Anal. Calcd for $C_{17}H_{17}NO_3$: C, 72.06; H, 6.06; N, 4.94. Found: C, 71.87; H, 6.22; N, 4.77.

2,3-Dimethyl-1,4-anthraquinone (8): ^1H NMR ($CDCl_3$) δ 2.25 (overlapping singlets, 6 H), 7.69 (m, 2 H), 8.04 (m, 2 H), 8.63 (s, 2 H); IR (KBr pellet) 1655, 1610, 1590 cm^{-1}; chemical ionization mass spectrum, m/z 237 ($M^+ + 1$).

Conversion of 7b to 8. A stirred solution of **7b** (6 mg) in methanol (10 mL) was heated to reflux for 20 h. ^1H NMR analysis of the crude concentrated reaction mixture indicated quantitative conversion to **8**. **7b** was stable in refluxing benzene solution for 12 h.

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Registry No. **1a**, 109243-48-3; **1b**, 109243-49-4; **2a**, 109243-50-7; **2b**, 109243-51-8; **2c**, 109243-52-9; **2d**, 109243-53-0; **2e**, 109243-54-1; **2f**, 109243-55-2; **3a**, 109243-56-3; **3b**, 109243-57-4; **4**, 109243-58-5; **6a**, 109243-59-6; **7a**, 109243-60-9; **7b**, 109243-61-0; **8**, 65869-73-0; **9a**, 106-51-4; **9b**, 527-61-7; **10**, 3376-23-6; 1,4-dimethoxy-2,6-dimethylbenzene, 14538-50-2; 1,4-dimethoxy-2,3-dimethylbenzene, 39021-83-5; monomethyl phthalate, 4376-18-5.

Supplementary Material Available: Tables of crystal structure data, atomic coordinates, bond lengths, bond angles, anisotropic parameters, and hydrogen atom coordinates for **6a** and **7a** (8 pages). Ordering information is given on any current masthead page.

Cycloaddition of Nitrones with Allenes. An Example of Steric Control of Regiochemistry

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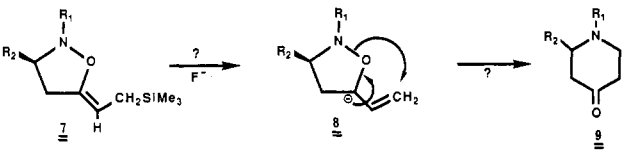
A study of the cycloaddition behavior of a series of electron-deficient allenes with *C*-phenyl-*N*-alkylnitrones has been carried out. The 1,3-dipolar cycloaddition proceeds in high yield with complete regiospecificity to produce 5-methylene substituted isoxazolidines. The reactions follow frontier orbital predictions. The orientation has been explained in terms of maximum orbital overlap of the nitrone HOMO-allene LUMO. In certain cases diastereomeric isoxazolidines were formed via different two-plane orientation complexes. The ratio of the diastereomers reflects the free energy difference of the two transition states. This difference comes from repulsive interactions caused by steric hindrance and attractive van der Waal forces associated with maximum π overlap of the substituent groups. The transition state that dominates in a particular case will depend on the nature of the groups attached to the N atom of the nitrone and to the dipolarophile π bond. An unusual regiochemical crossover occurred in the reaction of *N*-*tert*-butyl-*C*-phenylnitrone with methyl 2-methyl-2,3-butadienoate. In this case, the regiochemistry appears to be steric rather than stereoelectronic in origin. This contention was supported by molecular mechanics calculations.

The 1,3-dipolar cycloaddition reaction occupies a position of prominence in the arsenal of the synthetic organic chemist, as a consequence of its good yields, mild reaction conditions, high stereoselectivity, and predictability.[1] Nitrones represent a long-known and thoroughly investigated class of 1,3-dipoles.[2] Through the use of nitrone cycloaddition chemistry, numerous isoxazolidines have been prepared with excellent stereochemical control.[2] The 1,3-dipolar cycloaddition reaction has also attracted considerable attention as a convenient tool for the rapid construction of widely varied classes of natural products.[3-9]

Scheme I



The presence of a nitrogen atom within the isoxazolidine ring has made this heterocycle moiety especially attractive for the synthesis of the β-lactam ring.[10-15] The key feature of this approach generally involves a reductive cleavage of the isoxazolidine ring to give a γ-amino alcohol,[16-20]

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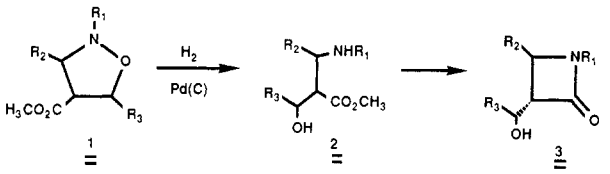
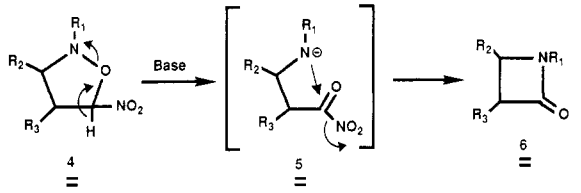
which undergoes subsequent cyclization with a neighboring carbomethoxy group.



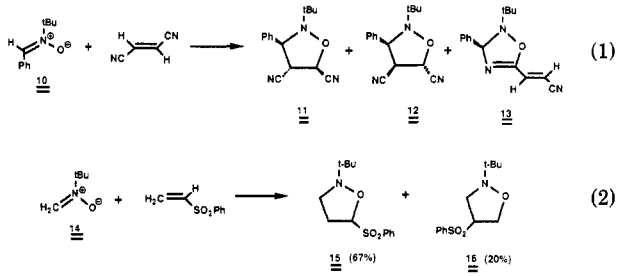
New methods of constructing the four-membered lactam ring continue to be of interest in connection with the synthesis of analogues of the naturally occurring antibiotics.[21-23] In a previous study we had reported that 5-nitro substituted isoxazolidines represent convenient reagents for the synthesis of β-lactams.[24] Removal of the acidic proton adjacent to the nitro group by a base followed by N–O bond cleavage and cyclization of the transient acyl nitro intermediate **5** was suggested as the mechanism to accommodate formation of the β-lactam ring system.[24]



As a continuation of our work in this area, we thought it worthwhile to study the reaction of several isoxazolidines that contain other electron-withdrawing substituents at the 5-position of the ring. Our hope was that these systems would also undergo a base-induced reorganization to produce β-lactams. In addition, we were also interested in the possible transformation depicted in Scheme I, in which the 5-exo methylene silyl substituted isoxazolidine **7** might serve as a precursor to allyl carbanion **8**.[25,26] By analogy with the results encountered with isoxazolidine **4**, we envisaged that this anion would undergo a tandem ring-opening–cyclization route to produce the 4-piperidinone ring system (**9**). Our intention was to synthesize isoxazolidine **7** via 1,3-dipolar cycloaddition of a nitrone with a silyl substituted allene. Although we did not find a way to accomplish the transformations outlined in Scheme I, we have observed that nitrones readily react with activated allenes to give 5-exo methylene substituted isoxazolidines.[27] In this paper, we report the results of this investigation.

Results and Discussion

As our first model we chose to investigate the cycloaddition behavior of the *N*-alkyl-*C*-phenylnitrone system with several monosubstituted alkenes possessing electron-withdrawing substituents. The reaction of *N*-*tert*-butyl-*C*-phenylnitrone (**10**) with fumaronitrile (eq 1) produced a mixture of trans (51%) and cis (16%) 5-cyano substituted isoxazolidines (**11**, **12**) as well as 1,2,4-oxadiazole **13** (16%). In a related fashion, treatment of *N*-*tert*-butylnitrone with phenyl vinyl sulfone afforded cycloadduct **15** as the major cycloadduct (67%) along with lesser quantities (i.e., ca. 20%) of the regioisomeric cycloadduct **16** (eq 2). This result is in general accord with the frontier orbital treatment of nitrone 1,3-dipolar cycloadditions.[28-30] Most dipolarophiles undergo cycloaddition to afford 5-substituted isoxazolidines with high regioselectivity. The orientation observed has been rationalized in terms of maximum overlap of the nitrone LUMO-dipolarophile HOMO.[31-35] As the ionization potential of the nitrone decreases or the electron affinity of the dipolarophile increases,[32] an increasing tendency toward production of 4-substituted isoxazolidines is found.[29] At some point, there must be a switch over from LUMO to HOMO control as one increases the electron-withdrawing power of the substituent on the alkene. That point is apparently approached with phenyl vinyl sulfone since regioisomeric mixtures of adducts are encountered with this dipolarophile. Unfortunately, all of our attempts to induce a base-catalyzed rearrangement of the 5-cyano and 5-sulfonyl substituted isoxazolidines to the β-lactam system failed and further work with these systems was abandoned.



We decided to probe an alternate nitrone approach for the synthesis of the β-lactam ring system. We expected that the cycloaddition of a nitrone with α-acetoxyacrylonitrile would provide a 5-substituted isoxazolidine. This heterocycle might be expected to undergo hydrolysis followed by a reductive ring opening and cyclization, thereby providing an alternate route to the azetidinone ring. In accord with FMO predictions, we find that nitrones **10**, **17**, and **18** readily react with α-acetoxyacrylonitrile to give the expected 5-acetoxy 5-cyano substituted isoxazolidines **19–21**. Unfortunately, all of our attempts to hydrolyze the resulting cycloadducts to the desired isoxazolidinone system failed to give characterizable material.

At this stage of our studies we decided to probe the viability of the sequence of reactions outlined in Scheme I. The ability of allenes to undergo bimolecular cyclo-

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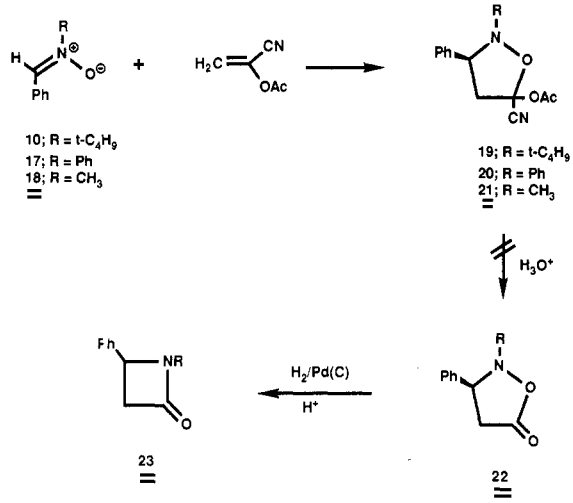
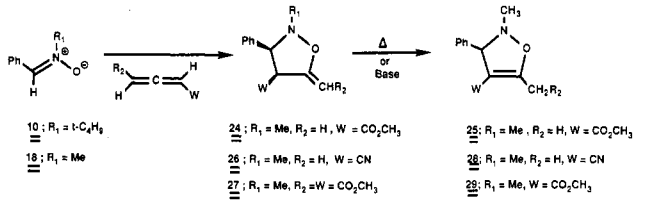


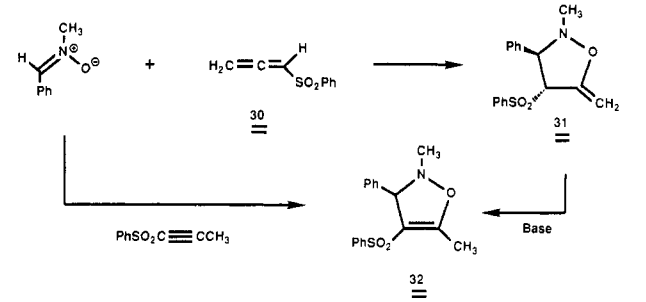
addition reactions with a variety of unsaturated π-systems has provided the synthetic chemist with a convenient route for the construction of complex ring systems.[36,37] While the Diels–Alder reaction of allenes with dienes has been studied in some detail,[38-40] the use of allenes in 1,3-dipolar cycloaddition has been severely limited as a consequence of their unreactive nature as dipolarophiles.[41-44] As part of our ongoing interest in the synthetic applications of nitrone cycloaddition chemistry, we have investigated the reaction of a variety of nitrones with different allenes.[27] All attempts to obtain a cycloadduct from the reaction of a wide assortment of nitrones with [(trimethylsilyl)-methyl]allene failed, even under high pressures (6 kbar). Nitrones generally react slowly with simple alkenes as a consequence of a large HOMO–LUMO gap.[29] On the basis of FMO theory, allenes possessing electron-withdrawing substituents are expected to undergo dipolar cycloaddition across the activated π-bond.[30] MNDO calculations of several substituted allenes (CN, CO_2CH_3, SO_2CH_3) (Table I) indicate that the introduction of an electron-withdrawing group on the double bond causes a significant lowering of the LUMO energy level compared with allene ($\Delta E \sim 1.3$ eV) and the largest LUMO coefficient resides on the central carbon and the next on the position bearing the activating group. This suggests that the reaction of nitrones with activated dienes will proceed in a highly regioselective fashion. This indeed proved to be the case.

The reaction of methyl 1,2-butadienoate with *N*-methyl-*C*-phenylnitrone (**18**) produced a mixture of two compounds (**24** and **25**) that could be separated by silica gel chromatography. Isoxazolidine **25** was readily formed from **24** on silica gel chromatography. This same isomerization could also be induced to occur by treating **24** with base. The stereochemical assignment of **24** as the cis isomer is made on the basis of the magnitude of the vicinal



coupling constant (J_{cis} = 9–11 Hz vs. J_{trans} = 7–8.5 Hz).[45] The isolation of cycloadduct **24** is of some interest since related 5-exo methylene substituted isoxazolidines have only been reported as transient species that rapidly rearrange to pyrrolidinones.[46-48] We have studied the thermolysis of **24** at 80 °C and find that it reacts via a 1,3-hydrogen shift to give **25** rather than by N–O bond scission.

We have also examined the regio- and stereochemical aspects of the cycloaddition of *N*-methyl- (**18**) and *N*-*tert*-butyl-*C*-phenylnitrone (**10**) with some additional allenes. Interaction of these nitrones with methyl 1,2-butadienoate, cyanoallene, and dimethyl 2,3-pentadienoate gave rise to a single cycloadduct (i.e., **26** and **28**). The structural assignment as the cis 5-exo methylene isomer is based on its spectroscopic properties (see Experimental Section). Surprisingly, the reaction of *N*-methyl-*C*-phenylnitrone (**18**) with (phenylsulfonyl)propadiene gave rise to the trans cycloadduct **31** (98%) as the exclusive product: NMR ($CDCl_3$, 360 MHz) δ 2.40 (s, 3 H), 4.23 (d, 1 H, J = 7.4 Hz), 4.37 (t, 1 H, J = 1.8 Hz), 4.48 (dt, 1 H, J = 7.4 and 1.8 Hz), 4.71 (t, 1 H, J = 1.8 Hz), and 6.7–7.30 (m, 10 H). When this material was treated with base, it rearranged to isoxazolidine **32**, which could be independently synthesized by the reaction of nitrone **18** with (1-phenylsulfonyl)propyne. The above results stands in marked contrast with the cycloaddition behavior of nitrone **18** with the other allenes which afford cis-substituted isoxazolidines.



Whereas *N*-methyl nitrone **18** and various allenes produce a single diastereomer, the cycloaddition reaction of the *N*-*tert*-butylnitrone **10** shows more complex behavior. With this nitrone a mixture of the cis and trans cycloadducts were obtained. Clearly, the presence of the bulky

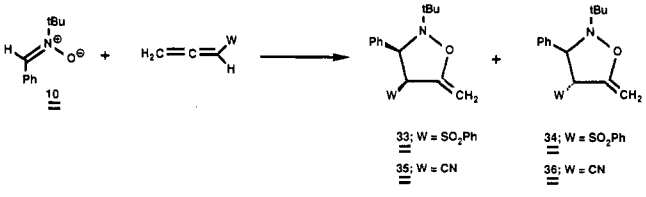


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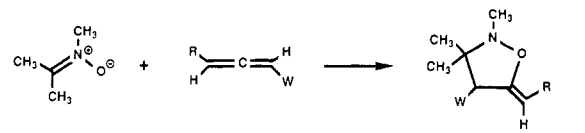
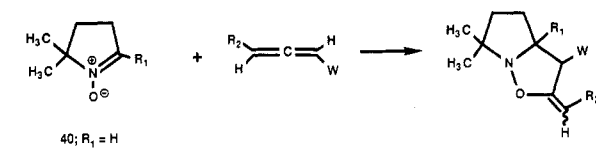
Table I. HOMO–LUMO Energies for Substituted Allenes and *N*-Alkylnitrones

	HOMO	LUMO	C_1	C_2	C_3
R_1 = H; R_2 = CN	−11.03		+0.17	−0.57	−0.63
	−10.44		−0.57	+0.49	+0.29
		−0.01	−0.49	+0.59	+0.04
		+0.50	+0.12	+0.59	−0.64
R_1 = H; R_2 = SO_2CH_3	−12.04		+0.05	+0.54	+0.51
	−11.57		−0.64	−0.44	+0.25
		−0.32	+0.56	−0.64	−0.09
		+0.15	+0.09	+0.44	−0.50
R_1 = H; R_2 = CO_2CH_3	−10.67		+0.23	−0.51	−0.57
	−10.62		+0.64	+0.52	−0.21
		−0.02	+0.46	−0.60	−0.04
		+0.57	−0.15	−0.59	+0.65
R_1 = CH_3; R_2 = CO_2CH_3	−10.70		+0.22	−0.49	−0.55
	−10.11		+0.58	+0.52	−0.19
		−0.008	+0.46	−0.60	−0.02
		+0.67	−0.16	−0.58	+0.62
	−8.47		+0.46	+0.26	−0.50
		−0.27	+0.37	−0.48	+0.33
	−8.69		+0.54	+0.25	−0.56
		−0.37	−0.31	+0.42	−0.29
	−8.34		+0.49	+0.27	−0.52
		−0.12	−0.36	+0.48	−0.33

N-tert-butyl group influences the distribution of diastereomers, although it does not effect the regiochemistry of the cycloaddition. In all of the cases involving monosubstituted allenes, the only regioisomer formed corresponds to the 5-exo methylene substituted isoxazolidine. This was also the case when aliphatic or cyclic nitrones were used. Thus, treatment of *N*-methyl-*C*-dimethylnitrone or pyrroline 1-oxides with carbomethoxy or cyano substituted allenes always produce the 5-exo methylene regioisomer (i.e., **37**–**44**).



37; R = H; W = CN
39; R = W = CO_2CH_3

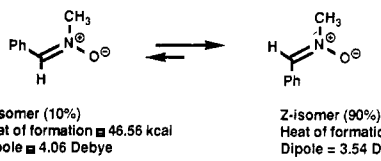


40; R_1 = H
43; R_1 = CH_3

41; R_1 = R_2 = H; W = CN
42; R_1 = H; R_2 = W = CO_2CH_3
44; R_1 = CH_3; R_2 = H; W = CN

The regio- and stereochemical outcome of the cycloaddition reactions of *N*-alkyl-*C*-phenylnitrones with alkenes have been extensively studied. Several generalizations can be made from these investigations. For monosubstituted dipolarophiles, where Z is aryl or alkyl, 5-substituted isoxazolidines are regiospecifically formed. With highly electron deficient olefins, a preference is seen for the formation of the 4-substituted isoxazolidines.[32] When electron-deficient allenes are used as dipolarophiles, however, the nitrone HOMO–dipolarophile LUMO interaction is of lowest energy. Our MNDO calculations also indicate that the largest LUMO coefficient resides on the central atom of the allene and the next on the position bearing the electron-withdrawing group (see Table I). This suggests that the reaction of nitrones with electron-deficient allenes will proceed in a highly regioselective fashion and give rise to the 5-exo methylene isoxazolidine.

There is strong evidence that nitrones derived from aromatic aldehydes possess a configuration in which the C-aryl and N-alkyl groups are in a trans relationship. This is based on a comparison of UV spectra of systems with fixed cis and trans geometry,[49] an X-ray crystal structure,[50] and intramolecular nuclear Overhauser enhancements. MNDO calculations on *N*-methyl-*C*-phenylnitrone show that the *E* and *Z* forms differ by 1.46 kcal in their heat of formation.[51] This would imply that the *E* isomer is

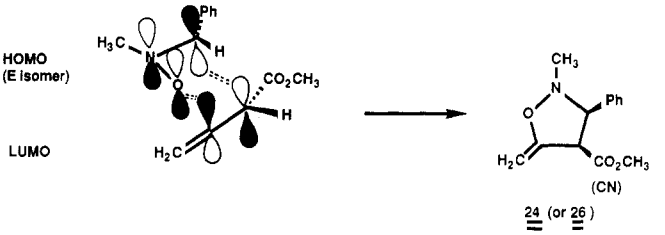


E-isomer (10%)
Heat of formation = 46.56 kcal
Dipole = 4.06 Debye

Z-isomer (90%)
Heat of formation = 45.10 kcal
Dipole = 3.54 Debye

present in solution in significant quantities, even at room temperature (i.e., ~10%). The *E* isomer has been proposed to undergo dipolar cycloaddition at a faster rate than the *Z* isomer due to steric reasons.[52,53] With the *N-tert*-butyl system, however, the *E* isomer is 6.3 kcal less stable and only the *Z* isomer exists in solution.

The stereochemistry of nitrone cycloaddition reactions has been the subject of several recent studies.[1-2] A generally accepted view of these reactions involves an approach of the addends in two parallel planes. Dipolar cycloadditions, like the Diels–Alder reaction, proceed through exo or endo transition states. Examination of the transition states involving certain electron-deficient allenes (i.e., cyano, carbomethoxy) from the perspective of FMO theory suggests that an endo transition state should be favored over its exo counterpart by a favorable secondary orbital interaction. We assume that the cycloadduct is derived from the minor *E* isomer of the *N*-methylnitrone. There is good literature precedence for this suggestion. Earlier work by Whitham and co-workers has shown that there is a significant barrier to rotation in nitrones but that this barrier is not sufficient to prohibit cis–trans interconversion under the conditions of dipolar cycloaddition.[52] The two-plane orientation complex leading to **24** (or **26**)



24 (or 26)

permits efficient π-overlap of the phenyl and ester groups that are located one above the other. The attractive van der Waals forces associated with maximal π-overlap are responsible for the preferred cycloaddition stereochemistry. The stereochemical outcome of the cycloaddition involving

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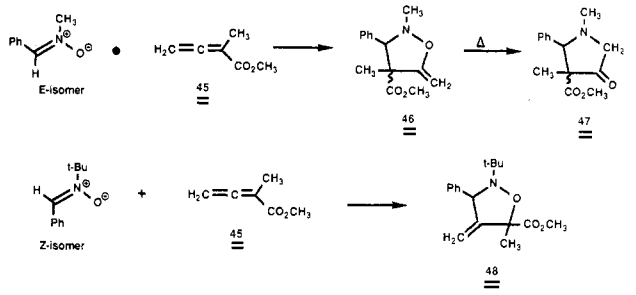
(50) Folting, K.; Lipscomb, W. N.; Jerslev, B. *Acta Chem. Scand.* **1963**, *17*, 2138.
(51) QCPE #506 (AMPAC) using the AM1 Hamiltonian. The calculations indicate that there is no significant difference in the coefficient size or HOMO/LUMO energies of the two geometric isomers.
(52) Boyle, L. W.; Peagram, M. J.; Whitham, G. H. *J. Chem. Soc. B* **1971**, 1728.
(53) Ali, S. A.; Wazeer, M. I. M. *J. Chem. Soc., Perkin Trans. 2* **1986**, 1789.

the reaction of *N*-methylnitrone **18** and (phenylsulfonyl)propadiene **30** is markedly different. Only a single adduct was detected, and this was shown to possess the trans structure **31**. In this case, the transition state leading to the cis isomer suffers repulsive interactions caused by steric hindrance with the bulky phenylsulfonyl group and consequently, the exo transition state is favored. When a *tert*-butyl group is present on the nitrogen atom of the nitrone, only the *Z* isomer exists in solution. With this system, the endo and exo transition states leading to the cis and trans isomers are of comparable energies. From these results it is clear that the interaction which dominates in a particular case will depend on the nature of the substituent groups attached to the nitrone and the allene.

During the course of our studies we encountered a most unusual regiochemical crossover in a study of the reaction of *N*-methyl- (**18**) and *N*-*tert*-butylnitrone (**10**) with methyl 2-methyl-2,3-butadienoate. The *N*-methylnitrone **10** gives the expected 5-exo methylene cycloadduct (**46**) as a 4:1 diastereomeric mixture of isomers (3*R*,4*S*/3*R*,4*R*). This



regiochemical assignment was supported by its thermal conversion (90 °C) to pyrrolidinone **47**.[54] In dramatic contrast to this result, cycloaddition of *N*-*tert*-butylnitrone **10** with **45** only afforded the 4-exo methylene isoxazolidine **48**. The assignment of **48** rests on its spectroscopic properties as well as its chemical behavior. The NMR spectrum ($CDCl_3$, 360 MHz) shows singlets at δ 1.05 (9 H), 1.70 (3 H), and 3.80 (3 H), doublets at 4.40 (1 H, J = 2.0 Hz), 5.10 (1 H, J = 2.0 Hz), and a triplet at 4.55 (1 H, J = 2.0 Hz). The appearance of the hydrogen at C_3 as a doublet is only compatible with this regiochemical assignment. All attempts to induce a thermal rearrangement of **48** to the pyrrolidione system failed. This results is also consistent with the structure assignment.

One possible explanation to account for the difference in regiochemistry in the cycloaddition of **45** with nitrones **10** and **18** is that there has been a crossover in the FMO interactions. We do not believe, however, that switching a methyl with a *tert*-butyl group would be sufficient to change the nature of the FMO interactions. Nevertheless, to probe this point, we have carried out some theoretical calculations. For economic reasons, we have utilized the semiempirical MNDO program, which has already been used successfully for the investigation of energy levels and coefficients of a series of dipoles and dipolarophiles.[1] Calculations were performed with the AMPAC program.[51] The net result of these calculations (see Table I) is that there is no evidence for any significant change in the coefficients or energy levels in the cycloaddition of nitrones **10** and **18** with methyl 2,3-butadienoate or 2-methyl-2,3-butadienoate.

Since the answer to regiochemical control does not seem to be attributable to FMO factors, we examined simple steric effects. Over the past 15 years, molecular mechanics

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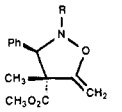
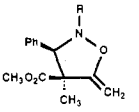
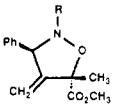
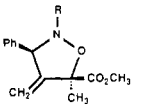
Table II. Molecular Mechanics Calculations of 4- and 5-Methylene Substituted Isoxazolidines

total energy, kcal/mol			
			
R = CH_3 24.48	R = CH_3 25.40	R = CH_3 26.67	R = CH_3 27.65
R = t-C_4H_9 28.96	R = t-C_4H_9 29.05	R = t-C_4H_9 27.73	R = t-C_4H_9 27.84

has developed into a powerful tool for the calculation of structures, energies, and sometimes other properties of molecules.[55] The MM2 program does a rather good job of such calculations with hydrocarbons and it has subsequently been extended to many other functionalized kinds of molecules,[56] including systems as complex as proteins.[57] Molecular mechanics treat molecular strain energy by using a classical model in which the strain energy is expressed as a sum of energies associated with particular molecular deformations. We have used the MMX86 program as parameterized by Gajewski and Gilbert[58] and implemented in the program Model 2.9[59] to calculate the total energy of the two regioisomeric cycloadducts for both the N-methyl and N-*tert*-butyl systems. We assume that the relative energy differences of the lowest energy conformations will parallel the energy differences in the transition state. The relevant total energies are given in Table II. The results for the N-methyl series show a fairly rigid set of structures in which the 5-exo methylene regioisomer is lower in energy (1.2 kcal) than the corresponding 4-exo methylene isomer. It is interesting to note that the MMX calculations also predict that the major diastereomer (**46a**) should have the phenyl and methyl groups in a cis disposition. This is indeed the case (**46a**:**46b** = 4/1). Most importantly, the relative energies of the two regioisomeric cycloadducts in the *tert*-butyl series have been switched relative to the methyl system (see Table II). Although the computed energy difference is less than 1.5 kcal, it does give credence to the idea that cycloadduct **48** is thermodynamically more stable than the alternate regioisomer in the *tert*-butyl series. Thus, regiochemical control in the cycloaddition of nitrones with methyl 2-methyl-2,3-butadienoate (**45**) appears to be steric rather than stereoelectronic in origin. Recognition of the importance of steric factors in controlling the regiochemistry of nitrone cycloaddition sets the stage for further studies with related systems.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were run on a Perkin Elmer Model 283 infrared spectrometer. Proton NMR spectra were obtained on a Varian EM-390 and Nicolet FT-360 spectrometer. ^{13}C NMR spectra were recorded

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(56) For some leading references, see: Profeta, S.; Allinger, N. L. *J. Am. Chem. Soc.* **1985**, *107*, 1907.

(57) Hagler, A. T.; Hyler, E.; Lifson, S. *J. Am. Chem. Soc.* **1974**, *96*, 5320.

(58) MMX86 will be avilable from Serena software, 489 Serena Lane, Bloomington, IN 47401. Calculations were performed on a Vax 11/785 (version 4.3). We are indebted to Professor J. Gajewski of the Unviersity of Indiana for a prerelease version of this program.

(59) We thank Professor Kosta Steliou of the University of Montreal for many fruitful discussions, helpful advice, and providing a copy of the extensively rewritten Still Model program.

on an IBM-200 MHz spectrometer. Microanalyses were performed at Atlantic Microlabs, Atlanta, GA. Mass spectra were determined with a Finnegan 4000 mass spectrometer at an ionizing voltage of 70 eV.

Reaction of *N*-*tert*-Butyl-*C*-phenylnitrone with Fumaronitrile. A solution containing 0.78 g of fumaronitrile and 1.77 g of *N*-*tert*-butyl-*C*-phenylnitrone[60] (**10**) in 25 mL of benzene was heated at reflux for 24 h. The solution was concentrated under reduced pressure and the residue was subjected to silica gel chromatography using a 10% ethyl acetate–hexane mixture as the eluent. The first fraction contained 1.31 g (51%) of *trans*-*N*-*tert*-butyl-4,5-dicyano-3-phenylisoxazolidene (**11**) as a white crystalline solid: mp 113–114 °C; IR (KBr) 2980, 2280, 1615, 1470, 1380, 1235, 1085, 980, 920, 850, 785, and 725 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 1.03 (s, 9 H), 3.58 (dd, 1 H, J = 6.8, 2.3 Hz), 4.25 (d, 1 H, J = 2.3 Hz), 4.98 (d, 1 H, J = 6.8 Hz), and 7.10–7.60 (m, 5 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 26.13, 30.81, 50.23, 59.51, 66.20, 68.57, 116.77, 117.00, 127.54, 129.44, and 137.85; UV (95% ethanol) 248 nm (ϵ 7000) and 280 (4900); MS, m/e 255 (M^+), 161, 121, and 77. Anal. Calcd for $C_{15}H_{17}N_3O$: C, 70.56; H, 6.71; N, 16.46. Found: C, 70.49; H, 6.72; N, 16.44.

The second fraction contained 0.37 g (16%) of *cis*-*N*-*tert*-butyl-4,5-dicyano-3-phenylisoxazolidine (**12**) as a white crystalline solid: mp 134–135 °C; IR (KBr) 2970, 2260, 1475, 1460, 1390, 1370, 1215, 1045, 980, 935, 765, and 710 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 1.10 (s, 9 H), 3.88 (dd, 1 H, J = 8.3 and 6.8 Hz), 4.58 (d, 1 H, J = 8.3 Hz), 4.95 (d, 1 H, J = 6.8 Hz), and 7.27–7.57 (m, 5 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 26.21, 30.84, 46.94, 60.13, 64.50, 66.16, 114.60, 114.68, 128.19, 128.97, 129.43, and 136.14; UV (95% ethanol) 246 nm (ϵ 9600) and 278 (7300); MS, m/e 255 (M^+), 156, 116, and 77. Anal. Calcd for $C_{15}H_{17}N_3O$: C, 70.56; H, 6.71; N, 16.46. Found: C, 70.54; H, 6.73; N, 16.44.

The third fraction contained 0.10 g (4%) of *N*-*tert*-butyl-2,3-dihydro-3-phenyl-5-(3-cyano-2-propenyl)-1,2,4-oxadiazole (**13**) as a white crystalline solid: mp 104–105 °C; IR (KBr) 3080, 2960, 2250, 1660, 1460, 1370, 1330, 1275, 1250, 1215, 1070, 1045, 975, 780, and 710 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 1.13 (s, 9 H), 6.04 (s, 1 H), 6.18 (d, 1 H, J = 16.5 Hz), 6.92 (d, 1 H, J = 16.5 Hz), and 7.20–7.50 (m, 5 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 24.93, 60.60, 86.19, 109.29, 115.56, 126.59, 128.43, 128.74, 134.33, 140.50, and 157.56; UV (95% ethanol) 250 nm (ϵ 9000) and 300 (1340); MS, m/e 256 (M^+), 200, 162, and 106. Anal. Calcd for $C_{15}H_{17}N_3O$: C, 70.56; H, 6.71; N, 16.27. Found: C, 70.43; H, 6.73; N, 16.42.

Reaction of *N*-*tert*-Butylnitrone with Phenyl Vinyl Sulfone. A solution containing 500 mg of *N*-*tert*-butylnitrone[31] (**14**) and 820 mg of phenyl vinyl sulfone in 25 mL of chloroform was heated at reflux for 3 h. The solution was concentrated under reduced pressure and the resulting yellow oil crystallized on standing. The resulting solid was fractionally recrystallized from methylene chloride–hexane to give 920 mg (67%) of *N*-*tert*-butyl-5-(phenylsulfonyl)isoxazolidine (**15**) as a white crystalline solid: mp 93–94 °C (lit.[31] mp 91–93 °C); NMR ($CDCl_3$, 90 MHz) δ 1.03 (s, 9 H), 2.50–3.16 (m, 4 H), 4.83–5.00 (m, 1 H), 7.40–7.70 (m, 3 H), and 7.87–8.03 (m, 2 H); IR (KBr) 2960, 1480, 1450, 1390, 1370, 1310, 1155, 1075, and 755 cm^{-1}; UV (95% ethanol) 215 nm (ϵ 9000) and 265 (1700); MS, m/e 269 (M^+), 143, 128, 126, 85, and 77. Anal. Calcd for $C_{13}H_{19}NO_3S$: C, 57.97; H, 7.11; N, 5.20. Found: C, 58.04; H, 7.12; N, 5.17.

Examination of the crude reaction mixture showed the presence of a regioisomeric cycloadduct (**i.e., 16**) in ca. 20% yield: NMR ($CDCl_3$, 90 MHz) δ 1.02 (s, 9 H), 3.0–3.4 (m, 2 H), 3.8–4.5 (m, 3 H), and 7.4–7.9 (m, 5 H). All attempts to separate this material from cycloadduct **14** failed to give pure material.

Preparation of 5-Acetoxy-*N*-*tert*-butyl-5-cyano-3-phenylisoxazolidine (19). A solution containing 313 mg of α-acetoxyacrylonitrile[61] and 500 mg of *N*-*tert*-butyl-*C*-phenylnitrone (**10**) in 25 mL of toluene was heated at reflux under a nitrogen atmosphere for 6 h. The solution was concentrated under reduced pressure and the residue was subjected to silica gel chromatography using a 25% ethyl acetate–hexane mixture as the eluent. The major fraction contained a white solid, which was recrystallized from ethyl acetate–hexane to give 510 mg (64%) of 5-acetoxy-*N*-*tert*-butyl-5-cyano-3-phenylisoxazolidine (**19**): mp 91–92 °C; NMR ($CDCl_3$, 90 MHz) δ 1.40 (s, 9 H), 2.03 (s, 3 H), 2.80 (dd, J = 15.0 and 9.0 Hz), 3.33 (dd, J = 15.0 and 9.0 Hz), 4.47 (t, J = 9.0 Hz), and 7.20–7.53 (m, 5 H); IR (KBr) 2980, 1760, 1375, 1210, 1175, 1020, 950, 860, and 780 cm^{-1}; UV (95% ethanol) 265 nm (ϵ 760); MS, m/e 288 (M^+), 190, 153, 131, 104, and 77. Anal. Calcd for $C_{16}H_{20}N_2O_3$: C, 66.65; H, 6.99; N, 9.72. Found: C, 66.74; H, 7.02; N, 9.71.

Preparation of 5-Acetoxy-5-cyano-2,3-diphenylisoxazolidine (20). A solution containing 560 mg of α-acetoxyacrylonitrile and 500 mg of *N*-phenyl-*C*-phenylnitrone (**17**) in 25 mL of toluene was heated at reflux under a nitrogen atmosphere for 6 h. The solution was concentrated under reduced pressure and the residue was subjected to silica gel chromatography using a 25% ethyl acetate–hexane mixture as the eluent. The major fraction contained a white solid, which was recrystallized from ethyl acetate–hexane to give 1.1 g (72%) of 5-acetoxy-5-cyano-2,3-diphenylisoxazolidine (**20**): mp 120–121 °C; NMR ($CDCl_3$, 90 MHz) δ 2.03 (s, 3 H), 3.05 (dd, J = 15.0 and 9.0 Hz), 3.47 (dd, J = 15.0 and 9.0 Hz), 4.70 (t, J = 9.0 Hz), and 6.93–7.53 (m, 5 H); IR (KBr) 2980, 1750, 1585, 1380, 1200, 1115, 1070, 1110, and 860 cm^{-1}; UV (95% ethanol) 235 nm (ϵ 6700); MS, m/e 308 (M^+), 266, 180, 157, 131, 116, 109, 105, and 77. Anal. Calcd for $C_{18}H_{16}N_2O_3$: C, 70.12; H, 5.23; N, 9.09. Found: C, 69.94; H, 5.28; N, 9.02.

Preparation of 5-Acetoxy-5-cyano-2-methyl-3-phenylisoxazolidine (21). A solution containing 313 mg of α-acetoxyacrylonitrile and 500 mg of *N*-methyl-*C*-phenylnitrone[60] (**18**) in 25 mL of toluene was heated at reflux under a nitrogen atmosphere for 6 h. The solution was concentrated under reduced pressure and the residue was subjected to silica gel chromatography using a 25% ethyl acetate–hexane mixture as the eluent. The major fraction contained a white solid which was recrystallized from ethyl acetate–hexane to give 900 mg (73%) of 5-acetoxy-*N*-*tert*-butyl-5-cyano-3-phenylisoxazolidine (**21**): mp 79–80 °C; NMR ($CDCl_3$, 90 MHz) δ 2.16 (s, 3 H), 2.66 (s, 3 H), 2.88 (dd, 1 H, J = 13.5 and 10.8 Hz), 3.43 (dd, 1 H, J = 13.5 and 6.9 Hz), 3.85 (dd, 1 H, J = 10 .8 and 6.9 Hz), and 7.33 (s, 5 H); IR (KBr) 2980, 1760, 1495, 1460, 1440, 1370, 1250, 1205, 1140, 1010, 960, 850, 765, and 705 cm^{-1}; UV (95% ethanol) 264 nm (ϵ 640); MS, m/e 246 (M^+), 205, 187, 177, 158, 136, 131, 116, 103, 91, and 77. Anal. Calcd for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.34; H, 5.76; N, 11.36.

Cycloaddition of *N*-Methyl-*C*-phenylnitrone with Methyl 2,3-Butadienoate. A solution containing 1.66 g of *N*-methyl-*C*-phenylnitrone and 1.50 g of methyl 2,3-butadienoate[62] was heated at 45 °C for 20 h under a nitrogen atmosphere. Concentration of the solution under reduced pressure followed by silica gel chromatography using a 2% ethyl acetate–hexane mixture as the eluent gave two fractions. The first fraction contained 0.63 g (18%) of 2-methyl-5-methylene-3-phenyl-4-carbomethoxyisoxazolidine (**24**) as a clear oil: IR (neat) 3070, 3040, 3000, 2960, 2880, 1745, 1670, 1500, 1440, 1350, 1260, 1165, 1085, 1030, 980, 960, 820, 760, and 705 cm^{-1}; NMR ($CDCl_3$, 360 MHz) δ 2.70 (s, 3 H), 3.71 (s, 3 H), 4.05 (dd, 2 H, J = 10.0 and 3.6 Hz), 4.18 (d, 1 H, J = 10.0 Hz), 4.36 (t, 1 H, J = 3.6 Hz), and 7.30–7.42 (m, 5 H); MS, m/e 235 (M^+), 216, 203, 186, 174, 156, 131, 118, 105, 89, and 82; HRMS calcd for $C_{13}H_{15}NO_3$ 233.1051, found 233.1050.

The second fraction isolated contained 1.12 g (32%) of 2,5-dimethyl-3-phenyl-4-carbomethoxyisoxazolidine (**25**) as a clear oil: IR (neat) 3030, 3015, 2950, 1700, 1645, 1495, 1435, 1375, 1355, 1330, 1230, 1190, 1125, 1090, 985, 850, 780, 760, 745, and 700 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 2.30 (s, 3 H), 2.85 (s, 3 H), 3.60 (s, 3 H), 4.85 (s, 1 H), and 7.20 (s, 5 H). Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.93; H, 6.48; N, 6.01. Found: C, 67.02; H, 6.46; N, 5.86. This same material was obtained from the base-catalyzed reaction of **24**.

Reaction of *N*-Methyl-*C*-phenylnitrone with Cyanoallene. A solution containing 1.45 g of *N*-methyl-*C*-phenylnitrone and 0.70 g of cyanoallene[63] in 20 mL of benzene was heated at 40 °C for 3 h. The solvent was removed under reduced pressure to give 2.13 g (99%) of 2-methyl-5-methylene-3-phenyl-4-isoxazolidinecarbonitrile (**26**) as a light yellow oil, which was used without

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(63) Kurtz, P.; Gold, H.; Disselnkotter, H. *Liebigs Ann. Chem.* **1959**, *624*, 1.

further purification: IR (neat) 3085, 3040, 3005, 2985, 2920, 2880, 2855, 2270, 1680, 1460, 1250, 970, 820, 750, and 700 cm^{-1}; NMR ($CDCl_3$, 360 MHz) δ 2.73 (s, 3 H), 3.86 (s, 1 H), 3.94 (d, 1 H, J = 10.8 Hz), 4.11 (dt, 1 H, J = 10.8 and 2.3 Hz), 4.28 (t, 1 H, J = 2.8 Hz), 4.53 (t, 1 H, J = 2.8 Hz), and 7.38–7.43 (m, 5 H).

To a solution containing 0.30 g of the above compound in 25 mL of anhydrous tetrahydrofuran at −78 °C under a nitrogen atmosphere was slowly added 1.20 mL of a 1.4 M solution of *n*-butyllithium in hexane. The resulting yellow solution was warmed to 0 °C, quenched by the addition of a saturated aqueous ammonium chloride solution, and extracted with ether. The organic phase was washed with water, dried over magnesium sulfate, and concentrated under reduced pressure to give a light brown oil, which was purified by silica gel chromatography using a 5% ethyl acetate–hexane mixture as the eluent. The major component contained 0.27 g (90%) 2,3-dihydro-2,5-dimethyl-3-phenyl-4-isoxazolecarbonitrile (**28**) as a yellow oil: IR (neat) 3070, 3040, 3005, 2970, 2920, 2215, 1660, 1500, 1460, 1440, 1390, 1265, 1020, and 980 cm^{-1}; NMR ($CDCl_3$, 360 MHz) δ 2.13 (s, 3 H), 2.94 (s, 3 H), 4.83 (s, 1 H), and 7.33–7.39 (m, 5 H); ^{13}C NMR ($CDCl_3$, 200 MHz), δ 75.28, 84.63, 126.62, 128.05, 128.18, 128.28, 128.39, 128.51, 128.64 and 138.32.

Reaction of *N*-Methyl-*C*-phenylnitrone with Dimethyl 2,3-Pentadienedioate. A solution containing 0.43 g of *N*-methyl-*C*-phenylnitrone and 0.50 g of dimethyl 2,3-pentadienedioate[64] in 25 mL of benzene was heated at 50 °C for 4 h. The solvent was removed under reduced pressure to give 0.90 g (97%) of methyl 5-(2-methoxy-2-oxoethylidene)-2-methyl-3-phenyl-4-isoxazolinecarboxylate (**27**) as a yellow oil: IR (neat) 3080, 3040, 3005, 2960, 2860, 1750, 1710, 1650, 1445, 1355, 1130, 915, 830, and 735 cm^{-1}; NMR ($CDCl_3$, 360 MHz) δ 2.84 (s, 3 H), 3.33 (s, 3 H), 3.65 (s, 3 H), 4.15 (d, 1 H, J = 8.1 Hz), 4.82 (dd, 1 H, J = 8.1 and 1.30 Hz), 5.44 (d, 1 H, J = 1.30 Hz), and 7.36–7.41 (m, 5 H); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 43.76, 44.01, 50.87, 51.79, 52.23, 54.18, 58.81, 74.36, 89.04, 89.76, 127.00, 127.36, 127.78, 128.13, 128.20, 128.27, 128.54, 128.76, 130.16, 130.37, 133.10, 134.86, 167.37, 167.45, 167.57, and 169.15.

To a solution containing 0.50 g of the above compound in 50 mL of anhydrous tetrahydrofuran at −78 °C under a nitrogen atmosphere was slowly added 1.35 mL of a 1.4 M solution of *n*-butyllithium in hexane. The resulting purple solution was warmed to 0 °C, quenched by the addition of a saturated ammonium chloride solution, and extracted with ether. The organic phase was washed with water, dried over magnesium sulfate, and concentrated under reduced pressure to give a brown oil, which was purifed by silica gel chromatography using a 5% ethyl acetate–hexane mixture as the eluent. The major component contained 0.43 g (86%) of methyl 2,3-dihydro-4-(methoxycarbonyl)-2-methyl-3-phenyl-5-isoxazoleacetate (**29**) as a clear oil: IR (neat) 3080, 3020, 3005, 2960, 2920, 1750, 1705, 1660, 1440, 1370, 1330, 1240, 1080, 855, 760, and 705 cm^{-1}; NMR ($CDCl_3$, 360 MHz) δ 2.95 (s, 3 H), 3.62 (s, 3 H), 3.77 (s, 3 H), 3.90 (s, 1 H), 3.95 (s, 1 H), 4.91 (s, 1 H), and 7.34 –7.38 (m, 5 H); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 32.10, 47.29, 52.31, 75.35, 77.08, 127.11, 127.18, 127.84, 128.39, 140.81, 159.30, 164.34, and 167.80; MS, m/e 291 (M^+), 214, 160, 132, and 118 (base); HRMS calcd for $C_{15}H_{17}NO_5$ 291.110, found, 291.1109.

Reaction of *N*-Methyl-*C*-phenylnitrone with (Phenylsulfonyl)propadiene. A solution containing 4.75 g of *N*-methyl-*C*-phenylnitrone and 7.00 g of (phenylsulfonyl)-propadiene[65] (**30**) in 100 mL of benzene was heated at 40 °C for 12 h. Concentration of the solution under reduced pressure gave a viscous oil, which solidified on standing. Recrystallization of this material from ether–hexane gave 2-methyl-5-methylene-3-phenyl-4-(phenylsulfonyl)isoxazolidine (**31**) in 98% yield: mp 88–89 °C; IR (KBr) 3080, 3020, 2995, 2880, 1650, 1600, 1315, 1155, 735, and 695 cm^{-1}; NMR ($CDCl_3$, 360 MHz) δ 2.40 (s, 3 H), 4.23 (d, 1 H, J = 7.4 Hz), 4.37 (t, 1 H, J = 1.8 Hz), 4.48 (dt, 1 H, J = 7.4 and 1.8 Hz), 4.71 (t, 1 H, J = 2.0 Hz), 6.74 (t, 1 H, J = 7.5 Hz), 6.85 (t, 1 H, J = 7.5 Hz), 6.96 (m, 1 H), 7.12 (m, 1 H), 7.18 (s, 5 H), and 7.30 (d, 1 H, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 43.4, 72.9, 75.7, 87.8, 127.8, 128.3, 128.5, 128.6, 128.9, 129.3, 134.0, 135.8, 136.8 and 151.0; MS, m/e 315 (M^+), 173, 118, and 77. Anal. Calcd for $C_{17}H_{17}NO_3S$: C, 64.74; H, 5.43; N, 4.44. Found: C, 64.82; H, 5.44; N, 4.43.

To a solution containing 0.2 g of the above compound in 20 mL of tetrahydrofuran at −78 °C was added 1.2 mL of a 1.4 M solution of *n*-butyllithium in hexane. The resulting yellow solution was warmed to 0 °C, quenched by the addition of water, and extracted with ether. The organic phase was concentrated under reduced pressure and the crude residue was purified by crystallization to give 0.18 g (90%) of 2,5-dimethyl-3-phenyl-4-(phenylsulfonyl)-4-isoxazolidine (**32**): mp 81–82 °C; IR (KBr) 3095, 3020, 2890, 1640, 1630, 1590, 1310, 1300, 1130, 730, 710, and 690 cm^{-1}; NMR ($CDCl_3$, 360 MHz) δ 2.40 (s, 3 H), 2.90 (s, 3 H), 4.90 (s, 1 H), and 7.0–7.4 (m, 10 H); MS, m/e 315 (M^+), 238, 173, 132, 118, and 77; ^{13}C NMR ($CDCl_3$, 50 MHz) δ 12.0, 47.1, and 76.9; UV (95% ethanol) 265 nm (ϵ 8200). Anal. Calcd for $C_{17}H_{17}NO_3S$: C, 64.75; H, 5.43; N, 4.44. Found: C, 64.65; H, 5.44; N, 4.43.

Reaction of *N*-*tert*-Butyl-*C*-phenylnitrone with (Phenylsulfonyl)propadiene. A solution containing 1.04 g of *N*-*tert*-butyl-*C*-phenylnitrone and 1.60 g of (phenylsulfonyl)-propadiene in 50 mL of benzene was heated at 40 °C for 48 h. Removal of the solvent under reduced pressure followed by silica gel chromatography using a 10% ethyl acetate–hexane mixture as the eluent gave a 14:1 mixture of *cis*- (**33**) and *trans*-*N*-*tert*-butyl-5-methylene-3-phenyl-4-(phenylsulfonyl)isoxazolidine (**34**). The trans isomer **34** showed the following spectral properties: IR (neat) 3060, 3040, 2980, 2940, 1650, 1610, 1590, 1320, 1160, 760, and 690 cm^{-1}; NMR ($CDCl_3$, 360 MHz) δ 0.98 (s, 9 H), 4.16 (dd, 1 H, J = 2.17 and 1.35 Hz), 4.38 (dt, 1 H, J = 6.4 and 1.33 Hz), 4.61 (d, 1 H, J = 6.4 Hz), 4.69 (dd, 1 H, J = 2.08 and 1.52 Hz), 7.20–7.30 (m, 3 H), 7.30–7.40 (m, 2 H), 7.55–7.62 (t, 2 H, J = 7.0 Hz), 7.70–7.75 (t, 1 H, J = 7.0 Hz)8, and 7.90–8.00 (d, 2 H, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 25.7, 60.0, 62.8, 78.2, 87.7, 126.4, 127.4, 127.8, 128.0, 128.1, 128.3, 128.5, 129.0, 130.0, 132.0, 134.0, 136.9, 141.3, and 150.3. Anal. Calcd for $C_{20}H_{23}NO_3S$: C, 67.21; H, 6.49; N, 3.92. Found: C, 67.04; H, 6.55; N, 3.86.

The cis isomer (**33**), mp 134–135 °C, showed the following spectral properties: IR (KBr) 3060, 2980, 1640, 1325, 1150, 730, and 700 cm^{-1}; NMR ($CDCl_3$, 360 MHz) δ 1.05 (s, 9 H), 4.10 (dd, 1 H, J = 2.34 and 1.21 Hz), 4.61 (dd, 1 H, J = 2.30 and 1.25 Hz), 4.79 (d, 1 H, J = 8.88 Hz), 4.85 (d, 1 H, J = 8.88 Hz), 7.10–7.20 (m, 3 H), 7.23–7.35 (m, 2 H), 7.35–7.40 (d, 2 H, J = 7.5 Hz), and 7.40–7.55 (m, 3 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 25.9, 61.6, 64.6, 73.7, 85.6, 127.7, 128.0, 128.4, 128.8, 129.3, 133.0, and 153.9. Anal. Calcd for $C_{20}H_{23}NO_3S$: C, 67.21; H, 6.49; N, 3.92. Found: C, 67.10; H, 6.53; N, 3.87.

Reaction of *N*-*tert*-Butyl-*C*-phenylnitrone with Cyanoallene. A solution containing 0.37 g of cyanoallene and 1.00 g of *N*-*tert*-butyl-*C*-phenylnitrone in 25 mL of benzene was heated at 40 °C for 2 h. The solvent was removed under reduced pressure and the resulting oil was purifed by silica gel chromatography using 5% ethyl acetate–hexane mixture as the eluent. The first fraction contained 0.56 g (41%) of *cis*-*N*-*tert*-butyl-5-methylene-3-phenyl-4-isoxazolinecarbonitrile (**35**) as an orange oil: IR (neat) 3065, 3015, 2980, 2940, 2905, 2880, 2255, 1675, 1455, 1365, 1215, 970, 815, 750, and 700 cm^{-1}; NMR ($CDCl_3$, 360 MHz) δ 1.04 (s, 9 H), 4.04 (dd, 1 H, J = 2.8 and 2.3 Hz), 4.18 (dd, 1 H, J = 2.8 and 2.3 Hz), 4.37 (d, 1 H, J = 10.6 Hz), 4.43 (t, 1 H, J = 2.8 Hz), and 7.34–7.39 (m, 5 H); MS, m/e 242 (M^+), 185, 171, 165, 143, 109, 104, 78, and 57 (base); HRMS calcd for $C_{15}H_{18}N_2O$ 242.141, found 242.1405.

The second fraction contained 0.72 g (53%) of *trans*-*N*-*tert*-butyl-5-methylene-3-phenyl-4-isoxazolinecarbonitrile (**36**) as a white solid: mp 92–93 °C; IR (KBr) 3070, 3040, 2980, 2940, 2220, 1675, 1370, 1205, 970, 815, and 725 cm^{-1}; NMR ($CDCl_3$, 360 MHz), δ 1.13 (s, 9 H), 4.23 (dd, 1 H, J = 2.73 and 1.93 Hz), 4.31 (dt, 1 H, J = 8.28 and 1.93 Hz), 4.58 (t, 1 H, J = 2.52 Hz), 4.60 (d, 1 H, J = 8.38 Hz), and 7.34–7.45 (m, 5 H). Anal. Calcd for $C_{15}H_{18}N_2O$: C, 74.35; H, 7.49; N, 11.56. Found: C, 74.25; H, 7.51; N, 11.52.

Reaction of *N*-Methyl-*C*,*C*-dimethylnitrone with Cyanoallene. A solution containing 1.80 g of *N*-methyl-*C*,*C*-dimethylnitrone and 1.35 g of cyanoallene in 30 mL of benzene was heated at 50 °C for 2.5 h. The solvent was removed under reduced pressure to give 3.12 g (99%) of 2,3,3-trimethyl-5-methylene-4-isoxazolidinecarbonitrile (**37**) as an orange oil, which was used

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in the next step without purification: IR (neat) 3020, 2990, 2945, 2900, 2260, 1680, 1380, 1240, 970, 825, and 690 cm^{-1}; NMR ($CDCl_3$, 360 MHz) δ 1.32 (s, 6 H), 2.66 (s, 3 H), 3.83 (t, 1 H, J = 2.1 Hz), 4.26 (dd, 1 H, J = 2.4 and 2.1 Hz), and 4.43 (t, 1 H, J = 2.4 Hz); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 14.79, 22.63, 37.26, 46.73, 65.66, 81.82, 115.87, and 128.13.

To a solution containing 0.50 g of the above compound in 50 mL of anhydrous tetrahydrofuran at −78 °C under a nitrogen atmosphere was added 2.40 mL of a 1.4 M solution of *n*-butyllithium in hexane. The resulting yellow solution was warmed to 0 °C, quenched by the addition of a saturated aqueous ammonium chloride solution, and extracted with ether. The organic phase was washed with water, dried over magnesium sulfate, and concentrated under reduced pressure to give a light brown oil, which was purified by silica gel chromatography using a 5% ethyl acetate–hexane mixture as the eluent. The major component contained 0.46 g (92%) of 2,3,5,5-tetramethyl-4-isoxazolecarbonitrile (**38**) as an orange oil: IR (neat) 2980, 2935, 2210, 1660, 1440, 1390, 1270, 970, 920, and 740 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 1.28 (s, 6 H), 1.96 (s, 3 H), and 2.66 (s, 3 H); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 12.13, 23.82, 29.56, 39.31, 68.62, 90.82, 114.89, and 165.63; MS, m/e 152 (M^+), 137 (base), and 95; HRMS calcd for $C_8H_{12}N_2O$ 152.0950, found 152.0946.

Reaction of *N*-Methyl-*C*,*C*-dimethylnitrone with Dimethyl 2,3-Pentadienedioate. A solution containing 0.75 g of *N*-methyl-*C*,*C*-dimethylnitrone and 1.35 g of dimethyl 2,3-pentadienedioate in 30 mL of benzene was heated at 40 °C for 4 h. The solvent was removed under reduced pressure to give 2.01 g (96%) of methyl 5-(2-methoxy-2-oxoethylidene)-2,3,3-trimethyl-4-isoxazolidinecarboxylate (**39**) as a yellow oil: IR (neat) 3020, 2985, 2960, 2900, 1745, 1710, 1650, 1440, 1360, 1260, 1145, 1110, 1040, 945, 830, and 735 cm^{-1}; NMR ($CDCl_3$, 360 MHz) δ 1.23 (s, 6 H), 2.69 (s, 3 H), 3.59 (s, 3 H), 3.71 (s, 3 H), 4.25 (s, 1 H), and 5.40 (s, 1 H); MS, m/e 243 (M^+), 228, and 196 (base); HRMS calcd for $C_{11}H_{17}NO_5$ 243.1107, found 243.1118.

Reaction of 5,5-Dimethyl-Δ^1-pyrroline 1-Oxide (40) with Cyanoallene. A solution containing 0.50 g of 5,5-dimethyl-Δ^1-pyroline 1-oxide[66] (**40**) and 0.29 g of cyanoallene in 20 mL of benzene was heated at 30 °C for 3.5 h. The solvent was removed under reduced pressure to give 0.75 g (95%) of hexahydro-6,6-dimethyl-2-methylenepyrrolo[1,2-*b*]isoxazole-3-carbonitrile (**41**) as a yellow oil: IR (neat) 2980, 2260, 1580, 1395, 1340, 1250, 1220, 980, 910, and 740 cm^{-1}; NMR ($CDCl_3$, 360 MHz) δ 1.11 (s, 3 H), 1.40 (s, 3 H), 1.62–1.73 (m, 2 H), 1.98–2.07 (m, 2 H), 4.22 (m, 1 H), 4.33 (ddd, 1 H, 6.50, 4.72, and 2.40 Hz), 4.42 (m, 1 H), and 5.03 (m, 1 H).

To a solution containing 0.50 g of the above compound in 50 mL of anhydrous tetrahydrofuran at −78 °C under a nitrogen atmosphere was slowly added 2.2 mL of a 1.4 M solution of *n*-butyllithium in hexane. The resulting yellow solution was warmed to 0 °C, quenched by the addition of a saturated aqueous ammonium chloride solution, and extracted with ether. The organic phase was washed with water, dried over magnesium sulfate, and concentrated under reduced pressure to give a light brown oil, which was purified by silica gel chromatography using a 5% ethyl acetate–hexane mixture as the eluent. The major component contained 0.46 g (92%) of 3a,4,5,6-tetrahydro-2,6,6-trimethylpyrrolo[1,2-*b*]isoxazole-3-carbonitrile as a yellow oil: IR (neat) 2990, 2940, 2880, 2220, 1660, 1625, 1265, 1020, 820, 800, and 740 cm^{-1}; NMR ($CDCl_3$, 360 MHz) δ 1.10 (s, 3 H), 1.32 (s, 3 H), 1.39 (m, 2 H), 1.70 (m, 2 H), 2.03 (s, 3 H), 2.10–2.19 (m, 1 H), and 4.73–4.78 (m, 1 H); MS, m/e 178 (M^+), 163, 142, 120, and 84 (base); HRMS calcd for $C_{10}H_{14}N_2O$ 178.110, found 178.1102.

Reaction of 5,5-Dimethyl-Δ^1-pyrroline 1-Oxide (40) with Dimethyl 2,3-Pentadienedioate. A solution containing 0.50 g of 5,5-dimethyl-Δ^1-pyrroline 1-oxide (**40**) and 0.69 g of dimethyl 2,3-pentadienedioate in 20 mL of benzene was heated at 40 °C for 3.5 h. The solvent was removed under reduced pressure and the resulting orange oil was passed through a silica gel scrub column using a 10% acetone–hexane mixture as the eluent. Removal of the solvent under reduced pressure gave 1.12 g (94%) of methyl hexahydro-2-(2-methoxy-2-oxoethylidene)-6,6-dimethylpyrrolo[1,2-*b*]isoxazole-3-carboxylate (**42**) as a yellow oil: IR (neat) 3020, 2980, 2960, 2880, 1750, 1710, 1650, 1445, 1380, 1135, and 1050 cm^{-1}; NMR ($CDCl_3$, 360 MHz) δ 1.10 (s, 3 H), 1.42 (s, 3 H), 1.65 (m, 2 H), 1.80 (m, 1 H), 2.33 (m, 1 H), 3.67 (s, 3 H), 3.79 (s, 3 H), 4.24 (ddd, 1 H, J = 9.16, 4.18, and 0.86 Hz), 4.68 (s, 1 H), and 5.41 (t, 1 H, J = 0.86 Hz); MS, m/e 269 (M^+), 154, 122, 110, and 96 (base); HRMS calcd for $C_{13}H_{19}NO_5$ 269.1263, found 269.1265.

Reaction of 1,5,5-Trimethyl-Δ^1-pyrroline 1-Oxide (43) with Cyanoallene. A solution containing 0.50 g of 1,5,5-trimethyl-Δ^1-pyrroline 1-oxide[60] (**43**) and 0.26 g of cyanoallene in 20 mL of benzene was heated at 35 °C for 3 h. The solvent was removed under reduced pressure to give a mixture of two isomers which were separated by silica gel chromatography using a 5% ethyl acetate–hexane mixture as the eluent. The first fraction contained 0.66 g (87%) of *cis*-hexahydro-3a,6,6-trimethyl-2-methylenepyrrolo[1,2-*b*]isoxazole-3-carbonitrile (**44a**) as a yellow oil: IR (neat) 2980, 2940, 2880, 2220, 1675, 1460, 1390, 1230, 980, and 825 cm^{-1}; NMR ($CDCl_3$, 360 MHz) δ 1.18 (s, 3 H), 1.22 (s, 3 H), 1.56 (s, 3 H), 1.82–1.98 (m, 4 H), 3.85 (t, 1 H, J = 2.4 Hz), 4.29 (dd, 1 H, J = 2.9 and 2.4 Hz), and 4.54 (t, 1 H, J = 2.9 Hz).

The second fraction contained 0.05 g (7%) of the trans stereoisomer **44b** as a yellow oil: IR (neat) 2980, 2940, 2880, 2220, 1675, 1470, 1390, 1230, 980, and 825 cm^{-1}; NMR ($CDCl_3$, 360 MHz) δ 1.34 (s, 3 H), 1.59 (s, 3 H), 1.81–1.96 (m, 4 H), 1.85 (s, 3 H), 3.98 (t, 1 H, J = 2.3 Hz), 4.22 (dd, 1 H, J = 2.7 and 2.3 Hz), and 4.42 (t, 1 H, J = 2.7 Hz).

To a solution containing 0.30 g of either of the above compounds in 25 mL of anhydrous tetrahydrofuran at −78 °C under a nitrogen atmosphere was slowly added 1.25 mL of a 1.4 M solution of *n*-butyllithium in hexane. The resulting yellow solution was warmed to 0 °C, quenched by the addition of a saturated ammonium chloride solution, and extracted with ether. The organic phase was washed with water, dried over magnesium sulfate, and concentrated under reduced pressure to give a brown oil, which was purified by silica gel chromatography using 5% ethyl acetate–hexane mixture as the eluent. The major component contained 0.25 g (83%) of 3a,4,5,6-tetrahydro-2,3a,6,6-tetramethylpyrrolo[1,2-*b*]isoxazole-3-carbonitrile as an orange oil: IR (neat) 3020, 2980, 2940, 2220, 1670, 1390, 1260, 1230, 920, and 740 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 1.19 (s, 3 H), 1.22 (s, 3 H), 1.51 (s, 3 H), 1.54–2.08 (m, 4 H), and 2.02 (s, 3 H); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 11.37, 23.02, 27.10, 28.50, 35.88, 36.76, 69.84, 88.92, 114.87, and 165.62; MS, m/e 192 (M^+), 177, 123 (base), and 70; HRMS calcd for $C_{11}H_{16}N_2O$ 192.1263, found 192.1264.

Cycloaddition of *N*-Methyl-*C*-phenylnitrone with Methyl 2-Methyl-2,3-butadienoate. A solution containing 0.65 g of *N*-methyl-*C*-phenylnitrone and 1.32 g of methyl 2-methyl-2,3-butadienoate (**45**) in 10 mL of benzene was heated at 45 °C for 10 h. Concentration of the solution under reduced pressure followed by silica gel chromatography using a 2% ethyl acetate–hexane mixture as the eluent gave two fractions. The first fraction contained 180 mg (17%) of a clear oil whose structure was assigned as (3*R*,4*R*)-2,4-dimethyl-5-methylene-3-phenyl-4-carbomethoxyisoxazolidine (**46a**) on the basis of its spectral data:[67] IR (neat), 3040, 3000, 2960, 2880, 1740, 1675, 1500, 1458, 1380, 1275, 1145, 1125, 990, 965, 825, 775, 755, and 710 cm^{-1}; NMR ($CDCl_3$, 360 MHz) δ 1.15 (s, 3 H), 2.70 (s, 3 H), 3.75 (s, 3 H), 3.90 (d, 1 H, J = 4.0 Hz), 4.22 (d, 1 H, J = 4.0 Hz), 4.50 (s, 1 H), and 7.25 (s, 5 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 43.75, 52.59, 59.22, 76.27, 76.90, 128.17, 128.32, 134.28, 162.64, and 172.15. Anal. Calcd for $C_{14}H_{17}NO_3$: C, 67.99; H, 6.93; N, 5.66. Found: C, 67.97; H, 6.94; N, 5.65.

The second fraction contained 770 mg (71%) of a crystalline solid whose structure was assigned as (3*R*,4*S*)-2,4-dimethyl-5-methylene-3-phenyl-4-carbomethoxyisoxazolidine (**46b**), mp 74–75 °C, on the basis of its spectral data: IR (KBr) 3005, 2960, 2860, 1730, 1670, 1605, 1445, 1390, 1340, 1285, 1250, 1150, 1130, 990, 930, 810, 760, and 710 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 1.45 (s, 3 H), 2.70 (s, 3 H), 3.45 (s, 3 H), 3.55 (s, 1 H), 3.80 (d, 1 H, J = 4.0 Hz), 4.30 (d, 1 H, J = 4.0 Hz), and 7.30 (s, 5 H); MS, m/e 247 (M^+), 188, 145, 132, 91, and 77. Anal. Calcd for $C_{14}H_{17}NO_3$: C, 67.99; H, 6.93; N, 5.66. Found: C, 68.02; H, 6.97; N, 5.66.

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(67) Experimental details dealing with the thermal rearrangement of **46** to pyrrolidinone **47** will be described in a subsequent manuscript.

Cycloaddition of *N*-*tert*-Butyl-*C*-phenylnitrone with Methyl 2-Methyl-2,3-butadienoate. A solution containing 1.00 g of *N*-*tert*-butyl-*C*-phenylnitrone and 0.67 g of methyl 2-methyl-2,3-butadienoate (**45**) in 15 mL of benzene was heated in a sealed tube at 80 °C for 8 h. Concentration of the solution under reduced pressure followed by silica gel chromatography using a 2% ethyl acetate–hexane mixture as the eluent gave 70 mg (20%) of *N*-*tert*-butyl-5-methyl-4-methylene-3-phenyl-5-carbomethoxyisoxazolidine (**48**) as a clear oil: IR (neat) 2995, 1745, 1455, 1370, 1285, 1225, 1130, 990, 910, 865, 760, and 705 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 1.05 (s, 9 H), 1.70 (s, 3 H), 3.80 (s, 3 H), 4.40 (d, 1 H, J = 2.0 Hz), 4.55 (t, 1 H, J = 2.0 Hz), 5.10 (d, 1 H, J = 2.0 Hz), and 7.18–7.38 (m, 5 H); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 24.72, 26.26, 52.55, 58.69, 67.78, 82.04, 108.29, 127.43, 128.33, 128.53, 141.84, 159.99, and 172.41; MS, m/e 289 (M^+), 274, 233, 174, 132, 115, and 84; HRMS calcd for $C_{17}H_{23}NO_3$ 289.1679, found 289.1678.

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Registry No. **10**, 3376-24-7; **11**, 108817-65-8; **12**, 108817-66-9; **13**, 108817-67-0; **14**, 41012-82-2; **15**, 43044-81-1; **16**, 43044-82-2; **17**, 1137-96-8; **18**, 3376-23-6; **19**, 108817-68-1; **20**, 108817-69-2; **21**, 108817-70-5; **24**, 108817-71-6; **25**, 108817-72-7; **26**, 108817-73-8; **27**, 108817-74-9; **28**, 108817-75-0; **29**, 108817-76-1; **31**, 108817-77-2; **32**, 107402-99-3; **33**, 108817-78-3; **34**, 108817-79-4; **35**, 108817-80-7; **36**, 108817-81-8; **37**, 108817-82-9; **38**, 108817-83-0; **39**, 108817-84-1; **40**, 3317-61-1; **41**, 108817-85-2; **42**, 4567-18-4; **44a**, 108817-87-4; **44b**, 108817-91-0; **45**, 18913-37-6; **46a**, 108817-88-5; **46b**, 108817-93-2; **48**, 108817-89-6; CH_2=C=CHC(O)OMe, 108817-89-6; $PhSO_2CH$=CH_2, 5535-48-8; fumaronitrile, 764-42-1; α-acetoxyacrylonitrile, 3061-65-2; cyanoallene, 1001-56-5; dimethyl 2,3-pentadienedioate, 1712-36-3; (phenylsulfonyl)propadiene, 2525-42-0; *N*-methyl-*C*-dimethylnitrone, 72552-73-9; 3a,4,5,6-tetrahydro-2,6,6-trimethylpyrrolo[1,2-*b*]isoxazole-3-carbonitrile, 108817-90-9; 3a,4,5,6-tetrahydro-2,3a,6,6-tetramethylpyrrolo-[1,2-*b*]isoxazole-3-carbonitrile, 108817-92-1.

Notes

Direct Synthesis of Ethers via Zinc Chloride Mediated Etherification of Alcohols in Dichloroethane

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Although the Williamson ether synthesis is one of the most widely used methods for synthesis of ethers, it requires initial conversion of alcohols into halides or tosylates and their displacement with alkoxides.[1] Several synthetic methods for the direct synthesis of ethers from alcohols are available, but each method has certain limitations with regard to scope and reaction conditions.[2]

Recently, Lau reported reductive deoxygenation of aromatic aldehydes and ketones with zinc iodide/sodium cyanoborohydride and briefly mentioned the preparation of bis(diphenylmethyl) ether from benzhydrol using zinc iodide in dichloroethane without describing precise reaction conditions and yield.[3,4] This information prompts us to report our results on zinc chloride mediated etherification of alcohols. It has been reported that benzylic, allylic, and tertiary alcohols can be activated with zinc halides to generate carbocationic species, which are trapped with thiols,[5] thio acids,[6] selenols,[7] and hydrides.[3] Similar behavior has been noted with benzylic, allylic, and tertiary halides when using zinc halides.[8]

We have found that the success of direct synthesis of ethers from alcohols is dependent critcally on solvents and Lewis acids. First, solvent effects were examined with α-methylbenzyl alcohol as a model compound with 1 equiv of zinc chloride. In dichloroethane, bis(α-methylbenzyl) ether was obtained in 91% yield at room temperature in 4 h, whereas no reaction occurred in other solvents such as tetrahydrofuran, ethyl ether, and acetonitrile. Among several Lewis acids tested in dichloroethane, zinc chloride gave the best results and is generally recommended. The reaction of α-methylbenzyl alcohol with 1 equiv of zinc iodide at room temperature for 24 h resulted in a less than 20% yield, and the reaction required 6 h in refluxing dichloroethane for completion.[9,10] This result is in contrast with previous reports in which zinc iodide is more effective than zinc chloride.[5,6] Furthermore, the use of boron trifluoride etherate[11] gave a mixture of several products along with the polymerized products, whereas the use of titanium

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(9) In order to explain the relatively low reactivity of zinc iodide, one of the reviewers suggested that trace amounts of water due to the hygroscopic nature of zinc chloride might participate for the reaction to occur rapidly. However, the use of commercially available zinc chloride without drying and wet zinc iodide [after anhydrous zinc iodide (2 mmol) was stirred in dichloroethane (10 mL) containing water (10 μl) at room temperature for 30 min, α-methylbenzyl alcohol was added] did not significantly change the reaction rates, as compared with the use of anhydrous zinc chloride and anhydrous zinc iodide, respectively.

(10) The use of zinc bromide required 8 h at room temperature for completion.

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