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Stereoselective Reduction of Ketones by Histidine-Alkoxysilane Complexes: The Role of Imidazole in Nucleophilic Substitution at Silicon

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Abstract: The reduction of carbonyl compounds with transient, hypervalent silicon hydrides is described. Trialkoxysilanes, upon activation by a catalytic amount of lithium imidazolide or the mono or dilithium salt of histidine, but not by neutral imidazole or histidine, reduced the carbonyl groups of various ketones. Enantiomerically enriched product alcohols were recovered in good to excellent yield (70 - 95%) with e.e.'s ranging from 5-75% when catalyzed by histidine derivatives.

INTRODUCTION

Simple hydrosilanes may be used as mild reducing agents for carbonyl compounds. They offer some distinct advantages over traditional metal hydrides. For instance, unlike most hydride reducing agents, these compounds are stable in water at neutral pH. Their activity is normally unleashed by transition metal catalysts, in which case the reduction can be enantioselective with appropriate chiral ligands on the transition metal.[2] Hydrosilanes also readily react with acidic or basic catalysis.

A conceptually different way to activate hydrosilanes is to form extracoordinate, usually pentacoordinate, hydrosiliconates. The hydride in these compounds is a much more nucleophilic reducing agent than in the analogous tetracoordinate silanes.[3,4] The traditional method to prepare extracoordinate hydrosilanes involves adding an alkoxide to a trifunctional hydrosilane, typically a trialkoxysilane. The pentacoordinate compounds formed from catechol are particularly easy to prepare.[5] These and related compounds[6,7] cleanly reduce carbonyl and α,β-unsaturated carbonyl compounds[5,8,9] preferentially in a 1,2-fashion. Hosomi *et al.*[10] and Kagan and coworkers,[11] respectively, demonstrated that extracoordinate hydrosilanes, formed from chiral diols or β-aminoalcohols, reduce ketones enantioselectively. For instance, the reduction of acetophenone to (*R*)-1-phenethyl alcohol by a mixture of $HSi(OEt)_3$ and a catalytic amount of (*S*)-prolinol occurred with 52% e.e.[10]

Imidazole and its derivatives play a special role in organosilicon chemistry. They activate silicon to nucleophilic attack with remarkable efficiency and are frequently employed as catalysts, for instance, in the preparation of silyl ethers from alcohols.[12] Bassindale *et al.* have established the pentacoordinate nature of the interaction between *N*-methylimidazole (NMI) and chlorodimethylsilane (DMCS) using ^{29}Si NMR.[13]

We were interested to examine with what efficiency imidazole could be used to facilitate the extracoordination of hydrosilanes to give compounds that would subsequently reduce carbonyl groups. We were additionally interested to discover if imidazole derivatives from the chiral pool, in particular histidine, would influence the stereoselectivity of the reduction. We report herein the use of catalytic amounts of lithium imidazolides (Li-IM) and the mono- (Li-His) and di-lithium salts of histidine (Li_2-His) to form extracoordinate silanes that reduce ketones and, in the case of the histidine salts, do so stereoselectively.

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RESULTS AND DISCUSSION

Extracoordinate hydrosilanes **1** (Scheme 1), were prepared *in situ* by mixing lithium imidazolide or the mono- or di-lithium salts of histidine with trialkoxysilane **2** in tetrahydrofuran (THF) solution. The extracoordinate nature of the resulting silicon species was demonstrated by the change in ^{29}Si NMR shift upon mixing of the reagents (Table 1), consistent with the work of Bassindale.[13] Note that the pentacoordinate systems derived from the mono- and dianions of histidine were identical by ^{29}Si NMR: hexacoordinate systems were not observed. This suggests a coincidental chemical shift for two different species, either mono or bidentate, or more likely the preferred formation of one isomeric structure (see below).

Table 1: ^{29}Si NMR chemical shifts of products of hydrosilane: imidazolide reactions

			^{29}Si NMR (δ ppm)		
Entry	$HSiR_3$	Solvent	Silane	L	Silane + L
1	$HSiMe_2Cl$	$CHCl_3$:hexane	12	NMI	-81[a]
5	$HSi(OEt)_3$	THF	-59	Li-IM	-83[b]
2	$HSi(OMe)_3$	THF/ TMEDA (30:1)	-56	Li-IM	-79[b]
3	$HSi(OMe)_3$	THF/ TMEDA (30:1)	-56	Li-His	-79[c]
4	$HSi(OMe)_3$	THF/ TMEDA (30:1)	-56	Li_2-His	-79[d]

[a] Reported by Bassindale *et al.*[13] and subsequently remeasured by us.

Neither imidazole nor histidine catalyzed the reaction between $HSi(OMe)_3$ and acetophenone: starting materials were recovered. However, ketone reduction took place at 0 °C over 24 hours when catalyzed by imidazolide or histidyl anions, via a pentacoordinate species (Scheme 1).[14] A preliminary screening of the reaction conditions necessary to effect reduction was performed with lithium imidazolide and acetophenone **3** using THF as the solvent (Table 2). In accord with the results obtained by Kagan *et al.*,[11] the use of TMEDA as cosolvent increased the yield of hydrosiliconate reductions, presumably by changing the aggregation behaviour of the organolithium salts (Table 2).[15]

Scheme 1

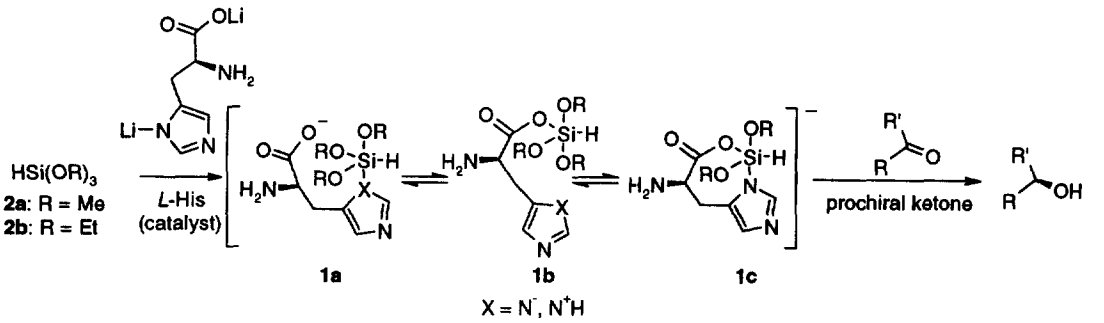

Table 2: Effect of TMEDA as additive for the reduction of acetophenone

Entry	Solvent	$(RO)_3SiH$	Conditions[a]	Yield (%)[b]
1	THF	$(EtO)_3SiH$ (**2a**)	6h, 0 °C then r.t. 17h	20
2	THF/TMEDA (30:1)	**2a**	6h, 0 °C then r.t. 17h	41
3	THF/TMEDA (30:1)	**2a**	6h, -78 °C then r.t. 17h	35
4	THF/TMEDA (30:1)	**2a**	12h, 0 °C	65

[a] 10 mol % of lithium imidazolide as catalyst and 1 eq of silane **2**. [b] Isolated yield after column chromatography on silica gel (pentane/ether = 3:1).

The enantioselective reduction of a variety of ketones was examined Table 3 using conditions optimized for the reduction of acetophenone (THF/TMEDA) with the di-lithium salt of *L*-histidine as catalyst (10 mol %). In the reduction of the acetophenone series, with the different steric requirements of the phenyl and methyl groups, it is not surprising that a reasonable level of stereoselectivity is observed. Pertinent to the discussion of the structure of the intermediate is the observation that as the distal group on the acetophenone becomes more electron donating, the preference for facial reduction of the ketone increases *p*-OMe (70) > *p*-Me (40) > *p*-H (26). Enantioselection is also observed in the benzophenone derivatives, where the only element for steric differentiation is far removed from the centre to be reduced. To a smaller degree, electronic effects appear to operate here as well. Somewhat surprisingly, opposite facial selectivity is observed in the reduction of the analogous compounds 4-phenyl-2-butanone and *trans*-4-phenyl-3-buten-2-one.

Table 3: Reduction of different ketones[a]

Entry	Ketone	$(RO)_3SiH$	Yield (%)[b]	e.e.(%)[c]
1	Acetophenone	$(EtO)_3SiH$ (**2a**)	70	26 (*S*)
2	Acetophenone	$(MeO)_3SiH$ (**2b**)[d]	85	26 (*S*)
2	Acetophenone	$(MeO)_3SiH$ (**2b**)	85	N.M.[e]
3	Benzophenone	**2b**	90	N.A.[f]
4	4,7-dimethyl-1-indanone	**2b**	66	30 (*R*)
5	4-phenyl-2-butanone	**2b**	91	28 (*R*)
6	*trans*-4-phenyl-3-buten-2-one	**2b**	78	70 (*S*)
7	4-(trifluoromethyl)acetophenone	**2b**	86	30 (*S*)
8	4-methyl-acetophenone	**2b**	80	40 (*S*)
9	4-methoxy-acetophenone	**2b**	89	70 (*S*)
10	4-(trifluoromethyl)benzophenone	**2b**	95	30 (*S*)
11	4-methyl-benzophenone	**2b**	82	5 (*S*)
12	4-methoxy-benzophenone	**2b**	78	5 (*S*)
13	Phenylacetone	**2b**	90	N.M.

[a] All reactions were conducted with 10 mol % of the di-lithium salt of *L*-histidine as catalyst and 1 eq of silane in THF/TMEDA = 30:1 solution. All reactions were run at 0 °C for 24 h. [b] Isolated yields, after chromatography on silica gel (pentane/ether=3:1). [c] Measured by ^1H NMR analysis of the Mosher ester of the corresponding alcohols.[16] Also measured by ^{19}F NMR of Mosher ester. Absolute configuration assigned from optical rotation of alcohol. [d] An equivalent histidine monoanion was added. [e] Not measured. [f] Not applicable.

Imidazole is commonly used to active silicon to nucleophilic attack when good leaving groups such as chloride are involved. With poorer leaving groups, such as hydride in the cases cited above, more powerful silanucleophiles are required, such as imidazolide or the histidyl dianion. While structural studies are ongoing, it is premature to predict the exact nature of the active intermediate. However, the fact that the mono- and dianion of histidine reduce acetophenone with the same enantioselectivity suggests that either monodentate structures **1a**, **1b** or bidentate structures **1c** are involved in both cases. These and related studies will form the basis of future reports.

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14 **General Procedure for Reduction** (example acetophenone):*Triethoxysilane 2b and especially trimethoxysilane 2b are rather toxic compounds and therefore care must be taken in their handling. Both are available commercially (Aldrich) and can be handled without problems via syringe techniques.* To a dry 100 mL round bottom flask flushed with nitrogen was added *L*-histidine (50 mg, 0.3 mmol) and THF (30 mL). At ambient temperature *n*-butyl lithium (2M, 0.32 mL, 0.6 mmol) was added slowly and the resulting suspension stirred for 30 min. The reaction mixture was cooled to 0 °C and TMEDA (1.0 mL, 6 mmol) was added and stirred for 10 min, then trimethoxysilane (0.38 mL, 3 mmol) was added and reaction stirred for an additional 10 min. Finally acetophenone (0.35 mL, 3 mmol) was added and the reaction mixture was kept at 0 °C for 24 h. The reaction was quenched by the addition of sodium hydrogen carbonate (0.1 M, 20 mL) and stirred vigorously for 30 min at room temperature. The biphasic system was transferred to a separatory funnel and extracted with ether (3 * 40 mL). The ether was removed without drying and the resulting crude product was purified by column chromatography on silica gel eluting with pentane/ether (3:1), to give (*S*)-phenethyl alcohol (0.31 g, 85%) as a colorless liquid. ^{1}H NMR ($CDCl_3$, 200 MHz) d 1.56 (d, 3H, J = 6.5 Hz, $PhCH(OH)CH_3$), 2.76 (bs, 1H, $PhCH(OH)CH_3$), 4.94 (q, 1H, J = 6.5 Hz, $PhCH(OH)CH_3$), 7.32-7.45 (m, 5H, Ph-H); ^{13}C NMR ($CDCl_3$, 200 MHz) d 24.97, 69.99, 125.24, 127.14, 128.24, 145.75; FTIR (neat, KBr disc) ν (cm^{-1}) 3364, 3065, 3031, 2974, 2929, 1728, 1603, 1494, 1452, 1371, 1287, 1204, 1077, 1030, 1011, 900, 762, 700, 607, 541; MS (EI) m/z (%): 122 (M^+, 10), 121 (40), 104 (68), 79 (28), 57 (7), 43 (100); (CI) m/z (%): 140 (M^+ + 18, 17), 122 (100), 105 (41), 78 (2), 44(1).

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16 **General experimental procedure for preparation of Mosher esters** (for (*S*)-1-phenylethanol)): (*S*)-1-phenylethanol (2 mg, 0.02 mmol) and MTPA-Cl (+) (4 mL, 0.02 mmol) were mixed with carbon tetrachloride (3 drops) and dry pyridine (3 drops). The reaction mixture was allowed to stand in a stoppered flask for 12 h at ambient temperature. Water (1 mL) was added and the reaction mixture transferred to a separatory funnel and extracted with ether (20 mL). The ether solution, after washing successively with HCl (1M, 20 mL), and saturated sodium carbonate solution (20 mL), and water (20 mL) was dried with sodium sulfate, filtered and solvent was removed *in vacuo*. The residue was dissolved in deuterated chloroform for NMR analysis. The integration(s) of the hydrogen on the carbon bearing the hydroxyl group was used as a measure to assess the enantioselection.