Tandem [4+2]/[3+2] Cycloadditions of Nitroalkenes

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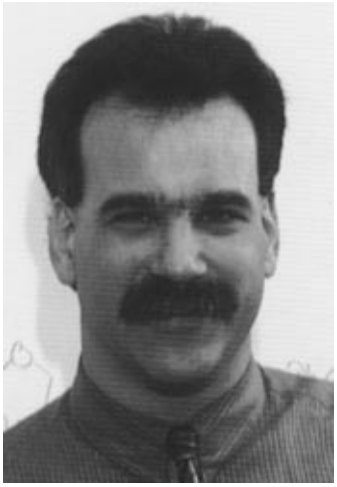
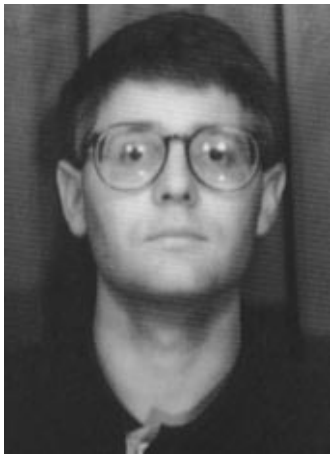


Scott E. Denmark was born in New York in 1953. He obtained an S.B. degree from MIT in 1975 and carried out research with Daniel Kemp and Richard Holm. His graduate studies at the ETH-Zürich with Albert Eschenmoser culminated with the D. Sc. Tech. degree in 1980. That same year he joined the faculty of the University of Illinois at Urbana—Champaign and was promoted to full professor in 1987. In 1991 he was named the Reynold C. Fuson Professor of Chemistry. His research interests are primarily in the invention of new synthetic reactions, structure and reactivity of organoelement reagents, and the origin of stereocontrol in fundamental carbon–carbon bond forming reactions.



Atli Thorarensen was born in 1965 in Reykjavik, Iceland. He received his B.S. degree in chemistry in 1990 from the University of Iceland. After a year's stay as a research associate with Professor Gudmundur G. Haraldsson at the University of Iceland, utilizing lipase's in the synthesis of glyceryl ether lipids and phospholipids, he entered the University of Illinois at Urbana—Champaign. He has been a graduate student in Professor Scott E. Denmark's group since 1991, where he has been involved in the application of the tandem [4+2]/[3+2] cycloaddition of nitroalkenes for the synthesis of natural products. His current research interests lie in the area of asymmetric catalysis, natural product synthesis and how to use the properties of natural products for further understanding of biological systems.

I. Introduction

Insofar as one of the fundamental objectives of organic synthesis is the construction of complex molecules from simpler ones, the importance of synthetic efficiency becomes immediately apparent and has been well-recognized.[1] The increase in molecular complexity[2] that necessarily accompanies the course of a synthesis provides a guide (and a measure) of synthetic efficiency. As a goal, one would like to optimally match the change in molecular complexity at each step with reactions of comparable synthetic complexity. Thus, the creation of many bonds, rings, and stereocenters in a single transformation is a necessary (though not sufficient) condition for high synthetic efficiency. The ultimate, perfect match would constitute single-step syntheses. More realistically, especially in view of the desire for *general* synthetic methods, the combination of mul-

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tiple reactions in single operations to increase molecular complexity is a powerful means to enhance synthetic efficiency.

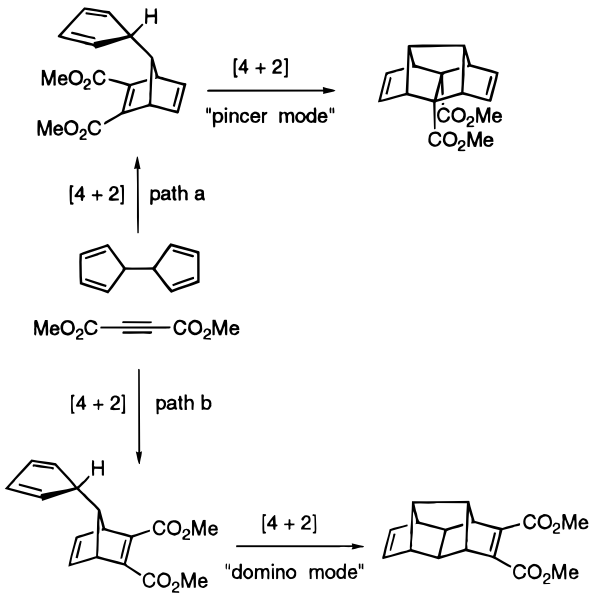
The concept of reactions in tandem as a strategy for the rapid construction of complex structures is well-known and has been reviewed.[3] In addition, a recent international symposium on "cascade chemistry" has attracted considerable attention,[4] and books dedicated to tandem reactions[5] and multicomponent cyclizations[6] have now appeared. Within the universe of tandem reactions, the constellation of consecutive pericyclic reactions is still vast. Consecutive pericyclic reactions involving at least one cycloaddition have enjoyed extensive application in synthesis as exemplified by tandem benzocyclobutene opening/Diels−Alder reactions,[7] Danheiser's aromatic annulation,[8] electrocyclic opening/1,3-dipolar cycloaddition,[9] and crowned by the endiandric acid cascade.[10] Our interest focuses on a member of this family in which *both* of the reactions are cycloadditions.

II. Definition of Tandem Reactions

The dictionary definition of tandem as "one behind the other"[11] is, in itself, insufficient since every reaction sequence would then be a tandem reaction. However, a rigorous and all encompassing definition of tandem or sequential reactions is very difficult to formulate because of the continuum of chemical reactivity. In other words, we must decide what constitutes a reactive intermediate or a stable, isolable entity which, given the circumstances of reactant structure or reaction conditions, undergoes a secondary transformation. What is unique about the type of tandem process exemplified by tandem pericyclic reactions is the structural change that accompanies the initial reaction and the creation of an intermediate with the necessary functionality to perform the second reaction. Furthermore, if the process involves sequential addition of reagents,[12] the second reagent has to be included into the product. In addition, new bonds and stereocenters have to be created in the second reaction.[5] Thus, any definition must make some arbitrary choice, and for our purposes the operational definitions suggested by Tietze are most appropriate.[3b] We have embellished them to include a third category as outlined below.

We propose to keep the all-encompassing definition of tandem as reactions that occur one after the other, and use the modifiers cascade (domino), consecutive, and sequential to specify how the two (or more) reactions follow. Thus, the family of tandem cycloaddition reactions can be divided into three categories with the following definitions: (1) *tandem cascade cycloadditions*, wherein the reactions are intrinsically coupled, i.e. each subsequent stage can occur by virtue of the structural change brought about by the previous step under the same reaction conditions; (2) *tandem consecutive cycloadditions*, wherein the first cycloaddition is necessary but not sufficient for the tandem process, i.e. external reagents or changes in reaction conditions are also required to facilitate propagation; and (3) *tandem sequential cycloadditions* wherein the second stage requires the addition of one of the cycloaddition partners or another reagent. These definitions serve to distinguish tandem from independent cycloadditions of substrates with multiple functional sites.[13]

Scheme 1



A. Tandem Cascade Cycloadditions

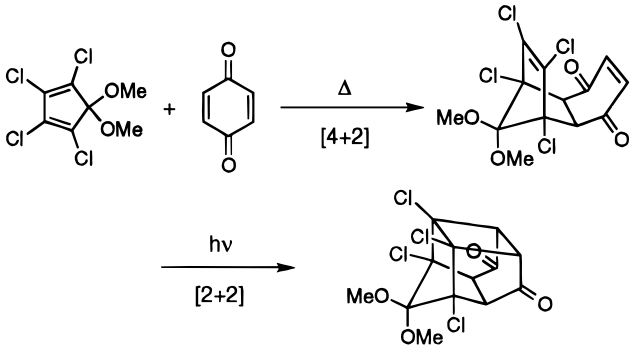
In tandem cascade cycloadditions, both processes take place without the agency of additional components or reagents. Everything necessary for both reactions is incorporated in the starting materials. The product of the initial stage may be stable under the reaction conditions; however, the intermediate cannot be an isolable species but rather is converted to the tandem product upon workup. The classic examples of tandem cascade cycloadditions are the "pincer"[14] (path a) and "domino"[15] (path b) mode of Diels−Alder reactions which have served as cornerstones in the syntheses of the formidable pagodane and dodecahedrane structures, respectively (Scheme 1). Despite the obvious potential of this process and the myriad of conceivable permutations, only a handful of tandem cascade cycloadditions have been developed,[16] most notably the intermolecular [3+2]/intramolecular [4+2] and double intermolecular [4+2] variety due to Tsuge.[17]

B. Tandem Consecutive Cycloadditions

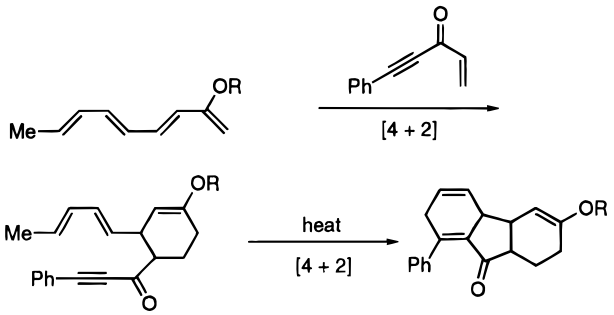
Tandem consecutive reactions differ from cascade reactions in that the intermediate is an isolable entity. The intermediate contains the required functionality to perform the second reaction, but additional promotion[18] in the form of energy (heat or light) is necessary to overcome the activation barriers. Many examples of such consecutive cycloadditions have been documented.[19−22] A particularly illustrative example is shown in Scheme 2.[23] The [4+2] cycloaddition produces a new olefin which is poised for an intramolecular [2+2] cycloaddition. Although, the first reaction is necessary, it is not sufficient for the tandem process, and a change in conditions (photochemical activation) is required as well.

Another example shown in Scheme 3 illustrates the problem of rigorous definitions.[24] While the first

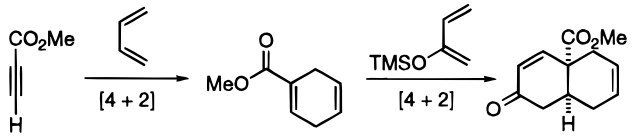
Scheme 2



Scheme 3



Scheme 4



[4+2] cycloaddition is not strictly necessary in that the components for the second [4+2] process are already present in the precursor, the important structural consequence of intramolecularity is probably equally significant for the success of the tandem process.

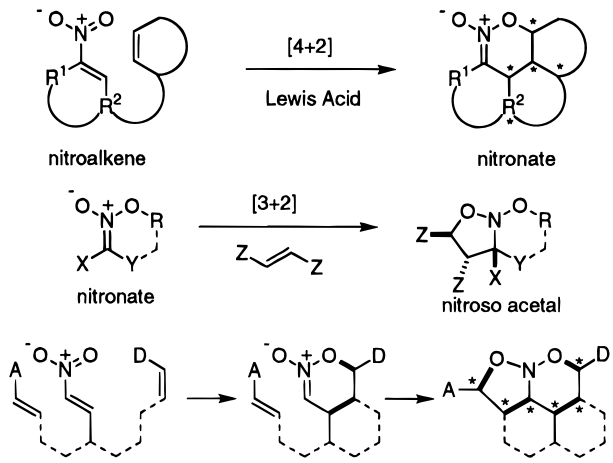
C. Tandem Sequential Cycloadditions

Tandem sequential cycloadditions require the addition of the second component for the tandem process in a separate step. To qualify as a tandem reaction, the first stage must create the functionality in the product to enable it to engage in the second reaction. The intermediate may be isolable, though this is not a necessity. This class of reaction is not as well-recognized[25] as the previous ones, but it is nonetheless clearly illustrated in the syntheses of vernolepin and vernomenin by Danishefsky (Scheme 4).[26]

D. Components of Tandem [4+2]/[3+2] Cycloadditions

The design of a tandem [4+2]/[3+2] cycloaddition process for nitroalkenes can be understood by recognizing the central role played by nitronates (Scheme 5). Early studies on the use of nitroalkenes as heterodienes (vide infra) led to the development of a general, high-yielding, and stereoselective method for the synthesis of cyclic nitronates. These dipoles are well-known to undergo 1,3-dipolar cycloadditions (vide infra); however, synthetic applications of this process are rare[27] in contrast to the functionally

Scheme 5

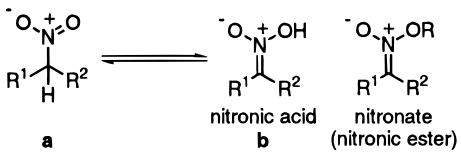


equivalent cycloadditions of nitrile oxides.[28] This is undoubtedly due to the lack of general methods for the preparation of nitronates and their instability. Thus, as illustrated in Scheme 5, the potential for a powerful tandem process is formulated in the combination of an inverse electron demand [4+2] cycloaddition of a donor dienophile (D = electron donating group) with a "normal electron demand" [3+2] cycloaddition of an acceptor dipolarophile (A = electron withdrawing group). The resulting tandem process can construct four new bonds, up to four new rings, and up to six new stereogenic centers (three of which bear heteroatoms).

The focus of this review is the development of the different classes of tandem [4+2]/[3+2] nitroalkene cycloadditions for the construction of highly functionalized nitrogen-containing heterocycles. The discussion of the scope, limitations, and applications of this protocol will be preceded by a summary of the background studies on each of the individual components along with a presentation of tandem [4+2]/[3+2] cycloadditions involving other functional groups.

III. Background

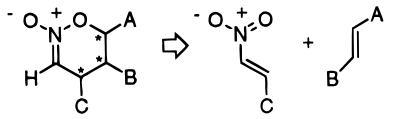
Aliphatic nitro compounds are versatile intermediates for organic synthesis. They can display either electrophilic or nucleophilic behavior at the α, *β* and *γ* position.[29] Furthermore the nitro group can easily be transformed into a wide range of functional groups such as amides, hydroxylamines, amines, nitrones, oximes, nitriles, nitrile oxides, and nitronates. Most importantly, however, the nitro group can be converted to a carbonyl compound by application of the Nef reaction.[30] A nitronate (also know as a nitronic ester) is the ester of a nitronic acid (eq 1). A nitronic



(1)

acid is a tautomer of an aliphatic nitro compound. Usually, at equilibrium the nitro tautomer (**a**) is favored, though there are notable exceptions wherein opportunities for conjugation or hydrogen bonding override the usual preference.[31]

Nitronates are well-studied compounds both in acyclic and cyclic form. They have been prepared by a wide variety of methods, though the more common approaches include *O*-alkylation and silylation of nitronate salts.[32] The cyclic, six-membered nitronates are of particular interest since they can be envisioned as the retron of a nitroalkene and an olefin by the agency of a hetero Diels−Alder reaction (eq 2). The Diels−Alder reaction is one of the more



(2)

important classes of cycloadditions due to its ability to construct complex six-membered rings with up to four contiguous stereocenters in a predictable manner. This construction has not escaped the attention of synthetic chemists, and several approaches have been devised for the preparation of six-membered cyclic nitronates (1,2-oxazine *N*-oxides).

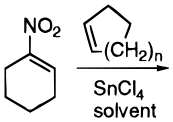
A. Nitroalkenes as Heterodienes in [4+2] Cycloadditions

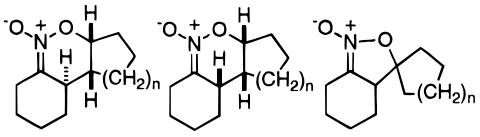
1. Unactivated Dienophiles

Several reports have appeared which describe the use of simple alkenes (unactivated dienophiles) in the hetero Diels−Alder reaction with nitroalkenes. Because of the relative non-nucleophilicity of the dienophile, all of these reactions require the addition of a Lewis acid as a promoter.[33−39]

One of the first systematic studies employed 1-nitrocyclohexene as the heterodiene together with several cyclic olefins (Table 1).[33] The reaction is found to be general in that five-, six-, or seven-membered cycloalkenes afforded nitronates in moderate to good yields. Two diastereomeric cycloadducts (**a** and **b**) along with a rearrangement product **c** are produced. The ratio of these components is both olefin and solvent dependent. The major diastereomer **a** (trans) arises from an exo approach of the olefin toward the nitroalkene and is in greatest proportion with cyclopentene. While the rate of the reaction and the exo/endo selectivity are dependent on the solvent, the proportion of the byproduct **c** is not. In dichloromethane, the reaction with cyclohexene is complete in only 5 h at −78 °C while the same reaction in toluene required 8 h at room temperature. The isolation of **c** and the demonstration that it is a primary product of the reaction shows that these cycloadditions are not concerted processes. Rather they can be viewed as stepwise processes which proceed via an intermediate zwitterion. The zwitterion can either collapse to form the six-membered nitronate or undergo a Wagner−Meerwein shift followed by collapse to afford the five-membered nitronate.

Table 1. Cycloaddition of 1-Nitrocyclohexene with Various Cycloalkenes





a **b** **c**

n	solvent	ratio **a**/**b**/**c**	yield %
1	CH_2Cl_2	23.7/2/1	80
2	CH_2Cl_2	14.3/1/2.3	53
2	toluene	5.1/1/1.1	
3	CH_2Cl_2	2.0/3.2/1	87

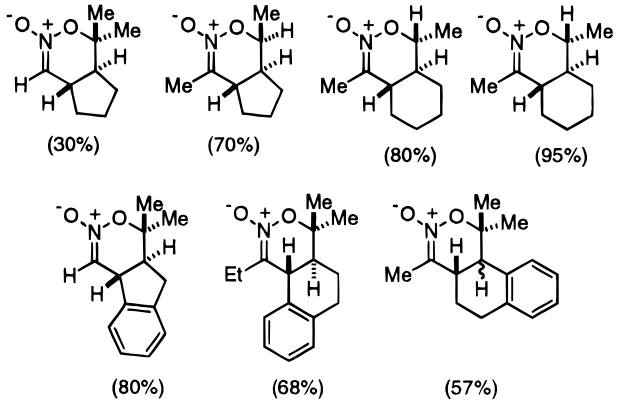
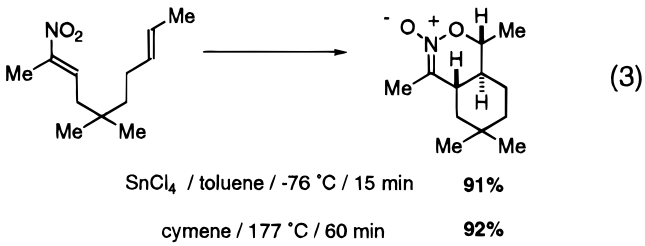


Figure 1. Products of intramolecular [4+2] cycloaddition of nitroalkenes.

Intramolecular cycloadditions have also been reported.[34−36,38] A collection of structures prepared by this approach is shown in Figure 1. The reaction is capable of forming five- and six- but not seven-membered rings. Substituents on the nitroalkene and tethered dienophile have a significant effect on reaction rate and stability of the product. As expected, the rate of reaction increases with increasing methyl substitution on the dienophile. In addition, nitronates bearing a non-hydrogen substituent at the nitronic carbon tend to be more stable. Both aliphatic and aromatic spacers in the tether can be used. In general, tin tetrachloride is found to be the most effective promoter.

The accelerating effect of the Lewis acid in the hetero Diels−Alder reaction has been documented in the intramolecular cycloaddition illustrated in eq 3.[36]



(3)

The substrate underwent a facile cycloaddition with tin tetrachloride as a promoter in 15 min at −76 °C to afford the nitronate in 91% yield. In dramatic contrast, the thermal reaction requires 177 °C for 60 min to produce the same nitronate in 92% yield. This experiment serves to demonstrate both the rate accelerating effect of the Lewis acid and, also, that the reaction is thermodynamically favorable. Thus, the Lewis acid does not provide a significant influence on the equilibrium by forming a strong complex to the nitronate.

Further understanding of the role of the Lewis acid is provided by a Hammett study of the cycloaddition rates with substituted nitrostyrenes.[38] Competition experiments reveal that electron rich nitroalkenes (4-methoxynitrostyrene) react 462 times faster than electron poor nitroalkenes (4-(trifluoromethyl)nitrostyrene) in cycloadditions promoted by tin tetrachloride in the presence of cyclopentene as the dienophile. Since these reactions are inverse electron demand cycloadditions, the relevant frontier orbital interactions are between the LUMO of the diene and the HOMO of the dienophile. The accelerating effect of a Lewis acid can be understood since complexation of the nitroalkene should decrease the HOMO−LUMO gap by lowering the LUMO of the diene. The observation that an electron deficient nitroalkene (with an expectedly lower LUMO) reacted slower than an electron-rich nitroalkene is inconsistent with this explanation. The contradiction can be resolved by considering how the basicity of the nitroalkene influences the concentration of the reactive Lewis acid−nitroalkene complex. The effective concentration of the reactive complex in the case of an electron-rich nitroalkene would be considerably greater and therefore outweighs the electronic influence of the nitroalkene substituent on the HOMO−LUMO gap.

Another important consequence of the Lewis acid activation has also been documented in the cycloaddition of nitroalkenes with cyclic dienes as dienophiles. It is well known that nitroalkenes are excellent dienophiles in the Diels−Alder reaction.[40] The use of nitrostyrene derivatives in combination with cyclohexadiene or cyclopentadiene in the presence of tin tetrachloride affords exclusively a nitronate.[38] Thus the periselectivity of the reaction is controlled by the complexation of the nitroalkene to the Lewis acid.

2. Nitrogen-Containing Dienophiles

In view of the powerful nucleophilicity of enamines, it is not surprising that one of the first examples of the creation of cyclic nitronates was the reaction of nitroalkenes with *N*-morpholinocyclohexene (Scheme 6).[41] This constitutes a formal [4+2] cycloaddition where the nitroalkene behaves as a diene. The successful isolation of the nitronate required that the nitroalkene bear an α substituent. In instances where no α-substituent is present, only the products of conjugate addition (Michael adducts) are isolated. Subsequent exploration of the use of other enamines

Scheme 6

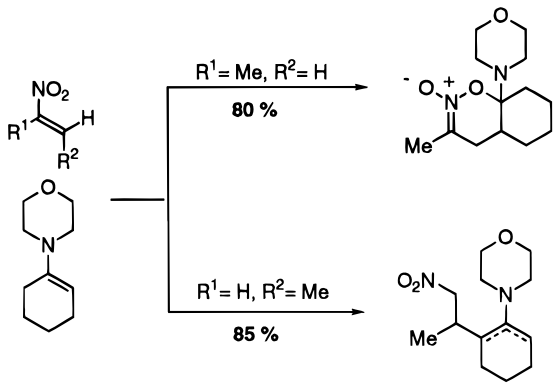
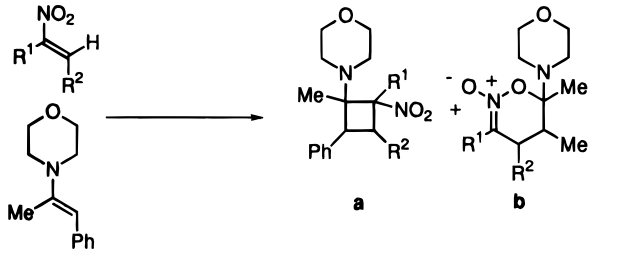
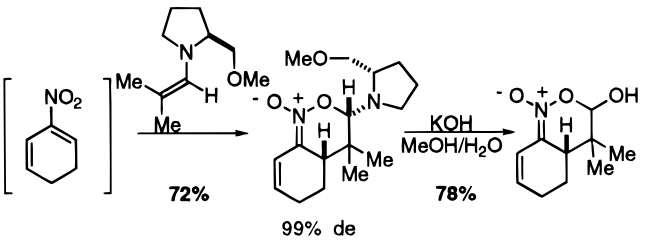


Table 2. Substrate Influence on Product Distribution in Reactions with Enamines



R^1	R^2	ratio **a**/**b**
H	Ph	1/0
Me	Ph	1/3
Ph	Me	0/1

Scheme 7



defined the scope of this reaction and further demonstrated the need for an α substituent for the successful isolation of the cyclic nitronate product.[42]

The stepwise nature of this formal [4+2] cycloaddition is shown by the isolation of either a *C*-alkylated cyclobutane or an *O*-alkylated nitronate as the product, depending on the substrate employed (Table 2).[43] The outcome of these reactions can be explained by the initial Michael addition of the enamine to the nitroalkene. The intermediate zwitterion has two fates: (1) it could add to the iminium ion through a *C*-alkylation to afford a cyclobutane (**a**) or (2) it could add to the iminium ion through an *O*-alkylation to afford the nitronate (**b**). The ratio of alkylation products is dependent on the steric environment at the α-carbon of the nitroalkene; sterically hindered substrates favor *O*-alkylation.

Further exploration of the utility of enamines in the preparation of nitronates has continued.[44] An interesting example was disclosed by Bäckvall which utilizes chiral enamines.[45] The addition of the (*S*)-2-(methoxymethyl)pyrrolidine enamine of isobutyraldehyde to in-situ-generated 2-nitro-1,3-cyclohexadiene affords a cyclic nitronate in good yield and excellent diastereoselectivity (Scheme 7). The auxiliary is then subsequently removed by basic hydrolysis. In a survey of the generality of the reaction, the authors found that with acyclic precursors the overall selectivity deteriorated.

The use of ynamines as dienophiles in [4+2] cycloadditions with nitroalkenes affords four-membered cyclic nitrones (**a**), as the isolated products (Figure 2).[46] The nitrones are proposed to be the products of a ring contraction from a six-membered cyclic nitronate. The isolation of nitronate **b** supports the hypothesis of intermediacy of six-membered ring structures. The structural assignment was tentatively made on the basis of IR and mass spectroscopic data. A range of achiral and chiral ynamines have

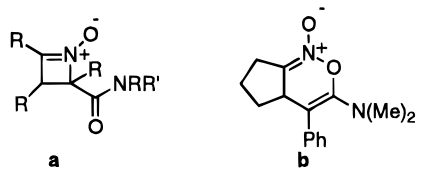


Figure 2. Products of cycloadditions between ynamines and nitroalkenes.

been employed with various nitroalkenes to afford modest to good selectivity of the corresponding nitrones.

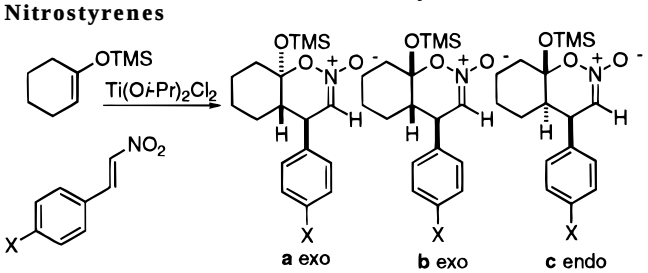
3. Oxygen-Containing Dienophiles

The use of oxygen-containing dienophiles in the form of enol ethers, silyl enol ethers, or ketene acetals has attracted considerable attention. An early report disclosed the Lewis acid-promoted addition of silyl enol ethers and silyl ketene acetals to nitroalkenes.[47] Many Lewis acids are effective promoters and the addition products obtained after workup are 1,4-dicarbonyl compounds. The mechanism of this reaction is assumed to involve a nitronate as an intermediate which, upon workup, hydrolyses to a 1,4-dicarbonyl compound. In support of this hypothesis, the authors reported the isolation of a nitronate under different workup conditions.[47d]

The use of silyl enol ethers as dienophiles has been further developed recently.[48] The trimethylsilyl enol ether of cyclohexanone reacted with several 2-nitrostyrenes in the presence of titanium dichloride diisopropoxide ($Ti(O\textit{i}\text{-}Pr)_2Cl_2$) (Table 3). The nitronates **a**−**c** were obtained in 55−81% yield as a mixture of diastereomers. Diastereomers **a** and **b** arise from an exo approach (with respect to the carbocyclic ring) in the cycloaddition while **c** is the corresponding adduct from an endo approach. The results clearly show that the endo approach is favored in the presence of $Ti(O\textit{i}\text{-}Pr)_2Cl_2$. The same authors found that titanium tetrachloride afforded the nitronates nonselectively. β-Furyl substituted nitroalkenes have been employed in a similar approach.[49]

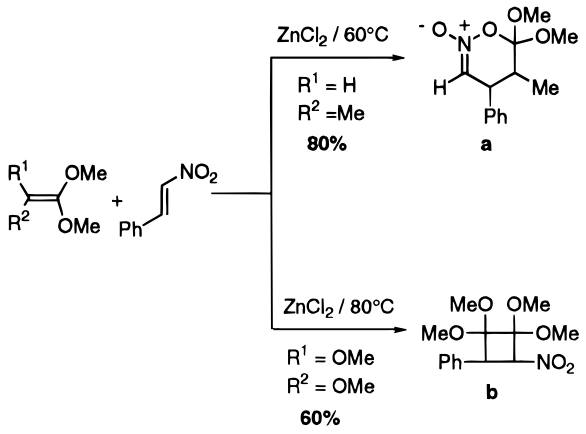
The use of the more nucleophilic ketene acetals has also been reported.[50] The *n*-propyl ketene acetal reacts with 2-nitrostyrene in the presence of zinc chloride to afford the cyclic nitronate ortho esters **a** in 80% yield (Scheme 8). When tetramethoxyethene is used instead, the sole product is the cyclobutane **b**. The cyclobutane is the equivalent of a formal

Table 3. Product Distribution in Cycloaddition with Nitrostyrenes



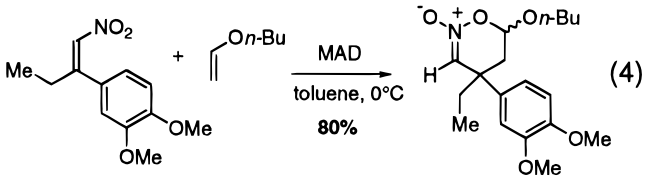
X	ratio **a**+**b**/**c**	yield %
H	1/3	81
Me	1/4	67
OMe	1/2	74
CN	3/8	55

Scheme 8



[2+2] cycloaddition or can be viewed as a stepwise [4+2] cycloaddition where the zwitterionic intermediate collapses through *C*-alkylation instead of *O*-alkylation of the iminium ion.

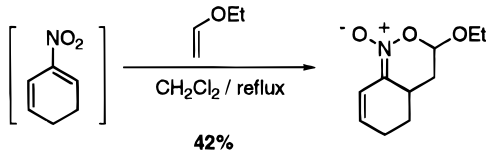
Alkyl enol ethers have been extensively employed as dienophiles in [4+2] cycloadditions with nitroalkenes.[39,51−58] The reactions can been promoted by a range of Lewis acids to afford the cyclic nitronates in good yields. A representative example (eq 4) is



(4)

the cycloaddition of a 2,2-disubstituted 1-nitrostyrene with *n*-butyl vinyl ether promoted by the bulky Lewis acid methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide) (MAD) to afford the nitronate in excellent yield.[53a] Interestingly the Wagner−Meerwin shift seen in the case of unactivated dienophiles has never been observed when enol ethers have been employed. Given the strong polarization due to the oxygen substituent, it is even more likely that these reactions proceed via zwitterionic intermediates. The lack of rearrangement products most likely results from the thermodynamic disadvantage of hydride migration which would generate a nonstabilized carbocation from an oxocarbenium ion.

A few examples of simple thermally activated cycloadditions of enol ethers and nitroalkenes have been reported.[59−62] An illustrative case is the cycloaddition of ethyl vinyl ether with in-situ-generated 2-nitro-1,3-cyclohexadiene in refluxing dichloromethane to afford the bicyclic nitronate in 42% yield (eq 5).[60] Several examples were reported and in all cases the nitronates were isolated in moderate yield.



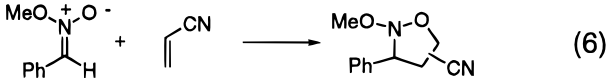
(5)

There are also a few alternative methods for the preparation of six-membered cyclic nitronates which do not involve cycloaddition reactions. These methods include intramolecular alkylation,[63] Mitsunobu reaction,[64] and hemiketal formation.[65]

B. Nitronates as Dipoles in [3 + 2] Cycloadditions

Dipolar cycloadditions are arguably the most powerful reactions for the construction of five-membered heterocycles.[66] A wide range of dipoles have been successfully employed for this purpose. In addition, frontier molecular orbital theory and more advanced theoretical treatments offer useful insights for making predictions and for understanding the effects of substituents on chemical reactivity and the stereo- and regioselectivity obtained in [3+2] cycloadditions.

In 1964, Tartakovskii first disclosed that nitronates could participate as dipoles in [3+2] cycloadditions.[67] This seminal report described the use of an acyclic nitronate prepared by *O*-alkylation of α-nitrotoluene with diazomethane (eq 6). The nitronate reacted

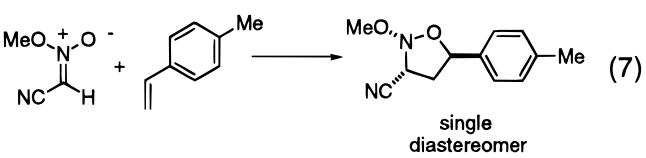


(6)

with acrylonitrile in a [3+2] cycloaddition to afford a 1-methoxyisoxazolidine (nitroso acetal). In subsequent years, Tartakovskii,[68,69] Carrié,[70,71] Torssell,[32d] and Seebach[48] have extensively explored the utility of these new dipoles in [3+2] cycloadditions.

The regioselectivity of the cycloaddition was established by Tartakovskii to be remarkably high (Table 4).[68] The cyclic nitronate reacted with several dipolarophiles to generate the nitroso acetals in excellent yields, except with allyl chloride, for which the yields were variable. In all instances the regiochemical course of the dipolarophile approach is such that the carbon bearing the substituent X always becomes attached to the oxygen of the dipole.

The stereochemical preferences for the approach of the dipolarophile (exo vs endo) has been established by a number of investigators. With a high degree of regularity, the preferred approach of the dipolarophile is exo, i.e., the activating (regiocontrolling) substituent on the double bond is oriented away from the underside of the dipole. An example provided by Carrié which utilizes an acyclic nitronate in a [3+2] cycloaddition with styrene afforded a single nitroso acetal, which is the result of an exo approach (eq 7).[70b] The preference for exo approach of the

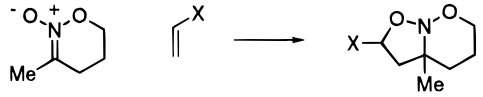


(7)

dipolarophile toward the dipole in [3+2] cycloadditions has been unambiguously established by X-ray crystallographic analysis of the resulting nitroso acetals in a number of cases.[34,48b,55,62]

Frontier molecular orbital theory has been useful in rationalizing the regio- and stereochemical outcome of these dipolar cycloadditions. The cycloaddition can be either $HOMO_{dipole}-LUMO_{dipolarophile}$ or

Table 4. Regiochemistry of the Dipolar Cycloaddition of Cyclic Nitronates



X	yield %
CO_2Me	85
Ph	80
CH_2Cl	10
CN	92

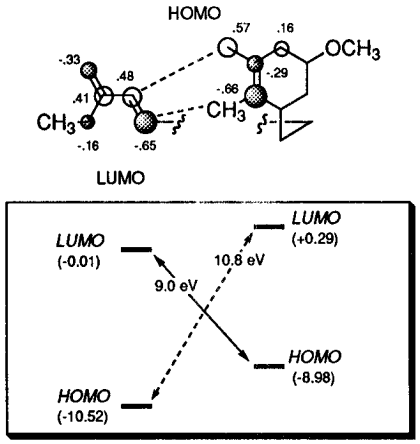


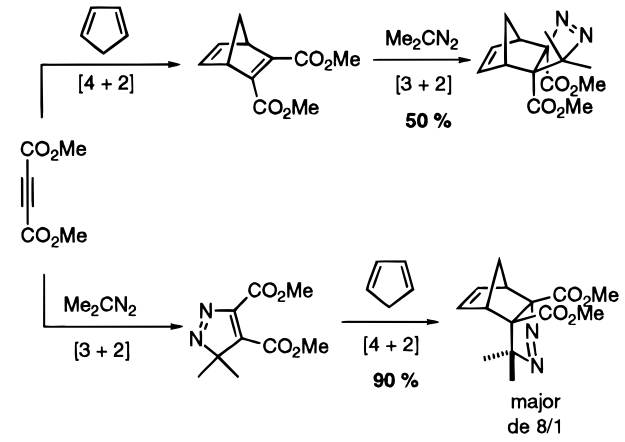
Figure 3. Frontier molecular orbitals (AM1) for [3+2] cycloaddition.

$LUMO_{dipole}-HOMO_{dipolarophile}$ controlled. To understand the nature of the dipoles, Carrié performed semiempirical (INDO) calculations.[71] A more advanced semiempirical treatment which employed calculations with the AM1 Hamiltonian has also been performed.[72] The results are in good agreement with the conclusions of Carrié. The relevant orbital interaction is dependent on the dipolarophile. With electron deficient dipolarophiles, the cycloaddition is under $LUMO_{dipole}-HOMO_{dipolarophile}$ control (Figure 3). The regiochemical outcome can be understood by examining the coefficients on the individual atoms. The optimal overlap of coefficients between the dipole and the dipolarophile occurs when the acrylate α carbon becomes attached to the oxygen. Further discussion of the use of nitronates as dipoles in other cases is beyond the scope of this review.[73]

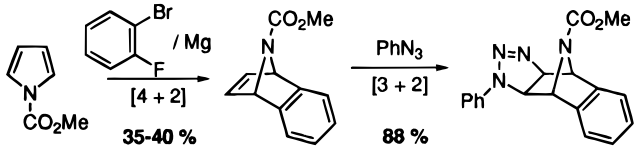
C. Tandem [4+2]/[3+2] Cycloadditions

The literature is replete with examples wherein the tandem [4+2]/[3+2] or [3+2]/[4+2] sequence has been employed. These tandem reactions fall primarily under our classification as tandem sequential cycloadditions. The use of the tandem sequence for any order of [4+2]/[3+2] cycloaddition has mainly involved the construction of functionalized norbornane structures.[74] Substituted norbornadiene derivatives are prepared by Diels–Alder cycloaddition of a substituted cyclopentadiene or its heteroatom analogs with the appropriate dienophile.[75] These compounds have then been employed as dipolarophiles with a range of dipoles such as nitrones,[76] azides,[77] thiocarbonyl ylides,[78] nitrile oxides[79] and diazoalkanes.[80] Neumann has devised a tandem [4+2]/[3+2] and [3+2]/[4+2] sequence by combining cyclopentadiene with a range of functionalized acetylenes and a diazoalkane (Scheme 9).[81] The reaction of dimethyl

Scheme 9



Scheme 10



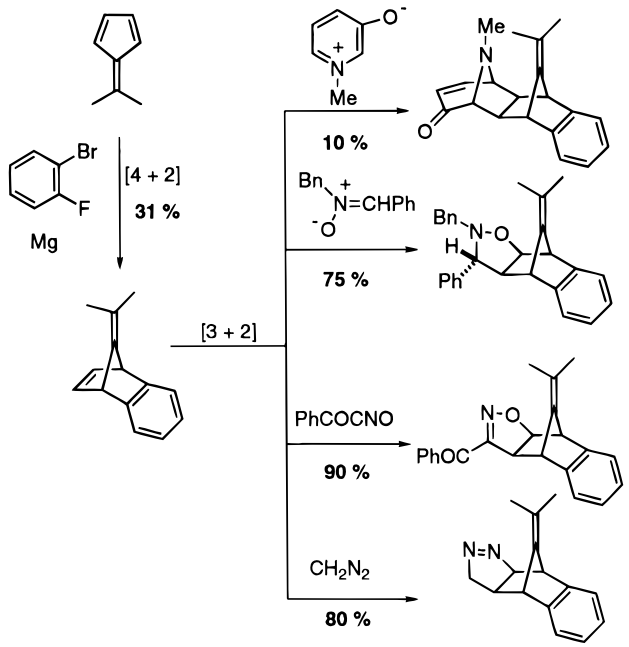
acetylenedicarboxylate with cyclopentadiene affords the corresponding Diels−Alder adduct which was subsequently treated with 2-diazopropane at 0 °C. The tandem cycloadduct is isolated in 50% yield as a single diastereomer. The pyrazoline results from an exo approach of the dipolarophile. Changing the sequence of reactions but maintaining the same components affords (as the major product) a stereoisomer of the same cycloadduct. This new product arises from the Diels−Alder reaction of the pyrazole such that the N−N linkage is endo with respect to the cyclopentadiene.

Another example of norbornadiene derivatives in tandem sequential cycloadditions is the preparation and use of 7-azabenzonorbornadiene as shown in Scheme 10.[82] Reaction of the 1-carbomethoxypyrrole with in-situ-generated benzyne afforded the [4+2] product in rather poor yield (35−40%). The 7-azanorbornadiene was then allowed to react with phenyl azide in a [3+2] cycloaddition to obtain the tandem adduct in 88% yield. Other dipoles such as azides, diazoalkanes, nitrones, and nitrile oxides have also been employed.[83]

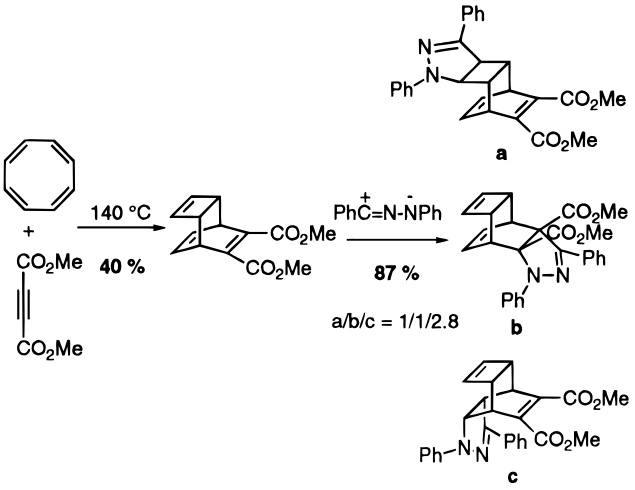
A more exotic example along similar lines is the preparation[84] and use of 7-isopropylidenebenzonorbornadiene as a dipolarophile.[85] This reactive alkene is prepared by a [4+2] cycloaddition of dimethylfulvene to benzyne (Scheme 11). The norbornadiene can then be combined with several dipoles such as azomethine ylides, nitrones, nitrile oxides, and diazomethane to afford the tandem products in rather variable yield (10−90%).

The Diels−Alder adduct from cyclopentadiene and quinone has been used as a dipolarophile with an azomethine ylide in the [3+2] cycloaddition.[86] Another interesting sequential [4 +2]/[3+2] cycloaddition involves the use of cyclooctatetraene. Reaction of cyclooctatetraene with dimethyl acetylenedicarboxylate affords an unusual tricyclic product which arises from an initial 6π electrocyclic ring closure followed by [4+2] cycloaddition in 40% overall yield

Scheme 11



Scheme 12

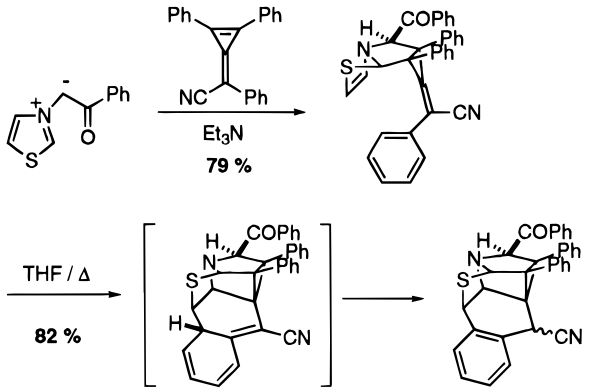


(Scheme 12).[87] Subsequent reaction with a nitrile imine affords a mixture of tandem cycloadducts **a**, **b**, and **c** in the ratio 1/1/2.8 and an overall yield of 87%. In addition, nitrones and thiocarbonyl ylides[88] have been used as dipoles with the tricyclic diester.

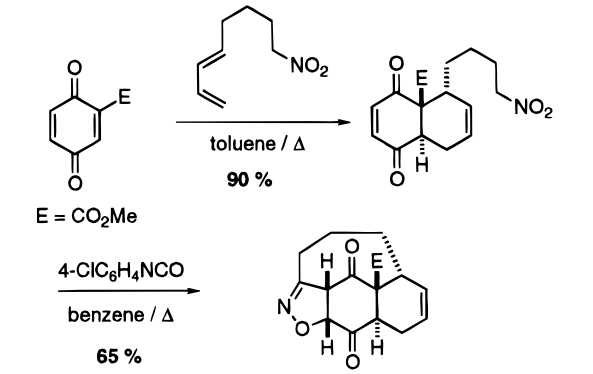
The tandem [4+2]/[3+2] or [3+2]/[4+2] sequence has only rarely been used to access systems not containing the norbornane subunit. Tsuge has extensively explored the use of alkylidenecyclopropenes as dipolarophiles in related tandem consecutive reactions.[17a,b] A spectacular example is depicted in Scheme 13.[89] Combination of the thiazolium ylide with the alkylidenecyclopropene affords the [3+2] cycloaddition product uniquely as the endo diastereomer in 79% yield. The resulting cycloadduct incorporates the required functionality for a subsequent [4+2] cycloaddition if one considers the aromatic ring. In refluxing THF, the tandem cycloadduct is formed in 82% yield as a 1.6/1 mixture of α/β epimers which results from a [4+2] cycloaddition and 1,3 hydride shift to rearomatize.

An interesting example of the tandem intermolecular [4+2]/intramolecular [3+2] process was reported

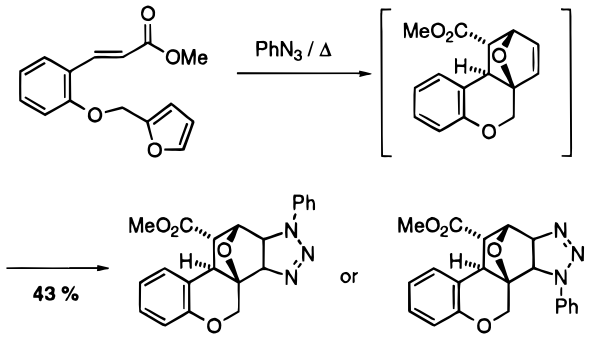
Scheme 13



Scheme 14



Scheme 15

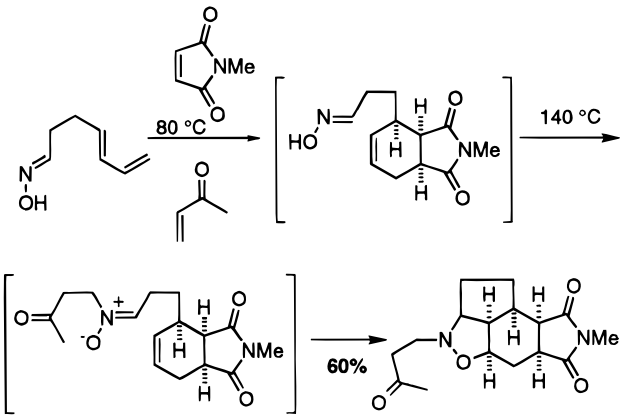


by Kozikowski (Scheme 14).[21] The Diels−Alder reaction between 2-carbomethoxyquinone and the ω-nitrodiene affords the expected bicyclic adduct in 90% yield. The nitro group is then transformed to a nitrile oxide which reacts in an intramolecular [3+2] cycloaddition exclusively with the more electron deficient olefin to produce the tetracyclic tandem cycloadduct in 65% yield.

Tandem intramolecular [4+2]/intermolecular [3+2] cycloadditions have also been used for the synthesis of polyaza-steroid type skeleta (Scheme 15).[17c] The intramolecular Diels−Alder reaction of the cinnamate with the appended furan diene in the presence of phenyl azide gives rise to a tandem product in 43% overall yield as a single (exo) stereoisomer of unknown regiochemistry.

A fascinating example of a triggered process has been disclosed in which both the dipole and dipolarophile are generated in situ (Scheme 16).[22b] A mixture of the dienyl oxime, *N*-methylmaleimide, and a Michael acceptor such as methyl vinyl ketone or a vinyl sulfone is heated at 80 °C to induce the [4+2]

Scheme 16



cycloaddition and generation of the dipolarophile. The temperature is then raised to 140 °C for 5−15 h to effect a Michael addition which transforms the oxime to a nitrone. The nitrone then reacts in an intramolecular [4+2] cycloaddition to afford the tetracyclic tandem [4+2]/Michael/[3 +2] product in ca. 60% yield.

IV. Tandem [4+2]/[3+2] Cycloadditions of Nitroalkenes

A. Definition of Families

As has been illustrated above, there are in principle four different permutations for any tandem [4+2]/[3+2] cycloaddition protocol. The permutations derive from the inter- or intramolecularity of each cycloaddition reaction and are illustrated in Figure 4: tandem intermolecular [4+2]/intermolecular [3+2], intramolecular [4+2]/intermolecular [3+2], intermolecular [4+2]/intramolecular [3+2], and intramolecular [4+2]/intramolecular [3+2] cycloadditions. For the tandem [4+2]/[3+2] cycloadditions of nitroalkenes, these families will serve as the organizational framework for the chapter. All of the permutations have been explored and are all feasible.

B. Tandem Intermolecular [4+2]/Intermolecular [3+2] Cycloadditions

1. Achiral Dienophiles

The tandem intermolecular [4+2]/intermolecular [3+2] cycloaddition creates bicyclic nitroso acetals with up to six stereogenic centers in a predictable fashion (Scheme 17). The [4+2] cycloaddition can create up to three contiguous stereogenic centers in the linchpin nitronate which further undergoes the

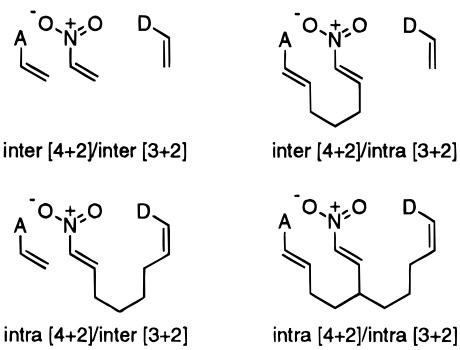


Figure 4. Families of tandem [4+2]/[3+2] cycloadditions of nitroalkenes.

Scheme 17

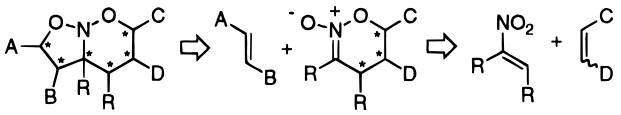
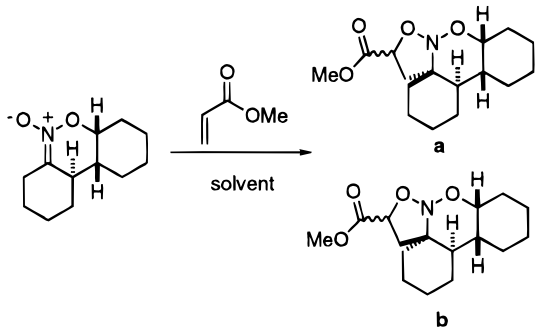
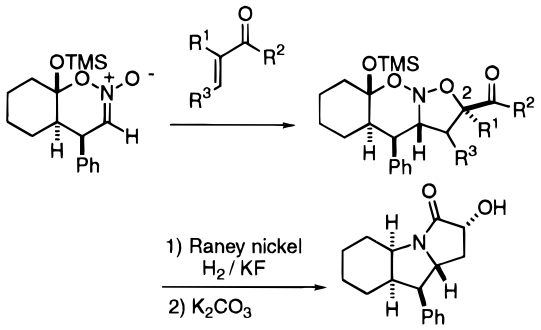


Table 5. Cycloadditions of Methyl Acrylate with a Tricyclic Nitronate



	yield %	
solvent	**a** (α/β)	**b** (α)
CH_2Cl_2	15/34	30
CH_3CN	17/25	39

Table 6. [3+2] Cycloadditions with Various Dipolarophiles



R^1	R^2	R^3	nitroso acetal, %	de, %
H	OMe	H	89	93
H	NH_2	H	59	83
Me	OMe	H	71	*a*
H	OMe	Ph	NR	
H	OMe	Me	NR	

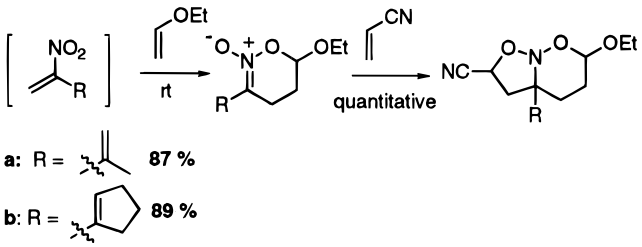
[a] 1/1 mixture at C(2).

[3+2] cycloaddition. Up to three additional centers are created as a consequence of this reaction as well.

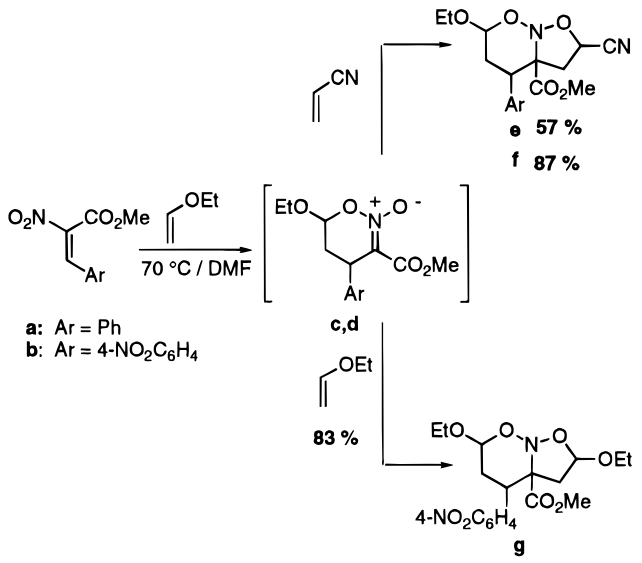
The tricyclic nitronate derived from 1-nitrocyclohexene and cyclohexene (cf. Table 1) undergoes rapid [3+2] cycloaddition with methyl acrylate to give a mixture of diastereomers **a** and **b** (Table 5).[33] The facial selectivity in the approach of the dipolarophile to the tricyclic nitronate is low. Further, the major diastereomers are the result of the expected exo preference in the approach of the dipolarophile to the dipole in ca. 4/1 exo/endo selectivity.

The nitronate derived from 2-nitrostyrene and [(trimethylsilyl)oxy]cyclohexene reacts with various dipolarophiles to create tricyclic nitroso acetals (Table 6).[48] While both acrylamide and methyl acrylate react readily, the ester is the more reactive dipolarophile, affording the nitroso acetals in good yields and

Scheme 18



Scheme 19

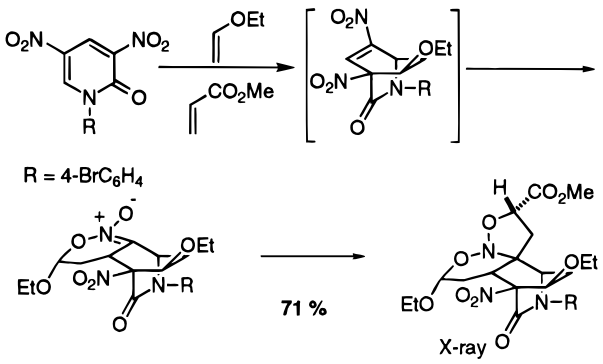


high diastereoselectivity. α-Substituted dipolarophiles give poor selectivity in the reaction while the β-substituted dipolarophiles, methyl cinnamate and methyl crotonate, fail to react. Interestingly, the nitroso acetal could be cleaved under hydrogenolytic conditions with Raney nickel in the presence of potassium fluoride to afford the tricyclic lactam in good yield. Thus, five new stereocenters are created in three steps from a acyclic precursors.

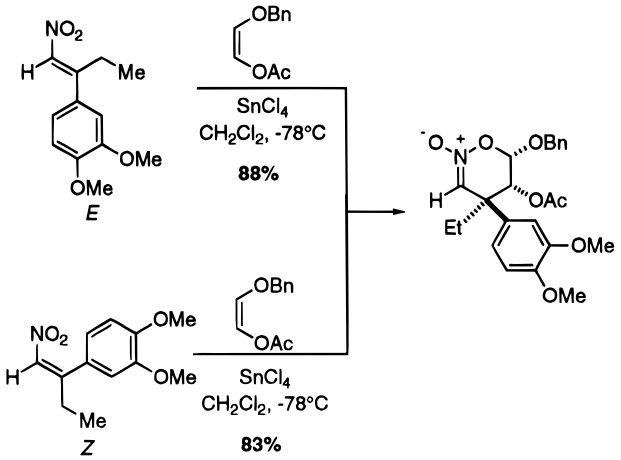
The highly-reactive, in-situ-generated nitrodienes shown in Scheme 18 react rapidly at room temperature with ethyl vinyl ether (as the solvent) to afford the alkoxy nitronates in excellent yield.[61] Reaction of the nitronates with acrylonitrile in DMF at 70 °C affords the nitroso acetals in quantitative yield.

A similar tandem process has been documented with the highly activated nitrostyrenes **a** and **b** shown in Scheme 19. Thus, heating each of the nitroalkenes in DMF at 70 °C with a mixture of ethyl vinyl ether and acrylonitrile affords the nitroso acetals **e** and **f**.[59a] On the other hand, treatment of the 2-nitrostyrene **a** with ethyl vinyl ether alone does not afford any nitronate **c** while the more electron deficient aryl nitroalkene **b** affords the nitronate **d** in good yield. Various enol ethers react with **b** and all afford isolable nitronates in moderate to good yields. In the absence of acrylonitrile and with longer reaction time the in-situ-generated nitronate **d** reacts with ethyl vinyl ether to produce the nitroso acetal **g** in 83% yield. This shows the ability of the dipole to react with both electron rich and electron deficient dipolarophiles, but as expected, the preference is to react with electron deficient dipolarophiles.

Scheme 20



Scheme 21



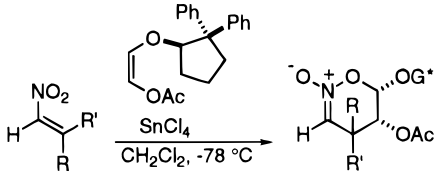
The same authors have reported the use of 3,5-dinitro-2-pyridone as a very electron deficient heterodiene.[59b] Under thermal conditions it reacts in tandem [4+2]/[4+2]/[3+2] cycloadditions forming highly functionalized tetracyclic frameworks (Scheme 20). The initial [4+2] cycloaddition is a stepwise reaction creating a very unstable intermediate when the reaction is performed with only 1 equiv of ethyl vinyl ether. Subsequent reaction with ethyl vinyl ether affords a nitronate which is isolable when the reaction mixture does not contain a reactive dipolarophile. In the presence of a dipolarophile such as methyl acrylate, the nitronate reacts to give the tetracyclic nitroso acetal. The structure of the tetracycle was established by X-ray crystallographic analysis. The nitronate does react with ethyl vinyl ether in a [3+2] cycloaddition, but the reaction is much slower than the corresponding reaction with methyl acrylate. Additional examples of thermal tandem [4+2]/[3+2] cycloadditions where ethyl vinyl ether is both the dienophile and dipolarophile are on record.[62]

2-(Acyloxy)vinyl ethers have been employed in the tandem cycloaddition for the installation of an additional heteroatom into the nitroso acetal skeleton (Scheme 21).[55] The (*E*)-β-disubstituted nitroalkene in Scheme 21 fails to react with 2-(acetoxy)vinyl benzyl ether when the reaction is promoted by the aluminum-based Lewis acid MAD or titanium dichloride diisopropoxide. However, in the presence of tin tetrachloride, reaction is observed at −78 °C which affords the nitronate in 88% yield with high diastereoselectivity. When the isomeric (*Z*)-nitroalkene is used, the same nitronate is isolated in high diastereomeric purity. Independent control experiments reveal that tin tetrachloride efficiently isomerizes the cis to the trans nitroalkene faster than it promotes the cycloaddition reaction.

2. Chiral Dienophiles

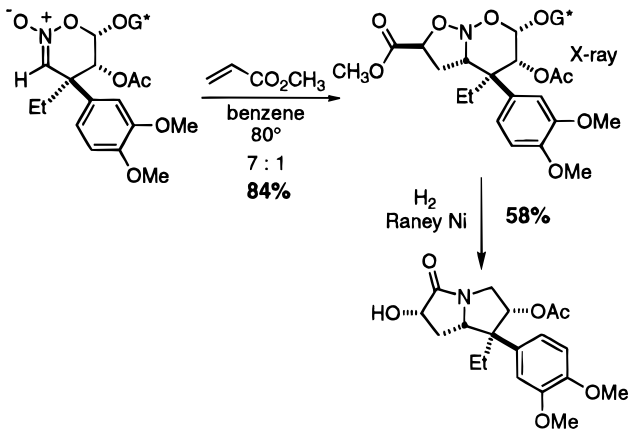
One of the most important advances in tandem cycloaddition methodology was the demonstration that chiral vinyl ethers are capable of distinguishing the enantiofaces of achiral nitroalkenes with high selectivity. The design and stereochemical analysis of these reactions will be discussed in detail below in the context of tandem intermolecular [4+2]/intramolecular [3+2] cycloadditions. When chirally modified 2-acyloxyvinyl ethers are employed to control absolute configuration it is found that those ethers derived from 2,2-diphenylcyclopentanol afford the resulting nitronate in good yields. A survey of several different 2-acyloxy substituted vinyl ethers reveals that the most selective reactions are achieved with a 2-acetoxy group; larger acyl groups give lower selectivity and are harder to prepare in good yields as well. Furthermore, when different β mono- or disubstituted aryl nitroalkenes are employed, the resulting nitronates are the result of an exo cycloaddition (Table 7). When the β-cyclohexyl nitroalkene is used, the reversed preference was observed and the major nitronate was the result of an endo selective cycloaddition. This method is limited to the use of substituted aryl nitroalkenes. Attempted employment of a disubstituted nitroalkene wherein both

Table 7. Cycloadditions of Chiral (2-Acyloxy)vinyl Ethers with Nitroalkenes

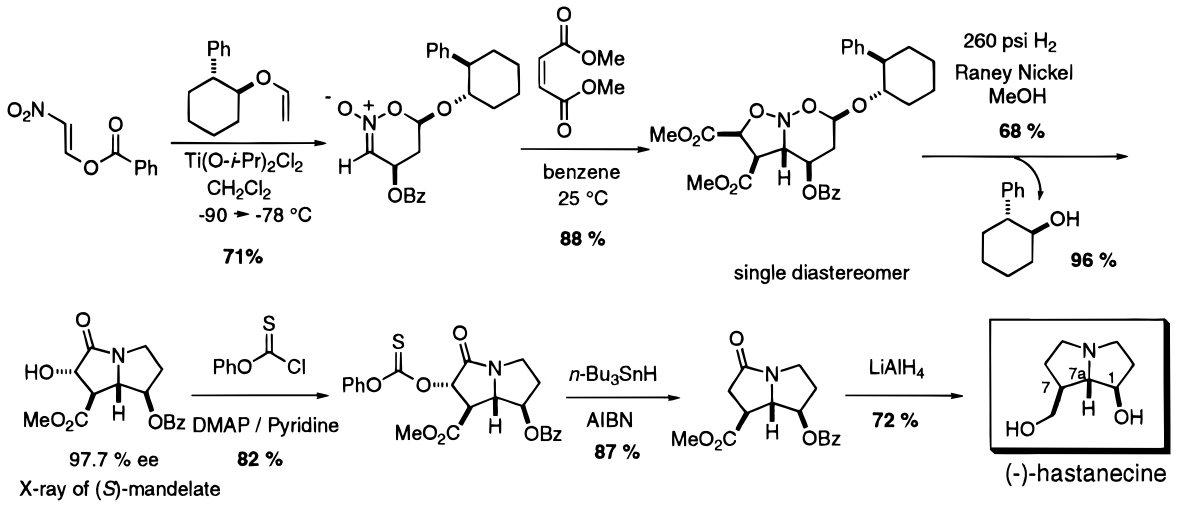


nitroalkene		nitronate yield, %	diastereomer	
R	R′		ratio	approach
ethyl	veratryl	90	40/1	exo
phenyl	H	86	1/1	exo
cyclohexyl	H	68	12/1	endo
n-pentyl	H	82	1/4/2/2	
cyclohexyl	ethyl	NR		

Scheme 22



Scheme 23



groups are alkyl substituents fails to provide any evidence of cycloadducts.

The veratryl-derived nitronate shown in Scheme 22 reacts smoothly with methyl acrylate to give a nitroso acetal in 84% yield as a 7/1 mixture of two diastereomers. The structure of the major diastereomer (confirmed by X-ray crystallographic analysis) arises as the result of a steric approach-controlled exo cycloaddition (i.e., to the face of the nitronate opposite the veratryl ring). It was further shown that the minor component is the result of a cycloaddition to the opposite face of the nitronate. When a pivaloyl group is employed instead of the acetate a single diastereomer is isolated.[72] Hydrogenolytic cleavage of the major nitroso acetal with Raney nickel gives the α-hydroxy lactam in 58% yield wherein four stereogenic centers are created with relative and absolute stereocontrol in only three steps from the simple starting materials.

The power of the tandem intermolecular [4+2]/intermolecular [3+2] nitroalkene cycloaddition has been demonstrated in the synthesis of (−)-hastanecine (Scheme 23).[54] (−)-Hastanecine is the necine portion of the pyrrolizidine alkaloid (−)-hastacine[90] and has been the subject of several total synthesis efforts.[91] Careful inspection of the relationships between the stereogenic centers C(1), C(7), and C(7a) of (−)-hastanecine dictates that both of the tandem cycloadditions should be intermolecular to afford the observed trans−trans relationship. Reaction of 2-(benzyloxy)nitroethene with the vinyl ether derived from (1*S*,2*R*)-2-phenylcyclohexanol in the presence of titanium diisopropoxide dichloride affords the nitronate in 71% yield. The major diastereomer is the result of an endo selective cycloaddition to the si face of the nitroalkene (vide infra). Treatment with dimethyl maleate affords the nitroso acetal as a single diastereomer through a steric approach-controlled, exo selective reaction in 88% yield. Unmasking of the nitroso acetal with hydrogen affords the α-hydroxy lactam containing all the required stereocenters of (−)-hastanecine with the correct relative and absolute stereochemistry as determined by X-ray analysis of the corresponding (*S*)-mandelate ester. Removal of the superfluous hydroxyl group was easily accomplished utilizing a radical deoxygenation. The reduction of the lactam affords (−)-hastanecine in only six steps and in 21% overall yield.

C. Tandem Intramolecular [4+2]/Intermolecular [3+2] Cycloadditions

The tandem intramolecular [4+2]/intermolecular [3+2] cycloaddition of nitroalkenes has not been extensively explored, so its full potential in organic synthesis cannot be assessed at the current time. The requirement of an intramolecular [4+2] cycloaddition dictates that the dienophile is tethered to either the α or β carbon of the nitroalkene, which, in turn creates bicyclic fused or bridged nitronates (Figure 5).

To date, the reactions of only β-tethered dienophiles has been reported (Scheme 24).[34] The substrates examined were either di- or trisubstituted nitroalkenes tethered by a three-methylene unit to disubstituted olefins as the dienophiles of either cis or trans configuration. Both the *Z*- and the *E*-disubstituted nitroalkenes react in the presence of tin tetrachloride to afford the nitronates in moderate to good yields but with poor diastereoselectivity. However, when trisubstituted nitroalkenes are used, both *E* and *Z* isomers give the *trans*- and *cis*-nitronates, respectively, in high selectivity through exclusive exo transition structures. The nitronates are combined

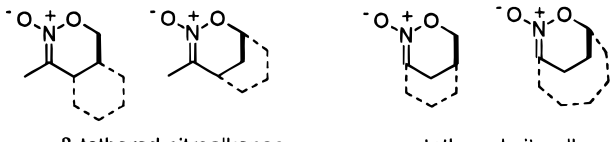
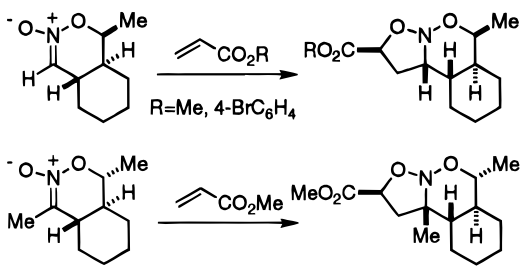


Figure 5. Classifications of tandem intramolecular [4+2]/intermolecular [3+2] cycloadditions.

Scheme 24



with acrylates to give the tricyclic nitroso acetals in 66−88% yield. The structure of the acetals has been established by X-ray analysis of the cycloadduct of the 4-bromophenyl acrylate.

D. Tandem Intermolecular [4+2]/Intramolecular [3+2] Cycloadditions

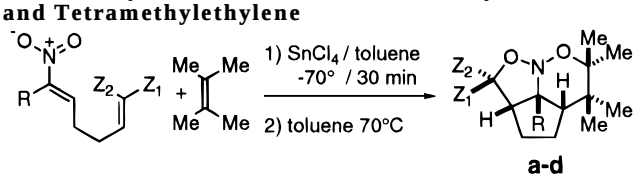
1. Definition of Subfamilies

The intermolecular [4+2]/intramolecular [3+2] cycloaddition of nitroalkenes is the family of tandem reactions that has been the most extensively explored. The versatility of this permutation derives in great measure from the fact that there exist four subfamilies of tandem cycloadditions which arise from the four different points of attachment of the dipolarophilic tether. These subfamilies, depicted in Scheme 25, are defined as fused, spiro, and bridged modes by virtue of the structure of the tricyclic nitroso acetal that is created. In the fused mode, the dipolarophile is tethered to the β-carbon of the nitroalkene (C(4) of the nitronate) and the product is a fused nitroso acetal. The spiro mode has the dipolarophile tethered to the α carbon of the nitroalkene (C(3) of the nitronate) and the product is a spirocyclic nitroso acetal. Finally, in the bridged mode, the dipolarophile is attached to either α or β carbon of the dienophile (C(6) or C(5) of the nitronate) and the resulting products are bridged tricyclic nitroso acetals.

2. Fused Mode Cycloadditions

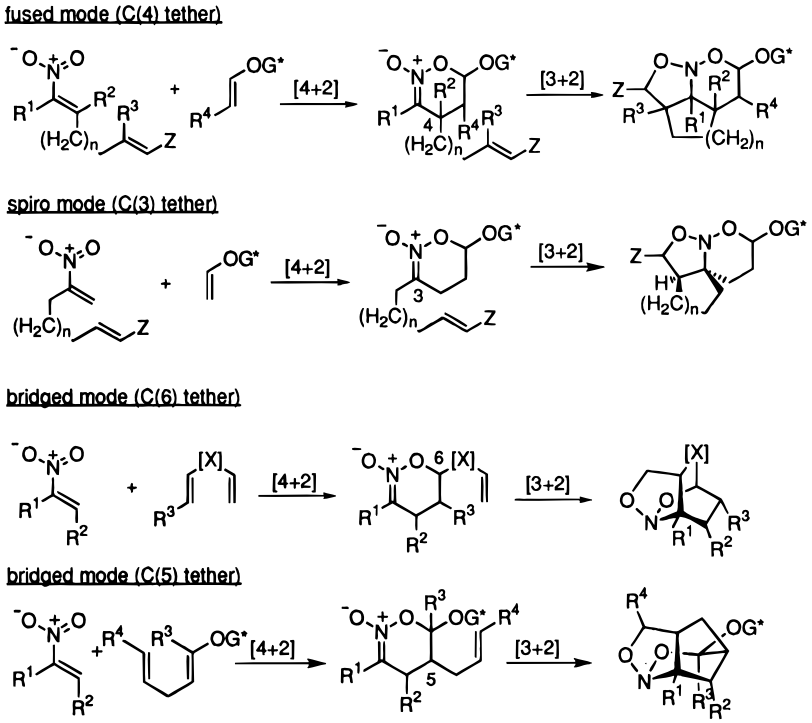
2.a. Unactivated Dienophiles. The initial exploration of this subfamily established the key structural attributes such as (1) the length of the tether between the dipole and the dipolarophile, (2) nitronate substitution, and (3) dipolarophile configuration. The survey of these structural variables in the tandem cycloaddition employed 2,3-dimethyl-2-butene as the test dienophile to avoid stereochemical complications.[37] The results for a two-methylene linking tether between heterodiene and dipolarophile are shown in Table 8. For both di- and trisubstituted nitroalkenes the *E*-enoate functions well as the dienophile to afford the tricyclic fused nitroso acetals **a** and **c** as single stereoisomers in good yields (68−72%). In neither case could the intermediate nitronate be isolated. The stereostructure of the cycloadduct **c** was confirmed by X-ray crystallography and revealed an all-cis ring system indicating a preferred endo fold for the side chain placing the ester in the preferred exo orientation in the [3+2] transition structure (vide infra). The corresponding *Z*-enoates react to give isolable intermediate nitronates after the initial [4+2] cycloaddition. The nitronates require heating in toluene at 70 °C to affect the [3+2] reaction, demonstrating their lesser reactivity compared to the trans-configured dipolarophiles. The tricyclic nitroso acetals are isolated in good yields (76−78%), but only **d** is formed with useful selectivity (20/1). That **c** and **d** possess the same gross stereostructure and differ only at the ester-bearing center has been proven by hydrogenolysis and oxidation of the resulting alcohols to a single ketone as shown in Scheme 26.

Table 8. Cycloaddition with a Two-Methylene Tether and Tetramethylethylene



R	Z_1	Z_2	time, h	product	de	yield %
H	CO_2Et	H	0	**a**	>100/1	68
H	H	CO_2Et	2.5	**b**	6/1/1.8	76
Me	CO_2Et	H	0	**c**	>100/1	72
Me	H	CO_2Et	3	**d**	20/1	78

Scheme 25



Scheme 26

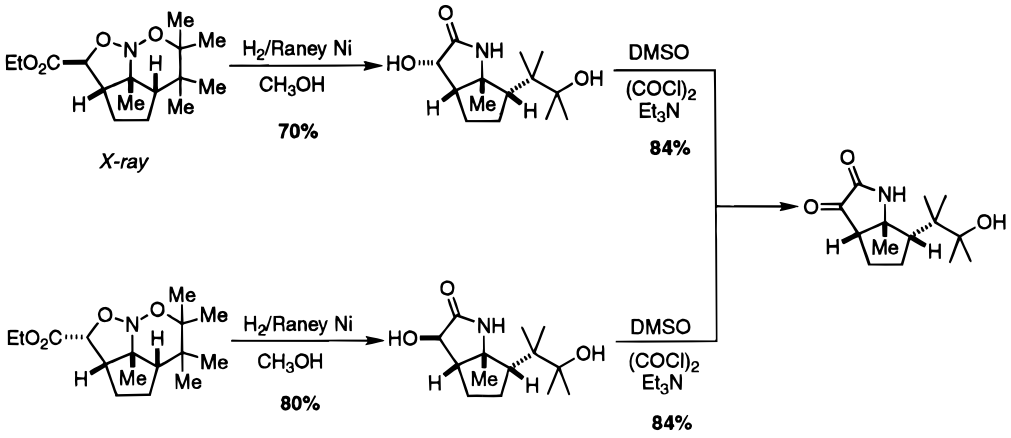
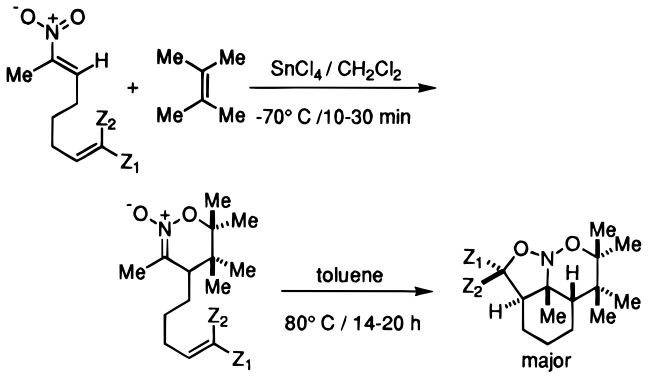


Table 9. Cycloadditions with a Three-Methylene Tether and Tetramethylethylene



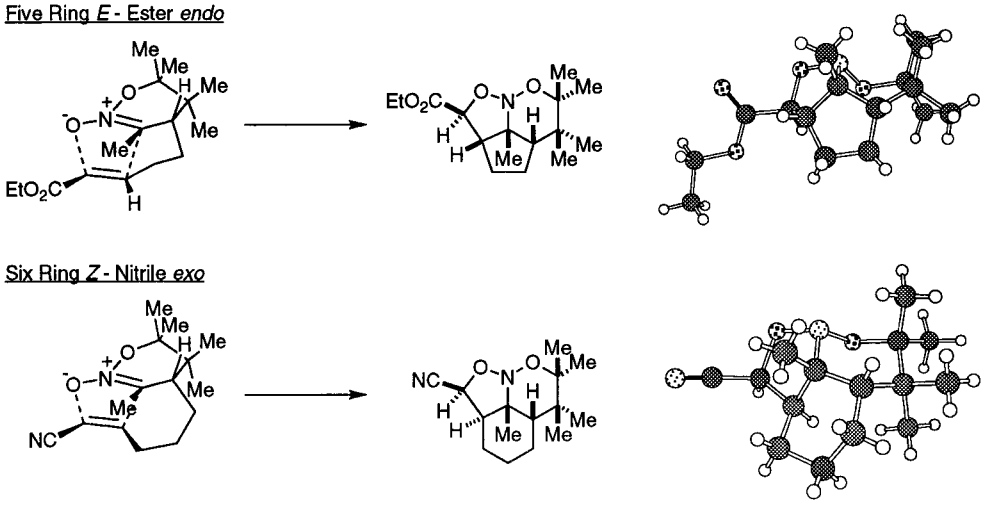
Z_1	Z_2	series	nitronate yield, %	de	nitroso acetal yield, %
CO_2Et	H	**a**	66	2.6/1	90
H	CO_2Et	**b**	72	>100/1	93
CN	H	**c**	83	2.8/1	97
H	CN	**d**	75	>100/1	95

For the homologous substrates bearing a three-methylene connecting tether, only the trisubstituted nitroalkenes were explored, but here the effect of the dipolarophile (ester versus nitrile) was compared (Table 9).[37] The results are complimentary to those above in an interesting way. First, in all cases the intermediate nitronates could be isolated. Warming these compounds to 80 °C is necessary to effect the [3+2] cycloaddition. For the trans dipolarophiles, the cycloaddition proceeds smoothly but unselectively (3/1). In this series, now the cis dipolarophiles reacted with high selectivity to provide a single stereoisomer. The rate and selectivity for the two dipolarophile activating groups are equivalent. Finally, the trans/cis ring fusion stereochemistry was proven by X-ray crystallography of nitroso acetal **d** (Scheme 27).

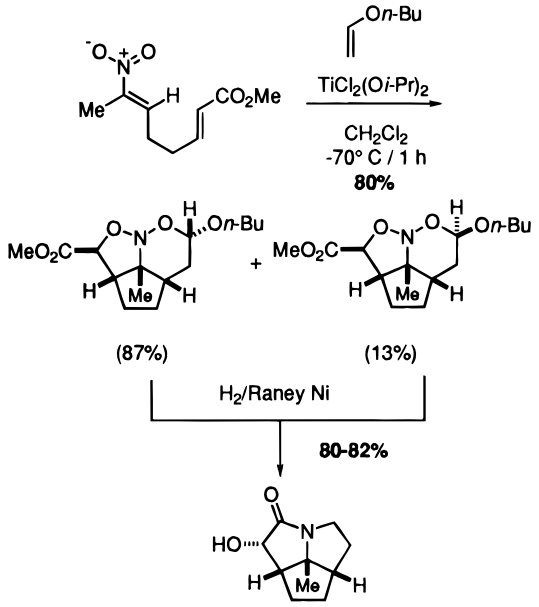
The dependence of rate and stereostructure on dipolarophile geometry can easily be rationalized by the change in folding of the side chain which depends on the length of the connecting tether (Scheme 27). Thus, the two-methylene tether can only support an endo fold, and therefore, the trans dipolarophile places the activating group in an exo orientation. The different behavior of the three-methylene tether can be understood since it adopts an exo fold. Thus, the cis-configured dipolarophile places the activating group in the preferred exo orientation, while in the trans series the activating group is forced to be in the less preferred endo orientation in the [3+2] transition structure resulting in diminished selectivity.

Incorporation of a four-carbon tether in the tandem sequence was attempted.[92] The [4+2] cycloaddition proceeded smoothly to afford the nitronate in 70−80% yield. However, the nitronates failed to undergo a thermal [3+2] cycloaddition to create a fused seven-membered ring.

Scheme 27



Scheme 28



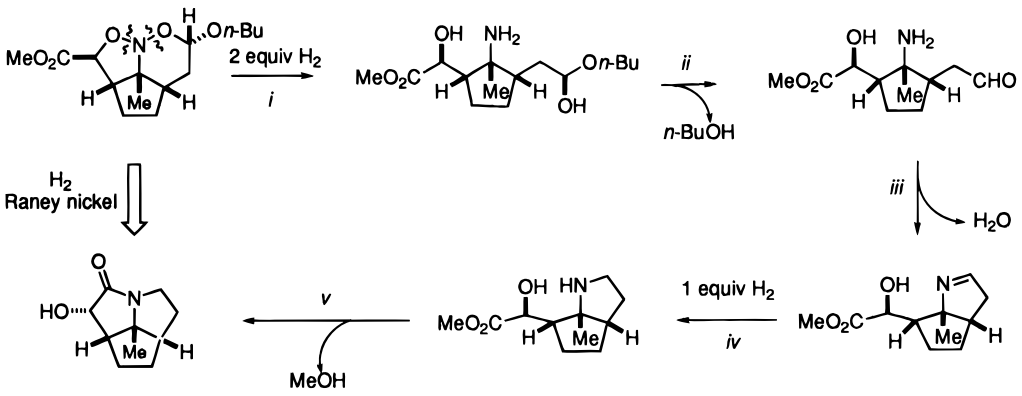
2.b. Oxygen-Containing Dienophiles (Achiral). The synthetic potential of the tandem [4+2]/[3+2] cycloaddition process is greatly enhanced by the employment of vinyl ether dienophiles.[37,52b] The initial survey of dienophile structure employed a trisubstituted nitroalkene and an *E*-enoate tethered by a two-methylene chain (Scheme 28). For the dienophiles, vinyl, (*Z*)-1-propenyl, and (*E*)-1-propenyl ethers were used. In all cases the mild Lewis acid $Ti(Oi\text{-}Pr)_2Cl_2$ or the hindered aluminum-based Lewis acids are the reagents of choice. In the simplest case, the reaction proceeds extremely well, affording a mixture of *n*-butoxy anomers in high yield.[37] Confirmation of the anomeric relationship has been established by independent hydrogenolysis with Raney nickel to afford the same tricyclic lactam in good yield. This remarkable series of transformations involves five discrete steps: (i) reductive N−O bond cleavage, (ii) hemiacetal breakdown, (iii) Schiff's base formation, (iv) saturation of the imine, and (v) lactam formation (Scheme 29). The stereostructure of the hydroxy lactam is assigned by analogy to the nitroso acetal derived from tetramethylethylene, the X-ray structure of which has been determined (Scheme 27). *Thus, in a two-stage transformation, two simple, acyclic molecules are transformed into a single tricyclic compound bearing four contiguous stereogenic centers in high yield.*

Extension of this tandem process to create *five* contiguous stereogenic centers is possible through the use of 2-substituted vinyl ethers.[52b] In addition to the obvious synthetic enhancement, the 2-substituted vinyl ethers also serve as a permanent stereochemical marker, preserving the memory of an endo or exo [4+2] transition state structure and allowing further understanding of the reaction. The results for the cycloaddition of the same nitroalkene substrate with ethyl (*Z*)-1-propenyl ether show a remarkable level of stereoselectivity in the creation of the fifth center (Scheme 30). The major isomer formed under conditions of kinetic control derives from an endo orientation of the ethoxy group in the [4+2] transition structure. Interestingly, the β-anomer formed under conditions of thermodynamic control has the same α-disposition of the methyl group, indicating that the two isomers are related by a simple epimerization at the acetal carbon. This was proven by independent hydrogenolysis of the two isomers to give a single tricyclic lactam. The position of the methyl group was established by the indicated NOE experiment. The thermodynamically more stable nitroso acetal has the ethoxy group disposed in an axial orientation, suggesting substantial stabilization due to the anomeric effect.

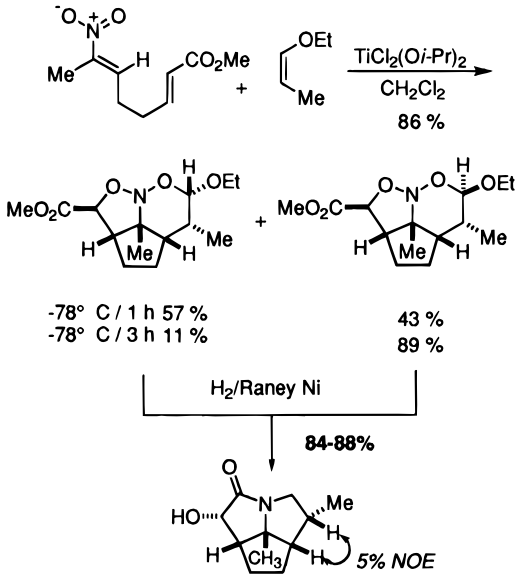
In an analogous fashion, ethyl (*E*)-1-propenyl ether reacts with the same nitroalkene in high selectivity to afford a 19/1 mixture of anomers (Scheme 31). The α-anomer is formed as the major isomer under all conditions and must arise from an endo orientation of the ethyl group. Hydrogenolysis of the anomeric mixture affords a single tricyclic lactam which is isomeric to the product obtained from the *Z*-propenyl ether, indicating that the methyl-bearing stereogenic center has changed. Thus, the propensity for an endo orientation of the ethoxy group is very strong and completely controls the ultimate position of the methyl group.

The cycloaddition of the three-methylene tethered nitroalkene with *n*-butyl vinyl ether was also examined using $Ti(Oi\text{-}Pr)_2Cl_2$ as the promoter.[37] Three important consequences of the additional methylene group are noteworthy (Scheme 32). First, unlike the two-methylene tethered substrate, in this case the intermediate nitronates could be isolated and were independently cyclized by heating in toluene. The two anomers behave similarly and provide the tricyclic products in good yield and high selectivity (>19/1). The assignment of stereostructure of the products

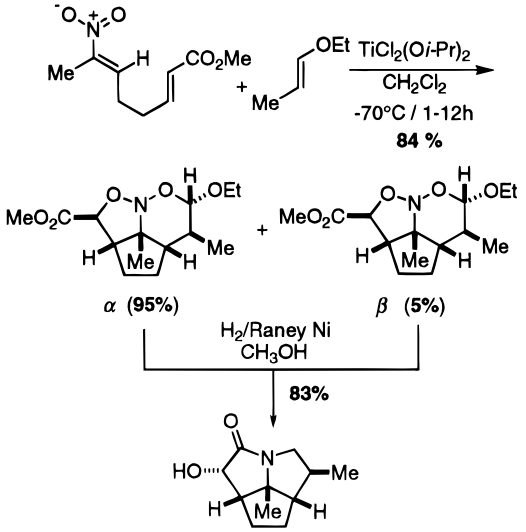
Scheme 29



Scheme 30



Scheme 31



was made on the basis of analogy to the X-ray structure of the tetramethylethylene adduct (Scheme 27). In these cases, the minor component was isolated and identified as the product of endo folding of the dipolarophile side chain.

The anomeric relationship of the two cycloadducts was proven as before by independent hydrogenolysis to the same pyrrolidino ester (Scheme 33). Herein, the second difference is noted in that the reduction is not complete at atmospheric pressure and intermediate reduction products could be isolated. A clean and complete conversion could be achieved at 160 psi. Finally, the third distinction was noted in that the pyrrolidino ester did not undergo spontaneous lactam formation. This is most certainly a consequence of the trans ring fusion stereochemistry since the ring closure would require a trans-fused lactam. This closure could be induced simply by heating the ester in toluene at 110 °C (Scheme 33).

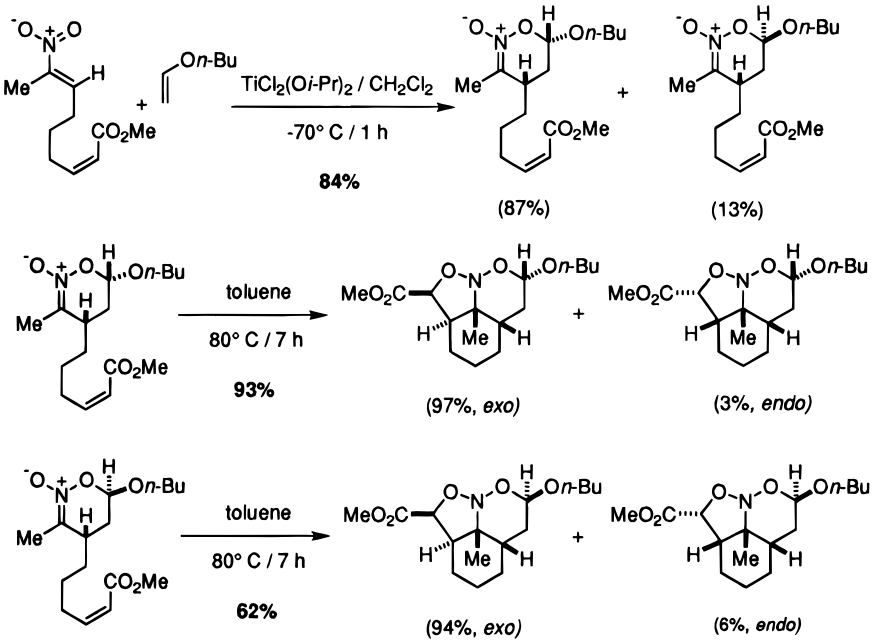
2.c. Unactivated Dipolarophiles. The success of the tandem intermolecular [4+2]/intramolecular [3+2] cycloaddition sequence rests in the complimentary electronic properties of the tethered dipolarophile and the enol ether dienophile. The inverse electron demand [4+2] cycloaddition is compatible with the unsaturated ester which is well-suited for the [3+2] cycloaddition component. The possibility of employing simple olefins as dipolarophiles represents an interesting challenge.[92] The key issue is whether the vinyl ether could compete with the intramolecularly tethered dienophile. Eight substrates were examined which bear two- and three-atom tethers, di- and trisubstituted nitroalkenes, and various substitution patterns on the tethered double bond (dipolarophile). The results of cycloadditions with nitroalkenes bearing the two methylene tethers are collected in Table 10. Remarkably, all substrates undergo clean cycloaddition with *n*-butyl vinyl ether; no products of intramolecular [4+2] cycloaddition are detected. In all cases the nitronates could be isolated (as anomeric mixtures). Subsequent heating (80 °C, toluene) effected the [3+2] cycloaddition uneventfully.

In this cycloaddition study, the remarkable effects of dipolarophile geometry and substitution on the rate of the [3+2] cycloaddition are observed. The rate of the cycloaddition with unactivated dipolarophiles is clearly slower than with activated dipolarophiles. The order of the cycloaddition rates is trans > monosubstituted > trisubstituted > cis. This trend is the same as that observed with activated dipolarophiles in which an *E*-unsaturated ester cyclizes faster than a *Z*-unsaturated ester dipolarophile. The endo cycloaddition is firmly established for ester dipolarophiles. Therefore, it is reasonable to assume that these cycloadditions also proceed with an endo transition structure during the [3+2] cycloaddition in which the connecting chain is oriented under the nitronate ring. Cycloaddition rates also imply that the reaction rate is sterically controlled. Comparison of the cycloaddition rates between the *E*- and the monosubstituted dipolarophiles and between the tri- and *Z*-substituted dipolarophile imply that addition of a methyl group (electron-donating group) accelerates the cycloaddition. Thus, the cycloaddition of a simple olefin to a nitronate appears to be $HOMO_{dipolarophile}-LUMO_{dipole}$-controlled

The [3+2] cycloadditions to form five-membered rings proceed with extremely high selectivity. In the case of the cycloadditions with the *E*-dipolarophile, only two anomers are obtained. However, in the cycloaddition with the *Z*-dipolarophile, a minor isomer is detected which most likely arises from a different side-chain folding. The higher selectivity for *E*-dipolarophiles is also observed in the ester series. In that case, an *E*-unsaturated ester gives >100/1 selectivity and a *Z*-unsaturated ester gives 19/1. The low selectivity for a *Z*-dipolarophile reflects the endo folding of the side chain during the cycloaddition. In an endo transition structure, the terminal substituent is placed in an unfavorable position under the dipole.

The cycloaddition of nitroalkenes tethered by three methylene units also proceed without difficulty. As expected, cycloaddition of *n*-butyl vinyl ether is faster than the intramolecular cycloaddition. The nitronates from disubstituted nitroalkenes (series **c** and **d**) underwent [3+2] cycloaddition slowly at room temperature. The mixtures of crude nitronates are

Scheme 32



Scheme 33

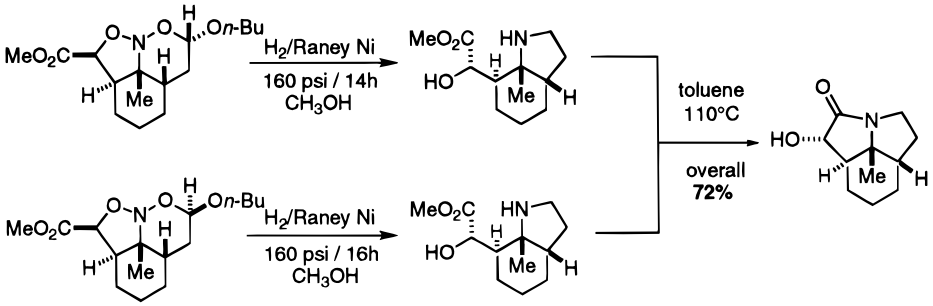
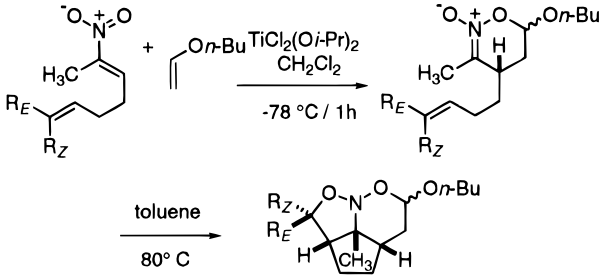
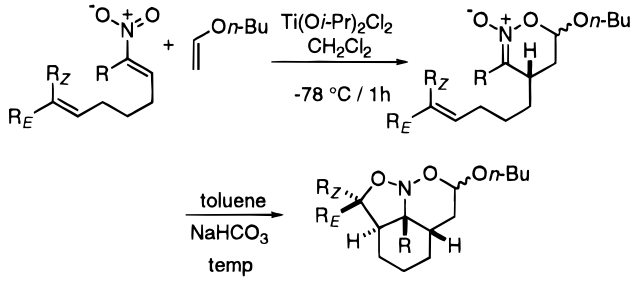


Table 10. Cycloaddition of Nitroalkenes Bearing a Two-Methylene Tether with an Unactivated Dipolarophile



series	nitroalkene R_E	nitroalkene R_Z	nitronate yield, %	time, h	nitroso acetal yield, % (ratio α/β)
a	H	H	85	13	70 (1/3.2)
b	Me	H	86	12	69 (1/5.8)
c	H	Me	88	33	70 (1/3)
d	Me	Me		18	70 (1/7)

Table 11. Cycloaddition of Nitroalkenes Bearing a Three-Methylene Tether with an Unactivated Dipolarophile



series	nitroalkene R_E	nitroalkene R_Z	nitroalkene R	nitronate temp, °C	nitronate time, h	nitroso acetal yield, % (ratio, α/β)
a	H	Me	Me	110	9	83 (5.5/1)
b	Me	H	Me	110	14	76 (15/1)
c	H	Me	H	80	18	76 (10.5/1)
d	Me	H	H	80	32	72 (2.7/1)

subjected to the thermal cycloaddition at 80 °C in toluene in the presence of $NaHCO_3$. The thermal [3+2] cycloaddition of nitronate anomers from trisubstituted nitroalkenes (series **a** and **b**) is very slow at 80 °C but does proceed at 110 °C in toluene in the presence of $NaHCO_3$. The results for these cycloadditions are summarized in Table 11.

The rates of reaction clearly reflect the effect of substituents on the [3+2] cycloaddition to form a six-membered ring. A disubstituted nitronate cyclizes faster than a trisubstituted nitronate and also a *Z*-dipolarophile cyclizes faster than an *E*-dipolarophile. These cycloaddition rates are in agreement with the previous trends observed with an activated dipolarophile. Therefore, it is reasonable to assume that the cycloaddition of an unactivated dipolarophile also proceeds via an exo transition structure. The

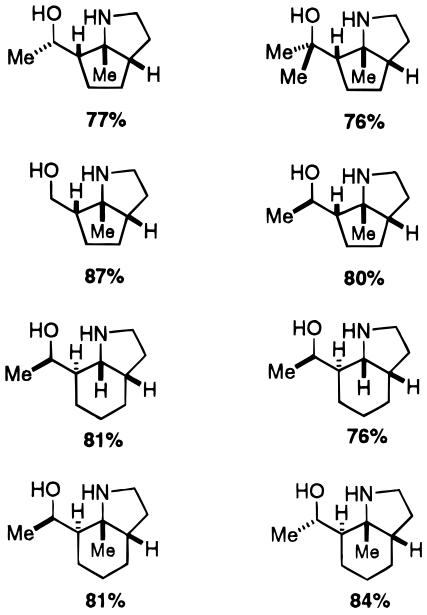


Figure 6. Hydrogenolysis products from cycloaddition with unactivated dipolarophiles.

stereoselectivity for the cycloadditions was extremely high. The anomeric mixtures of isolated nitroso acetals contained only the products of exo folding of the side chain. Minor components derived from endo folding could be detected in the crude cycloadducts. For disubstituted nitronates (**c** and **d**), the selectivity was greater than for a trisubstituted nitronates (**a** and **b)**. The cycloadditions with an activated dipolarophile showed that a *Z*-dipolarophile cyclizes with higher selectivity than an *E*-dipolarophile.

All of the nitroso acetals are amenable to the standard reductive transformation by hydrogenation in the presence of Raney nickel at atmospheric pressure. In these cases the mixture of anomeric nitroso acetals affords a single amino alcohol which demonstrates that the difference is only in the configuration at the acetal center. The process is analogous to that observed in the previous hydrogenolysis experiments. The only difference is that the sequence terminates after the imine saturation step due to the absence of an ester group. The structures and yields of the bicyclic amino alcohol products are collected in Figure 6.

2.d. Oxygen-Containing Dienophiles (Chiral). The extremely high selectivity for tandem cycloaddition, the ease of manipulation of the nitroso acetals, and the release of the vinyl ether appendage in the hydrogenolytic cleavage constitute ideal features for asymmetric modification of the cycloadditions with chiral vinyl ethers. The one permanent stereogenic center created in the [4+2] cycloaddition directs the formation of the other three centers. A number of candidates for the chiral alcohol which will serve as the auxiliary have been examined with the following criteria in mind. First, from a practical point of view the auxiliary (1) should be of low molecular weight, (2) easily prepared, and (3) both antipodes of the auxiliary should be available. From a stereochemical point of view, several additional criteria are critical. The chiral reagent should display a high exo/endo preference for the approach in the [4+2] cycloaddition and possess a high bias for reaction on one diastereoface of the vinyl ether. The vinyl ethers that have shown the greatest promise are derived from the chiral auxiliaries: bornanediol (**I**), 2-phenylcyclohexanol (**II**), and 2,2-diphenylcyclopentanol (**III**) (Figure 7).

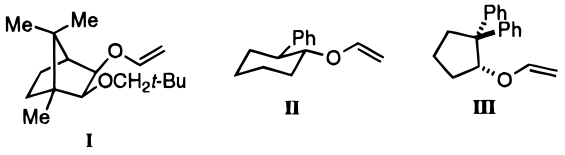
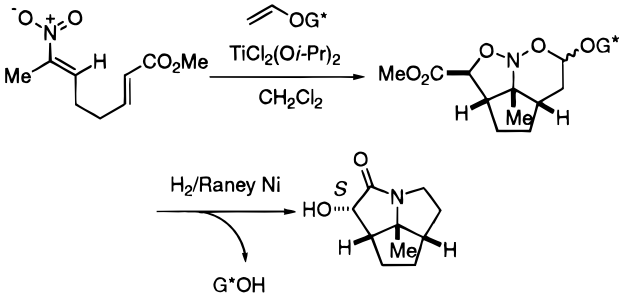


Figure 7. Chiral vinyl ethers employed in tandem nitroalkene cycloadditions.

Table 12. Cycloadditions with Chiral Vinyl Ethers

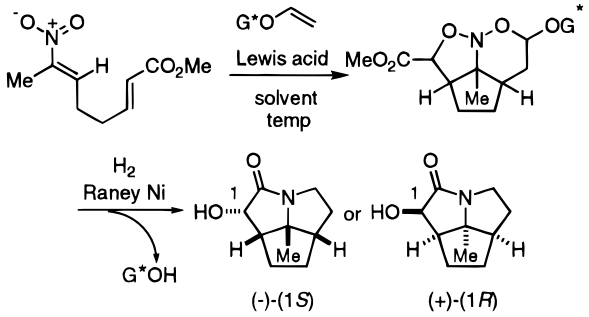


	nitroso acetal			lactam	
vinyl ether	yield, %	ds	G*OH yield, %	yield, %	ee, %
I	82	81/19	92	86	98
II	73	99/1	92	76	98
III	88	96/2/2	82	70	98

Thus, the chiral vinyl ether **I** derived from bornanediol is expected to be useful on the basis of its exquisite face selection properties illustrated in the Diels−Alder reaction.[93] The cycloaddition proceeds readily with the test nitroalkene shown in Table 12 in the presence of $Ti(O\textit{i}\text{-}Pr)_2Cl_2$ to afford an epimeric mixture of isomers in good yield. That these products are merely anomers is demonstrated as usual by hydrogenolytic cleavage and closure to afford the lactam shown in Table 12. Once again both anomers produce the known tricyclic lactam in excellent yield along with a high recovery of the camphor-derived auxiliary. The asymmetric induction was found to be excellent, >98% ee in both cases as judged by chiral HPLC analysis. The absolute configuration of the levorotatory tricyclic lactam has been established to be (−)-1*S* by the modified Mosher method.[94]

Despite the high selectivity obtained with **I**, the bornanediol-derived auxiliary is far from ideal due primarily to its size and the number of steps required for its synthesis. The simpler auxiliary, *trans*-2-phenylcyclohexanol, has shown great potential as well in the tandem cycloaddition. The smaller size, two step-synthesis,[95] and straightforward enzymatic resolution make it an attractive adjuvant. The stereoselectivity of reaction of the simple vinyl ether **II** with the standard nitroalkene substrate in the presence of $Ti(O\textit{i}\text{-}Pr)_2Cl_2$ is also shown in Table 12. The reaction proceeds cleanly, affording a mixture of anomers which heavily favors the α isomer. As before, the *β* isomer becomes predominant at extended reaction times, indicating that the α anomer is the kinetic product. Hydrogenolysis affords the familiar levorotatory lactam in good yield and with

Table 13. Lewis Acid Influence on Cycloadditions with Chiral Vinyl Ethers



chiral vinyl ether	Lewis acid	nitroso acetal yield, %	lactam yield, %	G*OH, yield, %	lactam ee, % (config.)
II	Ti(O*i*-Pr)$_2$Cl$_2$	73	76	92	98 (1*S*)
II	MAD	88	73	78	72 (1*S*)
II	MAPh	85	76	97	79 (1*R*)
I	Ti(O*i*-Pr)$_2$Cl$_2$	82	86	92	98 (1*S*)
I	MAD	86	67	81	2 (1*S*)
I	MAPh	83	88	86	99 (1*R*)
III	Ti(O*i*-Pr)$_2$Cl$_2$	88	70	82	98 (1*S*)
III	MAPh	86	74	94	93 (1*R*)

excellent enantiomeric enrichment. The sign of the optical rotation of the lactam reveals that the (1*R*,2*S*)-2-phenylcyclohexanol auxiliary produces the same absolute configuration of lactam as the camphor auxiliary.

In search of a general auxiliary for both endo and exo mode cycloadditions (vide infra), the diphenylcyclopentanol-derived vinyl ether has shown great potential due to the greater steric shielding of one face of the enol ether.[57] Subjecting **III** to the tandem sequence gave a mixture of nitroso acetals which favors the endo isomer. Hydrogenolysis then affords the α-hydroxy lactam in 98% enantiomeric purity. Therefore, the use of Ti(O*i*-Pr)$_2$Cl$_2$ as the Lewis acid promoter and any of the three auxiliaries affords the α-hydroxy lactam with very high asymmetric induction.

A remarkable dependence of the stereochemical course of the cycloaddition on the nature of the Lewis acid has been documented. In an attempt to reduce the amount of vinyl ether necessary for complete conversion, the hindered Lewis acids MAD and MAPh[96] were examined in the cycloaddition with **II** (Table 13). Although the selectivity observed with both of these reagents is inferior to that with Ti(O*i*-Pr)$_2$Cl$_2$, the lactam derived from reaction with MAPh is formed in the *enantiomeric dextrorotatory series!* Thus, from a single enantiomer of 2-phenylcyclohexanol, both antipodes of the lactam can be prepared.

The Lewis acid dependent reversal of selectivity is also verified in cycloadditions involving the camphor-derived vinyl ether (**I**) where even a stronger influence is observed (Table 13).[52c] In the cycloaddition promoted by MAPh, the same magnitude of asymmetric induction is observed as is seen with Ti(O*i*-Pr)$_2$Cl$_2$ but now in the opposite sense. The resulting α-hydroxy lactam is enriched in the (+)-(1*R*) enantiomer to the extent of 99% ee in contrast to 98% ee of the (−)-(1*S*)-enantiomer observed with Ti(O*i*-Pr)$_2$Cl$_2$.

Not unexpectedly, when vinyl ether **III** is employed in the cycloadditions promoted by MAPh, a reverse

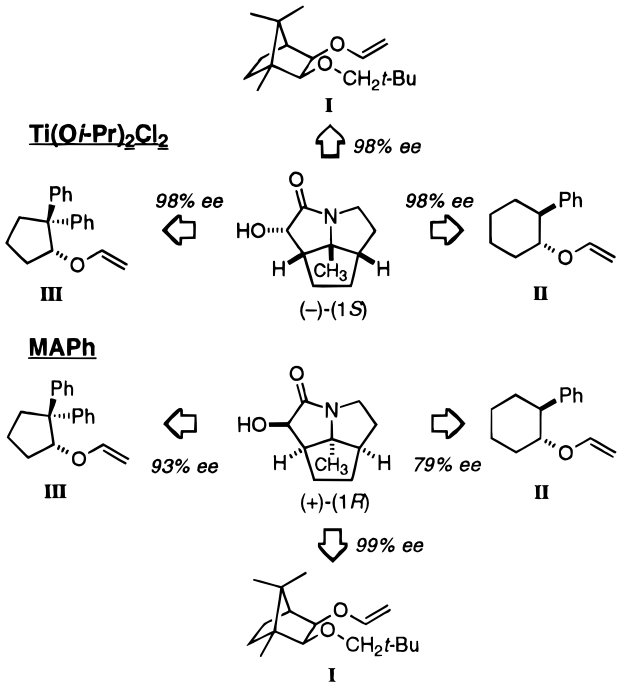


Figure 8. Comparison of chiral auxiliaries in vinyl ether cycloadditions.

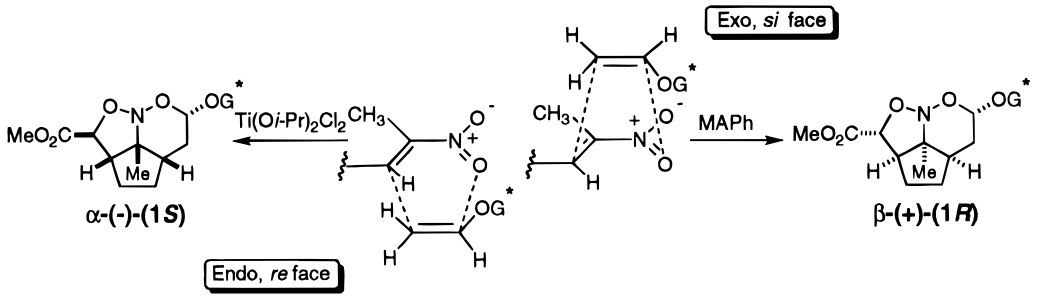
in selectivity is again observed, but in this instance, nearly the same magnitude of asymmetric induction for the (+)-(1*R*)-enantiomer (93% ee) with MAPh contrasts the 98% ee obtained for the (−)-(1*S*)-enantiomer with Ti(O*i*-Pr)$_2$Cl$_2$.[57]

The high levels and complimentary selectivities obtainable with the three chiral vinyl ethers and two different Lewis acids are summarized in Figure 8. The three auxiliaries all achieve very high asymmetric induction when the reactions are promoted by Ti(O*i*-Pr)$_2$Cl$_2$. The differences, however, manifest themselves in exo selective cycloadditions promoted by MAPh. Therefore, any synthetic planning must take into consideration the appropriate combination of a Lewis acid and chiral vinyl ether which will be substrate dependent. This feature is well-demonstrated in the synthesis of (−)-rosmarinecine (vide infra) wherein the substrate nitroalkene only tolerated aluminum-based Lewis acids, making diphenylcyclopentanol the auxiliary of choice.

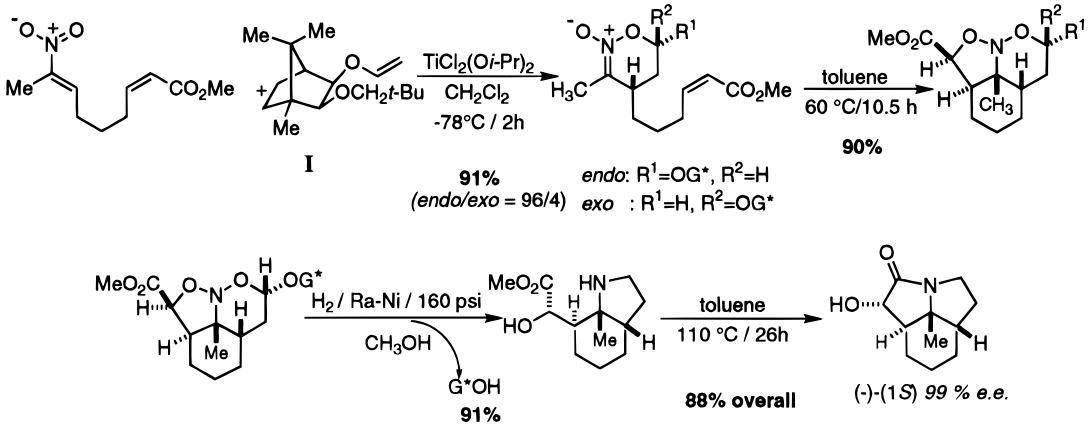
The striking inversion in enantiomeric composition can be simply explained by a reversal in the endo/exo selectivity of the [4+2] cycloaddition (Scheme 34). The preference for the endo orientation of a vinyl ether in inverse electron demand Diels−Alder reactions has been well-documented. However, the introduction of an extremely bulky Lewis acid coordinated to the substrate could alter the selectivity. On the basis of the formation of a single β anomer, the high stereoselectivity obtained with MAPh and the camphor-derived vinyl ether **I** is consistent with a *si* face, exo approach of the vinyl ether in an *s*-trans conformation. The enhanced selectivity from **I** and **III** compared to that from **II** arises from the greater bulk of the cyclic skeleton. Likewise, the phenyl substituents of MAPh can more effectively block the endo approach of the vinyl ether, therefore allowing MAPh to have a higher exo selectivity than MAD.

Since the origin of asymmetric induction derives from the [4+2] component of the tandem cycloaddi-

Scheme 34



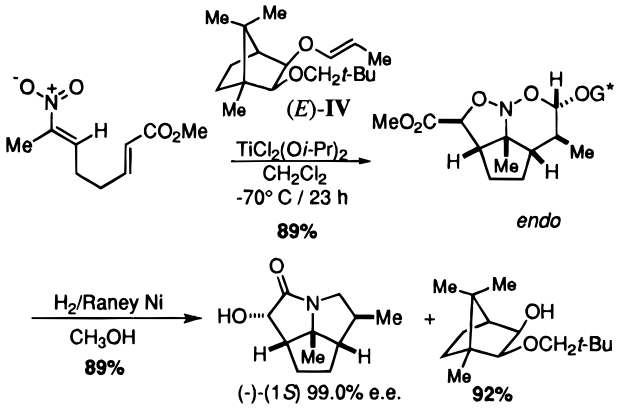
Scheme 35



tion process, a similarly high selectivity is expected from the asymmetric cycloaddition of the three-methylene tethered substrate as well.[51] This is indeed the case, as shown in Scheme 35. From the use of **I** and Ti(O*i*-Pr)$_2$Cl$_2$, the intermediate nitronate could be isolated as a 24/1 mixture of α and β anomers. This mixture is heated in toluene to afford the fused tricyclic nitroso acetals. Following the protocols described above, the mixture of nitroso acetals undergoes hydrogenolytic cleavage to afford the pyrrolidino ester (along with the auxiliary) which is then heated to produce the known hydroxy lactam in excellent overall yield. The stereoselectivity is again extremely high (99% ee) and the absolute configuration of the (−)-enantiomer was shown to be 1*S*. The stereochemical outcome of this reaction is in complete accord with the previous case and further supports the general formulation of the origin of asymmetric induction that will be discussed below.

Extension of the enantioselective cycloaddition methods to incorporate 2-substituted vinyl ethers has met with considerable success and has also served to highlight limitations. The synthesis of the 2-substituted vinyl ethers is possible by modification of the method of Greene[97] for the selective preparation of either (*E*)- or (*Z*)-propenyl ethers. The cycloaddition of the test nitroalkene shown in Scheme 36 with the chiral (*E*)-propenyl ether (*E*)-**IV** in the presence of Ti(O*i*-Pr)$_2$Cl$_2$ affords the tricyclic nitroso acetal as a single diastereomer in excellent yield. Hydrogenolysis of this intermediate cleanly produces the known hydroxy lactam in excellent yield, together with a good recovery of the auxiliary. The enantiomeric enrichment for the levorotatory lactam is, not surprisingly, extremely high. The absolute configuration was assigned ((−)-(1*S*)) by analogy and also on the basis of the elution order on chiral HPLC.

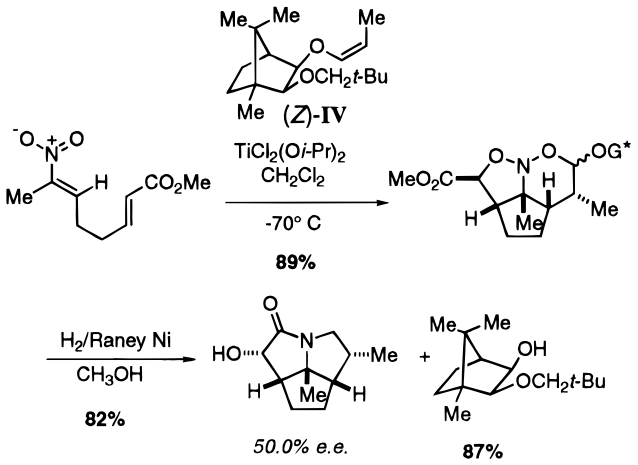
Scheme 36



Cycloaddition of the (*Z*)-propenyl ether (*Z*)-**IV** proceeds readily to afford a mixture of nitroso acetals in high yield (Scheme 37). Hydrogenolysis affords the known tricyclic lactam as a single diastereomer in good yield. However, the enantiomeric enrichment is very low (50% ee, (−)-(1*S*)), which indicates that the two anomers belong to opposite enantiomeric series.

The failure of (*Z*)-**IV** to react with high diastereofacial selectivity suggested the use of substituted vinyl ethers derived from 2-phenylcyclohexanol. In the presence of Ti(O*i*-Pr)$_2$Cl$_2$, (*E*)-propenyl ether (*E*)-**V** and (*Z*)-propenyl ether (*Z*)-**V** react to give a mixture of nitroso acetals derived from both exo and endo orientation (Table 14). The stereochemical analysis is confusing since product **a** derives from an endo orientation of (*E*)-**V** or an exo orientation of (*Z*)-**V** (and vice versa for **b**). The cycloaddition with (*E*)-**V** produces a ternary mixture of nitroso acetals in 86% yield. Hydrogenolytic cleavage produces the tricyclic lactams **a** and **b** in a 11.9/1 ratio, which is indicative

Scheme 37



of the endo/exo selectivity for the reaction. Chiral HPLC analysis of the mixture of isomers reveals that (−)-**a** is highly enriched (98% ee) in the expected 1*S* enantiomer. However, an erosion of selectivity was observed for (−)-**b**, which was found to be only 65% ee again in the 1*S* enantiomer.

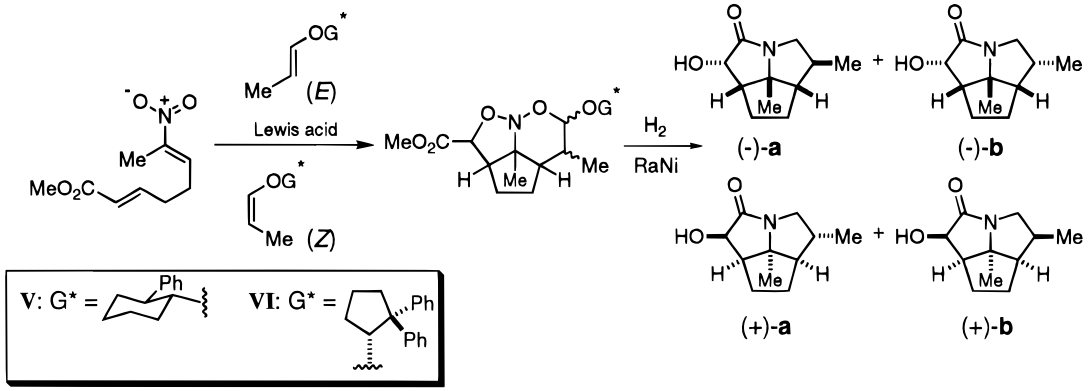
Similarly, the (*Z*)-propenyl ether (*Z*)-**V** reacts to give a quaternary mixture of nitroso acetals in 83% yield. Hydrogenolysis afforded a 10.7/1 mixture of lactams. Chiral HPLC analysis of the (inseparable) mixture of isomers again reveals a predominance of the 1*S* enantiomer in both endo and exo modes with a higher level of selectivity displayed in the endo (82% ee) compared to the exo (64% ee) mode. Although the vinyl and (*E*)-propenyl ethers reacted with high selectivity, the erosion in endo/exo control for (*E*)-**V** and the low enantiomeric excess seen for (*Z*)-**V** suggest that these are not suitable replacements of the camphor auxiliaries.

The (*Z*)-propenyl ether derived 2,2-diphenylcyclopentanol provides the best results for exo mode cycloadditions to date. Reaction of (*Z*)-propenyl ether (*Z*)-**VI** with Ti(O*i*-Pr)$_2$Cl$_2$ as the promoter affords the nitroso acetals in excellent yield (Table 14). Hydrogenolysis and derivatization as previously described reveal an endo/exo ratio of 8.2/1. The major diastereomer **b** is created very selectively (92% ee). With MAPh as the Lewis acid, the lactams formed after hydrogenation are now enriched in the exo diastereomer **a** (exo/endo, 10.2/1). In this case the exo diastereomer (+)-**a** is determined to be of 83% enantiomeric purity.

The full evaluation of 2,2-diphenylcyclpentanol as an auxiliary is seen in the examination of (*E*)-propenyl ether (*E*)-**VI** in the test cycloaddition with both Lewis acids, as shown in Table 14. Isolation of the nitroso acetals followed by hydrogenolysis and derivation reveals a rather unselective cycloaddition since the endo/exo ratio was only 2.3/1 as determined by HPLC. The major diastereomer **a** is derived from the endo mode and is created very selectively (96% ee) while an erosion is observed in the selectivity for the minor diastereomer **b**. With MAPh as the promoter, the nitroso acetals are formed in 83% yield but as a mixture of two diastereomers in a ratio of 7/1. Hydrogenolysis followed by derivatization reveals that both the diastereomers are derived from an exclusive exo selective orientation of the dienophile in the [4+2] cycloaddition. Therefore, the two nitroso acetal diastereomers must belong to the opposite enantiomeric family to explain the low enantiomeric purity observed for the α-hydroxy lactam (+)-**b**.

The success of cycloadditions of chiral propenyl ethers derived from the three auxiliaries is summarized in the comparison in Figure 9. To access the fused hydroxy lactam (−)-**a**, chiral auxiliaries (*E*)-**IV** and (*E*)-**V** provide the highest selectivities. In contrast, for the methyl epimer (−)-**b**, the Ti(O*i*-Pr)$_2$Cl$_2$-promoted cycloaddition of the (*Z*)-**VI** clearly provides the highest level of asymmetric induction (92% ee). The chiral auxiliary also allows for access

Table 14. Cycloadditions of Chiral Propenyl Ethers



enol ether	Lewis Acid	nitroso acetals yield, %	lactams yield, %	(endo/exo ratio)	endo % ee (config)	exo, % ee (config.)
(*E*)-**V**	Ti(O*i*-Pr)$_2$Cl$_2$	86	77	(−)-**a**/(−)-**b** (11.9/1.0)	98 (*S*)	65 (*S*)
(*Z*)-**V**	Ti(O*i*-Pr)$_2$Cl$_2$	83	70	(−)-**b**/(−)-**a** (10.7/1.0)	82 (*S*)	64 (*S*)
(*E*)-**V**	MAD	86	81	(−)-**a**/(−)-**b** (1.0/2.6)	100 (*S*)	72 (*S*)
(*Z*)-**V**	MAD	72	83	(−)-**b**/(+)-**a** (8.7/1.0)	100 (*S*)	17 (*R*)
(*Z*)-**VI**	Ti(O*i*-Pr)$_2$Cl$_2$	95	78	(−)-**b**/(−)-**a** (8.2/1.0)	92 (*S*)	65 (*R*)
(*Z*)-**VI**	MAPh	84	78	(−)-**b**/(+)-**a** (1.0/10.2)	38 (*S*)	83 (*R*)
(*E*)-**VI**	Ti(O*i*-Pr)$_2$Cl$_2$	93	84	(−)-**a**/(−)-**b** (2.3/1.0)	96 (*S*)	66 (*R*)
(*E*)-**VI**	MAPh	83	77	(−)-**a**/(+)-**b** (1.0/54.8)	41 (*S*)	74 (*R*)

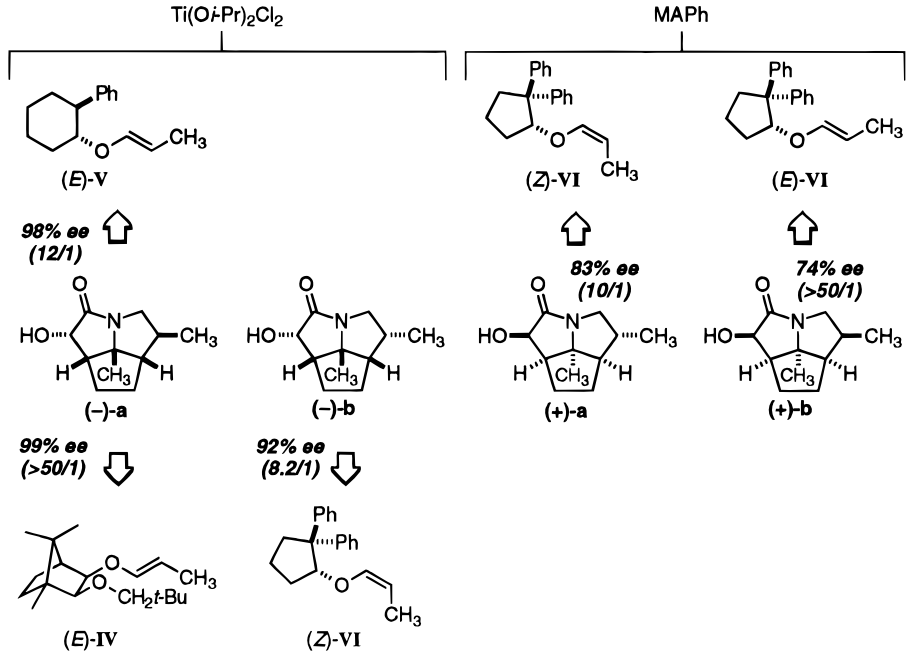


Figure 9. Isomeric α-hydroxy lactams accessible through propenyl ether cycloadditions.

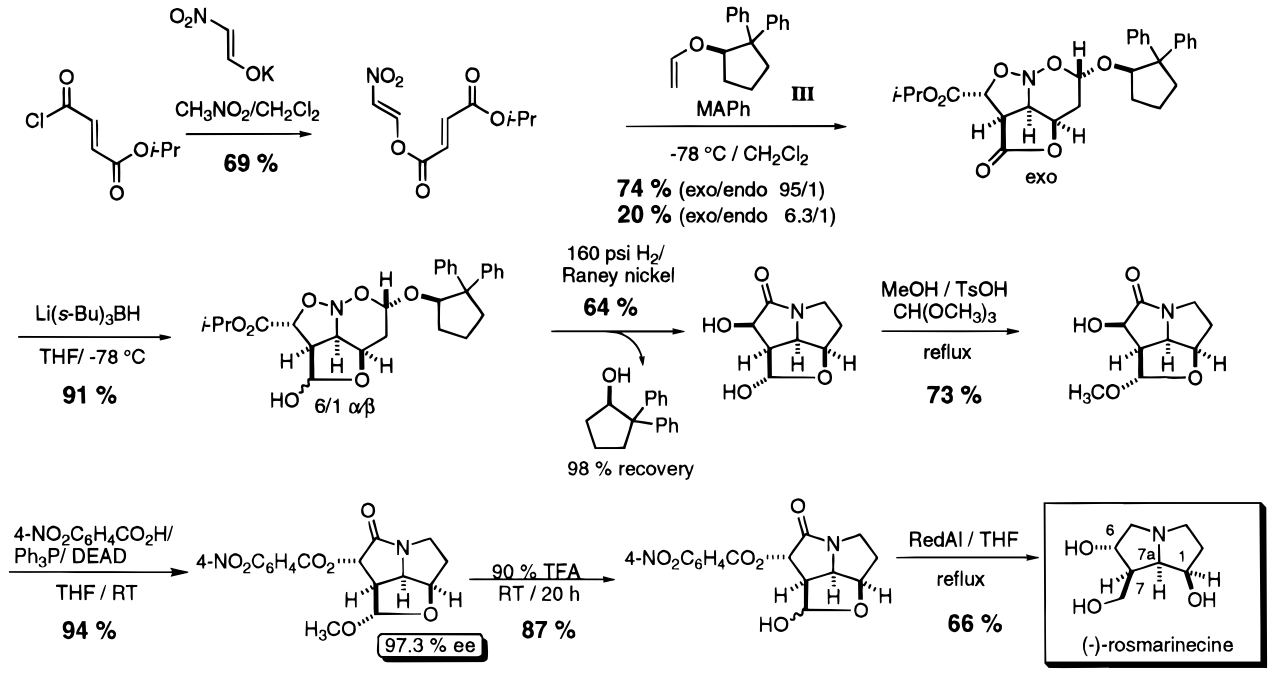
to the dextrorotatory enantiomers of **a** and **b** through the use of MAPh to promote the cycloaddition in 83% and 74% ee, respectively. The utility of such highly selective reactions for total synthesis of nitrogen-containing heterocycles is evident. Less evident is the origin of the asymmetric induction, and detailed analysis is beyond the scope of this review.

2.e. Synthesis of (−)-Rosmarinecine. The synthesis of the pyrrolizidine alkaloid (−)-rosmarinecine illustrates the power of the fused mode tandem cycloaddition method. One previous synthesis of rosmarinecine has been reported by Tatsuta[98] in 1983, which was accomplished in 17 steps from D-glucosamine.

The all-cis relationship at the three contiguous centers C(1), C(7), and C(7a) of (−)-rosmarinecine dictates that the [3+2] cycloaddition must be intramolecular. The configuration at C(2) is determined by the geometry of the dipolarophile, which in this scenario requires a *Z* configuration. This analysis simplifies the synthesis of (−)-rosmarinecine to two acyclic precursors: a β-maleoxynitroalkene and a chiral vinyl ether. This initial strategy was foiled by the difficulty in preparation of the maleate-derived nitroalkene and its inherent instability. The successful synthesis employed the fumarate half ester which necessitated the inelegance of a hydroxyl inversion.

The synthesis of (−)-rosmarinecine is detailed in Scheme 38.[58] The 2-(fumaryloxy)nitroethene is prepared by acylating the potassium salt of nitroacetaldehyde with isopropylfumaroyl chloride. Reaction of

Scheme 38



the nitroalkene with the chiral vinyl ether **III** in the presence of MAPh as the promoter affords the nitroso acetal in 94% yield and high diastereoselectivity (exo/endo 25/1). The tandem cycloaddition installs all the required stereocenters for (−)-rosmarinecine in a single pot reaction with the correct stereochemistry except at C(6).

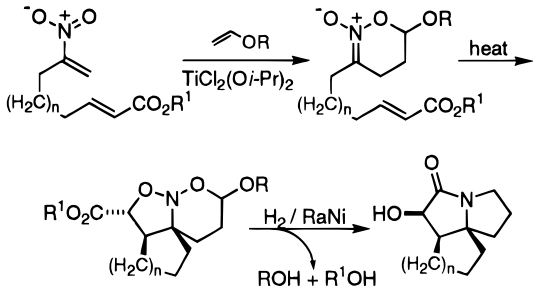
Direct hydrogenolysis of the lactone fails presumably due to competitive reduction and strain in the lactone ring. After an extensive survey of reducing agents and the size of the ester group, it was found that the lactone could be reduced very selectively with L-Selectride to afford the lactol in excellent yield (91%). The lactol could then be submitted to the standard hydrogenation conditions to afford the tricyclic α-hydroxy lactam−lactol in a very satisfying 64% yield together with excellent recovery of the auxiliary.

Since the lactam is derived from a fumarate dipolarophile, an inversion at C(6) is required for the correct configuration of (−)-rosmarinecine. After selective protection of the lactol as its methyl acetal, the inversion at C(6) is accomplished in excellent yield (94%) by a Mitsunobu reaction[99] with 4-nitrobenzoic acid as the nucleophile. The enantiomeric excess of the inverted ester is 97.3% by chiral HPLC. The synthesis is then completed by hydrolysis of the methyl acetal and exhaustive reduction of the resulting lactol with Red-Al. After extensive purification (−)-rosmarinecine was obtained as a analytically pure, white solid in 66% yield, thus completing the synthesis of (−)-rosmarinecine in eight steps and 14.8% overall yield.

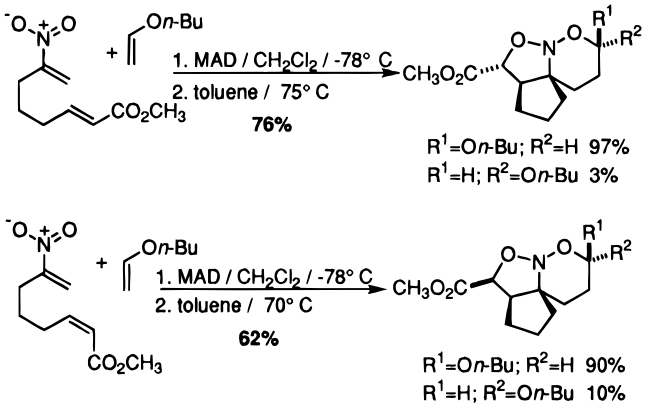
3. Spiro Mode Cycloadditions

In all of the examples of tandem [4+2]/[3+2] cycloadditions studied thus far the dipolarophile tether is attached at the β position of the nitroalkene (C(4) of the nitronate), which leads to fused tricyclic compounds. Should the tether extend from the α-position (C(3) of the nitronate), the [3+2] process creates spirocyclic systems.[56] This concept is illustrated by the family of α-tethered nitroalkenes bearing three and four methylene chains and ester-activated dipolarophiles as shown in Scheme 39. These new substrates offer interesting challenges in the prediction of stereochemical outcome (folding selectivity) and absolute stereocontrol. It should be recognized that the intermediate nitronate contains *only the anomeric center as the directing group for the second cycloaddition*. Thus, the previously observed selectivities in the tandem process were not expected in this case.

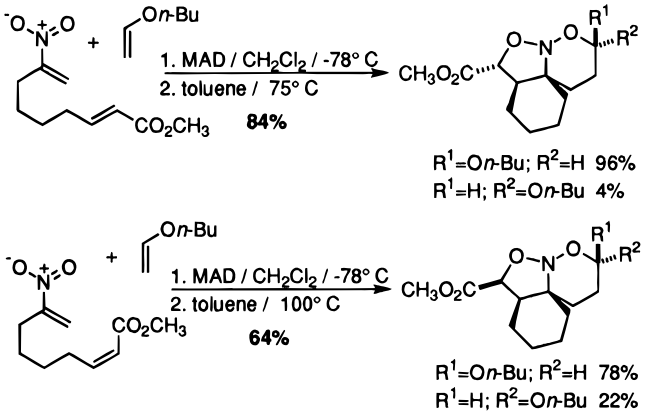
Scheme 39



Scheme 40



Scheme 41

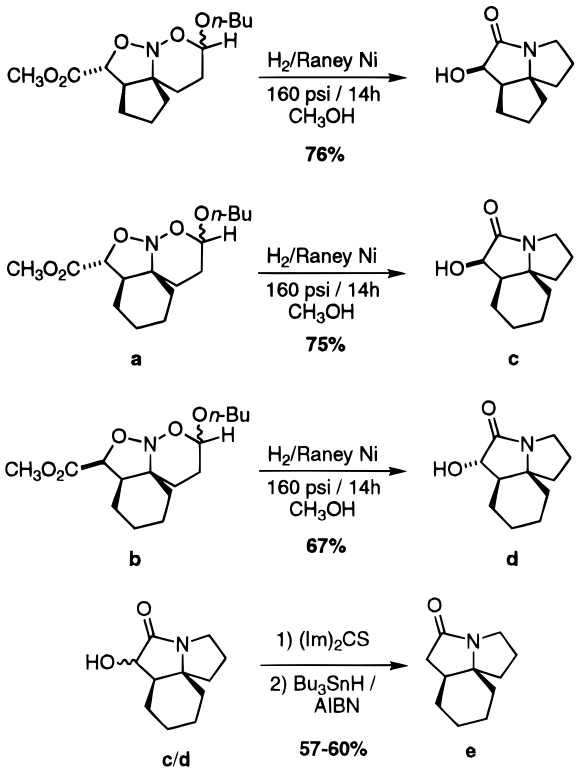


The cycloadditions of substrates bearing a three-methylene tether are shown in Scheme 40. Both substrates undergo smooth [4+2] cycloaddition with MAD as the Lewis acid of choice. The crude nitronates can be isolated and are warmed in toluene to effect complete [3+2] cycloaddition. The desired spiro tricyclic products are formed in good yield and with unexpectedly high diastereoselectivity. Apparently, the anomeric center exerts a strong influence on the folding of the side chain in the [3+2] process.

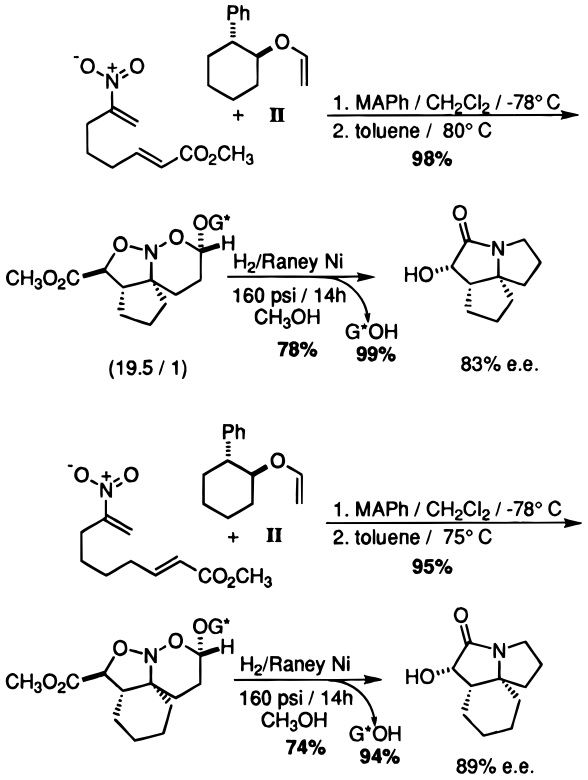
The cyclizations of the four-methylene tethered substrate follow analogously and afford the corresponding tricyclic products in good yield, albeit with diminished selectivity (Scheme 41). Interestingly, these substrates undergo [3+2] cycloaddition more slowly; higher temperatures and longer reaction times are needed to complete the closure. Both substrates bearing the *E*-dipolarophile react with higher diastereoselectivity. This is in accord with the unexpectedly high relative asymmetric induction observed due to the anomeric center. The anomeric relationship for all of these compounds was established by hydrogenolysis to single α-hydroxy lactams.

The reductive cleavage of the nitroso acetals at 160 psi in the presence of Raney nickel affords the tricyclic α-hydroxy lactams spontaneously (Scheme 42). That the hydroxy lactams **c** and **d** arising from cycloadducts **a** and **b** derived from *E*- and *Z*-enoates differ only at the hydroxyl-bearing center was proven by deoxygenation to a single tricyclic lactam **e**. The ability to carry out all of the transformations in this series along with the remarkable relative asymmetric induction due to the anomeric center made the auxiliary-based asymmetric synthesis feasible.

Scheme 42



Scheme 43



The potential for asymmetric induction in the spiro mode tandem cycloaddition with chiral vinyl ethers has been tested with **II** and aluminum-based Lewis acids. Substrates bearing both three and four methylene tethers with *E*-dipolarophiles were examined since they gave the highest selectivity with an achiral vinyl ether (Scheme 43). The yields of the tandem cycloadducts are excellent and the diastereoselectivities were found to be high. Hydrogenolytic cleavage of the nitroso acetals affords the known spirocyclic lactams in good yield with excellent recovery of the auxiliary alcohol. The enantiomeric excess of the products and their absolute configurations were established as above for the fused mode products. Given the remote nature of the stereodirecting group, the level of asymmetric induction (83−89% ee) is remarkable. Both products are formed with the same absolute configuration (1*S*), which is consistent with the sense of asymmetric induction observed with **II** in the fused mode series. The analysis of the origin of asymmetric induction in this case is more complex since only the configuration at the anomeric center is of significance, and this can only be inferred from the absolute configuration of the products.

From a detailed analysis of the conformation of the vinyl ether, the relative stereochemistry of the tricyclic products, and their absolute configuration, a transition state structure can be derived. To set the configuration of the anomeric center as 1*S* in the major product, the chiral vinyl ether **II** must react in an *s*-trans exo-oriented conformation. From here the side chain must fold in an exo fashion (in both cases) to the face of the nitronate in the half-space not containing the anomeric alkoxy substituent. This also nicely explains why the trans dipolarophiles react more selectively than the cis.

4. Bridged Mode Cycloadditions

The third member of the tandem intermolecular [4+2]/intramolecular [3+2] cycloaddition family differs fundamentally from the fused and spiro modes in that the dipolarophile is attached to the dienophile rather than the nitroalkene. Thus, the two 2π components of the two cycloadditions are part of the same molecule. This places stringent demands on the dienophile/dipolarophile to preordain which double bond will function in which role. Furthermore, the regiochemistry of the [4+2] cycloaddition is critical to set the [3+2] cycloaddition in either C(5) or C(6) bridging modes.[39] The products from the unmasking of the nitroso acetals are highly functionalized cyclohexanols or cyclopentanols (Scheme 44). This is a structural motif unlike any other previously accessed through the use of the tandem nitroalkene cycloaddition method.

4.a. α*-Tethered, Unactivated Dienophiles.* The bridged mode cycloaddition was first documented with 2-methyl-2-nitrostyrene and 3,3-dimethyl-1,4-pentadiene as the dienophile/dipolarophile. The *gem*-dimethyl substituent was chosen to eliminate potential isomerization under the strongly Lewis acidic conditions. Since the two double bonds are unactivated vinyl groups, harsher conditions are expected. Thus, the use of the powerful Lewis acid tin tetrachloride at elevated temperatures is necessary to induce [4+2] cycloaddition to afford the nitronate in 68% yield as a single diastereomer (Table 15). The nitronate is the result of an exo mode cycloaddition. Thermal promotion is required to affect the [3+2] cycloaddition of the nitronate to afford the strained tricyclic bridged nitroso acetal. The nitroso acetal is

Scheme 44

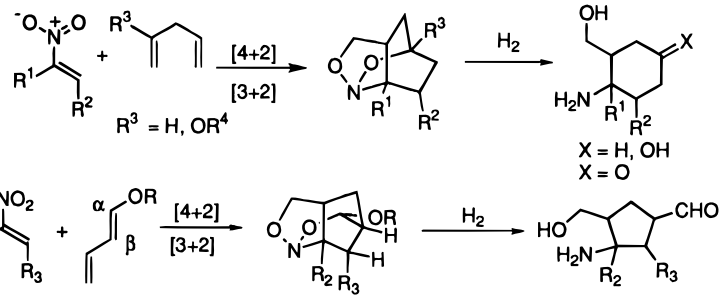
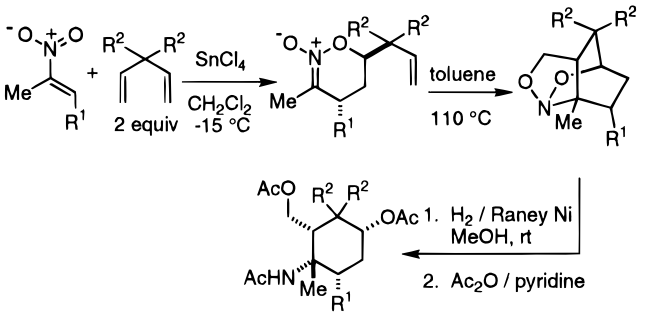


Table 15. Yields of Intermediates in Tandem [4+2]/[3+2] Cycloadditions

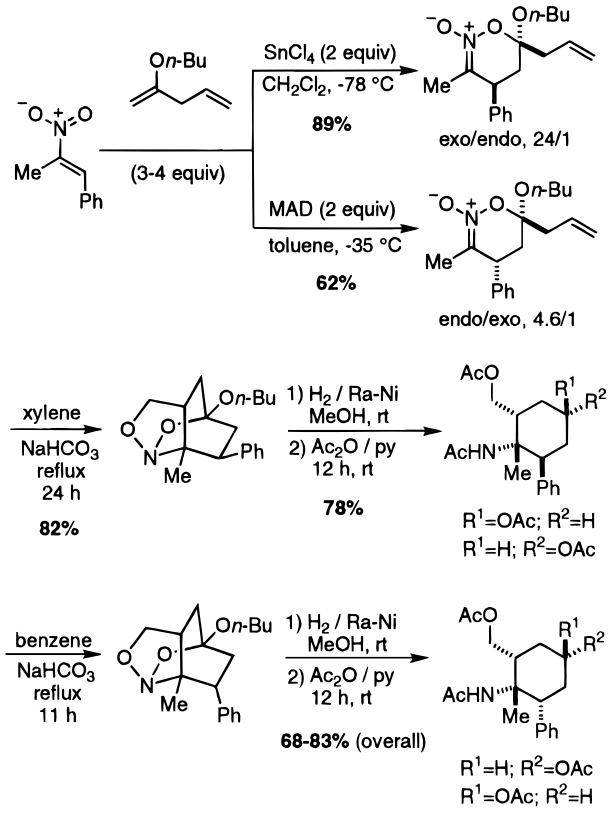


		nitronate			
nitroalkene R^1	diene R^2	yield, %	de, %	nitroso acetal yield, %	triacetate yield, %
Ph	Me	68	>100/1	79	59
Ph	H	91	>100/1	84	78
c-Hex	H	62	9/1	100	74
n-Pent	H	55	24/1	100	67

then unmasked under standard hydrogenolytic conditions to afford the aminocyclohexanemethanol, which is isolated in 59% yield as its triacetate. The reaction also proceeds smoothly with 1,4-pentadiene itself with a range of substituted nitroalkenes. The overall yields with the aliphatic nitroalkenes are similar through the sequence, but lower selectivity was observed in the [4+2] cycloaddition. The full stereostructure of the triacetate from 2-methyl-2-nitrostyrene and 1,4-pentadiene was determined by X-ray crystallographic analysis. This structure established the cis stereochemical relationship between the phenyl and the acetoxy groups, which further reveals that an exo mode [4+2] cycloaddition is operating.

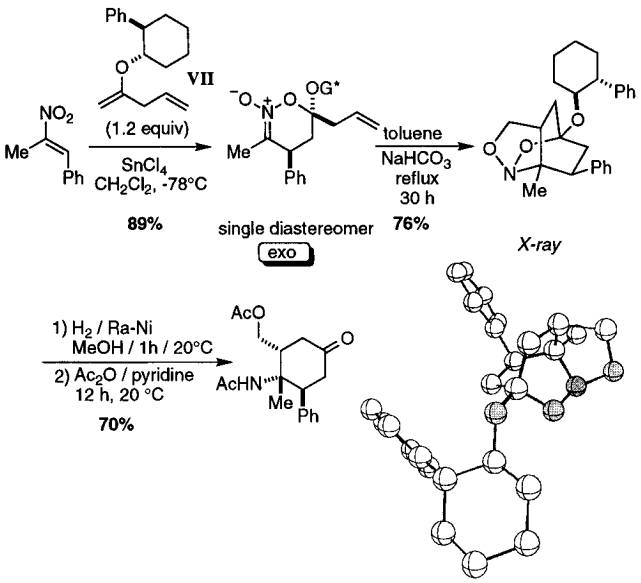
To control the absolute stereochemical course of this tandem process, a modification of the substrate structure is necessary since no obvious opportunity for stereocontrol is available. The employment of a chiral Lewis acid for absolute asymmetric induction has meet with very limited success in nitroalkene cycloaddition chemistry.[72,96,100] The use of chiral vinyl ethers as dienophiles, on the other hand, in both the spiro and the fused mode reactions has served admirably to control absolute stereochemistry. The incorporation of a chiral unit in this tandem mode must be at the 2-position of the 1,4-diene to ensure that the correct regiochemistry is obtained in the [4+2] process.

Scheme 45

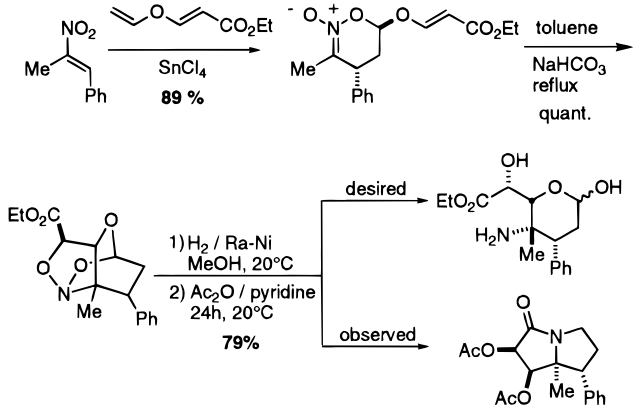


A test achiral substrate, 2-(butyloxy)-1,4-pentadiene, reacts smoothly under Lewis acid promotion in good yields (Scheme 45). The tin- and the aluminum-based Lewis acids show complimentary preference for orienting the enol ether in exo and endo mode cycloadditions, respectively. Both the endo and the exo diastereomers undergo [3+2] cycloaddition at elevated temperatures. The rate of cycloaddition for the two diastereomers is very different. This difference can easily be understood in terms of the relative ease of access to the reactive conformation required for the [3+2] cycloaddition in which the allyl group occupies an axial orientation. Hydrogenation of the nitroso acetals and acylation afford an epimeric mixture of triacetates arising through an unselective reduction of the intermediate ketone. The α-acetoxy epimer from the hydrogenation of the endo mode cycloadduct (MAD) was found to be identical to the product derived from 1,4-pentadiene, the stereostructure of which had previously been established by X-ray analysis.

Scheme 46



Scheme 47



The use of chiral 2-alkoxy-1,4-dienes has been demonstrated by the employment of (±)-**VII** (Scheme 46). Reaction of 2-methyl-2-nitrostyrene and (±)-**VII** in the presence of tin tetrachloride as the promoter results in a remarkably selective cycloaddition. The resulting nitronate is isolated in 89% yield as a single diastereomer. The intramolecular [3+2] cycloaddition is affected at elevated temperatures to afford the crystalline nitroso acetal, again as a single diastereomer. The full stereostructure of the tandem cycloadduct was determined by X-ray crystallographic analysis. The structure confirms that [4+2] cycloaddition proceeds through an exo mode wherein the chiral vinyl ether reacts in a *s*-cis conformation. The nitroso acetal can be unmasked by brief hydrogenolysis to allow isolation of the ketone. Acetylation afforded the target diacetate in 70% yield as a single diastereomer.

The bridged mode tandem cycloaddition can be expanded to incorporate divinyl ethers as shown in Scheme 47 to allow for the preparation of pyrans and ultimately amino sugars.[101] The tandem cycloaddition provided the tricyclic nitroso acetal in excellent yield as a single diastereomer. Unmasking of the nitroso acetal affords not the expected hydroxy pyran, but the pyrrolizidine in excellent yield. The construction and surprising stability of the oxatricyclic nitroso acetal clearly demonstrate the feasibility to distinguish the double bonds of a divinyl ether and to set the stage for the preparation of amino sugars. However, the hydrogenation needs further optimization to suppress the imine formation and allow for the isolation of the desired hydroxy pyran.

E. Tandem Intramolecular [4+2]/Intramolecular [3+2] Cycloadditions

The tandem intramolecular [4+2]/intramolecular [3+2] cycloaddition requires, by definition, that both the dipolarophile and the dienophile are tethered to the nitroalkene. There are five different permutations possible for the tethering through attachment at either the α or β carbon of the nitroalkene (Figure 10). Only one of these combinations has been explored so far. Nitroalkenes that have been employed are of the type where both the dienophile and the dipolarophile are tethered to the β carbon of the nitroalkene through a common substituent.[102]

The tandem cycloaddition precursor shown in Scheme 48 was prepared by a multistep sequence

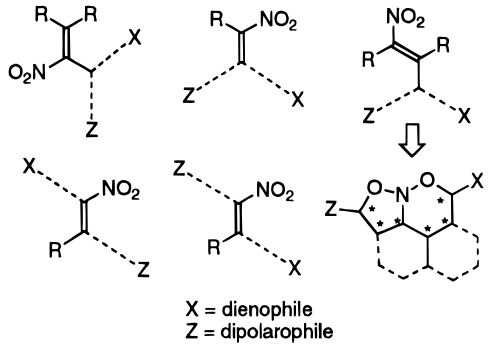
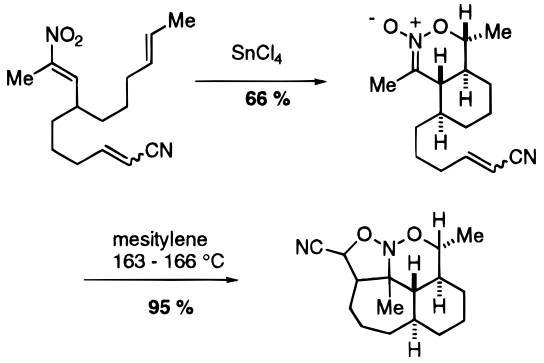
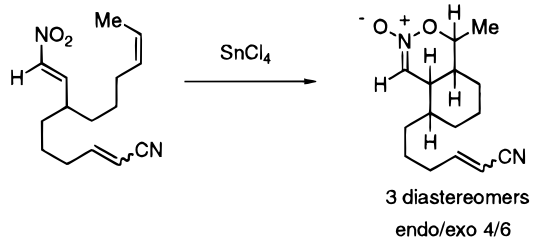


Figure 10. Possible combination of attachment of the dienophile/dipolarophile.

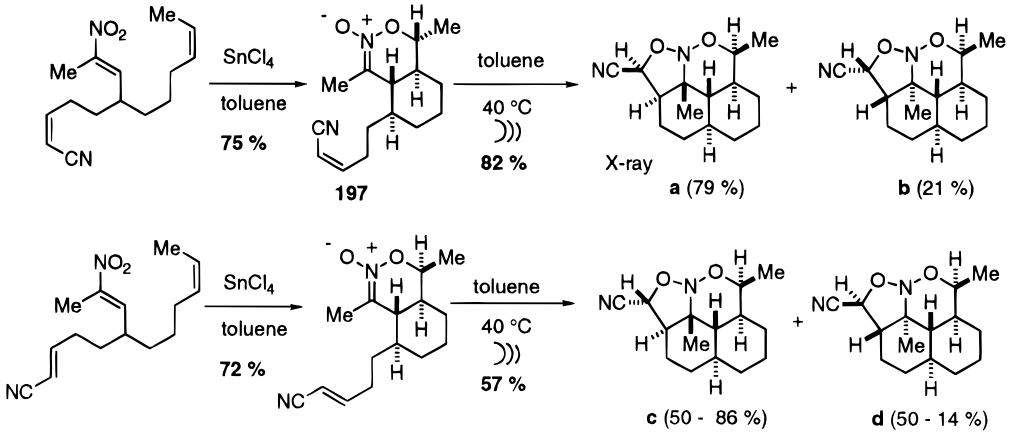
Scheme 48



Scheme 49



Scheme 50



which involved the alkylation of a lithio-2-methylthiazoline as an acetaldehyde anion equivalent. The roles of the dienophile and dipolarophile are clearly distinguished. Reaction in the presence of tin tetrachloride gives the nitronate in 66% yield. The nitronate requires heating in mesitylene (163−166 °C) to efficiently effect the [3+2] cycloaddition. The resulting nitroso acetal can be isolated in 95% yield, but the reaction shows poor stereoselectivity since four major and four minor diastereomeric nitroso acetals are detected by ^{1}H NMR analysis.

The analogous disubstituted nitroalkene was tested with the expectation that the methyl group was responsible for the poor selectivity in the [3+2] cycloaddition. Unfortunately, reaction of this nitroalkene with tin tetrachloride gives a mixture of three nitronates with little preference for either endo or exo approach in the [4+2] cycloaddition reaction (Scheme 49).

Therefore, to maintain the high selectivity in both the [4+2] and the [3+2] components, α-substituted nitroalkenes bearing shorter tethered dipolarophiles were considered. Reaction of the two nitroalkenes in Scheme 50 in the presence of tin tetrachloride afford, stereoselectively, the corresponding nitronates in good yields. The [3+2] cycloadditions could be effected at 40 °C in toluene under sonication to give a mixture of diastereomers. The nitronate bearing a *Z*-dipolarophile gives rise to two diastereomers in a 4/1 ratio. The structure of the major nitroso acetal **a** was determined by X-ray analysis, while the stereochemistry of the minor diastereomer **b** was determined by an NOE experiment. The nitronate bearing an *E*-configured dipolarophile gives nitroso acetals **c** and **d** in rather low selectivity (1/1 to 6/1).

The double intramolecular cycloaddition is feasible though serious limitations are encountered in the lengthy syntheses of the precursors and in the dependence of overall selectivity on the tether length and configuration of the dipolarophile.

V. Conclusion

Taken together these studies illustrate the power and potential of the tandem [4+2]/[3+2] cycloaddition process for the rapid and selective construction of highly functionalized polycyclic systems. Many other variations on this theme are currently being pursued, as are selected targets in a number of natural product families.

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