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Enantioselective Radical-Chain Hydrosilylation of Prochiral Alkenes Using Optically Active Thiol Catalysts

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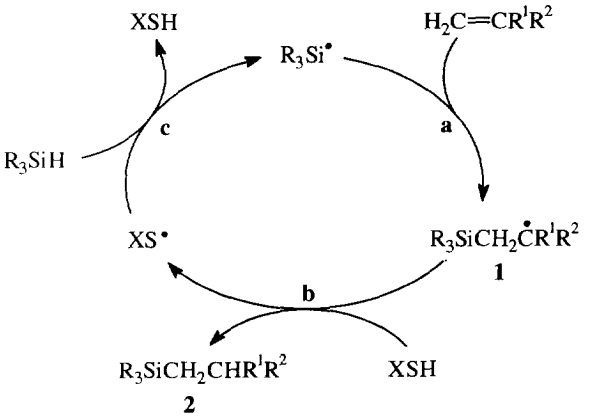
Abstract: *The radical-chain hydrosilylation of alkenes of the type $H_2C{=}CR^1R^2$, catalysed by small amounts of optically active thiols, affords functionalised organosilanes in moderate enantiomeric purity by a mechanism which involves enantioselective hydrogen-atom transfer from the thiol to a prochiral β-silylalkyl radical.*

We have reported recently that the radical-chain hydrosilylation of alkenes is catalysed by thiols.[1] In the presence of a thiol, the normally sluggish direct transfer of a hydrogen atom from the silane to the adduct radical **1** is replaced by the catalytic cycle of more rapid propagation reactions **b** and **c**, as shown in Scheme 1.[2,3] The hydrosilylation product



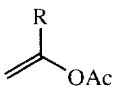
Scheme 1

2 is formed in step **b** by hydrogen-atom transfer from the thiol and thus, if the adduct radical **1** is prochiral and the thiol is optically active, step **b** should be enantioselective. In this paper we report preliminary results which show that functionalised chiral organosilanes can be obtained in moderate enantiomeric purity by this route, using only catalytic quantities of readily-available homochiral thiols.

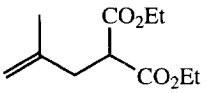
In accord with previous results,[1] radical-chain addition of dimethylphenylsilane (1.3 molar equiv.) to isopropenyl acetate **3** proceeded smoothly in hexane or dioxane solvent during 2.5 h at 60 °C, in the presence of di-*tert*-butyl hyponitrite[4] (TBHN; 0.05 equiv.) as initiator and *tert*-dodecanethiol[5] (0.05 equiv.) as catalyst, to give the adduct **7** in 85%

yield after purification by flash chromatography over silica gel. In order to maximise the yield,[1] the thiol in a small volume of solvent was added slowly to the reaction mixture during the first 2 h using a syringe pump; all reactions were carried out under anhydrous conditions and under an atmosphere of nitrogen. When the reaction was repeated in the absence of thiol, but under otherwise identical conditions, ^{1}H NMR spectroscopic analysis of the residue after evaporation of the solvent showed that only *ca.* 1% of the adduct **7** had been formed.

Similar results were obtained for the hydrosilylation of the alkenes **4-6** and the isolated yields of the corresponding adducts **8-10** are given alongside the formulae.[6] Interestingly, the yield of **10** was raised to 90% by the use of methyl thioglycolate ($HSCH_2CO_2Me$; 0.05 equiv.) as catalyst. When the reactions were repeated in dioxane solvent, using the



3, R = Me
4, R = Bu^t



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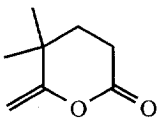

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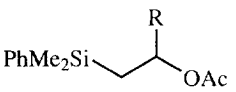
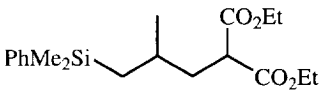
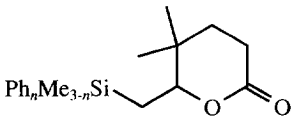


7, R = Me (85%)
8, R = Bu^t (82%)

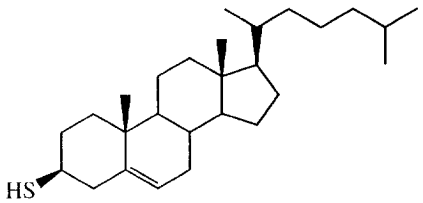


9 (88%)



10, n = 1 (80%)
11, n = 2
12, n = 3

commercially-available thiocholesterol **13** as catalyst, optically active adducts of low enantiomeric purity were obtained. The enantiomeric excesses (ees), determined by ^{1}H NMR spectroscopy in conjunction with an optically active shift reagent [Eu(hfc)$_3$] or by chiral-stationary-phase HPLC analysis, for **7-9** were 3, 5 and 10%, respectively.



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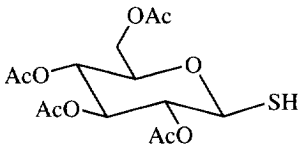

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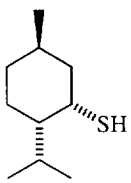

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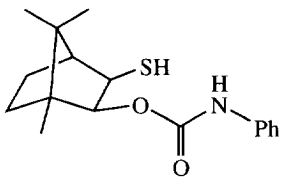

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A systematic investigation of the effects of varying the nature of the silane and of the thiol catalyst was made for hydrosilylation of the methylenelactone[7] **6** on a 5 mmol scale. In addition to **13**, commercially-available 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranose **14**, neomenthyl mercaptan[8] **15** and the thiol **16**, derived[11] from (1*R*)-(+)-camphor, were used in conjunction with the phenylsilanes $Ph_nMe_{3-n}SiH$ (n = 1-3). All reactions were carried out at 60 °C and the yields and enantiomeric purities of the adducts **10-12** are given in Table 1.[12] The ees of the products are generally small, except with the thioglucose derivative **14** as the catalyst, when enantiomeric purity increases with the degree of phenyl substitution at silicon. Considering the simplicity of the procedure and the preliminary nature of the work, the moderate degree of asymmetric induction obtained using **14** as catalyst is encouraging.

TABLE 1: Enantioselective hydrosilylation of the methylenelactone **6** using optically active thiol catalysts at 60 °C[a]

Entry	Silane[b]	Solvent	Thiol catalyst[c]	Product	Isolated yield (%)	Product ee (%)[d]
1	$PhMe_2SiH$	Dioxane	**13**	**10**	47	7
2	$PhMe_2SiH$	Dioxane	**14**	**10**	74	16
3	$PhMe_2SiH$	Hexane[e]	**14**	**10**	52	23
4	$PhMe_2SiH$	Hexane	**15**	**10**	39	0
5	$PhMe_2SiH$	Dioxane	**16**	**10**	40	6
6	Ph_2MeSiH	Dioxane	**13**	**11**	40	4
7	Ph_2MeSiH	Dioxane	**14**	**11**	78	26
8	Ph_2MeSiH	Hexane[e]	**14**	**11**	65	32
9	Ph_2MeSiH	Hexane	**15**	**11**	69	0
10	Ph_2MeSiH	Dioxane	**16**	**11**	76	10
11	Ph_3SiH	Dioxane	**13**	**12**	33	3
12	Ph_3SiH	Dioxane	**14**	**12**	63	40
13	Ph_3SiH	Hexane[e]	**14**	**12**	72	50[f]
14	Ph_3SiH	Hexane	**15**	**12**	36	3
15	Ph_3SiH	Dioxane	**16**	**12**	60	10

a TBHN (0.05 molar equiv.) initiator. *b* A small excess of silane (1.3 molar equiv.) was used. *c* All the thiol (0.05 molar equiv.) was added at the start of these reactions. *d* Determined by chiral-stationary-phase HPLC analysis using a Chiralcel-OJ column (Daicel Chemical Industries) for **10** and **11** and a Chiralcel-OD column for **12**. With thiols **13** and **15** as catalysts, the enantiomer present in excess was eluted second; with thiols **14** and **16**, the predominant enantiomer was eluted first. *e* Although the thiol **14** is only sparingly soluble in hexane at room temperature, all the catalyst dissolved in the reaction mixture at 60 °C. Towards the end of reaction, some of the adduct came out of solution and care was taken to recover all of the product for determination of the enantiomeric purity. *f* Enantiopure material, $[\alpha]_D^{22}$ = -77.5 (c = 1.78, $CHCl_3$), was obtained by recrystallisation from benzene-hexane.

A difference in the rates of hydrogen-atom transfer from a chiral thiol to the *Re* and *Si* faces of a prochiral carbon-centred radical such as **1** could, in principle, arise from various types of interaction present in the diastereoisomeric

transition states. Although the detailed nature of the transition state for hydrogen-atom transfer between a thiol and a carbon-centred radical is not yet firmly established,[13] in general, differences in steric (van der Waals), electrostatic and hydrogen-bonding interactions are the most likely causes of any deviation of (k_{Re}/k_{Si}) from unity. It might also prove possible to make use of Lewis acid complexation to link the thiol and the adduct radical **1** loosely and reversibly, thus rendering hydrogen-atom transfer effectively intramolecular and thereby (hopefully) increasing enantioselectivity. There is also potential for the design of radical-chain hydrosilylation reactions that are efficient at lower temperatures when enantioselectivity should be enhanced. For the thiols **13** and **15**, the differences in k_{Re} and k_{Si} are probably mainly steric in origin, while for the thioglucose tetraacetate **14** electrostatic interactions with the polar adduct radical derived from **6** may also be important and could be partly responsible for the relatively high ees obtained for hydrosilylation using this catalyst. Support for this suggestion is provided by the observation that the product ees increase on going from dioxane to hexane solvent in which the electrostatic binding should be tighter. More detailed investigations of this and related chain processes are in progress to establish the factors that govern enantioselectivity in hydrogen-atom transfer to prochiral carbon-centred radicals.

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5. This is the mixture of isomers *tert*-$C_{12}H_{25}SH$ as obtained from the Aldrich Chemical Company.
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12. *Representative procedure*: The lactone **6** (0.70 g, 5.0 mmol), triphenylsilane (1.69 g, 6.5 mmol), the thioglucose tetraacetate **14** (91 mg, 0.25 mmol) and TBHN (44 mg, 0.25 mmol) were dissolved in dry dioxane (4 cm^3). A short condenser was attached to the reaction flask, the apparatus was flushed briefly with nitrogen and the solution was stirred and heated under nitrogen for 2.5 h at 60 °C. After removal of the solvent under reduced pressure, the residue was subjected to chromatography over silica gel [petroleum spirit (b.p. 40-60 °C), followed by petroleum-diethyl ether (9:1), then petroleum-diethyl ether (4:1)] to give the adduct **12** as a microcrystalline solid (1.25 g, 63%), m.p. (racemate) 115-116 °C, $[\alpha]_D^{25}$ = -31.3 (*c* = 1.36, $CHCl_3$). (Found: C, 77.90; H, 7.11. $C_{26}H_{28}O_2Si$ requires: C, 77.96; H, 7.05%). HPLC analysis using a Chiralcel-OD column (hexane + 1% isopropyl alcohol eluent) showed the ee to be 40%, in favour of the faster-moving enantiomer. For this reaction, the yield was not improved by slow addition of the thiol during the reaction.
    NMR data (Varian VXR-400, $CDCl_3$ solvent): δ_H: 0.92 (s, 3H), 1.00 (s, 3H), 1.58 (m, 3H, CH^ASi + CH_2CMe_2), 1.79 (dd, 1H, *J* = 15.02, 11.55 Hz, CH^BSi), 2.40 (m, 2H), 4.11 (dd, 1H, *J* = 11.55, 2.39 Hz, *CH*O), 7.38 (m, 9H) and 7.59 (m, 6H); δ_C: 15.0, 19.3, 26.6, 27.4, 33.1, 34.0, 84.6, 127.8, 129.5, 134.5, 135.9 and 170.0.
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