Cycloaddition Reactions of Chiral 2-Amino-1,3-butadienes with Nitroalkenes: Synthesis of Enantiomerically Pure 4-Nitrocyclohexanones[1]

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2-Amino-1,3-butadienes bearing commercially available *S*-(+)-2-(methoxymethyl)pyrrolidine as chiral auxiliary undergo a [4 + 2] cycloaddition reaction with nitroalkenes to furnish 4-nitrocyclohexanones upon hydrolysis of the resulting enamine. The cycloadducts are obtained with good yields and very high enantiomeric excesses. The reaction has been performed with aromatic and aliphatic conjugated nitroalkenes. Moreover, a 2-amino diene which features a (*Z*) double bond undergoes a Michael addition reaction with nitroalkenes, which gives rise to open chain compounds with high enantioselectivity. After acidic hydrolysis, the open chain compounds cyclize to form chiral substituted furans.

Introduction

Enantioselective [4 + 2] cycloadditions constitute an excellent strategy for the preparation of functionalized optically active 6-membered rings. During the process, up to four new stereogenic centers can be created in a single synthetic operation. Asymmetric induction in these processes has been achieved by employing chiral catalysts (catalytic approach),[2] chirally modified dienophiles,[3] and chirally modified dienes[4] (stoichiometric approaches). While the usefulness of the first two methods—chiral catalysts and chiral dienophiles—has been widely demonstrated, optically active dienes have been employed less frequently in [4 + 2] cycloadditions. Most of the examples described in the literature rely on the use of dienes which carry the chiral information attached to the C-1 position of the diene.[5] However, these dienes are far from ideal; they usually present limitations in accessibility of the enantiomerically pure diene, poor reactivity, low stereoselectivity of the cycloaddition process, or cleavage of the chiral auxiliary.

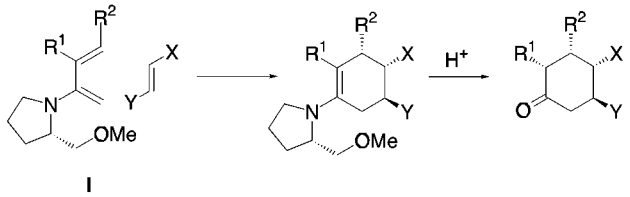

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Figure 1. Asymmetric synthesis with chiral 2-amino dienes.

Comparatively, few examples are known to date of the use of dienes with a chiral auxiliary linked to C-2 of the diene.[6] Recently our group, simultaneously with Enders *et al.*, introduced a new class of optically active 2-amino-1,3-butadienes **I**;[7] a type of diene that fulfills most of the requirements for an ideal chiral reagent: they are easily accessible by a variety of methods[8] in optically pure form, and the chiral auxiliary can be readily cleaved once the reaction has been carried out (Figure 1). In fact, chiral 2-amino dienes have been successfully employed in highly stereoselective [4 + 2] homo-[9] and hetero-Diels−Alder reactions,[10] and also in [4 + 3] cyclization processes

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involving α,β-unsaturated Fischer carbene complexes.[11]

On the other hand, conjugated nitroalkenes have been shown to be very potent dienophiles in [4 + 2] cycloadditions;[12] in particular, their reactivity toward 2-amino dienes is well-known.[13] It has been previously demonstrated that depending on the nature of the diene used, open chain 4-nitro ketones **II** (arising from a Michael type addition of the enamine moiety to the nitroolefin), or 4-nitrocyclohexanones **III** (formal [4 + 2] cycloaddition) can be obtained (Figure 2).[14] The chiral version of this reaction has received much less attention. As far as we know, only one contribution by the Enders' group restricted to the use of aromatic nitroolefins,[8c] apart from our previous communication, has been described.

Recently, we have been interested in the synthesis of enantiomerically pure compounds by using chiral 2-amino-1,3-butadienes bearing (*S*)-2-(methoxymethyl)pyrrolidine as chiral auxiliary. In our first communication in this field we introduced the reaction between chiral 2-amino dienes **1** and nitroolefins,[1] a process that afforded 4-nitrocyclohexanones in which four new stereocenters were created in good yields and high ee (82−90%). Encouraged by these promising results, as well as by the potential synthetic interest of these functionalized nitro derivatives, we set out to investigate the scope of this reaction with the purpose of developing a more general method for the preparation of substituted 4-nitrocyclohexanones.

In this paper we describe the reaction of substituted chiral 2-amino dienes with a variety of nitroalkenes with aromatic, heteroaromatic, and aliphatic substituents. The effect of the substituents on both the diene and dienophile on the enantiomeric excess has been studied. Additionally an enantioselective synthesis of substituted furans is reported.

Results and Discussion

As we are interested in the development of a method of synthesis of functionalized 4-nitrocyclohexanones, we decided to use 2-amino dienes **1**, which incorporate additional functionality as a protected hydroxymethyl substituent in position 4 of the diene (Scheme 1). The commercial precursor of these dienes is available in the form of both *E* and *Z* isomers. It turned out that the stereochemistry of the trisubstituted double bond of the diene is crucial for the outcome of the reaction; therefore we will discuss first the behavior of the dienes with an (*E*) double bond "(*E*)-dienes", and later the results obtained with "(*Z*)-dienes".

Reactions between (*E*)-Dienes and Nitroolefins: Synthesis of 4-Nitrocyclohexanones. The reactivity of dienes **1** was investigated toward a collection of nitroolefins, which were substituted with both aromatic and aliphatic groups. In a first run all cycloaddition reactions were carried out in MeOH as solvent at −80 °C for 12 h and then warmed to room temperature over 10 h. The initially formed enamines **3** were not isolated due to their moisture sensitivity but hydrolyzed with an acidic aqueous buffer (HOAc/NaOAc, pH = 4.6) to release the chiral auxiliary, yielding 4-nitrocyclohexanones **4** (Scheme 1). Both the cycloaddition process and the hydrolysis of the enamine moiety are highly diastereoselective, and in most of the cases a single diastereoisomer of all the possible combinations was isolated (83−99% de),[15] as deduced from the ^{1}H NMR spectra analysis of the crude reactions. Only for compound **4i** was a notable decrease in the selectivity observed (3:1 mixture of diastereoisomers). The facial diastereoselectivity of the cycloaddition is very high in most of the cases, ranging the enantiomeric excesses of compounds **4** from good to excellent. Enantiomeric excesses were determined by HPLC (unless otherwise indicated).[16] The racemic mixtures of compounds **4**, needed for the determination of the ee, were synthesized by following the same methodology, but using 2-morpholino-1,3-butadienes instead of chiral dienes **1**.[17] General results are summarized in Table 1.

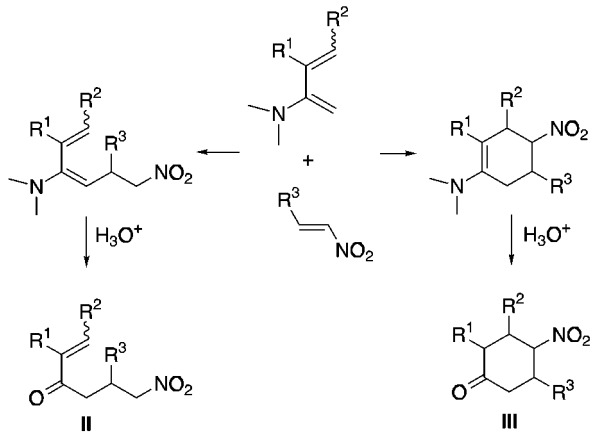

Figure 2. Reactivity of 2-amino dienes toward conjugated nitroalkenes.

From the data in Table 1 it can be observed that the substituents on both the diene and the nitroolefin exert some influence in the diastereoselectivity of the cycloaddition. It is interesting to discuss the effect of R^3 on the enantiomeric excesses of cycloadducts **4**. Electron rich aromatic rings (**4c**−**e**) provided lower enantiomeric excesses than the phenyl group itself (**4a**) or electron deficient aromatics (**4b**, **4f**). Very good ee's (92−95%) were obtained with all the aliphatic nitroalkenes tested, regardless of the substitution pattern on the olefin: α- and β-monosubstituted and α,β-disubstituted nitro-

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(15) Only compound **4i** was obtained with lower selectivity (3:1 mixture of diastereoisomers). Unfortunately, the structure of this minor diastereoisomer could not be unequivocally determined by NOESY experiments, as both the C2-epimer and the C4-epimer of **4i** match the observations. Additionally, compound **4k** was obtained along with a cyclic product [3-(((*tert*-butyldimethylsilyl)oxy)methyl)-2,4-dimethyl-4-nitro-6-(2-nitropropyl)-1-cyclohexanone, 4:1 mixture, 8% yield from ^{1}H NMR], derived from the reaction of the chiral diene with two molecules of 2-nitro-1-propene.

(16) The enantiomeric excesses of compounds **4l** and **4m** were determined by ^{1}H NMR of the Mosher's esters obtained by reduction of the carbonyl group, followed by esterification with (*R*)-(+)-MPTA chloride. Experimental details and spectrocopic data are available in the supplementary material of ref 1.

(17) For the synthesis of nonchiral 2-morpholino-1,3-butadienes, see ref 8a.

Scheme 1

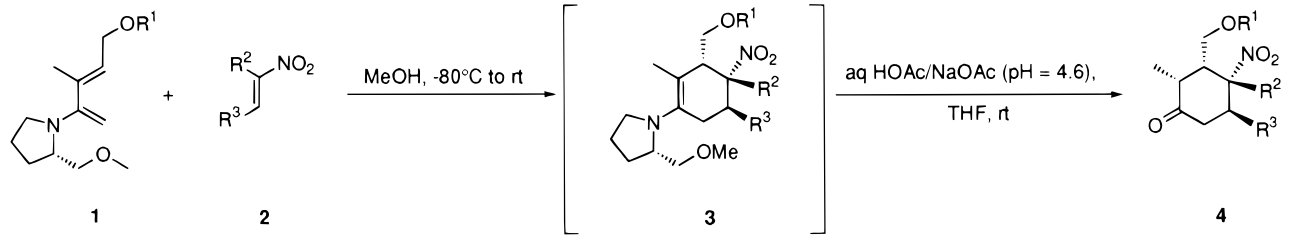

Table 1. 4-Nitro-1-cyclohexanones 4 Prepared According to Scheme 1

R^1	R^2	R^3	compd	yield, %	ee % (recryst)
TBDMS	H	Ph	**4a**	63[a]	94[b] (>99)
TBDMS	H	*o*-ClC_6H_4	**4b**	68[a]	98[b] (>99)
TBDMS	H	2-furyl	**4c**	88[a]	64[b]
TBDMS	H	3-furyl	**4d**	53[a]	89[b] (99)
TBDMS	H	*p*-$MeOC_6H_4$	**4e**	49[a]	83[b] (>99)
TBDMS	H	*p*-$NO_2C_6H_4$	**4f**	54[a]	94[b] (>99)
TBDMS	H	Me	**4g**	48[a]	95[b]
TBDMS	H	^{i}Pr	**4h**	56[a]	92[b]
TBDMS	H	$BnOCH_2$	**4i**	38[c]	94[b]
TBDMS	-$(CH_2)_4$-		**4j**	70[a]	94[b] (>99)
TBDMS	Me	H	**4k**	32[c]	94[b]
Me	H	Ph	**4l**	70[a]	82[d]
Me	H	*o*-ClC_6H_4	**4m**	76[a]	90[d]
Me	H	2-furyl	**4n**	42[a]	70[b]
Me	-$(CH_2)_4$-		**4o**	48[a]	>99[b]
MOM	H	2-furyl	**4p**	70[a]	56[b]

[a] Yield of the major diastereoisomer isolated after SiO_2 column chromatography. [b] ee determined by HPLC. [c] Yield of the major cycloadduct deduced from integration of the ^1H NMR spectra of the chromatographed mixture. [d] ee determined by ^1H NMR (see ref 16).

Table 2: Solvent Influence on the Synthesis of 4a and 4p

compd	solvent	yield, %[a]	ee %[b] (recryst)
4a	MeOH	63	94 (>99)
4a	Et_2O	31	99
4p	MeOH	63	56
4p	Et_2O	50	88 (>99)
4p	Tol	42	84 (>99)

[a] Yield of the major diastereoisomer isolated after SiO_2 column chromatography. [b] ee determined by HPLC.

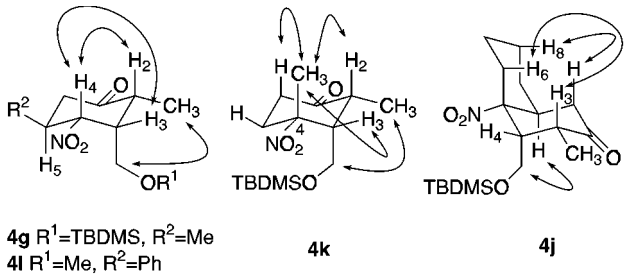

Figure 3. Some selected NOEs for compounds **4g**, **4l**, **4k**, and **4j**.

ethenes. However no reaction was observed for a β,β-disubstituted nitroolefin, probably due to sterical reasons.[18]

The influence of the substituent R^1 at the diene is not easy to rationalize. The methyl group provided better ee's than TBDMS and MOM with an electron rich aromatic substituted nitroalkene (R^3 = 2-furyl; **4n**, **4c**, **4p**) and also with an aliphatic substituted nitroolefin (R^2, R^3 = -$(CH_2)_4$-; **4o**, **4j**). However, TBDMS gave better results in reactions with β-nitrostyrene (**4a**, **4l**) and electron deficient aromatic nitroalkenes (**4b**, **4m**). From a synthetical point of view, we find the TBDMS ether a very interesting protecting group for this reaction. First, it can be easily cleaved to afford hydroxymethyl-substituted cyclohexanones; second, in most of the cases TBDMS-protected compounds **4** are crystalline solids that can be enantiomerically enriched up to ee >99% by crystallization.

It has been previously established with nonchiral dienes that the polarity of the solvent plays an important role in the course of this type of cycloaddition.[19] A similar behavior has been observed in this case. We studied the influence of the solvent for compounds **4a** (R^1 = TBDMS, R^3 = Ph) and **4p** (R^1 = MOM, R^3 = 2-furyl) for a series of solvents with increasing polarity: toluene, diethyl ether, methanol. The data summarized in Table 2 indicate that the yield of the major diastereoisomer increases with the polarity of the solvent, while less polar solvents provide a higher ee.[20] The remarkable decrease in the chemical yield obtained when Et_2O and toluene are employed is due to the lower selectivity of the process. Upon hydrolysis, along with compound **4**, the C-3 epimer of **4** and *Z*/*E* open chain products **6** (see following section) are formed as detected by ^1H NMR of the crude.

The relative configurations of the major cycloadducts **4** as depicted in Figure 3 were deduced from ^1H NMR data analysis. For instance, for compound **4l** the equatorial disposition of phenyl and nitro groups is indicated by the large axial−axial coupling constant between H_4 and H_5 ($J_{H4,H5}$ = 12.4 Hz) and the axial arrangement of CH_2OCH_3 group by the small equatorial−axial coupling constant between H_3 and H_4 ($J_{H3,H4}$ = 4.6 Hz); moreover, the positive NOE effect found between H_2 and H_4 indicated the axial orientation of H_2 and therefore the equatorial disposition of the methyl group. This particular structure was further confirmed by an X-ray structure determination.[21] The same relative configuration was deduced for **4a**−**f** (cycloadducts derived from aromatic nitroalkenes) and **4g**−**i** (cycloadducts derived from aliphatic nitroalkenes) in light of the values of the coupling constants, similar to those found for **4l**; NOE experiments carried out on **4g** also support the proposed structure (Figure 3). In compound **4k**, the methyl group at C_4

(18) When 2-amino diene **1** (R^1 = TBDMS) was reacted with 2-methyl-1-nitro-1-propene under the standard conditions, no reaction product was observed and the starting materials were recovered.

(19) In our previous paper dedicated to the reaction of nonchiral 2-amino dienes with β-nitrostyrene (see ref 14), we observed that very polar solvents such as MeOH favor the cyclization process, giving rise to a single diastereoisomer. However, less polar solvents like THF or chloroform lead to a mixture of three compounds: two diastereoisomers of nitrocyclohexanone and the open chain compound derived from the Michael type addition of the enamine to the electrophilic double bond.

(20) Similar observations have been reported by Enders *et al.* (ref 8c).

(21) Absolute configurations of **4l** and **4m** have been determined by X-ray using the anomalous dispersion technique and are available in the supplementary material of ref 1.

Scheme 2

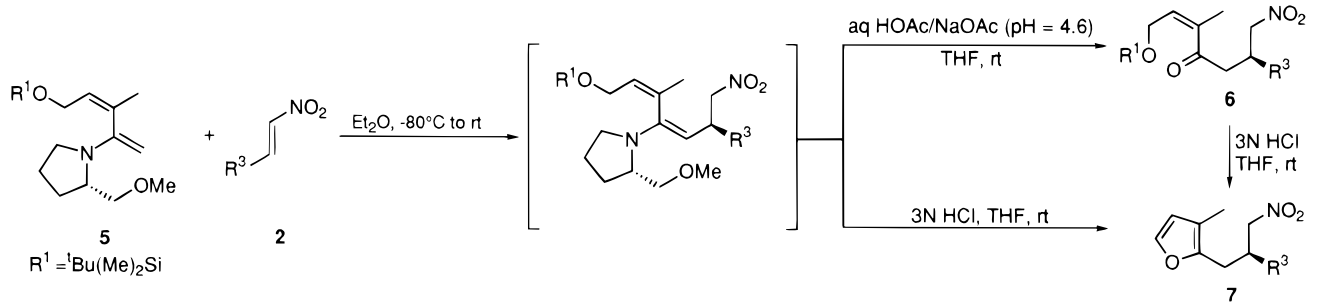

Table 3. Solvent and Substrate Influence in the Synthesis of Compounds 6 and 7

R^3	solvent	compd	yield, %[a]	% ee
Ph	Et_2O	**6a**	58	86[b]
Ph	MeOH	**7a**	65	78[b]
Ph	Et_2O	**7a**	69	85[b]
o-ClC_6H_4	Et_2O	**7b**	71	88[b]
Me	Et_2O	**7c**	56	75[c]

[a] Chemical yield of chromatographed compound. [b] Determined by HPLC. [c] Determined by NMR.

showed positive NOE with H_2, which points to an axial arrangement of both; a positive NOE between methyl group at C_4 and H_3 was also observed, consistent with an equatorial disposition of H_3. The determination of the stereochemistry of **4j** required COSY90 and HMQC experiments in order to assign the different protons in the ^1H NMR spectrum (400 MHz, $CDCl_3$). A phase sensitive NOESY experiment (with time proportional phase incrementation) showed NOE between H_3 and H_6, indicating that the methyl group at C_3 and the nitro substituent are in a *syn* equatorial arrangement. A coupling constant of 6.7 Hz between axial H_3 and H_4 pointed to an equatorial disposition of H_4. All other NOE signals observed were in agreement with the stereochemistry shown in Figure 3. Finally, the absolute configuration indicated in Scheme 1 for compounds **4** is based on X-ray determinations carried out for **4l** and **4m**.[21]

Influence of the Substituents on the Diene: Reactions with (*Z*)-Dienes. In our previous contribution dedicated to the reaction of nonchiral amino dienes toward nitroalkenes, we observed that the stereochemistry of the non-enaminic double bond on the 2-amino diene is decisive for the outcome of the reaction. Usually dienes with a *Z* double bond are unable to participate in cycloaddition processes; instead, open chain compounds are isolated. This is also the case here. When diene **5** was reacted with nitroolefins **2** followed by hydrolysis of the intermediate enamine under the same conditions (buffer HOAc/NaOAc, pH = 4.6) no cyclic compounds were detected, instead open chain compounds **6** were afforded (Scheme 2). Moreover, when stronger acidic conditions were employed (3 N HCl/THF) in the hydrolytic step, chiral 2-substituted furans **7** were obtained in good yields (Table 3). For these reactions, diethyl ether resulted in a more advantageous solvent than methanol, as it provided both better chemical yields and ee's.

Formation of furans **7** can be easily explained as a result of desilylation of compound **6** under the strong acidic conditions, followed by the formation of a cyclic hemiketal and subsequent aromatization through dehydration. This mechanism is supported by the fact that desilylation of pure **6a** under the same conditions affords **7a** in quantitative yield. The determination of the enantiomeric excesses[22] required the synthesis of the racemates of these compounds, which was achieved again starting from the corresponding 2-morpholino dienes. The enantiomeric excess of compound **7c** could not be obtained by HPLC, and it was determined by ^{19}F NMR following Mosher's procedure.[23] With that purpose the nitro group of furan **7c** was reduced[24] to give amine **8** in 71% yield (Scheme 3). Reaction of **8** with MPTA chloride yielded amide **9** as a 7.1:1 mixture of diastereoisomers, which corresponds to 75% ee of compound **7c**.

To establish the absolute configuration of the stereogenic center of compounds **6** and **7**, compound **7c** was transformed into pyrrolidinone **12**, a previously described compound with known absolute configuration and optical rotation value[25] (Scheme 3). With this purpose, the amino group of **8** was Boc-protected by treatment with $(Boc)_2O$ in CH_2Cl_2. Then the furan ring was converted into a carboxylic ester by ozonolysis in the presence of hydrogen peroxide, followed by esterification with diazomethane, to obtain ester **11**. Cleavage of the carbamate with TFA and subsequent basic aqueous workup afforded pyrrolidinone **12**. The measurement of the optical rotation and comparison with the literature value indicates the *S* configuration for the stereogenic center and confirms the ee value determined with the Mosher's ester method.

It is noteworthy that the same spatial arrangement of the substituents of this stereogenic center is obtained for both open chain nitroketones **6** and cycloadducts **4**. From this observation it can be postulated that both linear and cyclic compounds arise from a similar type of approximation of the nitroolefin to the enamine in the transition state. In fact, the model described by Seebach[26] *et al.* for the reactions of enamines and nitroalkenes takes account of the absolute configuration of this stereogenic center obtained in our reactions.

Two different mechanisms can be proposed for the [4 + 2] cycloaddition reaction between 2-amino-1,3-butadienes and nitroolefins: a concerted Diels−Alder process or a polar stepwise pathway which involves a Michael type 1,4-addition of the enamine to the nitroalkene, followed by an intramolecular vinylogous Mannich reaction. The strong dependence of chemical yields, products formed, rate of reaction,[14] and enantiomeric excesses upon the polarity of the solvent indicate that the polar stepwise reaction pathway *is more likely*. This mecha-

(22) Enantiomeric excesses were determined from furans **7** and not from open chain compounds **6** due to the unstability of the latter. Upon standing, compounds **6** undergo isomerization of the *Z* double bond.

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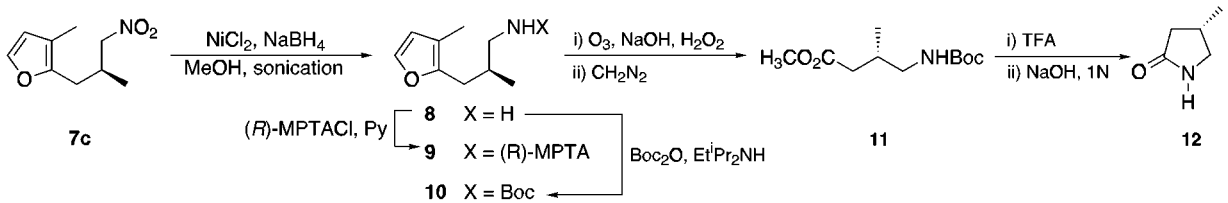
Scheme 3



nism is consistent with the well-known strong enaminic character of 2-amino dienes[27] and also with the fact that similar results are obtained in terms of yields, stereoselectivity, and face selectivity both when the [4 + 2] cycloadducts are formed (from *E*-dienes) and when open chain compounds are isolated (from *Z*-dienes). However a [4 + 2] concerted mechanism in which the nitroalkene would approach in an *endo* fashion (relative to the nitro group) to the diene[12b] also explains the relative stereochemistry of the final cycloadducts and therefore cannot be neglected in the absence of more rigorous mechanistical and theoretical studies.

Conclusion

We have described a highly enantioselective synthesis of 4-nitrocyclohexanones through an asymmetric [4 + 2] cycloaddition process between chiral 2-amino dienes and nitroalkenes. Moreover, if (*Z*)-dienes are employed, open chain compounds can be synthesized with good levels of stereocontrol, which upon hydrolysis lead to 2-substituted chiral furans. The compounds described herein are potentially interesting synthetic intermediates due to their high functionalization. The study of some of their applications in this direction is currently underway.

Experimental Section

General. All reactions were carried out under N_2 employing solvents dried following standard procedures.[28] For isolation, organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Column chromatography was carried out using 230−400 mesh silica gel (SiO_2). TLC analyses were performed on aluminum-backed silica gel 60 F_{254} plates, and compounds were visualized with UV light and by spraying with an acidic $Mo_7O_{24}(NH_4)_6 \cdot 4H_2O/Ce(SO_4)_2$ solution. Chiral HPLC analyses were carried out by employing a CHIRALCEL OD-H column (25 cm × 0.46 cm i.d., Daicel Chemical Industries) at rt with a Shimadzu photo diode array UV−vis detector (D_2 lamp, 200−300 nm); racemic compounds were used to choose the operating conditions [flow rate (F), solvent mixture] for the resolution of both enantiomer peaks, and ee's were determined at the wavelength of maximum absorbance. Semipreparative HPLC separations were performed on a Nucleosil 120-10 column (250 mm × 16 mm i.d.). Optical rotations were measured in CH_2Cl_2 or $CHCl_3$ at rt. All melting points are uncorrected. ^{1}H NMR spectra were recorded at 200 or 300 MHz at rt by employing $CDCl_3$ as solvent. Chemical shifts are reported in parts per million (ppm) relative to residual $CHCl_3$ peak; *J* values are given in hertz. ^{13}C NMR spectra were performed at 50 or 75 MHz. Elemental analyses were obtained on a Perkin-Elmer 240B microanalyzer. HRMS were determined on a Finnigan Mat-95 mass spectrometer. Chiral dienes **1** were synthesized as reported previously.[10b] Diene **5**, which had not been previously described, was prepared by following the same procedure: yield 40%, $[\alpha]^{20}_{589} = +46.8$ (*c* 2.9, CH_2Cl_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.0 (broad), 136.3, 128.2, 80.7 (broad), 73.5, 61.3, 59.0, 57.2, 48.7, 28.8, 26.0, 24.3, 23.3, 18.4, −5.2 ppm. Nitroolefins **2** were purchased from Aldrich [β-nitrostyrene, 2-chloro-ω-nitrostyrene, 1-(2-furyl)-2-nitroethylene, 4-nitro-ω-nitrostyrene, and 1-nitro-1-cyclohexene] or were prepared according to previously reported procedures: 3-(benzyloxy)-1-nitro-1-propene,[29] 2-nitro-1-propene;[30] 1-(3-furyl)-2-nitroethylene and 1-(*p*-methoxyphenyl)-2-nitroethylene analogously to β-nitrostyrene;[31] 1-nitro-1-propene was synthesized by following the same methodology employed for 3-methyl-1-nitro-1-butene.[32]

General Procedure for the Synthesis of Enantioenriched 4-Nitro-1-cyclohexanones 4. A solution of the corresponding nitroalkene **2** (1 mmol) in dry MeOH (10 mL) was cooled down to −80 °C. Pure chiral diene **1** (0.92 mmol) was added dropwise via syringe, and the stirred reaction mixture was kept at this temperature overnight with the aid of a cryocool apparatus (immersion cooler). The cooling equipment was then switched off, and the reaction mixture was permitted to reach rt slowly (10 h). Methanol was removed under vacuum (0.1 Torr), and the resulting oil was redissolved in THF (5 mL). The reaction was quenched with an aqueous AcOH/NaOAc solution (pH = 4.6, 5 mL), and after 10 min of stirring the aqueous layer was extracted with EtOAc (3 × 5 mL); the combined organic layers were washed with brine (5 mL), dried, and evaporated to dryness. The resulting crude product was purified by SiO_2 column chromatography.

(2*R*,3*S*,4*R*,5*R*)-3-(((*tert*-Butyldimethylsilyl)oxy)methyl)-2-methyl-4-nitro-5-phenyl-1-cyclohexanone (4a). Chiral diene **1** (R^1 = TBDMS, 0.30 g) and β-nitrostyrene (0.15 g) were employed. Compound **4a** was isolated as a white crystalline solid in 63% yield (220 mg): $R_f = 0.43$ (SiO_2, hexane/EtOAc 4:1); ee = 94% (determined by HPLC at 220 nm, hexane/EtOH 6:1, $F = 0.8$ mL/min; $t_{Rmajor} = 7.4$ min, $t_{Rminor} = 10.1$ min); recrystallized from CH_2Cl_2/MeOH, ee >99%, mp 154−155 °C; $[\alpha]^{20}_{589} = +26.5$ (*c* 1.3, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35−7.23 (m, 5H), 5.39 (dd, J = 12.5, 4.1, 1H), 4.44 (td, J = 12.5, 6.0, 1H), 3.83 (dd, J = 11.6, 2.2, 1H), 3.72 (d, J = 11.6, 1H), 2.75−2.68 (m, 3H), 2.44 (dd, J = 15.7, 13.1, 1H), 1.25 (d, J = 6.5, 3H), 0.95 (s, 9H), 0.16 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.0, 140.0, 128.7, 127.3, 126.6, 90.8, 57.9, 46.1, 46.0, 43.8, 42.5, 25.3, 17.8, 11.3, −6.3, −6.4. Anal. Calcd for $C_{20}H_{31}NO_4Si$ (377.56): C, 63.63; H, 8.28; N, 3.71. Found: C, 64.02; H, 8.34; N, 3.64.

(2*R*,3*S*,4*R*,5*R*)-3-(((*tert*-Butyldimethylsilyl)oxy)methyl)-5-(*o*-chlorophenyl)-2-methyl-4-nitro-1-cyclohexanone (4b). Chiral diene **1** (R^1 = TBDMS, 0.30 g) and 2-chloro-ω-nitrostyrene (0.18 g) were employed. Compound **4b** was isolated as a white crystalline solid in 68% yield (260 mg): $R_f = 0.36$ (SiO_2, hexane/EtOAc 4:1); ee = 98% (determined by HPLC at 215 nm, hexane/EtOH 6:1, $F = 0.8$ mL/min; $t_{Rmajor} = 7.8$ min, $t_{Rminor} = 10.7$ min); recrystallized in CH_2Cl_2/MeOH, ee >99%, mp 190−192 °C; $[\alpha]^{20}_{589} = +13.9$ (*c* 1.1, CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.42−7.16 (m, 4H), 5.63−5.42 (s, br, 1H), 5.16−4.91 (s, br, 1H), 3.85 (dd, J = 11.5, 3.3, 1H), 3.72 (dd, J = 11.5, 1.0, 1H), 2.90−2.66 (m, 3H), 2.30−2.06 (s, br, 1H), 1.28 (d, J = 6.7, 3H), 0.94 (s, 9H), 0.16 (s, 3H), 0.11 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 204.6, 137.9, 133.8, 130.2, 128.4, 127.5,

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124.9, 89.5, 57.9, 46.2, 44.8, 44.2, 37.9, 25.6, 18.1, 11.5, −4.7, −4.8. Anal. Calcd for $C_{20}H_{31}ClNO_4Si$ (412.01): C, 58.30; H, 7.34; N, 3.40. Found: C, 58.70; H, 7.34; N, 3.31.

(2*R*,3*S*,4*R*,5*S*)-3-(((*tert*-Butyldimethylsilyl)oxy)methyl)-5-(2-furyl)-2-methyl-4-nitro-1-cyclohexanone (4c). Chiral diene **1** (R^1 = TBDMS, 0.30 g) and 1-(2-furyl)-2-nitroethylene (0.14 g) were employed. Compound **4c** was isolated as a white crystalline solid in 88% yield (300 mg): mp 81−83 °C; R_f = 0.22 (SiO_2, hexane/EtOAc 8:1); ee = 64% (determined by HPLC at 230 nm, hexane/EtOH 6:1, F = 0.8 mL/min; t_{Rmajor} = 7.2 min, t_{Rminor} = 9.4 min); $[\alpha]^{20}_{589}$ = +28.4 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.30 (m, 1H), 6.27 (dd J = 3.1, 1.9, 1H), 6.11 (d, J = 3.1, 1H), 5.32 (dd, J = 12.1, 4.1, 1H), 4.55 (td, J = 12.1, 6.7, 1H), 3.79 (dd, J = 11.7, 2.0, 1H), 3.67 (dd, J = 11.7, 1.0, 1H), 2.78−2.53 (m, 4H), 1.21 (d, J = 6.0, 3H), 0.89 (s, 9H), 0.10 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 204.7, 152.4, 141.9, 110.2, 106.7, 89.1, 58.0, 46.0, 43.9, 42.9, 36.7, 25.5, 18.0, 11.5, −4.6, −4.7. Anal. Calcd for $C_{18}H_{29}NO_5Si$ (367.52): C, 58.83; H, 7.95; N, 3.81. Found: C, 58.52; H, 8.15; N, 3.76.

(2*R*,3*S*,4*R*,5*R*)-3-(((*tert*-Butyldimethylsilyl)oxy)methyl)-5-(3-furyl)-2-methyl-4-nitro-1-cyclohexanone (4d). Chiral diene **1** (R^1 = TBDMS, 0.30 g) and 1-(3-furyl)-2-nitroethylene (0.14 g) were employed. Compound **4d** was isolated as a white crystalline solid in 53% yield (180 mg): R_f = 0.24 (SiO_2, hexane/EtOAc 8:1); ee = 89% (determined by HPLC at 215 nm, hexane/EtOH 6:1, F = 0.8 mL/min; t_{Rmajor} = 7.8 min, t_{Rminor} = 9.9 min); recrystallized in Et_2O, ee = 99%, mp 105−106 °C; $[\alpha]^{20}_{589}$ = +29.3 (*c* 0.8, CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.36−7.34 (m, 1H), 7.29 (s, 1H), 6.29−6.28 (m, 1H), 5.09 (dd, J = 12.4, 3.9, 1H), 4.38 (td, J = 12.4, 5.8, 1H), 3.78 (dd, J = 11.4, 2.1, 1H), 3.69 (dd, J = 11.4, 1.0, 1H), 2.76−2.57 (m, 3H), 2.40 (dd, J = 15.9, 12.4, 1H), 1.21 (d, J = 6.0, 3H), 0.89 (s, 9H), 0.09 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.9, 143.3, 139.4, 124.3, 108.1, 91.5, 57.9, 45.9, 44.7, 43.9, 33.6, 25.3, 17.9, 11.4, −6.3, −6.4. Anal. Calcd for $C_{18}H_{29}NO_5Si$ (367.52): C, 58.83; H, 7.95; N, 3.81. Found: C, 59.15; H, 8.04; N, 3.72.

(2*R*,3*S*,4*R*,5*R*)-3-(((*tert*-Butyldimethylsilyl)oxy)methyl)-5-(*p*-methoxyphenyl)-2-methyl-4-nitro-1-cyclohexanone (4e). Chiral diene **1** (R^1 = TBDMS, 0.30 g) and 1-(*p*-methoxyphenyl)-2-nitroethylene (0.18 g) were employed. Compound **4e** was isolated as a white crystalline solid in 49% yield (180 mg): R_f = 0.28 (SiO_2, hexane/EtOAc 4:1); ee = 83% (determined by HPLC at 215 nm, hexane/EtOH 6:1, F = 0.8 mL/min; t_{Rmajor} = 8.6 min, t_{Rminor} = 10.7 min); recrystallized in EtOH, ee >99%, mp 132−136 °C; $[\alpha]^{20}_{589}$ = +22.4 (*c* 0.6, CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.14 (d, J = 8.6, 2H), 6.86 (d, J = 8.6, 2H), 5.30 (dd, J = 12.5, 3.9, 1H), 4.38 (td, J = 12.5, 6.0, 1H), 3.85−3.69 (m, 2H), 3.78 (s, 3H), 2.75−2.64 (m, 3H), 2.41 (dd, J = 15.9, 12.7, 1H), 1.24 (d, J = 6.4, 3H), 0.94 (s, 9H), 0.15 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 205.3, 158.7, 132.0, 127.9, 114.2, 91.6, 58.1, 55.0, 46.4, 46.2, 44.2, 41.9, 25.5 , 18.0, 11.5, −6.2, −6.3. Anal. Calcd for $C_{21}H_{33}NO_5Si$ (407.59): C, 61.88; H, 8.16; N, 3.44. Found: C, 62.06; H, 8.21; N, 3.40.

(2*R*,3*S*,4*R*,5*R*)-3-(((*tert*-Butyldimethylsilyl)oxy)methyl)-2-methyl-4-nitro-5-(*p*-nitrophenyl)-1-cyclohexanone (4f). Chiral diene **1** (R^1 = TBDMS, 0.30 g) and 1-(*p*-nitrophenyl)-2-nitroethylene (0.19 g) were employed. Compound **4f** was isolated as a white crystalline solid in 54% yield (210 mg): R_f = 0.47 (SiO_2, hexane/EtOAc 2:1); ee = 94% (determined by HPLC at 264 nm, hexane/EtOH 6:1, F = 0.8 mL/min; t_{Rmajor} = 14.4 min, t_{Rminor} = 18.2 min); recrystallized in CH_2Cl_2/EtOH, ee >99%, mp 224−226 °C dec; $[\alpha]^{20}_{589}$ = +13.1 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.22 (d, J = 8.9, 2H), 7.42 (d, J = 8.9, 2H), 5.39 (dd, J = 12.4, 4.3, 1H), 4.64 (td, J = 12.4, 5.9, 1H), 3.85 (dd, J = 11.5, 2.4, 1H), 3.68 (dd, J = 11.5, 1.0, 1H), 2.83−2.66 (m, 3H), 2.41 (dd, J = 15.9, 12.4, 1H), 1.26 (d, J = 6.4, 3H), 0.94 (s, 9H), 0.15 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.0, 147.4, 147.2, 127.9, 124.2, 90.4, 58.0, 46.3, 45.6, 44.2, 42.4, 25.5, 18.0, 11.5, −6.2, −6.3. Anal. Calcd for $C_{20}H_{30}N_2O_6Si$ (422.56): C, 56.85; H, 7.16; N, 6.63. Found: C, 57.11; H, 7.10; N, 6.49.

(2*R*,3*S*,4*R*,5*S*)-3-(((*tert*-Butyldimethylsilyl)oxy)methyl)-2,5-dimethyl-4-nitro-1-cyclohexanone (4g). Chiral diene **1** (R^1 = TBDMS, 0.30 g) and 1-nitro-1-propene (90 mg) were employed. Compound **4g** was isolated as a colorless oil in 48% yield (140 mg): R_f = 0.37 (SiO_2, hexane/EtOAc 4:1); ee = 95% (determined by HPLC at 215 nm, hexane/EtOH 6:1, F = 0.8 mL/min; t_{Rmajor} = 6.9 min, t_{Rminor} = 8.0 min); mp 49−50 °C; $[\alpha]^{20}_{589}$ = +14.7 (*c* 0.1, CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.71 (dd, J = 12.0, 4.5, 1H), 3.77 (dd, J = 11.5, 3.0, 1H), 3.58 (dd, J = 11.5, 1.1, 1H), 3.21 (ddd, J = 12.1, 6.5, 5.9, 1H), 2.63−2.45 (m, 3H), 1.98 (ddd, J = 16.0, 12.2, 1.0, 1H), 1.17 (d, J = 6.5, 3H), 1.03 (d, J = 6.5, 3H), 0.85 (s, 9H), 0.05 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 205.8, 93.2, 57.8, 46.4, 45.6, 44.0, 31.5, 25.4, 19.6, 17.9, 11.4, −4.6, −4.7. Anal. Calcd for $C_{15}H_{29}NO_4Si$ (315.49): C, 57.11; H, 9.27; N, 4.44. Found: C, 57.19; H, 9.33; N, 4.41.

(2*R*,3*S*,4*R*,5*R*)-3-(((*tert*-Butyldimethylsilyl)oxy)methyl)-2-methyl-4-nitro-5-isopropyl-1-cyclohexanone (4h). Chiral diene **1** (R^1 = TBDMS, 0.30 g) and 3-methyl-1-nitro-1-butene (0.12 g) were employed. Compound **4h** was isolated as a colorless oil in 56% yield (180 mg): R_f = 0.45 (SiO_2, hexane/EtOAc 8:1); ee = 92% (determined by HPLC at 210 nm, hexane/EtOH 20:1, F = 0.8 mL/min; t_{Rmajor} = 7.5 min, t_{Rminor} = 8.9 min); $[\alpha]^{20}_{589}$ = +18.0 (*c* 2.1, CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.94 (dd, J = 12.2, 4.2, 1H), 3.66 (m, 2H), 3.16 (tdd, J = 12.5, 6.1, 3.1, 1H), 2.55−2.33 (m, 3H), 1.98 (dd, J = 15.6, 12.8, 1H), 1.76 (m, J = 7.0, 3.1, 1H), 1.12 (d, J = 6.4, 3H), 0.84 (d, J = 7.0, 3H), 0.81 (s, 9H), 0.79 (d, J = 7.0, 3H), 0.01 (s, 3H), −0.03 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 206.6, 89.7, 57.9, 46.2, 44.1, 40.4, 36.5, 27.1, 25.4, 20.2, 17.9, 14.3, 11.4, -6.2, −6.3; HRMS (FAB) calcd for $C_{17}H_{34}NO_4Si$: 344.2257, found 344.2253.

(2*R*,3*S*,4*R*,5*S*)-5-((Benzyloxy)methyl)-3-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-methyl-4-nitro-1-cyclohexanone (4i). Chiral diene **1** (R^1 = TBDMS, 0.30 g) and 1-((benzyloxy)methyl)-2-nitroethylene (0.19 g) were employed. A mixture of compound **4i** and a diastereoisomer (3:1 by ^{1}H NMR) was isolated as a colorless oil in 52% yield (200 mg). Cycloadduct **4i** was separated by semipreparative HPLC (hexane/THF 20:1, F = 8 mL/min; t_R = 23.5 min): R_f = 0.24 (SiO_2, hexane/EtOAc 8:1); ee = 94% (determined by HPLC at 210 nm, hexane/EtOH 110:1, F = 0.9 mL/min; t_{Rmajor} = 16.0 min, t_{Rminor} = 17.1 min); $[\alpha]^{20}_{589}$ = +15.7 (*c* 0.2, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38−7.25 (m, 5H), 5.25 (dd, J = 11.8, 4.5, 1H), 4.49 (d, J = 12.0, 1H), 4.44 (d, J = 12.0, 1H), 3.76 (dd, J = 11.8, 3.0, 1H), 3.60 (dd, J = 11.6, 0.9, 1H), 3.53 (dd, J = 9.7, 3.2, 1H), 3.42−3.29 (m, 2H), 2.67−2.43 (m, 4H), 1.19 (d, J = 6.9, 3H), 0.86 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 206.6, 137.6, 128.3, 127.7, 127.5, 86.7, 73.1, 69.1, 58.0, 46.3, 43.9, 40.8, 36.9, 25.5, 18.0, 11.5, −6.2, −6.3; HRMS (FAB) calcd for $C_{22}H_{36}NO_5Si$ 422.2363, found, 422.2366.

(3*R*,4*S*,5*R*,10*S*)-4-(((*tert*-Butyldimethylsilyl)oxy)methyl)-3-methyl-5-nitro-2-decalone (4j). Chiral diene **1** (R^1 = TBDMS, 0.30 g) and 1-nitro-1-cyclohexene (113 μL, 1 mmol) were employed. Compound **4j** was isolated as a white crystalline solid in 70% yield (230 mg): R_f = 0.48 (SiO_2, hexane/EtOAc 4:1); ee = 94% (determined by HPLC at 210 nm, hexane/EtOH 6:1, F = 0.8 mL/min; t_{Rmajor} = 6.6 min, t_{Rminor} = 8.3 min); recrystallized in EtOH, ee >99%, mp 77−79 °C; $[\alpha]^{20}_{589}$ = +3.3 (*c* 1.1, CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.63 (dd, J = 11.8, 3.5, 1H), 3.48 (m, 1H), 3.22 (d, J = 11.8 , 1H), 2.59 (quintet, J = 6.4, 1H), 2.45−2.11 (m, 5H), 1.88−1.65 (m, 2H), 1.48−1.14 (m, 4H), 1.06 (d, J = 6.7, 3H), 0.76 (s, 9H), −0.07 (s, 3H), −0.09 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 207.4, 95.3, 59.5, 52.5, 42.1, 41.8, 34.2, 30.6, 26.4, 25.4, 22.3, 18.7, 17.9, 11.6, −3.5, −3.6. Anal. Calcd for $C_{18}H_{33}NO_4Si$ (355.55): C, 60.81; H, 9.35; N, 3.94. Found: C, 60.47; H, 9.73; N, 3.94.

(2*R*,3*S*,4*R*)-3-(((*tert*-Butyldimethylsilyl)oxy)methyl)-2,4-dimethyl-4-nitro-1-cyclohexanone (4k). Chiral diene **1** (R^1 = TBDMS, 0.30 g) and 2-nitro-1-propene (87 mg) were employed. A mixture of compound **4k** and a product of addition of two molecules of nitroalkene (4:1 by ^{1}H NMR) was isolated as a colorless oil in 39% yield (120 mg). Cycloadduct **4k** was separated by semipreparative HPLC (hexane/THF 10:1, F = 8 mL/min; t_R = 20.8 min): R_f = 0.39 (SiO_2, hexane/EtOAc 4:1); ee = 94% (determined by HPLC at 210 nm, hexane/^{i}PrOH 100:1, F = 0.9 mL/min; t_{Rmajor} = 17.6 min, t_{Rminor}

= 14.7 min); $[\alpha]^{20}_{589}$ = +32.3 (*c* 0.7, CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.70 (dd, *J* = 11.7, 3.7, 1H), 3.30 (dd, *J* = 11.7, 1.0, 1H), 3.13−2.97 (m, 1H), 2.60 (quintet, *J* = 6.7, 1H), 2.54−2.42 (m, 2H), 2.34−2.23 (m, 1H), 2.17−2.04 (m, 1H), 1.85 (s, 3H), 1.12 (d, *J* = 6.7, 3H), 0.78 (s, 9H), −0.05 (s, 3H), −0.06 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 206.9, 90.0, 59.3, 50.9, 41.3, 36.8, 30.5, 25.4, 25.3, 17.9, 11.9, −3.5, −3.6; HRMS (FAB) calcd for $C_{15}H_{30}NO_4Si$ 316.1944, found 316.1945.

(2*R*,3*S*,4*R*,5*R*)-3-(Methoxymethyl)-2-methyl-4-nitro-5-phenyl-1-cyclohexanone (4l). Chiral diene **1** (R^1 = Me, 0.23 g) and β-nitrostyrene (0.15 g) were employed. Compound **4l** was isolated as a white crystalline solid in 70% yield (180 mg): R_f = 0.37 (SiO_2, hexane/EtOAc 3:1); ee = 82% (determined by ^{1}H NMR over a Mosher derivative); mp 142 °C; $[\alpha]^{20}_{578}$ = +19.0 (*c* 0.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.3−7.1 (m, 5H), 5.3 (dd, *J* = 12.4, 4.6, 1H), 4.2 (td, *J* = 12.4, 6.0, 1H), 3.4 (t, 2H), 3.1 (s, 3H), 2.96 (m, 3H), 2.3 (dd, 1H), 1.1 (d, *J* = 7.0, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.1, 134.9, 127.9, 126.5, 126.1, 89.7, 66.3, 58.0, 45.4, 44.5, 43.4, 42.0, 10.5. Anal. Calcd for $C_{15}H_{19}NO_4$ (277.32): C, 64.96; H, 6.91; N, 5.05. Found: C, 64.72; H, 6.80; N, 5.12.

(2*R*,3*S*,4*R*,5*R*)-5-(*o*-Chlorophenyl)-3-(methoxymethyl)-2-methyl-4-nitro-1-cyclohexanone (4m). Chiral diene **1** (R^1 = Me, 0.23 g) and 2-chloro-ω-nitrostyrene (0.18 g) were employed. Compound **4m** was isolated as a white crystalline solid in 76% yield (220 mg): R_f = 0.28 (SiO_2, hexane/EtOAc 3:1); ee = 90% (determined by ^{1}H NMR over a Mosher derivative); mp 154 °C; $[\alpha]^{20}_{578}$ = −3.6 (*c* 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.4−7.1 (m, 4H), 5.45 (m, 1H), 3.5−3.3 (m, 3H), 3.23 (s, 3H), 2.5−2.3 (m, 3H), 2.2 (m, 1H), 1.13 (d, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.3, 137.4, 133.6, 130.9, 128.2, 127.5, 125.4, 88.9, 68.1, 59.8, 46.0, 45.5, 45.3, 37.9, 11.4. Anal. Calcd for $C_{15}H_{18}NO_4Cl$ (311.77): C, 57.79; H, 5.82; N, 4.49. Found: C, 57.99; H, 5.62; N, 4.30.

(2*R*,3*S*,4*R*,5*S*)-5-(2-Furyl)-3-(methoxymethyl)-2-methyl-4-nitro-1-cyclohexanone (4n). Chiral diene **1** (R^1 = Me, 0.23 g) and 1-(2-furyl)-2-nitroethylene (0.14 g) were employed. Compound **4n** was isolated as a yellow oil in 42% yield (100 mg): R_f = 0.18 (SiO_2, hexane/EtOAc 4:1); ee = 70% (determined by HPLC at 215 nm, hexane/EtOH 6:1, *F* = 0.9 mL/min; t_{Rmajor} = 9.9 min, t_{Rminor} = 13.0 min); $[\alpha]^{20}_{589}$ = +29.6 (*c* 0.3, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29−7.28 (m, 1H), 6.26−6.25 (m, 1H), 6.14−6.13 (m, 1H), 5.31 (dd, *J* = 12.0, 4.3, 1H), 4.40 (td, *J* = 12.0, 6.0, 1H), 3.49−3.40 (m, 2H), 3.24 (s, 3H), 2.76−2.53 (m, 4H), 1.18 (d, *J* = 6.9, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.1, 152.3, 141.8, 110.3, 106.8, 88.8, 66.9, 59.0, 44.9, 44.2, 42.9, 36.8, 11.4; HRMS (FAB) calcd for $C_{13}H_{17}NO_5$ 267.1107, found 267.1102.

(3*R*,4*S*,5*R*,10*S*)-4-(Methoxymethyl)-3-methyl-5-nitro-2-decalone (4o). Chiral diene **1** (R^1 = Me, 0.23 g) and 1-nitro-1-cyclohexene (113 μL, 1 mmol) were employed. Compound **4o** was isolated as a white crystalline solid in 48% yield (110 mg): R_f = 0.25 (SiO_2, hexane/EtOAc 4:1); ee > 99% [determined by HPLC at 210 nm, hexane/EtOH 6:1, *F* = 0.9 mL/min; t_{Rmajor} = 9.2 min, (t_{Rminor} = 11.2 min)]; mp 141−142 °C; $[\alpha]^{20}_{589}$ = +12.2 (*c* 0.8, CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.53−3.40 (m, 1H), 3.40 (dd, *J* = 11.1, 3.8, 1H), 3.14 (s, 3H), 3.05 (dd, *J* = 11.1, 1.5, 1H), 2.66 (m, *J* = 6.7, 1H), 2.52−2.16 (m, 5H), 1.95−1.71 (m, 2H), 1.53−1.22 (m, 4H), 1.12 (d, *J* = 6.7, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 207.8, 94.8, 68.4, 58.6, 51.4, 41.90, 41.85, 34.2, 30.3, 26.3, 22.1, 18.4, 11.4. Anal. Calcd for $C_{13}H_{21}NO_4$ (255.32): C, 61.16; H, 8.29; N, 5.49. Found: C, 61.53; H, 8.09; N, 5.21.

(2*R*,3*S*,4*R*,5*S*)-5-(2-Furyl)-3-((methoxymethoxy)methyl)-2-methyl-4-nitro-1-cyclohexanone (4p). Chiral diene **1** (R^1 = MOM, 0.26 g) and 1-(2-furyl)-2-nitroethylene (0.14 g) were employed. Compound **4p** was isolated as a white crystalline solid in 70% yield (190 mg): R_f = 0.35 (SiO_2, hexane/EtOAc 2:1); ee = 56% (determined by HPLC at 215 nm, hexane/EtOH 6:1, *F* = 0.8 mL/min; t_{Rmajor} = 13.5 min, t_{Rminor} = 16.3 min); recrystallized in EtOH, ee > 99%, mp 96−97 °C; $[\alpha]^{20}_{589}$ = +54.6 (*c* 0.3, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32−7.31 (m, 1H), 6.29−6.27 (m, 1H), 6.16−6.15 (m, 1H), 5.36 (dd, *J* = 12.0, 4.7, 1H), 4.55 (d, *J* = 6.9, 1H), 4.50 (d, *J* = 6.9, 1H), 4.46 (td, *J* = 12.0, 6.2, 1H), 3.71 (dd, *J* = 11.2, 3.4, 1H), 3.54 (dd, *J* = 11.2, 1.3, 1H), 3.38 (s, 3H), 2.87−2.59 (m, 4H), 1.21 (d, *J* = 6.9, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.0, 152.2, 141.8, 110.2, 106.6, 96.3, 88.6, 62.2, 55.6, 44.4, 43.9, 42.8, 36.9, 11.2. Anal. Calcd for $C_{14}H_{19}NO_6$ (297.31): C, 56.56; H, 6.44; N, 4.71. Found: C, 56.49; H, 6.50; N, 4.70.

General Procedure for the Synthesis of Enantiomerically Enriched Nitropropyl Vinyl Ketones 6 and (Nitropropyl)furans 7. These reactions were carried out as described above for cycloadducts **4**, but employing dry Et_2O as solvent. After the 22 h period, the reaction mixture was concentrated under reduced pressure and redissolved in dry THF (5 mL). Hydrolysis with 5 mL of a AcOH/NaOAc buffer solution (8 min stirring), usual extractive workup, followed by SiO_2 column chromatography afforded compound **6a** (R^3 = Ph). Alternatively, quenching with aqueous HCl (3 N, 5 mL, 10 min stirring) and exhaustive extractive workup afforded compounds **7**, which were purified by column chromatography.

(*Z*)-(6*R*)-1-((*tert*-Butyldimethylsilyl)oxy)-3-methyl-7-nitro-6-phenyl-2-hepten-4-one (6a). Chiral diene **5** (0.30 g) and β-nitrostyrene (0.15 g) were employed. Hydrolysis was accomplished with the acidic buffer solution. Compound **6a** was isolated after SiO_2 column chromatography as a yellow oil in 58% yield (200 mg): R_f = 0.34 (SiO_2, hexane/EtOAc 8:1); ee = 86% (determined by HPLC at 212 nm, hexane/EtOH 20:1, *F* = 0.8 mL/min; t_{Rmajor} = 13.5 min, t_{Rminor} = 15.4 min); $[\alpha]^{20}_{589}$ = −12.6 (*c* 0.8, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36−7.22 (m, 5H), 5.97−5.94 (m, 1H), 4.74 (dd, *J* = 12.4, 6.8, 1H), 4.61 (dd, *J* = 12.4, 7.8, 1H), 4.49−4.32 (m, 2H), 4.07 (quintet, *J* = 6.9, 1H), 3.03 (dd, *J* = 18.1, 6.5, 1H), 2.96 (dd, *J* = 18.1, 7.3, 1H), 1.96 (q, *J* = 1.7, 3H), 0.88 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.9, 145.2, 139.0, 131.9, 128.9, 127.7, 127.3, 79.4, 62.2, 43.7, 38.8, 25.8, 19.8, 18.1, −5.4; HRMS (EI) calcd for $C_{20}H_{31}NO_4Si$ 377.2022, found 377.2025.

3-Methyl-2-[(2*R*)-3-nitro-2-phenylpropyl]furan (7a). Chiral diene **5** (0.30 g) and β-nitrostyrene (0.15 g) were employed. Hydrolysis was accomplished with a 3 N HCl aqueous solution. Compound **7a** was isolated after SiO_2 column chromatography as a yellow oil in 69% yield (160 mg): R_f = 0.41 (SiO_2, hexane/EtOAc 8:1); ee = 85% (determined by HPLC at 215 nm, hexane/EtOH 20:1, *F* = 0.8 mL/min; t_{Rmajor} = 11.9 min, t_{Rminor} = 14.4 min); $[\alpha]^{20}_{589}$ = −8.4 (*c* 2.6, CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.33−7.15 (m, 6H), 6.15 (d, *J* = 1.5, 1H), 4.68 (d, *J* = 7.3, 2H), 3.90 (quintet, *J* = 7.3, 1H), 2.97 (d, *J* = 7.3, 2H), 1.77 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 146.5, 140.4, 138.8, 128.4, 127.3, 126.9, 116.2, 112.5, 78.7, 43.2, 30.0, 9.1; HRMS (EI) calcd for $C_{14}H_{15}NO_3$ 245.1052, found: 245.1054.

2-[(2*R*)-2-(*o*-Chlorophenyl)-3-nitropropyl]-3-methylfuran (7b). Chiral diene **5** (0.30 g) and *o*-chloro-ω-nitrostyrene (0.18 g) were employed. Hydrolysis was accomplished with a 3 N HCl solution. Compound **7b** was isolated after SiO_2 column chromatography as a yellow oil in 69% yield (180 mg): R_f = 0.33 (SiO_2, hexane/EtOAc 8:1); ee = 88% (determined by HPLC at 215 nm, hexane/EtOH 100:1, *F* = 0.9 mL/min; t_{Rmajor} = 16.6 min, t_{Rminor} = 19.5 min); $[\alpha]^{20}_{589}$ = +11.0 (*c* 1.2, CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.44−7.08 (m, 5H), 6.15 (d, *J* = 1.8, 1H), 4.81 (dd, *J* = 13.1, 8.5, 1H), 4.72 (dd, *J* = 13.1, 6.2, 1H), 4.44 (dq, *J* = 8.5, 6.7, 1H), 3.02 (d, *J* = 7.0, 2H), 1.77 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 146.3, 140.7, 136.1, 133.8, 129.9, 128.6, 127.5, 127.0, 116.7, 112.7, 77.1, 39.6, 28.5, 9.3; HRMS (EI) calcd for $C_{14}H_{14}ClNO_3$ 279.0662, found 279.0658.

3-Methyl-2-[(2*S*)-2-methyl-3-nitropropyl]furan (7c). Chiral diene **5** (0.30 g) and 1-nitro-1-propene (87 mg) were employed. Hydrolysis was accomplished with a 3 N HCl solution. Compound **7c** was isolated after SiO_2 column chromatography as a yellow oil in 66% yield (110 mg): R_f = 0.49 (SiO_2, hexane/EtOAc 8:1); ee = 75% (determined over Mosher derivative **9**); $[\alpha]^{20}_{589}$ = −3.4 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.25 (d, *J* = 1.8, 1H), 6.18 (d, *J* = 1.8, 1H), 4.36 (dd, *J* = 11.9, 5.5, 1H), 4.19 (dd, *J* = 11.9, 7.2, 1H), 2.79−2.61 (m, 3H), 1.96 (s, 3H), 1.04 (d, *J* = 6.1, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 147.3, 140.4, 115.9, 112.6, 80.3, 32.4, 29.7, 16.9, 9.6; HRMS (EI) calcd for $C_9H_{13}NO_3$ 183.0895, found 183.0890.

Determination of ee of Furan 7c. Reduction of the Nitro Group of Compound 7c: Synthesis of 2-[(2*S*)-3-Amino-2-methylpropyl]-3-methylfuran (8). The reaction

was carried out as described in ref 24 employing furan **7c** (100 mg, 0.55 mmol), except that the reaction mixture was stirred overnight. Methanol was evaporated at reduced pressure, and the resulting black solid was dissolved in H_2O (10 mL) and EtOAc (10 mL). The aqueous layer was extracted with EtOAc (2 × 10 mL), and the combined organic layers were washed with brine (5 mL), dried, and concentrated. Amine **8** was isolated after flash column chromatography as a colorless oil in 71% yield (60 mg): R_f = 0.21 (SiO_2, CH_2Cl_2/MeOH/NEt_3 9:1:0.01); ee = 75% (determined over Mosher derivative **9**); $[\alpha]^{20}_{589}$ = −4.44 (*c* 1.1, CH_2Cl_2); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.20 (d, *J* = 1.5, 1H), 6.14 (d, *J* = 1.5, 1H), 4.64 (s br, 1H), 2.81 (dd, *J* = 12.4, 5.7, 1H), 2.68−2.57 (m, 2H), 2.50 (dd, *J* = 15.0, 7.0, 1H), 2.07 (sextet, *J* = 6.7, 1H), 1.94 (s, 3H), 0.97 (d, *J* = 6.7, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.8, 140.1, 115.2, 112.6, 46.3, 34.2, 30.4, 17.3, 9.9; HRMS (EI) calcd for $C_9H_{15}NO$ 153.1154, found 153.1152.

Formation of Mosher's Amide from Amine 8: Synthesis of *N*-[2-Methyl-3-(3-methyl-2-furyl)propyl]-(*R*)-α-methoxy-α-phenyl-α-(trifluoromethyl)acetamide (9). The reaction was carried out as described in ref 23 employing amine **8** (40 mg, 0.26 mmol). Amide **9** was obtained quantitatively as a 7.1:1 mixture of diastereoisomers. NMR data of the major diastereoisomer were obtained from the mixture: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.23−7.08 (m, 6H), 6.03 (d, *J* = 1.8, 1H), 3.20 (q, *J* = 1.5, 3H), 3.06 (td, *J* = 6.7, 0.9, 2H), 2.39 (dd, *J* = 14.7, 6.4, 1H), 2.23 (dd, *J* = 14.7, 7.3, 1H), 1.96−1.80 (m, 1H), 1.77 (s, 3H), 0.73 (d, *J* = 6.7, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6, 150.2, 141.0, 134.4, 130.1, 129.0, 128.7, 116.0, 113.7, 85.3, 60.4, 55.5, 45.4, 34.6, 31.4, 18.2, 10.5.

Protection of the Amino Group of Aminofuran 8. Synthesis of 2-[(2*S*)-3-((*tert*-Butoxycarbonyl)amino)-2-methylpropyl]-3-methylfuran (10). A solution of (^{t}Boc)$_2$O (152 mg, 0.7 mMol) in 5 mL of CH_2Cl_2 was added dropwise to a solution of aminofuran **8** (100 mg, 0.66 mMol) in 15 mL of CH_2Cl_2 at room temperature. After 4 h of stirring the reaction was quenched with 10 mL of 0.1 N aqueous HCl. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The organic layers were combined, washed with 0.1 N HCl, and brine, and dried over Na_2SO_4. The solvents were evaporated under reduced pressure to afford a colorless oil which was purified by column chromatography in 84% yield (140 mg): R_f = 0.49 (hexane/EtOAc 5:1); ee = 75%; $[\alpha]^{20}_{589}$ = −2.5 (*c* 0.7, EtOH); ^{1}H NMR δ (300 MHz, $CDCl_3$) 7.20 (s, 1H), 6.15 (s, 1H), 4.66 (broad, 1H), 3.00 (dd, *J* = 7.3, 6.2, 1H), 2.53 (dd, *J* = 15.0, 6.2, 1H), 2.42 (dd, *J* = 15.0, 7.3, 1H), 1.95 (m, 1H), 1.93 (s, 3H), 1.43 (s, 9H), 0.88 (d, *J* = 6.9, 3H); ^{13}C NMR δ (75 MHz, $CDCl_3$) 155.9, 149.3, 139.8, 114.9, 112.6, 78.9, 45.8, 33.8, 30.3, 20.3, 17.4, 9.8; HRMS (EI) calcd for $C_{14}H_{23}NO_3$ 253.1678, found 253.1677.

Ozonolysis of the Furan Ring. Synthesis of Methyl (3*S*)-4-((*tert*-Butoxycarbonyl)amino)-3-methylbutanoate (11). Furan **10** (100 mg, 0.4 mmol) was dissolved in a mixture of 15 mL of CH_2Cl_2, 5 mL of ethanol, 1.25 mL of H_2O_2, and 120 mg of NaOH. The solution was stirred for 10 min and cooled to −78 °C. Then a stream of O_3/O_2 (300 L/h, 2.5 g of O_3) was bubbled through the solution using a gas diffusion tube. The ozone stream was mantained until complete dissapearance of the starting material was observed by TLC. The ozonizer was turned off, and oxygen was bubbled for 15 min. The mixture was stirred at room temperature for one additional hour, and the reaction was quenched with the aqueous buffer HOAc/NaOAc (pH = 4.6). After addition of 20 mL of CH_2Cl_2, the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried over Na_2SO_4, and the solvent was evaporated under reduced pressure. The crude acid obtained was dissolved in 15 mL of Et_2O, and a freshly prepared solution of diazomethane (1 mmol) in ether (5 mL) was added. After 15 min at room temperature 0.3 mL of AcOH and 10 mL of water were added succesively. The layers were separated, and the aqueous layer was extracted with ethyl acetate (2 × 15 mL). The organic layers were combined and dried with Na_2SO_4 and the solvent evaporated to afford a colorless oil that was purified by column chromatography (SiO_2, hexane:ethyl acetate, 2:1) to afford ester **11** in 65% yield (60 mg): R_f = 0.33 (hexane/EtOAc 1:1); ee = 75%; $[\alpha]^{20}_{589}$ = −1.3 (*c* 0.4, CH_2Cl_2); ^{1}H NMR δ (300 MHz, $CDCl_3$) 4.79 (m, 1H), 3.62 (s, 3H), 2.99 (m, 1H), 2.3−2.0 (m, 3H), 1.38 (s, 9H), 0.90 (d, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1, 155.9, 78.9, 51.3, 45.7, 38.6, 31.0, 28.2, 17.5; HRMS (EI) calcd for $C_7H_{12}NO_4$ (M^+ − ^{t}Bu) 174.0766, found 174.0771.

Synthesis of (4*S*)-4-Methyl-2-pyrrolidinone (12). Ester **11** (60 mg, 0.26 mmol) was dissolved in 3 mL of trifluoroacetic acid. After 30 min the trifluoroacetic acid was removed under reduced pressure and the residue treated with 5 mL of a 2 N NaOH aqueos solution and stirred for 5 min. Finally the organic compound was extracted with ethyl acetate (3 × 15 mL), and the combined organic layers were dried with Na_2SO_4. Removal of the solvents under reduced pressure afforded lactone **12** in 99% yield (25 mg): $[\alpha]^{20}_{589}$ = −15 (*c* 0.2, $CHCl_3$); ^{1}H NMR δ (300 MHz, $CDCl_3$) 5.95 (broad, 1H), 3.54 (dd, 1H), 2.95 (dd, 1H), 3.2−2.8 (m, 2H), 1.98 (dd, 1H), 1.06 (d, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.7, 49.5, 38.4, 29.3, 19.5; HRMS (EI) calcd for C_5H_9NO 99.0684, found 99.0682.

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Supporting Information Available: ^{13}C NMR spectra of compounds **4h**−**i**, **4n**, **6a**, **7a**−**c**, **8**, **10**, **11**, and **12** (12 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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