

The Application of Difunctional Organosilicon Compounds to Organic Synthesis; 1,3-Asymmetric Induction in the Reduction of β -Hydroxy-ketones

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A number of β -hydroxy-ketones were reduced to *anti*-1,3-diols with diastereoisomeric excesses exceeding 95%, by a method involving presumed intramolecular transfer of hydrogen from a silicon atom to the carbonyl carbon.

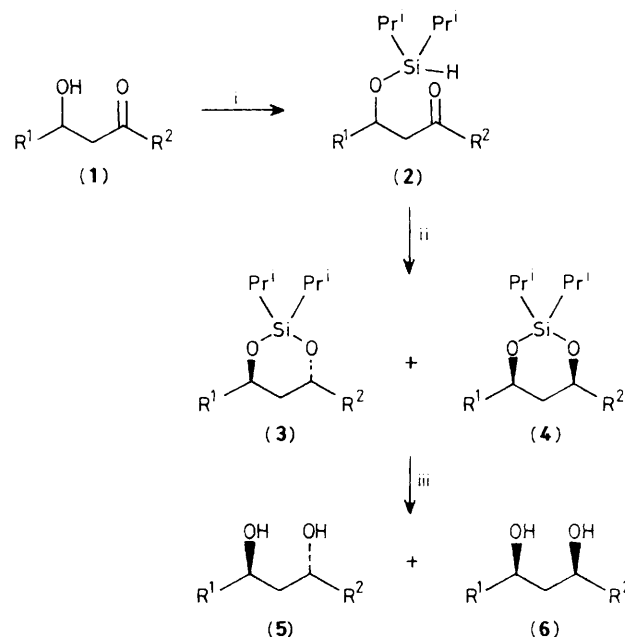
'Difunctional' silicon compounds of the form R_2SiAB , where both A and B have reactive potential, have received relatively little attention from synthetic organic chemists until quite recently.¹ An intriguing and lightly explored possibility is the use of the silicon atom effectively to attach a reagent to its substrate.² A variety of intermolecular reactions involving organosilicon compounds might thus be rendered intramolecular, profoundly affecting their regio- and stereo-selectivity. We report an application of this strategy to the reduction of a carbonyl group by an organosilane.

There is considerable current interest in remote asymmetric induction in addition reactions to carbonyl groups.^{3,4} Within this area, the stereoselective reduction of β -hydroxy-ketones⁴ may be seen as an especially attractive target because of the prevalence of 1,3-dioxygenated substructures in biologically active natural products and the advanced state of development of the directed aldol reaction.⁵ We have found that β -hydroxy-ketones can be reduced with a remarkable level of 1,3-asymmetric induction by employing the sequence shown in Scheme 1. The reducing agent is an organosilane which is initially attached to the hydroxy group of the β -hydroxy-ketone and then induced to react with the carbonyl group by a Lewis acidic catalyst. As shown in Table 1, treatment of a number of β -silyloxy-ketones (2) with $SnCl_4$ gave preferentially the *trans*-siladioxanes (3)[†] with diastereoisomeric excesses of 95% or better. After desilylation, the *anti*-diols (5) could be obtained in overall yields which are generally reasonable for a three-step, unoptimised procedure.[‡]

Although we have found $SnCl_4$ to be the most convenient and reliable catalyst for hydride transfer, it can be seen from Table 1 that other Lewis acids are also effective. Indeed, even greater stereoselectivity was achieved using $BF_3 \cdot OEt_2$ in one example, although the reaction was not entirely clean.

We have generally preferred to use the di-isopropylsilyl compounds specified in Scheme 1 for the following reasons: (i) di-isopropylchlorosilane, the initial reagent, is readily synthesised⁷ and is easy to store and handle, (ii) the silylated hydroxy-ketones (2) are also relatively easy to handle, being purifiable by chromatography on silica gel if required, (iii) the siladioxanes (3) and (4) are stable under the reaction conditions, readily analysable by g.l.c., and are recognised as useful protected forms of 1,3-diols.⁸ However, good results

can also be obtained with the commercially available dimethylchlorosilane; for example, silylation of (1; $R^1 = R^2 = Pr^i$) with the latter followed by treatment with $SnCl_4$ under our standard conditions (see Table 1) gave diols (5) and (6) ($R^1 = R^2 = Pr^i$) directly in a ratio of 30:1 (63% yield).



Scheme 1. i, Pr^i_2SiHCl , pyridine, benzene or hexane; ii, see Table 1; iii, $HF(aq.)$, $MeCN$.

Table 1. Results from the Lewis acid-catalysed rearrangements of β -silyloxyketones (2).

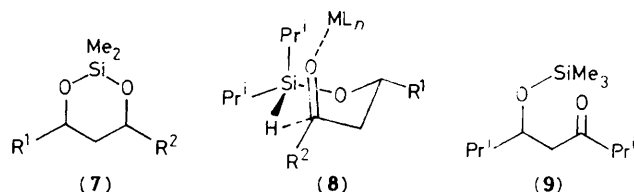
| R^1, R^2 | Catalyst | Ratio (3):(4) ^a | % Yield of <i>anti</i> -diol (5) ^b |
|------------|------------------------|----------------------------|---|
| Pr^i | $SnCl_4^b$ | 120:1 | 67 |
| Bu | $SnCl_4^b$ | 40:1 | 44 |
| Pr^i, Me | $SnCl_4^b$ | 50:1 | 61 |
| Me, Pr^i | $SnCl_4^b$ | 40:1 | 68 |
| Pr^i | $MgBr_2 \cdot OEt_2^c$ | 60:1 ^d | |
| Pr^i | $TiCl_4^e$ | 30:1 ^d | |
| Pr^i | $BF_3 \cdot OEt_2^f$ | 320:1 ^g | |

^a Determined by g.l.c. analysis. The ratio of diols formed on deprotection of the crude rearrangement products invariably reflected the figures in this column. ^b $SnCl_4$ (0.1 mol. equiv.), CH_2Cl_2 , $-80^\circ C$, 2 h. ^c $MgBr_2 \cdot OEt_2$ (0.1 mol. equiv.), CH_2Cl_2 , room temp., 24 h.

^d Formation of siladioxanes (3) and (4) was clean by g.l.c. ^e $TiCl_4$ (0.5 mol. equiv.), CH_2Cl_2 , $-80^\circ C$, 30 min. ^f $BF_3 \cdot OEt_2$ (0.5 mol. equiv.), $-80^\circ C$, 2 h. ^g Siladioxanes accompanied by unidentified impurity (ca. 30% by g.l.c. peak areas). ^h Overall yield based on hydroxy-ketone (1).

[†] The siladioxanes (3) and (4) ($R^1 = Me, R^2 = Pr^i$) were distinguished by comparison of the 1H n.m.r. spectra of the derived diols with literature data.⁶ The siladioxanes (3) and (4) ($R^1 = R^2 = Pr^i$ and $R^1 = R^2 = Bu$) were distinguished by comparison of their 1H n.m.r. spectra and those of the derived dimethylsiladioxanes (7). Selected 1H n.m.r. data, δ ($CDCl_3$): *trans*-(7; $R^1 = R^2 = Pr^i$) 0.1 (6H, s, SiMe) and 1.68 (2H, t, J 5 Hz, 5- H_2); *cis*-(7; $R^1 = R^2 = Pr^i$) 0.1 (3H, s, SiMe), 0.25 (3H, s, SiMe), and 1.50–1.82 (2H, m, 5- H_2); δ (5- H_2) for (3) and (4): (3; $R^1 = R^2 = Pr^i$) 1.70 (t, J 5 Hz); (4; $R^1 = R^2 = Pr^i$) 1.38–1.75 (m); (3; $R^1 = R^2 = Bu$) 1.70 (t, J 5 Hz); (4; $R^1 = R^2 = Bu$) 1.38–1.75 (m).

[‡] In each case the lowest yield in the sequence was for the first (silylation) step (yields 65–79%). An investigation of the many alternative methods for silylation may lead to significant improvements.



The stereoselectivity of the reaction can be understood on the assumption that it occurs *via* a chair-like transition state (8). The examination of molecular models clearly indicates that attack of the opposite face of the carbonyl group *via* alternative chair- or boat-like transition states is strongly disfavoured by steric and/or stereoelectronic effects. We presume that the catalyst is not chelated by the two oxygen atoms of the substrate, since $\text{BF}_3 \cdot \text{OEt}_2$ gives similar results to the other Lewis acids. Boron is generally assumed to be incapable of a co-ordination number greater than 4.⁹ Our presumption of intramolecularity was supported by control experiments in which we attempted the intermolecular reduction of cyclohexanone and the ketone (9) with diisopropylisopropoxysilane and SnCl_4 . Under our standard conditions, these reactions were apparently too slow to be observed.

In conclusion, we have demonstrated that the simultaneous use of a silicon atom as an activating influence and a link between reagent and substrate can form the basis of a synthetic method displaying impressive stereoselectivity. The *anti*-selective reduction of β -hydroxy-ketones described herein is unique in its capability, being complementary to the *syn*-selective reduction of Narasaka,⁴ and the level of 1,3-asymmetric induction is comparable with the best previously achieved for carbonyl addition reactions.^{3,4}

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