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

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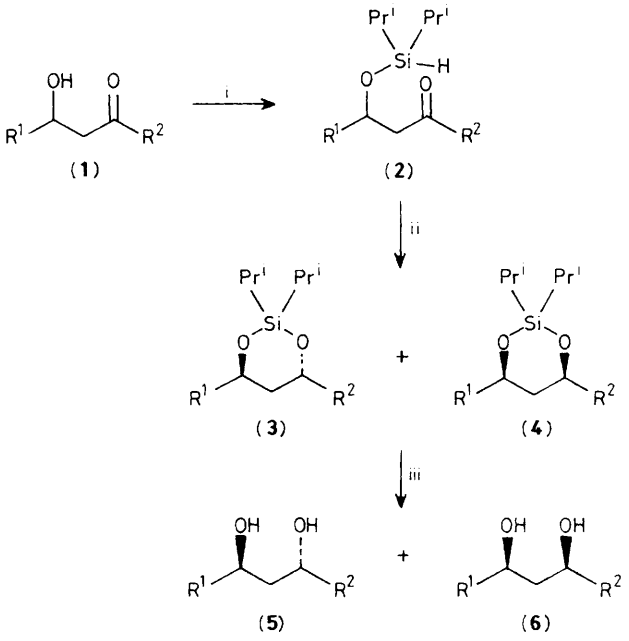
A number of β-hydroxy-ketones were reduced to *anti*-1,3-diols with diastereoisomeric excesses exceeding 95%, by a method involving presumed intramolecular transfer of hydrogen from a silicon atom to the carbonyl carbon.

'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-ketones[4] 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 synthesised[7] 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.

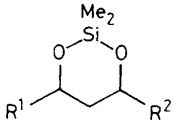
Table 1. Results from the Lewis acid-catalysed rearrangements of β-silyloxyketones (**2**).

R^1, R^2	Catalyst	Ratio (**3**) : (**4**)[a]	% Yield of *anti*-diol (**5**)[h]
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]	

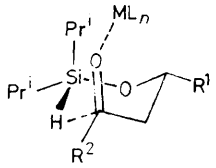
[a] Determined by g.l.c. analysis. The ratio of diols formed on deprotection of the crude rearrangement products invariably reflected the figures in this column. [b] $SnCl_4$ (0.1 mol. equiv.), CH_2Cl_2, −80 °C, 2 h. [c] $MgBr_2{\cdot}OEt_2$ (0.1 mol. equiv.), CH_2Cl_2, room temp., 24 h. [d] Formation of siladioxanes (**3**) and (**4**) was clean by g.l.c. [e] $TiCl_4$ (0.5 mol. equiv.), CH_2Cl_2, −80 °C, 30 min. [f] $BF_3{\cdot}OEt_2$ (0.5 mol. equiv.), −80 °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**; $R^1 = R^3$ = Bu) 1.70 (t, *J* 5 Hz); (**4**; $R^1 = R^2$ = Bu) 1.38—1.75 (m).

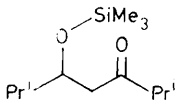
‡ In each case the lowest yield in the sequence was for the first (silylation) step (yields 65—79%). An investigation of the many alternative methods for silylation may lead to significant improvements.



(7)



(8)



(9)

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 $BF_3{\cdot}OEt_2$ 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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