JOC Article

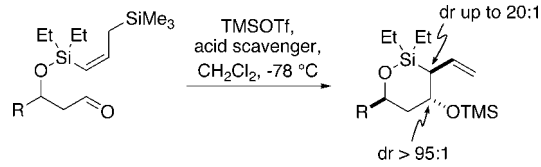
Temporary Silicon Connection Strategies in Intramolecular Allylation of Aldehydes with Allylsilanes

Julien Beignet, Peter J. Jervis, and Liam R. Cox*

School of Chemistry, The University of Birmingham, Edgbaston, Birmingham, B15 2TT, United Kingdom

l.r.cox@bham.ac.uk

Received April 14, 2008



Three γ-(amino)silyl-substituted allylsilanes **14a**−**c** have been prepared in three steps from the corresponding dialkyldichlorosilane. The aminosilyl group has been used to link this allylsilane nucleophile to a series of β-hydroxy aldehydes through a silyl ether temporary connection. The size of the alkyl substituents at the silyl ether tether governs the outcome of the reaction on exposure to acid. Thus, treatment of aldehyde (*E*)-**9aa**, which contains a di*methyl*silyl ether connection between the aldehyde and allylsilane, with a range of Lewis and Brønsted acid activators provides an (*E*)-diene product. The mechanism of formation of this undesired product is discussed. Systems containing a sterically more bulky di*ethyl*silyl ether connection react differently: thus in the presence of TMSOTf and a Brønsted acid scavenger, intramolecular allylation proceeds smoothly to provide two out of the possible four diastereoisomeric oxasilacycles, **23** (major) and **21** (minor). A diene product again accounts for the remaining mass balance in the reaction. This side product can be completely suppressed by using a sterically even more bulky di*isopropyl*silyl ether connection in the cyclization precursor, although this is now at the expense of a slight erosion in the 1,3-stereoinduction in the allylation products. The sense of 1,3-stereoinduction observed in these intramolecular allylations has been rationalized by using an electrostatic argument, which can also explain the stereochemical outcome of a number of related reactions. Levels of 1,4-stereoinduction in the intramolecular allylation are more modest but can be significantly improved in some cases by using a tethered (*Z*)-allylsilane in place of its (*E*)-stereoisomer. Oxidation of the major diastereoisomeric allylation product **23** under Tamao−Kumada conditions provides an entry into stereodefined 1,2-*anti*-2,4-*syn* triols **28**.

Introduction

The allylation of aldehydes to provide homoallylic alcohols represents a powerful transformation in organic synthesis and is a reaction that has been the focus of intense investigation.[1] Allylsilanes are particularly attractive agents for effecting this transformation owing to their low toxicity and relative ease of preparation and stability.[1d,2] Allyl*trialkyl*silanes generally exhibit fairly low nucleophilicity,[3] and as a consequence, usually only react with aldehydes in the presence of external activators such as Lewis or Brønsted acids.[4] By using this type of activation method, allylation proceeds through an open transition state in a stepwise, *anti* S_E' fashion in which there is no interaction between the carbonyl oxygen and the silicon atom in the nucleophile in the rate-determining addition step.[5,6] For its useful application in synthesis, the allylation of aldehydes needs to proceed stereoselectively.[1a,7] In the case of allyltrialkylsilanes,

* Corresponding author. Phone: +44 (0)121 414 3524. Fax: +44 (0)121 414 4403.

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

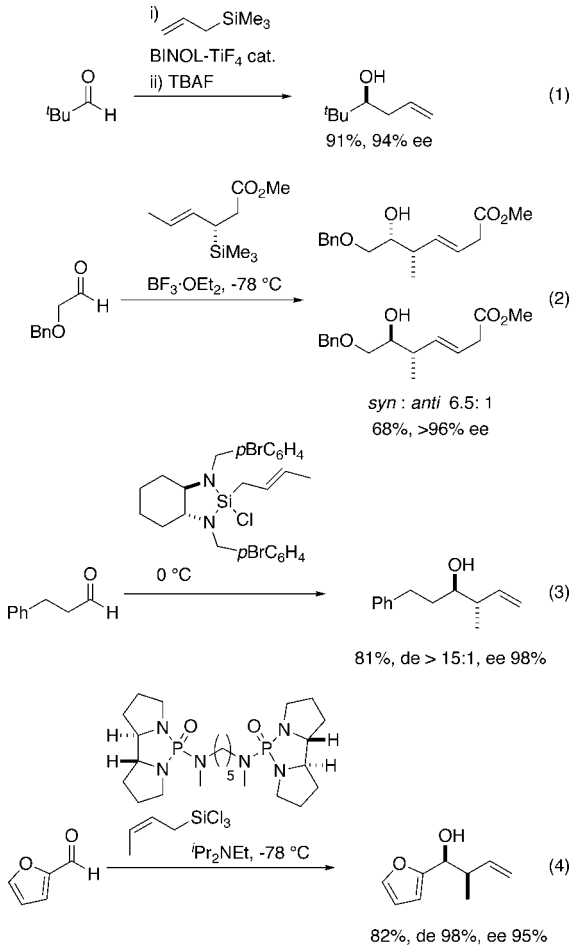
(2) (a) Kennedy, J. W. J.; Hall, D. G. *Angew. Chem., Int. Ed.* **2003**, *42*, 4732–4739. (b) Fleming, I.; Barbero, A.; Walter, D. *Chem. Rev.* **1997**, *97*, 2063–2192. (c) Masse, C. E.; Panek, J. S. *Chem. Rev.* **1995**, *95*, 1293–1316. (d) Fleming, I.; Dunoguès, J.; Smithers, R. *Org. React.* **1989**, *37*, 57–575.

(3) (a) Mayr, H.; Patz, M. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 938–957. (b) Mayr, H.; Hagen, G. *J. Chem. Soc., Chem. Commun.* **1989**, 91–92.

(4) Additives, such as fluoride, which activate the allylsilane, have occasionally been used. In these cases, the nucleophile may be an allyl anion, see: (a) Hosomi, A. Shirahata, A. Sakurai, H. *Tetrahedron Lett.* **1978**, 3043−3046. (b) Sarkar, T. K.; Andersen, N. H. *Tetrahedron Lett.* **1978**, 3513–3516.

10.1021/jo800824x CCC: $40.75
Published on Web 06/17/2008

SCHEME 1. Stereoselective Allylation of Aldehydes Employing Allylsilanes



the stereoselectivity of their reaction with aldehydes can be controlled in a variety of ways. Carreira and co-workers introduced a powerful chiral Lewis acid derived from TiF_4 and binol.[8] With use of this activation system, allylsilanes, which are unsubstituted at the γ-terminus, react with aldehydes with excellent levels of enantioselectivity (Scheme 1, eq 1).[8] This type of reagent-controlled strategy has rarely been extended to achiral crotylsilanes and other γ-substituted allylsilanes, where both diastereoselectivity and enantioselectivity need to be considered.[9] This is probably a result of (i) the relatively poorly defined open transition states through which allyltrialkylsilanes (type II allyl metals[10]) react, making the control of relative stereoselectivity difficult, and (ii) competition from type I allylating agents (crotylboranes[11] and crotylboronates[12] being the most important examples), which react with aldehydes through well-defined chair-like transition state conformations, and offer a straightforward route to both *syn* and *anti* homoallylic alcohol products through judicious choice of the appropriate crotylmetal stereoisomer. That said, crotylsilanes have been used successfully in enantio- and diastereoselective synthesis. Until recently, crotylsilanes, which incorporate a stereogenic center at the α-site,[2c,13] have been the most successful,[14] with the reagents developed by Panek and co-workers[2c,13a,b] providing the paradigm in this field (Scheme 1, eq 2). More recently, Leighton and co-workers have introduced crotylsilane reagents, which use chirality embedded in the silyl ligands to impart stereoselectivity (Scheme 1, eq 3),[15–17] while Denmark[18] and others[19] have introduced chiral Lewis base activators for use with allyl*trichloro*silanes (Scheme 1, eq 4). These last two strategies can both be used to effect highly enantio- and diastereoselective allylation reactions; however, these classes of crotylsilane react rather differently to the *anti* S_E' pathway followed by standard crotyltrialkylsilanes.[18a,b,20]

An alternative approach to controlling the stereoselectivity of reactions employing γ-substituted allyltrialkylsilanes is to incorporate the nucleophile into the same molecule as the electrophile and carry out an intramolecular allylation. Providing the number of atoms linking the two reacting functionalities is not too small, such that geometrical constraints prevent the nucleophile and electrophile from approaching sufficiently closely to one another to react, nor too large, such that the reaction resembles an intermolecular reaction or is disfavored on entropic grounds, this type of intramolecular allylation provides a powerful method for generating rings in a stereocontrolled fashion.[21] We have been interested in using a temporary silicon connection[22] to exploit the advantages associated with this type of intramolecularization strategy in

(5) (a) Buckle, M. J. C.; Fleming, I.; Gil, S.; Pang, K. L. C. *Org. Biomol. Chem.* **2004**, *2*, 749–769. (b) Denmark, S. E.; Almstead, N. G. *J. Org. Chem.* **1994**, *59*, 5130–5132. (c) Denmark, S. E.; Weber, E. J. *Helv. Chim. Acta* **1983**, *66*, 1655–1660.

(6) For computational investigations on the Lewis acid-mediated reaction of allyltrialkylsilanes with aldehydes see: (a) Tietze, L. F. Kinzel, T. Schmatz, S. *J. Am. Chem. Soc.* **2006**, *128*, 11483−11495. (b) Mayer, P. S.; Morton, T. H. *J. Am. Chem. Soc.* **2002**, *124*, 12928–12929. (c) Bottoni, A.; Costa, A. L.; Di Tommaso, D.; Rossi, I.; Tagliavini, E. *J. Am. Chem. Soc.* **1997**, *119*, 12131–12135.

(7) Yamamoto, Y. *Acc. Chem. Res.* **1987**, *20*, 243–249.

(8) Gauthier, D. R.; Carreira, E. M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2363–2365.

(9) See also: (a) Ishihara, K. Mouri, M. Gao, Q. Maruyama, T. Furuta, K. Yamamoto, H. *J. Am. Chem. Soc.* **1993**, *115*, 11490−11495. (b) Aoki, S.; Mikami, K.; Terada, M.; Nakai, T. *Tetrahedron* **1993**, *49*, 1783–1792.

(10) For the classification of allyl metals see: (a) Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1982***21*555−566. (b) Reference 5c.

(11) Brown, H. C.; Bhat, K. S.; Randad, R. S. *J. Org. Chem.* **1989**, *54*, 1570–1576.

(12) (a) Roush, W. R.; Adam, M. A.; Walts, A. E.; Harris, D. J. *J. Am. Chem. Soc.* **1986**, *108*, 3422–3434. (b) Roush, W. R.; Walts, A. E.; Hoong, L. K. *J. Am. Chem. Soc.* **1985**, *107*, 8186–8190.

(13) (a) Panek, J. S.; Cirillo, P. F. *J. Org. Chem.* **1993**, *58*, 999–1002. (b) Panek, J. S.; Yang, M. *J. Am. Chem. Soc.* **1991**, *113*, 6594–6600. (c) Suginome, M.; Iwanami, T.; Ito, Y. *J. Am. Chem. Soc.* **2001**, *123*, 4356–4357. (d) Hayashi, T.; Konishi, M.; Ito, H.; Kumada, M. *J. Am. Chem. Soc.* **1982**, *104*, 4962–4963. (e) Hayashi, T.; Konishi, M.; Kumada, M. *J. Am. Chem. Soc.* **1982**, *104*, 4963–4965.

(14) Chiral allylsilanes, which incorporate stereochemical information into the β- and γ-sites, have also been investigated: (a) Nativi, C.; Palio, G.; Taddei, M. *Tetrahedron Lett.* **1991**, *32*, 1583–1586. (b) Nishigaichi, Y.; Takuwa, A.; Jodai, A. *Tetrahedron Lett.* **1991**, *32*, 2383–2386.

(15) Hackman, B. M.; Lombardi, P. J.; Leighton, J. L. *Org. Lett.* **2004**, *6*, 4375–4377.

(16) The use of allylsilanes containing chiral ligands had previously met with little success: (a) Nativi, C.; Ravida, N.; Ricci, A.; Seconi, G.; Taddei, M. *J. Org. Chem.* **1991**, *56*, 1951–1955. (b) Wei, Z. Y.; Wang, D.; Li, J. S.; Chan, T. H. *J. Org. Chem.* **1989**, *54*, 5768–5774. (c) Chan, T. H.; Wang, D. *Tetrahedron Lett.* **1989**, *30*, 3041–3044. (d) Coppi, L.; Mordini, A.; Taddei, M. *Tetrahedron Lett.* **1987**, *28*, 969–972.

(17) Allylsilanes with Si-centered chirality have also been investigated: (a) Hathaway, S. J.; Paquette, L. A. *J. Org. Chem.* **1983**, *48*, 3351−3353.

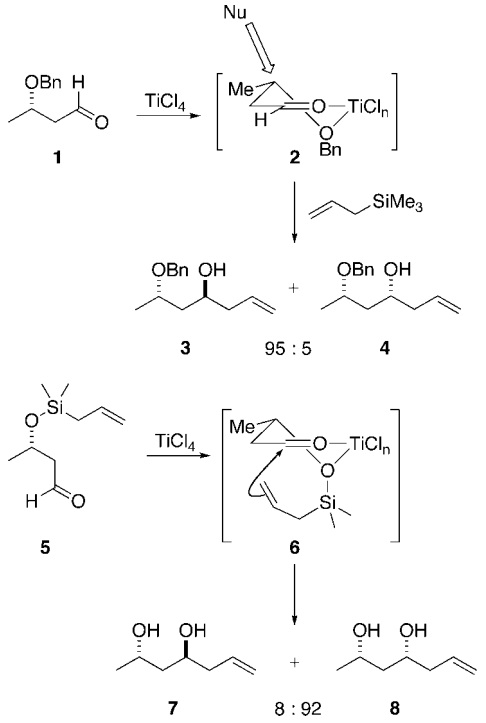
(18) (a) Denmark, S. E.; Fu, J. P.; Coe, D. M.; Su, X.; Pratt, N. E.; Griedel, B. D. *J. Org. Chem.* **2006**, *71*, 1513–1522. (b) Denmark, S. E.; Fu, J. P.; Lawler, M. J. *J. Org. Chem.* **2006**, *71*, 1523–1536. (c) Denmark, S. E.; Fu, J. P. *Chem. Commun.* **2003**, 167–170. (d) Denmark, S. E.; Fu, J. P. *J. Am. Chem. Soc.* **2001**, *123*, 9488–9489. (e) Denmark, S. E.; Coe, D. M.; Pratt, N. E.; Griedel, B. D. *J. Org. Chem.* **1994**, *59*, 6161–6163.

(19) For recent reviews see: (a) Malkov, A. V.; Kocovsky, P. *Eur. J. Org. Chem.* **2007**, 29–36. (b) Orito, Y.; Nakajima, M. *Synthesis* **2006**, 1391–1401, and references cited therein.

(20) Zhang, X.; Houk, K. N.; Leighton, J. L. *Angew. Chem., Int. Ed.* **2005**, *44*, 938–941.

(21) (a) Langkopf, E.; Schinzer, D. *Chem. Rev.* **1995**, *95*, 1385–1408. (b) Schinzer, D. *Synthesis* **1988**, 263–273.

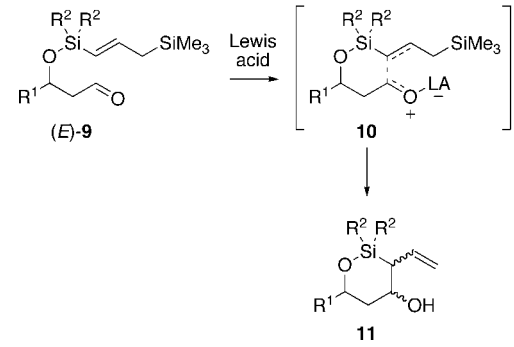
SCHEME 2. Reetz's Intramolecular Allylation Strategy Using a Silyl Ether Connection



stereoselective synthesis.[23] More specifically, by employing a silyl ether tethering group to connect an allylsilane to an electrophile, we aim to use the potentially more defined transition states associated with the formation of small rings to install new stereogenic centers in a controlled fashion. Being able to cleave the silyl ether connection post allylation then allows us to access a product that can be considered the result of a net intermolecular process.

At the outset of this project, allylsilanes had been previously tethered through a transient silyl ether connection to a small number of electrophile substrates.[24] In all cases, the silicon atom in the allylsilane had also served as the tethering unit connecting the nucleophile to the electrophile. A seminal study from Reetz and co-workers illustrates the concept and potential utility of this strategy (Scheme 2).[24g] Reaction of 3-benzyloxybutanal **1** with allyltrimethylsilane in the presence of $TiCl_4$ generated two homoallylic alcohol products, **3** and **4**. In this instance, excellent diastereoselectivity was observed for alcohol **3**, which contains

SCHEME 3. Relocating the Silyl Ether Connection to the γ-Terminus of the Allylsilane Generates an Oxasilacycle Containing Two New Stereogenic Centers, Ripe for Elaboration



a 1,3-*anti* relationship between the existing and newly formed stereogenic centers. The stereochemical outcome of this reaction was rationalized by invoking intermolecular addition of the allyl nucleophile on a chelated intermediate **2**. In an alternative approach, when aldehyde **5**, in which the allylsilane nucleophile is now tethered to the β-carbinol stereogenic center contained within the aldehyde, was treated with $TiCl_4$, the desired homoallylic alcohol products, **7** and **8**, were again obtained in good yield; however, this time, the favored diol product **8** now contained a 1,3-*syn* relationship between the two stereogenic centers (Scheme 2).[24g] Through judicious choice of reagents and reaction conditions, Reetz was able to access both 1,3-*anti* and 1,3-*syn* homoallylic alcohol diastereoisomers in a selective fashion.

In this pertinent example from Reetz, the temporary silicon connection is cleaved during the reaction, which removes the need to introduce a separate cleavage step into the synthetic sequence. While this is an attractive feature of this strategy, we reasoned that a more versatile product, ripe for chemical diversification, could be obtained if the temporary silicon connection were to remain in the allylation product. To achieve this, we elected to relocate the silyl ether connection to the γ-terminus of the allyl nucleophile (Scheme 3). This modification would serve a number of advantages. Although we would still be relying on the carbinol stereogenic center in **9** to control the stereochemical outcome of the allylation, substitution at the γ-terminus of the allylsilane nucleophile would necessarily introduce a second stereogenic center into the allylation product **11** and provide an added level of structural complexity. Retaining the silyl ether connection would also make available a number of potential elaboration strategies for the product. Moreover, since the allylsilane would now be reacting with the tethered aldehyde in an exocyclic fashion (**10**) (with respect to the ring being formed), the reaction would more closely resemble an intermolecular allylation. Assuming the substituent appended off the carbinol stereogenic center dictates the low-energy chair conformation for the formation of the six-membered ring, by analyzing the stereochemical relationship between the two new stereogenic centers in the product, we would be able to ascertain the relative orientation of the reacting π-systems in the aldehyde electrophile and allylsilane nucleo-

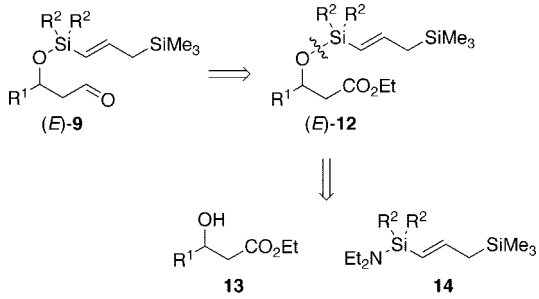
(22) (a) Cox, L. R.; Ley, S. V. In *Templated Organic Synthesis*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, Germany, 2000; Chapter 10, pp 275−375. (b) Bols, M.; Skrydstrup, T. *Chem. Rev.* **1995**, *95*, 1253–1277. (c) Fensterbank, L.; Malacria, M.; Sieburth, S. M. *Synthesis* **1997**, 813–854. (d) Gauthier, D. R., Jr.; Zandi, K. S.; Shea, K. J. *Tetrahedron* **1998**, *54*, 2289–2338.

(23) (a) Ramalho, R.; Jervis, P. J.; Kariuki, B. M.; Humphries, A. C.; Cox, L. R. *J. Org. Chem.* **2008**, *73*, 1631–1634. (b) Jervis, P. J.; Cox, L. R. *Beilstein J. Org. Chem.* **2007**, *3*, 6. (c) Ramalho, R.; Beignet, J.; Humphries, A. C.; Cox, L. R. *Synthesis* **2005**, 3389–3397. (d) Simpkins, S. M. E.; Kariuki, B. M.; Aricó, C. S.; Cox, L. R. *Org. Lett.* **2003**, *5*, 3971–3974. (e) Beignet, J.; Tiernan, J.; Woo, C. H.; Kariuki, B. M.; Cox, L. R. *J. Org. Chem.* **2004**, *69*, 6341–6356. (f) Beignet, J.; Cox, L. R. *Org. Lett.* **2003**, *5*, 4231–4234.

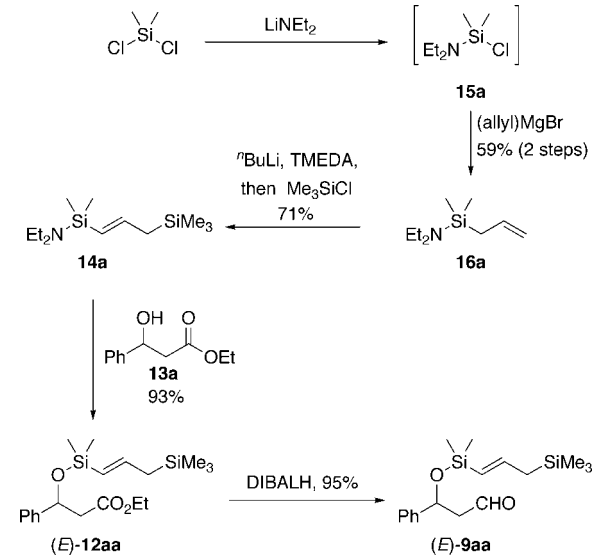
(24) (a) Robertson, J.; Hall, M. J.; Green, S. P. *Org. Biomol. Chem.* **2003**, *1*, 3635–3638. (b) Wipf, P.; Aslan, D. C. *J. Org. Chem.* **2001**, *66*, 337–343. (c) Pilli, R. A.; Riatto, V. B. *Tetrahedron: Asymmetry* **2000**, *11*, 3675–3686. (d) Fujita, K.; Inoue, A.; Shinokubo, H.; Oshima, K. *Org. Lett.* **1999**, *1*, 917–919. (e) Frost, L. M.; Smith, J. D.; Berrisford, D. J. *Tetrahedron Lett.* **1999**, *40*, 2183–2186. (f) Hioki, H.; Okuda, M.; Miyagi, W.; Itô, S. *Tetrahedron Lett.* **1993**, *34*, 6131–6134. (g) Reetz, M. T.; Jung, A.; Bolm, C. *Tetrahedron* **1988**, *44*, 3889–3898. (h) Martin, O. R.; Rao, S. P.; Kurz, K. G.; El-Shenawy, H. A. *J. Am. Chem. Soc.* **1988**, *110*, 8698–8700.

(25) For related approaches used to probe this aspect of the allylation reaction see: (a) Schlosser, M.; Franzini, L.; Bauer, C.; Leroux, F. *Chem. Eur. J.* **2001**, *7*, 1909−1914. (b) Keck, G. E.; Dougherty, S. M.; Savin, K. A. *J. Am. Chem. Soc.* **1995**, *117*, 6210–6223. (c) Denmark, S. E.; Weber, E. J.; Wilson, T. M.; Willson, T. M. *Tetrahedron* **1989**, *45*, 1053–1065.

SCHEME 4. Retrosynthetic Analysis of the Cyclization Precursor



SCHEME 5. Synthesis of the First-Generation Cyclization Precursor



phile.[5c,6,25,26] This would then allow us to probe a mechanistic detail of this type of reaction, specifically whether there is a preference for the allylsilane and aldehyde π-systems to adopt a synclinal orientation in a staggered transition state,[5c,25b,c,27] rather than an antiperiplanar orientation, which has also been proposed.[28] We have previously reported our initial results in this project[23,29] and now report the outcome of this study in full.

Results and Discussion

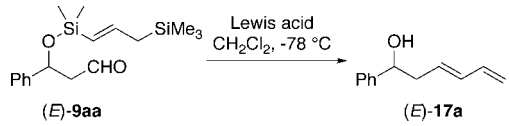
Retrosynthesis of the allylation precursor (*E*)-**9** was straightforward and is summarized in Scheme 4. Thus functional group interconversion of the aldehyde (*E*)-**9** to the corresponding ester (*E*)-**12**, followed by disconnection of the silyl ether in (*E*)-**12** provided us with our two reacting partners, namely a β-hydroxy ester **13** and a γ-silyl-substituted allylsilane **14**.

For our first generation of allylsilanes we chose to investigate a dimethylsilyl ether connection. The desired allylsilane **14a** was prepared in three steps following a modified procedure originally reported by Tamao and Ito (Scheme 5).[30] Thus addition of a THF solution of $LiNEt_2$ over 3 h to a solution of an equimolar quantity of Me_2SiCl_2 in Et_2O provided the desired aminochlorosilane **15a** in 51% yield after purification by reduced pressure distillation. In an effort to replace *n*-BuLi (used to generate the $LiNEt_2$) with a cheaper base, we also investigated the reaction of Me_2SiCl_2 with $HNEt_2$ in the presence of NaH. The NaCl precipitate generated in this reaction was more readily separated from the reaction mixture by Schlenk filtration than the LiCl generated in the reaction with $LiNEt_2$. While this simplified the workup and isolation of the highly moisture-sensitive aminochlorosilane product, at 40%, the isolated yield of aminosilane offered no significant improvement on our procedure employing $LiNEt_2$. Next, the chloro substituent in aminochlorosilane **15a** was selectively displaced with allyl magnesium bromide to afford allylsilane **16a** in good yield. Carrying out these two steps in a one-pot operation led to a further improvement in reaction efficiency (59% over two steps) probably owing to removing the need to handle the rather moisture-sensitive aminochlorosilane intermediate. In the final step, reaction of allylsilane **16a** with a strong base derived from equimolar quantities of *n*-BuLi and TMEDA in Et_2O provided the corresponding allyllithium species, which was trapped regioselectively with Me_3SiCl to provide γ-aminosilyl-substituted allylsilane **14a** as a single (*E*)-stereoisomer, as evidenced by a vicinal coupling constant of 18.3 Hz for the olefinic hydrogens. Although aminosilanes are nowadays only rarely used to form silyl ethers,[31–36] they are useful alternatives to more commonly employed silyl chlorides and silyl triflates. Moreover, since the byproduct from the reaction is an innocuous and volatile secondary amine, the reaction does not require the inclusion of acid scavengers. Thus the silyl ether in (*E*)-**12aa** was prepared by simply mixing equimolar quantities of aminosilane **14a** with β-hydroxyester **13a**. Since this silyletherification did not generate a strong exotherm, the two reactants could be combined in the absence of solvent, and after 3 h, silyl ether (*E*)-**12aa** was obtained in excellent yield. Chemoselective reduction of the ester in (*E*)-**12aa** with DIBALH proceeded uneventfully to provide the aldehyde cyclization precursor (*E*)-**9aa** (Scheme 5).

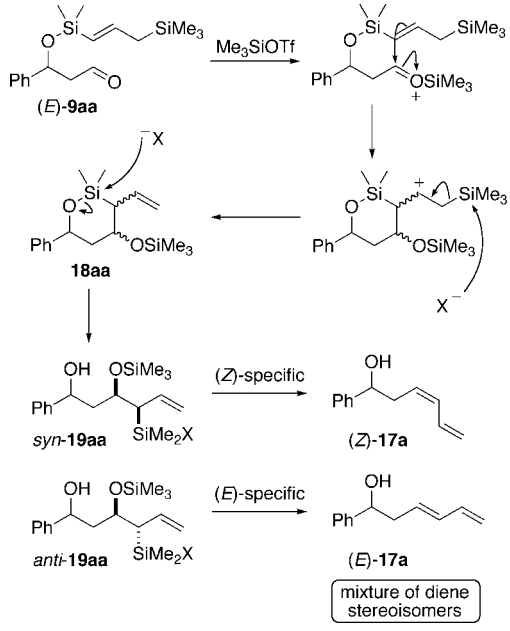
Since allylsilanes are susceptible to protodesilylation in the presence of Brønsted acids,[37] we elected to investigate the intramolecular allylation of (*E*)-**9aa** under Lewis acid activation. A wide range of Lewis acids[38] was screened with use of dichloromethane, which is the most commonly employed solvent for allylation reactions with allylsilanes, and MeCN as a

(26) For experimental studies employing related allyltrialkylstannanes see: Denmark, S. E.; Hosoi, S. *J. Org. Chem.* **1994**, *59*, 5133–5135.
(27) Mikami, K.; Kawamoto, K.; Loh, T.-P.; Nakai, T. *J. Chem. Soc., Chem. Commun.* **1990**, 1161–1163.
(28) Yamamoto, Y.; Yatagai, H.; Naruta, Y.; Maruyama, K. *J. Am. Chem. Soc.* **1980**, *102*, 7107–7109.
(29) Part of this work was presented at the 2007 ACS meeting in Chicago.
(30) Tamao, K.; Nakajo, E.; Ito, Y. *Tetrahedron* **1988**, *44*, 3997–4007.
(31) TMS protection by using an aminosilane: (a) Tanabe, Y.; Murakami, M.; Kitaichi, K.; Yoshida, Y. *Tetrahedron Lett.* **1994**, *35*, 8409–8412. (b) Rychnovsky, S. D.; Griesgraber, G. *J. Org. Chem.* **1992**, *57*, 1559–1563. (c) Kerwin, S. M.; Paul, A. G.; Heathcock, C. H. *J. Org. Chem.* **1987**, *52*, 1686–1695. (d) Yankee, E. W.; Bundy, G. L. *J. Am. Chem. Soc.* **1972**, *94*, 3651–3652. (e) Ruehlmann, K. *Synthesis* **1971**, 236–253.
(32) TES protection using an aminosilane: (a) Holton, R. A.; Zhang, Z.; Clarke, P. A.; Nadizadeh, H.; Procter, D. J. *Tetrahedron Lett.* **1998**, *39*, 2883–2886.
(33) TBDMS protection using an aminosilane: reference 31c.
(34) TIPS protection with an aminosilane: (a) Firouzabadi, H.; Iranpoor, N.; Shaterian, H. R. *Phosphorus, Sulfur Silicon Relat. Elem.* **2000**, *166*, 71–82.
(35) $PhMe_2Si$ protection with an aminosilane: Liepin'sh, E. E.; Birgele, I. S.; Zelchan, G. I.; Urtane, I. P.; Lukevits, E. *J. Gen. Chem. USSR (Engl. Transl.)* **1980**, *50*, 2212–2216.
(36) $(Allyl)Me_2Si$ protection with an aminosilane: reference 24g.
(37) (a) Chan, T. H.; Fleming, I. *Synthesis* **1979**, 761–786, and references cited therein. (b) Fleming, I.; Terrett, N. K. *Tetrahedron Lett.* **1983**, *24*, 4153–4156.
(38) $TiCl_4$, $SnCl_4$, $ZrCl_4$, $MgBr_2 \cdot OEt_2$, $Cu(OTf)_2$, $BF_3 \cdot OEt_2$, $Yb(OTf)_3$, $MeAlCl_2$, Me_3SiOTf, *t*-$BuMe_2SiOTf$, Me_3SiOTf/DTBMP, and TfOH were investigated.

SCHEME 6. Aldehyde (*E*)-9aa Containing a Dimethylsilyl Ether Temporary Connection Provides a Diene Product on Treatment with Lewis Acid



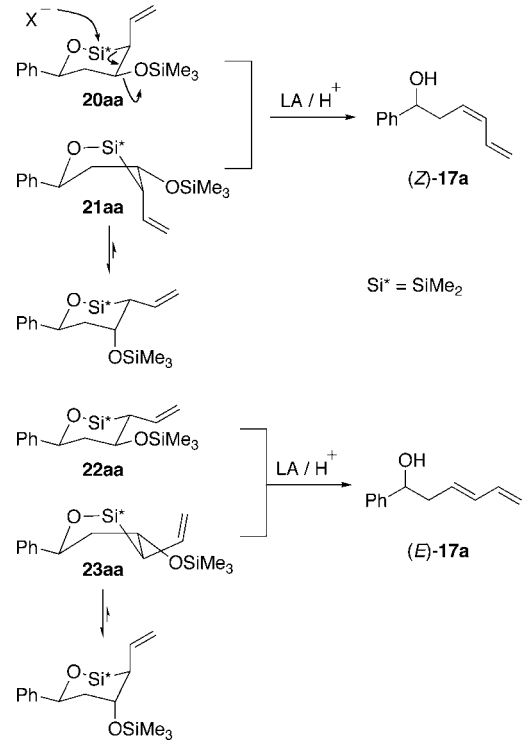
SCHEME 7. Ring-Opening of the Oxasilacycle Allylation Product Followed by Elimination Provides a Route to Diene Products



representative more polar solvent.[39] In all cases, we were disappointed to observe the desired oxasilacycle allylation product in only trace quantities, even in the best case, which employed Me_3SiOTf in the presence of 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) or 2,4,6-tri-*tert*-butylpyrimidine (TTBP),[40] both of which act as scavengers for adventitious triflic acid.[41] The starting aldehyde was always consumed rapidly at −78 °C to provide a diene (*E*)-**17a** as the major product (Scheme 6).

At this juncture, we felt it necessary to attempt to rationalize the product outcome to identify whether or not it might be possible to modify our system and redirect the course of reaction along the desired pathway. A number of mechanisms for diene formation were considered and are summarized in Schemes 7–9.[42] These essentially differ in the order in which the two silyl residues, namely the trimethylsilyl group and the silyl ether, are lost. In the first mechanism (Scheme 7), we proposed that allylation proceeds as desired to provide the oxasilacycle product **18aa**, potentially as a mixture of up to four diastereoisomers. Under the Lewis acidic conditions, we hypothesized that cleavage of the silyl ether connection might be occurring. The

SCHEME 8. Diene Formation Directly from the Oxasilacycle Allylation Products Is Conceivable



resulting conformationally flexible acyclic intermediates, *syn*-**19aa** and *anti*-**19aa** would then be susceptible to a further olefination reaction under the Lewis acidic reaction conditions. Since acid-mediated silicon olefination is a stereospecific process,[43] *syn*-**19aa** would be expected to collapse to diene (*Z*)-**17a** and *anti*-**19aa** to diene (*E*)-**17a** (Scheme 7).

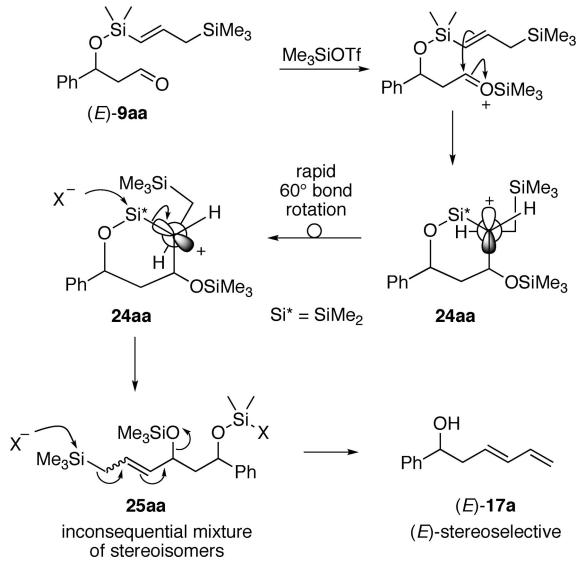
We also considered a mechanism in which elimination proceeds directly on the oxasilacycle allylation products (Scheme 8). The requirement for an antiperiplanar arrangement between the leaving group and the β-C−Si bond[43] would mean that the two diastereoisomers, **20aa** and **22aa**, in which the newly formed carbinol stereogenic center occupies an equatorial orientation, should eliminate readily in their low-energy chair conformations to provide (*Z*)-**17a** and (*E*)-**17a**, respectively, whereas elimination from the other two diastereoisomers, **21aa** and **23aa**, which contain an axially oriented C−O bond, would proceed after ring-flip to a boat-like conformation to afford (*Z*)-**17a** and (*E*)-**17a**, respectively (Scheme 8).

Since there was no reason to expect the initial allylation to be completely stereoselective (this was later borne out, see below) and analysis of the crude reaction mixture by ^1H NMR spectroscopy revealed the presence of a single diene stereoisomer, namely (*E*)-**17a**, we discounted these mechanisms and considered an alternative, which is summarized in Scheme 9. Not only does this mechanism rationalize the observed stereoselectivity of diene formation, more importantly it offered a potential way forward. In this third elimination pathway, we again proposed that the first step in the allylation of (*E*)-**9aa** proceeds as desired, to provide the carbocationic intermediate

(39) Kampen, D.; List, B. *Synlett* **2006**, 2589–2592.
(40) Crich, D.; Smith, M.; Yao, Q.; Picione, J. *Synthesis* **2001**, 323–326.
(41) The silyl ether tether decomposed rapidly in the presence of TfOH.
(42) No reaction was observed when (*E*)-γ-(*i*-PrO)Me_2Si-substituted allyltrimethylsilane was treated with PhCHO in CH_2Cl_2 in the presence of $TiCl_4$ at −78 °C for 24 h. The lack of product formation in this reaction, combined with the generation of the desired oxasilacycles when tethered allylsilanes containing bulkier groups at the silyl ether connection were employed, confirms that the mechanism of diene formation involves an intramolecular allylation step.

(43) (a) Ager, D. J. Product Subclass 37: β-Silyl Alcohols and the Peterson Reaction. In *Science of Synthesis*; Fleming, I., Ed.; Georg Thieme Verlag: Stuttgart, Germany, 2002; Vol. 4, Chapter 4.4.37, pp 789−809. (b) Ager, D. J. *Org. React.* **1990**, *38*, 1–223. (c) Hudrlik, P. F.; Peterson, D. *J. Am. Chem. Soc.* **1975**, *97*, 1464–1468. (d) Peterson, D. J. *J. Org. Chem.* **1968**, *33*, 780–784.

SCHEME 9. Preferential Collapse of the Carbocationic Intermediate by Attack at the Silyl Tether Provides an Acyclic Intermediate That Can Afford a Diene Product after a Vinylogous Silicon-Mediated Olefination



24aa.[44] While this cation will be stabilized by the exocyclic silyl group through the β-Si effect,[45] it only requires a 60° bond rotation[46] for the endocyclic silyl group to also adopt an orientation for this group to stabilize the carbocation optimally. If the presence of the oxygen substituent increases the electrofugacity of the endocyclic silyl ether, and in the absence of unfavorable steric effects, then collapse of this intermediate will proceed through preferential nucleophilic attack on the silyl ether silicon atom, to provide acyclic allylsilane intermediate **25aa**, potentially as an inconsequential (see below) mixture of olefin stereoisomers. Under the Lewis acidic reaction conditions, this intermediate would be susceptible to a vinylogous silicon-mediated olefination, which would lead to the diene product (*E*)-**17a** (Scheme 9).[47,48]

Vinylogous silicon-mediated reactions, when carried out under acidic conditions, are known to be highly (*E*)-stereoselective.[47] Elimination in allylsilane **25aa** should proceed on a reactive conformation in which the (smallest) hydrogen substituent at the stereogenic center α to the olefin sits in the plane of the olefin thereby minimizing A^{1,3}-interactions (Figure 1).[49] Irrespective of the stereoselectivity of the initial allylation step,

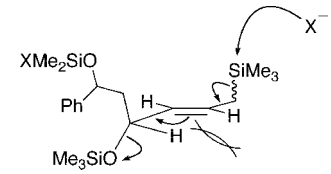
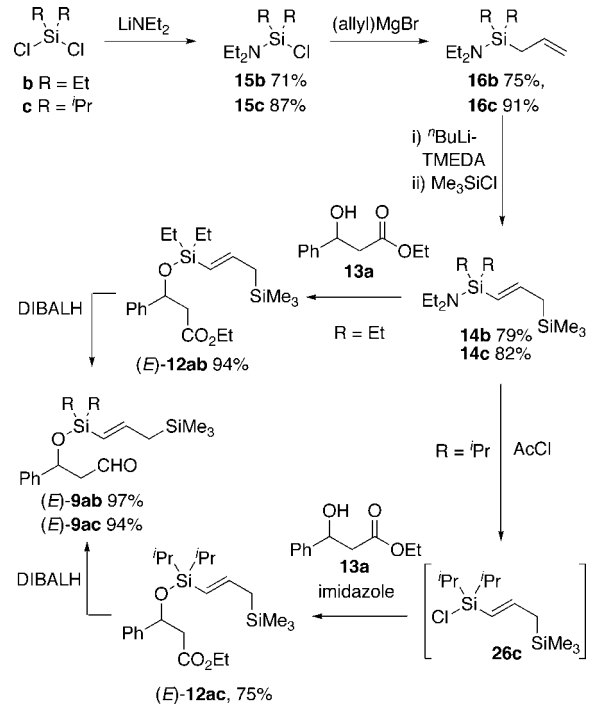


FIGURE 1. Vinylogous silicon-mediated olefination on a conformation that minimizes A^{1,3}-interactions leads to an (*E*)-diene product.

SCHEME 10. Synthesis of Cyclization Precursors Containing Bulkier Substituents at the Silyl Ether Connection



and of the olefin geometry in the acyclic allylsilane intermediate **25aa**, all products will then converge on a single diene product, (*E*)-**17a**.[50]

Were the mechanisms outlined in Schemes 7 and 8 to be operating, we reasoned that it would be difficult to stop the reaction at the oxasilacycle stage; however, if the diene product (*E*)-**17** were being generated via the mechanism described in Scheme 9, we postulated that using sterically more demanding substituents at the silyl ether tether would encourage the initially formed carbocationic intermediate **24aa** to collapse by nucleophilic attack at the less sterically hindered trimethylsilyl group. With this reasoning in mind, we prepared γ-aminosilyl-substituted allylsilanes **14b** and **14c**, which would allow the methyl substituents at the silyl ether connection in (*E*)-**9aa** to be replaced with ethyl groups and even bulkier isopropyl groups, respectively (Scheme 10). These compounds were prepared by using a similar approach to that employed in the synthesis of our first-generation silane (*E*)-**9aa** (Scheme 5); however, the presence of bulkier groups in the starting dialkyldichlorosilane required slight modifications to our previous methods (see the Experimental Section in the Supporting Information for full

(44) Evidence for a stepwise reaction mechanism in the reaction of allylsilanes with electrophiles: Fleming, I.; Langley, J. A. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1421–1423.

(45) Lambert, J. B.; Zhao, Y.; Emblidge, R. W.; Salvador, L. A.; Liu, X. Y.; So, J. H.; Chelius, E. C. *Acc. Chem. Res.* **1999**, *32*, 183–190.

(46) The energetic barrier to bond rotation will be very low.

(47) (a) Merten, J.; Hennig, A.; Schwab, P.; Fröhlich, R.; Tokalov, S. V.; Gutzeit, H. O.; Metz, P. *Eur. J. Org. Chem.* **2006**, 1144–1161. (b) Alcaide, B.; Almendros, P.; Aragoncillo, C. *Chem. Eur. J.* **2002**, *8*, 1719–1729. (c) Stragies, R.; Blechert, S. *Tetrahedron* **1999**, *55*, 8179–8188. (d) Qi, X.; Montgomery, J. *J. Org. Chem.* **1999**, *64*, 9310–9313. (e) Yamashita, K.; Sato, F. *Tetrahedron Lett.* **1996**, *37*, 7275–7278. (f) Angell, R.; Parsons, P. J.; Naylor, A.; Tyrrell, E. *Synlett* **1992**, 599–600. (g) Suzuki, K.; Hasegawa, T.; Imai, T.; Maeta, H.; Ohba, S. *Tetrahedron* **1995**, *51*, 4483–4494. (h) Angoh, A. G.; Clive, D. L. J. *J. Chem. Soc., Chem. Commun.* **1984**, 534–536.

(48) In our work on the synthesis of β-allyl-*C*-mannosyl derivatives using a related intramolecular allylation strategy, the isolation of intermediates along this mechanistic pathway supports this proposed mechanism: see reference 23e.

(49) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841–1860.

(50) We do not discount a non-concerted elimination pathway in which ionization first generates an allyl carbocationic intermediate, which then collapses to the diene through loss of the trimethylsilyl group. However, the carbocationic intermediate would again be expected to give rise to an (*E*)-diene product for similar reasons to those outlined in the text.

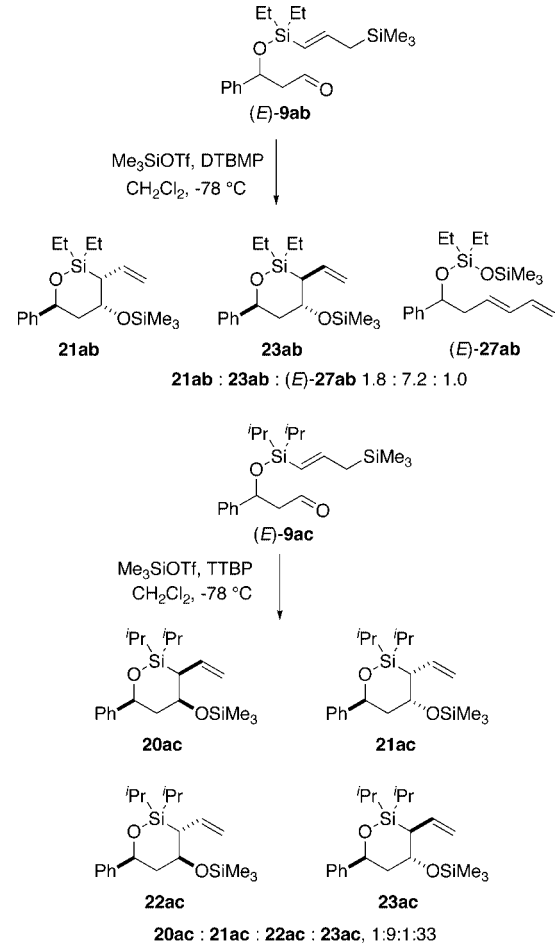
details). First, it is noteworthy that the final allylsilane products **14b** and **14c**, and the intermediates **15b** and **15c**, and **16b** and **16c**, were all appreciably less hydrolytically labile than their dimethylsilyl analogues, which made for more straightforward workup and purification procedures and led to improved yields of the products. In the case of diethylsilyl-substituted allylsilane **14b**, tethering to β-hydroxy ester **13a** was achieved in an identical fashion to that used for dimethylsilyl derivative **14a**; however, for the diisopropylsilyl analogue **14c**, the increased steric bulk of the isopropyl substituents resulted in a very slow reaction, which led to reduced yields of the silyl ether product owing to slow decomposition of both the ester (dehydration to the enoate) and amino silane (hydrolysis to the silanol) starting materials. To improve matters, aminosilane **14c** was therefore converted to the corresponding chlorosilane **26c** by treatment with acetyl chloride;[51] without isolation, addition of β-hydroxy ester **13a** and imidazole to the reaction mixture, provided the desired silyl ether (*E*)-**12ac** in greatly improved yield. The aldehyde precursors (*E*)-**9ab** and (*E*)-**9ac** were once again obtained in excellent yield by treating the corresponding esters with DIBALH (Scheme 10).

We were delighted to observe that treating aldehyde (*E*)-**9ab** with Me_3SiOTf,[52] in the presence of DTBMP, which was again necessary to avoid premature cleavage of the silyl ether by adventitious triflic acid, provided two of the possible four diastereoisomeric oxasilacycles, **21ab** and **23ab**, as the major products,[53] along with a small amount of the diene (*E*)-**27ab**[54] (Scheme 11). When aldehyde (*E*)-**9ac** containing the bulkier diisopropylsilyl tether was treated with Me_3SiOTf/DTBMP under the same reaction conditions, diene formation was suppressed completely, although the 1,3-stereoinduction (see below) was eroded slightly with all four possible diastereoisomers **20ac**, **21ac**, **22ac**, and **23ac** now being observed in the ratio 1:9:1:33 (Scheme 11). The relative stereochemistry in these products was determined by extensive NMR experiments, and in particular with NOE data (see the Supporting Information for full details).

Preferring to sacrifice an improvement in chemoselectivity for better stereoselectivity, we investigated a range of aldehydes (*E*)-**9ab**−(*E*)-**9hb**, all containing a diethylsilyl ether connection, to demonstrate the generality of the process. The cyclization precursors were prepared as outlined in Scheme 10, from aminosilane **14b** and the corresponding β-hydroxy esters **13a**−**h**, which were accessed uneventfully by a Reformatski reaction between ethyl bromoacetate and the corresponding aldehyde.[55] In all cases, only two out of the possible four diastereoisomers, **21** and **23**, were observed, owing to complete 1,3-stereoinduction in the cyclization. Levels of 1,4-induction were more modest ranging from 2.7:1 to 9.7:1 in the best case (Table 1). Dienes (*E*)-**27** were again obtained as minor side products.

As alluded to in the introductory paragraphs, retaining the silyl ether connection in the allylation products provided us with a compound that is ripe for elaboration. For our purposes, the presence of an electronegative substituent on the diethylsilyl group renders the C−Si bond in the oxasilacycle amenable to oxidation by using the Tamao−Kumada protocol.[56] Significantly, since this transformation is a stereospecific process in which the configuration at the carbon center, which is undergoing oxidation, is retained,[57] a single diastereoisomeric allylation product should furnish a single stereodefined 1,2,4-triol product on oxidation. In this way, a tether formation−allylation−oxidation sequence would provide a route to a net hydroxyallylation of an aldehyde.[58] Moreover, while extensive NMR experiments, in particular NOE measurements, had allowed us to assign the relative stereochemistry in the two allylation products, we were keen to use the triol oxidation products to confirm our assignments. Owing to the very low polarity of the oxasilacycles, which rendered separation of these products from the diene side product and Brønsted acid scavenger difficult,[59] the crude

SCHEME 11. Increasing the Steric Bulk of the Alkyl Groups at the Silyl Tether Suppressed Diene Formation



(51) Zechel, D. L.; Foucher, D. A.; Pudelski, J. K.; Yap, G. P. A.; Rheingold, A. L.; Manners, I. *J. Chem. Soc., Dalton Trans.* **1995**, 1893–1899.

(52) This Lewis acid had shown greatest promise in our early studies with **9aa**.

(53) One could argue that the other two diastereoisomers, which both contain an equatorially oriented $OSiMe_3$ substituent, undergo elimination and provide the source of diene; however, the exclusive formation of the (*E*)-diene would point against this.

(54) Diene (*E*)-**27** was not particularly stable; however, in some cases, small amounts of this side product could be isolated by HPLC and at least partially characterized (see the Supporting Information).

(55) Picotin, G.; Miginiac, P. *J. Org. Chem.* **1987**, *52*, 4796–4798.

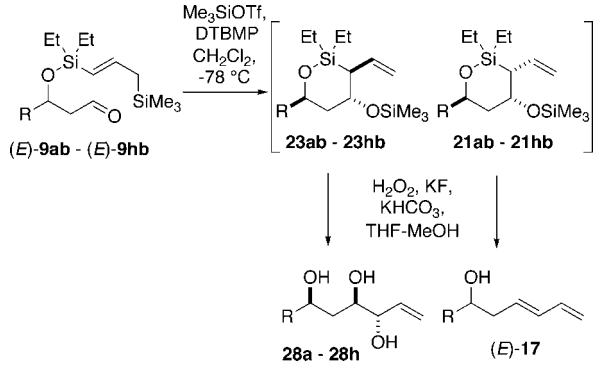
(56) (a) Tamao, K.; Ishida, N.; Kumada, M. *J. Org. Chem.* **1983**, *48*, 2120–2122. (b) Fleming, I. *Chemtracts: Org. Chem.* **1996**, *9*, 1–64.

(57) Tamao, K.; Kakui, T.; Akita, M.; Iwahara, T.; Kanatani, R.; Yoshida, J.; Kumada, M. *Tetrahedron* **1983**, *39*, 983–990.

(58) For related approaches see: (a) Toshima, K.; Arita, T.; Kato, K.; Tanaka, D.; Matsumura, S. *Tetrahedron Lett.* **2001**, *42*, 8873–8876. (b) Dankwardt, J. W.; Dankwardt, S. M.; Schlessinger, R. H. *Tetrahedron Lett.* **1998**, *39*, 4979–4982. (c) Shimura, T.; Komatsu, C.; Matsumura, M.; Shimada, Y.; Ohta, K.; Mitsunobu, O. *Tetrahedron Lett.* **1997**, *38*, 8341–8344. (d) Roush, W. R.; Grover, P. T. *Tetrahedron* **1992**, *48*, 1981–1998. (e) Barrett, A. G. M.; Malecha, J. W. *J. Org. Chem.* **1991**, *56*, 5243–5245. (f) Keck, G. E.; Boden, E. P.; Wiley, M. R. *J. Org. Chem.* **1989**, *54*, 896–906.

(59) Analytically pure samples of the allylation products were obtained by HPLC (see the Supporting Information).

TABLE 1. An Intramolecular Allylation/Tamao−Kumada Oxidation Sequence Provides a Route to Stereodefined 1,2,4-Triols



entry	aldehyde (*E*)-**9**	R	combined yield[a] of **21** + **23** (%)	**23**:**21** ratio[b]	isolated yield[c] of **28** (%)
1	**9ab**	Ph	88	3.9:1	73
2	**9bb**	2-furyl	86	4.0:1	61
3	**9cb**	cyclohexyl	83	4.9:1	51
4	**9db**	*n*-Bu	76	8.5:1	65
5	**9eb**	*i*-Bu	55	2.7:1	60
6	**9fb**	$BnOCH_2CH_2$	75	9.7:1	63
7	**9gb**	(*E*)-styryl	82	3.5:1	85
8	**9hb**	TIPS-alkynyl	92	6.7:1	34[d]

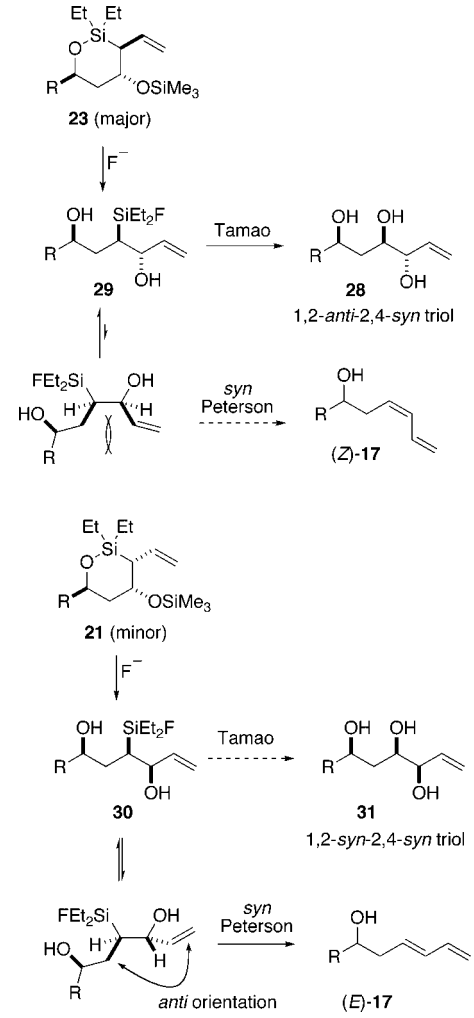
[a] Diene product accounted for the remaining material in the crude reaction mixture. [b] Ratio calculated from analysis of the crude reaction mixture by ^{1}H NMR. [c] Isolated yields following column chromatography. [d] The lower yield in this case can be attributed to competing decomposition of the TIPS-alkynyl group under the reaction conditions.

allylation product mixture was treated directly to the standard Tamao−Kumada conditions. The reaction was rather slow, requiring several days to reach completion. Notably, only the major oxasilacycles, **23ab**−**hb**, were converted efficiently to the desired 1,2,4-triol products, **28a**−**h** (Table 1); the minor allylation products, **21ab**−**hb**, were preferentially consumed in a competing Peterson olefination under the mildly basic reaction conditions.[43] This accounted for the increased amount of diene product, (*E*)-**17**, that was observed on ^{1}H NMR analysis of the crude reaction mixture.

That only the minor diastereoisomer, **21**, underwent elimination in preference to oxidation can be rationalized by considering the relative stability of the two conformers through which this reaction has to proceed to provide an elimination product (Scheme 12).[43c] In the case of the major diastereoisomer, **23**, adopting the synperiplanar alignment of the C−O and C−Si bonds in the intermediate **29**, required for the Peterson elimination, results in a build up of steric interactions (Scheme 12). As a consequence, this diastereoisomer is channeled along the oxidation pathway, leading to triol **28**. In the case of the minor diastereoisomer, **21**, the bulky substituents in the synperiplanar conformer **30**, required for olefination, are *anti* to one another, which allows this diastereoisomer to follow the competing olefination pathway (Scheme 12).

Acetonide protection of the crude triol oxidation products furnished inseparable mixtures of the corresponding 1,3-dioxolanes and 1,3-dioxanes, with the former predominating as expected.[60] Owing to the minor allylation product undergoing elimination preferentially (Scheme 12), an acetonide derived

SCHEME 12. Different Behavior of the Two Diastereoisomeric Allylation Products under the Tamao−Kumada Oxidation Reaction Conditions



from the minor triol **31** was observed in only two cases (**34a**, R = Ph, 4% and **34h**, R = TIPS-C≡C, 5%), and in these isolated examples, only the major 1,3-dioxolane product could be detected. All of the acetonide products were analyzed by ^{13}C NMR spectroscopy. The acetal resonance for the 1,3-dioxanes, **33a**−**h**, generated from the major oxidation products, **28a**−**h**, appeared in the region 98.4−99.1 ppm, which is consistent with a 1,3-*syn* diol relationship in the starting triol (Figure 2).[61] This conclusion was supported by the large difference in the chemical shifts (around 10 ppm) observed for the resonances for the two methyl groups in the protecting group (Figure 2).[61] NOE experiments supported this stereochemical assignment (Figure 2). A similar analysis of the 1,3-dioxolanes, **32a**−**h**, generated from the major oxidation products, **28a**−**h**, revealed a 1,2-*anti* relationship between these two stereogenic centers:[62] the two methyl resonances for the 1,3-dioxolanes, **32a**−**h**, appeared in two distinct regions at 25.0−25.7 and at 27.6−28.3 ppm, which is indicative of a 1,2-*anti* relationship between the vicinal alcohols in the major triol products, **28a**−**h**. Extensive NOE experiments on the minor oxasilacycle **21** had already allowed us to assign the relative stereochemistry in this

(60) (a) Kocienski, P. J.; Yeates, C.; Street, S. D. A.; Campbell, S. F. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2183–2187. (b) Mori, K.; Iwasawa, H. *Tetrahedron* **1980**, *36*, 87–90.

(61) Rychnovsky, S. D.; Rogers, B.; Yang, G. *J. Org. Chem.* **1993**, *58*, 3511–3515.

(62) Dana, G.; Danechpajouh, H. *Bull. Soc. Chim. Fr.* **1980**, 395–399.

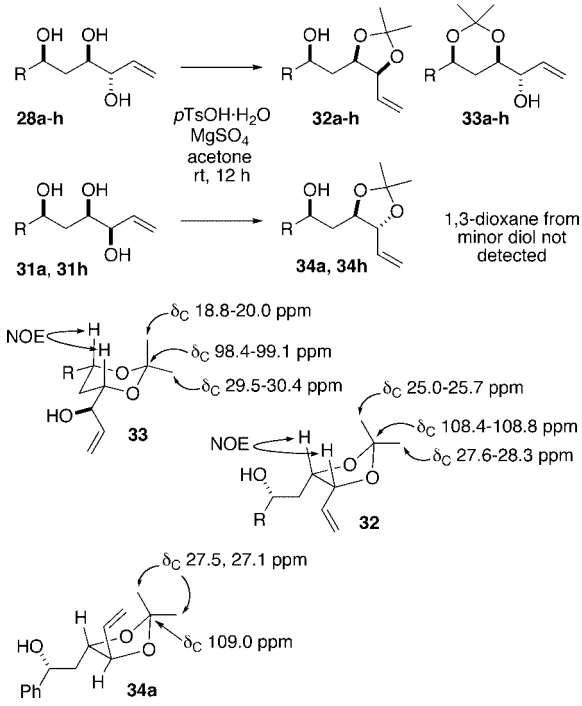
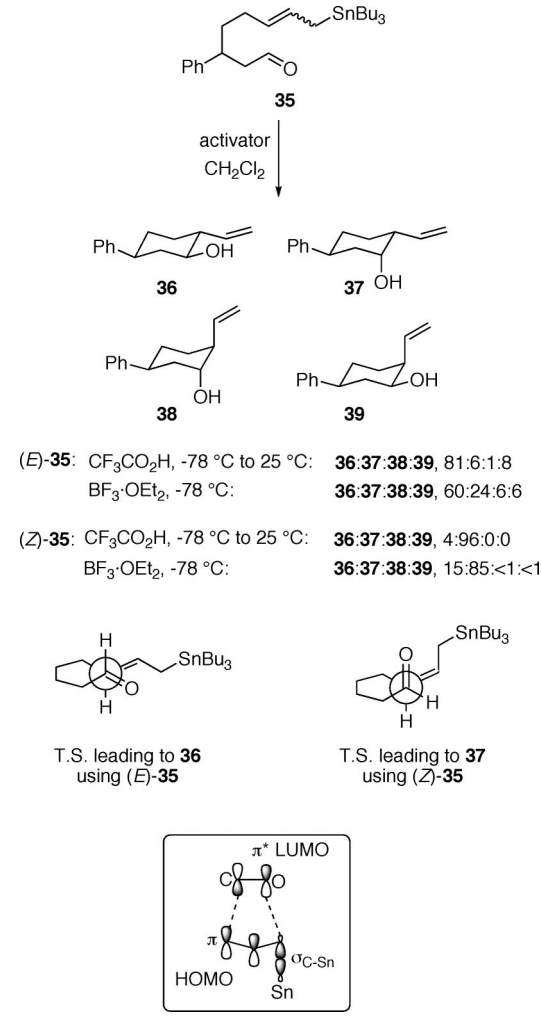


FIGURE 2. The relative stereochemistry in the products was determined by NMR spectroscopy.

product. However, the 1,2-*syn* relationship in the triol oxidation product from this diastereoisomer was confirmed by a similar analysis of the ^{13}C NMR spectra of the 1,3-dioxolanes, **34a** and **34h**, generated from **31a** and **31h**, respectively (Figure 2).[62] In these cases, the two methyl resonances for 1,3-dioxolane **34a** appeared at 27.1 and 27.5 ppm, while the two methyl resonances for 1,3-dioxolane **34h** appeared at 26.5 and 26.8 ppm. In both cases, similar chemical shifts for the two methyl resonances in the acetal protecting group are indicative of a vicinal diol displaying a 1,2-*syn* relationship.[62]

The Brønsted or Lewis acid-mediated reaction of crotylsilanes,[63] and their closely related stannane analogues[28,64] with aldehydes, has been shown to be *syn*-selective for both (*E*)- and (*Z*)-stereoisomers. It is likely that in the relatively poorly defined transition states through which this class of allylating agent reacts with aldehydes, steric,[28] stereoelectronic,[5c,25b,c] and electronic[25a,65] factors all play a role in governing the stereochemical outcome of the reaction. Furthermore, it is possible that this type of reaction proceeds through a number of low-energy reactive conformations, which are rather substrate-dependent. Mindful that gross generalizations need to be made with care, the origins of the *syn* selectivity in this type of crotylation reaction have been the subject of numerous studies, which have successfully elucidated the favored reactive conformations of type II allyl metals reacting with aldehydes.[5c,25] From these results, a range of factors that predispose the adoption of such low-energy arrangements has been proposed. One of the aims of our study was to examine whether in our tethered system, there was any preference for the reacting π-systems in the aldehyde and allylsilane to adopt a synclinal

SCHEME 13. Keck Invoked Secondary Orbital Interactions to Rationalize the Adoption of a *syn*-Synclinal Alignment of π-Systems in the Formation of the Major Diastereoisomer



or an antiperiplanar arrangement in the reactive conformation. While an antiperiplanar alignment of π-systems had been proposed originally for this type of allylation reaction,[28] synclinal alignments of the π-systems have also been shown to be important low-energy reactive arrangements that need to be considered.[5c,6,25] Keck has carried out a related study to ours using aldehyde **35** containing an allylstannane in the alkyl side chain (Scheme 13).[25a,b] Cyclization of (*E*)-**35** was effected with a variety of Lewis acid and Brønsted acid activators, and provided the corresponding 2-vinylcyclohexanols as a mixture of four diastereoisomers. In the case of allylstannane, (*E*)-**35**, which most closely resembles our own allylsilane (*E*)-**9**, the best stereoselectivity was obtained by using the Brønsted acid, CF_3CO_2H, which afforded cyclohexanols **36**, **37**, **38**, and **39** in the ratio 81:6:1:8 (Scheme 13). The stereoselectivity for the major diastereoisomer **36** was reduced when bulkier Lewis acids were employed; for example, with $BF_3 \cdot OEt_2$, cyclohexanols **36**, **37**, **38**, and **39** were now obtained in the ratio 60:24:6:6.[66] Improved stereoselectivity (for a different diastereoisomer, **37**) was observed when the (*Z*)-allylstannane was employed; thus (*Z*)-**35** reacted in the presence of CF_3CO_2H to provide cyclo-

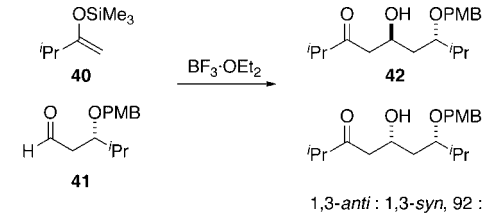
(63) Hayashi, T.; Kabeta, K.; Hamachi, I.; Kumada, M. *Tetrahedron Lett.* **1983**, *24*, 2865–2868.
(64) Keck, G. E.; Savin, K. A.; Cressman, E. N. K.; Abbott, D. E. *J. Org. Chem.* **1994**, *59*, 7889–7896.
(65) Gevorgyan, V.; Kadota, I.; Yamamoto, Y. *Tetrahedron Lett.* **1993**, *34*, 1313–1316.

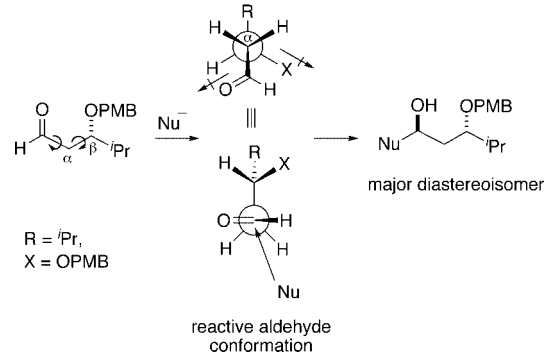
(66) The effect of size of the activator on the stereoselectivity of reactions between aldehydes and allylsilanes has also been observed by Denmark, see references 5b and 5c.

hexanols **36**, **37**, **38**, and **39** in the ratio 4:96:0:0, while with $BF_3 \cdot OEt_2$ the ratio of products was 15:85:<1:<1. To rationalize the observed stereoselectivity, Keck invoked transition state conformations in which the aldehyde and allylstannane assume a *syn*-synclinal orientation and proposed that these can benefit from a favorable interaction between the π^* LUMO of the aldehyde electrophile and the HOMO of the allylsilane nucleophile. In the absence of steric and other interactions, this frontier orbital effect could then account for the observed stereoselectivity (Scheme 13).[67]

Were such secondary orbital interactions controlling the stereochemical outcome of our cyclization, it would be the two diastereoisomers, **20** and **22**, which we do *not* observe (at least with the diethylsilyl tether) that would be expected to predominate; in our case, it is those two diastereoisomers, **21** and **23**, which *cannot* benefit from the proposed secondary orbital interaction that are observed. Keck's cyclization precursors differ principally in the atoms linking the electrophile and nucleophile. In Keck's substrates, an all-carbon chain connects the two reacting groups, whereas in our cyclization precursors the $-CH_2CH_2-$ unit is substituted for a $-OSiEt_2-$ motif. To rationalize the observed stereochemical outcome of our reactions, we therefore need to consider other factors that might affect the relative energies of the transition states leading to the four diastereoisomeric cyclization products. The intramolecular allylation reaction of aldehyde (*E*)-**9** containing a diethylsilyl ether tether exhibited complete 1,3-stereoinduction while 1,4-induction was more modest (Table 1). To rationalize the high 1,3-induction we propose that the reaction is governed by electronic factors and proceeds through a chair-like transition state in which the R substituent in the cyclization precursor adopts a pseudoequatorial orientation; this is in analogy to Keck's substrates (Scheme 13). To provide the observed sense of 1,3-induction, the aldehyde functionality must then adopt a pseudoaxial orientation. The addition of nucleophiles into aldehydes containing a β-carbinol stereogenic center has been investigated previously. Evans has looked at this problem in detail and proposed a model, which rationalizes the high stereoselectivity that can sometimes be observed in this type of addition reaction.[68,69] For example, he showed that the $BF_3 \cdot OEt_2$-mediated Mukaiyama aldol reaction of silyl enol ether **40** with β-silyloxy aldehyde **41** generates the corresponding aldol products with high stereoselectivity, favoring the diastereoisomer **42** in which there is a 1,3-*anti* relationship between the existing and new carbinol stereogenic centers (Scheme 14).[68] Under the rather apolar reaction conditions in which this (and our own) reaction is performed, Evans proposes a reactive conformation for **41** outlined in Scheme 14. Looking along the carbonyl-carbon$-C_\alpha$ bond, the conformation is very similar to that proposed by Felkin and Anh in which the bulky substituent lies orthogonal to the carbonyl functionality.[70] Next, considering rotation along the $C_\alpha - C_\beta$ bond, Evans favors a staggered conformation in which the dipole moments across the polar C—O and C═O bonds are opposed and steric interactions

SCHEME 14. Evans Proposes an Electrostatic Model to Rationalize the Diastereoselectivity





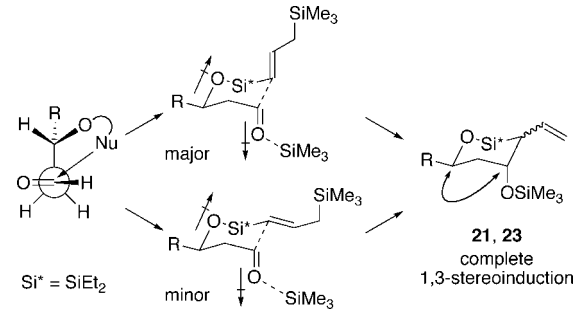


FIGURE 3. An electrostatic argument rationalizes the observed 1,3-stereoinduction.

minimized. Approach of the nucleophile along a Bürgi−Dunitz trajectory opposite the large group on this conformer then gives rise to the 1,3-*anti* diastereoisomer **42**.[68]

Our proposed chair-like transition state in which the aldehyde adopts a pseudoaxial position similarly minimizes electrostatic interactions (Figure 3); the 1,3-*syn* stereochemistry observed in our products, **21** and **23**, which is opposite to that obtained in Evans' study, can be explained by the fact that tethering the allylsilane to the aldehyde electrophile delivers the nucleophile to the opposite diastereoface (cf. Reetz's allylations in Scheme 2).

If electrostatic effects are responsible for the 1,3-stereoinduction in our allylation, one would expect that carrying out the reaction in solvents with higher dielectric constants might lead to an erosion in the level of 1,3-induction. Unfortunately, attempted cyclization of (*E*)-**9ab** in more polar solvents (MeCN, THF, acetone) led to a complex mixture of products, which was difficult to analyze. However, support for our proposals comes from some related work, which we have recently carried out on the synthesis of 2,4,5-tetrahydropyrans (Table 2).[71] In this study, the diethylsilyl tether present in aldehyde (*E*)-**9ab** was replaced with a methylene unit to provide **43**. Removal of the labile silyl ether linkage provided a more robust substrate that now allowed us to investigate the cyclization in a variety of

(67) Frontier orbital-controlled allylations have also been proposed by Denmark, see reference 25c.

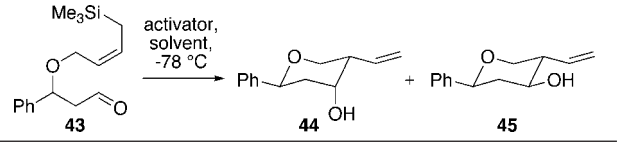
(68) (a) Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G. *J. Am. Chem. Soc.* **1996**, *118*, 4322–4343. (b) Evans, D. A.; Duffy, J. L.; Dart, M. J. *Tetrahedron Lett.* **1994**, *35*, 8537–8540. (c) Evans, D. A.; Dart, M. J.; Duffy, J. L. *Tetrahedron Lett.* **1994**, *35*, 8541–8544.

(69) This model has also been supported by computational calculations: Bonini, C.; Esposito, V.; D'Auria, M.; Righi, G. *Tetrahedron* **1997**, *53*, 13419–13426.

(70) (a) Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199–2204. (b) Anh, N. T.; Eisenstein, O. *Nouv. J. Chem.* **1977**, *1*, 61–70.

(71) Jervis, P. J.; Kariuki, B. M.; Cox, L. R. *Org. Lett.* **2006**, *8*, 4649–4652.

TABLE 2. Replacing the Diethylsilyl Tether with a Methylene Bridge Provides a Route to 2,4,5-Tetrahydropyrans Where the 1,3-Stereoinduction Exhibits a Strong Solvent Dependency



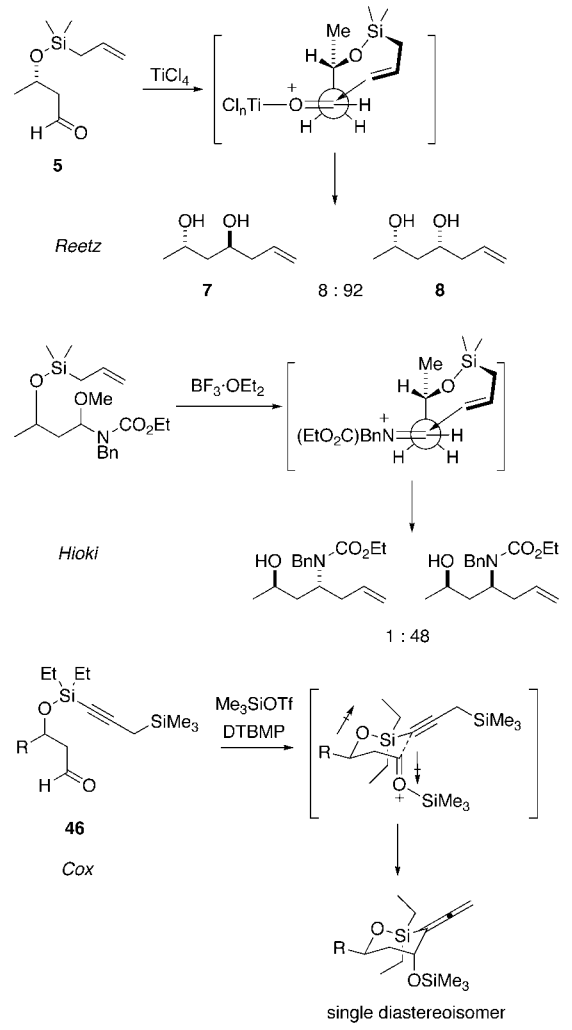
solvent	activator	**44**:**45** ratio
MeCN−CH_2Cl_2 1:1	Me_3SiOTf	5:1
CH_2Cl_2	Me_3SiOTf	12:1
CH_2Cl_2	TfOH	30:1
toluene	TfOH	>50:1

solvent systems. In the event, intramolecular allylation of **43** in the presence of TfOH or Me_3SiOTf afforded two out of the possible four diastereoisomers, **44** and **45**,[71] in this instance as a result of the cyclization proceeding with complete 1,4-induction. The levels of 1,3-induction proved to be strongly dependent on the dielectric constant of the solvent and on the activator employed (Table 2). The best results (leading to the same sense of 1,3-induction as observed in the present work, i.e., to the production of **44**) were observed when the reaction was performed in the apolar solvent, toluene, as would be predicted if the 1,3-stereoinduction was under electrostatic control. The size of the activator also influenced the level of 1,3-induction, with the Brønsted acid, which would minimize the size of the activated aldehyde functionality when it occupies a sterically less favorable pseudoaxial orientation, providing the best results.

Our proposed electrostatic model also rationalizes a number of related reactions. For example, having demonstrated the reaction was an intramolecular process, Reetz invoked chelation-control to account for the 1,3-*syn* selectivity, which was observed in the reaction of aldehyde **5** under $TiCl_4$ activation (Scheme 2).[24g] Ti(IV) Lewis acids are commonly used in chelation-controlled processes, although it is relatively unusual to invoke a silyl ether oxygen as a donor group, owing to their relatively low Lewis basicity (compared with alkyl ethers).[72] While it is not unreasonable to consider the allyldimethylsilyl group sufficiently small to permit the formation of the chelate intermediate **6** with the proximal carbonyl residue, intramolecular delivery of the allyl nucleophile to the *re* face (as drawn in Schemes 2 and 15) is stereoelectronically disfavored.[73] The electrostatic model, which rationalizes the sense of 1,3-stereoinduction in our system, also predicts the stereochemical outcome observed by Reetz in his system without the need to invoke chelation (Scheme 15). Results from a related study from Hioki and co-workers can also be explained by using a similar argument (Scheme 15),[24f,74] as can the observed 1,3-stereoinduction in the intramolecular allenylation of propargylsilane **46**, carried out in our own laboratories (Scheme 15).[23c]

Davis' reduction of β-hydroxy ketones using a tethered diisopropylsilane to deliver the hydride nucleophile intramolecularly to the proximal carbonyl group is one of the most stereoselective methods for forming 1,3-*anti* diols (Scheme

SCHEME 15. An Electrostatic Model Rationalizes the Stereochemical Outcome of Other Intramolecular Allylation and Allenylation Reactions



16).[75] Davis used a steric argument to explain the observed *anti* selectivity; thus reaction of ketone **47** proceeds through a chair-like transition state in which the carbonyl group adopts a pseudoaxial position, enabling the keto substituent to occupy a pseudoequatorial orientation and thereby minimize 1,3-diaxial interactions. However, it is not unreasonable to argue that the Lewis acid-complexed carbonyl group in the favored transition state is actually larger than the methyl substituent. If this is the case, then the proposed electrostatic arguments would still rationalize the high *anti* stereoselectivity that is observed in this reaction (Scheme 16).

As mentioned earlier, the reaction of aldehyde (*E*)-**9ac**, which contains a bulkier diisopropylsilyl ether tether, proceeded with the same sense of 1,3-stereoinduction although in this case there was a slight erosion in stereoselectivity (Scheme 11). We tentatively propose that this slight drop in selectivity is a consequence of increased 1,3-diaxial interactions between the pseudoaxially oriented aldehyde and the pseudoaxial isopropyl substituent (cf. Davis' reduction in Scheme 16).

The 1,4-induction in the reaction of aldehydes (*E*)-**9ab**−(*E*)-**9hb** (and aldehyde (*E*)-**9ac**) was modest, varying from 9.7:1 in the best case to 2.7:1 in the worst (Table 1). While rationalizing

(72) Certain aluminum Lewis acids have been proposed to form chelates between carbonyl groups and a β-silyl ether functionality: Evans, D. A.; Allison, B. D.; Yang, M. G.; Masse, C. E. *J. Am. Chem. Soc.* **2001**, *123*, 10840–10852.

(73) (a) Stevens, R. V. *Acc. Chem. Res.* **1984**, *17*, 289–296. (b) Deslongchamps, P. In *Stereoelectronic Effects in Organic Chemistry*; Baldwin, J. E., Ed.; Pergamon: Oxford, UK, 1983; Vol. 1, Chapter 6.

(74) A chelation-control argument cannot be used to rationalize the stereochemical outcome in this example.

(75) Anwar, S.; Davis, A. P. *Tetrahedron* **1988**, *44*, 3761–3770.

SCHEME 16. An Electrostatic Model Rationalizes the Observed 1,3-*anti* Selectivity in Davis' Reduction of *β*-Hydroxy Ketones

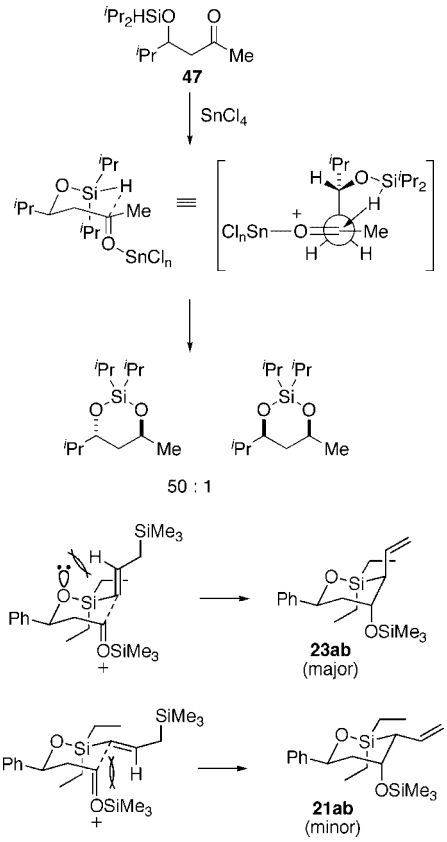
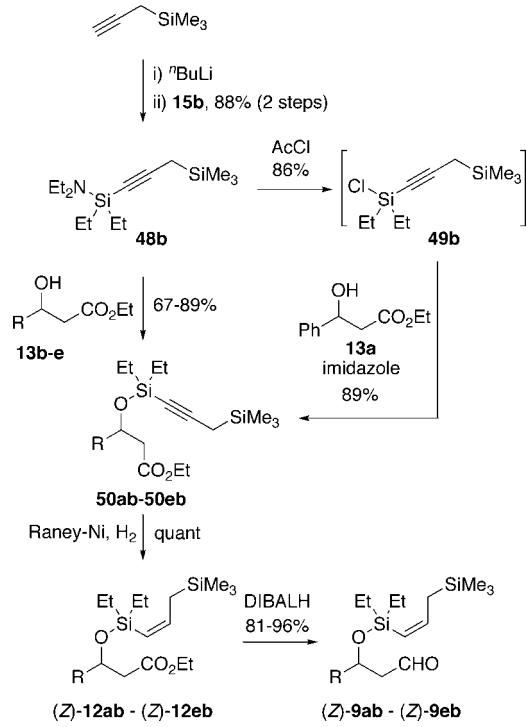


FIGURE 4. Steric interactions rationalize the observed 1,4-stereoinduction.

relatively small differences in selectivity needs to be made with care, we considered the two chair-like transition states leading to the observed products and propose that that leading to the minor diastereoisomer, **21**, is disfavored owing to steric interactions between the vinylic hydrogen in the allylsilane and the pseudoaxially oriented ethyl substituent in the silyl tether, and the pseudoaxially oriented activated aldehyde (Figure 4). Placing the allylsilane in a pseudoaxial orientation relieves these interactions as in this conformation, the vinylic hydrogen is now interacting with the axial lone pair on the silyl ether oxygen and potentially also the pseudoequatorial substituent at the silyl tether (Figure 4). The fact that the level of 1,4-stereoinduction was similar for (*E*)-**9ab** (**23ab**:**21ab**, 3.9:1) and (*E*)-**9ac** (**23ac**:**21ac** 3.5:1) could suggest that interactions between the vinylic hydrogen in the pseudoequatorially oriented allylsilane and the activated aldehyde are more significant than those with the pseudoaxial ligand at the silyl tether. Indeed the slight reduction in 1,4-induction on going from (*E*)-**9ab** to (*E*)-**9ac** might suggest additional unfavorable interactions are introduced into the transition state leading to **23** when the diisopropylsilyl tether is employed.

If the proposed steric interactions were indeed differentiating the two transition states leading to the oxasilacycles **21** and **23**, we postulated that changing the configuration of the double bond in the cyclization precursor **9** from (*E*) to (*Z*) would better differentiate these two transition states and lead to an increase in 1,4-induction in favor of **23** while having a negligible effect on the 1,3-induction. However, to counter this, we were mindful

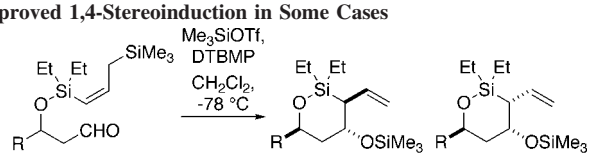
SCHEME 17. Synthesis of (*Z*)-Allylsilane Cyclization Precursors



that if Keck's frontier orbital interactions had any influence, the (*Z*)-allylsilane might lead to the preferential formation of the minor oxasilacycle **21** (cf. the reaction of (*Z*)-**35** in Scheme 13).[25b] Thus, a *change* in the degree of 1,4-induction observed in the cyclization of (*Z*)-**9** would allow us to probe the relative importance of steric and stereoelectronic effects in governing the stereochemical outcome of this intramolecular allylation.

Synthesis of this modified aldehyde precursor (*Z*)-**9** called for a slight change in the synthetic strategy, which is outlined in Scheme 17. *γ*-(Amino)silyl-substituted propargylsilane **48b** was prepared from the reaction of lithiated propargyltrimethylsilane with amino(chloro)silane **15b**. Stirring aminosilane **48b** with *β*-hydroxy esters **13b**−**e** in the absence of solvent at 40 °C for 2 days provided the desired silyl ethers **50bb**−**eb** in good to excellent yield. For the phenyl substrate, **50ab**, these silyletherification conditions led to preferential elimination so in this case, aminosilane **48b** was first converted to the corresponding chlorosilane **49b** by treatment with acetyl chloride.[51] Tether formation with alcohol **13a** could then be achieved by reaction with chlorosilane **49b** under standard conditions. Having formed the silyl ether tether in **50**, a number of methods was examined for effecting partial reduction of the alkyne functionality. Lead-poisoned Pd on $CaCO_3$ and quinoline-poisoned Pd on $BaSO_4$ under a hydrogen atmosphere led to a complex mixture of products resulting from over-reduction, translational isomerization of the olefin reduction product, and mixtures of both the (*Z*)- and (*E*)-stereoisomers. Raney nickel offered a more controlled hydrogenation, and with care, the reaction could be stopped before over-reduction to the alkane became a problem, to provide (*Z*)-**12** in good yield; however, even under these conditions we still observed varying amounts of the corresponding (*E*)-stereoisomer and trace amounts of an olefin product, which we tentatively suggest is an (*E*)-allylsilane resulting from translational isomerization of the double bond. DIBALH reduction of esters (*Z*)-**12ab**−(*Z*)-**12eb** once again

TABLE 3. Intramolecular Allylation with Allylsilane (*Z*)-9 Led to Improved 1,4-Stereoinduction in Some Cases



(*Z*)-**9ab** - (*Z*)-**9eb** **23ab** - **23eb** **21ab** - **21eb**

entry	aldehyde (*Z*)-**9**	R	combined yield[a] of **21** + **23** (%)	**23**:**21** ratio[b]
1	(*Z*)-**9ab**	Ph	92	15:1
2	(*Z*)-**9bb**	2-furyl	95	21:1
3	(*Z*)-**9cb**	cyclohexyl	50	14:1
4	(*Z*)-**9db**	*n*-Bu	79	9:1
5	(*Z*)-**9eb**	*i*-Bu	55	7:1

[a] Diene product accounted for the remaining material in the crude reaction mixture. [b] Ratio calculated from analysis of the crude reaction mixture by ^{1}H NMR.

proceeded uneventfully to provide the corresponding aldehyde cyclization precursors (*Z*)-**9ab**−(*Z*)-**9eb** in excellent yield (Scheme 17).

Aldehydes (*Z*)-**9ab**−**eb** were subjected to our standard cyclization conditions and generated the corresponding allylation products in good yield. Dienes, (*E*)-**27**, again accounted for the mass balance in these reactions. In all cases, we were pleased to observe the formation of just two diastereoisomers, **21** and **23**. Furthermore, in the majority of cases, the level of 1,4-stereoinduction was better, in some cases significantly so, than that observed in the reaction employing the corresponding (*E*)-stereoisomer, (*E*)-**9**; however, the increase in 1,4-induction was not uniform for all examples (Table 3). Substrates (*Z*)-**9ab** and (*Z*)-**9bb** containing an aryl substituent at the carbinol stereocenter showed the most dramatic improvement in 1,4-induction; the 1,4-induction in cyclohexyl derivative (*Z*)-**9cb** was also significantly better although in this case, the diene side product, (*E*)-**27cb**, was formed in higher amounts. Isobutyl derivative (*Z*)-**9eb** afforded a small but significant improvement in 1,4-induction, while perhaps most interestingly, the level of 1,4-induction for the *n*-butyl derivative, (*Z*)-**9db**, which had been one of the best substrates with use of the (*E*)-allylsilane (Table 1, entry 4), remained essentially unchanged when its (*Z*)-stereoisomer was employed.

It is difficult to account for these interesting observations and here we simply offer a few comments for consideration. It appears that the degree of improvement in 1,4-induction is a function of the steric bulk of the substituent at the carbinol stereogenic center, with the bulkiest groups (as measured by their *A* values) affording the most significant improvements. It would be expected that these groups provide the strongest conformational anchor in a chair-like transition state. The straight alkyl chain in (*Z*)-**9db** will provide a weaker anchoring effect, which may allow the reactive conformation to deviate significantly from a chair, in which case, additional factors that we have not considered may be more important in determining the 1,4-induction.

Conclusions

In summary, we set out to investigate the stereoselectivity of an intramolecular allylation reaction involving an allylsilane that had been tethered through the γ-terminus of the allyl nucleophile to a range of β-hydroxy aldehydes via a temporary silyl ether connection. By studying the relative stereochemistry in the product oxasilacycles we would then be able to ascertain the reactive conformation of the nucleophile and electrophile, and in doing so, probe the factors that control the stereochemical outcome of allylation reactions involving type II allyl metals. To this end, we have described the synthesis of a series of γ-aminosilyl-substituted allylsilanes and shown that these can be tethered to a selection of β-hydroxy aldehyde electrophiles. The size of the substituents in the silyl tether proved to be critical for governing the chemoselectivity of the allylation reaction: too small ($SiMe_2$) and a diene is the end product, too large (Si^iPr_2) and all four diastereoisomeric allylation products are obtained. A tether of intermediate steric bulk ($SiEt_2$) provides the best compromise. By analyzing the relative stereochemistry in the oxasilacycle products we have provided a rationale for the observed levels and sense of 1,3-stereoinduction based on Evans' dipole minimization model; thus it seems that in our case, the reaction is not controlled by frontier orbital interactions but by electrostatic effects. A model to account for the 1,4-stereoinduction based on minimization of steric interactions has also been proposed and from this we were able to predictably improve the 1,4-induction by using the stereoisomeric (*Z*)-allylsilane. That there is not a universal increase in 1,4-induction for all substrates suggests that our working transition state model may require modification, at least in some cases.

As an added bonus, the oxasilacycle allylation products are also ripe for elaboration. For example, we used an oxidative cleavage of the temporary silicon connection to verify the relative stereochemistry of the allylation products, and in the best cases with use of a (*Z*)-allylsilane, this intramolecular allylation/Tamao−Kumada oxidation sequence provides a highly stereoselective route to 1,2-*anti*-2,4-*syn* triols.

This study once again highlights the complexity of such a commonly used reaction as an allylation of an aldehyde. A multitude of factors can influence the stereochemical outcome of this reaction and steric, electronic, and stereoelectronic factors should all be considered. The relative importance of each depends on the reagents and reaction conditions; in the present study we advance an electrostatic controlling factor to be important and propose that this can be applied to a range of other stereoselective reactions.

Experimental Section

General Procedure for the Synthesis of Silyl Ether 12 from Alcohol 13 and Aminosilane 14. Alcohol **13** (50 mmol) and aminosilane **14** (50 mmol) were stirred at 40 °C for 2 d. Evaporation of the Et_2NH byproduct and purification of the residue by flash column chromatography (eluent Et_2O in hexane) afforded silyl ether **12** as a colorless liquid.

General Procedure for the Synthesis of Aldehyde 9 from Ester 12. DIBALH (31.7 mL, 1.5 M in toluene, 47.6 mmol) was added dropwise over 30 min to a solution of ester **12** (47.0 mmol) in CH_2Cl_2 (470 mL) at −78 °C. After 1 h, the reaction was quenched with MeOH (1.93 mL, 47.6 mmol) and H_2O (5.19 mL, 285.6 mmol) at −78 °C, and the resulting slurry was allowed to warm to rt. It was then filtered through $MgSO_4$ and Celite and the solvent was evaporated under reduced pressure to leave a yellow liquid, which was purified by flash column chromatography (eluent Et_2O in hexane) to afford aldehyde **9** as a colorless liquid.

General Procedure for Allylation Reaction: Synthesis of Oxasilacycles 23aa−ha and 21aa−ha. TMSOTf (1.0 equiv) was added dropwise (approximately one drop per second) via syringe to a solution of aldehyde **9** (1.0 equiv) and 2,6-DTBMP or TTBP (1.2 equiv) in CH_2Cl_2 (0.1 M reaction concentration) at −78 °C. The reaction mixture was stirred at −78 °C. TLC indicated

consumption of starting material within 8−16 h. The reaction mixture was then quenched by adding an equivalent volume of $NaHCO_3$ solution at −78 °C and allowed to warm to rt over 30 min. The two phases were separated and the aqueous phase was extracted with CH_2Cl_2 (two times the volume of aqueous phase). The combined organic extracts were successively washed with H_2O (one-third volume of organic phase) and brine (one-third volume of organic phase) and dried over $MgSO_4$. Filtration and evaporation of the volatiles under reduced pressure provided a yellow oil (quantitative mass recovery). This was used in the following Tamao−Kumada oxidation without further purification. Analytically pure samples of each oxasilacycle were obtained by preparative HPLC.

General Procedure for Tamao−Kumada Oxidation: Formation of Triols 28a−h. H_2O_2 (20 equiv, 60% in H_2O), $KHCO_3$ (3.0 equiv), and KF (5.0 equiv) were added to a solution of the products from the allylation of aldehyde **9** (1 equiv) in MeOH:THF (1:1) (0.1 M reaction concentration) and the resulting mixture was stirred at rt. The progress of the reaction was monitored by TLC and consumption of the starting material occurred within 4 to 7 d (an additional 5 equiv of H_2O_2 was sometimes added after a few days to drive the reaction to completion). The mixture was then poured into an equal volume of $Na_2S_2O_3$ solution and stirred for 30 min. The resulting mixture was extracted with EtOAc (3 × two volumes) and the combined organic extracts were washed with brine (ca. one-sixth volume of EtOAc) and dried ($MgSO_4$). Filtration and evaporation of the volatiles under reduced pressure afforded the triol **28** as a yellow oil that was purified by flash column chromatography.

Acknowledgment. We thank the Engineering and Physical Sciences Research Council (grant no. GR/N32556) for a studentship (to J.B.), the University of Birmingham and the Engineering and Physical Sciences Research Council for a studentship (to P.J.J.), and Astra Zeneca for an unrestricted award (to L.R.C).

Supporting Information Available: General experimental details, experimental procedures and complete compound characterization data for all new compounds, scanned ^1H NMR spectra, and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO800824X