Thermolysis of Bis[2-[(trimethylsilyl)oxy]prop-2-yl]furoxan (TOP-furoxan). The First Practical Method for Intermolecular Cycloaddition of an in Situ Generated Nitrile Oxide with 1,2-Di- and Trisubstituted Olefins

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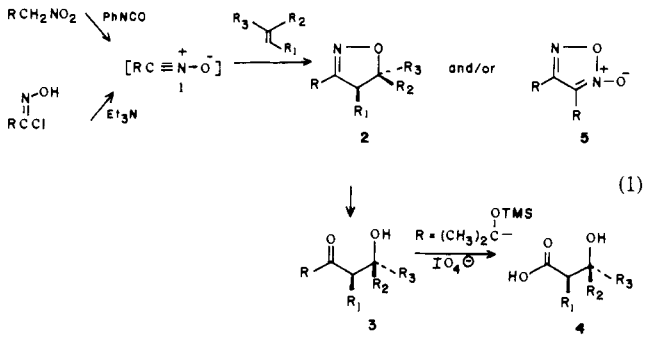
Abstract: Cycloaddition of in situ generated nitrile oxides with 1,2-di- and trisubstituted olefins to form Δ^2-isoxazolines is problematical due to dimerization of the nitrile oxides to form furoxans. It has been found that thermolysis of bis[2-[(trimethylsilyl)oxy]prop-2-yl]furoxan (TOP-furoxan) (**7**) in the presence of 1–2 equiv of mono-, di-, and trisubstituted olefins (165 °C, ϕH) produces the derived isoxazolines **9a–t** in good to excellent yields. Evidence is presented to support a mechanism involving reversible cycloreversion of the furoxan to 2-[(trimethylsilyl)oxy]-2-methylpropanenitrile oxide followed by irreversible [3 + 2]-dipolar cycloaddition with the olefin. The derived cycloadducts are readily converted to β-hydroxy acid derivatives.

We have recently developed a cycloadditive strategy to aldol-type adducts which complements in many ways the traditional carbonyl addition pathways.[2] The versatile sequence (eq 1)



(1)

involves olefin–nitrile oxide [3 + 2] dipolar cycloaddition and reduction of the resultant Δ^2-isoxazoline **2**. This basic route to β-hydroxy ketones **3** has recently been extended to β-hydroxy acid derivatives **4** by employing a substituted nitrile oxide capable of oxidative cleavage.[3] With general conditions now available for the reductive conversion of Δ^2-isoxazolines to β-hydroxy carbonyls, our experience has indicated that the major limitation in applying this strategy to synthesis lies in the nitrile oxide cycloaddition step. Nearly all nitrile oxides **1**[4] are generated by one of two methods: (1) dehydration of a 1° nitro compound[5] or (2) 1,3-dehydrohalogenation of an oximic acid halide.[4] Most nitrile oxides are quite unstable, rapidly dimerizing by presumed [3 + 2] dipolar cycloaddition to form furoxans **5** in the absence of an efficient trap. The ability of an olefin to competitively trap a transient nitrile oxide is largely a function of its substituent pattern. Both electron-donating and electron-withdrawing substituents activate olefins toward nitrile oxide cycloaddition. In our experience, yields of cycloadduct **2** are generally high with mono- or 1,1-disubstituted olefins; however, dimerization to the furoxan **5** becomes a serious competing reaction when trans-disubstituted olefins are employed. Cis-disubstituted olefins are significantly worse and unactivated trisubstituted alkenes are virtually useless in intermolecular cycloaddition reactions. Slow syringe pump addition of reagents does permit a marginal increase in yields as does the use of a bulky nitrile oxide which inhibits dimerization more than cycloaddition.[3] More commonly, a large excess of olefin (typically 20–50 equiv) is employed. One viable solution to this problem involves synthetic design with an *intra*molecular cycloaddition reaction.[6] *We now report the first method for nitrile oxide generation which permits intermolecular cycloadditions with near stoichiometric amounts of more highly substituted olefins.*

Furoxans **5**[7] have generally been regarded as stable "dead-end" side products from nitrile oxide cycloadditions. However, it has been known for almost 100 years that nitrile oxides can be regenerated from furoxans by thermolytic cycloreversion.[8–10] For example, flash vacuum pyrolysis (500 °C) of dimethylfuroxan gives methanenitrile oxide[8a] and thermolysis of the same furoxan with 1-decene at 260 °C yields the derived cycloadduct.[8b] Thus thermolysis of furoxans would appear to be an ideal method for cycloaddition since the nitrile oxide, now in equilibrium with the troublesome dimer, can be diverted to the desired cycloadduct (see eq 2). However, there is a limitation: nitrile oxides are well-known to rapidly rearrange to isocyanates at these high temperatures.[4] Thus, although dimerization is no longer a problem, the employment of less reactive di- and trisubstituted olefins as partners is likely not viable with most furoxans. With these considerations in mind, we established the following criteria for development of a successful method for nitrile oxide cycloaddition based on furoxan cycloreversion: (1) the furoxan must cyclorevert at reasonable temperatures, (2) the resultant nitrile oxide must then cycloadd with di- and trisubstituted olefins faster than re-

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(2) Curran, D. P. *J. Am. Chem. Soc.* **1983**, *105*, 5826. Curran, D. P. *Ibid.* **1982**, *104*, 4024.

(3) Curran, D. P.; Scanga, S. A.; Fenk, C. J. *J. Org. Chem.* **1984**, *49*, 3474.

(4) (a) Grundmann, C.; Grunanger, P. "The Nitrile Oxides"; Springer-Verlag: New York, 1981. (b) Caramella, P. In "1,3-Dipolar Cycloaddition"; Padwa, A., Ed.; Wiley: New York, 1983; Vol. 1, pp 291–392.

(5) Mukaiyama, T.; Hoshino, T. *J. Am. Chem. Soc.* **1960**, *82*, 5339. For modified conditions which permit very slow nitrile oxide generation, see: Müller, I.; Jäger, V. *Tetrahedron Lett.* **1982**, *23*, 4777.

(6) (a) Intramolecular cycloadditions can succeed even with trisubstituted olefins: see ref 2. (b) Kozikowski, A. P. *Acc. Chem. Res.* **1984**, *17*, 410.

(7) For a review of the chemistry of furoxans, see: Gasco, A.; Boulton, A. J. In "Advances in Heterocyclic Chemistry"; Academic Press: New York, 1981; Vol. 29, pp 251–340. Also: Sliwa, W.; Thomas, A. *Heterocycles* **1985**, *23*, 399.

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(9) Bisadamantylfuroxan cycloreverts at temperatures as low as 80 °C. Dondoni, A.; Barbaro, G.; Battaglia, A.; Biorgianni, P. *J. Org. Chem.* **1972**, *37*, 3196.

(10) (a) Reviews of 1,3-dipolar cycloreversions: Bianchi, G.; DiMicheli, C.; Gandolfi, R. *Angew. Chem., Int. Ed. Engl.* 1979, *18*, 721. (b) Bianchi, G.; Gandolfi, R. In "1,3-Dipolar Cycloaddition Chemistry"; Padwa, A., Ed.; Wiley: New York, 1984; pp 451–542.

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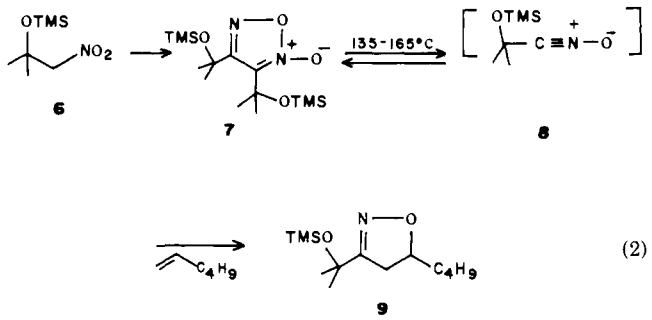


(2)

arrangement or decomposition, (3) this cycloaddition must not be reversible at the temperatures employed, and (4) the nitrile oxide must bear a group that will permit subsequent versatile synthetic transformations.

Results and Discussion

We have previously demonstrated that 2-[(trimethylsilyl)-oxy]-2-methylpropanenitrile oxide (**8**), generated by the Mukaiyama method from **6**, provides synthetically useful isoxazolines which are readily processed to β-hydroxy acid derivatives[3] (eq 1 and 2). The choice of a bulky substituent was dictated by the consideration that large groups should suppress the rate of dimerization to a greater extent than the rate of cycloaddition. Note that the bulky nitrile oxide substituents are placed on adjacent carbons in the dimer **7**. While modest increases in yields were observed with this hindered nitrile oxide relative to straight-chain analogues,[3] it was clear that this method hardly solved the problem of cycloaddition with 1,2-di- and trisubstituted olefins. For **9**, normal cycloaddition (PhNCO, ϕH, Δ) of **6** with *trans*-4-octene produced cycloadduct **9e** in <25% yield along with the furoxan **7**. Slow syringe pump addition of PhNCO (8 h) under otherwise identical conditions lead to **9e** in ~40% yield again accompanied by **7** as the major product. Coupling the synthetic versatility of isoxazolines **9** with the fact that bulky substituents on furoxans are known to lower the temperatures required for cycloreversion,[9] **7** appeared to be an ideal candidate for the investigation of a procedure for in situ nitrile oxide generation and cycloaddition based upon furoxan cycloreversion (eq 2).

Thus, bis[2-[(trimethylsilyl)oxy]prop-2-yl]furoxan (TOP-furoxan, **7**) was intentionally prepared by direct dimerization of **6** (itself readily available from acetone, nitromethane, and Me_3SiCl)[3] under standard Mukaiyama conditions[5] in the absence of olefin. After distillation and recrystallization from methanol, TOP-furoxan (**7**) was isolated in 70–80% yield as a low-melting white solid (mp 32–33 °C). The simple proton NMR clearly indicated the presence of an unsymmetrical dimer [($CDCl_3$) δ 1.76 (6 H, s), 1.72 (6 H, s), 0.22 (9 H, s), 0.13 (9 H, s)] and the IR stretching frequencies (see Experimental Section) were consistent with the furoxan ring system, by far the most commonly encountered nitrile oxide dimer.[4]

In a series of preliminary experiments, TOP-furoxan (**7**) was heated in a sealed NMR tube in C_6D_6 with 1.1 equiv[11] of 1-hexene. While no cycloadduct was detected at temperatures below 100 °C, we were pleased to find clean conversion to isoxazoline **9** in the range of 135–165 °C. While ~12 days was required for the completion at 135 °C, 3 days sufficed at 150 °C, and the reaction was complete in <16 h at 165 °C. In a subsequent experiment, **7** was heated with 1.1 equiv of 1-hexene in benzene at 165 °C for 17 h. Isoxazoline **9**, the sole detectable product, was isolated in 97% yield as an analytically pure oil after simple solvent removal and direct Kugelrohr distillation. The reaction is thought to proceed via slow cycloreversion of **7** to produce 2 equiv of 2-[(trimethylsilyl)oxy]-2-methylpropanenitrile oxide (**8**) followed by rapid and irreversible cycloaddition of **8** with 1-hexene (eq 2).[7,10]

Encouraged by these early results, we have investigated the utility of furoxan **7** under these standard conditions (ϕH, 165 °C, 17 h). The results are summarized in Table I. Since cycloadducts derived from mono- or 1,1-disubstituted olefins are readily available by standard methods of nitrile oxide generation, these were not extensively investigated. However, it is worth noting that good yields are produced (entries a and **b**) and chromatographic separation from diphenyl urea (required by the Mukaiyama method) is avoided. Also, isoxazoles are available from acetylenes (entry **d**). Finally, note the site selectivity based on olefin substitution observed with a diene (entry **c**).

Special emphasis was placed on 1,2-di- and trisubstituted olefins whose cycloadducts are more difficult to obtain by the standard routes. Clearly the thermolytic method is vastly superior. For example, compare the isolated yield of cycloadduct **9e** (81%) generated by the furoxan thermolysis method with that obtained by the standard method (40% maximum). This yield differential becomes even greater with cis-disubstituted and trisubstituted olefins. Note that the two stilbene isomers each provide a unique cycloadduct (entries **f** and **j**). This proves that the cycloaddition is stereospecific as expected and that olefin isomerization is not a problem under the reaction conditions. While cyclopentene generally provides good yields of cycloadducts via the normal procedures, cyclohexene is a notoriously poor dipolarophile. Under the thermolysis conditions, yields with the two olefins are only marginally different (entries **k** and **l**). Unprotected hydroxyl groups can survive the reaction conditions as illustrated with crotyl alcohol (entry **g**). Primary and secondary hydroxyl groups are not permitted in the isocyanate method. Not unexpectedly, both regioisomers are produced in essentially equal amounts.[12] Regioisomeric mixtures are also produced with methyl crotonate and *trans*-β-methylstyrene (entries **h** and **i**) which are typical of those produced by standard methods of nitrile oxide generation.[12] In contrast, cycloaddition with *cis*-4-methyl-2-pentene produces a *single* regioisomer (entry **m**). In accord with the observations of Martin,[13] the nitrile oxide oxygen becomes bonded to the more hindered olefinic site. Notably, the higher temperatures employed by us do not lead to detectable amounts of the alternate regioisomer. We anticipate that this combination of furoxan thermolysis with the Martin regiochemical observations will be the best way to prepare cis-3,4-disubstituted isoxazolines. These are then precursors to erythro β-hydroxy ketones. Finally, disubstituted olefins with an electron-donating group exhibit improved regioselectivity. Cycloaddition with dihydropyran (entry **n**) produces a readily separable 5.5/1 mixture of regioisomers at 165 °C (at 150 °C, the ratio was 10.5/1).[14] In summary, the method provides a valuable route to Δ^2-isoxazolines derived from both activated and unactivated disubstituted olefins.

Most importantly, reasonable yields of cycloadducts were also obtainable by thermolysis of TOP-furoxan (**7**) in the presence of trisubstituted olefins. For example, with 1.1 equiv of trimethylethylene, a 73% yield of cycloadduct is detected (entry **o**). Employing 2 equiv of olefin does increase the yield by ~10%. As such, 2 equiv of trisubstituted olefin was employed in the subsequent examples. As expected, the high regioselectivity obtained with trisubstituted olefins (in all cases only a single isomer was detected) was unaffected by the location of the "activating" group (entries **p–s**).[12] Note that, as with monosubstituted olefins, the nitrile oxide oxygen becomes bonded to the most substituted end of the alkene. Finally, even tetramethylethylene does produce some cycloadduct albeit in low yield with a larger excess of olefin (entry **t**). Overall, thermolysis of TOP-furoxan (**7**) with di- and trisubstituted olefins is presently the only useful method for intermolecular cycloaddition to form these more highly substituted Δ^2-isoxazolines.[15]

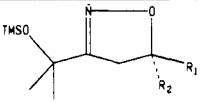
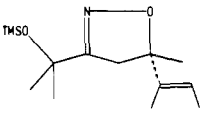
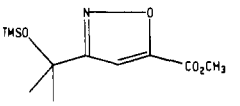
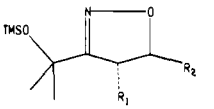
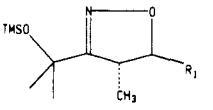
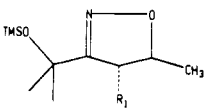
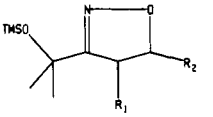
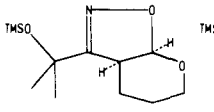
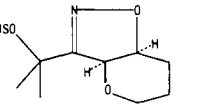
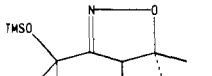
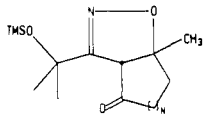
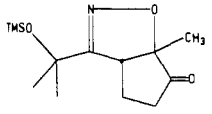
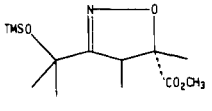
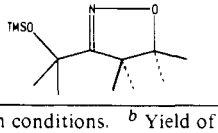
(11) Equivalents are calculated on the basis of the fact that one molecule of furoxan fragments to two molecules of nitrile oxide. Thus 1 equiv of olefin corresponds to 1 mmol of olefin to 0.5 mmol of furoxan.

(12) Houk, K. N.; Sims, J.; Duke, Jr., R. E.; Strozier, R. W.; George, J. K. *J. Am. Chem. Soc.* **1973**, *95*, 7287. Houk, K. N.; Sims, J.; Watts, C. R.; Luskus, L. J. *Ibid.* **1973**, *95*, 7301.

(13) Martin, S. F., Dupre, B. *Tetrahedron Lett.* **1983**, *24*, 1337.

(14) At room temperature, cycloaddition of nitrile oxides to dihydropyran was reported to give a single regioisomer in low yield accompanied by large amounts of dimer. Paul, R.; Techelitcheff, S. *Bull. Chem. Soc. Fr.* **1962**, 2215. Adachi, I.; Kano, H. *Chem. Pharm. Bull.* **1968**, *16*, 117.

Table I. Cycloadducts Formed by Thermolysis of TOP-Furoxan (7)[a]

entry	olefin (equiv)	cycloadduct 9	yield[b] (yield[c])
			
a	styrene (1.1)[d]	R_1 = H, R_2 = Ph	63%
b	2-methyl-1-pentene (1.1)	R_1 = CH_3, R_2 = *n*-Pr	79%
c	 (1.1)		68%
d	methyl propiolate (1.1)		58%
			
e	*trans*-4-octene (1.1)	R_1 = R_2 = *n*-Pr	81%
f	*trans*-stilbene[d] (1.1)	R_1 = R_2 = Ph	67%
		 	
		9 9′	
g	crotyl alcohol (1.1)	R_1 = CH_2OH (1/1)	47%
h	methyl crotonate (1.1)	R_1 = CO_2Me (1.25/1)	85%
i	*trans*-β-methylstyrene (1.1)	R_1 = Ph (3/2)	84%
			
j	*cis*-stilbene (1.1)	R_1 = R_2 = Ph	57%
k	cyclopentene (1.1)	R_1 = R_2 = $(CH_2)_3$	78%
l	cyclohexene (1.1)	R_1 = R_2 = $(CH_2)_4$	70%
m	 (1.1)	R_1 = CH_3, R_2 = *i*-Pr	59%
n	dihydropyran (1.1)	 	51% (5.5/1)[e]
		9 9′	
o	trimethylethylene (1.1)		(73%)
	(2.2)		(83%)
p	3-methylcyclopent-2-en-1-one *n* = 1		67%
q	3-methylcyclohex-2-en-1-one (2.2) *n* = 2		(78%)
r	2-methylcyclopent-2-en-1-one (2.2)		64%
s	methyl tiglate (2.2)		85%
t	tetramethylethylene (10)		6% (12%)

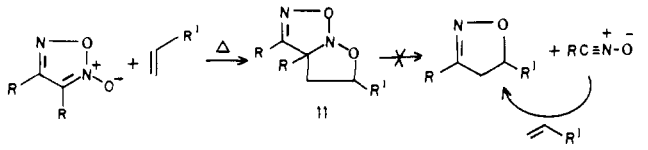
[a] Benzene, 165 °C, 17 h; see experimental for detailed reaction conditions. [b] Yield of isolated and purified product. [c] ^1H NMR yield. [d] Protected from light during thermolysis. [e] A 10.5/1 ratio was obtained at 150 °C (3 days).

Control experiments indicated that the dimer was not indefinitely stable under the reaction conditions. Heating in the absence of olefin lead to complete disappearance of **7**. Several products were formed as indicated by the presence of a variety of methyl and trimethylsilyl singlets in the ^{1}H NMR spectrum. The identity of these products was not pursued; however, thermolysis of di-*tert*-butylfuroxan (**10**) in C_6D_6 did produce a large *tert*-butyl singlet at correct chemical shift for *tert*-butyl isocyanate, along with several smaller unidentified *tert*-butyl peaks. Thus, as the rate of cycloaddition becomes extremely sluggish, furoxan decomposition (likely via the nitrile oxide) becomes a problem. Nonetheless, useful yields can still be obtained with trisubstituted olefins.

We feel that the mechanism is that outlined in eq 2. In a series of control experiments, the possibility for isoxazoline cycloreversion was tested. Heating of the trimethylethylene adduct **9o** in the presence of styrene at temperatures up to 200 °C produced no styrene cycloadduct. By the same token, the *cis*-stilbene adduct **9j** does not interchange with added *trans*-stilbene (up to 165 °C). Finally, when separately heated to 165 °C, pure **9h** and **9i** did not produce any of the alternate regioisomers (**9h′** and **9i′**). Thus, the isomeric ratios are kinetically controlled. Overall then, no evidence was obtained for isoxazoline cycloreversion at temperatures up to 200 °C. In contrast, related isoxazolidines can cyclorevert in this range, particularly when substituted with electron-withdrawing groups.[16]

The centrality of the bulky substituent to the success of the thermolysis was readily ascertained. Heating of diethylfuroxan with 1-hexene at 200 °C for 24 h produced no trace of cycloadduct and both starting materials were cleanly recovered.[17] The temperature is simply not sufficient for cycloreversion. Finally, although the furoxan **7** and nitrile oxide **8** are likely in equilibrium, not surprisingly the steady-state concentration of the nitrile oxide is very low. Thus, heating of di-*tert*-butylfuroxan (**10**) produced no detectable *tert*-butyl singlet for the nitrile oxide.[3]

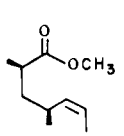
All of these observations are consistent with reversible cycloreversion of the furoxan **7** to two molecules of nitrile oxide **8** followed by irreversible cycloaddition of **8** with the appropriate olefin. With particularly sluggish olefins, rearrangement and/or decomposition of **8** becomes competitive.[15] An alternate mechanism which invokes initial olefin–furoxan cycloaddition, followed by cycloreversion of the resultant adduct **11** to give an isoxazoline and a nitrile oxide (eq 3), seems less likely since bulky substituents



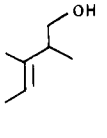
(3)

actually facilitate rather than hinder the reaction. In addition, adducts of the type **11** have been proposed (and in some cases isolated). Such adducts fragment by loss of RCN rather than RCNO.[18]

(15) With two more highly branched olefins, lower yields were obtained. In these cases, dimer decomposition products were observed and the starting olefins were recovered.



~20% Yield
Mixture of (stereo?) isomers

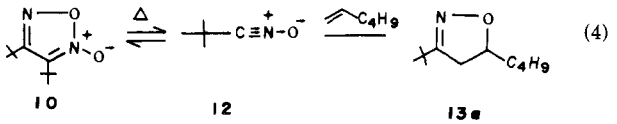


< 5% Yield

(16) See ref 10. See also: Tufariello, J. In ref 10b, p 107.

(17) Dialkyl furoxans have been shown to react directly with highly electron deficient dipolarophiles such as *N*-phenylmaleimide at ~135 °C. See ref 18.

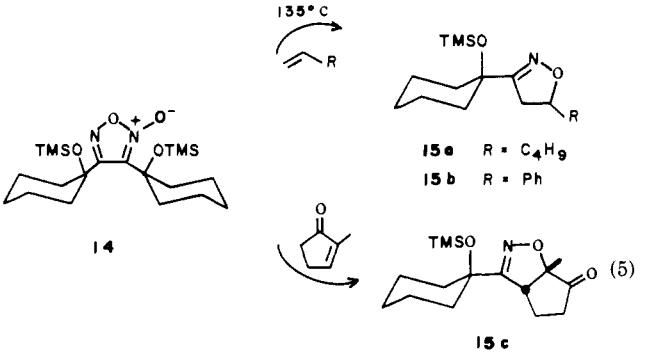
In order to gauge the effectiveness of TOP-furoxan (**7**) in the cycloreversion procedure, di-*tert*-butylfuroxan (**10**) was briefly investigated for comparison purposes (eq 4). Upon heating with



10 12 13a (4)

1-hexene (1.1 equiv, C_6H_6) at 135 °C for 21 h, di-tert-butylfuroxan (**10**) was completely consumed. Kugelrohr distillation of the crude reaction mixture gave a 78% yield of analytically pure cycloadduct **13a**, presumably via the intermediacy of 2,2-dimethylpropanenitrile oxide (**12**). Note that di-*tert*-butylfuroxan (**10**) fragments at a qualitatively similar rate to TOP-furoxan (**7**) at 30 °C lower temperature. Several cycloadducts were generated under these standard conditions and the results are compiled in Table II. We were somewhat surprised to learn that, *despite the lower fragmentation temperature, di-tert-butylfuroxan (**10**) consistently gave 20–40% lower yields when compared with TOP-furoxan (**7**).* For example, di-*tert*-butylfuroxan and 2.2 equiv of trimethylethylene were heated in C_6D_6 at 135 °C with a small amount of *p*-dimethoxybenzene as an internal standard. ^{1}H NMR integration indicated a 56% yield of cycloadduct **13d**. In a similar experiment at 165 °C with TOP-furoxan (**7**), an 83% yield of **9o** was indicated. This is not simply a temperature effect since repetition of the former experiment at 165 °C did not increase the yield of **13d** (54%). Thus, despite the higher temperatures required, the advantages of TOP-furoxan (**7**) over di-*tert*-butylfuroxan (**10**) are clear. One must conclude that 2,2-dimethylpropanenitrile oxide (**12**) either rearranges (decomposes) faster than or cycloadds slower than nitrile oxide **8**.

We have also prepared bis[1-[(trimethylsilyl)oxy]cyclohex-1-yl]furoxan (**14**) (mp 85–86 °C) with the anticipation that the bulky cyclohexyl groups might further lower the temperature required for a reasonable cycloreversion rate. Heating of furoxan **14** with 1-hexene at 135 °C for 36 h gave 90% isolated yield of **15a** (eq 5). A similar experiment conducted with styrene and



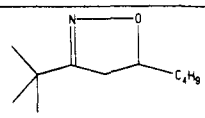
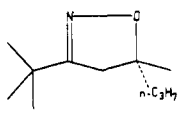
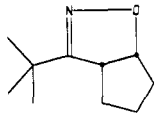
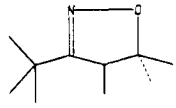
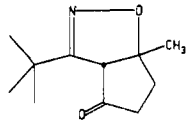
(5)

14 at 135 °C showed a $t_{1/2} \approx 9$ h. Under identical conditions the TOP-furoxan cycloaddition has a $t_{1/2} \approx 50$ h. Despite the lower temperatures employed with **14**, increases in yield were not apparent. For example, cycloaddition of **14** with 2-methylcyclopentenone at 135 °C provided **15c** in 62% yield as determined by ^{1}H NMR integration. This is virtually identical with the yield with TOP-furoxan and the same olefin (Table I, entry **r**). In addition, the purified yield of **15c** was substantially reduced due to difficulties in separation from decomposition products of dimer **14**. No such difficulties were encountered with TOP-furoxan. Thus, unless temperature is absolutely critical, TOP-furoxan is clearly the reagent of choice.

In conclusion, the cycloreversion of TOP-furoxan provides the first practical method of nitrile oxide generation which permits intermolecular cycloaddition with 1,2-di- and trisubstituted olefins. As expected, cycloadditions with trisubstituted olefins are highly

(18) Shimizu, T.; Hayashi, Y.; Teramura, K. *J. Org. Chem.* **1983**, *48*, 3053. Shimizu, T.; Hayashi, Y.; Taniguchi, T.; Teramura, K. *Tetrahedron* **1985**, *41*, 727.

Table II. Cycloadducts Formed by Thermolysis of Di-*tert*-butylfuroxan (**10**)[a]

entry	olefin (equiv)	cycloadduct **13**	yield[b] (yield[c])
a	1-hexene (1.1)		78%
b	2-methyl-1-pentene (1.1)		77%
c	cyclopentene (1.1)		40%
d	trimethylethylene (2.2) (10.0)		(56%) 59%
e	3-methylcyclopent-2-en-1-one (**1.1**) (2.2)		(42%) (65%)

[a] Benzene, 135 °C, 16 h. [b] Yield of isolated and purified product. [c] ^{1}H NMR yield.

regioselective. All available evidence points to a reversible cycloreversion of the furoxan to two molecules of nitrile oxide followed by irreversible [3 + 2] dipolar cycloaddition with the added olefin. The accessibility of the resultant Δ^2-isoxazolines, combined with the facile subsequent transformation to β-hydroxy acids, should significantly extend the utility of the cycloadditive strategy to aldol-type adducts.

Experimental Section[19]

Bis[2-[(trimethylsilyl)oxy]prop-2-yl]furoxan[20] (TOP-furoxan, 7). To a solution of 2-[(trimethylsilyl)oxy]-2-methyl-1-nitropropane (**6**)[3] (9.55 g, 50 mmol) and dry benzene (75 mL) was added phenylisocyanate (11.9 mL, 110 mmol) and triethylamine (1.40 mL, 10.0 mmol). This solution was refluxed for 18 h. Water (2.0 mL) was added and the resulting mixture was stirred 1 h, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude product was then dissolved in hexane and filtered through a column of Florisil. The eluent was concentrated under reduced pressure and purified by Kugelrohr distillation [bp 110 °C (0.5 mm)] to give 6.62 g (77%) of **7** as a white solid: mp 32–33 °C (MeOH); ^{1}H NMR δ 1.76 (6 H, s), 1.72 (6 H, s), 0.22 (9 H, s), 0.13 (9 H, s); IR 2950, 1670, 1455, 1380, 1360 cm^{-1}; MS, *m/e* calcd for $C_{13}H_{27}N_2O_4Si_2(M - CH_3)$ 331.1509, found 331.1512. Anal. Calcd for ($C_{14}H_{30}N_2O_4Si_2$): C, 48.52; H, 8.73. Found: C, 48.63; H, 8.71.

General Thermolysis Procedure. Cyclopentene Adduct 9k. A solution of TOP-furoxan (**7**) (173 mg, 0.50 mmol), cyclopentene (88.0 μL, 1.00 mmol), and benzene (1.0 mL) was placed into a glass pressure tube. The tube was sealed and immersed in silicon oil. Subsequently, the solution was heated to 165 °C for 17 h. The resulting solution was cooled, concentrated under reduced pressure, and purified by Kugelrohr distillation [bp 70–80 °C (0.2 mm)] to give 188 mg (78%) **9k**[6] as a colorless oil.

5-(But-2-en-2-yl)-5-methyl-3-[2-[(trimethylsilyl)oxy]prop-2-yl]-2-isoxazoline (9c) was prepared from (*E*)-2,3-dimethyl-1,3-pentadiene:[21] ^{1}H NMR δ 5.62 (1 H, q, J = 6.7 Hz), 3.02 (1 H, d, J = 17.1 Hz) and 2.75 (1 H, d, J = 17.1 Hz) (ABq), 1.65 (3 H, s), 1.62 (3 H, d, J = 6.7 Hz), 1.50 (3 H, s), 1.48 (3 H, s), 1.44 (3 H, s), 0.12 (9 H, s); IR (neat) 2985, 1605, 1370, 1355, 1295, 1160 cm^{-1}; MS, *m/e* calcd for $C_{14}H_{27}NO_2Si$-(M^+) 269.1811, found 269.1812.

5-Carbomethoxy-3-[2-[(trimethylsilyl)oxy]prop-2-yl]-2-isoxazole (9d) was prepared from ethyl propiolate and purified by semipreparative HPLC (3% EtOAc/hexane); ^{1}H NMR δ 6.97 (1 H, s), 4.43 (1 H, q, J = 6.75 Hz), 1.65 (6 H, s), 1.42 (3 H, t, J = 6.75 Hz), 0.11 (9 H, s); IR 1730, 1470, 1370, 1350 cm^{-1}; MS, *m/e* calcd for $C_{11}H_{18}NO_4Si(M - CH_3)$ 256.1005, found 256.1006.

4β,5α-Diphenyl-3-[2-[(trimethylsilyl)oxy]prop-2-yl]-2-isoxazoline (9f) was prepared from *trans*-stilbene and purified by MPLC (Lobar A column, 5% EtOAc/hexane): ^{1}H NMR δ 7.39 (10 H, m), 5.43 (1 H, d, J = 4.9 Hz), 4.48 (1 H, d, J = 4.9 Hz), 1.62 (3 H, s), 1.41 (3 H, s), −0.12 (9 H, s); IR 1600, 1495, 1455, 1380, 1360, 1040, 840 cm^{-1}; MS, *m/e* calcd for $C_{20}H_{24}NO_2Si(M - CH_3)$ 338.1576, found 338.1575.

4β-Methyl-5α-(hydroxymethyl)-3-[2-[(trimethylsilyl)oxy]prop-2-yl]-2-isoxazoline (9g) and 5β-methyl-4β-(hydroxymethyl)-3-[2-[(trimethylsilyl)oxy]prop-2-yl]-2-isoxazoline (9g′) were produced as a 1/1 mixture from crotyl alcohol and readily separable by flash chromatography (12% EtOAc/hexanes). **9g** (less polar): ^{1}H NMR δ 4.19 (1 H, m), 3.73 (1 H, m), 3.57 (1 H, m), 3.29 (1 H, m), 1.93 (1 H, br t, exchanges with D_2O), 1.57 (3 H, s), 1.49 (3 H, s), 1.35 (3 H, d, J = 7.88 Hz), 0.15 (9 H, s); irradiate 1.35, 3.29 collapses to a doublet, J = 8.9 Hz; IR 3500 (br), 1380, 1360 cm^{-1}. **9g′** (more polar): ^{1}H NMR δ 4.42 (1 H, m), 3.78 (1 H, m), 3.69 (1 H, m), 3.38 (1 H, dd, exchanges with D_2O), 1.68 (3 H, s), 1.53 (3 H, s), 1.38 (3 H, d, J = 6.75 Hz), 0.23 (9 H, s), irradiate 1.38, 4.42 collapses to a doublet, J = 8.9 Hz; IR 3400 (br), 1380, 1360 cm^{-1}; MS *m/e* calcd for $C_{10}H_{20}NO_3Si(M - CH_3)$ 230.1212, found 230.1213.

5α-Carbomethoxy-4β-methyl-3-[2-[(trimethylsilyl)oxy]prop-2-yl]-2-isoxazoline (9h) and 4β-carbomethoxy-5α-methyl-3-[2-[(trimethylsilyl)-oxy]prop-2-yl]-2-isoxazoline (9h′) were produced from methyl crotonate as a 1.25/1 mixture of **9h**/**9h′** which was readily separable (flash chromatography, 12% EtOAc/hexanes). **9h′** (less polar): ^{1}H NMR δ 4.57 (1 H, d, J = 5.63 Hz), 3.78 (3 H, s), 3.62 (1 H, m); 1.58 (3 H, s), 1.50 (3 H, s), 1.43 (3 H, d, J = 7.88 Hz), 0.15 (9 H, s); IR 1725, 1420, 1370, 1350 cm^{-1}; MS, *m/e* calcd for $C_{11}H_{20}NO_4Si(M - CH_3)$ 258.1162, found 258.1161. **9h** (more polar): ^{1}H NMR 4.82 (1 H, m), 3.73 (3 H, s, overlapping 1 H, d), 1.58 (3 H, s), 1.52 (3 H, s), 1.38 (3 H, d, J = 6.75 Hz), 0.13 (9 H, s); IR 1740, 1430, 1380, 1360 cm^{-1}.

5α-Phenyl-4β-methyl-3-[2-[(trimethylsilyl)oxy]prop-2-yl]-2-isoxazoline (9i) and 4β-phenyl-5α-methyl-3-[2-[(trimethylsilyl)oxy]prop-2-yl]-2-isoxazoline (9i′) were produced from *trans*-β-methylstyrene as an inseparable 60/40 mixture of **9i**/**9i′**: ^{1}H NMR 7.5–7.1 (10 H, m), 5.04 (1 H, d, J = 6.75 Hz), 4.56 (1 H, m), 3.97 (1 H, d, J = 4.5 Hz), 3.32 (1 H, m), 1.61 (3 H, s), 1.58 (3 H, s), 1.53 (3 H, s), 1.49 (3 H, s), 1.43 (3 H, d, J = 4.50 Hz), 1.34 (3 H, d, J = 6.75 Hz), 0.12 (9 H, s), −0.02 (9 H, s); IR (neat) 1600, 1495, 1450, 1380, 1360 cm^{-1}; MS, *m/e* calcd for $C_{15}H_{22}NO_2Si(M - CH_3)$ 276.1420, found 276.1420.

(19) **General.** All melting points and boiling points are uncorrected. Kugelrohr boiling points refer to oven temperature. All reactions were performed under nitrogen atmosphere. Benzene was distilled from Na/benzophenone. Phenyl isocyanate was vacuum distilled prior to use. All olefins employed were commercially available unless otherwise indicated. ^{1}H NMR spectra were recorded on a Bruker Model WH-300 spectrometer in $CDCl_3$. 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 by peak match on a Varian MATCH-5DF. Full characterization of compounds **9a,b,e,k,l**, and **13a,c** has been previously reported in ref 3.

(20) The preferred name for furoxan is 1,2,5-oxadiazole 2-oxide. The preferred name for Δ^2-isoxazoline (2-isoxazoline) is 4,5-dihydroisoxazole.

(21) The diene was prepared by addition of MeMgBr (2.1 equiv) to methyl tiglate followed by dehydration with pTSA.

4β-,5β-Diphenyl-3-[2-[(trimethylsilyl)oxy]prop-2-yl]-2-isoxazoline (9j) was prepared from *cis*-stilbene. Purified by MPLC (Lobar A column, 5% EtOAc/hexane) to give a white solid: mp 87–88 °C (MeOH); ^{1}H NMR δ 7.06 (8 H, m), 6.88 (1 H, s), 6.86 (1 H, s), 5.73 (1 H, d, J = 9.5 Hz), 4.51 (1 H, d, J = 9.5 Hz), 1.60 (3 H, s), −0.02 (9 H, s); IR 1600, 1490, 1450, 1380, 1360 cm^{-1}; MS, m/e calcd for $C_{20}H_{24}NO_2Si$(M − CH_3) 338.1576, found 338.1575.

5β-Methyl-4β(2-propyl)-3-[2-[(trimethylsilyl)oxy]prop-2-yl]-2-isoxazoline (9m) was prepared from *cis*-4-methyl-2-pentene and purified by semipreparative HPLC (3% EtOAc/hexane): ^{1}H NMR δ 3.79 (1 H, dd, J = 10.0 Hz, 2.25 Hz), 3.09 (1 H, m), 2.01 (1 H, m), 1.57 (3 H, s), 1.51 (3 H, s), 1.12 (3 H, d, J = 6.75 Hz), 1.09 (3 H, d, J = 6.75 Hz), 0.95 (3 H, d, J = 6.75 Hz), 0.16 (9 H, s); IR 1480, 1380, 1360 cm^{-1}; MS, m/e calcd for $C_{12}H_{24}NO_2Si$(M − CH_3) 242.1576, found 242.1573.

Dihydropyran cycloadducts 9n (major) and 9n′ (minor) were separated by flash chromatography (7.5% EtOAc/hexane). **9n**: ^{1}H NMR δ 5.70 (1 H, d, J = 6.87 Hz), 3.81 (1 H, m), 3.64 (1 H, m), 3.21 (1 H, q, J = 6.48 Hz), 2.21 (1 H, m), 1.93 (1 H, m), 1.68 (2 H, m), 1.60 (3 H, s), 1.52 (3 H, s), 0.16 (9 H, s); ^{13}C NMR δ 2.44, 19.7, 20.8, 29.0, 30.0, 44.3, 60.3, 73.0, 101.8, 166.9; IR (neat) 2960, 1470, 1385, 1365 cm^{-1}; MS, m/e calcd for $C_{11}H_{20}NO_3Si$(M − CH_3) 242.1212, found 242.1212. **9n′**: ^{1}H NMR δ 4.72 (1 H, d, J = 4.5 Hz), 4.08 (1 H, m), 3.74 (1 H, m), 3.40 (1 H, m), 2.30–1.40 (4 H, m), 1.59 (3 H, s), 1.53 (3 H, s), 0.14 (9 H, s); ^{13}C NMR δ 165.9, 78.63, 77.97, 72.56, 63.11, 30.12, 29.12, 21.31, 20.02, 2.42; IR (neat) 2960, 1460, 1440, 1380, 1360, 1255 cm^{-1}; MS, m/e calcd for $C_{11}H_{20}NO_3Si$(M − CH_3) 242.1212, found 242.1212.

4,5,5-Trimethyl-3-[2-[(trimethylsilyl)oxy]prop-2-yl]-2-isoxazoline (9o) was prepared from 2-methyl-2-butene. Purified by Kugelrohr distillation [bp 90 °C (2.2 mm)]; ^{1}H NMR δ 2.92 (1 H, q, J = 7.88 Hz), 1.57 (3 H, s), 1.52 (3 H, s), 1.28 (3 H, s), 1.26 (3 H, s), 1.18 (3 H, d, J = 7.88 Hz), 0.16 (9 H, s); IR 1450, 1380, 1365 cm^{-1}; MS, m/e 228, 200, 131. Anal. calcd for ($C_{12}H_{25}NO_2Si$): C, 59.21; H, 10.35. Found: C, 58.98; H, 10.40.

3-Methylcyclopentenone adduct 9p was purified by flash chromatography (14% EtOAc/hexane): ^{1}H NMR δ 3.51 (1 H, s), 2.7–2.3 (3 H, m), 1.98 (1 H, m), 1.53 (3 H, s), 1.50 (3 H, s), 1.48 (3 H, s), 0.13 (9 H, s); IR 1730, 1600, 1440, 1400 cm^{-1}; MS, m/e calcd for $C_{12}H_{20}NO_3Si$(M − CH_3) 254.1212, found 254.1212. Anal. Calcd for ($C_{13}H_{23}NO_3Si$): C, 57.96; H, 8.60. Found: C, 58.11; H, 8.55.

3-Methylcyclohexenone adduct 9q was purified by flash chromatography (10% EtOAc/hexane) to give 32 mg (23%) of product: ^{1}H NMR δ 3.71 (1 H, d, J = 1 Hz), 2.62 (1 H, m), 2.29 (1 H, m), 2.03 (2 H, m), 1.66 (2 H, m), 1.60 (3 H, s), 1.48 (3 H, s), 1.46 (3 H, s), 0.13 (9 H, s); IR 1710, 1460, 1380, 1365 cm^{-1}; MS, m/e calcd for $C_{14}H_{25}NO_3Si(M^+)$ 283.1604, found 283.1603.

2-Methylcyclopentenone adduct (9r) was purified by flash chromatography: ^{1}H NMR δ 3.64 (1 H, dd, J = 8.00, 2.50 Hz), 2.38 (3 H, m), 2.07 (1 H, m), 1.61 (3 H, s), 1.53 (3 H, s), 1.38 (3 H, s), 0.14 (9 H, s); IR 1760, 1380, 1360 cm^{-1}; MS, m/e calcd for $C_{13}H_{23}NO_3Si(M^+)$ 269.1447, found 269.1447.

5α-Carbomethoxy-5β,4a-dimethyl-3-[2-[(trimethylsilyl)oxy]prop-2-yl]-2-isoxazoline (9s) was purified by Kugelrohr distillation [bp 90 °C (0.2 mm)]: ^{1}H NMR δ 3.76 (3 H, s), 3.63 (1 H, q, J = 6.75 Hz), 1.56 (3 H, s), 1.51 (3 H, s), 1.47 (3 H, s), 1.25 (3 H, d, J = 6.75 Hz), 0.15 (9 H, s); IR 1725, 1440, 1380, 1360 cm^{-1}; MS, m/e calcd for $C_{12}H_{22}NO_2Si$(M − CH_3) 272.1318, found 272.1314.

4,4,5,5-Tetramethyl-3-[2-[(trimethylsilyl)oxy]prop-2-yl]-2-isoxazoline (9t) was purified by semipreparative HPLC followed by MPLC (Lobar A column, 3% EtOAc/hexane): ^{1}H NMR δ 1.58 (6 H, s), 1.18 (6 H, s), 1.17 (6 H, s), 0.18 (9 H, s); IR 1380, 1360, 1040 cm^{-1}; MS, m/e calcd for $C_{12}H_{24}NO_2Si$(M − CH_3) 242.1576, found 242.1584.

3,4-Bis(1,1-dimethylethyl)furoxan[20] (Di-*tert*-butylfuroxan, 10). To a solution of 2,2-dimethylpropanaldoxime chloride[22] (542 mg, 4.00 mmol) in benzene (10 mL) was added triethylamine (572 μL, 4.10 mmol). The reaction mixture was refluxed for 18 h, diluted with ether, and filtered through a column of florisil. The resulting solution was concentrated under reduced pressure and the solid obtained was recrystallized from methanol to give 265 mg of **10** (67%) as a white solid, mp 68.5–69 °C: ^{1}H NMR δ 1.50 (9 H, s), 1.48 (9 H, s).

5-Methyl-5-(1-propyl)-3-(2-methylprop-2-yl)-2-isoxazoline (13b) was prepared with 2-methyl-1-pentene and purified by Kugelrohr distillation: ^{1}H NMR δ 2.69 (2 H, AB quartet), 1.7–1.25 (4 H, m), 1.32 (3 H, s), 1.18 (9 H, s), 0.93 (3 H, t, J = 7.88 Hz); IR 1450, 1360, 910 cm^{-1}; MS, m/e calcd for $C_{11}H_{21}NO$ 183.1623, found 183.1624.

4,5,5-Trimethyl-3-(2-methylprop-2-yl)-2-isoxazoline (13d) was prepared from 2-methyl-2-butene and purified by semipreparative HPLC (5% EtOAc/hexane): ^{1}H NMR δ 2.76 (1 H, q, J = 6.75 Hz), 1.29 (3 H, s), 1.25 (9 H, s), 1.24 (3 H, s), 1.13 (3 H, d, J = 6.75 Hz), IR 1450, 1375, 1355 cm^{-1}; MS, m/e calcd for $C_{10}H_{19}NO(M^+)$ 169.1467, found 169.1470. Anal. Calcd for ($C_{10}H_{19}NO$): C, 70.96; H, 11.31. Found: C, 71.09; H, 11.30.

3-Methylcyclopentenone adduct 13e was purified by flash chromatography (15% EtOAc/hexane): ^{1}H NMR δ 3.38 (1 H, s), 2.61 (1 H, m), 2.43 (2 H, m), 1.99 (1 H, m), 1.47 (3 H, s), 1.24 (9 H, s); IR 1740, 1440, 1380, 1360 cm^{-1}; MS, m/e calcd for $C_{11}H_{17}NO_2(M^+)$ 195.1259, found 195.1261.

3,4-Bis[2-[(trimethylsilyl)oxy]cyclohex-1-yl]furoxan (14) was prepared in the same manner as furoxan **7**: mp 85–86 °C (MeOH); ^{1}H NMR δ 2.45 (4 H, m), 2.02 (4 H, m), 1.72 (4 H, m), 1.40 (8 H, m), 0.11 (9 H, s), 0.56 (9 H, s); IR 1560, 1430, 1210, 1030 cm^{-1}; MS, m/e calcd for $C_{19}H_{35}N_2O_4Si_2$(M − CH_3) 411.2134, found 411.2135.

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α-Deuterium and Carbon-13 Kinetic Isotope Effects Associated with the S_N2 Displacement of Iodide and Tosylate by Lithium Organocuprates[1a]

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Abstract: The secondary α-deuterium and ^{13}C isotope effects associated with the competitive methylation of two cuprates, (n-C_8H_{17})$_2$CuLi(PBu_3) and (n-C_8H_{17})$_4$CuLi$_3$(PBu_3), by CH_3X–CD_3X and $^{12,13}CH_3X$ (X = I or OTs) together with their related temperature dependences are reported.

The significance of the temperature dependence of primary hydrogen kientic isotope effects has recently received increased attention.[2] The corresponding influence on α-secondary hydrogen kinetic isotope effects is widely held to be less significant. In fact,

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