Tandem Cycloaddition Chemistry of Nitroalkenes: Probing the Remarkable Stereochemical Influence of the Lewis Acid†

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The influence of several Lewis acids on the stereochemical course of the [4 + 2] cycloaddition of nitroalkene **1** and chiral, nonracemic propenyl ether **8** has been examined. All of the Lewis acids examined favored *ul* relative diastereoselection ("exo" approach); $TiCl_4$, $TiBr_3$(O*i*-Pr), $SnCl_4$, and ATPh were the most selective. Within the titanium-based Lewis acids, it was found that increasing the halide-to-alkoxide ratio increased the degree of *ul* (relative) selectivity, as did switching from chloride to bromide. The internal diastereoselectivity was also dependent on the Lewis acid; most titanium isopropoxide−halides (bromide and chloride) and $SnCl_4$ were highly selective for (1,3-*lk*) approach, with the selectivity increasing with increasing halide content. Two aluminum-based Lewis acids (MAPh and ATPh) were selective for the opposite sense of internal diastereoselection. The high *lk* (relative) diastereoselectivity observed only with $TiCl_2$(O*i*-Pr)$_2$ is proposed to arise either from Coulombic stabilization of an endo approach or precomplexation of the vinyl ether to the Lewis acid. The switch in internal diastereoselectivity seen in the exo manifold is thought to arise from subtle changes in the steric nature of the Lewis acid−nitroalkene complex.

Introduction

The tandem [4 + 2]/[3 + 2] cycloaddition of nitroalkenes has emerged as a powerful method for the rapid and stereoselective construction of complex polyheterocyclic systems.[1] Of the four limiting permutations of this tandem sequence (Figure 1) the most extensively explored have been those utilizing the intermolecular [4 + 2] cycloaddition. A critical strategic feature in the intermolecular [4 + 2] cycloaddition with vinyl ethers is the ability of the Lewis acid to control the relative diastereoselectivity[2] of the reaction.[3] The ability to control the absolute configuration of the cycloadduct is allowed by the use of chiral nonracemic vinyl ethers.[4] Several total syntheses have relied on these two elements to selectively manipulate the stereochemical outcome of the tandem cycloaddition process.[5] Central to all issues of stereocontrol is the effect of the Lewis acid promoter (vide infra). From early studies using unactivated olefins as dienophiles, a small selection of efficient Lewis acids emerged. Although this small selection has admirably served synthetic needs, we thought it prudent to reexamine the reactivity and selectivity of a broader range of Lewis acids for two purposes: (1) to expand the repertoire of reagents that can be used in diverse synthetic endeavors, and (2) to formulate a clearer mechanistic understanding of the origin of stereocontrolling features.

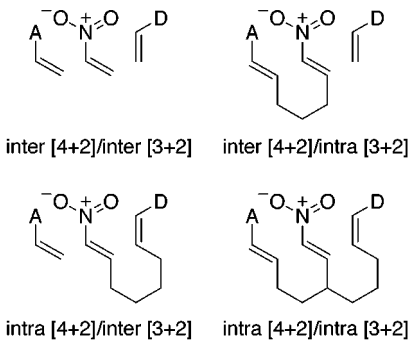

Figure 1. Family of tandem [4 + 2]/[3 + 2] cycloadditions (A = electron acceptor D = electron donor).

Background

Previous studies from these laboratories on the fused-mode tandem inter [4 + 2]/intra [3 + 2] cycloaddition[3,6] have demonstrated the ability of different Lewis acids to control the stereostructure of the nitroso acetal product. As shown in Scheme 1, [4 + 2]/[3 + 2] cycloaddition between nitroalkene **1** and chiral vinyl ether **2** promoted with methylaluminum bis(2,6-diphenylphenoxide) (MAPh) provided nitroso acetal **3a** (with a trans C(4a)−C(6)

† Tandem Inter [4 + 2]/Intra [3 + 2] Cycloaddition of Nitroalkenes. 23.

(1) Denmark, S. E.; Thorarensen, A. *Chem. Rev.* **1996**, *96*, 137.

(2) Helmchen, G. In *Stereoselective Synthesis, Methods of Organic Chemistry (Houben-Weyl)*; Edition E21a; Helmchen, G., Hoffmann, R., Mulzer, J., Schaumann, E., Eds.; Thieme: Stuttgart, 1995; Vol. 1, pp 1−74. This chapter uses the terms "simple" diastereoselectivity to describe the ratio of diastereomers with different relative configurations at the newly formed stereogenic centers, and "induced" diastereoselectivity to describe the ratio of diastereomers with the same relative configurations at the newly formed stereogenic centers (but, in this case, different relative to the preexisting stereogenic centers). We prefer the terms "relative" and "internal", respectively. Also, "external" diastereoselectivity (which is not relevant here) would refer to the absolute stereoselectivity imposed by an external chiral agent (such as a chiral Lewis acid).

(3) Denmark, S. E.; Schnute, M. E.; Senanayake, C. B. W. *J. Org. Chem.* **1993**, *58*, 1859.

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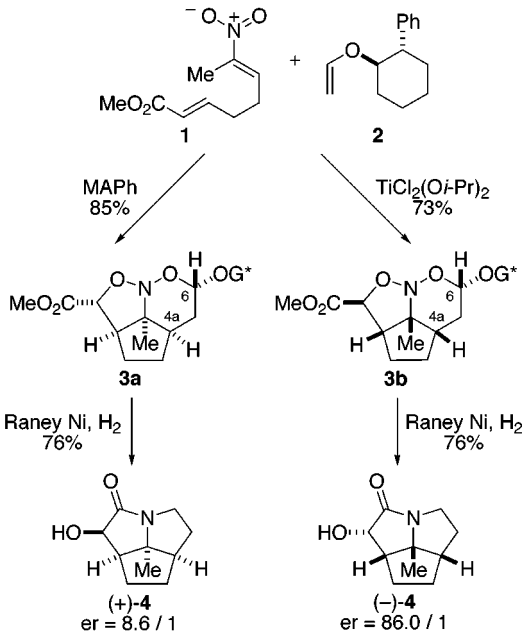
Scheme 1



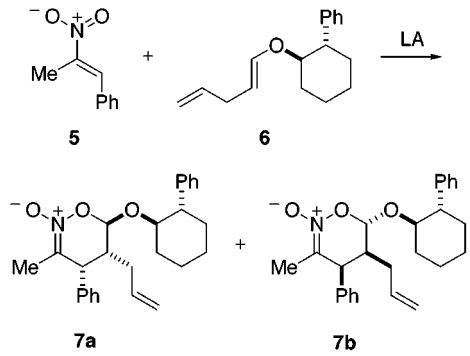
relationship), presumably via an "exo" approach of the *Si* face of **2** to **1**.

When $TiCl_2(O$*i*-$Pr)_2$ was employed as the Lewis acid, the major cycloadduct was cis nitroso acetal **3b**, which was interpreted as arising from an "endo" approach of the *Si* face of **2** to **1**. This switch in selectivity, which allowed lactams **4** of opposite absolute configuration to be produced from the same chiral nonracemic vinyl ether, was seen as a consequence of changing the face of the nitroalkene (**1**) which undergoes reaction while preserving the face of the dienophile (**2**) which reacts. The ability of a Lewis acid to control relative diastereoselectivity has been documented for a variety of [4 + 2] cycloadditions.[7]

Studies on the bridged-mode tandem inter [4 + 2]/intra [3 + 2] cycloaddition unveiled another dimension of stereocontrol (Table 1).[8] Whereas both $SnCl_4$ and MAPh provided trans (C(4a)−C(6)) nitroso acetals upon cycloaddition between **5** and **6**, they derived from reaction on the opposite faces of the dienophile. This switch in selectivity (which also allowed products of opposite absolute configuration to be produced with the same chiral nonracemic vinyl ether) was seen as a consequence of changing the face of the dienophile **6** which undergoes reaction while preserving the face of the nitroalkene **5** which reacts. The degree of stereocontrol of this mode was high and general for several nitroalkenes and vinyl ethers examined.

There are several examples of different Lewis acids causing a switch in the internal diastereoselectivities in [4 + 2] cycloadditions[9] and other reactions.[10] In all of these cases, the entity activated by the Lewis acid is the chiral substrate. These are fundamentally different from the example shown in Table 1, in which the activated species is the achiral nitroalkene **5**.

Table 1. Lewis Acid-Controlled π-Facial Selectivity



Lewis acid (equiv)	temp, °C	yield, %	**7a**/**7b**
MAPh (3)	−25	95	1/15
$SnCl_4$ (1)	−78	93	16/1

In view of the synthetic significance and mechanistic interest, we decided to systematically explore the ability of the Lewis acid to control the stereochemical outcome of the tandem [4 + 2]/[3 + 2] cycloaddition process. Nitroalkene **1** and propenyl ether **8** (Figure 2) were chosen as substrates; their high degree of stability to even harsh Lewis acids was expected to provide flexibility in the types of promoters to be tested. In addition, the methyl group of **8** could serve as a permanent stereochemical marker in the event a Lewis acid caused epimerization of the acetal center.

Stereochemical Nomenclature. Part 1. Product Configurations. A systematic nomenclature to describe the [4 + 2] cycloaddition is presented in Figure 2.[2,11] It is not necessary that one utilize this nomenclature to understand the results; however, a thorough understanding of the mechanistic ramifications requires a clear, concise method for describing all the stereochemical aspects of the [4 + 2] cycloaddition.

The first purpose (described here) served by this system is to provide for an unambiguous description of product configuration. As with most cycloadditions, there are several stereochemical elements, and thus many different possible products. There is then a need for clear nomenclature, based on a simple set of rules, to describe the relationship of the stereogenic centers in the product. The second purpose (described in Part 2 below) of this system is to define the reactive faces of the two substrates required by the configuration of the products. Finally, that configuration allows the formulation of a hypothetical arrangement of the two components in a stereodetermining transition structure.

The only possible products (assuming no epimerization of adducts or isomerization of starting materials) of cycloaddition between **1** and **8** are nitroso acetals **9a**−**d**. In the case of **9a**, the configuration of C(4a) is *S* and that of C(6) is *R*; thus, there is an unlike (*u*) relationship. The configuration of C(1′) of **9a** is the same as that of C(6); consequently, the 1,3-stereochemical relationship is like (*l*). The overall stereochemical designation for nitroso

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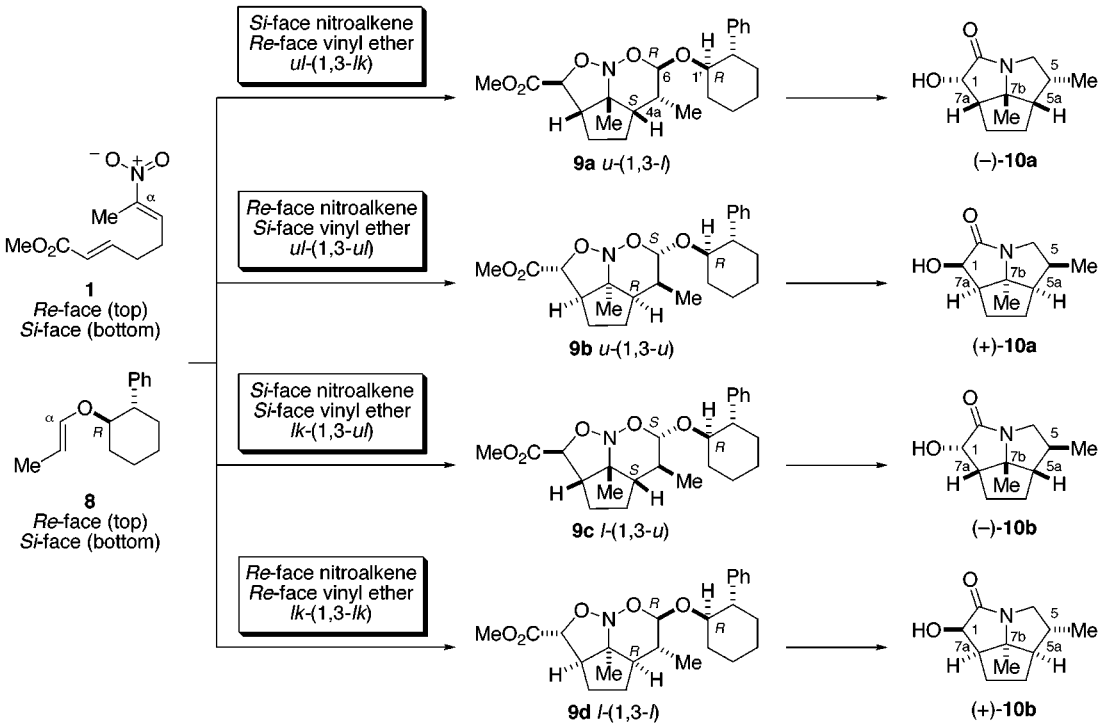


Figure 2. Stereochemical descriptors for the [4 + 2]/[3 + 2] cycloaddition.

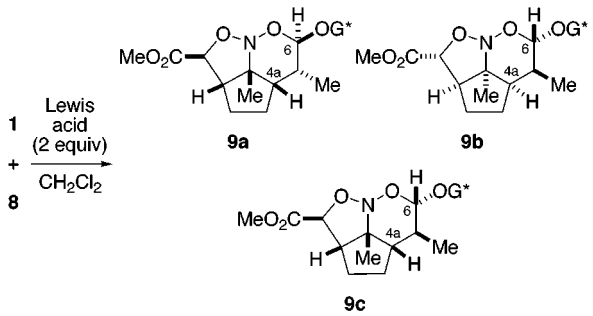
acetal **9a** is *u*-(1,3-*l*). All four cycloadducts are thus assigned unique, unambiguous designators.[12]

Results

General Aspects of [4 + 2]/[3 + 2] Cycloaddition. Tandem [4 + 2]/[3 + 2] cycloadditions of nitroalkene **1** and propenyl ether **8** were generally carried out at −78 °C in CH_2Cl_2 with 1.5−3 equiv of **8** and 2 equiv of Lewis acid.[3,6] In some cases, higher temperatures were required to effect cycloaddition. The overall yield and selectivity were often dependent on the order of addition of reagents; the best results were typically obtained by addition of Lewis acid last. After the [4 + 2] cycloaddition was complete, the Lewis acid was destroyed with either MeOH or a methanolic solution of NaOH. After aqueous workup, the crude nitronate was allowed to stand at room temperature for several hours to allow the intramolecular [3 + 2] cycloaddition to occur. Both the crude and purified mixtures of **9** were analyzed by ^{1}H NMR to determine the diastereomeric ratio of the nitroso acetals. Hydrogenolysis over Raney nickel afforded hydroxy lactams **10**, which were analyzed both by ^{1}H NMR and chiral stationary phase supercritical fluid chromatography (CSP-SFC).

Cycloadditions with Titanium-Based Lewis Acids. The results of cycloadditions of **1** and **8** promoted with several titanium(IV) halides are presented in Table 2. Each Lewis acid not only afforded products with differing selectivity (outlined below) but also promoted cycloaddition with varying degrees of reactivity; optimization of reaction conditions was required for each Lewis acid. Optimal conditions were found to be the addition of 2 equiv of the Lewis acid to a cold (−90 or −78 °C) solution of **1** and **8** in CH_2Cl_2. An exception was $TiCl_4$, which rapidly (<5 min) promoted both cycloaddition and destruction of the propenyl ether. For this reagent, the optimal procedure involved addition of 3 equiv of **8** in three equal portions every 15 to 20 min.[13] Titanium tetrabromide was found only to consume **8** without promoting cycloaddition. Both titanium trihalides were equally effective, affording cycloadduct **9** in good yield

Table 2. [4 + 2]/[3 + 2] Cycloadditions Promoted with Ti-Based Lewis Acids



Lewis acid	equiv **8**	temp, °C	time, h	yield[a] **9**, %	ratio[b] **9a**	**9b**	**9c**
$TiCl_4$[c]	3.0[d]	−78	1.0	86	25	1	
$TiCl_3(Oi\text{-}Pr)$	2.0	−78	1.1	95	17	1.3	1
$TiCl_2(Oi\text{-}Pr)_2$[e]	1.5	−90 → −78	2.5	86	2	1	24
$TiCl(Oi\text{-}Pr)_3$	2.0	−78 → rt	15.3	0			
$TiBr_4$[c]	1.5	−90 → −78	1.0	0			
$TiBr_3(Oi\text{-}Pr)$	2.0	−78	1.1	91	>25	1	
$TiBr_2(Oi\text{-}Pr)_2$	1.5	−78	2.0	82	7.7	1	7.9
$TiBr(Oi\text{-}Pr)_3$	3.5	−78 → 0	5.0	0			

[a] Isolated as a mixture of diastereomers. [b] Determined by ^{1}H NMR analysis. [c] One equivalent. [d] Added in 3 equal portions. [e] As reported previously.[3]

(12) In the event that epimerization or isomerization need be considered, stereochemical designators may be used to explicitly describe the C(4a)−C(5) and C(5)−C(6) relationships.

(13) Previous studies (ref 8) have shown that a substoichiometric amount of Lewis acid can promote nitroalkene cycloaddition in high yield. An attempt with 25 mol % of $TiCl_4$ provided the cycloadduct **9** with only 25% conversion.

(91−95%). Reactions with $TiBr_2(O$*i*-Pr$)_2$ were extremely capricious. Whereas 2 equiv of $TiBr_2(O$*i*-Pr$)_2$ promoted cycloaddition to about 85% conversion (based on nitroalkene), using either more or less Lewis acid caused the reaction to stall at lower conversion. Neither $TiCl(O$*i*-Pr$)_3$ nor $TiBr(O$*i*-Pr$)_3$ was an effective promoter. No change in the starting materials was observed at low temperatures; slow warming led only to destruction of **8** and no product formation. Attempts were also made with TiF_4 and $TiF_3(O$*i*-Pr), but these did not promote cycloaddition under any conditions.

In all cases, a greater halide-to-alkoxide proportion brought about an increase in both the relative and internal diastereoselectivity[2] (providing more of the *u*-(1,3-*l*) cycloadduct **9a**). With $TiCl_2(O$*i*-Pr$)_2$, the major (∼8/1) nitroso acetal **9c** was that with a cis (*l*) relationship between C(4a) and C(6); minor nitroso acetals **9a** and **9b** were produced in nearly equal amounts. Switching to $TiCl_3(O$*i*-Pr) caused a reversal in selectivity, favoring **9a** and **9b** over **9c** (18/1); the ratio of **9a** to **9b** also increased dramatically (from 2/1 for $TiCl_2(O$*i*-Pr$)_2$ to 13/1 for $TiCl_3(O$*i*-Pr)). Both of these trends continued with $TiCl_4$, which favored **9a** over **9b** by a wider margin (25/1), and afforded no detectable amount of **9c**. The same pattern was observed in the titanium bromide series. While $TiBr_2(O$*i*-Pr$)_2$ was only modestly selective for **9a**, $TiBr_3(O$*i*-Pr) was much more so (>25/1). Interestingly, the same trends noted by increasing the halide-to-alkoxide proportion (i.e. more **9a** relative to **9b**, and more **9a,b** relative to **9c**) were repeated upon switching from chloride to the corresponding bromide. Thus $TiBr_3(O$*i*-Pr) and $TiBr_2(O$*i*-Pr$)_2$ were much more selective than $TiCl_3(O$*i*-Pr) and $TiCl_2(O$*i*-Pr$)_2$, respectively.

Thus, two selectivity trends are evident which relate to the amount of [**9a** + **9b**] relative to **9c**, and the amount of **9a** relative to **9b**. Within each halide series (either bromide or chloride), increasing the halide-to-alkoxide ratio brought about an increase in both of these ratios. Likewise, switching from chloride to bromide (while maintaining the halide-to-alkoxide ratio) was also accompanied by an increase in both of these ratios.

Cycloadditions with Aluminum-Based Lewis Acids. Several aluminum-based Lewis acids were chosen to test their ability to promote [4 + 2] cycloaddition (Table 3); on the basis of previous results from these laboratories (vide supra), it was thought that the *u*-(1,3-*u*) nitroso acetal **9b** would be selectively produced. Two equivalents of Me_3Al, MAPh, and aluminum tris(2,6-diphenylphenoxide) (ATPh) promoted the cycloaddition, albeit at elevated reaction temperature (0 °C). Although an efficient promoter, Me_3Al was very unselective, modestly favoring nitroso acetal **9c**. Cycloaddition promoted with MAPh was more selective, providing **9b** with modest trans (*u*) selectivity (10/1) and *π*-facial (1,3-*u*) selectivity (∼6/1). The ATPh-promoted cycloaddition was found to be much more selective for the trans (*u*) cycloadducts (affording no detectable amount of **9c**), and with a slightly higher ratio of **9b** to **9a** (8/1). Two aluminum chlorides were examined, but found to be inadequate promoters. Even with a large excess of propenyl ether **8**, $EtAlCl_2$ provided cycloadduct **9** in only 30% conversion (all of **8** was consumed). Interestingly, the cycloadduct was produced in the same stereochemical sense as those from titanium halides.

Cycloadditions with Other Lewis Acids. To broaden the repertoire of available promoters, several other Lewis acids not based on titanium or aluminum were tested (Table 4). Tin tetrachloride, which has performed well in previous [4 + 2] nitroalkene cycloadditions,[1,8] provided **9a** in good yield with excellent selectivity. Although $Sc(OTf)_3$ did promote [4 + 2] cycloaddition, it did so with low selectivity. Both $ZnCl_2$ and BBr_3 provided cycloadduct **9** with only partial conversion. Zinc(II) chloride was unselective, while BBr_3 appeared to be slightly more selective; **9a** could clearly be identified (by ^{1}H NMR analysis) in the crude reaction mixture, but **9b** and **9c** could not. It was found that thermal [4 + 2] cycloaddition did occur without Lewis acid in refluxing xylenes, but the reaction was neither clean nor selective. Other Lewis acids employed that did not promote cycloaddition include $BF_3{\cdot}OEt_2$, TMSOTf, $ZrCp_2Cl_2$, and $SiCl_4$.

Table 3. [4 + 2]/[3 + 2] Cycloadditions Promoted with Al-Based Lewis Acids

Lewis acid	equiv **8**	temp, °C	time, h	yield[a] **9**, %	ratio[b] **9a**	**9b**	**9c**
MAPh	1.5	−78 → 0	1.5	82	1.5	8.2	1
ATPh	1.5	−78 → 0	1.5	91	1	8	
Me_3Al	1.2	−78 → 0	3.5	76	2	1	5
$EtAlCl_2$	2.8	−78	2	30[c]	5	1	
Et_2AlCl	1.4	−78 → rt	7	trace[c]		*d*	

[a] Isolated as a mixture of diastereomers. [b] Determined by ^{1}H NMR analysis. [c] Conversion based on ^{1}H NMR analysis. [d] Could not be determined.

Table 4. [4 + 2]/[3 + 2] Cycloadditions Promoted with Other Lewis Acids

Lewis acid	equiv **8**	temp, °C	time, h	yield[a] **9**, %	ratio[b] **9a**	**9b**	**9c**
$SnCl_4$	2	−78	0.3	95	>25	1	
$Sc(OTf)_3$	2.5	−78 → 0	4	75	4	1[c]	
$ZnCl_2$	1.6	−78 → rt	12	50[d]	1	1	1[c]
BBr_3	2	−78	5.5	33[d]	1[c]		
none	1.5	140[e]	21	100[d]		*f*	

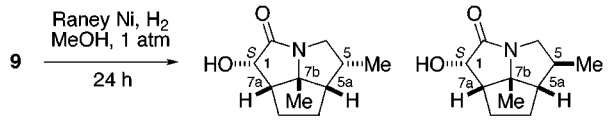
[a] Isolated as a mixture of diastereomers. [b] Determined by ^{1}H NMR analysis. [c] Several isomers present; ratios are approximate. [d] Conversion based on ^{1}H NMR analysis. [e] Xylenes used as solvent. [f] Could not be determined.

Hydrogenolyses of 9. Product ratios were also measured by transforming the nitroso acetals to the corresponding hydroxy lactams **10** (Table 5). This simplified the analysis by allowing for enantiomeric ratio (er[14]) determination by CSP-SFC.[15] Atmospheric pressure hydrogenation of nitroso acetals **9** over Raney nickel provided the hydroxy lactams **10a** and **10b** in good yield (along with recovered chiral auxiliary). All four compounds (i.e. each enantiomer of both diastereomers) were easily resolved, and the product ratios were in accord with the data presented in Tables 2−4 above. The most selective Lewis acid in the titanium series was $TiBr_3(O$*i*-Pr), which provided lactam (−)-**10a** in excellent dr (>99/1) and er (75.8/1). Because MAPh and ATPh pro-

(14) The enantiomeric ratio is simply the ratio of the major enantiomer to the minor, normalized to 1. The enantiomeric excess (% ee) can be calculated from the er by the equation % ee = (er − 1)/(er + 1) × 100. Because er is a direct measure of the relative rates of formation for two given products (and hence, the relative activation free energies leading to the respective transition structures) we believe it to be more useful than % ee when studying the stereochemical profile of a reaction. For a discussion of the relative merits of % ee and er, see Kagan, H. B. *Recl. Trav. Chim. Pays-Bas* **1995**, *114*, 203.

(15) Typical SFC conditions. Column: Chiralcel AD. Inlet pressure: 150 bar. Flow rate: 3 mL/min. Eluent composition: CO_2/MeOH (95/5). Detection wavelength: 220 nm. Retention times (min): (−)-**10b**, 3.18. (+)-**10b**, 3.56. (−)-**10a**, 4.04. (+)-**10a**, 4.66.

Table 5. Hydrogenolyses of 9



Lewis acid	yield[a] **10**, %	ratio[b,c] **10a**/**10b**	er[b] **10a** 1*S*/1*R*	er[b] **10b** 1*S*/1*R*
$TiCl_4$	62	>99/1	44.3/1	*d*
$TiCl_3(Oi\text{-}Pr)$	74	24.6/1	30.0/1	*d*
$TiBr_3(Oi\text{-}Pr)$	66	>99/1	75.8/1	*d*
$TiBr_2(Oi\text{-}Pr)_2$	74	1.6/1	14.8/1	>99/1
MAPh	82	15.1/1	1/6.2	*d*
ATPh	78	>99/1	1/9.0	*d*
$SnCl_4$	78	>99/1	44.1/1	*d*
$Sc(OTf)_3$	68	9.2/1	3.7/1	1.6/1

[a] Isolated as a mixture of diastereomers. [b] Determined by chiral stationary phase SFC analysis. [c] Determined by UV detection and not corrected for differing molar absorptivities; consistent with ^1H NMR analysis. [d] Could not be determined.

duced nitroso acetal **9b** as the major cycloadduct, hydroxy lactam **10a** was of the opposite enantiomeric series as that provided by titanium halides. Hydroxy lactam **10a** derived from $SnCl_4$ was enriched to a degree comparable to $TiCl_4$. The results from the $Sc(OTf)_3$-promoted cycloaddition confirmed the low selectivity it provided.[16]

Although the absolute configurations of **10a** and **10b** have not been directly proven (attempts to grow a single crystal of a derivative of (−)-**10a** were unsuccessful), their stereostructures can be reliably inferred from evidence amassed from within these laboratories. Studies with vinyl ethers derived from the same chiral auxiliary and a variety of nitroalkenes have demonstrated that the absolute stereochemical outcome (proven by X-ray crystallographic analysis) of [4 + 2] cycloadditions in those cases is controlled by the Lewis acid in the same sense as proposed here.[8] In addition, the absolute configuration of **10a** and **10b** have been inferred based on elution order (on a Whelk-O type column[17]) relative to a very similar hydroxy lactam.[3] All of the available evidence supports the configuration assignment depicted above.

Discussion

Stereochemical Nomenclature. Part 2. Reactant Topicities. The nomenclature defined in Part 1 allows for the unambiguous stereochemical description of the nitroso acetals **9** based on the configurations at C(4a) and C(6). The nomenclature presented here defines an unambiguous description of the reactive faces of nitroalkene **1** and propenyl ether **8** in the transition structure. It is this relationship which is the direct cause of the configurations of the kinetically controlled products of the tandem [4 + 2]/[3 + 2] cycloaddition.

The faces of both nitroalkene and vinyl ether are defined with respect to the α-carbon[18] (Figure 2). Combination of the *Re*-face of nitroalkene **1** with the *Re*-face of vinyl ether **8** corresponds to a "like" combination, and is designated as *lk*. An "unlike" combination is designated as *ul*. In the case presented in Figure 2, a concerted "endo" transition structure corresponds to one of two *lk* (relative) combinations and would give rise to nitroso acetal **9c** or **9d**.

The other stereochemical factor is the internal diastereoselectivity of the chiral auxiliary, which is defined as the relationship between the configuration of C(1′) and the reactive face of the vinyl ether. In the case of **8**, which is derived from (−)-(1*R*,2*S*)-phenylcyclohexanol, approach of either face of the nitroalkene to the *Re*-face of **8** is a "like" combination and is described as 1,3-*lk*. Thus, approach of the *Re*-face of **1** to the *Re*-face of **8** is defined as a *lk*-(1,3-*lk*) orientation and gives rise to nitroso acetal **9c**.

This definition of reactant topicities is simple enough to describe; however, it must be related directly to the specific experimental observations. The most direct stereochemical information gleaned from a given cycloaddition is the configuration of the product nitroso acetals **9** (see Figure 2 for complete numbering). The key stereochemical markers are the stereocenters at C(4a), C(5), and C(6). Although the center at C(5) has not been explicitly discussed, it served to confirm the topicity of the [4 + 2] cycloaddition at the dienophile and also served as a marker in the event of dienophile isomerization or post facto epimerization of C(6). This is an important issue for both modes of cycloaddition, since C(6) serves as a critical stereochemical marker and any inversion of this center would lead to erroneous interpretation. The relative stereoselectivity of the cycloaddition is apparent from inspection of the centers at C(4a) and C(6). The internal stereoselectivity is defined by the relationship between the centers C(6) and C(1′); this relationship is nearly impossible to discern from the cycloadduct, but can be deduced from the hydrogenation products (which, interestingly, contain neither of these centers). The key stereochemical feature is the absolute configuration of the reduction product. This is defined at C(1) of **10**, which through the suprafacial, endo [3 + 2] transition structure relates back to the configuration at C(5a) in **10** (C(4a) in **9**). Since we know the relationship between C(5a) and C(5) in **10**, we know the configuration of C(5) in **9**. Knowing the configuration of C(5) in **9** allows the deduction of which face of the propenyl ether must have reacted, and since we know the absolute configuration of the auxiliary, we can deduce the relationship between the reactive face of the propenyl ether (defined at the α-carbon) and C(1′) in **8** during the stereodetermining event.

Nitroso acetals **9a** and **9b**, which have an unlike (*u*) relationship between C(4a) and C(6), must derive from a *ul* arrangement of nitroalkene **1** and propenyl ether **8** in the transition state. Such an arrangement could be satisfied by a concerted exo-(alkoxy) approach of **8** to **1**, or by any number of nonconcerted transition structures. Likewise, an *lk* combination of faces could relate to an endo-(alkoxy) orientation of **8** (Figure 3).

The issue of internal diastereoselectivity arises as a consequence of the chirality of the auxiliary. In **8**, the

(16) The er for **10b** indicated the presence of a significant (~4%) amount of (+)-**10b** in the product mixture. This could be derived from an *l*-(1,3-*l*) nitroso acetal **9d**, which has never before been observed. Alternatively, isomerization of **8** to the *Z* isomer, followed by [4 + 2]/[3 + 2] cycloaddition could provide a *u*-(1,3-*u*) nitroso acetal which would be transformed to (+)-**10b** upon hydrogenolysis.

(17) Pirkle, W. H.; Pochapsky, T. C. *Chem. Rev.* **1989**, *89*, 347.

(18) Defining the topicity of the reactants at the other carbon would provide an explicit method to describe cycloadducts arising from epimerization or isomerization; however, this would create a nomenclature which is sensitive to the geometry of the alkene (whereas the cycloaddition is generally not) and which would be undefined in the case of monosubstituted dieneophiles.

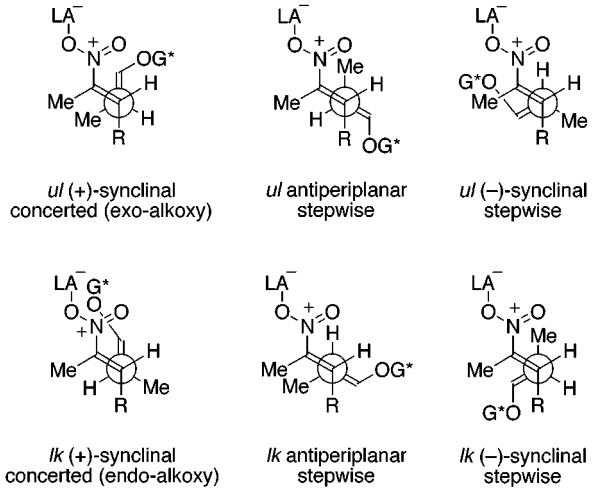


Figure 3. Limiting arrangements of *ul* and *lk* relative topicity.

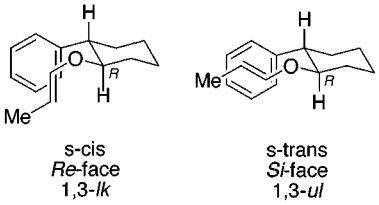


Figure 4. Accessible faces of **8** as a result of enol ether conformation.

faces of the vinyl ether are necessarily diastereotopic, and the internal diastereoselectivity is a measure of the preference for reaction on one of the faces over the other. Our system of nomenclature defines the relationship between the prochiral descriptor at the reactive face and the configuration at C(1′) of the auxiliary. Although the two faces of an olefin in a chiral environment are electronically different, it seems more likely that the unreactive face of the propenyl ether is rendered inaccessible due to steric shielding from the chiral auxiliary. As depicted in Figure 4 for the (1*R*,2*S*) auxiliary, the vinyl ether exists in one of two limiting conformations: s-cis or s-trans. In the s-cis conformation, the *Si*-face of the olefin is obscured by the phenyl group, leaving only the *Re*-face available (in the (1*R*,2*S*) auxiliary). Likewise, an s-trans conformation exposes the *Si*-face. Although these two selectivity factors are certainly interconnected to some extent, they will be discussed separately.

Relative Diastereoselection. In general, an endo approach in a cycloaddition brings about a more crowded, compact transition structure than the corresponding exo approach. If steric interactions between the reactive components dominate the selectivity, an exo approach will be favored. Electronic effects, which are also more pronounced with an endo pathway, can be either stabilizing or destabilizing. Thus, a cycloaddition controlled by electronic effects could favor either approach, depending on the specific nature of the interaction.

The bulky aluminum Lewis acid MAD was previously shown to promote modestly (~2/1) *ul* (exo) selective [4 + 2] cycloaddition between **1** and **8**.[3] Cycloaddition with MAPh was slightly (~10/1) more favorable to a *ul* combination of reactive faces. ATPh displayed the highest relative diastereoselectivity in the aluminum series; the ligands of this complex must occupy more space than those of MAPh. This trend is certainly consistent with a steric argument, which would predict that as the external bulk of the Lewis acid increased, the *ul* (relative) orientation would become more favorable. This consistency, however, cannot be used to rule out an electronic origin for the stereoselectivity.

A different picture is seen within the titanium series. If one accepts the assumption that the steric demand of these Lewis acids decreases in the series $TiCl_2(O\textit{i}\text{-}Pr)_2$ > $TiCl_3(O\textit{i}\text{-}Pr)$ > $TiCl_4$ (which would require that Cl be smaller than O*i*-Pr), then the results in Table 2 are counterintuitive. Further, if one accepts the assumption that $TiCl_x(O\textit{i}\text{-}Pr)_{4-x}$ is sterically congruent with its bromide analogue,[19] then another contradiction to expectation is found. Thus, it would appear that in the titanium series electronic effects dominate the relative topicity of the cycloaddition. Whatever the origin of that effect, it must be noted that $TiCl_2(O\textit{i}\text{-}Pr)_2$ is unique among all Lewis acids examined in that it is the only reagent that selectively promotes an *lk* combination of faces.

The nature of this electronic effect is not clear. Thermal nitroalkene cycloadditions with vinyl ethers have been shown to be *lk* (endo) selective.[20] One possible general effect of the Lewis acid is to create an overall destabilizing electronic interaction; this is consistent with the observation that most Lewis acids promote a highly selective cycloaddition with exo-alkoxy (*ul* relative) orientation. However, the origin of the uniqueness of $TiCl_2(O\textit{i}\text{-}Pr)_2$ is obscure. Because $TiCl_2(O\textit{i}\text{-}Pr)_2$ is certainly not electronically identical to the other Lewis acids employed, it should be expected that the nitroalkene−Lewis acid complex also be electronically different. It is possible that this unique electronic nature actually stabilizes an endo (*lk*) arrangement in the transition structure, whereas the electronic nature of other nitroalkene−Lewis acid complexes would destabilize an endo orientation. It is not at all apparent why this specific Lewis acid would generate a stabilizing effect; if true, one would expect (from the trends in Table 2) that $TiCl(O\textit{i}\text{-}Pr)_3$ would promote [4 + 2] cycloaddition with extremely high *lk* relative diastereoselectivity. Unfortunately, $TiCl(O\textit{i}\text{-}Pr)_3$ was not effective in promoting cycloaddition.

Another explanation for the endo (*lk* relative) diastereoselectivity involves a simultaneous complexation of **1** and **8**. During the course of the reaction, some of the Lewis basic propenyl ether **8** will certainly be coordinated to Lewis acid. In the case of Lewis acids which can accommodate two ligands (such as the titanium halides) there could be a significant population of Lewis acid coordinated to both nitroalkene **1** and propenyl ether **8** (Figure 5). The alkene unit of the coordinated vinyl ether would be less electron-rich, and hence less reactive, than that of an uncoordinated ether; this should in most cases nullify the favorable proximity brought about by dual coordination. However, a weak enough Lewis acid might bind both components, yet leave the vinyl ether reactive

(19) Cardin, C. J.; Cardin, D. J.; Morton-Blake, D. A.; Parge, H. E.; Roy, A. *J. Chem. Soc., Dalton Trans.* **1987**, 1641. A crystal structure of a mono-halide titanocene (with half of the molecules containing bromide, half with chloride) shows that the overall size and structure of the molecule is not significantly altered upon replacing chlorine with bromine, but rather governed primarily by the organic ligands.

(20) (a) Avalos, M.; Babiano, R.; Cintas, P.; Higes, F. J.; Jiménez, J. L.; Palacios, J. C.; Silva, M. A. *J. Org. Chem.* **1996**, *61*, 1880. (b) Tohda, Y.; Yamawaki, N.; Matsui, H.; Kawashima, T.; Ariga, M.; Mori, Y. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 461.

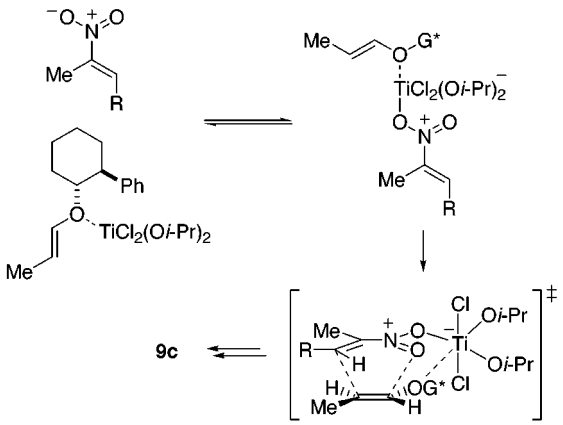


Figure 5. Simultaneous coordination of **1** and **8** to $TiCl_2(O$*i*-$Pr)_2$.

enough to undergo intramolecular cycloaddition. Inspection of molecular models shows that such an approach could lead only to *l*-(1,3-*u*) nitroso acetal **9c** (which arises from an *lk*-(1,3-*ul*) arrangement in the transition structure). The *ul* relative ("exo") arrangement is precluded by the temporary tethering effect of the Lewis acid, and approach of the face of the dienophile corresponding to a 1,3-*lk* (internal) arrangement would place the chiral auxiliary within the nitroalkene (regardless of the ether conformation). Again, it is not clear from these results why only $TiCl_2(O$*i*-$Pr)_2$ would favor this arrangement, nor can this rationale be distinguished from a Coulombic stabilization argument (vide supra). A detailed kinetic analysis (including information on entropy of activation) should be able to differentiate between the two proposals; however, this information is not yet available.

An additional possibility which must be considered is that the reaction proceeds through a nonconcerted, formal cycloaddition process. Previous work from these laboratories[21] has shown that simple, unactivated olefins react with nitroalkenes (at least in part) via a stepwise addition to afford a zwitterionic intermediate; the isolation of cycloadducts resulting from carbocation shifts indicated the presence of a long-lived zwitterionic intermediate. Although rearranged products have never been observed when vinyl ethers have been utilized, there is in principle no reason vinyl ethers would need to react through a concerted pathway.

The bond-forming event of an open transition structure would be addition of the enol ether in a Michael-type reaction to the electrophilic β-carbon of the nitroalkene; an analysis of the stereochemical environment around the β-carbon is presented in Figure 6 (the three limiting positions for staggering substituents are labeled **a**−**c**). With respect to the β-carbon, the two sectors which flank the smaller substituent (H in Figure 6) should be more sterically accessible; sector **c** would be the most congested. Of the two remaining, sector **b** is further from the rest of the nitroalkene, whereas sector **a** is in close proximity. Sector **b** would seem to be the least sterically encumbered. On the basis of this analysis, the preferred approach of the vinyl ether would be the antiperiplanar orientation; this would necessarily be true in the case of unsubstituted vinyl ethers, for which R_L and R_S are both H. The (−)-synclinal arrangement (Figure 3 above) would

(21) Denmark, S. E.; Cramer, C. J.; Sternberg, J. A. *Helv. Chim. Acta* **1986**, *69*, 1971.

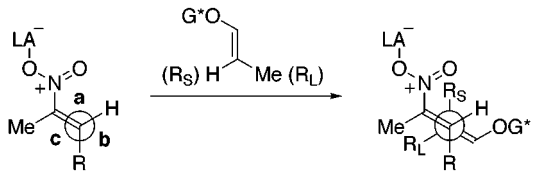


Figure 6. Steric environment of the nitroalkene.

place the alkoxy group in the least sterically accessible area (sector **c**) and can be discounted. The (+)-synclinal orientation would place the alkoxy group in sector **a**. Although this would be sterically less favorable, it would not be easily distinguished from a concerted transition structure, for which electronic effects would be expected to play a much more significant role. Thus, the question of whether certain Lewis acids promote cycloaddition through an open transition structure is probably best answered with respect to the steric requirements of an antiperiplanar approach.

Comparison of the *lk* antiperiplanar approach and the concerted orientation with respect to the methyl group of **8** would seem to favor the *lk* (+)-synclinal orientation. This orientation places the chiral auxiliary close to the nitro group (and the Lewis acid); for an operative *lk* (+)-synclinal orientation, this steric crowding would need to be overcome by an electronic stabilization. Switching from the (+)-synclinal to antiperiplanar approach moves the auxiliary into a much less crowded environment (from sector **a** to **b**), at the cost of moving the methyl group into a more crowded environment (from sector **b** to **c**). If this did occur, it would be because the steric requirements around the methyl group are not as severe as around the auxiliary. If the *lk* antiperiplanar orientation is the most reactive, then the origin of the internal diastereoselection becomes obvious. With the enol ether in an s-cis conformation (Figure 7), the chiral auxiliary is pointed back toward the nitroalkene β-carbon; this steric congestion would easily be relieved by orienting the auxiliary away from the nitroalkene. Thus, an s-trans conformation would be preferred and would lead to reaction on the *Si*-face of the propenyl ether (1,3-*ul* internal diastereoselection).

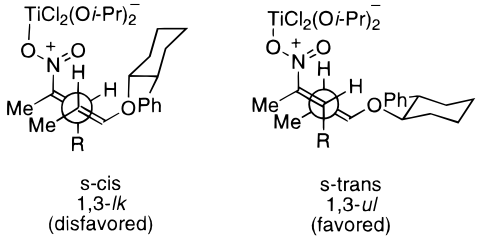


Figure 7. s-Cis and s-trans vinyl ether conformations with *lk* antiperiplanar orientation.

Whatever electronic properties make the *lk* (relative) approach favorable are seen primarily with $TiCl_2(O$*i*-$Pr)_2$. Increasing the halide-to-alkoxide ratio strongly disfavors *lk* approach, as does switching the chlorides to bromides. Likewise, the aluminum-based Lewis acids and $SnCl_4$ strongly disfavor *lk* approach. Whatever the origin, the electronic nature of the $TiCl_2(O$*i*-$Pr)_2$−nitroalkene (**1**) complex renders it fundamentally different from those of other Lewis acids examined.

Internal Diastereoselection. Just as there is a distinction between Lewis acids which favor *ul* (exo) or

lk (endo) relative diastereoselection, so too can one classify promoters by their ability to effect internal diastereoselection. The titanium halides (except for $TiCl_2(O\textit{i}\text{-}Pr)_2$), $SnCl_4$, and to a certain degree $EtAlCl_2$ and $Sc(OTf)_3$ all promote [4 + 2] cycloaddition via a 1,3-*lk* approach of propenyl ether **8**, whereas MAPh and ATPh favor 1,3-*ul* approach.

It is instructive to consider general differences between the Lewis acids in each group. An octahedral arrangement of ligands around $TiCl_4$[22] and $SnCl_4$[23] is generally favorable; aluminum aryloxides are generally limited to tetrahedral coordination.[24] Although the ligands around aluminum are bulkier than the ligands around Ti or Sn, they may actually be pushed farther from the reactive environment; π-electron donation from oxygen to aluminum causes shorter bond distances (Al−O compared to Al−alkyl) and larger bond angles (140−164° Al−O−C compared to other oxygen bond angles).[24]

Another general consideration is the strength of the Lewis acid. Although the nitro group is a very weak Lewis base,[25] it clearly must complex to various Lewis acids, and is thus activated toward cycloaddition.[26] However, complexation of the Lewis acid to stronger Lewis bases (such as enol ethers) should not be ignored. As discussed above, association of the enol ether to strong Lewis acids (such as $SnCl_4$) might render them unreactive, whereas enol ethers associated with weaker Lewis acids (such as $TiCl_2(O\textit{i}\text{-}Pr)_2$) might still be competent dienophiles. If so, it would not be surprising if propenyl ether **8**, when associated with a Lewis acid, reacted in a manner distinct from free enol ethers.

A few plausible hypotheses to explain the switch in internal diastereoselection are evident. Recent calculations on [4 + 2] cycloadditions with nitrosoethylene (without Lewis acid) support the hypothesis that enol ethers prefer to react with nitroalkenes in an s-trans conformation.[27] In this conformation, the *Si*-face (1,3-*ul* internal diastereoselectivity) of propenyl ether **8** is exposed and is presumably the reactive conformation when the [4 + 2] cycloaddition is promoted by MAPh and ATPh (Figure 4 explicitly shows how each face of the olefin is blocked). An s-trans conformation places the chiral auxiliary in close proximity to the bulky Lewis acid (Figure 8); however, due to the large Al−O−Ph bond angles, the phenoxide ligand may be pushed away from the auxiliary. In the case of Lewis acids such as $SnCl_4$, which point the octahedral ligands more directly at the auxiliary, the steric requirements of a reactive s-trans conformation may make it less favorable than an s-cis

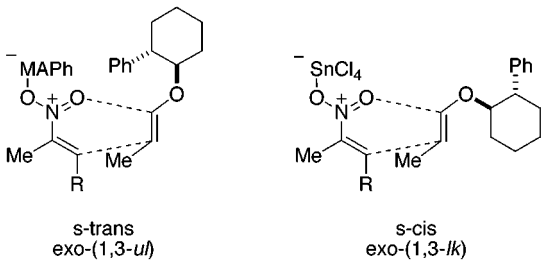


Figure 8. Reactive conformations of **8**.

conformation (Figure 8). In a certain sense, this argument implies that $SnCl_4$ (and other Lewis acids which selectively provide nitroso acetal **9a**) is "bulkier" than MAPh or ATPh. Although this is certainly not true with respect to the Lewis base to which it directly binds,[28] the exact nature of the environment around the ligands is not understood as well (in fact, although MAD is considerably "bulkier" than MAPh,[28b] it is often much less selective in the [4 + 2] cycloaddition[1]).

Another possibility (discussed above with respect to relative diastereoselection) is that one of the two "types" of Lewis acids causes a switch from a concerted to an open, nonconcerted transition structure (Figure 3). The argument that MAPh causes this change would be similar to the argument presented for $TiCl_2(O\textit{i}\text{-}Pr)_2$ with respect to relative diastereoselection (vide supra). The *ul* (−)-synclinal approach would again be expected to be unfavorable; placing the chiral auxiliary in that position is not an improvement over its location in the *ul* (+)-synclinal orientation. The alternative again would be the *ul* antiperiplanar arrangement. Switching to this orientation provides the most conformational freedom to the chiral auxiliary, while enforcing little additional steric strain upon the methyl group.

It must be noted that although either $TiCl_2(O\textit{i}\text{-}Pr)_2$ or MAPh could reasonably be thought to promote [4 + 2] cycloaddition through an open transition structure, it seems very unlikely that they both do. Both "families" of Lewis acid provide cycloadducts with the same sense of internal stereoselectivity, but they differ in the sense of relative stereoselectivity. If they both brought about an open, stepwise cycloaddition, there would be little steric effect of the Lewis acid on the orientation of the directing alkoxy portion of the vinyl ether.

Conclusion

The [4 + 2] cycloaddition of nitroalkene **1** and propenyl ether **8** was examined with a variety of Lewis acids. The high stability of both the substrates and the cycloadducts allowed for even harsh Lewis acids to be tested. Several titanium- and aluminum-based Lewis acids and $SnCl_4$ were found to be very efficient promoters, providing nitroso acetals in excellent yields (82−95%). All of the Lewis acids examined afforded cycloadducts arising from a *ul* (relative) orientation of reactants, with several (most notably $SnCl_4$, $TiCl_4$, $TiBr_3(O\textit{i}\text{-}Pr)$ and ATPh) providing the *u* (trans) products in excellent (>25/1) selectivity. The aryloxide aluminum-based Lewis acids promoted cycloaddition via approach to the *Si*-face (1,3-*ul*) of chiral propenyl ether **8** (presumably with the ether reacting in

(22) (a) Boyle, T. J.; Eilerts, N. W.; Heppert, J. A.; Takusagawa, F. *Organometallics* **1994**, *13*, 2218. (b) Oppolzer, W.; Rodriguez, I.; Blagg, J.; Bernardinelli, G. *Helv. Chim. Acta* **1989**, *72*, 123.

(23) Knight, C. T. G.; Merbach, A. E. *Inorg. Chem.* **1985**, *24*, 576.

(24) Healy, M. D.; Ziller, J. W.; Barron, A. R. *Organometallics* **1991**, *10*, 597.

(25) (a) Maria, P.-C.; Gal, J.-F. *J. Phys. Chem.* **1985**, *89*, 1296. (b) Catalán, J.; Díaz, C.; López, V.; Pérez, P.; de Paz, J.-L. G.; Rodríguez, J. G. *Liebigs Ann.* **1996**, 1785. (c) Gritzner, G. *J. Mol. Liq.* **1997**, *73*−*74*, 487.

(26) (a) Electron-rich nitroalkenes (which might be thought to react slower as heterodienes in an inverse-electron demand Diels−Alder reaction) in fact undergo cycloaddition more rapidly than electron-deficient nitroalkenes, presumably because of more efficient coordination to the Lewis acid. Denmark, S. E.; Kesler, B. S.; Moon, Y.-C. *J. Org. Chem.* **1992**, *57*, 4912. (b) The 1/1 complex of $SnCl_4$ to a nitroalkene has been examined with low-temperature NMR. Cramer, C. J. Ph.D. Thesis, University of Illinois, 1988. Ho, G.-D.; unpublished results from these laboratories.

(27) Liu, J.; Niwayama, S.; You, Y.; Houk, K. N. *J. Org. Chem.* **1998**, *63*, 1064.

(28) (a) Maruoka, K.; Nagahara, S.; Yamamoto, H. *J. Am. Chem. Soc.* **1990**, *112*, 6115. (b) Saito, S.; Yamamoto, H. *Chem. Commun.* **1997**, 1585.

an s-trans conformation), whereas the other Lewis acids caused a switch in selectivity, generally preferring reaction on the *Re*-face (1,3-*ul*) of the vinyl ether (with excellent selectivity again in the case of $SnCl_4$, $TiBr_3$(O*i*-Pr), and $TiCl_4$).

Experimental Section

General Experimental. See Supporting Information. All SFC analyses were performed on a Chiralcel AD column with UV detection (220 nm), a CO_2/MeOH (95/5) eluent, and an inlet pressure of 150 bar. Flow rates are listed individually below. Full analytical data for nitroso acetals **9a**, **9b**, **9c** and hydroxy lactams **10a**, and **10b** have been reported.[3,6]

Representative Procedure 1. [4 + 2]/[3 + 2] Cycloaddition of 1 and 8 Promoted with $TiBr_2$(O*i*-Pr)$_2$. (2*S*,-2a*S*,4a*S*,5*R*,6*R*,7b*R*)-, (2*R*,2a*R*,4a*R*,5*S*,6*S*,7b*S*)-, and (2*S*,-2a*S*,4a*S*,5*S*,6*S*,7b*R*)-Octahydro-5,7b-dimethyl-6-[(1*R*,2*S*)-2-(phenylcyclohexyl)oxy]-1,7-dioxa-7a-azacyclopent[*cd*]-indene-2-carboxylic Acid Methyl Ester (9a, 9b, and 9c). To a cold (−78 °C, internal) solution of **1** (196.2 mg, 1.0 mmol) and **8** (322.6 mg, 1.5 mmol, 1.5 equiv) in CH_2Cl_2 (5 mL) was added a solution (premixed at room temperature for 1 h) of $TiBr_4$ (382 mg, 1.0 mmol, 1.0 equiv) and Ti(O*i*-Pr)$_4$ (305 μL, 294 mg, 1.0 mmol, 1.0 equiv) in CH_2Cl_2 (8 mL) over 8 min. The resulting yellow solution was stirred at −74 °C for 2 h and then was quenched with 1 M NaOH in MeOH (4.2 mL). The mixture was poured into CH_2Cl_2 (200 mL), washed with water (2 × 100 mL), washed with brine (100 mL), and back extracted with CH_2Cl_2 (2 × 100 mL). The organic layer was dried (Na_2SO_4) and allowed to stand at room temperature overnight. The organic layer was concentrated in vacuo and purified by silica gel chromatography (hexane/acetone, 97.5/2.5, 95/5, 90/10) to afford 335.2 mg (82%) of a 7.7/1/7.9 mixture of **9a**, **9b**, and **9c** as a colorless oil. Data for the 7.7/1/7.9 mixture of **9a**, **9b**, and **9c**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39−7.16 (m, 5 H), 4.84 (d, *J* = 8.5, 1 H), 4.83 (d, *J* = 8.0, 1 H), 4.77 (d, *J* = 7.0, 1 H), 4.19−4.15 (m, 1 H), 4.12 (d, *J* = 6.5, 1 H), 4.07 (d, *J* = 7.5, 1 H), 3.84 (s, 3 H), 3.81 (s, 3 H), 3.75−3.70 (m, 1 H), 3.68−3.63 (m, 1 H), 2.73−2.69 (m, 2 H), 2.64−2.55 (m, 2 H), 2.35−2.29 (m, 2 H), 1.98−1.74 (m, 19 H), 1.63−1.31 (m, 13 H), 1.30 (s, 3 H), 1.21 (s, 3 H), 0.87 (d, *J* = 7.0, 3 H), 0.32 (d, *J* = 7.5, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.8, 169.7, 143.7, 143.4, 128.1, 127.6, 127.6, 127.5, 127.5, 127.3, 125.7, 125.0, 106.3, 105.8, 99.0, 86.3, 84.8, 84.8, 83.6, 81.9, 74.3, 73.6, 58.2, 56.3, 52.6, 51.7, 51.1, 50.2, 49.2, 49.0, 36.3, 35.5, 35.3, 34.6, 34.2, 33.2, 32.9, 31.1, 30.5, 27.7, 27.6, 27.5, 26.8, 25.7, 25.3, 24.7, 24.3, 23.1, 16.6, 16.2, 15.4.

Representative Procedure 2. Hydrogenolysis of 9. (1*S*,5*R*,5a*S*,7a*S*,7b*R*)- and (1*S*,5*S*,5a*S*,7a*S*,7b*R*)-Octahydro-1-hydroxy-5,7b-dimethyl-2*H*-cyclopenta[*gh*]pyrrolizin-2-one ((−)-10a and (−)-10b). To a solution of the mixture of **9** (335.2 mg, 0.81 mmol) in MeOH (20 mL) was added a slurry of a catalytic amount of Raney Ni (washed with MeOH) in MeOH (30 mL). This mixture was stirred at room temperature under an atmosphere of H_2 for 24 h, filtered through a pad of Celite along with MeOH (100 mL) and CH_2Cl_2 (100 mL), concentrated in vacuo, and purified by silica gel chromatography (EtOAc/hexane, 50/50, 100/0) to afford 117.2 mg (74%) of **10** as a crystalline white solid. Data for the 1.6/1 mixture of **10a** and **10b**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.67−4.63 (m, 1 H), 4.06 (dd, *J* = 11.5, 7.5, 1 H), 3.21 (d, *J* = 9.0, 2 H), 2.84−2.62 (m, 4 H), 2.56−2.52 (m, 2 H), 2.17−2.08 (m, 2 H), 1.85−1.77 (m, 3 H), 1.71−1.58 (m, 3 H), 1.53−1.43 (m, 2 H), 1.37 (s, 3 H), 1.35 (s, 3 H), 1.10−1.06 (m, 1 H), 1.08 (d, *J* = 7.0, 3 H), 1.04 (d, *J* = 7.0, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.3, 176.1, 77.4, 75.3, 72.4, 71.8, 58.0, 54.2, 51.8, 50.4, 50.2, 47.3, 42.0, 33.9, 30.8, 25.4, 25.2, 24.7, 24.0, 21.9, 17.4, 14.8; SFC t_R (−)-**10b**, 2.7 min (38.0%); t_R (+)-**10b**, 3.1 min (0.2%); t_R (−)-**10a**, 3.5 min (57.9%); t_R (+)-**10a**, 4.1 min (3.9%); (3.5 mL/min).

[4 + 2]/[3 + 2] Cycloaddition of 1 and 8 Promoted with $TiCl_4$. Following Representative Procedure 1, to **1** (196.9 mg, 1.0 mmol) and **8** (216.3 mg, 1.0 mmol, 1.0 equiv) in CH_2Cl_2 (14 mL) at −77 °C was added $TiCl_4$ (neat, 115 μL, 199 mg, 1.05 mmol, 1.05 equiv) to give an orange solution. After 15 min, **8** (216.8 mg, 1.0 mmol) in CH_2Cl_2 (2 mL) was added. After 20 min, **8** (215.9 mg, 1.0 mmol) in CH_2Cl_2 (2 mL) was added. After 15 min, the solution was quenched with 1 M NaOH in MeOH (4.2 mL). Workup and chromatography (hexane/EtOAc, 80/20) afforded 353.1 mg (86%) of a 25/1 mixture of **9a** and **9b**.

Following Representative Procedure 2, from **9** (353.1 mg, 0.85 mmol) in MeOH (50 mL), afforded 102 mg (62%) of **10**. Data for **10**: SFC t_R (−)-**10b**, 3.4 min (0.2%); t_R (+)-**10b**, 3.8 min (0.1%); t_R (−)-**10a**, 4.2 min (97.5%); t_R (+)-**10a**, 5.0 min (2.2%); (3.0 mL/min).

[4 + 2]/[3 + 2] Cycloaddition of 1 and 8 Promoted with $TiCl_3$(O*i*-Pr). Following Representative Procedure 1, to **1** (201.1 mg, 1.0 mmol) and **8** (433.1 mg, 2.0 mmol, 2.0 equiv) in CH_2Cl_2 (5 mL) at −74 °C was added a solution (premixed at room temperature for 50 min) of $TiCl_4$ (165 μL, 286 mg, 1.5 mmol, 1.5 equiv) and Ti(O*i*-Pr)$_4$ (150 μL, 145 mg, 0.5 mmol, 0.5 equiv) in CH_2Cl_2 (8 mL) over 10 min. The solution turned yellow and then brown during addition. After 1 h, the solution was quenched with 1 M NaOH in MeOH (6.0 mL). Workup and chromatography (hexane/EtOAc, 80/20) afforded 396.5 mg (95%) of a 17/1.3/1 mixture of **9a**, **9b**, and **9c**.

Following Representative Procedure 2, from **9** (396.5 mg, 0.95 mmol) in MeOH (50 mL), afforded 137.7 mg (74%) of **10**. Data for **10**: SFC t_R (−)-**10b**, 2.8 min (3.6%); t_R (+)-**10b**, 3.1 min (0.3%); t_R (−)-**10a**, 3.5 min (93.0%); t_R (+)-**10a**, 4.1 min (3.1%); (3.5 mL/min).

[4 + 2]/[3 + 2] Cycloaddition of 1 and 8 Promoted with $TiBr_3$(O*i*-Pr). Following Representative Procedure 1, to **1** (199.9 mg, 1.0 mmol) and **8** (433.3 mg, 2.0 mmol, 2.0 equiv) in CH_2Cl_2 (5 mL) at −75 °C was added a solution (premixed at room temperature for 40 min) of $TiBr_4$ (600 mg, 1.6 mmol, 1.6 equiv) and Ti(O*i*-Pr)$_4$ (160 μL, 154 mg, 0.5 mmol, 0.5 equiv) in CH_2Cl_2 (8 mL) over 5 min. The solution turned brown and then orange over time. After 1 h, the solution was quenched with 1 M NaOH in MeOH (6.5 mL). Workup and chromatography (hexane/EtOAc, 80/20) afforded 378.5 mg (91%) of a 30/1 mixture of **9a** and **9b**.

Following Representative Procedure 2, from **9** (378.5 mg, 0.91 mmol) in MeOH (50 mL), afforded 118.1 mg (66%) of **10**. Data for **10**: $[\alpha]^{24}_D = -65.5°$ (c = 1.012, CH_2Cl_2); SFC t_R (−)-**10b**, 3.3 min (0.1%); t_R (+)-**10b**, 3.7 min (0.1%); t_R (−)-**10a**, 4.2 min (98.5%); t_R (+)-**10a**, 5.0 min (1.3%); (3.0 mL/min).

[4 + 2]/[3 + 2] Cycloaddition of 1 and 8 Promoted with MAPh. Following Representative Procedure 1, to **1** (201.8 mg, 1.0 mmol) and **8** (327.5 mg, 1.5 mmol, 1.5 equiv) in CH_2Cl_2 (7 mL) at −76 °C was added a solution (premixed at room temperature for 1 h) of 2,6-diphenylphenol (983.7 mg, 4.0 mmol, 4.0 equiv) and Me_3Al (2 M in toluene, 1.0 mL, 2.0 mmol, 2.0 equiv) in CH_2Cl_2 (7 mL), resulting in a deep, dark brown color. The solution was warmed over 10 min to 0 °C (color changed to yellow), maintained at 0 °C for 1 h 20 min, cooled to −78 °C over 20 min, and quenched with MeOH (5.0 mL). Workup and chromatography (hexane/acetone, 97.5/2.5, 95/5, 90/10) afforded 344.6 mg (82%) of a 1.5/8.2/1 mixture of **9a**, **9b**, and **9c**.

Following Representative Procedure 2, from **9** (344.6 mg, 0.83 mmol) in MeOH (50 mL) afforded 132.5 mg (82%) of **10**. Data for **10**: SFC t_R (−)-**10b**, 2.7 min (5.9%); t_R (+)-**10b**, 3.1 min (0.3%); t_R (−)-**10a**, 3.6 min (13.0%); t_R (+)-**10a**, 3.9 min (80.9%); (3.5 mL/min).

[4 + 2]/[3 + 2] Cycloaddition of 1 and 8 Promoted with ATPh. Following Representative Procedure 1, to **1** (197.7 mg, 1.0 mmol) and **8** (325.4 mg, 1.5 mmol, 1.5 equiv) in CH_2Cl_2 (7 mL) at −76 °C was added a solution (premixed at room temperature for 1 h) of 2,6-diphenylphenol (1.4775 g, 6.0 mmol, 6.0 equiv) and Me_3Al (2 M in toluene, 1.0 mL, 2.0 mmol, 2.0 equiv) in CH_2Cl_2 (7 mL), resulting in a deep, dark brown color. The solution was warmed over 10 min to 0 °C (color slowly changed to yellow), maintained at 0 °C for 1 h 30 min, cooled to −78 °C over 10 min, and was quenched with MeOH (5.0 mL). Workup and chromatography (hexane/acetone, 97.5/2.5, 95/5, 90/10) afforded 374.2 mg (91%) of a 1/8 mixture of **9a** and **9b**.

Following Representative Procedure 2, from **9** (374.2 mg, 0.90 mmol) in MeOH (50 mL), afforded 137.3 mg (78%) of **10**. Data for **10**: SFC t_R (−)-**10b**, 2.8 min (0.3%); t_R (+)-**10b**, 3.1 min (0.1%); t_R (−)-**10a**, 3.6 min (10.0%); t_R (+)-**10a**, 4.0 min (89.6%); (3.5 mL/min).

[4 + 2]/[3 + 2] Cycloaddition of 1 and 8 Promoted with $SnCl_4$. Following Representative Procedure 1, to **1** (202.3 mg, 1.0 mmol) and **8** (417.5 mg, 1.9 mmol, 1.9 equiv) in CH_2Cl_2 (14.5 mL) at −77 °C was added $SnCl_4$ (neat, 235 μL, 524 mg, 2.0 mmol, 2.0 equiv) to give a yellow solution. After 20 min, the solution was quenched with 1 M NaOH in MeOH (8.0 mL). Workup and chromatography (hexane/EtOAc, 80/20) afforded 402 mg (95%) of a 40/1 mixture of **9a** and **9b**.

Following Representative Procedure 2, from **9** (389.5 mg, 0.94 mmol) in MeOH (50 mL), afforded 141.8 mg (78%) of **10**. Data for **10**: SFC t_R (−)-**10b**, 2.8 min (0.5%); t_R (+)-**10b**, 3.1 min (0.2%); t_R (−)-**10a**, 3.5 min (97.1%); t_R (+)-**10a**, 4.1 min (2.2%); (3.5 mL/min).

[4 + 2]/[3 + 2] Cycloaddition of 1 and 8 Promoted with $Sc(OTf)_3$. Following Representative Procedure 1, to $Sc(OTf)_3$ (987 mg, 2.0 mmol, 2.0 equiv) and 2,6-di-*tert*-butyl-4-methylpyridine (134 mg, 0.65 mmol, 0.65 equiv) in CH_2Cl_2 (5.0 mL) at −78 °C were added **1** (201.0 mg, 1.0 mmol) in CH_2Cl_2 (5.0 mL) (resulting in a yellow solution) and **8** (542.1 mg, 2.5 mmol, 2.5 equiv) in CH_2Cl_2 (4.0 mL). The solution was maintained at −78 °C for 30 min and then warmed to 0 °C and maintained for 3.5 h, cooled to −78 °C, and quenched with 1 M NaOH in MeOH (6.0 mL). Workup and chromatography (hexane/EtOAc, 80/20) afforded 316.1 mg (75%) of a 4/1 mixture of **9a** and **9b**.

Following Representative Procedure 2, from **9** (226.5 mg, 0.55 mmol) in MeOH (35 mL), afforded 71.9 mg (68%) of **10**. Data for **10**: SFC t_R (−)-**10b**, 3.2 min (6.0%); t_R (+)-**10b**, 3.6 min (3.8%); t_R (−)-**10a**, 4.0 min (71.2%); t_R (+)-**10a**, 4.7 min (19.0%); (3.0 mL/min).

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Supporting Information Available: General experimental, a full list of ^{1}H NMR and ^{13}C NMR resonances with assignments. This material is available free of charge via the Internet at http://pubs.acs.org.

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