mp 121–122 °C (dec). Anal. Calcd for $C_{20}H_{26}N_4O_8$ (M_r 450.45): C, 53.33; H, 5.82; N, 12.44. Found: C, 53.13; H, 5.93; N, 12.25.

For the synthesis of [^{15}N]-Boc-alanyl-prolyl-*O*-(*p*-nitrobenzoyl)hydroxylamine, Boc-alanyl-prolyl-methyl ester was treated in MeOH with ^{15}N enriched hydroxylamine (containing methanol solution). Mass spectrometric analysis gave 48 ± 2% ^{15}N enrichment in the final diacylated product.

Kinetics. The previously employed spectrophotometric procedure[1,2] was followed. The temperature dependence, the pH dependence, and solvent isotope effects for the decomposition of *N*-acyl-*O*-(*p*-nitrobenzoyl)hydroxylamines were measured with a Carl-Zeiss-Jena micropressor-controlled Specord M 40 spectrophotometer equipped with a jacketed cell compartment, containing electrical heater and temperature control. Temperatures were precise within ±0.1 °C. Data collected and stored in an internal buffer were analyzed with software packages provided on an application ROM for the instrument. The nitrogen isotope effect was determined with a Cary 118 spectrophotometer equipped with a jacketed cell holder and interfaced to a Zenith 158 personal computer for data acquisition. The temperature was maintained with a Lauda K4R circulating water bath and was monitored with a thermistor for direct electronic reading near the sample holder. Reactions were carried out in 1.0-cm Teflon-stoppered silica cells. For kinetic runs at temperatures distant from room temperature, sufficient thermal equilibration time was allowed. After the reaction was initiated by addition of the substrate-containing sample to the thermally equilibrated cell, the first 5 min of data aquisition was ignored for calculations. Stock solutions were made in H_2O (*N*-alanyl-alanyl-*O*-(*p*-nitrobenzoyl)- and *N*-alanyl-prolyl-*O*-(*p*-nitrobenzoyl)hydroxylamine), in methanol (*N*-Boc-alanyl-prolyl-*O*-(*p*-nitrobenzoyl)hydroxylamine), and acetonitrile (*N*-acetyl-*O*-(*p*-nitrobenzoyl)hydroxylamine. Final concentrations were achieved by dilution of the stock solution in the buffer-containing UV cell. All substrate solutions were (1.0–1.3) × 10^{-4} M. Reactions were monitored by following the absorbance of *p*-nitrobenzoic acid.[1,2] CHES and sodium phosphate buffer solutions were prepared in HOH and DOD as previously described;[17] KCl was used to maintain an ionic strength of 0.125. Data were collected over at least 4–6 half-times, and rate constants were calculated by nonlinear regression programs (Gauss–Newton–approximation method) on a Zenith 158 personal computer or a Hewlett-Packard 2598 A desktop computer.

pK_a Determinations. The UV maximum of 0.1 mM buffered solutions of *N*-acyl-*O*-(*p*-nitrobenzoyl)hydroxylamines shifted from 263 to 268 nm between pH 2.2 and pH 8.6. This allowed calculations of the pK_a's as previously described.[2]

NMR Spectra. ^{13}C NMR spectra were recorded on a Varian XL-300 spectrometer operating at 75.43 MHz, equipped with a 5-mm probe, thermally equilibrated at 20 ± 1 °C. In a typical ^{18}O trapping experiment, a 500-Hz sweep width, 90° pulse angle, 8.02-s acquisition time, and 8.5K data block were used. Protons were broad-band decoupled, and 1500–3000 transients accumulated. As standard parameters for natural-abundance ^{13}C product analysis, 0.6-s acquisition time, 16 500-Hz sweep width, 90° pulse angle, a 20K data block, and 2000–5000 transients were used. TMS was used as external standard.

Product Analysis. Solutions (30–60 mM) of diacyl hydroxamic acids were prepared in 0.5 mL of acetonitrile or 0.5 mL of dimethyl sulfoxide, 0.5 mL of 0.2 M sodium phosphate buffer (pH 7.0) was added, and the spectra were recorded. For the degradation studies, similar solutions were prepared and stored in 2.0-mL glass vials for 2–5 days at 37 °C in a shaking water bath. Before NMR analysis, organic solvent was added to undissolved precipitated *p*-nitrobenzoic acid. In ^{18}O trapping experiments, 10 mM solutions in acetonitrile were made, and 0.25 mL of 0.2 M sodium phosphate buffer (pH 7.0) and 0.25 mL of [^{18}O]water were added. Reference samples contained 0, 25, or 75% [^{18}O]-water. The solutions were kept in a shaking water bath at 50 °C. After 18–24 h, 0.1–0.2 mL of 10% HCl was added. A few crystals of precipitating *p*-nitrobenzoic acid were collected by centrifugation of the solution at 5000 rpm through a filter-containing plastic tube (Centrex, Keene, NH), dried, and supplied for mass spectrometric analysis. Residual solutions were transferred to 5-mm NMR tubes, and the carbonyl region was inspected.

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Registry No. 4-(O_2N)C_6H_4COONHAc, 123206-53-1; H-Ala-Ala-NHOCOC_6H_4-4-NO_2, 87620-98-2; H-Ala-Pro-NHOCOC_6H_4-4-NO_2, 87621-00-9; BOC-Ala-Ala-NHOCOC_6H_4-4-NO_2, 87620-99-3; H-Ala-Ala-NHOCOC_6H_4-4-NO_2·HCl, 123206-54-2; H-Ala-Pro-NHOCOC_6H_4-4-NO_2·HCl, 86030-65-1; HONH$_2$·HCl, 5470-11-1; AcNHOH, 546-88-3; 4-(O_2N)C_6H_4COCl, 122-04-3; BOC-Ala-Ala-OMe, 19794-10-6; BOC-Ala-Pro-OMe, 33300-71-9; BOC-Ala-Pro-^{15}NHOCOC_6H_4-4-NO_2, 123206-55-3; AcOH, 64-19-7; 4-(O_2N)C_6H_4COOH, 62-23-7; $MeNH_2$, 74-89-5.

Supplementary Material Available: First-order rate constants for decomposition and solvent isotope effects for selected compounds (3 pages). Ordering information is given on any current masthead page.

1,3-Dipolar Cycloadditions between Nitrile Oxides and Substituted 7-Oxabicyclo[2.2.1]heptenes

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1,3-Dipolar cycloadditions between aromatic nitrile oxides and a series of 7-oxabicyclo[2.2.1]heptenes have been studied. The reactivity of these systems is compared to that of related bicyclo[2.2.1]heptenes.

Bicyclic derivatives such as 1[1] add soft electrophiles in a regio- and stereoselective manner influenced by the substituents at C-2; however, this is not so clearly established for Diels–Alder cycloadditions.[2] Thus, this remote control appears to be highly reaction dependent. On the other hand, the effect of an oxygen bridge in position 7 should also be taken into account when comparing the higher reactivity of these systems toward electrophiles with that of the corresponding methylene analogues.[3] The

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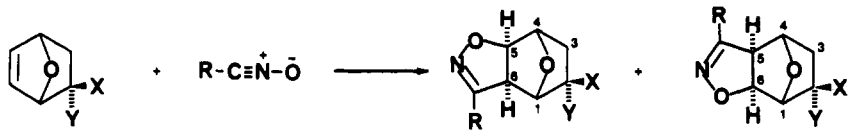
(1) These substrates are versatile synthetic intermediates; see: Auberson, Y.; Vogel, P. *Helv. Chim. Acta* **1989**, *72*, 278 and references therein.
(2) Black, K. A.; Vogel, P. *J. Org. Chem.* **1986**, *51*, 5341–5348.

0022-3263/89/1954-5883$01.50/0

Scheme I

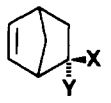


3 4

1a, X=CN, Y=OAc
1b, X, Y=O
1c, X, Y=OCH_2CH_2O

2a, R=C_6H_5
2b, R=2,4,6,$Me_3C_6H_2$

a, X=CN, Y=OAc, R=C_6H_5, (60:40)
b, X=CN, Y=OAc, R=2,4,6,$Me_3C_6H_2$, (50:50)
c, X, Y=O, R=C_6H_5, (65:35)
d, X, Y=O, R=2,4,6,$Me_3C_6H_2$, (55:45)
e, X, Y=OCH_2CH_2O, R=C_6H_5, (53:47)
f, X, Y=OCH_2CH_2O, R=2,4,6,MeC_6H_2, (55:45)



11a, X=CN, Y=OAc
11b, X, Y=O
11c, X, Y=OCH_2CH_2O

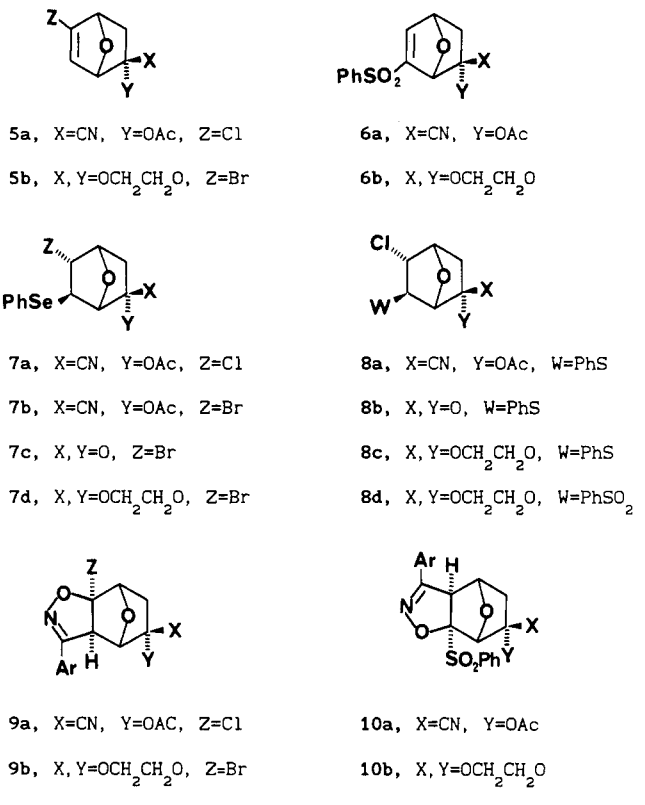
purpose of the present paper is to determine whether or not 1,3-dipolar cycloadditions of nitrile oxides to 7-oxanorbornenic systems[4] are subject to this remote control. Additionally, the reactivity of these systems is compared to that of the corresponding norbornene derivatives.

When benzonitrile oxide, BNO (**2a**), and mesitonitrile oxide, MNO (**2b**), were allowed to react with olefins **1a–c**, mixtures of the corresponding exo adducts **3** and **4** were obtained in nearly quantitative yields. No traces of the compounds resulting from the endo-face attack could be detected. In most cases, it was possible to isolate at least one of the two regioisomers by recrystallization. The isomer ratios obtained in the different reactions are indicated in parentheses in Scheme I. Cycloadditions with other nitrile oxides such as acetonitrile oxide (**2**, R = CH_3) or (ethoxycarbonyl)formonitrile oxide (**2**, R = CO_2Et) led to 1:1 regioisomeric mixtures of the corresponding cycloadducts.

The structural assignment of the cycloadducts was derived from their ^1H NMR spectra. The splitting pattern of H-1 (s) and H-4 (d, J = 5.5–6.0 Hz) conclusively proves the exo stereochemistry.[2] The regiochemistry of these adducts was determined by NOE measurements; thus, isomers **3** showed a NOE enhancement on H-1 upon irradiation of H-6 whereas isomers **4** displayed a NOE effect on H-4 upon irradiation of H-5. It should be pointed out that H-5 and H-6 may be readily assigned, since the proton attached to the carbon bearing the oxygen atom in the oxazoline ring appears significantly downfield relative to the other isoxazoline proton.

The lack of regioselectivity observed prompted us to consider ways to circumvent the problem. It was speculated that the introduction of substituents at positions 5 and 6 of the oxanorbornenic substrate could render the process highly regioselective and, therefore, increase its synthetic potential. Thus, halogenated derivatives **5** and vinyl sulfones **6** were prepared from precursors **7** and **8** by literature methods[2] (Scheme II), and their reactions with

Scheme II



5a, X=CN, Y=OAc, Z=Cl
5b, X, Y=OCH_2CH_2O, Z=Br

6a, X=CN, Y=OAc
6b, X, Y=OCH_2CH_2O

7a, X=CN, Y=OAc, Z=Cl
7b, X=CN, Y=OAc, Z=Br
7c, X, Y=O, Z=Br
7d, X, Y=OCH_2CH_2O, Z=Br

8a, X=CN, Y=OAc, W=PhS
8b, X, Y=O, W=PhS
8c, X, Y=OCH_2CH_2O, W=PhS
8d, X, Y=OCH_2CH_2O, W=$PhSO_2$

9a, X=CN, Y=OAC, Z=Cl
9b, X, Y=OCH_2CH_2O, Z=Br

10a, X=CN, Y=OAc
10b, X, Y=OCH_2CH_2O

Table I. Rate Constants for Cycloadditions of 1a–c and 11a–c with MNO (CCl_4, 40 °C)

substrate	$k_2 \times 10^3$, L mol^{-1} s^{-1}	substrate	$k_2 \times 10^3$, L mol^{-1} s^{-1}
1a	46 ± 6	11a	4.9 ± 0.1
1b	42 ± 1	11b	5.30 ± 0.05
1c	68 ± 2	11c	5.4 ± 0.1

(3) (a) Huisgen, R. *Pure Appl. Chem.* **1981**, *53*, 171–187. (b) Houk, K. N.; Paddon-Row, M. N.; Rondan, N. G.; Wu, Y.-D.; Brown, F. K.; Spellmeyer, D. C.; Metz, J. T.; Li, Y.; Loncharich, R. J. *Science* **1986**, *231*, 1108–1117.

(4) For previous work on dipolar cycloadditions to oxanorbornenic substrates, see: (a) Arjona, O.; Fernández de la Pradilla, R.; Peréz, R. A.; Plumet, J. *Tetrahedron* **1988**, *44*, 7199–7204. (b) Reymond, J. L.; Vogel, P. *Tetrahedron Lett.* **1988** *29*, 3695–3698. (c) Plumet, J.; Escobar, G.; Manzano, C.; Arjona, O.; Carrupt, P. A.; Vogel, P. *Heterocycles* **1986**, *24*, 1535–1538. (d) Fisera, L.; Kovac, J.; Patus, J.; Parlovic, D. *Collect. Czech. Chem. Commun.* **1983**, *48*, 1048–1056.

Table II. Rate Constants (40 °C, $k_2 \times 10^3$ L mol^{-1} s^{-1}) for Cycloadditions of 1b and 11b with MNO in Different Solvents

	solvent (E_T)		
	CCl_4 (32.5)	$CHCl_3$ (39.1)	$ClCH_2C$-H_2Cl (41.9)
1b	42 ± 1	13 ± 1	18 ± 1
11b	5.30 ± 0.05	2.2 ± 0.1	4.0 ± 0.1

MNO were found to be completely regioselective, affording exclusively adducts **9** and **10**.

The effect of an oxygen bridge in position 7 on the reactivity of some bicyclo[2.2.1]heptene systems in 1,3-dipolar cycloadditions has been dealt with in a previous publication.[5] We have now measured the rate constants for the reactions of **1a–c** and **11a–c** (Scheme I) with MNO, and the results obtained are shown in Table I.[6] Two conclusions may be drawn from these data: (1) the substitution pattern on C-2 does not appear to modify significantly the rate constant; and (2) an approximately 10-fold rate increase can be observed for oxanorbornenic substrates **1** relative to their norbornenic analogues **11**.

The effect of the solvent on the rate of the process[7] has been evaluated in the reactions of ketones **1b** and **11b** with MNO (Table II). A small variation of the rate constants in relation to the polarity parameter of the solvent E_T[8] can be observed.

Finally, in order to determine the activation parameters of the process, the rate constants of the reactions of **1b** and **11b** with MNO have been determined at four different temperatures (Table III). The moderate values of the activation enthalpies together with the very negative values of entropy are in agreement with a concerted process with an early transition state in the reaction coordinate.[9]

Conclusions. As a result of the present study, the following conclusions can be drawn: (1) A concerted pathway is definitely favored for 1,3-dipolar cycloadditions to 7-oxanorbornene systems. (2) Only those 7-oxanorbornene derivatives bearing substituents at the double bond display regioselectivity.

Experimental Section

General Methods. Melting points are uncorrected and were determined on a Büchi 512 melting point apparatus. Infrared spectra were recorded on a Perkin-Elmer 781 or 257 grating spectrophotometer in a KBr pellet unless otherwise stated. ^{1}H and ^{13}C NMR spectra were recorded on Varian FT-80A, Bruker AM-200, Varian XL-300, and Bruker WH-360FT instruments in $CDCl_3$ unless otherwise noted. Mass spectra were recorded on a Varian MAT-711 or HP-5890A instrument.

2-*endo*-Acetoxy-6-*exo*-(phenylselenenyl)-5-*endo*-bromo-7-oxabicyclo[2.2.1]heptane-2-*exo*-carbonitrile (7b). According to a previously described method,[2] **7b** was obtained from **1a**[10] and benzeneselenenyl bromide as a white solid after recrystallization from an ethanol–hexane mixture (85%): mp 78–79 °C; IR 1760 cm^{-1}; ^{1}H NMR δ 7.64 (m, 2 H, Ar H), 7.37 (m, 3 H, Ar H), 5.09 (s, 1 H, H-1), 4.69 (t_{ap}, 1 H, J = 5.1 Hz, H-4), 4.14 (td, 1 H, J = 4.9, 1.5 Hz, H-5), 3.47 (d, 1 H, J = 4.9 Hz, H-6), 2.76 (d, 1 H, J = 14.5 Hz, H-3$_{endo}$), 2.68 (ddd, 1 H, J = 14.5, 5.1, 1.5 Hz, H-3$_{exo}$), 2.07 (s, 3 H, CH_3); ^{13}C NMR δ 168.3, 134.8, 129.2, 128.5, 127.5, 117.3, 87.8, 80.3, 73.9, 50.5, 45.1, 38.0, 19.9.

6-*exo*-(Phenylselenenyl)-5-*endo*-bromo-7-oxabicyclo[2.2.1]heptan-2-one (7c). Saponification of **7b** with sodium methoxide in methanol in the presence of formaline[2,10] afforded **7c** (90%) as a light yellow oil: IR (neat) 1770 cm^{-1}; ^{1}H NMR δ 7.60 (m, 2 H, Ar H), 7.33 (m, 3 H, Ar H), 4.93 (ddm, 1 H, J = 5.9, 5.4 Hz, H-4), 4.31 (m, 1 H, $W_{1/2}$ = 3.5 Hz, H-1), 4.26 (ddd, 1 H, J = 5.4, 4.3, 1.5 Hz, H-5), 3.43 (d, 1 H, J = 4.3 Hz, H-6), 2.92 (d, 1 H, J = 18.0 Hz, H-3$_{endo}$), 2.51 (ddt, 1 H, J = 18.0, 5.9, 1.4 Hz, H-3$_{exo}$); ^{13}C NMR δ 206.2, 134.4, 129.2, 128.3, 127.5, 85.3, 79.8, 50.2, 46.7, 39.6.

6-*exo*-(Phenylselenenyl)-5-*endo*-bromo-2,2-(ethylenedioxy)-7-oxabicyclo[2.2.1]heptane (7d). Ketone **7c** (4 mmol), a catalytic amount of *p*-toluenesulfonic acid, and ethylene glycol (5 mmol) were refluxed in benzene by using a Dean–Stark trap. The reaction mixture was extracted with ethyl acetate, washed with sodium bicarbonate and brine, and dried over magnesium sulfate. Evaporation of the solvent afforded a white solid, which was purified by column chromatography (hexane–ethyl acetate, 3:1) to give **7d** (95%): mp 92–93 °C; IR 1025 cm^{-1}; ^{1}H NMR δ 7.60 (m, 2 H, Ar H), 7.30 (m, 3 H, Ar H), 4.59 (dd, 1 H, J = 6.0, 4.9 Hz, H-4), 4.11 (td, 1 H, J = 4.8, 1.5 Hz, H-5), 4.08 (s, 1 H, H-1), 4.03, 3.89 (m, m, 1 H, 1 H, OCH_2CH_2O), 3.84 (d, 1 H, J = 4.6 Hz, H-6), 3.75 (m, 2 H, OCH_2CH_2O), 2.61 (d, 1 H, J = 13.9 Hz, H-3$_{endo}$), 2.13 (ddt, 1 H, J = 13.9, 6.0, 1.5 Hz, H-3$_{exo}$); ^{13}C NMR δ 133.8, 129.0, 128.6, 127.6, 113.6, 86.0, 80.4, 65.1, 64.4, 51.6, 45.5, 37.6. Anal. Calcd for $C_{14}H_{15}O_3BrSe$: C, 43.10; H, 3.87; Br, 20.48. Found: C, 43.25; H, 3.55; Br, 20.37.

5-Bromo-2,2-(ethylenedioxy)-7-oxabicyclo[2.2.1]hept-5-ene (5b). According to a previously described method for **5a**,[2] **5b** was obtained from **7d** as a white solid. Recrystallization from an ether–hexane mixture afforded **5b** (96%): mp 110–111 °C; IR 1585, 1020 cm^{-1}; ^{1}H NMR δ 6.43 (d, 1 H, J = 1.9 Hz, H-6), 4.81 (dd, 1 H, J = 4.7, 0.7 Hz, H-4), 4.43 (dd, 1 H, J = 1.9, 1.0 Hz, H-1), 4.10, 3.91 (m, m, 1 H, 3 H, OCH_2CH_2O), 2.15 (dd, 1 H, J = 12.2, 4.7 Hz, H-3$_{exo}$), 1.75 (d, 1 H, J = 12.2 Hz, H-3$_{endo}$); ^{13}C NMR δ 131.5, 128.8, 114.3, 83.2, 82.6, 65.0, 64.3, 37.6. Anal. Calcd for $C_8H_9O_3Br$: C, 41.22; H, 3.89; Br, 34.28. Found: C, 41.24; H, 3.48; Br, 34.31.

6-*exo*-(Phenylsulfenyl)-5-*endo*-chloro-2,2-(ethylenedioxy)-7-oxabicyclo[2.2.1]heptane (8c). Treatment of **8b**[2] with ethylene glycol by the procedure described for **7d** afforded a white solid, which was purified by recrystallization from ethanol to give pure **8c** (75%): mp 93–94 °C; IR 1020 cm^{-1}; ^{1}H NMR δ 7.43 (m, 2 H, Ar H), 7.28 (m, 3 H, Ar H), 4.63 (ddm, 1 H, J = 6.0, 5.0 Hz, H-4), 4.05 (m, 3 H, H-1, H-5, OCH_2CH_2O), 3.84 (m, 4 H, H-6, OCH_2CH_2O), 2.54 (d, 1 H, J = 13.9 Hz, H-3$_{endo}$), 2.11 (ddt, 1 H, J = 13.9, 6.0, 1.2 Hz, H-3$_{exo}$); ^{13}C NMR δ 134.5, 130.1, 128.7, 126.6, 113.2, 85.3, 80.0, 65.1, 64.3, 61.4, 51.8, 36.2. Anal. Calcd for $C_{14}H_{15}O_3ClS$: C, 56.28; H, 5.06; Cl, 11.87; S, 10.73. Found: C, 56.21; H, 4.94; Cl, 11.79; S, 11.10.

6-*exo*-(Phenylsulfonyl)-5-*endo*-chloro-2,2-(ethylenedioxy)-7-oxabicyclo[2.2.1]heptane (8d). According to a previously described method,[2] treatment of **8c** with 3-chloroperbenzoic acid gave **8d** as a white solid, which was purified by recrystallization from ethanol (90%): mp 182–183 °C; IR 1105, 1020 cm^{-1}; ^{1}H NMR δ 7.95 (m, 2 H, Ar H), 7.66 (m, 3 H, Ar H), 4.64 (m, 2 H, H-1, H-4), 4.38 (t_{ap}, 1 H, J = 5.4 Hz, H-5), 4.09 (m, 1 H, OCH_2CH_2O), 3.87 (m, 4 H, H-6, OCH_2CH_2O), 2.44 (d, 1 H, J = 14.1 Hz, H-3$_{endo}$), 2.14 (dd, 1 H, J = 14.1, 5.4 Hz, H-3$_{exo}$); ^{13}C NMR δ 137.7, 134.1, 129.3, 128.4, 113.3, 80.4, 79.9, 69.8, 65.3, 64.7, 55.3, 36.2. Anal. Calcd for $C_{14}H_{15}O_5ClS$: C, 50.83; H, 4.57; Cl, 10.72; S, 9.69. Found: C, 50.80; H, 4.27; Cl, 10.50; S, 9.58.

6-(Phenylsulfonyl)-2,2-(ethylenedioxy)-7-oxabicyclo[2.2.1]hept-5-ene (6b). According to a previously described method (DBU, $CHCl_3$, 0 °C) for **6a**,[2] **6b** was obtained from **8d**. Recrystallization from ethanol afforded a white solid **6b** (90%): mp 169–170 °C; IR 1590 cm^{-1}; ^{1}H NMR δ 7.92 (m, 2 H, Ar H), 7.57 (m, 3 H, Ar H), 7.13 (d, 1 H, J = 1.9 Hz, H-5), 5.08 (dm, 1 H, J = 5.2 Hz, H-4), 4.64 (s, 1 H, H-1), 4.04, 3.87 (m, m, 1 H, 3 H, OCH_2CH_2O), 2.25 (dd, 1 H, J = 12.5, 5.2 Hz, H-3$_{exo}$), 1.72 (d, 1 H, J = 12.5 Hz, H-3$_{endo}$); ^{13}C NMR δ 150.4, 146.3, 140.0, 133.5,

(5) Cristina, D.; De Amici, M.; De Micheli, C.; Gandolfi, R. *Tetrahedron* **1981**, *37*, 1349–1357.

(6) No significant differences in regioselectivity could be observed between norbornene derivatives **11a–c** and the 7-oxanorbornene analogues.

(7) For a general discussion of the effect of the solvent on cycloaddition processes, see ref 3a and: Huisgen, R. *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; John Wiley and Sons: New York, 1984; Vol. 1, pp 76–87.

(8) Reichardt, C.; Harbush-Gervert, H. *Liebigs Ann. Chem.* **1983**, 721–743 and references therein.

(9) For a general discussion on activation parameters in 1,3-dipolar cycloadditions, see ref 7, pp 93–98.

(10) Black, K. A.; Vogel, P. *Helv. Chim. Acta* **1984**, *67*, 1612–1615.

Table III. Rate Constants ($k_2 \times 10^3$ L mol^{-1} s^{-1}) and Activation Parameters for Cycloadditions of 1b and 11b with MNO at Different Temperatures (CCl_4)

	T, °C						
	30	35	40	45	50	ΔH^*, kJ/mol	ΔS^*, J/mol K
1b	26 ± 1	33 ± 1	42 ± 1	52 ± 1		34.5 ± 0.5	−103.8 ± 1.15
11b		4.2 ± 0.1	5.30 ± 0.05	5.6 ± 0.2	6.0 ± 0.1	14.3 ± 5.2	−186.3 ± 16.4

129.0, 127.8, 113.2, 81.1, 79.5, 65.2, 64.5, 36.6. Anal. Calcd for $C_{14}H_{14}O_5S$: C, 57.13; H, 4.79; S, 10.89. Found: C, 56.80; H, 4.90; S, 10.74.

General Procedure for 1,3-Dipolar Cycloadditions. Olefins **1a–c**[10,11] (1 mmol) and benzonitrile oxide[12] (BNO) (1.2 mmol) of mesitonitrile oxide[13] (MNO) (1 mmol), dissolved in the minimum amount of carbon tetrachloride, were stirred at room temperature for 5–10 h. Removal of the solvent afforded the crude products, which were worked up as indicated in each case.

Reaction between 1a and BNO. An inseparable mixture of **3a** and **4a** (60:40, 96%) was obtained upon trituration of the crude product with cold ethanol: IR 1740 cm^{-1}; ^{1}H NMR (**4a**) δ 7.67 (m, 2 H, Ar H), 7.45 (m, 3 H, Ar H), 5.33 (s, 1 H, H-1), 5.12 (d, 1 H, J = 8.2 Hz, H-6), 4.86 (d, 1 H, J = 5.6 Hz, H-4), 4.02 (d, 1 H, J = 8.2 Hz, H-5), 2.83 (dd, 1 H, J = 15.0, 5.6 Hz, H-3$_{exo}$), 2.22 (s, 3 H, CH_3), 2.10 (d, 1 H, J = 15.0 Hz, H-3$_{endo}$); ^{1}H NMR (**3a**) δ 7.67 (m, 2 H, Ar H), 7.45 (m, 3 H, Ar H), 5.33 (s, 1 H, H-1), 4.91 (d, 1 H, J = 8.2 Hz, H-5), 4.60 (d, 1 H, J = 5.6 Hz, H-4), 4.12 (d, 1 H, J = 8.2 Hz, H-6), 2.78 (dd, 1 H, J = 15.0, 5.6 Hz, H-3$_{exo}$), 2.30 (s, 3 H, CH_3), 1.97 (d, 1 H, J = 15.0 Hz, H-3$_{endo}$). Anal. Calcd for $C_{16}H_{14}N_2O_4$: C, 64.42; H, 4.73; N, 9.39. Found: C, 64.31; H, 4.56; N, 9.31.

Reaction between 1b and BNO. A mixture of **3c** and **4c** (65:35, 96%) was obtained by washing the crude product with benzene and concentrating in vacuo: IR 1760 cm^{-1}. Anal. Calcd for $C_{13}H_{11}NO_3$: C, 68.12; H, 4.83; N, 6.11. Found: C, 68.02; H, 4.65; N, 6.05. Pure **3c** was isolated, after several recrystallizations from ethanol, as a white solid: mp 150–152 °C; ^{1}H NMR δ 7.71 (m, 2 H, Ar H), 7.45 (m, 3 H, Ar H), 5.16 (d, 1 H, J = 6.0 Hz, H-4), 5.10 (d, 1 H, J = 7.8 Hz, H-5), 4.52 (s, 1 H, H-1), 4.13 (d, 1 H, J = 7.8 Hz, H-6), 2.60 (dd, 1 H, J = 17.4, 6.0 Hz, H-3$_{exo}$) 2.19 (d, 1 H, J = 17.4 Hz, H-3$_{endo}$).

Reaction between 1c and BNO. A mixture of **3e** and **4e** (53:47, 98%) was obtained as described for **1b**. Anal. Calcd for $C_{15}H_{15}NO_4$: C, 65.92; H, 5.53; N, 5.13. Found: C, 65.98; H, 5.38; N, 5.21. Pure **4e** was isolated, after several recrystallizations from ethanol, as a white solid: mp 198–200 °C; IR 1600, 1030 cm^{-1}; ^{1}H NMR (**4e**) δ 7.70 (m, 2 H, Ar H), 7.43 (m, 3 H, Ar H), 5.37 (d, 1 H, J = 8.3 Hz, H-6), 4.75 (d, 1 H, J = 6.0 Hz, H-4), 4.44 (s, 1 H, H-1), 4.12–3.85 (m, 4 H, OCH_2CH_2O), 4.00 (d, 1 H, J = 8.0 Hz, H-5), 2.24 (dd, 1 H, J = 13.0, 6.0 Hz, H-3$_{exo}$), 1.93 (d, 1 H, J = 13.0 Hz, H-3$_{endo}$); ^{1}H NMR (**3e**, in the mixture) δ 7.70 (m, 2 H, Ar H), 7.43 (m, 3 H, Ar H), 4.96 (d, 1 H, J = 8.0 Hz, H-5), 4.82 (d, 1 H, J = 6.0 Hz, H-4), 4.41 (d, 1 H, J = 8.0 Hz, H-6), 4.24 (s, 1 H, H-1), 4.10–4.35 (m, 4 H, OCH_2CH_2O), 2.20 (dd, 1 H, J = 13.0, 6.0 Hz, H-3$_{exo}$), 1.76 (d, 1 H, J = 13.0 Hz, H-3$_{endo}$).

Reaction between 1a and MNO. A mixture of **3b** and **4b** (50:50, 96%) was obtained: IR 1755 cm^{-1}. Anal. Calcd for $C_{19}H_{20}N_2O_4$: C, 67.04; H, 5.92; N, 8.23. Found: C, 67.21; H, 5.94; N, 8.16. Pure **3b** was isolated after several recrystallizations from ethanol as a white solid: mp 214–216 °C; ^{1}H NMR (**3b**) δ 6.93 (s, 2 H, Ar H), 5.37 (s, 1 H, H-1), 5.17 (d, 1 H, J = 8.0 Hz, H-5), 4.60 (d, 1 H, J = 6.0 Hz, H-4), 3.87 (d, 1 H, J = 8.0 Hz, H-6), 2.77 (dd, 1 H, J = 13.0, 6.0 Hz, H-3$_{exo}$), 2.33, 2.27, 2.20 (s, s, s, 3 H, 6 H, 3 H, 4 CH_3), 1.87 (d, 1 H, J = 13.0 Hz, H-3$_{endo}$); ^{1}H NMR (**4b**, in the mixture) δ 6.90 (s, 2 H, Ar H), 4.90 (d, 1 H, J = 6.0 Hz, H-4), 4.85 (d, 1 H, J = 8.0 Hz, H-6), 4.80 (s, 1 H, H-1), 4.10 (d, 1 H, J = 8.0 Hz, H-5), 2.72 (dd, 1 H, J = 13.0, 6.0 Hz, H-3$_{exo}$), 2.33, 2.27, 2.10 (s, s, s, 3 H, 6 H, 3 H, 4 CH_3), 1.82 (d, 1 H, J = 13.0 Hz, H-3$_{endo}$).

Reaction between 1b and MNO. An inseparable mixture of **3d** and **4d** (55:45, 97%) was obtained: IR 1750 cm^{-1}; ^{1}H NMR δ 6.93, 6.91 (s, s, 2 H, 2 H, Ar H), 5.14 (d, 1 H, J = 6.0 Hz, H-4), 5.08, 5.05 (d, d, 1 H, 1 H, J = 8.7 Hz, H-5, H-6), 4.83 (d, 1 H, J = 6.0 Hz, H-4), 4.69, 4.21 (s, s, 1 H, 1 H, H-1), 3.98, 3.93 (d, d, 1 H, 1 H, J = 8.7 Hz, H-6, H-5), 2.52, 2.49 (dd, dd, 1 H, 1 H, J = 17.5, 6.0 Hz, H-3$_{exo}$), 2.29, 2.28, 2.25 (s, s, s, 18 H, 6 CH_3), 2.13, 2.09 (d, d, 1 H, 1 H, J = 17.5 Hz, H-3$_{endo}$). Anal. Calcd for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.31; N, 5.16. Found: C, 70.81; H, 6.20; N, 5.13.

Reaction between 1c and MNO. A mixture of **3f** and **4f** (55:45, 97%) was obtained. Anal. Calcd for $C_{18}H_{21}NO_4$: C, 68.55; H, 6.71; N, 4.44. Found: C, 68.71; H, 6.59; N, 4.32. Several recrystallizations from ethanol gave pure **4f**: IR 1030 cm^{-1}; ^{1}H NMR δ 6.90 (s, 2 H, Ar H), 5.30 (d, 1 H, J = 8.3 Hz, H-6), 4.50 (m, 2 H, H-1, H-4), 3.80 (m, 5 H, OCH_2CH_2O, H-5), 2.26 (s, 9 H, CH_3), 2.15 (dd, 1 H, J = 13.0, 6.0 Hz, H-3$_{exo}$), 1.67 (d, 1 H, J = 13.0 Hz, H-3$_{endo}$).

Reaction between 5a[2] and MNO. A solution of **5a** (1 mmol) and MNO (1.2 mmol) in methylene chloride (10 mL) was stirred at room temperature for 3 days. Evaporation of the solvent yielded a white solid, which was recrystallized from ethanol to give pure **9a** (75%): mp 180–181 °C; IR 1760 cm^{-1}; ^{1}H NMR δ 6.96 (s, 2 H, Ar H), 5.03 (d, 1 H, J = 5.9 Hz, H-4), 4.91 (s, 1 H, H-1), 4.06 (s, 1 H, H-6), 2.88 (dd, 1 H, J = 14.8, 5.9 Hz, H-3$_{exo}$), 2.65 (d, 1 H, J = 14.8 Hz, H-3$_{endo}$), 2.31, 2.28, 2.16 (s, s, s, 3 H, 6 H, 3 H, CH_3); ^{13}C NMR δ 168.2, 156.4, 139.8, 136.5, 128.8, 122.3, 116.9, 105.7, 85.3, 83.2, 72.8, 65.0, 39.8, 20.8, 20.0, 19.6. Anal. Calcd for $C_{19}H_{19}N_2O_4Cl$: C, 60.89; H, 5.11; N, 7.47; Cl, 9.46. Found: C, 60.55; H, 5.17; N, 7.22; Cl, 9.70.

Reaction between 5b and MNO. Under the same conditions as above, **9b** was obtained after 4 days. The crude product was recrystallized from ethanol to give pure **9b** as a white solid (78%): mp 165–166 °C; IR 1610, 1225, 1020 cm^{-1}; ^{1}H NMR δ 6.88 (s, 2 H, Ar H), 4.85 (d, 1 H, J = 6.13 Hz, H-4), 4.20 (s, 1 H, H-1), 3.94 (s, 1 H, H-6), 3.97, 3.78, 3.66 (m, m, m, 1 H, 2 H, 1 H, OCH_2CH_2O), 2.50 (d, 1 H, J = 13.0 Hz, H-3$_{endo}$), 2.24 (m, 10 H, H-3$_{exo}$, 3 CH_3); ^{13}C NMR δ 158.0, 139.3, 136.9, 128.6, 123.5, 112.8, 100.7, 86.2, 82.0, 67.4, 65.4, 64.7, 40.5, 20.9, 19.6; mass spectrum, m/e 395 (14.76), 393 (M, 15.11), 314 (17.39), 169 (base), 99 (42.67). Anal. Calcd for $C_{18}H_{20}NO_4Br$: C, 55.00; H, 5.13; N, 3.56; Br, 20.33. Found: C, 55.20; H, 5.13; N, 3.43; Br, 20.29.

Reaction between 6a[2] and MNO. Under the same conditions as above, **10a** was obtained in 2 days. The crude product was recrystallized from ethanol to give pure **10a** as a white solid (80%): mp 265–266 °C; IR 1760 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 8.25 (m, 2 H, Ar H), 7.96 (m, 3 H, Ar H), 7.10 (s, 2 H, Ar H), 5.89 (s, 1 H, H-1), 5.04 (d, 1 H, J = 6.4 Hz, H-4), 4.89 (s, 1 H, H-5), 3.21 (dd, 1 H, J = 14.4, 6.4 Hz, H-3$_{exo}$), 2.55 (d, 1 H, J = 14.4 Hz, H-3$_{endo}$), 2.43, 2.21 (s, s, 6 H, 6 H, 4 CH_3); ^{13}C NMR (DMSO-d_6) δ 169.3, 157.7, 139.4, 137.2, 136.3, 130.7, 129.3, 128.6, 122.52, 118.1, 107.5, 86.2, 80.7, 72.7, 64.9, 21.0, 20.6, 19.8; mass spectrum, m/e 480 (M, 22.72), 339 (base), 311 (36.36) 251 (95.45) 105 (70.45), 77 (40.90). Anal. Calcd for $C_{25}H_{24}N_2O_6S$: C, 62.49; H, 5.03; N, 5.83; S, 6.67. Found: C, 62.43; H, 4.97; N, 5.81; S, 6.59.

Reaction of 6b and MNO. Under the same conditions as above, **10b** was obtained in 7 days. The crude product was recrystallized from ethanol to give pure **10b** as a white solid (85%): mp 245–246 °C; IR 1610, 1100 cm^{-1}; ^{1}H NMR δ 8.04 (m, 2 H, Ar H), 7.54 (m, 3 H, Ar H), 6.77 (s, 2 H, Ar H), 4.57 (s, 1 H, H-1), 4.46 (d, 1 H, J = 6.3 Hz, H-4), 4.14 (s, 1 H, H-5), 4.04, 3.97, 3.88 (m, m, m, 2 H, 1 H, 1 H, OCH_2CH_2O), 2.30 (dd, 1 H, J = 14.1, 6.3 Hz, H-3$_{exo}$), 2.18, 2.08 (s, s, 3 H, 6 H, 3 CH_3), 2.05 (d, 1 H, J = 14.1 Hz, H-3$_{endo}$); ^{13}C NMR δ 156.6, 139.3, 137.2, 137.0, 134.0, 130.1, 128.6, 128.3, 122.7, 111.4, 107.4, 86.1, 78.9, 65.9, 65.6, 63.5, 39.6, 20.7, 19.8; mass spectrum, m/e 455 (M, 35.00), 200 (base), 169 (81.72), 115 (56.23), 86 (37.13). Anal. Calcd for $C_{25}H_{25}NO_6S$: C, 63.28; H, 5.53; N, 3.08; S, 7.04. Found: C, 63.15; H, 5.59; N, 2.95; S, 6.83.

Kinetic Study. The kinetics for the cycloadditions with MNO were determined by IR, using a Perkin-Elmer 781 spectropho-

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tometer with a 1-mm cell. The progress of the reaction was monitored by disappearance of the band at 2290 cm^{-1} of MNO. Concentrations of MNO for each time interval were obtained by means of a calibration plot (absorbance vs concentration). Rate constants for all the reactions were determined by means of a second-order-kinetics plot using equimolar amounts of both reagents.

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Registry No. **1a**, 79902-01-5; **1b**, 95530-78-2; **1c**, 107607-56-7; **2a**, 873-67-6; **2b**, 2904-57-6; **3a**, 107607-57-8; **3b**, 123075-84-3; **3c**, 107607-59-0; **3d**, 123075-85-4; **3e**, 107607-61-4; **3f**, 123075-86-5; **4a**, 107607-58-9; **4b**, 123075-87-6; **4c**, 123075-88-7; **4d**, 123075-89-8; **4e**, 107607-62-5; **4f**, 123075-90-1; **5a**, 123075-91-2; **5b**, 123075-92-3; **6a**, 123075-93-4; **6b**, 123075-94-5; **7b**, 123075-95-6; **7c**, 123075-96-7; **7d**, 123075-97-8; **8b**, 123163-88-2; **8c**, 123075-98-9; **8d**, 123075-99-0; **9a**, 123076-00-6; **9b**, 123076-01-7; **10a**, 123076-02-8; **10b**, 123076-03-9; benzeneselenenyl bromide, 34837-55-3.

Thioxanthene Dioxide Based Amino-Protecting Groups Sensitive to Pyridine Bases and Dipolar Aprotic Solvents[1,2]

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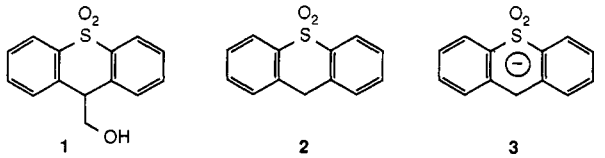
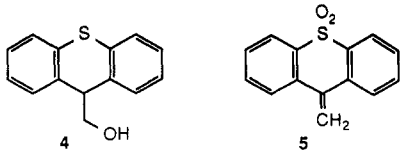
In pursuit of an analogy between fluorine and thioxanthene dioxide, the suitability of the D-TMOC and related functions as base-sensitive amino-protecting groups was examined. Such compounds were found to be cleaved by mild pyridine bases against which the analogous FMOC derivatives are stable. Deblocking gives as a byproduct the methylene sulfone **5** or its adducts with an appropriate secondary deblocking amine. Certain solvents such as DMSO, DMF, etc., were also found to deblock the D-TMOC group, especially on warming, whereas the compounds were stable in ordinary nonpolar solvents (e.g., CH_2Cl_2, benzene, THF). For practical use the D-TMOC function suffers from excessive solvent sensitivity and the low solubility of some derivatives. To overcome this problem *tert*-butyl groups were introduced into the 2,7-positions of the xanthene nucleus. The resulting DBD-TMOC function proved easier to handle in terms of both solubility and reactivity. The key alcohol **12** was synthesized from diphenyl sulfide **13** by *tert*-butylation followed by Friedel–Crafts cyclization using methyl dichloromethyl ether to give a 50–50 mixture of thioxanthene **15** and the corresponding thioxanthone **16**. Without separation of the mixture, oxidation gave a mixture of the dioxides **17** and **18**, and again without separation the mixture was reduced by P/HI to give the desired compound **17** in an overall yield of 60–65%. Formylation of **17** followed by reduction gave **12**, from which urethanes **11** were obtained in the normal manner via the chloroformate. The DBD-TMOC group was stable to strong acids (TFA, HBr–HOAc) but deblocked by catalytic hydrogenolysis as well as via mild bases and warming in dipolar aprotic solvents. Upon deblocking of **11** in DMSO the byproduct **27** separated completely, especially if 3–5% water is present or added subsequently. This process provides a clean solution of the deblocked amine, thus simplifying the use of the DBD-TMOC function in peptide synthesis. An example given is that of leucine enkephalin, in which all coupling steps were effected by acid chlorides and all deblocking steps by warming in DMSO. It was shown with model compounds that coupling could be effected under appropriate conditions without racemization.

In connection with studies aimed at developing a spectrum of base-sensitive amino-protecting groups subject to deblocking under nonhydrolytic conditions by organic bases of varying strengths, of which the FMOC group[3] is currently the most widely used representative, we have examined appropriate urethanes derived from sulfone alcohol **1** largely on the basis of the work of Pagani and associates[4] and the possible relationship between fluorene and the related sulfone **2**. It has been suggested that anion **3** may be subject to special "aromatic" stabilization as a completely conjugated cyclic six π-electron system.[5] Although the exact nature of anion **3** is not clear, the undisputed high kinetic acidity of **2** relative to acyclic analogues inspired our synthesis of alcohol **1** and its urethane derivatives.



Alcohol **1** was obtained by oxidation of known thioxanthyl alcohol **4**, which could be obtained by treatment of thioxanthene with n-butyllithium followed by reaction with paraformaldehyde.[6] Direct hydroxymethylation of



(1) Abstracted in part from the Ph.D. theses of H.-S.G. (1989) and G.-S.T. (1979), University of Massachusetts.

(2) A number of abbreviations are used in this paper. Those for natural amino acids and peptides follow the recommendations of the IUPAC-IUB Commission on Biochemical Nomenclature (*J. Biol. Chem.* **1971**, *247*, 997). Other abbreviations are as follows: TFA = trifluoroacetic acid, FMOC = (9-fluorenylmethoxy)carbonyl, DCC = dicyclohexylcarbodiimide, HOBT = *N*-hydroxybenzotriazole, HOSu = *N*-hydroxysuccinimide, PCA = *p*-chloroaniline, Phg = α-phenylglycine, TMOC = [(thioxanthen-9-yl)methoxy]carbonyl, D-TMOC = [10,10,10,10-tetrahydro-10,10-dioxothioxanthen-9-yl)methoxy]carbonyl, DBD-TMOC = 2,7-di-*tert*-butyl-D-TMOC.

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