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Transition metal catalyzed hydroboration

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Rice University, 1994
RICE UNIVERSITY

TRANSITION METAL CATALYZED HYDROBORATION

by

WILFRED VAN DER DONK

A THESIS SUBMITTED IN PARTIAL FULFILLMENT
OF THE REQUIREMENTS FOR THE DEGREE
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ABSTRACT

Transition Metal Catalyzed Hydroboration

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Wilfred van der Donk

Model studies on rhodium catalyzed hydroborations of sterically unbiased alkenes with catecholborane provided evidence for the role of dπ-π bonding in these transformations. Catalyzed hydroborations of 5-substituted-2-methylene adamantanes occurred predominantly from the face opposite the most electron withdrawing group, while uncatalyzed hydroborations gave the reversed selectivities.

Deuterium labeling studies on rhodium catalyzed hydroborations of allylic silyl ethers revealed some new mechanistic features. Vinylboronate esters were produced in these transformations in addition to the expected alkylboronate esters. The formation of such dehydrogenative borylation products can be explained by alkene insertion into the rhodium-boron bond of a metal complex produced from oxidative addition of catecholborane to the catalyst. Oxidation of the catalyst can have a pronounced effect on the product distributions. Catalyzed hydroboration of phenylethene produced 1-phenylethanol with freshly prepared Wilkinson's catalyst, but 2-phenylethanol was the predominant product if the catalyst had been in contact with oxygen.

Enantioselective hydroboration of prochiral alkenes in the presence of chiral phosphine ligands produced optically active alcohol products. The best results were obtained with DIOP or BDPP ligands. Asymmetric amplification was not observed in these reactions.

Bis(cyclopentadienyl)[tetrahydroborato(1-)]titanium promotes the addition of borohydride to alkenes. In the reaction of phenylethene the predominant products were tetraalkyborates. 1-Decene and β-pinene gave organoboron products that are involved in
a dynamic equilibrium with borohydride. A mechanism is proposed which explains the observed experimental characteristics of this reaction.

(o-Aminophenyl)diphenylphosphine was prepared from aniline in two steps. Optically pure (S) \( N-(\text{tert-} \text{butoxycarbonyl})-2\)-amino-3-diphenylphosphinoboranepropyl (\( p \)-nitrophenyl)carbonate was prepared from L-serine.
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List of Abbreviations

acac  acetylacetonate
Asp  aspartic acid
9-BBN  9-borabicyclo[3.3.1]nonane
BDPP  2,4-bis(diphenylphosphino)pentane
BINAP  2,2'-bis(diphenylphosphino)-1,1'-binaphthalene
Boc  tert-butyloxycarbonyl
BOP  benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate
Bz  benzoyl
cat  catechol
Cp  cyclopentadienyl
COD  cyclooctadiene
COE  cyclooctene
m-CPBA  m-chloroperbenzoic acid
Cy  cyclohexyl
DABCO  1,4-diazabicyclo[2.2.2]octane
DIBAL-H  diisobutylaluminum hydride
DIEA  diisopropylethylamine
DIOP  2,3-O-isopropylidene-2,3-dihydroxy-1,4-
bis(diphenylphosphino)butane
DIPAMP  1,2-ethanediylbis[(o-methoxyphenyl)phenylphosphine]
DMAP  4-dimethylaminopyridine
DME  dimethoxyethane (ethylene glycol dimethylether)
DMS  dimethylsulfide
dppe           diphenylphosphinoethane
EapBH₂         mono(ethylapoisopinocampheyl)borane
Fmoc           9-fluorenylethoxycarbonyl
Glu            glutamic acid
HOBt           hydroxybenzotriazole
HOMO           Highest Occupied Molecular Orbital
d¹IcrBH₂       dicaranylborane
Ipc₂BH         di(isopinocampheyl)borane
Lgf₂BH         dilongifolyborane
LimBH          limonylborane
LUMO           Lowest Unoccupied Molecular Orbital
Lys            Lysine
MDBH₂          2-(1,3-dithianyl)myrtanylborane
NBD            norbornadiene
PapBH₂         mono(phenylapoisopinocampheyl)borane
Siam           siamyl
TBS            tert-butyldimethylsilyl
Tf             trifluoromethylsulfonyl
TFA            trifluoroacetic acid
Thx            thexyl
TMEDA          tetramethylethylenediamine
TMS            trimethylsilyl
Chapter 1. Asymmetric Hydroboration

1.1. Introduction

Hydroboration has become indispensable in synthetic organic chemistry due to several factors. First, organoboranes from hydroboration of alkenes are produced by cis-stereospecific addition of the boron-hydride across the carbon-carbon double bond (equation 1.1). This characteristic makes the transformation useful for creation of stereocenters with high fidelity. Second, a large arsenal of hydroboring reagents has been developed, so that a wide spectrum of reactivities is available to effect a desired transformation.\(^1\)\(^2\) Finally, after the hydroboration step the organoboron products can be converted into a variety of functionalities including alcohols, amines,\(^3\) halides\(^4\) and homologation products (e.g. Scheme 1.1).\(^5\)

\[
\begin{align*}
\text{R}_2\text{BH} & \quad \rightarrow \\
\text{H} & \quad \text{R}_2\text{BH} \quad \text{(1.1)}
\end{align*}
\]

\[
\begin{align*}
\text{(a) R}_1\text{R}_2\text{BR}_2 & \quad \xrightarrow{\text{NaO}OH} \\
\begin{bmatrix}
\text{R}_1\text{R}_2\text{BR}_2 \\
\text{O} & \text{H}
\end{bmatrix}^{-} & \quad \rightarrow \ \\
\text{R}_1\text{R}_2 & \quad \text{OH}
\end{align*}
\]

\[
\begin{align*}
\text{(b) R}_1\text{R}_2\text{BR}_2 & \quad \xrightarrow{\text{I}_2} \\
\text{R}_1\text{R}_2 & \quad \text{I}
\end{align*}
\]

Scheme 1.1. (a) Conversion of organoboranes into alcohols generally occurs with retention of configuration at carbon; (b) however, halogenation takes place with inversion of stereochemistry.
This chapter focuses on the scope and limitations of hydroboration for stereocontrolled creation of new chiral centers. It gives an overview of current methodologies and provides a context for the results that are discussed in this thesis. In the hydroboration of an alkene, chiral centers can be formed at the position where the boron atom adds, at the adjacent carbon atom, or both (Scheme 1.2). An inherent problem frequently encountered in hydroborations of unsymmetrical, 1,2-disubstituted alkenes is regioselectivity (Scheme 1.2b). Two products may be formed, hence purification of the crude reaction mixtures may be required, reducing the yield of the desired regioisomers. This is not an issue however for symmetrically disubstituted 1,2-alkenes.

![Chemical Structures](image)

**Scheme 1.2.** Creation of new chiral centers in hydroborations of different alkenes.

Face selectivities in hydroboration reactions can be controlled by use of chiral hydroborating agents (reagent-controlled diastereoselectivity, section 1.2), or by asymmetric centers already present in the substrate (substrate-controlled diastereoselectivity, section 1.3). The final section of this chapter focuses on applications
of transition metal catalyzed hydroboration that were reported prior to the outset of the work described in this thesis. Several other relevant publications on catalyzed hydroborations have appeared since; these are discussed in relation to the findings in our laboratory in the appropriate chapters.

1.2 Reagent-Controlled Diastereoselectivity in Hydroborations

1.2.1 Scope and Limitations

Reagent-controlled diastereoselective reactions of prochiral substrates rely on a chiral reagent to induce asymmetry. For instance, reaction of a prochiral alkene with a chiral borane can lead to two different diastereomeric organoboranes. The transition state for production of the desired isomer must be favored over that for the undesired isomer for effective asymmetric induction to occur.

\[
\begin{align*}
\text{cis} & \quad \text{trans} \\
R^1R^2R^3R^4 & \quad R^1R^2R^3R^4 \\
R^1 & \quad R^1 \\
R^2 & \quad R^2 \\
R^3 & \quad R^3 \\
R^4 & \quad R^4
\end{align*}
\]

Reagent-controlled diastereoselective hydroborations have one inherent disadvantage: they require a stoichiometric amount of a chiral auxiliary. Besides the obvious cost factors, this means that the products obtained after oxidation are contaminated with materials derived from the chiral auxiliary. Consequently, purification of the crude reaction products is usually required.

1.2.2 Stereodiscriminating Hydroborating Reagents from Optically Active Alkenes

1.2.2.1 Syntheses and Properties of the Reagents

Most of the chiral hydroborating reagents used to date are alkylboranes produced via stereoselective hydroborations of naturally occurring optically active
alkenes. Terpenes and terpene derivatives have been used extensively due to their ready availability and the high face selectivities observed in the hydroboration of these cyclic alkenes. Figure 1.1 shows several chiral dialkylboranes prepared in this way.

![Chemical structures](image)

Figure 1.1. Asymmetric hydroborating agents and the terpenes from which they were derived.
In 1961, Brown described the first synthesis of a chiral hydroborating agent, diisopinocampheylborane (Ipc₂BH). In the subsequent three decades Ipc₂BH has become the most widely used chiral hydroborating agent in organic synthesis. One compelling advantage of Ipc₂BH over some similar reagents that have been developed, is the relative simplicity of its synthesis. Both enantiomers of the reagent can be conveniently prepared from borane and the readily available terpene, α-pinene. Commercial α-pinene is not optically pure, but it was found that reaction mixtures that are left for prolonged periods of time produced Ipc₂BH of higher enantiomeric purity than the α-pinene from which it was derived. This behavior was attributed to preferential incorporation of the major pinene enantiomer into the crystalline complex in an equilibrium process (equation 1.2), while the minor isomer accumulates in solution. During the synthesis, BH₃ and α-pinene reacted rapidly to form triisocampheylidiborane (Ipc₂B(μ-H)₂BHipc). Unfortunately, conversion of (Ipc₂B(μ-H)₂BHipc) to sym-tetraisopinocampheylidiborane (Ipc₂B(μ-H)₂BIPC₂) was slow, especially with dilute BH₃ solutions. Concentrated BH₃ in THF provided faster reaction times, but is not commercially available and is relatively hard to prepare. This problem was overcome by use of the stable borane-dimethylsulfide complex (BH₃·SMe₂), provided that the dimethylsulfide liberated during the reaction is removed by applying a vacuum. Using this procedure, the solid product can be obtained in 98 % ee or higher from α-pinene of only 92 % optical purity.

\[
(+\text{Ipc})\cdot\text{B}^\text{(-Ipc)}\cdot\text{H} \rightleftharpoons (+\text{Ipc})\cdot\text{B}^\text{(-Ipc)}\cdot\text{H} \rightleftharpoons (+\text{Ipc})\cdot\text{B}^\text{(-Ipc)}\cdot\text{H} \geq 98\% \text{ ee} \quad (1.2)
\]
The size of Ipc$_2$BH causes very sluggish additions to trisubstituted alkenes and otherwise sterically hindered substrates.$^9$ During these reactions Ipc$_2$BH partially disproportionates into IpcBH$_2$ and $\alpha$-pinene. Unfortunately, the IpcBH$_2$ produced reacts more rapidly with the substrates than Ipc$_2$BH, and gives products with the opposite configuration, so reducing the optical yields of the products (equation 1.3).$^9$ Disproportionation of Ipc$_2$BH proceeds more rapidly in THF than in diglyme, hence better enantioselectivities are often obtained in the latter solvent.

There have been numerous attempts to improve on the performance of Ipc$_2$BH. For instance, the chiral boraheterocycle limonylborane$^{10}$ (LimBH) was prepared from the cyclic hydroboration of limonene with monochloroborane etherate (CIBH$_2$.Et$_2$O) followed by reaction with lithium aluminum hydride (equation 1.4). The reagent exists as a relatively stable dimer. It is usually formed in situ from LimBCl, and, since limonene is readily available in both optical antipodes, both enantiomers of limonylborane can be prepared.
The other chiral dialkylboranes shown in Figure 1.1 were prepared via procedures similar to that described for Ipc₂BH. Only one optical isomer of longifolene, 2-carene and 3-carene is commercially available, therefore both enantiomeric forms of Lgf₂BH, 2-₅Ir₂BH and 4-₅Ir₂BH cannot be obtained, limiting their use in asymmetric hydroboration.

All dialkylboranes shown in Figure 1.1 tend to react very slowly with sterically demanding alkenes, so chiral monoalkylboranes have been investigated for their potentially higher reactivities. Attempted syntheses of IpcBH₂ by controlled addition of one equivalent of BH₃-THF to α-pinene derivatives produced significant amounts of Ipc₂BH. For instance, equilibration of BH₃-THF solutions with α-pinene for prolonged periods (ca 96 h at 25 °C) or at elevated temperatures (ca 50 °C) gives about 80% of IpcBH₂ and 5% of Ipc₂BH and BH₃-THF.¹¹ However, better, but more difficult, procedures for preparation of pure IpcBH₂ have been described. Thus, treatment of Ipc₂BH with TMEDA generated adduct I as a crystalline solid with 100% optical purity (equation 1.5). This material was converted into IpcBH₂ by reaction with BF₃·Et₂O, and the insoluble BF₃-amine adducts were easily removed by filtration (equation 1.6).¹² The reduced steric requirements of IpcBH₂ compared with Ipc₂BH indeed facilitated the hydroboration of trisubstituted and other hindered alkenes, and elimination of α-pinene was not a problem in these reactions.¹³
Figure I.2. Monoalkylboranes derived from hydroboration of α-pinene derivatives.

The IpcBH₂-homologues mono(ethylapoisopinocampheyl)borane (EapBH₂)¹⁴ and mono(phenylapoisocampheyl)borane (PapBH₂)¹⁵ were prepared via analogous sequences from (-)-2-ethylapinene and (-)-2-phenylapinene. These alkenes are not readily available and were synthesized from (-)-nopol and (-)-β-pinene, respectively (equations 1.7 and 1.8).
Another hydroborating reagent, 2-(1,3-dithianyl)myrtenylborane (MDBH₂), was obtained via hydroboration of alkene 2,¹⁶ prepared in two steps from myrtenol in 62 % yield (equation 1.9). Unlike the α-pinene derivatives discussed so far, the BH₃ hydroboration of 2 stopped at the monohydroboration stage. Optically pure MDBH₂ was obtained by recrystallization of the crude reaction product as a stable, monomeric solid that is not very sensitive to moisture even in the uncomplexed form. The ¹¹B NMR signal for this compound indicates significantly more shielding than expected for an uncomplexed monoalkylborane. These observations strongly implicate coordination of one of the sulfur lone pairs to the boron (Figure 1.3). Like other borane-sulfide complexes, MDBH₂ is a hydroborating reagent with good stability; it can be stored under an inert atmosphere at 0 °C for more than a year. A
disadvantage of this reagent is that while (-)-myrtenol is a common, commercially available natural product, (+)-myrtenol must be prepared from α-pinene.16

$$\text{(-)-myrtenol} \xrightarrow{\text{Ph}_3\text{PBr}_2} \text{Br} \xrightarrow{\text{Li}} \text{S} \xrightarrow{\text{BH}_3-\text{THF}} \text{MDBH}_2$$

Figure 1.3. Possible coordination of sulfur to boron in MDBH$_2$.

1.2.2.2 Effectiveness of the Reagents in Diastereoselective Reactions

Table 1.1 presents data for the hydroboration of five alkenes with chiral mono- and dialkylboranes. Excellent results are obtained for the reaction of cis-2-butene with Ip$_2$BH and 2-$d$Ir$_2$BH and high levels of asymmetric induction are not limited to this substrate, as both reagents perform well with a variety of other cis-alkenes.17,18 The costs of (+)-α-pinene and (+)-3-carene are comparable, but both enantiomers are only readily available for α-pinene.
Table 1.1. Asymmetric Hydroboration with Chiral Mono- and Dialkylboranes.

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Me(-)Me</th>
<th>Me(-)Me</th>
<th>Me(-)Me</th>
<th>Me(-)Me</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product</td>
<td>OH(\text{Me})</td>
<td>OH(\text{Me})</td>
<td>Me(-)Me</td>
<td>HO(\text{Me})</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reagent</th>
<th>% ee (config.)</th>
<th>% ee (config.)</th>
<th>% ee (config.)</th>
<th>% ee (config.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(+)Ipc(_2)BH</td>
<td>98 (R)</td>
<td>13 (S)</td>
<td>14 (S)</td>
<td>21 (R)</td>
</tr>
<tr>
<td>LimBH</td>
<td>55 (R)</td>
<td>59 (R)</td>
<td>67 (R)</td>
<td>5 (R)</td>
</tr>
<tr>
<td>(+)Lgf(_2)BH</td>
<td>78 (R)</td>
<td>25 (S)</td>
<td>70 (R)</td>
<td>1.5 (S)</td>
</tr>
<tr>
<td>2-(\text{d}l)cr(_2)BH</td>
<td>93 (S)</td>
<td>30 (R)</td>
<td>37 (S)</td>
<td>15 (S)</td>
</tr>
<tr>
<td>4-(\text{d}l)cr(_2)BH</td>
<td>50 (R)</td>
<td>40 (S)</td>
<td>0</td>
<td>5 (R)</td>
</tr>
<tr>
<td>(+)IpcBH(_2)</td>
<td>24 (S)</td>
<td>73 (S)</td>
<td>53 (R)</td>
<td>1 (S)</td>
</tr>
<tr>
<td>EapBH(_2)</td>
<td>30 (R)</td>
<td>76 (R)</td>
<td>68 (R)</td>
<td>2 (R)</td>
</tr>
<tr>
<td>PapBH(_2)</td>
<td>12 (R)</td>
<td>37 (R)</td>
<td>31 (R)</td>
<td>1 (R)</td>
</tr>
<tr>
<td>(-)MDBH(_2)</td>
<td>30 (R)</td>
<td>-</td>
<td>40 (R)</td>
<td>-</td>
</tr>
</tbody>
</table>

Comparison of the enantioselectivities in hydroborations of trans-2-butene (Table 1.1) reveals that the best results are obtained with IpcBH\(_2\) and EapBH\(_2\),\(^{12,14,19,20}\) but the optimal performance for trans-alkenes does not reach the same levels of asymmetric induction that are obtained in reactions of cis-alkenes with Ipc\(_2\)BH.\(^{12,19}\)
Overall, easier access to \( \alpha \)-pinene compared with 2-ethylapopinene makes IpcBH\(_2\) the reagent of choice for \textit{trans}-alkenes.

The trisubstituted alkenes 1-methylcyclopentene and 2-methyl-2-butene are hydroborated with fair levels of asymmetric induction using \( \text{Lgf}_2\text{BH}, \text{IpcBH}_2 \) or \( \text{EapBH}_2 \). Optimal enantiomeric purities in reactions of trisubstituted alkenes with IpcBH\(_2\) are obtained for substrates bearing a phenyl substituent (Scheme 1.3).\(^{21}\) The extent of chiral induction is comparable for both the \( E \)- and \( Z \)-isomers. \( E \)-Alkenes provide \textit{anti}-products, while \( Z \)-alkenes lead to the formation of \textit{syn}-products. With both isomers of the starting alkenes in hand it is therefore possible to synthesize all four product diastereomers in high optical yields using both enantiomers of IpcBH\(_2\) (Scheme 1.3). Moreover, dialkylboranes produced in reactions of 1:1 mixtures of IpcBH\(_2\) and hindered alkenes commonly exist as crystalline solids, so their optical purities often can be upgraded to near 100 \% by crystallization.\(^{22}\) Chemical yields may be compromised in this procedure, however.

![Scheme 1.3. Preparation of four diastereomers of 3-phenyl-2-butanol.](image)

All the asymmetric hydroborations of 2-methyl-1-butene shown in Table 1.1 resulted in poor asymmetric induction. This is a general observation for 1,1-
disubstituted alkenes, so the high selectivity obtained in the reaction of alkene 3 with Ipc₂BH is therefore surprising. Hydroboration of this substrate with (-)-Ipc₂BH afforded the syn product. The anti isomer was produced predominantly when the reaction was performed with (+)-Ipc₂BH, hence the stereoselectivity is genuinely reagent-controlled.

In general Ipc₂BH and IpcBH₂ are still the most useful chiral hydroborating reagents derived from asymmetric alkenes. In isolated cases, some of the other chiral mono- and dialkylboranes provide higher degrees of asymmetric induction, but the ready availability of both isomers of α-pinene and the well established synthetic procedures for Ipc₂BH and IpcBH₂ compensate overall.

Asymmetric hydroborations of cis- and trans-alkenes by Ipc₂BH and IpcBH₂, respectively, have been rationalized using the diastereomeric transition state models depicted in Figure 1.4 and 1.5. The geometries for the reactive conformations in these reactions were calculated using semi-empirical methods. Stereochemical preferences for the hydroboration of trans-alkenes with IpcBH₂ arise from steric repulsions between the substrate and the methyl group on the cyclohexyl ring of the reagent in the transition state leading to the minor isomers. In the preferred conformation (calculated ΔΔG = 1.0 kcal/mol) this methyl group points away from the alkene, i.e. the observed selectivities result from the size difference between the CH₂- and CHMe-moieties (Figure 1.4). If this model is correct, it is somewhat
surprising that the phenyl substituted IpcBH₂-analog (PapBH₂) gives lower degrees of asymmetric induction than the parent compound.\textsuperscript{15}

\begin{figure}[h]
\centering
\includegraphics[width=0.7\textwidth]{figure1_4.png}
\caption{Calculated transition states for reactions of trans-alkenes with IpcBH₂.}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=0.7\textwidth]{figure1_5.png}
\caption{(a) Schematic representation of steric factors controlling enantioselectivities for reactions of (a) trans-alkenes with IpcBH₂, and (b) cis-alkenes with Ipc₂BH.}
\end{figure}
Steric interactions also were postulated to determine the lowest energy transition state conformations for reaction of cis-alkenes with 1pc₂BH (Figure 1.4b). The major product isomer is generated from the conformation that places the largest substituent on the isopinocampheyl group closest to the alkene in the anti-orientation.

1.2.3 Resolution of a Chiral Borane

All the chiral hydroborating reagents discussed so far were obtained via face selective hydroborations of chiral alkenes. An alternative approach is depicted in Scheme 1.4, which shows the first resolution of a chiral borane.²⁵ Reaction of the Grignard reagent derived from 2,5-dibromo-hexane with (diethylamino)dichloroborane (Cl₂BNEt₂) and subsequent methanolysis lead to formation of a mixture of (2,5-dimethyl)methoxyborolanes 4. Precipitation of compound 5 formed from selective complexation of N,N-dimethylethanolamine with cis-4 was followed by distillation of the volatile, uncomplexed trans-isomer. The two enantiomers of trans-4 were resolved by treatment of the racemate with substoichiometric (S)-prolinol. This led to preferential formation of adduct 6 from the (R,R)-borolane. The volatile fraction was collected by distillation providing essentially pure (S,S)-4, and the (R,R)-methoxyborolane 4 was obtained by methanolysis of complex 6. Both enantiomers were transformed into the desired products by treatment with lithium aluminum hydride followed by reaction of the crystalline borates 7 with excess methyl iodide.
Scheme 1.4. Synthesis of both enantiomers of borolane 8.\textsuperscript{25}

The C\textsubscript{2}-symmetric borolane 8 gave uniformly good diastereoselection with all classes of prochiral alkenes except 1,1-disubstituted ones (Table 1.2). In terms of chiral induction this reagent was superior to any of the reagents derived from terpenes.\textsuperscript{25}
However, a relatively elaborate synthesis is required, and 8 is thermally unstable in solution rearranging to the dimer 9 (half-life of several days). For this reason, the borane is usually produced in situ from precursor 7 by treatment with two equivalents of methyl iodide (Scheme 1.4).

![Chemical Structures](Image)

**Table 1.2.** Asymmetric Hydroboration with Borolane \((R,R)-8\) of >95% ee.

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>product</th>
<th>% ee</th>
<th>config.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me=CHMe</td>
<td>Me-CH₂OH Me</td>
<td>98</td>
<td>S</td>
</tr>
<tr>
<td>2</td>
<td>Me-CH₂Me</td>
<td>Me-CH₂OH Me</td>
<td>100</td>
<td>S</td>
</tr>
<tr>
<td>3</td>
<td>Me-C(Me)</td>
<td>Me-C(OH) Me</td>
<td>100</td>
<td>1S,2S</td>
</tr>
<tr>
<td>4</td>
<td>Me=CHMe</td>
<td>Me-CH₂OH Me</td>
<td>98</td>
<td>S</td>
</tr>
<tr>
<td>5</td>
<td>Me-CH₂Me</td>
<td>Me-CH₂OH Me</td>
<td>1</td>
<td>S</td>
</tr>
</tbody>
</table>
1.3 Substrate-Controlled Diastereoselectivity in Hydroborations

In substrate-controlled diastereoselective hydroborations a chiral center in the alkene determines the face selectivity of the addition of the borane (equation 1.10). Therefore, this type of reaction can often be performed with achiral hydroborating reagents.

\[ \text{R}^1 \text{R}^2 \text{R}^3 \text{CH}_2 \xrightarrow{\text{R}_2 \text{BH}} \text{R}^1 \text{R}^2 \text{BR}_2 + \text{R}^1 \text{R}^2 \text{BR}_2 \] (1.10)

1.3.1 Intermolecular Reactions

1.3.1.1 Cyclic alkenes

Diastereoselective hydroborations of cyclic chiral alkenes are more easily accomplished than for acyclic ones, because the former tend to have better defined reactive conformations. In the absence of exceptional electronic or coordinative effects (see section 1.4.3.1), boranes tend to add to the least hindered face of a cyclic alkene. Thus, high face selectivities have been observed for reactions of terpenes with BH₃ (cf syntheses of the chiral hydroborating agents Ip₂BH, Lgf₂BH, dIcr₂BH, and 3-dIcr₂BH). Similarly, hydroborations of steroid derivatives often display good levels of substrate-controlled diastereoselectivity (e.g. equation 1.11).²⁶-²⁸
1.3.1.2 1,2-Induction for Acyclic Substrates

Several early examples of 1,2-asymmetric induction were presented by the Kishi group.\textsuperscript{29,30} The major diastereomer (\textasciitilde 8:1) from hydroboration of alkene 10 had the configuration shown in equation 1.12.\textsuperscript{29} Several other examples giving predominantly products with a \textit{syn} relationship between a methyl group at the allylic chiral center and the newly introduced alcohol functionality were reported (\textit{e.g.}, equation 1.13).

\begin{equation}
\begin{array}{c}
\text{Furan} \quad (\text{i) BH}_3\text{.THF} \\
\text{Me} \quad \text{Me} \\
\text{R}
\end{array}
\quad (\text{i) BH}_3\text{.THF} \\
\text{Me} \quad \text{Me} \\
\text{R} \\
\text{R} \quad \text{R} \\
\text{Me} \quad \text{Me} \\
\text{Me}
\end{equation}

10, \text{R} = \text{CO}_2\text{Et} \\
\text{85\%}

\begin{equation}
\begin{array}{c}
\text{Bz} \quad \text{Me} \quad \text{Me} \\
\text{R}
\end{array}
\quad (\text{i) BH}_3\text{.THF} \\
\text{Me} \quad \text{Me} \\
\text{R} \\
\text{Bz} \quad \text{R} \\
\text{Me} \quad \text{Me} \\
\text{Me}
\end{equation}

\begin{equation}
\begin{array}{c}
\text{Bz} \quad \text{Me} \quad \text{Me} \\
\text{R}
\end{array}
\quad (\text{i) BH}_3\text{.THF} \\
\text{Me} \quad \text{Me} \\
\text{R} \\
\text{Bz} \quad \text{R} \\
\text{Me} \quad \text{Me} \\
\text{Me}
\end{equation}

R = \text{CH}_2\text{OCH}_2\text{OMe} \\
3:1

Sterically hindered boranes can be used to hydroborate allylic alcohol derivatives with high \textit{anti} selectivity (equation 1.14).\textsuperscript{31} The degree of induction is enhanced by more electronegative O-protecting groups. For instance, acetate gives a
7.5:1 ratio of *anti* to *syn* products, while this ratio is increased to 14:1 for the corresponding trifluoroacetate.

(i) 9-BBN or ThxBH₂  
(ii) oxidation

\[
\begin{align*}
\text{Bu} & \quad \text{R}^1 \quad \text{R}^2 \quad \text{R}^3 \\
\text{OR}^1 & \quad \rightarrow & \quad \text{Bu} & \quad \text{R}^1 \quad \text{OH} \quad \text{R}^2 \quad \text{R}^3 \\
\text{(i) 9-BBN or ThxBH₂} & \quad \rightarrow & \quad \text{Bu} & \quad \text{R}^1 \quad \text{OH} \quad \text{R}^2 \quad \text{R}^3 & \quad + & \quad \text{Bu} & \quad \text{R}^1 \quad \text{OH} \quad \text{R}^2 \quad \text{R}^3 \quad \text{anti} \quad \text{syn}
\end{align*}
\]

\[
\begin{align*}
\text{R}^1 & \quad \text{R}^2 & \quad \text{R}^3 & \quad \text{anti:} \text{syn} \\
\text{H} & \quad \text{H} & \quad \text{Bu} & \quad >15:1 \\
\text{COCH}_3 & \quad \text{H} & \quad \text{H} & \quad 7.5:1 \\
\text{COCF}_3 & \quad \text{H} & \quad \text{H} & \quad 14:1
\end{align*}
\]

An elegant application of diastereoselective hydroboration of allylic alcohol derivatives is shown in equation 1.15. Alkene 11 was hydroborated with dicyclohexylborane providing an intermediate azido borane, which then underwent a cycloalkylation. The migrating alkyl moiety and the departing diazonium group are positioned antiperiplanar in the proposed intermediate (A) facilitating the rearrangement.

\[
\begin{align*}
\text{MeO} & \quad \text{C} & \quad \text{OH} \\
\text{N}_3 & \quad \rightarrow & \quad \text{MeO} & \quad \text{C} & \quad \text{OH} \\
\text{c-C}_6\text{H}_{11} \text{BH} & \quad \rightarrow & \quad \text{MeO} & \quad \text{C} & \quad \text{OH} \\
\text{11} & \quad \rightarrow & \quad \text{MeO} & \quad \text{C} & \quad \text{OH}
\end{align*}
\]
A few examples of stereocontrolled hydroborations of acyclic alkenes lacking heteroatom functionalities have been documented. One such case is the highly selective reaction of the steroid derivative 12 with sterically encumbered boranes like disiamylborane and dicyclohexylborane. The observed selectivity can be rationalized using the reactive conformation shown in Figure 1.6. The less reactive endo-cyclic double bond was not hydroborated in these reactions.

Figure 1.6. Preferred conformation for the hydroboration of 12 with hindered dialkylboranes.
1.3.1.3 1,3-Induction for Acyclic Substrates

In contrast to 1,2-asymmetric induction, only a few useful cases of substrate-controlled 1,3-induction have been reported for hydroboration reactions. For alkenes with a β-chiral center bearing a methyl group and a sterically more demanding substituent, only the stereochemistry of the proximal chiral center determines the outcome of the reaction (e.g., equations 1.16 and 1.15, the stereochemistry at C⁴ governs the face selectivity).³⁴,³⁵ Double asymmetric induction was not observed in the corresponding reactions with the chiral hydroborating reagents (+)- and (-)-IpcBH₂, because both enantiomers gave similar levels of asymmetric induction and provided the same major product.

\[
\begin{align*}
\text{(i) } & (\text{Sia})₂\text{BH} \\
\text{(ii) } & \text{H}_₂\text{O}_₂
\end{align*}
\]

\[
\begin{align*}
\text{HO} & \text{CH₂}₄\text{CH₂}₃\text{CO} & \text{R}' & + \text{HO} & \text{CH₂}₄\text{CH₂}₃\text{CO} & \text{R}' \\
87 & : 13
\end{align*}
\]

\[
\begin{align*}
\text{(i) } & (\text{Sia})₂\text{BH} \\
\text{(ii) } & \text{H}_₂\text{O}_₂
\end{align*}
\]

\[
\begin{align*}
\text{HO} & \text{CH₂}₄\text{CH₂}₃\text{CO} & \text{R}' & + \text{HO} & \text{CH₂}₄\text{CH₂}₃\text{CO} & \text{R}' \\
77 & : 23
\end{align*}
\]
1.3.2 Intramolecular Reactions

Still and co-workers showed the potential of stereocontrolled intramolecular delivery of boron-hydrides to chiral alkenes. These reactions involve cyclic intermediates with relatively rigid transition states, hence good stereoselection could be achieved from remote chiral centers (equation 1.18). In reactions of several non-conjugated dienes, a chiral center was created in the first hydroboration of the most reactive terminal alkene. Subsequently, the thexyl group was lost prior to cyclization, presumably via β-elimination, producing a monoalkylborane, which then reacted with the remaining alkene to form the second chiral center with excellent 1,3- and 1,4-asymmetric induction (equations 1.18 and 1.19 respectively). The observed preference was rationalized in terms of a boat-like transition state that positions ring substituents in equatorial positions and eclipses the boron-hydrogen bond with respect to the alkene π-system.

\[
\begin{align*}
\text{(i) ThxBH}_2 & \xrightarrow{} \text{OH} + \text{OH} \\
\text{(ii) NaOOH} & \text{OH} + \text{OH} \quad \text{(1.18)} \\
\text{OH} + \text{OH} & \quad 1:15 \\
\end{align*}
\]

\[
\begin{align*}
\text{(i) ThxBH}_2 & \xrightarrow{} \text{OH} + \text{OH} \\
\text{(ii) NaOOH} & \text{OH} + \text{OH} \quad \text{(1.19)} \\
\text{OH} + \text{OH} & \quad 6:1 \\
\end{align*}
\]
Cyclic hydroboration of allylic vinyl ether 15 produced alcohol 17 with >200:1 selectivity via initial reaction of the more reactive vinyl ether, and subsequent intramolecular addition of the second boron-hydrogen bond to the other alkene (Scheme 1.5). The seven-membered boraheterocycle 16 produced undergoes syn-elimination of ethene, hence oxidation of the resulting cyclic borinic ester yields the major product. The overall transformation provides products with opposite relative stereochemistry compared with intermolecular hydroborations of allylic alcohol derivatives (see section 1.3.1.2).

Scheme 1.5. Cyclic asymmetric hydroboration of allylic vinyl ether 15.

Another example of intramolecular asymmetric hydroboration of allylic alcohol derivatives is shown in Scheme 1.6. Addition of a hindered borane like thexylborane to alkene 18 occurred with good anti selectivity in the first hydroboration step, providing dialkylborane 19. Reaction of this intermediate with the second alkene furnished the seven membered boracycle 20 with high selectivity,
and diol 22 as the predominant product after oxidation. In contrast, hydroboration of alkene 18 with 9-BBN took place via two intermolecular processes that produced almost exclusively diol 21 after oxidation. \(^{40}\)

\[\text{Scheme 1.6. Cyclic asymmetric hydroboration of allylic silyl ether 18.}\]

Another highly stereoselective intramolecular hydroboration is the reaction of diene 23 with BH\(_3\), providing a 1:1 mixture of the diols 24. The random stereochemistry at C-2 is the result of the non-stereoselective initial hydroboration, but the stereocenters at C-4 and C-5 arise from preferential reaction via conformation B, avoiding the sterically unfavorable conformation A (Figure 1.7). \(^{37,38}\)
Figure 1.7. Minimization of 1,3-allylic strain governs the face selectivity in cyclic hydroboration of diene 23.

Intramolecular hydroboration of α-alkoxy-β, γ-unsaturated esters apparently occurs via initial reduction of the ester functionality.⁴¹ Alkoxycoboranes such as 26 are believed to be insufficiently reactive to hydroborate alkenes, but several observations support the postulated intermediacy of 26 in these reactions, such as the isolation of cyclic boronate ester 28 from the reaction with substrate 25. The stereochemistry at C-2 was shown to control the face selectivity of the hydroboration of the alkene (compare equations 1.21 and 1.22). Once more, the observed diastereoselectivity for these hydroborations can be explained on the basis of minimized 1,3-allylic strain.⁴²
1.4 Transition Metal Catalyzed Hydroborations

In 1985 Männig and Nöth reported hydroboration of alkenes with catecholborane at 25 °C catalyzed by Rh(I)-complexes.\(^{43}\) Catecholborane hydroborates alkenes only at elevated temperatures (ca 100 °C) in the absence of a catalyst.\(^ {44,45}\) In addition to the enhanced reactivity, the chemoselectivity of catecholborane was changed dramatically by addition of the catalyst (Scheme 1.7). Since the mechanism of the catalyzed process is likely to differ substantially from the uncatalyzed reactions, new chemo-, regio- and stereoselectivities were anticipated.
Scheme 1.7. Addition of a catalytic amount of rhodium catalyst changes the chemoselectivity in the reaction of catecholborane and 29.

1.4.1 Diastereoselective Rhodium Catalyzed Hydroboration

Stereocomplementary behavior of uncatalyzed and rhodium catalyzed hydroboration of allylic alcohol derivatives constitutes one of the most useful aspects emerging from transition metal catalyzed hydroboration. Thus, while the hydroboration of substrates 30 with 9-BBN gives good anti selectivity (section 1.3.1.2), the catalyzed reaction provides predominantly the syn alcohols (Table 1.3).46-50 This selectivity is enhanced by use of electronegative or sterically hindered O-protecting groups. The results of studies designed to probe stereoelectronic effects controlling face selectivities in catalyzed hydroborations of alkenes are described in chapter 2.
Table 1.3. Catalyzed and Uncatalyzed Hydroborations of Allylic Alcohol Derivatives

![Chemical structure diagram]

<table>
<thead>
<tr>
<th>R</th>
<th>reagents</th>
<th>anti:syn</th>
</tr>
</thead>
<tbody>
<tr>
<td>Si/BuMe₂</td>
<td>RhCl(PPPh₃)₃, catecholborane</td>
<td>4:96</td>
</tr>
<tr>
<td>Si/BuMe₂</td>
<td>9-BBN</td>
<td>90:10</td>
</tr>
<tr>
<td>COCH₃</td>
<td>[Rh(COD)Cl]₂/4 PPh₃, catecholborane</td>
<td>27:73</td>
</tr>
<tr>
<td>COCH₃</td>
<td>9-BBN</td>
<td>88:12</td>
</tr>
<tr>
<td>COCF₃</td>
<td>[Rh(COD)Cl]₂/4 PPh₃, catecholborane</td>
<td>12:88</td>
</tr>
<tr>
<td>COCF₃</td>
<td>9-BBN</td>
<td>93:7</td>
</tr>
<tr>
<td>CO/Me</td>
<td>[Rh(COD)Cl]₂/4 PPh₃, catecholborane</td>
<td>13:87</td>
</tr>
<tr>
<td>CO/Me</td>
<td>9-BBN</td>
<td>94:6</td>
</tr>
</tbody>
</table>

Optically active allylamine derivatives 31 prepared from α-amino acids also exhibit syn-selectivity in catalyzed hydroborations. More bulky N-(benzy1tosyl)-amines give better selectivities than the tosyl-protected allylamines. Presumably, these sterically demanding groups are positioned away from the approaching reactive metal complex and increased size of the substituents improves the observed syn selectivity. Reactions of these substrates with BH₃·THF yield anti products with high selectivities, whereas hydroborations with 9-BBN are non-selective or anti-selective.
Table 1.4. Catalyzed and Uncatalyzed Hydroboration of Allylic Amine Derivatives.

\[
\begin{align*}
\text{Table 1.4. Catalyzed and Uncatalyzed Hydroboration of Allylic Amine Derivatives.} \\
\end{align*}
\]

\[
\begin{align*}
\text{R} & \quad \text{R'} & \quad \text{reagents} & \quad \text{syn:anti} \\
\hline
\text{Bu} & \text{H} & \text{[Rh(COD)Cl]_2/4 PPh_3, catecholborane} & 84:16 \\
\text{^3PrCH}_2 & \text{H} & \text{[Rh(COD)Cl]_2/4 PPh_3, catecholborane} & 80:20 \\
\text{Bu} & \text{Bn} & \text{[Rh(COD)Cl]_2/4 PPh_3, catecholborane} & 91:1 \\
\text{^3PrCH}_2 & \text{Bn} & \text{[Rh(COD)Cl]_2/4 PPh_3, catecholborane} & 86:14 \\
\text{Bu} & \text{Bn} & \text{9-BBN} & 87:13 \\
\text{Bu} & \text{Bn} & \text{BH}_3 & 5:95 \\
\end{align*}
\]

1.4.2 Enantioselective Rhodium Catalyzed Hydroboration

The asymmetric hydrobating agents described in section 1.2 have proven to be successful in achieving high enantioselectivities for many substrates, but poor optical yields are obtained for some substrates, particularly 1,1-disubstituted alkenes. Furthermore, this methodology requires the use of stoichiometric or excess quantities of the chiral borane, which often necessitates purification of the crude reaction products. Unlike the aforementioned strategies, which give diastereomeric product boranes, catalyzed hydroboration in the presence of chiral ligands can afford product enantiomers directly (Figure 1.8). Moreover, the typical by-product, catechol, can be removed easily via partitioning with aqueous base, avoiding extra purification steps.
enantioselectivity in catalyzed hydroborations

\[
\begin{align*}
[\text{Rh(COD)Cl}_2]_{\text{cat}} & \xrightarrow{\text{(S,S)-DIOP}} \text{Bcat} \xrightarrow{\text{oxidation}} \text{two enantiomers} \\
\text{catecholborane} & \quad 57\% \text{ ee}
\end{align*}
\]

reagent-controlled diastereoselectivity in hydroborations

\[
\begin{align*}
(-)\text{-Ipc}_2\text{BH} & \xrightarrow{\text{oxidation}} \text{two diastereomers} \\
\text{Bipc}_2 & \quad 83\% \text{ ee}
\end{align*}
\]

Figure 1.8. True enantioselective hydroboration vs diastereoselective hydroboration.

Several reports have described asymmetric rhodium catalyzed hydroborations in the presence of chiral phosphine ligands. Enantioselectivities of >95% were achieved in hydroborations with BINAP and a cationic rhodium catalyst. However, these optical purities could only be obtained with phenylethene derivatives at -78°C.\textsuperscript{51,52}

Remarkably, rhodium catalyzed hydroboration and subsequent oxidation affords Markovnikov hydration for these substrates (equation 1.23).

\[
\begin{align*}
\text{PhCH}_2 & \xrightarrow{[\text{Rh(COD)_2}BF_4]} (R)\text{-}(-)\text{-BINAP catecholborane} \\
\text{oxidation} & \quad \text{OH} \\
\text{Me} & \quad 96\% \text{ ee}
\end{align*}
\]

(1.23)

Optical purities for hydroboration of other prochiral alkenes have not exceeded 80% ee.\textsuperscript{53} Therefore, a systematic study was undertaken to establish the factors
governing the enantioselectivity of rhodium catalyzed hydroboration. The results of this study are presented in chapter 4.

1.4.3 Hydroboration Catalysis with Other Transition Metals

The diastereo- and enantioselective catalyzed hydroboration of alkenes described above were all performed with Rh(I)-based catalysts. One study has reported hydroboration catalysis with Rh$_2$(OAc)$_4$. The involvement of rhodium-hydride intermediates in this process was proposed based on the observed isomerization of allylbenzene in the presence of catalyst and a deficiency of catecholborane (equation 1.24). As of yet, no useful applications of rhodium(II)-catalyzed hydroboration have been documented. A number of studies have been performed with other transition metal catalysts, and these will be discussed in the following sections.

\[
\begin{align*}
\text{Ph} & \quad \text{1 \% Rh}_2\text{(OAc)}_4 \\
\text{Ph} & \quad \text{3 \% catecholborane} \\
\rightarrow & \\
\text{Ph} & \quad \text{Ph} + \quad \text{Ph}
\end{align*}
\]

(1.24)

1.4.3.1 Iridium and Ruthenium based catalysts

Several iridium complexes are known to react with stoichiometric amounts of catecholborane (see also chapter 3), but only a few catalytic systems have been reported. Use of Crabtree’s iridium catalyst ([Ir(COD)(PCy$_3$)(py)]PF$_6$, COD = 1,4-cyclooctadiene) in hydroboration of substrates containing N-alkyl, or N,N-dialkyl amide functionalities lead to formation of products derived from transient coordination of the metal complex. Evidence for this assertion is predominant formation of cis products in hydroboration of some cyclohexenes functionalized with amide groups (i.e. approach from the most hindered face, equation 1.25). Similar effects in acyclic systems, and dampening of these
effects in coordinating solvents provide further support for a coordination directed process.

\[
\begin{align*}
\text{(i) } & \text{ HBO}_2\text{C}_6\text{H}_4, \\
& 4\% [\text{Ir(COD)(PCy}_3\text{(py))]PF_6 \\
\text{(ii) oxidation} & \\
\text{(iii) Ac}_2\text{O} \\
\end{align*}
\]

\[
\begin{align*}
\text{O} & \text{N} \\
\text{O} & \text{Ac}
\end{align*}
\]

\text{+ other isomers} \quad (1.25)

\text{44\%}

\text{cis:trans} = 19:1.0

In a second study, several iridium complexes were screened for catalytic activity in the reaction of 4-vinylanisole with catechochlorobane. The complexes [IrCl}_2(\eta^5\text{-C}_5\text{Me}_5)]}_2 and [Ir(\mu-\text{Cl})(\text{COE})_2]}_2 were extremely active hydroboration catalysts; complete conversion was observed within 0.5 h in the presence of 2 mol\% of catalyst (equation 1.26). The aforementioned Crabtree's catalyst was less reactive and produced more hydrogenation products for this particular transformation. Unfortunately, 4-vinylanisole was the only substrate studied, preventing more extensive comparison with uncatalyzed and rhodium catalyzed hydroboration.

Competitive hydrogenation and slow reaction rates were reported for hydroboration catalyzed by a number of ruthenium(II/III)-complexes (equation 1.26).\textsuperscript{56}
R 
catalyst 
mol %

time (h) 
31:32:33

OMe $[\text{IrCl}_2(\eta^5-\text{C}_5\text{Me}_5)])_2$ 2 0.5 98:0:2
OMe $[\text{Ir}(\mu-\text{Cl})(\text{COE})_2]_2$ 2 0.5 75:20:5
H $\text{RuCl}_2(\text{PPh}_3)_4$ 5 $6^a$ 90:0:10
H $\text{RuCl}_3(\text{PPh}_3)_2(\text{MeOH})$ 5 9 86:0:14

$^a$ 85 % Conversion.

1.4.3.2 Palladium and Nickel based catalysts

Rhodium(I)-complexes provide hydroboration products for reactions of catecholborane with alkenes, while conjugated dienes are virtually inert towards catecholborane in the presence of rhodium complexes because of their good ligating properties. Conversely, palladium complexes do accelerate the addition of catecholborane to conjugated dienes, but fail to show useful catalysis for hydroboration of isolated alkenes. Palladium catalyzed hydroboration of 1,3-dienes afford the terminal, allylic boronates with good regio- and stereoselectivities. The predominant formation of the (Z)-products suggests a reaction pathway as shown in Scheme 1.8. The boronate
intermediates can be conveniently trapped with aldehydes to provide homoallylic alcohols with high diastereoselectivity (>99 %).\textsuperscript{57}

\[
\begin{align*}
\text{R} & \quad \text{R'} \\
\text{H}_2\text{C} & \quad \text{CH}_2 \\
\text{C}_6\text{H}_6, 25 \degree \text{C}, 16 \text{ h} & \quad \text{Me} \\
\end{align*}
\]

\[
\begin{align*}
\text{PhCHO,} & \quad 0 \text{ to } 25 \degree \text{C}, 3 \text{ h} & \quad \text{R} = \text{H or Me} \\
\text{R'} & \quad \text{H, Me, or (CH}_2)_3\text{CH=CMe}_2 \\
\end{align*}
\]

\textbf{Scheme 1.8.} Palladium catalyzed addition of catecholborane with 1,3-dienes.

Hydroboration of conjugated enynes was promoted also by palladium complexes, providing allylboronates which were transformed into homopropargylic alcohols (\textit{e.g.} equation 1.27).\textsuperscript{57}

\[
\begin{align*}
\text{Me} & \quad \text{1 eq. HBO}_2\text{C}_6\text{H}_4, \\
\text{1.5 mol \% Pd(PPh}_3)_4 & \quad \text{Me} \\
\text{PhCHO, 60 \degree C} & \quad \text{Me} \\
\end{align*}
\]

(1.27)
Finally, a recent report described nickel-catalyzed hydroboration of disubstituted thioalkynes, affording β-(alkylthio)alkenyl boronates with high regioselectivity. This provides a useful addition to conventional hydroboration techniques, which usually produce mixtures of regioisomers.
Chapter 2. Stereoelectronic Effects in Catalyzed Hydroboration.

2.1 Introduction

The ability to predict the stereochemical outcome of a certain reaction is a major challenge in organic chemistry. Over the years many theories have been presented to explain observed selectivities and some have proven to be very valuable. This chapter concerns experimental probes of the stereoelectronic factors controlling selectivities in catalyzed and uncatalyzed hydroboration.

2.1.1 Stereoelectronic Effects in Nucleophilic Additions to α-Chiral Carbonyl Compounds

One of the first models to explain selectivities observed for reactions of metal hydrides and Grignard reagents with α-chiral aldehydes and ketones has become known as Cram's rule for open-chain transition states. The basis of this model was the assumption that the preferred conformation in the transition state is "reactant-like", and that attack of the nucleophile takes place perpendicular to the nodal plane of the carbonyl group (Figure 2.1a). For steric reasons the preferred conformation at the α-chiral center was proposed to place the smallest substituent (S) partially eclipsed with the nucleophile and the large substituent (L) pointing away from the carbonyl oxygen. Although this empirically derived rule was shown to be valid in many instances, several reactions were found to proceed with "anti-Cram" selectivity.

Felkin improved the Cram model by taking dipolar and steric factors into account. In the Felkin model the nucleophile still approaches the carbonyl perpendicular to the nodal plane of the π-system, but the substituents at the α-carbon occupy staggered rather than eclipsed positions with respect to the forming bond to avoid torsional strain. Furthermore,
electrostatic repulsion between the most electronegative group (L, M or S) and the
approaching nucleophile stabilizes the conformation that maximizes the separation between
these groups (i.e. the most electron withdrawing group (EWG) occupies the "anti-
position"). Steric factors govern the location of the other substituents (Figure 2.1b). For
carbonyl compounds in which the bulkiest group is also the most electronegative
substituent, the Felkin and Cram models predict the same stereochemical preference.
However, the outcome for substrates bearing small, electronegative substituents, such as
$\alpha$-chloro aldehydes and ketones, is predicted correctly only by the Felkin model.

![Figure 2.1. Preferred approach of nucleophiles to carbonyl compounds according to (a) Cram rule, (b) Felkin model, and, (c) Anh-Eisenstein model.](image)

Felkin's torsional strain model for nucleophilic attack on unsaturated trigonal
centers was supported by Anh and Eisenstein, who derived a similar lowest energy
transition state from orbital theories (Figure 2.1c).$^{60,61}$ The use of frontier molecular
orbitals (i.e. the energetically highest occupied orbital, HOMO, and lowest unoccupied
orbital, LUMO) in establishing selectivities of organic chemical reactions was first
introduced by Fukui and supplemented by others.$^{62-69}$ Fukui proposed perturbation of the
frontier orbitals of reactants by interaction with proximal $\sigma$-orbitals of correct symmetry.
In the Ahn-Eisenstein model this interaction involves the incipient $\sigma$-orbital of the forming
nucleophile-carbon bond and the vacant $\sigma^*$-orbital associated with the substituent that
occupies the anti-position on the $\alpha$-carbon (Figure 2.2). Best overlap will be achieved
when the $\sigma^*$-orbital is relatively close in energy to the $\sigma$-orbital, i.e. when the best electron acceptor occupies the anti position. The pioneering ab initio calculations by Ahn and Eisenstein suggested an attack angle of approximately 109.5°, and this assertion has been supported subsequently by several literature reports.\(^7\)

![Orbital interaction between the incipient $\sigma$-orbital and the empty $\sigma^*$ associated with the substituent in the anti position](image)

**Figure 2.2.** Orbital interaction between the incipient $\sigma$-orbital and the empty $\sigma^*$ associated with the substituent in the anti position

### 2.1.2 Stereoelectronic Effects in Uncatalyzed Hydroboration

The first model for face selectivity in hydroborations of $\alpha$-chiral alkenes (e.g. equation 2.1) was based on minimization of steric interactions. Alkenes differ from carbonyl compounds in that there is considerable steric hindrance (1,3-allylic strain)\(^4\) between the substituents on the alkene and the chiral center (Figure 2.3). Kishi proposed that minimization of 1,3-allylic strain leads to $A$ as the most reactive conformation for hydroborations of alkenes such as 10.\(^2\) Predominant attack on $A$ from the least hindered face correctly predicted the diastereoselectivity obtained in reactions with these substrates.
Figure 2.3. Kishi's model for uncatalyzed hydroborations of α-chiral alkenes.

Still and Barrish also attributed high face selectivities observed in hydroborations of protected allylic alcohol derivatives 34 to 1,3-allylic strain in conjunction with dipolar interactions (equation 2.2). The authors demonstrated increased stereoselection when the protecting group contains electron deficient functionalities. Based on these observations the model shown in Figure 2.4 was suggested as the preferred reactive conformation. This conformer has minimum 1,3-allylic strain and electrostatic repulsion between the nucleophile and the electronegative oxygen substituent.
Figure 2.4. Still's proposed preferred conformation for hydroboration of α-chiral allylic alcohol derivatives.

Houk and coworkers reported \textit{ab initio} calculations of the transition states for uncatalyzed hydroborations of α-substituted alkenes.\textsuperscript{71} In the lowest energy conformation the allylic substituents were staggered with respect to the forming bond (Figure 2.5). For allylic alcohol derivatives the oxygen preferentially occupies either the "inside" or "outside" position, but not the \textit{anti} position (Figure 2.5) which is occupied by the most electron donating group. With sterically demanding boranes the most reactive conformation (B) has the smallest substituent on the chiral center at the "inside" position resulting in predominant formation of the \textit{anti} -product. Reactions with small boranes like BH\textsubscript{3} can occur via either conformer A or B depending on more subtle steric and electronic effects. The results of these theoretical studies agree with the experimentally observed selectivities (\textit{e.g.} equations 1.12-1.14). The Houk model is most effective for compounds with small O-protecting groups in which the electronic preference of placing the most electron donating group in the \textit{anti} position is dominant. However, for alkenes with sterically demanding R' and O-protecting groups the outcome is not always predictable, because unfavorable steric interactions start to compete with electronic preferences.
Houk's staggered conformation for electrophilic attack on an alkene is similar to that proposed by Felkin and Anh for nucleophilic attack on carbonyl compounds, but the approach of the borane occurs at the "inside" position rather than the "outside", and the best electron donor instead of the best electron acceptor occupies the anti position. The sense of asymmetric 1,2-induction predicted by the Kishi and Still models, and by Houk's calculated transition state geometry is identical.

Finally, Burgess and Ohlmeyer established highly diastereoselective hydroborations for several allylic alcohol and amine derivatives using the sterically hindered borane 9-BBN. The proposed lowest energy transition state for these reactions was derived from frontier molecular orbital considerations. The HOMO orbital for this process is formed by the π-orbital associated with the alkene, while the empty p-orbital on the borane corresponds to the LUMO. The HOMO-LUMO overlap will be enhanced if their relative energies are closer to each other. For the reaction of a borane with an α-chiral alkene, this will be achieved by raising the energy of the HOMO through hyperconjugation
with the antiperiplanar $\sigma$-orbital of the substituent occupying the anti-position at the adjacent chiral center (Figure 2.6a). In the preferred reactive conformation the substituent with the highest energy $\sigma$-orbital (i.e. the strongest electron donating group) raises the HOMO orbital most and therefore occupies the anti-position (Figure 2.6b). This leads to the same conformations A and B as proposed from ab initio calculations (vide supra). The preference of conformer B over A is the result of steric interactions between the bulky 9-BBN reagent and the $O$-protecting group.

Figure 2.6. (a) Frontier orbitals involved in uncatalyzed hydroboration of $\alpha$-chiral allylic alcohol derivatives. (b) Preferred conformation for reaction of alkenes 34 with 9-BBN.
2.1.3 Stereoelectronic Effects in Rhodium Catalyzed Hydroborations

One of the most significant observations to emerge from studies of rhodium-mediated hydroboration reactions is that catalyzed hydroborations of the allylic alcohol derivatives 34 give syn products selectively whereas uncatalyzed reactions preferentially give the anti isomers (sections 1.3.2 and 1.4.1). 46-48,50,72-74

<table>
<thead>
<tr>
<th>X</th>
<th>HBO₂C₆H₄, Rh-cat</th>
<th>9-BBN</th>
<th>syn:anti</th>
<th>syn:anti</th>
</tr>
</thead>
<tbody>
<tr>
<td>COCH₃</td>
<td>2.7:1.0</td>
<td>1.0:7.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>COCF₃</td>
<td>7.5:1.0</td>
<td>1.0:14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CO₂Bu</td>
<td>6.5:1.0</td>
<td>1.0:15</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The data in Table 2.1 show increased diastereoselectivities for both catalyzed and uncatalyzed hydroboration of substrates 34 with more electronegative or more sterically demanding O-protecting groups. 48 The origin of this "stereocomplementary" behavior is an enigma in contemporary organic chemistry, and one which is difficult to address because details of the mechanism of catalyzed hydroborations are unknown (see chapter 3).

Two diastereomers can arise from complexation of a chiral alkene to a transition-metal. Burgess and Ohlmeyer suggested substrate-controlled diastereoselectivity in
catalyzed hydroborations of the allylic alcohol derivatives 34 and related substrates, may be dictated by the face selectivity of complexation in the formation of such η2-alkene complexes (equation 2.3).48,73 We assume that the minor diastereomer formed on complexation is not converted relatively fast into the major stereoisomer of the product, i.e. the peculiar type of situation observed in rhodium-mediated hydrogenations of dehydroamino acids75 is not applicable. On the basis of this assumption it is possible to account for diastereoselectivities observed in catalyzed hydroborations of allylic alcohols 34 by considering steric and electronic effects.

\[
n^\text{Bu} \quad \text{Me} \quad \overset{\text{OX}}{\substack{\text{complexation} \\ \rightarrow}} \quad n^\text{Bu} \quad \text{Me} \quad \overset{\text{[Rh]}}{\substack{\text{[Rh]} \\ \rightarrow}} + \quad n^\text{Bu} \quad \text{Me} \quad \overset{\text{[Rh]}}{\substack{\text{[Rh]} \\ \rightarrow}} \tag{2.3}
\]

Frontier orbitals controlling metal complexations of the type depicted in equation 2.3 (Figure 2.7a), are perturbed if one substituent of the chiral center is aligned perpendicular to the alkene such that a σ*-orbital at that chiral center overlaps with the π*-orbital of the alkene; this reduces the HOMO-LUMO energy gap. Maximum stabilization of the metal-to-alkene bond therefore will be achieved when the most electron-withdrawing substituent (OX) is placed in the anti-position, because this provides the lowest energy σ*-orbital for mixing with the alkene π* orbital (Figure 2.7c). On the basis of steric effects, the smallest of the other two substituents at the chiral center (hydrogen in this example) will preferentially occupy the "inside crowded"70 position in the metal-alkene complex, thus avoiding steric interactions between the rhodium center and the larger butyl group. Consequently, one would predict allylic alcohols 34 in catalyzed hydroborations to react predominantly via the conformation shown in Figure 2.7b.
The terms "kinetic-" and "thermodynamic-control" are ambiguous when applied to multi-step processes like catalyzed hydroboration, because each of the individual steps in the catalytic cycle can be either kinetically or thermodynamically controlled.

If the relative rates of the steps are such that complexation of the alkene is effectively irreversible, then the frontier orbital argument presented above may be applied to predict which diastereomeric alkene complex is formed fastest. Conversely, if the
diastereomeric complexes are rapidly interconverting, the orbital rationale provides a means to assess which is more stable; the observed selectivities could then be a consequence of a weighted equilibrium between two diastereomeric complexes which rapidly interconvert via a metal species without π-alkene ligands. However, product selectivities in such a process would arise from the energy difference for the transition states associated with the first irreversible step, which still has to be determined for rhodium catalyzed hydroborations of allylic alcohol derivatives.

The orbital hypothesis can also be used to explain the three-fold increase in syn selectivity observed on changing the protecting group from acetate (34, X = COCH₃) to trifluoroacetate (X = COF₃, see Table 2.1): the σ* orbital associated with C-OCOCH₃ bonding is higher in energy than that corresponding to the C-OCOCF₃ linkage, mixing with the alkene π* orbital is better in the latter case, and the preference for the reactive conformation (or bonding orientation) shown in Figure 2.7b is accentuated. Conversely, increased syn selectivity for the pivalate (34, X = COTBu) relative to the acetate (X = COCH₃) is probably due to steric repulsion between the ester and the metal center, which reinforces the electronic preference for placing the ester group in the anti position.

Increasing the electron-withdrawing capacity of the OX group of substrates 34 should also accelerate catalyzed hydroborations since this increases the affinity of the alkene for the metal (Figure 2.7c); Data from competition experiments designed to test this assertion are shown in Table 2.2. Replacement of n-butyl with n-propyl had no significant effect on the rate of hydroboration. Substitution of an acetate protecting group with a trifluoroacetate, however, caused a rate enhancement of more than 150 fold (entries 2 and 3). A similar competition experiment for uncatalyzed hydroborations of the same substrates showed the acetate to react approximately four times faster than the trifluoroacetate. This is not surprising, since electrophilic attack of a borane on an alkene is not expected to be facilitated by mixing of C-OCOR orbitals with the π-system; indeed,
uncatalyzed hydroborations of alkenes 34 should be slightly retarded when the σ-electron withdrawing properties of the allylic ester group are increased.\textsuperscript{24,31}

It is informative to correlate results obtained in these competition experiments with stereoselectivities in catalyzed hydroborations of the same substrates (Table 2.1). Syn:anti ratios observed in catalyzed hydroborations of butyl-substituted allylic alcohol derivatives increase when acetate is substituted with trifluoroacetate and with pivalate. The competition experiments presented in Table 2.2 indicate enhanced syn selectivities for the trifluoroacetate and pivalate are due to electronic and steric effects respectively.

\textbf{Table 2.2. Relative Rates of Hydroborations of Allylic Alcohol Derivatives 34.}

\begin{tabular}{|c|c|c|c|c|}
\hline
entry & R\textsuperscript{1} & R\textsuperscript{2} & conditions & Bu:Pr\textsuperscript{a} \\
\hline
1 & Me & Me & catalyzed\textsuperscript{b} & 1.0:1.2 \\
2 & Me & CF\textsubscript{3} & catalyzed & 1:160 \\
3 & CF\textsubscript{3} & Me & catalyzed & 210:1 \\
4 & CF\textsubscript{3} & Me & uncatalyzed\textsuperscript{c} & 1.0:4.9 \\
5 & Me & \textsuperscript{t}Bu & catalyzed & 2.7:1.0 \\
6 & \textsuperscript{t}Bu & Me & catalyzed & 1.0:3.5 \\
\hline
\end{tabular}
2.1.4 The Cieplak Effect

Cieplak suggested that attack of any reagent on an unsaturated center will be stabilized via overlap of the incipient $\sigma^*$-orbital with the highest energy $\sigma$-orbital of appropriate symmetry.\textsuperscript{78,79} This theory, which is essentially opposite to the Ahn-Eisenstein model, was proposed to explain the predominantly axial approach of a nucleophile to the carbonyl carbon of cyclohexanone derivatives, instead of the sterically favored equatorial approach. Cieplak assumed that the Baker-Nathan order of electron donating ability applies for this reaction, \textit{i.e.} carbon-hydrogen bonds are better donors than carbon-carbon bonds. Therefore axial attack results from better stabilization of the incipient $\sigma^*$-orbital by the $\sigma$-orbital associated with the C-H bond, compared with the interaction of the $\sigma^*$ with the C-C $\sigma$-orbital during equatorial attack (Figure 2.8a and b). Although the Cieplak postulate correctly predicts the stereoselectivity observed for a range of different reactions on rigid systems (\textit{vide infra}),\textsuperscript{80} reactions involving acyclic substrates usually provide \textit{anti}-Cieplak products.

\begin{center}
\begin{figure}
\begin{center}
\includegraphics[width=\textwidth]{figure2_8}
\end{center}
\end{figure}
\end{center}

\textbf{Figure 2.8.} (a) Explanation for preferential axial approach of cyclohexanone derivatives by a nucleophile according to the Cieplak postulate. (b) Energetically less favorable orbital interaction during equatorial approach.

Several reports have disputed the Cieplak model, particularly since the Baker-Nathan order was found to be reversed for gas phase reactions. This criticism was not
applicable, however, for reactions involving 5-substituted-2-methyleneadamantanes (Figure 2.9), which have only carbon-carbon bonds flanking the reaction center. The 5-substituents of these substrates are unlikely to have any steric influence on reactions at C(2), consequently 5-substituted adamantanes have been used to probe electronic effects in several different reaction types.\(^{81-86}\) The C(3)-C(4) and C(5)-X bonds in these compounds meet the stereo-electronic requirement of anti-planarity for \(\sigma\)-participation.\(^{87}\) Electronic perturbations resulting from such hyperconjugation lower (X = F or Ph) or elevate (X = SiMe\(_3\)) the energy of the C(3,4) bonds relative to the C(3,8) linkages on the opposite face of the alkene; this in turn may cause \(\pi\)-facial selectivities in reactions at the alkene group.

![Diagram](image)

**Figure 2.9.** (a) Preferential approach of a hydroborating reagent as predicted using the Cieplak postulate. (b) Preferential approach in rhodium catalyzed hydroboration deduced by consideration of secondary orbital effects involving d\(\pi\)-p\(\pi\) interactions.

Using Cieplak's hypothesis, one would predict hydroboration of these alkenes would occur preferentially on the face anti to the highest available \(\sigma\)-orbital, i.e. syn to a \(\sigma\)-electron withdrawing 5-substituent (e.g. Figure 2.9a), and anti to a \(\sigma\)-electron releasing one. These selectivities are likely to be small, but they are significant provided that they can be measured accurately. Cieplak's theory has gained experimental support for a range of reactions with different sterically unbiased, rigid substrates, including nucleophilic attack
on carbonyls,\,\textsuperscript{82,84,88,89} capture of radicals,\,\textsuperscript{90} cycloadditions,\,\textsuperscript{91} and the formation and capture of cations.\,\textsuperscript{81,83} Furthermore, NMR-studies on several adamantane derivatives have indicated the presence of hyperconjugation in these compounds.\,\textsuperscript{92} However, other reports have attributed the Cieplak selectivities in reactions with sterically unbiased substrates to electrostatic rather than hyperconjugative effects.\,\textsuperscript{93-95}

In contrast to the Cieplak theory, the Burgess/Ohlmeyer model predicts catalyzed hydroborations of rigid substrates with electronically perturbed, but sterically equivalent, alkene faces to occur via preferential delivery of the boron-hydride opposite the face flanked by the best $\sigma$-acceptor (Figure 2.8b). Therefore, we decided to study the face selectivities of both uncatalyzed and catalyzed hydroborations of 5-substituted -2-methylene adamantanes to test both hypotheses simultaneously.

\section*{2.2 Results and Discussion}

\subsection*{2.2.1 Syntheses of 5-Substituted-2-methylene Adamantanes}

The preparation of 5-substituted-2-methylene adamantanes involved some rather tedious chemistry (Scheme 2.1). 2-Adamantanone was oxidized to 5-hydroxy-adamantanone (35) by prolonged standing in 100 \% nitric acid (70 h) followed by distillation of the acid and heating in concentrated sulfuric acid to decompose the HNO\textsubscript{3}-adduct of the hydroxyketone.\,\textsuperscript{96} Conversion of 5-hydroxy-2-adamantanone into 5-bromo-2-adamantanone (36) was achieved in 80 \% yield by treatment with 48 \% aqueous HBr in HOAc.\,\textsuperscript{96} 5-Fluoro-2-methylene adamantane (38) had been synthesized previously by displacement of the bromide from compound 36 with anhydrous silver fluoride, followed by Wittig olefination.\,\textsuperscript{81} In this work, product 38 was obtained from the hydroxyketone 35 via the shorter route shown in Scheme 2.1. Wittig olefination and subsequent treatment of the olefin 37 with diethylamino sulfur trifluoride (DAST) provided the desired compound in 50 \% yield for two steps.
5-Bromo-2-adamantanone served as starting material for the synthesis of both 5-phenyl-2-methylene adamantane (40) and 5-trimethylsilyl-2-methylene adamantane (43). Friedel-Craft alkylation of benzene in the presence of aluminum tribromide\textsuperscript{96} followed by methylenation under the conditions described by Takai\textsuperscript{97} afforded 40. Protection of the carbonyl functionality of 36 and subsequent reaction with trimethylsilyl anion, generated from hexamethyldisilane and lithium wire, produced 5-trimethylsilyl-2-adamananone.\textsuperscript{83} About 10\% of an inseparable side product also was formed, which was indirectly characterized (see appendix 2) as compound 41 from competing cleavage of the C-Si bond of hexamethyldisilane by lithium metal. The crude material was converted to the product alkene in poor yield by either Takai or Wittig olefination. This may be due to fragmentation of 5-trimethylsilyl adamantanes which has been reported previously for electronically similar 5-trimethylstannyl adamantane derivatives.\textsuperscript{98}
Scheme 2.1. Synthesis of 5-substituted-2-methylene adamantanes.

2.2.2 Hydroborations of 5-Substituted 2-Methylene adamantanes

The stereoisomeric alcohols formed by hydroboration of alkenes 38, 40 and 43 could not be separated by chromatographic techniques. Fortunately, selectivities for hydroboration of the fluoro-alkene (38) were established by assigning the $^{13}$C NMR spectra of the crude reaction mixtures and correlating these with product ratios measured by
GC. The $^{13}$C NMR assignments were made by: (i) correlation of our results with le Noble's BH$_3$-hydroboration of the same substrate;\textsuperscript{85} (ii) deducing chemical shifts via the known shielding effects of the pendant hydroxymethylene group on an adamantane skeleton;\textsuperscript{99} and, (iii) assignment of chemical shifts via the "additivity rule for rigid structures".\textsuperscript{100}

The basis of this additivity rule is that the observed chemical shifts for carbon atoms of rigid compounds correlate well with that computed according to equation 2.4, where $\delta$(H,H) represents the chemical shift of the carbon in the unsubstituted parent compound.

\[
\delta(X,Y) = \delta(X,H) + \delta(H,Y) - \delta(H,H)
\]  \hspace{1cm} (2.4)

Le Noble and coworkers showed that the method is valid to about 0.5 ppm for 2-hydroxy-5-substituted adamantanes.\textsuperscript{100} The correlation between the observed and calculated chemical shifts for some diagnostic carbon atoms of the product alcohols in this work is presented in Table 2.3. Coupling of the $^{19}$F substituent in the hydroboration product from 38 to the carbons at C$^{(4)}$, but not to those at C$^{(8)}$, facilitated the assignment of $^{13}$C NMR signals in this case. Shielding effects and the additivity rule were also used to unambiguously assign the $^{13}$C NMR peaks of the phenyl-substituted product.

Unfortunately, the $^{13}$C NMR chemical shifts for the C$^{(4,9)}$ and C$^{(8,10)}$ carbons of the silyl-substituted compounds were very close, so direct correlation of the $^{13}$C NMR spectrum of
the crude reaction mixture and the GC ratios was inconclusive. Consequently, the sense of the diastereoselection for the silicon substituted compounds were assigned by inference, *i.e.* by assuming Cieplak selectivity in the uncatalyzed reaction (*vide infra*).

Table 2.3. Calculated and Observed Chemical Shifts in $^{13}$C NMR of Adamantanes.

<table>
<thead>
<tr>
<th>X, Y</th>
<th>C(4,9) $^{\delta}$ (ppm) obs.</th>
<th>C(4,9) $^{\delta}$ (ppm) calc.</th>
<th>C(8,10) $^{\delta}$ (ppm) obs.</th>
<th>C(8,10) $^{\delta}$ (ppm) calc.</th>
</tr>
</thead>
<tbody>
<tr>
<td>H,H</td>
<td>38.24</td>
<td>38.24</td>
<td>38.24</td>
<td>38.24</td>
</tr>
<tr>
<td>Z-OH,F</td>
<td>37.17</td>
<td>37.44</td>
<td>37.04</td>
<td>37.24</td>
</tr>
<tr>
<td>E-OH,F</td>
<td>43.53</td>
<td>44.06</td>
<td>30.31</td>
<td>30.29</td>
</tr>
<tr>
<td>Z-OH,Ph</td>
<td>37.32</td>
<td>36.84</td>
<td>37.98</td>
<td>37.49</td>
</tr>
<tr>
<td>E-OH,Ph</td>
<td>44.32</td>
<td>43.79</td>
<td>30.84</td>
<td>30.54</td>
</tr>
<tr>
<td>Z-OH,TMS</td>
<td>38.56</td>
<td>38.06</td>
<td>31.94</td>
<td>31.71</td>
</tr>
<tr>
<td>E-OH,TMS</td>
<td>31.25</td>
<td>31.11</td>
<td>38.91</td>
<td>38.66</td>
</tr>
</tbody>
</table>

Results in Table 2.4 show catalyzed hydroborations of alkenes 44 occur preferentially on the alkene face opposite to electron withdrawing substituents (giving excess *syn* product, entries 1, 2, 7, and 8), and on the same face as an electron releasing substituent (SiMe$_3$, entry 11). Hyperconjugation lowers the energy of the $\sigma^*$-orbital of the C(3)-C(4) bond relative to the C(3)-C(8) bond when the C(5) substituent is electron withdrawing (*e.g.* F or Ph). Conversely, the $\sigma^*$-orbital of the C(3)-C(4) bond is relatively high in energy when the 5-substituent is SiMe$_3$ (*i.e.* electron releasing). Consequently, the catalyzed hydroborations shown in Table 2.4 occur preferentially on the face opposite the
lowest lying $\sigma^*$-level, in perfect accord with the Burgess/Ohlmeyer hypothesis discussed above.

Table 2.4. Catalyzed and Uncatalyzed Hydroborations of Alkenes 44.

<table>
<thead>
<tr>
<th>entry</th>
<th>Z</th>
<th>solvent</th>
<th>conditions</th>
<th>anti:syn</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>THF</td>
<td>catalyzed$^a$</td>
<td>46:54</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>MePh</td>
<td>catalyzed</td>
<td>47:53</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>THF</td>
<td>uncatalyzed, BH$_3$$^b$</td>
<td>63:37</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>MePh</td>
<td>uncatalyzed, BH$_3$</td>
<td>57:43</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>THF</td>
<td>uncatalyzed, 9-BBN$^c$</td>
<td>68:32</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>THF</td>
<td>uncatalyzed, catecholboraned$^d$</td>
<td>65:35</td>
</tr>
<tr>
<td>7</td>
<td>Ph</td>
<td>THF</td>
<td>catalyzed</td>
<td>43:57</td>
</tr>
<tr>
<td>8</td>
<td>Ph</td>
<td>MePh</td>
<td>catalyzed</td>
<td>40:60</td>
</tr>
<tr>
<td>9</td>
<td>Ph</td>
<td>THF</td>
<td>uncatalyzed, BH$_3$</td>
<td>52:48</td>
</tr>
<tr>
<td>10</td>
<td>Ph</td>
<td>MePh</td>
<td>uncatalyzed, BH$_3$</td>
<td>53:47</td>
</tr>
<tr>
<td>11</td>
<td>SiMe$_3$</td>
<td>THF</td>
<td>catalyzed</td>
<td>75:25</td>
</tr>
<tr>
<td>12</td>
<td>SiMe$_3$</td>
<td>THF</td>
<td>uncatalyzed, BH$_3$</td>
<td>47:53</td>
</tr>
</tbody>
</table>

$^a$ Substrate: catecholborane = 1.0:1.5, 1 mol % [Rh(COD)Cl]$_2$, 4 mol % PPh$_3$. Throughout, product ratios determined via capillary GC of the silylated alcohols and checked via $^1$H, $^{13}$C, and, where appropriate, $^{19}$F NMR. $^b$ Equimolar amounts of substrate and BH$_3$.THF, THF, 0 °C to 20 °C, 12 h. $^c$ Substrate: 9-BBN = 1.0:1.5, THF, 0 °C to 20 °C, 36 h. $^d$ Substrate: catecholborane = 1.0:8.0, THF, 70 °C, 2 h.
Entry 2 in Table 2.4, confirms a result previously reported by le Noble and co-workers: hydroboration of this alkene with BH$_3$ gives predominantly the \textit{anti} product, just as one would predict using the Cieplak postulate. In fact, selectivities for all the uncatalyzed hydroboration presented in Table 2.4 are in accord with the model Cieplak described (entries 3 - 6, 9, 10 and 11). However, all the rhodium-mediated hydroboration of the same substrates give opposite stereochemistry, in contrast to the Cieplak postulate. Notably, hydroboration of 5-fluoro-2-methylene adamantane using catecholborane/rhodium catalyst gives a 46:54 \textit{syn} selectivity, whereas conventional hydroboration of the same substrate with catecholborane (no catalyst, higher temperature required) gives a 65:35 distribution in the opposite sense (Figure 2.10).

![Figure 2.10](image)

\textbf{Figure 2.10.} GC-traces of silylated crude reaction products from (a) BH$_3$ hydroboration of 38; (b) Rh-catalyzed hydroboration of 38; (c) hydroboration of 38 with catecholborane at 70 °C. Initial oven temperature 125 °C, then ramped 2 °C/min on 50 m fused silica column (see experimental for GC system).

The selectivities observed with the alkenes 44 are small ($\Delta\Delta$G$^\# = \sim 0.2$ kcal mol$^{-1}$), but this is not unexpected since the electronic perturbation by a substituent four bonds removed from the reaction center is not likely to be strong. More importantly, the observed selectivities proved highly reproducible and could be measured accurately by GC.
Computational studies have recently indicated that diastereofacial selectivities in other electronically perturbed alkenes can arise from solvation effects rather than the type of orbital interactions Cieplak proposes. The selectivities observed in this work, however, do not appear to be particularly sensitive to solvent change from THF to toluene (entries 1 and 2; 3 and 4; 7 and 8; and, 9 and 10); the uncatalyzed reactions are always selective in the sense predicted from the Cieplak postulate, and selectivities in the catalyzed reactions are opposite in every case. Solvent changes have been shown to have no effect in other tests of the Cieplak postulate.

The Cieplak model was formulated to explain results in kinetically controlled reactions. It is not clear that rhodium-catalyzed hydroborations of substrates 44 are kinetically controlled, so it is premature to describe them as exceptions to the Cieplak postulate. Indeed, Le Noble and Bodepudi have recently reported an apparent exception to the Cieplak hypothesis which they explain in terms of thermodynamic control. To establish whether overall catalyzed hydroboration process is irreversible excess 3,3-dimethylbut-1-ene 45 was subjected to catalyzed hydroboration until all the available catecholborane was consumed (equation 2.5); norbornene and more catalyst were added, and the mixture was allowed to stand for an additional 24 h, oxidized, and analyzed by GC. Competition experiments show norbornene reacts twice as fast as 3,3-dimethylbut-1-ene in catalyzed hydroborations, hence one would expect to observe norborneol at the end of this sequence if the catalyst reverses the hydroboration of 45. In fact, no norborneol was detected, implying that the reductive elimination step in catalyzed hydroboration of alkene 45 is irreversible. A similar experiment was reported recently by Evans and coworkers confirming this observation.
In a different experiment (equation 2.6), 5-fluoro-2-methyleneadamantane (38) was hydroborated with excess C₆H₄O₂BD, and the products obtained after oxidation were analyzed via ¹H and ²H NMR. No tertiary alcohol was detected, and almost all of the deuterium was located at the C(₂) position of the adamantane skeleton; this implies reversible formation of tertiary-rhodium alkyl complexes in these reactions is insignificant or does not occur at all. Others have suggested reversible formation of tertiary-alkyl rhodium complexes in these reactions (see chapter three), but such intermediates apparently are not formed under the conditions used in this study.
2.3 Conclusions

Results obtained in these experiments prove stereoselectivities of catalyzed hydroborations of alkenes are sensitive to electronic effects in a manner that can be anticipated by assuming metal complexation is determinant, then considering secondary orbital interactions involving dπ-pπ interactions. The theory originally proposed by Burgess and Ohlmeyer to account for stereoselectivities in rhodium-catalyzed hydroborations of allylic alcohols (and related substrates)\(^{48,72-74}\) facilitates prediction of rate differences, and of stereoselectivities arising from very weak electronic perturbations.

Recently, two other literature reports have described face selectivities for reactions related to this work. First, le Noble found that treatment of the adamantane derivative 46 with iron pentacarbonyl at 80 °C for 17 h, followed by refluxing the reaction mixture in n-butylether (b.p. 142 °C) predominantly produced the Z-isomer of 47 (E:Z = 2:3).\(^{86}\) Although this selectivity does not agree with that predicted for the complexation of transition metal complexes according to the Burgess/Ohlmeyer model, small electronic effects may not play a significant role under the harsh reaction conditions necessary for the reaction to proceed.

\[ \begin{align*}
46 \quad \text{Fe(CO)}_5 & \rightarrow \quad \text{(OC)}_3\text{Fe} \quad \downarrow \quad \text{Fe(CO)}_3 \\
\text{E-47} & \quad \text{Z-47} \\
\text{2 : 3} \\
\end{align*} \]

Ojima and coworkers observed moderate diastereoselectivity for rhodium catalyzed amidocarbonylation of allylic amine derivatives 48, leading to predominant production of
the syn-isomer 49. The results were accommodated using the proposed model for rhodium catalyzed hydroboration.

\[
\begin{align*}
\text{HRh(CO)(PPh}_3\text{)} & \quad \text{CO/H}_2, \text{HC(OEt)}_3 \\
\text{48} & \quad \text{syn} \quad \text{2 : 1} \\
& \quad \text{anti}
\end{align*}
\]

Finally, Cieplak's postulate implies all kinetically controlled reactions of alkenes should preferentially occur on the face syn to the best electron withdrawing group (Figure 2.9a). Results presented in Table 2.4 for catalyzed hydroboration provide a set of examples for which the Cieplak hypothesis is clearly not applicable. If these catalyzed hydrobortations are kinetically controlled, the stereoselectivities observed for substrates 44 are indicative of a fundamental flaw in the Cieplak postulate.
Chapter 3. Mechanistic Studies on Catalyzed Hydroboration

3.1 Introduction

After the original report on rhodium-catalyzed hydroboration of alkenes by Männig and Nöth in 1985, a large number of publications appeared documenting progress in chemoselective, diastereoselective, and enantioselective catalyzed hydroborations (section 1.3). However, the mechanism by which the borane is added to the substrate remained obscure. Männig and Nöth originally proposed the catalytic cycle shown in Scheme 3.1 for the reaction catalyzed by Wilkinson's catalyst, RhCl(PPh₃)₃.

Scheme 3.1. A possible mechanism for the hydroboration of alkenes mediated by RhCl(PPh₃)₃.

This model involves oxidative addition of the B-H bond to Rh(I), followed by
alkene insertion into the Rh-H bond and subsequent reductive elimination of the B-C bond. They characterized the oxidative addition product 50 from a stoichiometric reaction of RhCl(PPh$_3$)$_3$ with catecholborane by $^1$H NMR and IR, and showed that this complex reacts with alkenes resulting in hydroboration products and the rhodium complex 51. Compound 50 had been previously isolated by Kono and Ito in 1975 without recognizing its potential in catalysis.$^{105}$

Several model systems for catalyzed hydroboration have been reported providing support for some of the individual steps of the mechanism depicted in Scheme 3.1. Knorr and Merola isolated complex 52 from reaction of catecholborane with the iridium catalyst Ir(COE)(PMe$_3$)$_3$Cl (COE = cyclooctene).$^{106}$ Migratory insertion of phenylacetylene into the Ir-H bond of 52 led to the production of complex 53. This compound appears to be the resting state during the catalytic cycle and only very slow (6 turnovers in 2 days) reductive elimination of the vinyl and borate ligands of 53 was observed furnishing the hydroboration product 54.
Marder and Baker described oxidative addition of the boron-hydrogen bond of 9-BBN to the iridium complex 55.\textsuperscript{107} The analogous reaction of catecholborane with [Ir(μ-Cl)(COE)\textsubscript{2}]\textsubscript{2} in the presence of four equivalents of the electron-rich phosphine \textsuperscript{i}Pr\textsubscript{3}P yielded the trigonal bipyramidal complex 56.\textsuperscript{108} These same researchers also isolated and structurally characterized compound 58 from reaction of catecholborane with RhCl(N\textsubscript{2})(\textsuperscript{i}Pr\textsubscript{3})\textsubscript{2} (57).\textsuperscript{109} Both complexes (56 and 58) were shown to be active catalysts promoting the addition of catecholborane to alkenes.

\begin{equation}
\text{IrH(PMe}_3\text{)}\textsubscript{4} \underset{9\text{-BBN}}{\overset{\rightarrow}{\text{55}}} \begin{array}{c}
\text{Ir} \\
\text{H}
\end{array} \begin{array}{c}
\text{PMe}_3 \\
\text{H}
\end{array} \\
\begin{array}{c}
\text{B} \\
\text{H}
\end{array} \\
\begin{array}{c}
\text{H} \\
\text{PMe}_3
\end{array} \\
\begin{array}{c}
\text{PMe}_3 \\
\text{H}
\end{array} \\
\begin{array}{c}
\text{B} \\
\text{Ir}
\end{array} \\
\begin{array}{c}
\text{PMe}_3 \\
\text{H}
\end{array}
\end{equation}

(3.3)

\begin{equation}
\begin{array}{c}
\text{Cl} \\
\text{B} \\
\text{H}
\end{array} \begin{array}{c}
\text{N} \\
\text{N}
\end{array} \begin{array}{c}
\text{Rh} \\
\text{Cl}
\end{array} \begin{array}{c}
\text{H} \\
\text{iPr}_3\text{P}
\end{array} \\
\begin{array}{c}
\text{O} \\
\text{iPr}_3\text{P}
\end{array} \\
\begin{array}{c}
\text{O} \\
\text{iPr}_3\text{P}
\end{array} \\
\begin{array}{c}
\text{Cl} \\
\text{B} \\
\text{H}
\end{array} \begin{array}{c}
\text{N} \\
\text{N}
\end{array} \begin{array}{c}
\text{Rh} \\
\text{Cl}
\end{array} \begin{array}{c}
\text{H} \\
\text{iPr}_3\text{P}
\end{array} \\
\begin{array}{c}
\text{O} \\
\text{iPr}_3\text{P}
\end{array} \\
\begin{array}{c}
\text{O} \\
\text{iPr}_3\text{P}
\end{array}
\end{equation}

(3.4)

Marder and Baker also found that the reaction of Wilkinson's catalyst with catecholborane produces a number of rhodium complexes besides the expected oxidative addition product 50 (equation 3.5).\textsuperscript{110} Most notable is the isolation of the dihydride
complex 59, which accounts for the competing hydrogenation that is often seen in hydroboration processes catalyzed by RhCl(PPh₃)₃.

\[
\begin{align*}
\text{Cl}^-\text{Rh}^-\text{PPh}_3^- + \text{H-B-O} & \rightarrow \text{THF or CH}_2\text{Cl}_2 \\
\text{Ph}_3\text{P}^- \text{Rh}^-\text{PPh}_3^- \rightarrow \text{BH}_3\text{PPh}_3
\end{align*}
\]

The model systems described above give insight into the chemistry associated with stoichiometric hydroboration of alkenes mediated by metal complexes, but they do not give information about the insertion step of alkene during the catalytic transformation. Evans and Fu performed a series of deuterium labeling experiments in which substrates were treated with 0.1 equivalents of catecholborane-\(d_1\) in the presence of a catalytic amount of Wilkinson's catalyst.¹⁰²,¹⁰³ The presence of label in the recovered starting material was taken as evidence for reversibility of migratory insertion of alkenes into Rh-H(D) bonds (equations 3.6-3.8, numbers indicate % of deuterium found at each position).

\[
\begin{align*}
\text{nC}_8\text{H}_{17} \rightarrow \text{OHO} & \rightarrow \text{nC}_8\text{H}_{17} + \text{nC}_8\text{H}_{17} \\
86 \% & \rightarrow 14 \% \rightarrow 50 \% \rightarrow 50 \% \rightarrow 33 \%
\end{align*}
\]
The results for the allylic alcohol derivative 65 were particularly interesting (equation 3.8), because this substrate represents a class of compounds for which rhodium catalyzed hydroboration has been found to be a very useful reaction, providing high levels of diastereoselectivity (see chapter 1). No deuterium was found in the recovered alkene for this particular substrate, which is consistent with the Burgess/Ohlmeyer model, that alkene complexation and insertion for this class of substrates is stereodetermining (chapter 2).48,73 Nevertheless, the presence of deuterium in the starting material for other alkenes (i.e. 1-decene, equation 3.6) and in the α-position of alcohol 66 prompted the authors to question the validity of the Burgess-Ohlmeyer postulate. The absence of label in alkene 65 and in the methyl group of alcohol 66 coupled with significant levels of α-deuteration was explained as shown in Scheme 3.2.103
Scheme 3.2. Published rationale to explain observed label distribution in catalyzed hydroboration of substrate 65 with catecholborane-$d_I$.103

We had established the irreversibility of the reductive elimination step in the course of the work described in chapter 2.77 Evans and coworkers came to the same conclusion in a later publication using a similar approach.102 Therefore, label distribution into the products of rhodium-catalyzed hydroboration is limited to processes involving insertion/deinsertion of alkene into the Rh-D bond of metal-deuteride complexes present in solution.

Several of the conclusions drawn by Evans and Fu from the results of their labeling studies were not entirely satisfactory to us. First, the presence of rhodium-hydride complexes (e.g. 59, equation 3.5) which are capable of distributing deuterium label into the products of the overall process was not taken into account. Furthermore, the proposed
explanation for the label distribution in alcohol 66 requires 100 % diastereoselective β-elimination from the labeled methyl group, CH₂D, (as opposed to the diastereotopic methyl CH₃) since deuterium was not found in the CH₃ moiety (Schemes 3.2 and Figure 3.1). It also implies very high diastereofacial selectivity in addition of Rh-D to alkene, as addition to the opposite face would give an alkene-rhodium π-complex with deuterium in the vinylic methyl group (Figure 3.1). Finally, all labeling experiments were performed with Wilkinson's catalyst while the diastereoselectivity studies in our laboratory were usually carried out with the complex [Rh(μ-Cl)(COD)]₂ (COD = 1,4-cyclooctadiene) in the presence of two equivalents of triphenylphosphine per rhodium.⁴⁷,⁴⁸,⁷²,⁷⁴ Therefore we decided to reinvestigate the labeling study.

![Diagram](image_url)

**Figure 3.1** Expected label distribution from intermediate I.
3.2 Results and Discussion

3.2.1 Deuterium Labeling Studies with Commercial Wilkinson's Catalyst

Initial results obtained for the reaction of 1-decene and phenylethene with 0.1 equiv. of catecholborane-$d_7$ are shown in equations 3.9 and 3.10.\textsuperscript{111} GC and $^{13}$C NMR analysis of the crude reaction mixture of experiments with 1-decene revealed extensive isomerization of the starting material to various internal alkenes. Analysis of the product alcohols by $^2$H NMR after chromatographic removal of alkene also indicated a significant extent of deuterium incorporation along the alkyl chain of 1-decanol. Moreover, HRMS experiments showed that a considerable portion of the product alcohols contained more than one deuterium atom per molecule.

\[
\begin{align*}
\text{HO} - \text{C}_8\text{H}_{17} & \quad + \quad \text{C}_8\text{H}_{17} \quad + \quad \text{R} - \text{C}_8\text{H}_{17} \\
60 & \quad + \quad 60' & \quad 60'' \text{ (several products)} \quad (3.9) \\
60':60'' = 5:95
\end{align*}
\]

deuterium observed at all positions along alkyl chain of 61

Experiments with phenylethene produced 2-phenylethanol as the major product. This does not agree with the Evans' study, but Hayashi and coworkers previously had reported similar regioselective production of primary alcohol in the reaction of phenylethene with catecholborane mediated by Wilkinson's catalyst.\textsuperscript{51,52} Significant label incorporation into the starting material was observed and HRMS again indicated the presence of more than one deuterium atom per product molecule.
Finally, substrate 65 was reacted with catecholborane-d$_1$ in the presence of 0.02 equiv. of Wilkinson's catalyst or 0.01 equiv. of [Rh(COD)Cl]$_2$/4 PPh$_3$. No $\alpha$-deuteration was observed in either case and a small amount of deuterium was found in the starting alkene.

Most of the observations described above were in disagreement with the literature labeling study. Personal correspondence with Professor Evans revealed that the original work had been performed with freshly prepared Wilkinson's catalyst; our results, however, had been obtained with commercial RhCl(PPh$_3$)$_3$ or [Rh(COD)Cl]$_2$/4 PPh$_3$. We
decided to repeat the experiments described above with Wilkinson's catalyst prepared, isolated and stored with rigorous exclusion of oxygen. Equations 3.12 and 3.13 show that use of this material indeed produced results very similar to the original study for experiments with 1-decene and phenylethene. However, experiments with allylic silylether 65 gave some unexpected results, that were still different from the Evans' study. Although α-deuteration was observed, significant amounts of unlabeled aldehyde 67 were produced as well (equation 3.14).

\[
\begin{align*}
\text{60} & \xrightarrow{(i) \text{ 0.002 RhCl(PPh}_3)_3 \text{, 0.1 catecholborane-}d_1 \text{, (ii) oxidation}} \text{61, 60'} \\
\text{61} & \quad 89\% \quad 11\% \\
\text{60'} & \quad 50\% \quad 50\% \\
\% \text{ of total } D & \text{ 61:60'} = 70:30
\end{align*}
\]

\[
\begin{align*}
\text{62} & \xrightarrow{(i) \text{ 0.002 RhCl(PPh}_3)_3 \text{, 0.1 catecholborane-}d_1 \text{, (ii) oxidation}} \text{62''}, \text{63, 64} \\
\text{62''} & \quad 2\% \quad 49\% \quad \sim 0\% \\
\text{63} & \quad 100\% \\
\text{64} & \quad 100\% \\
\% \text{ of total } D & \text{ 62':63:64} = \text{trace:98:2}
\end{align*}
\]

\[
\begin{align*}
\text{65} & \xrightarrow{(i) \text{ 0.002 RhCl(PPh}_3)_3 \text{, 2.0 catecholborane-}d_1 \text{, (ii) oxidation}} \text{66, 67, 68} \\
\text{66} & \quad \text{93\%} \\
\text{67} & \quad \text{7\%} \\
\text{68} & \quad \text{2\%} \\
\% \text{ of total } D & \text{ 66:67:68} = 50:46:4
\end{align*}
\]

The following section describes experiments designed to investigate the origin of the disparate results obtained with different batches of catalyst.
3.2.2 Influence of Rhodium-to-Phosphine Ratios on Catalyzed Hydroboration

As described above, different results were obtained for catalyzed hydroborations using freshly prepared or "aged", commercial Wilkinson's catalyst, suggesting decomposition or oxidation of the catalyst for the latter material. While the chemistry associated with oxidation of RhCl(PPh₃)₃ in the solid state is unclear, in solution it is known to give RhCl(O₂)(PPh₃)₃ (69) which decomposes to [Rh(μ-Cl)(PPh₃)₂]₂ (70), [RhCl(O₂)(PPh₃)₂]₂, and triphenylphosphine oxide.¹¹²,¹¹³ Further oxidation presumably follows the same trend, lowering the phosphine to rhodium ratio by converting more triphenylphosphine to its oxide. Oxidized RhCl(PPh₃)₃ is known to have different properties to the parent material;¹¹⁴-¹¹⁶ significantly, it is a more active catalyst for alkene hydrogenations.¹¹⁷

Formation of 69 alone does not account for the change in regioselectivity as hydroboration of phenylethene catalyzed by pure, isolated 69 gave, after oxidation, almost exclusively 1-phenylethanol (63) (Table 3.1, entry 8). Primary alcohol 64 was the major product, however, when catalyst 69 was stirred for 1 h at 25 °C in THF under argon before phenylethene and catecholborane were added. 2-Phenylethanol (64) also predominated when a small amount of oxygen was introduced into the atmosphere above the hydroboration mixture (using either RhCl(PPh₃) or its dioxygen derivative 69 as catalyst, entries 6 and 9). Consequently, formation of the primary alcohol 64 appears to be due to complexes other than RhCl(PPh₃)₃ and RhCl(O₂)(PPh₃)₃. Higher selectivity for the secondary alcohol was observed when triphenylphosphine was added to oxidized catalyst (entry 7); Dai and coworkers have reported increased selectivity for the secondary product alcohol as more phosphine was added to [Rh(μ-Cl)(COD)]₂ catalyst for the same reaction (entries 10 and 11).¹¹⁸ All these observations are consistent with oxidative removal of triphenylphosphine in solution causing increased selectivity for the primary alcohol.
Similar results were obtained by Evans and coworkers in their investigation into the origin of reversal of regiochemistry upon oxidation. Isolated [RhCl(O$_2$)(PPh$_3$)$_2$]$_2$ gave a 60:40 ratio of primary to secondary alcohol.¹⁰² This complex has been reported to be only sparsely soluble in THF,¹¹²,¹¹⁹ however, and heterogeneous processes cannot be excluded.

Table 3.1. Catalyzed Hydroborations of Phenylenethane.

![Chemical structure](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst$^a$</th>
<th>additions</th>
<th>63:64</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>RhCl(PPh$_3$)$_3$⁵²</td>
<td>-</td>
<td>10:90</td>
</tr>
<tr>
<td>2</td>
<td>RhCl(PPh$_3$)$_3$¹⁰³</td>
<td>-</td>
<td>100:0</td>
</tr>
<tr>
<td>3</td>
<td>RhCl(PPh$_3$)$_3$¹¹¹</td>
<td>-</td>
<td>20:80</td>
</tr>
<tr>
<td>4</td>
<td>RhCl(PPh$_3$)$_3$ (A)</td>
<td>-</td>
<td>&gt;99:&lt;1</td>
</tr>
<tr>
<td>5</td>
<td>RhCl(PPh$_3$)$_3$ (B)</td>
<td>-</td>
<td>24:76</td>
</tr>
<tr>
<td>6</td>
<td>RhCl(PPh$_3$)$_3$ (A)</td>
<td>O$_2$</td>
<td>40:60</td>
</tr>
<tr>
<td>7</td>
<td>RhCl(PPh$_3$)$_3$ (B)</td>
<td>PPh$_3$</td>
<td>&gt;99:&lt;1</td>
</tr>
<tr>
<td>8</td>
<td>RhClO$_2$(PPh$_3$)$_3$</td>
<td>-</td>
<td>&gt;99:&lt;1</td>
</tr>
<tr>
<td>9</td>
<td>RhClO$_2$(PPh$_3$)$_3$</td>
<td>O$_2$</td>
<td>14:86</td>
</tr>
<tr>
<td>10</td>
<td>[Rh(COD)Cl]$_2$¹¹⁸</td>
<td>2 PPh$_3$</td>
<td>41:59</td>
</tr>
<tr>
<td>11</td>
<td>[Rh(COD)Cl]$_2$¹¹⁸</td>
<td>4 PPh$_3$</td>
<td>98:2</td>
</tr>
</tbody>
</table>

$^a$ Preparation A via the *Inorganic Syntheses* procedure, handled and manipulated under anaerobic conditions; preparation B is catalyst stored and manipulated in the air.
Table 3.2 shows results obtained for catalyzed hydroborations of phenylethene with 0.1 equivalents of DBO₂C₆H₄ in the presence of Wilkinson's catalyst that was: (A) freshly prepared; (B) exposed to air in the solid state; and, (C) the latter material plus three equivalents of PPh₃. Reactions mediated by oxidized catalyst in the absence of added PPh₃ gave more primary alcohol 64, and more deuterium incorporation in the recovered starting material (62'), relative to analogous reactions using freshly prepared catalyst.

<table>
<thead>
<tr>
<th>product/label</th>
<th>catalyst system(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>distribution</td>
<td>RhCl(PPh₃)₃ (A)</td>
</tr>
<tr>
<td>62(^1); α:β(^c):β(^i)</td>
<td>2:49:49</td>
</tr>
<tr>
<td>63; α:β</td>
<td>0:100</td>
</tr>
<tr>
<td>64; α:β</td>
<td>0:100</td>
</tr>
</tbody>
</table>

\(^a\) Preparation A via the Inorganic Syntheses procedure, handled and manipulated under anaerobic conditions; preparation B is catalyst stored and manipulated in the air.

3.2.3 Hydroboration of Phenylethene

Catalyzed hydroborations of phenylethene with two equivalents of catecholborane gave, after oxidation, carbonyl compounds, alcohols, and/or diols, depending on reaction
conditions (Table 3.3). At short reaction times isomeric carbonyl compounds predominated (entries 1 and 2), whereas extended periods favored formation of alcohols (entries 3 - 5). Formation of primary alcohol 64 originates presumably from hydrogenation of intermediate vinylboronate esters as the alternative, hydroboration of phenylethene, would give secondary alcohol 63 exclusively (vide supra).

**Table 3.3. Effect of Catalyst in Rhodium-Mediated Hydroborations of Phenylethene**

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst$^a$</th>
<th>reaction</th>
<th>product distribution (%)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>time (h)</td>
<td>$63$</td>
</tr>
<tr>
<td>1</td>
<td>RhCl(PPPh$_3$)$_3$</td>
<td>1.0</td>
<td>9</td>
</tr>
<tr>
<td>2</td>
<td>RhCl(PPPh$_3$)$_3$ + 1 PPh$_3$</td>
<td>1.5</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>RhCl(PPPh$_3$)$_3$</td>
<td>12</td>
<td>20</td>
</tr>
<tr>
<td>4</td>
<td>RhCl(PPPh$_3$)$_3$ + 1 PPh$_3$</td>
<td>15</td>
<td>29</td>
</tr>
<tr>
<td>5</td>
<td>[Rh(COD)Cl]$_2$ + 8 PPh$_3$</td>
<td>12</td>
<td>54</td>
</tr>
</tbody>
</table>

$^a$Prepared and handled under anaerobic conditions. $^b$Determined via $^1$H NMR, all figures ± 5%.

Formation of diol 73 in the catalyzed hydroboration of phenylethylene is interesting because it suggests vinylboronate ester intermediates can be hydroborated catalytically.
Direct evidence for this type of transformation has been obtained in experiments with allylsilyl ether and vinylarene substrates (*vide infra*).

To test for hydrogenation of vinylboronate esters under catalyzed hydroboration conditions, a vinylboronate ester was prepared and isolated from the uncatalyzed reaction of 1-hexyne with catecholborane. When this vinylboronate ester was subjected to catalytic hydroboration, the resulting mixture indeed contained significant amounts of 1-hexanol after oxidation (equation 3.15).

\[
\text{Pr} \quad \text{catecholborane} \quad 70 \, ^\circ\text{C} \quad \text{Pr} \quad \text{catecholborane}
\]

(i) \( \text{RhCl(PPh}_3\text{)}_3 \)  
(ii) \( \text{H}_2\text{O}_2/\text{NaOH} \)

\[
\begin{align*}
\text{Pr} & \quad \text{Pr} \\
\text{Pr} & \quad \text{Pr} \\
\text{Pr} & \quad \text{Pr} \\
\text{Pr} & \quad \text{Pr} \\
\end{align*}
\]

\[\text{(3.15)}\]

### 3.2.4 Deuterium Labeling studies for Allylic Alcohol Derivatives

After establishing that the phosphine content of the catalyst is important in rhodium catalyzed hydroborations of phenylethene (section 3.2.2), we decided to study this variable with respect to the hydroboration of allylic silyl ether 65. Freshly prepared \( \text{RhCl(PPh}_3\text{)}_3 \) manipulated in an inert atmosphere gave significant \( \alpha \)-deuteration (Fig. 3.2a). However, significant amounts of unlabeled aldehyde 68 were formed whenever \( \alpha \)-deuterium was observed in alcohol 66 (Figure 3.2a and b). Aldehyde 67 was not present in the reaction mixture before oxidation with alkaline hydrogen peroxide (by GC analysis). As described previously (section 3.2.1), neither \( \alpha \)-deuteration nor aldehyde production was observed in reactions using commercial Wilkinson’s catalyst or \( [\text{Rh(COD)Cl}]_2/4 \text{PPh}_3 \) (Fig 3.2b).
Table 3.4. Catalyzed Hydroboration of Silyl ether 65 with Catecholborane-$d_1$.

![Diagram showing reaction steps and products](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst system (method)$^a$</th>
<th>equivalents $^{66:67:68b}$</th>
<th>D-label$^c$</th>
<th>66$^b$ syn:anti</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>RhCl(PPh$_3$)$_3$ (A)</td>
<td>0.1</td>
<td>35:5:60</td>
<td>16:84</td>
</tr>
<tr>
<td>2</td>
<td>RhCl(PPh$_3$)$_3$ (B)</td>
<td>0.1</td>
<td>&gt;99:1:0</td>
<td>&lt;1: &gt;99</td>
</tr>
<tr>
<td>3</td>
<td>RhCl(PPh$_3$)$_3$ (A)</td>
<td>2.0</td>
<td>50:46:4</td>
<td>7:93</td>
</tr>
<tr>
<td>4</td>
<td>RhCl(PPh$_3$)$_3$ (B)</td>
<td>2.0</td>
<td>&gt;99:1:0</td>
<td>&lt;1: &gt;99</td>
</tr>
<tr>
<td>5</td>
<td>RhCl(PPh$_3$)$_3$ (A) + 1PPh$_3$</td>
<td>2.0</td>
<td>34:66:1</td>
<td>20:80</td>
</tr>
<tr>
<td>6</td>
<td>RhCl(PPh$_3$)$_3$ (B) + 1PPh$_3$</td>
<td>2.0</td>
<td>73:27:1</td>
<td>4:96</td>
</tr>
<tr>
<td>7</td>
<td>[Rh(COD)Cl)$_2$ + 8PPh$_3$</td>
<td>2.0</td>
<td>60:40$^d$</td>
<td>30:70</td>
</tr>
</tbody>
</table>

All samples of RhCl(PPh$_3$)$_3$ were prepared according to the *Inorganic Syntheses* procedures.$^{120,121}$ $^a$ Method A employs catalyst handled under an inert atmosphere at all times, method B uses Wilkinson's catalyst exposed to trace amounts of oxygen. All hydroboration reactions performed via either method were executed under an inert atmosphere, see experimental. $^b$ Determined by GC. $^c$ Determined by $^2$H NMR; throughout >99:<1 (or *vice versa*) indicates the minor component was not observed by NMR. $^d$ The amount of reduction product 68 was not determined.
Figure 3.2. GC-trace (top) and $^2$H NMR (bottom) from the crude product of hydroboration of 65 with catecholborane-$d_1$ catalyzed by (a) freshly prepared RhCl(PPh$_3$)$_3$, and (b) "aged" RhCl(PPh$_3$)$_3$. 
Product and label distributions changed dramatically when freshly prepared RhCl(PPh₃)₃ was allowed to react with trace amounts of oxygen (Table 3.3, entry 2), even though the amount of oxygen added was so small that the ³¹P NMR spectrum of this solution did not reveal any new features. Neither aldehyde formation nor α-deuteration was observed to any extent in reactions using this catalyst, and the hydroboration product 66 was formed in high yield. Addition of one equivalent of PPh₃ to the oxidized catalyst system (entry 6) restored the selectivity characteristic of freshly prepared RhCl(PPh₃)₃, i.e. α-deuteration and aldehyde formation was observed. Increased aldehyde formation and α-deuterium incorporation into product 66 were observed when one equivalent of PPh₃ was added to freshly prepared RhCl(PPh₃)₃ (compare entries 3 and 5).

The data presented in Table 3.3 and Figure 3.2 also show syn:anti diastereoselectivities decrease as the proportion of α-deuterium label in alcohol 66 increases (entries 3 and 5).

Three questions emerge from these data, specifically the origin of:

(i) α-deuteration;
(ii) aldehyde 65; and,
(iii) variance in syn:anti selectivity.

To obtain more information about the origin of α-deuteration, we investigated catalyzed hydroborations of the related achiral substrates 74 (Scheme 3.3). If a tertiary alkyl intermediate III is involved there can be no diastereoselection between β-elimination from the two enantiotopic methyl groups, consequently more deuterium should be observed in the γ-methyl than in the α-methylene.
Scheme 3.3. (a) Label distributions in the catalyzed hydroboration of substrate 74 indicate that intermediate II' cannot be present if β-elimination from II is 100% stereoselective. (b) The consequence of intermediate III in hydroboration of 20 would be a ca 2:3 α:γ ratio of deuterium distribution.

Silyl ether 74 (R = H, Table 3.4) gave at least three times more deuterium incorporation at the α-position than at the vinylic (γ) methyl group. These observations imply that formation of tertiary-alkyl intermediates III, followed by β-hydride elimination does not account for most of the α-deuterium incorporation in these substrates. For the
more hindered silyl ether 74 (R = Me), hydroboration was much slower, with less α-deuterium incorporation in the resulting alcohol and more alkene deuteration. The catalyzed hydroborations of 74 (R=H) gave only deuterated alkane when 0.1 equivalents of catecholborane-d$_1$ were used.

Table 3.5. Catalyzed Hydroboration of Silylethers 74 with Catecholborane-d$_1$.

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>catalyst system$^a$</th>
<th>75: label</th>
<th>75:76 distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>RhCl(PPh$_3$)$_3$</td>
<td>7:92:&lt;1</td>
<td>83:17</td>
</tr>
<tr>
<td>2</td>
<td>H</td>
<td>RhCl(PPh$_3$)$_3$ + 1 PPh$_3$</td>
<td>13:83:4</td>
<td>60:40</td>
</tr>
<tr>
<td>3</td>
<td>H</td>
<td>[Rh(COD)Cl]$_2$ + 8 PPh$_3$</td>
<td>16:79:5</td>
<td>60:40</td>
</tr>
<tr>
<td>4</td>
<td>Me</td>
<td>RhCl(PPh$_3$)$_3$</td>
<td>&lt;1:&gt;99;:b</td>
<td>93:7</td>
</tr>
<tr>
<td>5</td>
<td>Me</td>
<td>RhCl(PPh$_3$)$_3$ + 1 PPh$_3$</td>
<td>13:87;:c</td>
<td>50:50</td>
</tr>
</tbody>
</table>

$^a$ Catalyst prepared and manipulated under anaerobic conditions throughout; ratio of hydroboration to deuteration products (addition of D$_2$ to alkene) not established. $^b$ Conversion 43% after 18 h. $^c$ Conversion 5% after 18 h.

Formation of aldehyde in these catalyzed hydroborations is particularly surprising.

Aldehyde 67 cannot be formed from alcohol 66 in the oxidation step since 66 is deuterated
while 67 is not. Furthermore, GC experiments indicate the aldehyde is not present in the crude reaction mixture prior to oxidation. Therefore the aldehydes presumably arise from oxidation of vinylboronate esters formed via dehydrogenative borylation of silyl ethers 65 and 74. To investigate this we hydroborated alkene 74a catalytically, then added 2,3-dimethylbutan-2,3-diol (pinacol) instead of oxidizing. This gave the very stable boronate ester 77, which could be isolated via flash chromatography.\textsuperscript{122} A small amount of a compound tentatively characterized (see section 7.3) as the bis(boronate ester) 78 was also isolated.

![Chemical Structures](image)

Aldehydes isolated from hydroborations performed with catecholborane-$d_1$ were generally unlabeled. The exception, however, was 76a from hydroboration of allylsilyl ether 74a, which contained a small amount of deuterium label at the $\beta$-position and a trace at the $\alpha$-position (Figure 3.3). $\beta$-Deuteration presumably arises from hydroboration of the corresponding vinylboronate ester, \textit{i.e.} the bishydroboration process that led to the bisboronate ester 78 in the above experiment. Recently, bishydroboration has been observed also by other groups during rhodium catalyzed hydroboration processes (\textit{vide infra}).\textsuperscript{123}
Figure 3.3. $^2$H NMR from the crude product of hydroboration of 74a with catecholborane-$d_1$ catalyzed by RhCl(PPh$_3$)$_3$.

The experiments outlined above establish that vinylboronate esters are formed in these reactions. Furthermore, other experiments presented in this chapter and literature reports$^{125}$ indicate that vinylboronate esters can be hydrogenated under catalyzed hydroboration conditions. We propose $\alpha$-deuteration in the catalyzed hydroboration of substrate 65 (and 74) arises predominantly via addition of D$_2$ (or HD) to the vinylboronate ester IV (Scheme 3.4). Moreover, this would also explain the absence of deuterium label in the $\gamma$-position of products 66. Hydroboration product also can be formed via direct catalyzed hydroboration according to the mechanism previously outlined in Scheme 3.1, and the relative importance of each of these reaction pathways varies with conditions. This
accounts for the variable syn:anti diastereoselectivities in this reaction since each mechanism presumably has a different diastereofacial bias.

Rapid insertion/elimination relative to Rh-C bond rotation in the putative intermediates II (for 65) or III (for 74) could account for the higher degree of deuterium incorporation in the α-position than in the vinylic (γ) methyl group of alcohol 66 (or 75). In this case aldehyde and α-deuterated products would arise presumably from unrelated processes. However, we believe that this correlation is unlikely to be coincidental, since we have never observed substantial α-deuteration without aldehyde formation.

Scheme 3.4. The possible role of dehydrogenative borylation in the catalyzed hydroboration of substrate 65.

An attractive rationale for formation of vinylboronate esters in catalyzed hydroborations involves insertion of alkenes into rhodium-boron bonds, rather than Rh-H (Scheme 3.4). β-Hydride elimination from the resulting tertiary alkyl-intermediate could give the observed vinylboronate ester. Insertions of alkenes into transition metal-boron
bonds are presumed to be involved during platinum-catalyzed diboration of alkynes with 79 (equation 3.16), and alkene insertion into the metal-boron bond of trisboryliridium complex 80 has been observed.

![Chemical structure of 79 and 80](image)

Catalytic formation of vinylboranes from reactions of alkenes with pentaborane and borazine has been observed previously by Sneddon. Furthermore, J. Brown observed the formation of vinylboronate esters with comparable amounts of hydrogenation products from reactions of alkenes with boron-hydrides in the presence of phosphine-free rhodium catalysts. However more recently, Marder and Baker reported that the production of both vinylboronate and 1,1-bisboronate esters during hydroboration of α-
substituted vinylarenes (e.g. equation 3.17) increased with higher phosphine content of the catalyst.\textsuperscript{123}

\[
\begin{align*}
\text{Ph} & \quad \text{Me} \\
\text{Bcat} & \quad \text{Me} \\
\text{Ph} & \quad \text{Me} \\
\text{Ph} & \quad \text{Me} \\
\text{Ph} & \quad \text{Me} \\
\text{Ph} & \quad \text{Me} \\
\text{Ph} & \quad \text{Me} \\
\end{align*}
\]

\[2 \% \text{RhCl(PPh}_3)_3 \rightarrow \text{catecholborane}\]

\[\text{14\%} \quad 3\% \quad 53\% \quad 27\% \quad 3\%\]

Dehydrogenative borylation of alkenes is analogous to production of vinylsilanes via dehydrogenative silylation of alkenes.\textsuperscript{130-137} The mechanistic origin of the trans-addition of silanes to alkynes is also thought to involve insertion of the unsaturated organic fragment into the M-Si bond in preference to the M-H bond.

### 3.3 Conclusion

The results described herein underline the complexity of the Wilkinson’s catalyst/catecholborane hydroboration system.\textsuperscript{110} Combined with the results obtained in the laboratories of Marder and Baker it becomes clear that cleaner systems are required for catalyzed hydroborations to reach optimum chemo-, regio-, and stereoselectivities.

Deuterium labeling studies can provide useful information concerning the mechanism of catalyzed hydroborations, but reliable conclusions can only be obtained if these results are supported by other data, notably product distributions. Even then considerable care must be taken; hydroboration products can form via different mechanisms, and deuterium label can be delivered by a number of pathways and rhodium-deuteride species. Therefore label distribution in the products doesn’t necessarily provide information about individual steps in the mechanism(s) of catalyzed hydroboration.
Catalyst composition was found crucial in promoted hydroboration reactions, and addition of excess phosphine ligand can have a profound effect on product and label distribution.\textsuperscript{110}

Formation of vinylboronate esters in the catalyzed hydroboration of the unsaturated allylic silyl ethers 65 and 74 suggests insertion of alkenes into the rhodium-boron bond is a viable alternative to insertion into rhodium-hydride. This hypothesis is now supported by several literature reports documenting insertion of alkenes into metal-boron bonds. Rhodium-catalyzed deuteration of these vinylboronate esters \textit{in situ} offers an alternative explanation for $\alpha$-deuterium incorporation in the resulting alkylboronate esters. It is possible that insertion of some alkenes into the Rh-B bond may proceed at rates comparable to, or even greater than, insertion into the Rh-H bond. This is an important corollary to the accepted mechanism of catalyzed hydroboration.
Chapter 4. Enantioselective Rhodium Catalyzed Hydroborations.

4.1 Introduction

After metal promoted hydroboration of alkenes was initially reported in 1985, several laboratories recognized the potential of catalytic asymmetric hydroborations as an attractive alternative to methods which rely upon reagent-controlled diastereoselectivity (chapter 1, section 1.2).

\[
\text{81} \quad \text{[Rh(COD)Cl]_2 (R,R)-DIOP} \quad \text{catecholborane} \quad \overset{\text{oxidation}}{\rightarrow} \quad \text{76 \% ee}
\]

In the first report of catalytic enantioselective hydroborations Burgess and Ohlmeyer presented optical purities up to 76 %. The best result was obtained for the reaction of norbornadiene 81 with [Rh(COD)Cl]_2 and the chiral bidentate phosphine ligand (R,R)-DIOP (equation 4.1). Subsequently several other groups demonstrated that catalytic hydroboration can achieve enantiomerically enriched products. To date, however, enantiomeric excesses of over 95 % have only been obtained in catalyzed hydroborations of phenylethene derivatives. These substrates react extremely quickly (reaction temperatures of -78 °C can be used) and with high regioselectivity in favor of the secondary alcohol (equation 4.2) when cationic rhodium complexes are employed. Hayashi and co-workers proposed that the anomalous reactivity of these aryl alkenes could be due to formation of a \( \pi \)-allyl (i.e. \( \eta^3 \)-benzyl) complexes such as 82.
The challenge in the area of enantioselective catalyzed hydroboration is to understand the factors which control the levels of optical induction, and to use this knowledge to optimize the optical yields for other substrate types. This chapter presents a systematic study of enantioselective hydroborations using readily available phosphine ligands\textsuperscript{141} (Figure 4.1) and structurally diverse substrates. In the first phase of this research, seven optically active ligands were used in catalyzed hydroborations of three alkenes. Subsequent work focussed on the influence of varying rhodium-to-phosphine ratios (see also chapter 3) and the effect of the boron-hydride on the enantioselectivity of the reaction. The primary objective of these experiments was to correlate trends in the data with catalyst type, and to explore effects of variables one might manipulate to obtain higher enantioselectivities.

4.2 Results and Discussion

4.2.1 Variation of Chiral Phosphine

Figure 4.1 shows the phosphines used in this study. (R,R)-DIOP\textsuperscript{142}, (R,R)-2-MeO-DIOP\textsuperscript{143,144} and (R,R)-3-MeO-DIOP\textsuperscript{143} were synthesized according to literature procedures, while all other ligands were obtained from commercial sources.
Norbornene, indene, and 2-phenylpropene were selected as substrates since these alkenes have different structural features. Temperature effects were examined in a few examples. In most cases, however, the reaction components were mixed at -78 °C, warmed to -25 °C, and allowed to stand at this temperature; if no appreciable reaction occurred within 24 h, the reaction mixture was allowed to stand at -5 °C or 5 °C until the reaction was complete (TLC). Optical purities of the products were measured via HPLC with a chiral column, NMR analyses of 2-methoxy-3,3,3-trifluoropropanoate derivatives, or NMR/chiral shift experiments.  

Table 4.1 lists data for hydroborations of substrates 83-85 in the presence of the ligands shown in Figure 4.1. Comparison of the results indicates that DIOP is slightly
more effective than BINAP; this is perhaps surprising because the binaphthyl ligand is superior in many other reactions. The results with CHIRAPHOS and DIPAMP are relatively poor implying five-membered ring chelate structures are not favored for asymmetric induction in this process. The ligand BDPP is structurally analogous to CHIRAPHOS except that it forms six-membered ring chelates; catalysts based upon this give higher optical yields for each of the substrates 83-85. In view of these results, 2-MeODIOP and 3-MeODIOP were also screened in an attempt to improve on the selectivities obtained with the parent ligand DIOP. The ortho-substituted ligand (2-MeODIOP) was generally more effective giving 82 % ee with norbornene, the maximum observed in this series.

Throughout, norbornene (83) seems particularly amenable to asymmetric hydroboration. This substrate reacts relatively fast, the hydroboration processes are generally complete within 2 h at -25 °C. It may be significant that chiral induction in reactions of norbornene arises because the ends of the alkene linkage are enantiotopic, while induction for substrates 84 and 85 is determined by face selectivities. Enantioselectivities obtained for indene (84) vary widely with the nature of the chiral ligand. High optical yields are obtained in hydroborations of this substrate using DIOP-based catalysts, whereas trivial induction is observed when a BDPP system is used, even though this same system gives high optical yields with norbornene (83).

substrates
**Table 4.1** Enantioselective Hydroborations\(^a\) with Readily Available Chiral Phosphine Ligands.

<table>
<thead>
<tr>
<th>ligand</th>
<th>substrate</th>
<th>solvent</th>
<th>temp. (°C)</th>
<th>product</th>
<th>ee. (%)</th>
<th>method to determine ee.</th>
</tr>
</thead>
<tbody>
<tr>
<td>(R,R)-DIOP</td>
<td>83</td>
<td>THF(^b)</td>
<td>-5</td>
<td>1(R)-86</td>
<td>49</td>
<td>Eu(hfc)(_3)</td>
</tr>
<tr>
<td></td>
<td>83</td>
<td>THF</td>
<td>-25</td>
<td>1(R)-86</td>
<td>60</td>
<td>Eu(hfc)(_3)</td>
</tr>
<tr>
<td></td>
<td>84</td>
<td>THF</td>
<td>-25</td>
<td>S-87</td>
<td>76</td>
<td>HPLC</td>
</tr>
<tr>
<td></td>
<td>85</td>
<td>THF</td>
<td>-5</td>
<td>R-89</td>
<td>27</td>
<td>Eu(hfc)(_3)</td>
</tr>
<tr>
<td>R-BINAP</td>
<td>83</td>
<td>THF(^b,d)</td>
<td>-25</td>
<td>1(R)-86</td>
<td>65</td>
<td>Eu(hfc)(_3)</td>
</tr>
<tr>
<td></td>
<td>84</td>
<td>DME(^e)</td>
<td>-40</td>
<td>87</td>
<td>19</td>
<td>Eu(hfc)(_3)</td>
</tr>
<tr>
<td></td>
<td>85</td>
<td>THF</td>
<td>-25</td>
<td>S-89</td>
<td>25</td>
<td>Eu(hfc)(_3)</td>
</tr>
<tr>
<td>(S,S)-CHIRAPHOS</td>
<td>83</td>
<td>THF</td>
<td>-25</td>
<td>1(S)-86</td>
<td>4</td>
<td>Eu(hfc)(_3)</td>
</tr>
<tr>
<td></td>
<td>84</td>
<td>THF</td>
<td>-25</td>
<td>(___)</td>
<td>0</td>
<td>HPLC(^e)</td>
</tr>
<tr>
<td></td>
<td>85</td>
<td>THF</td>
<td>-25</td>
<td>R-89</td>
<td>25</td>
<td>Eu(hfc)(_3)</td>
</tr>
</tbody>
</table>
### Table 4.1 continued

<table>
<thead>
<tr>
<th>ligand</th>
<th>substrate</th>
<th>solvent</th>
<th>temp. (°C)</th>
<th>product</th>
<th>ee. (%)</th>
<th>method to determine ee.</th>
</tr>
</thead>
<tbody>
<tr>
<td>(R,R)-DIPAMP</td>
<td>83</td>
<td>THF</td>
<td>-25</td>
<td>-</td>
<td>0</td>
<td>Eu(hfc)₃</td>
</tr>
<tr>
<td></td>
<td>84</td>
<td>THF</td>
<td>-5</td>
<td>S-87&lt;sup&gt;h&lt;/sup&gt;</td>
<td>7</td>
<td>HPLC</td>
</tr>
<tr>
<td></td>
<td>85</td>
<td>THF</td>
<td>-5</td>
<td>-</td>
<td>0</td>
<td>Eu(hfc)₃</td>
</tr>
<tr>
<td>(S,S)-BDPP</td>
<td>83</td>
<td>THF</td>
<td>-25</td>
<td>1R-86</td>
<td>80</td>
<td>Eu(hfc)₃</td>
</tr>
<tr>
<td></td>
<td>84</td>
<td>THF</td>
<td>-5</td>
<td>S-87</td>
<td>4</td>
<td>HPLC</td>
</tr>
<tr>
<td></td>
<td>85</td>
<td>THF</td>
<td>-5</td>
<td>R-89</td>
<td>27</td>
<td>Eu(hfc)₃</td>
</tr>
<tr>
<td>(R,R)-2-MeODIOP</td>
<td>83</td>
<td>THF</td>
<td>-25</td>
<td>1R-86</td>
<td>82</td>
<td>Eu(hfc)₃</td>
</tr>
<tr>
<td></td>
<td>84</td>
<td>MePh&lt;sup&gt;b&lt;/sup&gt;</td>
<td>-25</td>
<td>S-87</td>
<td>59</td>
<td>Eu(hfc)₃</td>
</tr>
<tr>
<td></td>
<td>85</td>
<td>THF</td>
<td>25</td>
<td>R-89</td>
<td>15</td>
<td>Eu(hfc)₃</td>
</tr>
<tr>
<td>(R,R)-3-MeODIOP</td>
<td>83</td>
<td>THF</td>
<td>-25</td>
<td>1R-86</td>
<td>69</td>
<td>Eu(hfc)₃</td>
</tr>
<tr>
<td></td>
<td>84</td>
<td>THF</td>
<td>-25</td>
<td>S-87</td>
<td>55</td>
<td>HPLC</td>
</tr>
<tr>
<td></td>
<td>85</td>
<td>THF</td>
<td>-5</td>
<td>90</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

<sup>a</sup> Catalyst is 1 mol % [RhCl(COD)]₂ + 2 mol % ligand unless otherwise noted.  
<sup>c</sup> Chiral shift NMR experiment.  
<sup>d</sup> Catalyst is 0.5 mol % [RhCl(COD)]₂ + 1 mol % ligand.  
<sup>e</sup> Result from Dai and co-workers<sup>118</sup> using 2 mol % of [RhCl(COD)]₂ with ligand (mol % of ligand not specified).  
<sup>f</sup> 1-Indanol (87) and 2-indanol (88) were formed in a ratio of 1:1.  
<sup>g</sup> Chiralcel OB column from Daicel Industries.  
<sup>h</sup> 1-Indanol (87) and 2-indanol (88) were formed in a ratio of 2:1.  
<sup>i</sup> Less than 20 % of the primary alcohol 89 is formed, see Table 4.2.

#### 4.2.2 Variation of Rhodium-to-Phosphine Ratios

Analysis of the product mixtures from the catalyzed hydroborations of 2-phenylpropene revealed significant, and in some cases predominant, formation of tertiary alcohols (Table 4.2). Formation of secondary alcohols in the enantioselective
hydroboration of phenylethene has been reported by others,\textsuperscript{51,103} selective formation of tertiary alcohols in preference to primary ones is even more remarkable. As demonstrated in chapter 3, the ratio of secondary to primary alcohol in catalyzed hydroborations of phenylethene is dependant upon the concentration and nature of the phosphine ligands.\textsuperscript{110,118} Similar considerations seem to be applicable to catalyzed hydroborations of 2-phenylpropene (85): ratios of primary to tertiary alcohol products 89:90 are dependent upon the phosphine used. Data given in Table 4.2 indicates no correlation between chelating ring size and product distribution. However, increasing the phosphine to rhodium ratios from 1:1 to 2:1 for DIOP (entries 1 and 2) caused a reversal of the regioselectivity in favor of the tertiary alcohol.

**Table 4.2.** Regiochemistry of Enantioselective Hydroborations of 2-Phenylpropene .

![Reaction Scheme](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>ligand</th>
<th>ratio 89:90\textsuperscript{a}</th>
<th>ee of 89 (%)\textsuperscript{b}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(R,R)-DIOP</td>
<td>90:10</td>
<td>27 (R)</td>
</tr>
<tr>
<td>2</td>
<td>2 equiv. (R,R)-DIOP</td>
<td>11:89</td>
<td>n.d.</td>
</tr>
<tr>
<td>3</td>
<td>R-BINAP</td>
<td>85:15</td>
<td>25 (S)</td>
</tr>
<tr>
<td>4</td>
<td>(S,S)-CHIRAPHOS</td>
<td>&gt;95:5</td>
<td>25 (R)</td>
</tr>
<tr>
<td>5</td>
<td>(R,R)-DIPAMP</td>
<td>85:15</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>(S,S)-BDPP</td>
<td>48:52</td>
<td>27 (R)</td>
</tr>
<tr>
<td>7</td>
<td>(R,R)-3-MeODIOP</td>
<td>19:81</td>
<td>15 (R)</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Determined via \textsuperscript{1}H NMR analyses. \textsuperscript{b} Determined by HPLC of the corresponding acetates using a CHIRALCEL OB column.
The tertiary product obtained from hydroboration of 2-phenylpropene (85) is achiral. In view of the high enantioselectivities obtained by Hayashi and coworkers for the internal hydroboration product of phenylethene,\textsuperscript{51,52} we decided to attempt production of the chiral tertiary alcohols 93 and 96 via catalyzed hydroboration of 3,3,3-trifluoro-2-phenyl-1-propene (91) and 2-phenyl-1-butene (94). Table 4.3 shows data for rhodium catalyzed hydroboration of 2-phenyl-3,3,3-trifluoropropene in the presence of various chelating phosphine ligands. Collectively these results show that the regioselectivities are ligand dependent. Tertiary alcohols were always favored for BDPP (entries 1-4), whereas more primary alcohol was obtained when BINAP or DIOP were used (entries 5-9). Increasing the phosphine-to-rhodium ratio for the latter ligands gave more tertiary alcohol, but in the case of BINAP the reaction rate was severely retarded so that a diminished conversion was obtained (entry 6).

\[ \text{Ph} \quad \begin{array}{c} \text{R} \quad \text{(i) catecholborane,} \\
\text{91, R=CF}_3 \\
\text{94, R=E} \end{array} \quad \quad \begin{array}{c} \text{1 \% [RhCl(COD)]}_2 \\
\text{2 \% ligand} \\
\text{(ii) H}_2\text{O}_2, \text{NaOH}_{(aq)} \\
\text{92, R=CF}_3 \\
\text{95, R=E} \end{array} \quad \text{R} \quad \text{OH} \\
\text{93, R=CF}_3 \\
\text{96, R=E} \]
Table 4.3. Hydroborations of 2-Phenyl-3,3,3-trifluoropropene.

\[
\text{Ph} \quad \text{CF}_3 \\
\begin{array}{c}
\text{CF}_3 \\
\end{array}
\quad \xrightarrow{(i) \ 2 \text{ mol \% rhodium, 2.0 eq. catecholborane}} \\
\begin{array}{c}
\text{CF}_3 \\
\end{array}
\quad + \\
\begin{array}{c}
\text{M} & \text{H} \\
\text{OH} \\
\text{CF}_3 \\
\end{array}
\quad \xrightarrow{(ii) \text{ oxidation}} \\
\begin{array}{c}
\text{Ph} \\
\text{Ph} \\
\end{array}
\quad 92 \\
\quad \quad \quad + \\
\quad \quad \quad 93
\]

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>Rh:ligand</th>
<th>92:93$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[Rh(COD)Cl]$_2$/[(S,S)-BDPP]</td>
<td>1:2</td>
<td>14:86</td>
</tr>
<tr>
<td>2</td>
<td>Rh(COD)$_2$BF$_4$/[(S,S)-BDPP]</td>
<td>1:2</td>
<td>11:89</td>
</tr>
<tr>
<td>3</td>
<td>Rh(COD)$_2$BF$_4$/[(S,S)-BDPP]</td>
<td>1:1</td>
<td>14:86</td>
</tr>
<tr>
<td>4</td>
<td>Rh(COD)$_2$BF$_4$/[(S,S)-BDPP]</td>
<td>1:2</td>
<td>37:63$^b$</td>
</tr>
<tr>
<td>5</td>
<td>[Rh(COD)Cl]$_2$/[(R)-BINAP]</td>
<td>1:2</td>
<td>33:67</td>
</tr>
<tr>
<td>6</td>
<td>Rh(COD)$_2$BF$_4$/[(R)-BINAP]</td>
<td>1:2</td>
<td>80:20$^c$</td>
</tr>
<tr>
<td>7</td>
<td>Rh(COD)$_2$BF$_4$/[(R,R)-DIOP]</td>
<td>1:1</td>
<td>&gt;90:10</td>
</tr>
<tr>
<td>8</td>
<td>Rh(COD)$_2$BF$_4$/[(R,R)-DIOP]</td>
<td>1:2</td>
<td>72:28</td>
</tr>
<tr>
<td>9</td>
<td>Rh(COD)$_2$BF$_4$/[(R,R)-3MeO-DIOP]</td>
<td>1:2</td>
<td>74:26</td>
</tr>
</tbody>
</table>

$^a$ Determined by $^{19}$F NMR and capillary GC of the silylated products. $^b$ 30% conversion. $^c$ 45% conversion.

Catalyzed hydroborations of Ph(CF$_3$)C=CH$_2$ and of Ph(Et)C=CH$_2$ give chiral primary and chiral secondary alcohols. Table 4.4 shows different optical yields were obtained for the regioisomers in the enantioselective hydroborations of these 1,1-disubstituted alkenes.
Table 4.4. Simultaneous Enantioselective Syntheses of Primary and Tertiary Alcohols.

![Chemical structure](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>catalyst</th>
<th>1° (ee, config.): 3° (ee, config.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CF₃</td>
<td>Rh(COD)₂BF₄/(S,S)-BDPP</td>
<td>9 (13, R): 75 (0)</td>
</tr>
<tr>
<td>2</td>
<td>CF₃</td>
<td>[Rh(COD)Cl]₂/(S,S)-BDPP</td>
<td>15 (15, R): 85 (20)²</td>
</tr>
<tr>
<td>3</td>
<td>Et</td>
<td>[Rh(COD)Cl]₂/(S,S)-BDPP</td>
<td>53 (30, R): 47 (84, S)</td>
</tr>
<tr>
<td>4</td>
<td>Et</td>
<td>Rh(COD)₂BF₄/(R,R)-DIOP</td>
<td>73 (13, R): 27 (43, S)</td>
</tr>
</tbody>
</table>

² The absolute configuration of tertiary alcohol 93 (R = CF₃) was not determined.

For Ph(CF₃)C=CH₂ the levels of induction in both products 92 and 93 were too low to allow formulation of meaningful conclusions concerning the mechanism from the face selectivities. However, for Ph(Et)C=CH₂ the optical yields were higher and one important observation was made: the absolute configurations of the primary and tertiary alcohols are derived from addition to the same enantiotropic face of the alkene substrate, but the extent of asymmetric induction is greater for tertiary alcohols than primary alcohols.

It is not proven that η²-intermediates are involved in this process, the reaction could, for instance, proceed directly via η³-benzyl complexes (*cf* 82). It is certain, however, that the reaction does allow orientation of the metal on the two enantiotropic faces of the alkene to give both enantiomers of the two products. For the purpose of this discussion, we shall assume that the reaction proceeds via the rhodium-to-alkene π-complexes A and B and that these are intermediates in the formation of both primary and tertiary alcohols after oxidation (Scheme 4.1). Higher enantioselection was obtained for
tertiary product alcohols so formation of intermediates A and B cannot be
stereodeterminant (i.e. irreversible). It follows that alkene insertion to give primary
alcohols (V and VII) has little preference for intermediate A or intermediate B, but
insertion to give the tertiary-alkyl rhodium complexes is more favorable from A than from
B. These arguments are invalid if the reaction does not involve common intermediates for
formation of primary and secondary alcohols, but the conclusion is the same: there are
significant mechanistic differences for the formation of primary and tertiary alcohols in this
process.

Scheme 4.1. A possible reaction pathway for formation of primary and tertiary alcohols
in the hydroboration process.
An attempt was made to gain information about the catalytically active species in the hydroboration process, *i.e.* does it contain more than one chiral phosphine. Analogy with "asymmetric amplification" in other systems\textsuperscript{147-151} indicates that when catalysts of less than 100 % optical purity are used in catalyzed hydroboration, one of three outcomes are possible: (i) the enantiomeric excess of the product decreases proportionately *more* than that of the catalyst; (ii) the enantiomeric excess of the product decreases proportionately *less* than that of the catalyst; and, (iii) the two factors are linearly related. In the first case the active catalyst contains two (or more) ligands and the diastereomer with ligands of like chirality is *less* reactive. In the second case the active catalyst has two (or more) ligands but the diastereomer with ligands of like chirality is *more* reactive. The third case implies the catalytically active species has only one ligand, or that it has more than one and all possible diastereomers are equally reactive (Figure 4.2). Strictly, the term "asymmetric amplification" can only be applied to case (ii).

![Diagram](image)

**Figure 4.2.** Principles of asymmetric amplification.
To test this phenomenon in catalyzed hydroboration, an aryl substituted alkene was required for which the optical purity of the product alcohol could be determined accurately. Consequently, indene was selected (equation 4.4) because the optical purity of the product can be determined via HPLC on a CHIRALCEL OB column. Two catalyst formulations were used: [Rh(COD)Cl]_{2/2} equiv. DIOP and [Rh(COD)Cl]_{2/4} equiv. DIOP.

Intuitively, one would suspect that only one ligand per catalyst is involved in catalyzed hydroboration processes because the coordination sphere of rhodium would not simultaneously support two bidentate ligands, a coordinated alkene, and σ-hydride and a boryl ligand. However, another possibility is that the catalyst is a rhodium dimer with more than one ligand. The results for the asymmetric amplification experiments are shown in Figures 4.3a and 4.3b. Both catalyst formulations gave linear relationships between the optical activities of the product and of the ligand. Therefore, these experiments provide no evidence to suggest that more than one ligand per catalyst is involved.
Figure 4.3. Optical yields of 1-indanol as a function of the optical purity of the DIOP used in equation 4.4. (a) [Rh(COD)Cl\(_2\):(R,R\)-DIOP = 1:2; (b) [Rh(COD)Cl\(_2\):(R,R\)-DIOP = 1:4
4.2.3 Enantioselective Hydroborations with Different Boron-Hydrides

It is reasonable to assume that steric effects play a significant role in determining the sense and magnitude of asymmetric induction in catalyzed hydroboration reactions involving optically active ligands. Increasing the size of the boron-hydride component accentuates steric effects, hence compounds 97, 98, and 99 were screened (Table 4.5) to probe the effect of this change on induction in catalyzed hydroborations.

Figure 4.4. Alternative borohydrides for catalyzed hydroborations.

<table>
<thead>
<tr>
<th>boron-hydride</th>
<th>substrate</th>
<th>ligand</th>
<th>temp. (°C)</th>
<th>product</th>
<th>ee (%)</th>
<th>method to determine ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>97</td>
<td>83</td>
<td>(R,R)-DIOP</td>
<td>-25</td>
<td>1R-86</td>
<td>18</td>
<td>Eu(hfco)3</td>
</tr>
<tr>
<td>97</td>
<td>84</td>
<td>(R,R)-DIOP</td>
<td>-5</td>
<td>88a</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>98</td>
<td>83</td>
<td>(R,R)-DIOP</td>
<td>-25</td>
<td>1R-86</td>
<td>25</td>
<td>GCa</td>
</tr>
<tr>
<td>98</td>
<td>84</td>
<td>(R,R)-DIOP</td>
<td>-5</td>
<td>S-87</td>
<td>30</td>
<td>HPLC</td>
</tr>
<tr>
<td>99</td>
<td>83</td>
<td>(R,R)-DIOP</td>
<td>25</td>
<td>1S-86</td>
<td>19</td>
<td>Eu(hfco)3</td>
</tr>
<tr>
<td>99</td>
<td>83</td>
<td>(S,S)-DIOP</td>
<td>25</td>
<td>1R-86</td>
<td>16</td>
<td>Eu(hfco)3</td>
</tr>
<tr>
<td>99</td>
<td>83</td>
<td>(S,S)-CHIRAPHOS</td>
<td>25</td>
<td>1R-86</td>
<td>25</td>
<td>Eu(hfco)3</td>
</tr>
</tbody>
</table>

a Estimated via GC analysis on a Cyclodex-B column; base-line resolution was not obtained.
The highest enantiomeric excess obtained in this series was 30 %. The most surprising observation was for the ephedrine derivatives 99; here the catalyst formed from (R,R)-DIOP gave 1S-norborneol (86) whereas catecholborane under the same conditions gave the 1R product. When (S,S)-DIOP was used in conjunction with reagent 99, the sense of the asymmetric induction was opposite, i.e. the 1R-product was formed. Consequently, the ligand, not the ephedrine chirality, is the dominant feature in determining the outcome of the reaction, and the reversal of selectivity is a consequence of the structural properties of the hydroborating reagent. Another report\(^{140}\) has outlined similar observations for ephedrine-based oxazaborolidines (see chapter 1, section 1.3.2). Further modifications of the boron-hydride source may prove to be beneficial to the development of asymmetric hydroborations, but the compounds examined here are clearly not ideal. Moreover, there were some practical problems associated with these reagents: the reactions were relatively slow, presumably due to increased hindrance, and the relatively hydrophobic phenolic residues were difficult to separate from the products via simple base extractions.

### 4.2.4 Recent Developments in Enantioselective Catalyzed Hydroboration

A number of recent literature reports have presented enantioselective metal catalyzed hydroborations. Hydroboration of 1-phenyl-1,3-butadiene (100) with two equivalents of catecholborane in the presence of a rhodium catalyst and (R)-BINAP afforded diols 101 and 102 with modest optical purities, and in a 3:1 syn-to-anti ratio (equation 4.5).\(^{154}\)

\[
\begin{align*}
\text{Ph} & \quad \text{[Rh(COD)\(_2\)]BF}_4 \\
\text{(R BINA)P} & \quad \text{catecholborane} \\
\text{100} & \quad \text{[O]} \\
\text{Ph} & \quad \text{HO} \\
\text{HO} & \quad \text{OH} \\
\text{OH} & \quad \text{OH} \\
\text{Ph} & \quad 3 : 1 \\
\text{101, 40 % ee} & \quad \text{102, 44 % ee}
\end{align*}
\]
Palladium catalyzed reaction of enynes with catecholborane in the presence of monodentate ligand (S)-MeO-MOP, followed by trapping of the intermediate allenyl boronate with acetaldehyde provided homopropargylic alcohols 103 and 104 in a 3:1 ratio. However, the enantioselectivities of the products did not exceed 37 % ee.\textsuperscript{155}

\[
\begin{align*}
R & \quad \overset{1 \text{ eq. HBO}_2\text{C}_6\text{H}_4}{\rightarrow} \quad \overset{1 \text{ mol} \% \text{ Pd}_2(\text{dba})_3}{\rightarrow} \quad \overset{1 \text{ mol}\% \text{(S)-MeO-MOP}}{\rightarrow} \\
\text{PhCHO, -78 °C} & \\
\end{align*}
\]

Better results were reported in rhodium catalyzed hydroborations of vinylarenes with the axially chiral 1-(2-diphenylphosphino-1-naphthyl)isoquinoline 105.\textsuperscript{156} The enantioselectivities for phenylethene derivatives were similar to those using cationic rhodium-BINAP complexes (equations 4.6 and 4.7). With BINAP these selectivities could only be obtained at -78 °C, but the reactions using 105 afforded high optical purities at 20 °C. Lowering the temperature did not increase the enantioselectivities in reactions with 105, but reduced the regioselectivity, producing more achiral primary alcohol. Formation of this deleterious side product could be suppressed by using excess ligand, which restored the high selectivity for the secondary alcohol. This observation is similar to the results described in section 4.2.2.
Catalyzed hydroborations of indene (84) in the presence of 105 provided 1-indanol exclusively in 91 % optical purity, whereas BINAP-based catalyst systems give 1-indanol only in 13 % ee. 52

\[ \text{(4.7)} \]

(i) 1% [Rh(COD)(acac)]OTf 1% 105, catecholborane (ii) oxidation 94% ee

\[ \text{(4.8)} \]

(i) 1% [Rh(COD)(acac)]OTf 1% 105, catecholborane  
(ii) oxidation 91% ee

4.3 Conclusion

This work shows modest to good enantioselective hydroborations of alkenes are possible for combinations of certain ligands and substrates. However, none of the seven ligands tested gave uniformly good results with respect to asymmetric synthesis, but the combined data provides pointers to ligand designs that may be more successful. Ligands that give five-membered chelate rings (assuming that the catalyst has only one metal center per molecule) do not seem to be favorable for good chiral induction in these reactions.
Ligands which are simple modifications of DIOP, here 2-MeODIOp and 3-MeODIOp, may provide some surprisingly good results.

In view of the results described in chapter 3, it may not be surprising that high optical purities have been limited to reactive substrates like norbornene and phenylethene derivatives. Although the conclusions drawn for the RhCl(PPh3)3-mediated processes are not necessarily valid for catalyst systems derived from chiral chelating phosphines, slow reacting substrates will likely undergo side reactions similar to those found in the former system diminishing the optical purities of the products. To obtain uniformly good selectivities, development of catalysts that give cleaner performances are necessary. One such system has been reported recently by Marder and Baker for non-asymmetric hydroboration. Catalysis by the π-allyl complex 106 proved to be much cleaner than corresponding reactions promoted by Wilkinson's catalyst. Extrapolation of their results to enantioselective processes may provide the desired efficacies.

Asymmetric hydroboration of 1,1-disubstituted alkenes in the presence of higher phosphine-to-rhodium ratios favor formation of tertiary alcohols, and this preference is greater with BDPP than with BINAP or DIOP. Different enantioselectivities are obtained for primary and tertiary alcohols formed in these processes, indicative of fundamental mechanistic differences for the formation of the two products. "Asymmetric amplification"
experiments provide no evidence that more than one phosphine ligand per catalyst molecule is involved in enantioselective catalyzed hydroborations. The data described here does not eliminate this possibility, however, and the results show that phosphine-to-rhodium ratios have significant effects on the behavior of catalysts formed \textit{in situ} from [Rh(COD)Cl]_2.
Chapter 5. Titanium-Mediated Hydroboration

5.1 Introduction

Transition metal catalyzed hydroborations of alkenes are useful alternatives to classical (uncatalyzed) additions of boranes to alkenes and alkynes. Most of the catalyzed hydroborations reported to date involve complexes of late transition metals in a low oxidation state (see previous chapters), but there are some notable exceptions.

First, catecholborane additions can be accelerated by lanthanide cyclopentadienyl complexes like 107 and 108, in which the key step is believed to be combination of a lanthanide alkyl complex with the boron-hydride via a four center transition state. Recently, several lanthanide salts were reported also to promote the addition of catecholborane to alkenes. So far, these catalyzed hydroborations have no proven merits over the corresponding uncatalyzed transformations, but there is considerable potential for the control of relative and absolute stereochemistry.

\[ \text{Me}_2\text{Si} \quad \text{Sm} \quad \text{CH(TMS)}_2 \]

\[ \text{Ln} \quad R \]

107

108

\( \text{Ln} = \text{Sm, La} \)
\( R = \text{H, CH(TMS)}_2 \)
Scheme 5.1 Proposed mechanism for lanthanide catalyzed hydroboration of alkenes.

Second, a series of reactions, reported by Isagawa and coworkers, involve additions of borohydride to alkenes mediated by bis(cyclopentadienyl)dichlorotitanium (Cp₂TiCl₂) (Scheme 5.2). ¹⁶⁰-¹⁶²
catalyst formation

\[0.05 \text{Cp}_2\text{TiCl}_2 + 1.0 \text{LiBH}_4 \xrightarrow{\text{THF, 25 °C, 1h}} \text{"violet solution"} \]

or

\[0.2 \text{Cp}_2\text{TiCl}_2 + 0.2 \text{18-crown-6} + 1.0 \text{NaBH}_4 \xrightarrow{\text{THF, 65 °C, 1h}} \text{"violet solution"} \]

typical transformation

\[
\begin{array}{c}
\text{R} \\
\xrightarrow{\text{catalyst, THF}}
\end{array}
\xrightarrow{\text{putative borohydride intermediates}}
\xrightarrow{\text{H}_2\text{O}_2/\text{OH}^-}
\xrightarrow{\text{R}}
\begin{array}{c}
\text{R} \\
\text{O} \\
\text{H}
\end{array} + \begin{array}{c}
\text{R} \\
\text{OH} \\
\text{Me}
\end{array}
\]

Scheme 5.2 Original reports of titanium mediated hydroborations.

Nearly\textsuperscript{157} all rhodium catalyzed hydroboration reactions are complicated by disproportion of catecholborane and complex organometallic transformations (chapter 3),\textsuperscript{163,164} so they are hard to define and harder to manipulate into highly stereoselective transformations.\textsuperscript{110} Titanium mediated hydroborations, however, are potentially useful since the mechanism of these reactions must be different from the rhodium catalyzed processes. Certainly, use of borohydride circumvents the complications associated with disproportionation of catecholborane, and since BH\textsubscript{4}\textsuperscript{-} is a fundamental building block from which both diborane and catecholborane are made, the economic advantages and convenience of using borohydride are significant.

Despite their potential, an enigma surrounds the titanium mediated hydroboration reactions: the mechanistic pathway(s) by which borohydride adds to alkenes. Isagawa et al speculated that these reactions occur via addition of free borohydride to a titanium alkene complex.\textsuperscript{162} They also concluded that the products are alkylborohydrides (ie LiR\textsubscript{n}BH\textsubscript{(4-n)} from LiBH\textsubscript{4}) on the basis of the following experiment: 2-octene reacted with lithium borohydride at 45 °C and at 150 °C in the presence of Cp\textsubscript{2}TiCl\textsubscript{2} gave significant amounts
of 2-octanol after oxidation. 2-Octylborane is known to isomerize to 1-octylborane at 150 °C, so it could not have been an organoborane that was oxidized. Furthermore, the titanium mediated hydroboration of alkynes followed by protonolysis of the intermediates gave alkene products. This is different to the reaction of these substrates with BH$_3$, which usually produces dihydroboration products, suggesting that BH$_3$ is not the reactive species in the catalyzed process.

Two types of reaction conditions were used in Isagawa's original work on titanium promoted hydroborations (Scheme 5.2). In one typical experiment, $^{160}$ 5 mol % of Cp$_2$TiCl$_2$ was added to a solution of ca 1 equiv. (based on substrate) of LiBH$_4$ in THF, and the reaction mixture was stirred under argon for 1 h producing a violet solution. The alkene substrate was then added and the reaction mixture was stirred at 45-65 °C for 21 h or more. In the second modification, $^{161}$ 20 mol % Cp$_2$TiCl$_2$, 20 mol % 18-crown-6, and 1 equiv. of NaBH$_4$ were stirred at 65 °C for 1 h. A violet solution again formed. The substrate was added, and the reaction mixture was stirred at 65 °C for 5 or 24 h. None of the reaction intermediates were characterized.

Stoichiometric reactions of Cp$_2$TiCl$_2$ with borohydride have been studied in detail by other groups (equation 5.1). $^{166,167}$ This transformation was reported to produce diborane as a by-product. The protocols summarized above make no mention of steps to remove diborane that must have been produced in the catalyst formation steps. Consequently, despite Isagawa's assertions that borohydrides are formed, the conditions of the reaction suggest that some of the substrate should be consumed by diborane to give alkylboranes in transformations that do not intimately involve the metal. Specifically, 15 mol % uncatalyzed hydroboration could occur if 5 mol % of catalyst was used, and 60 mol % if 20 mol % of catalyst was used.
In summary, the mechanism of Ti-promoted hydroborations was unclear, and there were reasons to suspect they even might not involve catalysis of the B-H addition step. Therefore, titanium-mediated hydroborations merited further investigations. This chapter describes fundamental mechanistic probes, and attempts to dispel some of the ambiguities associated with these reactions. Some other titanium based systems are discussed also (section 5.2.2).

5.2 Results and Discussion

5.2.1 Catalyst Systems Involving $\text{Cp}_2\text{TiCl}_2$ or $\text{Cp}_2\text{Ti}(\mu-H)_2\text{BH}_2$

Equation 5.1 indicates $\text{Cp}_2\text{Ti}(\mu-H)_2\text{BH}_2$ is produced under conditions used in the "catalyst formation" step of the original titanium-mediated hydroborations. Isagawa and coworkers observed the catalyst solution was violet, which is the color of this titanium complex. Consequently, $\text{Cp}_2\text{Ti}(\mu-H)_2\text{BH}_2$ is strongly implicated for reactions in which $\text{Cp}_2\text{TiCl}_2$ is the starting material for the catalyst formation.

As a starting point in the current work, $\text{Cp}_2\text{Ti}(\mu-H)_2\text{BH}_2$ was synthesized via a literature procedure. This synthesis could be performed using Schlenk line techniques, but the complex was isolated in a glove box due to its sensitivity to air. Traces of oxygen rapidly transform the violet complex into a yellow material.

5.2.1.1 Reactions of $\text{Cp}_2\text{Ti}(\mu-H)_2\text{BH}_2$ and Phenylethene under Catalytic and Stoichiometric Conditions

Pure, isolated, $\text{Cp}_2\text{Ti}(\mu-H)_2\text{BH}_2$ indeed promoted additions of lithium borohydride to alkenes; for instance, GC experiments indicated 5 mol % of this material mediated 94 %
consumption of phenylethene after 9 h at 65 °C. Almost identical product distributions were obtained using catalytic Cp₂Ti(μ-H)₂BH₂ with lithium borohydride (Table 5.1, entry 1) compared with the original work wherein Cp₂TiCl₂ was used (entry 5). The transformation was slower, however, when a full equivalent of Cp₂Ti(μ-H)₂BH₂ and no borohydride was used (only 80 % conversion after 19 h at 65 °C, entry 2). The significant difference between these two sets of conditions is also apparent from the product distributions: more primary alcohol is formed (after oxidation) when 1.0 equiv. of catalyst and no borohydride is used.

Table 5.1. Regioselective hydroboration of phenylethene promoted by titanium complexes.

<table>
<thead>
<tr>
<th>entry</th>
<th>reagents</th>
<th>63:64</th>
<th>63:64:65</th>
<th>yield</th>
<th>conversion</th>
<th>time (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.05 Cp₂TiBH₄, 1.0 LiBH₄</td>
<td>31:69</td>
<td>26:58:16</td>
<td>51</td>
<td>94</td>
<td>9</td>
</tr>
<tr>
<td>2</td>
<td>1.0 Cp₂TiBH₄</td>
<td>17:83</td>
<td>14:66:20</td>
<td>60</td>
<td>80</td>
<td>19</td>
</tr>
<tr>
<td>3ᵇ</td>
<td>1.0 BH₃</td>
<td>19:81</td>
<td>19:81:0</td>
<td>90</td>
<td>100</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>0.2 BH₃, 1.0 LiBH₄</td>
<td>18:82</td>
<td>18:82:trace</td>
<td>85</td>
<td>100</td>
<td>2</td>
</tr>
<tr>
<td>5ᵇ</td>
<td>0.2 Cp₂TiCl₂, 1.0 NaBH₄</td>
<td>31:69</td>
<td>31:69:-d</td>
<td>70</td>
<td>_d</td>
<td>5</td>
</tr>
<tr>
<td>0.2 18-crown-6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ᵃ Product ratios accessed by ¹H NMR and by GC after silylation and calibration. ᵇ At 25 °C. ᶜ At 30 °C. ᵈ No data reported by Isagawa and coworkers.
Comparison of entries 1 and 3 reveal that hydroboration of phenylethene using 
Cp₂Ti(μ-H)₂BH₂/LiBH₄ or using BH₃·THF, gave different ratios of regioisomeric 
alcohols. Stoichiometric Cp₂Ti(μ-H)₂BH₂ hydroborated phenylethene with the same 
regioselectivity as BH₃·THF, however. Incidentally, borohydride and borane combine to 
form equilibrium quantities of B₂H₇⁺, but this makes no difference to the regioselectivity 
of the hydroboration of phenylethene with BH₃·THF, because both BH₃ and BH₃/BH₄⁺ 
gave the same ratio of regioisomers (entries 3 and 4).

5.2.1.2 Identification of the Organoboron Products Before Oxidation

Isagawa originally proposed lithium alkylborohydrides, not alkylboranes, were 
formed in the reactions they studied since one organoboron product did not isomerize at 
150 °C. However, the method used to form the catalysts implied the products could be 
alkylboranes from uncatalyzed BH₃ additions (vide supra). Identification of the 
organoborane products therefore was crucial to further comprehend these reactions.

In the current work, the catalytic reaction was monitored by ¹¹B NMR. A mixture 
of phenylethene, 1.0 eq. LiBH₄, and 0.05 eq. Cp₂Ti(μ-H)₂BH₂ after 9.5 h in THF 
showed a considerable amount of residual LiBH₄ and peaks at δ -14.4 and -12.3 ppm, 
characteristic of alkylborohydrides or tetraalkylborates. When more phenylethene was 
added, the LiBH₄ peak diminished, the resonances at -14.4 and -12.3 ppm were enhanced, 
and minor peaks at -10.1 ppm and -5.4 (doublet) emerged. No splitting was observed for 
the predominant peaks in the corresponding coupled spectrum (Figure 5.1).
Figure 5.1. (A) $^{11}$B NMR from Cp$_2$TiBH$_4$-catalyzed hydroboration of phenylethene with 0.2 equiv. of LiBH$_4$; (B) $^{11}$B NMR from Cp$_2$TiBH$_4$-catalyzed hydroboration of phenylethene with 1.0 equiv. of LiBH$_4$

Alkylborohydrides were formed via a different synthetic route to determine if these were the products of this catalyzed hydroboration as originally proposed. Thus phenylethene was reacted with borane in THF, and excess alkene was used to ensure conversion to trialkylboranes. If the ratio of anti-Markownikoff-to-Markownikoff hydroboration is approximately 4:1 (cf Table 5.1, entry 3), then the ratio of the trialkylboranes formed would be very roughly 64:16:4:1 for B(CH$_2$CH$_2$Ph)$_3$: B(CH$_2$CH$_2$Ph)$_2$(CH(Me)Ph):B(CH$_2$CH$_2$Ph)(CH(Me)Ph)$_2$:B(CH(Me)Ph)$_3$. The $^{11}$B NMR of this mixture was uninformative since the peaks were extremely broad and ill-defined. However, the reaction was then "quenched" by adding LiAlH$_4$/DABCO to
convert the alkylboranes to the corresponding trialkylborohydrides (109) (equation 5.2).\textsuperscript{170,171} The spectrum of the mixture formed after this process is shown in Figure 5.2B. There are three conspicuous peaks in this spectrum (8 -5.7 \{minor\}, -9.7 \{sharp\}, -13.5 \{broad\}) presumably corresponding to LiHB(CH\textsubscript{2}CH\textsubscript{2}Ph)(CH(Me)Ph)\textsubscript{2}, LiHB(CH\textsubscript{2}CH\textsubscript{2}Ph)\textsubscript{3} and LiHB(CH\textsubscript{2}CH\textsubscript{2}Ph)\textsubscript{2}(CH(Me)Ph). All these peaks are doublets ($J_{B-H} = 78 \pm 3$ Hz) in the coupled spectrum.

\[
\begin{align*}
\text{Ph} & \quad \text{BH}_3 \\
\text{Li} & \quad \text{DABCO} \\
\text{LiAlH}_4 & \quad \text{Li} \\
\text{Ph} & \quad \text{H} \\
\end{align*}
\]

Equilibria such as these are unlikely in the sample corresponding to Figure 5.2B since all the products were converted to alkylborohydrides via the addition of LiAlH\textsubscript{4}/DABCO.\textsuperscript{170,171,174} It was possible, however, that exchange processes could have had a bearing on the spectrum shown in Figure 5.2A, so the sample from the catalyzed hydroboration was also treated with LiAlH\textsubscript{4}/DABCO to quench exchange phenomena (Figure 5.2C). It gave almost the same \textsuperscript{11}B NMR as shown in Figure 5.2A; the predominant peaks in the original spectrum were unchanged, and were still singlets in the proton coupled spectrum. Minor shoulders at -9.7 and -13.6 ppm, and a triplet at -18.8 ppm were observed also. Therefore, differences between the spectra in Figure 5.2A and 5.2B are not due to exchange phenomena.
Figure 5.2. $^{11}$B NMR spectra ($^1H$-$^{11}$B decoupled) from (A) Cp$_2$TiBH$_4$-promoted hydroboration of phenylethene; (B) Hydroboration of phenylethene by BH$_3$, followed by treatment with LiAlH$_4$/DABCO (eq. 5.2); (C) Reaction mixture from spectrum A treated with LiAlH$_4$/DABCO; (D) BH$_3$ hydroboration followed by treatment with (2-phenylethyl)-lithium (eq. 5.4); and, (E) Lithium tetra(2-phenylethyl)borate from (eq 5.3).
The results up to this point indicated that the predominant products of the titanium mediated catalyzed hydroboration of phenylethene were not alkylboranes (from uncatalyzed addition of BH₃), and they were not the alkylborohydrides originally postulated. If not alkylboranes or alkylborohydrides, what were the major products formed in titanium promoted hydroboration of phenylethene? Tetraalkylborates were prepared to test for the presence of these by comparison. Thus, 2-lithiophenylethene was prepared from 2-phenylbromoethane,¹⁷⁵ and from 2-phenylidoethane¹⁷⁶,¹⁷⁷ in two sets of experiments. Both these samples of PhCH₂CH₂Li were transformed into LiB(CH₂CH₂Ph)₄ (110) via reaction with BF₃.OEt₂ (equation 5.3).

\[ \text{Ph} \quad \text{Li} \quad \text{BF₃.OEt₂} \quad \text{LiB(Ph)} \quad \text{(5.3)} \]

Analysis of samples from both these transformations by ¹¹B NMR showed sharp resonances at δ -16.3 ppm (Figure 5.2D),¹⁷⁸ which does not correspond to the major peak in Figure 5.2A. However, the "all-terminal" borate (110) is not necessarily a major product in this process, since the titanium mediated hydroboration of phenylethene gives a ca 7:3 mixture of primary:secondary alcohols after oxidation. Therefore, a mixture of isomers of LiB(CH₂CH₂Ph)₄ was prepared by treatment of borane with excess phenylethene to give a mixture of isomerictrialkylboranes (probably including B(CH₂CH₂Ph)₃, B(CH₂CH₂Ph)₂(CH(Me)Ph), B(CH₂CH₂Ph)(CH(Me)Ph)₂, and B(CH(Me)Ph)₃); this mixture was then reacted with PhCH₂CH₂Li to give the corresponding tetraalkylborates 111 (equation 5.4). The ¹¹B NMR spectrum of this mixture in Figure 5.2E matches well with Figure 5.2A except that LiB(CH₂CH₂Ph)₄ (-16.3 ppm) was not formed in the catalytic reaction, and the relative concentrations of the other peaks are different. The conclusion from these results is that the most conspicuous
products in the $^{11}$B NMR spectrum of the titanium promoted hydroboration of phenylethene were regioisomeric tetraalkylboronates.

\[
\begin{array}{c}
\text{Ph} \quad \xrightarrow{\text{BH}_3} \quad \left(\text{Ph}\right)_n \text{B} \left(\text{Me}\right)_{3-n} \\
\text{Ph} \quad \xrightarrow{\text{Li}} \quad \left(\text{Ph}\right)_{n+1} \text{B} \left(\text{Me}\right)_{3-n}
\end{array}
\]

(5.4)

Tetraalkylborates are not easily oxidized to alcohols. For example, when the crude reaction mixture represented in Figure 2A was treated with 30 % $\text{H}_2\text{O}_2$/3 M $\text{NaOH}$ (25 °C, 12 h) the $^{11}$B NMR showed only changes corresponding to transformation of $\text{BH}_4^-$ and trialkylborohydrides (-5.4 ppm) into $\text{B(OH)}_3$; the resonances assigned to tetraalkylborates (-14.4, -12.3, and -10.1) did not decrease appreciably relative to a $\text{BF}_3.\text{OEt}_2$ standard. Formation of tetraalkylborates should therefore lead to decreased yields of product alcohols. To accentuate the production of tetraalkylborates, phenylethene was reacted with only 0.5 equiv. of $\text{LiBH}_4$ instead of 1.0 equiv. which had been used for the reactions discussed so far. When the crude reaction mixture was oxidized, ca. 60 % of the phenylethene could not be accounted for in GC analyses. The implications of these observations is that 60 % of the phenylethene is converted into tetraalkylborates as indicated in equation 5.5, resulting in lower yield of alcohols and producing relatively more hydrogenation product.

\[
\begin{array}{c}
0.05 \text{Cp}_2\text{TiBH}_4, \text{0.5 LiBH}_4 \quad \xrightarrow{\text{THF, 16 h, 65 °C}} \quad \text{H}_2\text{O}_2, \text{OH}^-
\end{array}
\]

\[
\begin{align*}
\text{Ph} & \quad + \quad \text{Ph}^\text{Me} & \quad + \quad \text{Ph}^\text{Me} & \quad + \quad \text{Ph}^\text{OH} & \quad + \quad \text{tetraalkylborates (5.5)} \\
25 \% & \quad 4 \% & \quad 6 \% & \quad 60 \%
\end{align*}
\]
The quenching experiments with LiAlH₄/DABCO as described above exposed organoboron compounds which were previously "¹¹B NMR invisible" due to exchange processes. However, it was still necessary to check for alkylborohydrides with ¹¹B NMR chemical shifts close to the putative tetraalkylborates, since overlap potentially could have obscured alkylborohydride signals in the quenching experiments. Therefore, the reaction mixture resulting from catalyzed hydroboration of borohydride with phenylethene was reacted with ethanol to transform all alkylborohydrides into ethyl boronates and ethyl borinates which resonate in a different region of a ¹¹B NMR spectrum. New ¹¹B NMR peaks were seen corresponding to B(OEt)₃ (19.5 ppm), RB(OEt)₂ (32.5 ppm), and R₂B(OEt) (52.5 ppm). The latter compounds could be derived from reaction of ethanol with LiBH₃R and LiBH₂₂R₂, respectively. Alternatively these mono- and dialkylboronate esters could have been produced from RBH₂ and R₂BH after quenching with ethanol (vide infra). While dialkylborohydrides were observed in Figure 5.2C (minor triplet at -18.8 ppm) after LiAlH₄/DABCO quench of the crude metal promoted reaction, monoalkylborohydrides were not. Therefore these compounds must have been obscured by the signals from tetraalkylborate products.

5.2.1.3 Exchange Processes Involving Alkylboranes and Alkylborohydrides

Alcohols formed in the titanium mediated hydroboration processes could have been derived from either alkylboranes or alkylborohydrides, but not from tetraalkylborates (vide supra). Indeed, the experiments outlined in the previous sections indicate that one or both these compound types were present. Throughout, rapid chemical exchange on the NMR time scale could have precluded observation of some critical peaks, so limiting the value of direct ¹¹B NMR experiments. In fact, the ¹¹B NMR spectra of the crude reaction mixtures from the catalyzed hydroboration of phenylethene showed broad BH₄⁺ resonances and no
coupling was observed, whereas this signal normally appears as a well defined quintet in the coupled spectrum. In view of this evidence that exchange is occurring, it was extremely important to establish what exchange processes may have been operative in the metal promoted reactions to deduce what signals might have been lost. This section describes experiments undertaken to investigate possible exchange pathways.

First, the following experiment proved that exchange processes between alkylboranes and borohydride are very likely. When phenylethene was treated with a deficiency of BH₃ (0.35 equiv.), the ¹¹B NMR spectrum indicated the products were predominantly trialkylboranes (broad singlet at ppm 84 ppm in the proton-boron coupled ¹¹B NMR) and dialkylboranes (broad singlet at 54 ppm). Then catalytic Cp₂Ti(μ-H)₂BH₂ was added and the mixture was maintained at 65 °C for 12 h. The ¹¹B NMR of this material at ambient temperature was completely different to that before addition of the titanium complex. Predominant peaks in the reaction mixture at this stage were a number of weak, ill-defined broad singlets at 55 ppm, 32 ppm, 9 ppm and -18.6 ppm in addition to a broad singlet corresponding to LiBH₄. Consequently, exchange processes between BH₄⁻ and alkylboranes had been established.

In contrast to BH₄⁻/alkylborane exchange phenomena, the following experiment indicated alkylborohydrides and lithium borohydride in the presence of Cp₂Ti(μ-H)₂BH₂ do not interconvert rapidly on the NMR time scale. Thus, a mixture of lithium dialkyl- and trialkylborohydrides was prepared from phenylethene in the two step sequence shown in equation 5.6. These gave three doublets (-5.8, -9.9, and -13.6 ppm) and two triplets (-14.0 and -19.1 ppm) in the ¹¹B NMR. Then LiBH₄ and Cp₂Ti(μ-H)₂BH₂ were added and the mixture was stirred at 65 °C for 21 h. After this period the ¹¹B NMR was virtually unchanged: all the signals were still observable and splittings were well resolved in the boron-proton coupled spectra. This indicates that alkylborohydrides do not equilibrate with lithium borohydride under the titanium mediated reaction conditions. Furthermore, no
changes were observed in the ratios of the original signals within experimental limits, therefore isomerization of the alkylborohydrides had not occurred.

\[
\begin{align*}
\text{Ph} & \quad \xrightarrow{0.4 \text{ BH}_3, \text{THF}} \quad (\text{PhCHMe})_n(\text{PhCH}_2\text{CH}_2)_m\text{BH}_3-n-m \\
\text{LiAlH}_4 & \quad \xrightarrow{\text{DABCO}} \quad \text{Li}[(\text{PhCHMe})_n(\text{PhCH}_2\text{CH}_2)_m\text{BH}_4-n-m] \quad \text{0.05 Cp}_2\text{TiBH}_4 \\
 & \quad \xrightarrow{1.0 \text{ LiBH}_4, 65 \ ^\circ\text{C}, 21 \text{ h}} \quad \text{no reaction} \quad (5.6)
\end{align*}
\]

5.2.1.4 Isomerization Experiments

Various experiments were performed to test for possible isomerization processes that could influence the regioselectivity of the titanium-mediated hydroboration of phenylethene. The first experiment was to check for concomitant isomerization in the exchange of alkylboranes with LiBH₄ (see above). Phenylethene was treated with a deficiency of BH₃ (0.35 equiv.), catalytic Cp₂Ti(µ-H)₂BH₂ and 1.0 equiv. of lithium borohydride was added, and the mixture was maintained at 65 °C for 12 h. The ratio of 1-phenylethanol 63 to 2-phenylethanol 64 after oxidation was 20:80 (GC). Hydroboration of phenylethene with BH₃ is known to give this ratio of regioisomers (Table 5.1, entry 3), hence the product distribution was unaffected by treatment with the titanium catalyst and borohydride in the present experiment. Equilibration of alkylborane intermediates therefore cannot be invoked to account for the different ratios for the primary and secondary product alcohols for titanium catalyzed (BH₄⁻) and BH₃ hydroboration of phenylethene (cf Table 5.1 entries 1 and 3).

The previous sections showed that alkylboranes and alkylborohydrides obtained from phenylethene do not isomerize under the titanium mediated hydroboration conditions, but is this also true for tetraalkylborates? For instance, it was possible that
LiB(CH₂CH₂Ph)₄ (110) was not observed in the crude reaction mixture due to isomerization to regioisomeric borates, LiB(CH₂CH₂Ph)ₙ(CH(Me)Ph)₄₋ₙ. To test this, LiB(CH₂CH₂Ph)₄, prepared via equation 5.3, was subjected to the titanium mediated hydroboration conditions (equation 5.7). The only boron containing species observed (¹¹B NMR) were LiB(CH₂CH₂Ph)₄ and LiBH₄. Thus isomerization processes do not influence the regioselectivity of the Cp₂Ti(µ-H)₂BH₂-promoted hydroboration of phenylethene.

\[
\begin{align*}
\text{Li} & \quad \text{B} \quad \text{Ph} \\
110 & \quad \frac{\text{0.05 } \text{Cp}_2\text{TiBH}_4}{1.0 \text{ LiBH}_4} \\
& \quad 65^\circ\text{C}, 21 \text{ h} \quad \text{no reaction} \quad (5.7)
\end{align*}
\]

5.2.1.5 Time Dependence of Tetraalkylborate Production

Figure 5.3 shows concentration changes of phenylethene, tetraalkylborates, and ethylbenzene during the hydroboration of phenylethene with LiBH₄ in the presence of catalytic Cp₂Ti(µ-H)₂BH₂. Two notable qualitative features are apparent from this data. First, no appreciable induction time was observed. Secondly, tetraalkylborates are formed even at the very earliest stages of the reaction, implying that trialkylborohydrides, or other lesser substituted borates, do not accumulate.
Figure 5.3. Time dependence of Cp₂Ti(μ-H)₂BH₂ (0.05 eq.) catalyzed hydroboration of phenylethene (3 eq.) with LiBH₄ (1 eq.). (a) Consumption of phenylethene vs time; (b) Production of combined regioisomeric tetraalkylborates vs time; and, (c) Production of ethylbenzene vs time.
5.2.1.6 The Catalyst System: $^{11}$B NMR, EPR and Homogeneity Investigations

It was possible that the role of lithium borohydride in the catalytic reaction was to reduce Cp$_2$Ti($\mu$-H)$_2$BH$_2$ to colloidal titanium metal, especially since a similar reaction has been reported for TiCl$_4$ and LiEt$_3$BH.\textsuperscript{181,182} Heterogeneous catalysis by titanium metal could therefore not be ruled out. In the stoichiometric reaction, gradual decomposition of Cp$_2$Ti($\mu$-H)$_2$BH$_2$ to BH$_3$·THF (and titanium hydrides) could account for the relatively sluggish consumption of phenylethene. $^{11}$B NMR and homogeneity studies were performed specifically to address these issues.

The complex Cp$_2$Ti($\mu$-H)$_2$BH$_2$ is paramagnetic, hence it is inconspicuous in NMR experiments, at least in THF and other ethereal solvents.\textsuperscript{167} Thus, only borohydride was detected in the $^{11}$B NMR spectrum of a mixture of 1.0 Cp$_2$Ti($\mu$-H)$_2$BH$_2$ and 2.0 LiBH$_4$ after 12 h at 65 °C. If BH$_3$·THF was formed in this mixture, it was present in amounts smaller than the $^{11}$B NMR detection limits. Similarly, when Cp$_2$Ti($\mu$-H)$_2$BH$_2$ was heated alone (no LiBH$_4$) for 12 h at 65 °C, no signals at all were detected.

In general, as the Cp$_2$Ti($\mu$-H)$_2$BH$_2$ mediated hydroborations proceeded the solution changed from bright violet to deep blue/purple, and some solid material was deposited on the sides of the flask. To test homogeneity, two identical hydroborations of phenylethene were performed in parallel, except mercury was added to just one. The reaction rates and product distributions were followed by GC. Both transformations proceeded at approximately the same rate, and the product distribution was identical (\textit{i.e.} that shown in Table 5.1, entry 1). These observations imply that the catalysis is homogeneous assuming that titanium metal does amalgamate under these conditions, \textit{i.e.} that the "classical" mercury test\textsuperscript{183} is valid in this particular reaction.\textsuperscript{184}
5.2.1.7 Use of Other Borohydrides with Cp₂Ti(μ-H)₂BH₂ and Phenylethene

It was of interest to investigate other borohydrides for possible hydroborations of alkenes mediated by Cp₂Ti(μ-H)₂BH₂. Consequently, a reaction using sodium cyanoboroxyride was briefly investigated. A light blue solution formed immediately when 0.05 equiv. of Cp₂Ti(μ-H)₂BH₂ was mixed with 1.0 equiv. of NaBH₃CN at 65 °C. There was no reaction when 1.0 equiv. of phenylethene was added to this solution (GC vis internal standard).

\[ 0.2 \text{Cp}_2\text{Ti}(\mu-\text{H})_2\text{BH}_2 + 1.0 \text{NaBH}_3\text{CN} \xrightarrow{\text{THF, 65 °C, 0.5 h}} \text{"light blue solution"} \]

\[ 1.0 \text{Ph} \xrightarrow{\text{THF, 65 °C, 24 h}} \text{no reaction} \ (5.8) \]

The lack of reactivity described above could be due to some fundamental structural difference between complexes of BH₃⁻ and BH₃CN⁻. With regard to this, it may be significant, that Lippard has concluded that cyanoboroxyride tends to coordinate to transition metals via the nitrogen atom. Consequently, a reaction was attempted using LiBHÉt₃ as the borohydride source. Addition of this compound (1.0 equiv.) to 0.1 equiv. Cp₂Ti(μ-H)₂BH₂ gives a brown solution. A rapid reaction ensued at 25 °C when 1.0 equiv. of the phenylethene substrate was added to this solution. Most of the phenylethene consumed was converted to ethylbenzene, the hydrogenation product as indicated in equation 5.9. The reactions with LiBHÉt₃ were not pursued further since the amounts of hydroboration products in these process is relatively low.
5.2.1.8 Proposed Mechanism for Titanium Mediated Hydroboration of Phenylethene

A rationale to explain the observed characteristics of the Cp₂Ti(μ-H)₂BH₂-catalyzed hydroboration of phenylethene with LiBH₄ needs to accommodate the following experimental observations:

(i) the reaction of phenylethene with Cp₂Ti(μ-H)₂BH₂ proceeds faster under catalytic conditions (i.e., in the presence of excess borohydride) than under stoichiometric conditions (i.e., without borohydride);

(ii) regiochemistries for titanium mediated and BH₃ hydroboration of phenylethene are different, giving relatively more secondary alcohol for the catalyzed reaction;

(iii) the observed products of Cp₂Ti(μ-H)₂BH₂-mediated hydroboration of phenylethene are lithium trialkylborohydrides and lithium tetraalkylborates, which are produced from the very start of the transformation;

(iv) alkylborohydrides or tetraalkylborates derived from phenylethene do not isomerize under the reaction conditions; and,

(v) Isagawa’s hydroboration of phenylethene mediated by Cp₂TiCl₂ gave higher yield and a faster reaction rate than the corresponding Cp₂Ti(μ-H)₂BH₂-promoted reaction in the current work.
A mechanism that meets all of the criteria listed above is shown in Scheme 5.3. Lithium borohydride and Cp₂Ti(μ-H)₂BH₂ have been proposed to combine in a dynamic process that forms a bis(borohydride) complex 112 in a equilibrium favoring the starting materials.¹⁶⁷ We speculate that this complex could dissociate into the titanium-hydride 113 and LiBH₇. Such BH₃-abstraction from metal-borohydride complexes by Lewis bases has been observed previously for zirconium-borohydride complexes.¹⁸⁶ Thermal decomposition of metal-borohydride complexes into BH₃ and metal-hydrides is also well established and could be an alternative pathway.¹⁸⁷ The LiBH₇ formed reacts rapidly with phenylethene to produce several isomeric boranes 115 and LiBH₄. Meanwhile, highly regioselective insertion of phenylethene into the titanium-hydride bond of 113 produces the titanium-alkyl complex 114. Borohydride then displaces the alkyl group which is simultaneously transferred to the boron atom of boranes 115. This produces isomeric borates 116 with regeneration of the catalyst. Titanium-hydride 113 could be responsible for the observed competitive hydrogenation (cf. Table 5.1).¹⁸⁸⁻¹⁹⁰

Excess LiBH₄ is needed for the abstraction of BH₃ from Cp₂Ti(μ-H)₂BH₂, so reactions in the absence of LiBH₄ would be expected to proceed through a different reaction pathway. Indeed, the slower reaction rate observed in the stoichiometric reactions of Cp₂Ti(μ-H)₂BH₂ and phenylethene in the absence of excess LiBH₄ (Table 5.1, entry 2) is consistent with the fact that the first step in Scheme 5.3 is not possible under non-catalytic reaction conditions.
Scheme 5.3. Proposed mechanism for the formation of tetraalkylborates in the Cp$_2$Ti($\mu$-H)$_2$BH$_2$-mediated hydroboration of phenylethene.

The proposed high regioselectivity of alkene insertion into the titanium hydride bond of 113 in favor of the secondary titanium-alkyl complex 114 would prohibit the formation of LiB(CH$_2$CH$_2$Ph)$_4$ in the catalyzed reaction. Such selectivity is not without
precedent, since phenylethene has shown a tendency to form benzylic metal-alkyl compounds in several transition metal catalyzed transformations.

If, as suggested in Scheme 5.3, the initial event in the titanium-promoted hydroboration of phenylethene is simply BH$_3$ hydroboration of the alkene, it is necessary to explain differences in the regioselectivities for the BH$_3$ and the Ti-promoted processes (Table 5.1, entries 1 and 3). Our explanation for this is as follows. The postulated alkyl transfer from titanium to boron would be expected to proceed faster for less branched (and less hindered) boranes, as depicted in Figure 5.4. This would proportionally decrease the amounts of the less-hindered boranes leaving relatively more borane precursors to secondary alcohols (i.e. 115b and 115c).

\[
\begin{align*}
115a & \quad > \quad 115b \\
& \quad \text{fast} \\
& \quad > \\
& \quad 115c \\
& \quad \text{slow} \\
& \quad \downarrow \\
116a & \quad 116b \quad 116c \\
& \quad \text{slower}
\end{align*}
\]

Figure 5.4. Expected relative reactivity of isomeric trialkylboranes 115a-c towards alkyl transfer.
Higher yields and faster reaction rates for Isagawa's processes mediated by \( \text{Cp}_2\text{TiCl}_2 \), compared to the \( \text{Cp}_2\text{Ti}(\mu-\text{H})_2\text{BH}_2 \) catalyzed reaction, can be attributed to the fast initial formation of \( \text{BH}_3 \) in the former case (equation 5.1) leading to rapid initial hydroboration of alkene. After consumption of the \( \text{BH}_3 \) formed in equation 5.1, the second stage of the reaction proceeds through the mechanism depicted in Scheme 5.3, and fewer turnovers of \( \text{Cp}_2\text{Ti}(\mu-\text{H})_2\text{BH}_2 \) are needed to complete the reaction. Indeed, when the reaction of phenylethene with lithium borohydride in the presence of 0.1 equiv. of \( \text{Cp}_2\text{TiCl}_2 \) was monitored by GC, fast initial consumption of alkene was observed (40% conversion in 1 h) followed by a slower reaction rate (90% conversion after 10 h).

The proposed model thus explains the formation of tetraalkylborates from the early stages of the catalytic process, the regioselectivity of hydroboration of phenylethene, and the slower rate of the reaction with stoichiometric \( \text{Cp}_2\text{Ti}(\mu-\text{H})_2\text{BH}_2 \) and no borohydride. All steps in this mechanism have literature precedent, except we are unaware of any prior report of transmetallation from titanium to boron. An alternative mechanism could involve catalyzed additions of trialkylborohydrides to phenylethene. However, such a process would require simultaneous coordination of two cyclopentadienyl groups, an alkene, and a trialkylborohydride; this seems improbable for steric reasons.

5.2.1.9 Titanium Promoted Hydroborations of 1-Decene and \( \beta \)-Pinene

In some respects, different results were obtained for titanium promoted hydroborations of 1-decene and \( \beta \)-pinene compared with those of phenylethene. Visually, the reaction of these alkenes are very similar, i.e. a gradual change from bright violet to deep purple with deposition of solid material on the wall of the reaction flask. However, the reactions of 1-decene and \( \beta \)-pinene with \( \text{Cp}_2\text{Ti}(\mu-\text{H})_2\text{BH}_2 \) and borohydride were much slower than the corresponding transformation of phenylethene.
Attempts were made to characterize the products from the reaction of 1-decene using $^{11}$B NMR. When the crude reaction mixture of 1-decene with 0.05 equiv. of \( \text{Cp}_2\text{Ti}(\mu-\text{H})_2\text{BH}_2 \) and 1.0 equiv. of lithium borohydride was monitored after 36 h, only a very broad, non-resolved $^{11}$B-resonance corresponding to borohydride (-41 ppm) was observed; this signal showed no coupling in the coupled spectrum indicative of exchange processes. Three additional minor signals emerged on treatment of the crude reaction mixture with \( \text{LiAlH}_4/\text{DABCO} \): a quartet at -28.4 ppm, a triplet at -18.8 ppm and a singlet at -16.9 ppm.\(^{191}\) The BH\(_4^-\) signal at this stage is sharp and the coupling can be well resolved. Peaks corresponding to RB(OEt)\(_2\) (31.8 ppm) and R\(_2\)B(OEt) (54.2 ppm) were observed when the crude, incomplete reaction mixture after 20 h was quenched with ethanol instead of \( \text{LiAlH}_4/\text{DABCO} \), implying that LiBH\(_3\)R and LiBH\(_2\)R\(_2\) and/or RBH\(_2\) and R\(_2\)BH were present before ethanolysis.

Isagawa et al. reported that titanium mediated hydroboration of β-pinene, and the corresponding BH\(_3\) addition, followed by protonolysis gave different facial selectivities for the product alkanes (Table 5.2, entries 2 and 3; BH\(_3\) in entry 3 was formed \textit{in situ} from borohydride and boron trifluoride etherate).\(^{162}\) Similar selectivities were observed when these reactions were repeated in our laboratories, but using isolated \( \text{Cp}_2\text{Ti}(\mu-\text{H})_2\text{BH}_2 \) (Table 5.2, entry 1) as "catalyst". However, during the titanium mediated hydroboration of β-pinene we observed formation of significant quantities of pinane before protonolysis, presumably from metal catalyzed hydrogenation processes. Furthermore, \( \alpha \)-pinene produced from isomerization of β-pinene was also detected during the reaction (GC). Therefore, the alkane product distribution in entry 1 of Table 5.2 results from titanium catalyzed hydrogenation of \( \alpha \)-pinene and β-pinene, and from metal promoted hydroboration of these alkenes followed by protonolysis of the formed organoboranes.
Table 5.2. Diastereoselective hydroboration of β-pinene promoted by titanium complexes.

![Chemical structure](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>reagents</th>
<th>117:118</th>
<th>yield (%)</th>
<th>conversion (%)a</th>
<th>hydrogenation (%)a</th>
<th>time (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.05 Cp₂TiBH₄, 1.0 LiBH₄</td>
<td>77:23</td>
<td>62</td>
<td>94</td>
<td>35</td>
<td>25</td>
</tr>
<tr>
<td>2162</td>
<td>0.2 Cp₂TiCl₂, 1.0 NaBH₄, 0.2 18-crown-6</td>
<td>74:26</td>
<td>59</td>
<td><em>b</em></td>
<td><em>b</em></td>
<td><em>b</em></td>
</tr>
<tr>
<td>3c,d</td>
<td>0.25 NaBH₄, 0.33 BF₃.OEt₂</td>
<td>5:95</td>
<td>95</td>
<td>100</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

*a* By GC vs trans-decalin as internal standard.  
*b* No data reported.  
*c* The reactive species is BH₃.  
*d* At 25 °C.

To distinguish between the hydrogenation and hydroboration processes we decided to oxidize the crude reaction mixtures from the titanium mediated hydrobortions of β-pinene; in this way organoboron compounds would be converted into alcohols, while the hydrogenation products would be unchanged. Surprisingly, the observed ratio of cis- and trans-myrtanol (119 and 120) was 92:8 (equation 5.10), very close to the selectivity for BH₃ hydroboration of β-pinene. We also hydroborated β-pinene under the conditions...
originally published \((\text{Cp}_2\text{TiCl}_2:\beta\text{-pinene:BH}_4^- = 1:5:5, 65 \, ^\circ\text{C})\), and oxidized the crude reaction mixture. Once more, the ratio of cis- and trans-myrtanol (94:6) was very similar to that for BH\(_3\) hydroboration of \(\beta\)-pinene. The striking difference in the product ratios after protonolysis or oxidation of the crude reaction mixture suggests that isomerization of organoboron compounds during protonolysis in the presence of titanium complexes may occur.

\[
\begin{align*}
\text{CH}_2 & \\
\text{(i) catalyst, LiBH}_4 & \quad 65 \, ^\circ\text{C} \\
(\text{ii) H}_2\text{O}_2, \text{NaOH} & \\
\text{cis-myrtanol (119)} & + \\
\text{trans-myrtanol (119)} & \quad (5.10)
\end{align*}
\]

The proposed mechanism for the \(\text{Cp}_2\text{Ti}(\mu-\text{H})_2\text{BH}_2\)-promoted hydroboration of phenylethene must be modified when 1-decene and \(\beta\)-pinene are substrates. Only trace amounts of tetraalkylborates were observed in experiments with these aliphatic alkenes, and the reactions were also more sluggish compared with phenylethene. There could be several reasons for these observations. Insertion of 1-decene or \(\beta\)-pinene into the titanium hydride bond of 113 might be very slow. However, since hydrogenation products which also require insertions into titanium-hydride bonds were observed, the alkyltransfer from titanium to boron might be retarded instead. This decrease in reactivity of 1-decene (and other similar alkenes) compared with phenylethene probably reflects the electronic difference between alkyl- and aryl-substituted alkenes. Studies on titanocene catalyzed hydrogenation have shown that dicyclopentadienyl titanium hydrides readily dimerize to the
catalytically inactive species I and related polymeric materials. Therefore if alkene is not capable of insertion into the titanium hydride bond of 113, dimerization will break the catalytic cycle. The products of the reactions of 1-decene and β-pinene could still be generated via BH₃ hydroboration, as in the first steps of the proposed mechanism for phenylethene (Scheme 5.3). Regeneration of the catalyst, however, is suppressed leading to decreased reaction rates for 1-decene and β-pinene.

We propose that the borane products of the reactions of 1-decene and β-pinene are probably in equilibrium with borohydride and are not observable in the ¹¹B NMR spectra of the crude reaction mixtures. This equilibrium could explain the observation by Isagawa that products from titanium promoted hydroboration of 2-octene do not isomerize at 150 °C (see section 5.1). Finally, the observed predominant monohydroboration of alkynes can be explained by the slow rate of BH₃ production in the presence of a large excess of alkyne. After the first hydroboration produces vinylboranes, these products may enter the equilibrium with lithium borohydride preventing further reaction.

5.2.2 Other Titanium-Based Catalyst Systems

In the course of the work described in the previous sections, we briefly examined two other titanium-catalyst systems. The results of these studies are discussed below.
5.2.2.1 Hydroborations of Alkenes with Borohydride Mediated By TiCl₃/BH₄⁻

In addition to Cp₂TiCl₂-promoted hydroborations of alkenes, Isagawa also reported rate acceleration for reactions of alkenes with borohydride in the presence of TiCl₃. These transformations could be performed at milder reaction conditions (30 °C vs 65 °C) and afforded hydroboration products in shorter reaction times. For instance, 1-octene was consumed in 5 h, while the corresponding transformation with Cp₂TiCl₂ was complete after 24 h. Typically, 20 mol % of TiCl₃ was reacted with 1.0 equiv. of sodium borohydride in the presence of 20 mol % of 18-crown-6 (equation 5.11). After 1 h at 30 °C, the alkene was added and the reaction mixture was stirred until completion of the reaction.

\[ 0.2 \text{TiCl}_3 + 0.2 \text{18-crown-6} + 1.0 \text{NaBH}_4 \xrightarrow{\text{THF, 30 °C, 1h}} \text{"dark violet solution"} \ (5.11) \]

Two other groups have reported alkene hydroborations using TiCl₄/BH₄⁻ systems: Kano et al described hydroboration of alkenes using TiCl₄/NaBH₄,¹⁹⁶ and Kumar et al used TiCl₄/iBu₄NBH₄.¹⁹⁷ Stoichiometric amounts of titanium were used in these transformations. Kumar et al suggested that Ti(BH₄)₃ was the active catalyst in TiCl₄/iBu₄NBH₄ systems, and that the reaction occurred via a complex of type I.¹⁹⁷ In support of this, agostic-like type II bonding has been observed in crystallographic studies by Girolami and coworkers for a titanium borohydride phosphine complex.¹⁹⁸
A similar question arises for these systems as in hydroborations promoted by 
\( \text{Cp}_2\text{TiCl}_2 \): do \( \text{TiCl}_3 \) and \( \text{TiCl}_4 \) promoted hydroborations intimately involve the metal, since 
literature reports have described that stoichiometric reactions of titanium tetrachloride with 
borohydride give diborane as a by-product.\textsuperscript{199,200} In equation 5.12, one mole of BH\(_3\) is 
produced per mole of titanium; consequently a three fold excess of borane was produced in 
the work of Kano\textsuperscript{196} and of Kumar \textit{et al}\textsuperscript{197} wherein stoichiometric TiCl\(_4\) was used.

\[
2 \text{TiCl}_4 + 8 \text{LiBH}_4 \xrightarrow{\text{Et}_2\text{O, 25 °C}} 2 \text{Ti(BH}_3\text{)}_3 + 8 \text{LiCl} + \text{H}_2 + \text{B}_2\text{H}_6 \quad (5.12)
\]

5.2.2.2 The Catalyst System

Equation 5.12 strongly implies that Ti(BH\(_3\))\(_3\) and ClTi(BH\(_4\))\(_2\) are formed when 
TiCl\(_4\) is mixed with borohydride, and the color of the reaction mixture from TiCl\(_3\) ("dark 
violet" according to Isagawa \textit{et al})\textsuperscript{162} matches well with the reported color of the these 
complexes ("violet/purple").\textsuperscript{199,200}

In this work the reaction of TiCl\(_3\) with lithium borohydride was studied by \( ^{11}\text{B} \) 
NMR. Titanium complexes formed in this reaction are paramagnetic and NMR 
inconspicuous, so only the non-complexed boron containing products were evident. Peaks 
corresponding to BH\(_3\)·THF, B\(_2\)H\(_7\)\(^-\), and BH\(_4\)\(^-\) (equation 5.13), broadened by exchange 
processes, were observed after 3.5 h at 30 °C. A colorless precipitate was formed in this 
reaction, possibly corresponding to production of lithium chloride.

\[
0.2 \text{TiCl}_3 + 1.0 \text{LiBH}_4 \xrightarrow{\text{THF, 30 °C, 3.5 h}} \text{BH}_3 + \text{B}_2\text{H}_7\text{H}^- + \text{BH}_4\text{H}^- \quad (5.13)
\]

observed by \( ^{11}\text{B} \) NMR
5.2.2.3 Identification of the Organoboron Products

Titanium trichloride (0.2 equiv.) was treated with 1.1 equiv. of LiBH₄ in THF, for 1 h at 30 °C. Phenylethene (1.0 equiv.) was added, and the ¹¹B NMR was recorded after 12 h at 30 °C. Trace amounts of tetraalkylborates were observed, but the only other signal corresponded to BH₄⁻ and this was extremely broad. When the mixture was "quenched" with LiAlH₄/DABCO (vide supra) to trap alkylboranes as alkylborohydrides, the ¹¹B NMR of the resulting mixture was identical to that of a sample from BH₃ reacted with phenylethene then quenched with LiAlH₄/DABCO (i.e. Figure 5.2B). Furthermore, the ratio of the two regioisomeric alcohols formed after oxidation, PhCH₂CH₂OH and PhCH(OH)Me, was 4:1, exactly that formed in the conventional hydroboration of phenylethene with BH₃. Therefore, products of the hydroboration of phenylethene with BH₄⁻ and catalytic TiCl₃ probably arise from production of borane followed by classical hydroboration. However, appreciable amounts of tetraalkylborates and trialkylborohydrides were formed after 36 h at 65 °C if excess phenylethene was added. This suggest that alkyl transfer from titanium to boranes produced from BH₃ hydroboration of phenylethene does occur at elevated temperatures. Curiously, in the TiCl₃-promoted reaction the tetraalkylborate LiB(CH₂CH₂Ph)₄ (~15 %) was formed, in contrast to the reactions mediated by Cp₂Ti(μ-H)₂BH₂, suggesting that insertion of titanium-hydride complexes do provide a primary titanium-alkyl species in this reaction mixture (equation 5.14).
5.2.2.4 Hydroboration of Alkenes with Ti(O^iPr)_4/Catecholborane; The Catalyst System

During screening procedures to identify potential new hydroboration catalysts, we observed the production of hydroboration products when alkenes were treated with a combination of Ti(O^iPr)_4 and catecholborane. We decided to investigate these reactions in more detail and the results are discussed below.\textsuperscript{159}

When Ti(O^iPr)_4 was treated with catecholborane in THF, the solution rapidly turned deep red, and a red solid could be isolated after removal of the solvent and the excess catecholborane under reduced pressure. The $^{13}$C NMR spectrum of this material was similar to that published previously for Ti(O_2C_6H_4)_2,\textsuperscript{201} which was reported to show paramagnetic characteristics, presumably due to partial electron transfer of electrons from the aromatic catechol moieties to the metal center. Unfortunately, attempts to crystallize the red complex failed, and contamination with B_2(C_6H_4O_2)_3 prevented elemental analysis.

The $^{11}$B NMR spectrum of the reaction mixture from Ti(O^iPr)_4 and catecholborane (Figure 5.5A) showed that BH_3·THF and i^PrOBO_2C_6H_4 were also formed (the latter borate was prepared by reaction of catecholborane with i^PrOH for comparison). A possible rationale for these results is shown in equation 5.15.

\[
\text{Ti(O}^i\text{Pr)}_4 + 6 \text{ HBO}_2\text{C}_6\text{H}_4 \\
\xrightarrow{\text{THF, 25 °C, 12 h}} \text{Ti(O}_2\text{C}_6\text{H}_4)_2 + 4 \text{i^PrOBO}_2\text{C}_6\text{H}_4 + 2 \text{BH}_3\cdot\text{THF} \quad (5.15)
\]

Monitoring the progress of the reaction (equation 5.15) by $^{13}$C NMR in CDCl_3 revealed immediate consumption of Ti(O^iPr)_4 and initial formation of i^PrOBO_2C_6H_4 and a species that produces two signals in the $^{13}$C NMR (8 24.8 and 68.1 ppm) in addition to unreacted catecholborane. The intensities of the two unassigned signals in the $^{13}$C NMR decreased with time, eventually fading into the baseline after 6 h. During the same time
period, the $^{11}$B NMR of this reaction in THF showed signals of $^1$PrOBO$_2$C$_6$H$_4$ (23.1 ppm), catecholborane (doublet, 26.0 ppm) and BH$_3$·THF (quartet, 0.2 ppm) (Figure 5.5A). The intensity of the resonance corresponding to BH$_3$·THF slowly increased and an additional signal with relatively low intensity corresponding to B$_2$(O$_2$C$_6$H$_4$)$_3$ was observed also. We tentatively assign the unknown reaction intermediate as (O$^i$Pr)$_2$Ti(O$_2$C$_6$H$_4$) (III), the initial product from redistribution of the ligands on boron and titanium (Scheme 5.4).

\[
\begin{align*}
3 \text{O}_2\text{C}_6\text{H}_4\text{B-H} & \quad + \quad \text{Ti(O}^i\text{Pr)}_4 \\
\downarrow & \quad \\
2 \text{O}_2\text{C}_6\text{H}_4\text{B-O}^i\text{Pr} & + \quad \text{BH}_3\cdot\text{THF} & + \quad \text{O}_2\text{C}_6\text{H}_4\text{TiO}^i\text{Pr} \\
\text{III} & \\
\downarrow & \\
2 \text{O}_2\text{C}_6\text{H}_4\text{B-O}^i\text{Pr} & + \quad \text{BH}_3\cdot\text{THF} & + \quad \text{O}_2\text{C}_6\text{H}_4\text{TiO}^i\text{Pr} \\
\end{align*}
\]

**Scheme 5.4.** Possible formation of (C$_6$H$_4$O$_2$)$_2$Ti from catecholborane and Ti(O$^i$Pr)$_4$.

5.2.2.6 Identification of Organoboron Products from Ti(O$^i$Pr)$_4$-Promoted Hydroboration Reactions

Analysis of the $^{11}$B NMR recorded 12 h after 1.5 equiv. of catecholborane was added to a mixture of 1.0 equiv. of cyclohexene and 0.1 equiv. of Ti(O$^i$Pr)$_4$ indicated that
the major product of this reaction was tricyclohexylborane 121 (81 ppm). Only a very minor trace of CyB(O2C6H4)2 (36 ppm) was formed (Figure 5.5B). However, when the same procedure was repeated with 1-decene as substrate, clean production of \( n\text{-C}_{10}\text{H}_{21}\text{B(C}_{6}\text{H}_{4}\text{O}_{2}) \) 122 was observed (equation 5.17 and Figure 5.5C). Two more substrates were subjected to the reaction conditions. Phenylethene showed predominant formation of the boronic ester product, and 2-phenyl-propene produced about equal quantities of alkylboronates and tri- and dialkylboranes (equations 5.18 and 5.19).

\[
\begin{align*}
\text{cyclohexene} & \xrightarrow{\text{Ti(O^{i}Pr)\text{}}_{4}} \text{catecholborane} \quad \text{121} \\
n\text{-octene} & \xrightarrow{\text{Ti(O^{i}Pr)\text{}}_{4}} \text{catecholborane} \quad \text{122} \\
\text{Ph-ethene} & \xrightarrow{\text{Ti(O^{i}Pr)\text{}}_{4}} \text{catecholborane} \quad \text{123} \\
\text{Ph-propene} & \xrightarrow{\text{Ti(O^{i}Pr)\text{}}_{4}} \text{catecholborane} \quad \text{124}
\end{align*}
\]

These results suggest a competition between titanium catalyzed addition of catecholborane to alkenes and hydroboration of the substrates by BH\text{3}.THF, produced in redistribution of boron and titanium ligands. For fast reacting monosubstituted alkenes
such as 1-decene and phenylethene the predominant products appear to be formed via addition of catecholborane, while reactions with the less reactive, disubstituted alkenes 2-phenyl-propene and cyclohexene result in significant quantities of alkylboranes from BH$_3$ hydroboration. These results indicate that the Ti(O$^\text{i}$Pr)$_4$/catecholborane system is of limited general use.

Two alternative pathways for the production of alkyl boronate esters and alkylboranes were briefly investigated. For instance, observation of trialkylboranes does not prove that this material is formed from BH$_3$ hydroboration of the substrates. We decided to test if trialkylboranes can be formed from alkylboronate esters under the Ti(O$^\text{i}$Pr)$_4$-mediated reaction conditions. Thus, cyclohexene was hydroborated at 100 °C with catecholborane,$^{44,45}$ the crude product 123 was purified by vacuum distillation and 1.0 mmol of this compound was added to 0.1 mmol of Ti(O$^\text{i}$Pr)$_4$ in 2 mL of THF (equation 5.20). Catecholborane was then introduced and the reaction mixture was analyzed by $^{11}$B NMR after 12 h at 25 °C. This spectrum showed signals corresponding to BH$_3$.THF, catecholborane, $^i$PrB(O$_2$C$_6$H$_4$) and 123. No trialkylboranes were observed, indicating that tricyclohexylborane 121 produced in Ti(O$^\text{i}$Pr)$_4$-mediated hydroboration of cyclohexene was not derived from initially formed boronate ester 123.
Figure 5.5. Proton-boron decoupled $^{11}$B NMR spectra from (a, top) 1.0 equiv. of Ti($O^i$Pr)$_4$ and 6.0 equiv. of catecholborane after 6 h; (b, middle) 0.1 equiv. of Ti($O^i$Pr)$_4$, 1.5 equiv. of catecholborane and 1.0 equiv. of cyclohexene after 12 h; and, (c, bottom) 0.1 equiv. of Ti($O^i$Pr)$_4$, 1.5 equiv. of catecholborane and 1.0 equiv. of 1-decene after 12 h.
The previous paragraph showed that alkyl boronate esters are not transformed into trialkylboranes under titanium-promoted hydroboration conditions. We also tested the opposite scenario: can alkyl boronate esters be formed from BH$_3$-derived hydroboration products? Equation 5.21 shows a possible pathway for such a process. Therefore, both cyclohexene and 1-decene were hydroborated with an excess of BH$_3$ and after complete consumption of the substrate (GC), 0.1 equiv. of Ti(O$^t$Pr)$_4$ and catecholborane was added. The crude reaction mixture was analyzed by $^{11}$B NMR after 11 h at 25 °C. Clean conversion of the monoalkylboranes 124 and 125 into the corresponding boronate esters was observed for both reactions (equations 5.22 and 5.23). These results indicate that metal mediated esterification of alkylboranes into alkyl boronate esters is indeed feasible. However, since both intermediates 124 and 125 showed this reactivity, these esterifications do not account for the observed difference in products of Ti(O$^t$Pr)$_4$-promoted hydroborations of cyclohexene and 1-decene (equations 5.16 and 5.17).
5.3 Conclusion

This study addresses several key issues regarding titanium catalyzed additions of borohydride to alkenes. First, $\text{Cp}_2\text{Ti}(\mu-H)_2\text{BH}_2$ promotes the addition of LiBH$_4$ to alkenes, but is not directly involved in the hydroboration step. Second, the products of hydroboration of phenylethene were shown to consist primarily of regioisomeric tetraalkylborates, and minor amounts of trialkylborohydrides were produced also. The resulting ratio of primary to secondary alcohols after oxidation of the crude reaction mixture is decreased, because the non-oxidizable tetraalkylborates are predominantly formed from less branched trialkylboranes. A reaction mechanism is proposed that accommodates the observed characteristics for the titanium promoted hydroboration of phenylethene.

Organoboranes are produced in titanium mediated hydroboration of 1-decene and $\beta$-pinene. These products are involved in a dynamic equilibrium with lithium borohydride resulting in a mixture of alkylboranes and alkylborohydrides or in dimeric species. Tetraalkylborates are not formed to any significant extent for $\beta$-pinene and 1-decene. The organoboron products from titanium promoted reaction of $\beta$-pinene produce the same ratio of diastereomeric alcohols after oxidation as BH$_3$ hydroboration.

Reactions of alkenes and borohydride promoted by TiCl$_3$ produce BH$_3$ which is the actual hydroborating agent. At 25 °C, no tetraalkylborates were observed and the products are probably boranes in a dynamic equilibrium with lithium borohydride. At 65 °C the reaction of phenylethene and borohydride in the presence of TiCl$_3$ did produce
tetraalkylborates, which indicates that at elevated temperatures alkyl transfer from titanium to boron occurs in a similar way as described in detail for reactions with \( \text{Cp}_2\text{Ti(μ-H)}_2\text{BH}_2 \). In contrast to hydroborations of phenylethene promoted by this latter titanium complex, \( \text{TiCl}_3 \) promoted reactions do produce \( \text{Li(CH}_2\text{CH}_2\text{Ph})_4 \).

Finally, the reaction of titanium isopropoxide and catecholborane gives products of redistribution of their ligands and this leads to production of \( \text{BH}_3\cdot\text{THF} \). In the presence of reactive alkenes addition of catecholborane to the substrate was observed, but less reactive alkenes afforded mixtures of alkylborane products derived from \( \text{BH}_3 \) hydroboration and boronate esters produced from metal promoted addition of catecholborane.

6.1 Introduction.

Syntheses of optically pure molecules has become increasingly important in modern organic chemistry. Transition metal catalyzed asymmetric transformations are among the most successful methods to produce high levels of enantioselectivity.\textsuperscript{202} The ligands surrounding the metal play a critical role in such processes, creating a chiral environment that differentiates the transition state energies for the two possible enantiomeric products. Development of effective chiral ligands over the past two decades can be classified in two different schools of thought.

The first approach focusses on design and synthesis of stereochemically well defined ligands. This strategy has been applied successfully for ligands for both late and early transition metals. For instance, rhodium, ruthenium and palladium complexes with chiral bisphosphines BINAP,\textsuperscript{203,204} CHIRAPHOS,\textsuperscript{205} DIO\textsuperscript{206} and DIPAMP\textsuperscript{207} have been used to induce high degrees of enantioselectivity in the products of catalyzed hydrogenations,\textsuperscript{75,208} hydroborations\textsuperscript{51} and allylations.\textsuperscript{209,210} Salen and amino alcohol derived ligands \textbf{126} and \textbf{127} provide good results for manganese catalyzed epoxidations\textsuperscript{211,212} and copper catalyzed cyclopropanations\textsuperscript{213} and aziridinations\textsuperscript{214,215}
Despite the success of this approach, the performance of a ligand is rarely predictable, and is often limited to certain transformations or specific substrates. As a result, new ligands are reported constantly in the literature, but few provide sufficient selectivities for contemporary organic synthesis. The lack of correlation between design and actual performance provides a major obstacle for succesful application of this strategy.

The second approach relies on use of the "chiral pool", the stock of chiral molecules that nature has provided. In this case, metal catalyzed reactions are screened for high enantioselectivity in the presence of a variety of naturally occurring asymmetric ligands or simple derivatives of these. After a suitable molecule has been found, its performance is often fine-tuned by synthetic modifications until high selectivities are obtained. This methodology has been applied succesfully by the Sharpless group for titanium catalyzed epoxidations with diethyl tartrate,\textsuperscript{216-218} and for osmium catalyzed bishydroxylations with chinchona alkaloids.\textsuperscript{219-223}

This chapter describes foundations for new methodology to rapidly identify catalysts that give high chemical and optical yields for a desired transformation. This approach is based on the recent success of combinatorial libraries to screen a large pool of compounds with different chemical compositions for their biological activity.\textsuperscript{224-226} In these methods, rapid synthesis of a compound library is achieved by carrying out a series of consecutive chemical reactions on a lead compound attached to a solid support (Scheme 6.1). The size of the library is determined by the number of different transformations for each step. For example, if the synthesis consists of four steps with a choice of five different reagents for each step, the library will be composed of \(5^4\) different entities.
Scheme 6.1. Principle of solid phase combinatorial synthesis. Two steps with three different reagents provide $3^2$ different sequences.

The homogeneity of the entities attached to each resin is crucial for unequivocally determining a sequence that shows a positive interaction with a biological target. Therefore, the use of combinatorial libraries has been limited to compounds for which the yield of the individual steps is very high. This prerequisite is met by the modern technologies developed for solid phase peptide and oligonucleotide synthesis.\textsuperscript{227,228}
Several reports have appeared describing the introduction of ligating groups into amino acid derivatives.\textsuperscript{229,230} Incorporation of such amino acid surrogates into peptides can create a metal binding site, which potentially can function as a chiral center for asymmetric catalysis. Application of the combinatorial approach to the syntheses of peptides containing coordinative groups would enable the production of large numbers of possible catalysts in a relatively short time period. The screening of such a catalyst library can be performed conveniently in parallel experiments using an autosampler system and a chromatographic analyzer with a chiral stationary phase. In this way both chemical and optical yields of the products can be accessed accurately from small scale screening reactions.

For successful application of this methodology several requirements need to be fulfilled. First, a stable monomer needs to be synthesized possessing both a functionality capable of coordination to a transition metal, and an amine and/or carboxylate or similar group allowing incorporation into a peptide. Furthermore, metal binding has to be sufficiently strong to prevent leaching of the metal from solid phase into solution phase during catalysis, which could cause deleterious side reactions diminishing the optical yields of the products. We decided to focus on phosphine ligands, since these have relatively strong binding constants with most late transition metals especially if part of a chelating structure. Finally, these monomers and the peptides in which they are incorporated must be tolerant towards the conditions of peptide synthesis.

Two different screening processes could be used after incorporation of phosphine containing moieties into peptide sequences of a combinatorial library. The catalysis could be performed by coordination of transition metal complexes onto the supported ligands (heterogeneous catalysis). To project the catalytic site into solution, the resin must swell sufficiently in the solvent used during screening. Using a linker between the solid support and peptide will enhance the swelling properties of the resin and the accessibility of the
catalytic sites. Conversely, the peptide ligands can be cleaved from the solid support and complexed to transition metals in solution for homogeneous catalysis.

The use of metal binding peptides generated by a combinatorial approach on a solid support for asymmetric catalysis is unprecedented in the literature, but Inoue and coworkers have shown the potential of using peptide derivatives for several enantioselective, catalytic processes. For instance, the ligands 128 were used for titanium catalyzed hydrocyanation of aldehydes with enantioselectivities ranging from 25-90 % depending on the amino acid sequence used. Furthermore, asymmetric additions of diethylzinc and cyanotrimethylsilane to aldehydes and titanium catalyzed epoxidation of allylic alcohol derivatives were reported (equations 6.1-6.3).
In earlier work, Whitesides and coworkers attached a bisphosphine to biotin and used this compound after complexation with biotin's high-affinity, natural acceptor, avidin, for rhodium catalyzed asymmetric hydrogenation of N-acetamido dehydroalanine (Scheme 6.2). Modest enantioselectivities were obtained, and no optimization was attempted.\textsuperscript{236}

\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) {\includegraphics[width=0.5\textwidth]{image}};
\node (b) at (2,1) {avidin \textsuperscript{129}-Rh(NBD)OTf};
\node (c) at (2,-1) {\textsuperscript{130}};
\end{tikzpicture}
\end{center}

\textbf{Scheme 6.2.} Use of a biotinylated bidentate phosphine in asymmetric hydrogenation of dehydroalanine

\section{6.2 Results and Discussion}

\subsection{6.2.1 Synthesis of Achiral Phosphines with Amine or Carboxylic Acid Groups}

Phosphines containing an amine functionality can be used to introduce a coordination site at the side chains of Asp and Glu. Arylphosphines have greater stability towards oxidation than alkylphosphines, and therefore were chosen as targets for synthesis. Compound \textsuperscript{131} would fit both requirements and its preparation has been
reported (62% overall yield, Scheme 6.3).\textsuperscript{237,238} However, this synthesis is not very practical for small scale preparation of 131.

\[
\begin{align*}
\text{O} & \quad \text{EtOPPh}_2 \\
\text{Fe} & \quad \text{O} \\
\text{NH}_2 & \quad \text{PPh}_2
\end{align*}
\]

(i) methylpolysiloxane

\[
\begin{align*}
\text{Ni(NO}_3)_2, \text{MeOH} & \\
\text{C}_6\text{H}_6/\text{H}_2\text{O 90 }^\circ\text{C} & \quad \text{PPh}_2
\end{align*}
\]

\textbf{Scheme 6.3.} Literature synthesis of (o-Aminophenyl)diphenylphosphine.

We envisioned a different synthetic route to construct this compound using directed ortho-metalation (DOM) methodology.\textsuperscript{239} Aniline functioned as starting material in our work, and was protected with a tert-butyloxy carbonyl (tBoc) group. This group has been shown to have great potential as a directing ortho-metallation group (DMG),\textsuperscript{240} and a study optimizing the reaction conditions has appeared recently.\textsuperscript{241} Metallation with tert-butyl lithium in diethyl ether at -30 °C, followed by quenching with chlorodiphenylphosphine indeed produced compound 132. However, during work up and purification by flash chromatography a significant amount of phosphine oxide 133 was produced, diminishing the yield of the desired product. A combined yield of 91% for phosphine and phosphine oxide indicated that the ortho-metalation reaction proceeded with high efficiency (equation 6.4). Therefore, we decided to deprotect 132 to the free amine in a one-pot process following the directed ortho-metalation and quenching with chlorodiphenylphosphine. Attempted deprotection using trifluoroacetic acid in dichloromethane was unsuccessful providing unreacted starting material, but treatment with 4 M HCl in dioxane produced 131 in an overall yield of 50% from aniline (equation 6.5). Although this compares
unfavorably with the literature procedure in terms of chemical yield, the synthesis is much more economical with the present cost of aniline being more than 15 times lower than dinitrobenzene. Furthermore, the present route provides fewer chemical steps and purification procedures than the literature synthesis.

\[
\begin{align*}
&\text{NHBOc} \\
&\text{(i) } ^{t}\text{BuLi, Et}_{2}\text{O} \\
&\text{(ii) } \text{ClIPPh}_{2} \\
&\quad \text{NHBoc} \quad \text{NHBoc} \\
&\quad \text{PPh}_{2} \quad \text{P(O)Ph}_{2} \\
\text{132} & \quad \text{41 \%} \\
\text{133} & \quad \text{50 \%} \\
\end{align*}
\]

\[
\begin{align*}
&\text{NHBOc} \\
&\text{(i) } ^{t}\text{BuLi, Et}_{2}\text{O} \\
&\text{(ii) } \text{ClIPPh}_{2} \\
&\text{(iii) } 4 \text{ M HCl in dioxane} \\
&\quad \text{NH}_{2} \\
&\quad \text{PPh}_{2} \\
\text{131} & \quad \text{50 \%} \\
\end{align*}
\]

A phosphine containing a carboxylic acid functionality can be used to introduce a coordination site at either the side chain of Lys or at the N-terminal amine group of a peptide. 2-Diphenylphosphino-benzoic acid (134) was easily obtained according to a literature procedure as shown in equation 6.6\(^{242}\).

\[
\begin{align*}
&\text{CO}_{2}\text{H} \quad \text{Cl} \\
&\quad \text{NaPPPh}_{2}, \text{NH}_{3} \\
&\quad \text{CO}_{2}\text{H} \\
&\quad \text{PPh}_{2} \\
\text{134} & \quad (6.6) \\
\end{align*}
\]
6.2.2 Synthesis of an Optical Pure $\alpha$-Amino Acid Containing a Phosphine Functionality

Syntheses of unnatural $\alpha$-amino acids have attracted considerable interest in the past twenty years because of their use in peptidomimetics.$^{243-245}$ Several elegant methodologies have been developed to produce these compounds in optically pure form.$^{246}$ Two different approaches can be distinguished in which the amino acid backbone acts as either a nucleophile or as an electrophile.

Figure 6.1 shows our target molecule and readily available phosphorus-based electrophiles and nucleophiles. Compound 137 can be prepared from the corresponding diphenylphosphine borane by treatment with lithiated bases$^{247}$ or by reductive phosphorus-carbon bond cleavage of one of the phenyl groups of triphenylphosphine borane with lithium metal under ultrasound irradiation.$^{248}$ Phosphine boranes are air-stable compounds and are inert towards many reaction conditions. However, the borane can be easily removed via exchange with excess diethylamine under very mild conditions.$^{247}$ and in this work phosphine boranes have proven to be very convenient protected phosphine analogs.

![Figure 6.1. Possible phosphorus reagents for the synthesis of diphenylphosphino alanine.](image-url)

**Figure 6.1.** Possible phosphorus reagents for the synthesis of diphenylphosphino alanine.
Jackson and coworkers prepared protected L-iodoalanine in four steps from L-serine and converted this compound into the organozinc reagent \(138\).\(^{249,250}\) Coupling of this highly functionalized organometallic reagent with acyl chlorides in the presence of a palladium catalyst gave enantiomerically pure protected 4-oxo-\(\alpha\)-amino acids in 39-90\% yield (equation 6.7). The mild reaction conditions used in these transformations encouraged us to attempt a synthesis of our target molecule using this amino acid based nucleophile and chlorodiphenylphosphine as electrophile. Unfortunately, the only products that could be isolated from reactions performed under various reaction conditions (25 °C, 38 °C and -30 °C in THF or benzene) were protected dehydroalanine (139) and alanine (140) from elimination and protonation of the intermediates (equation 6.8).

Transmetallation of the organozinc reagent into a mixed copper/zinc organometallic by treatment with the THF soluble copper salt CuCN.2LiCl as described by Knochel\(^{251}\) prior to reaction with chlorodiphenylphosphine did not alter the outcome of the reaction.

\[
\begin{align*}
\text{BocNH}_2\text{COOBn} & \xrightarrow{\text{Zn/Cu}} \text{BocNH}_2\text{COOBn} \xrightarrow{(\text{PPh}_3)_2\text{PdCl}_2} \text{BocNH}_2\text{COOBn} \\
(6.7) & \text{RCOCl} \\
\text{BocNH}_2\text{COOBn} & \xrightarrow{\text{Zn/Cu}} \text{BocNH}_2\text{COOBn} \\
\text{Ph}_2\text{PCl} & \text{Ph}_2\text{PCl} \\
& \text{BocNH}_2\text{COOBn} + \text{BocNH}_2\text{COOBn} \xrightarrow{\text{Zn/Cu}} \text{BocNH}_2\text{COOBn} + \text{BocNH}_2\text{COOBn} \xrightarrow{(\text{PPh}_3)_2\text{PdCl}_2} \text{BocNH}_2\text{COOBn} \\
(6.8) & \\
\end{align*}
\]

We then turned our attention to combinations of phosphorus based nucleophiles and amino acid derived electrophiles. Displacement of the tosyl group from 3-(tosyloxy)alanine
by either Ph₂PLi or Ph₂P(BH₃)Li occurred readily providing compound 141 in unoptimized yields of 40-68%. However, assessment of the optical purities of the products by ¹H NMR after removal of the 'Boc protecting group and derivatization of the free amine with camphanic chloride showed that the stereochemical integrity was completely lost. When progression of the reaction with Ph₂P(BH₃)Li was followed closely by TLC, rapid consumption of the starting material with production of a new compound was observed. This intermediate was isolated and identified as dehydroalanine 140. Product 141 is presumably produced by Michael addition of another molecule of diphenylphosphide anion, explaining the loss of stereochemical integrity (equation 6.9).

Vederas and coworkers have described the use of serine derived β-lactone 142 in syntheses of a variety of α-amino acids.²⁵² They found that attack of organocuprates and a number of other soft nucleophiles causes ring opening with alkyl-oxygen cleavage to generate optically pure N-protected β-substituted alanines 143 (equation 6.10). Reaction of 142 with Ph₂PLi or Ph₂P(BH₃)Li led to a number of products, however, including compounds from nucleophilic attack at the carbonyl. Therefore, this approach was not further pursued.
Another strategy to synthesize α-amino acids has been reported by Garner using the serine derived oxazolidine ester 144. The aldehyde obtained via reduction\(^{253}\) of 144 has been used for a variety of transformations, including cyclocondensation\(^{254}\) (e.g. Scheme 6.4), Wittig olefination,\(^{253}\) and nucleophilic attack with organometallic compounds.\(^{253}\) The products of these reactions could then be converted into α-amino acids. For instance, acidic removal of the oxazolidine protecting group from 145 provided amino alcohol derivative 146, which was oxidized to the corresponding α-amino acid without loss of stereochemistry (Scheme 6.4).\(^{254}\)

Scheme 6.4. Synthesis of optically pure threo-β-hydroxy-L-glutamic acid.
In the present work, the ester 144 was reduced to the corresponding alcohol with lithium borohydride in THF and the alcohol produced was activated with *p*-toluenesulfonyl chloride (Scheme 6.5). Displacement of the tosyl group with lithium diphenylphosphide provided the desired phosphine 148 in 54 % yield. This reaction can be performed very conveniently as a dropwise titration at 0 °C with the red color of diphenylphosphide anion as indicator. Before complete conversion of the starting material this color rapidly disappears, but after completion of the reaction the red/orange color persists. The phosphine 148 could be protected from oxidation by reaction with borane-THF complex at 0 °C in 94 % isolated yield without any concomitant reduction of the carbamate functionality. A one-pot sequence from tosylate 147 to phosphine borane 149 improved the overall yield to 92 % for two steps. The \( ^1H, ^{13}C \) and \( ^{31}P \) NMR spectra of all compounds containing the oxazolidine ring showed two sets of signals at 25 °C similar to earlier observations by Garner.\(^{255} \) At elevated temperatures these signals merged into one set of signals indicating a dynamic equilibrium between two conformers at ambient temperature.
Scheme 6.5. Synthesis of phosphine borane 151.

The oxazolidine functionality was removed by methanolysis at 25 °C in the presence of a catalytic amount of p-toluenesulfonic acid. As observed previously, the 'Boc group is also slowly removed under these conditions and yields of the product amino alcohol 150 diminished with prolonged reaction times. Therefore, conversion was stopped before completion of the reaction (12 h) and the product and starting materials were separated by flash chromatography. The yield of isolated 150 was 61% based on recovered starting material. At higher reaction temperatures (60 °C) the reaction proceeded much faster but the chemoselectivity was greatly diminished providing significant amounts of the secondary amine 152, and the borane protecting group was partly removed.
The optical purity of amino alcohol 150 was checked at this stage by formation of the camphanate ester and subsequent removal of the borane protecting group (equation 6.11). Comparison of the $^1$H NMR spectrum of this material (153) with the ester formed from the racemic alcohol obtained by lithium borohydride reduction of 141 revealed complete preservation of stereochemistry during the synthesis of 150 (Scheme 6.5) within the limits of NMR detection.

\[
\begin{array}{c}
\text{BocHN} \quad \text{BH}_3 \\
\text{H} \quad \text{PPh}_2 \\
\end{array}
\quad \quad
\begin{array}{c}
\text{Cl} \\
\text{O} \\
\end{array}
\quad \quad
\begin{array}{c}
\text{(i) DMAP} \\
\text{(ii) Et}_2\text{NH} \\
\text{BocHN} \\
\text{O} \\
\end{array}
\quad \quad
\begin{array}{c}
\text{O} \\
\text{PPh}_2 \\
\end{array}
\quad \quad
\text{153}
\]

(6.11)

Recently, $p$-nitrophenyl carbonates from 1,3 amino alcohols have been shown to be excellent monomeric building blocks for a new type of polycarbonate polymer with biological activities similar to the natural polyamides (i.e. peptides). Furthermore, these polymers could be easily synthesized on a resin using conventional peptide synthesis techniques. With the optically pure, $N$-protected 1,3-amino alcohol (150) in hand we decided to pursue the synthesis of the corresponding $p$-nitrophenyl carbonate for incorporation in such polycarbonate polymers. Thus, alcohol 150 was transformed into carbonate 151 by reaction with $p$-nitrophenyl chloroformate in the presence of 4-
dimethylamino pyridine (Scheme 6.5), and the product was used for solid phase polymer synthesis (\textit{vide infra}).

A recent literature report indicated Jones oxidation of primary alcohols to carboxylic acids can be accomplished without concomitant oxidation of a phosphine-borane (equation 6.12).\textsuperscript{248} Jones oxidation of alcohol 150 is not possible because of removal of the \textit{t}Boc group under the strongly acidic conditions of this reaction. Attempted oxidation with pyridinium dichromate (PDC) in DMF did not lead to clean production of the anticipated amino acid.\textsuperscript{257}

\[
\begin{array}{c}
\text{BH}_3 \\
\text{Ph}_2\text{P}
\end{array}
\rightleftharpoons
\text{CrO}_3, \text{H}_2\text{SO}_4
\rightleftharpoons
\begin{array}{c}
\text{BH}_3 \\
\text{Ph}_2\text{P}
\end{array}
\]

\textbf{6.2.3 Peptide Synthesis and Catalyst Preparation}

After successful preparation of a number of phosphine containing monomers for incorporation into peptides or related polymers, we studied the stability of these compounds towards the conditions for solid phase peptide synthesis.

Compound 154 was prepared by coupling leucine methyl ester with 2-(diphenylphosphino)benzoic acid via Castro's method (BOP/HOBt).\textsuperscript{258} This compound was not oxidized to the corresponding phosphine oxide when exposed to 50 % TFA in dichloromethane, the conditions for \textit{t}Boc removal in solid phase peptide synthesis.\textsuperscript{228} It was, however, oxidized to the analogous phosphine sulfide by the "cocktail" often used to cleave peptides from the solid phase, \textit{i.e.} aqueous TFA, 1,2-ethanediol, and thioanisole.
Subsequently, the peptide H$_2$N-Leu-MBHA was prepared on MBHA amide resin$^{228,259}$ using BOP/HOBt.$^{258}$ This was then coupled with 2-(diphenylphosphino)-benzoic acid (134) using the same conditions furnishing 155. Completion of the coupling reactions was assured by quantitative Kaiser test with ninhydrin.$^{260}$
To determine if oxidation of the phosphine had occurred during the synthesis of 155, a sample of the resin was taken as a slurry in CDCl₃ and a ³¹P NMR spectrum was recorded. This is a two phase system, but in CDCl₃ the resin swells enough to allow tumbling of the peptide on the surface of the bead at a sufficient rate for NMR analysis; resonances with a bandwidth of approximately 35 Hz at half peak height are observed under these conditions. A signal at δ = -11.5 ppm was predominant, and the only other signal in the spectrum was a very small peak at +34 ppm (Figure 6.2a). These two resonances are typical of phosphines (-5 to -15 ppm) and phosphine oxides (30 to 40 ppm), respectively,²⁶¹,²⁶² hence the phosphine was incorporated without significant oxidation.

Finally, it was important to show that solid supported peptides could be complexed with transition metals, and that such coordination events could be monitored spectroscopically. Consequently, the beads in the above experiment were recovered and treated with [Rh(COD)Cl]₂ in CDCl₃. They turned from colorless to yellow, and the coloration persisted after several washings with THF. A ³¹P NMR spectrum of the resin was then recorded under the conditions described above. The signal at -11.5 had disappeared and was replaced by another a doublet at 27.5 ppm, typical of an arylphosphine coordinated to rhodium (¹J_Rh,P = 146 Hz). No change occurred to the minor signal at 34 ppm (Figure 6.2b). The beads were then filtered away and the ³¹P NMR of the supernatant was recorded; no signals were detected. Thus, resin bound phosphines can be complexed to rhodium, and the complexation can be analyzed spectroscopically.
Figure 6.2. $^{31}\text{P}$ NMR spectra from (a) resin 155 in CDCl$_3$; and, (b) resin 155 in the presence of 1.1 equiv. of [Rh(COD)Cl]$_2$ in CDCl$_3$.
Immobilized phosphine ligand 157 (Scheme 6.6) was prepared via standard techniques for Fmoc solid phase peptide synthesis. Thus, two Fmoc-protected glycine units were coupled to BHA (benzhydrylamine) resin, followed by incorporation of orthogonally protected Fmoc-Lys('Boc) producing the supported trimer 156 (Scheme 6.6). After removal of the N-terminal Fmoc group with piperidine, the first phosphine moiety was introduced by coupling the deprotected amine with 2-(diphenylphosphino)benzoic acid (134). Subsequently, the 'Boc-group on the side chain of the incorporated lysine was removed by treatment with 50 % TFA in dichloromethane, and the free amine generated was also coupled with 134 providing peptide analog 157 (Scheme 6.6).

We then attempted catalyzed hydrogenation of α-methyl cinnamic acid in the presence of 5 mol % 157 and 2 mol % of [Rh(COD)Cl]₂. Unfortunately, no reaction was observed (equation 6.13). There could be several reasons for this low reactivity. First, it is possible that BHA resin collapses in THF rendering the catalytic sites inaccessible. Second, harsher reaction conditions might be necessary for catalytic turnover, i.e. elevated reaction temperatures or higher hydrogen pressures.

\[
\begin{align*}
\text{Ph} & \quad \text{Me} \\
\text{COOH} & \\
1 \text{ atm} \text{ H}_2, \text{ THF} & \\
25 \degree \text{C} &
\end{align*}
\]

[Rh(COD)Cl]₂

157

no reaction

(6.13)
We tried to address the first possibility by using TentaGel S resin from RAPP Polymere as a solid support. This resin has glycol linkers capped with amine groups to project the substrate into solution, and it has shown good solvation characteristics in a number of commonly used organic solvents including THF. Moreover, the excellent kinetic properties of TentaGel resins accelerate coupling rates in peptide/peptidomimetic syntheses.

Tetrapeptide 158 was prepared as shown in Scheme 6.7. Two molecules of phenylalanine were coupled to Tentagel resin by standard tBoc-chemistry. The N-terminal tBoc protecting group was then removed with TFA, and after neutralization with diisopropylethylamine (DIEA) the free amino terminus was allowed to react for 4 h with 3 equiv. of the activated p-nitrophenylcarbonate 151 in N-methylpyrrolidine in the presence of 2 equiv. of HOBT. Ninhydrin test at this stage indicated complete coupling of the phosphoalanine derivative to the resin bound peptide. Subsequent treatment with 50 % TFA in CH₂Cl₂ resulted in a positive Kaiser test, lending further support for successful incorporation of 151. Repetition of the coupling procedure resulted in the desired N-protected tetramer.
Scheme 6.7. Solid phase synthesis of supported biopolymer 158.

Resin-bound ligand precursor 158 was activated by stirring with diethylamine at 40 °C for 1 h to displace the borane group from the phosphine, followed by evaporation of the excess amine under reduced pressure and repeated washing of the resin with THF to remove the formed diethylamine-borane complex. After loading the resin with [Rh(COD)Cl]₂, washing with THF and introduction of α-methylcinnamic acid, the reaction vessel was charged with hydrogen (1 atm). However, the anticipated hydrogenation of the substrate did not proceed.

6.3 Conclusions and Outlook

Synthesis of an optically pure phosphine which can be conveniently incorporated into resin-bound polymers was developed. Furthermore, preliminary results described in this chapter indicate that complexation of rhodium to a supported peptide derivative containing a metal coordination site is possible. At the present time, catalysis has not yet
been achieved using these types of immobilized ligands, but several improvements are being pursued in the Burgess laboratories.

First, a number of literature reports have indicated the difficulties associated with asymmetric metal catalysis using supported metal complexes,\textsuperscript{263,264} and heterogeneous asymmetric catalysis can only be achieved under optimum reaction conditions. An extensive investigation of suitable reaction conditions for transition metal catalysis with the supported ligands described above is therefore necessary. However, this would involve use of the relatively precious optically pure monomers, which can only be obtained after a multi-step synthesis. Equation 6.9 showed that \textit{racemic} amino acid derived phosphines are easily prepared from serine. After incorporation of these racemic derivatives into polypeptides they could be used to identify proper reaction types (\textit{e.g.} hydrogenation, hydrosilation, allylations) and reaction conditions (\textit{e.g.} temperature, pressure).

Second, asymmetric metal catalyzed reactions using surface-bound ligands pose several restrictions that are not encountered in solution phase reactions. Therefore, release of the peptide ligand into solution followed by screening for homogeneous catalytic activities might be a more successful approach. Exceptionally clean cleavage of polymers from resins has been achieved using photolabile linkers.\textsuperscript{265,266} In this strategy, the combinatorial approach can still be used for rapid generation of a large number of asymmetric ligands, but the catalysis can be performed in solution which provides better access of the substrates to the metal complexes.

This chapter has focused on the use of phosphine moieties to coordinate to transition metals, but several other functionalities could be used to accomplish this. For instance, the amino acid derivative \textbf{159} could be prepared from glutamic acid and an optically pure amino alcohol. After incorporation of this compound into peptides, the oxazolidine group would be able to bind transition metals in the similar way as ligand \textbf{127} (see section 6.1).
Finally, the only catalytic reactions tested so far have been rhodium catalyzed hydrogenations. A number of other transformations could be attempted using polymers containing phosphine functionalities like 157 and 158, including ruthenium catalyzed hydrogenations, rhodium catalyzed hydrosilations and palladium catalyzed allylations.
Appendix 1. General Experimental

High field NMR-spectra were recorded on a Bruker AF300 (1H at 300 MHz, 13C at 75.4 MHz), a Bruker AC250 (1H at 250 MHz, 13C at 62.9 MHz) instrument in CDCl3 or a Varian XL200 (1H at 200 MHz, 13C at 50 MHz). 1H chemical shifts are reported in δ ppm relative to CHCl3 (7.25 ppm) as an internal standard, and 13C chemical shifts are reported in δ ppm relative to CDCl3 (77.10 ppm) as an internal reference. 2H NMR spectra were recorded on a Bruker AMX-500 at 76.7 MHz with CDCl3 as an internal reference. 11B and 31P chemical shifts are reported in ppm relative to the external standards BF3 OEt2, and 85% H3PO4 respectively, and 19F chemical shifts are reported in ppm relative to C6F6 (-163.0 ppm). Low resolution (EI) and high resolution (EI) mass spectra were determined on a Finnigan 3300 mass spectrometer and a CAC 21/110 C high resolution mass spectrometer respectively. Melting points were determined on a Mel-Temp or an Electrothermal digital capillary melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Perkin-Elmer 1600 series FTIR or on a Nicolet 205 FTIR. HPLC was performed on a Rainin Rabbit HP using a Chiralcel OB column from Daicel Chemical Industries. GC was performed on a Shimadzu GC9A interfaced with an Apple Macintosh Plus using a 50 m (007 methyl phenyl (5%) silicone, 0.25 mm I.D. 0.25 μ film thickness) fused silica capillary column (Quadrex 007-2-50-0.25F). Thin layer chromatography was performed on silica gel 60 F254 plates from Whatman. Flash chromatography was performed on SP Silica Gel 60 (230-600 mesh ASTM).
Appendix 2. Experimental with Chapter 2.

Tetrahydrofuran and toluene was distilled immediately before use from sodium benzophenone ketyl. Borane, THF complex and 9-BBN solutions were purchased from Aldrich Chemical Co. and used as received. Catecholborane was purchased from Aldrich and distilled under reduced pressure before use. Organic solutions were dried over anhydrous magnesium sulfate. Trideuteroborane (BD₃) was purchased from Cambridge Isotope Laboratories and deuterocatecholborane was prepared according to literature procedures⁴²,⁴³ and distilled under reduced pressure before use.

5-Hydroxy-2-methyleneadamantane (37).

\[ \text{OH} \]

Procedure:
To a stirred suspension of methyltriphenylphosphine iodide (17.8 g, 44 mmol) in THF was added 22 mL of a 2.01 M solution of n-BuLi in hexane at -78 °C. After 10 min 5-hydroxy-2-adamantanone⁴⁶ (3.0 g, 18 mmol) in 30 mL of THF was added to the clear red solution. The reaction mixture was allowed to warm to 20 °C and was stirred at this temperature for another 3 h. The solution was then diluted with diethyl ether (100 mL) and washed with water (2x100 mL) and saturated ammonium chloride solution (75 mL). The organic layer was dried and a crude, yellow oil was obtained by removing the solvent under reduced pressure. Purification by flash chromatography (20 % EtOAc in hexane) gave 2.24 g (75 %) of a colorless crystalline solid.

\[
\begin{align*}
\text{m.p.} & \quad 112-113 \degree C \\
\text{R}_f & \quad 0.34 \text{ (EtOAc/hexane 20:80)}
\end{align*}
\]
$^1$H-NMR (CDCl$_3$):

300 MHz $\delta$ (ppm) = 1.65-1.80 (m, 10H), 2.20 (m, 1H), 2.64 (m, 2H), 4.55 (s, 2H)

$^{13}$C-NMR (CDCl$_3$):

75.4 MHz $\delta$ (ppm) = 30.60 (C7), 38.20 (C8+C10), 40.31 (C1+C3), 44.96 (C6),
46.42 (C4+C9), 68.05 (C5), 102.65 (C11), 155.38 (C2)

IR (KBr, CHBr$_3$):

$\nu$ (cm$^{-1}$) = 882 (s), 923 (s), 968 (s), 1065 (s), 1094 (s), 1109 (s), 1451 (m),
1657 (m), 2852 (s), 2915 (s), 3200-3500 (s br)

MS (EI, 70 eV):

m/z (%) = 164 (M$^+$ 12), 107 (64), 95 (80), 91 (69), 29 (73), 27 (100)

HRMS (EI):

calcd. for C$_{11}$H$_{16}$O 164.1201

found 164.1201
5-Hydroxy-2-methylene adamantane (37)

$^1$H NMR (CDCl$_3$)

$^{13}$C NMR (CDCl$_3$)
5-Hydroxy-2-methylene adamantane (37)

IR (CHBr₃)

MS (EI)
5-Fluoro-2-methyleneadamantane (38)

![Chemical Structure](image)


**Procedure:**
The procedure described here is considerably shorter than synthetic routes reported in the literature. A 100 mL flask was charged with 5-hydroxy-2-methyleneadamantane (37) (1.48 g, 9.0 mmol) and flushed with N₂, dichloromethane (30 mL) was added and the solution was cooled to -78 °C. Diethylaminosulfur trifluoride (1.62 g, 10.0 mmol) was added dropwise and the reaction mixture was allowed to warm to 20 °C. After stirring for 2 h, the reaction was quenched with water (1.0 mL) and diluted with diethyl ether (100 mL). The reaction mixture was washed with 1 M sodium bicarbonate (2 x 30 mL) and water (2 x 30 mL) and the organic layer was dried. Evaporation of the solvent under reduced pressure and purification by flash chromatography (hexane) gave 1.0 g (66 %) of the pure product.

\[
R_f \quad 0.52 \text{ (hexane)}
\]

\[
m.p. \quad 123 ^\circ C \text{ (lit. 125-125 } ^\circ C)
\]

\[
^1\text{H-NMR (CDCl}_3\text{):}
\]

250 MHz \[ \delta \text{ (ppm)} = 1.71 \text{ (m, 4H), 1.93 \text{ (m, 6H), 2.29 \text{ (m, 1H), 2.71 \text{ (m, 2H),}}}
\]

4.57 (s, 2H)
\(^{13}\text{C}-\text{NMR} (\text{CDCl}_3):\)

62.9 MHz \(\delta \ \text{(ppm)} = \)
31.17 (d, \(^3\text{J}_{\text{CF}} = 9.6 \text{ Hz}, \text{C7}), 37.98 (\text{C8+C10}), 40.55 \text{ (d, }^3\text{J}_{\text{CF}} = 10.2 \text{ Hz, C1+C3}), 42.35 \text{ (d, }^2\text{J}_{\text{CF}} = 17.2 \text{ Hz, C6}), 43.57 \text{ (d, }^2\text{J}_{\text{CF}} = 17.5 \text{ Hz, C4+C9}), 91.34 \text{ (d, }^1\text{J}_{\text{CF}} = 184.6 \text{ Hz, C5}), 103.38 \text{ (C11), 153.80 (C2)}

\(^{19}\text{F}-\text{NMR} (\text{CDCl}_3):\)

235 MHz \(\delta \ \text{(ppm)} = -134.06 \text{ (m)}\)

**HRMS (EI):**

calcd. for C\(_{11}\)H\(_{15}\)F
166.1158

found
166.1158

\(^{1}\text{H} \text{NMR} (\text{CDCl}_3)\)
5-Fluoro-2-methyleneadamantane (38)

$^{13}$C NMR (CDCl$_3$)

$^{19}$F NMR (CDCl$_3$)
5-Phenyl-2-methyleneadamantane (40)

Procedure:
A 250 mL round bottom flask was charged with 1.95 g of zinc powder (29 mmol) and flushed with Ar, THF (10 mL) was added followed by 4.4 g (16.5 mmol) of diiodomethane in dichloromethane (10 mL). The grey slurry was cooled to 0 °C and, after stirring for 30 min, 0.36 mL (1.5 mmol) of neat titanium tetrachloride was added. After 30 min 0.50 g (2.2 mmol) of 5-phenyl-2-adamantan-2-one\textsuperscript{96} in THF (5 mL) was added, the reaction mixture was allowed to warm to 20 °C, and was stirred overnight. The solution was then diluted with hexane (150 mL), filtered through Celite and washed with 1 M sodium bicarbonate solution (3x40 mL) and water (2 x 50 mL). The organic layer was dried and the crude product was obtained as a dark brown oil. The crude material was dissolved in diethyl ether (50 mL) and filtered over alumina (activity I). After removing the solvent under reduced pressure, 0.36 g (73 %) of pure title compound was obtained as a colorless oil which solidified upon cooling.

\textbf{m.p.} \hspace{1cm} 36-37 °C
\textbf{R}_f \hspace{1cm} 0.6 \ (hexane)

\textbf{\textsuperscript{1}H-NMR (CDCl}_3):\n
250 MHz \ \delta \ (ppm) = 1.91 (m, 4H), 2.06 (m, 6H), 2.20 (m, 1H), 2.70 (m, 2H), 4.64 (s, 2H), 7.37 (m, 5H)

\textbf{\textsuperscript{13}C-NMR (CDCl}_3):\n
$62.9 \text{ MHz}$  \hspace{1em} $\delta$ (ppm) = 29.0 (C7), 36.5 (C5), 38.8 (C8+C10), 39.4 (C1+C3),
42.7 (C6), 45.0 (C4+C9), 101.5 (C11), 124.9 (CH), 125.7
(CH), 128.2 (CH), 150.2 (C), 157.0 (C2)

**IR (KBr, CHBr$_3$):**

$\nu$ (cm$^{-1}$)

758 (s), 888 (s), 1019 (m), 1440 (s), 1495 (s), 1600 (w), 1651
(s), 2850 (s), 2915 (s), 2977 (s), 3065 (s)

**MS (EI, 70 eV):**

m/z (%) = 224 (M$^+$, 100)

**HRMS (EI):**

calcd. for C$_{17}$H$_{20}$ (M$^+$) 224.1565

found = 224.1565

$^1$H NMR (CDCl$_3$)
5-Phenyl-2-methyleneadamantane (40)

$^{13}$C NMR (CDCl$_3$)

IR (CHBr$_3$)
**5-Phenyl-2-methyleneadamantane (40)**

![Graph showing MS (EI)]

**5-Trimethylsilyl-2-methyleneadamantane (43)**

![Structural formula of 5-Trimethylsilyl-2-methyleneadamantane]

**Procedure:**

A 100 mL flask was charged with 1.8 g (4.5 mmol) of methyltriphenylphosphine iodide and flushed with N₂. THF (50 mL) was added and the mixture was cooled to -78 °C. After 5 min n-BuLi (2.0 mL of 2.01 M in hexanes) was added and the white suspension turned clear red. 5-Trimethylsilyl adamant-2-one (0.5 g, 2.2 mmol) in 10 mL of THF was added and the solution was allowed to warm to 20 °C. After stirring for 2 h, the reaction mixture was diluted with diethyl ether (100 mL) and washed with water (2 x 40 mL). The organic layer was dried and 200 mg of crude product was obtained after removing the solvent under reduced pressure. Purification by flash chromatography (hexane) yielded 100 mg (20 %) of the product as a yellow oil which was 85 - 90 % pure.
by capillary GC analysis. The contaminant was the pentamethyldisilyl compound shown in Scheme 2.1.

\[ R_f = 0.95 \text{ (hexane)} \]

\[ ^1\text{H-NMR (CDC}_3\text{)}: \]

200 MHz \[ \delta \text{ (ppm)} = -0.11 \text{ (s, 9H), 1.69-1.89 (m, 11H), 2.47 (m, 2H), 4.53 (s, 2H)} \]

\[ ^{13}\text{C-NMR (CDC}_3\text{)}: \]

75.4 MHz \[ \delta \text{ (ppm)} = -5.36 \text{ (SiMe}_3\text{), 21.55 (C5), 27.78 (C7), 36.82 (C4+C9), 38.82 (C1+C3), 39.59 (C8+C10), 40.93 (C6), 102.51 (C11), 158.73 (C2)} \]

\[ \text{IR (KBr, CHBr}_3\text{):} \]

\[ \nu \text{ (cm}^{-1}) = 687, 724, 744, 833, 853, 866, 947, 960, 1246, 1257, 1446, 1651, 2847, 2898 \]

\[ \text{MS (EI, 70 eV):} \]

\[ m/z \text{ (%)} = 205 \text{ (M-CH}_3\text{, 50), 73 (100)} \]

\[ \text{HRMS (EI):} \]

calcd. 220.1647 for C\textsubscript{14}H\textsubscript{24}Si (M\textsuperscript{+})

found 220.1646

\[ ^1\text{H NMR (CDC}_3\text{)} \]
5-Trimethylsilyl-2-methyleneadamantane (43)

$^{13}$C NMR (CDCl$_3$)

IR (CHBr$_3$)
5-Trimethylsilyl-2-methyleneadamantane (43)

General Procedure for Catalyzed Hydroborations of Alkenes

A Schlenk tube charged with a catalytic amount of 2.4 mg (0.005 mmol, 1%) of [Rh(COD)Cl]₂ and 5.2 mg (0.02, 4 %) of triphenylphosphine was three times evacuated/flushed with N₂. Toluene or THF (2 mL) was added, followed by 0.5 mmol of alkene in the same solvent (2 mL). The bright yellow solution was cooled to -78 °C and 120 mg (1 mmol, 2 eq) of catecholborane in THF or toluene (1 mL) was added. The reaction mixture was allowed to warm to 20 °C and was stirred at this temperature for 12 h. Ethanol (1 mL) was added at 0 °C followed by 1.7 mL of 3 M NaOH solution and 1 mL of 30 % H₂O₂. The mixture was stirred for 6 h at 20 °C and was then diluted with 10 mL of 1 M NaOH solution. Extraction with diethyl ether (3x75 mL), washing of the combined organic fractions with 1 M NaOH solution (50 mL), water (50 mL) and saturated NaCl solution (50 mL) and evaporating the solvent under reduced pressure after drying over MgSO₄ provided the crude product.
**General Procedure for Uncatalyzed Hydroborations**  To a solution of 0.5 mmol of substrate in THF or toluene (10 mL) was added 0.5 mL of 1.0 M BH₃·THF complex at 0°C. The reaction mixture was allowed to warm to 20°C and was stirred at this temperature for 6 h. Oxidation and work-up was carried out as described above for catalyzed hydroboration.
5-Fluoro-2-hydroxymethyl adamantane (44, X=F)

Procedure:
Yield after purification by flash chromatography (20% EtOAc in hexane): 68%. A small portion (5 mg) of the crude mixture was reacted with trimethylsilylchloride (0.05 mL) and hexamethyldisilazane (0.15 mL) in pyridine and the white suspension was analyzed by GC to determine the ratios of isomeric trimethylsilyl ethers. Ratio of syn:anti trimethylsilyl ether derivatives: 54:46

Rf 0.25 (EtOAc/hexanes 20:80)

NMR data for mixture of isomers throughout.

1H-NMR (CDCl3):
250 MHz δ (ppm) = 1.51-2.17 (m, 14H), 3.66 (d, 3JH-H = 7.5 Hz, 2H, syn-isomer), 3.70 (d, 3JH-H = 7.4 Hz, 2H, anti-isomer)

13C-NMR (CDCl3):
75.4 MHz δ (ppm) = 30.31 (C8 + C10, anti), 31.09 (d, 3JCF = 8.8 Hz, C7)/31.57 (d, 3JCF = 10.5 Hz, C7), 32.46 (d, 3JCF = 10.1, C1+C3)/32.61 (d, 3JCF = 9.4 Hz, C1+C3), 37.04 (C8+C10, syn), 37.44 (d, 2JCF = 17.5 Hz, C4+C9, syn), 43.14 (d, 2JCF = 20.3 Hz, C6), 43.53 (d, 2JCF = 17.7 Hz, C4+C9, anti), 45.48/45.70 (C2), 64.11/64.37 (C11), 92.59 (d, 1JCF = 183 Hz, C5)

19F-NMR (CDCl3):
235 MHz δ (ppm) = -132.42 (m, 1, syn), -129.77 (m, 1, anti)
**IR (KBr, CHBr₃):**

\[ v \text{ (cm}^{-1}\text{)} \]

904 (m), 939 (m), 952 (m), 999 (m), 1039 (s), 1057 (s), 1104 (s), 1354 (m), 1455 (m), 2861 (s), 2925 (s), 3379 (s br), 3597 (m br)

**MS (EI, 70 eV):**

\[ m/z \text{ (\%)} = \]

184 (M⁺, 7), 166 (100), 153 (47), 91 (27)

**HRMS (EI):**

calcd. for C₁₁H₁₇OF 184.1263

found 184.1263
5-Fluoro-2-hydroxymethyl adamantane (44, X=F)

$^{13}$C NMR (CDCl$_3$)

MS (EI)
$^{19}$F NMR (CDCl$_3$)

IR (CHBr$_3$)
5-Phenyl-2-hydroxymethyl-adamantane (44, Z=Ph)

![Chemical structure](image)

**Procedure:**

The general procedure described for the catalyzed and uncatalyzed hydroboration of 5-fluoro-2-methylen adamantane was followed. Yield for catalyzed reaction carried out in THF, after purification by flash chromatography (20 % EtOAc in hexane) 88 %. *Syn:anti* ratios of alcohols 57:43.

**m.p.**
59-60 °C

**R<sub>f</sub>**
0.35 (EtOAc/hexanes 15:85)

**<sup>1</sup>H-NMR (CDCl<sub>3</sub>):**

250 MHz

δ (ppm)= 1.58-2.08 (m, 14H), 3.74 (d, 3<sup>J</sup>HH = 7.3 Hz, 2H, anti), 3.80 (d, 3<sup>J</sup>HH = 7.3 Hz, 2H, syn)

**<sup>13</sup>C-NMR (CDCl<sub>3</sub>):**

75.4 MHz

δ (ppm)= 29.06/28.60 (C7), 29.80/29.96 (C1+C3), 31.08 (C8+C10, anti), 36.03/36.47 (C5), 37.32 (C4+C9, syn), 37.98 (C8+C10, syn), 43.69/43.92 (C6), 44.32 (C4+C9, anti), 45.87/46.09 (C2), 64.65/64.70 (CH<sub>2</sub>OH), 124.72/124.86 (CH), 125.65 (CH), 129.15 (CH), 150.65/150.83 (C)

**IR (KBr, CHBr<sub>3</sub>):**

ν (cm<sup>-1</sup>)

755 (s), 1007 (s), 1022 (m), 1068 (m), 1445 (m), 1451 (m), 1466 (m), 1600 (w), 2852 (s), 2919 (s), 3025 (s), 3300-3550 (s br)

**MS (EI, 70 eV):**
m/z (%) = 242 (M⁺, 87), 211 (31), 155 (100), 91 (67)

HRMS (EI):
calcd. for C₁₇H₂₂O 242.1671
found 242.1672
5-Phenyl-2-hydroxymethyl-adamantane (44, Z=Ph)

$^{13}$C NMR (CDCl$_3$)

IR (CHBr$_3$)
5-Trimethylsilyl-2-hydroxymethyl adamantane (44, Z=SiMe₃)

\[
\begin{align*}
\text{HO} & \quad \text{SiMe₃} \\
\end{align*}
\]

**Procedure:**


\( R_f \) 0.40 (EtOAc/hexanes 15:85)

NMR data, mixture of isomers throughout:

\(^1\text{H-NMR (CDCl₃):}\)

300 MHz  \( \delta \) (ppm)= -0.14 (s, 9H), 1.38-1.86 (m, 14H), 3.70 (m, 2H)

\(^{13}\text{C-NMR (CDCl₃):}\)

75.4 MHz  \( \delta \) (ppm)= 20.73/21.31 (C5), 27.44/27.84 (C7), 28.65/28.77 (C1+C3), 31.25, 31.94, 37.64, 38.56, 38.91, 46.88/47.11 (C2), 64.95/65.06 (C11)

**IR (KBr, CHBr₃):**

\( \nu \) (cm\(^{-1}\)) 651, 662, 834, 865, 1142, 1244, 2849, 2901, 3020, 3400 (br)

**MS (EI, 70 eV):**

\( m/z \) (%)= 238 (M⁺, 100),

**HRMS (EI):**

calcd. for C\(_{14}\)H\(_{26}\)OSi 238.1753

found 238.1753
5-Trimethylsilyl-2-hydroxymethyl adamantane (44, Z=SiMe₃)

¹H NMR (CDCl₃)

¹³C NMR (CDCl₃)
5-Trimethylsilyl-2-hydroxymethyl adamantane (44, Z=SiMe₃)

IR (CHBr₃)

MS (EI)
5-Pentamethyldisilyl-2-hydroxymethyl adamantane (44, $Z$=SiMe$_2$SiMe$_3$)

![Chemical Structure](image)

**Procedure:**

GC analysis of the silylated crude mixtures of the catalyzed and uncatalyzed hydroborations of 5-trimethylsilyl-2-methylene adamantane showed the presence of two contaminants, which could be isolated by careful flash chromatography (5-10% EtOAc in hexane). Spectral analysis and mass spectroscopy data showed that the contaminants consisted of the *syn* and *anti* isomers of 2-hydroxymethyl-5-pentamethyldisilyl adamantane (ratios from GC analysis: catalyzed 20:80, uncatalyzed 54:46). It was determined that these products originated from the corresponding alkene (44, $X$=SiMe$_2$SiMe$_3$), which was present as an impurity in the starting material for the hydroborations.

Data for isolated material (one isomer):

**$^1$H-NMR (CDCl$_3$):**

300 MHz $\delta$ (ppm) = -0.08 (s, 6H), 0.04 (s, 9H), 1.42-1.85 (m, 14 H), 3.67-3.72 (m, 2H)

**$^{13}$C-NMR (CDCl$_3$):**

75.4 MHz $\delta$ (ppm) = -6.47 (SiMe$_2$), -0.72 (SiMe$_3$), 22.39, 28.04, 28.88, 32.73, 38.89, 39.08, 46.96, 65.06

**MS (EI, 70 eV):**

m/z (%) = 296 (M$^+$, 26), 223 (M$^+$-SiMe$_3$, 77)
HRMS (EI):
calcd. 296.1992
found 296.1991

$^1$H NMR (CDCl$_3$)

$^{13}$C NMR (CDCl$_3$)
Catalyzed Hydroboration of 5-Fluoro-2-methylene Adamantane with Deuteriocatecholborane. Procedure as described above. Rf 0.25 (20 % EtOAc in hexane); $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 1.64-2.19 (m, 13H), 3.64 (s, 2H, syn), 3.68 (s, 2H, anti); $^{13}$C NMR (62.90 MHz, CDCl$_3$) $\delta$ 45.60 (m, CD); $^2$H NMR (76.7 MHz, CHCl$_3$) $\delta$ 1.72 (syn), 1.78 (anti); HRMS calcd for C$_{11}$H$_{16}$OFD (M$^+$): 185.1326. Found 185.1326.

Catalyzed Hydroboration of 3,3-Dimethyl-1-butene (45) A Schlenk tube charged with 2.5 mg (0.005 mmol, 1 %) of [Rh(COD)Cl]$_2$ and 5.2 mg (0.02 mmol, 2 %) of triphenylphosphine was evacuated/flushed three times with Ar, THF (2 mL) was added followed by 168 mg (2 mmol) of 3,3-dimethyl-1-butene. The solution was cooled to 0 $^\circ$C, 120 mg (1 mmol, 0.5 eq.) of catecholborane was added in THF (1 mL) and the solution was allowed to warm to 20 $^\circ$C. After stirring for 12 h, 282 mg (3 mmol) of norbornene was added with another 2.5 mg of [Rh(COD)Cl]$_2$ and 5.2 mg of triphenylphosphine in THF (2 mL). The resulting solution was stirred at 20 $^\circ$C for 24 h. Oxidation of the alkylboron species present in the reaction mixture and subsequent work-up was carried out as described under general procedure for catalyzed hydroboration. GC analysis of the crude material showed the absence of hydroboration product of norbornene.
Appendix 3. Experimental with Chapter 3

General Procedures

Wilkinson's catalyst (RhCl(PPh3)_3) and its oxygen adduct RhClO_2(PPh3)_3 were prepared according to literature procedures.\textsuperscript{113,121} Catecholborane-\textit{d}_1 was prepared in an analogous fashion to the published synthesis of catecholborane from trideuteroborane and catechol.\textsuperscript{44,45} Phenylethene, 1-decene and phenylacetylene were purchased from Aldrich Chemical Company.

General Procedure for Catalyzed Hydroborations with Catecholborane-\textit{d}_1

A Schlenk tube charged with 9.2 mg of Rh(PPh3)_3Cl (0.01 mmol, 0.002 eq) was evacuated/flushed three times with Ar, 2 mL of THF was added followed by 1.0 g (5 mmol) of alkene in 10 mL of THF. After stirring the bright yellow solution for 5 min, 60 mg (0.5 mmol, 0.1 eq) of C_6H_4O_2BD in 2 mL of THF was added. The reaction mixture was stirred at 20 °C for 12 h. Ethanol (1 mL) was added, followed by 1.7 mL of a 3 M NaOH solution and 1 mL of 30 % H_2O_2 at 0 °C. The mixture was stirred for 6 h at 20 °C, diluted with 100 mL of Et_2O, and washed with 1 M NaOH solution (50 mL). The aqueous layer was extracted with Et_2O (2 x 50 mL), and the combined organic fractions were washed with 1 M NaOH (50 mL), water (50 mL), and saturated NaCl solution (50 mL). The organic layer was dried, and the crude products were obtained by evaporating the solvent under reduced pressure. \textsuperscript{2}H NMR analysis of the crude products was performed prior to separation of the individual products by flash chromatography. The purified products were then characterized by \textsuperscript{1}H and \textsuperscript{13}C NMR.
$^2\text{H}$-NMR spectrum of catalyzed hydroboration of phenylethene 62 with commercial Wilkinson's catalyst

$^2\text{H}$-NMR spectrum of catalyzed hydroboration of phenylethene 62 with freshly prepared Wilkinson's catalyst
2-Deuterio-2-Methyl-3-((tert-Butyldimethylsilyl)-oxy)-butan-1-ol (66)

```
HO
OSi'BuMe₂

Me
D
Me
```


Procedure:
The syn isomer was obtained as the major product of the rhodium catalyzed hydroboration. Analytical data for the anti isomer were obtained from hydroboration of ?? with BD₃, which provides the anti diastereomer as the major product.

\[
R_f = 0.15 \text{ (EtOAc/hexanes 5/95)}
\]

Syn isomer

\[ ^1H-NMR \ (CDCl₃): \]

250 MHz \ \( \delta \ (ppm) = 0.06 \ (s, 3H), 0.07 \ (s, 3H), 0.75 \ (s, 3H), 0.88 \ (s, 9H), 1.11 \ (d, \ \ ^3J_{HH} = 6.4 \ Hz, 3H), 3.09 \ (br \ s, 1H), 3.44-3.55 \ (m, 1H), 3.66-3.70 \ (m, 1H), 3.96 \ (q, \ J=6.4 \ Hz, 1H) \]

\[ ^13C-NMR \ (CDCl₃): \]

75.4 MHz \ \( \delta \ (ppm) = -5.0 \ (CH₃), -4.5 \ (CH₃), 12.3 \ (CH₃), 17.9 \ (C), 18.3 \ (CH₃), 25.8 \ (C(CH₃)₃), 40.9 \ (t, \ ^1J_{CD}=18 \ Hz, \ CD), 65.6 \ (CH₂), 72.1 \ (CH) \]

\[ ^2H-NMR \ (CDCl₃): \]

76.7 MHz \ \( \delta \ (ppm) = 1.92 \ (14 \ %) \)
Anti-isomer

$^1$H-NMR (CDCl$_3$):

250 MHz $\delta$ (ppm) = 0.06 (s, 3H), 0.07 (s, 3H), 0.87 (s, 9H), 0.94 (s, 3H), 1.19 (d, $^3$J$_{HH}$ = 6.2 Hz, 3H), 2.91 (br s, 1H), 3.46-3.54 (m, 1H), 3.68-3.80 (m, 1H), 3.97 (q, $^3$J$_{HH}$ = 6.3 Hz, 1H)

$^{13}$C-NMR (CDCl$_3$):

75.4 MHz $\delta$ (ppm) = -5.0 (CH$_3$), -4.6 (CH$_3$), 17.9 (C), 22.1 (CH$_3$), 25.8 (CH$_3$), 41.7 (t, $^1$J$_{CD}$=19 Hz, CD, 65.8, CH$_2$), 73.9 (CH)

$^2$H-NMR (CDCl$_3$):

76.7 MHz $\delta$ (ppm) = 1.60

Data for mixture of isomers:

IR (KBr, neat):

$\nu$ (cm$^{-1}$) 775, 836, 1006, 1038, 1105, 1255, 2859, 2931, 3300-3400 (br OH)

MS (EI, 70 eV):

m/z (%) = 162 (M$^+$ - C$_4$H$_9$, 67), 118 (83), 75 (100)

HRMS (EI):

calcd. for C$_7$H$_{16}$O$_2$SiD 162.10605 (M-C$_4$H$_9$)

found 162.10606
$^{1}H$ NMR (CDCl$_3$)

$^{13}C$ NMR (CDCl$_3$)
2-Methyl-3-((tert-Butyldimethylsilyl)-oxy)-butan-1-al (67)

![Structural Formula](image)

**Procedure:**

The general procedure for catalyzed hydroborations of alkenes was followed (see above). The title compound was obtained from the crude reaction product by flash chromatography as an inseparable mixture of diastereomers.

\[ R^f \quad 0.4 \text{ (EtOAc/hexane 5/95)} \]

**\(^1\text{H-NMR (CDCl}_3\):**

250 MHz \[ \delta \text{ (ppm)} = 0.02 \text{ (s, 3H, Si(CH}_3)_2\), 0.86 \text{ (s, 9H, C(CH}_3)_3\), 1.02 \text{ (d, }^3\text{J}_{HH} = 8.4 \text{ Hz, 3H, two ov d from the two diastereoisomers), 1.13 \text{ (d, }^3\text{J}_{HH} = 10.1 \text{ Hz, 3H), 1.16 \text{ (d, J=9.9 Hz, 3H), 2.38 \text{ (m, 1H), 3.98 \text{ (m, 1H), 4.23 \text{ (m, 1H), 9.72 \text{ (d, J=1.4 Hz, 1H)}}}} \]

**\(^1\text{C-NMR (CDCl}_3\):**

62.9 MHz \[ \delta \text{ (ppm)} = -5.0 \text{ (SiCH}_3\), -4.2 \text{ (SiCH}_3\), 8.1 \text{ (CH}_3\), 10.7 \text{ (CH}_3\), 17.9 \text{ (C), 21.2 \text{ (CH}_3\), 21.8 \text{ (CH}_3\), 25.7 \text{ (C(CH}_3)_3\), 53.4 \text{ (CH}_3\), 53.7 \text{ (CH}_3\), 68.2 \text{ (CH), 69.9 \text{ (CH), 205.1 \text{ (CHO)}}}} \]

**IR (KBr, CHBr\(_3\):**

\[ \nu \text{ (cm}^{-1}) = 3022, 2380, 1746, 1712, 1500, 1143, 654 \]
IR (CHBr₃)
2-Methyl-3-((tert-butyldimethylsilyl)-oxy)prop-1-ene (74a)

\[
\begin{align*}
\text{Me} & \quad \text{OSi}^{\text{BuMe}_2} \\
\end{align*}
\]

Procedure:

2-Methyl-2-propen-1-ol (3.5 g, 48 mmol) was dissolved in 30 mL of DMF. Imidazole (5.0 g, 70 mmol) was added followed by chloro tert-butyldimethylsilane (10.8 g, 70 mmol) and the reaction mixture was stirred overnight at 25 °C. The reaction was quenched with saturated aqueous \( \text{NH}_4\text{Cl} \) solution, diluted with hexanes, and washed several times with water to remove DMF. After drying over \( \text{MgSO}_4 \), the solvent was removed and the crude reaction product was distilled to provide the title compound.

Yield: 68 %.

\( R_f \) 0.8 (hexanes)

\( ^1\text{H-NMR (CDCl}_3\): \)

250 MHz \( \delta \) (ppm) = 0.07 (s, 6H, SiMe_2), 0.92 (s, 9H, C(CH_3)_3), 1.69 (s, 3H, CH_3), 4.03 (s, 2H, CH_2OR), 4.80 (s, 1H), 4.98 (s, 1H)

\( ^{13}\text{C-NMR (CDCl}_3\): \)

62.9 MHz \( \delta \) (ppm) = -5.3 (Si(CH_3)_2), 18.5 (C), 19.0 (CH_3), 26.0 (C(CH_3)_3), 66.9 (CH_2OR), 109.3 (CH_2), 144.6 (C)

\( \text{IR (KBr, neat)}: \)

\( \nu \) (cm\(^{-1}\)) = 3022, 2380, 1746, 1712, 1500, 1143, 654
2-Methyl-3-((tert-Butyldimethylsilyl)-oxy)propan-1-ol (75)

![Chemical Structure](image)

**Procedure:**
The title compound was obtained from rhodium catalyzed hydroboration of 74 as described in the general procedure. The crude reaction product was purified by flash chromatography affording 75 as a yellow oil.

\[ R_f = 0.2 \text{ (EtOAc/hexanes 20:80)} \]

**\(^1\)H-NMR (CDCl\textsubscript{3}):**

300 MHz \( \delta \text{ (ppm)} = 0.04 \text{ (s, 6H, SiMe}_2\text{), 0.81 \text{ (d, J=6.9 Hz, 3H, CH}_3\text{), 0.87 \text{ (s, 9H, }^1\text{Bu), 1.89 \text{ (m, 1H), 2.99 \text{ (br s, 1H, OH), 3.60 \text{ (m, 4H)}}} \]

**\(^{13}\)C-NMR (CDCl\textsubscript{3}):**

75.4 MHz \( \delta \text{ (ppm)} = -5.6 \text{ (-5.52, SiMe}_3\text{), 13.1 \text{ (CH}_3\text{), 18.2 \text{ (C), 25.9 \text{ (C(CH}_3)_3\text{), 37.1 \text{ (CH), 68.1 \text{ (CH}_2\text{), 68.6 \text{ (CH}_2)}}} \]

**\(^2\)H-NMR (CDCl\textsubscript{3}):**

76.7 MHz \( \delta \text{ (ppm)} = 0.89 \text{ (CH}_2\text{D), 1.91 \text{ (CD), 3.61 \text{ (CHDOH)}}} \]

**IR (KBr, CHBr\textsubscript{3}):**

\( \nu \text{ (cm}^{-1} = 775, 837, 1361, 2860, 2885, 2956, 3300-3500 \text{ (br OH)}} \)
IR (CHBr$_3$)
2-Methyl-3-((tert-Butyldimethylsilyl)-oxy)propan-1-ol (76)

Procedure:
The title compound was obtained from rhodium catalyzed hydroboration of 74 as described in the general procedure. The crude reaction product was purified by flash chromatography affording 76 as a yellow oil.

Rf 
0.4 (EtOAc/hexanes = 20/80)

^1H-NMR (CDCl₃):
300 MHz δ (ppm) = 0.04 (s, 6H, Si(CH₃)₂), 0.86 (s, 9H, C(CH₃)₃), 1.07 (d, ^3J_HH = 7.1 Hz, 3H), 2.51 (m, 1H), 3.81 (m, 2H), 9.71 (d, ^3J_HH = 1.4 Hz)

^13C-NMR (CDCl₃):
75.4 MHz δ (ppm) = -5.5 (Si(CH₃)₃), 10.4 (CH₃), 18.3 (C), 25.9 (C(CH₃)₃), 48.9 (CH), 63.5 (CH₂), 204.8 (CHO)

IR (KBr, neat):
v (cm⁻¹) = 778, 838, 1098, 1255, 1334, 1389, 1471, 1736 (C=O), 2859, 2931, 2956
Catalyzed Hydroboration of 75 (R=H) Followed by Transesterification of the Intermediate Boronate ester. The general procedure as illustrated above was followed, and upon completion of the reaction (GC), 354 mg (3 mmol, 3 equiv) of pinacol in 2 mL of THF was added. The reaction mixture was stirred for 16 h, and the crude product was subjected to flash chromatography. Elution with 3% EtOAc in hexane gave an inseparable mixture of pinacol (2-methyl-3-((tert-butyldimethylsilyl)-oxy)-1-propyl) boronate and pinacol (2-methyl-3-((tert-butyldimethylsilyl)-oxy)-1-propenyl) boronate (77), while 78 was obtained pure.

**Pinacol (2-methyl-3-((tert-butyldimethylsilyl)-oxy)-1-propyl) boronate (77)**

R$_f$  
0.5 (EtOAc/hexanes = 3:97)

**1H NMR (CDCl$_3$)**

300 MHz  
$\delta$ (ppm) = 0.01 (s, 6H), 0.56 (dd, J=6.7 Hz, J=15.6 Hz, 2H), 0.88 (s, 9H), 0.89 (d, J=6.7 Hz, 3H), 1.16 (s, 12H), 1.78-1.85 (m, 1H), 3.29 (dd, J=7.2 Hz, J=9.6 Hz, 1H), 3.41 (dd, J=5.7 Hz, J=9.6 Hz, 1H);

**13C NMR (CDCl$_3$)**

62.9 MHz  
$\delta$ (ppm) = -5.2 (Si(CH$_3$)$_2$), 15.7 (br s, CH$_2$B), 18.5 (C), 19.1 (CH$_3$), 24.9 (CH$_3$), 25.0 (CH$_3$), 26.1 (C(CH$_3$)$_3$), 32.3 (CH), 70.1 (CH$_2$), 82.9 (C)

**MS (FAB)**

m/z (%) = 315 (M+1, ).
$^{1}H$ NMR (CDCl₃)

$^{13}C$ NMR (CDCl₃)
Bis-pinacol (2-methyl-3-((tert-butyldimethylsilyl)-oxy)-1,1-propyl) boronate (78).

Rf

0.35 (EtOAc/hexanes = 3:97)

\(^1\)H NMR (CDCl\(_3\))

250 MHz \(\delta\) (ppm)= 0.00 (s, Si(CH\(_3\))\(_2\), 6H), 0.66 (d, J=10.1 Hz, 1H), 0.86 (s, C(CH\(_3\))\(_3\), 9H), 0.97 (d, J=6.6 Hz, 3H), 1.20 (ov s, 24H), 1.97-2.03 (m, 1H), 3.21 (ov dd, 1H), 3.57 (dd, J=3.9 Hz, J=9.5 Hz, 1H);

\(^{13}\)C NMR (CDCl\(_3\))

62.9 MHz \(\delta\) (ppm)= -5.2 (Si(CH\(_3\))), -5.1 (Si(CH\(_3\))), 15.1 (br s, CHB\(_2\)), 18.4 (C), 19.4 (CH\(_3\)), 24.6 (CH\(_3\)), 25.0 (CH\(_3\)), 26.1 (C(CH\(_3\))\(_3\)), 33.8 (CH), 69.7 (CH\(_2\)), 83.0 (C)

MS (FAB)

m/z (%) 441 (M+1).

HRMS (FAB, 3NBA)

calc. 441.3379 for C\(_{22}\)H\(_{48}\)B\(_2\)O\(_5\)Si

found 441.3370
IR (CHBr₃)
Appendix 4. Experimental with Chapter 4

The catalyst precursors [Rh(COD)Cl]2 and Rh(COD)2BF4 were prepared as described in the literature. 205 3,3,3-Trifluoro-2-phenyl-1-propene was prepared according to a literature procedure. 268 (4S,5R)-3,4-dimethyl-5-phenyl-1,3,2-oxazaborolidine 153 and 4,6-di-t-butyl-1,3,2-benzodioxaborole 152 were prepared according to literature procedures; R-BINAP and (S,S)-CHIRAPHOS were purchased from Aldrich, (S,S)-BDPP was purchased from Strem Chemicals and (R,R)-DIOP was prepared according to a literature procedure. 142 3-MeO-(R,R)-DIOP 143 was prepared analogous to a published procedure for 2-MeO-(R,R)-DIOP. 143,144

General Procedure for Catalyzed Hydroboration

A Schlenk tube charged with a catalytic amount of [Rh(COD)Cl]2 and chiral phospine (1:2) was three times evacuated/flushed with N2. Solvent (2 mL) was added, followed by 1 mmol of substrate in 2 mL of solvent. The yellow solution was cooled to -78 °C, stirred for 10 min, and 2 equiv. of neat borane was added. The reaction mixture was stirred at this temperature for 30 min and then stored at a constant temperature (see Tables). The reaction was followed by TLC and upon completion of the reaction, 1 mL of ethanol was added at 0 °C followed by 1.7 mL of 3 M NaOH solution and 1 mL of 30% H2O2. The mixture was stirred for 6 h at 20 °C and then diluted with 10 mL of 1 M NaOH solution. Extraction with diethyl ether (3 x 75 mL), washing of the combined organic fractions with 1 M NaOH solution (50 mL), water (50 mL) and saturated NaCl solution (50 mL) and evaporating the solvent after drying provided the crude products. Analyses of the crude reaction mixtures indicated quantitative formation of the products in >95 % purity; the optical purities of the crude products were analyzed without further purification.
Determination of Optical Purities of Product Alcohols

Representative Chiral Shift Experiment with \textit{exo}-Norborneol \textit{(86)} and Eu(Hfc)\textsubscript{3}

$^1$H NMR (CDCl\textsubscript{3}) of racemic \textit{exo}-norborneol with Eu(hfc)\textsubscript{3}

$^1$H NMR (CDCl\textsubscript{3}) of \textit{exo}-norborneol of 38 \% \textit{ee} with Eu(hfc)\textsubscript{3}
Representative HPLC Analysis of 1-Indanol on Chiracel OB Column

(R)-1-indanol

24 min

50 min

Racemic 1-Indanol (87) (flow rate 0.5 mL/min, 4% iPrOH in hexanes)

(S)-1-indanol

(R)-1-indanol

24 min

50 min

1-Indanol (87) of 64% ee (flow rate 0.4 mL/min, 5% iPrOH in hexanes)
4-tert-Butyl-7-methyl-1,3,2-benzodioxaborole (98)

![Chemical structure](image)

**Procedure:**

The title compound was prepared following the method used for benzodioxaborole (catecholborane). A solution of 3-tert-butyl-6-methylcatechol (4 g, 22 mmol) in 30 mL of THF was added under argon at 0 °C to 23 mL of a 1.0 M solution of BH₃ in THF. The reaction mixture was stirred for 2 h at this temperature, then the THF was distilled off under Ar. The remaining brown oil was distilled under vacuum (0.3 Torr, b.p. 68 °C) yielding a colorless oil.

**¹H-NMR (CDCl₃):**

250 MHz \( \delta \) (ppm) = 6.83-6.95 (m, 2H), 2.37 (s, 3H), 1.42 (s, 9H)

**¹³C-NMR (CDCl₃):**

62.9 MHz \( \delta \) (ppm) = 146.3 (C), 145.1 (C), 133.9 (C), 123.9 (CH), 120.8 (C), 119.6 (CH), 34.0 (C), 29.8 (CH₃), 14.5 (CH₃)

**¹¹B-NMR (CDCl₃):**

96.3 MHz \( \delta \) (ppm) = 28.55 (br d, \( J_{BH} = 235 \) Hz)

**MS (EI, 70 eV):**

m/z (%) = M⁺ 190 (22), 175 (100)

**Elemental analyses:**

calcd. = C, 69.52 %; H, 7.95 %.

found = C, 69.66 %; H, 7.87 %.
$^1$H NMR (CDCl$_3$)

$^{13}$C NMR (CDCl$_3$)
Appendix 5. Experimental with Chapter 5

General Procedure for Hydroborations Catalyzed by Cp₂Ti(μ-H)₂BH₂

A Schlenk tube was charged with 19.4 mg (0.1 mmol, 0.05 equiv.) of Cp₂Ti(μ-H)₂BH₂ inside a dry box. The tube was transferred to a Schlenk line and 1.0 mL of THF was added under an atmosphere of Ar, followed by 2.0 mL of a 2.0 M solution of LiBH₄ in THF. The violet/purple solution was stirred at 25 °C for 10 min. prior to the addition of alkene (2 mmol, 1 equiv.) and a small amount of trans-decahydronaphthalene as internal standard. The tube was immersed in an oil bath kept at 65 °C, and the reaction mixture was stirred until the reaction was complete or conversion of starting material had ceased as monitored by GC versus internal standard. The reaction flask was cooled to 0 °C and 2 mL of ethanol was added followed by 2 mL of 3.0 M NaOH solution. After careful addition of 2 mL of 30% H₂O₂ (exothermic reaction and H₂ evolution) the oxidation mixture was stirred for 5-7 h, diluted with 50 mL diethyl ether and washed with 20 mL of 1 M NaOH solution and 20 mL of saturated NH₄Cl solution. The organic fraction was dried over Na₂SO₄ and the solvent was removed at reduced pressure.

General Procedure of Quenching with DABCO/LiAlH₄

The crude hydroboration reaction mixture was cooled to 0 °C and a solution of DABCO (1 equiv. with respect to the amount of boron present) in THF was added. After stirring for 15 min. a solution of LiAlH₄ in THF (1.0 M, 1 equiv.) was added dropwise. An exothermic reaction occurred when tricoordinate alkylboranes were present. The reaction was left at 25 °C to ensure complete conversion and the ¹¹B NMR of the reaction mixture was taken.

Preparation of LiHB(CH₂CH₂Ph)ₙ(CHCH₃Ph)₃-n (109)

Phenylethene (3.1 g, 3.0 mmol) was placed in a 50 mL round bottom flask purged with N₂. THF (20 mL) was added, the flask was cooled to 0 °C and 1.0 mL of borane-
dimethyl sulfide complex (10.0-10.2 M) was added dropwise. After stirring at 25 °C for 3 h the reaction mixture was cooled to 0 °C, and 1.12 g (10 mmol, 1 equiv.) of DABCO in 5 mL of THF was added. To the colorless, clear solution was added 10.0 mL of a 1.0 M solution of LiAlH₄ in THF at 0 °C, leading to an slightly exothermic reaction with the formation of a milky white emulsion. The reaction mixture was left at 25 °C for 12 h.

1¹B NMR (THF/benzene-δ₆) δ -5.7 ppm (d, J₆-H = 81.4 Hz, minor); -9.7 ppm (d, J₆-H = 78.0 Hz, major); -13.5 ppm (d, J₆-H = 73.6 Hz, major).

Preparation of LiB(CH₂CH₂Ph)ₙ(CHCH₃Ph)₄-n (111)

Phenylethene (16 mmol) was hydroborated with BH₃·THF as described above. A solution of 4 mmol (2-phenylethyl)lithium in 15 mL of diethyl ether/pentane, prepared according to literature procedures, was added at -78 °C to the crude phenylethene hydroboration product. Two layers form and after warming to 25 °C the bottom layer was transferred to a NMR tube. 1¹B NMR (THF/benzene-δ₆) δ -12.5 ppm (br s, minor); -14.6 ppm (br s, minor); -16.5 ppm (sh s, major).

Preparation of LiB(CH₂CH₂Ph)₄ (110)

A solution containing 50 mmol of (2-phenylethyl)lithium in 50 mL of diethyl ether/pentane was added at -78 °C to a solution of 10 mmol of BF₃·Et₂O in 5 mL diethyl ether. The solution was allowed to warm to 25 °C and the progress of the reaction was followed by ¹¹B NMR. The peak at 0 ppm corresponding to BF₃·Et₂O was slowly transformed into LiB(CH₂CH₂Ph)₄ at -16.3 ppm (sh s).

Time-dependence of Cp₂Ti(µ-H)₂BH₂ Catalyzed Hydroboration of Phenylethene

A large Schlenk tube was charged with 784 mg (4 mmol; 0.1 equiv.) of Cp₂Ti(µ-H)₂BH₂ inside a dry box. The tube was transferred to a Schlenk line and 10.0 mL of THF was added under an atmosphere of Ar, followed by 20.0 mL of a 2.0 M solution of LiBH₄ (40 mmol; 1 equiv.) in THF. The violet/purple solution was stirred at 25 °C for 10 min. prior to the addition of 8.15 g of phenylethene (80 mmol; 2 equiv.) and a small
amount of trans-decahydronaphthalene as internal standard. The reaction mixture was analyzed by GC and the tube was immersed in an oil bath kept at 65 °C. At regular time intervals 2.0 mL were transferred from the reaction mixture to a 10 mm quartz NMR tube equipped with an insert containing BF₃·Et₂O as internal standard. A ¹¹B NMR spectrum and a GC trace was taken and the consumption of starting materials and production of tetraalkylboronates were determined versus the internal standards.

**Homogeneity Test.** To a Schlenk tube charged with 38 mg of Cp₂Ti(μ-H)₂BH₂ was added 1.0 mL of a 2.0 M solution of lithium borohydride in THF and 3 mL of a solution of 208 mg (2.0 mmol; 1 equiv.) of phenylethene and 40 mg of trans-decahydronaphthalene in THF. Half of the resulting purple/violet solution was transferred to another Schlenk tube charged with 1.0 g of triple distilled metallic mercury and both flasks were immersed in an oil bath kept at 65 °C. At certain time intervals (every hour) the progress of both reactions were analyzed by GC. After completion of the reactions both mixtures were oxidized as described above and the ratio of primary to secondary alcohol in the crude product was established by GC.

**General Procedure for TiCl₃-Promoted Hydroboration of Alkenes**

A Schlenk tube was charged with 68 mg (0.44 mmol, 0.2 equiv.) of TiCl₃ inside a glove box, and the tube was transferred to a vacuum line and placed under an atmosphere of argon. THF (1 mL) was added followed by 1.1 mL of a 2.0 M solution of LiBH₄ in THF. The reaction mixture was stirred for 1 h at 30 °C, and a white fine precipitate was observed. Substrate (2.0 mmol) and internal standard were then introduced in 1.5 mL of THF, and the progress of the reaction was followed by GC. After completion half of the reaction the crude mixture was analyzed by ¹¹B NMR, while the other half was treated with LiAlH₄ and DABCO.
General procedure for Ti(OiPr)$_4$ Catalyzed Hydroboration of Alkenes

A Schlenk tube was evacuated/flushed with argon (3x), 1 mmol of freshly distilled substrate was introduced followed by 3 mL of THF. Distilled titanium isopropoxide (0.1 mmol) was then added by microsyringe and the colorless reaction mixture was stirred for 10 min prior to the addition of 1.5 mmol of catecholborane. Immediately upon addition, the reaction mixture turns deep red. This solution was stirred for 12 h and then analyzed by $^{11}$B NMR (see text of chapter 5).

$^{11}$B NMR spectrum of 0.2 equiv. of TiCl$_3$ and 1.0 equiv. of LiBH$_4$ in THF
$^{11}$B NMR spectrum of 0.2 equiv. of TiCl$_3$, 1.1 equiv. of LiBH$_4$ and 1.0 equiv. of phenylethene in THF after 16 h at 25 °C, followed by LiAlH$_4$/DABCO quench

$^{11}$B NMR spectrum of 0.2 equiv. of TiCl$_3$, 1.0 equiv. of LiBH$_4$ and 1.0 equiv. of phenylethene in THF after 48 h at 65 °C
$^{13}$C NMR of 6 equiv. of catecholborane and Ti($^{t}$OPr)$_4$ after 30 min

$^{13}$C NMR of 6 equiv. of catecholborane and Ti($^{t}$OPr)$_4$ after 48 h
$^{13}\text{C NMR of 10 equiv. of catecholborane and Ti(O\text{Pr})_4 after 12 h}$

$^{13}\text{C NMR of catecholborane and iPrOH (1:1)}$
$^{11}$B NMR of Ti(4OPr)$_4$ promoted addition of catecholborane to phenylethene

$^{11}$B NMR of Ti(4OPr)$_4$ promoted addition of catecholborane to 2-phenylpropene
Appendix 6. Experimental for Chapter 6

General Procedures

\([N-(\textit{tert}-\text{butyloxy carbonyl})]-\text{aniline},^{240} 2\text{-diphenylphosphino-benzoic acid (134, m.p. 185 °C, lit 186-187 °C)},^{242} \text{lithium diphenyl(borane)phosphide (137),}^{248} \text{benzyl (S)-}N-\text{tert-butyloxy carbonyl-2-amino-3-p-toluensulfonyloxy-propionate (m.p. 96 °C, lit. 95-96 °C)},^{249,250} \text{benzyl (R)-}N-\text{tert-butyloxy carbonyl-2-amino-3-iodopropionate (m.p. 78-79 °C, lit. 79-80 °C)},^{249,250} \text{N-(}N\text{-tert-butyloxy carbonyl)}-L\text{-serine β-lactone (142, m.p. 130-131 °C, lit. 133-134 °C)},^{252} \text{and 4-methyl (S)-}N-\text{tert-butyloxy carbonyl-3-amino-2,2-dimethyl-3,4-oxazolidinecarboxylate (144, [α]D -47.0 °, c=1.3 in CHCl}_3, \text{lit. -46.7 °})^{253}\]

were prepared according to literature procedures. Fmoc- and Boc-protected amino acids for peptide synthesis were purchased from Advanced Chemtech, and Tentagel resin was obtained from RAPP Polymere.

\((N\text{-tert-Butyloxy carbonyl-β-aminophenyl)}\text{diphenylphosphine oxide (133)}\)

\[
\begin{array}{c}
\text{PPh}_2 \\
\text{NH}_{\text{Boc}} \\
\end{array}
\]

Procedure:

A Schlenk tube charged with 0.50 g (2.59 mmol, 1 equiv.) of \(N\text{-tert-butyloxy carbonyl aniline was three times evacuated and purged with argon. Diethyl ether (8 mL) was added and the solution was cooled to -20 °C followed by dropwise addition of 3.35 mL of a 1.7 M solution of tert-butyllithium in pentane. The light yellow solution was stirred at -15 °C for 2 h and 45 min at which point the reaction mixture had turned into a creamy, yellow suspension. A solution of 0.63 g of chlorodiphenylphosphine in 2 mL of THF was added at -78 °C and the mixture was allowed to warm to 25 °C over 2.5 h. After quenching with saturated aqueous \text{NH}_4\text{Cl, the crude reaction was diluted with 50 mL of}}
\]
diethyl ether, washed with water and saturated aqueous NaCl and dried over MgSO₄. After filtration the ethereal solution was stirred in contact with air until all of the phosphine product (Rf 0.45 in 10 % EtOAc/hexanes) had been oxidized to the corresponding phosphine oxide (Rf 0.5 in 30 % EtOAc/hexanes). The solvent was removed under reduced pressure and the crude product was purified by recrystallization from ethanol. Yield 920 mg, 90 % from N-tert-butyloxycarbonyl aniline.

m.p. 152-154 °C

Rf 0.5 (EtOAc/hexanes = 30/70)

1H-NMR (CDCl₃):
200 MHz δ (ppm)= 1.40 (s, 3H), 6.88-6.95 (m, 2H), 7.40-7.68 (m, 12H), 8.31 (dd, 3JHH =4.7, 4.7 Hz, 1H)

13C-NMR (CDCl₃):
50 MHz δ (ppm)= 28.1 (CH₃), 80.1 (C(CH₃)₃), 120.7 (d, 7.4 Hz, CH), 121.5 (d, 12.6 Hz, CH), 128.7 (d, J = 12.3 Hz, CH), 132.0 (d, J = 105.1 Hz, CP(O)), 132.2 (d, J = 5.1 Hz, CH), 132.4 (d, J = 2.8 Hz, CH.), 132.8 (d, J =10.8 Hz, CH), 133.4 (d, J = 2.1 Hz, CH), 145.1 (d, J = 3.1 Hz, C), 153.3 (C)

31P-NMR (CDCl₃):
81 MHz δ (ppm)= 35.9

IR (KBr, CHBr₃):
ν (cm⁻¹) 3020, 1718, 1584, 1532, 1440, 1301, 1247, 1145, 654

MS (FAB, glycerol)):
m/z (%)= 394 (M+1, 36), 294 (100)

Elemental analyses:
calcd. = C, 70.22 % ; H, 6.15 %; N, 3.56, for C₂₃H₂₄NO₃P.

found = C, 69.83 % ; H, 6.16 %; N, 3.47.
(N-\textit{tert}-Butyloxycarbonyl-o-aminophenyl)diphenylphosphine oxide (133)

$^{1}$H-NMR (CDCl$_3$)

$^{13}$C-NMR (CDCl$_3$)
(N-tert-Butyloxycarbonyl-o-aminophenyl)diphenylphosphine oxide (133)

$^{31}$P-NMR (CDCl$_3$)

IR (CHBr$_3$)
(o-Aminophenyl)diphenylphosphine (131)

\[
\begin{array}{c}
\text{PPH}_2 \\
\text{NH}_2
\end{array}
\]

**Literature**


**Procedure:**

To a solution of crude N-tert-butyloxy carbonyl-2-diphenylphosphinoaniline (derived from 25 mmol of N-tert-butyloxy carbonyl aniline)\(^{242}\) in 10 mL of dichloromethane was added 10 mL of a 4.0 M solution of HCl in dioxane. The reaction mixture was stirred for 6 h at which time all starting material had been consumed as monitored by TLC. The solution was diluted with 70 mL of ethyl acetate, washed with 1 M aqueous NaOH solution and dried over MgSO\(_4\). The crude product was purified by flash chromatography eluting with 5% EtOAc in hexanes. The slightly yellow solid obtained was recrystallized from ethanol yielding 3.45 g of pure product (50% from N-tert-butyloxy carbonyl aminobenzene).

**m.p.**

81 °C (lit. 82.5-83.0 °C)

**R\(_f\)**

0.25 (EtOAc/hexanes = 5/95)

**\(^1\)H-NMR (CDCl\(_3\)):**

\[\text{200 MHz } \delta \text{ (ppm)= 3.92 (br s, 2H), 6.65-6.82 (m, 3H), 7.15-7.23 (m, 1H), 7.34-7.36 (m, 10H)}\]

**\(^{13}\)C-NMR (CDCl\(_3\)):**

\[\text{50 MHz } \delta \text{ (ppm)= 115.5 (d, 2.7 Hz, CH), 118.8 (d, 2.1 Hz, CH), 119.5 (d, 8.5 Hz, C), 128.6 (d, 7.1 Hz, CH), 128.9 (CH), 130.5 (C), 133.7 (d, 19.0 Hz, CH), 134.4 (d, 2.7, CH), 135.5 (d, 7.9, C), 149.8 (d, 19.8 Hz, C)}\]
$^{31}$P-NMR (CDCl$_3$):

81 MHz $\delta$ (ppm) = -20.6

$^1$H-NMR (CDCl$_3$)

$^{13}$C-NMR (CDCl$_3$)
(o-Aminophenyl)diphenylphosphine (131)

$^{31}$P-NMR (CDCl$_3$)
Benzyl 2-\([N\text{-}\text{tert-Butyloxycarbonyl}]\)amino-3-diphenylphosphinoborane-propionate

(141)

\[
\text{\includegraphics[width=0.2\textwidth]{boc-hn-o-bn}}
\]

**Procedure:**

To a solution of 1.0 g (3.8 mmol, 2 equiv.) of triphenylphosphine-borane in 18 mL of THF was added under a countercurrent of argon 260 mg (3.8 mmol, 2.0 equiv.) of lithium wire cut into small pieces. The reaction flask was immersed into a ultrasound sonication bath and sonicated for 45 min. The orange/brown solution was separated from the unreacted lithium and 385 mg (4.2 mmol, 2.2 equiv.) of tert-butyl chloride was added with stirring to remove the phenyllithium formed. Immediately after the addition, the solution was slowly transferred to a solution of 850 mg (1.9 mmol, 1 equiv.) of benzyl \((S)-N\text{-}\text{tert-Butyloxycarbonyl})\)-2-amino-3-p-toluenesulfonyloxy-propionate in 5 mL of THF at \(-78^\circ\text{C}\). The reaction mixture was quenched after 25 min with 0.4 M aqueous HCl and diluted with diethyl ether. The organic layer was washed with water and brine, and dried over MgSO₄. After removal of the solvent at a rotatory evaporator, the crude reaction mixture was purified by flash chromatography giving 750 mg (41 %) of a colorless, viscous oil.

\(R_f\) 0.4 (EtOAc/hexanes = 20/80)

**\(^1\text{H-NMR} (\text{CDCl}_3):**

200 MHz δ (ppm) = 1.29 (s, 9H), 2.91-3.04 (m, 2H, CH₂P(O)Ph₂), 4.44-4.62 (m, 1H, \(\alpha\)-CH), 4.96 (d, \(J = 12.2\) Hz, 1H, CHHOBn), 5.12 (d, \(J = 12.2\) Hz, 1H, CHHOBn), 5.24 (d, \(J = 7.6\) Hz, NH), 7.32 (s, 5H), 7.38-7.49 (m, 6H), 7.62-7.73 (m, 4H)
$^{13}$C-NMR (CDCl$_3$):

50 MHz  $\delta$ (ppm) = 27.6 (d, J = 37.3 Hz, CH$_2$P(BH$_3$)Ph$_2$), 28.2 (C(CH$_3$)$_3$), 50.4 (CH), 67.5 (CH$_2$), 80.0 (C(CH$_3$)$_3$), 128.3 (CH), 128.4 (CH), 128.5 (CH), 128.9 (d, J = 10.0 Hz, CH), 129.0 (d, J = 10.0 Hz, CH), 129.6 (ov d, C), 131.4 (d, J = 2.5 Hz, CH), 132.0 (d, J = 9.2 Hz, CH), 132.1 (d, J = 9.2 Hz, CH), 135.1 (C), 154.7 (C), 170.7 (d, J = 10.2 Hz, C)

$^{31}$P-NMR (CDCl$_3$):

81 MHz  $\delta$ (ppm) = 12.6 (br)

$^{11}$B-NMR (CDCl$_3$):

64 MHz  $\delta$ (ppm) = -39.0

IR (KBr, CHBr$_3$):

$\nu$ (cm$^{-1}$)  3022, 2380 (P-BH$_3$), 1746 (C=O), 1712 (C=O), 1500, 1143, 654

MS (FAB, 3NBA):

m/z (%) = 464 (M-BH$_3$+1, 21), 420 (44), 408 (37), 390 (47), 376 (46), 328 (44), 316 (44), 300 (100)

HRMS (EI):

calcd.  464.1991 for C$_{27}$H$_{31}$NO$_4$P (M-BH$_3$+1)

found  464.2045
$^{1}H$-NMR (CDCl$_3$)

$^{13}$C-NMR (CDCl$_3$)
IR (CHBr$_3$)

MS (FAB)
Benzyl 2-[\text{N-tert-Butyloxy carbonyl}]amino-3-diphenylphosphino-propionate

\[
\begin{aligned}
\text{BocHN} & \quad \text{O} \\
\text{Ph}_2\text{P} & \quad \text{OBn}
\end{aligned}
\]

Procedure:

A solution of 2.1 g (11.1 mmol, 2.5 equiv.) of diphenylphosphine in 10 mL of THF was cooled to -78 °C under an atmosphere of argon. To this stirred solution was added slowly 6.1 mL of a 1.6 M solution of \text{n-butyllithium} in hexanes. The red-orange solution was stirred at this temperature for 15 min and then warmed to 0 °C. Benzyl (\text{S-tert-butoxy carbonyl})-2-amino-3-\text{p-toluenesulfonyloxy-propionate} (2.0 g, 4.45 mmol, 1.0 equiv.) was dissolved in 10 mL of THF and the solution was cooled to -78 °C. To this solution was slowly added the solution of lithium diphenylphosphide. The red-orange color of the phosphide anion disappears instantly upon contact with the solution of the tosylate until half of the reagent has been added, after which point the color persists. When monitoring the reaction by TLC a new spot appears during the first stage of the reaction (R_f 0.7, EtOAc/hexanes 20:80) at the cost of starting material (R_f 0.35). This new spot later fades with the appearance of a spot with R_f 0.5, which corresponds to the phosphine product. After 30 min, the crude reaction mixture was quenched with 4.5 mL of a 1.0 M solution of HCl in diethyl ether, giving a clear light yellow solution. The reaction mixture was then diluted with ethyl acetate and rapidly washed with deoxygenated water and brine, and dried over MgSO_4. After removal of the solvent under reduced pressure, the crude product was purified by flash chromatography, yielding 1.30 g (63 %) of a colorless oil.

R_f \quad 0.2 \quad (\text{EtOAc/hexanes = 10/90})
$^1$H-NMR (CDCl$_3$):

200 MHz $\delta$ (ppm)= 1.44 (s, 9H, C(CH$_3$)$_3$), 2.58 (dd, $J$=7.2 Hz, $J$ = 14.3 Hz, 1H, CHHPPh$_2$), 2.75 (dd, $J$ = 4.9 Hz, $J$ = 9.0 Hz, 1H, CHHPPh$_2$), 4.57 (m, 1H, $\alpha$-CH), 4.93 (d, $J$ = 12.2 Hz, 1H, CHHOBn), 5.08 (d, $J$ = 12.2Hz, 1H, CHHOBn), 5.37 (d, $J$ = 7.3 Hz, 1H, NH), 7.30-7.52 (m, 15H)

$^{13}$C-NMR (CDCl$_3$):

50 MHz $\delta$ (ppm)= 28.2 (C(CH$_3$)$_3$), 31.9 (d, $J$ = 16.1 Hz, CH$_2$PPh$_2$), 51.8 (d, $J$ = 16.2 Hz, CH), 66.9 (CH$_2$OBn), 79.7 (C(CH$_3$)$_3$), 128.1 (CH), 128.2 (CH), 128.3-128.5 (4 ov CH), 128.6 (CH), 128.6 (CH), 132.5 (d, $J$ = 19.3 Hz), 132.8 (d, $J$ = 19.5 Hz), 135.2 (C) 137.6 (ov d, $J$ = 11.7, C), 154.8 (C), 171.8 (d, $J$ = 5.7 Hz)

$^{31}$P-NMR (CDCl$_3$):

81 MHz $\delta$ (ppm)= -23.7

IR (KBr, CHBr$_3$):

$\nu$ (cm$^{-1}$) 696, 737, 1164, 1498, 1712 (C=O), 1740 (C=O),

MS (EI, 70 eV):

m/z (%)= 464 (M$^+$, 5), 316 (100), 244 (72)

HRMS (EI):

calcd. 464.1984 for C$_{27}$H$_{30}$NO$_4$P (M + 1)

found 464.1991
$^{1}H$-NMR (CDCl$_3$)

$^{13}C$-NMR (CDCl$_3$)
$^{31}$P-NMR (CDCl$_3$)

IR (CHBr$_3$)
Benzyl N-tert-butyloxycarbonyl-2-amino-3-diphenylphosphinylpropionate

![Chemical Structure]

**Procedure:**

The title compound was obtained as a by product during the synthesis of benzyl N-tert-butyloxycarbonyl-2-amino-3-diphenylphosphinoylpropionate (see above).

**m.p.**

123-124 °C

**R**

0.2 (EtOAc/hexanes = 50/50)

**1H-NMR (CDCl₃):**

200 MHz  \( \delta \) (ppm)= 1.44 (s, 9H, C(CH₃)₃), 2.80-3.01 (m, 2H, CH₂P(O)Ph₂), 4.50-4.71 (m, 1H, α-CH), 4.81 (d, 12.4 Hz, 1H, CHHOBn), 4.92 (d, 12.4 Hz, 1H, CHHOBn), 6.23 (d, 7.0 Hz, NH), 7.27 (br s, 5H), 7.32-7.48 (m, 6H), 7.61-7.77 (m, 4H)

**13C-NMR (CDCl₃):**

50 MHz  \( \delta \) (ppm)= 28.1 (C(CH₃)₃), 30.7 (d, J = 70.3 Hz, CH₂P(O)Ph₂), 49.9 (d, J = 5.6 Hz, CH), 67.1 (CH₂), 79.5 (C(CH₃)₃), 127.9 (CH), 128.0 (CH), 128.2 (CH), 128.4 (d, J = 11.9 Hz, CH), 128.6 (d, J = 11.8 Hz, CH), 130.2 (d, J = 9.5 Hz, CH), 130.6 (d, J = 9.7 Hz, CH), 131.6-131.8 (ov d, CH), 132.2 (d, J = 99.3 Hz, C), 132.6 (d, J = 100.0 Hz, C), 135.0 (C), 155.2 (C), 170.6 (d, J = 8.5 Hz, C)

**31P-NMR (CDCl₃):**

81 MHz  \( \delta \) (ppm)= 30.2
IR (KBr, CHBr₃):

ν (cm⁻¹) 3023, 2954, 2928, 2852, 1740 (C=O), 1707 (C=O), 1500, 1254,
       1145, 839, 658

MS (FAB):

m/z (%)= 480 (M+1, 27), 424 (20), 380 (M-Me₂CCH₂-CO₂+1, 100)

Elemental analyses:

calcd. = C, 67.63 %; H, 6.31 %; N, 2.92.

found= C, 67.37 %; H, 6.45 %; N, 2.79.

¹H-NMR (CDCl₃)
$^{13}\text{C-NMR (CDCl}_3\text{)}$

$^{31}\text{P-NMR (CDCl}_3\text{)}$
Determination of Optical Purity of 141 via Camphanamide Derivatives

**Procedure:**

2-\([N\text{-}N\text{-}t\text{ert}-B\text{utyloxycarbonyl}]\text{amino-3-diphenylphosphinoyl benzylpropionate (0.5 mmol),}

obtained by stirring compound 141 in air after removal of the borane protecting group

with diethylamine, was dissolved in 4 mL of CH\(_2\)Cl\(_2\), and 1 mL of 50 % TFA in CH\(_2\)Cl\(_2\)

was added. After 1.5 h, the excess TFA was removed under vacuum and the resulting

yellow oil was dissolved in 2 mL of CH\(_2\)Cl\(_2\). Dimethylamino pyridine (0.5 mmol) and

triethylamine (0.5 mmol) in 1 mL of CH\(_2\)Cl\(_2\) was added, followed at 0 °C by 0.55 mmol

of camphanic chloride in 1 mL of CH\(_2\)Cl\(_2\). The resulting mixture was stirred for 24 h,

diluted with CHCl\(_3\), and washed with 0.4 M HCl solution, saturated aqueous NaHCO\(_3\)

solution and brine. After drying over Na\(_2\)SO\(_4\) and removal of the solvent under reduced

pressure, the \(^1\text{H NMR}\) of the crude product was recorded. The spectrum showed a 1:1

mixture of diastereomers indicating complete racemization during the synthesis of 141.
(S)\textit{N-}tert\textit{-Butyloxy carbonyl-4-}(p\textit{-toluenesulfonyloxy})\textit{methyl-2,2-dimethyl oxazolidine (147)}

\[
\begin{array}{c}
\text{Boc} \\
\text{Me}\textsuperscript{2} \\
\text{O} \\
\text{Me}\textsuperscript{2} \\
\end{array}
\]\n
\textbf{Procedure:}

A solution of 2.59 g (10.0 mmol, 1 equiv.) of 4-methyl (S)\textit{N-}tert\textit{-butyloxy carbonyl-2,2-dimethyl-4-oxazolidinecarboxylate (144)}\textsuperscript{255,257} in 10 ml of THF was added dropwise at 0 °C to a stirred suspension of 650 mg (30 mmol, 3 equiv.) of lithium borohydride in 15 mL of THF. The reaction mixture was allowed to warm to 25 °C and was stirred until all starting material had been consumed monitored by TLC. The mixture was cooled to 0 °C and equal amounts of ethyl acetate and 0.4 M aqueous HCl were added carefully. When H\textsubscript{2} evolution had ceased, more ethyl acetate was added and the two layers were separated. The organic layer was washed with brine, dried over MgSO\textsubscript{4}, and filtered. After removal of the solvent a colourles oil remained that was used without further purification. The oil was dissolved in 20 mL of dry pyridine under an atmosphere of argon, and cooled to -10 °C. To the stirred, colorless solution 2.9 g (mmol) of \textit{p-toluenesulfonyl chloride} was added against a countercflow of argon and the resulting light yellow solution was stored at -20 °C for 24 h. The reaction mixture was filtered and the precipitate washed with 70 mL of ethyl acetate. The filtrate was washed with 50 mL of 0.4 M aqueous HCl and brine, dried over MgSO\textsubscript{4} and filtered. After removal of the solvent an orange solid was obtained which was recrystallized from ethanol to give 3.39 g of colorless crystals (88 % overall).

\textbf{m.p.} \quad 108-109 °C.

\textbf{R}_{f} \quad 0.2 (EtOAc/hexanes 10:90)
$^1$H-NMR (CDCl$_3$, 25 °C):

200 MHz $\delta$ (ppm) = 1.30-1.42 (m, 15H), 2.36+2.40 (s, 3H), 3.72-4.12 (m, 3H), 7.25-7.35 (m, 2H), 7.71 (d, $^3$J$_{HH}$ = 8.3 Hz)+7.82 (d, $^3$J$_{HH}$ = 8.5 Hz)

$^1$H-NMR (C$_6$D$_6$, 60 °C):

200 MHz $\delta$ (ppm) = 1.37 (s, 12H), 1.52 (s, 3H), 1.91 (s, 3H), 3.52-3.59 (m, 1H), 3.73-3.78 (m, 1H), 3.88-4.08 (m, 2H), 4.22-4.27 (m, 1H), 6.80 (d, $^3$J$_{HH}$ = 8.0 Hz, 2H), 7.74 (d, $^3$J$_{HH}$ = 8.0 Hz, 2H)

$^{13}$C-NMR (C$_6$D$_6$, 25 °C):

50 MHz $\delta$ (ppm) = 21.3 (CH$_3$), 23.0+24.4 (CH$_3$), 26.9+27.5 (CH$_3$), 28.3 (C(CH$_3$)$_3$), 56.0+56.3 (CH), 64.7+65.0 (CH$_2$), 68.0+68.4 (CH$_2$), 80.1+80.3 (C(CH$_3$)$_3$), 93.9+94.4 (CH), 127.6 (CH), 128.1 (CH), 128.2 (CH), 128.4 (CH), 128.6 (CH), 130.1 (CH), 133.9 (C), 144.7+144.9 (C), 151.5+152.1 (C)

$^{13}$C-NMR (C$_6$D$_6$, 60 °C):

50 MHz $\delta$ (ppm) = 21.2 (CH$_3$), 23.6 (br, CH$_3$), 27.1 (CH$_3$), 28.4 (C(CH$_3$)$_3$), 56.2 (CH), 65.0 (CH$_2$), 68.3 (CH$_2$), 80.2 (C(CH$_3$)$_3$), 94.3 (CH), 127.6 (CH), 128.0 (CH), 128.5 (CH), 130.0 (CH), 134.3 (C), 144.6 (C), 151.8 (C)

IR (KBr, CHBr$_3$):

$\nu$ (cm$^{-1}$) = 653, 1175, 1366, 1377, 1389, 1692 (C=O), 3021

MS (FAB, glycerol):

$m/z$ (%) = 386 (M+1, 10), 330 (M-Me$_2$CCH$_2$, 46), 272 (100)

HRMS (FAB)

- calcd. = 385.4790 for C$_{18}$H$_{27}$NO$_6$S
- found = 385.4773
- $[\alpha]_D = -79.2^\circ$ (c=2.01, CHCl$_3$, 25 °C)
Elemental Analysis:

**calcd.** C 56.09; H 7.06; N 3.63 for C_{18}H_{27}NO_{6}S

**found** C 55.56; H 7.28; N 3.40
$^{13}$C NMR (C$_6$D$_6$, 25 °C)

$^{13}$C NMR (C$_6$D$_6$, 60 °C)
(S) N-tert-butyloxycarbonyl-4-methylenediphenylphosphino-2,2-dimethyl-oxazolidine (148)

**Procedure:**

A flask purged with argon was charged with 2.3 g (12.5 mmol, 1.6 equiv.) of diphenylphosphine (2.3 g, 12.5 mmol), followed by 5 mL of THF. The flask was cooled to -78 °C and 7.3 mL of a 1.6 M solution of n-butyllithium in hexanes was added dropwise to the solution, which colored bright red/orange. After stirring for 20 min the solution was warmed to 0 °C and added dropwise to a solution of 3.0 g (7.8 mmol, 1 equiv.) of (S)N-tert-butyloxycarbonyl-4-(p-toluenesulfonyloxy)methyl-2,2-dimethyl-oxazolidine (147) in 10 mL of THF. During the initial stages of the addition, the color of diphenylphosphide anion faded rapidly upon contact, and addition was stopped when the red color persisted in the reaction flask. TLC showed complete consumption of the starting material at this stage. The reaction mixture was then quenched with a minimum amount of saturated aqueous NH₄Cl solution, filtered through Celite and washed with THF. The solvent was then removed under reduced pressure and the remaining oil was loaded onto a silica column and purified by flash chromatography eluting with 5 % EtOAc in hexanes. Yield 1.9 g (60 %) of a white crystalline solid.

**m.p.** 98-99 °C

**Rf**

0.2 (EtOAc/hexanes 5:95)

0.6 (EtOAc/hexanes 10:90)

**1H-NMR (C₆D₆, 25 °C):**

200 MHz \( \delta \) (ppm)= 1.38-1.41 (m, 9H), 1.59+1.80 (s, 6H), 2.08-2.40 (m, 1H), 2.68-2.79 (m, 1H), 3.16-3.24 (m, 1H), 3.55-3.70 (m, 1H), 3.80-3.88
(m, 1H), 4.05-4.21 (m, 2H), 7.05-7.23 (m, 4H), 7.30-7.40 (m, 4H), 7.48-7.58 (m, 1H), 7.78-7.90 (m, 1H)

$^1$H-NMR (C$_6$D$_6$, 75 °C):

200 MHz  $\delta$ (ppm) = 1.40 (s, 9H), 1.47 (s, 3H), 1.67 (s, 3H), 2.18-2.32 (m, 1H), 2.89-
3.04 (m, 1H), 3.70 (ddd, J = 1.4 Hz, J = 5.7 Hz, J = 8.8 Hz, 1H),
3.88-4.60 (m, 2H), 7.06-7.22 (m, 6H), 7.36-7.47 (m, 2H), 7.58-
7.70 (m, 2H)

$^{13}$C-NMR (CDCl$_3$, 25 °C):

50 MHz  $\delta$ (ppm) = 23.4+24.7 (CH$_3$), 27.1+27.8 (CH$_3$), 28.6 (C(CH$_3$)$_3$), 31.9 (d, $^1$J$_{CP}$ = 15.0 Hz, CH$_2$)+33.1 (d, $^1$J$_{CP}$ = 14.5, CH$_2$), 55.4 (d, J =
23.2, CH)+55.7 (d, J = 21.8, CH), 67.0+67.2 (CH$_2$), 79.9
(C(CH$_3$)$_3$), 93.5+94.0 (CH), 128.6 (CH), 128.7 (CH), 129.0
(CH), 132.3 (CH), 132.7 (CH), 132.9 (CH), 133.3 (CH), 136.6-
139.0 (ov d from diastereotopic C of both conformers),
151.6+152.0 (C)

$^{13}$C-NMR (C$_6$D$_6$, 70 °C):

50 MHz  $\delta$ (ppm) = 24.4 (CH$_3$), 27.7 (CH$_3$), 28.7 (C(CH$_3$)$_3$), 33.5 (d, J = 16 Hz,
CH$_2$), 56.2 (d, J = 23.2 Hz, CH), 67.6 (d, J = 10.9 Hz, CH$_2$), 79.6
(C(CH$_3$)$_3$), 94.1 (CH), 127.5 (CH), 128.5 (CH), 128.7 (CH),
128.8 (CH), 128.85 (CH), 128.9 (CH), 129.0 (CH), 132.7 (CH),
133.1 (CH), 133.3 (CH), 133.7 (CH), 138.2 (C), 138.4 (C), 139.4
(C), 139.7 (C), 152.1 (C)

$^{31}$P-NMR (CDCl$_3$):

81 MHz  $\delta$ (ppm) = -22.1, -21.2

IR (KBr, CHBr$_3$):

$\nu$ (cm$^{-1}$)  653, 695, 1092, 1143, 1172, 1241, 1254, 1366, 1390, 1689, 2978
\textbf{MS (EI, 2.4 V):}

\begin{align*}
\text{m/z (%)=} & \quad 400 (M+1, 9), 399 (M^+, 6), 300 (M-\text{Me}_2\text{CCH}_2-\text{CO}_2+1, 100) \\
[\alpha]_D & \quad -64.4^\circ \text{ (c=2.53, CHCl}_3, 25 ^\circ \text{C)}
\end{align*}

\textbf{HRMS (EI):}

\begin{align*}
\text{calcd.} & \quad 399.1963 \text{ for } \text{C}_{23}\text{H}_{30}\text{NO}_3\text{P} (M^+) \\
\text{found} & \quad 399.1960 \\
\text{calcd.} & \quad 400.2041 \text{ for } \text{M+1 (C}_{23}\text{H}_{31}\text{NO}_3\text{P)} \\
\text{found} & \quad 400.2013
\end{align*}
$^1$H NMR (C$_6$D$_6$, 25 °C)

$^1$H NMR (C$_6$D$_6$, 70 °C)
$^{13}$C NMR (C$_6$D$_6$, 25 °C)

$^{13}$C NMR (C$_6$D$_6$, 70 °C)
$^{31}$P NMR (CDCl$_3$, 25 °C)

IR (CHBr$_3$)
(S) N-tert-Butyloxycarbonyl-4-methylenediphenylphosphinoborane-2,2-
dimethyloxazolidine (149)

Procedure:
The procedure was identical to that for (S) N-tert-butyloxycarbonyl-4-
methylenediphenylphosphino-2,2-dimethyl-oxazolidine (148), but instead of quenching
the crude reaction mixture with saturated aqueous NH₄Cl solution, the reaction mixture
obtained after addition of lithium diphenylphosphide was cooled to 0 °C, and a 1.0 M
solution of BH₃·THF was added dropwise until TLC showed conversion of the phosphine
product (Rᵢ = 0.6, EtOAc/hexanes 10:90) into the phosphine-borane (Rᵢ = 0.4,
EtOAc/hexanes 10:90). The crude reaction mixture was then quenched with water,
diluted with ethyl acetate and washed with brine. After drying over MgSO₄, the solvent
was removed, and the sticky oil purified by flash chromatography eluting with 7 %
EtOAc in hexanes. Yield 2.0 g (92 %) from 1.3 g of (147).

Rᵢ
0.4 (EtOAc/hexanes 10:90)

¹H-NMR (C₆D₆, 75 °C):
200 MHz δ (ppm) = 1.38 (s, 3H), 1.40 (s, 9H), 1.61, s, 3H), 2.32-2.54 (br m, 2H),
2.98-3.23 (m, 1H), 4.10, 4.40 (m, 2H), 7.01-7.17 (m, 6H), 7.60-
7.69 (m, 2H), 7.78-8.12 (m, 2H)

¹³C-NMR (C₆D₆, 60 °C):
50 MHz δ (ppm) = 24.4 (br, CH₃), 27.9 (CH₃), 28.6 (C(CH₃)₃), (29.9 (d, J = 30.1
Hz, CH₂), 54.7 (d, J = 7.3 Hz, CH), 67.7 (CH₂), 80.1 (C(CH₃)₃),
93.7 (CH), 127.6 (CH), 128.0 (CH), 128.5 (CH), 129.0 (CH),
129.2 (CH), 131.1-133.1 (ov d from diastereotopic C), 152.0 (C)
$^{31}$P-NMR (CDCl$_3$):
81 MHz $\delta$ (ppm) = 11.7 (br)

$^{11}$B-NMR (CDCl$_3$):
64.2 MHz $\delta$ (ppm) = -38.2 (br)

IR (KBr, CHBr$_3$):
\[ \nu (\text{cm}^{-1}) \]
702, 751, 1106, 1182, 1247, 1366, 1389, 1681 (C=O), 2385 (BH$_3$), 2978

MS (FAB, 3NBA):
\[ m/z (\%) \]
400 (M-BH$_3$+1, 27), 356 (100)

HRMS (EI):
calcd. 400.2041 for C$_{23}$H$_{31}$NO$_3$P (M-BH$_3$+1)
found 400.2020
$^1$H NMR (C$_{6}$D$_{6}$, 75 °C)

$^{13}$C NMR (C$_{6}$D$_{6}$, 60 °C)
$^{31}$P NMR (CDCl$_3$, 25 °C)

$^{11}$B NMR (CDCl$_3$, 25 °C)
IR (CHBr₃)

MS (FAB)
(S)-N-tert-Butyloxy carbonyl-2-amino-1-diphenylphosphino-3-propanol

![Chemical Structure]

**Procedure:**

(S) N-tert-Butyloxy carbonyl-4-methylenediphenylphosphinoborane-2,2-dimethyl-oxazolidine (148, 450 mg, 1.09 mmol) was placed in a flask equipped with a reflux condenser. The setup was three times evacuated and filled with argon, and p-toluene-sulfonic acid (100 mg) was added followed by 10 mL of freshly distilled, deoxygenated methanol. The reaction mixture was refluxed for 4 h, when all starting material had been consumed. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography, affording 180 mg (46%) of a white solid.

**Rf**

0.15 (EtOAc/hexanes 20:80)

**1H-NMR (CDCl3):**

200 MHz \( \delta \) (ppm): 1.39 (s, 9H), 2.32 (d, \( J = 6.9 \) Hz, 1H), 3.15 (br s, OH), 3.58-3.80 (m, 3H), 5.05 (br s, NH), 7.24-7.51 (m, 10 H)

**13C-NMR (CDCl3):**

50 MHz \( \delta \) (ppm): 28.4 (C(CH\(_3\))\(_3\)), 30.0 (d, \( J = 13 \) Hz, CH\(_2\)), 50.8 (d, \( J = 12.8 \) Hz, CH), 65.7 (CH\(_2\)), 79.6 (C), 128.5 (CH), 128.6 (CH), 128.8 (CH), 132.8 (d, \( J = 19.0 \) Hz, CH), 138.1 (d, \( J = 11.6 \) Hz, C), 155.9

**31P-NMR (CDCl3):**

81 MHz \( \delta \) (ppm): -22.9

**IR (KBr, CHBr\(_3\)):**

\( \nu \) (cm\(^{-1}\)): 696, 738, 1168, 1367, 1502, 1692 (C=O), 2967, 3300-3400 (br OH)
MS (EI, 9.4 V):

m/z (%) = 359 (M⁺, 5), 302 (M-Me₂CCH₂⁺1), 244 (100), 199 (95)

HRMS (EI):
calcd. 359.1650 for C₈₀H₂₆NO₃P (M⁺)
found 359.1654
(S)-N-tert-Butyloxycarbonyl-2-amino-1-diphenylphosphinoborane-3-propanol (150)

```
\[
\text{BocHN} \begin{array}{c}
- \text{BH}_3 \\
- \text{PPh}_2
\end{array} \\
\text{H}
\]
```

**Procedure:**

A Schlenk tube charged with 2.6 g (6.3 mmol) of (S) N-tert-butyloxycarbonyl-4-methylenediphenylphosphinoborane-2,2-dimethyloxazolidine (149) and 140 mg of p-toluene sulfonic acid was evacuated and filled with argon three consecutive times.

Freshly distilled, deoxygenated methanol (30 mL) was added and the suspension was stirred for 12 h. TLC analysis shows both product and starting material present at this stage, but only weak spots for N-deprotected materials were present. The solvent was removed under reduced pressure and the crude reaction product was subjected to flash chromatography. Yield 1.02 g (64 % based on recovery of 0.87 g of starting material).

**m.p.**

109-110 °C

**R**

0.15 (EtOAc/hexanes 30:70)

**1H-NMR (CDCl₃):**

200 MHz  \( \delta \) (ppm)= 1.36 (s, 9H), 2.42-2.80 (m, 2H), 3.62-3.90 (m, 3H), 5.03 (d, \( ^3J_{HH} = 6.7 \) Hz), 7.33-7.48 (m, 6H), 7.60-7.79 (m, 4H)

**13C-NMR (CDCl₃):**

50 MHz  \( \delta \) (ppm)= 27.4 (d, 34.5 Hz), 28.3 (C(CH₃)₃), 49.6 (CH), 65.2 (d, 7.8 Hz), 79.9 (C(CH₃)₃), 128.3, (C) 128.9 (CH), 129.0 (CH), 129.1 (CH), 129.2 (CH), 129.4 (C), 131.3 (CH), 131.4 (CH), 131.45 (CH), 131.5 (CH), 131.9 (CH), 132.1 (CH), 132.2 (CH), 132.4 (CH), 155.9 (C=O)

**31P-NMR (CDCl₃):**

81 MHz  \( \delta \) (ppm)= 11.3 (br d, \( ^1J_{PB} = 22.6 \) Hz)
$^{11}$B-NMR (CDCl$_3$):

64 MHz  -38 (br)

**IR (KBr, CHBr$_3$):**

$\nu$ (cm$^{-1}$)  
717, 1062, 1509, 1683 (C=O), 2384 (P-BH$_3$), 3300-3400 (br, OH)

**MS (FAB, 3NBA):**

$m/z$ (%) =  
372 (M-H$_2$ + 1, 20), 360 (M-BH$_3$+1, 13), 316 (M-(CH$_3$)$_2$CCH$_2$+1, 100)

**HRMS (EI, 3NBA):**

calcd.  360.1728 for C$_{20}$H$_{27}$NO$_3$P (M - BH$_3$ + 1))
found  360.1698

calcd  372.1900 for C$_{20}$H$_{28}$NO$_3$P (M-H$_2$+1)
found  372.1926

**Elemental Analyses**

calcd.  C 64.44; H 7.83; N 3.75 for C$_{20}$H$_{29}$BNO$_3$P
found  C 63.86; H 7.91; N 3.74
$^1$H NMR (CDCl$_3$)

$^{13}$C NMR (CDCl$_3$)
$^{31}\text{P NMR (CDCl}_3\text{)}$

$^{11}\text{B NMR (CDCl}_3\text{)}$
Determination of Optical Purity of 150 via Camphaneate Derivative

Procedure:

N-[(1,1-Dimethylethoxy)carbonyl]-3-amino-(S)-2-methylene(diphenylphosphinoborane)-propanol (150, 373 mg, 1 mmol) was dissolved in 2 mL of CH₂Cl₂ and the solution was cooled to 0 °C. Dimethylamino pyridine (122 mg, 1.0 mmol) in 1 mL of CH₂Cl₂ was added, followed by 216 mg (1.1 mmol) of camphaneic chloride in 1 mL of CH₂Cl₂. The resulting mixture was stirred for 9.5 h, diluted with CHCl₃, and washed with 0.4 M HCl solution, saturated aqueous NaHCO₃ solution and brine. After drying over Na₂SO₄ and removal of the solvent under reduced pressure the crude product was dissolved in 5 mL of Et₂NH and stirred at 40 °C until all phosphine-borane had been converted into the phosphine. The excess diethylamine was removed in vacuo and the¹H NMR of the crude product was recorded. The identity of the product was checked by MS (M⁺ at 540).

¹H NMR (CDCl₃) of optically pure camphaneate 153
$^1$H NMR (CDCl$_3$) of 1:1 ratio of diastereomers of camphanate 153

MS (EI)
(S) N-tert-Butyloxycarbonyl-2-amino-1-diphenylphosphinoborane-3-propanyl p-nitrophenylcarbonate (151)

\[
\begin{array}{c}
\text{BocHN} - \text{BH}_3 - \text{PPh}_2 \\
\text{O} - \text{O} - \text{NO}_2 \\
\end{array}
\]

Procedure:

(S) N-tert-Butyloxycarbonyl-2-amino-1-diphenylphosphinoborane-3-propanol (150, 1.4 mmol, 1.0 equiv.) was placed in a reaction flask purged with nitrogen. Dichloromethane (3 mL) was added and the solution was cooled to 0 °C. A solution containing 288 mg (1.4 mmol, 1.0 equiv.) of p-nitrophenyl chloroformate and 174 mg (1.4 mmol, 1.0 equiv.) of dimethylaminopyridine in 3 mL of CH₂Cl₂ was added and the reaction mixture was stirred at 25 °C for 13 h). The solution was diluted with ethyl acetate and washed with 0.2 M HCl solution and brine. After drying over MgSO₄, the solvent was removed and the crude product was purified by flash chromatography providing 665 mg (88 %) of product. A very small amount of impurity was still present after one chromatographic purification, which has a Rf-value very close to the product. This contaminant was removed by stirring the product in diethylamine at 35 °C to remove the borane group. The phosphine produced could be purified without difficulty by flash chromatography and this material was converted into the title compound by dropwise addition of BH₃·THF at 0 °C.

m.p. 57-59 °C

Rf 0.4 (EtOAc/hexanes 30:70)

\(^1\)H NMR (CDCl₃):
200 MHz  $\delta$ (ppm) = 1.39 (s, 9H), 2.50-2.84 (m, 2H), 4.23-4.36 (m, 3H), 4.94 (d, $^3J_{HH}$ = 6.9 Hz), 7.35 (d, $^3J_{HH} = 9.2$ Hz), 7.42-7.52 (m, 6H), 7.62-7.80 (m, 4H), 8.25 (d, $^3J_{HH} = 9.2$ Hz)

$^{13}$C-NMR (CDCl$_3$):

50 MHz  $\delta$ (ppm) = 28.3 (C(CH$_3$)$_3$), 46.4 (CH), 70.3 (d, $J = 7.4$ Hz, CH$_2$), 80.1 (C(CH$_3$)$_3$), 121.6 (CH), 125.2 (CH), 128.0 (d, $J = 3.6$ Hz, C), 128.8 (CH), 129.0 (CH), 131.46, 131.51 (CH), 131.8 (CH), 132.0 (CH), 132.2 (CH), 145.3 (C), 151.8 (C), 154.6 (C), 155.2 (C).

$^{31}$P-NMR (CDCl$_3$):

81 MHz  $\delta$ (ppm) = 12.1 (br)

$^{11}$B-NMR (CDCl$_3$):

64 MHz  -34 (br)

IR (KBr, CHBr$_3$):

$\nu$ (cm$^{-1}$)  735, 910, 1165, 1217, 1251, 1338, 1348 (NO$_2$), 1367, 1500, 1525 (NO$_2$), 1710, 1770, 2387 (P-BH$_3$)

MS (FAB, 3NBA):

m/z (%) = 525 (M-BH$_3$+1, 17), 481 (100),

HRMS (FAB):

calcld.  525.1791 for C$_{27}$H$_{32}$N$_2$O$_7$P (M - BH$_3$ + 1))

found  525.1823
$^{1}H$ NMR (CDCl$_3$)

$^{13}C$ NMR (CDCl$_3$)
$^{31}\text{P NMR (CDCl}_3\text{)}$

$^{11}\text{B NMR (CDCl}_3\text{)}$
Synthesis of supported tetramer 158

Introduction of two phenylalanine molecules onto Tentagel SS was achieved by shaking the resin with 3.0 equiv. of Boc-Phe-OH, 3.0 equiv. of BOP, 3.0 equiv. of HOBy and 3.0 equiv. of Nmm for 4 h in DMF. Deprotection of the terminal amino residue was done by reaction with 50 % TFA in CH₂Cl₂, followed by neutralization with diethylisopropylamine and the coupling procedure was then repeated with the second phenylalanine. The coupling with activated carbonate 151 was performed with 3.0 equiv. of 151, 1.5 equiv. of diethylisopropylamine and 6.0 equiv. of HOBy in 5 mL of NMP.

Attempted rhodium catalyzed hydrogenation of α-methyl-cinnamic acid

A Schlenk tube was charged with 300 mg (theoretically 0.067 mmol) of supported ligand 158, and 3 mL of freshly distilled, deoxygenated diethylamine was introduced. The suspension was stirred at 35 °C for 1 h and the diethylamine was removed under reduced pressure. The resin was washed 3x with 5 mL of THF, and 12.3 mg (0.025 mmol, 0.05 equiv.) of [Rh(COD)Cl]₂ in 2 mL of THF was introduced. The yellow solution was stirred at 25 °C for 30 min and the now faint yellow supernatant was removed by syringe. The resin was washed with two additional portions of THF prior to the introduction of α-methyl cinnamic acid in 2 mL of THF. The reaction flask was then flushed with hydrogen and the reaction mixture was stirred for 36 h. After removal of the resin by filtration, the ¹H NMR of the crude reaction product indicated that no reaction had taken place.
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180. We did not establish if the metal complex is actively involved in these processes.


184. EPR experiments showed identical signals before and after completion of the reaction. This result also is indicative that reduction of the titanium(II)-complex to titanium metal does not take place under the reaction conditions.


191. The dialkylborohydrides giving doublet and triplet resonances in this $^{11}$B NMR spectrum could be derived from alkyl transfer between trialkylborohydrides and AlH$_3$ (formed from the LiAlH$_4$), but this should have been suppressed by the DABCO (forms DABCO.AlH$_3$). The dialkylborohydrides giving doublet and triplet resonances in this $^{11}$B NMR spectrum could be derived from alkyl transfer between trialkylborohydrides and AlH$_3$ (formed from the LiAlH$_4$), but this should have been suppressed by the DABCO (forms DABCO.AlH$_3$).

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