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Intramolecular Cycloaddition Reactions of Allylic Cations

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Contents

I. Introduction

Allylic cations represent important intermediates in the biosynthesis of many interesting and significant carbocyclic and heterocyclic systems.[1] The use of allylic cations in carbon-carbon bond forming reactions which are biomimetic has been widely investigated.[2] Cycloaddition reactions of allylic cations have also been the subject of investigation and these reactions are of growing interest.

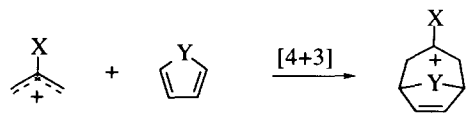
This review covers intramolecular versions of cycloaddition reactions of allylic cations. The term

"cycloaddition" is not meant to convey mechanistic information. Indeed, it is likely that many of the reactions discussed proceed in a stepwise fashion to give the "cycloaddition" products observed. Reactions which were intended to produce cycloaddition products but failed to do so will also be mentioned as the specific discussion demands. Reactions involving metal-stabilized allylic cations (e.g., pi allyl palladium) or those involving Lewis acid catalysis (e.g., many Diels-Alder reactions) are not covered. Literature coverage is through the autumn of 1996 and is meant to be comprehensive. Any omissions are unintentional and should be brought to the attention of the author.

II. Intramolecular 4+3 Cycloaddition Reactions

A. General

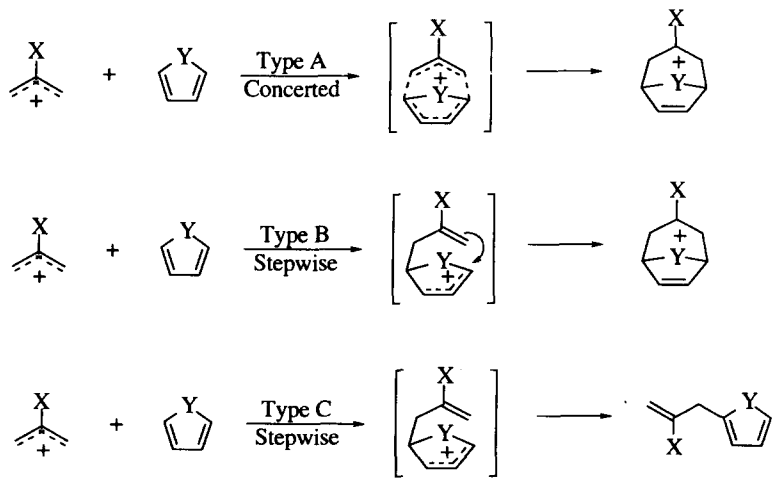
The reaction of an allylic cation with a diene to produce a seven-membered ring represents a highly convergent and potentially very useful route to such ring systems.[3] Intermolecular variants of this reaction are



(1)

well-known and research in this area is continuing. The intramolecular process has only relatively recently been accorded the attention it deserves based on its potential to produce complex polycyclic systems from relatively simple precursors.

Intermolecular 4+3 cycloaddition reactions have been classified into three types based on mechanistic considerations (Scheme 1).[3b] Concerted cycloadditions are categorized as Type A. Cycloadditions of the type



Scheme 1

B variety proceed in a stepwise fashion. Type C processes do not give cycloadducts but lead to products derived from electrophilic addition reactions.

These categorizations can also be applied to intramolecular 4+3 cycloadditions. However, subcategories based on the connectivity between the allylic cation and the diene can also be delineated. These are shown in

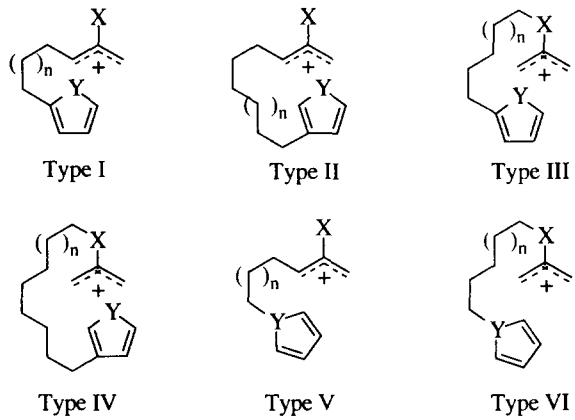


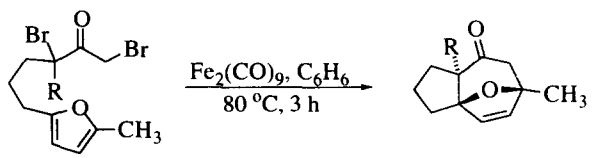
Figure 1. Types of intramolecular 4+3 cycloadditions.

Figure 1. It is also possible to devise systems in which two or more connectivity patterns are combined. For example, a transannular cycloaddition analogous to those carried out with the Diels-Alder reaction is easily imagined.[4] At this writing, only Type I intramolecular 4+3 cycloadditions have been reported.

B. Thermal Methods of Cation Generation

1. Acyclic Cations

The first example of an intramolecular 4+3 cycloaddition reaction was reported by Noyori and coworkers.[5] They reported that treatment of **1** or **2** with diiron nonacarbonyl in refluxing benzene for three



1, R=H
2, R=CH_3

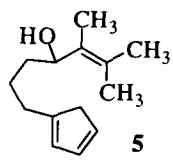
3, R=H, 41%
4, R=CH_3, 38%

(2)

hours gave **3** or **4** stereoselectively in 41% and 38% yields, respectively. No other examples of intramolecular 4+3 cycloaddition reactions using this methodology have been reported. This may be due to the rather lengthy route to the starting materials, the lachrymatory nature of α,α'-dibromoketones and the use of toxic iron carbonyls as reagents. A shorter synthesis of the precursor dibromoketones or an equivalent functional group

array would render this approach quite useful.

Another early contribution was made by Hoffmann and coworkers, who published a synthesis of norzizaene based on an intramolecular 4+3 cycloaddition approach.[6] Interestingly, this is the only published natural product synthesis which uses an intramolecular 4+3 cycloaddition reaction. Initial attempts to cyclize simple allylic alcohols such as **5** and **6** led to complex mixtures. To overcome some of the problems with these



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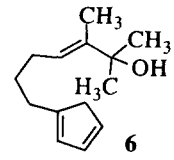
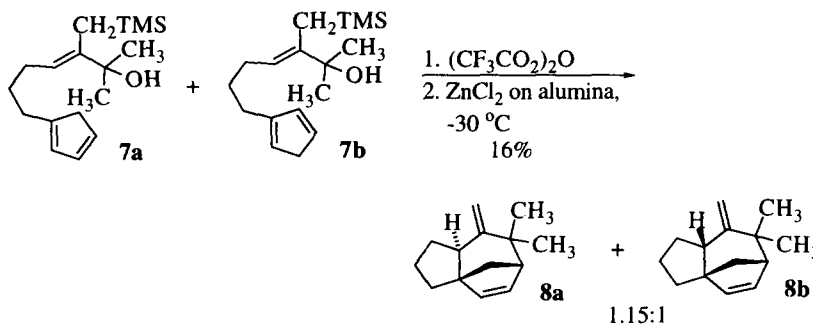


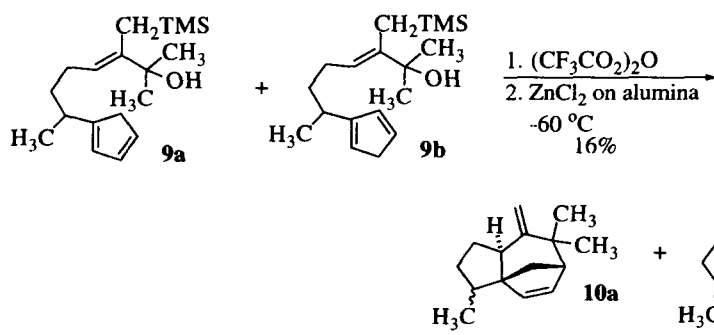
6

systems, **7** was prepared as a 44:56 mixture of **7a** and **7b**. Conversion of these compounds to the corresponding trifluoroacetates and reaction with anhydrous zinc chloride in acetonitrile at 0 °C gave a 1:1 mixture of **8a** and **8b** in 10% yield after chromatographic purification and distillation. Better results could be obtained by passing a pentane solution of **7** through a column of activity I neutral alumina coated with $ZnCl_2$ at -30 °C. Following such a procedure a 16% yield (36% based on **7a** alone) of cycloadducts **8a** and **8b** (1.15:1) was obtained.



(3)

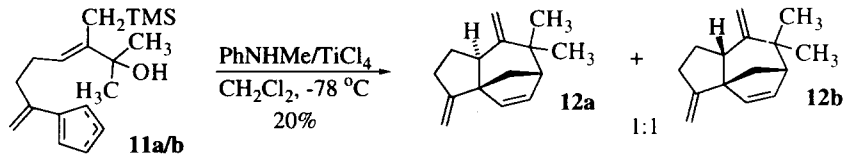
The same zinc chloride-based methodology was used to effect the cyclization of **9a/b** to give a 16% yield



(4)

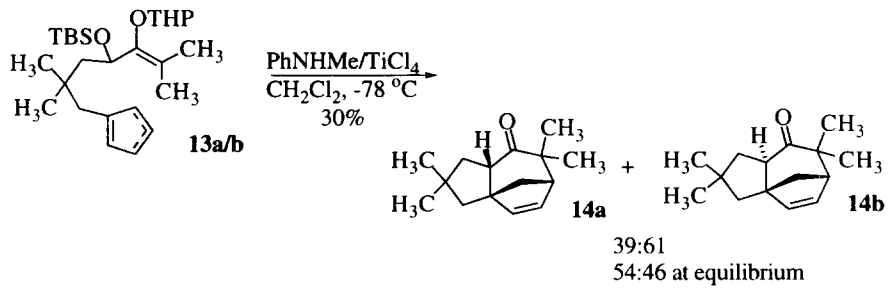
(30%, corrected) of a mixture of 4 cycloadducts **10a/b**. Neither internal asymmetric induction nor relative asymmetric induction was observed.[7]

A different ionization procedure was used to effect the closure of **11a/b**. Treatment of the alcohols **11a/b** with $TiCl_4$/PhNHMe in CH_2Cl_2 at -78 °C resulted in the formation of **12** as a 1:1 mixture of isomers in 20% yield. As expected, there was no diastereoselection. Application of this method to **7** afforded a 6% yield of the corresponding cycloadducts.[7]



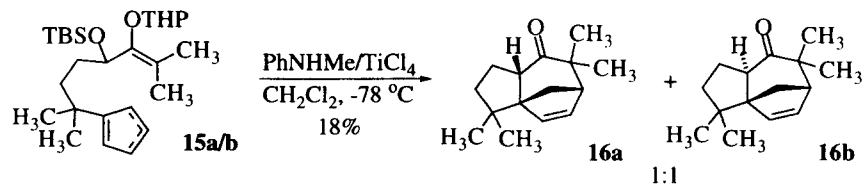
(5)

Hoffmann and coworkers also explored the use of alkoxy terminators in intramolecular 4+3 cycloadditions.[7] Treatment of silyl ether **13a/b** with $TiCl_4$/PhNHMe as per the above gave a 30% yield of **14a**



(6)

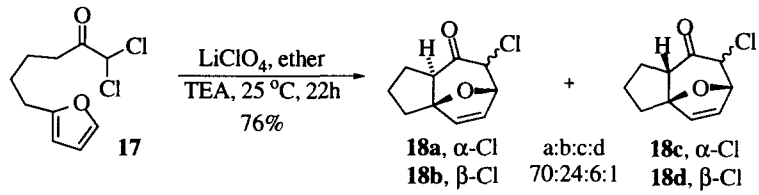
and **14b** in a ratio of 39:61. The equilibrium ratio of these epimers was found to be 54:46, suggesting that the cycloaddition occurred under kinetic control. In a similar fashion, an 18% yield of **16a** and **16b** was produced from **15** along with two unknown compounds.



(7)

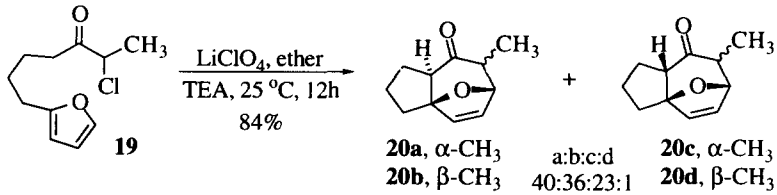
While the cycloadduct yields in these examples are not very good, the chemistry does lead to complex carbocyclic structures concisely. Because of the problems associated with cyclopentadienes involving valence isomerization and reactivity, it is difficult to judge the merits of the methods used to generate the allylic cations. It is likely that yields would improve with substrates containing dienes which are less prone to side reactions than cyclopentadienes.

Intramolecular 4+3 cycloaddition chemistry which is impressive in terms of yield as well as stereoselectivity was introduced by Föhlisch and coworkers.[8,9] Stirring an ethereal solution of **17** in the presence of excess of $LiClO_4$ and triethylamine at room temperature gave a 76% yield of 4 cycloadducts **18** in a



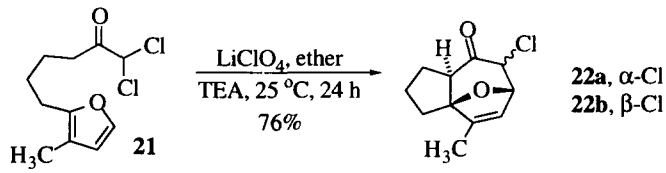
(8)

ratio of 70:24:6:1. If one only considers angular stereochemistry, the simple diastereoselection is excellent (94:6). Interestingly, the reaction of **19** also gave an excellent yield (84%) of 4 cycloadducts **20** but with a *trans:cis* selectivity of only 76:24. Treatment of the product mixture with base gave a 67:33 mixture of **20a** and **20b**, suggesting the cycloaddition reaction was kinetically controlled.



(9)

Similarly, **21** could be converted to a mixture of **22a** and **22b** in a ratio of 70:30 after 3 hours but in a ratio of 98:2 after 53 hours in an isolated yield of 70%. It is likely that under these reaction conditions an isomerization took place at C-7 to convert **22b** to the thermodynamically more stable **22a**. It should be noted that throughout the process the angular stereochemistry did not change.

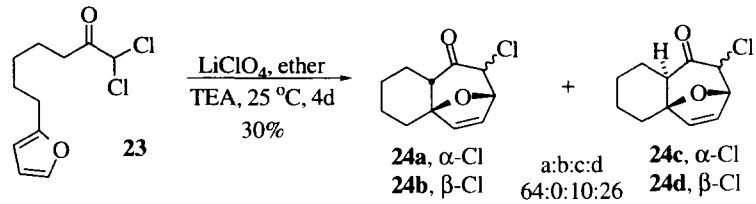


(10)

The dichloroketone **23** gave rise to three products **24** (a,c and d) in a ratio of 26:10:64 in 30% yield. Not surprisingly, the additional degree of freedom introduced by increasing the length of the tether resulted in a lower yield of cycloadduct. The stereochemical results reflect the decreased ring strain in the six-membered ring vis-à-vis the five-membered ring in cycloadducts such as **22**.

Some limitations exist with respect to this methodology. Chloroketone **25** gave only a 10% yield of the expected cycloadduct. Diene **26** apparently reacted to give a reasonable yield of cycloadducts of as mixture of a number of stereoisomers only two of which could be isolated and then only in low yield. The diene **27** gave a

low yield of a complicated reaction mixture resulting from stereoisomerism and the formation of elimination products.



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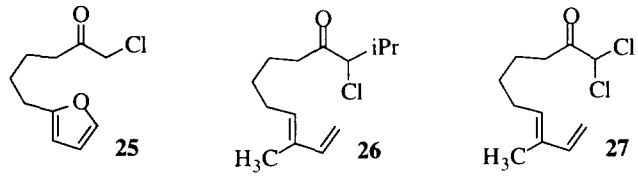
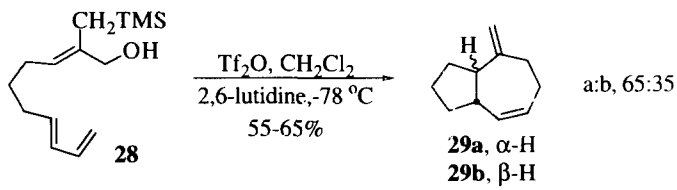


In most of the above cycloaddition processes, the stereochemistry of the allylic cation was undefined, though it could be inferred through stereochemical analysis of the cycloadducts and precedent in the intermolecular 4+3 cycloaddition reactions. However, all the successful reactions discussed up to now involved the use of the rigid cisoid dienes, furan or cyclopentadiene. Ring strain and steric effects associated with the use of these dienes make stereochemical results difficult to interpret.

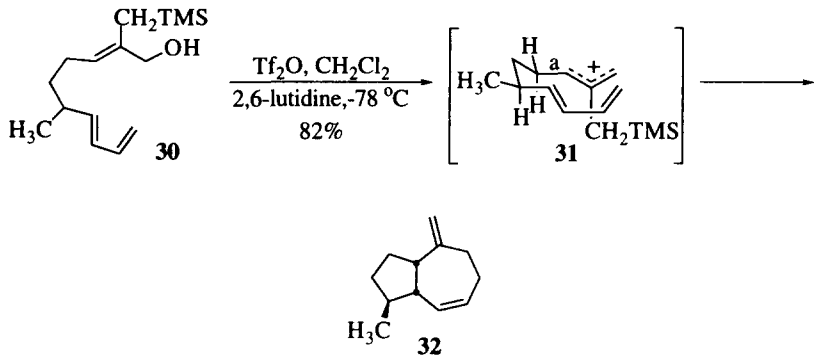
This problem has been addressed by Giguere, who demonstrated that allylic cation configuration can have a dramatic effect on the course of an intramolecular 4+3 cycloaddition reaction.[10,11] The diene **28**, prepared in 7 steps from 1,5-pentanediol, gave a 55-65% yield of cycloadduct **29** in a *trans:cis* ratio of 65:35 upon treatment with triflic anhydride in dichloromethane at -78 °C under conditions of high dilution. It is very likely that the reaction is kinetically controlled.



(12)

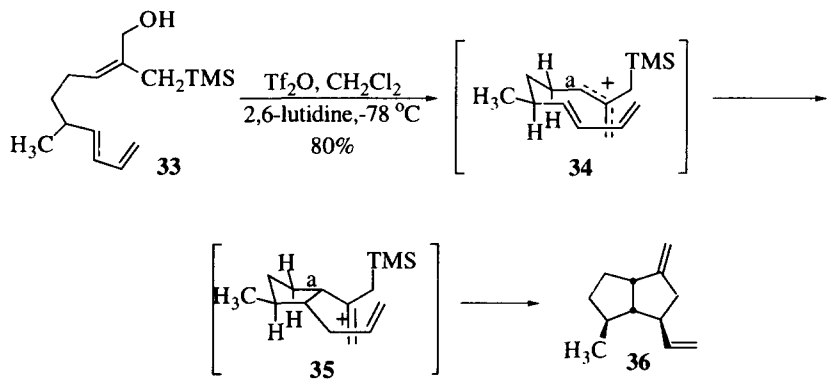
More significant was Giguere's report of the dramatic effect of allylic cation stereochemistry on the course of the cycloaddition reaction.[11] The isomers **30** and **33** were both readily available from citronellol. Treatment of **30** with Tf_2O under high dilution conditions gave an 82% yield of 4+3 cycloadduct **32** in a ratio of 92:5:3. The major isomer is shown. The stereochemistry of this reaction can be rationalized by proposing a concerted 4+3 cycloaddition of the allylic cation **31**, relative stereocontrol being dictated by conformational preferences of the reacting system. For example, in the transition state structure, the conformational preference about bond "a" is controlled by avoidance of 1,3-allylic strain.[12] The hydrogen prefers to be synplanar to the bulky

trimethylsilylmethyl group. Similarly, the conformation about the diene-tether bond is mediated by a preference



Scheme 2

of the diene to avoid gauche interactions with the tether and the methyl substituent. The resulting structure has a decided and favorable energetic bias relative to alternatives which would also lead to 4+3 cycloadducts.

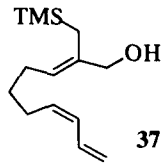


Scheme 3

Similar conformational criteria can be applied to **33**. However, in this case the allylic termini of the cation **34** are sterically prohibited from simultaneously interacting with both ends of the diene. Stepwise carbon-carbon bond formation leads to an intermediate cation **35** which is rapidly trapped intramolecularly to give the 3+2 cycloadduct **36** in 80% yield in a ratio of 93:7. The major isomer is shown. This study clearly demonstrated that high levels of regiochemical control and stereochemical control are available in both the intramolecular 4+3 and 3+2 cycloaddition reactions of allylic cations.

The importance of diene geometry in intramolecular 4+3 cycloadditions has also recently been addressed by Giguere and coworkers.[13] Neither **37** nor **38** led to 4+3 or 3+2 cycloadducts upon treatment with triflic anhydride. Only electrophilic addition and elimination products were isolated.

Harmata and Gamlath took advantage of the "chameleon" nature of sulfones to exploit that functionality in intramolecular 4+3 cycloadditions.[14] For example, treatment of **39** with 1.1 equivalents of $TiCl_4$ in CH_2Cl_2



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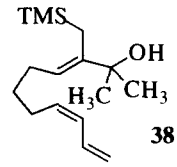

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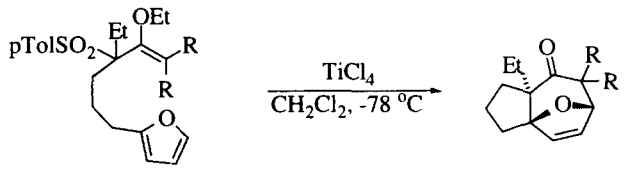
led to rapid consumption of starting material with concomitant formation of **40** as a single isomer, not surprising in view of precedent from the work of others (*vide supra*). In a similar fashion, **42** could be obtained from **41**.

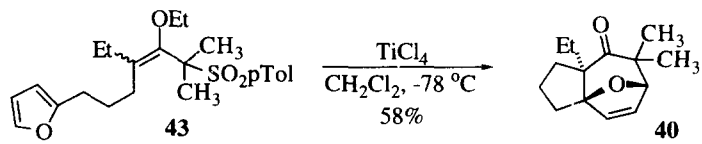


(13)

39: R=CH_3
41: R=-$(CH_2)_5$-

40: R=CH_3, 74%
42: R=-$(CH_2)_5$-, 66%

In order to answer questions concerning the stereochemistry of the putative allylic cations generated in these reactions, these investigators prepared both isomers of **43** and found that both gave cycloadduct **40** in 58% yield upon treatment with $TiCl_4$.[15] The lower yield of cycloadduct in these cases may have been due to the less efficient generation of the intermediate cation or to the formation of unidentified side products.

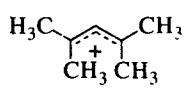


43 **40**

(14)

Regardless, these data show that there is no significant impact of stereochemistry in the allylic cation progenitors on the yield and diastereoselection of the intramolecular 4+3 cycloaddition process.

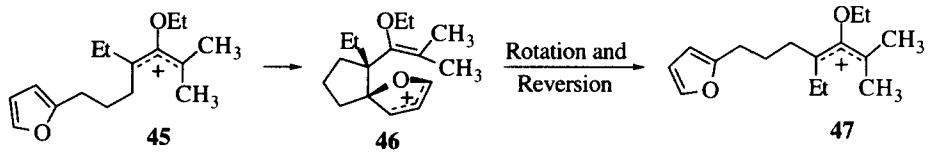
In order to rule out the possibility that the cations were converging to a single (or unique mixture of) cationic intermediate(s) through some isomerization process, Harmata and coworkers examined relative stereocontrol in this reaction.[17] With the heavily substituted allylic cations generated in this reaction, one could imagine an isomerization process taking place. For example, the activation energy for rotation in **44** has been



44

determined to be 16 kcal/mol.[16] It was further considered possible that reactions such as those illustrated in equations 15 and 16 might be taking place to scramble the stereochemistry of the intermediate cations.

To address these questions, cycloaddition substrates were prepared with independent stereochemical markers. Should cation stereochemistry and relative diastereoselection be related, it was anticipated that different mixtures of diastereomeric products would be obtained in the event that stereochemical leakage were slower than cycloaddition.[17]



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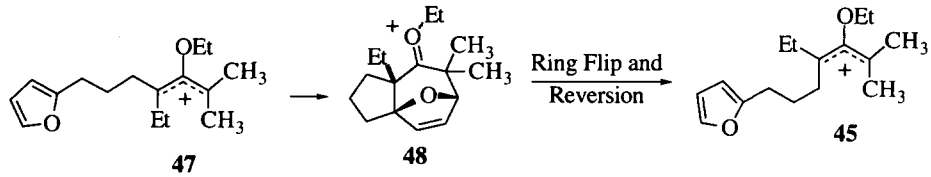
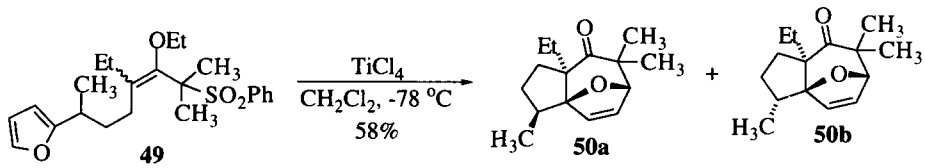


(16)

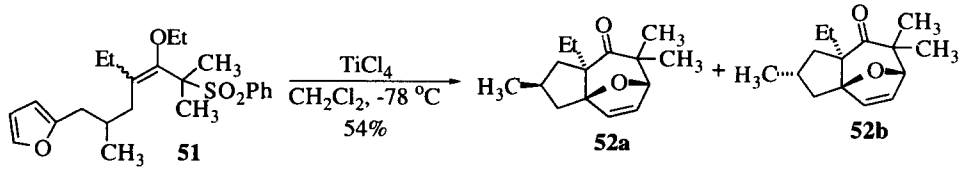
Separate treatment of the E and Z isomers of sulfone **49** with $TiCl_4$ under typical reactions conditions gave cycloadducts **50a** and **50b** in a ratio of 60:40 from (Z)-**49** and 71:29 from (E)-**49**. This result suggested that the intermediates generated from the individual stereoisomers of **49** maintained at least some of their stereochemical identity during the course of the reaction. Cycloaddition was faster than equilibration.



(17)

From (Z)-**49** : 60:40
From (E)-**49** : 71:29

A stronger case for this conclusion could be made by examining the cycloaddition of **51**. In this case, (Z)-**51** gave a 1:1 mixture of **52a** and **52b** while (E)-**51** led to a 74:26 mixture of the same isomers.

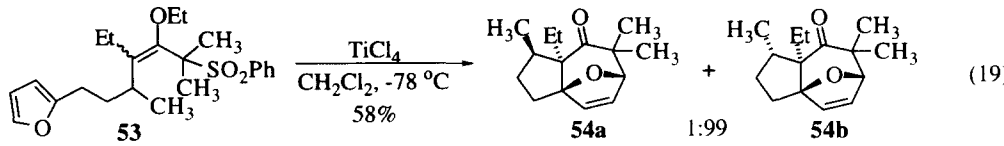


(18)

From (Z)-**51** : 50:50
From (E)-**51** : 74:26

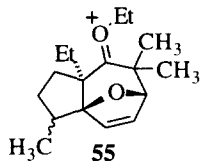
Interestingly, both isomers of **53** led to the same product **54b** as a single stereoisomer. This represented

only the second case of excellent relative diastereoselection in an intramolecular 4+3 cycloaddition reaction.



(19)

It is not a simple task to rationalize the stereochemical outcomes of the preceding reactions. The reactions appear to be kinetically controlled. Treatment of the cycloadducts under reaction conditions used to effect cycloaddition resulted in their recovery with no change in the stereochemistry. It is likely, however, that the initial products of the cycloaddition reaction are oxocarbenium ions such as **55** but no report of their generation and subsequent reactions has been made.



Harmata and coworkers have offered a rationalization for the preferential formation of **54a**.[17b] Two transition state structures for cycloaddition are possible from each of the two isomers of **53**. These are shown in Figure 2. For the allylic cation obtained from (E)-**53**, two conformers, **56a** and **56b**, represent the two possible transition state structures. While both would lead to a trans ring fusion, only **56b** leads to the observed product. It was proposed that 1,3-allylic strain in **56a** disfavored its participation in product formation. The cation derived from (Z)-**53** could cyclize via either **57a** or **57b**. Models suggested that the steric interaction indicated in **57b** was significant and would thus disfavor product formation via this structure. It was therefore concluded that steric effects operate in the same direction in both systems, leading to the same, single product from both allylic cation stereoisomers.

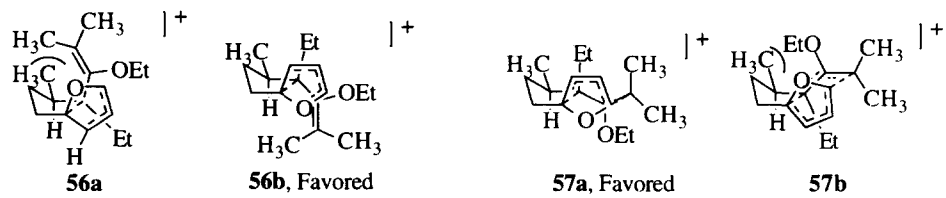
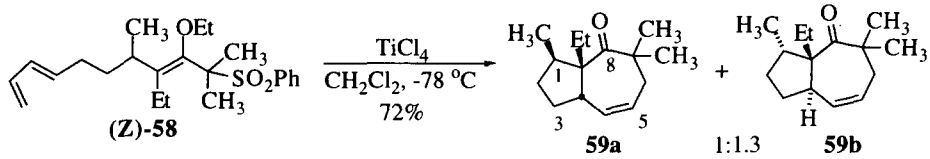


Figure 2. Proposed TS structures for the 4+3 cycloaddition reactions of (E)- and (Z)-53.

As a final test of stereochemical integrity, a system lacking a furan cation trap was examined.[17b] The results obtained supported the conclusion which had already been drawn. For example, treatment of (Z)-**58** with $TiCl_4$ gave a 72% yield of **59a** and **59b** in a ratio of 1:1.3. Complete relative diastereocontrol between C-1 and C-8a was observed but simple diastereoselection was essentially nonexistent. The *trans* isomer was

preferred, as was the case in a reaction reported by Giguere (equation 12).[10] This result was rationalized on the basis of the steric arguments presented above. In this case, however, the factor which led to *trans* ring fusion



(20)

in the formation of cycloadducts such as **54**, namely the oxygen bridge, is absent. There is only a small preference for an exo approach of the diene to the dienophile and the transition state structure **60b** is thus preferred on slightly to its isomer **60a**. This result supports the idea of a concerted cycloaddition, but the authors do not suggest this as being definitive.

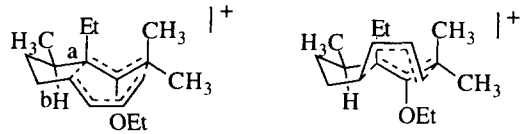
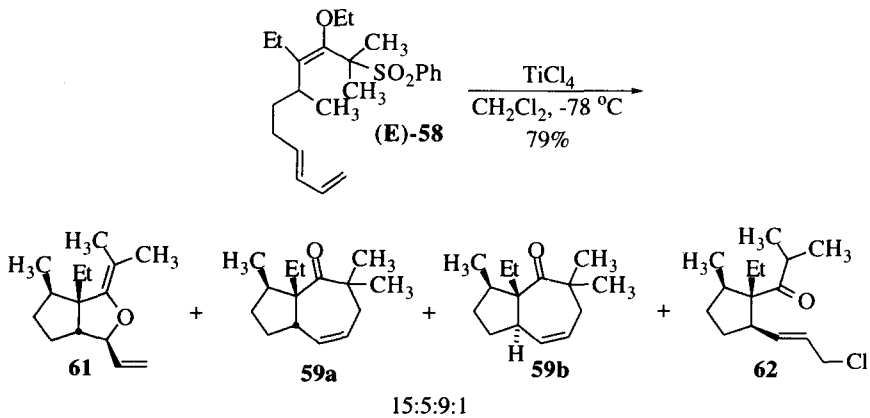


Figure 3. Proposed TS structures for the 4+3 cycloaddition reaction of (Z)-58.

Interestingly, treatment of (E)-**58** with $TiCl_4$ led to four products **61**, **59a**, **59b**, and **62** in a ratio of 15:5:9:1 in a total yield of 79%. The major product was **61**, a 3+2 cycloadduct presumably formed via a stepwise process since a concerted process of this type is thermally forbidden. The two 4+3 cycloadducts were

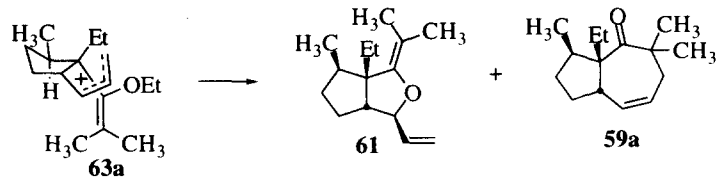


(21)

formed in a ratio of 1:1.8, suggesting that they arose from a path different from the cycloadducts derived from (Z)-**58**. Of course, the presence of the electrophilic addition product **62** strongly suggests a stepwise process was involved in this reaction.

These results have been explained by invoking many of the arguments already presented so that an

intermediate for the reaction would be represented by **63a** or **63b**, formed because simultaneous overlap of the



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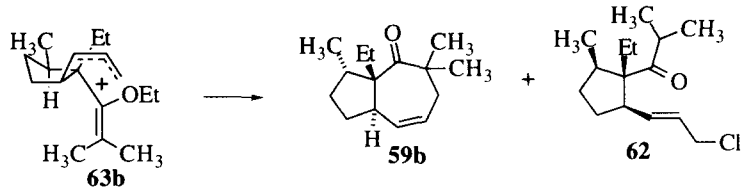
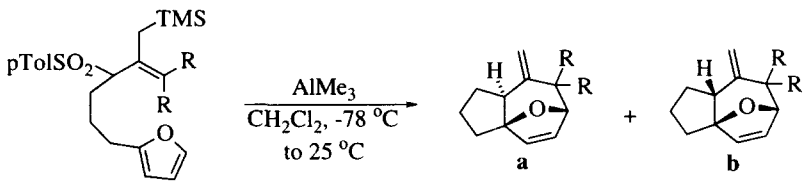


(23)

termini of the diene and dienophile (*i.e.*, allylic cation) is not possible. Intermediate **63a** closes to **59a** and the major product **61**. In **63a**, the oxygen of the enol ether is disposed very close to the secondary allylic carbocation resulting in rapid ring closure and dealkylation. Formation of **59a** is competitive. With **63b**, the formation of a 3+2 cycloaddition adduct would result in a high-energy, *trans*-fused bicyclo[3.3.0]octane ring system. Instead, intermolecular trapping with chloride occurs to give **62**, in addition to the formation of **59b**.

Citing problems sometimes associated with alkoxyallylic sulfones, Harmata and Herron have also investigated trimethylsilylmethyl allylic sulfones as progenitors of allylic cations for intramolecular 4+3 cycloaddition reactions.[18] For example, treatment of a dichloromethane solution of **64** with 1-2 equivalents of



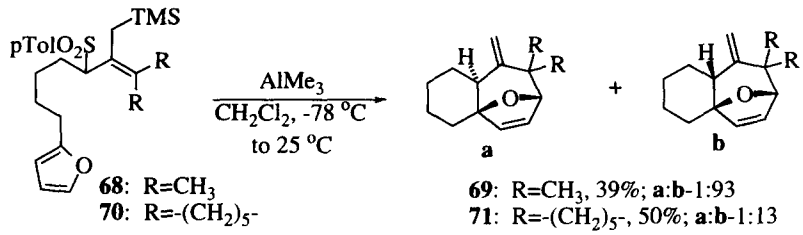
64: R=CH_3
66: R=-$(CH_2)_5$-

65: R=CH_3, 71%; **a**:**b**-1.7:1
67: R=-$(CH_2)_5$-, 71%; **a**:**b**-1.7:1

(24)

trimethylaluminum at -78 °C followed by warming to room temperature, resulted in the formation of cycloadducts **65a/b** as a 1.7:1 mixture in 71% yield (77%, corrected). Essentially the same result was obtained for **66**.

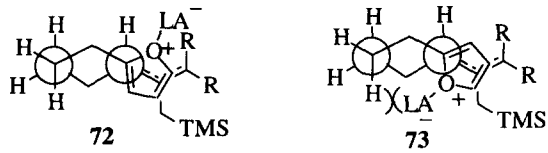
The formation of six-seven fused ring systems was also demonstrated with this methodology. Sulfone **68** gave cycloadduct **69** but only in 39% yield (46%, corrected). The low yield can be attributed to the extra degree of freedom afforded by the longer tether. However, the simple diastereoselection observed in this case and in the cyclization of **70** is noteworthy and without precedent. A possible, but speculative explanation might be that complex formation between the furan the the trimethylaluminum occurs. Such complexation would



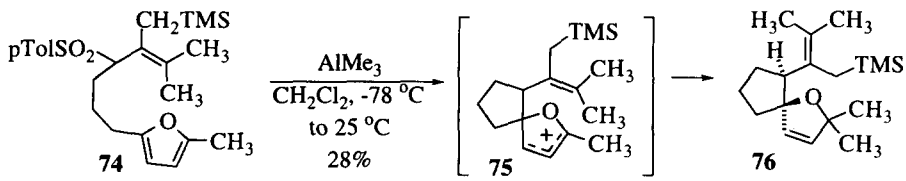
68: R=CH_3 **69**: R=CH_3, 39%; **a**:**b**-1:93
70: R=-$(CH_2)_5$- **71**: R=-$(CH_2)_5$-, 50%; **a**:**b**-1:13

(25)

change the steric features of the furan considerably and would favor a transition state structure resembling **72** over one such as **73**, in which the oxygen/Lewis acid complex is oriented in a pseudoaxial direction. No evidence for this proposition has yet been presented.



Two interesting examples of type C cycloadditions (no cycloaddition at all!) were published in the first report of this chemistry.[18a] Treatment of **74** with $AlMe_3$ resulted in the formation of the spiro ether **76** in 28% yield. Presumably, oxocarbenium ion **75** was formed after electrophilic addition to the furan ring. Ring closure was slowed due to the presence of the methyl group on the furan and delivery of a methyl group from $AlMe_3$ was competitive. This reaction was not optimized and this fact, coupled with the high degree of simple diastereoselection, makes it worthy of further study.

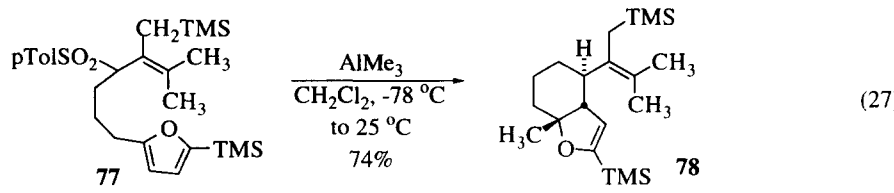


(26)

A different reaction path was seen with **77**. Treatment with $AlMe_3$ led to the formation of **78** in 74% yield with complete stereocontrol. A plausible mechanism is shown in Scheme 4. Apparently, steric effects preclude ring closure to 4+3 cycloadducts and may even direct electrophilic attack "ortho" to the tether-bearing carbon of the furan ring.

Another approach to solving problems with alkoxyallylic sulfones was based on the concept that a heteroatom (oxygen, nitrogen or sulfur) might be incorporated into the substrate to assist in the departure of the sulfone. Harmata and coworkers demonstrated the validity of this concept and went on to investigate other means of generating allylic cations stabilized by heteroatoms.

The heteroatom used initially by the Harmata group was sulfur.[19] The stereoisomeric sulfones (E)- and (Z)-**81** were prepared and subjected to treatment with $TiCl_4$. While the E isomer resulted in only a 12% yield



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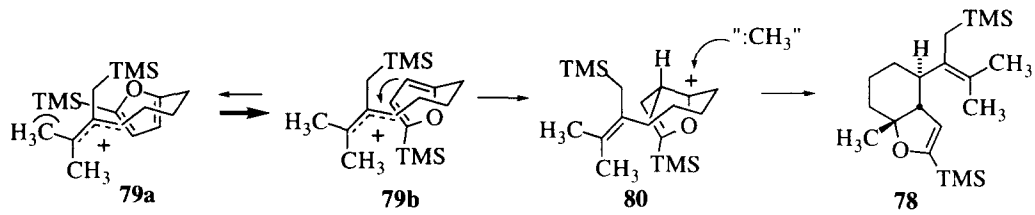
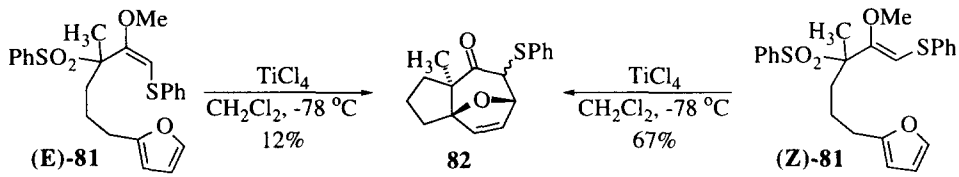


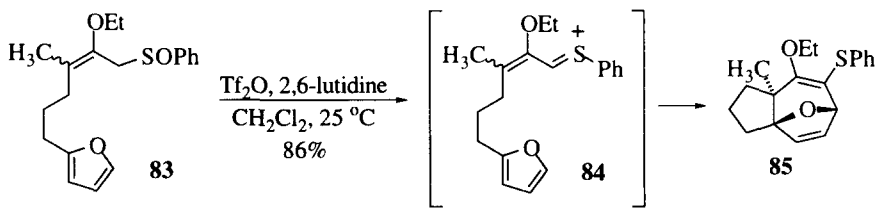
Scheme 4

of cycloadduct **82** as a mixture of epimers at C-7, the Z isomer gave the same compounds in a yield of 67%. Presumably, an intermediate vinylthionium ion is produced which cyclizes to give the observed product. The problems in the cyclization of (E)-**81** were ascribed to chelate formation with the Lewis acid.



(28)

Since the synthesis of (Z)-**81** always resulted in the formation of significant amounts of (E)-**81**, a different route to the cycloaddition intermediate in the reaction was sought. This resulted in the development of a tandem Pummerer/4+3 cycloaddition sequence.[19] For example, treatment of a 1:1 E/Z mixture of sulfoxide **83** with triflic anhydride and 2,6-lutidine in dichloromethane at room temperature resulted in the formation of cycloadduct **85** in 86% yield. The triene **86** gave cycloadduct **87** as a 1:1 mixture of stereoisomers in 53% yield under similar conditions.



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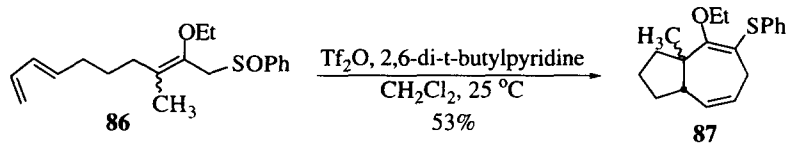
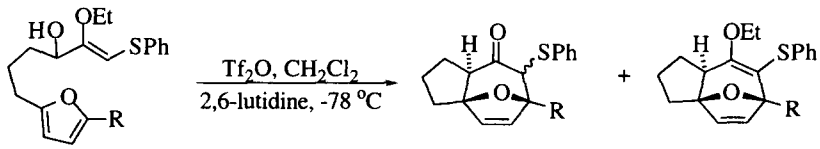


(30)

Quite recently, Harmata and Jones reported another route to vinylthionium ions for use in intramolecular 4+3 cycloaddition reactions.[20] Treatment of the readily accessible alcohol **88** with triflic anhydride and 2,6-lutidine in dichloromethane at -78 °C gave the ketone **89** and enol ether **90** in 49% and 37% yield, respectively. Interestingly, the alcohol **91** gave the cycloadduct **92** in 48% yield. Note that this result differs from that obtained with sulfone **74** in which no cycloadduct was formed. The yield of cycloadduct, however, is substantially lower than the overall yield of cycloadducts from **88**, indicating the importance of substituent effects in this reaction.



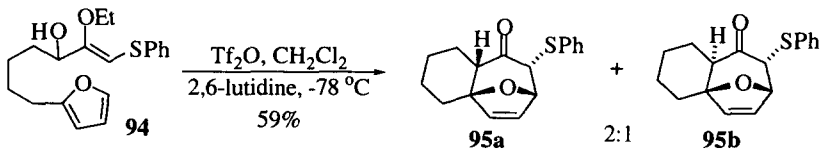
88: R=H
91: R=CH_3

89: R=H, 49%, 1:1
92: R=CH_3, 48%, 1.8:1

90: R=H, 37%
93: R=CH_3, 0%

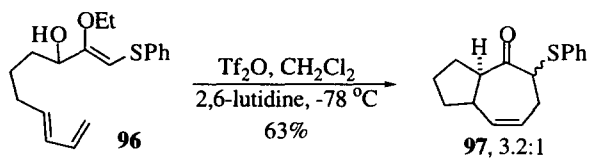
(31)

The preparation of a six-seven fused ring system using this methodology was reasonably successful. Alcohol **94** led to cycloadduct **95** in 59% yield. As in the case of **91**, only ketonic products were isolated. The reasons for this were not discussed.



(32)

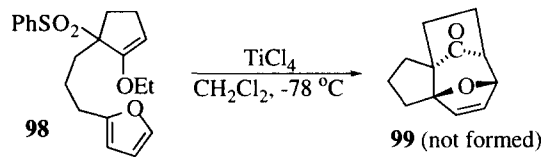
The triene **96** was cyclized to ketone **97** in 63% yield, though the precise stereochemistry of the cycloadducts was not defined. An attempt to use thiophene in the cycloaddition reaction led only to Friedel-Crafts alkylation product with no evidence of 4+3 cycloaddition.



(33)

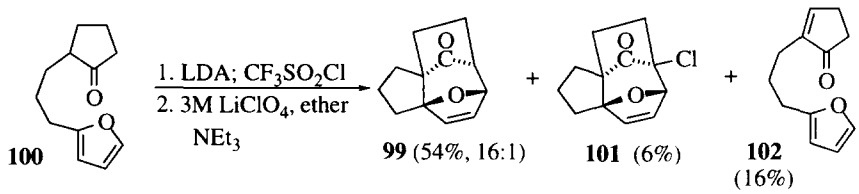
2. Cyclic Cations

The first example of a non-photochemical intramolecular 4+3 cycloaddition reaction involving a cyclic cation was reported by Harmata and coworkers.[21] Because the conversion of **98** to **99** was not successful, they adopted the methodology of Föhlisch and demonstrated the utility of the method for the intramolecular cycloaddition of cyclic oxyallylic cations.



(34)

For example, treatment of the readily available ketone **100** with LDA followed by triflyl chloride gave a chloroketone which was stirred in 3M $LiClO_4$ in the presence of 3 equivalents of triethylamine to give cycloadduct **99** in 54% yield, cycloadduct **101** in 6 % yield, 16% of the enone **102** and recovered starting material (6%). Parallel results were observed with ketones **103** and **106**.



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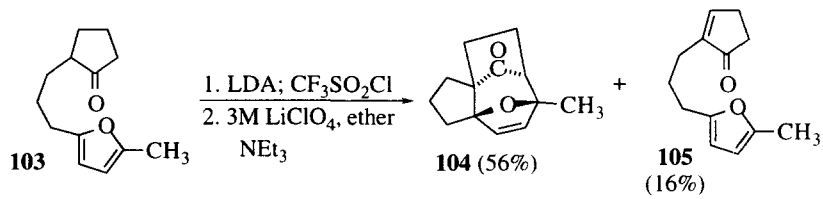

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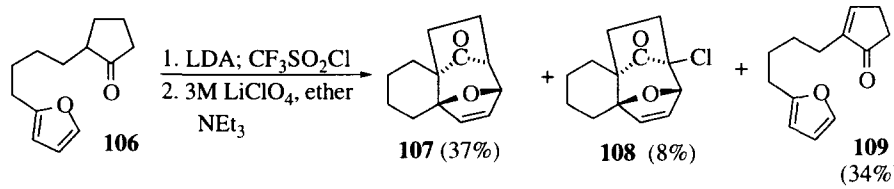
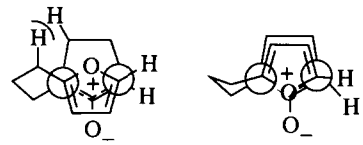


(37)

The cyclopentenyl oxyallylic cations which are intermediates in these reactions are particularly well-suited for deprotonation, hence relatively large amounts of elimination products were observed.[22] With **106** the

entropic demands on the cycloaddition increased and the relative amount of elimination product increased as well. The chlorinated cycloadducts **101** and **108** probably arose due to dichlorination of the starting material and this also accounts for the recovered starting material observed in these reactions. The successful cycloaddition of **103** is noteworthy given the failed cycloaddition attempt with **74**.

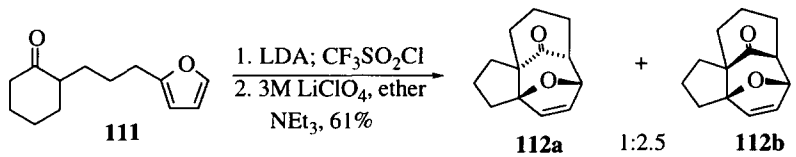
The high degree of simple diastereoselection observed in these cycloaddition reactions is in accord with precedent set by studies of related intermolecular processes.[23] Two approaches of the diene to the dienophile are possible: endo or exo. These are shown for the oxyallylic cation derived from **100** in Figure 4. The endo approach is preferred since it minimizes both dipole repulsion and untoward steric interactions.



110a: endo (preferred) **110b**: exo

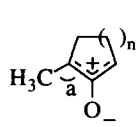
Figure 4. Endo and exo approaches in the cycloaddition of 100.

Larger ring oxyallylic cations were also examined. Using thé two step protocol described for **100**, cyclohexanone **111** was converted to a 1:2.5 mixture of cycloadducts **112a/b** in 61% yield. No elimination products were formed. Interestingly, the major stereoisomer from this reaction was that derived from an exo approach of the diene to the dienophile. This is in contrast to the corresponding intermolecular reaction.[23] The

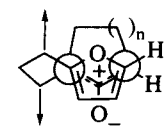


111 **112a** 1:2.5 **112b** (38)

authors demonstrated that the reaction was under kinetic control. They proposed that the change in stereochemistry was due to a change in relative strain in the exo and endo transition states as the ring size of the cyclic oxyallylic cations increased from 5 to 6. Molecular mechanics calculations indicated that for the model compound shown in Figure 5, the angle "a" decreased with increasing ring size. The consequence is that for a



n=1, a=127.8°
n=2, a=125.4°
n=3, a=121.7°
n=4, a=122.7°



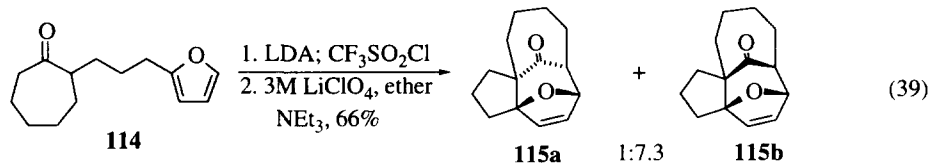
113

Figure 5. Change in "a" as a function of ring size.

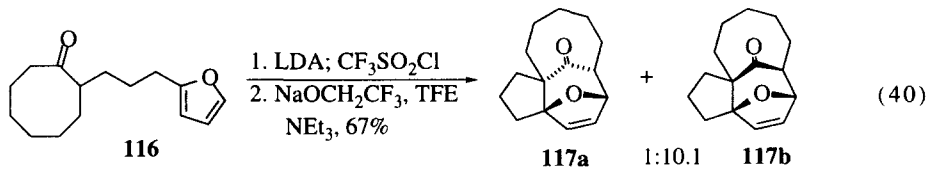
concerted cycloaddition, an increase in ring size of the oxyallyl should result in an increase in strain for the endo cycloaddition transition state as the two methylene groups are "pulled" in opposite directions as shown in **113**.

While this proposition received some circumstantial support in other cycloadditions (*vide infra*), it has not been fully scrutinized.

Cyclization of ketone **114** likewise resulted in a preference for the exo cycloadduct **115b**. Some difficulty was reported for the cyclization of the cyclooctanone **116**. The usual reaction conditions were not successful, only a 17% yield of cycloadduct **117a/b** being obtained. However, treatment of the appropriate chloroketone with sodium trifluoroethoxide in trifluoroethanol (25 °C to reflux) gave a 67% yield of

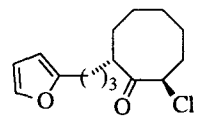


114 **115a** 1:7.3 **115b** (39)



116 **117a** 1:10.1 **117b** (40)

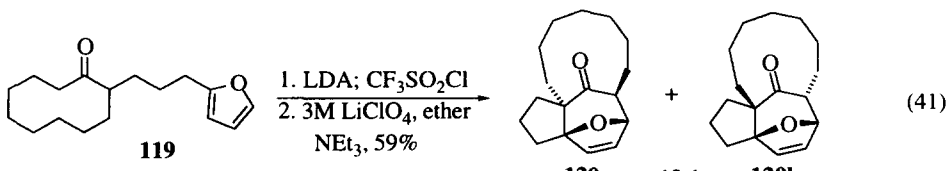
cycloadduct **117** as two stereoisomers in a ratio of 10.1:1. Again and as expected, the exo cycloadduct was preferred. The problems associated with the cycloaddition of this substrate were attributed to the corresponding chloroketone **118** which was expected (though not proven) to have the stereochemistry shown based on literature precedent.[24] The conformation of this molecule was predicted to be such that both of the hydrogens



118

alpha to the carbonyl were parallel to the carbon-oxygen double bond. A conformational change would be necessary to produce a structure which could be deprotonated to give the enolate precursor of the oxyallylic cation. The use of a stronger base and higher reaction temperatures were thus anticipated to lead to a successful reaction, as was observed.

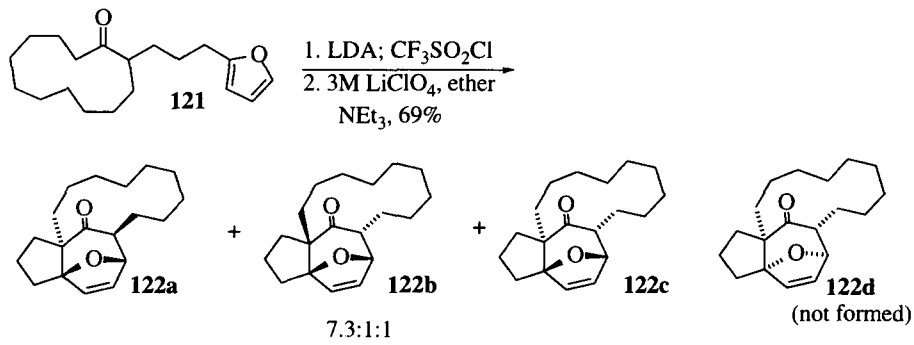
Larger ring systems worked well using the $LiClO_4$ method. Cyclodecanone **119** was cyclized following



119 **120a** 19:1 **120b** (41)

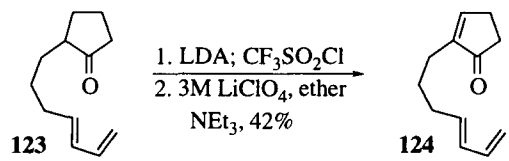
chlorination to give cycloadduct **120** in 59% yield (67%, corrected) with a 19:1 ratio of isomers. Although the origin of the stereochemistry in this reaction was originally questioned,[21b] work by Hoffman and coworkers suggests that the explanation one would derive based on the intermolecular precedent is applicable.[25] The reaction proceeds through a sickle-shaped oxyallylic cation via an exo transition state.

The cyclododecanone **121** likewise underwent smooth cycloaddition to give **122a**, **122b**, and **122c**, in 69% overall yield (72%, corrected) in a ratio of 7.3:1:1, respectively. All of the cycloadducts were stable to the reaction conditions and to treatment with stronger base. It was concluded that the cycloadducts **122a** and **122b** were obtained via a sickle-shaped oxyallylic cation, with **122a** arising from an exo approach of the cation to the diene. Cycloadduct **122c** was considered to arise from a W-shaped cation via an endo approach. The fact that **122d** was not formed supported this conjecture.



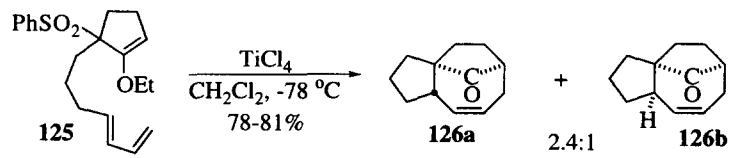
(42)

Attempts to apply the Föhlisch method to a substrate containing a substituted butadiene resulted only in elimination (equation 43). However, the authors found that the relatively less nucleophilic butadiene would



(43)

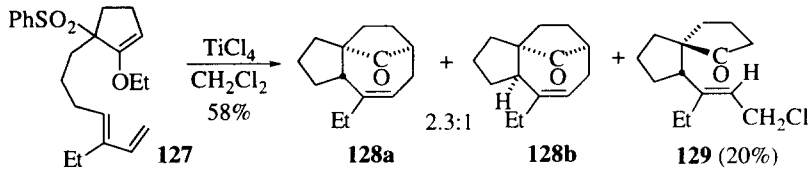
participate in a cycloaddition reaction with a more reactive cation. Thus, treatment of sulfone **125** with $TiCl_4$ resulted in the formation of cycloadduct **126** in about 80% yield as a 2.4:1 mixture of stereoisomers. The major product was derived from an endo approach of the diene to the cation.



(44)

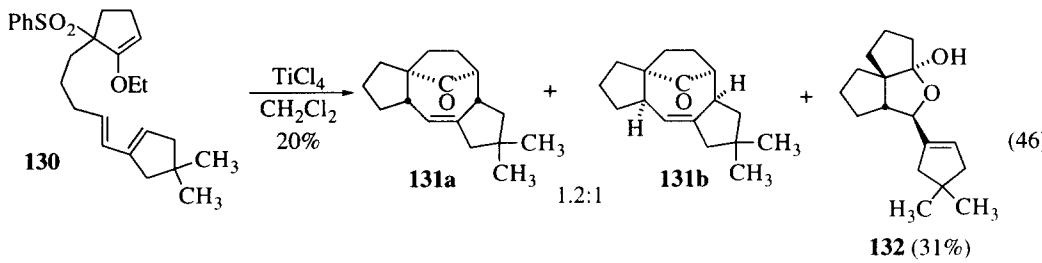
Sulfone **127** behaved similarly but, in addition to cycloadduct, a 20% yield of the electrophilic addition

product **129** was isolated as well. This suggested that substitution of the diene with electron-donating groups



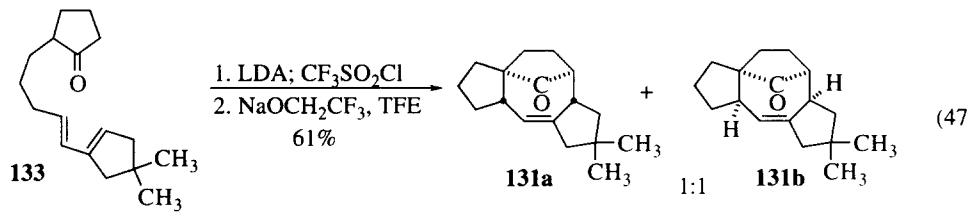
127 **128a** **128b** **129** (20%) (45)

was detrimental to the cycloaddition process for this particular methodology. This idea was supported by the attempted cycloaddition of **130**. Treatment with $TiCl_4$ gave cycloadduct **131** in only 20% yield, the major product (31%) being the hemiacetal **132**, a formal 3+2 cycloadduct.



130 **131a** 1.2:1 **131b** **132** (31%) (46)

This problem was addressed by recourse to the method of Föhlisch. Reaction of the chloroketone derived from **133** with $NaOCH_2CF_3$ gave cycloadduct **131** in 61% yield as a 1:1 mixture of stereoisomers. No further examples of this type of reaction were reported.



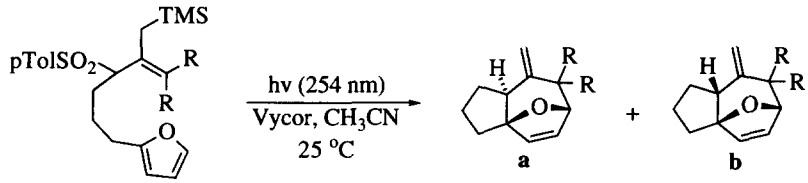
133 **131a** 1:1 **131b** (47)

C. Photochemical Methods of Cation Generation

1. Acyclic Cations

Only one example of the photochemical generation of acyclic allylic cations for intramolecular 4+3 cycloaddition has been reported. Harmata and Herron reported that photolysis of an acetonitrile solution of **64** (254 nm, Vycor filter) resulted in the formation of cycloadduct **65** in 35% yield (56%, corrected) in a ratio of 1:7.8.[26] The stereochemical outcome of this reaction is quite interesting but remains unexplained. The mechanism of this reaction was not established but a working hypothesis is shown in Scheme 5. A SET

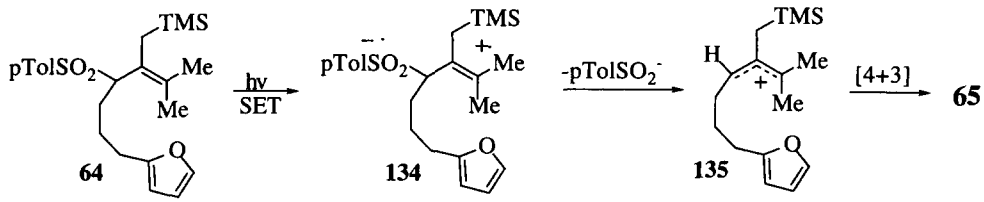
process followed by dissociation results in the formation of an allylic cation which undergoes cycloaddition. It was reported that no cycloaddition occurred at high dilution, suggesting that a bimolecular event might be involved in the reaction. This does not necessarily militate against the mechanism shown is Scheme 5, but



(48)

64: R=CH_3
66: R=-$(CH_2)_5$-

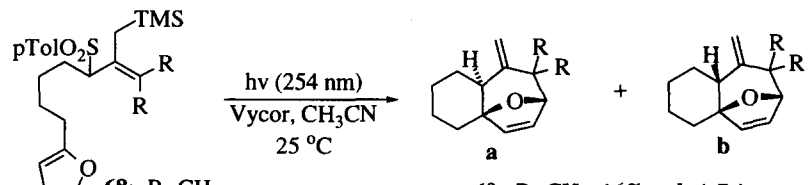
65: R=CH_3, 35%; **a**:**b**-1:7.8
67: R=-$(CH_2)_5$-, 11%; **a**:**b**-2.7:1



Scheme 5

might require an inter- rather than an intramolecular photoinitiated SET step. The cyclization of **66** took place as well, but in very low yield and with opposite stereochemical results.

The formation of six-seven fused ring systems was also investigated as shown in equation 49. Yields were low though simple diastereoselectivity was good. To make this process synthetically useful, more work will have to be done to optimize this reaction.



(49)

68: R=CH_3
70: R=-$(CH_2)_5$-

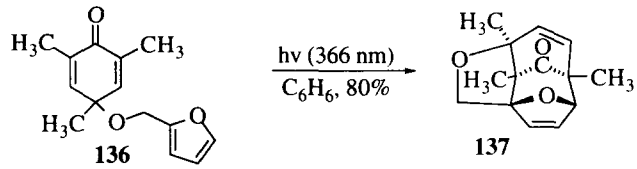
69: R=CH_3, 16%; **a**:**b**-1:7.1
71: R=-$(CH_2)_5$-, 22%; **a**:**b**-1:8

2. Cyclic Cations

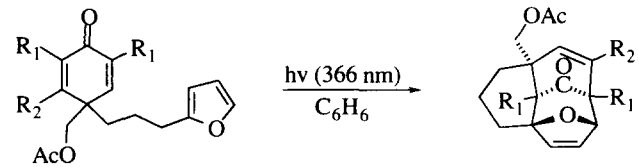
The photochemical generation of cyclic allylic cations for intramolecular 4+3 cycloadditions is more established than that for acyclic cations. In fact, the intramolecular cycloaddition reactions of such cations were among the earliest to be investigated.

For example, Schultz and coworkers showed that photolysis of a benzene solution of **136** at 366 nm gave an 80% yield of cycloadduct **137** as a single diastereomer.[27] This product results from an endo approach of the

reacting species as is observed with related cyclic oxyallylic cations in intermolecular cycloadditions.[23] Moreover, molecular models suggest that such an approach was mandatory, as an exo approach would entail considerably more strain.

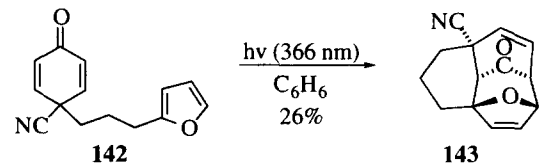


136 137 (50)

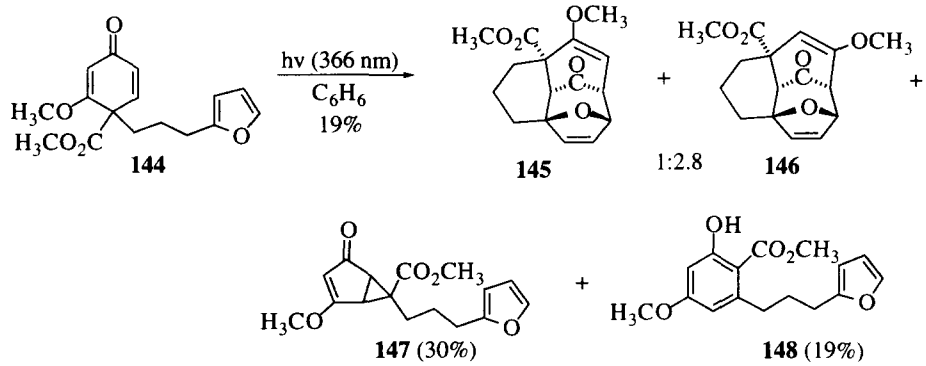


138: R_1=H, R_2=OCH_3
140: R_1=CH_3, R_2=H

139: R_1=H, R_2=OCH_3, 27%
141: R_1=CH_3, R_2=H, 100% (51)



142 143 (52)

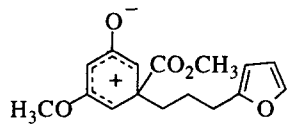


144 145 146 (53)

147 (30%) 148 (19%)

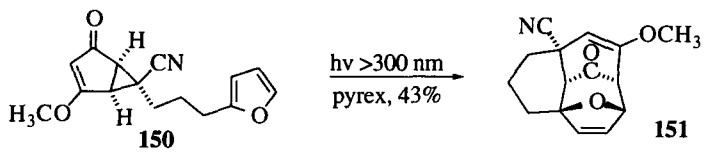
Some aspects of the scope and mechanism of this process have been delineated through a study of substituent effects. Photolysis of **138** gave 4+3 cycloadduct **139** in only 27% yield, while that of **140** resulted in the formation of **141** in quantitative yield. Substrate **142** led to **143** in 26% yield. Similar irradiation of **144** gave a mixture of **145** (5%) and **146** (14%). The major products of the reaction were the bicyclo[3.1.0]hexenone **147** (30%) and the phenol **148** (19%). The carbomethoxy group has a detrimental

effect on the 4+3 cycloaddition reaction, with a 1,2-shift of the group in the zwitterionic intermediate **149** competing very well with cycloaddition. The yield of this latter reaction could be slightly improved by extended irradiation of **144**. This gave **145** and **146** in 23% and 10% yields, respectively.



149

Interestingly, one of the bicyclo[3.2.1]hexenones formed as intermediates in these reactions also reacts upon photolysis to give rise to oxyallyls capable of 4+3 cycloaddition. For example, pyrex-filtered photolysis

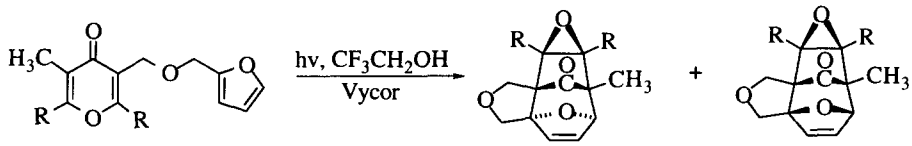


(54)

150 **151**

of **150** gave **151** in 43% yield.

West and coworkers have reported an intramolecular 4+3 cycloaddition reaction involving the photochemical conversion of 4-pyrones to cyclopentenyl oxyallylic cations.[28] Photolysis of **152** gave **153a** and **153b** in 30% and 20% yields, respectively. Facial selectivity was complete, the furan approaching the face



(55)

152: R=CH_3
154: R=H

153a: R=CH_3, 30%
155a: R=H, 0%

153b, R=CH_3, 20%
155b, R=H, 10%

of the oxyallylic cation from the convex side, away from the epoxide. The poor simple diastereoselection was attributed to unfavorable steric interactions between the tether and the "R" group in the endo cycloaddition transition state as shown in Figure 6.

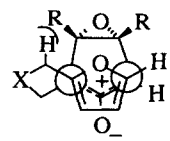
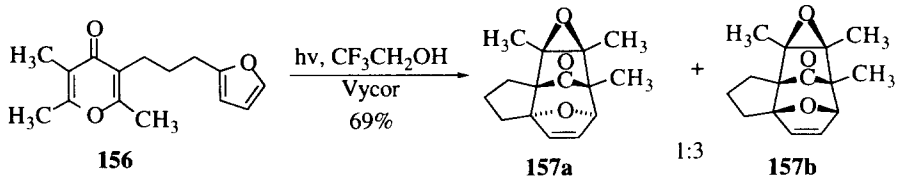


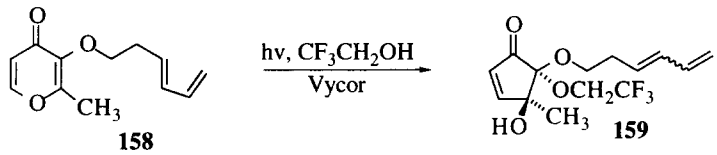
Figure 6. Steric interactions in the endo transition state for the cycloaddition of 152.

Heavy alkyl substitution on the pyrone appears to be required for effective cycloaddition. Irradiation of **154** led to cycloadduct **155b** in only 10% yield. Good yields of cycloadducts are obtainable as demonstrated

by the photolysis of **156**. Unfortunately, substrates such as **158** with either a tethered furan or butadiene gave products of solvent incorporation with no evidence of 4+3 cycloaddition.



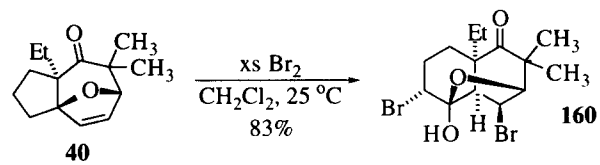
156 **157a** **157b** (56)



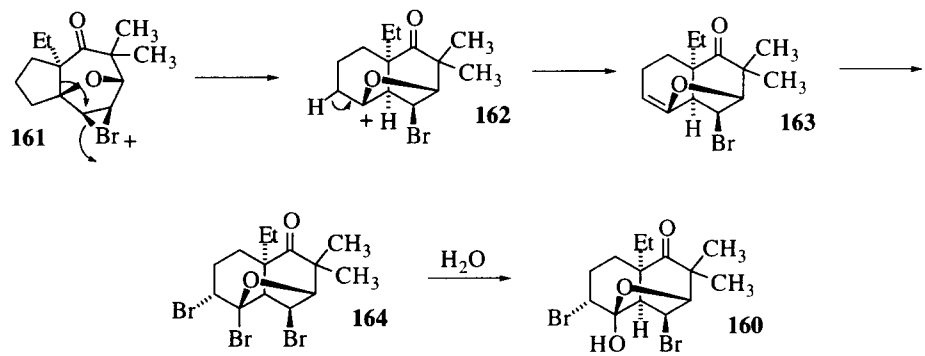
158 **159** (57)

D. Product Chemistry

In order to place the chemistry discussed in the preceding sections in some context, it is useful and informative to discuss some of the chemistry of the cycloaddition products which have been obtained by intramolecular 4+3 cycloaddition reactions of allylic cations.



40 **160** (58)



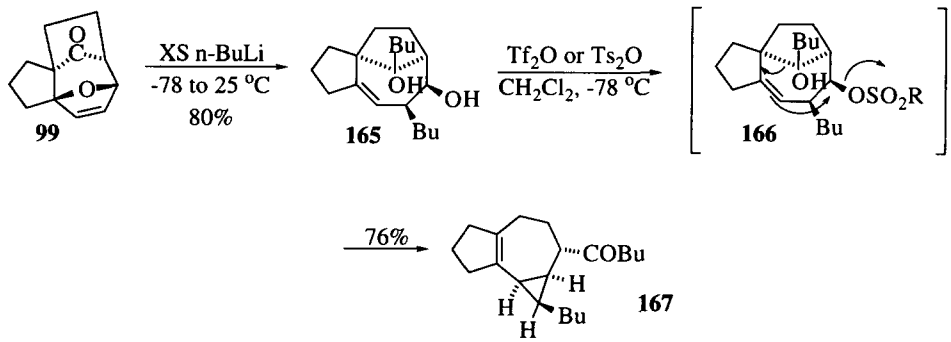
161 **162** **163** **164** **160**

Scheme 6

Not a great deal has been done with respect to cycloadduct chemistry. Some results have been forthcoming from Harmata and coworkers. For instance, as part of the characterization of **40**, this compound

was treated with excess bromine to give **160** in 83% yield.[15] Several other cycloadducts behave similarly and this rearrangement appears to be one which is general, though its occurrence with other electrophiles has not been established. The proposed mechanism for the formation of **160** is shown in Scheme 6. Bromonium ion **161** undergoes a 1,2-shift to give **162**. Loss of a proton leads to enol ether **163**. Bromination gives the α-bromo ether **164** which is hydrolyzed upon workup to afford **160**.

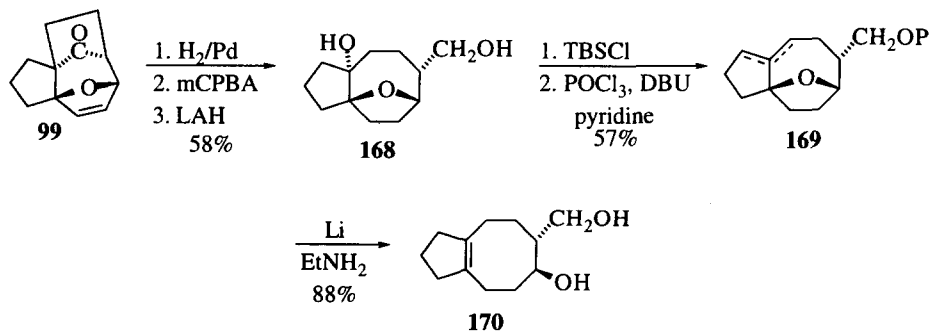
Harmata and Elahmad introduced a "vinylogous Grob" fragmentation process in the course of studies directed toward the synthesis of cyclooctanoids.[29] Treatment of **99** with excess n-BuLi resulted in ring opening in an S_N2' fashion to give diol **165** in 80% yield. Treatment of the diol with either triflic or tosic



Scheme 7

anhydride in the presence of base resulted in a rearrangement which appears to involve homoallylic participation in the departure of a sulfonate leaving group followed by a Grob-like carbon-carbon bond scission to give **167** in 76% yield. This polycyclic compound possesses the ring structure of the africane sesquiterpenes.[30] Only a single example of this process has been published.

Finally, Harmata and Elahmad demonstrated that certain cycloadducts derived from cyclic oxyallylic and alkoxyallylic cations could be converted to fused five-eight ring systems in a straightforward fashion.[31] For

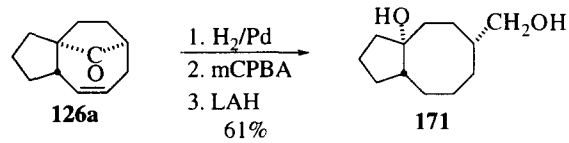


Scheme 8

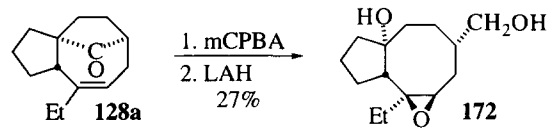
example, hydrogenation of **99** followed by regioselective Baeyer-Villiger oxidation and reduction gave diol **168**

in 58% yield (Scheme 8). Protection of the primary alcohol as a TBDMS ether followed by elimination gave a mixture of alkenes **169** in 57% yield. Treatment with excess lithium in ethylamine gave diol **170** in 88% yield. This sequence is rather long but does produce a stereoselectively functionalized 5,8 fused ring system. Other cycloadducts can be transformed in a similar fashion.

Another procedure makes use of cycloadduct **126a**. Hydrogenation, Baeyer-Villiger oxidation and reduction gave **171** in 61% yield. In a slightly more complex case, direct Baeyer-Villiger oxidation of **128a** with concomitant epoxidation and subsequent reduction gave **172** in 27% overall yield. The poor yield was attributed to considerable amounts of starting material which underwent Baeyer-Villiger oxidation, but not epoxidation.



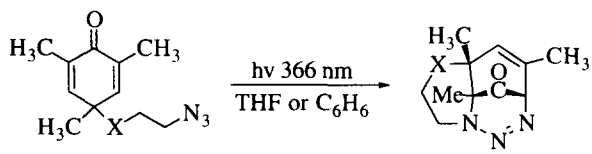
126a **171** (59)



128a **172** (60)

III. Intramolecular 3+3 Cycloadditions

There has been very little published concerning intramolecular 3+3 cycloadditions of allylic cations. The first examples were reported by Schultz and coworkers as part of their studies of cyclohexadienone photochemistry.[32] Photolysis of **173** gave **174** in 64% yield. Similarly, **175** gave triazene **176** in 75% yield. Subsequent studies of this process revealed limitations similar to those found in related work on intramolecular 4+3 cycloadditions (*vide supra*).[27b] Thus, irradiation of **177** and **178** afforded either phenolic byproducts such as **179** (from **177**) or the bicyclic species **180** (from **178**), no triazene being formed. Photolysis of **181** did give the expected cycloadduct, but only in 10% yield.

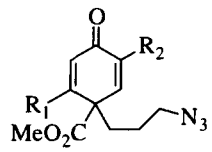


173: X=CH_2
175: X=O

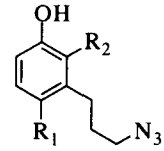
174: X=CH_2, 64%
176: X=O, 75% (61)

It was found, however, that problems associated with the high migratory aptitude of the methoxycarbonyl group could be overcome. Irradiation of acetate **183** gave the triazene **184** in 17% yield. This low yield was ascribed to decomposition upon attempted chromatographic purification. When crude **184** was exposed to the

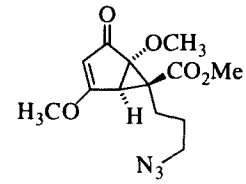
atmosphere (*i.e.*, H_2O), it was slowly transformed to **183**, which could be isolated in 75% yield.



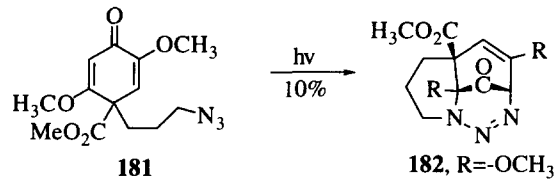
177: $R_1=R_2=H$
178: $R_1=OCH_3$, $R_2=H$



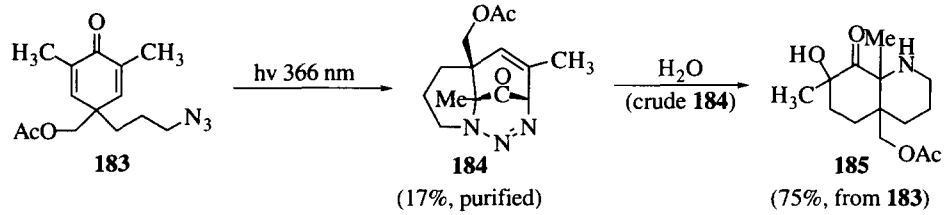
179a: $R_1=CO_2Me$, $R_2=H$
179b: $R_1=OCH_3$, $R_2=CO_2Me$



180



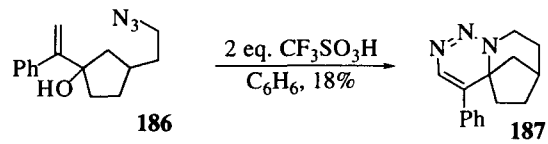
181 **182**, R=-OCH_3 (62)



183 **184** (17%, purified) **185** (75%, from **183**)

Scheme 9

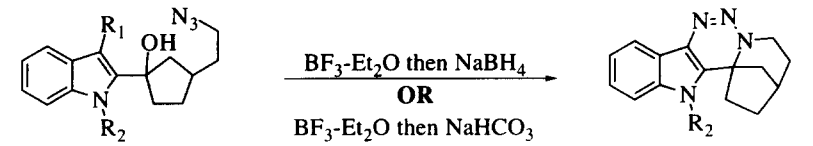
Pearson and coworkers found that allylic cations generated under Lewis acidic conditions react in a similar fashion.[33] Treatment of **186** with triflic acid resulted in the formation of **187** in 18% yield. The bulk of this



186 **187** (63)

study, however, focussed on cations which might be called "indolylic" rather than allylic. The results will nevertheless be discussed. For example, reaction of **188** with BF_3-Et_2O gave the triazene **189** in 44% yield. Yields were much improved when the 3-chloro group was removed. Thus, azide **192** led to triazene **191** in 85% yield. However, **193** gave only a 27% yield of **194**, perhaps suggesting that a certain degree of rigidity is necessary for a successful cycloaddition.

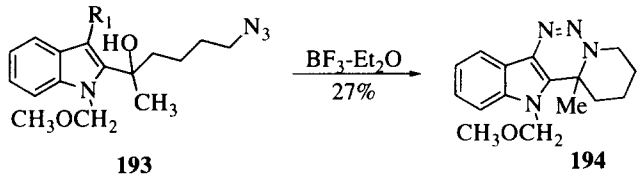
Substitution on the indole nitrogen played an important role in the regiochemical outcome of the reaction of the "indolylic" cations intermediate with the tethered azide. Treatment of **195** with 1.5 equivalents of $SnCl_4$ in dichloromethane at -78 °C gave the triazoline **196** as a 1.4:1 mixture of diastereomers. This appears to be an



188: R_1=Cl, R_2=-CH_3
190: R_1=Cl, R_2=-MOM
192: R_1=H, R_2=-MOM

189: R_2=-CH_3, 44%
191: R_2=-MOM
40% (from **190**)
85% (from **192**)

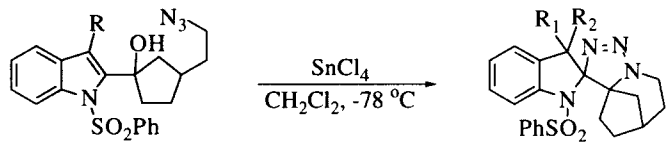
(64)



193 **194**

(65)

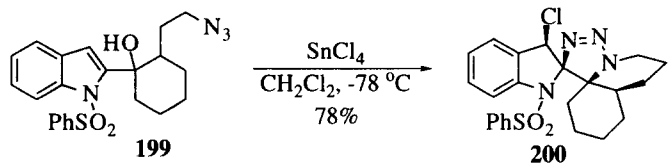
electronic effect such that as the donor ability of the indole nitrogen decreases, triazoline formation becomes preferred. Other examples support this conclusion. These are summarized in equations 67 and 68. These are formally intramolecular 3+2 dipolar cycloadditions to allylic cations. The full extent of regiocontrol available in this fashion remains to be determined.



195: R=H
197: R=-CH_3

196: R_1=H, R_2=Cl
75-95%, 1.4:1
198: R_1=R_2= (=CH_2)
31%, 1.3:1

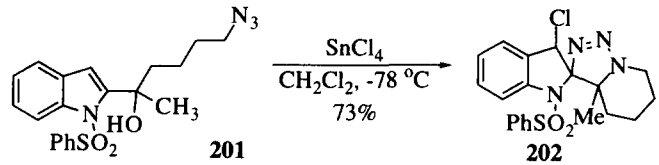
(66)



199 **200**

(67)

The mechanisms of these reactions have not been established and both stepwise and concerted pathways are conceivable. Further work in this area will doubtless be forthcoming.

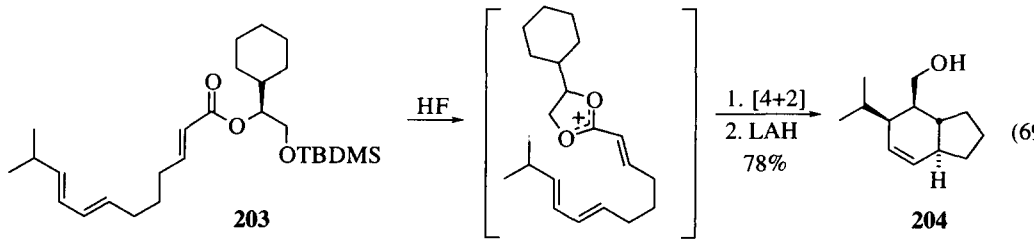


(68)

IV. Intramolecular 4+2 Cycloaddition Reactions

The intramolecular 4+2 cycloaddition or Diels-Alder reaction is quite an important process in organic synthesis and a great deal of attention has been paid to its synthetic and stereochemical aspects.[34] The use of allylic cations in this reaction is a relatively new occurrence and one can conclude that the study of this reaction is in its infancy.

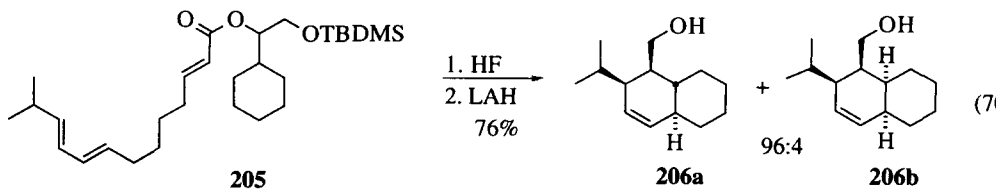
It appears that the first intramolecular 4+2 cycloaddition of an allylic cation was reported by Roush and coworkers.[35] During the course of studies involving Lewis acid mediated intramolecular Diels-Alder reactions it was discovered that treatment of **203** with HF in $CH_3CN/CH_2Cl_2/H_2O$ at 23 °C for 3 days gave rise to a cycloaddition product as a mixture of esters due to acyl transfer. Reduction of the mixture with lithium aluminum hydride gave alcohol **204** in 78% overall yield from **203**. Unfortunately, **204** was racemic.



(69)

It was proposed that the reaction took place via a reversibly-formed dioxolenium ion, which undergoes irreversible 4+2 cycloaddition. Control experiments supported this rationalization.

Bicyclo[4.4.0]decenes were also prepared using this methodology. High simple diastereoselectivity was again observed as shown in the reaction of **205**. A comparative study of **207**, **208**, and **209** revealed that the



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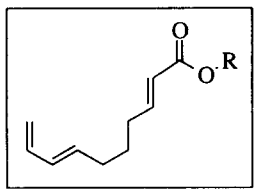
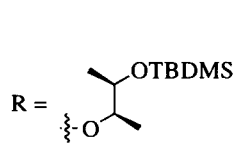
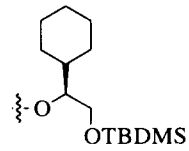
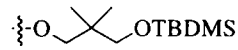
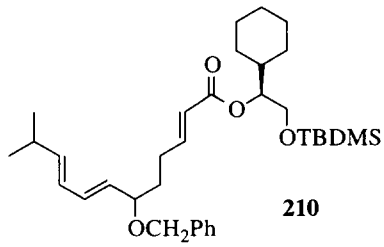
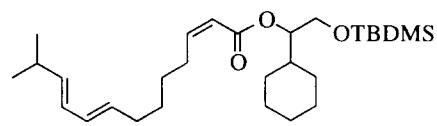
efficiency of cyclization correlated with the equilibrium constant for acetonide formation with the diols present as protected half-esters in these substrates. Thus, **207** led to cycloadducts in 44% yield, **208** in 24-36% yields,

207 **208** **209**

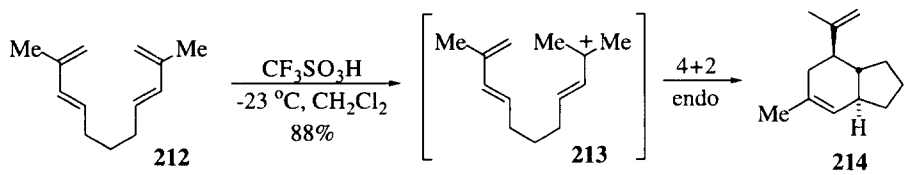
and **209** in 0% yield, only desilylation having taken place in this latter case. In those instances where cycloaddition was observed, very high endo selectivity was seen.

Some limitations uncovered included the inability of diene allylic ethers to survive the reaction conditions. Substrate **210** led to a quantitative yield of benzyl alcohol, but no cycloadducts, presumably via an El mechanism. Further, the (Z)-α,β-unsaturated ester **211** was shown to undergo desilylation and isomerization upon treatment with excess HF after a few hours. Longer reaction times resulted in cycloadduct formation, but from the (E)-α,β-unsaturated ester **203**.

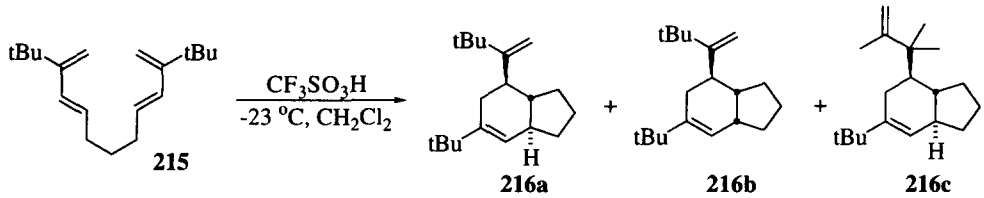
210 **211**

Gassman and Singleton demonstrated that simple allylic cations could serve as extremely efficient dienophiles in intramolecular Diels-Alder reactions.[36] Treatment of **212** with 4 mol% of triflic acid in dichloromethane at -78 °C gave an 88% yield of **214**, essentially as a single stereoisomer. Substrate **215** behaved similarly but gave more exo cycloadduct **216b** (23%) as well as the rearrangement product **216c** (8%). Product distributions for **215** were found to be mildly dependent on proton source.



212 **213** **214** (71)

Regiocontrol issues in this methodology were addressed by Gassman and Singleton through the use of allylic alcohols and ethers as progenitors of allylic cations.[37] For example, treatment of a dichloromethane solution of **217** with triflic acid for 20 minutes at -23 °C afforded the adduct **214** in 77% yield in nearly diastereomerically pure form. As expected, the reaction was highly endo selective. More functionalized allyl alcohols gave rise to good yields of cycloadducts with high degrees of stereoselectivity as illustrated for **218**



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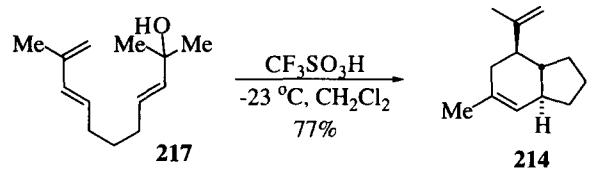
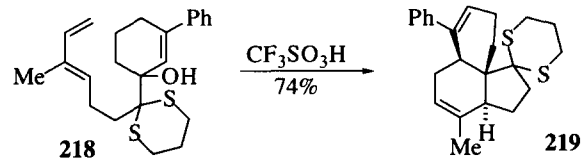


(73)

and **220**. The allylic ether **222** gave the bicyclo[4.4.0]decene **223** in lower yield. Hydrolysis and selective reduction of **223** led to **224**, a known precursor of γ_1-cadenene (Scheme 10).



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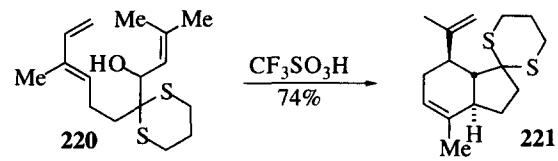

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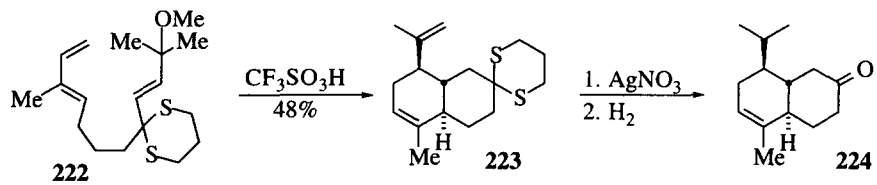
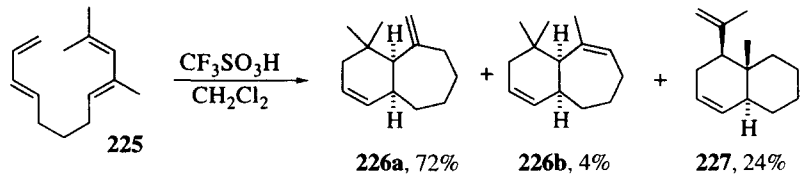


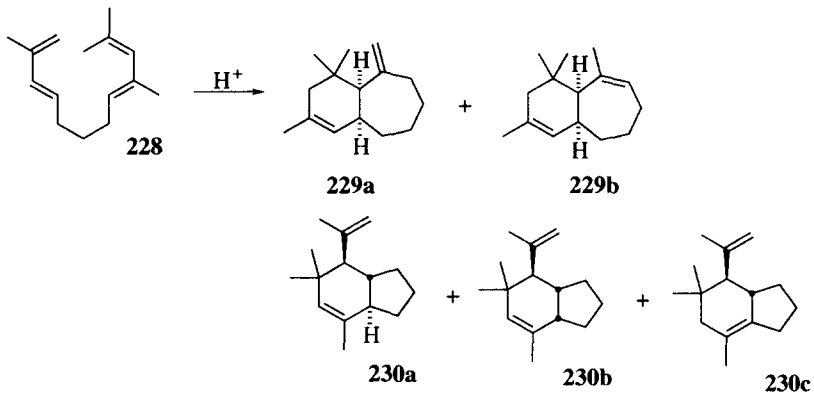
Scheme 10

The issue of regioselectivity both with respect to cation generation and subsequent cycloadditions was addressed in a unique way by Gassman and Gorman.[38] Treatment of **225** with 10 mol% of triflic acid at -23 °C for 10 minutes gave **226a**, **226b** and **227** in 72%, 4% and 24% yields (GC), respectively. Thus the more substituted diene was exclusively protonated to give the reactive dienophile. Interestingly, using one equivalent



(76)

of p-toluenesulfonic acid at room temperature gave 27%, 3% and 49% yields of the same compounds. So a change in temperature and acid resulted in a change of regiochemistry. This appears to be a consequence of kinetic, not thermodynamic, control. While **226b** is converted to **226a** under acidic conditions, no evidence was found in this or related studies to suggest reversibility in the cyclization/cycloaddition process.



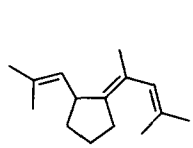
(77)

Complications arose with **228** since the protonation event was not chemoselective. Protonation occurred on both dienes to give two cations which underwent cycloaddition. Again, temperature and reagent control in product distribution was observed as summarized in Table 1.

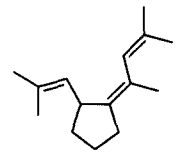
Table 1. Cycloaddition products from **228**.

Entry	Reagent	Time (min)	T °C	229a(%)	229b(%)	230a(%)	230b(%)	230c(%)
1	10% CF_3SO_3H	2	-23	43	5	15	15	14
2	10% CF_3SO_3H	90	-78	21	15	12	12	21
3	40% TsOH	60	23	4	2	20	20	30

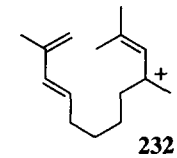
A closer investigation of the side products formed in the conversion of **228** to cycloadducts revealed the formation of **231a** and **231b** which were isolated as the major products of the reaction of **228** with p-toluenesulfonic acid at 23 °C for 30 minutes.[39] It was shown that both of these compounds could be converted to **230a-c**. The mechanistic conclusion was that two cations, **232** and **233**, are formed in the reaction of **228** with acid. Cation **232** gives rise to **229a/b** by either a concerted or stepwise mechanism. Cation **233** leads initially to **231a/b** which are subsequently reprotonated and go on to **230a/b**, either of which can isomerize to



231a



231b



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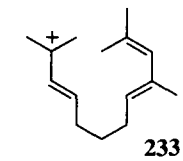
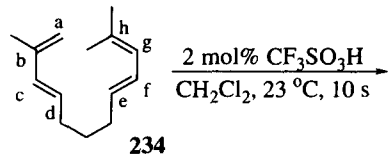


233

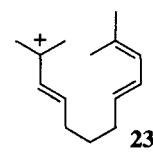
230c.

This study clearly demonstrated that stepwise processes should be seriously considered as mechanistically reasonable in the 4+2 "cycloaddition" reaction of such reactive dienes as allylic cations. This conclusion has received theoretical support from de Pascual-Teresa and Houk, who showed that, at least in the gas phase, the reaction of allyl cation with butadiene is a stepwise process.[40]



234 **(E)-235** + **(Z)-235** (78)

A number of other tetraene substrates have been examined to establish the scope and limitations of the reaction.[41] Treatment of **234** with 2 mol% of triflic acid in dichloromethane at 23 °C for 10 seconds resulted in the formation of (E)- and (Z)-**235** in 83% and 14% yields, respectively. It is interesting to note that the products could only have arisen from cation **236** via selective protonation of **234** at carbon "a". It appears that a kinetic preference for protonation at this site followed by a rapid cyclization is responsible for this result.



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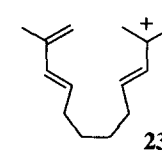
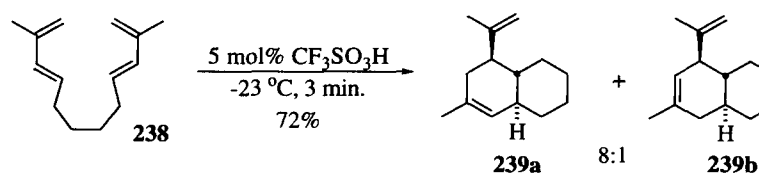


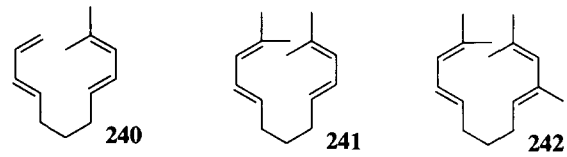
237

Interestingly, the cation which would have been produced by protonation of **234** at carbon "e" is accessible. Reaction of **238** with triflic acid (5 mol%, -23 °C, CH_2Cl_2, 3 min.) gave **239a** and **239b** as a 8:1 mixture in 72% yield. These data further indicate that the cation **237** was not formed in the reaction of **234**.



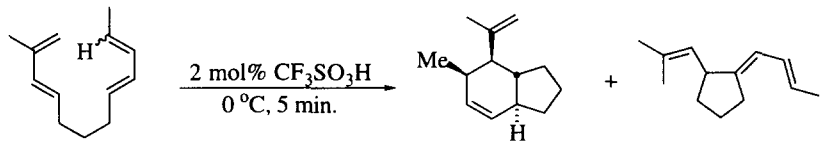
238 **239a** 8:1 **239b** (79)

The deleterious effect of geminal dimethyl substitution on the formation of cycloaddition products has some generality. Tetraenes **240**, **241**, and **242** led only to low yields of electrophilic addition/elimination products upon treatment with acid.



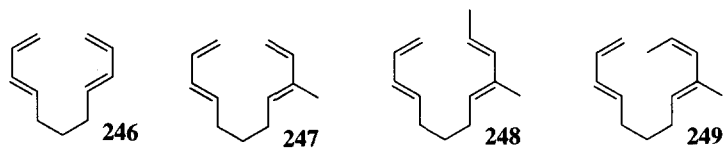
240 **241** **242**

However, substitution with a single methyl group was less problematic. For example, (E)- or (Z)- **243** afforded **244** in 45% yield upon exposure to acid. The electrophilic addition product **245** was formed in 39% yield. The fact that **244** was found as a single stereoisomer suggested that it was derived via a stepwise process, as the stereoisomers of **243** did not interconvert under the reaction conditions.



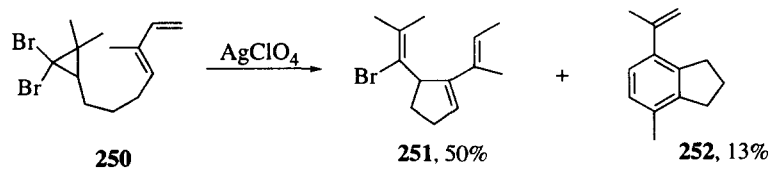
(E/Z)-243 **244**, 45% **245**, 39% (80)

Finally, it should be noted that acid treatment of **246**-**249** led to complex mixtures from which no products could be identified.

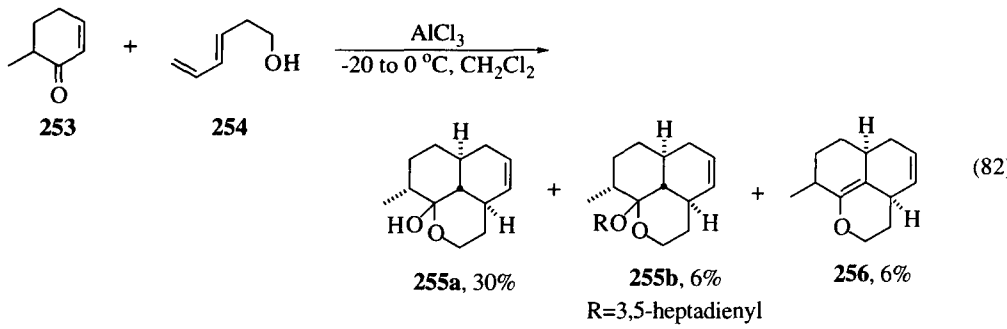


246 **247** **248** **249**

An interesting approach to allylic cation generation in the context of intramolecular 4+2 cycloaddition was investigated by Gassman, Hoye and Tan.[42] Silver ion-assisted ring opening of dibromocyclopropanes was used to access allylic cations. It was found, however, that the process was not useful for cycloaddition chemistry. For example, treatment of an ethereal solution of **250** with silver perchlorate gave a 50% yield of



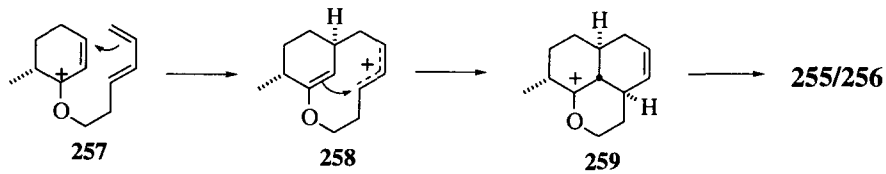
250 **251**, 50% **252**, 13% (81)



(82)

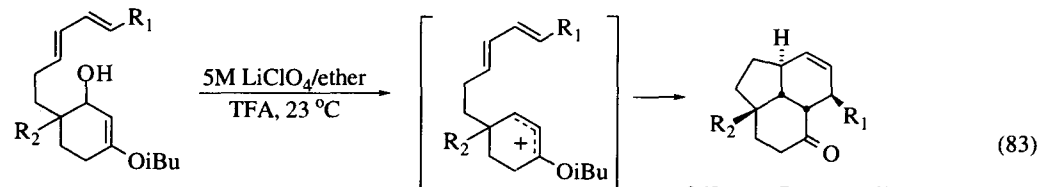
251 and a 13% yield of **252**. The latter presumably results from a formal cycloaddition (i.e., stepwise) followed by dehydrobromination and oxidation.

The use of heteroatom-stabilized allylic cations analogous to the aforementioned work of Roush is experiencing renewed attention. In the context of the synthesis of analogues of artemisinic acid, Haynes and coworkers examined the reaction of enone **253** and dienol **254**.[43] In the presence of one equivalent of $AlCl_3$, at -20 to 0 °C, **254** reacted with **253** to produce a 30% isolated yield of **255a** as well as 6% yields of **255b** and **256**. One equivalent of copper(II) triflate in acetonitrile gave **255a** in 42% yield as well as variable but low yields of **255b**. The reaction was rationalized on the basis of in-situ generation of heteroatom-stabilized allylic cation **257** which is trapped to give **258**. Subsequent ring closure then leads to oxocarbenium ion **259**, which can give rise to all of the observed products (Scheme 11). This mechanism remains to be rigorously established.



Scheme 11

Grieco and coworkers have made a more extensive study of the intramolecular Diels-Alder chemistry of heteroatom-stabilized allylic cations.[44] Reaction of **260** in 5M ethereal lithium perchlorate containing 10 mol%



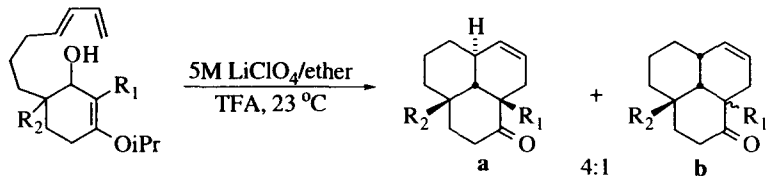
260: R_1=R_2=H
263: R_1=H, R_2=Me
265: R_1=Me, R_2=H

262: R_1=R_2=H, 87%
264: R_1=H, R_2=Me, 90%
266: R_1=Me, R_2=H, 92%

(83)

of trifluoroacetic acid gave the cycloadduct **262** in 87% yield. The proposed intermediate was oxocarbenium **261**. The completely diastereoselective formation of **262** resulted from exclusive exo approach of the diene to the dienophile, presumably for steric reasons. Control experiments supported the intermediacy of **261** and the related substrates **263** and **265** gave similar results, establishing the generality of the method.

An erosion of the exo selectivity was seen in the cyclization of **267** which gave **268a/b** in a ratio of 4:1 in 91% yield. The stability of these adducts to the reaction conditions and the cyclization of **269** and **271** to 4:1 mixtures of products suggested that the cycloadducts in these reactions were formed under kinetic control and presumably via a concerted process.

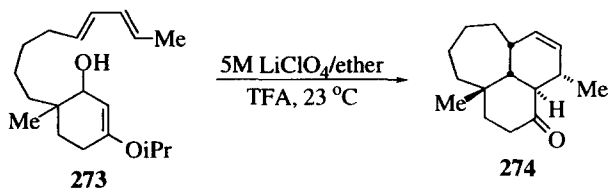


(84)

267: R_1=R_2=H
269: R_1=Me, R_2=H
271: R_1=H, R_2=Me

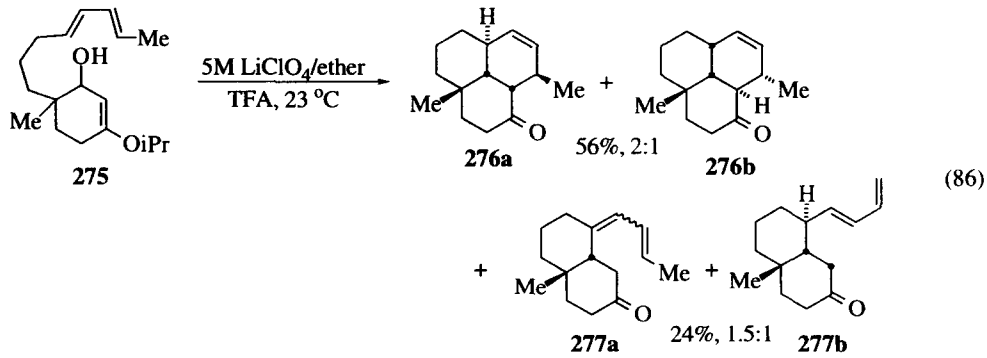
268: R_1=H (α in **b**); R_2=H, 91%
270: R_1=Me (β in **b**); R_2=H, 72%
272: R_1=H (α in **b**); R_2=Me, 95%

The formation of polycycle **274** was completely endo selective, indicating that removal of steric restrictions favors endo selectivity, as expected. Further, the result adds additional support to the idea that these reaction proceed via concerted mechanisms.



273 **274**

(85)

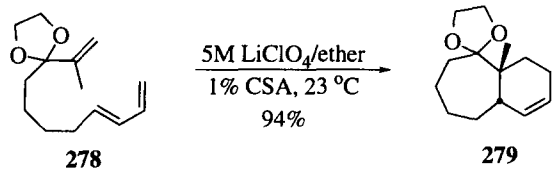


275 **276a** **276b** **277a** **277b**

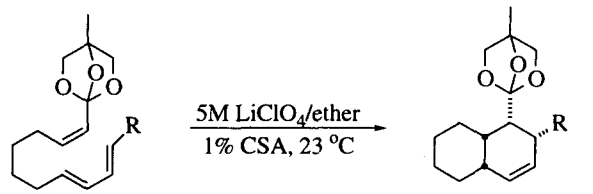
(86)

Nevertheless, in one example, evidence for a stepwise process was obtained. Substrate **275** gave rise to cycloadducts **276a/b** in 56% yield as well as dienes **277a/b**. The latter electrophilic addition/elimination products clearly result from a stepwise reaction.

Preliminary work by Grieco and coworkers also suggests that ketals and orthoesters will serve as excellent substrates for intramolecular 4+2 cycloadditions of heteroatom-stablized allylic cations.[45] Thus the reaction of **278** with 1 mol% of camphorsulfonic acid in ethereal 5M $LiClO_4$ gave the adduct **279** in 94% yield. Similarly, **280** gave **281** in 76% yield. The diasteroselectivity is impressive, particularly in the cases of **280** and **282**, where E/Z isomerization might have been anticipated.



278 **279** (87)



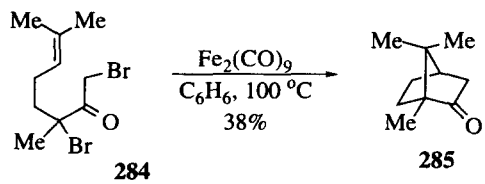
280: R=H
282: R=Me

281: R=H, 76%
283: R=Me, 65% (88)

V. Intramolecular 3+2 Cycloaddition Reactions

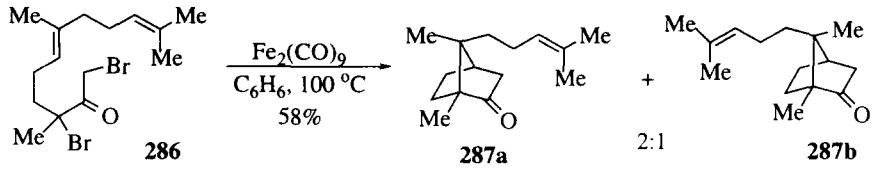
Intramolecular 3+2 cycloadditions of allylic cations have already been mentioned in the context of other cycloaddition reactions and these examples will not be presented again. Unlike the other processes discussed thus far, cycloadditions of this class are thermally forbidden in a concerted sense. Mechanistically, then, they should be viewed as stepwise processes.

As in the case of intramolecular 4+3 cycloadditions, Noyori and coworkers published the first examples of intramolecular 3+2 cycloadditions of allylic cations.[5] In an attempt to biomimetically synthesize some bicyclic terpenes, they treated a benzene solution of dibromide **284** with diiron nonacarbonyl in a pressure tube at ca. 100 °C and obtained racemic camphor (**285**) in 38% yield, along with a number of other monocyclic



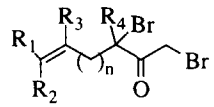
284 **285** (89)

products. Camphorenone **287a** and epicamphorenone **287b** could be prepared in a similar fashion as a 2:1 mixture in 58% yield from **286**. No other examples of intramolecular 3+2 cycloadditions using this



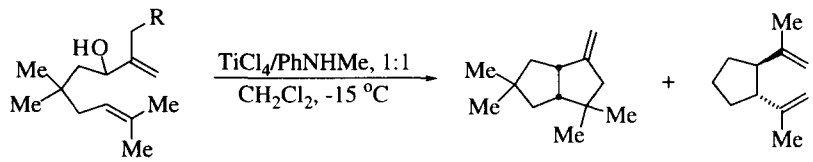
(90)

methodology are known. However, **288-290** did not afford the desired 3+2 cycloadducts upon treatment with $Fe_2(CO)_9$.



288: R_1=R_2=R_3=H; R_4=Me; n=2
289: R_1=R_2=R_4=Me; R_3=H; n=3
290: R_1=R_2=R_4=H; R_3=Me; n=3

Ipaktschi and Lauterbach showed that certain trimethylsilylmethyl-substituted allylic alcohols were excellent progenitors of allylic cations for intramolecular 3+2 cycloadditions.[46] Thus, reaction of **291** with $TiCl_4$/N-methylaniline (1:1) in dichloromethane at -15 °C gave the bicyclo[3.3.0]octane **292** in 55% yield, along with **293** (25%), a product of electrophilic addition/elimination, and small amounts of other materials. The importance of the trimethylsilyl group in this process was demonstrated by the attempted cyclization of **294** which led to **293** in only 17% yield.



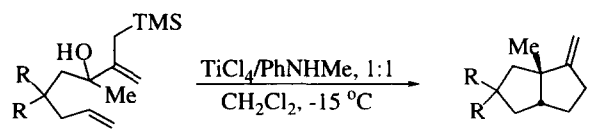
291: R=TMS
294: R=H

292, 55%

293, 25%

(91)

It is quite interesting that **295** reacted to provide **296** as the only isolated product in 70% yield, despite the fact that the nucleophilic alkene in **295** is only monosubstituted and the reaction appears to take place in an anti-Markownikoff fashion, though the timing of bond formation is not known. The importance of *geminal*

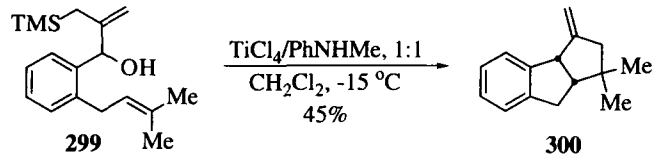


295: R=Me
297: R=H

296: R=Me, 70%
298: R=H, 15%

(92)

alkyl substitution in the tether was demonstrated by the low yield of product formed in the reaction of **297**. The polycycle **300** could, however, be prepared from **299** in 45% yield.



(93)

This methodology was further developed by Mann and coworkers, who studied the effect of alkene substitution on the reaction.[47] The results of these studies are compiled in Table 2. It was shown (Table 2, entries 4-6) that the stereochemical outcome of the reaction is independent of alkene geometry in the starting material. Detailed mechanistic questions, including cation stereochemistry, remain to be examined.

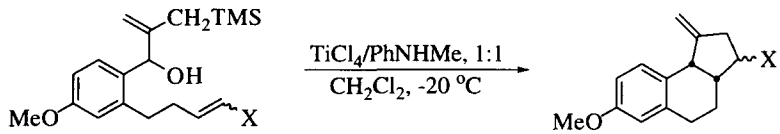
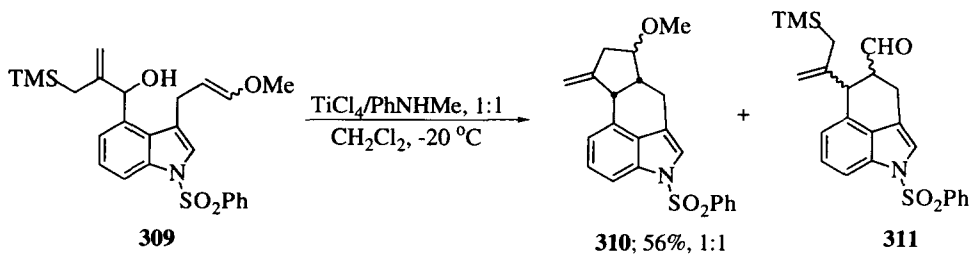


Table 2. Intramolecular 3+2 cycloaddition reactions.

Entry	Educt	X	Z/E	Product	Yield (%)	Ratio (X, β:α)
1	**301**	-Me_2	--	**302**	62	--
2	**303**	-SMe	2:3	**304**	40-50	--
3	**305**	-OCH_2Ph	3:7	**306**	30	1:5
4	**305**	-OMe	1:3	**308**	86	1:3
5	**305**	-OMe	0:1	**308**	81	1:3
6	**307**	-OMe	1:1	**308**	44	1:3

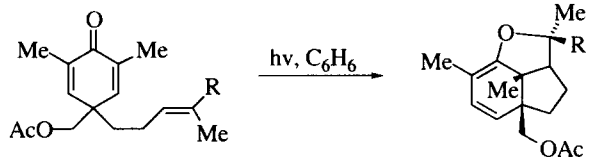
Mann and coworkers extended this work to studies aimed at the construction of ergot alkaloids.[48] It was shown that **309** afforded **310** as a 1:1 mixture of isomers in 56% yield under the usual reaction conditions. At lower temperatures, the electrophilic addition product **311** was obtained, but only in 25% yield.



(94)

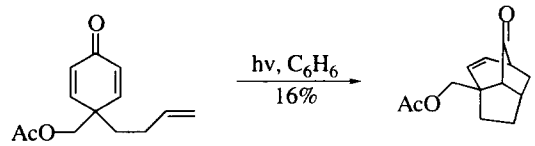
Finally, Schultz and coworkers showed that the oxyallylic cations available via photolysis could trap

alkenes.[49] Irradiation of **312** in benzene gave **313** in 71% yield. Unfortunately, much lower yields were obtained with **314** and **316**. Photolysis of **318** gave the 3+2 cycloadduct **319** in 16% yield, along with 5+2 cycloaddition products,[50] suggesting that steric crowding might be responsible for enol ether formation in the photolysis of **312** and related compounds.



(95)

312: R=CH_2OH **313**: R=CH_2OH, 71%
314: R=CHO **315**: R=CHO, 10%
316: R=Me **317**: R=Me, 20%



(96)

318 **319**

VI. Conclusions

The synthetic study of intramolecular allylic cation cycloadditions is not yet 20 years old. It offers many opportunities for mechanistic and synthetic investigation. Although it will doubtless find a fierce competitor in metal-catalyzed cycloaddition reactions,[51] there certainly will be instances where cationic reactions will compare favorably with their catalytic brethren. Further, the aim of chemistry, even synthetic organic chemistry, is not strictly utilitarian, especially in the short term. New and old reactions and processes offer the opportunity to learn about fundamental aspects of reactivity and mechanism. These aspects of organic chemistry are still often not easily predicted and are often subject to modification by serendipity. The careful and complete study of organic reactions provides information essential to the understanding of molecular behavior: synthetic organic chemistry is still a rich source of fundamental chemical information not available by other means. We anticipate a bright future for the many manifestations of allylic cation chemistry, especially their intramolecular cycloaddition reactions.

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50. A discussion of 5+2 cycloadditions of these and other (e.g., pyrilium) cations is beyond the scope of this review.

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Biographical Sketch

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Michael Harmata was born in 1959 in Chicago, Illinois. He attended St. Michael the Archangel Grammar School and Thomas Kelly High School, where his interest in organic chemistry was kindled by Mrs. Roberta Hanley. He earned an AB from the University of Illinois-Chicago, having done undergraduate research with Professor Jacques Kagan. Scott Denmark served as his Ph.D. advisor at the University of Illinois-Urbana/Champaign, from which he graduated in 1985. After an NIH postdoctoral experience with Paul Wender at Stanford University, he began his independent academic career at the University of Missouri-Columbia in 1986. He is now an Associate Professor of Chemistry at that institution. His research interests include allylic cation cycloaddition chemistry, the synthesis and study of chiral molecular clefts and tweezers based on Kagan's ether and the synthetic application of sulfonimidoyl chlorides. His hobbies include building and flying model rockets, stamp-collecting, reading science fiction and, more recently, trying to teach himself and his 4-year-old daughter German. Er hat Spass, aber die Sprachschwierigkeiten können frustrieren!