THE UNSYMMETRICAL SILAKETAL AS A NEUTRAL, REMOVABLE TETHER FOR EFFECTING INTRAMOLECULAR DIELS-ALDER REACTIONS.

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Summary: Silaketals, in which reactive dienes and dienophiles are linked, can participate in intramolecular Diels-Alder reactions to produce products with a high degree of stereocontrol and with regiochemistry opposite to that predicted by bond polarization models.

Intramolecular reaction processes which result from linking the reactive species frequently lead to higher expression of regio and stereochemical preferences¹. The subsequent removal of the linking species may produce compounds in which bond formation has been achieved with enhanced regio- and stereochemical control. However, tethers which impose intramolecularity frequently interfere with the bond forming process. In Diels-Alder chemistry, removable tethers such an esters², ethers³, amides⁴, ureas⁵, and carbamates⁵, have been examined and shown to have variable impact in controlling regio- and stereochemistry. The use of silaketals as tethers in the IntraMolecular-Diels-Alder reaction (IMDA) represents a novel means of achieving intramolecularity. It has demonstrated that such neutral, removable groups can convey a high degree of regio- and stereocontrol in the IMDA reaction^{6,7,8}.

We have recently described the synthesis of asymmetric silaketals based on stepwise functionalization of dichlorodiphenylsilane with different alcohols and phenols⁹. Similarly, enols^{10,11} have been transformed to silaketals. It was found that an appropriately linked silaketal (eq.1), derived by initial treatment of dichlorodiphenylsilane with ethyl 4-hydroxycrotonate¹² and subsequent treatment with the lithium enolate of butenal, could be induced to cyclize to give a mixture of 1,3-diols <u>3a</u> and <u>3b</u> (3:2) after deprotection of the silicon tether by treatment with fluoride¹³.



However, the use of diphenylsilaketals was unsatisfactory as a general synthetic operation due to difficulty in independently functionalizing diphenyldichlorosilane. This difficulty was also reported by Craig⁸. Allylic alcohols led to substantial (\geq 30%) symmetrical silaketal formation, also one of the products, <u>2b</u> trans, (bicyclo [4.4.0] siladioxadecene) was found to be unstable to chromatography. Therefore, we examined di-t-butylsilaketals as linking species. It is known that displacement of chloride by alcohols from di-t-butyldichlorosilane is very sluggish. Bis functionalization of di-t-butylsilanes has been accomplished through their conversion to silyl ditriflates¹⁴. Thus a logical step to achieve

independent bis-functionalization of the silane was through the formation of a di-t-butylchlorosilane monotriflate. This was achieved (eq.2) by selective protolysis of di-t-butylchlorosilane with triflic acid at low temperature, which led to the desired product 5a in good yield¹⁵ (b.p.=60°C, 0.3mm Hg). The subsequent displacement of the chloride to produce a ditriflate 5c is slow and requires elevated temperature.

$$\overset{\mathsf{Cl}}{\underset{\mathsf{H}}{\times}} \overset{\mathsf{Cl}}{\underset{\mathsf{I}_{\mathsf{b}}}{\times}} \overset{\mathsf{CF}_{\mathsf{3}}\mathsf{SO}_{\mathsf{3}}\mathsf{H}} (2.0 \text{ eq}) \xrightarrow{\mathsf{Cl}} \overset{\mathsf{Cl}}{\underset{\mathsf{I}_{\mathsf{b}}}{\times}} \overset{\mathsf{Cl}}{\underset{\mathsf{I}_{\mathsf{b}}}{\times}}} \overset{\mathsf{Cl}}{\underset{\mathsf{I}_{\mathsf{I}}}{\times}}} \overset{\mathsf{Cl}}{\underset{\mathsf{I}_{\mathsf{I}}}{\times}}} \overset{\mathsf{Cl}}{\underset{\mathsf{I}_{\mathsf{I}}}{\times}}} \overset{\mathsf{Cl}}{\underset{\mathsf{I}_{\mathsf{I}}}{\times}}} \overset{\mathsf{Cl}}{\underset{\mathsf{I}_{\mathsf{b}}}{\times}}} \overset{\mathsf{Cl}}{\underset{\mathsf{I}_{\mathsf{I}}}{\times}}} \overset{\mathsf{Cl}}{\underset{\mathsf{I}_{\mathsf{I}}}{\times}} \overset{\mathsf{Cl}}{\underset{\mathsf{I}}}} \overset{\mathsf{Cl}}{\underset{\mathsf{I}}}}} \overset{\mathsf{Cl}}{\underset{\mathsf{I}_{\mathsf{I}}}{\times}}} \overset{\mathsf{Cl}}{\underset{\mathsf{I}}}} \overset{\mathsf{Cl}}{\underset{\mathsf{I}}}} \overset{\mathsf{Cl}}{{\mathsf{I}}}} \overset{\mathsf{I}_{\mathsf{I}}}{\ast}} \overset{\mathsf{Cl}}{{\mathsf{I}}}} \overset{\mathsf{I}_{\mathsf{I}}}{{\mathsf{I}}}} \overset{\mathsf{I}_{\mathsf{I}}}{{\mathsf{I}}}}} \overset{\mathsf{I}_{\mathsf{I}}}{{\mathsf{I}$$

Due to the differing reactivity of the chloro and triflate groups, selective mono-functionalization was accomplished by displacing the triflate with the desired allylic alcohol, ethyl 4-hydroxycrotonate, which led to the chromatographically stable alkoxychlorosilane, <u>6</u> (Scheme 1). Reaction of <u>6</u> with a pre-formed lithium enolate of <u>7a</u> or <u>7b</u>, obtained by transmetallation of trimethylsiloxybuta-1,3-diene¹⁶ with methyl lithium, produced the requisite silaketals <u>8a</u> and <u>8b</u>. <u>SCHEME 1</u>



REGIOCHEMISTRY OF THE SILAKETAL IMDA REACTION

The intramolecular cycloaddition of <u>8a</u> in toluene at 160°-180°C, in a sealed tube, resulted in a -90% yield of <u>13a</u> and <u>13b</u>, (eq. 3), respectively, in a ratio of 9:1 as determined by NMR¹⁹. Both the regioisomers result from "head to tail" cyclization. In contrast, the <u>BIM</u>olecular <u>Diels-Alder</u> reaction (<u>BIMDA</u>) of diene <u>9</u>, (eq. 4) bearing a strong electron donor trimethylsilyloxy substituent and electron deficient dienophile <u>10</u> led us to expect that ortho¹⁷ adducts (head to head transition state) would result predominantly. In fact, only the compounds <u>11a</u> and <u>11b</u> (45:55) were found and no trace of the meta adduct <u>12</u> (resulting from a head to tail transition state) was observed. The polarisation of the diene/dienophile system, as well as the steric encumbrance of the two silicon protecting groups, inhibit attainment of this regiochemistry. This result and others¹⁸ show that it is difficult to induce a diene/dienophile system to react "head to tail". Constraining the system so that it is topologically impossible to achieve a "polarity preferred transition state" as seen in compounds like 8, achieves this regiochemical reversal.



STEREOCHEMISTRY OF THE SILAKETAL IMDA REACTIONS

The products of the Diels-Alder reaction of <u>8a</u> (eq. 3, 13a/13b 9:1) were separated by chromatography and the stereochemistry analysed¹⁹ by NMR. Compound <u>13a</u> was determined to have a <u>trans</u> relationship at the ring fusion which results from an <u>endo</u> transition state. This results in an all equatorial disposition of substituents of the final product. The favored <u>endo</u> cyclisation can be attributed to less steric restriction in the approach of the diene/dienophile in this transition state. The minor constituent (<u>13b</u>) was found to have a <u>cis</u> ring fusion resulting from an <u>exo</u> transition state. As seen in <u>Scheme 2</u> the <u>exo</u> transition state is encumbered by diene substituents and the bulky substituent on silicon. To further substantiate this interpretation, the analogous system with a methyl substituent at the C-2 position of the diene <u>8a</u>, was synthesized (<u>8b</u>) as described previously and subjected to the same cyclisation conditions. A comparable yield was obtained, however, the exclusive product was found to be <u>14a</u>, resulting from <u>endo</u> cyclisation only¹⁹. Evidently in this case, the steric factors imposed (Scheme 2) by the additional methyl group are sufficient to completely eliminate the <u>exo</u> transition state.

SCHEME 2

In summary, the unsymmetrical di-t-butyl silaketal is a thermally robust species, capable of linking a siloxydiene and a dienophile. As a neutral tether for effecting intramolecular reactions, it leads to products which are themselves, silaketals. These stable protected 1,3- diols can be futher functionalized or deprotected using published procedures^{13,14}. This silicon tether is a useful tool to be exploited for regio and stereocontrol in Diels-Alder reactions. It also has additional potential in other intra-molecular processes, such as radical cyclization²¹, which are currently being investigated.

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- 19. ¹H NMR (CDCl₃, δ =ppm) of <u>13a</u>: 5.66 (m,2H,H₄,H₅); 4.47 (m,1H,H₆); 4.31 (m,2H,-CO₂-<u>CH₂</u>CH₃); 4.09 (dd,1H,H₈,J_{H8-H7}=4Hz,J_{H8-H8}=10Hz); 3.72 (dd,1H,H₈,J_{H8-H7}=10Hz.); 2.78-2.50 (m,4H,H₇,H₃,H₃:H₂); 1.50 (t,3H,ethyl ester); 1.2(s,9H,t-Bu); 1.0 (s,9H,t-Bu). NOE showed a strong interaction between proton 2a, 6a, 8a, indicating 1,3 diaxial configuration. ¹H NMR (CDCl₃, δ =ppm) of <u>13b</u>: 5.75 (m,2H,H₄,H₅); 4.72 (m,1H,H₆); 4.18 (m,2H,-CO₂-<u>CH₂-CH₃); 4.02</u>

(d,2H,H₈,H₈), 2.88 (ddd,1H,H₂); 2.50 (ddt,1H,H₇); 2.35 (m,1H,H3); 2.23 (m,1H,H₃·); 1.25 (t,3H,ethyl ester); 1.03 (s,9H,t-Bu); 1.00 (s,9H,t-Bu).

- 20. ¹H NMR (CDCl₃, δ =ppm) of <u>14a</u>: 5.39 (m,1H,H₄); 4.46 (d,1H,H₆,J_{H6-H3a}=8.5hz); 4.58 (m,2H,-CO₂<u>CHH</u>CH₃); 4.11 (dd,1H,H_{8e},J_{H8e-H7}=4,3Hz,J_{H8e-H8a}=10.6Hz); 3.83 (dd,1H,H_{8a},J_{H8a-H7}=J_{H8a-H8e}=10.9Hz); 2.41-2.1 (m,4H,H₂,H_{3a},H_{3a},H₇); 1.66 (s,3H,Me-); 1.21 (t,3H,ethyl ester); 1.1 (s,9H,t-Bu); (0.90 (s,9H,t-Bu).
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