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On the stereochemical course of the addition of allylsilanes to aldehydes

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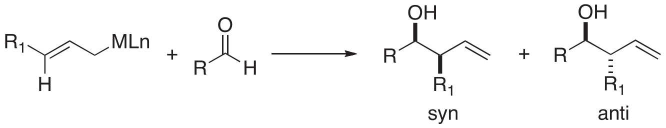
ABSTRACT

Model compounds **3** and **5** have been studied to determine the orientation of the reacting double bonds in the transition state of the allylmetal–aldehyde addition. These models were designed to remove any intrinsic steric bias for the formation of the bicyclic products that would obfuscate a stereoelectronic contribution to the transition states. Model system **3** revealed a modest preference for the synclinal transition state, albeit in very low yields. Model system **5** underwent selective and largely Lewis acid independent cyclization primarily via a synclinal transition state. The high proximal selectivity observed in these cyclizations likely reflects the selectivity of an unhindered allylmetal–aldehyde addition for the synclinal transition state and results from a stereoelectronic preference, not an intrinsic steric bias, for the synclinal arrangement of double bonds.

1. Introduction

The controlled construction of stereocenters in open-chain systems is of primary importance in the synthesis of acyclic natural and non-natural products. Many methods have been developed recently to synthesize the long sequences of stereocenters present in these molecules including the addition of allylmetal reagents to aldehydes.[1] The utility of the allylmetal–aldehyde addition is partly derived from the high yield, excellent site selectivity, and the mild conditions under which it can be employed.

The reaction of a substituted allylmetal reagent with an aldehyde can result in the formation of diastereomeric homoallylic alcohols (Scheme 1).[2] The allylmetal–aldehyde addition has proven to be successful with a wide variety of metals including boron,[3] tin,[4] silicon,[5] chromium,[6] and titanium.[7] The diastereoselectivity observed in the Lewis acid mediated allylmetal–aldehyde additions is dependent upon the allylmetal used. This dependence has been classified into three groups that relate the stereochemical outcome of the reaction to the geometry of the double bond.[1f,8] Type 1 reactions wherein the *syn*/*anti* ratio reflects the *Z*/*E* ratio of the starting allylmetal (B, Al, Sn); Type 2 reactions wherein the reaction is *syn*-selective independent of the geometry of the allylmetal (Sn, Si); and Type 3 reactions wherein the reaction is *anti*-selective independent of the geometry of the allylmetal (Cr, Ti, Zr).



Scheme 1.

Proposals for transition state geometry have been set forth for all three types of reactions,[1f,9] but those that fall in the Type 2 family are the focus of the studies described herein. Proposals for Type 2 reactions invoke an open chain arrangement of the reacting species.[1f] The two limiting hypotheses identify the torsional angle between the double bonds (synclinal (60°) and antiperiplanar (180°)) and minimization of nonbonded interactions as key features for relative diastereoselection (Scheme 2). The internal induction process is governed primarily by the relative disposition of the metal electrofuge and the aldehyde (*anti* or *syn* S_E') in the transition structure (Scheme 3). Thus, the orientation of the double bonds and the location of the metal in the transition structure uniquely define the stereochemical outcome of the reaction.

Previous investigations from these laboratories have described the synthesis and cyclization of a model system that *unambiguously* determined the stereochemical course of addition in an allylsilane–aldehyde reaction.[10] However, criticisms of this model focused on a potential inherent bias given the diastereomeric relationship of the products. We therefore undertook the investigation of two new model systems that remove this bias.

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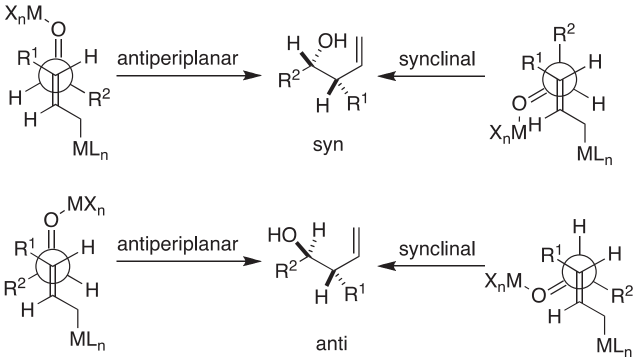
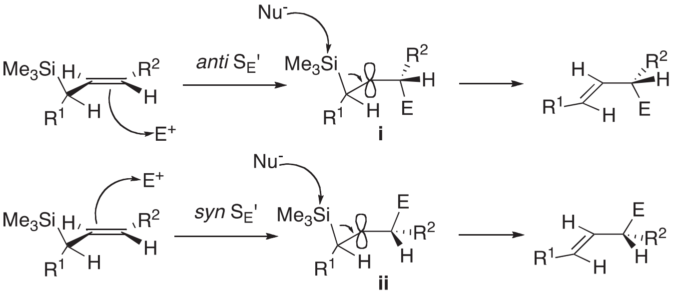


Scheme 2.



Scheme 3.

2. Background

The Lewis acid-mediated addition of electrophiles to allylsilanes has been extensively studied.[5] In most cases the addition of an electrophile to an allylsilane is an *anti* S_E' process. In the ground state, simple allylsilanes are known to prefer the conformation where the small substituent H eclipses the double bond.[11] The electrophile can then approach the double bond from the same side as the allylmetal (*syn* S_E') or from the side opposite the allylmetal (*anti* S_E'). The configuration of the newly formed stereogenic center is therefore dependent upon the directionality of attack (Scheme 3). After attack of the electrophile on the double bond only a slight rotation of the C–C bond is necessary for the formation of the intermediate **ii**, which is stabilized by hyperconjugation with the silicon atom (Scheme 3).[12] The silyl group is then released, resulting in the stereoselective formation of a *trans*-double bond.

The site selectivity and stereochemical course of electrophilic additions to allylsilanes have been modeled computationally by Hehre.[13] In this study, the conformational profile of 2-silylbut-3-ene was determined and three energy minima were observed (Chart 1). In the two most stable conformers the C–Si bond is perpendicular to the C–C double bond. The interaction of a point charge (α proton) and the allylsilane was next studied in the three low energy conformers. By using this 'test' electrophile an electrostatic potential map was developed. The electrophilic attack onto the two low energy conformers of 2-silylbut-3-ene, **iii** and **iv**, was shown to occur *anti* to the silyl group. In the high-energy conformer **v**, attack will occur *anti* to the methyl group.

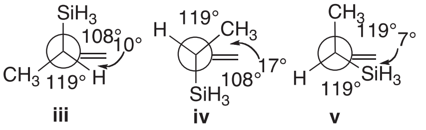
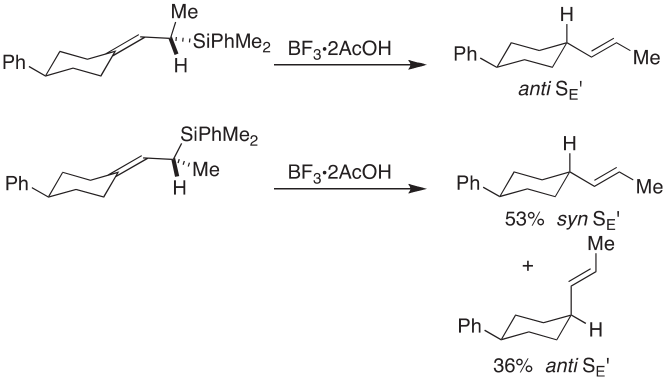


Chart 1.

The stereochemical course of the addition of electrophiles to allylsilanes has been studied to establish the position of the silicon electrofuge in the transition structure of these reactions.[14] In an early study, Fleming examined the additions of electrophiles to stereochemically-defined allylsilanes, which were constrained in either a five or six-membered ring.[15,16] The addition of an electrophile to these substrates resulted in the formation of products from both *anti* and *syn* S_E' pathways. Fleming concluded that the stereochemical constraints of the ring systems were likely the dominant influence in the observed stereoselectivity of these reactions. Therefore, these models cannot be used to elucidate the intrinsic preference of the S_E' reaction.

Fleming expanded the study of the S_E' reaction to include the use of acyclic allylsilanes.[17] In protiodesilylation experiments the allylsilane cleanly gives products from an *anti* S_E' reaction whereas the diastereomeric allylsilane affords a mixture of both *syn* and *anti* S_E' products (Scheme 4). Results from a deuteration study indicate that in addition to the *anti* selectivity of the allylsilane, the cyclohexyl ring has a preference for axial protonation. When this axial preference is in opposition to the *anti* selectivity of the allylsilane, the molecule will find an alternative reaction where the stereospecificity is lost.



Scheme 4.

Wetter[18] and Kitching[19] have also examined the stereochemical course of the S_E' reaction. In the studies performed by Wetter the reaction of a disilylalkene proceeds through either the *syn* or *anti* S_E' pathways depending upon the electrophile. Kitching examined the S_E' reaction of some cyclohexenylsilanes, -germanes, and -stannanes. For all three of the allylmetals, the results indicate that attack by proton occurred with *anti* selectivity except when a *trans*-4-*tert*-butylcyclohex-2-enyl derivative was used. In these reactions the approach of the electrophile *anti* to the metal is impeded by the presence of the *tert*-butyl substituent.

Kumada and Hayashi have carried out extensive studies to define all of the stereochemical features of the addition to aldehydes with titanium tetrachloride (Scheme 5).[20] The results from this study can be summarized as follows:[1] the enantiomeric excess of the products was essentially the same as the starting materials;[2] the *E*-allylsilanes reacted with high diastereoselectivity (*syn*/*anti*, 92:8–99:1);[3] the *Z*-allylsilanes were less selective with the resulting *syn*/*anti* ratio of products dependent upon the structure of the aldehydes (*syn*/*anti*, 50:50–99:1). The configuration of the products obtained for all of the reactions studied is interpreted in terms of an *anti* S_E' reaction. To explain the observed selectivities an acyclic transition structure was proposed in which the double-bonds are arranged in an antiperiplanar relationship. The observed diastereoselectivities are proposed to result from a minimization of steric interactions in the transition structures (Scheme 6).