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Tandem Aldol-Allylation Reactions: Double C-C Bond Formation Using Silicon-Tethered Dinucleophiles

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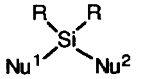
Abstract

A new tandem C-C bond forming process has been developed which utilises silicon-tethered dinucleophiles and acetals under Lewis acid conditions. The reaction incorporates a functionalised five carbon unit into both aromatic and aliphatic acetals, affording acyclic β-alkoxyhomoallylic alcohols in good yields.

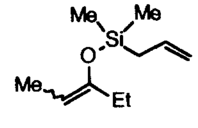
Keywords acetals; aldol reactions; allylation; silicon and compounds

Silicon chemistry continues to provide a wealth of useful synthetic methods. In particular, processes which result in the formation of new C-C bonds have particular value. Given the continued interest in total syntheses [1] of polypropionate-derived bioactive targets, aldol and allylation reactions of carbonyl compounds and their derivatives remain highly topical and silicon is an important controlling element in such chemistry. Tandem reactions [2,3], in which two or more bond-forming processes result from a single step, are particularly useful. By combining two steps into one, rapid syntheses of complex molecules are possible. The synthetic potential of tandem bond formation relies on the ability to control the fate of any reactive intermediate that is generated. Of course, silicon [3] can control the reactivity of unsaturated nucleophilic moieties (enol-, allyl-, and vinylsilanes) to synthetic advantage using the well-known β-effect [4]. Herein, we report the synthesis of particular classes of silicon-tethered dinucleophiles [5], in general represented by structure **1**, and the successful implementation of tandem reactions [2] which create two C-C bonds in a single step.



1 $Nu^1 \neq Nu^2$ (Nu = enol, allyl, crotyl, H)

The preparation of allyldimethylsilyl enol ethers and ketene acetals (*e.g.* **2**-**4**) is achieved [6] using standard lithium enolate chemistry [7] with quenching of the enolates with commercial allyldimethylchlorosilane. Tethered dinucleophiles derived from a range of ketones, esters, and thioesters, exemplified by **2**-**4**, can be prepared in good yields (up to 93%) typically as mixtures of geometric isomers.



67% (*E*):(*Z*) 67:33

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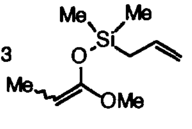

78% (*E*):(*Z*) 82:18

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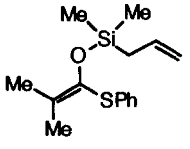

93%

4

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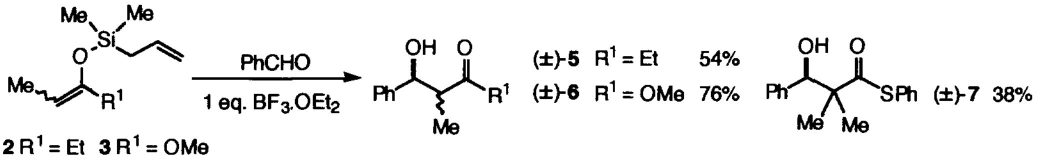
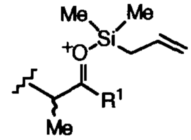
These Si-tethered compounds, represented by **2-4**, possess somewhat greater stability than their corresponding trimethylsilyl analogues. However, the silyl ketene acetals, exemplified by **3**, remain particularly prone to rapid hydrolysis. Initial experiments, illustrated (Scheme 1) for a typical case using PhCHO together with $BF_3.OEt_2$, revealed that reactions of these classes of dinucleophiles (**2-4**) with aldehydes and a range of Lewis acids (common B, Al, Sn, and Ti complexes) gave only the expected Mukaiyama aldol products (**5-7**) in variable yields with the predominant formation of the *syn* diastereoisomers, *e.g.* **5** *syn*:*anti* 95:5. No homoallylic alcohols or tandem products were observed.

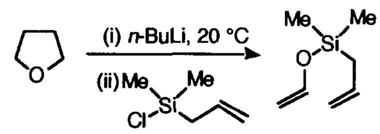
Scheme 1



Two important conclusions result from these experiments. Firstly, the relative nucleophilicity of the allyl and enolsilanes is generally, but not exclusively [8], as would be predicted based on the work of Mayr [9]. Normally, the allyl moiety is less reactive than the enol, explaining why no homoallylic alcohol is observed [8]. Secondly, as no tandem products result from these reactions, it is clear that the assumed intermediate of type **8** [10] (R^1 = alkyl, O-alkyl, S-aryl) is either: (i) too prone to adventitious breakdown by nucleophilic attack at silicon; or (ii) intrinsically too unreactive to undergo the second intramolecular allylation reaction. Indeed, we are unaware of good precedent for further reaction of **8** in the manner sought excepting when R^1 = H [11].



8 R^1 = alkyl, O-alkyl, S-aryl, H



9 84%

Based on this analysis we prepared silyl enol ether **9** from THF using the Jung methodology [12]. Enolsilanes formally derived from aldehydes are less nucleophilic than those derived from either ketones or esters. Accordingly, the first stage of the tandem addition will be less facile. However, it was expected that, if formed, intermediates of type **8** (R^1 = H) should possess greater reactivity towards intramolecular allylation than when R^1 = alkyl/O-alkyl. Gratifyingly, this expectation was verified by the reactions between **9** and various acetals promoted by Lewis acids [13] (Scheme 2; Table 1). The tandem reactions result in the formation of two new C-C bonds in a single step accompanied by the expulsion of the Si-linker giving **10-14** [14]. Under optimum conditions, no aldehydes of general type **15** are seen and the reactions are remarkably clean [14]. The best solvent from a number screened is dichloromethane. The temperature control is vital since the yields with certain acetals peak at sub-ambient temperatures (compare entries 1-3 with 8-9) but can suffer at higher or lower temperatures. Clearly, the required temperatures are substrate dependent. These results presumably reflect the balance between the activation barrier in the initial reaction with the acetal and the subsequent reactivity, or premature breakdown, of the assumed silyloxonium ion intermediate [10].

The Lewis acids of choice are $BF_3.OEt_2$ (entries 2, 8) or $MgBr_2.OEt_2$ (entries 5-7). A wide selection of other Lewis acids have been screened, including the common Ti and Al complexes, but amongst these only $SnCl_4$ was even moderately successful (entry 4). It should be noted from Table 1 that the reaction can be applied to both aromatic and acyclic aliphatic acetals for which only representative examples of a number screened are included. Substituted aromatic acetals (entry 6) can also be tolerated. Cyclic acetals, *e.g.* 1-methoxytetrahydropyran, afford tandem products, *e.g.* **14** (32% yield; -40 °C; $BF_3.OEt_2$), albeit rather slowly and are under further investigation. Preliminary experiments indicate that further substitution of the enolsilane moiety can be tolerated. In particular, the Si-enol ethers of phenylacetaldehyde (α-substituted) and *i*-butyraldehyde (α,α'-disubstituted) undergo tandem reactions [6].

Scheme 2

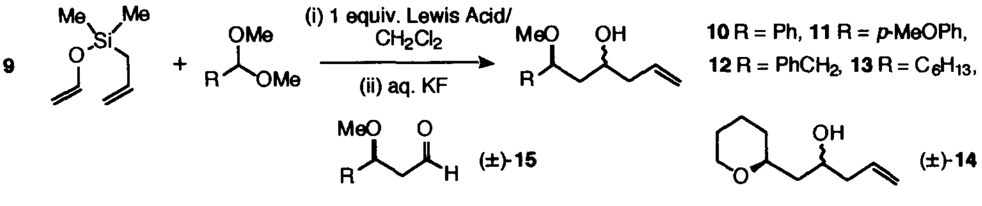
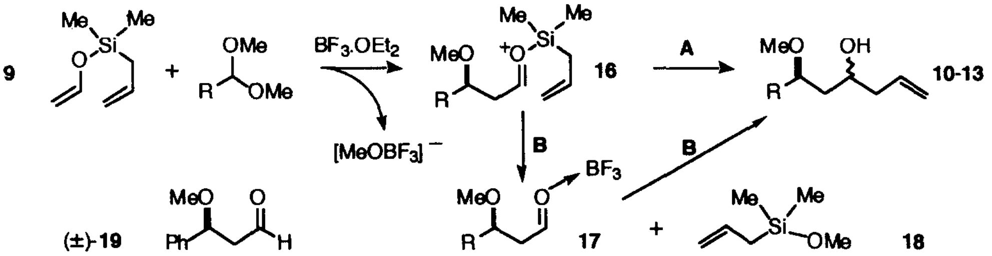


Table 1. Conditions and % yields for the tandem C-C bond forming process using **9** (Scheme 2).

Entry	*Acetal*	*Lewis Acid*	*Temperature*	*Product (Yield)*	*syn:anti ratio*
1	$PhCH(OMe)_2$	$BF_3.OEt_2$	-78 °C	**10** (58%)	58:42
2	$PhCH(OMe)_2$	$BF_3.OEt_2$	-40 °C	**10** (77%)	62:38
3	$PhCH(OMe)_2$	$BF_3.OEt_2$	-20 °C	**10** (65%)	61:39
4	$PhCH(OMe)_2$	$SnCl_4$	-78 °C	**10** (33%)	52:48
5	$PhCH(OMe)_2$	$MgBr_2.OEt_2$	0 °C	**10** (62%)	79:21
6	*p*-MeO-$PhCH(OMe)_2$	$MgBr_2.OEt_2$	0 °C	**11** (65%)	57:43
7	$PhCH_2CH(OMe)_2$	$MgBr_2.OEt_2$	0 °C	**12** (45%)	66:34
8	$C_6H_{13}CH(OMe)_2$	$BF_3.OEt_2$	-78 °C	**13** (78%)	73:27
9	$C_6H_{13}CH(OMe)_2$	$BF_3.OEt_2$	-40 °C	**13** (24%)	75:25

Diastereoselectivity in these reactions is moderate. The best diastereoisomeric ratio for **10** is 79:21 *syn:anti* using $MgBr_2.OEt_2$ [14]. The other Lewis acids screened to date offer reduced diastereoselectivity. The stereochemistry is assigned directly from published data [14] in the case of **10** and thereafter (**11**-**14**) by analogy. The optimisation of the reaction conditions and in particular, the incorporation of more sterically-demanding "spectator" groups other than Me on silicon may improve the diastereoselectivity of these reactions.

Scheme 3



We assume that the reactions proceed by intramolecular allylation of the silyloxonium ion **16** (Scheme 3; pathway **A**). Literature precedent [10] and other unpublished observations [6] support the premise that allylations of this type can occur. Moreover, Brook and Hiemstra [11] have performed calculations which suggest that the necessary approach pathway is ideal for efficient operation of the β-effect. While this mechanism is plausible, we note that the reaction may also proceed *via* breakdown of **16** (or a neutral complex derived from it) to regenerate the Lewis acid and produce β-methoxyaldehyde **17** and allyldimethylmethoxysilane **18** *in situ*. Lewis acid mediated intermolecular allylation of **17** could then occur (Scheme 3; pathway **B**). We suggest that the intermolecular mechanism is less likely given that, under conditions in which tandem addition occurs (Table 1; entry 1), authentic aldehyde **19** [15] and silane **18** do not undergo reaction to afford **10**. Further evidence for the intramolecular mechanism is currently being sought and will be reported in due course.

In summary, these results demonstrate the viability of tandem nucleophilic reactions of tethered enolallyl silanes and allow a number of conclusions to be drawn. Firstly, it is notable that the use of a removable Si-linker affords acyclic products following the loss of the silicon tether. Direct synthesis of multiple C-C bonds to give *acyclic* products are uncommon. Secondly, it may prove possible to use alternative electrophiles for the first stage, *e.g.* aldehydes and imines, and to control the absolute and relative stereochemistry of these reactions. Clearly, chiral Lewis acids may have a future role in such chemistry. Finally, these results provide further impetus to incorporate alternative combinations of nucleophilic [16] moieties directly onto silicon as a prelude to further tandem or consecutive reactions.

Acknowledgements. We are grateful to the EPSRC and Pfizer for a studentship for LMF.

References and Footnotes

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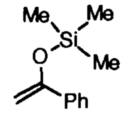
[6] Frost, L.M., Smith, J.D, Berrisford, D.J., unpublished results. All compounds reported herein are racemic.

[7] House, H.O., Czuba, L.J., Gall, M., Olmstead, H.D., *J. Org. Chem.* **1969**, *54*, 2324-2336.

[8] Competition experiments between trimethylsilylenol ether **20** and allyltrimethylsilane with aldehydes (equimolar amounts/-78 °C/1 equiv. $BF_3.OEt_2$) afford *only* the aldol products, *e.g.* **21**. In contrast, reactions of aldehydes with tethered silane **22** give homoallylic alcohols, *e.g.* **23**, as the sole products.



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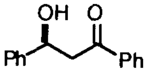

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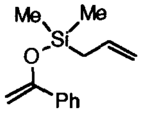

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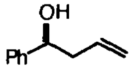

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[10] The anion may be associated with the silicon but is omitted for clarity. Similar intermediates in aldol reactions have been proposed in the literature: a) Hollis, T.K., Bosnich, B., *J. Am. Chem. Soc.* **1995**, *117*, 4570-4581; b) Ellis, W.W., Bosnich, B., *Chem. Commun.* **1998**, 193-194.

[11] Brook, M.A., Crowe, G.D., Hiemstra, H., *Can. J. Chem.* **1994**, *72*, 264-267.

[12] Jung, M. E., Blum, R. B., *Tetrahedron Lett.* **1977**, *18*, 3791-3794.

[13] Murata, S., Suzuki, M., Noyori, R., *Tetrahedron* **1988**, *44*, 4259-4275.

[14] *General procedure*: To a flame dried, argon flushed flask charged with a 0.3 M solution of the dimethylacetal (1 equiv.) in anhydrous DCM cooled to the temperature given (Table 1) was added the Lewis acid. (1 equiv.). This mixture was stirred at this temperature for 5 mins whereupon a 0.5 M solution of allyldimethylsiloxyethene (1 equiv.) in DCM was added dropwise. Stirring was continued for a further 4 hrs before quenching with 1 M KF solution (5 mL). The organics were diluted with ethyl acetate (2 x 20mL), washed with sat. $NaHCO_3$ sol. (5 mL), and dried ($MgSO_4$). The organics were concentrated in *vacuo* and purified by chromatography (SiO_2: hexane/ethyl acetate 4/1 v/v). The compounds were fully characterised by standard analytical techniques. The stereochemistry of **10** was assigned by comparison of the n.m.r. spectra with the literature (Hoffmann, R., Brückner, R., *Chem. Ber.* **1992**, *127*, 1471-1484).

[15] Aldehyde **19** is unstable to the reaction conditions. In contrast, no degradation products are observed using **9** (conditions as Table 1), suggesting that free aldehydes are not intermediates in the tandem reactions.

[16] We note the recent preparation and application of dialkylsilyl enol ethers by Hosomi (Miura, K., Sato, H., Tamaki, K., Ito, H., Hosomi, A., *Tetrahedron Lett.* **1998**, *39*, 2585-2589). These undergo aldol reactions in the absence of Lewis acids and the resulting β-siloxyketones are known precusors to *anti*-1,3-diols (Anwar, S., Bradley, G., Davis, A.P., *J. Chem. Soc. Perkin Trans. 1* **1991**, 1383-1389).