Tetrahydrofuran Synthesis

Bimetallic Reagents of Silicon: One-Pot Synthesis of 2,3,5-Trisubstituted Tetrahydrofurans by a Double Sakurai–Hosomi Reaction**

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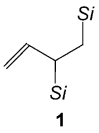
Unsaturated bimetallic reagents containing Group 14 metals, such as silicon and tin, have recently emerged as versatile coupling reagents in organic synthesis.[1,2] These reagents are particularly appealing when both metals employ a "ferryman" service to yield metal-free cyclic products in a one-pot reaction. However, examples of such reactions are rare.[2] As part of our interest in allyl organometallic compounds of silicon,[3] we envisioned that 1-silylmethyl allylic silanes **1** could be useful synthetic building blocks. In the presence of a Lewis acid, a bis-silyl reagent such as **1** affords a β-silyl carbocation **2** (Scheme 1) when treated with an aldehyde. This carbocation may then collapse to give an oxetane **3** (path a)[4] or, more likely, undergo a 1,2-silyl migration to give the thermodynamically favored bis-β-silyl carbocation **4**,[5] which produces a trisubstituted tetrahydrofuran **5** (path b).[6] The latter was realized recently by Peng and Woerpel.[7] Additionally, a third pathway is also conceivable wherein **2** collapses to give a new allylic silane **6**. The allylic silane **6** should be less reactive than the starting allylic silane **1** because its π bond is more hindered. Introduction of a second aldehyde should yield a silicon-free tetrahydrofuran **8** by trapping of the oxocarbenium ion **7** (path c). While our studies were in progress Smitrovich and Woerpel[8] reported a single experiment on the synthesis of a tetrahydrofuran lacking silyl groups by reaction of a substituted silylmethyl allylic silane and an aldehyde; however, a pure product could not be obtained and a furan structure was only tentatively assigned. Herein, we provide the first report that silylmethyl allylic silanes of type **1** can be channeled through path c to yield only 2,3,5-trisubstituted tetrahydrofurans.



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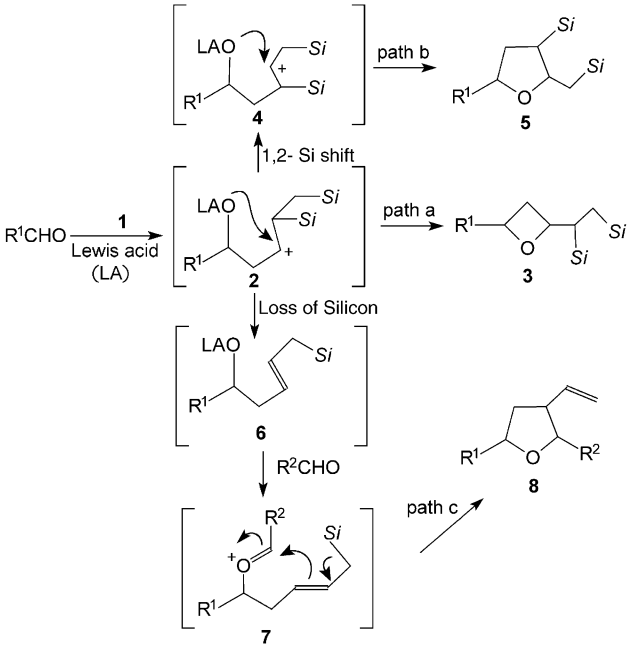
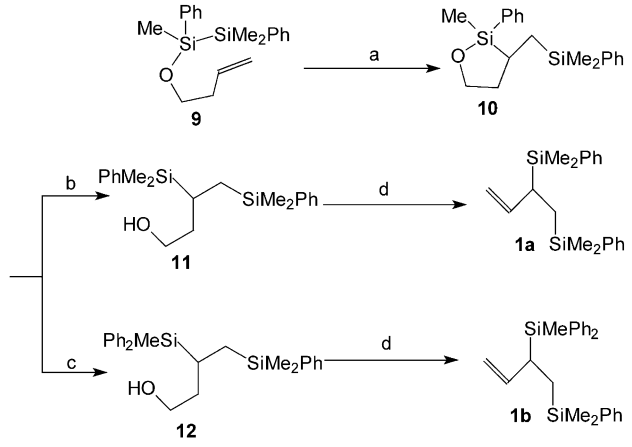


Scheme 1. Reaction of **1** with an aldehyde. *Si* = silyl group.

As the 1-silylmethyl allylic silanes **1a**,**b** (Scheme 2) selected for our study are novel, there were no reported procedures for their synthesis. Smitrovich and Woerpel experienced great difficulties in preparing similar compounds but eventually succeeded by employing allylic displacement,[9] which unfortunately could not be applied in our case since only carbamates from secondary allyl alcohols are amenable to it. Thus, a convenient synthetic methodology to this family of allylic silanes was our initial task. Our successful route (Scheme 2) involved heating disilanyl ether **9** (prepared in



Scheme 2. Reagents and conditions: a) Me_3CCN (8 mol%), $Pd(OAc)_2$ (2 mol%), toluene, reflux, 80% yield; b) MeLi, Et_2O, 75% yield; c) PhLi, Et_2O, 80% yield; d) 1. *o*-$NO_2C_6H_4SeCN$, nBu_3P, THF; 2. H_2O_2 (30%), pyridine, CH_2Cl_2, 60–68% yield over two steps.

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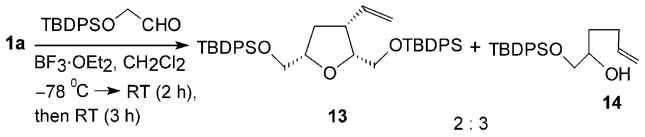
77% yield from 3-butene-1-ol and 1-chloro-1,2,2-trimethyl-1,2-diphenyldisilane) in the presence of $Pd(OAc)_2$ (2 mol%) and *tert*-butylisocyanide (8 mol%) under reflux in toluene. Intramolecular bis-silylation occurred readily to give the 1,2-oxasilolane **10** in good yield (80%).[10] Ring opening of **10** with either methyl- or phenyllithium in diethyl ether followed by Grieco dehydration[11] of the resulting alcohols **11** and **12** gave the desired allylic silanes **1a**,**b** in 45–55% overall yield from **10**.

Our initial idea for investigating the concept outlined in Scheme 1 was to treat the allylic silanes **1a**,**b** with an aldehyde containing a proximal heteroatom, such as oxygen, to allow the reaction to be performed under both chelation and nonchelation conditions. The choice of the aldehyde and reaction conditions were essential for the successful synthesis of tetrahydrofurans devoid of silicon appendages. Thus, in the presence of $BF_3{\cdot}OEt_2$,[12] **1a** was treated with (*tert*-butyldiphenylsilyloxy)ethanal to give tetrahydrofuran **13** (Scheme 3) admixed with the readily separable but undesired monoprotected glycol **14** (2:3, respectively). The latter was evidently

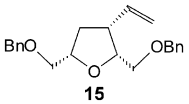
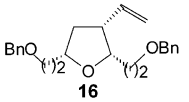
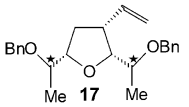
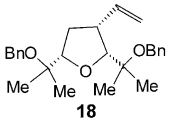


Scheme 3. The reaction of (*tert*-butyldiphenylsilyloxy)ethanal with allylic silane **1a**. TBDPSO = *tert*-butyldiphenylsilyloxy.

formed by protodesilylation of the in situ generated allylic silane (cf. **6**). Use of an additive, namely 2,6-di-*tert*-butyl-4-methylpyridine,[13] to remove traces of acid that would cause unwanted protodesilylation was ineffective. However, formation of **14** could be prevented by use of $BF_3{\cdot}OEt_2$ freshly distilled over calcium hydride to give only **13** in 50% yield. Additionally, **1b** was found to give **13** in a slightly higher yield (ca. 10%) under these conditions than did **1a**. Tetrahydrofuran **13** was formed as a single diastereomer, and the stereochemical outcome of the reaction is in accord with observations reported by Mohr.[14]

Encouraged by these findings, we investigated the scope and limitations of the one-pot tetrahydrofuran synthesis—the results of which are given in Table 1. $BF_3{\cdot}OEt_2$ was found to be the most effective Lewis acid (entry 1) and not $SnCl_4$ (entry 2), while $TiCl_4$ (entry 3) did not yield any traces of tetrahydrofuran **15**. The example in entry 4 shows the

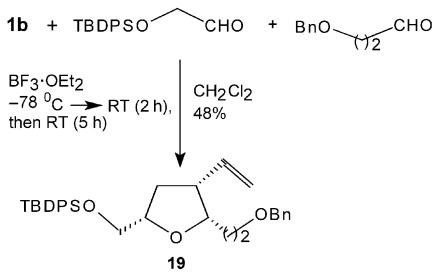
Table 1: Isolated yields for the reaction of allylic silane **1b** with aldehydes.

Entry	Aldehyde	Reaction conditions[a]	Products[b,c] (% yield)
1	BnO–CHO	$BF_3{\cdot}OEt_2$ −78 °C→RT (2 h), then RT (3 h)	 **15** (68%)
2		$SnCl_4$ −78 °C→RT (2 h), then RT (1 h)	(41%)
3		$TiCl_4$ −78 °C→RT (2 h), then RT (1 h)	(0%)
4	BnO–(CH2)2–CHO	$BF_3{\cdot}OEt_2$ −78 °C→RT (2 h), then RT (7 h)	 **16** (52%)
5	BnO–CH(Me)–CHO	$BF_3{\cdot}OEt_2$ −78 °C→RT (2 h), then RT (6 h)	 **17** (48%)
6	BnO–CMe2–CHO	$BF_3{\cdot}OEt_2$ −78 °C→RT (2 h), then RT (10 h)	 **18** (0%)

[a] All reactions were performed in CH_2Cl_2. [b] Yield of isolated pure material. [c] The product in entry 5 is a mixture of three diastereomers (3:1:1) with unknown configuration at the starred carbon atoms. LA = Lewis acid, RT = room temperature, Bn = benzyl.

compatibility of a β-alkoxy aldehyde to this reaction. Remarkably, **17** was obtained from 2-(benzyloxy)propanal as a mixture of three diastereomers (3:1:1, entry 5) from which the major one could be readily isolated by silica gel chromatography; however, the configuration at the extracyclic centers in this product remains undetermined at present. Incidentally, the reaction failed to give any tetrahydrofuran when the aldehyde is hindered (entry 6), although neither the aldehyde nor the starting allylic silane could be recovered.[15]

Finally, in our most dramatic result, three-component cyclizations were observed. For example, $BF_3{\cdot}OEt_2$ promoted the coupling of **1b** and two different aldehydes (Scheme 4) with the formation of a single product (**19**) in 48% yield uncontaminated by any regio- or stereoisomers. This synthesis was only possible because of the difference in reactivity between **1b** and the allylic silane formed in situ (cf. **6**) and between that of the two aldehydes.[16]



Scheme 4. Three-component reaction involving allylic silane **1b** with two different aldehydes. TBDPSO = *tert*-butyldiphenylsilyloxy, Bn = benzyl.

In summary, 1-silylmethyl allylic silanes have been developed as new bimetallic reagents for rapid access to a variety of 2,3,5-trisubstituted tetrahydrofurans in good yields and with high stereoselectivities. The synthesis allows two different groups to be introduced at the 2 and 5 positions of the furan ring, which should enhance the utility of tetrahydrofuran synthesis and help promote its application in organic synthesis.

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