Synthetic Methodology Based upon *N*-Sulfinyl Dienophile [4 + 2]-Cycloaddition Reactions

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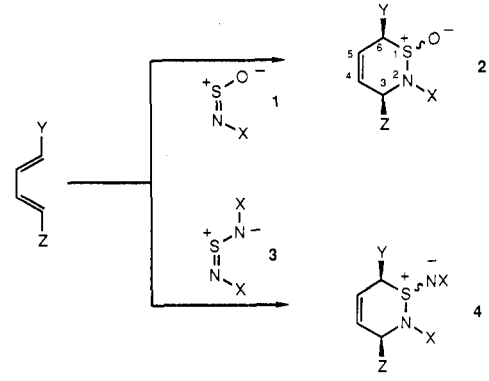
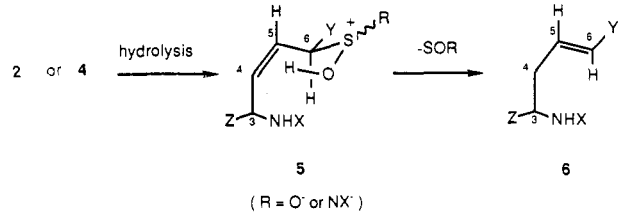
In the early 1950s Wichterle and Rocek[1] discovered that *N*-sulfinylaniline (**1**, X = Ph) reacts with conjugated 1,3-dienes in Diels–Alder fashion to give 3,6-dihydrothiazine 1-oxides **2** (Scheme I). Subsequent studies, notably by the groups of Kresze and Levchenko, demonstrated that this cycloaddition is quite general provided that the *N*-sulfinyl compound **1** bears an electron-withdrawing group.[2] These substituents, some of which are listed in Scheme I, impart sufficient reactivity to the dienophile that the cycloadditions usually occur at or below room temperature. Alkyl *N*-sulfinyl compounds, on the other hand, are reportedly unreactive as dienophiles. However, we have recently found that simple *N*-alkyl-*N*-sulfinylamines react at low temperatures with some dienes to give dihydrothiazine oxides if a Lewis acid catalyst or high pressure is employed.[3] A related type of *N*-sulfinyl dienophile is exemplified by bisimides **3**. In these cases, the products of [4 + 2] cycloaddition are 3,6-dihydrothiazin-1-imines **4**.[2]

Scheme I



Scheme II



Both reactions in Scheme I show excellent regiochemical control with many unsymmetrical dienes. However, a few of the early studies confused the issue of adduct regiochemistry, since it was not initially appreciated that in certain cases these cycloadditions are readily reversible.[4] Disparate mechanistic proposals have appeared for this reaction. Mock and Nugent have advocated a nonconcerted, stepwise mechanism.[5] More recently, Hanson and Stockburn proposed that these cycloadditions are concerted processes in line with FMO theory.[6] In fact, the regioselectivity of the kinetically formed cycloadducts can in principle be rationalized by either mechanism.

These *N*-sulfinyl Diels–Alder reactions are also highly stereoselective, giving products of syn addition to the 1,3-diene. However, very little data are available with regard to the stereochemical outcome at sulfur in adducts such as **2** and **4**. This paucity of information may be due in large part to the difficulty in establishing configuration by simple spectral methods. The nature of the *N*-sulfinyl dienophiles complicates interpretation of the sparse stereochemical data that are available. For example, although *N*-sulfinyl compounds such as **1** are known to exist in their ground states as the *Z* isomers, it has not been possible to determine unambiguously whether this geometry or a transient *E* form is the reactive species in the cycloaddition. Likewise, bisimides **3** usually exist in the *E,Z* geometry, but once again the reactive configuration is indeterminate and furthermore it is not known which S=N bond reacts with the diene. Moreover, the reversibility factor must also be considered, since one may not always be observing the kinetic cycloaddition product. Since chirality at sulfur plays a role in some of our synthetic methodology (vide infra), we hope that its genesis can eventually be clarified.

At the time we began work in this area only a few simple transformations of adducts **2** and **4** had been described. Interestingly, virtually all of the known reactions were reported over 3 decades ago in the original publications of Wichterle and Rocek.[1] One particularly intriguing transformation is the hydrolysis of these Diels–Alder adducts to afford homoallylic amines **6** (Scheme II). Our interest in this potentially useful process was stimulated by a paper of Mock and Nugent[7]

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(1) Wichterle, O.; Rocek, J. *Chem. Listy* **1953**, *47*, 1768. Wichterle, O.; Rocek, J. *Collect. Czech. Chem. Commun.* **1954**, *19*, 282.

(2) For comprehensive reviews of this cycloaddition, see: (a) Kresze, G. In *1,4-Cycloaddition Reactions, The Diels–Alder Reaction in Heterocyclic Syntheses*; Hamer, J., Ed.; Academic: New York, 1967; p 453. (b) Boger, D. L.; Weinreb, S. M. *Hetero Diels–Alder Methodology in Organic Synthesis*; Academic: San Diego, 1987; p 1. (c) Zibarev, A. V.; Yakobson, G. G. *Russ. Chem. Rev. (Engl. Transl.)* **1985**, *54*, 1706. (d) Bussas, R.; Kresze, G.; Munsterer, H.; Schwobel, A. *Sulfur Rep.* **1983**, *2*, 215.

(3) Bell, S. I.; Weinreb, S. M. *Tetrahedron Lett.*, in press.

(4) Kresze, G.; Wagner, U. *Justus Liebigs Ann. Chem.* **1972**, *762*, 93, 106.

(5) Mock, W. L.; Nugent, R. M. *J. Am. Chem. Soc.* **1975**, *97*, 6521, 6526.

(6) Hanson, P.; Stockburn, W. A. *J. Chem.* Soc., *Perkin Trans. 2* **1985**, 589.

(7) Mock, W. L.; Nugent, R. M. *J. Org. Chem.* **1978**, *43*, 3433.

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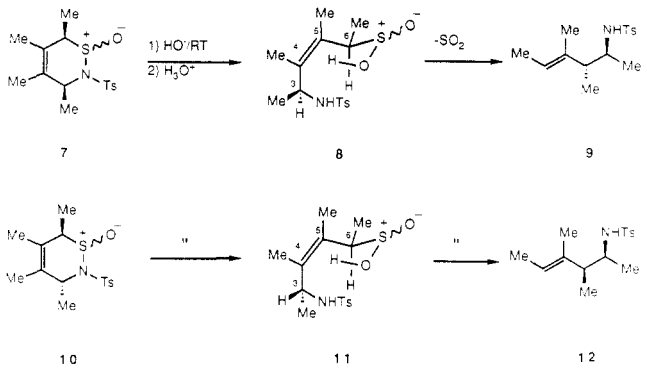
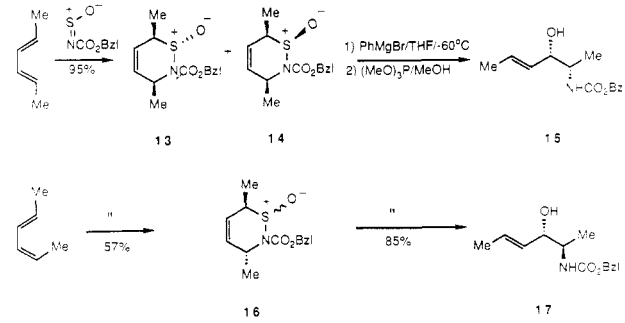
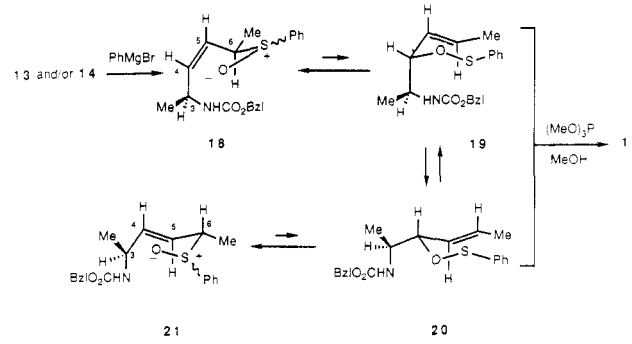
Scheme III



Scheme IV



Scheme V



in which they proposed that the allylic sulfinic acid **5**, formed by initial hydrolytic opening of the dihydrothiazine ring, undergoes retro-ene loss of sulfur dioxide (or its monoimine) via a chairlike transition state. In this conformation, group Y on the sulfur-bearing carbon (C-6) assumes a quasi-equatorial position, leading to the *E*-olefin configuration in **6**. This postulate was based upon deuterium labeling experiments, which, although strongly suggestive, were neither quantitative nor totally definitive.

On the basis of these preliminary results and in view of our longstanding interest in hetero Diels–Alder methodlogy as a synthetic tool,[1b,8] we considered dihydrothiazines such as **2** and **4** as potentially valuable synthetic intermediates and consequently undertook the research discussed below.

Homoallylic Amines

The basic strategy that we initially set out to test was the possibility of intimately coupling the syn selectivity of the [4 + 2]-cycloaddition step with a ring fragmentation process via a rigid chairlike transition-state conformation such as **5** to construct acyclic systems with multiple chiral centers in a stereorational manner. Toward this end, we first had to establish whether the Mock/Nugent retro-ene mechanism is correct.[9,10] Therefore, *N*-sulfinyltoluenesulfonamide was combined with (*E*,*E*)-tetramethylbutadiene to give adduct **7** in high yield (Scheme III). Hydrolysis of **7** afforded *exclusively* the *E*-homoallylic amine derivative **9** with the configuration shown. Similarly, (*E*,*Z*)-tetramethylbutadiene produced 3,6-dihydrothiazine oxide **10**, which was hydrolyzed to give *E*-homoallylic sulfonamide **12**. These results can in fact be nicely rationalized by the retro-ene transition-state conformers **8** and **11** (Scheme III), which lead to **9** and **12**, respectively. This chairlike conformation, which possesses a quasi-equatorial methyl group on the C-6 sulfur-bearing carbon, directs intramolecular protonation to one of the diastereotopic faces of the double bond. The alternative chairlike conformation is destabilized by an $A^{1,3}$ type interaction between a quasi-axial methyl group and the sulfonamide functionality. Thus chirality transfer from a 1,4- to a 1,2-sense is predictably controlled. Moreover, this same conformation explains the selective generation of the *E*-trisubstituted double bond in both **9** and **12**. This sequence also provides an efficient, stereoselective route to homoallylic amines from achiral 1,3-dienes, as well as providing strong support for the Mock/Nugent mechanism.

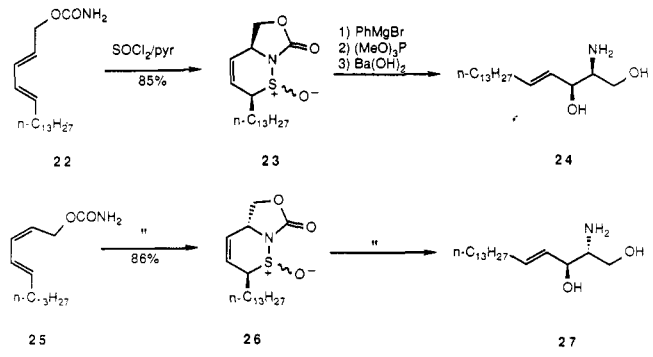
Vicinal Amino Alcohols

Development of Methodology. The stereochemical reasoning implicit in the Mock/Nugent retro-ene postulate was extended to other transformations, leading to a method for diastereoselective synthesis of unsaturated vicinal amino alcohol derivatives. Scheme IV shows some of the exploratory studies that were carried out.[11] Diels–Alder cycloaddition of (*E*,*E*)-hexadiene with benzyl *N*-sulfinylcarbamate gave a 15:1 mixture of epimeric adducts **13** and **14**, whose structures were established by X-ray crystallography. Treatment of either pure **13** or **14**, or the mixture of adducts, with phenylmagnesium bromide, followed by trimethyl phosphite, yielded a single unsaturated hydroxy carbamate shown to be the *E*-threo isomer **15**. Similarly, (*E*,*Z*)-hexadiene underwent the *N*-sulfinyl Diels–Alder reaction to give **16** (sulfur stereochemistry unknown), which could be cleanly transformed to *E*-erythro hydroxy carbamate **17** in an analogous series of reactions.

We believe that the conversion of the dihydrothiazine oxides to the acyclic amino alcohols proceeds via the sequence of steps shown in Scheme V.[11] Opening of **13** or **14** with the Grignard reagent initially affords an allylic sulfoxide **18**.[12] ^1H NMR studies showed that this sulfoxide rearranges to a new sulfoxide **21**, presumably via a [2,3]-sigmatropic rearrangement to a transient sulfenate ester **19** and its conformer **20**.[13] Treatment

(8) Weinreb, S. M. *Acc. Chem. Res.* **1985**, *18*, 16.
(9) Garigipati, R. S.; Morton, J. A.; Weinreb, S. M. *Tetrahedron Lett.* **1983**, *24*, 987.
(10) Weinreb, S. M.; Garigipati, R. S.; Gainor, J. A. *Heterocycles* **1984**, *21*, 309.
(11) Garigipati, R. S.; Weinreb, S. M. *J. Am. Chem. Soc.* **1983**, *105*, 4499. Garigipati, R. S.; Freyer, A. J.; Whittle, R. R.; Weinreb, S. M. *Ibid.* **1984**, *106*, 7861.
(12) 3,6-Dihydrothiazine 1-oxides had previously been opened with "hetero" nucleophiles, but not with carbon nucleophiles: Wucherpfennig, W. *Justus Liebigs Ann. Chem.* **1971**, *761*, 16.
(13) For reviews of the allylic sulfoxide/sulfenate ester [2,3]-sigmatropic rearrangement, see: Evans, D. A.; Andrews, G. C. *Acc. Chem. Res.* **1974**, *7*, 147. Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 563.

Scheme VI

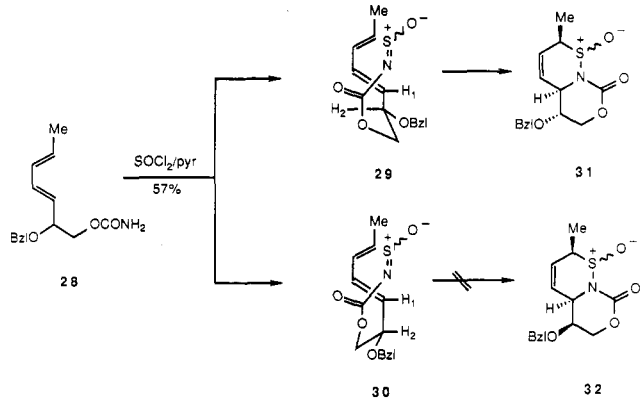


of either **18** or **21** with trimethyl phosphite produces *E*-threo unsaturated alcohol carbamate **15**. The transfer of stereochemical information from **13**/**14** to **15** is best rationalized by invoking envelope-like transition states for the [2,3]-sigmatropic rearrangements of **18** and **21** in which the methyl substituent at C-6 is quasi-equatorial. The erythro compound **17** is produced from Diels–Alder adduct **16** via an identical pathway involving intermediates epimeric at C-3. The net transformation accomplished in this synthetic method is the regioselective syn addition of N and O across one of the double bonds of a 1,3-diene.

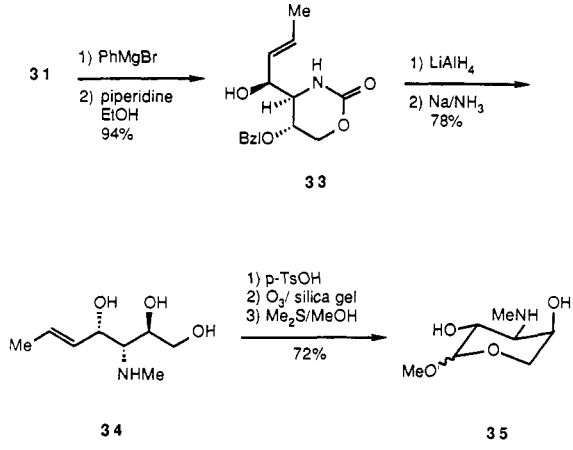
Applications Using Intramolecular *N*-Sulfinyl Cycloadditions. The methodology described above seemed ideally suited to synthesis of a number of natural products containing vicinal amino alcohol functionality. In particular, the sphingosine bases **24** and **27** were appealing targets. However, it was clear that in order to accomplish these syntheses it would be necessary to first effect regioselective Diels–Alder reactions with unsymmetrical 1,3-dienes bearing electronically similar substituents at the 1- and 4-positions. The obvious solution to this problem was to effect the Diels–Alder steps intramolecularly, although no examples of intramolecular *N*-sulfinyl [4 + 2] cycloadditions had been reported. In fact, such a strategy worked beautifully.[11] Treatment of *E,E*-diene carbamate **22** (Scheme VI) with thionyl chloride gave an intermediate *N*-sulfinyl carbamate that rapidly cyclized to dihydrothiazine oxide **23**. The compound was opened with a Grignard reagent to the allylic sulfoxide, which upon rearrangement and saponification yielded *threo*-sphingosine (**24**). Likewise, *E,Z*-diene carbamate cyclized to **26**, which could be transformed to *erythro*-sphingosine (**27**).

We have also utilized this methodology in the synthesis of some amino sugars.[14,15] In one study, diene carbamate **28** was converted to the corresponding *N*-sulfinyl carbamate, which cyclized intramolecularly to afford bicyclic dihydrothiazine oxide **31** as an inseparable 15:1 mixture of sulfur epimers (Scheme VII).[15] None of the adduct **32**, epimeric at the stereogenic center in the connecting chain, was detected. Assuming [4 + 2] cycloaddition occurs via a transition state having the carbamate carbonyl group endo the diene,[6] it appears from inspection of models that the chairlike conformer **30**, leading to adduct **32**, is destabilized relative to the boatlike conformation **29**, primarily due

Scheme VII



Scheme VIII



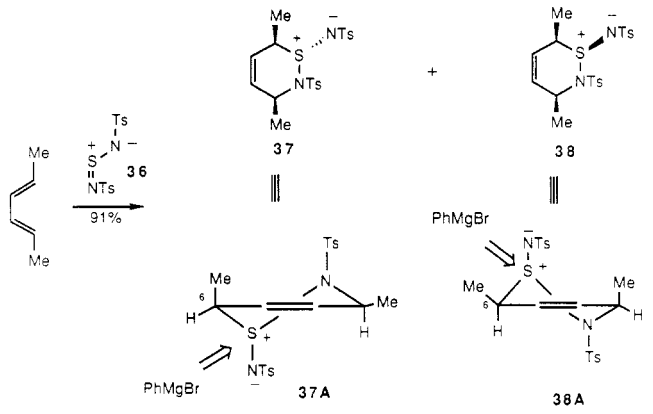
an eclipsing of H_1/H_2 in **30**. Molecular mechanics calculations indicated that conformer **29** has about 2.5 kcal/mol less strain energy than does conformer **30**. Diels–Alder adduct **31** was subsequently used to synthesize amino sugar **35**, a component of some aminoglycoside antibiotics. This adduct was opened to the allylic sulfoxide and rearranged, yielding unsaturated hydroxy carbamate **33** (Scheme VIII). The carbamate carbonyl group of **33** was reduced to produce an *N*-methylamine, and the *O*-benzyl protecting group was reductively removed, affording amino triol **34**. Oxidative cleavage of the olefinic double bond of **34** proved exceptionally difficult, but could eventually be effected by ozonolysis on silica gel, leading to pyranose **35** as a mixture of methyl anomers.

Vicinal Diamines

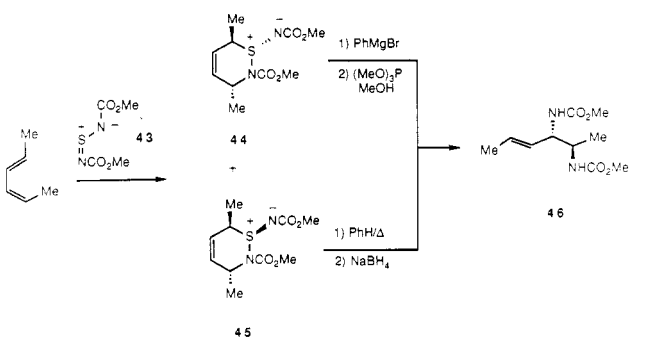
A variation of the above methodology that we have investigated in some detail involves the use of dihydrothiazinimines **4** (Scheme I) to stereoselectively synthesize unsaturated vicinal diamine derivatives. Some exploratory reactions were conducted with the adducts from (*E,E*)-hexadiene and bissulfonimide **36** (Scheme IX).[16] This cycloaddition afforded a separable 1.1:1 mixture of dihydrothiazinimines **37** and **38**. It should be noted that, as in the cases of cycloadditions with mono-*N*-sulfinyl compounds **1**, sulfur epimer ratios were dependent upon the particular diene and bisimide used and varied widely. Whereas the chemistry of dihydrothiazine oxides was generally independent of

(14) Remiszewski, S. W.; Whittle, R. R.; Weinreb, S. M. *J. Org. Chem.* **1984**, *49*, 3243.
(15) Remiszewski, S. M.; Stouch, T. R.; Weinreb, S. M. *Tetrahedron* **1985**, *41*, 1173.
(16) Natsugari, H.; Whittle, R. R.; Weinreb, S. M. *J. Am. Chem. Soc.* **1984**, *106*, 7867.

Scheme IX

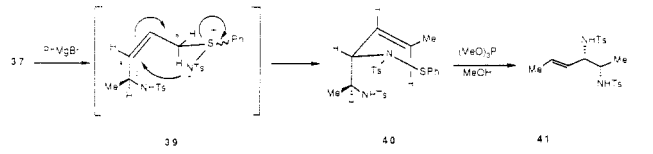


Scheme X



sulfur configuration, we found some dramatic effects of sulfur stereochemistry in the transformations of the corresponding dihydrothiazinimines (vide infra).

Treatment of adduct **37** with phenylmagnesium bromide, followed by trimethyl phosphite, as expected afforded the *E*-threo vicinal sulfonamide **41**. This

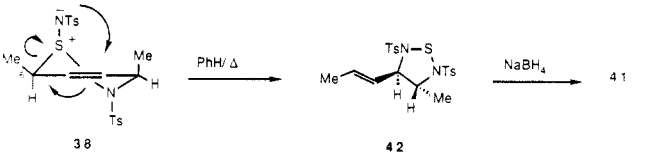


transformation was investigated in more detail, and an important difference from the vicinal amino alcohol synthesis via dihydrothiazine oxides was noted. If the Grignard product of **37** was isolated before desulfurization with phosphite, the expected allylic sulfilimine **39** was not observed, but rather the rearranged sulfenamide **40** was the only detectable product. Although the [2,3]-sigmatropic rearrangement of allylic sulfilimines predates the allylic sulfoxide rearrangement,[17] it has not been nearly as thoroughly investigated. It is therefore not widely appreciated that the equilibrium of the allylic sulfoxide/sulfenate ester system (cf. Scheme V) is totally reversed in the case of the nitrogen analogues.[18,19] In fact, we believe that the rearrangement of an allylic sulfilimine to the sulfenamide may be irreversible.[19]

We attempted to perform the identical chemistry on sulfur epimer **38**, but were very surprised to find that under the conditions used for the Grignard opening of **37**, **38** did not react. Under more forcing conditions, only a poor yield of *E*-threo product **41** could be isolated. This result was in sharp contrast to our observations in the dihydrothiazine oxide cases (vide supra) where sulfur stereochemistry played no role.

In order to help explain the difference in reactivity between epimers **37** and **38**, we established the configuration and conformation of these adducts by a combination of X-ray crystallography and LIS-NMR methods. Adduct **37** was found to have the structure shown in **37A**, and **38** as in **38A**. In both cases, the dihydrothiazine ring exists in a half-chair with the S–N bond quasi-axial, perhaps due to an anomeric effect. Assuming that the ring opening by the Grignard reagent occurs via an S_N2 process, it appears that the C-6 methyl substituent in **38A** interferes with the incoming nucleophile, whereas no such problem exists in **37A**. Indeed, in adducts with *no* C-6 substituent addition of phenylmagnesium bromide proceeds smoothly with both sulfur epimers (vide infra). Similar conformations were found for the dihydrothiazine oxides **13** and **14**, but these systems appear to be inherently more reactive, probably for reason of electronegativity, and therefore both epimers were opened rapidly by Grignard reagents.

Fortunately, we have been able to devise an alternative method for converting the "unreactive" isomer **38**



to a vicinal diamino compound. Simply heating **38** in benzene resulted in a quantitative conversion to thiadiazolidine **42** via a novel type of [2,3]-sigmatropic rearrangement. Reduction of **42** gave an excellent yield of bissulfonamide.

There are apparently two reasons why this sigmatropic rearrangement is so facile. One reason is the fact that adduct **38** prefers a conformation in which the S–N bond is quasi-axial and therefore is proximate to the C-4,5 double bond. The other is that the dihydrothiazinimine is structurally similar to an allylic sulfilimine (cf. **39**) and its rearrangement product **42** is analogous to the preferred allylic sulfenamide (cf. **40**). It should be emphasized here that in conversion of **37** to **40**, C-6 chirality is transferred to C-4, where in rearrangement of **38** to thiadiazoline **42**, it is actually the sulfur chirality that is relayed to C-4. In both sequences, the same *E*-threo vicinal bissulfonamide **41** happens to be the final product.

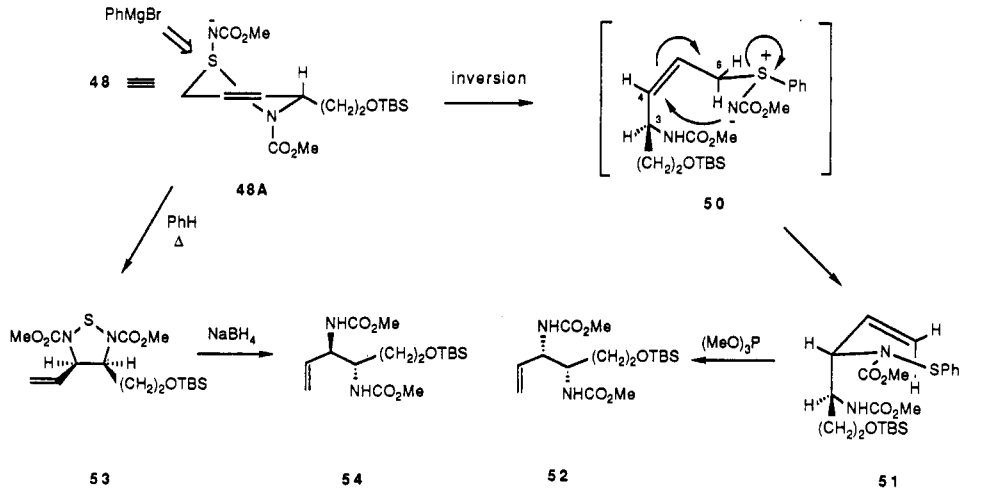
This strategy for synthesis of vicinal diamines could also be applied to (*E*,*Z*)-hexadiene (Scheme X).[16] Reaction of this diene with bisimide **43** gave a 1:2.4 mixture of adducts **44** and **45**. The minor adduct **44** underwent the Grignard addition/rearrangement sequence to provide *E*-erythro biscarbamate **46**. Epimeric adduct **45**, on the other hand, did not react with phenylmagnesium bromide, but did rearrange thermally to a thiadiazolidine, which could be converted to **46**. We believe that **44** and **45** exist in conformations similar to those of **37** and **38** (Scheme IX). The lack of reactivity of **45** vs **44** to Grignard reagents can be ascribed to the same type of steric factors mentioned above.

(17) Oae, S.; Furukawa, N. *Sulfilimines and Related Derivatives*; ACS Monograph 179; American Chemical Society: Washington, DC, 1983; pp 182–185.

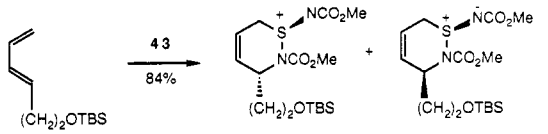
(18) Sharpless, K. B.; Hori. T. *J. Org. Chem.* **1976**, *41*, 176. Atkinson, R. S.; Awad, S. B. *J. Chem. Soc., Chem. Commun.* **1975**, 651.

(19) Natsugari, H.; Turos, E.; Weinreb, S. M.; Cvetovich, R. J. *Heterocycles* **1987**, *25*, 19.

Scheme XI



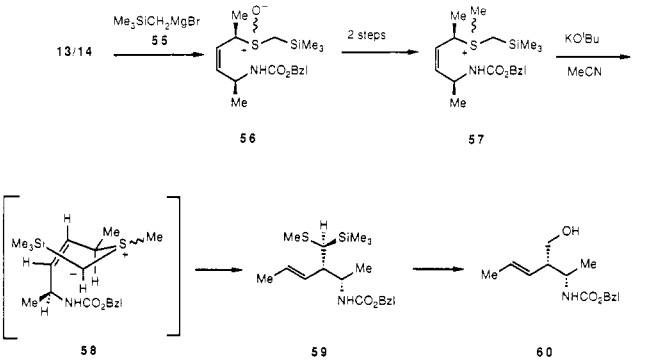
The important observation that sulfur chirality in **38** and **45** could be efficiently transferred to carbon led us to explore some transformations of dihydrothiazinimines derived from *monosubstituted* 1,3-dienes. The C-3 monosubstituted adducts **48** and **49** were easily prepared from diene **47** and bisimide **43**, which afforded a 10:1 mixture of epimers.[19] As anticipated, no other regioisomeric products were formed.[2]



We have been able to rationally convert *both* adducts **48** and **49** to *either* threo-vicinal biscarbamate **52** or the erythro isomer **54** (Scheme XI) with a high degree of diastereoselectivity.[19,20] For example, thermal [2,3]-sigmatropic rearrangement of *trans*-dihydrothiazinimine **48** (which undoubtedly exists as conformer **48A**) stereoselectively produced thiadiazolidine **53**, which was reduced to erythro biscarbamate **54**.

An even more interesting transformation of **48** involved its treatment with phenylmagnesium bromide, leading cleanly to threo sulfenamide **51**, which was then converted to threo biscarbamate **52**. We believe that this reaction sequence proceeds via Grignard opening of **48** (cf. **48A**, Scheme XI) with inversion at sulfur to give allylic sulfilimine **50**. This intermediate rearranges through an envelope-like conformation having the *S*-phenyl group quasi-equatorial, which gives the threo sulfenamide **51**. Thus, the rigid conformation of **50** and the irreversibility of its [2,3]-sigmatropic rearrangement to **51** combine to permit selective chirality transfer from sulfur to C-4. It should be pointed out that the 3,6-dihydrothiazine *oxide* corresponding to **48** (i.e., unsubstituted at C-6) reacts with phenylmagnesium bromide, followed by trimethyl phosphite, to give a 1:1 mixture of threo and erythro vicinal amino alcohol derivatives.[19] This lack of stereoselectivity results because sulfur chirality is transferred very inefficiently in [2,3]-sigmatropic rearrangements of allylic sulfoxides (cf. Scheme V) due to the rapid reversibility of that process.[13]

Scheme XII



The inverse sequence of reactions could be effected with the minor Diels–Alder adduct **49**. Thus, heating **49** gave a thiadiazolidine that upon $NaBH_4$ reduction afforded threo biscarbamate **52**. Alternatively, treatment of **49** with phenylmagnesium bromide, followed by trimethyl phosphite, yielded the erythro compound **54**.

A key feature of the approach to vicinal diamines from dihydrothiazinimines is that, depending upon the substitution pattern, one can utilize *either* C-6 or sulfur chirality to establish relative configuration in the final product.

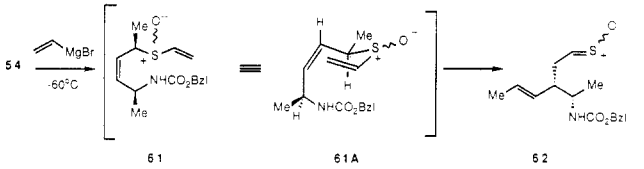
Other Fragmentation/Rearrangement Sequences

3,6-Dihydrothiazine oxides are also versatile intermediates for other transformations that involve initial ring opening by a carbon nucleophile, followed by a sigmatropic rearrangement to transpose 1,4- to 1,2-chirality and simultaneously create a new carbon–carbon bond. For instance, dihydrothiazine oxides **13/14** can be converted stereoselectively to alcohol carbamate **60** as shown in Scheme XII.[21] Treatment of **54** with Grignard reagent **55** gave silyl sulfoxide **56**, which was further elaborated into sulfonium salt **57** in two straightforward operations. Exposure of **57** to potassium *tert*-butoxide gave a *single* silyl sulfide **59**. This reaction probably takes place via ylide **58**, which undergoes a [2,3]-sigmatropic rearrangement to **59** via a conformation having the trimethylsilyl and C-6 methyl

(20) Turos, E.; Parvez, M.; Garigipati, R. S.; Weinreb, S. M. *J. Org. Chem.* **1988**, *53*, 1116.

(21) Garigipati, R. S.; Cordova, R.; Parvez, M.; Weinreb, S. M. *Tetrahedron* **1986**, *42*, 2979.

Scheme XIII



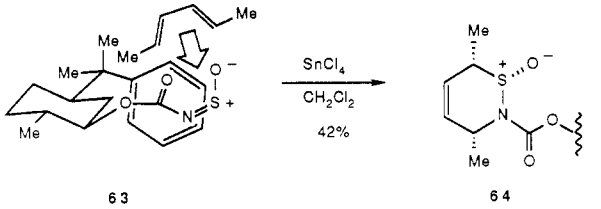
groups quasi-equatorial. It was possible to further elaborate **59** to the hydroxymethyl compound **60** using chemistry described by Ager.[22]

Another variation of this general theme involves the addition of vinylmagnesium bromide to dihydrothiazine oxide **54** (Scheme XIII).[21] Interestingly, the expected allyl vinyl sulfoxide **61** was not observed, but rather the sulfine **62** could be isolated in good yield. The sulfoxide **61** is undoubtedly the initial Grignard reaction product, but this compound undergoes a [3,3]-sigmatropic rearrangement at low temperature, probably via a chairlike conformation **61A**, to provide **62** as the stereoisomer shown. The ease with which this rearrangement occurs suggests that it may actually be an alkoxide-accelerated process. A similar observation has been made independently by Block and Ahmad.[23]

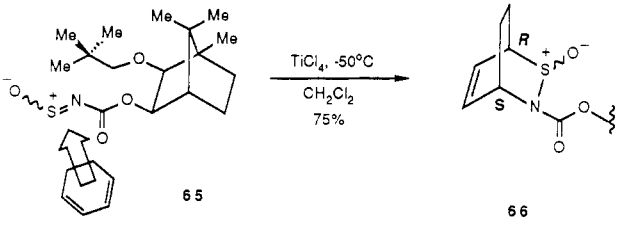
Enantioselective [4 + 2] Cycloadditions

In order to enhance the scope and synthetic utility of the above methodology, we have explored the possibility of effecting enantioselective *N*-sulfinyl dienophile cycloadditions.[24] Similar investigations have been carried out by Whitesell et al.[25]

Both we and Whitesell have prepared the *N*-sulfinyl carbamate **63** derived from 8-phenylmenthol.[24,25] The Whitesell group found that **63** reacts with (*E*,*E*)-hexadiene at room temperature to give four diastereomeric Diels–Alder adducts. However, if the cycloaddition was run at 0 °C in the presence of $SnCl_4$ *only* adduct **64** was produced. The best (but not only) rationale for formation of **64** is that the diene attacks a (*Z*)-*N*-sulfinyl carbamate in an endo mode from the least congested face. The role of the Lewis acid in this process is not at all clear. We have similarly been able to add 1,3-cyclohexadiene to **63** using $TiCl_4$ as catalyst to produce a single enantiomeric product (77%).[24]



Chiral *N*-sulfinyl dienophile **65**, derived from (+)-camphor,[26] has also proven to be effective in enantioselective cycloadditions.[24] Reaction of **65** with cyclohexadiene catalyzed by $TiCl_4$ gave adduct **66** as a single isomer (sulfur stereochemistry unknown). Once again, a reasonable explanation for formation of **66** is that endo attack by the diene occurs from the least hindered face of the dienophile.



Concluding Remarks

During the past several years there has been an increasing awareness of the potential of hetero Diels–Alder reactions in synthesis.[2b,27] The methodology described in this Account allows one to efficiently and stereospecifically prepare a variety of unsaturated, nitrogen-containing molecules. In particular, acyclic amine derivatives possessing multiple chiral centers are readily accessible by this chemistry. The research described here generally involves using a [4 + 2] cycloaddition to set up relative stereochemistry in a 3,6-dihydrothiazine, followed by a stereoselective ring fragmentation/rearrangement process to rationally manipulate stereochemistry and functionality. Other applications of *N*-sulfinyl dienophile cycloadducts have been explored,[28] but space limitations preclude discussion of this work. Suffice it to say that this once obscure Diels–Alder reaction provides useful, highly functionalized synthetic intermediates.

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