Asymmetric Nitroalkene [4 + 2] Cycloadditions: Enantioselective Synthesis of 3-Substituted and 3,4-Disubstituted Pyrrolidines

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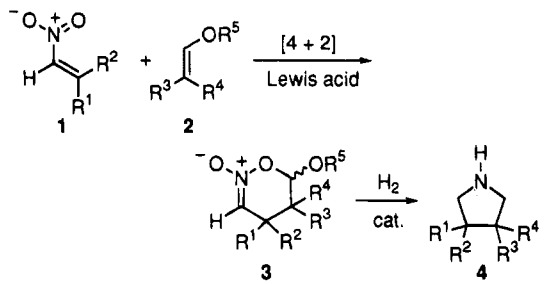
2-Substituted 1-nitroalkenes undergo highly diastereoselective, Lewis-acid-promoted, [4 + 2] cycloaddition with chiral vinyl ethers derived from (*R*)-2,2-diphenylcyclopentanol and (1*R*,2*S*)-2-phenylcyclohexanol to afford cyclic nitronates in high yields. The resulting nitronates were reduced with hydrogen at 160 psi in the presence of platinum oxide to afford enantiomerically enriched pyrrolidines (both as the free base and *N*-protected derivatives) in good yields. A series of 3-substituted pyrrolidines (71–97% ee) were prepared, as well as (3*S*,4*R*)-4-methyl-3-phenyl-*N*-(*p*-tolylsulfonyl)pyrrolidine (92% ee) and (3*S*,4*S*)-3,4-diphenylpyrrolidine (99% ee). The chiral auxiliaries can be recovered in nearly quantitative yields after hydrogenation.

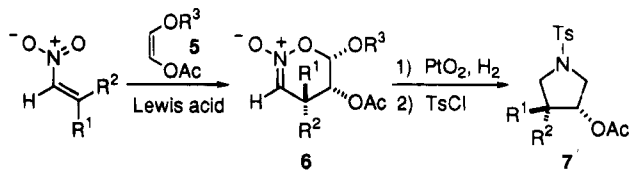
Introduction

Chiral, nonracemic pyrrolidines are common structural subunits found in many natural and unnatural products which possess interesting and important biological activity.[1] Depending on the substitution pattern and functionalization, pyrrolidines have been shown to be effective antibacterials,[2] neuroexcitatory agents,[3] potent venom,[4] glycosidase inhibitors[5] and fungicides.[6] In addition, enantiomerically enriched pyrrolidines have found use as auxiliaries for a number of different transformations.[7] Consequently, a significant effort has been directed toward the development of asymmetric methods for the synthesis of chiral pyrrolidines. Nonetheless, general and effective methods for the selective synthesis of 3-mono- and 3,4-polysubstituted pyrrolidines in enantiomerically enriched form are noticeably rare.[8,9] Since a number of pyrrolidines with this specific substitution pattern are of particular interest,[9] improved methods for their preparation are needed.

Scheme 1



Scheme 2



A recent report from these laboratories described a general method for the synthesis of 3,3- and 3,4-disubstituted pyrrolidines in racemic form from readily-available 1-nitroalkenes.[10] As shown in Scheme 1, cyclic nitronates **3**, obtained by Lewis acid promoted [4 + 2] cycloaddition of a variety of nitroalkenes **1** with vinyl ethers **2**, were reduced with hydrogen in the presence of a catalytic amount of platinum oxide to afford substituted pyrrolidines **4** in good yields. In a separate report, 4-substituted 3-hydroxypyrrolidines **7** were prepared in two steps from 1-nitroalkenes and (*Z*)-2-acetoxyvinyl ethers **5** (Scheme 2), thus demonstrating the ability to use functionalized vinyl ethers in nitroalkene [4 + 2] cycloadditions and to stereoselectively construct interesting oxygen-substituted pyrrolidines.[11]

From previous studies on nitroalkene tandem cycloadditions with chiral vinyl ethers we recognized the potential of the cycloaddition/reduction sequence for the *enantioselective* synthesis of substituted pyrrolidines. The use of chiral vinyl ethers in the tandem cycloaddition of nitroalkenes is extremely effective in providing enantiomerically enriched cycloadducts in good yield and with

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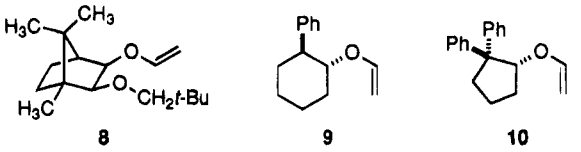

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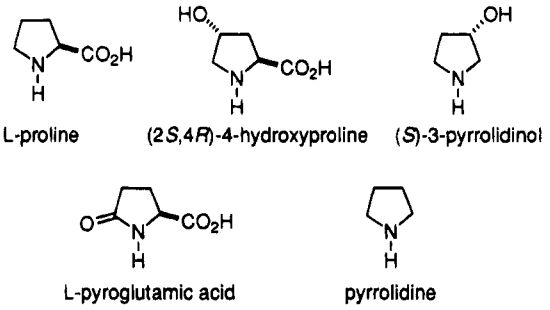
Figure 1. Chiral vinyl ethers employed in nitroalkene cycloaddition reactions.



L-proline (2S,4R)-4-hydroxyproline (S)-3-pyrrolidinol

L-pyroglutamic acid pyrrolidine

Figure 2. Common starting materials in pyrrolidine synthesis.

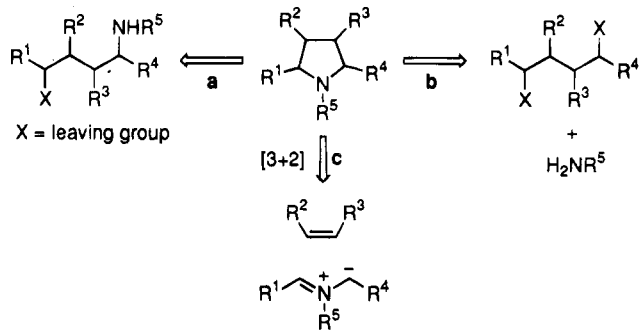
high diastereocontrol.[11,12] Specifically, vinyl ethers **8**–**10** derived from (+)-camphor, (1*R*,2*S*)-2-phenylcyclohexanol, and (*R*)-2,2-diphenylcyclopentanol, respectively, have proven to be very useful, Figure 1. In this paper, we detail the extension of the two-step cycloaddition/hydrogenolysis protocol to the *general* and *enantioselective synthesis* of 3-substituted and 3,4-disubstituted pyrrolidines.[13]

Background

Syntheses from Preexisting Rings. A number of synthetic strategies for the construction of substituted pyrrolidines in optically active form employ starting materials that embellish preexisting pyrrolidines. Although these approaches often benefit from the use of commercially available or easily obtained starting materials, the substitution patterns that can be accessed are often limited. A few of the more common starting materials include L-proline, (2*S*,4*R*)-4-hydroxyproline, L-pyroglutamic acid, (*S*)-3-pyrrolidinol, and pyrrolidine itself, Figure 2.

Syntheses that begin with L-proline are usually multistep sequences and are typically limited to the preparation of 2-substituted and 2,5-disubstituted pyrrolidines.[14] Preparations that commence from 4-hydroxyproline are primarily useful in the synthesis of substituted pyrrolidines that bear a hydroxyl group at the four position.[9d,f] (*S*)-3-Pyrrolidinol has been used exclusively in the synthesis of 3-substituted pyrrolidines.[9a] Routes that start with pyroglutamic acid provide access to 2,5-di- and 2,3,4-trisubstituted pyrrolidines.[15] Finally, a strategy that involves the asymmetric deprotonation and alkylation of achiral *N*-(*tert*-butoxycarbonyl)pyrrolidine is effective for the synthesis of nonracemic 2-substituted pyrrolidines.[16]

Scheme 3



Syntheses That Build the Pyrrolidine Ring. Strategies that assemble the heterocyclic ring allow access to a multitude of substitution patterns and are diverse in approach. The two most common methods are (1) intramolecular *N*-alkylation (cyclization) of chiral secondary amines,[17] and (2) the *N*,*N*-dialkylation of primary amines with enantiomerically enriched bis-alkylating agents,[8h,j,9b,18] Scheme 3, disconnections a and b, respectively. Although these approaches have been employed in the preparation of a number of polysubstituted pyrrolidines with high enantiomeric purity, their success is primarily dependent on the accessibility of the enantiomerically enriched precursors. The substrates are commonly obtained through the resolution of racemic intermediates or from the derivatization of carbohydrate-based starting materials. Regardless of how the starting materials are prepared, these approaches are usually multistep sequences.

Another route for the construction of the pyrrolidine ring system is based on asymmetric [3 + 2] dipolar cycloadditions of azomethine ylides with substituted olefins,[19] Scheme 3, disconnection c. The use of chrial ylides with achiral dipolarophiles as well as achiral ylides with chiral dipolarophiles has been explored. These strategies provide a rapid assembly of the pyrrolidine ring, but commonly suffer from low yields and poor levels of asymmetric induction.

The application of several other pericyclic reactions to asymmetric pyrrolidine synthesis has been successful as well. Representative examples include the hetero Diels–

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(13) A single example of this process has been disclosed in a previous report from these laboratories in which an *N*-tosyl-3-hydroxypyrrolidine was prepared in 96% enantiomeric excess (ee) from the use of a chiral, nonracemic 2-(acyloxy)vinyl ether.[11]

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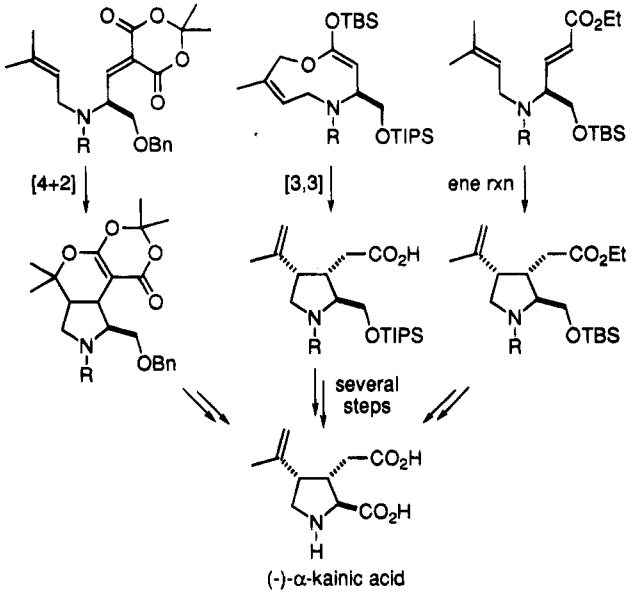
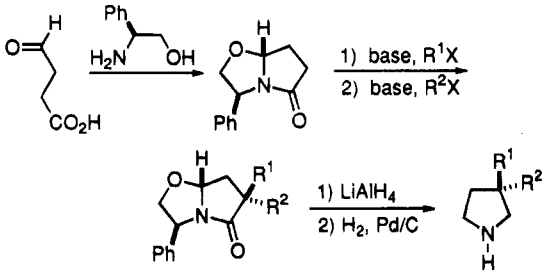
Scheme 4



Scheme 5

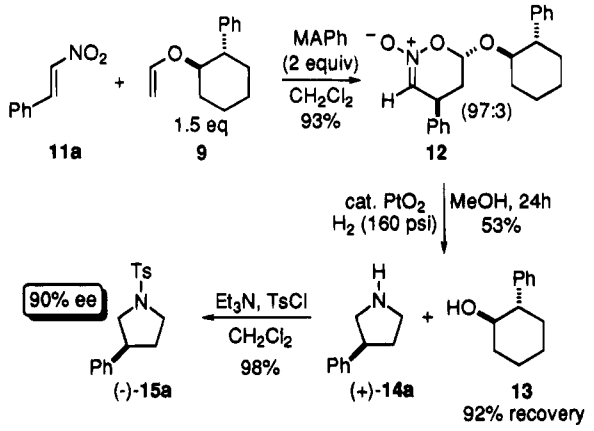


Alder reaction,[20] the ester enolate Claisen rearrangement,[21] and the ene reaction.[22] All of these reactions have been utilized in an intramolecular fashion and rely on relative asymmetric induction to control the configuration of the newly formed centers. Interestingly, these methods as well as one involving the Pauson–Khand bicyclization[23] have all been independently used as the key step in four total syntheses of (−)-α-kainic acid, a well known neurotoxin, Scheme 4. Unfortunately, these methods have not been developed as a general means of asymmetric pyrrolidine synthesis and have only been applied toward the total synthesis of selected molecules.

A recent strategy for enantioselective pyrrolidine synthesis involves the use of chiral bicyclic lactams derived from (*S*)-phenylglycinol.[8a,b] These chiral lactams can undergo diastereoselective mono- and dialkylation followed by lithium aluminum hydride reduction and palladium-catalyzed hydrogenolysis to afford enantiomerically pure 3-substituted and 3,3-disubstituted pyrrolidines, Scheme 5. A major limitation of this procedure is that the alkylations are not very diastereoselective. Thus, chromatographic separation of the product lactam diastereomers is required to obtain pyrrolidines with high enantiomeric purity.

Despite the significant number of existing methods for asymmetric pyrrolidine synthesis,[24] several problems still exist including: (1) lack of generality, (2) poor levels of asymmetric induction, (3) inability to access certain substitution patterns, and (4) overall efficiency. Thus, the need for new and selective methods for asymmetric pyrrolidine synthesis is apparent.

Scheme 6



Results

Synthesis of 3-Substituted Pyrrolines. Orienting experiments were focused on the asymmetric synthesis of 3-phenylpyrrolidine, since both enantiomers of this particular pyrrolidine have been fully characterized,[8h–j] and the precursor is simply (*E*)-2-nitrostyrene.[25] Initially, (1*R*,2*S*)-2-phenylcyclohexanol was explored as the chiral auxiliary.[26] The [4 + 2] cycloaddition of (*E*)-2-nitrostyrene (**11a**) with the chiral vinyl ether **9** (99% ee) was performed using methylaluminum bis(2,6-diphenylphenoxide) (MAPh)[27] as the Lewis acid promoter, Scheme 6. Nitronate **12** was isolated in 93% yield as a 97:3 mixture of diastereomers. Subsequent reduction of the diastereomeric mixture **12** with hydrogen, in the presence of a catalytic amount of platinum oxide, afforded optically active 3-phenylpyrrolidine ((+)-(**14a**)) in 53% yield and with 92% recovery of the chiral auxiliary **13**. The absolute configuration of the product was determined to be *S* by comparison of its specific rotation ($[\alpha]_D$ = +19.9) to that reported in the literature ($[\alpha]_D$ = +22.7).[8i] A portion of (*S*)-3-phenylpyrrolidine was *N*-protected as a *p*-toluenesulfonamide (−)-**15a** (98% yield) and was determined to be highly enantiomerically enriched (90% ee) by chiral HPLC analysis (DIACEL Chiralpak AD column).

Parallel studies documented in the preceding article have revealed that the vinyl ether derived from (*R*)-2,2-diphenylcyclopentanol can, in some cases, be more effective than (1*R*,2*S*)-2-phenylcyclohexanol in asymmetric nitroalkene cycloadditions.[12a] Therefore, the [4 + 2] cycloaddition of **11a** with the chiral vinyl ether **10** (97–98% ee) was next investigated, Table 1, entry 1. A

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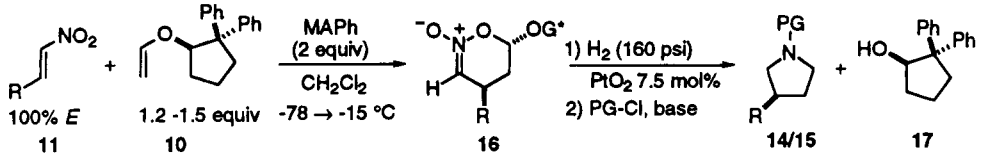
(25) Worral, D. E. *Org. Synth.* **1929**, *9*, 66.
(26) (−)-(1*R*,2*S*)-*trans*-2-Phenylcyclohexanol can be readily prepared on large scale by the following procedure: Schwartz, A.; Madan, P.; Whitesell, J. K.; Lawrence, R. M. *Org. Synth.* **1990**, *69*, 1. The vinyl ether derived from this alcohol has been found to be useful in nitroalkene tandem [4 + 2]/[3 + 2] cycloadditions; see refs 12b–d.
(27) (a) Maruoka, K.; Yamamoto, H. *Tetrahedron* **1988**, *44*, 5001. (b) Maruoka, K.; Itoh, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1985**, *107*, 4573.

Table 1. Synthesis of Optically Active 3-Substituted Pyrrolidines



entry	11, R	yield, % 16	de,[a] % 16	product	PG	yield, %	% ee[b,c]	recovery, % 17[d]
1	**a**, phenyl	95	90	**14a**	H	74	85 (88)	100
2	**a**, phenyl	89	98	**14a**	H	77	95 (98)	97
3	**a**, phenyl	89	94	**15a**	Ts	80	91 (93)	98
4	**b**, veratryl[e]	91	70	**15b**	Troc	76	71 (72)	63[f]
5	**c**, *n*-pentyl	88	94	**15c**	Troc	72	93 (95)	55
6	**d**, cyclohexyl	84	94	**15d**	Troc	79	91 (93)	69
7	**e**, *tert*-butyl	91	82	**15e**	Troc	80	77 (79)	54
8	**f**, $-(CH_2)_4CO_2$-*t*-Bu	92	98	**15f**	Troc	69	97 (99)	89

[a] Determined by ^{1}H NMR integration (major minus all minor diastereomers). [b] Determined by HPLC analysis of *N*-Ts or *N*-Troc derivatives (Daicel AD column). [c] Number in parentheses represents corrected enantioselectivity, based on the initial enantiomeric purity of **17**. [d] Reference 30. [e] 3,4-Dimethoxyphenyl. [f] Yield of *O*-Troc-2,2-diphencyclopentanol.

mixture of three diastereomeric nitronates **16a** (in a ratio of 95:4:1) was obtained in 95% overall yield.[28] Subsequent reduction of the diastereomeric mixture afforded enantiomerically enriched 3-phenylpyrrolidine ((+)-**14a**) in 74% yield along with a quantitative recovery of the chiral alcohol **17**. Again, the absolute configuration of the product was determined to be *S* by optical rotation.[29] Chiral HPLC analysis of the corresponding *p*-toluenesulfonamide **15a** revealed the pyrrolidine to be enantiomerically enriched to the extent of 85% ee. Alternatively, the [4 + 2] cycloadduct **16a** could be obtained in 89% yield and 98% diastereomeric excess after removal of the minor diastereomers by silica gel column chromatography, Table 1, entry 2. Reduction of the enriched mixture afforded (+)-**14a** in 77% yield and 95% ee (chiral HPLC analysis of **15a**).

Since (*R*)-2,2-diphenylcyclopentanol was found to be nearly as effective as *trans*-2-phenylcyclohexanol, and was readily available by means of a procedure optimized in these laboratories,[12a] subsequent experiments employed the corresponding vinyl ether **10**, entries 3–8 in Table 1. In these cases, the free pyrrolidines were not isolated but directly *N*-protected to afford derivatives **15** that could be easily purified, isolated, and fully characterized (free pyrrolidines are hygroscopic, air oxidizable, and in some instances volatile). The *N*-tosyl (Ts) and 2,2,2-trichloroethoxy (Troc) carbamate derivatives[31] were selected because these compounds could be prepared in near-quantitative yield and in all cases were amenable to chiral HPLC analysis. Six different *N*-protected 3-substituted pyrrolidines **15a–f** were synthesized in two steps from a number of readily obtained (*E*)-2-substituted 1-nitroalkenes **11a–f**.[32] In all of the examples investigated, the [4 + 2] cycloadducts **16** were isolated in high yield (84–92%) and with good diastereomeric excess (70–98%) as determined by 400 MHz ^{1}H NMR integration. Reduction of the nitronates followed by protection of the crude products afforded the *N*-Ts or *N*-Troc derivatives in yields of 69–80% and enantiomeric purities of 71–97% ee. The assignment of absolute configuration for compounds **15b–f** was made by analogy to **15a**.[33]

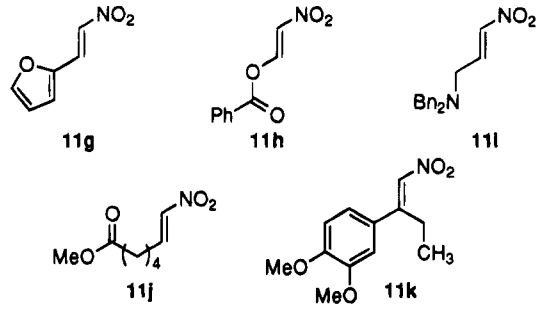


Figure 3. Incompatible functionalized nitroalkenes.

To further explore the scope of this construction, functionalized nitroalkenes **11g–k** were investigated in this sequence and for various reasons were found to be incompatible, Figure 3. For example, nitroalkenes **11g**, **11h**, and **11j** underwent high-yielding and diastereoselective [4 + 2] cycloadditions, but the corresponding nitronates could not be reduced to afford the pyrrolidines in preparatively useful yields (>50%). The dibenzylamino substrate **11i** was difficult to prepare and relatively unstable. Furthermore, the [4 + 2] cycloaddition of **11i** as well as the reduction of the product nitronate proceeded in low yield. Finally, a highly diastereoselective [4 + 2] cycloaddition of the 2,2-disubstituted 1-nitroalkene **11k** could not be realized; nevertheless, reduction of the corresponding nitronate proceeded smoothly. Interestingly, in the case of compound **11j**, the low yield in the hydrogenolysis could be overcome by the use of the *tert*-butyl ester analog **11f**.

By analogy to previous reports from these laboratories on the influence of Lewis acid on the product stereochemistry,[12c,d] we have demonstrated a switch in product configuration that complements the results in Table 1.

(28) The major diastereomer is assigned to the β-anomeric configuration (HC(6)) on the basis of previous studies with MAPh and **10**.[12a,c]

(29) Observed $[\alpha]^{26}_D = +18.3°$ (c = 1.21, EtOH) (lit.[8i] $[\alpha]^{20}_D = +22.7°$ (c = 2.36, EtOH).

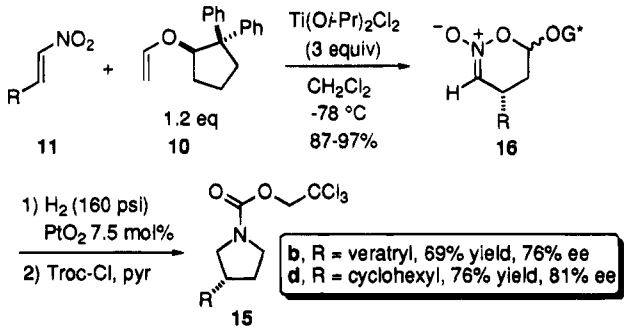
(30) The modest recoveries of the chiral aclohol entries 4–8 were the result of unavoidable *O*-Troc protection of the chiral alcohol under the reaction conditions. Thus, the net recovery of (*R*)-2,2-diphenylcyclopentanol in these examples was calculated after zinc-assisted hydrolysis of the corresponding carbonates.[31]

(31) Windholz, T. B.; Johnston, B. R. *Tetrahedron Lett.* **1967**, 2555.

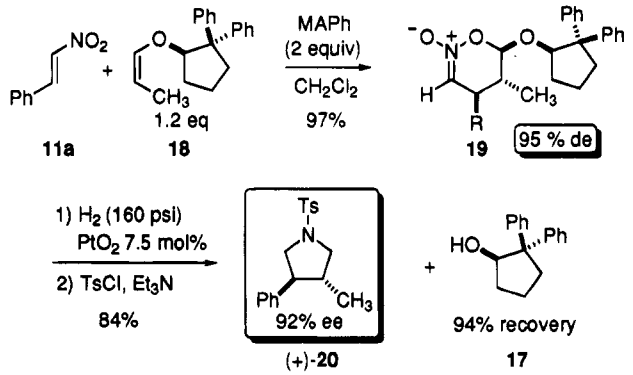
(32) For the preparation of **11b–f** see the following references: (a) **11b**: Seth, J. P.; Bhattacharyya, S. C. *Ind. J. Chem.* **1977**, *15B*, 595. (b) **11c** and **11d**: Denmark, S. E.; Marcin, L. R. *J. Org. Chem.* **1993**, *58*, 3850. (c) **11e** and **11f**: see the Experimental Section.

(33) Two independent trends support this assignment. First, the ^{1}H NMR chemical shift and splitting pattern for the anomeric proton (HC(6)) of the intermediate nitronates **16** is diagnostic for the major diastereomers and is consistent throughout. Second, the chiral HPLC elution order for the major and minor enantiomers of the *N*-protected pyrrolidine derivatives **15a–f** is consistent.

Scheme 7



Scheme 8

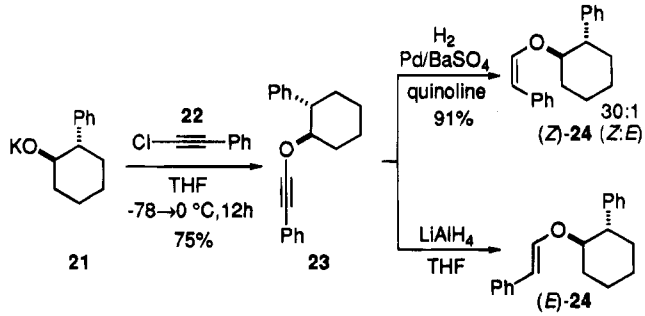


For example, when the cycloaddition of the cyclohexyl nitroalkene **11d** was promoted with $Ti(O\text{-}i\text{-}Pr)_2Cl_2$, a 37:55:8 ratio of diastereomeric nitronates **16d** was obtained, Scheme 7. Subsequent reduction of the mixture provided the corresponding *N*-protected pyrrolidine (−)-**15d** in 76% yield and 81% ee; however, the product was levorotatory indicating an excess of the *R* configuration.[34] Similar results were obtained with the veratryl-derived nitroalkene **11b**, where a 14:75:11 mixture of nitronate diastereomers **16b** provided the pyrrolidine **15b** in 69% yield and 76% ee.

Synthesis of 3,4-Disubstituted Pyrrolidines. This method has been extended to include the asymmetric synthesis of 3,4-disubstituted pyrrolidines. For example, the MAPh-promoted cycloaddition of **11a** with the (*Z*)-propenyl ether **18** (98% ee)[12a] provided a 20:1 mixture of diastereomeric nitronates in 97% yield, Scheme 8. Subsequent reduction of the combined diastereomers provided a 20:1 mixture of *trans*- and *cis*-4-methyl-3-phenylpyrrolidine. Since the pure *trans*-pyrrolidine was desired, the minor component was removed by silica gel chromatography and the major diastereomer reduced. After *N*-protection, diastereomerically pure *trans*-4-methyl-3-phenylpyrrolidine (+)-**20** was produced in 84% yield and 92% ee.[35]

We next targeted the synthesis of 3,4-diphenylpyrrolidine. This pyrrolidine is of interest because of its utility (in optically active form) as a chiral ligand in the asymmetric addition of Grignard reagents to aldehydes[36] as well as a ligand in asymmetric osmylations.[37] Furthermore, the published procedure for the synthesis of this pyrrolidine is lengthy and includes a resolution.[9b] Due to the flexibility of the nitroalkene cycloaddition strategy, the desired trans relationship between the two phenyl substituents at C(4) and C(5) in the nitronate cycloadduct could be established by two approaches through variation of enol ether geometry and the Lewis acid employed. One approach would require an endo-mode [4 + 2] cycloaddition of the (*E*)-styryl vinyl ether, while the second would entail an exo-mode [4 + 2] cycloaddition of the (*Z*)-styryl vinyl ether. Since the methods previously employed for the preparation of chiral propenyl ethers were not applicable, several different routes using well-established methods were explored.[38] Most of the approaches met with little or no success; however, a synthesis that provided access to both the (*E*)- and (*Z*)-styryl vinyl ethers of *trans*-2-phenylcyclohexanol and 2,2-diphenylcyclopentanol with high selectivity was developed. Following a modified literature procedure,[39] the potassium alkoxide of *trans*-2-phenylcyclohexanol **21** was combined with phenylchloroacetylene (**22**)[40] to afford the corresponding acetylenic ether **23** in 75% yield, Scheme 9. The acetylene was then subjected to a Lindlar reduction to provide the cis enol ether (*Z*)-**24** in 91% yield and 30:1 (*Z*:*E*) selectivity. After silica gel chromatography the geometrically pure *Z*-enol ether could be obtained in 85% yield. Alternatively, the *trans*-enol ether (*E*)-**24** could be prepared by a lithium aluminum hydride reduction of the acetylenic ether **23**.[41,42]

Scheme 9



Initial attempts at cycloaddition of **11a** and (*E*)-**24** promoted by $Ti(O\text{-}i\text{-}Pr)_2Cl_2$ were unselective. However, cycloaddition of (*E*)-2-nitrostyrene with (*Z*)-**24** promoted by MAPh proceeded in good selectivity (87:10:3) and high yield (96%) (Scheme 10).[43] Nitronates **25a** and **25b** were suspected to have the desired trans relationship between the two phenyl substituents according to analysis of their

(34) Pyrrolidine (+)-**15d** as prepared in Table 1 (using MAPh as the Lewis acid) was dextrorotatory and by analogy to **15a** was assigned to have an excess of the *S* configuration.

(35) The trans configurational assignment for compound **20** is made by comparison of ^1H NMR spectral data to that reported for racemic *trans*- and *cis*-4-methyl-3-phenyl-*N*-(*p*-tolylsulfonyl)pyrrolidine; see ref 10. The absolute configuration of (3*S*,4*R*) is assigned by analogy to compound **15a**.

(36) (a) Tomioka, K.; Nakajima, M.; Koga, K. *Chemistry Lett.* **1987**, 65. (b) Tomioka, K.; Nakajima, M.; Koga, K. *Tetrahedron Lett.* **1987**, *28*, 1291.

(37) Tomioka, K.; Nakajima, M.; Iitaka, Y.; Koga, K. *Tetrahedron Lett.* **1988**, *29*, 573.

(38) (a) Cabezas, J. A.; Oehlschlager, A. C. *Synthesis* **1994**, 432. (b) Löffler, A.; Himbert, G. *Synthesis* **1992**, 495. (c) Moyano, A. Charbonnier, F.; Greene, A. E. *J. Org. Chem.* **1987**, *52*, 2919. (d) Subramanyam, V.; Silver, E. H.; Soloway, A. H. *J. Org. Chem.* **1976**, *41*, 1272.

(39) Tanaka, R.; Miller, S. I. *Tetrahedron Lett.* **1971**, 1753.

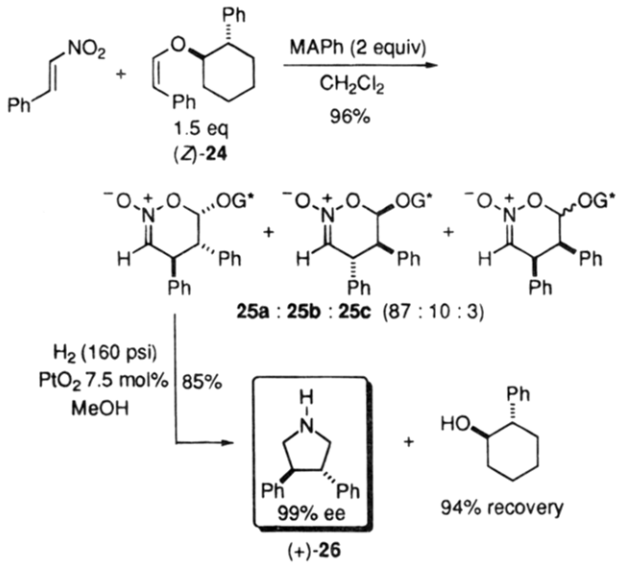
(40) Brandsma, L. *Preparative Acetylenic Chemistry*, 2nd ed.; Elsevier: New York, 1988; Chapter 8.

(41) The isomerically pure trans enol ether was prepared in an unoptimized yield of 49% by modification of the procedure of Solà; Solà, L.; Castro, J.; Moyano, A.; Pericàs, M. A.; Riera, A. *Tetrahedron Lett.* **1992**, *33*, 2863.

(42) In a similar fashion, samples of both the (*E*)- and (*Z*)-enol ethers derived from (*R*)-2,2-diphenylcyclopentanol were obtained.

(43) Cycloadditions of (*E*)-2-nitrostyrene (**11a**) with both the (*E*)- and (*Z*)-enol ethers derived from 2,2-diphenylcyclopentanol promoted by $Ti(O\text{-}i\text{-}Pr)_2Cl_2$ and MAPh, respectively, provided complex mixtures of four or more nitronate diastereomers.

Scheme 10



^{1}H NMR coupling constants. Both diastereomers exhibited a large (12.0 Hz) coupling between HC(4) and HC(5), while diastereomer **25c** displayed a smaller (8.5 Hz) coupling for the same protons. The major diastereomer **25a** was isolated in 79% yield by silica gel chromatography and subjected to reduction. After aqueous workup and distillation, pure 3,4-diphenylpyrrolidine ((+)-(**26**)) was obtained in 85% yield. The absolute configuration was established to be (3*S*,4*S*) by optical rotation,[44] and the enantiomeric purity was determined to be 99% ee by chiral HPLC analysis of the corresponding *N*-tosyl derivative **27**. In agreement with our expectations, reduction of diastereomer **25b** did provide *trans*-3,4-diphenylpyrrolidine of the opposite absolute configuration (3*R*,4*R*) in 97% ee.

Discussion

Origin of Diastereoselectivity in the Cycloaddition. From the analysis of asymmetric tandem cycloadditions, we have identified two principle criteria that govern the stereochemical course of an asymmetric nitroalkene [4 + 2] cycloaddition.[12] The first criterion involves the orientation of the chiral vinyl ether in its approach to the nitroalkene (exo or endo, with respect to the alkoxy group), Figure 4. The second criterion entails the stereodifferentiation of the chiral vinyl ether for one enantiotopic π-face (*si* or *re*) of the nitroalkene.[45] Typically, in cycloadditions involving (*E*)-2-substituted 1-nitroalkenes and vinyl ethers, it has been observed that the exo/endo selectivity is highly Lewis acid dependent. For example, the bulky, aluminum-based Lewis acid MAPh usually promotes exo-mode cycloadditions, while $Ti(O\text{-}i\text{-}Pr)_2Cl_2$, a relatively smaller Lewis acid, commonly promotes endo-mode cycloadditions. Facial selectivity in the [4 + 2] cycloaddition is dictated by the shape of the chiral auxiliary and as well as the vinyl ether reactive conformation, s-cis or s-trans.

From consideration of the aforementioned criteria we have developed models to rationalize the stereochemical course of the cycloadditions with the chiral vinyl ethers

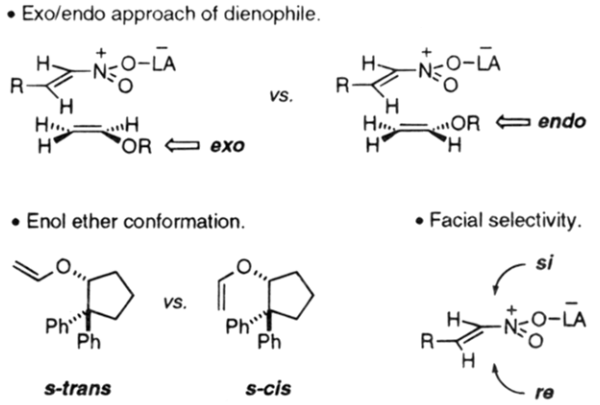


Figure 4. Components in cycloaddition diastereoselection.

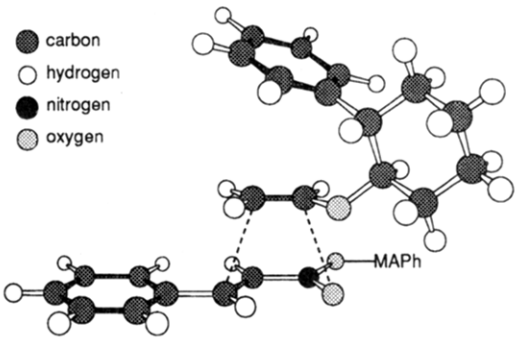


Figure 5. Exo-mode, *si*-face approach for cycloaddition of **9** with **11a**.

(1*R*,2*S*)-**9** and (*R*)-**10**. Illustrated in Figure 5 is a representation of the most favored approach of vinyl ether **9** to nitroalkene **11a**. The large Lewis acid has been omitted for clarity; however, its bulk is responsible for forcing the dienophile to approach in an exo-mode to minimize steric interactions. Importantly, the chiral vinyl ether is depicted in a low energy pseudo-s-trans conformation and approaches the *si*-face of the nitroalkene.[46] The facial selectivity is a consequence of the shielding of one face of the vinyl ether π-system by the phenyl substituent on the cyclohexane ring.

A similar model is proposed to explain the results with the (*R*)-diphenylcyclopentanol-derived chiral vinyl ether (*R*)-**10**, in an MAPh-promoted cycloaddition, Figure 6, structure **a**. In this model, the chiral vinyl ether (in a low energy pseudo-s-trans conformation)[47] approaches the *si*-face of the nitroalkene in an exo-mode. Once again, the bulky Lewis acid forces the chiral vinyl ether to be oriented in an exo fashion to minimize steric interactions, while a phenyl substituent on the cyclopentyl ring system effectively shields one face of the vinyl π-system. Conversely, transition state **b** in Figure 6, is believed to be favored when $Ti(O\text{-}i\text{-}Pr)_2Cl_2$ is used as the Lewis acid promoter. In this transition state structure, the chiral vinyl ether approaches the *re*-face of the nitroalkene in an endo orientation to allow for favorable columbic interactions between the electron rich enol ether oxygen and the positively charged nitrogen atom of the nitroalkene Lewis acid complex. This is possible since the

(44) Observed $[\alpha]^{23}_D = +228°$ (c = 1.05, $CHCl_3$) (lit.[9b] $[\alpha]^{20}_D = +226°$ (c = 1.50, $CHCl_3$).

(45) The *re*- and *si*-faces are defined at the β-carbon atom of the nitroalkene.

(46) Molecular mechanics (MM2) calculations performed on vinyl ether **9** determined that the minimized, ground state energies of both the s-trans and s-cis conformations are essentially identical.[12c] Although experimental results, using MAPh, implied that **9** is reacting through an s-trans conformation.[12c]

(47) Molecular mechanics (MM2) calculations have been performed on vinyl ether **10** and are discussed in ref 12a.

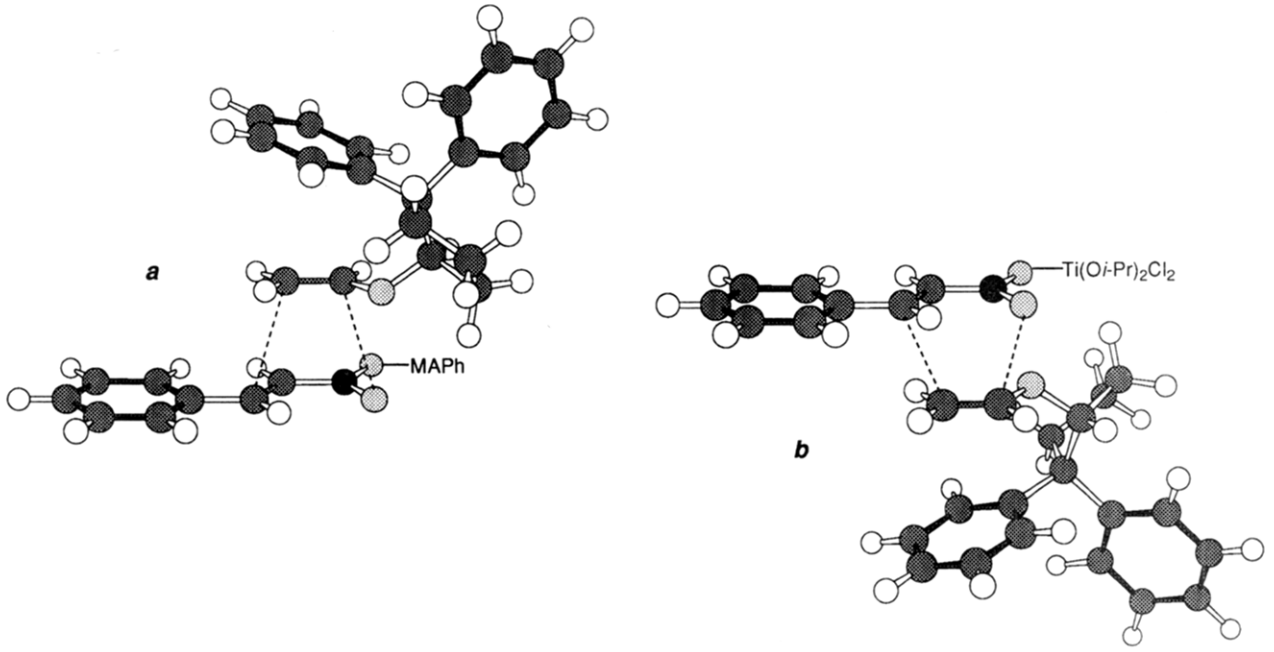


Figure 6. Exo-mode, *si*-face (**a**) and endo-mode, *re*-face (**b**) approaches of **11a** and **10**.

smaller Lewis acid, Ti(O-*i*-Pr)$_2$Cl$_2$, is able to accommodate the large chiral alkoxy substituent in an endo orientation.

A model very similar to that presented in Figure 6, structure **a**, can be used to rationalize the cycloaddition results of **11a** with the chiral propenyl ether (*Z*)-**18a**.[12a] Thus, (*Z*)-**18** is believed to react through an s-trans enol ether conformation and approaches the *si*-face of the nitroalkene in an exo-mode orientation.

The applicability of previously used models to rationalize the origin of diastereoselectivity in the cycloaddition of **11a** with the styryl vinyl ether (*Z*)-**24** was questionable. In (*Z*)-**24**, it was suspected that β-phenyl substituent might significantly alter the reactive conformation of the vinyl ether moiety. To gain further insight into this system, we performed molecular mechanics (MM3*) calculations on (*Z*)-**24**.[48] After a thorough conformational search, the calculations suggest that the ground state conformation (Figure 7) is a pseudo-s-trans geometry, $\Phi = -133.08°$ (the C=CO—C dinedral angle is defined as Φ), in which significant *re*-face shielding of the vinyl group is obtained.[49] Even though the calculations do not account for experimental conditions such as solvent effects and the presence of a Lewis acid, the computational results are in close agreement with experimental observations (stereochemical course of the reaction). Thus, we suspect that Figure 7 closely resembles the reactive conformation of styryl vinyl ether (*Z*)-**24** in a *si*-face, exo-mode approach to nitroalkene **11a**. Nonetheless, the minor diastereomers may result from exo-mode cycloaddition of other low energy conformers of the styryl vinyl ether.

Pyrrolidine Formation.[50] The results in Table 1 demonstrated that 3-substituted pyrrolidines with aryl,

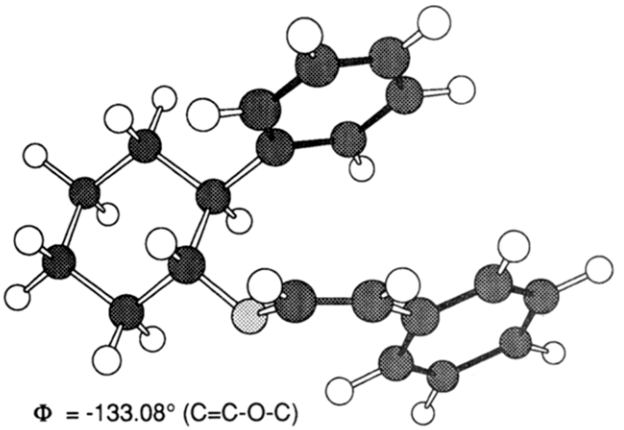


Figure 7. Lowest energy conformer of *Z*-**24** from MM3* calculations.

primary alkyl, secondary alkyl, and tertiary alkyl residues as well as functionalized derivatives (*tert*-butyl ester) could be prepared. Notably, in four of the six examples the enantiomeric purities were greater than 90% ee. However, in two cases the values dropped to 71 and 77% ee, entries 4 and 7. While the origin of this erosion is unclear, we suspect that a greater proportion of the endo-mode cycloaddition pathway led to the undesired nitronate diastereomers. In any event, the corrected enantioselectivities for the synthesis, based on the enantiomeric purity of the chiral auxiliary (97 or 98% ee), closely reflect the diastereoselectivities of the [4 + 2] cycloadditions.

Entry 2 in Table 1 was specifically included to exemplify the utility of this method as a useful route to enantiomerically pure pyrrolidines. In this example, the minor nitronate diastereomers were removed by silica gel column chromatography and discarded before the hydrogenolysis. In most of the other examples it would also have been possible to separate out the minor diastereomers before reduction. Nonetheless, from a practical standpoint, essentially enantiomerically pure pyrro-

(48) These calculations were conducted using the Allinger MM3 Force Field as implemented by MacroModel Version 3.5a. Allinger, N. L. *J. Am. Chem. Soc.* **1989**, *111*, 8551. Two closely related conformations were optimized which differ by only 0.16 kcal/mol; the lowest energy structure is depicted in Figure 7. The third lowest energy conformation (E_{rel} = 0.9 kcal/mol) exhibited very little π-facial shielding.

(49) The *si*- and *re*-faces of the enol ether are defined with respect to the C(1) alkoxy bearing carbon atom.

(50) For a discussion of the mechanism of pyrrolidine formation see ref 10.

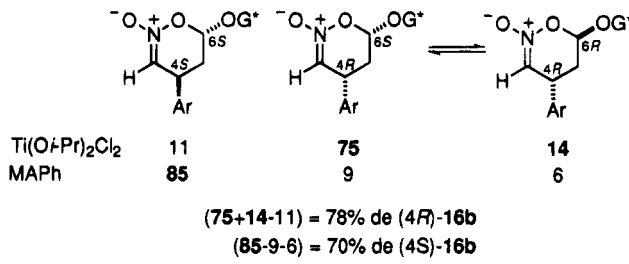


Figure 8. Lewis acid dependent diastereomeric ratios for nitronate **16b**.

lidines can be obtained following this protocol and the chiral alcohol can be recovered in nearly quantitative yield.

The reversal in the enantioselectivity when Ti(O-*i*-Pr)$_2$Cl$_2$ was used as the Lewis acid promoter was initially confusing since in both cases three diastereomeric nitronates were unselectively produced in the [4 + 2] cycloaddition, Scheme 7. Interestingly, we found that the nitronate diastereomeric ratio varied from trial to trial; however, consistent enantiomeric excesses of the final pyrrolidine products were obtained. This apparent dichotomy could be resolved if the epimerization of the acetal center in the two major diastereomers was occurring. Close inspection of the diastereomeric ratios revealed that the values closely correlate with the final pyrrolidine enantiomeric enrichment. For example, in the formation of nitronate **16b** the 11:75:14 ratio reflects a 89:11 (4*R*/4*S*) ratio of diastereomers or 78% de, Figure 8. Reduction of this mixture afforded (*R*)-**15b** with 76% ee. When MAPh was used to promote the cycloaddition, the 85:9:6 ratio of nitronate **16b** diastereomers was representative of a 70% de (4*S*), Table 1, entry 4. Reduction of this mixture produced (*S*)-**15b** with 70% ee. Importantly, the ability to access either antipode of final pyrrolidine product, by simple variation of the Lewis acid promoter in the [4 + 2] cycloaddition, further enhances the utility of this strategy for asymmetric pyrrolidine synthesis.

The ability to effectively use the two-step cycloaddition/hydrogenolysis protocol for the asymmetric synthesis of 3,4-disubstituted pyrrolidines was amply demonstrated by the synthesis of compounds **20** and **26**. In these examples it was necessary to remove the minor nitronate diastereomers prior to reduction to obtain diastereomerically pure pyrrolidine products. Fortunately, the cycloaddition yields are very high, and the isomers are easily separated. Using this methodology we have developed an alternative synthesis of enantiomerically pure *trans*-3,4-diphenylpyrrolidine (**26**) in two steps and 67% overall yield from (*E*)-2-nitrostyrene (**11a**) and the chiral enol ether (*Z*)-**24**. The geometrically pure chiral vinyl ether itself was prepared in two steps and 64% overall yield from (1*R*,4*S*)-2-phenylcyclohexanol which is recoverable in nearly quantitative yield after the hydrogenolysis.

Conclusion

We have developed a general, two-step protocol for the synthesis of chiral, nonracemic pyrrolidines that are substituted at the 3- and 4-positions. This approach utilizes simple 2-substituted 1-nitroalkenes and readily-prepared chiral, vinyl ethers derived from (*R*)-2,2-diphenylcyclopentanol and (1*R*,2*S*)-2-phenylcyclohexanol. The free and *N*-protected pyrrolidines can be obtained in good yield and high enantiomeric purity, and the chiral alcohol can be recovered in nearly quantitative amounts. Application of this method to the synthesis of natural and non-natural pyrrolidines is in progress.

Experimental Section

General. For general methods see the preceding paper in this issue.[12a]

Materials. 2-Methyl-2-propanol was fractionally distilled from $MgSO_4$. Nitromethane was distilled from $CaCl_2$. Triethylamine, trifluoroacetic anhydride, cyclohexene, pivalaldehyde, 2,2,2-trichloroethyl chloroformate, titanium(IV) chloride, and titanium(IV) isopropoxide were obtained from commerical sources and were distilled. *p*-Toluenesulfonyl chloride (TsCl) was obtained from a commercial source and recrystallized (benzene/hexane). Absolute ethanol, potassium *tert*-butoxide, and trimethylaluminum (2.0 M in toluene, Aldrich) were obtained from commercial sources and used as received. Platinum oxide was provided by the University of Illinois Redistributed Chemicals Service. 2,6-Diphenylphenol,[51] (*E*)-2-nitrostyrene,[25] (*E*)-1-nitro-1-heptene,[32b] (*E*)-1-nitro-2-cyclohexylethene,[32b] (*E*)-2-(3′,4′-dimethoxyphenyl)-1-nitrobutene,[32b] (*E*)-1-(3′,4′-dimethoxyphenyl)-2-nitroethene,[32a] methyl 6,6-dimethoxyhexanoate,[52] (1*R*,2*S*)-[(2-phenylcyclohexyl)-oxy]ethene (**9**),[12c] (*R*)-2,2-diphenylcyclopentoxyethene (**10**),[12a] and (*R*)-2,2-diphenyl-1-(1(*Z*)-propenyloxy)cyclopentane (**18**)[12a] were prepared by the literature methods.

3,3-Dimethyl-1-nitrobutan-2-ol. Potassium *tert*-butoxide (0.260 g, 2.32 mmol, 0.1 equiv) was added to a stirred solution of pivalaldehyde (2.00 g, 23.2 mmol), nitromethane (1.88 mL, 34.8 mmol, 1.5 equiv), THF (6.0 mL), and 2-methyl-2-propanol (6.0 mL) at 0 °C. The reaction mixture was stirred for 2 h at 0 °C, was allowed to warm to rt over 2 h, and was stirred for an additional 10 h at rt. The resulting solution was poured into water (100 mL) and extracted with TBME (3 × 100 mL). The combined organic layers were washed with brine (50 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The resulting slightly-yellow oil was purified by passage through a 5 cm × 2 cm column of silica gel (hexanes/EtOAc, 6/1) followed by bulb-to-bulb distillation to afford 2.75 g (81%) of analytically pure 3,3-dimethyl-1-nitrobutan-2-ol as a clear viscous oil which crystallized at rt. Data for 3,3-dimethyl-1-nitrobutan-2-ol: bp 110 °C (0.4 Torr, air bath temperature); mp 30−31 °C; ^{1}H NMR (400 MHz) 4.51 (dd, J = 12.6, 2.1, 1 H), 4.35 (dd, J = 12.8, 10.1, 1 H), 4.01 (m, 1 H), 2.62 (s, 1 H), 0.95 (s, 9 H); ^{13}C NMR (100.6 MHz) 78.21, 76.15, 34.23, 25.48; IR (CCl_4) 3627 (br, m), 2964 (s), 1556 (s); MS (CI, CH_4) 148 (M^+ + 1, 23); TLC R_f 0.25 (hexane/EtOAc, 6/1). Anal. Calcd for $C_6H_{13}NO_3$ (147.09): C, 48.95; H, 8.91; N, 9.52. Found: C, 48.93; H, 8.92; N, 9.50.

(*E*)-3,3-Dimethyl-1-nitro-1-butene (11e). Trifluoroacetic anhydride (1.01 mL, 7.14 mmol, 1.1 equiv) was added to a solution of 3,3-dimethyl-1-nitrobutan-2-ol (1.00 g, 6.80 mmol) in dichloromethane (8.5 mL) at −10 °C. The resulting solution was allowed to stir for 2 min, and then triethylamine (1.98 mL, 14.3 mmol, 2.1 equiv) was slowly added dropwise over 5 min and the reaction mixture was stirred for an additional 1 h at −10 °C. The resulting mixture was poured into dichloromethane (100 mL) and washed with saturated aqueous NH_4Cl solution (50 mL). The aqueous layer was back-extracted with dichloromethane (2 × 50 mL), and the combined organic layers were washed with brine (50 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. The light yellow oil was purified by silica gel column chromatography (hexanes/EtOAc, 20/1) followed by bulb-to-bulb distillation to afford 0.655 g (75%) of analytically pure **11e** as a light yellow oil. Data for **11e**: bp 140 °C (30 Torr, air bath temperature); ^{1}H NMR (400 MHz) 7.24 (d, J = 13.7, 1 H), 6.88 (d, J = 13.7, 1 H), 1.14 (s, 9 H); ^{13}C NMR (100.6 MHz) 151.99, 137.08, 32.66, 28.38; IR 2968 (s), 1643 (s), 1529 (s), 1352 (s); MS (CI, CH_4) 130 (M^+ + 1, 100); TLC R_f 0.37 (hexane/EtOAc, 20/1). Anal. Calcd for

(51) Dana, H. E.; Hay, A. S. *Synthesis* **1982**, 164−165.
(52) Claus, R. E.; Schreiber, S. L. *Org. Synth.* **1986**, *64*, 150−156.

$C_6H_{11}NO_3$ (129.08): C, 55.78; H, 8.59; N, 10.85. Found: C, 55.76; H, 8.59; N, 10.87.

1,1-Dimethylethyl 6,6-Dimethoxyhexanoate. Activated 3 Å molecular sieves (5.0 g) were added to a solution of methyl 6,6-dimethoxyhexanoate (5.00 g, 26.3 mmol) in 2-methyl-2-propanol (105 mL). The mixture was stirred at rt for 1 h, and then solid potassium *tert*-butoxide (14.7 g, 0.131 mol, 5.0 equiv) was added. After being stirred for 2.5 h at 33–35 °C the yellow reaction solution was decanted into a mixture of TBME (75 mL) and water (150 mL). The molecular sieves were rinsed with a fresh portion of TBME (75 mL) which was then added to the TBME/water mixture. After vigorous shaking, the organic layer was separated and the aqueous phase was extracted with fresh TBME (2 × 150 mL). The combined organic layers were washed with brine (50 mL), dried (Na_2SO_4), filtered and concentrated in vacuo. The resulting oil was purified by silica gel column chromatography (hexanes/EtOAc, 10/1) followed by bulb-to-bulb distillation to afford 2.47 g (40%) of analytically pure 1,1-dimethylethyl 6,6-dimethoxyhexanoate as a clear colorless oil. Data for 1,1-dimethylethyl 6,6-dimethoxyhexanoate: bp 135 °C (1.5 Torr, air bath temperature); ^{1}H NMR (400 MHz) 4.35 (t, J = 5.8, 1 H), 3.30 (s, 6 H), 2.21 (t, J = 7.6, 2 H), 1.59 (m, 4 H), 1.43 (s, 9 H), 1.36 (m, 2 H); ^{13}C NMR (100.6 MHz) 173.01, 104.23, 80.01, 52.60, 35.45, 32.14, 28.08, 24.89, 24.07; IR 2978 (s), 2936 (s), 1727 (s), 1368 (s), 1255 (s), 1225 (s), 1150 (s); MS (CI, CH_4) 201 ($M^+ + 1$ − MeOH, 64); TLC R_f 0.38 (hexane/EtOAc, 4/1); GC (column: HP-U2, 50 m, 150 °C isotherm) t_R 17.3 min. Anal. Calcd for $C_{12}H_{24}O_4$ (232.32): C, 62.04; H, 10.41. Found: C, 62.08; H, 10.38.

1,1-Dimethylethyl 6-Oxohexanoate. A 2.5 mL portion of 50% aqueous trifluoroacetic acid was added to a solution of 1,1-dimethylethyl 6,6-dimethoxyhexanoate (0.500 g, 2.15 mmol) dissolved in chloroform (5.0 mL) at 0 °C. The biphasic reaction mixture was vigorously stirred at 0 °C for 6 h and then was poured into saturated, aqueous $NaHCO_3$ solution (150 mL) and extracted with TBME (3 × 100 mL). The combined organic layers were washed with brine (50 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. GC analysis of the crude products indicated that approximately 2% of the starting dimethyl acetal remained. Thus, the clear crude material was resubjected to the reaction conditions (1.75 mL 50% trifluoroacetic acid; 2.5 mL chloroform) for 2 h. The reaction mixture was then worked up as described above. The resulting oil was purified by silica gel column chromatography (hexanes/EtOAc, 10/1) followed bulb-to-bulb distillation to afford 0.316 g (79%) of analytically pure 1,1-dimethylethyl 6-oxohexanoate as a clear colorless oil. Data for 1,1-dimethylethyl 6-oxohexanoate: bp 110 °C (3.0 Torr, air bath temperature); ^{1}H NMR (400 MHz) 9.75 (t, J = 1.6, 1 H), 2.24 (td, J_t = 7.1, J_d = 1.5, 2 H), 2.22 (t, J = 7.1, 2 H), 1.62 (m, 4 H), 1.42 (s, 9 H); ^{13}C NMR (100.6 MHz) 202.10, 172.61, 80.22, 43.52, 35.13, 28.04, 24.45, 21.41; IR 2978 (s), 2948 (s), 1731 (s), 1367 (s), 1152 (s), 1076 (s); MS (CI, CH_4) 187 ($M^+ + 1$, 47); TLC R_f 0.27 (hexane/EtOAc, 6/1); GC (column: HP-U2, 50 m, 150 °C isotherm) t_R 9.9 min. Anal. Calcd for $C_{10}H_{18}O_3$ (186.25): C, 64.49; H, 9.74. Found: C, 64.44; H, 9.76.

1,1-Dimethylethyl 6-Hydroxy-7-nitroheptanoate. Potassium *tert*-butoxide (9.0 mg, 0.84 mmol, 0.1 equiv) was added to a stirred solution of 1,1-dimethylethyl 6-oxohexanoate (0.115 g, 0.837 mmol), nitromethane (0.227 mL, 4.19 mmol, 5.0 equiv), THF (1.0 mL), and 2-methyl-2-propanol (1.0 mL) at 0 °C. The reaction mixture was allowed to warm to rt over 2 h and then was stirred for an additional 4 h at rt. The resulting solution was poured into water (50 mL) and extracted with TBME (3 × 50 mL). The combined organic layers were washed with brine (50 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. The resulting white solid was purified by silica gel column chromatography (hexanes/EtOAc, 4/1) to afford 0.155 g (75%) of analytically pure 1,1-dimethylethyl 6-hydroxy-7-nitroheptanoate as a microcrystalline white solid. Data for 1,1-dimethylethyl 6-hydroxy-7-nitroheptanoate: mp 62–65 °C (EtOAc/hexane); ^{1}H NMR (400 MHz) 4.43–4.33 (m, 3 H), 2.99 (m, 1 H), 2.22 (t, J = 7.3, 2 H), 1.62–1.48 (m, 6 H), 1.42 (s, 9 H); ^{13}C NMR (100.6 MHz) 173.07, 80.60, 80.38, 68.27, 35.11, 28.04, 24.52, 24.38; IR (CCl_4) 3425 (br, w), 2982 (s), 2938 (s), 1720 (s), 1555 (s), 1369 (s), 1151 (s); MS (CI, CH_4) 248 ($M^+ +$ 1, 6); TLC R_f 0.27 (hexane/EtOAc, 2/1). Anal. Calcd for $C_{11}H_{21}NO_5$ (247.29): C, 53.43; H, 8.56; N, 5.66. Found: C, 53.32; H, 8.64; N, 5.70.

1,1-Dimethylethyl (*E*)-7-Nitro-6-heptenoate (11f). Trifluoroacetic anhydride (0.215 mL, 1.62 mmol, 1.1 equiv) was added to a solution of 1,1-dimethylethyl 6-hydroxy-7-nitroheptanoate (0.360 g, 1.46 mmol) in dichloromethane (2.0 mL) at −10 °C. The resulting solution was allowed to stir for 5 min, and then triethylamine (0.428 mL, 3.23 mmol, 2.1 equiv) was slowly added dropwise over 5 min and the reaction mixture was stirred for an additional 30 min at −10 °C. The resulting mixture was poured into dichloromethane (150 mL) and washed with saturated aqueous NH_4Cl solution (100 mL). The aqueous layer was back-extracted with dichloromethane (2 × 100 mL), and the combined organic layers were washed with brine (50 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. The light yellow oil was purified by silica gel column chromatography (hexanes/EtOAc, 6/1) to afford 0.272 g (81%) of analytically pure **11f** as a light yellow oil. Data for **11f**: ^{1}H NMR (400 MHz) 7.26 (dt, J_d = 13.4, J_t = 7.3, 1 H), 6.99 (dt, J_d = 13.4, J_t = 1.5, 1 H), 2.32–2.23 (m, 4 H), 1.65–1.52 (m, 4 H), 1.44 (s, 9 H); ^{13}C NMR (100.6 MHz) 172.50, 142.14, 139.73, 80.39, 34.94, 28.17, 28.07, 27.09, 24.42; IR 2978 (s), 2935 (s), 1727 (s), 1527 (s), 1366 (s), 1353 (s), 1256 (s), 1150 (s); MS (CI, CH_4) 230 ($M^+ + 1$, 70); TLC R_f 0.24 (hexane/EtOAc, 10/1). Anal. Calcd for $C_{11}H_{19}NO_4$ (229.28): C, 57.63; H, 8.35; N, 6.11. Found: C, 57.56; H, 8.35; N, 6.07.

General Procedure for MAPh-Promoted [4 + 2] Cycloadditions (General Procedure I). The preparation of **12** from **11a** will serve to illustrate the general procedure utilized.

(4*S*,6*S*)-4-Phenyl-6-[[(1*R*,2*S*)-(2-phenylcyclohexyl)]oxy]-5,6-dihydro-4*H*-[1,2]oxazine *N*-Oxide (12). Trimethylaluminum (2.0 M in toluene, 1.65 mL, 3.30 mmol, 2.0 equiv) was added dropwise to a solution of 2,6-diphenylphenol (1.63 g, 6.60 mmol, 4.0 equiv) in dichloromethane (23 mL) at rt. Gas evolution (CH_4) was observed as the solution stirred at rt for 1 h. The resulting Lewis acid solution (MAPh) was cooled to 0 °C and transferred, via cannula, to a second reaction vessel containing a solution of nitroalkene **11a** (0.246 g, 1.65 mmol) in dichloromethane (2.0 mL) at 0 °C. The resulting dark purple solution was cooled to −78 °C, and chiral ether **9** (0.500 g, 2.47 mmol, 1.5 equiv, 99% ee) was added neat. The reaction was allowed to stir for 4 h, at −78 °C, and the cold bath was removed. As the reaction vessel warmed, the color disappeared within 7 min. The reaction vessel was placed in a 0 °C bath and immediately quenched with water (10 mL). The resulting gelatinous mixture was poured into dichloromethane (100 mL) and washed with water (3 × 100 mL). The aqueous layers were back-extracted with dichloromethane (3 × 100 mL) and the combined organic layers washed with brine (50 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude material was purified by silica gel column chromatography (hexane/EtOAc, 3/1) to afford 0.538 g (93%) of **12** as an off-white solid. The product was determined to be a 97:3 mixture of diastereomers by ^{1}H NMR integration. A small sample was recrystallized (EtOAc/hexane) to obtain an analytical sample. Data for **12**: mp 110–111 °C; ^{1}H NMR (400 MHz) 7.34–7.12 (m, 10 H), 6.31 (d, J = 3.2, 1 H), 4.58 (s, 1 H), 3.91–3.79 (m, 2 H), 2.58 (m, 1 H), 2.25 (m, 1 H), 1.94–1.26 (m, 9 H); ^{13}C NMR (100.6 MHz) 143.63, 139.64, 129.01, 128.27, 127.76, 127.65, 127.48, 126.56, 114.63, 102.31, 83.34, 51.30, 36.09, 34.17, 32.46, 31.69, 25.59, 25.02; IR 2934 (s), 1624 (s), 1237 (s), 1107 (s), 1003 (s), 862 (s); MS (CI, CH_4) 352 ($M^+ + 1$, 4); TLC R_f 0.21 (hexane/EtOAc, 3/1); $[\alpha]^{22}_D$ = 44.8° ($CHCl_3$, c = 0.54). Anal. Calcd for $C_{22}H_{25}NO_3$ (351.45): C, 75.19; H, 7.17; N, 3.99. Found: C, 75.21; H, 7.20; N, 3.98.

(4*S*,6*S*)-6-[[(1*R*)-(2,2-Diphenylcyclopentyl)oxy]]-4-phenyl-5,6-dihydro-4*H*-[1,2]oxazine *N*-Oxide (16a). According to general procedure I, a solution of MAPh (2.68 mmol, 2.0 equiv) in dichloromethane (8.0 mL), at 0 °C, was added to a mixture of nitroalkene **11a** (0.200 g, 1.34 mmol) and chiral vinyl ether **10** (0.529 g, 2.01 mmol, 1.5 equiv, 98% ee) in dichloromethane (1.5 mL) at −78 °C. The dark reaction mixture was stirred at −78 °C for 1.5 h and then was warmed to 0 °C as the color faded to light brown. After quenching with

water and aqueous extractive workup, the crude organic concentrate was purified by silica gel column chromatography (hexane/EtOAc, 3/1) to afford 0.490 g (89%) of **16e** as a white solid. The product was determined to be a 97:3 mixture of diastereomers by ^{1}H NMR integration. An analytical sample of **16a** was obtained after recrystallization from EtOAc/hexane. An additional run under similar conditions (with **10**, 97% ee) afforded 0.491 g (95%) of the desired nitronate **16a** as a 4:95:1 mixture of diastereomers. A third experiment (with **10**, 97% ee) provided 0.449 g (89%) of nitronate **16a** as a 99:1 mixture of diastereomers after enrichment by silica gel column chromatography. Data for **16a**: mp 149–151 °C (EtOAc/hexane); ^{1}H NMR (400 MHz) 7.35–7.10 (m, 15 H), 6.31 (d, J = 2.9, 1 H), 5.09 (s, 1 H), 4.94 (dd, J = 5.8, 2.6, 1 H), 3.75 (ddd, J = 11.6, 7.2, 2.9, 1 H), 2.66 (dt, J_d = 12.7, J_t = 9.0, 1 H), 2.40–2.27 (m, 2 H), 2.01 (m, 1 H), 1.89 (m, 1 H), 1.69–1.48 (m, 3 H); ^{13}C NMR (100.6 MHz) 146.08, 144.95, 139.51, 129.04, 128.35, 128.27, 127.69, 127.49, 126.84, 126.08, 125.86, 114.49, 102.66, 86.62, 59.99, 36.12, 35.12, 31.84, 31.76, 20.39; IR (CCl_4) 2973 (m), 1626 (s), 1493 (m), 1294 (m), 1237 (s), 1113 (s); MS (CI, CH_4) 414 (M^+ + 1, 1); TLC R_f 0.11 (hexane/EtOAc, 4/1); $[\alpha]^{26}_D$ = −12.8° (c = 0.75, $CHCl_3$). Anal. Calcd for $C_{27}H_{27}NO_3$ (413.52): C, 78.42; H, 6.58; N, 3.39. Found: C, 78.38; H, 6.60; N, 3.36.

(4*S*,6*S*)-4-(3,4-Dimethoxyphenyl)-6-[[(1*R*)-(2,2-diphenylcyclopentyl)]oxy]]-5,6-dihydro-4*H*-[1,2]oxazine *N*-Oxide (16b). According to general procedure I, a solution of MAPh (3.34 mmol, 2.0 equiv) in dichloromethane (10 mL), at 0 °C, was added to a mixture of nitroalkene **11b** (0.350 g, 1.67 mmol) and chiral vinyl ether **10** (0.529 g, 2.00 mmol, 1.2 equiv, 98% ee) in dichloromethane (1.6 mL) at −78 °C. The deep red reaction mixture was stirred at −78 °C for 5 min, warmed to −15 °C, and stirred for 1 h. After quenching with water (5 mL) and aqueous extractive workup, the crude organic concentrate was purified by silica gel column chromatography (hexane/EtOAc, 3/2) to afford 0.718 g (91%) of analytically pure **16b** as a white solid. The product was determined to be a 90:10 mixture of diastereomers by ^{1}H NMR integration. An additional run under similar conditions (with **10**, 98% ee) afforded 0.442 g (98%) of the desired nitronate **16b** as a 6:85:9 mixture of diastereomers. Data for **16b**: mp 64–70 °C; ^{1}H NMR (400 MHz) 7.34–7.07 (m, 10 H), 6.80–6.51 (m, 3 H), 6.30 (d, J = 2.9, 0.9 H), 5.83 (d, J = 2.9, 0.1 H), 5.49 (s, 0.1 H), 5.33 (m, 0.1 H), 5.08 (s, 0.9 H), 4.94 (dd, J = 5.9, 2.4, 0.9 H), 3.85 (m, 6 H), 3.68 (ddd, J = 11.7, 7.1, 2.9, 1 H), 2.65 (m, 1 H), 2.48–1.10 (m, 7 H); ^{13}C NMR (100.6 MHz) major diastereomer only: 149.24, 148.41, 145.99, 144.95, 131.75, 128.31, 128.22, 127.64, 126.77, 126.04, 125.79, 119.65, 114.82, 111.25, 110.14, 102.65, 86.57, 59.95, 55.87, 55.84, 35.74, 35.04, 31.86, 31.69, 20.34; IR (CCl_4) 2956 (m), 1625 (s), 1517 (s), 1267 (s), 1247 (s), 1239 (s); MS (FAB, magic bullet) 474 (M^+ + 1, 44); TLC R_f 0.21 (hexane/EtOAc, 1/1); $[\alpha]^{26}_D$ = −31.6° (c = 1.59, $CHCl_3$). Anal. Calcd for $C_{29}H_{31}NO_5$ (473.57): C, 73.55; H, 6.60; N, 2.96. Found: C, 73.54; H, 6.60; N, 2.94.

(4*R*,6*S*)-6-[[(1*R*)-(2,2-Diphenylcyclopentyl)]oxy]-4-pentyl-5,6-dihydro-4*H*-[1,2]oxazine *N*-Oxide (16c). According to general procedure I, a solution of MAPh (3.50 mmol, 2.0 equiv) in dichloromethane (13 mL), at 0 °C, was added to a mixture of nitroalkene **11c** (0.255 g, 1.78 mmol) and chiral vinyl ether **10** (0.555 g, 2.10 mmol, 1.2 equiv, 98% ee) in dichloromethane (3.0 mL) at −20 °C. The dark black reaction mixture was stirred at −20 °C for 15 min as the color dissipated to light brown. After quenching with water and aqueous extractive workup, the crude organic concentrate was purified by silica gel column chromatography (hexane/EtOAc, 2/1) to afford 0.635 g (88%) of analytically pure **16c** as a heavy, clear oil. The product was determined to be a 7:85:8 mixture of diastereomers by ^{1}H NMR integration. An additional run under similar conditions (with **10**, 98% ee) afforded 0.401 g (94%) of the desired nitronate **16c** as a 2:97:1 mixture of diastereomers. Analytical data for **16c**: ^{1}H NMR (400 MHz) 7.28–7.11 (m, 10 H), 6.25 (d, J = 3.9, 0.07 H), 6.18 (d, J = 2.9, 0.85 H), 5.74 (t, J = 1.3, 0.08 H), 5.42 (s, 0.08 H), 5.27 (m, 0.08 H), 5.01 (s, 0.85 H), 4.98 (t, J = 3.7, 0.07 H), 4.86 (dd, J = 4.9, 2.7, 0.85 H), 4.82 (dd, J = 5.8, 1.6, 0.07 H), 2.61–1.16 (m, 17 H), 0.88 (m, 3 H); ^{13}C NMR (100.6 MHz) major diastereomer only: 146.13, 144.98, 128.34, 128.20, 127.61, 126.79, 125.99, 125.73, 115.98, 102.67, 86.46, 59.84, 35.03, 32.95, 31.65, 31.39, 29.24, 28.54, 25.78, 22.38, 20.27, 13.92; IR (CCl_4) 2959 (s), 2932 (s), 1626 (s); MS (CI, CH_4) 408 (M^+ + 1, 40); TLC R_f 0.25–0.14 (hexane/EtOAc, 2/1); $[\alpha]^{23}_D$ = −64.8° (c = 0.95, $CHCl_3$). Anal. Calcd for $C_{26}H_{33}NO_3$ (407.55): C, 76.62; H, 8.16; N, 3.44. Found: C, 76.63; H, 8.15; N, 3.42.

(4*S*,6*S*)-4-Cyclohexyl-6-[[(1*R*)-(2,2-diphenylcyclopentyl)]oxy]-5,6-dihydro-4*H*-[1,2]oxazine *N*-Oxide (16d). According to general procedure I, a solution of MAPh (3.22 mmol, 2.0 equiv) in dichloromethane (12 mL), at 0 °C, was added to a mixture of nitroalkene **11d** (0.250 g, 1.61 mmol) and chiral vinyl ether **10** (0.510 g, 1.93 mmol, 1.2 equiv, 98% ee) in dichloromethane (3.0 mL) at −78 °C. The dark reaction mixture was stirred at −78 °C for 30 min and then immediately warmed to −20 °C and stirred for an additional 30 min as the color dissipated to light brown. After quenching with water and aqueous extractive workup, the crude organic concentrate was purified by silica gel column chromatography (hexane/EtOAc, 2/1) to afford 0.564 g (84%) of **16d** as a white solid. The product was determined to be a 95:5 mixture of diastereomers by ^{1}H NMR integration. An analytical sample of **16d** was obtained after recrystallization from hexane. An additional run under similar conditions (with **10**, 98% ee) afforded 0.501 g (93%) of the desired nitronate **16d** as a 97:3 mixture of diastereomers. Data for **16d**: mp 133–134 °C (hexane); ^{1}H NMR (400 MHz) 7.28–7.11 (m, 10 H), 6.23 (d, J = 2.7, 1 H), 5.00 (s, 1 H), 4.86 (dd, J = 5.6, 2.4, 1 H), 2.58 (dt, J_d = 12.2, J_t = 9.0, 1 H), 2.42–2.22 (m, 3 H), 1.94–0.94 (m, 16 H); ^{13}C NMR (100.6 MHz) 146.14, 144.98, 128.35, 128.20, 127.61, 126.82, 126.00, 125.74, 115.27, 102.78, 86.45, 59.89, 40.17, 35.04, 34.81, 31.70, 29.63, 29.52, 26.06, 25.56, 20.31; IR (CCl_4) 2928 (s), 1624 (s), 1240 (s); MS (CI, CH_4) 420 (M^+ + 1, 13); TLC R_f 0.22 (hexane/EtOAc, 2/1); $[\alpha]^{23}_D$ = −25.6° (c = 0.70, $CHCl_3$). Anal. Calcd for $C_{27}H_{33}NO_3$ (419.57): C, 77.29; H, 7.93; N, 3.34. Found: C, 77.29; H, 7.94; N, 3.35.

(4*S*,6*S*)-4-(1,1-Dimethylethyl)-6-[[(1*R*)-(2,2-diphenylcyclopentyl)]oxy]-5,6-dihydro-4*H*-[1,2]oxazine *N*-Oxide (16e). According to general procedure I, a solution of MAPh (3.88 mmol, 2.0 equiv) in dichloromethane (15 mL), at 0 °C, was added to a mixture of nitroalkene **11e** (0.250 g, 1.94 mmol) and chiral vinyl ether **10** (0.613 g, 2.32 mmol, 1.2 equiv, 98% ee) in dichloromethane (2.0 ML) at −78 °C. The dark reaction mixture was stirred at −78 °C for 1 h, was immediately warmed to −20 °C and stirred for 30 min, then was warmed to rt and stirred for an additional 20 min. After quenching with water and aqueous extractive workup, the crude organic concentrate was purified by silica gel column chromatography (hexane/EtOAc, 2/1) to afford 0.696 g (91%) of **16e** as a white solid. The product was determined to be a 84.16 mixture of diastereomers by ^{1}H NMR integration. An analytical sample of **16e** was obtained after recrystallization from EtOAc/hexane. An additional run under similar conditions (with **10**, 98% ee) afforded 0.568 g (98%) of the desired nitronate **16e** as a 91:9 mixture of diastereomers. Data for **16e**: mp 122–124 °C (EtOAc/hexane); ^{1}H NMR (400 MHz), 7.28–7.11 (m, 10 H), 6.32 (d, J = 3.2, 0.95 H), 5.80 (t, J = 1.2, 0.05 H), 5.43 (s, 0.05 H), 5.25 (d, J = 4.4, 0.05 H), 5.02 (s, 0.95 H), 4.86 (dd, J = 6.0, 2.3, 0.95 H), 2.59 (m, 1 H), 2.34–2.21 (m, 3 H), 1.94–1.80 (m, 2 H), 1.45–1.14 (m, 3 H), 0.84 (s, 9 H); ^{13}C NMR (100.6 MHz), 146.11, 145.00, 128.34, 128.20, 127.60, 126.83, 126.00, 125.75, 114.50, 102.70, 86.52, 59.96, 39.65, 35.08, 32.43, 31.74, 26.82, 24.35, 20.35; IR (CCl_4) 2965 (s), 1624 (s), 1244 (s), 1117 (s); MS (CI, CH_4) 394 (M^+ + 1, 100); TLC R_f 0.23 (hexane/EtOAc, 2/1); $[\alpha]^{23}_D$ = −67.0° (c = 0.89, $CHCl_3$). Anal. Calcd for $C_{25}H_{31}NO_3$ (393.53): C, 76.30; H, 7.94; N, 3.56. Found: C, 76.15; H, 8.16; N, 3.54.

(4*R*,6*S*)-4-[4-[[(1,1-Dimethylethyl)oxy]carbonyl]butyl]-6-[[(1*R*)-(2,2-diphenylcyclopentyl)]oxy]-5,6-dihydro-4*H*-[1,2]oxazine *N*-Oxide (16f). According to general procedure I, a solution of MAPh (1.64 mmol, 2.5 equiv) in dichloromethane (10 mL), at 0 °C, was added to a mixture of nitroalkene **11f** (0.150 g, 0.654 mmol) and chiral vinyl ether **10** (0.216 g, 0.818 mmol, 1.3 equiv, 98% ee) in dichloromethane (1.0 mL) at −78 °C. The dark reaction mixture was stirred at −78 °C for 1 h and then immediately warmed to −15 °C and

stirred for an additional 15 min, as the color faded to light rust. After quenching with water and aqueous extractive workup, the crude organic concentrate was purified by silica gel column chromatography (hexane/EtOAc, 1.5/1.0) to afford 0.298 g (92%) of analytically pure **16f** as a clear colorless oil. The product appeared to be a single diastereomer (>99:1) by ^{1}H NMR analysis. An additional run under similar conditions (with **10**, 98% ee) afforded 0.631 g (90%) of the desired nitronate **16f** as a single diastereomer (>99:1). Data for **16f**: ^{1}H NMR (400 MHz) 7.28−7.10 (m, 10 H), 6.16 (d, J = 2.9, 1 H), 5.29 (s, 1 H), 4.86 (dd, J = 5.9, 2.4, 1 H), 2.61−2.50 (m, 2 H), 2.34−2.17 (m, 4 H), 2.00−1.80 (m, 2 H), 1.57−1.47 (m, 2 H), 1.44 (s, 9 H), 1.42−1.22 (m, 7 H); ^{13}C NMR (100.6 MHz) 172.69, 146.15, 145.01, 128.37, 128.24, 127.66, 126.84, 126.04, 125.79, 115.60, 102.64, 86.51, 80.22, 59.92, 35.10, 35.06, 32.79, 31.71, 29.19, 28.56, 28.08, 25.64, 24.66, 20.32; IR (CCl_4) 3008 (s), 2979 (s), 1720 (s), 1625 (s), 1368 (s), 1237 (s), 1153 (s); MS (CI, CH_4) 478 ($M^+ + 1 - CH_4$, 3); TLC R_f 0.30 (hexane/EtOAc, 1/1); $[\alpha]^{28}_D = -21.2°$ (c = 2.0, $CHCl_3$). Anal. Calcd for $C_{30}H_{39}NO_5$ (493.65): C, 72.99; H, 7.96; N, 2.84. Found: C, 72.81; H, 8.00; N, 2.83.

General Procedure for the Reduction of Nitronates to Substituted Pyrrolidines (General Procedure II). The preparation of **14a** from **12** will serve to illustrate the general procedure utilized.

(+)-(*S*)-3-Phenylpyrrolidine (14a). Preparation of 14a from 12. Platinum oxide (small spatula tip) was placed in a 25 × 150 mm test tube equipped with a magnetic stirring bar and charged with a solution of nitronate **12** (0.370 g, 1.05 mmol) in methanol (12 mL). The test tube was placed in a steel autoclave which was then flushed and filled with hydrogen to a pressure of 160 psi. After the reaction mixture was stirred for 24 h at rt, the autoclave was slowly depressurized and purged with nitrogen. The heterogeneous reaction solution was filtered through a small pipet Celite plug, and the reaction vessel was rinsed with fresh methanol (10 mL). The filtrate was concentrated to afford a yellow oil which was purified by silica gel chromatography (hexane/EtOAc, 4/1; hexane/EtOAc, 1/1; MeOH/$CHCl_3$, 1/1; MeOH 100%) to obtain 0.171 g (92% recovery) of **13** as a white solid and ~0.100 g of **14a** as a slightly yellow oil. Bulb-to-bulb distillation of the oil afforded 82 mg (53%) of **14a** as a clear colorless oil. The recorded ^{1}H NMR spectrum as well as optical rotation data are consistent with that previously reported for (*S*)-3-phenylpyrrolidine.[8i] Data for **14a**: bp 100 °C (0.4 Torr, air bath temperature); ^{1}H NMR (400 MHz) 7.25 (m, 5 H), 3.36 (dd, J = 10.7, 7.6, 1 H), 3.24−3.06 (m, 3 H), 2.85 (dd, J = 10.7, 8.3, 1 H), 2.17 (m, 1 H), 1.91 (br, 1 H), 1.85 (m, 1 H); ^{13}C NMR (100.6 MHz) 144.29, 128.43, 127.18, 126.13, 55.30, 47.46, 45.64, 34.54; TLC R_f 0.15 ($CHCl_3$/MeOH/Et_3N, 80/10/1); $[\alpha]^{23}_D$ = +19.9° ($CHCl_3$, c = 0.98).

Preparation of 14a from 16a. According to general procedure II, a sample of nitronate **16a** (0.453 g, 1.11 mmol, 4:95:1 (diastereomeric ratio)) in methanol (75 mL) was reduced with hydrogen in the presence of platinum oxide (19 mg, 83 μmol, 7.5 mol %). After filtration (using a Büchner funnel lined with Whatman #1 filter paper) and treatment with 6 M H_2SO_4 (94 μL, 0.57 mmol, 0.5 equiv), the resulting solution was concentrated in vacuo. Benzene (~60 mL) was added to the residue, and the solution was concentrated again to facilitate the removal of methanol. The clear residue was dissolved in TBME (100 mL) and 1 M HCl (50 mL), and the layers were separated. The organic layer was washed with an additional portion of 1 M HCl (50 mL) and the combined aqueous layers were back-extracted with TBME (40 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude concentrate was purified by silica gel column chromatography (hexane/EtOAc, 10/1) to provide 0.265 g (100% recovery) of **17**. The acidic aqueous washings were made basic (to litmus) with aqueous 10% NaOH solution (50 mL) and extracted with dichloromethane (4 × 40 mL). The combined organic layers were washed with brine (15 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. The yellow, oily residue was purified by bulb-to-bulb distillation to afford 0.120 g (74%) of **14a** as a clear, thin oil. The recorded ^{1}H NMR spectrum was consistent with that previously reported for compound **14a** prepared from nitronate **12**. Data for **14a**: $[\alpha]^{26}_D$ = +18.3° (c = 1.21, EtOH).

Preparation of 14a from Diastereomerically Enriched 16a. According to general procedure II, a sample of nitronate **16a** (0.437 g, 1.06 mmol, 99:1 (diastereomeric ratio)) in methanol (60 mL) was reduced with hydrogen in the presence of platinum oxide (17 mg, 74 μmol, 7.5 mol %). After filtration and treatment with 6 M H_2SO_4 (90 μL, 0.54 mmol, 0.51 equiv), the reaction mixture was concentrated in vacuo and subjected to acid/base extractions. The crude concentrate of the TBME extract was purified by silica gel column chromatography (hexane/EtOAc, 10/1) to provide 0.246 g (97% recovery) of **17**. The dichloromethane concentrate was purified by bulb-to-bulb distillation to afford 0.120 g (77%) of **14a** as a clear, thin oil. The recorded ^{1}H NMR spectrum was consistent with that previously reported for compound **14a** prepared from nitronate **12**. Data for **14a**: $[\alpha]^{26}_D$ = +21.2° (c = 1.41, EtOH).

(−)-(*S*)-1-[(4-Methylphenyl)sulfonyl]-3-phenylpyrrolidine (15a). Preparation of 15a (90% ee) from 14a. The free pyrrolidine **14a** (52 mg, 0.35 mmol, $[\alpha]^{23}_D$ = +19.9°) was dissolved in dichloromethane (4 mL) and cooled to 0 °C, and triethylamine (75 μL, 0.53 mmol, 1.5 equiv) was added, followed by a solution of TsCl (74 mg, 0.39 mmol, 1.1 equiv) in dichloromethane (1 mL). The mixture was allowed to stir for 1 h, and then it was poured into dichloromethane (75 mL) and washed successively with dilute aqueous HCl solution (0.2 M, 50 mL), saturated aqueous $NaHCO_3$ solution (50 mL), and brine (20 mL). The organic layer was dried ($MgSO_4$), filtered through a pad of Celite, and concentrated. The crude concentrate was purified by silica gel column chromatography (hexane/EtOAc, 10/1) to afford 0.104 g (98%) of **15a** as white solid. The enantiomeric excess was determined to be 90% by chiral HPLC. A small sample was recrystallized (EtOAc/hexane) to obtain an analytical sample. Data for **15a**: mp 101−102 °C; ^{1}H NMR (400 MHz) 7.75 (d, J = 8.0, 2 H), 7.36 (d, J = 8.0, 2 H), 7.23 (m, 3 H), 7.09 (m, 2 H), 3.75−3.17 (m, 5 H), 2.45 (s, 3 H), 2.20 (m, 1 H), 1.86 (m, 1 H); ^{13}C NMR (100.6 MHz) 143.45, 140.61, 133.85, 129.69, 128.61, 127.52, 126.93, 126.91, 54.05, 47.79, 43.79, 32.88, 21.53; IR (CCl_4) 3031 (m), 1499 (m), 1356 (s), 1165 (s), 1094 (m), 1030 (m); MS (CI, CH_4) 302 ($M^+ + 1$, 100); TLC R_f 0.13 (hexane/EtOAc, 10/1); $[\alpha]^{22}_D$ = −6.6° ($CHCl_3$, c = 0.49); chiral HPLC (column: DIACEl Chiralpak AD (hexane/EtOH, 96/4), 1.0 mL/min) t_R (*S*)-**15a** 20.14 min (94.8%); t_R (*R*)-**15a** 23.8 min (5.2%); 90% ee. Anal. Calcd for $C_{17}H_{19}NSO_2$ (301.41): C, 67.75; H, 6.35; N, 4.65. Found: C, 67.68; H, 6.31; N, 4.64.

Preparation of 15a (85% ee) from 14a. (*S*)-3-Phenylpyrrolidine (**14a**) (62 mg, 0.42 mmol, $[\alpha]^{26}_D$ = +18.3°) was dissolved in dichloromethane (1.0 mL) and cooled to 0 °C. Triethylamine (0.118 mL, 0.857 mmol, 2.0 equiv) was added, followed by a solution of TsCl (88 mg, 0.46 mmol, 1.1 equiv) in dichloromethane (1.5 mL). The mixture was allowed to stir for 2 h at 0 °C and was poured into dichloromethane (75 mL) and washed with aqueous 0.1 M HCl (2 × 50 mL). The aqueous washings were back-extracted with dichloromethane (2 × 50 mL), and the combined organic layers were washed with brine (15 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude concentrate was purified by silica gel column chromatography (hexane/EtOAc, 6/1) to afford 0.124 g (98%) of **15a** as white solid. The recorded ^{1}H NMR spectrum was consistent with that previously reported for compound **15a** prepared in two steps from nitronate **12**. Data for **15a**: chiral HPLC (column: DIACEL Chiralpak AD, (hexane/EtOH, 96/4), 1.0 mL/min) t_R (*S*)-**15a** 30.9 min (92.6%); t_R (*R*)-**15a** 36.5 min (7.4%); 85% ee.

Preparation of 15a (95% ee) from 14a. A sample of (*S*)-3-phenylpyrrolidine (**14a**) (58 mg, 0.39 mmol, $[\alpha]^{26}_D$ = +21.2°) was treated with TsCl (79 mg, 0.41 mmol, 1.1 equiv) in the presence of triethylamine (0.109 mL, 0.784 mmol, 2.0 equiv) to afford after workup and purification 0.117 g (99%) of **15a** as a white solid. The recorded ^{1}H NMR spectrum was consistent with that previously reported for compound **15a** prepared in two steps from nitronate **12**. Data for **15a**: chiral HPLC (column: DAICEL Chiralpak AD, (hexane/EtOH, 96/4), 1.0 mL/min) t_R (*S*)-**15a** 31.3 min (97.3%); t_R (*R*)-**15a** 37.0 min (2.7%); 95% ee.

Preparation of 15a (91% ee) from 16a. According to general procedure II, a sample of nitronate **16a** (0.243 g, 0.588 mmol, 97:3 (diastereomeric ratio)) in ethanol (20 mL) was reduced with hydrogen in the presence of platinum oxide (10 mg, 44 μmol, 7.5 mol %). After filtration and concentration, the clear oil was placed under high vacuum for 15 min. The residue was dissolved in dichloromethane (3 mL), cooled to 0 °C, and treated with triethylamine (0.123 mL, 0.882 mmol, 1.5 equiv) followed by TsCl (0.104 g, 0.647 mmol, 1.1 equiv). After the mixture was stirred for 1 h, followed by aqueous extractive workup, the crude organic concentrate was purified by silica gel column chromatography (hexane/EtOAc, 10/1) to provide 0.139 g (98% recovery) of **17** and 0.141 g (80%) of **15a** as a white solid. The recorded ^{1}H NMR spectrum was consistent with that previously reported for compound **15a** prepared in two steps from nitronate **12**. Data for **15a**: chiral HPLC (column: DIACEL Chiralpak AD (hexane/EtOH, 96/4), 1.0 mL/min) t_R (*S*)-**15a** 23.4 min (95.5%); t_R (*R*)-**15a** 27.1 min (4.5%); 91% ee.

(−)-(*S*)-3-(3,5-Dimethoxyphenyl)-1-[(2,2,2-trichloroethoxy)carbonyl]pyrrolidine (15b) and (1*R*)-[1-(2,2-Diphenylcyclopentyl)]-2′,2′,2′-trichloroethyl Carbonate. According to general procedure II, a sample of nitronate **16b** (0.350 g, 0.739 mmol, 6:85:9 (diastereomeric ratio)) in ethanol (20 mL) was reduced with hydrogen in the presence of platinum oxide (13 mg, 55 μmol, 7.5 mol %). After filtration and treatment with 6 M H_2SO_4, (92 μL, 0.55 mmol, 0.75 equiv), the reaction mixture was concentrated in vacuo and placed under high vacuum for several hours. The crude products were dissolved in pyridine (5 mL) and treated with TrocCl (0.407 mL, 2.96 mmol, 4.0 equiv) at rt for 5 h. The resulting red, heterogeneous mixture was dissolved in dichloromethane (100 mL) and washed with aqueous 1 M HCl (2 × 50 mL). The aqueous washings were back-extracted with dichloromethane (2 × 50 mL), and the combined organic layers were washed with brine (40 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo to afford a red oil. The oil was purified by silica gel column chromatography (hexane/EtOAc, 3/1) to afford 0.514 g of impure[53] *O*-Troc-2,2-diphenylcyclopentanol as a white solid and 0.216 g (76%) of analytically pure **15b** as a clear, colorless oil. The protected chiral auxiliary was further purified by MPLC (hexane/EtOAc, 99/1) to provide 0.205 g (63%) of analytically pure (1*R*)-[1-(2,2-diphenylcyclopentyl)]-2′,2′,2′-trichloroethyl carbonate as a viscous, clear, colorless oil. Data for **15b**: ^{1}H NMR (400 MHz) 6.84−6.74 (m, 3 H), 4.76 (m, 2 H), 3.94−3.86 (m, 7 H), 3.74 (m, 1 H), 3.53 (m, 1 H), 3.44−3.31 (m, 2 H), 2.30 (m, 1 H), 2.04 (m, 1 H); ^{13}C NMR (100.6 MHz) mixture of rotamers: 152.83, 152.79, 148.96, 148.92, 147.93, 147.84, 133.12, 133.08, 118.84, 118.78, 111.16, 111.11, 110.24, 110.13, 95.76, 95.71, 74.78, 74.76, 55.88, 55.86, 55.81, 52.52, 52.45, 46.34, 45.90, 43.82, 42.87, 33.21, 32.56; IR (CCl_4) 2952 (m), 1726 (s), 1519 (s), 1416 (s), 1125 (s); MS (EI, 10 eV) 381 (M^+, 100); TLC R_f 0.28 (hexane/EtOAc, 2/1); $[\alpha]^{25}_D$ = −11.1° (*c* = 1.27, $CHCl_3$); chiral HPLC (column: DIACEL Chiralpak AD (hexane/EtOH, 96/4), 1.0 mL/min) t_R (*S*)-**15b** 19.2 min (85.3%), t_R (*R*)-**15b** 22.6 min (14.7%); 71% ee. Anal. Calcd for $C_{15}H_{18}NO_4Cl_3$ (381.03): C, 47.24; H, 4.76; N, 3.68; Cl, 27.53. Found: C, 47.15; H, 4.75; N, 3.67; Cl, 27.46.

Data for (1*R*)-[1-(2,2-diphenylcyclopentyl)]-2′,2′,2′-trichloroethyl carbonate: ^{1}H NMR (400 MHz, $CDCl_3$) 7.56−7.09 (m, 10 H), 6.03 (d, *J* = 5.4, 1 H), 4.60 (q, *J* = 12.0, 2 H), 2.67−2.54 (m, 2 H), 2.25−2.20 (m, 1 H), 1.97−1.92 (m, 2 H), 1.62−1.55 (m, 1 H); ^{13}C NMR (100.6 MHz) 153.49, 144.76, 143.97, 128.48, 128.01, 127.91, 126.45, 126.32, 126.03, 94.43, 85.45, 76.45, 59.64, 34.63, 30.55, 20.31; IR (CCl_4) 2976 (w), 1756 (s), 1379 (m), 1255 (s), 1227 (m); MS (CI, CH_4) 412 (M^+, 3); TLC R_f 0.31 (hexane/EtOAc, 40/1); $[\alpha]^{28}_D$ = −85.3° (*c* = 1.01, $CHCl_3$). Anal. Calcd for $C_{20}H_{19}O_3Cl_3$ (412.04): C, 58.06; H, 4.63; Cl, 25.71. Found: C, 58.06; H, 4.64; Cl, 25.62.

(+)-(*R*)-3-Pentyl-1-[(2,2,2-trichloroethoxy)carbonyl]pyrrolidine (15c). According to general procedure II, a sample of nitronate **16c** (0.384 g, 0.942 mmol, 2:97:1 (diastereomeric ratio)) in ethanol (20 mL) was reduced with hydrogen in the presence of platinum oxide (16 mg, 71 μmol, 7.5 mol %). After filtration and treatment with 6 M H_2SO_4 (0.157 mL, 0.942 mmol, 1.0 equiv), the reaction mixture was concentrated in vacuo and placed under high vacuum for several hours. The crude products were dissolved in pyridine (5 mL) and treated with TrocCl (0.518 mL, 3.77 mmol, 4.0 equiv) at rt for 4.5 h. After aqueous extractive workup, the resulting oil was purified by silica gel column chromatography (hexane/EtOAc, 40/1) to afford 0.552 g of impure *O*-Troc-2,2-diphenylcyclopentanol as a white solid and 0.219 g of **15c** as a clear, colorless oil. An analytical sample 0.215 g (72%) of **15c** was obtained after bulb-to-bulb distillation. The impure protected chiral alcohol was treated with zinc dust (500 mg) in refluxing methanol (10 mL) for 1 h. The reaction mixture was cooled, filtered (Celite), and poured into TBME (100 mL). The mixture was washed with water (2 × 100 mL), and the aqueous phase was back-extracted with TBME (2 × 50 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), filtered, and concentrated. The crude concentrate was purified by silica gel column chromatography (hexane/EtOAc, 10/1) to afford 0.124 g (55% recovery based on nitronate) of **17** as a white solid. Data for **15c**: bp 80 °C (0.5 Torr, air bath temperature); ^{1}H NMR (400 MHz) 4.72 (m, 2 H), 3.67−3.53 (m, 2 H), 3.37 (m, 1 H), 2.97 (m, 1 H), 2.14 (m, 1 H), 2.02 (m, 1 H), 1.53 (m, 1 H), 1.39−1.29 (m, 8 H), 0.88 (m, 3 H); ^{13}C NMR (100.6 MHz) mixture of rotamers: 152.88, 152.86, 95.83, 74.72, 51.96, 51.48, 46.22, 45.77, 39.06, 38.30, 32.97, 32.96, 31.86, 31.82, 31.72, 30.99, 27.84, 27.81, 22.53, 14.03, 14.02; IR 2955 (s), 2927 (s), 1727 (s), 1417 (s), 1122 (s); MS (EI, 10 eV) 315 (M^+, 19); TLC R_f 0.28 (hexane/EtOAc, 10/1); $[\alpha]^{22}_D$ = +19.8° (*c* = 1.12, $CHCl_3$); chiral HPLC (column: DIACEL Chiralpak AD (hexane/EtOH, 99/1), 1.4 mL/min) t_R (*R*)-**15c** 10.2 min (96.4%); t_R (*S*)-**15c** 14.63 min (3.6%); 93% ee. Anal. Calcd for $C_{12}H_{20}NO_2Cl_3$ (315.06): C, 45.52; H, 6.37; N, 4.42; Cl, 33.59. Found: C, 45.60; H, 6.47; N, 4.34; Cl, 33.36.

(+)-(*S*)-3-Cyclohexyl-1-[(2,2,2-trichloroethoxy)carbonyl]pyrrolidine (15d). According to general procedure II, a sample of nitronate **16d** (0.501 g, 1.19 mmol, 97:3 (diastereomeric ratio)) in ethanol (20 mL) was reduced with hydrogen in the presence of platinum oxide (21 mg, 89 μmol, 7.5 mol %). After filtration and treatment with 6 M H_2SO_4 (0.150 mL, 0.900 mmol, 0.8 equiv), the reaction mixture was concentrated in vacuo and placed under high vacuum for several hours. The crude products were dissolved in pyridine (7 mL) and treated with TrocCl (0.656 mL, 4.76 mmol, 4.0 equiv) at rt for 12 h. After aqueous extractive workup, the resulting oil was purified by silica gel column chromatography (hexane/EtOAc, 40/1) to afford 0.805 g of impure *O*-Troc-2,2-diphenylcyclopentanol as a white solid and 0.309 g (79%) of analytically pure **15d** as a clear oil which crystallized at rt. The impure protected chiral alcohol was treated with zinc dust (500 mg) in glacial acetic acid (9 mL) for 4 h. The reaction mixture was filtered, and the vessel and salts were washed with TBME (150 mL). The filtrate was washed with water (2 × 100 mL), and the aqueous phase was back-extracted with TBME (100 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution (100 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude concentrate was purified by silica gel column chromatography (hexane/EtOAc, 10/1) to afford 0.197 g (69% recovery based on nitronate) of **17** as a white solid. Data for **15d**: mp 38−40 °C; ^{1}H NMR (400 MHz) 4.73 (m, 2 H), 3.66 (m, 2 H), 3.32 (m, 1 H), 2.99 (m, 1 H), 2.04 (m, 1 H), 1.84 (m, 1 H), 1.70 (m, 5 H), 1.50 (m, 1 H), 1.18 (m, 4 H), 0.98 (m, 2 H); ^{13}C NMR (100.6 MHz) mixture of rotamers: 152.85, 152.84, 95.82, 74.71, 50.69, 50.10, 46.61, 46.14, 45.29, 44.53, 41.51, 31.99, 31.91, 31.46, 31.39, 29.90, 29.19, 26.28, 26.02; IR 2928 (s), 1725 (s), 1416 (s), 1127 (s); MS (CI, CH_4) 328 (M^+ + 1, 100); TLC R_f 0.27 (hexane/EtOAc, 10/1); $[\alpha]^{26}_D$ = +25.2° (*c* = 1.37, $CHCl_3$); chiral HPLC (column: DIACEL Chiralpak AD (hexane/EtOH, 98/2), 0.8 mL/min) t_R (*S*)-**15d** 12.2 min (95.5%); t_R (*R*)-**15d** 19.9 min (4.5%); 91% ee. Anal. Calcd for $C_{13}H_{28}NO_2Cl_3$ (327.06): C, 47.51; H, 6.13; N, 4.26; Cl, 32.36. Found: C, 47.64; H, 6.20; N, 4.14; Cl, 32.07.

(−)-(*S*)-3-(1,1-Dimethylethyl)-1-[(2,2,2-trichloroethoxy)carbonyl]pyrrolidine (15e). According to general

(53) Contaminated with bis(2,2,2-trichloroethyl) carbonate: He, X.-S.; Brossi, A. *Synth. Commun.* **1990**, *20*, 2177−2179.

procedure II, a sample of nitronate **16e** (0.567 g, 1.44 mmol, 91:1 (diastereomeric ratio)) in ethanol (20 mL) was reduced with hydrogen in the presence of platinum oxide (25 mg, 0.11 mmol, 7.5 mol %). After filtration and treatment with 6 M H_2SO_4 (0.180 mL, 1.08 mmol, 0.8 equiv), the reaction mixture was concentrated in vacuo and placed under high vacuum for several hours. The crude products were dissolved in pyridine (7 mL) and treated with TrocCl (0.792 mL, 5.76 mmol, 4.0 equiv) at rt for 4 h. After aqueous extractive workup, the resulting oil was purified by silica gel column chromatography (hexane/EtOAc, 49/1) to afford 0.552 g of impure *O*-Troc-2,2-diphenylcyclopentanol as a white solid and 0.348 g (80%) of analytically pure **15e** as a clear, colorless oil. The impure *O*-Troc protected alcohol was treated with zinc dust (500 mg) in glacial acetic acid (9 mL) for 4 h. After filtration and aqueous extractive workup, the crude organic concentrate was purified by silica gel column chromatography (hexane/EtOAc, 10/1) to afford 0.186 g (54% recovery based on nitronate) of **17** as a white solid. Data for **15e**: ^{1}H NMR (400 MHz) 4.73 (m, 2 H), 3.65 (m, 1 H), 3.53 (m, 1 H), 3.33 (m, 1 H), 3.11 (m, 1 H), 2.04 (m, 1 H), 1.86 (m, 1 H), 1.66 (m, 1 H), 0.92 (s, 9 H); ^{13}C NMR (100.6 MHz) mixture of rotamers 152.89, 95.79, 74.69, 74.67, 49.70, 48.98, 47.57, 46.91, 46.71, 46.26, 30.98, 30.94, 27.49, 26.59, 25.94; IR 2958 (s), 1724 (s), 1417 (s), 1128 (s), MS (CI, CH_4) 302 (M^+ + 1, 100); TLC R_f 0.33 (hexane/EtOAc, 10/1); $[\alpha]^{24}_D = -20.5°$ (c = 1.58, $CHCl_3$); chiral HPLC (column: DAICEL Chiralpak AD (hexane/EtOH, 98/2), 0.8 mL/min) t_R (*S*)-**15e** 11.9 min (88.7%); t_R (*R*)-**15e** 15.3 min (11.3%); 77% ee. Anal. Calcd for $C_{11}H_{18}NO_2Cl_3$ (301.04): C, 43.66; H, 6.00; N, 4.63; Cl, 35.14. Found: C, 43.71; H, 6.02; N, 4.63; Cl, 35.09.

(+)-(1,1-Dimethylethyl) 5-[(3*R*)-3-[1-[(2,2,2-Trichloroethoxy)carbonyl]pyrrolidinyl]]pentanoate (15f). According to general procedure II, a sample of nitronate **16f** (0.605 g, 1.22 mmol, >99:1 (diastereomeric ratio)) in methanol (50 mL) was reduced with hydrogen in the presence of platinum oxide (22 mg, 96 μmol, 7.8 mol %). After filtration and concentration in vacuo, benzene (125 mL) was added and the solution reconcentrated to facilitate the removal of methanol and water. The crude products were placed under high vacuum for several hours and then dissolved in pyridine (7 mL) and treated with TrocCl (0.672 mL, 4.88 mmol, 4.0 equiv) at rt for 24 h. After aqueous extractive workup, the resulting oil was purified by silica gel column chromatography (hexane/EtOAc, 20/1) to afford 0.848 g of impure *O*-Troc-2,2-diphenylcyclopentanol as a white solid and 0.360 g (69%) of analytically pure **15f** as a slightly yellow oil. The impure *O*-Troc-protected alcohol was treated with zinc dust (750 mg) in glacial acetic acid/THF (15 mL/6 mL) for 4 h. After filtration and aqueous extractive workup, the crude organic concentrate was purified by silica gel column chromatography (hexane/EtOAc, 10/1) to afford 0.258 g (89% recovery based on nitronate) of **17** as a white solid. Data for **15f**: ^{1}H NMR (400 MHz) 4.72 (m, 2 H), 3.61 (m, 2 H), 3.37 (m, 1 H), 2.97 (m, 1 H), 2.23–2.00 (m, 4 H), 1.61–131 (m, 16 H); ^{13}C NMR (100.6 MHz) mixture of rotamers 172.98, 152.85, 95.81, 95.43, 80.07, 74.73, 51.89, 51.41, 46.19, 45.72, 38.87, 38.11, 35.33, 31.64, 30.95, 28.08, 27.60, 27.54, 25.04, 25.01; IR (neat) 2976 (s), 1727 (s), 1455 (s), 1355 (s), 1249 (s), 1127 (s); MS (CI, CH_4) 402 (M^+ + 1, 27); TLC R_f 0.23 (hexane/EtOAc, 6/1); $[\alpha]^{28}_D = +15.5°$ (c = 1.05, $CHCl_3$); chiral HPLC (column: DIACEL Chiralpak AD (EtOH/hexane, 85/15), 1.3 mL/min) t_R (*R*)-**15f** 12.2 min (98.6%); t_R (*S*)-**15f** 21.0 min (1.4%); 97% ee. Anal. Calcd for $C_{16}H_{26}NO_4Cl_3$ (401.09): C, 47.72; H, 6.51; N, 3.48; Cl, 26.40. Found: C, 47.71; H, 6.50; N, 3.48; Cl, 26.40.

(+)-(*R*)-3-(3,5-Dimethoxyphenyl)-1-[(2,2,2-trichloroethoxy)carbonyl]pyrrolidine (15b). Titanium(IV) chloride (0.199 mL, 1.82 mmol) was added to a stirred solution of titanium(IV) isopropoxide (0.540 mL, 1.82 mmol) in dichloromethane (8 mL) at rt. The resulting solution was allowed to stir for 1 h at rt, and then 3.48 mL (1.45 mmol, 3.0 equiv) of the prepared Lewis acid solution was added to a mixture of nitroalkene **11b** (0.101 g, 0.484 mmol), chiral vinyl ether **10** (0.192 g, 0.726 mmol, 1.5 equiv, 98% ee), and dichloromethane (2 mL) at −78 °C. The yellow reaction mixture was allowed to stir at −78 °C for 1.5 h, and then −40 °C for 2 h, and finally −15 °C for 1.5 h. After being quenched with 1 N methanolic sodium hydroxide solution (5 mL), followed by aqueous extractive workup (identical to that used in general procedure I), the crude organic concentrate was purified by silica gel column chromatography (hexanes/EtOAc, 1/1) to afford 0.223 g (97%) of **16b** as a white solid. The product was determined to be a mixture of diastereomers in a ratio of 14:75:11 by ^{1}H NMR.

According to general procedure II, a sample of nitronate **16b** (0.223 g, 0.471 mmol, 14:75:11 (diastereomeric ratio)) in ethanol (15 mL) was reduced with hydrogen in the presence of platinum oxide (8.0 mg, 35 μmol, 7.5 mol %). After filtration and treatment with 6 M H_2SO_4 (59 μL, 0.35 mmol, 0.8 equiv), the reaction mixture was concentrated in vacuo and placed under high vacuum for several hours. The crude products were dissolved in pyridine (5 mL) and treated with TrocCl (0.259 mL, 1.88 mmol, 4.0 equiv) at rt for 6 h. After aqueous extractive workup, the resulting oil was purified by silica gel column chromatography (hexane/EtOAc, 2/1) to afford 0.335 g of impure *O*-Troc-2,2-diphenylcyclopentanol as a white solid and 0.125 g (69%) of **15b** as a slightly yellow oil. The recorded ^{1}H NMR spectrum was consistent with that previously reported for (−)-**15b**. The impure *O*-Troc-protected alcohol was treated with zinc dust (0.500 g) in glacial acetic acid (10 mL) for 1 h. After filtration and aqueous extractive workup, the crude organic concentrate was purified by silica gel column chromatography (hexane/EtOAc, 10/1) to afford 0.065 g (58% recovery based on nitronate) of **17** as a white solid. Data for (+)-**15b**: $[\alpha]^{25}_D = +11.4°$ (c = 1.08, $CHCl_3$); chiral HPLC (column: DIACEL Chiralpak AD (hexane/EtOH, 94/6), 1.0 mL/min) t_R (*S*)-**15b** 18.1 min (11.7%); t_R (*R*)-**15b** 20.5 min (88.3%); 76% ee.

(−)-(*R*)-3-Cyclohexyl-1-[(2,2,2-trichloroethoxy)carbonyl]pyrrolidine (15d). Titanium(IV) chloride (0.318 mL, 2.90 mmol) was added to a stirred solution of titanium(IV) isopropoxide (0.863 mL, 2.90 mmol) in dichloromethane (12 mL) at rt. The resulting solution was allowed to stir for 1 h at rt, and then 6.59 mL (2.90 mmol, 3.0 equiv) of the prepared Lewis acid solution was added to a mixture of nitroalkene **11d** (0.153 g, 0.986 mmol), chiral vinyl ether **10** (0.383 g, 1.45 mmol, 1.5 equiv, 98% ee), and dichloromethane (1.5 mL) at −78 °C. The yellow reaction mixture was allowed to stir at −78 °C for 1 h and was warmed to −15 °C for 1 h. After being quenched with 1 N methanolic sodium hydroxide solution (5 mL), followed by aqueous extractive workup (identical to that used in general procedure I), the crude organic concentrate was purified by silica gel column chromatography (hexanes/EtOAc, 2/1) to afford 0.361 g (87%) of **16d** as a white solid. The product was determined to be a mixture of diastereomers in a ratio of 37:55:8 by ^{1}H NMR.

According to general procedure II, a sample of nitronate **16d** (0.345 g, 0.822 mmol, 37:55:8 (diastereomeric ratio)) in ethanol (15 mL) was reduced with hydrogen in the presence of platinum oxide (14 mg, 62 μmol, 7.5 mol %). After filtration and treatment with 6 M H_2SO_4 (0.103 mL, 0.780 mmol, 0.8 equiv), the reaction mixture was concentrated in vacuo and placed under high vacuum for several hours. The crude products were dissolved in pyridine (6 mL) and treated with TrocCl (0.453 mL, 3.29 mmol, 4.0 equiv) at rt for 12 h. After aqueous extractive workup, the resulting oil was purified by silica gel column chromatography (hexane/EtOAc, 40/1) to afford 0.538 g of impure *O*-Troc-2,2-diphenylcyclopentanol as a white solid and 0.205 g (76%) of **15d** as a white solid. The recorded ^{1}H NMR spectrum was consistent with that previously reported for (+)-**15d**. The impure *O*-Troc-protected alcohol was treated with zinc dust (0.538 g) in refluxing methanol (10 mL) for 1 h. After filtration and aqueous extractive workup the crude organic concentrate was purified by silica gel column chromatography (hexane/EtOAc, 10/1) to afford 0.133 g (48% recovery based on nitronate) of **17** as a white solid. Analytical data for (−)-**15d**: $[\alpha]^{25}_D = -22.6°$ (c = 1.47, $CHCl_3$); chiral HPLC (column: DIACEL Chiralpak AD (hexane/EtOH, 99:1), 1.0 mL/min) t_R (*S*)-**15d** 13.7 min (9.6%); t_R (*R*)-**15d** 20.4 min (90.4%); 81% ee.

(4*S*,5*R*,6*S*)-5-Methyl-4-phenyl-6-[(1*R*)-[(2,2-diphenylcyclopentyl)oxy]]-5,6-dihydro-4*H*-[1,2]oxazine *N*-Oxide (19). According to general procedure I, a solution of MAPh (2.30

mmol, 2.0 equiv) in dichloromethane (13 mL), at 0 °C, was added to a mixture of nitroalkene **11a** (0.172 g, 1.15 mmol) and chiral propenyl ether **18** (0.400 g, 1.44 mmol, 1.3 equiv, 98% ee) in dichloromethane (2.0 mL) at −78 °C. The dark, heterogeneous reaction mixture was stirred at −78 °C for 30 min and then immediately warmed to −15 °C and stirred for 20 min as the color dissipated. After quenching with water and aqueous extractive workup, the crude organic concentrate was purified by silica gel column chromatography (hexane/EtOAc, 2/1) to afford 0.482 g (97%) of **19** as a white solid. The product was determined to be a 20:1 mixture of diastereomers by ^{1}H NMR integration. An analytical sample of **19** was obtained after recrystallization from EtOAc/hexane. The product was further purified by a second silica gel chromatography (hexane/EtOAc, 2/1) to obtain the pure major nitronate. Data for **19**: mp 164−165 °C (EtOAc/hexane); ^{1}H NMR (400 MHz) 7.33−7.08 (m, 15 H), 6.26 (d, J = 2.7, 1 H), 5.08 (d, J = 2.2, 1 H), 5.01 (dd, J = 5.5, 2.3, 1 H), 3.24 (dd, J = 11.2, 2.9, 1 H), 2.65 (dt, J_d = 12.9, J_t = 9.3, 1 H), 2.39 (m, 2 H), 2.01 (m, 1 H), 1.88 (m, 2 H), 1.48 (m, 1 H), 0.23 (d, J = 6.8, 3 H); ^{13}C NMR (100.6 MHz) 146.19, 145.20, 138.56, 128.89, 128.34, 128.28, 127.90, 127.82, 126.62, 126.01, 125.79, 114.55, 106.12, 85.99, 60.10, 43.47, 35.81, 35.10, 31.77, 20.27, 12.52; IR (CCl_4) 3030 (m), 2971 (m), 1628 (s), 1604 (m), 1246 (m); MS (CI, CH_4) 428 (M^+ + 1, 38); TLC R_f 0.32 (hexane/EtOAc, 2/1); $[\alpha]^{22}_D$ = +1.6° (c = 0.75, $CHCl_3$). Anal. Calcd for $C_{28}H_{29}NO_3$ (427.21): C, 78.66; H, 6.84; N, 3.28. Found: C, 78.68; H, 6.85; N, 3.30.

(+)-(3*S*,4*R*)-4-Methyl-1-[(4-methylphenyl)sulfonyl]-3-phenylpyrrolidine (20). According to general procedure II, a sample of nitronate **19** (0.198 g, 0.463 mmol) in ethanol (30 mL) was reduced with hydrogen in the presence of platinum oxide (7.4 mg, 32 μmol, 7.5 mol %). After filtration, the reaction mixture was concentrated in vacuo and placed under high vacuum for 15 min. The crude product was dissolved in dichloromethane (3 mL), cooled to 0 °C, and treated with triethylamine (0.129 mL, 0.926 mmol, 2.0 equiv) followed by TsCl (97 mg, 0.51 mmol, 1.1 equiv) for 1 h. After aqueous extractive workup, the crude organic concentrate was purified by silica gel column chromatography (hexane/EtOAc, 12/1) to afford 0.103 g (94% recovery) of **17** as a white solid and 0.122 g (84%) of **20** as a clear, colorless oil. The recorded ^{1}H NMR spectrum was consistent with that previously reported for (±)-*trans*-4-methyl-1-[(4-methylphenyl)sulfonyl]-3-phenylpyrrolidine.[10] Data for **20**: ^{1}H NMR (400 MHz, $CDCl_3$) 7.75 (d, J = 8.0, 2 H), 7.36 (d, J = 8.0, 2 H), 7.26 (m, 3 H), 7.09 (m, 2 H), 3.70 (m, 2 H), 3.28 (t, J = 10.0, 1 H), 2.92 (t, J = 10.0, 1 H), 2.65 (td, J_t = 10.0, J_d = 8.3, 1 H), 2.47 (s, 3 H), 2.17 (m, 1 H), 0.87 (d, J = 6.6, 3 H); $[\alpha]^{26}_D$ = +16.8° (c = 0.76, $CHCl_3$); chiral HPLC (column: DIACEL Chiralpak AD (hexane/EtOH, 89/11), 1.0 mL/min) t_R (3*S*,4*R*)-**20** 11.0 min (96.1%), t_R (3*R*,4*S*)-**20** 16.3 min (3.9%), 92% ee.

(−)-(1*R*,2*S*)-2-Phenyl-1-[(2-phenylethynyl)oxy]cyclohexane (23). A solution of chiral alcohol **13** (2.49 g, 14.1 mmol, 99% ee) dissolved in THF (15 mL) was added to a suspension of oil-free potassium hydride (0.567 g, 14.1 mmol, 1.0 equiv) in THF (15 mL) at rt. The heterogeneous mixture was allowed to stir for 15 min (while H_2 evolution was observed) and then warmed to 35−40 °C for 30 min. The resulting clear solution was transferred, via cannula, to a separate flask charged with phenyl chloroacetylene (2.41 g, 17.6 mmol, 1.3 equiv) dissolved in THF (10 mL) at −78 °C. After complete addition the cold bath was removed and the reaction mixture allowed to warm to rt and stir for 12 h. The resulting dark mixture was poured into water (150 mL) and extracted with TBME (3 × 150 mL). The combined organic extracts were washed with brine (50 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. The orange-yellow oil was purified twice by silica gel column chromatography (first with hexanes/EtOAc, 99/1; second with 100% hexanes) to afford 2.45 g of **23** as a clear oil which eventually solidified. Two additional chromatographic purifications of the mixed fractions on silica gel (100% hexanes) provided an additional 0.250 and 0.218 g, respectively, of pure **23** as a white solid for a combined mass of 2.92 g (75%) of analytically pure **23**. Data for **23**: mp 53−55 °C; ^{1}H NMR (400 MHz) 7.34−7.20 (m, 10 H), 4.24 (td, J_t = 10.9, J_d = 4.6, 1 H), 2.86 (ddd, J = 12.5, 10.7, 3.9, 1 H), 2.52 (m, 1 H), 2.00 (m, 2 H), 1.76 (m, 2 H), 1.64−1.33 (m, 3 H); ^{13}C NMR (100.6 MHz) 142.40, 131.36, 124.46, 128.04, 127.55, 126.73, 126.93, 124.83, 96.96, 89.90, 49.16, 33.84, 31.13, 25.49, 24.72; IR (CCl_4) 2939 (s), 2257 (s), 1327 (s), 1065 (s); MS (70 eV) 276 (M^+, 1); TLC R_f 0.20 (hexane/EtOAc, 40/1); $[\alpha]^{22}_D$ = −90.3° (c = 2.03, $CHCl_3$). Anal. Calcd for $C_{20}H_{20}O$ (276.38): C, 86.29; H, 7.29. Found: C, 85.99; H, 7.24.

(−)-(1*R*,2*S*)-2-Phenyl-1-[((*Z*)-2-phenylethynyl)oxy]cyclohexane ((*Z*)-24). A suspension of 5% Pd/$BaSO_4$ (0.376 g, 0.176 mmol, 7 mol %) in MeOH/hexanes (5 mL/5 mL) was stirred under 1 atm of hydrogen for 15 min. In a separate flask, acetylenic ether **23** was dissolved in MeOH/hexanes (10 mL/10 mL) and treated with quinoline (0.348 mL, 2.94 mmol, 1.0 equiv). The solution containing **23** was then added to the palladium mixture, via syringe, and the resulting heterogeneous reaction mixture stirred for 1.5 h at rt. The reaction vessel was purged with N_2 and the mixture was filtered through a small pad of Celite. The vessel and Celite were washed with fresh portions of hexanes and MeOH (20 mL each), and the clear filtrate was concentrated in vacuo. The slightly yellow concentrate was then passed through a silica plug (99/1, hexane/EtOAc) and concentrated in vacuo. Residual solvents were removed under high vacuum (0.2 Torr, 30 min) to afford 0.712 mg (96%) of **24** as a 30:1 (*Z*/*E*) mixture as determined by ^{1}H NMR integration. The product was further purified by silica gel column chromatography (hexanes) to afford 0.629 g (85%) of pure (*Z*)-**24** as a clear oil and 0.050 g (7%) of a 7:1 (*Z*/*E*) mixture of **24**. Data for (*Z*)-**24**: ^{1}H NMR (400 MHz) 7.37 (m, 2 H), 7.28 (m, 4 H), 7.19 (m, 3 H), 7.07 (m, 1 H), 5.99 (d, J = 7.1, 1 H), 4.94 (d, J = 6.8, 1 H), 3.81 (td, J_t = 10.5, J_d = 4.4, 1 H), 2.77 (ddd, J = 12.5, 10.2, 3.8, 1 H), 2.27 (m, 1 H), 1.95 (m, 2 H), 1.81 (m, 1 H), 1.67−1.36 (m, 4 H); ^{13}C NMR (100.6 MHz) 145.53, 143.46, 136.15, 128.27, 127.99, 127.87, 127.71, 126.39, 104.54, 85.85, 50.69, 33.37, 32.97, 25.74, 24.84; IR 2931 (s), 1649 (s), 1090 (s), 1076 (s); MS (70 eV) 278 (M^+, 27); TLC R_f 0.25 (hexane/EtOAc, 40/1); $[\alpha]^{22}_D$ = −447.5° (c = 1.87, $CHCl_3$). Anal. Calcd for $C_{20}H_{22}O$ (278.40): C, 86.29; H, 7.97. Found: C, 86.30; H, 7.84.

(+)-(4*R*,5*R*,6*S*)-4,5-Diphenyl-6-[((1*R*,2*S*)-2-phenylcyclohexyl)oxy]-5,6-dihydro-4*H*-[1,2]oxazine *N*-Oxide (25a). According to general procedure I, a solution of MAPh (2.50 mmol, 2.0 equiv) in dichloromethane (14 mL), at 0 °C, was added to a mixture of ntiroalkene **11a** (0.186 g, 1.3 mmol) and chiral enol ether (*Z*)-**24** (0.520 g, 1.87 mmol, 1.5 equiv) in dichloromethane (3.0 mL) at 0 °C. The resulting deep red solution was allowed to stir for 3 h at 0 °C and then 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 0.510 g (96%) of **25** as a white foam. The product was determined to be 87:10:3 (**25a**/**25b**/**25c**) mixture of diastereomers by ^{1}H NMR integration. The material was further purified by silica gel column chromatography (hexanes/EtOAc, 5/1) to afford 0.423 g (79%) of **25a** as a white foam (trace solvent present). An analytical sample was obtained by heating a small sample of **25a** at 80 °C for 4 h in vacuo (0.2 Torr). Data for **25a**: ^{1}H NMR (400 MHz) 7.13−6.89 (m, 13 H), 6.75 (m, 2 H), 6.42 (d, 1 H), 4.75 (d, J = 2.2, 1 H), 4.07 (dd, J = 12.0, 2.9, 1 H), 3.99 (td, J_t = 10.5, J_d = 4.4, 1 H), 2.95 (dd, J = 12.0, 2.4, 1 H), 2.56 (ddd, J = 12.5, 10.3, 3.7, 1 H), 2.33 (m, 1 H), 2.04−1.26 (m, 7 H); ^{13}C NMR (100.6 MHz) 143.27, 138.04, 135.01, 129.78, 128.17, 128.07, 128.05, 127.58, 127.53, 127.23, 126.07, 115.01, 103.64, 81.65, 51.11, 48.39, 42.63, 34.06, 33.78, 25.55, 24.95; IR (CCl_4) 2933 (s), 1627 (s), 1244 (s); MS (70 eV) 428 (M^+ + 1, 26); TLC R_f 0.17 (hexane/EtOAc, 3/1); $[\alpha]^{22}_D$ = 197.1° (c = 0.92, $CHCl_3$). Anal. Calcd for $C_{28}H_{29}NO_3$ (427.54): C, 78.66; H, 6.84; N, 3.28. Found: C, 78.38; H, 6.77; N, 3.57.

(+)-(3*S*,4*S*)-3,4-Diphenylpyrrolidine (26). A sample of nitronate **25a** (0.500 g, 1.17 mmol) in methanol (30 mL) was reduced with hydrogen in the presence of platinum oxide (20 mg, 88 μmol, 7.5 mol %). After filtration, the reaction mixture was concentrated in vacuo, and the clear residue was dissolved in CH_2Cl_2 (50 mL). The solution was poured into TBME (100 mL) and extracted with 1 M HCl (3 × 25 mL), and the combined aqueous layers were back-extracted with TBME (50 mL). The organic layer was washed with brine (20 mL), dried

($MgSO_4$), filtered, and concentrated in vacuo. The crude concentrate was purified by silica gel column chromatography (hexanes/EtOAc, 6/1) to afford 0.193 g (94%) of chiral alcohol **17** as a white solid. The acidic aqueous washes were made basic (to litmus) with 10% aqueous NaOH solution and extracted with dichloromethane (5 × 100 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. The off-white solid was purified by bulb-to-bulb distillation to afford 0.221 g (85%) of **26** as a white solid. The recorded ^1H NMR spectrum and optical rotation data are consistent with that previously reported for compound (3*S*,4*S*)-3,4-diphenylpyrrolidine.[9b] Data for **26**: ^1H NMR (400 MHz) 7.27−7.14 (m, 10 H), 3.58 (m, 2H), 3.35 (m, 2 H), 3.15 (m, 2 H), 2.16 (br m, 1 H); ^{13}C NMR (100.6 MHz) 142.42, 128.41, 127.34, 126.31, 56.04, 54.17; $[\alpha]^{23}_D$ = +227.8° (*c* = 1.05, $CHCl_3$).

(+)-(3*S*,4*S*)-1-[(4-Methylphenyl)sulfonyl)]-3,4-diphenylpyrrolidine (27). The free pyrrolidine **26** (37 mg, 0.17 mmol) was dissolved in dichloromethane (1 mL) and cooled to 0 °C, and triethylamine (58 μL, 0.42 mmol, 2.5 equiv) was added, followed by a solution of TsCl (0.035 g, 0.182 mmol, 1.1 equiv) in dichloromethane (1 mL). The mixture was allowed to stir for 1 h and then was poured into dichloromethane (50 mL) and was washed with dilute 0.1 N HCl solution (50 mL). The acidic aqueous layer was back-extracted with dichloromethane (2 × 50 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4), filtered, and concentrated. The crude concentrate was purified by silica gel column chromatography (hexane/EtOAc, 6/1) to afford 0.056 mg (100%) of **27** as white solid. The ^1H NMR spectrum was consistent with that previously reported for compound (±)-*trans*-3,4-diphenyl-*N*-(*p*-tolylsulfonyl)pyrrolidine.[10] Data for **27**: ^1H NMR (400 MHz) 7.80 (d, *J* = 8.2, 2 H), 7.39 (d, *J* = 7.8, 2 H), 7.23−7.14 (m, 6 H), 7.02 (m, 4 H), 3.90 (m, 2 H), 3.41 (m, 2 H), 3.39 (m, 2 H), 2.49 (s, 3 H); $[\alpha]^{23}_D$ = +87.0° ($CHCl_3$, *c* = 0.575); chiral HPLC (column: DAICEL Chiralpak AD (hexane/EtOH, 80/20), 1.0 mL/min) t_R (3*S*,4*S*)-**27** 10.58 min (100%); t_R (3*R*,4*R*)-**27** 24.14 min (0%); >99% ee.

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Supplementary Material Available: Complete ^1H and ^{13}C NMR assignments, IR and MS data for all characterized compounds (15 pages). This material is contained in libraries on microfiche, immediately following this article in the microfilm version of the journal, and can be ordered from the ACS; see and current masthead page for ordering information.

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