

# Recent Developments in Catalytic Asymmetric Hydrogenation Employing P-Chirogenic Diphosphine Ligands

Karen V. L. Crépy, Tsuneo Imamoto\*

Department of Chemistry, Faculty of Science, Chiba University, Yayoi-cho, Inage-ku, Chiba 263-8522, Japan  
Fax: (+81)-43-290-2791, e-mail: imamoto@scichem.s.chiba-u.ac.jp

Received: July 26, 2002; Accepted: October 18, 2002

**Abstract:** Rhodium- and ruthenium-catalyzed asymmetric hydrogenations reactions employing  $C_2$ -symmetric chiral diphosphine ligands have a long history, and exceedingly high enantioselectivities have been reported. On the other hand, metal complexes containing P-chirogenic, electron-rich diphosphine ligands such as 1,2-bis(alkylmethylphosphino)ethane (BisP\*) and bis(alkylmethylphosphino)methane (MiniPHOS) have been tested only recently, and proved greatly successful. These results prompted intensive research amongst organic chemists, and the scope and limitations of the use of ligands bearing the chiral center at phosphorus atoms is presented in this review. The most recent data have been collected and summarized. In terms of ligand design, it is necessary to address an important question: "which properties are responsible for very high enantioselectivity in hydrogenation reactions?". To this extent, a full discussion of new aspects on the mechanism, in particular the demonstration of a dihydride mechanism for enantioselective hydrogenation as opposed to the unsaturated mechanism widely accepted so far, also constitutes an important part of this review.

- 1 Introduction
- 2 Asymmetric Hydrogenation: Historical Overview
- 3 Some Outstanding Chiral Ligands
  - 3.1 BPE and DuPHOS: Phosphine Ligands with Pseudo-Chirality at Phosphorus
  - 3.2 BisP\* and MiniPHOS: Synthesis and Characteristic Features
- 4 Metal-Catalyzed Enantioselective Hydrogenation Reactions
  - 4.1 Rh-Catalyzed Asymmetric Hydrogenations
  - 4.2 Ru-Catalyzed Asymmetric Hydrogenation of  $\beta$ -Keto Esters using BisP\*
- 5 Mechanism of Enantioselective Hydrogenation Catalyzed by Chiral Rh Complexes: General Considerations
- 6 Origin of High Enantioselectivity
  - 6.1 Empirical Rules
  - 6.2 Mechanistic Studies with BisP\*
  - 6.3 Reaction of Rh-MiniPHOS with  $H_2$
- 7 Conclusion

**Keywords:** catalysts; P-chirogenic ligands;  $C_2$ -symmetry; enantioselective hydrogenation; mechanism; rhodium

## 1 Introduction

Biologically active compounds, such as pharmaceuticals, agrochemicals, flavors, and fragrance, as well as advanced materials, such as liquid crystals, are indispensable in our daily life. The majority of the biological responses and physical functions engendered by these key molecules stem from specific molecular and chirality recognition, and thus, preparation of optically active substances is a challenging task for synthetic chemists. Synthesis of such vital compounds relies to major extent on the piling up of optically active building blocks, which must be endowed with suitable functionality, configuration, and conformational rigidity or flexibility to produce the desired stereoselectivity in the target molecule.

Catalytic enantioselective hydrogenation of unsaturated bonds, which employs dihydrogen and small

amounts of transition-metal complexes modified intrinsically by chiral ligands, is now recognized as being the most promising strategy for the synthesis of large amounts of enantiomerically pure products, and thus enormous progress has been achieved in this area.<sup>[1–3]</sup> Moreover, hydrogenation is economical and environmentally friendly, and most importantly provides an ideal route to optically active alkanes, alcohols, and amines, which can be structurally modified to desired building blocks.

Typically, rhodium(I) and ruthenium(II) complexes and, most often, diphosphine-based chiral ligands have been extensively employed in asymmetric hydrogenation, achieving high reaction rate and excellent enantioselectivity under optimized reaction conditions. Given the fact that the chiral information is transferred from the chiral catalysts to the organic products, special care has to be given to the design of efficient chiral agents. As

*Karen Crépy* was born in 1974 in Bourges, France. She studied chemistry in Rouen at the Institut Universitaire de Technologie, then at the Institut National des Sciences Appliquées. After graduating in 1997, she joined the research group of Andrew N. Cammidge at the University of East Anglia in Norwich (England), devoting most of her efforts to the construction of chiral (atropisomeric) biaryls. There, she demonstrated the first examples of an asymmetric Suzuki coupling reaction. After completing her Ph.D. in 2001, she moved to her current position as a post-doctoral associate with Tsuneo Imamoto at Chiba University, Japan. Her research there involves the development of highly efficient P-chirogenic phosphine ligands for application in asymmetric catalysis.



*Tsuneo Imamoto* was born in Yaizu, Shizuoka prefecture, Japan in 1942, and received his B. S. from Shizuoka University and his Ph. D. in 1972 from Osaka University. After one year post-doctoral work with Professor T. Mukaiyama at Tokyo Institute of Technology, he joined the Faculty of Osaka University. In 1975 he moved to Wayne State University, where he studied asymmetric synthesis under the guidance of Professor Carl R. Johnson. In 1978 he joined the research group of Professor Mukaiyama at the University of Tokyo and in 1980 he moved to Chiba University, where he is currently Professor of Chemistry. His research interests are methodology, synthesis, and mechanism, particularly in the context of asymmetric catalysis. He received the Synthetic Organic Chemistry Award, Japan (1997) and the Rare Earth Society Award, Japan (2001).



as a result, the efforts of synthetic organic chemists over the course of the past three decades have been focused on the search for new chiral catalysts or the tuning of existing ligands to permit almost perfect selectivity, excellent reactivity, and high productivity.

A comparative literature study led to the observation that the most effective catalysts present some similar structural requirements. Indeed, it is almost universally observed that ligands with  $C_2$  symmetry elements

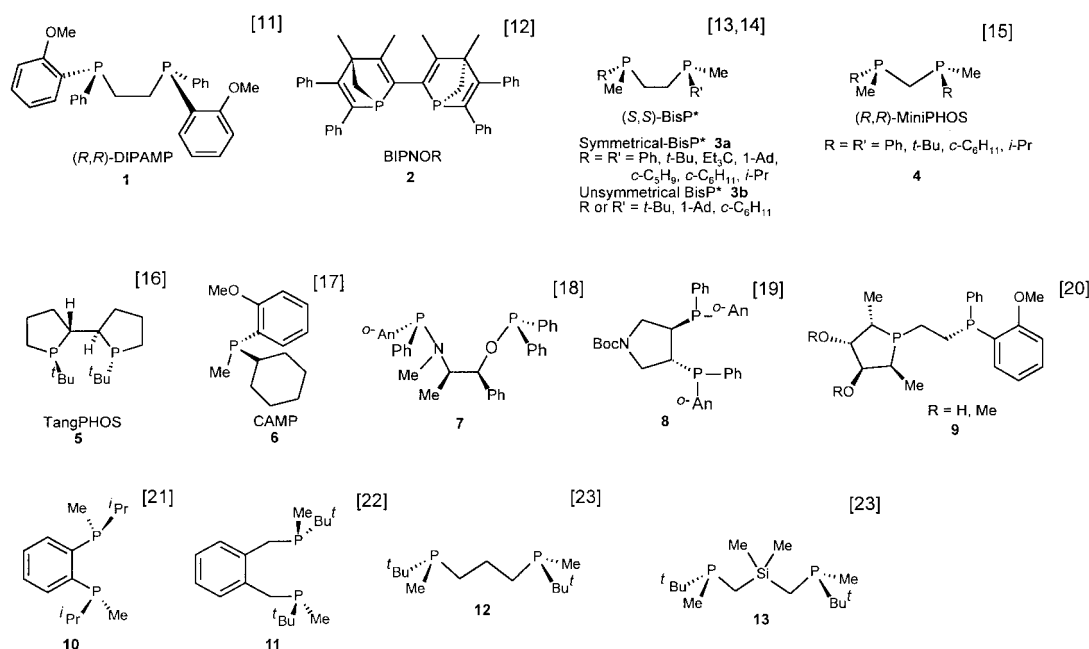
perform excellent stereochemical control because the number of conformations of the catalyst-substrate complexes is reduced to half as compared to those formed from  $C_1$ -symmetry catalysts.<sup>[4,5]</sup> For the same reason, ligands used in enantioselective catalyses are usually bidentate. Finally, optically active phosphines play a key role as chiral ligands in enantioselective hydrogenation reactions,<sup>[2,3]</sup> because of their intrinsic electronic properties and steric variability.

The chiral center of most optically active phosphines<sup>[6]</sup> resides within the ligand backbone and the chirality is transferred to the metal coordination sphere through a chiral array of aryl groups on the phosphorus.<sup>[7-9]</sup> The correct orientation of these aryl substituents in the coordination sphere has been identified as a stereochemically important feature contributing to the “recognition ability” of the metal complex.<sup>[10]</sup> In contrast, in P-chirogenic ligands, in which the chiral center exists at the phosphorus atom itself, the chirogenic atoms bind directly to the metal atom. This factor eliminates potentially inefficient secondary transfer of chirality from the ligand backbone and, thus, provides a more efficient chiral environment at the site where the enantioselection takes place. Phosphine ligands such as DIPAMP **1**,<sup>[11]</sup> BIPNOR **2**,<sup>[12]</sup> BisP\* **3**,<sup>[13,14]</sup> MiniPHOS **4**,<sup>[15]</sup> and TangPHOS **5**,<sup>[16]</sup> which belong to this category of chiral ligands (Figure 1), exhibit excellent enantioselection in asymmetric hydrogenations, and the scope of their usefulness is still an area of ongoing research.

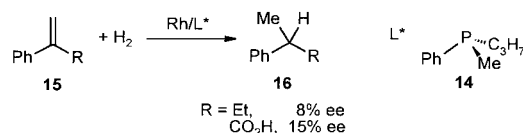
Attempts to bring insight to the mechanism and the stereoselection of enantioselective hydrogenation using various types of ligands have also been well documented, and numerous seminal reports are available to date.<sup>[1-3,24]</sup> Therefore, it is not the intention here to overlap with them, nor to cover in depth this extraordinarily large area, but rather to describe recent advances in the field. Thus, we limit the topic to transition metal-catalyzed stereoselective hydrogenation reactions performed in the presence of P-chirogenic ligands, for which no comprehensive review has been published yet. After presenting a brief overview of the most striking findings in this field, this account attempts to provide an analysis of the catalytic efficiency of newly designed P-chirogenic phosphine ligands—their scope and limitations—and most importantly an update on mechanisms.

## 2 Asymmetric Hydrogenation: Historical Overview

Asymmetric hydrogenation has a history long of over three decades. The discovery by Wilkinson<sup>[25]</sup> that chlorotris(triphenylphosphine)rhodium,  $[\text{RhCl}(\text{PPh}_3)_3]$ , is a soluble hydrogenation catalyst for some olefins, gave the idea to several research groups to substitute  $\text{PPh}_3$  by a chiral phosphine ligand in the Wilkinson catalyst and to directly perform asymmetric



**Figure 1.** P-Chirogenic phosphine ligands employed recently (except DIPAMP and CAMP) in asymmetric hydrogenation reactions.



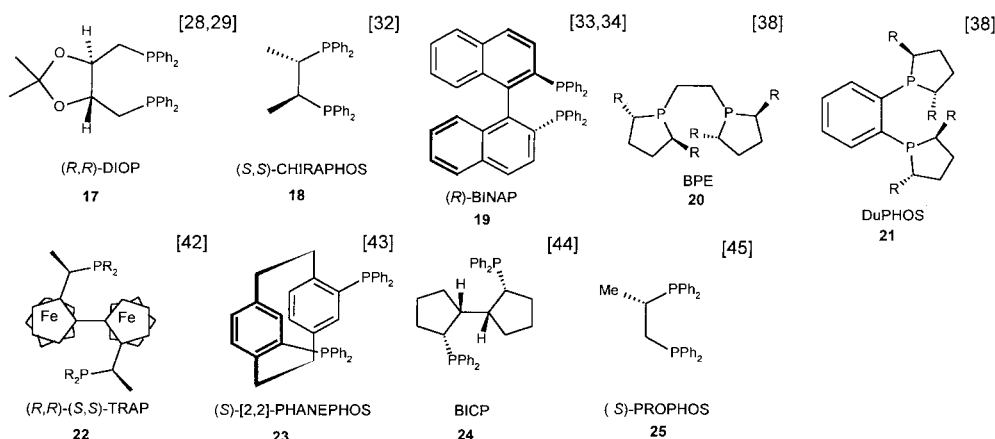
**Scheme 1.** The first Rh-catalyzed enantioselective hydrogenations.

hydrogenation. Thus, Horner<sup>[26]</sup> and Knowles<sup>[27]</sup> independently demonstrated that low but definite enantioselectivities were produced in the rhodium-catalyzed asymmetric hydrogenation of simple alkenes using the known methylpropylphenylphosphine **14** as the chiral ligand (Scheme 1). The issue then became one of finding the correct match between ligand and substrate, and thus the design of chiral ligands became a stimulating enterprise for synthetic chemists.

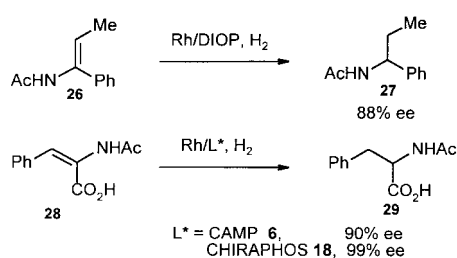
In the early 1970's, Kagan et al. first demonstrated the efficiency of DIOP **17** (Figure 2) as a C<sub>2</sub>-symmetric chelating diphosphine capable of, by complexation with rhodium metal, generating enantioselectivities up to 88% in the hydrogenation reaction of enamides (Scheme 2).<sup>[28,29]</sup> The potential of a C<sub>2</sub>-symmetric ligand bearing two diphenylphosphino groups to confer a suitable asymmetric environment has since been widely explored.<sup>[4]</sup> Around the same time, some chiral monophosphines, such as CAMP **6** and neomenthyldiphenylphosphine, led to enantioselectivity up to 90% in the reduction of *N*-acetyldehydrophenylalanine **28** (Scheme 2) and modest enantioselectivity in asymmetric hydrogenation of various conjugated acids, respectively.<sup>[17,30]</sup>

A real breakthrough in the early history of asymmetric hydrogenation was the preparation, in 1975, of DIPAMP **1** by Knowles et al.<sup>[11]</sup> This ligand simultaneously presents C<sub>2</sub>-symmetry elements and bears two chelating asymmetric phosphorus atoms, generating a closer chiral environment to the site where the reaction takes place. Consequently, the asymmetric hydrogenation of dehydroamino acids reached ees of up to 90–96%. The discovery of DIPAMP also enabled the first industrial asymmetric synthesis, and thus the commercial process for the amino acid (*S*)-DOPA (3,4-dihydroxyphenylalanine), a drug used for treating Parkinson's disease.<sup>[31]</sup> CHIRAPHOS **18**, another simple C<sub>2</sub>-symmetric diphosphine prepared by Fryzuk and Bosnich,<sup>[32]</sup> permitted the hydrogenation of *N*-acetyldehydrophenylalanine with an ee approaching 99%. The discovery of BINAP significantly expanded the scope of olefinic substrates for asymmetric hydrogenation.<sup>[33,34]</sup> When complexed to transition metals like rhodium, but most spectacularly with ruthenium, this fully aromatic diphosphine ligand furnished excellent to almost perfect enantioselectivity in the reduction of various C=C and C=O double bonds,<sup>[35,36]</sup> and also allowed the successful isomerization of allylamines into enamines.<sup>[37]</sup>

A significant advance was also achieved with the preparation of 1,2-bis(phospholano)ethane **20** (BPE) and 1,2-bis(phospholano)benzene **21** (DuPHOS) by Burk et al.<sup>[38]</sup> Their metal, especially rhodium, complexes serve as highly efficient catalyst precursors for the hydrogenation of a wide selection of many types of unsaturated systems.<sup>[38,39]</sup>



**Figure 2.** Optically active phosphine ligands (with backbone chirality) mentioned in this review.



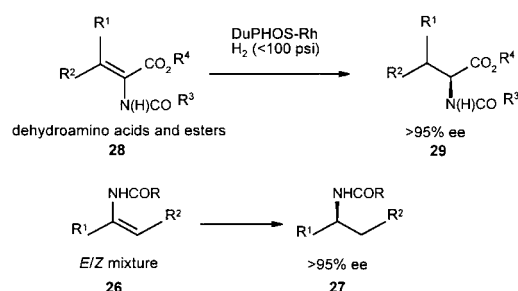
**Scheme 2.** The first successful asymmetric hydrogenations.

Overall, the synthetic value of asymmetric hydrogenation has been greatly improved, affording enantioselectivities in the range of 95–99% with a broad scope. On the other hand, combining high enantioselectivities and high catalytic activity (TOF or TON) is required to facilitate the transfer of asymmetric hydrogenation to industrial applications. Yet, there is still no universal catalyst that ensures both requirements, and thus the area of enantioselective hydrogenation is subject to constant developments due to the synthesis of new generations of chiral ligands or of new catalysts. This ongoing progress constitutes the topic on the presented account. In the following sections, highlighted examples have been selected from the outstanding results achieved with BPE and DuPHOS.<sup>[40,41]</sup> The discussion will then gradually progress to recent advances made possible by the new  $C_2$ -symmetric P-chirogenic phosphine ligands designed in our laboratory in the past four years.

### 3 Some Outstanding Chiral Ligands

#### 3.1 BPE and DuPHOS: Phosphine Ligands with Pseudo-Chirality at Phosphorus

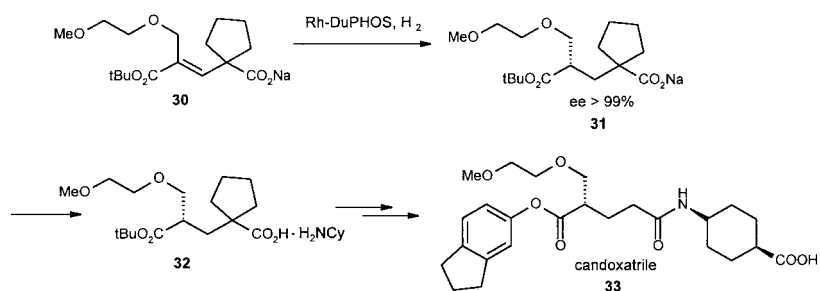
Two main distinctive features embodied by these ligands, as compared to other known chiral diphosphine



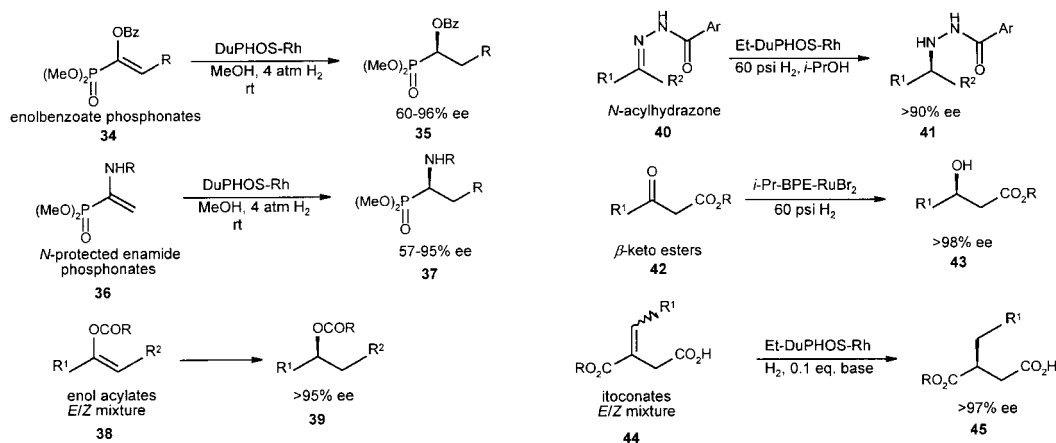
**Scheme 3.** Asymmetric hydrogenation reactions of dehydroamino acids derivatives with DuPHOS.

ligands, are the electron-rich character of the phosphorus atoms on the one hand and the pseudo-chirality at phosphorus atoms on the other hand. These properties are responsible for both the high activity of the corresponding metal complexes and enantioselection independent of the conformation properties of the chelate cycle.<sup>[38]</sup>

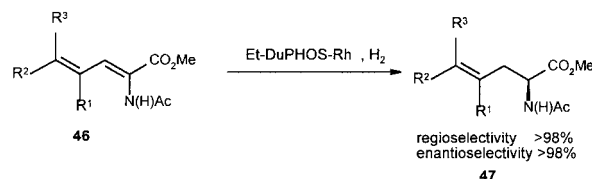
In the asymmetric hydrogenation of  $\alpha$ -dehydroamino acids and their esters **28**, high enantioselectivities (93–98%) were observed with the initially designed BPE, demonstrating that relatively efficient asymmetric induction based on the phospholane moieties could be achieved.<sup>[38]</sup> Owing to the flexibility of the ethano bridge, BPE (complexed to Rh) presents a dynamic structure in solution, giving rise to conflictual stereochemical communication between the ligand and an incoming substrate. On the other hand, the rigid backbone of DuPHOS firmly positions the phospholane alkyl groups close to the metal coordination sphere, reducing the number of possible conformations in the transition state. The added rigidity of the DuPHOS ligand was translated to almost perfect enantioselectivity in the rhodium-catalyzed asymmetric hydrogenation of a wide range of *N*-protected enamide esters and acids (Scheme 3).<sup>[38]</sup> Catalyst productivities displayed were excellent [substrate-to-catalyst (S/C) ratios up to 50,000]. The use of DuPHOS also permitted the hydro-



**Scheme 4.** Improved synthesis of the key intermediate of candoxtrile.



**Scheme 5.** Representative examples employing DuPHOS and BPE.



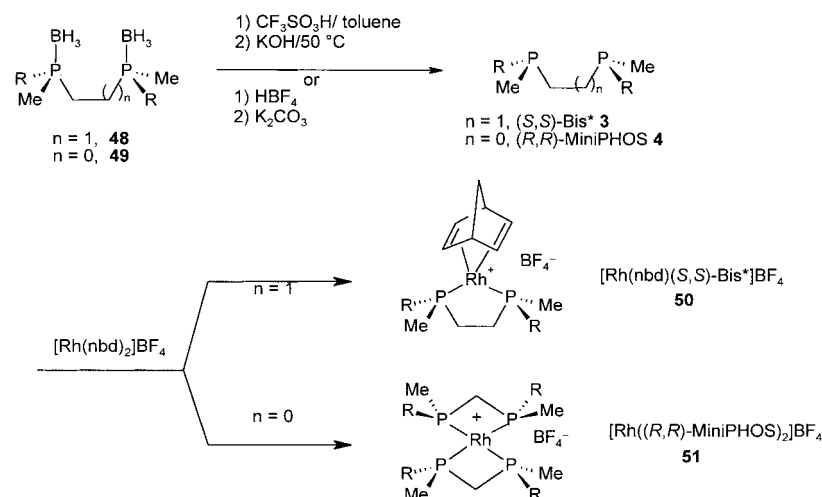
**Scheme 6.** Reduction of enamides containing multiple conjugated alkene functions.

genation reaction of both (*E*)- and (*Z*)-enamides to afford hydrogenated products of identical absolute configuration, saving necessary separation of isomeric mixtures prior to hydrogenation.<sup>[38]</sup>

Recently, the cationic (*R,R*)-Me-DuPHOS-Rh catalyst was also found to allow highly efficient and enantioselective hydrogenation of carboxylate **30** to afford the (*S*)-cyclopentaneglutarate **31**, a key intermediate required for Pfizer's drug candoxatril,<sup>[46,47]</sup> in enantioselectivity exceeding 99% and high yield (95%),<sup>[39]</sup> the best results obtained until then (Scheme 4). It is noted that, in contrast with other catalyst systems, no isomerization of the starting material **30** occurred. The Me-DuPHOS-Rh catalyst system operated with high catalytic efficiency (*S/C* = 3500, initial TOF = 6000 h<sup>-1</sup>) under low pressure, and the process was validated on a multi-kilogram scale.

Similar Rh catalysts of DuPHOS and BPE have also demonstrated the ability to hydrogenate a series of  $\alpha$ -benzoyloxyethenephosphonic esters in ees ranging from 60 to 96%,<sup>[39i]</sup> *N*-protected enamido phosphonates (57 to 95% ee),<sup>[39i]</sup> enol acylates (> 95% ee),<sup>[48]</sup> *N*-acylhydrazones (> 90% ee),<sup>[39a, b]</sup>  $\beta$ -keto esters (> 98% ee with Ru metal and under high pressure),<sup>[39c]</sup> and itaconate derivatives (> 97% ee).<sup>[39h]</sup>

Of interest, the DuPHOS-Rh catalysts offer excellent regioselectivity in the reduction of enamides containing multiple conjugated alkene functions (Scheme 6):<sup>[38,39g]</sup> only the enamide double bond is hydrogenated over distant C=C double bonds, most likely because the chelation of the alkene and the carbonyl oxygen atom of the *N*-acyl group to the metal center directs the hydrogenation.



**Scheme 7.** Formation of the Rh catalysts of BisP\* and MiniPHOS.

### 3.2 BisP\* and MiniPHOS: Synthesis and Characteristic Features

On the basis of the conclusions accumulated with BPE and DuPHOS, we have elaborated a new class of  $C_2$ -symmetric electron-rich P-chirogenic phosphine ligands, the 1,2-bis(alkylmethylphosphino)ethanes **3** (abbreviated as BisP\*)<sup>[13]</sup> and the 1,2-bis(alkylmethylphosphino)methanes **4** (abbreviated as MiniPHOS).<sup>[15]</sup> Similar to BPE, BisP\* ligands contain an ethylene bridge, although they form conformationally more rigid rhodium complexes owing to the presence of bulky groups disposed in a quasi-equatorial fashion. In contrast, the four-membered ring chelate that MiniPHOS forms with Rh is more rigid. The striking size difference between the two alkyl groups attached to the phosphorus atoms constitutes a powerful stereoregulating tool, as will be discussed in the following sections.

We have used the well-developed chemistry of phosphine-boranes<sup>[49–53]</sup> to prepare air-stable di(phosphine-boranes) **48** (Scheme 7).<sup>[13]</sup> The phosphorus-boron bond of **48** was cleaved by conventional methods<sup>[54,55]</sup> to leave the free  $(S,S)$ -diphosphines in almost quantitative yields. Precatalysts **50** were obtained from the immediate complexation of free phosphines **3** and  $[\text{Rh}(\text{nbd})_2]\text{BF}_4$ . The structures of enantiomerically pure  $[\text{Rh}(\text{BisP}^*)(\text{nbd})]\text{BF}_4$  precatalysts **50** were examined by X-ray crystallography, which testified that a single molecule of BisP\* binds to the rhodium metal. The following important structural features of the newly designed catalysts were confirmed: (i) the coordinated bisphosphines are  $C_2$ -symmetric and possess an  $(S,S)$ -configuration; (ii) the bulky alkyl groups occupy the quasi-equatorial positions and the methyl groups the quasi-axial positions, fixing the chelate cycles in a  $\lambda$ -conformation.

Employing a similar strategy to the synthesis of BisP\*, enantiomerically pure MiniPHOS ligands **4**, the next smaller analogues to BisP\*, were prepared.<sup>[15]</sup> Reaction of free diphosphines **4** with  $[\text{Rh}(\text{nbd})_2]^+\text{X}^-$  ( $\text{X} = \text{BF}_4, \text{PF}_6$ )

afforded in all cases and independently of the reaction conditions bischelate complexes **51**, which were expected to exhibit high enantioselection in asymmetric reactions. Indeed, James et al. demonstrated that, although slower, rhodium-catalyzed asymmetric hydrogenation employing bis(DIOP) species led to higher optical yields than the corresponding monochelate complex.<sup>[56]</sup> Observation of the X-ray structure of the rhodium complex **51** with  $\text{R} = t\text{-Bu}$  showed evidence for the  $(R,R)$ -configuration and an overall  $C_2$ -symmetric environment, where the two bulky groups occupy two diagonal quadrants and the smaller groups the two other quadrants.<sup>[31]</sup>

One of the important features of BisP\* and MiniPHOS is that the steric bulk imposed by the substituents born on the phosphorus atoms may be readily changed without affecting the electronic nature of the metal. Facile variation of the substituents enables optimization of the enantioselectivity by conferring correct steric matching between the ligand and the incoming substrate. However, for almost all substrates studied,  $t\text{-Bu}$ -BisP\* and  $t\text{-Bu}$ -MiniPHOS provide the best known enantioselectivities.<sup>[57]</sup> The catalytic activity of the BisP\*-Rh complexes is comparable to that of the best DuPHOS-Rh catalysts.<sup>[38]</sup>

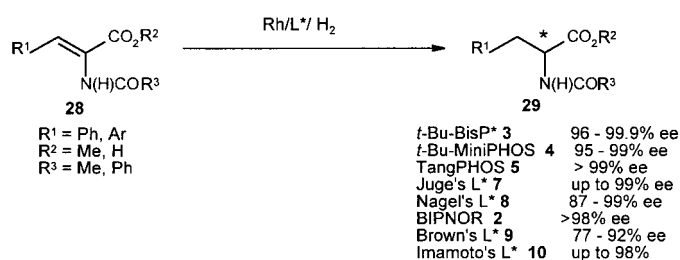
## 4 Metal-Catalyzed Enantioselective Hydrogenation Reactions

### 4.1 Rh-Catalyzed Asymmetric Hydrogenations

#### 4.1.1 Dehydroamino Acids and Itaconic Acid

##### 4.1.1.1 BisP\* and MiniPHOS

Asymmetric hydrogenations of dehydroamino acids have become a routine test reaction for evaluation of the effectiveness of new chiral ligands.<sup>[3,8,9,32,33,39]</sup> In



**Scheme 8.** Recent results in Rh-catalyzed asymmetric hydrogenation reactions of dehydroamino esters.

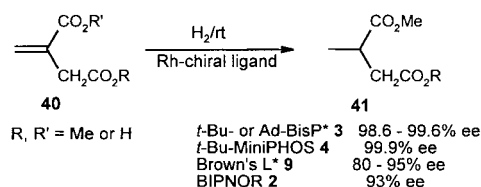
addition to being a test reaction, it stands as one of the most powerful and economic methods for the production of enantiomerically pure  $\alpha$ -amino acid derivatives. Our group<sup>[13,15,21,22,57]</sup> and others<sup>[12,16,18–20]</sup> have carried out an extensive series of hydrogenation reactions of dehydroamino acids using the rhodium complexes of P-chirogenic ligands, achieving enantiomeric excesses up to 99.9% (BisP\* **3**),<sup>[13,57]</sup> 99% (MiniPHOS **4**),<sup>[15,57]</sup> TangPHOS **5**,<sup>[16]</sup> Jugé's ligand **7**<sup>[18]</sup> and Nagel's ligand **8**<sup>[19]</sup>, 92% (Brown's ligand **9**),<sup>[20]</sup> and 84% (BIPNOR **2**),<sup>[12]</sup> as shown in Scheme 8.

Conclusions which were drawn from our screening are that the Rh-BisP\* and Rh-MiniPHOS are extremely efficient catalysts for the asymmetric hydrogenation of various dehydroamino acids, allowing enantioselectivities of over 97% for  $\beta$ -monosubstituted unsaturated substrates **28a**, over 98% for  $\beta$ -unsubstituted enamides **28b**, and over 90% for the  $\beta$ -branched ones **28c** (Table 1).<sup>[13,15,57]</sup> On the other hand, BisP\*-Rh catalysts present higher catalytic activity than the corresponding MiniPHOS analogues so that hydrogenations are completed in short reaction time (1–2 h) under moderate  $H_2$  pressure (2 atm) and ambient temperature. Yet, hydrogenation of  $\beta$ -branched dehydroamino acids requires higher pressure and a longer reaction time.

The conversion times of reaction employing MiniPHOS are long (24 h), although similar to those obtained with CHIRAPHOS-Rh catalyst.<sup>[58,59]</sup> MiniPHOS, however, exhibited greater enantioselection than CHIRAPHOS. The relatively lower catalytic activity of MiniPHOS as compared to BisP\* can be compensated by carrying out hydrogenation at high pressure, without any loss of optical purity. Interestingly, in contrast with Ojima's observation that hydrogen

**Table 1.** Enantioselective hydrogenations of dehydroamino acids derivatives with BisP\* and MiniPHOS.

Entry	Substrate	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	Precatalyst	ee [%]
1		Ph	Me	Me		<i>t</i> -Bu- or Ad-BisP*	99.9
2						<i>t</i> -Bu- or Ad-MiniPHOS	99
3						<i>t</i> -BuAd-BisP*	99.2
4						<i>t</i> -Bu-BisP*	98.4
5						Ad-BisP*	98.6
6						<i>t</i> -Bu-MiniPHOS	97
7						<i>t</i> -Bu-BisP*	95.9
8						<i>t</i> -Bu-BisP*	97.7
9		Ar	H	Me		<i>t</i> -Bu-BisP*	97.3
10						<i>t</i> -Bu-MiniPHOS	95
11						<i>t</i> -Bu-BisP*	99.8
12						<i>t</i> -Bu-MiniPHOS	> 99.9
13		H	Me			<i>c</i> -C <sub>6</sub> H <sub>11</sub> MiniPHOS	99.1
14						<i>t</i> -Bu-BisP*	98.1
15						Ad-BisP*	> 99.9
16						<i>t</i> -Bu-MiniPHOS	> 99.9
17		Me	Me	Me	Me	<i>t</i> -BuAd-BisP*	96.2
18						<i>c</i> -C <sub>6</sub> H <sub>11</sub> BisP*	90.9
19						<i>c</i> -C <sub>5</sub> H <sub>9</sub> BisP*	91
20						AdCy-BisP*	94.0
21		-(CH <sub>2</sub> ) <sub>5</sub> -		Me	Me	-(CH <sub>2</sub> ) <sub>5</sub> -	93.0
22						<i>t</i> -Bu-MiniPHOS	97
23						AdCy-BisP*	98.2
24						AdCy-BisP*	87.6
25		-(CH <sub>2</sub> ) <sub>4</sub> -		Me	Me	<i>t</i> -Bu-MiniPHOS	94
26							



**Scheme 9.** Enantioselective hydrogenation of itaconic acid and its methyl ester.

pressure influences the enantioselectivity,<sup>[60]</sup> we found only a marginal pressure dependence on the stereoselectivity outcome. This suggests that a dihydride mechanism may be involved, without competition with the unsaturated mechanism (cf. Section 6).

Methanol is the solvent usually chosen for the best compromise between enantioselection and reaction yields. *t*-Bu-BisP\* and *t*-Bu-MiniPHOS provide optimal results for the hydrogenation of  $\beta$ -unsubstituted and  $\beta$ -monosubstituted dehydroamino acids with almost perfect enantioselectivity.<sup>[57]</sup> Ad-BisP\* and cyclohexyl-MiniPHOS show similar efficiency. On the other hand, the cyclopentyl- and cyclohexyl-substituted BisP\*-Rh catalysts as well as *t*-Bu-MiniPHOS prove the most effective catalysts for the reduction of  $\beta$ -disubstituted dehydroamino acids. Enantiomeric excesses of the products obtained in the latter reduction may be compared with results obtained with Me-DuPHOS (99.4% ee),<sup>[61]</sup> Me-BPE (98.6% ee),<sup>[61]</sup> BuTRAP (88% ee),<sup>[42]</sup> DiPAMP (55% ee)<sup>[62]</sup> and [2,2]-PHANEPHOS (51% ee)<sup>[43]</sup> which were the highest ee values for the enantioselective hydrogenations of  $\beta,\beta$ -disubstituted derivatives.

Although the asymmetric hydrogenation of itaconic acid derivatives **40** is a potential synthetic approach to many useful products,<sup>[39h]</sup> lower enantioselectivities are often reported. In contrast with other catalysts, *t*-Bu-BisP\*, Ad-BisP\*, *t*-Bu-MiniPHOS,<sup>[57]</sup> BIPNOR,<sup>[12]</sup> and Brown's ligand **9**<sup>[20]</sup> gave high to almost perfect enantioselectivities in the hydrogenation of these substrates (Scheme 9).

#### 4.1.1.2 Unsymmetrical *P*-Chirogenic Bisphosphine Ligands

[(*S*)-1-(*R*<sup>1</sup>)methylphosphino-(*S*)-2-(*R*<sup>2</sup>)methylphosphino]ethanes serve as the non-*C*<sub>2</sub>-symmetric version of BisP\* since they bear different groups on both phosphorus atoms, breaking the *C*<sub>2</sub> symmetry character of BisP\*.<sup>[14]</sup> It is interesting to notice that, similar to the trend observed in the case of symmetrical BisP\*,<sup>[13,57]</sup> the unsymmetrical BisP\*-Rh precatalysts which give the worse results in the asymmetric hydrogenation of  $\beta$ -monosubstituted  $\alpha$ -dehydroamino acids **28a** or  $\beta$ -unsubstituted ones **28b** give the best enantioselectivities for the asymmetric hydrogenation of  $\beta$ -disubstituted  $\alpha$ -dehydroamino acids **28c**, and *vice versa*.<sup>[63]</sup> Thus, asymmetric hydrogenation of **28a** and **28b** gave optimal

optical yields (96.2 to 99.2% ee) when Ad-*t*-BuBisP\* was the ligand employed, whereas AdCyBisP\* or *t*-BuCyBisP\* (for which similar tendency of enantioselectivity is observed) are the ligands of choice for the reduction of  $\beta,\beta'$ -disubstituted substrates **28c**.<sup>[14,63]</sup> It should also be pointed out that a quantitative yield of *N*-acetyl- $\alpha$ -cyclohexylglycine methyl ester with extremely high ee (98.2%) was obtained using AdCyBisP\*.<sup>[14]</sup> This enantioselectivity exceeds or is similar to the best one obtained for the same reaction employing symmetric CyBisP\*, the best ligand for this substrate (93% ee),<sup>[13]</sup> (*S,S*)-Me-DuPHOS (96.2% ee),<sup>[61]</sup> or (*R,R*)-Me-BPE (98.6% ee).<sup>[61]</sup>

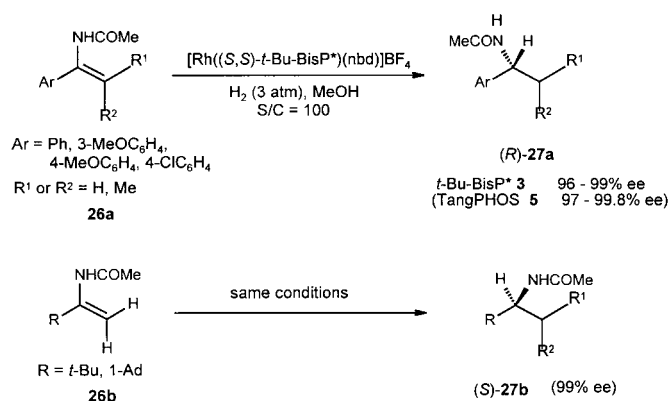
#### 4.1.1.3 1,2-Bis(isopropylmethylphosphino)benzene

Burk and coworkers demonstrated that the added rigidity of DuPHOS, as compared to BPE, was translated to excellent enantioselectivity in the rhodium-catalyzed asymmetric hydrogenation of a wide range of *N*-protected enamide esters and acids with selectivity approaching 100%.<sup>[38]</sup> (*S,S*)-1,2-Bis(isopropylmethylphosphino)benzene **10**, which is a rigid analogue to BisP\* thanks to the 1,2-phenylene backbone, was therefore synthesized from 1,2-bis(methylphosphino)benzene, and tested in our hands.<sup>[21]</sup> Enantiomerically pure [Rh((*S,S*)-**10**)(cod)]BF<sub>4</sub> was found to be effective in the asymmetric hydrogenation of dehydroamino acid methyl esters and excellent enantioselectivities (up to 98%) were achieved even in the reduction of  $\beta,\beta$ -disubstituted derivatives.

#### 4.1.2 Enamides

Several interesting results stemmed from the hydrogenation of various aryl-substituted and alkyl-substituted enamides **26** catalyzed by Rh-BisP\* and Rh-MiniPHOS. First, phenylenamides gave the corresponding optically active amides with 96–99% ee (Scheme 10).<sup>[64,65]</sup> However, optical yields of *ortho*-substituted compounds were drastically decreased as compared to the *meta*- or *para*-substituted ones, suggesting that less steric hindrance around the double bond is favorable for successful asymmetric catalysis. Second, all the studied aryl-substituted enamides gave the *R*-hydrogenated products whereas the enamides bearing bulky alkyl groups such as *t*-butyl or adamantyl gave the *S*-products under the same reaction conditions (Scheme 10).<sup>[64,65]</sup> This striking difference in the sense of stereoselection was first reported by Burk et al. in the rhodium-catalyzed asymmetric hydrogenation of 1-acetamido-1-phenylethene and 2-acetamido-3,3-dimethyl-1-butene employing (*S,S*)-Me-DuPHOS.<sup>[39d,66]</sup> The *R* absolute configuration was also assigned when the Rh-TangPHOS **5** system was employed for the hydrogenation of  $\alpha$ -arylenamides, with exceedingly





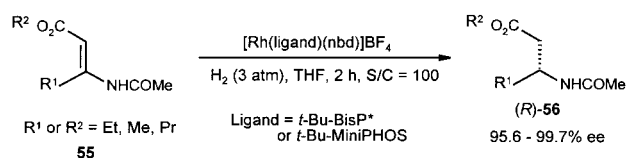
**Scheme 10.** Enantioselective hydrogenation of enamides.

high TON (10000) and ees (up to 99.8%).<sup>[16]</sup> From these results, it seems that the stereochemical environment of the double bond of the enamide considerably affects the sense of the stereoselection. In the structure of an enamide, the carboxy group of the dehydroamino acids mentioned earlier is substituted by an aryl or alkyl group. Still, a high degree of enantioselectivity is also obtained, implying intervention of different stereoregulating factors, which are the subject of Section 6.2.3. In this study, the [Rh(BisP\*)(nbd)]BF<sub>4</sub> catalyst again revealed better results compared to the corresponding (S,S)-MiniPHOS catalyst, and is actually one of the best catalysts for the asymmetric hydrogenation of enamides reported so far.

The rhodium complex of the (R,R)-counterenantiomer of (S,S)-BisP\* enabled asymmetric hydrogenation of 3-methoxy-substituted substrate **52** in high ee (97%), which constitutes a precursor to the acetylcholinesterase inhibitor SDZ-ENA-713 (**54**) (Scheme 11).<sup>[65]</sup>

#### 4.1.3 (E)-β-(Acylamino)acrylates

As just described above, a wide range of optically active natural and unnatural α-amino acids have been synthesized in excellent ees by catalytic asymmetric hydrogenation. On the other hand, the same approach for the preparation of β-amino acids has been the subject of less attention. Yet, these are key precursors to the synthesis



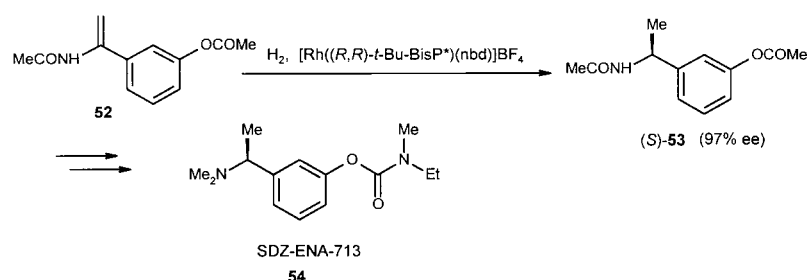
**Scheme 12.** Enantioselective hydrogenation of (E)-β-(acylamino)acrylates.

of β-lactams,<sup>[67]</sup> β-peptides,<sup>[68–70]</sup> and some medicinally important natural products.<sup>[71–73]</sup> Note, however, that good to excellent optical yields of β-amino acids were reported by Noyori<sup>[74]</sup> and Zhang<sup>[44]</sup> using Ru-BINAP **19**, Rh-DuPHOS **21**, and Rh-BICP **24**. We also demonstrated that the rhodium complexes of (S,S)-BisP\* and (R,R)-MiniPHOS are excellent catalysts for the asymmetric hydrogenation of (E)-β-(acylamino)acrylates, affording both excellent to almost perfect R-enantioselectivity and remarkably high catalytic efficiency (Scheme 12).<sup>[75]</sup> The reaction proceeds smoothly, and is tolerant to both change in solvent and variation in the nature of the substituents (ester and alkyl groups) of the starting substrate. The electron-rich character of BisP\* and MiniPHOS results in an increased affinity of their rhodium complexes to dihydrogen and thus faster hydrogenation as compared to BICP or (R,R)-Me-DuPHOS.<sup>[44]</sup> In contrast, the hydrogenation of the corresponding (Z)-isomers required high pressure and long reaction time, and afforded only moderate S-enantioselection.<sup>[75]</sup>

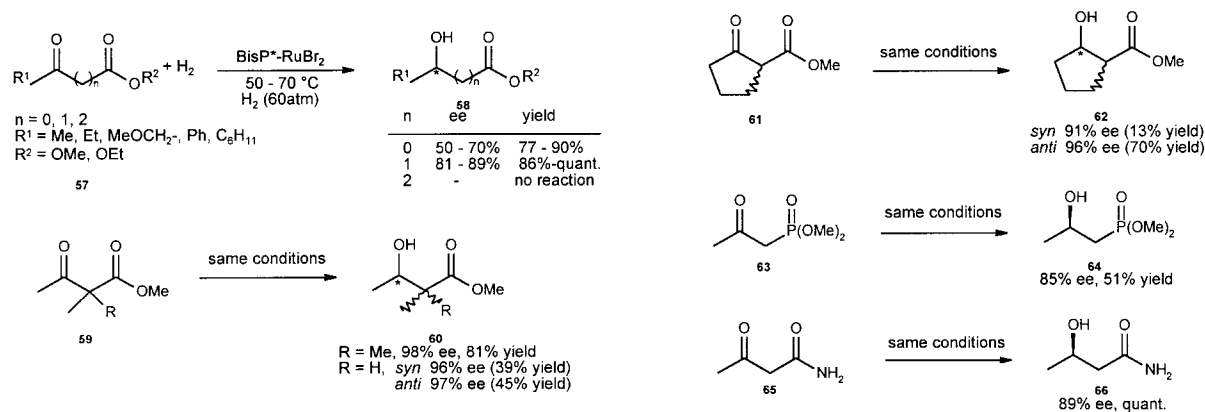
Interestingly, the sense of the enantioselection of the asymmetric hydrogenation of (E)-β-dehydroamino acids is opposite to that found in the corresponding α-analogues.<sup>[13,15,57]</sup> The origin affording the opposite enantioselection was clarified by the means of NMR experiments, as will be discussed in Section 6.2.

#### 4.1.4 Structurally Flexible Ligands

It is well-known that the most successful catalysts including in their structure chiral ligands with backbone chirality contain seven-membered chelate cycles (e.g., DIOP **17**<sup>[29]</sup> and BINAP **19**<sup>[34]</sup>), whereas those bearing P-chirogenic or pseudo-chiral phosphorus atoms contain



**Scheme 11.** Synthesis of the key intermediate of SDZ-ENA-713.



**Scheme 13.** Ru-catalyzed enantioselective hydrogenation of keto esters.

five-membered chelates (e.g., DIPAMP **1**,<sup>[31]</sup> DuPHOS **21**,<sup>[38]</sup> BisP\* **3**<sup>[13]</sup>). Therefore, we recently prepared the novel P-chirogenic diphosphine **11**, the rhodium-chelate complex of which forms a seven-membered ring.<sup>[22]</sup> The X-ray structure of this complex reveals a very distorted chelate ring, in which the two identical alkyl groups born on each phosphorus atom (the two *t*-butyl on the one hand and the two methyl on the other hand) become unequivalent (one is pseudo-equatorially positioned and the other one occupies a pseudo-axial position).<sup>[22]</sup> The catalytic potential of this new ligand was surveyed in asymmetric hydrogenations of four structurally different olefins. Thus, methyl (*Z*)- $\alpha$ -acetamidocinnamate (**28**, with  $R^1 = \text{H}$ ,  $R^2 = \text{Ph}$ ,  $R^3 = \text{Me}$  and  $R^4 = \text{Me}$ ) and 1-acetamido-1-phenylethene (**26a**, with  $R^1 = R^2 = \text{H}$  and  $\text{Ar} = \text{Ph}$ ) gave modest enantioselection (*R*-hydrogenation products, 68% and 76% ee, respectively), whereas 2-acetamido-3,3-dimethyl-1-butene (**26b**, with  $R = t\text{-Bu}$ ) and dimethyl 1-benzoyloxyethenephosphonate **98** afforded very low ee (*S*-hydrogenation products, 37% and 19% ee, respectively).<sup>[22]</sup> Similarly, Rh-catalyzed hydrogenation of **28** with structurally flexible 1,3-bis(*tert*-butyl(methyl)phosphino)propane **12** and its silicon-substituted derivative **13** (Figure 1) proceeded very rapidly. However, almost racemic products were obtained (14% and 0% ee, respectively), suggesting that the conformational flexibility of the six- or seven-membered chelate ring favoring conformations deviating from  $C_2$ -symmetry is a detrimental factor to high enantioselectivity.<sup>[23]</sup>

#### 4.2 Ru-Catalyzed Asymmetric Hydrogenation $\beta$ -Keto Esters using BisP\*

The broad applicability of BisP\* complexed to a transition metal was further exemplified by the ruthenium-catalyzed asymmetric hydrogenation of keto esters,<sup>[76]</sup> which has been the subject of various re-

ports.<sup>[2,3,77]</sup> The BisP\*-RuBr<sub>2</sub> precatalyst was readily prepared by reaction between BisP\* and Ru(2-methylallyl)<sub>2</sub>(COD), followed by treatment with methanolic HBr, as reported by Burk et al. for the preparation of BPE-RuBr<sub>2</sub> complex.<sup>[39c,78]</sup> Several kinds of keto esters were subjected to asymmetric hydrogenations under mild conditions (6 atm H<sub>2</sub>, 50–70 °C), yet only  $\beta$ -keto esters were smoothly hydrogenated, with high chemical yields and enantioselectivities up to 98% (Scheme 13). In contrast,  $\alpha$ -keto esters gave hydrogenation products of moderate ee, whereas  $\gamma$ - and  $\delta$ -derivatives remained unreactive even under harsh conditions. The general trend was that the best ees were obtained with *t*-Bu-BisP\*.  $\beta$ -Keto amides and  $\beta$ -keto phosphonates provided also high enantioselectivities. Given the fact that  $\alpha$ -mono- or  $\alpha$ -disubstituted- $\beta$ -keto esters were smoothly hydrogenated providing excellent results in terms of chemical and optical yields (Scheme 13), it seems that the hydrogenation catalyzed by BisP\*-Ru complex proceeds *via* a keto form rather than enol form.<sup>[76,79]</sup> Finally, the BisP\*-Ru complex enabled the synthesis of ethyl (*S*)-3-hydroxy-3-phenylpropionate, which is a key intermediate for the synthesis of (*R*)-(-)-tomoxetine (an anti-depressant and an agent for urinary disorder),<sup>[80]</sup> with 85% ee and in reasonable yield. Note also that the Ru-BIPNOR complex permitted ees between 74 and 95% in the hydrogenation of acetophenone and acetophenanthone.<sup>[12]</sup>

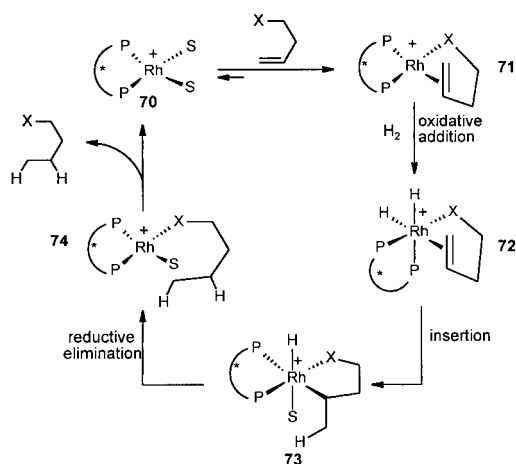
These studies revealed that rhodium(I) complexes of BisP\* and MiniPHOS have enabled the achievement of high optical yields for a wide series of substrates together with an attractive catalytic activity. Consequently, these catalysts are now ranged amongst the leading catalysts employed in asymmetric catalytic hydrogenation reactions. These results promoted mechanistic studies, which are the focus of the following sections.

## 5 Mechanism of Enantioselective Hydrogenation Catalyzed by Chiral Rh-Complexes: General Considerations

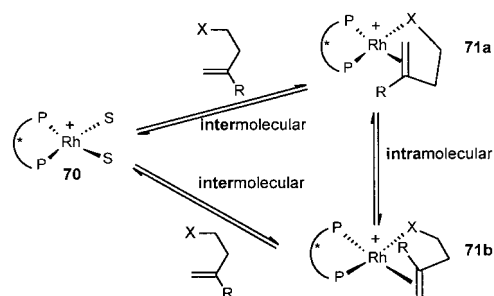
Wilkinson first reported that hydrogenation of  $\text{RhCl}(\text{PPh}_3)_3$  generates a stable dihydride complex,  $\text{RhH}_2\text{Cl}(\text{PPh}_3)_3$ ,<sup>[81]</sup> prior to coordination of the substrate.<sup>[25]</sup> On the other hand, Halpern et al. did not detect any stable hydride complexes upon hydrogenation of  $[\text{Rh}(\text{dppe})(\text{nbd})]\text{BF}_4$ , and observed dimer **68**, which dissociated in solution to produce solvate complex **69** (Scheme 14).<sup>[82]</sup> Further evidence showed that hydrogenation of rhodium(I) complexes containing diphosphine ligands generally produces the complexes of the type **69**,<sup>[60,83–87]</sup> while *trans*- and *cis*-chelating diphosphine rhodium complexes should be differentiated. Indeed, the formation of a dihydride complex has been observed for diphosphine ligands capable of *trans*-coordination,<sup>[88,89]</sup> suggesting that addition of the dihydrogen to rhodium precedes the alkene association (hydride mechanism).<sup>[90,91]</sup> In contrast, it seems that, in the case of diphosphines coordinating to the metal in a *cis*-fashion, alkene complexation is the primary addition step (unsaturated mechanism).<sup>[82,84,92,93]</sup>

The unsaturated mechanism for hydrogenation reaction depicted in Scheme 15 is generally accepted.<sup>[82,84,92,93]</sup> Typically, the alkene coordinates to the solvate complex **70** to produce catalyst-substrate complex **71**, many of which have been observed by spectroscopic methods<sup>[60,83,84,86,87,92,94–99]</sup> and X-ray crystallography.<sup>[82,84,100]</sup> Subsequently, molecular hydrogen oxidatively adds to the metal to furnish dihydride intermediate **72** from which insertion of one hydrogen atom to the olefin is possible, giving hydridoalkyl species **73**. Subsequent reductive elimination (addition of the other hydrogen atom) and solvation of the rhodium complex liberates the hydrogenation product.

When a chiral ligand is complexed to the transition metal, asymmetric addition of dihydrogen takes place due to the chiral environment imposed around the metal center. Moreover, when the diphosphine ligand exhibits  $C_2$  symmetry, as it is the case in the majority of the most successful ligands in the field of enantioselective hydrogenation, it has been demonstrated that the stereochemistry of the hydrogenation is controlled by the relative reactivity of the two possible diastereoisomers of catalyst-substrate complexes **71** (**71a** and **71b**) interconvert inter-<sup>[95,97]</sup> or intramolecularly,<sup>[94e,97]</sup> as depicted



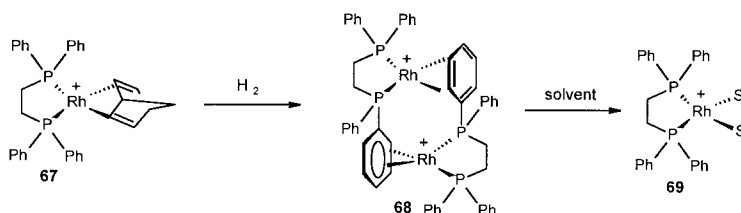
**Scheme 15.** Accepted unsaturated mechanism for the hydrogenation reaction.



**Scheme 16.** Interconversion of the catalyst-substrate complexes.

in Scheme 16), rather than their relative abundance.<sup>[93]</sup> Indeed, although only one diastereomer usually predominates in solution, the configuration of the product does not necessarily arise from the major diastereomeric complex present in solution. For example, at low temperature, the minor (i.e., less stable) diastereomer of the catalyst-substrate complex **71** of  $[\text{Rh}(\text{DIPAMP})]^+$  and methyl (*Z*)- $\alpha$ -acetamidocinnamate **28** ( $\text{R} = \text{Me}$ ) was shown to be much more reactive than the major one.<sup>[94]</sup> In the case of CHIRAPHOS and ethyl (*Z*)- $\alpha$ -acetamidocinnamate **28** ( $\text{R} = \text{Et}$ ), spectroscopic evidence also confirmed that the configuration of the hydrogenation product was irrelevant to the configuration of the major diastereomer.<sup>[84,101]</sup>

Therefore, it is generally believed that the interconversion of the diastereoisomers **71** as well as the



**Scheme 14.** Hydrogenation of  $[\text{Rh}(\text{dppe})(\text{nbd})]\text{BF}_4$ .

oxidative addition of dihydrogen are very important parameters to take into consideration for understanding the mechanism and to explain variation in enantioselectivity.

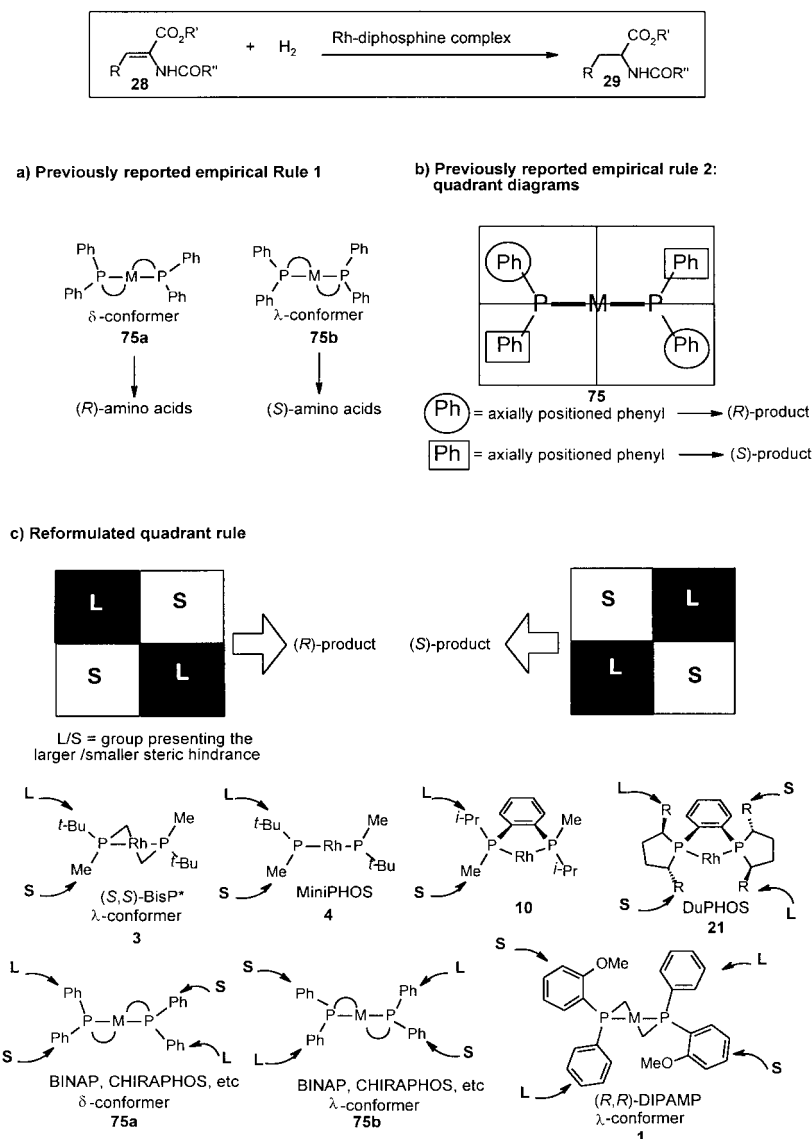
## 6 Origin of High Enantioselectivity

### 6.1 Empirical Rules

In terms of ligand design, it is necessary to ask oneself an important question: “which properties are responsible for very high enantioselectivity in hydrogenation reactions?”. Given the fact that the origin of the enantioselectivity is still not yet fully understood, empirical rules to predict the stereochemical outcome of rhodium-cata-

lyzed hydrogenation reactions employing diphosphine ligands have been proposed. Because theoretical studies are generally accepted until ruled out by experimental evidence, it is considered safe to start the discussion on the mechanism of hydrogenation with speculated conclusions.

In the early history of the hydrogenation, Fryzuk and Bosnich prepared (*S,S*)-CHIRAPHOS **18**, the rhodium chelate of which is chiral and fixed in a stable  $\delta$ -conformation, due to the quasi-equatorial disposition of the methyl groups.<sup>[32]</sup> Because this complex produced only (*R*)-*N*-acylamino acids in hydrogenation reactions, they speculated that (*R*)-PROPHOS **25**, the rhodium chelate of which presents a stable  $\lambda$ -conformation [i.e., opposite chirality of (*S,S*)-CHIRAPHOS], would give only (*S*)-*N*-acylamino acids.<sup>[45]</sup> Their assumption proved correct,<sup>[45]</sup> and similar observations were reported by



**Figure 3.** Empirical rules explaining the enantioselection.

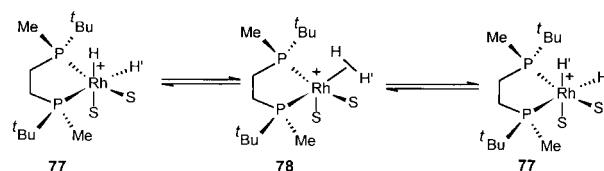
Kagan for other ligands.<sup>[102]</sup> These experimental facts developed into a very general empirical rule (Figure 3a), which was supported by X-ray data.<sup>[103]</sup>

The origin of enantioselection in transition metal-catalyzed asymmetric hydrogenation reactions employing  $C_2$ -symmetric chelating diphosphine bearing aryl substituents on each phosphorus atom (chirality located on the backbone) has also been predicted using an additional empirical rule, most commonly known as the “quadrant diagrams” (Figure 3b).<sup>[31]</sup> The chiral environment of the rhodium atom is divided into symmetry-related pairs of quadrants, in which the two  $C_2$ -correlated pairs of phenyls take positions to constitute a sterically different “wall” to the approach of the substrate. The two phenyls axially disposed expose their edge to the substrate, whereas the two phenyls equatorially disposed expose their face, and such a difference in orientation was considered to be the most important stereoregulating tool. Thus, when the upper left and bottom right quadrant are occupied with axial phenyls, (*R*)-amino acids are produced and the opposite combination gives the opposite enantioselection.

Since the majority of the mechanistic studies had been carried out for the catalysts with diarylalkylphosphine ligands, these rules seemed to correlate well with the reality. Unfortunately, contradictory results were obtained with newly designed electron-rich (trialkyl-substituted) diphosphine ligands. For instance, although the  $[\text{Rh}((S,S)\text{-}t\text{-Bu-BisP}^*)(\text{nb})]\text{BF}_4$  chelate shows a  $\lambda$ -conformation, (*R*)-amino acids were produced in excellent ees.<sup>[13]</sup> Moreover, predictions made by applying the quadrant rule to the rhodium complex of, for example, (*R,R*)-Me-DuPHOS,<sup>[38]</sup> (*S,S*)-*t*-Bu-BisP\*,<sup>[13]</sup> (*R,R*)-*t*-Bu-MiniPHOS,<sup>[15]</sup> (*S,S*)-1,2-bis(isopropylmethylphosphino)benzene,<sup>[21]</sup> BPE,<sup>[38]</sup> and BIPNOR<sup>[12]</sup> do not correlate to experimental facts. Following the classification of Knowles<sup>[31]</sup> and considering our new mechanistic findings,<sup>[104]</sup> the quadrant rule was reformulated and thus made applicable to both catalysts with backbone chirality and P-stereogenic catalysts (Figure 3c).<sup>[104]</sup> That is: (i) bulky substituents born on the phosphorus atoms and disposed in the upper-left corner and bottom-right quadrant produce *R*-stereoselectivity; (ii) the opposite orientation gives hydrogenation products of opposite (*S*)-absolute configuration; (iii) in the case where all four substituents present the same or a similar steric bulk, the quasi-axially disposed substituents should be regarded as the bulky groups.

## 6.2 Mechanistic Studies with BisP\*

Because the complete understanding of the mechanism of enantioselection in asymmetric hydrogenation certainly provides useful hints about the design of the ligands, extensive studies have been carried out over the last three decades, especially with bis(diarylalkylphos-



**Figure 4.** Inter-exchange of the hydrides in the hydrogenated catalyst.

phine) ligands.<sup>[1]</sup> Only very recently mechanistic studies with DuPHOS were undertaken.<sup>[39],105]</sup> Previous suggestions were based on accumulated experimental facts rather than the study of intervening species. However, neither reasons for the exceptionally high activity of the bis(trialkylphosphine)-based catalysts nor rules that govern the stereoselection were well understood. Therefore, we undertook the mechanistic study on asymmetric hydrogenation using the rhodium complexes of BisP\* and MiniPHOS. We also searched for a correlation between the observed stereochemistry of the products and the properties of the characterizable intermediates using extensive hydrogenation data and analyzing a wide series of intermediates. Before considering in detail the mechanistic issues for asymmetric induction, it is deemed necessary to bring some background on exchanges occurring between the catalyst and the different species involved in the process. Initial focus is devoted to BisP\*-rhodium complexes.

### 6.2.1 Hydrogenation of $\alpha$ -Dehydroamino Acids

#### 6.2.1.1 Hydrogenation of the Precatalyst

Usually the solvated Rh(I)-diphosphine complexes are readily generated by hydrogenation of appropriate catalytic precursors, and  $[\text{Rh}(\text{BisP}^*)(\text{nb})]\text{BF}_4$  **50** is no exception. Thus, this complex was hydrogenated in deuteriomethanol at  $-20^\circ\text{C}$  to produce a solvate complex  $[\text{Rh}(\text{BisP}^*)(\text{CD}_3\text{OD})_2]\text{BF}_4$  **76**, the spectral characteristics of which were demonstrated by multinuclear NMR (Scheme 17).<sup>[104]</sup> We demonstrated that upon hydrogenation at  $-90^\circ\text{C}$ , the solvate complex **76** reacts stereoselectively and reversibly with dihydrogen to afford the two isomeric dihydrides **77** and **77'** in *ca.* 10:1 ratio in equilibrium with **76** and dihydrogen.  $[\text{RhH}_2(\text{BisP}^*)(\text{CD}_3\text{OD})_2]$  (**77**) constitutes the first observable dihydride of a rhodium(I) complex with a diphosphine ligand.<sup>[104]</sup> The electron-rich character of the phosphorus atoms was believed to be responsible for the stability of the octahedral dihydride complex **77**, and a rather rapid equilibration between **76** and **77** was observed. The hydrides in **77** can interchange their positions without complete dissociation of the hydrogen *via* intermediate **78** (Figure 4), as suggested by a previously reported mechanism for a structurally related  $[\text{RhH}_2(\text{P}(\text{CH}_2\text{CH}_2\text{PPh}_2)_3)]^+$  complex<sup>[106]</sup> and com-

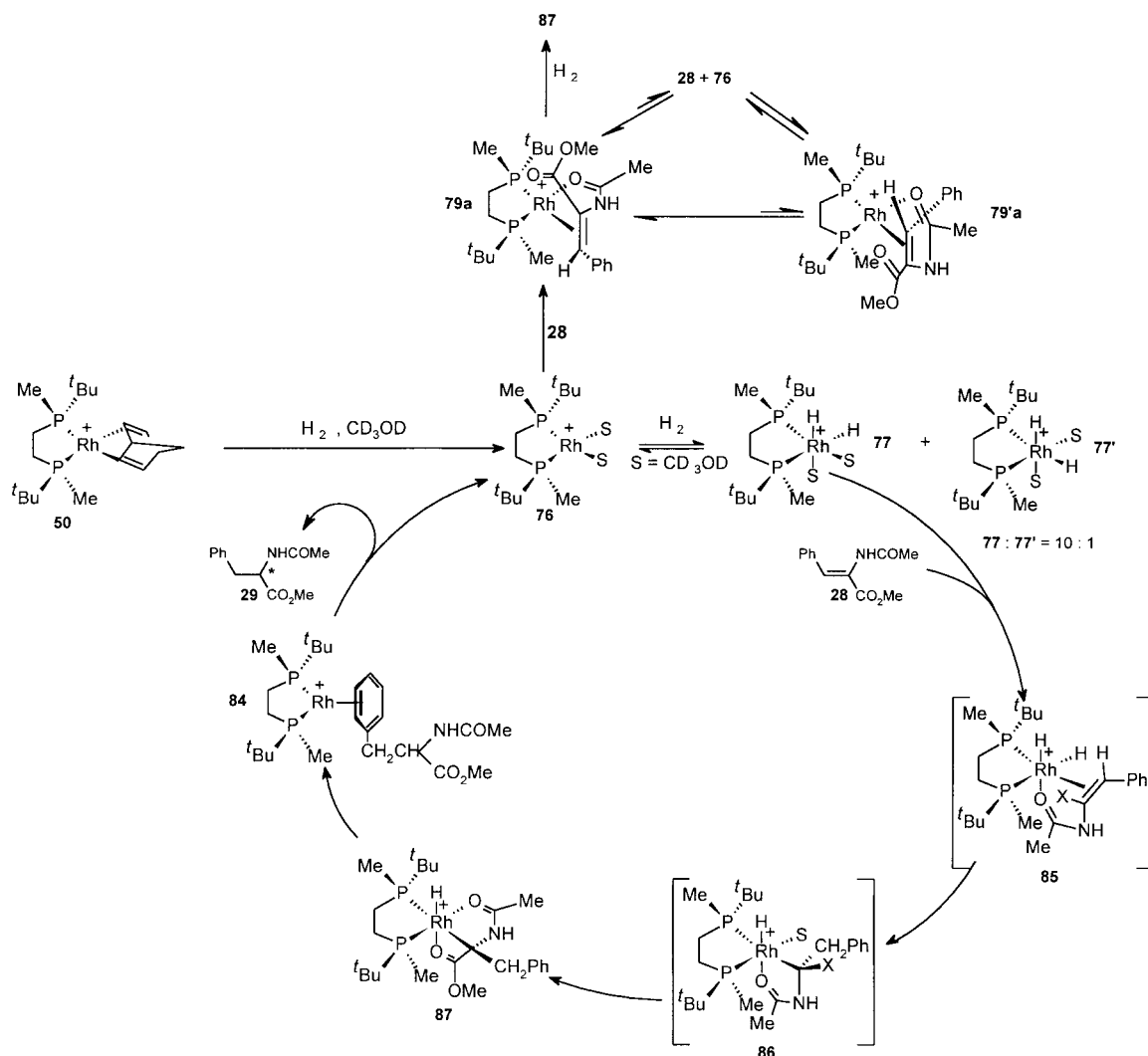
putational studies.<sup>[107]</sup> The stereoselectivity observed in the hydrogenation catalyzed by BisP\*-Rh complex is likely to be governed by the steric factors rather than the electronic properties of the ligand.<sup>[104]</sup>

### 6.2.1.2 Catalyst-Substrate Complex

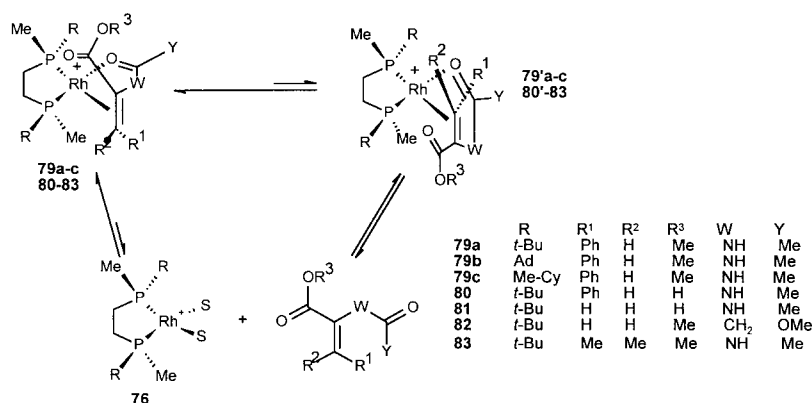
The catalyst-substrate complexes can also easily be produced by adding the substrate to a solution of a solvate complex. We studied the dynamic behavior of several catalyst-substrate complexes, produced by the reaction between a series of  $\alpha$ -hydroxycarbonyl- or  $\alpha$ -alkoxycarbonyl-substituted enamides and itaconic esters and precursor **50** containing bisP\* bearing different alkyl groups (Scheme 18).<sup>[57,104]</sup> NMR studies confirmed that the substrate is bound to the metal by both the alkene double bond and the amide group. As mentioned earlier in the general description of the mechanism of hydrogenation, diastereomers **79a** and **79'a** interconvert both inter- and intramolecularly *via* a complete and rapid dissociation-recoordination process between the

substrate and solvate complex **76**. Observation of spectral data of the major isomer **79** gave enough reasons to assign their structures and deduce that the enamides are in all cases reassociated in equilibrium. However, *R*-amino acids are produced in excellent enantioselectivity, confirming conclusions drawn from the asymmetric hydrogenation with other bis(diarylalkylphosphine)Rh(I) complexes where the major diastereomer's conformation is not necessarily the stereo-determining parameter.

The dynamic behavior of the catalyst-substrate **80**, from the coordination of (*Z*)- $\alpha$ -acetamidocinnamic acid **28** to **76**, is somewhat more complex, and a tetracoordination (binding by the double bond, the carboxylic and acetamido groups)<sup>[94b]</sup> has been proposed.<sup>[57]</sup> In contrast to the strong binding observed in complexes **79a–c** and **81**, dimethyl itaconate binds to the metal more weakly (catalyst-substrate **82**) and the equilibrium concentration of free **76** is mainly observed (Scheme 18). The dynamic behavior of **82** depends on the temperature, as previously reported.<sup>[108]</sup>



**Scheme 17.** Dihydride mechanism of asymmetric hydrogenation.



**Scheme 18.** Catalyst-substrate complexes.

Although the solution behaviors of the bisP\*-substrate complexes **79a–c** and **80–82** differ in many respects, methyl (*Z*)- $\alpha$ -acetamidocinnamate, (*Z*)- $\alpha$ -acetamidocinnamic acid,  $\alpha$ -acetamidoacrylic acid, and dimethyl itaconate all afford excellent enantioselectivities (over 98%), strongly suggesting that the dynamic behavior of the catalyst-substrate is not the stereo-regulating tool in the asymmetric hydrogenation catalyzed by **76**. However, reasonably strong binding is believed to be necessary for the success of asymmetric hydrogenation, as testified by the poor selectivity obtained with the catalyst-substrate **83** [from methyl  $\beta,\beta$ -dimethyl( $\alpha$ -acetamido)acrylate and **76**] in which very poor substrate binding was found.<sup>[57]</sup>

#### 6.2.1.3 Catalyst-Product Complex

NMR evidence showed that solvate complex **76** is able to weakly coordinate reversibly with the hydrogenation product to produce a  $\eta^6$ -aryl catalyst-product complex **84**, as exemplified by the hydrogenation of methyl (*Z*)- $\alpha$ -acetamidocinnamate depicted in Scheme 17.<sup>[104]</sup>

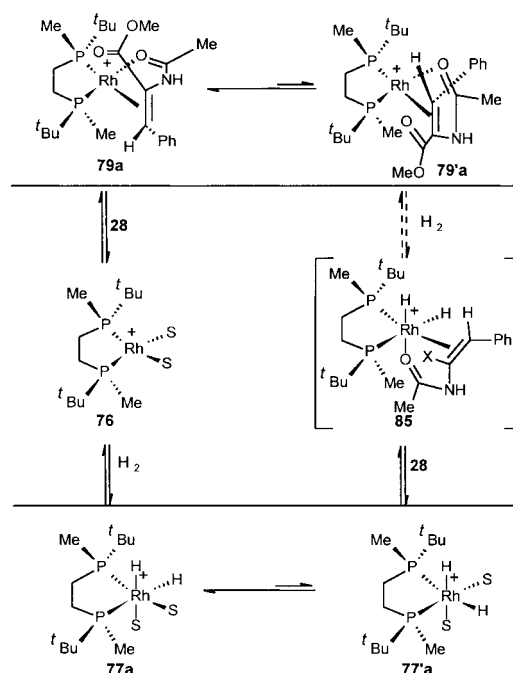
With the nature of the intermediates produced from the reactions between the catalyst, H<sub>2</sub>, the substrate, or the product, it is possible to examine more closely the mechanism of asymmetric hydrogenation as well as the origin of the stereoselection. The enantioselective hydrogenation of methyl (*Z*)- $\alpha$ -acetamidocinnamate (**28**, with R<sup>1</sup> = H, R<sup>2</sup> = Ph, R<sup>3</sup> = Me and R<sup>4</sup> = Me) serves as illustration.

#### 6.2.1.4 Dihydride Mechanism of Asymmetric Hydrogenation

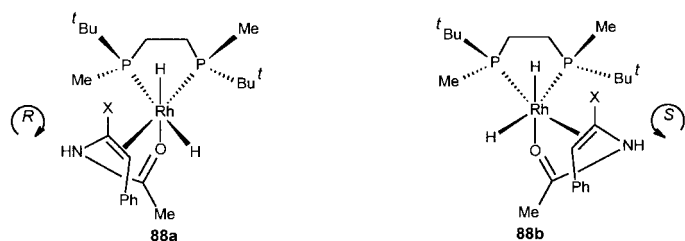
We demonstrated by multinuclear NMR studies that dihydride **77** itself rapidly reacts with methyl *N*-acetylcinnamate (MAC) **28** to generate the hydrogenation product **29** in 99% ee, accompanied with solvate complex **76** and  $\eta^6$ -arene complex **84**.<sup>[104]</sup> Careful observations led to firm conclusions that dihydride **77** coordinates to a molecule of MAC **28** giving rise to the

existence of a considerably unstable dihydride **85** which rapidly converts into a new monohydride species, likely to be isomer **86**, by migratory insertion. Rearrangement (rotation around the Rh–C bond) of **86** into the more stable **87**, in which both carbonyl groups coordinate to the rhodium metal, and subsequent reductive elimination complete the catalytic cycle (Scheme 17).

On the other hand, it was found that hydrogenation of the catalyst-substrate complex **79** also produces monohydride **87**, though at a much smaller kinetic rate even at higher temperature (Scheme 19). The slowness of the process is attributed to a slow and reversible dissociation of **79** to generate **76** which is then hydrogenated to dihydride complex **77**, which immediately reacts with the substrate **28** as mentioned earlier (Scheme 19).



**Scheme 19.** Hydrogenation of the catalyst-substrate complexes.



**Figure 5.** Origin of the stereoselection in the asymmetric hydrogenation of dehydroamino acid derivatives.

Direct hydrogenation of **79** might also be envisaged. Nevertheless, it is reasonable to consider that the dihydride mechanism (i.e., addition of hydrogen to rhodium precedes the alkene association) is favored as compared to the unsaturated mechanism (i.e., addition of the alkene precedes the  $H_2$  addition) owing to the considerably high reactivity of **77**, even at  $-100\text{ }^\circ\text{C}$ .

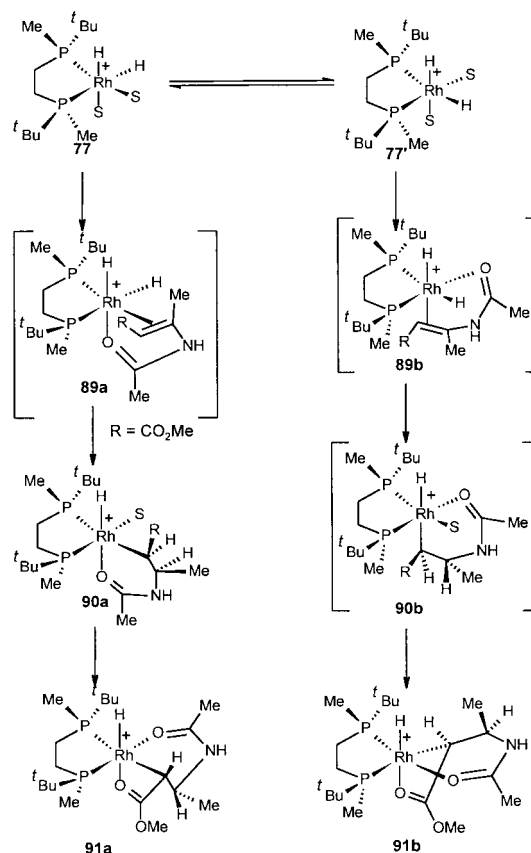
Whether hydrogenation proceeds *via* **77** + **28** or **79** +  $H_2$  (or by equilibrium phenomenon between them), the same monohydride intermediate **87** and the same high (*R*)-stereoselectivity are produced, suggesting that the enantiodetermining step is the migratory insertion (i.e., very unstable intermediate **85**).<sup>[104]</sup>

Interestingly, the isomer ratio of monohydrides **87** correlates almost perfectly with the ee measured in the catalytic hydrogenation,<sup>[104]</sup> showing evidence, and in agreement with computational results,<sup>[109]</sup> that the migratory insertion step is indeed the stereodetermining step. This conclusion would be ruled out in the case of a reversible reaction. This ambiguity prompted isotope-labeling experiments. Indeed, deuteration studies provide an efficient way to understand mechanistic pathways. For example, the reversibility or not of a step involved in the mechanism may be investigated by simple analysis of the products of catalytic deuteration: unequal distribution of deuterium between two sites attests to reversibility.<sup>[110,111]</sup> In the case of the present study, the complete absence of deuterium scrambling demonstrated the irreversibility of this step.<sup>[57]</sup>

As for the origin of the stereoselection, the nature of the alkyl group in close contact to the incoming substrate is proposed to be responsible for the discrimination of **88a** (interaction with the methyl substituent) and **88b** (interaction with the bulky *t*-butyl substituent), which are the only two precursors (among eight possible ones) to the observed  $\alpha$ -alkyl monohydride with *trans*-positioned hydride and oxygen atoms (Figure 5).<sup>[104]</sup> It becomes clear that migratory insertion occurring on **88a** is energetically preferred. Migratory insertion from this intermediate also predicts (*R*)-stereoselectivity. In other words, the main stereoregulating factor is the minimization of the steric repulsion in the unstable dihydride intermediate between the chelate ring made by the substrate and one of the alkyl groups of the ligand.<sup>[104]</sup>

## 6.2.2 Hydrogenation of $\beta$ -Dehydroamino Acids

In the case of the rhodium-catalyzed hydrogenation of  $\beta$ -dehydroamino acids, low-temperature NMR experiments testified that monohydrides with the  $\beta$ -carbon atom of the substrate bound to the rhodium (i.e., the first hydrogen atom is transferred to the  $\alpha$ -position) are involved in the catalytic cycle,<sup>[75]</sup> whereas hydrogenation of  $\alpha$ -dehydroamino acids takes place in the opposite manner. In this case, the following plausible mechanism was suggested (Scheme 20): the two solvent molecules in solvate dihydride **77** (equilibrium between isomers **77** and **77'**) are substituted for the double bond and the amide carbonyl group to produce **89a** and **89b**, which are the only diastereomeric dihydride precursors of  $\beta$ -bound monohydrides with *R*-configuration at the  $\alpha$ -carbon atom. Migratory insertion leads to monohydride intermediates **90a** and **90b**, which rapidly isomerize to produce the more stable **91a** (terdentate coordination) and **91b**, respectively. NMR data testified that the structures of monohydrides **90**–**91** are  $\beta$ -monohydrides and that the hydrides occupy a position *trans* to the electronegative oxygen atom.<sup>[75]</sup> After reductive elimination, all these intermediates liberate the hydrogenation product with *R*-configuration at the  $\alpha$ -carbon atom, justifying the high ee (98%) obtained, and regenerate solvate complex **77**.



**Scheme 20.** Suggested mechanism of asymmetric hydrogenation of  $\beta$ -dehydroamino acid derivatives.



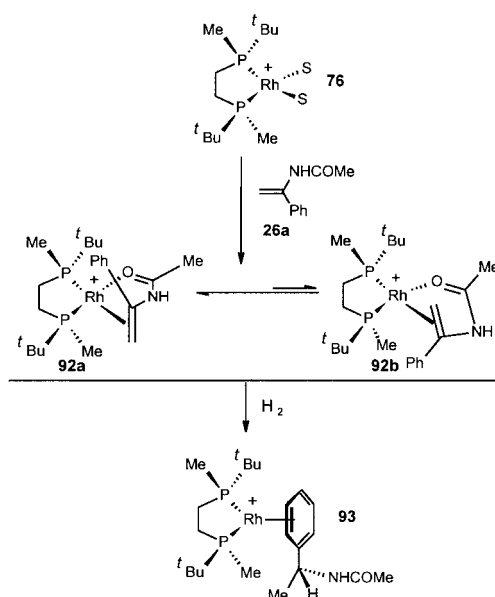
### 6.2.3 Hydrogenation of Phenyl- and *t*-Butyl-Substituted Enamides

As mentioned previously in Section 4.1.2, a completely different substrate discrimination is observed in the asymmetric hydrogenation of aryl-substituted enamides and enamides bearing bulky alkyl groups, provoking a total switch in the sense of stereoselection.<sup>[39d,64,66]</sup> Therefore, we carried out isotope-labeling experiments to rationalize this striking difference.<sup>[65]</sup>

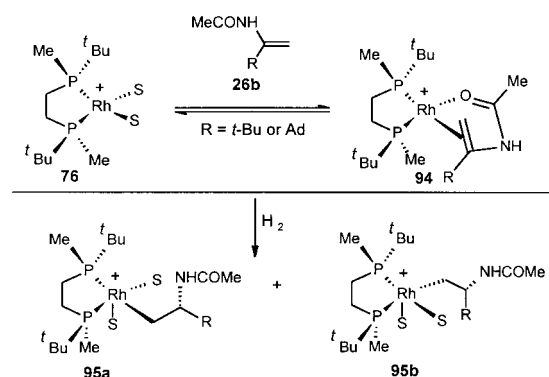
#### 6.2.3.1 Observed Intermediates

Similarly to dehydroamino acids, enamides form a catalyst-substrate in the presence of solvate complex **76**. In the case of phenylenamide **26a**, two diastereomers of tightly bound catalyst-substrate complexes **92** in a ratio depending on the temperature are produced (Scheme 21). Spectral evidence showed that, quite unexpectedly, **92a** is the major isomer, suggesting that the phenyl ring spatially places itself in such a way to minimize steric interactions with the bulky *t*-butyl group. Isomers **92a** and **92b** are in equilibrium and interconvert *via* both intra- and intermolecular pathways, as demonstrated earlier in the case of complexes of dehydroamino acids.<sup>[57,95,97,104,112]</sup>

On the other hand, catalyst-substrate complexes **94** (Scheme 22), obtained similarly by reacting **76** and enamide **26b** bearing bulky groups like *t*-Bu- or 1-Ad substituents, respectively, present a relatively weak binding of the double bond of the enamide to the metal, most likely owing to the bulkiness of the *t*-butyl and adamantyl groups. Therefore, complex **94** is in equilibrium with solvate complex **76**. Another striking differ-



**Scheme 21.** Observed intermediates in the asymmetric hydrogenation of 1-acetylamino-1-phenylethene.

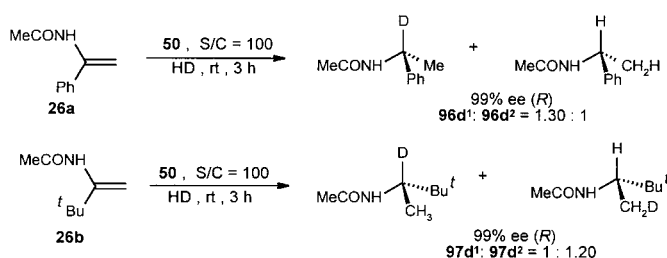


**Scheme 22.** Observed intermediates in the asymmetric hydrogenation of alkyl-substituted enamides.

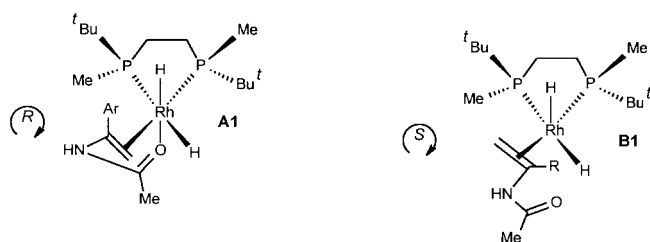
ence is the existence of solely one isomer **94**, the configuration of which was deduced from the DFT calculations of simplified molecules.<sup>[65]</sup> Moreover, although the catalyst-product complex **93** (in equilibrium with solvate **76**) was produced directly in the case of phenylenamides, formation of two isomers of the monohydride intermediates **95** (major **95a** and minor **95b**) were observed upon hydrogenation of **94** (in equilibrium with **76** and **26b**). Atom labeling and meticulous NMR research led to the conclusion that **95** is a monohydride complex in which the amide binds to the metal by the CH<sub>2</sub> group and that the  $\alpha$ -position is hydrogenated. A binding difference is observed in the coordination of **94** and **95** to the metal, in that the coordination of the carbonyl group of **94** to the metal is lost to give place to solvent coordination in **95a**. Monohydrides **95a** and **95b**, which are diastereomers with the same absolute configuration at the carbon atom, undergo reductive elimination with increase in temperature to afford the respective hydrogenation product and the regenerated solvate complex **76**.

#### 6.2.3.2 Mechanism of the Stereoselection

We undertook a mechanistic investigation with deuterium labeling (HD and D<sub>2</sub>).<sup>[64,65]</sup> The D-labeling experiments enable unambiguous conclusions. Indeed, if the interconversion of the isomeric intermediates is slower than the coordination of the substrate and the migratory insertion, the partitioning of deuterium should indicate the way the substrate coordinates to the metal. As mentioned earlier, the migratory insertion step is irreversible.<sup>[104]</sup> Further observation in the experiment using HD led to the conclusion that the deuterium distribution at  $\alpha$ - and  $\beta$ -positions in the products and intermediates obtained from **26a** and **26b** is unequal and opposite:<sup>[57,104,111]</sup> aromatic hydrogenated products are predominantly  $\alpha$ -deuterated, and the *t*-Bu-substituted enamide **26b** is predominantly  $\beta$ -deuterated, showing evidence that the stereochemical outcome of the reaction arises from different mechanistic pathways



**Scheme 23.** Unequal and opposite deuterium-partitioning in the hydrogenation of enamides.



**Figure 6.** Origin of the opposite enantioselection in the reduction of aryl- and alkyl-substituted enamides.

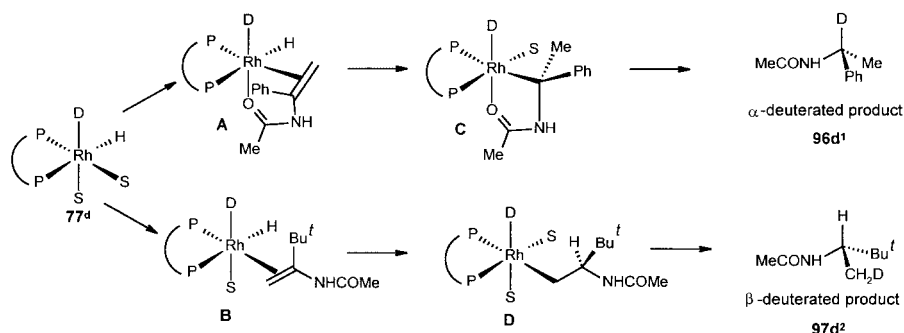
(Scheme 23).<sup>[64]</sup> As previously confirmed with NMR evidence,<sup>[104]</sup> the only coordination fashion of the enamide to the metal is the double bond binding at the equatorial position. Thus, an  $\alpha$ -deuterated product (aromatic enamides) originates from coordination of type **A** (Scheme 24), and most likely **A1** (Figure 6), since the steric interaction between the chelate ring made by the substrate and the adjacent alkyl group of the catalyst is minimized (stereoregulating factor). Products bound in such a fashion form a monohydride species bound to Rh by the tertiary carbon.<sup>[65]</sup> On the other hand, a  $\beta$ -deuterated product (enamides bearing the bulky *t*-butyl and adamantyl groups) originates from coordination of type **B** (most likely **B1** of Figure 6) and formation of a monohydride species bound to Rh by the  $\text{CH}_2$  group (Scheme 24). In other words, the mechanism of stereoselection for **26a** follows the same process as the one presented for methyl (*Z*)- $\alpha$ -acetamidocinnamate,<sup>[104]</sup> whereas the enhanced steric bulk imposed by the *t*-butyl group constrains the substrate to complex to

the metal in such a way that the amide carbonyl is not chelated in the monohydride intermediate **95**. This different mode of coordination explains the difference in stereoselectivity.

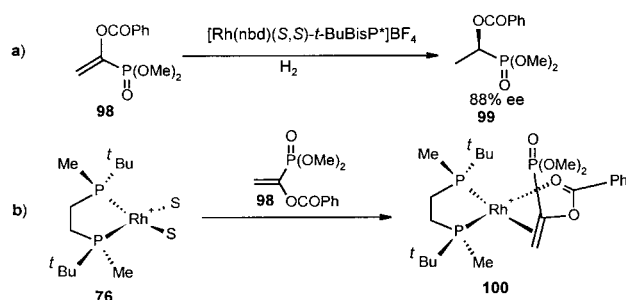
#### 6.2.4 Interconversion of the Monohydride Intermediates

The first experimental (NMR) evidence for the interconversion of the monohydride intermediates, which are, as discussed previously, the intermediates responsible for the observed enantioselection, was presented in the course of our studies of the Rh(I)-catalyzed asymmetric hydrogenation of dimethyl 1-benzoyloxyethenephosphonate **98** using *t*-Bu-BisP\* as the chiral ligand.<sup>[113]</sup> The corresponding (*S*)-product **99** was obtained with 88% ee (Scheme 25a), enantioselectivity which is comparable to those observed by Burk et al.<sup>[39]</sup> Generation of the catalyst-substrate complex **100** from reaction between phosphonate **98** and complex **76** is fast and irreversible, and we showed that the substrate binds to the metal by both the double bond and the benzoyloxy moiety (Scheme 25b). The reaction between dihydride **77**<sup>[104]</sup> and phosphonate **98** carried out at very low temperature affords the two monohydride intermediates **101a** and **101b** (in 100:5 ratio), which interconvert upon heating into **102a** and **102b** (respectively) via the non-chelating complexes **103a** and **103b** (respectively), as depicted in Scheme 26. However, no cross-exchange between **102a** and **102b** or **103a** and **103b** is observed. On the basis of isotope labeling and spectral evidence, the structures of monohydride intermediates **101–103** are as depicted in Scheme 26: the hydrides bind to the metal to adopt a *cis*-arrangement with both phosphorus atoms, and the  $\alpha$ -carbon atom is attached to the metal atom.

It is reasonable to consider that the monohydride intermediate **101** is the direct consequence of the unobservable dihydride intermediate **104** (not detectable due to the low energy barrier of the migratory insertion).<sup>[112,114]</sup> Furthermore, the isomer of type **a** is responsible for the (*S*)-absolute configuration observed



**Scheme 24.** Suggested mechanism of asymmetric hydrogenation of substituted enamides.



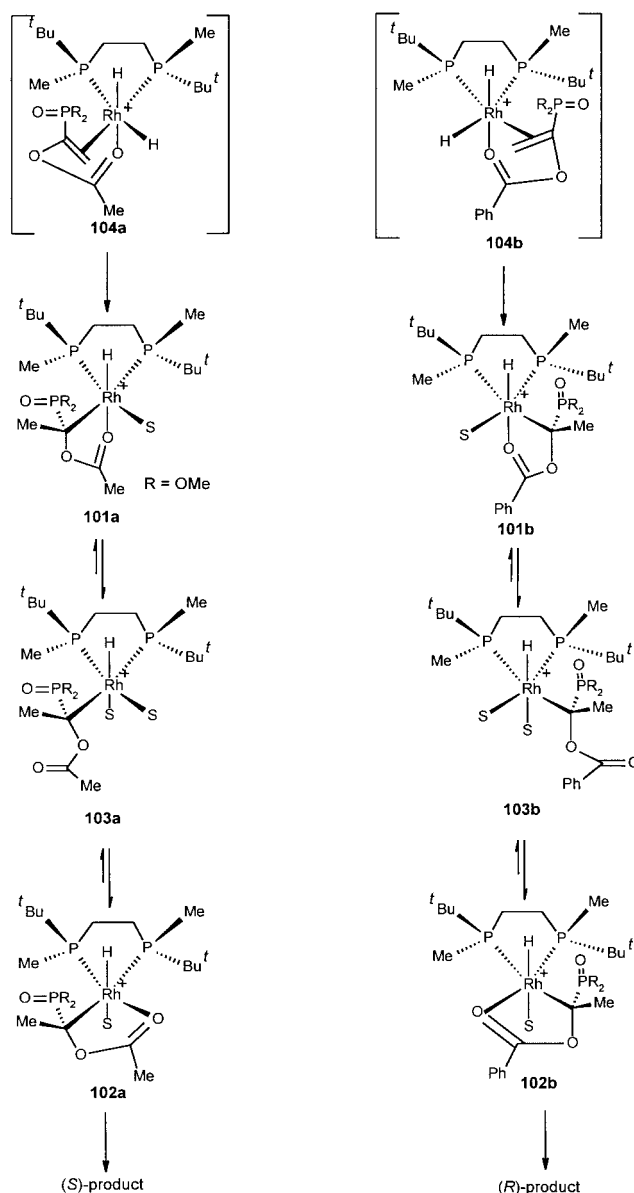
**Scheme 25.** a) Asymmetric hydrogenation of an ethene-phosphonate derivative. b) Catalyst-substrate complex.

in the hydrogenated product whereas the type **b** gives minor amounts of (*R*)-hydrogenation product. This stereoselection is actually expected if one considers that the increased steric hindrance disfavors the migratory insertion through the dihydride intermediate **104b**.

### 6.3 Reaction of Rh-MiniPHOS with $\text{H}_2$

Although the catalytic activity of the rhodium complex of MiniPHOS has shown to be lower than the corresponding BisP\* complex, very high enantioselectivities (up to 99.9%) have been achieved in asymmetric reactions.<sup>[15]</sup> X-ray analysis of the Rh-MiniPHOS complex shows a double coordination of the ligand to the metal, and the apparent lack of vacant coordination sites for subsequent substrate binding implies that the catalytic cycle completes through a process different from the one presented for BisP\*.

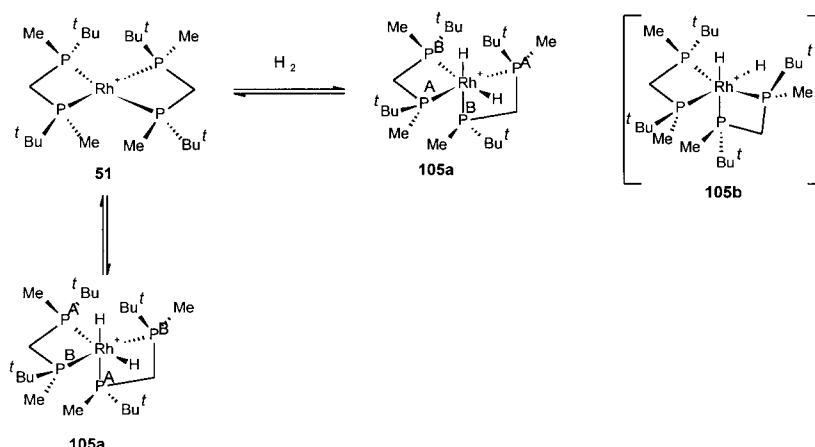
The structures of dihydride complexes of general formula  $[\text{RhH}_2(\text{Ph}_2\text{P}(\text{CH}_2)_n\text{PPh}_2)]^+\text{X}^-$  ( $n > 3$ ) containing six- or seven-membered chelate rings are isolable,<sup>[56,115,116]</sup> and it has been suggested that partial ligand dissociation occurred in the dihydride  $[\text{RhH}_2(\text{DIOP})_2]\text{BF}_4$  to free a coordinating site in the metal coordination sphere.<sup>[56]</sup> Because previously reported trials failed to produce any significant conclusions on the smaller corresponding ring chelates ( $n = 1, 2$ ), we undertook meticulous NMR and computational studies to understand the mechanism of rhodium-catalyzed hydrogenation employing MiniPHOS.  $[\text{Rh}((R,R)\text{-Me}(t\text{-Bu})\text{PCH}_2\text{PMe}(t\text{-Bu}))_2]\text{BF}_4$  in deuteriomethanol was hydrogenated at low temperature ( $-90^\circ\text{C}$ ) and examined by NMR. Data suggested that the two hydrogen atoms bind to the metal in a *cis*-fashion (*cis*-dihydride chelate **105**) and that only one of the two possible diastereomers is produced (Scheme 27).<sup>[117]</sup> The relative stability of **105**, as opposed to the failure in detecting other ring chelates of similar size,<sup>[56,115,116]</sup> can be attributed to the electron-rich character of this ligand, increasing the affinity of **51** to  $\text{H}_2$ .<sup>[107,118]</sup> Intensive theoretical calculations carried out on the optimized geometries of the Rh-diphosphine complex suggested that the steric strain imposed by



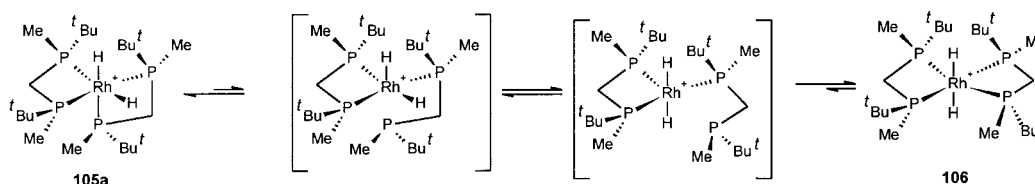
**Scheme 26.** Interconversion of monohydride intermediates.

double close contacts of the bulky *t*-butyl groups in **105b** is higher than in **105a**. The binding fashion of the hydride in isomer **105a** allows more space between one pair of *t*-butyl groups, and thus **105a** is less distorted and more stable. We also concluded that **105a** equilibrates relatively rapidly with **51** with exchange of the positions of the phosphorus atoms (Scheme 27).<sup>[117]</sup>

When Rh-MiniPHOS complex was hydrogenated at higher temperature ( $-20^\circ\text{C}$ ), *cis*-dihydride chelate **105a** was accompanied by *trans*-dihydride chelate **106** which gradually decomposes affording **51**. Because **106** can obviously not be obtained by direct oxidative addition of dihydrogen to **51**, the origin of **106** is likely to be the consequence of isomerization of **105a**, occurring *via* reversible dissociation and reorganization of the strained four-membered ring chelate



**Scheme 27.** Hydrogenation of the Rh-MiniPHOS precatalyst



**Scheme 28.** Isomerization of the hydrogenated Rh-MiniPHOS complex.

(Scheme 28).<sup>[118,119]</sup> The stability of **108** correlates to the rate for interconversion from **108** to **105a**, since direct reductive elimination to produce **51** is only possible *via* the *cis*-dihydride **105**.

The fact that  $[\text{RhH}_2(\text{MiniPHOS})_2]\text{BF}_4$  can be reversibly and stereoselectively hydrogenated to give either the *cis*-dihydride chelate **105a** at low temperature, or *cis*-**105a** in equilibrium with its *trans*-isomer **106**, suggests that the binding MiniPHOS to the rhodium metal is fairly weak and, as was previously reported by James et al. in the case of  $[\text{Rh}(\text{DIOP})_2]\text{BF}_4$ ,<sup>[56]</sup> one vacant coordination site is made available by partial dissociation of the ligand to allow complexation of the substrate. We also speculated that two free sites might be created by disconnection of the two phosphorus atoms in *trans*-position to the hydrides to produce a substrate-catalyst complex with two pendant ligands.<sup>[117]</sup> In conclusion, our studies demonstrated that the mechanism of the asymmetric hydrogenation catalyzed by MiniPHOS-Rh catalysts follows the pathway first suggested with the Wilkinson catalyst.<sup>[1,120]</sup>

## 7 Conclusion

We hope that, thanks to the numerous examples of asymmetric hydrogenation reactions analyzed in this review, the readers will become aware of the exciting potential of chiral phosphine ligands bearing the chiral center at the phosphorus atom. Exceedingly high enantioselectivity and great reactivity have been achieved using (mainly) new rhodium(I) complexes containing

P-chirogenic ligands such as BisP\* and MiniPHOS for a wide range of unsaturated substrates, most likely because of the direct contact between the chiral center and the transition-metal (i.e., the reaction site). These are among the most effective catalysts known today in this area. Considerable important findings regarding the mechanism of enantioselective hydrogenation have been reported recently. The electronic properties of the Rh-complexes of BisP\* and MiniPHOS stipulate the relative stability of the solvate dihydrides. Evidence for a dihydride mechanism has been supported by multinuclear NMR studies, ruling out the theory for the unsaturated mechanism accepted until now. Nonetheless, since the enantioselection is determined during the migratory insertion, i.e., at a later stage in the catalytic cycle, these striking findings do not interfere much with the former considerations.

Although DIPAMP was designed thirty years ago, it is not untrue to say that P-stereogenic ligands have a ten year history in terms of number of ligands synthesized and application in asymmetric reactions. Therefore, the full potential of these chiral catalysts has not been explored yet, but it is expected that exceptionally high enantio-, diastereo-, regio-, and chemoselectivities may be obtained in future.

## Acknowledgements

The authors are grateful to the European Commission (European Union Science and Technology Fellowship Programme in Japan–EU S&T FPJ 15) for the fellowship of K. V. L. C.

## References

- [1] J. M. Brown, in *Comprehensive Asymmetric Catalysis*, Vol. 1 (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **1999**, Chap. 5.1.
- [2] R. Noyori, *Asymmetric Catalysis in Organic Synthesis*, John Wiley & Sons, New York, **1994**.
- [3] T. Ohkuma, M. Kitamura, R. Noyori, in *Catalytic Asymmetric Synthesis*, 2nd edn., (Ed.: I. Ojima), Wiley-VCH, Weinheim, **2000**, Chap. 1.
- [4] J. K. Whitesell, *Chem. Rev.* **1989**, 89, 1581-1590.
- [5] H. Brunner, *Topics in Stereochemistry*, Vol. 18, (Eds.: E. L. Eliel, S. H. Wilen), John Wiley & Sons, New York, **1988**, 129-247.
- [6] Y. Yamanoi, T. Imamoto, *Rev. Heteroat. Chem.* **1999**, 20, 227-248.
- [7] *Asymmetric Catalysis*, (Ed.: B. Bosnich), Martinus Nijhoff Publishers, Dordrecht, **1986**.
- [8] H. B. Kagan, in *Asymmetric Synthesis*, Vol. 5, (Ed.: J. D. Morrison), Academic Press, New York, **1985**, Chap. 1.
- [9] K. E. Koenig, in *Asymmetric Synthesis*, Vol. 5, (Ed.: J. D. Morrison), Academic Press, New York, **1985**, Chap. 3.
- [10] J. M. Brown, P. A. Chaloner, in *Homogeneous Catalysis with Metal Phosphine Complexes*, (Ed. L. H. Pingolet), Plenum, New York, **1983**.
- [11] a) W. S. Knowles, M. J. Sabacky, B. D. Vineyard, D. J. Weinkauff, *J. Am. Chem. Soc.* **1975**, 97, 2567-2568; b) B. D. Vineyard, W. S. Knowles, G. L. Bachman, D. J. Weinkauff, *J. Am. Chem. Soc.* **1977**, 99, 5946-5952.
- [12] F. Robin, F. Mercier, L. Ricard, F. Mathey, M. Spagnol, *Chem. Eur. J.* **1997**, 3, 1365-1369.
- [13] T. Imamoto, J. Watanabe, Y. Wada, H. Masuda, H. Yamada, H. Tsuruta, S. Matsukawa, K. Yamaguchi, *J. Am. Chem. Soc.* **1998**, 120, 1635-1636.
- [14] A. Ohashi, T. Imamoto, *Tetrahedron Lett.* **2001**, 42, 1099-1101.
- [15] Y. Yamanoi, T. Imamoto, *J. Org. Chem.* **1999**, 64, 2988-2989.
- [16] W. Tang, X. Zhang, *Angew. Chem.* **2002**, 114, 1682-1684.
- [17] W. S. Knowles, M. J. Sabacky, B. D. Vineyard, *J. Chem. Soc. Chem. Commun.* **1972**, 10-11.
- [18] D. Moulin, C. Darcel, S. Jugé, *Tetrahedron: Asymmetry* **1999**, 10, 4729-4743.
- [19] U. Nagel, T. Krink, *Angew. Chem. Int. Ed. Engl.* **1993**, 32, 1052-1054.
- [20] D. Carmichael, H. Doucet, J. M. Brown, *Chem. Commun.* **1999**, 261-262.
- [21] T. Miura, T. Imamoto, *Tetrahedron Lett.* **1999**, 40, 4833-4836.
- [22] I. D. Gridnev, N. Higashi, T. Imamoto, *Organometallics* **2001**, 20, 4542-4553.
- [23] K. Nagata, T. Imamoto, unpublished results.
- [24] J. Halpern, in *Asymmetric Synthesis*, Vol. 5, (Ed.: J. M. Morrison), Academic Press, New-York, **1985**, Chap. 2.
- [25] J. A. Osborn, F. S. Jardine, J. F. Young, G. Wilkinson, *J. Chem. Soc. A* **1966**, 1711-1732.
- [26] L. Horner, H. Siegel, H. Buthe, *Angew. Chem. Int. Ed. Engl.* **1968**, 7, 942-942.
- [27] W. S. Knowles, M. J. Sabacky, *J. Chem. Soc. Chem. Commun.* **1968**, 1445-1446.
- [28] T. P. Dang, H. B. Kagan, *J. Chem. Soc. Chem. Commun.* **1971**, 481-481.
- [29] H. B. Kagan, T. P. Dang, *J. Am. Chem. Soc.* **1972**, 94, 6429-6433.
- [30] J. D. Morrison, R. E. Barnett, A. M. Aguiar, C. J. Morrows, C. Phillips, *J. Am. Chem. Soc.* **1971**, 93, 1301-1303.
- [31] W. S. Knowles, *Acc. Chem. Res.* **1983**, 16, 106-112.
- [32] M. D. Fryzuck, B. Bosnich, *J. Am. Chem. Soc.* **1977**, 99, 6262-6267.
- [33] A. Miyashita, A. Yasuda, H. Takaya, K. Toriumi, T. Ito, T. Souchi, R. Noyori, *J. Am. Chem. Soc.* **1980**, 102, 7932-7934.
- [34] R. Noyori, H. Takaya, *Acc. Chem. Res.* **1990**, 23, 345-350.
- [35] T. Ohta, H. Takaya, M. Kitamura, K. Nagai, R. Noyori, *J. Org. Chem.* **1987**, 52, 3174-3176.
- [36] a) R. Noyori, T. Ohkuma, M. Kitamura, H. Takaya, N. Sayo, H. Kumobayashi, S. Akutagawa, *J. Am. Chem. Soc.* **1987**, 109, 5856-5158; b) R. Noyori, T. Ohkuma, *Angew. Chem. Int. Ed.* **2001**, 40, 40-73.
- [37] K. Tani, T. Yamagata, S. Akutagawa, H. Kumobayashi, T. Taketomi, H. Takaya, A. Miyashita, R. Noyori, T. Otsuka, *J. Am. Chem. Soc.* **1984**, 106, 5208-5217.
- [38] M. J. Burk, J. E. Feaster, W. A. Nugent, R. L. Harlow, *J. Am. Chem. Soc.* **1993**, 115, 10125-10138.
- [39] a) M. J. Burk, J. E. Feaster, *J. Am. Chem. Soc.* **1992**, 114, 6266-6267; b) M. J. Burk, J. P. Martinez, J. E. Feaster, N. Cosford, *Tetrahedron* **1994**, 50, 4399-4428; c) M. J. Burk, T. G. P. Harper, C. Kalberg, *J. Am. Chem. Soc.* **1995**, 117, 4423-4424; d) M. J. Burk, Y. M. Wang, J. R. Lee, *J. Am. Chem. Soc.* **1996**, 118, 5142-5143; e) M. J. Burk, M. F. Gross, T. G. P. Harper, C. S. Kalberg, J. R. Lee, J. P. Martinez, *Pure Appl. Chem.* **1996**, 68, 37-44; f) M. J. Burk, C. S. Kalberg, A. Pizzano, *J. Am. Chem. Soc.* **1998**, 120, 4345-4353; g) M. J. Burk, J. G. Allen, F. Kiesman, *J. Am. Chem. Soc.* **1998**, 120, 657-663; h) M. J. Burk, F. Bienewald, M. Harris, A. Zanotti-Gerosa, *Angew. Chem. Int. Ed. Engl.* **1998**, 37, 1931-1933; i) M. J. Burk, T. A. Stammers, J. A. Straub, *Organic Letters* **1999**, 1, 387-390; j) M. J. Burk, F. Bienewald, S. Challenger, A. Derrick, J. Ramsden, *J. Org. Chem.* **1999**, 64, 3290-3298; k) M. J. Burk, K. M. Bedigfield, W. F. Kiesman, J. G. Allen, *Tetrahedron Lett.* **1999**, 40, 3093-3096.
- [40] M. J. Burk, in *Handbook of Chiral Chemicals*, (Ed.: D. J. Ager), Dekker, New York, **1999**.
- [41] M. J. Burk, *Acc. Chem. Res.* **2000**, 33, 363-372.
- [42] M. Sawamura, R. Kuwano, Y. Ito, *J. Am. Chem. Soc.* **1995**, 117, 9602-9603.
- [43] P. J. Pye, K. Rossen, R. A. Beamer, N. N. Tsou, R. P. Volante, P. J. Reider, *J. Am. Chem. Soc.* **1997**, 119, 6207-6208.
- [44] G. Zhu, Z. Chen, X. Zhang, *J. Org. Chem.* **1999**, 64, 6907-6910.
- [45] M. D. Fryzuck, B. Bosnich, *J. Am. Chem. Soc.* **1978**, 100, 5491-5494.

- [46] J. C. Danilewicz, M. T. Williams, *Eur. Patent* 0342850; *Chem. Abstr.* **1990**, 112, 197688r.
- [47] I. T. Barnish, J. C. Danilewicz, K. James, G. M. B. Samuels, N. K. Terrett, M. T. Williams, M. J. Wythes, *U. S. Patent* 5,192,800, **1993**.
- [48] M. J. Burk, *J. Am. Chem. Soc.* **1991**, 113, 8518-8519.
- [49] T. Imamoto, T. Kusumoto, N. Suzuki, K. Sato, *J. Am. Chem. Soc.* **1985**, 107, 5301-5303.
- [50] T. Imamoto, T. Oshiki, T. Onozawa, T. Kusumoto, K. Sato, *J. Am. Chem. Soc.* **1990**, 112, 5244-5252.
- [51] S. Jugé, M. Stephan, J. A. Laffite, J. P. Genêt, *Tetrahedron Lett.* **1990**, 31, 6357-6360.
- [52] H. Yang, N. Lugan, R. Mathieu, *Organometallics* **1997**, 16, 2089-2095.
- [53] B. Carboni, L. Monnier, *Tetrahedron* **1999**, 55, 1197-1248.
- [54] L. McKinstry, T. Livinghouse, *Tetrahedron Lett.* **1994**, 35, 9319-9322.
- [55] L. McKinstry, T. Livinghouse, *Tetrahedron* **1994**, 50, 6145-6154.
- [56] B. R. James, D. Mahajan, *J. Organomet. Chem.* **1985**, 279, 31-48.
- [57] I. D. Gridnev, Y. Yamanoi, N. Higashi, H. Tsuruta, M. Yasutake, T. Imamoto, *Adv. Synth. Catal.* **2001**, 343, 118-136.
- [58] U. Nagel, E. Kinzel, J. Andrade, G. Prescher, *Chem. Ber.* **1986**, 119, 3326-3343.
- [59] J. D. Oliver, D. P. Riley, *Organometallics* **1983**, 2, 1032-1038.
- [60] I. Ojima, T. Kogure, N. Yoda, *J. Org. Chem.* **1980**, 45, 4728-4739.
- [61] M. J. Burk, M. F. Gross, J. P. Martinez, *J. Am. Chem. Soc.* **1995**, 117, 9375-9376.
- [62] J. W. Scott, D. D. Keith, G. J. Nix, D. R. Parrish, S. Remington, G. P. Roth, J. M. Townsend, D. J. Valentine, R. Yang, *J. Org. Chem.* **1981**, 46, 5086-5093.
- [63] A. Ohashi, T. Imamoto, *Org. Lett.* **2001**, 3, 373-375.
- [64] I. D. Gridnev, N. Higashi, T. Imamoto, *J. Am. Chem. Soc.* **2000**, 122, 10486-10487.
- [65] I. D. Gridnev, M. Yasutake, N. Higashi, T. Imamoto, *J. Am. Chem. Soc.* **2001**, 123, 5268-5276.
- [66] M. J. Burk, G. Casy, N. B. Johnson, *J. Org. Chem.* **1998**, 63, 6084-6085.
- [67] *Enantioselective Synthesis of B-Amino Acids*, (Ed.: E. Juaristi), Wiley-VCH, New York, **1997**.
- [68] S. H. Gellman, *Acc. Chem. Res.* **1998**, 31, 173-180.
- [69] D. C. Cole, *Tetrahedron* **1994**, 50, 9517-9582.
- [70] D. J. Hart, D.-C. Ha, *Chem. Rev.* **1989**, 89, 1447-1465.
- [71] L. Deng, E. N. Jacobsen, *J. Org. Chem.* **1992**, 57, 4320-4323.
- [72] Z.-M. Wang, H. C. Kolb, K. B. Sharpless, *J. Org. Chem.* **1994**, 59, 5104-5105.
- [73] D. Guenard, F. Guéritte-Voegelein, P. Potier, *Acc. Chem. Res.* **1993**, 115, 160-167.
- [74] W. D. Lubell, M. Kitamura, R. Noyori, *Tetrahedron: Asymmetry* **1991**, 2, 543-554.
- [75] M. Yasutake, I. D. Gridnev, N. Higashi, T. Imamoto, *Organic Lett.* **2001**, 3, 1701-1704.
- [76] T. Yamano, N. Taya, M. Kawada, T. Huang, T. Imamoto, *Tetrahedron Lett.* **1999**, 40, 2577-2580.
- [77] T. Ohkuma, R. Noyori, in *Comprehensive Asymmetric Catalysis*, Vol. 1, (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **1999**, Chap 6.1.
- [78] J. P. Genêt, C. Pinel, S. Mallart, S. Jugé, S. Thorimbert, J. A. Laffite, *Tetrahedron: Asymmetry* **1991**, 2, 555-567.
- [79] R. Noyori, T. Ikeda, T. Ohkuma, M. Widhalm, M. Kitamura, H. Takaya, S. Akutagawa, N. Sayo, T. Saito, T. Taketomi, H. Kumobayashi, *J. Am. Chem. Soc.* **1989**, 111, 9134-9135.
- [80] A. Kumar, D. H. Ner, S. Y. Dike, *Tetrahedron Lett.* **1991**, 32, 1901-1904.
- [81] J. F. Young, J. A. Osborn, F. H. Jardine, G. Wilkinson, *Chem. Commun.* **1965**, 131-132.
- [82] J. Halpern, D. P. Riley, A. S. C. Chan, J. J. Pluth, *J. Am. Chem. Soc.* **1977**, 99, 8055-8057.
- [83] J. M. Brown, P. A. Chaloner, *Tetrahedron Lett.* **1978**, 1877-1880.
- [84] A. S. S. Chan, J. J. Pluth, J. Halpern, *J. Am. Chem. Soc.* **1980**, 102, 5952-5954.
- [85] J. M. Brown, P. A. Chaloner, *J. Am. Chem. Soc.* **1980**, 102, 3040-3048.
- [86] A. Miyashita, H. Takaya, T. Souchi, R. Noyori, *Tetrahedron* **1984**, 40, 1245-1253.
- [87] D. G. Allen, S. B. Wild, D. L. Wood, *Organometallics* **1986**, 5, 1009-1015.
- [88] J. M. Brown, P. A. Chaloner, A. G. Kent, B. A. Murrer, P. N. Nicholson, D. Parker, P. J. Sidebottom, *J. Organomet. Chem.* **1981**, 216, 263-276.
- [89] G. Descotes, D. Lafont, D. Sinou, J. M. Brown, P. A. Chaloner, D. Parker, *Nouv. J. Chim.* **1981**, 5, 167-173.
- [90] D. Sinou, *Tetrahedron Lett.* **1981**, 22, 2987-2990.
- [91] R. Kuwano, Y. Ito, *J. Org. Chem.* **1999**, 64, 1232-1237.
- [92] A. S. C. Chan, J. Halpern, *J. Am. Chem. Soc.* **1980**, 102, 838-840.
- [93] J. Halpern, *Science* **1982**, 217, 401-407.
- [94] a) J. M. Brown, P. M. Chaloner, *J. Chem. Soc. Chem. Commun.* **1980**, 344-346; b) J. M. Brown, D. Parker, *J. Chem. Soc. Chem. Commun.* **1980**, 342-344; c) J. M. Brown, D. Parker, *J. Org. Chem.* **1982**, 47, 2722-2730; d) J. M. Brown, P. A. Chaloner, G. A. Morris, *J. Chem. Soc. Chem. Commun.* **1983**, 664-666; e) J. M. Brown, P. A. Chaloner, *J. Chem. Soc. Perkin Trans. 2* **1987**, 1583-1588.
- [95] C. R. Landis, J. Halpern, *J. Am. Chem. Soc.* **1987**, 109, 1746-1754.
- [96] B. R. Bender, M. Koller, D. Nanz, W. von Philipsborn, *J. Am. Chem. Soc.* **1993**, 115, 5889-5890.
- [97] H. Bircher, B. R. Bender, W. von Philipsborn, *Magn. Res. Chem.* **1993**, 31, 293-298.
- [98] J. S. Giovannetti, C. M. Kelly, C. R. Landis, *J. Am. Chem. Soc.* **1993**, 115, 4040-4057.
- [99] T. V. RajanBabu, B. Radetich, K. Y. Kamfia, T. A. Ayers, A. Casalnuovo, J. C. Calabrese, *J. Org. Chem.* **1999**, 64, 3429-3447.
- [100] B. McCulloh, J. Halpern, M. R. Thompson, C. R. Landis, *Organometallics* **1990**, 9, 1392-1395.

- [101] P. S. Chua, N. K. Roberts, B. Bosnich, S. J. Okrasinski, S. J. Halpern, *J. Chem. Soc. Chem. Commun.* **1981**, 1278-1280.
- [102] O. Samuel, R. Couffignal, M. Lauer, S. Y. Zhang, H. B. Kagan, *Nouv. J. Chim.* **1981**, 5, 15-20.
- [103] H. B. Kagan, in *Comprehensive Organometallic Chemistry*, Vol. 8, (Eds.: G. Wilkinson, F. G. A. Stone, E. W. Abel), Pergamon, Oxford, **1982**, pp. 463-498.
- [104] I. D. Gridnev, N. Higashi, K. Asakura, T. Imamoto, *J. Am. Chem. Soc.* **2000**, 122, 7183-7194.
- [105] S. K. Armstrong, J. M. Brown, M. J. Burk, *Tetrahedron Lett.* **1993**, 34, 879-882.
- [106] D. M. Heinekey, M. van Roon, *J. Am. Chem. Soc.* **1996**, 118, 12134-12140.
- [107] C. R. Landis, P. Hilfenhaus, S. Feldgus, *J. Am. Chem. Soc.* **1999**, 121, 8741-8754.
- [108] R. Kadyrov, T. Freier, D. Heller, M. Michalik, R. Selke, *J. Chem. Soc. Chem. Commun.* **1995**, 1745-1746.
- [109] J. R. Bleeke, A. J. Donaldson, *Organometallics* **1988**, 7, 1588-1596.
- [110] C. R. Landis, T. W. Brauch, *Inorg. Chim. Acta* **1998**, 270, 285-297.
- [111] J. M. Brown, D. Parker, *Organometallics* **1982**, 1, 950-956.
- [112] C. R. Landis, S. Feldgus, *Angew. Chem. Int. Ed.* **2000**, 39, 2863-2866.
- [113] I. D. Gridnev, N. Higashi, T. Imamoto, *J. Am. Chem. Soc.* **2001**, 123, 4631-4632.
- [114] S. Feldgus, C. R. Landis, *J. Am. Chem. Soc.* **2000**, 122, 12714-12727.
- [115] B. R. James, D. Mahajan, *Can. J. Chem.* **1980**, 58, 996-1004.
- [116] R. G. Ball, B. R. James, D. Mahajan, J. Trotter, *Inorg. Chem.* **1981**, 20, 254-261.
- [117] I. D. Gridnev, T. Imamoto, *Organometallics* **2001**, 20, 545-549.
- [118] A. L. Sargent, M. B. Hall, M. F. Guest, *J. Am. Chem. Soc.* **1992**, 114, 517-522.
- [119] N. Koga, S. Q. Jin, K. Morokuma, *J. Am. Chem. Soc.* **1988**, 110, 3417-3425.
- [120] S. B. Duckett, C. L. Newell, R. Eisenberg, *J. Am. Chem. Soc.* **1994**, 116, 10548-10556.