Electrochemical silicon-directed aldol condensation by a β-destabilizing effect

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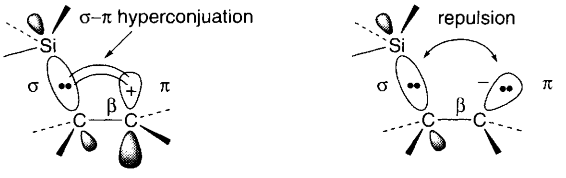
A pass of electricity (4.0 F mol^{-1}, constant 1.5 A current) through a cell containing β-silyl cycloalkanone 1, 2 or 10 in anhydrous methanol with NaOMe at −10 °C in the anodic chamber gives the corresponding aldols with hydroxymethyl groups exclusively at the α′-position; the silicon β-destabilizing effect on the intermediate enolate ion results in high regioselectivity.

Silicon-controlled reactions have a high potential for use in the development of new materials of value to industry and life sciences.[1] To investigate these reactions we studied photolysis, thermolysis, catalysis and electron transfer reactions.[2] The β-stabilizing effect of a silyl group is often utilized to control organic reactions involving carbocationic intermediates (Scheme 1).[3] Few successful examples, however, exist of the use of its β-destabilizing effect to direct reactions involving anionic intermediates.

Fleming *et al.*[4] reported that the directing effect of a β-silyl group is detectable but minimal on base-catalysed enolization of an unsymmetrical ketone; the effect appears to be largely steric in origin. We considered that an organic anionic species may associate with its counter cation to a lesser extent under electrochemical conditions than in normal solution. Thus the electronic effect resulting from a β-silyl group could destabilize the highly dissociated anions to a greater extent than those tightly associated with a metal cation. Based on this concept, we have successfully developed the first electrochemical aldol condensation directed by silicon.

Electricity (4.0 F mol^{-1}, constant current 1.5 A, 0.2 A cm^{-2}, average voltage *ca.* 19 V) was passed through an anhydrous methanol solution (40 mL) containing NaOMe (15 mmol) and 3-(trimethylsilyl)cyclohexanone **1** (10 mmol) at −10 °C in an undivided cell equipped with two platinum electrodes.[5] After 2 h, the reaction mixture was worked up with HCl (0.30 mol dm^{-3}) and water. Purification of the crude products by silica gel chromatography gave the pure aldols **4** (30%) and **5** (35%, Scheme 2). By the same procedure, β-silylated ketone **2** gave aldols **6** (31%), **7** (18%) and **8** (11%) in 63% overall yield. Furthermore, 3-(trimethylsilyl)cyclopentanone **10** gave aldols **11** (29%) and **12** (30%) in 59% overall yields (Scheme 3). On the other hand, in a control experiment, we applied the same electrochemical conditions to 3-(isopropyl)cyclohexanone **3**. Within 3 h, hydroxymethylation took place at the α-position exclusively to afford **9** in 31% yield as the only alkylated product; the starting material **3** was recovered in >50% yield.

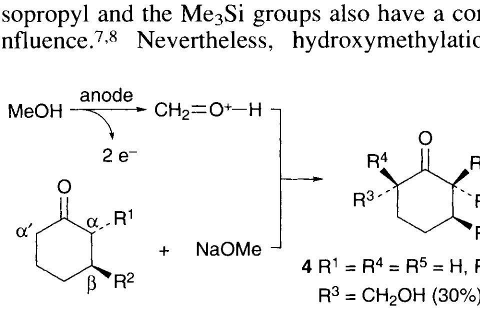


β-stabilizing effect β-destabilizing effect

Scheme 1

The products were identified by ^{1}H NMR, ^{13}C NMR, IR and mass spectrometry. To confirm the aldol skeleton, we carried out single-crystal X-ray diffraction analysis of crystalline aldol **5** (mp 110–112 °C). Fig. 1 shows its molecular framework,† which possessed an α′-geminal dihydroxymethyl moiety in 3-(trimethylsilyl)cyclohexanone.

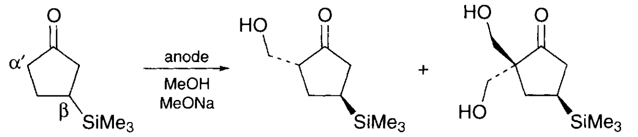
In these reactions, the enolates generated from cycloalkanones and NaOMe reacted with $CH_2{=}O^+H$, which was produced from the solvent MeOH by electrochemical oxidation.[6] The isopropyl and the Me_3Si groups also have a comparable steric influence.[7,8] Nevertheless, hydroxymethylation took place



1 R^1 = H, R^2 = $SiMe_3$
(intact 20%)
2 R^1 = Me, R^2 = $SiMe_3$
(intact 22%)
3 R^1 = H, R^2 = Pr^i
(intact 55%)

4 R^1 = R^4 = R^5 = H, R^2 = $SiMe_3$,
R^3 = CH_2OH (30%)
5 R^1 = R^5 = H, R^2 = $SiMe_3$,
R^3 = R^4 = CH_2OH (35%)
6 R^1 = Me, R^2 = $SiMe_3$,
R^3 = R^4 = CH_2OH, R^5 = H (31%)
7 R^1 = Me, R^2 = $SiMe_3$, R^3 = CH_2OH,
R^4 = CH_2OMe, R^5 = H (18%)
8 R^1 = Me, R^2 = $SiMe_3$, R^3 = CH_2OMe,
R^4 = CH_2OH, R^5 = H (11%)
9 R^1 = CH_2OH, R^2 = Pr^i,
R^3 = R^4 = H, R^5 = CH_2OH (31%)

Scheme 2



10 (intact 35%) **11** (29%) **12** (30%)

Scheme 3

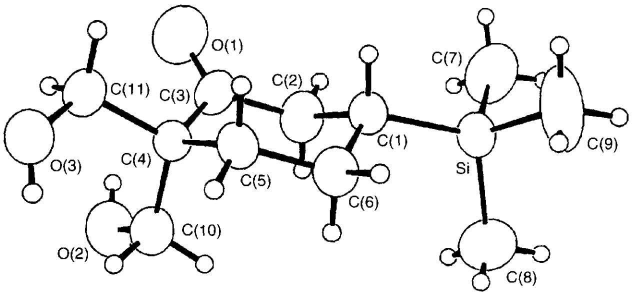


Fig. 1 Molecular framework of aldol **5** revealed by single-crystal X-ray analysis

exclusively at the α′-position in the β-silylated cyclohexanones **1**, **2** and **10**. This outcome can be explained by the silicon β-destabilizing effect towards enolate ions and contrasts sharply with those being hydroxymethylated at the α-position for non-silylated cyclohexanone **3**.

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Footnote

[†] *Crystal data* for **5**: $C_{11}H_{22}O_3Si$; M = 230.38. The crystals were grown from a THF solution. Triclinic, space group $P\bar{1}$, a = 6.265(2), b = 9.784(2), c = 11.148(2) Å, α = 100.64(2)°, β = 89.42(2)°, γ = 98.01(2)°, V = 665.0(2) Å^3, Z = 2, D_c = 1.151 Mg m^{-3}, T = 298 K, absorption coefficient (ψ scan): μ(Mo-Kα) = 0.16 m^{-1}, Enraf-Nonius CAD4-diffractometer, $2\theta_{max}$ = 44.8°, 1743 reflections measured, 1733 symmetry-independent reflections, 1207 observed reflections (R = 0.062, R_w = 0.047). The intensity data were collected by use of a CAD4 diffractometer with $\omega-\theta$ scans. The unit-cell parameters were determined by a least-squares refinement on diffractometer angles for 25 (17.20–28.00°) automatically centred reflections. The structure was solved by direct methods associated with the NRCSDP program package.[9] All non-hydrogens were anisotropically refined by the least-squares Fourier-method. The H atoms were found by a Fourier difference map. The ORTEP[10] program was used for drawing the molecules. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Information for Authors, Issue No. 1.

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