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Stereospecificity in the silicon tethered α-(methyl)allylation of aldehydes †

Jeremy Robertson,*[a] Michael J. Hall[a] and Stuart P. Green[b]

[a] *Dyson Perrins Laboratory, South Parks Road, Oxford, UK OX1 3QY*

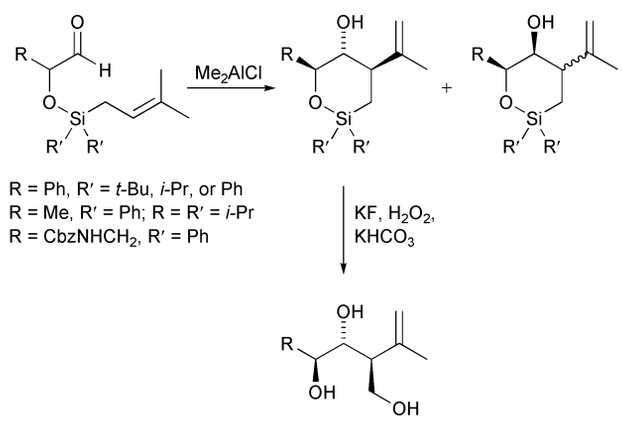
[b] *Chemical Research & Development Department, Pfizer Global Research and Development, Sandwich, Kent, UK CT13 9NJ*

Received 17th June 2003, Accepted 15th August 2003
First published as an Advance Article on the web 3rd September 2003

Heating *E*- and *Z*-crotyl(diphenyl)silyloxy aldehydes, in the absence of an added catalyst, results in stereospecific intramolecular allyl transfer with moderate to high stereoselectivity.

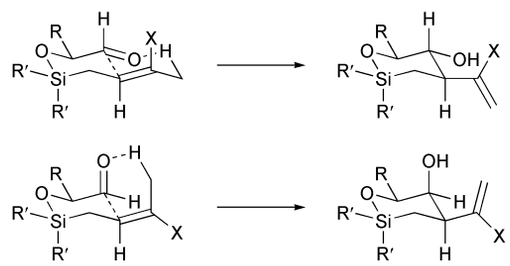
Introduction

We have described Lewis acid-mediated silicon tethered ene cyclisations of β-prenylsilyl aldehydes that proceed with moderate stereoselectivity in favour of a *trans*-disposition of the newly-formed hydroxyl and isopropenyl groups.[1] More recently, we have observed that α-prenylsilyloxy aldehyde precursors show broadly similar behavior and benefit from an easy oxidative cleavage pathway to generate stereodefined triols (Scheme 1).[2]



Scheme 1

Diastereomeric ene cyclisation products could arise by proton abstraction from either of the diastereotopic methyl groups on the prenyl substituent in either a *trans*- or *cis*-decalin-like transition structure (Scheme 2, X = Me).[3] On this basis we sought to prepare the *E*- and *Z*-crotyl analogues in the belief that these would cyclise with improved ratios of diastereomeric products (Scheme 2, X = H).[4] In this communication we describe the successful preparation of suitable substrates in order to test this proposal, and report their behaviour under both Lewis acidic and thermal conditions.

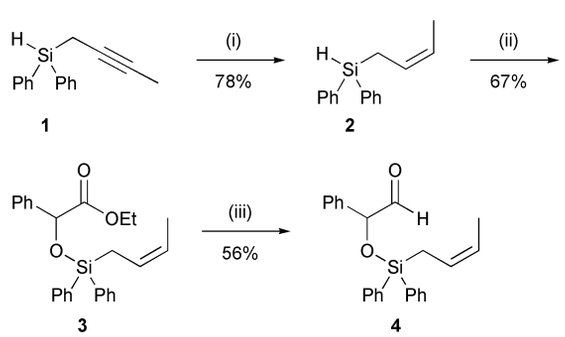


Scheme 2 Prediction of improved stereoselectivity in the ene cyclisation of crotylsilyl precursors (X = H) compared with that of prenylsilyl precursors (X = Me).

† This is one of a number of contributions from the current members of the Dyson Perrins Laboratory to mark the end of almost 90 years of organic chemistry research in that building, as all its current academic staff move across South Parks Road to a new purpose-built laboratory.

Stereoselective synthesis of *E*- and *Z*-crotyl precursors

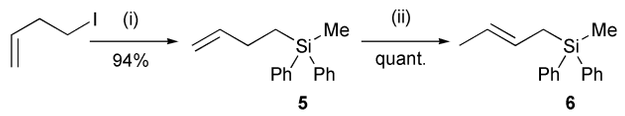
Substrates **4** (Scheme 3) and **10** (see Scheme 5) were identified as the initial targets since our earlier work had shown that phenyl substituents on silicon offered the optimum balance of stability and eventual ease of oxidative cleavage of the C–Si bond.[5] In addition, we had found that Piers' method[6] for hydroxyl silylation could be relied upon even with allylic silanes, therefore access to the *Z*-crotyl derivative **4** required the preparation of *Z*-crotyldiphenylsilane. The requisite silane (**2**) was prepared by reduction[7] of 2-butynyldiphenylsilane (**1**)[8] and, after purification by chromatography, was found to be free of the *E*-isomer as judged by examination of the 600 MHz ^{1}H NMR spectrum. (±)-Ethyl mandelate was successfully silylated with this reagent and the ester (**3**) reduced to provide the desired *Z*-crotyl precursor (**4**) in acceptable yield (Scheme 3).



Scheme 3 *Reagents:* (i) DIBAL; H_3O^+; (ii) $PhCH(OH)CO_2Et$, $B(C_6F_5)_3$ cat.; (iii) DIBAL.

Efficient access to the *E*-analogue proved to be more problematic since existing methods[9] for *E*-crotylsilane synthesis were either inapplicable to our specific requirements or gave poor results in our hands. However, inspired by Hodgson's report[10] that the double bond in 1,1-bis(trialkylsilyl)alkenes could be migrated into the allylic position we proposed that it might be possible to isomerise the double bond in readily-prepared 3-butenylsilanes (*i.e.* homoallylic silanes) into the allylic position. Indeed, there was good precedent to this concept in the work of Matsuda in which a range of Ir(I) and Rh(I) complexes had been evaluated for their potential in the isomerisation of several simple tetraalkylsilanes.[11] A short model study established that commercially-available $[(COD)Ir(PPh_2Me)_2]^+PF_6^-$ was effective in achieving complete isomerisation of 3-butenylsilane **5** (Scheme 4) to give *E*-crotylsilane **6**, even though this was not identified as the optimum pre-catalyst

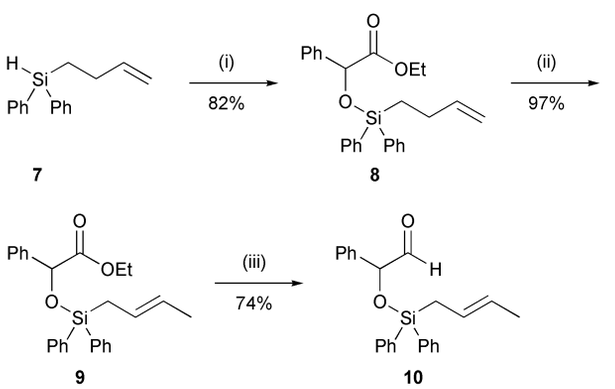
DOI: 10.1039/b306920f



Scheme 4 *Reagents:* (i) *t*-BuLi; $Ph_2MeSiCl$; (ii) $[(COD)Ir(PPh_2Me)_2]^+PF_6^-$ cat.

in Matsuda's study. Key to the success of this reaction was careful control of activation of the pre-catalyst with hydrogen, removal of excess hydrogen, and identification of the correct temperature (0 °C) and time (*ca.* 30–45 min) for the isomerisation; in this way, the product was obtained free of vinylsilyl contaminants and accompanied by only *ca.* 2–3% of the *Z*-crotylsilyl isomer.

Subsequently we were delighted to find that the product (**8**) of silylation of ethyl mandelate with 3-butenyldiphenylsilane (**7**)[12] could be isomerised under these optimised conditions to provide *E*-crotyl substrate **9** in high yield. DIBAL reduction of the ester to give aldehyde **10** proceeded well to complete a practical and efficient synthesis of the *E*-crotyl precursor (Scheme 5).

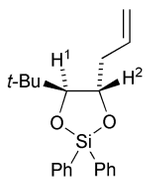


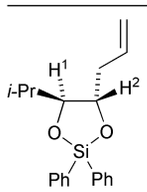
Scheme 5 *Reagents:* (i) $PhCH(OH)CO_2Et$, $B(C_6F_5)_3$ cat.; (ii) $[(COD)Ir(PPh_2Me)_2]^+PF_6^-$ cat.; (iii) DIBAL.

Cyclisations

Having expended considerable effort in developing short, efficient routes to both *E*- and *Z*-crotyl precursors we were disappointed to find that they were totally unsuited to ene cyclisation both under the "standard" conditions (Me_2AlCl, CH_2Cl_2, RT) and with a variety of alternative Lewis acids at various temperatures; in all cases the precursors either decomposed completely or gave rise to complex product mixtures that were of no synthetic value. To try to effect ene cyclisation under conditions in which the substrates would not be prone to decomposition, aldehydes **4** and **10** were heated at 80 °C in $CDCl_3$ and the reactions monitored by ^1H NMR. Interestingly, in each case, there was a smooth progression from the

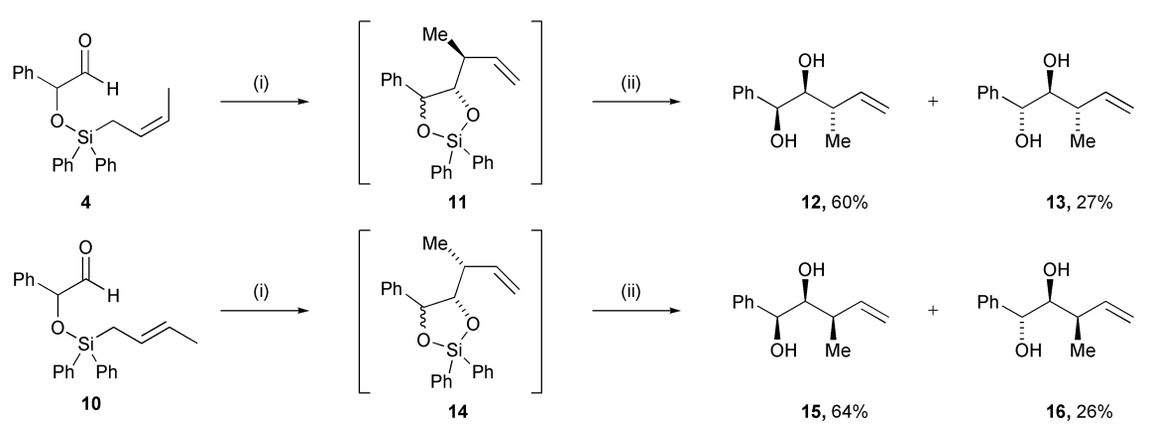
Table 1

		Enhancement/%			
	Irradiate	H^1	H^2	CH_2CH=	Me_3C
	H^1	—	1.5	4.8	6.9
	H^2	2.0	—	4.9	8.6
	CH_2CH=	8.3	6.9	—	2.3
	t-Bu	19.7	21.7	4.6	—
27					

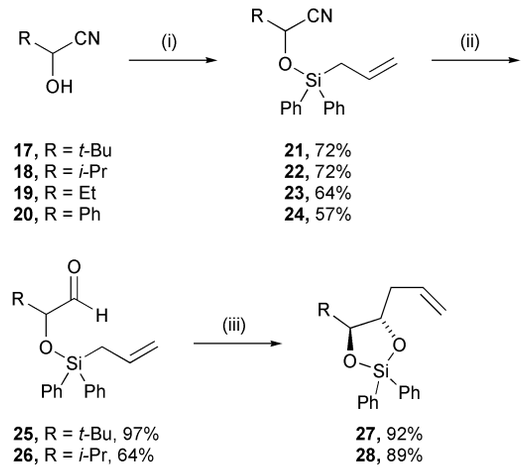
		Enhancement/%			
	Irradiate	H^1	H^2	CH_2CH=	Me_2CH
	H^1	—	2.3	5.5	6.3
	H^2	2.2	—	5.1	4.7
	CH_2CH=	5.5	5.0	—	0.7
	$CHMe_2$	4.0	3.4	—	—
28					

α-silyloxyaldehyde to a pair of 2-sila-1,3-dioxolanes, which were tentatively assigned, on the basis of subsequent results, as being epimeric at the benzylic position, the stereochemistry at the allylic position being determined by that of the crotyl unit in the starting material (Scheme 6). Desilylation of these intermediates gave a high yield of the diols **12** and **13** (from **4**) and **15** and **16** (from **10**) that could be readily separated by chromatography.

Confirmation of the stereochemistry in these compounds was sought by correlation with simpler analogues and, initially, unsubstituted allyl substrates were examined so that the predominant formation of siladioxolane precursors of *syn*-diols could be established. Preparation of test substrates was most easily achieved by silylation of cyanohydrins **17**–**20**[13] (Scheme 7) with allyldiphenylchlorosilane (prepared *in situ* from dichlorodiphenylsilane and allylmagnesium bromide) followed by DIBAL reduction.[14] This sequence worked well for cyanohydrins **17** and **18**, derived respectively from pivalaldehyde and isobutyraldehyde, but the DIBAL reductions were not productive in generating the more labile aldehydes derived ultimately from propionaldehyde and benzaldehyde. Nevertheless, the two substrates **25** and **26** proved sufficient for the purposes of this study, behaving as expected when heated to 80 °C and, after 36 h at this temperature, removal of the solvent gave a single compound in each case (**27** and **28** respectively), the stereochemistry being confirmed by NOE experiments, as indicated (Table 1).



Scheme 6 *Reagents:* (i) $CHCl_3$, 80 °C, 36 h; (ii) KF, $KHCO_3$, aq. MeOH–Et_2O.



17, R = *t*-Bu
18, R = *i*-Pr
19, R = Et
20, R = Ph

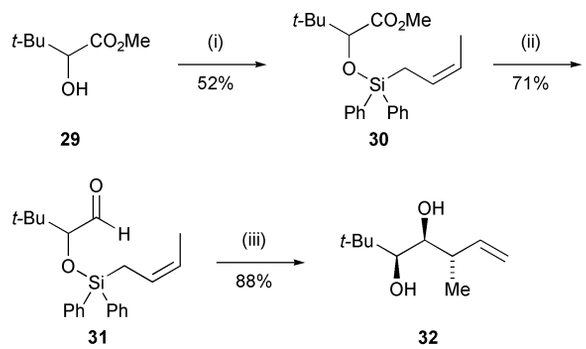
21, 72%
22, 72%
23, 64%
24, 57%

25, R = *t*-Bu, 97%
26, R = *i*-Pr, 64%

27, 92%
28, 89%

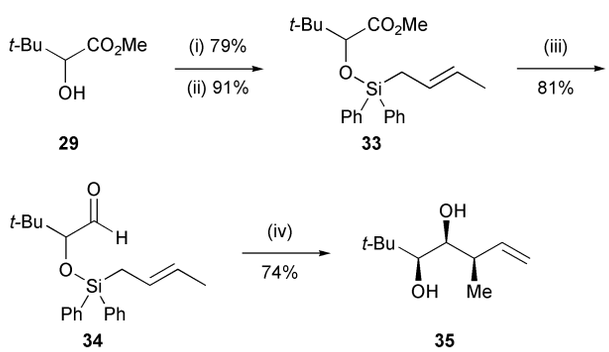
Scheme 7 *Reagents:* (i) Ph_2(allyl)SiCl, imidazole; (ii) DIBAL; (iii) C_6H_6, 80 °C, 36 h.

Because the *tert*-butyl-substituted compounds were stable, easy to handle, gave essentially perfect stereocontrol during the rearrangement step and simple NMR spectra with the minimal amount of coupling of the ring protons, *tert*-butyl variants (**31**, Scheme 8 and **34**, Scheme 9) of the *Z*- and *E*-crotyl precursors were prepared. Once again, cyclisation proceeded extremely cleanly, this time to give single diastereoisomers of the siladioxolane intermediates (not shown) which were desilylated in the presence of hydrogen peroxide to facilitate separation of the diols from phenylsilyl residues.



29 **30** **31** **32**

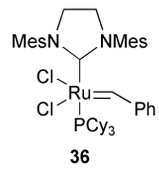
Scheme 8 *Reagents:* (i) silane **2**, $B(C_6F_5)_3$ cat.; (ii) DIBAL; Swern oxidation; (iii) C_6H_6, 80 °C, 36 h then KF, H_2O_2, aq. MeOH–Et_2O.



29 **33** **34** **35**

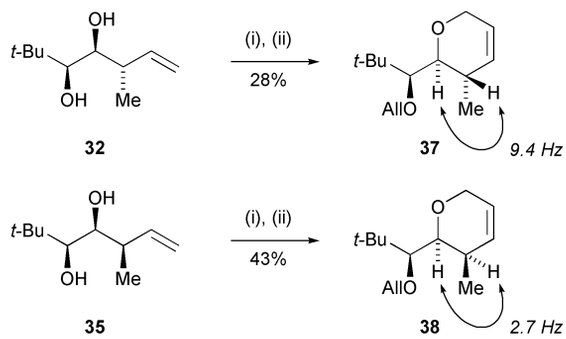
Scheme 9 *Reagents:* (i) silane **7**, $B(C_6F_5)_3$ cat.; (ii) $[(COD)Ir(PPh_2Me)_2]^+PF_6^-$ cat.; (iii) DIBAL; Swern oxidation; (iv) C_6H_6, 80 °C, 36 h then KF, H_2O_2, aq. MeOH–Et_2O.

Whilst the relative stereochemistry at the two hydroxylated positions was clear by NMR analysis of the intermediate siladioxolanes, to secure the stereochemistry at the allylic position diols **32** and **35** were bis-allylated and the allyl ethers subjected to ring closing metathesis (RCM) with the second generation Grubbs' catalyst **36** (Fig. 1) to give samples of the dihydropyrans **37** and **38** (Scheme 10). The modest yields in



36

Fig. 1



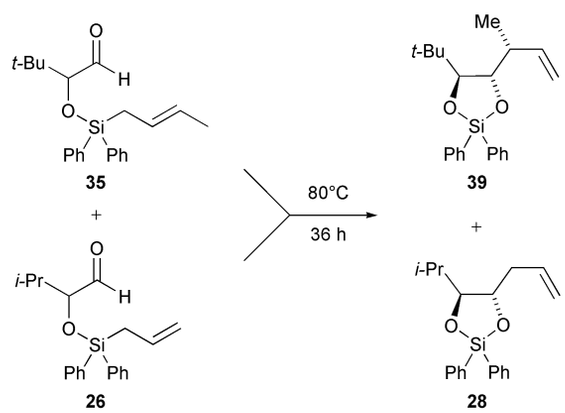
32 **37** **35** **38**

Scheme 10 *Reagents:* (i) NaH, allyl bromide; (ii) **36** cat., 20 °C, 4 h.

these unoptimised RCM reactions result from competing cyclisation to give seven membered ring products (not shown).[15] The coupling constant between the allylic and ring-oxygen methine protons was large (*J* 9.4 Hz) in the case of **37** and small (*J* 2.7 Hz) in the case of **38** which supported *anti*- and *syn*-assignments respectively of the precursor diols **32** and **35**.

Mechanism and stereochemistry

In view of the observed stereochemistry of the siladioxolanes, the process seems most likely to be intramolecular and to be sure that intermolecular processes could not compete a mixture of *tert*-butyl/*E*-crotyl substrate **35** and isopropyl/allyl substrate **26** was heated for 36 h at 80 °C. Analysis of the reaction mixture both by high field ^{1}H NMR spectroscopy and high resolution GC mass spectrometry revealed that only two siladioxolanes (**39** and **28**) had been produced in support of a purely intramolecular reaction (Scheme 11).



35 **39** **26** **28**

Scheme 11 Crossover experiment.

Our working model for these reactions involves cooperative[16] pre-activation of both the aldehyde and silicon atom by their mutual coordination and subsequent allylic transfer through a chair-like assembly from the face opposite the alkyl substituent (Fig. 2). This arrangement results in anti-Felkin–Anh selectivity and, because the group bound to the acyl carbon is forced into a pseudoaxial position, the usual sense of stereoselectivity between the allylic and newly-formed hydroxylated positions (*E* ⟶ *anti, Z* ⟶ *syn*) is reversed when compared with nominally intermolecular allylations that proceed *via* coordinated nucleophilic delivery within a six-membered ring transition state.[17]

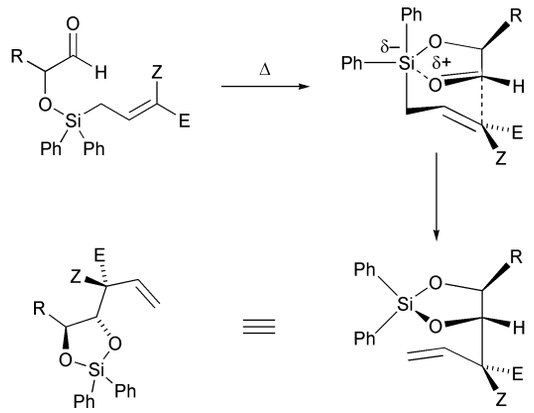


Fig. 2

This model predicts that the level of facial selectivity should be determined by the effective size of the alkyl group and, indeed, the *t*-Bu and *i*-Pr cases proceeded with excellent stereoselectivity in contrast to the Ph cases.

Summary

This process is closely related to an increasing number of allylations that proceed in the absence of added catalysts. For example, if the silicon atom is rendered sufficiently Lewis acidic, either by virtue of attached electronegative substituents[18] or by being constrained within a four membered ring,[16,19] then complexation to an aldehyde precedes allyl delivery and an ordered intramolecular reaction follows with consequently high stereocontrol. More recently, Leighton has been very active in this general field and has reported, *inter alia*, a variety of elegant systems for intramolecular carbonyl allylation from silicon intermediates.[20] Nevertheless, these examples appear to be the first in which a simple diarylsilyloxy substituent activates the proximal carbonyl group in this way.

A full description of these results is currently in preparation that will include β-silyloxyaldehyde analogues, substrates bearing functionalised side-chains, and examples of α-(trialkylsilyl)-allyl transfer.

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