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NUCLEOPHILIC SUBSTITUTION AT SILICON: EVIDENCE FOR ELECTRONIC FACTORS AS DRIVING FORCE OF THE STEREOCHEMISTRY

R.J.P. CORRIU and C. GUERIN

Laboratoire des Organométalliques, ERA 554, Université des Sciences et Techniques du Languedoc, Place Eugène Bataillon, 34060 Montpellier Cédex (France)

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Summary

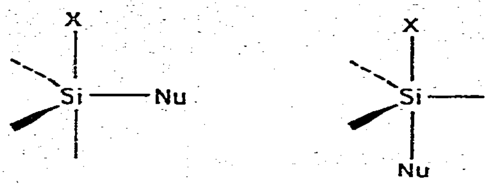
The relationship between the stereochemistry of nucleophilic substitution at silicon and the electronic character of the attacking nucleophile has been studied. It is shown that the reagents which favour 1,2-addition to α-enones react with retention of configuration, whereas those which favour 1,4-addition react with inversion at silicon. This is consistent with our hypothesis suggesting that the dominant influence on the stereochemistry at silicon for a given leaving group is the electronic character of the nucleophile: inversion would be a frontier-orbital process, and retention a charge-controlled mechanism.

I. Introduction

Coupling reactions of various organometallic reagents (RLi, RMgX, RNa) and of $LiAlH_4$ with optically active silicon compounds have been studied previously [1,2]; it was shown that the stereochemistry of these reactions depends not only on the nature of the leaving group [3], but also on the electronic character of the nucleophile. For instance, inversion of configuration is the stereochemical path for acyclic R_3Si^*Cl in reactions with all kinds of organometallic reagents (R'Li and R'MgX). For R_3Si^*F, however, simple alkyllithium reagents give retention of configuration whereas allyl- and benzyl-lithium give inversion of configuration. Also relevant are the differences of stereochemistry of reactions of the allyl anion (inversion of configuration) and n-alkyl anions (retention of configuration) with an optically active oxasilacyclopentane [2a].

In order to explain the dependence of stereochemistry on the nature of the organometallic reagents for a given leaving group we suggested two possibilities for nucleophilic attack at silicon [4]. Hard nucleophiles (such as n-alkyl anions) which have a localized negative charge, attack equatorially at silicon; the stereochemistry is retention (Scheme 1). In contrast, softer nucleophiles (such as benzyl or allyl anions) which have a delocalized negative charge, prefer apical attack at silicon, and give predominant inversion of configuration (Scheme 1).

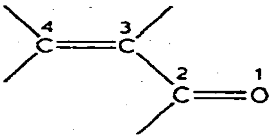
SCHEME 1



Retention Inversion

Both processes involve the rate-determining formation of a pentacoordinate intermediate [5]. The electronic interactions at silicon due on the one hand to the lability of the leaving group [5] and on the other hand to the electronic structure of the nucleophile (soft or hard) determine the stereochemistry.

The literature provides other examples of reactions for which the stereochemistry [6] or regioselectivity [7,8] are dependent on the nature of the reactive species. Our interest was in nucleophilic additions to α-enones, which are ambident electrophiles, the two reactive sites being carbon-2 (carbonyl addition) and carbon-4 (Michaël type addition):



The regioselectivity of these reactions has been extensively studied [7] and it is easy to find nucleophilic additions for which kinetic control is confirmed. Theoretical interpretations have been proposed in terms of the Klopman theory [9] by Anh and Seyden-Penne [10—13]. Simply stated, in the absence of complexation reactions at carbon-2 are under charge control (hard site) while reactions at carbon-4 are under frontier orbital control (soft site).

In the present paper, we report some parallel studies of nucleophilic reactions at a silicon center and α-enones: the close parallel observed between the two sets of reactions provides good support for our hypothesis of the electronic character of the nucleophilic reagents the dominant influence on the stereochemistry of nucleophilic displacements at silicon for a given leaving group.

II. Results and discussion

Two kinds of reactions were chosen for the present study: (1) Reactions with organolithium, Grignard, and organocuprate reagents, and (2) reductions with some alanes $AlH_{3-n}(Y)_n$ (Y = OR, SR or I), which were recently proposed by Ashby et al. [14—16]. The cyclohexenone and benzalacetone were chosen as representative enones. The optically active silanes used are compounds I—V.

(1) Coupling reactions with organolithium, organomagnesium and organocuprate reagents

Table 1 summarizes the results for substitutions at silicon.

It is again evident that the stereochemistry is related to the lability of the

(α-Np)PhMeSiOMe

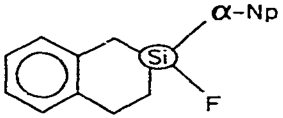
(I) $[\alpha]_D$ −16.5°

(α-Np)PhMeSiF

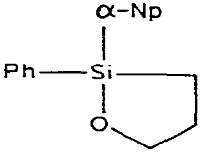
(II) $[\alpha]_D$ +47°

(α-Np)PhMeSiSPh

(III) $[\alpha]_D$ +27°



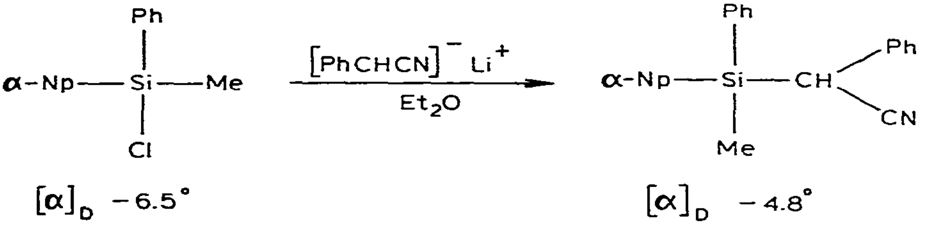
(IV) $[\alpha]_D$ −34°

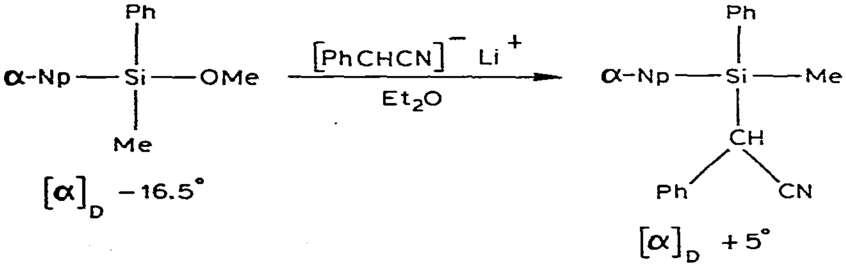


(V) $[\alpha]_D$ −16°

leaving group; the poor leaving group OR reacts with retention of configuration, while the better leaving groups F and SPh react with inversion. As for the influence of the nature of the nucleophile, we observe a displacement from retention to inversion of configuration in the order: $R'_2CuMgX > R'MgX > R'Li$. Examination of data given in the literature for α-enones leads to similar conclusions: viz. (a) organolithium derivatives give 1,2-addition [7], (b) organocuprates lead only to attack at carbon 4 [8], and (c) organomagnesium reagents show intermediate behaviour [7].

This parallel is strengthened by the inversion at silicon observed in the substitution of the Si—OMe bond by $[PhCHCN]^-Li^+$. This reagent is known to give predominant 1,4 addition with α-enones [18].





The (—)-chloro and (—)-methoxysilane have opposite configurations [1], and we get substitution products which also have opposite configurations. A chlorosilane, whatever the nucleophile used, always reacts with inversion of configuration [1,2]: therefore we conclude that the Si—OMe bond is substituted with in-

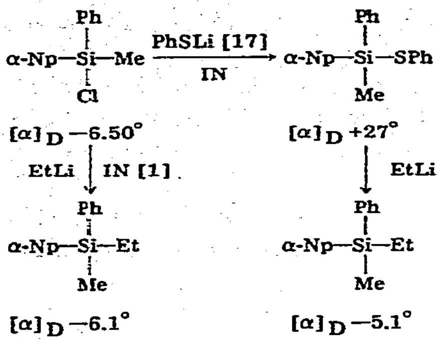
TABLE 1

SUBSTITUTION AT SILICON

$R_3SiX + R'M \rightarrow R_3Si{-}R'$
($R'M = R'Li, R'MgX$ or R'_2CuMgX)

Reagents	III [a]	IV [b]	V [c]
MeLi			$[\alpha]_D$ −8° RN [2e]
MeMgBr			$[\alpha]_D$ −8° RN [2e]
$Me_2CuMgBr$			Rac.
EtLi	92% RN	96% RN [2b]	
EtMgBr	95% IN	61% RN [2a]	
$Et_2CuMgBr$	95% IN	84% IN	
PhLi		96% RN [2b]	
PhMgBr		95% RN [2a]	
$Ph_2CuMgBr$		55% RN	

[a] The following method was used for determining the stereochemistry and the stereoselectivity ($[\alpha]_D$ of the optically pure (−)(α-Np)Ph(Me)SiEt is known [1]: $[\alpha]_D$ −6.1°):



[b] Predominant stereochemistries for IV were determined previously [2a,2b]: the $[\alpha]_D$ of the optically pure substitution product is known.

[c] Predominant stereochemistry for V [2e]: we give the $[\alpha]_D$ of the alcohol VI:

$$V \xrightarrow{MeM} (\alpha\text{-}Np)Ph(Me)Si(CH_2)_3OH$$

(VI)

version of configuration. The stereoselectivity of the reaction is as good for Si—OMe as for Si—Cl bonds.

(2) Reduction reactions

Table 2 gives the stereochemical results for reduction of the optically active silanes I, II, IV and V ($R_3SiX + AlH_{3-n}(Y)_n \rightarrow R_3SiH$), and ratios of 1,2 and 1,4 additions to the representative enones, cyclohexenone and benzalacetone.

The observed stereochemistry of the optically active silanes is related to the lability and to the structure of the leaving group: (a) alkoxy groups which are poor leaving groups, give retention of configuration, whereas there is predominant inversion with fluorosilanes; (b) a cyclic structure with an exocyclic functional group, such as in fluorosilane IV, favours retention of configuration; and (c) the intracyclic alkoxy functional group in silane V is more labile than an acyclic one

TABLE 2

RESULTS OF REDUCTION REACTIONS OF THE OPTICALLY ACTIVE SILANES I, II, IV AND V AND OF THE REPRESENTATIVE ENONES

Reaction number	Reagent (solvent) [a]	I [b]	II [b]	IV [b]	V [d]	Cyclohexenone [c]	Benzalacetone [c]
1	Dibah (hexane)	100% RN [19]	98% RN [19]	100% RN	$[\alpha]_D$ +19° RN [2c]	100% 1,2	100% 1,2
2	Dibah (Et_2O)	99% RN [19]	90% IN [19]	80% RN	$[\alpha]_D$ +16° RN	92% 1,2	75% 1,2
3	Dibah (TMD/hexane)	95% RN [19]	90% IN [19]	70% RN	$[\alpha]_D$ +15° RN	60% 1,2	14% 1,2
4	Dibah (THF)				$[\alpha]_D$ +10° RN	85% 1,2	10% 1,2
5	AlH_3 (Et_2O)	92% RN	96% IN	100% RN	$[\alpha]_D$ +16° RN	97% 1,2	80% 1,2
6	AlH_3 (THF)	90% RN	100% IN	70% IN	$[\alpha]_D$ +8° RN	87% 1,2	25% 1,2
7	$HAl(O\text{-}t\text{-}Bu)_2$ (Et_2O)	90% RN	100% IN	75% IN		87% 1,2	10% 1,2
8	$HAl(O\text{-}t\text{-}Bu)_2$ (THF)	90% RN	100% IN	80% IN	$[\alpha]_D$ −14° IN	80% 1,2	8% 1,2
9	$HAl(SEt)_2$ (THF)	85% RN	100% IN	85% IN	$[\alpha]_D$ −16° IN	40% 1,2	6% 1,2
10	H_2AlH(THF)	55% RN		80% IN	$[\alpha]_D$ −18° IN	no reaction [14]	0% 1,2

[a] TMD = tetramethylethylenediamine, THF = tetrahydrofuran, Dibah = $HAl(i\text{-}Bu)_2$. [b] Predominant stereochemistry (I, II, IV): the $[\alpha]_D$ for optically pure R_3Si^*H are known [1]. A predominant stereochemistry of 90% inversion indicates a reaction path that is 90% invertive and 10% retentive, giving a product that is 80% optically pure. [c] % 1,4-addition = 100% − (1,2-addition) %, the reactions giving quantitative yields. [d] Predominant stereochemistry for V: we give the $[\alpha]_D$ of the alcohol VII

$$V \xrightarrow{H_{3-n}Al(Y)_n} (\alpha\text{-Np})Ph(H)Si(CH_2)_3OH$$

(VII)

($[\alpha]_D$ max. obtained for VII −2.1°)

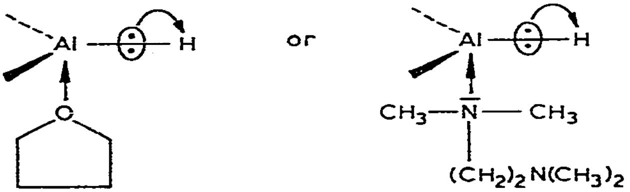
[20] (silane I) and the stereochemistry is somewhat displaced towards inversion *.

Similarly the 1,2 addition ratio depends on the nature of the studied α-enones, and so we get more 1,2-addition for cyclohexenone than for benzalacetone. However in all cases, we observe a very close parallel between the stereochemistry at silicon and the distribution of addition products on α-enones: an increase of 1,4-addition ratio corresponds with a displacement of the stereochemistry towards inversion of configuration.

Two interesting effects must be discussed in greater detail, viz. substituant and solvent effects on the reactivity of the alanes. Ashby et al. [15] reported changes in the regioselectivity of α,β-enone reduction with changes in the nature of the substituents on the aluminium atom. For some alanes $H_{3-n}Al(Y)_n$, these changes in the 1,4-addition ratio are very close to those for their stereochemical behaviour at silicon. For instance, substitution of hydrogen atoms by OR or SR groups leads to an increase in the proportion of 1,4-addition and at the same time to increased inversion at silicon (experiments 6, 8, 9 or 5 and 7). In the case of H_2AlI there is only 1,4-addition with benzalacetone, and a very high selectivity towards inversion of configuration. These observations are in good agreement with our hypothesis: a change in the nature of the Y groups leads to a change of the electronic character of the Al—H bond. We observe an increase of 1,4-addition for the reduction of α-enones, which parallels the increase in inversion at silicon.

The solvent effect is very clear: for AlH_3, $HAl(O\text{-}t\text{-}Bu)_2$ and $HAl(SEt)_2$, an increase of the basicity of solvent leads to increased 1,4-addition and increased inversion at silicon (experiments 5 and 6, 7 and 8). $HAl(i\text{-}Bu)_2$ is especially interesting in this respect (experiments 1, 2, 3 and 4); in hexane it is a very efficient reagent for 1,2-addition to α-enones, and it substitutes all Si—X bonds (X = Cl, SR, F and OR) with retention [19]. However, the addition at carbon-4 of α-enones and the percentage of inversion at silicon increase with the basicity of the solvent (hexane < Et_2O < THF) or on use of a complexing agent such as TMD. These observations are well explained by the modification of the electronic character of the Al—H bond due to complexation at the aluminium atom (Scheme 2).

SCHEME 2



In hexane there is no coordination of solvent to Al. When Et_2O or THF is used, the coordination of solvent at Al increases with the basicity of solvent, and the delocalization of the negative charge on hydrogen is in the order: hexane < Et_2O < THF (Scheme 2) **.

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* This point will be discussed in more detail in a later paper.

** Stereochemical results obtained with $LiAlH_4$ are not presented. The parallel with α-enone reduction is more complex and must take into account the complexation of the carbonyl group by the hard cation Li^+ [21]. This will be discussed in a subsequent paper.

III. Conclusion

The results reveal a very close parallel as the reactive species is varied between the stereochemistry of S_N2 reactions at a silicon center and the regioselectivity of attack on α-enones. In all cases, reagents which favours 1,2-addition to α-enones (a charge-controlled process), react with retention of configuration at silicon, whereas nucleophiles which give predominant 1,4-addition (frontier-orbital controlled process) react with inversion of configuration.

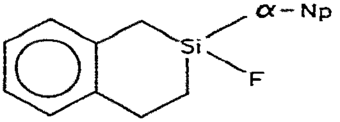
This parallel is consistent with our hypothesis that the dominant factor in the change of stereochemistry for a given leaving group is the electronic character of the nucleophile: hard nucleophiles prefer to attack equatorially at silicon, in a charge-controlled process, and softer reagents apically in a frontier-orbital controlled process.

It is noteworthy that in the case of tetrahedral phosphorus compounds the stereochemistry of nucleophilic substitution is explained very differently. The nucleophile attacks apically giving the most stable intermediate, the leaving group is also displaced apically with possible intervention of pseudorotation. We are making a more detailed comparison between the stereochemistries at silicon and at phosphorus.

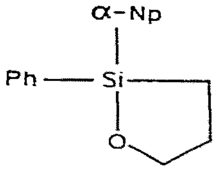
IV. Experimental

Materials

Commercial cyclohexenone and benzalacetone were used after distillation. The preparation of the optically active silyl derivatives I, II, IV, V have been described elsewhere: (α-Np)PhMeSiOMe [22], (α-Np)PhMeSiF [23],



[24] and



[19]

Preparation of (α-Np)PhMeSiSPh. To a solution of the (—)-chlorosilane (2.82 g, 10 mmol), $[\alpha]_D$ −6.5° (c_{10} in pentane) in anhydrous ethyl ether, an ethereal solution of PhSLi (15 mmol in 10 ml of ethyl ether) was added with stirring. The mixture was stirred at room temperature under dry nitrogen for one hour. The solvent was removed at reduced pressure. The resulting oil was dissolved in pentane and the solution filtered to remove lithium salts. Evaporation of the pentane at reduced pressure gave (+)-(α-Np)PhMeSiSPh, 3.2 g (90% yield), $[\alpha]_D$ +27° (c_{10} pentane).

RMN (δ, ppm): 7.5 (17 H,m), 0.8 (3 H,s). Anal. Found: C, 77.20; H, 5.92; Si, 8.81. $C_{23}H_{20}SSi$ calcd.: C, 77.52; H, 5.61; Si, 7.86%.

A. Coupling reactions with organolithium, organomagnesium and organocuprate reagents

(1) Ethereal solutions of organolithium and organomagnesium reagents were prepared from the appropriate halides and standardized by the Jolibois method

[25]. Ethereal solutions of organocuprates $R'_2CuMgBr$ were prepared as previously described [8]. To an ethereal solution of the organometallic reagent at room temperature the optically active silyl compound ($R'Li$ or $R'MgX/R_3SiX = 2$ and $R'_2CuMgBr/R_3SiX = 15$) was added dropwise under dry nitrogen. After hydrolysis with cold, dilute hydrochloric acid and extraction with ethyl ether, the organic layer was dried over anhydrous Na_2SO_4. Ether was removed at reduced pressure and the resulting oil was purified by column chromatography (silica gel, eluent benzene). The optically active products were identical with authentic samples [1,2a,2b,13].

The experimental results are listed in Table 1.

(2) Reactions with $[PhCHCN]^-Li^+$.

$[PhCHCN]^-Li^+$ was prepared at —25°C as described [26], a solution of phenylacetonitrile (6 mmol) being added to a stirred ethereal solution of 7.5 ml of 0.08 *M* n-butyllithium. A solution of the (—)-chlorosilane ($[\alpha]_D$ —6.5°, c_{10} pentane, 0.5 mmol) or of (—)-methoxysilane ($[\alpha]_D$ —16.5°, c_{10} pentane) in ethyl ether was added dropwise at —25°C to the solution of $[PhCHCN]^-Li^+$. The mixture was allowed to warm to room temperature to ensure complete reaction. After hydrolysis with cold, dilute hydrochloric acid and extraction with ethyl ether, the organic layers were dried (Na_2SO_4). Ether was removed at reduced pressure and purification of the resulting oil by column chromatography yielded (α-Np)Ph(PhCHCN)SiMe: from (—)-chlorosilane $[\alpha]_D$ —4.8°, from (—)-methoxysilane $[\alpha]_D$ +5°.

RMN (δ, ppm): 7.5 (17 H,m), 4 (1 H, s), 0.9 (3 H, s). Anal. $C_{25}H_{21}NSi$ calcd.: C, 82.64; H, 5.78; Si, 7.71. Found: C, 82.27; H, 5.91; Si, 7.98%.

B. Reduction reactions

Solutions of AlH_3 [16], $AlH(O\text{-}t\text{-}Bu)_2$ [15] in ethyl ether or tetrahydrofuran as solvents were prepared as described by Ashby et al. The $LiAlH_4/4\ CuI/THF$ reagent was prepared according to ref. 14.

A commercial solution of $HAl(i\text{-}Bu)_2$ in hexane was employed: $HAl(i\text{-}Bu)_2$ in ethyl ether or tetrahydrofuran was obtained by adding a large excess of these solvents. $HAl(i\text{-}Bu)_2/TMD/hexane$ was obtained by addition of an equimolecular amount of purified TMD to a known amount of $HAl(i\text{-}Bu)_2$ in hexane. $HAl(SEt)_2$ in THF was obtained by dropwise addition of THF solution of EtSH (2 equivalents by AlH_3) to an AlH_3 solution: the mixture was stirred for 3 hours to ensure complete reaction.

(1) Reduction of silyl derivatives

To the standardized solutions of the alane derivatives, a solution of the optically active silyl compound was added dropwise under nitrogen (molar ratios: AlH_3/R'_3SiX 1/1, $AlH(Y)_2/R_3SiX$ 21; $LiAlH_4/4CuI/R_3SiX$ 2/8/1).

The reaction was allowed to proceed at 0°C to ensure complete reaction. After hydrolysis with cold, dilute hydrochloric acid and extraction with ethyl ether, the organic layers were dried (Na_2SO_4). After evaporation of the ether at reduced pressure, the resulting oil was purified by column chromatography (silica gel, eluent benzene). The optically active products were identical with authentic samples [20,24,27].

The experimental results are shown in Table 2.

(2) Reduction of α-enones

The α-enone was added dropwise to a standardized solution of the alane derivative, under dry nitrogen. After 1 h the reaction was quenched with a minimum of distilled water and the organic layer was dried (Na_2SO_4). Analysis of the product was by VPC (10% carbowax 20M, Chromosorb W AW DMSO 60/80, 4 m). Authentic samples were used to give the retention times of 1,4- and 1,2-reduction products (molar ratios: AlH_3/α-enone 1/3, $AlH(Y)_2$/α-enone 2/1, $LiAlH_4$(CuI/α-enone 1/4/1).

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