JOC Article

# Carbocation-Forming Reactions in Dimethyl Sulfoxide

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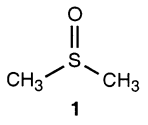
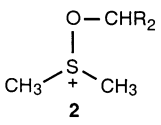
Mesylate derivatives of 3-aryl-3-hydroxy-$\beta$-lactams and thiolactams react in DMSO-$d_6$ by first-order processes to give alcohol products. Substituent effect studies implicate carbocation intermediates (ion-pairs) that are captured by DMSO-$d_6$ to give transient oxosulfonium ions. Rapid reaction of the oxosulfonium ions with trace amounts of water leads to the alcohol product and regenerates DMSO-$d_6$. $H_2{}^{17}O$ labeling studies show that $^{17}O$ is incorporated into the DMSO. The mesylate derivatives of *endo*- and *exo*-2-hydroxy-2-phenylbicyclo[2.2.1]heptan-3-one also react in DMSO-$d_6$ to give the alcohol products. Ion-pair intermediates that capture DMSO giving unstable oxosulfonium ions are again proposed. *Exo*-2-phenyl-*endo*-bicyclo[2.2.1]heptyl trifluoroacetate readily eliminates trifluoroacetic acid in DMSO-$d_6$ via a cationic mechanism involving loss of the *endo*-trifluoroacetate leaving group as well as an *exo*-hydrogen. The *O*-methyl oxime derivative of α-chloro-α,α-diphenylacetophenone reacts in DMSO-$d_6$ to give 1-methoxy-2,3-diphenylindole, a product derived from cyclization of a cationic intermediate. A common ion rate suppression provides further evidence for a cationic mechanism. The triflate derivative of pivaloin reacts by a cationic mechanism in DMSO-$d_6$ to give rearranged products. The rate is even faster than in highly ionizing solvents such as trifluoroethanol or trifluoroacetic acid. 1-Adamantyl mesylate reacts in DMSO-$d_6$ by a first-order process ($Y_{OMs} = -4.00$) to give a long-lived oxosulfonium ion, 1-Ad-OS$(CD_3)_2{}^+$, which can be characterized spectroscopically. This oxosulfonium ion reacts only slowly with water at elevated temperatures to give 1-adamantanol. DMSO is therefore a viable solvent for $k_s$, $k_C$, and $k_\Delta$ cationic processes.

## Introduction

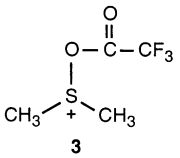
Dimethyl sulfoxide (DMSO), **1**, is a common solvent and reagent in organic chemistry.[1] Organic compounds tend to be quite soluble in this solvent, and the deuterated analogue $CD_3SOCD_3$ (DMSO-$d_6$) is a commonly used solvent for recording NMR spectra. DMSO is also characterized by its high dielectric constant ($E = 48.9$), and many ionic substances have relatively high solubility in this solvent. Due to the inability to hydrogen bond, many anions have extraordinary nucleophilic reactivity as well as basicity in DMSO. $S_N2$ and E2 reactions tend to occur much more rapidly in this solvent. DMSO is quite hygroscopic, and it is therefore difficult to exclude all traces of water. In fact, DMSO at high temperature is an effective dehydrating agent for certain alcohols.[2] DMSO can also act as an oxidizing agent, and the Kornblum oxidation, which proceeds via the alkylated DMSO **2**, is a facile method for conversion of alkyl halides and tosylates to carbonyl compounds.[3] Reagents derived from activation of DMSO with reagents such as trifluoroacetic anhydride, **3**, or oxalyl chloride can also lead to oxidation processes. Such reagents have proven to be the method of choice for conversion of certain alcohols to aldehydes and ketones.[4]



**1**



**2**



**3**

Over the years, we have carried out numerous solvolytic studies in protic solvents on substrates that react readily at room temperature by carbocationic mechanisms. Recording NMR spectra of these substrates in the aprotic solvent DMSO-$d_6$ was often problematic since these substrates also react in this solvent by a mechanism that we now conclude is carbocationic in nature. Indeed, reactions that involve capture of tropylium cation[5] and *tert*-butyl cation[6] by DMSO have been proposed in the past. However, there has been no systematic study of reactions that proceed via carbocationic intermediates in DMSO. The compounds selected for study

(1) For reviews and leading references, see: (a) Buncel, E.; Wilson, H. *Adv. Phys. Org. Chem.* **1977**, *14*, 133. (b) Martin, D.; Weise, A.; Niclas, H.-J. *Angew Chem., Int. Ed. Engl.* **1967**, *6*, 318.

(2) (a) Traynelis, V. J.; Hergenrother, W. L.; Livingston, J. R.; Valicenti, J. A. *J. Org. Chem.* **1962**, *27*, 2377. (b) Traynelis, V. J.; Hergenrother, W. L.; Hanson, H. T.; Valicenti, J. A. *J. Org. Chem.* **1964**, *29*, 123. (c) Traynelis, V. J.; Hergenrother *J. Org. Chem.* **1964**, *29*, 221.

(3) (a) Kornblum, N.; Powers, J. W.; Anderson, G. J.; Jones, W. J.; Larson, H. O.; Weaver, W. M. *J. Am. Chem. Soc.* **1957**, *79*, 6562. (b) Kornblum, N.; Jones, W. J.; Anderson, G. J. *J. Am. Chem. Soc.* **1959**, *81*, 4113. (c) Johnson, A. P.; Pelter, A. *J. Chem. Soc.* **1964**, 520.

(4) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165.

(5) Garfunkel, E.; Reingold, I. D. *J. Org. Chem.* **1979**, *44*, 3725.

(6) Dossena, A.; Marchelli, R.; Casnati, G. *J. Chem. Soc., Chem. Commun.* **1979**, 370.

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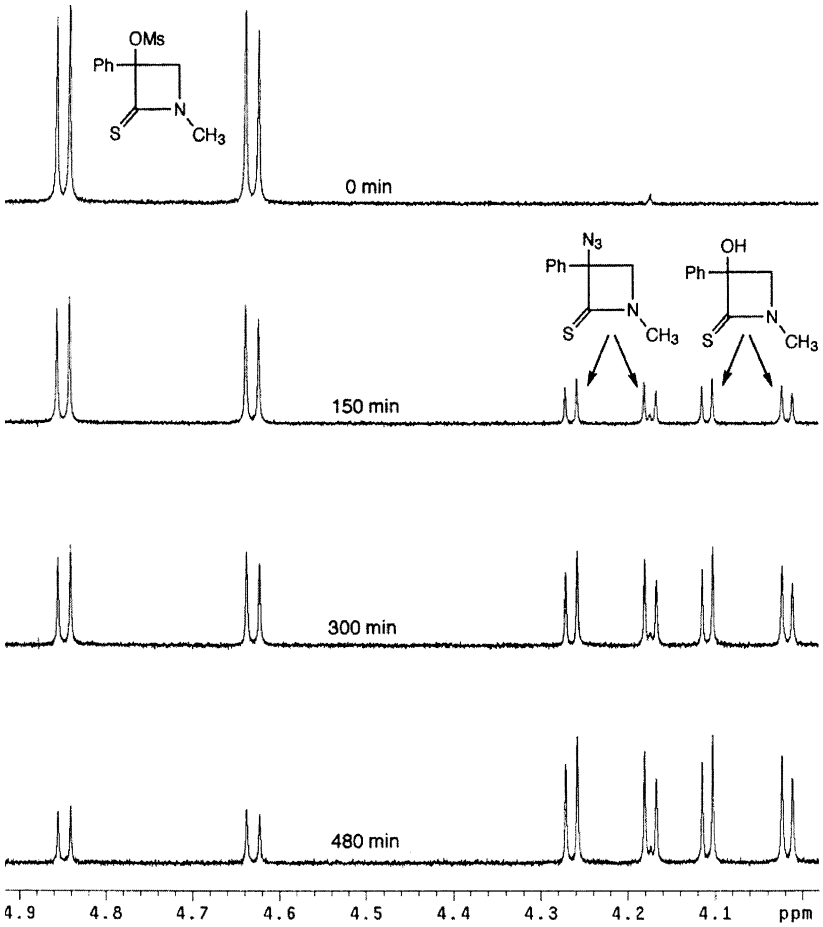
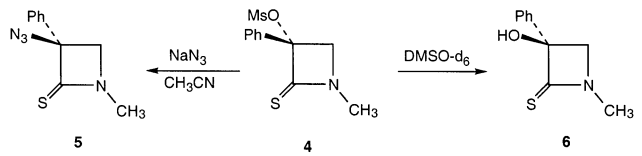



**FIGURE 1.** Evolving $^1$H NMR spectra during reaction of **4** with 0.10 M $NaN_3$ in DMSO-$d_6$ at 50 °C.

in this paper were readily available in our laboratory, having been examined by us in the past in protic solvents where they have relatively high reactivity. Reported here are some reactions of mesylates, trifluoroacetates, and chlorides in DMSO-$d_6$, many of which proceed via carbocation intermediates.

## Results and Discussion

***β*-Thiolactam and *β*-Lactam Systems.** We recently reported on the reaction of mesylate **4** with azide ion in dimethyl formamide, which proceeds to give azide substitution product **5** with clean inversion.[7] We have now employed DMSO as a solvent and found that the reaction of **4** with excess sodium azide gives varying amounts of azide product **5** along with alcohol **6**. Figure 1 shows a typical reaction using 0.1 M $NaN_3$, where comparable amounts of **5** and **6** are formed.




As the $NaN_3$ concentration is increased, the pseudo first-order rate constant for the disappearance of **4** increased

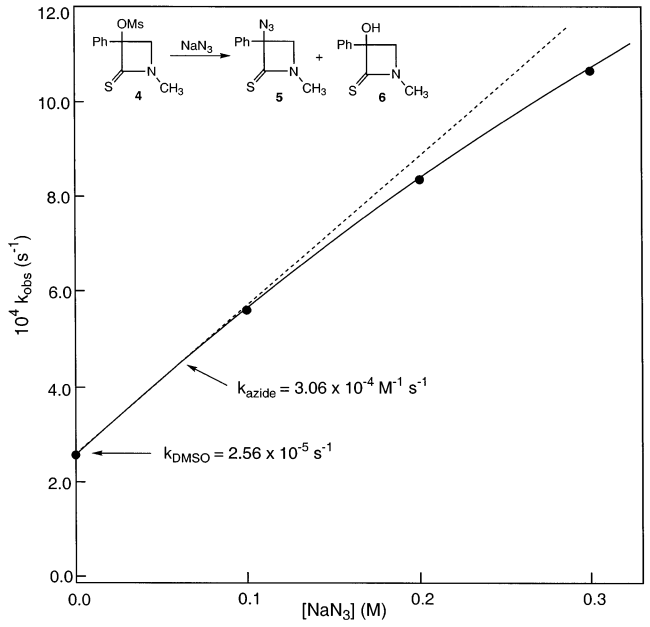



**FIGURE 2.** Plot of the observed pseudo first-order rate constant for reaction of **4** with $NaN_3$ in DMSO-$d_6$ at 50.0 °C versus [$NaN_3$].

(Figure 2) and less of alcohol **6** was formed. The limiting slope of the plot shown in Figure 2 is $3.06 \times 10^{-4}$ $M^{-1}$ $s^{-1}$ and corresponds to the second order rate constant for

(7) Creary, X.; Zhu, C.; Jiang, Z. *J. Am. Chem. Soc.* **1996**, *118*, 12331.

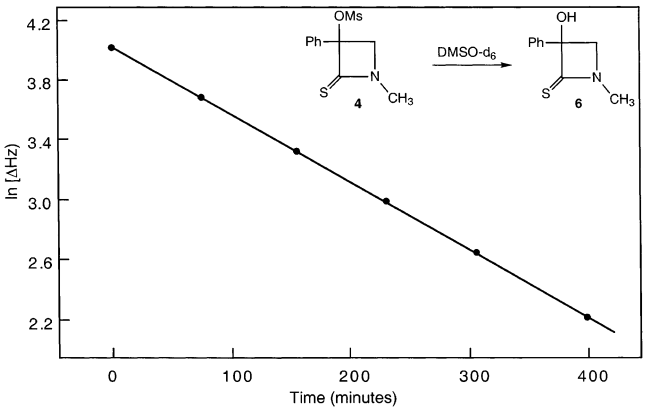
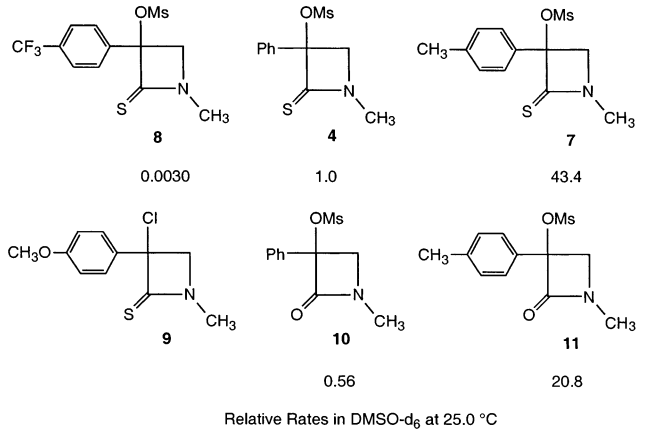



**FIGURE 3.** First-order kinetic plot for reaction of mesylate **4** in DMSO-$d_6$ at 60.0 °C.

the azide reaction. The small deviations from linearity at higher azide concentrations are probably due to aggregation phenomena in the more concentrated solutions.

When mesylate **4** was reacted in DMSO-$d_6$ without added $NaN_3$, **4** disappeared in a clean pseudo first-order process[8] (Figure 3), and alcohol **3** was the only product formed. A study on the optically active mesylate **4** showed that the alcohol product was 94% inverted (6% racemized). To shed further light on the origin of this alcohol product, a limited substituent effect study on the rate was carried out. *p*-$CH_3$ analogue **7** reacted 43 times faster than **4**, and *p*-$CF_3$ analogue **8** reacted 333 times more slowly than **4** (Table 1). The *p*-$OCH_3$ substituted mesylate analogue could not be prepared due to its high reactivity, but the corresponding chloride **9** can be prepared and reacted in DMSO-$d_6$. All of these substrates react in DMSO-$d_6$ to give the corresponding alcohol products. If one assumes a mesylate/chloride rate ratio[9] of $3 \times 10^4$, then the Hammett $\rho^+$ value based on **4** and **7**−**9** is −4.9 (correlation coefficient = 0.998). If data for **9** are omitted, then the $\rho^+$ value is −4.6.

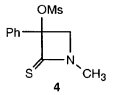
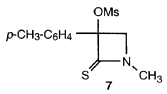
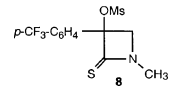
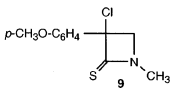
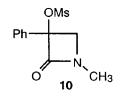
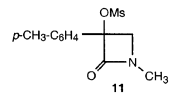
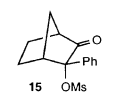
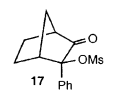
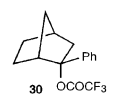
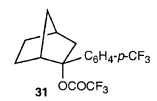
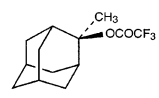
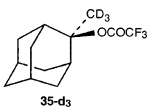
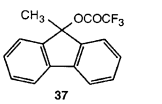
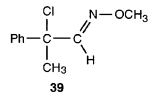
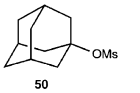
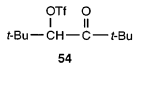



It is proposed that these data are consistent with a carbocation mechanism, where the solvent DMSO-$d_6$ has an "ionizing power" that is not insignificant. This belief

(8) Reaction is easily monitored by integration of the signals in Figure 1 or by adding $Et_3N$ and monitoring the changing shift of the methyl group of $Et_3N$. See Experimental Section for details.

(9) Noyce, D. S.; Virgilio, J. A. *J. Org. Chem.* **1972**, *37*, 2643.

**TABLE 1. Rates of Reaction of Substrates in DMSO-$d_6$**

| Compound | Temp (°C) | k ($s^{-1}$) | $k_{rel}$ |
|---|---|---|---|
|  **4** | 60.0 | $7.52 \times 10^{-5}$ | |
| | 50.0 | $2.56 \times 10^{-5}$ | |
| | 40.0 | $8.18 \times 10^{-6}$ | |
| | 50.0 | $5.62 \times 10^{-5}$ (0.10 M $NaN_3$) | |
| | 50.0 | $8.35 \times 10^{-5}$ (0.20 M $NaN_3$) | |
| | 50.0 | $1.06 \times 10^{-4}$ (0.30 M $NaN_3$) | |
| | 25.0 | $1.27 \times 10^{-6}$ | 1.00 |
|  **7** | 25.0 | $5.52 \times 10^{-5}$ | 43.4 |
|  **8** | 100.0 | $1.98 \times 10^{-5}$ | |
| | 80.0 | $2.88 \times 10^{-6}$ | |
| | 25.0 | $3.82 \times 10^{-9}$ | $3.00 \times 10^{-3}$ |
|  **9** | 80.0 | $1.59 \times 10^{-4}$ | |
| | 60.0 | $2.64 \times 10^{-5}$ | |
| | 25.0 | $6.40 \times 10^{-7}$ | |
|  **10** | 70.0 | $1.02 \times 10^{-4}$ | |
| | 50.0 | $1.33 \times 10^{-5}$ | |
| | 25.0 | $7.17 \times 10^{-7}$ | 0.56 |
|  **11** | 25.0 | $2.65 \times 10^{-5}$ | 20.8 |
|  **15** | 50.0 | $2.00 \times 10^{-4}$ | |
| | 25.0 | $9.85 \times 10^{-6}$ | |
|  **17** | 25.0 | $1.41 \times 10^{-4}$ | |
|  **30** | 25.0 | $1.37 \times 10^{-3}$ | |
|  **31** | 25.0 | $9.35 \times 10^{-6}$ | |
|  **35** | 70.0 | $2.53 \times 10^{-4}$ | |
| | 50.0 | $2.10 \times 10^{-5}$ | |
| | 25.0 | $5.85 \times 10^{-5}$ | |
|  **35-d3** | 50.0 | $9.70 \times 10^{-6}$ | |
|  **37** | 25.0 | $7.35 \times 10^{-4}$ | |
|  **39** | 25.0 | $6.59 \times 10^{-5}$ | |
|  **50** | 70.0 | $1.08 \times 10^{-4}$ | |
| | 50.0 | $1.11 \times 10^{-5}$ | |
| | 25.0 | $4.21 \times 10^{-7}$ | |
|  **54** | 25.0 | $1.41 \times 10^{-3}$ | |

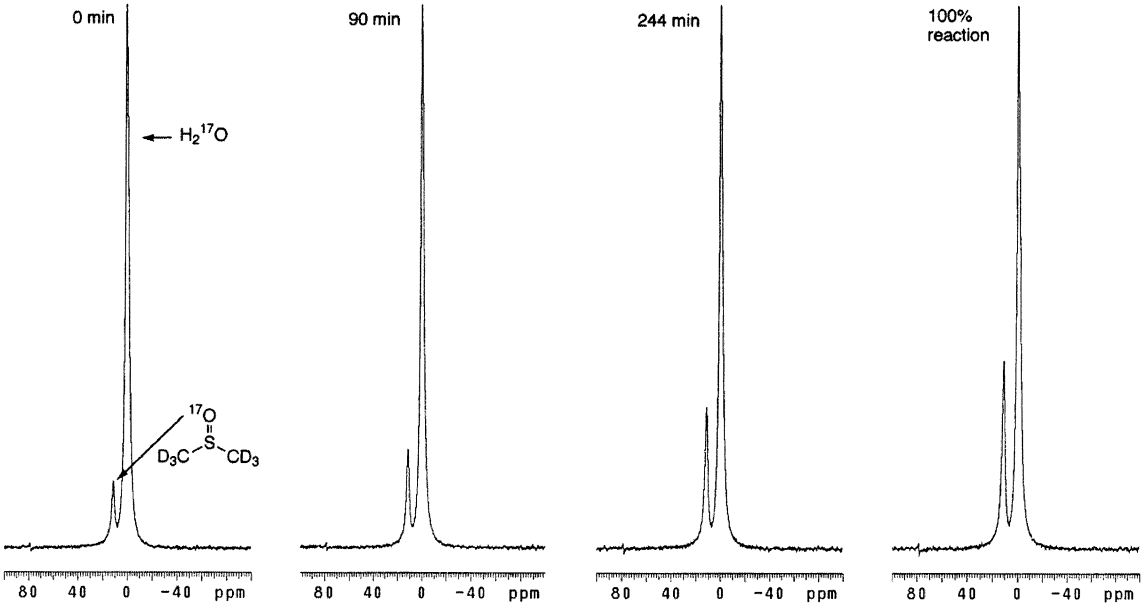


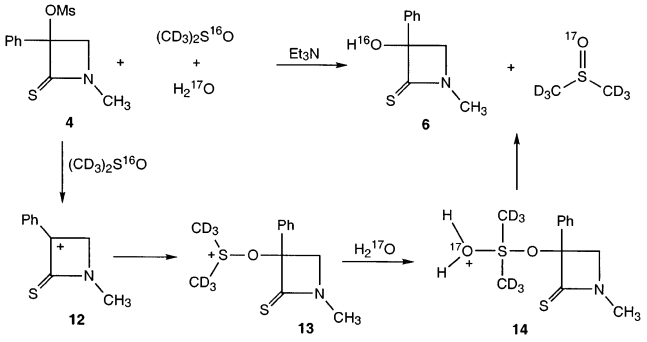

**FIGURE 4.** Evolving $^{17}O$ NMR spectra during reaction of **4** in DMSO-$d_6$ containing 0.5% $H_2{}^{17}O$ at 60 °C. The peak at $\delta$ 11.5 at time = 0 is due to naturally occurring $^{17}O$ in the DMSO-$d_6$ solvent.

is based partially on the $\rho^+$ value of −4.9. This value is quite large and consistent with a transition state with significant positive charge. The stereochemical course of the reaction of optically active **4** suggests that a minimum of 6% of this reaction proceeds via a carbocation mechanism (racemization). In fact, we suggest that the entire reaction proceeds via a tight ion-pair mechanism where nucleophile capture occurs preferentially from the opposite side of the departing mesylate leaving group. This ion-pair is short-lived and strongly solvated by the DMSO-$d_6$ solvent from the rear of the leaving group. Solvolysis reactions proceeding through such ion-pair mechanisms, which give large amounts of net inversion, have been observed in the past.[10] Hence, the formation of the largely inverted product **6** is not inconsistent with a carbocation mechanism.

The rates of these substrates (Table 1) are all somewhat less than the previously reported rates[6] in acetic acid, a very common solvent in solvolysis studies. Carbonyl analogue **10** was also examined and reacts in a similar fashion in DMSO-$d_6$ to give the alcohol product at a rate that is slightly slower than that of **4**. *p*-$CH_3$ analogue **11** reacts 37 times faster than **10**, and this substituent effect is also consistent with an analogous ion-pair mechanism.

A question arises as to the origin of the alcohol products in DMSO-$d_6$ as a solvent. Substitution product **6** has incorporated an OH group (and not OD) as can be clearly observed in the $^1H$ NMR spectrum in DMSO-$d_6$ before workup. The logical source of **6** is the trace of water (0.04%) present in the commercial "dry" DMSO-$d_6$. To probe this question in more detail, the reaction of **4** was carried out in DMSO-$d_6$ containing an added trace of $H_2{}^{17}O$ (0.6%) and some buffering $Et_3N$. The reaction was then monitored by $^{17}O$ NMR. Figure 4 shows that $^{17}O$ is incorporated *into the DMSO*. Control experiments show that (in the absence of mesylate **4**) the oxygen atom of DMSO-$d_6$ does not undergo exchange with $H_2{}^{17}O$ even when heated under the reaction conditions and even when a trace of $CH_3SO_3H$ is added. Examination of alcohol product **6** reveals *no* $^{17}O$ incorporation, while an authentic sample of the $^{17}O$-labeled **6** showed an $^{17}O$ signal at $\delta$ 39.1. The source of the oxygen atom in alcohol product **6** is therefore not residual water in the DMSO-$d_6$ but the DMSO-$d_6$ itself.

A reasonable mechanism accounting for the results of the labeling study involves capture of cationic intermediate **12** by DMSO-$d_6$ to give oxosulfonium intermediate **13**.[11] Intermediate **13** could then react with water to give **14**, which then breaks down to give $^{17}O$-labeled DMSO-$d_6$ and unlabeled alcohol product **6**. Alternatively, **13** could react with water by nucleophilic attack at sulfur and directly displacing the unlabeled oxygen, thereby avoiding hypervalent intermediate **14**.

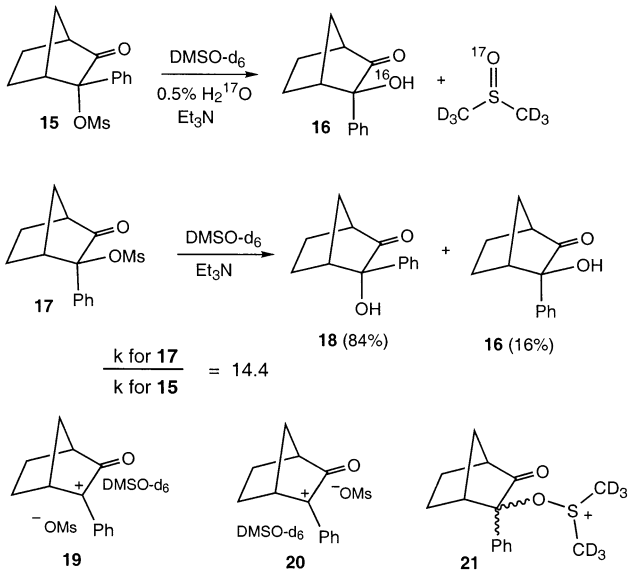



**Other Carbocation-Forming Substrates.** To further probe DMSO as a solvent for carbocation-forming

(10) (a) Weiner, H.; Sneen, R. A. *J. Am. Chem. Soc.* **1965**, *87*, 287. (b) Streitwieser, A.,Jr.; Walsh, T. D.; Wolfe, J. R., Jr. *J. Am. Chem. Soc.* **1965**, *87*, 3682. (c) Hughes, E. D.; Ingold, C. K.; Martin, R. J. L.; Meigh, D. F. *Nature* **1950**, *166*, 679.

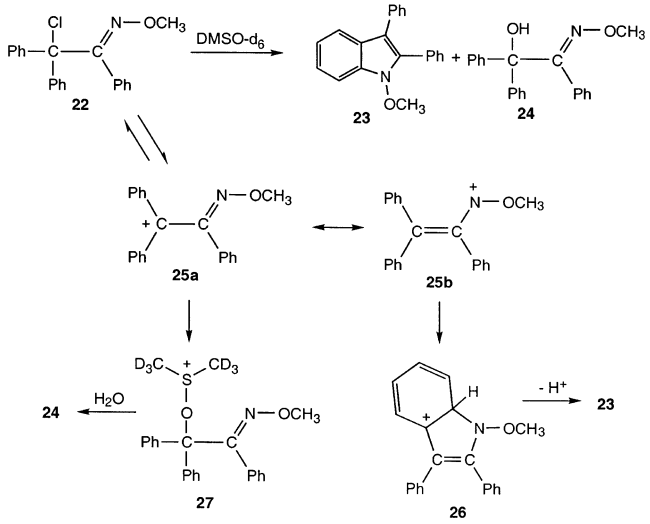
(11) Oxosulfonium ions analogous to **9** have been proposed as intermediates in reaction of $R_2SO$ and triflic anhydride with carbohydrates. These intermediates react with nucleopliles at carbon to displace $R_2SO$. See: Nguyen, H. M.; Chen, Y.; Duron, S. G.; Gin, D. Y. *J. Am. Chem. Soc.* **2001**, *123*, 8766.

reactions, mesylate **15** was examined. Solvolysis reactions of **15** in protic solvents proceed via α-keto carbocationic intermediates that lead to *exo*-substitution products.[12] Mesylate **15** disappears in a clean pseudo first-order process in DMSO-$d_6$, and rate data are given in Table 1. Mesylate **15** in DMSO-$d_6$ is 8 times less reactive than in ethanol and 40 times less reactive than in acetic acid. The product formed in DMSO-$d_6$ (containing a slight excess of triethylamine) is exclusively *exo*-alcohol **16**. No buildup of intermediates could be detected spectroscopically over the course of the reaction. An analogous labeling experiment using 0.5% $H_2{}^{17}O$ in DMSO-$d_6$ showed that $^{17}O$ is again incorporated into the DMSO-$d_6$ and not into the alcohol product. The suggested mechanism to account for the $^{17}O$ labeling result again involves formation of an oxosulfonium ion intermediate derived from capture of DMSO-$d_6$ from the *exo*-face. The resultant oxosulfonium ion then reacts with the trace of water present in the DMSO-$d_6$, which results in the observed alcohol product and label incorporation into the DMSO-$d_6$. The stereochemistry of **16** is consistent with either an $S_N2$ process utilizing DMSO-$d_6$ as the nucleophile or an ion-pair process where the cation preferentially captures DMSO-$d_6$ from the *exo*-face.




The reaction of *exo*-mesylate **17** in DMSO-$d_6$ sheds further light on the mechanism. Mesylate **17** reacts 14.4 times faster than *endo*-analogue **15**. However, the inversion of stereochemistry in this reaction is not clean and an 84:16 ratio of alcohols **18** and **16** is produced. The exo/endo rate ratio of 14.4 is inconsistent with $S_N2$ processes. In fact, *exo*-2-norbornyl brosylate is slightly *less reactive* than *endo*-2-norbornyl brosylate in $S_N2$ reactions.[13] The significant amount of *exo*-alcohol **16** derived from **17** is also inconsistent with an $S_N2$ mechanism. On the other hand, an ion-pair mechanism analogous to that proposed for **4** nicely accounts for the rate and stereochemical results. It is well established that *exo*-2-norbornyl derivatives solvolyze via cationic intermediates more rapidly than *endo*-2-norbornyl derivatives.[14] Our exo/endo rate ratio of 14.4, although on the small side,[15] is completely consistent with ion-pair mechanisms for reactions of **15** and **17**, where the ion-pairs are quite short-lived. The complete inversion in the solvolysis of **15** suggests, as expected, complete capture of ion-pair **19** from the *exo*-face. On the other hand, solvation of ion-pair **20** from the *endo*-side is not as effective and some solvent finds its way to the *exo*-side. These stereochemical studies suggest that ion-pairs **19** and **20** are quite short-lived and readily collapse to covalent oxosulfonium ions **21**.

Reaction of chloride **22** provides further evidence for carbocation formation in DMSO-$d_6$. At room temperature, **22** is cleanly converted to a mixture of indole **23** (83%) and alcohol **24** (17%). As before, the minor alcohol product is suggested to be derived from rapid reaction of the trace amount of water with intermediate **27**. Indole **23** is a product of cationic cyclization and indicative of the intermediacy of the resonance-stabilized carbocation **25**. This type of resonance stabilization of α-oximino cations has been previously proposed,[16] and the observation of **23** supports this notion. Cyclization of **25** also provides an interesting route leading to the indole nucleus. Thus, treatment of **24** with catalytic $CF_3CO_2H$ in chloroform also leads to a high yield of indole **23**.

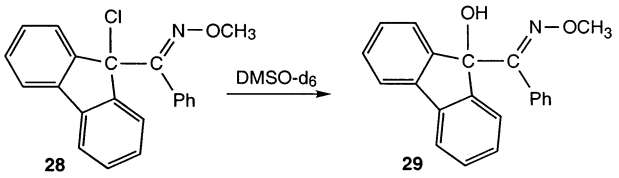



When the reaction of **22** in DMSO-$d_6$ is monitored by $^1H$ NMR spectroscopy (0.01 M in **22**), the rate is subject to a common ion rate suppression,[17] i.e., the apparent first-order rate constant for disappearance of **22** decreases as the reaction proceeds. Also, the addition of tetramethylammonium chloride (0.1 M) at the beginning of the reaction greatly suppresses the rate. This provides additional evidence for the involvement of a cationic intermediate. Intermediate **25** must live long enough to arrive at the dissociated ion-pair stage, where externally

(12) Creary, X. *J. Org. Chem.* **1979**, *44*, 3938.
(13) Banert, K.; Kirmse, W. *J. Am. Chem. Soc.* **1982**, *104*, 3766.
(14) For leading references, see: Brown, H. C. *The Nonclassical Ion Problem*; Plenum Press: New York, 1977.
(15) Although the exo/endo ratio of 20.x for **17** and **15** might be considered small, comparable values are seen in other 2-norbornyl systems solvolyzing via cationic mechanisms. See: Wilcox, C. F.; Jesaitis, R. G. *Tetrahedron Lett.* **1967**, 2567. (b) Wilcox, C. F.; Jesaitis, R. G. *Chem. Commun.* **1967**, 1056. (c) Traylor, T. G. Perrin, C. L. *J. Am. Chem. Soc.* **1966**, *88*, 4934.
(16) (a) Creary, X.; Wang, Y.-X.; Jiang, Z. *J. Am. Chem. Soc.* **1995**, *117*, 3044. (b) Creary, X.; Jiang, Z. *J. Org. Chem.* **1996**, *61*, 3482.
(17) Smith, M.; March, J. *March's Advanced Organic Chemistry*; Wiley-Interscience: New York, 2001; p 395.

added chloride can trap **25** and thereby return to starting chloride **22**.

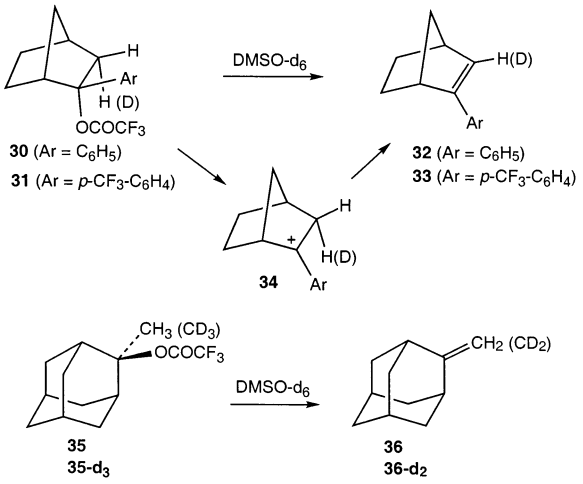
Fluorenyl system **28** is another example of a substrate that reacts in DMSO-$d_6$ to give the corresponding alcohol as the exclusive product. The rate of reaction of chloride **28** is also subject to a common ion rate suppression, and addition of tetramethylammonium chloride at the beginning of the reaction greatly slows the rate. Presumably, ring strain precludes indole formation from the cationic intermediate involved in this reaction. Although strict first-order rate behavior is not observed due to the common ion effect, the rate of reaction of **28** is qualitatively much slower than that of analogue **22**. The time required for 50% of **22** (0.01 M) to react at 50 °C is 32 min,[18] while a temperature of 112 °C is required to achieve comparable reactivity in **29**. The features leading to decreased solvolytic reactivity in fluorenyl systems analogous to **28** have been discussed.[19]




**28** **29**

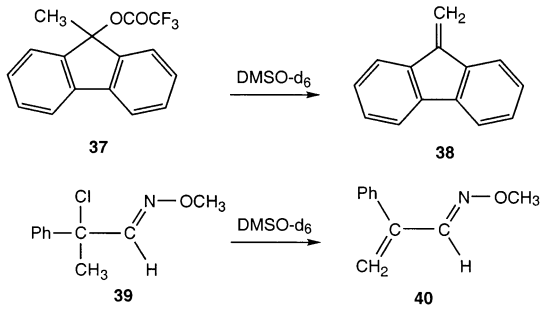
**Solvolytic Eliminations.** Trifluoroacetates **30** and **31** undergo facile solvolytic eliminations in DMSO-$d_6$ at room temperature to give exclusively alkenes **32** and **33**. To probe these elimination processes in more detail, the *endo*-deuterated substrates were also prepared and allowed to react in DMSO-$d_6$. The exclusive products were the deuterated alkenes, where the *exo*-hydrogens are lost in the elimination processes. These products are consistent with stepwise mechanisms proceeding via carbocations **34**, which preferentially lose the *exo*-hydrogen.[20] Products **32** and **33** are inconsistent with concerted eliminations of trifluoroacetic acid from **30** and **31**. Concerted eliminations such as E2 or ester pyrolysis-type mechanisms should be cis elimination processes.[21] Rate data (Table 1) are also consistent with the intermediacy of cation **34** since *p*-$CF_3$ analogue **31** reacts 146 times more slowly than unsubstituted analogue **24**.

Trifluoroacetate **35** solvolyzes readily in DMSO-$d_6$ at slightly elevated temperatures to give elimination product **36** exclusively. No alcohol product or oxosulfonium ion intermediate could be detected. By way of contrast, solvolyses of 2-chloro-2-methyladamantane in protic solvents give mainly solvent capture products and only smaller amounts of the elimination product.[22] To shed further light on this elimination reaction of **35**, we have measured the $\beta$-deuterium isotope effect in DMSO-$d_6$




using $CD_3$ analogue **35**-$d_3$. Replacement of the methyl hydrogens by deuterium slows the rate by a factor of 2.11 ± 0.06. Previously determined α-$CH_3$/$CD_3$ isotope effects for 2-chloro-2-methyladamantane in protic solvents ranged from 1.48 to 1.68.[22] Our value of 2.11 in DMSO-$d_6$ is considered to be too large for simple rate-determining cation formation, where the expected value is 1.46.[22] It is therefore suggested that the reaction of **35** in DMSO-$d_6$ proceeds via the $E2_{C+}$ mechanism,[23] where the rate limiting step is proton loss from the reversibly formed 2-methyladamantyl cation.

Trifluoroacetate **37** and chloride **39** also react readily at room temperature in DMSO-$d_6$ to give elimination products **38** and **40**, respectively, with no alcohol products being formed. It therefore appears that, when feasible, $\beta$-proton loss from cationic intermediates can be more facile than capture of the carbocation by DMSO.




**Other Benzylic Substrates. $k_s$ Substrates.** Attention was next turned to the reaction of mesylate **41** in DMSO-$d_6$. Our previous studies have shown that solvolyses of this substrate in polar alcohol solvents proceed via carbocationic intermediates.[24] We wanted to evaluate the potential for carbocation formation in DMSO-$d_6$. Also of interest is the relationship between our observed carbocation-forming reactions in DMSO-$d_6$ and the Kornblum oxidation. This classic oxidation involves reaction on benzylic chlorides with DMSO and presumably involves nucleophilic displacement of halide with DMSO,

(18) Rates of reaction of **16** and **22** are extremely concentration dependent due to the common ion effect. Chloride **16** (0.0015 M) is 50% reacted in 70 min at 25 °C.

(19) Creary, X.; Wolf, A. *J. Phys Org. Chem.* **2000**, *13*, 337.

(20) Protonation of norbornenes from the *exo*-face is well established. Microscopic reversibility requires that *exo*-deprotonation of norbornyl cations be much faster than *endo*-deprotonation. See: (a) Kropp, P. J. *J. Am. Chem. Soc.* **1973**, *95*, 4611. (b) Stille, J. K.; Hughes, R. D. *J. Org. Chem.* **1971**, *36*, 340. (c) Brown, H. C.; Liu, K.-T. *J. Am. Chem. Soc.* **1975**, *97*, 2469. (d) Brown, H. C.; Kawakami, J. H. *J. Am. Chem. Soc.* **1975**, *97*, 5521.

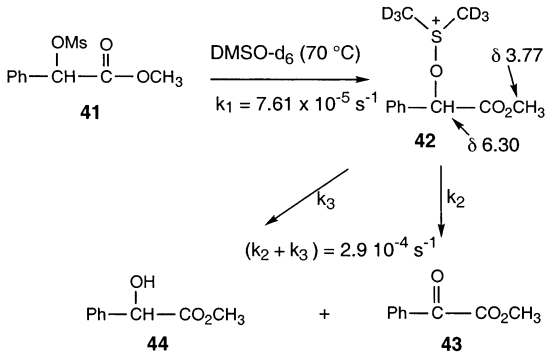
(21) Coke, J. L.; Cooke, M. P., Jr. *J. Am. Chem. Soc.* **1967**, *89*, 6701.

(22) Fisher, R. D.; Seib, R. C.; Shiner, V. J., Jr.; Szele, I.; Tomic, M.; Sunko, D. E. *J. Am. Chem. Soc.* **1975**, *97*, 2408.

(23) (a) Ingold, C. K. In *Structure and Mechanism in Organic Chemistry*, 2nd ed.; Cornell University Press: Ithica, New York, 1969; p 955. (b) Jansen, M. P.; Koshy, K. M.; Mangru, N. N.; Tidwell, T. T. *J. Am. Chem. Soc.* **1981**, *103*, 3863. (c) Creary, X.; Geiger, C. C.; Hilton, K. *J. Am. Chem. Soc.* **1983**, *105*, 2851.

(24) Creary, X.; Geiger, C. C. *J. Am. Chem. Soc.* **1982**, *104*, 4151.

followed by $\beta$-elimination of dimethyl sulfide from the oxosulfonium intermediate. Mesylate **41** reacts readily in DMSO-$d_6$ at 70 °C to give oxidation product **43** (83%) as well as the substitution product, methyl mandelate, **44** (17%). The starting mesylate disappears in a clean pseudo first-order process and, contrary to the previously discussed substrates, oxosulfonium intermediate **42**, which builds up to a maximum concentration of 17%, can be observed by $^1$H NMR.[25] Unlike the reactions of substrates **4**, **7**−**11**, **15**, and **17**, intermediate **42** is probably formed *not* by a carbocationic process but by an $S_N2$ process. This intermediate partitions readily between elimination of dimethyl sulfide and alcohol formation. The pseudo first-order rate constants shown can be extracted by fitting the NMR data to a kinetic scheme involving consecutive pseudo first-order processes. Of interest is the reaction of **42** with the water in the DMSO-$d_6$ solvent, which leads to **44**. Adding 0.5% water to the DMSO-$d_6$ increased the amount of **44** formed to 38%. The rate of reaction of **42** with water is many orders of magnitude slower than the reaction of intermediate **13** with water. While intermediate **42** lives long enough to allow spectroscopic identification, no trace of analogous intermediate **13** (or intermediates derived from **7**−**11**, **15**, **17**, or **28**) can be detected. This is presumably due to the high rate of reaction of **13** with water. The origin of this large rate difference for reactions of **42** and **13** with water is unclear.




We have now prepared benzyl mesylate, **45**, and found that the products formed when this substrate reacts with DMSO-$d_6$ are highly dependent on the reaction conditions. When benzyl mesylate is dissolved in DMSO-$d_6$ containing no added base, oxosulfonium intermediate **46** is initially formed ($k = 6.2 \times 10^{-5}$ s$^{-1}$). This intermediate does not react readily with trace amounts (0.04%) of water present, and this allows **46** to be characterized in situ by $^1$H and $^{13}$C NMR spectroscopy. Under the reaction conditions, this intermediate converts slowly to sulfonium salt **47** ($k = 6.7 \times 10^{-6}$ s$^{-1}$). Figure 5 shows the buildup of intermediate **46** as a function of time as well as the slower conversion of **46** to the final product **47**. This figure shows that the initial rate of formation of **47** is quite slow, but the rate of formation of **47** increases as intermediate **46** builds up. This kinetic behavior is consistent with a mechanism where **47** is formed via intermediate **46** and *not* by direct reaction of benzyl

(25) An oxosulfonium intermediate [$Ph_2S$−O−sugar]$^+$ has been spectroscopically characterized at low temperatures. See: Garcia, B. A.; Gin, D. Y. *J. Am. Chem. Soc.* **2000**, *122*, 4269.

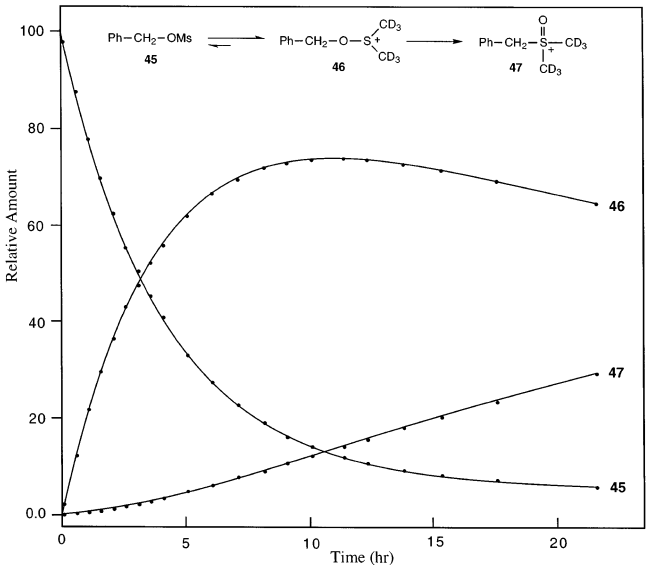
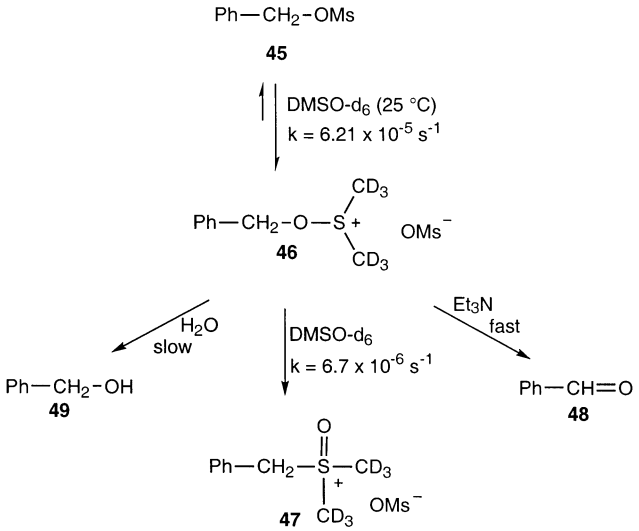



**FIGURE 5.** Conversion of $PhCH_2OMs$ **45** to **46** and **47** in DMSO-$d_6$ at 60 °C.

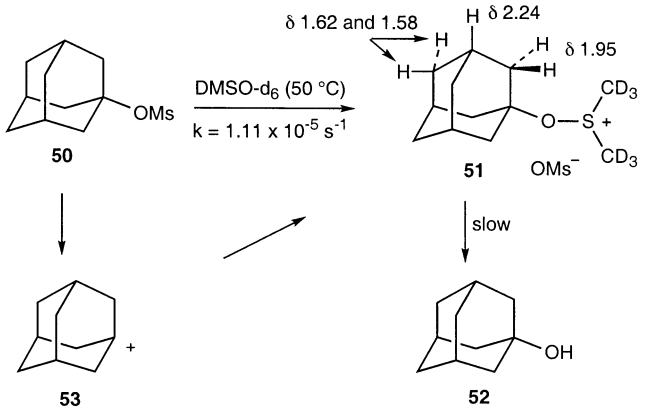
mesylate with DMSO-$d_6$. In other words, DMSO-$d_6$ can be displaced from **46** by solvent DMSO-$d_6$, where the sulfur is now the nucleophilic end of the solvent. The formations of both **46** and **47** are probably $S_N2$ processes.

When $Et_3N$ is added to the DMSO-$d_6$ at the beginning of the reaction, no buildup of **46** is observed and the observed product of the reaction is then benzaldehyde, **48**. If there is no $Et_3N$ present and larger amounts of water (1−2%) are added, then **46** can be intercepted and converted to benzyl alcohol, **49**, in competition with conversion to **47**. Thus, in DMSO-$d_6$ containing 2% $H_2O$, **46** partitions to give comparable amounts of **47** and **49**. However, the reactivity of **46** with water is many orders of magnitude lower than that of **13** with water. While **46** can be easily observed in the NMR even with 2% water present, oxosulfonium intermediate **13** cannot be detected even when water is present to the extent of only 0.04%.




**1-Adamantyl Mesylate: A $k_C$ Substrate.** 1-Adamantyl and 2-adamantyl systems have become standards for evaluation of reactions proceeding via $k_C$ (carbocat-

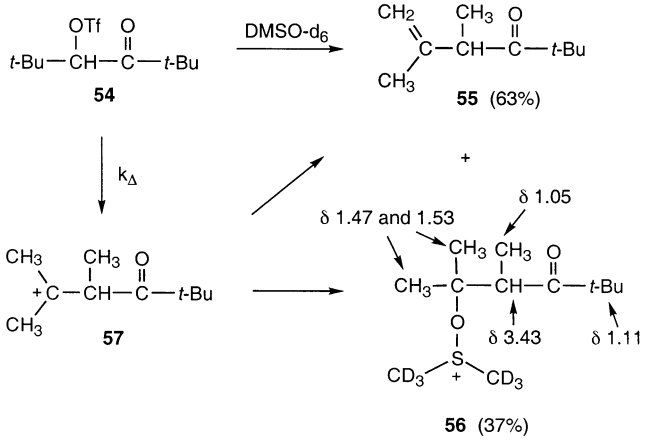
ionic) mechanisms.[26] These systems react in solvolysis reactions without backside assistance due to nucleophilic solvent properties. A series of solvent ionizing power values (*Y* values) have been developed on the basis of adamantyl systems. It was therefore of interest to determine the reactivity of 1-adamantyl mesylate in DMSO-$d_6$.




1-Adamantyl mesylate, **50**, reacts in DMSO-$d_6$ at 50 °C to give oxosulfonium salt **51**, which is relatively unreactive under the reaction conditions. The activation parameters calculated from the data in Table 1 ($\Delta H^{\ddagger}$ = 24.4 kcal/mol; $\Delta S^{\ddagger} = -5.8$ eu) are unexceptional. The extrapolated rate constant for disappearance of **50** ($4.21 \times 10^{-7}$ s$^{-1}$ at 25 °C DMSO-$d_6$) is $10^4$ times slower than reaction of **50** in 80% aqueous ethanol,[27] and this corresponds to a $Y_{OMs}$ value of −4.00 for DMSO-$d_6$. The rate of reaction of mesylates **4**, **7**, **10**, and **11** in DMSO-$d_6$ are all somewhat faster than predicted on the basis of this $Y_{OMs}$ value for DMSO-$d_6$ derived from **50**. It is suggested that **50**, which is quite reactive in protic solvents, is relatively unreactive in DMSO-$d_6$ due to the inability of DMSO-$d_6$ to solvate the developing mesylate anion as effectively as hydrogen-bonding solvents.

The fact that oxosulfonium salt **51** does not react rapidly with water in DMSO-$d_6$ at 50 °C allows it to be characterized in situ by $^1$H as well as $^{13}$C NMR. However, **46** is slowly converted to 1-adamantyl alcohol, **52**, at 100 °C, presumably by reaction with the trace of water present. Thus, adding 1% water to the DMSO-$d_6$ and heating at 100 °C for 4 h gives complete conversion of **51** to **52**.

**Triflate Derivative of Pivaloin: A $k_\Delta$ Substrate.** Reaction of the triflate derived from pivaloin, **54**, is of special interest due to the high reactivity of this substrate in DMSO-$d_6$. Triflate **54** disappears in a clean first-order process with a half-life of only 15 min at 25 °C in this solvent. Previous solvolysis studies on **54** have been carried out in solvents ranging from the relatively "poorly ionizing" solvents ethanol and acetic acid (half-life of **54** = 46 h in HOAc) to the "highly ionizing" solvents formic acid, hexafluoroisopropyl alcohol, and trifluoroacetic acid (half-life of **54** = 58 min in $CF_3CO_2H$).[28] Triflate **54** solvolyzes in DMSO-$d_6$ at a rate that *exceeds* rates in all of these solvents. Hence the $Y_{OMs}$ value of −4.00 for DMSO-$d_6$ is of little value in predicting the reactivity of triflate **54** in DMSO-$d_6$. The products of reaction of **54** in DMSO-$d_6$ are also of interest. The major product (63%) is the rearranged elimination product **55**, and this attests to the cationic nature ($k_\Delta$) of the reaction in DMSO-$d_6$. Also formed is a smaller amount of oxosulfonium salt **56**, which is derived from solvent capture of the rearranged cation **57**. Of note is the fact that **56** can be easily detected under the reaction conditions and none of the corresponding rearranged alcohol product is observed. This represents a rare example where DMSO capture successfully competes with $\beta$-proton loss from the cationic intermediate.

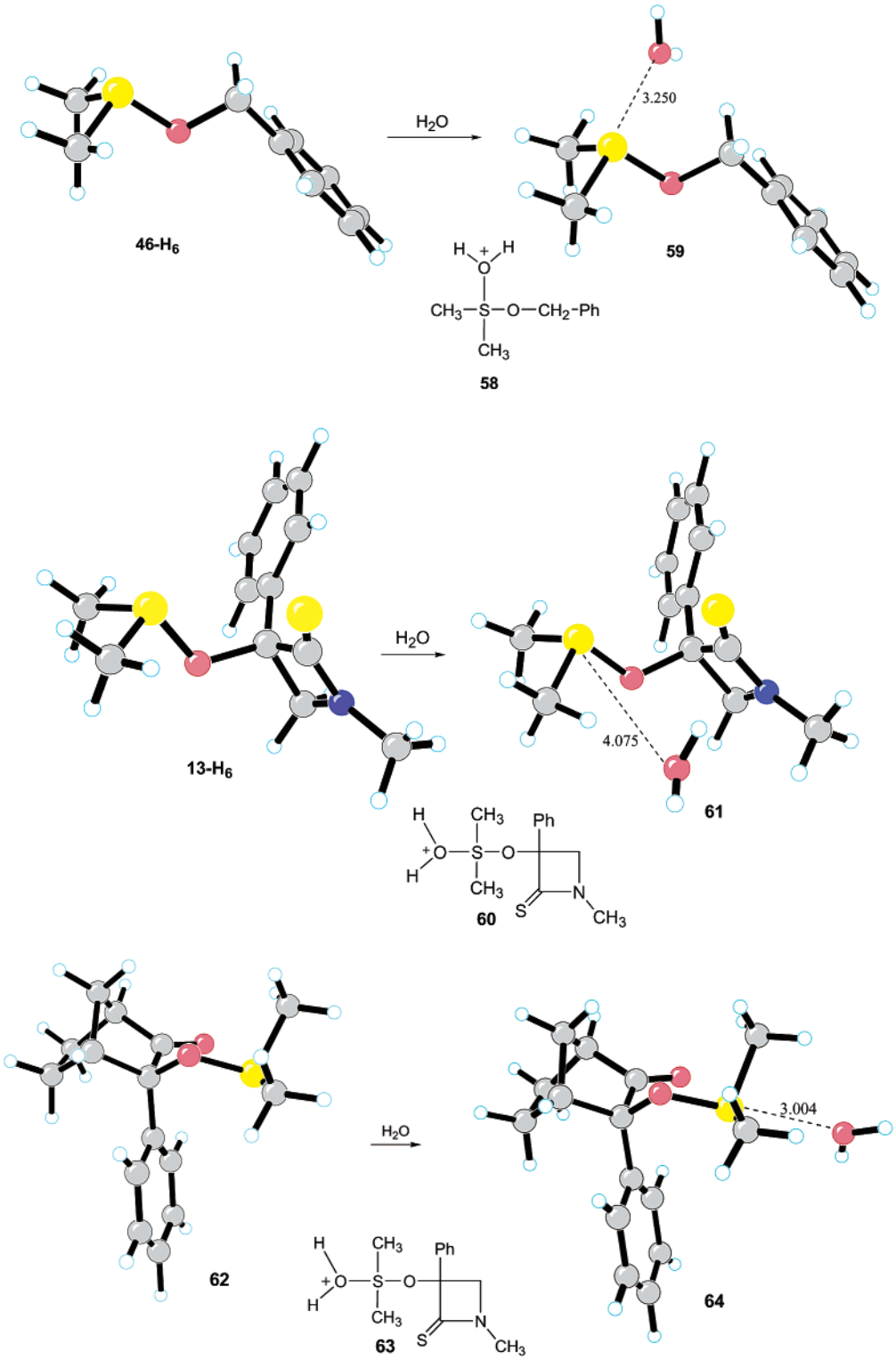



**Computational Studies.** To shed further light on the reaction of substrates with DMSO and water, computational studies were carried out at the B3LYP/6-31G* level.[29] Shown is the geometry-optimized structure of the adduct $[Ph{-}CH_2{-}O{-}S(CH_3)_2]^+$, **46**-$H_6$, derived from O-benzylation of DMSO. Covalent product **58** potentially formed by reaction of water with **46**-$H_6$ could not be located as an energy minimum at any computational level attempted. Starting with a geometry where water is within covalent bonding distance of sulfur, attempted geometry optimization led to the energy minimum structure **59** shown. The $H_2O$−sulfur distance is quite long (3.250 Å) and indicative of an ion/dipole attractive interaction. The covalent form represented by **58** contains a hypervalent sulfur, and this computational study casts doubt on the involvement of such species in reactions of **13** and **27** (and other oxosulfonium intermediates) with water.

To probe for subtle structural differences that might lead to facile reaction with water, computational studies were also carried out at the B3LYP/6-31G* level on unlabeled oxosulfonium ion **13**-$H_6$, as well as on oxosul-

(26) For reviews, see: (a) Bentley, T. W.; Schleyer, P. v. R. *Adv. Phys. Org. Chem*. **1977**, *14*, 1. (b) Kamlet, M. J.; Abboud, J. L. M.; Taft, R. *Prog. Phys. Org. Chem*. **1981**, *13*, 485.
(27) Bentley, T. W.; Carter, G. E. *J. Org. Chem*. **1983**, *48*, 579.
(28) Creary, X.; McDonald, S. R. *J. Org. Chem*. **1985**, *50*, 474.

(29) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B. G.; Chen, W.; Wong, M. W.; Andres, J. L.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, revision A.7; Gaussian, Inc.: Pittsburgh, PA, 1998.




fonium ion intermediate **62** derived from mesylate **15**. Optimized structures are shown. As before, the computational studies indicate that covalent water adducts **60** and **63** are not energy minima because water is not within covalent bonding distance of sulfur in minimized forms **61** and **64**. How then do oxosulfonium ions react with water? The obvious alternative is a concerted pathway where nucleophilic attack of water on sulfur occurs with simultaneous sulfur−oxygen bond breaking. An additional water molecule may well be hydrogen-bonded to oxygen in the departing alcohol to avoid formation of anionic $RO^-$. However, these calculations do not offer an obvious reason as to why certain oxosulfonium intermediates such as **13** and **27** react so much more readily with water than oxosulfonium ions **42**, **46**, **51**, and **56**.

## Conclusion

Certain mesylates, triflates, trifluoroacetates, and chlorides react at reasonable rates in DMSO-$d_6$ to give

products derived from carbocationic intermediates. These carbocations can suffer proton loss leading to elimination products or they can be captured by DMSO-$d_6$ to give oxosulfonium intermediates. These oxosulfonium intermediates then undergo rapid reaction with trace amounts of water present in the DMSO-$d_6$ to give alcohol products. Reaction in the presence of $H_2{}^{17}O$ leads to $^{17}O$ incorporation into the DMSO-$d_6$ and no $^{17}O$ in the alcohol product. Reaction of the *O*-methyl oxime derivative of α-chloro-α,α-diphenylacetophenone in DMSO-$d_6$ gives an indole as the major product, and this finding supports the involvement of a delocalized α-oximino carbocation. Solvolysis of 1-adamantyl mesylate in DMSO-$d_6$ allows determination of a $Y_{OMs}$ value (−4.00) for DMSO-$d_6$. Capture of the 1-adamantyl cation by DMSO-$d_6$ gives a long-lived oxosulfonium intermediate which can be characterized by $^1$H and $^{13}$C NMR. This intermediate reacts slowly with residual water in the solvent at 100 °C. Hence, oxosulfonium intermediates possess remarkably differing reactivities toward water. In some cases, they cannot be detected at room temperature, while in other cases they survive for significant periods of time at 100 °C.

## Experimental Section

**Reaction of Mesylate 4 with $NaN_3$ in DMSO-$d_6$. Kinetic Studies.** Mesylate **4**[7] (2.4 mg) was dissolved in 2.0 mL of 0.1 M $NaN_3$ in DMSO-$d_6$, and a portion of this solution was sealed in an NMR tube. The tube was immersed in a water bath at 50.0 °C for a given amount of time. The tube was then cooled to room temperature and analyzed by 600 MHz $^1$H NMR. The amounts of unreacted **4** and products **5** and **6** were determined by integration of signals at $\delta$ 4.63, 4.27, and 4.11. Figure 1 shows some representative spectra as a function of time at 50.0 °C. Pseudo first-order rate constants for disappearance of **4** were calculated by standard least squares procedures. Correlation coefficients were all greater than 0.9999. Kinetic studies in 0.20 and 0.30 M $NaN_3$ were carried out in a completely analogous fashion.

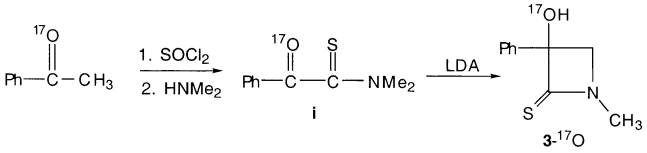
**Reaction of Mesylates 4, 7, 8, 10, 11, 15, and 17 in DMSO-$d_6$. Kinetic Studies.** Rates of reaction of these mesylates[7,12] were determined by $^1$H NMR using two methods.

Method 1: approximately 5 mg of the appropriate mesylate was dissolved in 1 mL of 0.06 M $Et_3N$ in DMSO-$d_6$, and the sample was sealed in an NMR tube. The tube was placed in a constant-temperature bath at the appropriate temperature or in the probe of the NMR at 25.0 °C. At appropriate time intervals, the tube was analyzed by $^1$H NMR, and the shift of the upfield triplet due to the $Et_3N$ was determined. The shift of the $Et_3N$, which moves downfield as a function of time, was monitored. After 10 half-lives, a final reading was taken. First-order rate constants for disappearance of mesylates were calculated by standard least squares procedures. Correlation coefficients were all greater than 0.9999. Rates of **4**, **7**, **9**, **15**, and **17** were measured by this method.

Method 2: approximately 5 mg of the appropriate mesylate was dissolved in 1 mL of DMSO-$d_6$, and a portion of the solution was sealed in an NMR tube. The tube was placed in a constant-temperature bath at the appropriate temperature. At appropriate time intervals, the tube was analyzed by 600 MHz $^1$H NMR and areas due to starting mesylate and alcohol product were measured. First-order rate constants for disappearance of mesylates were calculated by standard least squares procedures. Correlation coefficients were all greater than 0.9999. Rates of **8**, **10**, and **11** were measured by this method.

**Reaction of Mesylate 4 in DMSO-$d_6$ with 0.5% $H_2{}^{17}O$.** A solution was prepared by dissolving of 40.3 mg of mesylate **1** in 2.31 g of DMSO-$d_6$ containing 11.2 mg of $H_2{}^{17}O$ (20.1 atom % $^{17}O$) and 28 mg of $Et_3N$. This solution was sealed in two NMR tubes, and the tubes were immersed in a water bath at 60.0 °C. One of the tubes was periodically withdrawn from the water bath and analyzed by $^{17}O$ NMR spectroscopy. The evolving NMR spectra are shown in Figure 4. The signal at $\delta$ 0.0 is due to the $H_2{}^{17}O$, while the signal at $\delta$ 11.5, which increases with time, is due to $(CD_3)_2S^{17}O$. After 22 h at 60 °C, the contents of the NMR tubes were added to water and extracted into ether. The ether extract was washed with water and saturated NaCl solution and dried over $MgSO_4$. After solvent removal using a rotary evaporator, the residue was analyzed by $^1$H NMR, which showed **6** as the sole product. $^{17}O$ NMR spectroscopy of **6** showed no signals.

**Preparation of an Authentic Sample of 6-$^{17}$O.** The preparation of **6**-$^{17}O$ was analogous to the preparation of unlabeled **6** from acetophenone as shown below. Thionyl chloride (2.20 g) was added to 410 mg of acetophenone-$^{17}O$ (20 at. % $^{17}O$)[30] containing 5.6 mg of pyridine.




The mixture was stirred for 2.25 h at room temperature, and the excess $SOCl_2$ was removed using a rotary evaporator. The crude residue was dissolved in 5 mL of ether, and the ether solution was added dropwise to a stirred solution of 2.0 g $HN(CH_3)_2$ in 10 mL of ether at −78 °C. The mixture was slowly warmed to room temperature with stirring and then taken up into ether and water. The ether extract was washed with water and saturated NaCl solution and dried over $MgSO_4$. The ether solvent was removed using a rotary evaporator, and 537 mg (81%) of thioamide **i** was obtained as a yellow solid. The $^{17}O$ NMR spectrum of **i** ($CDCl_3$) showed a signal at $\delta$ 497.4.

A solution of 489 mg of thioamide **i** in 3 mL of THF was added dropwise to a solution of lithium diisopropyl amide (LDA) prepared from 329 mg of diisopropylamine and 1.90 mL of 1.6 M *n*-BuLi in 3 mL of THF at −78 °C. The mixture was slowly warmed to room temperature, and an aqueous workup followed with ether extraction. The ether extract was dried over $MgSO_4$ and filtered, and the solvent was removed using a rotary evaporator. The crude product was chromatographed on 5 g of silica gel, and 236 mg (48%) of **6**-$^{17}O$ eluted with 30% ether in hexanes. The $^{17}O$ NMR spectrum of **6**-$^{17}O$ (DMSO-$d_6$) showed a signal at $\delta$ 39.1.

**Reaction of (*S*)-(+)-Mesylate 4 in DMSO-$d_6$.** (*S*)-(+)-Mesylate **4** (15 mg) (prepared from optically pure (*S*)-(+)-**6**)[7] was dissolved in 1.9 mL of DMSO-$d_6$ containing 10.8 mg of $Et_3N$. The solution was sealed in a tube and heated at 60.0 °C for 17 h and then at 64 °C for 5.5 h. After a standard aqueous workup, the crude alcohol product was passed through a small amount of silica gel in a pipet and then analyzed by 600 MHz $^1$H NMR. The ratio of the enantiomers present was determined by addition of the chiral shift reagent Eu(hfc)$_3$. The ratio of (*R*)- to (*S*)- enantiomers was 97.1:2.9 as determined by integration of the *o*-hydrogens of the phenyl group, which appeared at $\delta$ 7.86 for (*R*)-**6** and $\delta$ 7.99 for (*S*)-**6**. This corresponds to 94.2% inversion and 5.8% racemization.

**Preparation of Chloride 22.** A mixture of 1.78 g of α-hydroxy-α,α-diphenylacetophenone[31] and 0.670 g of methoxylamine hydrochloride in 5 mL of pyridine was sealed in a tube and heated at 120 °C for 48 h. The contents of the tube were then added to 30 mL of water and extracted into ether. The ether extract was washed with dilute HCl solution, saturated NaCl solution, and dried over $MgSO_4$. After solvent

(30) Creary, X.; Inocencio, P. A. *J. Am. Chem. Soc.* **1986**, *108*, 5979.
(31) Greene, J. L.; Zook, H. D. *J. Am. Chem. Soc.* **1958**, *80*, 3629.

removal using a rotary evaporator, the residue was chromatographed on silica gel and the column was eluted using 10% ether in hexanes. The (*Z*)-isomer of the *O*-methyloxime eluted first (250 mg) followed by 1.612 mg of the pure (*E*)-*O*-methyloxime **24**. $^1$H NMR of **24** ($CDCl_3$): $\delta$ 7.40 (m, 4 H), 7.29 (m, 6 H), 7.24 (t, $J$ = 7.4 Hz, 1 H), 7.19 (t, $J$ = 7.4 Hz, 2 H), 6.82 (m, 2 H), 4.23 (s, 1 H), 3.86 (s, 3 H). $^{13}$C NMR ($CDCl_3$): $\delta$ 160.2, 143.0, 132.1, 128.63, 128.60, 128.3, 127.85, 127.81, 127.7, 81.5, 62.6.

A mixture of 280 mg of alcohol **24**, 157 mg of $SOCl_2$, and 468 mg of $Na_2CO_3$ in 3 mL of ether was stirred at room temperature for 3 days. The mixture was filtered, and the solvent was removed using a rotary evaporator. The NMR of the crude solid showed 6% of the (*Z*)-chloride along with 94% of **22**. The solid was slurried with ether, and the ether was decanted. The solid was collected using a Büchner funnel, washed with a small amount of ether, and dried under vacuum. $^1$H NMR of **22** ($CDCl_3$): $\delta$ 7.50 (m, 4 H), 7.39−7.32 (m, 6 H), 7.30−7.22 (m, 3 H), 6.95 (m, 2 H), 3.79 (s, 3 H). $^{13}$C NMR of **22** ($CDCl_3$): $\delta$ 159.5, 141.7, 133.1, 129.2, 128.6, 128.4, 128.1, 127.7, 127.5, 79.7, 62.7. Exact mass (EI) calcd for $C_{21}H_{18}$NOCl 335.1077, found 335.1059.

**Preparation of Indole 23.** A solution of 237 mg of alcohol **24** in 5 mL of $CDCl_3$ was stirred as 58 mg of $CF_3CO_2H$ was added. After 4 days at room temperature, the solvent was removed using a rotary evaporator and the residue was passed through a short silica gel column with ether elution. Solid indole **23** (224 mg; 95% yield) was collected, mp 134−135 °C. $^1$H NMR of **23** ($CDCl_3$): $\delta$ 7.72 (d of t, $J$ = 8.0, 0.9 Hz, 1 H), 7.52 (m, 3 H), 7.38−7.29 (m, 8 H), 7.24 (t, $J$ = 7.2 Hz, 1 H), 7.18 (t of d, $J$ = 8.0 Hz, 1.0 H), 3.694 (s, 3 H). $^{13}$C NMR of **23** ($CDCl_3$): $\delta$ 134.5, 133.3, 132.8, 130.4, 130.1, 129.7, 128.4, 128.3, 128.0, 126.1, 123.8, 123.0, 121.0, 119.8, 112.5, 108.9, 64.2. Exact mass (EI) calcd for $C_{21}H_{17}NO$ 299.1310, found 299.1311. Anal. Calcd for $C_{21}H_{17}NO$: C, 84.25; H, 5.72; N, 4.68. Found: C, 84.69; H, 5.94; N, 4.48.

**Preparation of Chloride 28.** A solution containing 2.271 g of 9-cyano-9-trimethylsiloxyfluorene (8.13 mmol)[32] in 5 mL of ether was stirred while 9.8 mL of 1.0 M phenylmagnesium bromide (9.8 mmol) in ether was added dropwise. After 15 min at room temperature, the reaction was quenched with 10 mL of saturated $NH_4Cl$ solution. The mixture was taken up into ether, and the ether extract was washed with water and saturated NaCl solution. The ether phase was dried over $MgSO_4$ and filtered, and the solvent was removed using a rotary evaporator. The crude residue was dissolved in 16 mL of tetrahydrofuran, and 4 mL of water was added followed by 0.716 g of $H_2SO_4$. The mixture was stirred at room temperature for 7 h and then taken up into ether. The ether extract was washed with saturated $NaHCO_3$ solution and saturated NaCl solution and then dried over $MgSO_4$. Filtration and removal of solvent by rotary evaporator gave 1.753 g of an oil, which was purified by chromatography on 30 g of silica gel. The column was eluted with increasing amounts of ether in hexanes. 9-Benzoyl-9-hydroxyfluorene (1.00 g; 57% yield), mp 132−134 °C, eluted with 6−15% ether in hexanes. $^1$H NMR ($CDCl_3$): $\delta$ 7.74 (d of m, $J$ = 7.5 Hz, 2 H), 7.41 (t of d, $J$ = 7.2, 1.2 Hz, 2 H), 7.35 (d of m, $J$ = 8.1, 2 H), 7.31−7.20 (m, 5 H), 7.07 (t of m, $J$ = 7.5, 2 H), 5.67 (br, 1H). $^{13}$C NMR ($CDCl_3$): $\delta$ 199.7, 146.0, 141.2, 133.3, 133.0, 129.9, 129.2, 128.7, 128.2, 124.5, 120.8, 86.52.

A solution of 205 mg of 9-benzoyl-9-hydroxyfluorene (0.715 mmol) and 71.8 mg of methoxylamine hydrochloride (0.857 mmol) in 4 mL of pyridine was stirred at 60 °C for 10 h. The mixture was taken up into ether and extracted with water, 2% hydrochloric acid, and saturated NaCl solution. The ether extract was dried over $MgSO_4$ and filtered, and the solvent was removed using a rotary evaporator to give 160 mg (71% yield) of *O*-methyloxime derivative **29**. $^1$H NMR of **29** ($CDCl_3$): $\delta$ 7.59−7.53 (m, 2 H), 7.46−7.39 (m, 2 H), 7.33−7.26 (m, 4 H), 7.03 (t of t, $J$ = 7.5, 1.2 Hz, 1 H), 6.93 (t of m, $J$ = 7.5, 2 H), 6.44 (d of m, $J$ = 8.2 Hz, 2 H), 5.18 (br, 1 H), 3.99 (s, 3 H). $^{13}$C NMR of **29** ($CDCl_3$): $\delta$ 157.7, 145.7, 140.8, 130.6, 129.4, 128.2, 127.9, 127.6, 127.2, 124.5, 120.0, 83.8, 62.8. Anal. Calcd for $C_{21}H_{17}NO_2$: C, 79.98; H, 5.43. Found: C, 79.77; H, 5.47.

A mixture of 108 mg of *O*-methyloxime derivative **29** prepared above and 100 mg of $Na_2CO_3$ in 3 mL of ether was stirred as 133 mg of thionyl chloride in 0.5 mL of ether was added. After the mixture was stirred for 10 h at room temperature, the $Na_2CO_3$ was removed by filtration and the solvent was removed using a rotary evaporator to give 93 mg (81% yield) of chloride **28**, mp 81−82 °C. $^1$H NMR ($CDCl_3$): $\delta$ 7.52 (d of m, $J$ = 7.6 Hz, 2 H), 7.46 (d of m, $J$ = 7.5 Hz, 2 H), 7.32 (t of d, $J$ = 7.8, 1.5 Hz, 2 H), 7.24 (t of d, $J$ = 7.2, 1.2 Hz, 2 H), 7.19−7.09 (m, 3 H), 6.80 (d of m, $J$ = 8.1, 2H), 3.89 (s, 3 H). $^{13}$C NMR ($CDCl_3$): $\delta$ 155.6, 144.8, 139.4, 131.7, 129.5, 128.6, 128.4, 127.8, 127.5, 136.7, 120.0, 72.1, 62.6. Exact mass (EI) calcd for $C_{21}H_{16}NOCl$ 333.0920, found 333.0927.

**Preparation of Trifluoroacetates 35, 35-*d*$_3$, and 37. General Procedure.** A solution of the appropriate alcohol (1.0 equiv) and 2,6-lutidine (1.5 equiv) in ether was cooled to −10 °C, and 1.3 equiv of trifluoroacetic anhydride was added dropwise to the stirred solution. The mixture was warmed to 0 °C, and after 5 min, water was added. The mixture was rapidly transferred to a separatory funnel using ether, and the ether extract was washed with dilute HCl solution, $NaHCO_3$ solution, and saturated NaCl solution and dried over $MgSO_4$. After filtration, the ether solvent was removed using a rotary evaporator to give the crude trifluoroacetates that were used without further purification. The trifluoroacetates decompose upon prolonged standing at room temperature and were therefore used immediately after solvent removal. The following procedure is representative.

Reaction of 97 mg of 2-methyl-2-adamantanol[22] and 121 mg of 2,6-lutidine in 2 mL of ether with 161 mg of trifluoroacetic anhydride gave of 2-methyl-2-adamantyl trifluoroacetate, **35**. $^1$H NMR ($CDCl_3$); $\delta$ 2.36 (m, 2 H), 1.99 (br d, 2 H), 1.93−1.78 (m, 6 H), 1.74 (m, 2 H), 1.707 (s, 3 H), 1.63 (br d, 2 H). $^{13}$C NMR ($CDCl_3$); $\delta$ 155.9 (q, $J$ = 41 Hz), 114.6 (q, $J$ = 287 Hz), 94.0, 37.9, 36.0, 34.6, 32.8, 27.1, 26.4, 22.0.

**Computational Studies.** Ab initio molecular orbital calculations were performed using the Gaussian 98 series of programs.[29] Structures were characterized as minima via frequency calculations that showed no negative frequencies.

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**Supporting Information Available:** B3LYP calculated structures, energies, and Cartesian coordinates of **46**-$H_6$, **59**, **13**-$H_6$, **61**, **62**, and **64**, $^1$H and $^{13}$C NMR spectra of compounds **22**, **24**, **28**, and **35**, as well as experimental procedures for reactions of **22**, **28**, **30**, **31**, **35**, **37**, **39**, **41**, **45**, **50**, and **54**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(32) Gassman, P. G.; Talley, J. J. *Organic Syntheses*; Wiley: New York, 1990; Collect. Vol. VII, p 20 .