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SELECTIVITY OF BIFUNCTIONAL ANNULATING REAGENTS: ADDITIONAL RULES FOR RING CLOSURE

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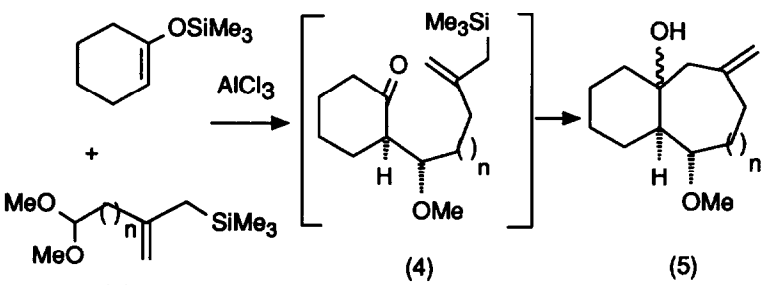
Summary:- From a consideration of the products of cyclisation of allylsilanes it is concluded that stereoelectronic effects play a dominant rôle and that descriptors, similar to those for predicting intramolecular aldol cyclisations, could be used for intramolecular cyclisations of allylic species.

Multi-functional compounds are becoming increasingly important in organic synthesis, not least because of the potential they offer for performing highly efficient multi-bond forming reactions. For instance we have recently introduced a novel bifunctional annulation strategy for the synthesis of carbocyclic compounds. The new process involves the chemoselective *intermolecular* reaction of the acetal function of an allylsilane such as **1-3** with an enolsilane to form stereoselectively the ketone **4**, which is *not*



(4) (5)

(1) n = 0

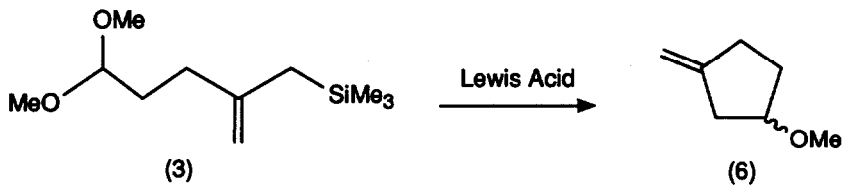
(2) n = 1

(3) n = 2

isolated, but reacts under the same conditions of Lewis acid, to form, via an *intramolecular* ring closure, the annulated product **5**. The stereochemistry about the new ring junction depends upon the ring size of the enol and the chain length of the allylsilane but in most cases is highly selective. By using a range of bifunctional reagents of this type, we have developed a one-pot construction of fused five [1,2], six [3], seven [3], eight [4], and nine-membered [4] rings, and of five, six, and seven-membered spirocyclic ring systems [2,5].

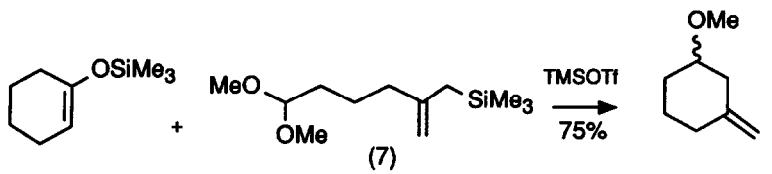
These bifunctional reagents are *inherently* interesting because of the fact that under the above conditions the functionality in such as **3**, and its homologues, could also undergo an irreversible "self destruction" in an intramolecular manner, to form **6** [6]. However their preference for *intermolecular* attack by an enol, followed by sequential attack of the allylsilane on the thus newly formed ketone, provides a more

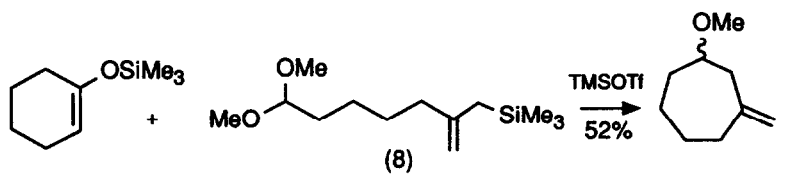
productive pathway for the bifunctional nature of these reagents.

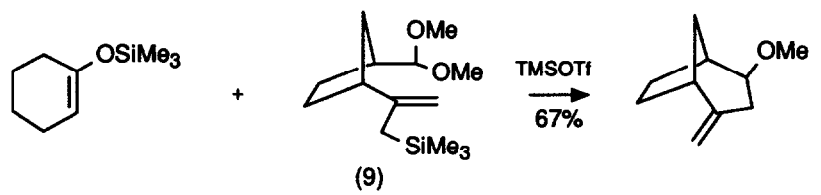


(3) (6)

These observations pose two related questions. Firstly, what is the underlying cause of this selectivity? And secondly, does it extend to longer acetal-allylsilane chains? The lack of intramolecular cyclisation seen for **1**, **2**, and, in particular **3** (which should react the fastest), suggests, that on the grounds of enthalpic and entropic factors [7], intramolecular cyclisation of the next two higher homologues, **7** and **8** [8], should not be favoured either. However, reaction of **7** and **8**, and the cyclic analogue **9**, with TMSOTf in the presence of an enolsilane gave only the products derived from intramolecular cyclisation of the allylsilanes [9]. This indicates that factors beyond enthalpy and entropy, i.e. stereoelectronic effects, are the dominant factors controlling the cyclisation of allylsilanes.

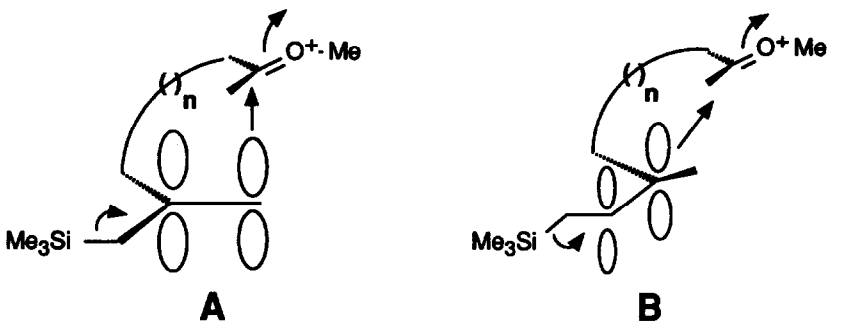






A consideration of the stereoelectronics for cyclisation suggests that the topology **A** (Fig.1) is required for intramolecular reaction. The similarity between this situation and a description of the stereoelectronic requirements of the intramolecular aldol condensation [10] leads us to suggest that analogous descriptors could be used for predicting intramolecular cyclisations of allylic species. Based on this we can describe situation **A** as representing an (Allylendo)-Exo-Trig closure, which for n= 3-5 is not favoured, but for n = 6 and 7 is favoured [10]. Therefore intramolecular cyclisation of **1** to **3** is not kinetically favoured, thus allowing intermolecular enolsilane attack to predominate, whereas **7**, **8**, and **9** undergo a stereoelectronically favoured intramolecular reaction.

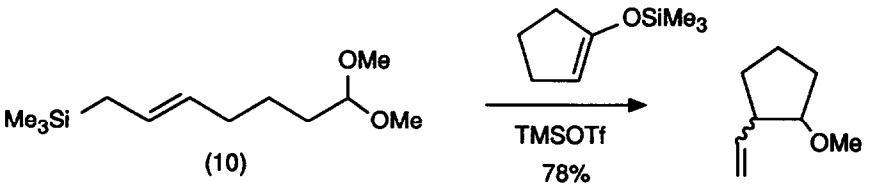
Fig.1



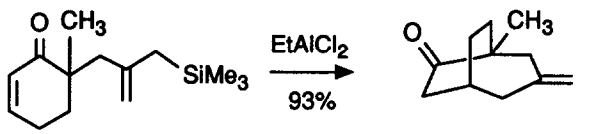
(Allylendo)-Exo-Trig (Allylexo)-Exo-Trig

A corollary to this analysis is that the situation for which we have an (Allylexo)-Exo-Trig ring closure, given by topology **B**, should be favoured for cyclisations of n = 3-7 membered rings [10], and such allylsilanes would not react intermolecularly with enolsilanes.

To test this we prepared and reacted the allylsilane **10**[11] with TMSOTf, in the presence of an enolsilane, and observed exclusive intramolecular cyclisation, as predicted, with no trace of the product derived from attack by the enolsilane.



5-(Allylexo)-Exo-Trig

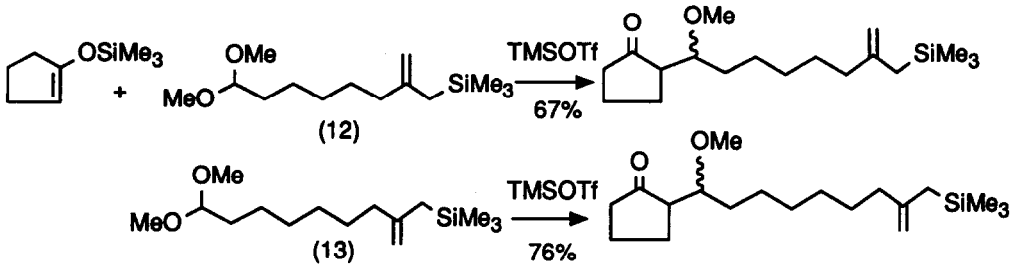


(11)

5 v 7-(Allylendo)-Exo-Trig

Additionally, the literature does show that the importance of stereoelectronic effects in intramolecular closure of allylic compounds has been realised[12], but not described in this more precise manner, that considers the structure of the allylsilane. For example, closure of the enone **11**[13], which displays competition between a 5- and a 7-(Allylendo)-Exo-Trig reaction gives only the latter cyclisation as predicted by these additional rules for ring closure.

Not unexpectedly, a brief investigation of even longer acetal allylsilane chains **12** and **13**, results once more in preferential attack of an enolsilane. Presumably in these cases the entropic factors for intramolecular attack now begin to dominate and "self destruction" becomes a slow process. The products of this selectivity are potentially highly useful for the synthesis of medium and large rings.



From these results we conclude that the selectivity shown by these bifunctional annulating reagents, under *electrophilic* conditions, is controlled mainly by the stereoelectronic requirements for intramolecular cyclisation of allylsilanes. These are such that for (Allylendo)-Exo-Trig cases, n = 3-5 closure is disfavoured to an extent that allows competitive intermolecular attack of an enolsilane to predominate. In contrast 6 and 7-(Allylendo)-Exo-Trig and 3 to 7-(Allylexo)-Exo-Trig will all be favoured processes which precludes intermolecular attack by an enolsilane.

To test this idea more thoroughly we are currently studying the competitive cyclisation of a range of additional allylsilane based bifunctional reagents. Furthermore, these controlling factors should extend to reactions of bifunctional reagents that possess other reactive electrophilic and nucleophilic centres, and we are studying this possibility. However, in the case of 3 to 5-(Allylendo)-Exo-Trig closures, we can already benefit from the synthetic consequences of this selectivity, as outlined above.

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REFERENCES AND NOTES.

1. Lee, T.V; Boucher, R.J; Porter, J.R; Taylor, D.A, *Tetrahedron*, **1988**, 44, 4233.
2. Lee,T.V; Richardson, K.A; Taylor, D.A, *Tetrahedron Letters*, **1986**, 27, 5021 and Lee, T.V; Ellis, K.L; Richardson, K.A; Visani, N, *Tetrahedron* **1989**, 45, 1167.
3. Lee, T.V; Boucher, R.J; Porter, J.R, *Tetrahedron* **1989**, 45, 5887.
4. Lee, T.V; Roden, F.S; Porter, J.R, *J.Chem.Soc., Perkin Trans. 1*, **1989**, 2139.
5. Lee, T.V and Cregg, C, *Synlett* ..... submitted for publication.
6. Fleming, I; Pearce, A; Snowden, R.L, *J. Chem. Soc. Chem. Communs*. 1976, 182.
7. Eliel. E, *Stereochemistry of Carbon Compounds*, pp 198-202.
8. All allylsilanes, except **10**, were prepared according to:- Lee,T.V; Channon,J; Cregg,C; Porter,J.R; Roden,F.S; Yeoh,H, *Tetrahedron* **1989**, 45, 5877.
9. All new compounds gave satisfactory analytical and/or spectroscopic data.
10. Baldwin, J.E and Lusch, M.J, *Tetrahedron*, **1982**, 38, 2939, and references therein.
11. Prepared according to Fleming, I and Paterson, I, *Synthesis*, 1979, 446.
12. Majetich, G; Defauw, J; Ringold, C, *J. Org. Chem.*, **1988**, 53, 50.
13. Majetich, G in *Organic Synthesis: Theory and Application*, Vol.1, p. 173, (JAI Press, **1989**), and references therein.

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