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Divergent Stereoselectivity in the Reduction of α,β-Epoxy Ketones Using Hydridosilicates¹

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Abstract: α,β -Epoxy ketones are reduced by trimethoxysilane in the presence of a catalytic amount of lithium methoxide to yield the corresponding alcohols. This reaction system reveals divergent selectivity depending on the solvent; both *anti*-selectivity and *syn*-selectivity are observed in less polar Et₂O and in polar HMPA, respectively.

Highly coordinate organosilicon compounds show interesting feature of both structures and reactivities in comparison with normal tetracoordinate silicon compounds.² Among them, organosilicates coordinated by fluorine atom as electron-negative ligands are successfully applied for organic synthesis.³ In the course of our investigation concerning highly coordinate silicon compounds bearing alkoxy-ligands, we previously reported novel allylation reactions by the use of pentacoordinate alkoxyallylsilicates and reductions using alkoxysilanes activated by an additional alkoxy group.⁴ In such a context, we tried to draw out more characteristics of alkoxyhydridosilicates, and apply these species to the organic synthesis as novel hydride-reagents. Now we wish to report divergent selectivity depending on the reaction medium in the reduction of α,β -epoxy ketones with trimethoxysilane activated by a catalytic amount of lithium methoxide.



At first, we examined the reduction of α,β -epoxy ketone 1 with trimethoxysilane in Et₂O. No reaction took place at room temperature. However upon addition of a catalytic amount of lithium methoxide to this mixture, the reaction smoothly proceeded even at -20 °C and the corresponding α,β -epoxy alcohol 2 was obtained quantitatively. This suggests that hydridosilicates coordinated by methoxy groups are produced as reactive species.⁵ Moreover we found that the *anti*- α,β -epoxy alcohols *anti*-2 were predominant by the

spectroscopic analysis of a crude reaction mixture (Scheme 1, eq. 1). Contrary to this *anti*-selectivity in Et₂O, highly *syn*-selective reduction giving the *syn*- α , β -epoxy alcohols *syn*-2 can be attained only by changing a solvent, from Et₂O to HMPA (Scheme 1, eq. 2). These results are summarized in Table 1.⁶

R¹_	R ¹ → R ³ R ⁴ Li			O) ₃ Si-H (1.2 m Me (0.04 r	moi) mmol) R				
	l R ²	N Ö		solvent	_ _	R ² OH	+ R ²	о́н	
	1	(1 mm	nol)			syn- 2	а	nti-2	
				in Et ₂ O			in HMPA		
Substrate 1				Conditions	svn / anti ^s	Product 2	Conditions	svn/anti	a)Product 2
R ¹	R ²	R ³	R ⁴	Conditions	Synn and	Yield/% ^{b)}	Conditions	Synn and	Yield/%b
н	н	н	Ph	-20 °C, 9 h	8/92	100	0 °C, 22 h	90 / 10	98
н	н	Ме	Ph	-20 °C, 18 h	34 / 66	91	0 °C, 22 h	72 / 28	91
Me	н	н	Ph	-20 °C, 6 h	9/91	99	0 °C, 22 h	93/7	99
Me	Me	н	Ph	-20 °C, 2 h	0 / 100	88	0 °C, 22 h	60 / 40	100
н	н	н	Bu	-20 °C, 2 h	11/ 89	78	0 °C, 23 h	81 / 19	80
н	н	Me	Bu	-20 °C, 2 h	11/ 89	84	0 °C, 23 h	44 / 56	90

Table 1. Anti - and Syn-Selective Reduction of α,β-Epoxy Ketone 1

a) Determined by ¹H NMR integration of α proton to hydroxyl group. b) Isolated yield by column chromatography on silica gel.

The general procedure is as follows: to a two-necked flask purged with nitrogen, a solution of methanol in a solvent (0.04 mmol/ 1.2 ml of Et₂O or HMPA) was introduced and a solution of *n*-butyllithium (0.04 mmol) in hexane was added at -20 °C. After stirring the mixture for 30 min, an α , β -epoxy ketone 1 (1 mmol) and trimethoxysilane (1.2 mmol) were successively added and the resultant mixture was stirred at -20 °C until ketone disappeared by checking using TLC. After evaporation of easily volatile materials, saturated KF solution, methanol, and Et₂O were added to the flask and the mixture was stirred for several hours. Raw products were obtained by usual operation and a diastereomeric ratio was determined by ¹H NMR integration of α proton to hydroxyl group. Products were purified by chromatography on silica gel.

Anti-selectivity and the tendency on this selectivity to increase in the presence of substituent \mathbb{R}^2 and to decrease by \mathbb{R}^3 can be explained by considering that this reaction proceeds *via* the chelation model in less polar Et₂O, although it is not clear which metal of silicon or lithium atom participates in the conformational fixing (Scheme 2).⁷ In this reaction, a catalytic amount of methoxide is sufficient for completion of the reaction and this seems that some alkoxide regenerates as an activator for trimethoxysilane. Lithium methoxide and lithium alkoxide derived from the produced epoxy alcohol **2** may be possible candidates, and Table 2 shows results of the reaction in Et₂O (*anti*-selective) with a catalytic and stoichiometric amount of lithium alkoxide derived from methanol and product epoxy alcohol **2**.⁸ In the cases using lithium methoxide as an activator, reactions proceed with different selectivity and efficiency depending on a catalytic or stoichiometric amount of the activator. This means active species in a catalytic system are not hydridosilicates activated by only methoxide. On the other hand, hydridosilicates with lithium α,β -epoxy alcoholate show similar reactivity independent on the amount of

an activator and these results strongly suggest epoxy alcoholate is incorporated in the active species of a catalytic system. On the basis of these observations, a plausible catalytic cycle is proposed in Scheme 3.⁹



Table 2. Effect of Alkoxides on Anti-Selective Reduction of α , β -Epoxy Ketone

Syn-selectivity in HMPA may be stemmed from a polar solvent breaking the above mentioned chelation, and reactions may proceed via Felkin-Anh model¹¹ by which lowering selectivity in the presence of substituent R^2 and R^3 can be reasonably rationalized (Scheme 2). Reactions using DMPU (N,N'-dimethylpropyleneurea) as a solvent also showed similar syn-selectivity and yields to those in HMPA. Unfortunately we cannot get any information concerning the active species because similar experiments in HMPA to those in Table 2 show the same results between both alkoxides.

In conclusion, trimethoxysilane is indeed activated by the addition of lithium alkoxides and these alkoxyhydridosilicates act as hydride-reagents reducing α,β -epoxy ketones to alcohols. In these reactions, a catalytic amount of alkoxide is enough for completion of the reaction. As a characteristic feature, both *anti*- and *syn*-selective reductions can be attained only by the choice of a solvent. Further applications of these reaction systems to organic synthesis are now under investigation.

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- 5. In our previous investigations, ketones were not reduced with trimethoxysilane in the presence of a stoichiometric amount of a *monodentate* alkoxide such as alkali metal methoxide and a *bidentate* ligand such as pinacolate and amino alcoholate was necessary for the reduction.^{4d,e}
- 6. Satisfactory spectral and analytical data were obtained for all compounds.
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- 8. Reactions with a stoichiometric amount of lithium methoxide are somewhat sluggish and lacking reproducibility, but commonly have a tendency to show low selectivity and yields. On the other hand, reactions using a stoichiometric amount of lithium alkoxide derived from epoxy alcohols provide *anti-*alcohol with similar selectivity to that in a catalytic reaction, in high yield, independent on the diastereometric ratio of epoxy alcohol used as an activator.
- 9. For the simplicity, a speculative catalytic cycle is presented in Scheme 3 in consistent with the present results shown in Table 1 and 2, regenerating an epoxy alcoholate. However a second molecule of trimethoxysilane may participate in the catalytic cycle of the present reduction to form an active species^{4g,h} like the active species in the reduction using oxazaborolidine.¹⁰
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