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DIASTEREOSELECTIVE NITRILE OXIDE AND NITRONE ADDITIONS

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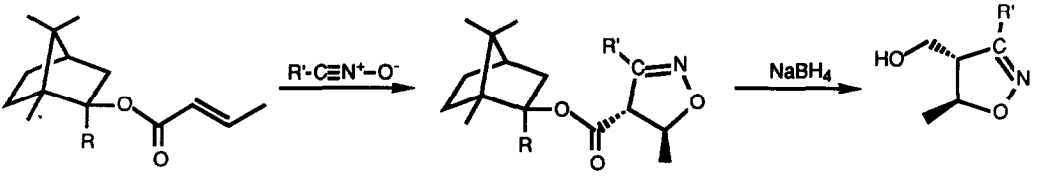
Summary: *With simple chiral esters, cycloaddition reactions are performed in high yields with considerable diastereoselectivities. Evidence for the preferred conformation of the enoates in the transition state of the nitrile oxide addition is provided and the stereoselectivity of nitrone additions is discussed.*

Introduction

Several groups are presently involved in asymmetric dipolar cycloaddition chemistry, since the reactions constitute powerful tools for constructing heterocyclic systems. The heterocycles obtained can be cleaved in numerous ways to provide different functionalities, which thereafter can be elaborated to produce the framework of various natural products.

A method for asymmetric 1,3-dipolar cycloadditions of nitrile oxides using optically active crotonates was recently reported by us.[1] The nitrile oxides were added to chiral esters **1** with substantial diastereoselectivities, the diastereomers separated, and the ester bonds subsequently cleaved to obtain enantiomerically pure isoxazolines **2** (Scheme 1).

Scheme 1



1a R = Phenyl
b R = Naphthyl

R' = Methyl

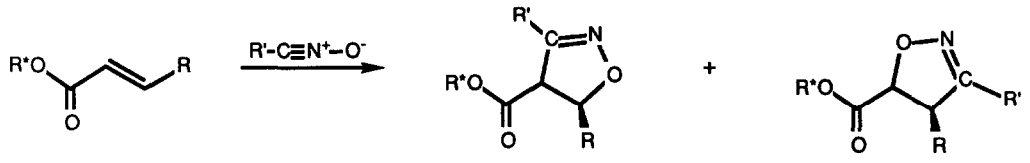
2

In this paper we describe the extension of this method to include nitrile oxide additions to the corresponding chiral acrylates and nitrone additions to the same esters. The nitrile oxide additions gave reasonable results, comparable to those obtained with chiral crotonates, and the nitrone additions gave diastereoselectivities up to 97%.

Nitrile Oxide Additions

Two differently substituted isoxazolines **3** and **4** result from the two possible orientations of the nitrile oxide in the cycloaddition reaction (Scheme 2).

Scheme 2

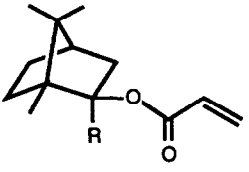


R = H, Methyl

3 **4**

The regioselectivity of 1,3-dipolar cycloadditions is controlled by electronic and steric effects.[2] Thus, in the acrylate additions where the two ends of the double bonds are spatially very different, the sterically favored cycloadducts **3** are produced almost exclusively. In the addition to crotonates, the sterical environment of the two carbon atoms of the double bond is more alike, and the HOMO-LUMO interactions of the reactants become important, reversing the regiochemistry of the reactions to yield isoxazolines **4** as major products. The regioselectivity in the crotonate additions is only about 3:1, why the addition to acrylates has been considered a synthetically more interesting reaction. The crotonate additions, however, are useful since an additional stereocenter is introduced as compared to the acrylates. The two new stereocenters are formed stereospecifically in the cycloaddition reaction, leading to 4,5-disubstituted isoxazolines with defined relative configuration.

Curran *et al.* have undertaken a study[3] in which they tested the acrylates of some known chiral auxiliaries in nitrile oxide addition reactions to obtain asymmetric induction. The results varied from 4 - 56% d.e. In order to compare the diastereoselectivities obtained by our method with these results, we synthesized the acrylic esters **5** and subjected them to nitrile oxide addition conditions. The results of acetonitrile oxide addition to crotonates **1** and acrylates **5** are summarized in Table 1.



5a R = Phenyl
b R = Naphthyl

Table 1. Yields and Diastereoselectivities of 1,3-Dipolar Cycloadditions of Acetonitrile Oxide to Chiral Enoates

Chiral enoate	Yield **3**(%)[a]	d.e.(%)[b]	Yield **4**(%)[a]	d.e.(%)[b]
1a	46	54	25	30
5a	-	-	79	22
1b	76	47	24	75
5b	-	-	94	68

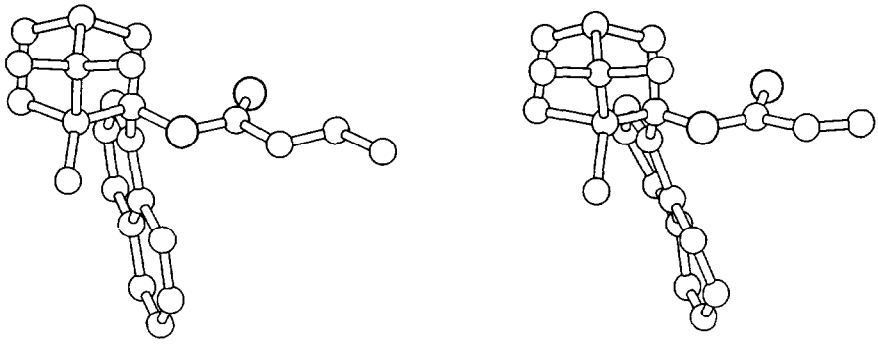
[a] Isolated yields after chromatographic purification.

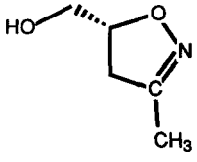
[b] Determined from the ^{1}H-NMR spectra of the crude reaction mixtures.

Acetonitrile oxide reacted with chiral acrylates **5** in high yields, giving regioisomeric ratios greater than 13:1. The diastereoselectivities were determined by integration of the isoxazoline proton signals in the ^{1}H-NMR spectra of the crude products. The d.e. observed for addition of acetonitrile oxide to esters **5a** and **5b** follow the results obtained for the corresponding regioisomers from addition to the crotonates **1a** and **1b** so closely that a strong resemblance between the transition states of the acrylate and crotonate substrates might be concluded.

The question of ester conformation has previously been addressed by Curran[3,4] and by us.[1] It was found that the absolute configuration of the major cycloaddition products agreed with attack by the dipole from the least hindered side of the enoates with the esters in the *s-cis* conformation. According to MM-calculations,[5] the lowest energy *s-cis* conformation of ester **1b** was only a few kJ/mol higher in energy than the corresponding *s-trans* conformer. X-ray diffraction proved the crystal ground state of ester **1b** to be very much alike the lowest energy *s-cis* conformation presented in ref. 1. The crystal structure of **5b** was also determined by X-ray diffraction and, although the crystals were of to low a quality to assure the accuracy of the resulting structure, this structure bears a close resemblance to the structure of **1b** (Fig. 1).

***Figure 1.** X-ray Diffraction Structures of Esters **1b** and **5b**.*





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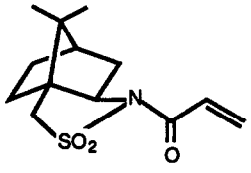
The absolute configuration of the major isoxazoline resulting from addition of acetonitrile oxide to ester **5a** was concluded by reduction of the diastereomeric product mixture with $NaBH_4$ to the known hydroxymethyl isoxazoline **6**[4] and determination of the sign of the optical rotation of the product.

The preferred direction of attack again proved to be in accord with addition from the least hindered side of a conformation similar to the one in Figure 1. We have also used these esters successfully in organocopper additions, and the experimental results indicate that monoorganocopper compounds add to the crotonates **1** with the esters in the *s-trans* conformation, at least as long as

free lithium iodide is present, while cuprates show a temperature dependency with *s-trans* addition at -60 °C and *s-cis* addition at 0 °C.[6]

Possible addition to the *s-cis* and *s-trans* rotamers of the chiral enoates leads to a lower diastereomeric selectivity than the shielding of one face of the double bond would suggest. This has already been pointed out by Curran *et al.*, who solved the problem by using Oppolzer's chiral sultam **7**, in which the ester is forced to adopt the *s-cis* conformation.[4,7] Indeed, the results obtained with this chiral auxiliary were excellent!

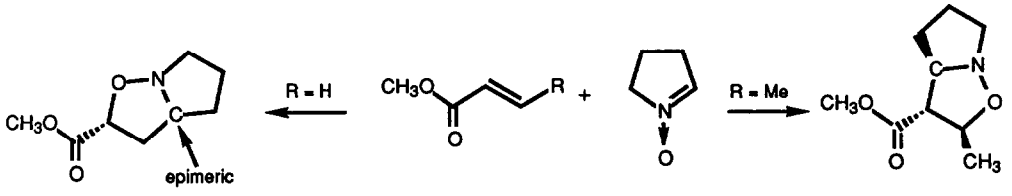


7

Nitrone Additions

Nitrones add to unsymmetrical olefins in the same way as nitrile oxides to yield two regioisomers. Addition of 1-pyrroline-1-oxide **8** to methyl acrylate mainly gave regioisomer **9**, while the addition to methyl crotonate proceeded with the opposite regiochemistry to yield isoxazolidine **10** as the major product (Scheme 3).

Scheme 3



9 **8** **10**

Further, nitrones can add in an *endo* or *exo* fashion to the double bond, leading to two diastereomeric products with the protons on C3 and C5 of the isoxazolidine ring in a *cis* or *trans* relationship. The acrylate reaction showed no *endo/exo* selectivity, but gave a roughly 1:1 diastereomeric mixture of *cis* and *trans* substituted isoxazolidine **9**.[8] When methyl crotonate was used as the substrate, the product contained only one isomer, which, according to Tufariello *et al.*,[9] was the isomer **10** resulting from *endo* addition.

The lack of diastereoselectivity in the acrylate reaction can be understood, as the reaction is believed to be controlled by steric effects and not by frontier orbital interactions. The highly selective crotonate reaction, on the contrary, is thought to proceed with frontier orbital control and evidence for secondary orbital interactions has been forwarded.[10]

There are four conceivable products when nitrone **8** is added to chiral acrylates **5a** and **5b**; two diastereomeric 3,5-*cis* substituted isoxazolidines resulting from *endo* addition to different sides of the olefinic bond and two 3,5-*trans* substituted diastereomers from *exo* addition (Fig. 2). Both reactions yielded crude products with two well-separated spots on TLC, and flash chromatography gave a minor fraction, containing the diastereomeric *trans* isomers, ahead of a larger fraction with *cis* substituted cycloadducts for the addition to **5b**, and two equally sized fractions for the addition to **5a**. The relative configurations of the different isomers were concluded from ^{1}H-NMR data as described below, and the

isomeric compositions obtained in the two reactions are presented in Table 2.
The large chiral auxiliary influenced the *cis/trans* ratio only to a very small extent, but high diastereofacial selectivity was obtained for both *endo* and *exo* addition to acrylate **5b**, implying substantial shielding of one side of the double bond by the auxiliary.

Figure 2. *Isomers resulting from* Endo *and* Exo *Addition, Respectively.*

cis (*endo*-addition) *trans* (*exo*-addition)

Table 2. *Stereoselectivities of Nitrone Additions to Chiral Enoates.*

Chiral enoate	*cis/trans* ratio[a]	*cis* d.e.[b] (%)	*trans* d.e.[b] (%)
5a	1:1	40	15
5b	2:1	91	>97[c]

[a] Determined from the ^{1}H-NMR spectrum of the crude product.
[b] Determined from the ^{1}H-NMR spectrum of the product after flash chromatography.
[c] Only one diastereomer could be detected in the ^{1}H-NMR spectrum.

The noteworthy diastereoselectivities obtained in the nitrone addition to naphthyl substituted ester **5b** are subject to further investigation. Our results so far indicate that one single conformer of **5b** participates in the reaction.
The relative configurations around the isoxazolidine rings were decided as follows: Molecular mechanics minimization of the energies of the possible *cis* and *trans* substituted isomeric cycloadducts, resulting from *endo* or *exo* addition, and inspection of the bond angles on a Hewlett Packard graphics workstation[11] gave at hand that the coupling between H_A and H_D (Fig. 2) in the ^{1}H-NMR spectrum ought to be of the same magnitude as the coupling H_B - H_C for the *trans* substituted isomers. The coupling constants J_{AC} and J_{BD} should also be about the same. For the *cis* isomers, the couplings H_A - H_C, H_A - H_D, H_B - H_C, and H_B - H_D should all be of comparable size.[12] The two fractions of almost diastereomerically pure adducts, obtained on addition to ester **5b**, gave well resolved ^{1}H-NMR spectra in which the couplings for H_A, H_B, H_C, and H_D (Table 3) could readily be determined by decoupling experiments.
The data for the fastest eluated fraction obtained upon nitrone addition to ester **5b** correspond well to the restrictions outlined above for the *trans* isomer. The data for the second fraction are consistent with *cis* substitution since all couplings are 8 Hz. The ^{1}H-NMR spectra of the two fractions produced on ad-

dition to ester **5a** appeared very similar to those of the corresponding fractions after addition to **5b**. Hence, the two fractions from addition to phenyl substituted ester **5a** were assigned to be *trans* and *cis* isoxazolidines in analogy with the products from addition to ester **5b**.

Table 3. ^{1}H-NMR Shifts and Coupling Constants for Isoxazolidine Protons.

Chiral enoate	Product fraction	Proton shifts[a] (ppm from TMS) H_A	H_B	H_C	H_D	Coupling constants (Hz) J_{AC}	J_{AD}	J_{BC}	J_{BD}
5a	1	4.42	3.73	2.76[b]	2.11[b]	8	8	-[c]	-[c]
	2	4.48	3.69	2.71	2.22	6	8	8	-[c]
5b	1	4.47	3.66	2.61[b]	1.97[b]	8	8	8	8
	2	4.49	3.59	2.64	2.06	4.5	8	8	3.5

[a] The peaks were assigned according to the coupling patterns of the ^{1}H-NMR 2D COSY spectra.

[b] The shifts of H_C and H_D could be the other way around.

[c] These coupling constants could not be measured in the spectra.

The crotonates **1**, in our hands, failed to react with nitrone **8** despite high temperatures and prolonged reaction times. The reason could be that the bulky camphor group disfavors *endo* addition and the barrier to *exo* addition is to high. If this is the case, the experiment actually provides further evidence for the *endo* mode of nitrone addition to crotonates.

Acknowledgements

We are grateful to Mr. Mikael Bergdahl and Mr. Ingvar Lagerstedt for valuable discussions and comments on the manuscript.

Experimental Section

All reactions were carried out in an argon atmosphere with oven-dried equipment. Solvents were dried by distillation from sodium/bensophenone prior to use. IR spectra were recorded on a Perkin-Elmer 1600 FT-IR instrument and NMR spectra were recorded on a Varian VXR-5000 or a Bruker WH-270 in $CDCl_3$ with TMS as internal reference. The NMR-shifts are given as δ-values (ppm from TMS). Merck silica gel (230-400 mesh ASTM) was used for flash chromatography. Butyl lithium (Aldrich) was used as purchased.

The chiral esters were synthesized from (+)-camphor in two simple steps. A Grignard-reaction with RMgBr afforded the bornyl alcohols[13] which were esterified with BuLi/propenoic acid chloride[14] to yield substituted bornyl propenoates **5**. No effort was made to optimize the yields reported below.

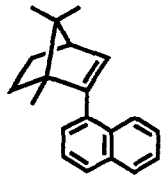
Acetonitrile oxide was generated *in situ* from nitroethane and phenyl isocyanate[15] and 1-pyrroline-1-oxide was generated *in situ* from pyrrolidine and hydrogen peroxide.[16] 1-Pyrroline-1-oxide was selected for the nitrone additions since it does not *cis/trans* isomerize.

Propenoic acid chloride. About 3 ml of propenoic acid chloride was distilled on a short column at 60-90 °C from a mixture of 20 ml bensoyl chloride and 5 ml acrylic acid. An oil bath was heated to

150 °C prior to the rapid distillation, since acrylic acid polymerized if it was heated slowly. The acid chloride was used immediately in the next step.

1-(1-*endo*-Phenyl)bornylpropenoate (5a). 1-(1-*endo*-Phenyl)borneol (1.0 g, 4.3 mmol) was dissolved in 10 ml THF and cooled in an ice-bath. BuLi (1.6 M in hexane, 3.3 ml, 5.2 mmol) was added dropwise. The reaction mixture was kept at 0 °C for 1h. Propenoic acid chloride (0.7 ml, 8.7 mmol) in 5 ml THF was added. Stirring was continued at 0 °C another 4 h. Water was added, the mixture extracted twice with diethyl ether, and the combined organic layers were washed with water, brine, and dried with Na_2SO_4. Evaporation of the solvent yielded a pale yellow oil, which was subjected to flash chromatography with 10% diethyl ether/pentane as the eluent. Some solid material remained which turned out to be polymerized bornyl acrylate. A 767 mg yield (63%) of colorless oil was isolated.
IR (neat) 3059, 3018, 2958, 1727, 1635, 1618, 1403, 1179, 1048 cm^{-1}.
^{1}H-NMR 0.95 (m, 1H), 0.96 (s, 3H), 1.02 (s, 3H), 1.16 (s, 3H), 1.20 (m, 1H), 1.32 (m, 1H), 1.75 (m, 1H), 1.91 (t, 1H, J = 4 Hz), 2.47 (dt, 1H, J = 15, 4 Hz), 2.62 (d, 1H, J = 15 Hz), 5.79 (dd, 1H, J = 1.5, 10 Hz), 6.09 (dd, 1H, J = 10, 17 Hz), 6.33 (dd, 1H, J = 1.5, 17 Hz), 7.30 (b, 3H), 7.52 (d, 2H, J = 4Hz).
^{13}C-NMR 10.0 (CH_3), 20.7 (CH_3), 21.3 (CH_3), 25.8 (CH_2), 42.0 (CH_2), 45.1 (CH), 50.1 (C), 53.8 (C), 93.5 (C), 125.3 (CH), 126.5 (2 CH), 127.3 (CH), 127.6 (C), 129.7 (CH, CH_2), 141.8 (C), 163.8 (C).

1-(1-*endo*-(1-Naphthyl))bornylpropenoate (5b). The procedure described above was used with the following amounts: 1-(1-*endo*-(1-Naphthyl))borneol (2.5 g, 8.9 mmol), BuLi (1.6 M in hexane, 6.7 ml, 10.7 mmol), propenoic acid chloride (1.7 ml, 21.7 mmol). Chromatographic purification yielded a first fraction of elimination product **11** and a second fraction which on crystallization from ethanol yielded 951 mg ester (32%), white crystals; m.p. 119-125°C.



11

IR ($CHCl_3$) 3050, 2938, 1723, 1590-1640, 1400, 1183, 1044 cm^{-1}.
^{1}H-NMR 0.92 (m, 1H), 1.00 (s, 3H), 1.06 (m, 1H), 1.21 (s, 3H), 1.30 (s, 3H), 1.43 (m, 1H), 1.79 (m, 1H), 1.98 (t, 1H, J = 3 Hz), 2.56 (dt, 1H, J = 15, 3 Hz), 3.00 (d, 1H, J = 15 Hz), 5.80 (dd, 1H, J = 1.5, 10 Hz), 6.12 (dd, 1H, J = 10, 17 Hz), 6.35 (dd, 1H, J = 1.5, 17 Hz), 7.36 (dd, 1H, J = 7, 8 Hz), 7.46 (t, 2H, J = 8 Hz), 7.77 (d, 2H, J = 8 Hz), 7.81 (d, 1H, J = 7 Hz), 8.57 (d, 1H, J = 8 Hz).
^{13}C-NMR 14.3 (CH_3), 21.0 (CH_3), 21.9 (CH_3), 25.6 (CH_2), 30.8 (CH_2), 42.4 (C), 45.5 (CH_2), 51.4 (CH), 55.4 (C), 94.8 (C), 124.3 (CH), 124.7 (CH), 124.8 (CH), 125.5 (CH), 127.9 (CH), 128.9 (CH_2), 129.3 (CH), 129.7 (CH), 130.1 (CH), 131.6 (C), 135.0 (C), 137.6 (C), 163.5 (C).
Anal. Calcd for $C_{23}H_{26}O_2$: C, 82.60; H, 7.84. Found: C, 82.6; H, 7.8.

Cycloaddition of Acetonitrile Oxide. Addition to **5a**. 1-(1-*endo*-Phenyl)bornylpropenoate (374 mg, 1.3 mmol) was dissolved in 5 ml benzene. Phenyl isocyanate (0.35 ml, 2.9 mmol) was added. Nitroethane (110 mg, 1.5 mmol) and triethyl amine (1 drop) in 5 ml benzene was added over a period of 3h. Stirring was maintained during 8h. The precipitated N,N-diphenylurea was filtered off and washed thoroughly with benzene. Evaporation of the solvent yielded a colorless syrup. Integration of isoxazoline C5-protons at $\delta \approx 4.9$ and $\delta \approx 4.4$ in the ^{1}H-NMR spectrum gave a regioisomeric ratio 13:1 and decoupling of the C4-protons at $\delta = 3.10$ followed by integration of the C5-protons at $\delta = 4.86$ and $\delta = 4.90$ gave a diastereomeric excess of 22% for the major regioisomer. Flash chromatography with 50% diethyl ether/pentane yielded 351 mg (79%) of one pure regioisomer, enriched in d.e. to 32%. When this oil was dissolved in ethanol, white crystals precipitated, which turned out to be the pure minor diastereomer; m.p. 131-133°C.

Major diastereomer 1-(1-*endo*-phenyl)bornyl-((5R)-3-methyl-2-isoxazolin-5-yl)-carboxylate:
IR (CHCl3) 3054, 2954, 2871, 1734, 1442, 2225 cm^{-1}.
^{1}H-NMR[17] 0.86 (s, 3H), 0.93 (s, 3H), 1.02 (s, 3H), 2.00 (s, 3H), 2.48 (dt, 1H, J = 4, 15 Hz), 2.61 (d, 1H, J = 15 Hz), 3.10 (m, 2H), 4.86 (dd, 1H, J = 6, 10 Hz), 7.32 (m, 3H), 7.55 (d , 2H, J = 4 Hz).
Minor diastereomer 1-(1-*endo*-phenyl)bornyl-((5S)-3-methyl-2-isoxazolin-5-yl)-carboxylate:
^{1}H-NMR 0.82 (m, 1H), 0.95 (s, 3H), 1.01 (s, 3H), 1.15 (m, 1H), 1.16 (s, 3H), 1.28 (m,1H), 1.73 (m,1H), 1.90 (t, 1H, J = 4 Hz), 2.00 (s, 3H), 2.43 (dt, 1H, J = 4, 15 Hz), 2.61 (d, 1H, J = 15 Hz), 3.11 (m, 2H), 4.90 (dd, 1H, J = 6, 9 Hz), 7.31 (bm, 3H), 7.48(bd , 2H).
Anal. Calcd for $C_{21}H_{27}NO_3$: C, 73.87; H, 7.97; N, 4.10. Found: C, 72.9; H, 8.0; N, 4.3.
Addition to **5b.** The procedure above was followed with 1-(1-*endo*-(1-naphthyl))bornylpropenoate (300 mg, 0.9 mmol) and phenyl isocyanate (0.3 ml, 2.8 mmol) in 7 ml benzene. Nitroethane (0.1 ml, 1.4 mmol) and triethyl amine (1 drop) in 3 ml benzene was added during 2h. The crude product contained cycloadducts with a regioisomeric ratio of 15:1 and a diastereomeric excess of 68% according to ^{1}H-NMR. Chromatographic purification (50% diethyl ether/pentane) gave 332 mg (94%) of the major regioisomer with a d.e. of 74%.
Major diastereomer: ^{1}H-NMR 0.97 (s, 3H), 1.00 (m, 1H), 1.20 (s, 3H), 1.21 (m, 1H), 1.28 (s, 3H), 1.43 (m, 1H), 1.77 (m, 1H), 1.95 (s, 3H), 1.96 (m, 1H), 2.46 (m, 1H), 2.99 (m, 3H), 4.90 (dd, 1H, J = 7, 11 Hz), 7.42 (m, 3H), 7.78 (m, 3H), 8.64 (d, 1H, J = 8 Hz).
Minor diastereomer: ^{1}H-NMR (significant peaks) 2.84 (dd, 1H, J = 6, 17 Hz), 3.08 (m, 1H), 4.95 (dd, 1H, J = 6, 11 Hz), 8.57 (d, 1H, J = 8 Hz).

Addition of 1-Pyrroline-1-oxide. Addition to **5a.** Freshly distilled pyrrolidine (310 mg, 4.0 mmol) and SeO_2 (24 mg, 0.2 mmol) in 5 ml acetone was cooled to 0°C. Aqueous 30% H_2O_2-solution (367 mg, 3.3 mmol) was added during 30 min. and the mixture was stirred at room temperature for 3h.
1-(1-*endo*-Phenyl)bornylpropenoate (204 mg, 0.7 mmol) in 5 ml CH_2Cl_2 was added and the reaction was stirred for 8 h. The solvents were removed by evaporation and the remaining mixture was extracted between diethyl ether and water twice, and the combined organic layers were dried with $MgSO_4$. Evaporation of the solvent gave a brown oil, which according to ^{1}H-NMR contained a 1:1 mixture of *cis* and *trans* isomers of 1-(1-*endo*-phenyl)bornyl-(pyrrolidino[1,2-*c*]isoxazolidin-2-yl)carboxylate. Flash chromatography with 75% diethyl ether/pentane gave two major fractions; 92 mg (37%) *trans* isomer and 80 mg (32%) *cis* isomer.
Trans isomer: ^{1}H-NMR[17] 0.82 (m, 1H), 0.94 (s, 3H), 1.01 (s, 3H), 1.17 (s, 3H), 1.27 (m, 1H), 1.59 (m, 1H), 1.73 (m, 2H), 1.90 (t, 1H, J = 4 Hz), 2.22 (m, 1H), 2.44 (d, 1H, J = 15, 4 Hz), 2.61 (d, 1H, J = 15 Hz), 2.71 (ddd, 1H, J = 6, 8, 12 Hz), 3.03 (dt , 1H, J = 13, 8 Hz), 3.28 (ddd, 1H, J = 4, 6.5, 13 Hz), 3.69 (m, 1H), 4.48 (dd, 1H, J = 6, 8 Hz), 7.29 (b, 3H), 7.47 (b, 2H).
Cis isomer: IR (neat) 3062, 2930, 1736, 1453, 1180, 1044 cm^{-1}.
^{1}H-NMR[17] 0.79 (m, 1H), 0.92 (s, 3H), 0.97 (s, 3H), 1.11 (s, 3H), 1.20 (m, 1H), 1.59 (m, 1H), 1.68 (m, 2H), 1.89 (t, 1H, J = 4 Hz), 2.11 (m, 1H), 2.42 (dt, 1H, J = 15, 4 Hz), 2.59 (d, 1H, J = 15 Hz), 2.76 (m, 1H), 2.97 (m , 1H), 3.40 (m, 1H), 3.73 (m, 1H), 4.42 (t, 1H, J = 8 Hz), 7.28 (b, 3H), 7.47 (b, 2H).
Anal. Calcd for $C_{23}H_{31}O_3N$: C, 74.76; H, 8.46; N, 3.79. Found: C, 73.2; H, 8.3; N, 3.7.
Addition to **5b.** Same procedure and work-up as above, with 1-(1-*endo*-(1-naphthyl))bornylpropenoate (212 mg, 0.6 mmol). A 2:1 ratio between the *cis*/*trans* isomers of 1-(1-*endo*-(1-naphthyl))bornyl-(pyrrolidino[1,2-*c*]isoxazolidin-2-yl)carboxylate was measured by ^{1}H-NMR spectroscopy. Separation of the isomers with flash chromatography (75% diethyl ether/pentane) yielded 54 mg (20%) *trans* isomer and 94 mg (36%) *cis* isomer.

Trans isomer: ^{1}H-NMR[17] 0.98 (s, 3H), 1.20 (s, 3H), 1.35 (s, 3H), 1.42 (m, 1H), 1.55 (m, 1H), 1.72 (m, 2H), 1.90 (m, 1H), 1.96 (t, 1H, J = 3 Hz), 2.06 (ddd, 1H, J =12, 8, 3.5), 2.52 (dt, 1H, J = 16, 3Hz), 2.64 (ddd, 1H, J = 4.5, 8, 12 Hz), 2.96 (d, 1H, J = 16 Hz), 2.99 (dt , 1H, J = 13, 8 Hz), 3.32 (ddd, 1H, J = 4.5, 7.5, 13, Hz), 3.59 (m, 1H), 4.49 (dd, 1H, J = 4.5, 8 Hz), 7.36 (m, 2H), 7.43 (t, 1H, J = 7 Hz), 7.75 (d, 2H, J = 7 Hz), 7.81 (m, 1H), 8.63 (m, 1H).
Cis isomer: ^{1}H-NMR[17] 0.97 (s, 3H), 1.18 (s, 3H), 1.29 (s, 3H), 1.42 (m, 1H), 1.54 (m, 1H), 1.67 (m, 2H), 1.78 (m, 2H), 1.94 (m, 1H), 1.96 (t, 1H, *J* = 4 Hz), 2.49 (dt, 1H, *J* = 15.5, 3Hz), 2.61 (dt, 1H, *J* = 12, 8 Hz), 2.97 (dt, 1H, *J* = 12, 8 Hz), 2.98 (d, 1H, *J* = 15.5 Hz), 3.37 (ddd, 1H, *J* = 4.5, 7.5, 12, Hz), 3.66 (t, 1H, *J* = 5,8), 4.47 (t, 1H, *J* = 8 Hz), 7.38 (m, 2H), 7.44 (t, 1H, *J* = 7 Hz), 7.74 (m, 2H), 7.82 (m, 1H), 8.56 (m, 1H).
Additions to **1a** and **1b.** The procedure described above was tried for both substrates, but no trace of product could be detected. A small amount of methanol was added for the sake of homogeneity and the reaction mixture was refluxed, but still no reaction occurred. The solvent was exchanged for toluene and the reaction mixtures refluxed for several days, but the crotonate substrates still failed to react and were completely recovered. Attempts to first isolate the nitrone and then react it with **1a** also failed. The reaction of 1-pyrroline-1-oxide with methyl crotonate was performed in refluxing toluene.

X-ray Crystallography of Esters 1b and 5b. Colorless crystals of **1b** were obtained from an ethanolic solution and a crystal with the dimensions 0.42x0.42x0.20 mm was used for data collection on an Enraf-Nonius CAD4F-11 diffractometer. The angular settings of 25 reflections with 2 θ in the range of 30-55° were measured to calculate the cell parameters. Intensity data for reflections with θ < 65° were collected by the θ/2θ scan mode using monochromated Cuα radiation. Three intensity control reflexions, which were measured every 2 h, dropped to about 70% of their original values. The intensities were rescaled to account for this decay. A total of 1918 unique reflexions satisfying I > 2.5σ(I) were considered observed. No absorption correction was made.
Crystal data: $C_{24}H_{30}O_2$, M = 350.38, orthorhombic, $P2_12_12_1$, *a* = 9.759(4), *b* = 13.664(5), *c* = 14.774(5) Å, V = 1966.0 Å^3, Z = 4, d_{calc} = 1.184 gcm^{-3}, μ = 0.57 mm^{-1}.
The NRCVAX system[18] was used for all calculations. Application of direct methods provided the non-hydrogen atom positions. Hydrogen atoms (except those connected to methyl groups) were included at expected positions. Refinement was carried out by the full-matrix least-squares refinement using anisotropic temperature factors for the non-hydrogen atoms. The hydrogen atom parameters were not refined. After refinement the *R* and R_w values were 0.120 and 0.106, respectively. A final difference electron density map exhibited no peaks higher than 0.36 and -0.35 eÅ^{-3}.
The crystal structure of **5b** was determined in the same way as **1b.**
Crystal data: $C_{23}H_{28}O_2$, M = 336.36, triclinic, $P2_1$, *a* = 9.050(3), *b* = 7.187(7), *c* = 14.456(5) Å, β = 104.29(3)°, V = 911.1 Å^3, Z = 2, d_{calc} = 1.226 gcm^{-3}, μ = 0.56 mm^{-1}.
The refinement, however, did not converge properly. The temperature factors of the naphthyl group became abnormally large indicating a possible disorder of this moiety. The refinement was terminated with *R* = 0.166 and R_w = 0.123.

References and Notes

1. Olsson, T.; Stern, K.; Sundell, S. *J. Org. Chem.*, **1988**, *53*, 2468.
2. Huisgen, R. *J. Org. Chem.*, **1976**, *41*, 403.
3. Curran, D. P.; Kim, B. H.; Piyasena, H. P.; Loncharich, R. J.; Houk, K. N. *J. Org. Chem.*, **1987**, *52*, 2137.

4. Curran, D. P.; Kim, B. H., Daugherty, J., Heffner, T. A. *Tetrahedron Letters*, **1988**, *29*, 3555.
5. Allinger, N. L.; Yuh, Y. *QCPE*, **1976**, *12*, 318.
6. Bergdahl, M.; Nilsson, M.; Olsson, T.; Stern, K. *Manuscript.*
7. Oppolzer, W.; Poli, G.; Starkemann, C.; Bernardinelli, G. *Tetrahedron Letters*, **1988**, *29*, 3559.
8. The product composition has been thoroughly analyzed in: Ali, Sk.; Khan, J. H.; Wazeer, M. I. H. *Tetrahedron*, **1988**, *44*, 5911.
9. Tufariello, J. J.; Lee, G. E.; Senaratne, A. P.; Al-Nuri, M. *Tetrahedron Letters*, **1979**, 4359.
10. Joucla, M.; Tonnard, F.; Grée, D.; Hamelin, J. *J. Chem. Res. (M)*, **1978**, 290.
11. A program package for molecular modeling on the HP SRX-series has recently been developed by T. Olsson.
12. Based on the Karplus equations.
13. Coxon, J. M.; Steele, P. J.; Coddington, J. M.; Rae, I. D.; Jones, A. J. *Aust. J. Chem.*, **1978**, *31*, 1223.
14. Kaiser, E. M.; Woodruff, R. A. *J. Org. Chem.*, **1970**, *35*, 1198.
15. Mukaiama, T.; Hoshino, T. *J. Am. Chem. Soc.*, **1960**, *82*, 5339.
16. Murahashi, S.-I.; Shiota, T. *Tetrahedron Letters*, **1987**, *28*, 2383.
17. Not all protons of the borneol part of the molecule are listed.
18. Gabe, E. J.; Lee, F. L., LePage, Y. *The NRCVAX Crystal Structure System.* In *Crystallographic Computing 3, Data Collection, Structure Determination, Proteins and Databases*, edited by G. M. Sheldrick, C. Kruger, and R. Goddard, Clarendon Press, Oxford, **1985**, 167-174.