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1,3-γ-Silyl-elimination in electron-deficient cationic systems†

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Placement of an electron-withdrawing trifluoromethyl group (–CF_3) at a putative cationic centre enhances γ-silyl neighbouring-group participation (NGP). In stark contrast to previously studied γ-silyl-substituted systems, the preferred reaction pathway is 1,3-γ-silyl elimination, giving ring closure over solvent substitution or alkene formation. The scope of this cyclopropanation reaction is explored for numerous cyclic and acyclic examples, proving this method to be a viable approach to preparing CF_3-substituted cyclopropanes and bicyclic systems, both containing quaternary centres. Rate-constants, kinetic isotope effects, and quantum mechanical calculations provided evidence for this enhancement and further elaborated the disparity in the reaction outcome between these systems and previously studied γ-silyl systems.

Introduction

The construction of highly-strained ring systems and the creation of quaternary centers are arduous processes coveted by synthetic chemists. One unique unexplored route to *simultaneously* perform these tasks exploits 1,3-γ-silyl elimination. In 1946, Sommer and Whitmore reported on the ability of a γ-silyl substituent to donate electron density to the α-carbon, thereby enhancing the reactivity of this centre.[1] Subsequently, this type of interaction has been observed in a wide variety of γ-silyl scaffolds, particularly in carbocationic systems.[2,3] Shiner and others reported on homohyperconjugative stabilization of the developing p-orbital of a cationic centre by back-lobe ("percaudal") participation of the C–Si bond of the γ-silyl substituent.[2,3] Unfortunately, this transient percaudal interaction has not been effectively harnessed for ring closure to access substituted cyclopropanes. Shiner and others have shown that the major product-forming pathways in the solvolysis studies of γ-silyl substituted sulfonate esters were solvent substitution with retention of stereochemistry (Fig. 1, Product **IV**) and rearrangement to give β-silyl elimination (Product **III**), with 1,3-γ-silyl elimination to give cyclopropanation (Product **II**) being a minor path.[2g] Even cyclic systems, wherein the leaving group and the γ-silyl substituent are in the ideal *cis* "W" conformation for maximum percaudal interaction, gave only slightly higher percentages of cyclopropanation (Product II).[3a]

One logical solution to enhance cyclopropanation would be to increase the electron-donating character of the γ-substituent. Indeed, Kuivila reported that the solvolysis of 1-aryl-3-trimethylstannyl 3,5-dinitrobenzoates led exclusively to cyclopropanation *via* 1,3-γ-stannyl elimination.[4] Elimination

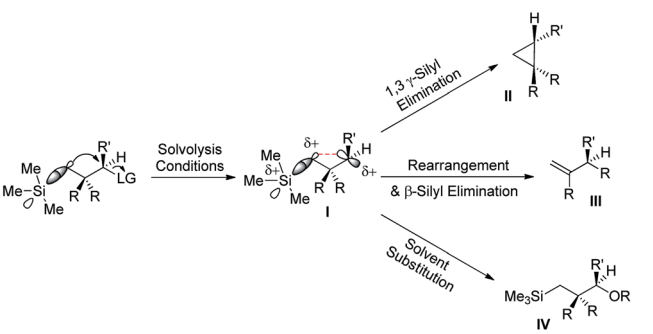

Fig. 1 Possible pathways of γ-silyl stabilized carbocations.

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products in Yoshida's competitive study of a dual γ-stannyl and γ-silyl system arose solely from the γ-stannyl substituent.[5] However, potentially toxic organostannanes limit the synthetic utility of this solvolytic reaction. As a potential surrogate for a γ-stannyl group, we hypothesized that an umpolung strategy would be to augment the γ-silyl percaudal interaction by installing a CF_3 group at the α-carbon. Work by Gassman and others supports this hypothesis by suggesting that "the placement of a strongly electron-withdrawing group at the incipient cationic centre can magnify the influence of a related series of neighbouring groups" by generating an "electron-deficient" carbocation.[6] This strategy is supported by the known delocalization of electron density from adjacent π- and σ-orbitals into the C–F σ*-orbital.[7]

We recently validated our strategy by synthesizing the highly strained 1-(trifluoromethyl)bicyclo[1.1.0]butane *via* exclusive 1,3-γ-silyl elimination (Fig. 2 eqn (1)).[8] This result was in stark contrast to studies by Creary and co-workers on analogous γ-trimethylsilyl alkyl cyclobutyl systems in which no 1,3-γ-silyl elimination was observed.[2h] We therefore wished to explore the generality of our method in the context of a potential synthetic route to trifluoromethylcyclopropanes (CF_3 cyclopropanes) containing a quaternary centre.

CF_3 cyclopropanes are highly attractive synthetic targets for medicinal chemists due to their compact, rigid structure and their lipophilic properties.[9,10] This small-ring motif can be found in a variety of recent candidates for the treatment of cancer,[11a] hepatitis,[11b] HIV,[11c] obesity,[11d,e] diabetes,[11e,f] and inflammatory diseases[11g] as well as in potential pharmacons for management of cholesterol levels[11h] and pain.[11i] Likewise, CF_3 cyclopropane-containing substances have found use as pesticides[12a,b] and parasiticides.[12c,d] Recently, the CF_3 cyclopropyl group has been found to be a suitable replacement for the *tert*-butyl group, but with enhanced metabolic stability.[13]

Current methods for CF_3 cyclopropane synthesis (Fig. 2) primarily rely on anionic or carbene/carbenoid approaches (Fig. 2 eqn (2)–(4)).[14,15] However, nearly all of these reactions involve the use of potentially explosive and/or harsh reagents/conditions to facilitate ring formation. Therefore, we sought to bolster the limited repertoire available for constructing CF_3 cyclopropanes by utilizing 1,3-γ-silyl elimination to effect ring closure. We explored a broad scope of substrates and performed comprehensive product, rate-constant, isotope effect, and computational studies. The results of our investigations are presented here.

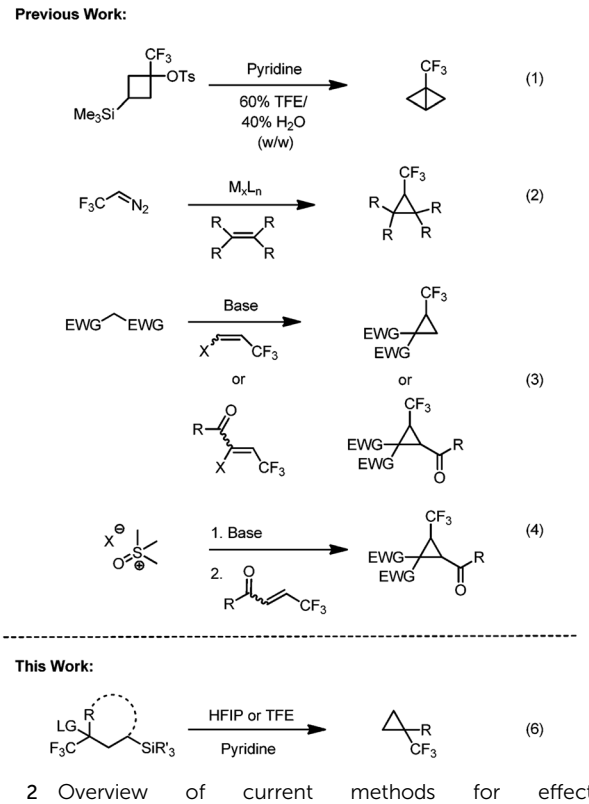


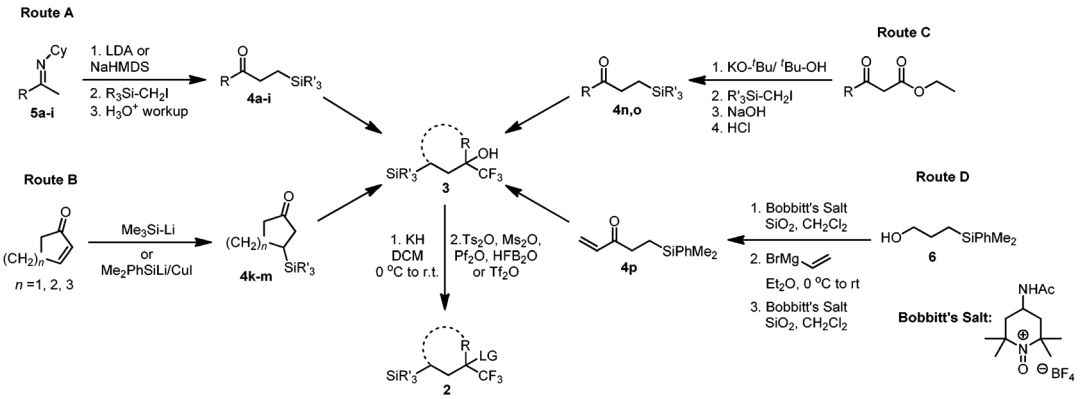
Fig. 2 Overview of current methods for effecting trifluoromethylcyclopropanation.

Synthetic results and discussion

Seeking to develop a generalized route for the synthesis of our substrates, we modeled our strategy on our previous preparation of cyclobutyl tosylates.[8] Thus, we would first prepare a carbonyl compound containing a γ-silyl moiety (–$SiMe_3$, –$SiPhMe_2$) and subsequently introduce the CF_3 group *via* the Ruppert–Prakash reagent (TMS–CF_3).[16] The resulting α-CF_3 carbinol could then be converted to the desired leaving group.

Drawing on the work of Fleming and coworkers, we found that a variety of substrates could be synthesized using Route A in good overall yield (Scheme 1).[2c,i] Alkylation of cyclohexyl imines with Me_3Si–CH_2I or $PhMe_2Si$–CH_2I, reagents that are easily prepared from the corresponding commercially available chlorides by a Finkelstein reaction with NaI, proved to be a facile and rapid methodology for silyl group introduction.[2k] To prepare other non-aryl substituted systems, we elected to utilize either Michael additions of Me_3Si–Li or the cuprate of $PhMe_2Si$–Li to α,β-unsaturated carbonyl derivatives (Route B).[17] Another route involving alkylation of β-ketoesters with Me_3Si–CH_2I or $PhMe_2Si$–CH_2I followed by decarboxylation (Route C) was also used to access straight chain alkyl systems.[2b] Lastly, we devised a modified route to prepare an allyl system *via* a series of alkylations and oxidations (Route D). Subsequent trifluoromethylation of the intermediate ketones using TMS–CF_3 followed by deprotonation[6c] with KH and functionalization of the alkoxide with the appropriate anhydride[8] gave us the desired substrates for solvolysis. The results of our solvolytic studies utilizing these compounds are presented in Table 1.

Due in part to the relative ease in their preparation, we first examined straight-chain systems with an α-phenyl ring. We were initially concerned that the stabilization afforded by the aromatic system would deter 1,3-γ-silyl participation. However, the solvolytic reaction of **2a** proceeded smoothly in 97 T [97% 2,2,2-trifluoroethanol (TFE)/3% H_2O (w/w)] giving 1,3-γ-silyl elimination as the major product of solvolysis. But, even using TFE as the sole solvating agent, minor amounts of substitution products were detected. To mitigate formation of unwanted substitution products, we conducted the reaction in the even



Scheme 1 Generalized routes to access potential cyclopropane precursor solvolytic substrates.

less nucleophilic solvent hexafluoroisopropanol (HFIP) at a relatively high substrate concentration (1 mmol per mL of HFIP). This led to cyclopropanation as the exclusive reaction pathway for **2a** (Table 1, Entry 1). We explored the –$SiMe_2Ph$ group as an alternative γ-silyl substituent (Entry 2) and obtained identical yield. Thus, it is likely that a wide range of silyl groups can be used so long as they do not lead to unfavorable conformational restriction or reduction in electron availability on silicon. Moreover, having a less volatile silyl byproduct may be advantageous when isolating lower molecular weight CF_3 cyclopropanes.

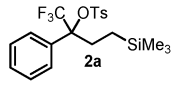
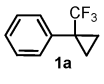
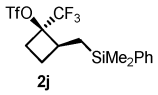
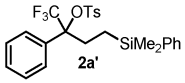
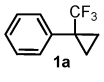
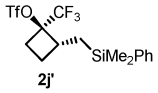
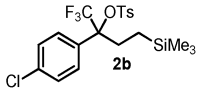
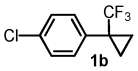
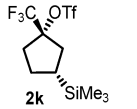
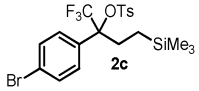
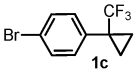
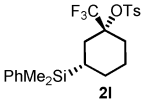
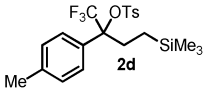
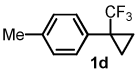
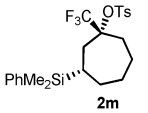
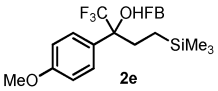
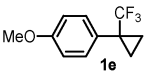
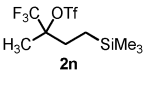
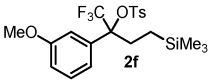
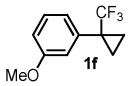
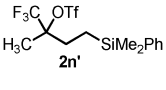
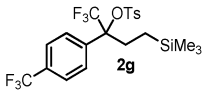
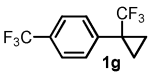
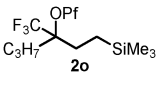
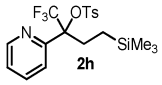
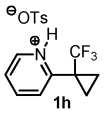
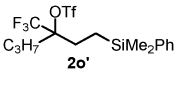
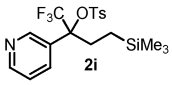
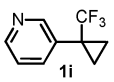
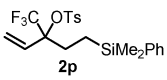
To probe the effect of electronic changes on 1,3-γ-silyl participation we screened a series of additional aromatic systems. Both electron-deficient (Entries 3, 4, 8) and moderately electron-rich (Entries 5 & 7) arenes underwent facile γ-silyl elimination to afford the corresponding CF_3 cyclopropanes in good to excellent yield. Of particular note are the pyridyl systems (Entries 9 & 10). Because of the disparity in electronics between the 2- and 3-positions on the pyridine rings, heating was needed to facilitate the ionization of the 2-pyridyl system while the 3-pyridyl system reacted, albeit slowly, at room temperature. We were also pleased to find that the pyridyl substituent itself could successfully serve as the base for the reaction (Entry 9), yielding the pyridinium salt after solvent removal. The salt facilitated product isolation as it decreased volatility (compare yield of Entry 9 to Entry 10 or 1 and 2). The tosylate of the 3-pyridyl system could not be obtained as a pure material as it was contaminated with ≈20% of its alcohol precursor. However, the solvolysis reaction could still be conducted with impure material because the cyclopropane product was easily separated from this impurity. This demonstrates the overall robustness of this protocol. Likewise of note are the 4-bromo and 4-chloro systems (Entries 3 & 4) as they could potentially be further utilized in transition-metal-mediated coupling reactions to prepare more complex systems. Not all α-aryl substrates underwent cyclopropanation successfully. No cyclopropane products could be obtained in the case of the 4-methoxy substituted system (Entry 6). Even when using a less-reactive heptafluorobutyrate (–OHFB) leaving group, solvolysis occurred rapidly and gave a complex mixture of S_N1 substitution, E1 elimination, and β-silyl elimination (*via* a Wagner–Meerwein rearrangement).

We next explored 1,3-γ-silyl elimination in cyclic systems to determine if ring closure was possible in systems other than cyclobutyl. Both six- and seven-membered ring systems (Entries 14 and 15) exhibited bridging. In contrast, the cyclopentyl system (Entry 13) gave mostly elimination (80% E1 elimination, 20% β-silyl elimination following rearrangement) with trace amounts of substitution products. We suspect none of the low-energy cyclopentyl conformers permit the "W" orbital conformation to facilitate percaudal participation.[2h,8] In the case of the cyclohexyl system, **2h**, which adopts the correct "W" conformation,[3a] mild heating (40 °C), yielded the highly strained bicyclo[3.1.0]hexane as the sole product of solvolysis. The increased degrees of freedom in the larger cycloheptyl ring system, **2m**, provides access to a favorable conformation for bridging. This flexibility still did not, however, permit the *trans* isomer, **2m′**, to bridge.

In an attempt to circumvent the conformational issues arising from the cyclopentyl system, we solvolysed **2j** and **2j′** (Entries 11 & 12). Rather than obtaining the desired housane, we serendipitously obtained **1j**. A mechanistic rationale for this result can be seen in Fig. 3. Due to the rapidity of this reaction and its highly selectivity towards ring contraction, we suggest that, in addition to the known NGP by C–C σ-bonds in cyclobutyl systems,[18] there is a transient cation-stabilizing interaction between the γ-silyl group and the forming cation. This is evidenced by a substantial rate difference (≈12 times) between the two diastereomers, indicating that the putative carbocation formed from isomer **2j′** is benefiting from additional NGP stabilization. However, ultimately the product determining pathway is dictated by the C–C σ-bond NGP which yields a highly stabilized β-silyl cyclopropylcarbinyl cation. Subsequent β-silyl elimination gives the alkenyl CF_3 cyclopropane in both cases.

We next turned our attention to linear aliphatic systems (Entries 16–20), which required trifluoromethylsulfonate (OTf) leaving groups to facilitate solvolysis.[19] In general, these reactions proceeded smoothly, with cyclopropanation being the sole reaction pathway. NMR yields were high, but due to the

Table 1 Solvolysis studies of various γ-trimethylsilyl-α-trifluoromethyl systems[a]

Entry	Substrate	Product	Yield[b] (%)	Entry	Substrate	Product	Yield[b] (%)
1[c]	 2a	 1a	58	11[c,i]	 2j	 1j	(84)
2[c]	 2a'	 1a	58	12[c,i]	 2j'	 1j	(87)
3[c]	 2b	 1b	76	13[f,g]	 2k	 1k	—
4[c]	 2c	 1c	74	14[f,g,h]	 2l	 1l	(95)
5[c]	 2d	 1d	72	15[d,e,f]	 2m	 1m	(92)
6[c]	 2e	 1e	—	16[f,h]	 2n	 1n	29 (91)
7[c]	 2f	 1f	74	17[e,f]	 2n'	 1n	64 (95)
8[c,d]	 2g	 1g	95	18[j]	 2o	 1o	(91)
9[c,d,e]	 2h	 1h	100	19[j]	 2o'	 1o	35 (98)
10[c]	 2i	 1i	65	20[k]	 2p	 1j	(68)[l]

[a] Reaction conditions unless otherwise noted: hexafluoroisopropanol (HFIP), cyclopropane precursor (1 equiv., 1 M in HFIP), pyridine (2 equiv.); OTs: *p*-toluenesulfonate, OTf: trifluoromethanesulfonate, OPf: pentafluorobenzenesulfonate, OHFB: heptafluorobutyrate. [b] Isolated yield; yields in parentheses indicate yields determined by ^{1}H NMR spectroscopy. [c] Prepared *via* Route A. [d] Reaction was performed at 50 °C. [e] No pyridine was used. [f] Solvolysis was performed in TFE. [g] Prepared *via* Route B. [h] Reaction was performed at 40 °C. [i] While both substrates gave the same product, **2j′** reacted ≈12 times faster than **2j** (**2j**: $k = 1.49 \times 10^{-4}$ s^{-1}; **2j′**: $k = 1.83 \times 10^{-3}$ s^{-1}). [j] Prepared *via* Route C. [k] Prepared *via* Route D. [l] 20% yield of S_N1' product, 12% yield of the S_N1 product.

Fig. 3 Possible pathways of γ-silyl stabilized carbocations.

volatility of the products, isolation and purification were extremely difficult. Altering the silyl group (Me_3Si to Me_2PhSi), minimized complications in product purification of several volatile systems (by raising the boiling point of silyl ether by-products) and led to improved yields. NMR yields were obtained exclusively in some cases as the desired cyclopropanes were nearly inseparable from either silyl-ether byproducts or extraction solvents. As an alternative route to the vinyl cyclopropane **1j** obtained from **2j** and **2j′**, we screened the corresponding straight-chain allyl system **2p**. This system gave a mixture of cyclopropanation and substitution [both at the cationic center (S_N1) and γ-carbon on the olefinic moiety (S_N1')]. Increased substitution is likely a combination of the enhanced stability of the resonance-stabilized ion, and decreased participation of the

silyl group due to reduced conformational restriction in the straight-chain system.

Kinetic results and discussion

To determine the extent of γ-silyl participation during the course of these reactions, we obtained first-order solvolytic rate-constants (using conductometric methods) for several representative systems and corresponding carbon analogs. We also prepared β-d_2 labeled analogs of some of these systems to probe secondary β-deuterium kinetic isotope effects (KIE). These secondary KIEs measure rate changes due to isotopic substitutions at a site other than the bond breaking/formation site in the rate determining step of the reaction, providing transition-state conformational and charge distribution information. The results of these studies and values of relevant literature compounds are shown in Table 2.[20,21]

The greatly enhanced rate effects seen for the silyl systems provide strong evidence of percaudal participation during the transition state for this reaction. The most striking enhancement is for our α-CF_3 cyclobutyl system[8] (Table 2, Entry 2). The rate acceleration of more than 6×10^6 represents the largest γ-silyl enhancement measured to date. The largest rate enhancement previously measured was reported by Creary[2h] to be 1×10^5 for a secondary γ-silyl cyclobutyl system. Our extreme case results from a combination of increased demand for silyl participation and ideal orbital overlap due to the locked "W" conformation.

Shiner reported similar (although less drastic) effects for the less rigid cyclohexyl systems lacking a CF_3 group (Entries 8 & 9).[3a] Rate enhancements for the straight chain systems in this work also seem to correspond to the stability of the putative carbocation and therefore inversely to the demand being placed on the silyl group for stabilization. The rate increase of over 200 for **2n** over **2t** is the largest ever observed for any acyclic γ-silyl system to date (Entries 9 & 10). An analogous comparison using systems lacking an α-CF_3 group (Entries 11 & 12) showed only a mere doubling in rate in the silyl system. Presumably, this is because the inherent stability of the tertiary carbocation places very little demand on the silyl group.[2k] The marked decrease in rate enhancement for the more stable phenyl systems (compare Entries 15 & 16) seems to initially be indicative of greatly diminished silyl participation during the ionization step. However, the major product from the silyl-substituted phenyl system was still the cyclopropane (see Table 1 Entries 1 & 2), although as noted above for these systems (as well as the allylic one) substitution was also observed in TFE.

Consequently, we envisioned an electron-demand dependent mechanistic spectrum for these reactions. This ranges from either a concerted or "nonclassical" ion-containing process in systems analogous to **2n** where strong γ-silyl demand exists to a stepwise process with a clearly extant "classical" carbocation intermediate with reduced demand in systems analogous to **2v**.[22] To further substantiate this concept, we examined Raber–Harris plots and secondary β-d_2 KIEs. Raber–Harris plots for **2n** and **2t** (see ESI†) show a clear difference in mechanism for these systems; **2n** is not dependent upon solvent nucleophilicity (as would be expected for extensive participation) whereas **2t** exhibits nucleophilic solvent assistance.[23] In contrast, Raber–Harris plots of **2u** and **2v** are very similar, showing very little if any nucleophilic solvent assistance for either system, as might be expected during formation of a benzylic cation (see ESI†).

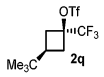
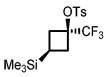
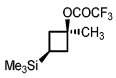
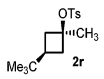
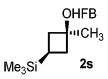
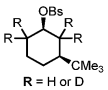
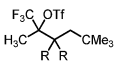
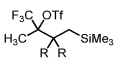
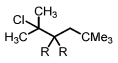
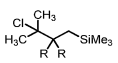
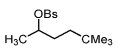
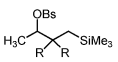
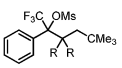
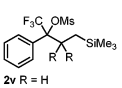
Secondary β-d_2 KIE data are also consistent with greater participation *via* a "nonclassical" cation type or concerted mechanism for straight chain aliphaitc CF_3 systems and reduced (but not absent) participation in straight-chain α-aryl systems. The magnitude of the β-d_2 KIE depends on both the extent of positive charge at the potential cationic centre and the dihedral angle between the incipient p-orbital and the adjacent C–H/C–D bonds.[24] In cases with large percaudal participation this dihedral angle is such that virtually no hyperconjugative stabilization exists. The absence of hyperconjugation results in little or no difference between isotopically-labelled and -unlabelled compounds, giving secondary KIEs of one or less. Inverse KIEs (*i.e.* less than one) result from inductive effects of deuterium, as Shiner has reported previously (Entries 8 & 14).[3a,24] Thus extensive percaudal participation would result in in very small secondary β-d_2 KIEs. This participation can occur either *via* a concerted process in which the C–Si bond acts as an internal nucleophile in an S_N2-like fashion or a stepwise process leading to a conformationally-bridged ion with extensive charge delocalization.

Our systems **2n**/**2n**′ exhibit virtually no KIE (Entry 10). The large KIE seen for the carbon analog in system **2t**/**2t**′ is consistent with literature values.[2k] In the case of α-aryl systems, the isotope effects for both systems **2u**/**2u**′ and **2v**/**2v**′, are quite small. The small normal KIE for the carbon analog is in line with the resonance delocalization of the positive charge into the aromatic system expected as a result of the greatly increased demand for electron density created by the α-CF_3 in that system (Entry 15).[6,25] The inverse (*i.e.* non-unity) isotope effect for the silyl system likely indicates the presence of an intermediate ion that is stabilized both by percaudal participation (requiring conformational restriction and reduced hyperconjugation) and resonance with the phenyl group. Thus, while the phenyl group deters participation, it is not completely removed. A similar deterrence in silyl participation (and thereby a diminished rate enhancement) has also been observed in α-phenyl-β-silyl cationic systems.[26]

Our isotope effects provide a nice comparison to reports by Kuivila[4] and by Davis[27] who observed similarly small secondary β-d_2 KIEs for deoxystannylation of both aliphatic and aryl straight chain systems. Both reports concluded the mechanisms to be concerted.[4,27] Because in our case only the aliphatic systems show extensive participation, the stronger effect of the stannyl group must be such as to preclude the formation of an intermediate benzyl cation. Thus we suggest that the electronic influence on percaudal participation in our unique γ-silyl α-CF_3 system lies between those of γ-silyl and γ-stannyl groups alone and results from a combined push-pull effect based on the electronics of the α-carbon.

The influence of the CF_3 group itself may be further extracted utilizing rate data from the cyclobutyl and straight-chain

Table 2 First order rate constants and secondary β-d_2 KIE data for solvolytic studies of representative γ-silyl sulfonic esters and their carbon analogues at 25 °C in 97 T

Entry	Compound	Rate (s^{-1})[a]	β-d_2 KIE (k_H/k_D)	γ-Silyl group acceleration[b]
1	 **2q**	1.00×10^{-5}	—	—
2		6.12×10^{-4}	—	6.0×10^{6}[c]
3[d]		3.38×10^{-9}[e]	—	—
4[d]		1.55×10^{-4}[e]	—	4.6×10^{4}
5	 **2r**	2.00×10^{-1}	—	—
6	 **2s**	4.40×10^{-2}	—	2.2×10^{4}[f]
7[g]	 **R** = H or D	1.64×10^{-5}	2.06	—
8[g]	 **R** = H or D	1.76×10^{-3}	0.972	107.5
9	 **2t** R = H **2t'** R = D	1.39×10^{-5}	1.85	—
10	 **2n** R = H **2n'** R = D	2.90×10^{-3}	1.00	208
11[h]	 **R** = H or D	5.58×10^{-4}	1.452	—
12[h]	 **R** = H or D	1.31×10^{-3}	1.159	2.35
13[i]		8.44×10^{-4}	—	—
14[i]	 **R** = H or D	6.54×10^{-6}	0.975	129
15	 **2u** R = H **2u'** R = D	2.48×10^{-3}	1.02	—
16	 **2v** R = H **2v'** R = D	9.43×10^{-3}	0.98	3.8

[a] Values in parentheses indicate percent error of the obtained rate constant. [b] Ratio of rates between the silyl sulfonate ester and its carbon analog. [c] Assuming $k_{OTf}/k_{OTs} = 1 \times 10^5$ (conversion factor obtained from ref. 20). [d] Ref. 2*h*. [e] Solvent was CD_3CO_2D. [f] Assuming $k_{OTs}/k_{Cl} = 2 \times 10^5$ and $k_{OHFB}/k_{Cl} = 2$ (ref. 20 and 21). [g] Ref. 3*a*. [h] Ref. 2*k*. [i] Ref. 2*g*.

aliphatic systems. Creary reported[2h] a γ-silyl rate acceleration of 4.6×10^4 for tertiary cyclobutyl systems (Entries 3 & 4) lacking a cation-destabilizing α-CF_3 group. We supplemented Creary's data by preparing and solvolyzing the more sterically-analogous 1-methyl-3-*tert*-butyl systems (Entries 5 and 6), which showed a similar enhancement of 2.2×10^4 based purely on conformational locking. Consequently, the rate enhancement ratio for Entries 2 and 1 to Entries 6 and 5 ($6.0 \times 10^6/2.2 \times 10^4 = 130$) allows the demand created by the α-CF_3 for homo-hyperconjugative stabilization by the γ-silyl group to be extracted and inferred to be roughly a factor of 10^2. Application of this approach to the corresponding acyclic aliphatic systems, wherein the added variable of conformational restriction is removed, gives a remarkably similar result. The rate enhancement ratio for Entries 11 and 10 to Entries 13 and 12 ($208/2.35 = 88.5$) shows a demand for silyl participation created by the α-CF_3 group that is identical in order of magnitude ($\approx 10^2$).

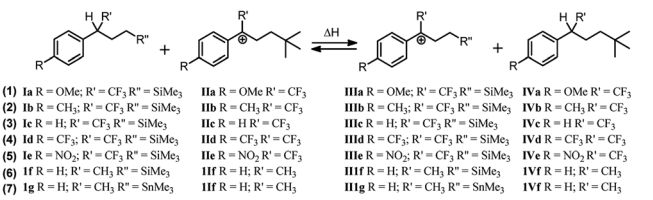
Thus, fine tuning of the electronics by modification of the substitution pattern at the α-carbon can induce dramatic mechanistic changes. However, there must still be sufficient percaudal interaction to allow cyclopropanation to be the lowest energy product-forming pathway. This intermediate reactivity level between traditional γ-silyl and γ-stannyl systems (lacking α-CF_3 groups) allows for preparation of relatively stable, tin-free substrates while still providing regioselective product control.

Computational results and discussion

The aryl and vinyl systems clearly proceed *via* a carbocation intermediate, because solvent substitution was observed and secondary KIEs supported reduced participation. We used computational modeling to predict secondary KIEs for **2v** and **2n** and found them to be in excellent accord with experiment (computed KIE for **2n** = 0.98; **2v** = 0.96). Density functional theory (DFT) calculations were performed with Gaussian 09[28] at the B3LYP level of theory[29] with the 6-31+g(d) basis set.[30] The polarizable continuum model (PCM)[31] was used to better evaluate solvated cationic species. TFE was chosen as the solvent used for our solvation model as it was representative of the solvents used experimentally. Further details on the calculations can be found in the ESI.†

Although our mechanistic (and computed KIEs) results on the aliphatic and carbocyclic systems indicate extensive participation, the lack of substitution does not provide sufficient evidence to unambiguously conclude a mechanistic pathway. Exclusive 1,3-γ-silyl elimination could result from either poor solvent nucleophilicity preventing substitution on a bridged ion intermediate, or because of a concerted pathway. To further glean mechanistic insight, the electronic and conformational effects on γ-silyl participation (and subsequent 1,3-elimination) in α-CF_3 cationic systems were investigated by additional computational modeling.

An isodesmic study[32] of α-aryl systems (Scheme 2) was conducted to elucidate the balance between phenyl resonance- and γ-silyl-mediated carbocation stabilization. In all cases γ-silyl cations were slightly more stable than their carbon analogs (Table 3). A clear inverse correlation can be observed between



Scheme 2 Isodesmic calculations evaluating γ-silyl stabilization of cations **IIIa–g**.

the degree of γ-silyl stabilization and the available electron density of the aryl ring. **IIIa** and **IIIb** are only slightly more energetically stable than **IIa** and **IIb**, respectively, due to more available ring electron density and, in the case of **IIIa**, an additional resonance contributor. This stabilization thereby mitigates the need for γ-silyl cation stabilization. However, **IIId** and **IIIe** are ~2 kcal mol^{-1} more stable than **IId** and **IIe**, respectively, due to diminished available ring electron density thereby necessitating enhanced γ-silyl participation. Comparison to the corresponding α-CH_3 substituted γ-silyl and γ-stannyl systems **IIIf** and **IIIg** leads further credence to the electronic intermediacy of our α-CF_3 γ-silyl system in terms of the γ-substituents ability to participate in cation stabilization. Little difference between **IIIf** and **IIf** confirms minimal participation[2k] of the γ-silyl group in the 3° system while the γ-stannyl system is ~2 kcal mol^{-1} more stabilizing and is consistent[4,27] with its ability to contribute significantly *via* bridging in the aromatic systems even without the added demand of the α-CF_3 group. Energetically, the contribution of the γ-stannyl substituent appears to be equivalent to that of a γ-silyl system with both an α-CF_3 and a 4-CF_3-substituted-α-aryl substituent.

To further probe these electronic effects, the relative degree of aromaticity of the α-aryl ring as a function of cation structure was assessed using the *Harmonic Oscillator Model of Aromaticity* (HOMA; eqn (1)) for **IIa**, **IIIa**, **IIb**, **IIIb**, *etc.*[33] In eqn (1), α is a normalization constant ($\alpha = 257.7$ for C–C bonds), n is the number of C–C bonds included in the summation, $R_{opt} = 1.388$ Å, and R_i = length of successive C–C bonds. Using HOMA, the degree of aromatic character of a system relative to benzene can be assessed numerically. A HOMA value of 0 corresponds to a completely nonaromatic system, while a HOMA of 1 is equal in aromatic character to benzene.

Analysis of the ΔHOMA values confirmed that in all cases the aryl ring had more aromatic character in γ-silyl systems than in their carbon analogues. This implies that the extent of aryl stabilization is diminished in these systems because of compensatory γ-silyl participation. As dispersal of charge into the aryl ring becomes less favourable, γ-silyl stabilization is enhanced and allows the ring system to retain a higher degree of aromaticity. With the removal of the CF_3 decreasing electronic demand, **IIIf** and **IIIg** both show little difference from the carbon analogue **IIf**; with the slightly higher degree of aromaticity **IIIg** consistent with participation from the tin.

$$\mathrm{HOMA} = 1 - \frac{a}{n}\sum_{i=1}^{n}\left(R_{opt} - R_i\right)^2 \quad (1)$$

Table 3 Relative stabilization energies[a] and HOMA values for γ-metalloidal carbenium ions and the corresponding carbon analogues

Entry	Eqn in Scheme 2	ΔH^b kcal mol^{-1}	HOMA[c] **IIa–g**	HOMA[c] **IIIa–g**	ΔHOMA[d] (**III–II**)
a	(1)	−0.37	0.487	0.511	0.0242
b	(2)	−0.68	0.633	0.663	0.0296
c	(3)	−1.00	0.714	0.747	0.0335
d	(4)	−1.67	0.781	0.825	0.0448
e	(5)	−2.18	0.812	0.872	0.0609
f	(6)	−0.53	0.834	0.846	0.0111
g	(7)	−1.60	0.834	0.860	0.0257

[a] In kcal mol^{-1} at 298 K. [b] A negative value indicates that the γ-silyl carbenium ion **IIa–e** is more stabilized than the corresponding carbon analog carbenium ion **IIIa–e**. [c] HOMA values range from 0–1. HOMA = 0 for completely nonarmoatic system and HOMA = 1 for fully aromatic system (all C–C bonds R_{opt} = 1.388 Å). [d] Difference between HOMA **IIa–e** and HOMA **IIIa–e**. Positive values indicate a higher degree of aromaticity.

For the 4-CF_3, 4-CH_3, and 4-H systems, thermodynamically favorable isodesmic values correlated with empirical cyclopropanation as did the γ-stannyl[4] system **IIIg**. However, experimental solvolysis of the 4-OMe system resulted in predominant solvent substitution, suggesting some thermodynamic threshold had been crossed. To better understand the relative energetics of the cyclization and solvolytic pathways, we populated the free energy surface (Fig. 4). Initial attempts to locate transition state structures involved chemical intuition and or serendipity. If these attempts proved fruitless, QST3 calculations were employed where the reactant, product, and initial guess of the transition state were inputted. Transition states were confirmed by IRC analysis.[34] The ionization step of **Va–c** is an exergonic process (summing cation and leaving-group anion energies), but is energetically unfavorable for **Vd** and **Ve**. This explains the need for heating in the solvolysis study of **Vd**. In the case of **Va**, however, the extremely electron rich nature of the methoxy substituent indicates a potentially competing rate-determining second step, which can further explain the preferential solvent substitution in this system.

In all observed cases the energetics of the second step controls product formation. In this "product-determining" step of the solvolysis, the cyclization is exergonic for **VIIb–e**. Cyclization of cationic intermediates **VIIc–e** proceeds *via* **TS-VIIIc–e**, the energy barrier for which decreases systematically as the aryl substituent becomes more deactivating. Once the 4-Me system is reached, the activation energy increases slightly compared to **VIIc**. This is likely due to the increased stability of the

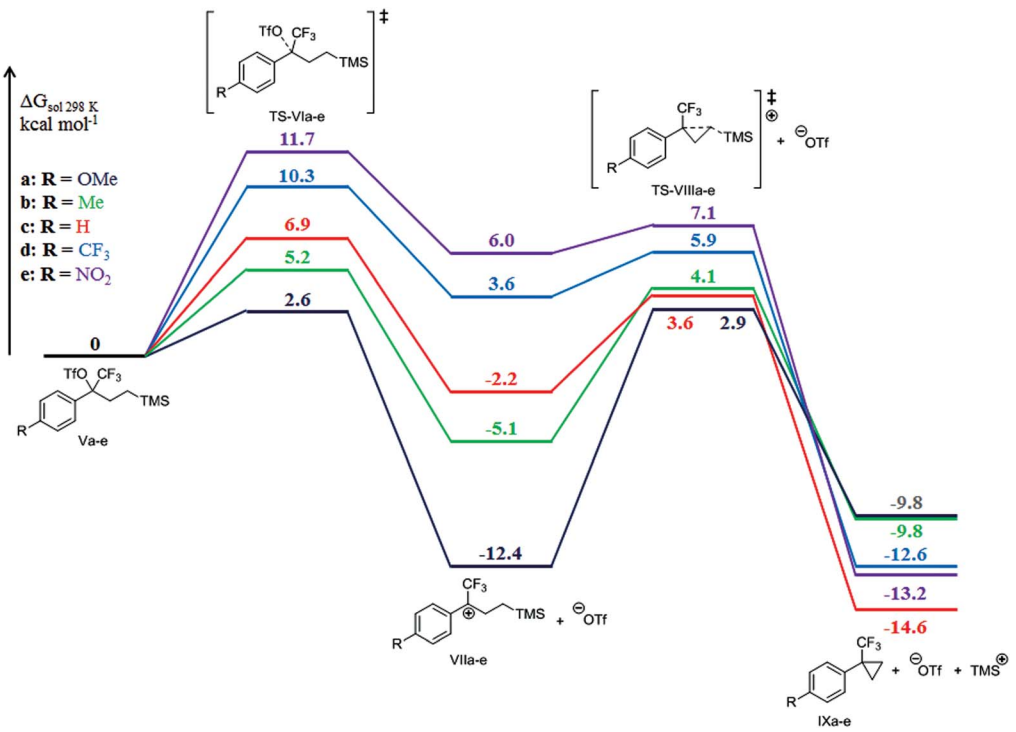


Fig. 4 Calculated energy profile for the cyclopropanation of **Va–e**. Figures of the optimized transition state geometries for both the ionization and cyclization steps are provided in the ESI.†

intermediate **VIIb** starting to disfavor the cyclization pathway. Indeed, in the case of **VIIa**, the predicted cyclization step becomes rate determining. This change in energetics suggests either a longer-lived cation for this pathway (allowing for competing substitution) or simply other potentially lower energy "product-determining" pathways. These alternative reaction pathways are consistent with our experimental observation that solvent substitution predominates. Efforts to locate a transition state for a substitution pathway were unsuccessful.

Attempts to perform analogous isodesmic studies of the straight-chain aliphatic and carbocyclic systems did not provide the expected results based on the assumption of a stable bridged ion-intermediate. Optimization of the ground state structures of the γ-silyl cations of these systems resulted in spontaneous cyclization. No stable carbocationic intermediate could be located.[35] Since the optimized ground state-structures of the silyl systems had different bond arrangements than their carbon analogs (which were located as the expected carbocations), isodesmic studies could not be performed. The inability to locate a bridged ion pointed toward a concerted mechanism or at least an ionization step with a very early transition state. Furthermore, in our attempts to locate a transition state corresponding to an ionization step, we discovered a transition state corresponding to both ionization and cyclization.

We therefore explored the potential energy surfaces of the straight-chain and carbocyclic systems with the premise that there is a single transition state involving both ionization and cyclization (Fig. 5). In all cases the ring-closing reaction was exergonic and a marked difference in the activation barrier was observed between cyclic and acyclic systems (compare **TS-XIIIa** to **TS-XIIIc-e**). This disparity in energy likely stems from conformational restriction and is consistent with experimental requirements for less reactive leaving groups in the cyclic systems. In a select case we also explored a concerted β-hydride elimination reaction pathway and compared it to the γ-silyl elimination path. Comparing the two pathways from straight chain systems leading to **TS-XIa** and **TS-XIIIa**, it is clear that the controlling factor for elimination in γ-silyl α-CF_3 cationic systems is almost certainly kinetic. While the cyclopropane **XIVa** is ultimately higher in energy, its activation barrier is significantly lower than the barrier leading to **XIIa** ($\Delta\Delta G^{\ddagger} = 3.0$ kcal mol^{-1}), allowing this pathway to predominate. Additionally, the so-called "perfluoroalkyl effect" initially described by Lemal, may provide some kinetic stability to this strained system by preventing electrophilic degradation and raising activation energies of isomerization.[36] In the case of the cyclopentyl system we could not locate a transition-state for cyclopropanation. The structure of the system is such that the preferred stabilizing interaction was hyperconjugation of the β C–H bond, leading to concerted elimination (**XIb**). This pathway is consistent with our prediction of unfavorable ring conformation forbidding cyclization and preferring elimination as seen experimentally.

While treatment of most cyclic systems with assumption that both steps were concerted was viable, the cyclobutyl system proved to be an exception (Fig. 6, **XVII**). Indeed, even unsubstituted cyclobutyl systems are known to receive anchimeric assistance from the C–C σ-bonds in the ring.[18] Such assistance would diminish the dependency on direct γ-silyl-promoted elimination and lead to a longer-lived ion. However, analysis of the ground state structure **XVII** still showed the hallmarks of

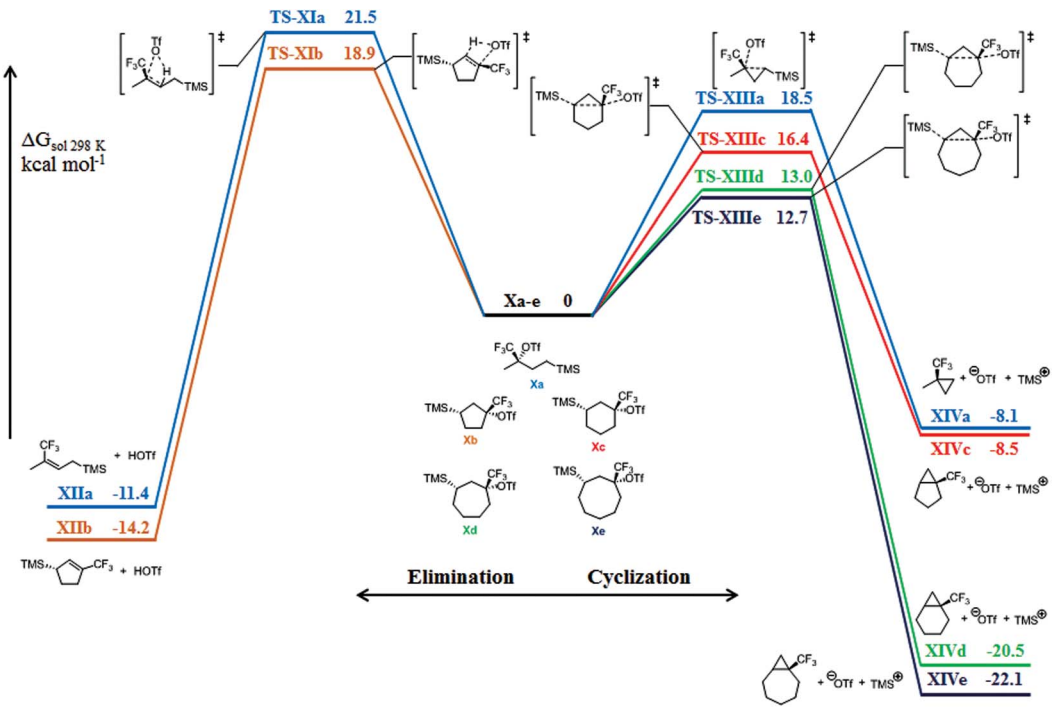


Fig. 5 Calculated energy profile for the possible pathways for straight chain and carbocyclic γ-silyl α-CF_3 cations. Figures of the optimized transition state geometries for the cyclization steps are provided in the ESI.† Numeric values indicate energies in kcal mol^{-1}.

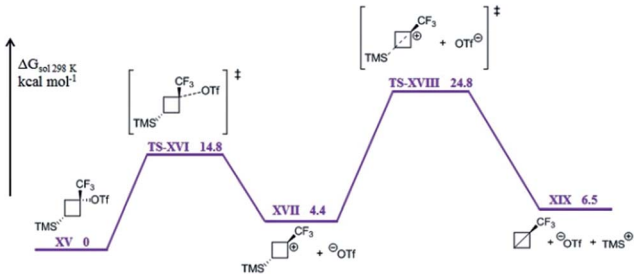


Fig. 6 Calculated energy profile for the ring closure of XV. Figures of the optimized transition state geometries for the cyclization steps are provided in the ESI.† Numeric values indicate energies in kcal mol^{-1}.

γ-silyl stabilization (*e.g.* ring contraction, elongation of the C–Si bond). To quantify the degree of γ-silyl stabilization in this system, we conducted an isodesmic study in a manner similar to our previous study of the α-phenyl system (Fig. 7). This study revealed that not only was γ-silyl stabilization present, but it was quite substantial as compared to the straight-chain α-phenyl systems (−15.4 kcal mol^{-1} *vs.* −0.37 to −2.18 kcal mol^{-1}) and significantly more than the corresponding α-CH_3 system. To give a comparison of disparate stabilizing effects (resonance *vs.* anchimeric assistance), an isodesmic study was conducted using an α-vinyl substituent. This study produced stabilization energy more in line with the α-phenyl systems (−2.25 kcal mol^{-1}). Additionally, we were able to quantify the amount of energetic stabilization afford by the α-CF_3 group in this system by comparing it to its α-CH_3 congener (5.58 kcal mol^{-1}). Therefore, while stabilizing, the anchimeric assistance of C–C σ-bonds is not nearly as competitive to γ-silyl homo-hyperconjugative stabilization as resonance stabilization.

Finally, to address the discrepancy between the endothermic nature of the potential energy surface (Fig. 6) for the cyclobutyl system and the highly successful bridging under laboratory conditions, we offer the following rationales: (1) the high Baeyer strain of **XIX** in the resulting bicyclobutyl system dramatically increases the energy of this system; (2) the γ-silyl homo-hyperconjugative stabilization is very significant in this system leading to a highly electropositive silicon; (3) the formation of the bond between the electropositive silicon and the solvent, which was not accounted for in these computations, may offset the energetic cost of forming this system and would allow this reaction to be permissible from a thermodynamic standpoint; (4) the "perfluoroalkyl effect," may provide some kinetic stability to this resulting strained system thereby trapping it in a potential energy well.[36]

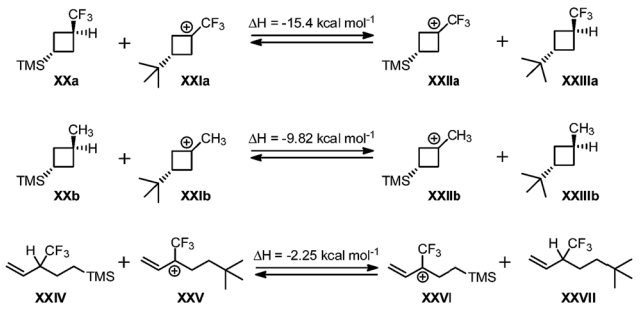


Fig. 7 Isodesmic calculations evaluating γ-silyl stabilization of cations XXIIa/b and XXVI.

Conclusions

These studies evince that placement of a cation-destabilizing group adjacent to the α-carbon in a γ-silyl systems leads to a much stronger γ-silyl interaction. This enhanced interaction allows the 1,3-γ-silyl elimination pathway to predominate, yielding a method for cyclopropanation in most systems. A strategy for the preparation of CF_3 cyclopropanes was developed to demonstrate the synthetic value of this enhancement. Using kinetic studies and hybrid density functional theory calculations, the entire mechanistic spectrum was elucidated. Solvolyses of the straight chain aliphatic, cyclohexyl and cycloheptyl systems appear to be concerted with a transition state involving significant charge delocalization by percaudal participation, whereas the cyclobutyl system proceeds through a percaudally-stabilized bridged ion intermediate. The difference between these systems can be accounted for by the high demand for silyl participation in the former without the added stabilizing factors of maximal conformational restriction and neighbouring σ-bond participation found in the latter. The stabilization provided by the adjacent π system in both the α-aryl and α-vinyl systems begins to dominate enough to allow for a more classical ion. However, the complementary directing effects of the γ-silyl and α-CF_3 substituents are still sufficient (excepting the most electron-donating *p*-methoxy system, **2e**) to favour 1,3-silyl elimination over substitution.

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