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GEOMETRICAL LIMITATIONS IN THE INTRAMOLECULAR ADDITION OF UNSYMMETRICAL ALLYLSILANES TO ENONES

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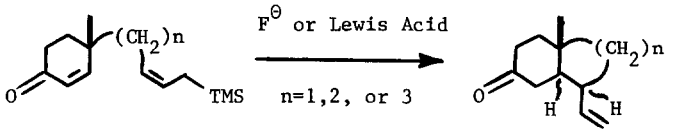
SUMMARY: The geometrical constraints of the fluoride-initiated and Lewis acid-catalyzed intramolecular addition of allylsilanes to enone systems were shown to be governed by kinetic-ring-size preferences. Molecules containing adjacent quaternary carbon atoms can be prepared using this method.

The potential for regio- and stereochemical control in the intramolecular version of a reaction is an important consequence of the geometrical requirements. We previously reported the first example of ring formation via a fluoride-induced intramolecular addition[1] of a symmetrical allylsilane to a Michael acceptor.[2] In this Letter, we report our systematic investigation of the geometrical requirements in the intramolecular addition of unsymmetrically substituted allylsilanes[3] to α,β-unsaturated enones (e.g. **i**→**ii**). These early results indicate that the regiochemical control exhibited in these ring closures depends solely on kinetic-ring size biases.[4]

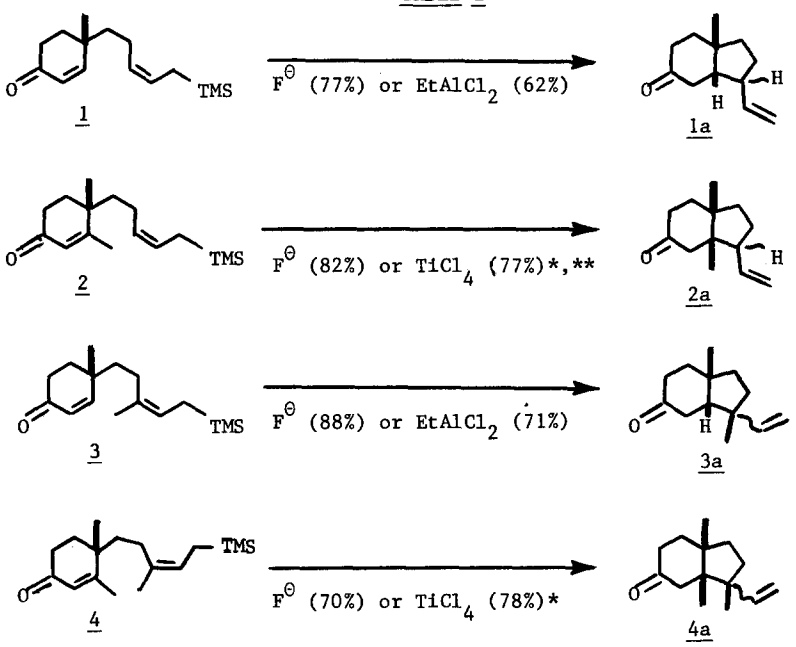


i **ii**

Trajectory analysis of an intramolecular Michael addition requires that the nucleophile attack approximately perpendicular to the plane of the electron-deficient olefin.[5] Cyclizations which readily accommodate this trajectory are favored. Inspection of models of **iii** (where n=1, 2,3) suggests that this geometrical requirement is difficult to attain unless the two olefin units are separated by at least two carbons. Substrate **1** meets this prerequisite, with its three carbon tether, and has the potential to cyclize at either terminus of the allyl moiety (see Table I). In this situation, cyclization via the primary center of the ambident allylic nucleophile would generate a seven-membered ring, whereas reaction at the secondary terminus would result in a five-membered ring. In 1978 Sakurai and co-workers reported that during the intermolecular fluoride-induced allylation reaction, alkyl substituted allylsilanes reacted at the less-substituted nucleophilic site with aldehydes and ketones.[6] This precedent suggested that ring formation would occur at the α-carbon of the allylsilane unit. We anticipated, however, that cyclization of **1** would produce only hydrindanone **1a** because of the ring sizes involved and because substituted allylic organometallic reagents undergo intermolecular reaction at the γ-carbon atom.[7] Indeed, treatment of substrate **1** with fluoride ion afforded only the expected product,

1a, in 65% yield.[8,9] Analogous cyclizations are shown in Table I.[10] The regiospecific γ-substitution of allylsilanes with carbon electrophiles has been rigorously established,[11] and it was correctly anticipated that reaction of substrates 1→4 under Lewis acid catalysis would generate the same products as the fluoride-induced process.

TABLE I [9,10]



1 → 1a; 2 → 2a; 3 → 3a; 4 → 4a

* No reaction with $EtAlCl_2$

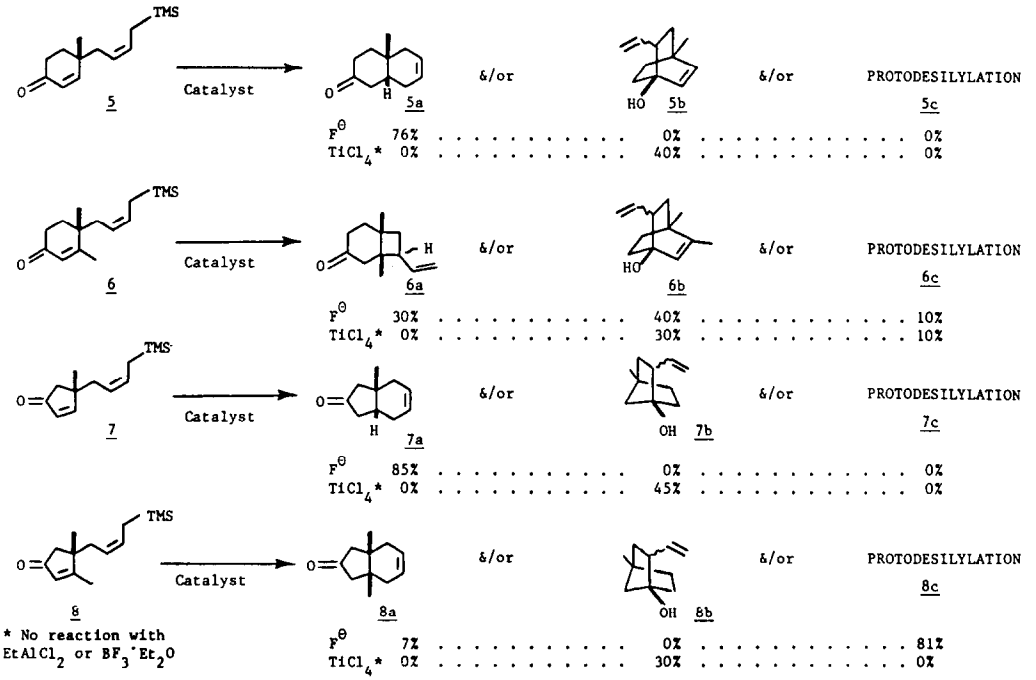
** No reaction with $BF_3 \cdot Et_2O$

Several of the fluoride-initiated reactions merit further comment. First, note that the cyclization of entries 3 and 4 involves a tertiary carbon nucleophile,[12] thus creating a new quaternary carbon atom. Although the construction of quaternary centers by the conjugate addition of nucleophiles to β,β-disubstituted Michael acceptors is a well accepted method,[13] steric effects strongly influence this procedure.[14] **The cyclization of 4 generates three contiguous quaternary centers in a single step with remarkable efficiency (73% yield).**[15] Second, the stereoelectronically favored axial approach of the allylic nucleophile leads directly to the generation of only cis fused bicyclic products. Furthermore, in each case two stereoisomers were obtained; **the ratio of these epimers is controlled by the choice of reaction catalyst.**[9] Finally, these results suggest that the fluoride-induced additions proceed via an S_E2' mechanism.[16]

Table II[17] presents several examples where the two reactive centers are connected by only two carbons. Note that under fluoride catalysis, ring closure occurs at the less-substituted terminus of the allyl unit for substrates **5**,**7** and **8**, whereas substrate **6** cyclizes via an S_E2' mechanism to produce a cyclobutane ring.[9] These results suggest that the transition states for the cyclization of substrates 5, 7, and 8 via direct displacement (as in an S_N2-Si reaction) possess less steric and/or strain energy than the related transition states for the S_E2' process. A β-alkyl substituent, however, introduces severe steric interactions between the reactive sites and this facilitating ring closure

via the intrinsically preferred S_E2' process. The failure of compound **8** to undergo fluoride-induced conjugate addition is consistent with related studies using a symmetrical allylsilane unit.[18] In general, the results of the intramolecular Sakurai reactions indicate that the γ-carbon of the allylsilane moiety has difficulty adopting a spatial position favorable for 1,4 attack, and instead 1,2-addition occurs.

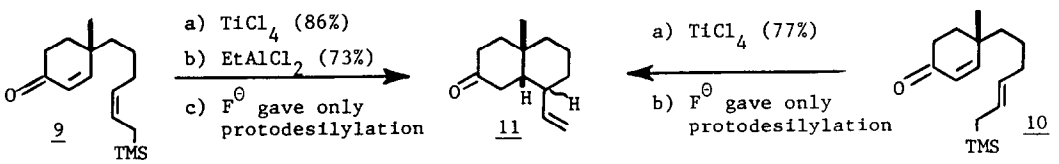
TABLE II [17]



Finally, substrates possessing a four-carbon tether have the potential to form either an eight- or a six- membered ring (Table III[19]). We were not surprised that the Lewis acid-catalyzed cyclizations of **9** and **10** gave exclusively octalones **11**, since the formation of a six-membered ring is kinetically favored over creation of an eight-membered ring by a factor of about 10^4. The failure of the fluoride-induced process to produce bicyclic products is a significant limitation of this ring-forming procedure.

In conclusion, these studies have shown that simple geometric limitations offer a general solution to the regiochemical problems associated with the intramolecular addition of allylsilanes to Michael acceptors. The course of cyclization shows a marked dependency upon the choice of reaction catalysis and ring size.

TABLE III [19,9]



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References:

1. The first example of an intramolecular addition of an intramolecular Sakurai reaction was reported by: Wilson, S.R.; Price, M.F. J. Am. Chem. Soc., **1982**, 104 1124.
2. Majetich, G.; Desmond, R.; Casares, A. M. Tetrahedron Lett., **1983** 24, 1913.
3. We define unsymmetrically substituted allylsilanes as those which have different substitutents on the α- and γ- carbon atoms of the allylic system (the TMS group is on the α-carbon).
4. a) Galli, C.; Illuminati, G.; Mandolini, L.; Tamborra, P. J. Am. Chem. Soc., **1977**, 99, 2591; b) Illuminati, G.; Mandolini, L.; Masci, B. ibid., **1975**, 97, 4960.
5. Baldwin, J. E.; Thomas, R. C.; Kruse, L. I.; Silberman, L. J. Org. Chem., **1977**, 42, 3846.
6. Hosomi, A.; Shirhata, A.; Sakurai, H. Tetrahedron Lett., **1978**, 3043.
7. For numerous examples see: Yamamoto, Y.; Maruyama, K. J. Org. Chem., **1983**, 48, 1565.
8. a) Spectroscopic data obtained for all new compounds were fully consistent with the assigned structures; b) Reaction conditions have not been optimized; and c) All yields are isolated yields.
9. These cyclizations occurred with remarkable diastereoselection. Our rationalization for the selectivity observed will be discussed more extensively in a future manuscript.
10. The allylsilane moiety of enones **1** and **2** was prepared by alkylating the kinetic enolate of 3-ethoxy-2-cyclohexenone (**iii**) with 1-iodo-2-butyne. KH in 1,3-diaminopropane isomerized the triple bond to the terminal position (Brown, C. A.; Yamashita, A.; J. Am. Chem. Soc., **1975**, 97, 891). Generation of the lithium salt of the alkyne, followed by alkylation with trimethylsilylmethyl triflate (Chiu, S. K.; Peterson, P. E. Tetrahedron Lett., 1980, 4047) and Lindlar reduction provided the cis allylsilanes. Alkylation of **iii** with 1-iodo-3-methyl-3-butene, followed by oxidative cleavage of the olefin and condensation with the Wittig salt (1-trimethylsilyl-2-propylidenephosphorane) efficiently generated the required trisubstituted allylsilane moiety for substrates **3** and **4**.
11. For a comprehensive review of allylsilanes in organic synthesis see: Sakurai, H. Pure Appl. Chem., **1982**, 54, 1.
12. In Sakurai's original manuscript[6] the nucleophilic species was described as a free allylic carbanion. We, however, believe that a hypervalent silicon intermediate is more plausible. For examples of penta- or hexacoordinate silicon species see: a) Voronkow, M. G.; Deriglazov, N. M.; Broadskaya, E. I.; Kalistratova, E. F.; Gubanova, L. I. J. Fluorine Chem. **1982**, 19, 299; b) Schomburg, D.; Frebs, R. Inorg. Chem. **1984**, 23, 1378; c) Tamao, K.; Mishima, M.; Yoshida, J.; Takahashi, M.; Ishida, N.; Kumada, M. J. Organomet. Chem., **1982**, 225, 151.
13. For a comprehensive review of methods for preparing quaternary centers see: Martin, S. F. Tetrahedron, **1980**, 36, 419.
14. Unfavorable steric interactions in the initial Michael adduct greatly faciliate the retrograde Michael reaction.[13]
15. Only cycloaddition reactions have proven capable of creating compounds possessing several quaternary centers in a single step; eg., the intramolecular Diels Alder reaction, the photochemical 2 + 2 reaction, and the cycloadditions of allyl cations.
16. Sleezer, B.; Winstein, R.; Young, J.; J. Am. Chem. Soc., **1963**, 85, 1980.
17. Enones **5**→**8** were conveniently prepared using the sequenced described in ref 10 from **iii** or the kinetic enolate of 3-ethoxy-5-methyl-cyclopentenone.
18. A comphehensive study of the fluoride-induced cyclization of a series of substituted cyclohexenones and cyclopentenones has been carried out; MS thesis, Richard Desmond, University of Georgia, **1984**.
19. Enone **9** was prepared by alkylating **iii** with propargyl bromide. Alkylation of the lithium salt of the alkyne with ethyl iodide and alkyne migration permitted the introduction of the allylsilane unit via the sequence described in ref. 10. Alkylation of **iii** with 6-iodo-2-(E)-hexene trimethylsilane led to the preparation of enone **10** using standard transformations.

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