# Hydrosilylation of ketones catalyzed by $C_2$-symmetric proline-derived complexes[1]

**Li Gan and Michael A. Brook**

**Abstract:** Extracoordinate chiral hydrosilanes were generated in situ from triethoxysilane and a $C_2$-symmetric ligand derived from bisproline 7. In the presence of a catalytic amount of ligand **7**, prochiral ketones were reduced in moderate yield with moderate enantioselectivity (up to 64% ee). Alternatively, $TiF_4$ complexes of **7** were used to provide higher enantioselectivity and with improved yields. The copper complex of ligand **7** and $^{29}Si$ NMR data provide some guidance as to the key factors responsible for the observed reactivity at the silicon and at the ligand centre.

*Key words:* extracoordinate chiral silane, $C_2$-symmetry, enantioselectivity, Lewis acid titanium catalysis.

**Résumé :** On a effectué une génération *in situ* d'hydrosilanes chiraux extracoordinés à partir du triéthoxysilane et d'un ligand de symétrie $C_2$ dérivé de la bisproline **7**. En présence d'une quantité catalytique du ligand **7**, les cétones prochirales sont réduites avec des rendements moyens et un énantiosélectivité modérée, allant jusqu'à 64 % d'excès énantiomère. D'une façon alternative, on a utilisé des complexes du tétrafluorure de titane du ligand **7** qui ont fourni une énantiosélectivité supérieure et de meilleurs rendements. Le complexe de cuivre du ligand **7** et les données de la RMN du $^{29}Si$ donnent des indications sur les facteurs clés responsables au niveau de l'atome de silicium et du centre du ligand pour la réactivité observée.

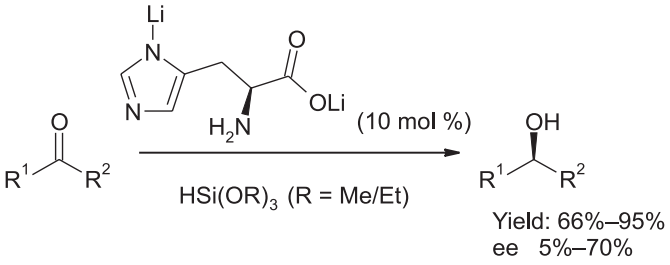
*Mots clés :* silane chiral extracoordiné, symétrie $C_2$, énantiosélectivité, catalyseur de titane agissant comme acide de Lewis.

[Traduit par la Rédaction]

## Introduction

The enantioselective reduction of carbonyl groups remains one of the fundamental operations in organic synthesis (1). Typical catalytic systems utilize a chiral ligand complexed with a transition metal (2). With the exception of boron, such as the well-developed chiral boron catalyst (CBS) (3), the use of chiral catalytic motifs based on main group elements is uncommon (4). However, in a process related to that reported by Shiffers and Kagan (5) and Hosomi and co-workers (6), we previously demonstrated that the complex derived from hydrosilanes and a catalytic amount of amino acids can reduce ketones enantioselectively (Scheme 1) (7).

**Scheme 1.** Histidine-catalyzed ketone reduction.




These reactions with hydrosilanes occur via extracoordinate silicon in the presence of anionic catalysts. Sakurai and co-workers (8a, 8b) has demonstrated that diastereoselective allylation of carbonyl groups in the presence of pentacoordinate silicon hydrides, for example, can best be explained by invoking six-membered ring transition states (Scheme 2). Coordination of the nucleophile, the carbonyl group, to the extracoordinate silicon is followed by allyl group transfer. As a departure point, we proposed that a related assembly of ketone and carboxylate on an extracoordinate silicon 1 could be used to explain the observed stereoselectivity in the hydrosilane reduction of acetophenone, although related bidentate structures could also be envisaged. While the mechanisms of these reactions have not yet been clearly established, the presence of extracoordinate

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*It is a great pleasure to dedicate this paper to the superb career of Alfred Bader. I learned about his passion for chemistry and chemists when we met several times when I was a graduate student and postdoctoral fellow. It meant a great deal to me then, and now, that "Please Bother Us" meant anyone interested in chemistry, not just the professors. I thank him for sharing his vision and enthusiasm for chemistry with me then and many times since. The example he set has profoundly affected the way my career has evolved.*

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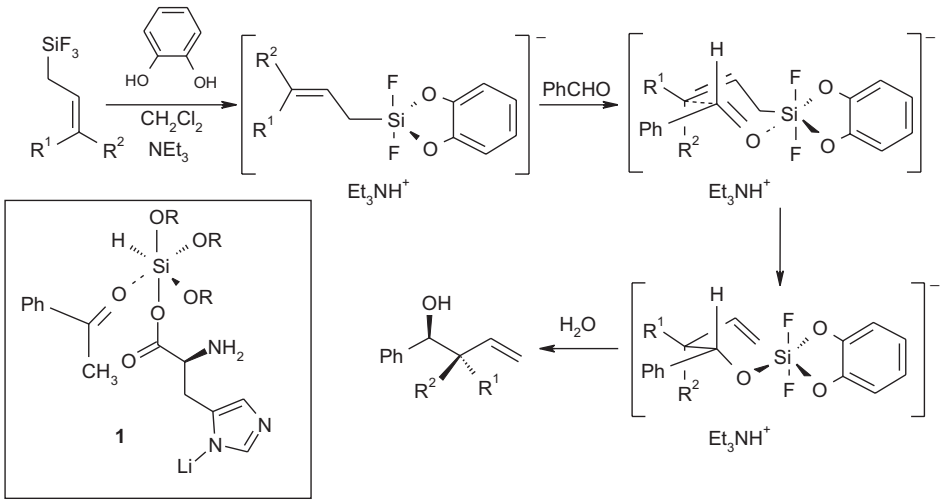
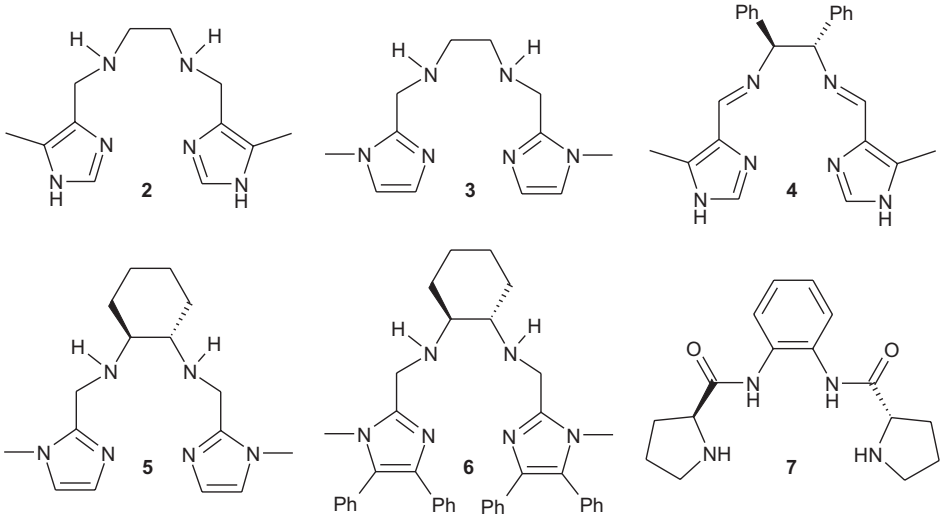
**Scheme 2.**



**Scheme 3.**



silicon, particularly the pentacoordinate species, is evident from Si NMR.

In an attempt to better understand the processes involved in the reduction, recent research has turned to the utilization of multidentate ligands that, on binding, would have fewer degrees of freedom and, additionally, would be more amenable to structural characterization. The use of $C_2$-symmetry, in particular, provides a more highly structured environment for enantioselective reactions (9), a strategy we recently utilized with silane-medicated reductions (**2**–**6**, Scheme 3) (10). Unfortunately, only moderate ee were observed in these reactions.

In this study, we developed a $C_2$-symmetric multidentate ligand that utilizes proline, perhaps the most widely utilized amino acid chiral template (11). We report the synthesis of the $C_2$-symmetric compound **7** (Scheme 3), the formation of pentacoordinate silicon complexes on reaction of **7** with $HSi(OEt)_3$, as shown by $^{29}Si$ NMR, the ability of this complex to reduce ketones, and the characterization of its copper complex **13** by an X-ray structure. In addition, the behaviour of the Lewis acidic derivative formed from the reaction of **7** with $TiF_4$ is described in the same carbonyl reduction process.[3]

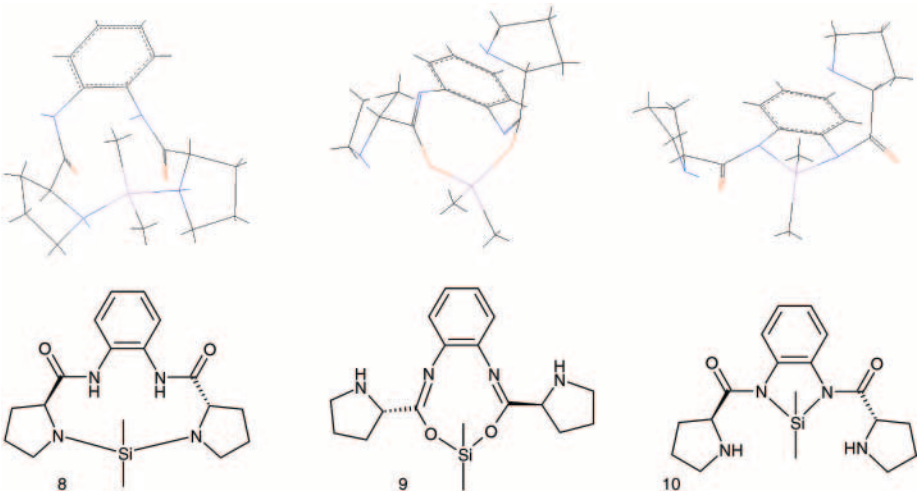
## Results and discussion

### Preparation and characterization of the ligands

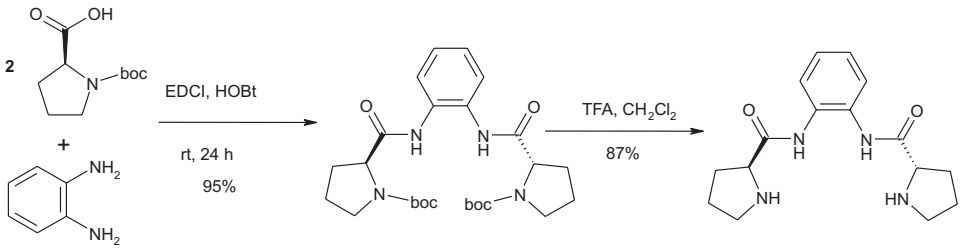
A series of molecular modeling experiments were undertaken with $C_2$-symmetric diamino acid derivatives. Preliminary studies compared the geometries of bidentate

[3] Supplementary data for this article are available on the journal Web site (http://canjchem.nrc.ca) or may be purchased from the Depository of Unpublished Data, Document Delivery, CISTI, National Research Council Canada, Ottawa, ON K1A 0R6, Canada. DUD 5079. For more information on obtaining material refer to http://cisti-icist.nrc-cnrc.gc.ca/irm/unpub_e.shtml. CCDC 601366 and 601367 contain the crystallographic data for this manuscript. These data can be obtained, free of charge, via http://www.ccdc.cam.ac.uk/conts/retrieving.html (Or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax +44 1223 336033; or deposit@ccdc.cam.ac.uk).

**Fig. 1.** Molecular models of dimethylsilyl derivatives of **7.**




**Scheme 4.** Preparation of bisproline **7**.



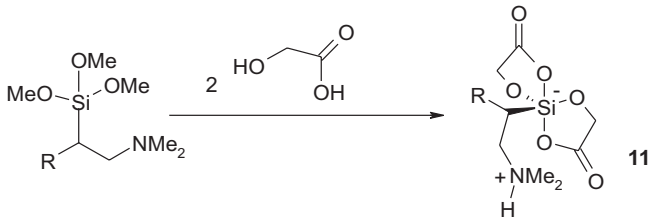

dimethylsilicon complexes based on various amino acid complexes of 1,2-diaminobenzene. Among the amino acids examined (phenylalanine, histidine, alanine, and proline), the latter had a more tightly constrained structure, irrespective of whether the linkages occurred through the proline nitrogen **8**, amide oxygen **9**, or amide nitrogen **10** (Fig. 1). All of the derivatives had more rigid and compact chiral environments than structures based on the structural motifs found in **4** or **5** (Scheme 3). Therefore, the bisproline ligand **7** was prepared by coupling 1,2-diaminobenzene with commercially available N-protected L-proline (Scheme 4). The optically pure ligand was obtained, after deprotection by trifluoroacetic acid, by recrystallization from methanol in an overall yield of 83% and structurally characterized by NMR ($^1$H, $^{13}$C), HRMS, and IR.

## Mechanistic study

Silicon compounds undergo extracoordination in the presence of silaphilic nucleophiles, particularly oxygen, fluoride, and aromatic amines (12). Coordination expansion is facilitated by electron-withdrawing groups on silicon, especially fluoride and oxygen ligands. Thus, the facility of trialkoxysilanes to undergo extracoordination lies between that of trialkyl- and trihalo-silanes (12). Tacke and co-workers (13), in a beautiful series of papers, demonstrated that bidentate nucleophiles are particularly efficacious in inducing coordination expansion. A broad variety of pentacoordinate amino and hydroxy acid derivatives, exemplified by **11**, have been isolated in crystalline form (Scheme 5) (13, 14).

Complexes of **7** and $HSi(OEt)_3$ were characterized by $^{29}$Si NMR. The $^{29}$Si NMR of the neutral mixture gave a singlet at

**Scheme 5.** Formation of extracoordinate silicon with α-hydroxy acids.




–58.68 ppm, consistent with reported data for triethoxysilane (15). Thus, the amine groups are insufficiently basic to engender extracoordination at silicon. By contrast, when the bisproline tetraanion of **7** was mixed with triethoxysilane in a ratio of 1:2 (sensitivity of the NMR precluded lower concentrations of the silicon compound and higher concentration of the bisproline tetraanion led to precipitates) $^{29}$Si NMR showed two singlets at –84.27 and –98.83 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, as does each exchange of N by O. For example, the addition of the anionic ligand of **7** to $HSi(OEt)_3$ to give a pentacoordinate species $(HSi(OEt)_3\text{-}N\mathbf{7})^-$ would lead to an upfield shift of about 20 ppm. However, displacement of the $EtO^-$ by the same nitrogen to give a tetracoordinate species $(HSi(OEt)_2\text{-}N\mathbf{7})$ would lead to a downfield shift of about 15 ppm (16). The observed peaks are consistent with a pentacoordinate species ($HSiX_4^-$, –84.27 ppm) and an oxidized pentacoordinate species ($SiX_5^-$) or a hydrido hexacoordinate species ($HSiX_5^{2-}$,

**Fig. 2.** ORTEP drawing of the structure of **12**, a copper complex **13**, and a possible structure of the hydridosiliconate **14**.

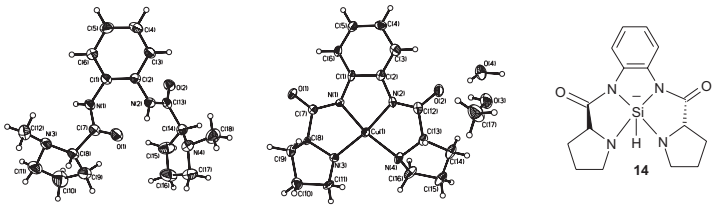


**Table 1.** Selected crystallographic data for ligand **7**.

| | |
|---|---|
| Identification code | CCDC 601366 |
| Empirical formula | $C_{18}H_{26}N_4O_2$ |
| Formula weight (g mol$^{-1}$) | 330.43 |
| Crystal system | Monoclinic |
| Space group | *C*2 |
| *a* (Å) | 20.259(8) |
| *b* (Å) | 8.751(3) |
| *c* (Å) | 10.929(4) |
| α (°) | 90 |
| β (°) | 113.066(6) |
| γ (°) | 90 |
| Volume (Å$^3$) | 1782.6(12) |
| *Z* | 4 |
| Density$_{calcd.}$ (Mg/m$^3$) | 1.231 |
| Absorption coefficient (mm$^{-1}$) | 0.082 |
| *F*(000) | 712 |
| Crystal size (mm$^3$) | 0.38 × 0.18 × 0.08 |
| θ range for data collection (°) | 2.03–26.48 |
| Reflections collected | 7556 |
| Independent reflections | 3346 |
| $R_{int}$ | 0.0346 |
| Data, restraints, parameters | 3346, 1, 218 |
| Goodness-of-fit on $F^2$ | 1.009 |
| Final *R* indices [$I > \sigma(I)$] | $R_1$ = 0.0419, $wR_2$ = 0.0898 |
| *R* indices (all data) | $R_1$ = 0.0702, $wR_2$ = 0.0993 |
| Largest diff. peak and hole (e Å$^{-3}$) | 0.116 and –0.118 |

**Table 2.** Selected crystallographic data for **13**.

| | |
|---|---|
| Identification code | CCDC 601367 |
| Empirical formula | $C_{17}H_{24}CuN_4O_4$ |
| Formula weight | 411.94 |
| Space group | *P*2(1)2(1)2(1) |
| Crystal system | Orthorhombic |
| Crystal size (mm$^3$) | 0.20 × 0.18 × 0.06 |
| *a* (Å) | 8.3234(4) |
| *b* (Å) | 11.7554(5) |
| *c* (Å) | 18.5682(8) |
| α (°) | 90 |
| β (°) | 90 |
| γ (°) | 90 |
| Volume (Å$^3$) | 1816.80(14) |
| *Z* | 4 |
| Density$_{calcd.}$ (Mg/m$^3$) | 1.506 |
| Absorption coefficient (mm$^{-1}$) | 1.233 |
| *F*(000) | 860 |
| θ range for data collection (°) | 2.05–28.31 |
| Reflections collected | 16 688 |
| Independent reflections | 4359 |
| $R_{int}$ | 0.0891 |
| Completeness to θ = 28.31° (%) | 98.00 |
| Data, restraints, parameters | 4359, 0, 248 |
| Goodness-of-fit on $F^2$ | 1.042 |
| Final *R* indices [$I > 2\sigma(I)$] | $R_1$ = 0.0593, $wR_2$ = 0.1036 |
| *R* indices (all data) | $R_1$ = 0.1041, $wR_2$ = 0.1152 |
| Largest diff. peak and hole (e Å$^{-3}$) | 0.526 and –0.555 |

–98.83 ppm), respectively. Since extracoordinate hydridosiliconates are required to reduce ketones (see later), it is anticipated that these peaks represent penta- and hexacoordinate silicon hydrides; after the ketone reduction, $^{29}$Si NMR showed only one peak at –82.39 ppm.

It did not prove possible to prepare crystals of sufficient quality for an X-ray analysis. By contrast, the *N*,*N*-dimethyl derivative **12** gave suitable crystals (Fig. 2, for crystallographic parameters and typical bond lengths and angles see Table 1). To explore complexed ligand structures that would be related to the reduction process, the copper complex **13** of ligand **7** was prepared by the reaction of the ligand with copper(II) chloride in methanol in the presence of excess potassium carbonate (Fig. 2). An X-ray crystal structure of the compound showed a nearly square planar arrangement of the $C_2$-symmetric nitrogen ligands around copper (Tables 2 and 3). The ligand in **13** forms a compact complex with short Cu—N bond lengths that brings the stereodirecting chiral centres in closer proximity to the metal centre. This structure was very encouraging as it suggests that analogous $C_2$-symmetric structures, such as **14**, may be formed. Extensive attempts to isolate various silicon complexes of **7** in crystalline form were unsuccessful.

## Reductions of acetophenone

Previous work demonstrated that ketone reduction with hydrosilanes could be initiated with carboxylate or other anions to activate the silicon (7). A series of reductions of acetophenone was undertaken to establish the key factors required for efficacy in the presence of **7** (Table 4). Negative controls included a set of reactions in which each of the key ingredients was selectively absent. Notable among the results is the reduction of acetophenone with the proline anion, which resulted in 50% yield and 15% ee (Table 4, entry 3). This is a result that is related to, but less efficient than, reductions in the presence of anions of histidine and particularly phenylalanine that occurred in yields typically of 80% and ee up to 70% (7). A series of experiments demonstrated that the best compromise for yield and ee occurred at 55 °C, higher than would be expected for a reaction run under ki-

**Table 3.** Selected bond lengths (Å) and angles (°) for **13** (esds in parentheses).

| | |
|---|---|
| **Bond lengths (Å)** | |
| Cu(1)—N(1) | 1.924(4) |
| Cu(1)—N(4) | 2.006(4) |
| C(12)—C(13) | 1.526(7) |
| C(7)—C(8) | 1.517(7) |
| N(3)—C(8) | 1.525(6) |
| Cu(1)—N(2) | 1.925(4) |
| N(1)—C(7) | 1.342(6) |
| N(2)—C(2) | 1.413(6) |
| N(2)—C(12) | 1.305(6) |
| Cu(1)—N(3) | 1.997(4) |
| N(1)—C(1) | 1.410(6) |
| C(1)—C(2) | 1.426(6) |
| N(4)—C(13) | 1.511(6) |
| **Bond angles (°)** | |
| N(1)-Cu(1)-N(2) | 83.38(16) |
| N(1)-Cu(1)-N(4) | 168.95(17) |
| C(7)-N(1)-C(1) | 127.5(4) |
| C(6)-C(1)-N(1) | 127.5(4) |
| C(12)-N(2)-Cu(1) | 116.8(3) |
| N(2)-C(2)-C(1) | 114.4(4) |
| C(8)-N(3)-Cu(1) | 106.5(3) |
| C(13)-N(4)-Cu(1) | 107.2(3) |
| N(1)-C(7)-C(8) | 113.5(4) |
| C(9)-C(8)-N(3) | 103.8(4) |
| N(2)-C(12)-C(13) | 115.2(4) |
| C(15)-C(14)-C(13) | 103.8(5) |
| N(1)-Cu(1)-N(3) | 85.66(17) |
| N(2)-Cu(1)-N(4) | 85.60(16) |
| C(7)-N(1)-Cu(1) | 116.7(3) |
| N(1)-C(1)-C(2) | 113.0(4) |
| C(2)-N(2)-Cu(1) | 114.2(3) |
| C(11)-N(3)-C(8) | 106.4(4) |
| C(16)-N(4)-C(13) | 105.5(4) |
| O(1)-C(7)-N(1) | 128.0(4) |
| C(7)-C(8)-C(9) | 114.1(4) |
| O(2)-C(12)-N(2) | 127.3(5) |
| N(4)-C(13)-C(12) | 112.3(4) |
| N(2)-Cu(1)-N(3) | 166.91(16) |
| N(3)-Cu(1)-N(4) | 105.17(17) |
| C(1)-N(1)-Cu(1) | 115.1(3) |
| C(12)-N(2)-C(2) | 127.9(4) |
| C(3)-C(2)-N(2) | 125.8(4) |
| C(11)-N(3)-Cu(1) | 118.2(3) |
| C(16)-N(4)-Cu(1) | 117.7(3) |
| O(1)-C(7)-C(8) | 118.5(4) |
| C(7)-C(8)-N(3) | 113.0(4) |
| O(2)-C(12)-C(13) | 117.5(4) |
| C(12)-C(13)-C(14) | 114.3(4) |

netic control. The reactions further confirmed that extracoordinate hydrosilanes are more reactive towards a variety of electrophiles than their four-coordinate counterparts (12). For example, neutral $HSi(OEt)_3$ is not able to reduce acetophenone in the absence of nucleophilic activation (Table 4, entry 1). Neutral bisproline **7** is similarly unable to activate triethoxysilane to undergo the reduction (Table 4, entry 2) as was also shown by $^{29}Si$ NMR experiments (see earlier). By contrast, the most effective reduction took place with the tetraanion of **7** (Table 3, entry 4). While the tetraanion of **7** can make a tight complex with silicon, it can do so with loss of chirality because of amino acid epimerization.

While the yields of these reactions were acceptable, the ee were marginal. Although the crystal structure of the copper complex **13** shows that the stereochemistry of the amino acids are maintained in the complex, it is also conceivable that α-amido epimerization occurs under the more basic conditions used for these reductions. To reduce this possibility, the efficacy of the reaction was tested as a function of the equivalents of base added (from 1 to 4 equiv.). The most interesting results came with 2 equiv. of base, which should deprotonate the amide NHs, possibly leading to bidentate complexes **15** (Table 4) and **16** (analogous to **9** and **10**, Fig. 3) without affecting the chiral centres. The reaction was more sluggish and it can be seen that, in one case, the ee improved, but at the expense of reaction yield (Table 4, entries 5–7).

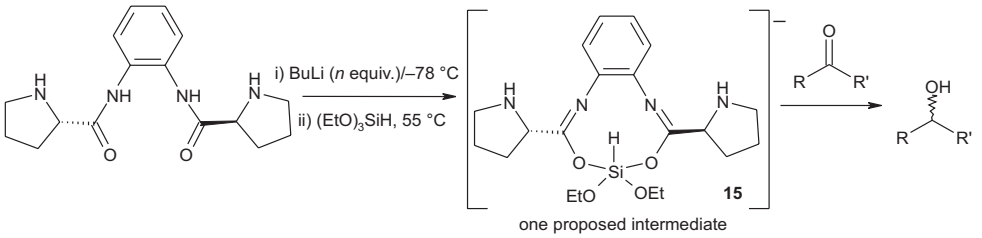
Hydrosilanes are very stable at neutral conditions, but significantly less so away from neutrality, particularly under basic conditions. Exchangeable hydrogens under these conditions serve as excellent electrophiles, with the result that $H_2$ is normally released (e.g., $R_3SiH + HY \rightarrow R_3SiY + H_2$) (17). This process is particularly favoured when multidentate ligands are utilized (14) and can be exploited as a method for generating $H_2$ in situ on demand (18).

In the current case, the design of the ligand is challenged by this reactivity. Tetradentate complexation giving compounds such as **14** could also result in loss of chirality through epimerization **17**. By contrast, a bidentate chiral $C_2$-symmetric complex such as **16** is subject to loss of hydride through the processes just described (**16** → **18**, Fig. 3).

Si-H groups are significantly less reactive to acidic than basic conditions (19). It was reasoned that these problems could be mitigated or avoided by changing from basic to acidic conditions. That is, the same ligand could be complexed by a Lewis acid that would fit into the chiral pocket of the ligand and direct reduction. An important precedent for this approach is the observation by Cozzi and coworkers (20) that Lewis acidic titanium fluoride complexes **19**, based on readily accessible chiral bisoxazoline complexes of Evans, will catalyze carbonyl reductions (Scheme 6). The titanium complex of ligand **7** is expected to be tetradentate (Table 5) based on the structure of the copper complex **13**. Carbonyl complexation will preferentially occur at the more Lewis acidic site (titanium) and the locus of the reduction reaction will be taken away from silicon. These proposals were tested by complexing ligand **7** with titanium-based Lewis acids and examining the reduction reaction in the absence and presence of base (Table 5) in the presence of 5 mol% of the chiral catalyst.

The relative Lewis acidity of simple titanium catalysts follows the order $Ti(OiPr)_4 < TiCl_4 < TiF_4$. Replacement of halides or alkoxy groups with amines will further moderate Lewis acidity. No reduction was observed under any conditions when the first two less acidic compounds were employed as catalysts (Table 5). When 2 equiv. of BuLi were

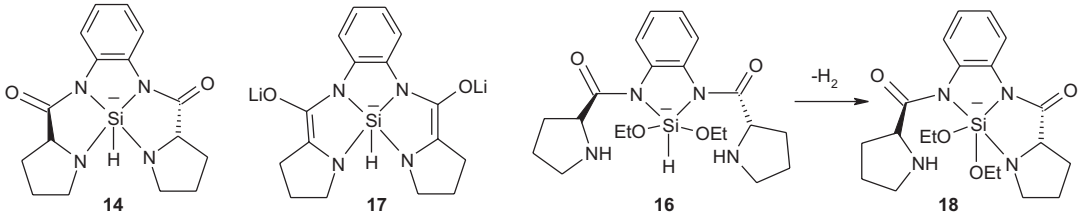
**Table 4.** Basic reduction of acetophenone by $(EtO)_3SiH$ in the presence of **7**.



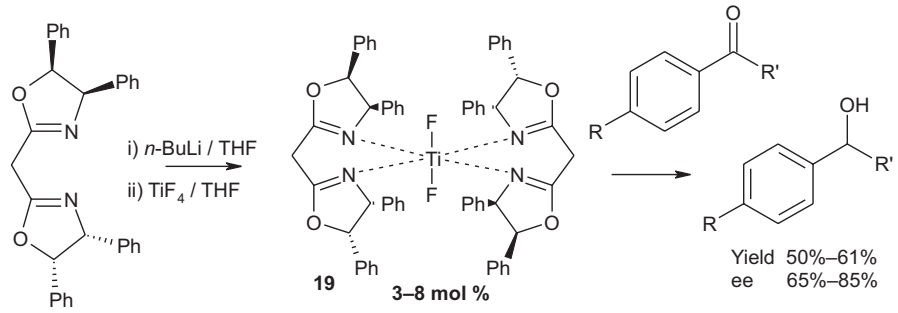

| Entry | A | Conditions | *n* (equiv. base) | Yield (%) | ee (%) |
|---|---|---|---|---|---|
| 1 | Acetophenone | 55 °C, 72 h | 0 | NR[a] | — |
| 2 | Acetophenone | **7**, 55 °C, 12 h | 0 | NR | — |
| 3 | Acetophenone | proline, BuLi, 55 °C, 24 h | 2 | 50 | 15 |
| 4 | Acetophenone | **7**, BuLi, rt, 12 h | 4 | 85 | 5 |
| 5 | Acetophenone | **7**, BuLi, rt, 72 h | 2 | 35 | 64 |
| 6 | 2-Bromoacetophenone | **7**, BuLi, rt, 72 h | 2 | 20 | 20 |
| 7 | 4-Methoxyacetophenone | **7**, BuLi, rt, 72 h | 2 | 48 | 5 |

[a]NR = No reaction.

**Fig. 3.** Possible pentacoordinate intermediates prior to and following reduction.




**Scheme 6.**

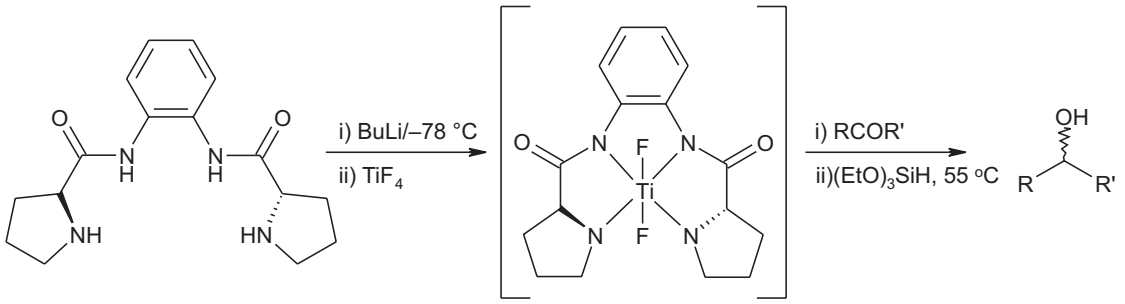



used to facilitate formation of the titanium–**7** complex, only marginal reduction yields were observed, in general worse than in the absence of the titanium compound (Table 4). Of the three reducing agents $H_2$, $Ph_2SiH_2$, and $HSi(OEt)_3$, only the last was somewhat efficient. $H_2$ was used as a negative control. Of the two silanes, $HSi(OEt)_3$ is generally more reactive than $Ph_2SiH_2$. It has a greater facility for coordination expansion, and as discussed earlier, silylhydrides are more reactive as five- rather than four-coordinate silicon. Improved results were obtained when 4 equiv. of base was used to create the titanium–**7** complex. Yields increased as did enantioselectivity as determined using Mosher ester synthesis (21), although not to levels sufficient for practical application.

A bidentate adduct could form from addition of the dianion **20** to $TiF_4$ (Scheme 7), which will be a less rigid structure than a tridentate complex such as **21** or the $C_2$-symmetric catalyst tetradentate titanium complex **22** that should form when 4 equiv. of base are added (Scheme 7). The more rigid structures with proximal chiral groups should have improved enantioselectivity, as was observed with the system derived from the tetraanion.

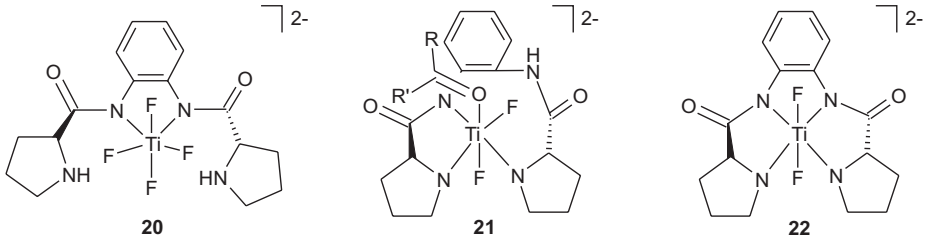
Several observations provide guidance about the role of the titanium complex **20**. Oxophilic titanium will preferentially jettison nitrogen groups to form a complex with the carbonyl oxygen to give a motif such as **21**, which is widely exploited in titanium-catalyzed aldol and related reactions (22), but in doing so will lose $C_2$-symmetry. The attempt to crystallize **20** or carbonyl complexes of it were unfortunately unfruitful. Hydrosilanes are normally insufficiently reactive

**Table 5.** Enantioselective reduction of ketones using a bisproline-Ti catalytic system.




| Entry | Ketone | 7 (mol%) | Metal catalyst (equiv.) | Reaction time (h) | Temp. (°C) | Reducing agent | *n* (equiv. BuLi) | Yield | ee |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Acetophenone | 5 | None | 12 | 25 | $HSi(OEt)_3$ | 4 | 85 | 5 |
| 2 | Acetophenone | 0 | $TiF_4$ (5) | 24 | 55 | $HSi(OEt)_3$ | 0 | NR | — |
| 3 | Acetophenone | 5 | $TiCl_4$ (10) | 24 | 55 | $HSi(OEt)_3$ | 2 | NR | — |
| 4 | Acetophenone | 10 | $TiF_4$ (10) | 24 | 25 | $H_2$ | 2 | NR | — |
| 5 | Acetophenone | 5 | None | 24 | 55 | $Ph_2SiH_2$ | 2 | NR | — |
| 6 | Acetophenone | 5 | $TiF_4$ (5) | 24 | 55 | $Ph_2SiH_2$ | 2 | 17 | — |
| 7 | Acetophenone | 5 | $TiF_4$ (5) | 24 | 55 | $(EtO)_3SiH$ | 2 | 10 | — |
| 8 | Acetophenone | 5 | $TiCl_4$ (5) | 24 | 55 | $(EtO)_3SiH$ | 4 | NR | — |
| 9 | Acetophenone | 5 | $RhCl_3$ (5) | 24 | 55 | $HSi(OEt)_3$ | 4 | 20 | — |
| 10 | Acetophenone | 5 | $TiF_4$ (5) | 12 | 25 | $HSi(OEt)_3$ | 4 | 80 | 2 |
| 11 | Acetophenone | 5 | $TiF_4$ (5) | 24 | 55 | $HSi(OEt)_3$ | 4 | 80 | 20 |
| 12 | Acetophenone | 5 | $TiF_4$ (5) | 12 | 55 | $(EtO)_3SiH$ | 4 | 80 | 20 |
| 13 | 2-Bromoacetophenone | 5 | $TiF_4$ (5) | 12 | 55 | $(EtO)_3SiH$ | 4 | 60 | 20 |
| 14 | 2-Methoxyacetophenone | 5 | $TiF_4$ (5) | 12 | 55 | $(EtO)_3SiH$ | 4 | 40 | 2 |
| 15 | *trans*-4-Phenyl-3-buten-2-one | 5 | $TiF_4$ (5) | 12 | 55 | $(EtO)_3SiH$ | 4 | 90 | 2 |

**Scheme 7.**




to reduce such titanium carbonyl complexes. By contrast, carbocations can be trapped to give C—H bonds (23).

While the specific role of the hydrosilane has not yet been established in the Ti-catalyzed reductions, it seems likely, as with the basic conditions, that extracoordinate silicon is responsible for reduction. The inability of the $TiCl_4$ complex of **7** to catalyze reduction is instructive in this context. The formation of a Lewis acidic chiral complex will liberate the halide $Cl^-$, which is normally not able to facilitate extracoordination at silicon (12). Thus, while a chiral carbonyl–Ti complex may form, the only reducing agent present is $HSi(OEt)_3$, which is a not viable reducing agent for ketones.

As reported by many researchers, fluoride activates silicon hydrides to reduce carbonyls (24). Formation of compounds such as **22** with $TiF_4$ serves two purposes. It first provides a chiral Lewis acidic pocket that serves as the locus of reduction and further liberates 2 equiv. of $F^-$. Fluoride is key, as it can convert the hydrosilane into an active reducing agent, $HSi(OEt)_3F^-$. The obvious disadvantage of this process is that the activated fluoride complex $HSi(OEt)_3F^-$ can directly reduce the ketone outside the sphere of the chiral ligand, leading to a reduction in the overall enantioselectivity of the process.

Of the two very mild approaches examined, the Lewis acidic approach was more efficacious than the extracoordinate hydrosiliconate, with respect to both yields and enantioselectivity. Our current focus is to develop ligands that provide chirality and intramolecular activation to the silicon. Such a system will constrain all reactions to the proximity of the chiral environment.

## Conclusion

A $C_2$-symmetric bisproline ligand can be used as a cata-

lyst to induce enantioselective induction as an anionic extracoordinate silicon complex or after complexation with $TiF_4$. The Lewis acid catalyzed route led to high yields because side reactions are reduced and showed higher ee.

## Experimental section

### Reagents and physical methods

The following materials were obtained from Sigma-Aldrich and were used without further purification: acetophenone, *n*-butyllithium (1.6 mol/L solution in cyclohexane), (*S*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (MTPA-Cl (+)), 2-methoxyacetophenone, *trans*-4-phenyl-3-buten-2-one, sodium sulfate, triethoxysilane, 1,2-diaminobenzene, *N*-BOC-(*S*)-proline, hydroxybenztriazole (HOBt), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC), rhodium(III) chloride, titanium(IV) fluoride, and titanium(IV) chloride.

All solvents were thoroughly dried before use; THF was 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.

$^1$H and $^{13}$C NMR spectra were recorded on a Bruker AC-200 (at 200 MHz for protons, 50.32 MHz for $^{13}$C) Fourier transform spectrometer. $^{29}$Si NMR was performed on a Bruker DRX-300 (at 75.44 and 59.60 MHz for carbon and silicon, respectively). $^1$H-NMR was also performed on a Bruker DRX-500 (at 500 MHz for hydrogen). $^1$H chemical shifts are reported either with respect to tetramethylsilane as an external standard set to 0 ppm or $CDCl_3$ as an internal standard set to 7.26 ppm. $^{13}$C NMR chemical shifts are reported either with respect to $CDCl_3$ as an internal standard set to 77.26 or THF-$d_8$ as an internal standard set to 67.57 ppm. Coupling constants (*J*) are recorded in Hertz (Hz). The abbreviations singlet (s), doublet (d), triplet (t), quartet (q), doublet of doublets (dd), doublet of triplets (dt), multiplet (m) 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 (Waters Corporation, Milford, Massachusetts) mass spectrometer using a heated probe. High-resolution mass spectral (HRMS) data were obtained using the EI method calibrant with perfluorotributyl amine. Molecular modeling calculations were undertaken using the MM2 molecular mechanics parameter set, using Hyperchem 5.01 from Hypercube Inc. (Gainesville, Florida).

X-ray crystallographic data for **7** and **13** were collected from suitable samples mounted with epoxy on the end of thin glass fibers. Data collections were performed at 273 K.

Data for **7** were collected on a Bruker P4 diffractometer equipped with a Bruker SMART 1K CCD area detector (using the program SMART (25)) and a rotating anode utilizing graphite-monochromated Mo Kα radiation (λ = 0.710 73 Å). Data processing was carried out by use of the program SAINT (26), while the program SADABS (27) was utilized for the scaling of diffraction data, the application of a decay correction, and an empirical absorption correction based on redundant reflections. The structures were solved by using the direct methods procedure in the Bruker SHELXTL (28) program library and refined by full-matrix least-squares methods on $F^2$. All non-hydrogen atoms were refined using anisotropic thermal parameters and hydrogen atoms were added as fixed contributors at calculated positions, with isotropic thermal parameters based on the atom to which they are bonded.

Data for **13** were collected on a three-circle D8 Bruker diffractometer equipped with a Bruker SMART 6000 CCD area detector (using the program SMART (25)) and a rotating anode utilizing cross-coupled parallel focusing mirrors to provide monochromated Cu Kα radiation (λ = 1.541 78 Å). Data processing and structure solving were carried out as noted previously.

### Preparation of the bis(L)prolinyl amide of 1,2-diaminobenzene

A solution of 1,2-diaminobenzene (0.36 g, 3.3 mmol) and *N*-(*tert*-butoxycarbonyl)-L-proline (1.5 g, 6.9 mmol) in $CH_2Cl_2$–DMF (10:1, 30 mL) was treated at 0 °C with HOBt (0.93 g, 6.9 mmol) and EDC (1.35 g, 6.9 mmol). The reaction mixture was stirred at 0 °C for 2 h and allowed to warm up to room temperature (rt) overnight. Solvents were removed under reduced pressure. $CH_2Cl_2$ (20 mL) was added to the yellow residue and stirred for 2 h. TFA (10 mL) was added dropwise at rt to the solution, which was stirred for another 2 h. Saturated $K_2CO_3$ solution (20 mL) neutralized the solution (pH 9). The aqueous layer was extracted with $CH_2Cl_2$ (3 × 20 mL). The combined organic layer was dried over anhydr. $Na_2SO_4$. After removing the solvents under reduced pressure, the product was recrystallized from methanol and dichloromethane (20:1). The product, a colourless crystal, was formed in 83% yield. $^1$H NMR ($CDCl_3$, 500 MHz) δ: 1.73–1.80 (m, 4H, $R_1$-C*H*-$R_2$), 2.02–2.13 (m, 2H, NH), 2.18–2.24 (m, 4H, $R_2$-C*H*-$R_3$), 2.95–3.10 (m, 4H, C$H_2$-NH), 3.86–3.93 (q, 2H, *CH*-NH), 7.13–7.19 (m, 2H, Ph-*H*), 7.65–7.70 (m, 2H, Ph-*H*). $^{13}$C NMR ($d_6$-DMSO, 200 MHz) δ: 33.27, 37.76, 54.07, 67.92, 131.03, 132.11, 137.72, 181.25. LRMS (EI) *m*/*z* (%): 302 ($M^+$, 13), 232 (62), 205 (53), 188 (100), 91 (92), 70 (83), 45 (87). HRMS (ES) *m*/*z* calcd. for $(C_{16}H_{23}N_4O_2)^+$: 303.1808; found: 303.1821.

### Preparation of the *N*,*N*′-dimethyl bis(L)prolinyl amide of 1,2-diaminobenzene (12)

To a stirred solution of **7** (1 g, 3.3 mmol) and 37% aqueous formaldehyde (2 mL, 25 mmol) in 20 mL acetonitrile was added sodium cyanoborohydride (0.8 g, 10 mmol). Glacial acetic acid was added until the solution reached neutrality. The reaction was stirred at ambient temperature for 3 h. The reaction mixture was poured into 50 mL of ether and washed with 3 × 30 mL portions of 1 N KOH and one 30 mL portion of brine. The ether solution was dried ($Na_2SO_4$) and evaporated under reduced pressure. The desired product was recrystallized from MeOH and ether (1:10). The product, a colourless crystal, was formed in 80% yield, mp 206 °C. $^1$H NMR ($CDCl_3$, 300 MHz) δ: 1.77–1.80 (m, 4H, $R_1$-C$H_2$-$R_2$), 1.82–1.99 (m, 2H, CH-C$H_2$-$CH_2$), 2.25–2.42 (m, 4H, CH-C$H_2$-$CH_2$), 2.46 (s, 6H, C$H_3$-N), 3.02 (q, 2H, *J* = 5.1, 10.2 Hz, C$H_2$-$NHCH_3$), 3.14–3.19 (m, 2H, C$H_2$-$NHCH_3$), 3.29–3.32 (m, 2H, C*H*-$NCH_3$), 7.20–7.25 (m, 2H, Ph-*H*), 7.62–7.67 (m, 2H, Ph-*H*), 9.38 (s, 2H, CON*H*). $^{13}$C NMR ($CDCl_3$, 200 MHz) δ: 24.38, 31.15, 41.79, 56.67, 69.23, 124.25, 125.80, 129.77, 173.43. LRMS (ES) *m*/*z* (%): 331.6 ($M^+$, 100), 147.0 (5), 65 (10). HRMS (ES) *m*/*z* calcd.

for $(C_{18}H_{27}N_4O_2)^+$: 331.2134; found: 331.2139. For X-ray data, see Table 1.

**Preparation of the copper complex of the bis(L)prolinyl amide of 1,2-diaminobenzene (13)**

Ligand **7** (0.03 g, 0.1 mmol) was dissolved in methanol (5 mL) before the addition of anhydr. $K_2CO_3$ (0.055 g, 0.4 mmol) and $CuCl_2 \cdot 2H_2O$ (0.017 g, 0.1 mmol). The resulting system was stirred overnight, then the solid was filtered off and the clear blue solution was layered with ether. After 2 weeks, purple crystals were isolated, mp 295 °C (dec.). HRMS (ES) *m/z* calcd. for $(C_{16}H_{21}N_4O_2Cu)^+$: 364.0961; found: 364.0957. For X-ray data, see Tables 2 and 3.

**General procedure for the $^{29}$Si NMR experiment (example ligand 7–triethoxysilane, 1:2)**

To a dry NMR tube was added **7** (0.039 g, 0.13 mmol) and $d_8$-THF (0.3 mL). This solution was cooled to –78 °C and *n*-butyllithium (0.16 mL, 1.6 mol/L 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 up to rt for 30 min. $^{29}$Si NMR was examined in proton decoupled mode using the Bruker DRX-500.

**General procedure for basic reduction of ketone in the presence of 7 (example acetophenone) (Table 4)**

To a dry 10 mL round-bottomed flame-dried flask protected by argon was added **7** (0.016 g, 0.05 mmol) and THF (5 mL). This solution was cooled to –78 °C and *n*-butyllithium (0.13 mL, 1.6 mol/L 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 at which point $(EtO)_3SiH$ (0.38 mL, 2.06 mmol) was added. The resulting clear solution was stirred for 1 h at rt, then acetophenone (0.12 mL, 1.02 mmol) was added. The solution was stirred at rt and product development was monitored by TLC. The reaction mixture was acidified by adding 1 N HCl at 0 °C and carefully made to pH 6 (29). The organic phase collected. The aqueous phase was extracted with ethyl acetate (3 × 10 mL). The organic layers weree combined, dried over sodium sulfate, and then concentrated to give the crude product, which was purified by column chromatography eluting with hexanes – ethyl acetate (5:1). $^1$H 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). MS (CI) *m/z* (%): 140 ($(M + 18)^+$, 17), 122 (100), 105 (41), 78 (2), 52 (1), 44(1).

**General procedure for Lewis acid catalyzed reduction of ketone (example acetophenone) (Table 5)**

To a dry 10 mL round-bottomed flame-dried flask protected by argon was added **7** (0.016 g, 0.05 mmol) and THF (5 mL). This solution was cooled to –78 °C and *n*-butyllithium (0.13 mL, 1.6 mol/L solution in hexanes, 0.2 mmol) was added dropwise. The resulting yellowish solution was stirred for 5 min at –78 °C and warmed to 0 °C for 15 min. To this yellow solution was added $TiF_4$ (6 mg, 0.05 mmol) and the mixture was vigorously stirred until the salt was completely dissolved. The resulting yellow mixture was stirred for 1 h at rt and triethoxysilane (0.38 mL, 2.06 mmol) and acetophenone (0.12 mL, 1.02 mmol) were added. The solution was stirred at 55 °C 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 mol/L of sodium hydroxide (30). The solid was separated by filtration and the organic phase was 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 which was purified by column chromatography eluting with hexanes – ethyl acetate (5:1).

**2-Bromophenethyl alcohol**

$^1$H NMR ($CDCl_3$, 200 MHz) δ: 2.69 (bs, 1H, O*H*), 3.69–3.45 (m, 2H, C$H_2$Br), 4.90 (dd, *J* = 3.5, 8.6 Hz, 1H, Ph*CH*(OH)), 7.36 (s, $5H_{arom}$). $^{13}$C NMR ($CDCl_3$, 200 MHz) δ: 40.12, 73.78, 125.95, 128.43, 128.65, 140.31. MS (EI) *m/z* (%): 202 ($(M + 2)^+$, 2), 200 ($M^+$, 2), 185 (5), 183 (5), 121 (5), 107 (100), 91 (10), 79 (78), 51 (29).

***trans*-4-Phenyl-3-buten-2-ol**

$^1$H NMR ($CDCl_3$, 200 MHz) δ: 1.38 (d, 3H, *J* = 6.4 Hz, PhCH=CHCH(OH)*CH*$_3$), 2.26 (bs, 1H, PhCH=CHCH(*OH*)$CH_3$), 4.48 (dp, 1H, *J* = 0.9, 6.3 Hz, PhCH=CHC*H*(OH)$CH_3$), 6.26 (dd, 1H, *J* = 6.3, 16.0 Hz, PhCH=C*H*CH(OH)$CH_3$), 6.56 (d, 1H, *J* = 16.0 Hz, PhC*H*=CHCH(OH)$CH_3$), 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-Methoxyphenethyl alcohol**

$^1$H NMR ($CDCl_3$, 200 MHz) δ: 1.41 (d, 3H, *J* = 6.4 Hz, $CH_3O$-$C_6H_4$CH(OH)*CH*$_3$), 2.64 (bs, 1H, $CH_3OC_6H_4$CH(O*H*)$CH_3$), 3.74 (s, 3H, C$H_3OC_6H_4$-CH(OH)$CH_3$), 4.76 (q, 1H, *J* = 6.4 Hz, $CH_3OC_6H_4$*CH*(OH)$CH_3$), 6.85 (d, 2H, *J* = 8.0 Hz, 2 × $CH_3$OC-CH-*CH*), 7.25 (d, 2H, *J* = 8.0 Hz, 2 × $CH_3$OC-*CH*-CH). $^{13}$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).

**2-Methoxyphenethyl alcohol**

$^1$H NMR ($CDCl_3$, 200 MHz) δ: 2.81 (s, 1H, OH), 3.43 (s, 3H, $CH_3O$), 3.53 (dd, 2H, *J* = 1.2, 4.1 Hz, $CH_3$O-C$H_2$-CH(OH)), 4.88 (dd, 1H, *J* = 1.2, 1.7 Hz, C*H*(OH)), 7.30–7.40 (m, $5H_{arom}$). $^{13}$C NMR ($CDCl_3$, 200 MHz) δ: 24.12, 26.89, 57.69, 115.62, 129.53, 139.00. MS (EI) *m/z* (%): 144 ($M^+$, 9), 113 (31), 96 (68), 77 (78), 67 (70), 31 (100).

**General procedure for reduction of ketone using rhodium chloride and titanium chloride**

The general procedure for Table 5 was followed except that $RhCl_3$ (10 mg, 0.05 mmol) or $TiCl_4$ (9.5 mg, 0.05 mmol) were used, respectively.

**General experimental procedure for preparation of Mosher esters (example (*S*)-1-phenylethanol)**

(*S*)-1-Phenylethanol (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 mol/L, 20 mL), saturated sodium carbonate solution (20 mL), and water (20 mL), was dried with sodium sulfate, filtered, and the 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.

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