159. On the Stereochemistry of Allylmetal-Aldehyde Condensations[1])

Preliminary Communication

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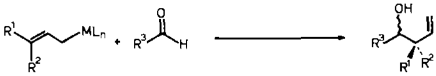
Summary

The stereochemical course of the intramolecular allylsilane-aldehyde condensation of **1a** has been investigated. A modest preference for the product arising from a synclinal orientation of double bonds was observed with *Lewis*-acid catalysts. Cyclization induced by fluoride ion resulted in stereochemical reversal.

The stereoselective formation of C–C bonds between prochiral centers is one of the most important processes in synthetic organic chemistry[3]), and is becoming of greater significance in relation to macro- and acyclic molecules adorned with contiguous chiral centers [2]. One of the more synthetically useful examples of this reaction is the condensation of allylmetal derivatives with aldehydes to give homoallylic alcohols [3] *(Scheme 1)*. This reaction succeeds with a wide variety of metals (B, Al, Si, Ti, Cr, Zr, Sn)[4]) and the stereochemical outcome is, to some extent, dependent on the nature of the metal and the reaction conditions. This dependence can be classified into three groups[5]).

Scheme 1



Type 1: the *ul*/*lk* ratio reflects the *(Z)*/*(E)* ratio in the allyl moiety (B, Al, Sn).
Type 2: *ul*-selective reactions independent of allyl geometry (Sn, Si).
Type 3: *lk*-selective reactions independent of allyl geometry (Ti, Cr, Zr).

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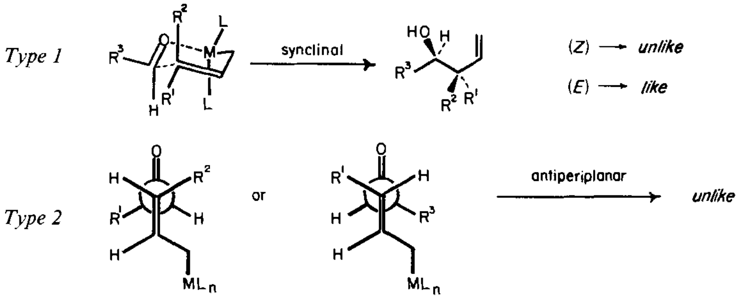
[3]) For a recent discussion of the variety of reaction included in this process see [1].

[4]) In addition to those examples cited in [3] see [4].

[5]) The nomenclature employed has been proposed recently [5] to unambiguously define relative stereochemistry and to recognize topological families.

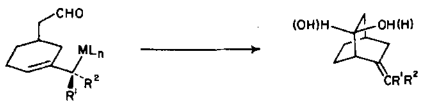
Transition state structures have been proposed for all three types [3a] *(Scheme 2)*. These proposals invoke very different geometries of reacting double bonds to explain stereoselectivity. Thus, the rigid, chair-like transition state^{6}) in *Type 1* reactions requires a synclinal orientation of double bonds while the 'open' or 'extended' [7] transition states for *Type 2* reactions suggest an antiperiplanar relationship. *Type 3* reactions with Cr[4n,o], Zr[4m] and Ti[4j-l] derivatives are suggested to involve preequilibration to the more stable *(E)*-double bond geometry followed by reaction *via* a cyclic *(Type 1)* transition state^{7}). However, nearly all cases examined involve intermolecular reactions, precluding an unambiguous assignment of transition-state geometry. We have, therefore, initiated a program to study the stereochemistry of these reactions in a system which defines all stereochemical relationships and examined the dependence of transition state geometry as a function of metal and reaction conditions.

Scheme 2



The general model selected (**1**, *Scheme 3*) incorporates two stereochemical variables and defines, *simultaneously*, relative topicity [5] and S'_E-stereochemistry^{8}). Inspection of *Dreiding* models of **1a** reveals that the two limiting reactive conformations of the aldehyde carbonyl group correspond to antiperiplanar *(lk)* and synclinal *(ul)* transition-state geometries. We now report: *1)* a versatile synthesis of **1a** amenable to the incorporation of various organometallic groups ML_n, *2)* stereochemical analysis of the products **2**, and *3)* preliminary results involving the relative topicity of cyclization.

Scheme 3



1a $R^1 = R^2 = H$, $ML_n = Si(CH_3)_3$ **2**
b $R^1 = R^2 = H$, $ML_n = Sn(Bu)_3$

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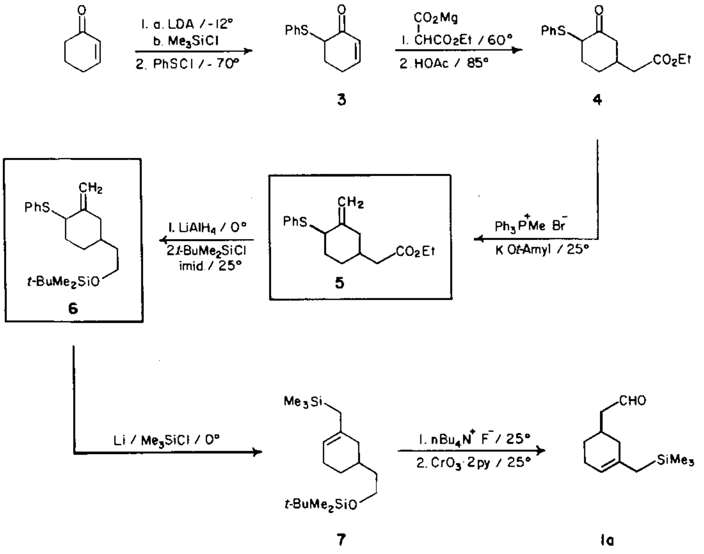
^{6}) For a discussion of the steric and energetic details of this arrangement in the context of the aldol condensation see [6].

^{7}) Recent ^{1}H-NMR studies suggest that $(C_5H_5)_2Zr\ (CH_2CH{=}CHCH_3)_2$ complexes are η' (σ-bound) and allylically labile [4m].

^{8}) The stereochemistry of S_E2'-substitution with allyl organometallics has been addressed with both experimental (Si[4a-d] [8] [9], Sn [10] and theoretical [11] methods.

The synthesis of **1a** *(Scheme 4)* highlights branch points (boxed structures) where intermediates can be used to incorporate other metals. Phenylsulfenylation [12] of 2-trimethylsilyloxy-1,3-cyclohexadiene [13] afforded **3**[9] (79–90% yield) which was transformed into **4**[9][10] (64–80%) by the method of *McMurry et al.* [14]. Methylidenation of **4** under protic conditions [15] (49–88%) afforded **5**[9] which serves as a precursor for allylsilanes and -stannanes. $LiAlH_4$-reduction of **5** and protection of the resulting alcohol produced **6**[9] (81–93%) also a precursor for allylic Cr, Zr, and Ti organometallics. Reductive silylation [16] of **6** afforded allylsilane **7**[9] as a single regioisomer (65–75%). Selective deprotection of **7** with fluoride ion and *Collins* oxidation [17] afforded **1a**[9] (65–67%).

Scheme 4



The model system was surprisingly stable, surviving chromatography (SiO_2) and distillation (120°/0.07 Torr), but cyclized readily in the presence of *Lewis* acids. The product mixtures were analyzed by capillary gas chromatography[11] and the stereochemical assignments made by coinjection with independently prepared samples[12][13].

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[9] All new compounds have been characterized by ^1H-NMR (220 or 360 MHz), IR, mass spectrometry and combustion analysis (± 0.3%).

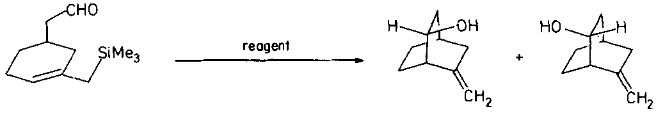
[10] A 3:2 mixture of diastereoisomers which was not separated.

[11] Column: 23 m *OV-101. WCOT.*

[12] Authentic samples of *syn*- and *anti*-**2a**[9] ($R^1 = R^2 = H$) were obtained by $NaBH_4$-reduction of 6-methylidenebicyclo[2.2.2]octan-2-one [18] and flash-chromatographic separation of the alcohols. Stereochemistry was assigned based on the slope of LIS of the methylidene group with $Eu(fod)_3$: *syn*-**2a**, 6.61 ppm/equiv; *anti*-**2a**, 2.81 ppm/equiv.

[13] *syn*-**2a** has also been prepared by unambiguous synthesis, *D. Gremaud*, unpublished results from these laboratories.

Table. *Cyclization of* **1a**



1a *syn*-**2a** *anti*-**2a**

Reagent	Solvent	Temp (°C)	% *syn*	% *anti*
$SnCl_4$	CH_2Cl_2	–70	49	51
Et_2AlCl	CH_2Cl_2	–70	66	34
$FeCl_3$	CH_2Cl_2	–70	70	30
$AlCl_3$	CH_2Cl_2	–70	79	21
$BF_3 \cdot OEt_2$	CH_2Cl_2	–70	80	20
$nBu_4N^+F^-$	THF	67	30	70

The results of intramolecular cyclization[14]) are summarized in the *Table.* To obtain clean reactions free from skeletal rearrangement [20], quenching at –70° with NaOH-solution was necessary[15]). Control experiments with TMS-ethers of *syn*- and *anti*-**2a** demonstrated that the product ratios represent kinetically controlled reactions. The predominance of the *l*-diastereomer (*syn*-**2a**) with *Lewis* acids resulting from a synclinal transition state geometry (*ul*-topicity) is contrary to expectation based on recent results with optically active silanes [4a, d]. *Kumada et al.* invoke antiperiplanar double bond alignments to explain the *ul*-selectivity *(Scheme 2),* but these workers unambiguously establish only the relative (and absolute) topicity, not the angular disposition of reactants. The dependence of stereoselectivity on *Lewis* acid serves as a cautionary note; any mechanism claiming to explain the stereochemistry of these reactions must intimately incorporate the reagents which bring them to bear. In our system there is a crude correlation between covalent radius of the *Lewis* acid metal atom[16]) and the stereoselectivity, *i.e.* the larger the metal, the less selective the reaction. Accordingly we have examined molecular models of the reactive complex **1a** · *Lewis* acid for $SnCl_4$ and BF_3[17]). Assuming association gives the *(E)*-complex[18]) *(Scheme 5)* it is seen that the major steric contribution arises from interaction between the *Lewis* acid and the

Scheme 5

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[14]) For other intramolecular allylsilane-aldehyde (ketone) cyclizations see [19].

[15]) Even with this precaution $TiCl_4$ gave only rearranged products.

[16]) Covalent radii (Å) B, 0.82; Fe, 1.17; Al, 1.18; Sn, 1.41.

[17]) While BF_3 forms stable 1:1 complexes with aldehydes [21a, b] $SnCl_4$ prefers a 1:2 stoichiometry [21c–e].

[18]) Little is known about the stereochemistry of these complexes, for recent speculations see [22]. Protonated aldehydes prefer the *(E)*-configuration (H-atoms *cis*) [23].

(trimethylsilyl)methylene group. Indeed, it is surprising that *syn*-products are observed at all for $SnCl_4$. We interpret this to suggest a stereoelectronic advantage for synclinal orientation of reactants under electrophilic conditions. The reversal in stereoselectivity in the fluoride-induced cyclization[19]) suggests a change in mechanism with attendant changes in stereoelectronic demands. Nucleophilic attack on the aldehyde by the allyl fluorosiliconate or allyl anion [24] most probably prefers a trajectory not unlike that suggested by *Burgi et al.* [25]. This is readily accommodated only in the antiperiplanar alignment (*lk*-topicity) of double bonds.

Work is in progress on the synthesis of the analogous allylstannane **1b** and the complete model system with a deuterium label (R^1 or $R^2 = D$). The stereochemical results from a model which eliminates the diastereoisomeric bias inherent in **2** will be reported.

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