Competitive Substitution Reactions at Extracoordinate Silicon during Asymmetric Hydrosilylation

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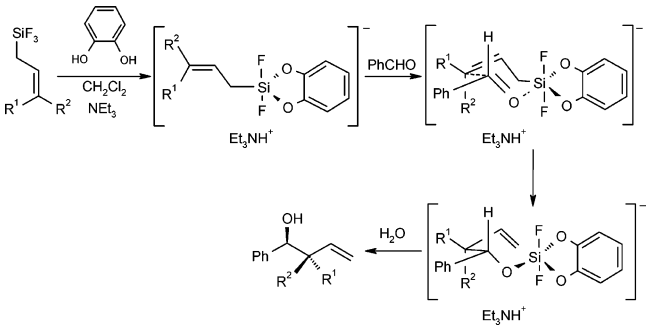
Proline-derived small molecules were utilized as organic catalysts in the asymmetric hydrosilylation of ketones. Extracoordinate chiral hydrosilicates were generated in situ as shown by ^{29}Si NMR. These active species reduce prochiral ketones enantioselectively in good yield but only moderate enantiomeric excess (up to 40%). The parameters affecting stereoselectivity have been studied in detail. By isolating some of the intermediates and performing a series of control reactions, the relative efficiency of alkoxy group exchange reactions and the ability of ketones to complex to extracoordinate hydrosilicates have been discovered to be critical factors. The proline catalyst is a poorer leaving group from the initial pentacoordinate product than the product of reduction, $PhMeCHO^-$, which leads subsequently to several competitive hydrosilylation pathways.

Introduction

Silicon compounds undergo extracoordination in the presence of nucleophiles, particularly oxygen, fluoride, and aromatic amines.[1] The facility of trialkoxysilanes to undergo extracoordination lies between that of trialkyl- and trihalosilanes.[2] Alkoxy group exchange reactions, an example of this process, can be facilitated by multidentate ligands.[3] When both nucleophile and leaving groups are alkoxy groups, the process (tetravalent to hypervalent to tetravalent) is reversible and the products ultimately formed are controlled by the relative basicity and steric demands of the alcoholates involved.[4]

There are a variety of consequences, with respect to reactivity, in forming extracoordinate silicon. Corriu,[5] Bassindale,[6] and others have shown that the extracoordinate silicon compounds are more susceptible to nucleophilic addition than tetracoordinate silicon compounds and that the ligands on silicon are more nucleophilic. For example, Sakurai demonstrated that diastereoselective allylation of carbonyl groups is efficient at pentacoordinate silicon (Scheme 1).[7] Coordination of the nucleophile, the carbonyl group, to the extracoordinate silicon is followed by allyl group transfer.

Scheme 1



The reducing properties of hypervalent hydrosilicon compounds are enhanced compared to simple hydrosilanes, especially toward ketones.[8−11] In a process related to that reported by Kagan and co-workers[4] and Hosomi et al.,[12] we previously demonstrated that the complex derived from hydrosilanes and a catalytic amount of imidazolide anion can reduce ketones enantioselectively (Scheme 2A).[13,14] While the mechanisms of these reactions have not yet been clearly established, the presence of extracoordinate silicon, for example, pentacoordinate species such as **1**, was evident from ^{29}Si NMR. Although the reactions were generally efficient, they were not very enantioselective.

One of the challenges in obtaining high enantioselectivity may be related to the limited stability of the five-coordinate silicon

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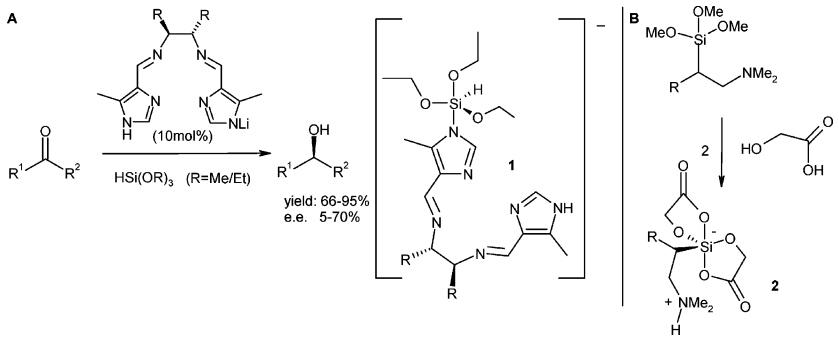
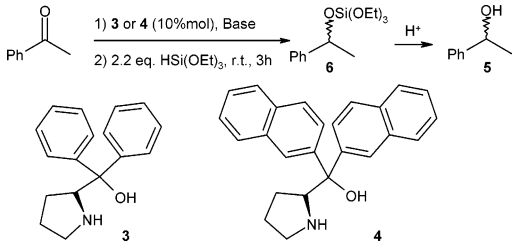
Scheme 2. Imidazolide-Catalyzed Ketone Reduction



Scheme 3. Prolinol Ligands



species (e.g., **1**). With a good leaving group such as imidazole, it is possible that decomposition of the complex competes with complexation of the ketone, which is necessary for reduction. Alternatively, the weak complex formed by the imidazole may be insufficiently rigid to induce effective stereoselective control during reduction.

Tacke has demonstrated that bidentate nucleophiles that lead to the generation of small cyclic structures are particularly efficacious in inducing coordination expansion at silicon and lead to stable complexes when a zwitterionic structure can be formed from a linked amine. A broad variety of pentacoordinate amino and hydroxy acid derivatives, exemplified by **2**, have been isolated in crystalline form (Scheme 2B).[15−17]

We reasoned that related extracoordinate alkoxysilicon species derived from more basic β-aminoalkoxides should form readily and have sufficiently long lifetimes to permit complexation with ketones, leading to subsequent reduction. To test this hypothesis, a series of experiments were undertaken with the catalytic system derived from a chiral bidentate pyrrolidine alcoholate (Scheme 3), which induces the hydrosilylation of ketones enantioselectively. During the optimization process, which involved a systematic screen of silanes, ketone substrates, temperature, and the steric effect of ligands, and which included examination of isolated reduction intermediates by ^{29}Si NMR, it was discovered that the enantioselectivity was affected by both the ease of formation of the substrate ketone complex with the chiral extracoordinate silicon intermediate and its competitive decomposition.

Results

Two ligands derived from proline, **3** and **4**, were utilized in this study (Scheme 3), taking advantage of a natural source of chirality. Proline derivative **3** has previously been used to complex with metals (Sn, Ti) to generate Lewis acid catalysts in situ. However, our interest has been focused on using this ligand as an organic catalyst. The analogous, but more sterically congested, compound **4** was also examined. A typical reduction procedure included the use of 10 mol % of **3** or **4**, after treatment of a cooled solution with 1 equiv of base (NaH or BuLi). Triethoxysilane or H_2SiPh_2 was then added, and the solution was warmed to room temperature; the reduction started when the ketone substrate was added. The reductions proceeded smoothly to give phenethanol **5** with high conversion but with marginal stereoselectivity, as measured by conversion of the reduction products into Mosher esters (Table 1). The stereoselectivities of the reduction were shown to be independent of the amount (1 or 2 equiv) or nature of the base (BuLi or NaH) or counterion (Li^+ or Na^+) used (entry 1, 3), although they were improved in the presence of a quantitative amount of base at the expense of chemical yield (entry 5, 6). Similarly, the use of diethyl ether as solvent improved the stereoselectivity, but led to a decrease in reaction rate and overall yield.

Modification of several features of the reaction was undertaken in an effort to improve the enantioselectivity including the nature of the reducing agent, the size of the chiral ligand (**3** vs **4**), and the temperature. A comparison of the reactivity of different hydrosilanes, $D_{4'}$ ($(MeHSiO)_4$), poly(methylhydrosiloxane) (PMHS, $Me_3SiO(MeHSiO)_nSiMe_3$), Ph_3SiH, Me_2PhSiH, Ph_2SiH_2, and $HSi(OEt)_3$, was instructive. Reduction was observed only with Ph_2SiH_2, PMHS, and $HSi(OEt)_3$, but even this depended on solvent: reactions were much more efficacious in THF than diethyl ether. The relative reaction rates were $HSi(OEt)_3$ (THF) ≈ PMHS (THF) > H_2SiPh_2 (THF) > $HSi(OEt)_3$ (diethyl ether) ≫ PMHS (diethyl ether), Me_2HSiPh, $HSiPh_3$, $D_{4'}$ (either THF or diethyl ether). As discussed below, these observations show a direct link between ease of coordination expansion—the facility for which increases as the number of heteroatom linkages at silicon is increased—and the efficiency of reduction at silicon.

With either Ph_2SiH_2 or $HSi(OEt)_3$ as the reducing agent, it was possible to isolate product silyl ethers $(PhMeCHO)Si(OEt)_3$, **6**, or $(PhMeCHO)_2SiPh_2$, **7**,***7RS***, respectively, following careful chromatography. The hydrolysis of tetraalkoxysilanes is typically facile except at neutrality,[18] conditions that are not met on the silica gel column used for purifying the compounds. Thus, it was surprising that these compounds could be isolated in good yield using column chromatography.

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Table 1. α,α-Diaryl-2-pyrrolidinemethanol (3 or 4)-Catalyzed Hydrosilylations (Scheme 3)

entry	substrate	conditions[a]	yield (%)	ee (%)
1	acetophenone	**3**, 2 equiv BuLi, $HSi(OEt)_3$, rt, 3 h	80	4 *R*
2	*trans*-4-phenyl-3-buten-2-one	**3**, 2 equiv BuLi, $HSi(OEt)_3$, rt, 3 h	87	3 *S*
3	acetophenone	**3**, 1 equiv NaH, $HSi(OEt)_3$, rt, 3 h	90	6 *R*
4	acetophenone	**3**, 1 equiv BuLi, $HSi(OEt)_3$, rt, ether, 72 h	65	30 *R*
5	acetophenone	100% **3**, 1 equiv NaH, 1 equiv $HSi(OEt)_3$, rt, 3 h	47	38 *R*
6	acetophenone	100% **3**, 1 equiv BuLi, 1 equiv $HSi(OEt)_3$, rt, 72 h	55	25 *R*
7	4′-(trifluoromethyl)acetophenone	**4**, 1 equiv NaH, Me_2PhSiH, rt/50 °C, 72 h	no reaction	
8	4'-trifluoromethyl-acetophenone	**4**, 1 equiv NaH, Ph_3SiH, 50 °C, 72 h	no reaction	
9	acetophenone	**4**, 1 equiv NaH, D_4, rt, 72 h	no reaction	
10	acetophenone	**4**, 1 equiv NaH, PMHS, rt, 72 h	no reaction	
11	acetophenone	**4**, 1 equiv NaH, $HSi(OEt)_3$, rt, 3 h	87	40 *R*
12	acetophenone	**4**, 1 equiv NaH, $HSi(OEt)_3$, 0 °C, 3 h	93	23 *R*
13	4′-(trifluoromethyl)acetophenone	**4**, 1 equiv NaH, $HSi(OEt)_3$, rt, 2 h	96	1 *S*
14	4′-(trifluoromethyl)acetophenone	**4**, 1 equiv NaH, Ph_2SiH_2, rt, 2 h	75	7 *R*
15	4′-nitroacetophenone	**4**, 1 equiv NaH, Ph_2SiH_2, rt, 2 h	72	13 *R*
16	4′-methoxyacetophenone	**4**, 1 equiv NaH, $HSi(OEt)_3$, rt, 6 h	84	7 *S*
17	2′,4′-dimethylacetophenone	**4**, 1 equiv NaH, $HSi(OEt)_3$, rt, 6h	81	2 *S*

[a] Catalysts were present at a concentration of 10 mol % unless otherwise noted.

Table 2. Effect of Temperature on Reduction with $HSi(OEt)_3$ Using 4 (Scheme 3)

entry	conditions	yield (%)	ee (%)
1	1 equiv NaH, −78 °C, 5 h	no reaction	
2	1 equiv NaH, −50 °C, 5 h	no reaction	
3	1 equiv NaH, −40 °C, 5 h	no reaction	
4	1 equiv NaH, −35 °C, 0.5 h	90	11 *R*
5	1 equiv NaH, −35 °C, 0.2 h	8	18 *R*
6	1 equiv NaH, 0 °C, 2 h	93	23 *R*
7	1 equiv NaH, rt, 2 h	87	40 *R*
8	1 equiv NaH, 50 °C, 2 h	75	15 *R*

The traditional way to improve enantioselectivity when using a chiral auxiliary is to bias one transition state over the other either by exaggerating steric or electronic effects in one diastereotopic transition state over another or by reducing the temperature so that kinetic control favors the pathway with the lowest activation energy. The former process was somewhat effective: the more sterically bulky ligand **4** gave improved selectivity over the reaction initiated with **3** (40% ee, Table 1, entry 11), but only with acetophenone: higher enantioselectivity was not observed with other ketones under the same conditions, irrespective of the electronic or steric characteristics present in the ketone.

The effect of temperature was initially rather surprising. As can be seen in Table 2, the hydrosilylation reaction started to occur only at −35 °C. However, the stereoselectivity was not improved at this lower temperature. Even in the first 30 min, low enantiomeric excesses were obtained (11%, entry 4). At low conversion (8%) the ee was 18%, higher but not substantially so than the complete reaction. Interestingly, the ee became larger with an increase in temperature, reaching the maximum value at approximately 25 °C, after which the ee started to drop. Thus, this is not a case of classic kinetic control.

Nucleophilic substitution at silicon is generally understood to occur via a pentacoordinate, trigonal bipyrimidal (TBP) silicon intermediate.[19−21] Nucleophiles generally attack from the axial position, and poor leaving groups, such as hydrogen, normally occupy equatorial positions. When a nucleophilic catalyst is also present, addition of the catalyst is generally followed by addition of the nucleophile, in this case the ketone, to form a hexacoordinate species (as in a sequence such as **3** → **8** → **10** → **11** → **5**, Scheme 4). Stereochemical control in the ketone reduction occurring at such a center will depend on the disposition of the chiral ligand at silicon.

In the absence of a basic activator, triethoxysilane was not able to reduce ketones. ^{29}Si NMR shows a singlet at −59 ppm for triethoxysilane and −58 ppm for the $HSi(OEt)_3$ in the presence of either **3** or **4**, consistent with previously reported data for the tetracoordinate silane.[13] Hypervalent hydrosilicates were detected when the anion of **3** was mixed with trialkoxysilane. When the ratio of triethoxysilane to the monoanion of **3** was 2:1, ^{29}Si NMR showed three singlets at −57.5 ($HSi(OEt)_3$), −82.1, and −96.5 ppm, respectively.

It is challenging to assign putative structures to compounds with these chemical shifts. Each exchange at silicon of H by O or N leads to an upfield shift in the NMR, as does each exchange of N by O. For example, addition of the anion **3** to $HSi(OEt)_3$ to give a pentacoordinate species such as **8** would lead to an upfield shift by about 20 ppm. However, displacement of the EtO^- by the same ligand to give a tetracoordinate species would lead to a downfield shift of about 15 ppm (Scheme 4).[22] The observed peaks are consistent with a pentacoordinate species ($HSiX_4^-$, −84.2 ppm) and a hydrido hexacoordinate species ($HSiX_5^{2-}$, −98.8 ppm such as **9**), respectively. After the ketone reduction, but before workup, ^{29}Si NMR showed only one peak, at −82.4 ppm, consistent with $(RO)_4Si$, e.g., $PhMeCHOSi(OEt)_3$.

These observations are consistent with a reaction mechanism analogous to that proposed by Kagan.[4] The formation of a chiral complex such as **8**, followed by complexation of the ketone to give a hexacoordinate structure such as **10**, is followed by reduction leading to pentacoordinate structure **11** (Scheme 4), which is ultimately converted into a tetraalkoxysilanes (see below).

To probe other sources for the low enantioselectivity, the "back end" of the reaction with $HSi(OEt)_3$ was examined. An effective enantioselective process requires that **11** decomposes to regenerate the chiral catalyst and produce **6** (which was isolated). However, if **11** were to decompose instead to generate EtO^- or $PhMeCHO^-$, either alkoxide could serve to initiate other reduction processes (e.g., $RO^- + HSi(OEt)_3 + PhCOMe$

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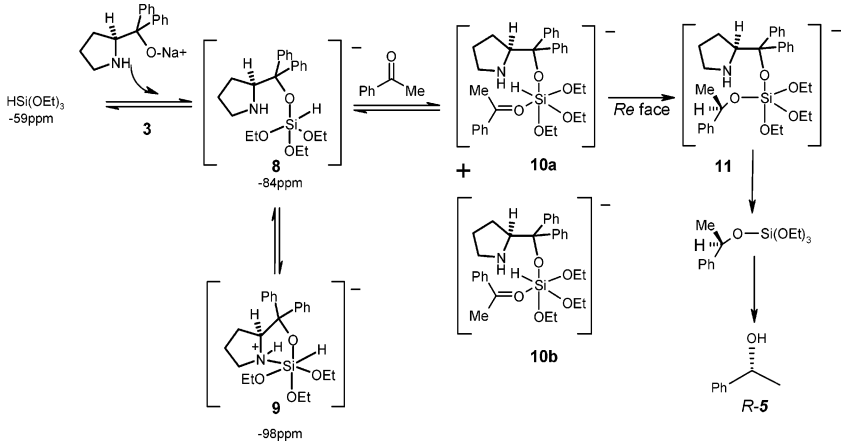
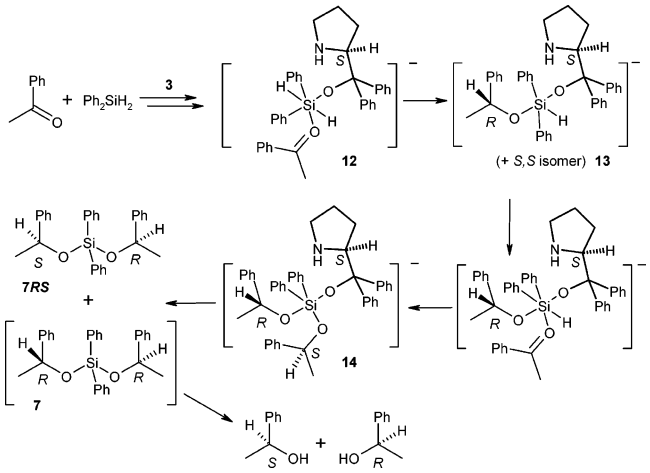
Scheme 4



Scheme 5



→ RO^- + $(EtO)_3SiOCHMePh$). These possibilities are addressed in turn.

When the reduction of acetophenone was performed with Ph_2SiH_2 and 10 mol % of the anion of **3**, low enantioselectivity was observed (Table 1). Since the presence of EtO^- is precluded in this case, unlike with $HSi(OEt)_3$, other competitive reactions are the source of poor stereoselectivity. The reaction provided other interesting information. As noted above, the isolated product was a mixture of two dialkoxysilanes, *R*,*R*/*S*,*S* **7** and **7*RS*** (Scheme 5), respectively, as shown in the ^1H NMR: the mixtures could not be separated chromatographically. Note that even if an excess of Ph_2SiH_2 was used, it was not possible to observe or isolate monohydridosilane intermediates. Instead, during workup, extracoordinate complexes decomposed to give **7** and **7*RS***, recovered Ph_2SiH_2, and **5**: silyl compounds containing the ligand **3** were not present in the ^1H NMR. The diastereoselectivity for the formation of **7** and **7*RS*** was 10%, based on ^1H NMR (Figure 1). By contrast, after workup, the ee of **5** was about 1%.

These data are consistent with a process in which Ph_2SiH_2 is activated by **3** to give compounds such as **12**, followed by ketone reduction to generate the monohydrido diastereomers **13**; these compounds, more reactive than **12**, then reduce a second ketone rather than decomposing to tetracoordinate products. The stereoinduction is thus a consequence of both the initial control provided by *S*-**3** (preferentially leading to *R*-**5**) and the secondary reduction in which **13** complexes and then reduces another acetophenone. Clearly, the combination of the fixed chirality at **3** and induced chirality from the first reduction lead to a loss, rather than a gain, in stereocontrol, as the diastereoselectivity in forming **7** versus **7*RS*** is higher than the ultimate enantioselectivity of the overall process forming **5**.

To test the effect of the presence of the product alcohol **5** on the reaction, a negative control reaction was performed using enantiopure *S*-1-phenylethoxide + $HSi(OEt)_3$ to catalyze the hydrosilylation of PhCOMe under the same conditions. A moderate enantiomeric excess was obtained (21% ee), giving in this case the *R*-enantiomer (cf. the reaction initiated by **3**, which gave a 4% ee under the same conditions of Table 1). Thus, the alkoxide *S*-**5** can catalyze the asymmetric hydrosilylation efficiently and, in doing so, preferentially give the product of opposite stereochemistry, *R*-**5**.

Discussion

The use of **3** as a chiral catalyst leads to a modest enantioselective induction in the hydrosilylative reduction of arylketones by hydrosilanes that can readily undergo extracoordination. The use of *S*-**3** as catalyst leads to the moderate preferential formation of *R*-**5**. Larger groups on the chiral auxiliary improve the outcome, for instance when naphthyl groups replace phenyl groups, as with **4**. These observations are consistent with ketone complex intermediates, such as **10** (Scheme 4), that have more restricted mobility because of steric interactions between the aryl group on the ketone and phenyl or naphthyl groups on the chiral auxiliary. Although binding the chiral ligand to the silane activates the ketone to reduction, the subsequent stereochemical induction remains low.

It was initially anticipated that formation of a silicon-based chiral complex using **3** or **4** would lead to efficient stereocontrol in ketone reduction. However, an efficient stereoselective catalytic process also requires that the chiral auxiliary prefer-

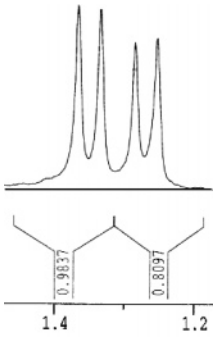
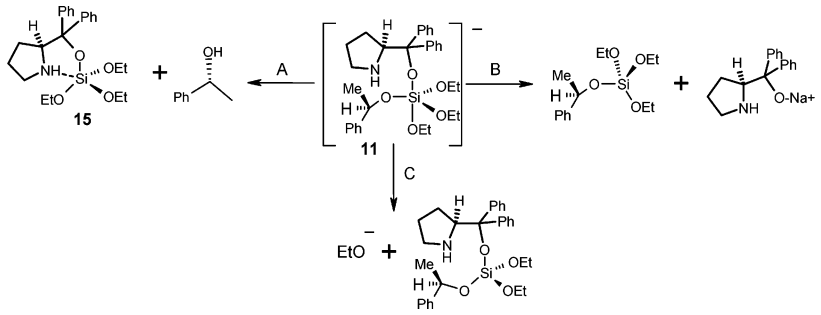


Figure 1. ^1H NMR showing the diastereomeric mixture of methyl group signals of the two dialkoxydiphenylsilanes **7** and **7*RS***.

Scheme 6. Decomplexation Routes of Pentacoordinate Silicon



entially decomplexes from intermediates so that it can initiate subsequent reactions. When Ph_2SiH_2 was used as the reducing agent, however, a secondary reduction on the same complex occurred before the chiral catalyst could be liberated, for example, **12** → **13** → **14** (Scheme 5). Any induction occurring in the initial step, which shows up as the diastereoselectivity in the formation of **7** and **7*RS***, is lost because the silane complex of *R*-**5** induces the formation of *S*-**5**, and vice versa, as noted above. Thus, the effects of chiral induction by the product **5** are much more powerful than those of **3** or **4** and lead to competitive racemization. This may be associated with the closer proximity between Si and the chiral center in **5**, when compared to **3** and **4** (two bonds versus three).

In the case of reduction with $HSi(OEt)_3$ a related mechanism occurs. At low temperatures, the initial reduction leads to an extracoordinate complex such as **11**. However, there are several decomposition routes for such a complex (Scheme 6). If the generation of the alkoxides of **5** is more efficient than the regeneration of the anion of **3** (or **4**) (Scheme 6A), then a reduction in stereochemical induction in the reaction is expected because, in addition to **3**, subsequent reactions are also catalyzed by enantiomers of **5**, which induce the opposite sense of reduction (i.e., *R*-**5** + $HSi(OEt)_3$ + PhMeCO → *R*-**5** + *S*-**5**-Si-$(OEt)_3$).

This process can be biased at higher temperatures. The improvement in stereochemical outcome is consistent with a change in rate-determining step. At higher temperatures, decomplexation of the alkoxides of **3** (or **4**) more effectively competes with those of **5**. The improved concentration of **3** (or **4**) (Scheme 6B), among the group of available chiral molecules, leads to an increase in enantioselectivity as the temperature is raised from <0 to 25 °C. If EtO^- is formed during these processes (Scheme 6C), it will catalyze ketone reduction nonstereoselectively.

Nucleophilic substitution reactions at silicon have been extensively studied, primarily with respect to the role played by electronic characteristics of ligands on silicon.[5,6] The reactions described above demonstrate that some subtlety exists in the efficiency of decomplexation reactions of alkoxysilanes. The stereochemical outcomes described above are consistent with different leaving group abilities resulting from steric bulk and the abilities of the ligand to form monodentate or bidentate complexes.

It was initially anticipated that the relative rates of reaction B are greater than those of A (Scheme 6), because of the steric encumbrance provided by the adjacent diphenylalkoxy group. Instead, the lowest reaction barrier exists for reaction A, perhaps both because significant steric pressure is relieved by the ejection of the secondary phenethanol and because of the internal assistance provided by dative interactions from the pyrrolidine nitrogen, which can stabilize compound **15** through extracoordination: recent studies by Kost have similarly shown the ability of multidentate nitrogen compounds to stabilize hexacoordinate silicon compounds.[23]

The use of multidentate ligands provides opportunities to tune the stability of extracoordinate species at silicon and to modify the reactivity, including enantioselectivity, of reactions at that site. However, the results presented above are instructive, in that relative rates of ligand addition and leaving from these sites are subtly different. Unless great care is made to bias the system such that there is a great disparity in the leaving group ability of the directing group and reaction products, exquisite control is not possible. Future work will elaborate multidentate ligand designs that more effectively discriminate between the substitution pathways at silicon.

Conclusion

Bidentate, enantiopure catalysts derived from proline induced only moderate degrees of enantioselectivity in the reduction of arylketones with either $HSi(OEt)_3$ or Ph_2SiH_2. The reaction did not operate under typical kinetic control: improved enantioselectivity was observed at higher temperatures. While the prolinol ligand readily generated pentacoordinate species and facilitated enantioselective reduction of the ketone, competitive decomplexation of different alkoxy groups from a pentacoordinate intermediate led to the presence of multiple catalysts. For example, *R*-phenethoxide induced formation, in a subsequent ketone reduction, of *S*-phenethanol. Thus, stereocontrol in these systems requires catalysts that are both better nucleophiles and leaving groups at silicon than normal alkoxides.

Experimental Section

Reagents and Physical Method. The following materials were obtained from Aldrich and were used without further purification: *n*-butyllithium (1.6 M solution in hexanes) (titrated with diphenylacetic acid before use), *S*-(+)-α-methoxy-α-(trifluoromethyl)-phenylacetyl chloride (MTPA-Cl (+)), acetophenone, *trans*-4-phenyl-3-buten-2-one, 4′-trifluoromethylacetophenone, 2′,4′-dimethylacetophenone, 4′-nitroacetophenone, 4′-methoxyacetophenone, triethoxysilane, diphenylsilane, triphenylsilane, dimethylphenylsilane, $D_{4'}$, poly(methylhydrosiloxane) (Dow Corning 1107), *S*-1-phenylethanol, *S*-diphenyl-2-pyrrolidinylmethanol, *S*-di(2-naphthyl)-2-pyrrolidinylmethanol, sodium hydride, sodium sulfate, and tetrabutylammonium fluoride.

^1H and ^{13}C NMR spectra were recorded on a Bruker AC-200 Fourier transform spectrometer (at 200 MHz for protons and 50.32 MHz for ^{13}C). ^{29}Si NMR was performed on a Bruker DRX-500 at 99.35 MHz for silicon. ^1H NMR was also performed on a Bruker DRX-500 (at 500 MHz for hydrogen). ^1H chemical shifts are reported with respect to either tetramethylsilane as an external

(23) Kalikhman, I.; Gostevskii, B.; Botoshansky, M.; Kaftory, M.; Tessier, C. A.; Panzner, M. J.; Youngs, W. J.; Kost, D. *Organometallics* **2006**, *25*, 1252−1258.

standard, set to 0 ppm, or $CDCl_3$ as an internal standard, set at 7.26 ppm. ^{13}C chemical shifts are reported with respect to either $CDCl_3$ as an internal standard, set at 77.26, or THF-d_8 as an internal standard set at 67.57 ppm. Coupling constants (*J*) are recorded in hertz (Hz). The abbreviations s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, dt = doublet of triplets, m = multiplet are used to report spectra.

Electron impact (EI) and chemical ionization (CI, NH_3) mass spectra were recorded at 70 eV with a source temperature of 200 °C on a Micromass GCT mass spectrometer using a heated probe. High-resolution mass spectral (HRMS) data were obtained using the EI method calibrant with perfluorotributyl amine.

All solvents were thoroughly dried before use: THF and diethyl ether were dried from Na/benzophenone. All reactions were carried out in flame-dried apparatus under an argon atmosphere with the use of septa and syringes for the transfer of reagents.

General Procedure for Reduction Using BuLi (example acetophenone + 3, Table 1). To a dry 10 mL round-bottomed flame-dried flask protected by argon were added **3** (0.025 g, 0.1 mmol) and THF (3 mL). This solution was cooled to −78 °C, and then *n*-butyllithium (0.125 mL, 1.6 M solution in hexanes, 0.2 mmol) was added dropwise. The resulting yellowish solution was stirred for 5 min at −78 °C and then warmed to 0 °C for 15 min. To this yellow solution were added triethoxysilane (0.38 mL, 2.06 mmol) and acetophenone (0.12 mL, 1.02 mmol). The solution was stirred at ambient temperature, and product development was monitored by TLC. The reaction mixture was diluted with ethyl acetate (5 mL) and carefully made basic (pH = 9) with 1 M sodium hydroxide. The solid was separated by filtration and the organic phase collected. The aqueous phase was extracted with ethyl acetate (3 × 10 mL). The organic layers were combined, dried over sodium sulfate, and then concentrated to give the crude product of silyl ether, which was purified by column chromatography eluting with hexanes/ethyl acetate (10:1). The silyl ether product was dissolved in THF (5 mL) and then treated by aqueous HCl solution (1 N) at 0 °C for 1 h. Ethyl acetate (20 mL) was added to the solution, and the aqueous phase was extracted with ethyl acetate (2 × 10 mL). The organic layers were combined, dried over sodium sulfate, and then concentrated to give the crude product (1-phenylethanol), which was purified by flash column chromatography eluting with hexanes/ethyl acetate (5:1): ^1H NMR ($CDCl_3$, 200 MHz) δ 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, Ph*CH*(OH)CH_3), 7.32−7.45 (m, $5H_{arom}$); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 24.97, 69.99, 125.24, 127.14, 128.24, 145.75; 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), 52 (1), 44(1).

General Procedure for Reduction Using NaH (example acetophenone + 3). To a dry 10 mL round-bottomed flame-dried flask protected by argon were added **3** (0.025 g, 0.1 mmol) and THF (3 mL). This solution was cooled to 0 °C, and then sodium hydride (4 mg, 0.1 mmol, 60% dispersion in mineral oil) was added. The resulting suspension (because of the mineral oil with NaH) was stirred for 30 min at 0 °C. To this suspension was added dropwise triethoxysilane (0.38 mL, 2.06 mmol). The reaction mixture was stirred for 15 min at 0 °C and then warmed to ambient temperature for 30 min. Acetophenone (0.12 mL, 1.02 mmol) was then added at ambient temperature. The solution was stirred at ambient temperature, and product development was monitored by TLC. After 3 h, the reaction mixture was diluted with THF (5 mL) and cooled to 0 °C. Aqueous HCl solution (1 N) was added carefully to neutralize the mixture, which was stirred at 0 °C for 1 h. Ethyl acetate (20 mL) was added to the solution, and the aqueous phase was extracted with ethyl acetate (2 × 10 mL). The organic layers were combined, dried over sodium sulfate, and then concentrated to give the crude product, which was purified by flash column chromatography eluting with hexanes/ethyl acetate (5:1).

Procedure for Reduction Using Ph_2SiH_2 (example 4′-trifluoromethylacetophenone + 3). To a dry 10 mL round-bottomed flame-dried flask protected by argon was added **3** (0.025 g, 0.1 mmol) and THF (3 mL). This solution was cooled to 0 °C, and then sodium hydride (4 mg, 0.1 mmol, 60% dispersion in mineral oil) was added. The resulting suspension (because of the mineral oil with NaH) was stirred for 30 min at 0 °C. To this suspension was added diphenylsilane (0.40 mL, 2.06 mmol) dropwise, and the reaction mixture was stirred for 15 min at 0 °C and then warmed to ambient temperature for 30 min. Trifluoromethylacetophenone (0.19 g, 1.00 mmol) was then added at ambient temperature with stirring, and product development was monitored by TLC. After 5 h, the reaction mixture was diluted with THF (5 mL) and cooled to 0 °C, tetrabutylammonium fluoride (TBAF, 1.0 M in THF) was added carefully, and the solution was stirred at 0 °C for 1 h and then at ambient temperature for another 2 h. Ethyl acetate (20 mL) was added to the solution, the organic phase was washed by water (20 mL), and the aqueous layer was extracted with ethyl acetate (2 × 10 mL). The organic layers were combined, dried over sodium sulfate, and then concentrated to give the crude product, which was purified by flash column chromatography eluting with hexanes/ethyl acetate (5:1).

Procedure for Reduction Using *R*-(+)-PhMeCHOH (5) and NaH (example acetophenone). To a dry 10 mL round-bottomed flame-dried flask protected by argon were added *R*-PhMeCHOH (from Aldrich) (0.01 mL, 0.1 mmol) and THF (3 mL). This solution was cooled to 0 °C, and then sodium hydride (4 mg, 0.1 mmol, 60% dispersion in mineral oil) was added. The resulting suspension was stirred for 30 min at 0 °C. To this suspension was added triethoxysilane (0.38 mL, 2.06 mmol) dropwise, and the reaction mixture was stirred for 15 min at 0 °C and then warmed to ambient temperature for 30 min. Acetophenone (0.12 mL, 1.02 mmol) was then added at ambient temperature. The solution was stirred at ambient temperature, and product development was monitored by TLC. After 3 h, the reaction mixture was loaded on a flash column for chromatography and the intermediate silyl ether was isolated by eluting with hexanes/ethyl acetate (5:1). The purified silyl ether intermediate was diluted with THF (5 mL), the solution was cooled to 0 °C, an aqueous HCl solution (1 N) was added carefully, and the solution was stirred at 0 °C for 1 h. Ethyl acetate (20 mL) was added to the solution, and the aqueous phase was extracted with ethyl acetate (2 × 10 mL). The organic layers were combined, dried over sodium sulfate, and then concentrated to give the pure product (yield, 87%).

***trans*-4-Phenyl-3-buten-2-ol:** ^1H NMR ($CDCl_3$, 200 MHz) δ 1.38 (d, 3H, J = 6.4 Hz, PhCHCHCH(OH)CH_3), 2.26 (bs, 1H, PhCHCHCH(*OH*)CH_3), 4.48 (dp, 1H, J = 0.9, 6.3 Hz, PhCHCH-C*H*(OH)CH_3), 6.26 (dd, 1H, J = 6.3, 16.0 Hz, PhCHC*H*CH(OH)-CH_3), 6.56 (d, 1H, J = 16.0 Hz, PhC*H*CHCH(OH)CH3), 7.20−7.41 (m, $5H_{arom}$); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 23.27, 68.68, 126.34, 127.47, 128.44, 129.16, 133.51, 136.61; MS (EI) *m*/*z* (%) 148 (M^+, 63), 131 (66), 115 (26), 105 (100), 91 (49), 77 (37), 55 (15), 43 (71).

4′-Trifluoromethylphenylethanol: ^1H NMR ($CDCl_3$, 200 MHz) δ 1.46 (d, 3H, J = 6.5 Hz, $F_3CC_6H_4CH(OH)CH_3$), 2.33 (bs, 1H, $F_3CC_6H_4CH(OH)CH_3$), 4.90 (q, 1H, J = 6.5 Hz, $F_3CC_6H_4CH(OH)$-CH_3), 7.43 (d, 2H, J = 8.1 Hz, $F_3CC_6H_2H_2$), 7.61 (d, 2H, J = 8.1 Hz, $F_3CC_6H_2H_2$); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 25.77, 69.93, 125.00, 127.29, 129.91, 134.32, 148.88; MS (EI) *m*/*z* (%) 190 (M^+, 5), 175 (40), 159(2), 145 (7), 128 (5), 127 (30), 109 (3), 95 (5), 77(8), 69 (5), 51 (8), 43 (100).

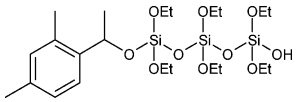
4′-Methoxyphenylethanol: ^1H NMR ($CDCl_3$, 200 MHz) δ 1.41 (d, 3H, J = 6.4 Hz, $H_3COC_6H_4CH(OH)CH_3$), 2.64 (bs, 1H, H_3-$COC_6H_4CH(OH)CH_3$), 3.74 (s, 3H, $H_3COC_6H_4CH(OH)CH_3$), 4.76 (q, 1H, J = 6.4 Hz, $H_3COC_6H_4CH(OH)CH_3$), 6.85 (d, 2H, J = 8.0 Hz, $H_3COC_6H_2H_2$), 7.25 (d, J = 8.0 Hz, $H_3COC_6H_2H_2$); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 24.88, 55.09, 69.61, 113.62, 126.53, 138.00,

158.70; MS (EI) *m*/*z* (%) 152 (M^+, 6), 135 (37), 109 (78), 105 (50), 84 (17), 77 (74), 51 (42), 43 (100).

4′-Nitrophenylethanol: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.51 (d, 3H, J = 6.4 Hz, $NO_2C_6H_4CH(OH)CH_3$), 2.00 (bs, 1H, $NO_2C_6H_4CH(OH)CH_3$), 5.01 (q, 1H, J = 6.4 Hz, $NO_2C_6H_4CH(OH)CH_3$)), 7.53 (d, J = 8.0 Hz, $NO_2C_6H_2H_2$), 8.19 (d, J = 8.0 Hz, $NO_2C_6H_2H_2$); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 26.14, 70.14, 124.39, 126.73, 128.49, 134.93, 154.40; MS (ES) *m*/*z* (%) 185 ($[M + NH_4]^+$, 100), 102 (18), 79 (45), 65 (18), 47 (4).

2′,4′-Dimethylphenylethanol: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.45 (d, 3H, J = 6.4 Hz, $(CH_3)_2C_6H_3CH(OH)CH_3$), 1.80 (bs, 1H, $(CH_3)_2C_6H_3CH(OH)CH_3$), 2.32 (s, 6H, $(CH_3)_2C_6H_3CH(OH)CH_3$), 5.09 (q, 1H, J = 6.4 Hz, $(CH_3)_2C_6H_3CH(OH)CH_3$), 6.97 (s, 1H, $(CH_3)_2C_6HHH$), 7.05 (d, 1H, J = 9.1 Hz, $(CH_3)_2C_6HHH$), 7.39 (d, 1H, J = 9.1 Hz, $(CH_3)_2C_6HHH$); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 18.81, 20.92, 23.92, 66.67, 124.45, 126.96, 131.14, 134.14, 136.74, 140.83; MS (ES) *m*/*z* (%) 150 (M^+, 49), 133 (100), 79 (23), 65 (10).

5-(2,4-Dimethylphenyl)ethoxyl-1,1-3,3-5,5-hexaethoxytrisiloxanol. If hydrolysis was not properly undertaken, partially condensed alkoxysilanes were isolated.



^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.09−1.33 (m, 18H, $(CH_3)_2$-PhCHO[$Si(OCH_2CH_3)_2$]$_3$(OH)CH_3), 1.44 (d, 3H, J = 5.4 Hz, [$Si(OCH_2CH_3)_2$]$_3$(OH)CH_3), 2.13 (bs, 1H, −[$Si(OCH_2CH_3)_2$]$_3$(OH)-CH_3), 3.68−3.91 (m, 12H, $(CH_3)_2$PhCHO[$Si(OCH_2CH_3)_2$]$_3$(OH)CH_3), 5.28−5.31 (m, 1H, $(CH_3)_2$PhCHO[$Si(OCH_2CH_3)_2$]$_3$(OH)CH_3), 6.91 (s, 1H, Ph-*H*), 7.01 (d, 1H, Ph-*H*), 7.42 (s, 1H, Ph-*H*); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 18.17, 18.96, 21.08, 25.41, 59.27, 68.09, 125.28, 125.91, 130.88; MS (CI) *m*/*z* (%) 554.2 ($[M + NH_4]^+$, 1), 535.2 (8), 505.3 (7), 491.1 (4), 417.2 (23), 401.2 (93), 283.1 (32), 269.1 (33), 133.1 (100), 119.1 (55), 105.1 (24), 91.1 (16); FTIR ν (cm^{-1}) 2976, 2885, 2885, 1392, 1079, 1085, 971, 795.

Bis(1-(4-(Trifluoromethyl)phenyl)ethoxy)diphenylsilane: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.27 (d, 3H, J = 6.4 Hz, $F_3CC_6H_4$-$CH(OSi-)CH_3$), 1.35 (d, 3H, J = 6.4 Hz, $F_3CC_6H_4CH(OSi-)$-CH_3), 4.92 (q, 1H, J = 6.4 Hz, $F_3CC_6H_4CH(OSi-)CH_3$), 4.98 (q, 1H, J = 6.4 Hz, $F_3CC_6H_4CH(OSi-)CH_3$), 7.20−7.69 (m, 14H, F_3-CC_6H_4, $Si(C_6H_5)_2$); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 25.77, 26.11, 69.93, 70.19, 124.60, 125.00, 127.29, 129.91, 131.85, 134.32, 148.88; HRMS (ES) exact mass calcd for $(C_{30}H_{26}NO_2F_6Si + NH_4)^+$ requires *m*/*z* 578.1950, found *m*/*z* 578.1982; LRMS (ES) *m*/*z* (%) 578 (M^+, 7), 364 (24), 179 (100), 165 (58), 100 (79), 77 (74), 65 (48).

(1-Phenylethoxy)triethoxysilane: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.10−1.25 (m, 9H, PhCHOSi$(OCH_2CH_3)_3CH_3$), 1.29−1.54 (m, 3H, PhCHOSi$(OCH_2CH_3)_3CH_3$), 3.68−3.92 (m, 6H, PhCHOSi-$(OCH_2CH_3)_3CH_3$), 5.08−5.14 (m, 1H, PhCHOSi$(OCH_2CH_3)_3CH_3$), 7.26−7.41 (m, Ph-*H*); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 18.00, 26.25, 59.11, 71.27, 125.29, 126.96, 128.09, 145.52; MS (ES) *m*/*z* (%) 307.2 ($[M + Na]^+$, 69), 302.3 (37), 139.0 (95), 105.1 (100).

General Experimental Procedure for Preparation of Mosher Esters (example *S*-1-phenethanol 5). *S*-1-Phenethanol **5** (2 mg, 0.02 mmol) and MTPA-Cl (+) (4 μL, 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 (1 M, 20 mL), saturated sodium carbonate solution (20 mL), and water (20 mL), was dried with sodium sulfate and filtered, and solvent was removed in vacuo. The residue was dissolved in deuterated chloroform for NMR analysis. The integration of the hydrogen on the carbon bearing the hydroxyl group was used as a measure to assess the enantioselection.

General Procedure for the ^{29}Si NMR Experiment (example triethoxysilane:3, 2:1). To a dry NMR tube were added **3** (0.034 g, 0.13 mmol) and d_8-THF (0.3 mL). This solution was cooled to −78 °C, and then *n*-butyllithium (0.18 mL, 1.6 M solution in hexanes, 0.26 mmol) was added dropwise. The resulting yellowish solution was warmed to 0 °C for 15 min. To this yellow solution was added triethoxysilane (0.05 mL, 0.26 mmol). The solution was allowed to stand at 0 °C, then warmed to room temperature for 30 min. ^{29}Si NMR was examined under proton-decoupled mode using a Bruker DRX-500.

Acetophenone (0.015 mL, 0.13 mmol) was then added to the solution at ambient temperature, and ^{29}Si NMR was examined every 2 h under proton-decoupled mode with the Bruker DRX-500.

Procedure for Low-Conversion Reduction of Acetophenone ($(EtO)_3SiH$ + 4). To a dry 10 mL round-bottomed flame-dried flask protected by argon were added **4** (0.035 g, 0.1 mmol) and THF (3 mL). This solution was cooled to 0 °C, and then sodium hydride (4 mg, 0.1 mmol, 60% dispersion in mineral oil) was added. The resulting suspension was stirred for 30 min at 0 °C. To this suspension was added triethoxysilane (0.38 mL, 2.06 mmol) dropwise, and the reaction mixture was stirred for 30 min at 0 °C and then cooled to −19 °C for 30 min. Acetophenone (0.12 mL, 1.02 mmol) was then added at −19 °C. The solution was stirred at −19 °C, and product development was monitored by TLC. After 20 min, the reaction mixture was diluted with cold THF (5 mL, 0 °C), a cold aqueous HCl solution (1 N, 0 °C) was added dropwise, and the solution was stirred for 1 h with the temperature allowed to increase gradually from −19 °C to room temperature. Ethyl acetate (20 mL) was added to the solution, and the aqueous phase was extracted with ethyl acetate (2 × 10 mL). The organic layers were combined, dried over sodium sulfate, and then concentrated to give the crude product, which was purified by flash column chromatography eluting with hexanes/ethyl acetate (5:1).

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