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The Reaction of Acylsilane–Enolates with Benzaldehyde: Reaction Cascade Leading to α-Benzoyloxy-γ-hydroxysilanes

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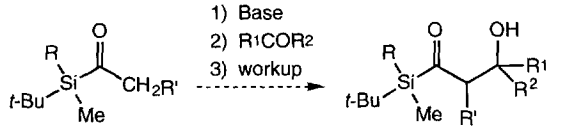
Abstract: The reaction of acylsilane–enolates with benzaldehyde gives rise to α-benzoyloxy-γ-hydroxysilanes in a reaction cascade involving aldol addition, hemiacetal formation, stereospecific intramolecular Cannizarro type disproportionation, and transesterification. This reaction pathway is supported by the separate transformation of proposed intermediates to the final products.

INTRODUCTION

In connection with our ongoing investigation of diastereoselective transformations using chiral alkoxymethyl-substituted silyl groups as chiral auxiliaries[3,4] we were interested to study the potential of such subsidiaries as inducers of stereoselectivity in aldol type reactions. Metal enolates of chiral acetylsilanes of the type **1** (R ≠ Me) were expected to yield – upon treatment with carbonyl electrophiles, like, *e.g.*, benzaldehyde – unequal amounts of diastereoisomeric β-hydroxyacylsilanes of the type **2** and, hence, optically active aldol products when using enantiomerically pure starting silanes (Scheme 1).



1a R = BnOCH$_2$ R' = H
1b R = Me R' = H

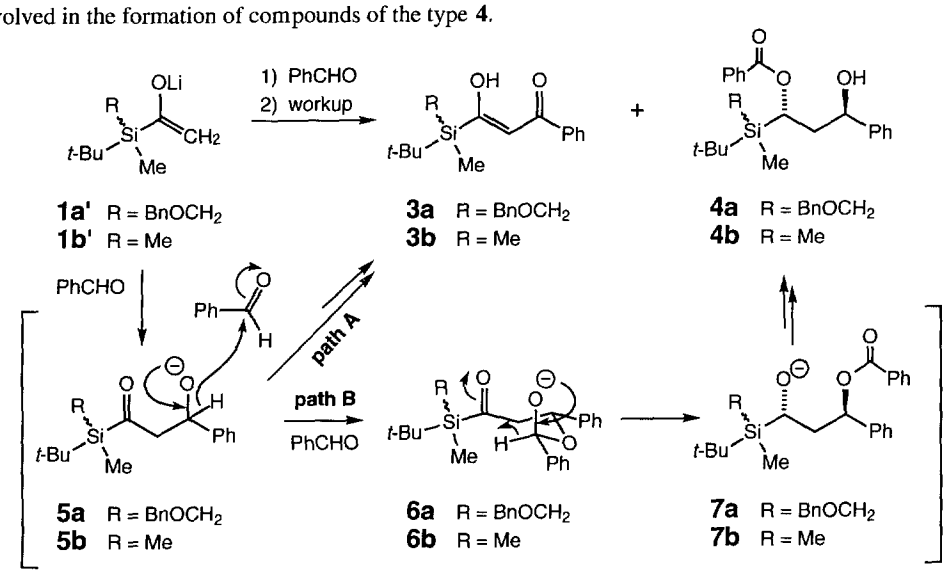
2a R = BnOCH$_2$ R' = H
2b R = Me R' = H

Scheme 1

RESULTS AND DISCUSSION

The reaction of the lithium enolate **1a'**, prepared by deprotonation of **1a** with lithium diisopropyl amide (LDA), with an excess of benzaldehyde (THF, –78° to 23°C), however, did not afford any trace of the desired compounds **2a**, but a rather complex mixture of products consisting mainly of the two diastereoisomeric α-benzoyloxy-γ-hydroxysilanes (R_{Si}*,S*,R*)-**4a** and (S_{Si}*,S*,R*)-**4a** (16% each) (Scheme 2) and the fully enolized β-diketone **3a** (35%). Similar products were obtained with nonchiral **1b** as the acylsilane component,

namely, (*S**,*R**)-**4b** (20%) and **3b** (10%), in this case as minor components, together with the normal aldol product **2b** (60%). The yields of the unusual products of the type **3** and **4**, however, could be improved by using a greater excess of benzaldehyde. Interestingly, none of the compounds (R_{Si}*,*R**,*R**)-**4a**, (S_{Si}*,*R**,*R**)-**4a**, or (*R**,*R**)-**4b** were found. These latter compounds differ from the observed products in the relative configurations at the chiral centers on the carbon framework. The results indicate that a stereospecific process is involved in the formation of compounds of the type **4**.



Scheme 2

The exclusive creation of the (R_{Si}*/S_{Si}*,*S**,*R**)-configured compounds **4a**, the structures of which were secured by single crystal X-ray analyses (Figure 1), the (*S**,*R**)-configured **4b**, as well as the formation of the products of the type **3**, is explained by the reaction cascades outlined in Scheme 2. It is proposed that the enolates **1'** react in an initial non-stereoselective step with one equivalent of benzaldehyde to give a 1:1-mixture of the aldolate anions **5**, which are not stable under the reaction conditions. In the presence of additional benzaldehyde they could either act as hydride donors giving rise to the diketones **3** and benzyl alcohol (path A), or add to the carbonyl double bond of benzaldehyde to produce intermediary hemiacetal anions **6**. These are then, in a stereospecific way, able to transfer intramolecularly – *via* a six-membered cyclic transition state – a hydride to the silyl ketone moiety, which initially affords alkoxy anions **7** and, after transesterification and protic workup, the final products **4** (path B).

The proposed mechanism for the formation of the compounds **4** is supported by several additional findings: aldolates **5**, generated from the corresponding aldols that have been obtained by Mukaiyama aldol reaction[5], gave rise to **7** upon treatment with benzaldehyde followed by protic workup. These compounds were further converted to the final transesterified products **4** by the action of LDA and benzyl alcoholate. The presence of an external alcoholate was found to be crucial for the final rearrangement. Its effect could possibly be explained by the decomposition of a supposedly rather stable alkali cation chelate of the anions **7** by the action of a good nucleophile; the driving force for the transesterification, however, is unclear. Evidently, the anions of the type **7** are less stable than the alcoholate anions of the corresponding compounds **4**.

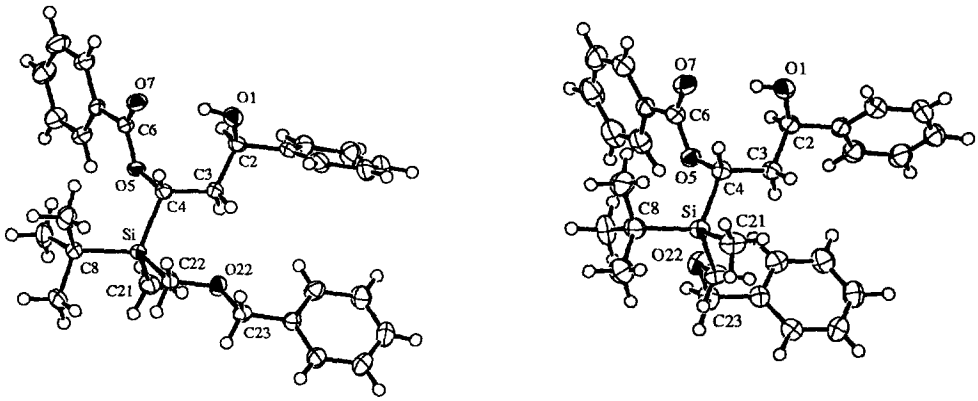
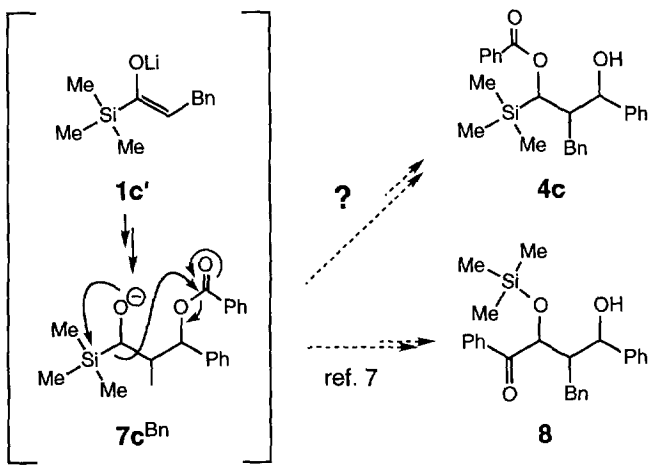


Figure 1: X-ray structures of (R_{Si}*,S*,R*)-**4a** (left) and (S_{Si}*,S*,R*)-**4a** (right)[6].

A reaction cascade similar to that described above is already discussed in the literature[7]: Kuwajima *et al.* have reported that the treatment of enolate **1c'** with benzaldehyde formed – similarly to **1a** or **1b** shown above – the intermediary alcoholate **7c**, which, according to the authors, gave rise to **8** after Brook rearrangement[8,9] and intramolecular acylation (Scheme 3). We assume, however, that Kuwajima and his collaborators have misinterpreted their spectra (which unfortunately are not published) and actually have obtained **4c**, a



Scheme 3

product which is similar to ours. Since the starting acylsilane **1c** for their reaction is structurally not too distinct from the acylsilanes **1a** and **1b** investigated in our laboratories and because the reaction conditions leading apparently to **8** are identical with ours, which unambiguously gave rise to **4**, the completely different behavior of intermediate **7c** as compared with **7a** or **7b** cannot be rationalized.

EXPERIMENTAL

General Remarks. Where not remarked differently: all reactions were carried out under a blanket of inert gas. During the workup, all extracts were dried over disodium sulfate prior to evaporation of the solvents *in vacuo*. Chromatography was performed on Merck Kieselgel 60 (230–400 mesh). Infrared spectra (IR) were taken on a Perkin-Elmer 297 or 781 (frequencies given in cm^{-1}), ^1H (200 or 300 MHz) and ^{13}C NMR (50.4 MHz) on a Bruker AM-300 or a Varian XL-200 in $CDCl_3$ as the solvent (δ in ppm relative to the solvent: δ_H ($CHCl_3$) = 7.26, δ_C ($CDCl_3$) = 77.0; coupling constants (J) in Hertz, multiplicities of the ^{13}C NMR signals from DEPT experiments), mass spectra in *m/z* (rel.%) on a Varian MAT 112S (chemical ionization (CI-MS) with NH_3 as the reactant gase and electron impact ionization (EI-MS) at 70 eV).

Acylsilane–Enolate Reaction with Benzaldehyde. A soln. of the respective acylsilane (**1a** or **1b**) in tetrahydrofuran (1.0 eq, *ca.* 2M) was added dropwise to a soln. of freshly prepared lithium diisopropyl amide in tetrahydrofuran (1.2 eq, *ca.* 0.1M) at –78°C and the resulting soln. was warmed to –30°C for 30 min. After re-cooling to –78°C, benzaldehyde (1.2 eq, neat) was added dropwise, and the soln. was allowed to warm to 23°C overnight. It was quenched with aqueous NH_4Cl soln., extracted with ether, and the crude products, obtained after evaporation of the organic solvent, were chromatographed with hexane/ethyl acetate (20:1) to give **3a** (35%), (*R*$_{Si}$*,*S**,*R**)-**4a** (16%), and (*S*$_{Si}$*,*S**,*R**)-**4a** (16%) from **1a**, and **2b** (60%), **3b** (10%), and (*S**,*R**)-**4b** (20%) from **1b**. The pure compounds (*R*$_{Si}$*,*S**,*R**)-**4a** and (*S*$_{Si}$*,*S**,*R**)-**4a** were gained by fractional crystallization from hexane/ethyl acetate.

Stepwise Transformation of 2a Into 4a: To a soln. of 48 mmol of freshly prepared lithium diisopropyl amide in 4 ml of tetrahydrofuran at –78°C, 100 mg (0.27 mmol) of aldol **2a**[10] and 450 mg (4.6 mmol) of benzaldehyde were added. Reaction and workup as above gave 53 mg (41%) of **7a**. Treatment of 129 mg (0.27 mmol) of **7a** with 48 mmol lithium diisopropyl amide and 0.27 mmol of benzaldehyde as above gave quantitatively **4a**.

[(*tert*-Butyl)dimethylsilyl] [2-Hydroxy-2-phenylethyl] Ketone (2b): Colorless oil; ^1H NMR ($CDCl_3$): 8.11–7.26 (*m*, 5 arom. H); 5.22–5.17 (*m*, PhC*H*OH); 3.42 (*d*, *J* = 2.6, OH); 3.08–2.93 (*m*, $SiCOCH_2$); 0.95 (*s*, CMe_3); 0.202, 0.200 (2*s*, $SiMe_2$).

1-{[(Benzyloxy)methyl](*tert*-butyl)methylsilyl}-3-hydroxy-3-phenyl-2-propen-1-one (3a): Orange-yellow oil; IR (neat): 1600*m*, 1570*s*; ^1H NMR ($CDCl_3$): 15.12 (br. s, OH, exchanged with D_2O, enol of diketone); 7.73–7.70 (*m* app. *d*, 2 arom. H); 7.41–7.00 (*m*, 8 arom. H); 6.42 (*s*, =CH); 4.39 (*s*, $PhCH_2O$); 3.32 (*s*, $SiCH_2O$); 0.89 (*s*, CMe_3); 0.14 (*s*, SiMe); ^{13}C NMR ($CDCl_3$): 192.52 (*s*, CO); 191.88 (*s*, =COH); 138.45, 137.12 (2*s*, arom. C); 132.60 (*d*, arom. C); 128.53, 128.28, 127.74, 127.62 (4*d*, 8 arom. C); 127.50 (*d*, arom. C); 107.30 (*d*, =CH); 77.50 (*t*, $PhCH_2O$); 59.21 (*t*, $SiCH_2O$); 26.83 (*q*, CMe_3); 16.78 (s, CMe_3); –10.03 (*q*, SiMe); CI-MS (NH_3): 369 [*M* + NH_4]$^+$; Anal. Calcd. for $C_{22}H_{28}O_3Si$ (368.55): C 71.70, H 7.66. Found: C 70.50, H 7.60.

1-[(*tert*-Butyl)dimethylsilyl]-3-hydroxy-3-phenyl-2-propen-1-one (3b): Orange-yellow oil; IR (neat): 1600*m*, 1565*s*; ^1H NMR ($CDCl_3$): 15.19 (br. *s*, OH); 7.84–7.82 (*m* app. *d*, 2 arom. H); 7.45–7.34 (*m*, 3 arom. H); 6.33 (*s*, =CH); 0.91 (*s*, CMe_3); 0.14 (*s*, $SiMe_2$); ^{13}C NMR ($CDCl_3$): 194.33 (*s*, CO); 192.52 (*s*, =COH); 137.29 (*s*, arom. C); 132.61 (*d*, arom. C), 128.57, 127.70 (2*d*, 4 arom. C); 106.33 (*d*, =CH); 26.42 (*q*, CMe_3);

16.53 (*s*, *C*Me$_3$); –7.29 (*q*, SiMe$_2$); CI-MS (NH_3): 263 [M + H]$^+$; Anal. Calcd. for $C_{15}H_{22}O_2Si$ (262.43): C 68.65, H 8.45. Found: C 68.56, H 8.54.

(Si*R,1*S**,3*R**)-1-{[(Benzyloxy)methyl](*tert*-butyl)methylsilyl}-3-hydroxy-3-phenylpropyl Benzoate** [(*R*$_{Si}$*,*S**,*R**)-**4a**]: Colorless crystals,;m.p. (hexane/AcOEt 10:1): 89–90°C; IR (neat): 3500*s*, 1690*s*, 1270*s*; ^{1}H NMR ($CDCl_3$): 8.12–8.10 (*m* app. *d*, 2 arom. H); 7.62–7.26 (*m*, 13 arom. H); 5.70 (*dd*, *J* = 12.6, 2.8, SiC*H*OBz); 4.56 (*ddd*, *J* = 10.6, 3.2, 2.8, PhC*H*OH); 4.47 (*s*, PhCH_2O); 3.87 (*d*, *J* = 3.2, OH); 3.38, 3.34 (*AB*, *J* = 12.6, SiCH$_2$O); 2.21 (*ddd*, *J* = 15.0, 12.6, 2.8, 1 CHCH_2); 2.04 (*ddd*, *J* = 15.0, 10.6, 2.8, 1 CHCH_2); 1.03 (*s*, CMe$_3$); 0.22 (*s*, SiMe); ^{13}C NMR ($CDCl_3$): 168.38 (*s*, CO); 143.86, 138.34 (2*s*, arom. C); 133.14 (*d*, arom. C); 129.79, 128.42 (2*d*, 4 arom. C); 128.22 (*d* and *s*, 3 arom. C); 128.16, 127.60 (2*d*, 4 arom. C); 127.34, 127.03 (2*d*, arom. C); 125.63 (*d*, 2 arom. C); 77.29 (*t*, PhCH_2O); 69.21 (*d*, PhCHOH); 63.26 (*d*, SiCHOBz); 59.44 (*t*, SiCH$_2$O); 42.18 (*t*, CHCH_2); 27.26 (*q*, C*Me*$_3$); 16.85 (*s*, *C*Me$_3$); –10.55 (*q*, SiMe); CI-MS (NH_3): 494 (20, [*M* + NH_4]$^+$), 459 (100, [*M* + 1 – H_2O]$^+$); Anal. Calcd. for $C_{29}H_{36}O_4Si$ (476.69): C 73.07, H 7.61. Found: 73.10, H 7.42.

(Si*R,1*S**,3*R**)-3-{[(Benzyloxy)methyl](*tert*-butyl)methylsilyl}-3-hydroxy-1-phenylpropyl Benzoate** [(*R*$_{Si}$*,*S**,*R**)-**4a**]: Colorless crystals; m.p. (hexane/AcOEt 10:1): 79–82°C; IR (neat): 3500*s*, 1690*s*, 1270*s*; ^{1}H NMR ($CDCl_3$): 8.17–8.05 (*m* app. *d*, 2 arom. H); 7.61–7.26 (*m*, 13 arom. H); 5.63 (*dd*, *J* = 12.8, 2.4, SiC*H*OBz); 4.50 (*ddd*, *J* = 10.4, 3.2, 2.5, PhC*H*OH); 4.34, 4.31 (*AB*, *J* = 12.6, PhCH_2O); 3.93 (*d*, *J* = 3.2, OH); 3.51, 3.41 (*AB*, *J* = 12.9, SiCH$_2$O); 2.30 (*ddd*, *J* = 14.0, 12.8, 2.5, CHCH_2); 1.94 (*ddd*, *J* = 14.0, 10.4, 2.4, 1 CHCH_2); 1.10 (*s*, CMe$_3$); 0.16 (*s*, SiMe); ^{13}C NMR ($CDCl_3$): 168.57 (*s*, CO); 143.84, 138.53 (2*s*, arom. C); 133.18 (*d*, arom. C); 129.90, 128.83, 128.45 (3*d*, 6 arom. C); 128.29 (*s*, arom. C); 128.26, 127.59 (2*d*, 4 arom. C); 127.38, 127.08 (2*d*, arom. C); 125.61 (*d*, 2 arom. C); 77.05 (*t*, PhCH_2O); 69.07 (*d*, PhCHOH); 63.43 (*d*, SiCHOBz); 59.23(*t*, SiCH$_2$O); 42.43 (*t*, CHCH_2); 27.27 (*q*, C*Me*$_3$); 16.88 (s, *C*Me$_3$); –10.50 (*q*, SiMe); CI-MS (NH_3): 494 (20, [*M* + NH_4]$^+$), 459 (100, [*M* + 1 – H_2O]$^+$).

(1*S,3*R**)-1-[(*tert*-Butyl)dimethylsilyl]-3-hydroxy-3-phenylpropyl Benzoate** [(*S**,*R**)-**4b**]: Colorless oil; IR: 3490 br. *s*, 1695*s*, 1270*s*; ^{1}H NMR ($CDCl_3$): 8.04–8.00 (*m* app. *d*, 2 arom. H); 7.54–7.19 (*m*, 8 arom. H); 5.45 (*dd*, *J* = 13.0, 1.9, SiC*H*OBz); 4.43 (*ddd*, *J* = 10.7, 3.5, 2.3, PhC*H*OH); 3.76 (*d*, *J* = 3.5, OH); 2.01 (*ddd*, *J* = 14.7, 13.1, 2.3, 1 CHCH_2); 1.78 (*ddd*, *J* = 14.7, 10.7, 1.9, 1 CHCH_2); 0.87 (*s*, CMe$_3$); 0.07, 0.00 (2*s*, SiMe$_2$); ^{13}C NMR ($CDCl_3$): 168.58 (*s*, CO); 143.84 (*s*, arom. C); 133.25 (*d*, arom. C); 129.85, 128.51, 128.33 (3*d*, 6 arom. C); 128.1 (*s*, arom. C); 127.16 (*d*, arom. C), 125.62 (*d*, 2 arom. C); 69.14 (*d*, PhCHOH); 64.09 (*d*, SiCHOBz); 42.38 (*t*, CHCH_2); 26.93 (*q*, C*Me*$_3$); 16.73 (*s*, *C*Me$_3$); –7.14, –8.05 (2*q* Si(Me)$_2$); CI-MS (NH_3): 353 [*M* + 1 – H_2O]$^+$; Anal. Calcd. for $C_{22}H_{30}O_3Si$ (370.57): C:, 71.31, H 8.16 Found: C 69.04, H 10.72.

(Si*S/*R**,1*R*,*3*S**)-1-{[(Benzyloxy)methyl](*tert*-butyl)methylsilyl}-3-hydroxy-3-phenylpropyl Benzoate** [(*S*/*R*$_{Si}$*,*R**,*S**)-**7a**]: Colorless oil; ^{1}H NMR ($CDCl_3$, mixture of two diastereoisomers): 8.04–7.93 (*m*, 2 arom. H); 7.56–7.15 (*m*, 13 arom. H); 6.31–6.23 (*m*, PhC*H*OBz); 4.35 (*s*, PhCH_2O); 3.89–3.61 (*m*, SiC*H*OH); 3.43–3.13 (*m*, SiCH$_2$O); 2.22–2.00 (*m*, CHCH_2); 0.91 (*s*, CMe$_3$); 0.01, –0.44 (2*s*, SiMe).

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