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Using a Temporary Silicon Connection in Stereoselective Allylation with Allylsilanes: Application to the Synthesis of Stereodefined 1,2,4-Triols

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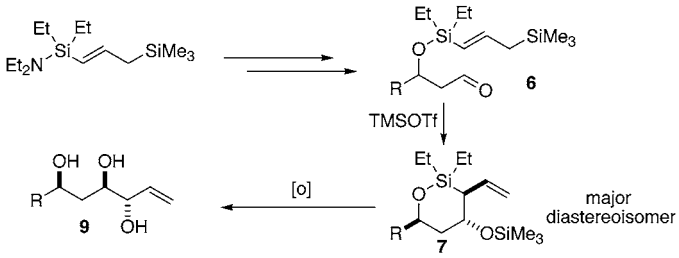
ABSTRACT



Treatment of aldehyde 6 with TMSOTf, in the presence of a Brønsted acid scavenger, effects an intramolecular allylation to provide the oxasilacycle 7 as the major diastereoisomer. Tamao oxidation of the C–Si bond in 7 affords the corresponding 1,2,4-triol 9.

The reaction between an aldehyde and an allylmetal to provide a homoallylic alcohol remains one of the most powerful and widely used methods for the stereoselective formation of C−C bonds.[1] Nucleophilic allyl reagents can be grouped into three classes according to the mechanism by which they react with aldehydes.[1,2] This classification is not only a function of the metal; it is also dependent on the coordinating ligands, the presence of additives, and the reaction conditions. We are interested in employing so-called Type II allylmetals, specifically allyltrialkylsilanes, in stereoselective synthesis.[1c,3] These are potentially very attractive reagents for synthesis, owing to their ease of preparation, relatively high stability, and low toxicity. Unfortunately, the inherently low nucleophilicity of allyltrialkylsilanes offsets some of these advantages. Thus, to use these reagents as nucleophiles in synthesis, it is usually necessary to either increase the nucleophilicity of the allylsilane (e.g. with fluoride[4]), or improve the reactivity of the participating electrophile (usually with a Lewis acid). This requirement, in combination with the weak Lewis acidity of the metal center, has important ramifications for the reaction mechanism: allyltrialkylsilanes invariably[5] react with aldehydes through an open, acyclic T. S.[1c] This type of T. S. is poorly defined when compared with the closed Zimmerman-Traxler T. S.s through which reactions between Type I allylmetals (e.g. allylboranes) and aldehydes proceed.[1b] Nevertheless the reaction between a Type II allylmetal and an aldehyde can

(1) (a) Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763−2794. (b) Roush, W. R. in *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Volume 2, Chapter 1.1, pp 1−53. (c) Fleming, I. in *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Volume 2, Chapter 2.2, pp 563−593. (d) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207−2293.

(2) Denmark, S. E.; Weber, E. J. *Helv. Chim. Acta* **1983**, *66*, 1655−1660.

(3) Fleming, I.; Dunoguès, J.; Smithers, R. *Org. React.* **1989**, *37*, 57−575.

(4) Hosomi, A.; Shirahata, A.; Sakurai, H. *Tetrahedron Lett.* **1978**, 3043−3046.

(5) Silacyclobutane systems would be an important exception: (a) Denmark, S. E.; Griedel, B. D.; Coe, D. M.; Schnute, M. E. *J. Am. Chem. Soc.* **1994**, *116*, 7026−7043. (b) Myers, A. G.; Kephart, S. E.; Chen, H. *J. Am. Chem. Soc.* **1992**, *114*, 7922−7923.

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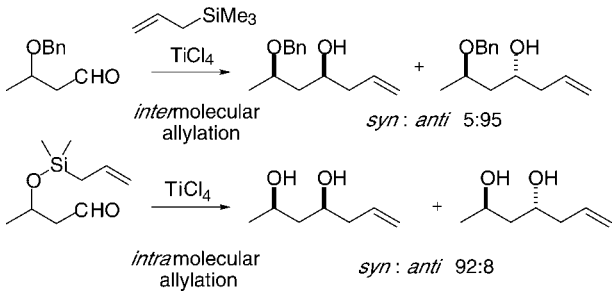
sometimes be highly diastereoselective.[1,3] Moreover, chiral Lewis acids can render the reaction highly enantioselective which further increases the synthetic utility of these reagents.[1a,6]

A number of approaches have been devised for overcoming some of the shortfalls associated with allylsilanes. One of the most successful is to modify the ligands on the allylic silicon center such that reaction proceeds through a closed T. S. and behaves more like a Type I allyl reagent.[7] We are interested in retaining the alkyl ligands around the silicon and investigating an alternative strategy, namely to use a temporary connection, for controlling the stereoselectivity of an allylation reaction.[8] By employing a silyl ether connection to temporarily tether the two reacting partners, a sequence of tether formation, followed by reaction, and finally tether cleavage, provides a product that is the result of a net *inter*molecular reaction, yet one that has benefited from all the advantages associated with an *intra*molecular process. Thus, by using this approach we will have an allylsilane that retains the attractive properties of Type II reagents, but one that should exhibit increased reactivity and react through a better defined − and hopefully more predictable − T. S., leading to improved − or different − levels of stereocontrol to the analogous intermolecular process.

Reetz has shown that tethering an allylsilane through the carbinol center of a β-hydroxy aldehyde led to the 1,3-syn diol allylation product on activation with $TiCl_4$ (Scheme 1).[9]

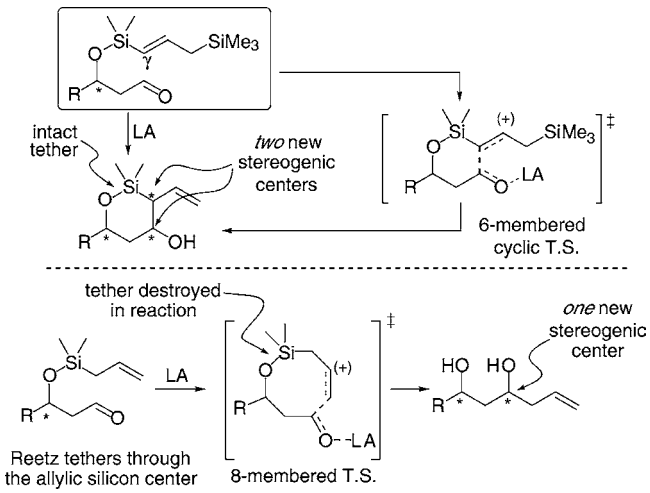
Scheme 1. Tethering an Allylsilane to an Aldehyde Electrophile Leads to a Different Sense of Stereoinduction (Ref 9)



This result was significant in that the sense of induction in this intramolecular process[9] was opposite that found in the analogous intermolecular reaction.[10] This, and other studies,[11] clearly demonstrate that temporarily tethering an allylsilane in this fashion leads to consistently higher (or opposite in the Reetz example) levels of stereocontrol compared to the analogous intermolecular reactions.

We envisaged that relocating the silyl ether tether from the allylic silicon group to the γ-position of the allylsilane would confer a number of potential advantages over the system employed by Reetz and others (Scheme 2).

Scheme 2. Relocating the Silyl Ether Tether to the γ-Position of the Allylsilane Provides an Oxasilacyclic Product Rather than an Acyclic 1,3-Diol as is Obtained in the Reetz System



In our modified system, the reacting allyl group would now be exocyclic in the T. S. and therefore more closely resemble the corresponding intermolecular reaction. Reaction would also proceed through a tighter, and better-defined, T. S. to provide a cyclic product in which the tether remains intact. Furthermore, by preserving the tether in the reaction we would generate two − as opposed to one − new stereogenic centers and therefore obtain improved stereochemical transcription. Finally, the oxasilacycle product is a very versatile intermediate ripe for further elaboration (Scheme 2).

The γ-(amino)silyl-substituted allylsilane **1** was readily synthesized according to the procedure of Tamao et al. as outlined in Scheme 3.[12] Aminosilanes are attractive silylating agents: treatment of β-hydroxy ester **2** with aminosilane **1** provided the desired silyl ether **3** in excellent yield after purification by chromatography (Scheme 3). Silylation was neither particularly rapid nor exothermic, and was best achieved by simply mixing equimolar quantities of the two reagents in the absence of solvent and with slight warming of the reaction mixture to aid mixing of the two reactants. Since the only byproduct in the reaction is a volatile secondary amine, acid scavengers are not required which facilitates workup. DIBALH reduction of the ester in **3** then

(6) For an enantioselective allylation reaction employing allyltrialkylsilanes: Gauthier, D. R.; Carreira, E. M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2363−2365.

(7) For some very recent examples: (a) Denmark, S. E.; Fu, J. *Chem. Commun.* **2003**, 167−170. (b) Kubota, K.; Leighton, J. L. *Angew. Chem., Int. Ed.* **2003**, *42*, 946−948. (c) Yamasaki, S.; Fujii, K.; Wada, R.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2002**, *124*, 6536−6537.

(8) Cox, L. R.; Ley, S. V. in *Templated Organic Synthesis*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1999; Chapter 10, pp 275−395 and references therein.

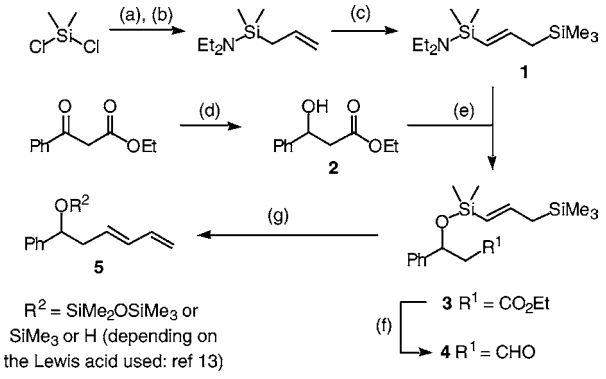
(9) Reetz, M. T.; Jung, A.; Bolm, C. *Tetrahedron* **1988**, *44*, 3889−3898. The choice of $TiCl_4$ as a Lewis acid was important here for ensuring an intramolecular allylation. A T. S. in which the Ti Lewis acid coordinates to both the aldehyde and silyl ether oxygen was invoked for rationalizing the stereochemical outcome of the reaction.

(10) Reetz, M. T.; Jung, A. *J. Am. Chem. Soc.* **1983**, *105*, 4833−4835.

(11) See for example: (a) Hioki, H.; Okuda, M.; Miyagi, W.; Itô, S. *Tetrahedron Lett.* **1993**, *34*, 6131−6134. (b) Martin, O. R.; Rao, S. P.; Kurz, K. G.; El-Shenawy, H. A. *J. Am. Chem. Soc.* **1988**, *110*, 8698−8700.

(12) Tamao, K.; Nakajo, E.; Ito, Y. *Tetrahedron* **1988**, *44*, 3997−4007.

Scheme 3. Synthesis of Allylsilane **1**, Tethering, and Initial Cyclization Studies[a]



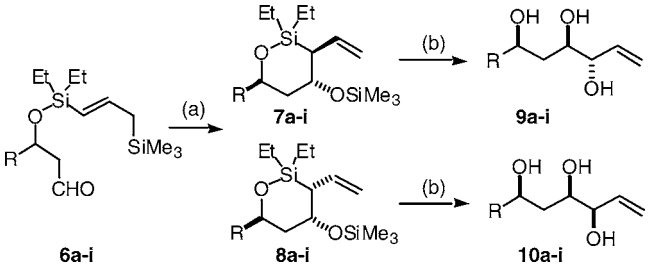
[a] Reaction conditions: (a) $LiNEt_2$ (1.0 equiv), THF, 0 °C; (b) (allyl)MgBr (1.0 equiv), Et_2O, reflux; (c) ^{n}BuLi (1.1 equiv), TMEDA (1.0 equiv), Et_2O, −5 °C, then TMSCl (1.0 equiv), −5 °C to rt (19%, three steps); (d) $NaBH_4$ (1.1 equiv), EtOH, 0 °C (81%); (e) **1** (1.0 equiv), **2** (1.0 equiv), 40 °C (90%); (f) DIBALH (1.1 equiv), CH_2Cl_2, −78 °C (93%); (g) Lewis acid (ref 13), CH_2Cl_2, −78 °C or MeCN, −40 °C, **5** (>95% crude).

provided the corresponding aldehyde **4** ready for investigating the intramolecular allylation. Unfortunately however, all attempts to effect cyclization using a range of Lewis and Brønsted acids[13] in CH_2Cl_2 and MeCN at a range of temperatures only ever provided the desired oxasilacyclic products in trace amounts; in every case dienes **5** were isolated as the major products and as single (*E*)-stereoisomers (Scheme 3).

We reasoned that our problem was associated with preferential collapse of the silyl ether in the carbocationic intermediate[14] and that, by increasing the steric bulk of the ligands around the silyl ether tether, we would redirect the course of the reaction to the desired products. We were therefore delighted to observe that allylsilane **6a**[15] containing Et substituents at the silyl tether efficiently suppressed the formation of diene products and provided the desired cyclization products **7a** and **8a** in very good yield (Table 1). Similar reactions were carried out on a range of aldehydes. The results are summarized in Table 1.

As already discussed, relocating the silyl ether to a position where it is retained in the initial allylation product, generates a product ripe for further elaboration. In a first investigation we chose to oxidatively cleave the Si−C bond in our allylation products using a Tamao oxidation[16] to provide a route into stereodefined 1,2,4-triols. Treatment of the crude

Table 1. An Intramolecular Allylation/Tamao Oxidation Sequence Provides a Route to Stereodefined 1,2,4-Triols[a]



entry	aldehyde	R	combined yield **7** + **8**[b] (%)	ratio[c] **7**:**8**	isolated yield **9**[d] (%)
1	**6a**	Ph	88	3.9:1	73
2	**6b**	2-furyl	86	4.0:1	61
3	**6c**	cinnamyl	82	3.5:1	85
4	**6d**	TIPS-C≡C−	92	6.7:1	34
5	**6e**	cyclohexyl	83	4.9:1	51
6	**6f**	^{n}Bu	76	8.5:1	65
7	**6g**	^{s}Bu	55	2.7:1	60
8	**6h**	$BnOCH_2CH_2$−	75	9.7:1	63
9	**6i**	Me	trace[e]		

[a] Reaction conditions: (a) TMSOTf (1.0 equiv), 2,6-DTBMP (1.2 equiv), CH_2Cl_2, −78 °C; (b) H_2O_2 (60% aq) (20 equiv), KF (5 equiv), $KHCO_3$ (3 equiv), THF/MeOH (1:1). [b] Diene products accounted for the remaining material in the crude reaction mixture. [c] Ratio calculated from analysis of the crude reaction mixture by ^{1}H NMR. [d] Isolated yields following column chromatography. [e] (*E*)-Dienes were the major products from this reaction. It is not clear at the present time why this substrate does not provide the desired oxasilacycles.

reaction mixture from the allylation to the standard Tamao oxidation conditions effected a relatively slow cleavage of the tether to give the desired triol products **9** in moderate to good yield (Table 1). Interestingly, under the mildly basic reaction conditions of the oxidation process, the minor diastereoisomer **8** was found to be particularly susceptible to elimination (to provide (*E*)-dienes)[17] and only small quantities of the minor triol product **10** were identified. It is unclear at the present time why the two diastereoisomeric allylation products behave so differently; however the result fortuitously allowed the isolation of essentially diastereoisomerically pure triol product **9**.

In all cases, only two of the four possible diastereoisomers were observed by analysis of the crude reaction mixture by HPLC and ^{1}H NMR. A series of nOe experiments was used to elucidate the structure of the minor diastereoisomer **8** (Figure 1). However, we were unable to use similar procedures for confirming the relative stereochemistry in the major diastereoisomer **7**. Fortunately since the Tamao oxidation is a stereospecific process that proceeds with retention of configuration, we were able to identify the relative stereochemistry of the major diastereoisomer indirectly using the triol oxidation products. Exposure of triol **9a** to acetone in the presence of *p*TSA and Na_2SO_4 led to the formation of the two acetonides **11a** and **12a** with the

(13) The following activators were tried: $TiCl_4$, $SnCl_4$, BF_3·OEt_2, $Yb(OTf)_3$, $MeAlCl_2$, TMSOTf with/without 2,6-DTBMP, TBDMSOTf with/without 2,6-DTBMP, $Cu(OTf)_2$, $ZrCl_4$, $MgBr_2$·OEt_2, TfOH.

(14) Diene **5** may be formed in a variety of ways. We currently favor a mechanism involving a vinylogous silicon-mediated olefination as this best accounts for the excellent (*E*)-stereoselectivity observed. (a) Stragies, R.; Blechert, S. *Tetrahedron* **1999**, *55*, 8179−8188. (b) Bradley, G. W.; Thomas, E. J. *Synlett* **1997**, 629−631. (c) Angoh, A. G.; Clive, D. L. J. *J. Chem. Soc., Chem. Commun.* **1984**, 534−536.

(15) **6a** was prepared according to Scheme 3 starting from Et_2SiCl_2 in place of Me_2SiCl_2.

(16) For a detailed review on this reaction: Fleming, I. *Chemtracts: Org. Chem.* **1996**, *9*, 1−64.

(17) Ager, D. J. *Org. React.* **1990**, *38*, 1−223 and references therein.

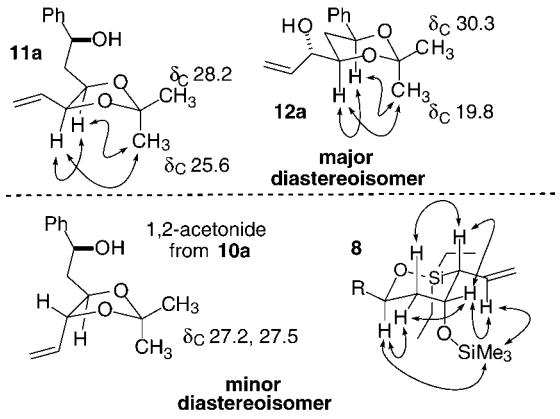


Figure 1. Selected nOes and δ_C resonances used to elucidate the relative stereochemistry of the two diastereoisomers.

dioxolane predominating as expected (Figure 1). NMR spectroscopy (^{13}C NMR[18] and nOe experiments) on this mixture readily allowed the identification of the relative stereochemistry in these products and therefore in the major allylation diastereoisomer **7** (Figure 1).

It is worthwhile to compare the diastereoselectivity of this set of reactions with those from a similar study carried out by Keck.[19] The results are rather different. In Keck's very detailed study employing an allylstannane linked through an all-carbon chain to the reacting aldehyde, the diastereoselectivity of the reaction with the analogous (*E*)-allylstannane was heavily dependent on the Lewis acid employed, although generally, all four possible diastereoisomers were observed in varying amounts.[19] In our system, only two out of the possible four diastereoisomeric allylation products were ever observed. We believe this difference is a consequence of the C−O bond and its associated dipole affecting the relative energies of the reacting T. S.s, a controlling factor that is absent in the substrates employed by Keck. Thus, levels of 1,3-stereoinduction are excellent − there is a clear preference for the aldehyde to adopt a pseudoaxial orientation in the reacting chairlike T. S. (Figure 2). Levels of 1,4-

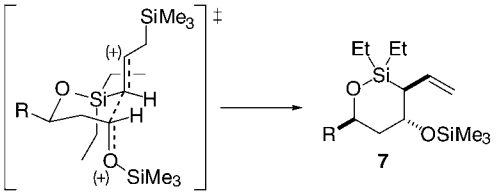


Figure 2. Transition state leading to the major diastereoisomer **7**. The transition state has the aldehyde and allylsilane adopting pseudoaxial orientations.

stereoinduction, however, are more modest with the major diastereoisomer resulting from the allylsilane also preferentially adopting a pseudoaxial orientation in the reacting T. S. (Figure 2). We believe that this is a consequence of the allylsilane minimizing steric interactions with the ethyl substituents at the silyl tether. We expect that the (*Z*)-stereoisomeric allylsilane will better differentiate the two T. S.s leading to **7** and **8** and improve the levels of 1,4-induction. Efforts are currently underway to synthesize this novel allylsilane.

Acknowledgment. We thank the Engineering and Physical Sciences Research Council (Grant No. GR/N32556) for a studentship (to J.B.).

Supporting Information Available: Experimental procedures and full characterization data for allylation products **7** and **8**, triols **9**, and acetonides **11** and **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) For elucidating the 1,3-relative stereochemistry: Rychnovsky, S. D.; Rogers, B.; Yang, G. *J. Org. Chem.* **1993**, *58*, 3511−3515; and the 1,2-relative stereochemistry: Dana, G.; Danechpajouh, H. *Bull. Soc. Chim. Fr.* **1980**, *2*, 395−399.

(19) Keck, G. E.; Dougherty, S. M.; Savin, K. A. *J. Am. Chem. Soc.* **1995**, *117*, 6210−6223.