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On the Mechanism of Stereoselection in Rh-Catalyzed Asymmetric Hydrogenation: A General Approach for Predicting the Sense of Enantioselectivity

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ABSTRACT
This account brings together the recent experimental and computational data on the mechanism of Rh-catalyzed asymmetric hydrogenation of activated double bonds. Two alternative reaction pathways (unsaturated and dihydride) are compared. It is suggested that the differences in these mechanisms are not primarily important for stereoselection, since they join in a single pathway before stereoselection occurs. This approach was used to rationalize the present discrepancies in the prediction of the sense of enantioselection for the P-stereogenic ligands and the ligands with backbone chirality.

Introduction

Over 30 years, the mechanism of rhodium-catalyzed asymmetric hydrogenation has been actively investigated. The practical and theoretical importance,[1,2] coupled with numerous intercepted intermediates, maintains great interest in the mechanistic aspects of this reaction. Success in this field is evident—reaction pathways have been studied with all possible accuracy both experimentally and theoretically. However, as often happens in science, our achievements in acquiring new knowledge nurture an understanding of our real ignorance of the genuine and intricate ways in which nature works. This is well illustrated by the history of the views on reaction pathways and on the prediction of the sense of enantioselectivity in the course of Rh-catalyzed asymmetric hydrogenation. In the last 5 years the number of publications in the field has doubled, demonstrating new experimental findings and computational achievements. In particular, our own studies[3−9] and others' studies[10,11] show that the so-called "dihydride mechanism" of Rh-catalyzed asymmetric hydrogenation is of greater relevance than previously accepted. On the other hand, extensive high-level computational studies on the alternative "unsaturated pathway" has brought a deeper understanding of the molecular mechanisms responsible for creating enantioselectivity in this catalytic reaction.[12−15] However, we are still quite far from definite conclusions on the mechanistic details in each particular case and from confident recommendations on ligand design.

This paper presents a comparative analysis of the alternative mechanistic pathways of Rh-catalyzed asymmetric hydrogenation, both from a historical perspective

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Ilya Gridnev received his Ph.D. degree in 1989 from Moscow University. In 1990−1998 he was employed by the Russian Academy of Science (Institute of Organic Chemistry and Institute of Organoelement Compounds). After two postdoctoral stays in Japan (JSPS Fellowship, Hokkaido University) and Germany (A. v. Humboldt Fellowship, Goettingen University) he received his Dr. Sci. degree ("Habilitation") from A. V. Nesmeyanov Institute of Organoelement Compounds, Moscow, Russia. In 1998−2003 he was employed as a Research Associate at the University of Rennes, France, Chiba University, Japan, and Oxford University, U.K., before he took his present position as Associate Professor at Tohoku University, Sendai, Japan. His research interests cover organometallic chemistry, reaction mechanisms, and NMR spectroscopy.

Tsuneo Imamoto was born in Yaizu, Shizuoka prefecture, Japan, in 1942 and received his B.S. degree from Shizuoka University and his Ph.D. degree in 1972 from Osaka University. After 1 year of postdoctoral 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 methodologies, synthesis, and mechanisms, particularly in the context of asymmetric catalysis. He received the Synthetic Organic Chemistry Award, Japan (1997), and the Rare Earth Society Award, Japan (2001).

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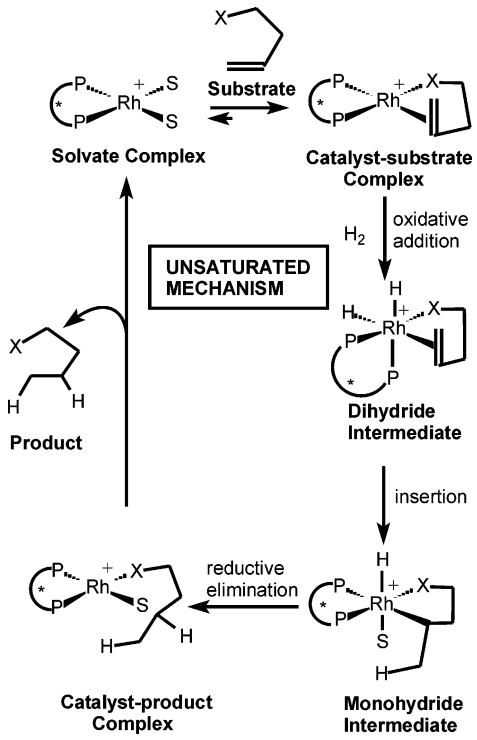
Scheme 1



and considering the most recent results. This area is being actively reviewed[16−19] and highlighted.[20,21] We did not attempt, therefore, to either cover all aspects of the mechanism of Rh-catalyzed asymmetric hydrogenation or provide a complete citation list. Instead, we attempted to bring together different pieces of research to elaborate a generalized view on the catalytic cycle and the mechanism of stereoselection in this important reaction.

Unsaturated Mechanism of Rh-Catalyzed Asymmetric Hydrogenation

After successful characterization of the dihydride complex obtained by the oxidative addition of dihydrogen to Wilkinson's catalyst,[22,23] it was expected that similar intermediates would be found upon hydrogenation of the catalytic precursors to Rh-catalyzed asymmetric hydrogenation. However, no hydride complexes were detected when the diene rhodium complexes of tetraaryl-substituted diphosphines were hydrogenated in solution.[24] Instead, cationic 16e complexes were characterized in which either two solvent molecules or a phenyl ring from another molecule of the complex compensated for the deficit of electrons on the rhodium atom (Solvate Complex in Scheme 1).[24,25]

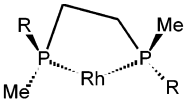
It was immediately realized that in catalytic conditions, when a substrate significantly exceeds the catalyst in concentration, the two vacant coordination sites on the rhodium atom must be occupied by a molecule of the substrate coordinated in a chelate manner (Catalyst−substrate Complex in Scheme 1). Moreover, a prochiral substrate can coordinate with the metal with two different enantiofaces, giving rise to two diastereomeric catalyst−substrate complexes. Reasonably supposing that the hydrogen will always arrive from the side of the metal, one can conclude that the hydrogenation of these isomers would give the opposite enantiomers of the product.[26] This is the idea of the "unsaturated mechanism" in which the coordination of the substrate occurs before the hydrogen activation step (Scheme 1). Following the first example provided by Brown and Chaloner,[26] numerous catalyst−substrate rhodium complexes of chiral diphosphines and prochiral olefins have been described. The stability of the catalyst−substrate complexes compared to the elusiveness of the solvate dihydrides led to a general acceptance of the unsaturated mechanism for Rh-catalyzed asymmetric hydrogenation.[27,28] This was further supported by low-temperature hydrogenations of catalyst−substrate complexes that produced essentially the same stereochemical results as the true catalytic reactions using the same catalyst.[29,30] Important monohydride intermediates have been characterized during these experiments, thus bringing the catalytic cycle of the unsaturated pathway almost to completion. The only uncharacterized species is the "dihydride intermediate". There is little doubt that this structure must appear on the reaction pathway, but its low stability retards proper characterization.

All catalyst−substrate complexes without exception demonstrated stereodifferentiation in solution with the ratio of diastereomers varying from 5:1 to almost 100:1. However, it was shown by Halpern and Chan that the difference in the thermodynamic stabilities is not the cause of enantioselection, since the major diastereomer of the catalyst−substrate complex studied in their experiments had an opposite mode of coordination of the prochiral substrate compared to the experimental outcome of catalytic hydrogenation using the same ligand.[31,32] This was sufficient to disprove the idea of thermodynamic control of enantioselectivity at the stage of catalyst−substrate complexes.

If the unsaturated pathway is accepted, the inconsistency between the structure of the major diastereomer of the catalyst−substrate complex and the stereochemical outcome of the asymmetric hydrogenation automatically means that the reactivity of the minor diastereomer of the catalyst−substrate complex toward dihydrogen must be dramatically higher compared to that of the major diastereomer. Experimental observations of this difference in reactivity between major and minor diastereomers[29,30] have been accepted as evidence for the unsaturated mechanism. The kinetic observations were accommodated to the unsaturated pathway,[33] and recent extensive quantum chemical computations have outlined the structural reasons for the higher reactivity of the minor diastereomer within the unsaturated pathway.[12−15]

Characterization of Rh Solvate Dihydride Complexes: The Dihydride Mechanism of Asymmetric Hydrogenation

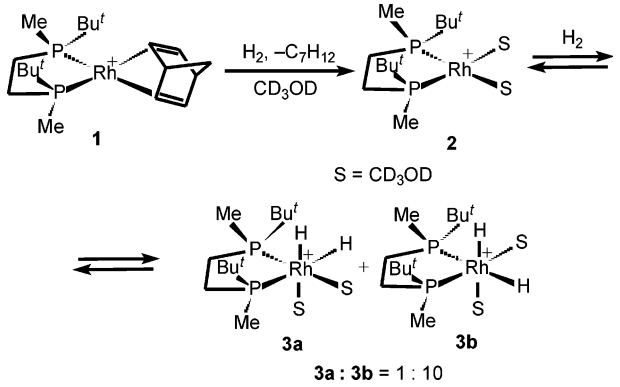
We were motivated to conduct new mechanistic studies in the field of Rh-catalyzed asymmetric hydrogenation by very promising synthetic results obtained with new P-



R = *t*-Bu, 1-adamantyl, 1-methylcyclohexyl, Et_3C, *i*-Pr, *c*-C_5H_9, c-C_6H_{11}

FIGURE 1. Schematic representation of the Rh complex of a BisP* ligand utilizing the difference in size between a bulky alkyl substituent and the smallest possible alkyl group for stereoselection.

Scheme 2



stereogenic diphosphine ligands, BisP*.[34] The structure of BisP* ligands (Figure 1) stipulates the distinctly settled asymmetric environment around the Rh atom in their rhodium complexes. The different substituents at phosphorus atoms can be easily distinguished in the NMR spectra of the intermediates, and the stereochemical assignment of any intermediate complexes is a much easier task compared to that of the complexes of tetraphenyl-substituted ligands.[35]

We intended not to look for the solvate dihydrides at the beginning of our study but have attempted to conduct experiments with the *t*-Bu-BisP* rhodium complex in line with previous research in this field. We very soon found that, unlike all previously studied catalytic precursors, [Rh(nbd)BisP*]BF_4 (**1**) cannot be cleanly hydrogenated to a solvate complex (**2**) at ambient temperature; attempts produced darkly colored reaction mixtures with multipart contents. Decreasing the temperature of hydrogenation to −20 °C afforded the expected solvate complex and allowed further preparation of the catalyst−substrate and catalyst−product complexes. However, all samples prepared by this procedure invariably contained notable amounts of impurities, which are always very undesirable in any mechanistic studies aimed at the characterization of supposedly unstable and low-concentrated intermediates. This led us to perform hydrogenation of the catalytic precursor at still lower temperatures, which resulted in characterization of the solvate dihydrides (**3**) (Scheme 2). The optimal procedure for the preparation of **3** is the removal of the norbornadiene ligand by hydrogenation at −20 °C and then application of 1−2 atm of H_2 at −90 °C to the resulting solution of **2**. If a solution of **2** free of dihydride **3** is needed, the hydrogen must be changed to argon after hydrogenation at −20 °C. The formation of dihydrides **3a** and **3b** is reversible; the equilibrium parameters were obtained from the series of NMR spectra taken at temperature intervals from −90 to −60 °C.[3]

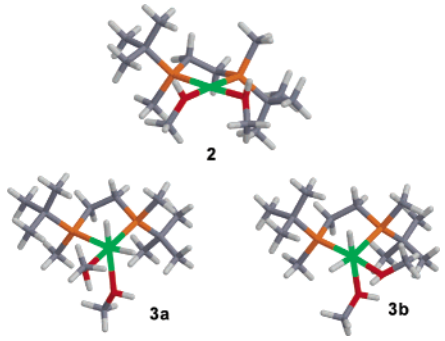


FIGURE 2. Structures of intermediates **2**, **3a**, and **3b** optimized at the B3LYP/LANL2DZ level.

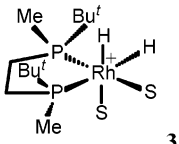
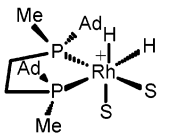
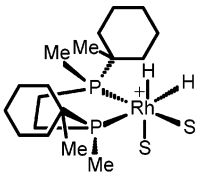
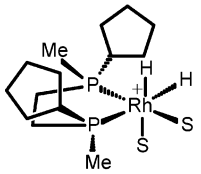
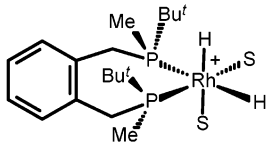
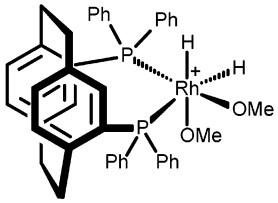
We later demonstrated the scope of dihydride formation, extending similar observations for the other BisP* ligands,[8] whereas Brown and co-workers observed the formation of solvate dihydride for the PHANEPHOS−Rh complex.[10] The equilibrium parameters are quite similar for the series of the structurally related dihydride complexes (Table 1). The catalytic precursor with the benzylic-type BisP*-like ligand gives dihydride **7** irreversibly; it is stable up to 0 °C, and the reactions that take place at higher temperatures are not accompanied by hydrogen loss.[6] These results show the importance of the electronic properties of the diphosphine ligand for the stability of the solvate dihydrides; apparently, the electron-donating substituents in the ligand increases the affinity of its rhodium complex to dihydrogen.

The relatively small size of the BisP* ligand allowed us to carry out the complete optimization of the structures of solvate complex **2** and dihydrides **3a**,**b** at the B3LYP/LANL2DZ level of theory (Figure 2).[36] The computed enthalpy of formation (−8.2 kcal mol^{-1}) is in reasonably good agreement with the experimental value (−6.3 kcal mol^{-1}). The small difference in energies between two diastereomers of the solvate dihydride was also reproduced in the computations (computed value 0.7 kcal mol^{-1} in favor of **3b**).

Low-Temperature Reactions Simulating Dihydride and Unsaturated Mechanisms

Having at hand the solvate dihydrides, we were interested in simulating the dihydride mechanism (Scheme 3) of the Rh-catalyzed asymmetric hydrogenation by reacting them with various prochiral substrates. Thus, the reaction of **3** with methyl (*Z*)-α-acetamidocinnamate (MAC) at −100 °C was immediate and quantitative, giving a single isomer of monohydride intermediate, and after quenching a hydrogenation product with 99% ee and the same configuration as obtained in the catalytic reaction. Similar observations were made for reactions of **3** with other α-dehydroamino acids,[8] enamides,[4,9] (*E*)-β-dehydroamino acids,[37] and dimethyl 1-benzoyloxyethenephosphonate.[5] In the last two cases, several interconverting monohydride intermediates were observed; nevertheless, the enantiomeric excesses of the products from the experiments simulating the dihydride pathway were always over 98% ee. These experiments demonstrated that the stereose-

Table 1. Structure and Equilibrium Parameters of Rh Solvate Dihydride Complexes

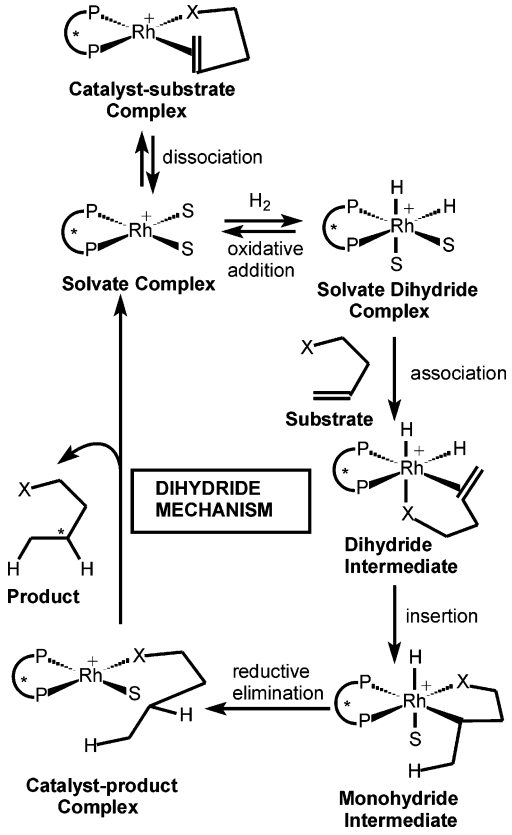
Dihydride	% in equilibrium mixture	Ratio of diatereomers	ΔH, kcal mol^{-1}	ΔS, kcal mol^{-1}, K^{-1}	Reference
 **3**	20	1 : 10	–6.3[a]	–23.7	3,8
 **4**	24	1 : 20	-6.6	–25.7	8
 **5**	30	1 :12	-7.4	–28.5	8
 **6**	20	[b]	[b]	[b]	8
 **7**	100	1 : 14	[b]	[b]	6
 **8**	45	1 : 2	[b]	[b]	10

[a] The computed value is −8.2 kcal mol^{-1}. [b] Not determined.

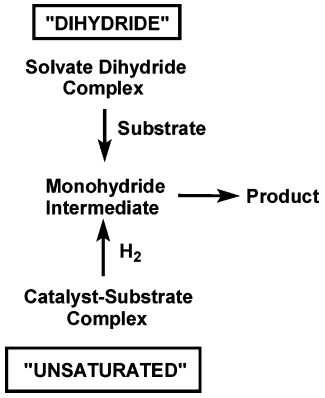
lection equivalent in sense and value to that observed in the catalytic conditions is possible via reaction of the equilibrium mixture of solvate dihydrides with substrates, and hence, the dihydride mechanism (Scheme 3) can be regarded as a possible pathway of Rh-catalyzed asymmetric hydrogenation.

Another set of experiments was designed to create conditions that favor the direct hydrogenation of the catalyst−substrate complexes (Scheme 4). The loosely bound complexes of Rh-*t*-Bu-BisP* with enamides[9] and β-dehydroamino acids[37] can be hydrogenated at the same temperature as the reaction of dihydride with the substrate, i.e., at −100 °C. In these cases the ee's obtained in both procedures were identical. A very different situation is observed when the catalyst−substrate complex is tightly bound, as in the case of dimethyl 1-benzoyloxyethenephosphonate. In this case, hydrogenation of the catalyst−substrate complex could be achieved only at −30 °C and provided the product with notably lower ee (75% ee) than the reaction of the solvate dihydride with the substrate at −100 °C (97% ee). The catalytic hydrogenation of the dimethyl 1-benzoyloxyethenephosphonate yields a product with 88% ee, which is an intermediate value between the results of two mechanistic experiments.

Scheme 3



Scheme 4



Another interesting fact is the striking difference in the ee's of the low-temperature reaction of the dihydride **7** with dimethyl 1-benzoyloxyethenephosphonate (92%) and the catalytic reaction using the corresponding catalytic precursor (19%).[6] The low ee obtained under catalytic conditions in this reaction can be attributed to competing flux from a nonselective unsaturated pathway.

Thus, our mechanistic data for the hydrogenations that were catalyzed by Rh-complexes of *t*-Bu-BisP* and its analogues suggest that in the case of these electron-rich ligands with different in size substituents bound directly to the stereogenic phosphorus atoms, the dihydride pathway seems to carry the main flux of the catalytic reaction and determine the high enantioselectivity. Under the artificially created conditions that favor the direct hydrogenation of the catalyst−substrate complexes (unsaturated mechanism), lower ee's of the products are observed. Additional experiments are required to make similar conclusions for other catalytic systems.

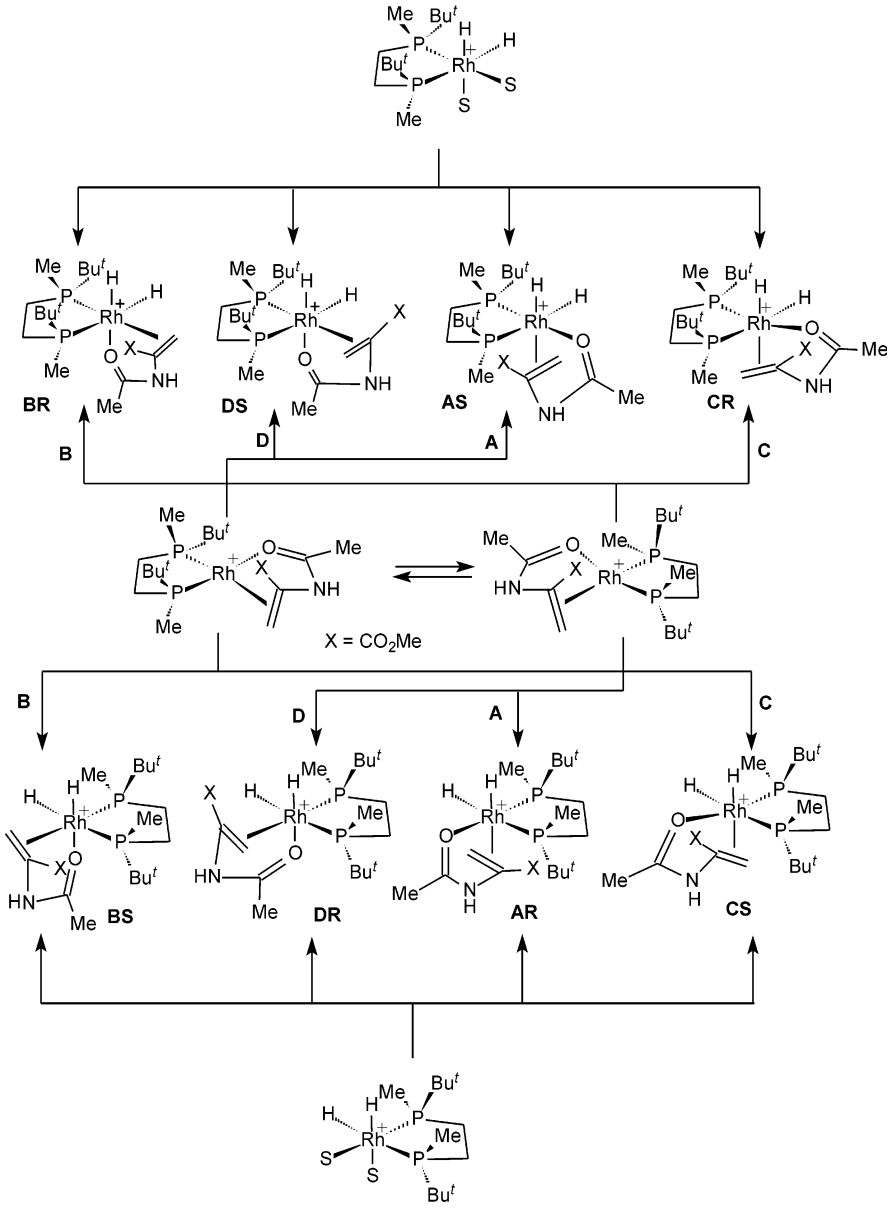
Before analyzing the sophisticated stereochemical features of both mechanisms, we address the issue of the experimentally observed higher reactivities of the minor diastereomers of the catalyst−substrate complexes that were often regarded as evidence for the unsaturated pathway. We argue that this experimental fact is also in accord with the dihydride mechanism (see Figure 3). Indeed, it is well known that the diastereomers of the catalyst−substrate complexes can interconvert via complete dissociation,[3,33,38] i.e., producing the solvate complex. If the dihydride pathway takes place, this dissociation is an essential step in the catalytic cycle (Scheme 3); the solvate complex formed by the dissociation is being further hydrogenated to the solvate dihydride. Thus, the relatively fast consumption of the minor diastereomer of the catalyst−substrate complex is an expected phenomenon within the dihydride mechanism, since the minor diastereomer dissociates faster than the major diastereomer.

Stereochemical Features of Both Pathways

In the case of a C_2-symmetric diphosphine ligand, either the coordination of a prochiral substrate or the oxidative addition of dihydrogen to the complex gives two diastereomeric species: a catalyst−substrate complex or a solvate dihydride, respectively. At the next stage of the catalytic cycle (the oxidative addition of H_2 in the case of the unsaturated mechanism or coordination of the substrate in the case of the dihydride pathway), eight dihydride intermediates can be produced (Scheme 5). These intermediates are extremely unstable, but the structure of the formed dihydride intermediate is essential for the configuration of the hydrogenation product and is unique for a certain pathway within either the unsaturated or dihydride mechanism. In Scheme 5, the origin of all eight possible dihydride intermediates is analyzed, taking the (*S*,*S*)-*t*-BisP*−Rh complex as an example and assigning the different reaction routes according to the papers of Landis et al.[12−15]

The detailed computational studies of Landis convincingly show that only route **A** is viable within the unsaturated pathway.[12,15] The activation barriers transforming the catalyst−substrate complexes into corresponding dihydride intermediates via pathways **B** and **D** are too high (around 30 kcal/mol). Although the dihydride intermediate can be generated with a reasonably low barrier via route **C**, the migratory insertion in this intermediate is strongly disfavored (the activation barrier is approximately 20 kcal/mol higher than the migratory insertion in intermediate generated by pathway **A**). The lower reactivity of the major diastereomer of the catalyst−substrate complex within pathway **A** (in terms of the unsaturated mechanism) is explained by the steric interactions between the α-substituent on the prochiral double bond and the hindered quadrant (see next section and Figure 8 for the definition)

Scheme 5



of the catalyst in the course of the oxidative addition of H_2. In the case of the minor diastereomer, the oxidative addition of dihydrogen does not imply that it is necessary for the α-substituent to pass through the hindered quadrant, and therefore, the reactivity is higher.[15]

The computational results of Landis can also be applied to analysis of the dihydride pathway. In this case, coordination of the substrate (ultimately determining the enantioface of further migratory insertion and the configuration of the product) occurs at the later stage of the reaction. Hence, it is sufficient to consider the association step shown in Scheme 5 to obtain conclusions on the mechanism of stereoselection within the dihydride mechanism. Exactly the same analysis is applicable to the unsaturated pathway if a fast equilibrium between the dihydride intermediates is viable, e.g., via the dissociation−association of the substrate.

Proper computations of the association step are retarded by the necessity to consider solvation effects. Nevertheless, since our experimental results demonstrate that the consequence of the association and the migratory insertion steps is practically instantaneous at −100 °C, it is natural to accept that the enantioselective reaction can occur without involvement of any considerable activation barriers. Therefore, both the relative stability of a dihydride intermediate and the transition state of migratory insertion must be minimal. Figure 4, redrawn from the original paper of Landis, shows that route **B** is the most probable pathway of migratory insertion if all dihydride intermediates are kinetically accessible.

To reveal a possible origin of the stereoselection within pathway **B**, we optimized the geometries of the dihydride intermediates **BR** and **BS** for the Rh−*t*-Bu-(*S,S*)-BisP*-catalyzed asymmetric hydrogenation of methyl α-acetamidoacrylate, which gives a hydrogenation product with 98% ee (*R*) (Figures 5 and 6). Dihydride **BR** is 1.5 kcal mol^{-1} more stable with respect to dihydride **BS** ($\Delta E_{\mathbf{BR/BS}}$ in Figure 6). Considering the energy difference between

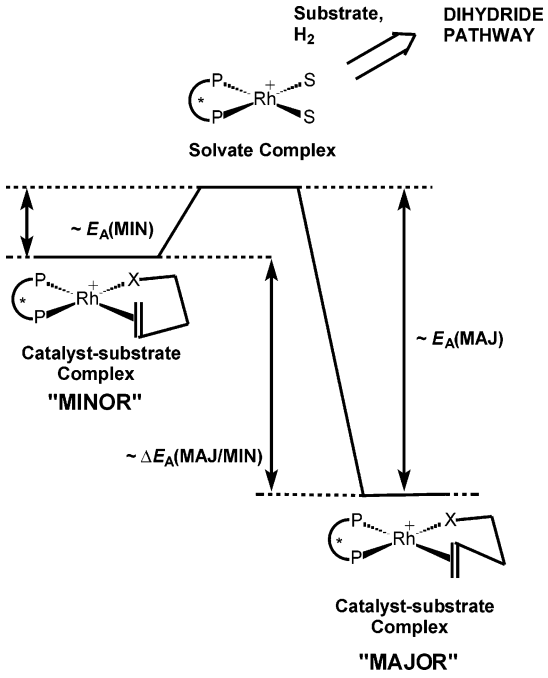


FIGURE 3. Schematic representation of the PPE of the equilibrium between the solvate complex and two diastereomers of the catalyst−substrate complex. The association is very fast, so the barriers may be neglected.

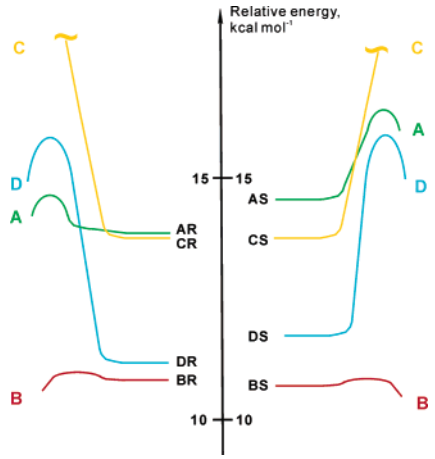


FIGURE 4. Section plots (migratory insertion step) of the profile of potential energy (PPE) describing the asymmetric hydrogenation of acrylonitrile catalyzed by Rh−DUPHOS. The PPE sections are redrawn from ref 12; the dihydride intermediates are marked according to Scheme 5.

the starting dihydrides (0.3 kcal mol^{-1}, $\Delta E_{3a/3b}$ in Figure 6), we obtain the association step being 1.8 kcal mol^{-1} ($\Delta E_R - \Delta E_S$) favored for the production of the hydrogenation product with the correct stereochemistry (Figure 6). This approach does not consider the possible difference in the activation barriers of the migratory insertion step. We believe, however, that this can be justified in view of the extremely flat transition states for pathway **B** (Figure 4), implying that the structure of the transition state must be very close to the structure of the dihydride intermediate.[39] In our opinion, the low-temperature experiments for the simulation of the dihydride mechanism convincingly demonstrate that stereoselection can occur after the

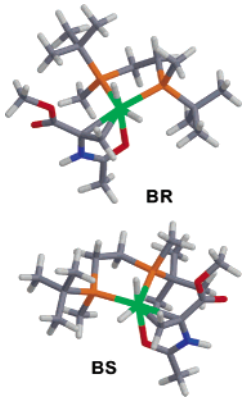
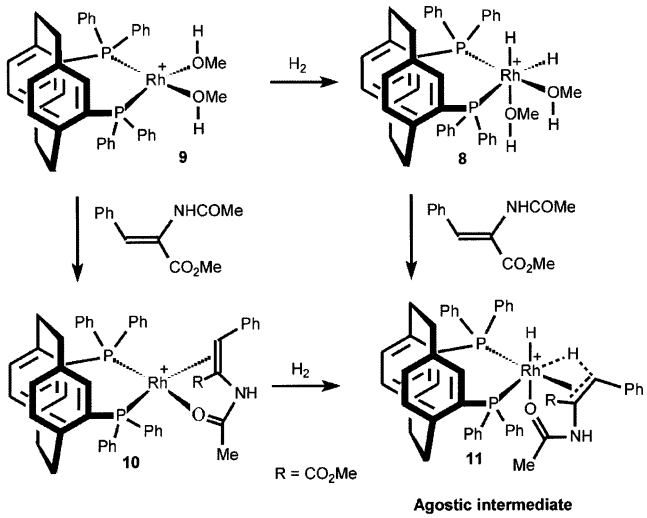


FIGURE 5. Structures of dihydride intermediates **BR** and **BS** optimized at the B3LYP/LANL2DZ level.

Scheme 6



hydrogen activation step, and the discussion in this section illustrates how this can be achieved.

The difference between pathways **A** (unsaturated mechanism) and **B** (dihydride mechanism or unsaturated mechanism with fast interconversion of the dihydride intermediates) is essential for a conclusion on the importance of the α-substituent of the substrate in stereoselection. In pathway **A**, the double bond of the substrate takes place over the plane of the Rh complex chelate cycle, i.e., in the close vicinity of the substituents on the stereogenic phosphorus atoms. Accordingly, the hindrance created by the α-substituent for this arrangement is an important stereoregulating factor. On the other hand, in the dihydride intermediate generated via pathway **B,** the double bond is effectively distanced from the substituents on the phosphorus atoms and the α-substituent can easily acquire a conformation that is free of steric hindrance in both dihydride intermediates (precursors of the product with opposite chirality). In this case, the steric hindrance of the entire chelate cycle produced by the substrate becomes decisive for stereocontrol.

Significant evidence for the importance of pathway **B** has been discovered by Brown et al. in their recent work on the detection of agostic intermediates in the asymmetric hydrogenation of dehydroamino acids catalyzed by

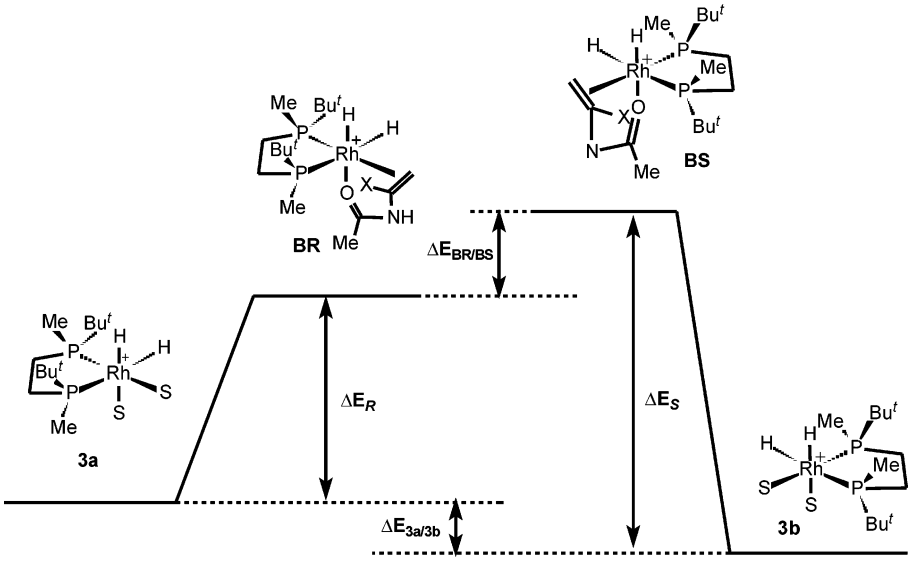


FIGURE 6. Schematic representation of our computational results providing an explanation of the enantioselection within the dihydride pathway.

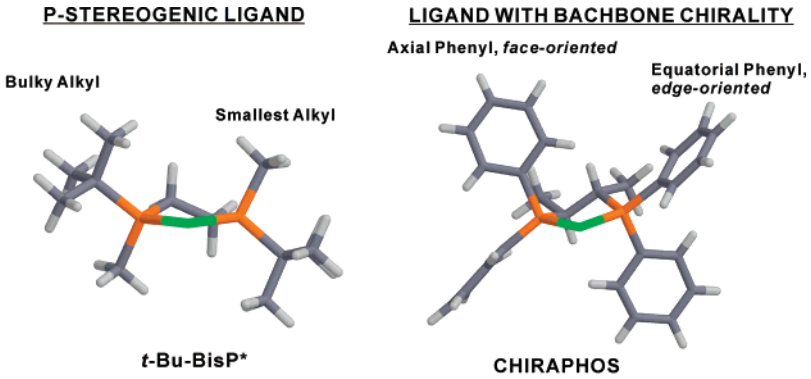


FIGURE 7. Difference between the Rh complexes with P-stereogenic ligands (e.g., BisP*, left) and backbone chirality ligands (e.g., CHIRAPHOS, right).

Rh−PHANEPHOS complex.[10,11] Low-temperature hydrogenation of catalyst−substrate complex **10** led to complete characterization of the agostic intermediate **11** using PHIP NMR spectroscopy (Scheme 6). With the characterization of this intermediate, the asymmetric hydrogenation was "photographed" during the migratory insertion step. The spectral evidence clearly shows that the hydride being delivered to the double bond is simultaneously bound to rhodium and carbon, whereas the second dihydride is evidently *trans* to the oxygen atom, which is consistent with the structure of the intermediates for pathway **B** rather than pathway **A**. At the later stages of hydrogenation, solvate dihydride **8** has been detected.[10] Moreover, agostic intermediate **11** can be generated by reaction of **8** with the substrate at −80 °C; **11** was shown to be in reversible equilibrium with the substrate, solvate complex **9,** and solvate dihydride **8**.[10]

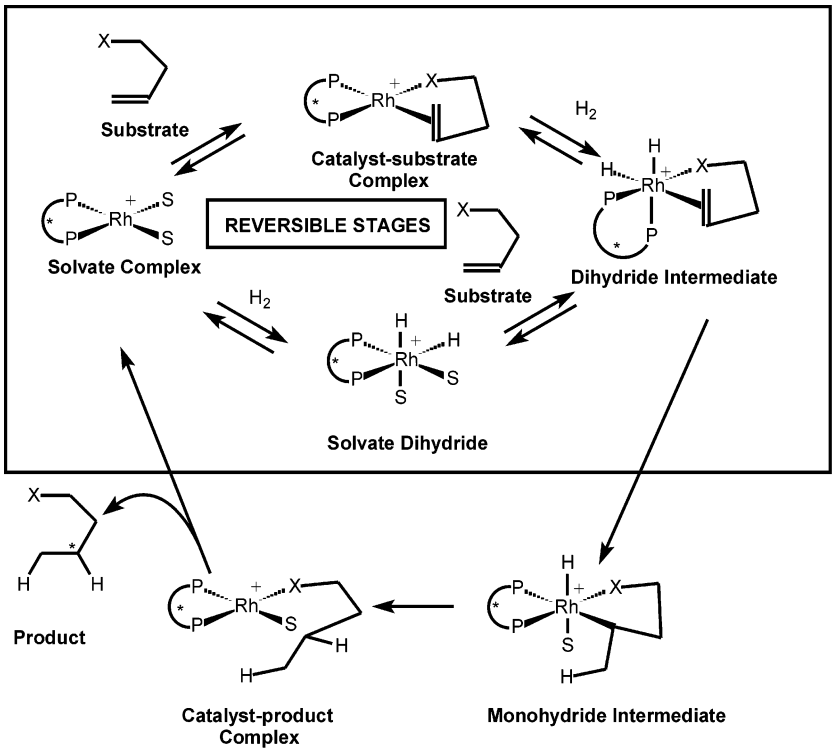
Hence, the data of Brown et al. unequivocally prove the reversibility of all stages of the hydrogenation that precede the formation of the monohydride. This means that the difference between unsaturated and dihydride mechanisms is not important for stereoselection since they join in a single pathway before the irreversible stereodetermining step occurs (Scheme 7). As Brown pointed out, "...INEPT experiments demonstrated that the agostic intermediate is in reversible equilibrium with the solvate complex and substrate. This makes the discrimination between the two pathways quite subtle."[10]

Thus, we conclude that although solid computational support has been obtained for the possibility of a proper stereoselection within pathway **A** (direct hydrogenation of the catalyst−substrate complexes not involving equilibration of the dihydride intermediates), the experimental data available so far instead indicate the stereoselection via pathway **B** (dihydride route or dissociation−association of the dihydride intermediates). Further studies are necessary to support or disprove the general character of this conclusion.

Sense of Stereoselection in the Case of Catalysts with Backbone Chirality

All the mechanistic studies discussed above have dealt with reactions catalyzed by Rh complexes of the P-stereogenic (or pseudo-stereogenic) ligands where the substituents on the phosphorus atoms are evidently different in size and the structure of the asymmetric environment around the rhodium atom is quite clear. It

Scheme 7



is more difficult to make definite conclusions in the case of the diphosphine ligands with backbone chirality when all four substituents on the two phosphorus atoms are identical (Figure 7). The conformation of the chelate cycle (fixed by the backbone substituents) makes these four phenyls pairwise nonequivalent (pseudo-axial and pseudo-equatorial), thus securing the C_2-symmetrical environment around the rhodium atom essential to accomplish asymmetric catalysis. However, the question of which of these two types of spatially nonequivalent phenyls provides the necessary hindrance to realize stereoselection is a source of a considerable controversy.

Originally the question emerged when Knowles introduced his famous quadrant diagrams as an illustration of the empirical correlation predicting the chirality of the product based on the chirality of the catalytic precursor.[40] The early mechanistic interpretation of the quadrant rule in terms of the effective size of the substituents was inspired by the spectacular leaning of the equatorial phenyls from the plane orthogonal to the chelate cycle of the known catalytic precursors and the fact that these phenyls are *edge*-oriented in their solid state, in contrast to the *face*-oriented axial phenyls (e.g., Figure 7).[41] However, an empirical explanation of the relative stability of the square-planar catalyst−substrate complexes based on the proposal of the relative bulkiness of the equatorial phenyls did not work. As Knowles puts it in his Nobel lecture on the structure of the catalyst−substrate complex, "...it was with considerable eagerness we awaited the X-ray crystallographic analysis results. It turned out that the enamide was lying nicely in the hindered quadrant."[1]

After a decade of successful studies on the asymmetric hydrogenation catalyzed by the rhodium complexes of the P-stereogenic (or pseudo-stereogenic) ligands, we can approach the problem of stereodifferentiation of the

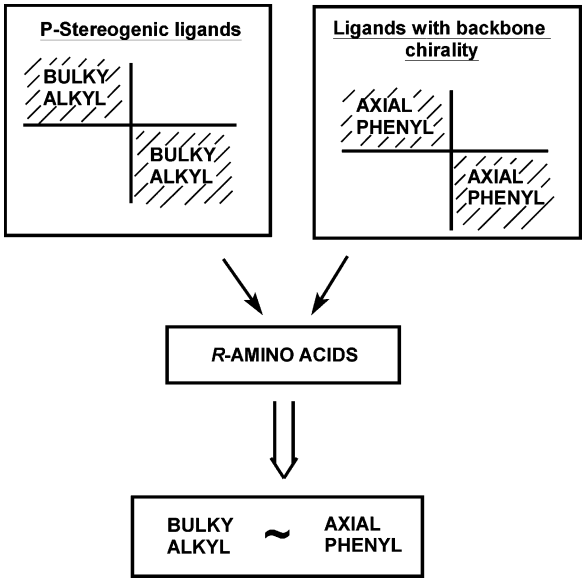


FIGURE 8. Knowles' quadrant diagrams for the rhodium complexes of the P-stereogenic ligands (left) and the ligands with backbone chirality (right). The rhodium atom is considered to be positioned in the center of the diagrams viewed from the side of the free coordination space. The asymmetric environment created by the C_2-symmetrical ligands can then be divided in four quadrants; two of them are "hindered" (dashed in the figure). Comparing the sense of enantioselection observed in the asymmetric hydrogenations catalyzed by rhodium complexes of the P-stereogenic ligands and of the ligands with backbone chirality, one can conclude that the axial phenyls of the tetraphenyl-substituted ligands play the same role in the enantioselection as the bulky alkyl groups of the P-stereogenic ligands.

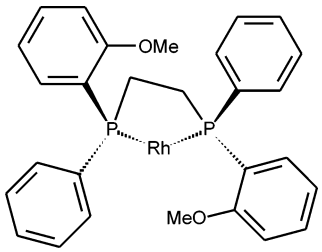


FIGURE 9. Schematic representation of the Rh complex of DIPAMP.

chemically equivalent phenyl groups from another angle. Indeed, we know now that in terms of Knowles' quadrant diagrams, a bulky substituent in the upper left corner will always give rise to *R* α-amino acids. Turning back to the structural relationship established by Knowles and building a quadrant diagram for a catalyst that provides *R*-enantioselectivity, we must conclude that the axial phenyls of the Rh complexes made by C_2-symmetrical diphosphines with backbone chirality operate in a similar way to the bulky substituents in P-stereogenic ligands (Figure 8).

This conclusion allowed us to unify the predictions of the Knowles' quadrant rule for the vast majority of known C_2-symmetrical diphosphine ligands.[3] Within pathway **B** (see discussion in the previous section), the chelate cycle produced by the substrate is axially oriented and the importance of axially oriented substituents is quite natural.[42,43]

Sense of Stereoselection in the Hydrogenations Catalyzed by Rh Complexes of DIPAMP and Structurally Related Ligands

The famous DIPAMP ligand (Figure 9) does not obey the modified quadrant rule described in the previous paragraph. For more than 20 years it remained the most successful diphosphine ligand in Rh-catalyzed asymmetric hydrogenation.[1] It is not surprising that Knowles based his deductions on the originally formulated quadrant rule using the results of hydrogenations catalyzed by Rh–DIPAMP complexes. Assuming that the *o*-anisyl substituents are "bulkier" than simple phenyls, the sense of enantioselection will be opposite of that obtained with BisP*, DuPHOS, and all other modern P-stereogenic ligands with a clearly settled asymmetric environment around the rhodium atom.

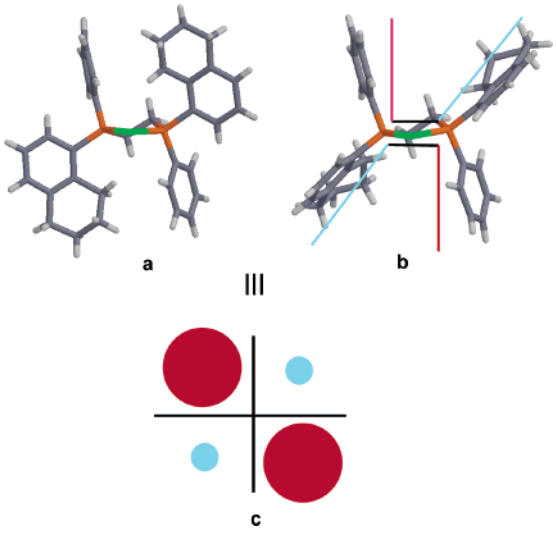
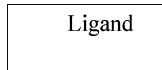
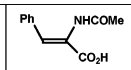
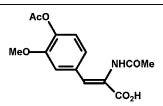
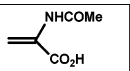
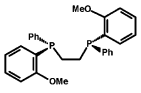
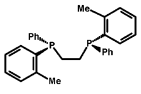
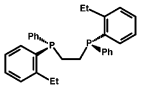
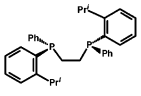
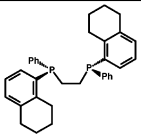


FIGURE 10. Models built using the X-ray structure of the cyclooctadienylrhodium complex of the diphosphine **16**: (a) X-ray structure without the cod ligand; (b) Structure obtained by rotation around P–C bonds of the tetrahydronaphthalenyl substituent; (c) Quadrant diagram corresponding to the upper structure—hindered quadrants are made by axial phenyls.

Table 2. Results of Asymmetric Hydrogenations (ee (configuration of the product)) Catalyzed by the Rh Complexes of Diphosphines 12–16

Ligand					Ref.
 **12**	97 (*R*)	96 (*R*)	94 (*R*)	90 (*R*)	44
 **13**	92 (*R*)	89 (*R*)	90 (*R*)	90 (*R*)	46
 **14**	97 (*R*)	90 (*R*)	91 (*R*)	93 (*R*)	45,46
 **15**	>99 (*R*)	92 (*R*)	91 (*R*)	96 (*R*)	46
 **16**	>99 (*R*)	93 (*R*)	92 (*R*)	94 (*R*)	46

The origin of the high stereogenic potential of the DIPAMP ligand has long fascinated researchers in this field. Indeed, the difference in size between *o*-anisyl and phenyl groups seems too insignificant for the excellent stereoselection observed in the hydrogenations catalyzed by Rh−DIPAMP complex. Knowles himself suggested that the *o*-methoxy group of the anisyl substituent might participate in the coordination of the DIPAMP ligand to rhodium, thus securing the higher stereoselection.[44]

However, analysis of the hydrogenation results for DIPAMP (**12**) and a series of DIPAMP-like diphosphine ligands **13**−**16** (Table 2) shows that very similar ee's are achieved with ligands that do not have any donor atoms capable for additional coordination in the rhodium complexes.[45,46] Moreover, the results shown in Table 2 demonstrate the uniformity of the sense of enantioselection observed in asymmetric hydrogenations utilizing these ligands; if the substituted phenyl ring is regarded as a bulky substituent, then predictions of the quadrant rule are opposite for the ligands listed in Table 2 and all other P-stereogenic ligands.

The conformation of the chelate cycle of the catalyst in solution must be determined in Rh complexes of ligands **12**−**16** by the substituents on phosphorus. The substituted phenyls would therefore preferentially occupy the equatorial positions. This is confirmed by the X-ray structure for the rhodium complex of **16** (Figure 10).[46] In solution, the tetrahydronaphthalene substituents can easily acquire a conformation where they would not create any hindrance above the chelate cycle whereas the axial positions of the phenyls would be fixed by the conformational locks (Figure 10b). Accepting this line of argument, it can be concluded that the unsubstituted phenyls in the Rh complex of **16** act as stereoregulating substituents. This, in turn, gives a quadrant diagram that coincides with the general quadrant rule (see above). In other words, being formally P-stereogenic ligands, DIPAMP (**12**) and its analogues (**13**−**16**) work as the catalysts with backbone chirality in asymmetric hydrogenation.

Summary and Outlook

The amount of data, experimental, computational, etc., on the mechanism of Rh-catalyzed asymmetric hydrogenation is outstanding. It can be seen, nevertheless, that the reaction deserves this attention since we are beginning to enjoy the possibility of having a broader and wiser view on the reaction mechanism. In this account, we suggested an approach for overcoming the existing contradictions in the prediction of the sense of enantioselectivity. The key mechanistic assumption to open the door to this general approach is the fast equilibrium of the dihydride intermediates followed by the stereodetermining migratory insertion step. On one hand, this assumption smoothes the difference between unsaturated and dihydride mechanisms since they join in a single pathway before stereoselection occurs. On the other, it manifests the primary importance of the area above the axially oriented substituents for stereoselection. This in turn makes possible a unified approach to predict the sense of enantioselection via the Knowles quadrant diagrams while also explaining the reasons for earlier uncertainties.

Despite its dignified maturity, research in this area seems to be far from being complete. New effective ligands continue to appear regularly and the synthetic scope of the Rh-catalyzed asymmetric hydrogenation grows further. Hence, additional mechanistic experimental data clarifying the validity of the conclusions made in this account can be expected soon.

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