Asymmetric Induction in Nitrile Oxide Cycloadditions to Optically Active Acrylates. Comparisons of Acrylate Conformations in Thermal and Acid-Catalyzed 1,3-Dipolar and Diels-Alder Cycloaddition Transition States

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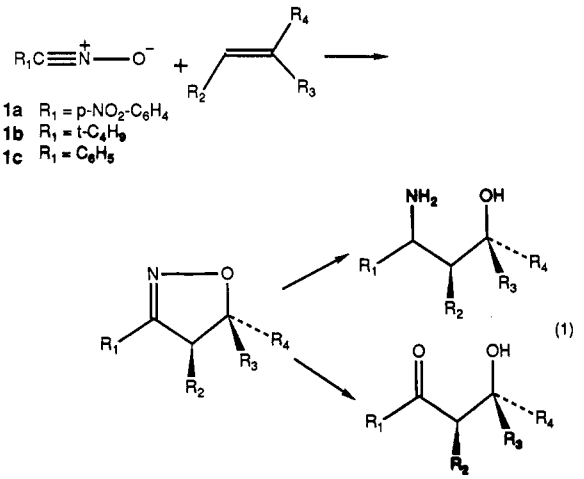
Nitrile oxides undergo cycloadditions to several different chiral acrylates to give 0–56% π-facial stereoselectivity. In cases where stereoselectivity is significant, the structure of the major product is consistent with a transition state with an s-cis conformation of the acrylate. Thermal Diels–Alder reactions of cyclopentadiene with these acrylates have also been studied, since the literature only gives results of catalyzed reactions. The major products are consistent with transition states which involve a small s-cis preference, by contrast to the substantial s-trans preferences required to explain results found by Oppolzer for the catalyzed reactions of the same acrylates. Model theoretical calculations also are in accord with these models, favoring an s-cis preference in the thermal reaction and an s-trans in the catalyzed.

Introduction

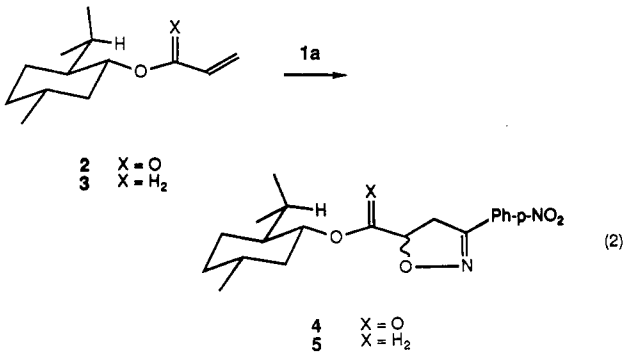
The products of nitrile oxide cycloadditions to alkenes (2-isoxazolines) are versatile intermediates in synthesis.[2] For example, reductive cleavage of the heterocyclic ring can be controlled to provide either β-amino alcohols or β-hydroxy ketones selectively (eq 1). Overall, this approach provides a strategic alternative to aldol-based reaction sequences. The utility of the cycloaddition strategy would be greatly enhanced if 2-isoxazolines could be prepared readily in optically active form. The use of optically active nitrile oxides for this purpose has been investigated by others.[3] Although nitrile oxides are relatively small cycloaddends and there was no a priori reason to expect high stereoselectivities, we felt that the reaction could be important, if successful. Since our two laboratories, housed in the same department at the time, independently conceived this project, we anticipate that many other laboratories are involved in similar studies.



We now report that optically active isoxazolines can be prepared through the cycloadditions of nitrile oxides to optically active acrylates. Only modest degrees of asymmetric induction are presently achievable, even with acrylates which give very high stereoselectivities in Lewis acid catalyzed Diels–Alder reactions. Nevertheless, the results are of considerable mechanistic interest, because they provide information about the conformation of the acrylate in the transition state of the reaction. For comparison, we have also investigated the thermal Diels–Alder reaction of cyclopentadiene with one of the optically active acrylates used in our nitrile oxide studies.[4] Our experimental results indicate that the preferred conformation of the acrylate in both thermal, 1,3-dipolar and Diels–Alder cycloadditions is s-cis. By contrast, the s-trans conformation is known to be favored for Lewis acid catalyzed Diels–Alder reactions. Computational models support these conclusions.

Results

A variety of chiral auxiliaries have been developed which are suitable for use in the asymmetric Diels–Alder reaction.[4,5] We have studied whether these are useful in the nitrile oxide 1,3-dipolar cycloaddition reaction. Reactions of *p*-nitrobenzonitrile oxide (**1a**) with optically active menthyl acrylate (**2**) or menthyl allyl ether (**3**), both prepared from (−)-menthol, gave mixtures of diastereomeric adducts **4** and **5**, respectively (eq 2). The diastereomer ratio was readily ascertained from NMR spectra. There



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(2) Leading references: (a) Curran, D. P. *J. Am. Chem. Soc.* **1983**, *105*, 5826. (b) Kozikowski, A. P. *Acc. Chem. Res.* **1984**, *17*, 410. (c) Jäger, V.; Müller, I. *Tetrahedron* **1985**, *41*, 3519. (d) Ko, S. S.; Confalone, P. *Tetrahedron* **1985**, *41*, 3511. (e) Torssell, K. B.; Hazell, R. C.; Hazell, R. G. *Tetrahedron* **1985**, *41*, 5569. (f) Curran, D. P.; Scanga, S. A.; Fenk, C. J. *J. Org. Chem.* **1984**, *49*, 3474.

(3) Kozikowski, A. P.; Kitagawa, Y.; Springer, J. P. *J. Chem. Soc., Chem. Commun.* **1983**, 1460. Jones, R. H.; Robinson, G. C.; Thomas, E. J. *Tetrahedron* **1984**, *40*, 177. Larsen, K. E.; Torssell, K. B. G. *Tetrahedron* **1984**, *40*, 2985.

(4) Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 876.

(5) Paquette, L. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: New York, 1984; Vol. 3, pp 455–478.

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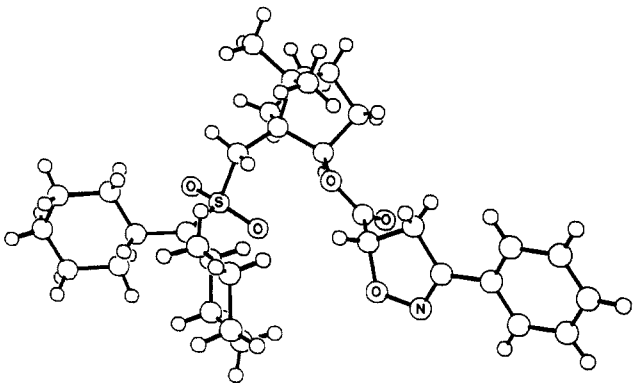
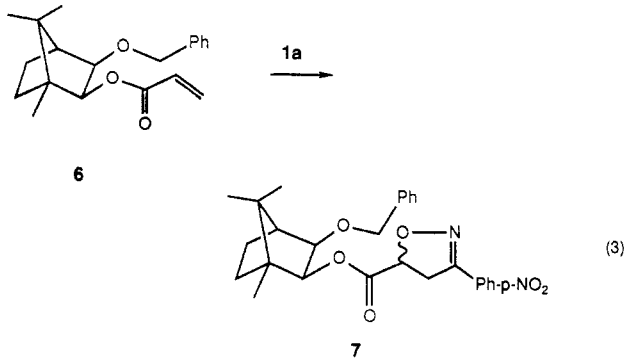


Figure 1. ORTEP drawing of X-ray structure of 14.[11]

was less than 4% excess of one diastereomer over the other in either cycloaddition. For this reason, no attempt was made to assign the configuration of the major products of these reactions. In the thermal Diels–Alder reaction of menthyl acrylate with cyclopentadiene, less than 10% stereoselectivity is observed, but this can be increased to 85% by Lewis acid catalysis.[6]

Acrylate **6** was prepared according to the method of Oppolzer.[7] The cycloaddition of **1a** with **6** gave **7** as a 55/45 mixture of diastereomers (10% de) as determined by NMR (eq 3). Again, the configuration of the major

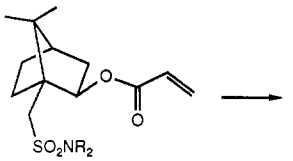


(3)

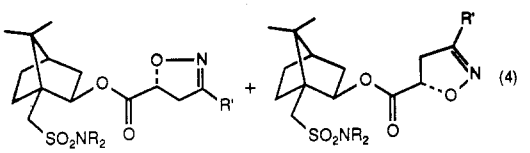
diastereomer was not determined. By contrast, Oppolzer has reported an 88% de in the Lewis acid catalyzed ($TiCl_4$) Diels–Alder reaction of **6** with cyclopentadiene.[7] Helmchen has reported similar asymmetric induction levels with related acrylates.[8]

Undaunted by our continuing, if not surprising, lack of success, we next prepared the Oppolzer sulfonamides **8a** and **8b** from (+)-camphorsulfonyl chloride.[9] These acrylates exhibit extremely high selectivities in Lewis acid catalyzed Diels–Alder reactions with cyclopentadiene, presumably because one face of the acrylate is nearly completely inaccessible due to shielding by the bulky sulfonamide. In order to account for the structure of the major product, Oppolzer has suggested that this face shielding must be the result of a preferred conformation of the acrylate in the transition state. In particular, Oppolzer postulates (1) a relatively rigid s-trans conformation of the acrylate, (2) a syn conformation of the ester (dihedral angle O=COC = 0°), and (3) the eclipsing of the CH bond of the chiral auxilary with the O–C bond (dihedral angle COCH = 0°).[4,9]

Cycloaddition of *p*-nitrobenzonitrile oxide (**1a**) to **8a** produced diastereomers **9** and **10** in a 66/34 ratio (32% de) as determined by integration of the NMR spectrum (eq 4). Once again, the configurations were not rigorously determined. However, the results outlined below leave little doubt as to the correctness of the assigned structures.



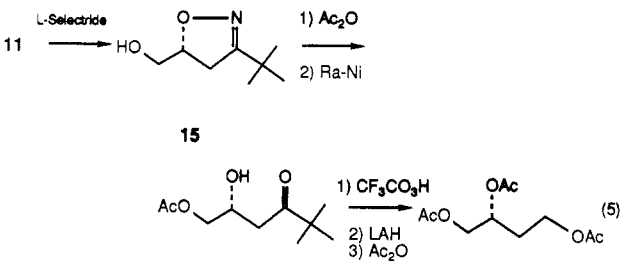
8a R = i-Pr
8b R = cyclohexyl



(4)

9	R = i-Pr ; R' = p-NO_2-C_6H_4	**10**
11	R = C_6H_{11} ; R' = t-C_4H_9	**12**
13	R = C_6H_{11} ; R' = C_6H_5	**14**

The reaction of 2,2-dimethylpropanenitrile oxide (pivalonitrile oxide) (**1b**) with the dicyclohexylsulfonamide **8b** produced **11** and **12** in a ratio of 77/23 (54% de). In this case, unequivocal proof of the configuration of the major diastereomer was secured as outlined in eq 5.[2f]



(5)

Separation of the diastereoisomers was accomplished by medium-pressure liquid chromatography (MPLC) to give homogeneous **11** and **12** in 43% and 13% yields, respectively. Reduction of **11** with L-Selectride cleaved the auxiliary selectively to produce optically pure **15**. Notably, the isoxazoline ring was stable to these reduction conditions. Acetylation, followed by standard isoxazoline cleavage, gave hydroxy ketone **16**. Baeyer–Villiger oxidation, followed by reduction and acetylation provided (*R*)-(+)-butanetriol triacetate (**17**) [α_D = +19.6 ($CHCl_3$, c 0.46)]. This compares favorably to the literature value[10] for the enantiomer, (*S*)-(−)-**16** [α_D = −20.9 ($CHCl_3$, c 1.84)], prepared from (*S*)-(−)-malic acid.

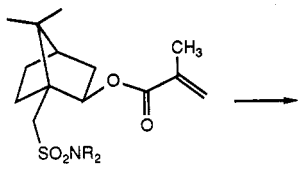
Cycloaddition of benzonitrile oxide (**1c**) with **8b** provided a similar (78/22, 56% de) ratio of diastereometers **13** and **14**. Again the diastereomers were separated by MPLC and, in this case, suitable crystals for X-ray analysis were obtained from the minor isomer **14**.[11] An ORTEP drawing of this structure is shown in Figure 1.[11] In both

(6) Morrison, J. D.; Mosher, H. S., *Asymmetric Organic Reactions*; Prentice-Hall: New York, 1971; pp 252–257.
(7) Oppolzer, W.; Chapuis, C.; Dao, G. M.; Reichlin, D.; Godel, T. *Tetrahedron Lett.* **1982**, *23*, 4781.
(8) Poll, T.; Helmchen, G.; Bauer, B. *Tetrahedron Lett.* **1984**, *25*, 2191.
(9) Oppolzer, W.; Chapuis, C.; Bernardinelli, G. *Tetrahedron Lett.* **1984**, *67*, 1397.
(10) Poulter, C. D.; Muscio, O. J.; Goodfellow, R. *Biochemistry* **1974**, *13*, 1530.
(11) X-ray data were obtained at the Pittsburgh Diffraction Laboratory by Jamie Abola and Jeffrey Mandel and will be reported in full in the Ph.D. dissertation of B.H.K. Additional experimental details are also available in the Ph.D. dissertation of H.P.P, University of Pittsburgh, 1985.

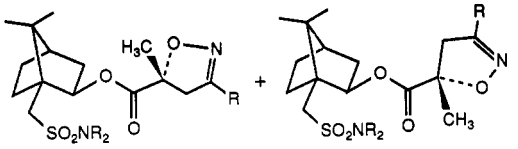
cases, the major isomer possesses the same configuration at the newly generated stereogenic center. Assuming that attack occurs primarily from the side of the acrylate away from the sulfonamide moiety, the acrylate must have the s-cis conformation in the transition state for formation of the major product.

The diastereomeric ratio observed was relatively constant under a variety of reaction conditions. Cycloadditions of **1c** with **8b** at 0 or −20 °C showed no detectable increase in product selectivity, while a cycloaddition with **1b** at 185 °C showed only a modest decrease in selectivity (11/12, 66/34). Variation of solvent also had little effect. Maximum selectivity for **1c** was obtained in benzene or toluene (77/23) with marginally lower ratios in hexane (76/24), ether (72/28), and dichloromethane (70/30). Finally, while Lewis acid additives provide dramatic rate and stereoselectivity increases in analogous Diels–Alder reactions,[4] no such effects were observed in the nitrile oxide cycloadditions. Attempted catalysis of the cycloaddition of **1b** with **8b** gave uniformly unsuccessful results. Addition of Et_2AlCl, $EtAlCl_2$, or $TiCl_4$ all resulted in significant decreases in both the rate of cycloaddition and the isolated yield of the products, without noticeably changing the diastereomer ratio. This is likely due to the fact that the nitrile oxide is an excellent Lewis base, and complexation effectively inhibits the reaction.

The cycloaddition of the α-methacrylate derivative **8c** with both **1b** and **1c** provided a 57/43 ratio of isomers. On the basis of similarities of the NMR spectra to those of previously assigned adducts (see Experimental Section), the major stereoisomers are tentatively assigned structures **18** and **20**, respectively. The major stereoisomers in the



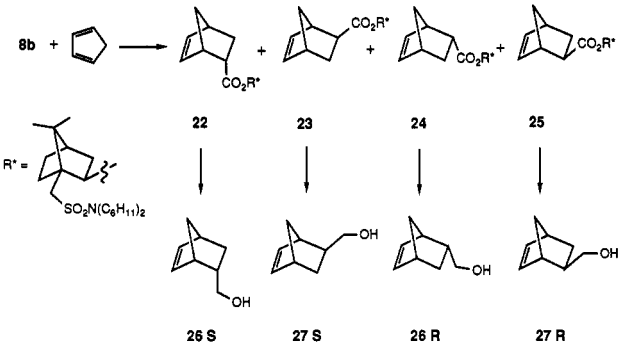
8c R = cyclohexyl



18 **20** R = Ph R = t-butyl **19** **21**

reaction of methacrylates have the same stereogenicity at the newly formed stereogenic center as the acrylate cycloadducts, but the selectivity is lower than in the acrylate cases. Assuming that nitrile oxide attack occurs only from the backside (away from the sulfonamide moiety), the methacrylate must have a very slight preference for the s-cis conformation in the transition state of the cycloaddition.

In order to determine whether the preference for a s-cis reactive conformation is a unique feature of nitrile oxide cycloadditions to acrylates or is normal for thermal cycloadditions, an investigation of the thermal Diels–Alder reaction of **8b** with cyclopentadiene was undertaken. The reaction occurs in benzene at room temperature to give all four possible products, **22–25**, in a 4.6/1.3/2.2/1 ratio as determined by analytical HPLC analysis of the crude reaction mixture. Structural assignments were made by diastereomer separation, reduction of the esters to primary alcohols, and correlation to the appropriate enantiomers



of endo- and *exo*-4-(hydroxymethyl)norbornenes[12] (**26** and **27**) as described in the Experimental Section. In the absence of catalyst, the overall endo/exo ratio is only 2.9/1, whereas only endo adducts are found in the catalyzed reaction. The diastereoselectivity in the endo adduct is very low (35% de), and for the exo adduct it is even smaller (13% de). Assuming that attack only occurs from the backside (away from the sulfonamide), there is a slight preference for the acrylate to have the s-cis conformation in the transition state of the uncatalyzed reaction. By contrast, the catalyzed reactions must involve a very high preference for the s-trans conformation.

Discussion and Computational Results

Assuming a high degree of π-face shielding in additions to acrylate **8b**, the results prove the preferred conformation of the acrylate in the transition states of thermal cycloadditions. The major 1,3-dipolar cycloadducts are derived from the s-cis conformer of the acrylate, while the minor cycloadducts are derived from the *s*-trans conformer. Furthermore, both major cycloadducts from the Diels–Alder reaction (endo and exo) are also derived from the s-cis conformer. A modest preference for thermal cycloadditions to proceed via the s-cis conformer is evident. This contrasts to the considerable s-trans preference deduced from Lewis acid catalyzed Diels–Alder cycloadditions of acrylates.[4]

In order to investigate these conformational preferences further, theoretical calculations were performed on the conformations of free acrylates, and on models for the transition states of acrylate cycloadditions. Full geometry optimizations with the 3-21G basis set and single-point calculations using the 6-31G* basis set[13] are described elsewhere.[14] The s-cis conformations of acrylic acid and methyl acrylate are predicted to be 0.6 and 0.7 kcal/mol, respectively, more stable than the s-trans conformations in the gas phase. In connection with the results reported here, we have optimized the geometries of various conformations of methacrylic acid. An α-methyl substituent on acrylic acid makes the s-trans conformation slightly more stable than the s-cis. The 3-21G calculations predict that the s-trans conformation of α-methacrylic acid is 0.3 kcal/mol more stable than the s-cis.[15]

The trends identified for the ground states are parallel to those found for the transition states. Thus, whereas acrylates prefer the s-cis conformation, there is essentially

(12) Berson, J. A.; Walia, J. S.; Remanick, A.; Suzuki, S.; Reynolds-Warnhoff, P.; Willner, D. *J. Am. Chem. Soc.* **1961**, *83*, 3986.

(13) Binkley, J. S.; Frisch, M.; Raghavachari, K.; DeFrees, D. J.; Schlegel, H. B.; Whiteside, R.; Fluder, E.; Seeger, R.; Pople, J. A. GAUSSIAN 82, Carnegie-Mellon University, Pittsburgh, PA.

(14) Loncharich, R. J.; Schwartz, T. R.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 14. Experimental studies, which disagree about the preferred conformations of acrylates in solution, are discussed there.

(15) Similar trends in conformations are found in unsaturated ketones: Chamberlin, A. R.; Reich, S. H. *J. Am. Chem. Soc.* **1985**, *107*, 1440.

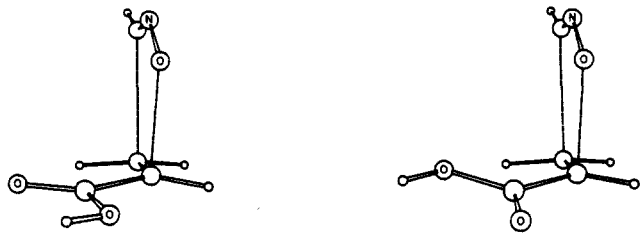


Figure 2. Partially optimized transition-state models for the reactions of fulminic acid with *s-cis*- and *s-trans*-acrylic acid.

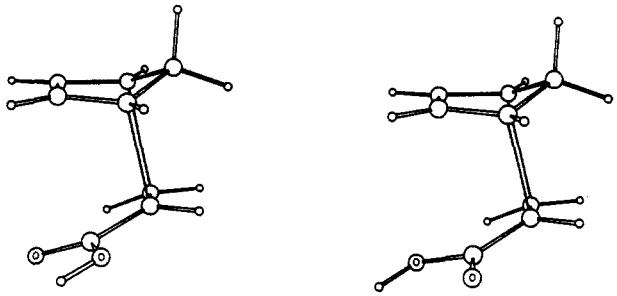


Figure 3. Partially optimized transition-state models for the reactions of cyclopentadiene with *s-cis*- and *s-trans*-acrylic acid.

no preference for methacrylate. The effect of the α-methyl on the ground-state conformation is to disfavor the s-cis conformation by about 1 kcal/mol, and the effect on the transition state is probably similar. The aforementioned computational study on acrylates[14] predicts a very large trans preference upon Lewis acid complexation, in accord with Oppolzer's deductions from catalyzed cases.[4]

As part of this project, we have also carried out calculations on the preferred conformation of ester groups in the transition states of nitrile oxide and cyclopentadiene cycloadditions. These are huge systems, so only model calculations can be performed. We described earlier a 3-21G transition structure for the cycloaddition of fulminic acid to ethylene.[16] We have also located a constrained-synchronous (C_s) transition structure by MNDO techniques for the cycloaddition of cyclopentadiene to ethylene.[17] In each case, one of the hydrogens was replaced by a carboxyl group, and the carboxyl group was optimized starting from s-cis and s-trans conformations, using the 3-21G basis set.[13] These partially optimized structures are shown in Figures 2 and 3. The partially optimized s-cis transition state in the fulminic acid cycloaddition (Figure 2) is predicted to be 1.2 kcal/mol more stable than the s-trans. For the endo Diels–Alder reaction of cyclopentadiene, the s-cis transition-structure model is found to be 1.7 kcal/mol more stable than the s-trans. While these energy differences are not expected to be very accurate, we believe that these are qualitatively correct and account for the significant stereoselectivities calculated for such reactions.

We have also reported elsewhere the effect of Lewis acid complexation on the conformation of acrylates.[14] Our calculations indicated that the small preference for the s-cis conformation in acrylic acid and its esters becomes a large preference for the s-trans conformation upon complexation.[14] While we have not carried out transition-model calculations, we believe that the large s-trans preference of complexed acrylates will survive in these transition states. The preference for the s-cis conformation in the thermal reactions and s-trans in the catalyzed thus parallel the ground-state preference observed for the isolated dienophiles.

(16) Brown, F. K.; Houk, K. N.; Kozikowski, A. P., in preparation.
(17) Brown, F. K.; Houk, K. N.; Burnell, J. D.; Valenta, Z. *J. Org. Chem.*, in press.

Experimental Section

General. All melting points and boiling points are uncorrected. Kugelrohr boiling points refer to oven temperature. All reactions were performed under nitrogen atmosphere. ^{1}H NMR spectra were recorded on a Bruker Model WH-300 spectrometer in $CDCl_3$ unless otherwise indicated. Infrared spectra were obtained on a Beckman Acculab 4 or a Perkin-Elmer Model 247 spectrophotometer in $CHCl_3$. Low-resolution mass spectra were obtained on an LKB-9000, and high-resolution spectra were obtained on a Varian MATCH-5DF. Optical rotations were measured at ambient temperature on a Perkin-Elmer Model 241 polarimeter. X-ray structures were obtained on a Nicolet P3 diffractometer. All reactions were performed under nitrogen atmosphere with the exception of the Raney nickel reductions, which were conducted under hydrogen. Reagents and solvents were purified as follows: triethylamine, dichloromethane, and toluene, distilled from calcium hydride; benzene, THF, and ether, distilled from sodium/benzophenone. Stable solutions of 2,2-dimethylpropane nitrile oxide were prepared by addition of triethylamine to trimethylacetaldoxime chloride in toluene followed by centrifugation. With storage at −20 °C, the solution remained useful for about 3 weeks.

Flash and medium-pressure (MPLC) column chromatography were performed with Keiselgel 60 (230–400 mesch ASTM). Medium-pressure chromatography was also done on prepacked EM lobar LiChroprep Si 60 columns. Semipreparative HPLC refers to separation on a Waters PrepLC/System 500A with a 25-mm steel column packed with Keiselgel 60 (230–400 mesh). Analytical HPLC was performed with Waters Porasil steel column (8 mL/min) or Radial-Pak B liquid chromatography cartridge (2 mL/min).

2,2-Dimethylpropanenitrile Oxide Cycloadducts 11 and 12. To a solution of the acrylate **8b** (302.2 mg, 0.699 mmol) in toluene (10 mL) was added 2,2-dimethylpropanenitrile oxide (11.9 mL, 0.068 M in toluene, 0.803 mmol). The reaction mixture was stirred at room temperature for 6 h. Evaporation of solvent gave 433.7 mg of the crude diastereomeric mixture of **11** and **12**. The diastereomer ratio (77:23) was determined by HPLC. Two diastereomers were separated by MPLC (14% EtOAc/hexane). Major product **11** (more polar, 158 mg, 43%): mp 76–78 °C; ^{1}H NMR ($CDCl_3$) δ 5.05–4.88 (2 H, m), 3.42–3.12 (5 H, m), 2.65 (1 H, d, J = 13 H), 2.10–1.10 (27 H, m), 1.20 (9 H, s), 1.00 (3 H, s), 0.87 (3 H, s); IR ($CHCl_3$) 1730 cm^{-1}; MS m/e 550 (M^+), calcd for $C_{30}H_{50}N_2O_5S$ 550.3770, found 550.3436. Minor product **12** (less polar, oil, 49.1 mg, 13%): ^{1}H NMR ($CDCl_3$) δ 5.13–5.01 (1 H, m), 4.90 (1 H, dd, J = 11, 7.5 Hz), 3.40–3.21 (4 H, m), 3.14 (1 H, dd, J = 16.8, 11.3 Hz), 2.67 (1 H, d, J = 13.4 Hz), 2.10–1.10 (27 H, m), 1.20 (9 H, s), 1.00 (3 H, s), 0.87 (3 H, s); IR ($CHCl_3$) 1730, 1450, 1320 cm^{-1}.

Benzonitrile Oxide Cycloadducts 13 and 14. To a mixture of the acrylate **8b** (21.9 mg, 0.0485 mmol) and phenylhydroximic acid chloride (11.0 mg, 0.07 mmol) in benzene (4 mL) at 0 °C was added triethylamine (9.4 μL, 0.07 mmol). The reaction mixture was stirred at 0 °C for 6 h, diluted with toluene, and poured into water. The reaction mixture was washed with water (×3) and brine and then dried over $MgSO_4$. Solvent evaporation gave 32.9 mg of the crude diastereomeric mixture of **13** and **14**. The diastereomer ratio (78:22) was determined by HPLC. The two diastereomers were separated by MPLC (12% EtOAc/hexane). Major product **13** (more polar): mp 102–104 °C; ^{1}H NMR ($CDCl_3$) δ 7.80–7.63 (2 H, m), 7.53–7.35 (3 H, m), 5.16 (1 H, dd, J = 11.5, 6.2 Hz), 5.04 (1 H, m), 3.74 (1 H, dd, J = 17, 6.2 Hz), 3.60 (1 H, dd, J = 17, 11.6 Hz), 3.48–3.20 (3 H, m), 2.66 (1 H, d, J = 13.3 Hz), 2.10–1.03 (27 H, m), 0.97 (3 H, s), 0.87 (3 H, s); IR ($CHCl_3$) 3010, 1730, 1520, 1320 cm^{-1}; MS, m/e 570 (M^+), calcd for $C_{32}H_{46}N_2O_5S$ 570.3127, found 570.3130. Minor product **14** (less polar): mp 226–228 °C; ^{1}H NMR ($CDCl_3$) δ 7.76–7.61 (2 H, m), 7.50–7.35 (3 H, m), 5.21–5.05 (2 H, m), 3.75 (1 H, dd, J = 17, 8.7 Hz), 3.57 (1 H, dd, J = 17, 12.2 Hz), 3.37–3.12 (3 H, m), 2.66 (1 H, d, J = 13 Hz), 2.10–1.10 (27 H, m), 1.02 (3 H, s), 0.88 (3 H, s); IR ($CHCl_3$) 3020, 1730, 1520, 1420 cm^{-1}. This minor product **14** was analyzed by X-ray structure analysis. A single-crystal for X-ray was

prepared by the vapor diffusion technique.

(*N*,*N*-Dicyclohexylsulfamoyl)isobornyl Methacrylate 8c. To 2-chloro-*N*-methylpyridinium iodide (532.9 mg, 2.02 mmol) was added to a mixture of the isoborneol sulfonamide (111.6 mg, 0.28 mmol), $N(n\text{-Pr})_3$ (746 μL, 3.92 mmol), and methacrylic acid (166 μL, 1.96 mmol) in toluene (8 mL). The reaction mixture was heated at reflux for 5 h, and then additional 2-chloro-*N*-methylpyridinium iodide (243 mg, 0.95 mmol), methacrylic acid (81 μL, 0.95 mmol), and $N(n\text{-Pr})_3$ (362 μL, 1.9 mmol) were added. After the mixture was heated for 6 h, 2-chloro-*N*-methylpyridinium iodide (289 mg, 1.13 mmol) was added and the mixture refluxed overnight. The reaction mixture was then diluted with toluene and washed with 10% HCl, saturated $NaHCO_3$, and brine. Solvent evaporation gave 318.8 mg of the crude product **8c**. The product was purified by flash chromatography (SiO_2, 7% EtOAc/hexane). Early fractions gave the recovered starting alcohol (42 mg) followed by **8c** (34.5 mg, 26%): mp 166–168 °C; ^1H NMR ($CDCl_3$) δ 6.03 (1 H, s), 5.54 (1 H, s), 5.09 (1 H, dd, J = 8.3, 3.4 Hz), 3.37–3.10 (3 H, m), 2.68 (1 H, d, J = 13.2 Hz), 1.97 (3 H, s), 1.97–0.97 (27 H, m), 1.04 (3 H, s), 0.90 (3 H, s); IR ($CHCl_3$) 2940, 1710, 1330 cm^{-1}; MS, m/e 465 (M^+), calcd for $C_{26}H_{43}NO_4S$ 465.2913, found 465.2912.

Benzonitrile Oxide Cycloadducts with the Methacrylate 8c. To a mixture of the methacrylate **8c** (5.8 mg, 0.0125 mmol) and phenyl hydroximic acid chloride (11.0 mg, 0.07 mmol) in toluene (4 mL) was added triethylamine (9.9 μL, 0.07 mmol). The reaction mixture stirred at room temperature for 9 h. Filtration and solvent removal gave the crude products **18** and **19**. The diastereomer ratio (56:44) was determined by analytical HPLC and ^1H NMR (300 MHz): ^1H NMR ($CDCl_3$, mixture of **18** and **19**) δ 7.75–7.35 (5 H, m), 5.09, 5.00 (1 H, both dd, J = 9, 2 Hz), 4.02, 3.85 (1 H, both d, J = 16.6 Hz), 3.42–3.00 (4 H, m), 2.66, 2.61 (1 H, both d, J = 4.4 Hz), 2.10–1.00 (30 H, m), 1.03, 0.89 (3 H, both s), 0.97, 0.87 (3 H, both s).

2,2-Dimethylpropionitrile Oxide Cycloadducts with 8c. To a mixture of the methacrylate **8c** (7.5 mg, 0.016 mmol) and trimethylacetaldoximic acid chloride (12.1 mg, 0.089 mmol) in toluene (4 mL) was added triethylamine (12.4 μL, 0.089 mmol). The reaction mixture stirred at room temperature for 9 h. The diastereomer ratio of **20**/**21** (57:43) was determined by analytical HPLC and ^1H NMR (300 MHz): ^1H NMR ($CDCl_3$, mixture of **20** and **21**) δ 5.05, 4.95 (1 H, both m), 3.68–3.20 (4 H, m), 2.86–2.55 (2 H, m), 2.10–0.83 (36 H, m), 1.20, 1.18 (9 H, both s).

(*R*)-(−)-3-(1,1-Dimethylethyl)-5-(hydroxymethyl)-2-isoxazoline (15). To a solution of the cycloadduct **11** (628 mg, 1.14 mmol) in THF (12 mL) was added L-Selectride (1.0 M in THF, 4.56 mL, 4.56 mmol). The reaction mixture was stirred at room temperature overnight, transferred to an Erlenmeyer flask, and diluted with THF. After the addition of H_2O (1.0 mL), ethanol (3.7 mL), 3 N NaOH (4.95 mL), and 30% H_2O_2 (3.7 mL) at 0 °C, the aqueous phase was saturated with K_2CO_3. Extraction with Et_2O/THF (1:1), drying over $MgSO_4$, and evaporation of solvent gave 786.2 mg of the crude product. Flash chromatography (SiO_2, 300 mL, 15% EtOAc/hexane) gave 90% recovery of the isoborneol sulfonamide. Further elution with 55% EtOAc/hexane (400 mL) gave 160.4 mg (90%) of **15** as a clear oil: ^1H NMR ($CDCl_3$) δ 4.67 (1 H, m), 3.76 (1 H, dd, J = 11, 4.4 Hz), 3.55 (1 H, dd, J = 11, 5.3 Hz), 3.02 (1 H, dd, J = 16.8, 10.5 Hz), 2.88 (1 H, dd, J = 16.8, 7.4 Hz), 1.95 (1 H, br s), 1.21 (9 H, s); IR ($CHCl_3$) 3400 (br), 1480, 1460, 1370 cm^{-1}; $[\alpha]^{25}_D$ −127.96° (*c* 1.395, $CHCl_3$). The spectra were identical with those of racemic **15** prepared from allyl alcohol and 2,2-dimethylpropionitrile oxide.

(*R*)-2,2-Dimethyl-5-hydroxy-6-(acetyloxy)-3-hexanone (16). To the optically pure **15** (144 mg, 0.92 mmol) were added pyridine (920 μL) and acetic anhydride (460 μL). The reaction mixture was stirred at room temperature for 1.5 h and then diluted with ethyl acetate. The organic layer was washed with 5% Na_2CO_3 and H_2O, dried over $MgSO_4$, and concentrated to afford 169.2 mg (93%) of the crude product. This acetate was used directly for the next reaction: ^1H NMR ($CDCl_3$) δ 4.78 (1 H, m), 4.11 (2 H, m), 3.09 (1 H, dd J = 17.5, 11 Hz), 2.77 (1 H, dd, J = 17.5, 6.6 Hz), 2.10 (3 H, s), 1.21 (9 H, s). To a solution of the acetate (169.2 mg, 0.85 mmol) in 5/1 methanol/water (7 mL) was added boric acid (262.9 mg, 4.25 mmol) and three spatula tips of W-2 Raney nickel. The reaction mixture was placed under hydrogen, stirred vigorously for 11 h, and then filtered through Celite into a separatory funnel containing brine and dichloromethane. The reaction mixture was extracted with dichloromethane (×4), dried over $MgSO_4$, and concentrated to give 170.9 mg of the crude product. Flash chromatography (SiO_2, 40% EtOAc/hexane) gave 163.3 mg (96%) of the reduced product **16** [^1H NMR ($CDCl_3$) δ 4.29 (1 H, m), 4.10 (2 H, m), 3.30 (1 H, br s), 2.70 (2 H, d, J = 5.9 Hz), 2.11 (3 H, s), 1.16 (9 H, s)] mixed with the acyl transfer product 2,2-dimethyl-5-(acetyloxy)-6-hydroxy-3-hexanone (ca. 10%) [δ 5.29 (m), 3.74 (m), 2.86 (m), 2.06 (s), 1.15 (s)].

(*R*)-(+)-1,2,4-Butanetriol Triacetate (17). To the above mixture (125 mg, 0.628 mmol) and Na_2HPO_4 in dichloromethane (10 mL) was added a mixture of $(CF_3CO)_2O$ (1.08 mL) and 90% H_2O_2 (229 mg) in dichloromethane (5 mL). After an initial exothermic reaction, the mixture was heated at reflux for 1 h, then diluted with ethyl acetate, washed with aqueous $NaHCO_3$ (×3), and dried over $MgSO_4$. Solvent evaporation gave 87.2 mg of the crude product (partially trifluoroacetylated). To a suspension of lithium aluminum hydride (58.5 mg, 1.54 mmol) in THF (10 mL) was added the above crude product (87.2 mg) in THF (5 mL). The reaction mixture was heated at reflux for 7 h and then filtered through a Florisil column with ethanol. Solvent evaporation gave 23.2 mg of 1,2,4-butanetriol. To this triol was added pyridine (2 mL) and acetic anhydride (1 mL). The reaction mixture was stirred at room temperature overnight, and then diluted with ethyl acetate. The reaction mixture was washed with 5% Na_2CO_3 and water, dried over $MgSO_4$, and concentrated to give 25.6 mg of the crude triacetate **17**. This was purified by flash chromatography (SiO_2, 20% EtOAc/hexane) to yield pure **17**: ^1H NMR ($CDCl_3$) δ 5.20 (1 H, m), 4.29 (1 H, dd, J = 11.9, 3.5 Hz), 4.19–4.02 (3 H, m), 2.08 (6 H, s), 2.06 (3 H, s), 1.96 (2 H, m); IR ($CHCl_3$) 1730, 1370 cm^{-1}; $[\alpha]^{25}_D$ +19.6° (*c* 0.455, $CHCl_3$). Spectra were identical with those of an authentic sample of **17** prepared from *S*-malic acid.[10]

Thermal Diels–Alder Reaction of Cyclopentadiene with 8b. To a solution of **8b** (58.6 mg, 0.13 mmol) in benzene (25 mL) was added freshly cracked cyclopentadiene (2.5 mL). The reaction mixture was stirred at room temperature for 20 h. Evaporation of the solvent gave 82.9 mg of the crude products **22**, **23**, **24**, and **25**. The ratio by analytical HPLC (10% EtOAc/hexanes) was 4.6:1.3:2.2:1.0. The ratio between the exo products **23** and **25** and endo products **22** and **24** was 1:2.9. These diastereomers were partially separated by MPLC and each fraction was analyzed by analytical HPLC. Characterization of **22**–**25** was accomplished by reduction to the optically active hydroxymethyl norbornenes.

LAH Reductions of Diels–Alder Cycloadducts. To a suspension of LAH (35 mg, 0.88 mmol) in THF (2 mL) was added the endo Diels–Alder products (**22**/**24** = 12:1, free of exo products) (16 mg, 0.031 mmol) in THF (13 mL). The reaction mixture was stirred at room temperature for 2 h and then quenched with water (35 μL), 15% NaOH (35 μL), and water (105 μL). The mixture was filtered and washed with ether, and the crude products were separated by flash chromatography [SiO_2, 15% EtOAc/hexane (100 mL) and 40% EtOAc/hexane (100 mL)] to give 3.3 mg (86%) of enantiomeric mixture enriched in **26S**, $[\alpha]^{25}_D$ −75° (*c* 0.02, 95% EtOH).[12]

Similarly the endo Diels–Alder product (endo minor product **24** enriched, free of exo products) was reduced to give a mixture enriched in **26R**, $[\alpha]^{25}_D$ +34° (*c* 0.085, 95% EtOH).[12]

Finally, the exo Diels–Alder products (exo major product **23** enriched, free of endo products) were also reduced to give a mixture enriched in **27S**, $[\alpha]^{25}_D$ +13° (*c* 0.015, 95% EtOH).[12]

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