HOMOGENEOUS ASYMMETRIC CATALYSIS BY MEANS OF CHIRAL RHODIUM COMPLEXES

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Abstract - Synthetic and mechanistic aspects of homogeneous asymmetric
hydrogenation and hydrosilylation catalyzed by rhodium complexes with
chiral phosphine ligands are described. The following aspects are dis-
cussed: (i) Asymmetric reduction of α,β-enones and keto esters via hydro-
silylation, (ii) Asymmetric reduction of α-keto esters and ketopantoyl
lactone by hydrogenation, the latter reaction provides D-(-)-pantoyl lac-
tone which is further converted to pantothenate, a vitamine B, (iii) Asym-
metric hydrogenation of N-acyldehydro-α-amino acids; (a) remarkable ef-
fects of hydrogen pressure on the stereoselectivity, (b) crucial factors
for effective asymmetric induction, (iv) Asymmetric hydrogenation of de-
hydropeptides; (a) efficiency of typical chiral diphosphine ligands, (b)
effects of chiral centers, protecting groups and functional groups at N-
and C-termini on the asymmetric induction, (c) application to stereoselec-
tive labeling of peptides, and (d) application to the synthesis of bio-
logically active oligopeptides such as analogs of Enkephalin, a peptide
hormone isolated from brain.

INTRODUCTION

During the last decade, there have been revolutionary advances in catalytic asymmetric syn-
thesis. For instance, asymmetric hydrogenation, epoxidation, hydrosilylation, hydrocarbonyl-
ation, cyclopropanation, Grignard cross coupling, dimerization and isomerization have
achieved to date very high stereoselectivities by the catalysis of chiral transition-metal
complexes (Refs. 1-3). Among such chiral transition-metal complexes, rhodium complexes with
chiral phosphine ligands have played a key role in the asymmetric hydrogenation (Ref. 4),
hydrosilylation (Ref. 5), hydroformylation (Ref. 6) and isomerization (Ref. 7). We have been
particularly interested in the catalysis of chiral rhodium complexes in the asymmetric hy-
drogenation and hydrosilylation for a decade.
As for the asymmetric hydrogenation of prochiral olefins, a great breakthrough was realized
in the asymmetric synthesis of L-dopa (a drug for Perkinson's disease) by Monsanto research-
ers in early 1970s (Ref. 8). Since then a good deal of investigations have been made on the
asymmetric hydrogenation of N-acyldehydroamino acids, which rivals the stereoselectivity of
enzymic reactions (Ref. 4). Quite recently the mechanism of the asymmetric hydrogenation of
N-acyldehydroamino acids has been precisely studied on the basis of organometallic and coor-
dination chemistry of such chiral rhodium complexes to give us clear understanding for the
mechanism of effective chiral recognition in some cases (Refs. 9-11). Advances have also
been brought about in the synthetic application of the asymmetric hydrogenation: The asym-
metric synthesis of oligopeptides has recently been successfully achieved by means of the
asymmetric hydrogenation (Refs. 12-17).
On the other hand, the catalytic asymmetric reduction of carbonyl compounds seems to be still
a challenging reaction although excellent stereoselectivities rivaling the corresponding
enzymic reactions have been achieved in a few cases. One successful approach has been the
asymmetric hydrosilylation of carbonyl compounds and imines followed by hydrolysis, which has
been extensively studied in the last decade (Ref. 5). In some cases, the asymmetric hydro-
genation of carbonyl compounds has been shown to achieve excellent results, e.g., the asym-
metric syntheses of epinephrine (Ref. 18) and pantoyl lactone (Ref. 19). Quite recently
rhodium complexes with chiral diphosphine ligands bearing dialkylphosphino groups have showed
up as powerful candidate for effective chiral catalyst for the asymmetric hydrogenation of
carbonyl compounds (Ref. 20).
We will describe here our recent advances in the synthetic and mechanistic aspects of the
homogeneous asymmetric hydrogenation and hydrosilylation catalyzed by chiral rhodium complex-
es.

ASYMMETRIC REDUCTION OF α,β-ENONES VIA HYDROSILYLATION

One of the most striking features of RhCl(PPh$_3$)$_3$-catalyzed hydrosilylation is the fact that the reaction of α,β-unsaturated ketones and aldehydes with monohydrosilanes gives 1,4-adducts while that with dihydrosilanes or trihydrosilanes gives 1,2-adducts with extremely high selectivity, and the 1,4-adducts and the 1,2-adducts are readily hydrolyzed to afford the corresponding saturated products and allylic alcohols, respectively (Refs. 21,22).
This finding has resulted in studies on two kinds of selective asymmetric hydrosilylation of α,β-unsaturated carbonyl compounds: The 1,4-addition induces asymmetry on a β-carbon to afford optically active saturated carbonyl compounds while the 1,2-addition gives optically active allylic alcohols (Eq. 1). The former reaction was performed by Kumada et al. (Ref. 23) and the latter by us (Ref. 24): A typical result on the asymmetric synthesis of allylic alcohol is exemplified in Eq. 2.

$$(1)$$

(R)-carvone   carveol

$$(2)$$

Et$_2$SiH$_2$-(-)DIOP-Rh[N]	15.5	84.5
αNpPhSiH$_2$-(+)DIOP-Rh[N]	78.7	21.3
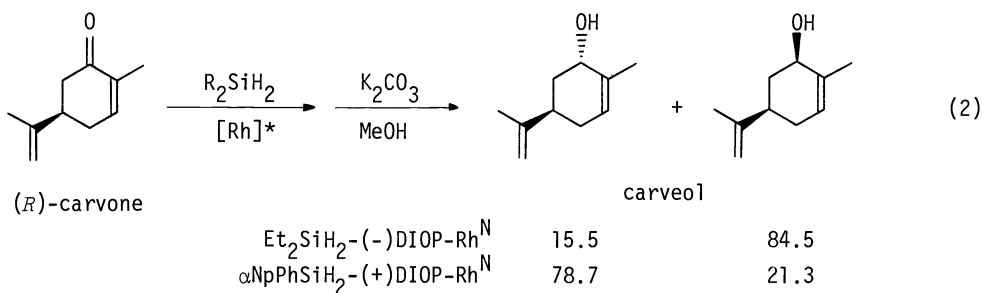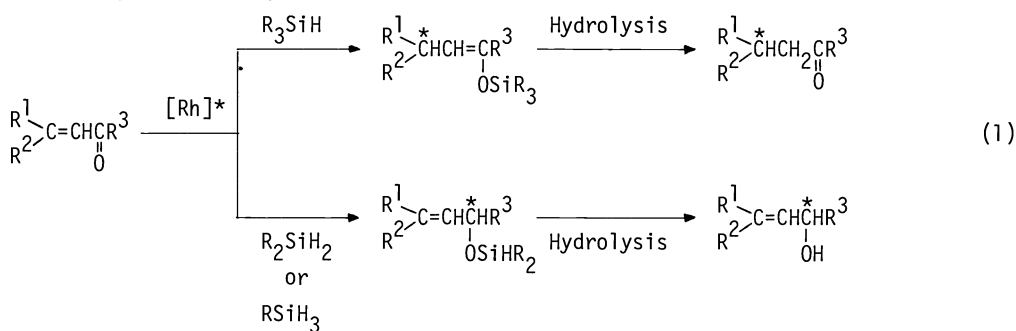
Recently, Et$_3$SiH-RhCl(PPh$_3$)$_3$ combination was successfully applied to the regio- and stereoselective reduction of dehydrofaranal even in a μg scale, which gave an insect pheromone, faranal (Eq. 3) (Ref. 25). The ratio of 3(S),4(R)/3(R),4(R)-faranal was found to be 11/2 by GLC analysis. The reaction was crucial to determine the absolute configuration of natural faranal: 3(S),4(R)-faranal turned out to be natural product. This is another type of asymmetric hydrosilylation.

$$(3)$$
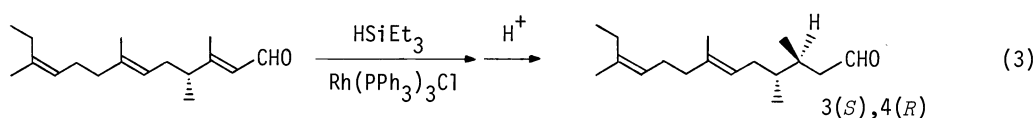
Although we found this interesting selective reaction in 1972, the mechanism of the reaction was left unclarified for a decade. Thus, we have recently carried out some mechanistic study on this highly selective reaction and proposed a rational mechanism (Ref. 22). As to the mechanism of the hydrosilylation of simple carbonyl compounds catalyzed by Wilkinson type rhodium complexes, we and others proposed the one which involved an initial silicon migration from the oxidative adduct to the carbonyl oxygen of the coordinated substrate giving α-siloxyalkylrhodium hydride as key intermediate (Ref. 26). A spin trapping experiment done by Kagan et al. also supports the proposed mechanism (Ref. 27). Thus, it is quite reasonable to assume that the hydrosilylation of α,β-unsaturated ketones and aldehydes also follows the proposed mechanism basically. In addition, the possible isomerization of the produced 1,2-adduct to 1,4-adduct was excluded by a controlled experiment.
The most rational mechanism which can accommodate the observed regioselectivity is illustrated in Fig. 1. The mechanism involves an α-siloxyallylrhodium hydride (5a) as key intermediate and a hydrogen shift from 5a gives the 1,2-adduct (2) whereas an isomerization of 5a gives the other intermediate, γ-siloxyallylrhodium hydride (5b), and a hydrogen shift from 5b then affords the 1,4-adduct (1).
In connection with the proposed mechanism (Fig. 1), we carried out the spin trapping experiment in the hope of obtaining supporting evidence of the intermediacy of 5a and 5b (Ref. 22). EPR spectra were measured by adding nitrosodurene to the hydrosilylation system which con-

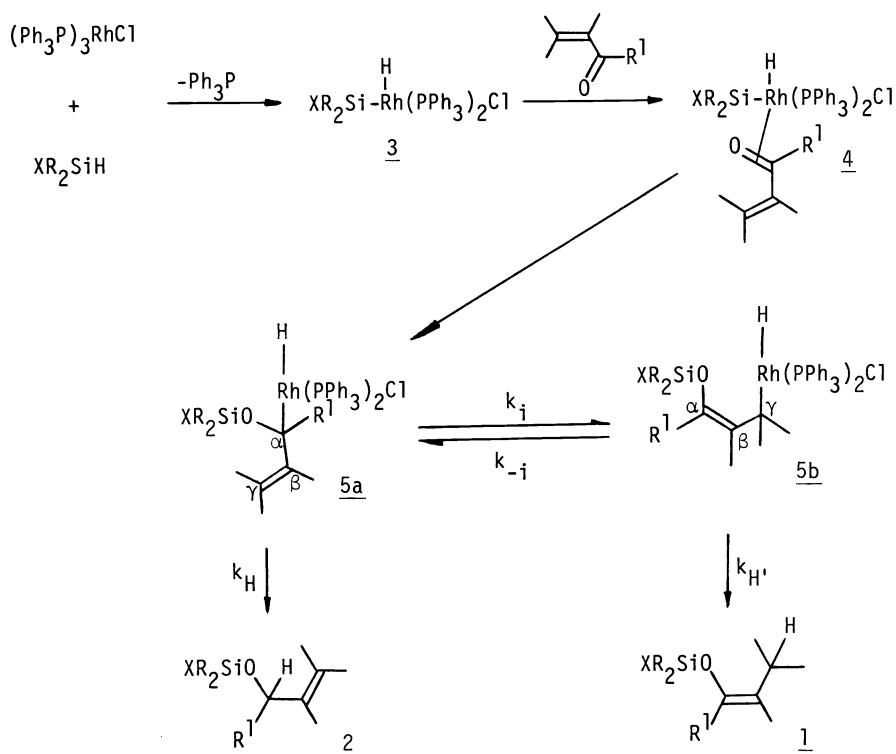Fig. 1. Proposed mechanism for the selective hydrosilylation of α,β-enones.

sists of β-ionone, Ph_2SiH_2 and $(Ph_3P)_3RhCl$. The EPR spectrum measured at 15 min period after the mixing of reagents indicates that there are two sets of signals, i.e., one triplet (g=2.0069, a_N=12.6 G) and one doublet of triplet (g=2.0069, a_N=12.9 G, a_H=8.4 G). When the spectrum was measured at 30 min period, the triplet diminishes and the doublet of triplet becomes predominant. It is quite reasonable that the triplet is ascribed to α-siloxyallyl-nitroxide (6), and the doublet of triplet is assigned to γ-siloxyallylnitroxide (7). The results strongly suggest the intermediacy of α- and γ-siloxyallylrhodium hydride complexes (5a and 5b) as well as the possible isomerization of 5a to 5b.
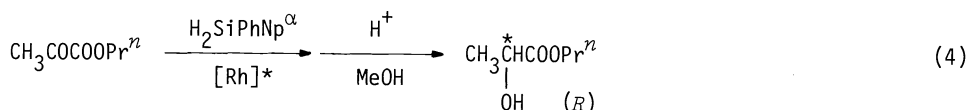

Consequently, the selectivity should be governed by the relative easiness of the hydride shift from 5a toward the isomerization of 5a: The 1,4-addition takes place exclusively when the isomerization is by far faster than the hydride shift, i.e., $k_i \gg k_H$, and the exclusive 1,2-addition occurs when the hydride shift is by far faster than the isomerization, i.e., $k_i \ll k_H$.
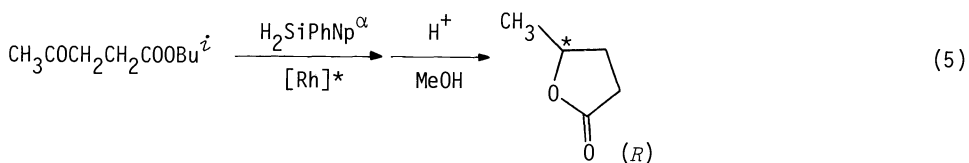
ASYMMETRIC REDUCTION OF KETO ESTERS VIA HYDROSILYLATION

The asymmetric reduction of α-keto esters, typically pyruvates and phenylglyoxylates, is easily achieved by the chiral rhodium complex-catalyzed hydrosilylation (Eq. 4) (Ref. 26a). Generally, optical yields of lactates are high (>80% e.e.) and much better than those obtained for simple prochiral ketones. The marked increase in optical yield in the reaction of pyruvates compared with simple prochiral ketones can probably be ascribed to a ligand effect of the ester moiety in the key intermediate or transition state. Further support for this hypothesis comes from the results for asymmetric hydrosilylation of levulinates (Ref. 26a). The hydrosilylation of levulinates followed by acid solvolysis afforded 4-methyl-γ-butyro-lactone with more than 80% e.e. through silyl ether of 4-hydroxybutyrates (Eq. 5).
With regard to the possible mode of the ligand effect of the ester moiety, we have found an

interesting clear difference between neutral and cationic rhodium(I) complex catalysts in the asymmetric hydrosilylation of a pyruvate. Namely, the use of a cationic complex, $[(DIOP)Rh(COD)]^+ClO_4^-$, in the hydrosilylation of n-propyl pyruvate brought about a remarkable decrease in the optical yield compared with that obtained by using the corresponding neutral catalyst (Eq. 4). The result clearly indicates that chlorine ligand of the neutral catalyst plays a significant role in the induction of asymmetry, i.e., the active species of neutral catalyst is shown to be different from that of the cationic catalyst. However, such a difference in optical yield was not observed in the case of i-butyl levulinate (Eq. 5).

$$CH_3COCOOPr^n \xrightarrow[\text{[Rh]*}]{H_2SiPhNp^\alpha} \xrightarrow[\text{MeOH}]{H^+} CH_3\overset{*}{C}HCOOPr^n \quad \underset{OH \quad (R)}{|} \tag{4}$$

(a) [Rh]* = $[((-)DIOP)Rh(COD)]^+ClO_4^-$: 41% e.e.

  [Rh]* = $[(-)DIOP]Rh(COD)Cl$: 85% e.e.

(b) [Rh]* = $[((-)BPPM)Rh(COD)]^+ClO_4^-$: 23% e.e.

  [Rh]* = $[(-)BPPM]Rh(COD)Cl$: 78% e.e.

$$CH_3COCH_2CH_2COOBu^i \xrightarrow[\text{[Rh]*}]{H_2SiPhNp^\alpha} \xrightarrow[\text{MeOH}]{H^+} \tag{5}$$

[Rh]* = $[((-)DIOP)Rh(COD)]^+ClO_4^-$: 85% e.e.

[Rh]* = $[(-)DIOP]Rh(COD)Cl$: 84% e.e.

These results may well be accommodated by taking into account two possible modes for the postulated ligand effect of ester moiety in the key intermediate: The α-siloxyalkylrhodium intermediate arising from levulinate (8) can form a six-membered ring chelate by the strong coordination of ester moiety, which gets rid of chlorine to the outer sphere as counter anion, while the ester moiety of the key intermediate from pyruvate (9) may only interact with rhodium electronically because of the unfavorable four membered ring chelate and this electronic interaction is not strong enough to liberate chlorine from rhodium.
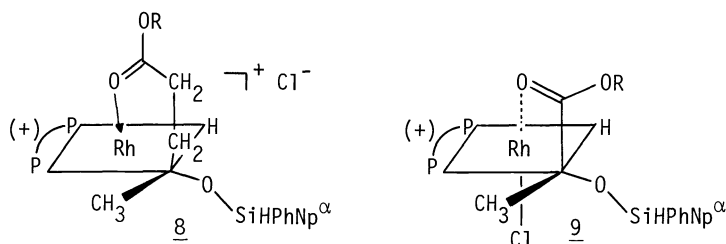
ASYMMETRIC HYDROGENATION OF KETOPANTOYL LACTONE

It is known that, in general, the Wilkinson type neutral rhodium(I) complexes lack catalytic activity toward the hydrogenation of carbonyl functionalities under mild conditions (Ref. 28). Accordingly, the studies on the asymmetric hydrogenation of ketones were made mainly by using cationic chiral rhodium complexes as catalyst in 1970s although recently it has been shown that chiral neutral rhodium complex-amine combination can realize high enantio-selectivity (Ref. 29). In 1976, Hayashi et al. developed a unique chiral ferrocenyldiphos-phine, BPPFOH, which brought about the effective asymmetric hydrogenation when it was employ-ed as a ligand in a rhodium catalyst, and high optical yields were realized for the hydrogen-ation of pyruvic acid (Ref. 30) and aminoketones (Ref. 31). However, the asymmetric hydro-genation of methyl pyruvate catalyzed by the same catalyst resulted in only 10% asymmetric induction (Ref. 32).

We found that the neutral Wilkinson type catalysts were quite effective for the hydrogen-ation of α-keto esters as a special case (Ref. 33) and have applied it successfully to the asymmetric synthesis of lactates (Ref. 33) and D-(-)-pantoyl lactone which is further con-verted to D-(+)-pantothenate (Ref. 18) (Fig. 2).
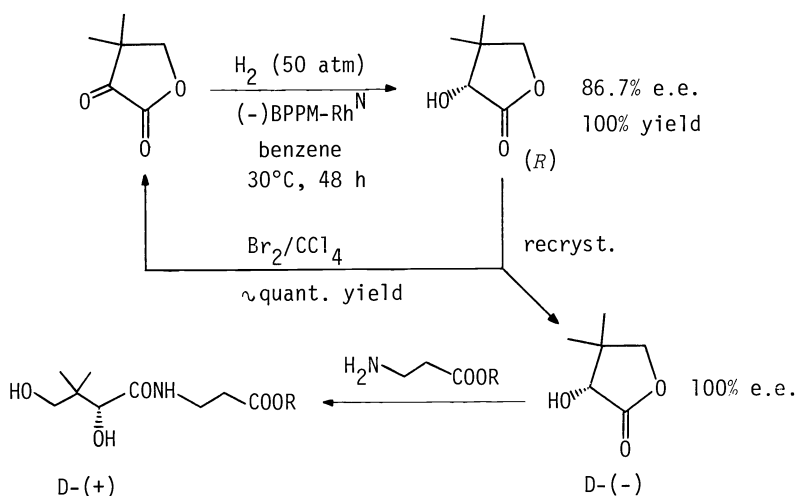
Fig. 2. Asymmetric synthesis of pantothenate

Pantothenic acid is a member of the B complex vitamines and is an important constitute of Coenzyme A. The biosynthesis of pantothenic acid from valine has been postulated (Refs. 34,35) to involve the asymmetric reduction of ketopantoyl lactone to pantoyl lactone. Among several steps involved in the biosynthetic route, the asymmetric reduction step is the most signifi-cant step since only D-(-)-pantoyl lactone has the biological activities (Ref. 36).
The asymmetric hydrogenation of ketopantoyl lactone was carried out by using neutral rhodium catalyst with (-)BPPM as chiral ligand to afford D-(-)-pantoyl lactone with the optical puri-ty of 86.7% e.e. in quantitative yield under optimum conditions. The pantoyl lactone thus obtained was easily purified to the pure D-isomer by recrystallization from n-hexane-benzene. Accordingly, pure sample of D-(-)-pantoyl lactone was obtained in 70-78% yield from keto-pantoyl lactone. The pure sample of D-(-)-pantoyl lactone was converted to ethyl ester of D-(+)-panthothenic acid by the reaction with β-alanine ethyl ester. The transformation of ethyl D-(+)-pantothenate to D-(+)-pantothenic acid is a known process (Ref. 36). As the optical yield of the reduction of ketopantoyl lactone using baker's yeast has been reported (Ref. 37) to be ca. 72%, our chiral rhodium catalyst is shown to be superior to baker's yeast in this reaction. Although Lanzilotta et al. found that specific strains of the ascomycete, *Byssochlamys fulva*, could achieve exceedingly high optical yield production of the D-isomer (Ref. 37), the isolation procedure from aqueous reaction media, i.e., extraction, recovery of raw materials, and purification, is very troublesome because of the high solubility of the product in water. Thus, the present process has some advantages in a synthetic point of view, e.g., i) conversion of the reaction is virtually 100%, ii) the isolation of the product is quite simple and convenient since the reaction is carried out in small quantity of non-aqueous media, and iii) the D-(-)-pantoyl lactone with low optical purity, which is remained in the mother liquor in the recrystallization, is easily oxidized to the starting ketopantoyl lactone.
Mechanistic study on the asymmetric hydrogenation of pyruvates and ketopantoyl lactone re-vealed that i) the Schrock-Osborn mechanism (Ref. 38) was not operative at all since no ac-celeration of the reaction rate by the addition of water (1%) was observed, ii) there was a clear difference between cationic and neutral rhodium catalysts in their enantioselectivity: neutral catalysts realized much better results than the corresponding cationic catalysts, and iii) there was a remarkable solvent effect on the extent and direction of asymmetric induc-tion (Ref. 39).

ASYMMETRIC HYDROGENATION OF N-ACYLDEHYDRO-α-AMINO ACIDS

Remarkable effects of hydrogen pressure on the stereoselectivity
Although homogeneous asymmetric hydrogenation of dehydroamino acids has been extensively studied (Ref. 1), little attention has been focused on the pressure dependency of stereo-selectivity in these reactions (Ref. 8c). Accordingly, we carried out the asymmetric hydro-genation of (Z)-α-benzamidocinnamic acid (10), (Z)-α-acetamidocinnamic acid (11), methyl (Z)-α-acetamidocinnamate (12), α-acetamidoacrylic acid (13) and itaconic acid (14) under a varie-ty of hydrogen pressures using rhodium complexes with (-)BPPM, (-)DIOP and diPAMP under a variety of hydrogen pressures. Then, we have found that the hydrogen pressure exerts a sig-nificant influence on the stereoselectivity and the pressure dependency is sensitive to the structure of substrate. Results are exemplified in Table 1. For example, (R)-N-benzoyl-phenylalanine is a predominant product of the asymmetric hydrogenation of 10 at 25°C and 1 atm of hydrogen whereas the production of S-isomer is preferred under high pressures such as 50 atm and 100 atm of hydrogen on using either (BPPM)Rh(COD)Cl prepared in situ or [(BPPM)Rh-(COD)]+ClO4- (II). The pressure effect on the DIOP complex catalyzed reaction is closely similar to that on the BPPM complex catalyzed one, while the pressure effect is considerably

smaller for the diPAMP complex catalyzed one. This may be due to the fact that the former two complexes have rather fluxional seven-membered-ring chelate structures whereas the latter forms a rigid five-membered-ring chelate with a C_2 axis.

TABLE 1. Dependency of stereoselectivity on hydrogen pressure (% e.e.) (Configuration)

Substrate	Catalyst	Solvent	Pressure of hydrogen (atm)			
			1	20	50	100
Ph C=C NHCOPh / H COOH **10**	II	EtOH	83.8(R)	21.2(R)	4.7(S)	8.4(S)
	II(Et$_3$N)	EtOH	93.3(R)	78.7(R)	66.2(R)	64.2(R)
	I	EtOH	84.0(R)	12.9(R)	8.6(S)	14.4(S)
	I(Et$_3$N)	EtOH	91.8(R)	75.5(R)	66.6(R)	63.2(R)
Ph C=C NHCOMe / H COOH **11**	II	EtOH	87.1(R)	82.3(R)		
	II(Et$_3$N)	EtOH	93.5(R)	93.1(R)		
	I	EtOH	91.6(R)	83.6(R)		
	I(Et$_3$N)	EtOH	93.1(R)	90.9(R)		
Ph C=C NHCOMe / H COOMe **12**	II	EtOH	95.0(R)	89.7(R)		
	II(Et$_3$N)	EtOH	95.9(R)	89.1(R)		
	I	EtOH	95.2(R)	59.6(R)		
	I(Et$_3$N)	EtOH	96.8(R)	59.3(R)		
H C=C NHCOMe / H COOH **13**	II	MeOH	95.2(R)	21.8(S)		
	II(Et$_3$N)	MeOH	98.5(R)	7.3(S)		
	I	MeOH	86.3(R)	5.8(S)		
	I(Et$_3$N)	MeOH	88.7(R)	5.7(S)		
H C=C CH$_2$COOH / H COOH **14**	II	MeOH	91.3(S)	85.3(S)		
	II(Et$_3$N)	MeOH	94.8(S)	93.1(S)		
	I	MeOH-PhH	92.3(S)	'79.7(S)		
	I(Et$_3$N)	MeOH-PhH	94.5(S)	91.3(S)		

We found that the addition of a small amount of triethylamine to the reaction system not only increases the optical yield under a given hydrogen pressure, but also markedly attenuates the pressure dependency of stereoselectivity. It also turns out that the marked effects of added triethylamine are observed only for the free acid substrates and virtually no effects are observed for the ester 12. We also looked at the effects of temperature on the pressure dependency of stereoselectivity. To our surprise, a higher temperature (50°C) brings about the higher stereoselectivity than a lower temperature (25°C) does in almost all cases examined and as a result, the higher temperature considerably releases the pressure dependency of stereoselectivity. The temperature effect is remarkable for the neutral complex catalyzed reactions but it is relatively mild for the cationic complex catalyzed ones. The observed temperature effects on stereoselectivity are rather unusual since it has been generally accepted in these reactions that the higher the temperature, the lower is the stereoselectivity at the given hydrogen pressure (Ref. 8c).

These phenomena could be caused by either i) a change in the rate determining step or ii) an exchange of one mechanism for another, provided that the reaction proceeds via two competitive mechanisms.

According to the mechanism of the hydrogenation catalyzed by a rhodium complex with a *cis* chelating diphosphine ligand proposed by Halpern et al. (Ref. 40), the rate determining step should be the oxidative addition of molecular hydrogen to the pre-formed rhodium-substrate complex, i.e., step (a) in Fig. 3. Thus, if the former were the case, a high hydrogen pressure makes the oxidative addition of hydrogen [step (a)] easy, and the rate determining step may change to the second hydride migration [step (c)]. Namely, an isomerization of the coordinating olefinic substrate may occur to facilitate the formation of the other enantiomer. The reaction paths involved in this mechanism are shown in Fig. 3. In order to examine this possibility, we carried out the dideuteration of 13 in methanol at 20 atm of dideuterium at which pressure the production of the *S*-isomer was preferred: If there were such an equilibrium in step (b), at least 3,3-dideuterio-N-acetylalanine should be produced and further deuterated products are also possible to be formed. We found that there was no scrambling of deuterium at all. Consequently, the first assumption is unlikely in the present reaction from our point of view.

Rh*
 + $\xrightarrow{\text{(d)}}$ Rh*(>C=C<) $\xrightarrow{\text{H}_2 \ \text{(a)}}$ Rh*(>C=C<)(H$_2$) $\overset{\text{(b)}}{\underset{}{\nearrow}}$ Rh*(-C-C-H)*(H) $\xrightarrow{\text{(c)}}$ H-C*-C-H + Rh* (R)
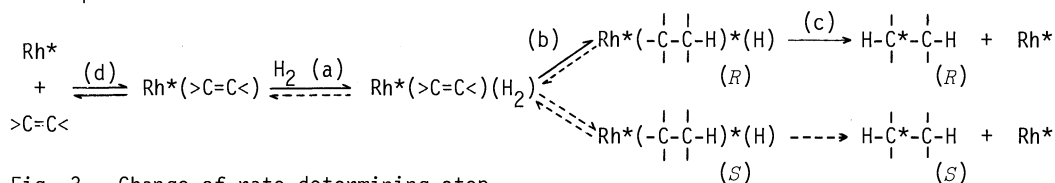 >C=C< $\searrow$ Rh*(-C-C-H)*(H) ----> H-C*-C-H + Rh* (S)

Fig. 3. Change of rate-determining step

The observed results are well accommodated by taking into account the competitive mechanisms, A and B, shown in Fig. 4. Mechanism A follows the one proposed by Halpern et al. (Ref. 40), in which the rate determining step is the oxidative addition of molecular hydrogen to the intermediate complex 15. Mechanism B follows the one which has been widely accepted for the hydrogenation of olefins catalyzed by $(Ph_3P)_3RhCl$ (Ref. 41). Mechanism A is exclusively operative at 1 atm of hydrogen whereas Mechanism B becomes predominant at higher pressures. Namely, it is reasonable to assume that the dihydride complex 18 is stable and is formed at high pressures of hydrogen even though the formation of 18 is unfavorable for a complex with chelating diphosphines (Ref. 40). As for the stereoselectivity of these mechanisms, Mechanism A should extremely favor the production of R-isomer (S-isomer for diPAMP) while Mechanism B should prefer the other isomer in order to accommodate the results. In the formation of 15, the olefinic substrate occupies the coordination site most favorable to the reaction, and then molecular hydrogen undergoes oxidative addition keeping the orientation of the substrate to give 16, and ii) in the formation of 18, hydrogens occupy the most favorable site first, and then the olefinic substrate comes into the coordination sphere to give 19 in which the preferable orientation for the substrate may well be opposite to that of 16. Although it seems to be generally considered that Mechanism A is always operative for cis chelating diphosphine ligands, our results strongly indicate that Mechanism B makes a significant contribution at higher hydrogen pressures even when cis chelating diphosphines are employed.

Mechanism A (favorable under low hydrogen pressure)
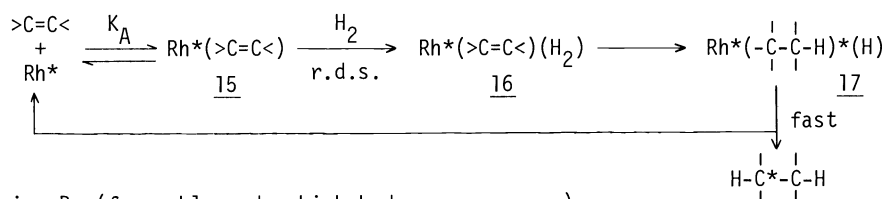
Mechanism B (favorable under high hydrogen pressure)
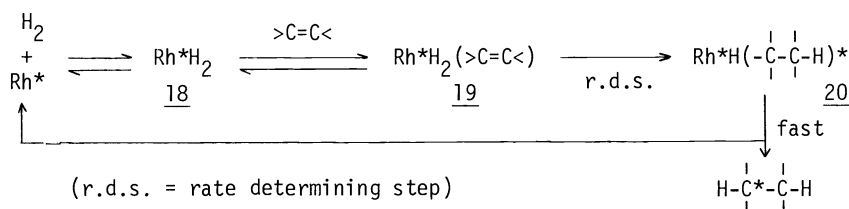

(r.d.s. = rate determining step)

Fig. 4. Competitive mechanisms

The observed effects of added triethylamine and temperature on the pressure dependency of stereoselectivity are also well explained based on the competitive mechanisms mentioned above. The results shown in Table 1 may imply that the amine generates the carboxylate anion of the free acid substrate, which has much larger binding (equilibrium) constant with the rhodium catalyst to give 15 than the non-ionized substrate does, i.e., $K_A \gg K_B$, and as a result, the formation of 18 is suppressed and Mechanism A predominates over Mechanism B. As for the temperature effects on the pressure dependency of stereoselectivity, it is reasonable to assume that the formation of the dihydride complex 18 is unfavorable at higher temperatures because of its inherent instability as far as cis chelating ligands are concerned: This means that a higher temperature favors Mechanism A.
Our results show that one should be very careful about the pressure dependency of optical yield when discussing precisely the stereochemistry of a given chiral catalyst in asymmetric hydrogenations.
As for the pressure effect we observed, Halpern explains it by taking the possibility of the change in the rate-determining step from (a) to (d) (Fig. 3), which also seems to be able to accommodate the results (Ref. 9a). Accordingly, further studies are necessary to clarify the "real" mechanism.

"Induced-fit" action of chiral rhodium complexes
During our study on the crucial factors for the effective asymmetric induction on the basis of ^{31}P NMR spectroscopy we observed a very interesting phenomena with regard to the behavior of BPPM-complexes in solution (Ref. 11). Namely, from the ^{31}P NMR spectra of $[(BPPM)Rh(COD)]^+$ ClO_4^- (II) and $[(BPPM)Rh(CD_3OD)_n]^+ClO_4^-$ (III), it turns out that i) there are two species in nearly equal amount in methanol-d_4 at ambient temperature since there appear two sets of doublets of doublets in either $^\alpha P$ or $^\beta P$ regions as shown in Fig. 5, ii) the ratio of the two species is changed by changing the solvent or the temperature and iii) the coalescence of the two sets of signals is observed when the solution of the complex is warmed up in the case of II: The coalescence temperature for II is found to be 318 K. The results clearly show that

there are two conformational isomers
in solution. However, when α-acet-
amidoacrylic acid, for example, was
added to <u>III</u>, the features of the
spectrum changed dramatically and
the predominant formation of one
diastereomeric complex was observed
(Fig. 5). Namely, the rhodium com-
plex takes a preferred conformation
when α-acetamidoacrylic acid comes
into the coordination sphere. The
result is best interpreted as the
"induced-fit" action of the chiral
rhodium complex by the complexation
of the substrate. The observed two
conformers could be ascribed to
either the quasi-chair or the quasi-
boat conformers with regard to the
seven-membered ring or the rotational
isomers arising from the slow rota-
tion of the *tert*-butoxycarbonyl group
around the N-C(O) bond, which is
characteristic of an amide or car-
bamate structure. The variable tem-
perature NMR study strongly indicated
that the conformers should be as-
cribed to the rotational isomers.
Inspection of CPK models clearly
shows that the interconversion be-
tween the quasi-chair and the quasi-
boat conformers is impossible once
the chelating substrate comes into
the coordination sphere to form the
substrate-rhodium complex. Only the
quasi-chair conformer is accessible
for the complexation of the chelating
substrate, which happens to corre-
spond exactly to the X-ray structure
of [(PPPM)Rh(COD)]+ClO4- (<u>IV</u>) (Refs.
11,42).
It should be noted that even the
rotation of the distal *tert*-butoxy-
carbonyl group around the N-C(O) bond
in BPPM is found to be fixed by the
complexation of the prochiral sub-
strate, and this fixation is obserbed
as the "induced-fit" action of the
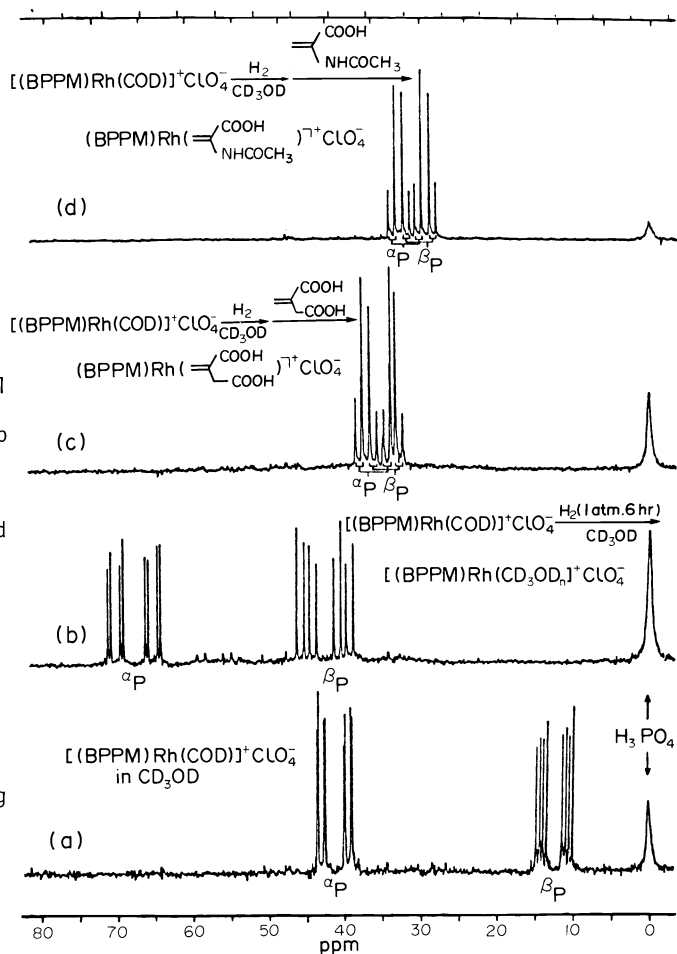chiral rhodium complex.

Fig. 5. "Induced-fit" phenomenona of (-)BPPM-Rh[+]
complexes

ASYMMETRIC HYDROGENATION OF DEHYDROPEPTIDES

Recently, it has been shown that significant modifications of biological activities can be
effected through inversion of configuration at one or more chiral centers, or through re-
placement of one or more "natural" amino acid residue by "unnatural" amino acid components in
a biologically active polypeptide such as Enkephalin, Vasopressin, Angiotensin II, Gonadoli-
berin and other hormones (Ref. 43). In order to obtain such synthetic polypeptides by the
conventional methods mentioned above, it is indispensable to prepare chiral amino acids with
"unnatural" configuration or "unnatural" substituents. As an approach to the synthesis of
chiral oligo- and polypeptides with desired structures, we have been trying to develop facile
approaches to obtaining chiral building blocks. The catalytic asymmetric hydrogenation of
dehydropeptides is one of such approaches.

Efficiency of typical chiral diphosphine ligands
Asymmetric hydrogenation of the N-acyldehydrodipeptides was carried out by using rhodium
complexes with a variety of chiral diphosphines such as *p*-Br-Phenyl-CAPP, Ph-CAPP, (-)BPPM,
(+)BPPM, (-)DIOP, (+)DIOP, diPAMP, Chiraphos, Prophos and BPPFA. The chiral catalysts were
prepared in situ from chiral diphosphine ligand with [Rh(NBD)2]+ClO4- (Ref. 14). As Table 2
shows, the efficiency of each chiral diphosphine ligand exhibited in the asymmetric hydrogen-
ation of dehydrodipeptides is considerably different from that reported for the reaction of
N-acyldehydroamino acids, especially in the case of Chiraphos and BPPFA. When Ac-ΔPhe-(S)-
Phe-OH was employed as substrate, Chiraphos induced S configuration (Entry 17) and BPPFA led
to R configuration (Entry 19) with low stereoselectivities; in both cases, the directions of
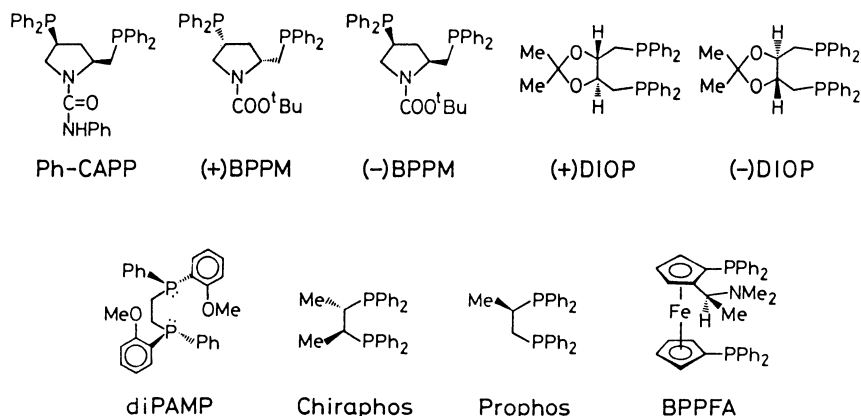asymmetric induction are opposite to those observed for α-acetamidocinnamic acid. Prophos

CHART 1. Typical Chiral diphosphine ligands

induced high stereoselectivity with Bz-ΔPhe-(S)-Phe-OMe (Entry 8) whereas it was no longer a very good chiral ligand for Ac-ΔPhe-(S)-Phe-OH (Entry 18). Pyrrolidinodiphosphines and diPAMP achieved extremely high stereoselectivities. There seems to be a trend that the chiral ligands which form seven-membered-ring chelates with rhodium give rise to much better results than those forming rigid five-membered-ring chelates or quasi five-membered-ring chelates except diPAMP. The results may imply that the seven-membered-ring chelate has flexibility for "induced-fit" action like an enzyme, which is quite an important factor for a chiral complex catalyst when the substrate is polyfunctional (Ref. 11).

TABLE 2. Efficiency of chiral diphosphine ligands in the asymmetric hydrogenation of typical dehydrodipeptides[a]

Entry	Substrate	Ligand	Conditions (H_2 press., Temp., Time)			Conversion (%)[b]	Dipeptide (R,S)/(S,S)[b]
1		p-Br-Phenyl-CAPP	1 atm,	40°C,	3 h	100	99.2/0.8
2		(-)BPPM	1 atm,	40°C,	1 h	100	98.7/1.3
3		(+)BPPM	1 atm,	40°C,	1 h	100	0.9/99.1
4		(-)DIOP	5 atm,	25°C,	18 h	100	84.1/15.9
5	Bz-ΔPhe-(S)-Phe-OMe	(+)DIOP	5 atm,	25°C,	18 h	100	15.0/85.0
6		diPAMP	10 atm,	50°C,	15 h	100	2.2/97.8
7		Chiraphos	5 atm,	40°C,	10 h	82	85.1/14.9
8		Prophos	5 atm,	40°C,	10 h	99	4.1/95.9
9		BPPFA	5 atm,	40°C,	10 h	51	18.7/81.3
10		dppb	1 atm,	40°C,	5 h	85	37.8/62.2
11		Ph-CAPP	5 atm,	40°C,	20 h	100	98.0/2.0
12		(-)BPPM	10 atm,	50°C,	20 h	100	96.2/3.8
13		(+)BPPM	10 atm,	50°C,	20 h	97	0.6/99.4
14		(-)DIOP	5 atm,	40°C,	20 h	100	81.8/18.2
15	Ac-ΔPhe-(S)-Phe-OMe	(+)DIOP	5 atm,	40°C,	20 h	89	5.9/94.1
16		diPAMP	5 atm,	50°C,	20 h	86	1.4/98.6
17		Chiraphos	10 atm,	50°C,	20 h	96	39.1/60.9
18		Prophos	10 atm,	50°C,	20 h	95	18.8/81.2
19		BPPFA	50 atm,	50°C,	20 h	23	61.2/38.8
20		dppb	10 atm,	50°C,	20 h	99	34.1/65.9

[a] All reactions were run with 5.0 × 10^{-4} mol of substrate and 5.0 × 10^{-6} mol of catalyst.
[b] Determined by HPLC.

Effects of functional groups at N- and C-termini on the asymmetric induction
We carried out the asymmetric hydrogenations of Ac-ΔAA-AA'-OMe, Ac-ΔTyr(Ac)-Ala-Gly-OMe, Ac-ΔTyr(Ac)-Ala-Gly-Phe-OMe, Ac-ΔPhe-NH-$\overset{*}{C}$H(R)-CH_2OCH_2Ph, HCO-ΔPhe-AA-OMe, X-AA-ΔPhe-AA'-OMe, (X = tBOC, CBZ, TFA), and tBOC-AA-ΔPhe-AA'-NH-Y (Y = H, NH_2, NHPh) catalyzed by [L*Rh(NBD)]$^+$-ClO_4^- (L* = chiral diphosphine) and looked at the effects of chiral centers, protecting groups and functional groups on the efficiency of asymmetric induction. Considerably large double asymmetric inductions were observed in some cases. Among the observed effects of the functional groups in the substrates, the remarkable effects of the protecting groups at N-termini

are interesting to note.

The asymmetric hydrogenations of X-Gly-ΔPhe-Leu-OMe (21: X = ^{t}BOC, CBZ, TFA) and N_3CH_2CO-ΔPhe-Leu-OMe (22) were carried out by using Ph-CAPP-Rh$^+$ as catalyst. As typically exemplified in Table 3, 21 bearing ^{t}BOC group brings about saliently the best stereoselectivity as well as catalyst efficiency. It should be noted that a distal protecting group exerts a remarkable influence on the asymmetric hydrogenation of dehydroamino acid residue in the present systems.

TABLE 3. Asymmetric hydrogenation of 21 and 22 by using Ph-CAPP-Rh$^+$ as catalyst^a

Entry	Substrate	Catalyst (mol%)	H_2 press. (atm)	Conversion^b (%)	$(R,S)/(S,S)^b$
1	^{t}BOC-Gly-ΔPhe-(S)-Leu-OMe	1.0	10	100	96.9/3.1
2	CBZ-Gly-ΔPhe-(S)-Leu-OMe	2.0	10	82	86.4/13.6
3	TFA-Gly-ΔPhe-(S)-Leu-OMe	5.0	50	93	61.5/38.5
4	N_3CH_2CO-ΔPhe-(S)-Leu-OMe	5.0	50	0	——

^{a} Reactions were run with 0.30 mmol of substrate in ethanol at 40°C for 40 h.
^{b} Determined by HPLC analysis.

Stereoselective labeling of peptides

In connection with the regiospecific and stereoselective labeling of polypeptides, we carried out the dideuteration of 21 (X = ^{t}BOC) as a model system by using Ph-CAPP-Rh$^+$ and diPAMP-Rh$^+$ as catalyst. The reactions were run with 1.0 mol% of the chiral catalyst in ethanol at 40°C and 10 atm of dideuterium for 18 h, and the corresponding dideuteriotripeptides were obtained in quantitative yields without any scrambling of deuterium (Eq. 6); Ph-CAPP-Rh$^+$: $(R,R,S)/(S,S,S) = 93.0/7.0$; diPAMP-Rh$^+$: $(R,R,S)/(S,S,S) = 2.6/97.4$.

$$(6)$$
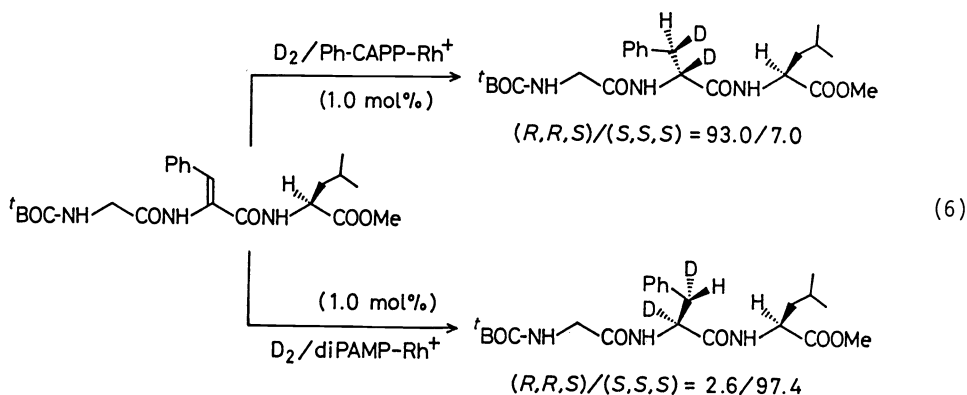
As for the highly stereoselective labeling of N-acyldipeptides, we reported the dideuteration of Ac-ΔPhe-(S)-Ala-OMe (Ref. 14) and Levine-Pinto et al. reported the ditritiation of Ac-ΔPhe-(S)-Phe-OMe (Ref. 15), but the present system may provide a better model for the specific labeling of a certain amino acid residue in a polypeptide. As it has been shown that the introduction of deuterium to the chiral center of certain amino acids, e.g., 3-fluoro-2-deuterio-(R)-alanine, increases the metabolic stability remarkably (Ref. 43), the stereoselective dideuteration may provide a convenient device for this kind of modification of bioligical activity. Tritiation of peptides is, of course, very important for the study on metabolism, and if tritium could be introduced into polypeptides specifically in the very late stage of polypeptide synthesis, such a method would give us big benefits since the method can keep the amounts of radioactive side products at minimum level in sharp contrast with the stepwise synthesis of the labeled polypeptides starting from tritiated amino acids. In this respect, the catalytic asymmetric ditritiation of dehydropeptides may provide a potentially useful method for this problem.

Asymmetric synthesis of Enkephalin analogs

We applied the asymmetric hydrogenation of dehydropeptides to the synthesis of the analogs of Enkephalin (Ref. 44) which is an opioid hormone isolated from brain through fragment condensation. Tow examples are shown in Fig. 6 and Eq. 7, which demonstrate the wide applicability of the catalytic asymmetric hydrogenation to peptide synthesis.
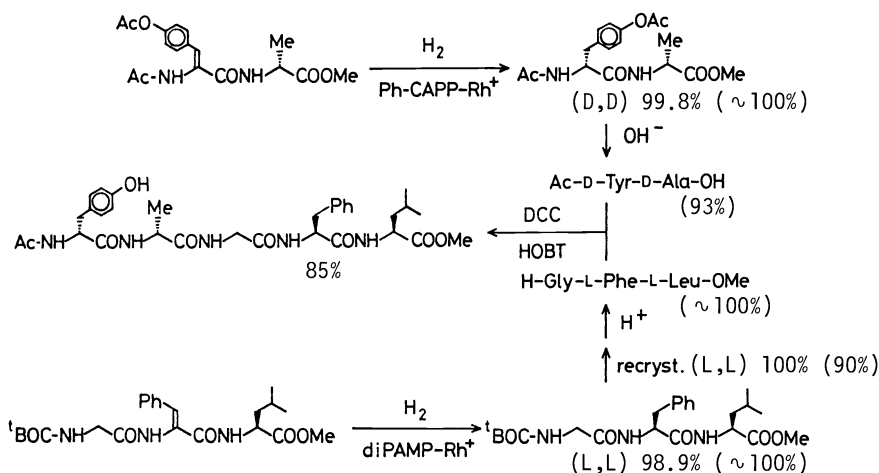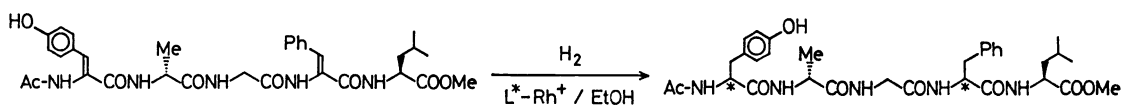
Fig. 6. Synthesis of [Ac-D-Tyr^1, D-Ala^2, Leu^5-OMe]Enkephalin

Ph-CAPP-Rh$^+$ (10 atm, 40°C, 21 hr.) : 100% yield

$(R,R,R,S)/(R,R,S,S)/(S,R,R,S)/(S,R,S,S) = 93.3/6.0/0.7/0.0$

diPAMP-Rh$^+$ (10 atm, 40°C, 18 hr.) : 100% yield

$(R,R,R,S)/(R,R,S,S)/(S,R,R,S)/(S,R,S,S) = 0.4/2.7/0.9/96.0$

(7)

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