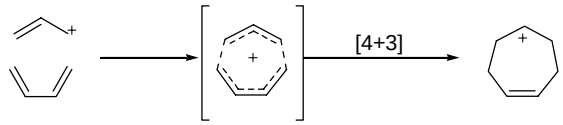
[4 +3] CYCLOADDITIONS: SEVEN MEMBERED RINGS FROM ALLYL CATIONS

Reported by Christopher S. Regens November 29, 2004

INTRODUCTION

Cycloaddition reactions represent one of the most powerful methods in organic chemistry for the synthesis of cyclic structures. The high fictionalization and stereoselectivity imparted to the products frequently characterize these processes and make them particularly useful in complex molecule synthesis. Five and six-membered rings are typically constructed by the well-known [3+2] dipolar and [4+2] Diels-Alder cycloaddition reactions, respectively.[1a] Seven-membered rings are more difficult to prepare than their smaller homologs due to increased ring strain and entropy.[1g] Developing a method to construct seven-membered rings in an straightforward manner would allow access to a commonly found framework in biologically active natural products. Electronically, the [4+3] cycloaddition is related to the Diels-Alder reaction and can be viewed as a [4π(4C) + 2π(3C)] combination in which an allyl cation participates as the reactive dienophile for the formation of a seven-membered ring (Scheme 1).[1]

Scheme 1



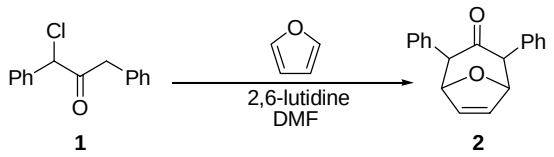
This report examines the scope and limitations of the [4+3] cycloaddition. Oxyallyl cations derived from the dehalogenation of haloketones or generated from aldehydes and acetals have been demonstrated to be reactive dienophiles. The versatility of the [4+3] cycladdition allows this methodology to be applied to intramolecular, distereoselective and enantioselective cycloaddition reactions.

GENERATION AND USE OF ALLYL CATIONS IN [4+3] CYCLOADDITONS

The development of [4+3] cycloadditions has focused on methods to generate allyl[2] or oxyallyl cations[3] as reaction partners with a wide range of 1,3-dienes such as: furans, pyrroles, cyclopentadienes and butadienes. [4-6]

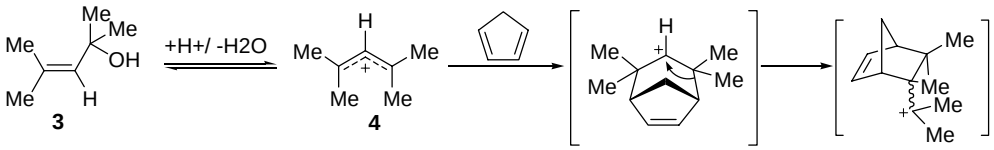
Since 1962 when Fort[7] reported the generation of oxyallyl cations and their subsequent trapping with furan, the [4+3] cycloadditon has been one of the most straightforward and powerful approaches of constructing seven-membered rings (Scheme 2). Over the years, numerous methods for the generation of allyl cations have been reported.[8] Conditions for the generation of the parent allyl cation typically

Scheme 2



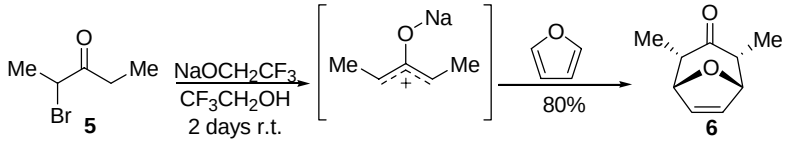
employ Lewis acids in nonnucleophilic solvents (SbF_5-SO_2) or concentrated aqueous acid (H_2SO_4).[9] Although these conditions produce the allyl cation, they are not suitable for cycloaddition reactions.[3] In addition, Hoffmann demonstrated that hydrolysis of **3** to give the allyl cation; upon reaction with cyclopentadiene rearranged to the more stable tertiary carbocation (Scheme 3).[10] To produce allyl cations that afford [4+3] cycloadducts, a number of new milder techniques were developed for the generation of substituted allyl cations.

Scheme 3



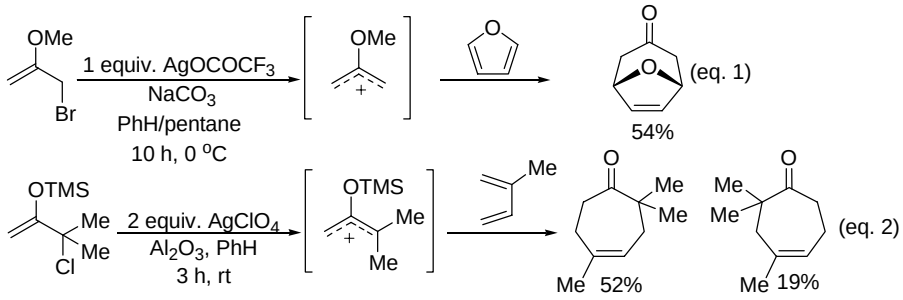
Utilizing Fort's initial findings, oxyallyl cations have been generated using base methods. Exposure of α-bromoketone **5** to triflouroethoxide in the presence of furan, cycloadduct **6** was isolated in 80% yield (Scheme 4).[11]

Scheme 4



A more direct route to allyl cations involves heterolysis of allyl halides promoted by Lewis acids. Silver salts are especially useful due to their mild Lewis acidity if highly reactive allyl cations are employed. Silver (I) promoted heterolysis of monohalo ketones is mild enough to allow less substituted allyl cations to undergo cycloaddition, albeit in modest yields (Scheme 5, eq. 1 and 2). Use of these allyl cations is problematic under other methods of generation. [12, 13]

Scheme 5

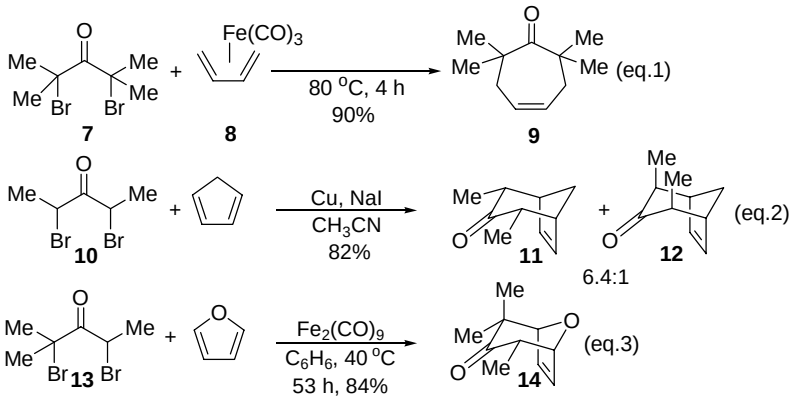


The principal

method for preparing oxyallyl cation intermediates is the reduction of dihaloketones. A variety of reducing agents can be employed; however, the mechanism of the subsequent cycloadditon is critically dependent upon the specific reducing agent utilized.[1g] When α,α'-dihaloketones are reduced with iron carbonyls or zinc/copper couple in the presence of acyclic dienes, 4-cycloheptenones are obtained. Diene ironcarbonyl **8** in benzene is conventionally employed as the reducing agent affording cycloadduct **9** in 90% yield (Scheme 6, eq. 1).[4]

Reductively activated cycloaddition reactions of dibromo ketone **10** with cyclopentadiene affords rise to cyclo[3.2.1]oct-6-en-3-ones in generally high yields.[1e] The combination of copper and sodium iodide in acetonitrile gives an 82% yield of cylcoadducts **11** and **12** (Scheme 6, eq. 2).[14] diiron carbonyl ($Fe_2(CO)_9$) is the most widely used reducing agents for the cycloaddition of dibromo ketones providing the corresponding cycloadduct **14** in 84% yield (Scheme 6, eq. 3).[4]

Scheme 6



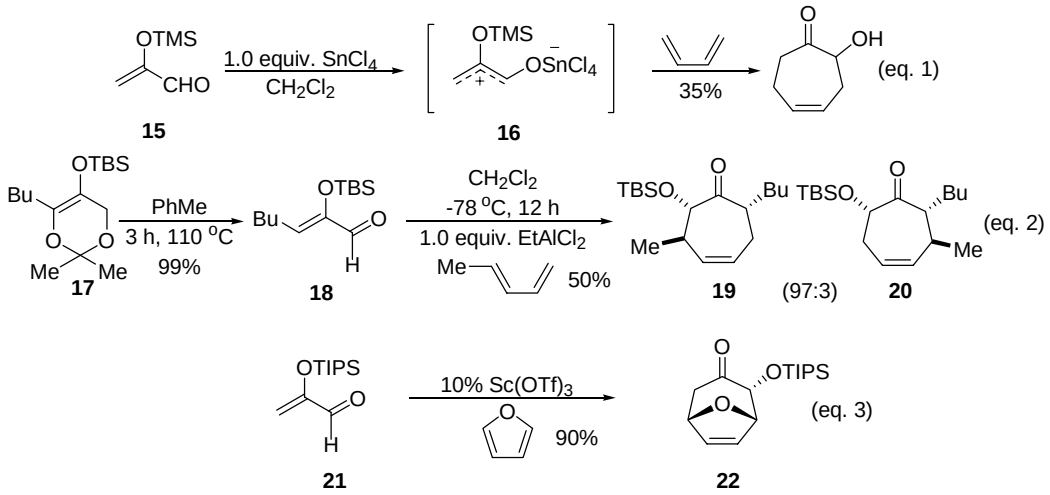
The above methods for the generation of allyl cations are well established, reproducible and their scope is amply demonstrated for a range of dienes and allyl cations. These methods suffer from several limitations including sensitivity to solvents, low yields, heterogeneous reaction mixtures, long reaction times and the use of stoichometric metal reagents.[1a]

Recent advances have focused on milder generation of the oxyallyl cation and the development of heteroatom-functionalized oxyallyl cations. Some common precursors that achieve this goal are: α-silyloxy acroleins and allylic acetals. In addition, 2-alkoxy allylic sulfones, sulfoxides or alcohols are utilized for intramolecular [4+3] cyclizations. These progenitors of allylic cations are also more stable and easier to handle than α,α'-dihaloketones.[1b]

Complexation of α-silyloxy acrolein **15** with a strong Lewis acid ($SnCl_4$) generates a dialkoxy allylic cation **16** that undergoes [4+3] cycloaddition with butadiene (Scheme 7, eq. 1).[15] High levels of regioselectivity are observed using 2-trialkyl-1-siloxy-2-alkenals, derived from retro-Diels Alder of 1,3-dioxins. For example, heating dioxin **17** in toluene gave rise to aldehyde **18** in 99% yield.[16] Treatment of **18** with one equivalent of $EtAlCl_2$ in the presence of isoprene afforded 50% yield of **19** and **20** in 97:3 regioselectivity (Scheme 7, eq. 2).[16] In a seminal discovery, Harmata demonstrated activation of

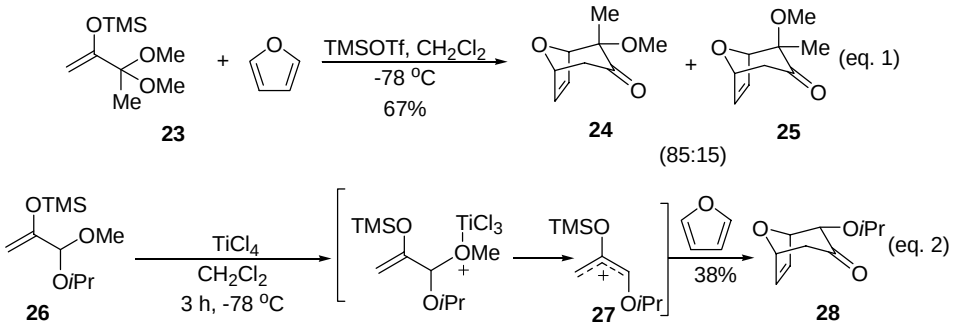
2-(triisopropylsilyloxy)acrolein **21** with a catalytic Lewis acid $Sc(OTf)_3$ providing **22** in 90% yield as a single stereoisomer (Scheme 7, eq. 3).[17]

Scheme 7



The use of allylic acetals has become increasingly popular, particularly as building blocks for use in diasteroselective [4+3] cycloaddition reactions. In an early contribution, Föhlish showed that treatment of 1-chloro-1-methoxy ketones with base in the presence of a diene resulted in the formation of [4+3] cycloadducts, presumably through the intermediacy of a methoxy-stabilized oxyallyl cation.[18] For example, treatment of acetal **23** with TMSOTf in the presence of furan affords cycloadducts **24** and **25** in 67% yield as a 85:15 mixture of diasteroisomers (Scheme 8, eq. 1).[19] A discovery of paramount importance was made by Hoffmann using trimethylsilyl stabilized mixed acetal **26**.[19] It was shown that the sterically least demanding methoxide substituent of **26** was removed chemoselectively by $TiCl_4$. The trimethylsilyoxy allyl cation **27** underwent [4+3] cycloaddition with furan to yield 38% of **28** as a single isomer (Scheme 8, eq. 2).[19]

Scheme 8

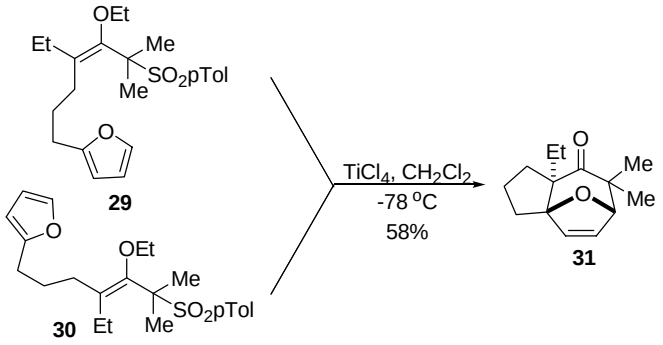


This discovery led to the development of mixed acetals as precursors to chiral oxyallyl cations.

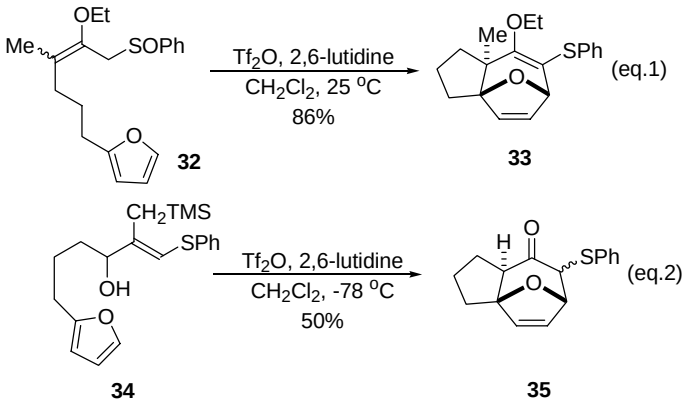
Harmata and coworkers developed the first Lewis acid assisted intramolecular cycloaddition using alkoxyallylic sulfones with furan.[1b] This method is a straightforward approach to the formation of functionalized seven-membered tricyclic systems in high diastereoselectivities. For example, both *E* and *Z*-alkoxyallylic sulfones lead to the same cycloadduct, **31**, in 58% yield (Scheme 9).[20] However, it was observed that only α-dialkyl

substituted allylic sulfones led to [4+3] cycloadducts. These findings prompted investigation into other leaving groups for the generation of oxyally cations. The reaction of phenyl thio-substituted allylic sulfoxide **32** with triflic anhydride and 2,6-lutidine at room temperature affords the cycloadduct **33** in

Scheme 9



Scheme 10



86% yield (Scheme 10, eq. 1).[21] A more straightforward approach involves heterolysis of the appropriate allylic alcohols. Alcohol **34** reacted to afford the corresponding cycloadduct **35** in 50% yield (Scheme 10, eq. 2).[22]

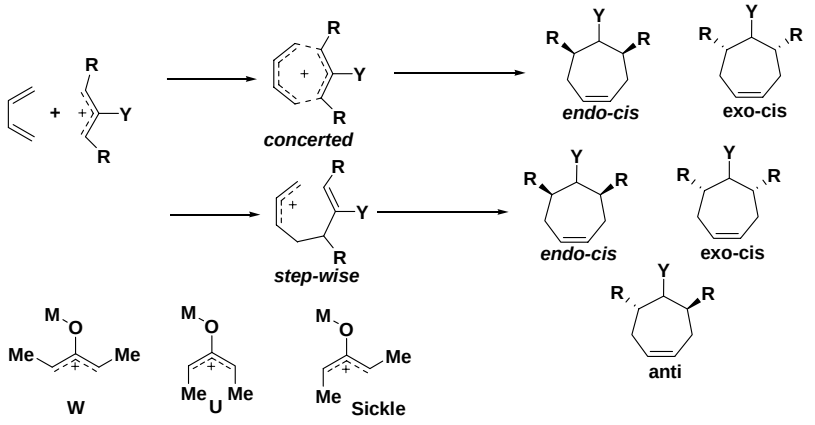
MECHANISM AND STEREOCHEMISTRY

The [4+3] cycloaddition reaction has been proposed to proceed through two principal mechanistic categories, either a concerted bond-formation (A) or a stepwise process (B) (Scheme 11).[23] For those reactions proceeding by the stepwise process (B), the lifetime of the allyl cation determines the stereochmical outcome (Scheme 11).[23] The concerted process can proceed through two topologically distinct transition states an extended (*endo*) transition state or a compact (*exo*) arrangement (Scheme 12).[24]

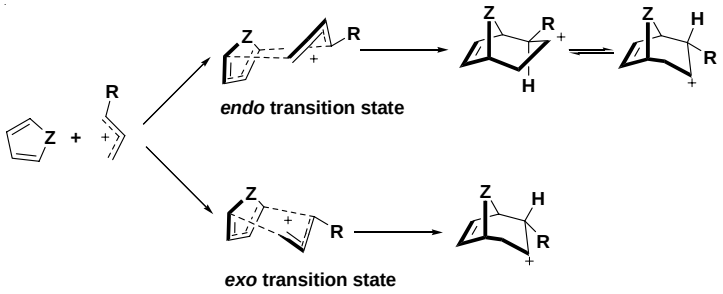
The stereoselectivity in [4+3] cycloaddition reactions is variable relative to other cycloaddition reactions. The geometry of the allyl cation is not defined and can exist in a W, U or sickle configuration (Scheme 12).[24] This could lead to multiple stereochemical outcomes based on the configuration of the allyl cation. Careful choice of reactants and reaction conditions can lead to control of the regio- and stereoselectivity of the [4+3] cycloaddition.[1d]

Recently Cramer and co-workers have investigated the mechanism of the [4+3] cycloaddition using computational methods. Cramer found that the mechanism is dependent on the electrophilicity of the oxyallyl cation and the nucleophilicity of the diene. Cramer and co-workers suggest that the mechanism is still ambiguous and may involve either an concerted asynchronous or step-wise [3+2] cycloaddition followed by Claisen rearrangement to generate a formal [4+3] cycloadduct.[25,26]

Scheme 11



Scheme 12

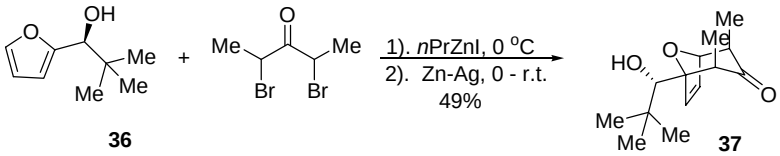


DIASTEROSELECTIVE AND ENANTIOSELECTIVE [4+3] CYCLOADDITION REACTION

There are two direct approaches for the development of diastereoselective [4+3] cycloadditions. Initial approaches involve asymmetric induction through the reaction of a chiral diene with achiral allyl cations.[27] The second method reverses the roles, generating a chiral allyl cation which is subsequently captured by an achiral dienes.[27] If the chiral information from the diene or allyl cation can be cleaved, enantiomerically enriched products can be obtained.

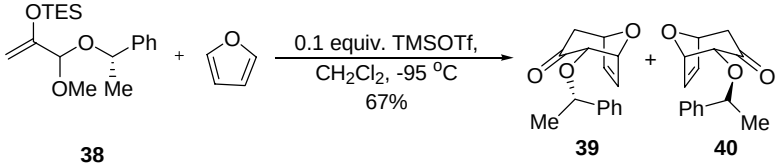
The chiral furyl alcohol **36** has been utilized in diasteroselective [4+3] cycloadditions with furan affording cycloadducts **37** in 49% total yield and 94% diastereoselectivity (Scheme 13).[28]

Scheme 13



36 **37**

Scheme 14



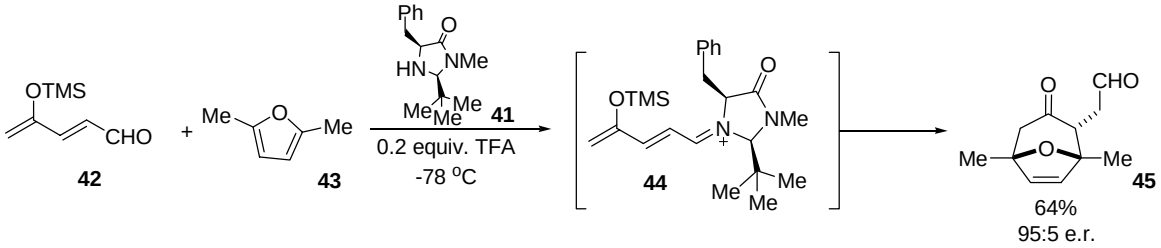
38 **39** **40**

The use of chiral information on the allyl cation allows for easier cleavage of the auxiliary giving pseudo-enantioselective reactions.[29] Given the success in [4+3]

cycloadditon of acetals and dienes, mixed chiral acetals are utilized for the direct introduction of a stereogenic center α to the carbonyl group of the C_3 bridge.[30] TMSOTf facilitated chemoselective removal of the methoxide from the mixed chiral acetal **38** which underwent cycloaddition to afford a 7.5:1.0 ratio of cycloaducts **39** and **40** in 67% yield (Scheme 14).[31] Cleavage of the chiral information is achieved under hydrogenation conditions giving the enantioenriched product.

The use of an organocatalyst has allowed for the development of catalytic, asymmetric [4+3] cycloaddition.[32] The *in-situ*-generated chiral iminium ion **44** functions as a stabilized oxyallyl cation. Combination of **42** with 2,5-dimethylfuran results in the formation of keto aldehyde **45** in 64% yield and 95:5 e.r (Scheme 15).[31]

Scheme 15

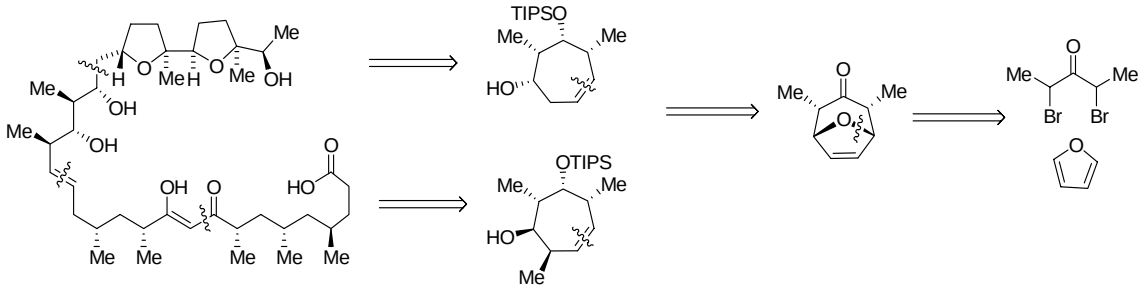


The chiral amine **41** is turned over by acid-promoted hydrolysis, thus only a catalytic amount (0.2 equiv) is required. Despite the high enantioselectivities, this approach is limited by the low yields and the need to use 2,5-disubstituted furans as the diene component (Scheme 15).

[4+3] IN TOTAL SYNTHESIS

The interest in [4+3] cycloaddition chemistry has fostered intresting applications in synthesis. For example, Lautens has demonstrated the utility of the ring-opening of oxabicyclic alkenes as an alternative to the synthesis of 1,3 *syn*-dimethyl moiety of C1-10 and C17-C23 fragments of ionomycin. The [3.2.1] oxabicyclic alkenes are prepared by a [4+3] cycloaddition between furan and an oxyallyl cation. The rigidly of the bicyclic structure was used to introduce functional groups in a highly

Scheme 16



stereoselective manner. After ring-opening the cycloheptene ring was cleaved by ozonolysis to give the dialdehyde that was further manipulated to give substituted 1,3-*syn*-dimethyl fragments (Scheme 16).[26]

CONCLUSION

The [4+3] cycloaddition between dienes and allylic cations has shown potential for the selective construction of seven-membered rings. In addition, the [4+3] cycloaddition has been utilized for the construction of many natural products. The many factors that control the stereochemical outcome and substrate dependence are limitations to this method.

Future investigations should include development of a general catalytic process to achieve enantioselectivity similar to Diels-Alder processes. In addition, the mechanistic subtleties of the [4+3] cycloadditon have to be understood in order to predict the outcome of a particular cycloaddition. The [4+3] cycloaddition reaction between allyl cations and dienes has been and continues to one to the most power approaches for the construction of seven-membered rings.

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