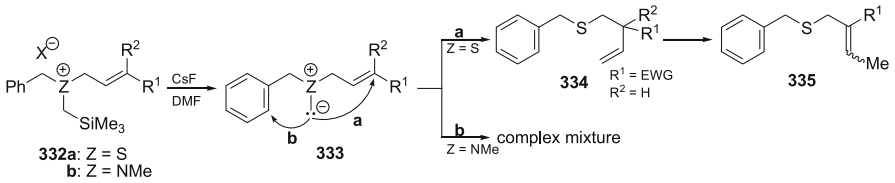
Scheme 80 Ring enlargement via Sommelet–Hauser rearrangement

lylic sulfonium ylides (Scheme 78). Most of these carbenoids were generated by decomposition of diazo compounds possessing α-carbonyl groups. Solutions for simple methylene carbenoids are rare [192]. One of these rare cases appeared in the literature in 1998 (Scheme 81) [193]. With sulfides **309** the carbenoid generated from CH_2I_2 and samarium iodide initiated ylide formation which finally led to homoallylic sulfides **331**. When the γ-position was unsubstituted (R^i = H) the yield dropped dramatically from 97% (R^i = CH_3) to 59%.



Scheme 81 Type **M** rearrangement with unsubstituted ylide carbon

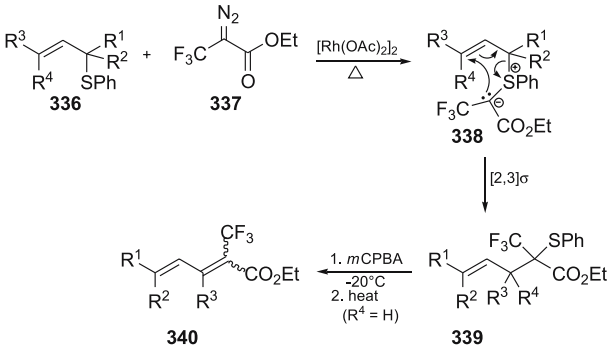
In a comparative study between allylbenzyl*sulfonium* ylides and allylbenzyl*ammonium* ylides interesting results were achieved (Scheme 82) [194]. Contrasting the behavior of *N*-methylides **333b**, the *S*-methylides **333a** cleanly rearranged toward the allyl group. No products resulting from Sommelet–Hauser or Stevens rearrangements occurred. If R^2 is hydrogen and R^1 is an electron-withdrawing group (e.g., CO_2Me or CN), rearrangement to olefins **335** was observed.



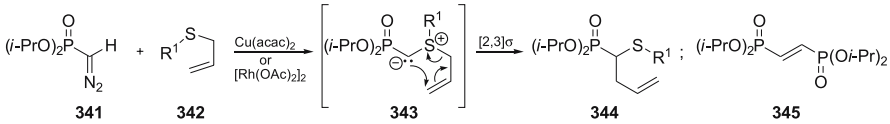
Scheme 82 Different behavior of sulfonium and ammonium ylides

Diazo compound **337** can be used as a starting material to convert allylic sulfides **336** via [2,3]-sigmatropic rearrangement followed by sulfinate extrusion into highly substituted trifluoromethylated dienoic esters **340** (Scheme 83) [195]. When R^2 = H, *E*-configured rearrangement products **339** were observed, as expected. The geometry of the double bond generated after sulfinate elimination is poorly controlled.

Phosphorus-functionalized homoallyl sulfides have been prepared using either base-promoted ylide generation [196] or, more recently, the carbenoid route (Scheme 84) [197]. When diazomethylphosphonate **341** [198] was reacted with allylic sulfides **342**, the rearranged α-phosphorylated sulfides **344**



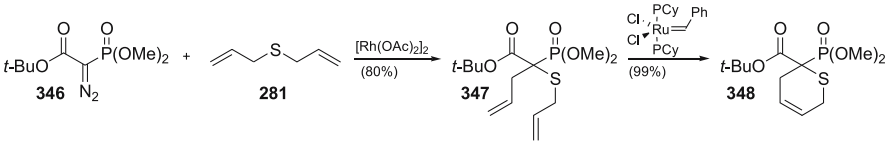
Scheme 83 Type **M** rearrangement followed by sulfinate extrusion



Scheme 84 Rearrangement of phosphorus-functionalized sulfonium ylides

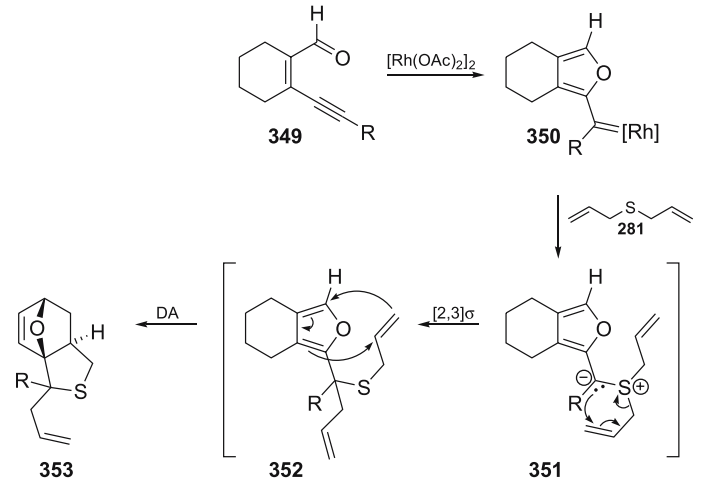
were obtained in variable yields depending on the substituents R^1 and the catalyst used. Under optimized conditions (mainly with the Rh catalyst) 60–75% yields were achieved. An important side reaction was the formation of the carbene dimer **345**. The synthesis of an eight-membered ring derivative delivered the target compound only in moderate yield.

In 2001 Hanson et al. described an alternative way to cyclic α-thiophosphonates involving a sequence of [2,3]-sigmatropic rearrangement followed by ring-closing metathesis (RCM) (Scheme 85) [199]. High yields in the RCM step are achieved only with quaternary rearrangement products like **347**.



Scheme 85 Combined application of a Type **M** rearrangement and RCM

In 2003 Uemura reported on a domino reaction, including a Type **M** rearrangement and a Diels–Alder reaction, which efficiently generates complex polycyclic ring systems (Scheme 86) [200]. Enynal **349** was transformed to 2-furyl carbenoid species **350** [201–203], which formed ylide **351** after treatment with diallyl sulfide **281**. After [2, 3]-sigmatropic rearrangement of the latter, furan **352** was formed which readily underwent an intramolecular Diels–Alder reaction furnishing adducts **353** that were epimeric at the

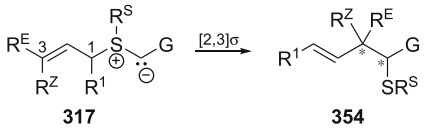


Scheme 86 Enynals as carbenoid precursor

nondesignated position bearing substituent R. When R was an electron-withdrawing group excellent yields (80–92%) were achieved.

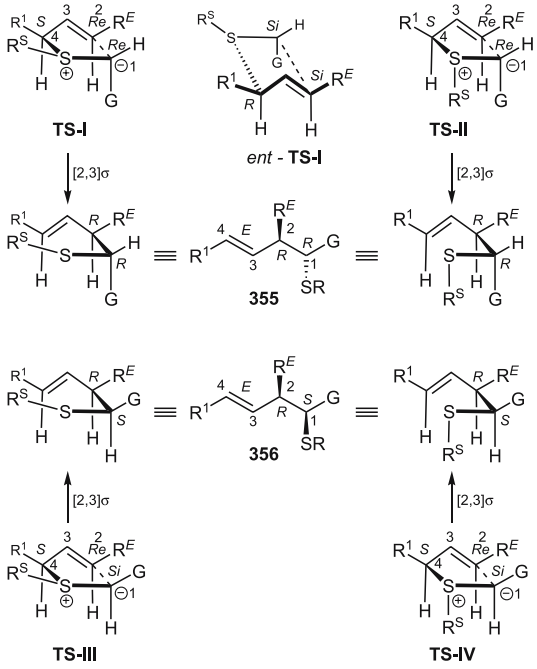
3.7.2 Stereoselective Type M Rearrangements

In the course of a sulfonium ylide rearrangement a maximum number of three stereogenic units can be generated (Scheme 87). The resulting homoallylic sulfide **354** contains up to two stereogenic centers and one stereogenic double bond. Based on the work of Houk [204] with R^Z = H, the following simplified transition-state models can be discussed (Scheme 88).



Scheme 87 Stereogenic elements in Type **M** rearrangements

The relative configuration of the newly created stereogenic centers at C1 and C2 depends on the relative topicity of attack of the reactive sites 1 and 2 (**TS-I**–**TS-IV**) on each other (simple diastereoselectivity if R^1 = H). This in turn is determined by double bond geometry in the starting material and the disposition of G in the transition state. If C4 in the transition state (C1 in starting material **317**) is not stereogenic (missing R^1) or both configurations are present, the enantiomorphic transition states will lead to *ent*-**355**

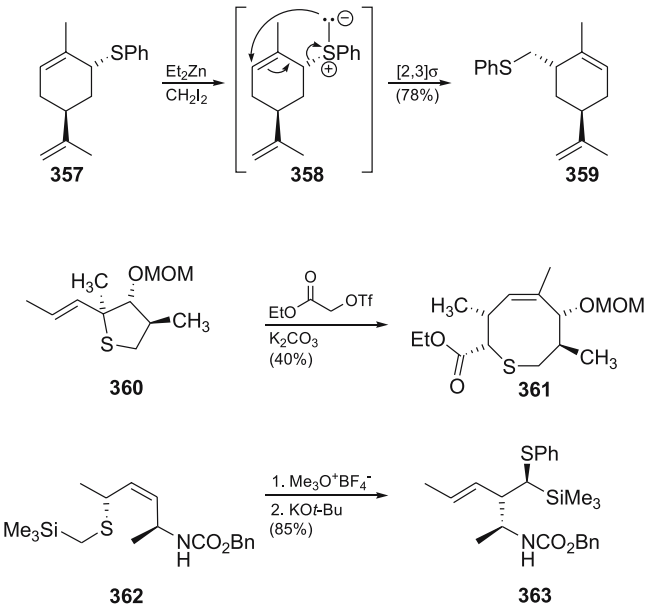


Scheme 88 Transition-state models for the Type **M** rearrangement with CIP priorities

and *ent*-**356**, exemplified by *ent*-**TS-1**. If one furthermore assumes that the R^{1eq} conformation is preferred (avoids $A^{1,3}$ interactions [205] with H2 or R^Z if present), the new double bond must be *E* configured. Another consequence of this assumption is that a uniform absolute configuration at C4 in the transition state entails a uniform *absolute* topicity of attack onto olefinic C2 (1,3-chirality transfer). Finally, if the sulfur atom is configurationally stable on the timescale of the subsequent rearrangement, the reaction is expected to proceed via $R^{S\text{-endo}}/G^{exo}$ (**TS-I**) or $R^{S\text{-exo}}/G^{endo}$ (**TS-IV**) transition states (see also discussion in Sect. 3.7.2.2, Scheme 95). Any other mode of stereoselection will be called induced stereoselection (e.g., evoked by chiral nonracemic G groups).

3.7.2.1
1,3-Chirality Transfer and Induced Diastereoselectivity

The possibility to "transfer chirality" using secondary sulfides has not been exploited very much (Scheme 89). Carveol-derived sulfide **357** has been converted into ylide **358** by the Simon–Smith-type reagent combination



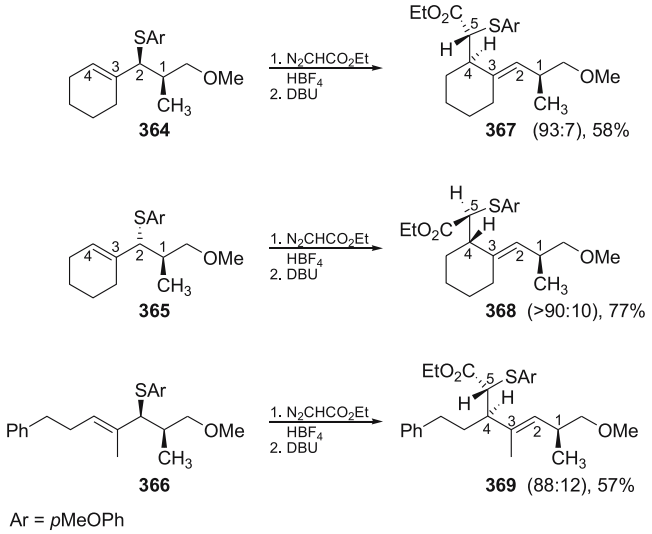
Scheme 89 1,3-Chirality transfer with secondary sulfides

Et_2Zn/CH_2I_2 which rearranged to **359** as a single isomer [192]. In the context of a methinolide synthesis [206] the possibility of using the Type **M** rearrangement in ring expansion reactions has been superpositioned with stereocontrol by 1,3-chirality transfer. In the event, cyclic sulfide **360** has been transformed to eight-membered ring **361** again as a single isomer [207].

One of the first examples of an excellent stereoselectivity in open-chain allylic sulfides was published in 1986 by Weinreb [208]. In this remarkable paper a diastereoselective "Diels–Alder reaction" of a sulfinyl dienophile with a substituted diene delivered cycloadducts as described earlier (Sect. 3.5.3, Scheme 59). After ring opening and reduction *Z*-olefin **362** was produced which, after *S*-methylation and base treatment rearranged to isomerically pure homoallyl sulfide **363**.

In a series of publications Warren et al. demonstrated the usefulness of 1,3-chirality transfer in the context of Type **M** rearrangements to synthesize 1,4,5-stereotriads with *E*-configured double bonds (Scheme 90) [209–211]. Based on their successful work on diol syntheses with 1,4-related stereogenic centers across *E*-configured double bonds [212, 213] involving the Mislow–Evans rearrangement (Sect. 3.5), the authors developed a procedure for the stereoselective synthesis of *E*-homoallylic sulfides.

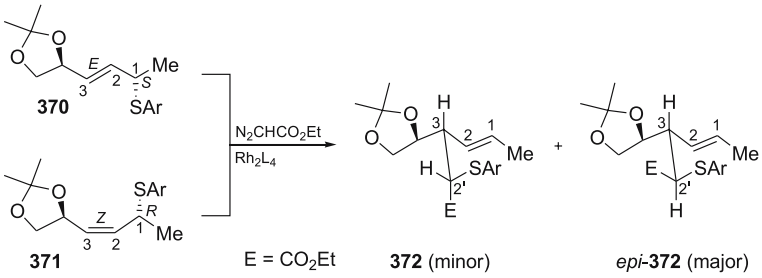
The required diastereomerically pure allylic sulfides **364–366** were prepared by a combination of stereoselective aldol additions and 1,2-arylsulfanyl migrations [214]. Under carefully controlled conditions [211] they could be



Scheme 90 1,4,5-Stereotriads by combined application of stereoselective aldol reactions and Type **M** rearrangements

converted into the corresponding sulfonium salts, which in turn delivered sulfonium ylides after base treatment. Their rearrangement furnished homoallylic sulfides **367**–**369** with high diastereomeric purity. The relative topicity of attack (ylide carbon onto allylic terminus) was *lk* in all cases; thus, the *relative* configuration of the newly formed stereogenic centers at C4 and C5 was always the same irrespective of the relative configuration in the starting material. On the other hand, the inversion of the *absolute* configuration at the sulfanylated carbon (e.g., going from **364** to **365**) entails an inversion of the *absolute* topicity of attack of the reactive sites on each other (see **TS-I**/*ent*-**TS-I**). This in turn led to an inversion of the C4/C5 configuration in the products (**367**/**368**). As expected the *S* configuration plays only a minor role (if any) in systems capable of 1,3-chirality transfer [6]). Moreover, diastereoselectivity induced by the stereogenic C1 can obviously be neglected, too.

This overriding effect of 1,3-chirality transfer as compared to induced diastereoselectivity was also observed in chiral, nonracemic, secondary allylic sulfides bearing a remote chiral dioxolanyl moiety (Scheme 91) [215]. The reactions of *E*-(*S*)-**370** and *Z*-(*R*)-**371** with ethyl diazoacetate under the influence of various Rh catalysts delivered ylides which rearranged to products **372** and 2′-*epi*-**372**. From the analysis of the products it was deduced that 1,3-chirality was almost complete, whereas the stereochemical outcome at C2′ differed somewhat with the catalysts used and was only modest in all cases. Obviously the reaction of **370** to the major diastereomer *epi*-**372** involves **TS-I** or **TS-II** (Scheme 88) (R^E = dioxolanyl moiety, R^1 = Me, G = CO_2Et) with the absolute topicity of attack being *Re* (C2′)/*Si* (C3). After desulfanylation only

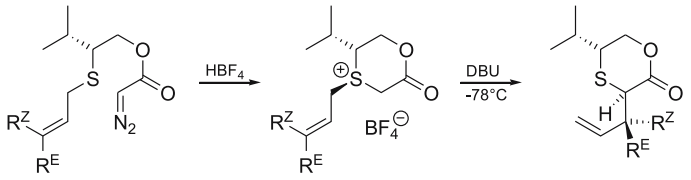


Scheme 91 Dominance of 1,3-chirality over induced diastereoselectivity

one isomer remains, demonstrating complete 1,3-chirality transfer but incomplete control at C2′. This in turn indicates that the transition-state energy is more sensitive to the position of R^1 (pseudo-equatorial to avoid $A^{1,3}$ strain) than to those of G (*trans* or *cis* to R^E).

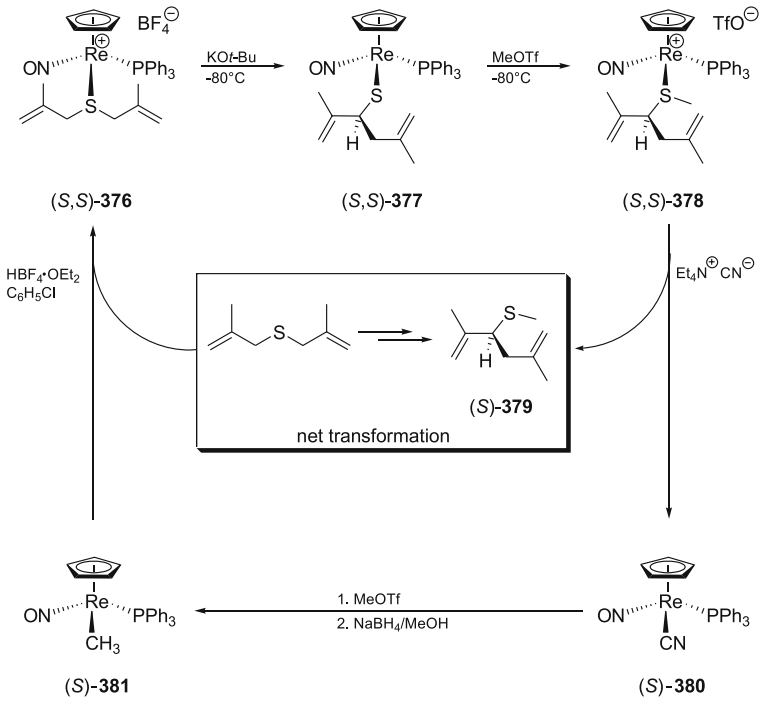
Z-(*R*)-sulfide **371** rearranges to the same products because both relevant stereogenic units are inverted as compared to **370** entailing conservation of the absolute topicity of attack. In experiments without stereogenic C1 all four possible diastereomers were obtained with essentially no stereoselection, indicating the minor influence of the C4 stereogenic center (virtually no induced diastereoselectivity).

On the other hand, when R^S (Scheme 88) contains a stereogenic center, high induced diastereoselectivities have been observed (Scheme 92) [216]). The valine-derived chiral, nonracemic sulfides **373a** and **373b** cyclized after HBF_4 treatment to diastereomerically pure sulfonium salts **374**, which rearranged after DBU addition to **375a** (94% *ds*) and **375b** (93% *ds*), respectively. The authors interpret the stereochemical outcome of the reaction as a diastereoselective cyclization (induced diastereoselectivity) yielding sulfonium salt **374** with *trans*-oriented crotyl and isopropyl side chains followed by chirality transfer from sulfur to carbon (see also Sect. 3.7.2.2).



Scheme 92 Induced diastereoselectivity with chiral R^S -group

An interesting alternative to stereogenic carbon-based auxiliaries is the application of chiral Lewis acidic transition metal fragments (Scheme 93) [217–



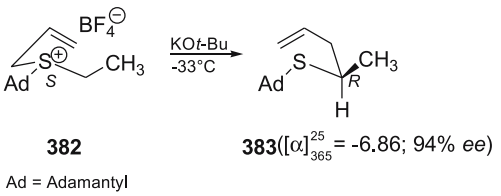
Scheme 93 Centrochiral rhenium complexes in the Type **M** rearrangement

219]. Complex **376** can be prepared from enantiomerically pure rhenium precursor **381**. The former can be deprotonated at low temperatures initiating the [2,3]-sigmatropic rearrangement to diastereomerically pure homoallylic sulfide complex **377**. After *S*-alkylation, cyanide treatment releases the *S* ligand as product **379**. As an extension of this work the authors showed that iron and ruthenium complexes can be used, too [219].

3.7.2.2 S → C Chirality Transfer

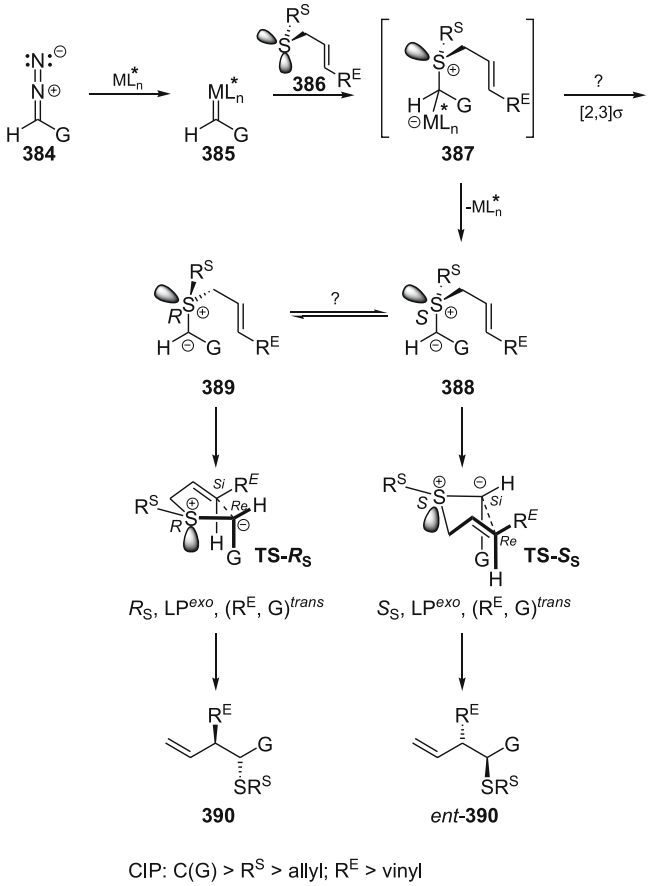
In a seminal paper published in 1973, Trost reported on the preparation of highly enantioenriched sulfonium tetrafluoroborates by resolution of the corresponding dibenzoylhydrogen tartrates (Scheme 94) [220]. When the resolved allyl sulfonium salt **382** was treated with base the rearrangement product **383** was obtained and its absolute configuration was determined by chemical correlation. Furthermore, it was deduced that **383** had 94% *ee*, which denotes that the rearrangement should be fast on the timescale of ylide inversion and indicates at least 94% asymmetric induction.

Despite its mechanistic significance this approach to S → C chirality transfer implies resolved sulfonium salts, which obviously is not as practical as



Scheme 94 First example of sulfur to carbon chirality transfer in a Type **M** rearrangement

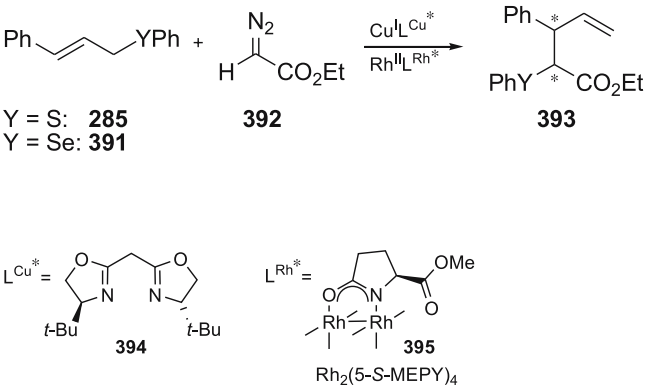
a catalytic variant involving chiral transition metals would be. Therefore, in recent years major efforts were undertaken to develop this kind of chemistry using enantioselective carbenoid addition to organosulfur compounds (Scheme 95) [177, 178, 184, 221, 222].



Scheme 95 Transition-state models for sulfur to carbon chirality transfer in Type **M** rearrangements

The reaction of a diazo compound **384** with (chiral) transition metal complexes (M = Cu, Rh, Co) delivers a metal carbene species **385** ("Doyle–Kirmse" reaction [223, 224]) which reacts with sulfides **386** to generate metal-bound sulfonium ylides **387**. If sulfide **386** was prochiral, then in ylide **387** sulfur becomes stereogenic with an excess configuration being dependent on the efficiency of the enantiotopos differentiation of the sulfur lone pairs (LPs). Whether or not this species undergoes directly the subsequent [2,3]-shift is a matter of debate (see below). There is plenty of evidence that the metal dissociates from the complex generating the free ylide **388**, which may or may not be configurationally stable on the timescale of the rearrangement. An additional problem could be the question of the configurational stability at the ylide carbon! Under the assumption that **388** is configurationally stable and the preferred transition-state conformation is LP^{exo} and displays R^E and G in a *trans* relation [204], *ent*-**390** should be the product produced in excess. Consequently the enantiomer **390** should be produced via R_S-configured ylide **389**. Unfortunately things are more complicated than that. Due to the usually small energy differences involved in five-membered ring transition states, variations in the substitution pattern may invalidate the assumptions given above entailing changes in the topicity of attack (including the relative topicity). This in turn invalidates a direct relation of the enantiomeric excess observed in the products with the efficiency of the enantiotopos differentiation during ylide formation.

In 1995 the first examples of enantioselective, metal-catalyzed [2,3]-sigmatropic sulfurylide rearrangements appeared (Scheme 96) [225]. When *E*-cinnamylphenyl sulfide **285** was reacted with ethyl diazoacetate in the presence of a catalytic amount of CuOTf and bisoxazoline **394** [226], a diastereomeric mixture close to 1 : 1 of homoallylic sulfides **393** was produced with 20% *ee* for the major diastereomer (configuration was not assigned).

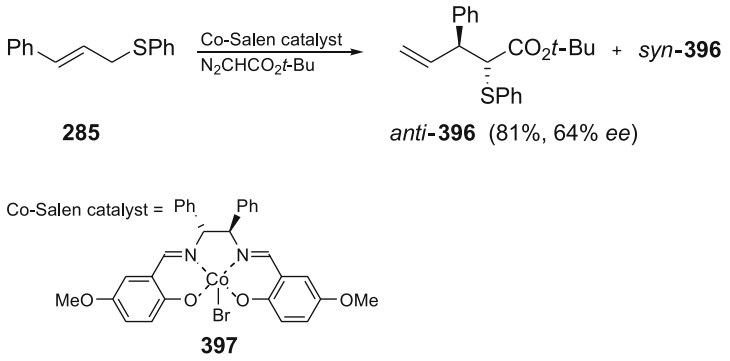


Scheme 96 First example of an enantioselective transition metal catalyzed Type **M** rearrangement

With the selenium compound **391** the minor diastereomer was generated with 34% *ee*. Changing the catalyst system to Rh_2(5*S*-MEPY) (MEPY = methyl 2-oxopyrrolidine-5-carboxylate) [227, 228] increased the maximum *ee* to 41% for **391**.

In 2000 this work was extended by a systematic screening of the influence of the *S*-bound substituent [229]. It was found that replacing the *S*-phenyl group in allyl phenyl sulfide with 2,6-dimethylphenyl increases the *ee* of the major diastereomer from 14 to 52% in Cu^I/bisoxazoline-catalyzed rearrangements.

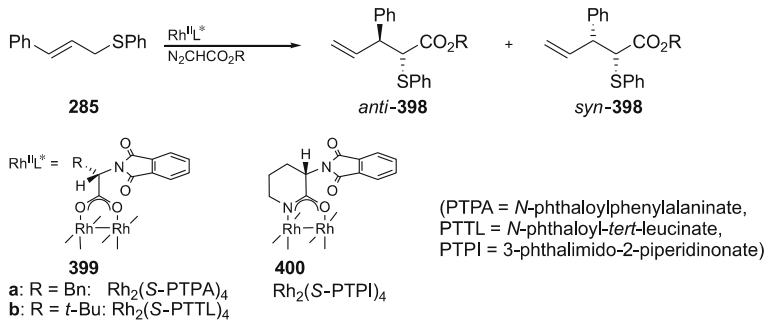
In 1997 Katsuki found a considerably better system (Scheme 97) [230]. This time *E*-cinnamyl phenyl sulfide **285** was converted under Co catalysis using a salen ligand to generate *anti*-**396** and *syn*-**396** (85 : 15) with much improved diastereoselectivity and 65% *ee*, in favor of the (2*R*,3*S*)-*anti* diastereomer (presumably via **TS**-$\boldsymbol{R}_S$, Scheme 95, see also [231]). When *t*-Bu in the diazo compound was replaced by (–)-menthyl, the *anti* isomer was generated with 74% *ee* and 93% *ds* in a matched double stereodifferentiating reaction.



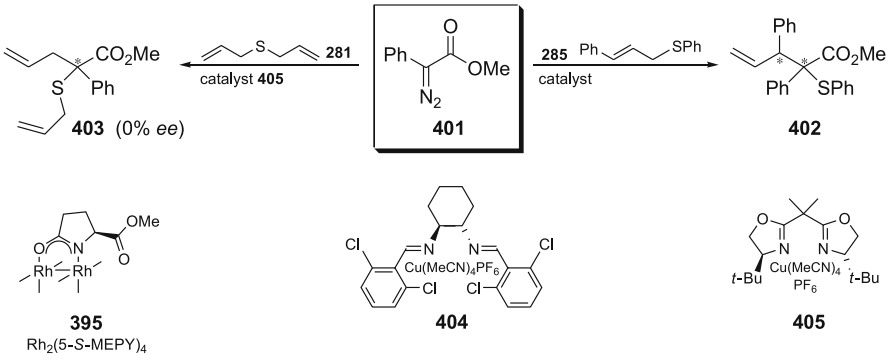
Scheme 97 Application of cobalt salen complexes for sulfonium ylide rearrangements

Important work concerning the question of the intermediacy of metal-bound ylides was published in 2001 (Scheme 98) [232]. It was found that the diastereoselectivity of the reaction was independent of the catalyst used, but markedly influenced by the size of the ester groups. (With R = CH(*i*Pr)$_2$ and Rh_2(*S*-PTPI)$_4$ the *anti*-**398** : *syn*-**398** ratio was 94 : 6.) From these results it was deduced that after the enantiotopos differentiating ylide formation, the metal dissociates off and the absolute topicity of attack of the reactive sites on each other is controlled by the factors discussed for the free ylide pathway, as illustrated in Scheme 95.

The same conclusion was drawn from a study by Wang et al. (Scheme 99) [233]. In the metal-catalyzed reaction of *E*-cinnamyl phenyl sulfide **285** with diazo compound **401** the diastereoisomeric ratios in the re-



Scheme 98 Studies concerning the question of the intermediacy of metal-bound ylides in the sulfonium ylide rearrangement

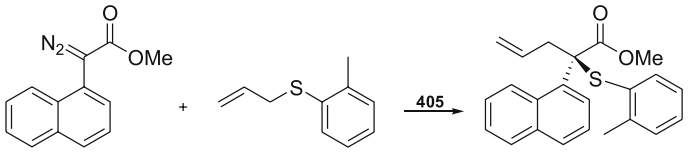


Scheme 99 More evidence for metal-catalyzed Type **M** rearrangements via free ylides

arrangement products **402** were found to be independent of the catalyst used ($Rh_2(OAc)_4$, **395**; $Cu(MeCN)_4PF_6$, **404** or **405**). Next, the symmetric diallyl sulfide **281** with homotopic lone pairs was used. In this case the initially formed ylide is only chiral when the metal remains bound to it. Therefore, any asymmetric induction must be due to catalyst-bound species. In the event, the rearrangement product **403** was isolated with 0% *ee* using chiral copper complex **405**.

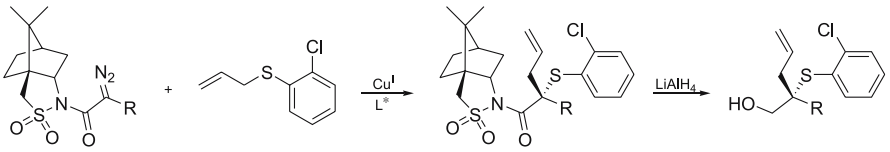
Although this is not *conclusive* evidence for the ylide-free mechanistic variant, it is at least strongly in favor of it. It is worth mentioning that in the same paper the momentary *ee* "world record" for this type of reaction was reported (Scheme 100).

In a recent paper from the same group another attempt (see also [230]) was made to improve the stereoselectivity by double asymmetric induction (Scheme 101) [234]. In this remarkable study it was found that the asymmetric induction exerted by the camphor sultam auxiliary [235] alone delivers, after reduction of the rearrangement product **411a**, alcohol **412a** with 30% *ee* in the given absolute configuration. With (*S*, *S*)-**413** as chiral ligand **412a** was

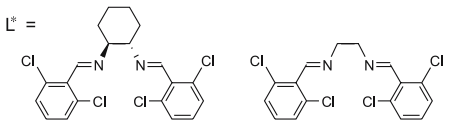


406 **407** **408** (66%, 78% ee)

Scheme 100 Highest *ee* reported to date for a transition metal catalyzed Type **M** rearrangement



409a: R = Ph **410** **411a**: R = Ph **412a**: R = Ph

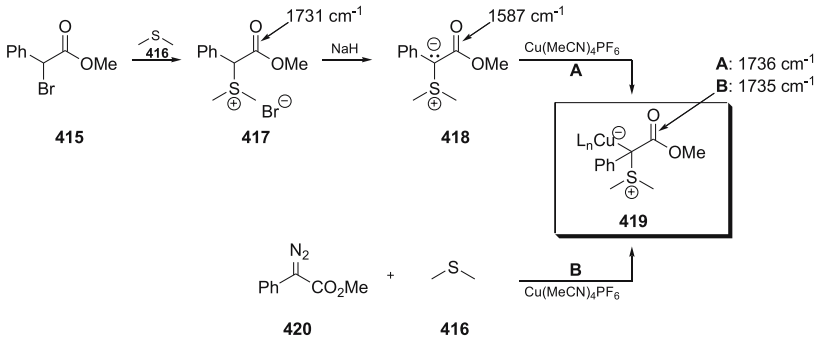


(*S*,*S*)-**413** **414**

Scheme 101 Double asymmetric induction with the camphor sultam auxiliary

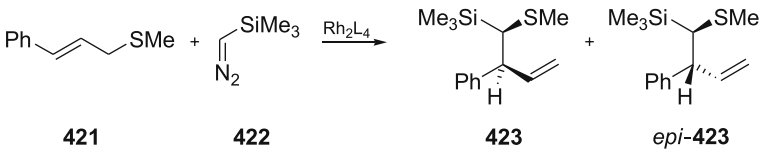
produced with 90% *ee* (70% yield) and with (*R*,*R*)-**413** it was found to have 80% *ee* (same absolute configuration!). These data suggest that the sense of the asymmetric induction is dominated by the auxiliary and not by the chiral ligands. Nonetheless, the ligands reinforce the "inductive power" of the sultam with the *S*,*S* isomer of **413** being more effective than its enantiomer (matched combination). A possible explanation could be the induction of a chiral conformation in the ligands by the auxiliary entailing an increased ability of the copper complex to choose between the enantiotopic lone pairs of sulfur. This interpretation is corroborated by the fact that *achiral* ligand **414** can be influenced by the auxiliary to produce **412a** with 92% *ee* (slightly better than with the chiral (*S*, *S*)-**413**!). Furthermore, the authors demonstrate that the system tolerates quite a broad range of substituents R in the diazo compound (substituted aryl, methyl, alkenyl). In most cases enantioselectivities above 80% *ee* were achieved. Most interestingly, the authors found evidence for a tight complexation of the ylide with the copper complex (a little bit hidden in the supporting material) (Scheme 102).

This evidence is based on IR-spectroscopic measurements on the copper–ylide complex prepared by two independent routes. First, sulfonium salt **417** was made by alkylation of dimethyl sulfide **416** with bromide **415**. The



Scheme 102 IR spectroscopic evidence for ylide–copper complexes

C = O stretching frequency was found to be υ(C = O) = 1731 cm^{-1}. After deprotonation yielding ylide **418**, this frequency dropped dramatically to υ(C = O) = 1587 cm^{-1} and after treatment of the ylide with Cu(MeCN)$_4$PF$_6$ (path A) it was restored to υ(C = O) = 1736 cm^{-1}, strongly indicating complex formation to **419**. To show that this species is relevant also for the carbenoid route to ylides, diazo compound **420** was reacted with dimethyl sulfide in the presence of the copper source. Indeed, a species with nearly the same υ(C = O) was produced (path B). Although these data suggest that the [2,3]-sigmatropic rearrangement occurs from the complexed ylide, this conclusion is not stringent. It cannot be ruled out that the rearrangement proceeds from the fractional free ylide that is in equilibrium with the complexed one (Curtin–Hammett principle). This latter scenario is in accordance with most observations made in the context of transition metal catalyzed [2,3]-sigmatropic rearrangements of 2-alkenyl sulfonium ylides (see above). Nevertheless, it should be mentioned that there is a single observation in the literature pointing to rearrangement processes involving complexed ylides (Scheme 103) [236].



Scheme 103 Type **M** rearrangement via Rh-complexed sulfonium ylide?

In the Rh-catalyzed reactions of sulfide **421** with trimethylsilyldiazomethane **422**, a pronounced dependence of the diastereoisomeric ratio on the catalyst used was observed (ranging from 90 : 10 to 49 : 51 for the **423** : *epi*-**423** ratio). These data, together with the above-mentioned mechanistic study of Wang, point to an influence of the ylide substituents on both the position of the equilibrium between complexed and free ylide and a possible influence

on the relative rates by which both components undergo the rearrangement reaction.

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Top Curr Chem (2007) 275: 67–101
DOI 10.1007/128_047

Published online: 10 June 2006

[2,3]Sigmatropic Rearrangements of Propargylic and Allenic Systems

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Abstract [2,3]Sigmatropic rearrangements of propargyl sulfonium ylides along with recent advances in the corresponding sulfenate–sulfoxide and sulfinate–sulfone type rearrangements are reviewed. Some new additional examples of these types of transformations, including rearrangements of propargylic dialkoxy disulfides are also surveyed.

Keywords [2,3]Sigmatropic rearrangements · Sulfonium ylide · Sulfoxide/sulfenate · Sulfone/sulfinate · Dialkoxy disulfide

Abbreviations

S-TBSP 1-[(4-*t*-Butylphenyl)sulfonyl]-(2*S*)-pyrrolidinecarboxylate)
S-DOSP 1-[(4-Alkyl(C_{11}-C_{13})phenyl)sulfonyl]-(2*S*)-pyrrolidinecarboxylate)
NB 2-Nitrophenyl
BMCB Bis(methylene)cyclobutene
dpph Bis(diphenylphosphino)hexane
dppb Bis(diphenylphosphino)butane

1 Introduction

As a natural extension of the [2,3]sigmatropic rearrangement of allylic sulfinates [1–3] and sulfenates [4, 5], the [2,3]sigmatropic rearrangements of propargylic sulfinates [6, 7] and sulfenates [8] to allenic sulfones and sulfoxides, respectively, were reported by us in the mid 1960s. During the past four decades, the field of sigmatropic rearrangements of propargylic esters of sulfur acids at various oxidation states has proven to be a rich source of synthetically valuable and mechanistically intriguing reactions, often yielding novel and surprising products. However, since the relevant literature for the first two decades has been reviewed before [9–12], the present account concentrates on the more recent studies and developments. The appearance of tandem multiple sigmatropic rearrangements followed by intramolecular cycloadditions and formation of complex structures resembling biologically active organosulfur compounds isolated from the allium species is a good example of such recent developments.

Interestingly, the [2,3]sigmatropic rearrangements of propargylic sulfonium ylides [13] was also inspired by the allylic analogs [14] at about the same time as the rearrangements of propargylic sulfenates and sulfinates, mentioned above. Due to their great synthetic utility, high stereoselectivity and mechanistic interest these rearrangements have also received wide attention in the past four decades. Recently, a nitrogen analog of this rearrangement has also been reported (Sect. 2.5).

2 [2,3]Sigmatropic Rearrangements of Propargylic Sulfonium Ylides and Related Systems

Propargyl sulfonium ylides can undergo symmetry-allowed thermal [2,3]sigmatropic rearrangement to generate β-allenyl sulfides [13, 14]. Although less known then its allylic counterpart, this rearrangement was recognized as powerful bond reorganization processes leading to simultaneous C – C bond formation and C – S bond cleavage. The reaction has been applied as a use-

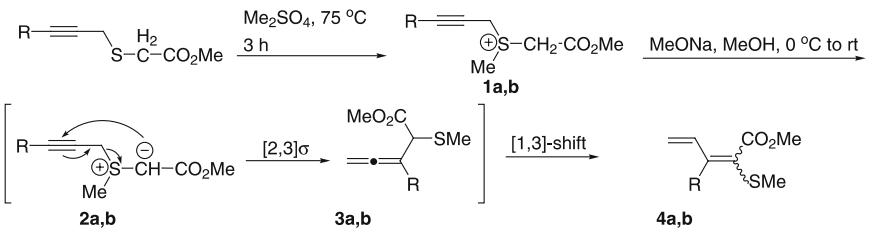
ful synthetic tool for the preparation of allenyl and conjugated dienic sulfides since its discovery in the late 1960s [13–17]. In addition, the [2,3]sigmatropic rearrangement of sulfonium ylides can be used to transfer chirality from sulfur to carbon [18]. Since propargyl sulfonium ylides are reactive intermediates, they should be generated in situ either via a base-promoted approach involving alkylation of sulfides, followed by base-induced deprotonation of corresponding sulfonium salts, or by the transition metal catalyzed reaction of sulfides with carbenes or carbenoid systems.

2.1 Sulfonium Ylides Generated via Alkylation/Deprotonation

Alkylation of propargylic sulfides with usual alkylating agents such as dimethyl sulfate or trialkyloxonium tetrafluoroborates leads to the corresponding sulfonium salts. The latter can be easily deprotonated in a basic media to propargylic sulfonium ylides, which undergo spontaneous [2,3]sigmatropic rearrangement resulting in the formation of terminal or internal allenyl sulfides. Both propargyl and dipropargyl systems can participate in this kind of transformations. Baldwin was the first to report that *sp*-hybridized bonds participate in the electrocyclic rearrangement of sulfonium ylide with formation of allenes [13].

Latter, an alkylation–deprotonation approach has been used for the preparation of synthetically useful 1,1-captodative substituted butadienes (**4**) [19]. Sodium methoxide deprotonation of propargylic sulfonium salts (**1**) followed by [2,3]sigmatropic rearrangement of the resulting sulfonium ylides (**2**) give the corresponding allenes (**3**), which under the reaction conditions undergo spontaneous isomerization by 1,3-hydrogen shift to the thermodynamically more stable 1,3-butadiene derivatives (**4**) (Scheme 1).

The reactivity of bis-γ-substituted and unsubstituted dipropargylic sulfonium salts under various basic conditions was investigated by Braverman [20]. Formally, two modes of reactivity are possible for sulfur-bridged



Compound	R	Yield (%)	*E/Z*
4a	H	61	0/100
4b	Me	65	55/45

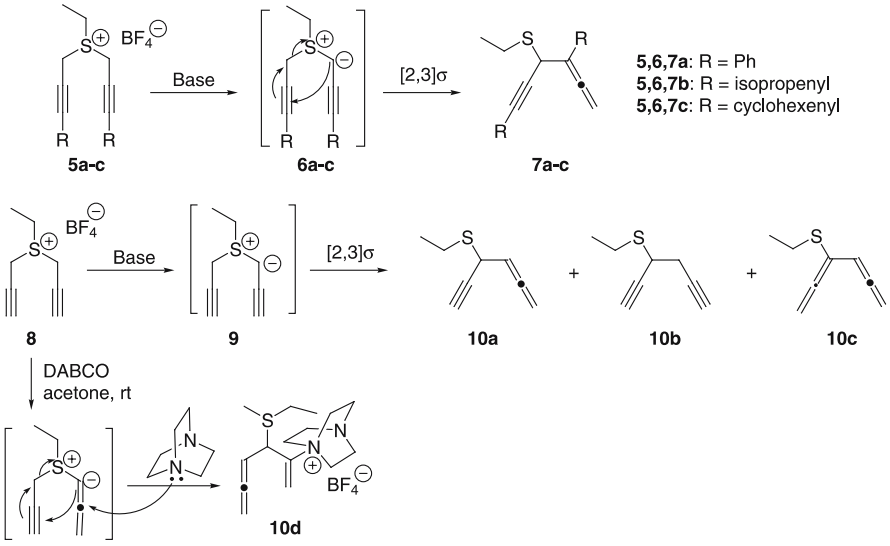
Scheme 1 Butadienyl sulfides via [3,2]sigmatropic rearrangement of sulfonium ylides

bis-propargylic systems under basic conditions. The first one includes isomerization to the corresponding diallene, followed by cyclization and aromatization via a diradical intermediate, similar to bis-propargyl sulfones and sulfoxides [21]. The second one involves [2,3]sigmatropic rearrangement of an sulfonium ylide generated in situ. No cyclization was observed for any of the investigated sulfonium salts. The bis-γ-substituted compounds (**5**) reacted only by [2,3]sigmatropic rearrangement of the corresponding sulfur ylides (**6**). For example, reaction of ethyl bis-γ-cyclohexenylpropargyl sulfonium tetrafluoroborate (**5c**) with DBU in $CHCl_3$ at room temperature resulted in practically spontaneous and quantitative [2,3]sigmatropic rearrangement, affording the sulfide derivative **7c**. However, unsubstituted bis-propargylic

Table 1 Base-catalyzed [2,3]sigmatropic rearrangement of dipropargylic sulfonium salt

Base/solvent	**10a** Yield (%)	**10b** Yield (%)	**10c** Yield (%)	**10d** Yield (%	Refs.
NaOMe/MeOH [a]	33	67	0	0	[20]
t-BuOK/*t*-BuOH-acetone [a]	85	0	0	0	[20]
DBU/acetone [b]	0	30	70	0	[20]
DABCO/acetone [a]	0	0	0	100	[20]

[a] Isolated yield
[b] Determined by NMR

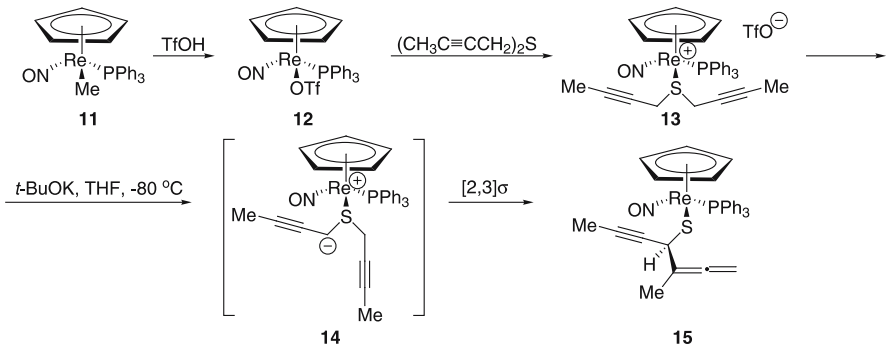


Scheme 2 Base-catalyzed [2,3]sigmatropic rearrangement of dipropargylic sulfonium salts

sulfonium salt (**8**) exhibited a wider range of reactivity, which depends on the nature of the base (Table 1). For example, using strong bases leads to sigmatropic rearrangement and prototropic isomerization, while with weaker base (such as DABCO) nucleophilic addition–displacement of the base to allene takes place (Table 1 and Scheme 2).

2.2 Sulfonium Ylides Generated via Alkylation/Deprotonation: Asymmetric Version

An asymmetric version of the [2,3]sigmatropic rearrangement of sulfonium ylides can be successfully used for the preparation of sulfides in an enantioselective manner from sulfonium salts that lack resolved carbon stereocenters. This is accomplished via sulfur-bonded chiral auxiliaries, controlling the carbon configuration of the products. In one such approach chiral rhenium Lewis acid $[(\eta^5\text{-}C_5H_5)Re(NO)(PPh_3)]^+$ (**12**) serves as a highly effective and readily recycled auxiliary for the conversion of achiral symmetrical dipropargyl sulfides to chiral rearranged sulfides of high enantiomeric purities [22–24]. First, air-stable metal sulfide complex (**13**) was obtained with a yield of 79% from racemic methyl complex (**11**). *t*-BuOK in THF deprotonates this cationic sulfide adduct **13** to sulfur ylide (**14**), which has a sulfur stereocenter. The latter undergoes spontaneous low-temperature [2,3]sigmatropic rearrangement to neutral thiolate complex (**15**) with efficient transfer of chirality to the new carbon stereocenter (Scheme 3). The rearranged thiolate complex **15** was obtained with a yield of 95% and as 87 : 13 mixture of Re,C configurational diastereomers. The relative Re,S*C* configuration of the major diastereomer was presumed to be identical with the corresponding diallyl derivative (established from the X-ray structure) and assigned as *SR,RS* [24]. The thiolate ligand can be likely S-alkylated and detached as



Scheme 3 Generation and rearrangement of rhenium-substituted dipropargyl sulfonium ylide

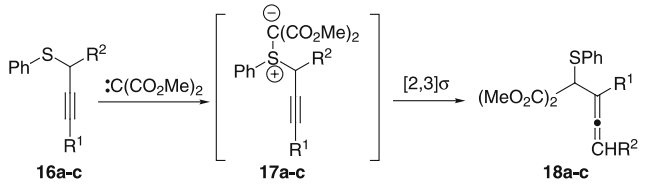
free sulfide of high enantiomeric purity, as for a number of allyl derivatives [22–24]. The Re auxiliary is easily recovered and recycled without loss of configuration.

2.3
Sulfonium Ylides Generated via Carbene or Carbenoid Precursors

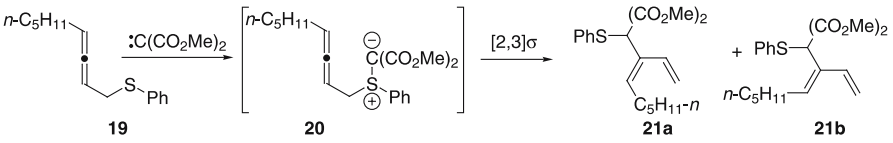
An elegant and efficient way for preparation of sulfonium ylides under mild conditions is the so-called Doyle–Kirmse reaction [25, 26], which involves transition metal catalyzed decomposition of diazo compounds (usually α-diazocarbonyls) in the presence of sulfides. For the catalytic generation of matallocarbenes from diazo compounds, copper catalysts have traditionally been employed. More recently, rhodium and ruthenium compounds were reported to be efficient catalysts, especially for the generation of sulfonium ylides [27–29].

Employing this procedure, terminal and internal allenyl sulfides (**18a–c**) can be conveniently prepared via the copper salt catalyzed thermal decomposition of diazomalonates in acetylenic sulfides (**16**). The rearrangements are carried out in the absence of solvent by heating a mixture of methyl diazomalonate and acetylenic sulfide **16** in the presence of catalytic amount of anhydrous cupric sulfate at 95–100 °C (Scheme 4) [15]. Similarly, the [2,3]sigmatropic rearrangement of sulfonium ylides can be successfully applied to allenic systems, as demonstrated by the smooth conversion of allenic sulfide (**19**) into a 4 : 1 mixture of conjugated dienes (**21a** and **21b**) (Scheme 4) [15].

The [2,3]sigmatropic rearrangement of sulfonium ylide (**24**) derived from rhodium-catalyzed decomposition of ethyl 3,3,3-trifluoro-2-diazopropanoate (**23**) in the presence of propargyl sulfide (**22a**) affords the corresponding functionalized CF_3-containing carboxylic ester sulfide (**25a**). The latter was



a: R^1= Et, R^2=H, yield 71 %; **b:** R^1= *n*-Bu, R^2=H, yield 80 %; **c:** R^1= Et, R^2=Me, yield 60 %

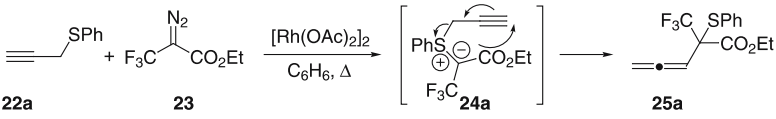


Scheme 4 [2,3]Sigmatropic rearrangement of acetylenic and allenic sulfonium ylides via copper salt catalyzed thermal decomposition of diazomalonates

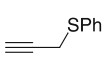
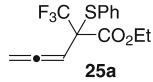
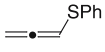
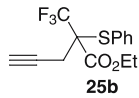
further converted to the synthetically useful trifluoromethylated conjugated ester via the dehydrosulfenylation sequence, thus giving a new approach to trifluoromethylated aliphatic compounds under mild conditions and with a tolerance of functionalities [30]. As above, the [2,3]sigmatropic rearrangement of CF_3-containing carboxylic ester sulfonium ylides **24** works well with allenic systems and results in the high yield transformation of allenyl phenyl sulfide (**22b**) to the propargyl trifluoromethylated sulfide (**25b**) (Scheme 5) [30].

The [2,3]sigmatropic rearrangement was carried out by stirring a mixture of sulfide **22** and catalytic amounts of rhodium(II) acetate in dry benzene until the solution became homogenous. Then the diazo compound **23** was added and the reaction mixture heated at the temperature at which a smooth nitrogen evolution was maintained. Sulfonium ylide **24** generated by trapping of CF_3-substituted carboethoxy carbenoid intermediate with the corresponding sulfide undergoes the expected [2,3]sigmatropic rearrangement and affords the trifluoromethylated sulfide **25** with good yield.

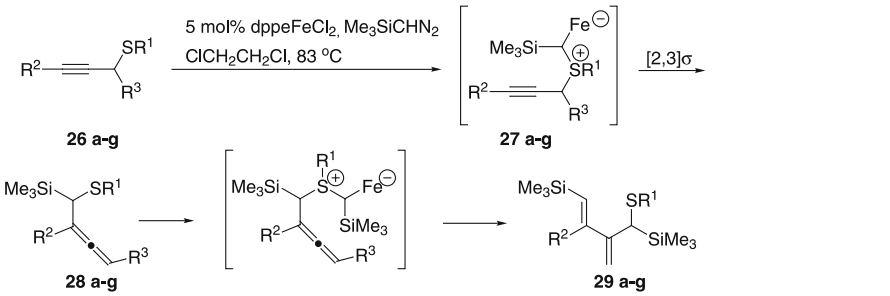
Iron-catalyzed carbene generation/[2,3]sigmatropic rearrangement of propargyl sulfonium ylides have also been reported [31]. Thus, catalysis by ferrous salts has been efficiently applied to the synthesis of homoallenylsilanes (**28**) via addition/[2,3]sigmatropic rearrangement reactions of propargyl sulfides (**26**) with trimethylsilyldiazometane (Scheme 6). Adding Me_3SiCHN_2 after premixing the catalyst with sulfide **26** gave significantly higher yields and lower reaction times than comparable reactions without premixing. While dppe$FeCl_2$ was a convenient catalyst precursor, phosphine ligand was not necessary for the reaction and simple ferrous salts such as $FeBr_2$ can be used. An additional product, diene **29**, was obtained as a mixture of *E* and *Z* isomers, probably from addition of a second molecule of trimethylsilyldiazometane to the homoallenyl sulfide moiety of **28**. Larger



22a **23** **24a** **25a**

Sulfide	equiv of **23**	T °C/t (h)	Product	Yield (%)
 **22a**	1.3	60/0.5	 **25a**	85
 **22b**	2.0	35/0.7	 **25b**	82

Scheme 5 [2,3]Sigmatropic rearrangement of sulfonium ylides via rhodium-catalyzed decomposition of ethyl 3,3,3-trifluoro-2-diazopropionate

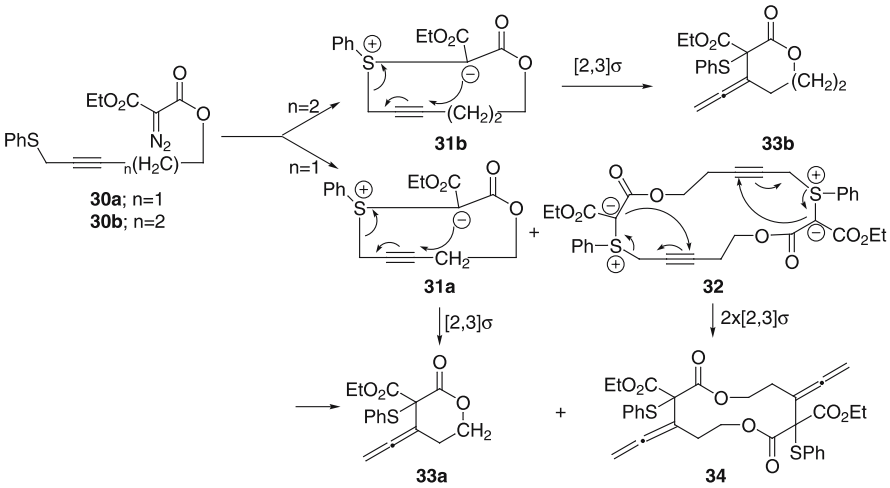


	R^1	R^2	R^3	Time (h)	Yield (%) **28**
a	4-$MeOC_6H_4CH_2$	H	H	1	73
b	4-$MeOC_6H_4CH_2$	Me	H	1	76
c	4-$MeOC_6H_4$	Me	H	7	78
d	4-$MeOC_6H_4CH_2$	CHPh(OAc)	H	0.5	73
e	2,5-$Me_2C_6H_3$	CHPh(OAc)	H	1	90
f	4-$MeOC_6H_4CH_2$	H	Me	5	48
g	4-$MeOC_6H_4CH_2$	CO_2Me	H	5	18

Scheme 6 Iron-catalyzed carbene generation/[2,3]sigmatropic rearrangement of propargyl sulfonium ylides

substituents on the alkyne gave allene products in higher yields, presumably because they disfavor this second addition. Concerning diastereoselectivity, low diastereoselection was observed when a stereogenic center was adjacent to sulfur (reaction of sulfide **26f** proceeds with a mere 2 : 1 diastereocontrol), while no diastereoselectivity was seen at all when stereogenic centers were far. Thus chiral acetates **26d** and **26e** both gave good yields of the corresponding allenes **28d** and **28e**, but as a 1 : 1 mixture of diastereomers.

In an interesting application [32], the [2,3]sigmatropic rearrangement of propargyl sulfonium ylides has been used as a ring-forming reaction. Thus, acyclic acetylenic diazomalonates (**30**) having both a propargyl sulfide substituent and a diazomalonyl group as a carbene-generating function at the terminal positions give the novel allenic lactones (**33** and **34**) via a rhodium-catalyzed formation of the cyclic sulfonium ylides (**31**, **32**) followed by the [2,3]sigmatropic rearrangement (Scheme 7). Formation of cyclic sulfonium ylide was strictly determined by ring size. Thus, reaction of diazomalonate **30a** ($n = 1$) with rhodium(II) acetate in refluxing benzene resulted in the formation of two products: allenic six-membered lactone **33a** and a diastereomeric mixture of bis-lactones **34** via bimolecular bis-ylide (**32**) formation followed by the double [2,3]sigmatropic rearrangement. Diazomalonate **30b** ($n = 2$) afforded the seven-membered lactone **33b** as the single isolable product with 24% yield, whereas diazomalonate **30c** ($n = 0$) under similar reaction conditions gave a mixture of polar products in which no allenic lactones were detected.

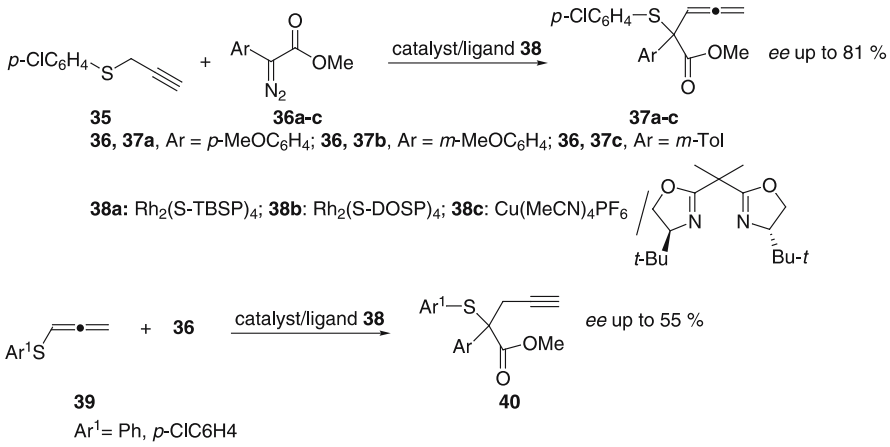


Scheme 7 [2,3]Sigmatropic rearrangement of propargyl sulfonium ylides as a ring forming reaction

2.4 Sulfonium Ylides Generated via Carbene or Carbenoid Precursors: Asymmetric Version

Due to availability of new chiral catalysts for carbene-generating decomposition of diazocarbonyl compounds, catalytic enantioselective rearrangements involving sulfonium ylides have attracted considerable attention in recent years [27, 28]. The main issue concerning the asymmetric catalysis in [2,3]sigmatropic rearrangement of sulfonium ylides is whether the rearrangement proceeds through a metal-associated ylide or a free ylide, and it still remains unsettled. Consequently, asymmetric induction in ylide transformations is possible either if the ylide remains attached to metal and its chiral ligand, or the free chiral ylide is relatively stable and therefore, subsequent rearrangement is faster than its racemization. Thus, in 1995 Uemura et al. reported the first example of catalytic asymmetric [2,3]sigmatropic rearrangement of allylic sulfonium ylides derived from trans-cinnamyl phenyl sulfide with ethyl diazoacetate catalyzed by copper(I) or rhodium catalyst [33]. However, the enantioselectivity was low. Later this approach was extended to the related propargylic systems and the enantioselectivity of the reaction substantially improved.

Allenic sulfides (**37**) have been obtained with moderate to good enantioselectivities (up to 81%) in sigmatropic rearrangements of sulfonium ylides generated from propargyl aryl sulfide (**35**) and aryldiazoacetates (**36**) as carbenoid source catalyzed by chiral Rh(II) (**38a**,**b**) and Cu(I) (**38c**) catalysts [34] (Scheme 8).



Scheme 8 Catalytic asymmetric [2,3]sigmatropic rearrangements of propargyl sulfonium ylides

A number of catalysts were investigated in terms of catalytic activity and enantioselectivity and it was shown that Rh_2(*S*-TBSP)$_4$ (tetrakis[1-[(4-*t*-butylphenyl)sulfonyl]-(2*S*)-pyrrolidinecarboxylate)dirhodium) **38a** and Rh_2(*S*-DOSP)$_4$(tetrakis[1-[(4-alkyl(C_{11}-C_{13})phenyl)sulfonyl]-(2*S*)-pyrrolidinecarboxylate)dirhodium) **38b** were the most effective in promoting the rearrangements. However, the Cu(MeCN)$_4$$PF_6$/bisoxazoline system **38c** gave the best enantioselectivity. Thus, when chiral Rh(II) catalysts were used, the reaction became faster and approximately the same level of enantioselectivity as compared to Cu(I) could be achieved in some cases (Table 2, entries 2, 3). However, Cu(I) catalysts gave higher ee values for diazosubstrates bearing a *meta* substituent (Table 2, entries 4, 7).

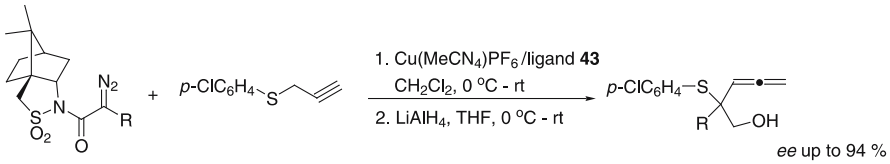
A similar approach has been applied to the [2,3]sigmatropic rearrangements of sulfonium ylides derived from allenic sulfides (**39**) [35]. Rh(II) catalysts **38a,b** are found to be more effective than Cu (I) catalysts **38c.** Homopropargylic sulfides (**40**) were obtained in moderate to good yields and moderate enantiomeric excess in optimized conditions in *n*-hexane at 0 °C (Scheme 8).

More recently, a double asymmetric induction approach was applied to achieve highly stereoselective rearrangement of sulfonium ylides generated from propargyl 2-chlorophenyl sulfides **35** and diazoacetamides bearing camphor sultam auxiliary (**41**) in the presence of Cu(I) catalyst. This double asymmetric induction approach involves the combination of a chiral camphor sultam auxiliary and Cu(I) catalyst with chiral or achiral ligands (**43**) (Scheme 9, Table 2) [36]. When the reaction was carried out in the absence of a ligand, it gave low selectivity. Allenic sulfides (**42**) were isolated with good overall yields and high enantiomeric excess after removing chiral auxiliary by reduction with $LiAlH_4$.

Table 2 Enantioselectivity of the catalytic reaction of propargyl 2-chlorophenyl sulfide and diazo compounds

Entry	Diazo compound	Catalyst/ ligand	Time/T (h/°C)	ee (%) [b]	Yield (%)	Refs.
1	**36a**	**38c**	18/0–25	80	79	[34]
2	**36a**	**38a**	1/0	70	89	[34]
3	**36a**	**38b**	1/0	67	87	[34]
4	**36b**	**38c**	20/0–25	75	89	[34]
5	**36b**	**38a**	5/0	36	44	[34]
6	**36b**	**38b**	5/0	27	48	[34]
7	**36c**	**38c**	20/25	81	82	[34]
8	**41a**	**43a**	5/– 25 [a]	94	87 [c]	[36]
9	**41a**	**43b**	5/– 25 [a]	82	85 [c]	[36]
10	**41b**	**43a**	5/– 25 [a]	91	92 [c]	[36]
11	**41b**	**43b**	5/– 25 [a]	88	90 [c]	[36]
12	**41c**	**43a**	3/– 25 [a]	84	86 [c]	[36]
13	**41d**	**43a**	0.25/5/0–25 [a]	93	95 [c]	[36]
14	**41d**	**43b**	0.25/5/0–25 [a]	92	88 [c]	[36]
15	**41e**	**43a**	0.25/5/0–25 [a]	91	70 [c]	[36]
16	**41e**	**43b**	0.25/5/0–25 [a]	90	65 [c]	[36]

[a] Refers to the first step only
[b] ee values determined by chiral HPLC
[c] Isolated yields for two steps



41a-e **35** **42a-e**

41, 42a: R = Ph; **41, 42b**: R = 4-BrC_6H_4; **41, 42c**: R = 3,4-$Cl_2C_6H_3$; **41, 42d**: R = Me; **41, 42e**: R = $CH_3CH{=}CH$

43a **43b**

Scheme 9 Double asymmetric induction in [2,3]sigmatropic rearrangements of propargyl sulfonium ylides

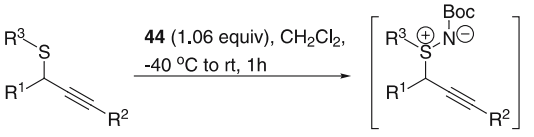
Since a similar level of enantioselectivity and the same absolute configuration of the product could be achieved regardless the stereochemistry of the chiral ligand **43a** (*R*,*R* and *S*,*S*) and even with achiral ligand **43b** (Table 2,

entries 11, 14, 16), it was concluded that the sense of the asymmetric induction was dictated by chiral auxiliary, rather than the chiral ligand of the Cu(I) catalyst.

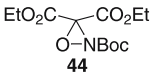
2.5 Sulfimide–Sulfenimide [2,3]Sigmatropic Rearrangement

Recent advances in the [2,3]sigmatropic rearrangements of the propargylic sulfonium ylides have prompted to apply this methodology to their nitrogen analogues, sulfimides and, thus, open an attractive synthetic route to highly functionalized allene systems. First evidence of this process was reported by Tamura [37]. S-Amination of phenyl propargyl sulfide with ethyl *N*-[(trifluoromethanesulfonyl)oxy]carbamate followed by treatment of the reaction mixture with sodium bicarbonate results in the formation of the corresponding *N*-allenylsulfenimide produced via [2,3]sigmatropic rearrangement of initially formed propargyl sulfimide. More recently, ketomalonate-derived oxaziridine **44**, which effected efficient amination and rearrangement of allyl sulfides [38], was successfully applied to the propargylic systems [39]. A wide range of propargyl sulfides (**45**) easily react with oxaziridine **44** under metal-free conditions to give *N*-allenylsulfenimides (**47**) via [2,3]sigmatropic rearrangement of the corresponding propargylic sulfimides (**46**) (Scheme 10).

Yield of allenes **47a–e** from sulfides unbranched in α-position to sulfur are moderate to high. However, α-branching to sulfur lead to lower yields (allenes **47f–h**) and is accompanied by competing formation of sulfoxides by O-transfer from oxaziridine **44**. The metal-free reaction conditions allow synthesis of particularly sensitive allenes or those derived from sensitive sulfides



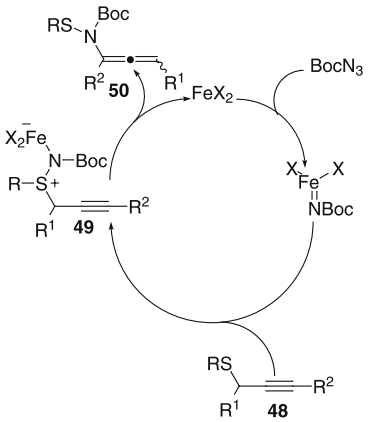
45a-h **46a-h** **47a-h**



44

	R^1	R^2	R^3	Yield (%)
a	H	H	Ph	87
b	H	Me	Ph	55
c	H	CO_2Bu^t	Ph	66
d	H	Ph	Ph	88
e	H	I	Ph	85
f	Me	H	Ph	31
g	Me	H	n-C_6H_{13}	37
h	Me	Me	n-C_6H_{13}	13

Scheme 10 Conversion of propargyl sulfides to *N*-allenylsulfenimides via [2,3]sigmatropic rearrangement of propargylic sulfimides



R = Ph, R^1= H, R^2= H, Me, TMS, CHPh(OH), CHPh(OAc);
R = $PhCH_2CH_2$, R^1= H, R^2= Me;
R = Ph, R^1= Me, R^2= H.

Scheme 11 Iron-catalyzed sulfimidation and [2,3]sigmatropic rearrangements of propargyl sulfides

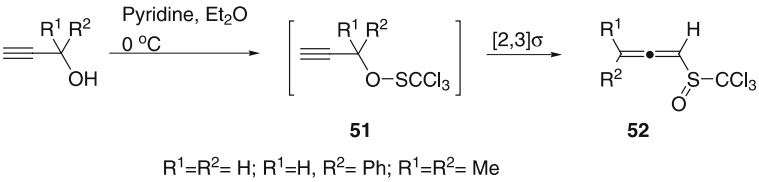
(e.g. **47c**) that are likely to be difficult to obtain using metal-mediated sulfimidation systems.

Another approach to *N*-allenylsulfenimides via [2,3]sigmatropic rearrangement of propargyl sulfimide involves a metal-catalyzed nitrogen atom transfer reaction, based on the Bach reaction [40–42]. The iron(II)-catalyzed Bach reaction of *t*-butoxycarbonyl azide ($BocN_3$) and propargyl sulfides (**48**) gives *N*-allenylsulfenimide products (**50**) (Scheme 11) [43]. Using 10 mol % $dppeFeCl_2$ as catalyst the reaction proceeds at 0 °C with a number of different propargyl sulfides **48** in 31–73% isolated yield. It is suggested that stable Fe · NBoc complex is formed, which reacts with sulfide to produce a sulfimide **49**. The latter rearranges to *N*-allenylsulfenimide **50** and liberates the iron catalyst to continue the catalytic cycle. The reaction is limited by product instability toward the iron catalyst and termination of the catalytic cycle by excess $BocN_3$, which leads to catalyst destruction.

3
[2,3]Sigmatropic Rearrangements Involving Sulfenates and Sulfoxides

3.1
Introduction

Since its discovery by Braverman and Stabinsky in 1967 [8], the [2,3]sigmatropic rearrangement of propargylic sulfenates to allenic sulfoxides, like the analogous rearrangement of propargylic sulfinates [6, 7], has become one of the best-known [2,3]sigmatropic rearrangements. Certainly, this is not only because of the considerable mechanistic and stereochemical interest involved,



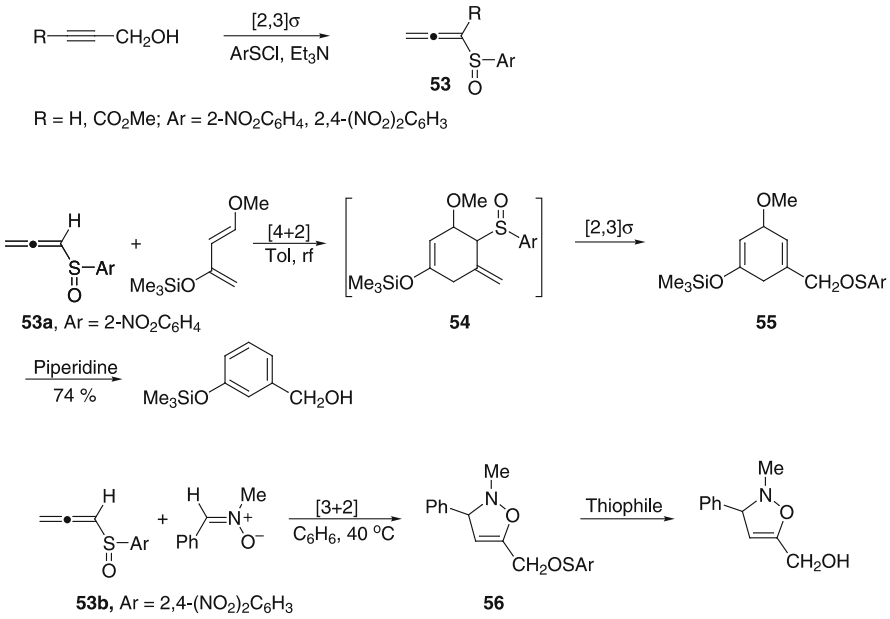
Scheme 12 [2,3]Sigmatropic rearrangement of propargylic trichloromethanesulfinates to allenic sulfoxides

but also because of its remarkable synthetic utility. Since this kind of sulfur-mediated rearrangement has been extensively reviewed by one of the present authors scanning the literature through 1988 [9, 12], only brief statements of the mechanistic aspects are presented here with special attention on recent synthetic achievements.

Braverman and Stabinsky [8] first reported that a number of propargyl trichloromethanesulfenates (**51**) are transformed spontaneously at low temperature to the corresponding allenyl trichloromethyl sulfoxides (**52**) (Scheme 12). This observation is suggestive of a concerted mechanism for this [2,3]sigmatropic rearrangement as well. The great enhancement in rate of rearrangement of propargyl sulfenates as compared with the corresponding sulfinates [6] is reasonably ascribed to the greater nucleophilicity of the sulfur atom in the first compounds. In support of the postulated concerted mechanism, it was subsequently shown [44] that treatment of (R)-(+)-α-methylpropargyl alcohol with *p*-toluenesulfenyl chloride in pyridine at – 75 °C gave (S)-(–)-γ-methylallenyl *p*-tolyl sulfoxide as predicted for a stereospecific suprafacial [2,3]sigmatropic shift.

3.2 Synthetic Utility of the Propargylic Sulfenate-to-Allene Sulfoxide Rearrangement

The synthetic utility of the [2,3]sigmatropic rearrangements of propargylic sulfenates has been further demonstrated in a variety of preparations and interesting reactions of allenyl sulfoxides. In one such preparation [45, 46], activated (nitroaryl)sulfinyl-substituted allenes (**53**), conveniently prepared by treating the corresponding propargyl alcohol or methyl 3-hydroxy-2-butynoate with (nitroaryl)sulfenyl chloride and Et_3N via spontaneous [2,3]sigmatropic rearrangement of the intermediate propargyl sulfenate, undergo [4 + 2] cycloaddition across the C_1C_2 π-bond. The initially formed allylic sulfoxide (**54**) readily undergoes a [2,3]sigmatropic rearrangement to produce a stable sulfenate ester (**55**) that is easily cleaved with thiophilic reagents (Scheme 13). The (2,4-dinitrophenyl)sulfinyl-substituted allene **53b** was found to react smoothly with a variety of nitrones to give sulfenate esters of isoxazolidine (**56**) (Scheme 13). These allenyl sulfoxides serve as formal

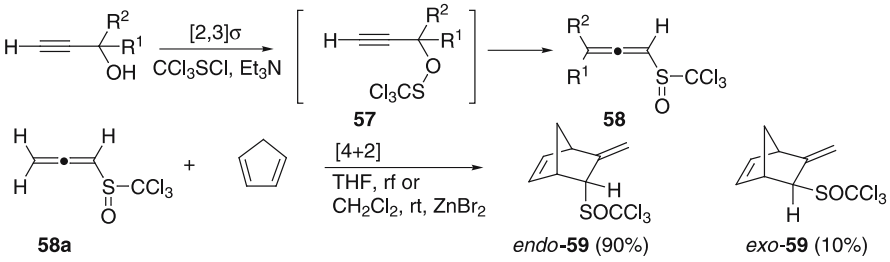


Scheme 13 [2,3]Sigmatropic rearrangements of nitroaryl propargyl sulfenates to allene sulfoxides and their cycloaddition reactions

equivalents of propargyl alcohols in both Diels–Alder and 1,3-dipolar cycloadditions. The dienophilic reactivity of the allenyl sulfoxides **53** is much greater than that of the corresponding alkyne and the cycloaddition also proceeds with high regioselectivity.

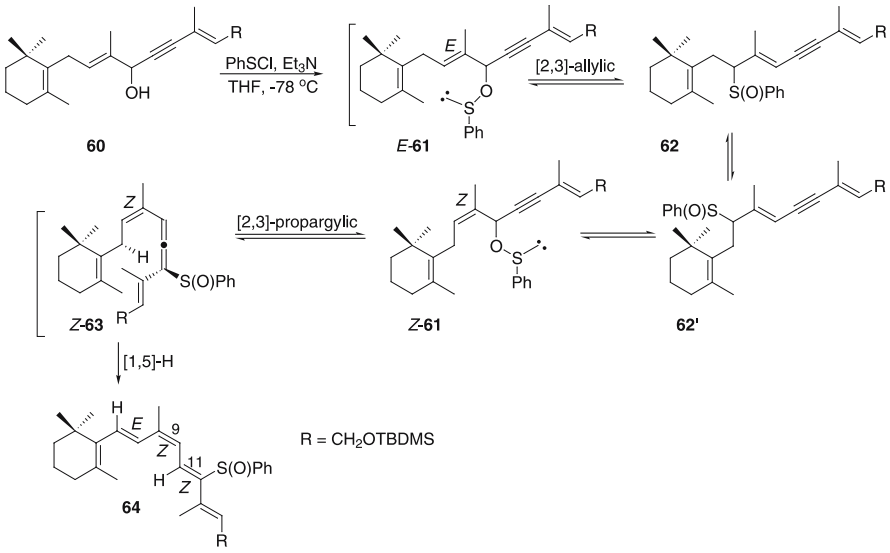
In a somewhat related approach, the dienophilic reactivity of allenes (**58**), obtained spontaneously by [2,3]σ rearrangement of the appropriate propargyl trichloromethanesulfenates (**57**) during its preparation from propargyl alcohol and trichloromethanesulfenyl chloride at 0 °C, is drastically increased by introduction of the powerful electron-withdrawing trichloromethylsulfinyl substituent [47]. Thus, the [4 + 2]-cycloaddition of trichloromethanesulfinylpropadiene (**58a**) proceeds in a highly regioselective fashion across the activated C_1C_2 π-bond. Reaction with cyclopentadiene in refluxing THF is complete after 2 h at atmospheric pressure to give the expected cycloadduct (**59**) as a mixture of *endo*- and *exo*-products [47] (Scheme 14). With the use of catalytic amounts of $ZnBr_2$ in dichloromethane, the reaction is complete after 1 h at room temperature.

[2,3]Sigmatropic rearrangement of propargylic sulfenates was a key step in the straightforward one-pot stereocontrolled synthesis of 9-*cis*-retinoids [48] (Scheme 15). A domino reaction that is pericyclic in nature is thought to be triggered upon treatment of alkenynol (**60**) with arylsulfenyl chlorides. The process comprises an ordered sequence of sigmatropic rearrangements:



a, R^1= R^2= H; **b**, R^1=H, R^2= Me; **c**, R^1= R^2= Me

Scheme 14 [4 + 2]Cycloaddition of trichloromethanesulfinylpropadiene



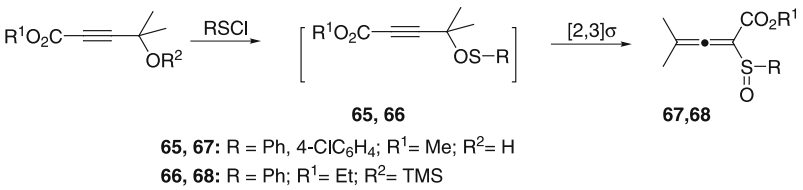
Scheme 15 One-pot stereocontrolled synthesis of 9-*cis*-retinoids via [2,3]sigmatropic rearrangement of propargylic sulfenates

a reversible [2,3]sigmatropic shift of allyl sulfenate (*E*-**61**) to allyl sulfoxide (**62**) (with concomitant double bond isomerization arising from conformer **62**′), followed by propargylic sulfenate to vinylallenyl sulfoxide [2,3]σ rearrangement from (*Z*-**61**) to provide (*Z*-**63**), and finally, irreversible doubly stereoselective [1,5]-sigmatropic hydrogen migration leading to polyene (**64**) (Scheme 15). Although vinylallenyl sulfoxide *Z*-**63** could not be isolated due to the facile [1,5]-H rearrangement induced by the sulfoxide group, its involvement was inferred from the stereoselective generation of the $C_{11} - C_{12}$ *Z*-olefin geometry as well as by the isolation of the similar allenyl phosphine oxides.

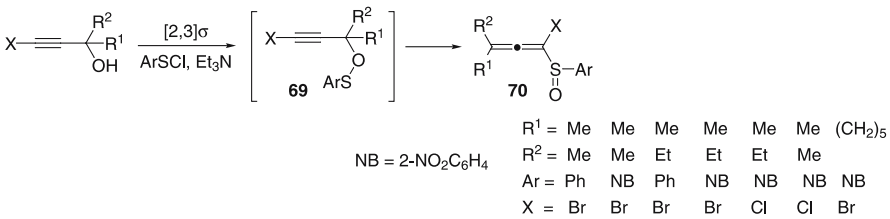
The [2,3]sigmatropic rearrangement of propargylic sulfenates can be applied for the preparation of a variety of functionalized allenes, not readily acceptable by other routs. Thus, a number of sulfinyl allenecarboxylates (**67**, **68**), as new 1,1-diacceptor-substituted allenes, were prepared via a [2,3]sigmatropic rearrangement of the corresponding sulfenate esters (**65**, **66**) (Scheme 16) [49, 50].

Similarly, 1-haloallenyl 1-sulfoxides (**70**) have been prepared by a spontaneous [2,3]sigmatropic rearrangement of the in situ generated corresponding alkynyl sulfenates (**69**) (Scheme 17) [51].

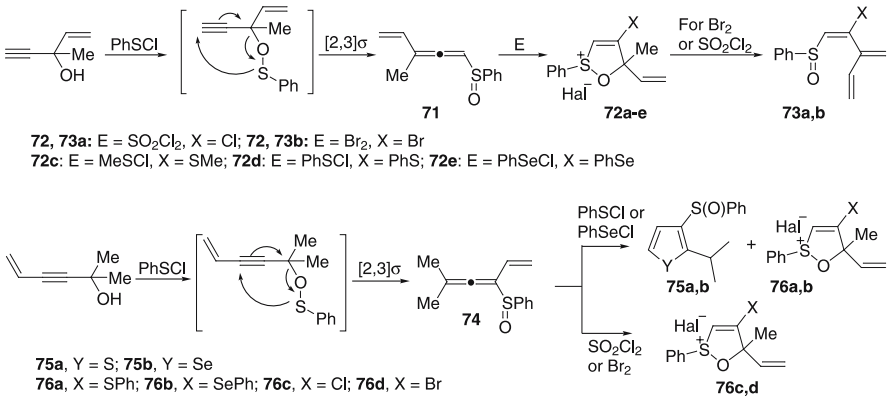
The sulfenate-to-sulfoxide sigmatropic rearrangement has also been explored for the preparation of alkatrienyl sulfoxides (**71**, **74**) [52, 53]. The latter undergo a five-membered heterocyclization in electrophile-induced reactions leading to the synthesis of either 5H-1,2-oxathiol-2-ium salts (**72**) and/or 1,4-pentadienyl phenyl sulfoxide derivatives (**73**). Alternatively, 3-(benzenesulfinyl)thiophene and -selenophene (**75**) and/or cyclic sulfoxonium salts (**76**) can be obtained, depending on the nature of the applied electrophile, as well as on the structure of the vinylallenes **71** and **74** (Scheme 18). Interestingly, while the electrophile-promoted cyclization of vinylallene **71** takes place exclusively by neighboring group participation of the sulfoxide group as an internal nucleophile, in the case of allene **74** two types of heterocyclization by neighboring group participation take place. The first one involves the vinyl group and leads to thiophene (selenophene) **75**, whereas the second involves the sulfoxide group and leads to cyclic sulfoxonium salts **76** (Scheme 18).



Scheme 16 Sulfinylallenecarboxylates via a [2,3]sigmatropic rearrangement of sulfenate esters



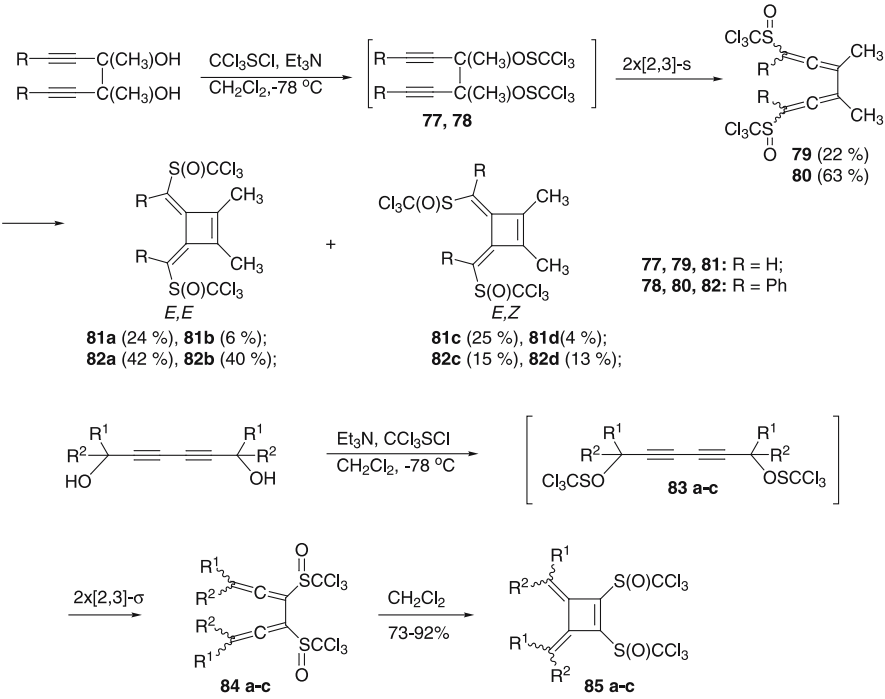
Scheme 17 1-Haloallenyl 1-sulfoxides via [2,3]sigmatropic rearrangement alkynyl sulfenates



Scheme 18 Alkatrienyl sulfoxides via sulfenate-to-sulfoxide sigmatropic rearrangement and their electrophile-induced reactions

3.3
Double Sigmatropic Rearrangements of Propargyl Sulfenates

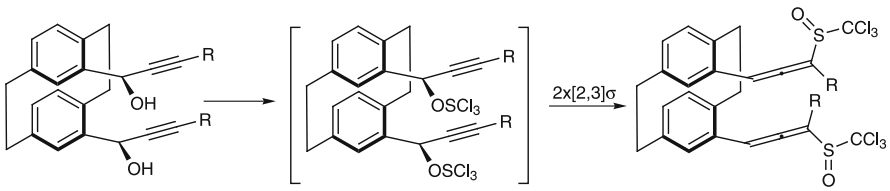
A double [2,3]sigmatropic rearrangement of bis(propargyl sulfenates) (**77**, **78**, **83a–c**) to bis(allenic sulfoxides) (**79**, **80**, **84a–c**) was shown to be a convenient and effective method for the preparation of conjugated diallene systems bearing two electron-withdrawing trihalomethyl sulfoxide substituents either on C-1 and C-6 (**79**, **80**), or on C-3 and C-4 (**84a–c**) [54] (Scheme 19). Thus, the reaction of the corresponding acetylenic diols with trichloromethanesulfenyl chloride in the presence of triethylamine at – 78 °C resulted in complete rearrangement of the first formed propargyl sulfenate esters **77**, **78** and **83** to diallenic disulfoxides **79**, **80** and **84** and in part, by subsequent cyclization, to the respective isomeric bis(methylene)cyclobutenes (BMCB) (**81**, **82**, **85**). However, if the reaction was carried out for 0.5 h at – 78 °C, followed by rapid work-up at 0 °C and trituration with hexane, it was possible to isolate conjugated bis-allenes **79**, **80** and **84b,c** as mixtures of stereoisomers, observed in their NMR spectra and expected from the stereochemical analysis based on the suprafacial nature of the [2,3]σ rearrangement [12], as well as on the assumption of the stereochemical independence of the two rearrangements due to the distance between two sulfoxide functions. In contrast to the high temperature Cope rearrangements that are commonly used to convert hexadiyne systems into conjugated diallenes and thereafter into BMCBs, this one-pot synthesis utilizes the convenient low-temperature conversion of readily accessible bis-propargylic sulfenates to conjugated bisallenic sulfoxides and subsequent rapid electrocyclization to BMCB bis-sulfoxides. Electron-withdrawing trihalomethyl sulfoxide substituents facilitate cyclization to bis(methylene)cyclobutenes (**81**, **82**, **85**) and stabilize the latter kinetically, and presumably also thermodynamically. The EWG substitution on



Scheme 19 Double [2,3]sigmatropic rearrangement of bis(propargyl sulfenates)

the exocyclic methylene extremities in compounds **81**, **82** proved more effective than similar substitution on the endocyclic double bond in **85**. Attempts at chromatographic separation of isomeric BMCB **85** lead to decomposition. The stereochemistry of **81** and **82** (Scheme 19), determined on the basis of X-ray structures and 2D-NMR analysis, are in keeping with expectations based on the known suprafacial nature of the [2,3]σ rearrangement of β,γ-unsaturated sulfenate esters [12], and the known conrotatory path of the ring closure of diallenes to BMCBs [55–58].

The double [2,3]sigmatropic rearrangement of propargylic sulfenates to the corresponding allenyl sulfoxides has also been applied to the synthesis of the first *pseudo-geminally*-substituted bisallenic [2.2]paracyclophane systems (**88**) [59]. Starting from the bis-propargylic alcohols (**86**) in a *meso*-form, the reaction proceeds easily at low temperature and produces *pseudo-geminal* bis-allenyl trichloromethyl sulfoxides **88** in good yields via rearrangement of the initially formed *pseudo-geminal* bis-propargylic trichloromethanesulfenates (**87**) (Scheme 20). Both bis-allenyl sulfoxides **88** have been obtained as mixtures of four inseparable diastereomers. Since upon oxidation of sulfoxides **88** with DMDO to the corresponding bis-allenyl sulfones, a single



86a, b **87a, b** **88a, b**

a, R = *n*-Pr, 84 %; **b**, R = *n*-Bu, 80 %.

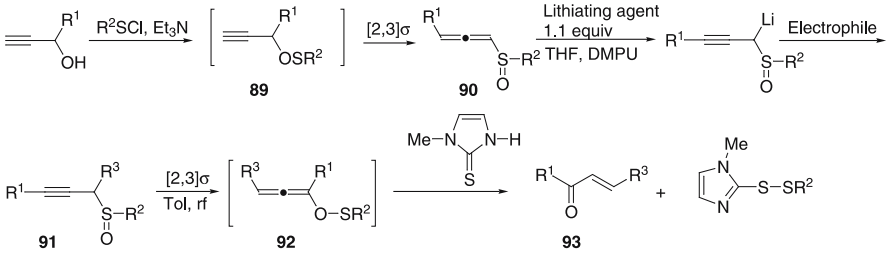
Scheme 20 *pseudo-geminally*-Substituted bisallenic [2.2]paracyclophane systems via double [2,3]sigmatropic rearrangement of propargylic sulfenates

compound was isolated, it has been concluded that all stereogenicity was due to two sulfoxide chiral centers in the starting material. To explain a reasonable stability of these symmetrical *pseudo-geminally*-substituted bisallenic [2.2]paracyclophanes, the less hindered *meso*-form, where the bulky trichloromethyl sulfone groups point away from the closest ethano bridge and allenic protons are located in the interannular space of the cyclophane core, are suggested.

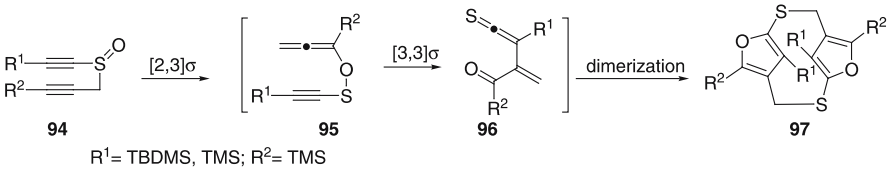
3.4
Propargylic Sulfoxide-to-Allenyl Sulfenate Rearrangement

Unlike the rearrangements of propargylic sulfenates to sulfoxides, the rearrangements of propargylic sulfoxides to allenic sulfenates has received relatively little attention, possibly due to instability of the latter. In one interesting application, such sulfoxide-to-sulfenate rearrangement has been involved in the synthesis of conjugated enones (**93**) [60, 61]. The reaction sequence includes first preparation of allenic sulfoxides (**90**) via [2,3]σ rearrangement of the appropriate propargylic sulfenates (**89**). Then, the γ-substituted allenic sulfoxides **90** are converted into the disubstituted propargylic sulfoxides (**91**) by deprotonation with methyl lithium or LDA and reaction with electrophilic reagents (primary alkyl halides or aldehydes) in the presence of DMPU. Smooth thermal [2,3]sigmatropic rearrangement of **91**, using 2-mercapto-1-methylimidazole as thiophilic reagent for trapping of the intermediate allenic sulfenate (**92**), yielded enones **93** (Scheme 21). Similar allenic benzenesulfenates have also been reported as reactive intermediates [62].

Propargylic sulfoxide-to-allenic sulfenate rearrangement is assumed to be involved in the reaction sequence leading to the formation of furanophane structures (**97**) [63]. Thermal reaction of alkynyl propargyl sulfoxides (**94**), derived by the oxidation of the corresponding sulfides possessing silyl groups at both terminals, affords a ten-membered cyclic structure **97** in moderate yield. This tandem transformation includes a [2,3]sigmatropic rearrange-



Scheme 21 Sulfoxide-to-sulfenate rearrangement in the synthesis of conjugated enones



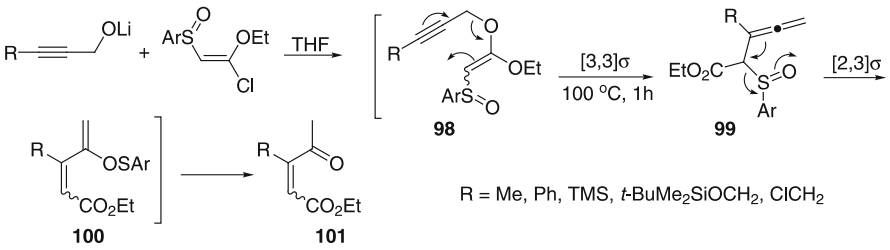
Scheme 22 [2,3]Sigmatropic rearrangement of propargylic sulfoxide to allenic sulfenate

ment of sulfoxide **94** to the allenic sulfenate **95**, followed by a [3,3]sigmatropic rearrangement to the thioketene (**96**) and dimerization of the latter to the furanophane **97** (Scheme 22).

3.5 Rearrangement of β-Allenic Sulfoxides

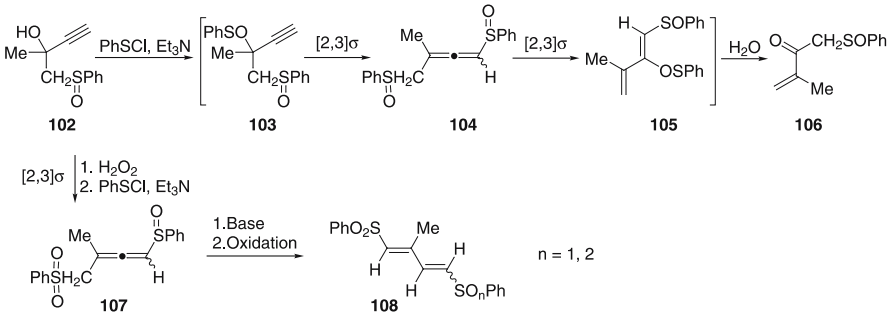
Posner was the first to exploit the potential of the [2,3]sigmatropic rearrangement in the context of β-allenic sulfoxides and apply this transformation to the one-pot synthesis of functionalized 4-oxo-2-alkenoate esters (**101**) [64]. Thus, both primary and secondary propargylic alcohols react with (arylsulfinyl)vinyl chloride at 100 °C for 1 h to give the corresponding 4-oxo-2-alkenoates **101** in good yields and as a mixture of *E* and *Z* isomers (Scheme 23). This one-pot conversion also involves several steps: replacement of chloride in sulfinyl vinyl chloride to produce ethers (**98**), [3,3]sigmatropic rearrangement of these propargylic ethers **98** to produce β-allenic sulfoxides (**99**), and, finally, transformation of the latter to the corresponding ketones **101**. The conversion of the intermediate β-allenic aryl sulfoxides **99** into 4-oxo-2-alkenoates **101** is presumed to proceed via [2,3]sigmatropic rearrangement of the allylic sulfoxide moiety of **99** to the intermediate vinyl sulfenate **100**, although attempts to intercept this diene intermolecularly or intramolecularly were unsuccessful.

A somewhat related [2,3]sigmatropic rearrangement of β-allenic sulfoxides to vinyl sulfenates has been reported by Padwa and coworkers [65].



Scheme 23 β-Allenic sulfoxides in the one-pot synthesis of functionalized 4-oxo-2-alkenoate esters

When β-benzenesulfinyl propargylic alcohol **102** was treated with benzenesulfenyl chloride and excess of triethylamine, enone **106** was isolated in 75% yield. The reaction proceeds via the initial formation of sulfenate **103**, which then undergoes the expected [2,3]sigmatropic rearrangement to produce β-allenic sulfoxide **104**. This transient species undergoes another [2,3]sigmatropic shift to form vinyl sulfenate **105**, which eventually hydrolyzes to enone **106** upon aqueous workup (Scheme 24). Interestingly, with β-benzenesulfonyl propargylic alcohols the reaction proceeds by an entirely different course. Oxidation of the sulfoxide moiety of β-benzenesulfinyl propargylic alcohols to sulfone, followed by sulfenate formation with benzenesulfenyl chloride, produces, after [2,3]sigmatropic rearrangement, γ-sulfonyl-substituted α-allenic sulfoxides (**107**). In certain cases these allenes could be isolated, but they were usually isomerized in situ with excess of base to the dienes (**108**) and further oxidized to give 1,4-bis(phenylsulfonyl)-1,3-butadienes (Scheme 24).



Scheme 24 [2,3]Sigmatropic rearrangement of β-allenic sulfoxides to vinyl sulfenates

4
[2,3]Sigmatropic Rearrangements Involving Sulfinates and Sulfones

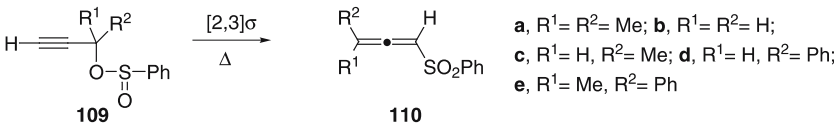
[2,3]Sigmatropic rearrangements of propargylic sulfinates to allenic sulfones have been widely studied and are well documented [10, 11], covering the most significant aspects and most important advances through the late 1980s.

4.1
Mechanistic Aspects

Braverman and coworkers [66] were the first to report that propargyl arenesulfinates rearrange to allenyl aryl sulfones (Scheme 25). Thus, α,α-dimethylpropargyl benzenesulfinate (**109a**) undergoes facile thermal rearrangement to γ,γ-dimethylallenyl phenyl sulfone (**110a**) with high yield even under solvolytic conditions (Scheme 25). Detailed mechanistic studies [6, 7] revealed low sensitivity of the rate of rearrangement to the change in ionizing power of the solvent and substituent effect. In the light of this evidence and a negative value of the entropy of activation ($\Delta S^{\ddagger} = -12.8$ eu) obtained for the reaction of **109a** in acetonitrile, the authors [6, 7, 66] suggested a concerted mechanism for this rearrangement.

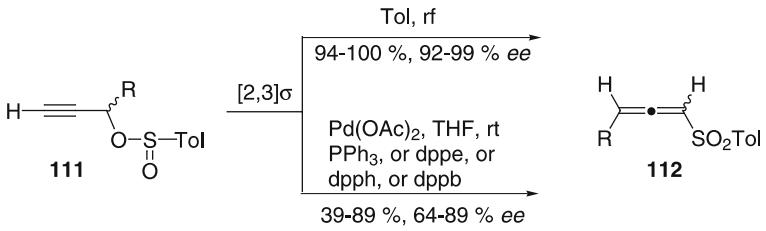
The suggested mechanism is also supported by the work of Stirling and Smith [44, 67], who reported that γ-deuteriopropargyl *p*-toluenesulfinate rearranged to α-deuterioallenyl *p*-tolyl sulfone on heating at 130 °C, and that under similar conditions R-(+)-α-methylpropargyl *p*-toluenesulfinate rearranged to (–)-γ-methylallenyl *p*-tolyl sulfone whose absolute configuration, predicted on the basis of a concerted mechanism, agrees with the calculated from the polarizability sequence of substituents attached to the allene system.

Diastereomerically pure 2-alkynyl *p*-toluenesulfinates (**111**), possessing chirality on both the α-carbons of the 2-alkynyl groups and the sulfur atoms of the sulfinates, were transformed into chiral allenyl sulfones (**112**) with high stereospecificity in almost quantitative yields under heating at reflux in toluene. It was also shown that the rearrangement could be facilitated by applying palladium catalysts. Thus, treatment of sulfinates **111** with palladium acetate in the presence of phosphine ligands at room temperature gives both enantiomers of optically active sulfonyl allenes **112**, but in somewhat lower chemical and optical yields than those of thermal rearrangement (Scheme 26) [68, 69]. A plausible mechanism for the palladium-catalyzed



109 **110**

Scheme 25 [2,3]Sigmatropic rearrangement of propargyl benzenesulfinates

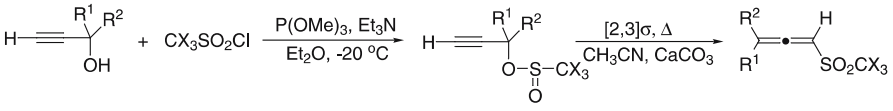


Scheme 26 Palladium-catalyzed asymmetric transformation of chiral 2-alkynyl sulfinates into allenyl sulfones

transformation includes a five-membered-like palladium-containing cyclic intermediate.

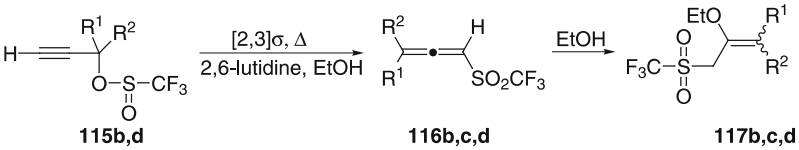
Similar to propargyl arenesulfinates, but unlike allylic trichlinates [70], propargyl trihalomethanesulfinates (trichlinates **113** and triflinates **115**) undergo full [2,3]sigmatropic rearrangement to allenyl trihalometanesulfones (**114**, **116**) [70–72]. Sulfinates **113** and **115** have been obtained by the reaction of the appropriate propargyl alcohol with trihalomethanesulfinyl chloride generated in situ by reduction of the corresponding sulfonyl chloride with trimethyl phosphite at – 20 °C [73]. Interestingly, α-methyl-α-phenylpropargyl esters **113c** and **115c** could not be isolated because of spontaneous low temperature rearrangement to γ-methyl-γ-phenylallenyl trichlone **114c** [70] and triflone **116c** [71], respectively, as expected from a concerted [2,3]sigmatropic shift (Scheme 27). Furthermore, the rearrangement of optically active trichlinate **113a** affords optically active γ-methylallenyl trichlone **114a**, when conducting in toluene [70].

The rate of rearrangement of triflinate **115b** in acetonitrile at 40 °C is twice as rapid as in chloroform [71]. This result is similar to that found for propargylic arenesulfinates [6]. The low sensitivity to solvent ionizing power can also be used as evidence for a concerted [2,3]sigmatropic shift for the rearrangement. Similarly, the exclusive rearrangement of these esters to allenic products may also be used as evidence for such a mechanism. Interestingly, the comparison of the reactivity of triflinate **115b** [71] and benzenesulfinate



113, 114: a, R^1= H, R^2= Me; **b**, R^1= R^2= Me; **c**, R^1= Ph, R^2= Me;
115, 116: a, R^1= H, R^2= Me; **b**, R^1= R^2= Me; **c**, R^1= Ph, R^2= Me; **d**, R^1= Me, R^2= Et

Scheme 27 Synthesis and [2,3]sigmatropic rearrangement of propargyl trihalomethyl sulfinates



Scheme 28 Propargyl trifluoromethanesufinates under solvolytic conditions

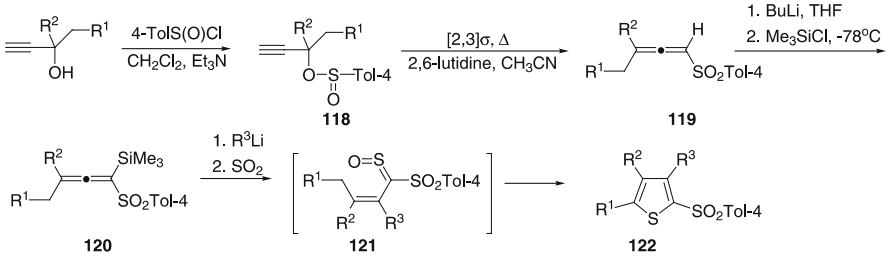
109a [6] shows that the former is faster by a factor of about five. In fact, the decreased nucleophilicity of the sulfur atom in the triflinates might be expected to decrease the rate of the concerted rearrangement. However, since precisely the same shift also involves cleavage of a better leaving group in the transition state, this may compensate in the opposite direction. For comparison, substitution of the aryl group by a trichloromethyl group in the case of benzylic sulfinates results in a much higher rate enhancement, for both solvolysis and rearrangement to sulfone, which proceed by an ionic mechanism [74–76].

It should be noted that even under solvolytic conditions (heating at 60 °C in ethanol) esters **115b** and **115d** undergo rearrangement and yield β-ethoxy allyl triflones **117**, produced by the rearrangement to allenic triflones **116b** and **116d**, followed by nucleophilic addition of ethanol to the allenic β-carbon (Scheme 28) [71]. Similarly, γ-methyl-γ-phenylallenyl triflone **116c**, when tested under the same conditions, also affords the corresponding product of nucleophilic addition **117**, obtained as a mixture of *E* and *Z* isomers in the ratio of 1 : 1.5 (Scheme 28).

4.2
Synthetic Utility of the Propargylic Sulfinate-to-Sulfone Rearrangements

The synthetic utility of the [2,3]sigmatropic rearrangement of propargylic sulfinates has been demonstrated in a variety of preparations and reactions of allenyl sulfones. In one such preparation [77] allenyl sulfones (**119**), synthesized by [2,3]sigmatropic rearrangement of the appropriately substituted prop-2-ynyl sulfinates (**118**), have been applied to the synthesis of 2-sulfonylthiophenes (**122**) via intermediate formation of α,β-unsaturated sulfines (**121**) (Scheme 29). The treatment of the allenyl sulfones **119** with BuLi and chlorotrimethylsilane gives α-silylated allenyl sulfones (**120**) in almost quantitative yield, which, on heteroconjugate addition of organolithium reagents, gives the desired α-silyl carbanions. These reacted with sulfur dioxide to give the α,β-unsaturated sulfines **121**, which underwent in situ rearrangement to 2-sulfonylthiophenes **122**. The yield of the thiophenes depended on the organolithium reagents used.

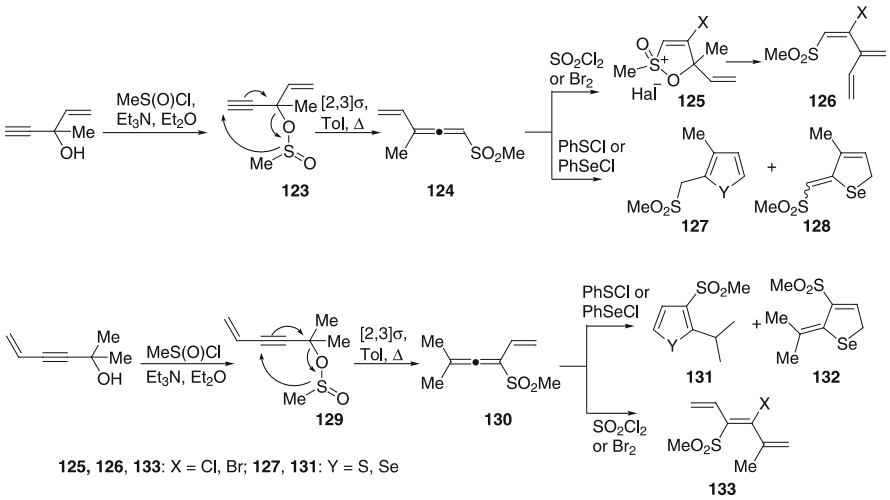
The sulfinate-to-sulfone sigmatropic rearrangement has also been employed for the preparation of alkatrienyl sulfones (**124, 130**) [78, 79]. Electro-



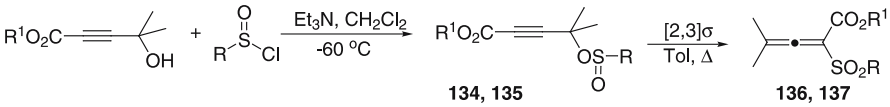
Scheme 29 Synthesis of 2-sulfonylthiophenes via [2,3]sigmatropic rearrangement of prop-2-ynyl sulfinates

phile-induced reactions of thus obtained vinylallenyl sulfones **124** and **130** occur in different pathways depending on the electrophiles (Scheme 30). Halogenation leads to formation of halotrienes (**126**) and (**133**), respectively, and probably proceeds through cyclic sulfoxonium salts (e.g., **125**). Reactions with benzenesulfenyl and benzeneselenenyl chlorides afford only heterocyclic products (**127**, **128** and **131**, **132**) via electrophile-promoted cyclization by neighboring participation of the $C_4 - C_5$ double bond and ring closure.

A further application of the [2,3]sigmatropic rearrangement of propargylic sulfinates involves the preparation of a variety of functionalized allenes, hardly accessible by other routes. Thus, a number of sulfonylallenecarboxylates (**136**, **137**), as new 1,1-diacceptor-substituted allenes, were prepared via a [2,3]sigmatropic rearrangement of the corresponding sulfinate esters (**134**, **135**) (Scheme 31) [49, 50].



Scheme 30 Synthesis and electrophile-induced reactions of alkatrienyl sulfones



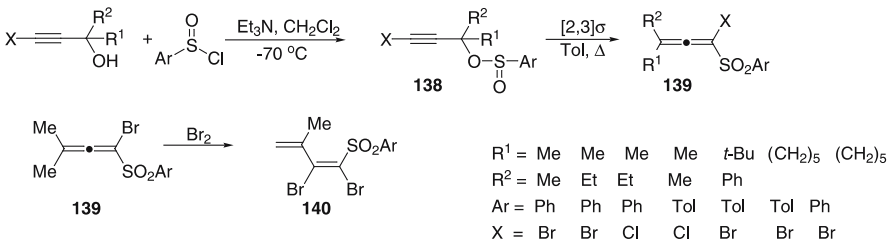
134, 136 : R = Ph, 4-ClC_6H_4, Me; R^1= Me;
135, 137 : R = CCl_3; R^1= Et;

Scheme 31 Sulfonylallenecarboxylates via [2,3]sigmatropic rearrangement

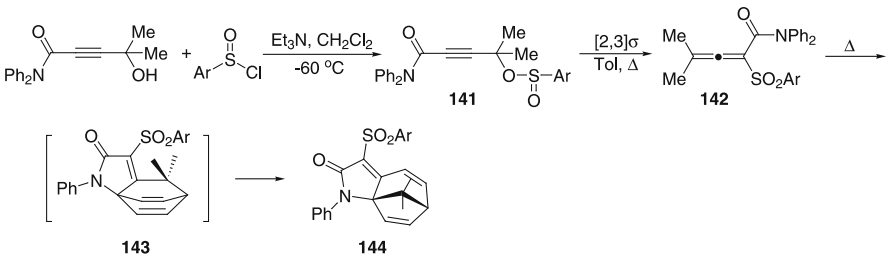
Similarly, 1-halo-1-sulfonylallenes (**139**) have been prepared by heating in toluene at 80 °C of propargyl esters (**138**) via [2,3]sigmatropic rearrangement of the latter (Scheme 32) [51]. 1-Bromo-1-sulfonylallenes **139**, when treated with bromine, undergo attack on central allenic carbon with formation of intermediate carbenium bromide followed by hydrogen bromide elimination, and afford stereospecifically the 2,3-dibromo-1-sulfonyl-1,3-dienes **140**.

In another interesting application, thermal [2,3]sigmatropic rearrangement of sulfinic ester **141** affords *N*,*N*-diphenyl-1-sulfonylallene carboxanilide **142**. On heating the latter undergoes intramolecular Diels–Alder reaction of the terminal allenic double bond and one of the *N*-phenyl rings acting as a diene, affording intermediate [2.2.2]bicycle **143**, which isomerizes to the [3.2.1]bicycle **144** [80] (Scheme 33).

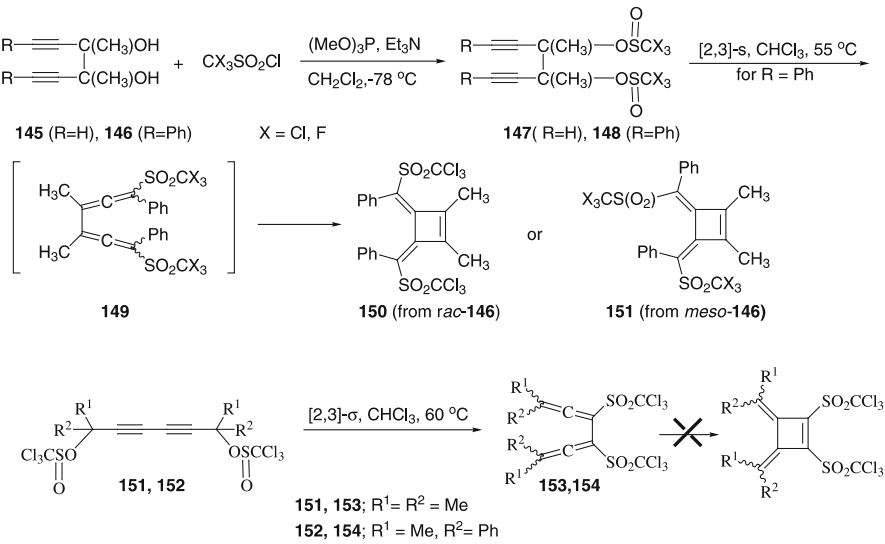
Double [2,3]sigmatropic rearrangements of bis(propargyl sulfinates) (**147**, **148** and **151**, **152**) to bis(allenic sulfones) (**149** and **153**, **154**) are found



Scheme 32 1-Halo-1-sulfonylallenes via [2,3]sigmatropic rearrangement



Scheme 33 Synthesis and IMDA of *N*-phenyl-1-sulfonylallene carboxanilide

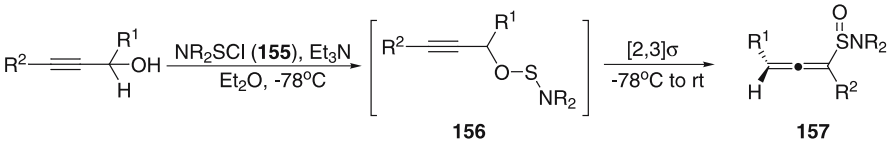


Scheme 34 Double [2,3]sigmatropic rearrangements of bis(propargyl sulfinates)

to be a convenient and effective method for the preparation of conjugated diallene systems bearing two electron-withdrawing trihalomethyl sulfone substituents either on C-1 and C-6 (**149**), or on C-3 and C-4 (**153**, **154**) (Scheme 34) [54]. Such substituents are shown to facilitate cyclization to bis(methylene)cyclobutenes (BMCB), and to stabilize the latter. Thus, it required heating at ~ 55 °C in chloroform solution to complete rearrangement of sulfinates **148**. However, the formation of intermediate allenes **149** could only be detected by NMR spectroscopy because of their rapid cyclization to BMCBs **150** and **151**. Interestingly, sulfinate **147** did not undergo the [2,3]sigmatropic rearrangement in refluxing chloroform. Refluxing in acetonitrile caused decomposition. Obviously the stabilizing effect of the phenyl substituent on the transition state is necessary in these cases to reduce the temperature required for rearrangement below the decomposition temperature. Similarly, the rearrangement of sulfinates **151** and **152** to the corresponding conjugated diallenyl sulfones **153** and **154**, respectively, has been achieved by heating in diluted chloroform solution at 60 °C. However, unlike the diallenyl sulfones **149**, diallenyl sulfones **153** and **154** do not cyclize to BMCBs, most probably due to the steric hindrance arising from the two bulky *cis* 1,2-bis(trichloromethylsulfonyl) substituents.

5
[2,3]Sigmatropic Rearrangements Involving Sulfinamides and Amidosulfenates

Similar to propargylic sulfenates, propargylic amidosulfenate esters undergo facile [2,3]sigmatropic rearrangement to the corresponding allenyl sulfinamide. Thus, several substituted propargylic alcohols have been converted into the corresponding allenic sulfinamides (**157**) by the reaction with *N*,*N*-dialkylamido sulfenyl chloride (**155**) in the presence of triethylamine (Scheme 35) [81, 82]. The reaction proceeds with good chemical yields, but low diastereoselectivity to give the allenes **157** as a mixture of diastereomers, whose ratios have been detected by ^{1}H NMR spectroscopy and depend essentially on the size of the substituents of the propargyl alcohols as well as of sulfenyl chloride **155**. As can be seen from the data of Table 3, the larger *N*,*N*-



Scheme 35 [2,3]Sigmatropic rearrangement of propargylic amidosulfenates to allenyl sulfinamides

Table 3 [2,3]Sigmatropic rearrangement of propargylic amidosulfenates to allenyl sulfinamides

Entry	R^1	R^2	R_2	Yield of **157** (%)	Diastereomers ratio [a]	Refs.
1	Me	Me	Me	66	60 : 40	[82]
2	Me	Me	$[(CH_2)_2]_2O$	98	65 : 35	[82]
3	Me	Me	*i*-Pr	72	70 : 30	[82]
4	*n*-C_7H_{15}	Me	Me	31	65 : 35	[82]
5	*n*-C_7H_{15}	Me	$[(CH_2)_2]_2O$	75	75 : 25	[82]
6	*n*-C_7H_{15}	Me	*i*-Pr	57	80 : 20	[82]
7	*n*-C_7H_{15}	*i*-Pr	$[(CH_2)_2]_2O$	77	75 : 25	[82]
8	*n*-C_7H_{15}	*t*-Bu	$[(CH_2)_2]_2O$	85	75 : 25	[82]
9	*i*-Pr	Me	Me	41	75 : 25	[82]
10	*i*-Pr	Me	$[(CH_2)_2]_2O$	77	60 : 40	[82]
11	*i*-Pr	Me	*i*-Pr	72	> 95 : 5 <	[82]
12	*t*-Bu	Me	Me	55	70 : 30	[82]
13	*t*-Bu	Me	$[(CH_2)_2]_2O$	76	85 : 15	[82]
14	*t*-Bu	Me	*i*-Pr	48	> 95 : 5 <	[82]

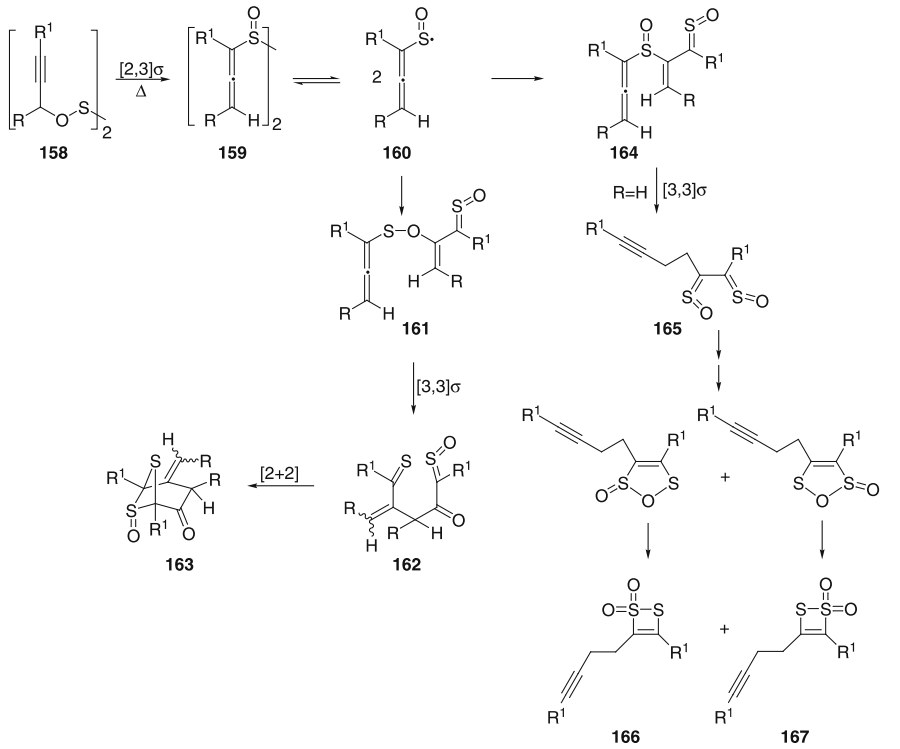
[a] Determined by ^{1}H NMR.

diisopropyl group leads to the best diastereoselectivity. The rearrangement becomes highly stereoselective when both substituents R^1 and R are large (Table 3, entries 11, 14). When the substituents on nitrogen in **155** are small or medium-sized (methyl or morpholine), the rearrangement of the intermediate *N*,*N*-dialkylamidosulfenate esters (**156**, $R_2 = Me_2$, morpholine) are fast (1–2 h) in contrast to the *N*,*N*-diisopropylsulfenate esters (**156**, $R_2 = i$-Pr), which required 24–48 h for complete conversion [82].

6
[2,3]Sigmatropic Rearrangements of Alkoxy Disulfides

The [2,3]sigmatropic rearrangement was found to be a key step in an unprecedented transformation of bis-propargylic dialkoxy disulfides to 6,7-dithiabicyclo[3.1.1]heptane-2-one 6-oxide derivates (**163**), which are structurally related to the zwiebelanes, first isolated from freshly cut onion by Block [83]. Bis-propargylic dialkoxy disulfides (**158**) have been recently prepared in high yields (91–98%) and proved to be stable in chloroform solution at – 18 °C for extended periods of time [84]. Under heating in chloroform, compounds **158** undergo a sequence of several [2,3]- and [3,3]sigmatropic shifts followed by an intramolecular [2 + 2] cycloaddition and afford a mixture of novel complex products (Scheme 36) [84, 85]. Investigation of the reactivity of various γ- and α-substituted bis-propargylic dialkoxy disulfides **158** under mild thermal conditions revealed that the behavior of these novel compounds is strongly dependent on the nature and position of substituents. Thus, heating of dialkoxy disulfides **158a–d** afforded the novel 6,7-dithiabicyclo[3.1.1]heptane-2-one 6-oxide derivates **163a–d** (30–65% isolated yield, Scheme 35). For unsubstituted dipropargyloxy disulfide **158e**, formation of **163e** was accompanied by two isomeric α,β-unsaturated four-membered cyclic thiosulfonates **166e** and **167e**. Substitution at the γ-position of the propargyl moieties significantly affected the ratio of the products. A tentative reaction mechanism is presented in Scheme 36.

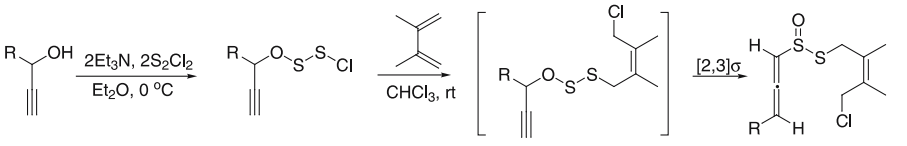
First, a double [2,3]sigmatropic rearrangement converts dipropargyloxy disulfide **158** to *vic*-disulfoxide **159**, which dissociates to two allenesulfinyl radicals, **160**. Recombination of two such radicals via the sulfinyl oxygen of one and C-2 of the other gives **161**, which converts to **163** by tandem [3,3]sigmatropic rearrangement (**161** → **162**) and [2 + 2] cycloaddition (**162** → **163**). Alternatively, two radicals **160** recombine via the sulfinyl sulfur of one and C-2 of the other to yield **164**. The [3,3]sigmatropic rearrangement **164** produces the disulfine **165**, intramolecular disproportionation of which (in a manner analogous to that found in the intermolecular dimerization of sulfines [83] and in the conversion of α-disulfoxides to thiosulfonates [86, 87]) leads to **166** and **167**.



a, R = Me, R^1 = H; **b**, R = $CHPh_2$, R^1 = H; **c**, R = H, R^1 = Me; **d**, R = H, R^1 = Ph; **e**, R = R^1 = H; **f**, R = H, R^1 = CH_3CH_2; **g**, R = H, R^1 = *t*Bu; **h**, R = H, R^1 = Me_3Si

Scheme 36 [2,3]Sigmatropic rearrangement of bis-propargylic dialkoxy disulfides

[2,3]Sigmatropic rearrangement of monoalkoxydisulfides is involved in the reaction sequence leading to the mixed allyl allenethiosulfinates [88]. On a first step, unstable propargyloxy chlorodisulfides (**168**) are prepared by the addition of an ether solution of the appropriate propargyl alcohol to a mixture of two equivalents of triethylamine and S_2Cl_2 in ether under high dilution conditions. Facile 1,4-electrophilic addition of **168** to 2,3-dimethyl-1,3-butadiene, followed by [2,3]sigmatropic rearrangements of the interme-



R = Me, Et, *n*-C_5H_{11}, *i*-Pr, *i*-Bu, neopentyl

Scheme 37 [2,3]Sigmatropic rearrangement of monoalkoxydisulfides

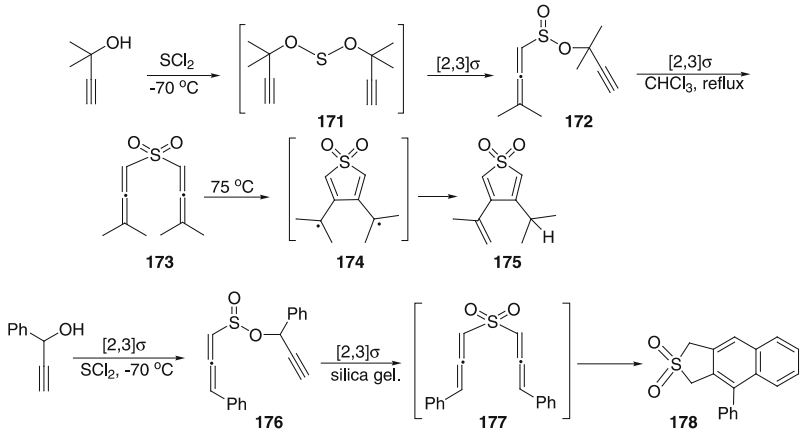
diate propargyloxy disulfide (**169**), affords allyl allenethiosulfinates (**170**) as a mixture of diastereomers (Scheme 37).

7
[2,3]Sigmatropic Rearrangements of Propargylic Sulfoxylates

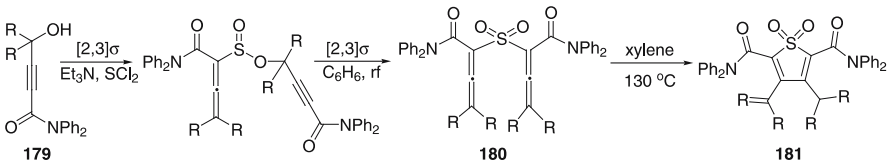
The double [2,3]sigmatropic rearrangement of bis-propargylic sulfoxylate ester (**171**) to bis-γ,γ-dimethylallenyl sulfone (**173**) (Scheme 38) discovered by the present author three decades ago [89] can be regarded as a natural extension of the above mentioned [2,3]sigmatropic rearrangements of propargylic sulfenates and sulfinates. While rearrangement of **172** requires moderate heating for several hours, the rearrangement of its sulfoxylate precursor **171** proceeds spontaneously at low temperature. Diallenyl sulfone **173** further undergoes a quantitative cyclization on heating in chloroform to the thiophene-1,1-dioxide derivative **175** via a 2,2′-bisallyl-type diradical **174.**

Similarly, bis-allenyl sulfones (**180**), prepared in an analogous way from alkynol *N*-phenylanilides (**179**) undergo thermal cyclization to the corresponding thiophene 1,1-dioxides (**181**) on heating in xylene at 130 °C (Scheme 39) [51]. However, when double [2,3]sigmatropic rearrangement of the corresponding sulfoxylate ester was applied for the preparation of bis-γ-phenylallenyl sulfone **177**, the latter could not be isolated since, during attempted isolation and purification by column chromatography of the precursor **176**, a spontaneous tandem rearrangement, cyclization, and aromatization to the naphthalene derivative **178** took place (Scheme 38) [90].

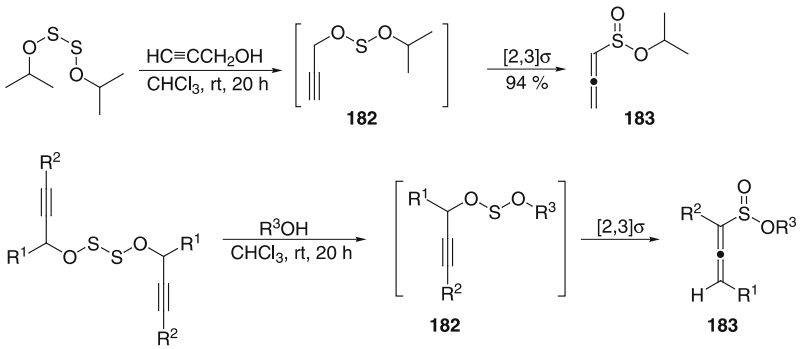
Finally, mixed alkyl propargyl sulfoxylates (**182**) also undergo spontaneous [2,3]sigmatropic rearrangement and produces mixed alkyl allenesulfinates



Scheme 38 Tandem [2,3]sigmatropic rearrangement/cyclization of bis-propargylic sulfoxylate



Scheme 39 Double [2,3]sigmatropic rearrangement of sulfoxylate esters



Scheme 40 [2,3]Sigmatropic rearrangement of mixed alkyl propargyl sulfoxylates

(**183**), which are not readily available by other routes, in good yield [91]. Mixed sulfoxylates **182** have been prepared in situ by a new, general, and efficient method via treatment of symmetrical saturated dialkoxy disulfides with propargyl alcohols at room temperature, or alternatively, by the reaction of substituted propargylic dialkoxy disulfides with saturated alcohols (Scheme 40).

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Top Curr Chem (2007) 275: 103–129
DOI 10.1007/128_059

Published online: 29 July 2006

Sulfur Participation in [3,3]-Sigmatropic Rearrangements

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Abstract The thio-Claisen rearrangement is a general and facile process that is often advantageous over the standard Claisen rearrangement. Several asymmetric variants of the thio-Claisen rearrangement have been reported. The rearrangement of sulfonium salts and sulfoxides takes place even more readily. Alkenyl sulfoxides and sulfilimines undergo a highly stereocontrolled cyclization to lactones and lactams, respectively, upon reaction with haloketenes; this synthetically useful process entails a [3,3]-sigmatropic rearrangement of a zwitterionic intermediate. Sulfur-containing functionalities located at the periphery of the Claisen substrates exert a powerful influence on the outcome of the process.

Keywords Sulfur · [3,3]-sigmatropic rearrangements · Thio-Claisen · Sulfoxides · Sulfilimines

1 Introduction

This review aims to summarize and update the various roles exerted by sulfur-containing functionalities in [3,3]-sigmatropic rearrangements. Some of the subject matter discussed herein has been reviewed before [1–5], therefore, we have made an effort to discuss in depth just the more recent results, as well as mechanistically related transformations that were not included in previous reviews on Claisen and thio-Claisen rearrangements.

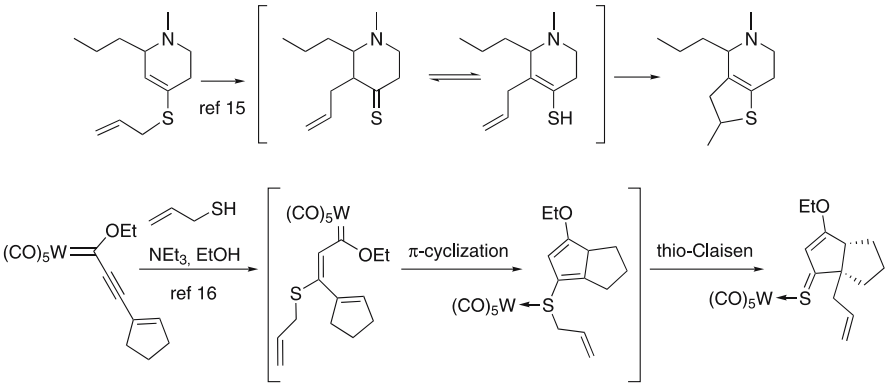
2
Thio-Claisen Rearrangement of Allyl Vinyl Sulfides and Related Compounds

The thio-Claisen rearrangement is a general process that has served for the formation of new carbon–carbon bonds in a great variety of compounds. Numerous studies were directed to establish the mechanism and scope of the rearrangement of allyl vinyl sulfides (Scheme 1) and their conclusions are gathered in different publications [6–9]. In terms of kinetics, the thio-Claisen rearrangement ($\Delta H^{\neq}$ close to 20 kcal/mol) is more favored than the oxy-Claisen rearrangement [6], mainly due to the weaker character of the C – S bond (65 kcal/mol) compared to the C – O bond (85 kcal/mol). In contrast, the sulfur-containing rearrangement is in general less exothermic than the oxy-Claisen [7] and structural factors such as conjugation and strain will drive the equilibrium to the thio-Claisen side (thiocarbonyl compound) or to the retro-Claisen side (allyl vinyl sulfide). In fact, some examples of retro thio-Claisen rearrangement, also referred as thia-Cope, have been studied [10–13].

Simple allyl vinyl sulfides are commonly available from thio-carbonyl compounds by base-induced *S*-allylation [6]; however other methods have been reported such as addition of the lithium carbanion of diethyl allylthiomethylphosphonate to a ketone [14]. Frequently, the final γ,δ-unsaturated thiocarbonyl compound undergoes tautomerization and the transient enethiol cyclizes onto the new double bond generating sulfur-containing heterocycles. This has been observed in the synthesis of functionalized piperidines [15]. Recently the group of Aumann has examined the behavior of allyl vinyl sulfides containing Fisher carbenes [16]. Thus, the addition of allylthiol to alkynyl carbene tungsten complexes containing a cycloalkene fragment afforded cyclopentene-1-thione tungsten complexes, which are stable to be isolated by chromatography on silica gel since the $W(CO)_5$ fragment acts as protecting group of the α, β-unsaturated thiocarbonyl moiety. Probably, the process takes place by nucleophilic addition of sulfur onto the alkyne followed by π-cyclization and finally a thio-Claisen rearrangement that places the allyl group attached to the bridge carbon atom (Scheme 2).

Base-induced *S*-allylation of dithioesters [17, 18], thionoselenoesters [19] as well as tertiary thioamides [20–23] with allylic halides and alcohols [24] have been commonly used to generate *S*-allyl ketene-*S*,*W*-acetals (W = S, Se, N), which are prone for a thio-Claisen rearrangement. In fact, the marked trend of the starting thiocarbonyl compounds to render the *cis*-

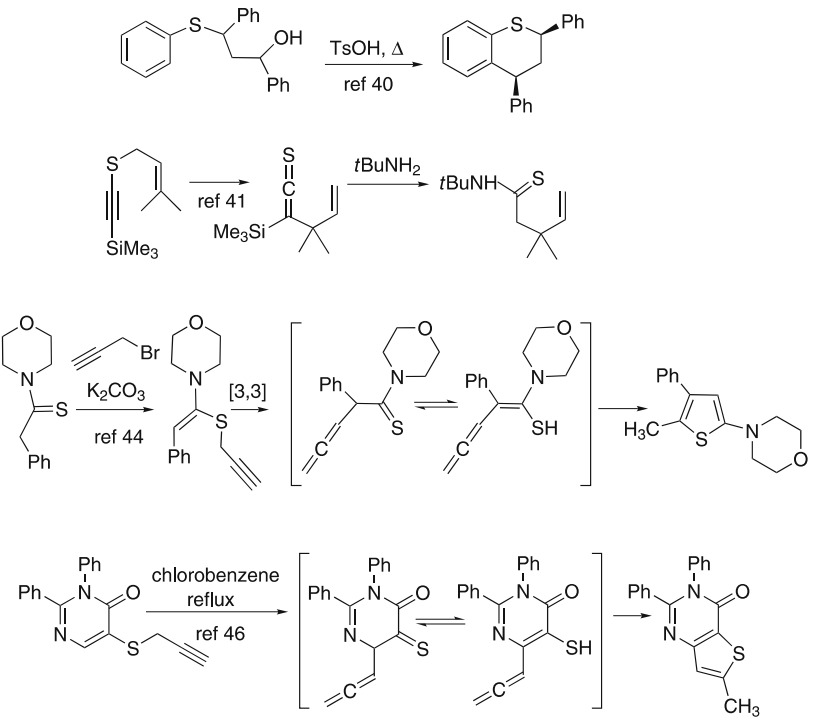
Scheme 1



Scheme 2

thienolate upon deprotonation is responsible of the stereoselectivity found in the thio-Claisen rearrangement [25–28].

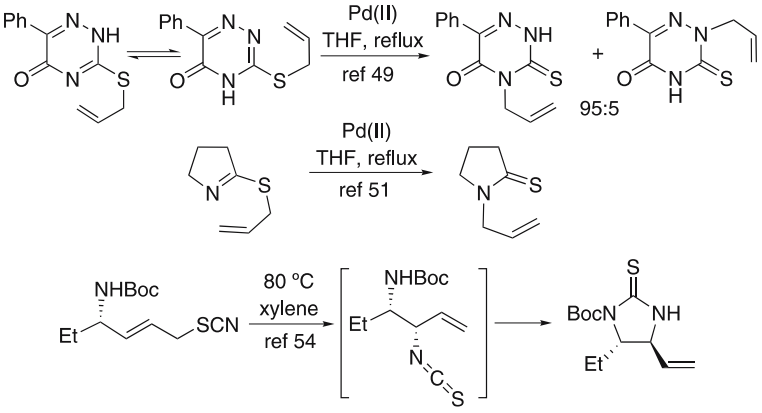
The thio-Claisen rearrangement also takes place when the nature of the unsaturations of the carbon-chain is modified. One of the most important versions of the thio-Claisen rearrangement comes from changing the vinyl group by an aromatic group. In fact, the early studies in this field were focused on the aromatic thio-Claisen rearrangement [29, 30]. The pyrolysis of allyl aryl sulfides, prepared from allyl bromide and the sodium salt of the arylthiol, was independently studied by Hurd and Karaulova affording *o*-allylthiophenols through an aromatic thio-Claisen rearrangement along with undetermined amounts of a cyclization product whose structure was a matter of controversy. Later in the early 1960s, Kwart and Meyers independently reported that after the [3,3]-sigmatropic rearrangement the formation of a dihydrobenzothiophene or a thiochroman as a major product can take place depending on the isolation procedures [31, 32]. Since then, a good number of studies have been published [33, 34] dealing with the mechanism and the nucleophilic triggering of the [3,3]-sigmatropic rearrangement. The structural scope of the aromatic thio-Claisen has also been studied by several groups. The aromatic group can be modified by bearing different substituents [33] or be changed by heteroaromatic groups such us indoles [35, 36] and quinolines [37–39] among others. One of the more recent contributions [40] in the aromatic thio-Claisen describes the formation of the thiochroman ring system by heating 3-thiophenyl-1-propanols or 4-thiophenyl-2-butanols in toluene with catalytic amounts of *p*-toluenesulfonic acid, generated from sulfur stabilized carbanions and epoxides. However, apparently this time the process involves an intramolecular electrophilic aromatic substitution rather than the sequential thio-Claisen/cyclization commonly proposed (Scheme 3).



Scheme 3

Beyond aromatic and heteroaromatic substrates, other structural modifications can be introduced. Thus, the vinyl fragment can be substituted by an alkyne [41] and the allyl fragment can be replaced by an allenyl group [42] or a propargyl group [43–45] and in these cases after the [3,3]-sigmatropic rearrangement and tautomerization of the resulting thione, the cyclization onto the allene renders thiophene rings. Recent contributions are due to the group of Mahajan [46] and Majumdar [47] in the context of synthesis of heterocycles. Two examples are gathered in Scheme 3.

In addition, some reports describe the polyhetero-Claisen rearrangement of systems containing more that one heteroatom (Scheme 4). In 1974, Balasubramanian [48] examined the thio-Claisen rearrangement of 2-propargylthio benzimidazoles and then in 1983 Sanemitsu described a parallel sigmatropic rearrangement in triazines gathered in Scheme 4 [49]. In both cases the vinyl fragment is replaced by a C – N double bond as part of a heterocyclic unit. The retro thio-Claisen rearrangement has also been observed in related heterocyclic systems [50]. *S*-allyl thioimidates generated from secondary thioamides are also prone for the S → N [3,3]-sigmatropic rearrangement using palladium(II) salts as catalyst [51], although in some cases competence with the S → C has been reported by means of tautomerization of

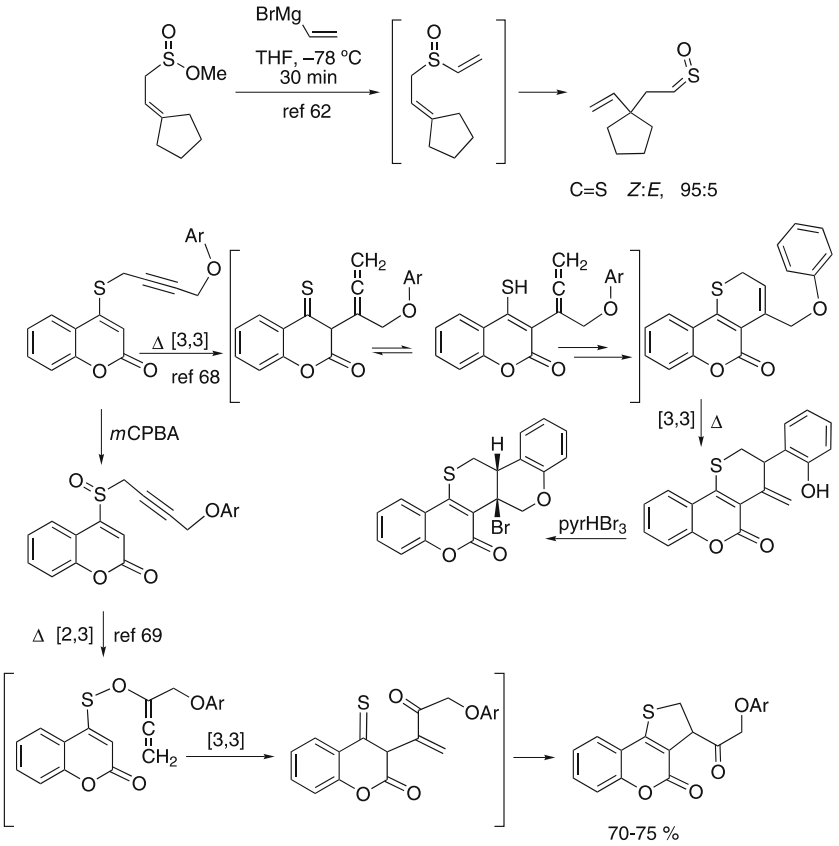


Scheme 4

the initial thioimidate previous to the sigmatropic shift [52, 53]. More recently the group of Gonda has described that δ-amino allylic thiocyanates undergo sequential asymmetric [3,3]-sigmatropic rearrangement and intramolecular cyclization onto the transient isothiocyanate to afford diastereomerically pure 1*H*-2-imidazolethiones [54]. This reactivity has also been applied in the synthesis of the 5′-aminofuranoside moiety of polyoxins [55].

In general, the oxidation state of sulfur exerts a crucial role in the reactivity of the substrates. While the thio-Claisen rearrangement of sulfides [56] and sulfones [57] requires heating at temperatures higher than 150 °C, the [3,3]-sigmatropic rearrangement of their sulfoxide counterparts usually takes place below 0 °C, affording isolable thiocarbonyl *S*-oxides (sulfines) [58]. This remarkable acceleration has been attributed to the polarized nature of the S – O bond that provides simultaneously two known charge accelerating effects: one from the sulfonium salt and the other from the anionic oxygen. A number of studies have been focused on the mechanism of the sulfoxide-accelerated thio-Claisen [59, 60]. Furthermore, it has been proposed that this process is responsible of the biosynthesis of bis(sulfines) isolated from onion extracts [61]. The group of Baudin [62] has used the sulfoxide-accelerated thio-Claisen for the synthesis of γ-unsaturated thioaldehyde and thioketone-*S*-oxides from sulfinates (Scheme 5). Thus, the addition of a vinyl Grignard reagent to the allyl sulfinate at – 78 °C generates a transient allyl vinyl sulfoxide that undergoes the [3,3]-sigmatropic rearrangement. A parallel behavior is observed for allenyl sulfinates. In spite of the chiral nature of sulfoxides, the potential asymmetric induction of these substrates has been scarcely explored [63].

In the above examples, in spite of the allylic nature of the starting sulfoxides, the [2,3]-sigmatropic rearrangement does not interfere with the thio-Claisen process. In this context, the group of Majumdar recently found contradicting results (Scheme 5). These authors examined the thermally pro-



Scheme 5

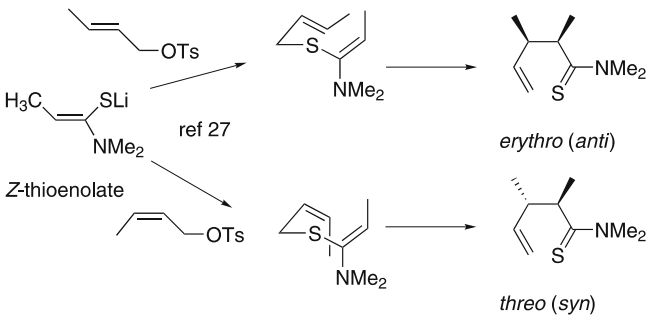
moted thio-Claisen rearrangement of allyl and propargyl benzopyran-4-ones and quinolon-2-1*H*-ones [64–67]. Interestingly, 4-(4′-aryloxybut-2′-ynylthio) benzopyran-2-ones allow for the competition study of the thio-Claisen and oxy-Claisen rearrangements [68]. Upon heating, these substrates undergo a thio-Claisen rearrangement followed by enolization, [1,5] proton shift, and electrocyclic ring closure to afford thiopyrano[3,2-*c*][1]benzopyran-5(2*H*)-ones and then after a second heating period suffer a second aromatic oxy-Claisen rearrangement onto the pending aryloxy group yielding phenolic benzopyranones. Finally, bromoetherification of these substrates on the exocyclic double bond using pyridine trihydrobromide produces pentaheterocyclic systems difficult to access by other synthetic routes. However, when sulfur is oxidized to sulfoxide the thio-Claisen shift does not take place [69]. Instead a [2,3] sulfoxide–sulfenate reaction occurs first onto the propargylic fragment upon heating to give an allenyl sulfenate that undergoes the polyhetero [3,3]-sigmatropic rearrangement followed by enolization and cycli-

zation onto the enone moiety affording dihydrothieno[3,2-*c*][1]benzopyran-4-ones in 70–75% yields. A parallel reactivity was observed in pyrimidine systems [70].

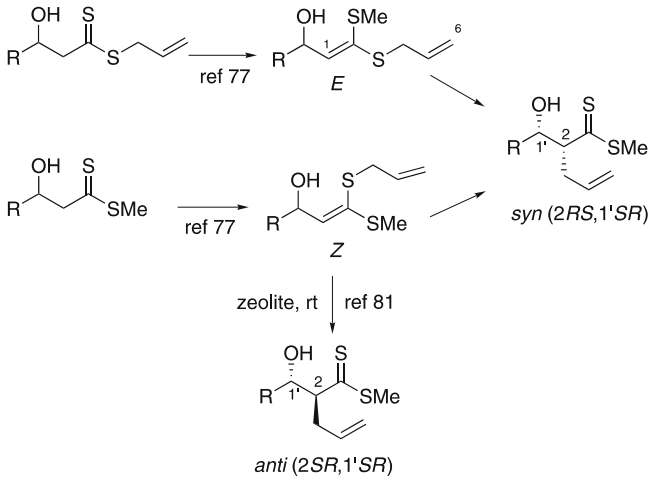
3
Asymmetric Thio-Claisen Rearrangement

Like other [3,3]-sigmatropic rearrangements, the thio-Claisen rearrangement offers excellent opportunities to create new carbon skeletons with stereocontrol and it has been used in the synthesis of complex products such as an analog of prostaglandin I_2 [71]. These transformations have an intrinsic stereoselectivity in the formation of double [72] as well as single carbon–carbon bonds. In fact, the thio-Claisen rearrangement of allyl vinyl sulfides generated by deprotonation of dithiopropanoates and thiopropanamides with *n*Buli, LDA or *i*PrMgBr and then capture with (*E*) crotyl electrophiles, takes place with a moderate *anti* (*erythro*) diastereoselectivity (Scheme 6). This is mainly due to the particular tendency of the starting thiocarbonyl compounds to render *Z*-thioenolates as major products upon kinetic deprotonation as well as to the stereospecific character of the [3,3]-sigmatropic rearrangement [25–28, 73].

Chirality transmission can also be induced in thio-Claisen reactions by a chiral center adjacent to the allyl vinyl sulfide core. The group of Metzner examined the diastereoselectivity of the rearrangement of acyclic *S*-allyl ketene dithioacetals bearing a chiral center adjacent to carbon 6. In these substrates, the sigmatropic shift proceeded smoothly and with modest *syn* : *anti* diastereoselectivity [74]. In contrast, higher selectivities are found for thio-Claisen precursors bearing a chiral center adjacent to carbon 1 mainly due to steric effects and allylic strain [75]. In 1991, the group of Beslin examined the effect of a hydroxyl substituted chiral center attached to C-1 of *Z* and *E S*-allyl ketene dithioacetals [76, 77] (Scheme 7). Under the reaction conditions, these



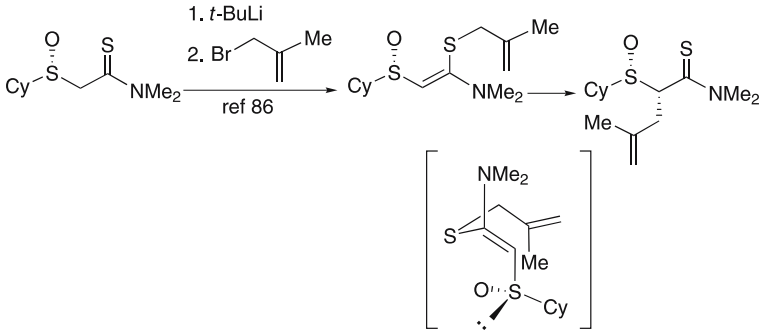
Scheme 6



Scheme 7

substrates smoothly undergo the expected thio-Claisen rearrangement with a high level of *syn* stereoselectivity (24 : 1 to 9 : 1) in contrast to the related oxy-Claisen rearrangement that affords mainly the *anti* product. The *syn*-stereoselectivity is independent of the stereochemistry of the starting ketene dithioacetal (*E* or *Z*) and apparently obeys to the approach of the allylic terminus to the ketene *anti* to the R group that is suitably placed to minimize allylic strain. These authors have studied the scope and generality of the above findings by introducing stereogenic centers contiguous to the hydroxyl group and placing *S*-crotylic fragments in the starting compounds [78, 79]. In addition, a similar trend was observed for (*Z*)-*S*-allyl ketene-*S*,*N*-acetals, prepared from the corresponding *N*,*N*-dimethyl β-hydroxythioamides, which afford *syn* β-hydroxy α-allylic thioamides [80]. However the *syn*-selectivity found for ketene dithioacetals can be reversed. In 1997, Sreekumar reported that *S*-allyl γ-hydroxy ketene dithioacetals render exclusively *anti* α-allyl β-hydroxy dithioesters upon thio-Claisen rearrangement over zeolites [81]. The *anti* stereochemical assignment was secured by comparison with previous NMR data [77] as well as by chemical correlation with the known *anti*-ethyl α-allyl β-hydroxy butanoate [82]. The authors have proposed that the *anti* stereochemical outcome is the result of the adsorption of the starting compound inside the channels of the zeolite by a simultaneous complexation of the sulfur and hydroxyl groups placing the bulky substituents away from the catalytic support. Computational models have also been applied to understand the above findings [83].

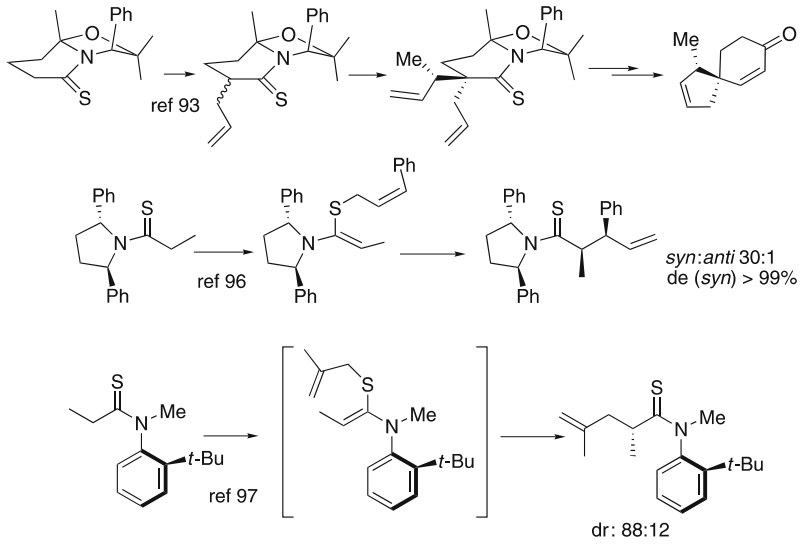
Asymmetric induction can be caused by the presence of a sulfinyl group within the system [63]. In 1997, the group of Metzner reported the first examples of a thio-Claisen rearrangement stereocontrolled by a sulfinyl group



Scheme 8

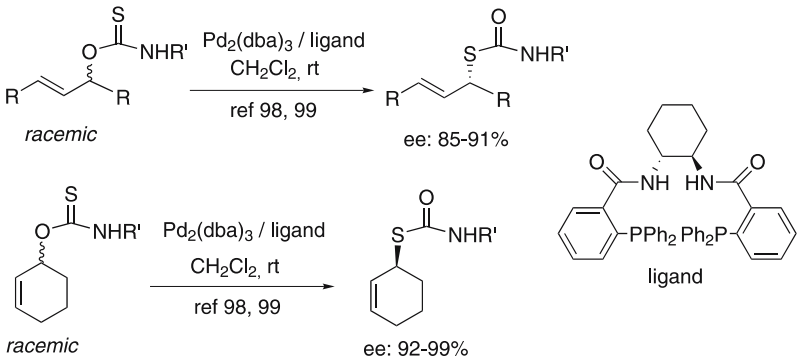
attached to the double bond of *S*-allyl ketene dithioacetals and *S*,*N*-acetals (Scheme 8). Thus, deprotonation of α-sulfinyl dithioesters with LDA, followed by capture with allyl electrophiles led mainly to *Z*-ketene dithioacetals that rearranged smoothly at room temperature affording γ-unsaturated α-sulfinyl dithioesters with very high diastereoselectivity [84]. The steric bulk of the alkyl group attached to the sulfoxide has little influence on the diastereomeric ratio, therefore the authors invoke an stereoelectronic control of the [3,3]-sigmatropic rearrangement. Thus considering a chair-like transition state, the approach of the allyl terminus would take place *anti* to the electron pair of the sulfoxide that adopts a conformation that places the alkyl group R^1 in an outside position. The scope of this diastereoselective thio-Claisen has been expanded to ketene-*S*,*N*-acetals, generated from α-sulfinyl tertiary thioamides, which render α-sulfinyl γ,δ-unsaturated thioamides with high asymmetric induction [85, 86].

Within this context, asymmetric induction can also be promoted in tertiary thioamides by placing stereogenic centers attached to nitrogen. Thus, thioamides generated from aminoacids such us proline, valine and pyroglutamate have provided modest diastereomeric excesses [87–89]. In 1994, Meyers reported [90, 91] the first examples of highly diastereoselective thermal thio-Claisen rearrangement of chiral bicyclic thiolactams that render γ-unsaturated bicyclic thiolactams (de $> 99:1$). The methodology has been used for the synthesis of vicinal stereogenic quaternary centers and further applied in the asymmetric synthesis of the sesquiterpene (–)-trichodiene [92] and in an approach to chiral cyclohexenones with spiro-connected cyclopentenes [93] (Scheme 9). Later, this group found that nickel and palladium-catalyzed thio-Claisen rearrangement of the above chiral bicyclic thiolactams occurred under milder conditions; however, a decrease in the diastereoselectivity of the new chiral centers was also observed [94]. However, Metzner reported that for *Z*-ketene dithioacetals, catalysis by other metals such as $CeCl_3$ improves the yield as well as the diastereoselectivity [95].



Scheme 9

C_2-symmetric amines have also been used as source of stereocontrol in the reaction [96]. Thus, from (+)-*trans*-2,5-diphenylpyrrolidine and after three synthetic steps are obtained ketene-*N*,*S*-acetals which undergo the [3,3]-sigmatropic rearrangement with high diastereocontrol generating up to two new stereogenic centers with excellent *syn* : *anti* selectivity when crotyl and cinnamyl bromides are used to trap the *Z*-thioenolate (Scheme 9). Recently, the group of Metzner reported the use of axial chirality to induce asymmetry in the thio-Claisen of atropoisomeric thioamides. After deprotonation and allylation, thioamides from *ortho-tert*-butylaniline provided γ, δ-unsaturated thioamides with moderate diastereoselectivity (from 80 : 20 to



Scheme 10

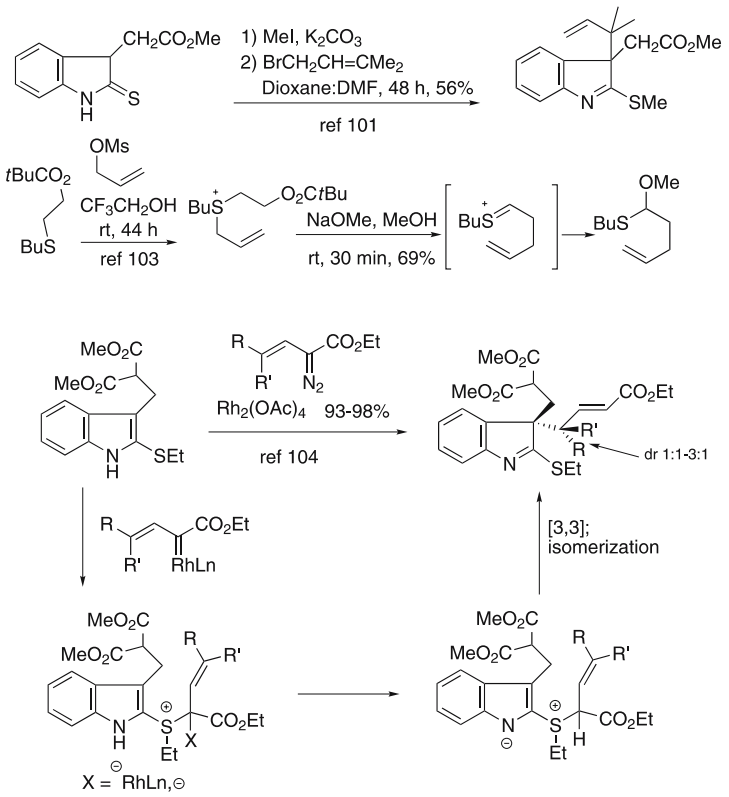
86 : 14). The intermediate (*S*)-allyl keteneaminothioacetals were not detected in these transformations [97] (Scheme 9).

Finally, within the context of catalytic and enantioselective rearrangements, the group of Gais reported in 1999 the first examples of palladium(0)-catalyzed enantioselective *O*, *S*-rearrangement in *O*-allylic thiocarbamates in the presence of a C_2-symmetric bisphosphane as chiral bidentate ligand [98, 99], that allow for the synthesis of chiral *S*-allylic thiocarbamates with ee values ranging from 85 to 99% for acyclic and cyclic substrates, respectively, (Scheme 10). While these *O*, *S*-rearrangements could be understood as formal retro thio-Claisen shifts, some evidence points to an ionization–substitution mechanism involving π-allylpalladium complexes as intermediates.

4
Sulfonium Ion Participation in [3,3]-Sigmatropic Rearrangements

A positive charge at position 3 of a Claisen system can accelerate the rearrangement and this variant has been applied to indolyl allyl sulfonium ions [100]. This methodology has been used within the context of a synthetic approach to the alkaloid amauromine; thus, methylation of a thioamide, followed by allylation results in a sulfonium ion that undergoes a smooth sigmatropic rearrangement at rt to afford an inverted prenyl derivative [101, 102]. Similarly, allylation of a β-pivalyloxy sulfide, followed by treatment with base produces an allyl vinyl sulfonium ion that undergoes a facile sigmatropic rearrangement with incorporation of methoxide [103]. Finally, the coupling of rhodium carbenoids with 2-thio-3-alkyl indoles generates substituted indolines via a thionium ylide-initiated [3,3]-sigmatropic rearrangement [104] (Scheme 11).

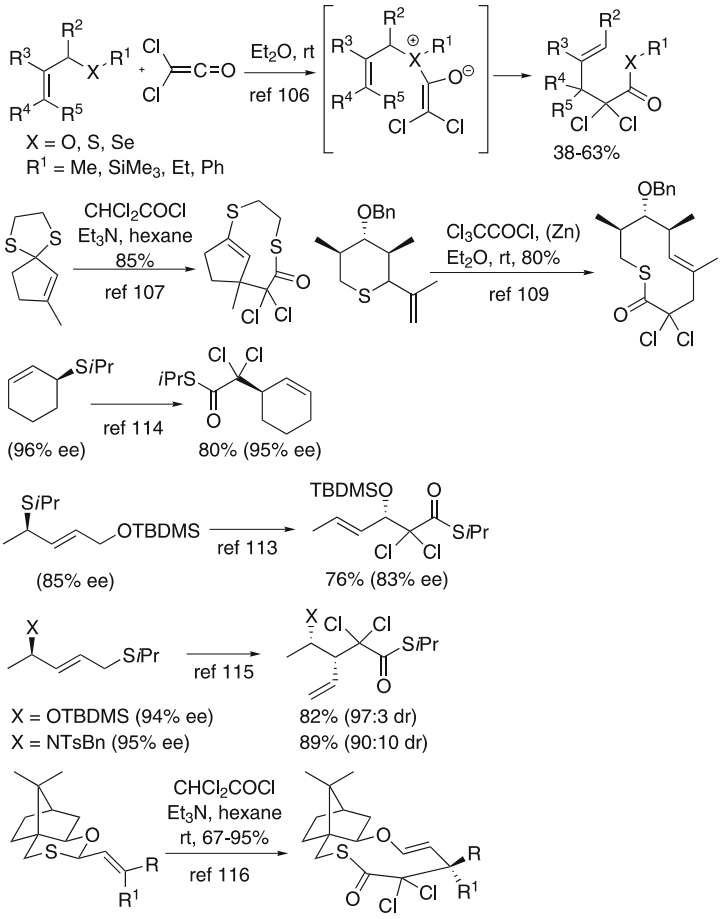
In 1978, Belluš reported [105] the first examples of the ketene-Claisen rearrangement (Scheme 12) that entailed the treatment of allylic ethers, sulfides and selenides with dichloroketene to generate a zwitterion that undergoes a [3,3]-sigmatropic rearrangement under very mild conditions due to the presence of a positive charge at position 3 and a negative charge at position 2 of the Claisen system. The competing [2 + 2] cycloaddition was observed in a few cases and as minor products [106]. This protocol is particularly useful for promoting ring enlargements of cyclic thioketals [107], and while the enlargement of cyclic sulfides was initially low-yielding [108], subsequent experimental modifications introduced by Vedejs rendered the process synthetically useful [109, 110]. When the ketene is generated by dehalogenation with Zn, the $ZnCl_2$ produced facilitates the sigmatropic rearrangement; interestingly, addition of dimethoxyethane complexes $ZnCl_2$ and, in some cases, allows for a clean [2 + 2] cycloaddition [111]. The stereochemical aspects of this rearrangement have been addressed for systems where the sulfide is attached to a chiral center and for sulfides with an allylic chiral center bearing oxygen



Scheme 11

and nitrogen-based substituents; the process was found to occur with a good degree of chirality transfer in all cases and may be rationalized in terms of the favored chair-like reactive intermediates [112–115]. Finally, Aggarwal recently described the ring expansion of camphor-derived 1,3-oxathianes in excellent yields and diastereoselectivities, provided dichloroketene was generated by elimination with Et_3N [116].

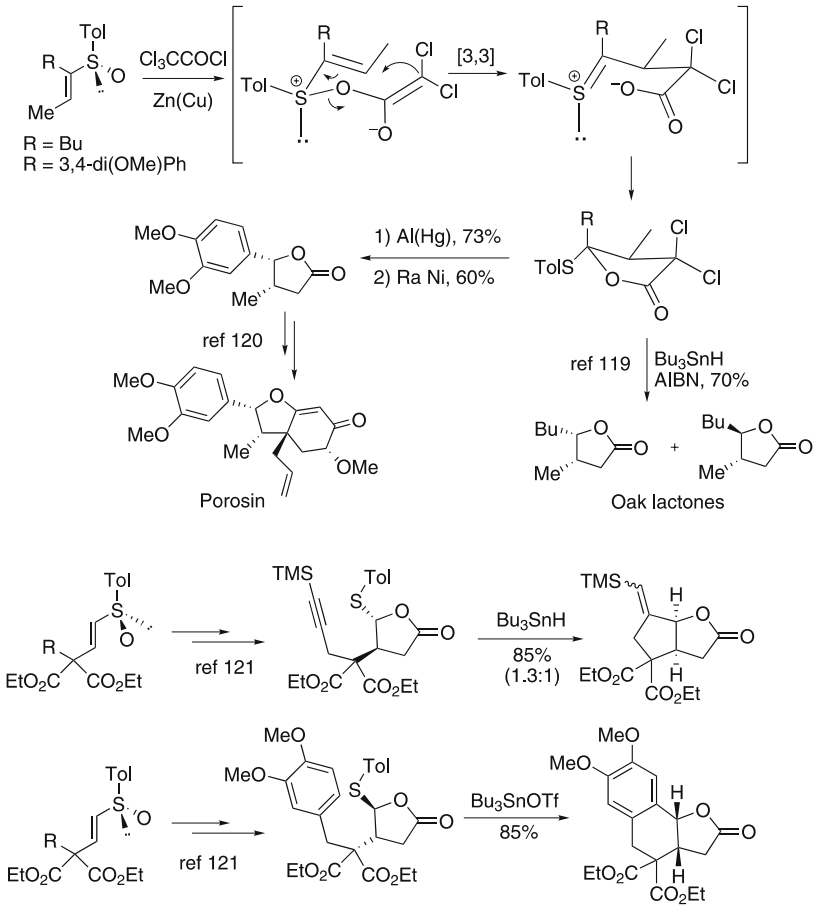
In 1981 Marino reported a lactonization of readily available vinyl sulfoxides and haloketenes to produce γ-butyrolactones (Scheme 13) [117]. Subsequent work showed the reaction to transfer the chirality of sulfur to the newly created centers, resulting in enantiopure lactones from enantiopure sulfoxides [118, 119]. The synthesis of oak lactones from a sulfoxide of known configuration defined the absolute sense of the chirality transfer and allowed for the proposal of a reaction pathway that entails a highly stereocontrolled [3,3]-sigmatropic rearrangement of the *O*-acylated intermediate, with the bulky tolyl group in an equatorial arrangement, followed by a stereoselective intramolecular trapping of the sulfonium intermediate by the carboxylate [120]. Reductive dechlorination and desulfurization with Bu_3SnH brings about par-



Scheme 12

tial epimerization at C-4; alternatively, dehalogenation with Al(Hg), followed by desulfurization with Ra Ni takes place with retention of configuration at C-4 and this resulted in a formal synthesis of porosin [120]. The synthetic utility of the lactonization was further demonstrated by the efficient preparation of fused butyrolactones by intramolecular cyclizations of adequately functionalized lactones promoted either under free radical conditions or with Bu_3SnOTf [121]. The substrates of this study were prepared uneventfully by the sulfoxide directed lactonization of the readily available malonyl vinyl sulfoxides [122].

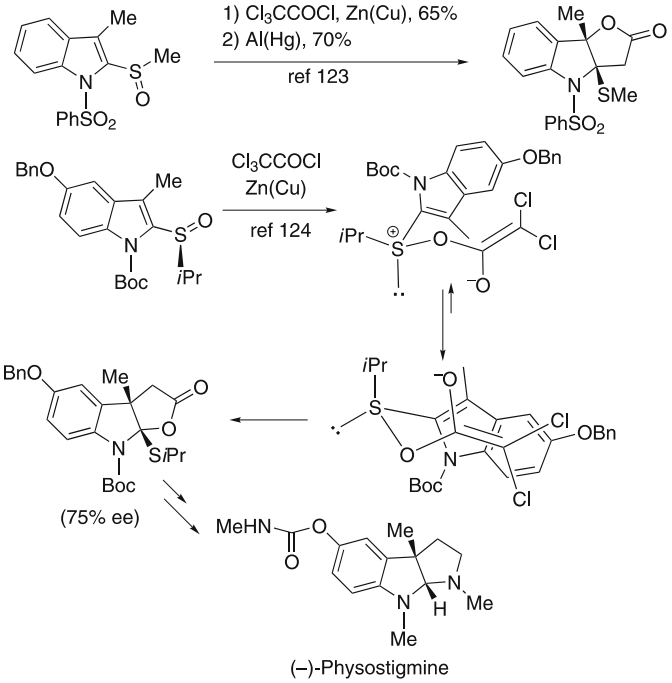
This lactonization was later extended to indole derivatives [123], and the influence of different groups on sulfur on the process was explored within an application to the total synthesis of the alkaloid physostigmine [124] (Scheme 14). Thus methyl indolyl sulfoxides rendered practically racemic



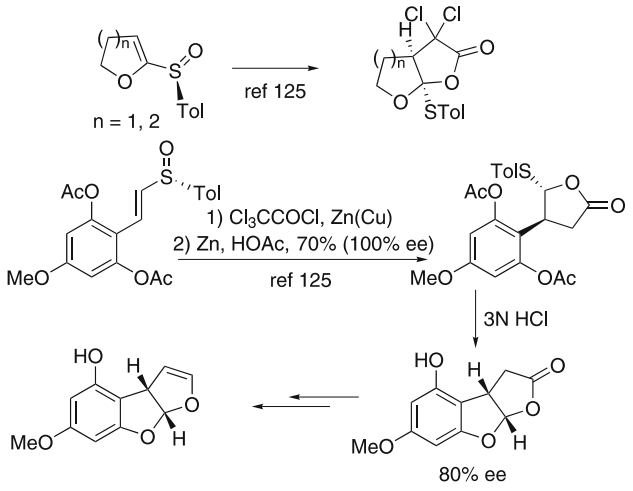
Scheme 13

material, the phenyl indolyl substrate did not undergo lactonization and the isopropyl sulfoxide gave the product in 75% ee. Considering the absolute configuration of the starting alkenyl sulfoxide, it was expected that the unnatural enantiomer would be obtained but, surprisingly, the natural (–)-physostigmine was instead produced. This can be understood by considering that in this particular case the 1,2-diequatorial interaction between the Boc and isopropyl groups may render the alternative conformer, with an axial isopropyl moiety, more favorable.

To extend the methodology to the synthesis of aflatoxins and related products containing a benzodihydrofuran fused to another dihydrofuran, the lactonization of model dihydrofuranyl and dihydropyranyl sulfoxides was explored with excellent results (Scheme 15); in contrast, the 2-sulfoxide of benzofuran did not yield the desired lactone [125]. In an alternative ap-



Scheme 14

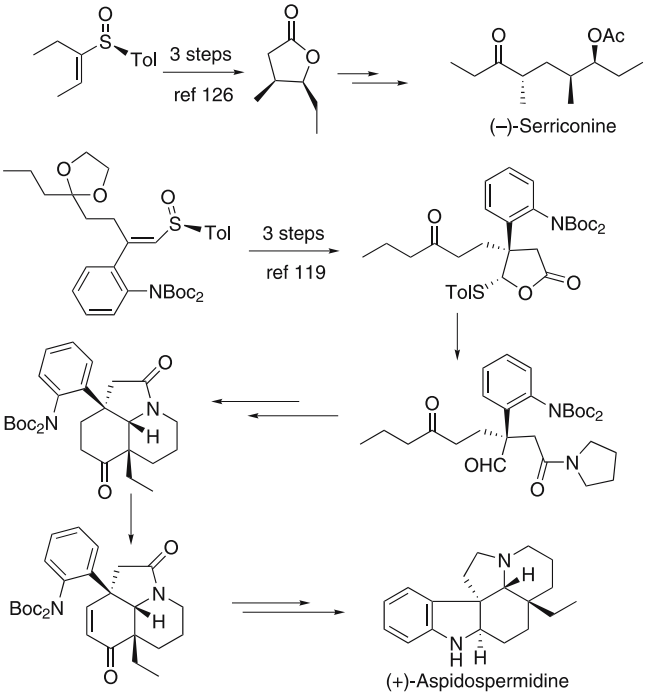


Scheme 15

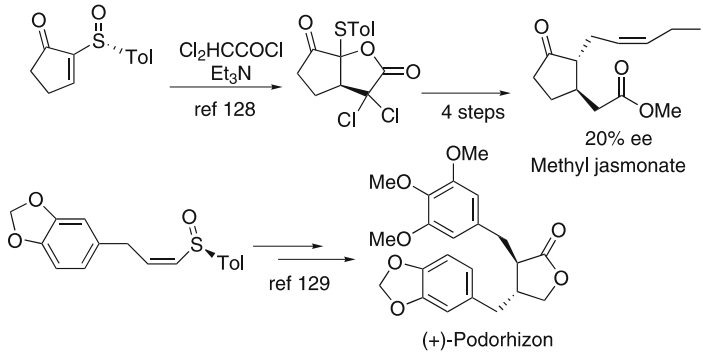
proach, the lactonization of a functionalized alkenyl sulfoxide, followed by reductive dechlorination afforded an enantiopure lactone that underwent an acid-catalyzed cyclization with partial racemization to produce the desired fused lactone that was further elaborated to a dihydrofuran.

This methodology has also been applied to the formal synthesis of serriconine [126]. A remarkable feature of this lactonization is the enantiospecific production of quaternary centers [119] that was later utilized in a synthesis of the alkaloid aspidospermidine [127] (Scheme 16).

Other groups have contributed to defining the scope and limitations of this unique transformation (Scheme 17). Posner prepared enantioenriched



Scheme 16

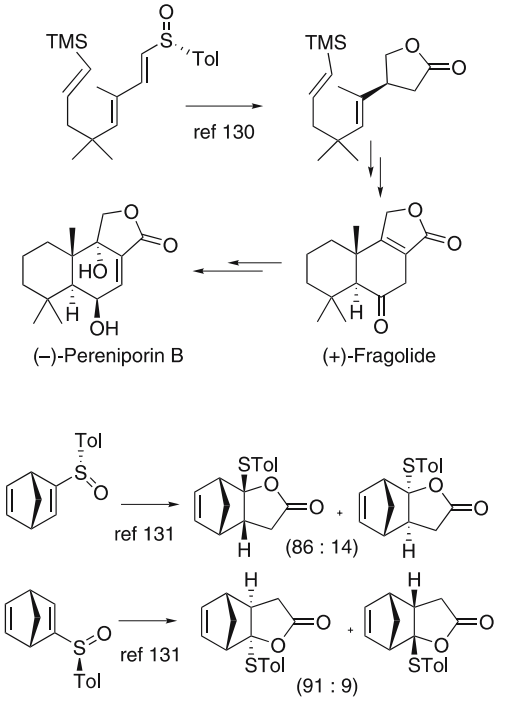


Scheme 17

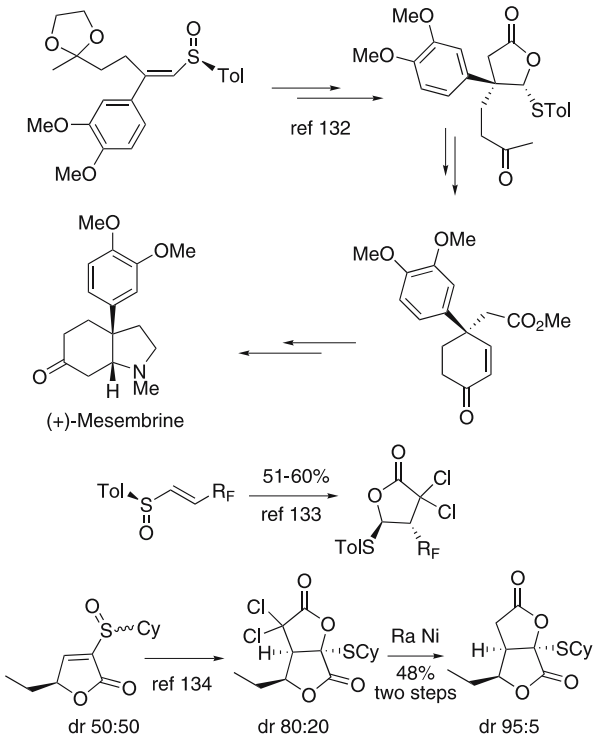
methyl jasmonate from a 2-sulfinyl cyclopentenone and dichloroketene generated by dehydrohalogenation [128]. The scope of the lactonization of a variety of alkenyl sulfoxides was examined by Kosugi and Uda and, in one case, the lactone obtained after dehalogenation and desulfurization was metalated with LDA and reacted with the appropriate acid chloride to produce an excellent yield of the lignan podorhizon [129].

The use of 1-sulfinyl dienes as substrates for this lactonization was illustrated within the context of a synthesis of fragolide and pereniporin B [130]. Norbornadienyl sulfoxides were also examined and the expected lactones were produced after dehalogenation in a predominantly sulfur-directed process [131] (Scheme 18).

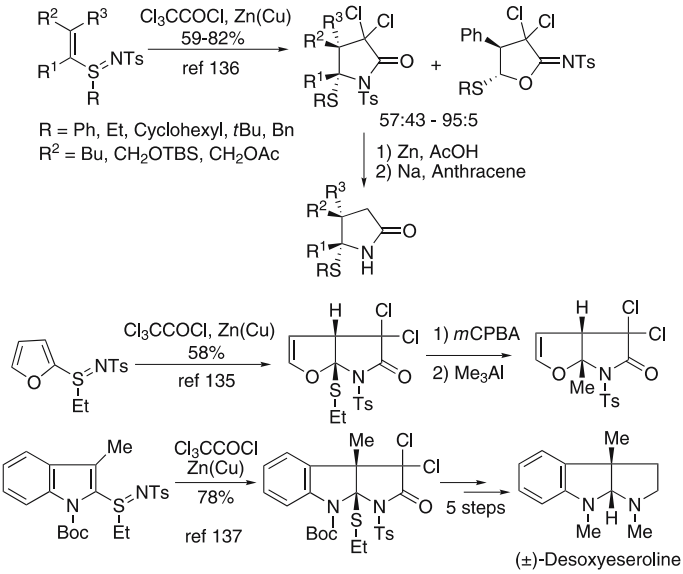
The production of quaternary centers was also utilized by Kosugi to develop a synthesis of mesembrine [132]. Lactones bearing fluorinated sidechains are also available by this methodology [133]. The lactonization of a 50 : 50 mixture of cyclohexylsulfinyl butenolides has been examined. It was expected that a mixture of bis-lactones would be produced in 50 : 50 ratio. Instead, an 80 : 20 mixture of dichloro bis-lactones was obtained and, dehalogenation with Ra – Ni gave the lactone shown as the major isomer of a 95 : 5 mixture [133] (Scheme 19).



Scheme 18



Scheme 19



Scheme 20

A novel extension of this chemistry that entails the transformation of alkenyl and aryl sulfilimines to γ-butyrolactams upon reaction with dichoroketene was recently reported by the groups of Padwa [134] and Marino [136] (Scheme 20). The scope of the process is rather broad and the relative stereochemistry of the alkene is transferred to the products. This suggests the involvement of a [3,3]-sigmatropic rearrangement followed by intramolecular trapping of the cation by the amido anion. Interestingly, just in the case of styryl sulfilimines, variable amounts of the related iminolactones are obtained as minor products. The chemistry of these adducts has been explored and conditions to dechlorinate, desulfonylate and remove the sulfide with concurrent methylation have been outlined. The methodology has been applied to the synthesis of the alkaloid (±)-desoxyeseroline [137].

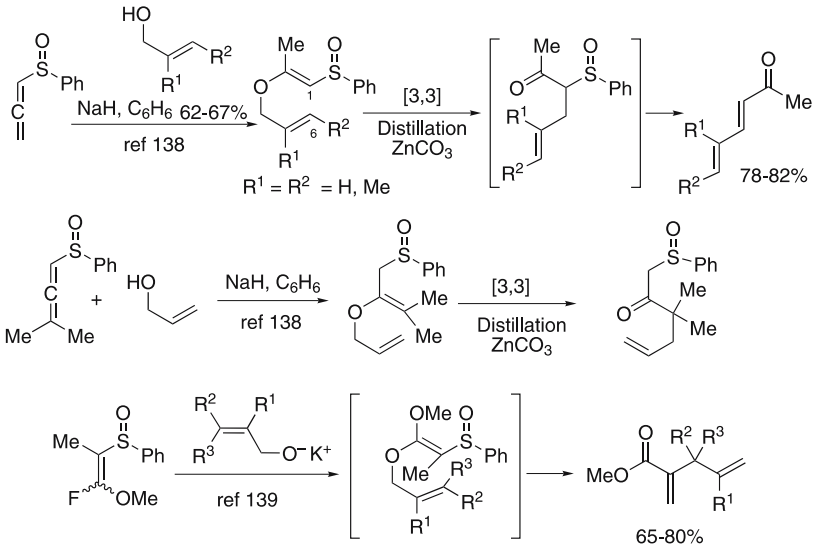
5
External Sulfur Participation in [3,3]-Sigmatropic Rearrangements

5.1
Sulfur on Vinyl Fragment

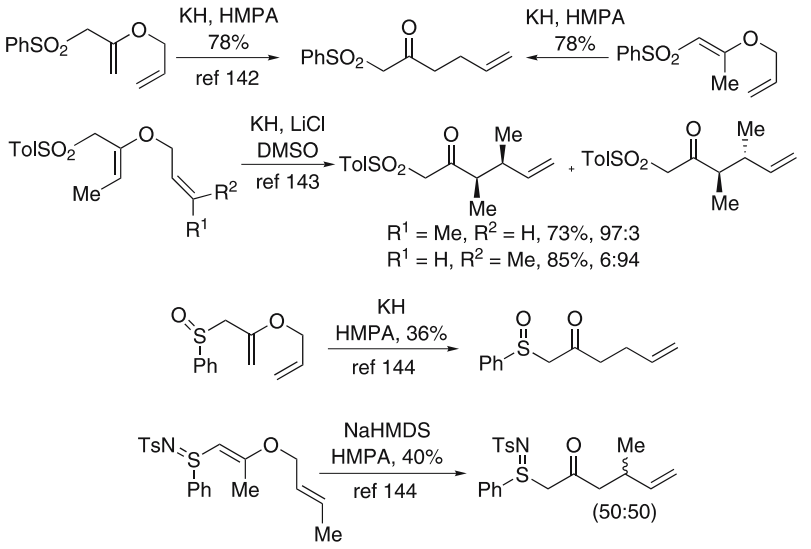
The addition of an allyl alcohol to racemic allenyl sulfoxides results in vinyl ethers with the sulfinyl moiety at C-1 that undergo sigmatropic rearrangements upon distillation to produce 2,4-dienones after elimination of sulfenic acid. In one example, an isomeric vinyl ether was obtained with a sulfinyl methyl substituent at C-2 that gave rise to a sulfinyl enone upon rearrangement [138]. In related work, the addition–elimination of an allyl alkoxide to a functionalized vinyl sulfoxide results in a sulfinyl enol ether that rearranges with loss of sulfenic acid to the unsaturated ester [139–141] (Scheme 21).

Sulfone stabilized carbanions attached at C-2 substantially accelerate the Claisen rearrangement (Scheme 22); these species may be generated from either regioisomeric precursors [142]. These processes take place with high levels of internal asymmetric induction [143], and the scope of the process is broad and it has been extensively studied. This acceleration was also noted for the related sulfinyl carbanions, albeit with low yields and in the case of sulfilimines no internal asymmetric induction was observed [144].

A mercury-free route to allyl vinyl ethers that relies on the Michael addition of allyl alcohols to unsubstituted alkenyl sulfoxides, followed by thermal loss of sulfenic acid and concurrent Claisen rearrangement has been described [145]. This methodology has been applied to the synthesis of isocarbacyclin [146]. Posner reported an acid-catalyzed protocol that produces conjugated dienoate esters from allylic alcohols and a sulfinyl orthoester [147]. Additionally, the use of propargyl alcoholates and a chloro alkenyl sulfox-



Scheme 21

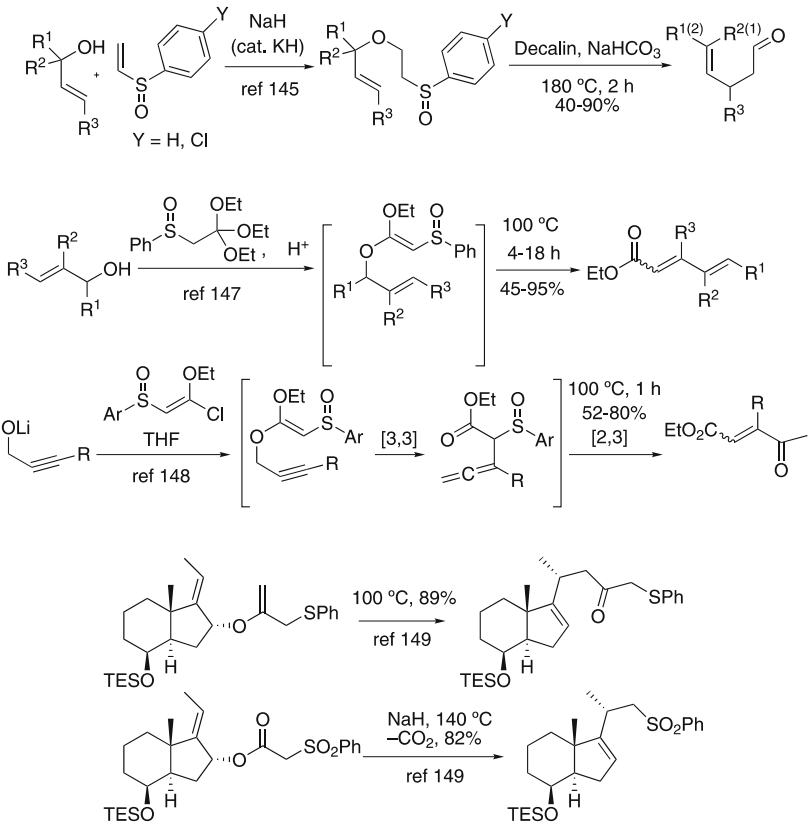


Scheme 22

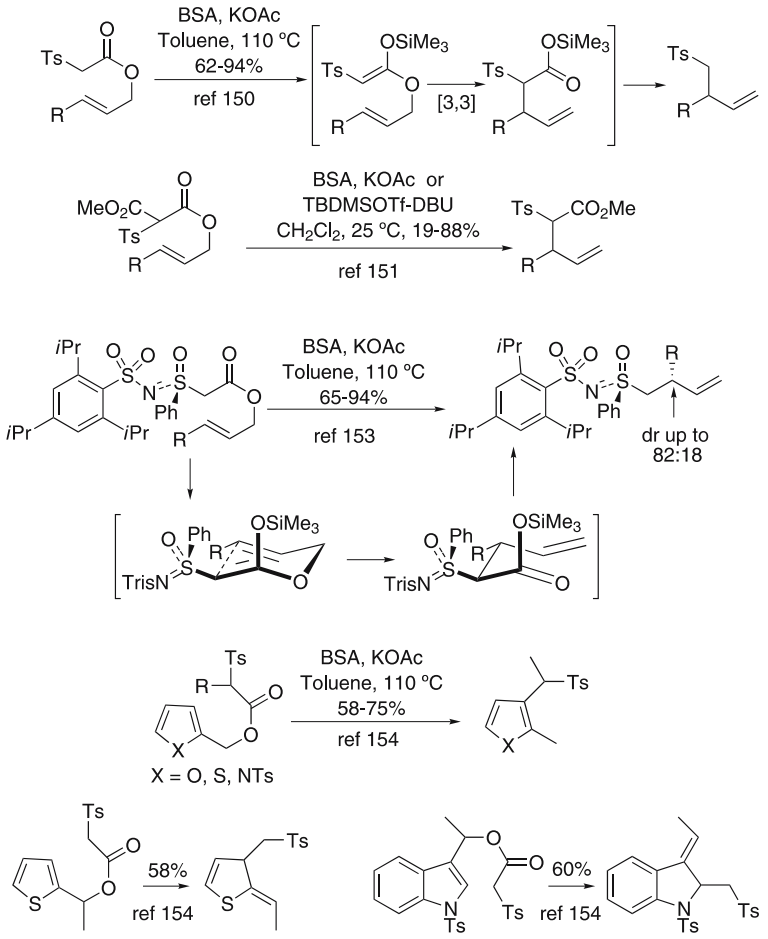
ide presumably triggers a Claisen [3,3] rearrangement to produce an allenyl sulfoxide that undergoes a sequential [2,3]-sigmatropic rearrangement and hydrolysis of the enol sulfenate affording oxo unsaturated esters [148]. Finally, several variants of the Claisen rearrangement were examined within the

context of the synthesis of functionalized vitamin D_3 side-chain units; interestingly, the Carroll-like rearrangement of a sulfonyl acetate unit took place with concurrent decarboxylation [149] (Scheme 23).

Craig recently reported a novel procedure to effect the decarboxylative Claisen rearrangement of allyl tosylacetates to produce homoallylic sulfones under exceptionally mild conditions (Scheme 24). Optimal conditions involve the use of *N*,*O*-bis(trimethylsilyl)acetamide (BSA) and KOAc in refluxing toluene [150]. In a subsequent report the method was extended to tosylmalonate derivatives that reacted readily under two sets of conditions at room temperature [151, 152]. Furthermore, an asymmetric variant of this method that entails the use of chiral sulfoximines has been developed and the rearrangement products can be obtained in up to 82 : 18 dr [153]. The method has been applied to furan, thiophene and pyrrole derivatives with good results, and, in some cases, the exo methylene non-aromatic derivatives are isolated in good yields and as single isomers [154].



Scheme 23

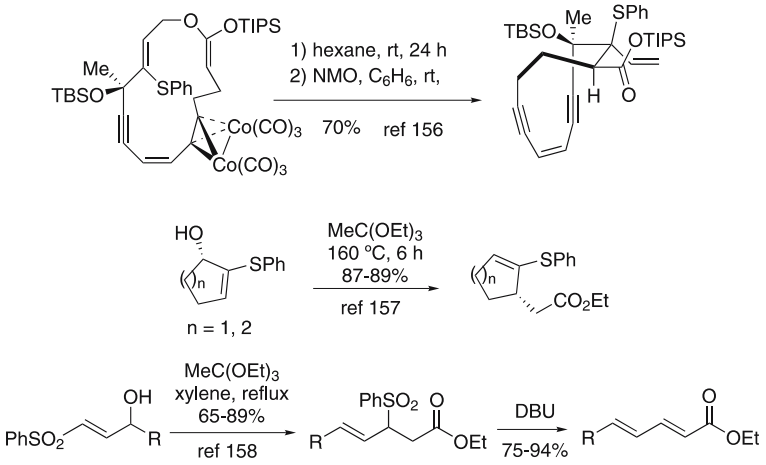


Scheme 24

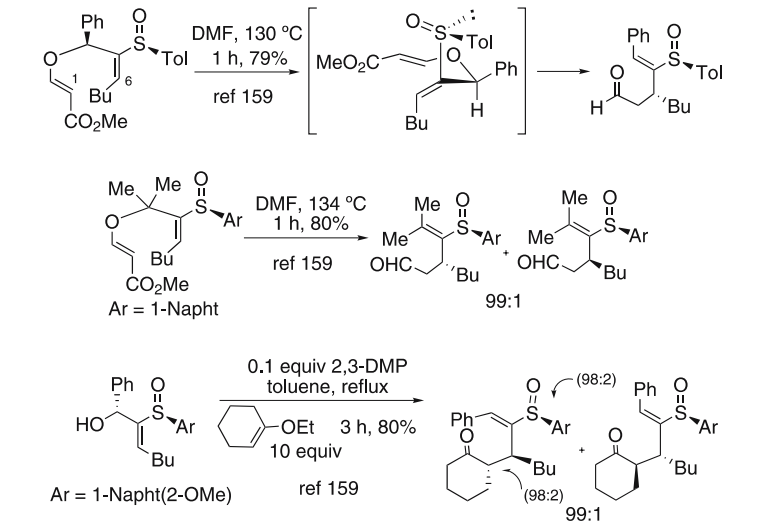
5.2
Sulfur on Allyl Fragment

The $Co_2(CO)_6$ complex of a sulfenyl substituted ketene acetal underwent a remarkably mild and stereoselective Claisen rearrangement to produce, after decomplexation, an 11-membered enediyne as a single isomer. It should be pointed out that thermolysis of the related uncomplexed ketene acetal gives a completely different product derived from a rare [1,3] rearrangement [155, 156]. Cyclic sulfenyl allylic alcohols undergo a facile Claisen–Johnson rearrangement [157], and acyclic hydroxy vinyl sulfones give rise to sulfonyl unsaturated esters that readily undergo elimination to produce dienoic esters [158] (Scheme 25).

Our group described the highly diastereoselective Claisen rearrangement of alkoxy acrylates bearing a chiral sulfoxide at C-5 that takes place under relatively mild conditions and with concurrent decarboxylation to generate a synthetically useful vinyl sulfoxide (Scheme 26). The scope of the process was studied with regard to the influence of the alkene geometry at the allylic moiety, the use of different groups on sulfur and the possibility of creating two adjacent chiral centers. The stereochemical outcome of the process was rationalized in terms of reinforcing and nonreinforcing relationships between



Scheme 25



Scheme 26

the chiral sulfur and the allylic stereocenter, with the sulfinyl moiety being a powerful stereodirecting group [159].

6 Conclusion

Sulfur participation in [3,3]-sigmatropic rearrangements allows for a broad variety of unique and synthetically useful transformations that often take place under mild conditions. We hope this article will encourage researchers to continue the development of new processes and applications within this field.

Acknowledgements This article was supported by DGICYT (BQU2003-02921 and CTQ2005-04632). We thank JANSSEN-CILAG for generous additional support. Also, we would like to thank Prof. Meztner for providing a preprint of his manuscript [3].

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Top Curr Chem (2007) 275: 131–161
DOI 10.1007/128_065

Published online: 12 September 2006

Thione–Thiol Rearrangement: Miyazaki–Newman–Kwart Rearrangement and Others

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Abstract Thione-to-thiol rearrangements represent a general route for the synthesis of sulfur compounds from hydroxyl functionalities. In particular, the Miyazaki–Newman–Kwart rearrangement has been widely used for the synthesis of aromatic thiols from the corresponding phenols.

Keywords Thermal rearrangement · Newman–Kwart rearrangement · Aromatic thiols

Abbreviations
DMF Dimethylformamide
DABCO 1,4-Diazabiciclo[2.2.2]octane

DMAP Dimethylaminopyridine
DMTCl Dimethylthiocarbamoyl chloride
DETCl Diethylthiocarbamoyl chloride
PTC Phase transfer catalyst
BINOL Binaphthol
MOP 2-(Diphenylphosphino)-2′-alkoxy-1,1′-binaphthyl

1 Introduction

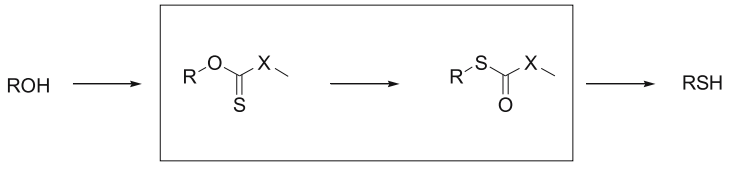
Thione-to-thiol rearrangements are reactions of thiocarbonates and related compounds in which oxygen and sulfur are mutually exchanged (Scheme 1).

Since the thiocarbonate derives from an alcohol or phenol, the rearrangement represents a general method for transforming an hydroxyl group into a thiol group. X in Scheme 1 is an heteroatom, typically nitrogen, but oxygen and, to a lesser extent, sulfur are used as well. In view of the seminal contributions by Newman [1] and Kwart [2] the reaction is usually referred to as the Newman–Kwart rearrangement.

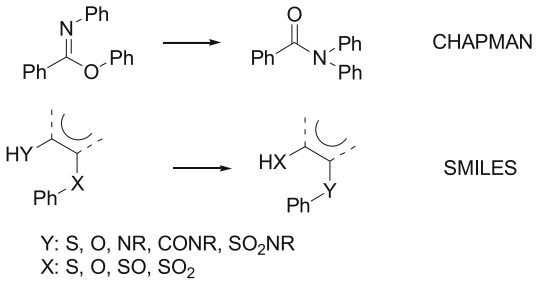
However, during the bibliographical search we became aware of a previous report, followed by other important contributions on the subject, by Miyazaki [3]. For this reason we propose the name Miyazaki–Newman–Kwart (MNK) for the rearrangement.

Over the years, the MNK reaction has emerged as a reliable method, especially for the conversion of aromatic hydroxides into aromatic thiols (and oxidised derivatives). It has received less attention in the aliphatic field because of the existence of alternative methods for transforming alcohols into thiols, namely via aliphatic nucleophilic substitution. Nonetheless, in the aliphatic field, it represents a valuable alternative in the presence of other functional groups and has also been shown to be susceptible to catalysis by a number of compounds.

Historically, the possibility of obtaining intramolecular rearrangement came from the tautomeric irreversible rearrangements observed by Chapman (Scheme 2) [4, 5]. In his early work, Chapman was able to demonstrate that the reaction undertakes an intramolecular pathway, i.e. via a spirocyclic intermediate. Not much later Smiles found another reaction causing the 1,3 shift of the substituent in the aromatic ring, involving a similar intermediate [6, 7].



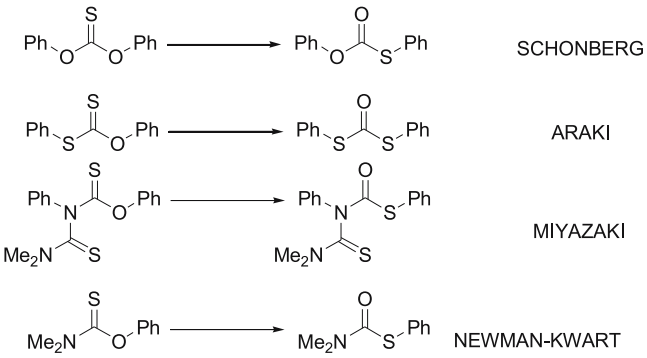
Scheme 1 Thione to thiol rearrangement



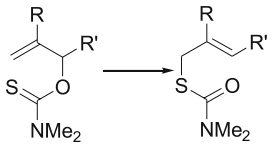
Scheme 2 Chapman and Smiles rearrangements

The first observation of a rearrangement involving a thiocarbonyl group was made by Schönberg in the thermal reaction of symmetric xanthates [8]. The following hydrolysis furnished one molecule of rearranged thiophenol and one molecule of starting phenol [9]. Later, Araki expanded the method to dithiocarbonates, showing that the heteroatom flanking the thiocarbonyl group in the starting reagent may be different from oxygen. However, the greatest improvement in terms of efficiency (e.g. yields) was obtained by the introduction of a nitrogen atom. In fact, with the previous methods only one of the two phenols present in the thiocarbamates could be converted into the corresponding thiophenol. Newman and Kwart reported, in two different contributions, the possibility of using the dimethylthiocarbamoyl group for the rearrangement; to date the preferred starting materials for the MNK rearrangement [1, 2]. An independent study, which actually was first announced prior to the Newman and Kwart report, was given by Miyazaki [3] who also further contributed to the mechanistic understanding of the reaction (Scheme 3) [10].

This review is divided into three parts. The first part concerns the aromatic thione–thiol rearrangement, i.e. the typical MNK rearrangement, which since



Scheme 3 Examples of thione–thiol rearrangement



Scheme 4 Example of [3.3] sigmatropic reaction giving thione–thiol rearrangement

its discovery has been widely applied in organic synthesis. The second part concerns the use of the MNK rearrangement in industrial processes. Since industrial applications imply a thorough search of the best reaction conditions and require detailed optimisation studies, we judged them useful for gaining insight into the reaction outcome, even for small laboratory preparations. The third part deals with the equivalent aliphatic rearrangement which, as mentioned, has been less extensively exploited and often requires different reaction conditions and reagents.

It should be mentioned that, among the examples of thione-to-thiol rearrangements, many of them occur via a [3,3]-sigmatropic rearrangement (Scheme 4).

Such reactions, which have been extensively exploited to produce thiols efficiently from allyl dithiocarbamates, have been excluded from the present review to focus only on those cases where sulfur is exchanged for oxygen at the same carbon atom [11, 12].

In a similar way, the reaction of xanthates under radical conditions leads to products and selectivities that are totally different from those in thermal rearrangements. The radical transformation usually furnishes unsubstituted hydrocarbons as reaction products. The major accomplishment of the reaction is the deoxygenation of secondary alcohols to furnish the corresponding hydrocarbons when tributylstannane is used with *O*-cycloalkyl thiobenzoates or *S*-methyl dithiocarbamates [13]. However, the rearranged product may be observed as a byproduct [14, 15].

2
Aromatic

2.1
General Considerations

2.1.1
Mechanism

Since its discovery, it has been widely accepted that the mechanism of the tautomeric MNK rearrangement consists of a nucleophilic displacement of the oxygen substituent on the aromatic ring by the sulfur atom through

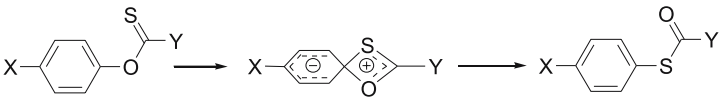
a four-membered ring transition state. The stronger nucleophilicity of sulfur compared to oxygen is the driving force of the reaction towards the single product where sulfur is completely substituted for oxygen (Scheme 5) [16].

Strong support for such a mechanistic proposal is the observation that the reaction rate depends on the capability of the substituent of the aromatic ring to stabilise the negative charge (e.g. 4-nitro > 2,4-dichloro > 2- and 4-chloro > 4-bromo > 2,4- and 2,6-dimethyl > 2- and 4-methoxy) as well as by the capability of the substituent Y to stabilise the positive charge [17]. Indeed, Newman and Kwart noticed that *N*-alkyls (and *N*-alkylaryl) substituents furnished the best yields in the rearranged products and, beside ameliorating the reaction conditions, they improved the synthetic potential because the products were easily cleaved to the corresponding thiols via reductive hydrolysis (Scheme 6).

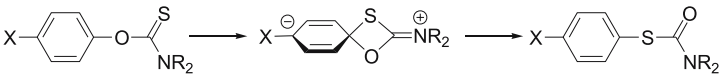
The strong contribution of the reaction rate due to substituents at the aromatic ring and the beneficial effect of the alkylamido group was confirmed by Miyazaki, who reported a detailed work based on the influence on the rate of reaction on different substituents at the 3 or 4 positions (Scheme 7) [10, 18].

The importance of the electronic effect is most evident in pyridine systems bearing nitrogen at the 2 and 4 positions, which activate the rearrangement by protonation, as exemplified by *O*-2-pyridyl thiocarbamate (Scheme 8) [6]. The activation is such that the reaction occurs at room temperature. In contrast, where nitrogen is at the 3 position the temperature at which rearrangement occurs is lowered by 60 °C, from 210 to 150 °C in the case of phenyl.

Even small structural changes in the starting materials can result in major reactivity differences, as demonstrated by a series of diversely substituted chromanones, the sulfur analogs of the natural precocenes [19, 20]. A sim-



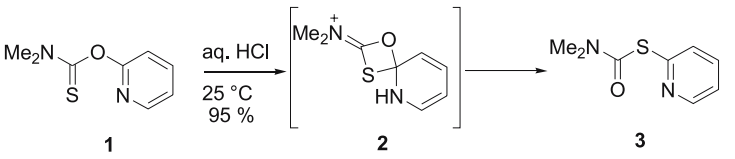
Scheme 5 Four-member intermediate present in the thione–thiols rearrangements



Scheme 6 Stabilisation of the positive charge by *N*,*N*-dialkyl groups in the intermediate

Rate of reaction X: 4-NO_2 > 4-CN > 4-SO_2Me > 4-COOEt > 3-NO_2
R: i-But > n-Pr > Et > Me

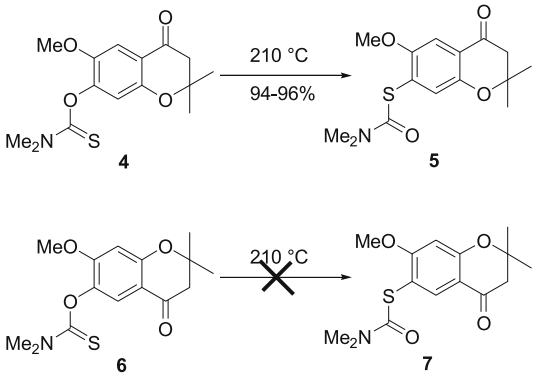
Scheme 7 Correlation of the rate of reaction with the substituents



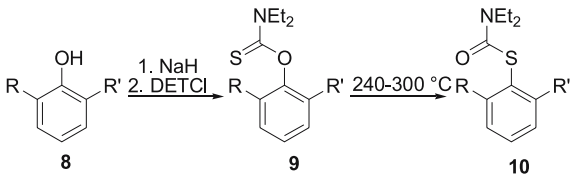
Scheme 8 Room temperature MNK in 2-pyridine derivative

ple shift of the carbonyl functionality from *para* to *meta* as shown Scheme 9 strongly varies the electron density of the aromatic ring and, as a consequence, the reaction outcome.

Besides electronic effects, steric effects have also been investigated. Contrary to expectations, the presence of reasonably hindered substituents at the *ortho* position, favours the reaction, preorganising the formation of the spirocyclic intermediate. In the presence of a single *ortho* substitution, the rate of reaction follows the trend *t*-butyl > *i*-propyl > methyl [21]. The



Scheme 9 Reactivity of chromanones



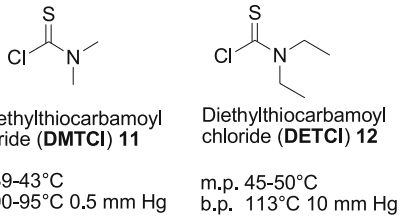
a R = Me; R' = H;	53 %	90%
b R = *i*-Pr; R' = H;	40 %	95%
c R = *t*-Bu; R' = H:	24 %	21%
d R = Me; R' = Me:	45 %	90%
e R = *t*-Bu; R' = Me:	29 %	95%

Scheme 10 Effect of steric hindrance in the reaction yield

yields of 2,5-dialkyl substituted rings are generally excellent for the MNK rearrangement but sometimes modest for the formation of the starting thiocarbamate, independent of the dialkylthiocarbamoylating agent used [22]. The presence of two *t*-butyl groups is probably excessive, reducing the yields of the rearrangements to about 40%, (Scheme 10) [23, 24]. The presence of one adamantyl group at the *ortho* position reduces the yield of the rearrangement to 23% [25].

2.1.2
Preparation of the Starting Materials

The preparation of typical substrates consists of the thiocarbamoylation of the corresponding phenol (Scheme 11). Usually the phenolic starting material is added to a solution of NaH in DMF at 0 °C [26]. The commercially available dialkylthiocarbamoyl chloride is added to the reaction mixture, the temperature raised to 80–85 °C and the reaction left to stir for 1 h



Scheme 11 Common carbamoylating agents

Alternative base/solvent couples can be selected among DABCO/DMF [27], $NaOH/K_2CO_3$/DMF/PTC (phase transfer catalyst), KOH/MeOH [28], DMAP/NEt_3/DMTCl [29] and quinoline [30, 31]. For optimal results, the choice of the most appropriate couple depends on solubility and acidity issues. The yields are usually from good to excellent, the only exceptions arising when the phenol is excessively hindered or additional acidic protons are present in the molecule.

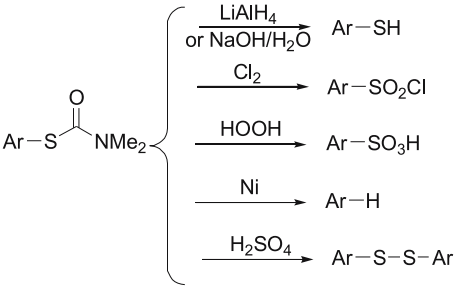
2.1.3
Reaction Conditions

The reaction is usually carried out in the neat state at high temperatures for short times under inert atmosphere. Alternatively, high boiling point solvents are often used, such as diphenyl ether, dichlorobenzene, sulfolane, dimethyl aniline or diethyl aniline. The best conditions are those that avoid unnecessarily heating the product. Recently, microwave irradiation has been used with interesting results [32].

2.1.4 Products

The product of the rearrangement can be treated with different reagents to obtain different sulfur compounds. The typical reaction is reductive hydrolysis ($LiAlH_4$) or basic hydrolysis (NaOH/water) leading to the thiol products.

However, a plethora of other conditions have been developed for the synthesis of other *S*-derivatives. The crude thiocarbamates can be readily converted to the corresponding sulfonyl chlorides via oxidative chlorination under mild conditions [33]. Oxidation to the corresponding arylsulfonic acid has been carried out using 30% hydrogen peroxide as oxidising agent and formic acid as solvent [34, 35]. Acidic conditions lead to the corresponding disulfide (Scheme 12) [36]. Desulfurisation can be obtained using nickel [20].



Scheme 12 The product of the rearrangement can be alternatively functionalised to give a different product

2.2 Examples

2.2.1 General Thiols

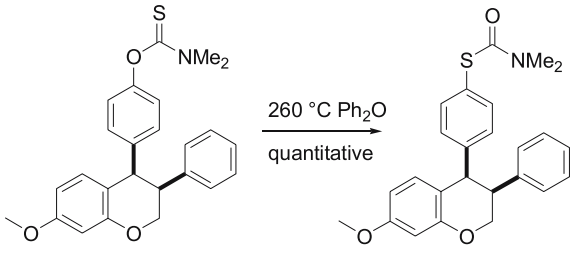
The MNK rearrangement is the most widely used method for the production of aromatic thiols. The reaction often represents the method of choice for the synthesis of thiols due to its high yields and good tolerance towards the aromatic ring substituents such as aldehydes [37, 38], esters [39], halogens [40] and pyrones [41, 42].

For example, the transformation of thiocarbamate **13** not only proves to be compatible with the 3-chromane substituent, but also retains the initial product distereoisomeric ratio (Scheme 13) [43].

Due to the presence of sulfur atoms in numerous biologically active compounds, the reaction has been extensively carried out for the synthesis of

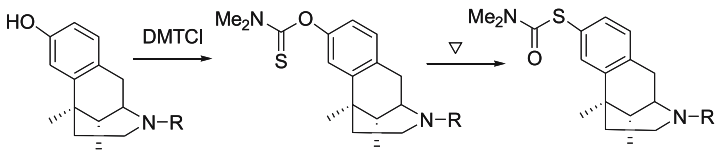
several medicinal chemistry targets. The reaction tolerance to aromatic ring substituents, in the lead discovery phase, facilitates the production of libraries of "phenol" candidates and their corresponding "thiophenol" analogues, via the MNK rearrangement. For example, this approach has been applied in a study directed towards the synthesis of 2′-alkylthio-6,7-benzomorphans (Scheme 14) [44].

As shown in Scheme 14, the reaction is tolerant to the presence of most functional groups. Only the prenyl and cyclopropylmethyl groups seem to be sensitive to the high temperatures involved in the rearrangement, lead-



(±)**13** (±)**14**

Scheme 13 MNK rearrangement in a chromane subunit



	15	**16** yield %	Temp	min	**17** yield %
	(±) a	85	300	5	92
a R= Me	S(+) a	64	300	5	73
b R= CH_2CH_2Ph	R(-) a	83	300	5	85
c R= CH_2CH_2	b	100	320	6	96
d R= $CH_2CH{=}C(CH_3)_2$	c	81	310	5	96
e R= CH_2Ph	(±) d	84	325	0.5	11
f R = $CH_2C_3H_5$	S(+) d	77	325	0.5	8
	R(-) d	75	325	0.5	8
	e	72	315	4	74
	f	96			

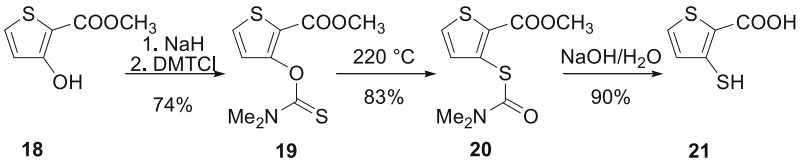
Scheme 14 Preparation of alkylthiobenzomorphanes

ing to unidentified tars. The authors, during the optimisation of conversions and yields, monitored the reaction by TLC and ^{1}H-NMR spectroscopy, in particular focusing their attention on dimethylamino group ^{1}H-NMR signals. As a general rule, the ratio between the area of the singlet belonging to the newly formed dimethylamino **17** (at 3.04 ppm for this example) and the area of the two singlets belonging to the starting dimethylamino group **16** (3.33 and 3.46 ppm in deuterochloroform) furnishes the reaction conversion and is the most widely used method for following the reaction outcome. They found the reaction to proceed above 250 °C and selected the optimum conditions at 300 °C for 5 min. Interestingly, a comparison of the MNK rearrangement with alternative methods for the synthesis of thiol derivatives showed the superiority of this method [45].

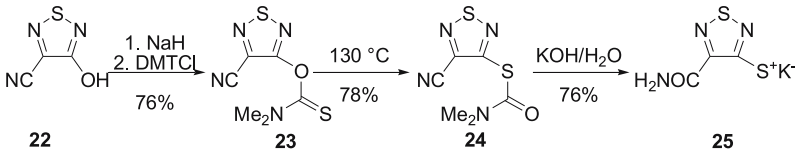
Besides functional group tolerance, high yields and ease of monitoring the reaction outcome, the MNK rearrangement has been widely used to obtain selective introduction of sulfonyl functionalities, whereas other methods have failed. For example, direct sulfonylation often yields mixtures of isomeric compounds difficult to separate [46, 47]. In contrast, subjecting a starting phenol to MNK rearrangement and oxidising the obtained carbamate with hydrogen peroxide and formic acid as the solvent, it is possible to selectively obtain the desired sulfonyl derivative.

2.2.2 Heterocyclic Substrates

Heterocyclic substrates have also proved to be viable starting materials for the rearrangement. The reaction has been used for the synthesis of 3-mercaptothiophene derivatives furnishing the desired products in high yields (Scheme 15) [48, 49].



Scheme 15 Formation of β-thiol in a thiophene derivative



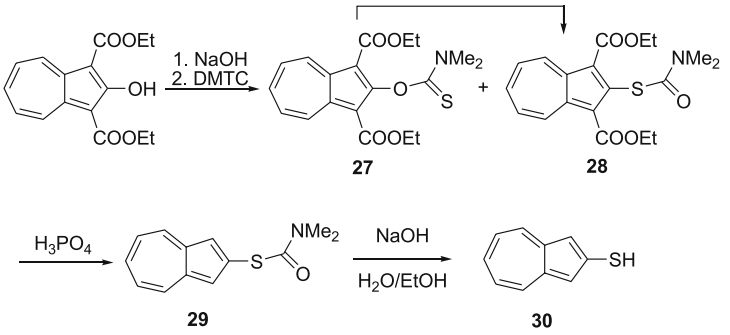
Scheme 16 Formation of β-thiol in a thiadiazole derivative

3-Hydroxy-4-cyano-1,2,5-thiadiazole **22** was subjected to thiocarbamoylation and subsequent thermal rearrangement for the production of the nitrile intermediate, which upon hydrolysis gave 3-thiolate-4-amide-1,2,5-thiadiazole **25** (Scheme 16) [50].

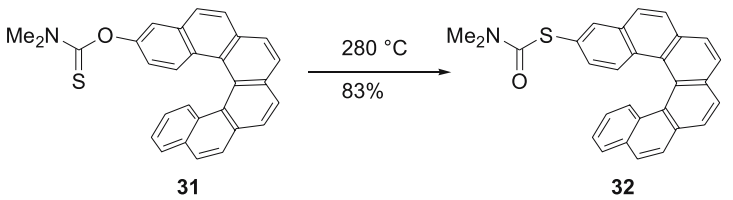
2.2.3 Aromatic Fused Rings

MNK rearrangement is also a widespread method for the conversion of hydroxyl-substituted aromatic fused rings, such as the naphthalene and quinoline ring systems. For these substrates, a different trend in reactivity was observed for aromatic fused rings bearing the hydroxyl group at the alpha or beta position. Whereas conversion of 1-naphthol failed [51], good results were obtained for 2-naphthol conversion [52]. The MNK transformation was, however, possible for quinoline derivatives bearing the hydroxyl functionality at the 2-position [53, 54].

The rearrangement has been applied to the synthesis of 2-, and 6-azulenethiols [55]. In this case, however, it was not possible to start from the corresponding hydroxyazulenes. In fact, the reaction of the alcoholic functional group with dimethylthiocarbamoyl chloride in the presence of sodium hydroxide afforded a complex reaction mixture, involving electrophilic substitution at various positions. In order to avoid this problem, the correspond-



Scheme 17 Functionalisation in an azulene molecule



Scheme 18 MNK rearrangement in a [6]-helicene

ing 2-hydroxy-1,3-dicarboxylate was used as starting material, which gave product **27** and **28** in 23% and 48% yields, respectively (Scheme 17).

The first compound mentioned underwent rearrangement at high temperature affording **28** quantitatively. The diester was then subjected to decarboxylation in phosphoric acid, affording the aromatic thiol in 86% yield. Similarly, the reaction has been carried out for 6-azulenethiol.

Inherently chiral compounds, such as helicens, gave good conversion to the corresponding thiols using the MNK rearrangement (Scheme 18) [56].

2.2.4 2-Substituted Thiocarbamates

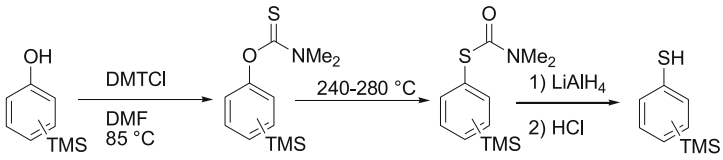
In the MNK rearrangement, *ortho* substituents usually play a key role in modulating the reaction pathway (e.g. yield) and directing further product reactivity (e.g. subsequent ring formation).

The position of a trimethylsilyl substituent in phenols **33** determines great yield differences in both thiocarbamate formation and rearrangement [57, 58]. The required TMS-substituted phenols, which were prepared from the respective bromophenols, were tested under standard conditions (Scheme 19). The yield of the rearrangement decreased as the substituent moved from *para* to *ortho*.

Good yields were always obtained for the final hydrolysis step. Moreover, the silyl group had a remarkable effect in reducing the thiophenol smell. More recently, longer alkyl chains instead of TMS have been used in the preparation of other odourless thiols [59].

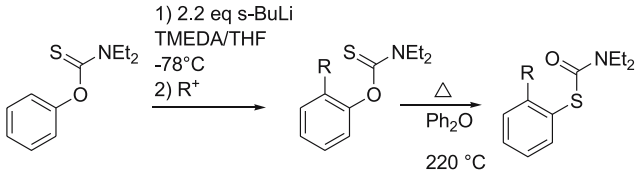
The starting thiocarbamates can also be used for selective introduction of further substitution at 2-position via 2-directed metallation [60]. Indeed, *s*-BuLi in TMEDA selectively furnished the 2-lithiated product, which was reacted with electrophiles to produce the corresponding compounds shown in Scheme 20 [61].

The presence of a nitro group at the *ortho* position can be strategically useful for the production of oxothiazole fused rings or for the synthesis of thio



	33	**34**	**35**	**36**
a:*para*		100	82	71
b:*meta*		100	53	82
c:*ortho*		60	30	84

Scheme 19 MNK rearrangement for the production of silyl thiocarbamates and the resulting yields

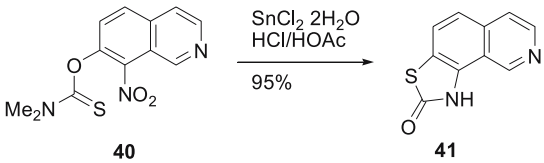


37	38	39
a:R = CHO	30	66
b:R = $CONEt_2$	84	78
c:R = SPh	85	87
d:R = I	66	87
e:R = $SiMe_3$	80	91

Scheme 20 *ortho*-Metallation followed by MNK rearrangement

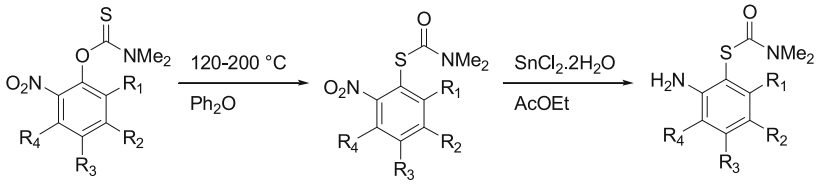
anilines. For example, in the synthesis of a series of phenylethanolamine-*N*-methyltransferase inhibitors, Girard and coworkers developed a strategy for the construction of 2-oxothiazoles [54]. Reaction of *O*-aryl dimethylthiocarbamate under reductive conditions smoothly furnished 2-oxothiazole **41** in high yields (Scheme 21).

In another example, Shinkai was able to reduce an *ortho* nitro group to the corresponding amino in the presence of the rearranged product. This demonstrates again the stability of *S*-aryl thiocarbamates to moderate reducing agents such as tin chloride (Scheme 22) [62].



40 **41**

Scheme 21 Synthesis of oxathiazole **41**



42 **43** **44**

R_1=H,F; R_2=H,F,Cl,CF_3,CN,OMe; R_3=H,F; R_4=H,F

Scheme 22 Reduction of *ortho*-nitro aromatic thiocarbamates to corresponding anilines

The presence of 2-halo functionalities opens new reaction pathways. This is the case of the trihalosubstituted substrates studied by Reineke (Scheme 23) [63].

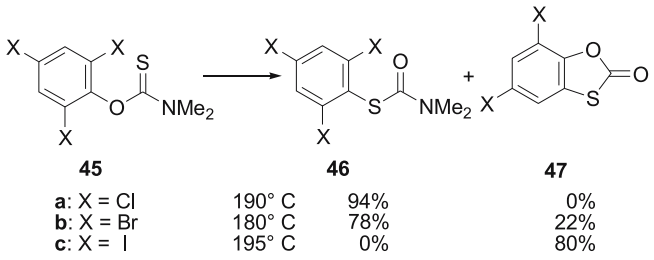
Among the halogen series, the greater the ability of the leaving group of the substituent, the easier is the formation of the byproduct benzoxathiol. Benzoxathiol-2-ones are formed by the nucleophilic attack of the thiocarbonyl group to the carbon of the halogen atom. In the case of chlorine, only the uncyclised rearranged product was observed. However, a bromo functionality in the *para* position did not affect the reaction and it could be used after the rearrangement for a Stille coupling [64].

Along with the synthesis of reductase inhibitors, it was demonstrated that tetrahalo-trityl substrates are stable to the reaction conditions (Scheme 24) [65, 66].

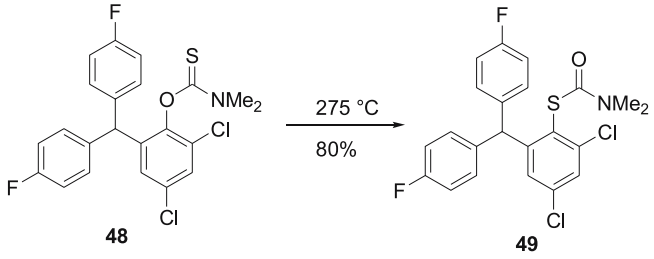
Benzoxathiol-2-one formation can in turn be the desired reaction pathway. This compound can be similarly prepared when a methoxy group is present at the 2 position [67]. The cyclisation is carried out using hydroiodic acid or pyridine hydrochloride as demethylating agents (Scheme 25).

The presence at the *ortho* position of an aldehyde function has been used for the synthesis of substituted benzothiophenes (Scheme 26) [68, 69].

Since the original paper by Newman, it has been well known that the presence of an acetyl group in the 2 position gives very poor yields of rearranged products [70]. The problem was solved by performing the reaction in re-

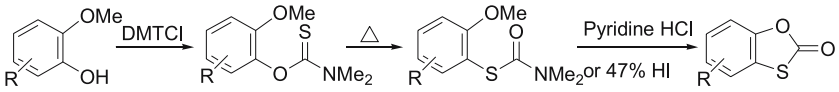


Scheme 23 Effect of 2-halogen substituents in the rearrangement



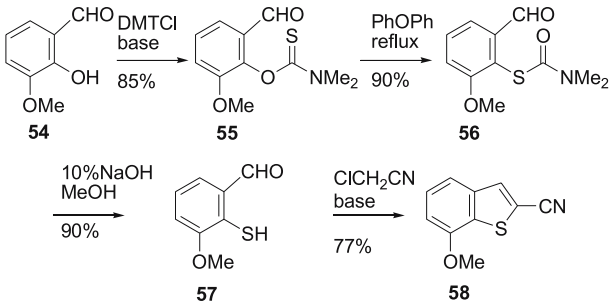
Scheme 24 Tetrahalo-trityl substrates stable under the MNK reaction conditions

fluxing dichlorobenzene. As shown in Scheme 27, the electronegativity of the substituent is crucial for the final reaction yield. The rearrangement in neat leads exclusively to the thiochromone ring (Scheme 27).

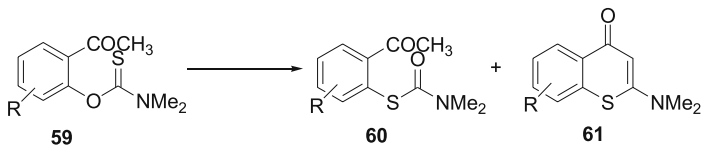


50	51	52	53	
a: R = H	42%	72%		88%
b: R = 4-Me	49%	56%		100%
c: R = 4-Cl	42%	21%		81%
d: R = 3-OMe	51%	55%	R = 7-OH	87%
e: R = 6-OMe	39%	39%	R = 4-OH	64%

Scheme 25 Rearrangement and synthesis of oxothiazoles



Scheme 26 MNK rearrangement for the synthesis of substituted benzothiophenes



a: R = H	dichlorobenzene reflux	55%	4%
b: R = 5-MeO	dichlorobenzene reflux	41%	7%
c: R = 3-OH	dichlorobenzene reflux	25%	5%
d: R = 3-OH	neat	0%	50%
e: R = 3-MeO	dichlorobenzene reflux	45%	
f: R = OTf	dichlorobenzene reflux	91%	
g: R = 3-OAc	dichlorobenzene reflux	66%	

Scheme 27 Synthesis of the thiochromone ring

2.2.5 Biaryls

Substrates with 2-naphthyl or 2-phenyl groups to the reacting hydroxyl functionality represent one of the most fruitful applications of the MNK rearrangement. In fact, this reaction has been extensively used as a key step for the synthesis of BINAS compounds sulfur analogous to BINOL or BINAP.

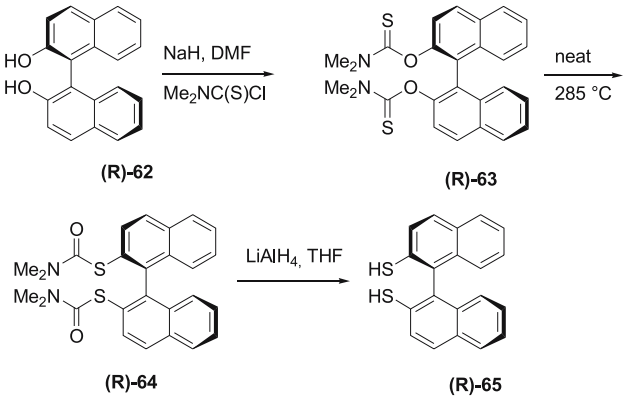
Racemic binaphthol was first converted to binaphthodithiol by Cram [71]. In order to obtain enantiopure BINAS. Modena prepared the racemic thioether and then resolved it via diasteromeric separation of the corresponding sulfoxides [72].

It is important to note that enantiopure BINOL was converted to the corresponding enantiopure dithiol in high yields, proving atropoisomeric conservation for binaphthyl substrates during the MNK rearrangement [73, 74]. The result can be explained because of the high energy barrier for bis-thiocarbamate and *O*-naphthyl thiocarbamate racemisation via rotation through the atropoisomeric bond (Scheme 28).

The ease of performance and the reaction stereoconservation led to the synthesis of a large variety of compounds such as functionalised biphenylenes [75], biphenanthrenes [76] and octahydro-binaphthyl [77].

The MNK rearrangement can be applied successfully to the synthesis of asymmetrically substituted 1,1′-binaphthyls with the thiol group being one of the substituents (Scheme 29) [78].

Whereas at > 260 °C the reaction mainly furnished the doubly rearranged product, the mono-rearranged *O*,*S*-derivative was obtained as the major product (40%) at 240 °C. In the same study the *N*,*S* derivatives have also been similarly prepared (Scheme 29).



Scheme 28 Synthesis of (R)-BINAS

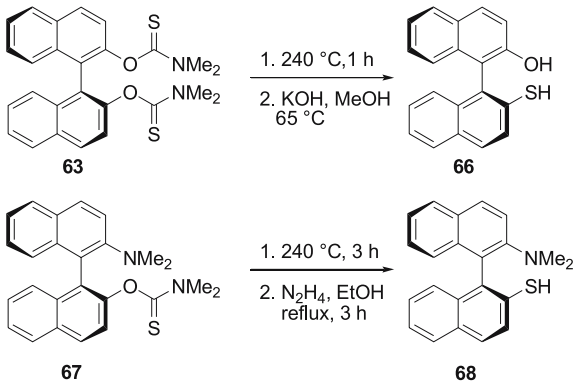
An alternative method was offered by Woodward who was able to perform the monoacylation of the diol and consequently performed the rearrangement to *O*,*S* binaphthol (Scheme 30) [79].

A further alternative procedure for the mono rearrangement, was developed by Gladiali and consists in using one equivalent of base for the preparation of the thiocarbamates [80]. The procedure led to the synthesis of *O*,*S*-binaphthol in five steps with an overall 67% yield.

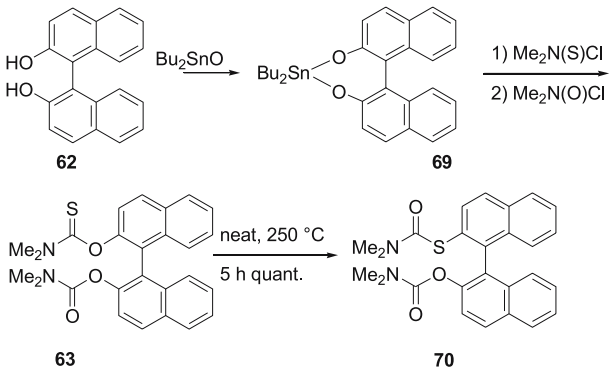
For the preparation of chiral ligand **72**, with a pendant achiral oxazoline, the thiocarbamate **71** was subjected to MNK rearrangement (280 °C, 17 min) to the corresponding thiocarbamate (S)-**72** in 57% yield (Scheme 31).

Further hydrolysis of (S)-**72** afforded the thiol **73**, which was alkylated to the target ether **74** with 85% ee [81]. The MNK rearrangement was also used for the synthesis of thiophosphines, sulfur analogues of MOP [82].

The thiophene derivative usually presents as an impurity, and the binaphthyl derivative may be produced as the main product in the rearrangement of



Scheme 29 Synthesis of mixed BINAS

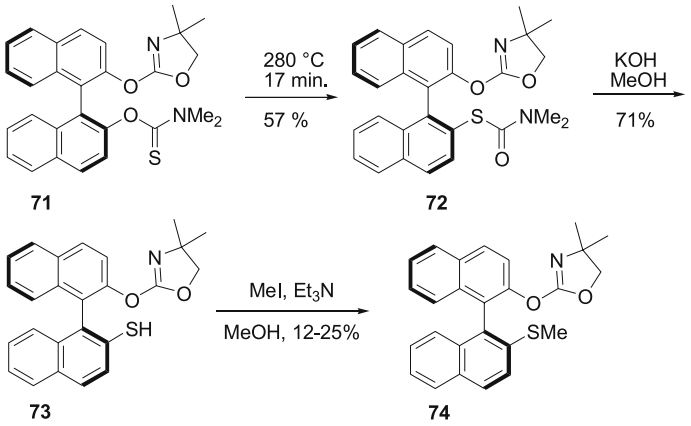


Scheme 30 Procedure for the synthesis of mixed BINAS

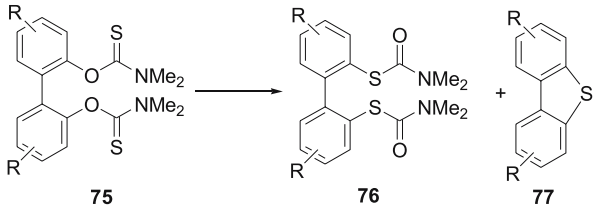
biphenyl derivatives upon changing reaction the conditions (Scheme 32) [74, 83, 84].

In general, long reaction times and high reaction temperatures favour the thiophene derivative **77**, as shown in Scheme 32.

Asymmetrical compounds have been obtained by the Ni-catalysed ring-opening of diphenylthiophenes with a Grignard reagent. These are produced from rearrangement of the carbamate and the subsequent elimination to form the corresponding dibenzothiophenes. The pure thiophene is produced in high yield and used as starting material to synthesise functionalised chiral ligands by Grignard cross-coupling catalysed by nickel complexes (Scheme 33).

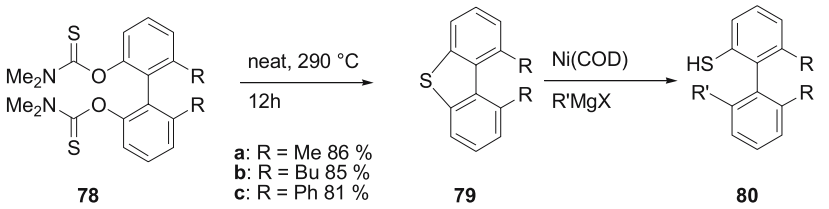


Scheme 31 Synthesis of mixed BINAS

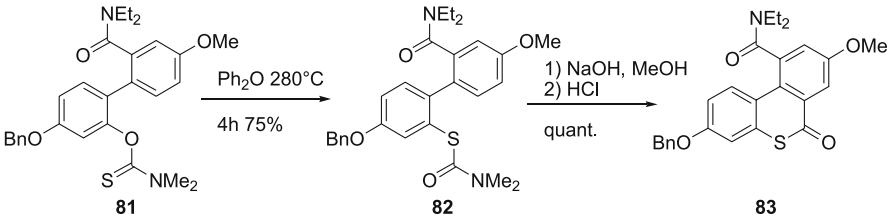


	Temp (°C)	Time (min)	**76** (yield)	**77** (yield)
a: R = H	310	25	72	-
b: R = 3-Me	285	22	80	20
c: R = 6-OMe	285	22	74	8
d: R = 6-Me	290	720	-	82
e: R = 6-Bu	290	720	-	85
f: R = 6-Ph	290	720	-	81

Scheme 32 Biaryl rearrangement



Scheme 33 Synthesis of thiophene derivative followed by functionalisation



Scheme 34 Rearrangement and cyclisation

Axially chiral bidentate ligands have been extensively developed for their use in asymmetric catalysis [85, 86].

An elegant example of rearrangement followed by cyclisation has been recently reported by Kim. In a study directed towards the development of dihydrobenzoxathiin as antagonist for osteoporosis, the MNK rearrangement was utilised to achieve the chemical synthesis of its major metabolite, confirming its structure (Scheme 34) [87].

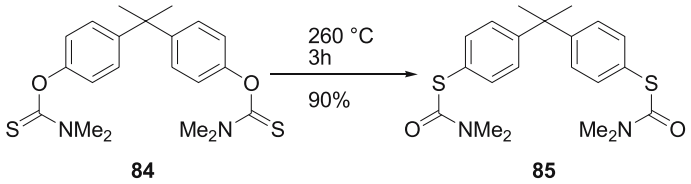
The MNK rearrangement proceeded smoothly to furnish *S*-aryl dimethylthiocarbamate. A temperature of 280 °C was necessary for clean conversion. Eventual hydrolysis with sodium hydroxide and acidification with dilute acid chloride promoted the cyclisation to thiocoumarin **83**.

2.2.6 Supramolecular Chemistry/Polymers

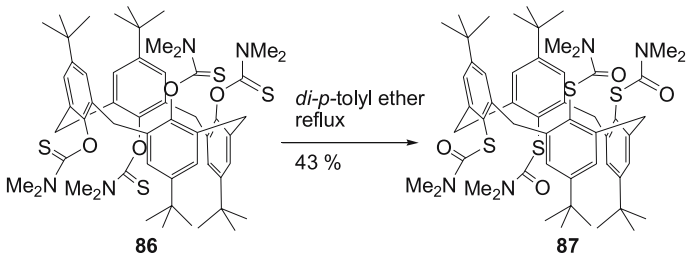
Particular interest has been directed towards the use of the MNK reaction in supramolecular chemistry. The possibility of modifying a substrate backbone, by substituting an oxygen atom with sulfur, can be of extreme importance for changing a molecule's recognition properties. Indeed, this transformation has been exploited in typical hosts such as crown ethers and calixarenes via the MNK rearrangement.

The variation in the complexation properties by this substitution (polyether to polythioether) was used by Cram for ion complexation and by Inouye for the synthesis of macrocycles for sugar recognition (Scheme 35) [71, 88].

In particular, this reaction has been applied to the synthesis of thiocalixarenes (Scheme 36) [89, 90].



Scheme 35 Rearrangement for the synthesis of a precursor for a macrocycle



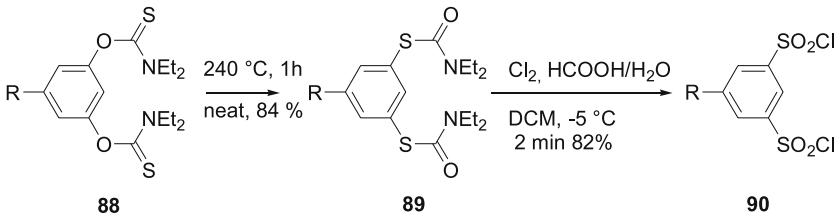
Scheme 36 Rearrangement in calixarene

The synthesis of the carbamoyl derivative and the subsequent rearrangement have to be carried out simultaneously at four centres [91]. In an analogous manner, the same observations have been carried for the mercaptothiacalix[4]arene [92, 93]. Interestingly, in systems where multiple functionalities are present, the metal counterion for the deprotonation of the phenols plays an important role.

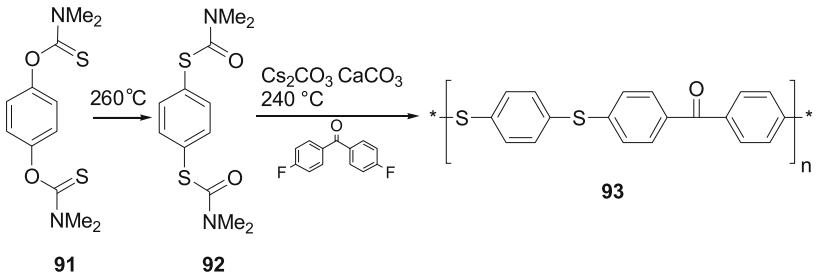
The reaction has been extensively applied to the synthesis of precursors of dendrimers. Due to the possibility of converting the obtained thiol directly to sulfonyl chlorides, Percec widely investigated this chemistry for the preparation of multisulfonyl chlorides [33]. These compounds exhibit important applications in synthetic and supramolecular chemistry (Scheme 37).

Another application of the rearrangement in dendrimers focuses on the development of novel polythioether dendrons on a solid support for supported catalysis applications [94].

The use of the MNK rearrangement proved particularly useful in the synthesis of polyarylene-thioethers by a one-pot polymerisation of *N*, *N*-



Scheme 37 Synthesis of building block for the development of dendrimers



Scheme 38 Synthesis of polyarylenethioethers by MNK rearrangement followed by polymerisation

dimethyl-*S*-carbamate masked bisthiols. These compounds can be conveniently prepared by the MNK rearrangement of the corresponding phenols (Scheme 38) [28].

The reaction is a consequence of the capability of the *N*,*N*-dimethyl-*S*-carbamates to be cleaved to the corresponding thiols, carbon dioxide and dimethylamine at high temperature in the presence of cesium carbonate [30, 31, 95].

The rearrangement has also been used in the synthesis of multidentate ligands [96].

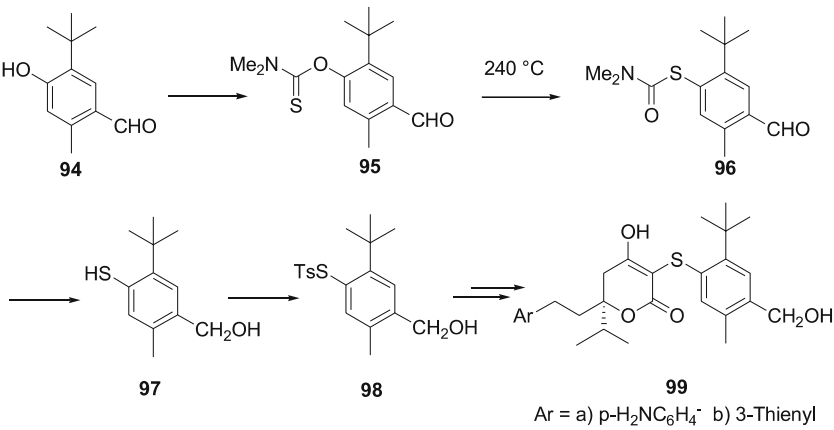
2.3 Scaled Reactions

Because the MNK rearrangement is the method of choice for the formation of aromatic thiols, a study directed towards the scale-up to industrial production was pursued.

In the continuous quest for new generations of HIV inhibitors, Pfizer identified the thiosubstituted pyrones as a new class of non-peptidic protease inhibitors [97].

3-Arylthio-4-hydroxy-5,6-dihydropyrones such as CI-1029 **99a** and PD 190497 **99b** were selected as lead candidates and their synthesis scaled-up. In particular, a method for the preparation of intermediate **97**, was developed on the kilogram scale using the MNK rearrangement as a key step (Scheme 39) [98].

The development of a large scale preparation resulted in discovery of a practical and reliable method of synthesis. The thiocarbamylation of the phenol with the *t*-butyl group at the *ortho* position is not a straightforward reaction to accomplish. For example, the unfavourable effect on the reaction rate of the bulky group was overcome by controlling the pH to 11.5–12.5, while carrying out the simultaneous additions of KOH and the tetrahydrofuran solution of DMTCl. This major technical and synthetic advance was developed for the MNK rearrangement step. The reaction was originally car-

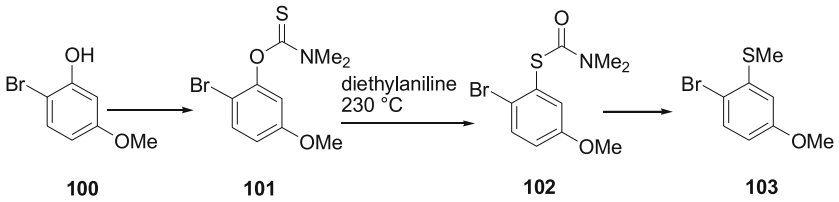


Scheme 39 Synthesis of product **99**

ried out in diphenyl ether at 270 °C. However, the reaction outcome generated two major impurities whose removal proved difficult to accomplish, leading to high impurity profiles for the final active pharmaceutical ingredient. A systematic study of process variables followed, comprising substrate concentration (25–75%), temperature (250–300 °C) and reaction time (20–180 min). The major effect was produced by the reaction dilution: the higher the dilution the better the product quality. The study showed as well that a temperature increase shortened the reaction time, raising throughput to acceptable levels. Another improvement dealt with the use of tetraethylene glycol as reaction solvent, which after water addition during work-up constituted the right medium for product precipitation and further isolation. The last improvement was obtained using a continuous tubular reactor to execute the rearrangement. This allowed for a more efficient temperature control and increased per day productivity. On a laboratory scale the process was conducted in a GC oven. Hot tube conditions have been largely used for the scale-up of thermal rearrangements [99].

Another description of large scale analysis come from AstraZeneca in a study directed towards the synthesis of a neurokinin inhibitor of the central nervous system [100]. The synthesis inherited from the research stage already contained a Newman–Kwart rearrangement for the introduction of the sulfur atom (Scheme 40). This step was maintained in the reaction scale-up [101, 102].

The development of the process is thoroughly described in the paper and several hits can be discovered. The authors demonstrated that degassing the solvent before thermal rearrangement resulted in lower impurity profiles. Subsequent hydrolysis and methylation gave the corresponding drug precursor.



Scheme 40 Synthesis of **103**

An interesting possibility is offered by the implementation of microreactors for this rearrangement. In fact, preliminary results has shown interesting productivity for this reaction [103].

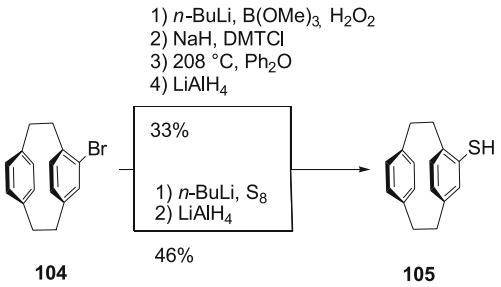
The method has proved to be valuable for the synthesis of basic thiophenols in industrial synthesis, as shown by the manufacture of the starting material dimethylthiocarbamoyl chloride [104].

2.4 Alternatives

Various method are available in the literature for the synthesis of thiophenols [105]. In some cases, the high temperature of rearrangement or the presence of sensitive functional groups call for alternative ways of introducing the sulfur functionality.

This is the case for the synthesis of a thiol derivative of a paracyclophane starting from the corresponding bromine-substituted aromatic ring (Scheme 41) [106].

The MNK route displayed difficulties in the rearrangement, showing the formation of two byproducts coming from ring opening. Cyclophanes are indeed not stable at high temperatures. The alternative procedure using sublimed sulfur on the metallated substrate furnished the product in higher yield. The introduction of the sulfur atom using this methodology has also been used as alternative of MNK elsewhere [107].



Scheme 41 Comparative rearrangement using two different methods

3
Aliphatic

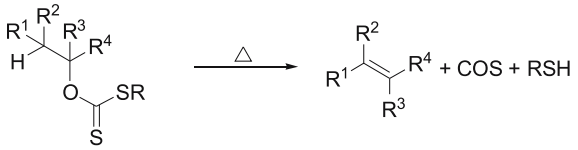
3.1
General Considerations

The rearrangement of thiocarbamates has been less used in the synthesis of thiols in aliphatic molecules. This is due to the availability of different methods and by the fact that when Newman tried the same reaction on aliphatic molecules he observed complete conversion to olefins [108]. In fact, in the case of aliphatic molecules, alcohol xanthates afford the corresponding olefins at high temperature if β-hydrogen atoms are present. This reaction, known as the Chugaev elimination, proceeds via an unimolecular *syn* elimination (Scheme 42) [109, 110]. Small percentages of the corresponding rearranged product are sometimes detected [111, 112].

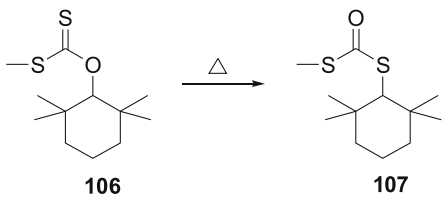
However, as shown by Taguchi, xanthates rearrange to the corresponding dithiocarbonates when no β-hydrogens are present (Scheme 43) [113, 114].

The rearrangement is also possible as a side reaction when olefin formation is sought. In this case, the difficulty in obtaining a planar transition state and the participation of a neighbouring group play important roles. In the case shown in Scheme 44 the rearrangement takes place only if the reacting substrate possesses an anchimeric group adjacent to the xanthate.

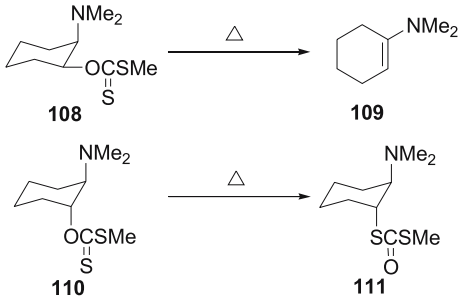
Most probably an ion pair mechanism is involved in which the anchimeric group stabilises the positive charge. This is confirmed by the simultaneous presence of products giving 1,2 shift and products resulting through an SNi (intramolecular nucleophilic substitution) type mechanism (Scheme 45) [115].



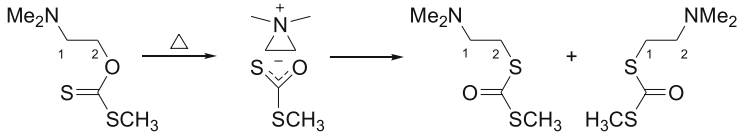
Scheme 42 Elimination reaction (Chugaev reaction)



Scheme 43 Rearrangement in a molecule where β-hydrogens are not present



Scheme 44 Influence of the anchimeric group in the rearrangement



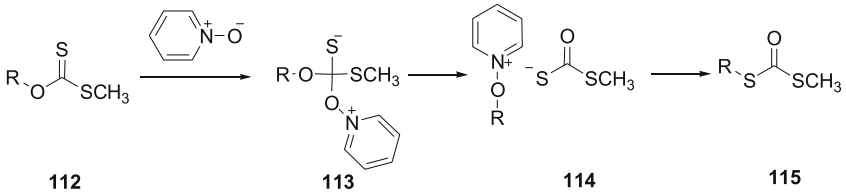
Scheme 45 Mechanism of the rearrangement

A wide variety of catalysts have been used to increase the rate of the desired reaction pathway, among which are Lewis acids, protic acids, phenols and pyridine *N*-oxides. Due to the different characteristics and products of the different catalysts, the examples will be grouped according to the catalyst used.

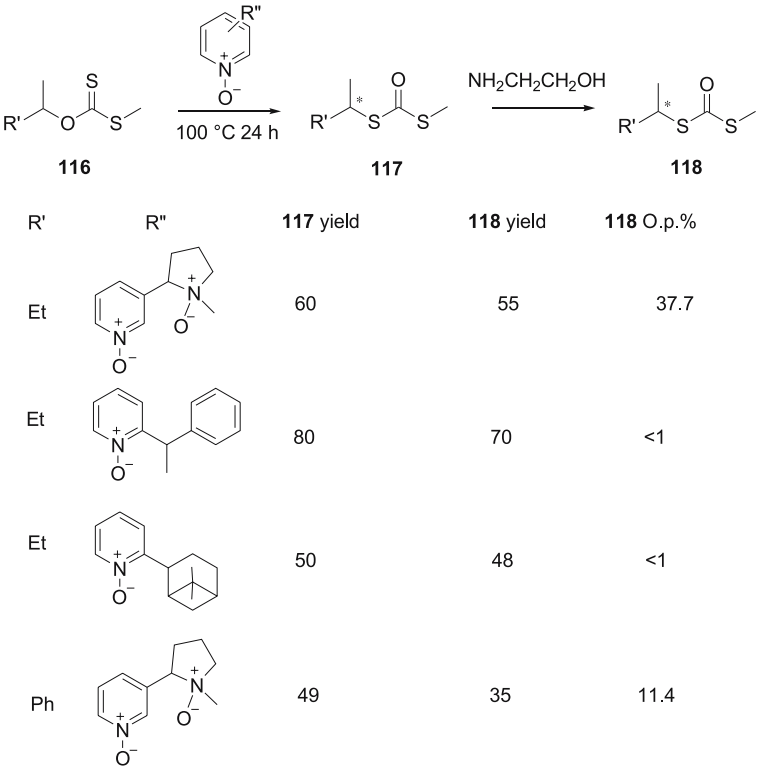
3.2 Examples

3.2.1 Pyridine *N*-Oxides

Pyridine *N*-oxides proved to be good catalysts for the rearrangement, confirming the formation of an ion pair intermediate followed by an intermolecular attack (Scheme 46) [116].



Scheme 46 Rearrangement catalysed by pyridine *N*-oxide



Scheme 47 *N*-oxide catalysed rearrangement

Hisano developed a solid phase copolymer incorporating the *N*-oxide functionality that was able to catalyse the reaction, furnishing good yields of thiols [117]. The method has been used recently for the enantioselective synthesis of thiols catalysed by optically active pyridine *N*-oxides (Scheme 47) [118].

Starting from racemic alcohols it was possible to obtain the corresponding thiols with optical purities up to 38%.

3.2.2 Acids

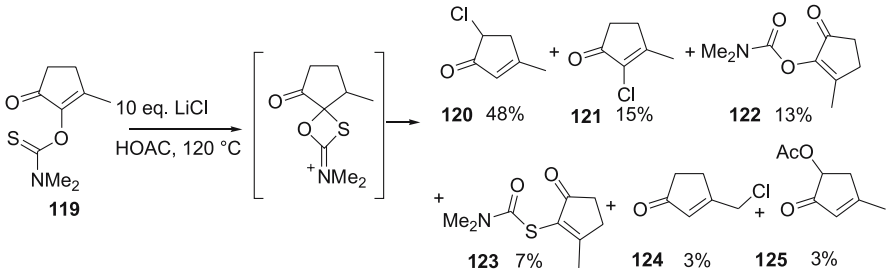
The role played by a protic acid catalyst in the rearrangement has been observed by Olah [119]. The protonation site has been proved to be the thiocarbonyl sulfur. A wide variety of acids have been used for the reaction, such as phenols or picric acid [120, 121] (and references cited therein).

Another rearrangement has been observed by Ponaras in acetic acid in the presence of ten equivalents of lithium chloride [122]. This reaction has not

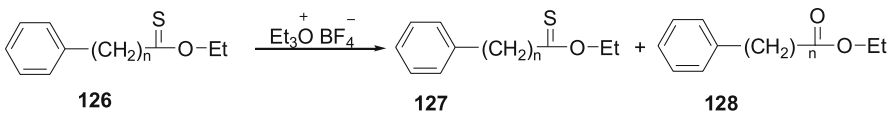
been used further for the synthesis of thioaliphatic compounds (Scheme 48). Most probably, the cationic intermediate evolves in different ways such as rearrangement, halogen quenching or elimination.

Lewis acids are supposed to act similarly and promote rearrangement. For example, thiono esters have been converted to the corresponding thiol esters using the oxonium salt $Et_3O^+ BF_4^-$ (Scheme 49) [123]. Kawata et al. have shown the possibility of using standard Lewis acids such as $AlCl_3$ for the rearrangement of xanthates, giving mixed dithiolcarbonates in good yields at room temperature [124].

More recently, Barton was able to convert cyclododecylxanthate **129** into the corresponding dithiocarbonate at room temperature using trimethylaluminium as catalyst (Scheme 50) [125]. The reaction takes place only with secondary xanthates, the linear hexadecyl *S*-methyl xanthate not furnishing

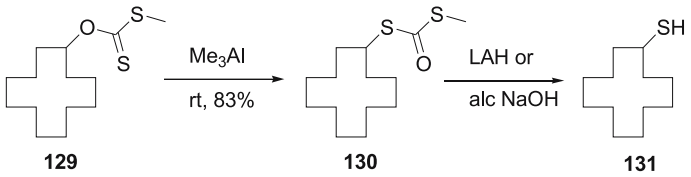


Scheme 48 Rearrangement in acetic acid



a: n=0	94 %	0%
b: n=1	86%	14%
c: n=2	67%	33%

Scheme 49 Rearrangement using $Et_3O^+BF_4^-$



Scheme 50 Rearrangement using trimethylaluminium

any rearranged product. In order to gain a deeper insight into the reaction mechanism, the selectivity towards two epimers on a cholestanyl derivative was studied. Along the reaction pathway, the reactivity was related to the conformation of the ionic pair in which the trimethylaluminium is linked to the carbonyl oxygen.

Acknowledgements This work was co-founded by MIUR within the PRIN national framework.

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Top Curr Chem (2007) 275: 163–250
DOI 10.1007/128_049

Published online: 10 June 2006

The Smiles Rearrangement and the Julia–Kocienski Olefination Reaction

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Abstract Molecular rearrangements consisting of base- or acid-induced dislocation of aromatic or heteroaromatic rings are reviewed. The emphasis is given to recent developments and, in particular, to synthetic application of the rearrangement. A novel

classification has been applied in order to discuss systematically rather diverse published data. The rearrangements are reviewed according to atoms entering and leaving the *ipso*-position of the migrating ring. The Julia–Kocienski olefination reaction is presented in other parts of this volume.

Keywords Amines · Aromatic compounds · Ethers · Heteroaromatic compounds · Meisenheimer complexes · Molecular rearrangements · Olefination reaction · Sulfides · Sulfones

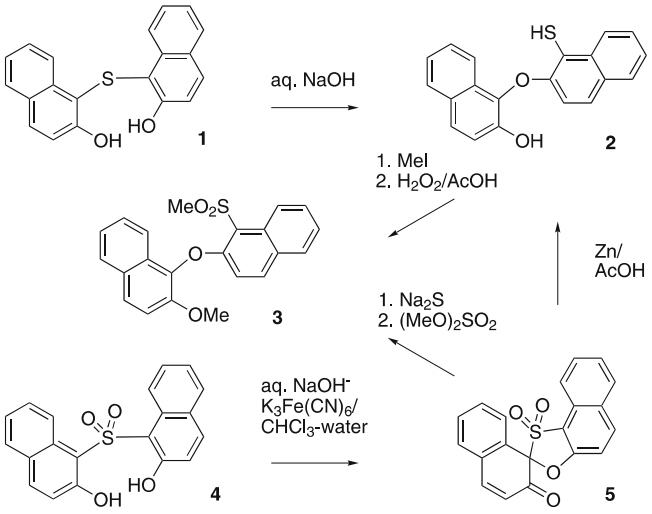
Abbreviations

BT	1,3-benzothiazol-2-yl
BTFP	3,5-bis-(trifluoromethyl)-phenyl
DCM	dichloromethane
DMA	dimethylacetamide
PT	1-phenyl-1*H*-tetrazol-5-yl
Pyr	pyrid-2-yl
P2-Et	1-ethyl-2,2,4,4,4-pentakis(dimethylamino)-2^5,4^5-catenadi(phosphazene)
P4-*t*-Bu	1-*tert*-butyl-4,4,4-tris(dimethylamino)-2,2-bis[tris(dimethylamino)-phosphoranylidenamino]-2^5,4^5-catenadi(phosphazene)
SES	β-trimethylsilylethanesulfonyl
TASF	difluoro-tris(dimethylamino)(trimethylsilyl)sulfide
TES	triethylsilyl

1 Introduction

In 1930 Smiles and Warren [1, 2] documented that "iso-β-naphthol sulfide" **1** (Scheme 1), when heated in aqueous sodium hydroxide solution, undergoes rearrangement to hydroxy mercaptane **2.** The corresponding sulfone **4**, when treated with aq. sodium hydroxide solution containing potassium ferricyanide, gave spirocyclic product **5** that was then transformed into **2** by reduction. Both products **2** and **5** were also correlated through sulfone **3** (Scheme 1). Studies of the behavior of sulfide **1** and sulfone **4** under alkaline conditions concluded with the discovery of the rearrangement that occurs via nucleophilic attack on the migrating ring *ipso*-carbon atom. Migration of an aromatic or hetero-aromatic ring via a spirocyclic intermediate is a general phenomenon presently known as the Smiles rearrangement.

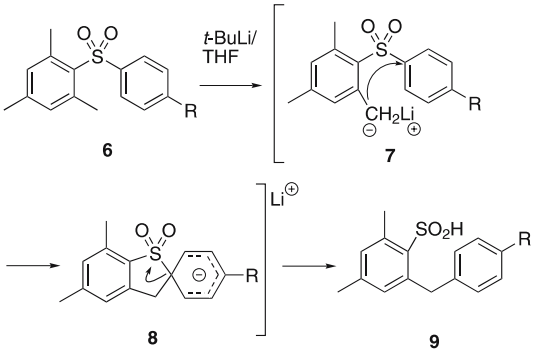
Extensive work by Smiles and his collaborators and by other groups clarified the main features of the rearrangement involving nitro-, sulfonyl- and halo-substituted aromatic rings. Rearrangement of 2-amino-pyridine derivatives has also been extensively studied. Reactions involved the replacement of hetero-substituents, a C – O bond by a C – N bond (N – O), C – S by C – N (N – S) and C – S by C – O (O – S), etc. Early work has been reviewed by Bunnett [3] (1951) and Truce [4] (1970).



Scheme 1

Extension of the rearrangement to carbanion chemistry was of particular significance. Truce and coworkers [5, 6] discovered that treatment of biaryl sulfone **6** (Scheme 2) with *tert*-butyllithium in diethyl ether results in a rearrangement with the formation of a new carbon–carbon bond to give sulfinic acid **9.** In mechanistic terms, the carbanion generated by abstraction of a proton from the *ortho*-methyl group had attacked the *ipso*-position in the other ring to form the spirocyclic anion **8** that fragments with cleavage of the carbon–sulfur bond. The rearrangements involving carbanions are called by some authors the Smiles–Truce rearrangement.

Perhaps the most important feature in the modern development of the Smiles rearrangement is its application to heterocyclic chemistry. Various heterocyclic compounds have been approached both with the intended or with "unexpected" rearrangements.

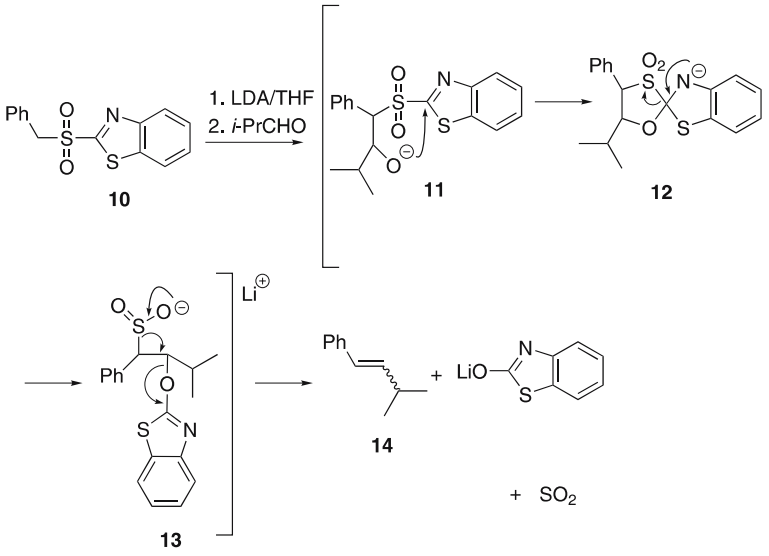


Scheme 2

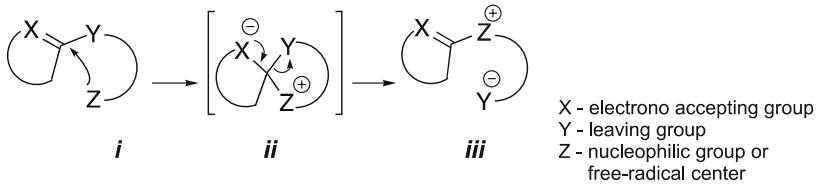
During the 1990s Sylvestre Julia and coworkers [7–9] discovered and developed a new reaction of alkyl benzothiazolyl sulfones and some related alkyl heteroaromatic sulfones with carbonyl compounds. The reaction is illustrated in Scheme 3. The carbanion generated (LDA) from benzyl benzothiazol-2-yl sulfone **10** with isobutyric aldehyde formed adduct **11** that isomerized to the spirocyclic and then *O*-benzothiazolyl derivatives **12** and **13**, respectively. The latter fragmented with extrusion of SO_2 to form alkene **14** and the lithium salt of 1,3-benzothiazol-2-ol. In the transformation of **11** into **13**, the Smiles rearrangement had occurred. The Julia reaction had opened new prospects in the synthesis of olefins, in particular, in combining building blocks in target-oriented synthesis through a carbon–carbon double bond.

The S. Julia olefination reaction modified and optimized by P. Kocienski [10] became the premiere fragment linkage reaction in construction of functionally complex targets. It has frequently been referred to as the Julia–Kocienski reaction.

The general form of the Smiles rearrangement is presented in Scheme 4. The rearrangement may be brought about by various factors: base or acid catalysts, thermolysis, irradiation or free radical initiators. The classical Smiles rearrangement involving aryl or hetero-aryl group migration in ***i*** usually refers to base- or acid-catalyzed processes. Free radical rearrangements are usually classified as *ipso*-substitution reactions or radical aryl migration reactions (in earlier terminology spirodiene rearrangements). Progress in this area has been recently reviewed [11, 12].



Scheme 3

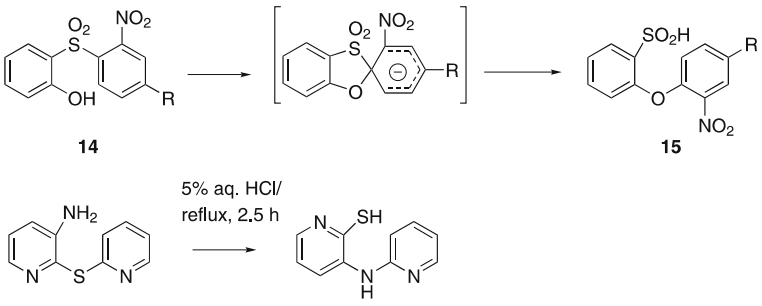


Scheme 4

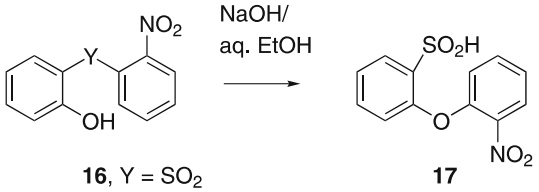
Studies by Smiles, Bunnett [3], Truce [4] and others revealed the basic requirements for the structure *i* to rearrange. Conveniently, the following features are discussed: (a) activation of the migrating ring, (b) replaceability of the leaving group (Y), (c) nucleophilicity of the entering group (Z), and acidity of the nucleophilic function, when Z stands for the amino or acylamino groups. Naturally, the factors influencing the rearrangement are inter-related. Some important conclusions from the early work are as follows:

a) Activation of the migrating ring
Electronic activation of the aromatic ring is a prerequisite for a rearrangement, catalyzed by weak bases or acids in protic solvents. For example [13], sulfone **14**, R = NO_2 (Scheme 5) rearranges to the sulfinic acid **15** rapidly, R = COPh, in 0.5 min, R = CO_2Na, in 50 min, R = Cl, 70 min, R = H, 255 min. Common activating groups include the *o*- or *p*-nitro group, the sulfonyl group, or halogen substituents. Migration of an unsubstituted 2-pyridyl ring under acidic conditions has also been recorded [14] in early studies (Scheme 5).

b) Replaceability of the leaving group (Y)
The importance of the leaving group, Y, was documented in early studies [15]. For example, in the *o*-nitro diaryl system **16** where Y = SO_2, (Scheme 6) rearrangement occurred. However, when Y = SO or S, the starting material was recovered unchanged. Groups Y exert activation in the order of activation of the β-elimination reactions, thus SO_2 > SO > S.



Scheme 5



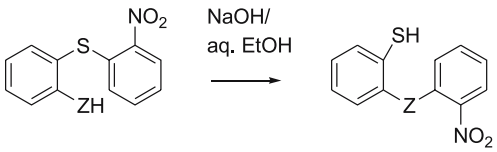
16, Y = SO_2 **17**

Scheme 6

c) Nucleophilicity of the entering group

The nucleophilicity of the entering group is also an important factor. Out of the derivatives shown in Scheme 7, only those with Z = acetamido or 4-nitrobenzamido underwent the rearrangement under the standard conditions [16]. It was suggested that derivatives with Z = NHMe and NH_2 do not provide sufficient concentration of the respective anion whereas those with picric and sulfamidic residue form non-nucleophilic salts. In contrast to the sulfide, the respective amino sulfone (SO_2 in the place of S, Z = NH_2) smoothly rearranged indicating that when Y is a better leaving group, the nucleophilicity of Z may be diminished. However, the relation between the acidity of the NH group and the rate of the rearrangement is more complex.

The present review refers mainly to the work published in the last ten years. Emphasis is given to hetero-aromatic systems and sulfur-mediated rearrangements although broader prospects were thought desirable. As the criteria for classification, the entering group Z (Scheme 4) and the leaving group Y were chosen, as O – S, N – O, etc. The abbreviation O – S refers to a case where O is the entering group and S is the leaving group (a C – O bond has been generated in place of the C – S bond). Thus, for comparison also Smiles and related rearrangements are included where cleavage of a carbon–sulfur bond is not involved. Anionic and cationic rearrangements are discussed but free radical rearrangements are not included. The Julia–Kocienski reaction is presented elsewhere in this chapter (Sect. 5.)



18 **19**

rearrange: Z = NHAc, NH-2-(NO_2)Bz

do not rearrange: Z = NHMe, NH_2, NH-2,4,6-(NO_2)$_3$Ph, $NHSO_2$Ph

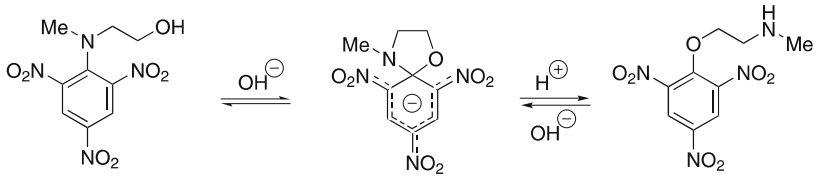
Scheme 7

2
N – O Rearrangements

When base was added to a solution of *N*-methyl-*N*-β-hydroxyethyl picramide **20** in a polar solvent, the isolable cyclic Meisenheimer complex **21** was formed (Scheme 8). At pH $\geq$ 12 the conversion is virtually complete. Rapid protonation of **21** causes quantitative formation of picryl ether **22** trapped as an ammonium ion. The corresponding free base was unstable and tended to rearrange in the opposite direction [17].

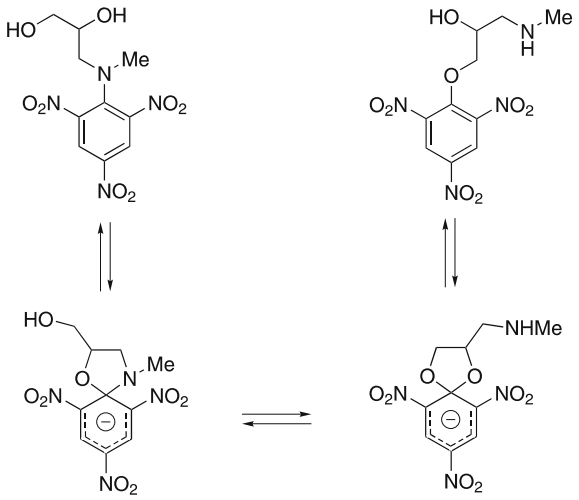
Reversible double Smiles rearrangement through intermediate formation of tautomeric Meisenheimer spiro-complexes was observed in the system of 1-methylamino-3-picryloxy-2-propanol [18] (Scheme 9).

Addition of picric acid to a solution of diisopropylcarbodiimide in DCM afforded stable fluorescent Meisenheimer complex **23** (Scheme 10) along with 1 : 1 adduct **24**, each with 16% yield [19]. The structure of **23** was derived

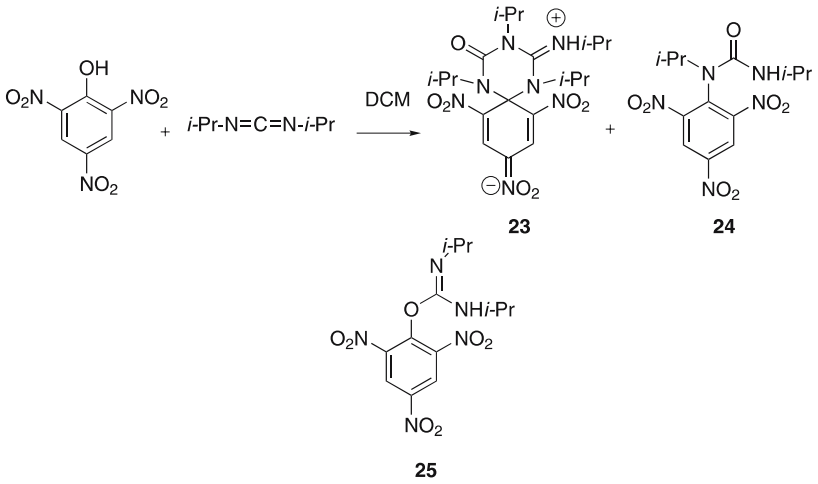


20 **21** **22**

Scheme 8



Scheme 9

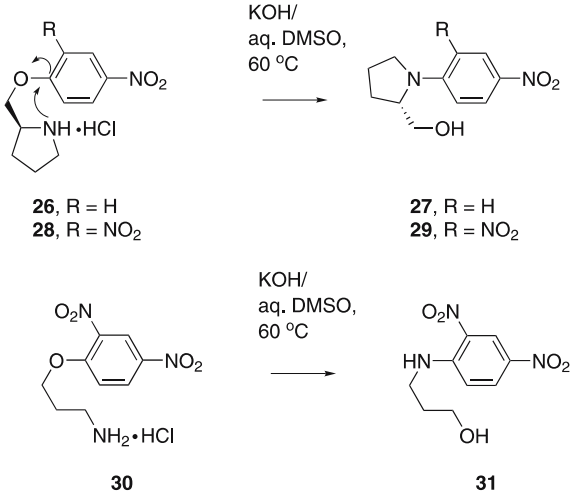


Scheme 10

from X-ray analysis. The reaction is likely to proceed through isourea derivative **25** and O – N rearrangement.

Mononitro compound **26** (Scheme 11) required several hours of heating to effect complete rearrangement into **27** [20]. The dinitro derivative **28** under analogous conditions rearranged to **29** in 15 min. Transformation **30** to **31** occurred in 4 h. In the later case, the six-membered spiro-intermediate was involved.

It has been shown [21, 22] that desulfonation of l-*N*-(2-hydroxyethyl)-4-nitrobenzenesulphonamide proceeds via two consecutive Smiles rearrange-



Scheme 11

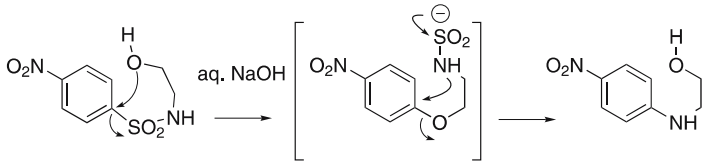
ments, as indicated in Scheme 12. First the rearrangement O – S occurs and then, after extrusion of SO_2, the C – O bond was replaced by the C – N bond. Derivatives with alkyl substituents on the C- or N-atom of the hydroxyethylamino side chain react in a similar way (Table 1). 2-Nitrophenyl-2-hydroxyethyl sulfonamide gave a very low yield of the rearrangement product. Interestingly, 2-[sulfonamido(2-hydroxyethyl)]benzothiazole undergoes desulfonation on the same route (Table 1, entry 7).

It has been reported [23] that the anion generated from 2-(*N*-alkylamino)-ethanol with dimsyl sodium in DMSO reacted with 4-chloronitrobenzene to afford ether **32**. Rearrangement of **32** into **33** took place after water was added. Accordingly, **32** rearranged in high yield when NaOH in aq. DMSO at 60 °C was used (Scheme 13).

Kinetic measurements gave evidence for deprotonation of the spiro-Meisenheimer intermediate **35** as the rate-limiting step during the rearrangement of 2-(4-nitrophenoxy)ethylamine **32** into **33** in aqueous alkali [23] (Scheme 14, R = H). The kinetic effect of *N*-alkyl substitution [24–26] (Scheme 14, R = Me, Et, *i*-Pr) has also been investigated.

[^{13}C] or [^{18}O] enriched **32** were prepared and kinetic isotope effects have been measured [27] in their hydroxide ion-catalyzed rearrangements into **33**.

2-Aryloxy-2-methylpropionamides **36** (Scheme 15) underwent the rearrangement in anhydrous dioxane or, faster, in DMF in the presence of sodium hydride [28]. An important observation was made: the presence



Scheme 12

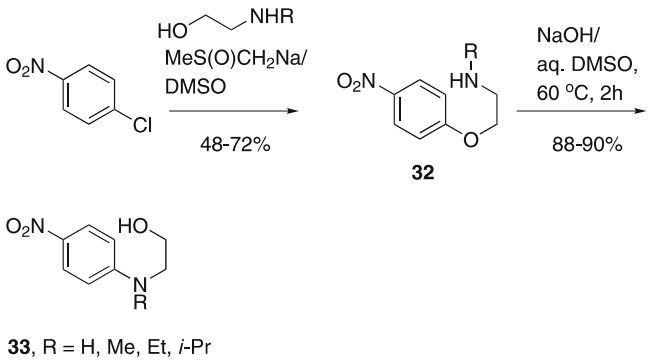
Table 1 Desulfonation of l-*N*-(2-hydroxyethyl)-4-nitrobenzenesulphonamides according to Scheme 12

	Sulfonamide	Yield(%)
1	4-(NO_2)Ph – SO_2 – NH – CH_2CH_2OH	96
2	4-(NO_2)Ph – SO_2 – N(CH_3) – CH_2CH_2OH	89
3	4-(NO_2)Ph – SO_2 – N$(CH_2CH_2OH)_2$	87
4	4-(NO_2)Ph – SO_2 – NH – $CH_2CH(CH_3)OH$	91
5	4-(NO_2)Ph – SO_2 – NH – $C(CH_3)_2CH_2OH$	92
6	4,5-Cl_2 – 2 – (NO_2)Ph – SO_2 – NH – CH_2CH_2OH	60
7	2-Benzothiazolyl–SO_2 – NH – CH_2CH_2OH	82

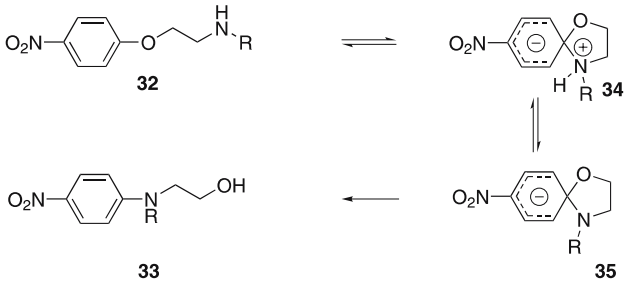
of geminal methyl groups facilitates the rearrangement. Since then the 2-methylpropionamide auxiliary has been commonly used. Results are presented in Table 2.

However, when the aromatic ring was deactivated, prolonged heating in HMPA (Table 2, entry 8) [29] or in DMF-DMPU (Table 2, entry 9) [30] solution was necessary for the rearrangement to occur.

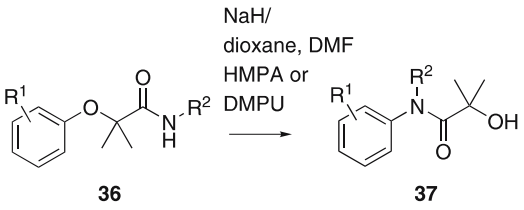
Synthesis [31] of hydroxy amides **39** and **41**, that were intermediates on the route to dopamine D_3/D_5 receptor antagonists, involved the Smiles re-



Scheme 13



Scheme 14



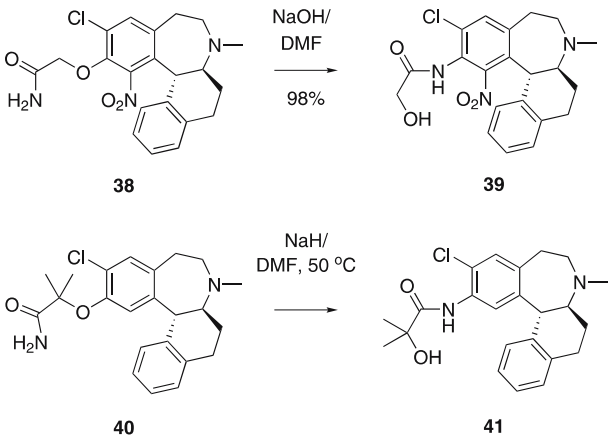
Scheme 15

Table 2 Rearrangement of 2-aryloxy-2-methylpropionamides **36**

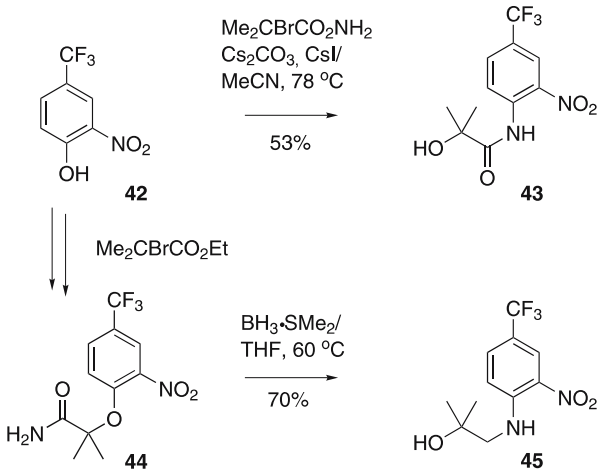
	R^1	R^2	NaH (equiv)	Solvent	Temp. (°C)/Time (h)	Yield (%)
1	4-NO_2	H	1.1	dioxane	100/6	75
2	4-PhCO	H	1.0	dioxane	100/16	50
3	4-PhCO	H	4.0	DMF	25/2	65
4	4-NO_2	Me	2.0	dioxane	100/140	25
5	H	H	1.1	DMF	100/16	80
		H	1.1	HMPA	100/1	85
6	4-Cl	H	1.1	DMF	100/16	80
		H	1.1	HMPA	25/16	85
7	4-Me	H	1.1	DMF	100/16	45
		H	1.1	HMPA	100/1	60
8	4-MeO	H	1.1	HMPA	100/16	50
9	4-MeO	H	1.1	DMF-DMPU	100/1	31

arrangement (Scheme 16). In compound **40** the migrating ring was activated by a chlorine atom only.

2-Nitro-4-(trifluoromethyl)-phenol **42** (Scheme 17) in reaction with 2-bromo-2-methyl-propionamide in the presence of cesium carbonate and cesium iodide in acetonitrile afforded 2-hydroxy-2-methylpropionamide **43**, apparently via derivative **44** as the intermediate [32]. Amide **44**, prepared on a circuitous route, on reduction with borane-dimethylsulfide complex, gave amine **45** as the only isolated product. The parent 2-hydroxy-2-methyl-*N*-(2-



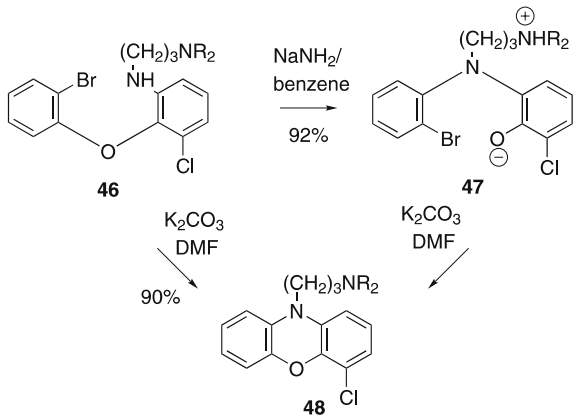
Scheme 16



Scheme 17

nitrophenyl)propionamide (**43**, H in place of the CF_3 group) as well as its 4-Me, 5-Me, 5-F and (4-Cl, 5-Me) derivatives, on reduction with the borane complex, gave the respective rearrangement products in high yields.

Bromo-aryl ether **46** (Scheme 18), on treatment with one equivalent of sodium amide in boiling benzene, underwent rearrangement into **47** in 92% yield. The presence of an *N*-alkyl substituent on the aniline nitrogen atom was essential for the rearrangement. However, **46** heated with potassium carbonate in dimethylformamide afforded 2-chloro-10-(3-dimethylaminopropyl)phenoxazine **48** in 90% yield [33]. It was later proved [34] that the cyclization of **46** into **48** involves the rearrangement via **47**. Rearrangements of *ortho*-aminodiphenyl ethers have been reviewed [35].



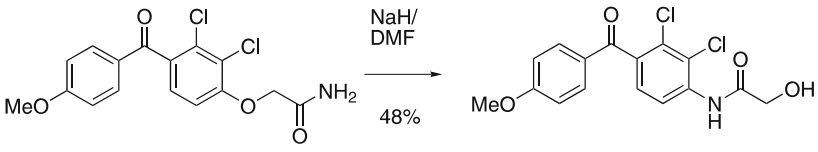
Scheme 18

Aryloxyacetamide **49** rearranged to **50** in 48% yield when stirred with NaH in DMF for 75 min at room temperature [36] (Scheme 19).

On the route to benzo[c]phenanthridine alkaloids [37], naphthol **51** (Scheme 20) was *O*-alkylated with 2-bromo-2-methylpropionoamide under forcing conditions to give **52** in 93% yield. The rearrangement of **52** was executed with sodium hydride in DMF-DMPU and the hydroxy-amide **53** was hydrolyzed to give the aminonaphthyl derivative **54**.

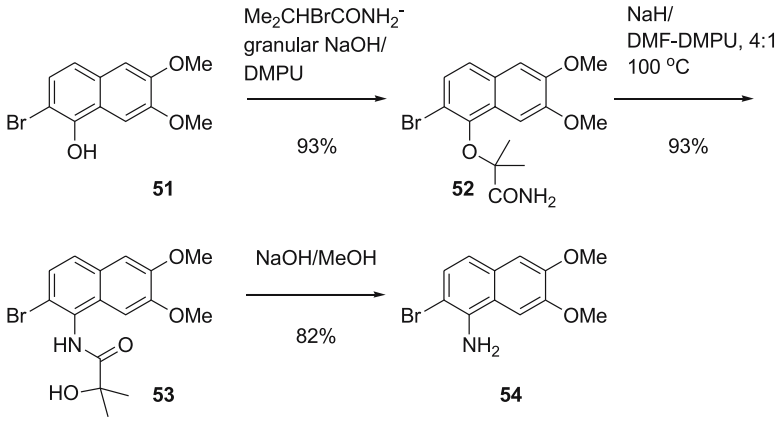
Attempted *N*-alkylation of 2,4,6-trichlorophenoxyacetamide **55** (Scheme 21) with various alkyl bromides in the presence of potassium hydroxide and tris(3,6-dioxaheptylamine) (TDA-1) as the phase-transfer catalyst, in toluene at reflux temperature, yielded the corresponding *N*-alkylated 2,4,6-trichlorophenylamine derivatives **56**. 2,4,6-Trichloro substitution on the phenyl ring was essential for the rearrangement [38].

2,6-Dichloro-*N*-phenylaniline **59a** that is used for the production of anti-inflammatory drug Voltaren (Diclofenac) can be conveniently prepared through intermediates **57a** and **58a**, as indicated in Scheme 22. The synthesis can be carried out in one pot [39–42]. The same reaction scheme applies to the synthesis of 2-chloro-6-fluoro-*N*-(4-tolyl)aniline **59b**, an intermediate



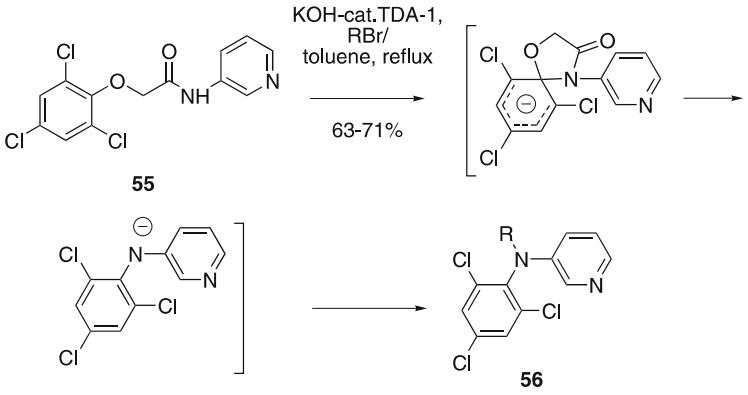
49 **50**

Scheme 19

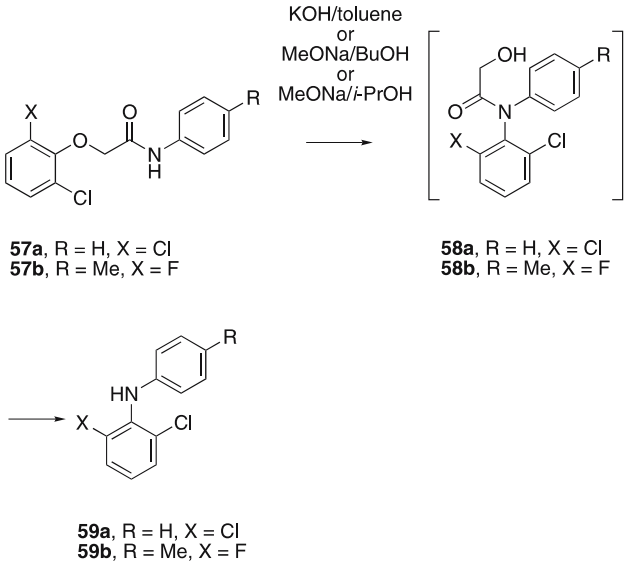


51 **52** **53** **54**

Scheme 20



Scheme 21

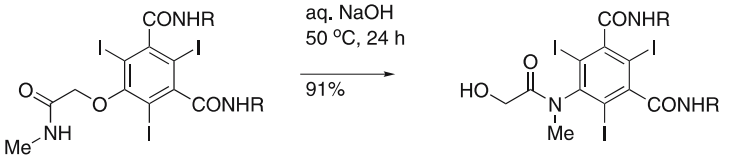


Scheme 22

in the production [43] of Prexige (Lumiracoxib). Some other alkylarylamines and diarylamines have been prepared in a similar way [44].

The iodinated X-ray contrast agent **61** (Iomeprol) is prepared on an industrial [45] scale from easily available aryloxyamide **60** (Scheme 23).

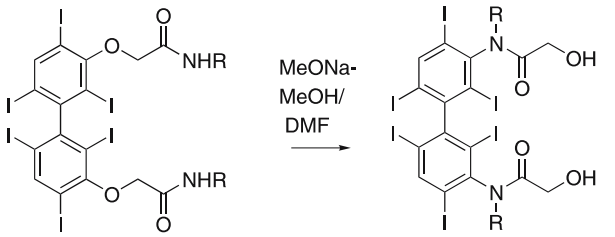
In a similar way polyiodinated biphenyl derivative **62** (Scheme 24) rearranged upon treatment with sodium methoxide in DMF to give **63.** Along with **63** a "partly rearranged" product in which one acetamide moiety remained unchanged, was obtained [46].



60 **61**

R = $CH_2CH(OH)CH_2OH$

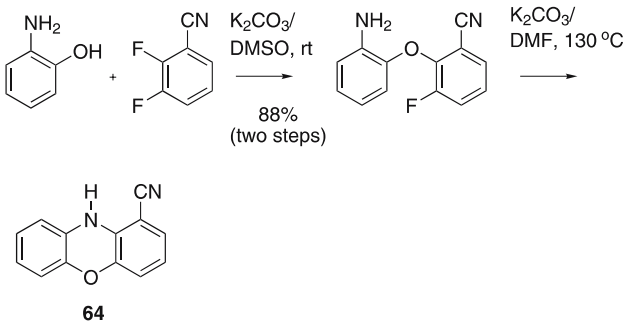
Scheme 23



62 **63**

R = $(CH_2CH_2O)_2H$

Scheme 24

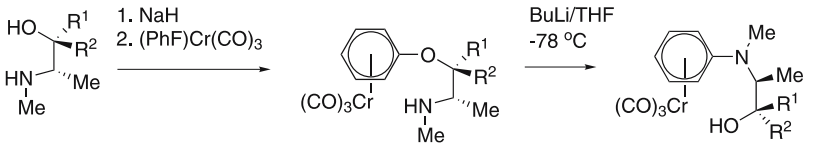


64

Scheme 25

2,3-Difluorobenzonitrile and 2-aminophenol were used [47] in a synthesis of cyanophenoxazines **64** (Scheme 25). After displacement of the fluorine atom activated by the cyano-group, rearrangement and cyclization were carried out. Analogous reaction sequences involving catechol, 2-aminothiophenol and benzene-1,2-dithiol have also been studied.

Complexing with chromium tricarbonyl provided activation of the aromatic ring for nucleophilic substitution of a fluorine atom with β-aminoalkoxides and then for rearrangements of the initially formed products. Thus,



65, R^1 = Ph, R^2 = H
66, R^1 = H, R^2 = Ph

67, R^1 = Ph, R^2 = H (81%)
68, R^1 = H, R^2 = Ph (89%)

69, R^1= Ph, R^2 = H (96%)
70, R^1 = H, R^2 = Ph (98%)

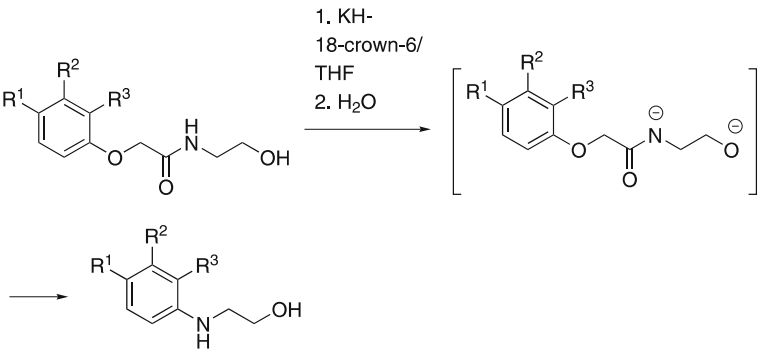
Scheme 26

fluorobenzene, on treatment with alkoxide generated from ephedrine **65** or pseudoephedrine **66**, afforded β-aminoether derivatives **67** or **68**, respectively (Scheme 26). The later products, on treatment with *n*-butyllithium in THF at –78 °C, smoothly rearranged to phenylamine derivatives **69** or **70** in high yields [48].

Baker [36] reported that the presence of the *N*-(2- or 3-hydroxyalkyl) group in the molecule accelerates the N – O type rearrangement (Scheme 27). Potassium hydride—18-crown-6 was used as the base in THF. Some results are presented in Table 3. It is noteworthy that the rearrangement occurred (although with poor yield) for substrates devoid of activating substituents on the aromatic ring (entry 5) as well as for derivatives with electron-donating substituents (entries 6 and 7). It was suggested that electrostatic repulsion between the alkoxide and amide anions in the intermediates contribute to this effect.

Inactivated aromatic ring migration was observed on attempted metalation of a crown ether-type ligand [49]. Treatment of bis[2-(2-methoxyethylamino)phenyl] ether **71** with sodium hydride in toluene containing some HMPA at elevated temperature gave the corresponding derivative with a free phenolic hydroxyl group **72** (Scheme 28).

Replacement of the phenolic hydroxyl in estrone **73** by an amino group was reported [30, 50]. A one-pot procedure was developed in which the amide

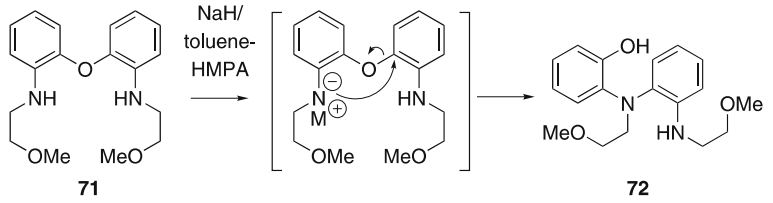


Scheme 27

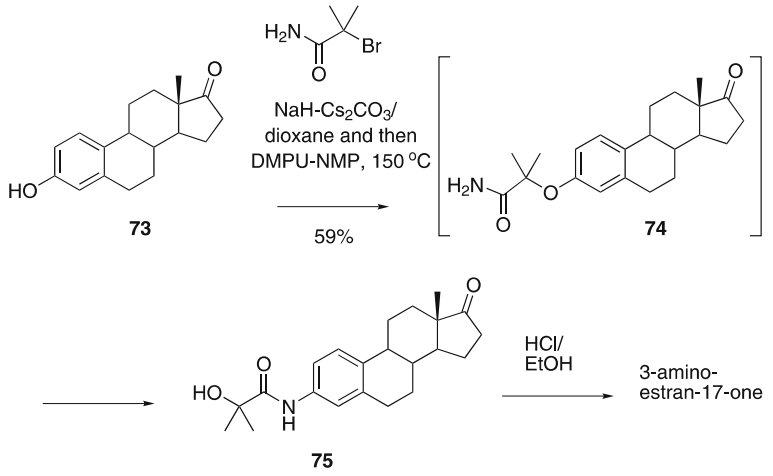
Table 3 Rearrangement of 2-aryloxy-*N*-(2-hydroxyethyl)propionamides

	R^1	R^2	R^3	Temp. (°C)	Time (h)	Yield (%)
1	NO_2	H	H	–40 to –30	1	63
2	H	Cl	Cl	–20 to 0	1	63
3	Cl	H	H	20	18.5	50
4	H	H	Br	20	0.1	39
5	H	H	H	45 to 50	20	21
6	Me	H	H	50 to 55	40	28
7	MeO	H	H	90	19	35

auxiliary was attached using sodium hydride and cesium carbonate in dioxane. The rearrangement was affected by sodium hydride in NMP-DMPU at 150 °C (Scheme 29) [50]. For analogous exchange of the hydroxyl for the amino group in a dihydronaphthalene derivative, DMA was used as the solvent [51].



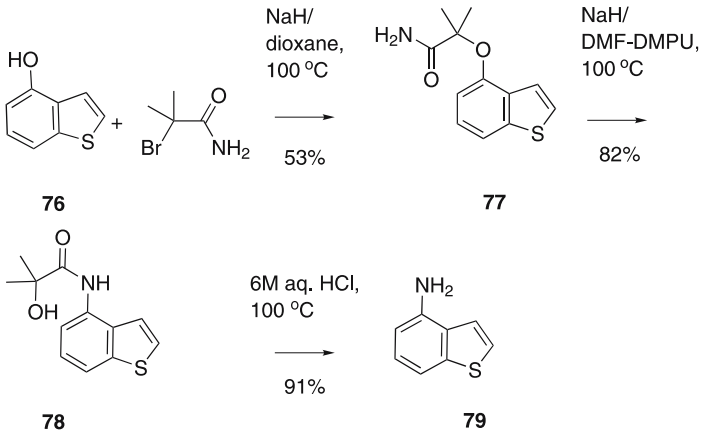
Scheme 28



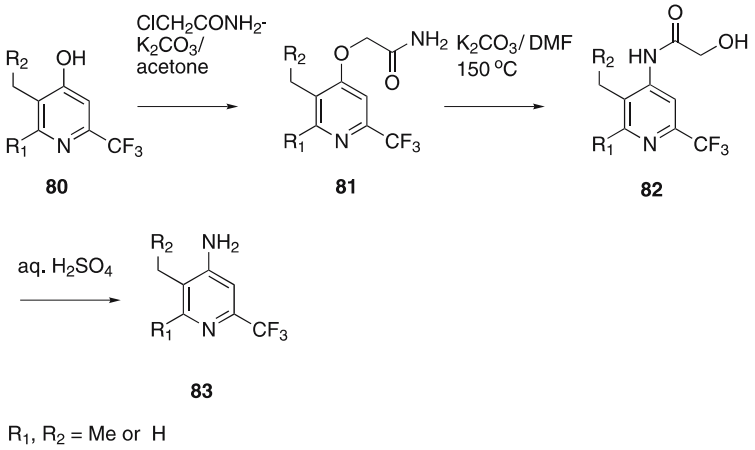
Scheme 29

Benzothiophene-4-ol **76** was transformed into 4-amino-benzothiophene **79** via 2-methylpropionamide derivative **77** (Scheme 30). The rearrangement was carried out under harsh conditions using sodium hydride in HMPA [29] or in DMF-DMPU [52], at 100 °C.

4-Hydroxy-2-(trifluoromethyl)pyridine derivatives **80** (Scheme 31) were linked [53] to the acetamide moiety in the usual way. Pyridyloxy-acetamides **81** smoothly rearranged into the respective 4-aminopyridines **82** when heated with potassium carbonate in DMF at 150 °C. Acid hydrolysis provided amines **83**. In a similar way, hydroxy-quinolines and hydroxy-acridines were transformed into the respective amines [50, 54].



Scheme 30

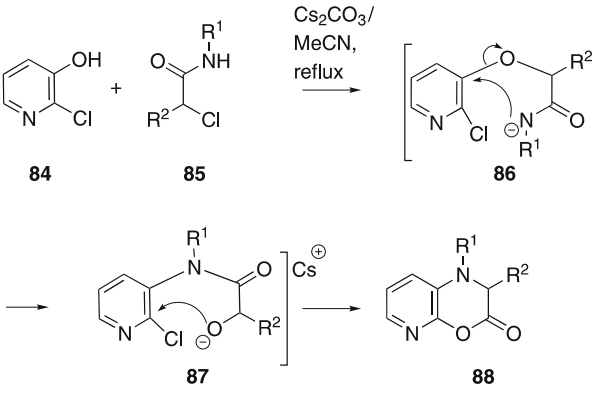


Scheme 31

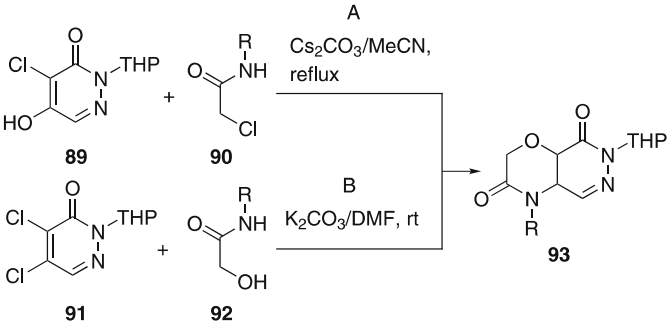
Pyrido[2,3-b] [1, 4]oxazin-2-ones **88** were prepared [55] from 2-chloro-3-hydroxypyridine **84** and 2-chloroacetamide derivatives **85** (Scheme 32). In principle, the intermediate anion **86** could cyclize through the pyridine C-2 or C-3 carbon atoms (the Smiles rearrangement). The best results were obtained when cesium or rubidium carbonate in boiling MeCN or cesium carbonate in DMF at 90–100 °C were used as the base (Table 4).

The synthesis of pyridazino[4,5-*b*] [1, 4]oxazine derivatives **93** (Scheme 33) from either 4-chloro-5-hydroxy- or 4,5-dichloro-2*H*-pyridazin-3-one derivatives **89** and **91**, respectively, was examined [56]. The hydroxy derivative **89** was condensed with chloroacetamide derivative using cesium carbonate in acetonitrile whereas for the complementary experiments, potassium carbonate in DMF was used. In both routes the rearrangement was effective. In route B markedly shorter reaction times were needed and higher yields were obtained. Some examples are shown in Table 5.

An interesting acid-catalyzed migration of a dimethoxy pyrimidine ring has been recently studied [57]. Compounds **94**, when treated with acetic acid in acetone, afforded the respective derivatives **96** in excellent



Scheme 32



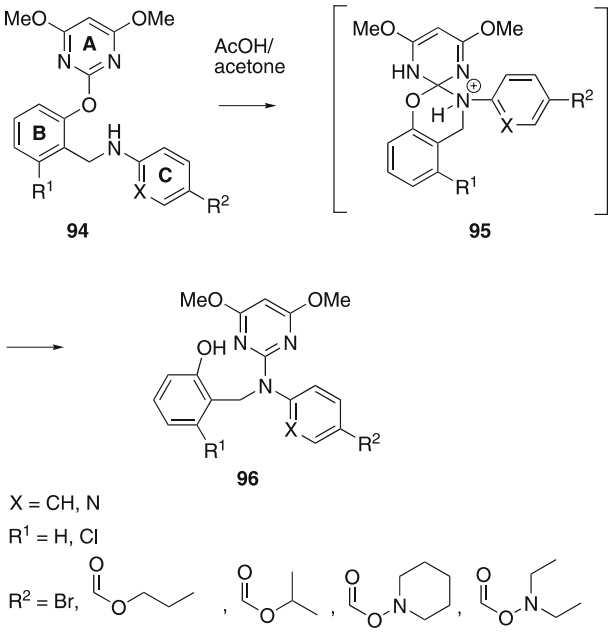
Scheme 33

Table 4 Representative product yields in the reaction according to Scheme 32

R^1	R^2	Yield (%)
Ph	H	90
Ph	Me	91
Bn	H	90
Bn	Me	87
c-hexyl	H	90
c-hexyl	Me	93

Table 5 Comparison of the reaction time and yields for the syntheses of **93** according to Scheme 33

R	Time (min)		Yields (%)	
	Route A	Route B	A	B
n-Pr	49	4	65	92
c-hexyl	42	5	53	93
Bn	48	3	55	94



Scheme 34

yields (Scheme 34). The rearrangement involves the six-membered spiro-intermediate **95**. It has been documented that compounds with a chlorine substituent at the ring B ($R^1 = Cl$) rearrange twice as fast as their counterparts with $R^1 = H$. 2-Aminopyridine derivatives (X = N) rearrange slower than aniline derivatives (X = CH). Interestingly, 2-bromoaniline derivatives (X = CBr) remained unchanged under the conditions.

3
N – S Rearrangements

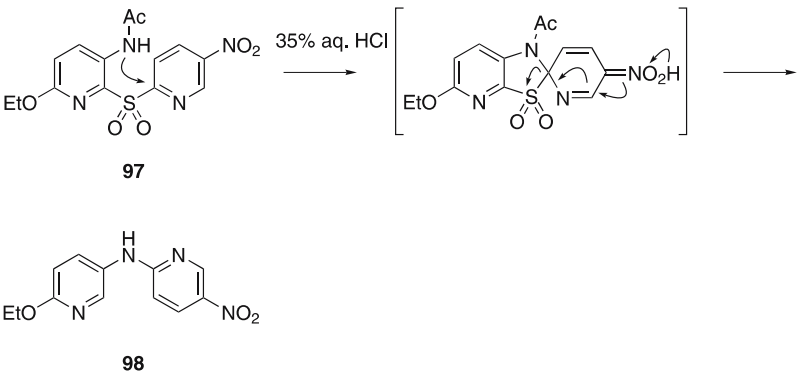
Attempted hydrolysis [58] of the acetamide moiety in **97** (Scheme 35) in 35% hydrochloric acid instead resulted in rearrangement and desulfonation to afford the 2-aminopyridine derivative **98**.

Sulfides **99** (Scheme 36) rearranged [14] into thiols **100** under alkaline (KOH/EtOH, reflux), acidic (5% aq. HCl, reflux), or neutral (EtOH or water, reflux) conditions. Selected results are presented in Table 6.

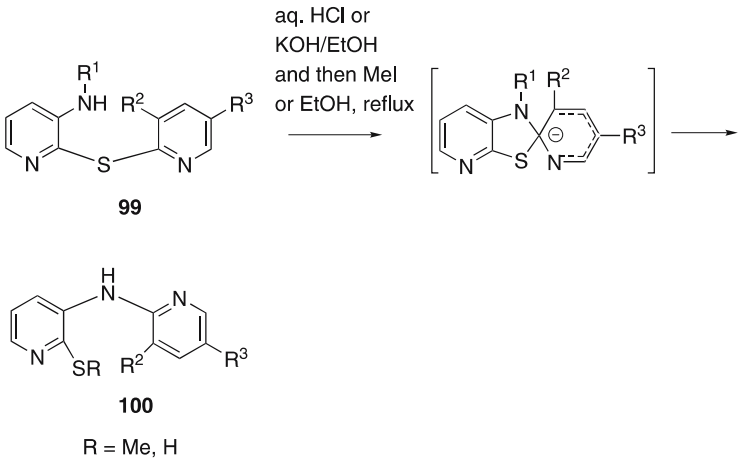
Higher yields of products were usually obtained under acidic conditions. Free amines ($R^1 = H$) and acetamides ($R^1 = Ac$) behave in a similar manner. It was suggested that hydrolysis is concerted with rearrangement. As expected, the transformation under neutral conditions occurred markedly slower.

Tetrazolyl ring migration in **101** (Scheme 37) under acidic conditions was studied [59]. It was shown that the nature of the substituent R influences the fragmentation of the spiro-intermediate **103**. When R was an alkyl- or alkylphenyl, the fragmentation followed route A leading to **104**, but when R was aryl, **105** was obtained via route B. It should be noted that the same products were obtained under alkaline conditions but yields were lower.

Vinylic sulfide **106** (Scheme 38) was methylated with methyl iodide—silver tetrafluoroborate to give [60] sulfonium salt **107** that on treatment with DBU



Scheme 35



Scheme 36

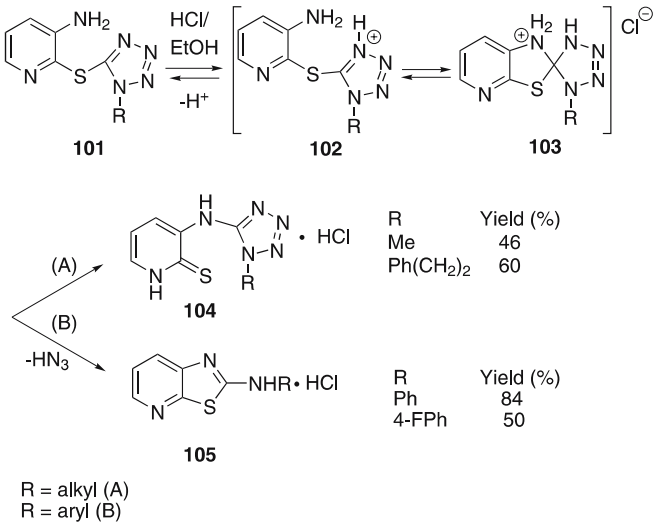
Table 6 Rearrangement of sulfides **99** into thiols **100** according to Scheme 36

R^1	R^2	R^3	Yield (%) KOH/EtOH	5% HCl aq.
H	NO_2	H	48	95
H	NO_2	Me	60	92
H	Me	NO_2	55	82
Ac	NO_2	Me	61	67
Ac	Me	NO_2	54	93

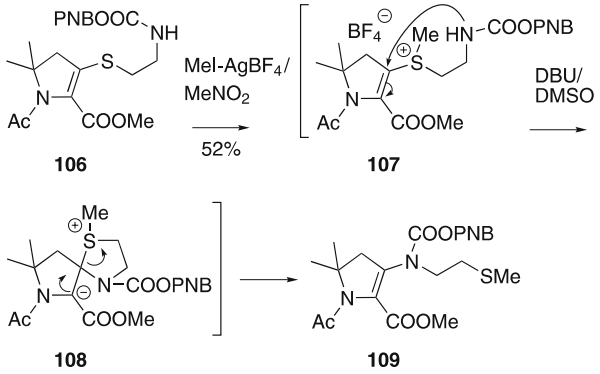
in DMSO provided enamine derivative **109**. An analogue of **107** with sulfonyl in the place of the sulfonium group resisted changes when treated with DBU in DMSO. However, the rearrangement did occur when the sulfone was treated with sodium hydride in DMF to give the respective sulfinic acid salt (isolated as methyl sulfone in 52% yield).

The same authors rearranged β-lactam amino-sulfone **110** (Scheme 39) with DBU in DMF but the yield of the respective methyl sulfone **111** amounted to only 14%.

Acetamide derivatives of *N*-methyl-1*H*-tetrazol-5-thiol **112** (X = S, R = H, Ph or Bn, Scheme 40), upon heating in ethanolic sodium hydroxide, rearranged into the respective tetrazol-5-yl amides **114** (Y = SH) that were isolated in high yields [61]. Sulfones **112** (X = SO_2) rearranged at room temperature and the resultant sulfinic acid salt underwent desulfonation to give the respective products **114** (Y = H) in 80–95% yields. The rearrangement was also brought about by *N*-methylpiperidine in boiling toluene. Sulfoxides



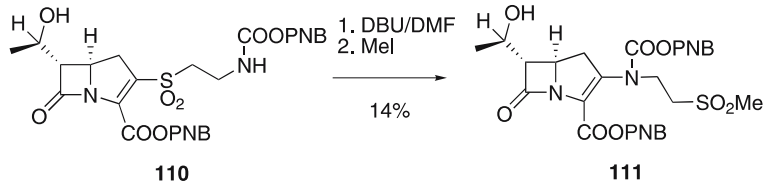
Scheme 37



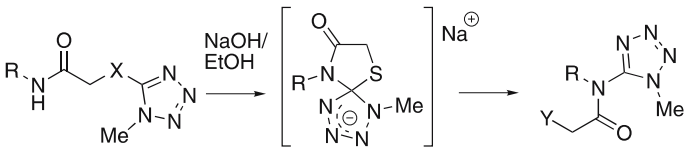
Scheme 38

112 (X = SO) decomposed on heating in alcoholic sodium hydroxide. However, small amounts (11%) of rearranged products **114** (Y = H) could be isolated when a two-phase system, aq. $NaHCO_3$-DCM was applied.

Reaction of 5-bromo-6-chloroisocytosine **115** (Scheme 41) with 2-aminoethanethiol derivatives has been extensively studied by Maki and coworkers [62, 63] aimed at the synthesis of folic acid analogues. Treatment of **115** with amino-thiol **116** ($R^1 = R^2 = H$) in ethanol at reflux temperature in the presence of phosphate buffer at pH 7 provided bicyclic product **121** ($R^1 = R^2 = H$) in 50% yield. An analogous reaction of aminothiols **116** ($R^1 = CH_2OH$, $R^2 = H$) and **116** ($R^1 = H$, $R^2 = CH_2OH$) provided products in 37 and 67% yield, respectively. The mechanism of the reaction is indicated in the scheme.

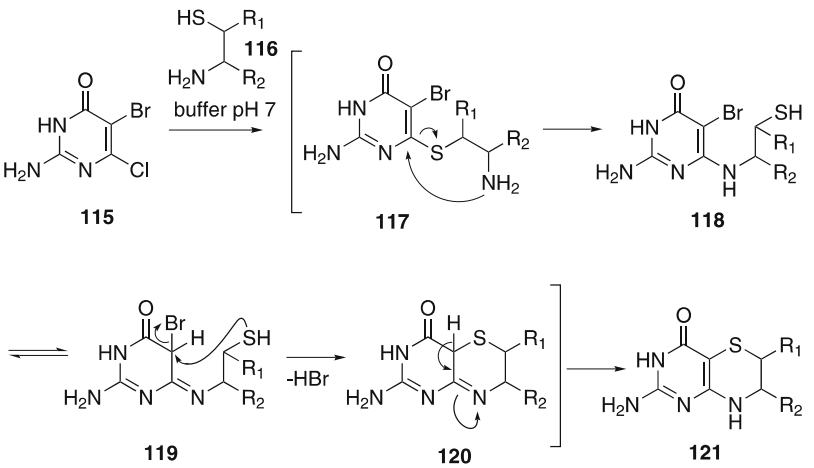


Scheme 39



X = S, SO or SO_2
R = H, Ph, Bn

Scheme 40



R^1 = H or CH_2OH
R^2 = H or CH_2OH

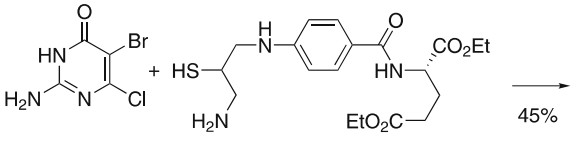
Scheme 41

Complex aminothiol **123** in reaction with **122** under similar conditions afforded the thio-analogue **124** (X = S) of tetrahydrofolic acid **125** (X = NH) in 45% yield (Scheme 42).

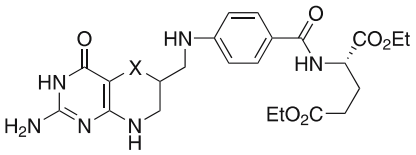
C.E. Song and coworkers [64, 65] found that treatment of *N*-[2-(1*H*-benzimidazol-2-ylthio)phenyl]thioureas **126** (Scheme 43) with DCC in acetonitrile at reflux results in cyclization with elimination of hydrogen sulphide to afford **127**. It is noteworthy that the respective 1*H*-[1,2,4]-triazole-3-thiol

derivatives under similar conditions provided products of straight cyclization with no rearrangement.

Treatment of hydrazide derivative **128** (Scheme 44) with powdered iron in acetic acid afforded benzimidazole **129** as the sole product [66]. The likely mechanism of this reaction is indicated in the scheme.

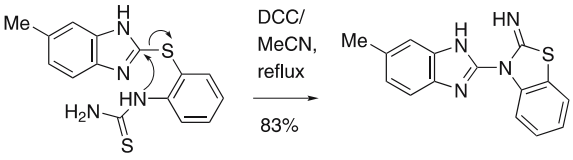


122 **123**



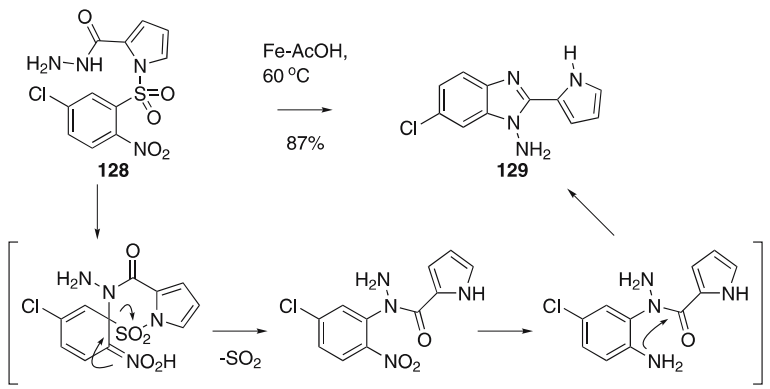
124, X = S
125, X = NH

Scheme 42



126 **127**

Scheme 43



128 **129**

Scheme 44

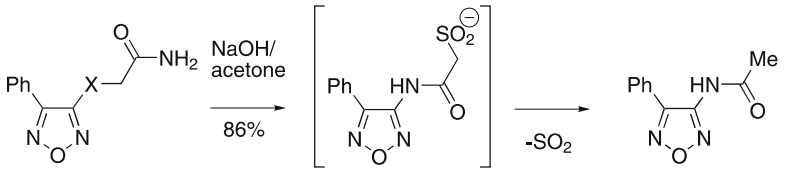
Rearrangement of furazan derivatives were studied by Boschi and coauthors [67]. 4-Phenyl-1,2,5-oxadiazole sulfone **130** (Scheme 45) heated in acetone containing sodium hydroxide rearranged to sulfinic acid derivative **132.** After expulsion of SO_2, 3-acetamido-4-phenylfurazan **133** was formed in 86% yield. Amido-sulfide **131** under similar conditions underwent hydrolysis only to afford the respective acid.

Similarly, the sulfonyl derivative of oxadiazole-oxide **134** (Scheme 46) rearranged to give **136** in 40% yield. In the respective sulfide **135** the amido group was hydrolyzed only.

However, oxido-oxadiazole **137** (Scheme 47) fragmented to give nitrile **138.** The mechanism of this transformation is not clear. The respective sulfide **139** in ethanolic solution of sodium hydroxide at room temperature fragmented to give 4-phenyl-1,2,5-oxadiazo-3-thiol **143** in 74% yield. It was suggested that this transformation occurs via thiirane **141**, as indicated in the scheme.

A symmetrical tricyclic 1,3,6-thiadiazepine derivative **152** (Scheme 48) has been synthesized [68, 69] in 54% yield starting from 5-bromo-thiadiazole derivative **144** and 1,2-diaminobenzene **145**. The synthesis embraces two types of molecular rearrangements: Smiles' and Dimroth's.

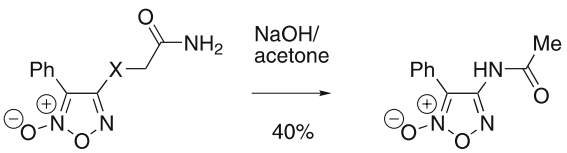
Condensation of **144** and **145** in DMF afforded 5-amino-thiadiazole **146** that was subjected to the Dimroth rearrangement. The resultant 5-thio-thiadiazole derivative **147** was coupled with another molecule of starting bromide **144** to give **148.** Compound **148,** on treatment with triethylamine in ethanol, underwent Smiles' N – S rearrangement via an intermediate with a seven-membered ring **149** to generate thiolate anion **150.** The latter subsequently rearranged to **151** as indicated in the scheme (Dimroth's rearrange-



130, X = SO_2
131, X = S

132 **133**

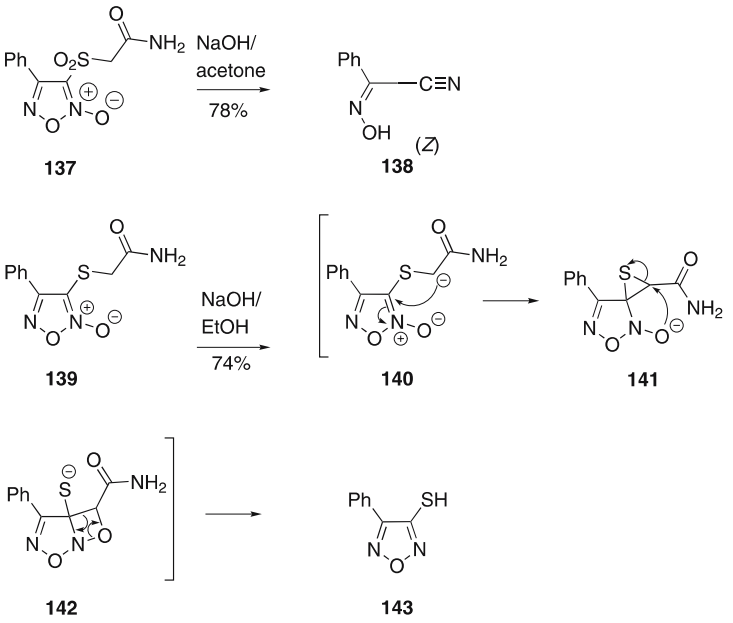
Scheme 45



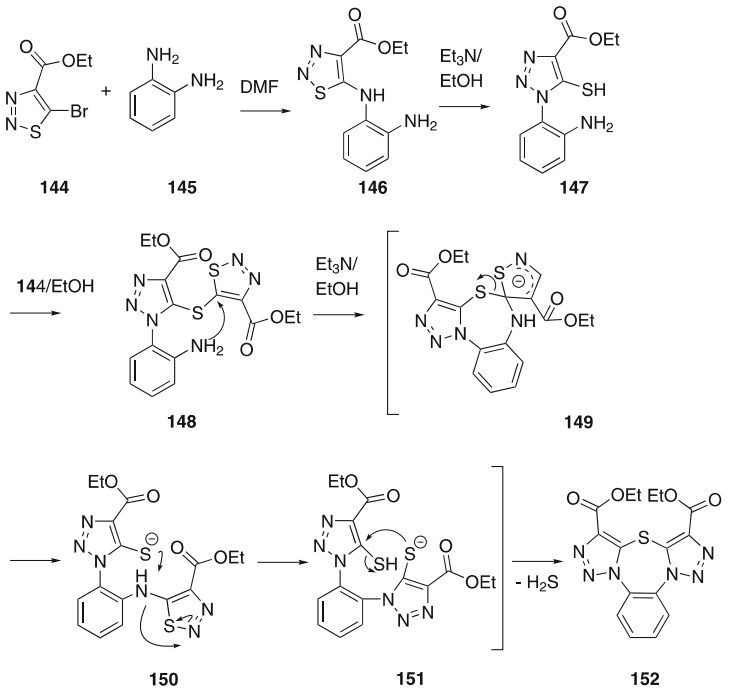
134, X = SO_2
135, X = S

136

Scheme 46



Scheme 47



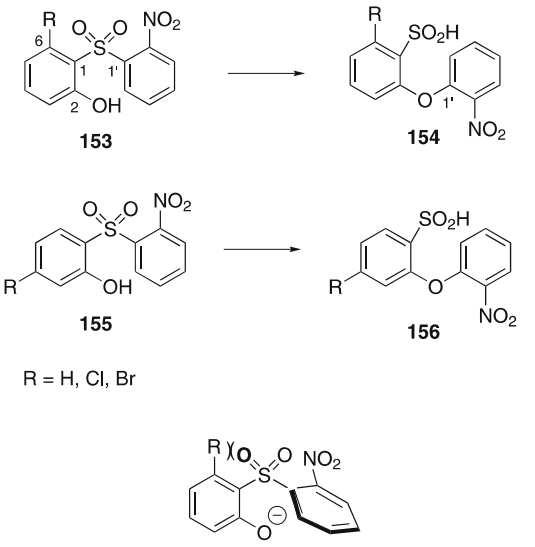
Scheme 48

ment). Finally, cyclization with elimination of hydrogen sulfide took place to furnish **152**. Analogous transformations of other derivatives of thiadiazole and diaminobenzene into the respective thiadiazepine were also studied; yields in the range 15–70% were attained.

4
O – S Rearrangements

McClement and Smiles [70] noted as early as 1937 that the rate of rearrangement of 2-hydroxy-2′-nitrodiphenyl sulfone **153** (Scheme 49) is accelerated by the presence of a methyl group in the 6-position. The origin of this acceleration was studied by Bunnett and Okamoto [71]. To distinguish between electronic and steric effects, isomers **153** and **155** differing in the position of the substituent R (Me, Cl and Br) were chosen with an assumption that the inductive effect upon nucleophilicity of the phenolic oxygen from both *meta* positions is roughly the same. It was found that both methyl (electron donating) and halogen (electron withdrawing) substituents in position 6 accelerate the rearrangement. In fact, a remarkable acceleration of magnitude 10^5–10^6 was measured for all substrates **153**.

The results suggested a steric origin of the C-6 substituent effects. The authors analyzed conformations of the basic substrate **153** (R = H) and concluded that the conformation with the aromatic rings located on perpendicular planes and phenolic oxygen in a remote position from the sulfone oxygens



Scheme 49

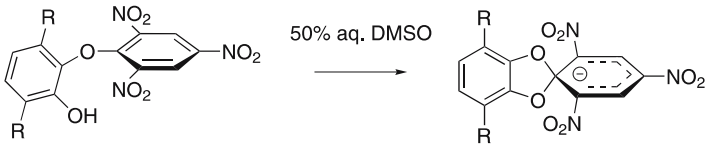
presents the lowest energy (Scheme 49). Introduction of a 6-substituent (R) brings the C-2 hydroxy group in close proximity to C-1′ radically decreasing the energy required for the activation of the rearrangement process.

The relevant kinetic studies of spiro Meisenheimer complex formation from 2,4,6-trinitrophenyl ether of 3,6-dimethylcatechol (**157**, R = H or Me) was reported [72] (Scheme 50). It was found that the presence of methyl groups, accelerates the rearrangement, although the increase in the rate was not so dramatic as in the case of sulfone **153** (Scheme 49). It was suggested that the steric effect of the methyl groups increases the population of the conformation leading to rearrangement. The authors discussed two mechanisms for Meisenheimer complex formation—diffusion and pre-association controlled.

The activation energy for rearrangement of **153** (R = H, Me, *i*-Pr and *t*-Bu) (Scheme 49), was derived from ab initio calculations based upon an equation relating reaction rate and the distance between the reacting atoms in the ground state [73]. The derived values shown in Table 7 confirm the purely steric nature of the enhanced rate of the rearrangement by the substituent in position 6. A study of the gas-phase rearrangement with labeled substrates was reported [74].

The application of nitro-sulfide rearrangements in heterocycle synthesis has been more recently reported [75].

An interesting version of the rearrangement [76] is presented in Scheme 51. The base-induced reaction of 2,4-dinitrobenzenesulfonamide with various acyl chlorides provides *N*-(2,4-dinitrobenzenesulfonyl) acylamide derivatives **159** that rearrange and fragment in situ to afford the respective nitriles **160.** The reaction has been used for derivatization of complex crown ethers.

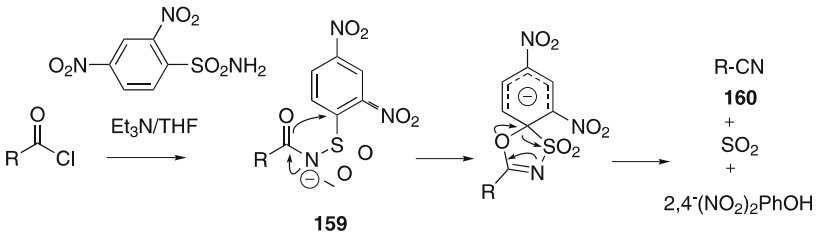


157 **158**

Scheme 50

Table 7 Geometric and energy data for rearrangement of **153** (Scheme 49)

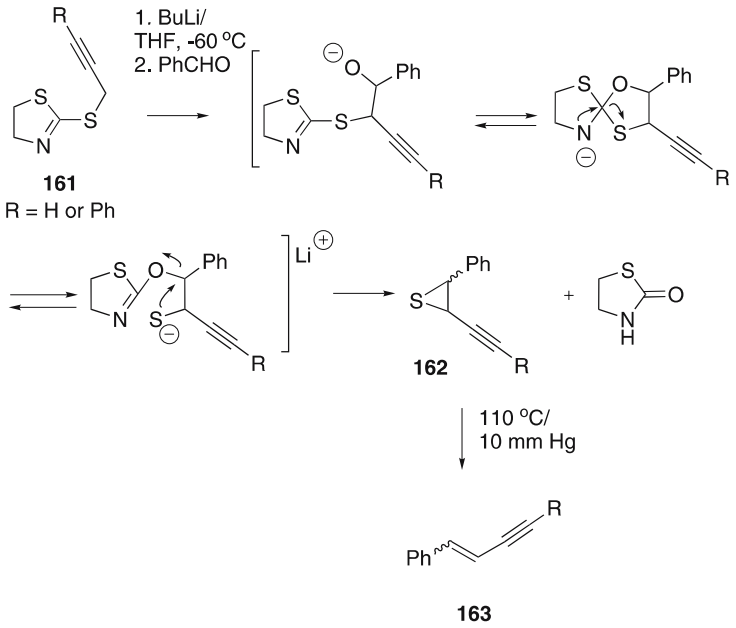
R	Distance O*-C1, Å	*E* kcal mol^{-1}
H	3.05	6.6
Me	2.80	1.5
i-Pr	2.67	0.3
t-Bu	2.58	0.2



Scheme 51

To the best of our knowledge, the first indication that the Smiles rearrangement could be applied to olefination reactions emerged from the work of Hirai and coworkers [77] in 1972. These authors reported that anion generated from the thiazole-2-thiol derivatives **161** (R = H or Ph) (Scheme 52) and *n*-butyllithium (when R = H, two equivalents were used) reacted with benzaldehyde to provide, after chromatography, thiirane **162** and 1,3-thiazolidin-2-one. Distillation of the thiirane gave the respective olefin **163** (which was also detected in the crude product). The authors realized that the reaction occurred through a spiro-bicyclic intermediate.

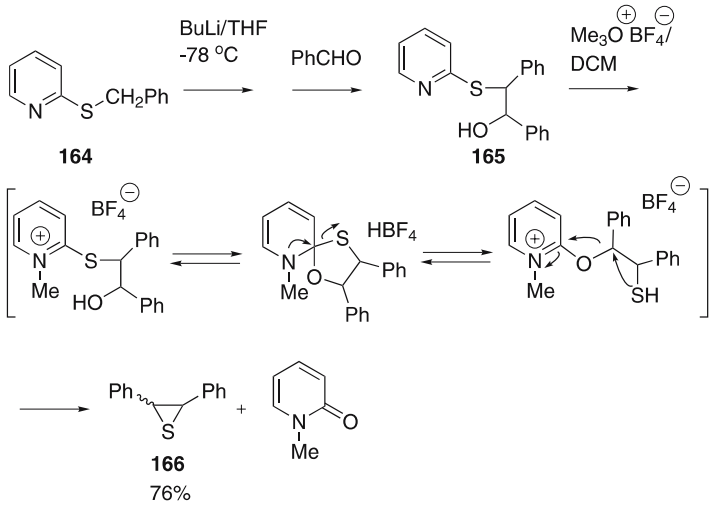
C.R. Johnson et al. [78] confirmed that 2-methylthio- or 2-benzylthiothiazole derivatives react with benzaldehyde or acetone to afford the respective adducts that could be transformed into thiiranes. It has also been shown



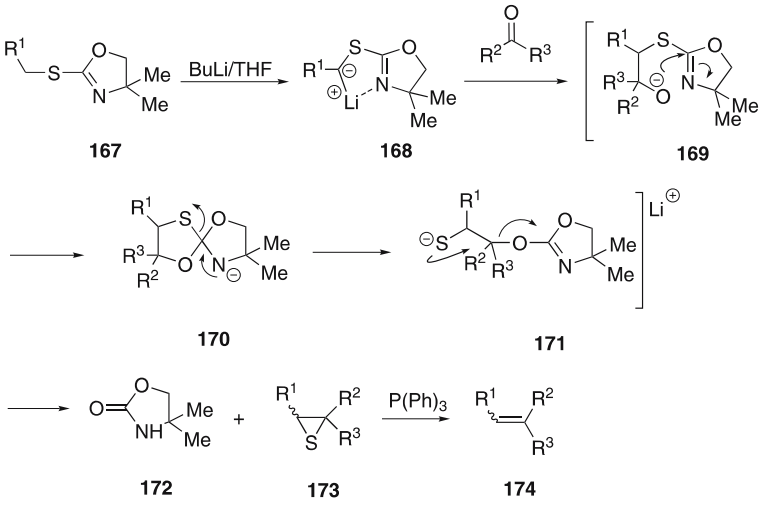
Scheme 52

that 2-thiopyridine derivatives may serve as a template in thiirane synthesis (Scheme 53). When benzyl-pyrid-2-yl sulfide **164** (Scheme 53) was treated with *n*-butyllithium and then with benzaldehyde, adduct **165** was obtained in 71% yield. Methylation of the adduct with the Meerwein salt followed by alkaline treatment gave thiirane **166** in 76% yield as a mixture of *cis*- and *trans*-isomers in a ratio of 1 : 1, and *N*-methyl-2-pyridone.

Meyers and Ford [79, 80] reported that anions generated from 1,3-oxazolyl sulfides **167** (Scheme 54) react with carbonyl compounds to give thiiranes **173**



Scheme 53



Scheme 54

and oxazolidinone **172.** Reduction of the thiiranes (isolated or in situ) with triphenylphosphine or triethyl phosphite [81] provided olefins **174.** Selected examples are shown in Table 8.

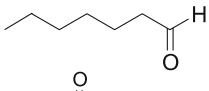
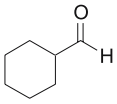
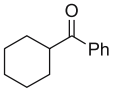
The thiirane synthesis was also studied using optically active oxazoline **175** in which the methoxy group oxygen atom provides additional complexation of Li^+. However, asymmetric induction was rather low. Enantiomeric excesses and configuration of the prevailing enantiomers are indicated in Scheme 55.

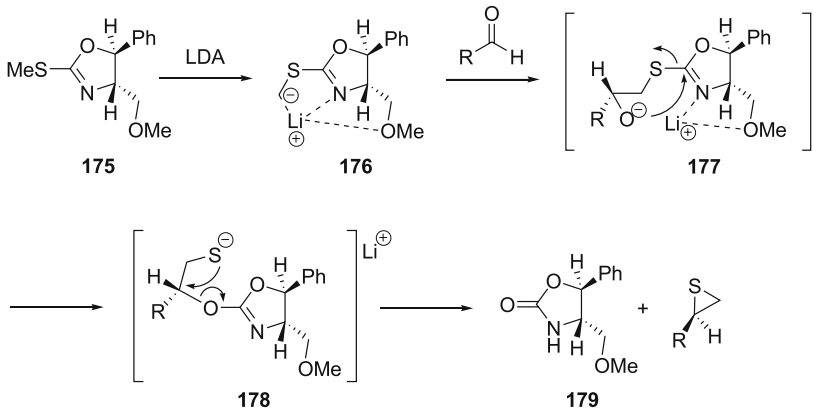
Tominaga and coworkers [82, 83] reported a thiirane synthesis starting from 2-mercapto-1,3-thiazole derivative **180** bearing a trimethylsilyl group (Scheme 56). Treatment of **180** with CsF in acetonitrile and then with an aldehyde provided adducts **182** that fragmented via the spiro-isomer **183.** Interestingly, the use of TASF as the fluorine anion source provided alcohols **185.** The latter products were slowly transformed into the respective thiiranes **184** and thiazolidinone on storage (Table 9).

Similar results were obtained using (2-pyridyl)-[(trimethylsilyl)methyl] sulfides instead of **180.**

Gasco et al. [67] reported detailed studies on O – S and N – S rearrangements in furazan and furoxan systems. 4-Phenylfurazan (3-phenyl-1,2,5-oxadiazole) bearing thio-(2-hydroxyethyl) group **186** (Scheme 57) in ethanolic NaOH, at reflux temperature, generated thiirane and 3-hydroxy-4-phenylofurazan **188** (74% yield). Apparently, rearrangement of **186** into **187** and fragmentation of the latter had occurred.

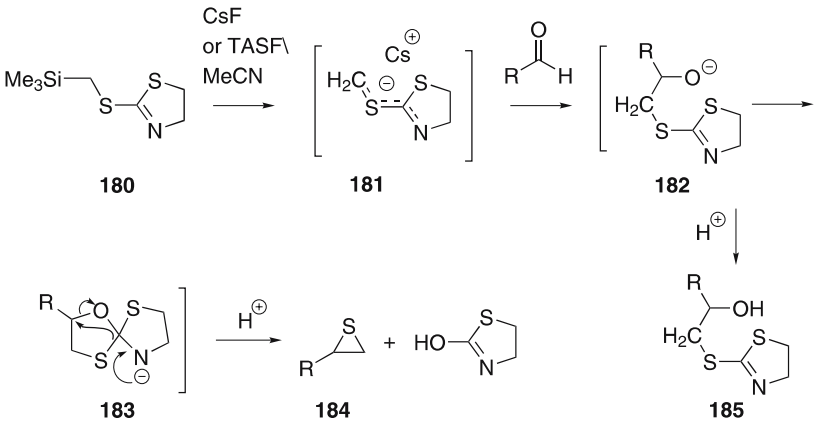
Table 8 Synthesis of thiiranes and olefins according to Scheme 54

R^1	R^2COR^3	Yield (%) Thiirane	Olefin
H		73	69
H		78	69
Ph		71	81
H		61	56
PhCH(Me)		–	51



R	Yield (%)	*ee*
n-hexyl	53	21 (*R*)
c-hexyl	64	32 (*R*)
Ph	48	19 (*R*)

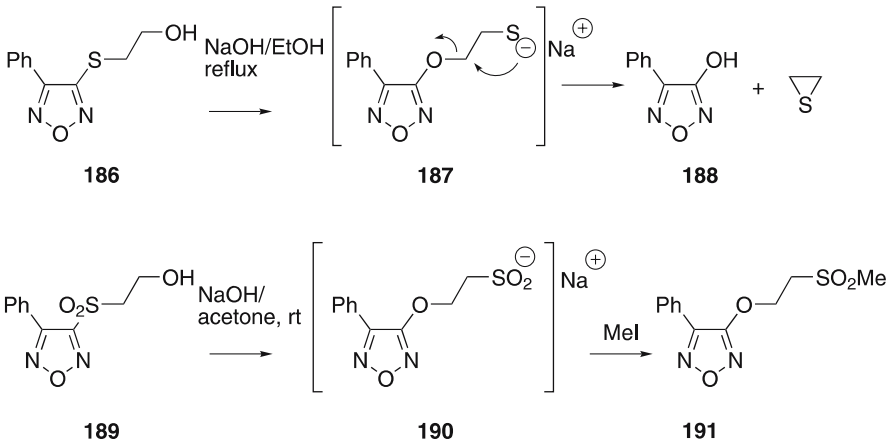
Scheme 55



Scheme 56

The related sulfone **189**, when treated with sodium hydroxide in acetone, smoothly rearranged into sulfinic acid **190** (isolated as methyl sulfone **191**, 70% yield) at room temperature. As expected, the sulfone rearranged more readily than the sulfide.

Replacement of the 4-phenylfurazan with a 3-phenylfuroxan moiety does not affect the rearrangement since sulfide **192** (Scheme 58) in ethanolic NaOH at reflux temperature yielded the hydroxy derivative **193** (61%) and thiirane.



Scheme 57

Table 9 The reaction of sulfide **180** with aldehydes

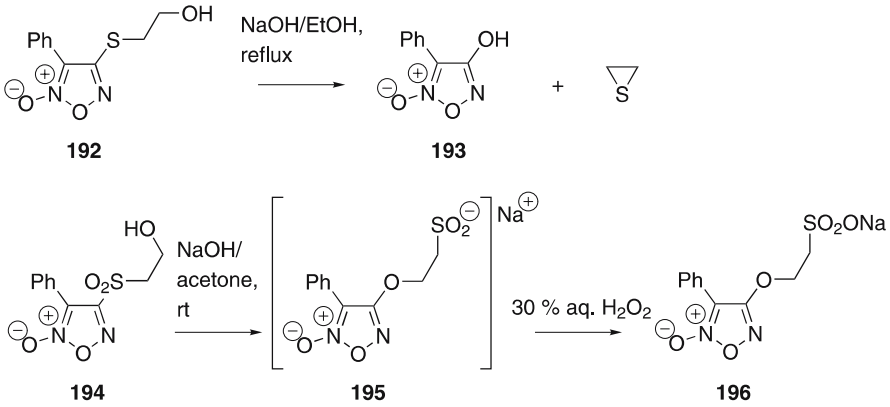
R	Reagent	Yield (%) **184**	**185**
Ph	CsF	40	–
4-PhPh	CsF	75	–
1-naphthyl	CsF	59	–
Ph	TASF	–	90
4-PhPh	TASF	–	81
4-(MeO)Ph	TASF	–	80

Accordingly, sulfone **194** changed into the respective sulfinic acid salt **195** that after oxidation gave sulfonate **196** (92%).

However, 4-phenylfuroxan (2-oxido-4-phenyl-1,2,5-oxadiazole) derivatives behave in a different way. Sulfide **197** (Scheme 59) as well as sulfone **198** decompose with evolution of NO in alkaline conditions. It was suggested that the N – O bond is cleaved in the spirocyclic intermediate **199** to give the fragile nitroso derivative **200**.

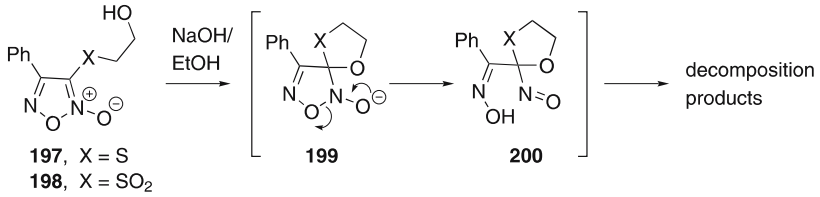
The N – S rearrangements of furazan and furoxan derivatives will be discussed in the appropriate section.

The Smiles-type rearrangement in acyclic systems was recorded in the already discussed work of C.R. Johnson and coworkers [78] (Scheme 53 and the relevant text). Reaction of an anion generated from dithiocarbamate **201** (Scheme 60) with propionaldehyde afforded adducts **202** (95% yield). Treatment of this product with NaH in THF gave thiirane **205** in 78% yield as a mixture of *cis*/*trans* isomers.



192 193 194 195 196

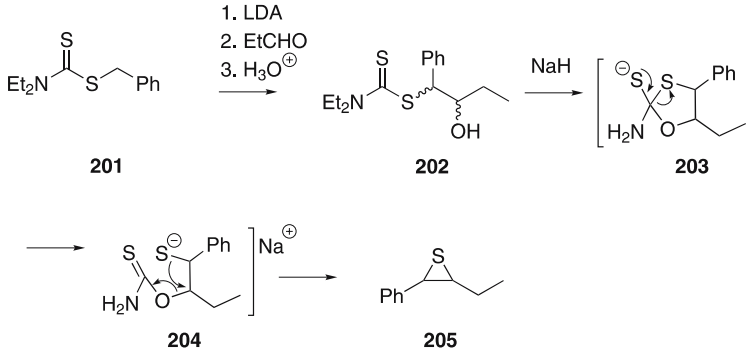
Scheme 58



197, X = S
198, X = SO_2

199 **200**

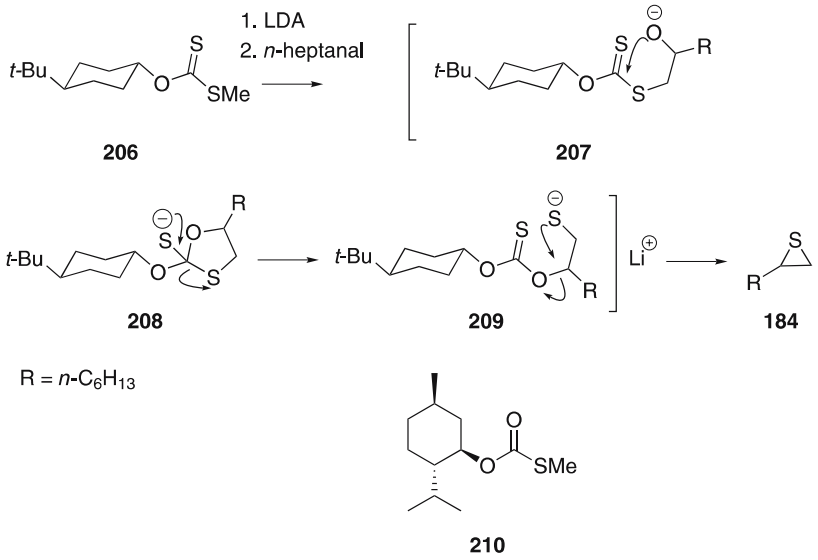
Scheme 59



201 **202** **203** **204** **205**

Scheme 60

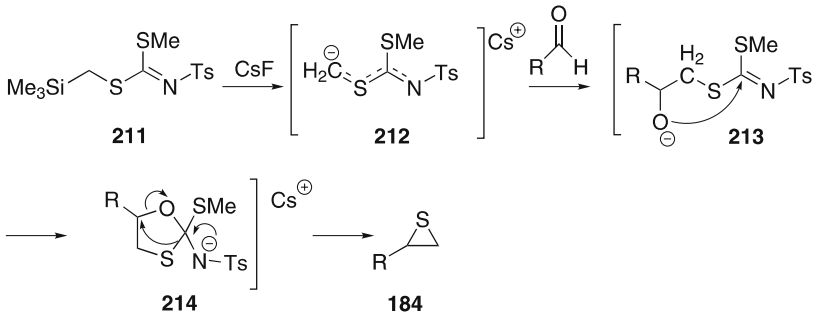
The same authors have shown that xanthates **206** (Scheme 61) may also be used for thiirane synthesis as in the case of the adduct **207** which fragmented under the reaction conditions to give **184**. Attempted use [78] of a chiral auxiliary failed—reaction of *O*-menthyl thiocarbonate **210** with various aldehydes and ketones provided the respective thiiranes in good yields but with a negligible enantiomeric excess.



Scheme 61

Tominaga et al. [84] reported the synthesis of thiiranes by reaction of aldehydes with an anion generated from silylated *N*-(4-toluenesulfonyl)dithiocarboimides **211** (Scheme 62). Treatment of **211** with CsF and an aldehyde gave adducts **213** and then the spirocyclic derivative **214** that fragmented according to the usual scheme.

A combination of Pummerer-type and Smiles rearrangement has been recorded [85]. For an earlier discussed O – S rearrangement, see Scheme 12 and the relevant text.



Scheme 62

5
The Julia–Kocienski Olefination Reaction

5.1
Introduction. Sulfone-based Olefination Reactions

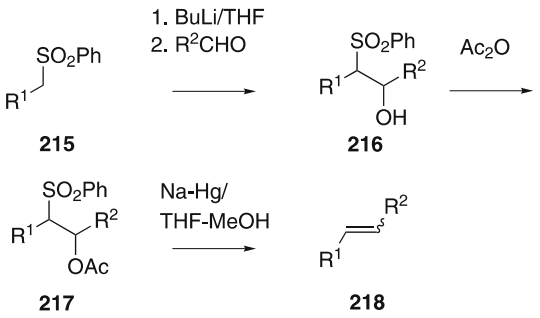
The advantages of sulfur-based olefination reactions in syntheses of complex targets stem from the relative ease of generating the C – S bond in various building blocks and from the compatibility of sulfur-containing functional groups with many chemical transformations.

In 1973 Marc Julia and J.M. Paris [86] developed an olefination protocol involving three distinctive steps (Scheme 63): (1) reaction of an anion generated from alkyl phenyl sulfone **215** and *n*-butyllithium with an aldehyde to provide the adduct **216**; (2) acetylation (or benzoylation) of **216**; and (3) sodium amalgam reductive elimination of sulfonyl–ester **217**.

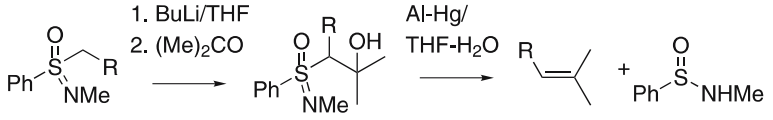
Lythgoe, Kocienski and their coworkers investigated the scope, stereochemistry and mechanism of the "classical Julia olefination" (also called the Julia–Lythgoe olefination) and paved the way for its broad application in target-oriented synthesis [87–90]. The bias towards *E*-olefins, with the isomer ratio being typically in the range 7/3 to 9/1 for primary unhindered sulfones and aldehydes, marks a distinctive stereochemical feature of the reaction.

Reductive elimination of β-hydroxysulfoximines provided the basis for a related olefination method put forward by C.R. Johnson and coworkers [91] (Scheme 64).

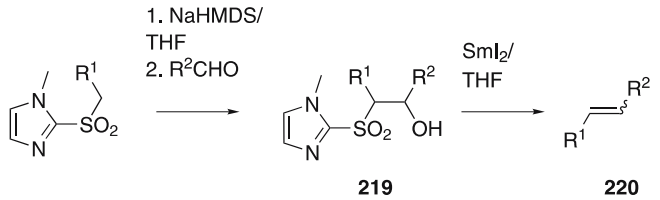
Several modifications and improvements of the classical Julia methodology are currently available. In particular, sulfoxides were used in the place of sulfones [92–95], milder reducing agents were employed in the place of sodium amalgam [96], and a 1-methyl-1*H*-imidazolyl-2 sulfone (Scheme 65) was used in the place of the phenyl sulfone in order to facilitate the reduction step [97]. The latter modification is of particular interest since, in principle,



Scheme 63



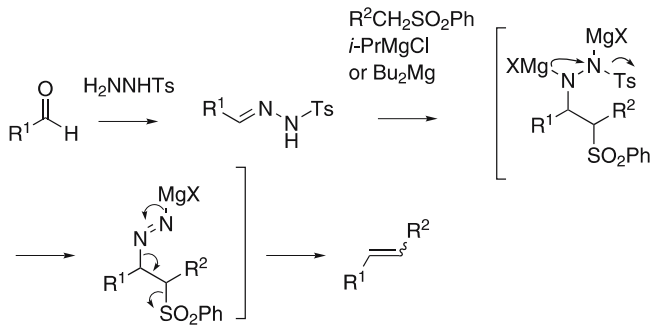
Scheme 64



Scheme 65

the Smiles rearrangement of the hydroxy sulfone **219** could occur. Reexamination of the original procedure [98] showed that, indeed, olefin **220** was formed directly from lithiated sulfone and aldehyde when the reaction was carried out at higher temperature. The migratory aptitude of the methylimidazole ring turned out to be too low for the rearrangement to occur at low temperature.

Wicha and co-workers showed that the reduction step could be circumvented altogether by initial conversion of the aldehyde into the respective tosylhydrazone [99–101] (Scheme 66). The tosylhydrazone was treated with an excess of a magnesium derivative of an alkyl phenyl sulfone to give an adduct that fragments by the mechanism indicated in Scheme 66. The magnesium derivatives of sulfones were generated separately or in situ using *iso*-propylmagnesium chloride or dibutylmagnesium. The method is based upon the observation [102] that aldehyde tosylhydrazones react with some sterically unshielded alkyl phenyl sulfones in the presence of LDA to produce olefins. However, with the use of LDA as the base, fragmentation of the to-



Scheme 66

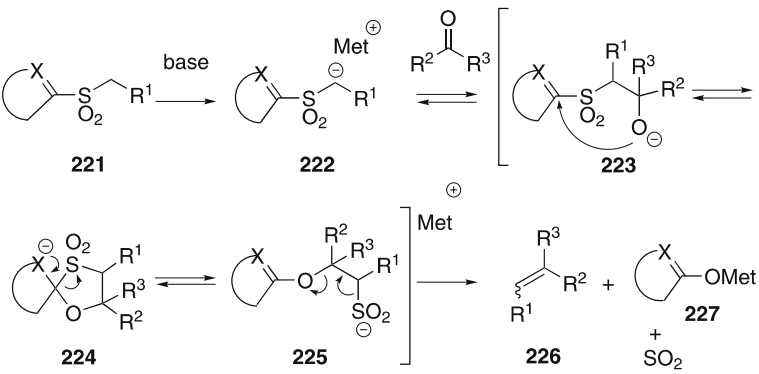
sylhydrazone (the Shapiro reaction) prevailed when more complex reaction partners were involved. The nature of the counterion turned out to be crucial in this case.

5.2
Olefination Involving the Smiles' Rearrangement

In 1991 Sylvestre Julia and coworkers [7] published a communication on a direct synthesis of olefins by reaction of carbonyl compounds with lithio derivatives of 2-(alkylsulfonyl)-benzothiazoles. The olefin is accompanied by 2-hydroxy-benzothiazole and sulfur dioxide. The reaction was carried out using LDA as the base in THF, with the separate generation of the sulfonyl anion or by adding the base to the solution of sulfone and the carbonyl compound ("Barbier approach"). As has already been discussed in the introductory part of this chapter, the Smiles rearrangement and fragmentation of the rearrangement product are involved. This new general method allowed for the preparation of olefins from carbonyl compounds in one step, using readily accessible reagents. In the full account of the French group studies [8, 9] successful application of 2-pyridyl and 2-pyrimidyl sulfones to alkene synthesis was also described. The generalized scheme of the reaction is presented below (C = X stands for a carbon–heteroatom or activated C = C bond).

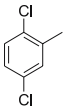
In a pivotal modification of the "direct olefination reaction" Kocienski and his coworkers [10] showed that the use of 1-phenyl-1*H*-tetrazol-5-yl sulfones, preferentially with NaHMDS or KHMDS as the base and DME as the solvent, provides olefins in excellent yields and stereoselectivity with respect to *E*-isomers. The modified version of the direct olefination reaction has frequently been referred to as the Julia–Kocienski olefination reaction.

Presently, several heterocyclic and aromatic sulfones have been tested in the reaction. Their structures, names and common abbreviations are compiled in Table 10.



Scheme 67

Table 10 Heterocyclic and aromatic sulfones used in the Julia–Kocienski olefination reaction

Structure	Name, abbreviation	Refs.
	benzothiazol-2-yl (BT)	[8, 9]
	pyridin-2-yl (Pyr)	[8, 9]
	pyrimidin-2-yl	[8, 9]
	1-phenyl-1*H*-tetrazol-5-yl (PT)	[10]
	1-*tert*-butyl-1*H*-tetrazol-5-yl (TBT)	[103]
	1*H*-benzoimidazo-2-yl	[104]
	1-methyl-1*H*-benzoimidazo-2-yl	[104, 105]
	3,5-bis-(trifluoromethyl)-phenyl (BTFP)	[106]
	pentachlorophenyl	[a]
	2,5-dichlorophenyl	[a]
	4-nitrophenyl	[a]
	4-cyjanophenyl	[a]
	2-(trifluoromethyl)-phenyl	[a]

[a] Judka and Makosza, 2006, personal communication

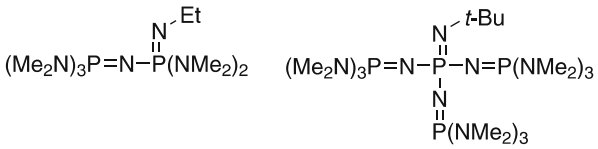
3,5-Bis-(trifluoromethyl)-phenyl plays the role of migrating ring in the Smiles rearrangement in the Nájera and co-workers [106, 107] modification of the olefination reaction. Judka and Makosza (Judka and Makosza, 2006, personal communication) have shown that pentachlorophenyl and some very simple phenyl derivatives may be conveniently used in the olefination reactions under mild conditions. Indubitably, several other aromatic and heterocyclic systems will be established as the templates in the direct olefination reaction, allowing for convenient choice of experimental conditions and stereochemical bias.

5.3 Experimental Methods and Conditions

Julia and coworkers made use of two protocols for carrying out the reaction: (A) the sulfone in THF, at – 78 °C, was treated with LDA (in the case of pyridyl sulfones *n*-butyllithium could also be used) and then (usually after 0.5 to 1 h) an aldehyde (a slight excess) was added; the mixture was kept for a certain time at – 78 °C and then it was allowed to warm to room temperature and (B) ("Barbier procedure") a solution of LDA was slowly added to a solution of both reacting components in THF at – 78 °C. In general, the methods were equivalent. However, in some cases the side reactions could be minimized by using the method B.

Commercially available solutions of lithium–sodium- and potassium hexamethyldisilazides (LHMDS, NaHMDS, KHMDS) were applied in the Kocienski laboratory [10] using as the reaction medium DME, THF, Et_2O, or MePh.

A range of other base–solvent combinations were applied with various sulfones. Judka and Makosza have used *t*-BuOK, *t*-BuOLi and EtONa in THF or DMF. Reactions of ethyl (benzothiazol-2-yl-sulfonyl)acetate [108] with carbonyl compounds were conveniently carried out using DBU as a base in DCM at reflux (2 molar excess of the sulfone was used). Reaction of methyl *tert*-butyltetrazolyl sulfones [109] was executed by Cs_2CO_3 in THF-DMF at reflux.



P2-Et P4-*t*-Bu

Fig. 1

Spanish authors [106] amongst other bases have used triaminoiminophosphonates P2-Et and P4-*t*-Bu (Fig. 1) in THF or potassium hydroxide—tetra-(*n*-butyl)ammonium bromide (TBAB) in THF at room temperature.

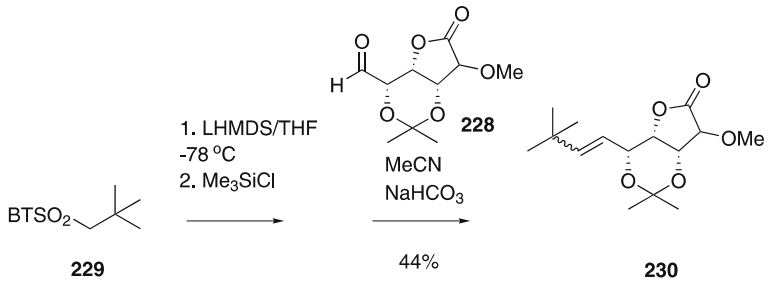
The sulfones and the corresponding bases are compiled in Table 11. It should be noted that the Kocienski protocol (PT-sulfones, Li- or NaHMDS in THF or DME) appears to be the method most often used at present.

A large-scale olefination of a sparingly soluble aldehyde **228** (Scheme 68) required some modifications of the standard procedure [110]. The anion generated from BT-sulfone **229** and LHMDS, in THF at – 78 to – 55 °C, was treated with trimethylsilyl chloride (or with $BF_3 \cdot Et_2O$) and the mixture was added to a pre-cooled solution of **228** in acetonitrile. The mixture was allowed to warm to room temperature and then was briefly heated to 50 °C. After aqueous workup, the product **230** was obtained in 44% yield.

Table 11 Typical conditions for Julia–Kocienski olefination, sulfones, bases, solvents and the temperature

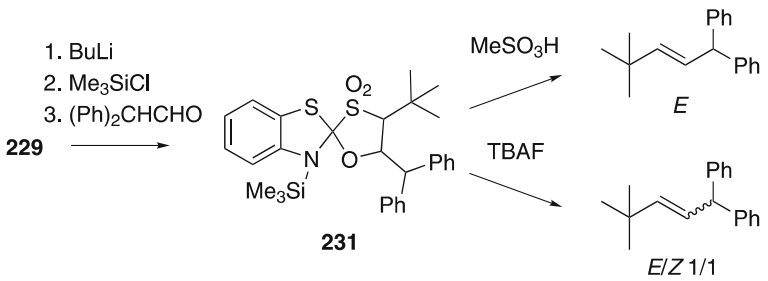
Sulfones	Base	Solvent	Temp. (°C)
All	LDA	THF	– 78
Pyr	BuLi	THF, THF-MeCN	– 78
All	MetHMDS [a]	THF, DME, PhMe, Et_2O	– 78 → rt
TBT, BT	Cs_2CO_3	THF, THF-DMF	reflux
BT	DBU	THF, Et_2O, DCM, MeOH, EtOH, MeCN	rt
aromatic	*t*-BuOK	DME, DMF, THF	rt
BTFP	P2-Et	THF	– 78
BTFP, BT, PT, TBT	P4-*t*-Bu	THF	– 78, rt
BTFP, PT, TBT	KOH-TBAB	DME, THF	rt

[a] Met = Li, Na, K



229 230

Scheme 68



Scheme 69

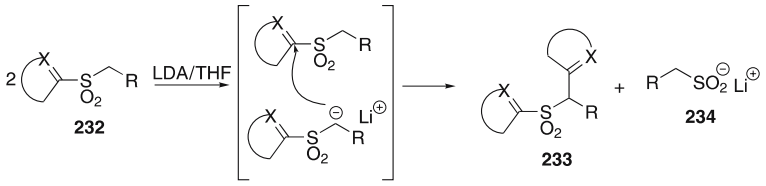
In related experiments the authors isolated an intermediate (a solid) to which the structure **231** was assigned (Scheme 69). On treatment of **231** with acids, such as $MeSO_3H$, an *E*-olefin was formed exclusively while TBAF ("anhydrous" reagent) provided a mixture of geometric isomers in a ratio of 1/1.

The additives (Me_3SiCl or $BF_3 \cdot Et_2O$) may activate the carbonyl compound or stabilize the intermediate. $BF_3 \cdot Et_2O$ has been used as an activator in the reaction of aldehydes with lithiated phenylsulfones [111] although its function remains vague. It may be noted that acyclic products were formed on silylation of the hydroxy sulfides obtained in the reaction of oxazol-2-yl sulfides with aldehydes [80].

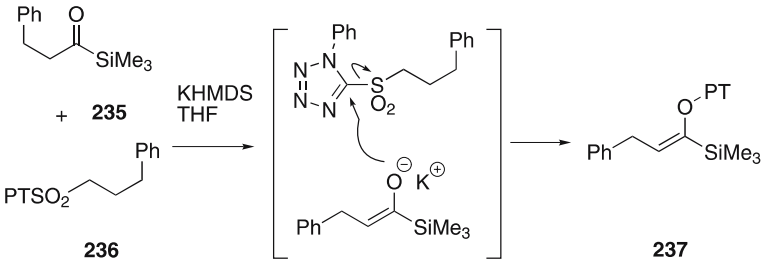
5.4 The Side Reactions

The main-stream reactions of metalated heterocyclic sulfones with carbonyl compounds afford the respective olefins in high yields. However, important side reactions were recorded.

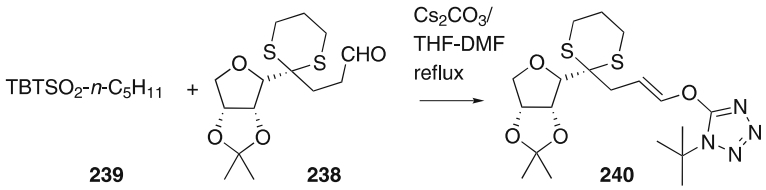
1. Autocondensation of sulfones
   Autocondensation of sulfones in the anion formation step was recorded by the Julia group [9]. The reaction consists of nucleophilic substitution of the sulfonyl moiety by a sulfonyl anion, as indicated in Scheme 70.
   The relative vulnerability of BT, PT and TBT sulfones to autocondensation was estimated in a set of experiments [103]. Anions were generated with KHMDS in THF at – 60 °C. After 2 h no BT sulfone and only 20% of the starting PT sulfone could be recovered while TBT sulfone remained largely unchanged (91% was recovered).
   Branching of the sulfone in the α or β position slows down autocondensation; however, the reaction with a carbonyl partner is also retarded, presumably to a lesser extent. Pyr sulfones exhibit notable resistance towards autocondensation. As was already mentioned, in this case anions may be generated even with the use of relatively nucleophilic *n*-butyllithium without forming a detectible amount of 2-butylpyridine.



Scheme 70



Scheme 71

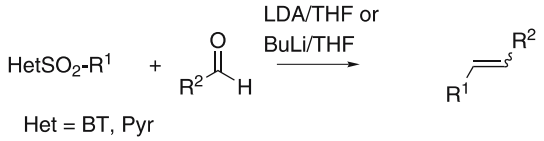


Scheme 72

2. Addition of the carbonyl compound enol to heterocyclic sulfone.
   Reaction of PT sulfone **236** with acylsilane **235** in the presence of KHMDS leads to the enol derivative **237** (*E* isomer, Scheme 71) [112], isolated in 68% yield. The enol **237** showed low reactivity towards acids and bases and could be stored indefinitely without decomposition.
   A similar reaction of aldehyde **238** with TBT sulfone induced by cesium carbonate has recently been noted [109] (Scheme 72).

5.5
Systematic Studies on Benzothiazolyl, 2-Pyridyl and Phenyltetrazolyl Sulfones

Julia and coworkers conducted extensive studies [7–9] of the reaction of benzothiazolyl and pyridyl sulfones, with emphasis given to the former, and selected carbonyl compounds, mainly aldehydes. Some pyrimidyl sulfones were also examined. A large number of experiments were summarized in ta-



Scheme 73

bles and discussed. Below we present selected examples of the Julia results that illustrate the scope, efficiency and stereochemical aspects of the reaction developed.

Representative results for the reaction of benzothiazolyl and pyridyl sulfones with unbranched aliphatic and benzylic aldehydes are shown in Table 12. Anions were generated in situ with LDA (BT sulfones) or separately using *n*-butyllithium (Pyr sulfones). The yields vary between low and 95%. High stereoselectivities with *E*-isomers favored were recorded for aromatic aldehydes.

Selected examples of the reaction of unsaturated sulfones with aldehydes are compiled in Table 13.

Benzothiazolyl anions were generated in situ (method B) or pre-formed with LDA (method A); for Pyr sulfones method A with *n*-butyllithium was used. High yields were obtained for some allylic and propargylic sulfones. In general, relatively high stereochemical preferences were noted.

In 1998 Kocienski et al. [10] reported the results of systematic studies on the reaction of selected heterocyclic sulfones with carbonyl compounds. The best results were obtained using 1-phenyl-1*H*-tetrazol-5-yl (PT) sulfones. In the first series of experiments, the representative PT sulfone **241** (Scheme 74) was compared with its benzothiazolyl (BT) counterpart. The comparison was

Table 12 Reaction of benzothiazolyl and pyridyl sulfones with unbranched aliphatic and benzylic aldehydes according to Scheme 73 (BT sulfones—under Barbier conditions, Pyr—sulfones with premetalation)

Het	R^1	R^2	Yield (%)	E/Z	Base
BT	Me	*n*-C_9H_{19}	20	–	LDA
BT	Et	*n*-C_8H_{17}	48	49/51	LDA
Pyr	Et	*n*-C_9H_{19}	47	52/48	BuLi
BT	Bn	*n*-C_8H_{17}	80	23/77	LDA
Pyr	Bn	*n*-C_8H_{17}	51	10/90	BuLi
BT	Et	4-MeOPh	54	98/2	LDA
BT	*n*-Pr	4-MeOPh	95	99/1	LDA
BT	Et	3,4-$(MeO)_2$Ph	39	98/2	LDA
BT	*t*-BuO-$(CH_2)_2$	Ph	15	93/7	LDA

Table 13 The reaction of BT and Pyr sulfones with aldehydes involving unsaturated groups, according to Scheme 73

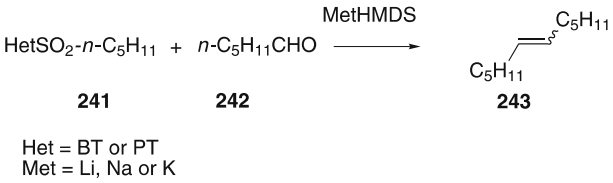
Het	R^1	R^2	Yield (%)	E/Z	Method/Base
BT	$CH_2 = CHCH_2$	Bn	50	31/69	A/LDA
BT	$CH \equiv CCH_2$	*n*-C_7H_{15}	26	1/99	A/LDA
			22	1/99	B/LDA
BT	Bn	$MeC = CH_2$	93	90/10	A/LDA
BT	*c*-hexyl		26	99/1	A/LDA
			20	99/1	B/LDA
Pyr	$CH_2 = CHCH_2$	*n*-C_8H_{17}	25	19/81	BuLi[a]
Pyr	$Me_2C = CHCH_2$	*n*-C_6H_{13}	73	7/93	BuLi[a]

[a] Premetalation

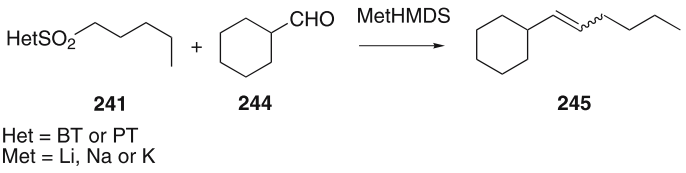
conducted using *n*-hexanal **242**, LHMDS, NaHMDS and KHMDS as bases in THF, toluene, Et_2O or DME. It should be noted that the product yields and the isomer ratios were determined by GC with dodecane as the internal standard. The results are presented in Table 14.

As shown in Table 14, the highest proportion of the *E*-isomer was recorded for both sulfones when DME was the solvent. The PT sulfone showed the best selectivity with K as the countercation whereas the BT sulfone was less sensitive to change in the base. The PT sulfone provided over 90% yield (Li and K-bases) whereas the best yield with BT sulfone amounted to 68%.

The effect of aldehyde chain branching was examined using cyclohexanecarboxaldehyde **244** (Scheme 75). The results are shown in Table 15.



Scheme 74



Scheme 75

Table 14 Comparison of PT- and BT-sulfones in reaction with hexanal

Met	Het	Isomer ratio, *E*/*Z*; yield (%) Toluene		Et_2O		THF		DME	
Li	BT	40/60	5	43/57	7	60/40	42	55/45	3
	PT	57/43	55	73/27	76	75/25	97	77/23	95
Na	BT	51/49	29	53/47	17	–	0	77/23	27
	PT	59/41	80	57/43	90	76/24	89	86/14	92
K	BT	47/53	15	51/49	68	55/45	24	75/25	6
	PT	64/36	13	72/28	30	86/14	71	94/6	71

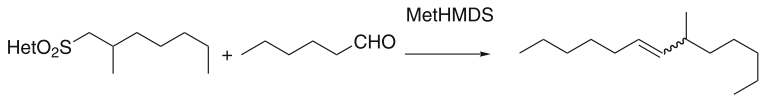
Table 15 The aldehyde chain branching effects

Met	Het	Isomer ratio, *E*/*Z*; yield (%) Toluene		Et_2O		THF		DME	
Li	BT	50/50	1	49/51	2	66/34	6	70/30	2
	PT	51/49	90	61/39	66	69/31	90	72/28	94
Na	BT	54/36	20	50/50	17	62/38	19	75/25	32
	PT	65/35	51	65/35	83	73/27	92	89/11	95
K	BT	54/36	13	51/49	57	54/46	27	76/24	4
	PT	77/23	22	89/11	46	97/3	71	99/1	81

As shown in the Table, aldehyde branching in the α-position does not affect markedly the reaction yield or stereoselectivity. The relative efficiency of the sulfones remained, in principle, the same.

The reactions of β-branched sulfones were examined with **246** (Scheme 76). The results are compiled in Table 16.

Introduction of β-branching into the sulfones resulted in higher yields of the olefination product, in general. The steric course of the reaction depends upon the counterion and the solvent. The high yields of the product with *E*-isomer dominating could be attained under various conditions, although the BT sulfone and KHMDS in THF furnished a mixture with the *Z*-isomer prevailing.



246 **242** **247**

Het = BT or PT
Met = Li, Na or K

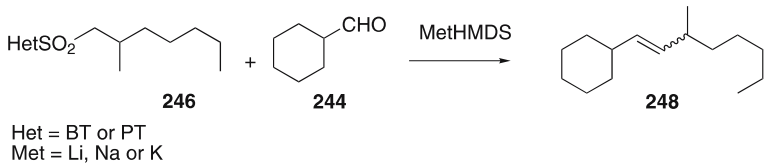
Scheme 76

Table 16 Effect of β-branching in sulfone on the reaction course

Met	Het	Isomer ratio, *E*/*Z*; yield (%) Toluene		Et_2O		THF		DME	
Li	BT	54/56	86	60/40	74	57/43	98	44/56	100
	PT	43/57	96	48/52	61	67/33	100	60/40	100
Na	BT	57/43	78	58/42	84	39/61	89	64/36	87
	PT	38/62	65	32/68	98	32/68	88	78/22	100
K	BT	26/74	31	36/64	46	25/75	68	46/54	63
	PT	62/38	25	37/63	20	76/24	23	96/4	22

Table 17 Effect of branching in the sulfone and aldehyde on the reaction course

Met	Het	Isomer ratio, *E*/*Z*; yield (%) Toluene		Et_2O		THF		DME	
Li	BT	70/30	88	67/33	74	72/28	87	58/42	83
	PT	39/61	85	41/59	74	53/47	90	40/60	100
Na	BT	86/14	66	87/13	75	67/33	84	55/45	96
	PT	67/33	83	53/47	98	48/52	71	84/16	100
K	BT	76/24	48	78/22	68	40/60	85	36/64	100
	PT	98/2	68	92/8	28	97/3	58	99/1	59



Scheme 77

Finally, the reactions of branched sulfone **246** with branched aldehyde **244** were scrutinized (Scheme 77, Table 17).

The experiments revealed the major trends in the reaction. The following general conclusions were formulated by the authors.

(a) Branched alkyl benzothiazoyl sulfones (BT) often gave better yields than their unbranched counterpart.

(b) Alkyl phenyltetrazolyl (PT) sulfones gave clearly better yields than alkyl benzothiazolyl sulfones.

The authors suggest that the differences (a and b) reflect the stability of the metalated sulfones as olefination efficiency is lower when the sulfone is prone to self condensation.

(c) In the BT series, the stereoselectivity of the reaction was not markedly sensitive to changes in counteranion whereas in the PT series, an increase of *E*/*Z* ratio was observed in the series Li, Na, K.
(d) Branching of the alkyl chain in either the reaction partners did not affect markedly the steric course of the reaction.
(e) For PT sulfones the highest yields were attained using Li- or NaHMDS in THF or DME. As the polarity and coordinating ability of the solvent increased (DME > THF > Et_2O > PhMe), the *E*-selectivity of the reaction increased. The highest proportion of the *E*-isomer was recorded when KHMDS in DME was used. The authors suggest that the best compromise between yield and stereoselectivity is provided by NaHMDS in DME.

It could be added that reaction of BT sulfones with α,β-unsaturated aldehydes provided dienes in high yields. Pyridyl- and *tert*-butyltetrazolyl-sulfones afford olefins in moderate yields but with noticeable preference of *Z*-isomers.

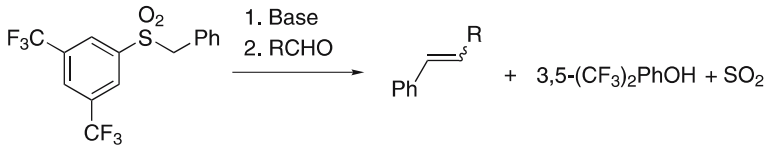
5.6 Progress in Diversification of the Sulfones

Studies by Julia and by Kocienski have shown that the nature of the sulfone may exert a decisive effect on the efficiency of the olefination reaction. Diversification of the migrating rings in the Smiles rearrangement could be benefactions for extending the scope of application of the reaction.

Nájera and coworkers [106, 107, 113] have successfully applied aromatic 3,5-bis(trifluoromethyl)phenyl (BTFP) sulfones in olefination reactions. The sulfones are readily prepared using commercially available 3,5-bis(trifluoromethyl)thiophenol and the respective precursors of the aliphatic or benzylic portion of the molecule.

The stability of the BTFP sulfonyl carbanions generated with a variety of bases including LDA, KHMDS, phosphazene bases (P4-*t*-Bu) and KOH-TBAB towards autocondensation was studied. It was shown that the sulfone recovery from the respective anions was higher than recovery of BT and PT sulfones.

Selected examples of benzyl BTFP sulfone **249** (Scheme 78) with aromatic and aliphatic aldehydes with the use of P4-*t*-Bu, P2-Et or KOH-TBAB in THF are shown in Table 18.



249

Scheme 78

Table 18 Selected results of studies on the reaction of **249** with aldehydes according to Scheme 78

	R	Base	Temp. (°C)	Yield (%)	*E*/*Z*
1	Ph	P4-*t*-Bu	– 78	65	98/2
2	Ph	KOH	rt	78	84/16
3	4-(MeO)Ph	P4-*t*-Bu	– 78	67	94/6
4	4-(MeO)Ph	KOH	rt	52	86/14
5	4-(NO_2)Ph	P4-*t*-Bu	0	76	30/70
6	4-(NO_2)Ph	KOH	rt	12	66/34
7	*c*-hexyl	P4-*t*-Bu	rt	86	50/50
8	*c*-hexyl	P2-Et	rt	75	25/75
9	*c*-hexyl	KOH	rt	14	34/66

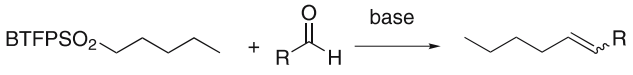
Olefination of aromatic and aliphatic aldehydes was achieved using either P4-*t*-Bu or KOH-TBAB as the base. Aromatic aldehydes gave the products in which the *E* isomer is dominant, with the exception of 4-nitrobenzaldehyde—P4-*t*-Bu (Table 18, entry 5). In reaction with cyclohexanecarboxaldehyde, stereoselectivity was lower and the *Z*-isomer was obtained as the major product.

Examples of the reaction of pentyl BTFP sulfone **250** (Scheme 79) with various aldehydes are presented in Table 19.

The olefination product was obtained in 70% yield in reaction with aromatic as well as aliphatic aldehyde using phosphazene bases or KOH-TBAB. Both aldehydes gave the *E*-isomer predominantly. Cinnamaldehyde gave the corresponding diene with lower yields.

The olefination reaction of BTFP sulfones could be performed with aldehydes and ketones. Efficiency and stereoselectivity of the process was influenced by various factors, such as structural features, base, solvent, etc. General trends are summarized in Table 20.

Judka and Makosza (Judka and Makosza, 2006, personal communication) found that the reaction of 1-(pentachlorophenylsulfonyl)-3-chloropropane with benzaldehyde in the presence of *t*-BuOK in THF gave the respective olefin with the halogen atom in the aliphatic part remaining untouched (Scheme 80, $R^1 = CH_2CH_2Cl$, R^2 = Ph). Following this observation, reaction of pentachlorophenyl- and some other selected aromatic sulfones with alde-



250

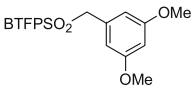
Scheme 79

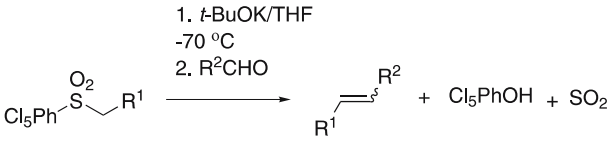
Table 19 Examples of the reaction of *n*-pentyl BTFP sulfone **250** with aldehydes (THF)

	R	Base	Temp. (°C)	Yield (%)	*E*/*Z*
1	Ph	P4-*t*-Bu	rt	45	75/25
2	Ph	KOH[1]	rt	70	67/33
3	(*E*)-PhCH = CH	P4-*t*-Bu	– 78	28	50/50
4	(*E*)-PhCH = CH	KOH[1]	rt	30	12/88
5	*n*-hexyl	P2-Et	rt	70	90/10
6	*n*-hexyl	KOH[1]	rt	50	75/25

[1]TBAB was added

Table 20 Olefination of aldehydes with BTFP sulfones. General trends with regard to yields and stereoselectivity

Sulfone	Aldehyde	Base	Temp. (°C)	Olefine Yield	*E*/*Z*-preference
	aliphatic	P2-Et	rt	good	moderate, *Z*
	aromatic neutral or electron-rich	P4-*t*-Bu	– 78	good	high, *E*
	aromatic electron-poor	P4-*t*-Bu	0	good	moderate, *Z*
	aromatic	KOH	rt	moderate	moderate to high, *E*
	aliphatic	KOH or P2-Et	rt	good	moderate to high, *E*
	aromatic	KOH	rt	good	moderate, *E*
	α,β-unsaturated	KOH	rt	low	high, *Z*



Scheme 80

hydes, using *t*-BuOK in THF as the solvent were studied. Selected results are presented in Table 21.

Olefins were generated in excellent yields and, in some cases, with a clear stereochemical preference. The reaction outcome showed little sensitivity to-

Table 21 Reactions of alkyl pentachlorophenyl sulfones with aldehydes

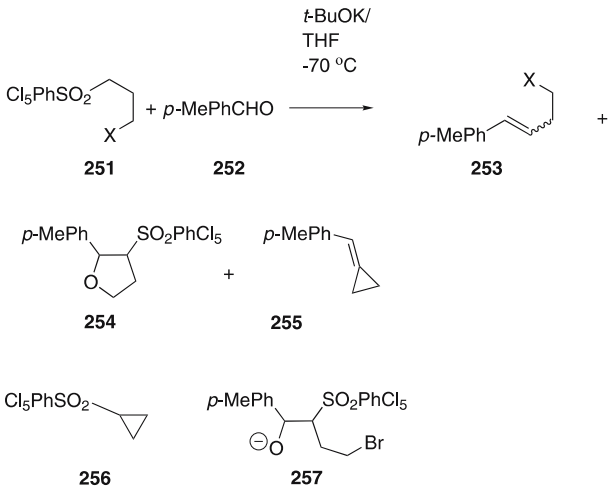
	R^1	R^2	Yield (%)	*E*/*Z*
1	H	4-MePh	85	–
2	*n*-Pr	4-MePh	90	74/26
3	$ClCH_2CH_2$	Ph	90	25/75
4	Bn	4-MePh	92	33/67
5	Ph	Ph	77	100/0
6	Ph	*s*-Bu	78	15/85
7	Cl	4-MePh	93	0/100

Table 22 Yields of products in the reaction according to Scheme 81

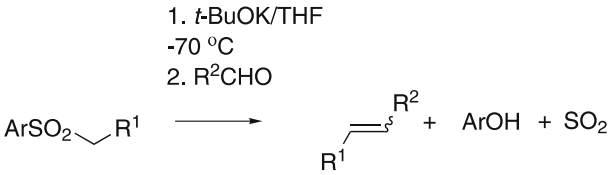
X	Yield (%) **253**	**254**	**255**
Cl	69	0	12
Br	4	50	5

wards changing of the base and the solvent (*t*-BuOK, *t*-BuOLi or EtONa in THF or DMF).

The behavior of γ-haloalkyl pentachlorophenyl sulfones has been studied in detail. Reaction of the anion generated from sulfone **251** (X = Cl (Table 22), Scheme 81) with 4-methylbenzaldehyde affords two products: direct olefina-



Scheme 81



Scheme 82

Table 23 Reaction of substituted phenylsulfones with aldehydes according to Scheme 82

Ar	R^1	R^2	Yield (%)	*E*/*Z*
4-(NO_2)Ph	Et	4-MePh	80	96/4
	Ph	Pr	89	25/75
2,5-Cl_2Ph	Et	4-MePh	81	89/11
2-(CF_3) – Ph	Et	4-MePh	77	92/8
4-(CN)Ph	Ph	Ph	69	100/1

tion product **253** (69% yield) and benzylidene cyclopropane derivative **255** (12% yield). The latter has been formed via cyclization of the haloalkene to afford **256**, prior to the olefination reaction. Under analogous conditions, **251**, X = Br, affords the furane derivative **254** as the major product (50% yield) along with olefins **253** (X = Br, 4%) and **255** (5%). Apparently, in the intermediate adduct **257**, the anion attack on the carbon bearing the bromine atom occurs faster than on the *ipso*-carbon atom.

Judka and Makosza (Judka and Makosza, 2006, personal communication) have also shown that phenyl sulfones with very simple modifications of the aromatic ring may conveniently be used in the direct olefination reaction (Scheme 82, Table 23).

All listed sulfones gave the products with high yields, in the majority of cases with the *E*-isomer predominating.

5.7 Mechanism of the Reaction

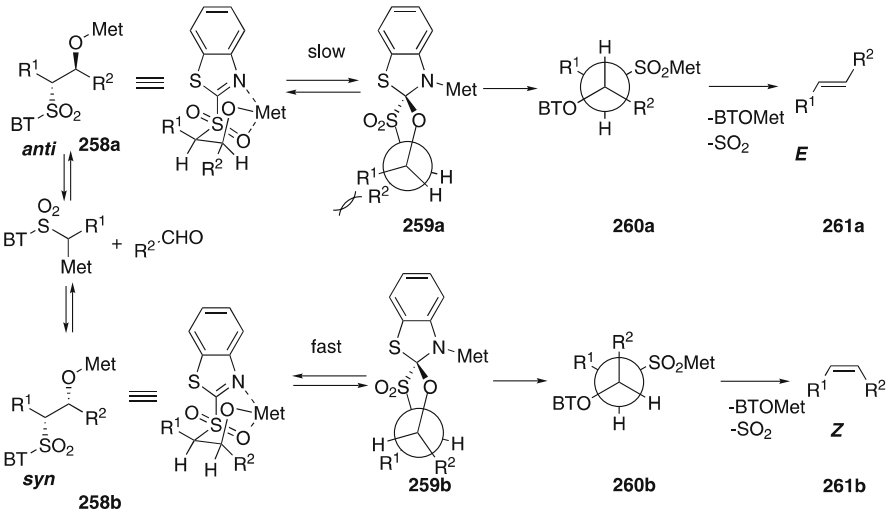
Mechanistic and stereochemical aspects of the reaction of benzothiazolyl sulfones with aldehydes were thoroughly analyzed in the Julia works [8, 9] and in the Blakemore review [98].

The reaction involves several steps. The absolute and relative rate of the separated steps depend upon the nature of the heterocyclic (aromatic) portion of the sulfone. Reactions of benzothiazolyl- and pyridylsulfones were compared by Julia. However, there are only a few direct mechanistic comparisons with other sulfones.

In the reaction of metalated BT-sulfone with an aldehyde (Scheme 83), diastereomeric adducts *syn* and *anti*, **258b** and **258a**, respectively, are formed. For the Li derivatives, chelating of the metal by the oxygen atom of the SO_2 group and the nitrogen atom of the heterocycle atom occurs. For large cations such as K^+, participation of an "open" transition state **259c** (Fig. 2) appears likely.

As demonstrated by Julia, the addition step in the reaction of unbranched sulfones with unbranched aldehydes is virtually irreversible. Since all further transformations of the adducts **258a** and **258b** occur stereoselectively, the mode of addition is the decisive step for the reaction outcome.

However, in reactions of sulfones equipped with anion-stabilizing groups, the addition step may be reversible. For example, hydroxysulfone **262** (Scheme 84, prepared from *trans* stilbene oxide and 2-mercapto-benzothiazole) when treated with LDA in the presence of 4-nitrobenzaldehyde, afforded styrene **263** and nitrostyrene **264**. Consequently, the stereochemical outcome of the reaction is decided in the following steps.



Scheme 83

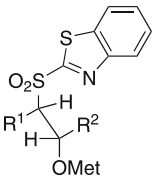
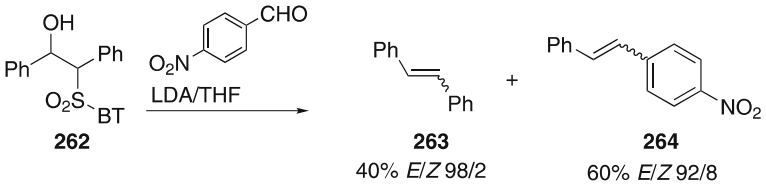


Fig. 2



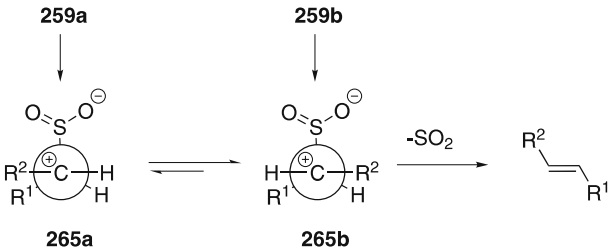
Scheme 84

Coming back to Scheme 83, hydroxy sulfones **258a** and **258b** isomerize to the spirocyclic structures **259a** and **259b**, respectively. Nonbonding repulsive interactions are higher in **259a** due to the close proximity of the substituents R^1 and R^2 (versus the interactions of R^1 and R^2 with the respective protons). It may be assumed that **259a** will be formed faster than its diastereomer **259b.** Accordingly, in the reaction of stabilized sulfones (reversibility of the addition step), the Smiles rearrangement step would determine the proportion of isomeric olefins.

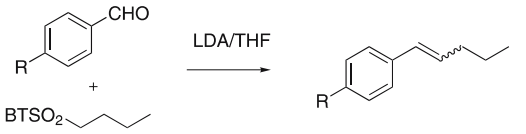
The subsequent step involves cleavage of the C – S bond in the spirointermediates and rotation around the central C – C bond to place the $-SO_2$ and benzothiazolyloxy group in an *anti*-periplanar orientation. The bulk of the data collected by Julia indicated that final elimination was entirely *anti*-periplanar when R^1 and R^2 were saturated aliphatic chains (or for **258a** where $R^1 = R^2 = Ph$). However, when carbocation stabilizing substituent R^2 is involved, the zwitterionic intermediate may collapse to the olefin directly, as shown in Scheme 85. Rotation around the carbon–carbon bond in a stabilized carbocation is also feasible.

The carbocationic mechanism may be involved in the reaction of aliphatic sulfones with benzaldehyde and its derivatives leading preferentially to *E*-styrenes (Scheme 86). The electronic nature of the aromatic ring substituents shows little effect on the product composition.

As regards solvent effects, it seems likely that in nonpolar solvents, rotation around the central bond in the Smiles rearrangement product will be retarded by intramolecular bounding of the lithium cation by SO_2 and the benzothiazolyl group.



Scheme 85



R	Yield (%)	*E*/*Z*
H	68	94/6
Cl	51	77/13
MeO	95	99/1

Scheme 86

The final step of the carbocationic mechanism discussed involves elimination of SO_2 and lithium benzothiazolylate. This step is irreversible and does not influence the isomer ratio.

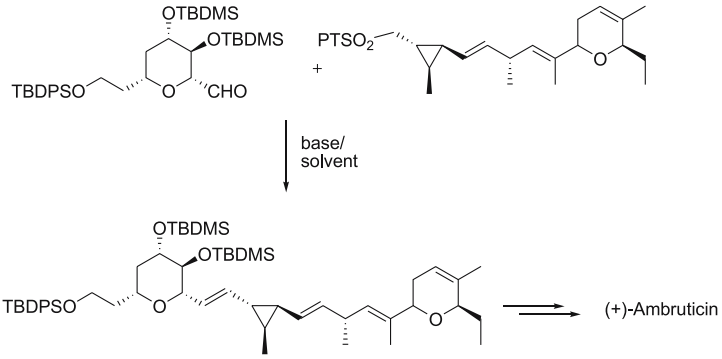
5.8 Application to Natural Product Synthesis. Selected Examples

The olefination based upon the reaction of benzothiazolyl- and phenyltetrazolyl sulfones with carbonyl compounds is widely used in the target-oriented synthesis. In order to illustrate the reaction scope, yields and stereoselectivities, in this section we present selected examples of these reactions. The examples include reactions of saturated sulfones with saturated aldehydes, saturated sulfones with α,β-unsaturated carbonyl compounds, β,γ-unsaturated sulfones with saturated aldehydes, and β,γ-unsaturated sulfones with α,β-unsaturated aldehydes. The emphasis is given to recent work. A complete account of earlier applications of the modified Julia reaction has been given in the Blakemore review [98].

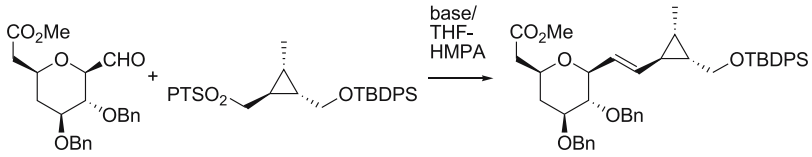
In the synthesis of novel antifungal agent Ambruticin by Jacobsen and coworkers [114] the major building blocks were connected using the Julia–Kocienski olefination reaction (Scheme 87). It was found that high selectivity for either double bond isomer could be obtained: NaHMDS in THF providing *Z* alkene (Table 24, entries 1 and 2) whereas LHMDS in polar solvents afforded the desired *E* isomer almost exclusively (entries 3 and 4).

In the Ambruticin synthesis reported somewhat later by E. Lee et al. [115, 116], cyclopropane—PT-sulfone building block **267** (Scheme 88) was condensed with aldehyde **266** in THF containing some HMPA. The effect of the countercation on the reaction course was examined. LHMDS provided 78% yield with a ratio of isomers *E*/*Z* 80/20. The change to NaHMDS resulted in higher selectivity *E*/*Z* 90/10; however, at the expense of the yield (63%). With KHMDS the selectivity turned out lower (63% yield, *E*/*Z* 50/50).

In the synthesis of Ambruticin developed by other authors, the modified Julia olefination was also used [117, 118]. Application of BT sulfones



Scheme 87



266 **267** **268**

Base	Yield (%)	*E*/*Z*
LHMDS	78	80/20
NaHMDS	63	90/10
KHMDS	63	50/50

Scheme 88

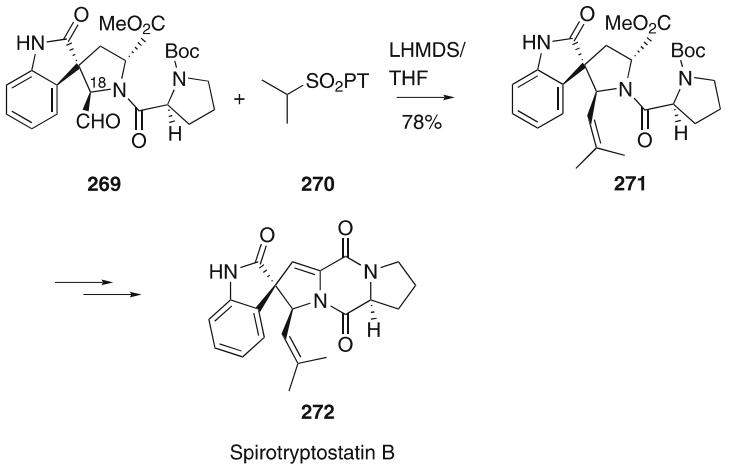
Table 24 Selected reaction conditions for PT sulfone and aldehyde reaction according to Scheme 87. In all cases the yields were greater than 90%

	Base, solvent and temperature	*E*/*Z* ratio
1	NaHMDS, THF – 78 °C	1/8
2	NaHMDS, THF – 35 °C	1/6
3	LHMDS, DMF-HMPA, 4 : 1, – 35 °C	> 30/1
4	LHMDS, DMF-DMPU, 1 : 1, – 35 °C	> 30/1

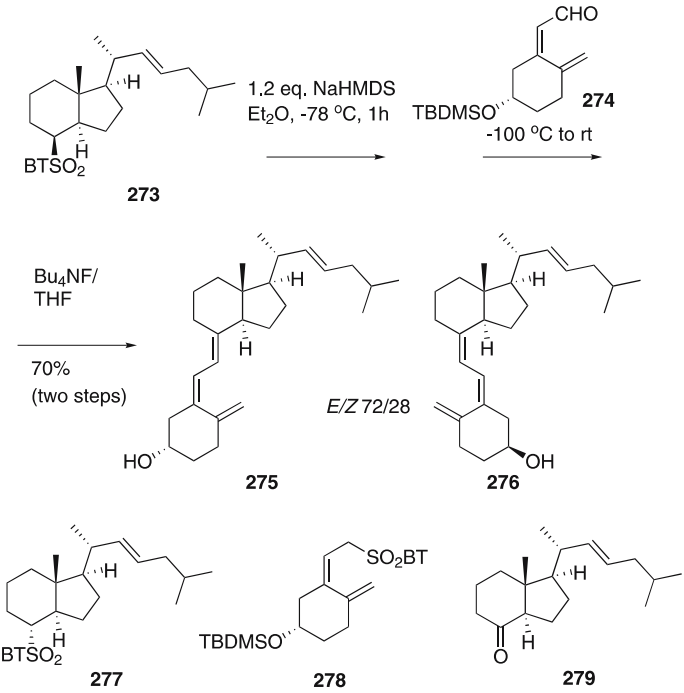
for the construction of vinylcyclopropanes was pioneered by Charette and Lebel [119] in an important earlier work.

Marti and Carreira [120] reported the total synthesis of natural cytostatic agent Spirotryptostatin B **272** (Scheme 89). The isobutene side chain was constructed by the reaction of aldehyde **269** with isopropyl PT sulfone **270.** The product **271** was obtained in 78% yield. It is noteworthy, that an attempted use

of the Wittig or "classical Julia" reaction for transformation of **269** into **271** failed. In both cases epimerization (at C-18) and considerable decomposition of the starting aldehyde occurred.



Scheme 89



Scheme 90

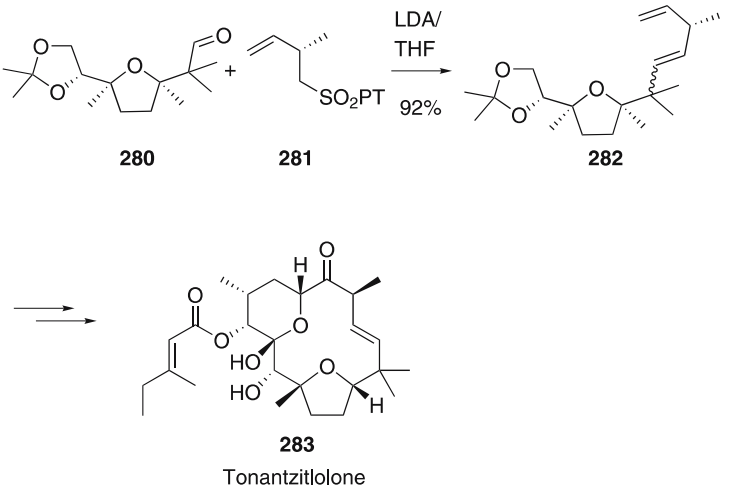
The relevant use of BT and PT sulfones in arranging prenyl [121] and other tri-substituted olefin patterns has been recently reported [122, 123].

In a study on vitamin D_2 synthesis [124], a sterically very hindered sulfone **273** (Scheme 90) with the axially oriented sulfonyl group was transformed into an anion (NaHMDS) and subjected to reaction with diene-aldehyde **274** used in excess. After deprotection, vitamin D_2 **275** and its unstable C7-C8 *Z*-isomer **276**, were obtained in 70% yield, ratio of 72/28, respectively. Some BT-sulfone **277** generated by epimerization of **273** was also isolated. An attempt to carry out the reaction with the reverse allotment of the functional groups (sulfone **278** with ketone **279**) failed. With regard to the isomer ratio **275** and **276**, it is of interest that the "classical" Julia reaction of phenylsulfone corresponding to **277** and aldehyde **274** occurs with somewhat lower selectivity towards the *E*-isomer [125].

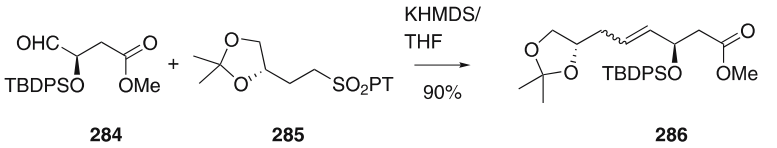
Sterically shielded aldehyde **280** (Scheme 91) in reaction with a branched sulfone **281** provided the coupling product **282** in 92% yield as a mixture of *E*/*Z* isomers 9/1. This product was further used for synthesis of Tonantzitlolone [126].

Paquette and coworkers [127], in a synthesis of the complex polyol antibiotic amfidinolu-3, made masterly use of the Julia–Kocienski olefination reaction. Two examples taken from that work are presented below. Reaction of sulfone **285** with aldehyde **284** (Scheme 92) carried out with KHMDS in THF (at – 78 °C to rt) gave the building block **286** with 90% yield but with relatively poor selectivity, *E*/*Z* 3/1. Free-radical isomerization of the mixture (benzene, AIBN, reflux) increased the isomer ratio, *E*/*Z* 6/1.

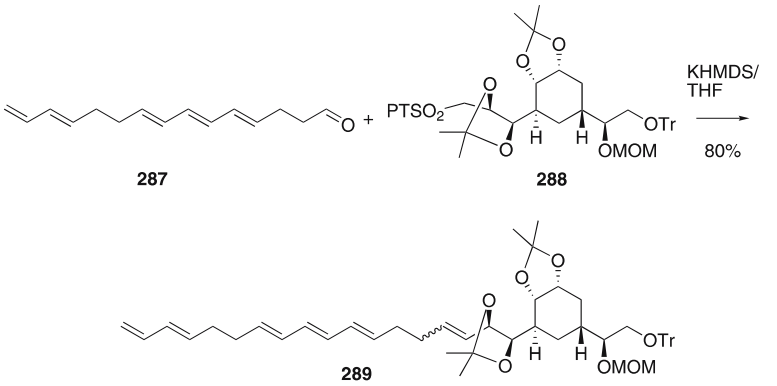
Reaction of aldehyde **287** with sulfone **288** (Scheme 93) [128] using the same base provided product **289** in 80% yield and with the isomer ratio, *E*/*Z* 20/1.



Scheme 91

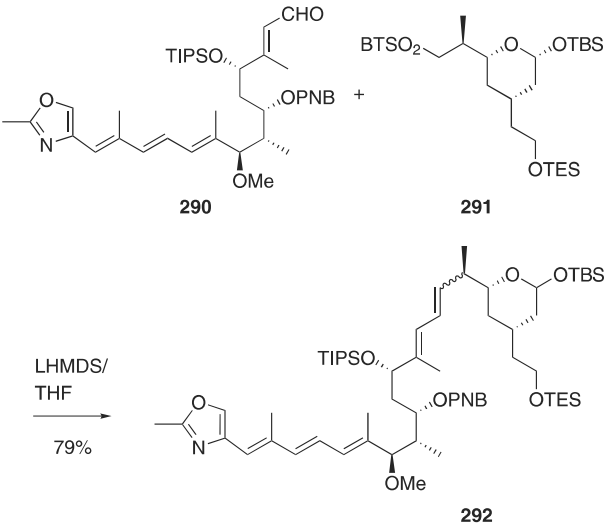


Scheme 92



Scheme 93

The segment linkage step in a synthesis of Rhizoxin D [129] consists of the coupling of β-branched saturated sulfone **291** (Scheme 94) with α,β-unsaturated aldehyde **290.** The reaction was carried out with LHMDS in THF.



Scheme 94

Product **292** was obtained in 79% yield as a mixture of isomers with an excess of the *E* isomer.

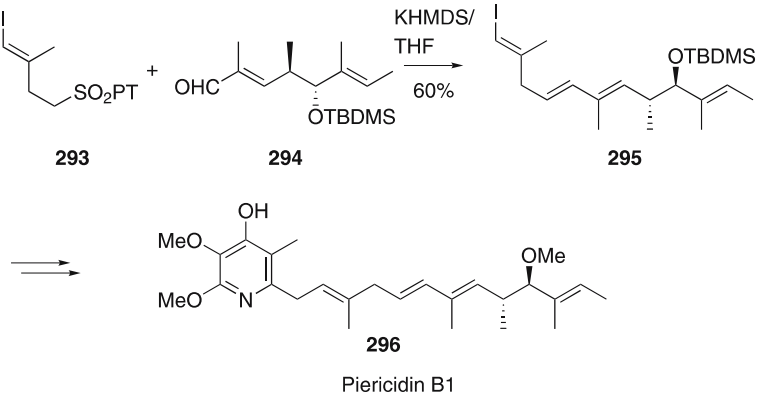
In another approach to Rhizoxin D, olefination with the use of a BT sulfone was also used [130].

Most recently Schnermann and Boger [131] reported that reaction of PT sulfone **293** with unsaturated aldehyde **294**, induced by KHMDS in THF (Scheme 95), afforded exclusively the *E*-isomer of conjugate diene **295** in 60% yield. This product was then transformed into Piericidin B1 **296**.

Albrecht and Williams [132, 133] developed an interesting synthetic approach to macrocyclic proteasome inhibitors TMC-95A/B, involving reaction of BT sulfone **297** with activated ketone **298** (Scheme 96). The reaction was carried out using LHMDS, in DMF containing DMPU as the co-solvent, at 0 °C. The olefination product **299** was obtained in 79% yield, *E*/*Z* 5/1.

Kocienski and coworkers [134] at a certain stage of the Rapamacin synthesis used dienyl aldehyde **300** and saturated sulfone **301**, as indicated in Scheme 97. Triene **302** was obtained, 68% yield, *E*/*Z* 95/5.

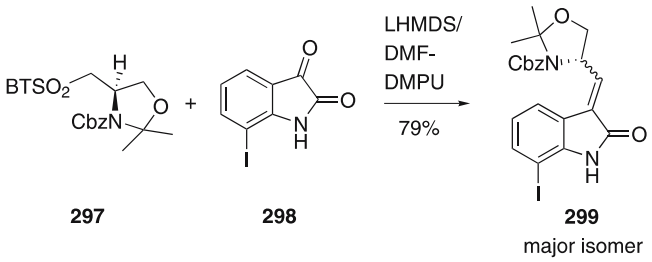
An example [135] of the reaction of β,γ-unsaturated sulfones and saturated aldehydes is shown in Scheme 98. The anion was generated using



293 **294** **295** **296**

Piericidin B1

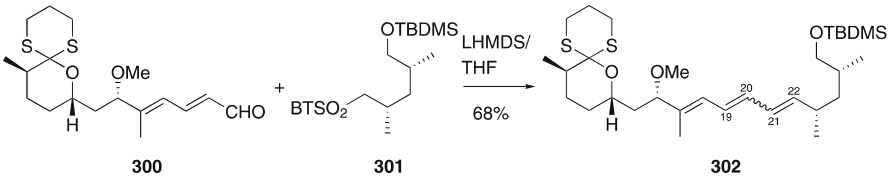
Scheme 95



297 **298** **299**

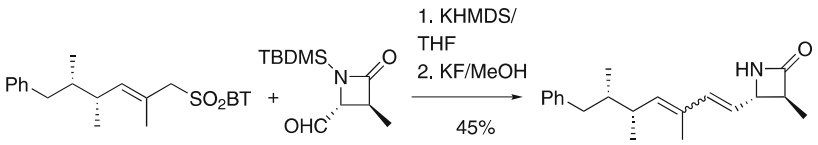
major isomer

Scheme 96



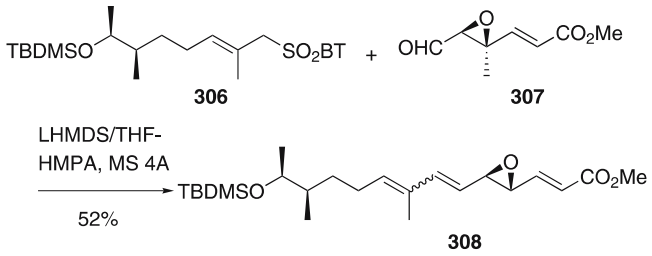
300 301 302

Scheme 97



303 304 305

Scheme 98



306 307 308

Scheme 99

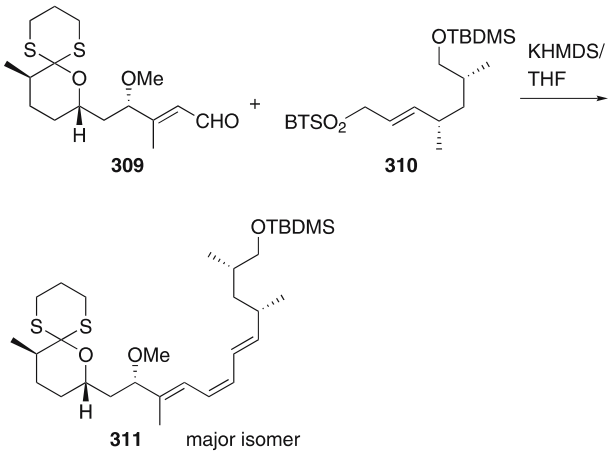
KHMDS in THF. The product **305** was isolated (45% yield, *E*/*Z* 75/25) after deprotection of the β-lactam amide group.

Kitahara et al. [136] reported olefination using the α,β-epoxy aldehyde **307** and the unsaturated sulfone **306** (Scheme 99). The anion was generated with LHMDS in THF in the presence of HMPA and molecular sieves 4Å. Epoxydiene **308** was obtained as a mixture of isomers, 52% yield, *E*/*Z* 70/30. This product was further used in the synthesis of Cineromycin B.

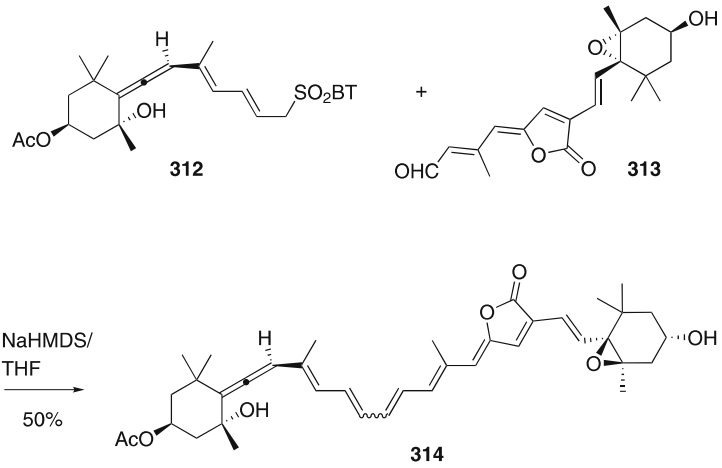
Reaction [134] of α,β-unsaturated aldehyde **309** (Scheme 100) and β,γ-unsaturated sulfone **310** with the use of KHMDS as the base provided triene **311**; the *Z*-isomer predominated, *E*/*Z* 18/82. When NaHMDS was used, the olefination product was obtained in 79% yield (*E*/*Z* 56/44).

Katsumura and collaborators [137–139] reported the total synthesis of a polyfunctional carotenoid, Peridinin **314** (Scheme 101). Diene-allenyl sulfone **312** was combined with unsaturated aldehyde **313** using NaHMDS in THF. The product was obtained in 50% yield as a mixture of isomers *E*/*Z* 25/75.

Other syntheses of carotenoids via direct olefination have been recently reported [140].



Scheme 100



Scheme 101

5.9 Specific Applications

5.9.1 Methylenation Reaction

Julia [8, 9] showed that methyl BT sulfone reacts with benzaldehyde in the presence of LDA under Barbier conditions to give styrene in 20% yield. Similarly, the methyl sulfone in the reaction 4-(*t*-butyl)-cyclohexanone provided the respective methylidene derivative.

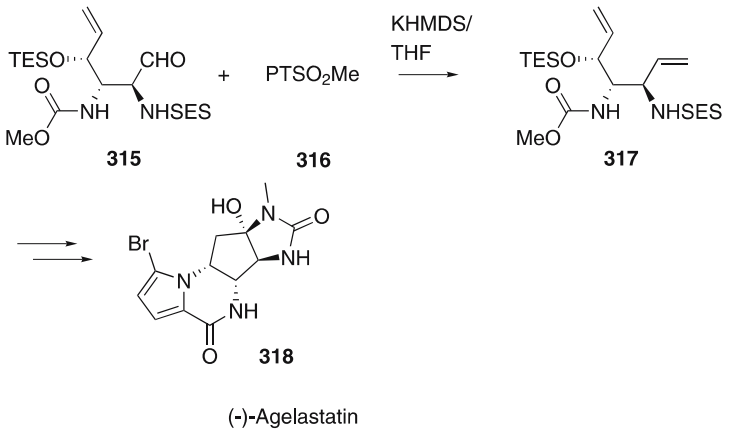
Methylenation of complex aminoaldehyde derivative **315** (Scheme 102) has been achieved [141] using methyl PT sulfone and KHMDS in THF. Noteworthy, neither Wittig, Tebbe nor Peterson olefination could be employed in this case. The diene **317** was further used in the synthesis of (–)-Agelastatin **318.**

Nájera's methyl BTFP sulfone **319** has been applied in the synthesis of terminal olefins [106] (Scheme 103, cf. Scheme 78 and the relevant text). Reaction of **319** (1 molar equivalent) with aldehydes or ketones (1.1 molar equivalent) could be conveniently carried out using P4-*t*-Bu (1.2 molar equivalent) or KOH-TBAB (9 molar equivalent) under Barbier conditions. Some examples are shown in Table 25.

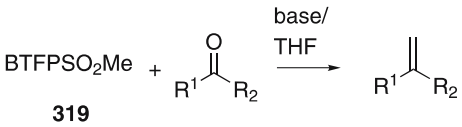
Aromatic aldehydes gave the respective methylene derivatives in good yields using either KOH-TBAB or P4-*t*-Bu. The method also proved effective in the reaction of relatively unhindered ketones. Apparently, aliphatic aldehydes exemplified by dihydrocinnamaldehyde were less favorable substrates for this reaction.

tert-Butyltetrazolyl (TBT) methyl sulfone has been used [109] for methylenation of aldehydes and some ketones. The reactions were conducted using either NaHMDS in THF under Barbier conditions or cesium carbonate in THF-DMF at reflux temperature (Scheme 104). Selected results are shown in Table 26.

In several cases the products were obtained in excellent yields, both starting from aldehydes or ketones. TBS- (entry 3), 4-methoxybenzyl (entry 4) and

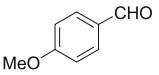
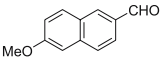
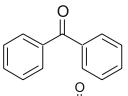
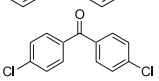
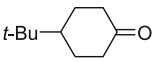
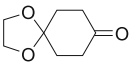
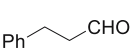


Scheme 102



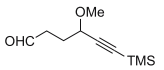
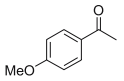
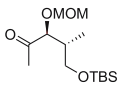
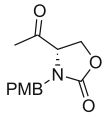
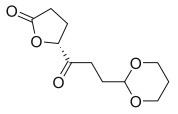
Scheme 103

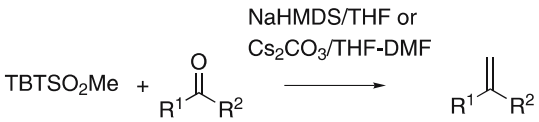
Table 25 The reaction of methyl BTFP sulfone with aldehydes or ketones under Barbier conditions, according to Scheme 103

R^1COR^2	Base	Temp. (°C)	Yield (%)
	KOH [a]	rt	60
	KOH [a] P4-*t*-Bu	rt – 78–rt	80 82
	P4-*t*-Bu	0–rt	36(57 [b])
	P4-*t*-Bu	0–rt	50
	P4-*t*-Bu	0–rt	74
	P4-*t*-Bu	0–rt	41
	P4-*t*-Bu	– 78–rt	30

[a] Catalytic amount of TBAB was added.
[b] Two equivalents of the sulfone were used.

Table 26 Methylenation reaction according to Scheme 104

	R^1COR^2	Base	Yield (%)
1		Cs_2CO_3	96
2		NaHMDS Cs_2CO_3	77 63
3		NaHMDS	77
4		NaHMDS	85
5		NaHMDS Cs_2CO_3	59 93



Scheme 104

lactone groups (entry 5) remained unaffected in the process. With NaHMDS no epimerization on the chiral center in the α-position to the carbonyl group was noted (entries 3–5).

5.9.2 Synthesis of α,β-unsaturated Esters

Blakemore and coworkers [108] developed a convenient method for synthesis of α,β-unsaturated esters in the reaction of ethyl BT-sulfonylacetate **320** (Scheme 105) with aldehydes. For generation of the doubly stabilized anions DBU in DCM was used.

As shown in Table 27, from aromatic and branched aliphatic aldehydes the respective olefins were obtained in excellent yields and with high preference for *E*-isomers. Unbranched aldehydes tend to give products with a low yield and the preference for *Z*-isomers. It is noteworthy that neither phenyltetrazolyl (PT) nor *tert*-butyltetrazolyl (TBT) sulfones could be applied in this reaction.

Scheme 105

Table 27 Selected examples of synthesis of α,β-unsaturated esters by the Blakemore method

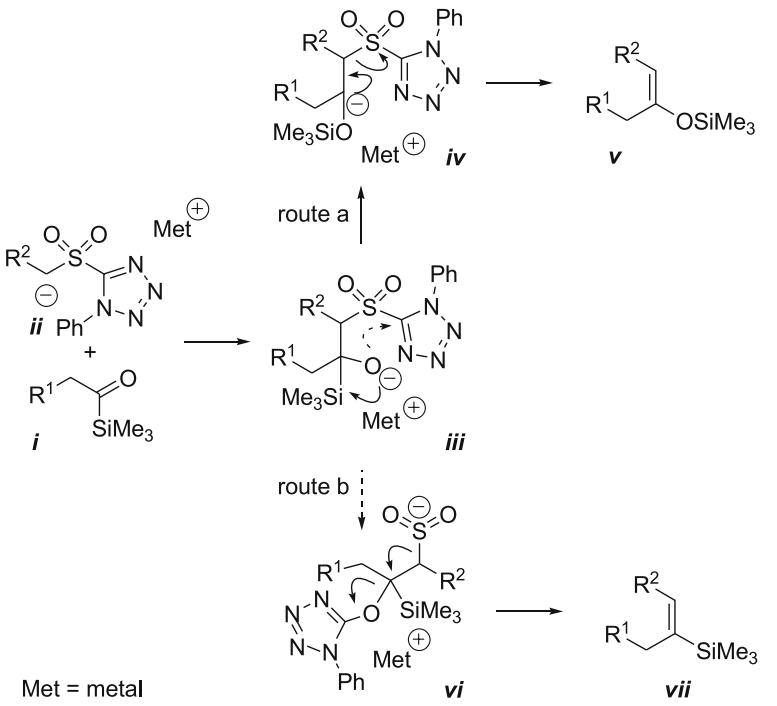
R	Yield (%)	*E*/*Z*
4-(NO_2)Ph	89	98/2
4-(MeO)Ph	93	92/8
n-C_5H_{11}	41	19/81
c-hexyl	80	80/20
Et_2CH	88	98/2
Bn	80	98/2

5.9.3
Synthesis of Vinylsilanes

Synthesis of vinylsilanes by the reaction of alkyl PT or BT sulfones with acylsilanes has been studied [112]. Addition of sulfonyl anion ***ii*** (Scheme 106) to acylsilane ***i*** provides adduct ***iii*** that may rearrange by two routes: (1) migration of the trimethylsilyl group from carbon to oxygen (the Brook rearrangement, route a) and β-elimination of the sulfonyl to give silyl enol ether (***v***) or (2) the Smiles rearrangement (route b) followed by extrusion of SO_2 and elimination of phenyltetrazolol to provide vinylsilanes. The reaction pathway depends upon several factors: the nature of alkyl groups R^1 and R^2, the base, the solvent and the reaction conditions.

Reaction of unbranched alkyl PT sulfones with unbranched acylsilanes using LHMDS as the base in THF or toluene afforded vinylsilanes in high yields. In THF the *E*-isomer was formed in excess; in toluene stereochemical preferences are reversed. Representative results are shown in Table 28.

On branching of alkyl chains in either of the reagents, mixtures of vinylsilanes and silyl enol ethers or silyl enol ethers alone were formed.



Scheme 106

Table 28 Synthesis of vinylsilanes from acylsilanes and PT-sulfones using LHMDS under Barbier conditions at – 78 °C

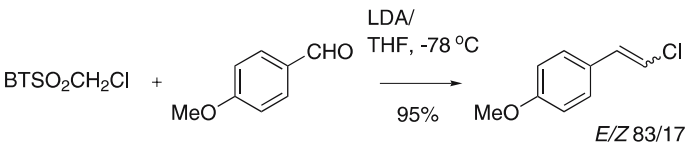
R^1	R^2	Solvent	Yield (%)	*E*/*Z*
Bn	*n*-$C_{11}H_{23}$	THF	79	65/35
		PhMe	69	39/61
$Ph(CH_2)_2$	$Ph(CH_2)_2$	THF	78	62/38
		PhMe	76	32/68
$Ph(CH_2)_2$	*n*-$C_{11}H_{23}$	THF	84	68/32
		PhMe	61	42/58

5.9.4 Synthesis of Vinyl Halides

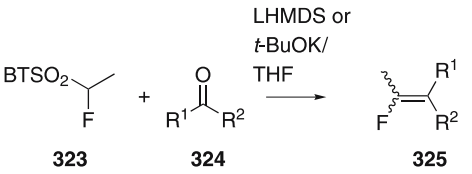
It has been shown by Julia et al. [9] that chloromethyl BT sulfone, in reaction with anisaldehyde, affords the respective vinyl chloride (Scheme 107) in almost quantitative yield and with the *E*-isomer predominating.

Pazenok et al. [142] have reported that the reaction of α-fluoroethyl BT-sulfone **323** (Scheme 108) with aldehydes or ketones **324** affords vinyl fluorides **325**. Sulfonyl anions were generated either with NaHMDS or with *t*-BuOK in THF. In general, high chemical yields could be attained but the selectivity was poor. Representative applications of this reaction are shown in Table 29.

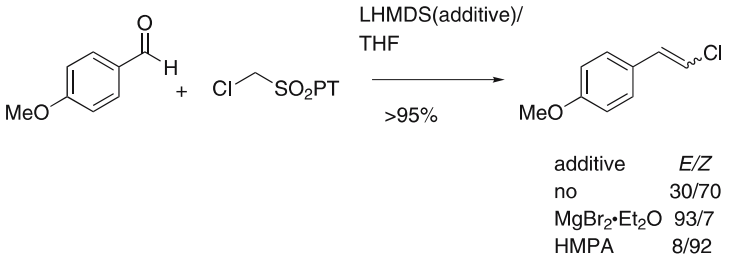
Berthelette et al. [143] reported a detailed study on the stereochemistry of vinyl halide (chlorides and bromides) synthesis by the Julia–Kocienski method. In the model experiments using chloromethyl PT sulfone and anisaldehyde (Scheme 109), the isomer ratio depends on the countercation,



Scheme 107

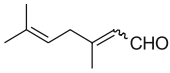
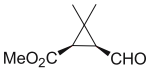
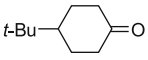
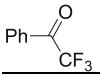


Scheme 108



Scheme 109

Table 29 Selected examples of vinyl fluorides synthesis according to Scheme 108

R^1COR^2	Base	Yield (%)	*E*/*Z*
4-(NO_2)PhCHO	*t*-BuOK	88	61/39
	t-BuOK	55	62/38
	LHMDS	74	52/48
	*t*-BuOK	80	45/55
	LHMDS	49	–
	LHMDS	69	–
	LHMDS	45	not indicated

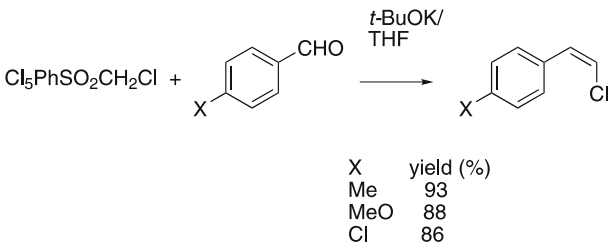
solvent and other factors. Notably, the reaction outcome may be controlled by some additives: when LHMDS was used as the base in THF at rt, a mixture of isomers with an *E*/*Z* ratio of 30/70 was obtained (in all experiment yields over 95% were attained) but adding to the reagents 2 mole equivalents of HMPA prior to the addition of the base resulted in an *E*/*Z* ratio of 8/92 whereas addition of $MgBr_2 \cdot Et_2O$ resulted in an *E*/*Z* ratio of 93/7.

In further work it turned out that the method for preparation of *Z*-halides has a general value whereas preparation of *E*-isomers suffered from some limitations. Some examples of synthesis of *Z*-vinylhalides are shown in Table 30.

Reaction of chloromethyl pentachlorophenyl sulfone with aromatic aldehydes provided *Z* vinyl chlorides exclusively in high yields (Judka and Makosza, 2006, personal communication).

Table 30 Reaction of halomethyl PT sulfones ($PTSO_2CH_2X$) with aldehydes induced by LHMDS (2 mol equivalents) in the presence of HMPA (2 mol equivalents)

R^1	X	Yield (%)	*E*/*Z*
2-(MeO)Ph	Cl	95	10/90
	Br	70	5/95
naphthyl	Cl	86	9/91
	Br	79	5/95
3-MePh	Cl	99	10/90



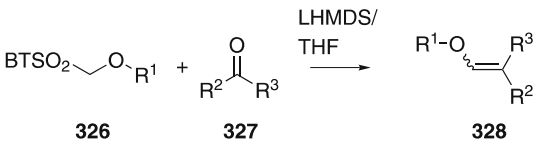
Scheme 110

5.9.5 Synthesis of Vinyl Ethers

Berthelette and coworkers [144] developed the synthesis of vinyl ethers **328** (Scheme 111) from α-alkoxymethyl BT sulfones **326** and various aldehydes or ketones **327**. The olefination reaction was carried out using LHMDS in THF at 0 °C. In general, very good chemical yields and poor stereoselectivities were recorded. Selected examples are presented in Table 31.

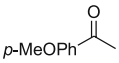
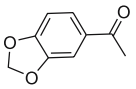
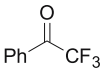
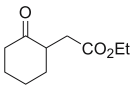
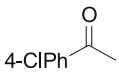
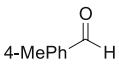
5.9.6 Synthesis of Tin-substituted Dienes

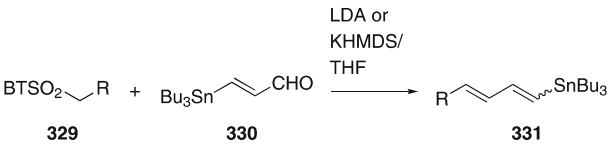
Brückner and coworkers [145] examined the reaction of BT-sulfones with α,β-unsaturated aldehydes, bearing a tributyltin substituent at the β-position (Scheme 112). The reactions were carried out either with premetalation or under Barbier conditions using LDA or KHMDS in THF. With both methods



Scheme 111

Table 31 Synthesis of vinyl ethers according to Scheme 111

R^1	R^2COR^3	Yield (%)	*E*/*Z*
Bn		87	50/50
Bn		86	50/50
Bn		82	64/36
Bn		71	67/33
$MeOCH_2CH_2$		86	57/43
$MeOCH_2CH_2$		87	62/38
4-$MePhCH_2$		83	55/45



Scheme 112

appreciable yields of tributylstannyl dienes were obtained. Selected results are shown in Table 32.

Saturated unbranched sulfones in reaction with **330** gave the olefination products in high yield but with poor selectivity as illustrated in Table 32, entry 1. β,γ-Unsaturated sulfones provided the products with moderate yields (entries 2 and 4). However, a remarkable selectivity in favor of the *Z*-isomer was observed. In the reaction of the relatively bulky sulfone (entry 3), a considerable drop in the yield and selectivity occurred.

The reaction of γ-(tributyltin)-β,γ-unsaturated BT sulfone **332** with aldehydes has also been examined (Scheme 113). Selected results are presented in Table 33.

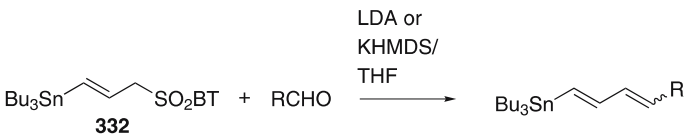
The steric course of the reaction depended markedly upon the countercation. KHMDS provided high selectivity for saturated (entry 1) and allyl

Table 32 Reaction of BT-sulfones with β-tributylstannyl-α,β-unsaturated aldehydes

	R	Base	Yield (%)	*E*/*Z*
1	Et	LDA	78	53/47
		KHMDS	78	61/39
2	$CH_2 = CH$	LDA	59	9/91
		KHMDS	60	10/91
3	$(Me)_2C = CH$	LDA	41	29/71
		KHMDS	43	61/39
4	$Bu_3SnCH = CHCH_2$	KHMDS	66	4/96

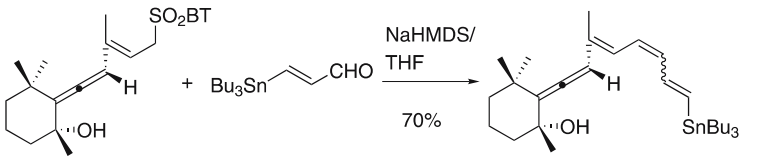
Table 33 Reaction of β,γ-unsaturated sulfone **332** with aldehydes, according to Scheme 113

	R	Base	Yield (%)	*E*/*Z*
1	Et	LDA	60	40/60
		KHMDS	50	91/9
2	$MeCH = CH$	LDA	58	78/22
		KHMDS	55	93/7
3	$PhCH = CH$	LDA	62	60/40
		KHMDS	50	6/94



332

Scheme 113



333 **330** **334** *E*/*Z* 25/75

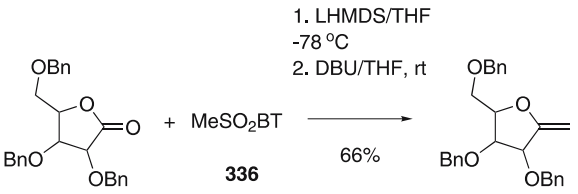
Scheme 114

(entry 2) sulfone in favor of the *E*-isomers, whereas for the styrenyl sulfone (entry 3)—the *Z*-isomer predominated. LDA-induced reaction occurred with some preference for *E*-products.

De Lera et al. reported [140, 146] the synthesis of triene **334** (Scheme 114) in the reaction of complex BT sulfone with β-(tributyltin)-acrolein. The work concluded in the total synthesis of 6′-*epi*-Peridinin [147].

5.9.7
Methylenation of Lactones

Methylenation of tri-*O*-benzyl-D-arabinolactone **335** (Scheme 115) with BT methyl sulfone gave [148] the expected adduct (not shown in the scheme) under the standard conditions in 78% yield. However, the rearrangement step was retarded. Methylene exoglycal **337** was eventually obtained in 66% yield when the reagents were treated first with LHMDS in THF at – 78 °C and then with DBU at rt. The method was applied to various sugar lactones with pyranose or furanose rings to give the respective methylene derivatives in 46–74% yields.



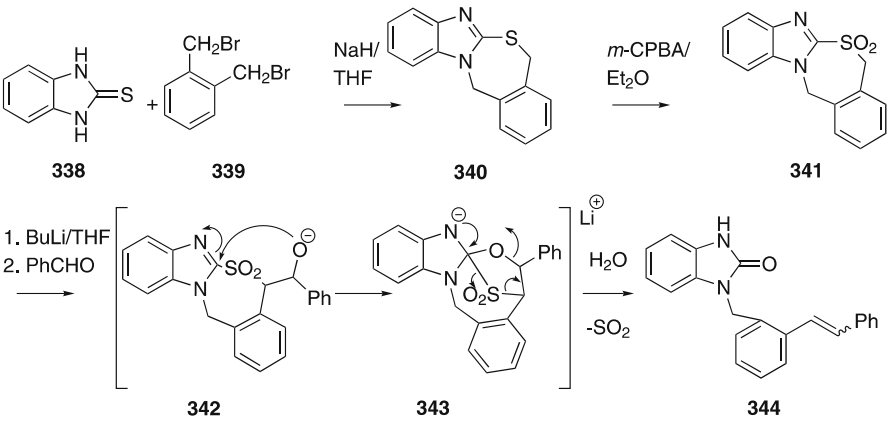
335 **337**

Scheme 115

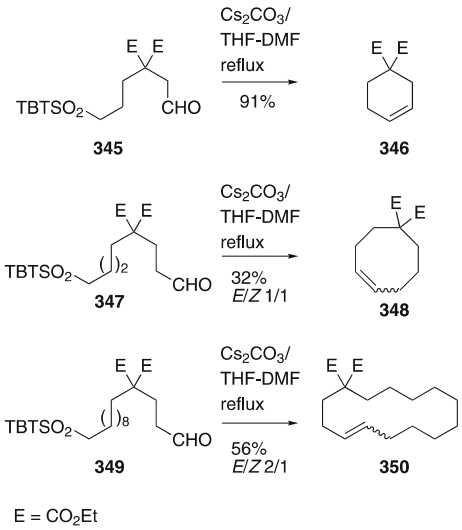
5.9.8
Intramolecular Olefination Reactions

Yoon and Kim [149] reported synthesis of benzimidazole derivatives **344** (Scheme 116) involving the Smiles rearrangement. Alkylation of benzimidazole **338** with α,α'-dibromo-*o*-xylene **339** and NaH in THF gave the tetracyclic sulfide **340** that was subsequently oxidized with *m*-CPBA to sulfone **341**. Treatment of **341** with *n*-butyllithium and then with benzaldehyde afforded adduct **342** that underwent isomerization into the spiro-derivative **343** and the fragmentation with expulsion of SO_2, as indicated in the scheme. Several other aromatic aldehydes were also used to give the respective olefins in excellent yields. It should be noted that the rearrangement occurs in a relatively strained polycyclic system.

Aissa reported [109] that a combination of *tert*-butyltetrazolyl as the migrating ring and cesium carbonate as the base in THF–DMF, at reflux temperature, enables cyclization reactions. As indicated in Scheme 117, a six-membered ring was formed in an excellent yield. Cyclization of **347** pro-



Scheme 116

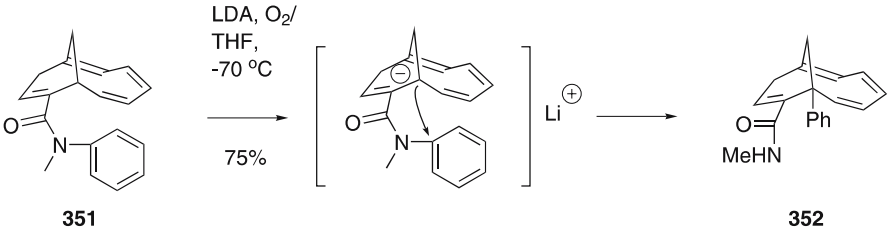


Scheme 117

vided a mixture of *E*- and *Z*-cyclooctene derivatives. Macrocyclization of **349** occurred with a relatively good yield and with a clear preference for the *E*-isomer.

6
The Smiles–Truce Rearrangement

On attempted aerial oxidation of 1,5-methano [10]annulene carboxylic acid anilide **351** (Scheme 118) Sho Ito and co-workers [150] obtained the prod-

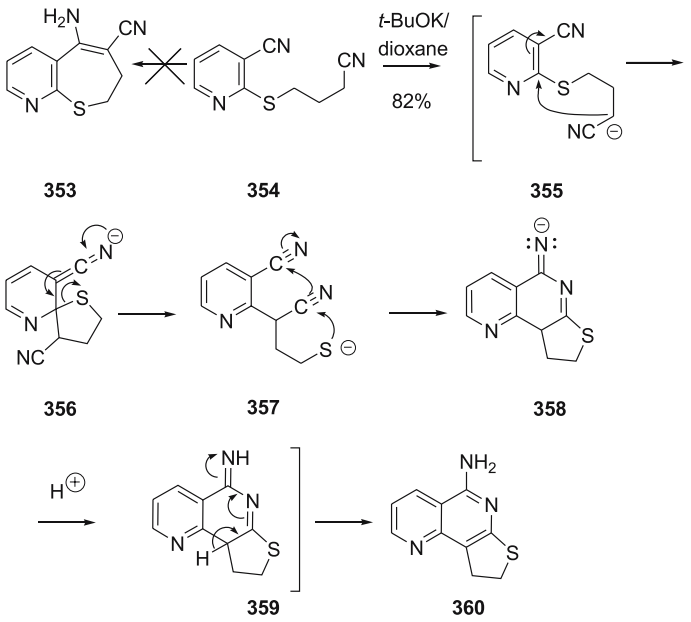


Scheme 118

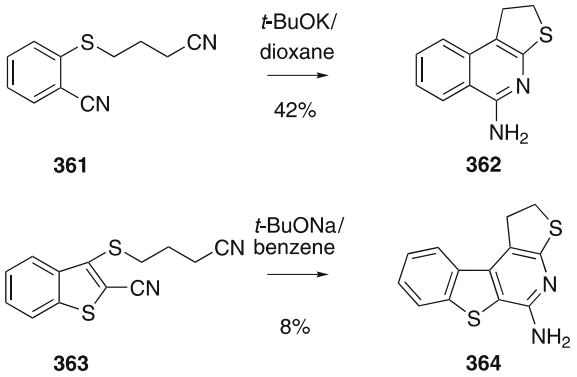
uct of intramolecular C-arylation **352.** The rearrangement involved a bulky tertiary carbanion and migration of a nonactivated phenyl ring. The authors suggest that coordination of Li cation by the nitrogen atom facilitated the rearrangement. However, a free-radical mechanism cannot be ruled out.

Hirota and coworkers [151–153] discovered an interesting rearrangement on the attempted Dieckmann cyclization of **354** (Scheme 119). Instead of **353**, a tricyclic product **360** lacking the cyano group was obtained in 82% yield. The rearrangement was explained by the pyridyl ring migration and then "domino" cyclization, as indicated in the scheme.

The related benzene **361** and benzothiophene **363** derivatives (Scheme 120) also rearranged [154] but the yields of the respective products were markedly lower.



Scheme 119

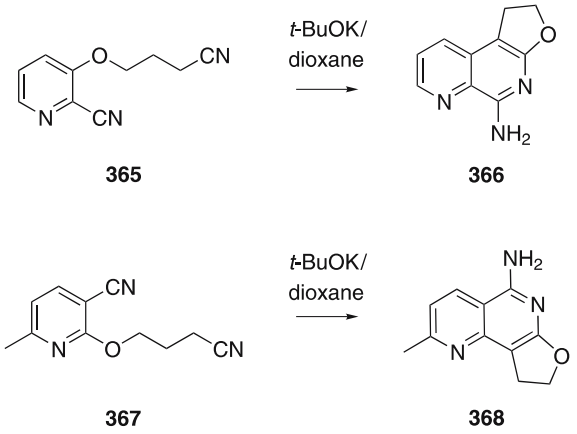


Scheme 120

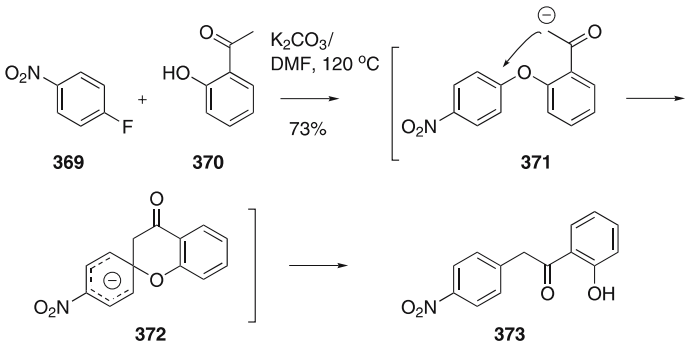
Likewise, treatment of 2-cyano-3-pyridyl ether **365** or 3-cyano-2-pyridyl ether **367** (Scheme 121) with *t*-BuOK in dioxane resulted in rearrangement and cyclization to afford the respective tricyclic products [155].

When three isomers of hydroxyacetophenone were treated separately with 4-fluoronitrobenzene [156] **369** (Scheme 122) and potassium carbonate (DMF, 120 °C) the *para*- and *meta*-isomers gave the respective diaryl ethers (*O*-arylation products). The *ortho*-isomer **370** behaves in a different way: the *C*-arylation product **373** was formed exclusively (isolated in 73% yield). *O*-Arylation of **370** occurred first to give diaryl ether (protonated **371**) and this is followed by the rearrangement through the intermediate **372.** At lower temperature (60 °C) **371** (protonated) could be isolated in 21% yield along with unchanged **370.**

Reaction of **370** with 2-fluoronitrobenzene provided, likewise, the *C*-arylated (rearranged) product but the yield was only 33%.



Scheme 121



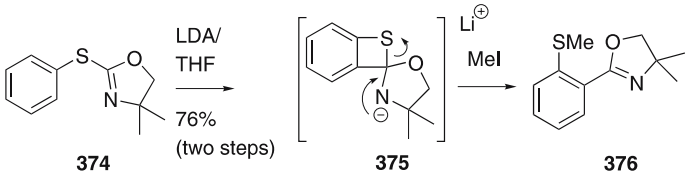
Scheme 122

Chenard [157] reported that lithiation of phenyl oxazolinyl thioether **374** (Scheme 123) with LDA in THF at – 78 °C and then warming the derivative to room temperature afforded an oxazoline ring migration product. Trapping of the product with methyl iodide gave the methylthio derivative **376** in 76% yield. The rearrangement occurred via four-membered spirocyclic intermediate **375.** Interestingly, attempted metalation of **374** with either BuLi, *t*-BuLi or PhLi failed to provide the rearranged product; decomposition of the starting material was observed instead.

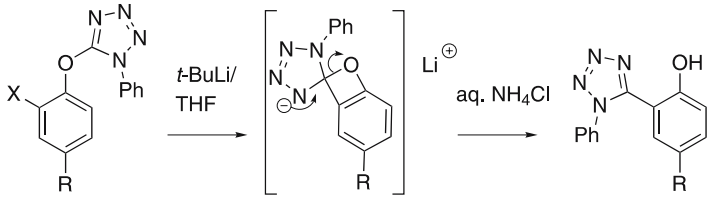
Metalation of phenyl tetrazolyl ethers **377** (Scheme 124), either direct or by bromine–metal exchange, triggered the heterocycle migration from oxygen to carbon [158]. Products were obtained in excellent yields for all examined derivatives (84–93%). Again, a spirocyclic four-membered ring intermediate was involved. Similarly, naphthyl derivative **380** smoothly rearranged to **381.**

On treatment of the 2-hydroxypyridine derivative **382** (X = Y = Z = H, Scheme 125) with potassium hydride in THF, Erickson and coworkers [159] obtained the pyridine ring migration product **386** (X = Y = Z = H). The rearrangement has been confirmed for several derivatives of **382**, as indicated in the scheme. However, the yields were not disclosed.

Metalation of amino-functionalized tertiary phosphine **388** with BuLi in THF afforded quantitatively [160] the rearranged product **391** (Scheme 126). Both intermediate lithium derivatives **389** and **390** form stoichiometric complexes with THF. No product of methylene group insertion into the C – P bond in **389** was detected.

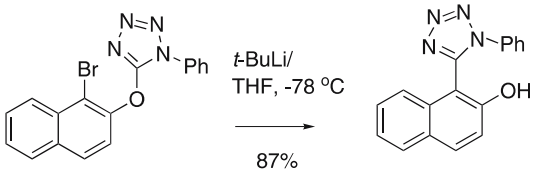


Scheme 123



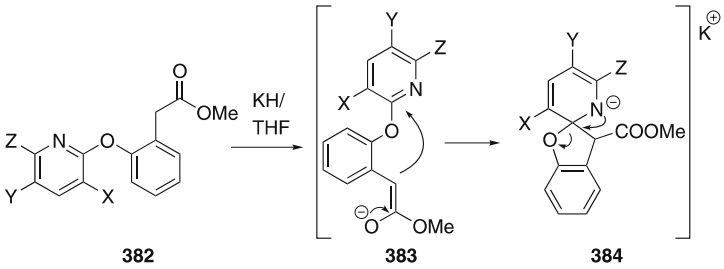
377 **378** **379**

X = Br, H
R = Cl, OMe, H

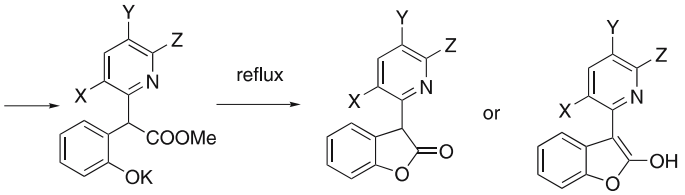


380 **381**

Scheme 124



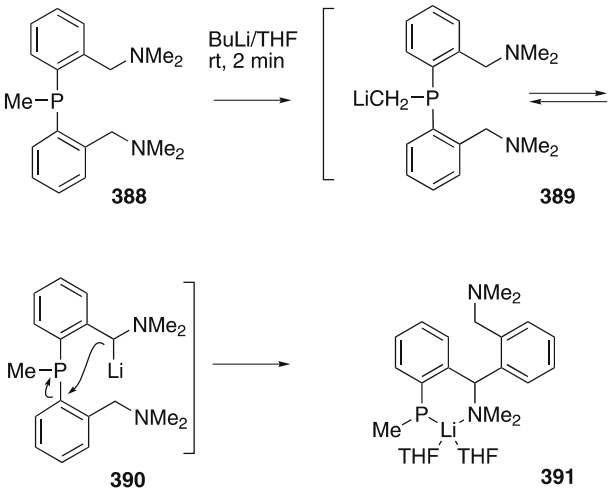
382 **383** **384**



385 **386** **387**

a) X = H, Y = H, Z = H
b) X = H, Y = H, Z = CF_3
c) X = CF_3, Y = Cl, Z = H
d) X = Cl, Y = H, Z = H

Scheme 125

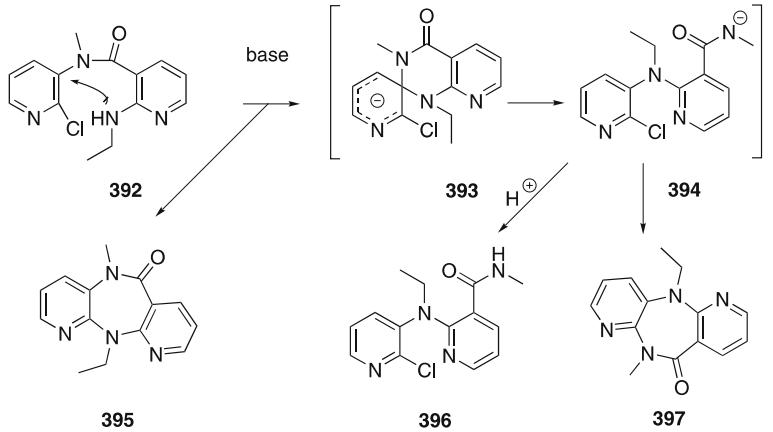


Scheme 126

7
Rearrangements Involving Alike Atoms (X – X′)

7.1
N – N′ Rearrangements

In the synthesis of the Nevirapine ring system [161], cyclization of chloro-amine **392** (Scheme 127) afforded diazepinone derivatives **395** and **397** along with chloro-amide **396.** Products **396** and **397** were formed via spirocyclic intermediate **393.** The relative amounts of **395, 396** and **397** could be subjected



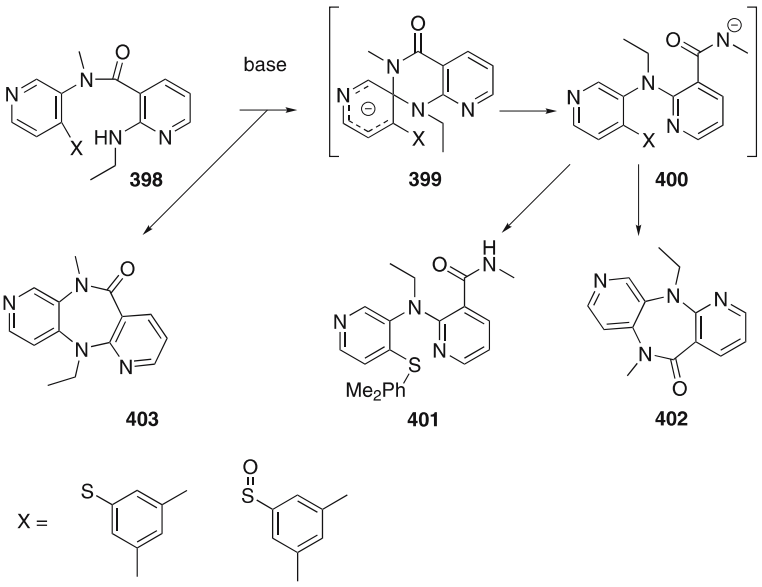
Scheme 127

to some control by variation of base and reaction conditions. Selected results are shown in Table 34.

For an approach to other diazepinone isomers, the authors chose 4-arylthio-derivative **398**, (X = 3,5-Me_2PhS) as the starting material (Scheme 128). It was expected that the carbanion stabilizing effect of the sulfur substituent would facilitate the rearrangement. This was not the case—under all conditions examined the sulfide underwent direct cyclization to give **403**. However, the corresponding sulfoxide, **398**, (X = 3,5-Me_2PhSO), followed the rearrangement-cyclization pathway to give **402** in 79% yield. The difference is likely to reflect higher ability of sulfoxide to act as a leaving group. Selected results are presented in Table 35.

Table 34 Cyclization of 2-chloropyridine derivative **392** according to Scheme 127

Conditions	Product yields (%)		
	395	**397**	**396**
LHMDS/THF, rt	20	39	34
NaHMDS/THF, rt	41	48	8
NaH/xylene, 155 °C	51	32	–
t-BuOK/THF, rt	54	22	–



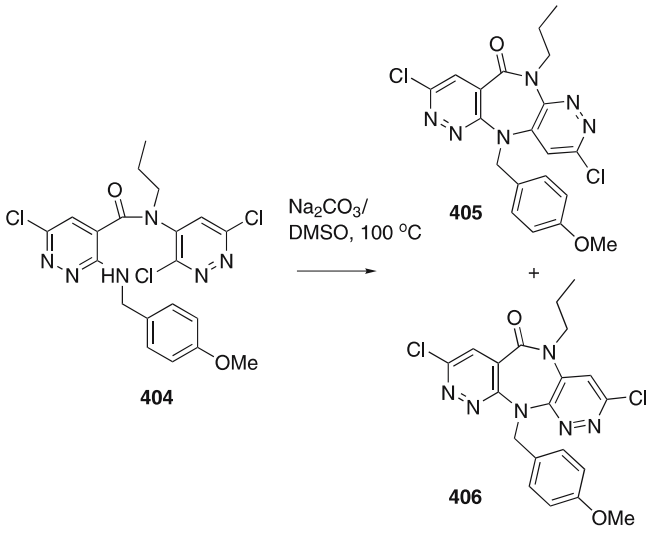
Scheme 128

Table 35 Reaction of sulfide **398**, X = 3,5-Me_2PhS and sulfoxide **398**, X = 3,5-Me_2PhSO, according to Scheme 128

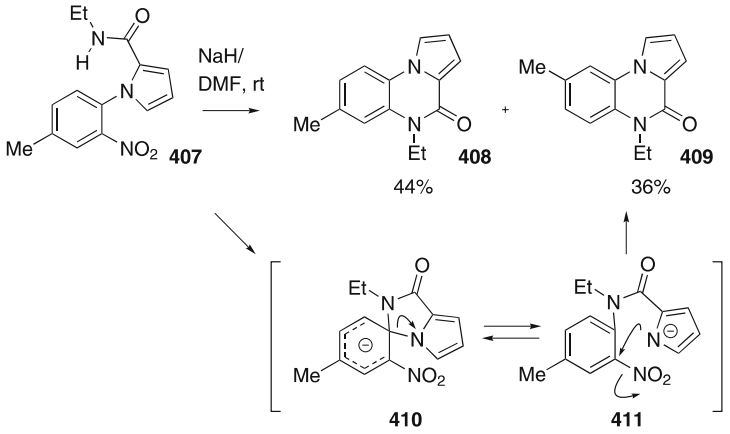
Sulfur group	Conditions	Product yields (%) **403**	**402**	**401**
S	NaH/xylene, 155 °C	50	21	–
S	NaHMDS/THF, – 20 °C	75	–	8
SO	KHMDS/benzene, rt	39	39	–
SO	LHMDS/THF	< 5	79	–

Matuszczak and coworkers [162] reported that cyclization of 3,6-dichloropyridazine **404** (Scheme 129) leads to isomeric products **406** and/or **405** (80–100% yields). For example, when Na_2CO_3 was used as the base in DMSO at 100 °C, a mixture of both products was obtained in a ratio of 1 : 1. The use of NaH in dioxane (100 °C) shifted the reaction outcome in favor of the rearranged component **405/406** 1 : 0.4, whereas Na_2CO_3 in *N*-methylformamide provided **405** as the exclusive product.

1-(2-Nitrophenyl)-1*H*-pyrrole-2-carboxamide derivative **407** (Scheme 130), on treatment with sodium hydride in DMF [163], afforded two isomeric pyrroloquinoxalinones, **408** and **409**, in 44 and 36% yields. While **408** could be obtained by a direct displacement of the nitro group by the carboxamide nitrogen atom, formation of the isomer **409** was more involved. Spirocyclic anion **410** generated by the *ipso*-attack, isomerized to anion **411** that cyclized



Scheme 129



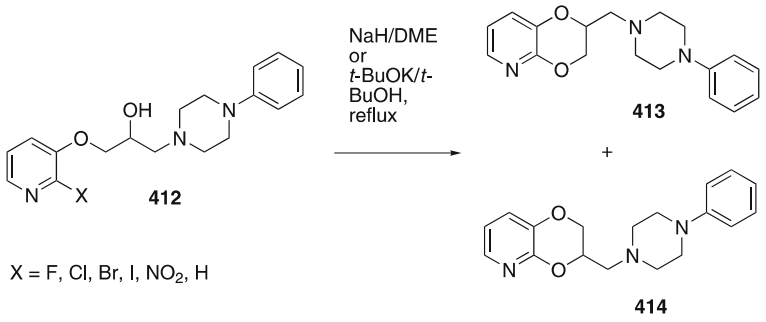
Scheme 130

with displacement of the nitro group. Formation of some other pyrroloquinoxalinones by the rearrangement route was also examined.

7.2
O – O′ Rearrangements

Guillaumet and coworkers [164, 165] showed that base-induced cyclization of pyridine derivatives **412** (Scheme 131) affords isomeric dioxino-pyridines **413** and/or **414**. The cyclization mode depends upon the nature of the substituent X and reaction conditions. Selected results are presented in Table 36.

Direct cyclization products were obtained mainly or exclusively when X was a halogen atom. Only small differences in the product composition were recorded upon changing the halogen atom. The nitro-derivative gave the rearranged product in excess (Table 36, entry 3). Inactivated pyridine derivative (X = H) remained unchanged under the reaction conditions. Some other



Scheme 131

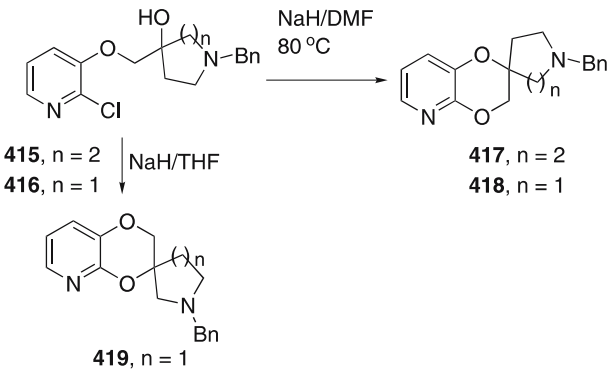
Table 36 Effects of the substituent X and the base on the isomer distribution in the reaction according to Scheme 131

	X	Reaction conditions	Yield (%) **413**	**414**
1	F	NaH/DME	–	58
		t-BuOK/*t*-BuOH	7	50
2	Cl	NaH/DME	–	62
		t-BuOK/*t*-BuOH	15	45
3	NO_2	NaH/DME	59	30
		t-BuOK/*t*-BuOH	52	44
4	H	NaH/DME	–	–

nitro-analogues of **412** with modified side chain and other bases (LiH or KH in DME) were also examined.

The same authors [166] used 2-chloropyridine derivatives **415** and **416** as precursors in the synthesis of **417** and **418** (Scheme 132), respectively. Rearrangement-cyclization of **415** ($n = 2$) was effected with NaH in DMF at 80 °C to give **417** ($n = 2$) in 44% yield (no direct cyclization product was detected). Rearrangement-cyclization of **416** leads to the product **418** in 57% yield contaminated by some **419**. Chloro-pyridine derivative **416**, when treated with sodium hydride in THF at 55 °C, afforded mainly the respective direct cyclization product **419**. Several other base-solvent combinations were also examined. Another O – O′ rearrangement has been recently recorded [167].

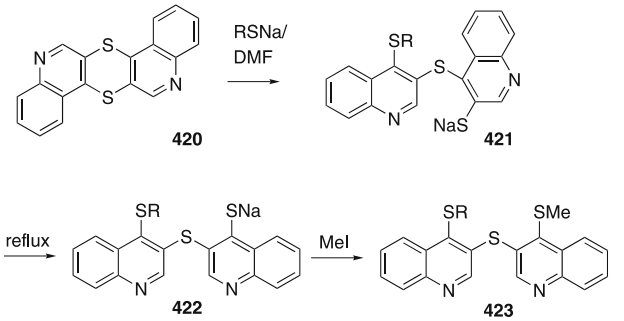
The kinetics and mechanism of Meisenheimer complex formation involving O – O exchange has been studied [74, 168–171].



Scheme 132

7.3
S – S′ Rearrangements

Pluta and coworkers [172, 173] reported application of a S – S rearrangement in the synthesis of various complex quinoline derivatives. This work is illustrated by rearrangement of the dithiine **420** (Scheme 133). Treatment of **420** with sodium alkanethiolates in DMF or DMSO provided the respective substitution product **421**, that rearranged on heating to give **422** and, after methylation, **423**.



Scheme 133

Acknowledgements We thank Professor Philip Kocienski for reading the manuscript and editorial corrections.

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