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Cycloaddition reactions of vinyl oxocarbenium ions

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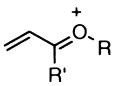
Contents

1. Introduction

Vinyl oxocarbenium ions can be described as allylic cations that are substituted at one terminus by at least one oxygen atom. In the broadest sense, the literature is replete with examples of the cycloaddition chemistry of such species, particularly their behavior as dienophiles in the Diels–Alder reaction. This is the case because any α,β-unsaturated carbonyl compound complexed to a Lewis acid can be represented in one of its resonance forms as a vinyl oxocarbenium ion (Fig. 1). With a few exceptions in the area of 4+3 cycloaddition chemistry, the cycloaddition chemistry of such intermediates will not be discussed in this review. Instead, we will focus on systems represented by **1**, in which the 'R' group is some alkyl substituent and generation of the cation involves loss of a leaving group, not coordination to a carbonyl group oxygen.



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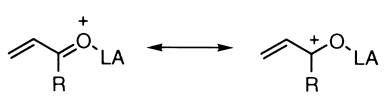

Figure 1.

This review is intended to be comprehensive and we would like to be informed of any omissions that have occurred as an oversight on our part. Data will be presented loosely in chronological order.

2. 4+2 (Diels–Alder) cycloaddition reactions

The 4+2 cycloaddition or Diels–Alder reaction is perhaps the most effective way of constructing six-membered ring systems. The reaction has been well studied since it was discovered in 1928.[1] Extensive research in the area of stereo- and regiocontrol, as well as application to the synthesis of natural products, has been conducted during the last few decades.[2] In an ordinary or 'normal' Diels–Alder reaction, the interaction between the HOMO of an electron-rich diene and the LUMO of an electron-poor dienophile is a major factor in determining the rate and regiochemical outcome of the reaction. Since there is no other carbon-based electron-withdrawing group better than a carbocation, an olefin bearing an adjacent carbocation would be expected to act as an excellent dienophile. Diels–Alder reactions involving allylic cations as dienophiles are referred to as ionic Diels–Alder reactions. Many variations on this theme are possible, but we will mention only those cation 'substituents' which are further stabilized by one or more alkoxy groups.[3]

What appears to be the first example of an oxocarbenium ion in a 4+2 cycloaddition reaction came from the laboratories of Sasaki and co-workers.[4] They showed that methyl vinyl ketone underwent a 4+2 cycloaddition

Keywords: Diels–Alder reaction; oxocarbenium ion; Lewis acid; cycloaddition.

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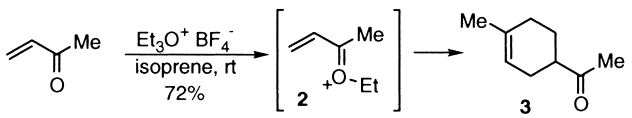
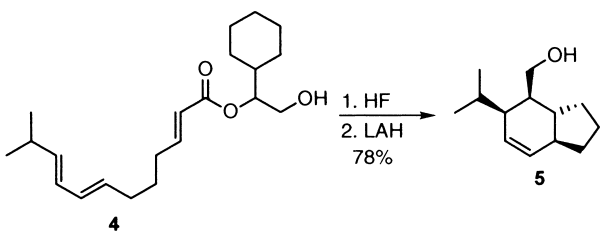
reaction with isoprene at room temperature in the presence of triethyloxonium tetrafluoroborate to afford cycloadduct **3** in 72% yield. It is not clear, however, that the vinyl oxocarbenium ion **2** was indeed an intermediate in the reaction (Scheme 1).



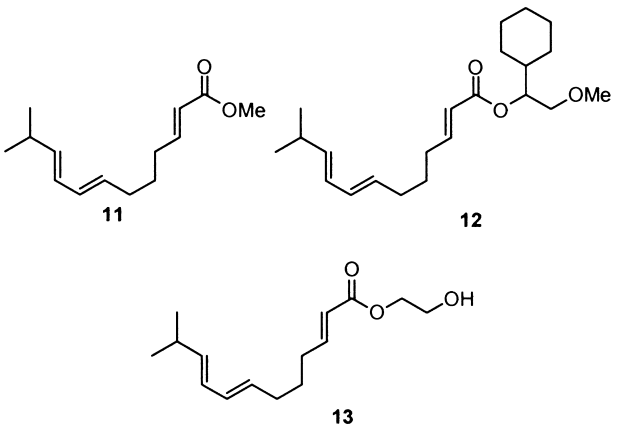
Scheme 1.

Subsequently, Roush and co-workers convincingly demonstrated the intermediacy of an oxocarbenium ion in certain intramolecular Diels–Alder reactions catalyzed by hydrofluoric acid.[5] For example, treatment of **4** with HF in acetonitrile at ambient temperature resulted in a cycloadduct as a mixture of esters, which upon reduction gave alcohol **5** in 78% overall yield (Scheme 2).

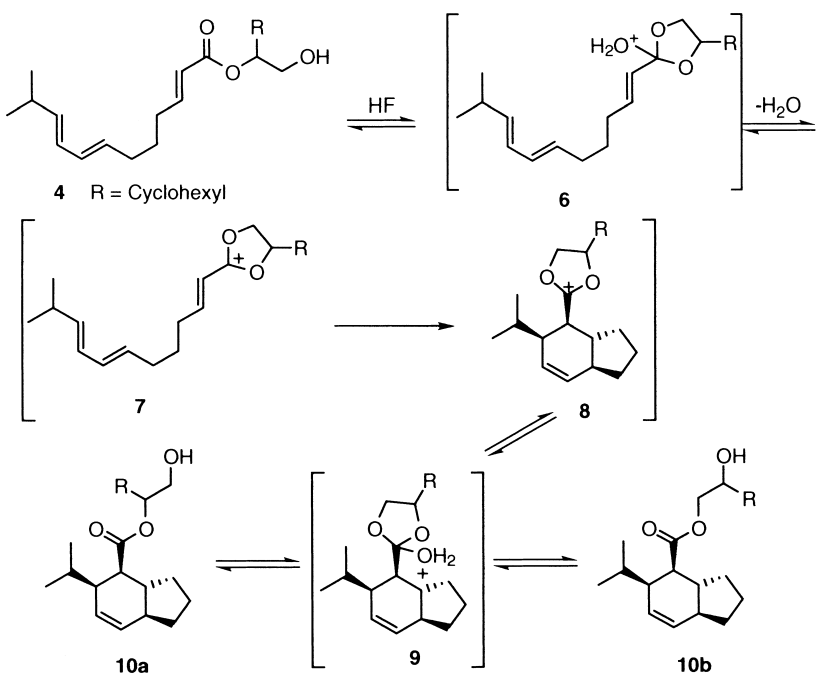


Scheme 2.

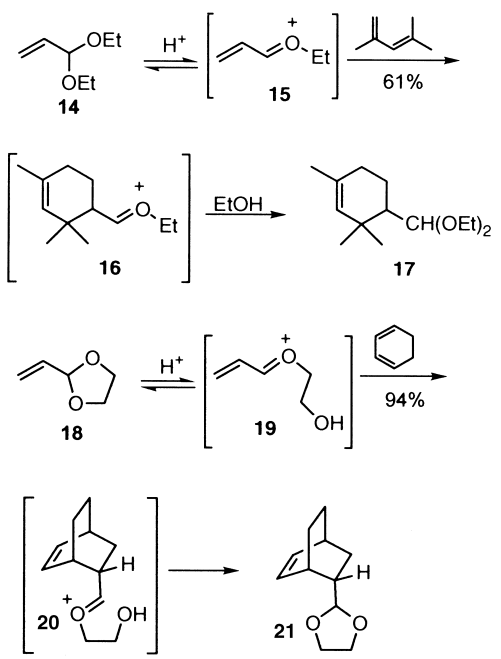
The proposed mechanism for this reaction involved the reversible formation of vinyloxocarbenium ion **7** which cyclized irreversibly to **8** (Scheme 3). The hydrolysis of this intermediate gave rise to a mixture of cycloadducts **10a** and **10b**. Both free hydroxy and cyclohexyl groups in **4** were essential for the cyclization to proceed as the substrates **11**, **12**, and **13** failed to give the expected products upon treatment with HF. This accounts for the intermediacy of **6** and the fact that alkyl groups are known to increase the rate of formation and the thermodynamic stability of many ring systems. The presence of a bulky alkyl group might promote closure to the dioxolane ring and increase the stability of **6**. This would also increase the equilibrium concentration of **6**, and consequently the overall rate of cyclization. Unfortunately, this methodology was not useful when applied to intermolecular Diels–Alder reactions.



However, other approaches to the use of vinyl oxocarbenium ions in intermolecular 4+2 cycloadditions have met with success. For example, the problem of polymerization that often accompanies thermal Diels–Alder reactions with acrolein was addressed by Gassman and co-workers. They used acrolein acetals as vinyl oxocarbenium precursors and were successful in achieving rapid, synthetically useful Diels–Alder reactions.[6] Thus, treatment of 3,3-diethoxypropene (**14**) or 2-vinyl-1,3-dioxolane (**18**) with various dienes in the presence of catalytic amounts of trifluoromethanesulfonic acid in CH_2Cl_2 at −78°C gave rise to the corresponding cycloadducts. Examples are shown in



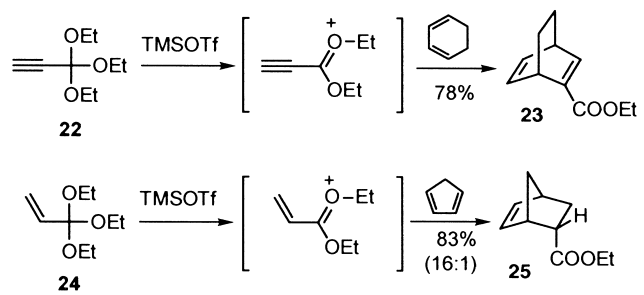
Scheme 3.



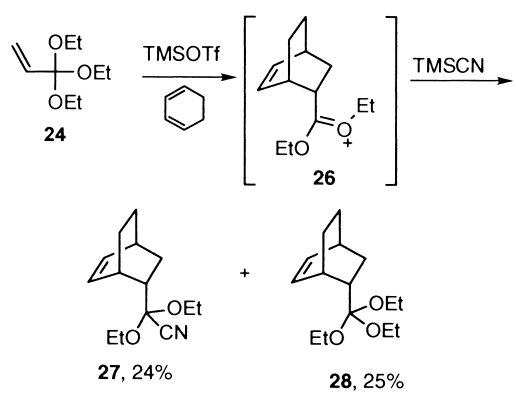
Scheme 4.

Scheme 4. It is interesting that cyclic acetals usually gave better yields than acyclic acetals. This was attributed to the intramolecular trapping of an intermediate like **20**, a process likely to be much more efficient than an intermolecular trapping required of intermediates like **16**.

The same research group used both vinyl as well as ethynyl orthoesters as precursors to the corresponding oxocarbenium ions.[7,8] For instance, the reaction of **22** or **24** with dienes in the presence of trimethylsilyl triflate in CH_2Cl_2 at −78°C gave the corresponding cycloadducts in good yields (Scheme 5). Interestingly, in these reactions the orthoester functional group was not retained, ethyl esters being formed in the cycloadducts. To establish that ethyl acrylate was not serving as the dienophile, it was shown that ethyl acrylate failed to react with 1,3-cyclohexadiene under the reaction conditions. Furthermore, when the reaction of **24** with cyclohexadiene was conducted in the presence of trimethylsilyl cyanide, nitrile **27** was isolated in 24% yield along with cycloadduct **28** (Scheme 6). The exact mechanism of the loss of an ethoxy group in the course of the reaction was not determined.



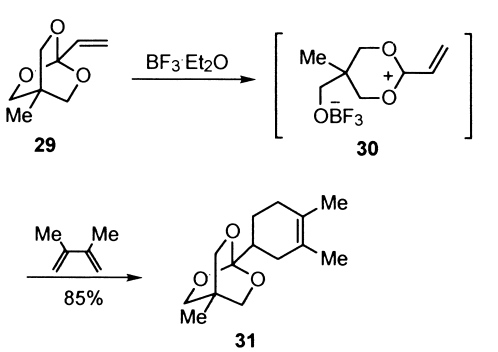
Scheme 5.



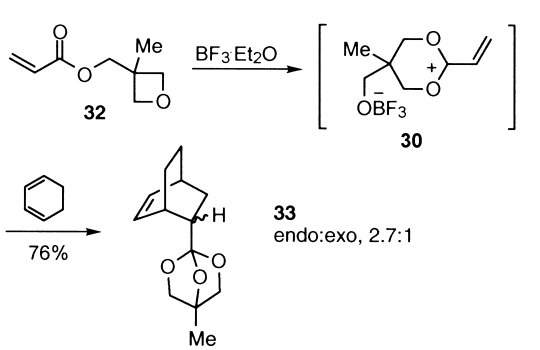
Scheme 6.

Since the orthoester functional group is a protecting group for an ester or carboxylic acid, it was deemed of interest to see if a system could be found which allowed for cycloaddition via oxocarbenium ion formation, but facilitated regeneration of the orthoester functionality. This issue could be addressed through the use of a bicyclic orthoester as embodied in 1-vinyl-4-methyl-2,6,7-trioxobicyclo-[2.2.2]octane (**29**). Thus, reaction of **29** with dienes in the presence of boron trifluoride etherate afforded cycloadducts containing the bicyclic orthoester functional group in good yield (Scheme 7).[9] Interestingly, when **32** was treated with $BF_3{-}OEt_2$ in the presence of cyclohexadiene, the cycloadduct **33** was obtained in 76% yield, presumably via the intermediacy of **30** (Scheme 8). Control experiments supported this conclusion.

The allene functionality can participate as a dienophile in the Diels–Alder reaction.[10] Gassman and Lottes showed that, in the case of the ethylene acetal of cyclonona-1,2-dien-4-one, Lewis acid catalyzed generation of an oxocarbenium ion produced an intermediate that reacted rapidly

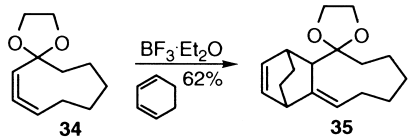


Scheme 7.



Scheme 8.

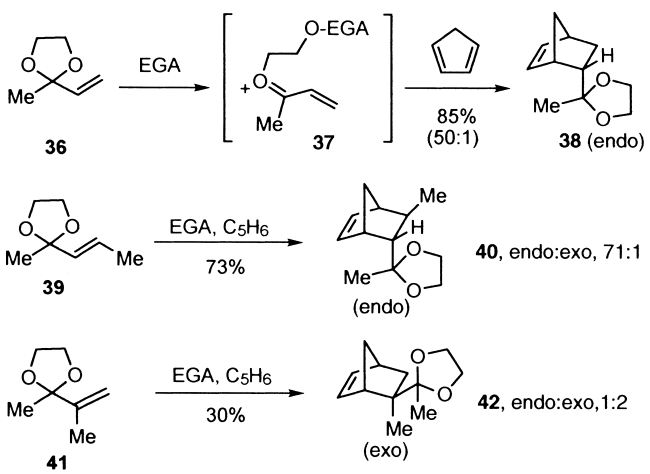
with dienes to produce 4+2 cycloadducts, as exemplified in Scheme 9.[11] In the case shown, the product **35** was produced with essentially no *endo*/*exo* selectivity, though high *endo* selectivity was observed with both cyclopentadiene and cycloheptadiene. It was estimated that the presence of the cationic center adjacent to the diene provided an accelerating effect of 10^6!



Scheme 9.

Several attempts to develop the most convenient reaction conditions that can achieve higher yields and stereoselectivity in the 4+2 cycloaddition reactions of allylic acetals have been reported in the literature. A group of Japanese chemists reported a high *endo* selectivity in the ionic Diels–Alder reaction between enone or enal acetals with dienes catalyzed by electrogenerated acid (EGA).[12] The reaction was performed by using platinum electrodes in CH_2Cl_2 containing $LiClO_4$ and Bu_4NClO_4 as a source of acid catalyst. The electrolysis of acetal **36** and cyclopentadiene at −78°C under an applied voltage of 15 V afforded cycloadduct **38** in 85% yield with the *endo*/*exo* ratio as high as 50:1 (Scheme 10). The substitution pattern of the alkyl group on the olefin also tremendously affected the stereoselectivity of the reaction. Under the same conditions, the reaction of **39** afforded the corresponding cycloadduct **40** with a diastereoselectivity of 71:1 in favor of the *endo* isomer, while the reaction of **41** produced the adduct in a 2:1 ratio in favor of the *exo* isomer. This remarkable change in the *endo*–*exo* ratio was rationalized on the basis of models which suggest that the α-methyl group of the oxocarbenium ion derived from **41** experiences a steric interaction with the methylene group of cyclopentadiene in the *endo* transition state, while the β-methyl group of the cation from **39** is less affected. This is illustrated in Figure 2.

Grieco and co-workers demonstrated that the ethylene ketals of various α,β-unsaturated ketones would react with dienes in 4 M $LiClO_4$ in ether in the presence of a catalytic



Scheme 10.

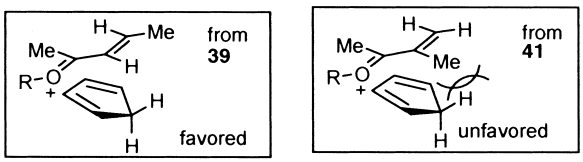
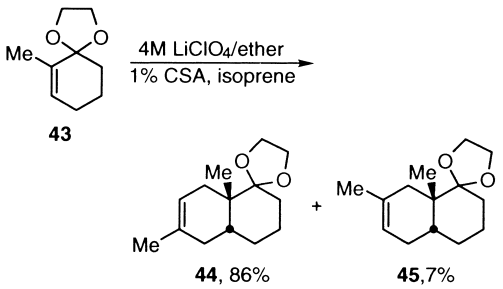


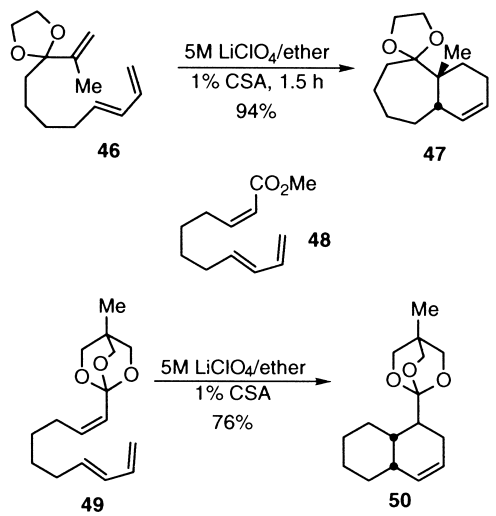
Figure 2.

amount of camphorsulfonic acid (CSA).[13] For example, the ethylene acetal of 2-methyl-2-cyclohexenone (**43**) afforded the cycloadducts **44** and **45** in 86 and 7% yields, respectively, upon reaction with isoprene (Scheme 11). Interestingly, 3 M $LiClO_4$ gave slower reaction rates, and catalytic amounts of camphorsulfonic acid in ether were ineffective in bringing about cycloaddition. The reactions took place between room temperature and 0°C.



Scheme 11.

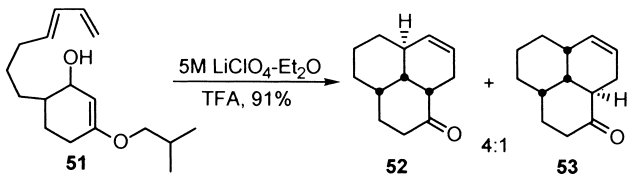
Other examples demonstrated the general utility of the method. Treatment of **46** with catalytic camphorsulfonic acid in 5 M $LiClO_4$ gave cycloadduct **47** in 94% yield as a single stereoisomer. The ketone corresponding to **46** required a reaction temperature near 200°C to undergo cycloaddition. Similarly, while the methyl ester **48** was known to react at high temperatures but with little selectivity to afford a Diels–Alder cycloadduct, the reaction of the orthoester **49** in 5 M $LiClO_4$ led to **50** in 76% yield as the only product (Scheme 12).



Scheme 12.

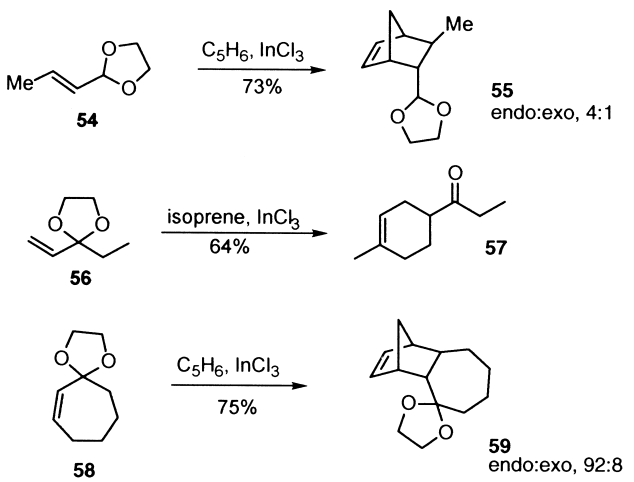
A different approach to vinyl oxocarbenium ions using the same reaction conditions was also introduced by the Grieco group. In this case, readily prepared hydroxy enol ethers

were exposed to acid in 5 M $LiClO_4$ in ether to generate oxocarbenium ions, which underwent rapid cycloaddition.[14] For example, the reaction of **51** produced cycloadducts **52** and **53** in a ratio of 4:1 in 91% yield (Scheme 13). The former cycloadduct was the result of an *exo* transition state and the latter from an *endo* transition state followed by a post-cyclization epimerization. With but one exception, it appeared that all of the intramolecular cycloadditions studied in this work proceeded in a concerted fashion.

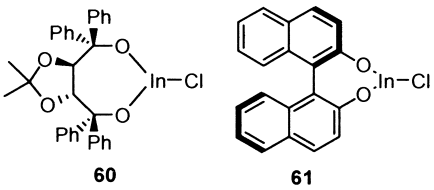


Scheme 13.

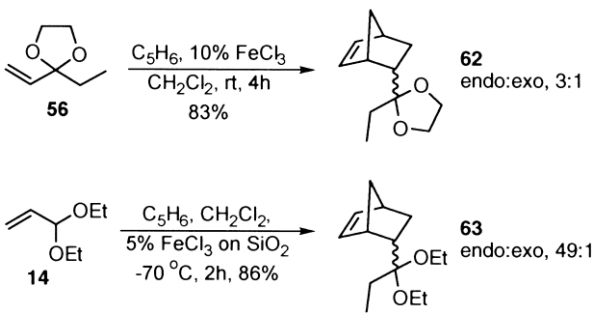
Other catalysts for the generation of vinyl oxocarbenium ions from vinyl acetals have been introduced by Vankar and co-workers.[15] They showed that $InCl_3$ (20 mol%) in nitromethane at room temperature was able to activate allylic acetals to afford cycloadducts in the presence of dienes. Some examples are shown in Scheme 14. Attempts to use chiral indium catalysts such as **60** and **61** failed to result in the formation of cycloadducts, suggesting that these Lewis acids were not sufficiently electrophilic to generate vinyl oxocarbenium ions from allylic acetals.



Scheme 14.

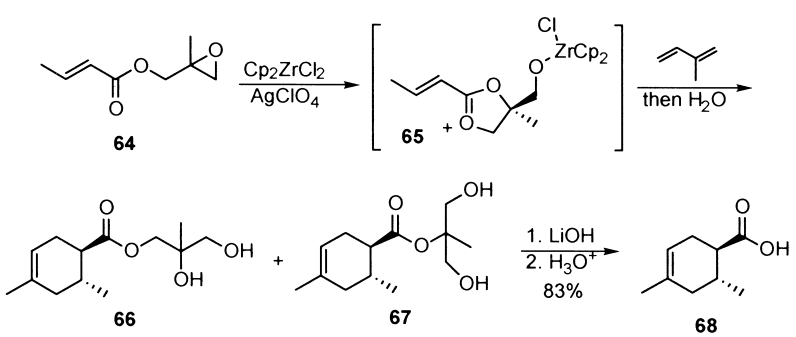


Chavan and Sharma have recently introduced $FeCl_3$ and $FeCl_3$ adsorbed on silica as effective Lewis acids for the ionic Diels–Alder reaction.[16] Thus, the reaction of **56** with cyclopentadiene in the presence of 10 mol% $FeCl_3$ in CH_2Cl_2 at room temperature afforded cycloadduct **62** in 83% yield as a 3:1 mixture of *endo* and *exo* isomers. In order to circumvent some problems associated with $FeCl_3$ as a catalyst, its adsorption on silica was considered as a means of mitigating its reactivity. Indeed, when 0.1 mol% of 5 wt% $FeCl_3$ on silica was stirred in the presence of acetal **14** and cyclopentadiene in CH_2Cl_2 at −70°C, the cycloadduct **63** was obtained in 86% yield in an *endo*/*exo* ratio of 49:1 (Scheme 15). The acetal **14** was not compatible with $FeCl_3$ alone, affording only decomposition products on attempted cycloaddition. It was shown that silica alone was not sufficient to induce cycloaddition.

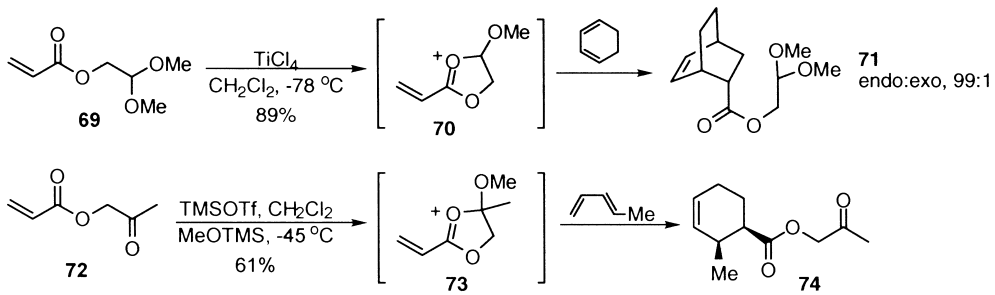


Scheme 15.

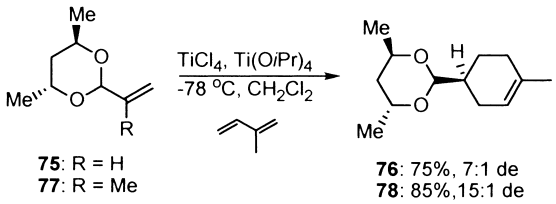
The in situ generation of a cationic organozirconocene is another useful catalytic method for an ionic Diels–Alder reaction.[17] Wipf and Xu showed that halide abstraction from Cp_2ZrCl_2 with $AgClO_4$ in the presence of epoxyester **64** in CH_2Cl_2 at room temperature resulted in vinyloxocarbenium ion **65** that rapidly reacted as a dienophile. Aqueous workup provided diols **66** and **67**, which were hydrolyzed to carboxylic acid **68** (Scheme 16). The reaction was found highly regioselective (>98:2 by GC and NMR) compared to the thermal cycloaddition of methyl crotonate, which provided a 76:24 mixture of two regioisomers. Other



Scheme 16.



Scheme 17.



Scheme 18.

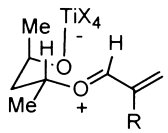
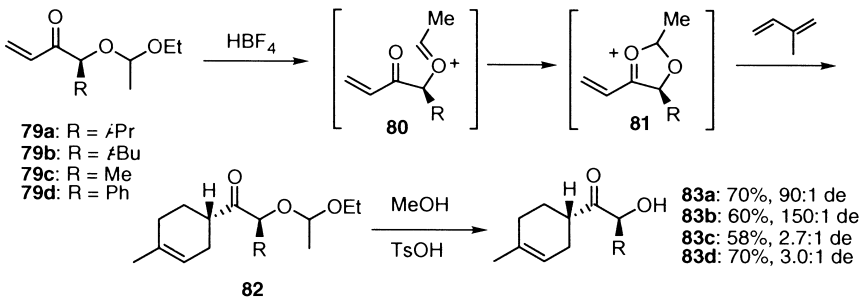


Figure 3.



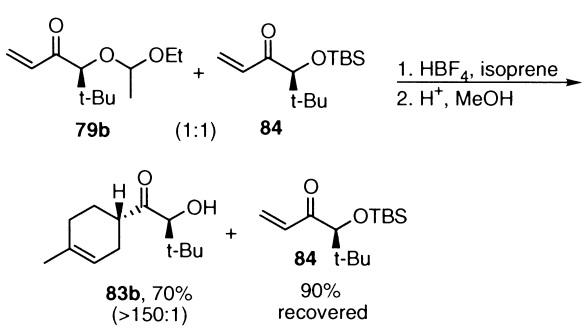
Scheme 19.

examples illustrated that the dioxolenium ion intermediate reacted with a variety of dienes with good regioselectivity and *endo*/*exo* selectivity. Control experiments supported the intermediacy of a dioxolenium ion and suggested that simple Lewis acid activation of the substrate was not contributing to the cycloaddition process.

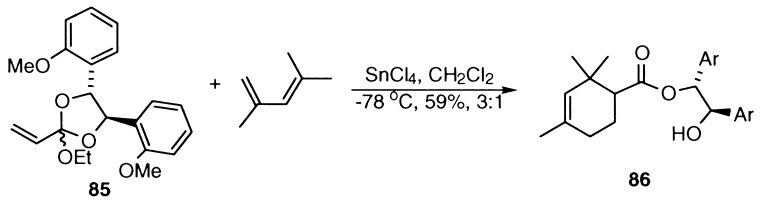
Two other simple and reliable paths to vinyl oxocarbenium species from acyclic substrates were reported by Saigo and co-workers.[18,19] They have shown that a cationic species suitable for ionic Diels–Alder reactions could be prepared from 2,2-dimethoxyethyl acrylate (**69**) by treatment with $TiCl_4$ in CH_2Cl_2 at −78°C. Other Lewis acids including TMSOTf and trityl perchlorate were also effective in the reaction. With cyclohexadiene, for example, both $TiCl_4$ and TMSOTf afforded the cycloadduct **71** as essentially a single stereoisomer in excellent yield (Scheme 17). These workers also found that the ketoester **72** afforded Diels–Alder cycloadducts when treated with TMSOTf and TMSOMe in the presence of dienes at −45°C in CH_2Cl_2. It was proposed that the intermediate **73** was formed and that this species was responsible for the chemistry observed. Importantly, no reaction took place in the absence of TMSOMe, supporting the idea that **73** is formed and that simple Lewis acid activation of the ester is not responsible for the results observed. In general, cycloadditions using this protocol gave good to excellent yields of cycloadducts with high *endo*/*exo* selectivity and regioselectivity.

The issue of diastereoselectivity in the ionic Diels–Alder reaction has been studied by Sammakia and Berliner using chiral α,β-unsaturated acetals derived from 2,4-pentanediol.[20] The reaction of **75** and **77** with isoprene catalyzed by a $TiCl_4$–$Ti(OiPr)_4$ mixture gave **76** and **78** in 7:1 and 15:1 diastereomeric ratios, whereas the activation of the acetal with protic acid resulted in no facial selectivity (Scheme 18). Figure 3 illustrates the preferred conformation of the vinyloxocarbenium ion intermediate that should give rise to the major isomer as a result of 1,4-asymmetric induction.

An extension of the preceding work was the generation of five-membered cyclic vinyloxocarbenium ions from acyclic substrates.[21] Treatment of ketones **79a–d** with HBF_4 in CH_2Cl_2 resulted in the formation of acyclic oxonium ions,

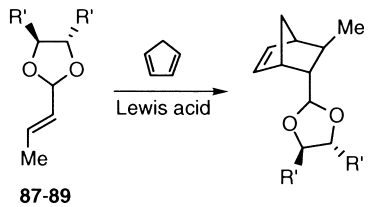


Scheme 20.



Scheme 21.

Table 1. Some Diels–Alder reactions of acetals **87–89** with cyclopentadiene

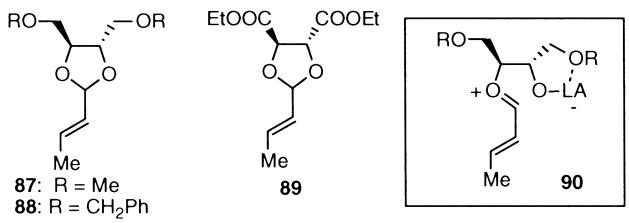


87-89

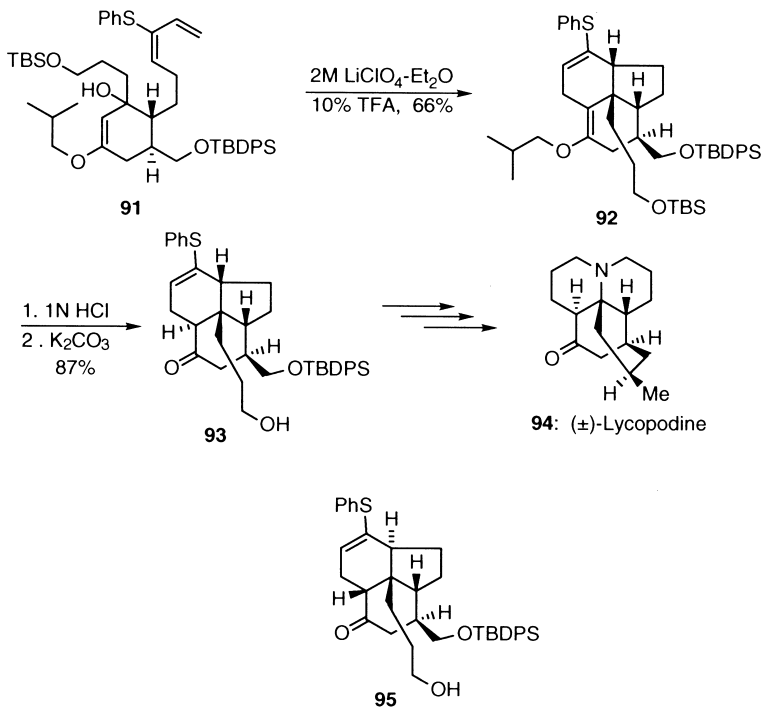
Acetal	Lewis acid	Yield (%)	*endo*/*exo*	*endo* de
87	$TiCl_4$	67	60:40	68
87	$TiCl_2(iPrO)_2$	76	74:26	78
87	$BF_3{\cdot}Et_2O$	59	60:40	60
88	$TiCl_2(iPrO)_2$	71	60:40	62
89	$TiCl_2(iPrO)_2$	65	65:35	54

which cyclized to form a cyclic oxocarbenium possessing a reactive dienophile. The 4+2 cycloaddition reactions with isoprene followed by hydrolysis of acetals provided **83a–d** in good yields (Scheme 19). Several other dienes were also used to ensure the generality of the transformation. The size of the substituent on the α'-carbon has a major effect on the diastereoselectivity. A competition experiment confirmed the intermediacy of the proposed vinyloxocarbenium ion. Thus, treatment of a 1:1 mixture of **79b** and **84** with HBF_4 and isoprene afforded only **83b** as the cycloadduct formed, **84** being recovered from the reaction mixture (Scheme 20).

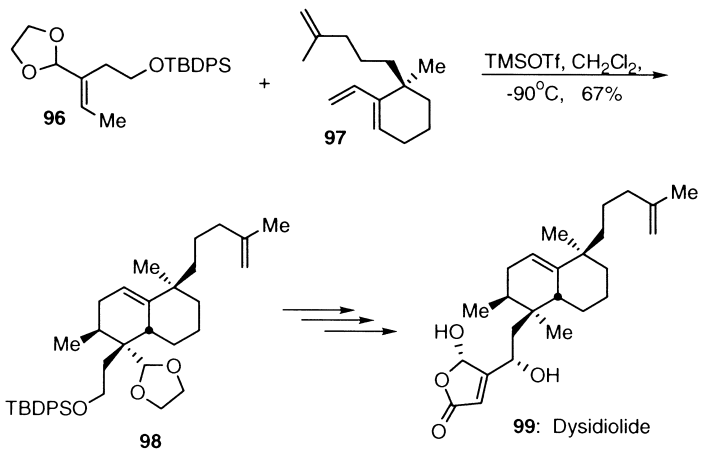
Langlois and co-workers published a study involving the generation and cycloaddition of chiral dioxolenium ions.[22] In the best case reported, treatment of orthoester **85** with 1.5 equiv. of $SnCl_4$ for 30 min at −78°C in the presence of 2,4-dimethyl-1,3-pentadiene afforded cycloadduct **86** in 59% yield as a 3:1 mixture of diastereomers (Scheme 21). Other examples using a variety of ortho esters, dienes and different reaction conditions showed no improvement in the stereochemical outcome of the reaction.



More recently, Vankar and co-workers have studied chiral allylic acetals **87–89** as precursors to chiral vinyl oxocarbenium ions for diastereocontrol in the ionic Diels–Alder reaction.[23] The anticipation was that the extra oxygens in the acetal side chain would chelate with the Lewis acid and lead to high facial selectivity in the



Scheme 22.



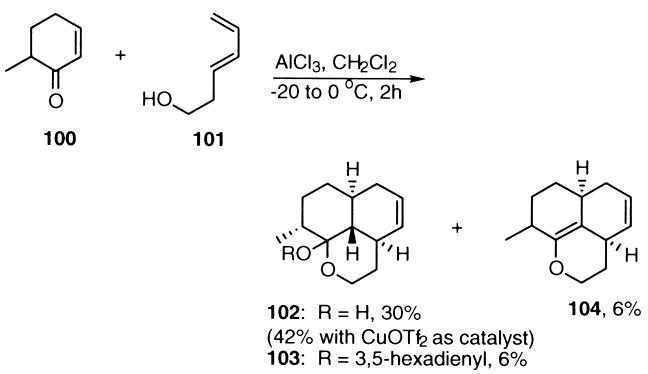
Scheme 23.

cycloaddition reaction of an intermediate like **90**. The results were fair to good with respect to diastereoselectivity, and some data are shown in Table 1. In this paper the authors also reported that Nafion H could be used to generate vinyl oxocarbenium ions from simple allylic acetals when the reaction was conducted in dichloromethane. They also demonstrated that 4 M $LiClO_4$ in nitromethane provided a medium for the direct generation of vinyl oxocarbenium ions from allylic acetals for ionic DA reactions, no acid catalyst being required.

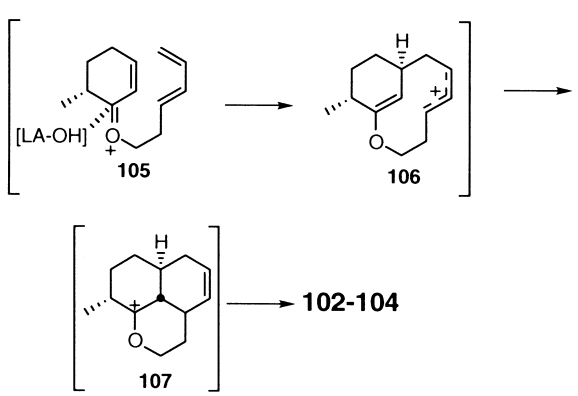
Applications of the methodologies thus far presented have not yet been extensive.[24] Grieco and Dai used methodology introduced by that group for a total synthesis of the racemic alkaloid lycopodine.[25a] The key step involved treatment of the tertiary alcohol **91** with 10 mol% trifluoroacetic acid in 2 M ethereal $LiClO_4$ to give a 66% yield of **92**. This intramolecular Diels–Alder cycloaddition product arose from an *exo* transition state. Hydrolysis and equilibration afforded **93** exclusively from **92**. Compound **93** was converted over the course of several steps to (+/−)-lycopodine (**94**). A 20% yield of the ketone **95** was also obtained during enol ether hydrolysis and equilibration. The formation of this product was rationalized on the basis of the isomerization of **91** to the corresponding (*Z*)-diene, followed by cycloaddition via an *exo* transition state (Scheme 22).

Danishefsky and co-workers have used an intermolecular ionic Diels–Alder reaction in a synthesis of dysidiolide.[25b] The acetal **96** was treated with TMSOTf in CH_2Cl_2 at −90°C in the presence of diene **97**. An *endo* selective, regioselective Diels–Alder reaction of the vinyl oxocarbenium ion derived from **96** led to the isolation of **98** in 67% yield as well as an isomer of undetermined structure in about 5% yield. Conversion of **98** to dysidiolide **99** occurred over five steps (Scheme 23).

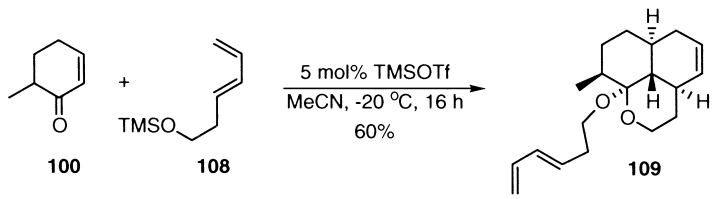
All of the cycloaddition reactions discussed up to this point have involved intermolecular reactions or intramolecular reactions in which the diene is connected to the vinyl oxocarbenium ion via a tether of carbon atoms. However, several examples exist of intramolecular cycloadditions in which the diene is joined to the vinyl oxocarbenium ion via the oxygen of the oxocarbenium ion intermediate. For example, during the course of the synthesis of an analogue of artemisinic acid, Haynes and co-workers examined the Lewis acid catalyzed ionic Diels–Alder reaction of 6-methyl-2-cyclohexenone **100** and hydroxy diene **101**.[26] In the presence of $AlCl_3$, enone **100** reacted with diene **101** to provide *trans*-fused octalin **102** (30%), acetal **103** (6%) and dehydration product **104** (6%) (Scheme 24). When the reaction was catalyzed by $Cu(OTf)_2$ in MeCN, **102** (42%) and variable amounts of **103** (up to 8%) were obtained. The relative stereochemistry of **102** was established by X-ray crystallography.[27] The mechanism of this reaction was proposed to involve the formation of a vinyloxocarbenium ion (**105**) followed by a cyclization to form **106**, which



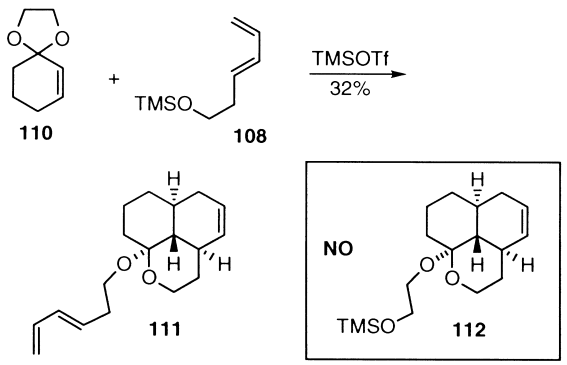
Scheme 24.



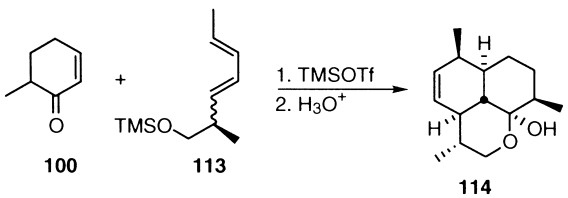
Scheme 25.



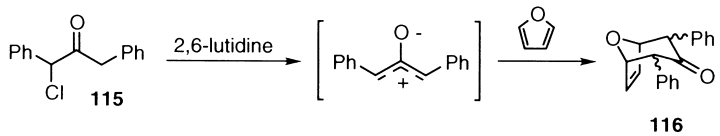
Scheme 26.



Scheme 27.



Scheme 28.



Scheme 29.

underwent ring closure to afford **107**. This cation then proceeded to the products isolated (Scheme 25).

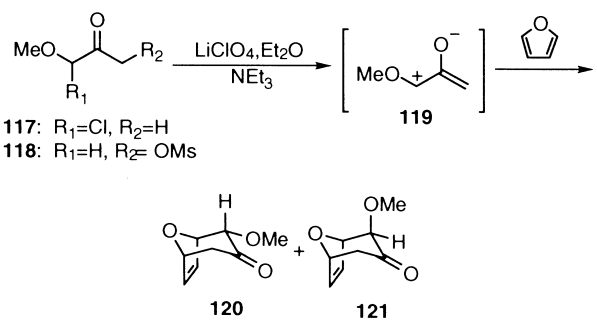
Improvements in this chemistry have been made.[28] For example, the reaction of 6-methyl-2-cyclohexonone with 2 equiv. of silyl ether **108** in the presence of 5 mol% of TMSOTf afforded cycloadduct **109** in 60% yield (Scheme 26). This product is different both structurally (acetal vs hemiacetal) and configurationally from that obtained in the $AlCl_3$-catalyzed reaction. The methyl group in **109** is axial and calculations suggest that for the acetal functional group, the axial methyl is more stable than the equatorial methyl. The opposite situation obtains when the hemiacetal functionality is present, as in **102**, and in fact hydrolysis of **109** and treatment of the resulting hemiacetal with $AlCl_3$ results in the formation of **102**.

A small number of other enones were found to react under the modified reaction conditions to afford cycloadducts. Attempts to limit the amount of silyl ether needed for the reaction by using the ethylene ketal were not promising. Treatment of **110** with 1 equiv. of **108** in the presence of TMSOTf afforded only **111** in just 32% yield, no **112** having been formed (Scheme 27). Use of a chiral acetal resulted in the formation of racemic **111**, suggesting that complete acetal exchange occurred before ring formation.

Finally, the reaction of a mixture of TMS ethers of (2*R*)-2-methylheptadien-1-ols (*E*/*Z* mixture at position 3) with racemic 6-methyl-2-cyclohexenone afforded a mixture of cycloadducts in 25% yield which upon hydrolysis afforded **114** as a single, enantiomerically pure compound (Scheme 28). The formation of **114** supports the idea of an *endo* transition state in the cycloaddition process in which initial attack on the dienophile occurs on the face *cis* to the methyl group. This contrasts with the initial mechanistic formulation in which attack was assumed to occur trans to the methyl group (see Scheme 25). In any case, the result bodes well for the development and application of relative stereocontrol in reactions of this type.

3. 4+3 Cycloaddition reactions

Seven-membered ring systems are a synthetically and theoretically interesting class of carbocycles that can be synthesized by a variety of routes, including the 4+3 cycloaddition reaction between allylic cations and dienes.[29] Discovered by Fort in 1962, the 4+3 cycloaddition reaction between allylic cations and dienes has been one of the most straightforward and powerful approaches of constructing seven-membered rings.[30] In his approach, a chloroketone was treated with a base in the presence of a diene (Scheme 29). The overall process involves an electron rich ($4\pi e^-$, 4C) diene reacting with a reactive allylic cation ($2\pi e^-$, 3C).

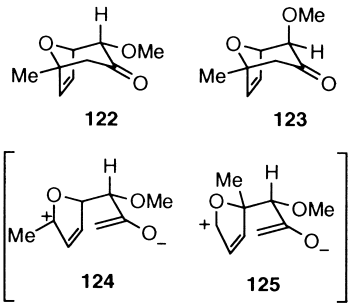


Scheme 30.

Even though there are a number of different methods existing for the generation of allylic cations in the 4+3 cycloaddition, further development of the methodological research in this area is needed to explore new aspects of the reaction and to make it as useful, convenient, and general as the 4+2 cycloaddition (Diels–Alder reaction).[31]

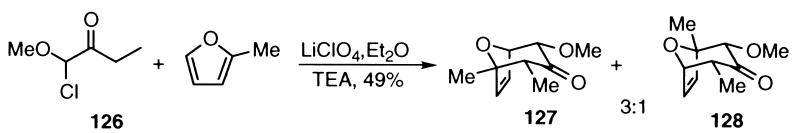
The use of vinyloxocarbenium ions in the 4+3 cycloaddition reaction has gained attention since Föhlisch and co-workers reported the formation of an oxyallylic cation intermediate by heterolysis of **117**.[32] In the presence of furan, this intermediate (**119**) reacted as a dienophile to afford 4+3 cycloaddition products (**120**,**121**) in 44% yield (Scheme 30). Although the chemical yield was modest, GC and ^{13}C NMR analysis suggested a high degree of diastereoselectivity (95:5) in favor of the *endo* isomer (**120**). The same products were obtained, although in only 12% yield, when **117** was replaced by **118**.

The question of regioselectivity was studied in the reaction between **117** and 2-methylfuran. A mixture of three cycloadducts was produced in 38% yield in a ratio of 80:18:2. The major product was **122**. The high regioselectivity (98:2) could be rationalized based on a stepwise mechanism in which the most stable zwitterion **124** was produced as an intermediate in favor of **125**. Similarly, the reaction of **126** with 2-methylfuran gave 49% yield of two regioisomeric products, **127** and **128**, in a ratio of 3:1 (Scheme 31).

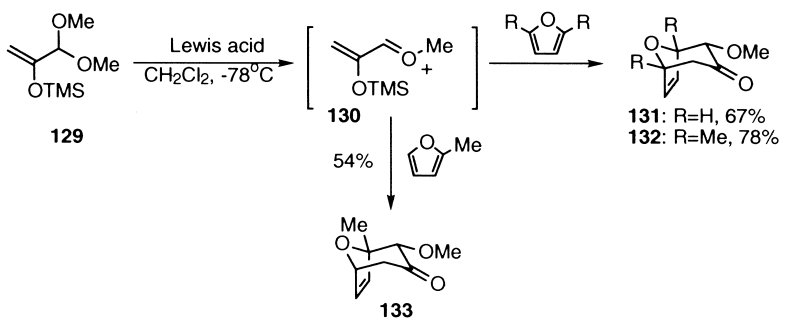


Albizati and co-workers reported the formation of vinyloxocarbenium ions from allylic acetals.[33] Treatment of **129** with a Lewis acid, such as TMSOTf, $SnCl_4$, $TiCl_4$, or BCl_3, in the presence of furan or 2,5-dimethylfuran led to cycloadduct **131** or **132** in 67 and 78% yield, respectively. The reaction with an unsymmetrical diene such as 2-methylfuran produced **133** in 54% yield as a single isomer (Scheme 32). The major differences between this result and that observed by the Föhlisch group are the complete diastereoselectivity and the opposite regiochemical outcome of the reaction. This suggests a mechanistic difference between the two reactions, but there is as yet neither sufficient data to assess the generality of the regioselectivity of both reactions, nor a good model to explain the different outcomes.

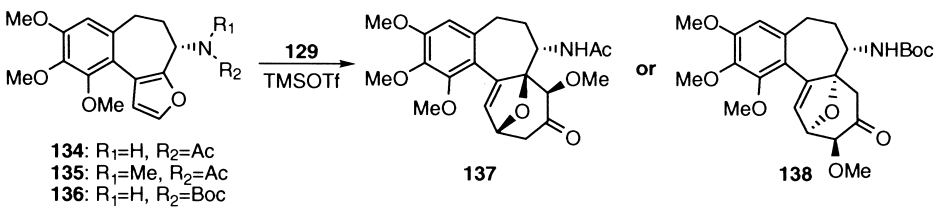
The method for the generation of vinyl oxocarbenium ions



Scheme 31.



Scheme 32.



Scheme 33.

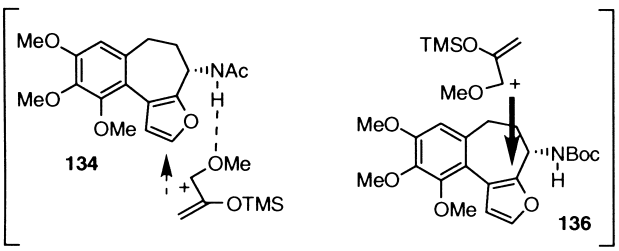
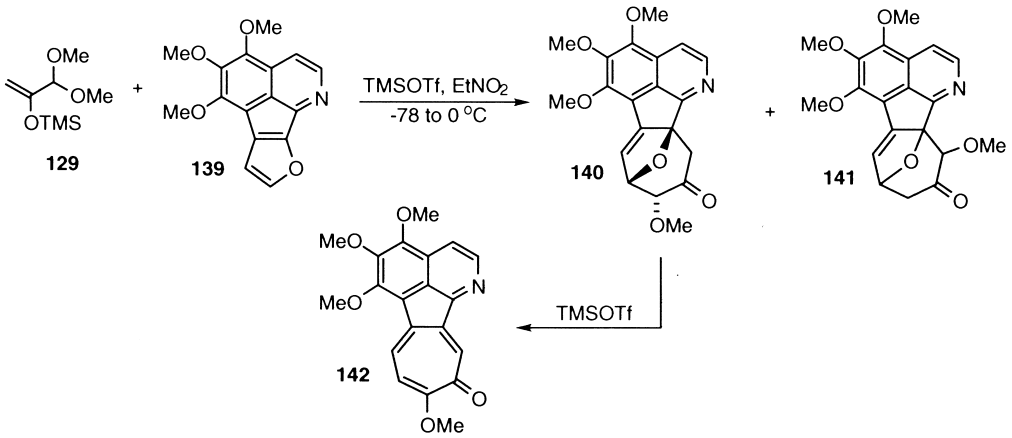


Figure 4.

would engage in 4+3 cycloaddition reactions.[36] For example, treatment of **143** with $TiCl_3(OiPr)$ in the presence of excess furan in dichloromethane at 0°C afforded the cycloadduct **144** in 70% yield as a single diastereomer (Scheme 35). The reaction with cyclopentadiene produced **145** in 50% yield.

Other alkyl-substituted allylic acetals were studied by Hoffmann and co-workers.[37] Treatment of acetal **146** with TMSOTf in the presence of furan at −78°C in nitroethane



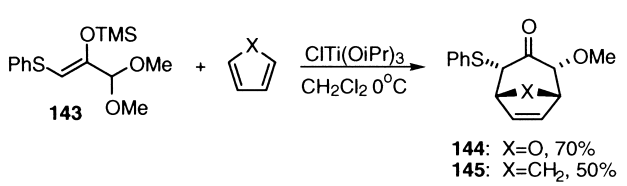
Scheme 34.

developed by Albizati was later exploited in a natural product synthesis. During the synthesis of alkaloid (−)-colchicine, Cha and co-workers observed an interesting effect of an adjacent substituent on the diene in a highly diastereoselective cycloaddition.[34] For example, the reaction of furan **134** with **129** gave the undesired isomer **137** in 60% yield (50% conversion) (Scheme 33). It was suggested that hydrogen bonding between the acetamide N–H proton and the methoxy group of the W-shaped oxyallyl cation was responsible for the regio- and diastereoselectivity (Fig. 4). This was supported by the fact that the experiment with *N*-methyl acetamide **135** resulted in only recovered starting material. The stereochemical outcome was altered when the amine was protected by a Boc group (**136**), in which case cycloadduct **138** was obtained as a sole product in 45% yield (50% conversion). The result is consistent with the *endo* approach of the W-shaped oxyallyl cation from the less hindered face of the furan.

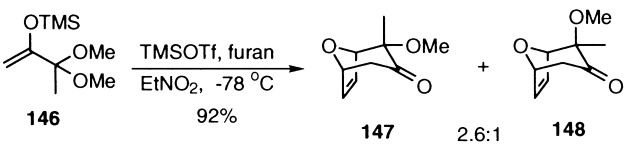
This basic approach was extended to the synthesis of various tropoloisoquinolines.[35] Reaction of **129** with furan **139** in the presence of TMSOTf produced the cycloadducts **140** and **141** in 26 and 29% yields, respectively, along with 42% of recovered starting material (Scheme 34). The reaction showed no regioselectivity. While the stereochemistry of **140** could be assigned via NMR, that of **141** remained undefined. Compound **140** could be converted to imerubrine **142** in 76% yield by treatment with TMSOTf. Compound **141** did not undergo elimination under similar conditions.

Harmata and Carter recently demonstrated that vinyloxocarbenium ions bearing additional electron donating substituents could be generated and that these intermediates afforded cycloadducts **147** and **148** in 92% yield as a 2.6:1 mixture of isomers (Scheme 36). The major product **147** was calculated to be the less stable isomer by 0.93 kcal/mol. Chemical yields and selectivities in this reaction depended upon the solvents and Lewis acids used. For example, use of CH_2Cl_2 as solvent afforded the cycloadducts in a 4.4:1 ratio (**147/148**), but only in 55% yield, when the reaction was conducted at −90°C. Other acetals were also used in the course of this study. The reaction of **149** with furan, cyclopentadiene and 2,5-dimethylfuran afforded cycloadducts with complete diastereoselectivity, but in relatively low yields (Scheme 37). The more substituted acetal **154** reacted with furan in the presence of TMSOTf to give cycloadduct **156** in only 10% yield (Scheme 38).

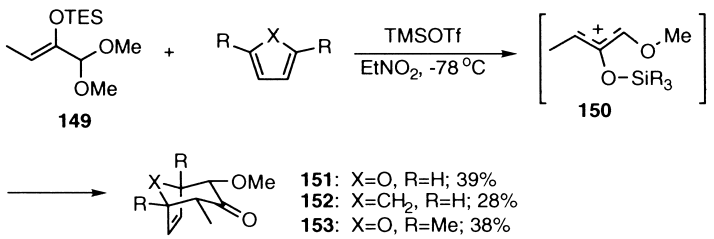
A result related to one in Hoffman's work was obtained by Harmata and Rashatasakhon.[38] They demonstrated that



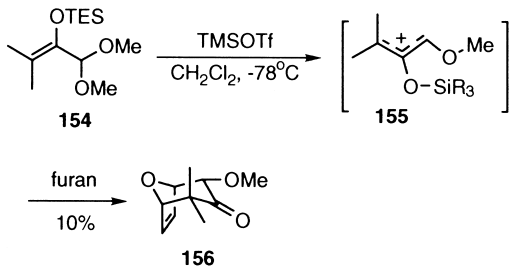
Scheme 35.



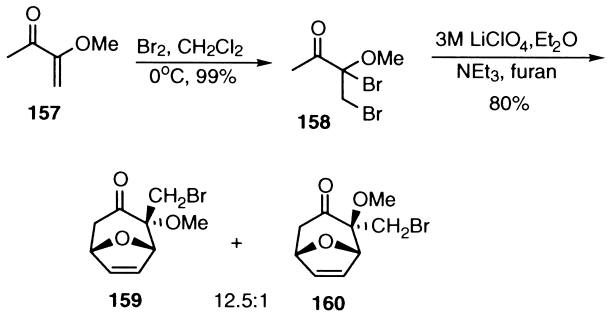
Scheme 36.



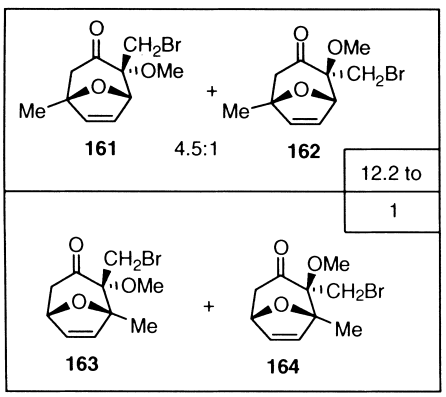
Scheme 37.



Scheme 38.



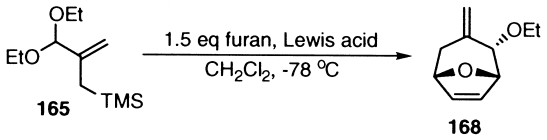
Scheme 39.



treatment of the readily available dibromide **158** with triethylamine in 3 M ethereal $LiClO_4$ in the presence of furan afforded cycloadducts **159** and **160** in 80% yield as a 12.5:1 mixture of diastereomers (Scheme 39). The reaction was performed at room temperature, making the diastereoselectivity even more noteworthy. A similar reaction with 2,5-dimethylfuran afforded a good yield of two cycloadducts, but only with low diastereoselectivity (1.8:1), but the reaction with cyclopentadiene proceeded well (67% yield, 6.2:1 diastereoselectivity). Finally, the reaction with 2-methylfuran proved interesting. Four products **161**–**164** as two sets of regioisomers were obtained in a ratio of 12.2:1 in over 70% yield. This regioselectivity is the same as that observed by the Föhlisch group in its studies of the 4+3 cycloaddition reaction using 2-methylfuran as a diene (see **122**–**123**). The major stereoisomer of the major product was **161**, as expected based on the reaction of **158** with furan.

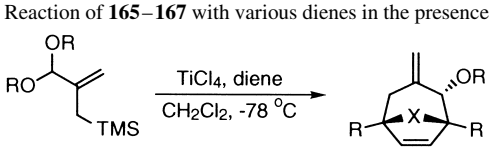
Other investigations of allylic acetals have focused on systems with a substituent at the 2 position which differs from a trialkylsilyloxy group. In 1997, Harmata and Jones prepared a series of (trimethylsilyl)methyl allylic acetals (**165**–**167**) by Peterson olefination and used these species as

Table 2. Reaction of **165** with furan to form **168**



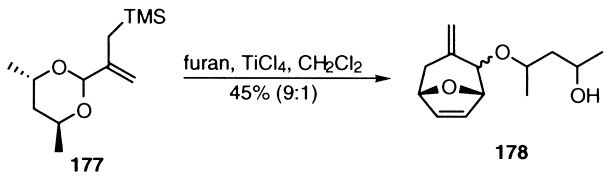
Entry	Lewis acid	Equiv.	Yield (%)
1	$TiCl_4$	1.1	99
2	$TiCl_4/Ti(OiPr)_4$ (1:1)	2	55
3	$TiCl_4/Ti(OiPr)_4$ (7:5)	2	82
4	$TiCl_4/Ti(OiPr)_4$ (11:5)	2	89
5	$TiCl_4/Ti(OiPr)_4$ (13:5)	2	84
6	$TiCl_4/Ti(OiPr)_4$ (15:5)	2	71
7	$AlEt_3$	1.1	0
8	$AlEt_2Cl$	1.1	29
9	$AlEtCl_2$	1.1	52
10	$AlMeCl_2$	1.1	61
11	$AlCl_3$	1.1	53
12	TMSOTf	0.1	65
13	TfOH	1.1	60
14	$SbCl_5$	1.1	32
15	$SnCl_4$	1.1	93

Table 3. Reaction of **165**–**167** with various dienes in the presence of $TiCl_4$



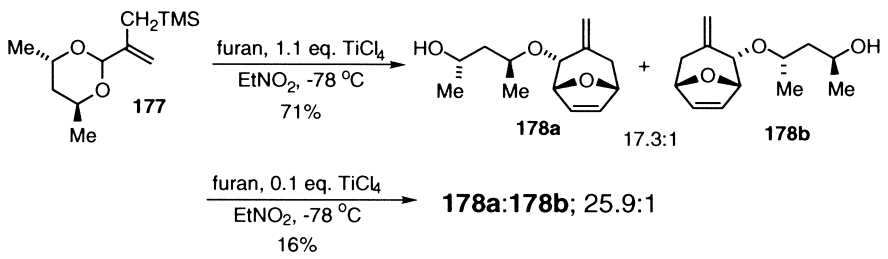
165: R=Et
166: R=Me
167: R=*i*Pr

Entry	Acetal	Diene	X	R	Product	Yield (%)
1	**165**	Furan	O	H	**168**	99
2	**165**	Cyclopentadiene	CH_2	H	**169**	62
3	**165**	2,5-Dimethylfuran	O	Me	**170**	47
4	**166**	Furan	O	H	**171**	62
5	**166**	Cyclopentadiene	CH_2	H	**172**	43
6	**166**	2,5-Dimethylfuran	O	Me	**173**	51
7	**167**	Furan	O	H	**174**	50
8	**167**	Cyclopentadiene	CH_2	H	**175**	53
9	**167**	2,5-Dimethylfuran	O	Me	**176**	0

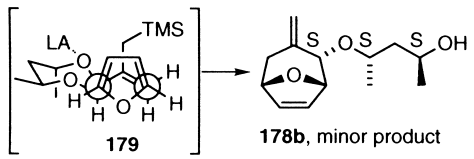


Scheme 40.

precursors for vinyl oxocarbenium ions.[39] An examination of the various Lewis acids for the reaction between **165** and furan showed that much variation was possible, though the best results came from $TiCl_4$ and $SnCl_4$ (Table 2). The scope of the reaction was examined with a small number of simple dienes as summarized in Table 3. Steric effects were evident as the reaction between **167** and 2,5-dimethylfuran failed to produce cycloadducts (Table 3, entry 9).



Scheme 41.

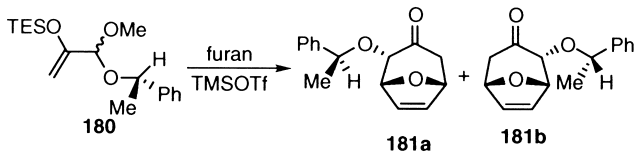


Scheme 42.

The first example of an asymmetric 4+3 cycloaddition reaction using a chiral allylic acetal was also demonstrated in this work (Scheme 40). Treatment of acetal **177** with $TiCl_4$ in the presence of furan gave rise to a 9:1 mixture of two diastereomers in 45% yield. This promising result ensured the feasibility of the chiral auxiliary-based approach to asymmetric 4+3 cycloaddition reaction.

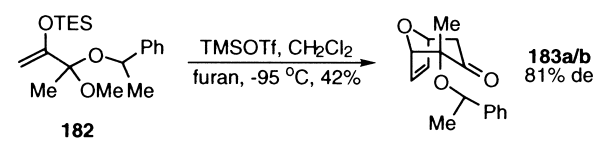
Subsequent studies demonstrated that the reaction of **177** with furan could proceed with diastereoselectivities as high at 17.3:1 (71%) yield to afford cycloadducts **178a** and **178b**.[40] Even higher diastereoselectivity could be achieved using catalytic amounts of $TiCl_4$ in nitroethane at −78°C, but the yield was quite low (Scheme 41). Interestingly, while it was anticipated that the stereochemical outcome of the reaction would be determined by an acetal/Lewis acid complex such as **179**, ring-opening with inversion directing the formation of the major stereoisomer, this was shown not to be the case (Scheme 42). A clear rationalization of the stereochemical outcome of the reaction has not yet been published. A number of Lewis acids were examined in this reaction and they all produced that same major diastereomer, though diastereomeric ratios varied considerably. Interestingly, the reaction with cyclopentadiene proceeded well in terms of yield, but was not very diastereoselective.

Table 4. Reaction of **180** with furan and TMSOTf

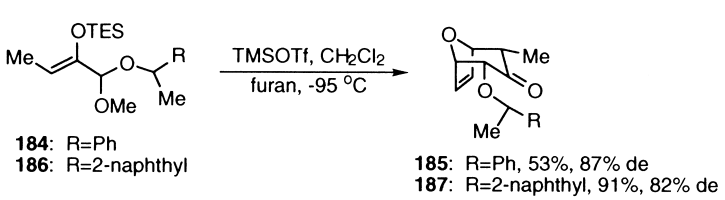


Entry	Solvent	T (°C)	Yield (%)	**181a/181b**	de (%)
1	CH_2Cl_2	−20	55	2.9:1	49
2	CH_2Cl_2	−78	58	5.3:1	68
3	CH_2Cl_2	−95	67	7.5:1	76
4	Et_2O	−95	10	12.:1	10
5	THF	−95	14	1.3:1	13
6	Pentane	−95	21	2.1:1	36
7	Furan (neat)	−78	54	2.9:1	49
8	$MeNO_2$	−95	36	4.1:1	61
9	CH_2Cl_2/pentane	−110	37	8.2:1	78

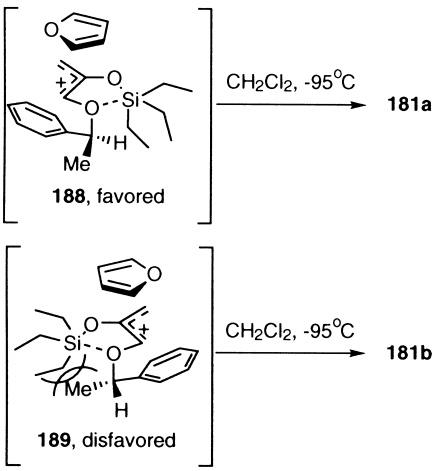
Other chiral acetals have been examined in the context of asymmetric 4+3 cycloaddition processes. For example, Hoffmann and co-workers investigated a 4+3 cycloaddition protocol using mixed, chiral allylic acetals based on the methodology introduced by Albizati (see Scheme 32).[41] The reaction of acetal **180** with furan and catalytic amount of TMSOTf produced cycloadducts **181a/181b** in varied yields



Scheme 43.



Scheme 44.



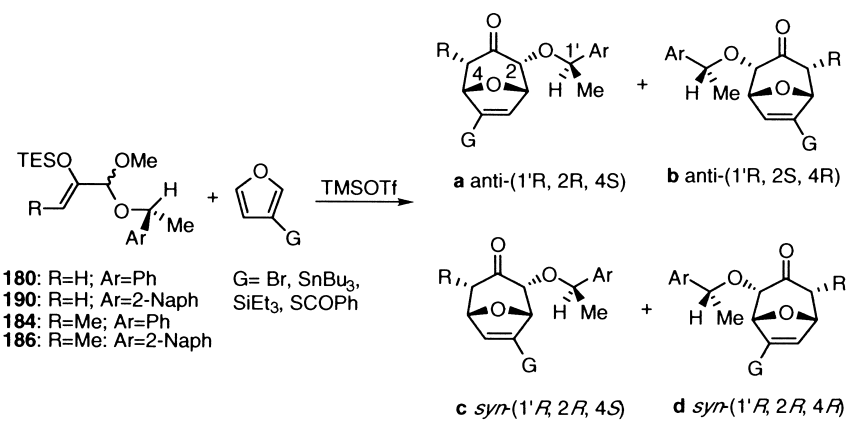
Scheme 45.

and selectivities depending upon the choices of solvent and temperature (Table 4). Changing from the phenyl group to a 2-naphthyl group led to complete diastereoselection.[42] The reaction of other chiral acetals was also investigated. Acetal **182** afforded two products **183a/b** with 81% de in 42% yield (Scheme 43). Interestingly, acetal **184** gave cycloadduct **185** in 53% yield in 87% de while its naphthyl analog **186** afforded a higher yield (91%) of the corresponding cycloadduct **187** but with a de of only 82% (Scheme 44). Both reactions were conducted at −95°C.

The origin of the stereochemical outcome in these reactions was rationalized by the two diastereomeric transition states having the allylic cation stabilized by the aromatic moiety of the chiral auxiliary as illustrated in Scheme 45 for the formation of **181a/b**. Assuming silicon–oxygen chelation and a steric interaction between –Me and $-SiEt_3$ groups, structure **188b**, which would lead to the minor product, would be less favored.

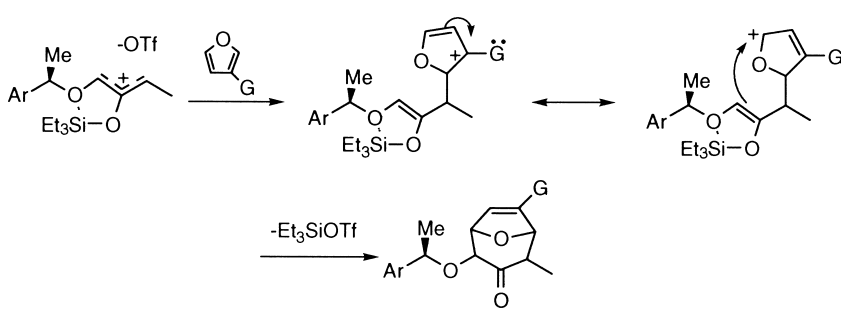
The compatibility of substituted furans with this cycloaddition procedure was studied recently.[43] Furans with substituents such as bromine, silicon, tin, and sulfur at the 3-position reacted rapidly with the allylic cation generated from chiral allylic acetals (Table 5). It was postulated that the reactions proceeded in a stepwise fashion (or via a highly asynchronous transition state) as a means of rationalizing the very high levels of regioselectivity

Table 5. Reaction of chiral acetals **188**–**191** with substituted furans

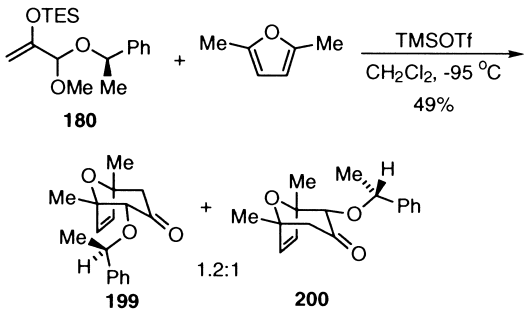


Entry	Acetal	G	Product	Diastereoselectivity (a+c)/(b+d)	Regioselectivity (a+b)/(c+d)	Overall yield (%)
1	**180**	Br	**191**	7:1	10:1	50
2	**184**	$SnBu_3$	**192**	–	–	51[a]
3	**180**	$SiEt_3$	**193**	7:1	1.3:1	74
4	**190**	$SiEt_3$	**194**	6:1	1.3:1	73
5	**180**	SCOPh	**195**	1.2:1	6:1	79
6	**190**	SCOPh	**196**	1.5:1	6:1	74
7	**184**	SCOPh	**197**	17:1	17:1	75
8	**186**	SCOPh	**198**	13:1	14:1	75

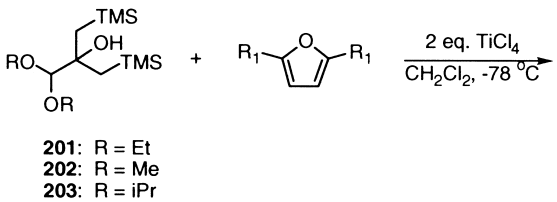
[a] Only **192a** was isolated cleanly due to side product formation.

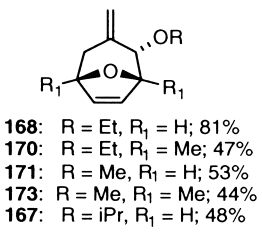


Scheme 46.



Scheme 47.





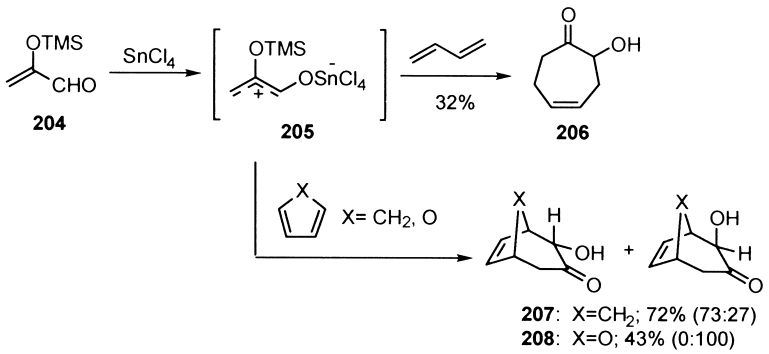
Scheme 48.

observed (Scheme 46). However, a steric effect from bulky substituents (such as a TBDMS group) prevented the *endo* approach of the allylic cation. A high selectivity was obtained from 3,4-dibromofurans with slightly lower yield. The reaction with 2,5-dimethylfuran with **180** afforded cycloadduct in reasonable yield, but with low selectivity (Scheme 47). This was rationalized on the basis of inhibition of stacking between the allylic dienophile and the diene due to untoward steric interactions between the methyl groups and the dienophile.

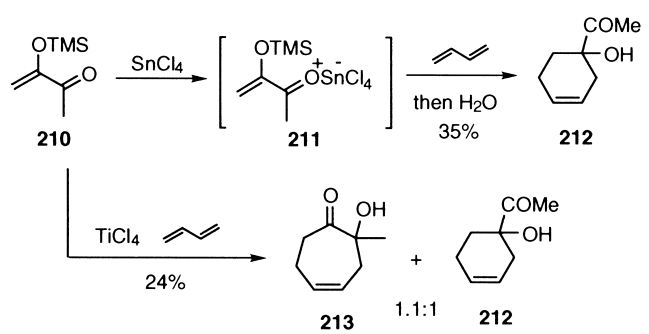
A unique approach to vinyl oxocarbenium ions for 4+3 cycloaddition was introduced by Harmata and Jones.[44] Treatment of **201** with $TiCl_4$ presumably resulted in an initial Peterson reaction to form the corresponding allylic acetal **165** (see Table 2) that gave a vinyl oxocarbenium ion upon reaction with additional Lewis acid. With furan as the diene, cycloadduct **168** was obtained in 81% yield. Other dienes were also successful, illustrating that the reaction possessed some scope (Scheme 48).

While we mentioned that Lewis acid complexes of α,β-unsaturated carbonyl compounds would not be covered in detail, their application in 4+3 cycloaddition reactions is sufficiently limited and fascinating to warrant a presentation of the results in that area.

Some 20 years ago, two different groups studied the Lewis acid-catalyzed formation of vinyl oxocarbenium ions from α,β-unsaturated carbonyl compounds in the context of 4+3 cycloaddition chemistry. Sasaki and co-workers reported the $SnCl_4$-catalyzed reaction of silyloxyaldehyde **204** with dienes.[4] The reaction worked well with several dienes and gave fair to good yields of α-hydroxy 4+3 cycloadducts



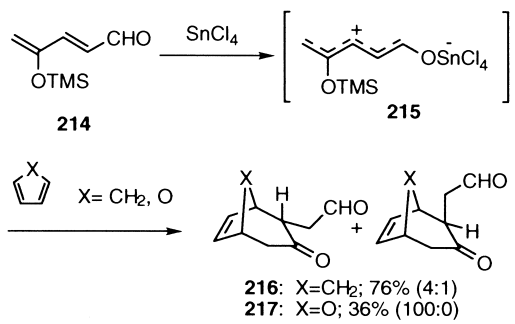
Scheme 49.



Scheme 50.

(**206**–**208**) after aqueous workup (Scheme 49). In contrast, the reaction of ketone analog **210** gave only 4+2 cycloadduct (Scheme 50) due to the difference in the two resultant intermediates (**205** vs. **211**), the latter being formulated as a polarized unsaturated ketone, the former as an allyl cation. However, Childs and co-workers found that the $TiCl_4$ catalyzed reaction of **210** with 1,3-butadiene actually produced a mixture of 4+2 and 4+3 cycloadducts (Scheme 50).[45] Ketone **213** could be converted to **212** under acidic conditions or at high temperature.

A related study was reported by Eguchi and co-workers.[46] A vinylogous congener of **205** was generated by reacting the



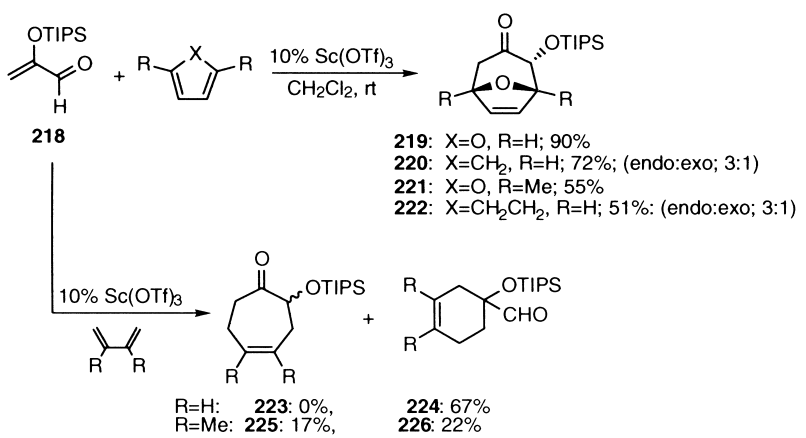
Scheme 51.

silyl enol ether **214** with $SnCl_4$ (Scheme 51). This afforded **215**, which underwent cycloaddition reactions with furan and cyclopentadiene. The *endo* product **216** was predominant in the case of cyclopentadiene and complete *endo* stereoselectivity was observed in the case of furan.

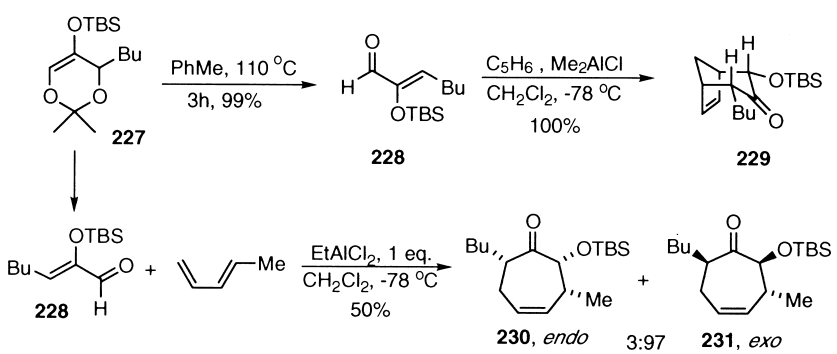
Much more recently, Harmata and Sharma published a report on the ability of $Sc(OTf)_3$ to catalyze the 4+3 cycloaddition reaction of 2-(triisopropylsilyloxy)acrolein (**218**).[47] The procedure consisted of treating a solution of **218** and 2.5 equiv. of diene in CH_2Cl_2 with 10 mol% $Sc(OTf)_3$ at room temperature. The best case was the reaction with furan, which produced a single diastereoisomer of cycloadduct (**219**) in 90% yield. Reasonable yields and diastereoselectivities were obtained with several other dienes (Scheme 52). In the case of acyclic dienes such as butadiene, however, 4+2 cycloadducts were formed either exclusively or as a significant byproduct.

Funk and Aungst reported the preparation of 2-trialkylsilyloxy-2-alkenals from 1,3-dioxin-5-ones and their utility in 4+3 cycloadditions.[48] For example, heating dioxin **227** in refluxing toluene gave rise to aldehyde **228** as a single stereoisomer in 99% yield (Scheme 53). Such stereoselectivity appears to be general. Treatment of **228** with 1 equiv. of Me_2AlCl in the presence of cyclopentadiene in CH_2Cl_2 at −78°C afforded a quantitative yield of **229** as a single stereoisomer. With $SnCl_4$ as the Lewis acid, a lower yield of product was obtained (73%) with an *endo*/*exo* ratio of 4:1. Interestingly, high levels of regiocontrol were possible using this chemistry. The reaction of **228** with piperylene in the presence of $EtAlCl_2$ afforded a 50% yield of **230** and **231** in a ratio of 3:97, the major product being the *exo* isomer. The intramolecular version of this reaction was also demonstrated (Scheme 54). It required direct exposure of dioxin **232** or **233** to Lewis acid, suggesting Lewis acid catalysis of both the retro-Diels–Alder reaction required to generate **234** and of the subsequent intramolecular 4+3 cycloaddition of this α,β-unsaturated aldehyde. As in certain intermolecular reactions, *endo*/*exo* selectivity was a function of the nature of the silyloxy substituent.

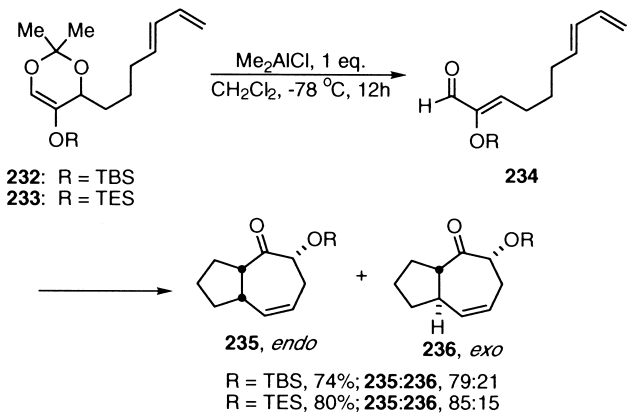
Finally, some miscellaneous reactions need to be presented. Hoffmann and co-workers published a study of the 4+3 cycloaddition chemistry of certain acyl cyanides.[49] For example, the reaction of **237** and **238** with cyclopentadiene afforded the cycloadducts **241** and **242** in 36 and 70% yields, respectively (Scheme 55). Presumably, the reactive intermediate was a Lewis acid complex such as **239** or an acylium ion like **240**.



Scheme 52.



Scheme 53.

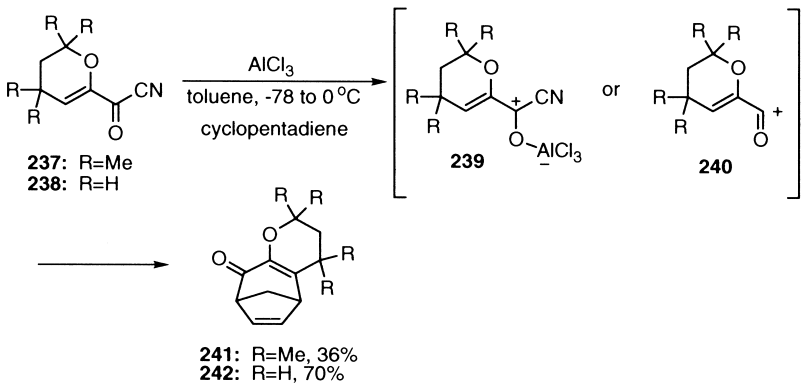


Scheme 54.

In some very recent work, Avenoza, Peregrina and coworkers showed that certain oxazolones could function as dienophiles in 4+3 cycloaddition reactions with cyclopentadiene upon Lewis acid activation.[50] Thus, the reaction of **243** with 1.5 equiv. of $EtAlCl_2$ in the presence of cyclopentadiene afforded **245**, presumably via initial 4+3 cycloaddition to afford cation **244** and subsequent trapping with cyclopentadiene to give **245** (Scheme 56). Unfortunately, at this stage this reaction is limited to the use of cyclopentadiene as the diene reactant.

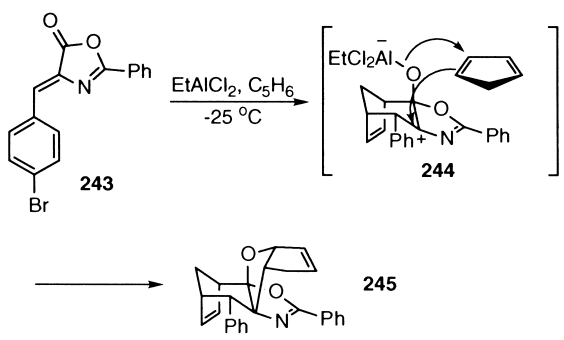
4. 2+2 Cycloaddition reactions

The use of vinyl oxocarbenium ions in 2+2 cycloadditions



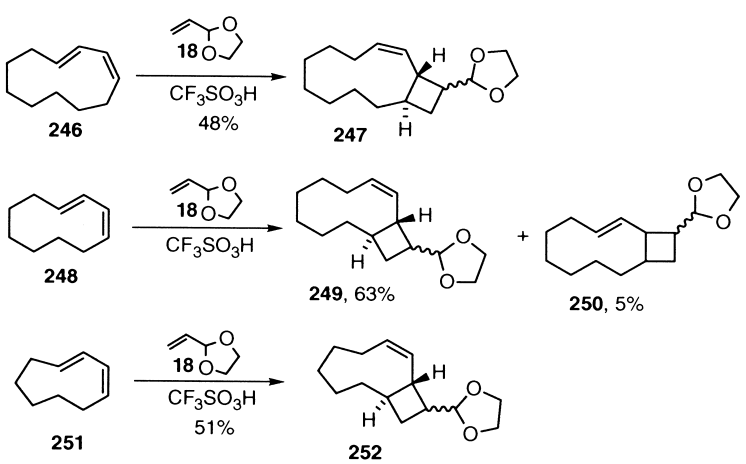
Scheme 55.

is virtually unexplored, save for two publications from the Gassman group. These workers showed that vinyl oxocarbenium species can indeed engage in what appears to be a stepwise reaction with select dienes and alkenes to afford cyclobutanes.

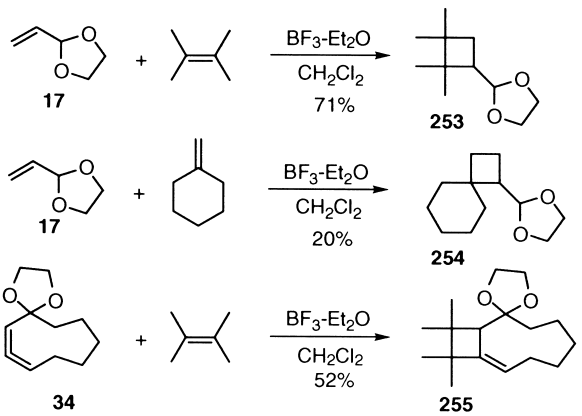


Scheme 56.

For example, with a small series of cyclic (E,Z) conjugated dienes, it was found that acetal **18** reacted to afford 2+2 rather than 4+2 cycloadducts (Scheme 57).[51] The result suggested, however, that the reactions of vinyl oxocarbenium ions with dienes might generally proceed in a stepwise fashion, regardless of the ultimate periselectivity. The regioselectivity of the process was not rationalized.



Scheme 57.



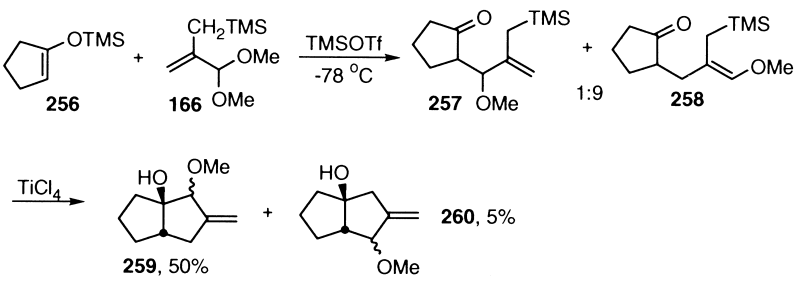
Scheme 58.

The scope of this process was broadened when it was demonstrated that various substituted alkenes could lead to cyclobutanes upon reaction with vinyl oxocarbenium ions (Scheme 58).[52] Yields were high for tetrasubstituted alkenes, but low for 1,1-disubstituted systems.

5. 3+2 Cycloaddition reactions

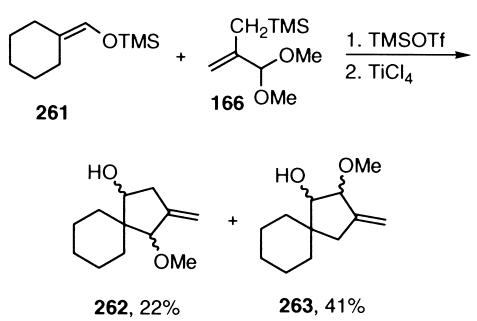
Also relatively rare are the 3+2 cycloadditions of vinyl oxocarbenium ions, though what might be called a special class of such intermediates has received a reasonable amount of recent attention.

The first examples of 3+2 cycloadditions involving vinyl oxocarbenium ions were reported by Lee and co-workers.

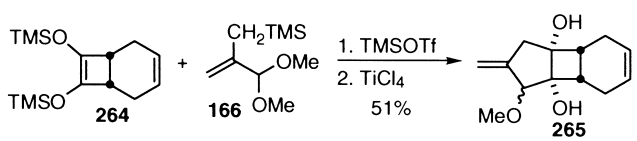


Scheme 59.

These reactions are distinctly stepwise and involve a one-pot, two-operation process to lead to annulation products that look like 3+2 cycloaddition adducts. For example, the reaction of **166** with enol ether **256** in the presence of TMSOTf afforded **257** and **258** as a 1:9 mixture of isomers.[53] Subsequent treatment with $TiCl_4$ gave adducts **259** and **260** in 50 and 5% yields, respectively (Scheme 59). The major product of the first step of the reaction sequence arises from conjugate addition of the silyl enol ether **256** to the vinyl oxocarbenium ion derived from **166**. The regioselectivity is high in the case shown, but is not universally so. It was found that products such as **258** react faster with Lewis acids than products like **257**. This formed the basis for the separation of these two species. In the case of **261**, it was mentioned that TMSOTf is sufficiently strong as a Lewis acid to effect both carbon–carbon bond forming steps, without recourse to $TiCl_4$, to afford **263** directly, though details were not given (Scheme 60).[54] The general development of the reaction as a one-pot, one-operation process has apparently not been reported.



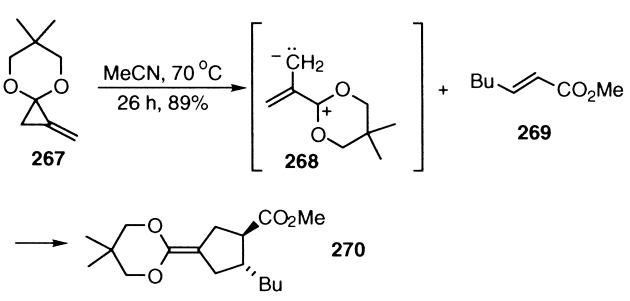
Scheme 60.



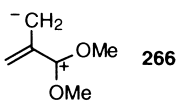
Scheme 61.

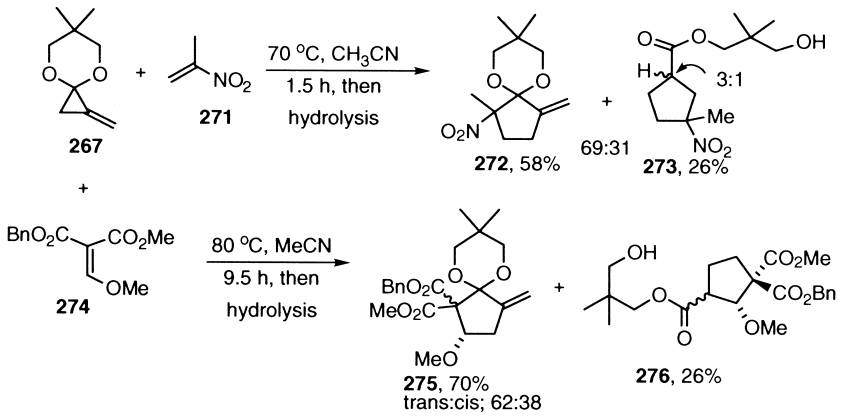
This chemistry was extended to other enol ethers as shown in Scheme 61.[55] The product diols obtained in this way could be oxidatively cleaved to afford medium ring systems.

Trimethylenemethane species such as **266** can be viewed as vinyl oxocarbenium ions substituted by a carbanion. The cycloaddition chemistry of these species is reasonably well developed. As this report was being written, a review on the chemistry of these species appeared.[56] Consequently, we will only present several highlights in this section.

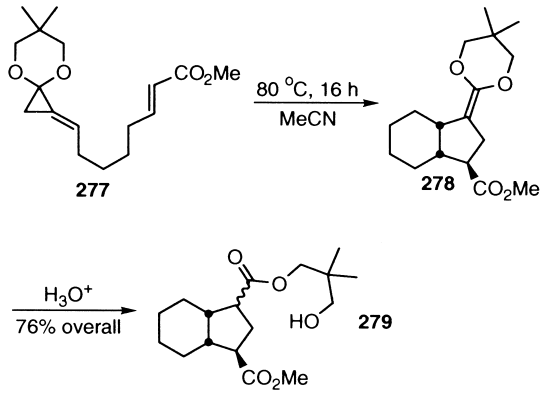


Scheme 62.

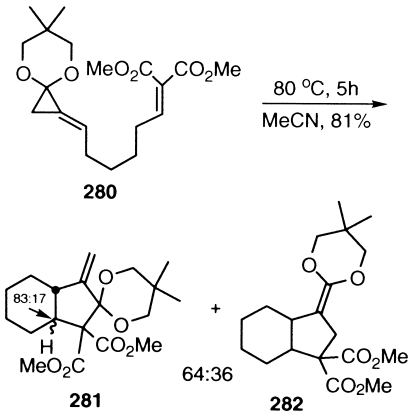




Scheme 63.



Scheme 64.



Scheme 65.

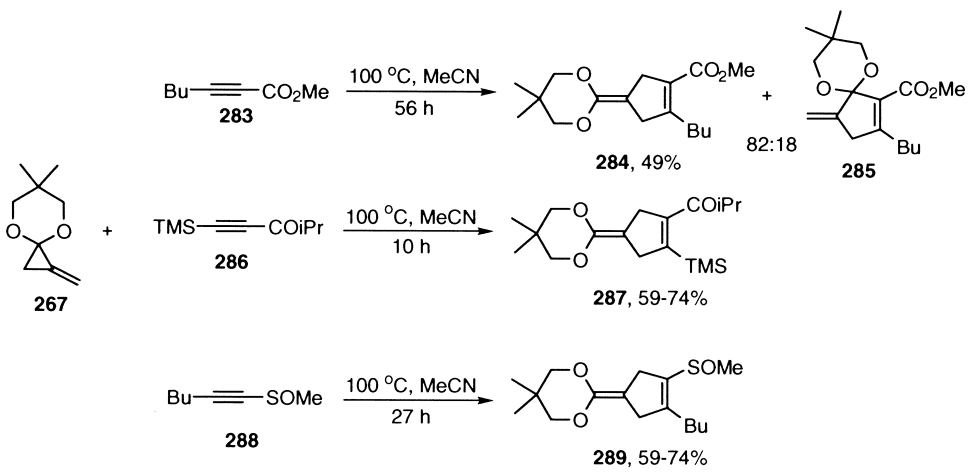
All of the work to be discussed was performed by the Nakamura group. In 1989, this group demonstrated that thermolysis of **267** in the presence of electron deficient alkene **269** afforded 3+2 cycloadducts as exemplified in Scheme 62.[57] Retention of alkene configuration in this example and with the corresponding *Z* alkene implied a concerted mechanism. Studies with substituted trimethylenemethanes demonstrated that alkenes reacted in an *endo* fashion.[58] With more highly electrophilic alkenes, a mechanistic and concomitant regiochemical change in the reaction was observed. For example, reaction of **267** with nitroalkene **271** afforded a mixture of **272** and **273** in a ratio of 69:31 in an overall yield of 84% (Scheme 63). With methoxymethylenemalonates such as **274**, it was found that the cycloaddition process proceeded with loss of alkene stereochemistry to the extent of about 20% initially, though further erosion was due to product equilibration. Alkene **274** and its *Z* congener isomerized during the cycloaddition, but were thermally stable in the absence of **267**. These and other data suggested that the reaction was not concerted but in fact proceeded by a SET mechanism. It was suggested that alkenes with reduction potentials less negative than −1.8 V (vs SCE) will react with **267** via this mechanism.

An intramolecular version of this cycloaddition process has been published.[59] Thermolysis of **277** gave the cycloadduct **279** after hydrolysis in 76% yield (Scheme 64). On the other hand, similar treatment of **280** afforded an 81% yield of **281** and **282** as a 64:36 mixture of regioisomers (Scheme 65). The ratio of stereoisomers of the major regioisomer was 83:17. The differences between the reactions shown in Schemes 64 and 65 were ascribed to a change in mechanism from a concerted cycloaddition to a stepwise SET process.

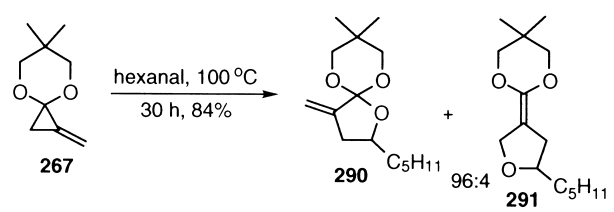
Alkynes react with **267**, though more slowly than alkenes, to afford ketene acetal products as the major, but not always exclusive, regioisomer. Examples are shown in Scheme 66. The ketene acetals shown in this and other schemes were unstable and yields reported are generally for esters obtained after acidic hydrolysis, even if these esters are not explicitly shown.

Aldehydes, ketones and certain imines also react with **267** and its congeners in a 3+2 cycloaddition fashion. Thermolysis of **267** in toluene in the presence of hexanal afforded an 84% yield of two products in ratio of 96:4.[60] The major product was orthoester **290**, typical of the structure of the major products obtained in the study (Scheme 67). A study of the regiochemistry in this reaction was not pursued in great detail, but the reaction of **292** with benzaldehyde gave an 85% yield of **293** and **294** in a ratio of 2:1 (Scheme 68).

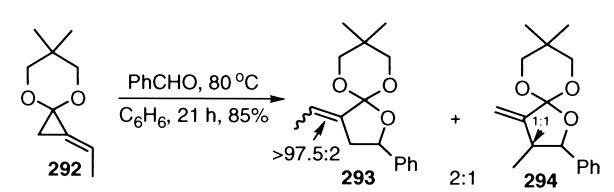
Imines are less electrophilic than their corresponding ketones or aldehydes and this was reflected in the reactivity of imines towards **267**. The *N*-phenylimine of benzaldehyde



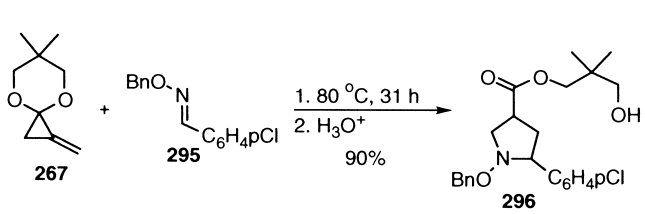
Scheme 66.



Scheme 67.



Scheme 68.

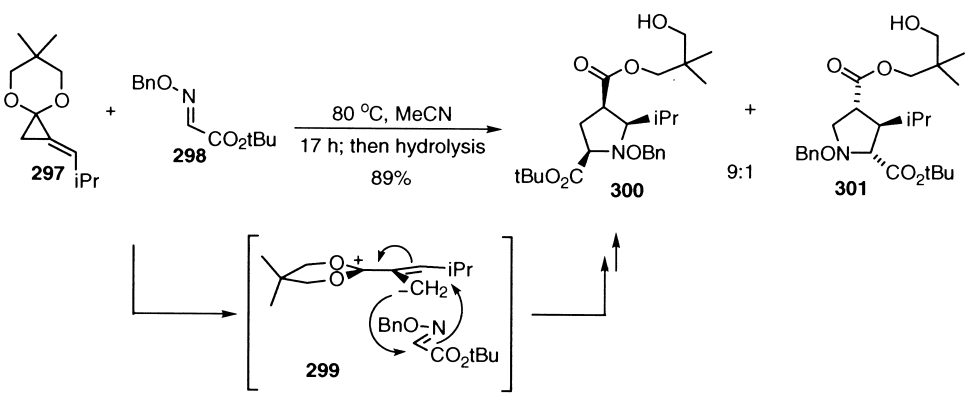


Scheme 69.

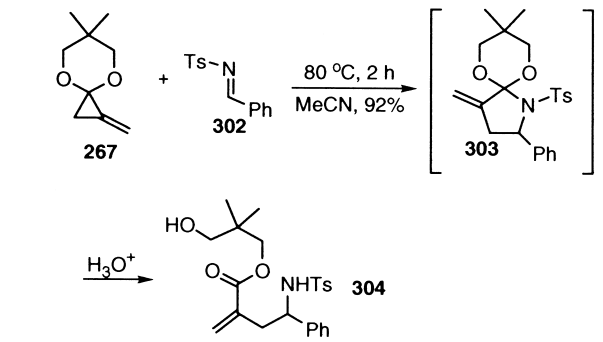
did not react with **267**. However, *O*-alkyloximes were sufficiently reactive to afford excellent yields of products.[61] Thermolysis of **267** at 100°C in acetonitrile in the presence of **295** afforded **296** in 90% yield after hydrolysis of the ketene acetal formed directly from the cycloaddition (Scheme 69). Solvent was not necessary for the reaction to proceed. Regioselectivity and stereoselectivity were often only fair in these reactions, but good results could be obtained when sterically bulky substituents were present in the reactants. Thus, reaction of **297** with **298** gave a 9:1 mixture of the cycloadducts **300** and **301** (Scheme 70). Both cycloadducts were formed with very high levels of stereoselectivity. The origin of both selectivities was ascribed to steric interactions in the transition states (e.g. **299**) leading to the products. More electrophilic imines such as sulfonyl- and acylimines also reacted to form cycloadducts with **267**, but with a different regioselectivity from that observed with *O*-alkylimines.[62] Thus, thermolysis of **267** and **302** at 80°C afforded the ester **304**, after hydrolysis of the orthoamide **303**, in 92% yield (Scheme 71). The mechanism in this case was considered to involve SET rather than the concerted process considered operative with *O*-alkyloximes.

6. 5+2 Cycloaddition reactions

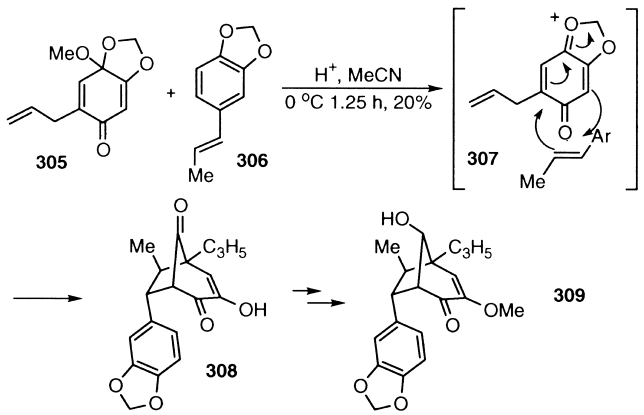
Cycloadditions from this class are not common, except with oxidopyrylium ions. These species can be classified as



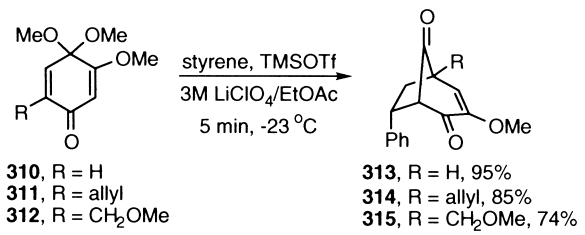
Scheme 70.



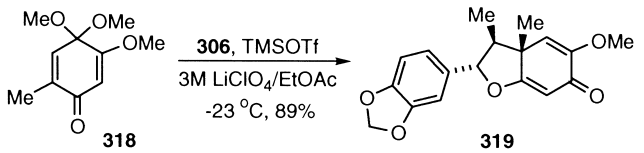
Scheme 71.



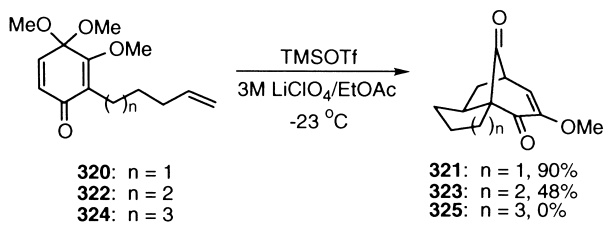
Scheme 72.



Scheme 73.



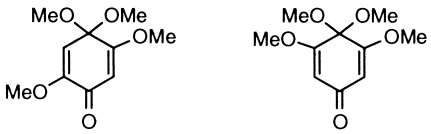
Scheme 74.



Scheme 75.

oxocarbenium ions, but their reactivity pattern with alkenes is basically that of a carbonyl ylide. An excellent, timely review on the chemistry of these species has been published.[63]

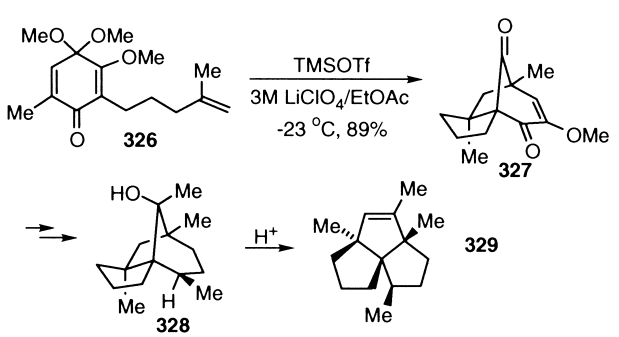
Some cationic 5+2 cycloaddition reactions are known, however. Büchi and Mak performed syntheses of various neolignans starting with quinone monoketals.[64] For example, the reaction of **305** with isosafrole (**306**) in the presence of 2,4,6-trinitrobenzenesulfonic acid in acetonitrile at 0°C afforded the cycloadduct **308** in 20% yield, along with other products. This cycloadduct was converted to racemic guianin (**309**) over several steps (Scheme 72). An obvious problem with this reaction is the low yield of the cycloaddition step. Related cycloadditions using quinones and Lewis acid activation also suffered from this problem.



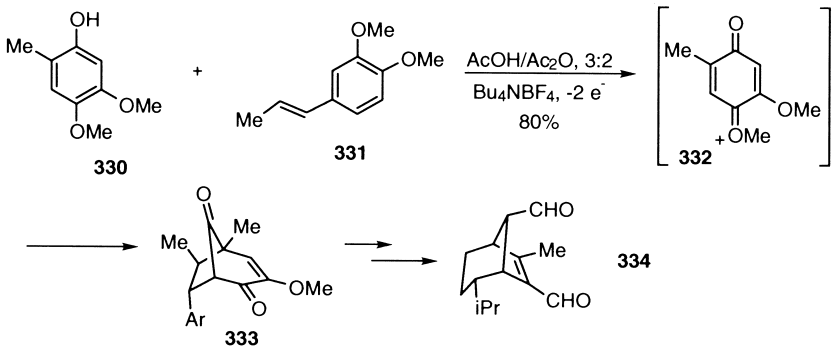
A breakthrough in the area which solved this difficulty was published recently by the Grieco group. They showed that conducting the cycloaddition reaction in highly polar media can result in extremely high yields of product.[65] Thus, the reaction of ketals **310**–**312** with styrene in 3 M $LiClO_4$ in ethyl acetate in the presence of a stoichiometric amount of TMSOTf afforded cycloadducts **313**–**315** in excellent yields and selectivity (Scheme 73). The reactions were complete in 5 min or less at −23°C. Some limitations were described. Quinone monoketals **316** and **317** did not give cycloadducts with styrene. And while the ketal **318** reacted with a number of alkenes successfully to afford a 5+2 cycloadduct, its reaction with isosafrole resulted only in the formation of **319** in 89% yield (Scheme 74).

The reaction was extended to an intramolecular version by Grieco and Walker.[66] Treatment of a solution of **320** in 3 M $LiClO_4$ in ethyl acetate with TMSOTf at −23°C afforded the cycloadduct **321** in 90% yield in 5 min (Scheme 75). The homologous **322** gave the corresponding cycloadduct **323** in 48% yield at best, along with side products, while **324** afforded no 5+2 cycloadduct. Other substrates with three carbon tethers between the alkene and oxocarbenium ion gave cycloadducts in very high yields. The cycloadduct **327** was obtained in 89% yield from **326**. It was converted over several steps to the natural product isocomene (**329**) (Scheme 76).

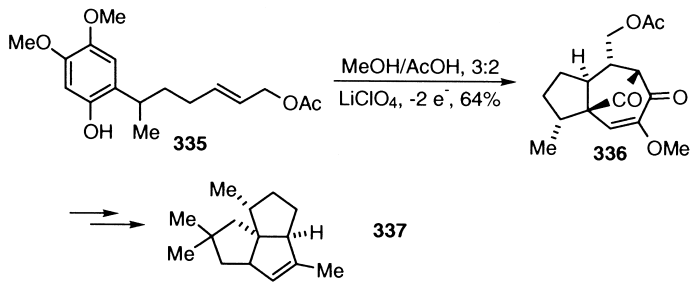
Other approaches to the generation of intermediates like **307** have been made using electrochemical oxidation of the appropriate phenols. This area has been recently reviewed,[67]



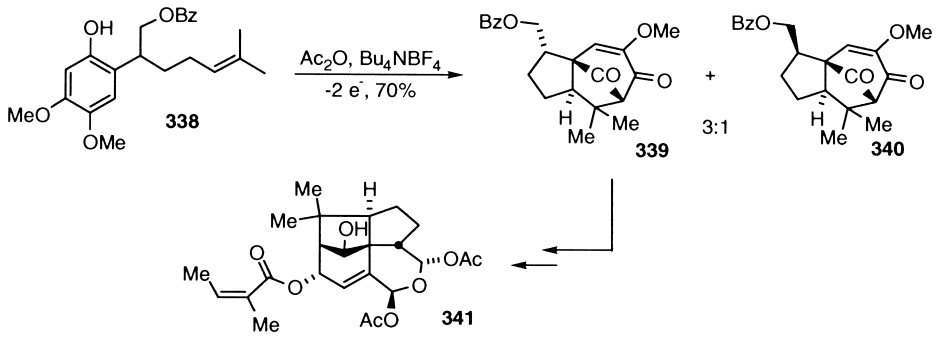
Scheme 76.



Scheme 77.



Scheme 78.



Scheme 79.

so only a few examples of the chemistry will be presented. All of these examples are the result of work from the Yamamura group.

An example of an intermolecular cycloaddition was published in the context of a synthesis of helminthosporal.[68] Anodic oxidation of **330** in the presence of **331** afforded the cycloadduct **333** in 80% yield (Scheme 77). This was converted to helminthosporal **334** over several steps.

Intramolecular cycloadditions based on electrochemical oxidation of phenols have seen application. A synthesis of pentalenene began with the oxidation of **335** to afford **336** in 64% yield (Scheme 78).[69] This intermediate was converted to the sesquiterpene natural product pentalenene. An isocedrane natural product **341** was prepared from the cycloadduct **339**. The cycloadduct **339** was prepared as part of a 3:1 mixture with **340** in 70% yield from the phenol **338**. Relative stereocontrol in this case was rather low, but the yield of the cycloaddition was sufficiently high to enable application of the process to the synthesis of **341** (Scheme 79).

7. Conclusion

Work on the generation of vinyl oxocarbenium ions, further methodological developments with respect to their cycloaddition chemistry, particularly with respect to stereochemical control, and especially the application of the methodology should provide ample impetus for continued work in the area. A little funding would not hurt either. While there are cycloaddition processes that are catalytic and quite elegant, they do not yet fill every synthetic need. Thus, the development of reactive species capable of cycloaddition is and will remain important for some time to come. Further, chemists, including synthetic ones, are in the business of exploring the nature of molecules, their structure and reactivity; not making only technological contributions, but fundamental ones as well. The creation, generation and study of reactive intermediates is but one of

many areas where synthetic organic chemists have and will continue to make important contributions to Science.

Acknowledgements

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Biographical sketch

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Paitoon Rashatasakhon was born in Samut-Sakhon, Thailand in 1975. He attended Chulalongkorn University (Bangkok) in 1993, received his B.S. degree in chemistry in 1997, and joined the Department of Chemistry at the University of Missouri-Columbia later that year. He worked under the guidance of Professor Michael Harmata and earned his PhD degree in 2002 for his work on 4+3 cycloaddition reactions, including the synthetic utility of vinyl oxocarbenium ions and cyclopentenyl oxyallyl zwitterions. Paitoon is currently working as a postdoctoral research fellow with Professor Albert Padwa at the Emory University in Atlanta, Georgia. His other interests include tennis, volleyball, and most importantly, badminton, which he has played casually and as a tournament participant since 1989.