Tandem Inter [4 + 2]/Intra [3 + 2] Cycloadditions of Nitroalkenes. 15. The Bridged Mode (α-Tether)

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A new variant of the tandem inter [4 + 2]/intra [3 + 2] cycloaddition of nitroalkenes is described in detail. The scope and limitations of the bridged mode tandem cycloaddition in which the diene and dienophile are part of the same molecule are documented. Simple 1,4-pentadienes as well as 2-alkoxy-1,4-pentadienes can function effectively as dienophile and dipolarophile combinations with excellent chemical selectivity and regio- and diastereoselectivities. Hydrogenation of the bridged nitroso acetals produces aminocyclohexanemethanol derivatives in high diastereo- and enantioselectivities. Further, insights into the mechanistic aspects of the Raney nickel promoted hydrogenation are reported. An intriguing influence of the nitro olefin α-substituent on the diastereoselectivity in the [4 + 2] cycloaddition has been documented. The reactivity of the α-chloro-substituted nitroalkene **26** as the heterodiene in the Diels−Alder reaction is assayed, and the use of the chlorine atom as a hydrogen surrogate is described.

Introduction

The hetero Diels−Alder reaction represents one of the most important tools for the stereoselective construction of highly functionalized heterocyclic systems.[1] Furthermore, the heteroatomic [4 + 2] cycloaddition allows for the simultaneous formation of carbon−carbon and carbon−heteroatom bonds, as well as the creation of stereogenic centers in a predictable fashion. In recent years, we have extensively investigated the asymmetric tandem inter [4 + 2]/intra [3 + 2] cycloaddition sequence using chiral vinyl ethers as the dienophiles and nitroalkenes with pendant dipolarophiles as the heterodienes.[2] The Lewis acid promoted [4 + 2] cycloadditions result in the highly stereoselective formation of nitronates which can either be cleaved by hydrogenolysis to afford substituted pyrrolidines[3] or, owing to their dipolar nature, undergo [3 + 2] cycloadditions to afford the corresponding nitroso acetals.[2] Depending on the point of attachment of the dipolarophile to the nitroalkene, two subclasses of inter [4 + 2]/intra [3 + 2] cycloadditions have been documented: the fused mode (β tether) and the spiro mode (α tether) constructions, Scheme 1. Each mode is responsible for the formation of a particular class of polycyclic nitroso acetals which can be unmasked by a simple hydrogenation reaction to reveal interesting tricyclic structures.[2] In both cases, the use of chiral dienophiles derived from optically active alcohols G*OH led to the production of enantiomerically enriched α-hydroxy lactams.

A recent report from our laboratories disclosed a new construction named the bridged mode, which arises from the attachment of the dipolarophile to the α position of the *dienophile*, Scheme 2.[4] Thus, a Lewis acid promoted cycloaddition affords nitronates bearing a tethered olefin at the C(6) position. Subsequent intramolecular [3 + 2] cycloaddition leads to bridged tricyclic nitroso acetals which can be converted by hydrogenolysis into highly substituted aminocyclohexanes. Since these compounds occur as subunits in clinically useful therapeutic agents,[5] a general route to their preparation would be desirable. Our initial studies sought to demonstrate the feasibility of the overall construction ([4 + 2]/[3 + 2]/cleavage) with the use of simple 1,4-pentadienes. Furthermore, the use of 2-alkoxy-1,4-pentadienes as the 2π component in the tandem sequence was of considerable interest since ultimately optically active 2-alkoxy-1,4-pentadienes could be employed to access the aminocyclohexane derivatives in enantiomerically enriched form. The following report provides a detailed account of our studies directed toward defining the scope and limitation of the bridged (α-tether) construction.

Results

Preparation of 2-Alkoxy-1,4-pentadienes 1 and 4a−c. The substrates for our initial survey, 1,4-penta-

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(5) (a) Rinehart, K. L.; Shield, L. S., Eds.; *Aminocyclitol Antibiotics*; ACS Symposium Series 125; ACS: American Chemical Society: Washington, DC, 1980. (b) Suami, T.; Ogawa S. *Advances in Carbohydrate Chemistry and Biochemistry* **1990**, *48*, 21. (c) Hudlicky, T.; Olivo, H. F.; McKibben, B. *J. Am. Chem. Soc.* **1994**, *116*, 5108.

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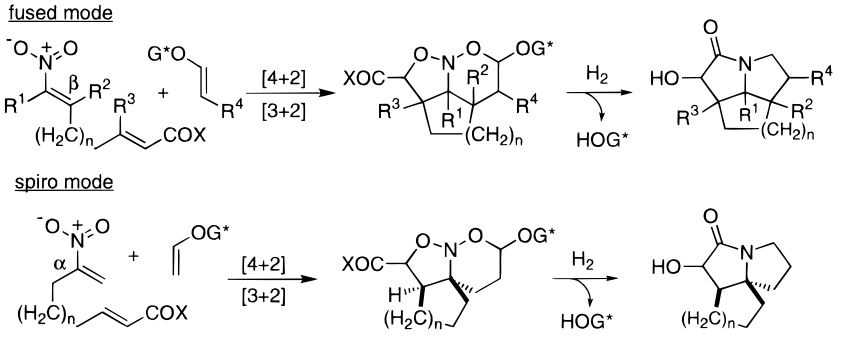
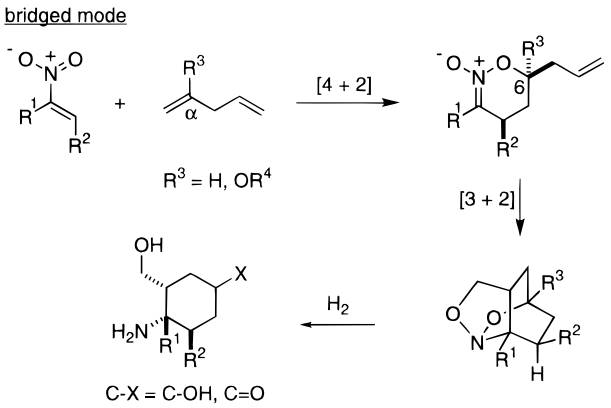
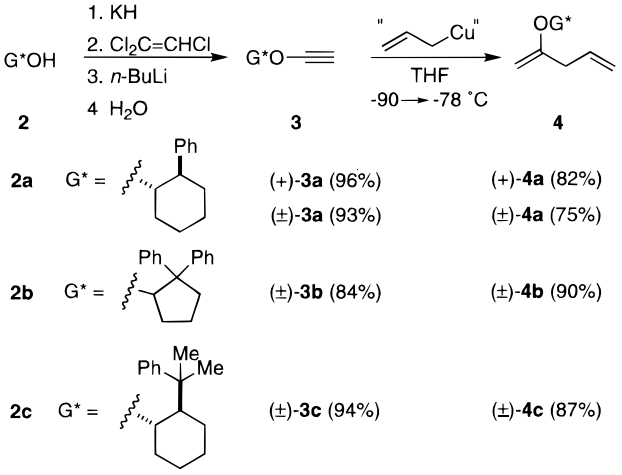
Scheme 1



Scheme 2

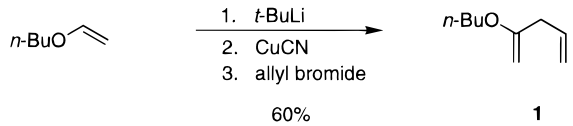


Scheme 4



diene and 3,3-dimethyl-1,4-pentadiene, were readily available either commercially or by literature procedures.[6] In addition, the functionalized substrate 2-butoxy-1,4-pentadiene (**1**) could be prepared in one step by modification of a known procedure.[7] Treatment of *n*-butyl vinyl ether with *tert*-butyllithium (*t*-BuLi) followed by copper cyanide and subsequent reaction of the corresponding cyanocuprate with allyl bromide afforded the desired product in 60% yield after fractional distillation, Scheme 3.

Scheme 3



Unfortunately, this procedure could not be applied to the synthesis of chiral 2-alkoxy-1,4-pentadienes because of the inability of *t*-BuLi to metallate vinyl ethers of secondary alcohols. An alternative strategy for the preparation of these compounds involves the allylboration of the corresponding alkoxyacetylenes.[8] However, the difficult accessibility of allylboranes and the limitation associated with the use of unfunctionalized allyl chains prompted us to explore a different synthetic route, based on the use of a more versatile and functional-group-tolerant organometallic reagent. Thus, vinyl ethers **4a**−**c** were prepared by allylcupration of alkoxyacetylenes **3a**−**c.** The alkynyl ethers **3a**−**c** were synthesized from the corresponding chiral alcohols **2a**−**c** according to a modified literature procedure, Scheme 4.[9] It should be noted that enol ethers **4a**−**c** are moisture sensitive and are prone to undergo isomerization to the corresponding 1,3-pentadiene. Finally, despite the extensive use of allylcopper reagents in the 1,4-conjugated addition to α,β-unsaturated ketones[10] and despite the known regio- and stereoselective reactions of ethoxyacetylene with alkyl-, 1-alkenyl-, and arylcopper(I) compounds,[11] no example of allylcupration of alkoxyacetylenes has been previously reported.

Cycloadditions with 1,4-Pentadienes. In orienting experiments, (*E*)-(2-nitro-1-propenyl)benzene (**5a**)[12] was selected as the test nitroalkene and 3,3-dimethyl-1,4-pentadiene[6] as the dienophile. The choice of dienophile was guided by the initial concern that the Lewis acid could promote isomerization to a conjugated 1,3-pentadiene. In no previous study on tandem cycloaddditions has a simple vinyl group been successfully employed as a dienophile, although examples of substituted olefinic dienophiles[2a,13] and unactivated vinyl dipolarophiles are on record.[14] A brief survey of Lewis acids[15] indicated that $SnCl_4$ was the promoter of choice for the [4 + 2] cycloaddition. According to the preferred protocol, the cycloaddition was carried out in CH_2Cl_2 at −15 °C for

(6) Eilbracht, P.; Acker, M.; Totzauer, W. *Chem. Ber.* **1983**, *116*, 238.
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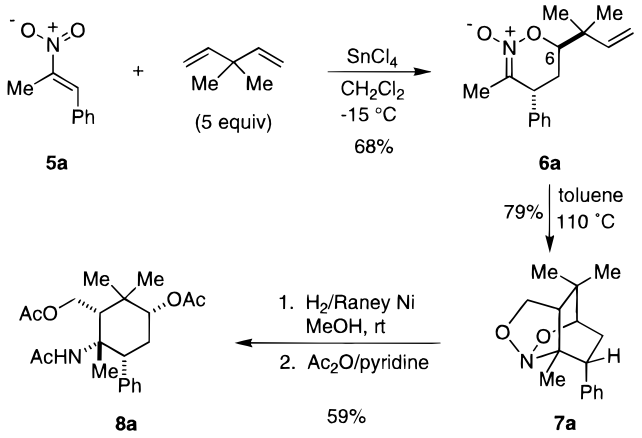
(12) Denmark, S. E.; Kesler, B. S.; Moon, Y.-C. *J. Org. Chem.* **1992**, *57*, 4912.
(13) (a) Denmark, S. E.; Cramer, C. J.; Sternberg, J. A. *Helv. Chim. Acta.* **1986**, *69*, 1971. (b) Denmark, S. E.; Moon, Y.-C.; Cramer, C. J.; Dappen, M. S.; Senanayake, C. B. W. *Tetrahedron* **1990**, *46*, 7373.
(14) Denmark, S. E.; Senanayake, C. B. W. *Tetrahedron* **1996**, *35*, 11579.
(15) Other Lewis acids examined were $BF_3{\cdot}OEt_2$, $TiCl_4$, and $AlCl_3$.

Scheme 5



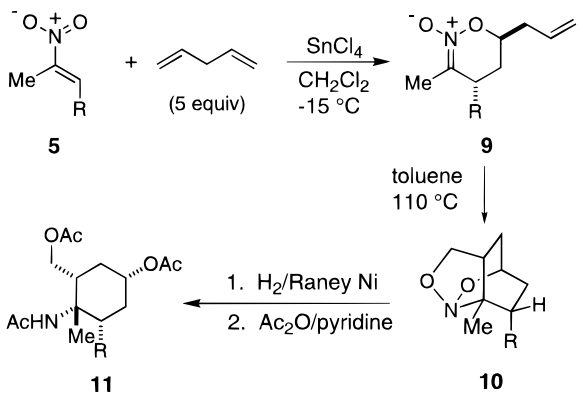
36−48 h, using a ratio of 1.0/2.0/1.7 for **5a**/pentadiene/$SnCl_4$, Scheme 5. The stable, crystalline nitronate **6a** was obtained in 68% yield as a single stereoisomer. The regiochemical course of the [4 + 2] cycloaddition was revealed by the appearance of a low-field methine hydrogen at 4.08 ppm (dd, J = 11.8, 1.6 Hz) corresponding to HC(6). The trans stereochemistry depicted for the nitronate (arising form an exo-mode cycloaddition) was subsequently assigned by X-ray analysis of the final product.

The isolation and stability of nitronate **6a** supports the notion that the intramolecular [3 + 2] cycloaddition in the bridged mode series is not a facile process. This is not unexpected as the dipolarophile is unactivated[14] and the nitronate must adopt a conformation with an axial C(6) substituent for the cycloaddition to take place. Thus, heating nitronate **6a** in toluene at 110 °C induced a [3 + 2] cycloaddition to afford nitroso acetal **7a** in 79% yield. The bridged tricyclic structure of **7a** (an unprecedented ring system) was easily confirmed by 2D NMR spectroscopy. This rather strained nitroso acetal was unstable to silica gel chromatography but could be purified by crystallization. Hydrogenolysis of the nitroso acetal in the presence of Raney nickel, followed by acetylation, afforded the highly functionalized cyclohexanemethanol triacetate **8a** as a single stereoisomer in 59% yield.

The reactivity of the simplest dienophile/dipolarophile was next examined. 1,4-Pentadiene was not plagued by the expected isomerization to 1,3-pentadiene and was found to be a superior partner in the Diels−Alder reaction, Table 1, entry 1. The $SnCl_4$-promoted cycloaddition of **5a** with 1,4-pentadiene afforded nitronate **9a** as a single diastereomer in 91% yield. The intramolecular [3 + 2] cycloaddition of **9a** and subsequent hydrogenolysis/acetylation produced the triacetate **11a** in 66% yield. The stereostructure of triacetate **11a** was established by X-ray analysis which in turn provided confirmation of the basic structures of **9a** and **10a**, Figure 1. Moreover, the determination of the structure of **11a** demonstrated that this compound arose from a preferred exo-mode cycloaddition, as expected on the basis of the results of a previous investigation.[13] The exo selectivity in the analogous reaction of nitroalkene **5a** and 3,3-dimethyl-1,4-pentadiene was established by ^{1}H NMR correlation between nitronates **6a** and **9a**, Figure 2.

To evaluate the scope of the tandem process, secondary and primary β-alkyl substituted nitroalkenes were employed as the heterodienes in the [4 + 2] cycloaddition. Gratifyingly, the tandem [4 + 2]/[3 + 2] sequence proved to be general. The $SnCl_4$-promoted cycloadditions of nitroalkenes **5b**[12] and **5c**[12] with 1,4-pentadiene provided nitronates **9b** and **9c** in 62% and 55% yield and nitroso acetals **10b** and **10c** in quantitative yield, respectively, Table 1, entries 2−3. Furthermore, the hydrogenolyses

Table 1. Yields of Products in Tandem [4 + 2]/[3 + 2] Cycloadditions[a]



entry	**5** (R)	**9** (yield, %)	**10** (yield, %)	**11** (yield, %)
1	**5a** (Ph)	**9a** (91)[b]	**10a** (84)	**11a** (78)
2	**5b** (c-Hex)	**9b** (62)[b]	**10b** (100)	**11b** (74)
3	**5c** (*n*-Pent)	**9c** (55)[b]	**10c** (100)	**11c** (67)

[a] Yields of analytically pure material. [b] Chromatographically homogenous, nondistillable oil.

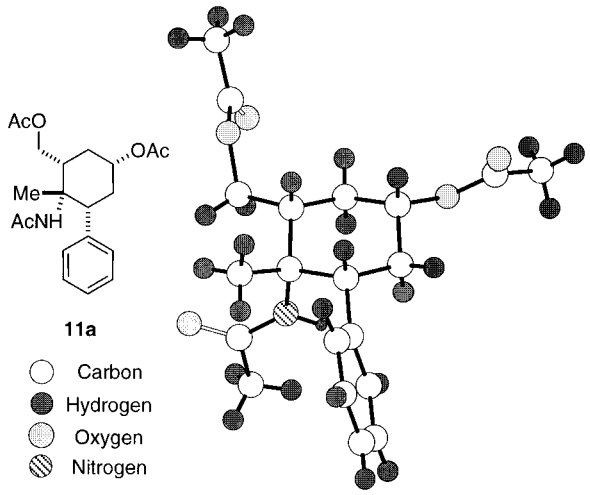
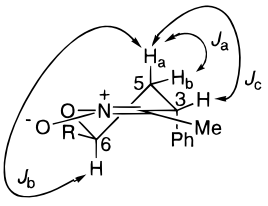
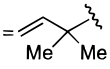


Figure 1. Chem 3D representation of the X-ray structure of **11a**.



6a R =  HC(6): 4.08 (dd, J = 11.8, 1.6 Hz)

$H_aC(5)$: 2.11 (ddd, J_a = 13.7, J_b = 11.7, J_c = 7.1)

9a R =  HC(6): 4.15-4.10 (m)

$H_aC(5)$: 2.18 (ddd, J_a = 13.8, J_b = 10.9, J_c = 7.1)

Figure 2. ^{1}H NMR correlation between nitronates **6a** and **9a**.

Scheme 6

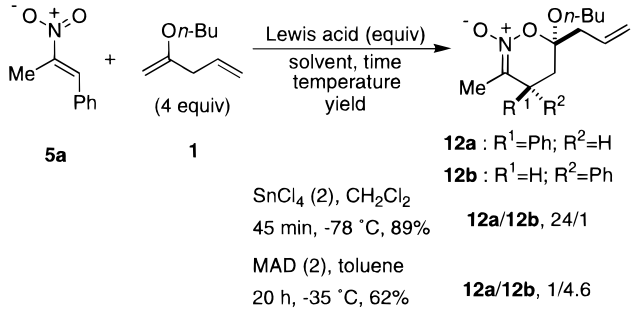
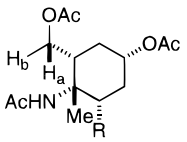


Table 2. Selected ^{1}H NMR Data for Triacetates 11a−c



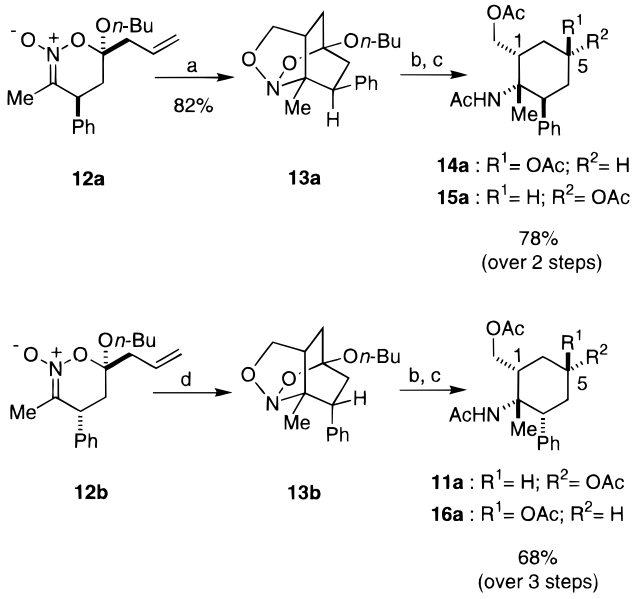
11

11	R	H_a ppm (J, Hz)	H_b ppm (J, Hz)
11a	Ph	4.57 (dd, 11.5, 3.9)	3.95 (ddd, 11.5, 8.6)
11b	*c*-Hex	4.51 (dd, 11.6, 3.8)	3.87 (ddd, 11.5, 8.3)
11c	*n*-Pent	4.53 (dd, 11.5, 3.9)	3.91 (ddd, 11.5, 8.5)

of these nitroso acetals proceeded as expected to afford good yields of the functionalized aminocyclohexanemethanols as their triacetates, **11b** and **11c** (Table 2).

Cycloadditions of Nitroalkene 5a with 2-Butoxy-1,4-pentadiene (1). The development of an asymmetric variant of the highly stereoselective tandem sequence required the introduction of a stereocontrolling element in one of the three participants (heterodiene, dienophile, and Lewis acid) in the [4 + 2] cycloaddition. Taking into account the successful use of chiral vinyl ethers as the carriers of the chiral modifier group in both fused and spiro mode cycloadditions,[2b,c,d,f,g] a chiral dienophile in the form of a 2-alkoxy-1,4-pentadiene appeared to be the best candidate. The 2-alkoxy group would serve to enhance the reactivity of the dienophile (due to the inverse electron demand nature of the cycloaddition) and also would assure the proper regiocontrol in the [4 + 2] process to place the dipolarophile at C(6) of the nitronate. Thus, 2-butoxy-1,4-pentadiene (**1**) was first tested as the dienophile/dipolarophile in the tandem cycloaddition process. The $SnCl_4$-promoted cycloaddition of nitroalkene **5a** and enol ether **1** proceeded in a highly selective manner, producing nitronate **12a** as the major diastereomer in 89% yield, Scheme 6. The assignment of stereostructure could not be assured until completion of the synthetic sequence as described below. In agreement with previous observations,[2f] the Lewis acid played a crucial role in determining the diastereoselectivity in the reaction. Nitronate **12b** now became the major component of the diastereomeric mixture when methylaluminum bis(2,6-di-*tert*-4-methylphenoxide) (MAD)[16] was used as the Lewis acid promoter, Scheme 6. However, it was found that careful control of reaction parameters was essential for reproducibility. A solution of MAD in toluene was added over a 10 h period to a solution of nitroalkene **5a** and vinyl ether **1** in toluene at −35 °C. After the mixture was stirred for an additional 10 h period, the reaction provided nitronates **12b** and **12a** as a 4.6/1 (**12b**/**12a**) mixture in 62% yield, Scheme 6. The minor diastereomer **12a** was found to be identical by ^{1}H NMR spectroscopy to the major nitronate obtained from the analogous cycloaddition promoted by $SnCl_4$. Interestingly, partial isomerization of **1** to the corresponding 4-butoxy-1,3-pentadiene occurred when the cycloaddition was carried out at temperatures higher than −30 °C. The MAD-induced isomerization of pentadiene **1** was established by the ^{1}H NMR detection of a nitronate deriving from the cycloaddition of nitro olefin **5a** and the isomerized pentadiene.

Scheme 7

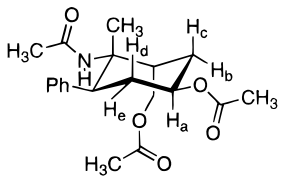


a. xylene, $NaHCO_3$, reflux, 24 h. b. H_2 (1 atm), Ra-Ni, MeOH, rt. c. pyridine, Ac_2O, 12 h, rt. d. benzene, $NaHCO_3$, reflux, 11 h.

Both nitronates **12a** and **12b** underwent thermal [3 + 2] cycloaddition, though optimization of addition rate, time, and temperature was necessary, Scheme 7. The rates of cycloaddition for the two diastereomers were quite different; **12b** was consumed within 11 h in refluxing benzene, while **12a** required 24 h in refluxing xylene. The resulting nitroso acetals **13a** and **13b** are extremely acid sensitive, and it was critical to have solid $NaHCO_3$ present in the reaction vessel as well as for any manipulation of the isolated nitroso acetals. Other bases ($CaCO_3$, $CsHCO_3$, Cs_2CO_3, 2,6-lutidine) were found to be less satisfactory in the [3 + 2] cycloaddition. Nitroso acetal **13a** was obtained in 82% yield after chromatography on basic alumina. However, its congener **13b** was not isolated and was carried on directly in the next step. Thus, the crude nitroso acetal **13b** was immediately hydrogenated in the presence of Raney nickel to afford, after acetylation, a diastereomeric mixture of triacetates **11a**/**16a** (**11a**/**16a**, 1/1.8) in 68% overall yield (from **13a**), Scheme 7. Similarly, the hydrogenation/acetylation sequence performed on nitroso acetal **13a** produced the triacetates **14a**/**15a** (**14a**/**15a**, 1/1.6) in 78% overall yield. The triacetates in each diastereomeric pair (**11a**/**16a** and **14a**/**15a**) were found to be epimeric at the C(5) position, as a result of the unselective reduction of the ketone (vide infra).

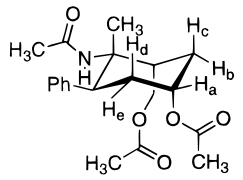
While the unselective (and unwanted) reduction of the ketone function provided a temporary inconvenience it did allow for an unambiguous assignment of the stereostructures of **14a**/**15a** and **11a**/**16a**. The minor (less

(16) Maruoka, K.; Itoh, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1985**, *107*, 4573.



14a

H_a : δ = 5.02 ppm, tt
$J_{ac} = J_{ad}$ = 12.0 Hz
$J_{ab} = J_{ae}$ = 5.0Hz



15a

H_a : δ = 5.16 ppm, quint
$J_{ab} = J_{ae} = J_{ac} = J_{ad}$ = 3.3 Hz

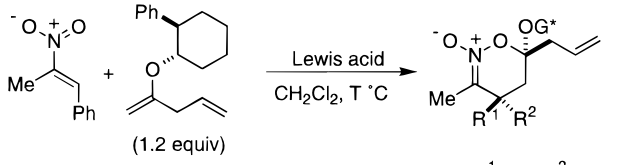
Figure 3. Coupling patterns of H_a with H_{b-e} in **14a** and **15a**.

polar) triacetate formed by hydrogenation of **13b** was found to be identical in all respects to **11a**, the product triacetate from the cycloaddition of 1,4-pentadiene. Since the stereostructure of **11a** was established by X-ray analysis, the structures of nitronate **12b** and nitroso acetal **13b** can be easily deduced. Thus, the cis relationship of acetoxymethyl and phenyl substituents must arise from a trans relationship of allyl and phenyl substituents in **12b**. This series therefore arises from an endo (butoxy) [4 + 2] cycloaddition. Furthermore, **12a** must arise from an exo (butoxy) cycloaddition which confirms the full structure of **13a**. It therefore remained to establish the configuration of the acetoxy group in **14a**/**15a** which was deduced by analyzing the coupling patterns of the triacetates, Figure 3. The axial hydrogen H_a in triacetate **14a** appears in the ^{1}H NMR spectrum as a triplet of triplets by virtue of its coupling with the four vicinal hydrogens (H_{b-e}), of which two are axial ($J_{ac} = J_{ad} = 12.0$ Hz) and two are equatorial ($J_{ab} = J_{ae} = 5.0$ Hz). Alternatively, the coupling constants of the corresponding equatorial hydrogen (H_a) in triacetate **15a** with the adjacent hydrogens H_{b-e} are virtually identical ($J = 3.3$ Hz); thus the multiplicity of the H_a ^{1}H NMR signal is a quintet, Figure 3.

Cycloaddition of Nitroalkene 7a and Alkoxypentadiene (±)-4a. The ability to control the absolute stereochemical course of the bridged mode tandem cycloadditions could be achieved through the use of a chiral nonracemic 2-alkoxy-1,4-pentadiene. Previous reports from our laboratories have illustrated the successful use of chiral vinyl or propenyl ethers as the 2π components in [4 + 2] cycloadditions, although no α-substituted enol ether had yet been examined.[2f,3c] From previous experience, *trans*-2-phenylcyclohexanol (**3a**) represented the logical first choice due to availability and ease of preparation.[17] The enantiofacial discrimination of the selected dienophile/dipolarophile (±)-**4a** was tested in the $SnCl_4$-promoted cycloaddition with nitroalkene **5a**, Table 3, entry 1. The reaction resulted in the completely stereoselective formation of a single cycloadduct (**17a**) which was isolated in 89% yield. It is noteworthy that as little as 1.2 equiv of (±)-**4a** could be used for the complete consumption of **5a**. On the basis of the stereochemical outcome of the analogous reaction of vinyl ether **1**, nitronate **17a** is expected to be the product of an exo (butoxy) [4 + 2] pathway. In agreement with the results reported in the previous section, the use of MAD as the Lewis acid promoter afforded a different nitronate (which is assumed to arise from an endo mode cycloaddition in analogy to the MAD-promoted cycloaddition of **5a** and

(17) Schwartz, A.; Madan, P.; Whitesell, J. K.; Lawrence, R. M. *Org. Synth.* **1990**, *69*, 1.

Table 3. Influence of the Lewis Acid on Cycloadditions with (±)-4a



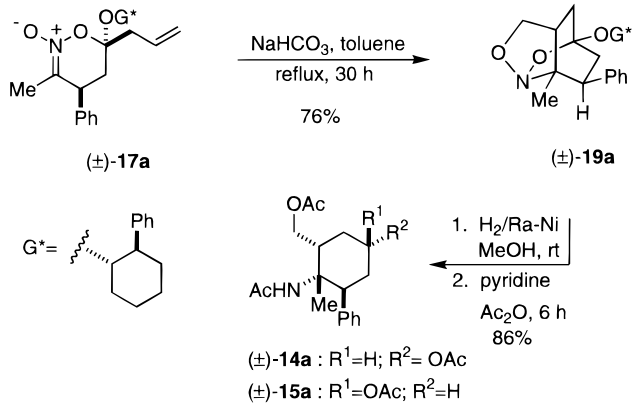
5a (±)-**4a**

17a : R^1=Ph; R^2=H
18a : R^1=H; R^2=Ph

entry	Lewis acid (equiv)	*T* (°C)	**17a**/**18a**	yield (%)[a]
1	$SnCl_4$ (2)	−74	1/0	89
2	MAD (1.3)[b]	−67	1/40.7/3.8[c]	55(48)[d]
3	$Ti(O\text{-}i\text{-}Pr)_2Cl_2$ (2.4)	−74	8.8/0/1[c]	52[e]

[a] Isolated as a mixture of diastereomers. [b] Reaction carried out in toluene. [c] Unassigned diastereomer. [d] Yield of the analytically pure major diastereomer. [e] 79% Conversion of **5a** as determined by ^{1}H NMR analysis of crude reaction mixture.

Scheme 8



(±)-**17a** (±)-**19a**

(±)-**14a** : R^1=H; R^2= OAc
(±)-**15a** : R^1=OAc; R^2=H

1) as the major component of a diastereomeric mixture, Table 3, entry 2. The modest yield of the nitronate is the consequence of the chemical incompatibility between **4a** and MAD. When $Ti(O\text{-}i\text{-}Pr)_2Cl_2$ was employed, the cycloaddition was moderately exo selective (the major component of the diastereomeric mixture of nitronates showed ^{1}H NMR identical to that of **17a**, obtained from the $SnCl_4$-promoted cycloaddition). The complete conversion of the nitroalkene **5a** was not achieved since the ^{1}H NMR spectrum of the crude reaction mixture revealed the presence of unreacted **5a** (21%), Table 3, entry 3.

The [3 + 2] dipolar cycloaddition of the nitronate (±)-**17a** was performed under the optimized conditions employed for the analogous reaction of nitronate **12a**. After slow addition (12 h) of a solution of nitronate **17a** in xylene to a suspension of sodium bicarbonate in refluxing xylene, additional (12 h) heating of the reaction mixture, and purification by column chromatography, nitroso acetal **19a** was isolated in 47% yield, Scheme 8. Reasoning that the prolonged heating could be responsible for a thermal decomposition of the starting nitronate and/or of the product, several experiments were performed to improve the yield in the preparation of the nitroso acetal. The highest yield (80%) of **19a** was achieved when a solution of the nitronate in toluene was heated at reflux for 30 h in the presence of 7 equiv of $NaHCO_3$. Other combinations of base (K_2CO_3, $NaHCO_3$) and equivalents of base (0.1 to 10) provided the nitroso acetal **19a** in comparable yields at similar reaction times in refluxing toluene.

A descriptive preparation of nitroso acetal (±)-**19a** was

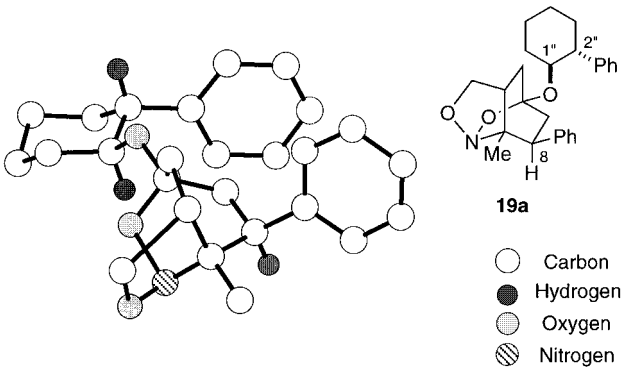


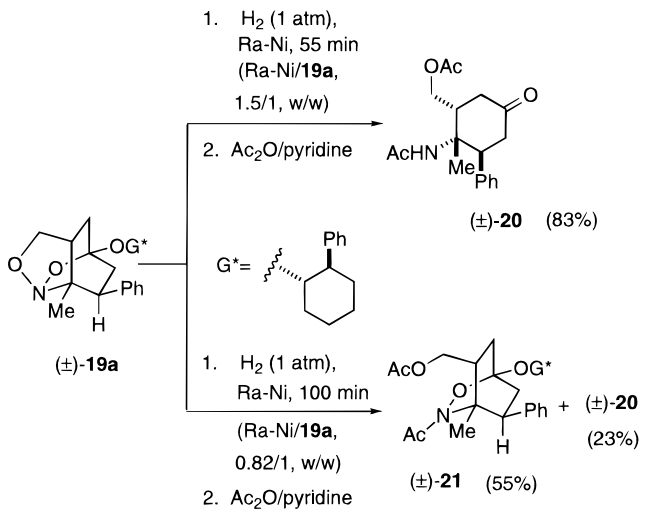
Figure 4. Chem 3D representation of the X-ray crystal structure of (±)-**19a**. All hydrogens (except hydrogens on C(8), C(1″), C(2″)) are removed for clarity.

carried out under the optimized experimental conditions, and the desired compound was obtained in analytically pure form in 76% yield, Scheme 8. The full stereostructure of (±)-**19a,** obtained by X-ray crystallographic analysis, Figure 4, confirmed the original assignment of (±)-**17a** as having arisen from an exo (alkoxy) [4 + 2] cycloaddition and also established the sense of asymmetric induction from the chiral auxiliary. Hydrogenolysis of (±)-**19a** followed by acetylation of the resulting crude amino diol afforded a mixture of triacetates **14a**/**15a** (**14a**/**15a**, 1.8/1) in 86% yield along with an 85% recovery of *trans*-2-phenylcyclohexyl acetate, Scheme 8.

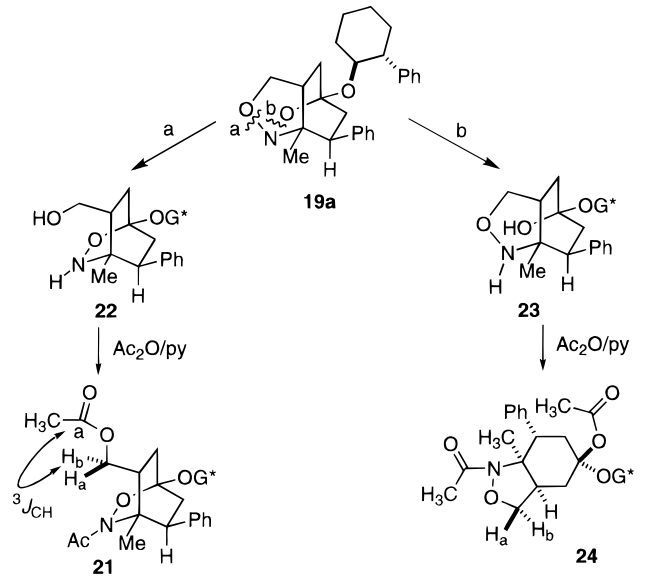
Synthesis of Optically Active Amino Cyclohexanone 20. The assessment of the enantiomeric excess of the triacetates **14a**/**15a**, obtained as a mixture of epimers, would require the oxidation of the epimeric alcohols to a single ketone. The introduction of additional steps in the tandem sequence would reduce the efficiency of this new construction and overshadow its intrinsic utility. Therefore, the ability to isolate the ketone before unselective reduction could occur in the hydrogenation of nitroso acetal **19a** became the next challenge.

The nitroso acetal hydrogenolysis is a critical reaction whose success relies upon the suitable choice of three parameters (hydrogen pressure, solvent, and amount of the promoter). Considering that our goal was to avoid the reduction of a carbonyl group to the corresponding hydroxyl functionality, it seemed logical to carry out the hydrogenation of **19a** under 1 atm of hydrogen. Furthermore, the choice of methanol as the reaction solvent was dictated by the results of previous observations. Thus, the influence of the amount of the Raney nickel on the course of the hydrogenolysis of **19a** was examined. A strict dependence of the rate of the nitroso acetal hydrogenation on the Raney nickel loading was observed. The selective unmasking of the nitroso acetal to afford the corresponding ketone could be achieved by stirring a methanolic suspension of commercially available Raney Ni (W2) (Ra-Ni) and nitroso acetal **19a** (Ra-Ni/**19a**, 1.5/1, w/w) under 1 atm of H_2 at room temperature for 55 min, Scheme 9. The crude product, obtained after removal of the nickel catalyst by filtration, was acetylated to give aminocyclohexanone **20** in 83% yield. Interestingly, during the optimization, it was found that the hydrogenation of **19a** proceeds through a partially reduced intermediate, which could be detected by thin-layer chromotographic (TLC) analysis. This new compound, whose bicyclic structure was confirmed by spectroscopic and analytical data, was obtained as a diacetate derivative, according to the following protocol. The hydrogenation of the nitroso acetal **19a** was performed in methanol, under 1 atm of H_2, for 100 min, using a Ra-Ni/**19a** ratio of 0.82/1, w/w, Scheme 9. The complete conversion of **19a** could not be achieved since TLC analysis of the reaction mixture showed the concomitant slower formation of ketone **20**. The crude product underwent acetylation to afford 55% of the diacetate derivative **21**.

Scheme 9

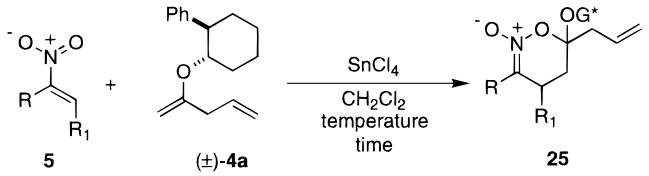


Scheme 10



The assignment of the structure of **21** presented a challenge. It should be noted that two distinct bicyclic compounds (**22** and **23**) can be obtained depending on which N−O bond is cleaved first, Scheme 10. Although the analytical data confirmed that **21** is the product of a single N−O bond cleavage, these data did not allow for a definitive assignment of its structure. However, under the reaction conditions hemiacetal **23** is expected to be a nonisolable species that would immediately collapse to the corresponding ketone **24**. Both the ^{13}C NMR or the IR spectra of the diacetate did not indicate the presence of a carbonyl functionality. Furthermore, the spectroscopic data revealed that the intermediate still retained the chiral auxiliary. A characteristic feature that distinguishes the bridged derivative **21** from the fused structure **24** is the existence, in the former, of a correlation ($^3J_{CH}$) between the alkoxy methylenic hydrogens H_a and H_b and the sp^2 carbon of the acetoxy group, Scheme

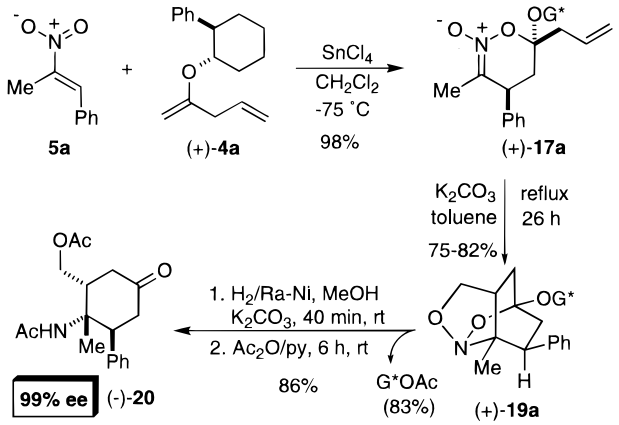
Table 4. Cycloadditions of Nitroalkenes 5b−e with (±)-4a



entry	**5** (R) (R_1)	**4a** (equiv)	$SnCl_4$ (equiv)	*T* (°C)	time (h)	diastereomeric ratio[a]	**25** (yield, %)[b]
1	**5b** (Me) (c-Hex)	1.2	2	−74 → 0	1.5		**25ba** (0)
2	**5b** (Me) (c-Hex)	3	1	−65	20		**25ba** (0)
3	**5c** (Me) (*n*-Pent)	3	2	−74	0.75	9.7/1.1/1.0	**25ca** (70.7)
4	**5c** (Me) (*n*-Pent)	1.3	2	−74	0.75		**25ca** (54.7)
5	**5d** (H) (Ph)	1.5	2	−74	0.25	14.0/6.0/1.0	**25da** (84)
6[c]	**5e** (H) (OBz)	1.5	2	−74	3	1.4/1.0	**25ea** (92)[d]

[a] Determined by ^{1}H NMR. [b] Isolated as a mixture of diastereomers. [c] The reaction was carried out in toluene. [d] Contaminated by 2-phenylcyclohexanol.

Scheme 11

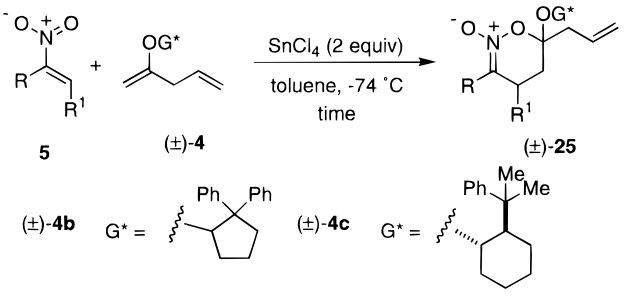


10. This correlation was established by performing a HMBC experiment which helped to unambiguously determine the structure of diacetate **21**.

With reproducible conditions for the selective hydrogenation of the nitroso acetal in hand, the synthesis of optically active aminocyclohexanone **20** was undertaken. The $SnCl_4$-promoted cycloaddition of nitroalkene **5a** with 1.2 equiv of vinyl ether (+)-**4a** provided nitronate (+)-**17a** as a single diastereomer, in 98% yield, Scheme 11. The thermal, intramolecular [3 + 2] cycloaddition was carried out by refluxing a solution of nitronate (+)-**17a** in anhydrous toluene, in the presence of an insoluble base (K_2CO_3). After workup and purification, the nitroso acetal (+)-**19a** was isolated in 75% yield. The hydrogenolysis of **19a** was accomplished under the usual protocol (H_2/Ra-Ni) in a 0.002 N methanolic solution of K_2CO_3. After acetylation, aminocyclohexanone **20** was isolated in 86% yield and 99% ee as determined by chiral HPLC, Scheme 11. The acetylated chiral alcohol was recovered in 83% yield.

Cycloadditions of Nitroalkenes 5b−e and Dienophiles (±)-4a−c. The generality of this remarkably stereoselective sequence was examined by performing $SnCl_4$-promoted [4 + 2] cycloadditions of selected nitroalkenes with 2-alkoxy-1,4-pentadiene (±)-**4a**. The results of this study, shown in Table 4, underline the poor reactivity of the secondary alkyl *β*-substituted nitroalkene **5b**, Table 4, entry 1, and a general decrease of the selectivity in the cycloadditions of nitroalkenes **5c−e**. The erosion in the diastereoselectivity of the cycloaddition becomes dramatic in the nitroalkenes **5d**[12] and **5e**[2j] bearing no α-substituent. A low exo/endo selectivity (exo/endo, 2.4/1, Table 4, entry 5) was observed in the $SnCl_4$-promoted cycloaddition of nitrostyrene (**5d**) with (±)-**4a**, whereas the analogous reaction of **5a** displayed exclusive exo selectivity.

Table 5. Cycloadditions of Nitroalkenes 5c−e with Dienophiles (±)-4b,c



entry	**5** (R) (R^1)	(±)-**4** (equiv)	time (h)	diastereomeric ratio[a]	**25** (yield, %)[b]
1	**5c** (Me) (*n*-Pent)	**4b** (3.0)	0.75	17.1/3.0/1.6/1.0	**25cb** (71)
2	**5c** (Me) (*n*-Pent)	**4c** (3.0)	0.75	7.1/1.0/1.0	**25cc** (85)[c]
3	**5d** (H) (Ph)	**4b** (1.3)	0.25	1.1/1.0	**25cb** (83)
4	**5d** (H) (Ph)	**4c** (1.5)	0.25	1.9/1.0	**25dc** (84)
5	**5e** (H) (OBz)	**4b** (2.0)	3.00	2.4/2.1/1.0	**25eb** (100)
6	**5e** (H) (OBz)	**4c** (3.0)	3.00	16.8/1.4/1.0	**25ec** (37)[d]

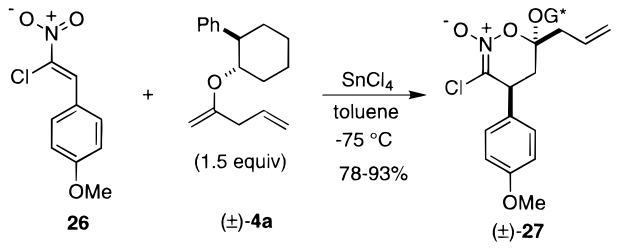
[a] Determined by ^{1}H NMR. [b] Isolated as a mixture of diastereomers. [c] Contaminated by *trans*-2-(1-methyl-1-phenylethyl)cyclohexanol (**4c**). [d] Partially decomposed.

No improvement in the diastereoselectivity was observed when dienophiles derived from 2,2-diphenylcyclopentanol,[2h] (±)-**4b**, or 2-(1-methyl-1-phenylethyl)-cyclohexanol,[18] (±)-**4c** (whose application to the fused mode tandem cycloadditions has provided remarkable results[2f,19]), were employed, Table 5. In all cases, $SnCl_4$-promoted [4 + 2] cycloaddition of nitroalkenes **5c−e** with vinyl ethers **4b,c** afforded mixtures of diastereomeric nitronates in varying yields and selectivity.

It should be noted that the nitronates derived from nitroalkenes **5d** and **5e** proved to be more thermally labile and acid-sensitive than the methyl-substituted nitronate **17a**. The chemical behavior of these delicate nitronates in the [3 + 2] cycloaddition was nonetheless assayed. The two diastereomeric nitronates **25dc** could be separated by column chromatography, but only the

(18) Comins, D. L.; Salvador J. M. *Tetrahedron Lett.* **1993**, *34*, 801.
(19) Denmark, S. E.; Thorarensen *J. Org. Chem.* **1996**, *61*, 6727.

Scheme 12



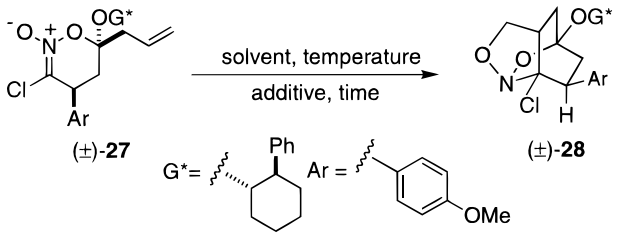
minor one was recovered in analytically pure form. The minor diastereomer was then subjected to a refluxing suspension of potassium carbonate in toluene. Unfortunately, no [3 + 2] cycloadduct could be isolated, even when the reaction was carried out at lower temperatures.

Cycloaddition of Nitroalkene 26 and (±)-4a. The low selectivities observed in the cycloadditions of **5**c and **5d** directed our attention to the use of heterodienes which incorporate a "hydrogen surrogate". According to this strategy, a group attached to C(1) of the nitroalkene would act as stereochemical director to achieve high selectivity in the [4 + 2] cycloaddition. The group would then be replaced by a hydrogen atom. This strategy has been used previously to control the exo/endo selectivity in intramolecular [4 + 2] cycloadditions[20] with groups such as Me_3Si, $PhSO_2$, and PhS. Unfortunately, the nitroalkenes which incorporate these moieties proved to be either difficult to prepare or unreactive toward cycloaddition.

(2-Chloro-2-nitroethenyl)arenes are heterodienes which contain a potential hydrogen surrogate. This novel class of compounds has been extensively explored by Dauzonne et al. in conjugate addition reactions.[21] To assess the potential of the chlorine atom as a hydrogen surrogate in the tandem sequence, the reactivity of nitroalkene **26**[21b] in the [4 + 2] cycloadditions was investigated. We were pleased to find that the $SnCl_4$-promoted [4 + 2] cycloaddition of **26** with vinyl ether (±)-**4a** afforded the corresponding nitronate **27** as a single diastereomer in 78% yield after recrystallization, Scheme 12. Interestingly, the nitronate displayed improved crystallinity and relative stability. This may be attributed to the presence of a chlorine substituent. On the basis of the stereochemical outcome of the cycloaddition of nitroalkene **5a** and the dienophile (±)-**4a**, the nitronate is assumed to arise from an exo-mode cycloaddition. This assumption is supported by ^{1}H NMR data (vide infra). The [3 + 2] cycloaddition of nitronate **27** was carried out according to the usual protocol in refluxing toluene and in the presence of K_2CO_3. Under these conditions, extensive decomposition occurred and no product could be isolated. Performing the reaction at lower temperatures resulted in a slower but complete destruction of the nitronate.

A summary of the optimization experiments for the synthesis of the nitroso acetal **28** is shown in Table 6. The use of polar solvents and mild temperatures seemed to be crucial, although in solvents with high donor number,[22] the starting nitronate decomposed. The formation of many byproducts was observed with additives such as LiBr and $LiClO_4$. Nitromethane, despite its thermal instability, appeared to be a promising solvent,

Table 6. Optimization of [3 + 2] Cycloadditions with (±)-27



entry	K_2CO_3 (equiv)	solvent	*T* (°C)[a]	additive (equiv)	time (h)	yield (%)
1	1	nitromethane	82		41	40
2	1	acetonitrile	reflux	$LiClO_4$ (100)	1	0
3	1	acetonitrile	reflux		22	30
4	2	acetonitrile	73[b]		79	60

[a] Temperature of the oil bath. [b] Internal temperature.

owing to its high polarity and low donor number. However, the partial polymerization of CH_3NO_2, favored by the presence of K_2CO_3, occurred and the nitroso acetal **28** was isolated only in modest yield, Table 6, entry 1. Finally, higher and more reproducible yields of **28** could be obtained by heating a mixture of the nitronate **27** and K_2CO_3 (2 equiv) in acetonitrile at 72−73 °C (internal temperature) for 79 h, Table 6, entry 4. Under these conditions, the nitroso acetal was isolated in 60% yield.

The hydrogenolysis of nitroso acetal **28**, carried out in methanol under H_2 (1 atm) at room temperature and in the presence of NaOH (3 equiv), afforded after acetylation a diastereoisomeric mixture of the aminocyclohexanones **29**/**30** (**29**/**30**, 1/1) in 63% yield, Scheme 13. Separation by radial chromatography and spectroscopic analysis of each stereoisomer revealed that the two compounds were epimers at the C(2) (amino-bearing) carbon.

The assignment of the relative configuration of the two epimeric aminocyclohexanones **29**/**30** was accomplished by analysis of the coupling patterns between HC(2) and the adjacent hydrogens HC(1) and HC(3), respectively, Figure 5. The less polar epimer **29** exhibits an axial−equatorial coupling between H_a and H_b (J_b = 5.0 Hz) and a coupling between the two equatorial hydrogens H_a and H_c (J_a = 10.4 Hz). In diacetate **30**, there exists a diaxial coupling between H_a and H_b (J_b = 10.0 Hz) and an axial−equatorial coupling H_a and H_c (J_a = 3.8 Hz).

We next directed our efforts toward the selective cleavage of only the C−Cl bond in **28** as a solution to the formation of epimeric products. The following reagents, which have been previously employed in the reduction of the C−X bond in tertiary bridged halides, were tried: Pd/C (10%),[23] $Zn(BH_4)_2$,[24] Bu_3SnH/AIBN (thermally and photochemically initiated),[25] Na(Hg),[26] Al(Hg),[27] $LiAlH_4$/

(20) (a) Jacobs, R. T. Unpublished observations in these laboratories. (b) Wilde, R. G. Unpublished observations in these laboratories.

(21) Dauzonne, D.; Demerseman, P. *J. Heterocycl. Chem.* **1990**, *27*, 1581. (b) Dauzonne, D.; Demerseman, P. *Synthesis* **1990**, 66. (c) Dauzonne, D.; Josien, H; Demerseman, P. *Synthesis* **1992**, 309.

(22) Donor number (or donicity) has been defined as the negative ΔH values for 1/1 adduct formation between antimony pentachloride and electron pair donor solvents in dilute solution in the noncoordinating solvent 1,2-dichloroethane (Reichardt, C. *Solvents and Solvents Effects in Organic Chemistry*; VCH Verlagsgesellschaft mbH: Weinhein, 1988).

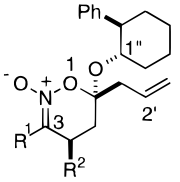
(23) Imamoto, T. In *Comprehensive Organic Synthesis*, Vol. 8, Reduction; Paquette, L. A., Ed.; Pergamon Press: Oxford, 1991; Chapter 4.1

(24) Kim, S.; Hong, C. Y.; Yang, S. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 562.

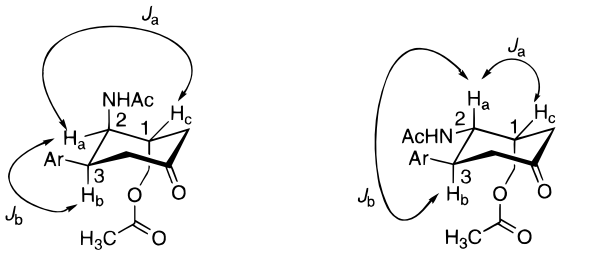
(25) (a) Della, E. W.; Patney, H. K. *Synthesis* **1976**, 251. (b) Fort, R. C., Jr.; Hiti, J. *J. Org. Chem.* **1977**, *42*, 3968. (c) Duri, Z. H.; Fraga, B. M.; Hanson, J. R. *J. Chem. Soc., Perkin Trans. 1* **1981**, 161.

(26) Austin, E.; Alonso, R. A.; Rossi, R. A. *J. Chem. Res., Synop.* **1990**, 190.

Table 7. Selected ^{1}H NMR Data for Nitronates 17a, 27, and 32



nitronate	R^1	R^2	HC(2′) ppm (*J*, Hz)	HC(1″) ppm (*J*, Hz)
17a	Me	Ph	5.78 (ddt, 17.2, 10.4, 7.1)	4.16 (dt, 4.0, 10.0)
27	Cl	4-MeOC$_6$H$_4$	5.76 (ddt, 17.0, 10.2, 7.2)	4.15 (dt, 4.0, 10.0)
32	Br	Ph	5.69 (ddt, 17.2, 10.4, 7.1)	4.07 (dt, 4.3, 9.8)



29

R_f 0.40 ($CHCl_3$/MeOH)

J_a = 10.4 Hz

J_b= 5.0 Hz

30

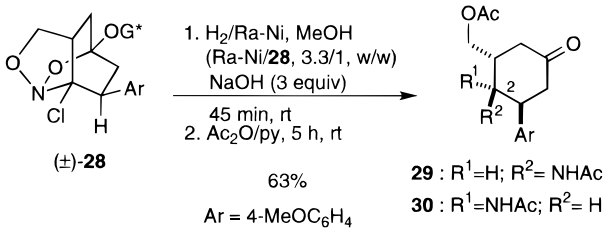
R_f 0.35 ($CHCl_3$/MeOH)

J_a = 3.8 Hz

J_b= 10.0 Hz

Figure 5. Coupling patterns of HC(2) in **29** and **30**.

Scheme 13



(±)-**28**

1. H_2/Ra-Ni, MeOH (Ra-Ni/**28**, 3.3/1, w/w) NaOH (3 equiv) 45 min, rt
2. Ac_2O/py, 5 h, rt

63%

Ar = 4-MeOC$_6$H$_4$

29 : R^1=H; R^2= NHAc

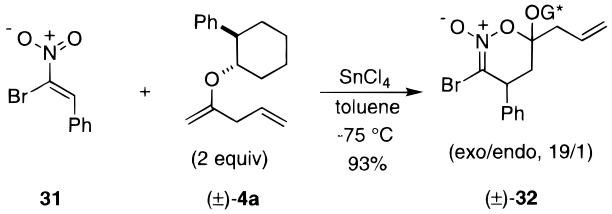
30 : R^1=NHAc; R^2= H

$NiCl_2$(cat),[28] and SmI_2/HMPA.[29] In all cases, either an intractable mixture of products was obtained or decomposition of the nitroso acetal **28** occurred.

To facilitate the selective cleavage of the halogen surrogate, a bromine substituent was introduced at C(1). Thus, the [4 + 2] cycloaddition of (2-bromo-2-nitroethenyl)benzene[30] (**31**) and vinyl ether (±)-**4a** was performed, Scheme 14. The resulting nitronate **32** was isolated in high yield (93%), although the selectivity (exo/endo, 19/1) was slightly lower than that observed in the analogous reaction of **27**. The [3 + 2] cycloaddition of **32**, performed using the same conditions employed for nitronate **27**, resulted in the poor mass recovery of a mixture of products.

The exo selectivity in the cycloadditions of the chloro- and bromo-substituted nitroalkenes **27** and **31** can be inferred by comparison of ^{1}H NMR data of the nitronates **27**, **32**, and **17a**, Table 7. The chemical shifts and the coupling patterns of the olefinic hydrogen H(2′) and the hydrogen H(1″) on the chiral auxiliary are diagnostic for

Scheme 14



31 (±)-**4a** (2 equiv)

$SnCl_4$, toluene, -75 °C, 93%

(exo/endo, 19/1) (±)-**32**

the distinction between the trans (exo approach) and the cis (endo approach) nitronates. Nitronate **17a** was established to have arisen from an exo approach of the vinyl ether **4a** to the nitro olefin **5a** by correlation to nitroso acetal **19a** whose stereostructure was unambiguously determined by X-ray analysis, Figure 4.

Discussion

[4 + 2] Cycloaddition: Exo/Endo Selectivity and Asymmetric Induction. The stereochemical course of the [4 + 2] cycloaddition is governed by two factors: (1) the exo or endo approach of the dienophile to the nitroalkene (with respect to the alkoxy group) and (2) the facial selectivity of the dienophile (with respect to the chiral auxiliary). It has also been demonstrated that both the rate of the [4 + 2] cycloaddition and its stereochemical outcome are profoundly affected by the Lewis acid.[1] The first effect can be rationalized in terms of frontier molecular orbital theory and has been discussed previously.[31] The influence of the Lewis acid on the stereochemical outcome of the reaction is more complex and not completely understood. It has been shown that the Lewis acid influences not only the exo/endo selectivity of the [4 + 2] cycloaddition but also which conformation of the dienophile (vinyl ether) is the most reactive, which, in turn, dictates the sense of the asymmetric induction.[2f] The exo preference in $SnCl_4$-promoted cycloadditions of substituted olefinic dienophiles is not unusual, and it has been documented in previous studies.[3b,12] High exo selectivity was observed in the cycloadditions of nitroalkenes **5a** with 1,4-pentadienes, 3,3-dimethyl-1,4-pentadiene, and the 2-alkoxy-1,4-pentadienes **1** and **4a**. Furthermore, (2-chloro-2-nitroethenyl)benzene (**26**) underwent exclusively an exo-mode cycloaddition with vinyl ether **4a** in the presence of $SnCl_4$. The exo selectivity in the cycloadditions of nitroalkene **5a** and simple pentadienes is easily understood in terms of the avoidance of steric interactions between the allyl chain of the dienophile and the heterodiene in the transition structure leading to trans nitronate. The exo (alkoxy) preference observed

(27) Hudlicky, T.; Olivo, H. F. *Tetrahedron Lett.* **1991**, *32*, 6077.

(28) (a) Ashby, E. C.; Lin, J. J. *J. Org. Chem.* **1978**, *43*, 1263. (b) Ganem, B.; Osby, J. O. *Chem. Rev.* **1986**, *86*, 763.

(29) Inanaga, J.; Ishikawa, M.; Yamaguchi, M. *Chem. Lett.* **1987**, 1485.

(30) (a) Devlin, C. J.; Walker, B. J. *J. Chem. Soc., Perkin Trans. 1* **1973**, 1428. (b) Parham, W. E.; Bleasdale, J. L. *J. Am. Chem. Soc.* **1951**, *73*, 4664.

(31) Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; John Wiley and Sons: New York, 1976.

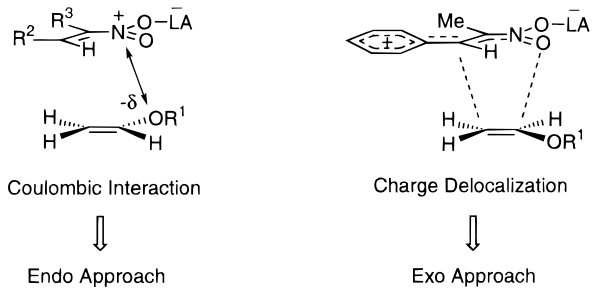


Figure 6. Preferred exo approach of a vinyl ether to the nitroalkene **5a**−Lewis acid complex.

in the reactions with the alkoxypentadienes **1** and **4a** is more intriguing and deserves a more detailed discussion. Coulombic interactions between diene and dienophile in the transition state have been invoked by Houk[32] and Hehre[33] to rationalize the exo/endo selectivity in Diels−Alder reactions. This model has allowed for an interpretation of the selectivity observed in the Lewis acid promoted cycloadditions of nitroalkenes with simple or β-substituted vinyl ethers.[2f,3b] In this context it has been pointed out that the nature of the substituent on the β-position on the nitroalkene can influence the exo/endo selectivity of the cycloaddition. Thus, attractive electrostatic interactions between the electron poor nitrogen of the diene and the partially electron rich oxygen of the dienophile would be responsible for the selective formation of the endo cycloadduct, Figure 6. However, the presence of an extended π-conjugation in aryl-substituted nitroalkenes could modify the electronic environment of the nitrogen and allow for a delocalization of the positive charge into the aryl ring. A consequent weakening of the attractive interaction would be expected, such that the less sterically demanding exo approach would be preferred, Figure 6.[3b]

Obviously, the application of this model to the cycloadditions of the α-substituted vinyl ethers **1** and **4a** with nitroalkene **5a** provides a convenient rationalization for the high exo selectivity observed in these reactions. However, this simplistic view does not take into account both the nature of the nitroalkene−Lewis acid complex[34] and the reactive conformation of the dienophile. In addition, it fails to explain the complementary selectivities observed in the reactions promoted by $SnCl_4$ and MAD of **5a** and the 2-alkoxy-1,4-pentadienes **1** and **4a**.

The predominance of the endo selectivity in the [4 + 2] cycloadditions promoted by the bulky aluminum-based Lewis acid MAD is surprising since one would expect the exo approach of the vinyl ether to the nitroalkene−MAD complex to be preferred on steric grounds. It could be argued that, depending on the reactive conformation of the enol ether, steric interactions between the methylenic hydrogens in the allyl chain and the Lewis acid could develop such that the endo approach is favored. However, this hypothesis is not convincing since the nonsynchronous nature of the [4 + 2] cycloaddition process attenuates the significance of such nonbonded interactions.[13a]

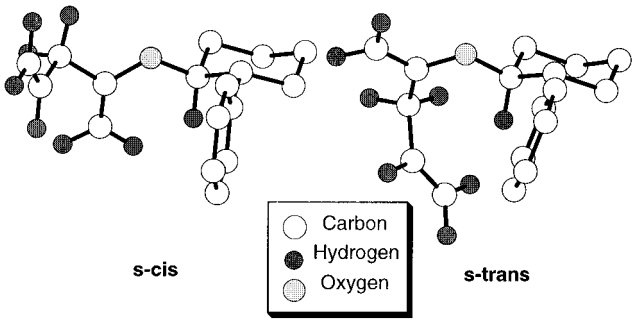


Figure 7. MOPAC (PM3) calculated *s*-cis and *s*-trans conformations of **4a**.

The interpretation of the influence of the α-substituent on the nitro olefin on the selectivity of the [4 + 2] cycloaddition is even more problematic and difficult to rationalize. The low selectivities observed in the cycloadditions of α-hydrogen substituted nitroalkenes (Tables 4 and 5) indicate that the α-substituent affects the orientation of the β-substituent which in turn might determine the conformation of the dienophile in the transition structure. An exclusive exo approach of the dienophile **4a** occurs in the $SnCl_4$-promoted cycloadditions of methyl- and chloro-substituted nitroalkenes **5a** and **26**. Furthermore, the analogous reaction of the bromo-substituted heterodiene **31** shows a slight decrease in selectivity (exo/endo, 19/1).

The exo/endo selectivity is only one of the two components that dictate the stereochemical outcome of the [4 + 2] cycloaddition with chiral vinyl ethers. The second contribution is given by the dienophile face selectivity, i.e., the stereodifferentiation provided by the auxiliary. This stereodifferentiation arises from the interaction of the dienophile with the Lewis acid−substrate complex and also the structure of the chiral auxiliary. Enol ethers have been shown to exist in two limiting conformations, *s*-cis and *s*-trans.[35] The semiempirical calculated ground state structure (PM3) for the *s*-cis and *s*-trans conformations of 2-alkoxy-1,4-pentadiene **4a** show that a different face of the enol ether is shielded in each conformation, Figure 7.

The reactive conformation of the vinyl ether **4a** in the [4 + 2] cycloaddition with **5a** can be inferred by the X-ray crystal structure of nitroso acetal (±)-**19a**, which in turn reveals the sense of the asymmetric induction provided by the chiral auxiliary. The crystallographically determined cis relationship between the phenyl (C(4)) and the allyl group (C(6)) in nitronate **17a** is uniquely established by an exo-mode orientation of the vinyl ether with respect to the heterodiene in the [4 + 2] cycloaddition. Moreover, since the relative configuration of the auxiliary (1*S**,2*R**)-2-phenylcyclohexanol is known, the relative configurations of C(4) and C(6) in **17a** can both be assigned as *S**. To obtain the 4*S** configuration, the 2-alkoxy-1,4-pentadiene **4a** must approach the *si* face of nitroalkene **5a**, whereas the C(6) configuration implies the approach of **5a** to the *re* face of the vinyl ether. The high selectivity observed in the [4 + 2] cycloaddition is a consequence of the very efficient shielding provided by the chiral auxiliary to the *si* face of the vinyl ether. As shown in Figure

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(34) Early studies employing variable-temperature NMR experiments suggested that the tin tetrachloride complex with 1-nitrocyclohexene has a 1/1 stochiometry; however, the complex was still dynamic at −120 °C (Cramer, C. J. Ph.D. Thesis; University of Illinois, Urbana, IL, 1988).

(35) (a) Bond, D.; Schleyer, P. v. R. *J. Org. Chem.* **1990**, *55*, 1003. (b) For a review, see: Fischer, P. Enol Ethers-Structure, Synthesis, and Reaction. In *The Chemistry of Ethers, Crown Ethers, Hydroxyl Groups, and their Sulphur Analogs*; Patai, S., Ed.; Wiley: New York, 1980; Part 2, p 761.

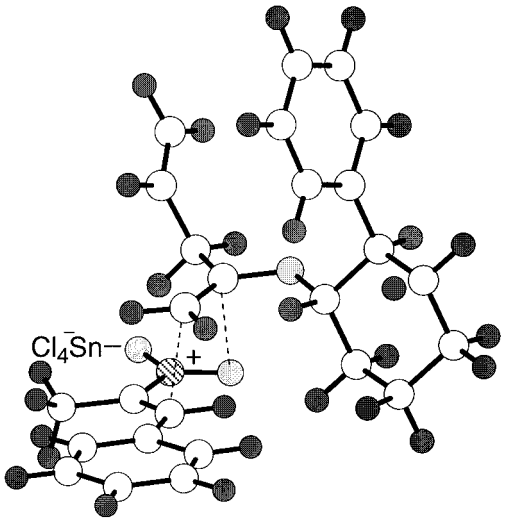

Figure 8. Facial selectivity and reactive *s*-cis conformation of alkoxypentadiene **4a**.

8, only the *s*-cis conformation of **4a** exposes the reactive face of the alkoxypentadiene in the cycloaddition. Therefore, the dienophile reacts in a cisoid conformation, exposing its *re* face and approaching the *si* face of **5a**, Figure 8. It is noteworthy that these α-substituted enol ethers react in an *s*-cis conformation while simple vinyl ethers or *β*-substituted enol ethers prefer an *s*-trans conformation.[2f] However, we have recently discovered that this behavior is actually a consequence of the Lewis acid employed in the cycloaddition.[36] The preference for a *s*-cis reactive conformation appears to be characteristic for $SnCl_4$-promoted reactions (except for (*Z*)-*β*-substituted enol ethers where the *s*-cis orientation is sterically inaccessible).

[3 + 2] Cycloaddition. The activation energy required for the [3 + 2] dipolar cycloaddition is influenced by the reactivity of the dipolarophile and the accessibility of a suitable reactive conformation of the nitronate. A previous study has documented the significant effects of dipolarophile geometry and substitution on the rate of the intramolecular [3 + 2] cycloadditions of cyclic nitronates bearing a pendant dipolarophile on the C(4).[14] The rate of the cycloaddition with unactivated dipolarophiles is considerably slower than that with activated dipolarophiles. Furthermore, the order of the cycloaddition rates has been found to be trans disubstituted > monosubstituted > trisubstituted > cis disubstituted (a similar trend has also been observed with activated dipolarophiles). Thus, the intramolecular cycloadditions of nitronates **9a**−**c**, **12a,b**, and **17a** are energetically disfavored processes since they involve the reaction of a nitronate dipole with an unactivated, monosubstituted olefin as the dipolarophile. Both the trans and cis nitronates are believed to adopt a half-chair conformation in the ground state in which the phenyl group is placed in a pseudoequatorial (trans nitronate) or in a pseudoaxial position (cis nitronate), while the alkoxy group is pseudoaxially oriented, by virtue of the anomeric effect, Figure 9. A suitable approach of the dipolarophile to the dipole can be accommodated only in a higher energy boat-like conformation, which is particularly unfavorable in the trans nitronate due to the nonbonded interactions between the methyl and phenyl groups (Figure 9). The

(36) Dixon, J. A. Unpublished observations in these laboratories.

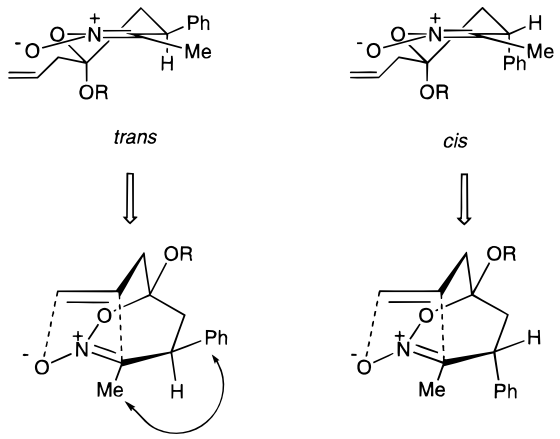

Figure 9. Proposed ground state and reactive conformations for exo and endo nitronates.

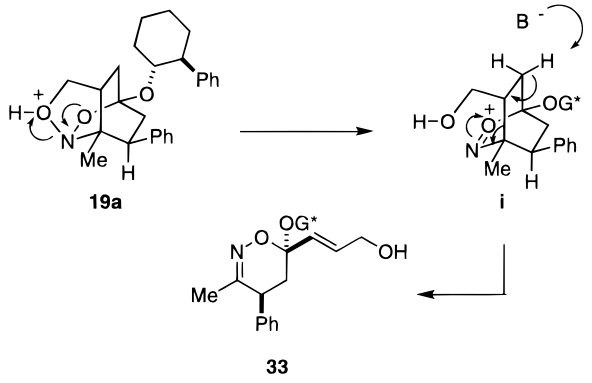

Figure 10. Proposed mechanism for formation of **33**.

difference in the experimental conditions (temperature and reaction time), under which the [3 + 2] cycloadditions of **12a** and **12b** (Scheme 6) are carried out, bears out the difference in energies for reaction of the two nitronates.

The use of an insoluble base ($NaHCO_3$ or K_2CO_3) in the [3 + 2] cycloadditions of the nitronates derived from 2-alkoxy-1,4-pentadienes was essential for the success of the reactions. Presumably, the base neutralizes acidic products generated by the thermal destruction of the nitronate, which in turn could accelerate the decomposition of both the nitroso acetal and nitronate. Interestingly, the dipolar cycloaddition of nitronate (±)-**17a**, conducted either in the absence of the base or in the presence of a soluble and non-nucleophilic base (2,6-lutidine), afforded a new compound which was identified as the 1,2-oxazine **33**. As shown in Figure 10, compound **33** could arise from the acid-catalyzed opening of the five-membered ring of the tricyclic nitroso acetal **19a** to give intermediate **i**. Subsequent deprotonation and concomitant bridge opening would lead to the observed product.

Hydrogenolysis. The studies on the selective hydrogenolysis of nitroso acetal **19a** to afford cyclohexanone **20** revealed an important insight into the mechanism of the process. As shown in Scheme 9, the rate of the Raney-nickel-promoted hydrogenation of **19a** could be modulated by a judicious choice of the catalyst loading and the reaction time. The isolation of the diacetate **21** demonstrated that the two nitrogen−oxygen bonds in the nitroso acetal are cleaved at different rates. Although the isolation of **21** implies **22** as an intermediate, it does not necessarily exclude the operation of the alternative oxazine N−O bond cleavage pathway. Inspection of the X-ray crystallographic structure of **19a** revealed that the

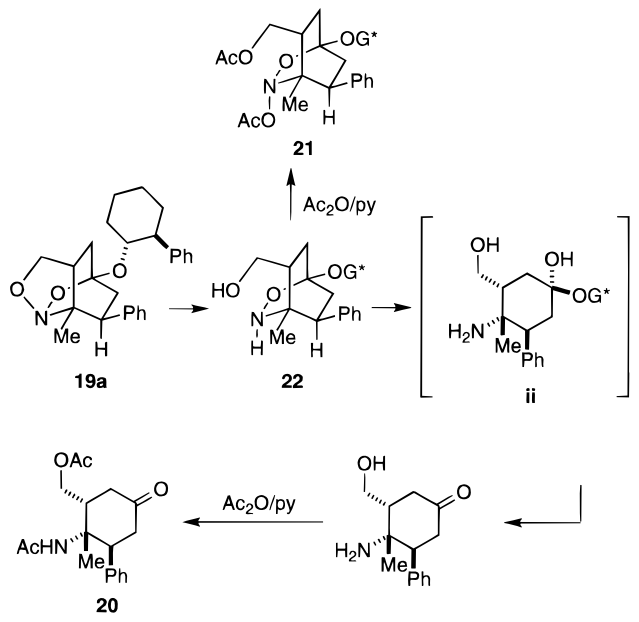

Figure 11. Mechanism of nitroso acetal **19a** hydrogenolysis.

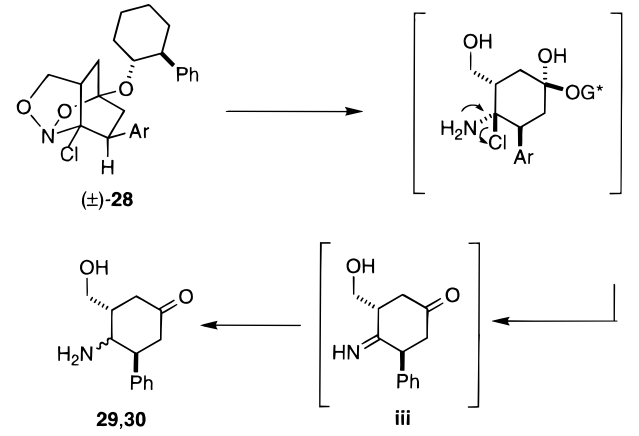

Figure 12. Proposed mechanism for nitroso acetal **28** hydrogenolysis.

N−O bond in the oxazine ring is 0.051 Å longer than the one in the five-membered ring. The longer and weaker N−O bond would be expected to undergo reductive cleavage more easily to afford, after acylation, the fused bicyclic compound **24**, Scheme 10. However, since only diacetate **21** was isolated as an intermediate, one can rationalize that **22** is the kinetic product and that the cleavage of the N−O bond in the six-membered ring is the slow step of the reaction, Figure 11.

The formation of the epimeric mixture of ketones **29**/**30**, upon hydrogenolysis of (±)-**28**, can be explained on the basis of the unselective reduction of the intermediate imine **iii** which originates from the extrusion of the chlorine atom after cleavage of the N−O bonds, Figure 12.

Conclusion

The feasibility of the bridged (α-tether) mode of the tandem inter [4 + 2]/intra [3 + 2] cycloaddition has been demonstrated. Simple 1,4-pentadienes as well as 2-alkoxy-1,4-pentadienes can function effectively as dienophile and dipolarophile combinations with excellent chemical selectivity and, regio- and diastereoselectivities. Chiral 2-alkoxy-1,4-pentadienes undergo the tandem process with excellent asymmetric induction. The range of useful nitroalkene components is currently limited to those containing α-substituents. The hydrogenolytic unmasking of the unusual tricyclic nitroso acetals proceeds cleanly under mild conditions to afford highly substituted aminocyclohexanemethanols as single stereoisomers. Application of this method to the synthesis of aminocyclitols is under investigation.

Experimental Section

General. See Supporting Information.

Materials. See Supporting Information.

2-Butoxy-1,4-pentadiene (1). To a cold (−70 °C) solution of *n*-butyl vinyl ether (13.0 g, 16.8 mL, 130 mmol, 2.0 equiv) in THF (84 mL) was added *tert*-butyllithium (1.43 M in heptane, 70 mL, 100 mmol, 2.0 equiv), via an addition funnel. The resulting bright yellow mixture was allowed to warm to 0 °C over a 3 h period. The almost colorless mixture was cooled to −78 °C and transferred via cannula to a mechanically stirred suspension of CuCN (4.48 g, 50.0 mmol, 1.0 equiv) in THF (45 mL). The resulting tan suspension was allowed to warm to −50 °C over a 2 h period and subsequently recooled to −78 °C. Allyl bromide (6.10 g, 4.30 mL, 50 mmol) was added dropwise over a 25 min period. The resulting orange-red suspension was stirred for 1.5 h at −78 °C, allowed to warm to rt, and quenched with aqueous NH_4OH solution (pH = 8, 100 mL). The mixture was diluted with diethyl ether (500 mL), and the organic phase was successively washed with an aqueous NH_4OH solution (pH = 8, 3 × 100 mL), water (6 × 100 mL), and brine (100 mL), then was dried (K_2CO_3), filtered, and concentrated in vacuo. Fractional distillation of the residue afforded 4.20 g (60%) of **3** as a clear, colorless liquid: bp 72 °C (40 Torr); ^{1}H NMR (400 MHz) δ 5.88 (ddt, J_d = 17.1, 10.3, J_t = 6.8, 1 H), 5.12−5.03 (m, 2 H), 3.87−3.85 (m, 2 H), 3.66 (t, J = 6.6, 2 H), 2.84 (d, J = 6.8, 2 H), 1.69−1.62 (m, 2 H), 1.46−1.37 (m, 2 H), 0.94 (t, J = 7.3, 3 H); ^{13}C NMR (100 MHz) δ 161.95, 134.87, 116.30, 80.98, 67.03, 39.52, 30.99, 19.34, 13.85; IR (neat) 2960, 2936, 1656, 1645, 1303, 1229, 1079, 1035; MS (70 eV) 140 (M^+ + 1, 7), 42 (100). Anal. Calcd for $C_9H_{16}O$ (140.23): C, 77.09; H, 11.50. Found: C, 77.11; H, 11.60.

Representative Procedure for the Preparation of Chiral 2-Alkoxy-1,4-pentadienes 4a−c (Representative Procedure I). The preparation of (+)-**4a** will serve to illustrate the general procedure utilized.

2-[(1*S*,2*R*)-*trans*-(2-Phenylcyclohexyl)oxy]-1,4-pentadiene ((+)-4a). Representative Procedure I. A cold (−90 °C) solution of allylmagnesium chloride (2 M in THF, 8 mL, 15.90 mmol, 1.20 equiv) in THF (35 mL) was transferred via a precooled cannula into a 3-neck, 250 mL, round-bottom flask containing a cold (−90 °C) yellow-green solution of LiBr (1.45 g, 16.70 mmol, 1.26 equiv) and CuBr (2.40 g, 16.7 mmol, 1.26 equiv) in THF (35 mL). A solution of (+)-**3a**[9] (2.50 g, 13.30 mmol) in THF (3.5 mL) was added to the orange solution of the allylcopper reagent (−90 °C). The dark brown reaction mixture was warmed to −78 °C and stirred for 90 min. The reaction was quenched by the addition of a NH_4Cl solution containing ammonium hydroxide (NH_4Cl/NH_4OH, pH = 8, 80 mL). After warming to room temperature, the dark green mixture was poured into pentane (800 mL) and washed with the NH_4Cl/NH_4OH solution (4 × 100 mL). The aqueous layer was back-extracted with pentane (3 x 100 mL). The combined organic extracts were washed with brine (3 × 150 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo to afford a black oil. The crude product was purified by column chromatography on Activity IV neutral alumina (hexane) to give 2.67 g (83%) of (+)-**4a** as a colorless oil: ^{1}H NMR (400 MHz) δ 7.40−7.10 (m, 5 H), 5.45 (ddt, J_d = 17.2, 10.4, J_t = 6.4, 1 H), 4.88−4.76 (m, 2 H), 4.04 (dt, J_d = 4.0, J_t =10.0, 1 H), 3.84 (d, J = 1.6, 1 H), 3.77 (d, J = 1.6, 1 H), 2.70 (ddd, J = 12.4, 10.2, 3.9, 1 H), 2.54 (d, J = 6.4, 2 H), 2.39−2.31 (m, 1 H), 1.98−1.90 (m, 1 H), 1.89−1.83 (m, 1 H), 1.81−1.73 (m, 1 H), 1.60−1.22 (m, 4 H); ^{13}C NMR (100 MHz) δ 160.50, 144.04, 134.83, 128.03, 127.51, 125.97, 115.64, 81.03, 78.62, 50.27, 39.72, 34.10, 31.02,

26.08, 24.76; IR (CCl_4) 3085, 2934, 2857, 1660, 1603, 1451, 1293, 1226, 1070, 1060; MS (CI, CH_4) 243 ($M^+ + 1$, 6), 159 (100); $[\alpha]^{22}_D$ +14.2° ($CHCl_3$, $c = 1.45$). Anal. Calcd for $C_{17}H_{22}O$ (242.36): C, 84.25; H, 9.15. Found: C, 84.01; H, 9.34.

Representative Procedure for the Preparation of Chiral Alkoxy Alkynes 3b,c (Representative Procedure II). The preparation of (±)-**3b** will serve to illustrate the general procedure utilized.

(±)-[(2,2-Diphenylcyclopentyl)oxy]ethyne ((±)-3b). Representative Procedure II. A 3-neck, 250-mL, round-bottom flask equipped with magnetic stir bar was charged with a suspension of potassium hydride (KH) in mineral oil. The KH was washed with hexane (2 × 20 mL), and the residual solvent was removed under high vacuum (0.1 Torr). (±)-2,2-Diphenylcyclopentanol[2h] ((±)-**2b**) (4.45 g, 18.70 mmol) dissolved in 20 mL of THF was added dropwise to the cold (0 °C) suspension of KH (1.50 g, 37.4 mmol, 2.0 equiv) in THF (20 mL). The reaction mixture was stirred for 16 h at room temperature and then was cooled to −74 °C. A solution of trichloroethylene (2.0 mL, 22.40 mmol, 1.0 equiv) in THF (6.0 mL) was slowly added, maintaining the internal temperature below −70 °C. The reaction mixture was warmed to room temperature, stirred for 1 h, and cooled to -74 °C. *n*-Butyllithium (1.6 M in hexane, 35.3 mL, 56.1 mmol, 3.0 equiv) was added dropwise to the resulting dark brown mixture. The reaction mixture was stirred for 1 h at −74 °C, warmed to 0 °C, quenched with water (25 mL), and then poured into a mixture of brine (50 mL) and pentane (200 mL). The aqueous layer was back-extracted with pentane (3 × 50 mL). The combined organic extracts were washed with brine (50 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. The resulting black oil was purified by vacuum filtration through a plug of Activity III basic alumina (hexane) to give 4.12 g (84%) of analytically pure (±)-**3b** as a light yellow solid, which could be stored at −25 °C (**3b** decomposes at room temperature): ^{1}H NMR (400 MHz) δ 7.40−7.05 (m, 10 H), 5.29−5.25 (m, 1 H), 2.65−2.57 (m, 1 H), 2.54−2.43 (m, 1 H), 2.36−2.25 (m, 1 H), 2.07−1.87 (m, 2 H), 1.73−1.59 (m, 1 H), 1.54 (s, 1 H); ^{13}C NMR (100 MHz) δ 144.48, 143.99, 128.50, 128.05, 127.84, 126.32, 126.24, 126,01, 95.08, 89.93, 59.54, 33.64, 28.44, 27.84, 19.90; IR (CCl_4) 3330, 2975, 2148, 1494, 1124, 1107; MS (FAB) 263 ($M^+ + 1$, 9), 117 (100); TLC R_f 0.69 (hexane/TBME, 24/1). Anal. Calcd for $C_{19}H_{18}O$ (262.35): C, 86.99; H, 6.92. Found: C, 87.05; H, 7.05.

2-[(±)-(2,2-Diphenylcyclopentyl)oxy]-1,4-pentadiene ((±)-4b). Following representative procedure I, from allylmagnesium chloride (2 M in THF, 4.6 mL, 9.15 mmol, 1.20 equiv) in THF (25 mL), LiBr (0.834 g, 9.60 mmol, 1.26 equiv), CuBr (1.38 g, 9.60 mmol, 1.26 equiv) in THF (25 mL), and (±)-**3b** (2.00 g, 7.62 mmol, 1 equiv) in THF (4 mL) was obtained 2.08 g (90%) of (±)-**4b** as a clear, colorless oil after column chromatography on Activity IV neutral alumina (hexane): ^{1}H NMR (400 MHz) δ 7.35−7.15 (m, 10 H), 5.55 (ddt, $J_d = 17.2$, 10.0, $J_t = 6.8$, 1 H), 5.03−4.98 (m, 1 H), 4.96−4.85 (m, 2 H), 3.96−3.92 (m, 2 H), 2.66−2.42 (m, 4 H), 2.05−1.76 (m, 3 H), 1.70−1.58 (m, 1 H); ^{13}C NMR (100 MHz) δ 160.24, 146.36, 145.41, 134.80, 128.30, 128.23, 127.56, 126.70, 125.88, 125.38, 115.95, 82.18, 81.78, 59.29, 39.78, 34.65, 28.47, 20.49; IR (CCl_4) 2972, 1654, 1598, 1495, 1447, 1303, 1292, 1267, 1227, 1074, 1034; MS (CI, CH_4) 305 ($M^+ + 1$, 1), 221 (100). Anal. Calcd for $C_{22}H_{24}O$ (304.44): C, 86.80; H, 7.95. Found: C, 86.74; H, 8.01.

(1*R,2*S**)-*trans*-[(2-(1-Methyl-1-phenylethyl)cyclohexyl)oxy]ethyne ((±)-3c).** Following representative procedure II, from (±)-**2c**[18] (2.26 g, 10.35 mmol) in THF (20 mL), KH (0.830 g, 20.70 mmol, 2.0 equiv) in THF (20 mL), trichloroethylene (1.12 mL, 12.42 mmol, 1.2 equiv) in THF (4.0 mL), and *n*-butyllithium (1.6 M, in hexane, 20 mL, 31.10 mmol, 3 equiv) was obtained 2.36 g (94%) of (±)-**3c** as a yellow oil after vacuum filtration through a compressed pad of Activity III basic alumina (hexane): ^{1}H NMR (400 MHz) δ 7.40−7.10 (m, 5 H), 3.92 (dt, $J_d = 4.4$, $J_t = 10.8$, 1 H), 2.34−2.26 (m, 1 H), 1.89 (ddd, $J = 11.8$, 10.1, 3.6, 1 H), 1.80−1.70 (m, 1 H), 1.60−1.48 (m, 3 H), 1.45 (s, 3 H), 1.42−1.34 (m, 4 H), 1.15 (qt, $J_q = 12.8$, $J_t = 3.6$, 1 H,), 1.03 (qt, $J_q = 12.8$, $J_t = 3.6$, 1 H), 0.83 (ddd, $J = 25.8$, 12.6, 3.6, 1 H); ^{13}C NMR (100 MHz) δ 149.76, 127.91, 125.86, 125.38, 89.70, 89.34, 51.08, 40.50, 31.80, 29.38, 28.01, 27.33, 25.40, 24.59, 24.22; IR (CCl_4) 3329, 2967, 2941, 2934, 2861, 2143, 1496, 1118, 1088, 1014; MS (CI, CH_4) 243 ($M^+ + 1$, 2), 201 (100); TLC R_f 0.79 (hexane/TBME, 24/1). Anal. Calcd for $C_{17}H_{22}O$ (242.36): C, 84.25; H, 9.15. Found: C, 84.46; H, 9.32.

2-[(1*R,2*S**)-*trans*-(2-(1-Methyl-1-phenylethyl)cyclohexyl)oxy]-1,4-pentadiene ((±)-4c).** Following representative procedure I, from allylmagnesium chloride (2 M in THF, 4.9 mL, 9.71 mmol, 1.20 equiv) in THF (30 mL), LiBr (0.890 g, 10.23 mmol, 1.26 equiv), CuBr (1.47 g, 10.23 mmol, 1.26 equiv) in THF (30 mL), and (±)-**3c** (1.97 g, 8.12 mmol, 1.0 equiv) in THF (4 mL) was obtained 2.01 g (87%) of (±)-**4c**, as a clear, colorless oil after column chromatography on Activity IV neutral alumina (hexane): ^{1}H NMR (400 MHz) δ 7.38−7.06 (m, 5 H), 5.74 (ddt, $J_d = 15.2$, 10.0, $J_t = 6.8$, 1 H), 5.04−4.96 (m, 2 H), 3.86−3.79 (m, 3 H), 2.51 (d, $J = 7.2$, 2 H), 2.22−2.12 (m, 1 H), 1.97 (ddd, $J = 12.2$, 10.0, 3.4, 1 H), 1.70−1.63 (m, 1 H), 1.62−1.54 (m, 1 H), 1.52−1.43 (m, 1 H), 1.37 (s, 3 H), 1.25 (s, 3 H), 1.18−1.08 (m, 3 H), 0.98−0.86 (m, 1 H); ^{13}C NMR (100 MHz) δ 159.22, 151.41, 134.97, 127.71, 125.68, 124.88, 116.24, 80.37, 76.66 , 51.67, 40.31, 39.69, 31.01, 27.93, 27.51, 26.22, 25.77, 24.68; IR (CCl_4) 2966, 2934, 2857, 1654, 1644, 1599, 1496, 1446, 1330, 1292, 1210, 1062, 1050, 1040; MS (CI, CH_4) 284 (M^+, 2), 119 (100). Anal. Calcd for $C_{20}H_{28}O$ (284.44): C, 84.45; H, 9.92. Found: C, 84.29; H, 10.12.

Representative Procedure for the [4 + 2] Cycloadditions of Nitroalkenes 5a−c and 3,3-Dimethyl-1,4-pentadiene and 1,4-Pentadiene. Representative Procedure III. The preparation of (±)-**6a** will serve to illustrate the general procedure utilized.

(4*R,6*R**)-3-Methyl-6-(2-methyl-3-buten-2-yl)-4-phenyl-5,6-dihydro-4*H*-[1,2]oxazine *N*-Oxide ((±)-6a). Representative Procedure III.** To a cold (−78 °C) solution of nitroalkene **5a**[12] (0.489 g, 2.99 mmol) and 3,3-dimethyl-1,4-pentadiene (0.565 g, 5.87 mmol, 2.0 equiv) in CH_2Cl_2 (4.0 mL) was added dropwise $SnCl_4$ (1.36 g, 0.60 mL, 5.20 mmol, 1.74 equiv). The yellow mixture was stirred at −78 °C for 20 min and was then allowed to stand at −15 °C for 40 h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution (6 mL), stirred for 5 min, allowed to warm to rt, and diluted with CH_2Cl_2 (100 mL). The organic layer was washed with a saturated aqueous $NaHCO_3$ solution (2 × 50 mL) and brine (50 mL). The combined aqueous layers were back-extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Purification by column chromatography on neutral alumina (hexane/EtOAc, 2/1) afforded 0.526 g (68%) of nitronate (±)-**6a** as a light yellow solid. An analytical sample was obtained after recrystallization (TBME) of a portion to afford (±)-**6a** as a crystalline solid: mp 115−116 °C (TBME): ^{1}H NMR (400 MHz) δ 7.39−7.26 (m, 3 H), 7.16−7.14 (m, 2 H), 5.73 (dd, $J = 17.3$, 10.8, 1 H), 5.01 (dd, $J = 10.9$, 1.0, 1 H), 4.97 (dd, $J = 17.5$, 1.0, 1 H), 4.08 (dd, $J = 11.8$, 1.6, 1 H), 3.80 (d, $J = 6.8$, 1 H), 2.11 (ddd, $J = 13.7$, 11.7, 7.1, 1 H), 1.98 (d, $J = 1.0$, 3 H), 1.82 (dt, $J_d = 13.7$, $J_t = 1.5$, 1 H), 1.09 (s, 3 H), 1.02 (s, 3 H); ^{13}C NMR (100 MHz) δ 142.67, 141.48, 129.04, 127.80, 127.42, 120.74, 113.56, 82.81, 42.76, 39.51, 29.17, 23.43, 22.12, 18.67; IR (KBr) 3065, 2974, 1606, 1275, 1238, 1014; MS (CI, CH_4) 260 ($M^+ + 1$, 41), 230 (100); TLC R_f 0.15 (hexane/EtOAc, 2/1). Anal. Calcd for $C_{16}H_{21}NO_2$ (259.35): C, 74.10; H, 8.16; N, 5.40. Found: C, 73.96; H, 8.15; N, 5.31.

Representative Procedure for the [3 + 2] Cycloadditions of Nitronates 6a and 9a−c. Representative Procedure IV. The preparation of (±)-**7a** will serve to illustrate the general procedure utilized.

(1*R,6*R**,7*S**,8*R**)-3-Aza-7,10,10-trimethyl-2,4-dioxa-8-phenyl-tricyclo[4.3.1.0^{3,7}]decane ((±)-7a). Representative Procedure IV.** A solution of nitronate (±)-**6a** (0.384 g, 1.62 mmol) in toluene (23 mL) was allowed to stir at 110 °C (oil bath) for 3 h. After being cooled to rt, the mixture was concentrated in vacuo and the residue recrystallized (TBME) to afford 0.305 g (79%) of nitroso acetal (±)-**7a** as a white solid: mp 164−165 °C (TBME): ^{1}H NMR (400 MHz) δ 7.46−7.39 (bs, 1 H), 7.33−7.29 (m, 2 H), 7.25−7.21 (m, 2 H), 4.06 (d, $J = 8.1$, 1 H), 3.95 (dd, $J = 8.1$, 5.1, 1 H,), 3.53 (t, $J = 2.7$, 1 H), 3.30 (dd, $J = 11.5$, 7.8, 1 H), 2.36 (ddd, $J = 11.9$, 11.8,

2.1, 1 H), 2.09 (d, J = 5.1, 1 H), 2.00−1.91 (m, 1 H), 1.19 (s, 3 H, CH_3), 1.13 (s, 3 H, CH_3), 0.82 (s, 3 H); ^{13}C NMR (100 MHz) δ 143.59, 129.56, 128.75, 126.98, 76.09, 70.39, 70.13, 51.96, 41.86, 36.71, 33.94, 28.81, 25.91, 21.46; IR (KBr) 2938, 2874, 1493, 1456, 1388, 1230; MS (10 eV) 259 (M^+, 2), 69 (100). Anal. Calcd for $C_{16}H_{21}NO_2$ (259.35): C, 74.10; H, 8.16; N, 5.40. Found: C, 74.00; H, 8.16; N, 5.43.

Representative Procedure for the Hydrogenation/Acetylation of Nitroso Acetals 7a and 10a−c. Representative Procedure V. The preparation of (±)-**8a** will serve to illustrate the general procedure utilized.

[(1*R,2*S**,3*R**,5*R**)-5-Acetoxy-2-(acetylamino)-2,6,6-trimethyl-3-phenylcyclohexyl]methyl Acetate ((±)-8a). Representative Procedure V.** To a suspension of a small amount of Raney nickel (washed with methanol (4 × 5 mL)) in methanol (6 mL) was added nitroso acetal (±)-**7a** (0.061 g, 0.24 mmol). The suspension was stirred for 23 h under 1 atm of hydrogen at rt. The cloudy suspension was filtered through a cotton plug, washing with copious amounts of methanol. The filtrate was concentrated in vacuo to afford a white solid (0.069 g). The crude product was dissolved in pyridine (2 mL), and a catalytic amount of DMAP was added followed by acetic anhydride (2 mL). The mixture was allowed to stir for 46 h at rt and concentrated in vacuo. The residue was dissolved in 100 mL of CH_2Cl_2 and washed successively with a saturated aqueous $NaHCO_3$ solution (2 × 30 mL), brine (30 mL), 2 M HCl (2 × 30 mL), and brine (30 mL). The organic phase was then dried ($MgSO_4$) and concentrated in vacuo. The crude organic concentrate was purified by silica gel column chromatography (EtOAc/hexane, 2/1) to afford 0.054 g (59%) of analytically pure (±)-**8a** as a white solid: mp 171 °C (hexane/EtOAc): ^{1}H NMR (400 MHz) δ 7.34−7.24 (m, 3 H), 7.16−7.12 (m, 2 H), 5.26 (bs, 1 H), 4.74 (dd, J = 11.5, 4.4, 1 H), 4.71 (dd, J = 12.5, 4.2, 1 H), 4.36 (dd, J = 12.5, 3.7, 1 H), 2.77 (dd, J = 13.7, 3.2, 1 H), 2.23−2.00 (m, 1 H), 2.07 (s, 3 H), 2.04 (s, 3 H), 1.92 (dt, J_d = 13.4, J_t = 3.6, 1 H), 1.86 (s, 3 H), 1.61 (dd, J = 3.9, 3.7, 1 H), 1.53 (s, 3 H), 1.09 (s, 3 H), 1.02 (s, 3 H); ^{13}C NMR (100 MHz) δ 170.66, 170.48, 169.44, 139.33, 128.84, 128.22, 127.40, 78.53, 63.00, 59.04, 55.81, 52.42, 38.42, 28.55, 27.39, 24.97, 24.32, 21.18, 21.07, 16.50; IR (KBr) 3427, 3400, 2980, 1738, 1664, 1531, 1369, 1248, 1022; MS (70 eV) 389 (M^+, 2), 43 (100); TLC R_f 0.18 (hexane/EtOAc, 1/1). Anal. Calcd for $C_{22}H_{31}NO_5$ (389.49): C, 67.84; H, 8.02; N, 3.60. Found: C, 67.83; H, 8.01; N, 3.58.

(4*R,6*S**)-3-Methyl-4-phenyl-6-(2-propenyl)-5,6-dihydro-4*H*-[1,2]oxazine *N*-Oxide ((±)-9a).** Following representative procedure III, to a cold (−78 °C) solution of nitroalkene **5a**[12] (0.098 g, 0.58 mmol) and 1,4-pentadiene (0.198 g, 0.30 mL, 2.90 mmol, 5.0 equiv) in CH_2Cl_2 (1.7 mL) was added dropwise $SnCl_4$ (0.249 g, 0.11 mL, 0.950 mmol, 1.7 equiv). Usual workup, followed by column chromatography purification on basic alumina (hexane/EtOAc, 1/1), afforded 0.125 g (91%) of nitronate (±)-**9a** as a thick, red oil: ^{1}H NMR (400 MHz) δ 7.40−7.28 (m, 3 H), 7.18−7.15 (m, 2 H), 5.80−5.69 (m, 1 H), 5.11−5.05 (m, 2 H), 4.45−4.42 (m, 1 H), 3.80 (d, J = 3.8, 1 H), 2.49−2.41 (m, 1 H), 2.38−2.28 (m, 1 H), 2.18 (ddd, J = 13.8, 10.9, 7.1, 1 H), 1.98 (d, J = 1.0, 3 H), 1.88 (dt, J_d = 13.9, J_t = 2.0, 1 H); ^{13}C NMR (100 MHz) δ 141.33, 131.63, 129.03, 127.71, 127.43, 120.76, 118.70, 76.29, 42.53, 37.41, 32.90, 18.50; IR (Neat) 3065, 3026, 2926, 1730, 1606, 1495, 1284, 1240, 993, 918; MS (CI, CH_4) 232 (M^+ + 1, 100); TLC R_f 0.28 (hexane/EtOAc, 2/1).

(1*R,6*R**,7*S**,8*R**)-3-Aza-7-methyl-2,4-dioxa-8-phenyltricyclo[4.3.1.0^{3,7}]decane ((±)-10a).** Following representative procedure IV, from a solution of nitronate (±)-**9a** (0.327 g) in toluene (23 mL) was obtained 0.283 g (84%) of nitroso acetal (±)-**10a** as a white solid after recrystallization (TBME): mp 161−162 °C (TBME); ^{1}H NMR (400 MHz) δ 7.48−7.36 (bs, 1 H), 7.35−7.28 (m, 2 H), 7.26−7.20 (m, 2 H), 4.27 (ddd, J = 8.1, 5.4, 1.0, 1 H), 4.15−4.10 (m, 1 H), 3.93 (d, J = 7.1, 1 H), 3.29 (dd, J = 11.0, 7.6, 1 H), 2.56 (dd, J = 9.3, 5.2, 1 H), 2.25 (dd, J = 13.6, 9.6, 1 H), 2.15−2.03 (m, 3 H), 0.90 (s, 3 H); ^{13}C NMR (100 MHz) δ 143.00, 129.00, 128.35, 126.56, 77.51, 68.38, 64.23, 41.61, 40.02, 37.66, 35.77, 20.88; IR (KBr) 2951, 2914, 1495, 1454, 1252, 1093, 1074, 1028, 987; MS (70 eV) 231 (M^+, 11), 104 (100). Anal. Calcd for $C_{14}H_{17}NO_2$ (231.29): C, 72.70; H, 7.41; N, 6.06. Found: C, 72.59; H, 7.40; N, 6.07.

[(1*R,2*S**,3*R**,5*R**)-5-Acetoxy-2-(acetylamino)-2-methyl-3-phenylcyclohexylmethyl Acetate ((±)-11a).** Following representative procedure V, from nitroso acetal (±)-**10a** (0.096 g, 0.41 mmol) was obtained 0.117 g (78%) of (±)-**11a** as a white, crystalline solid: mp 205−206 °C (hexane/EtOAc, 20/1); ^{1}H NMR (400 MHz) δ 7.33−7.24 (m, 3 H), 7.14−7.12 (m, 2 H), 5.28 (bs, 1 H), 4.92−4.84 (m, 1 H), 4.57 (dd, J = 11.5, 3.9, 1 H), 3.95 (dd, J = 11.5, 8.6, 1 H), 2.66 (dd, J = 12.6, 4.5, 1 H), 2.14−2.08 (m, 1 H), 2.17−2.00 (m, 2 H), 2.05 (s, 3 H), 2.04 (s, 3 H), 1.97−1.86 (m, 1 H), 1.93 (s, 3 H), 1.62 (dd, J = 24.8, 12.4, 1 H) 1.48 (s, 3 H); ^{13}C NMR (100.6 MHz) δ 170.88, 170.27, 169.57, 139.30, 128.83, 128.19, 127.39, 71.08, 65.47, 56.37, 52.58, 46.38, 32.88, 30.76, 24.86, 23.22, 21.30, 21.02; IR (KBr) 3352, 2953, 1726, 1649, 1545, 1383, 1250, 1032; MS (70 eV) 301 ($M^+ - CH_3CO_2$, 6), 43 (100); TLC R_f 0.12 (hexane/EtOAc, 1/1). Anal. Calcd for $C_{20}H_{27}NO_5$ (361.44): C, 66.46; H, 7.53; N, 3.88. Found: C, 66.46; H, 7.51; N, 3.91.

(4*R,6*S**)-4-Cyclohexyl-3-methyl-6-(2-propenyl)-5,6-dihydro-4*H*-[1,2]oxazine *N*-Oxide ((±)-9b).** Following representative procedure III, from nitroalkene **5b**[12] (0.173 g, 1.02 mmol) in CH_2Cl_2 (1 mL), 1,4-pentadiene (0.197 g, 0.30 mL, 2.89 mmol, 2.3 equiv) in toluene (0.3 mL), and $SnCl_4$ (0.565 g, 0.25 mL, 2.17 mmol, 2.1 equiv) was obtained a yellow oil (mixture of diastereomers, 91/9 by ^{1}H NMR). Purification by column chromatography on neutral alumina (hexane/EtOAc, 2/1) afforded 0.149 g (62%) of nitronate (±)-**9b** as a thick, colorless oil: ^{1}H NMR (400 MHz) δ 5.85−5.75 (m, 1 H), 5.17−5.12 (m, 2 H), 4.35−4.29 (m, 1 H), 2.53−2.46 (m, 1 H), 2.36−2.28 (m, 2 H), 2.06 (d, J = 1.0, 3 H), 1.92 (ddd, J = 14.4, 3.4, 3.2, 1 H), 1.81−1.62 (m, 5 H), 1.57−1.50 (m, 2 H), 1.35−1.20 (m, 4 H), 1.00−0.84 (m, 1 H); ^{13}C NMR (100 MHz) δ 131.91, 123.58, 118.50, 78.40, 40.72, 40.03, 37.39, 31.01, 28.53, 26.70, 26.13, 25.83, 25.37, 17.50; IR (neat) 2930, 2851, 1601, 1448, 1252, 998; MS (CI, CH_4) 238 (M^+ + 1, 100); TLC R_f 0.17 (hexane/EtOAc, 1/1), 0.11 (hexane/EtOAc, 2/1).

(1*R,6*R**,7*S**,8*R**)-3-Aza-8-cyclohexyl-7-methyl-2,4-dioxatricyclo[4.3.1.0^{3,7}]decane ((±)-10b).** Following representative procedure IV, from nitronate (±)-**9b** (0.342 g, 1.44 mmol) in toluene (21 mL) was obtained 0.342 g (100%) of analytically pure nitroso acetal (±)-**10b** as a white solid: mp 149−150 °C (toluene); ^{1}H NMR (400 MHz, C_6D_6) δ 3.81 (t, J = 6.0, 1 H), 3.64−3.39 (m, 1 H), 3.47 (d, J = 7.1, 1 H), 2.25 (d, J = 12.9, 1 H), 1.78−1.65 (m, 2 H), 1.64−1.48 (m, 4 H), 1.34−1.26 (m, 2 H), 1.25−0.85 (m, 8 H), 0.84 (s, 3 H); ^{13}C NMR (100 MHz, C_6D_6) δ 79.19, 68.31, 63.47, 41.35, 38.58, 38.31, 35.89, 31.36, 28.76, 27.33, 26.78, 26.43, 25.96, 19.78; IR (KBr) 2993, 2920, 2847, 1448, 930; MS (70 eV) 237 (M^+, 8), 55 (100). Anal. Calcd for $C_{14}H_{23}NO_2$ (237.34): C, 70.85; H, 9.77; N, 5.90. Found: C, 70.80; H, 9.78; N, 5.88.

[(1*R,2*S**,3*R**,5*R**)-5-Acetoxy-2-(acetylamino)-3-cyclohexyl-2-methylcyclohexyl]methyl Acetate ((±)-11b).** Following representative procedure V, from nitroso acetal (±)-**10b** (0.087 g, 0.37 mmol) was obtained a white solid, which was washed with hexane/EtOAc and filtered to give 0.100 g (74%) of (±)-**11b**. An analytical sample was obtained after recrystallization (ethanol) of a portion to afford (±)-**11b** as a crystalline solid: mp 216 °C (ethanol); ^{1}H NMR (400 MHz) δ 5.12 (bs, 1 H), 4.76−4.68 (m, 1 H), 4.51 (dd, J = 11.6, 3.8, 1 H), 3.87 (dd, J = 11.5, 8.3, 1 H), 2.06 (s, 3 H), 2.04 (s, 3 H), 2.03−1.89 (m, 2 H), 1.95 (s, 3 H), 1.71−1.31 (m, 6 H), 1.71 (s, 3 H), 1.22−0.96 (m, 9 H); ^{13}C NMR (100 MHz) δ 170.86, 170.34, 169.52, 71.80, 65.32, 57.04, 51.75, 46.67, 36.37, 34.57, 30.72, 29.37, 28.35, 26.94, 26.65, 26.27, 25.08, 22.07, 21.31, 20.99; IR (KBr) 3350, 2924, 1743, 1724, 1653, 1537, 1369, 1248, 1034; MS (70 eV) 367 (M^+, 3), 43 (100); TLC R_f 0.12 (hexane/EtOAc, 1/1), 0.26 (hexane/EtOAc, 1/2). Anal. Calcd for $C_{20}H_{33}NO_5$ (367.48): C, 65.37; H, 9.06; N, 3.81. Found: C, 65.24; H, 9.17; N, 3.80.

(4*S,6*S**)-3-Methyl-4-pentyl-6-(2-propenyl)-5,6-dihydro-4*H*-[1,2]oxazine *N*-Oxide ((±)-9c).** Following representative procedure III, to a cold (−78 °C) solution of nitroalkene **5c**[12] (0.154 g, 0.92 mmol) in CH_2Cl_2 (1 mL) was added a solution of 1,4-pentadiene (0.197 g, 0.30 mL, 2.89 mmol, 2.3 equiv) in toluene (0.30 mL) followed by $SnCl_4$ (0542 g, 0.24 mL, 2.08

mmol, 2.1 equiv). After being stirred at −78 °C for 5 min, the deep yellow reaction mixture was allowed to stand at −15 °C for 14 h. After usual workup, a crude yellow oil (mixture of diastereomers, 94/6 by ^{1}H NMR) was obtained. Purification by column chromatography on neutral alumina (hexane/EtOAc, 2/1, 1/1) afforded 0.120 g (55%) of nitronate (±)-**9c** as a thick, colorless oil: ^{1}H NMR (400 MHz) δ 5.86−5.76 (m, 1 H), 5.18−5.13 (m, 2 H), 4.37−4.31 (m, 1 H), 2.53−2.47 (m, 1 H), 2.39−2.32 (m, 2 H), 2.05 (d, J = 1.0, 3 H), 1.82−1.60 (m, 3 H), 1.41−1.24 (m, 7 H), 0.89 (t, J = 6.9, 3 H); ^{13}C NMR (100 MHz) δ 131.78, 123.45, 118.59, 76.89, 37.49, 35.92, 32.47, 31.32, 27.76, 26.48, 22.26, 17.72, 3.77; IR (neat) 2961, 2933, 2846, 1605, 1460, 1273, 997; MS (CI, CH_4) 226 ($M^+ + 1$, 100); TLC R_f 0.17 (hexane/EtOAc, 1/1), 0.11 (hexane/EtOAc, 2/1).

(1*R,6*R**,7*S**,8*S**)-3-Aza-9-methyl-2,4-dioxa-8-pentyltricyclo-[4.3.1.0^{3,7}]decane ((±)10c).** Following representative procedure IV, from nitronate (±)-**9c** (0.200 g, 0.89 mmol) in toluene (13 mL) was obtained 0.200 g (100%) of analytically pure nitroso acetal (±)-**10c** as a white solid: mp 69 °C (toluene); ^{1}H NMR (400 MHz, C_6D_6) δ 3.89 (t, J = 6.4, 1 H), 3.95−3.61 (m, 1 H), 3.53 (d, J = 7.1, 1 H), 1.68−1.00 (m, 14 H), 0.90 (t, J = 7.2, 3 H), 0.87 (s, 3 H); ^{13}C NMR (100 MHz, C_6D_6) δ 77.30, 68.33, 63.23, 40.24, 35.99, 34.27, 33.81, 32.26, 32.24, 26.57, 23.03, 20.82, 14.33; IR (KBr) 2955, 2912, 2858, 1462, 1340, 1230, 1095; MS (10 eV) 225 (M^+, 7), 69 (100). Anal. Calcd for $C_{13}H_{23}NO_2$ (225.33): C, 69.30; H, 10.29; N, 6.22. Found: C, 69.26; H, 10.34; N, 6.20.

[(1*R,2*S**,3*S**,5*R**)-5-Acetoxy-2-(acetylamino)-2-methyl-3-pentylcyclohexyl]methyl Acetate ((±)-11c).** Following representative procedure V, from nitroso acetal (±)-**10c** (0.117 g, 0.52 mmol) was obtained 0.124 g (67%) of (±)-**11c** as a white solid after column chromatography on silica gel (EtOAc/hexane, 3/1). An analytical sample was obtained after recrystallization (hexane/EtOAc) to afford (±)-**11c** as a crystalline solid: mp 100−102 °C (hexane/EtOAc): ^{1}H NMR (400 MHz) δ 5.00 (bs, 1 H), 4.76−4.62 (m, 1 H), 4.53 (dd, J = 11.5, 3.9, 1 H), 3.91 (dd, J = 11.5, 8.5, 1 H), 2.10−2.00 (m, 2 H), 2.04 (s, 3 H), 2.02 (s, 3 H), 1.97 (s, 3 H), 1.80−1.65 (m, 2 H), 1.65 (s, 3 H), 1.40−1.05 (m, 9 H), 0.98−0.93 (m, 1 H), 0.87 (t, J = 7.1, 3 H); ^{13}C NMR (100 MHz) δ 170.77, 170.25, 169.85, 70.96, 65.33, 56.28, 46.62, 46.19, 32.30, 31.80, 30.51, 29.47, 27.62, 24.71, 22.47, 21.75, 21.20, 20.92, 13.92; IR (KBr) 3348, 2934, 1740, 1656, 1543, 1367, 1248, 1030; MS (70 eV) 355 (M^+, 1), 43 (100); TLC R_f 0.14 (hexane/EtOAc, 1/1). Anal. Calcd for $C_{19}H_{33}NO_5$ (355.48): C, 64.20; H, 9.36; N, 3.94. Found: C, 64.19; H, 9.35; N, 3.96.

Representative Procedure for the $SnCl_4$-Promoted [4 + 2] Cycloadditions of Nitroalkenes and 2-Alkoxy-1,4-pentadienes 1 and 4a. Representative Procedure VI. The preparation of (±)-**12a** will serve to illustrate the general procedure utilized.

(4*S,6*S**)-6-Butoxy-3-methyl-4-phenyl-6-(2-propenyl)-5,6-dihydro-4*H*-[1,2]oxazine *N*-Oxide ((±)-12a). Representative Procedure VI.** To a cold (−78 °C) solution of nitroalkene **5a**[12] (0.250 g, 1.50 mmol) in CH_2Cl_2 (10 mL) was added $SnCl_4$ (0.780 g, 0.35 mL, 3.00 mmol, 2.0 equiv), and a bright yellow solution resulted. After the solution was stirred for 15 min at −78 °C, a solution of vinyl ether **1** (0.840 g, 6.00 mmol, 4.0 equiv) in CH_2Cl_2 (2 mL) was added over a 30 min period. The mixture was allowed to stir for an additional 15 min and then was quenched with a solution of Et_3N (0.5 mL) in methanol (10 mL). The cold reaction mixture was diluted with CH_2Cl_2 (200 mL), and the organic phase was washed with water (3 × 200 mL). The combined aqueous layers were back-extracted with CH_2Cl_2 (3 × 100 mL), and the combined organic phase was washed with brine (100 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. The cloudy, yellow oil was purified by silica gel column chromatography (hexane/EtOAc, 5/1) to afford 0.388 g of (±)-**12a** as a white solid and 0.016 g of (±)-**12b** as a clear oil, for a combined yield of 0.404 g (89%) and a diastereomeric ratio of 24/1 (**12a**/**12b**). The ^{1}H NMR spectral data for the more polar nitronate were consistent with those reported for (±)-**12b** obtained through an MAD-promoted cycloaddition of nitroalkene **5a**[12] with vinyl ether **1** (see next preparation): mp 49−50.5 °C (hexane): ^{1}H NMR (400 MHz) δ 7.34−7.24 (m, 3 H), 7.17−7.14 (m, 2 H), 5.69 (ddt, J_d = 16.9, 10.5, J_t = 7.3, 1 H), 5.14−5.09 (m, 2 H), 3.86−3.78 (m, 2 H), 3.65 (dt, J_d = 9.0, J_t = 5.9, 1 H), 2.72−2.66 (m, 1 H), 2.48 (dd, J = 14.7, 7.6, 1 H), 2.28 (dd, J = 13.9, 7.7, 1 H), 1.85 (dd, J = 13.9, 11.7, 1 H), 1.82 (d, J = 1.5, 3 H), 1.63−1.46 (m, 2 H), 1.41−1.31 (m, 2 H), 0.91 (t, J = 7.3, 3 H); ^{13}C NMR (100 MHz) δ 140.02, 130.28, 129.02, 127.86, 127.46, 122.99, 119.86, 104.45, 61.59, 41.86, 38.46, 37.78, 31.61, 19.10, 17.22, 13.70; IR (CCl_4) 3050, 2960, 1615, 1455, 1280, 1240, 1086; MS (CI, CH_4) 304 ($M^+ + 1$, 100); TLC R_f 0.50 (hexane/EtOAc, 2/1). Anal. Calcd for $C_{18}H_{25}NO_3$ (303.405): C, 71.26; H, 8.31; N, 4.62. Found: C, 71.27; H, 8.30; N, 4.62.

Representative Procedure for the MAD-Promoted [4 + 2] Cycloadditions of Nitroalkene 5a and 2-Alkoxy-1,4-pentadienes 1 and (±)-4a. Representative Procedure VII. The preparation of (±)-**12b** will serve to illustrate the general procedure utilized.

(4*R,6*S**)-6-Butoxy-3-methyl-4-phenyl-6-(2-propenyl)-5,6-dihydro-4*H*-[1,2]oxazine *N*-Oxide ((±)-12b). Representative Procedure VII.** To a solution of BHT (1.46 g, 8.00 mmol, 4.0 equiv) in toluene (8 mL) was added dropwise a solution of trimethylaluminum (2.0 M in toluene, 2.0 mL, 4.00 mmol, 2.0 equiv). Gas evolution was observed as the solution was stirred at rt for 1 h. The resulting clear solution was added over a 10 h period, via syringe pump, to a cold (−35 °C), stirred solution of nitroalkene **5a**[12] (0.328 g, 2.00 mmol, 1 equiv) and vinyl ether **1** (1.12 g, 8.00 mmol, 4.0 equiv) in toluene. The resulting pale-yellow reaction mixture was stirred an additional 10 h at −35 °C and then was quenched with water (5 mL) and poured into CH_2Cl_2 (200 mL). The organic layer was washed with water (3 × 150 mL), and the combined aqueous layer was back extracted with CH_2Cl_2 (3 × 100 mL). The combined organic phase was washed with brine (100 mL), dried (Na_2SO_4/$NaHCO_3$, 1/1), filtered, and concentrated in vacuo to afford a yellow oil. The crude residue was purified by silica gel column chromatography (hexane/EtOAc, 4/1) to afford a 4.6/1 (**12b**/**12a**) ratio of diastereomers as determined by ^{1}H NMR integration. After a second silica gel column chromatography (hexane/EtOAc, 5/1), 0.042 g of nitronate **12a**, 0.087 g of a mixture of nitronates **12a** and **12b**, and 0.243 g of analytically pure nitronate **12b** were obtained to give a combined yield of 0.377 g (62%). The ^{1}H NMR data for the less polar nitronate were consistent with those previously reported for **12a** obtained through a tin(IV) chloride promoted cycloaddition of nitroalkene **5a**[12] and vinyl ether **1**. (±)-**12b**: ^{1}H NMR (400 MHz) δ 7.34−7.23 (m, 5 H), 5.70 (ddt, J_d = 17.1, 9.8, J_t = 7.1, 1 H), 5.19−5.14 (m, 2 H), 3.88 (dt J_d = 9.0, J_t = 6.4, 1 H), 3.75−3.72 (m, 1 H), 3.59 (dt, J_d = 8.8, J_t = 6.8, 1 H), 2.70 (ddt, J_d = 14.7, 6.8, J_t = 1.2, 1 H), 2.52 (dd, J = 14.9, 7.6, 1 H), 2.43 (dd, J = 13.9, 8.8, 1 H), 2.12 (dd, J = 13.9, 4.6, 1 H), 1.91 (d, J = 1.5, 3 H), 1.61−1.49 (m, 2 H), 1.36−1.26 (m, 2 H), 0.90 (t, J = 7.3, 3 H); ^{13}C NMR (100 MHz) δ 140.58, 130.77, 128.75, 128.58, 127.23, 123.74, 119.78, 105.59, 62.38, 41.92, 38.79, 37.23, 31.72, 19.22, 17.37, 13.90; IR (CCl_4) 3050, 2960, 2874, 1613, 1495, 1281, 1250, 1217, 1079, 1005; MS (CI, CH_4) 304 ($M^+ + 1$, 100); TLC R_f 0.35 (hexane/EtOAc, 2/1). Anal. Calcd for $C_{18}H_{25}NO_3$ (303.405): C, 71.26; H, 8.31; N, 4.62. Found: C, 71.26; H, 8.31; N, 4.63.

(1*R,6*R**,7*S**,8*S**)-3-Aza-1-butoxy-7-methyl-2,4-dioxa-8-phenyltricyclo[4.3.1.0^{3,7}]decane ((±)-13a).** A solution of nitronate (±)-**12a** (0.285 g, 0.94 mmol) in xylenes (10 mL), was added over an 8 h period, via syringe pump, to a stirred suspension of $NaHCO_3$ (0.552 g, 6.57 mmol, 7.0 equiv) in refluxing xylenes (84 mL). After the addition was complete, the resulting mixture was heated at reflux for an additional 24 h. The suspension was cooled to rt, and the solvent was removed in vacuo (0.5 Torr) to afford a brown solid. The crude organic concentrate was dissolved in benzene (20 mL) and filtered through a cotton plug into a round-bottom flask charged with $NaHCO_3$ (100 mg). After concentration in vacuo (0.5 Torr), the crude residue was purified by column chromatography on Activity III basic alumina (hexane/TBME, 5/1), and fractions were collected in 13 × 100 mm tubes charged with $NaHCO_3$ (~0.05 g). The fractions containing the product were concentrated in vacuo (0.5 Torr) and filtered through a cotton plug into a preweighed round-bottom flask containing $NaHCO_3$ (0.05 g). The solvent was removed in vacuo (0.5 Torr)

to afford 0.234 g (82%) of nitroso acetal (±)-**13a** as a white solid in the presence of $NaHCO_3$: ^{1}H NMR (400 MHz, C_6D_6) δ 7.15−7.06 (m, 3 H), 6.96 (d, J = 7.8, 2 H), 3.76−3.73 (m, 1 H), 3.65 (d, J = 6.8, 1 H), 3.58 (dt, J_t = 6.6, J_d = 1.7, 2 H), 3.35 (dd, J = 12.0, 6.1, 1 H), 2.40 (dt, J_t = 12.5, J_d = 3.4, 1 H), 2.08−1.96 (m, 2 H), 1.87 (dd, J = 12.9, 3.4, 1 H), 1.54−1.46 (m, 3 H), 1.35−1.26 (m, 2 H), 0.79 (t, J = 7.3, 3 H), 0.64 (s, 3 H); ^{13}C NMR (100 MHz, C_6D_6) δ 142.85, 128.97, 128.91, 127.11, 96.13, 79.09, 69.31, 62.44, 44.21, 40.57, 40.02, 38.81, 32.55, 20.23, 19.54, 14.05.

[(1*R,2*S**,3S*,5*S**)-5-Acetoxy-2-(acetylamino)-2-methyl-3-phenylcyclohexyl]methyl Acetate ((±)-14a) and [(1*R**,2*S**,3*S**,5*R**)-5-Acetoxy-2-(acetylamino)-2-methyl-3-phenylcyclohexyl]methyl Acetate ((±)-15a).** Following representative procedure V, a suspension of nitroso acetal (±)-**13a** (0.210 g, 0.69 mmol), $NaHCO_3$ (0.05 g), and Raney nickel (2.00 g), in methanol (60 mL) was stirred for 40 h under 1 atm of hydrogen at rt. The cloudy suspension was filtered through a Büchner funnel lined with Whatman no. 1 filter paper, washed with methanol (30 mL), and concentrated in vacuo. The residue was treated with pyridine (8 mL) and acetic anhydride (8 mL) at rt for 32 h. After usual workup, the resulting crude oil was purified by silica gel column chromatography (hexane/EtOAc, 1/1) to afford 0.195 g (78%) of a mixture of triacetates (±)-**14a** and (±)-**15a** as a 1/1.6 (**14a**/**15a**) ratio of diastereomers (determined by ^{1}H NMR integration). A small amount of the triacetate mixture was separated using MPLC (hexane/EtOAc, 3/2) to provide diastereomerically pure samples of **14a** (first eluted) and **15a** (second eluted). Compound **14a** was recrystallized being dissolved in EtOAc (1 mL) and then precipitated with hexane (3 mL) to afford an analytically pure white crystalline solid. Diastereomer **15a** was further purified by silica gel column chromatography (hexane/EtOAc, 1/1). **(±)-14a**: mp 166−168°C (hexane/EtOAc); ^{1}H NMR (400 MHz) δ 7.40−7.30 (m, 3 H), 7.19−7.16 (m, 2 H), 5.37 (s, 1 H), 5.02 (tt, J = 12.0, 5.5, 1 H), 4.30 (dd, J = 11.2, 9.5, 1 H), 4.16 (dd, J = 11.1, 4.8, 1 H), 3.31 (dtd, J_d = 10.0, 3.0, J_t = 5.0, 1 H), 2.90 (dd, J = 12.5, 3.9, 1 H), 2.21−2.16 (m, 1 H), 2.13−2.01 (m, 8 H) 1.83−1.75 (m, 4 H), 1.53 (s, 3 H); ^{13}C NMR (100 MHz) δ 171.39, 170.35, 169.69, 138.95, 128.98, 128.93, 127.92, 68.67, 63.44, 56.98, 46.18, 40.06, 33.31, 28.90, 24.30, 21.29, 21.09, 18.98; IR ($CHCl_3$) 3421, 2994, 2256, 1732, 1678, 1504, 1368, 1256, 1034; MS (FAB) 362 (M^+ + H, 96), 302 (100); TLC R_f 0.22 (EtOAc/hexane, 2/1). Anal. Calcd for $C_{20}H_{27}NO_5$ (361.44): C, 66.46; H, 7.53; N, 3.88. Found: C, 66.51 H, 7.61 N, 4.05. **(±)-15a**: ^{1}H NMR (400 MHz) δ 7.41−7.34 (m, 3 H), 7.35−7.31 (m, 2 H), 5.44 (s, 1 H), 5.16 (q, J = 3.3, 1 H), 4.51 (t, J = 10.4, 1 H), 4.13 (dd, J = 10.5, 5.6, 1 H), 3.21 (dd, J = 12.8, 3.3, 1 H), 3.15 (dtd, J_d = 10.0, 3.0, J_t = 5.0, 1 H), 2.30−2.20 (m, 2 H), 2.06 (s, 3 H) 2.01 (s, 3 H) 1.96−1.89 (m, 1 H,), 1.85 (dt, J_d = 15.8, J_t = 4.4, 1 H), 1.78 (s, 3 H), 1.47 (s, 3 H); ^{13}C NMR (100 MHz) δ 171.43, 170.20, 169.64, 139.42, 129.15, 128.94, 127.80, 69.09, 65.03, 57.07, 42.11, 38.68, 32.52, 26.74, 24.31, 21.40, 20.96, 18.84; IR ($CHCl_3$) 3421, 2957, 2258, 2250, 1732, 1678, 1504, 1380, 1369, 1263, 1034; MS (FAB) 362 (M^+ + H, 27), 119 (100); TLC R_f 0.22 (EtOAc/hexane, 2/1); exact mass calcd for $C_{20}H_{27}NO_5$ + H 362.1967, found 362.1961 (FAB).

(1*R,6*R**,7*S**,8*R**)-3-Aza-1-butoxy-7-methyl-2,4-dioxa-8-phenyltricyclo[4.3.1.0^{3,7}]decane ((±)-13b).** A solution of nitronate (±)-**12b** (0.200 g, 0.66 mmol) dissolved in benzene (10 mL) was added to a suspension of $NaHCO_3$ (0.388 g, 4.61 mmol, 7.0 equiv) in benzene (56 mL). The resulting reaction mixture was heated to reflux for 11 h. After being cooled to rt, the mixture was concentrated in vacuo (0.5 Torr) to afford nitroso acetal (±)-**13b** as a white solid: ^{1}H NMR (400 MHz, C_6D_6) δ 7.20−7.15 (m, 3 H), 7.08−7.04 (m, 2 H), 3.88−3.85 (m, 1 H), 3.66 (dt, J_d = 9.0, J_t = 6.6, 1 H), 3.64 (d, J = 7.1, 1 H), 3.49 (dt, J_d = 9.0, J_t = 6.6, 1 H), 2.89 (dd, J = 11.5, 6.8, 1 H), 2.13−2.07 (m, 1 H), 1.93−1.80 (m, 4 H), 1.54−1.47 (m, 2 H), 1.36−1.27 (m, 2 H), 0.81 (t, J = 7.6, 3 H), 0.64 (s, 3 H); ^{13}C NMR (100.6 MHz, C_6D_6) δ 143.85, 129.46, 128.74, 126.99, 96.66, 77.29, 68.98, 62.49, 43.56, 41.94, 41.20, 40.08, 32.50, 20.27, 19.53, 14.05.

[(1*R,2*S**,3*R**,5*R**)-5-Acetoxy-2-(acetylamino)-2-methyl-3-phenyl-cyclohexyl]methyl Acetate ((±)-11a) and [(1*R**,2*S**,3*R**,5*S**)-5-Acetoxy-2-(acetylamino)-2-methyl-3-phenylcyclohexyl]methyl Acetate ((±)-16a).** Following representative procedure V as described for the preparation of **14a**/**15a**, from a suspension of nitroso acetal (±)-**13b** (0.66 mmol) and *ca.* 1.0 g of Raney nickel in methanol (16 mL) was obtained, after acetylation, a light brown oil which was purified by silica gel column chromatography (hexane/EtOAc, 1/1) to afford 0.038 g of **11a**, 0.028 g of a mixture of triacetates **16a** and **11a**, and 0.094 g of analytically pure **16a**, for a combined yield of 0.160 g (68%) and an overall diastereomeric ratio of 1.8:1 (**16a**/**11a**). The ^{1}H NMR spectral data for the less polar triacetate were consistent with those previously reported for (±)-**11a** obtained through the hydrogenolysis of nitroso acetal (±)-**10a**. **(±)-16a**: ^{1}H NMR (400 MHz) δ 7.32−7.21 (m, 3 H), 7.15−7.14 (m, 2 H), 5.28 (s, 1 H), 5.23 (bt, J = 2.7, 1 H), 4.53 (dd, J = 11.5, 4.1, 1 H), 3.93 (dd, J = 11.5, 8.1, 1 H), 2.95 (dd, J = 13.9, 3.4, 1 H), 2.25 (dt, J_d = 14.7, J_t = 2.7, 1 H), 2.20−2.13 (m, 1 H), 2.08−1.96 (m, 7 H), 1.90−1.80 (m, 5 H), 1.48 (s, 3 H); ^{13}C NMR (100 MHz) δ 170.94, 170.34, 169.86, 139.73, 129.05, 128.09, 127.23, 68.49, 65.75, 57.17, 48.41, 42.15, 31.35, 29.47, 24.80, 24.13, 21.40, 21.01; IR (CCl_4) 3400, 2920, 1741, 1698, 1366, 1238, 1033; MS (70 eV) 361 (M^+, 2), 150 (100), 142 (100); TLC R_f 0.30 (EtOAc/hexane, 2/1). Anal. Calcd for $C_{20}H_{27}NO_5$ (361.44): C, 66.46; H, 7.53; N, 3.88. Found: C, 66.27; H, 7.68; N, 3.82.

(4*S*,6*S*)-3-Methyl-4-phenyl-6-[(1*S*,2*R*)-(2-phenylcyclohexyl)oxy]-6-(2-propenyl)-5,6-dihydro-4*H*-[1,2]oxazine *N*-Oxide ((+)-17a). Following representative procedure VI, a mixture of nitroalkene **5a**[12] (0.490 g, 3.00 mmol), $SnCl_4$ (0.70 mL, 6.00 mmol, 2.0 equiv), and (+)-**4a** (0.870 g, 3.60 mmol, 1.2 equiv) in CH_2Cl_2 (23 mL) was stirred for 10 min at −74 °C and then quenched by the addition of a methanolic solution of triethylamine (52 mL, 0.5 M). The clear, cold (−75 °C) mixture was poured into a separatory funnel containing H_2O (50 mL) and CH_2Cl_2 (250 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 200 mL). The combined organic extracts were dried (Na_2SO_4), filtered through a compressed pad of Celite, and concentrated in vacuo. The resulting crude product was purified by silica gel column chromatography (hexane/EtOAc, 4/1) to give 1.19 g (98%) of (+)-**17a** as white crystals. Analytically pure (+)-**17a** (1.13 g, 93%) was obtained after recrystallization from hexane/CH_2Cl_2: mp 137−138 °C (hexane/CH_2Cl_2); ^{1}H NMR (400 MHz) δ 7.40−7.10 (m, 8 H), 6.90−6.84 (m, 2 H), 5.78 (ddt, J_d = 17.2, 10.4, J_t =7.1, 1 H), 5.13−5.02 (m, 2 H), 4.16 (dt, J_d = 4.0, J_t =10.0, 1 H), 2.74−2.67 (m, 1 H), 2.66−2.57 (m, 3 H), 2.46−2.38 (m, 1 H), 1.92 (dd, J = 13.6, 6.4, 1 H), 1.88−1.70 (m, 3 H), 1.68−1.42 (m, 4 H), 1.40−1.28 (m, 4 H); ^{13}C NMR (100 MHz) δ 145.01, 139.73, 131.72, 128.83, 128.37, 128.07, 127.71, 127.34, 126.19, 122.30, 119.50, 104.10, 75.84, 51.71, 43.55, 39.75, 36.85, 35.16, 34.25, 25.74, 24.82, 17.94; IR (CCl_4) 3029, 2934, 2859, 1613, 1494, 1455, 1278, 1238, 1130, 1078; MS (CI, CH_4) 406 (M^+ + 1, 12), 159 (100); TLC R_f 0.30 (hexane/EtOAc, 2/1); $[\alpha]^{22}_D$ +284.5° ($CHCl_3$, c = 1.10). Anal. Calcd for $C_{26}H_{31}NO_3$ (405.54): C, 77.01; H, 7.71; N, 3.46. Found: C, 77.01; H, 7.79; N, 3.29.

(4*R,6*S**)-3-Methyl-4-phenyl-6-[(1*S**,2*R**)-(2-phenylcyclohexyl)oxy]-6-(2-propenyl)-5,6-dihydro-4*H*-[1,2]-oxazine *N*-Oxide ((±)-18a).** Following representative procedure VII, a solution of MAD (1.04 mmol, 1.3 equiv) in toluene (3.5 mL) was added over a 20 h period, via syringe pump, to a cold (−67 °C), stirred solution of nitroalkene **5a**[12] (0.131 g, 0.80 mmol, 1.0 equiv) and vinyl ether (±)-**4a** (0.252 g, 1.04 mmol, 1.3 equiv) in toluene. The resulting yellow-green reaction mixture was stirred for an additional hour at −67 °C and then was quenched with methanol (5 mL) and poured into a mixture of CH_2Cl_2 (400 mL) and H_2O (100 mL). The aqueous layer was extracted with washed with CH_2Cl_2 (2 × 200 mL). The combined organic phase was dried over Na_2SO_4, filtered through a compressed pad of Celite, and concentrated in vacuo to afford a yellow oil. The crude residue was purified by silica gel column chromatography (hexane/EtOAc, 4/1) to afford a diastereomeric mixture (**17a**/**18a**/**18a′**, 1/40.7/3.8, as determined by ^{1}H NMR integration) of nitronates **17a**/**18a**/**18a′** in 55% yield. The ^{1}H NMR spectrum of nitronate (±)-**17a** were consistent with those previously reported for (+)-**17a** (obtained through a tin(IV) chloride promoted cycloaddition of nitroalk-

ene **5a** and vinyl ether (+)-**4a**. Recrystallization of the diastereomeric mixture (hexane/CH_2Cl_2/Et_2O) afforded nitronate (±)-**18a** in analytically pure form and in 48% yield: mp 124−125 °C (hexane/CH_2Cl_2/Et_2O); ^{1}H NMR (400 MHz) δ 7.46−7.22 (m, 5 H), 7.12−7.05 (m, 3 H), 6.68−6.60 (m, 2 H), 5.10−4.89 (m, 1 H), 4.81 (d, J = 8.8, 1 H), 4.72 (d, J = 16.8, 1 H), 3.76−3.64 (m, 2 H), 2.60−2.50 (m, 1 H), 2.28 (dd, J = 14.8, 6.4, 1 H), 2.24−2.15 (m, 1 H), 2.10 (dd, J = 14.0, 8.8, 1 H), 2.04 (s, 3 H), 1.94−1.58 (m, 5 H), 1.54−1.22 (m, 4 H); ^{13}C NMR (100 MHz) δ 143.73, 141.64, 131.38, 128.87, 128.23, 127.57, 126.80, 125.98, 122.02, 118.82, 105.72, 76.97, 50.30, 41.44, 38.59, 35.64, 34.69, 31.42, 25.75, 25.08, 18.38; IR (CCl_4) 3082, 2933, 1615, 1494, 1451, 1289, 1253, 1137, 1074, 1004; MS (CI, CH_4) 406 (M^+ + 1, 15), 159 (100); TLC R_f hexane/EtOAc, 2/1). Anal. Calcd for $C_{26}H_{31}NO_3$ (405.54): C, 77.01; H, 7.71; N, 3.46. Found: C, 76.77; H, 7.64; N, 3.46.

[4 + 2] Cycloaddition of 7a and (±)-6a Promoted by Ti(O-*i*-Pr)$_2$Cl$_2$. (4*S,6*S**)-3-Methyl-4-phenyl-6-[(1*S**,2*R**)-(2-phenylcyclohexyl)oxy]-6-(2-propenyl)-5,6-dihydro-4*H*-[1,2]oxazine *N*-Oxide ((±)-17a).** A freshly prepared solution of Ti(O-*i*-Pr)$_2$Cl$_2$ (0.48 mmol, 2.4 equiv) in CH_2Cl_2 (0.3 mL) was slowly added to a cold (−74 °C) solution of **5a**[12] (0.033 g, 0.2 mmol, 1 equiv) in CH_2Cl_2 (1 mL), and the resulting solution was allowed to stir for 15 min. Subsequently, (±)-**4a** (0.063 g, 0.26 mmol, 1.3 equiv) in CH_2Cl_2 (0.5 mL) was added. The reaction mixture was stirred for 30 min at −74 °C and then quenched by addition of a methanolic solution of triethylamine (0.5 M, 3 mL). The mixture was diluted with CH_2Cl_2 (250 mL), washed with H_2O (50 mL), dried over Na_2SO_4, filtered through a compressed pad of celite, and concentrated in vacuo. ^{1}H NMR of the crude product revealed the presence of unreacted nitroalkene **5a** (20%). Purification of the crude mixture by silica gel column chromatography (hexane/EtOAc, 4/1) afforded 0.042 g (52%) of a diastereomeric mixture of nitronates **17a**/**18a**′ (**17a**/**18a**′, 8.8/1). The ^{1}H NMR data for the major diastereomer were consistent with those reported for (+)-**17a** obtained through the $SnCl_4$-promoted cycloaddition of **5a** and (+)-**4a**.

(1*R*,6*R*,7*S*,8*S*)-3-Aza-7-methyl-2,4-dioxa-8-phenyl-1-[(1*S*,2*R*)-(2-phenylcyclohexyl)oxy]tricyclo[4.3.1.0^{3,7}]-decane ((+)-19a). A 250-mL, round-bottom flask equipped with magnetic stir bar and a condenser was charged with K_2CO_3 (1.28 g, 9.10 mmol, 7.0 equiv). Potassium carbonate was dried in the reaction apparatus in vacuo (200 °C, 0.1 Torr, 10 min). The apparatus was allowed to cool to room temperature, and K_2CO_3 was suspended in 90 mL of toluene. A solution of the nitronate (+)-**17a** (0.527 g, 1.30 mmol, 1.0 equiv) in toluene (40 mL) was then added, and the resulting mixture was refluxed for 26 h. The grey-blue reaction mixture was cooled to room temperature, filtered through a glass-sintered (medium frit) funnel, and concentrated in the presence of a small amount of fresh K_2CO_3. The crude product was purified by column chromatography on Activity III basic alumina (hexane/TBME, 2/1) to give 0.395 g (75%) of (+)-**19a** as a white solid: mp 142−144 °C; ^{1}H NMR (400 MHz, C_6D_6) δ 7.20−6.70 (m, 10 H), 3.79 (dt, J_d = 4.3, J_t = 10.1, 1 H), 3.68−3.57 (m, 2 H), 3.20 (dd, J = 12.0, 6.0, 1 H), 2.70−2.62 (m, 1 H), 2.54 (ddd, J = 13.0, 9.8, 3.4, 1 H), 2.10 (dt, J_d = 3.5, J_t = 12.4, 1 H), 1.96 (dd, J = 13.6, 10.4, 1 H), 1.82−1.70 (m, 3 H), 1.66−1.55 (m, 2 H), 1.52−1.36 (m, 2 H), 1.30−1.16 (m, 1 H), 1.14−1.04 (m, 1 H), 0.61 (s, 3 H), 0.48 (dd, J = 12.8, 6.0, 1 H); ^{13}C NMR (100 MHz, C_6D_6) δ 144.86, 142.73, 128.78, 128.69, 128.64, 128.00, 126.93, 126.25, 96.69, 78.94, 76.51, 69.27, 51.44, 44.20, 43.30, 38.62, 37.59, 36.27, 32.88, 26.12, 25.39, 20.31; IR (CCl_4) 3031, 2934, 2858, 1496, 1450, 1351, 1176, 1122, 1093, 1040, 1026; MS (FAB) 406 (M^+ + 1, 12), 154 (100); TLC R_f 0.40 (hexane/EtOAc, 2/1); $[\alpha]^{23}_D$ +103.7° (CH_3OH, c = 1.010). Anal. Calcd for $C_{26}H_{31}NO_3$ (405.54): C, 77.01; H, 7.71; N, 3.46. Found: C, 77.09; H, 7.90; N, 3.41.

(1*R,6*R**,7*S**,8*S**)-3-Aza-7-methyl-2,4-dioxa-8-phenyl-1-[(1*S*,2*R*)-(2-phenylcyclohexyl)oxy]tricyclo[4.3.1.0^{3,7}]-decane ((±)-19a).** A 1-neck, 250-mL, round-bottom flask equipped with magnetic stir bar and a condenser was charged with $NaHCO_3$ (0.76 g, 9.1 mmol, 7 equiv), 90 mL of toluene, and a solution of the nitronate **17a** (0.53 g, 1.3 mmol) in toluene (40 mL). The resulting mixture was refluxed for 30 h and subsequentely cooled to room temperature, and the reaction mixture was filtered through a glass-sintered (medium frit) funnel and concentrated in vacuo, in the presence of a small amount of fresh $NaHCO_3$. The crude product was purified by column chromatography on basic alumina Activity III (hexane/EtOAc, 1/2) to give 0.298 g (76%) of (±)-**19a** as a white solid. A suitable crystal for X-ray analysis was obtained by diffusion crystallization in EtOAc/pentane: mp 138−139 °C; ^{1}H NMR (400 MHz) δ 7.19−6.88 (m, 8 H), 6.81−6.76 (m, 2 H), 3.79 (dt, J_d = 4.3, J_t = 10.2, 1 H), 3.68−3.57 (m, 2 H), 3.20 (dd, J = 12.0, 6.0, 1 H), 2.70−2.62 (m, 1 H), 2.58−2.50 (m, 1 H), 2.10 (dt, J_d = 3.5, J_t = 12.8, 1 H), 1.97 (dd, J = 13.8, 10.2, 1 H), 1.82−1.70 (m, 3 H), 1.66−1.55 (m, 2 H), 1.52−1.36 (m, 2 H), 1.30−1.16 (m, 1 H), 1.14−1.04 (m, 1 H), 0.61 (s, 3 H), 0.49 (dd, J = 13.2, 6.0, 1 H); ^{13}C NMR (100 MHz) δ 144.86, 142.74, 128.77, 128.68, 128.64, 128.00, 126.91, 126.24, 96.68, 78.94, 76.51, 69.26, 51.44, 44.21, 43.31, 38.62, 37.61, 36.27, 32.89, 26.12, 25.39, 20.31; IR (KBr) 3028, 2977, 2926, 2856, 1494, 1459, 1383, 1344, 1326, 1321, 1256, 1168, 1122, 1094, 1019, 796, 754; MS (FAB) 406 (M^+ + 1, 19), 154 (100); TLC R_f 0.40 (hexane/EtOAc, 2/1). Anal. Calcd for $C_{26}H_{31}NO_3$ (405.54): C, 77.01; H, 7.71; N, 3.46. Found: C, 76.93; H, 7.48; N, 3.64.

Hydrogenation/Acetylation of Nitroso Acetal (±)-19a. [(1*R,2*S**,3*S**,5*S**)-5-Acetoxy-2-(acetylamino)-2-methyl-3-phenylcyclohexyl]methyl Acetate ((±)-14a) and [(1*R**,2*S**,3*S**,5*R**)-5-Acetoxy-2-(acetylamino)-2-methyl-3-phenylcyclohexyl]methyl Acetate ((±)-15a).** Following representative procedure V, from a suspension of nitroso acetal (±)-**19a** (0.390 g, 0.96 mmol) and *ca*. 1.2 g of Raney nickel in methanol (33 mL) was obtained, after acetylation, a yellow oil which was purified by silica gel column chromatography (hexane/EtOAc, 1/2) to afford 0.298 g (86%) of a mixture of triacetates (±)-**14a** and (±)-**15a** as a 1.8/1 (**14a**/**15a**) ratio of diastereomers (determined by ^{1}H NMR integration) along with 0.212 g (61%) of acetylated chiral auxyliary. The ^{1}H NMR data for the triacetates were consistent with those reported for (±)-**14a** and (±)-**15a** obtained through the analogous reaction sequence from nitroso acetal (±)-**13a**.

[(1*R*,2*S*,3*S*)-2-(Acetylamino)-2-methyl-5-oxo-3-phenylcyclohexyl]methyl Acetate ((−)-20). A solution of nitroso acetal (+)-**19a** (0.434 g, 1.07 mmol) in a 0.002 M methanolic solution of K_2CO_3 (48 mL) was added to a suspension of 0.675 g of Raney nickel (prewashed with methanol and dried under stream of nitrogen, rt, 1 atm). The reaction mixture was stirred for 40 min under 1 atm of hydrogen at room temperature and then filtered through a compressed pad of Celite. The catalyst was washed with methanol. The solvent was removed in vacuo, and the residue was dissolved in pyridine (14 mL) and treated with acetic anhydride (14 mL). The resulting reaction mixture was stirred for 6 h at room temperature. Pyridine and acetic anhydride were removed by bulb-to-bulb distillation (40 °C, 0.1 Torr), and the residual yellow oil was purified by silica gel column chromatography (hexane/EtOAc, 1/1) to give 0.292 g (86%) of ketone (−)-**20** in 99% enantiomeric excess (by chiral HPLC): ^{1}H NMR (400 MHz) δ 7.42−7.25 (m, 3 H), 7.20−7.15 (m, 2 H), 5.71 (bs, 1 H), 4.31 (dd, J = 11.4, 4.2, 1 H), 4.07 (dd, J = 11.4, 6.2, 1 H), 3.99 (dd, J = 11.4, 4.6, 1 H), 2.97 (dd, J = 16.0, 8.8, 1 H), 2.90−2.83 (m, 1 H), 2.79 (dd, J = 16.6, 11.8, 1 H), 2.66−2.54 (m, 2 H), 2.05 (s, 3 H), 1.95 (s, 3 H), 1.40 (s, 3 H); ^{13}C NMR (100 MHz) δ 209.47, 170.54, 170.18, 138.55, 128.92, 128.55, 127.60, 64.09, 57.12, 44.80, 42.33, 40.42, 40.09, 24.23, 21.57, 20.74; IR (CCl_4) 3425, 3032, 1736, 1719, 1510, 1369, 1232; MS (CI, CH_4) 318 (M^+ + 1, 22), 258 (100); TLC R_f 0.19 (hexane/EtOAc, 1/2); $[\alpha]^{23}_D$ −48.66° ($CHCl_3$, c = 1.695). Anal. Calcd for $C_{18}H_{23}NO_4$ (317.38): C, 68.12; H, 7.30; N, 4.41. Found: C, 67.97; H, 7.41; N, 4.27.

(1*R,4*S**,5*S**,8*R**)-8-(Acetoxymethyl)-*N*-acetyl-3-aza-2-oxa-5-phenyl-1-[(1*R**,2*S**)-(2-phenylcyclohexyl)oxy]-bicyclo[2.2.2]octane ((±)-21).** A solution of nitroso acetal (±)-**19a** (0.171 g, 0.42 mmol) in methanol (16 mL) was added to a suspension of 0.166 g of Raney nickel (prewashed with methanol and dried under stream of nitrogen, rt, 1 atm). The reaction mixture was stirred for 100 min under 1 atm of hydrogen at room temperature and then filtered through a plug of Celite. The catalyst was washed with methanol (5 ×

20 mL). The solvent was removed in vacuo. The crude product was dissolved in pyridine (5.5 mL) and treated with acetic anhydride (5.5 mL). The resulting reaction mixture was stirred for 6 h at room temperature. Pyridine and acetic anhydride were removed by bulb-to-bulb distillation (30 °C, 0.1 Torr), and the residual yellow oil was purified by column chromatography on Activity III neutral alumina (hexane/EtOAc, 3/1) to afford 0.114 g (55%) of (±)-**21**, as a white solid. Diacetate (±)-**21** (0.108 g, 42%) was obtained in analytically pure form after two recrystallizations from hexane/CH_2Cl_2: mp 172−173 °C (hexane/CH_2Cl_2); ^{1}H NMR (400 MHz) δ 7.30−7.20 (m, 7 H), 7.15−7.10 (m, 1 H), 6.96−6.90 (m, 2 H), 4.15 (dd, J = 10.8, 4.8, 1 H), 4.00 (dd, J = 10.6, 9.4, 1 H), 3.69 (dt, J_d = 4.4, J_t = 10.4, 1 H), 3.53 (dd, J = 11.2, 3.6, 1 H), 2.57 (ddd, J = 12.4, 10.2, 3.4, 1 H), 2.25−2.16 (m, 1 H), 2.06 (s, 3 H), 1.97 (s, 3 H), 2.02−1.64 (m, 8 H), 1.50 (s, 3 H), 1.58−1.46 (m, 1 H), 1.44−1.24 (m, 2 H), 0.69 (dd, J = 14.4, 3.6, 1 H); ^{13}C NMR (100 MHz) δ 173.73, 170.82, 143.62, 138.52, 128.48, 128.36, 128.05, 127.86, 126.93, 126.40, 104.96, 77.42, 65.95, 61.93, 50.51, 46.52, 37.72, 35.63, 35.44, 32.12 31.38, 25.58, 25.17, 22.96, 22.59, 20.78; IR ($CHCl_3$) 3030, 3009, 1736, 1732, 1656, 1450, 1384, 1234; MS (FAB) 493 (M^+ + 2, 29), 492 (86), 154 (100); TLC R_f 0.69 (hexane/EtOAc, 2/1). Anal. Calcd for $C_{30}H_{37}NO_5$ (491.63): C, 73.29; H, 7.59; N, 2.85. Found: C, 73.55; H, 7.61; N, 2.93.

6-[(1*R,2*S**)-(2-(1-Methyl-1-phenylethyl)cyclohexyl)-oxy]-4-phenyl-6-(2-propenyl)-5,6-dihydro-4*H*-[1,2]-oxazine *N*-Oxide (25dc).** Following representative procedure VI, a mixture of **5d**[12] (0.191 g, 1.28 mmol), $SnCl_4$ (0.30 mL, 2.56 mmol, 2.0 equiv), and (±)-**4c** (0.555 g, 1.92 mmol, 1.5 equiv) in toluene (11 mL) was stirred for 15 min at −74 °C and then quenched by the addition of a methanolic solution of triethylamine (20 mL, 0.5 M). The cold (−74 °C) mixture was poured into a mixture of H_2O (150 mL) and TBME (500 mL). The aqueous layer was back-extracted with TBME (3 × 150 mL). The combined organic phase was dried (Na_2SO_4), filtered through a compressed pad of Celite, and concentrated in vacuo. Purification of the crude product by silica gel column chromatography (hexane/EtOAc, 9/1) afforded 0.308 g (55.5%) of nitronate **25dca** as a pale yellow foam and 0.159 g (28.7%) of analytically pure nitronate **25dcb** as a white foam. **25dca**: ^{1}H NMR (400 MHz, C_6D_6) δ 7.75−7.68 (m, 2 H), 7.38−6.88 (m, 6 H), 6.72−6.64 (m, 2 H), 5.93 (d, J = 2.4, 1 H), 5.55 (ddt, J_d = 16.8, 10.0, J_t = 7.2, 1 H), 4.91 (dd, J = 10.0, 1.6, 1 H), 4.81 (dd, J = 17.2, 1.6, 1 H), 4.36−4.28 (m, 1 H), 3.73 (ddd, J = 12.2, 6.9, 2.8, 1 H), 2.40−2.33 (m, 1 H), 2.32−2.16 (m, 2 H), 1.88 (ddd, J = 13.2, 6.9, 0.7, 1 H), 1.78−1.38 (m, 15 H); ^{13}C NMR (100 MHz, C_6D_6) δ 150.48, 140.61, 131.58, 129.03, 128.35, 127.86, 127.45, 127.07, 125.82, 119.44, 111.86, 104.64, 69.74, 48.71, 41.11, 39.79, 37.76, 36.76, 29.76, 28.45, 28.09, 23.13, 22.61, 20.21; IR (CCl_4) 3088, 2936, 2933, 2866, 1625, 1497, 1454, 1319, 1234, 1106, 1002; MS (CI, CH_4) 434 (M^+ + 1, 6), 105 (100); TLC R_f 0.72 (hexane/EtOAc, 3/1); exact mass calcd for C_{28} H_{35} NO_3 + H 434.2692, found 434.2695. **25dcb**: ^{1}H NMR (400 MHz, C_6D_6) δ 7.30−6.80 (m, 10 H), 5.99 (d, J = 2.9, 1 H), 5.80−5.66 (m, 1 H), 5.04−4.90 (m, 2 H), 3.77 (dt, J_d = 4.0, J_t = 9.2, 1 H), 3.29 (ddd, J = 12.0, 6.8, 3.1, 1 H), 2.86−2.75 (m, 1 H), 2.67 (dd, J = 14.2, 5.8, 1 H), 2.10−1.94 (m, 2 H), 1.74−1.44 (m, 5 H), 1.41−1.09 (m, 9 H), 0.98−0.88 (m, 1 H); ^{13}C NMR (100 MHz, C_6D_6) δ 152.74, 141.15, 132.25, 129.01, 128.10, 127.93, 127.37, 125.68, 125.33, 119.40, 111.53, 105.35, 75.00, 51.63, 40.01, 39.36, 37.28, 36.35, 34.04, 29.77, 27.08, 25.98, 24.68, 24.53; IR (CCl_4) 3087, 2930, 1626, 1496, 1454, 1235, 1111, 1096, 1006; MS (FAB) 434 (M^+ + 1, 19), 105 (100); TLC R_f 0.54 (hexane/EtOAc, 3/1). Anal. Calcd for $C_{28}H_{35}NO_3$ (433.60): C, 77.56; H, 8.14 N, 3.23. Found: C, 77.54; H, 8.42 N, 2.98.

(4*S,6*S**)-3-Chloro-4-(4-methoxyphenyl)-6-[(1*R**,2*S**)-(2-phenyl-cyclohexyl)oxy]-6-(2-propenyl)-5,6-dihydro-4*H*-[1,2]oxazine *N*-Oxide ((±)-27).** Following representative procedure V as described for the preparation of **25dc**, from a mixture of nitroalkene **26**[21b] (0.253 g, 1.28 mmol), $SnCl_4$ (0.30 mL, 2.56 mmol, 2.0 equiv), and (±)-**4a** (0.419 g, 1.73 mmol, 1.35 equiv) in toluene (14 mL) was obtained a yellow solid which was purified by silica gel column chromatography (hexane/EtOAc, 4/1) followed by recrystallization from hexane/CH_2Cl_2 to afford 0.457 g (78%) of (±)-**27** as a pale yellow solid: mp 140 °C (hexane/CH_2Cl_2); ^{1}H NMR (400 MHz) δ 7.40−7.17 (m, 5 H), 6.85−6.78 (m, 4 H), 5.76 (ddt, J_d = 17.0, 10.2, J_t = 7.2, 1 H), 5.16−5.04 (m, 2 H), 4.15 (dt, J_d = 4.0, J_t = 10.0, 1 H), 3.77 (s, 3 H), 2.93 (dd, J = 12.4, 6.0, 1 H), 2.68−2.57 (m, 3 H), 2.44−2.36 (m, 1 H), 2.05 (dd, J = 13.8, 6.2, 1 H), 1.92−1.71 (m, 4 H), 1.70−1.24 (m, 4 H); ^{13}C NMR (100 MHz) δ 159.01, 144.30, 131.21, 130.27, 129.16, 128.70, 127.29, 126.57, 120.11, 119.96, 114.05, 105.23, 76.42, 55.18, 51.54, 42.89, 41.35, 38.68, 34.88, 34.02, 25.61, 24.73; IR (CCl_4) 3020, 2936, 1597, 1514, 1252, 1177, 1034, 1004; MS (CI, CH_4) 456 (M^+ + 1, 10), 159 (100); TLC R_f 0.65 (hexane/EtOAc, 2/1). Anal. Calcd for $C_{26}H_{30}ClNO_4$ (455.98): C, 68.49; H, 6.63; N, 3.07; Cl, 7.78. Found: C, 68.64; H, 6.69; N, 2.93; Cl, 7.49.

[(1*R,6*S**,7*R**,8*S**)-3-Aza-7-chloro-8-(4-methoxyphenyl)-2,4-dioxa-1-[(1*R**,2*S**)-(2-phenylcyclohexyl)oxy]tricyclo-[4.3.1.0^{3,7}]decane ((±)-28).** A suspension of (±)-**27** (0.474 g, 1.04 mmol) and K_2CO_3 (0.288 g, 2.08 mmol, 2.0 equiv) in CH_3-CN (120 mL) was stirred for 79 h at 72−73 °C. The reaction mixture was cooled to room temperature, filtered through a glass-sintered (medium frit) funnel, and concentrated in vacuo in the presence of a small amount of fresh K_2CO_3. The crude product was purified by column chromatography on Activity II basic alumina (pentane/Et_2O, 1/1) to give 0.284 g (60%) of (±)-**28** as a white solid: mp 107−108 °C; ^{1}H NMR (400 MHz) δ 7.30−7.05 (m, 5 H), 7.02−6.95 (m, 2 H), 6.88−6.80 (m, 2 H), 4.31 (dd, J = 6.4, 3.6, 1 H), 4.02 (d, J = 6.4, 1 H), 3.80 (s, 3 H), 3.69 (dt, J_d = 4.3, J_t = 10.3, 1 H), 3.60 (dd, J = 12.0, 6.0, 1 H), 2.78 (dd, J = 10.0, 4.0, 1 H), 2.54−2.44 (m, 1 H), 2.32−2.15 (m, 3 H), 2.00−1.56 (m, 5 H), 1.52−1.22 (m, 3 H), 0.60 (dd, J = 13.0, 5.8, 1 H); ^{13}C NMR (100 MHz) δ 158.82, 143.91, 131.53, 129.89, 128.20, 127.76, 126.22, 113.67, 96.29, 95.07, 78.51, 77.38, 55.16, 50.64, 43.55, 42.86, 41.38, 37.33, 35.44, 31.92, 25.64, 25.01; IR (CCl_4) 3024, 2937, 2859, 1515, 1353, 1250, 1231, 1173; MS (FAB) 456 (M^+ + 1, 6), 154 (100); TLC R_f 0.30 (hexane/EtOAc, 3/1). Anal. Calcd for $C_{26}H_{30}ClNO_4$ (455.98): C, 68.49; H, 6.63; N, 3.07; Cl, 7.78. Found: C, 68.40; H, 6.67; N, 3.18; Cl, 7.82.

[(1*R,2*R**,3*S**)-2-(Acetylamino)-3-(4-methoxyphenyl)-5-oxocyclohexyl]methyl Acetate ((±)-29) and [(1*R**,-2*S**,3*S**)-2-(Acetylamino)-3-(4-methoxyphenyl)-5-oxocy-clohexyl]methyl Acetate ((±)-30).** A solution of nitroso acetal (±)-**28** (0.249 g, 0.54 mmol) in a 0.03 M methanolic solution of NaOH (55 mL) was added to a suspension of 0.822 g of Raney nickel (prewashed with methanol and dried under stream of nitrogen, rt, 1 atm). The reaction mixture was stirred for 45 min under 1 atm of hydrogen at room temperature, filtered through a plug of Celite, and concentrated. Acetylation of the crude residue by treatment with pyridine (10 mL) and acetic anhydride (10 mL) afforded a yellow oil which was purified by silica gel column chromatography (hexane/EtOAc, 1/1, 1/2, 1/3, 1/4). A second silica gel column chromatography ($CHCl_3$/MeOH, 15/1) provided 0.115 g (63%) of a diastereomeric mixture of ketones **29**/**30** (**29**/**30**, 1.1/1) in analytically pure form. Anal. Calcd for $C_{18}H_{23}NO_5$ (333.38): C, 64.85; H, 6.95; N, 4.20; Found: C, 64.84; H, 7.13; N, 4.20. The two diastereomeric products were separated by radial chromatography ($CHCl_3$/MeOH, 99/1) and characterized by spectroscopic methods. Ketone **29** was recrystallized from hexane/CH_2Cl_2/Et_2O. **(±)-29**: mp 122−124 °C (hexane/CH_2-Cl_2/Et_2O); ^{1}H NMR (400 MHz) δ 6.96 (d, J = 8.4, 2 H), 6.86 (d, J = 8.4, 2 H), 5.14 (d, J = 8.8, 1 H), 4.50 (dt, J_d = 4.7, J_t = 10.2, 1 H), 4.00−3.88 (m, 2 H), 3.72 (m, 3 H), 3.52−3.47 (m, 1 H), 2.82 (dd, J = 16.0, 6.8, 1 H), 2.68−2.56 (m, 2 H), 2.45 (dd, J = 15.2, 12.0, 1 H), 2.15−2.02 (m, 1 H), 1.98 (s, 3 H), 1.88 (s, 3 H); ^{13}C NMR (100 MHz) δ 209.25, 170.75, 169.61, 158.85, 130.92, 129.88, 114.01, 64.69, 55.22, 49.50, 44.51, 43.12, 42.96, 36.04, 23.28, 20.77; IR ($CHCl_3$) 3427, 3026, 2937, 1738, 1715, 1673, 1514, 1254; MS (CI, CH_4) 334 (M^+ + 1, 100); TLC R_f 0.40 ($CHCl_3$/MeOH, 15/1). **(±)-30**: ^{1}H NMR (400 MHz) δ 7.05 (d, J = 8.4, 2 H), 6.79 (d, J = 8.4, 2 H), 6.07 (d, J = 7.6, 1 H), 4.64−4.52 (m, 1 H), 4.15 (dd, J = 11.4, 4.2, 1 H), 3.97 (dd, J = 11.2, 5.6, 1 H), 3.72 (s, 3 H), 3.20−3.10 (m, 1 H), 2.72−2.62 (m, 2 H), 2.61-2.54 (m, 2 H), 2.52−2.41 (m, 1 H), 1.97 (s, 3 H), 1.77 (s, 3 H); ^{13}C NMR (100 MHz) δ 208.22, 171.00, 170.03, 158.66, 132.57, 128.08, 114.24, 63.66, 55.17, 51.92, 46.74,

43.98, 41.60, 36.48, 23.06, 20.80; IR ($CHCl_3$) 3436, 3026, 2961, 1736, 1731, 1720, 1673, 1514, 1372, 1252, 1036; MS (CI, CH_4) 334 ($M^+ + 1$, 56), 274 (100); TLC R_f 0.35 ($CHCl_3$/MeOH, 15/1).

(4*S,6*S**)-3-Bromo-4-phenyl-6-[(1*R**,2*S**)-(2-phenylcyclohexyl)oxy]-6-(2-propenyl)-5,6-dihydro-4*H*-[1,2]-oxazine *N*-Oxide ((±)-32).** Following representative procedure V as described for the preparation of **25dc**, from a mixture of nitroalkene **31**[30] (0.390 g, 1.71 mmol), $SnCl_4$ (0.40 mL, 3.42 mmol, 2.0 equiv), and (±)-**4a** (0.829 g, 3.42 mmol, 2.0 equiv), in toluene (15 mL) was obtained a pale yellow solid which was purified by column chromatography (hexane/EtOAc, 9/1) to afford 0.750 g (93%) of analytically pure (±)-**32** as a mixture of diastereomers (**32a**/**32b**, 19/1): mp 132 °C (hexane/EtOAc). Anal. Calcd for $C_{25}H_{28}BrNO_3$ (470.41): C, 63.83; H, 6.00; N, 2.98; Br, 16.99. Found: C, 63.89; H, 6.17; N, 2.89; Br, 16.97. **(±)-32a**: ^{1}H NMR (400 MHz) δ 7.40−7.05 (m, 8 H), 6.90−6.75 (m, 2 H), 5.69 (ddt, J_d = 17.2, 10.4, J_t = 7.1, 1 H), 5.10−4.97 (m, 2 H), 4.07 (dt, J_d = 4.3, J_t = 9.8, 1 H), 2.94 (dd, J = 12.0, 6.0, 1 H), 2.61−2.52 (m, 3 H), 2.36−2.29 (m, 1 H), 1.98 (dd, J = 14.0, 6.0, 1 H), 1.84−1.74 (m, 3 H), 1.72−1.64 (m, 1 H), 1.62−1.20 (m, 4 H); ^{13}C NMR (100 MHz) δ 144.29, 139.79, 131.22, 128.75, 128.64, 128.17, 127.70, 127.34, 126.60, 119.91, 111.07, 105.34, 76.45, 51.37, 43.72, 42.92, 38.74, 34.72, 33.83, 25.54, 24.63; IR ($CHCl_3$) 3019, 2936, 1595, 1584, 1494, 1455, 1234, 1120, 1078, 1004; MS (CI, CH_4) 472 ($M^+ + 2$, 3), 471 (1), 159 (100); TLC R_f 0.38 (hexane/EtOAc, 4/1).

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Supporting Information Available: General experimental as well as complete ^{1}H NMR, ^{13}C NMR, IR, MS, and microanalytical data for all characterized compounds, spectroscopic data for (±)-**33** and **25**, and a tabular listing of the fractional coordinates and thermal parameters for **11a** and (±)-**19a** (66 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from ACS; see any current masthead page for ordering information.

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