MECHANISM AND STEREOCHEMISTRY OF ASYMMETRIC CATALYSIS BY
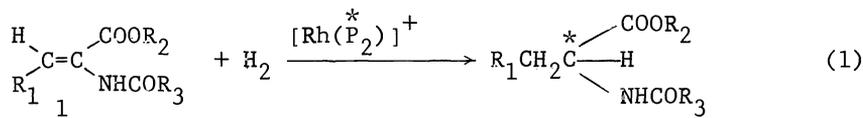METAL COMPLEXES

Jack Halpern

Department of Chemistry, The University of Chicago
Chicago, Illinois 60637, U.S.A.

Abstract - The use of chiral catalysts to effect the asymmet-
ric hydrogenation of prochiral olefinic substrates with high
optical yields represents one of the most impressive achieve-
ments to date in catalytic selectivity. Notably high optical
yields, approaching 100% enantiomeric excess, have been
achieved in the hydrogenation of prochiral enamides to the
corresponding amino acid derivatives, using homogeneous cat-
ionic rhodium catalysts containing chiral phosphine, especi-
ally bis(tertiaryphosphine), ligands. The following aspects
of such systems are discussed: (a) the coordination chemistry
of the cationic rhodium phosphine catalysts, (b) the mechanism
of catalytic hydrogenation, and (c) the origin of the enan-
tioselection. A remarkable conclusion of the studies de-
scribed is that, contrary to the hitherto prevailing "lock and
key" view concerning these and related stereoselective cata-
lysts, the enantioselection in these systems is determined not
by the preferred initial binding of the prochiral substrate to
the chiral catalyst but, rather, by the much higher reactivity
of the minor diastereomer of the catalyst-substrate adduct cor-
responding to the less favored binding mode.

INTRODUCTION

The use of chiral catalysts to effect the asymmetric hydrogenation of pro-
chiral olefinic substrates with high optical yields represents one of the
most remarkable achievements to date in catalytic selectivity, rivaling the
corresponding stereoselectivity of enzymic catalysts (1). Notably high opti-
cal yields, approaching 100% enantiomeric excess (e.e.), have been obtained
in the hydrogenation of α-acylaminoacrylic acid derivatives such as 1 to the
corresponding amino acid derivatives (eq. 1) using cationic rhodium complexes
containing chiral phosphine (especially chelating diphosphine) ligands as
catalysts (1-4). The commercial synthesis of L-dopa (3,4-dihydroxyphenyl-
alanine) by such a route exemplifies an important practical application of
this extraordinarily stereoselective catalysis.

$$H \underset{R_1}{\overset{}{\diagdown}}C=C\overset{COOR_2}{\underset{NHCOR_3}{\diagup}} + H_2 \xrightarrow{[Rh(\overset{*}{P}_2)]^+} R_1CH_2\overset{*}{C}\overset{COOR_2}{\underset{NHCOR_3}{\diagdown}}H \qquad (1)$$
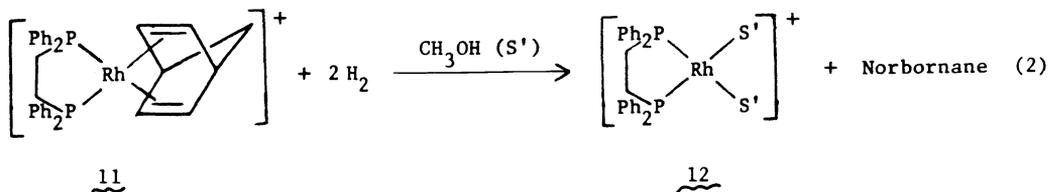
Examples of some of the chiral ligands that have been found to be effective
in such asymmetric catalytic hydrogenation reactions are depicted by 2 to 7
(1-6). These catalyst systems are impressive not only for their remarkable
stereoselectivities but also for their very high activities. Extrapolation
from low temperature measurements (7) yields turnover frequencies under sat-
uration conditions approaching 10^2 sec^{-1} at room temperature for reaction 1
catalyzed by cationic Rh rhodium complexes of DIPHOS (8) and its chiral de-
rivatives. Even higher catalytic activities are exhibited by rhodium com-
plexes of chelating diphosphine ligands that form larger chelate rings, e.g.,
DIOP (3) (8). Such activities are unusually high for homogeneous hydrogena-
tion catalysts (9) and, indeed, lie well up on the scale of activities cha-
racteristic 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.

(PAMP)   (DIOP)   (BPPM)

2   3   4

(DIPAMP)   (CHIRAPHOS)   (PROPHOS)   (DIPHOS)

5   6   7   8
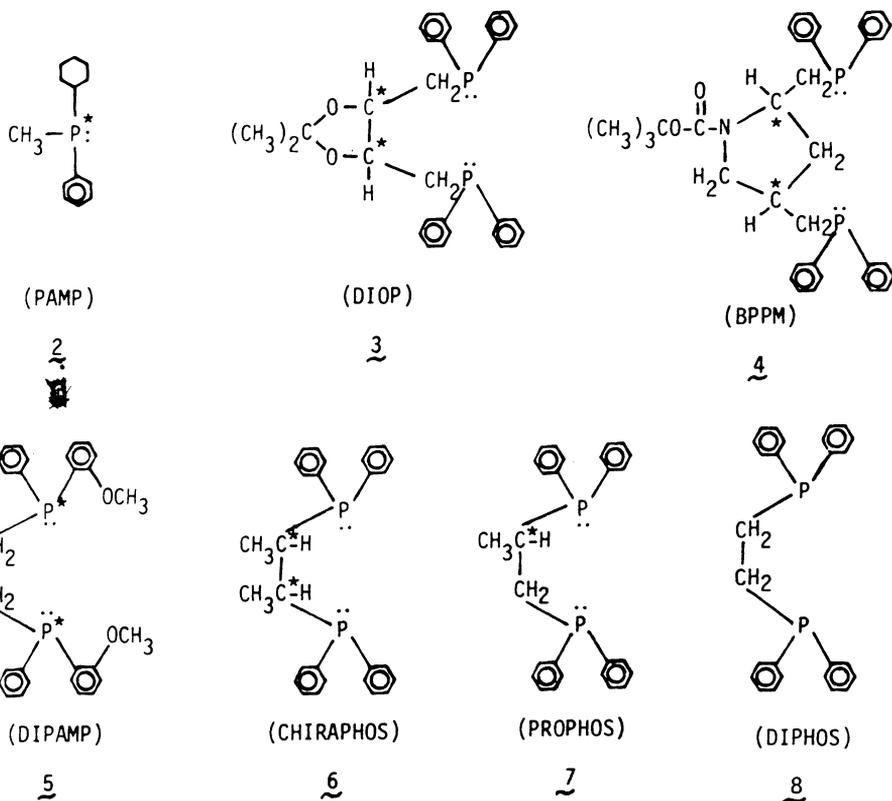
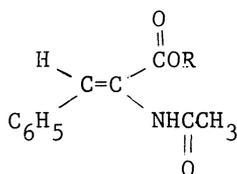## MECHANISM OF [Rh(DIPHOS)]$^+$-CATALYZED HYDROGENATION

Various earlier studies have served to define the scope of asymmetric cata-
lytic hydrogenation and to delineate the empirical dependence of the rates
and stereoselectivities of these reactions on electronic and structural fea-
tures of the catalysts and substrates (1-6). However, a fundamental under-
standing of these themes, and a rational approach to the design and modifica-
tion of such catalysts, must rest ultimately upon a detailed understanding of
the catalytic mechanisms.

Since several of the most effective and widely used chiral ligands for homo-
geneous catalytic hydrogenation (e.g., 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). The catalyst precursors employed in such hydrogenation reactions
typically are diene adducts such as [Rh(DIPHOS)(NOR)]$^+$ (11, NOR = norborna-
diene). H$_2$ was found to react rapidly with such complexes in methanol (S')
and related solvents according to eq. 2 and form the solvated complex
[Rh(DIPHOS)S$_2'$]$^+$ (12, abbreviated [Rh(DIPHOS)]$^+$). The latter, accordingly, is
the starting point of the catalytic hydrogenation cycle (10).

$$\left[\begin{array}{c} Ph_2P \\ \\ Ph_2P \end{array} Rh \right]^+ + 2\,H_2 \xrightarrow{\ CH_3OH\ (S')\ } \left[\begin{array}{c} Ph_2P \\ \\ Ph_2P \end{array} Rh \begin{array}{c} S' \\ \\ S' \end{array}\right]^+ + \ Norbornane \quad (2)$$

11   12

The catalytic mechanism, as deduced from studies encompassing kinetic measure-

ments as well as the characterization of several intermediates by spectro-
scopic (notably NMR) and structural methods, is depicted in Fig. 1 (10, 7)
for the prototype substrate methyl-(Z)-α-acetamidocinnamate (MAC, 13a). The
kinetic parameters are summarized in Table 1 (7,8).

$$
\begin{array}{c}
\text{O} \\
\parallel \\
\text{H} \qquad\qquad \text{COR} \\
\diagdown \quad \diagup \\
\text{C=C} \\
\diagup \quad \diagdown \\
C_6H_5 \qquad \text{NHCCH}_3 \\
\parallel \\
\text{O}
\end{array}
$$

13a (MAC), R = CH$_3$; 13b (EAC), R = C$_2$H$_5$

The formation of the [Rh(DIPHOS)(MAC)]$^+$ adduct (15) is rapid and essentially
complete (K_1eq = k_1/k_{-1} = [15]/[14][MAC] = ca 2 $\times$ 10^4 M^{-1} at 25°C) even at
moderate ($\gtrsim$ 0.1 M) MAC concentrations. The structure of 15, depicted in
Fig. 1, was established by NMR (^{31}P, ^{13}C and ^{1}H) spectroscopy and by single
crystal X-ray analysis of the BF$_4$ salt, revealing chelation of the MAC sub-
strate to the Rh atom through the carbonyl oxygen of the amide group as well
as through symmetrical side-on (η^2) coordination of the C=C bond (11).

At room temperature the second step of the catalytic cycle (corresponding to
k_2), i.e., the oxidative addition of H$_2$ to [Rh(DIPHOS)(MAC)]$^+$, was found to be
rate-determining for the overall catalytic hydrogenation cycle. However, the
final product-forming step, corresponding to the rate-law, -d[17]/dt = k_4[17],
exhibited a sufficiently higher activation enthalpy compared with k_2 (17.0 vs
6.3 kcal/mol) that this step became rate-limiting below -40°C, permitting the
intermediate 17 to be intercepted and characterized at low temperatures.
Fig. 1 depicts the structure of 17 as deduced from ^{1}H, ^{31}P and ^{13}C NMR spec-
tral measurements (7). Although such hydridoalkyl complexes frequently have
been posutlated as intermediates in homogeneous catalytic hydrogenation re-
actions (12,9) this represents the first instance in which such an intermedi-
ate actually has been intercepted and characterized, and the product-forming
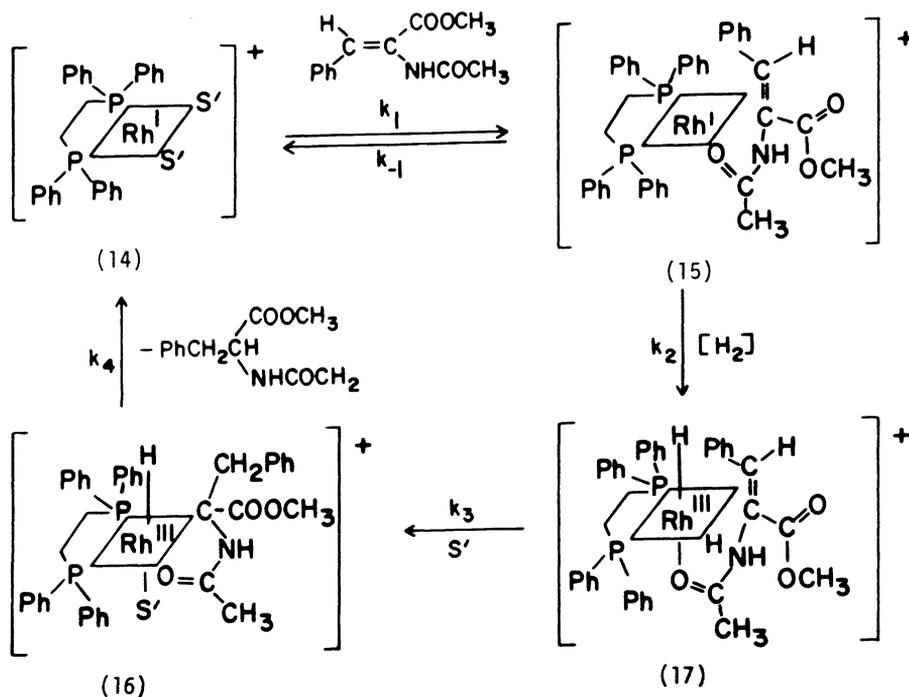C-H bond-forming reductive elimination step directly observed.

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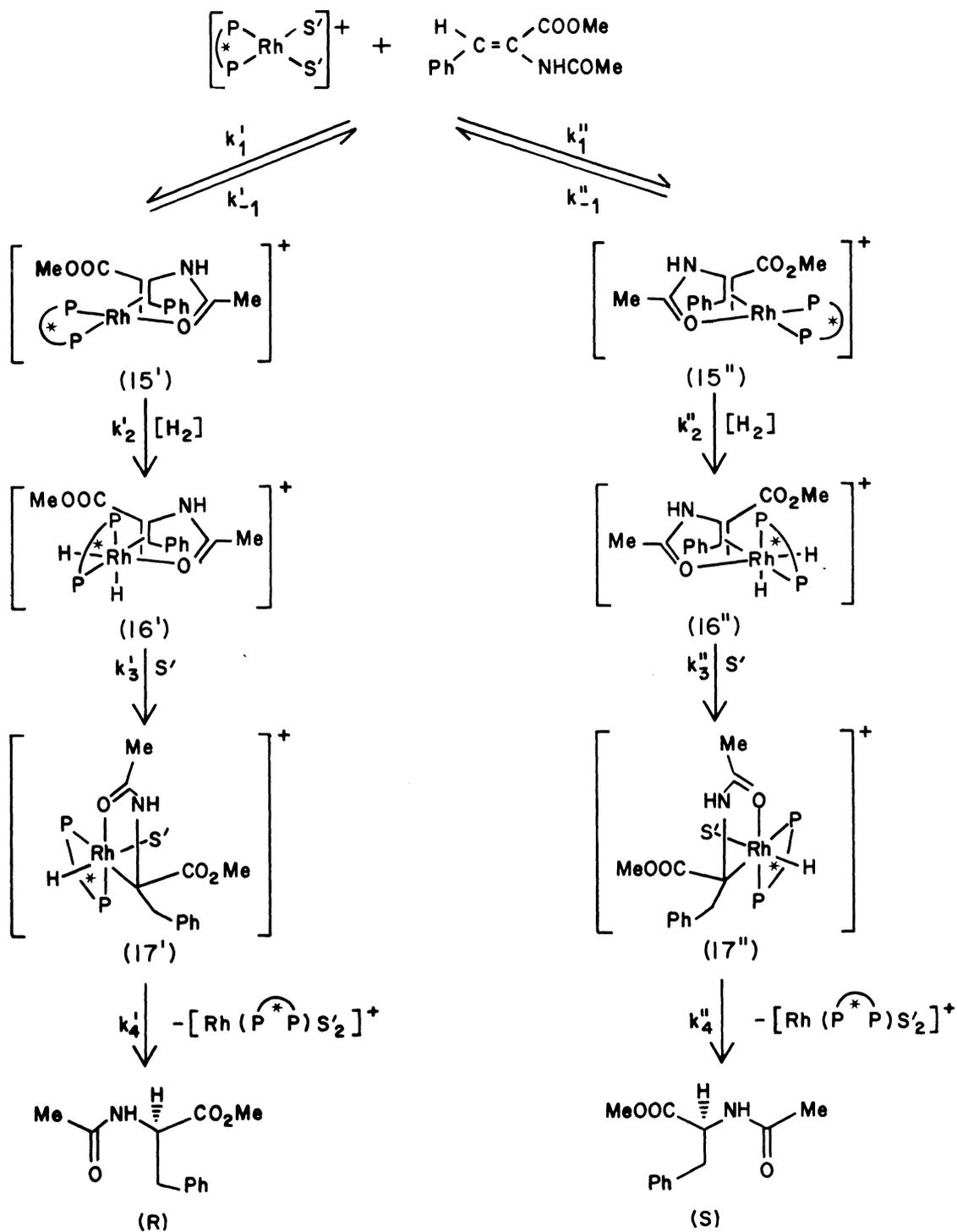   α-acetamidocinnamate (MAC).

Fig. 2.   Mechanistic scheme for the hydrogenation of a prochiral substrate
          (MAC) with a catalyst containing a chiral chelating diphosphine
          ligand.   (P*P = CHIRAPHOS or DIPAMP: S' = methanol.)

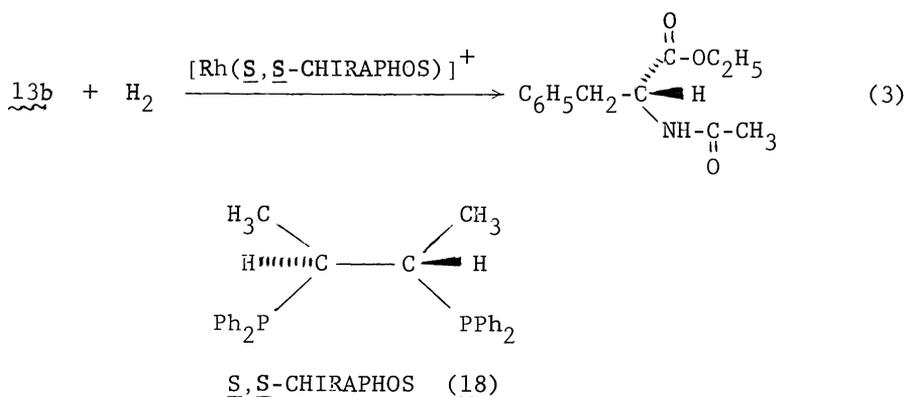TABLE 1. Kinetic parameters for the $[Rh(DIPHOS)]^+$-catalyzed hydrogenation of MAC in methanol according to Fig. 1

Rate constant (units)	$k(25^{\circ}C)$	$\Delta H^{\ddagger}$ (Kcal/mol)	$\Delta H^{\ddagger}$ (cal/mol$^{\circ}$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

ORIGIN OF ENANTIOSELECTION

When the mechanistic scheme of Fig. 1 is extended to catalysts containing chiral ligands it must be modified according to Fig. 2 to accommodate the formation of diastereomeric forms of the adduct corresponding to 15 (i.e., 15' and 15") and of the further reaction intermediates. This scheme permits the stereochemistry of the product to be correlated with that of the adduct diastereomer from which it is derived, i.e., 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: (a) the prevailing product chirality is determined by the preferred mode of initial binding of the substrate to the catalyst, i.e., the predominant enantiomer of the product arises from the predominant diastereomer of the catalyst-substrate adduct; (b) 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.

The determination of which of the above alternatives prevails was first achieved for the hydrogenation of ethyl-(Z)-α-acetamidocinnamate (EAC, 13b) catalyzed by the rhodium complex of S,S-CHIRAPHOS (18) according to eq. 3 (14). This reaction was shown to proceed with high enantioselectivity yielding N-acetyl-(R)-phenylalanine (>95% e.e.).

$$13b \;+\; H_2 \;\xrightarrow{\;[Rh(\underline{S},\underline{S}\text{-CHIRAPHOS})]^+\;}\; C_6H_5CH_2-\underset{\underset{O}{\overset{|}{NH-C-CH_3}}}{\overset{\overset{O}{\overset{\|}{C-OC_2H_5}}}{C}}\!\!\blacktriangleleft H \qquad (3)$$

$$H_3C\diagdown\diagup CH_3$$
$$H\text{''''''}C \;—\; C\blacktriangleleft H$$
$$Ph_2P\diagup\diagdown PPh_2$$

S,S-CHIRAPHOS (18)

The essential features of reaction 3 were found to parallel those of the corresponding $[Rh(DIPHOS)]^+$-catalyzed reaction, as depicted by Fig. 1 (13). Formation of a $[Rh(S,S\text{-}CHIRAPHOS)(EAC)]^+$ 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 $[Rh(S,S\text{-}CHIRAPHOS)(EAC)]^+$ could be identified in solution by NMR and, hence, it was concluded that the other diastereomer (which was ex-

pected to exhibit a distinguishable NMR spectrum) must be present to the ex-
tent of less than 5%. 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 es-
sentially 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. 2), would yield N-acetyl-(S)-phenyl-
alanine ethyl ester. Instead it was found that the predominant product of
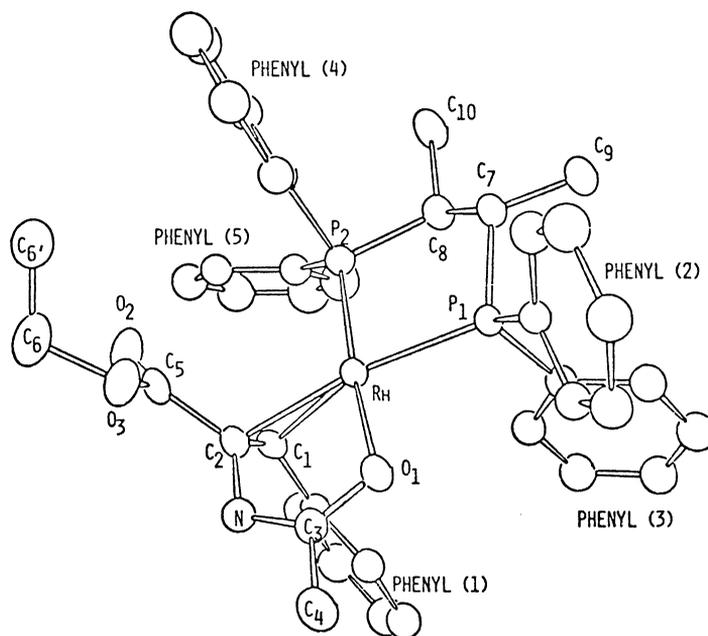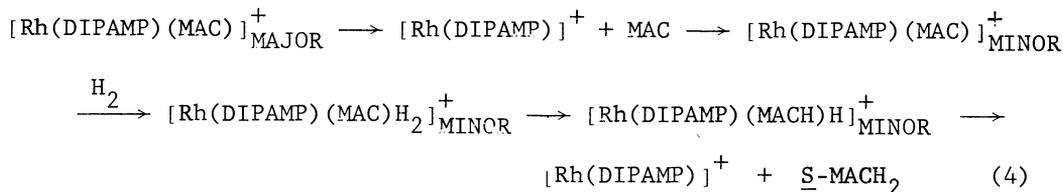reaction 3 (>95% e.e.) was the R isomer (3,19).

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

We are, accordingly, led to the conclusion that, contrary to earlier inter-
pretations (14-18), 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 ad-
ducts 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.

Evidence for the same conclusion concerning the origin of the enantioselec-
tion in the [Rh(R,R-DIPAMP)]$^+$-catalyzed hydrogenation of MAC and related sub-
strates is provided by yet another line of evidence. In the case of this
catalyst both diastereomers of the catalyst-substrate adduct can be detected
in solution by NMR (although their absolute configurations cannot be assigned)
(15,8). At 25°C the equilibrium ratio of the two diastereomers is ca 11:1.
By reacting H_2 with such a mixture of diastereomers (i.e., [Rh(R,R-DIPAMP)-
(MAC)]$^+$) at low temperatures (ca -40°C), where the interconversion of di-
astereomers is frozen out, it was found that only the minor diastereomer
reacts directly with H_2 (to form initially the hydridoalkyl complex corre-
sponding to 17 and then, by reductive elimination, the hydrogenated product)
(16,8).

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

$$\xrightarrow{H_2} [Rh(DIPAMP)(MAC)H_2]^+_{MINOR} \longrightarrow [Rh(DIPAMP)(MACH)H]^+_{MINOR} \longrightarrow$$

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

OTHER CONSEQUENCES AND INDIRECT CRITERIA

The demonstration of the origin of the enantioselection in the two cases con-
sidered above depended on either (a) the isolation and structural characteri-
zation of the catalyst-substrate adduct (in the case of CHIRAPHOS), or (b)
the detection and monitoring of both diastereomers of the adduct in solution
(in the case of 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 enantio-
selection deduced above, the reversibility of the initial catalyst-substrate
adduct formation step, 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 con-
centrations (i.e., when $k_2[H_2][15] \gg k_{-1}[15]$), the rate and stereochemistry
of the reaction should become determined by the initial binding rates of the
prochiral substrate to the catalyst (i.e., 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 the predominant product chiral-
ity, with increasing H_2 pressure. This has been quantitatively confirmed for
the $[Rh(DIPAMP)]^+$-catalyzed hydrogenation of MAC (8). Furthermore, such an
inverse dependence of optical yield on the H_2 pressure has been observed for
virtually all the asymmetric hydrogenation catalysts that have thus far been
examined (2,20,21,8). 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 enantio-
selection in such reactions probably extends to this whole class of catalysts
and substrates.

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 upon
rapid interconversion of the diastereomeric catalyst-substrate adducts com-
pared with the rates of their reactions with H_2. Since the adduct dissocia-
tion step through which such interconversion occurs typically has a much
higher activation enthalpy than reaction with H_2 (18.3 vs 6.3 kcal/mol 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%) the optical yield may actually de-
crease with decreasing temperature. Such an unusual dependence of enantio-
selectivity on temperature indeed has been reported, e.g., for the hydrogena-
tion of MAC and related substrates catalyzed by rhodium complexes containing
several chiral phosphine ligands (20,21,6). In one particularly dramatic
case the optical yield increases from 0 to 60% e.e. in going from 0° to
100°C (21).

ORIGIN OF THE DIFFERENCES IN STABILITY AND REACTIVITY OF THE
DIASTEREOMERIC CATALYST-SUBSTRATE ADDUCTS

The conclusion that we have reached concerning the origin of enantioselection
in these systems implies very large differences in reactivity toward H_2 be-
tween the two diastereomeric forms of the catalyst-substrate adduct. 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 stabil-
ity (i.e., than the equilibrium concentration difference) of the diastereo-

mers, indeed at least 50 times greater to accommodate an optical yield of 96% e.e. 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)]$^+$) still is 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..

REFERENCES

1. For reviews, see: H. B. Kagan, Pure Appl. Chem., 43, 401 (1975). J. D. Morrison and W. F. Masler, Advan. Catalysis, 25, 81 (1976). P. Pino and G. Consiglio, in Fundamental Research in Homogeneous Catalysis, M. Tsutsui and R. Ugo, Eds., Plenum, New York (1977), p. 147. H. B. Kagan and J. C. Ciaud, Topics Stereochem., 10 175 (1978). D. Valentine, Jr. and J. W. Scott, Synthesis, 329 (1978). B. Bosnich and M. D. Fryzuk, Topics Stereochem., 12, 119 (1981). H. Wynberg, Recueil, J. Roy. Netherlands Chem. Soc., 100, 399 (1981).
2. W. S. Knowles, M. J. Sabacky and B. D. Vineyard, Advan. Chem. Ser., 132, 274 (1974). B. D. Vineyard, W. S. Knowles, M. J. Sabacky, G. L. Bachman and D. J. Weinkauff, J. Am. Chem. Soc., 99, 5946 (1977).
3. M. D. Fryzuk and B. Bosnich, J. Am. Chem. Soc., 99, 6262 (1977). P. A. MacNeil, N. K. Roberts and B. Bosnich, J. Am. Chem. Soc., 103, 2273 (1981).
4. I. Ojima, T. Kogure and N. Yoda, J. Org. Chem., 45, 4728 (1980).
5. H. B. Kagan, Ann. N. Y. Acad. Sci., 333, 1 (1980). L. Marko and J. Bakos, in Aspects of Homogeneous Catalysis, Vol. 3, R. Ugo, Ed., Reidel, Dordrecht (1981), p. 145. R. E. Merill, Chem. Tech., 118 (1981).
6. W. C. Christophel and B. D. Vineyard, J. Am. Chem. Soc., 101, 4406 (1979). K. E. Koenig, G. L. Bachman and B. D. Vineyard, J. Org. Chem., 45, 2362 (1980).
7. A. S. C. Chan and J. Halpern, J. Am. Chem. Soc., 102, 838 (1980).
8. C. Landis, S. Okrasinski and J. Halpern, unpublished results.
9. J. Halpern, Inorg. Chim. Acta, 50, 11 (1981).
10. J. Halpern, D. P. Riley, A. S. C. Chan and J. J. Pluth, J. Am. Chem. Soc., 99, 8055 (1977).
11. A. S. C. Chan. J. J. Pluth and J. Halpern, Inorg. Chim. Acta, 37, 2477 (1979).
12. B. R. James, Homogeneous Hydrogenation, Wiley, New York (1969), and references therein.
13. A. S. C. Chan, J. J. Pluth and J. Halpern, J. Am. Chem. Soc., 102, 5952 (1980).
14. J. M. Brown and P. A. Chaloner, Tetrahed. Lett., 1877 (1978).
15. J. M. Brown and P. A. Chaloner, J.C.S. Chem. Comm., 321 (1978).
16. J. M. Brown and P. A. Chaloner, J.C.S. Chem. Comm., 344 (1980).
17. I. Ojima and T. Kogure, Chem. Lett., 1175 (1978); 641 (1979).
18. W. S. Knowles, B. D. Vineyard, M. J. Sabacky and B. R. Stults, in Fundamental Research in Homogeneous Catalysis, Vol. 3, M. Tsutsui, Ed., Plenum, New York (1979), p. 537. K. E. Koenig, M. J. Sabacky, G. L. Bachman, W. C. Christophel, H. D. Barnstorff B. B. Friedman, W. S. Knowles, B. R. Stults, B. D. Vineyard and D. J. Weinkauff, Ann. N. Y. Acad. Sci., 333, 16 (1980).
19. P. S. Chua, N. K. Roberts, B. Bosnich, S. J. Okrasinski and J. Halpern, J.C.S. Chem. Comm., 1278 (1981).
20. I. Ojima, T. Kogure and N. Yoda, Chem. Lett., 495 (1979); J. Org. Chem., 45, 4728 (1980).
21. D. Sinou, Tetrahed. Lett., 22, 2987 (1981).