Asymmetric Reduction of Ketones with Catecholborane Using 2,6-BODOL Complexes of Titanium(IV) as Catalysts

Ian Sarvary,[a] Fredrik Almqvist,[b] and Torbjörn Frejd*[a]

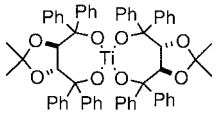
Abstract: Reductions performed with Ti^{IV} complexes of ligands based on bicyclo[2.2.2]octane diols **5** and **6** are effective catalysts in the reduction of prochiral ketones to optically active alcohols, with catecholborane as the reducing agent. Methyl ketones are favored and enantiomeric excesses (*ee*) of $\leq 98\,\%$ have been achieved with acetophenone as the substrate. Several other substrates were tested, among them 2-octanone, which gave 2-octanol in 87 % *ee*. Further details of the method were examined, for example, temperature, solvent composition, amount of molecular sieves (4 Å), and catecholborane quality, as well as the sensitivity of the ligands towards acids. NMR spectroscopic methods were used to gain some insight into the complexes formed between the ligands and $[Ti(O\mathit{i}Pr)_4]$. A dimeric structure is proposed for the pre-catalyst.

Keywords: asymmetric catalysis · diol ligands · ketones · reduction · structure elucidation · titanates

Introduction

One of the most studied transformations in asymmetric catalysis is the asymmetric reduction of prochiral ketones. Several reasons may be found for this interest; the product alcohols are often used as starting materials in the synthesis of drugs, as ligands for catalysis, and in the synthesis of large, complicated target molecules. Moreover, this reaction also serves as a test for new catalysts and their ligand systems. Some of the most efficient catalysts for this transformation utilize oxazaborolidines as ligands and boranes as reductants (CBS reduction).[1, 2] Modifications of these ligands have improved the enantioselectivities so that very high levels can be achieved, often better than 98 % *ee*.[3]

Systems that employ Ti^{IV}-based Lewis acids for reductions with boranes have not been investigated to the same degree. In 1994, Lindsley et al. showed that the addition of $[Ti(O\mathit{i}Pr)_4]$ accelerated the reduction of ketones with several boranes.[4] In their investigation, a Ti-TADDOLate (**1**: TADDOL = $\alpha,\alpha,\alpha',\alpha'$-tetraaryl-1,3-dioxolane-4,5-dimethanol) produced a low *ee* (24 %) in the catalytic asymmetric reduction of acetophenone. Shortly thereafter, Giffels et al. tested several ligands together with $[Ti(O\mathit{i}Pr)_4]$; this lead to increased enantioselectivities.[5] The highest values, $\leq 84\,\%$ *ee*, were obtained with bicyclic TADDOL analogues (**2**) and aromatic ketones as the substrate. However, much lower *ee*'s were obtained with nonaromatic ketones.



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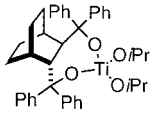

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Other combinations of electron-deficient metals and diol ligands have been tried recently. Huang et al. employed Zn^{II} as the electron-deficient metal center and reached *ee*'s of $\leq 80\,\%$ for aromatic ketones with a polybinaphthol (**3**) as the chiral ligand and catecholborane as the reductant.[6] In addition to the diol ligands mentioned above, a Ga^{III} complex that contained two monothiobinaphthol ligands (**4**) was reported by Ford and Woodward to give moderate-to-high *ee*'s ($\leq 93\,\%$) in the reduction of ketones with catecholborane.[7, 8]

In connection with another project, we became interested to see whether 1,3-diol systems, based on the bicyclo[2.2.2]octane framework, could be used as ligands for the Ti^{IV}-catalyzed reduction of ketones with catecholborane as the reductant. The rigidity of the bicycles and the many possible orientations of metal-coordinating atoms or groups constitute interesting qualities for ligand construction.

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Supporting information for this article is available on the WWW under http://www.wiley-vch.de/home/chemistry/or from the author.

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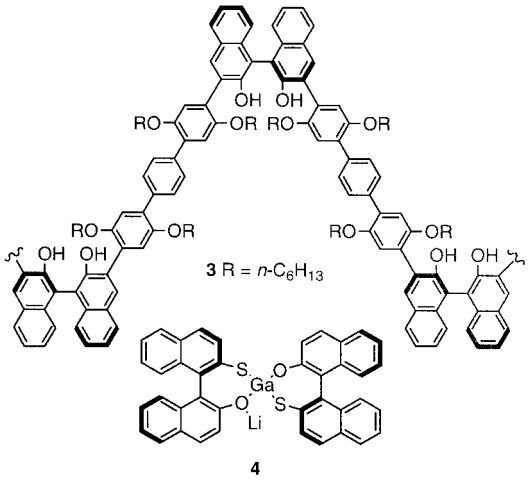

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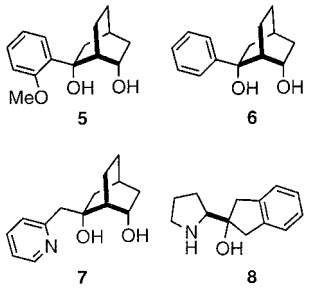
These bicyclic 1,3-diols may form metal chelates with a six-membered ring, in contrast to the seven-membered-ring chelates of the BINOLs[9] and TADDOLs.[10] Thus, different geometries of the metal complexes would result and, in consequence, different properties of the active catalysts could be expected. Although the structure of the catalyst is not known, it was noted in our earlier report that straight-chain aliphatic methyl ketones were reduced with higher *ee*'s by the titanium isopropoxide complexes of the 1,3-diols **5** and **6** as compared to those of **2**.[11] Several other methyl ketones were successfully reduced with high yields and *ee*'s. At the time it seemed necessary to apply rigorous reaction conditions in terms of dryness and quality for all of the reagents (it seemed crucial to distill the [Ti(O*i*Pr)$_4$], as well as the ketones and solvents before use). Moreover, the use of large amounts of molecular sieves seemed necessary to achieve the best results. Despite these measures, we experienced difficulties with the reproducibility. The yields and *ee*'s varied and the catalytic reaction sometimes failed for no apparent reason.

The reaction system has now been investigated thoroughly and several details have been changed with respect to our earlier communication. This provides a reliable and more robust method for catalytic asymmetric reductions of prochiral ketones. In addition, the synthesis of the ligands has been improved.

Results and Discussion

After some experimentation, it was discovered that the order of addition of the reagents was important and the following procedure was found to be reliable. Firstly, [Ti(O*i*Pr)$_4$] was added to a solution of the ligand in *t*BuOMe, that contained the molecular sieves, followed by stirring at 45 °C for 1.5 h. During this time we believe that ligand exchange takes place to generate the catalyst, the structure of which is not known at present (see below). Subsequently, the ketone was added followed by a waiting time of 30 min to allow for the formation of a complex with the chiral Lewis acid. Finally, the reaction mixture was cooled to −20 °C before a pre-cooled solution of catecholborane was added. This generated a reddish reaction mixture, which was quenched after 24 h at −20 °C. The alcohol formed was then isolated by chromatography. A more detailed discussion concerning the reaction conditions is found below.

The ligand selected for this investigation was based on a previous observation that anisyl-BODOL (**5**)[12] produced higher *ee*'s than phenyl-BODOL (**6**) (Scheme 1). Picolyl



5 **6** **7** **8**

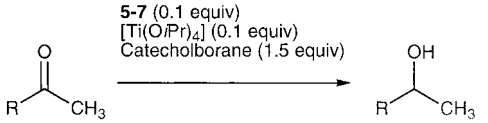
Scheme 1. The BODOL ligands: anisyl-BODOL (**5**), phenyl-BODOL (**6**) and picolyl-BODOL (**7**), and the amino alcohol (**8**) used by Demir et al.[14]

-BODOL (**7**) has a coordinating pyridine nitrogen at approximately the same distance from the hydroxy groups as the oxygen of the methoxy group of **5**. However, reductions performed with **7** as the ligand only resulted in traces of the expected alcohols. When the procedure described above was followed, a gel-like mass was formed on addition of the catecholborane. This impaired the stirring process, and the reaction medium did not seem to allow a proper mixing of the reactants. Therefore, **5** is used as the preferred ligand throughout this work, unless otherwise stated.

Good-to-excellent enantioselectivity was achieved for most of the aromatic methyl ketones used as the substrate when **5** was employed as the ligand in the reductions (entries 1A, 2A, 2B, and 3A–3D, Tables 1–3).

When the nonaromatic part of the ketones was changed to ethyl (entry 2A), the yield decreased; however, it did not significantly influence the enantioselectivity. 1-Tetralone, in which the alkyl chain is tied back into a 6-membered ring, gave the same yield and *ee* as acetophenone (entry 2B). In contrast, a somewhat lower *ee* was found in the case of the five-membered ring in 1-indanone (entry 2C). The sterically

Table 1. Asymmetric reduction of methyl ketones with catecholborane by Ti-BODOLate complexes of **5**, **6**, and **7**.



Entry	Ligand	R	Yield [%][a]	*ee* [%]	Configuration[d]
1A	**5**	Ph	quantitative	96[b]	*R*
1B	**5**	*n*hexyl	82	87[c]	*R*
1C	**6**	Ph	92	89[b]	*R*
1D	**6**	*n*hexyl	80	72[c]	*R*
1E	**7**	Ph	< 5	–	
1D	**7**	*n*hexyl	< 5	–	

[a] Isolated yields. [b] Determined by HPLC on Chiralcel OD-H. [c] Determined by GC analysis of the Mosher ester on Supelco alpha-DEX. [d] Established by optical rotation.

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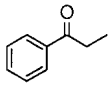
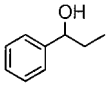
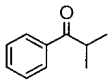
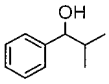
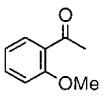
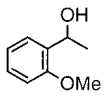
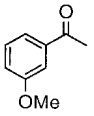
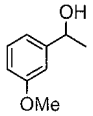
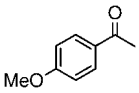
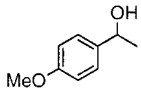
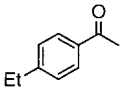
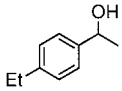
Table 2. Catalytic asymmetric reduction of aromatic ketones.

Entry	Ketone	Alcohol	Yield [%][a]	*ee* [%][b]	Configuration[c]
2A			50	95	*R*
2B			quantitative	96	*R*
2C			89	87	*R*
2D			88	86	*R*
2E			–	–	–

[a] Isolated yields. [b] Determined by HPLC, Chiralcel OD-H. [c] Established by optical rotation.

Table 3. Catalytic asymmetric reduction of aromatic ketones, continued.

Entry	Ketone	Alcohol	Yield [%][a]	*ee* [%][b]	Configuration[c]
3A			Quant.	91	*R*
3B			85	98	*R*
3C			quantitative	94	*R*
3D			93	96	*R*

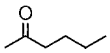
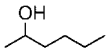
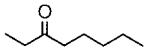
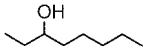
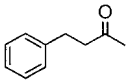
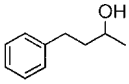
[a] Isolated yields. [b] Determined by HPLC on Chiralcel OD-H. [c] Established by optical rotation.

more hindered 1-acetonaphthone also gave a lower yield and *ee* than acetophenone (entry 2D). In the case of isobutyrophenone (entry 2E), the yield of the alcohol produced was very low, without any noticeable *ee*. The amount of product formed in this case was comparable to that of the background reduction, that is, the reduction with just the catecholborane.[13] Apparently, the catalyst did not seem to tolerate steric hindrance at both α-positions of the carbonyl group. For isobutyrophenone, there was not even a catalytic effect of $[Ti(OiPr)_4]$ without the ligand, at either $-20\,^{\circ}C$ or $0\,^{\circ}C$. Again, low conversions comparable to those of the background reaction were observed; for example, after 12 h reaction time at the higher temperature, only 18% of the alcohol was formed (Table 2).

Four aromatic ketones with substituents in the aromatic ring were tested next; they all gave quite high *ee*'s and yields (Table 3). The two *p*-substituted acetophenones (*p*-methoxy and *p*-ethyl, entries 3C and 3D) gave similar results, with high *ee*'s and yields. In all cases, the (*R*) configuration was obtained.

Reductions catalyzed by chiral, nonracemic Lewis acids frequently do not produce high *ee*'s for linear, nonconjugated ketones. However, some rather high values have been reported. For the CBS reduction, Demir et al. reported the highest *ee* in the reduction of 2-octanone (91% *ee* and 78% yield) that used **8** with BH_3 as the reducing agent.[14] In our experiments, the linear methyl ketones (entries 4A and 1B) produced fairly good *ee*'s. A lower *ee* was obtained when an ethyl ketone, 3-octanone (entry 4B), was the substrate. It is also interesting to note that 1-acetyl-1-cyclohexene (entry 4C) was reduced with a good yield and *ee*. The alkene moiety was intact, showing that there was no over-reduction (Table 4).

Table 4. Catalytic asymmetric reduction of non-benzylic ketones.

Entry	Ketone	Alcohol	Yield [%][a]	*ee* [%]	Configuration[e]
4A			80	85[b]	*R*
4B			91	48[b]	*R*
4C			97	96[c]	*R*
4D			quantitative	56[d]	*R*

[a] Isolated yields. [b] Determined by GC analysis of the corresponding Mosher ester on Supelco alpha-DEX column. [c] Determined by GC, Supelco beta-DEX column. [d] Determined by HPLC on Chiralcel OD-H. [e] Established by optical rotation.

The reduction of benzylacetone (entry 4D) resulted in an unexpectedly low *ee*, although the yield was still high. Lowering the temperature to $-40\,^{\circ}C$ did not lead to any detectable improvement of the *ee*, while the yield remained the same.

Reaction conditions: We generally used a catalyst loading of 10% in our reactions; this amount can be decreased to 2.5% without loss of enantioselectivity or yield, as tested with acetophenone.

In our preliminary experiments, the reaction temperature was set to $-50\,^{\circ}C$, as measured in the external cooling bath (ethanol/solid CO_2). However, a cryostat gave better temperature control and allowed the reaction to be performed at $-20\,^{\circ}C$ without loss of enantioselectivity. At $-10\,^{\circ}C$ the *ee* was lower, and it is therefore recommended to cool the catecholborane solution to $-20\,^{\circ}C$ before addition, in order to achieve the best *ee*'s. No significant change in yield or *ee* was noticed when the reaction temperature was $-40\,^{\circ}C$, but the reaction rate was considerably lower.

Catecholborane was used as a 1M solution in THF, which makes it convenient to use THF as the bulk solvent, although the reactions may be performed in mixtures of THF and diethyl ether, toluene, or *t*BuOMe without significant loss of *ee*'s and yields. To any of the mentioned solutions, varying

0947-6539/01/0710-2160 $ 17.50+.50/0 *Chem. Eur. J.* **2001**, *7*, No. 10

amounts of aliphatic hydrocarbons (pentane, hexane, or heptane) may be used as co-solvents, as long as the substrate does not precipitate. It is also important to ensure that the solvents are well dried.

The ligand sensitivity towards Brönsted acids became evident when performing NMR spectroscopic analysis in $CDCl_3$: the ligands deteriorated. NMR investigations were therefore carried out in solvents in which HCl formation could not occur (toluene, benzene, etc.). Dissolution of the ligands in CH_2Cl_2 for HPLC analysis also caused deterioration. Thus, the use of halogenated solvents should be avoided. As expected, picolyl-BODOL (**7**) was not acid sensitive and its NMR data were recorded in $CDCl_3$.

To estimate the acid sensitivity of **5** and **6**, we studied their decomposition in the presence of HCl, TFA, and HOAc by ^{1}H NMR spectroscopy (integration of the H_c signal at $\delta = 4$). Not surprisingly, on account of its electron-donating substituent in the aromatic ring, **5** was more sensitive than **6** towards acidic conditions. Thus, both of the ligands rapidly deteriorated in contact with 0.1M HCl (Table 5, entries 5A and 5B).

Table 5. Acidic deterioration of **5** and **6** in [D_4]methanol measured by ^{1}H NMR spectroscopy.

Entry	Ligand	Acid	Concn [M]	$t_{1/2}$ [min]
5A	**5**	HCl	0.1	< 3
5B	**6**	HCl	0.1	< 3
5C	**5**	TFA	0.1	< 3
5D	**6**	TFA	0.1	45
5E	**5**	HOAc	0.15	10 %[a]
5F	**6**	HOAc	0.15	no degradation[a]

[a] Observed deterioration during 5 h.

The use of TFA caused the same rapid deterioration of **5**, while **6** could withstand this acid a little better (entries 5C and 5D). Both ligands could withstand prolonged exposure to HOAc. Only small amounts of **5** had deteriorated in this solvent after 5 h, whereas no destruction of **6** was observed, even after longer periods (entries 5E and 5F).

Because of the sensitivity towards Brönsted acids (see above), the reaction mixtures were quenched with saturated NH_4Cl. We previously used HCl, but this caused deterioration of the ligands and resulted in several byproducts that were difficult to separate from the alcohols produced. Quenching with NH_4Cl left the ligand essentially intact, enabling its isolation by chromatography and recycling. Thus, normally > 90 % of the ligand could be isolated after the reductions, but small amounts of impurities accumulated on repeated recovery. As a result, the ligand may be reused only five times before the *ee* starts to drop. An interesting alternative to improve the ligand recycling may be to immobilize it on a solid support; this may also simplify the isolation of the product alcohols. These measures are now being tested.

In our preliminary experiments, the use of quite a large amount of molecular sieves appeared to be important to obtain the best results. Their role could have been to facilitate the ligand–alkoxy exchange, as has been proposed in the gyloxylate-ene reaction that employs [(iPrO)$_2$TiCl$_2$]/BINOL as a catalyst.[15] However, during our further investigations it became evident that there was only a minor dependence on the amount of the molecular sieves. Thus, the reactions may be performed without the molecular sieves, with only a minor loss of *ee* (≈2 %, Table 6); however, in this case the dryness of the solvent is very important. Such a minor effect of the molecular sieves has also been observed in Diels–Alder reactions with [(iPrO)$_2$TiCl$_2$]/TADDOL as the catalyst.[16] We believe that the molecular sieves only act as a drying agent before the addition of [Ti(OiPr)$_4$].

Table 6. Enantiomeric excess (*ee*) versus loading of the 4 Å molecular sieves (ms) in the reduction of acetophenone with **5**.

Entry	ms [g][a]	Yield [%][b]	*ee* %[c]
6A	0.25	98	96.4
6B	0.10	95	95.7
6C	0.05	96	94.3
6D[d]	0	95	94.6

[a] Amount of ms per mmol ketone. [b] Isolated yields. [c] Determined by HPLC on Chiralcel OD-H. [d] The solvents were dried over sodium/benzophenone.

The *ee*'s of the alcohols produced in the reductions was rather insensitive to the *ee* of the ligand. Anisyl-BODOL (**5**), purified only by flash chromatography (95 % *ee*), produced the same *ee* in the reduction of acetophenone as the more rigorously purified sample that had been purified both by chromatography and recrystallization (> 99 % *ee*). When the reaction was carried out with a ligand of 60 % *ee*, the alcohol produced had an *ee* of 90 %. This pronounced positive nonlinear effect[17] is shown in Figure 1.

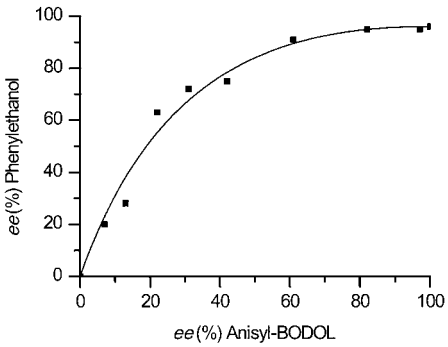


Figure 1. The nonlinear effect in the reduction of acetophenone with catecholborane/[Ti(OiPr)$_4$] in the presence of **5** in various enantiomeric purities.

We also noticed that the reduction was catalyzed by the ligand without addition of [Ti(OiPr)$_4$]; however, the alcohols produced in these reactions showed no or negligible *ee*. It is possible that **5** formed borates with catecholborane and that these may act as Lewis acids, catalyzing the reductions. The yields from these reactions were, however, much lower (50 %)

compared with those obtained in the presence of both the ligand and $[Ti(OiPr)_4]$.

A further modification of our earlier experimental details resulted after we had noticed that the distillation of $[Ti(OiPr)_4]$ was not necessary to achieve good results. Therefore, we used undistilled $[Ti(OiPr)_4]$ in stock solutions (*t*BuOMe) in all reductions. These solutions are stable and can be kept at room temperature for weeks under dry conditions without any noticeable negative influence on the reductions.

The ketones used were usually not distilled and we found that a surprisingly large amount of impurities were tolerated. Ketones kept in our chemical storage for decades were used with good results. Most impurities were removed after the reaction by flash chromatographic purification of the alcohols. A few percent better yields may be obtained by the use of freshly distilled ketones.

After our first report on this reduction, we encountered severe problems with its reproducibility. After elimination of several of the evident possible causes, we were left with the suspicion that the quality of the catecholborane solutions was crucial. ^1H, ^{13}C, and ^{11}B NMR spectroscopy was used to check the quality and large quantities of several species were revealed in those batches of catecholborane that had given inferior results (Figure 2).

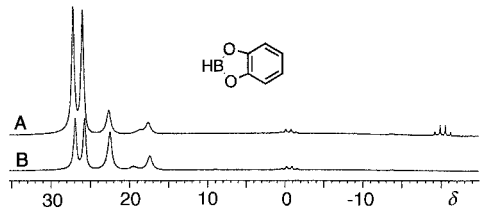
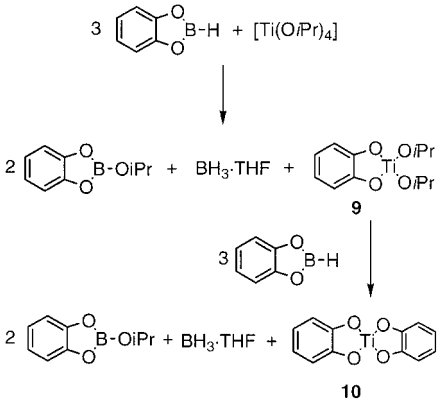


Figure 2. ^{11}B NMR of 50% catecholborane solution (1M in THF) and 50% $[D_8]$toluene. A: Good quality of the catecholborane, B: bad quality of the catecholborane. Both spectra were recorded on a Bruker DRX 500 MHz spectrometer at 25 °C with $Et_2O \cdot BF_3$ in $[D_8]$toluene as the reference.

As seen in the ^{11}B NMR spectrum of the catecholborane solutions of good quality, the resonance of catecholborane itself ($\delta = 26.5$) dominated relative to the signals from the impurities. However, in the catecholborane solutions of bad quality the area of signal was approximately of the same magnitude as those of the impurities. These signals at $\delta = 15-25$ may originate from $B(OR)_3$ compounds formed on unintended contact of catecholborane with water. It should also be noted that the quartet at $\delta = -0.5$ in the solutions of both good and bad quality most likely originated from $BH_3 \cdot THF$. However, the quartet located at $\delta = -20$ in the good quality catecholborane is not identified, but it is evidently an indication of the presence of free BH_3 or another of its complexes.[4, 18] Apparently, the storage and handling of catecholborane solutions must be more carefully controlled and checked than we anticipated. After we had established the importance of the catecholborane quality, the reductions turned out to be very reproducible.

Two other common boranes were tested as reducing agents: 9-BBN and $BH_3 \cdot THF$. The more bulky 9-BBN gave low yields and no *ee*, despite the presence of $[Ti(OiPr)_4]$. The yield was essentially the same as that of the background reaction.[13] In contrast, the use of $BH_3 \cdot THF$ resulted in a rapid reduction of the ketones, but produced no or negligible *ee*.

It has been proposed that the actual reducing agent in the $[Ti(OiPr)_4]$-catalyzed hydroboration of olefins with catecholborane might be BH_3, formed by disproportionation between catecholborane and $[Ti(OiPr)_4]$.[18] Naturally, the question arises as to whether a species formed from BH_3 was the real reducing agent, despite the fact that reductions that used $BH_3 \cdot THF$ directly did not produce any noticeable *ee*. The deep red color observed in our reductions with catecholborane indicated the formation of Ti catecholates; this could be the result of disproportionation (Scheme 2).



Scheme 2. Possible formation of Ti-catecholates and $BH_3 \cdot THF$ from catecholborane and $[Ti(OiPr)_4]$, as proposed by Burgess and van der Donk.[18]

The Ti catecholate formed may be essential for the asymmetric reductions by being part of the catalyst. For example, Ti catecholates **9** or **10** could exchange two ligand sites for the diol of the BODOLs. In order to test this idea, catechol was added to the $[Ti(OiPr)_4]$/BODOL mixture to test whether the Ti catecholate was formed. Indeed, this was indicated since the same red color appeared as in the catecholborane reductions. Next, acetophenone was added and then the mixture was cooled to -20 °C followed by the addition of $BH_3 \cdot THF$ (pre-cooled to -20 °C). This resulted in a rapid consumption of the ketone; however, the alcohol formed was completely racemic. The addition of catechol before or after the acetophenone or a reduction of the temperature further (-50 °C) did not produce any *ee* either. Thus, the red complex, whatever its structure may be, did not have any influence on the stereoselectivity when $BH_3 \cdot THF$ was used as the reductant. We may conclude that the effective reducing agent in our reductions was not BH_3. With this in mind, it is very remarkable that (despite the presence of $BH_3 \cdot THF$ in the good catecholborane solution) the reductions produce such high *ee*'s.

Maturation periods in titanium chemistry are quite common and this was also observed in our reductions. However, NMR experiments did not show any evident changes during several hours after the initial complex formation from a mixture of **5** and $[Ti(OiPr)_4]$ in toluene.

0947-6539/01/0710-2162 $ 17.50+.50/0 *Chem. Eur. J.* **2001**, *7*, No. 10

We generally allowed the mixture of the molecular sieves (4 Å), the ligand, and the solvent to stir for 2–4 hours before the addition of the [Ti(O*i*Pr)$_4$]; although if the solvents had been rigorously dried, this drying period was not necessary. After the addition of [Ti(O*i*Pr)$_4$], a maturation period of 1.5 h at 45 °C, or 10–12 hours at room temperature was used (Table 7, entries 7C and 7F). When this period was less than 1 hour at room temperature, there was a drop in *ee* of 17% (entry 7A). A mixture kept at 45 °C for 30 min or at room temperature (≈21 °C) for 4 h gave approximately the same results (entries 7E and 7B). The maturation period must not be too long, however, because when the mixture was kept at room temperature for more than 24 hours, the reaction became sluggish and gave a considerably lower *ee* (entry 7D). It should be mentioned that sonication of the mixture for 30 min (entry 7G) did not improve the *ee*.

Table 7. The effect of varying the catalyst aging conditions for the reduction of acetophenone with **5**.

Entry	Ageing period [h]	*T* [°C]	*ee* [%][a]	Yield [%][b]
7A	0.5	23	80	73
7B	4	23	89	92
7C	11	23	96.7	95
7D	48	23	75	85
7E	0.5	45	90	90
7F	1.5	45	96.9	97
7G	0.5	25 (sonication)	77	75

[a] Determined by HPLC on Chiralcel OD-H. [b] Isolated yields.

To test the reliability of the method, a reaction was performed on a somewhat larger scale (3 g) for 4-methoxy-acetophenone with a 5% catalyst loading. There was no significant change in either *ee* or chemical yield, relative to the 150 mg experiments. Therefore, we do not expect any special difficulties for the application of the method on even larger scales.

Structure of the pre-catalyst: In the absence of more precise data concerning the structure of the active catalyst, it could still be of interest to acquire structural information of the pre-catalyst, that is the complex(es) formed on mixing the metal component with the ligand. As already discussed, our catalyst showed a nonlinear behavior; the *ee* of the product was considerably higher than that of the ligand. This indicated that the actual catalyst may contain more than one ligand. Unfortunately, the solid material obtained from equimolar portions of **5** and [Ti(O*i*Pr)$_4$] was not suitable for an X-ray analysis. Only amorphous material has hitherto been obtained.

Since the reactions were performed in toluene with good results, we studied the complexes formed in [D$_8$]toluene solution by NMR spectroscopy. Thus, addition of one equivalent [Ti(O*i*Pr)$_4$] to the pure enantiomer **5** resulted in several downfield shifts of the ligand resonances (Figure 3, traces A and B), which suggests coordination to Ti^{IV}. The most noticeable changes were the following: a large downfield shift of the methoxy signal (0.4 ppm), a smaller downfield shift of the aromatic region and a large downfield shift of H$_c$ (0.55 ppm). We also noted that the signal of the bridgehead proton at $\delta = 2.55$ was not shifted (not shown). It was also clear that CH signals of two different *i*PrO groups appeared at $\delta = 4.95$ and 4.3 (Figure 3, trace B). The large downfield shift of the methoxy protons indicated that the ether oxygen acted as an extra coordination site to make **5** a tridentate ligand. This extra coordination site is not available in **6** and may be related to the fact that **6** is a less efficient ligand than **5** in most cases.

As judged by its NMR spectrum, this initially formed complex seemed to be quite stable for several hours and was not effected by the addition of three equivalents of *i*PrOH. However, when this complex was kept in toluene solution for 48 h at room temperature, other complexes were formed. These aged complexes could account for the decreased *ee* and yield mentioned above (Table 7, entry 7D).

Further structural information on the pre-catalyst was obtained by the use of a partially enantiomerically enriched sample of the ligand. If the complex contained two ligands, two diastereomeric complexes would be formed that could be detected by their NMR spectra. We therefore recorded the ^{1}H MNR spectrum of a sample prepared by the addition of one equivalent of [Ti(O*i*Pr)$_4$] to a 40% enantiomerically enriched sample of **5**, which had been obtained by mixing the two enantiomers of **5** in the proper portions (70:30). The resulting ^{1}H NMR spectrum clearly showed that two complexes were formed. They had similar, but different spectral features (Figure 3, trace C). The appearance of the signals at $\delta = 3.6$,

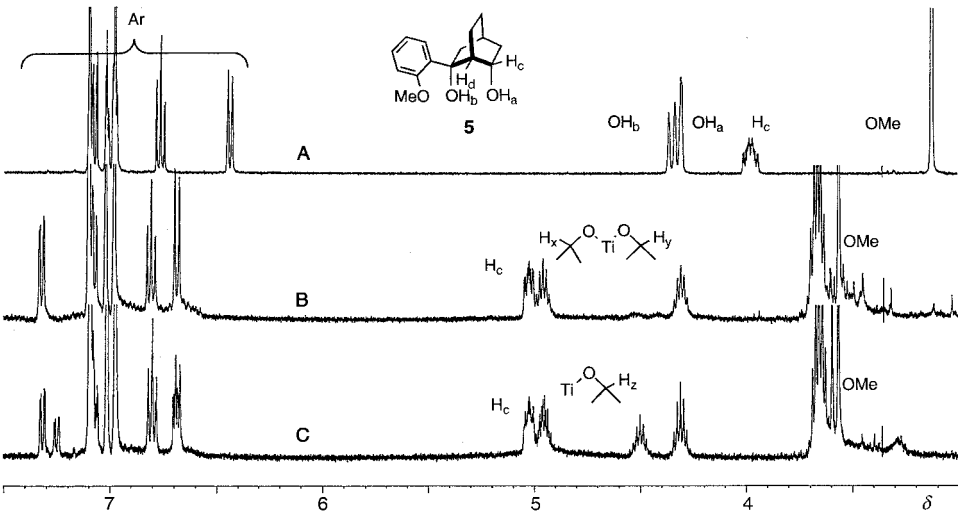
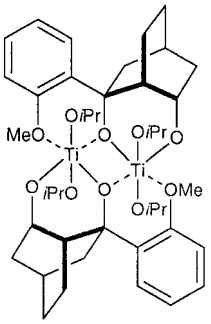


Figure 3. ^{1}H NMR spectra in [D$_8$]toluene of A: free ligand, B: mixture of enantiopure **5** and one equivalent of [Ti(O*i*Pr)$_4$], C: mixture of **5** (40% *ee*) and one equivalent of [Ti(O*i*Pr)$_4$].

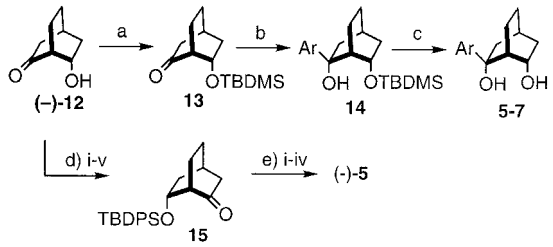
4.5, and 7.25, which have the expected areas of the minor diastereomeric component, indicated a structure which contains two ligands.

Complexes involved in the Sharpless Ti–tartrate-catalyzed asymmetric epoxidation of allylic alcohols have been studied with NMR spectroscopic methods by Potvin et al.[19] These structures have the possibility of extra coordination to Ti from the carbonyl of the ester or amide groups. Despite the fact that there is no X-ray data available for the Ti–diethyltartrate esters, it is assumed that they coordinate in a tridentate fashion. It is also assumed that these complexes are dimers,[20–23] [$(TiL)_2$], although it has been disputed that these are the active catalysts.[24] The situation has been summarized recently.[25] Naturally, similar questions arise in our case. Thus, when all the data is taken into consideration, it seems likely that the dominating species is a rather stable C_2-symmetric complex, such as **11**, which is composed of two ligands and two titanium atoms. However, further spectroscopic evidence must be obtained before a more rigorous structure determination of the pre-catalyst system can be made.



11

Synthesis of the ligands: BODOLs **5**–**7** were synthesized according to a published procedure with some adjustments (Scheme 3).[11] Although this scheme seems straightforward,



Scheme 3. Synthetic route to the BODOL ligands. a) TBDMSCl, DMF, imidazole; b) ArLi, $CeCl_3$, THF, $-78\,^{\circ}C \rightarrow RT$; c) Bu_4NF, THF. Synthetic route to (−)-**5**: d) i) DHP (dihydro-2*H*-pyran), PPTS (pyridinium-*p*-toluenesulfonate), CH_2Cl_2; ii) $NaBH_4$, MeOH/THF; iii) TBDPSCl, DMF, imidazole; iv) PTS, *i*PrOH; v) Swern oxidation; e) i) Bu_4NF, THF; ii) TBDMSCl, DMF, imidazole; iii) ArLi, $CeCl_3$, THF, $-78\,^{\circ}C \rightarrow RT$; iv) Bu_4NF, THF.

some comments should be made. The treatment of the protected keto-alcohol **13** with aromatic Grignard and lithium reagents did not result in a 1,2-addition to give **14** unless $CeCl_3$ was added to the reagent.[26] The most likely explanation for this is the formation of an enolate in the absence of $CeCl_3$ since **13** could be recovered after aqueous work-up (Scheme 3).

It was also necessary to introduce the lithium by direct metalation, since ArLi syntheses based on a halogen–metal exchange with BuLi were nonproductive, even in the presence of $CeCl_3$. The reason for this is unclear; however, it is possible that LiBr is formed in a Wurtz coupling between ArLi and BuBr and then may form an "ate" complex with $CeCl_3$ to give $Li^+[CeCl_3Br]^-$, which may not give a useful Ar–Ce reagent.

Our previously described method of inversion of (−)-**12** gave access to (+)-**12**.[27] During these transformations, we observed that the ArLi–$CeCl_3$ reaction with **15**, which has a bulky TBDPS (*tert*-butyldiisopropylsilyl) protective group, did not work under the same reaction conditions that were used for the synthesis of **14**. The starting material was recovered to a large extent. Therefore, it was necessary to change the protective group from TBDPS to TBDMS (*tert*-butyldimethylsilyl) for the conversion of **15** to (−)-**5**.

Conclusion

The presented enantioselective reduction conditions are mild and provides a useful method for the catalytic asymmetric reduction of ketones. It is also worth noting that, although sensitive towards branching at the carbonyl α-position, the Ti–anisyl-BODOL complex (Ti-**5**) is quite substrate tolerant and produced good enantioselectivities and chemical yields for a wide range of substrates. Based on preliminary structural data, a tentative structure of the pre-catalyst is suggested to be the dimeric complex **11**.

Experimental Section

General remarks: GC analyses was performed with either an alpha- or beta-DEX column (Supelco, 30 m × 0.25 mm i.d. × 0.25 μm film thickness). HPLC analyses were performed on a Chiralcel OD-H column (0.46 cm × 25 cm, 5 μm particle size), with *i*PrOH and hexane as the eluents. NMR spectra were recorded at 400 MHz (Bruker DRX spectrometer), if not stated otherwise. Optical rotations were measured with a Perkin–Elmer 241 LC polarimeter at 23 °C. Preparative chromatographic separations were performed on normal-phase silica gel 60 (0.035–0.070 mm, Matrex Amicon). Thin-layer chromatography was performed on TLC plates precoated with silica gel 60 F-254, 0.25 mm (Merck). After elution, the TLC plates were visualized with UV light followed by spraying with a solution of *p*-methoxybenzaldehyde (26 mL), glacial acetic acid (11 mL), concentrated sulfuric acid (35 mL), and 95% ethanol (960 mL), followed by heating. All solvents were dried over 4 Å molecular sieves (5% m/w) for 24 h prior to use, unless stated otherwise. The molecular sieves were activated at 400 °C for 6 h and then allowed to cool under argon. [$Ti(OiPr)_4$] (97%, Aldrich), phenyllithium (2.0 M in benzene/ether, Aldrich), and catecholborane (1 M in THF, Aldrich) were used as delivered. In our laboratory, the catecholborane solutions were stored at −20 °C. The reductions have not been optimized for any particular reaction; however, the temperature selected was that which was best suited to acetophenone.

(1*R*,2*R*,4*S*,6*S*)-2-(2-Anisyl)-bicyclo[2.2.2]octane-2,6-diol (5): $CeCl_3$ (3.6 g, 9.7 mmol) was placed in a round-bottomed flask and dried at 110 °C under vacuum (< 1 mm Hg) overnight (14 h). The flask was cooled on ice under Ar, then ice-cold, dry THF (25 mL) was added. The resulting mixture was stirred for 5 min at 0 °C and then for at least 4 h at RT before use. This should result in a "milky suspension" without any large fragments.[28] The suspension was then cooled to −78 °C, followed by addition of anisyllithium [prepared by addition of *n*BuLi (1.6 mL, 12 mmol), to anisole (1.6 mL, 15 mmol) in THF(20 mL)] and the resulting yellow mixture was stirred for 1 h. A solution of (1*R*,4*S*,6*S*)-6-(*t*-butyldimethylsilyloxy)bicyclo[2.2.2]octane-2-one (**13**, 1.5 g, 5.9 mmol) in THF (5 mL) was then added, and the mixture was allowed to reach RT overnight. A saturated aqueous solution of NH_4Cl (25 mL) was added, the phases were separated, and the water phase was extracted with ether (2 × 20 mL). The combined organic phases were dried (Na_2SO_4) and filtered through a pad of SiO_2, in order to remove

0947-6539/01/0710-2164 $ 17.50+.50/0 *Chem. Eur. J.* **2001**, *7*, No. 10

inorganic cerium salts. The solvent was removed under vacuum, and the residue was diluted with cold, dry THF (30 mL). Bu_4NF (3 g, 9.5 mmol) was added to this solution and the deprotection was monitored by TLC. The reaction was complete after 4 hours. The reaction mixture was concentrated under reduced pressure to yield an orange oil, which was diluted with EtOAc (50 mL). The organic solution was washed with brine (3×20 mL) and dried (Na_2SO_4). Filtration and removal of the solvent under reduced pressure gave an oil that was purified by flash chromatography (SiO_2, heptane/EtOAc 50:50, $R_f = 0.26$). The resulting clear syrup crystallized in the refrigerator to give 1.18 g (81%) of white crystals, which were recrystallized (*t*BuOMe/hexane, 20:80) to afford **5**, m.p. 82–83 °C. ^{1}H NMR data in $CDCl_3$ were identical with those previously reported.[11] However, since we found that the compound was acid sensitive, we give here the NMR data in benzene: ^{1}H NMR ([D$_6$]benzene, 25 °C): $\delta = 7.08$ (dd, J(H,H) = 1.65, 7.74 Hz, 1H), 7.01 (ddd, J(H,H) = 1.65, 7.43, 8.2 Hz, 1H), 6.83 (td, J(H,H) = 7.47, 1.2, Hz, 1H), 6.45 (dd, J(H,H) = 1.2, 8.2 Hz, 1H), 4.55 (d, J(H,H) = 11.2 Hz, 1H; OH), 4.45 (s, 1H; OH), 4.07 (m, 1H; C*H*OH), 3.05 (s, 3H; OMe), 2.56 (m, 1H), 2.2 (m, 2H), 2.02 (dt, J(H,H) = 14.7, 2.5 Hz, 1H), 1.93 (m, 1H), 1.25 (m, 2H), 1.08 (m 2H); ^{13}C NMR ([D$_6$]benzene, 25 °C): $\delta = 157.9$, 135.8, 128.2, 126.8, 121.0, 112.0, 78.3, 71.0, 54.8, 42.8, 39.8, 39.5, 26.5, 23.5, 21.8.

(1*R*,2*R*,4*S*,6*S*)-2-Phenyl-bicyclo[2.2.2]octane-2,6-diol (6): This compound was prepared by the procedure described for **5** except that phenyllithium in benzene/ether was used instead of anisyllithium. Flash chromatography (SiO_2, heptane/EtOAc 2:1, $R_f = 0.21$) gave a clear syrup which crystallized in the refrigerator (78%). Recrystallization from *t*BuOMe/hexane (20:80) gave **6**, m.p. 85–87 °C. ^{1}H NMR data in $CDCl_3$ were identical to those previously reported.[11] However, since we found that the compound was acid sensitive we give here the NMR data in benzene solution: ^{1}H NMR ([D$_6$]benzene, 25 °C): $\delta = 7.35$ (br d, J(H,H) = 6.6 Hz, 2H), 7.2 (br t, J(H,H) = 7.7 Hz, 2H), 7.1 (tt, J(H,H) = 7.3, 1.9 Hz, 1H), 4.1–3.7 (br s; 1H; OH), 3.8 (m; 1H; CH), 3.8–3.5 (br d, 1H; OH), 2.19 (m, 1H), 1.99 (m, 1H), 1.9 (m, 1H), 1.76 (m, 1H), 1.66 (m, 2H), 1.2–0.84 (m, 4H); ^{13}C NMR ([D$_6$]benzene, 25 °C): $\delta = 148.0$, 128.4, 127.3, 126.8, 76.9, 71.0, 42.7, 42.5, 38.3, 26.4, 23.3, 20.7.

(1*R*,2*R*,4*S*,6*S*)-2-(2-Picolyl)-bicyclo[2.2.2]octane-2,6-diol (7): This compound was prepared by the procedure described for **5** except that 2-picolyllithium was used instead of anisyllithium. Flash chromatography (SiO_2, heptane/EtOAc 20:80, $R_f = 0.29$) resulted in a light yellow syrup (77%). $[\alpha]_D^{21} = 23.8$ ($c = 6.5$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 25 °C): $\delta = 8.37$ (br d, J(H,H) = 4.7 Hz, 1H), 7.66 (td, J(H,H) = 7.7, 1.8 Hz, 1H), 7.2 (dd, J(H,H) = 7.7, 5.6 Hz, 1H), 7.16 (d, J(H,H) = 7.8 Hz, 1H), 4.93 (br s, 1H; OH), 3.8 (br s, 1H; CH), 2.97 (ABq, J(H,H) = 14.9 Hz), 2.13 (m, 1H), 1.81 (m, 2H), 1.65–1.5 (m, 4H), 1.4–1.20 (m, 4H); ^{13}C NMR ($CDCl_3$, 25 °C): $\delta = 159.5$, 148.6, 137.6, 124.8, 122.2, 76.5, 71.0, 47.1, 44.0, 39.3, 38.9, 26.1, 23.6, 21.3; HRMS (FAB+, direct inlet) calcd: 234.1494; found: 234.1493.

(±)-*endo*-6-Hydroxy-bicyclo[2.2.2]octane-2-one: The synthetic sequence was adopted from the literature.[29] The first step, the synthesis of 3-allyl cyclohexanone, was performed according to the literature[30] from 2-cyclohexenone (3.0 g, 31 mmol), $TiCl_4$ (3.7 mL, 33 mmol), and allyltrimethylsilane (5.0 mL, 32 mmol), with the exception that after the addition of water (200 mL) the mixture was filtered through Celite to remove the thick precipitate of titanium oxide. In the second step, the crude product from above (4 g) was diluted with MeOH (100 mL) and cooled to −76 °C, and O_3 was bubbled through the stirred solution until it turned blue-violet. The solution was purged with argon gas until colorless, followed by the addition of methyl sulfide (5.0 mL, 68 mmol). The temperature was then allowed to rise slowly to reach RT (over 14 h). Concentration under reduced pressure gave an yellow oil (4.3 g) that was diluted with acetone (40 mL) and HCl (40 mL, 1M). This solution was heated under reflux (1 h) and then allowed to cool to room temperature. The mixture was diluted with brine (75 mL) and then extracted with EtOAc (4×25 mL). The combined organic phases were washed with saturated $NaHCO_3$ (25 mL) and brine (25 mL), and then dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The oily residue was purifed by chromatography (SiO_2, heptane/EtOAc 1:3) to yield the compound as a white solid (0.93 g, 6.5 mmol, 21%). M.p 200–203 °C (sublimation and decomp); lit.: m.p. 201[31] and 165.3–167.2[32]). ^{1}H NMR and ^{13}C NMR spectral data were in full agreement with those reported.[32]

(±)-*o*-Anisyl-2,6-BODOL: The same procedure was used as for the synthesis of (1*R*,2*R*,4*S*,6*S*)-2-(2-anisyl)-bicyclo[2.2.2]octane-2,6-diol, except that racemic *endo*-6-hydroxy-bicyclo[2.2.2]octan-2-one was employed instead of the optically active material. The product was obtained as white crystals, m.p. 101–102 °C. ^{1}H and ^{13}C NMR spectral data were identical to those of **5**.

General method for the reduction of the ketones: A solution of the ligand (25 mg, 0.1 mmol) in *t*BuOMe was dried by stirring with activated 4 Å molecular sieves (0.4 g) for 2 h at room temperature. Then [Ti(O*i*Pr)$_4$] (0.5 mL, 0.19 M in *t*BuOMe, 95 μmol) was added. The mixture was kept for 1.5 h at 45 °C before addition of the ketone (1 mmol, neat or dissolved in a minimum amount of THF). The wall of the reaction vessel was rinsed with hexane (0.75 mL) to ensure that all of the ketone had been added to the reaction mixture. The mixture was stirred at room temperature for another 30 min and was then cooled to −20 °C. Cold (−20 °C, from the freezer) catecholborane (1.5 mL, 1M in THF, 1.5 mmol) was added, and the reaction was monitored by TLC. After 24 h, only traces of the starting material could be detected. Aqueous saturated NH_4Cl (5 mL) was added at −20 °C to the reaction mixture, which was then stirred for 10 min. Diethyl ether (25 mL) and another portion of aqueous saturated NH_4Cl (15 mL) were added at RT, followed by stirring for 1 h. The phases were separated, and the aqueous phase was extracted with diethyl ether (2×25 mL). The combined ether phases were washed with NaOH (1M, 2×25 mL), dried (Na_2SO_4), and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (SiO_2, diethyl ether/pentane, and then diethyl ether) to elute the unreacted ketone, then the alcohol, and then the ligand. This procedure was used for the preparation of the following alcohols: (1*R*)-1-phenylethanol (entry 1A), (2*R*)-octan-2-ol (entry 1B), (1*R*)-1-phenyl-propan-1-ol (entry 2A), (1*R*)-1,2,3,4-tetrahydronaphth-1-ol (entry 2B), (1*R*)-indan-1-ol (entry 2C), (1*R*)-1-(1-naphthyl)-ethanol (entry 2D), (1*S*)-1-(2-methoxyphenyl)-ethanol (entry 3A), (1*R*)-1-(3-methoxyphenyl)-ethanol (entry 3B), (1*R*)-1-(4-methoxyphenyl)-ethanol (entry 3C), (1*R*)-1-(4-ethylphenyl)-ethanol (entry 3D), (2*R*)-hexan-2-ol (entry 4A), (3*R*)-octan-3-ol (entry 4B), (1*R*)-1-(cyclohex-1-en-1-yl)-ethan-1-ol (entry 4C), (2*R*)-4-phenylbutan-2-ol (entry 4D). For further details see Tables 1–7 and the Supporting Information.

Reductions for the investigation of the nonlinear effect: Samples that contained the ligand in different enantiomeric compositions were prepared as stock solutions (0.10 M) by mixing the appropriate amounts of the racemate and the pure enantiomer in *t*BuOMe. The enantiomeric compositions of the product and the purity of the ligand samples were determined by HPLC analysis (Chiralcel OD-H, hexane/*i*PrOH 80:20) before the reductions, and for the ligand also after the reductions. This showed that the ligand retained its enantiomeric composition.

Acknowledgements

We thank the Swedish Natural Science Research Council, the Crafoord Foundation, the Knut and Alice Wallenberg Foundation, and the Royal Physiographic Society in Lund (Sweden) for financial support.

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Note added in proof: For a recent method for the enantioselective reduction of linear ketones see: B. A. Persson, A. L. E. Larsson, M. Le Ray, J.-E. Bäckvall, *J. Am. Chem. Soc.* **1999**, *121*, 1645 – 1650.

Received: August 4, 2000
Revised version: December 21, 2000 [F2647]

  0947-6539/01/0710-2166 $ 17.50+.50/0