Stereoselective Synthesis of 2,3,5-Trisubstituted Tetrahydrofurans by an Allyl Silane Metathesis - Nucleophilic Addition Sequence

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This paper is dedicated to Professor C. W. Rees, F.R.S. on the occasion of his 70th birthday.

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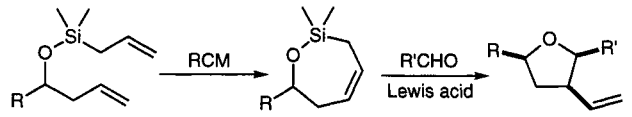
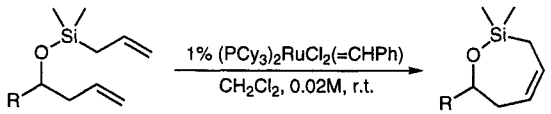
Abstract: Functionalised cyclic allyl silanes have been prepared by the ring closing metathesis of allyldimethylsilyl ethers of homoallylic alcohols. Treatment of these allyl silanes with aldehydes in the presence of boron trifluoride etherate gives high yields of 2,3,5-substituted tetrahydrofurans. Stereoselectivities are excellent for aldehydes with primary substituents, good for secondary substituents and modest for tertiary substituents.

Substituted tetrahydrofurans are ubiquitous in nature, occurring in a wide range of biologically active substances such as C-nucleosides[1] and ionophore antibiotics.[2] There has therefore been much interest in the development of methods for the stereoselective synthesis of these subunits. A common strategy is to prepare a substrate containing all five ring atoms which is then cyclised by nucleophilic, electrophilic, radical or transition metal mediated processes.[3] A more convergent and flexible approach involves the construction of the ring from two precursors in a one-step [3+2] annulation.[4] Herein we disclose a new [3+2] approach to the synthesis of 2,3,5-trisubstituted tetrahydrofurans based upon the Lewis acid mediated condensation of aldehydes with cyclic allylsilanes, prepared by the ring closing metathesis (RCM) of allyldimethylsilyl protected homoallylic alcohols (Scheme 1).



Scheme 1

The utility of allylsilanes in synthesis is well documented.[5] However, the synthesis of functionalised allylsilanes can still be problematic, often requiring the use of strongly basic reagents, and hence new methods for the preparation of these compounds would be of great utility. The recent explosion of interest in the synthetic applications of transition metal promoted olefin metathesis[6] prompted us to question whether we could prepare cyclic allylsilanes by the ring closing metathesis (RCM) of allyldimethylsilyl protected homoallylic alcohols. As we began this work, we were encouraged that allyl silanes might be viable participants in ring closing metathesis by reports in the literature concerning the molybdenum alkylidene catalysed ring opening polymerisation of silacyclopent-3-enes[7] and the cross metathesis of allyltrimethylsilane with various olefins.[8] Since the completion of our work, Grubbs and co-workers have published the results of their related studies concerning the RCM of a range of allyl and vinyl siloxanes bearing pendant olefins.[9] The allyldimethylsilyl protected homoallylic alcohols **1a-c** were readily prepared by standard methods,[10] and we set about identifying the optimum conditions for cyclisation. We were delighted to find that the ring closed siloxane was obtained as the only observable product after treatment with 1 mol% of Grubbs' ruthenium benzylidene catalyst $(PCy_3)_2RuCl_2(=CHPh)$ in dichloromethane at room temperature for one hour (Scheme 2).[11]



Scheme 2

The cyclic siloxanes could be isolated by chromatography on silica gel as shown, but it was often most convenient to use the crude products from these reactions (>98% pure by ^1H nmr) for our further studies.

With these functionalised allyl silanes in hand, we wished to examine their reactivity towards various electrophiles. In our first attempts, we found that reaction of allyl silane **2a** with benzaldehyde in the presence of a variety of Lewis acids gave, as the sole identifiable product, the 2,3,5-trisubstituted tetrahydrofuran as a mixture of two diastereomers **3a/4a** (Table 1).

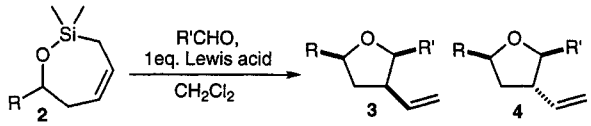


Table 1. Tetrahydrofuran formation with allyl silane **2a**

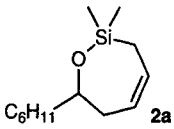
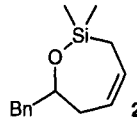
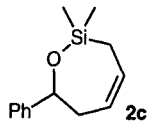
Entry	R	R'	Lewis Acid	Temp.	Yield	dr[a]
1	C_6H_{11}	Ph	BF_3·OEt	-78°C	73%	92:8
2	C_6H_{11}	Ph	$TiCl_4$	-78°C	76%	75:25
3	C_6H_{11}	Ph	Et_2AlCl	-78°C	73%	90:10
4	C_6H_{11}	^iPr	BF_3·OEt	-78°C	84%	84:16
5	C_6H_{11}	^iPr	BF_3·OEt	r.t.	82%	52:48

a) Ratios **3a:4a** (entries 1-3) and **3b:4b** (entries 4,5) were determined by ^1H nmr spectroscopy

The use of different Lewis acids (entries 1-3) gave comparable yields of **3**, but the stereoselectivity of the reaction varied and was found to be highest when boron trifluoride etherate was employed (entry 1). Aliphatic aldehydes were also effective partners in the reaction, as evidenced by the preparation of **3b/4b** by reaction of **2a** with isobutyraldehyde (entry 4). The temperature of the reaction was found to be crucial to the selectivity, since when the latter reaction was carried out at room temperature the stereoselectivity decreased from 84:16 to 52:48 (entry 5).

We then examined the reactions of allyl silanes **2a-c** with a range of aldehydes under the optimum conditions,[12] and found that the reaction was applicable to a broad range of substrates. The results of this survey are shown in Table 2.

Table 2. Scope and substituent effects on tetrahydrofuran formation *via* the [3+2] annulation[a]

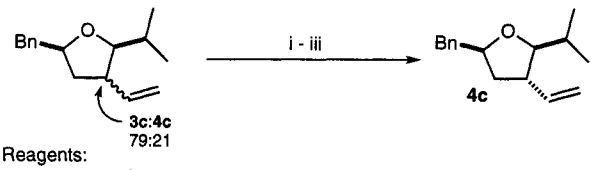
Aldehyde / Allyl silane	^{n}BuCHO	PhCH$_2$CHO	^{i}PrCHO	PhCHO	^{t}BuCHO
 **2a**	97% (>98:2)	92% (>98:2)	84% (84:16)	73% (92:8)	87% (63:37)
 **2b**	87% (>98:2)	89% (>98:2)	89% (79:21)	70% (80:20)	86% (67:33)
 **2c**	83% (>98:2)	79% (>98:2)	78% (85:15)	65% (81:19)	74% (77:23)

a) Reactions carried out with one equivalent each of allyl silanes **2a-c**, aldehyde and $BF_3{\cdot}OEt_2$ in DCM at -78°C

Several points concerning the reaction are noteworthy. Firstly, the yields are good to excellent in all cases, with aliphatic aldehydes giving slightly higher yields than their aromatic counterparts. Secondly, the stereochemical outcome of the reaction is dependent upon the degree of branching of the aldehyde substituent: aldehydes with primary substituents yield essentially a single diasteroisomer, whereas with secondary or aromatic substituted aldehydes small amounts (8-21%) of a second diastereoisomer are formed, and with pivaldehyde this increases further (23-37%). Thirdly, the nature of the substituent on the allyl silane appears to have little impact upon reactivity or stereoselectivity.

The stereochemistry of the adduct of **2b** and pentanal was determined to be all-*cis* by nOe experiments;[13] at this stage we assign this stereochemistry to all of the major isomers.

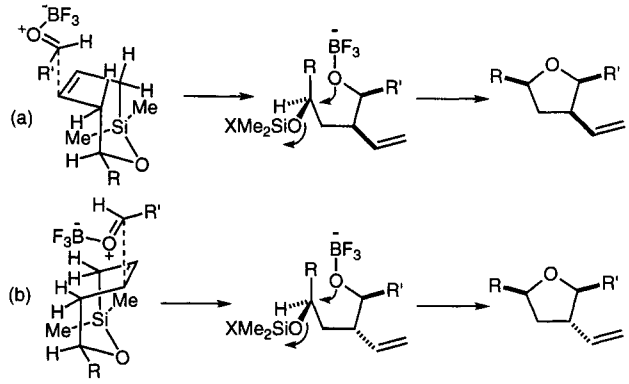
The identity of the minor isomer in the mixture of **3c/4c** (from the condensation of **2b** and isovaleraldehyde) was deduced to be the C3-epimer by the sequence of reactions shown in Scheme 3. Oxidative cleavage of the vinyl group was achieved by osmium tetroxide catalysed dihydroxylation followed by treatment with sodium periodate. Epimerisation of the resulting aldehyde was achieved by exposure to catalytic potassium *tert*-butoxide in *tert*-butanol/THF.[14] Finally, Wittig methylenation returned the tetrahydrofuran **4c** as a single isomer which was identical by ^{1}H nmr spectroscopy to the minor isomer in the original mixture. We tentatively assign all of the minor isomers to be the C3-epimers.



Reagents:
i) OsO_4, NMO, ^{t}BuOH/acetone/water, then $NaIO_4$ (83%); ii) 0.1 eq. KO^{t}Bu, 0.1 eq. ^{t}BuOH, THF (100%); iii) $Ph_3P{=}CH_2$, THF, -78°C (54%)

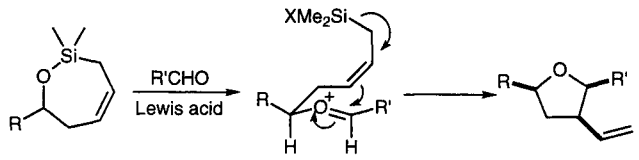
Scheme 3

The precise mechanism of the reaction is not known at this time. Our current favoured mechanism is depicted in Scheme 4, and involves the face selective addition of the aldehyde to the allylsilane, followed by the S_N2-like displacement of siloxide (with inversion of configuration) by the resulting alkoxide. The favoured sense of addition is that shown in path (a), with the Lewis acid-coordinated aldehyde undergoing *anti*-addition to the allyl silane through a syn-clinal arrangement which places the least bulky group (the formyl hydrogen) over the ring. The R' group of the aldehyde is situated adjacent to the allylic methylene unit, to avoid unfavourable interactions between the Lewis acid and the *endo*-hydrogen of the methylene group. However, as R' gains branching the repulsion between R' and the methylene group increases, and a second pathway (b) becomes competitive. In this route, the allylsilane is in a less stable conformation (due to electronic repulsion between the olefin and an oxygen lone pair) but the *endo*-hydrogen is flattened towards the plane of the olefin, thus accomodating the Lewis acid over the ring, with the bulky R' substituent situated in free space.



Scheme 4

An alternative possibility involves the partial acetalisation of the aldehyde by the silyl ether to yield an oxonium ion (Scheme 5) which is then trapped in an intramolecular Sakurai reaction to yield the observed tetrahydrofuran. A similar mechanism has been proposed by Mohr[15] and Oriyama[16] for the synthesis of tetrahydrofurans by the condensation of dialkyl acetals with 5-alkyl-5-hydroxy(silyloxy)-2-pentenylsilanes under protic acid or silyl triflate catalysis.



Scheme 5

However, several factors concerning our reaction lead us to discount this mechanism at this stage. Firstly, both Mohr and Oriyama observed the formation of essentially single stereoisomers of their tetrahydrofurans, regardless of the nature of the acetal side chain used. This is in stark contrast to the erosion of selectivity seen in our case as the steric bulk of the side chain increases. Secondly, their reactions remained highly stereoselective at ambient temperatures (0 °C to room temperature), whereas ours exhibit a strong temperature dependence. Thirdly, the stereoselectivity of our reaction is dependent upon the identity of the Lewis acid used indicating that, unlike the Mohr/Oriyama reactions, the acid is still intimately involved in the stereochemistry determining step of the reaction.

In summary, we have demonstrated the synthesis of a range of substituted cyclic allyl silanes by ring closing metathesis, and demonstrated their application in a novel, stereoselective synthesis of 2,3,5-trisubstituted tetrahydrofurans. The reaction appears to be applicable to a range of substrates. Further work on this reaction, including studies to elucidate the mechanism and applications to target systems, is currently being undertaken.

Acknowledgements

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(3) For a recent review of the synthesis of 2,5-disubstituted tetrahydrofurans, see: Harmange, J.-C.; Figadere, B. *Tetrahedron, Asymmetry* **1993**, *4*, 1711.

(4) For example, carbonyl ylide-olefin cycloaddition (Padwa, A; Fryxell, G.E.; Zhi, L. *J. Am. Chem. Soc.* **1990**, *112*, 3100); trimethylenemethane-aldehyde condensation (Trost, B.M.; King, S.A.; Schmidt, T. *J. Am. Chem. Soc.* **1989**, *111*, 5902); allyl silane addition to aldehydes with silicon migration (Panek, J.S.; Yang, M. *J. Am. Chem. Soc.* **1991**, *113*, 9868).

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(8) Crowe, W.E.; Goldberg, D.R.; Zhang, Z.J. *Tetrahedron Lett.* **1996**, *37*, 2117.

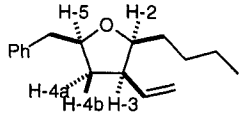
(9) Chang, S.B.; Grubbs, R.H. *Tetrahedron Lett.* **1997**, *38*, 4757.

(10) The cyclisation precursors **1a-c** were prepared by treatment of the homoallylic alcohols (from addition of allylmagnesium chloride to the appropriate aldehyde) with allyldimethylchlorosilane in DCM in the presence of triethylamine. Yields are in the range 77 to 79%.

(11) Representative procedure: to a thoroughly degassed solution of 2-(allyldimethylsilyloxy)-1-phenyl-4-pentene (52 mg, 0.2 mmol) in dry DCM (10 ml) was added $(PCy_3)_2RuCl_2(=CHPh)$ (2 mg, 0.002 mmol) in one portion. The mixture was stirred at room temperature for one hour, then evaporated *in vacuo* and purified by passage through a short pad of silica (eluant 15% EtOAc:hexane) to yield **2b** as a clear oil (42 mg, 91%): IR (film) 3026, 2929, 1637, 1496, 1455, 1251, 1088 cm^{-1}; ^1H nmr ($CDCl_3$, 250 MHz) δ 7.30 (5H, m, Ar-H), 5.81 (1H, dt, J = 10.6, 7.0, C=CH), 5.52 (1H, dt, J = 10.6, 6.6, C=CH), 4.12 (1H, p, J = 6.0 Hz, -CHO-), 2.77 (1H, dd, J = 13.3, 6.4, CH_2Ph), 2.69 (1H, dd, J = 13.3, 6.8, CH_2Ph), 2.28 (2H, t, J = 6.1, C=CHCH_2), 1.55 (2H, m, $SiCH_2$), 0.10 (3H, s, $SiCH_3$), 0.02 (3H, s, $SiCH_3$); ^{13}C nmr ($CDCl_3$, 62.5 MHz) δ 139.3, 138.6, 129.4, 128.1, 126.2, 126.0, 73.9, 44.8, 35.8, 18.2, -0.2, -1.7; MS m/z 232, 214, 177, 163, 141, 91; found $[MH]^+$ 233.1350, $C_{14}H_{21}OSi$ requires 233.1361.

(12) Representative procedure: To a -78 °C solution of **2b** (66 mg, 0.20 mmol) in dry DCM (2 ml) was added $BF_3{\bullet}OEt_2$ (20 µl, 0.22 mmol) and the solution stirred for five minutes prior to the addition of isovaleraldehyde (22 µl, 0.20 mmol). The mixture was allowed to warm to room temperature and stirred for 18 hours. The reaction was quenched by the addition of brine (10 ml) and the mixture was extracted into EtOAc (3 x 10 ml). The combined organic layers were washed with water (10 ml), dried over magnesium sulfate, filtered and the solvent evaporated *in vacuo*. The residue was purified by chromatography on silica gel (eluant 1% Et_2O:petrol) to yield the diastereomeric tetrahydrofurans **3c/4c** (5:1 ratio) as a clear oil (41 mg, 89%): IR (film) 2960, 2931, 1640, 1455, 1257, 1158 cm^{-1}; ^1H nmr ($CDCl_3$, 250 MHz) (Signals for **3c**) δ 7.30 (5H, m, Ar-H), 5.76 (1H, dt, J = 17.6, 9.7, CH=CH_2), 4.98 (2H, m, CH=CH_2), 4.03 (1H, m, BnCHO-), 3.31 (1H, dd, J = 9.2, 5.6, ^iPrCHO), 3.08 (1H, dd, J = 13.4, 5.8, $PhCH_2$), 2.71 (2H, m, inc. dd, J = 13.4, 7.4, $PhCH_2$ and $CHCH{=}CH_2$), 2.17 (1H, dt, J = 13.0, 8.0, CH_2), 1.76 (1H, m, $CH(CH_3)_2$), 1.46 (1H, ddd, J = 13.0, 7.0, 3.8, CH_2), 1.01 (3H, d, J = 6.5, CH_3), 0.83 (3H, d, J = 6.6, CH_3); (Signals for **4c** visible at δ 3.40 (1H, dd, J = 7.1, 5.9) and 2.96 (1H, dd, J = 13.4, 3.4, $PhCH_2$); ^{13}C nmr ($CDCl_3$, 62.5 MHz) (Signals for **3c** only) δ 139.1, 138.8, 129.4, 128.2, 126.1, 114.5, 45.8, 42.5, 38.3, 32.4, 28.9, 20.4, 18.8; MS m/z 248 ($M+NH_4$), 231, 139, 95, 91; found $[MH]^+$ 231.1742, $C_{16}H_{23}O$ requires 231.1749.

(13) Irradiation of the signal for H-2 gave enhancements of the signals for H-5 and H-3; irradiation of H-3 gave enhancements of the signals for H-2, H-5 and H-4a. Irradiation of H-5 gave enhancements of the signals for H-2, H-3, and H-4a.



(14) Epimerisation of C-3 aldehydes of all-*cis* 2,3,5-trisubstituted tetrahydrofurans to the more stable 2,3-*trans* isomer is known. See, for example: Frauenrath, H.; Runsink, J. *J. Org. Chem.* **1987**, *52*, 2707.

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