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Straightforward one-pot stereoselective synthesis of substituted tetrahydrofurans from 1,3-butadienes and aldehydes

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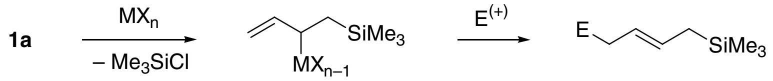
Abstract—A new and efficient multicomponent reaction involving a double-allylation sequence is reported. In situ generated bimetallic reagents are prepared from disilane **1** and added onto a range of aliphatic aldehydes to afford a direct access to trisubstituted tetrahydrofurans in good to excellent diastereoselectivity (up to 70%).

Multicomponent reactions (MCRs) are transformations of great interest in organic synthesis.[1] The ability to form stereoselectively two or more carbon–carbon and/or carbon–heteroatom bonds in a single operation is an exciting challenge in chemistry. To gain high atom economy, selectivity, and low levels of by-products, MCRs have been already an active area of research. In this regard, the development of multifunctional reagents that display chemodivergent reactivity is of interest for the rapid preparation of novel organic compounds. In this field, polyallylsilanes have proven to be very efficient building blocks, for example in a one-pot double Sakurai addition reaction.[2] Allylsilanes are useful and safe reagents to transfer an allyl unit to an electrophilic center.[3] But, except for a few commercially available compounds, preparation of substituted allylsilanes is not generally easy. A very simple procedure is the reductive disilylation of 1,3-dienes using lithium/chlorotrimethylsilane giving rise to 1,4-bis(trimethylsilyl)-2-butenes as **1a**–**c**.[4,5] Unfortunately, addition of **1a** or **1b** to various electrophilic reagents in the presence of Lewis acids led to compounds bearing a 4-trimethylsilyl-1-butene moiety in which the second silyl group occupies a non allylic position and is therefore not activated to further reaction (Scheme 1).[6]



To explore more extensively the reactivity of **1** and to keep intact the intrinsic information of the two allyl metal bonds, we thought that one way to circumvent the non reactivity of the second carbon silicon bond, would be to transmetallate **1** via an allylic process. The intermediate species would then react with an electrophile affording a new allyl silane moiety.

As part of our research program directed to the application of allyldisilanes in organic synthesis,[7] we planned the use of **1** as C4 dianions. In this communication, we describe a one-pot procedure to obtain tri- and tetrasubstituted tetrahydrofurans using a sequence involving trans-metallation of **1** and two S_E2' reactions of aldehydes.

A way to activate the two trimethylsilyl groups can be the use of tin tetrachloride as Lewis acid because, in this case, a metathesis reaction (ligand exchange) occurred with allylic transposition.[8] Investigation of the literature revealed little precedent for the transmetallation of allylsilanes. In 1999, Diaz et al. reported the transmetallation of allyltrimethylsilane with tin tetrachloride evidenced by ^{1}H NMR studies[8a] while similar studies realized by

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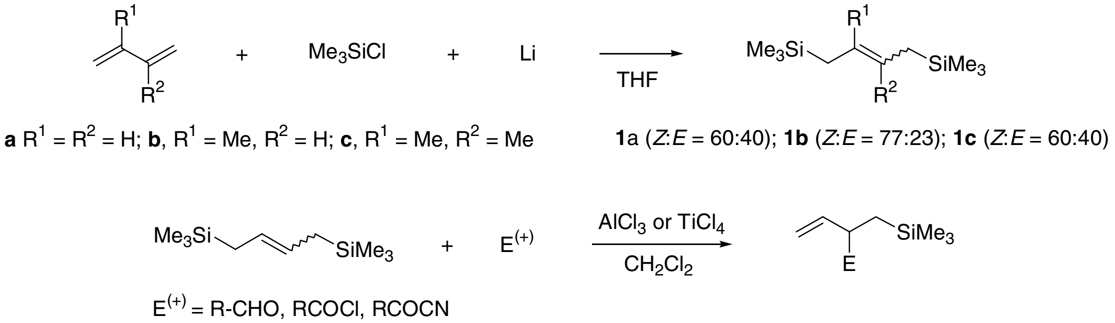


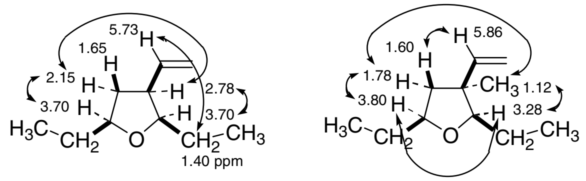
Scheme 1. Synthesis of 1,4-bis(trimethylsilyl)-2-butenes **1a**–**c** from 1,3-dienes and addition of **1a** to various electrophilic reagents.

Denmark with titanium tetrachloride indicated the absence of the metathesis reaction. Moreover, we recently found that allenyltrimethylsilane was transmetallated with tin tetrachloride affording 2-trichlorostannyl-1,3-butadiene in quantitative yield.[9] In first experiments, when $SnCl_4$ was added to a solution of **1** in deuterated chloroform and stirred at room temperature for 2 min, the proton NMR spectra evidenced the formation of chlorotrimethylsilane and the reduction of the signal intensity corresponding to the methylene hydrogens to a silicon atom. Nevertheless, the reaction conducted in $CDCl_3$ and followed by ^1H NMR spectroscopy revealed low conversion even after 5 h. Similarly, with titanium tetrachloride, only a small amount of trimethylsilyl chloride was detected. As a possible explanation, we thought that an equilibrium could take place between the couple tin tetrachloride/**1a** and allyltrichlorostannane **6**/trimethylsilyl chloride.[10]

Accordingly to these first experiments, we carried out the reaction of disilane **1a**,**b** and various aldehydes in the presence of tin tetrachloride. We have observed that the $SnCl_4$-mediated addition of **1a**,**b** led to tri- or tetra-substituted tetrahydrofurans **2**–**5** resulting from the successive reaction of two moles of aldehyde.[11] Reactions with **1a** led to major all-cis-diastereoisomers with two minors products **3**, **4** when normal aldehydes were used (Scheme 2 and Table 1).[12] In the case of branched aldehydes, the reaction with **1a** or **1b** proceeds with a total diastereoselectivity leading to **2** as a single isomer.

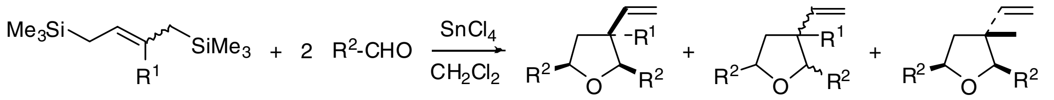
We did not obtain tetrahydrofuran when aromatic aldehydes such as benzaldehyde and 4-fluorobenzaldehyde were employed.

The stereoselectivity increased with prenyldisilane **1b** in which case, only two diastereoisomeric tetrahydrofurans



2 (R^1 = H; R^2 = Et) **2** (R^1 = Me; R^2 = Et)

Figure 1. Selected NOE interactions for the determination of the relative configuration of **2** ($R^1 = H$, $R^2 = Et$) and **2** ($R^1 = Me$, $R^2 = Et$).

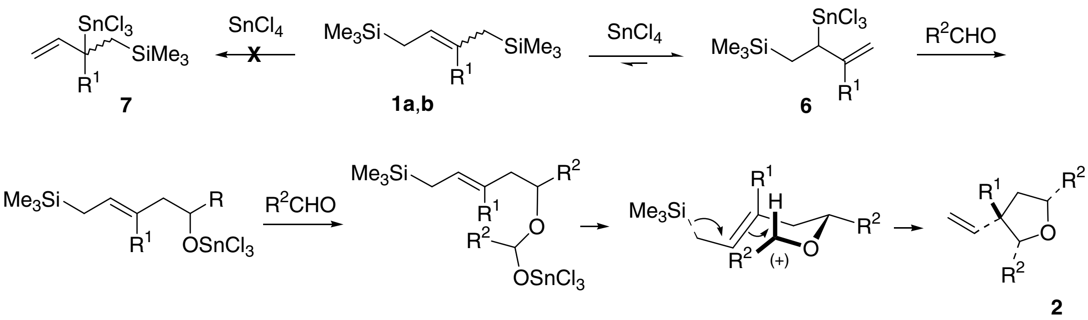


2, major isomer **3**, **4**, minor isomers **5**, minor isomer

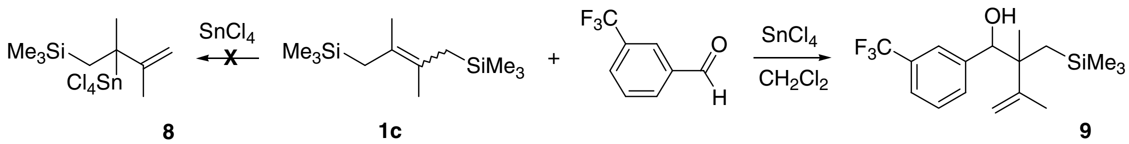
Scheme 2. Addition reaction of **1a** or **1b** to various aldehydes.

Table 1. Obtention of 2,5-dialkyl- and 2,3,5-trialkyl-3-vinyl-tetrahydrofurans **2**

Entry	R^1	Aldehyde	Tetrahydrofuran	Ratio **2**:**3**:**4**	Ratio **2**:**5**	**2**, Isolated yield (%)
1	H	Propanal	$R^2 = Et$	84:8:8		66
2	H	Pentanal	$R^2 = n$-Bu	88:6:6		56
3	H	*iso*Butanal	$R^2 = i$-Pr	100:0:0		48
4	H	Nonanal	$R^2 = n$-Octyl	86:7:7		51
5	H	Hydrocinnamaldehyde	R^2 = 2-Phenylethyl	88:6:6		56
6	Me	Propanal	$R^2 = Et$		87:13	68
7	Me	Pentanal	$R^2 = n$-Bu		88:12	71
8	Me	*iso*Butanal	$R^2 = i$-Pr		>98:<2	54
9	Me	Nonanal	$R^2 = n$-Octyl		89:11	56
10	Me	Hydrocinnamaldehyde	R^2 = 2-Phenylethyl		90:10	52



Scheme 3. Proposed route to the synthesis of **2**.



Scheme 4. Addition of **1c** to *m*-trifluoromethylbenzaldehyde.

2 and **5** were obtained (Scheme 2 and Table 1, entries 6–10). Previously, Mohr has observed that 1-trimethylsilyl-pent-2-en-5-ols react with acetals under protic catalysis via a transacetalization-ring closure reaction to afford all cis-trisubstituted tetrahydrofurans.[13] A similar result has been observed by Meyer and Cossy from cyclic allylsilyloxanes and aldehydes or ketones in the presence of trimethylsilyl triflate.[14] The stereochemistry of the obtained tetrahydrofurans **2** and **3**–**5** has been determined by NOESY NMR experiments as indicated for **2**[15] (Fig. 1).

The reaction mechanism leading to tetrahydrofurans begins with a metathesis step which gives regioselectively the secondary allyltin intermediate **6**, followed by the addition of the more reactive allylstannane moiety to aldehydes. In the case of disilane **1b**, the total regioselectivity for the S_E2' reaction (absence of product resulting from the formation of the tertiary allyltin derivative **7**) is governed by the stability of the generated cation. Then, the stannyl alcoholate would quickly add a second equivalent of aldehyde and then an intramolecular substitution by the allylsilane moiety gives rise to tetrahydrofurans through a cyclic transition state with a chair-like structure (Scheme 3).

In contrast to **1a** and **1b**, the substituted 1,4-disilane **1c** does not lead to a tetrahydrofuran derivatives from aliphatic propanal, *iso*-butanal, pentanal and benzaldehyde. Only, powerful electrophilic *m*-trifluoromethylbenzaldehyde reacts to give alcohol **9** (2 isomers, 70:30)[16] coming from a direct addition of **1c** without preliminary metathesis. It seems that the metathesis leading to a tertiary allylstannane such as **8** is more difficult than the formation of secondary allylstannanes **6** (Scheme 4).[17]

In conclusion, we have disclosed a new multicomponent reaction affording the synthesis of tri- or tetrasubstituted furans from a disilane (obtained in one step from 1,3-dienes) and aldehydes. Previous results in this area used elaborate precursors.[13,14] Moreover, a good control of the stereochemistry is observed and these results may be applied in the synthesis of more complex products.[18]

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10. In the case of the allyltrimethylsilane, the total exchange reaction occurred after 140 min (Ref. 8a).
11. Tetrahydrofurans were the only products when 1 equiv of aldehyde was used.

12. At −78 °C, to a flame-dried 20 mL Schlenck tube was added disilane **1** (2.5 mmol), CH_2Cl_2 (5 mL) and then $SnCl_4$ (0.30 mL, 2.5 mmol). The solution was stirred at −40 °C for 1.5 h. then aldehyde (5 mmol) was added. The reaction mixture was stirred further 2 h at −0 °C and then quenched with an aqueous NaCl solution. The reaction mixture was extracted with ether (3 × 5 mL), dried over $MgSO_4$ and the organic layers were removed under vacuum. The products were purified by flash chromatography.
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15. Compound **2** (**1a**+propanal), ^{1}H NMR (300 MHz, $CDCl_3$), δ 5.74 (dt, $J = 17.1$, 10.0 Hz, 1H), 4.97 (d, $J = 17.1$ Hz, 1H), 4.96 (d, $J = 10.0$ Hz, 1H), 3.77–3.64, (m, 2H), 2.78 (apparent quint. $J = 7.9$ Hz, 1H), 2.15 (apparent quint. $J = 6.85$ Hz, 1H), 1.74–1.28 (m, 5H), 0.95–0.86 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.8 (d), 114.8 (t), 83.1 (d), 79.9 (d), 46.6 (d), 37.8 (t), 29.3 (t), 25.6 (t), 10.5 (q), 10.2 (q). Compound **2** (**1b**+propanal), ^{1}H NMR (300 MHz, $CDCl_3$), δ 5.86 (dd, $J = 17.4$, 10.8 Hz, 1H), 4.94 (dd, $J = 10.8$, 1.3 Hz), 4.91 (dd, $J = 17.4$, 1.3 Hz, 1H), 3.80 (quint. $J = 8.1$ Hz, 1H),3.28 (t, $J = 7.1$ Hz, 1H), 1.78 (dd, $J = 12.6$, 7.1 Hz, 1H), 1.71–1.27 (m, 5H), 1.12 (s, 3H), 0.98–0.86 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.1 (d), 111.5 (t), 89.8 (d), 79.1 (d), 47.2 (s), 45.3 (t), 29.8 (t), 25.0 (t), 23.4 (q), 11.8 (q), 10.9 (q).
16. Major isomer, ^{1}H NMR (300 MHz, $CDCl_3$), δ 7.51–7.33 (m, 4H), 4.79 (br s, 1H), 4.60 (s, 1H), 1.75 (s, 1H), 1.04 (s, 3H), 0.90 (s, 3H), −0.04 (s, 9H), −0.08 (s, 2H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.9 (s), 143.6 (s), 131.2 (d), 129.7 (d), 127.4 (d), 124.8 (d), 124.0 (d, $J_{C\text{–}F} = 271$ Hz), 123.7 (d), 112.5 (t), 80.2 (d), 44.6 (s), 24.9 (t), 23.7 (q), 22.7 (q), 21.2 (q), 0.04 (q).
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