

# Exploration of Fundamental and Synthetic Aspects of the Intramolecular 4 + 3 Cycloaddition Reaction†

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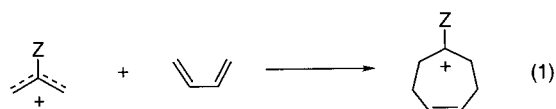
## ABSTRACT

In this Account, a summary of our work in the exploration and development of intramolecular 4 + 3 cycloaddition reactions between dienes and allylic cations is presented. Alkoxyallylic sulfones are useful precursors for the generation of allylic cations which are good dienophiles. Such substrates allowed a number of important pieces of data concerning the cycloaddition to be obtained. The evolution of the work has involved pursuing other methods for allylic cation generation, an investigation of stereochemical variables and applications, including the total syntheses of aphanamol I, widdrol, and (+)-dactylol.

## Introduction

The 4 + 3 cycloaddition reaction of allylic cations and dienes constitutes a convenient way to prepare relatively complex seven-membered rings from simple starting materials.<sup>1</sup> For this reason, it continues to be investigated as a means of preparing complex systems such as natural products which contain seven-membered rings.

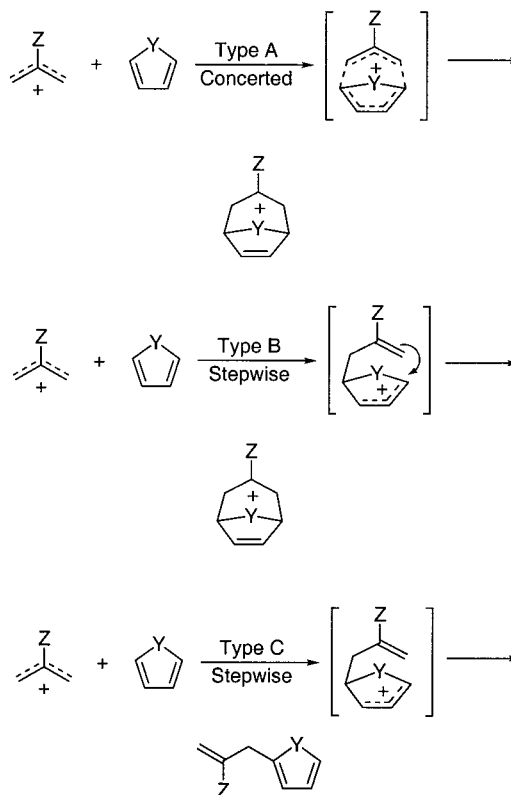
A generic process is shown in eq 1. There are several features of this reaction that are noteworthy. First, the



product ultimately formed from the reaction depends on the nature of the “Z” group on the 2 position of the allylic cation. Typically, this group is an oxygen-bearing functionality, and the product formed is a cycloheptenone. However, the trimethylsilylmethyl group has been used in this role, and the range of terminating groups which could, in principle, be used is quite large. Second, one could inquire about the nature of the reaction from a mechanistic point of view. In what might be called the early days of 4 + 3 cycloaddition reactions, Hoffmann defined three categories for the reaction of allylic cations with dienes.<sup>2</sup> Type A processes are concerted reactions

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Scheme 1

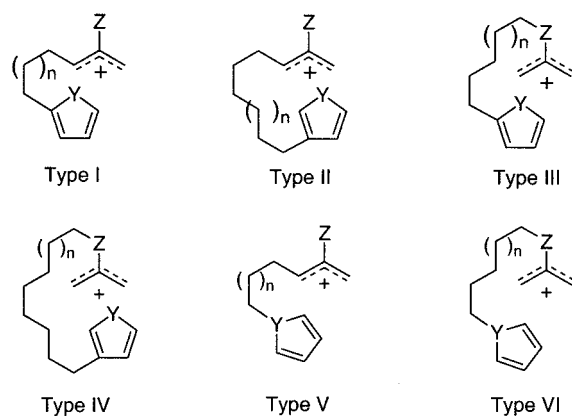


which lead to 4 + 3 cycloadducts. Type B processes also give rise to 4 + 3 cycloadducts, but through a stepwise mechanism. Finally, type C products arise via a stepwise process in which the final bond-forming step is thwarted in favor of a competitive reaction, leading to products of electrophilic addition or substitution (Scheme 1). Recent theoretical studies by Cramer and co-workers suggest that both stepwise and concerted mechanisms are possible.<sup>3</sup> The pathway followed by the reaction depends on the nature of the allylic cation and the diene. Reactive, strongly electrophilic allylic cations and nucleophilic dienes tend to react via stepwise mechanisms, while less electrophilic cations and less nucleophilic dienes tend to react via concerted processes.

A variant of the 4 + 3 cycloaddition reaction that we have been studying over the past several years is the intramolecular 4 + 3 cycloaddition reaction. As with other reactions, we expected that intramolecularity would provide advantages that were otherwise not easily obtained in the intermolecular process. At the time we began our studies, very little had been done with respect to the intramolecular 4 + 3 cycloaddition reaction. Given the number of natural products which possessed seven-membered rings fused to other rings, we thought it would be useful to examine this process from both a synthetic and mechanistic perspective, with particular emphasis on stereochemical control.

Early on, we defined different categories of the intramolecular 4 + 3 cycloaddition reaction based not on

† This paper is dedicated to the memory of Professor Norman Rabjohn (May 1, 1915–September 2, 2000).



**FIGURE 1.** Types of intramolecular 4 + 3 cycloaddition reactions based on connectivity between the diene and dienophile.

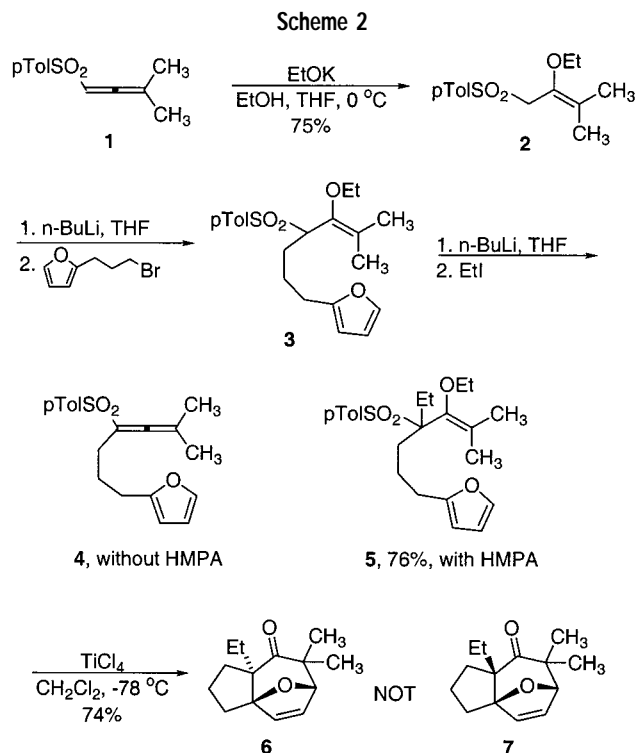
mechanistic considerations, but on the connectivity between the diene and the dienophiles. These types are shown in Figure 1, and it is noteworthy that it is still the case that most of these reaction types have not been explored.

At the outset of our work, we were aware of the work by Noyori, Hoffmann, Föhlisch, and Mann, among others, in the area of 4 + 3 cycloaddition reactions.<sup>1</sup> We were concerned that many of the progenitors of allylic cations used for 4 + 3 cycloaddition reactions, such as the  $\alpha,\alpha'$ -dibromoketones used by Noyori and Hoffmann, were unstable and/or unpleasant to work with. We thus set as our first goal to develop a cation precursor that was stable and easily synthesized and purified, and that could be stored for long periods of time. Experience suggested that  $\beta$ -alkoxyallylic sulfones might provide suitable precursors.

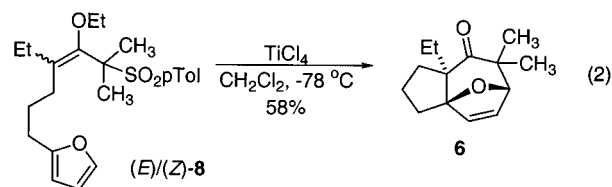
## Synthesis and 4 + 3 Cycloaddition Chemistry of Alkoxyallylic Sulfones

A few years before we began our studies, we realized that alkoxyallylic sulfones were interesting species which had been only extensively studied from a synthetic point of view within the context of the carbanion-accelerated Claisen rearrangement.<sup>4</sup> Given that knowledge and the contributions by Trost in the development of the sulfone functional group as a chemical chameleon,<sup>5</sup> the application of alkoxyallylic sulfones in 4 + 3 cycloaddition chemistry seemed a natural next step.

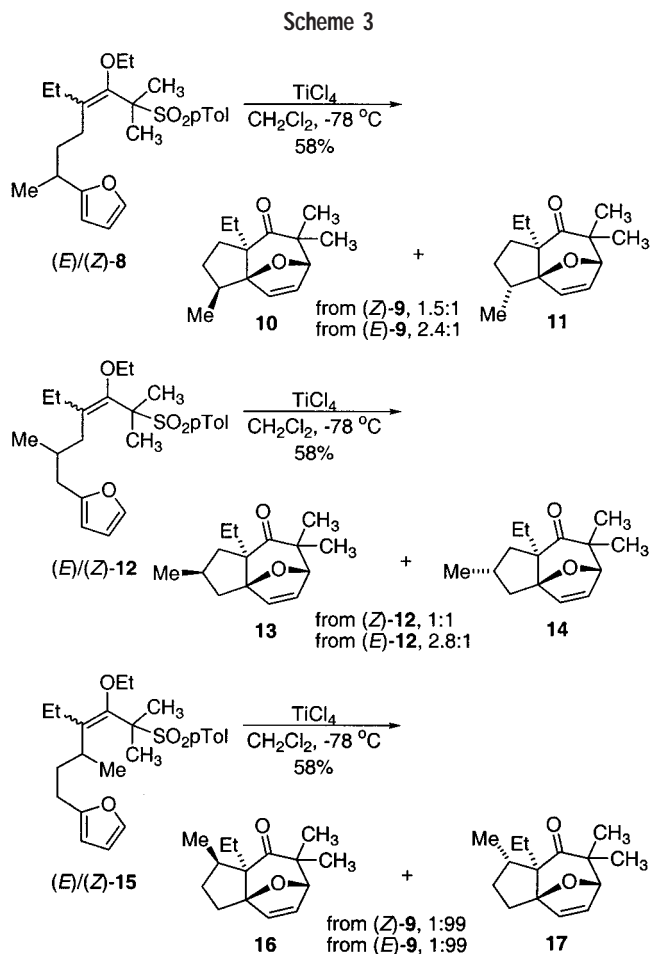
Alkoxyallylic sulfones were prepared via the addition of alkoxides to the corresponding sulfonyl allenes. The alkylation of alkoxyallylic sulfones was found to be a relatively simple reaction. Deprotonation with *n*-BuLi led to the corresponding organolithium which could be alkylated in good to excellent yields. Only in the case of sulfones such as **3** did we experience problems. Treatment of **3** with *n*-BuLi in THF at  $-78\text{ }^{\circ}\text{C}$  followed by slow warming afforded not the expected alkylation product **5**, but the elimination product **4**. This problem was easily solved by the inclusion of HMPA as an additive in the alkylation reaction. This increased the reactivity of the metalated sulfone and allowed alkylation to take place at temperatures at which the elimination process was not competitive. Using this basic approach, we were able to



prepare a number of cycloaddition precursors to examine the viability of the reaction and its scope, at least with respect to substitution on the alkoxyallylic sulfone. Our initial efforts focused on systems with a three-carbon tether between the alkoxyallylic sulfone and the diene, a furan. For example, treatment of **5** with 1 equiv of titanium tetrachloride in dichloromethane at  $-78\text{ }^{\circ}\text{C}$  afforded the cycloadduct **6** as a single stereoisomer in 74% yield (Scheme 2).<sup>6</sup> This beautiful result led us to ask a number of questions, including ones associated with the mechanism of the bond-forming process(es) and the origin of the high levels of simple diastereoselection. The latter might be explained simply in terms of product development control. The observed product is 7.5 kcal/mol (AM1) more stable than the isomer **7**. The reaction appeared to be under kinetic control, and stability differences in potential products could be used to explain different rates of formation of those products. However, there were and in fact still are a number of questions about the reaction. We realized that **5** could lead to two isomeric allylic cations upon treatment with a Lewis acid. When (*E*)- and (*Z*)-**8** were prepared and individually treated with  $\text{TiCl}_4$ , both led to the cycloadduct **6** in 58% yield (eq 2).<sup>7</sup> This suggested that the stereochemical outcome of the reaction was independent of allylic cation stereochemistry, although the possibility of isomerization of the cation under the reaction conditions could not be ruled out.

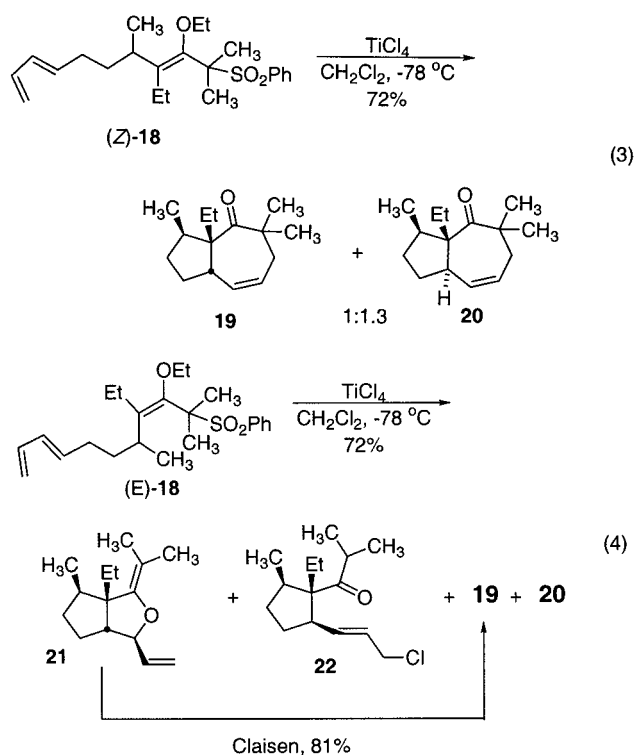


Scheme 3



To address this question, we prepared six different cycloaddition precursors bearing two stereochemical markers, one of which was not subject to any change during the course of the cycloaddition reaction. Their cycloaddition reactions are summarized in Scheme 3. As can be seen, the *E* and *Z* isomers of the first sets of educts give rise to a unique set of products in a reproducible fashion. The numbers are not so different as to suggest a definitive answer to the question posed, yet the *E/Z* isomers within each series give rise to unique intermediates which react without undergoing complete conversion to a common intermediate. The results do not rule out, however, partial interconversion of the cations derived from the *E* and *Z* cations. In the case of **15**, both isomers led to the same, single diastereomer of cycloadduct. This result was rationalized on the basis of steric effects that happened to lead to the same diastereomer of cycloadduct regardless of allylic cation configuration.

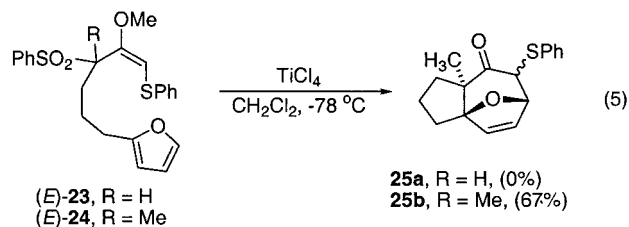
A more profound example of the dependence of allylic cation geometry on the reaction was found in the cycloaddition reaction of the geometrical isomers of **18** (eqs 3 and 4).<sup>8</sup> While (*Z*)-**18** afforded 4 + 3 cycloadducts **19** and **20** in good yield, the *E* isomer gave four different products, highly suggestive of a stepwise process. Noteworthy are the following: First, in both reactions, the 4 + 3 cycloadducts are formed with little to no simple (endo/exo) selectivity, but excellent relative stereocontrol. Second, the 3+2 cycloadduct **21** could be converted to **19** via a thermal



Claisen rearrangement in excellent yield. Finally, the isolation of **22** strongly supports the formation of a cationic intermediate which is probably relevant to the formation of cycloadducts derived from (*E*)-**18**.

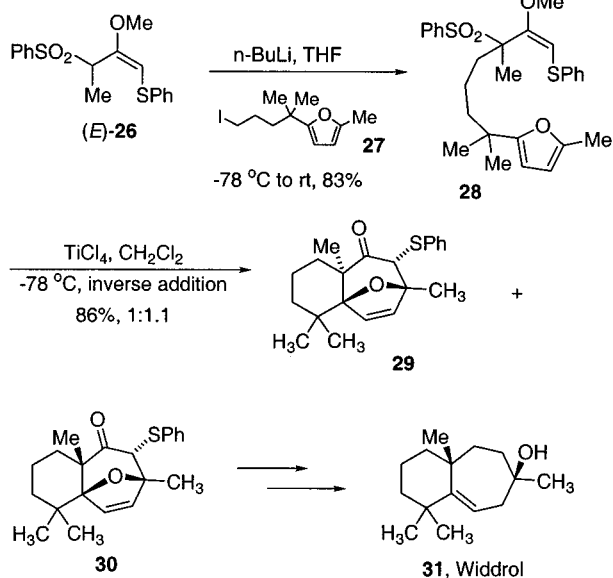
Notwithstanding all of the aforementioned results, the methodology we developed has some problems. Most importantly, only highly substituted allylic sulfones led to cycloadducts. The problem is that the sulfone functional group is not a very good leaving group. This is, of course, the reason alkoxyallylic sulfones are easily handled and stored. In considering a solution to this problem, we decided to pursue the synthesis of heteroatom-substituted allylic sulfones, in the hope of using lone pairs of electrons to facilitate ionization to give the allylic cation.

We therefore prepared (*E*)-**23** in a rather straightforward fashion, and in the process we were able to show that deprotonation/alkylation could take place.<sup>9</sup> We have not been able to induce the cycloaddition of (*E*)-**23** successfully, but we did find that treatment of (*E*)-**24** with  $\text{TiCl}_4$  afforded cycloadduct **25b** in 67% yield (eq 5). The *Z* isomer of **24** was shown to react only poorly in this reaction.<sup>10</sup>



We have exploited this methodology as described in Scheme 4. Alkylation of (*E*)-**26** with **27** in THF/HMPA afforded (*E*)-**28** as a single geometrical isomer in 83% yield.

Scheme 4

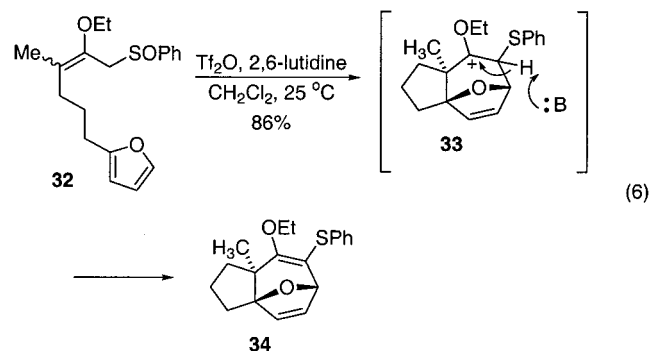


Treatment of (*E*)-**28** with  $\text{TiCl}_4$  gave cycloadducts **29** and **30** as a 1:1.1 mixture of diastereomers, respectively. The latter has been converted to the natural product, widdrol.<sup>11</sup> It is important to note that in the formation of 12-oxatricyclo[7.2.1.0]dodecenones, simple diastereoselection is generally poor.

## Alkoxy Allylic Sulfoxides and Alkoxy Allylic Alcohols

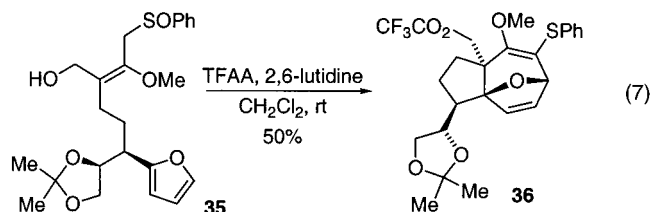
The intermediate generated from the reaction of phenylthio-substituted allylic sulfones with a Lewis acid is presumably a vinylthionium ion. An obvious extension of the work we were conducting was to consider other methods for generating such an intermediate.

One approach involved the synthesis of alkoxy allylic sulfides such as **32**. We anticipated that a Pummerer reaction would result in the formation of a vinylthionium ion which would cyclize. Indeed, treatment of **32** with triflic anhydride and 2,6-lutidine at room temperature afforded the cycloadduct **33** in 86% yield (eq 6).<sup>9</sup> The presence of the base favors formation of the enol ether over dealkylation products, so that **33** affords **34** as shown.



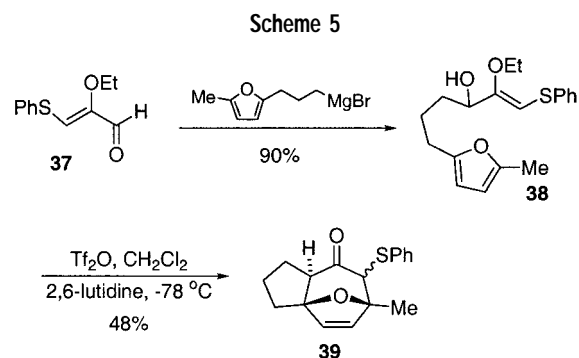
While we have not intensively investigated this methodology, we were gratified and excited to see a recent application from Bai's group.<sup>12</sup> In an approach toward the

synthesis of pseudolaric acid **A**, these workers treated the allylic sulfoxide **35** with trifluoroacetic anhydride and 2,6-lutidine to obtain the cycloadduct **36** in 50% yield (eq 7). The high level of relative stereocontrol observed in this reaction is impressive.



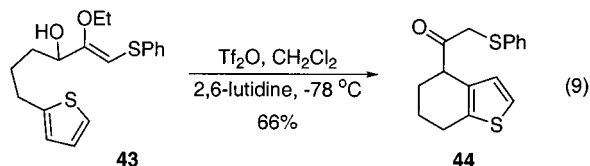
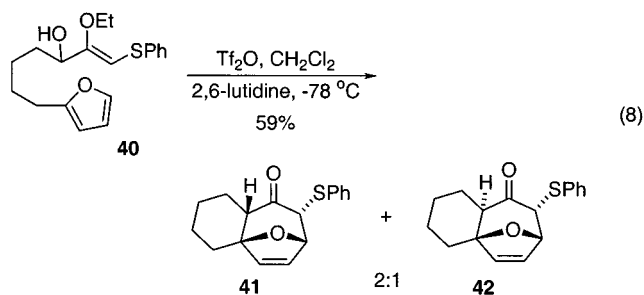
A more straightforward approach to vinylthionium ions would involve heterolysis of the appropriate allylic alcohols. Allylic alcohols or their derivatives had been used as precursors to allylic cations in the context of intramolecular 4 + 3 cycloaddition reactions, and this precedent suggested this idea would work.<sup>13,14</sup> One particular motivation for pursuing this approach was that we hoped that sulfur-based chiral auxiliaries might ultimately be incorporated into cycloaddition precursors and that this would be a means of achieving asymmetric 4 + 3 cycloaddition reactions.

We prepared aldehyde **37** in seven steps from ethyl pyruvate and found that Grignard reagents added to the aldehyde in good yields to afford cycloaddition precursors. Treatment of these alcohols with triflic anhydride and 2,6-lutidine gave cycloadducts in moderate yields.<sup>15</sup> Three examples should suffice in making some important points. Alcohol **38** reacted to afford the corresponding cycloadduct **39** in 48% yield, with what can be described as the typical stereochemical relationship between the angular positions (Scheme 5). The cycloaddition of **40** gave



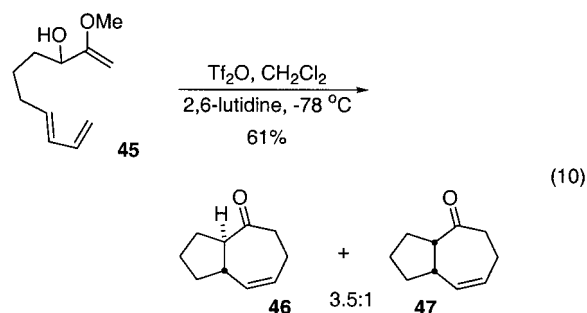
two products, in a 2:1 ratio, consistent with the observation that low simple diastereoselection is to be expected in the formation of 12-oxatricyclo[7.2.1.0]dodecenones (eq 8). Finally, thiophene **43** afforded only the electrophilic aromatic substitution product **44** in 66% yield (eq 9). This is an important observation. In general, thiophene is not a good diene for 4 + 3 cycloaddition reactions.

In performing this work, we also considered it appropriate to examine the cycloaddition chemistry of alkoxyallylic alcohols which bore no sulfur substituents. Although this would remove the potential utility of incorporation of a sulfur substituent as, for example, a



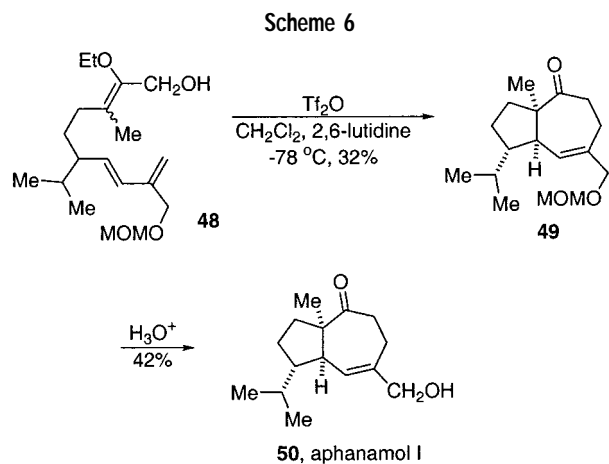
chiral auxiliary, it would provide information about the reactivity and stereoselectivity when no sulfur substituent was present.

As an example, the reaction of allylic alcohol **45** with triflic anhydride resulted in the formation of cycloadducts **46** and **47** in 61% yield in a ratio of 3.5:1, respectively (eq 10).<sup>16</sup> Despite the moderate yield, the ease with which

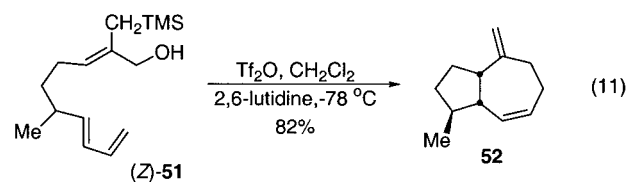


cycloaddition precursors such as **45** can be assembled makes this methodology extremely attractive. Work on expanding this methodology is currently in progress in our group.

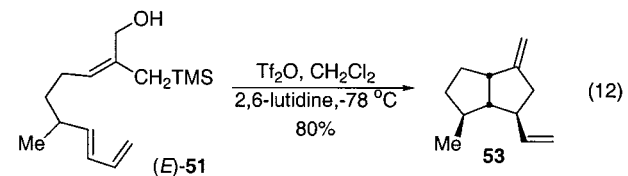
Further studies in this area have been focused on applications and determining the relationship between cation geometry and the regiochemical outcome (4 + 3 vs 3 + 2) of the cycloaddition reaction. We were able to show that a 1:1 mixture of the *E* and *Z* isomers of **48**



afforded the cycloadduct **49** exclusively, albeit in relatively poor yield (32%). This compound could be deprotected to afford **50**, the natural product aphanamol I (Scheme 6).<sup>17</sup> It was somewhat surprising that the yield of **49** was so low and that the reaction apparently produced no 3 + 2 cycloadducts, particularly in view of what has been reported in the literature. In a seminal contribution, Giguere and co-workers established a relationship between the configuration of a 4 + 3 cycloaddition precursor and the regiochemical outcome of the reaction.<sup>18</sup> The reaction of alcohol (*Z*)-**51** with triflic anhydride in the presence of base afforded the cycloadduct **52** as the major product of the reaction, along with some minor byproducts (eq 11). The reaction was both regio- and stereo-

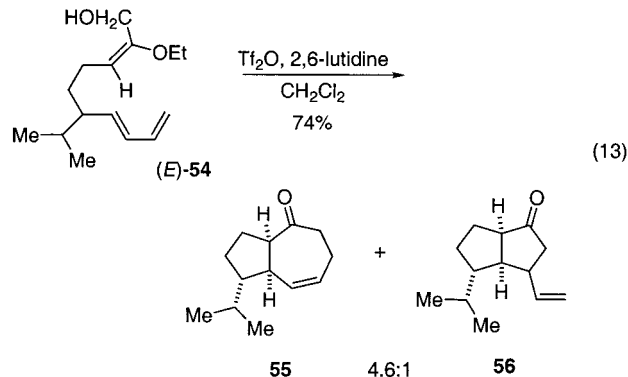


selective. Further, reaction of (*E*)-**51** under the same conditions gave the 3 + 2 cycloadduct **53** as the major product (eq 12). The results suggest that the configuration



of the allylic cation intermediate in intramolecular 4 + 3 cycloaddition reactions plays an important role in the regiochemical outcome of the reaction. We have observed similar results (cf. eqs 3 and 4).

To study this effect in more detail, we have examined cycloaddition substrates related to **48** and have found that yields could be quite acceptable and, more interestingly, that the regioselectivity generally favored 4 + 3 cycloadducts independent of cation geometry. For example, alcohol (*E*)-**54** gave cycloadducts **55** and **56** in a 4.6:1 ratio in 74% yield (eq 13).<sup>17</sup> Note that the stereochemistry of

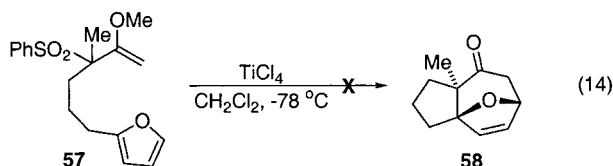


(*E*)-**54** is such that one might predict the formation of the 3 + 2 cycloadduct as the major product of the reaction, using the result in eq 12 as precedent. Interestingly, the *Z* isomer of **54** gave only a 17% yield of the same

regioisomers in a ratio of 17.6:1. Further studies have shown that substituents strongly affect the course of the cycloaddition reactions of substrates related to **48** and **54**, but many, regardless of the configuration of the enol ether portion of the molecule, serve as useful precursors to 4 + 3 cycloadducts.

## Trimethylsilylmethyl Allylic Sulfones and Alcohols

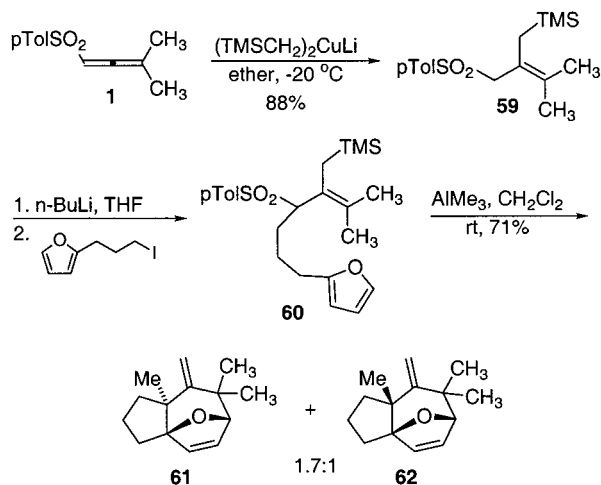
The use of the trimethylsilylmethyl group as a terminator in 4 + 3 cycloaddition reactions is known (see eqs 11 and 12).<sup>1,13,14,18</sup> We engaged in studies using such a terminator principally because of concerns that the enol ethers in many of our alkoxyallylic sulfones appeared to be labile in the presence of Lewis acids, particularly when these sulfones were not heavily substituted. For example, the reaction of **57**, a tertiary allylic sulfone, with Lewis acids resulted in either no reaction or destruction of the starting material, with no evidence for the formation of a 4 + 3 cycloadduct (eq 14). We speculated that part of the



problem was related to the reactivity of the enol ether in the presence of the Lewis acid and hoped that a switch to an allylmetal might allow a broader range of allylic sulfones to serve as cation precursors for 4 + 3 cycloaddition reactions.

The cycloaddition precursors for this work were easily prepared by the addition of the appropriate cuprates to the corresponding sulfonyl allenes, as exemplified by the synthesis of **59**.<sup>19</sup> Attempts to directly alkylate the cuprate addition product were not successful. We also failed at attempts to alkylate **60** via a deprotonation–alkylation sequence. Deuterium oxide quenching experiments suggested that deprotonation with *n*-BuLi in THF was very

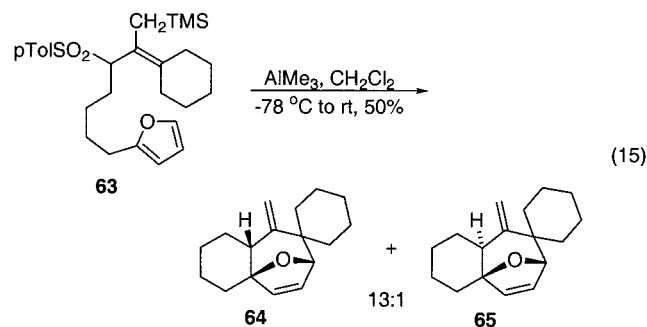
Scheme 7



slow. We thus used **60** directly in our cycloaddition studies. This was important since we knew that a related secondary alkoxyallylic sulfone afforded only low yields of 4 + 3 cycloaddition products upon treatment with various Lewis acids, and we were interested to see if a change in the terminating group would give any improvement.

While TiCl<sub>4</sub> was not an effective Lewis acid for the cycloaddition of **60**, we found that the reaction with 2 equiv of trimethylaluminum (TMA) resulted in the formation of cycloadducts **61** and **62** in 71% yield (Scheme 7).<sup>20</sup> The low simple diastereoselection in this case does not appear to strongly parallel the stability differences of the products (4.4 kcal/mol, AM1), though the more stable product **61** is produced in a slight excess.

A number of interesting observations were made in the course of these studies. First, we found some high diastereoselection in the formation of 12-oxatricyclo[7.2.1.0]-dodecenes. For example, the reaction of **63** with trimethylaluminum afforded the cycloadducts **64** and **65** in a ratio of 13:1 (eq 15). We rationalized this result initially



as one in which complexation between the furan and the trimethylaluminum resulted in steric interactions in the transition state represented by **67**, which correspondingly favored the less encumbered **66**. Simple overlap differences between the diene and dienophile in structures **68** and **69** may be sufficient to explain the stereoselection, however, and the need to invoke the complexation of furan by a Lewis acid is questionable (Figure 2).

We also uncovered several examples in which unusual relative diastereoselectivity was observed. In a representative case, reaction of **70** with TMA in CH<sub>2</sub>Cl<sub>2</sub> afforded the

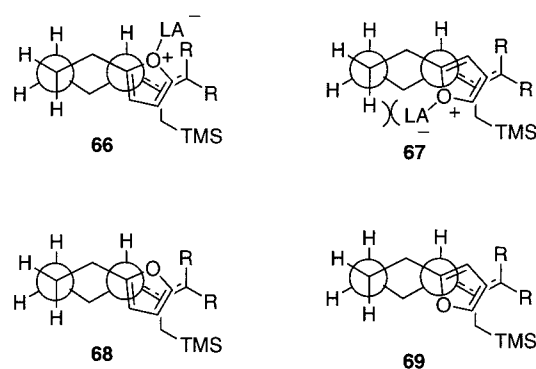
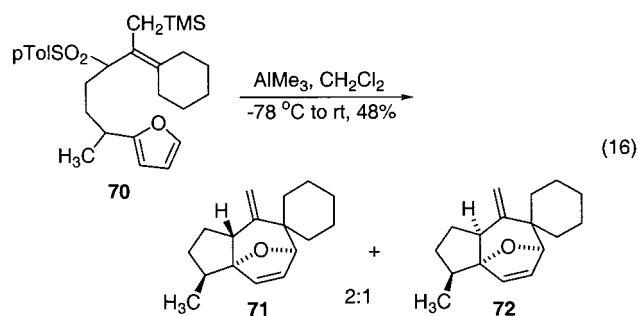


FIGURE 2. Possible transition-state structures for the cycloaddition of an allylic cation in the presence and in the absence of Lewis acid coordination to the furan.

cycloadducts **71** and **72** in 48% yield (eq 16).<sup>21</sup> In view of



the cycloaddition results of **8** (see Scheme 3), the fact that both of these cycloadducts possess a trans relationship between the oxygen bridge and the methyl substituent is noteworthy. Transition-state structures such as **73** and **74** were used to rationalize the outcome, the latter possessing severe steric interactions and thus being disfavored (Figure 3). We were able to show via NMR studies that furan itself

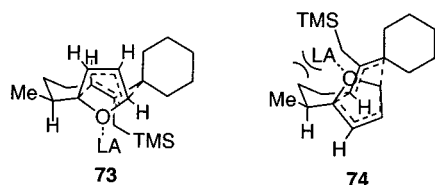
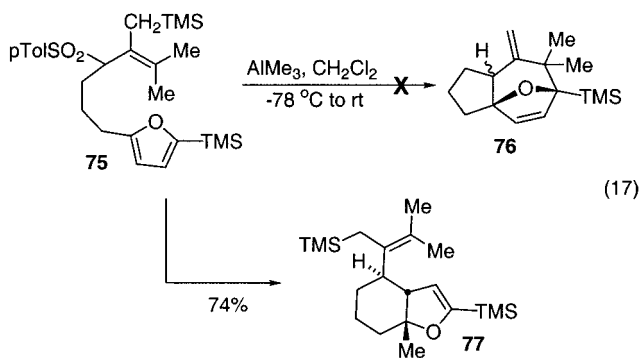


FIGURE 3. Transition-state structures rationalizing high relative stereocontrol in an intramolecular 4 + 3 cycloaddition reaction.

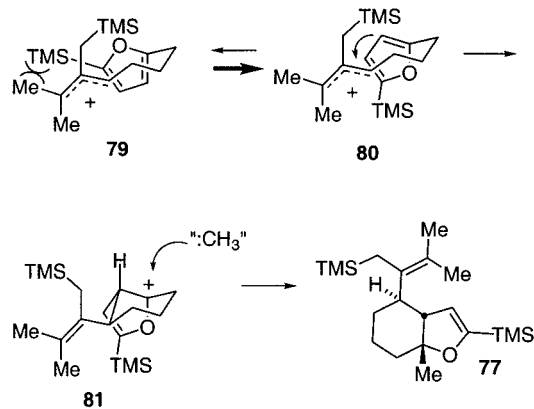
is stable in the presence of TMA at room temperature in  $\text{CH}_2\text{Cl}_2$  and apparently forms a complex with it. The actual relevance of this result to the stereochemical outcome of the cycloaddition reaction of substrates such as **70** remains unclear.

We also observed steric effects in this work which changed the course of the reaction from one of net cycloaddition to one of electrophilic addition.<sup>20,21</sup> A nice example involves the reaction of **75** with TMA. Instead of producing the 4 + 3 cycloadduct **76**, the dihydrofuran **77** was formed, a product of electrophilic addition and subsequent trapping of the resulting  $\sigma$  complex (eq 17).

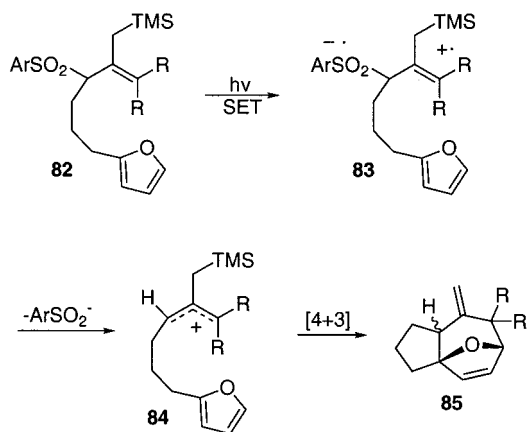


This product was produced as a single diastereomer. Scheme 8 shows a rationalization for this outcome. Allylic cation conformer **80** is preferred to **79**, thus alleviating untoward steric interactions between the TMS group on the furan ring and the allylic cation. Cyclization proceeds

Scheme 8

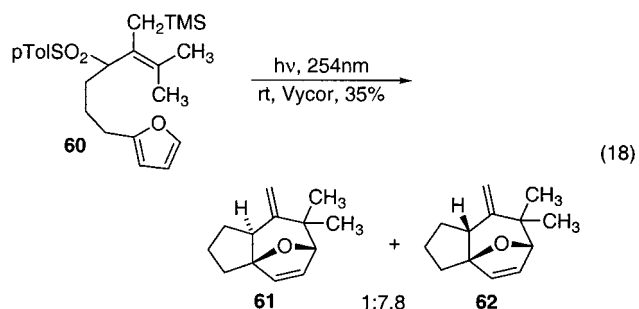


Scheme 9



to give the oxocarbenium ion **81**, which reacts with TMA or an "ate" complex thereof to afford **77**.

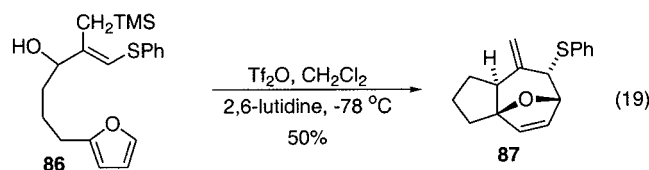
Another unique aspect of trimethylsilylmethyl allylic sulfones which was recognized was their potential as progenitors of carbocations via photochemical activation. We believed that an electron-transfer process such as that illustrated in Scheme 9 would take place upon photolysis of such substrates. This would lead to an intermediate which would ultimately eject a sulfinate anion to produce an allylic cation which would cyclize. In the event, irradiation of an acetonitrile solution of **60** at 254 nm through a Vycor filter afforded the cycloadducts **61** and **62** in 35% yield (56% based on recovered starting material) in a ratio of 1:7:8, respectively (eq 18).<sup>22</sup> Although the yield



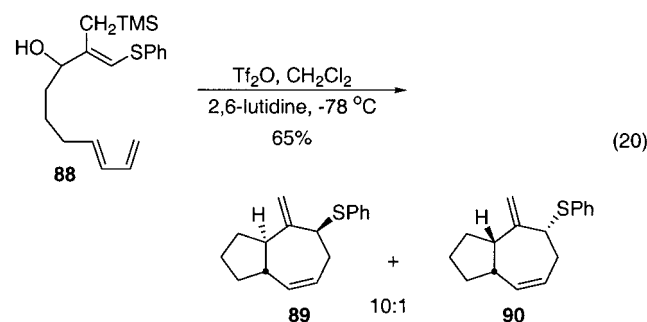
was low, the observation of high levels of simple diastereoselection was intriguing, particularly since the major diastereomer was not the same as that found in the TMA-

mediated reaction of **60** (cf. Scheme 7). Other substrates gave similar results upon irradiation, but yields were too low for the reaction to be considered synthetically useful.

While most of our work with trimethylsilylmethyl termination of the 4 + 3 cycloaddition reaction has focused on allylic sulfones, we recently investigated a small number of alcohols in order to produce cycloadducts which would be less subject to epimerization than the ketones typically produced from cycloaddition substrates such as **38**.<sup>23</sup> Both examples investigated are interesting for the high simple diastereoselectivity observed in the reactions. For example, treatment of **86** with triflic anhydride and 2,6-lutidine gave the cycloadduct **87** exclusively (eq 19). This high stereoselectivity should be compared



to the result obtained with **60** (Scheme 7), which is typical of the results we observed with sulfones of this type. More interesting was the fact that **88** afforded **89** and **90** as a 10:1 mixture of isomers in 65% yield (eq 20). Such high simple diastereoselectivity has not been observed in related systems previously.



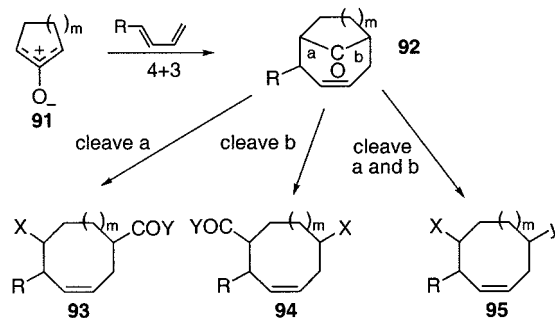
## A Special Case: Cyclic Allylic Cations and Cyclooctanoid Synthesis

Relatively early on in our work in this area, we realized that cyclic allylic cations such as **91** offered the possibility of doing not only 4 + 3 cycloadditions, but 4 + (3 + m) cycloadditions as well.<sup>24</sup> The actual course of the process depended on the ring size of the cation and our ability to excise the carbonyl group from cycloadducts such as **92** by either one- or two-bond cleavages to afford products corresponding to **93–95** (Scheme 10).

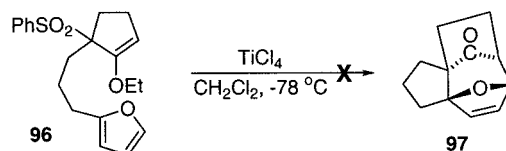
Given the large and growing number of cyclooctanoid natural products, we focused on developing a formal 4 + 4 cycloaddition using 4 + 3 methodology. Hence, we explored the intramolecular 4 + 3 cycloaddition chemistry of cyclopentenyl allylic cations.<sup>25</sup>

One of our first reactions in this area involved the treatment of sulfone **96** with  $\text{TiCl}_4$ . This resulted in complete consumption of the starting material, with little

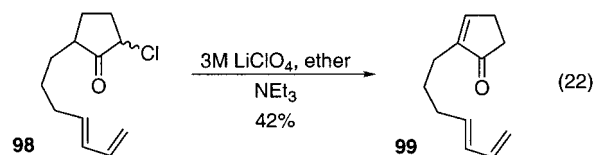
Scheme 10



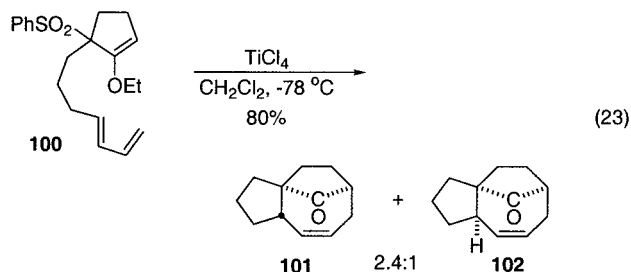
of any type of product being isolable, much less the desired cycloadduct **97** (eq 21). Another early experiment



involved treatment of the chloroketone **98** with base in ethereal 3 M  $\text{LiClO}_4$  (eq 22). This gave the elimination product **99** as the major product of the reaction. There was no sign of any cycloaddition products.

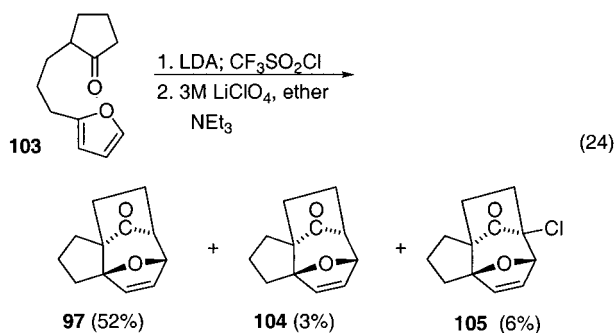


We overcame this problem by switching dienes. We thought that the cation from the allylic sulfone would be highly electrophilic and might behave better with the less nucleophilic tethered butadiene. The product would also be less strained than **97** and more likely to survive in the presence of a Lewis acid. Similarly, we anticipated that the oxyallylic zwitterion derived from a chloroketone would be less electrophilic and would react faster with a more nucleophilic diene, such as furan. In the event, treatment of **100** with  $\text{TiCl}_4$  gave cycloadducts **101** and **102** in 81% yield in a ratio of 2:4:1, respectively (eq 23).



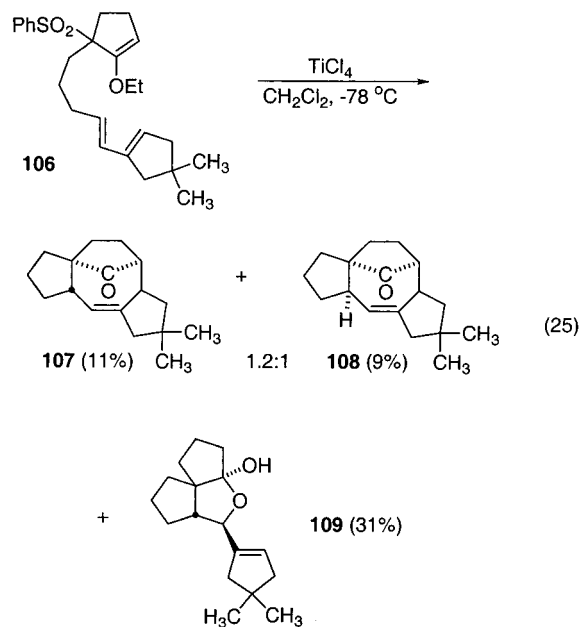
The reaction of **103** with triethylamine afforded three cycloadducts as well as some recovered starting material (6%), as shown in eq 24. The yield of expected cycloadducts was reasonable and the simple diastereoselectivity high, around 17:1 in favor of the cycloadduct **97** derived via a compact (endo) transition state. The formation of **105** presumably resulted from the presence of small





amounts of dichloroketone in the starting material. Its formation served to inspire studies on intermolecular 4 + 3 cycloaddition reactions by our group.<sup>26</sup> Elimination product was still formed in a fairly significant amount (16%). More recent studies suggest that elimination products in reactions such as these can be minimized through appropriate choice of the reaction medium. The bottom line is that 3 M ethereal lithium perchlorate does not appear to be the best solvent system for reactions of this type. A 1:1 mixture of trifluoroethanol and ether generally gives superior results.

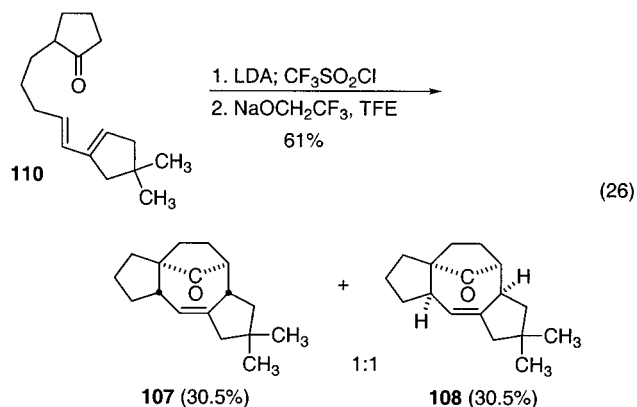
Cyclopentenyl cations derived from allylic sulfones have a potentially broad range of applications. However, as we evaluated their ability to productively afford 4 + 3 cycloadducts, we discovered some problems. A good example is shown in eq 25. Upon reaction with TiCl<sub>4</sub>,



sulfone **106** gave the cycloadducts **107** and **108** containing the 5-8-5 ring system prevalent in many cyclooctanoid natural products.<sup>27</sup> Unfortunately, the yield was only 20%, and there was basically no simple diastereoselectivity associated with the process. The major product of the reaction was the hemiacetal **109**, a 3 + 2 cycloadduct (eq 25). The formation of this compound could be rationalized via a stepwise mechanism, suggesting that increasingly substituted, and correspondingly more nucleophilic, dienes would react with the cation produced via this methodol-

ogy in a stepwise fashion, affording a variety of products, of which 4 + 3 cycloadducts might be only minor components.

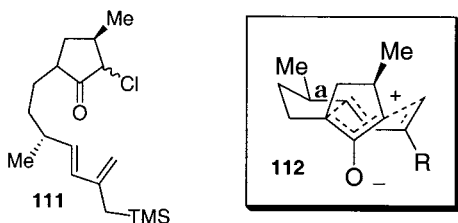
In addressing this difficulty, we decided to see if alkylated butadienes would react with a cyclopentenyl oxallylic zwitterion. The ketone **110** was assembled easily. Its chlorination and subsequent cycloaddition afforded the cycloadducts **107** and **108** in 61% yield (eq 26).<sup>27</sup> The problem was that the products were formed in a 1:1 ratio.



This was a problem that appeared to be general. With tethered butadienes, as opposed to tethered furans, no significant simple diastereoselection was observed in the intramolecular 4 + 3 cycloaddition reactions of cyclopentenyl cations. We considered this a problem with respect to applying the methodology to total synthesis. It is this situation which led to our considering methods for achieving better stereocontrol in cycloadditions of this type.

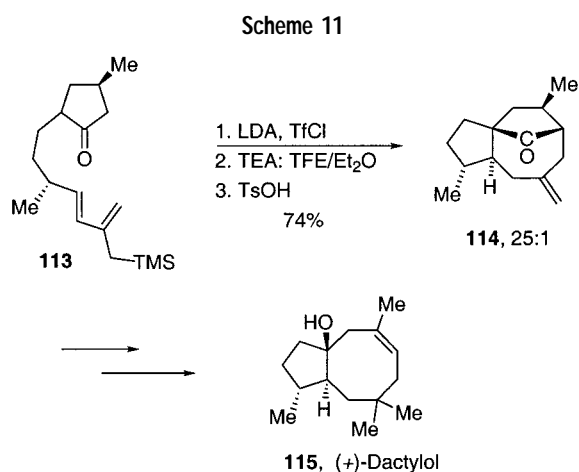
Two pieces of data were significant in our devising a system which we believed would provide for high diastereoselection. First, the result by Giguere and co-workers shown in eq 12 indicated that a dienyl substituent could have profound stereochemical consequences on an intramolecular 4 + 3 cycloaddition reaction.<sup>18</sup> Second, we knew that in intermolecular and intramolecular 4 + 3 cycloaddition reactions of cyclic allylic cations bearing a stereogenic center, the diene approached the cation from the face opposite the larger substituent at the stereocenter.<sup>28</sup> If we could combine these two stereochemical features into one molecule, we should see high diastereoselectivity. We wanted to do the study in the context of a natural product synthesis and soon found a target that was suitable.

That target was (+)-dactyol. Its successful synthesis depended on our ability to prepare **111** and enabling it to perform a stereoselective cycloaddition. We anticipated that an oxallylic zwitterion derived from **111** would cyclize preferentially via the transition state **112**. In this transition-state structure, the incipient five-membered ring is chairlike and puckered to place the methyl substituent in a pseudoequatorial orientation. The diene approaches the dienophile from the face opposite the methyl group on the cyclopentenyl cation. The conformation about the bond marked "a" is as shown. Flipping the diene 180° would result in unfavorable gauche interactions



between the diene and the methyl group as well as the methylene group in the incipient five-membered ring.

Compound **113** could be prepared relatively easily with absolute stereocontrol at the stereocenters bearing the methyl substituents. Chlorination and cycloaddition gave a mixture of products, complicated by the fact that some of the cycloadducts had apparently undergone a desilylation reaction. This was, in fact, desired, and to make analysis easier, the entire reaction mixture was treated with acid to effect complete desilylation. Proton NMR (500 MHz) analysis of crude material after these three steps showed two cycloadducts in a ratio of 25:1, the major product being that predicted by our model, the minor product remaining unidentified. This cycloadduct could be converted to (+)-dactylol (Scheme 11).<sup>29</sup>



More recent studies have shown that both stereocenters are necessary for the high diastereoselectivity to be observed. The key cycloaddition step leading to dactylol is thus a nice example of a case of double diastereoselection. Our findings provide good justification for further applications of the methodology in cyclooctanoid synthesis and for further studies of new methods to control the stereochemical outcome of such reactions. Studies of larger ring systems as dienophiles have been successful, so the range of potential higher-order cycloaddition reactions that are possible using this approach should be quite substantial.<sup>27,30</sup>

## Conclusion

The intramolecular 4 + 3 cycloaddition reaction is a powerful method for producing complex molecular systems from simple starting materials. Our research and that of others have shown that fickle allylic cation cycloaddition chemistry can be made to work quite well.

Mechanistic studies, methodological developments, and especially applications remain areas where meaningful contributions can be made in the intramolecular 4 + 3 cycloaddition arena. While other methodologies, such as metal-catalyzed processes,<sup>31</sup> may offer a superior approach to certain cycloadducts, it is unlikely that such reactions will be sufficiently general to render traditional 4 + 3 cycloaddition chemistry obsolete. More generally, for synthetic organic chemists there are aspects of many reactions, new and old, which demand investigation and refinement, to increase our collection of "useful" reactions and add to our knowledge of fundamental aspects of reactivity and mechanism. We hope our future studies in the area of 4 + 3 cycloaddition chemistry will continue to add to the knowledge base of synthetic organic chemistry in a meaningful way.

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