tamate 43, the calcium ion, and the substrate as well as the roles of the glutamate and calcium ion in catalysis may not be precisely those inferred from the X-ray studies. Despite unsuccessful attempts to trap a covalent intermediate[6,17] a mechanism involving formation of an intermediate cannot be eliminated on the basis of our stereochemical result. Nucleophilic attack of glutamate 43 on the phosphorus of NPpT would result in formation of an acyl 4-nitrophenyl phosphate intermediate, with hydrolysis of the acyl phosphate ester intermediate yielding pNP. The stereochemical course of the overall hydrolysis reaction could be either retention or inversion, depending upon whether hydrolysis of the intermediate involves P–O or C–O bond cleavage, respectively. Carboxylate groups are known to be effective nucleophilic catalysts in the intramolecular hydrolysis of phosphate esters.[18] In addition, the hydrolysis of 5′-adenosyl benzoyl phosphate[19] and the methanolysis of phenyl acetyl phosphate[20] both occur with C–O bond cleavage; however, the effect of metal ion coordination on the position of bond cleavage is unknown.

The importance of this mechanism can be evaluated either by performing a single turnover experiment, in which the origin of the oxygen atom incorporated into the product can be established, or by determining whether catalysis is accompanied by the incorporation of solvent isotope into enzyme carboxylate groups.[21] Such experiments are feasible with the nuclease, since it can be isolated in gram quantities; the results of these and other experiments designed to further probe the mechanism of the reaction catalyzed by this enzyme will be reported in the future.

Since most phosphohydrolases cannot be purified in amounts compatible with such mechanistic investigation, the disconcerting possibility that an inversion of configuration may not be sufficient evidence to rule out the participation of a covalent intermediate in these reactions cannot be easily discarded. The potential occurrence of acyl phosphate ester intermediates in hydrolysis reactions does provide, however, a plausible hypothesis to explain the lack of stereochemical uniformity that has been observed for two types of phosphohydrolase reactions.[2,22]

Acknowledgment. We thank Professors Samuel Danishefsky and John Kozarich for helpful comments. Dr. Hiroshi Taniuchi (NIH) generously provided us with a sample of staphylococcal nuclease. We thank David Hansen, Stephen Buchwald, and Professor Jeremy Knowles for instruction in their method of phosphomonoester configurational analysis and the hospitality extended to S.M. during a brief tutorial at Harvard. The high-field ^{1}H NMR spectra essential to this research were obtained at the NSF Northeast NMR Facility at Yale University (CHE-7916120); the high-field ^{31}P NMR spectrum was obtained through the continuing cooperation of Professor Philip Bolton at Wesleyan University. This research was supported by a grant from the National Institutes of Health (GM-22350).

Registry No. Labeled *syn*-4-methyl-1,3,2-dioxaphospholane methyl ester, 66943-87-1; labeled *anti*-4-methyl-1,3,2-dioxaphospholane methyl ester, 78780-75-3.

(17) We have observed that incubation of nuclease with 7 mM NPpT, 0.5 M hydroxylamine, and 10 mM $CaCl_2$ in 0.1 M borate buffer, pH 8.8, causes no inactivation of the enzyme, as judged by assaying aliquots of the incubation mixture with heat-denatured calf thymus DNA as substrate. This inability to intercept an acyl phosphate intermediate does not exclude its participation, since the intermediate need not be accessible to the solvent. For example, water coordinated to the calcium ion could serve as the nucleophile, and this coordination site may be unable to accommodate hydroxylamine.

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Nucleophilic Attack on Olefins Initiated by Dimethyl(methylthio)sulfonium Fluoroborate (DMTSF). Azasulfenylation

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Madison, Wisconsin 53706

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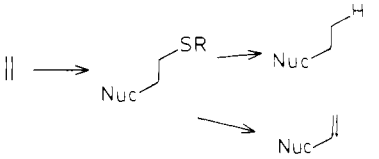
While the concept of elaboration of olefins with electrophiles is well accepted, the converse, i.e., elaboration by nucleophiles, is not, except for Michael-type systems. Reversal of olefin reactivity by use of transition metals has been a particularly exciting area of study.[1] The general utility of organosulfur substituents in terms of subsequent elimination, reduction, or substitution reactions led us to consider an RS^+ equivalent that would simultaneously invert the electronic characteristics of an olefin and permit the introduction of a wide variety of nucleophiles. Such reactions would constitute the equivalent of nucleophilic addition or substutition (see eq 1). We report that dimethyl(methyl-



(1)

thio)sulfonium fluoroborate (DMTSF, **1**)[2,3] is such a conjunctive reagent. In conjunction with nitrogen nucleophiles, an extraordinary level of regiocontrol can be exercised in an azasulfenylation reaction[4] whose products not only permit an overall olefin amination (by reductive cleavage of sulfur) but also constitute an oxazoline synthesis, a cis hydroxyamination of an olefin, and an aziridine synthesis as a result of the leaving-group properties of the sulfur.

The procedure is experimentally quite simple. A solution of the olefin in methylene chloride, nitromethane, or acetonitrile is treated with 1 equiv of **1** at 0 °C to room temperature. In some instances, addition of 1% (v/v) of dimethyl sulfide helps minimize side reactions. Addition of the nitrogen nucleophile, normally at room temperature, led to smooth, albeit slow (1–4 days) substitution to give excellent yields of the desired products. The results are summarized in Table I.

Three types of nitrogen nucleophiles were examined: amines, azide, and nitrite. The stereochemistry of the addition is trans, as has been shown for both cis- and trans-disubstituted olefins (Table I, entries 1–7, 14). For example, in the case of the acetamide derived from **2**, the ^{1}H NMR spectra showed two ^{1}H signals, at δ 3.72 (tdd, J = 10.6, 7.9, 4.1 Hz) and δ 2.38 (td, J = 10.9, 3.7 Hz), a fact only consistent with the stereochemistry depicted. Further transformations (vide infra) confirm these stereochemical assignments.

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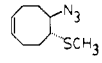
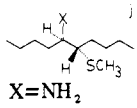
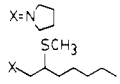
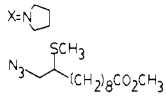
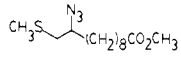
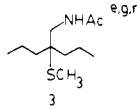
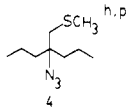
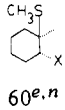
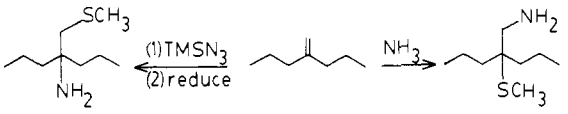
Table I. Azasulfenylation of Olefins

entry	olefin	nucleophile	solvent	product[d]			yield,[o] %
1				2			
a	cyclohexene	NH_3	CH_3CN	2, $n = 2$; X = NH_2[i]			76
b		NH_4OH	CH_3CN, H_2O[a]	2, $n = 2$; X = NH_2[i]			92
2	cyclohexene	NaN_3	CH_3NO_2, H_2O[a]	2, $n = 2$; X = N_3			95
3	cyclohexene	$NaNO_2$	CH_2Cl_2-DMS,[b] H_2O[a]	2, $n = 2$; X = NO_2			54
4	cyclopentene	NH_4OH	CH_3CN, H_2O	2, $n = 1$; X = NHAc[e]			96
			CH_2Cl_2, H_2O				86
5	cyclooctene	NH_4OH	CH_3NO_2, H_2O[a]	2, $n = 3$; X = NH_2			50
6	1,5-cyclooctadiene	NaN_3	CH_3NO_2-DMS[b]				70
7	(*E*)-5-decene	NH_4OH	CH_3CN-DMS,[b] H_2O	 X=NH_2			97
8	(*E*)-5-decene	pyrrolidine	CH_3CN-DMS,[b] CF_3CO_2H[c]-H_2O				91
9	1-heptene	NH_4OH	CH_3CN-DMS,[b] H_2O	X = NHAc[e,f]			94
10	1-heptene	pyrrolidine	CH_3CN, H_2O				59
11	methyl 10-undecylenate						
a		NaN_3	CH_3NO_2	56	44		96
b		NaN_3	CH_3CN	63	37		89
c		Me_3SiN_3	CH_2Cl_2	48	52		95
12	2-propyl-1-pentene	NH_3	CH_2Cl_2-DMS[b]	 3			84
13	2-propyl-1-pentene	Me_3SN_3	CH_2Cl_2	 4			82
14	(*E*)-1-phenylpropene	NH_3	CH_2Cl_2-DMS[b]				98
15	1-methylcyclohexene	NH_3	CH_2Cl_2-DMS[b]	X = NHAc	40[e,m]	 60[e,n]	91
16	1-methylcyclohexene	pyrrolidine	CH_2Cl_2		33	67	82
17	1-methylcyclohexene						
a		KN_3	CH_3NO_3	X = N_3	71	29	98
b		$(n\text{-}C_4H_9)_4N^+N^-$	CH_2Cl_2	X = N_3	82	18	
c		Me_3SiN_3	CH_2Cl_2	X = N_3	95	5	92

[a] After initial reaction of **1** with the olefin, the organic solvent was evaporated and an aqueous solution of the nucleophile added. [b] DMS = dimethyl sulfide. [c] One equivalent of trifluoroacetic acid added. [d] Full characterization of each product was obtained including IR, ^1H and sometimes ^{13}C NMR, and mass spectra as well as determination of elemental composition by high-resolution mass spectroscopy and/or combustion analysis. [e] The initial amine was characterized after acetylation with Ac_2O in pyridine. [f] An 88:12 mixture of the two regioisomers was obtained; the major isomer is depicted. [g] An 85:15 mixture of the two regioisomers was obtained; the major isomer is depicted and shows d for 2 H at δ 3.25 ($J = 5.4$ Hz). [h] A 95:5 mixture of the two regioisomers was obtained; the major isomer is depicted. [i] Also characterized as its acetamide, mp 100.7–101.5 °C. [j] Also characterized as its acetamide, mp 53–55 °C. [k] Also characterized as its acetamide, mp 60.5–61.5 °C. [l] Also characterized as its acetamide, mp 111.5–113.5 °C. [m] Mp 108.5–109.5 °C. [n] Mp 85.5–86.7 °C. [o] All yields are for pure products isolated by distillation, crystallization, and/or chromatography. [p] Also converted to its amine and characterized as the corresponding acetamide, mp 78.5–79.8 °C, and the NMR spectrum shows a singlet for 2 H at δ 2.98.

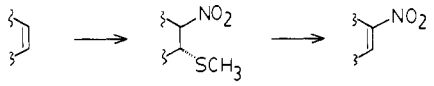
Regioselectivity and the ability to control it represents a most fascinating facet of this azasulfenylation reaction. NMR and mass spectroscopy permit confident assignment of regiochemistry. In general, the higher the nucleophilicity of the attacking reagent, the higher the tendency for an anti-Markovnikov product and vice versa. Olefin substitution also clearly plays a major role. Monosubstituted olefins show a propensity for anti-Markovnikov addition and trisubstituted olefins for Markovnikov addition. 1,1-Disubstituted olefins permit virtually complete control either way. For example, 2-propyl-1-pentene gives mainly the anti-Markovnikov product **3** with ammonia, whereas, use of the much less nucleophilic Me_3SiN_3 gives the Markovnikov product **4**. From subsequent reduction of **4** as shown in eq 2, both regioisomers are available in good yields.



(2)

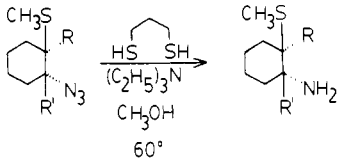
5

While we have only examined ammonia and pyrrolidine, it would appear that primary amines should be equally efficacious. Although we have limited ourselves at this time to only one example of nitrite, it appears highly promising. With the ability of sulfur to serve as a leaving group (see eq 3), this technique may



(3)

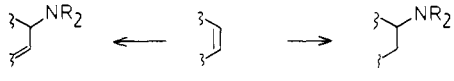
serve as a valuable entry to the synthetically versatile nitroolefins.[5] In the case of azide, sodium or potassium azide, either finely ground for anhydrous reaction or dissolved in water, sufficed. However, reducing the nucleophilicity by switching to Me_3SiN_3 enhanced the Markovnikov regioselectivity (see table, entry 17). Chemoselective reduction of the azido sulfides to amino sulfides was easily achieved with propylenedithiol[6] (see eq 2 for **4** → **5** and eq 4). Thus, azidosulfenylation is the equivalent of aminosulfenylation.



R	R'	%
H	H	96
CH_3	H	86
H	CH_3	86

(4)

The well-known procedures to desulfurize via reduction or elimination methods converts this reaction into an addition of amines to an olefin or a substitution with double-bond migration (eq 5). We focused on a new application: cis hydroxy amination.[7]



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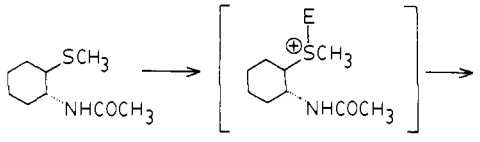
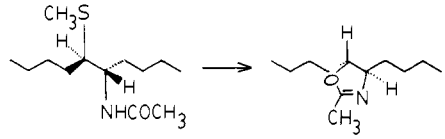


6 7

(6)

8

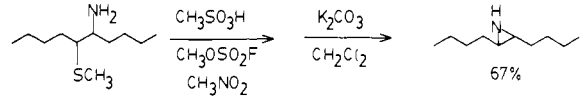
Alkylation of **6** with trimethyloxonium fluoroborate to give **7** (E = CH_3) followed by heating at 80 °C for several days ($t_{1/2}$ ~ 40 h) gave the oxazoline **8**[7b,8] after basic workup. A much more efficient route utilized **1** in which **7** (E = SCH_3) decomposed much more rapidly in acetonitrile at 80 °C ($t_{1/2}$ ~15 min) to give **8** in 72% yield. The adduct **9** generated the oxazoline **10** (30 min at 0 °C, 30 min at room temperature, then diisopropylethylamine in acetonitrile at 80 °C) with trimethyloxonium fluoroborate in 93% yield (see eq 7). The NMR spectrum δ 4.03 (td, J = 6.8,



(7)

9 10

5.1 Hz), 3.55 (td, J = 6.1, 5.1 Hz)] confirms the E stereochemistry.[7b] A second new reaction of these adducts is their conversion to aziridines[9] (eq 8) initiated by chemoselective alkylation of the sulfide.



(8)

The question of mechanism of the azasulfenylation obviously arises. Whether these reactions occur via the known type of olefin adducts of **1**[3] or episulfonium ions[4b,10,11] is debatable. Several notable differences from the reactions of authenticated episulfonium ions are to be noted. First, mono- and 1,1-disubstituted episulfonium ions almost invariably give Markovnikov-type products upon reaction with nucleophiles,[11] in contrast to our results. Second, carbonium ion rearrangement products are frequently seen with episulfonium ions.[11] The absence of such products in the case of cycloocta-1,5-diene in our case is quite noteworthy in this respect.[12] Third, acetonitrile efficiently reacts with episulfonium ions[4b] but does not do so with the intermediates of this reaction. On the other hand, the trans stereochemistry of the products is inconsistent with the direct reaction of the olefin adducts of **1** with the nucleophile.

Over and above the control of selectivity that this simple one-pot operation offers, the convenience offered by **1**, a stable crystalline solid that can be easily manipulated on small and large scales, imparts special importance to this approach. The instability of sulfenyl halides[13] makes the multistep procedures proceeding via their adducts to olefins much less satisfactory. Synthetic procedures passing through isolable episulfonium ions suffer from the requirements of sulfenyl halides and/or silver salts.[4b,10,11] In addition, different selectivity is observed.[11] The chemoselectivity offered by **1** and its olefin adducts may make this approach a general solution to nucleophilic attack on olefins. This goal is under active investigation in these laboratories.

Acknowledgment. We thank the National Science Foundation for their generous support of our programs.

Registry No. 1, 5799-67-7; **2** (n = 2, x = NH_2), 81230-50-4; **2** (n = 2, x = NH-Ac), 41578-08-9; **2** (n = 2, x = N_3), 81230-51-5; **2** (n = 2, x = NO_2), 81230-52-6; **2** (n = 1, x = NH-Ac), 81230-53-7; **2** (n = 3, x = NH_2), 81230-54-8; **3**, 81230-55-9; **4**, 81230-56-0; **5**, 81230-57-1; **8**, 23236-44-4; **9**, 81230-58-2; **10**, 81230-59-3; NH_3, 7664-41-7; NH_4OH, 1336-21-6; NaN_3, 26628-22-8; $NaNO_2$, 7632-00-0; TMS-N_3, 4648-54-8; KN_3, 20762-60-1; $(n\text{-}C_4H_9)_4N^+N_3^-$, 993-22-6; pyrrolidine, 123-75-1; cyclohexene, 110-83-8; cyclopentene, 142-29-0; cyclooctene, 931-88-4; 1,5-cyclooctadiene, 111-78-4; (E)-5-decene, 7433-56-9; 1-heptene, 592-76-7; methyl 10-undecylenate, 111-81-9; 2-propyl-1-pentene, 15918-08-8; (E)-1-phenylpropene, 873-66-5; 1-methylcyclohexene, 591-49-1; *trans*-2-azido-1-(methylthio)-5-cyclooctene, 81230-60-6; (R^*,S^*)-5-amino-6-(methylthio)decane, 81230-61-7; (R^*,S^*)-1-(1-butyl-2-(methylthio)-

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Nucleophilic Attack on Olefins Initiated by Dimethyl(methylthio)sulfonium Fluoroborate (DMTSF). Cyanosulfenylation and Oxy- and Oxosulfenylation

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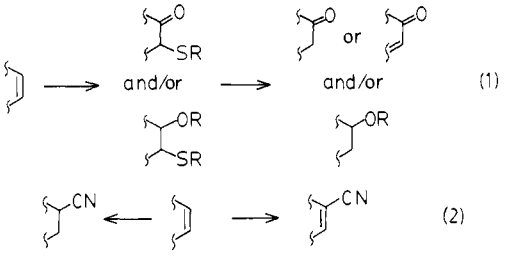
Nucleophilic addition to and substitution in olefins enhances synthetic flexibility by complementing the more usual electrophilic reactions. In exploration of new avenues for such a strategy, attention was focused on nucleophilic introduction of an oxygen substituent and a nitrile group. While the versatile β-hydroxy and β-keto sulfides normally derive from sulfenylation of a carbonyl compound,[1,2] the ready availability of olefins as basic building blocks stimulates a search for simple methods to introduce such functionality directly via the carbon–carbon double bond (eq 1).[3-5] Similarly, very limited methods exist for cyanation of olefins



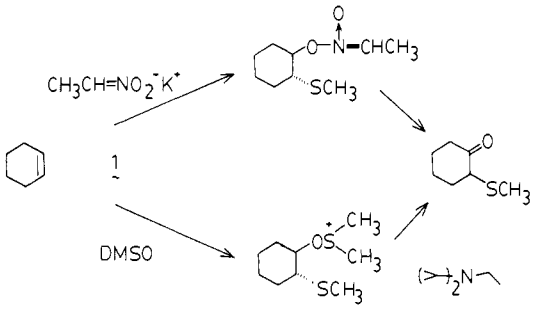
(1)

(2)

(eq 2), again a versatile type of substituent.[6-8] The chemoselective activation of olefins for nucleophilic attack by dimethyl(methylthio)sulfonium fluoroborate[9] (DMTSF, **1**), a readily available and convenient reagent that to date has found virtually no synthetic applications,[10,11] offers an attractive solution to both problems.

Three types of oxygen nucleophiles were examined—hydroxide, carboxylate, and Me_2SO as summarized in Table I. Typically, for hydroxide and acetate as the nucleophiles, the olefin and **1** were mixed in the stated organic solvent. Subsequently, either an aqueous carbonate solution (for hydroxide) or anhydrous powdered potassium acetate was added at ambient temperature. While reactions were slow (3–5 days), they were very clean, and pure products were isolated in high yield. In two cases (entries 4 and 6), an advantageous effect on the yield was noted by the addition of a small amount of dimethyl sulfide. Entries 7 and 14 illustrate the chemoselectivity. Complementary regioselectivity is exhibited by these two nucleophiles with hydroxide giving mainly Markovnikov addition (entries 2–4 and 7) and acetate giving mainly anti-Markovnikov addition (entry 5). Entries 4 and 5 nicely illustrate the ability of obtaining both types of products selectively from the same olefin by this simple manipulation of reaction conditions. Spectral analysis allows easy assignment of both the regiochemistry and stereochemistry (i.e., a clean trans addition; see entries 1, 2, 6).

While the hydroxy sulfides can be envisioned as precursors to β-keto sulfides, direct conversion to β-keto sulfides would be desirable. Two approaches were examined (eq 3). In the first,



O-alkylation of a nitronate salt by the olefin-**1** complex followed by elimination of nitrosoethane would generate the desired product. While this expectation was fulfilled, substantial amounts of the corresponding β-hydroxy sulfide, which presumably arose by simple hydrolysis of the nitronate intermediate, accompanied it. Surprisingly, Me_2SO proved to be a sufficient nucleophile.[12,13] Addition of diisopropylethylamine to the initial adduct completed the conversion to the desired β-keto sulfide. Three procedures were employed. In the first, the olefin was reacted sequentially with **1**, Me_2SO, and then base at room temperature (entries 8, 13, 14). In the second, the olefin was mixed with **1**, Me_2SO, and base in CCl_4 and then heated to 60 °C (entry 9). In the third and preferred method, the olefin and **1** were mixed in methylene chloride and, after 15 min, Me_2SO, HgO, and diisopropylethylamine added in rapid succession (entries 10–13), all at room temperature.

A typical procedure for cyanosulfenylation involves mixing DMTSF (1 equiv) with the olefin (1–2 equiv) in acetonitrile followed by addition of finely powdered sodium cyanide at room temperature. Use of acetonitrile containing 1–3% (v/v) of dimethyl sulfide sometimes improved the yield. While this reaction is slow (1–3 days), it proceeds cleanly, which allows isolation of the products in good yield by simple distillation as summarized

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