[2+3] Cycloadditions Between Nitroalkenes and Camphor-Derived Oxazoline *N*-Oxides and Radical Denitration of the Adducts

Arnaud Voituriez, Julien Moulinas, Cyrille Kouklovsky,* Yves Langlois*

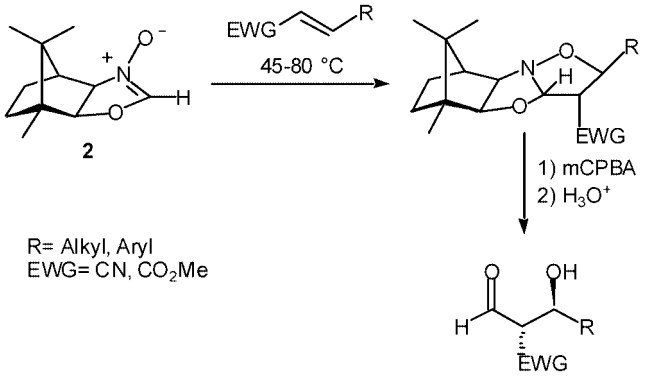
Laboratoire de Synthèse Des Substances Naturelles Associé au CNRS, ICMMO, Bâtiment 410, Université de Paris-Sud, 91405 Orsay, France
Fax +33(1)69154679; E-mail: cykouklo@icmo.u-psud.fr; E-mail: langlois@icmo.u-psud.fr
Received 28 April 2003

Abstract: [2+3] Cycloadditions between camphor-derived oxazoline *N*-oxide **2** and nitroalkenes **3a**–**f** afforded stereoselectively adducts **4a**–**f**. Radical denitration followed by acidic hydrolysis gave rise to *anti*-aldols **8a**,**b**. The radical intermediate was also trapped by a suitable alkene, giving rise to a single stereoisomer.

Key words: cycloaddition, asymmetric synthesis, radical

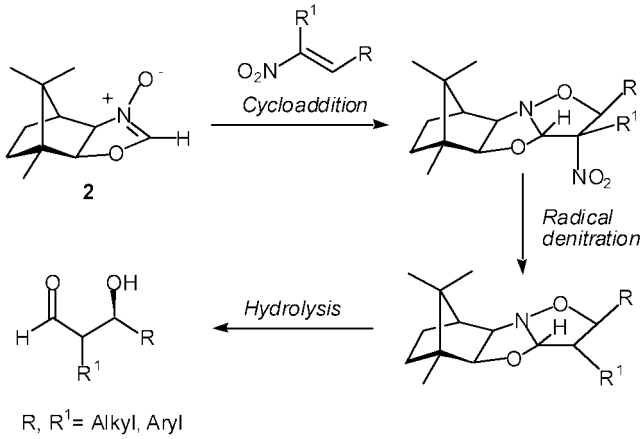
Introduction

In the recent years, we have investigated the asymmetric [2+3] cycloaddition reaction between camphor-derived oxazoline *N*-oxide **2** and various electron-deficient alkenes. This reaction proceeds in a highly regio- and stereoselective fashion, a single isomer often being obtained via an *endo*-transition state.[1,2] Oxidative cleavage of the chiral auxiliary gives rise to enantiomerically pure β-hydroxy aldehydes, which can be used as chirons for the synthesis of natural products (Scheme 1); this reaction sequence has been applied, using either α,β-unsaturated esters or nitriles, to the synthesis of pheromones, of β-lactones and β-lactams.[3]



Scheme 1

Recently, we have turned our attention to the cycloaddition reactions with nitroalkenes as dipolarophiles, because of the high reactivity of these compounds, and the nitro function can be transformed into various other functional groups. Particularly, we were interested in the radical denitration of nitro-substituted cycloadducts since [2+3] cycloaddition reactions of oxazoline *N*-oxide **2** are limited in most cases to electron-deficient alkenes as dipolarophiles, even the use of cyclopentadiene[4] or intramolecular cycloadditions[5] can overcome the poor reactivity observed with other alkenes. In this context, it appears that cycloadditions between dipole **2** and nitroalkenes, followed by denitration of the adducts should constitute an equivalent of this type of cycloaddition between **2** and unfunctionalized alkenes (Scheme 2).



Scheme 2

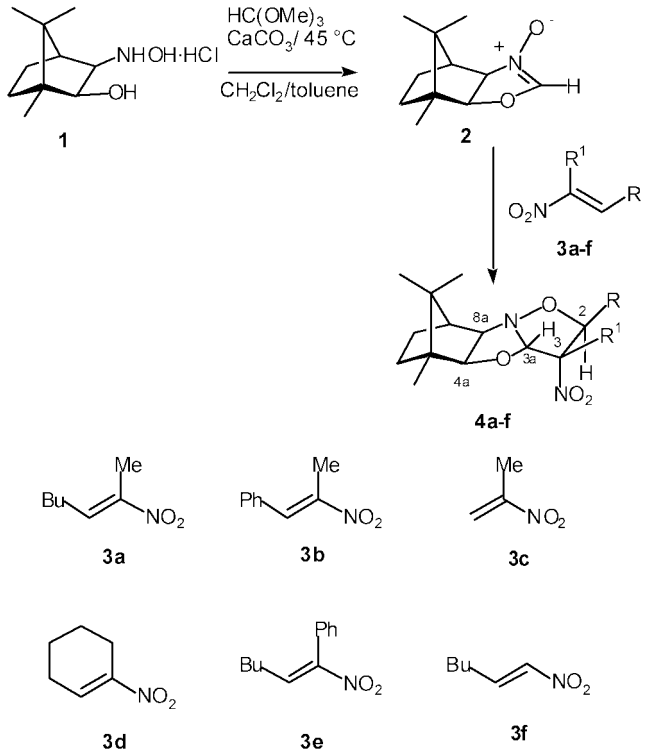
In the present article, we report several new examples of asymmetric [2+3] cycloadditions between **2** and various nitroalkenes, and a study of the stereoselective denitration of the resulting adducts, as well as their transformation into *anti*-β-hydoxyesters.

Asymmetric [2+3] Cycloaddition Reaction with Nitroalkenes

Previous results from this laboratory have shown that nitroalkenes display good reactivity in the asymmetric [2+3] cycloaddition with dipole **2**, the reaction occuring in refluxing dichloromethane to give cycloadducts with good yields and high selectivity.[2] This reaction may be extended to the use of trisubstituted nitroalkenes, which gives rise to cycloadducts without loss of reactivity or regioselectivity.

Synthesis 2003, No. 9, Print: 03 07 2003.
Art Id.1437-210X,E;2003,0,09,1419,1426,ftx,en;C01403SS.pdf.

Dipolarophiles used in the present study were nitroalkenes **3a–f** which were either commercially available (**3f**) or prepared according to known procedures.[6,7] The chiral dipole **2** was prepared in situ by reaction of hydroxylamino isoborneol hydrochloride **1** with trimethyl orthoformate following the described procedure. After stirring for 4 hours at 45 °C, the nitroalkene (3 equiv) was added and the reaction was followed by TLC (Scheme 3).



Scheme 3

Reaction conditions and results are summarized in Table 1. As previously observed,[2] cycloaddition reactions between nitroalkenes **3a–f** and oxazoline *N*-oxide **2** gave in a regio- and stereoselective fashion *endo* adduct **4a–f** (major). The structure of adducts **4a–f** were deduced after NOE experiments as exemplified in adduct **4a**, thus confirming the *endo* transition state of the cycloaddition reaction (Figure 1).

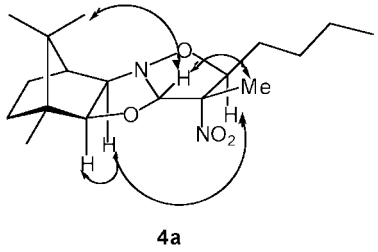


Figure 1 Principle effects in ^{1}H NMR

These results illustrate the remarkable reactivity of nitroalkenes in the asymmetric [2+3] cycloaddition reaction with dipole **2**, as a great variety of substitution onto the double bond is allowed, including alkyl or aryl substituents, without any loss of regio- or stereoselctivity.

Radical Denitration of Nitro Substituted Cycloadducts

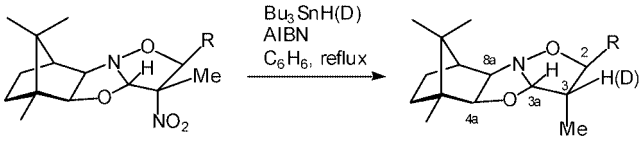
With cycloadducts **4a–f** in hand, their radical denitration was studied. This reaction has been throughly investigated,[8] and is known to proceed under standard radical conditions (Bu_3SnH, AIBN) at high temperature (generally in refluxing toluene), giving good yields with tertiary nitroalkenes as substrates, whereas secondary nitroalkenes give low yields and conversions.[9] The radical denitration may be associated with inter- or intramolecular addition to a radical acceptor.[10]

Cycloadducts **4a** and **4b**, when treated with excess tributyl tin hydride and AIBN, underwent the radical denitration under slightly milder conditions than described (refluxing benzene) to give the unfunctionalized adducts **5a** and **5b** in good yields and stereoselectivity. Compound **5a** (R^2 = Ph) was obtained as a single stereoisomer, whereas compound **5b** (R^2 = *n*-Bu) was obtained as a 9:1 mixture of stereoisomers. ^{1}H NMR analysis of the products (with NOESY) showed inversion of configuration at the carbon C_3, the methyl substituent being in the *endo* position. Performing the reaction at higher temperature resulted in partial degradation of the reaction mixture, whereas the use of bulkier hydride reagents (eg. Ph_3SnH) did not improve selectivity. When radical denitration of cycloadduct **4b**

Table 1 Compounds **4a–f** Prepared

Entry	Alkene	Solvent	Time (h) (Temp, °C)	Adduct	*Endo* /*Exo*	Yield (%)
1	**3a**	CH_2Cl_2	18 (45)	**4a**	>95/5	75
2	**3b**	PhMe	18 (60)	**4b**	>95/5	73
3	**3c**	CH_2Cl_2	18 (45)	**4c**	84/16	80
4	**3d**	CH_2Cl_2	18 (45)	**4d**	>95/5	67
5	**3e**	CH_2Cl_2	18 (45)	**4e**	>95/5	43
6	**3f**	CH_2Cl_2	2 (45)	**4f**	>95/5	70

was perfomed with tributyltin deuteride, complete incorporation of deuterium on carbon C_3 was observed, thus indicating there was no hydride abstraction from the radical intermediate during the radical-chain process. The stability of the radical intermediate (α to an oxazolidine ring) is note worthy (Scheme 4).

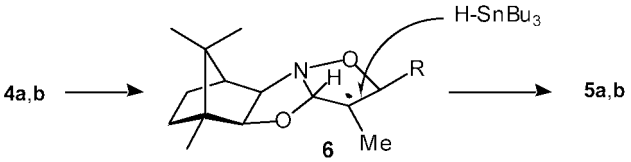


4a R=Bu
4b R=Ph

5a R=Bu 70% de: 90/10
5b R=Ph 95% de>95/5

Scheme 4

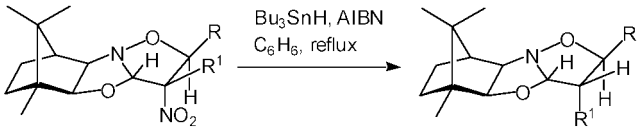
The stereoselectivity of this radical reaction may be explained by the formation of a bowl-shaped radical intermediate **6**, which undergoes attack by tin hydride from the *exo*-face (convex face). Although the role of the substituent at carbon C_2 is not clearly understood, its absence results in complete loss of selectivity, as illustred by the radical denitration of cycloadduct **4c** (Scheme 5).



6

Scheme 5

Results for the denitration of cycloadducts **4a**–**f** are summarized in Table 2. Tertiary nitroalkanes gave good yields and stereoselectivity, whereas denitration of secondary nitroalkane **4f** gave as expected low yields. Denitration of cycloadduct **4d** required a slow addition of tin hydride and AIBN in order to prevent recombination of radical intermediate with the isobutyronitrile radical (Scheme 6).



4a-f **5a-f**

Scheme 6

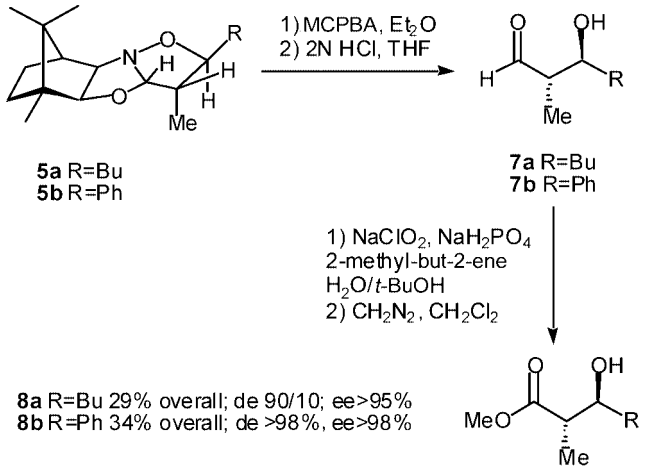
These results demonstrate the efficiency of the asymmetric [2+3] cycloaddition-radical denitration sequence for the preparation of unfunctionalized cycloadducts **5** when trisubstitued nitroalkenes are used as dipolarophiles for the cycloaddition reaction. The radical denitration occurs with high stereoselectivity, leading to *trans*-alkyl- or aryldisubstituded cycloadducts. The synthetic utility of this sequence was further demonstrated by the transformation of compounds **5a**,**b** into the known β-hydroxy esters **8a**,**b**.[11,12] Accordingly, following previously described conditions, compounds **5a**,**b** were oxidized with excess MCPBA. The resulting nitrone intermediates were hydrolyzed under acidic conditions to give β-hydoxy aldehydes **7a**,**b**, which were in turn oxidized to the corresponding carboxylic acids. After diazomethane esterification, the β-hydroxy esters **8a** and **8b** were isolated in 29% and 34% overall yield respectively (Scheme 7).

Diastereo- and enantiomeric excess of esters **8a** and **8b** were measured by NMR.[11,12] The *anti*/*syn* ratio of **8a** was 90:10 based on ^{13}C NMR chemical shifts at 14.0 ppm and 45.2 ppm for the major *anti*-isomer and at 10.2 ppm and 43.3 ppm for the minor *syn*-isomer. In the presence of (+) $Eu(Hfc)_3$, the ^1H NMR spectrum of **8a** showed peaks for the OMe group at 4.07 ppm (major *anti*-isomer) and 4.15 ppm (minor *syn*-isomer) respectively. The enantiomeric purity of each isomer was found to be up to 98%. The same analysis for compound **8b** showed both diastereo- and enantiomeric purities to be up to 98%.

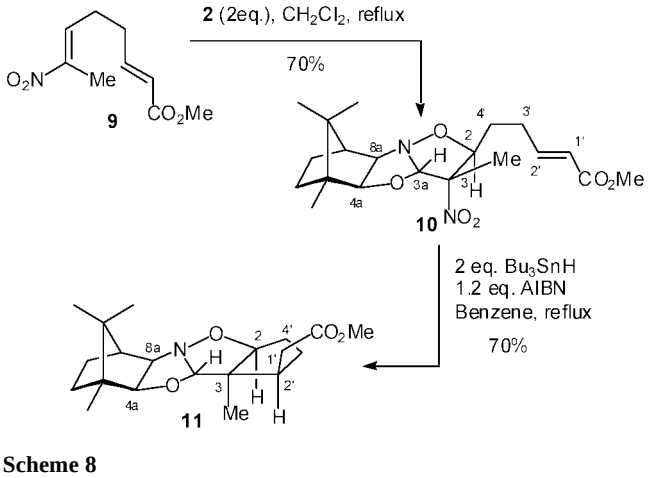
Table 2 Denitration of Cycloadducts **4a**–**f**[a]

Entry	Cycloadduct	R	R^1	Product	Yield%	ds[d]
1	**4a**	Bu	Me	**5a**	70	90/10
2	**4b**	Ph	Me	**5b**	95	>95/5
3	**4c**	H	Me	**5c**	48	50/50
4	**4d**		$-(CH_2)_4-$	**5d**	69[b]	>95/5
5	**4e**	Bu	Ph	**5e**	53	>95/5
6	**4f**	Bu	H	**5f**	14[c]	–

[a] Conditions:Bu_3SnH (2equiv), AIBN (1.2 equiv), benzene, reflux.
[b] AIBN was added over 10 h (syringe pump).
[c] In refluxing toluene, reaction gave 25% yield.
[d] Ratio was determined by NMR.



Scheme 7

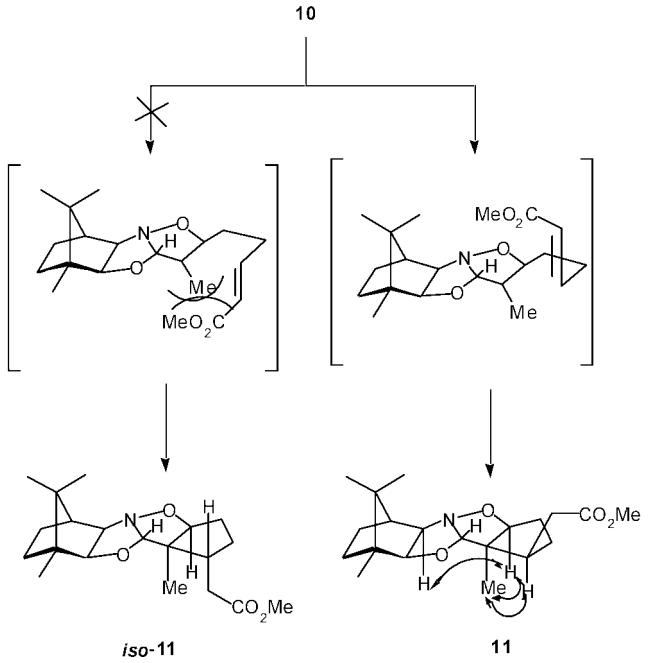


Scheme 8

Tandem Radical Denitration-Cyclization Reaction

Having demonstrated the good stereoselectivity of the radical denitration of nitro-substituted cycloadducts, we attempted a tandem radical denitration-cyclization reaction. This radical sequence has often been used for the stereoselective preparation of cyclic compounds, and involves the intramolecular addition of the radical onto an activated double bound.[13] The application of this sequence to a nitro-substituted cycloadducts therefore requires the preparation of a dipolarophile with a nitroalkene function and another electron-deficient double bond. The known α,β-unsaturated ester **9**[14] was therefore prepared and reacted with excess dipole **2** under standard conditions (CH_2Cl_2, reflux), to give the cycloadduct **10** as a single isomer in 70% yield (Scheme 8). The reaction showed remarkable chemoselectivity since despite being more substituted, only the nitroalkene function reacts in the cycloaddition. No trace of cycloadduct with the α,β-unsaturated ester was detected in the crude product. Upon treatment of **10** with excess tin hydride and AIBN in refluxing benzene, a 5-*exo*-trig cyclization occured, leading to the cyclopentane product **11** as a single stereoisomer (70% yield). Extensive NMR analysis of compound **11** (with COSY, NOESY and HSQC) proved the *syn* relationship between the proton at carbon C_2, the methyl substituent at C_3, and the proton at $C_{2'}$, thus establishing the (3*R*,1′*R*) configurations for the newly created stereogenic centers.

The high stereoselectivity of this radical cyclization may be explained considering steric interactions between the ester function in the radical acceptor and the methyl substitutent on the radical, leading to an attack of the radical on the *Re*-face of the double bond (Scheme 9); as observed in the simple denitration reaction, the radical trapping is *exo*-selective, leading to an inversion of the methyl substituent at C_3. These two factors account for the high stereoselectivity of the 5-*exo*-trig radical cyclization of the nitro compound **10**.



Scheme 9

Conclusion

A new asymmetric [2+3] cycloaddition-radical denitration sequence was developed for the preparation of unfunctionalized cycloadducts, formally resulting from cycloaddition with simple alkenes. This sequence is efficient when various trisubstituted nitroalkenes are used, and shows excellent stereoselectivity, as a single isomer is obtained in most cases. This sequence may also be associated with a radical cyclization process, as shown for the preparation of compound **11**, with complete stereocontrol, thus allowing the formation of three contiguous stereogenic centers. The nitro function may therefore be considered as a removable activating group for cycloaddition reactions; further methological studies as well as synthetic applications of this sequence are currently in progress

^{1}H and ^{13}C NMR spectra were recorded at 200, 250 or 400 MHz and 50, 62.5 or 100 MHz, respectively. Optical rotation were recorded at 25 °C. Chromatographic purifications were performed on 230–400 mesh silica gel (Merck 9385) using the indicated solvent system. CH_2Cl_2 and trimethyl orthoformate were distilled from CaH. Toluene was distilled from sodium metal. Et_2O and THF were distilled from sodium metal/benzophenone ketyl. $CHCl_3$ used for optical measurements was filtered through basic alumina before use. 2-Nitropropene was prepared by dehydration (phthalic anhydride, 150 °C) of commercial 2-nitro-propanol[8]. 1-Nitro-hexene and 2-nitro-hept-2-ene were prepared by Henry condensation (Al_2O_3) of nitromethane and nitroethane with valeraldehyde, followed by dehydration (PPh_3, CCl_4).[7] All non-aqueous reactions were performed under an argon atmosphere using oven-dried glassware.

Asymmetric [2+3] Cycloadditions Between Oxazoline *N*-Oxide 2 and Nitroalkenes 3a–f; General Procedure

A suspension of 3-hydroxylaminoisoborneol hydrochloride **1** (1 equiv) and powdered $Ca(CO_3)_2$ (l equiv) in either CH_2Cl_2 or toluene (5ml/mmol) was heated at 45 °C with stirring and trimethyl orthoformate (4 equiv) was added via syringe. The mixture was stirred at 45 °C for 4 h then the nitroalkene **3** was added (4 equiv). The mixture was stirred vigorously at the appropriate temperature and for the appropriate time (see Table 1). The completion of the reaction was monitored by TLC. After cooling to r.t., the mixture was filtered through a plug of celite and the filtrate concentrated in vacuo. The residue was purified by flash chromatography on silica gel (10% EtOAc–heptane,1:9) to give the pure cycloadduct (except for products **4b** and **4e**, vide infra).

(2*S*,3*S*,3a*S*,4a*S*,5*R*,8*S*,8a*R*)-2-Butyl 3-nitro-3,5,10,10-tetramethyl- 5,8-methanooctahydro-2*H*- isoxazolo[3,2-*b*]benzoxazole (4a)

After the addition of 2-nitrohept-2-ene (**3a**) the reaction was heated to 80 °C in toluene for 18 h to give the product **4a** as a single stereoisomer; yield: 75%; $[\alpha]_D^{20}$ –172 (*c* 1.1, $CHCl_3$).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 4.96 (1 H, s), 4.77 (1 H, t, *J* = 6 Hz), 4.00 (1 H, d, *J* = 7.5 Hz), 3.45 (1 H, d, *J* = 7.5 Hz), 2.10 (1 H, d, *J* = 4.5 Hz), 1.63 (3 H, s), 1.80–1.30 (10 H, m), 0.90 (3 H, t, *J* = 7 Hz), 0.90, 0.85 and 0.80 (9 H, 3 × s).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 103.9, 95.9, 91.2, 79.6, 76.6, 49.3, 48.7, 45.6, 31.3, 28.2, 26.5, 25.4, 22.6, 22.1, 18.7, 17.8, 13.8, 10.7.

MS (CI, NH_3): *m*/*z* = 339 (MH^+).

Anal. Calcd for $C_{18}H_{30}N_2O_4$ (338.22054): C, 63.88; H, 8.93; N, 8.28. Found: C, 64.23; H, 9.24; N, 8.41.

(2*S*,3*S*,3a*S*,4a*S*,5*R*,8*S*,8a*R*)-3-Nitro 2-phenyl 3,5,10,10-tetramethyl-5,8-methanooctahydro-2*H*-isoxazolo[3,2-*b*]benzoxazole (4b)

After addition of 2-nitro-1-phenylpropene (**3b**) the reaction was refluxed in CH_2Cl_2 for 18 h. The crude product consists of an inseparable mixture of cycloadduct **4b** and excess dipolarophile. Separation of both compounds was accomplished as follows: the crude product was redissolved in a THF–water mixture (1:1, 5mL/mmol). $NaHCO_3$ (5 equiv to the starting dipolarophile) was added, followed by hydroxylamine hydrochloride (5 equiv); gas evolution was observed, and the yellow solution progressively faded to pale yellow; after stirring for 24 h at r.t., THF was removed in vacuo, and the mixture was extracted EtOAc (2 × 30 mL); the combined organic layers were washed with brine (50 mL), dried (Na_2SO_4), filtered, and concentred in vacuo. The pure cycloadduct **4b** was obtained as a single isomer after chromatography;[15] yield: 73%; $[\alpha]_D^{20}$ –161 (*c* 1.2, $CHCl_3$).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.29 (5 H, br s, ArH), 6.06 (1 H, s), 5.06 (1 H, s), 4.13 (1 H, d, *J* = 8 Hz), 3.62 (1 H, d, *J* = 8 Hz), 2.16 (1 H, d, *J* = 5 Hz), 1.70–1.42 (4 H, m), 1.34 (3 H, s), 0.91, 0.87, 0.80 (9 H, 3 × s).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 132.4, 128.9, 128.5, 126.5, 103.6, 97.5, 91.2, 80.7, 76.1, 49.3, 48.8, 45.7, 31.3, 25.4, 22.1, 19.1, 18.8, 10.7.

MS (CI, NH_3): *m*/*z* = 359 (MH^+).

HRMS: *m*/*z* calcd for $C_{20}H_{26}N_2O_4$, 358.18924; found, 358.18922.

(3*S*,3a*S*,4a*S*,5*R*,8*S*,8a*R*)-3-Nitro-3,5,10,10-tetramethyl-5,8-methanooctahydro-2*H*-isoxazolo[3,2-*b*]benzoxazole (4c)

After the addition of 2-nitropropene (**3c**) the reaction was refluxed in CH_2Cl_2 for 18 h. The crude product was purified by chromatography. First to elute was **4c** (R_f 0.35; yield 64%), followed by a small amount of *exo*-adduct **5c** (R_f 0.29; yield: 16%); combined yield: 80%; $[\alpha]_D^{20}$ –202.1 (*c* 1.89, $CHCl_3$).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 4.94 (1 H, s), 4.73 (1 H, d, *J* = 10 Hz), 3.94 (1 H, d, *J* = 7.5 Hz), 3.79 (1 H, d, *J* = 10 Hz), 3.42 (1 H, d, *J* = 7.5 Hz), 2.09 (1 H, d, *J* = 4.5 Hz), 1.78 (3 H, s), 1.80 and 1.65 (4 H, 2 × m), 0.87, 0.83 and 0.77 (3 s, 9 H, 3 × CH_3).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 102.8, 94.9, 91.4, 75.6, 72.1, 49.2, 48.9, 45.8, 31.4, 25.5, 22.8, 22.6, 18.9, 10.8.

Mass (CI NH_3): *m*/*z* = 301 (MNH_4^+), 283 (MH^+);

Anal. Calcd for $C_{14}H_{22}N_2O_4$ (282.34244): C, 59.56; H, 7.85; N, 9.92. Found: C, 59.71; H, 8.11; N, 9.42.

(2*S*,3*S*,3a*S*,4a*S*,5*R*,8*S*,8a*R*)-3-Nitro 3,5,10,10-tetramethyl-5,8-methanoperhydrobenzo[*d*]isoxazolo[3,2-*b*]benzoxazole (4d)

After the addition of 1-nitrocyclohexene (**3d**) the reaction was refluxed in CH_2Cl_2 for 18 h to give the product **4d** as a single stereoisomer; yield: 67%; $[\alpha]_D^{20}$ –163 (*c* 0.99, $CHCl_3$).

^{1}H NMR (250 MHz with COSY and NOESY, $CDCl_3$): δ = 4.82 (1 H, s), 4.59 (1 H, s), 3.81 (1 H, d, *J* = 8 Hz), 3.41 (1 H, d, *J* = 8 Hz), 2.59 (1 H, d, *J* = 14 Hz), 1.96 (1 H, d, *J* = 5 Hz), 1.87 (1 H, m), 1.70–1.50 (4 H, m), 1.36 (1 H, m), 1.31–1.20 (2 H, m), 094 (1 H, m), 0.90–0.80 (2 H, m), 0.75, 0.70, 0.65 (3 s, 9 H, 3 × CH_3).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 102.4, 94.5, 91.4, 77.8, 73.7, 49.5, 49.0, 45.5, 31.3, 30.5, 25.7, 23.4, 22.2, 21.2, 19.3, 18.7, 10.8.

MS (CI NH_3): *m*/*z* = 345 (MH^+).

HRMS: *m*/*z* calcd for $C_{17}H_{26}NaN_2O_4$ (M + Na), 345.17983; found, 345.17903.

(2*S*,3*S*,3a*S*,4a*S*,5*R*,8*S*,8a*R*)-2-Butyl-3-nitro-3-phenyl-5,10,10-trimethyl-5,8-methanooctahydro[2*H*]isoxazolo[3,2-*b*]benzoxazole (4e)

After the addition of l-nitro-1-phenylhexene (**3e**) the reaction was refluxed in CH_2Cl_2 for 2 h. Purification of the crude product was accomplished as for the purification of cycloadduct **4b** to give the product **4e** as a single stereoisomer; yield: 43%; $[\alpha]_D^{20}$ –161 (*c* 1, $CHCl_3$).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.29 (5 H, br s), 5.48 (1 H, s), 4.58 (1 H, d, *J* = 9 Hz), 3.89 (1 H, d, *J* = 8 Hz), 3.48 (1 H, d, *J* = 8 Hz), 2.09 (1 H, d, *J* = 5 Hz), 1.40–1.05 (10, m), 0.80 (3 H, s, Me-C_2), 0.78, 0.75, 0.65 (3 s 9 H, 3 × CH_3).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 133.5, 130.3, 128.4, 126.4, 103.6, 103.1, 91.1, 79.6, 79.0, 49.5, 49.1, 45.2, 31.3, 28.2, 27.4, 25.7, 22.4, 22.2, 13.8, 10.8;

MS (CI, NH_3): *m*/*z* = 401 (MH^+).

HRMS: *m*/*z* calcd for $C_{23}H_{32}N_2O_4$, 400.23621; found, 400.23623.

(2*S*,3*S*,3a*S*,4a*S*,5*R*,8*S*,8a*R*)-2-Butyl 3-nitro-5,10,10-trimethyl-5,8-methanooctahydro[2*H*]isoxazolo[3,2-*b*]benzoxazole (4f)
After the addition of 1-nitrohexene (**3f**), the reaction was refluxed in CH_2Cl_2 for 2 h to give the product **4f** as a single stereoisomer; yield: 70%; $[\alpha]_D^{20}$ –161 (*c* 1.47, $CHCl_3$).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 5.55 (1 H, d, *J* = 7 Hz), 4.80 (1 H, dd, *J* = 7, 8 Hz), 4.65 (1 H, dt, *J* = 6, 8 Hz), 4.05 (1 H, d, *J* = 7.5 Hz), 3.45 (1 H, d, *J* = 7.5 Hz), 2.10 (1 H, d, *J* = 4.5 Hz), 1.80–1.30 (10 H, m), 0.90 (3 H, t, *J* = 7 Hz), 0.95, 0.88, 0.80 (3 s 9 H, 3 × CH_3).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 96.4, 92 4, 91.4, 78.0, 75.7, 49.1, 48.7, 45.8, 31.3, 30.6, 27.3, 25.2, 22.4, 22.0, 18.7, 13.7, 10.6.

MS (CI, NH_3): *m*/*z* = 325 (MH^+).

HRMS: *m*/*z* calcd for $C_{17}H_{28}N_2O_4$, 324.20489; found, 324.20491.

Radical Denitration of Cycloadducts 4a–e
AIBN (1.2 equiv) was added to a solution of the nitro cycloadduct **4** and Bu_3SnH (2 equiv) in anhyd benzene (5 mL/mmol). The mixture was stirred at reflux for 2 h, then cooled to r.t. Excess hydride reagent was destroyed by the addition of CCl_4 (1 mL), and this was subsequently stirred for 20 min. The solvents were removed in vacuo (in a well ventilated hood) and the residue redissolved in EtOAc (25 mL). Sat. aq KF solution was added and the mixture was stirred for 30 min. The white precipitate was removed by filtration through cotton wool, and the layers were separated. The organic layer was washed with brine (25 mL), dried (Na_2SO_4), filtered and concentred in vacuo. The crude product was purified by chromatography (EtOAc–heptane, 1:9) to give the pure denitrated products **5**.

(2*S*,3*S*,3a*S*,4a*S*,5*R*,8*S*,8a*R*)-2-Butyl-3,5,10,10-tetramethyl-5,8-methanooctahydro[2*H*]isoxazolo[3,2-*b*]benzoxazole (5a)
Denitration of cycloadduct **4a** according to the procedure described above gives a 90:10 mixture of **5a** and its *exo* isomer; yield: 70%.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 5.14 (1 H, d, *J* = 6.9 Hz), 3.74 (1 H, d, *J* = 8 Hz), 3.41 (1 H, m), 3.25 (1 H, d, *J* = 8 Hz), 2.07 (1 H, d, *J* = 5 Hz), 1.93 (1 H, ddq with J_3-J_{3a} = 6.9 Hz), 1.75–1.20 (10 H, m) 1.15 (3 H, d), 1.12 (3 H, t), 0.95, 0.80, 0.75 (3 s, 9 H, 3 × CH_3).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 100.8, 90.4, 82.8, 77.7, 50.1, 49.3, 46.9, 46.3, 32.3, 32.0, 28.8, 26.3, 23.5, 22.9, 19.6, 14.6, 11.7, 10.7.

MS (CI, NH_3): *m*/*z* = 294 (MH^+).

(2*S*,3*S*,3a*S*,4a*S*,5*R*,8*S*,8a*R*)-2-Phenyl-3,5,10,10-tetramethyl-5,8-methanooctahydro[2*H*]isoxazolo[3,2-*b*]benzoxazole (5b)
Denitration of cycloadduct **4b** according to the described procedure gives compound **5b** as a single isomer; white solid; yield: 90%; $[\alpha]_D^{20}$ –67 (*c* 0.47, $CHCl_3$).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.32 (5 H, br s), 5.33 (1 H, d, *J* = 6.8 Hz), 4.34 (1 H, d, *J* = 10 Hz), 3.89 (1 H, d, *J* = 8 Hz), 3.46 (1 H, d, *J* = 8 Hz), 2.24 (1 H, ddq with J_3-J_{3a} = 6.8 Hz), 2.13 (1 H, d, *J* = 5 Hz), 1.75–1.10 (4 H, m), 1.05, 0.85, 0.82 (3 s, 9 H, 3 × CH_3).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 137.3, 129.3, 128.4, 126.8, 100.2, 89.9, 84.7, 77.3, 50.1, 49.5, 48.8, 45.7, 31.7, 25.7, 22.2, 19.0, 11.0, 9.4;

MS (ESI): *m*/*z* = 336 (M + Na).

HRMS: *m*/*z* calcd for $C_{20}H_{27}NaNO_2$ (M + Na), 336.19380; found, 336.19395.

(2*S*,3*R*,3a*S*,4a*S*,5*R*,8*S*,8a*R*) 3,5,10,10-tetramethyl-5,8-methanoperhydrobenzo[*d*]isoxazolo[3,2-*b*]benzoxazole (5d)
A solution of nitrated cycloadduct **4d** (142 mg, 0.44 mmol) and Bu_3SnH (0.26 mL, 0.88 mmol, 2 equiv) in benzene (1 mL) was stirred at reflux and a solution of AIBN (82 mg, 0.52 mmol, 1.2 equiv) in benzene (2.5 mL) was added with a syringe pump over 10 h. After completion of the addition, the solution was refluxed for a further 4 h before being cooled to r.t., CCl_4 (1 mL) was added, and the mixture was treated as usual. Purification of the crude product by chromatography (EtOAc–heptane, 1:19) gave compound **5d** as a single stereoisomer; colorless oil; yield: 69% (85 mg); $[\alpha]_D^{20}$ –124 (*c* 0.34, $CHCl_3$).

^{1}H NMR (250 MHz, $CDCl_3$): 5.27 (1 H, d, *J* = 4 Hz), 3.87 (1 H, d, *J* = 8 Hz), 3.49 (1 H, d, *J* = 8 Hz), 3.21 (1 H, ddd, *J* = 2, 6, 13 Hz), 2.05 (1 H, d, *J* = 6 Hz), 2.00–0.80 (13 H, m), 0.96, 0.95, 0.81 (3 s, 9 H, 3 × CH_3).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 100.2, 92.1, 79.6, 79.5, 53.7, 50.5, 49.8, 45.8, 32.5, 30.1, 26.7, 25.9, 24.7, 24.6, 23.0, 19.5, 11.8.

MS (ESI): *m*/*z* = 300 (M + Na), 278 (MH^+).

HRMS: *m*/*z* calcd for $C_{17}H_{27}NaO_2$ (M + Na), 300.19386; found, 300.19385.

Hydrolysis of Chiral Auxiliary
A solution of the denitrated cycloadduct **5a**,**b** (1 mmol) in anhyd Et_2O (20 mL) was treated with MCPBA (4 mmol, 4 equiv). The colorless solution was stirred at r.t. After 1 h, excess peroxy reagent was destroyed by the addition of an aq 5% $NaHCO_3$–5% $Na_2S_2O_3$ solution (25 mL) and the resulting mixture was stirred for 1 h. The layers were separated, the organic layer was washed with 5% $NaHCO_3$ solution (15 mL), brine (15 mL), then dried (Na_2SO_4), filtered and concentred in vacuo. The crude product was redissolved in THF (10 mL), and a 2 N HCl solution (10 mL) was added. The resulting pale yellow solution was stirred for 30 min, before being diluted with H_2O (15 mL), and extracted with EtOAc (3 × 20 mL). The combined organic layer was washed with brine (50 mL), dried (Na_2SO_4), filtered, and concentred in vacuo to give a crude mixture of the β-hydroxy-aldehyde **7** and the recovered chiral auxiliary.

For the sake of characterization, the aldehyde **7** was transformed into the corresponding methyl ester in a two-step sequence: the crude aldehyde was redissolved in *t*-BuOH (8 mL), 2-methyl-2-butene (3 mL) was added, followed by a freshly prepared aq 10% $NaClO_2$ –10% NaH_2PO_4 (4.5 mL). The solution was stirred at r.t. for 1 h, then diluted with H_2O (20 mL), and extracted with EtOAc (4 × 20 mL). The combined organic layer was washed with brine (50 mL), dried (Na_2SO_4), filtered, and concentred in vacuo. The crude carboxylic acid was redissolved in aq $NaHCO_3$ solution (50 mL) and extracted with Et_2O (2 × 10 mL). The organic layer (containing the recovered chiral auxiliary) was discarded, the aqueous layer was acidified with 6 N HCl solution, and extracted with EtOAc (4 × 20 mL). The combined organic extracts were washed with brine (50 mL), dried (Na_2SO_4), filtered, and concentred in vacuo to give the pure carboxylic acid, which was redissolved in Et_2O (5 mL) and treated with etheral diazomethane until the yellow color persisted. After concentration in vacuo, pure methyl ester **8** was obtained.

(2*S*, 3*S*)-Methyl 3-hydroxy 2-methylheptanonate (8a)
This ester was prepared from denitrated cycloadduct **5a** according to the four-step sequence previously described; overall yield: 29%. This product consists of a mixture of *anti*- and *syn*-isomers in a ratio of 90:10.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.72 (3 H, s), 3.65 (1 H, m), 2.54 (1 H, dq, *J* = 7.5, 6.5 Hz), 1.60–1.28 (6 H, m), 1.22 (3 H, d, *J* = 7.5 Hz), 0.91 (3 H, t, *J* = 7 Hz).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 176.5, 73.3, 51.7, 45.2, 34.4, 37.6, 22.6, 14.3, 14.0; small peaks at 43.3 and 10.2 ppm are characteristic of the minor *syn*-isomer.

Enantiomeric purity was checked by ^{1}H NMR in the presence of tris [3-(heptafluoropropyl)hydroxymethylene]-*d*-camphorato europium. The chemical shifts for the OMe group at 4.07 ppm (major isomer) and 4.15 ppm (minor isomer) are assigned as (2*S*,3*S*) and

(2*R*,3*S*) isomers respectively. Chemical shifts for (2*S*,3*R*) and (2*R*,3*R*) isomers are not detected.

(2*S*, 3*S*)-Methyl 3-hydroxy 2-methylphenylpropionate (8b)
This ester was prepared from denitrated cycloadduct **5b** according to the four-step sequence previously described as a single isomer; overall yield: 34%.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.34 (5 H, br s), 4.73 (1 H, d, *J* = 8.5 Hz), 3.71 (3 H, s), 2.90 (1 H, s, exchangeable with D_2O), 2.83 (1 H, m), 1.00 (3 H, d, *J* = 7 Hz). In the presence of Eu(hfc)$_3$, the OMe signal shifts to 4.1 ppm, no other signal corresponding to another enantiomer was detected.

MS (ESI): *m*/*z* = 217 (M + Na).

HRMS: *m*/*z* calcd for $C_{11}H_{14}NaO_3$ (M + Na), 217.08398; found, 217.08046.

(2*S*,3*S*,3a*S*,4a*S*,5*R*,8*S*,8a*R*,1′*E*)-2-(1′-Methoxycarbonyl-1′buten-4′-yl) 3-nitro 3,5,10,10-tetramethyl 5,8- methano octahydro[2*H*]isoxazolo[3,2-*b*]benzoxazole (10)
Trimethylorthoformate (2.2 mL, 20 mmol, 8 equiv) was added to a suspension of hydroxylamino isoborneol hydrochloride (1.1 g, 5 mmol, 2 equiv) and $Ca(CO_3)_2$ (500 mg, 5 mmol, 2 equiv) in CH_2Cl_2 (15 mL). The resulting suspension was stirred at reflux for 4 h, then (2*E*,7*E*)-methyl 7-nitro-2,6-octadienoate (**9**) (504 mg, 2.5 mmol, 1 equiv), was added in one protion. The reaction mixture was stirred at reflux for 16 h, then cooled to r.t. and filtered through a short pad of celite, eluting with CH_2Cl_2. The filtrate was concentred in vacuo and the crude product purified by chromatography on silica gel (EtOAc–heptane, 3:1) to give the cycloadduct **10** as a single stereoisomer; yield: 70% (660 mg); $[\alpha]_D^{20}$ –129 (*c* 0.3, $CHCl_3$).

IR ($CHCl_3$): 3055, 2956, 1723, 1548, 1267, 1132, 1111, 738 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, with COSY and NOESY): δ = 6.90 (1 H, m, with $J_{1'}$-$J_{2'}$ = 13 Hz, $C_{2'}$-H), 5.83 (1 H, d, $J_{1'}$-$J_{2'}$ = 13 Hz, $C_{1'}$-H), 4.94 (1 H, s, C_{3a}-H), 4.71 (1 H, dd, *J* = 9, 4 Hz, C_2-H), 3.93 (1 H, d, *J* = 8 Hz, C_{4a}-H), 3.70 (3 H, s, OMe), 3.37 (1 H, d, *J* = 8 Hz, C_{8a}-H), 2.29 (2 H, m, 2 × $C_{3'}$-H), 2.07 (1 H, d, *J* = 5 Hz, C_8-H), 1.68 (3 H, m, 2 × $C_{4'}$-H, one of C_6-H), 1.61 (3 H, s, Me-C_3), 1.37 (1 H, m, one of C_6-H), 0.92 (2 H, m, 2 × C_7-H), 0.86, 0.80, 0.73 (3 s, 9 H, 3 × CH_3).

^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 166.4 (CO), 146.8 ($C_{2'}$), 121.8 ($C_{1'}$), 103.7 (C_{3a}), 95.6 (C_2), 91.1 (C_{4a}), 78.4 (C_{8a}), 76.6 (OMe), 53.3 (C_3), 49.1 (C_8), 48.6 (C_5), 45.4 (C_{10}), 31.1 (C_6), 28.6, 25.3 ($C_{3'}$, $C_{4'}$), 25.1 (C_7), 22.0 (Me-C_3), 18.5, 17.7, 10.6 (3 × CH_3).

MS (ES): *m*/*z* = 417 (M + Na).

Cyclization Product 11
AIBN (82 mg, 0.5 eq.) and Bu_3SnH (290 μL, 1 mmol) were added to a solution of nitro cycloadduct **10** (197 mg, 0.5 mmol) in benzene (5 mL), and the colorless solution was stirred at reflux. After 1.5 h, the reaction mixture was cooled to r.t., CCl_4 (0.5 mL) was added and the mixture treated as usual. After purification by chromatography (EtOAc–heptane, 4:1), the cyclized product **11** was obtained as a colorless oil that solidified on standing to give the product as a single isomer; yield: 70% (122 mg); $[\alpha]_D^{20}$ –115.2 (*c* 1.1, $CHCl_3$).

IR ($CHCl_3$): 2958, 1732, 1457, 1438, 1090 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$, with COSY, NOESY and HSQC): δ = 4.92 (1 H, s, C_{3a}-H), 4.20 (1 H, d, *J* = 4 Hz, C_2-H), 4.09 (1 H, d, *J* = 8 Hz, C_4-H), 3.64 (3 H, s, OMe), 3.23 (1 H, d, *J* = 8 Hz, C_{8a}-H), 2.55 (1 H, dd, *J* = 5, 15 Hz, one of $C_{1'}$-H), 2.34 (1 H, dd, *J* = 10, 15 Hz, one of $C_{1'}$-H), 2.06 (1 H, m, $C_{2'}$-H), 2.02 (1 H, d, *J* = 5 Hz, C_8-H), 1.86 (1 H, m, one of $C_{3'}$-H), 1.75 (1 H, m, one of $C_{4'}$-H), 1.67 (1 H, m, one of C_7), 1.61 (1 H, m, one of $C_{4'}$-H), 1.46 (1 H, m, one of $C_{3'}$-H), 1.35 (1 H, m, one of C_6-H), 1.28 (1 H, m, one of C_7-H), 1.11 (3 H, s, Me-C_3), 0.88 (1 H, m, one of C_6-H), 0.94, 0.92, 0.77 (3 s, 9 H, 3 × CH_3).

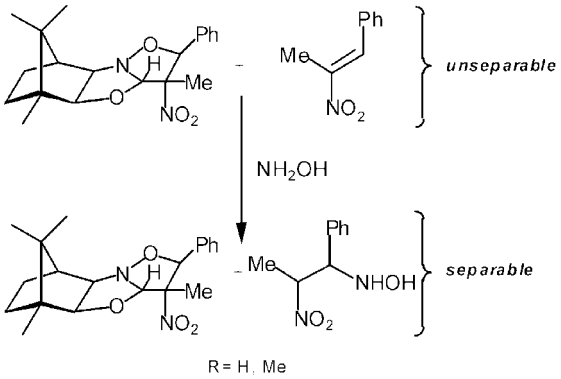
^{13}C NMR (100 MHz, $CDCl_3$) δ = 173.4 (CO), 100.9 (C_{3a}), 90.6 (C_2), 89.9 (C_{4a}), 74.6 (C_{8a}), 58.0 (C_3), 51.8 (OMe), 49.0 (C_8), 48.6 (C_5), 46.7 ($C_{2'}$), 46.2 (C_{10}), 35.8 ($C_{1'}$), 31.9 (C_6), 31.2 ($C_{3'}$), 29.7 ($C_{4'}$), 25.3 (C_7), 21.1 (Me-C_3), 22.3, 19.3, 10.9 (3 × CH_3).

MS (ESI): *m*/*z* = 721.5 (2 M + Na), 372 (M + Na).

References

(1) Berranger, T.; Langlois, Y. *J. Org. Chem.* **1995**, *60*, 1720.
(2) Kouklovsky, C.; Dirat, O.; Berranger, T.; Langlois, Y.; Tran Huu Dau, M.-E.; Riche, C. *J. Org. Chem.* **1998**, *63*, 5123.
(3) For a review: Dirat, O.; Kouklovsky, C.; Mauduit, M.; Langlois, Y. *Pure Applied Chem.* **2000**, *72*, 1721.
(4) Berranger, T.; Langlois, Y. *Tetrahedron Lett.* **1995**, *36*, 5523.
(5) Kobayakawa, M.; Langlois, Y. *Tetrahedron Lett.* **1992**, *33*, 2353.
(6) Nitroalkenes **3a**, **3e**, and **3f** were prepared in two steps, Henry condensation in the presence of basic alumina, followed by dehydration of the nitroalcohol by treatment with PPh_3–CCl_4: (a) Ballini, R.; Chatagnani, R.; Petrini, M. *J. Org. Chem.* **1992**, *57*, 2160. (b) Saikia, A. K.; Barua, N. C.; Sharma, R. P.; Ghosh, A. C. *Synthesis* **1994**, 685.
(7) Nitroalkene **3c** was prepared by dehydration of commercially available 2-nitropropanol with phthalic anhydride: Ranganathan D., Bhushan Rao C., Ranganathan S., Mehrotra A.K., Iyengar R.; *J. Org. Chem.;* **1980**, 45: 1185.
(8) (a) Ono, N.; Miyake, H.; Fuji, H.; Kaji, A. *Tetrahedron Lett.* **1984**, *23*, 3477. (b) Review: Ono, N.; Kaji, A. *Synthesis* **1986**, 693. (c) For a tin-catalyzed procedure: Torno, J.; Hays, D. S.; Fu, G. C. *J. Org. Chem.* **1998**, *63*, 5296.
(9) Recently Mioskowski and co-workers reported good yields in the denitration of secondary *N*-2-nitroalkyl oxazolidinones: Leroux, M.-L.; Le Gall, T.; Mioskowski, C. *Tetrahedron: Asymmetry* **2001**, *12*, 1817.
(10) For an example of intermolecular addition: Dupuis, J.; Giese, B.; Hartung, J.; Leising, M.; Korth, H. G.; Sustmann, R. *J. Am. Chem. Soc.* **1985**, *107*, 4332.
(11) Matteson, D. S.; Man, H. W. *J. Org. Chem.* **1994**, *59*, 5734.
(12) Gennari, C.; Colombo, L.; Bertolini, G.; Schimherna, G. *J. Org. Chem.* **1987**, *52*, 2754.
(13) For reviews see inter alia: (a) Giese, B.; Kopping, B.; Göbel, T.; Dickhaut, J.; Thoma, G.; Kulicke, K. J.; Trach, F. *Org. React.* **1996**, *48*, 301. (b) Curran, D. P.; Porter, N. A.; Giese, B. In *Stereochemistry of Radical Reactions*; VCH: Weinheim, **1986**. (c) Giese, B. In *Radicals in Organic Synthesis Formation of C-C Bonds*; Pergamon: Oxford, **1986**.
(14) Denmark, S. E.; Senanayake, C. B. W. *J. Org. Chem.* **1993**, *58*, 1853.

(15)



Scheme 10 Note: this special purification procedure applies whenever phenyl-substituted nitroalkenes are used in the cycloaddition (Scheme 10).