Stereoge Phosphorus Containing Phosphine-Phosphite Ligands in Asymmetric Catalysis.
Deerenberg, S.

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Chapter 6

Chiral Phosphine–Phosphite Ligands in the Rhodium–Catalyzed Asymmetric Hydrogenation of methyl (N)-acetylaminoacrylate and methyl (Z)-(N)-acetylaminocinnamate

Sirk Deerenberg, Oscar Pàmies, Montserrat Diéguez, Carmen Claver, Paul C. J. Kamer, Piet W. N. M. van Leeuwen

Abstract

A series of enantiopure phosphine–phosphite ligands (P₁–P₂ = ligands 1–4) was investigated in the rhodium-catalyzed asymmetric hydrogenation reaction. Intermediate [Rh(P₁–P₂)(cod)]BF₄ and [Rh(P₁–P₂)(maaa)]BF₄ complexes (cod = 1,5-cyclooctadiene; maaa = methyl acetamidoacrylate ester) were observed by $^{31}$P{¹H} NMR. The [Rh(P₁–P₂)(cod)]BF₄ complexes were precursors to active catalysts of the asymmetric hydrogenation reaction of several prochiral dehydroamino acid derivatives, at room temperature under 1 bar of hydrogen. The highest enantiomeric excess obtained was 99 %.
6.1 Introduction

Since the discovery by Iguchi in 1939 that certain rhodium(III) complexes catalyze the hydrogenation of organic substrates, the addition of hydrogen ($H_2$) to an unsaturated moiety is one of the most extensively studied reactions involving homogeneous catalysis.\(^1\)

$\alpha$-Acylaminoacrylic acid derivatives were the first olefinic substrates successfully used in the asymmetric hydrogenation reaction.\(^2\)–\(^5\) Complexation of the substrate is stabilized by the additional coordination of the carbonyl group. This first success was followed by a large effort in ligand synthesis to broaden the scope of the reaction by other substrates. Nowadays, synthetic routes are abundantly available and the electronic character of the catalyst can be tuned at will,\(^6\)–\(^11\) which broadens the scope of the reaction. The electronic properties of the rhodium center can be modified such that a strong rhodium–substrate bond and thus a short metal–substrate bond distance is obtained.\(^11\)

The majority of the rhodium–catalysts used in the hydrogenation reaction contain bidentate phosphorus ligands, having $C_2$–symmetry, e.g. DIOP\(^3\) and DIPAMP.\(^4,12,13\)

![Scheme 6.1 Catalytic cycle of the asymmetric hydrogenation reaction](image)

The mechanism of the asymmetric hydrogenation reaction catalyzed by rhodium complexes containing $C_2$ symmetric diphosphines has been studied in considerable detail (Scheme 6.1).\(^14\)–\(^27\) The first step in the asymmetric hydrogenation involves the coordination of the substrate, giving a mixture of diastereomeric $\text{Rh(1)(P_1-P_2)(substrate)}$ species, (B). The
next step in the hydrogenation sequence involves the irreversible oxidative addition of dihydrogen to the alkene complex (B) affording a Rh(III)(P1–P2)(substrate)(H2) complex, (C). Migration of the hydride, forming complex Rh(III)(P1–P2)(substrate–H)(H) (D), locks the configuration of the stereogenic center. The last step is the reductive elimination of the product from complex (D), giving the product and complex (A), which can re-enter the catalytic cycle.

Kinetic and spectroscopic studies\textsuperscript{17} clearly indicate that the rate-limiting step is enantiodetermining, and it is generally accepted that this is the oxidative addition reaction of dihydrogen.\textsuperscript{7,11,15,16} The enantioselection is determined by the relative rates of reaction of the diastereomeric adducts (B) with H\textsubscript{2} and by their equilibrium constants. Hydrogenation of the minor adduct is faster than of the major and leads to the observed product.\textsuperscript{17}

Previously, we have shown that the use of ligands with different donor atoms, \textit{viz.} an electron donating phosphine and an electron withdrawing phosphite, affects the reactivity and selectivity of the catalyst.\textsuperscript{28-30} The ligands consist of a phosphine moiety and a phosphite having an atropisomeric bisphenol group, which are connected to a 3 or 4 atom linker containing a stereocenter. In this Chapter, we describe investigations on the influence of a series of optically pure phosphine–phosphite ligands 1–4 on rate and enantioselectivity of the asymmetric hydrogenation reaction of methyl (\textit{N})-acetylaminoacrylate and methyl (\textit{Z})-(\textit{N})-acetylaminocinnamate. The steric and electronic character of the phosphine moiety, as well as the substituents and configuration of the stereocenter at the backbone have been varied systematically. Finally, ligands containing a shorter linker, thus enforcing a smaller P–Rh–P angle, have been examined. Under hydrogenation conditions intermediate rhodium complexes will be discussed and kinetic studies are conducted to get more insight in the mechanism of the asymmetric hydrogenation reaction.
Chapter 6

6.2 Results and Discussion

6.2.1 Ligands

The phosphine-phosphite ligands consist of a phosphine group and a phosphite moiety having a bulky atropisomerically chiral tetra(t-buty1)bisphenol group as reported in Chapters 2 and 3. The donor atoms are connected by a linker, which contains a stereogenic carbon. The phosphine moiety of ligands 1a and 1b contains two phenyl substituents, whereas ligand 1c has an o-anisyl and a phenyl substituent and contains a stereogenic phosphorus atom. The stereocenter at the backbone contains a phenyl group for ligands 1a and 1c and a methyl group for ligand 1b. The electronic character is expected to be similar for ligands 1 and therefore, the influence of the substituent of the backbone on the enantioselectivity can be investigated.
Ligands 2 are more electron donating due to the t-buty1 group. Furthermore, they have a stereogenic P-atom. The influence of the stereogenic phosphorus atom will be investigated by comparing diastereomeric ligands 2a and 2b and ligand 2c, which is a mixture of epimers of opposite configuration at the bridge stereocenter and of R-configured phosphine moiety. Ligand 2d contains the smaller methyl substituent at the stereogenic carbon.

The two t-buty1 substituents of the phosphine moiety make ligand 3 even stronger electron donating than ligands 2 and the π-electron accepting properties are diminished.

Ligands 4a and 4b resemble ligands 2a and 2b, respectively, but have a shorter backbone, thus enforcing a smaller P–Rh–P angle. The orientation of the substituents at the carbon stereocenter is similar, despite the absolute configuration of the carbon stereocenters.

6.2.2 Synthesis of the alkene complexes

The reaction of chiral phosphine–phosphite ligands (1–4) with [Rh(cod)2]BF4 in a dichloromethane solution proceeded readily to provide high yields of [Rh(P1–P2)(cod)]BF4 (P1 = phosphite, P2 = phosphine) cationic complexes (Scheme 6.2). At 293 K the 31P{1H} NMR spectra for complexes [Rh(P1–P2)(cod)]BF4 (P1–P2 = 1–3) (Table 6.1) showed a sharp double doublet in the phosphite region due to the J[P1–P2] and J[P1–Rh] couplings, while in the phosphine region a broad doublet was obtained (Δω1/2 = 40 Hz). These coupling constants suggest fluxional processes on the NMR time-scale, which was confirmed by low temperature 31P{1H} NMR spectroscopy. At 193 K the 31P{1H} NMR spectra showed sharp double doublets in the phosphine and in the phosphite region, indicating that only one complex was present.

\[
[Rh(cod)2]BF_4 + P_1-P_2 \xrightarrow{CH_2Cl_2} [Rh(P_1-P_2)(cod)]BF_4 + cod
\]

Scheme 6.2
Table 6.1 $^{31}$P{H} NMR data for complexes [Rh(P$_1$−P$_2$)(cod)]BF$_4$ (P$_1$−P$_2$ = 1−3)$^{a,b}$

<table>
<thead>
<tr>
<th>Ligand</th>
<th>P$_1$ = phosphite</th>
<th>P$_2$ = phosphine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\delta$(P$_1$)</td>
<td>$J$(P$_1$−Rh)</td>
</tr>
<tr>
<td>1a</td>
<td>130.9</td>
<td>263.1</td>
</tr>
<tr>
<td>1b</td>
<td>126.5</td>
<td>269.2</td>
</tr>
<tr>
<td>1c</td>
<td>130.5</td>
<td>262.3</td>
</tr>
<tr>
<td>2a</td>
<td>130.0</td>
<td>260.5</td>
</tr>
<tr>
<td>2b</td>
<td>130.3</td>
<td>261.2</td>
</tr>
<tr>
<td>2c</td>
<td>130.1</td>
<td>259.8</td>
</tr>
<tr>
<td>2d</td>
<td>129.8</td>
<td>261.2</td>
</tr>
<tr>
<td>3</td>
<td>129.9</td>
<td>260.8</td>
</tr>
</tbody>
</table>

$^a$ Chemical shifts ($\delta$) in ppm, coupling constants ($J$) in hertz. $^b$ The spectra were recorded at ambient temperature.

At ambient temperature, $^{31}$P{H} NMR spectra for complexes [Rh(P$_1$−P$_2$)(cod)]BF$_4$ (P$_1$−P$_2$ = 4a and 4b) (Table 6.2) showed two sharp double doublets. When the temperature was lowered, the presence of two sets of signals was observed in different proportions (Table 6.2). These results are consistent with the presence of two isomeric forms (a and b) in fast exchange on the NMR time-scale at room temperature. The formation of different isomers can be caused by two diastereoisomers obtained from the atropisomerism of the bispheno l in the phosphite moiety, by different conformers for the six-membered chelate ring or by a combination of both. Even though the rapid ring inversion of the seven membered dioxaphosphenin rings has been detected on the NMR time-scale in the free ligands,28,29 we expect the bispheno l moiety to be in one configuration in the related cationic complexes [Rh(P$_1$−P$_2$)(cod)]BF$_4$, as is the case in other complexes.28−30,32 This suggests the presence of different conformers of the six-membered chelate ring.
**Table 6.2** $^{31}$P [$^1$H] NMR data for complexes [Rh(P$_1$–P$_2$)(cot)]BF$_4$ (P$_1$–P$_2$ = 4a and 4b)$^a$

<table>
<thead>
<tr>
<th>Ligand</th>
<th>P$_1$ = phosphite</th>
<th>P$_2$ = phosphine</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td>124.1 248.4 21.0</td>
<td>140.2 54.4</td>
</tr>
<tr>
<td>4a (65 %)$^b$</td>
<td>122.4 248.6 22.1</td>
<td>141.2 52.3</td>
</tr>
<tr>
<td>4a (35 %)$^b$</td>
<td>127.3 248.9 18.5</td>
<td>140.1 55.3</td>
</tr>
<tr>
<td>4b</td>
<td>127.3 249.7 20.0</td>
<td>136.8 53.5</td>
</tr>
<tr>
<td>4b (55 %)$^b$</td>
<td>126.1 251.3 15.1</td>
<td>132.2 53.1</td>
</tr>
<tr>
<td>4b (45 %)$^b$</td>
<td>128.3 250.2 23.8</td>
<td>138.9 54.1</td>
</tr>
</tbody>
</table>

$^a$ Chemical shifts ($\delta$) in ppm, coupling constants ($J$) in hertz. $^b$ T = 213 K. Relative abundance between brackets.

6.2.4 Asymmetric Hydrogenation results

The catalytic performance of the complexes with the phosphine–phosphite ligands was tested in the enantioselective rhodium–catalyzed hydrogenation reactions of methyl (N)-acetylaminoacrylate 5 and methyl (Z)-(N)-acetylaminoacrylate 7 under 1.2 bar of H$_2$. The catalyst was formed *in situ* from [Rh(cot)$_2$]BF$_4$ and 1.1 equivalent of the ligands 1-4. The results of this study are presented in Table 6.3 and 6.4. For both methyl (N)-acetylaminoacrylate 5 and methyl (Z)-(N)-acetylaminoacrylate 7 high enantioselectivities were achieved up to 99 % and 97 %, respectively. Other products than (N)-acetyl-alanine methylester 6 and (N)-acetyl-phenylalanine methylester 8 were not observed. In general, the hydrogenation of methyl (N)-acetylaminoacrylate 5 was somewhat faster than that of methyl (Z)-(N)-acetylaminoacrylate 7.

The hydrogenation of methyl (N)-acetylaminoacrylate was performed in several solvents. Rhodium–catalyzed asymmetric hydrogenation reactions are commonly performed in methanol. For the reaction in methanol using 1a a high enantioselectivity of 93 % and a high rate were observed (TOF = 30.1). The reaction in tetrahydrofuran showed similar ee, but the rate was lower (TOF = 22). For the reactions performed in dichloromethane/methanol (9/1) and pure dichloromethane the enantiomeric excess increased to 98 % and 99 %, respectively. However, the reaction rate decreased and the highest ee corresponded with the slowest reaction (TOF = 7.4). Since phosphite ligands are known to decompose in protic solvents, further hydrogenation reactions were studied using dichloromethane.
Table 6.3 Asymmetric Hydrogenation of methyl (N)-acetylaminoacrylate.\textsuperscript{a}

\[
\begin{align*}
\text{H}_2\text{CO}_2\text{C} & \quad \text{NHAc} \\
\text{H}_3\text{CO}_2\text{C} & \quad \text{NHAc}
\end{align*}
\]

\[
\begin{align*}
\text{[Rh(cod)_2]BF}_4 \quad \text{Ligands 1-4} \\
\text{2 atm H}_2, \text{RT} \quad \text{H}_3\text{CO}_2\text{C} \quad \text{NHAc}
\end{align*}
\]

<table>
<thead>
<tr>
<th>Ligands</th>
<th>Solvent</th>
<th>TOF\textsuperscript{b}</th>
<th>Conv. [%] (h)\textsuperscript{c}</th>
<th>Ee [%] (conf.)\textsuperscript{d}</th>
</tr>
</thead>
<tbody>
<tr>
<td>(S\textsubscript{C})-1\text{a}</td>
<td>CH\textsubscript{2}Cl\textsubscript{2}</td>
<td>7.4</td>
<td>77 (14)</td>
<td>99 (R)</td>
</tr>
<tr>
<td>(S\textsubscript{C})-1\text{a}</td>
<td>MeOH</td>
<td>30.1</td>
<td>97 (4)</td>
<td>93 (R)</td>
</tr>
<tr>
<td>(S\textsubscript{C})-1\text{a}</td>
<td>CH\textsubscript{2}Cl\textsubscript{2}/MeOH\textsuperscript{e}</td>
<td>9.2</td>
<td>78 (14)</td>
<td>98 (R)</td>
</tr>
<tr>
<td>(S\textsubscript{C})-1\text{a}</td>
<td>THF</td>
<td>22</td>
<td>84 (4)</td>
<td>94 (R)</td>
</tr>
<tr>
<td>(S\textsubscript{C})-1\text{a}</td>
<td>CH\textsubscript{2}Cl\textsubscript{2}</td>
<td>18.1</td>
<td>39 (2.5)</td>
<td>96 (S)</td>
</tr>
<tr>
<td>(S\textsubscript{P},S\textsubscript{C})-1\text{c}</td>
<td>CH\textsubscript{2}Cl\textsubscript{2}</td>
<td>12.3</td>
<td>100 (14)</td>
<td>4 (S)</td>
</tr>
<tr>
<td>(R\textsubscript{P},R\textsubscript{C})-2\text{a}</td>
<td>CH\textsubscript{2}Cl\textsubscript{2}</td>
<td>42.2</td>
<td>100 (2.5)</td>
<td>96 (S)</td>
</tr>
<tr>
<td>(R\textsubscript{P},S\textsubscript{C})-2\text{b}</td>
<td>CH\textsubscript{2}Cl\textsubscript{2}</td>
<td>41.3</td>
<td>100 (2.5)</td>
<td>95 (R)</td>
</tr>
<tr>
<td>(R\textsubscript{P})-2\text{c}</td>
<td>CH\textsubscript{2}Cl\textsubscript{2}</td>
<td>41.2</td>
<td>100 (2.5)</td>
<td>6 (R)</td>
</tr>
<tr>
<td>(R\textsubscript{P},S\textsubscript{C})-2\text{d}</td>
<td>CH\textsubscript{2}Cl\textsubscript{2}</td>
<td>52.1</td>
<td>100 (2.5)</td>
<td>95 (S)</td>
</tr>
<tr>
<td>(S\textsubscript{C})-3</td>
<td>CH\textsubscript{2}Cl\textsubscript{2}</td>
<td>4.8</td>
<td>21 (5)</td>
<td>58 (R)</td>
</tr>
<tr>
<td>(R\textsubscript{P},S\textsubscript{C})-4\text{a}</td>
<td>CH\textsubscript{2}Cl\textsubscript{2}</td>
<td>19.1</td>
<td>32 (2.5)</td>
<td>61 (S)</td>
</tr>
<tr>
<td>(R\textsubscript{P},R\textsubscript{C})-4\text{b}</td>
<td>CH\textsubscript{2}Cl\textsubscript{2}</td>
<td>36\textsuperscript{c}</td>
<td>100 (1)</td>
<td>96 (R)</td>
</tr>
</tbody>
</table>

\textsuperscript{a} All reactions were run at ambient temperature under 1 bar of H\textsubscript{2}. Cinnamate to rhodium ratio is 100. Ligand to rhodium ratio is 1.1. \textsuperscript{b} After 1 hour [in mol·mol\textsuperscript{-1}·h\textsuperscript{-1}]. \textsuperscript{c} Percentage conversion of cinnamate determined by GC. \textsuperscript{d} Enantiomeric excess determined by GC. Absolute configuration drawn in parenthesis. \textsuperscript{e} Ratio 9/1.

The hydrogenation reaction performed with ligand 1\text{a}, containing a phenyl substituent at the stereocenter of the backbone, gave the R-enantiomer in 99 % ee. Using ligand 1\text{b}, having a methyl substituent, in a different spatial arrangement than the phenyl, afforded the S-configured product in 96 % ee. The changed configuration of the products indicates that the enantioselectivity is mainly controlled by the configuration of the substituent in the backbone.\textsuperscript{31} The ee decreased slightly due to the smaller methyl group of ligand 1\text{b}, but the reaction rate is enhanced. Using ligand 1\text{c}, containing a phosphine moiety with an anisyl substituent, resulted in a low ee (4 %). Since the substituents of the phosphorus and carbon...
Rhodium-Catalyzed Hydrogenation

Stereocenters are similarly oriented for ligand 1c and 2b, this indicates that the anisyl group is responsible for the decrease in rate and enantioselectivity.

For ligands 2, which contain a strongly electron-donating stereogenic phosphine, the reaction rate was higher than that found for ligands 1. Complexes containing ligands 2a and 2b afforded in the hydrogenation reaction almost similar ee’s of 96 % (S) and 95 % (R), respectively. Since the ligands only differ in configuration of the stereocenter in the backbone, this indicates that the stereogenic phosphine moiety does not influence the enantioselectivity. Therefore, we conclude that the enantioselectivity is predominantly controlled by the stereocenter of the backbone. This was confirmed by the use of ligand 2c, which is the mixture of 2a and 2b, and for which a low ee of 6 % was obtained. Ligand 2d, which has a small methyl substituent at the bridge, gave a higher reaction rate than 1b, which contains a phenyl substituent. The ee obtained using 2d was almost similar to that obtained when ligand 2a was applied.

The use of ligand 3, containing a more basic phosphine moiety than ligands 1 and 2, resulted in a moderate ee of 58 % and a relatively low reaction rate in the hydrogenation. This more strongly σ-donating ligand affects both reaction rate and enantioselectivity. The enantioselectivity might also be influenced by the steric hindrance of the bulky t-butyl groups at the phosphine moiety.

Using ligand 4b, having a shorter linker between the phosphine and the phosphite moieties we observed the highest reaction rate of all ligands used and an ee of 96 %. The use of diastereomer 4a gave a lower ee of 61 % and a slower reaction. The difference in reactivity and selectivity between rhodium complexes containing ligands 4a and 4b is remarkable compared to ligands 2a and 2b, which both afforded similar ee’s of different enantiomers. We propose that the small bite angles of the rhodium complexes containing ligands 4 enhance a cooperative effect between the stereocenters, which results in a matched combination for ligand 4b and a mismatched combination for ligand 4a. Ligands 1–3 have a larger bite angle and therefore the substituents of the phosphine moiety and the carbon stereocenter are not in close proximity.
Table 6.4 Asymmetric Hydrogenation of methyl (Z)-(N)-acetylaminocinnamate.\(^a\)

<table>
<thead>
<tr>
<th>Ligands</th>
<th>TOF(^b)</th>
<th>Conv. [%] (h)(^c)</th>
<th>Ee [%] (conf.)(^d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(S(_C))-1a</td>
<td>6.2</td>
<td>100 (24)</td>
<td>97 (R)</td>
</tr>
<tr>
<td>(S(_C))-1b</td>
<td>14</td>
<td>100 (24)</td>
<td>92 (S)</td>
</tr>
<tr>
<td>(S(_p),S(_C))-1c(^e)</td>
<td>9</td>
<td>100 (24)</td>
<td>6 (S)</td>
</tr>
<tr>
<td>(R(_p),R(_C))-2a</td>
<td>34.8</td>
<td>100 (12)</td>
<td>95 (S)</td>
</tr>
<tr>
<td>(R(_p),S(_C))-2b</td>
<td>35</td>
<td>100 (12)</td>
<td>95 (R)</td>
</tr>
<tr>
<td>(R(_p))-2c(^e)</td>
<td>33.9</td>
<td>100 (12)</td>
<td>3 (R)</td>
</tr>
<tr>
<td>(R(_p),S(_C))-2d(^e)</td>
<td>44.3</td>
<td>100 (12)</td>
<td>89 (S)</td>
</tr>
<tr>
<td>(S(_C))-3</td>
<td>3.9</td>
<td>85 (24)</td>
<td>63 (R)</td>
</tr>
<tr>
<td>(R(_p),S(_C))-4a(^e)</td>
<td>9.6</td>
<td>100 (12)</td>
<td>65 (S)</td>
</tr>
<tr>
<td>(R(_p),R(_C))-4b(^e)</td>
<td>100</td>
<td>100 (1)</td>
<td>95 (R)</td>
</tr>
</tbody>
</table>

\(^a\) All reactions were run at ambient temperature under 1 bar of H\(_2\). Cinnamate to rhodium ratio is 100. Ligand to rhodium ratio is 1.1. \(^b\) After 1 hour [mol-molRh\(^{-1}\)-h\(^{-1}\)]. \(^c\) Percentage conversion of cinnamate determined by GC. \(^d\) Enantiomeric excess determined by GC. Absolute configuration drawn in parenthesis. \(^e\) substrate / rhodium = 1 / 50

The results from the rhodium–catalyzed hydrogenation of methyl (Z)-(N)-acetylaminocinnamate are shown in Table 6.4. In general, the hydrogenation of methyl (Z)-(N)-acetylaminocinnamate follows the same trend as observed for methyl (N)-acetylaminoacrylate. However, the enantiomeric excesses obtained are somewhat smaller and the reaction rates are lower. Application of the same ligand in the hydrogenation reaction of methyl (N)-acetylaminoacrylate and methyl (Z)-(N)-acetylaminocinnamate resulted in the same configuration of the corresponding products 6 and 8, respectively, and similar ee. The catalyst containing ligand 1a gave the highest ee of 97% (R) for this series at a low reaction rate. The use of ligand 4b afforded the highest reaction rate and a cooperative effect was observed between the stereogenic phosphine moiety and the stereocenter at the backbone.
Complexes containing ligands 2 and 4 afforded the highest reaction rates together with high enantioselectivities of all ligands used. We propose that an electron–donating ligand enhances the oxidative addition of dihydrogen.7,11,15–17

6.2.3 Mechanistic Considerations

As depicted in Scheme 6.1 the generally accepted mechanism of Rh–diphosphine catalyzed hydrogenation involves the so–called alkene pathway.17,20,22,33–43 Since phosphine–phosphite ligands have different properties compared to diphosphines, the catalytic pathway may be different. In order to learn more about the catalytic cycle we monitored the hydrogenation of methyl acetamidoacrylate ester (maaa) with ligand 2a by $^{31}$P{$^1$H} NMR. A solution of [Rh(2a)(cod)]BF$_4$ in dichloromethane–d$_2$ was examined at 1.2 bars of dihydrogen, but a [Rh(2a)(cod)H$_2$] species was not detected. After addition of methyl acetamidoacrylate ester two new double doublets at 136.02 and 35.57 ppm were observed in the $^{31}$P{$^1$H} NMR spectrum. These new signals were assigned to the cationic rhodium complex [Rh(2a)(maaa)]$^+$. After the hydrogenation reaction, only [Rh(2a)(maaa)]$^+$ was observed. The formation of hydride species was not observed in the $^1$H NMR spectrum, from which we conclude that the subsequent migratory insertion and reductive elimination steps are very fast. Halpern’s classic studies$^{17}$ on hydrogenation have shown that the enantioselectivity is determined by the ratio of the initially formed diastereoisomers of [Rh(P$_1$–P$_2$)(substrate)]$^+$ complexes (Figure 6.1) and their respective reactivities of these intermediates towards H$_2$. 

![Scheme 6.1](image)
Figure 6.1 Diastereomeric \([\text{Rh}(\text{P}_1-\text{P}_2)(\text{maaa})]\) complexes. When ligand is \(C_2\)-symmetric, 1 and 3 and also 2 and 4 are equivalent.

In a NMR experiment using \([\text{Rh}(2a)(\text{cod})]\text{BF}_4\) and 5 equivalents maaa, an equilibrium between the starting compound, \([\text{Rh}(2a)(\text{cod})]\text{BF}_4\) and an amido complex, \([\text{Rh}(2a)(\text{maaa})]^+\), was observed (Equation 6.1). After 5 hours the equilibrium has shifted for 95% towards the \([\text{Rh}(2a)(\text{maaa})]^+\) species \((K_O = 288 \text{ Lmol}^{-1})\). In a similar experiment, addition of 20 equivalents of maaa immediately shifted the equilibrium totally towards the \([\text{Rh}(2a)(\text{maaa})]^+\) species.

\[
[\text{Rh(cod)(2a)}]\text{BF}_4 + \text{aaaCH}_3 \rightleftharpoons [\text{Rh}(2a)(\text{aaaCH}_3)]\text{BF}_4 \\
K_O = 288 \text{ Lmol}^{-1}
\]

Equation 6.1

Variable-temperature \(^{31}\text{P}\{^1\text{H}\}\) NMR spectra between 303 and 193 K showed that only one diastereoisomer is present. For the \([\text{Rh}(\text{P}_1-\text{P}_2)(\text{maaa})]\) complexes two signals were observed in the \(^{31}\text{P}\{^1\text{H}\}\) NMR spectrum at 35.57 ppm and 136.02 ppm, attributed to the phosphine and the phosphite, respectively. For the \(\text{P}_1-\text{P}_2\) coupling constant a value of 56 Hz is found, whereas \(J(\text{P}_1-\text{Rh})\) and \(J(\text{P}_2-\text{Rh})\) are found to be 241 Hz and 161 Hz, respectively. The shift of the phosphite signal in the \(^{31}\text{P}\{^1\text{H}\}\) NMR spectrum of complex \([\text{Rh}(2a)(\text{maaa})]\text{BF}_4\) is consistent with a diastereoisomer containing the phosphite trans to the C=O fragment and the phosphine trans to the C=C fragment.\(^{17}\)
Scheme 6.6

From these results the so-called alkene pathway (pathway A, Scheme 6.6) seems the preferred route. Pathway B (Scheme 6.6), in which a dihydrogen complex is formed, however, can not be excluded, since species $[\text{Rh}(2a)(\text{cod})\text{H}_2]\text{BF}_4$ could be present in amounts under the detection limit of the NMR equipment.

In order to get more insight in the sequence of the cycle, we studied the rate dependence on the substrate and rhodium concentration. We assumed that the rate dependence of the reaction on the $\text{H}_2$ concentration is in line with literature and is first order. From Figure 6.2 it is clear that the rate of the formation of hydrogenation products is linearly proportional to the rhodium precursor concentration. For a typical hydrogenation reaction, performed at standard conditions, the formation of hydrogenated product shows a zeroth-order dependency in substrate (maaa) concentration as shown in Figure 6.3. Neither the $[\text{Rh}(2a)(\text{maaa})\text{H}_2]\text{BF}_4$ species nor the $[\text{Rh}(2a)(\text{alkyl})\text{H}]\text{BF}_4$ have been observed under hydrogenation conditions and it seems reasonable to assume that the addition of $\text{H}_2$ is the rate determining step. However, further investigations on the equilibrium constant are necessary to understand why the hydrogenation reaction shows a pseudo zeroth-order in substrate in between 80 and 100 % conversion.
Figure 6.2 Influence of rhodium concentration on the reaction rate (TOF is turnover frequency in mol·(mol Rh)$^{-1}$·h$^{-1}$, [Rh] is rhodium concentration in mol·L$^{-1}$).

Figure 6.3 Hydrogenation of methyl (N)-acetylaminoacrylate.

Since the order of the reaction is zeroth–order in the concentration of methyl acetamidoacrylate ester and the fact that [Rh(2a)(maaa)]$^+$ is always the only observed species under hydrogenation conditions, we conclude that the rate determining step is the addition of H$_2$ to the catalyst precursor [Rh(2a)(maaa)]$^+$ (pathway A). In spite of this, pathway B cannot
be discarded, because it is possible that the intermediate species are formed under the
detection limit of the NMR equipment.

Figure 6.5 Quadrant diagrams showing the steric hindrance exerted by a C\textsubscript{2} symmetric ligand

6.2.5 Origin of enantioselectivity

In the past, the enantioselectivity achieved with several known C\textsubscript{2}–symmetric
diphosphine–rhodium catalysts has been explained through the use of quadrant diagrams.\textsuperscript{44} This simple method does not explain why a reaction involving such a small dihydrogen molecule can lead to such enormous differences in rate for the diastereomeric alkene adducts present. Investigations by Brown, Burk and Landis resulted in the “rotation mechanism” as depicted in Figure 6.6.\textsuperscript{40–42,45,46} The prochiral enamide substrate coordinates in a bidentate fashion and the square planar Rh–complex is formed. Due to steric hindrance of the ligand towards the substrate one of the diastereomeric complexes is energetically more favored and formed in excess. The oxidative addition of dihydrogen can take place from the top or the bottom of the complex and dihydrogen will coordinate in a cis fashion. The carbonyl fragment migrates together with rotation of the alkene fragment. The steric hindrance exerted by the ligand determines which diastereomeric rhodium–dihydride complex will be formed and thus leads to the enantiomeric product. It is often found that the minor diastereomeric rhodium–substrate species leads to the product.\textsuperscript{14,17,37,38}
Using our phosphine–phosphite ligand the alkene is coordinated cis towards the sterically more demanding phosphate moiety. The hydrogenation experiments have shown that the substituent of the stereogenic carbon has the major effect on the enantioselectivity. Since the substituent of the backbone is positioned at the back of the complex and it has been shown from previous work, that the substituent at the backbone controls the phosphate moiety, which on its turn determines the enantioselectivity, we expect that the bulky biphenol moiety influences the enantioselectivity.

6.3 Conclusions

We have investigated the rhodium catalyzed asymmetric hydrogenation reaction of methyl (N)-acetilaminocrylate and methyl (Z)-(N)-acetilaminocinnamate using a series of enantiopure phosphine–phosphite ligands (1–4). Good enantioselectivities up to 99 % were obtained under mild conditions. Systematic variation of the steric and electronic properties of the ligands showed that the enantioselectivity is determined by the stereogenic carbon in the backbone. Even though the phosphine moiety has no influence on the enantioselectivity, an
electron-donating phosphine enhances the reaction rate. Studies on intermediates of the catalytic cycle of the reaction using $^{31}\text{P}[^1\text{H}] \text{NMR}$ indicate that the $[\text{Rh}(\text{P}_1\text{P}_2\text{P}	ext{amaa})]^+$ species is the resting state of the reaction and that the rate dependence is first order in rhodium and zeroth order in substrate. The alkene coordinates $trans$ to the phosphine moiety and we propose that the phosphite moiety determines the enantioselectivity of the reaction controlled by the substituent of the stereogenic carbon. With ligands 4 enforcing a smaller bite angle, a cooperative effect was observed between the two stereogenic groups.

6.4 Experimental Section

General Considerations

Chemicals were obtained from Acros Chimica and Aldrich. All syntheses were performed by standard Schlenck techniques under argon atmosphere. Complex $[\text{Rh(cod)}_2]\text{BF}_4$ and ligands 1–4 were prepared by previously described methods. Solvents were distilled and deoxygenated before use. NMR–spectra were recorded on a Varian Gemini 300 MHz spectrometer.

Preparation of rhodium cationic complexes

In a general procedure, phosphine–phosphite ligand (0.05 mmol) was added to a solution of $[\text{Rh(cod)}_2]\text{BF}_4$ (20.2 mg, 0.05 mmol) in dichloromethane (2 mL). After 5 minutes, the desired products were obtained by precipitation with hexane as orange solids in good yields (around 90\%).

In situ NMR characterization experiments

$[\text{Rh(cod)}(\text{P}_1\text{P}_2)]\text{BF}_4$ under $H_2$–pressure

Procedure A. Hydrogen was bubbled through a solution of $[\text{Rh(cod)}(\text{P}_1\text{P}_2)]\text{BF}_4$ (0.015 mmol) in dichloromethane–$d_2$ (1.0 mL) at room temperature in an NMR tube. The reaction was followed by NMR.

Procedure B. In a typical experiment a sapphire tube ($\Phi=10$ mm) was filled under argon with a solution of $[\text{Rh(cod)}(\text{P}_1\text{P}_2)]\text{BF}_4$ (0.02 mmol) in dichloromethane–$d_2$ (1.5 mL).
The tube was purged twice and pressurized to 1.2 bar of H₂. The reaction was followed under H₂ pressure.

[Rh(cod)(P₁–P₂)]BF₄ and methyl acetamidoacrylate ester

In a typical experiment a sapphire tube (Φ = 10 mm) was filled under argon with a solution of [Rh(cod)(P₁–P₂)]BF₄ (0.02 mmol) and methyl acetamidoacrylate ester (0.1 mmol or 0.25 mmol) in dichloromethane–d₂ (1.5 mL). The reaction was followed by ³¹P{¹H} NMR.

Asymmetric hydrogenation reactions

In a typical run a Schlenk filled with a solution of substrate (1 mmol), catalyst precursor [Rh(cod)₂]BF₄ (0.01 mmol) and the ligand (molar ratio P₁–P₂/Rh = 1.1) in dichloromethane (6 mL) was purged three times with H₂. The reaction mixture was then shaken under H₂ (1 atm) at 298K. After the desired reaction time, the conversion and enantioselectivity were measured by GC (fused silica capillary column 25 m x 0.25 mm permabond L–Chirasil–Val).

6.5 References
Rhodium-Catalyzed Hydrogenation