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A Three-Component Coupling Strategy for Tetrahydrofuran Synthesis: Application of the Diisopropyl Tartrate Modified (*E*)-γ-(Dimethylphenylsilyl)allylboronate as an α,γ-Allyl Dianion Equivalent

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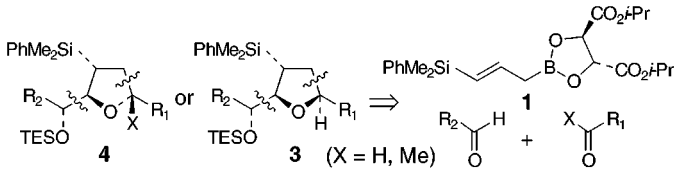
ABSTRACT



A highly convergent three-component coupling strategy for the stereocontrolled synthesis of 2,3,5-trisubstituted tetrahydrofurans is described. After allylboration of the first aldehyde with 1, the chiral, nonracemic allylsilanes 2 are coupled with a second aldehyde or ketone with Lewis acid catalysis to give tetrahydrofurans 3 or 4 with excellent selectivity. The 2,5-stereochemistry is controlled by operating under nonchelate (e.g., 3) or chelate (e.g., 4) conditions.

The stereoselective synthesis of substituted tetrahydrofurans, which are present in many biologically interesting natural products, remains a topic of considerable interest.[2] Studies from several laboratories have demonstrated that the [3 + 2] annulations of allylic and allenic silanes with enone, carbonyl, and imine electrophiles represent a powerful method for the synthesis of both carbocyclic and heterocyclic five-membered rings.[3−5] However, widespread application of this methodology in natural products synthesis has been impeded by the lack of simple, general, and highly stereoselective methods for synthesis of chiral, nonracemic allylic silanes, especially the parent allylsilanes.[3,6,7]

We have demonstrated that tartrate ester modified (*E*)-γ-silylallylboronates are useful reagents for the formal α- and γ-hydroxyallylation of aldehydes following Tamao oxidation or epoxidation−Peterson elimination of the intermediate allylsilanes.[8,9] However, it was readily apparent that this allylboration sequence also constituted an exceptionally simple route to chiral, nonracemic allylsilanes of general structure **2**. Herein we demonstrate the utility of allylsilanes **2** in the highly stereocontrolled synthesis of 2,3,5-trisubsti-

(1) Holder of the 1999−2000 American Chemical Society Division of Organic Graduate Fellowship sponsored by Eli Lilly.

(2) Elliot, M. C. *J. Chem. Soc., Perkin Trans. 1* **1998**, 4175.
(3) Masse, C. E.; Panek, J. S. *Chem. Rev.* **1995**, *95*, 1293, and literature cited therein.
(4) (a) Danheiser, R. L.; Kwasigroch, C. A.; Tsai, Y.-M. *J. Am. Chem. Soc.* **1985**, *107*, 7233. (b) Panek, J. S.; Yang, M. *J. Am. Chem. Soc.* **1991**, *113*, 9868. (c) Akiyama, T.; Ishikawa, K.; Ozaki, S. *Chem. Lett.* **1994**, 627.
(5) Roberson, C. W.; Woerpel, K. A. *J. Org. Chem.* **1999**, *64*, 1434.
(6) Suginome, M.; Matsumoto, A.; Ito, Y. *J. Am. Chem. Soc.* **1996**, *118*, 3061.
(7) Smitrovich, J. H.; Woerpel, K. A. *J. Am. Chem. Soc.* **1998**, *120*, 12998.
(8) Roush, W. R.; Grover, P. T. *Tetrahedron* **1992**, *48*, 1981.
(9) Hunt, J. A.; Roush, W. R. *J. Org. Chem.* **1997**, *62*, 1112.
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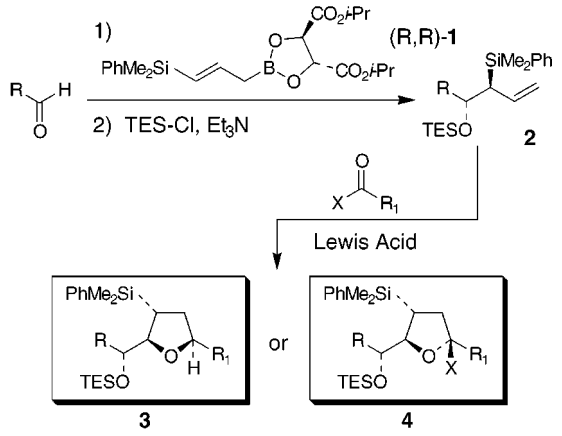
tuted tetrahydrofurans via [3 + 2] annulations with aldehydes, α-keto esters, and 1,2-diketones (Scheme 1). We also

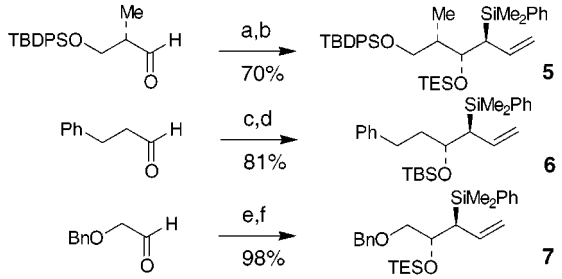
Scheme 1



demonstrate that the stereoselectivity of the annulation event can be reversed by appropriate choice of Lewis acid catalyst, thereby providing access to both 2,5-*cis*- and 2,5-*trans*-substituted tetrahydrofurans **3** and **4** with exceptional stereoselectivity.

Allylsilanes **5**−**7** were synthesized in 75−99% yield by the allylboration reactions summarized in Scheme 2.[8] The

Scheme 2

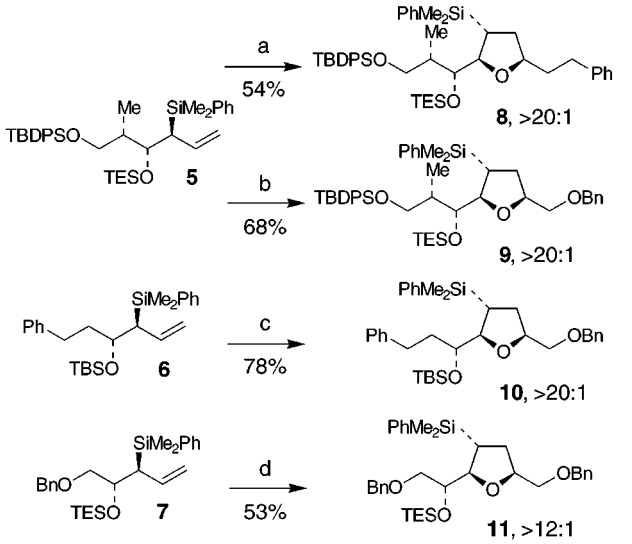


(a) **1**, PhMe, —78 °C, 4 Å mol. sieves (75%); (b) TESCl, Et_3N, DMAP, CH_2Cl_2 (93%); (c) **1**, PhMe, —78 °C, 4 Å mol. sieves (86%); (d) TBSCl, Et_3N, DMAP, $Cl(CH_2)_2Cl$, reflux (94%); (e) **1**, PhMe, —78 °C, 4 Å mol. sieves (99%); (f) TESCl, Et_3N, DMAP, CH_2Cl_2 (99%).

β-hydroxylallylsilane precursor to **5** is the product of a matched double asymmetric allylboration and was obtained with high diastereoselectivity. The enantiomeric purity of the *β*-hydroxyallylsilane corresponding to **6** was 75% ee. However, the same intermediate can be prepared in greater than 90% ee by using the chiral allylborating agent generated from $PhMe_2SiCH_2CH{=}CH_2$, KO-*t*-Bu, *n*-BuLi, and MeOB-(Ipc)$_2$ using the standard procedure for synthesis of allyl-(diisopinocampheyl)boranes.[10,11] Protection of the *β*-hydroxysilanes was achieved by using either TES-Cl or TBS-Cl in the presence of Et_3N and DMAP in CH_2Cl_2 or $Cl(CH_2)_2Cl$ (93−99% yield).

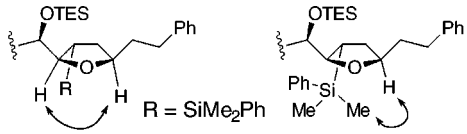
Treatment of allylsilane **5** with either hydrocinnamaldehyde or α-(benzyloxy)acetaldehyde in CH_2Cl_2 at −78 °C in the presence of $BF_3{\cdot}OEt_2$ (0.5 equiv) provided the 2,5-*cis*-tetrahydrofurans **8** and **9** in 54% and 68% yields, with >20:1 diastereoselectivity in each case (Scheme 3). Similarly, $BF_3{\cdot}$

Scheme 3



a) $Ph(CH_2)_2CHO$, $BF_3{\cdot}OEt_2$, CH_2Cl_2, —78 °C; b) $BnOCH_2CHO$, $BF_3{\cdot}OEt_2$, CH_2Cl_2, —78 °C; c) $BnOCH_2CHO$, $BF_3{\cdot}OEt_2$, CH_2Cl_2, —78 °C; d) $BnOCH_2CHO$, $BF_3{\cdot}OEt_2$, CH_2Cl_2, —78 °C.

nOe's observed for **8**:



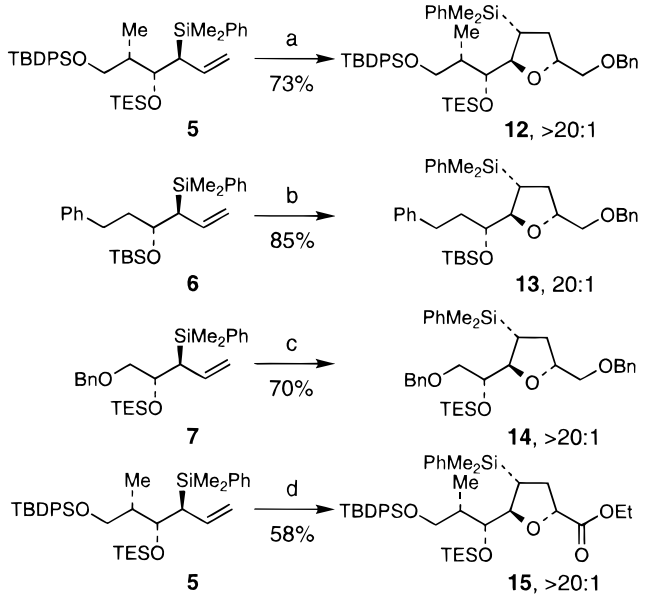
OEt_2-catalyzed [3 + 2] annulation of allylsilanes **6** and **7** with α-(benzyloxy)acetaldehyde furnishes the 2,5-*cis*-substituted tetrahydrofurans **10** and **11** in 78% and 53% yields, again with excellent diastereoselectivity. The stereochemistry within the 2,5-*cis*-tetrahydrofuran rings in each case was assigned by NOE, as summarized in Scheme 3 for the NOE's observed for **8**.

A reversal in stereoselectivity was observed when the [3 + 2] annulations with α-(benzyloxy)acetaldehyde were

(12) Denmark, S. E.; Almstead, N. G. *J. Org. Chem.* **1994**, *59*, 5130.
(13) Fleming, I.; Dunogues, J.; Smithers, R. *Org. React.* **1989**, *37*, 57.
(14) Panek, J. S.; Yang, M. *J. Am. Chem. Soc.* **1991**, *113*, 9868.
(15) Panek, J. S.; Beresis, R. *J. Org. Chem.* **1993**, *58*, 809.
(16) The stereochemistry of **18** has been fully assigned by NOE studies of the tetraisopropyldisiloxane derivative prepared from diol **19** (see Supporting Information). These data verify that inversion of the original C−Si center occurred during the [3 + 2]-cycloaddition reaction, consistent with previous literature documentation in refs 14 and 15.
(17) Mikami, K.; Kawamoto, K.; Loh, T.-P.; Nakai, T. *J. Chem. Soc., Chem. Commun.* **1990**, 1161.
(18) Panek, J. S.; Cirillo, P. F. *J. Org. Chem.* **1993**, *58*, 999.
(19) Liu, P.; Panek, J. S. *Tetrahedron Lett.* **1998**, *39*, 6143.
(20) We are also aware of one example in which the stereoselectivity of the Mukaiyama aldol reaction of a thioketene acetal and an aldehyde is reversed when performed under nonchelate- vs chelate-controlled conditions: Gennari, C.; Bernardi, A.; Scolastico, C.; Potenza, D. *Tetrahedron Lett.* **1985**, *26*, 4129.

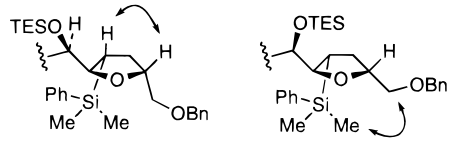
performed using $SnCl_4$ as the Lewis acid catalyst (Scheme 4). These reactions provided the 2,5-*trans*-tetrahydrofurans

Scheme 4



(a) $BnOCH_2CHO$, $SnCl_4$, CH_2Cl_2, —55 °C;(b) $BnOCH_2CHO$, $SnCl_4$, CH_2Cl_2, —55 °C; (c) $BnOCH_2CHO$, $SnCl_4$, CH_2Cl_2, —55 °C; (d) EtO_2CCHO, $SnCl_4$, CH_2Cl_2, —78 °C.

nOe's observed for **14**:

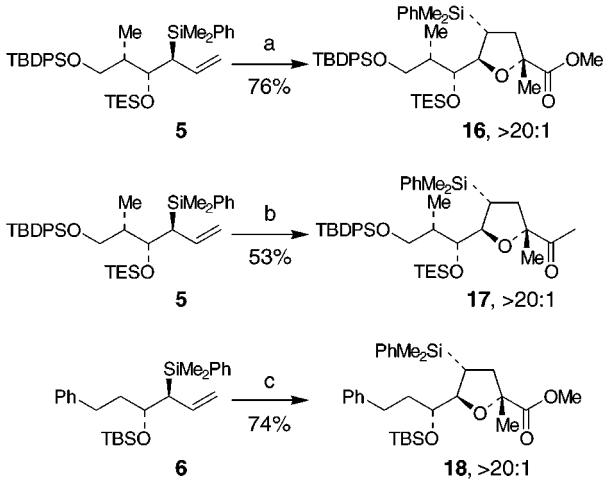


12−**14** in 70−85% yields and with >20:1 selectivity. Similar results were obtained in the reactions of allylsilanes **7** with ethyl glyoxalate (see Scheme 4). The stereochemistry in all cases was assigned by NOE experiments, as summarized for the specific case of **14**.

The chelate-controlled [3 + 2] annulation may also be extended to electron deficient ketones, thereby providing access to more highly substituted tetrahydrofurans containing a quarternary center (Scheme 5). Thus, reactions of **5** and **6** with methyl pyruvate or 2,3-butanedione promoted by $SnCl_4$ proceed in 53−76% yield, furnishing the 2,5-*trans*-substituted tetrahydrofurans **16**, **17**, and **18**, again with excellent diastereoselectivity.

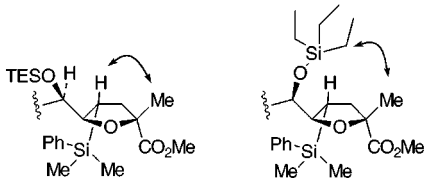
The [3 + 2] annulation reaction proceeds via stepwise *anti* S_E' addition[12,13] of the allylsilane to the Lewis acid-complexed aldehyde, followed by suparafacial 1,2-silyl migration and intramolecular ether formation, with inversion of the original C−Si stereocenter.[14−16] Our demonstration that the stereoselectivity of the [3 + 2] annulation can be reversed by selection of Lewis acid catalysts that support chelate- vs nonchelate-controlled addition is striking. Several earlier papers have demonstrated that the diastereoselectivity of Lewis acid-catalyzed reactions of substituted allylsilanes

Scheme 5



(a) $CH_3C(O)CO_2Me$, $SnCl_4$, CH_2Cl_2, —78 °C; (b) $CH_3C(O)C(O)CH_3$, $SnCl_4$, CH_2Cl_2, —78 °C; (c) $CH_3C(O)CO_2Me$, $SnCl_4$, CH_2Cl_2, —78 °C.

nOe data employed in the structure determination of **16**:



and carbonyl electrophiles may be reversed as a function of chelation vs nonchelation control.[17−20] However, all of the previous examples have involved substituted allylsilanes (of the methallyl, (*E*)-crotyl, or tiglyl types), and the interpretations provided have assumed that the olefin substituents play a role in the reversal in stereoselectivity.[17,18,21] Our results, all of which were obtained with allylsilanes lacking substituents on the double bond, indicate that the reversal of selectivity is much more fundamental in nature.[22]

Keck has provided compelling arguments that the *syn*-synclinal transition state (i.e., transition states **A** and **A′** in Figure 1, in which the carbon bearing the silicon substituent is syn to the carbonyl oxygen) are the lowest energy transition states available in the BF_3-catalyzed reactions of (*E*)-crotylstannanes and aldehydes.[21,23] We consider the quadrant of space bearing the complexed Lewis acid to be the most sterically demanding and therefore that the BF_3•Et_2O-promoted reactions should proceed preferentially via ts **A**. In the case of the chelate-controlled reactions, the *syn*-

(21) Keck, G. E.; Savin, K. A.; Cressman, E. N. K.; Abbott, D. E. *J. Org. Chem.* **1994**, *59*, 7889.

(22) Although Panek has demonstrated a reversal of stereoselectivity in the [3 + 2] cycloaddition of a chiral (*E*)-crotylsilane and a chiral aldehyde, it must be noted that the stereochemical outcome in this case was highly dependent on the relative stereochemistry of the chiral crotylsilane and the chiral aldehyde. Thus, whereas the (2*S*,3*R*)-(*E*)-crotysilane and (*S*)-2-benzyloxypropanal exibited a reversal of selectivity in reactions performed with BF_3 vs $SnCl_4$ as catalysts, the reaction of the enantiomeric (2*R*,3*S*)-(*E*)-crotysilane and (*S*)-2-benzyloxypropanal gave the same product with either BF_3 or $SnCl_4$ as catalyst. See ref 15.

(23) Denmark, S. E.; Weber, E. J.; Wilson, T.; Willson, T. M. *Tetrahedron* **1989**, *45*, 1053.

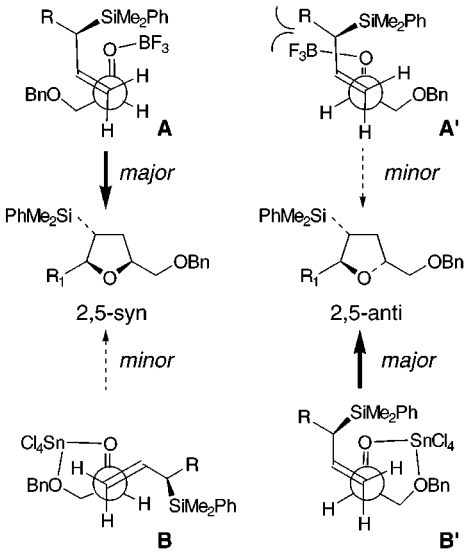


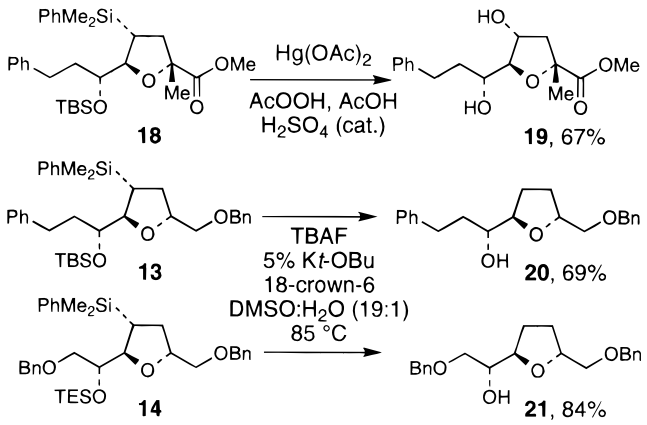
Figure 1. Synclinal transition states leading to the 2,5-*cis*- and 2,5-*trans*-tetrahydrofurans.

synclinal ts **B′** is viewed as the lowest energy pathway, since this transition structure benefits from the most favorable HOMO−LUMO interactions (as discussed by Keck).[21] We recognize that other transition structures could in principle contribute to the production of the minor isomers from each reaction (e.g., antiperiplanar arrangements), but defer a more detailed discussion of this topic to a subsequent paper.

The dimethylphenylsilyl group is a well-known surrogate for the hydroxyl group.[24] Application of the Fleming−Tamao oxidation to substrates such as **18** proceeds smoothly (Scheme 6). It is also possible to remove the silyl substituent altogether, giving tetrahydrofurans that are unsubstituted at this position. This is smootly accomplished by using a modified version of the Hudrlik procedure[25] (TBAF, 5% KO-*t*-Bu, 18-c-6, DMSO, H_2O), as illustrated by the conversion of **13** and **14** to tetrahydrofurans **20** and **21** in 69−84% yields (Scheme 6).

In summary, we have demonstrated that chiral allylsilanes of general structure **2**, generated by the allylboration of aldehydes with (*E*)-γ-(dimethylphenylsilyl)allylboronate **1** [or the analogous $(Ipc)_2$allylborane], are useful precursors for the synthesis of highly functionalized tetrahydrofurans via [3 + 2] annulations with a second carbonyl component. This methodology constitutes a general and highly convergent route to tetrahydrofurans. We have demonstrated that the stereochemistry of this annulation process can be controlled by selection of the appropriate Lewis acid catalyst, so as to produce either the 2,5-*cis*- or 2,5-*trans*-substituted tetrahydrofurans via nonchelate- and chelate-controlled pathways, respectively. The observed stereodivergence is consistent with the proposition that these annulations proceed by way of *syn*-synclinal ts's. We have shown that the silyl substituent of the products can be converted to functionality (e.g., -OH or -H) present in a range of tetrahydrofuran-containing natural products. Finally, this work clearly illustrates the potential of allylboronate **1** and the derived allylsilanes **2** for use in complex fragment assembly problems in organic synthesis, extending the scope of this chemistry beyond conventional allyl transfer reactions. Applications of this methodology in total synthesis will be reported in due course.

Scheme 6



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Supporting Information Available: Experimental details for the [3 + 2] annulations and tabulated spectroscopic data for tetrahydrofurans **12**−**21**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL9913082

(24) Jones, G. R.; Landais, Y. *Tetrahedron* **1996**, *52*, 7599.
(25) (a) Hudrlik, P. F.; Holmes, P. E.; Hudrlik, A. M. *Tetrahedron Lett.* **1988**, *29*, 6395. (b) Hudrlik, P. F.; Hudrlik, A. M.; Kulkarni, A. K. *J. Am. Chem. Soc.* **1982**, *104*, 6809.