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Mechanism and Stereoselectivity of Asymmetric Hydrogenation

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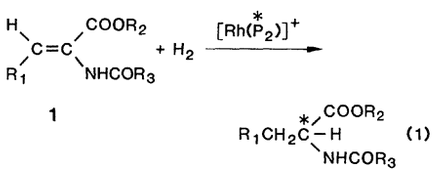
Summary. Rhodium complexes containing chiral phosphine ligands catalyze the hydrogenation of olefinic substrates such as α-aminoacrylic acid derivatives, producing chiral products with very high optical yields. Elucidation of the mechanisms of such reactions leads to the conclusion that the stereoselection is dictated not by the preferred initial binding of the substrate to the chiral catalyst, but rather by the much higher reactivity of the minor diastereomer of the catalyst-substrate adduct corresponding to the less favored binding mode.

The use of chiral catalysts to obtain high optical yields in the asymmetric hydrogenation of prochiral olefinic substrates represents one of the most impressive achievements to date in catalytic selectivity, rivaling the corresponding stereoselectivity of enzymic catalysts (*1*). Notably high optical yields, approaching 100 percent enantiomeric excess (that is, the excess of one of the mirror-image isomers) have been achieved in the hydrogenation of α-acylaminoacrylic acid derivatives such as **1**



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to the corresponding amino acid derivatives (reaction 1) with cationic rhodium complexes containing chiral phosphine (especially chelating diphosphine) ligands as catalysts (*1–4*). The commercial synthesis of L-dopa (3,4-dihydroxyphenylalanine) by such a route constitutes an important practical application of this extraordinarily stereoselective catalysis.

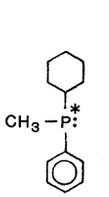
Examples of some of the chiral ligands that are effective in such asymmetric catalytic hydrogenation reactions are depicted by structures **2** to **7**.

These catalyst systems are impressive not only for their remarkable stereoselectivities, but also for their very high activities. Extrapolation from low-temperature measurements (*5*) yields turnover frequencies under saturation conditions approaching 10^2 per second at room temperature for reaction 1 catalyzed by cationic rhodium complexes of DIPHOS (**8**) and its chiral derivatives. Even higher catalytic activities are exhibited by rhodium complexes of chelating diphosphines that form larger chelate rings, for example, DIOP (**3**) (*6*). Such activities are unusually high for homogeneous hydrogenation catalysts (*7*) and, indeed, lie well up on the scale of activities characteristic of enzymes. Thus, in respect of both selectivity and rate, the behavior of these synthetic catalysts rivals, to an unprecedented degree, that of enzymic catalysts.

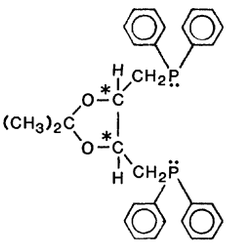
This article deals with the kinetic and mechanistic features of these catalyst systems and with the origin of their remarkable stereoselectivities.

Scope of Asymmetric Catalytic Hydrogenation

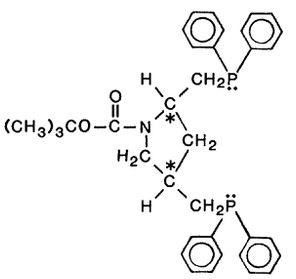
Asymmetric induction has been achieved with a wide variety of chiral homogeneous hydrogenation catalysts and with a considerable range of substrates (*1–4*). However, only with a relatively limited combination of catalysts



(PAMP)
2



(DIOP)
3



(BPPM)
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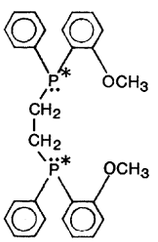
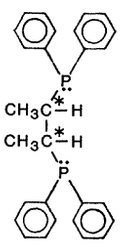


(DIPAMP)
5



(CHIRAPHOS)
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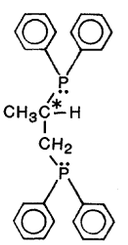
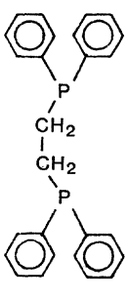


(PROPHOS)
7



(DIPHOS)
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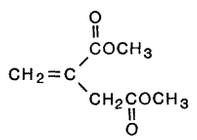
and substrates have very high optical yields ($\gtrsim$ 95 percent enantiomeric excess) been obtained—most readily and consistently in the hydrogenation of (*Z*)-α-acylaminoacrylic acids or esters (**1**) catalyzed by cationic rhodium phosphine complexes in polar solvents such as alcohols or acetone. Such catalytic complexes typically contain a chelating diphosphine ligand, although reasonably high optical yields also have been obtained with catalysts containing two monodentate phosphine ligands such as **2** (in both cases Rh:P = 1:2). The range of chiral phosphine ligands, exemplified by **2** to **7**, is extensive and varied (*1, 8*). However, one common feature appears to be the presence on each coordinating phosphorus atom of two ring substituents, such as a phenyl, a substituted phenyl or, occasionally, a cyclohexyl ring. Equally satisfactory results ($\gtrsim$ 95 percent enantiomeric excess) have been achieved whether the site of chirality is the coordinating phosphorus atom (**5**) or a substituent or backbone carbon atom (**3**, **4**, **6**, or **7**). To date only a few other prochiral



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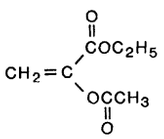

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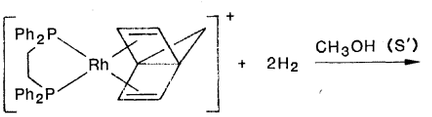
substrates, for example, certain itaconic acid derivatives (**9**) and certain vinyl acetate derivatives (**10**), have been successfully hydrogenated with high optical yields (*9*).

Mechanism of [Rh(DIPHOS)]$^+$–Catalyzed Hydrogenation

The various studies cited above have served to define the scope of asymmetric catalytic hydrogenation and to delineate the empirical dependence of the rates and stereoselectivities of these reactions on electronic and structural features of the catalysts and substrates. However, a fundamental understanding of these themes, and a rational approach to the design and modification of such catalysts, must rest ultimately upon a detailed understanding of the catalytic mechanisms. Furthermore, to accommodate the stereochemical features of the reactions, such a mechanistic description must encompass the actual interception and structural characterization of the stereoregulating intermediates as well as the kinetic information necessary to define the reaction pathway and to establish the roles (if any) in the actual catalytic cycle of species that are identified as being present in the reaction system. Kinetic measurements are essential for the elucidation of any catalytic mechanism since catalysis, by definition and significance, is purely a kinetic phenomenon.

Since several of the most effective and widely used chiral ligands for homogeneous catalytic hydrogenation (for example, **5**, **6**, and **7**) are simple derivatives of the familiar achiral ligand, 1,2-bis(diphenylphosphino)ethane (DIPHOS, **8**), our initial studies were directed at catalytic systems containing the latter (*10*). As subsequent studies demonstrated, the use of such an achiral "model" as a reference constitutes not only a matter of convenience, but also may be important for the recognition, through appropriate comparisons, of those features of the chiral systems that are distinctively associated with their chiral properties (for example, rates).

The catalyst precursors used in such hydrogenation reactions typically are diene adducts such as [Rh(DIPHOS)(NOR)]$^+$ (**11**) (NOR, norbornadiene). We found that H_2 reacts rapidly with such complexes in methanol (S′) and related solvents according to reaction 2 and forms the solvated complex [Rh(DIPHOS)S_2']$^+$ (**12**; abbreviated [Rh(DIPHOS)]$^+$). The latter, accordingly, is the starting point of the catalytic hydrogenation cycle (*10*).



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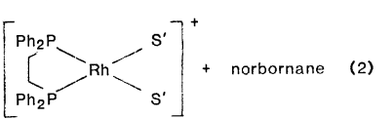

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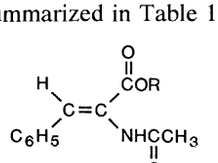
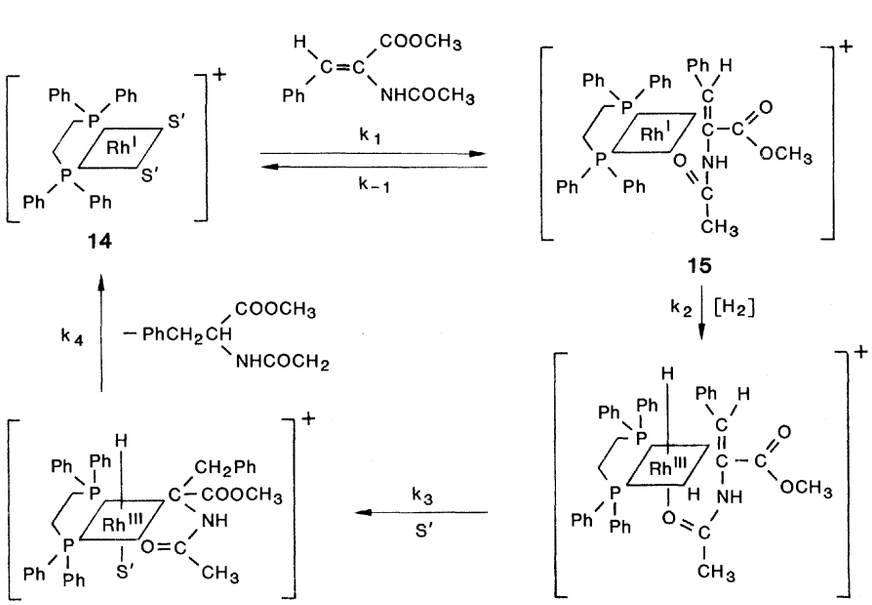
The catalytic mechanism, as deduced from studies encompassing kinetic measurements as well as the characterization of several intermediates by spectroscopic [notably nuclear magnetic resonance (NMR)] and structural methods, is depicted in Fig. 1 (*5, 10*) for the prototype substrate methyl-(*Z*)-α-acetamidocinnamate (MAC, **13a**). The kinetic parameters are summarized in Table 1 (*5, 6*).



13a (MAC) R = CH_3

13b (EAC) R = C_2H_5

The formation of the [Rh(DIPHOS)(MAC)]$^+$ adduct (**15**) is rapid and essentially complete ($K_1 = k_1/k_{-1}$ = [**15**]/[**14**][MAC] $\approx 2 \times 10^4 M^{-1}$ at 25°C, where K_1 is the equilibrium constant, and k_1 and k_{-1} are rate constants) even at moderate ($\gtrsim 0.1M$) MAC concentrations. The structure of **15** (Fig. 1) was established by NMR (^{31}P, ^{13}C, and ^1H) spectroscopy and by single crystal x-ray analysis of the BF_4 salt, revealing chelation of the MAC substrate to the Rh atom through the carbonyl oxygen of the amide group as well as through normal



14 **15** **16** **17**

Fig. 1. Mechanism of the [Rh(DIPHOS)]$^+$–catalyzed hydrogenation of methyl-(*Z*)-α-acetamidocinnamate (MAC).

symmetrical (η^2) coordination of the C=C bond (*11*).

At room temperature, the second step of the catalytic cycle (corresponding to k_2), the reaction of [Rh(DIPHOS)-(MAC)]$^+$ with H_2, was found to be rate-determining for the overall catalytic hydrogenation reaction. However, the final product-forming step, corresponding to the rate law $-d[\mathbf{17}]/dt = k_4[\mathbf{17}]$ exhibited a sufficiently higher activation enthalpy compared with k_2 (17.0 as compared with 6.3 kilocalories per mole) that this step became rate-limiting below −40°C, permitting the intermediate **17** to be intercepted and characterized. Figure 1 depicts the structure of **17** as deduced from ^1H, ^{31}P, and ^{13}C NMR spectral measurements (*5*). These measurements also served to establish that H-transfer from Rh during the migratory insertion step (**16** → **17**) occurs to the β-carbon atom of the C=C bond while the α-carbon atom becomes bonded to Rh. Although such hydridoalkyl complexes frequently have been postulated as intermediates in homogeneous catalytic hydrogenation reactions (*7, 12*), this is the first time that such an intermediate has actually been intercepted and characterized, and the product C–H bond–forming reductive elimination step has been directly observed.

The only intermediate in the proposed catalytic cycle that has not thus far been intercepted and directly characterized is **16**. The formation of such an intermediate seems highly likely by analogy with the well-recognized oxidative addition reactions of H_2 with other Rh^I and related d^8 complexes, particularly in view of the similarity of the activation parameters of k_2 to those that have been determined directly for such oxidative addition reactions (*7, 13*). Failure to intercept **16** apparently reflects the very rapid transformation of **16** to **17**. Indeed, it is the high rate of this step which accounts for the unusually high activity of these catalyst systems and which made possible the interception of the hydridoalkyl intermediate **17**.

The mechanism depicted by Fig. 1 extends also to the [Rh(DIPHOS)]$^+$–catalyzed hydrogenation of other olefinic substrates including simple olefins such as 1-hexene (*10*). However, while such olefins also form intermediate adducts analogous to **15**, the formation constants (corresponding to k_1/k_{-1}) typically are much lower than for (*Z*)-α-acylaminoacrylic acid derivatives; for example, $2M^{-1}$ for 1-hexene and $3M^{-1}$ for methyl acrylate, compared to approximately $2 \times 10^4 M^{-1}$ for MAC.

Origin of Enantioselection

With the exception of the features identified below that are specifically related to the formation of diastereomers of the adduct corresponding to **15**, the chemistry of cationic complexes of chiral derivatives of DIPHOS, notably of DIPAMP (**5**) and CHIRAPHOS (**6**), and the mechanisms of catalysis by these complexes of the hydrogenation of prochiral substrates such as MAC parallel closely those of the corresponding DIPHOS complexes (*6, 14*). When the mechanistic scheme of Fig. 1 is extended to catalysts containing such chiral ligands, it must be modified in accordance with Fig. 2 to accommodate the formation of diastereomeric forms of the adduct corresponding to **15** (**15′** and **15″**) and of the further reaction intermediates. Invoking the plausible assumptions (i) that the oxidative addition of H_2 and subsequent steps in the catalytic cycle are irreversible (supported by the absence of isotopic exchange with unreacted substrate when D_2 is used instead of H_2), and (ii) that the observed *cis*-addition of H_2 to the coordinated olefin is *endo*, that is, to the Rh-coordinated face, permits the stereochemistry of the product to be correlated with that of the adduct diastereomer from which it is derived in accord with Fig. 2, namely,

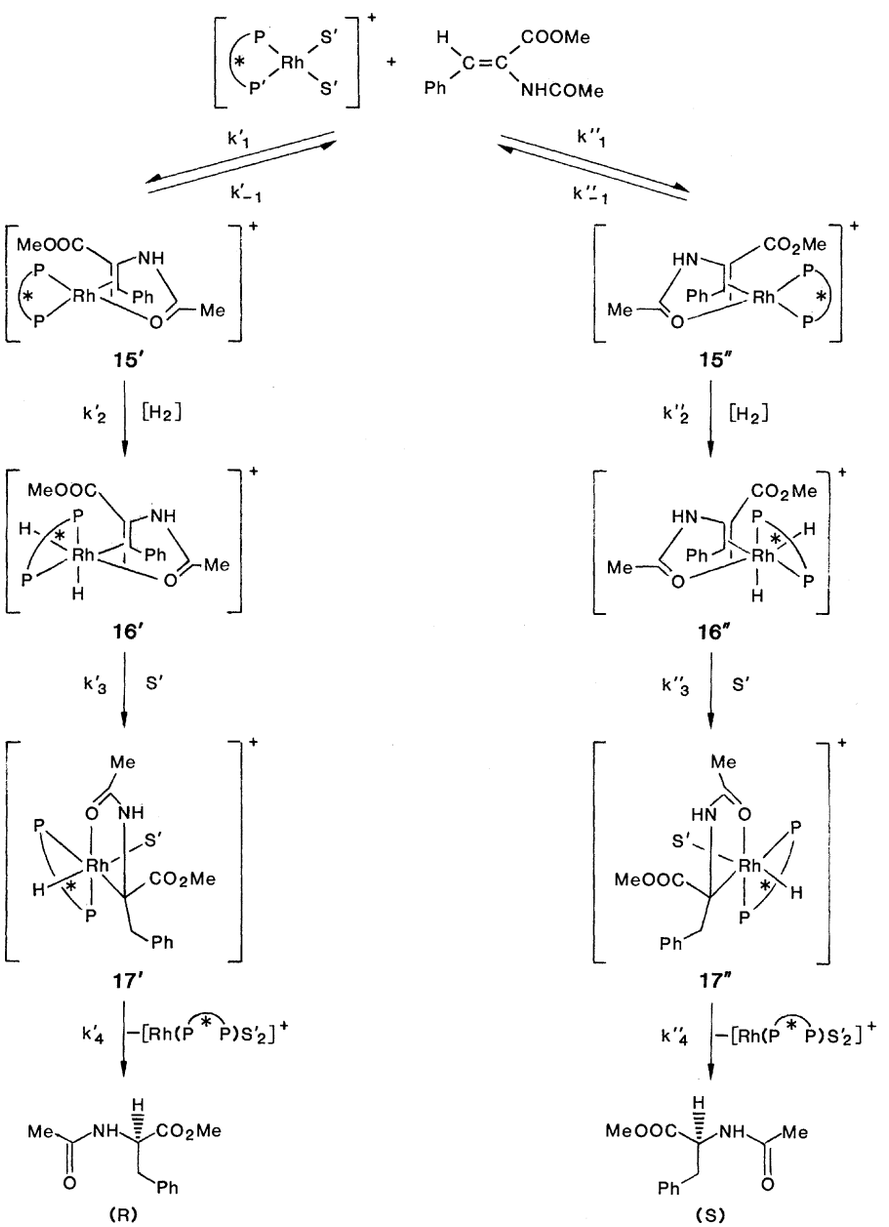


Fig. 2. Mechanistic scheme for the hydrogenation of a prochiral substrate (MAC) with a catalyst containing a chiral chelating diphosphine ligand ($\widehat{P^*P}$, CHIRAPHOS or DIPAMP: *S′*, methanol).

the *N*-acetyl-(*R*)-phenylalanine ester product from **15′** and the *S*-product from **15″**.

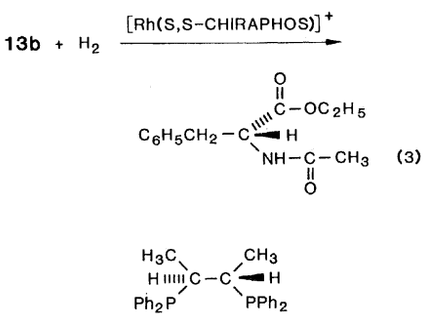
Two possible limiting interpretations may be accorded to the origin of the enantioselection in such systems, namely:

1) The prevailing product chirality is determined by the preferred mode of initial binding of the substrate to the catalyst; that is, the predominant enantiomer of the product arises from the predominant diastereomer of the catalyst-substrate adduct.

2) The predominant enantiomer of the product arises from the minor diastereomer of the catalyst-substrate adduct by virtue of the much higher reactivity of the latter, compared with that of the predominant diastereomer, toward H_2.

Because the formation and dissociation of the catalyst-substrate adducts, and hence interconversion and equilibration of their diastereomeric forms, is rapid (compared with their reactions with H_2) at ambient temperatures and pressures, these two alternatives are kinetically indistinguishable under the usual catalytic conditions. In the absence of definitive proof, several lines of indirect evidence originally were interpreted as favoring the first of the above alternatives (*15–18*). This interpretation also seemed more attractive on conceptual grounds since it corresponds to the familiar lock-and-key concept that has been invoked so widely to explain the characteristically high selectivities of enzymic catalysts.

To resolve this ambiguity, it was necessary to correlate the absolute configurations of the products with those of the intermediate catalyst-substrate adducts. This was first achieved for the hydrogenation of ethyl-(*Z*)-α-acetamidocinnamate (EAC, **13b**) catalyzed by the rhodium complex of *S,S*-CHIRAPHOS (**18**) in



accordance with reaction 3 (*14*). This reaction was shown to proceed with high enantioselectivity yielding *N*-acetyl-(*R*)-phenylalanine (> 95 percent enantiomeric excess).

Table 1. Kinetic parameters (rate constant; $\Delta H‡$, the enthalpy of activation; and $\Delta S‡$, the entropy of activation) for the [Rh(DIPHOS)]$^+$–catalyzed hydrogenation of MAC in methanol according to Fig. 1.

Rate constant (units)	k (25°C)	$\Delta H‡$ (kcal/mole)	$\Delta S‡$ (cal/mole °K)
k_1 (M^{-1} sec^{-1})	1.4×10^4		
k_{-1} (sec^{-1})	5.2×10^{-1}	18.3	+2
k_2 (M^{-1} sec^{-1})	1.0×10^2	6.3	−28
k_3 (sec^{-1})	> 1		
k_4 (sec^{-1})	23	17.0	+6

The essential features of reaction 3 were found to parallel those of the corresponding [Rh(DIPHOS)]$^+$–catalyzed reaction, as depicted by Fig. 1 (*14*). Formation of a [Rh(*S,S*-CHIRAPHOS)(EAC)]$^+$ adduct (**19**) analogous to **15** occurred with a similar equilibrium constant. The electronic spectrum and ^{31}P NMR spectrum of **19** also were virtually identical to those of **15**. Only a single diastereomer of [Rh(*S,S*-CHIRAPHOS)(EAC)]$^+$ could be identified in solution by NMR and, hence, the other diastereomer (which is expected to exhibit a distinguishable NMR spectrum) must be present to the extent of less than 5 percent.

The rate law for reaction 3 was found to be similar to that for the [Rh(DIPHOS)]$^+$–catalyzed reaction, namely, $-d[H_2]/dt = k_5[H_2][\mathbf{19}]$, with $k_5 = 1.6M^{-1}$ sec^{-1}; that is, only about 1/60 the corresponding value (k_2) for the [Rh(DIPHOS)]$^+$–catalyzed reaction. This rate difference represents the only significant disparity revealed by the various solution measurements on the [Rh(DIPHOS)]$^+$ and [Rh(*S,S*-CHIRAPHOS)]$^+$ systems (*14*).

The structure of the predominant diastereomer of the [Rh(*S,S*-CHIRAPHOS)(EAC)]$^+$ ion, determined by x-ray analysis of single crystals of the perchlorate salt, is depicted in Fig. 3 (*14, 19*) and is essentially identical to that previously determined for **15** (*11*). Of crucial significance in the present context is the finding that the C_α-re face of EAC is coordinated to the Rh atom. Addition of H_2 to this face, in accord with the mechanism deduced above (Fig. 1), would yield *N*-acetyl-(*S*)-phenylalanine ethyl ester. Instead it was found that the predominant product of reaction 3 (> 95 percent enantiomeric excess) was the *R* isomer (*3, 14*).

We are, accordingly, led to the conclusion that it is not the preferred mode of initial binding of the prochiral olefinic substrate to the catalyst but, rather, differences in the rates of subsequent reactions of the diastereomeric catalyst–substrate adducts with H_2, that dictates the enantioselectivity of these catalyst systems. Apparently the minor diastereomer is sufficiently more reactive than the major one that it determines the predominant chirality of the product.

This conclusion also is consistent with, and serves to explain, the observation that, although the structural, equilibrium, and spectroscopic (electronic and NMR) properties of the predominant [Rh(*S,S*-CHIRAPHOS)(EAC)]$^+$ diastereomer are virtually identical with those of the analogous [Rh(DIPHOS)(EAC)]$^+$ complex, its apparent reactivity toward H_2 (k_5) is only about 1/60 of the latter (k_2). In contrast, the reactivity toward H_2 of the [Rh(*S,S*-CHIRAPHOS)]$^+$ adduct of a simple olefin (1-hexene) actually was found to be about three times higher than that of the corresponding [Rh(DIPHOS)]$^+$ adduct. This suggests that the low value of k_5 compared with k_2 is due not to the intrinsically lower reactivity of the *S,S*-CHIRAPHOS–derived catalyst but, rather, to the low concentration of the "reactive" minor diastereomer of the EAC adduct (*14*).

Evidence for the same conclusion concerning the origin of the enantioselection in the [Rh(*R,R*-DIPAMP)]$^+$–catalyzed hydrogenation of MAC and related substrates is provided by yet another line of evidence. With this catalyst, both diastereomers of the catalyst-substrate adduct can be detected in solution by NMR (although their absolute configurations cannot be assigned) (*6, 15*). At 25°C, the equilibrium ratio of the two diastereomers is about 11:1. Since this is also approximately the ratio of the two enantiomers derived from the hydrogenation of such solutions, the conclusion originally was drawn that the enantioselectivity of the reaction was determined by the ratio of the diastereomeric adduct precursors, the prevailing chirality of the product being that derived from the major diastereomer (*15*). However, by having H_2 react with a solution containing such a mixture of diastereomers of [Rh(*R,R*-DIPAMP)(MAC)]$^+$ at low temperatures (around −40°C), where the interconversion of diastereomers is frozen out, it was found that only the minor diastereomer reacts directly with H_2 (to form initially the hydridoalkyl complex corresponding to **17** and then, by reductive elimination, the hydrogenated product (*6, 16*). The subsequent slow reaction of the major diastereomer occurred at a rate independent of the H_2 concentration and approximating the rate of dissociation of the adduct. Thus, consistent with the high enantioselectivity of the reac-

tion (> 95 percent *S* amino acid ester), product formation appears to proceed predominantly through the minor diastereomer in accordance with reaction 4 (*6*).

$$[Rh(DIPAMP)(MAC)]^+_{major} \longrightarrow$$

$$[Rh(DIPAMP)]^+ + MAC \longrightarrow$$

$$[Rh(DIPAMP)(MAC)]^+_{minor} \xrightarrow{H_2}$$

$$[Rh(DIPAMP)(MAC)H_2]^+_{minor} \longrightarrow$$

$$[Rh(DIPAMP)(MACH)H]^+_{minor} \longrightarrow$$

$$[Rh(DIPAMP)]^+ + S\text{-}MACH_2 \quad (4)$$

Kinetic measurements (*6*) on the [Rh(*R*,*R*-DIPAMP)]$^+$–catalyzed hydrogenation of MAC in methanol at 25°C yielded the following values for the parameters defined in Fig. 2 (where k' and k'' refer to the major and minor [Rh(*R*,*R*-DIPAMP)(MAC)]$^+$ diastereomers, respectively); $k'_1 = 5.3 \times 10^3 M^{-1}$ sec^{-1}; $k'_{-1} = 0.15$ sec^{-1}; $k'_2 = 1.1 M^{-1}$ sec^{-1}; $k''_1 = 1.1 \times 10^4 M^{-1}$ sec^{-1}; $k''_{-1} = 3.2$ sec^{-1}; $k''_2 = 6.4 \times 10^2 M^{-1}$ sec^{-1}; K'_1(eq) $= k'_1/k'_{-1} = 3.5 \times 10^4 M^{-1}$; K''_1(eq) $= k''_1/k''_{-1} = 3.3 \times 10^3 M^{-1}$. The approximately 580-fold higher reactivity of the minor diastereomer (k''_2/k'_2) more than offsets its lower concentration ([**15**″]/[**15**′]) = 0.09) and results in a product ratio of about 60:1 (> 96 percent enantiomeric excess) in favor of the *S*-enantiomer which is derived from the minor diastereomer.

Other Consequences and Indirect Criteria

The demonstration of the origin of the enantioselection in the two cases considered above depended on either (i) the isolation and structural characterization of the catalyst-substrate adduct (for CHIRAPHOS), or (ii) the detection and monitoring of both diastereomers of the adduct in solution (for DIPAMP). In general, for other catalyst systems, neither of these circumstances may be realized, so that it is necessary to resort to less direct criteria to ascertain whether the same conclusions apply.

One such criterion relates to the dependence of the optical yield on the H_2 concentration. According to the interpretation of the origin of enantioselection deduced above, the reversibility of the initial step of catalyst-substrate adduct formation, through which interconversion of the diastereomeric adducts apparently occurs, should be reduced by increasing the rate of the subsequent H_2 oxidative addition step. Thus, at sufficiently high H_2 concentrations (when $k_2[H_2][\mathbf{15}] \gg k_{-1}[\mathbf{15}]$), the rate and stereochemistry of the reaction should become determined by the initial binding rates of the prochiral substrate to the catalyst (that is, by k'_1/k''_1). For systems of the type we have described, this predicts that the enantioselectivity should decrease, with the possibility of eventual reversal of predominant product chirality, with increasing H_2 pressure. This has been quantitatively confirmed for the [Rh(DIPAMP)]$^+$–catalyzed hydrogenation of MAC (*6*). Furthermore, such an inverse dependence of optical yield on the H_2 pressure, exemplified by the results in Table 2, has been observed for virtually all of the asymmetric hydrogenation catalysts that have thus far been examined (*2*, *6*, *20*, *21*). This feature of the behavior of these systems limits the scope of achieving higher rates, while still maintaining high optical yields, by increasing the H_2 pressure. Insofar as this inverse dependence of optical yield is fairly general for the catalytic hydrogenation of α-acylaminoacrylic acid derivatives with catalysts containing a variety of chiral phosphine ligands, we conclude that our interpretation of the enantioselection in such reactions probably extends to this whole class of catalysts and substrates.

Table 2. Effect of H_2 pressure on the optical yield of the [Rh(diphosphine)]$^+$–catalyzed hydrogenation of (*Z*)-α-benzamidocinnamic acid (*20*).

H_2 pressure (atm)	Optical yield (percent enantiomeric excess)		
	S,*S*-BPPM	*R*,*R*-DIOP	*R*,*R*-DIPAMP
1	83.8 (*R*)	55.2 (*R*)	
5	62.3 (*R*)	8.4 (*R*)	63.6 (*S*)
20	21.2 (*R*)	0.5 (*S*)	29.9 (*S*)
50	4.7 (*S*)	4.9 (*S*)	
100	8.4 (*S*)		

A related, and somewhat surprising, consequence of our analysis concerns the temperature dependence of the optical yield. According to our interpretation of the origin of the enantioselection, high enantioselectivity depends on rapid interconversion of the diastereomeric catalyst-substrate adducts compared with the rates of their reactions with H_2. Since the adduct dissociation step through which such interconversion occurs typically has a much higher activation enthalpy than reaction with H_2 (18.3 compared to 6.3 kcal/mole for **15**), the diastereomer interconversion process should become "frozen out" at sufficiently low temperatures. This leads to the prediction that, provided the major diastereomer exhibits some reactivity toward H_2 (as it must if the enantiomeric excess is less than 100 percent), the optical yield may actually decrease with decreasing temperature. Such an unusual dependence of enantioselectivity on temperature has been reported, for example, for the hydrogenation of MAC and related substrates catalyzed by rhodium complexes containing several chiral phosphine ligands (*6*, *20*, *21*). In one particularly dramatic case, the optical yield increases from 0 to 60 percent enantiomeric excess in going from 0° to 100°C (*21*).

Origin of Stability and Reactivity Differences of Diastereomeric Adducts

The conclusion that we have reached concerning the origin of enantioselection in these systems implies very large differences in reactivity toward H_2 between the two diastereomeric forms of the catalyst-substrate adduct. With [Rh(*S*,*S*-

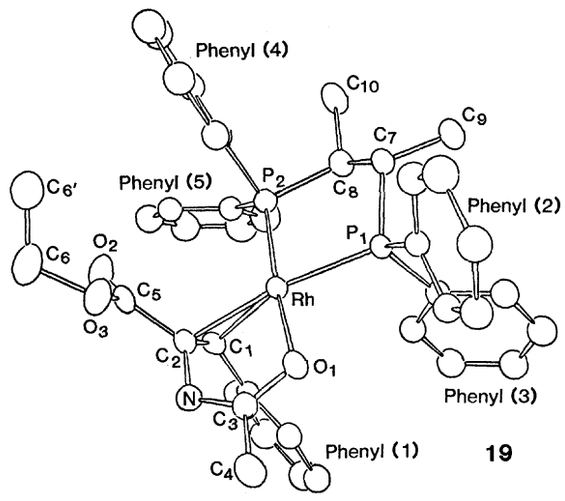
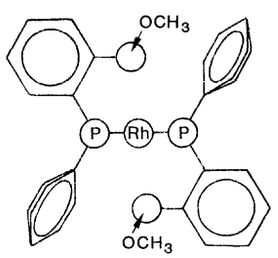


Fig. 3. Structure of the predominant diastereomer of [Rh(*S*,*S*-CHIRAPHOS)(EAC)]$^+$.

CHIRAPHOS)(EAC)]$^+$, the minor (less stable) diastereomer must be at least 10^3 times as reactive toward H_2 at 25°C as the major (more stable) diastereomer in order to account for the observed optical yield. In the case of [Rh(*R*,*R*-DIPAMP)-(MAC)]$^+$, where both diastereomers are observed, the corresponding reactivity difference has been directly measured to be about 580. The origin of these marked differences in reactivity clearly constitutes an important aspect of the behavior of these systems.

It has been pointed out (*18*) that a general feature of the conformations of the diarylphosphine ligands that are common to these catalysts is the arrangement of the four phenyl groups in a chiral alternating "edge-face" array depicted schematically (**20**) for [Rh(*R*,*R*-DIPAMP)]$^+$ and also re-



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vealed by the structure of Fig. 3. The enantiorecognition involved in the binding of prochiral substrates such as (*Z*)-α-acylaminocinnamic acid derivatives to such a chiral template and the differences in stability between the diastereomers of the resulting adducts (for example, of [Rh(*R*,*R*-DIPAMP)(MAC)]$^+$ or [Rh(*S*,*S*-CHIRAPHOS)(EAC)]$^+$) has been attributed to the "matching" of the two faces of the substrate to the chiral "template" formed by this array of phenyl rings. The chirality and rigidity of this template, in turn, are determined by the nature of the chiral centers in the phosphine ligand and of the backbone connecting the phosphorus atoms. This model, as reflected in the structure depicted in Fig. 3, appears to provide a satisfactory basis for interpreting the stability difference between the diastereomers of the initial catalyst-substrate adducts; for example, $\Delta G° = 1.4$ kcal/mole, $\Delta H° = 2.2$ kcal/mole, $\Delta S° = 2.7$ cal/mole °K for [Rh(*R*,*R*-DIPAMP)-(MAC)]$^+$ (*6*), where $\Delta G°$, $\Delta H°$, and $\Delta S°$ are the standard free energy change, the standard enthalpy change, and the standard entropy change, respectively.

The origin of the striking differences between the reactivities of the diastereomeric adducts toward H_2 is more difficult to understand. It is, of course, not unexpected that the less stable of a pair of diastereomers will exhibit the higher reactivity by virtue of its higher initial free energy. However, to account for the enantioselectivity of the reaction, the difference in reactivity must be much greater than the difference in stability (that is, the difference in equilibrium concentration) of the diastereomers, indeed at least 50 times greater to accommodate an optical yield of 96 percent enantiomeric excess. At this stage, the origin of this marked reactivity difference (corresponding to $\Delta\Delta G^‡ = 4$ kcal in the case of [Rh(*R*,*R*-DIPAMP)(MAC)]$^+$) is still a matter of speculation. A reasonable suggestion is that the reactivity difference has its origin in the stability difference of the diastereomers of the initial product of the oxidative addition of H_2, the relative stabilities of the diastereomeric products being opposite to that of the parent catalyst-substrate adducts. Thus, the greater stability of the diastereomer of the dihydride, RhH_2(*R*,*R*-DIPHOS)(MAC)]$^+$, derived from the less stable diastereomer of [Rh(*R*,*R*-DIPHOS)(MAC)]$^+$, enhances the driving force and rate of the reaction of the former with H_2, compared with the rate of the more stable diastereomer. The reaction profiles corresponding to this situation are depicted schematically in Fig. 4. Examination of space-filling models provides some support for such an interpretation and suggests that a systematic reason for the inverted stabilities of the diastereomers of the initial catalyst-substrate adducts and the dihydrides derived from them, may be the *trans*-disposition of the substrate and diphosphine chelate rings in the former case and *cis*-disposition in the latter (Fig. 4). However, the space-filling models of these complexes (particularly of **16**) are extremely crowded and conclusions based on such models must be considered to be of limited reliability. Efforts are being made to explore this theme further and more directly, by actually intercepting and characterizing the dihydride intermediates in question.

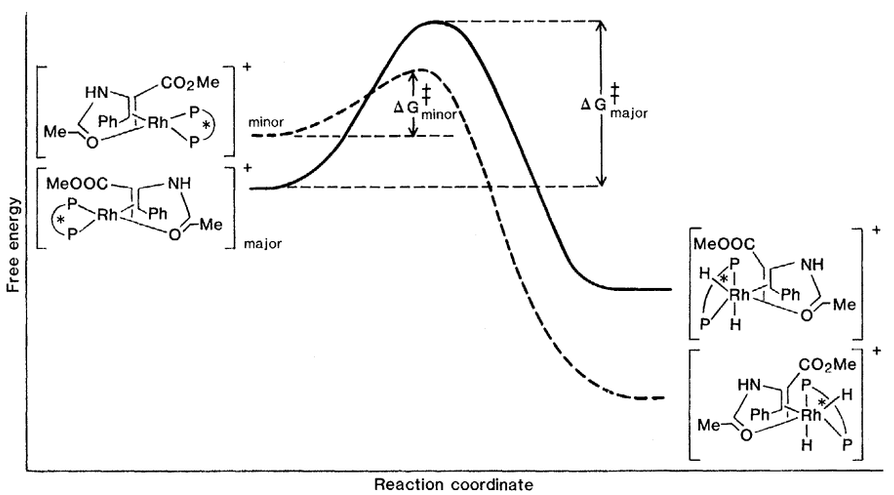

Fig. 4. Schematic reaction coordinate profiles for the enantiodetermining reactions of the diastereomeric [Rh(DIPAMP)(MAC)]$^+$ catalyst-substrate adducts with H_2 ($\Delta G^‡$, the free energy of activation).

Concluding Remarks

This article has dealt with a relatively restricted class of asymmetric catalytic reactions, namely, the hydrogenation of α-acylaminoacrylic acid derivatives and related substrates, catalyzed by rhodium complexes containing chiral phosphine ligands. The scope of asymmetric catalysis by metal complexes is considerably more extensive, and other substrates as well as other reactions, such as hydroformylation (*22*), hydrosilylation (*23*), and olefin coupling (*24*), have been studied. While moderate optical yields, in some cases up to 70 percent, have been achieved in such reactions, only in one other case do these consistently approach the high enantioselectivities (> 90 percent enantiomeric excess) characteristic of the hydrogenation reactions discussed in this article. This case involves the epoxidation of allylic alcohols by *tert*-butylhydroperoxide, catalyzed by titanium alkoxides in the presence of a tartarate ester as the chiral component (*25*). The latter catalyst system, like those discussed in this article, exhibits high enantioselectivity only for a restricted class of substrates. Furthermore, in each case, the effective substrates are characterized by the presence, in addition to the reactive olefin site, of a neighboring binding site (a

carbonyl and hydroxyl substituent, respectively) which, in combination with the olefin site can effect the anchoring of the substrate to the catalyst through chelation.

The studies described in this article constitute a detailed elucidation of the mechanism of such an asymmetric catalytic reaction. The most significant and surprising conclusion yielded by these studies is that, contrary to the view generally held previously, it is not the preferred mode of the initial binding of the prochiral substrate to the chiral catalyst, but rather overcompensating differences in the rates of the subsequent reactions of the diastereomeric catalyst-substrate adducts that dominate the enantioselectivity of asymmetric catalytic hydrogenation. The predominant product enantiomer arises from the minor (less stable) diastereomer of the adduct, which frequently does not accumulate in sufficient concentration to be detected. In contrast, the major diastereomer, whose stability reflects the optimal fitting of the prochiral substrate to the chiral template of the catalyst and which is the principal species present under catalytic conditions, is unreactive and corresponds to a "dead-end" complex. Based on a variety of criteria, including the temperature- and H_2 pressure–dependence of the optical yield, this conclusion appears to be quite general for the variety of chiral catalysts identified for this class of reactions. It also finds parallels in the conclusions reached in studies on the mechanisms of other homogeneous catalytic reactions, for example, the $[Rh(PPh_3)_3Cl]$-catalyzed hydrogenation of olefins. In the latter case, it also was demonstrated that virtually none of the species that accumulate under the conditions of the catalytic reactions in sufficient concentrations to be detected actually are intermediates in the catalytic reaction (*7*). This serves to underscore the unreliable, and often misleading, mechanistic conclusions that may be derived by simply identifying the species present in a catalytic system unless such observations are coupled with kinetic and other appropriate (for example, stereochemical) evidence to define the role of such species in the reaction mechanism.

An important question that remains to be addressed is how widely our conclusion concerning the origin of enantioselection applies to other stereoselective catalyst systems. This question is particularly significant in the context of enzymic reactions where a contrary interpretation (embodied in the familiar lock-and-key concept) often is assumed; namely, that the stable adducts that are formed by optimal fitting of the substrate to the enzyme, and that so frequently are the focus of direct observation and characterization, are intermediates in the enzymic reactions. Since the formation of such adducts usually is rapid compared with the catalytic reaction, direct support for such a conclusion often is lacking, and the results of our studies on asymmetric hydrogenation raise serious questions about its widely accepted plausibility. The criteria for distinguishing between the alternative interpretations that need to be considered are not readily realized for many catalytic reactions, but the studies described in this article provide some leads as to how such criteria might be developed.

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