Nitroalkene [4 + 2] Cycloaddition as a General and Stereoselective Route to the Synthesis of 3,3- and 3,4-Disubstituted Pyrrolidines

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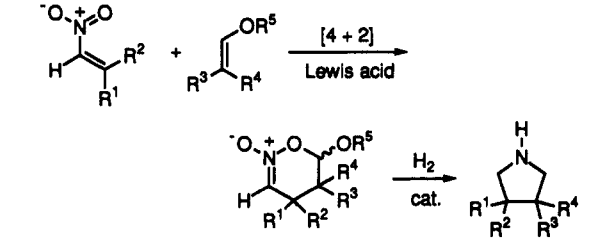
2,2-Disubstituted 1-nitroalkenes **12** undergo Lewis acid-promoted [4 + 2] cycloadditions with *n*-butyl vinyl ether to afford cyclic nitronates **14** as anomeric mixtures in good yields. The resulting nitronates were reduced with hydrogen in the presence of Adam's catalyst to afford 3,3-disubstituted pyrrolidines which were isolated in good yield as their *N*-*p*-toluenesulfonamides **17**. Cycloadditions of (*E*)-2-nitrostyrene with ethyl (*E*)- and (*Z*)-1-propenyl ethers provided for the stereoselective synthesis of *cis*- and *trans*-3-phenyl-4-methyl-*N*-(*p*-tolylsulfonyl)pyrrolidine. Similarly, *trans*-3,4-diphenyl-*N*-(*p*-tolylsulfonyl)pyrrolidine was prepared from (*E*)-2-nitrostyrene and ethyl (*E*)-2-styryl ether.

Introduction

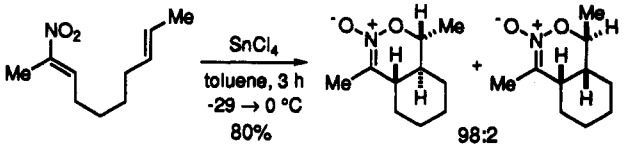
Substituted pyrrolidines have attracted the attention of synthetic organic chemists for many years. Among the reasons for interest in this class of compounds, the more important are the following: (i) isolated pyrrolidine rings are contained in many families of alkaloid natural products,[1] (ii) certain classes of substituted pyrrolidines possess significant biological activity,[1] ranging from effective antibacterial agents[2] to potent venom[3] and neuroexcititory agents,[4] and (iii) chiral pyrrolidines have found considerable utility as auxiliaries and ligands in asymmetric reactions.[5] Consequently, the development of general and selective methods for the synthesis of pyrrolidines with various levels of substitution has been an active field of research.[6]

As part of our program on the chemistry of cyclic nitronates, resulting from [4 + 2] cycloaddition of nitroalkenes with vinyl ethers, we became interested in demonstrating their potential for the direct conversion to pyrrolidines by hydrogenolysis, Scheme I. Variation of nitroalkene substitution and enol ether composition would provide for the synthesis of 3,4-di-, tri-, or tetrasubstituted pyrrolidines in two steps from nitroalkenes. Indeed, we have recently documented that considerable stereocontrol

Scheme I



Scheme II



is often observed with (*E*)- and (*Z*)-1-propenyl ethers as the dienophiles in [4 + 2]/[3 + 2] tandem cycloadditions.[7]

The construction of cyclic nitronates from [4 + 2] cycloaddition of a nitroalkene (acting as a 4π component) together with an unactivated olefin was reported from our laboratories in 1986, Scheme II.[8] Subsequent reports have documented the generality of this transformation[8b] in intermolecular modes[9a,b] as well as with 2-nitrostyrenes,[9c] and showed the utility of simple alkenes and vinyl ethers as dienophiles.[10] The products of the cycloaddition, cyclic nitronate esters, were studied for their synthetic potential by subjecting them to a variety of transformations, including hydrogenolysis to hydroxy ketones, oxidation to diketones, deoxygenation to 1,2-dihydrooxazines and reduction to amino alcohols.[9a]

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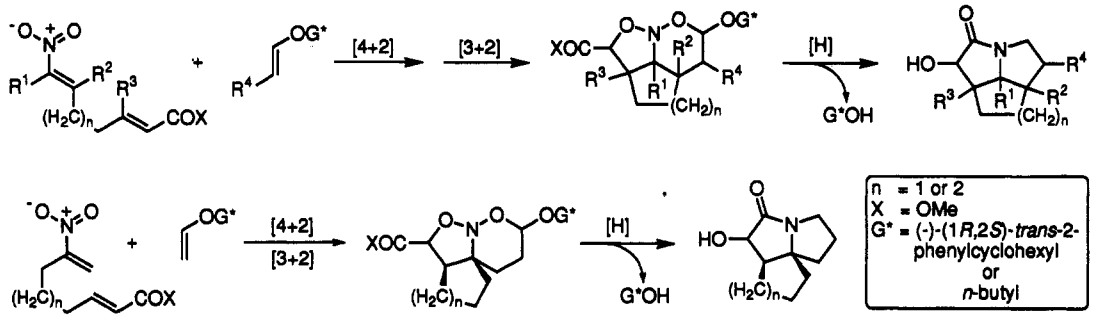
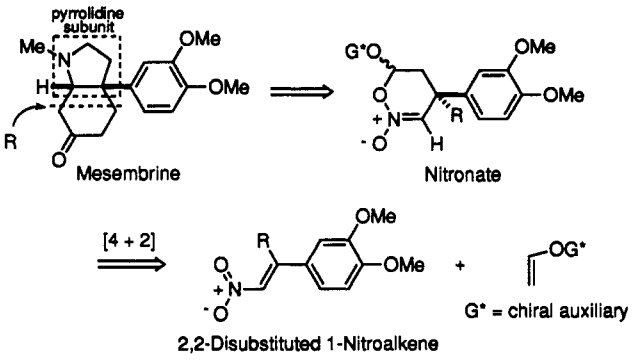
Scheme III



Scheme IV



Following the pioneering studies of Tartakovskii,[11] we recognized the dipolar character of the nitronates and have amply demonstrated their utility in [3 + 2] cycloadditions,[10d] Scheme III. A key transformation of the resulting nitroso acetals is their catalytic reduction in the presence of Raney nickel. Those nitro acetals derived from vinyl ether dienophiles afforded fused-ring pyrrolidines upon hydrogenation, Scheme III. We speculated that isolated pyrrolidines might result from the catalytic reduction of the parent nitronates derived from enol ethers. The realization of that strategy is disclosed in detail below.

Another interesting challenge for substituted pyrrolidine synthesis is posed by consideration of the quaternary center in the *Scletium* alkaloid mesembrine.[12] The synthesis of such alkaloids by nitroalkene technology would require the successful cycloaddition of a 2,2-disubstituted 1-nitroalkene, Scheme IV. The preceding article in this issue described the general and high-yielding synthesis of the requisite 2,2-disubstituted 1-nitroalkenes.[13] In this contribution we describe the use of substituted nitroalkenes and vinyl ethers for the stereoselective synthesis of 3,3- and 3,4-disubstituted pyrrolidines by the cycloaddition/hydrogenolysis protocol.

Background

Pyrrolidine Synthesis. Pyrrolidine syntheses can be classified into two major categories: (1) those that build on (or embellish) preexisting pyrrolidine rings and (2) those that construct the heterocyclic ring. Procedures that begin with the intact pyrrolidine ring are numerous and rely on commercially available or easily obtained starting materials (e.g. pyrrolidine itself or L-proline). This type of strategy has found widespread use and benefits from the ease of accessing optically active products from inexpensive starting materials. However, these approaches are often limited to the preparation of 2- and 2,5-disubstituted pyrrolidines. Some of the more useful methods include: alkylation of carbanions α to nitrogen,[14] nucleophilic addition to *N*-acyliminium ions,[15] and syntheses from proline[16] or pyroglutamic acid.[17]

The second approach, in which the pyrrolidine ring is constructed, is more versatile and allows for access to pyrrolidine products with more varied substitution. The most prevalent method in this category is the [3 + 2] cycloaddition of stabilized or nonstabilized azomethine ylides with substituted olefins.[18] This construction provides access to a wide variety of substituted pyrrolidines but suffers from the lack of a highly selective, asymmetric variant.[19] In addition to [3 + 2] cycloadditions, other pericyclic reactions have been effectively employed in pyrrolidine synthesis. Some other methods that involve pericyclic reactions include: enolate Claisen rearrangements of azalactones,[20] ene reactions,[21] tandem aza-Cope/Mannich reactions,[22] and even Diels–Alder reactions.[23] Pericyclic reactions are often desirable, since these reactions can be highly stereoselective and can provide for the synthesis of optically active pyrrolidines.

Another common strategy employed in pyrrolidine synthesis is the use of various cyclization reactions.

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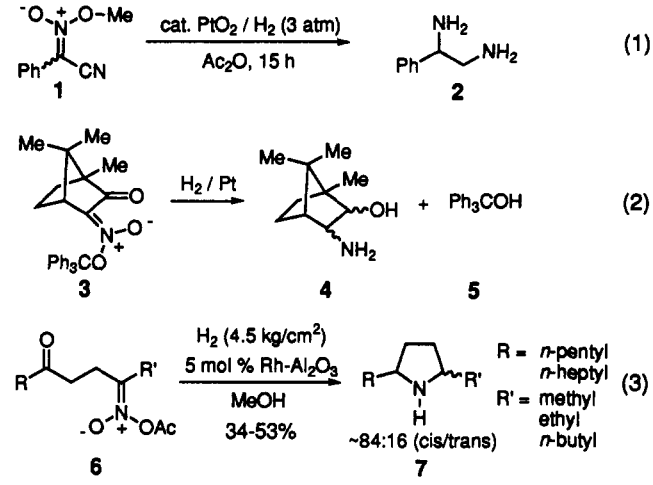
Electrophilically initiated cycloamidation reactions have been widely investigated, in which metals (Hg^{+2}, Ag^{+}, Pd^{+2}) and other electrophilic reagents (PhSeCl, I_2) promote intramolecular cyclization of δ-alkenylamines.[24] Likewise, aminyl radicals (generated by anodic oxidation of lithium amides) have been used to effect ring closure.[25] In addition to aminyl radicals, intramolecular cyclization of carbon radicals has been reported as a viable route to substituted pyrrolidines.[26] Notably, Baldwin et al. have developed an enantioselective route to Kanoid analogues via cobalt-mediated cyclizations of serine-derived substrates.[27]

A more basic approach to pyrrolidine synthesis relies on intramolecular N-alkylation to close the heterocyclic ring.[28] Kibayashi and co-workers have utilized intramolecular N-alkylations of sugars or tartrate-derived substrates in the enantioselective total synthesis of several pyrrolidine alkaloid natural products.[29] Also, intramolecular nucleophilic addition of amides to alkynes,[30] allenes,[31] and epoxides[32] have been explored as methods of forming pyrrolidine rings.

Finally, Meyers' multistep approach to pyrrolidine synthesis employing easily obtained chiral bicyclic lactams (phenyl glycinol derived) is useful for the general preparation of optically active 2- and 3-substituted pyrrolidines.[33]

Despite the numerous methods already described for pyrrolidine synthesis, the importance of this class of compounds continues to stimulate much activity. Noticeably absent are general methods that allow for substitution at the 3- and 4-position with high diastereoselectivity and the potential for absolute stereocontrol.

The Reduction of Nitronates. Surprisingly, there is little precedent for the direct reduction of nitronates to their respective amines.[34] To the best of our knowledge, there are only three examples of this transformation and they all deal with *acyclic* nitronates. Thurston and Shriner documented the catalytic reduction of an acyclic methyl nitronic ester **1** to phenylethyldiamine **2** in the presence of platinum oxide[34a] (eq 1). Unfortunately, no yield for this transformation was provided. Later, Larson et al. reported the reduction of a camphor-derived trityl nitronic ester **3** with platinum and hydrogen to afford triphenylcarbinol **5** and a diastereomeric mixture of β-amino alcohols **4**,[34b] (eq 2). Once again, no yield for the formation of the amino alcohol was provided. More recently, Yoshikoshi and co-workers have described the hydrogenolysis of nitronic anhydrides **6** to mixtures of the corresponding *cis*- and *trans*-2,5-disubstituted pyrrolidines **7** with 5% $Rh-Al_2O_3$ in methanol,[34c,d] (eq 3). The yields for this



transformation are rather poor ranging from 34–53% and the diastereoselectivities are low. Thus, only limited success has been reported for the reduction of nitronates to their respective amines, and no examples involving cyclic nitronates have appeared.

Given the close structural similarity between nitronates and nitroso acetals it is not surprising to find examples of the hydrogenolysis of O–N–O structures to amines. Our own studies in this area have amply demonstrated the facile reductive cleavage of nitroso acetals. Hydrogenolysis of nitroso acetals of the type **8** is a general, high-yielding transformation to fused,[10a] and spiro tricyclic[10d] pyrrolidines, eq 4 and Scheme III. Similarly, Seebach and Brook have reported the reduction of tricyclic nitroso acetals to substituted octahydroindoles with hydrogen at elevated pressures in the presence of Raney nickel catalyst,[35] eq 5.

Results

Cycloadditions of 2,2-Disubstituted 1-Nitroalkenes. Isomeric *E*/*Z* mixtures of 2,2-disubstituted 1-nitroalkenes were prepared in good yields as described in the preceding article.[13] Cycloadditions of these nitroalkenes were performed using methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide) (MAD),[36] as the Lewis acid promoter,

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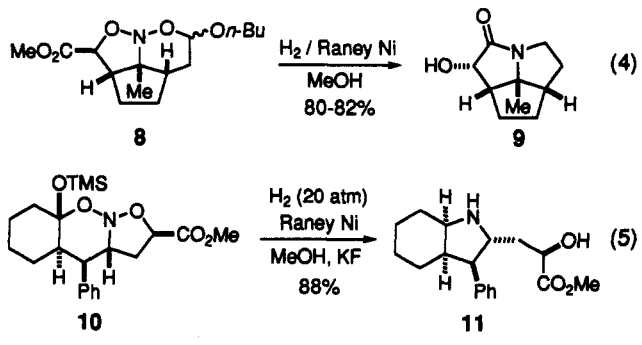


Figure 1. We have described the use of MAD, as well as methylaluminum bis(2,6-diphenylphenoxide) (MAPh),[37] as effective Lewis acids for promoting nitroalkene cycloadditions.[7b,10c] Other Lewis acids, such as $TiCl_4$, $SnCl_4$, and $TiCl_2(O\text{-}i\text{-}Pr)_2$, failed to promote the cycloaddition of 2,2-disubstituted 1-nitroalkenes. Interestingly, with the titanium- and tin-based Lewis acids, highly colored reaction solutions resulted, indicating a strong complexation of the nitro group by the Lewis acid.

The results of cycloadditions performed using *E*/*Z* mixtures of 2,2-disubstituted 1-nitroalkenes **12a–g** with *n*-butyl vinyl ether (**13**) are summarized in Table I. Reactions conducted under the standard protocol (−78 °C, 3 equiv of vinyl ether, and 3 equiv of Lewis acid) were very slow and led to only trace amounts of cycloadducts. However, reactions conducted at 0 °C, with 6 equiv of vinyl ether and 3 equiv of Lewis acid, proceeded to completion within 30–120 min. Analytically pure, cyclic nitronates **14a–g** were isolated as anomeric mixtures in good yields (76–91%).

Assignment of the relative cofiguration of the nitronate diastereomers was not possible on the basis of ^1H NMR coupling constants. Since stereochemical assignments were not necessary for our subsequent purposes, they were left undetermined. It is worthy of note that the product nitronates are relatively stable compounds and can be stored in the freezer for prolonged periods of time (~2 weeks or more). However, nitronates are typically labile species and will undergo decomposition if exposed to heat and/or acidic conditions.[38]

Preparation of 3,3-Disubstituted Pyrrolidines. Our initial attempts to carry out the reduction of cyclic nitronates to pyrrolidines with Raney nickel as the catalyst, at varying hydrogen pressures, were unsuccessful. However, the use of platinum oxide (Adams' catalyst),[39] at moderately elevated hydrogen pressures (>40 psi), afforded the desired pyrrolidines in good yields. For example, nitronate **14a** was reduced in the presence of 10 mol% platinum oxide, at a pressure of 160 psi, to afford the corresponding 3-alkyl-3-arylpyrrolidine **15** in 78% yield, Scheme V.

Later, it was discovered that the addition of 1 equiv of acetic acid to the reaction, as well as direct *N*-protection of the crude pyrrolidine products as their *p*-toluenesulfonamides, resulted in good yields of protected pyrrolidines. Surprisingly, variation of pressure had little effect on the outcome of the hydrogenolysis. Reactions were conducted at a range of hydrogen pressures from 14.7 psi (atmospheric pressure) to 240 psi for the reduction of nitronate **14b**. The reaction performed at atmospheric pressure afforded none of the desired pyrrolidine. However, the reactions conducted at pressures of 40–240 psi afforded the *N*-tosylpyrrolidine **17b** in 70–82% yield, presumably all within experimental error.

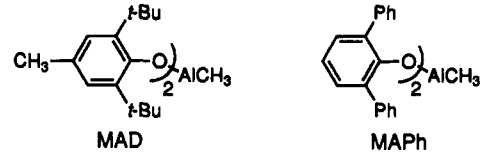


Figure 1.

The results obtained for the hydrogenolysis of nitronates **14a-g** are summarized in Table II. All reactions were carried out in a steel autoclave at a pressure of 160 psi at room temperature for 24 h. (These reactions could also be performed in a glass bottle Parr shaker at 40 psi.) The optimized conditions called for the use of 5–10 mol% of platinum oxide together with 1 mol equiv of glacial acetic acid in freshly distilled methanol. The crude pyrrolidines were isolated as their acetate salts **16**, after filtration of the clear reaction solutions through Celite and solvent evaporation. The pyrrolidines were directly treated with tosyl chloride in the presence of triethylamine or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). Analytically pure *N*-tosylpyrrolidines **17** were isolated in good yields (70–83%) after silica gel column chromatography and recrystallization or distillation.

Synthesis of 3,4-Disubstituted Pyrrolidines. To access vicinally disubstituted pyrrolidines, a stereoselective cycloaddition between a 2-monosubstituted nitroalkene and a 2-substituted vinyl ether is necessary Scheme VI. The resulting *trans*- or *cis*-4,5-disubstituted nitronates would then be reduced to the corresponding *trans*- or *cis*-3,4-disubstituted pyrrolidines.

Orienting experiments were conducted with (*E*)-2-nitrostyrene[40] (**18**) and commercially available ethyl (*E*)- and (*Z*)-1-propenyl ethers (**19**), Table III. The propenyl ether was obtained as a 3:1 (*E*/*Z*) mixture and could be separated by spinning band distillation to provide samples of both isomers with greater than 99% purity as determined by capillary GC analysis.[41] Initial results with MAD as the Lewis acid promoter were disappointing (poor yields and little diastereoselectivity). The use of MAPh,[35b] a bulkier and slightly less reactive Lewis acid, afforded products in excellent yields with better, but still disappointing diastereoselectivity, Table III, entries 1 and 2. Drawing analogy from our success with $TiCl_2(O\text{-}i\text{-}Pr)_2$ in tandem [4 + 2]/[3 + 2] cycloaddition reactions with propenyl ethers,[7a] we found that this Lewis acid promoted stereoselective and high-yielding cycloaddition reactions for both *E* and *Z* isomers of 1-propenyl ether with (*E*)-2-nitrostyrene, Table III, entries 3 and 4. Analytically pure nitronates **20a–d** were isolated by silica gel column chromatography and were individually characterized. However, the ^1H NMR data was insufficient to unam-

(37) 2,6-Diphenylphenol is no longer commercially available so it was prepared by the procedure of Dana, H. E.; Hay, A. S. *Synthesis* **1982**, 164–165.

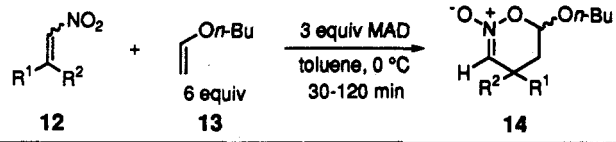
(38) (a) Torssell, K. B. G. *Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis*; VCH: New York, 1988; Chapter 4. (b) Breuer, E.; Aurich, H. G.; Nielsen, A. *Nitrones, Nitronates and Nitroxides*; John Wiley & Sons: New York, 1989; Chapter 4.

(39) Adams, R.; Voorhees, V.; Shriner, R. L. In *Organic Syntheses*, 2nd ed.; Blatt, A. H., Ed.; John Wiley & Sons: New York, 1941; Collect. Vol. 1, pp 463–470.

(40) Worral, D. E. In *Organic Syntheses*, 2nd ed.; Blatt, A. H., Ed.; John Wiley & Sons: New York, 1941; Collect. Vol. 1, pp 413–414.

(41) Ethyl (*E*/*Z*)-1-propenyl ether (3:1, (*E*:*Z*)) was purchased from Fluka. *E*: bp = 75.0 °C. *Z*: bp = 69.0 °C. GC (Hewlett Packard HP-5 column, 35 °C isotherm) t_R *E* isomer 6.98 min, t_R *Z* isomer 6.25 min.

Table I. Cycloadditions of 2,2-Disubstituted 1-Nitroalkenes



12 13 14

entry	R^1	R^2	starting alkene ratio (*E*/*Z*)	yield (%) 14	anomer ratio[a] 14
a	3,4-dimethoxyphenyl	ethyl	0:1.0	80	1.1:1.0
b	3,4-dimethoxyphenyl	*n*-butyl	1.0:2.2	76	1.0:1.0
c	3,4-dimethoxyphenyl	*i*-butyl	1.0:1.0	80	2.3:1.0
d	*n*-pentyl	ethyl	1.0:1.0	91	*b*
e	cyclohexyl	ethyl	1.0:1.5	90	1.5:1.0
f	phenyl	$(CH_2)_4CO_2Et$	1.0:1.8	88	2.5:1.0
g	phenyl	ethyl	1.0:1.5	83	1.1:1.0

[a] Anomer ratios were determined by ^1H NMR integration of the acetal proton. [b] Could not be determined by ^1H NMR.

Scheme V

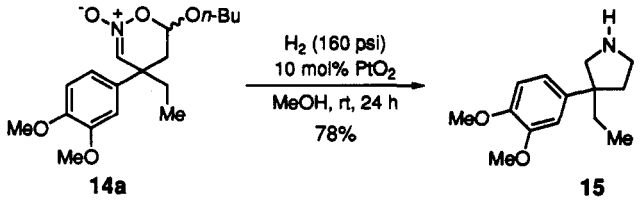
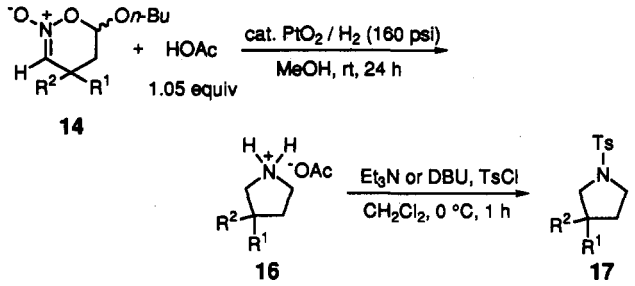


Table II. Preparation of 3,3-Disubstituted Pyrrolidines from the Reduction of Nitronates



entry	R^1	R^2	yield 17 (%)[a]
a	3,4-dimethoxyphenyl	ethyl	83
b	3,4-dimethoxyphenyl	*n*-butyl	70 (50)
c	3,4-dimethoxyphenyl	*i*-butyl	73 (46)
d	*n*-pentyl	ethyl	77
e	cyclohexyl	ethyl	80 (55)
f	phenyl	$(CH_2)_4CO_2Et$	78

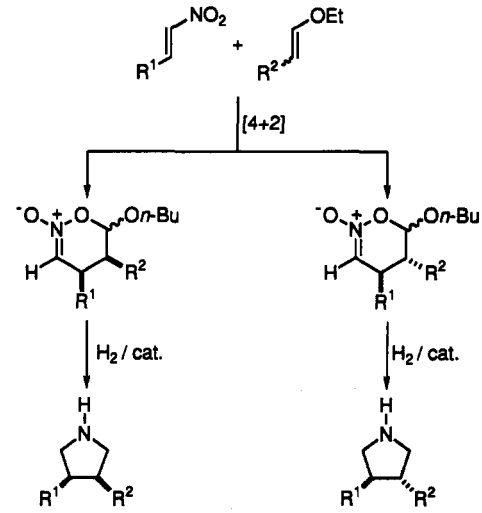
[a] Numbers in parentheses represent yields obtained from hydrogenolyses conducted in the absence of acetic acid.

biguously establish the relative configuration of the phenyl and methyl ring substituents.

Configurational assignments for nitronates **20a–d** were determined only after reduction to the corresponding pyrrolidines. Both isomers **20a** and **20b** were independently reduced under standard conditions to afford the *trans*-pyrrolidine **21a** in good yield (78–79%), Scheme VII. Likewise, independent hydrogenolysis of isomers **20c** and **20d** produced the *cis*-pyrrolidine **21b** in 65–83% yield. Interestingly, unlike the previously mentioned reductions to produce 3,3-disubstituted pyrrolidines, the addition of *acetic acid resulted in decreased yields of pyrrolidine* products and was therefore omitted.

Stereostructural assignments of **21a** and **21b** were inferred by analysis of their ^1H NMR coupling constants extracted from 400-MHz spectra, Figure 2. The pyrrolidine **21a** has a 10.0-Hz coupling between the methine protons on C(3) and C(4), where as, the pyrrolidine **21b** has a 6.6-Hz coupling constant between the same two protons. On the basis of similar values reported in the literature for pyrrolidines, we assigned the trans configuration to **21a** and the cis configuration to **21b**.[42]

Scheme VI



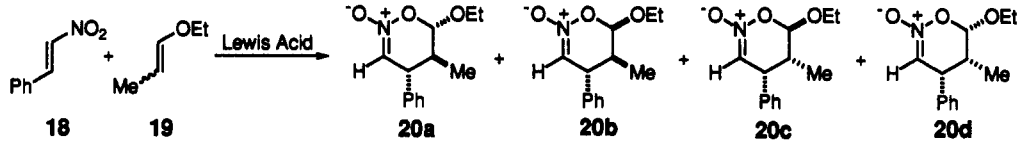
Our next target, *trans*-3,4-diphenylpyrrolidine, was of interest because of its utility (in optically active form) as a chiral ligand in the asymmetric addition of Grignard reagents to aldehydes,[5f,g] as well as in asymmetric osmylations.[5h] Synthesis of this compound would require a nitroalkene [4 + 2] cycloaddition between (*E*)-2-nitrostyrene and ethyl 2-styryl ether (**22**), Scheme VIII. Ethyl 2-styryl ether was prepared in 76% yield by a Wittig benzylidenation of ethyl formate.[43] The enol ether was obtained as an 86:14 (*E*/*Z*) mixture of isomers and was enriched to 93:7 (*E*/*Z*) by spinning band distillation. The ratio of isomers was determined by capillary GC analysis.[44] Reaction of (*E*)-2-nitrostyrene and the *E*-enriched enol ether **22**, promoted by MAPh, afforded nitronate **23** as a 1:1 mixture of diastereomers in 65% yield. *However, the use of $TiCl_2(O\text{-}i\text{-}Pr)_2$ as the Lewis acid promoter afforded nitronate 23, as a single product, in 91% yield.* Hydrogenolysis of nitronate **23**, followed by *N*-protection as the tosylamide, proceeded smoothly to provide *trans*-3,4-diphenyl-*N*-(*p*-tolylsulfonyl)pyrrolidine (**24**) in 83% yield.

Discussion

Cycloadditions of 2,2-Disubstituted 1-Nitroalkenes. Cycloaddition of 2,2-disubstituted 1-nitroalkenes **12a–g**

(42) Deprez, P.; Royer, J.; Husson, H. P. *Synthesis* **1991**, 759–762.
(43) Subraman, V.; Silver, E. H.; Soloway, A. H. *J. Org. Chem.* **1976**, *41*, 1272–1273.
(44) GC (Hewlett-Packard Ultra-2 column, 150 °C, 5 min, 5 °C/min, 200 °C, 10 min) t_R *E* isomer 9.60 min, t_R *Z* isomer 9.24 min.

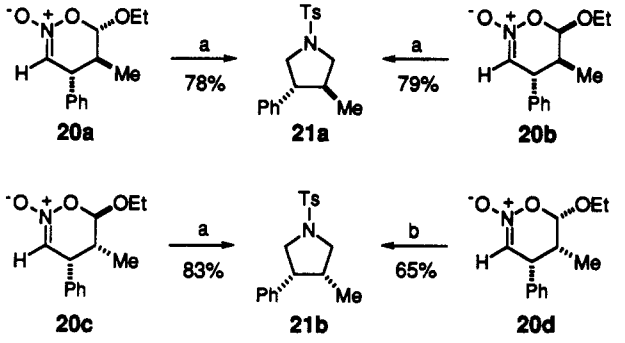
Table III. Cycloadditions of (*E*)- and (*Z*)-1-Propenyl Ethers with (*E*)-2-Nitrostyrene



				product distribution[a]				
entry	Lewis acid (equiv)	enol ether 19	combined 20 yield (%)	20a	20b	20c + 20d	ratio exo/endo	ratio cis/trans
1	MAPh (2.0)	*E*	88	1.0	–	1.4 (**20c**)	58:42	58:42
2	MAPh (3.0)	*Z*	92	–	7.5	1.0 (**20d**)	88:12	12:88
3	$TiCl_2(O\text{-}i\text{-}Pr)_2$ (3.0)	*E*	89	28	1.0	2.0	6:94	6:94
4	$TiCl_2(O\text{-}i\text{-}Pr)_2$ (3.0)	*Z*	84	1.0	12	113	10:90	90:10

[a] Ratios for entries 1 and 2 represent isolated quantities. Ratios for entries 3 and 4 were determined in part by ^1H NMR integrations of product mixtures.

Scheme VII[a]



[a] (a) (i) H_2/PtO_2, (ii) Et_3N, TsCl; (b) (i) H_2/PtO_2, (ii) DBU, TsCl.

proceeded rather slowly in comparison to 2-monosubstituted nitroalkenes previously investigated by these laboratories. On the basis of electronic effects alone, one might expect that an additional alkyl substituent would raise the nitroalkene reactivity by making the heterodiene more electron-rich. Previous Hammett studies conducted on a series of 4-substituted nitrostyrenes have shown that electron-rich nitroalkenes are *more* reactive in Lewis acid-promoted cycloadditions than their electron-deficient analogs.[9c] Therefore, the lower reactivity of 2,2-disubstituted 1-nitroalkenes must be attributed to a significant steric effect. The second alkyl substituent on the β-position of the heterodiene lowers the diene reactivity by contributing additional nonbonded interactions with the dienophile in the polarized [4 + 2] transition structure. Experimental and computational studies of heterodiene [4 + 2] cycloadditions support the notion of an unsymmetrical transition state wherein bond formation at the β-carbon is further advanced than at the α-carbon.[45] This would tend to amplify the steric effects of substituents at those positions.

The poor diastereoselectivity observed in the cycloaddition of 2,2-disubstituted 1-nitroalkenes with *n*-butyl vinyl ether can be attributed to poor exo/endo selectivity in cycloaddition or possibly isomerization of the nitroalkene under the reaction conditions. The origin of the poor selectivity was not investigated, since anomer mixtures were found to be suitable for our subsequent purposes.

Preparation of 3,3-Disubstituted Pyrrolidines. The hydrogenolysis of nitronates to pyrrolidines is interesting and deserves some comment. While no mechanistic studies

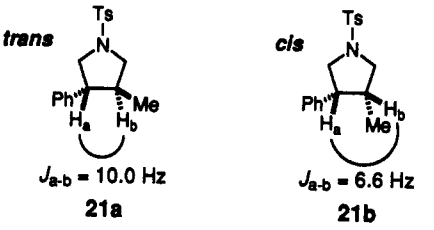
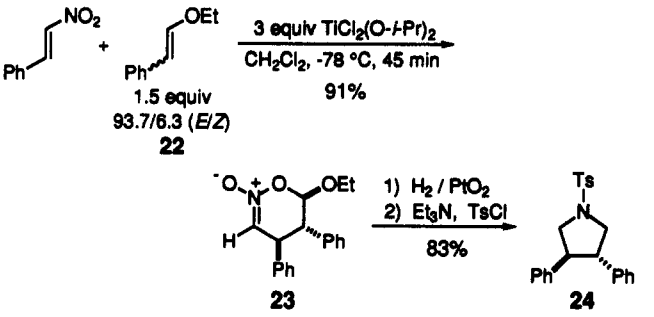
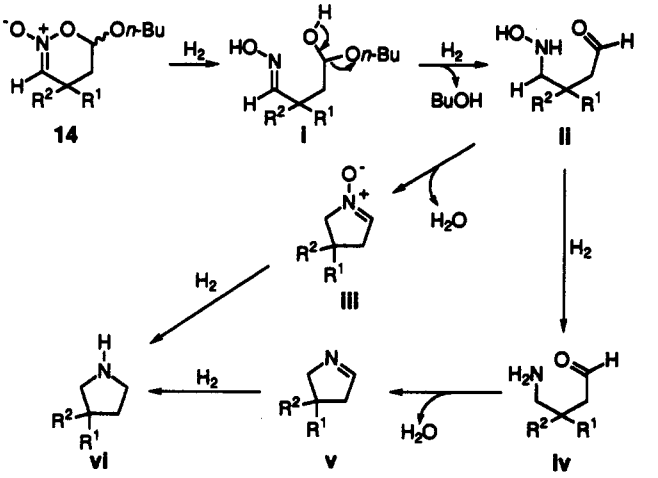


Figure 2. ^1H NMR couplings for **21a** and **21b**.

Scheme VIII



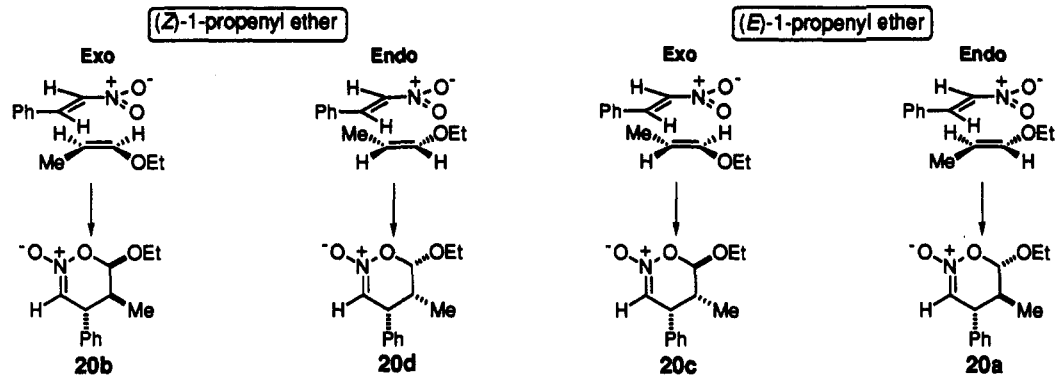
Scheme IX



of this reaction have been conducted, a plausible mechanistic proposal is outlined in Scheme IX. The first step involves the addition of molecular hydrogen to the nitronate **14** to cleave the internal N–O bond and afford the oxime hemiacetal **i**. This intermediate can also be accessed by saturation of the C=N bond followed by elimination. The unstable hemiacetal breaks down to the parent aldehyde by loss of *n*-butanol, and a second equivalent of hydrogen reduces the oxime to produce the

(45) (a) Tietze, L.-F.; Bumbry, T.; Brand, S.; Bratz, M. *Chem. Ber.* **1988**, *121*, 499–506. (b) Tietze, L.-F.; Fennen, J.; Wichmann, J. *Chem. Ber.* **1992**, *125*, 1507–1511.

Scheme X



hydroxylamine aldehyde **ii**. It is unclear at this point as to whether the intermediate **ii** would spontaneously cyclize to afford the nitrone **iii** or be further reduced to the amido aldehyde **iv**. Regardless, the nitrone **iii** would be readily reduced to the pyrrolidine **vi**. Likewise, the amino aldehyde **iv** would cyclize to the imine **v** and would be saturated to afford the same pyrrolidine product **vi**. Considering the number of intermediates involved in this transformation (regardless of the precise mechanism), it is remarkable that such good yields of pyrrolidines are obtained.

The level of nitronate substitution also had little or no effect on the outcome of the hydrogenolysis reaction. Variation of substitution from aryl to alkyl and α-branched alkyl resulted in little change in the yield or rate of the reaction. However, the effect of added acetic acid was dramatic. The yields of *N*-tosylated pyrrolidines improved by 20–35% when conducting the reaction in the presence of 1 equiv of acetic acid, Table III, entries b, c, and e. The role of acetic acid in the reaction is unclear, since many intermediates contain a basic nitrogen atom. It is well known that basic nitrogen functions can foil hydrogenations by poisoning the catalyst.[46] However, there are other, potentially acid-catalyzed processes involved in the overall sequence, such as nitrone or imine formation and dehydration. Moreover, the saturation of the azomethine functions can also be acid catalyzed.

Synthesis of 3,4-Disubstituted Pyrrolidines. The mode of cycloaddition of (*E*)- and (*Z*)-1-propenyl ether with (*E*)-2-nitrostyrene (exo versus endo) and attendant stereostructure of the final products was dependent on the configuration of the vinyl ether and the Lewis acid employed. The methyl group of the propenyl ether serves as a stereochemical marker preserving the memory of an exo or endo [4 + 2] transition structure. Thus, knowing the starting enol ether geometry and the final relationship between the 3-phenyl and 4-methyl substituents on the pyrrolidine products, we could deduce the configuration of the nitronates and thereby establish if they arose from exo or endo [4 + 2] transition structures.

Reactions performed utilizing MAPh produced nitronates that were enriched in isomers derived from an exo (ethoxy) approach of the dienophile (**20b** and **20c**) in the [4 + 2] cycloaddition, Scheme X. A preference for the exo orientation of a vinyl alkoxy group in nitroalkene [4 + 2] cycloadditions promoted by MAPh has been our general experience.[7b,10c] It is believed that the bulk of the aluminum-based Lewis acid forces the ethoxy group to take up an exo orientation to minimize nonbonded interactions. However, the difference in the magnitude of selectivity for the *E*-vinyl ether (58:42 (exo/endo)) and the *Z*-vinyl ether (88:12 (exo/endo)) deserves some comment. It is suspected that in transition state for the *E*-propenyl ether, a significant steric interaction exists between the vinyl methyl group and the nitroalkene which may be responsible for the erosion of selectivity. This interaction is absent in the transition state with the Z-propenyl ether. Thus, a delicate balance of steric effects between the Lewis acid–nitroalkene complex and the vinyl ether is responsible for the stereochemical outcome.

In contrast, reactions conducted with $TiCl_2(O\text{-}i\text{-}Pr)_2$ produced nitronates that were enriched in isomers derived from an endo (ethoxy) approach of the dienophile (**20a** and **20d**), Scheme X. For (*E*)-**19** and (*Z*)-**19**, a 94:6 and a 90:10 endo/exo diastereoselectivity was observed, respectively. The strong preference for an endo orientation of the alkoxy group in $TiCl_2(O\text{-}i\text{-}Pr)_2$-promoted nitroalkene cycloadditions has been discussed in detail.[7,8,10] It is believed that the transition structure of the titanium-promoted nitroalkene [4 + 2] cycloaddition is highly polarized, placing a partial positive charge on the nitrogen atom of the alkene. Therefore, the participating vinyl ether assumes an endo orientation of the electron-rich alkoxy due to stabilizing interactions. Unlike the bulky aluminum-based Lewis acid, the relatively small titanium-based Lewis acid can accommodate the endo orientation of the alkoxy group.

In reactions which employed $TiCl_2(O\text{-}i\text{-}Pr)_2$, the formation of varying amounts of all four possible diastereomers was observed. This can be attributed to epimerization of the acetal center in the nitronate products by the excess Lewis acid present. Isomerization of the starting enol ether can be ruled out, since Schnute and Senanayake have observed that enol ethers are not susceptible to isomerization under the reaction conditions.[7a]

The hydrogenolysis of the individual nitronate diastereomers **20a–d** was straightforward providing the corresponding *trans*- or *cis*-pyrrolidines **21a,b** in good yields. The decreased yield of pyrrolidines obtained when 1 equiv of acetic acid was employed in the reduction was surprising. We suspect that in these examples the added acid decomposed a significant portion of the acid-labile nitronates into unproductive intermediates before hydrogenolysis could occur.

The highly diastereoselective [4 + 2] cycloaddition reaction of (*E*)-2-nitrostyrene with trans-enriched styryl ether **22** to afford nitronate **23** was intriguing, Scheme VIII. A 93:7 (*E*/*Z*) ratio of the styryl ether was utilized

(46) Rylander, P. N. *Catalytic Hydrogenation in Organic Syntheses*; Academic Press: New York, 1979; p 154.

and only a single diastereomer of nitronate was isolated in 91% yield. This requires that the *E*-enol ether is more reactive than the *Z*-enol ether, and a kinetic resolution occurred in which the *E*-enol ether reacted preferentially, consuming all of the nitroalkene before *Z*-enol ether could react (the enol ether was used in excess). The stereostructure of the cycloaddition product indicates an endo (ethoxy) orientation of the dienophile in the transition state and is consistent with the previous observations with (*E*)-2-nitrostyrene and (*E*)-1-propenyl ether.

Conclusion

2,2-Disubstituted 1-nitroalkenes are effective heterodienes in MAD-promoted [4 + 2] cycloadditions with *n*-butyl vinyl ether. The cycloadducts were produced as anomeric mixtures in good yields. Significantly, this work comprises the first examples of the formation of a quaternary center by nitroalkene cycloaddition chemistry.

In addition, we have accomplished the selective reduction of cyclic nitronates to substituted pyrrolidines. 3,3-Disubstituted and *cis*/*trans*-3,4-disubstituted pyrrolidines were prepared in good yield and high diastereoselectivity from nitroalkene cycloaddition products. Importantly, this scheme constitutes a general and useful route to 3,3- and 3,4-substituted pyrrolidines from nitroalkenes and vinyl ethers in two steps. Current studies in our laboratories are focused on the enantioselective synthesis of 3-substituted pyrrolidines by the use of chiral dienophiles in the [4 + 2] cycloaddition and on the application of this method to the total synthesis of selected alkaloids.

Experimental Section

General. For general methods see the preceding paper in this issue.

Materials. *n*-Butyl vinyl ether, triethylamine, 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU), ethyl 1-propenyl ether, titanium(IV) chloride, and titanium(IV) isopropoxide were obtained from commercial sources and were distilled. 2,6-Di-*tert*-butyl-4-methylphenol (BHT) and *p*-toluenesulfonyl chloride (TsCl) were obtained from commercial sources and recrystallized. Trimethylaluminum (2.0 M in toluene, Aldrich) and glacial acetic acid (99.7%) were obtained from commercial sources and used as received. 2,6-Diphenylphenylphenol[37] and (*E*)-2-nitrostyrene[40] were prepared by the literature methods.

^{1}H and ^{13}C NMR chemical shifts are reported as δ values. IR absorption frequencies are reported in cm^{-1}.

General Procedure for the [4 + 2] Cycloaddition of 2,2-Disubstituted 1-Nitroalkenes (12a–g) with Butyl Vinyl Ether (General Procedure I). The preparation of **14a** from **12a** will serve to illustrate the general procedure utilized.

6-Butoxy-4-(3′,4′-dimethoxyphenyl)-4-ethyl-5,6-dihydro-4*H*-[1,2]-oxazine *N*-Oxide (14a). To a solution of BHT (1.23 g, 5.79 mmol, 6 equiv) in toluene (6 mL) was added dropwise trimethylaluminum (2.0 M in toluene, 1.45 mL, 2.90 mmol, 3 equiv). Gas evolution was observed as the solution was stirred at room temperature for 1 h. The resulting clear solution was transferred, via cannula, to a second reaction vessel containing a solution of nitroalkene **12a** (0.229 g, 0.956 mmol, 100% *Z*) and *n*-butyl vinyl ether (0.749 mL, 5.79 mmol, 6 equiv) in toluene (0.4 mL) at 0 °C. The dark red reaction mixture was allowed to stir for 1 h as the color faded to a light rust. The reaction was quenched with water (5 mL), poured into CH_2Cl_2 (150 mL) and washed with water (3 × 100 mL). The aqueous layers were back-extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4), and concentrated. The crude organic concentrate was purified by silica gel column chromatography (hexane/EtOAc, (3/2)) to afford 0.260 g (80%) of analytically pure **14a** as a clear, heavy oil, in a ratio of 1.0:1.1 (**14aa**/**14ab**) by ^{1}H NMR integration. The anomers were separated by a second silica gel column provide **14aa** as a white solid and analytically pure **14ab** as a heavy oil. An analytical sample of **14aa** was obtained after recrystallization (hexane) to afford a white microcrystalline material. **14aa**: mp 61–62 °C; ^{1}H NMR (300 MHz), 6.84–6.70 (m, 3 H, Ph), 6.62 (s, 1 H, HC(3)), 5.22 (dd, J = 3.7, J = 5.7, 1 H, HC(6)), 3.97 (dt, J_t = 6.7, J_d = 9.4, 1 H, $H_aC(9)$), 3.88 (s, 3 H, OCH_3), 3.87 (s, 3 H, OCH_3), 3.52 (dt, J_t = 6.7, J_d = 9.4, 1 H, $H_bC(9)$), 2.39 (dd, J = 3.7, J = 13.9, 1 H, $H_aC(5)$), 2.11 (dd, J = 5.7, J = 13.9, 1 H, $H_bC(5)$), 1.99 (m, 2 H, $H_2C(7)$), 1.59 (m, 2 H, $H_2C(10)$), 1.36 (m, 2 H, $H_2C(11)$), 0.91 (t, J = 7.3, 3 H, $H_3C(12)$), 0.78 (*t*, J = 7.4, 3 H, $H_3C(8)$); ^{13}C NMR (75.5 MHz) 149.19 (C(3′)), 148.02 (C(4′)), 135.96 (C(1′)), 118.48 (C(6′)), 117.50 (C(3)), 111.06 (C(5′)), 109.14 (C(2′)), 102.63 (C(6)), 69.88 (C(9)), 55.99 (OCH_3), 55.81 (OCH_3), 43.09 (C(4)), 38.85 (C(5)), 33.83 (C(7)), 31.39 (C(10)), 19.06 (C(11)), 13.72 (C(12)), 8.43 (C(8)); IR (CCl_4) 2963 (s), 1620 (s); MS (CI, CH_4) 338 (M^+ + 1, 8); TLC R_f 0.22 (hexane/EtOAc, (1/1)). Anal. Calcd for $C_{18}H_{27}NO_5$ (337.42): C, 64.07; H, 8.07; N, 4.15. Found: C, 64.24; H, 8.08; N, 4.27. **14ab**: ^{1}H NMR (300 MHz) 6.79–6.75 (m, 3 H, Ph), 6.62 (s, 1 H, HC(3)), 5.35 (t, J = 3.3, 1 H, HC(6)), 3.91–3.85 (m, 7 H, $H_aC(9)$, OCH_3, OCH_3), 3.45 (dt, J_t = 6.6, J_d = 9.4, 1 H, $H_bC(9)$), 2.28 (dd, J = 3.3, J = 14.1, 1 H, $H_aC(5)$), 2.23 (dd, J = 3.3, J = 14.1, 1 H, $H_bC(5)$), 1.89 (m, 2 H, $H_2C(7)$), 1.39 (m, 2 H, $H_2C(10)$), 1.16 (m, 2 H, $H_2C(11)$), 0.80 (t, J = 7.3, 6 H $H_3C(8)$, $H_3C(12)$); ^{13}C NMR (75.5 MHz) 148.76 (C(3′)), 147.63 (C(4′)), 136.78 (C(1′)), 118.39 (C(6′)), 117.81 (C(3)), 110.75 (C(5′)), 109.73 (C(2′), 102.27 (C(6)), 69.42 (C(9)), 55.89 (OCH_3), 55.80 (OCH_3), 41.98 (C(4)), 37.85 (C(5)), 34.89 (C(7)), 31.33 (C(10)), 18.90 (C(11)), 13.62 C(12)), 8.55 (C(8)); IR (CCl_4) 2963 (s), 1622 (s); MS (CI, CH_4) 338 (M^+ + 1, 32); TLC R_f 0.15 (hexane/EtOAc, (1/1)); Anal. Calcd for $C_{18}H_{27}NO_5$ (337.42): C, 64.07; H, 8.07; N, 4.15. Found: C, 63.92; H, 8.06; N, 4.14.

6-Butoxy-4-butyl-4-(3′,4′-dimethoxyphenyl)-5,6-dihydro-4*H*-[1,2]-oxazine *N*-Oxide (14b). General Procedure I. A solution of MAD (2.83 mmol, 3 equiv) in toluene (5 mL) was added to a mixture of nitroalkene **12b** (0.250 g, 0.942 mmol, 1.0: 2.2 (*E*/*Z*)) and *n*-butyl vinyl ether (0.760 mL, 5.65 mmol, 6 equiv) in toluene (0.8 mL) at −78 °C. The reaction mixture was warmed to 0 °C, allowed to stir for 45 min, and then quenched with water (5 mL). After aqueous workup, the crude organic concentrate was purified by silica gel column chromatography (hexane/EtOAc, (2/1)) to afford 0.263 g (76%) of an anomeric mixture of nitronates, as a clear oil, in a ratio of 1.0:1.0 (**14ba**/**14bb**) by ^{1}H NMR integration. **14ba**, **14bb**: ^{1}H NMR (300 MHz) 6.84–6.69 (m, 3 H, Ph), 6.63 (m, 1 H, HC(3)), 5.36 (t, J = 3.4, 0.5 H, $HC_a(6)$), 5.21 (dd, J = 3.7, J = 5.7, 0.5 H, $HC_b(6)$), 3.99–3.87 (m, 7 H, $H_aC(11)$, OCH_3, OCH_3), 3.53–3.45 (m, 1 H, $H_bC(11)$), 2.41–1.94 (m, 2 H, $H_2C(5)$), 1.89–1.80 (m, 2 H, $H_2C(7)$), 1.61–1.54 (m, 2 H, $H_2C(12)$), 1.46–1.10 (m, 6 H, $H_2C(8)$, $H_2C(9)$, $H_2C(13)$), 0.94–0.80 (m, 6 H, $H_3C(10)$, $H_3C(14)$). ^{13}C NMR (75.5 MHz) **14ba**: 149.02 (C(3′)), 147.48 (C(4′)), 136.22 (C(1′)), 118.14 (C(6′)), 117.62 (C(3)), 110.68 (C(5′)), 109.58 (C(2′)), 102.45 (C(6)), 69.22 (C(11)), 55.74 (OCH_3), 42.59 (C(4)), 41.50 (C(7)), 38.11 (C(5)), 31.22 (C(12)), 26.03 (C(8)), 18.73 (C(13)), 13.61, 13.53. **14bb**: 148.61 (C(3′)), 147.85 (C(4′)), 137.02 (C(1′)), 118.18 (C(6′)), 117.87 (C(3)), 110.96 (C(5′)), 108.99 (C(2′)), 102.11 (C(6)), 69.62 (C(11)), 58.82 (OCH_3), 41.83 (C(4)), 40.66 (C(7)), 38.90 (C(5)), 31.18 (C(12)), 25.89 (C(8)), 18.89 (C(13)), 13.58, 13.44. **14ba**, **14bb**: 55.63 (OCH_3), 22.67 (C(9)); IR (neat) 2957 (s), 1617 (s); MS (70 eV) 365 (M^+, 15); TLC R_f 0.16 (hexane/EtOAc, (2/1)). Anal. Calcd for $C_{20}H_{31}NO_5$ (365.47): C, 65.73; H, 8.55; N, 3.83. Found: C, 65.55; H, 8.60; N, 3.85.

6-Butoxy-4-(*i*-butyl)-4-(3′,4′-dimethoxyphenyl)-5,6-dihydro-4*H*-[1,2]-oxazine *N*-Oxide (14c). General Procedure I. A solution of MAD (1.60 mmol, 3 equiv) in toluene (2.8 mL) was added to a mixture of nitroalkene **12c** (0.140 g, 0.528 mmol, 1.0: 1.0 (*E*/*Z*)) and *n*-butyl vinyl ether (0.426 mL, 3.16 mmol, 6 equiv) in toluene (0.3 mL) at −78 °C. The reaction mixture was warmed to 0 °C, allowed to stir for 105 min, and then quenched with water (5 mL). After aqueous workup, the crude organic concentrate was purified by silica gel column chromatography (hexane/EtOAc, (3/2)) to afford 0.155 g (80%) of an anomeric mixture of nitronates, as a clear oil, in a ratio of 2.3:1.0 (**14ca**/**14cb**) by ^{1}H NMR integration. **14ca**, **14cb**: ^{1}H NMR (300 MHz), 6.78–6.25 (m, 4 H, HC(3), Ph), 5.30 (t, J = 3.3, 0.7 H, $HC_a(6)$), 5.12 (dd, J = 3.3, J = 5.7, 0.3 H, $HC_b(6)$), 3.92–3.80 (m, 7 H, $H_aC(11)$, OCH_3, OCH_3), 3.47–3.37 (m, 1 H, $H_bC(11)$), 2.39–1.70

(m, 4 H, $H_2C(5)$, $H_2C(7)$), 1.50 (m, 2 H, $H_2C(12)$), 1.29 (m, 2 H, $H_2C(13)$), 1.09 (m, 1 H, HC(8)), 0.86–0.66 (m, 9 H, $H_3C(9)$, $H_3C(10)$, $H_3C(14)$). ^{13}C NMR (75.5 MHz) **14ca**: 148.93 (C(3′)), 147.87 (C(4′)), 136.29 (C(1′)), 118.32 (C(6′)), 110.87 (C(5′)), 109.17 (C(2′)), 102.47 (C(6)), 69.61 (C(11)), 55.85 (OCH_3), 49.67 (C(7)), 42.88 (C(4)), 39.45 (C(5)), 31.23 (C(12)), 24.50, 24.39, 24.03, 18.89 (C(13)), 13.54 (C(14). **14cb**: 148.51 (C(3′)), 147.49 (C(4′)), 137.18 (C(1′)), 118.27 (C(6′)), 110.59 (C(5′)), 109.60 (C(2′)), 102.07 (C(6)), 69.17 (C(11)), 55.77 (OCH_3), 41.76 (C(7)), 38.60 (C(5)), 31.16 (C(12)), 24.57, 24.46, 24.08, 18.73 (C(13)), 13.46 (C(14)). **14ca, 14cb**: 118.10 (C(3)), 55.64 (OCH_3); IR (neat) 2957 (s); MS (70 eV) 365 (M^+, 27); TLC R_f 0.21 (hexane/EtOAc, (2/1)). Anal. $C_{20}H_{31}NO_5$ (365.47): C, 65.73; H, 8.55; N, 3.83. Found: C, 65.60; H, 8.58; N, 3.83.

6-Butoxy-4-ethyl-4-pentyl-5,6-dihydro-4*H*-[1,2]-oxazine *N*-Oxide (14d). General Procedure I. A solution of MAD (8.76 mmol, 3 equiv) in toluene (15 mL) was added to a mixture of nitroalkene **12d** (0.500 g, 2.92 mmol, *E*/*Z* mixture) and *n*-butyl vinyl ether (1.18 mL, 8.76 mmol, 3 equiv) in toluene (2.5 mL) at 0 °C. The reaction mixture was stirred for 30 min, at 0 °C, and then was quenched with water (10 mL). After aqueous workup, the crude organic concentrate was purified by silica gel column chromatography (hexane/EtOAc, (3/1)) to afford 0.719 g (91%) of analytically pure **14d** (mixture of anomers) as a heavy oil. **14da, 14db**: ^1H NMR (400 MHz) 6.19 (s, 1 H, HC(3)), 5.30 (t, J = 3.7, 1 H, HC(6)), 3.96 (m, 1 H, $H_aC(14)$), 3.55 (m, 1 H, $H_bC(14)$), 1.86 (m, 2 H, $H_2C(5)$), 1.66–1.20 (m, 14 H), 0.93–0.86 (m, 9 H, $H_3C(11)$, $H_3C(13)$, $H_3C(17)$). ^{13}C NMR (100.6 MHz) **14da**: 119.69 (C(3)), 69.61 (C(14)), 38.21, 37.91 (C(4)), 33.82 (C(5)), 31.70, 22.98, 22.41, 19.13 (C(16)), 13.95 (C(11)), 13.72 (C(17)), 7.79 (C(13)). **14db**: 119.76 (C(3)), 69.63 (C(14)), 38.57, 37.83 (C(4)), 33.80 (C(5)), 31.27, 23.51, 22.42, 19.11 (C(16)) 13.93 (C(11)), 13.73 (C(17)), 8.27 (C(13)). **14da, 14db**: 102.52 (C(6)), 32.11, 31.40; IR (Neat) 2957 (s), 1622 (s); MS (CI, CH_4) 272 (M^+ + 1, 100); TLC R_f 0.13, 0.25 (hexane/EtOAc, (4/1)). Anal. Calcd for $C_{15}H_{29}NO_3$ (271.40): C, 66.38; H, 10.77; N, 5.16. Found: C, 66.31; H, 10.77; N, 5.17.

6-Butoxy-4-cyclohexyl-4-ethyl-5,6-dihydro-4*H*-[1,2]-*N*-Oxide (14e). General Procedure I. A solution of MAD (4.08 mmol, 3.0 equiv) in toluene (5 mL) was added to mixture of nitroalkene **12e** (0.250 g, 1.36 mmol, 1.0/1.5 (*E*/*Z*) mixture) and *n*-butyl vinyl ether (0.55 mL, 4.08 mmol, 3 equiv) in toluene (0.5 mL) at 0 °C. The reaction mixture was stirred for 2 h, at 0 °C, and then was quenched with water (5 mL). After aqueous workup, the crude organic concentrate was purified by silica gel column chromatography (hexane/EtOAc, (4/1)) to afford 0.347 g (90%) of an anomeric mixture of nitronates, as a heavy oil, in a ratio of 1.5:1.0 (**14ea/14eb**). **14ea, 14eb**: ^1H NMR (400 MHz) 6.19 (s, 0.4 H, $HC_b(3)$), 6.16 (s, 0.6 H, $HC_a(3)$), 5.26–5.20 (m, 1 H, HC(6)), 3.94 (m, 1 H, $H_aC(9)$), 3.53 (m, 1 H, $H_bC(9)$), 2.01–0.83 (m, 25 H). ^{13}C NMR (100.6 MHz) **14ea**: 120.22 (C(3)), 103.09 (C(6)), 69.98 (C(9)), 44.25 (C(1′)), 41.68 (C(4)), 33.09 (C(5)), 31.39 (C(10)), 30.70, 27.71, 26.57, 26.26, 19.04 (C(11)), 8.57 (C(8)). **14eb**: 119.64 (C(3)), 102.59 (C(6)), 69.53 (C(9)), 43.71 (C(1′)), 40.76 (C(4)), 31.65 (C(5)), 31.36 (C(10)), 29.98, 27.61, 26.42, 26.20, 19.09 (C(11)), 7.73 (C(8)). **14ea, 14eb**: 26.49, 26.47, 13.72 (C(12)); IR (neat) 2928 (s), 1622 (s); MS (CI, CH_4) 284 (M^+ + 1, 100); TLC R_f 0.12, 0.16 (hexane/EtOAc, (4/1)). Anal. Calcd for $C_{16}H_{29}NO_3$ (283.41): C, 67.81; H, 10.31; N, 4.94. Found: C, 67.95; H, 10.49; N, 4.82.

6-Butoxy-4-[(ethoxycarbonyl)butyl]-4-phenyl-5,6-dihydro-4*H*-[1,2]-oxazine *N*-Oxide (14f). General Procedure I. A solution of MAD (5.4 mmol, 3.0 equiv) in toluene (10 mL) was added to mixture of nitroalkene **12f** (0.500 g, 1.36 mmol, 1.0/1.8 (*E*/*Z*) mixture) and *n*-butyl vinyl ether (1.45 mL, 10.8 mmol, 6 equiv) in toluene (0.8 mL) at 0 °C. The reaction mixture was stirred for 30 min, at 0 °C, and was quenched with water (5 mL). After aqueous workup, the crude organic concentrate was purified by silica gel column chromatography (hexane/EtOAc, (2/1)) to afford 0.595 g (88%) of an anomeric mixture of nitronates, as a heavy oil, in a ratio of 2.5:1.0 (**14fa/14fb**). **14fa, 14fb**: ^1H NMR (400 MHz) 7.33–7.15 (m, 5 H, Ph), 6.64 (s, 0.7 H, HC(3)), 6.61 (s, 0.3 H, HC(3)), 5.31 (t, J = 3.2, 0.7 H, HC(6)), 5.18 (dd, J = 5.2, J = 4.0, 0.3 H, HC(6)), 4.04 (q, J = 7.1, 1.4 H, OCH_2CH_3), 4.03 (q, J = 7.1, 0.6 H, OCH_2CH_3), 3.92 (m, 0.3 H, C(12)), 3.82 (m, 0.7 H, $H_2C(12)$), 3.47 (m, 0.3 H, $H_2C(12)$), 3.37 (m, 0.7 H, $H_2C(12)$), 2.41–2.08 (m, 4 H, $H_2C(5)$, $H_2C(10)$), 1.86 (m, 2 H, $H_2C(7)$), 1.52 (m, 3 H), 1.35–1.01 (m, 8 H), 0.87 (t, J = 7.3, 0.9 H, $H_3C(15)$), 0.74 (t, J = 7.2, 2.1 H, $H_3C(15)$). ^{13}C NMR (100.6 MHz) **14fa**: 144.21 (Ph), 128.27 (Ph), 126.51 (Ph), 125.80 (Ph), 117.40 (C(3)), 102.08 (C(6)), 69.14 (C(12)), 41.76 (C(4)), 41.81, 37.60 (C(5)), 33.70, 31.08 (C(13)), 24.83, 23.48, 18.72 (C(14)), 13.51 (C(15)). **14fb**: 143.49 (Ph), 128.84 (Ph), 127.07 (Ph), 125.75 (Ph), 117.53 (C(3)), 102.41 (C(6)), 69.70 (C(12)), 42.84 (C(4)), 40.53, 38.71 (C(5)), 33.72, 31.26 (C(13)), 24.88, 23.38, 18.98 (C(14)), 13.64 (C(15)). **14fa, 14fb**: 173.08 (C(11)), 60.15 (CH_2CH_3), 14.05 (CH_2CH_3); IR (neat) 2957 (s), 1730 (s), 1619 (s); MS (CI, CH_4) 378 (M^+ + 1, 100); TLC R_f 0.14, 0.27 (hexane/EtOAc, (2/1)). Anal. Calcd for $C_{21}H_{31}NO_5$ (377.48): C, 66.82; H, 8.28; N, 3.71. Found: C, 66.61; H, 8.30; N, 3.86.

6-Butoxy-4-ethyl-4-phenyl-5,6-dihydro-4*H*-[1,2]-oxazine *N*-Oxide (14g). General Procedure I. A solution of MAD (5.88 mmol, 3 equiv) in toluene (10 mL) was added to a mixture of nitroalkene **12g** (0.350 g, 1.96 mmol, 1.0:1.5 (*E*/*Z*)) and *n*-butyl vinyl ether (1.58 mL, 11.76 mmol, 6 equiv) in toluene (2 mL) at −78 °C. The reaction mixture was warmed to 0 °C, stirred for 15 min, and then quenched with water (5 mL). After aqueous workup, the crude organic concentrate was purified by silica gel column chromatography (hexane/EtOAc, (4/1)) to afford 0.234 g of **14ga** and 0.218 g of **14gb** as clear oils. The products were isolated in a ratio of 1.1:1.0 (**14ga/14gb**) and in a combined yield of 0.562 g (83%). **14ga**: ^1H NMR (400 MHz) 7.33–7.19 (m, 5 H, Ph), 6.61 (s, 1 H, HC(3)), 5.17 (dd, J = 4.0, J = 5.5, 1 H, HC(6)), 3.91 (dt, J_t = 6.7, J_d = 9.5, 1 H, $H_aC(9)$), 3.69 (dt, J_t = 6.7, J_d = 9.5, 1 H, $H_bC(9)$), 2.40 (dd, J = 4.0, J = 13.9, 1 H, $H_aC(5)$), 2.09 (dd, J = 5.5, J = 13.9, 1 H, $H_bC(5)$), 1.95 (m, 2 H, $H_2C(7)$), 1.53 (m, 2 H, $H_2C(10)$), 1.31 (m, 2 H, $H_2C(11)$), 0.86 (t, J = 7.3, 3 H, $H_3C(12)$, 0.72 (t, J = 7.4, 3 H, $H_3C(8)$); ^{13}C NMR (100.6 MHz) 143.76 (C(1′)), 128.71 (C(3′)), 126.93 (C(4′)), 125.88 (C(2′)), 117.51 (C(3)), 102.48 (C(6)), 69.63 (C(9)), 43.24 (C(4)), 38.49 (C(5)), 33.62 (C(7)), 31.23 (C(10)), 18.92 (C(11)), 13.57 (C(12)), 8.25 (C(8)); IR (neat) 2961 (s), 1619 (s); MS (CI, CH_4) 278 (M^+ + 69); TLC R_f 0.32 (hexane/EtOAc, (2/1)). Anal. Calcd for $C_{16}H_{23}NO_3$ (277.36): C, 69.29; H, 8.36; N, 5.05. Found: C, 69.04; H, 8.37; N, 5.04. **14gb**: ^1H NMR (400 MHz) 7.28–7.14 (m, 5 H, Ph), 6.63 (s, 1 H, HC(3)), 5.31 (t, J = 3.2, 1 H, HC(6)), 3.82 (dt, J_t = 6.3, J_d = 9.3, 1 H, $H_aC(9)$), 3.37 (dt, J_t = 6.3, J_d = 9.3, 1 H, $H_bC(9)$), 2.31 (dd, J = 3.2, J = 14.1, 1 H, $H_aC(5)$), 2.21 (dd, J = 3.4, J = 13.9, 1 H, $H_bC(5)$), 1.88 (m, 2 H, $H_2C(7)$), 1.32 (m, 2 H, $H_2C(10)$), 1.07 (m, 2 H, $H_2C(11)$), 0.75 (m, 6 H, $H_3C(8)$, $H_3C(12)$); ^{13}C NMR (100.6 MHz) 144.13 (C(1′)), 128.17 (C(3′)), 126.40 (C(4′)), 126.00 (C(2′)), 117.30 (C(3)), 102.11 (C(6)), 69.10 (C(9)), 42.11 (C(4)), 37.22 (C(5)), 34.80 (C(7)), 31.08 (C(10)), 18.69 (C(11)), 13.45 (C(12)), 8.38 (C(8)); IR (neat) 2961 (s), 1619 (s); MS (CI, CH_4) 278 (M^+ + 1, 100); TLC R_f 0.16 (hexane/EtOAc, (2/1)). Anal. Calcd for $C_{16}H_{23}NO_3$ (277.36): C, 69.29; H, 8.36; N, 5.05. Found: C, 69.05; H, 8.40; N, 4.99.

3-(3′,4′-Dimethoxyphenyl)-3-ethylpyrrolidine (15). Platinum oxide (24.0 mg, 0.110 mmol, 0.1 equiv) was added to a 25 mm × 150 mm test tube equipped with a magnetic stir bar and charged with a solution of nitronate **14a** (0.358 g, 1.06 mmol) in methanol (10 mL). The test tube was placed in a steel autoclave which was then flushed and filled with hydrogen to a pressure of 160 psi. The reaction mixture was stirred for 24 h at room temperature. Afterwards, the steel autoclave was carefully depressurized (this must be done slowly to avoid effervescing the reaction solution out of the test tube) and the clear reaction solution filtered through a short Celite plug. The reaction vessel and Celite were washed with 10 mL of methanol, and the combined filtrate was concentrated to afford a yellow oil. The yellow oil was purified by MPLC ($CHCl_3$/MeOH/Et_3N, (80/10/1)) to afford 0.196 mg (78%) of **15** as a clear colorless oil. An analytical sample was obtained after bulb-to-bulb distillation: bp 160 °C (0.1 Torr); ^1H NMR (400 MHz) 6.77–6.70 (m, 3 H, Ph), 3.83 (s, 3 H, OCH_3), 3.81 (s, 3 H, OCH_3), 3.08–2.94 (m, 4 H, $H_2C(2)$, $H_2C(5)$), 2.36 (br, 1 H, NH), 2.06 (m, 1 H, $H_aC(4)$), 1.89 (m, 1 H, $H_bC(4)$), 1.62 (m, 2 H, $H_2C(6)$), 0.62 (t, J = 7.4, 3 H, $H_3C(7)$); ^{13}C NMR (100.6 MHz) 148.42 (C(3′)), 146.93 (C(4′)), 139.04 (C(1′)), 118.90 (C(6′)), 110.48 (C(5′)), 110.44 (C(2′)), 57.89 (C(2)), 55.78 (OCH_3), 55.69 (OCH_3), 51.44 (C(3)), 45.63 (C(5)), 36.95 (C(4)), 33.31 (C(6)), 9.61 (C(7)); IR (neat) 3350 (br, m), 2959 (s); MS (10 eV) 235 (M^+, 49); TLC R_f 0.18 ($CHCl_3$/MeOH/Et_3N, (80/10/1)). Anal. Calcd for $C_{14}H_{21}$-

NO_2 (235.33): C, 71.46; H, 8.99; N, 5.95. Found: C, 71.39; H, 9.01; N, 5.91.

General Procedure for the Preparation of 3,3-Disubstituted Pyrrolidines from the Reduction of Nitronates (14a–f) (General Procedure II). The preparation of **17a** from **10a** will serve to illustrate the general procedure utilized.

3-(3′,4′-Dimethoxyphenyl)-3-ethyl-*N*-(*p*-tolylsulfonyl)-pyrrolidine (17a). Acetic acid (39.0 μL, 0.678 mmol, 1.05 equiv) was added to a 25 mm × 150 mm test tube equipped with a magnetic stirring bar and charged with a solution containing platinum oxide (small spatula tip) and nitronate **14a** (0.218 g, 0.646 mmol) in methanol (10 mL). The test tube was placed in a steel autoclave which was then flushed and filled with hydrogen to a pressure of 160 psi. The reaction mixture was stirred for 24 h at room temperature. Afterwards, the steel autoclave was depressurized and the clear reaction solution filtered through a pipet Celite plug, washing with 10 mL of methanol. The filtrate was concentrated to afford a clear oil. Residual solvent was removed under high vacuum. The clear oil was dissolved in dichloromethane (2.5 mL) and cooled to 0 °C, and DBU (0.234 mL, 1.62 mmol, 2.5 equiv) was added, followed by a solution of TsCl (0.114 g, 0.711 mmol, 1.1 equiv) in dichloromethane (1 mL). The mixture was stirred for 1 h, poured into dichloromethane (75 mL), and washed with dilute aqueous HCl solution (0.2 M, 50 mL). The aqueous layer was back-extracted with dichloromethane (20 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), filtered through a pad of Celite, and concentrated. The crude organic concentrate was purified by silica gel column chromatography (hexane/EtOAc, (2/1)) and recrystallized (EtOAc/hexane) to afford 0.210 g (83%) of analytically pure **13a** as a white crystalline solid: mp 135–136 °C; ^{1}H NMR (400 MHz) 7.68 (d, J = 8.0, 2 H, HC(9)), 7.26 (d, J = 8.0, 2 H, HC(10)), 6.72 (d, J = 7.8, 1 H, HC(5′)), 6.57 (m, 2 H, HC(2′), HC(6′)), 3.82 (s, 6 H, OCH_3, OCH_3), 3.52 (d, J = 9.5, 1 H, $H_aC(2)$), 3.41–3.30 (m, 3 H, $H_bC(2)$, $H_2C(5)$), 2.39 (s, 3 H, $H_3C(12)$), 2.00 (m, 2 H, $H_2C(4)$), 1.50 (m, 2 H, $H_2C(6)$), 0.54 (t, J = 7.4, 3 H, $H_3C(7)$); ^{13}C NMR (100.6 MHz) 148.50 (C(3′)), 147.33 (C(4′)), 143.23 (C(11)), 136.38 (C(1′)), 133.96 (C(8)), 129.50 (C(10)), 127.20 (C(9)), 118.42 (C(6′)), 110.49 (C(5′)), 109.61 (C(2′)), 57.20 (C(2)), 55.78 (OCH_3), 55.70 (OCH_3), 49.86 (C(3)), 46.22 (C(5)), 35.31 (C(4)), 32.13 (C(6)), 21.41 (C(12)), 9.07 (C(7)); IR (CCl_4) 1354 (s), 1169 (s); MS (CI, CH_4) 390 (M^+ + 1, 100); TLC R_f 0.35 (hexane/EtOAc, (2/1)). Anal. Calcd for $C_{21}H_{27}NSO_4$ (389.51): C, 64.76; H, 6.99; N, 3.60. Found: C, 64.73; H, 7.06; N, 3.57.

3-Butyl-3-(3′,4′-dimethoxyphenyl)-*N*-(*p*-tolylsulfonyl)-pyrrolidine (17b). General Procedure II. A sample of nitronate **14b** (0.150 g, 0.410 mmol) in methanol was reduced with hydrogen in the presence of platinum oxide and 1 mol equiv of acetic acid. After reduction, the crude concentrated reaction mixture was dissolved in methylene chloride and reacted with triethylamine and TsCl. After acidic workup, the crude organic concentrate was purified by silica gel column chromatography (hexane/EtOAc, (3/1)) to afford 0.120 g (70%) of analytically pure **17b** as a clear heavy oil: ^{1}H NMR (400 MHz) 7.68 (d, J = 8.0, 2 H, HC(11)), 7.26 (d, J = 8.1, 2 H, HC(12)), 6.71 (d, J = 8.7, 1 H, HC(5′)), 6.56 (m, 2 H, HC(2′), HC(6′)), 3.82 (s, 6 H, OCH_3, OCH_3), 3.51–3.30 (m, 4 H, $H_2C(2)$, $H_2C(5)$), 2.38 (s, 3 H, $H_3C(14)$), 2.00 (m, 2 H, $H_2C(4)$), 1.36 (m, 2 H, $H_2C(6)$), 1.00 (m, 2 H, $H_2C(7)$), 0.82 (m, 2 H, $H_2C(8)$), 0.69 (t, J = 7.2, 3 H, $H_3C(9)$); ^{13}C NMR (100.6 MHz) 148.47 (C(3′)), 147.27 (C(4′)), 143.21 (C(13)), 136.75 (C(1′)), 133.97 (C(10)), 129.46 (C(12)), 127.17 (C(11)), 118.27 (C(6′)), 110.51 (C(5′)), 109.53 (C(2′)), 57.45 (C(2)), 55.78 (OCH_3), 55.65 (OCH_3), 49.35 (C(3)), 46.22 (C(5)), 39.28 (C(4)), 35.77 (C(6)), 26.74 (C(7)), 22.75 (C(8)), 21.34 (C(14)), 13.72 (C(9)); IR (CCl_4) 2932 (s), 1354 (s); MS (10 eV) 417 (M^+, 96); TLC R_f 0.25 (hexane/EtOAc, (2/1)). Anal. Calcd for $C_{23}H_{31}NSO_4$ (417.56): C, 66.16; H, 7.48; N, 3.35. Found: C, 66.08; H, 7.57; N, 3.40.

3-(*i*-Butyl)-3-(3′,4′-dimethoxyphenyl)-*N*-(*p*-tolylsulfonyl)-pyrrolidine (17c). General Procedure II. A sample of nitronate **14c** (0.150 g, 0.410 mmol) in methanol was reduced with hydrogen in the presence of platinum oxide and 1 mol equiv of acetic acid. After reduction, the crude, concentrated reaction mixture was dissolved in methylene chloride and reacted with triethylamine and TsCl. After acidic workup, the crude organic concentrate was purified by silica gel column chromatography (hexane/EtOAc, (3/1)) to afford 0.126 g (73%) of **17c**. An analytical sample was obtained after recrystallization (EtOAc/hexane) to afford a white crystalline solid: mp 78–79 °C; ^{1}H NMR (400 MHz) 7.67 (d, J = 8.0, 2 H, HC(11)), 7.26 (d, J = 8.0, 2 H, HC(12)), 6.72–6.61 (m, 3 H, HC(2′), HC(5′), HC(6′)), 3.84 (s, 3 H, OCH_3), 3.82 (s, 3 H, OCH_3), 3.56–3.23 (m, 4 H, $H_2C(2)$, $H_2C(5)$), 2.40 (s, 3 H, $H_3C(14)$), 2.01 (m, 2 H, $H_2C(4)$), 1.53 (dd, J = 5.5, J = 14.0, 1 H, $H_aC(6)$), 1.40 (dd, J = 6.2, J = 14.0, 1 H, $H_bC(6)$), 1.32 (m, 1 H, HC(7)), 0.61 (d, J = 6.8, 3 H, $H_3C(8)$ or $H_3C(9)$), 0.57 (d, J = 6.8, 3 H, $H_3C(9)$ or $H_3C(8)$); ^{13}C NMR (100.6 MHz) 148.54 (C(3′)), 147.35 (C(4′)), 143.10 (C(13)), 136.35 (C(1′)), 134.23 (C(10)), 129.42 (C(12)), 127.14 (C(11)), 118.33 (C(6′)), 110.49 (C(5′)), 109.70 (C(2′)), 58.24 (C(2)), 55.78 (OCH_3), 55.63 (OCH_3), 49.46 (C(3)), 48.52 (C(5)), 37.03 (C(4)), 24.96, 24.29, 23.81, 21.34 (C(14)); IR (CCl_4) 2955 (s), 1354 (s), 1169 (s); MS (10 eV) 417 (M^+, 100); TLC R_f 0.25 (hexane/EtOAc, (3/1)). Anal. Calcd for $C_{23}H_{31}NSO_4$ (417.56): C, 66.16; H, 7.48; N, 3.35. Found: C, 66.19; H, 7.50; N, 3.36.

3-Ethyl-3-pentyl-*N*-(*p*-tolylsulfonyl)pyrrolidine (17d). General Procedure II. A sample of nitronate **14d** (0.320 g, 1.18 mmol) in methanol was reduced with hydrogen in the presence of platinum oxide and 1 mol equiv of acetic acid. After reduction, the crude concentrated reaction mixture was dissolved in methylene chloride and reacted with triethylamine and TsCl. After acidic workup, the crude organic concentrate was purified by silica gel column chromatography (hexane/EtOAc, (10/1)) followed by bulb-to-bulb distillation to afford 0.296 g (77%) of analytically pure **17d** as a clear heavy oil: bp: 220 °C (0.5 Torr); ^{1}H NMR (400 MHz) 7.69 (d, J = 8.0, 2 H, HC(14)), 7.30 (d, J = 8.0, 2 H, HC(15)), 3.23 (m, 2 H, $H_2C(5)$), 2.96 (s, 2 H, $H_2C(2)$), 2.41 (s, 3 H, $H_3C(17)$), 1.55 (t, J = 7.0, 2 H, $H_2C(4)$), 1.19 (m, 4 H), 1.06 (m, 6 H), 0.83 (t, J = 7.2, 3 H, $H_3C(10)$ or $H_3C(12)$), 0.71 (t, J = 7.4, 3 H, $H_3C(12)$ or $H_3C(10)$); ^{13}C NMR (100.6 MHz) 143.14 (C(16)), 133.75 (C(13)), 129.46 (C(15)), 127.37 (C(14)), 57.50 (C(2)), 46.65 (C(5)), 45.00 (C(3)), 35.60 (C(4)), 34.86, 32.31, 27.95, 23.79, 22.44, 21.43 (C(17)), 13.98 (C(10)), 8.63 (C(12)); IR (neat) 2959 (s), 1345 (s), 1159 (s); MS (70 eV) 323 (M^+, 2); TLC R_f 0.10 (hexane/EtOAc, (20/1)). Anal. Calcd for $C_{18}H_{29}NSO_2$ (323.50): C, 66.83; H, 9.04; N, 4.33. Found: C, 66.84; H, 9.11; N, 4.24.

3-Cyclohexyl-3-ethyl-*N*-(*p*-tolylsulfonyl)pyrrolidine (17e). General Procedure II. A sample of nitronate **14e** (0.375 g, 1.32 mmol) in methanol was reduced with hydrogen in the presence of platinum oxide and 1 mol equiv of acetic acid. After reduction, the crude concentrated reaction mixture was dissolved in methylene chloride and reacted with triethylamine and TsCl. After acidic workup, the crude organic concentrate was purified by silica gel column chromatography (hexane/EtOAc, (20/1)) followed by recrystallization (EtOAc/hexane) to afford 0.355 g (80%) of analytically pure **17e** as a white crystalline solid: mp 101–103 °C; ^{1}H NMR (400 MHz) 7.69 (d, J = 8.0, 2 H, HC(9)), 7.31 (d, J = 8.0, 2 H, HC(10)), 3.19 (m, 2 H, $H_2C(5)$), 3.02 (d, J = 9.8, 1 H, $H_aC(2)$), 2.93 (d, J = 9.8, 1 H, $H_bC(2)$), 2.42 (s, 3 H, $H_3C(12)$), 1.73–1.48 (m, 8 H), 1.28–0.91 (m, 7 H), 0.71 (t, J = 7.5, 3 H, $H_3C(7)$); ^{13}C NMR (100.6 MHz) 143.19 (C(11)), 133.34 (C(8)), 129.46 (C(10)), 127.52 (C(9)), 55.64 (C(2)), 47.78 (C(3)), 47.46 (C(5)), 43.66 (C(1′)), 32.96 (C(4)), 28.01, 27.90, 27.72, 26.90, 26.83, 26.44, 21.49 (C(12)), 8.91 (C(7)); IR (CCl_4) 2930 (s), 1354 (s), 1167 (s); MS (10 eV) 335 (M^+, 22); TLC R_f 0.17 (hexane/EtOAc, (20/1)). Anal. Calcd for $C_{19}H_{29}NSO_2$ (335.51): C, 68.02; H, 8.71; N, 4.17. Found: C, 68.18; H, 8.81; N, 4.10.

Ethyl 5-[3-[3-Phenyl-*N*-(*p*-tolylsulfonyl)pyrrolidinyl]]-pentanoate (17f). General Procedure II. A sample of nitronate **14f** (0.250 g, 0.662 mmol) in methanol was reduced with hydrogen in the presence of platinum oxide and 1 mol equiv of acetic acid. After reduction, the crude, concentrated reaction mixture was dissolved in methylene chloride and reacted with DBU and TsCl. After acidic workup, the crude organic concentrate was purified by silica gel column chromatography (hexane/EtOAc, (4/1)) to afford 0.221 g (78%) of analytically pure **17f** as a clear heavy oil: ^{1}H NMR (400 MHz) 7.71 (d, J = 8.3, 2 H, *ortho* H on tosyl group), 7.30–7.15 (m, 5 H, Ph), 7.23 (d, J = 7.6, 2 H, *meta* H on tosyl group), 4.04 (q, J = 7.1, 2 H, OCH_2CH_3), 3.55 (d, J = 9.5, 1 H, $H_aC(2')$), 3.43–3.31 (m, 3 H, $H_bC(2')$, $H_2C(5')$), 2.40 (s, 3 H, *p*-CH_3 on tosyl), 2.10–1.98 (m, 4 H, $H_2C(4')$, $H_2C(2)$), 1.46–1.29 (m, 4 H), 1.18 (t, J = 7.1, 3 H, OCH_2CH_3), 0.89 (m, 2 H); ^{13}C NMR (100.6

MHz) 173 (C(1)), 143.96 (Ph), 143.35 (C(4″)), 133.83 (C(1″)), 129.59 (C(3″)), 128.27 (Ph), 127.27 (C(2″)), 126.36 (Ph), 126.13 (Ph), 60.11 (OCH_2CH_3), 57.03 (C(2′)), 46.63 (C(5′)), 39.13, 35.59, 33.90, 24.99, 24.10, 21.42 (C(5″)), 14.13 (OCH_2CH_3); IR (neat) 2940 (s), 1730 (s), 1372 (s), 1163 (s); MS (CI, CH_4) 430 (M^+ + 1, 100); TLC R_f 0.17 (hexane/EtOAc, (4/1)). Anal. Calcd for $C_{24}H_{31}NSO_4$ (429.58): C, 67.10; H, 7.27; N, 3.26. Found: C, 67.13; H, 7.29; N, 3.25.

Cycloaddition of (*E*)-2-Nitrostyrene and (*E*)-19-Promoted by MAPh. *rel*-(4*R*,5*R*,6*R*)-6-Ethoxy-5-methyl-4-phenyl-5,6-dihydro-4*H*-[1,2]-oxazine *N*-Oxide (20a) and *rel*-(4*R*,5*S*,6*S*)-6-Ethoxy-5-methyl-4-phenyl-5,6-dihydro-4*H*-[1,2]-oxazine *N*-Oxide (20c). General Procedure I. A solution of MAD (6.70 mmol, 2 equiv) in dichloromethane (28 mL) was cooled to −30 °C and a solution of (*E*)-2-nitrostyrene (0.500 g, 3.35 mmol) in dichloromethane (2.0 mL) was added. The resulting dark red solution was stirred for 5 min and then (*E*)-**19** (0.739 mL, 6.7 mmol, 2 equiv) was added. The reaction was allowed to stir for 20 min, as the color faded to light brown, and then it was quenched with water (5 mL). After aqueous workup, the crude organic concentrate was purified by silica gel column chromatography (hexane/EtOAc, (2/1)) to afford 0.399 g of analytically pure **20c**, as a white solid, and 0.295 g of analytically pure **20a**, as a heavy oil, for a total combined mass of 0.694 g (88%) (ratio 1.4:1.0, **20a**/**20c**). **20a**: ^{1}H NMR (400 MHz) 7.38–7.18 (m, 5 H, Ph), 6.41 (d, J = 3.4, 1 H, HC(3)), 5.08 (d, J = 5.1, 1 H, HC(6)), 4.10 (m, 1 H, $H_aC(8)$), 3.70 (m, 1 H, $H_bC(8)$), 3.29 (dd, J = 3.7, J = 8.5, 1 H, HC(4)), 2.13 (m, 1 H, HC(5)), 1.27 (t, J = 7.1, 3 H, $H_3C(9)$), 1.08 (d, J = 7.1, 3 H, $H_3C(7)$); ^{13}C NMR (100.6 MHz) 138.82 (C(1′)), 128.98 (C(3′)), 128.32 (C(2′)), 127.81 (C(4′)), 116.17 (C(3)), 108.13 (C(6)), 65.85 (C(8)), 46.67 (C(4)), 40.82 (C(5)), 15.88 (C(9)), 14.90 (C(7)); IR (neat) 1622 (s); MS (CI, CH_4) 236 (M^+ + 1, 97); TLC R_f 0.13 (hexane/EtOAc, (2/1)). Anal. Calcd for $C_{13}H_{17}NO_3$ (235.28): C, 66.36; H, 7.28; N, 5.98. Found: C, 66.27; H, 7.30; N, 5.96. **20c**: mp 90–91 °C; ^{1}H NMR (400 MHz) 7.38–7.16 (m, 5 H, Ph), 6.45 (d, J = 2.9, 1 H, HC(3)), 5.17 (d, J = 1.0, 1 H, HC(6)), 4.30 (dd, J = 2.9, J = 6.3, 1 H, HC(4)), 4.10 (m, 1 H, $H_aC(8)$), 3.75 (m, 1 H, $H_bC(8)$), 2.19 (m, 1 H, HC(5)), 1.30 (t, J = 7.1, 3 H, $H_3C(9)$), 0.76 (d, J = 7.3, 3 H, $H_3C(7)$); ^{13}C NMR (100.6 MHz) 137.21 (C(1′)), 128.79 (C(3′)), 128.30 (C(2′)), 127.51 (C(4′)), 113.70 (C(3)), 106.29 (C(6)), 65.01 (C(8)), 39.81 (C(4)), 32.82 (C(5)), 15.04 (C(9)), 12.66 (C(7)); IR (CCl_4) 1630 (s); MS (CI, CH_4) 236 (M^+ + 1, 85); TLC R_f 0.21 (hexane/EtOAc, (2/1)). Anal. Calcd for $C_{13}H_{17}NO_3$ (235.28): C, 66.36; H, 7.28; N, 5.98. Found: C, 66.51; H, 7.34; N, 5.94.

Cycloaddition of (*E*)-2-Nitrostyrene and (*Z*)-19 Promoted by MAPh. *rel*-(4*R*,5*S*,6*R*)-6-Ethoxy-5-methyl-4-phenyl-5,6-dihydro-4*H*-[1,2]-oxazine *N*-Oxide (20b). General Procedure I. A solution of MAD (6.62 mmol, 3 equiv) in dichloromethane (21 mL) was added to a mixture of (*E*)-2-nitrostyrene (0.400 g, 2.21 mmol) and (*Z*)-**19** (0.731 mL, 6.62 mmol, 3 equiv) in dichloromethane (2.0 mL) at −78 °C. The reaction solution was stirred at −78 °C for 1 h, the −78 °C bath was replaced with a 0 °C bath, and after 7 min the reaction was quenched with water (10 mL). After aqueous workup the crude organic concentrate was purified by silica gel column chromatography (hexane/EtOAc, (1/1)) to afford 0.417 g of analytically pure **20b**, as a white crystalline solid after recrystallization (EtOAc/hexane), and 59.0 mg of **20d**, as a clear oil, for a total combined mass of 0.476 g (92%) (ratio 7.1:1.0, **20b**/**20d**). **20b**: mp 110–111 °C; ^{1}H NMR (400 MHz) 7.34–7.15 (m, 5 H, Ph), 6.26 (d, J = 2.9, 1 H, HC(3)), 5.17 (d, J = 2.4, 1 H, HC(6)), 4.04 (m, 1 H, $H_aC(8)$), 3.70 (m, 1 H, $H_bC(8)$), 3.48 (dd, J = 2.9, J = 11.2, 1 H, HC(4)), 2.10 (m, 1 H, HC(5)), 1.25 (t, J = 6.8, 3 H, $H_3C(9)$), 1.08 (d, J = 6.8, 3 H, $H_3C(7)$); ^{13}C NMR (100.6 MHz) 138.54 (C(1′)), 128.84 (C(3′)), 128.24 (C(2′)), 127.75 (C(4′)), 114.35 (C(3)), 104.97 (C(6)), 65.15 (C(8)), 43.26 (C(4)), 35.60 (C(5)), 14.80 (C(9)), 13.39 (C(7)); IR (CCl_4) 1628 (s); MS (70 eV) 235 (M^+, 4); TLC R_f 0.35 (hexane/EtOAc, (1/1)). Anal. Calcd for $C_{13}H_{17}NO_3$ (235.28): C, 66.36; H, 7.28; N, 5.98. Found: C, 66.46; H, 7.32; N, 5.97. The spectral data for **20d** matches that reported for **20d** resulting from the cycloaddition of (*Z*)-**19** and (*E*)-2-nitrostyrene promoted by Ti(O-*i*-Pr)$_2$Cl$_2$.

Cycloaddition of (*E*)-2-Nitrostyrene and (*Z*)-19 Promoted by Ti(*O*-*i*-Pr)$_2$Cl$_2$. *rel*-(4*R*,5*R*,6*S*)-6-Ethoxy-5-methyl-4-phenyl-5,6-dihydro-4*H*-[1,2]-oxazine *N*-Oxide (20d). Titanium(IV) chloride (0.220 mL, 2.01 mmol, 1.5 equiv) was added to a solution of titanium(IV) isopropoxide (0.598 mL, 2.01 mmol, 1.5 equiv) in dichloromethane (7 mL) at room temperature. The resulting solution was allowed to stir for 1 h and then added to a slurry of (*E*)-2-nitrostyrene (0.200 g, 1.34 mmol) and (*Z*)-**19** (0.222 mL, 2.01 mmol, 1.5 equiv) in dichloromethane (1 mL) at −78 °C. The reaction mixture was stirred for 30 min at −78 °C, and then quenched with a methanolic sodium hydroxide solution (1 N, 3 mL). After aqueous workup, the crude organic concentrate was purified by silica gel column chromatography (hexane/EtOAc, (1.5/1.0 → 1/1) to afford 0.189 g of **20d** as a heavy oil and 75.0 mg of a 1.0:11.5:22.6 mixture of **20a**/**20b**/**20c** as determined by ^{1}H NMR integration, for a total combined mass of 0.264 g (84%) (ratio 1.0:12:23:90, **20a**/**20b**/**20c**/**20d**). **20d**: ^{1}H NMR (400 MHz) 7.32–7.24 (m, 5 H, Ph), 6.48 (d, J = 3.8, 1 H, HC(3)), 5.23 (d, J = 2.4, 1 H, HC(6)), 4.07 (m, 1 H, $H_aC(8)$), 3.86 (dd, J = 3.9, J = 8.5, 1 H, HC(4)), 3.65 (m, 1 H, $H_bC(8)$), 2.52 (m, 1 H, HC(5)), 1.25 (t, J = 7.1, 3 H, $H_3C(9)$), 0.76 (d, J = 7.1, 3 H, $H_3C(7)$); ^{13}C NMR (100.6 MHz) 136.70 (C(1′)), 130.07 (C(3′)), 128.08 (C(2′)), 127.45 (C(4′)), 114.55 (C(3)), 105.18 (C(6)), 65.75 (C(8)), 42.32 (C(4)), 32.65 (C(5)), 14.83 (C(9)), 12.04 (C(7)); IR (neat) 1624 (s); MS (CI, CH_4) 236 (M^+ + 1, 79); TLC R_f 0.13 (hexane/EtOAc, (2/1)). Anal. Calcd for $C_{13}H_{17}NO_3$ (235.28): C, 66.36; H, 7.28; N, 5.98. Found: C, 66.28; H, 7.38; N, 5.92.

Cycloaddition of (*E*)-2-Nitrostyrene and (*E*)-19 Promoted by Ti(O-*i*-Pr)$_2$Cl$_2$. Titanium(IV) chloride (0.441 mL, 4.02 mmol, 1.5 equiv) was added to a solution of titanium(IV) isopropoxide (1.19 mL, 4.02 mmol, 1.5 equiv) in dichloromethane (14 mL) at room temperature. The resulting solution was allowed to stir for 1 h and then added to a slurry of (*E*)-2-nitrostyrene (0.400 g, 2.68 mmol) and (*E*)-**19** (0.444 mL, 4.02 mmol, 1.5 equiv) in dichloromethane (2.0 mL) at −78 °C. The reaction mixture was stirred for 5 min at −78 °C and then quenched with a methanolic sodium hydroxide solution (1 N, 10 mL). After aqueous workup, the crude organic concentrate was purified by silica gel column chromatography (hexane/EtOAc, (2/1)) to afford 0.380 g of **20a** as a heavy oil and 0.186 g of a 7.2:1.0:1.8 mixture of **20a**/**20b**/**20c,d** as determined by ^{1}H NMR integration, for a total combined mass of 0.566 g (89%) (ratio 28:1.0:2.0, **20a**/**20b**/**20c,d**).

Reduction of Nitronate 20a to *cis*-Pyrrolidine 21a. *trans*-3-Phenyl-4-methyl-*N*-(*p*-tolylsulfonyl)pyrrolidine (21a). General Procedure II (acid free). A sample of nitronate **20a** (0.220 g, 0.935 mmol) in methanol was reduced with hydrogen in the presence of platinum oxide. After reduction, the crude concentrated reaction mixture was dissolved in methylene chloride and reacted with triethylamine and TsCl. After acidic workup, the crude organic concentrate was purified by silica gel column chromatography (hexane/EtOAc, (10/1)) to afford 0.230 g (78%) of **21a** as a clear heavy oil. An analytical sample was obtained after bulb-to-bulb distillation: bp 200 °C (0.2 Torr); ^{1}H NMR (400 MHz) 7.75 (d, J = 8.0, 2 H, HC(8)), 7.36 (d, J = 8.0, 2 H, HC(9)), 7.26 (m, 3 H, Ph), 7.09 (m, 2 H, Ph), 3.70 (m, 2 H, $H_aC(2)$, $H_aC(5)$), 3.28 (t, J = 10.0, 1 H, $H_bC(2)$), 2.92 (t, J = 10.0, 1 H, $H_bC(5)$), 2.65 (dt, J_d = 8.3, J_t = 10.0, 1 H, HC(3)), 2.47 (s, 3 H, $H_3C(11)$), 2.17 (m, 1 H, HC(4)), 0.87 (d, J = 6.6, 3 H, $H_3C(6)$); ^{13}C NMR (100.6 MHz) 143.43 (C(10)), 139.14 (C(1′)), 133.92 (C(7)), 129.69 (C(9)), 128.67 (C(2′)), 127.51 (C(8)), 127.45 (C(3′)), 127.17 (C(4′)), 54.96 (C(2)), 54.88 (C(3)), 52.07 (C(5)), 40.79 (C(4)), 21.57 (C(11)), 15.44 (C(6)); IR (neat) 2959 (s), 1455 (s), 1165 (s); MS (10 eV) 315 (M^+, 32); TLC R_f 0.15 (hexane/EtOAc, (10/1)). Anal. Calcd for $C_{18}H_{21}NSO_2$ (315.43): C, 68.54; H, 6.71; N, 4.46. Found: C, 68.59; H, 6.67; N, 4.41.

Reduction of Nitronate 20b to *cis*-Pyrrolidine 21a. General Procedure II (acid free). A sample of nitronate **20b** (0.143 g, 0.608 mmol) in methanol was reduced with hydrogen in the presence of platinum oxide. After reduction, the crude concentrated reaction mixture was dissolved in methylene chloride and reacted with triethylamine and TsCl. After acidic workup, the crude organic concentrate was purified by silica gel column chromatography (hexane/EtOAc, (10/1)) to afford 0.151 g (79%) of **21a** as a clear heavy oil. The spectral data matches that reported for **21a** resulting from the reduction of **20a**.

Reduction of Nitronate 20c to *trans*-Pyrrolidine 21b. *cis*-3-Phenyl-4-methyl-*N*-(*p*-tolylsulfonyl)pyrrolidine (21b). General Procedure II (acid free). A sample of nitronate **20c** (0.250 g, 1.06 mmol) in methanol was reduced with hydrogen in the

presence of platinum oxide. After reduction, the crude concentrated reaction mixture was dissolved in methylene chloride and reacted with triethylamine and TsCl. After acidic workup, the crude concentrate was purified by silica gel column chromatography (hexane/EtOAc, (10/1)) to afford 0.277 g (83%) of **21b** as a clear heavy oil. An analytical sample was obtained after bulb-to-bulb distillation: bp 250 °C (0.2 Torr); ^{1}H NMR (400 MHz) 7.79 (d, J = 8.0, 2 H, HC(8)), 7.36 (d, J = 8.0, 2 H, HC(9)), 7.23 (m, 3 H, Ph), 6.97 (m, 2 H, Ph), 3.67 (dd, J = 7.2, J = 9.9, 1 H, $H_aC(2)$), 3.59 (dd, J = 6.0, J = 9.9, 1 H, $H_bC(2)$), 3.53 (dd, J = 6.8, J = 9.9, 1 H, $H_aC(5)$), 3.29 (q, J = 6.6, 1 H, HC(3)), 3.09 (dd, J = 6.6, J = 9.9, 1 H, $H_bC(5)$), 2.46 (s, 3 H, $H_3C(11)$), 2.39 (m, 1 H, HC(4)), 0.52 (d, J = 7.1, 3 H, $H_3C(6)$); ^{13}C NMR (100.6 MHz) 143.37 (C(10)), 138.83 (C(1')), 134.01 (C(7)), 129.68 (C(9)), 128.27 (C(2')), 127.82 (C(8)), 127.38 (C(3')), 126.66 (C(4')), 53.61 (C(2)), 51.53 (C(3)), 47.20 (C(5)), 37.15 (C(4)), 21.49 (C(11), 13.62 (C(6)); IR (neat) 2967 (s), 1341 (s), 1161 (s); MS (10 eV) 315 (M^+, 26); TLC R_f 0.17 (hexane/EtOAc, (10/1)); Anal. Calcd for $C_{16}H_{21}NSO_2$ (315.43): C, 68.54; H, 6.71; N, 4.46. Found: C, 68.46; H, 6.71; N, 4.39.

Reduction of Nitronate 20d to *cis*-Pyrrolidine 21a. General Procedure II (acid free). A sample of nitronate **20d** (0.173 g, 0.735 mmol) in methanol was reduced with hydrogen in the presence of platinum oxide. After reduction, the crude concentrated reaction mixture was dissolved in methylene chloride and reacted with DBU and TsCl. After acidic workup, the crude organic concentrate was purified by silica gel column chromatography (hexane/EtOAc, (10/1)) to afford 0.150 g (65%) of **21b** as a clear heavy oil. The spectral data matches that reported for **21b** resulting from the reduction of **20c**.

***rel*-(4*S*,5*S*,6*R*)-6-Ethoxy-4,5-diphenyl-5,6-dihydro-4*H*-[1,2]-oxazine *N*-Oxide (23).** Titanium(IV) chloride (0.441 mL, 4.02 mmol, 1.5 equiv) was added to a solution of titanium(IV) isopropoxide (1.19 mL, 4.02 mmol, 1.5 equiv) in dichloromethane (14 mL) at room temperature. The resulting solution was allowed to stir for 1 h and then added to a slurry of (*E*)-2-nitrostyrene (0.400 g, 2.68 mmol) and **22** (0.596 g, 4.02 mmol, 1.5 equiv, 93.7:6.3 (*E*/*Z*)) in dichloromethane (2.0 mL) at −78 °C. The reaction was stirred for 45 min and quenched with a methanolic sodium hydroxide solution (1 N, 15 mL). After aqueous workup, the crude organic concentrate was purified by silica gel column chromatography (hexane/EtOAc, (3/1)) to afford 0.729 g (91%) of **23** as an off-white solid. An analytical sample was obtained after recrystallization (EtOAc/hexane) to afford a white crystalline solid: mp 89–90 °C; ^{1}H NMR (400 MHz) 7.31–7.04 (m, 10 H, Ph, Ph), 6.60 (d, J = 3.8, 1 H, HC(3)), 5.48 (d, J = 4.0, 1 H, HC(6)), 4.09 (m, 1 H, $H_aC(7)$), 3.82 (dd, J = 3.8, J = 8.8, 1 H, HC(4)), 3.63 (m, 1 H, $H_bC(7)$), 3.19 (dd, J = 4.0, J = 8.8, 1 H, HC(5)), 1.22 (t, J = 7.1, 3 H, $H_3C(8)$); ^{13}C NMR (100.6 MHz) 138.84, 138.28, 128.80, 128.78, 128.19, 127.92, 127.63, 127.58, 116.51 (C(3)), 107.98 (C(6)), 65.68 (C(7)), 54.49 (C(4)), 47.23 (C(5)), 14.77 (C(8)); IR (CCl_4) 1628 (s); MS (FAB) 298 (M^+ + 1, 38); TLC R_f 0.30 (hexane/EtOAc, (2/1)). Anal. Calcd for $C_{18}H_{19}NO_3$ (297.36): C, 72.71; H, 6.44; N, 4.71. Found: C, 72.58; H, 6.48; N, 4.61.

***trans*-3,4-Diphenyl-*N*-(*p*-tolylsulfonyl)pyrrolidine (24).** General Procedure II (acid free). A sample of nitronate **23** (0.255 g, 0.858 mmol) in methanol was reduced with hydrogen in the presence of platinum oxide. After reduction, the crude concentrated reaction mixture was dissolved in methylene chloride and reacted with triethylamine and TsCl. After acidic workup, the crude organic concentrate was purified by silica gel column chromatography (hexane/EtOAc, (10/1)) to afford 0.268 g (83%) of **24** as a white solid. An analytical sample was obtained after recrystallization (EtOAc/hexane): mp 133–134 °C; ^{1}H NMR (400 MHz) 7.80 (d, J = 8.0, 2 H, HC(7)), 7.40 (d, J = 8.0, 2 H, HC(8)), 7.19 (m, 6 H, Ph), 7.03 (m, 4 H, Ph), 3.90 (m, 2 H, $H_aC(2)$, $H_aC(5)$), 3.40 (m, 2 H, $H_bC(2)$, $H_bC(5)$), 3.33 (m, 2 H, HC(3), HC(4)), 2.49 (s, 3 H, $H_3C(10)$); ^{13}C NMR (100.6 MHz) 143.67 (C(9)), 138.64 (Ph), 133.69 (C(6)), 129.81 (C(8)), 128.60, 127.61 (C(7)), 127.31, 127.15, 54.88 (C(2) and C(5)), 51.19 (C(3) and C(4)), 21.62 (C(10)); IR ($CHCl_3$) 1345 (s), 1161 (s); MS (70 eV) 377 (M^+, 8); TLC R_f 0.15 (hexane/EtOAc, (10/1)). Anal. Calcd for $C_{23}H_{23}NSO_2$ (377.51): C, 73.18; H, 6.14; N, 3.71. Found: C, 73.16; H, 6.15; N, 3.72.

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Supplementary Material Available: A description of general experimental methods along with complete listings of infrared absorbances and mass spectral fragments for all compounds described are provided (4 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 the ACS; see any current masthead page for ordering information.