

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

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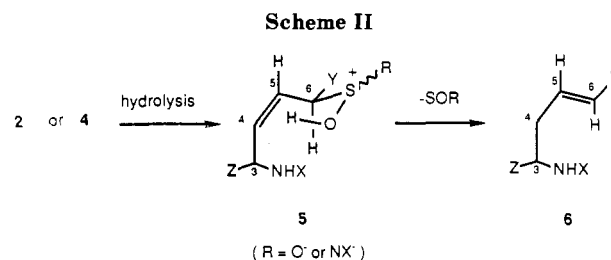
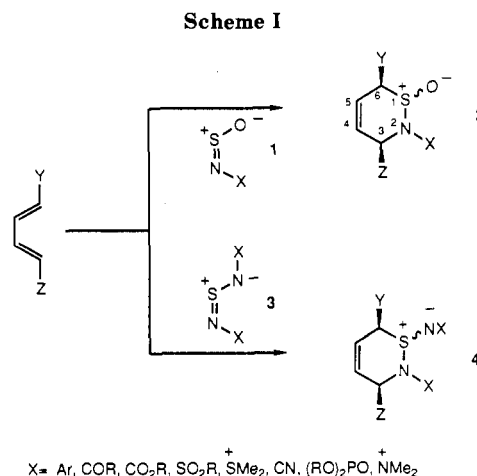
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In the early 1950s Wichterle and Rocek<sup>1</sup> discovered that *N*-sulfinylaniline (1, X = Ph) reacts with conjugated 1,3-dienes in Diels-Alder fashion to give 3,6-dihydrothiazine 1-oxides 2 (Scheme I). Subsequent studies, notably by the groups of Kresze and Levchenko, demonstrated that this cycloaddition is quite general provided that the *N*-sulfinyl compound 1 bears an electron-withdrawing group.<sup>2</sup> 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.<sup>3</sup> 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.<sup>2</sup>

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.<sup>4</sup> Disparate mechanistic proposals have appeared for this reaction. Mock and Nugent have advocated a nonconcerted, stepwise mechanism.<sup>5</sup> More recently, Hanson and Stockburn proposed that these cycloadditions are concerted processes in line with FMO theory.<sup>6</sup> 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

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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.<sup>1</sup> 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<sup>7</sup>

(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.

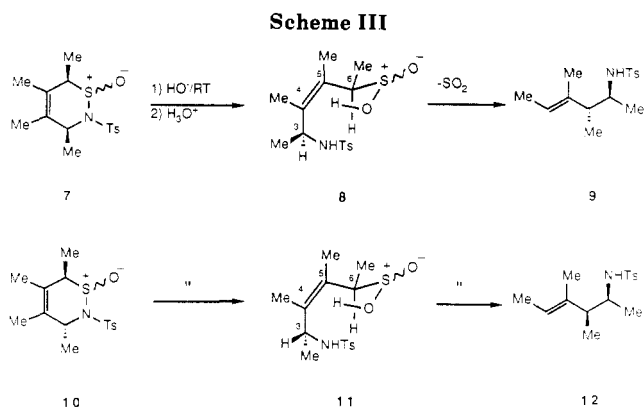
(3) Bell, S. I.; Weinreb, S. M. *Tetrahedron Lett.*, in press.

(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.



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 methodology as a synthetic tool,<sup>1b,8</sup> we considered dihydrothiazines such as **2** and **4** as potentially valuable synthetic intermediates and consequently undertook the research discussed below.

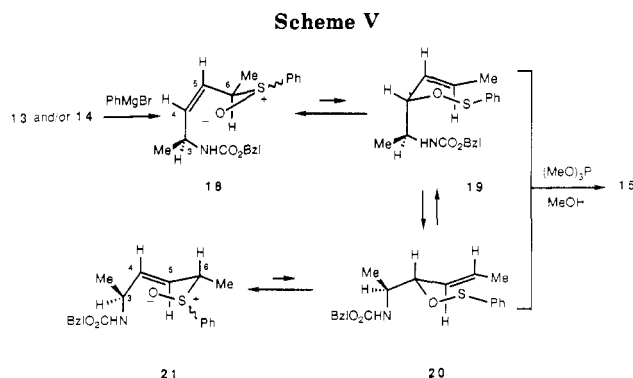
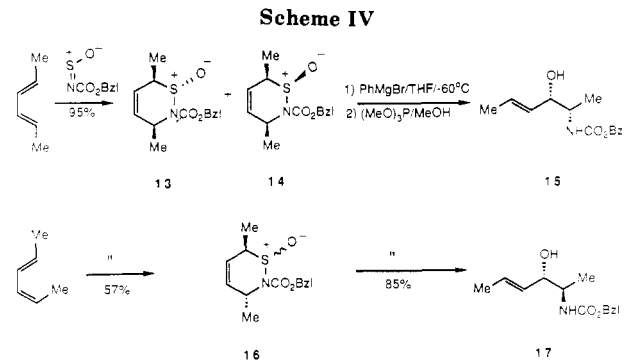
### Homoallylic Amines

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.<sup>9,10</sup> 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<sup>1,3</sup> 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

(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.



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.<sup>11</sup> 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.

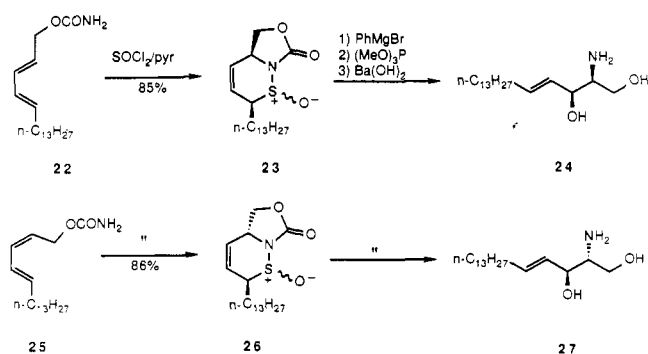
We believe that the conversion of the dihydrothiazine oxides to the acyclic amino alcohols proceeds via the sequence of steps shown in Scheme V.<sup>11</sup> Opening of **13** or **14** with the Grignard reagent initially affords an allylic sulfoxide **18**.<sup>12</sup> <sup>1</sup>H NMR studies showed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

(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: Wucherpennig, W. *Justus Liebig's Ann. Chem.* **1971**, *761*, 16.

(13) For reviews of the allylic sulfoxide/sulfenyl 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

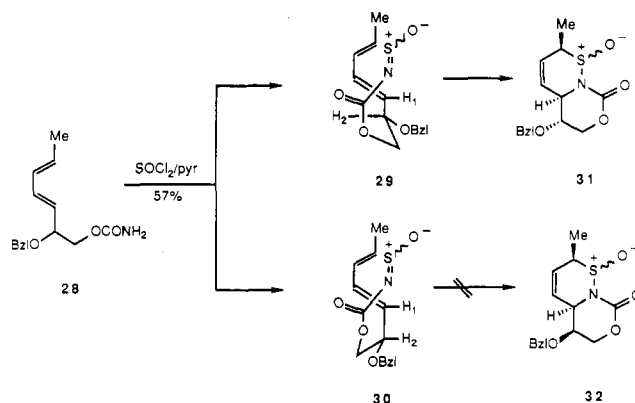


of either 18 or 21 with trimethyl phosphite produces *E*-threo unsaturated alcohol carbamate 15. The transfer of stereochemical information from 13/14 to 15 is best rationalized by invoking envelope-like transition states for the [2,3]-sigmatropic rearrangements of 18 and 21 in which the methyl substituent 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.

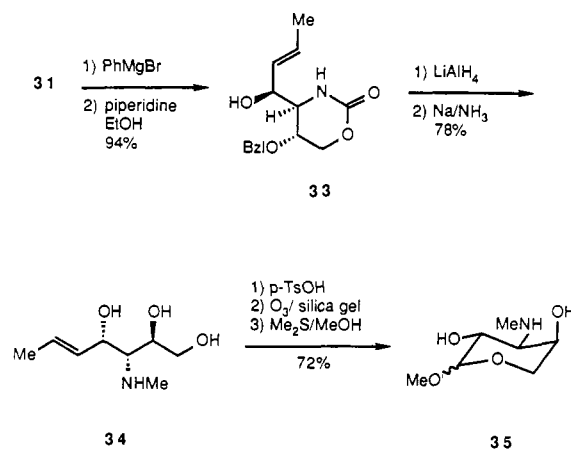
**Applications Using Intramolecular *N*-Sulfinyl Cycloadditions.** The methodology described above seemed ideally suited to synthesis of a number of natural products containing vicinal amino alcohol functionality. In particular, the sphingosine bases 24 and 27 were appealing targets. However, it was 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.<sup>11</sup> 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.<sup>14,15</sup> 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).<sup>15</sup> 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,<sup>6</sup> 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<sub>1</sub>/H<sub>2</sub> 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 bisulfonimide 36 (Scheme IX).<sup>16</sup> 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

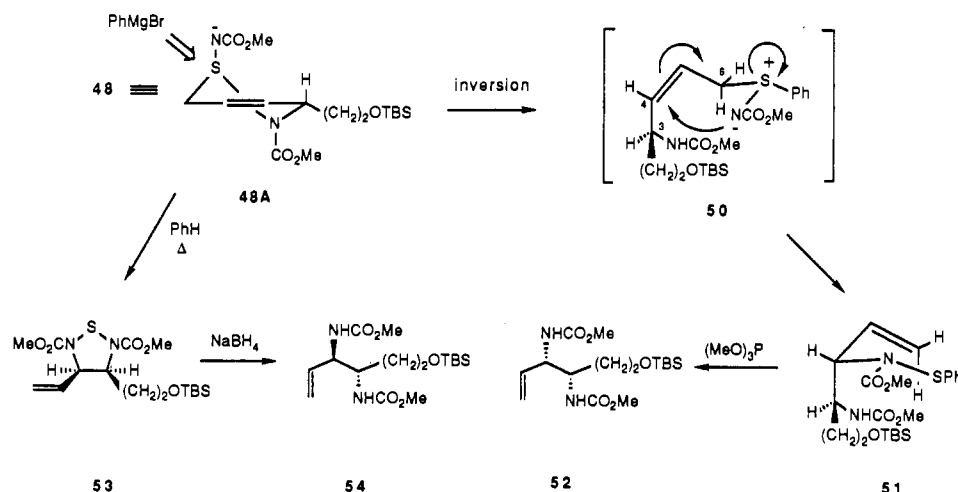
(14) Remiszewski, S. W.; Whittle, R. R.; Weinreb, S. M. *J. Org. Chem.* 1984, 49, 3243.

(15) Remiszewski, S. M.; Stouch, T. R.; Weinreb, S. M. *Tetrahedron* 1985, 41, 1173.

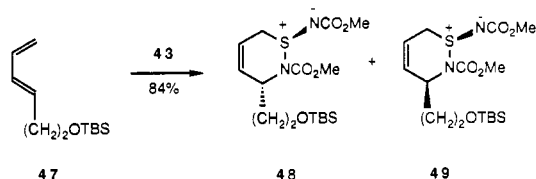
(16) Natsugari, H.; Whittle, R. R.; Weinreb, S. M. *J. Am. Chem. Soc.* 1984, 106, 7867.



Scheme 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.<sup>19</sup> As anticipated, no other regioisomeric products were formed.<sup>2</sup>

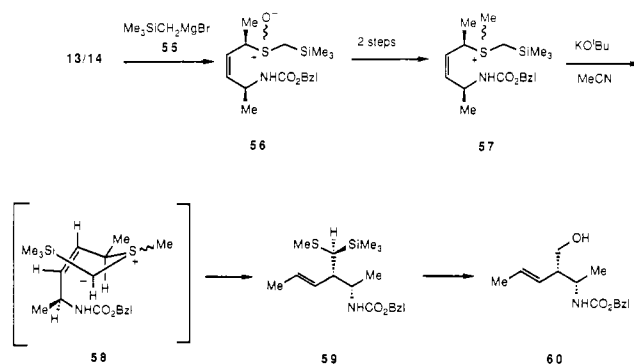


We have been able to rationally convert *both* adducts **48** and **49** to *either* threo-vicinal biscarbamate **52** or the erythro isomer **54** (Scheme XI) with a high degree of diastereoselectivity.<sup>19,20</sup> For example, thermal [2,3]-sigmatropic rearrangement of *trans*-dihydrothiazinimine **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.<sup>19</sup> 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.<sup>13</sup>

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

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<sub>4</sub> reduction afforded threo biscarbamate **52**. Alternatively, treatment of **49** with phenylmagnesium bromide, followed by trimethyl phosphite, yielded the erythro compound **54**.

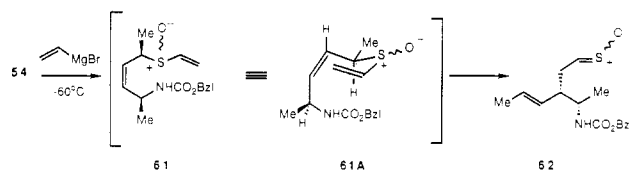
A key feature of the approach to vicinal diamines from dihydrothiazinimines is that, depending upon the substitution pattern, one can utilize *either* C-6 or sulfur chirality to establish relative configuration in the final product.

### 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.<sup>21</sup> 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

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

Scheme XIII



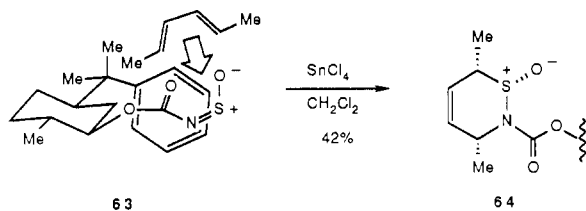
groups quasi-equatorial. It was possible to further elaborate **59** to the hydroxymethyl compound **60** using chemistry described by Ager.<sup>22</sup>

Another variation of this general theme involves the addition of vinylmagnesium bromide to dihydrothiazine oxide **54** (Scheme XIII).<sup>21</sup> 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.<sup>23</sup>

### 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.<sup>24</sup> Similar investigations have been carried out by Whitesell et al.<sup>25</sup>

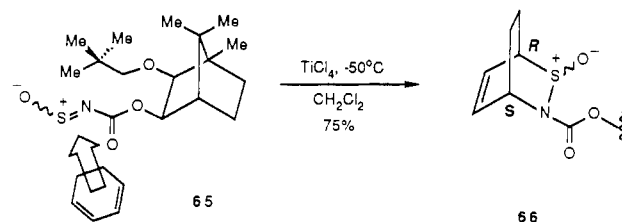
Both we and Whitesell have prepared the *N*-sulfinyl carbamate **63** derived from 8-phenylmenthol.<sup>24,25</sup> The Whitesell group found that **63** reacts with (*E,E*)-hexadiene at room temperature to give four diastereomeric Diels-Alder adducts. However, if the cycloaddition was run at  $0^{\circ}\text{C}$  in the presence of  $\text{SnCl}_4$  only adduct **64** was produced. The best (but not only) rationale for for-



mation 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  $\text{TiCl}_4$  as catalyst to produce a single enantiomeric product (77%).<sup>24</sup>

Chiral *N*-sulfinyl dienophile **65**, derived from (+)-camphor,<sup>26</sup> has also proven to be effective in enantioselective cycloadditions.<sup>24</sup> Reaction of **65** with cyclohexadiene catalyzed by  $\text{TiCl}_4$  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.<sup>2b,27</sup> 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,<sup>28</sup> 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.

*I wish to thank my talented colleagues Ravi Garigipati, Judith Morton, Stacy Remiszewski, Ed Turos, and Hideaki Natsugari for their invaluable contributions to this research program. The important services of M. Parvez (X-ray crystallography), Alan Freyer (NMR spectroscopy), and Robert Minard (mass spectrometry) are also warmly acknowledged. This research was generously supported by the National Science Foundation.*

(22) Ager, D. J. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1131.

(23) Block, E.; Ahmad, S. *J. Am. Chem. Soc.* **1985**, *107*, 6731. See also: Hwu, J. R.; Anderson, D. A. *Tetrahedron Lett.* **1986**, *27*, 4965.

(24) Remiszewski, S. W.; Yang, J.; Weinreb, S. M. *Tetrahedron Lett.* **1986**, *27*, 1853.

(25) Whitesell, J. K.; James, D.; Carpenter, J. F. *J. Chem. Soc., Chem. Commun.* **1985**, 1449.

(26) Oppolzer, W.; Chapuis, C.; Dao, G. M.; Reichlin, D.; Godel, T. *Tetrahedron Lett.* **1982**, *23*, 4781.

(27) Kametani, T.; Hibino, S. *Adv. Heterocycl. Chem.* **1987**, *42*, 246.

(28) See also: Weinreb, S. M.; Gainor, J. A.; Joyce, R. P. *Bull. Soc. Chim. Belg.* **1986**, *95*, 1021. Joyce, R. P.; Parvez, M.; Weinreb, S. M. *Tetrahedron Lett.* **1986**, *27*, 4885. Joyce, R. P.; Gainor, J. A.; Weinreb, S. M. *J. Org. Chem.* **1987**, *52*, 1177.