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γ-Silyl Cyclobutyl Carbocations

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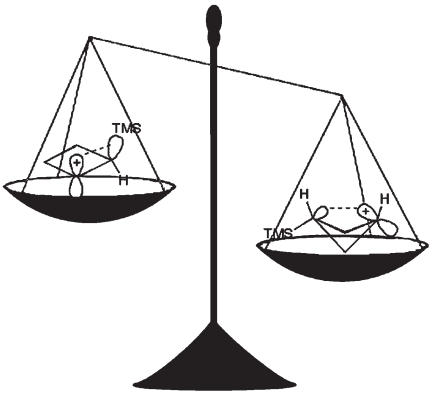

A series of 3-trimethylsilyl-1-substituted cyclobutyl trifluoroacetates have been prepared and reacted in CD_3CO_2D. Rate data indicate that the substrates with the trimethylsilyl group cis to the leaving group react with assistance due to γ-silyl participation. Rate enhancements range from a factor of 209 for α-phenyl-substituted cations to 4.6×10^4 for α-methyl-substituted cations to $>10^{10}$ for the unsubstituted γ-trimethylsilylcyclobutyl cation. Acetate substitution products are formed with net retention of stereochemistry. These experimental studies, as well as B3LYP/6-31G* computational studies, are consistent with the involvement of carbocations where the rear lobe of the γ-Si−C bond interacts strongly with the developing cationic center. Solvolytic rate studies, as well as computational studies, suggest that the secondary γ-trimethylsilylcyclobutyl cation is even more stable than the β-trimethylsilylcyclobutyl cation, i.e., the γ-silyl effect actually outweighs the potent β-silyl effect. Although computational studies suggest the existence of certain isomeric cations, where the front lobe of the Si−C bond interacts with the cationic center, solvolytic evidence for the involvement of these front lobe stabilized cations is less compelling.

Introduction

The β-silyl effect on carbocations of type **1** is a well-studied phenomenon.[1] Cations **1** are formed much more readily than unsilylated analogues and rate enhancements up to 10^{11} have been observed in quantitative studies by Lambert.[2] These cations **1** are tremendously stabilized by a very favorable interaction between the cationic center and the adjacent carbon−silicon bond. Computational studies,[3,4] as well as a recent X-ray crystallographic study,[5] also point to this mode of stabilization, as opposed to a potential stabilization mode involving silicon bridging as in **2**. Less well studied is the effect of a silyl group one carbon further removed from the carbocationic center, i.e., "the γ-silyl effect". Shiner[6]

(1) For reviews and early studies, see: (a) Colvin, E. W. *Silicon in Organic Synthesis*; Butterworths: London, UK, 1981. (b) White, J. M. *Aust. J. Chem.* **1995**, *48*, 1227. (c) Ushakav, S. N.; Itenberg, A. M. *Zh. Obshch. Khim.* **1937**, *7*, 2495. (d) Sommer, L. H.; Dorfman, E.; Goldberg, G. M.; Whitmore, F. C. *J. Am. Chem. Soc.* **1946**, *68*, 488. (e) Sommer, L. H.; Bailey, D. L.; Whitmore, F. C. *J. Am. Chem. Soc.* **1948**, *70*, 2869. (f) Sommer, L. H.; Baughman, G. A. *J. Am. Chem. Soc.* **1961**, *83*, 3346. (g) Davis, D. D.; Jacocks, H. M. III *J. Organomet. Chem.* **1981**, *206*, 33.

(2) (a) Lambert, J. B.; Wang, G.-t.; Finzel, R. B.; Teramura, D. H. *J. Am. Chem. Soc.* **1987**, *109*, 7838. (b) Lambert, J. B.; Chelius, E. C. *J. Am. Chem. Soc.* **1990**, *112*, 8120. (c) Lambert, J. B. *Tetrahedron* **1990**, *46*, 2677. (d) Lambert, J. B.; Liu, X. *J. Organomet. Chem.* **1996**, *521*, 203. (e) Lambert, J. B.; Zhao, Y.; Emblidge, R. W.; Salvador, L. A.; Liu, X.; So, J. H.; Chelius, E. C. *Acc. Chem. Res.* **1999**, *32*, 183.

(3) (a) Wierschke, S. G.; Chandrasekhar, J.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1985**, *107*, 1496. (b) Ibrahim, M. R.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1989**, *111*, 819.

(4) Creary, X.; Kochly, E. D. *J. Org. Chem.* **2009**, *74*, 2134.

(5) Klaer, A.; Saak, W.; Haase, D.; Müller, T. *J. Am. Chem. Soc.* **2008**, *130*, 14956.

(6) Shiner, V. J. Jr.; Ensinger, M. W. *J. Am. Chem. Soc.* **1986**, *108*, 842.

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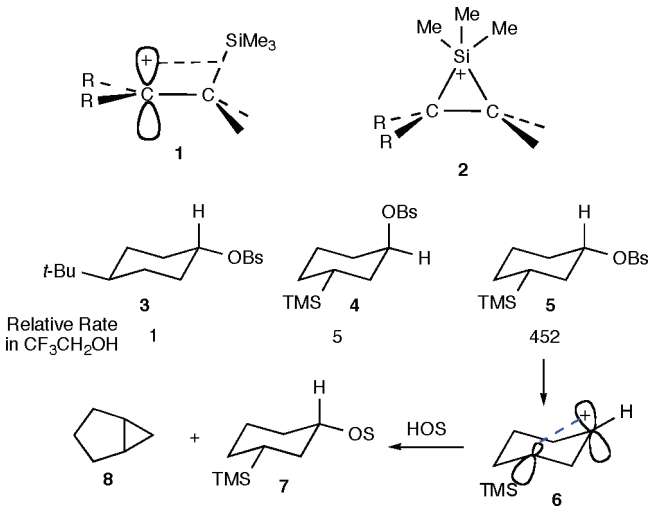
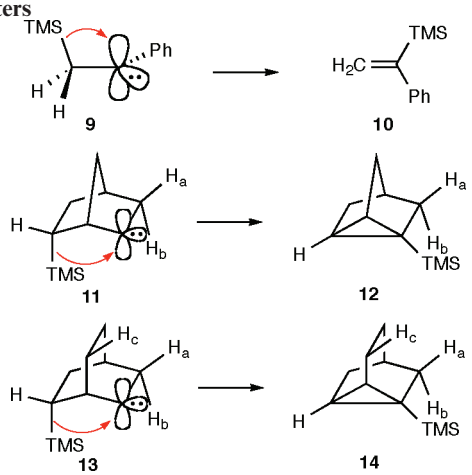
examined this phenomenon in a study of brosylate **5**, which was found to solvolyze 452 times faster than the unsilylated analogue **3** in 97% trifluoroethanol. A negligible rate enhancement was observed for the *trans*-brosylate **4**.



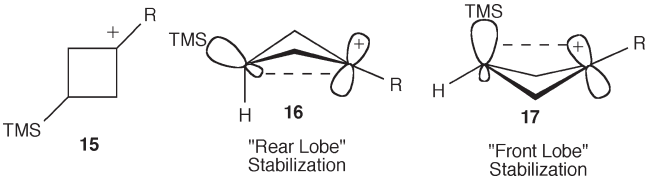
The major product from solvolysis of **5** was the solvent capture product **7**, with retention of configuration. The observed rate enhancement, along with the observed products, can be explained by a γ-silicon stabilized intermediate **6** formed by assistance involving the rear lobe of the carbon−silicon orbital in a "W" fashion. Computational studies also provided evidence for carbocation stabilization by a γ-trimethylsilyl group.[7] Other studies by Shiner[8] and Grob[9] support this type of γ-silyl stabilization of cations.

Our laboratory has extensively studied the effect of both β- and γ-silyl groups on a variety of carbenes (Scheme 1).[10] It was found that a β-silyl group migrated preferentially to the carbenic center of **9**.[10a,d] The bicyclo [2.2.1] and [2.2.2] systems **11** and **13** were used as a probe for γ-trimethylsilyl interactions.[10b] The products **12** and **14** formed from these carbenes indicate that 1,3-trimethylsilyl migration to the carbenic center occurs much more readily than either 1,2- or 1,3-hydrogen migration. From these studies it was concluded that the γ-trimethylsilyl group interacts quite effectively with a carbenic center. This γ-interaction of silicon with carbenes is quite different from the γ-stabilization of carbocations described by Shiner. Whereas Shiner's stabilization of carbocations occurs via the "rear lobe" of the carbon−silicon σ-orbital, our carbene studies demonstrate "front lobe" interaction of carbenes analogous to the β-silyl effect seen in carbocations of type **1**.

SCHEME 1. Migration of Neighboring Silyl Groups to Carbenic Centers



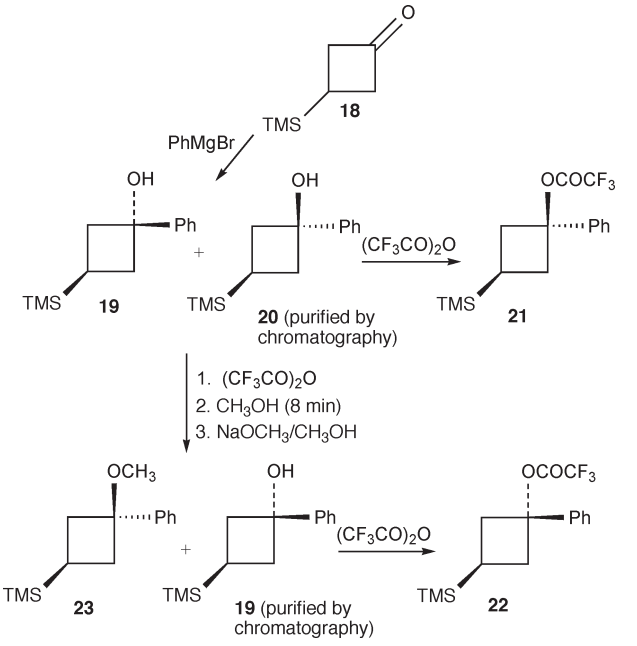
We therefore wanted to study carbocations of type **15**. What kind of stabilization will be involved? We can envisage two types of stabilization, i.e., "rear lobe" stabilization, **16**, analogous to that previously proposed by Shiner, as well as "front lobe" stabilization, **17**, analogous to that suggested in our previous carbene studies. Reported here are the results of these studies.



Results and Discussion

The 1-Phenyl-3-(Trimethylsilyl)cyclobutyl Carbocation. Synthesis. Synthesis of precursors to cation **15** (R = Ph) (Scheme 2) involved the cyclobutanone **18**, which is readily available by addition of excess diazomethane to trimethylsilyl

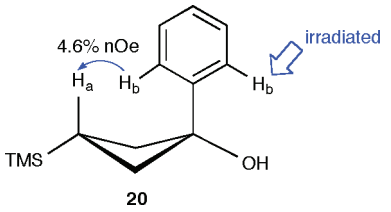
SCHEME 2. Synthesis of Trifluoroacetates 21 and 22



(7) Davidson, E. R.; Shiner, V. J. Jr. *J. Am. Chem. Soc.* **1986**, *108*, 3135.
(8) (a) Shiner, V. J. Jr.; Ensinger, M. W.; Rutkowske, R. D. *J. Am. Chem. Soc.* **1987**, *109*, 804. (b) Shiner, V. J. Jr.; Ensinger, M. W.; Huffman, J. C. *J. Am. Chem. Soc.* **1989**, *111*, 7199.
(9) Grob, C. A.; Sawlewicz, P. *Tetrahedron Lett.* **1987**, *28*, 951.
(10) (a) Creary, X.; Wang, Y.-X. *Tetrahedron Lett.* **1989**, *19*, 2493. (b) Creary, X.; Wang, Y.-X. *J. Org. Chem.* **1994**, *59*, 1604. (c) Creary, X.; Butchko, M. A. *J. Org. Chem.* **2001**, *66*, 1115. (d) Creary, X.; Butchko, M. A. *J. Org. Chem.* **2002**, *67*, 112.

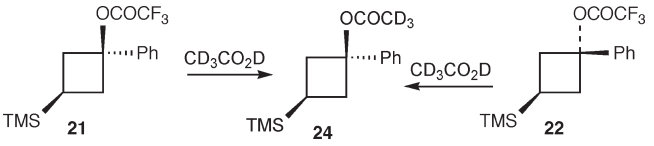
ketene.[11] Addition of phenylmagnesium bromide to this silylated cyclobutanone gave a mixture of alcohols **19** and **20**. Chromatography of the mixture gave pure alcohol **20**. However, pure **19** could not be completely separated from **20**. Therefore an enriched mixture of **19** and **20** was converted to a mixture of trifluoroacetates **21** and **22**. These trifluoroacetates have significantly different reactivity in methanol, where **21** converts completely to methyl ether **23**, while trifluoroacetate **22** remained intact at room temperature. Addition of sodium methoxide to the reaction mixture resulted in transesterification of unreacted **22**. Chromatography of the resulting mixture of **19** and **23** gave pure alcohol **19**, which was then converted to the pure trifluoroacetate **22**.

The stereochemistry of alcohol **20** was confirmed by nuclear Overhauser effect (NOE) studies. Irradiation of the ortho hydrogens (H_b) on the phenyl ring caused a 4.6% increase in the signal due to H_a. This confirmed the cis-orientation of the phenyl group relative to H_a.



Solvolytic Studies. Solvolyses of trifluoroacetates **21** and **22** were carried out in CD_3CO_2D, where both substrates gave the same product, the acetate **24** (Scheme 3). The structure of **24** was verified by independent synthesis of the protio

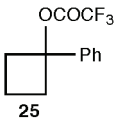
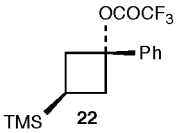
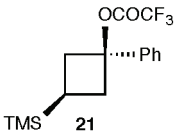
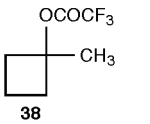
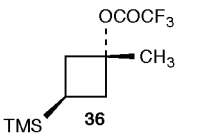
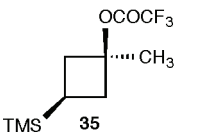
SCHEME 3. Solvolyses of Trifluoroacetates 21 and 22



analogue by acetylation of alcohol **20** with acetic anhydride. The isomeric acetate was also synthesized from **19** to verify that it was *not* present as a solvolysis product. This common product **24** suggests that the same cationic intermediate is involved in both solvolyses.

Solvolyses of **21** and **22** in CD_3CO_2D were monitored by ^1H NMR and data for these and the unsilylated analogue **25** are summarized in Table 1. As can be seen from the relative rates, both silylated compounds are somewhat rate enhanced relative to the unsilylated analogue **25**.[12] Although the enhancement in trifluoroacetate **22** is relatively small, the enhancement seen for trifluoroacetate **21** is more significant. What is the nature of the cationic intermediate in these solvolyses? While the factor of 209 for **21** suggests stabilization of the intermediate by the neighboring silyl group, the rate enhancement of 13 is hardly compelling evidence for

TABLE 1. Solvolysis Rates for Substrates in CD_3CO_2D

Compound	T (°C)	k (s^{-1})	k_{rel}
 **25**	25.0	4.54×10^{-5}	1
 **22**	25.0	5.85×10^{-4}	13
 **21**	16.6	3.06×10^{-3}	
	19.6	4.45×10^{-3}	
	22.6	6.97×10^{-3}	
	25.0	9.47×10^{-3} [a]	209
 **38**	90.0	1.73×10^{-5}	
	70.0	1.76×10^{-6}	
	25.0	3.38×10^{-9} [a]	1
 **36**	90.0	9.65×10^{-5}	
	70.0	9.18×10^{-6}	
	25.0	1.48×10^{-8} [a]	4.4
 **35**	25.0	1.55×10^{-4}	46,000

[a] Extrapolated from data at other temperatures.

participation by silicon in the ionization step for **22**. Therefore further information was desirable.

Computational Studies. To further understand the carbocation intermediates in the solvolyses of **21** and **22**, density functional calculations were carried out at the B3LYP/6-31G* level. Two energy minima, corresponding to cations **26**

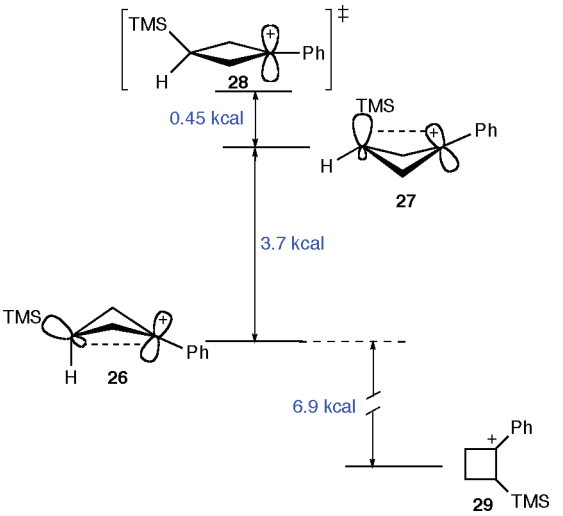


FIGURE 1. B3LYP/6-31G* calculated energies of 1-phenylsilylcyclobutyl cations.

(11) Zaitseva, G. S.; Bogdanova, G. S.; Baukov, Yu. I.; Lutsenko, D. F. *J. Organomet. Chem.* **1976**, *121*, C21.

(12) For kinetic data on chloride and *p*-nitrobenzoate analogues of **25**, see: (a) Tanida, H.; Tsushima, T. *J. Am. Chem. Soc.* **1970**, *92*, 3397. (b) Brown, H. C.; Ravindranathan, M.; Peters, E. N.; Rao, C. G.; Rho, M. M. *J. Am. Chem. Soc.* **1977**, *99*, 5373.

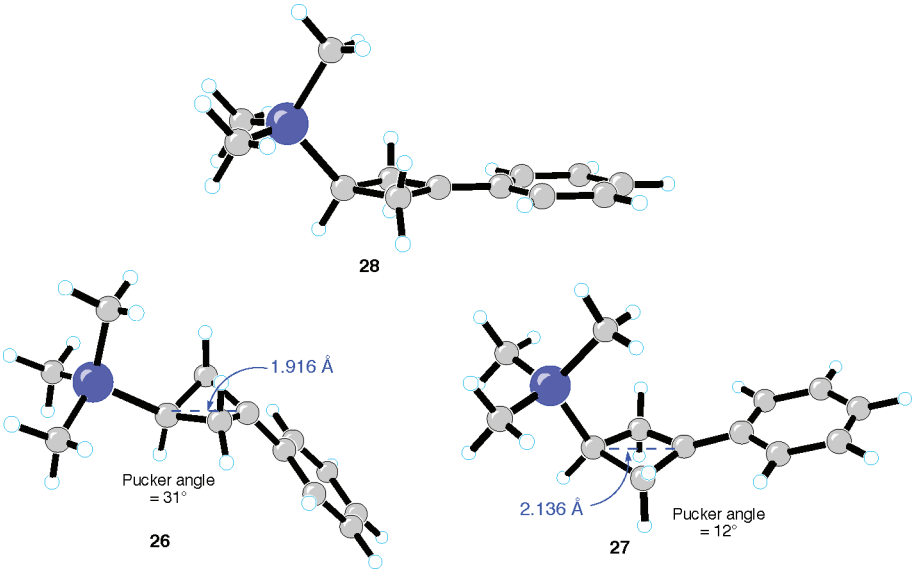
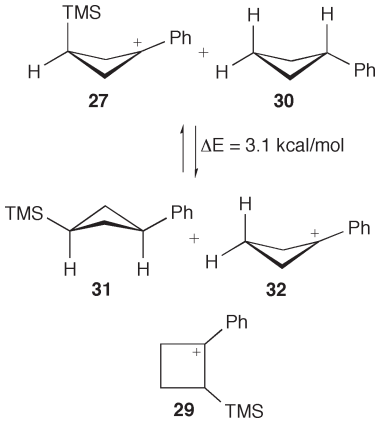


FIGURE 2. B3LYP/6-31G* calculated structures of 1-phenylsilylcyclobutyl cations.

and **27**, were located on the potential energy surface. The "rear lobe" form **26** is 3.7 kcal/mol more stable than the "front lobe" form **27** (Figures 1 and 2). Structurally, this can be seen in the contraction of the distance between the cationic center and the carbon bonded to the TMS group, as well as in the pucker angle of the cyclobutyl backbone. The more stable "rear lobe" conformation **26** is more puckered and more contracted (1.916 Å) than the "front lobe" conformation **27** (2.316 Å). The structure of the transition state **28** for the interconversion of **26** and **27** was also calculated at the B3LYP/6-31G* level. This transition state lies 0.45 kcal/mol above the "front lobe" stabilized form **27**.

How do the stabilites of these γ-silyl-stabilized cations **26** and **27** compare with that of the β-silyl cation? The analogous β-silyl cation **29** is 6.9 kcal/mol lower in energy than the rear lobe stabilized cation **26** at the B3LYP/6-31G* level. The isodesmic calculation shown in Scheme 4 was used to further evaluate stabilization of cation **27** relative to the

SCHEME 4. Isodesmic Calculation Evaluating Trimethylsilyl Stabilization of Cation 27

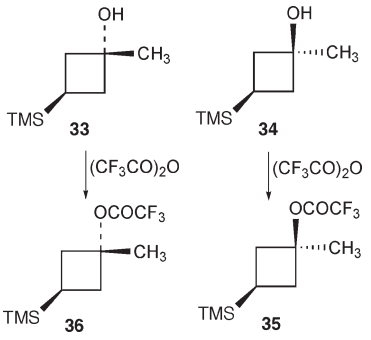


unsilylated analogue **32**. The cation **27**, which utilizes front lobe γ-silyl participation, was found to be stabilized by 3.1 kcal/mol relative to the unsilylated cation **32**. The more stable cation **26**, which utilizes rear lobe γ-silyl participation, is stabilized by 6.8 kcal/mol relative to **32**. Computational studies, as well as rate studies, therefore suggest that the γ-silyl effect in this system is real, albeit not as large as the β-silyl effect.

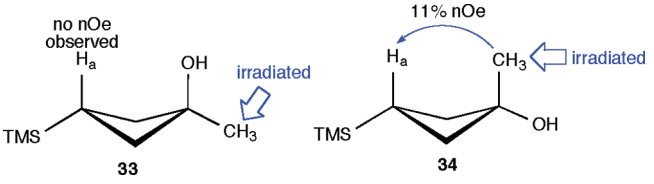
How do these computational studies fit with our solvolytic studies? It is suggested that the faster reacting trifluoroacetate **21** ionizes with assistance from the rear lobe of the γ-Si−C bond leading directly to the more stabilized cation **26**. Cation **26** then captures solvent from the rear of this delocalized cation, giving net retention of stereochemistry in the product **24**. The slower reacting trifluoroacetate **22** could ionize with assistance from the front lobe of the Si−C bond leading to the less stabilized conformation of the cation **27**, but the case is less compelling. The calculated barrier for inversion of **27** to the more stable **26** is so small (0.45 kcal/mol) that this inversion should occur much faster than other potential pathways. Cation **26** (derived from **22**) should then capture solvent, ultimately giving **24** (a product of net inversion from **22**). Alternatively, trifluoroacetate **22** could solvolyze via a simple unassisted (k_C) pathway to give a benzylic cation not further stabilized by the γ-silyl group. This cation should rapidly reorganize to **26**. The small rate enhancement factor of 13 does not allow a clear distinction between these two ionization modes for **22**.

The 1-Methyl-3-(trimethylsilyl)cyclobutyl Carbocation. Synthesis. The next objective was to replace the phenyl groups in **21** and **22** with methyl groups, thereby forcing the resulting cation to rely more heavily on stabilization from the γ-trimethylsilyl group. It was anticipated that larger γ-trimethylsilyl rate enhancements would result. The required alcohols **33** and **34** were prepared and purified (Scheme 5) in a similar fashion to their phenyl analogues. Reaction of 3-trimethylsilylcyclobutanone **18** with methylmagnesium iodide gave a mixture of alcohols **33** and **34**, which were not completely separated by column chromatography. A separation procedure analogous to that used to prepare pure alcohol **19**, based on the higher reactivity of trifluoroacetate **35** in methanol, was again employed.

SCHEME 5. Synthesis of Trifluoroacetates 35 and 36



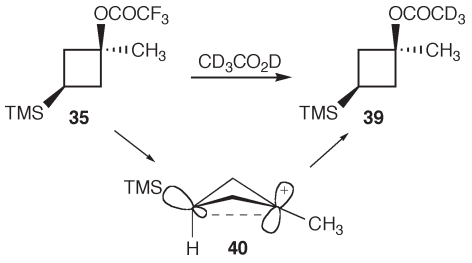
As in the case of the phenyl analogues, stereochemistry of alcohols **33** and **34** was again confirmed by NOE studies. Irradiation of the methyl signal of **34** gave an increase of 11% in the signal due to *cis*-H_a. Conversely, when the methyl signal of **33** was irradiated, no change was seen in the intensity of the signal due to *trans*-H_a. These alcohols were converted to trifluoroacetates **35** and **36** in a straightforward fashion.



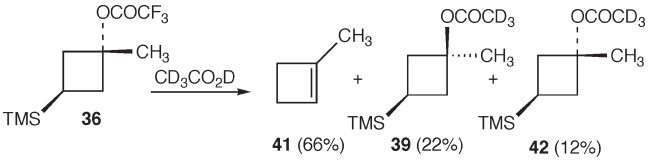
Solvolytic Studies. Solvolyses of trifluoroacetates **35**, **36**, and the unsilylated analogue **38** were carried out in CD_3CO_2D. The faster reacting substrate **35** gave the completely retained acetate **39** as the exclusive product. Rate data are summarized in Table 1. The rate enhancement of 46 000 seen for trifluoroacetate **35** is much larger than the value of 209 seen for the phenyl analogue **21**. This is presumably due to the fact that methyl is a less effective carbocation stabilizing group than phenyl. The carbocation intermediate demands more stabilization from the γ-trimethylsilyl group, thus leading to a larger rate enhancement. When one considers the fact that the model compound, unsilylated **38**, is itself "rate enhanced" due to the nature of the delocalized cyclobutyl carbocation,[13,14] the actual anchimeric assistance in solvolysis of **35** is probably even greater than the factor of 46 000. The exclusively retained product, and the large rate enhancement, are completely consistent with the rear lobe stabilized γ-silyl cation **40** as the intermediate in this reaction (Scheme 6).

In contrast to the exclusive product formed on solvolysis of **35**, the slower reacting trifluoroacetate **36** gave three products (Scheme 7). The major product was the desilylated 1-methylcyclobutene, **41**. Also formed were acetates **39** (net inversion) and **42** (net retention). The differing behavior of trifluoroacetates **35** and **36** indicates that a common cationic intermediate is *not* involved in these solvolyses. There is no

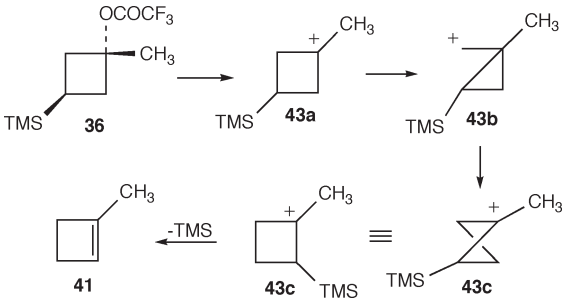
SCHEME 6. Solvolysis Product from Trifluoroacetate 35



SCHEME 7. Solvolysis Products from Trifluoroacetate 36



SCHEME 8. Solvolysis of Trifluoroacetate 36: Mechanistic Analysis



strong evidence for a front lobe stabilized γ-silyl cation. Instead, it is suggested that **36** enters the cyclobutyl-cyclopropylcarbinyl-homoallylic cation manifold,[15] as illustrated in Scheme 8. Rearrangement of cyclobutyl cation **43a** to cyclopropylcarbinyl cation **43b** to cyclobutyl cation **43c** allows access to β-silyl stabilization. The expected fate of **43c** is desilylation to give the observed major product **41**. Capture of a cyclobutyl cation **43a**, where there is no rear lobe or front lobe γ-silyl stabilization, accounts for the isomeric mixture of acetates **39** and **42**.

Computational Studies. B3LYP/6-31G* calculations again provide insight into the nature of the cationic intermediates derived from trifluoroacetates **35** and **36**. As with the phenyl-substituted cations **26** and **27**, two energy minima were located on the potential energy surface (Figures 3 and 4). These correspond to rear lobe and front lobe γ-trimethylsilyl cations **40** and **44**. Both cations show a larger pucker angle and a shorter distance between the cationic carbon and the silicon-substituted carbon than their phenyl counterparts. This indicates a greater interaction of the cationic center with the silyl-substituted carbon in **40** and **44** relative to the phenyl analogues **26** and **27**. Cation **40** is 16.0 kcal/mol more stable than **44**. This calculated stabilization is consistent with the relatively large solvolysis rate of trifluoroacetate **35**, which presumably solvolyzes via rear lobe γ-silyl participation to give cation **40**.

(13) Cox, E. F.; Caserio, M. J.; Silver, M. S.; Roberts, J. D. *J. Am. Chem. Soc.* **1961**, *83*, 2719.
(14) Nikoletic, M.; Borçic, S.; Sunko, D. E. *Tetrahedron* **1967**, *23*, 649.
(15) For reviews, see: (a) Richey, H. G., Jr. *Carbonium Ions*; Olah, G. A., Schleyer, P. v. R., Eds.; John Wiley & Sons: New York, 1972; Vol. III, Chapter 25. (b) Wiberg, K. B.; Hess, B. A., Jr.; Ashe, A. J., III *Carbonium Ions*; Olah, G. A., Schleyer, P. v. R., Eds.; John Wiley & Sons: New York, 1972; Vol. III, Chapter 26.

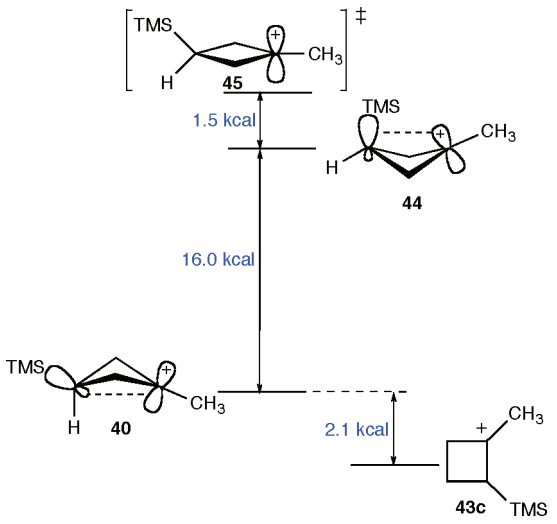


FIGURE 3. B3LYP/6-31G* calculated energies of 1-methylsilylcyclobutyl cations.

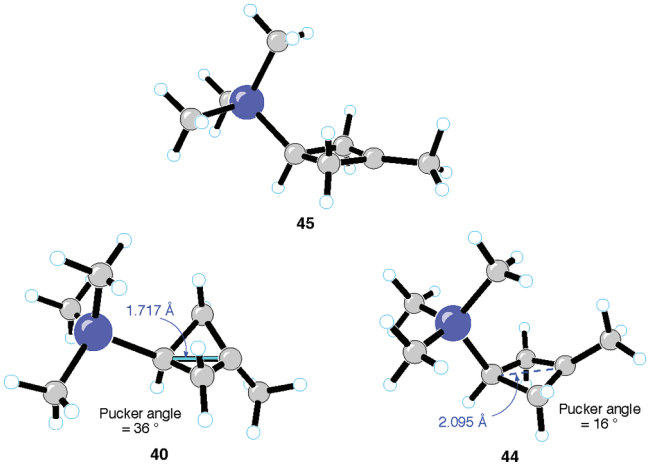
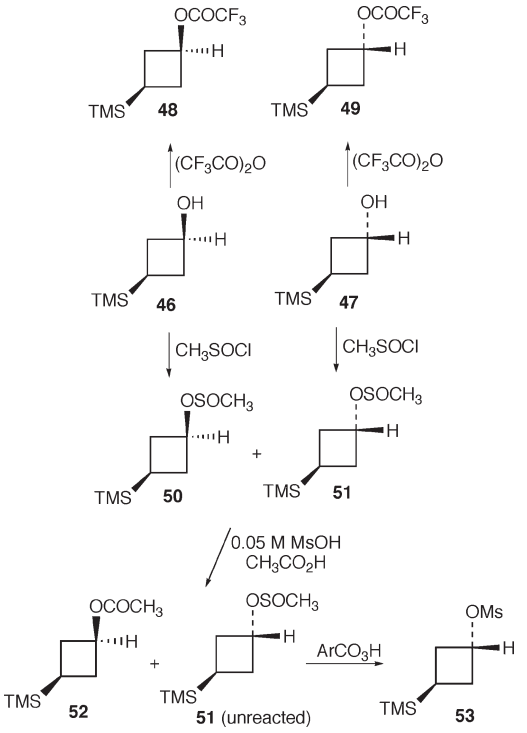


FIGURE 4. B3LYP/6-31G* calculated structures of 1-methylsilylcyclobutyl cations.

The transition state **45** in the inversion of **44** to **40** was also located, and this barrier is 1.5 kcal/mol. This is somewhat larger than the barrier to inversion for phenyl analogues **27** and **26**. The structure of the β-silyl-stabilized cation **43c** was also calculated and it is only 2.1 kcal/mol more stable than **40**. Apparently rear lobe γ-silyl stabilization can be a much larger effect than was originally anticipated.

The 3-(Trimethylsilyl)cyclobutyl Carbocation. Lithium aluminum hydride reduction of ketone **18** gave *cis*- and *trans*-3-trimethylsilylcyclobutanols **46** and **47** in a 85:15 ratio, while $NaBH_4$ reduction gave a 93:7 ratio. These alcohols were converted to the corresponding trifluoroacetates **48** and **49** as shown in Scheme 9. The *cis*-trifluoroacetate **48** reacted conveniently in CD_3CO_2D at 70 °C. However, the *trans*-trifluoroacetate **49** was quite unreactive and the more reactive *trans*-mesylate derivative **53** was desired. Since chromatography was not successful in completely separating a pure sample of the trans-alcohol **47**, an alcohol mixture was converted to a mixture of sulfinate esters **50** and **51** (Scheme 9). Methanesulfonic acid catalyzed reaction in acetic acid led to facile conversion of the *cis*-sulfinate

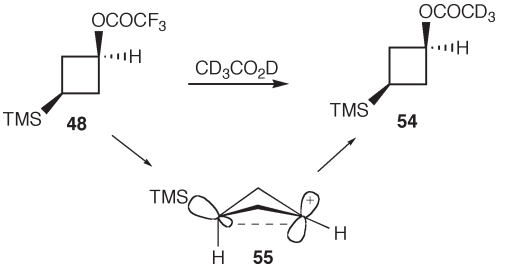
SCHEME 9. Synthesis of Trifluoroacetate 48 and Mesylate 53



50 to the acetate **52**. This transformation presumably occurs via protonation of **50** followed by loss of CH_3SO_2H to generate a carbocation intermediate.[16] Under conditions where *cis*-**50** reacts readily, the *trans*-sulfinate **51** is unreactive. This allows for isolation of **51** with no **50** present. Oxidation of **51** with peracid to the *trans*-mesylate **53** was straightforward.

Trifluoroacetate **48** reacted in CD_3CO_2D at 70 °C to give the retained acetate **54** exclusively (Scheme 10). No bicyclobutane was observed, nor was any cyclopropylcarbinyl

SCHEME 10. Solvolysis of Trifluoroacetate 48: Mechanistic Analysis

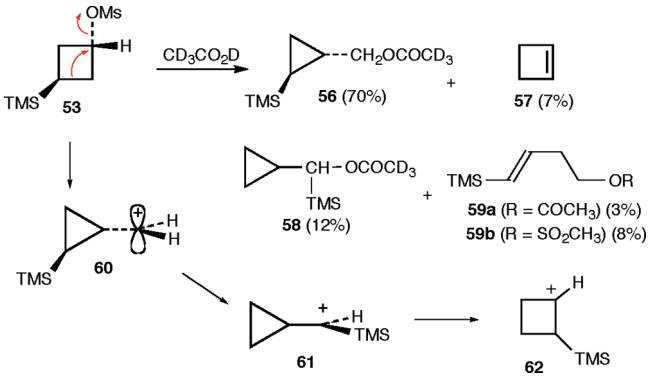


acetate formed. This latter product would have formed from addition of acetic acid to bicyclobutane.[17] The retained acetate product **54** is completely consistent with the involvement of the rear lobe silyl stabilized cation **55**.

On the other hand, the behavior of mesylate **53** is quite different from that of **48**. Acetolysis of **53** (Scheme 11) gives the cyclopropylcarbinyl acetate **56** as the major product along with smaller amounts of cyclobutene, **57**, and the acetates **58** and **59a**, and the mesylate **59b** from internal

(16) Creary, X. *J. Org. Chem.* **1985**, *50*, 5080.
(17) Wiberg, K. B.; Szeimies, G. *J. Am. Chem. Soc.* **1970**, *92*, 571.

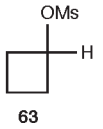
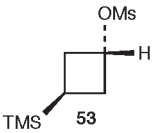
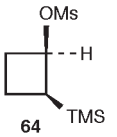
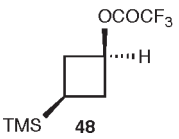
SCHEME 11. Solvolysis of Mesylate 53: Mechanistic Analysis



return. Front lobe silyl stabilization of the developing cationic intermediate does not appear to be a factor. Instead, mesylate **53** appears to enter the cyclobutyl-cyclopropylcarbinyl-homoallylic cation manifold, where the ionization of **53** is assisted by participation of a cyclobutane σ-bond. Solvent capture of cyclopropylcarbinyl cation **60** leads to **56**, while further rearrangement, involving cations **61** and **62**, leads to the minor products **57**−**59**.

Rate data for trifluoroacetate **48**, mesylate **53**, cyclobutyl mesylate, **63**, and β-trimethylsilylcyclobutyl mesylate, **64**, are summarized in Table 2. The rate difference between *cis*-**48** and *trans*-**49** can be estimated from the rate of the *trans*-mesylate **53**. If one assumes a mesylate/trifluoroacetate rate ratio[18] of 10^5, then the rate enhancement in **48** relative to **49** is about 10^3. Comparison of **48** with the unsubstituted cyclobutyl mesylate **63** is also informative. Since the solvolysis rate of cyclobutyl tosylate is enhanced by σ-participation, the

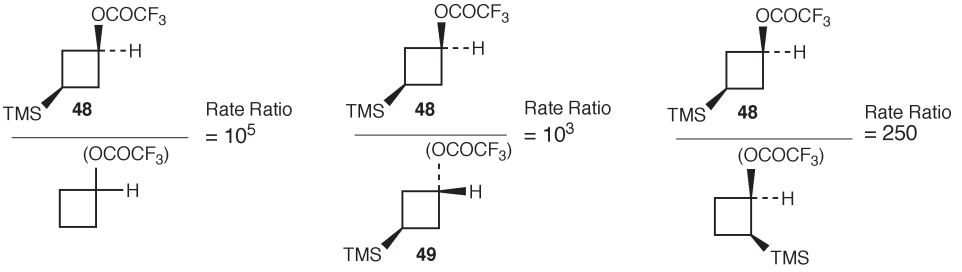
TABLE 2. Solvolysis Rates for Substrates in CD_3CO_2D[a]

Compound	T (°C)	k (s^{-1})	k_{rel}
 **63**	25.0	2.12×10^{-6}	1.0
 **53**	25.0	1.11×10^{-4}	53
 **64**	25.0	6.37×10^{-4}	300
 **48**	25.0	1.57×10^{-6}	10^5 [a]

[a]Estimated relative rate of mesylate assuming $k_{ROMs}/k_{ROCOCF_3} = 10^5$.

the well-studied β-silyl group, which can offer rate enhancements as large as 10^{12} in the cyclohexyl system.

Computational Studies. The B3LYP/6-31G* structures and energies of potential γ-silyl-stabilized cations derived from **48** and **53** are of interest. Energies of these and related



$R(OCOCF_3)$ rates are estimated from mesylate rates

estimated rate enhancement due to the γ-trimethylsilyl group in *cis*-trifluoroacetate **48** is much larger than the rate ratio of 10^5. The rate enhancement in cyclobutyl systems[19] has been estimated to be as low as 10^5 and as high as 10^{10}. Hence the actual rate enhancement in trifluoroacetate **48** relative to an "unassisted rate" is probably in the range of 10^{10} to 10^{15}.

Rate data allow for a comparison of the enhancement due to γ-silyl participation with enhancement due to β-silyl stabilization. The γ-silyl rate enhancement is actually much larger, as shown in Table 2. This again points to an enormous stabilization of the cationic intermediate derived from **48** due to the γ-silyl group, a stabilization that even exceeds that of

cations are shown in Figure 3. Calculations have also been carried out with a larger basis set (B3LYP/6-311+G**) as well as at the MP2/6-311+G** level. The general trends are quite similar to those shown in Figure 3.[20] The rear lobe stabilized cation **55** has been located as an energy minimum at the B3LYP/6-31B* level (Figure 5). This cation **55** appears to be a corner protonated 1-trimethylsilylbicyclobutane. The bond between the cationic carbon and the carbon carrying the silyl group is only 1.662 Å. In valence bond terms, the bicyclobutane form **55b** is a major resonance contributor.

In contrast to the Ph and CH_3 analogues, the analogous front lobe stabilized cation **63** is not an energy minimum but is a transition state (4.5 kcal/mol above **64**) for the interconversion of cyclopropyl carbinyl cations **64a** and **64b**.

(18) (a) Noyce, D. S.; Virgilio, J. A. *J. Org. Chem.* **1972**, *37*, 2643. (b) Creary, X. *J. Org. Chem.* **1979**, *44*, 3938. (c) Creary, X.; Jiang, Z. *J. Org. Chem.* **1996**, *61*, 3482.

(19) (a) Foote, C. S. *J. Am. Chem. Soc.* **1964**, *86*, 1853. (b) Schleyer, P. V. R. *J. Am. Chem. Soc.* **1964**, *86*, 1856.

(20) B3LYP/6-311+G** and MP2/6-311+G** calculated energies of cations **55**, **62**, **63**, **64**, **65**, and **66** are shown as Supporting Information.

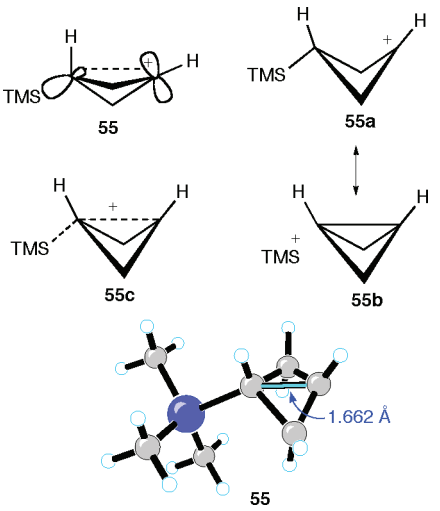


FIGURE 5. B3LYP/6-31G* calculated structure and valence bond description of cation **55**.

A second minimum energy cyclopropylcarbinyl cation, **65**, has also been located on the potential energy surface (Figure 6).

Of note is the relative energy of the γ-silyl cation **55**. The B3LYP/6-31G* energy of this cation is actually 1.0 kcal/mol lower than that of the β-silyl cation **62** and 5.9 kcal/mol lower than the cyclopropylcarbinyl cation **64** (Figure 7). This computational study is in line with the kinetic study, where the rate enhancing effect in the acetolysis of **48** exceeds the β-silyl rate enhancing effect in **64**. This computational result contrasts with that of the Ph and CH_3 analogues **26** and **40** and demonstrates that indeed, γ-silyl stabilization can be an enormous cation stabilizing effect. In fact, a planar transition state **66** has been located, where there is presumably no cross ring γ-silyl stabilization, and this structure lies 28.8 kcal above **55**.

Conclusions. γ-Trimethylsilylcyclobutyl systems with a leaving group cis to the silyl group ionize with assistance due to a cation-stabilizing interaction with the rear lobe of the γ-carbon−silicon bond. Rate enhancements relative to unsilylated analogues range from a small factor (209) for the phenyl-substituted system **21**, to a very large factor (10^5) for the more demanding unsubstituted system **48**. The γ-silyl-stabilized cation **55** derived from **48** is even more stable that the β-silyl cation **62**, as revealed by solvolytic rate studies as well as B3LYP/6-31G* computational studies. While computational studies suggest the existence of cations **27** and **44**, which are stabilized by an interaction of the vacant orbital

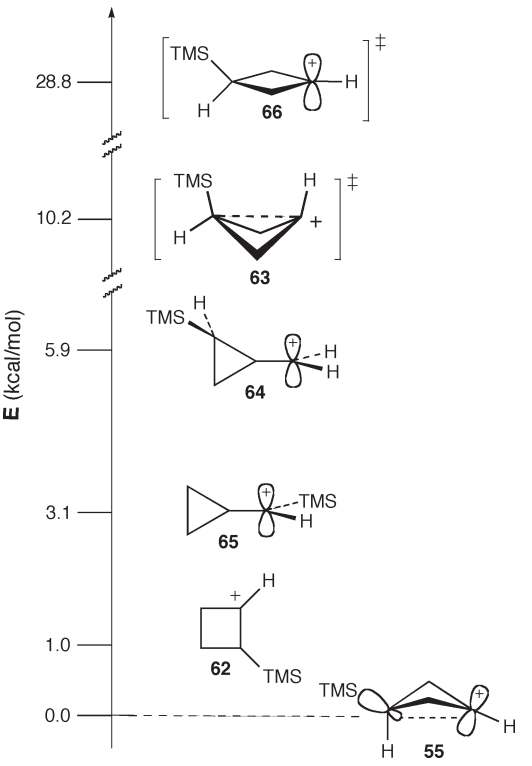


FIGURE 7. B3LYP/6-31G* calculated energies of silylcyclobutyl and silylcyclopropylcarbinyl cations.

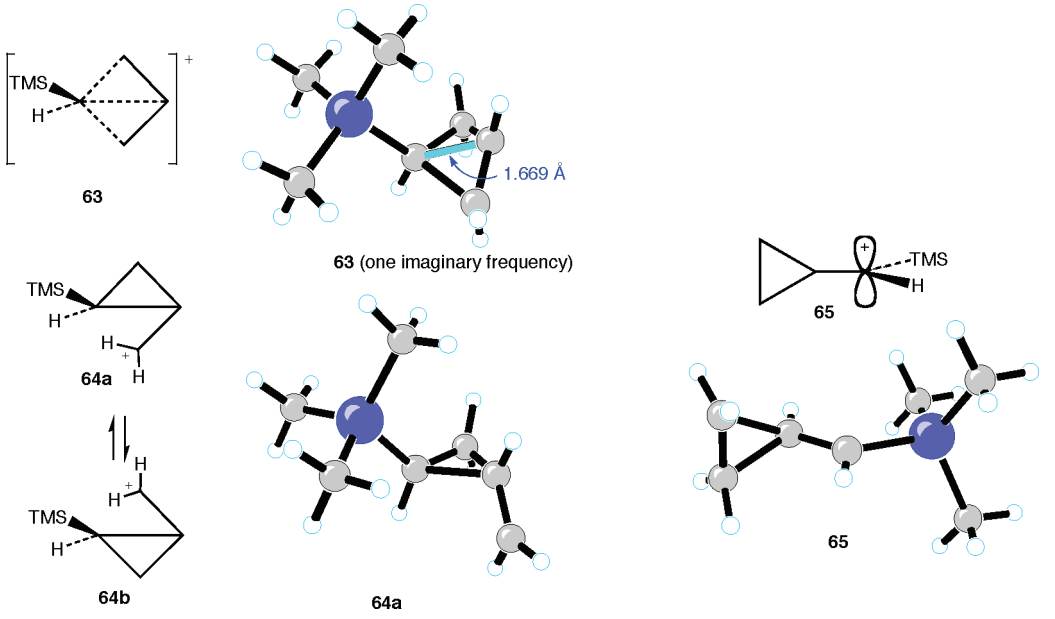


FIGURE 6. B3LYP/6-31G* calculated structures of cations **63**, **64**, and **65**.

with the front lobe of the γ-carbon−silicon bond, solvolytic studies are less conclusive. *trans*-Silyl systems **22**, **36**, and **53** do not solvolyze with significant rate enhancements relative to unsilylated analogues. The systems **36** and **53** lead to cations in the cyclobutyl-cyclopropylcarbinyl manifold. The front lobe silyl stabilized cation **63** is not an energy minimum at the B3LYP/6-31G* level, and is significantly higher in energy than the rear lobe γ-silyl stabilized cation **55**.

Experimental Section

Preparation of Alcohol 20. A mixture of 2-trimethylsilylcyclobutanone and 3-trimethylsilylcyclobutanone (**18**[11]) (1.03 g, 1:1.5 ratio) was dissolved in 8 mL of anhydrous ether and the solution was cooled to 0 °C. Phenylmagnesium bromide (8.2 mL of a 1.0 M solution in ether) was then added. The solution was warmed to room temperature for 2 h and then recooled to 0 °C. The mixture was then quenched with dilute NH_4Cl solution. The ether phase was separated, washed with saturated NaCl solution, and dried over a mixture of Na_2SO_4 and $MgSO_4$. After filtration, solvent was removed with a rotary evaporator. The crude product mixture was chromatographed on 15 g of silica gel and eluted with increasing amounts of ether in hexanes. 1-Phenyl-2-trimethylsilylcyclobutanol (360 mg, 22% yield) eluted with 4% ether in hexanes. A mixture of alcohols **19** and **20** (717 mg, 45% yield) coeluted with 8% ether in hexanes. This mixture was rechromatographed on 10 g of silica gel and the column was eluted with 4% ether in hexanes. A fraction containing 23 mg of pure **20** eluted first, followed by fractions containing **20** contaminated with increasing amounts of alcohol **19**. The final fractions contained alcohol **19** as the major component, but contaminated with **20**. ^{1}H NMR of **20** ($CDCl_3$) δ 7.60 (d, J = 8.3 Hz, 2 H), 7.40 (t, J = 7.8 Hz, 2 H), 7.31 (t, J = 7.3 Hz, 1 H), 2.60 (m, 2 H), 2.22 (m, 2 H), 2.13 (s, 1 H), 1.17 (t of t, J = 11.4, 8.7 Hz, 1 H), 0.02 (s, 9 H). ^{13}C NMR of **20** ($CDCl_3$) δ 145.9, 128.6, 127.6, 125.5, 75.9, 38.6, 11.7, −3.2. ESI exact mass ($M + Na^+$) calculated for $C_{13}H_{20}NaOSi$ 243.1176, found 243.1173.

Preparation of Alcohol 19. A mixture of alcohols **19** and **20** (213 mg of a 55:45 ratio) was dissolved in 5 mL of ether and 285 mg of 2,6-lutidine was added. The solution was cooled to 0 °C and 373 mg of trifluoroacetic anhydride was added. After 10 min, a cold aqueous workup ensued with ether extraction. The ether extract was washed with cold aliquots of water, dilute HCl solution, water, aqueous $NaHCO_3$ solution, and saturated NaCl solution. The ether solution was then dried over a mixture of Na_2SO_4 and $MgSO_4$ and filtered. The solvent was removed with a rotary evaporator to give a mixture of trifluoroacetates **21** and **22** (291 mg, 95% yield) in a 45:55 ratio.

A solution of 54 mg of 2,6-lutidine in 4 mL of methanol was added to 271 mg of the trifluoroacetate mixture prepared above. After the mixture was stirred for exactly 8 min at 26 °C, 1.4 mL of 0.50 M $NaOCH_3$ in methanol was added. After 10 min at room temperature, the methanol was removed with a rotary evaporator and the crude mixture was chromatographed on 7 g of silica gel. The column was eluted with increasing amounts of ether in hexanes. Methyl ether **23** (99 mg) eluted with 2% ether in hexanes. The alcohol **19** (92 mg, 89% yield based on the amount of trifluoroacetate **22** in the starting mixture) eluted with 6−10% ether in hexanes, mp 86−87 °C. ^{1}H NMR of **19** ($CDCl_3$) δ 7.38 (d, J = 8.4 Hz, 2 H), 7.35 (t, J = 7.7 Hz, 2 H), 7.26 (t, J = 7.2 Hz, 1 H), 2.44 (m, 2 H), 2.32 (m, 2 H), 2.08 (quin, J = 9.9 Hz, 1 H), 2.02 (s, 1 H), −0.04 (s, 9 H). ^{13}C NMR of **19** ($CDCl_3$) δ 147.0, 128.6, 127.3, 124.9, 78.5, 37.0, 15.0, −3.3. Exact mass (FAB) calculated for $C_{13}H_{20}OSi$ 220.1283, found 220.1289.

Preparation of Alcohol 34. A pure sample of 3-trimethylsilylcyclobutanone, **18**, was isolated by silica gel chromatography of the mixture of 2- and 3-trimethylsilylcyclobutanone.[11] Ketone **18** (191 mg) was dissolved in 2 mL of ether and the solution was cooled to 0 °C. Methylmagnesium iodide (1.5 mL of a 1.0 M solution in ether) was then added. The solution was warmed to room temperature for 1 h and then recooled to 0 °C. Aqueous NH_4Cl solution was then added. The ether phase was separated, washed with water and saturated NaCl solution, and dried over a mixture of Na_2SO_4 and $MgSO_4$. After filtration, solvent was removed with a rotary evaporator leaving 192 mg (91% yield) of a mixture of alcohols **33** and **34** in a 36:64 ratio. This mixture was chromatographed on 8 g of silica gel and eluted with increasing amounts of ether in hexanes. Eluting with 8% ether in hexanes gave a fraction containing 81% alcohol **34**. This mixture was used for further studies. ^{1}H NMR of **34** ($CDCl_3$) δ 2.03 (m, 2 H), 1.84 (m, 2 H), 1.59 (br s, 1 H), 1.42 (t, J = 0.8 Hz, 3 H), 1.11 (t of t, J = 11.1, 8.6 Hz, 1 H), −0.04 (s, 9 H). ^{13}C NMR of **34** ($CDCl_3$) δ 72.7, 39.4, 26.5, 11.7, −3.2. ESI exact mass ($M + Na^+$) calculated for $C_8H_{18}NaOSi$ 181.1019, found 181.0998.

Preparation of Alcohol 33. A mixture of alcohols **33** and **34** (38:62 ratio, 249 mg) was dissolved in 5 mL of ether and 294 mg of 2,6-lutidine was added. The solution was cooled to 0 °C and 435 mg of trifluoroacetic anhydride was added. After 36 min, a fast, cold aqueous workup ensued with ether extraction. The ether extract was washed with ice-cold aliquots of water, dilute HCl solution, water, aqueous $NaHCO_3$ solution, and saturated NaCl solution. The ether solution was dried over a mixture of Na_2SO_4 and $MgSO_4$ and filtered. The solvent was removed by rotary evaporator to give a mixture of trifluoroacetates **36** and **35** (347 mg, 87% yield) in a 39:61 ratio.

A solution of 72 mg of 2,6-lutidine in 4 mL of methanol was added to 254 mg of the trifluoroacetate mixture prepared above. After the mixture was stirred for 16 h at room temperature, 1.6 mL of 0.50 M $NaOCH_3$ in methanol was added. After 20 min at room temperature, the methanol was removed with a rotary evaporator and the crude product was chromatographed on 7 g of silica gel. The column was eluted with increasing amounts of ether in hexanes. 1-Methoxy-1-methyl-3-trimethylsilylcyclobutane (derived from **35**) (58 mg) eluted with 3% ether in hexanes. The alcohol **33** (60 mg; 88% yield based on the amount of trifluoroacetate **36** in the starting mixture) eluted with 8−10% ether in hexanes. ^{1}H NMR of **33** ($CDCl_3$) δ 2.09 (m, 2 H), 1.98 (m, 2 H), 1.78 (br s, 1 H), 1.74 (t of t, J = 10.7, 9.2 Hz, 1 H), 1.26 (s, 3 H), −0.04 (s, 9 H). ^{13}C NMR of **33** ($CDCl_3$) δ 74.9, 37.5, 29.1, 12.2, −3.2. ESI exact mass ($M + Na^+$) calculated for $C_8H_{18}NaOSi$ 181.1019, found 181.0983.

Preparation of Alcohol 46. A solution of 42 mg of ketone **18** in 1 mL of methanol was cooled in an ice bath and 15 mg of $NaBH_4$ was added in one portion with stirring. The mixture was warmed to room temperature for 1 h and about 2/3 of the methanol was then removed with a rotary evaporator. Dilute NaOH solution was then added and the mixture was extracted with ether. The ether extract was washed with saturated NaCl solution then dried over $MgSO_4$, and the solvent was removed with a rotary evaporator to give 39 mg (93% yield) of alcohols **46** and **47** in a 93:7 ratio. This mixture was used for conversion to the trifluoroacetate **48**. ^{1}H NMR of **46** ($CDCl_3$) δ 4.27 (sextet, J = 7 Hz, 1 H), 2.29 (m, 2 H), 1.71 (d, J = 7 Hz, 1 H), 1.65 (m, 2 H), 1.01 (t of t, J = 11.6, 7.8 Hz, 1 H), −0.04 (s, 9 H). ^{13}C NMR of **46** ($CDCl_3$) δ 67.2, 35.1, 11.6, −3.3. ESI exact mass ($M + H_2O + Na^+$) calculated for $C_7H_{18}NaO_2Si$ 185.0968, found 185.1001.

Preparation of Mesylate 53. A solution of 96 mg of a mixture of alcohols **46** and **47** (82% of **46** and 18% of **47**) was dissolved in 2 mL of CH_2Cl_2 and 118 mg of Et_3N in 0.5 mL of CH_2Cl_2 was added. The mixture was cooled to −35 °C and 95 mg of CH_3SOCl in 0.5 mL of CH_2Cl_2 was slowly added. The mixture was warmed to room temperature for about 5 min and then transferred to a separatory funnel with ether. The mixture was then washed successively with cold water, cold dilute HCl, cold

water, and saturated NaCl solution. The organic phase was dried over a mixture of Na_2SO_4 and $MgSO_4$. After filtration, the solvents were removed with a rotary evaporator to give 137 mg (100% yield) of a mixture of crude sulfinate esters **50** and **51**. ^{1}H NMR of **50** ($CDCl_3$) δ 4.73 (t of t, J = 8.3, 7.1 Hz, 1 H), 2.59 (s, 3 H), 2.33 (m, 2 H), 1.99 (m, 1 H), 1.92 (m, 1 H), 1.15 (t of t, J = 11.7, 7.9 Hz, 1 H), −0.03 (s, 9 H). ^{13}C NMR of **50** ($CDCl_3$) δ 71.6, 44.4, 33.4, 32.8, 12.9, −3.4. ^{1}H NMR of **51** ($CDCl_3$) δ 4.65 (quintet of doublets, J = 7.3, 1.1 Hz, 1 H), 2.60 (s, 3 H), 2.48 (m, 1 H), 2.40 (m, 1 H), 2.26 (m, 2 H), 1.50 (t of t of d, J = 12.1, 4.3, 1.3 Hz, 1 H), −0.01 (s, 9 H). ^{13}C NMR of **51** ($CDCl_3$) δ 72.4, 44.5, 32.3, 31.9, 12.7, −3.3.

The mixture of sulfinate esters **50** and **51** obtained above (132 mg) was dissolved in 3.2 mL of 0.05 M CH_3SO_3H in acetic acid. After 90 min at room temperature, the sample was diluted with 25 mL of pentane and the solution was cooled to 0 °C. The solution was extracted with 2 portions of cold water and then with $NaHCO_3$ solution. The pentane extract was washed with saturated NaCl solution and dried over a mixture of Na_2SO_4 and $MgSO_4$. Solvent removal by rotary evaporator gave 108 mg of a mixture of acetate **52** and unreacted sulfinate ester **51**.

The mixture of sulfinate ester **51** and acetate **52** obtained above was dissolved in 2 mL of $CDCl_3$ and the solution was cooled in a water bath at 15 °C. *m*-Chloroperbenzoic acid (25 mg of 86% peracid) was added and the mixture was kept at room temperature for 3.5 h. The mixture was diluted with 20 mL of pentane and the solution was cooled in an ice bath. The solution was extracted with a cold $Na_2S_2O_3$/NaI/Na_2CO_3 solution containing about 10 mg of NaOH. The pentane extract was dried over $MgSO_4$. The solvent was removed with a rotary evaporator to give 105 mg of a mixture of acetate **52** and mesylate **53**. Further evacuation of this residue at 0.1 mm (to remove the more volatile acetate **52**) gave 24 mg of mesylate **53**. ^{1}H NMR of **53** ($CDCl_3$) δ 4.92 (d of quintets, J = 7.4, 1.3 Hz, 1 H), 2.97 (s, 3 H), 2.56 (m, 2 H), 2.32 (m, 2 H), 1.56 (t of t of d, J = 12.3, 4.3, 1.3 Hz, 1 H), 0.01 (s, 9 H). ^{13}C NMR of **53** ($CDCl_3$) δ 74.3, 38.4, 31.6, 12.8, −3.3. ESI exact mass ($M + Na^+$) calculated for $C_8H_{18}NaO_3SSi$ 245.0638, found 245.0613.

Preparation of Mesylate 64. The preparation of mesylate **64** was analogous to the preparation of **53**. Thus, a mixture of 2-trimethylsilylcyclobutanone and 3-trimethylsilylcyclobutanone was reduced with $NaBH_4$ in CH_3OH. The resulting alcohol mixture was converted to a mixture of methanesulfinate esters by reaction with CH_3SOCl and Et_3N as described above. This mixture of sulfinate esters was allowed to react in 0.05 M CH_3SO_3H in acetic acid for 90 min, which gave acetate **52**, a small amount of sulfinate **51**, as well as the sulfinate derivative of *cis*-2-trimethylsilylcyclobutanol. Oxidation of this mixture with *m*-chloroperbenzoic acid gave acetate **52**, a small amount of mesylate **53**, along with mesylate **64**. Kinetic studies on **64** were carried out with this mixture. Removal of the acetate **52** under vacuum led to autocatalytic decomposition of the highly reactive mesylate **64**.

Solvolyses of Trifluoroacetates and Mesylates. Kinetics Procedures. Rate constants reported in Tables 1 and 2 were all determined using a 600 MHz ^{1}H NMR spectrometer. A solution was prepared by dissolving approximately 5 mg of the appropriate substrate in 400 mg of CD_3CO_2D containing approximately 1.5 equiv of 2,6-lutidine. The sample was sealed in an NMR tube and the tube was placed in the probe of an NMR spectrometer at 25.0 °C or at the appropriate temperature. For slower reactions, the sample was placed in a constant temperature bath at 25.0 °C between readings. At appropriate time intervals, the sample was analyzed by ^{1}H NMR and relative areas due to starting trifluoroacetate or mesylate were measured. For runs at higher temperatures, the tube was placed in a constant temperature bath at the appropriate temperature. At appropriate time intervals, the tube was then quenched in a water bath at 15 °C and rapidly analyzed by ^{1}H NMR at ambient temperature.

For trifluoroacetate **21** in CD_3CO_2D, the rate of disappearance of the TMS singlet at δ 0.03 was monitored. For trifluoroacetate **22**, the TMS singlet at δ −0.07 was monitored. For trifluoroacetate **25**, the area of the *m*-H's of **25** at δ 7.40 was monitored by using the 2,6-lutidine signal at δ 8.24 as an internal standard. The reaction of trifluoroacetate **35** was monitored by measuring the area of the CH_3 singlet at δ 1.68. Trifluoroacetate **36** was monitored by measuring the area of the TMS singlet at δ 0.00. Trifluoroacetate **38** was monitored by measuring the decrease in the area of the multiplet at δ 2.22, using the 2,6-lutidine signal at δ 7.59 as an internal standard. For trifluoroacetate **48**, the rate of disappearance of the quintet at δ 5.26 was monitored.

In the case of mesylates **53**, **63**, and **64** in CD_3CO_2D, the rates of disappearance of the singlets due to the $ROSO_2\mathbf{CH_3}$ group at δ 3.00, 2.99, and 2.99, respectively, were monitored with use of the 2,6-lutidine as an internal standard.

Typical data illustrating the reaction of trifluoroacetates **21**, **35**, and **48**, and mesylate **53** in CD_3CO_2D are given as Supporting Information. First-order rate constants for disappearance of substrates were calculated by standard least-squares procedures. Correlation coefficients were all greater than 0.9998. The maximum standard deviation in duplicate runs was ±2%.

Computational Studies. Ab initio molecular orbital calculations were performed using the Gaussian 03 series of programs.[21] All structures were characterized as energy minima via frequency calculations that showed no negative frequencies, or as transition states that showed one negative frequency.

Supporting Information Available: Complete ref 21, experimental procedures for preparation of trifluoroacetates, experimental procedures for solvolysis reactions and product analyses, the B3LYP/6-31G* calculated structures, energies, and Cartesian coordinates of **26**, **27**, **28**, **29**, **40**, **43c**, **44**, **45**, **55**, **62**, **63**, **64**, **65**, and **66**, B3LYP/6-311+G** and MP2/6-311+G** calculated energies of cations **55**, **62**, **63**, **64**, **65**, and **66**, ^{1}H and ^{13}C NMR spectra of compounds **19**, **20**, **21**, **22**, **24**, **33**, **34**, **35**, **36**, 39, **42**, **46**, **48**, **53**, **54**, **56**, **58**, **59a**, and **59b**, as well as evolving ^{1}H NMR spectra during solvolyses of **21**, **35**, **48**, and **53** in CD_3CO_2D. This material is available free of charge via the Internet at http://pubs.acs.org.

(21) Frisch, M. J. et al. *Gaussian 03*, Revision C.01; Gaussian, Inc., Wallingford, CT, 2004.