Catalytic Asymmetric Synthesis by Means of Secondary Interaction between Chiral Ligands and Substrates

Masaya Sawamura and Yoshihiko Ito*

Department of Synthetic Chemistry, Faculty of Engineering, Kyoto University, Kyoto 606-01, Japan

Received February 19, 1992 (Revised Manuscript Received May 20, 1992)

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Masaya Sawamura was born in 1961. He was graduated from Kyoto University, where he also received his Doctor Degree in 1989 under the direction of Prof. Y. Ito with the thesis *Gold(I)-Catalyzed Asymmetric Aldol Reaction of α-Isocyanocarboxylates*. He is now an assistant professor of the department of Synthetic Chemistry, Kyoto University. His research interests are in the development of new synthetic methods with organometallic and biological molecules. He is currently engaged in catalytic asymmetric synthesis promoted by transition metal complexes.

Yoshihiko Ito was born in 1937. He was graduated from Kyoto University, where he received his Doctor Degree of Engineering under the supervision of Prof. R. Oda in 1966. His thesis is entitled *New Synthetic Reactions with Isonitriles, Ylides and Carbenes*. He is now a full professor of the department of Synthetic Chemistry, Kyoto University. His research group is involved in the study of a broad range of topics covering the general area of synthetic organic chemistry with emphasis on development of new synthetic methodologies by means of organometallic compounds. Synthesis and synthetic methods of new silicon compounds and functionally interesting molecules are also current topics in his group.

I. Introduction

In the past two decades, there has been great progress in asymmetric synthesis employing a chiral metal catalyst, so-called catalytic asymmetric synthesis, which is one of the most promising methods of obtaining an optically active compound, since a small amount of chiral material can produce a large amount of chiral product.[1]

As seen in many successful examples of catalytic asymmetric reactions such as rhodium- and ruthenium-catalyzed asymmetric hydrogenations, asymmetric epoxidation and dihydroxylation of olefins, palladium-catalyzed asymmetric allylic alkylations, and asymmetric alkylations with organozinc reagents, the achievement of highly enantioselective reaction by chiral metal catalyst meets at least one of the following two requirements in general: (1) The prochiral center of a reaction substrate is in close proximity to a central metal. In most cases, the prochiral functional group is in coordination with the central metal directly, e.g., π-coordination of olefins in the asymmetric hydrogenations and σ-coordination of aldehydes in the asymmetric alkylation with organozinc reagents. (2) The reacting substrate, to which asymmetry of a chiral catalyst should be induced, has a secondary coordination site to form a chelate complex at the enantiodifferentiating transition state. Such a secondary interaction *between the reacting substrate and the central metal* suppresses the degree of freedom in the transition state and makes it easy to control the stereochemistry of the product.

On the other hand, a new type of chiral ligands, which has been designed and synthesized so as to interact with the reacting substrates by means of *secondary interactions between functional groups on the chiral ligands and substrates* and to overcome the above-

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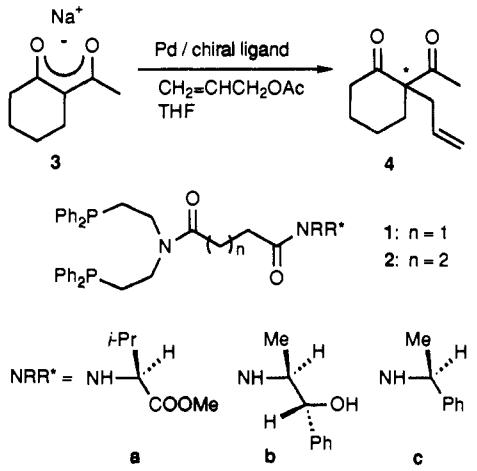
Scheme 1



mentioned requirements, has recently been of much interest. An interesting point of the asymmetric synthesis with the new functionalized chiral ligands is the resemblance to enzymes in the manner of stereoselection, which are excellent chiral catalysts in biological systems. The multipoint interaction of the transition state with convergent functional groups of the enzyme is the essence of the stereospecific enzyme catalysis.

In this review, we would like to describe the usefulness of the secondary ligand–substrate interaction by collecting the examples of catalytic asymmetric reactions, which seem to be in accord with the concept.[2]

II. Palladium-Catalyzed Asymmetric Allylic Alkylation

A. Asymmetric Induction at Carbon Nucleophiles

Studies on the stereochemistry of the palladium-catalyzed allylic alkylation have revealed that stabilized carbon nucleophiles such as acetylacetonate attack a π-allyl carbon from the side opposite to palladium atom in a π-allylpalladium(II) intermediate.[3-5] Accordingly, it is apparent that a chiral ligand on palladium is far from the attacking nucleophile and has only a limited effect on the asymmetric allylation reaction where a new asymmetric center is created at the nucleophile.[6,7]

Hayashi et al. have designed new types of chiral diphosphine ligands which possess a *chirotopic functional group* at an appropriate distance from an achiral diphosphine moiety and demonstrated them to be fairly effective for the asymmetric allylic alkylation.[8] Phosphine ligands **1** and **2** were examined for the stereoselectivity in the palladium-catalyzed reaction of sodium enolate of 2-acetylcyclohexanone (**3**) with allyl acetate (Scheme 1, Table 1). Optically active allylation product **4** with high enantiomeric purity can be obtained in the reaction with phosphine ligands **1a** and **1b**. The reaction with **1a** at −50 °C gives **4** in the highest enantiomeric excess (52% ee). The coordinative interaction between the chiral functional groups and the sodium enolate has been proposed for the stereoselection (Figure 1a). The low selectivity with **2a**, which has 1-phenylethyl group as a chiral source, supports the proposed chelation. The importance of linker chain length is shown by lower selectivity of **2a**, which is a long-chain version of **1a**.

Table 1. Palladium-Catalyzed Asymmetric Allylation of Sodium Enolate of 2-Acetylcyclohexanone (3) (Scheme 1)[a]

chiral ligand	T (°C)	% ee	chiral ligand	T (°C)	% ee
1a	rt	19 (*R*)	**1c**	−30	15 (*R*)
1a	−30	45 (*R*)	**2**	rt	5 (*R*)
1a	−50	52 (*R*)	(−)-DIOP	−30	2 (*R*)
1b	−30	31 (*R*)	(*S*)-prophos	−30	11 (*R*)

[a] 3/allyl acetate/[(π-allyl)PdCl]$_2$/chiral ligand = 1/1.4/0.004/0.008.

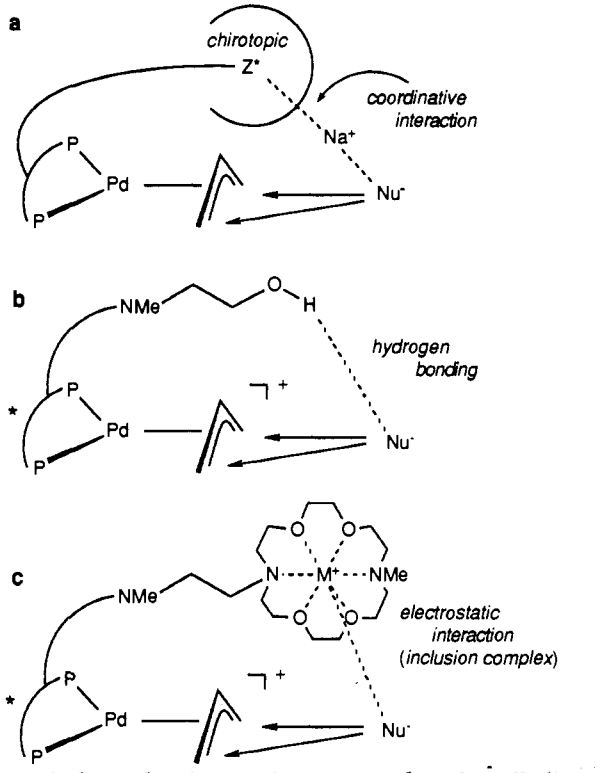
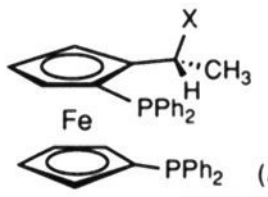


Figure 1. Secondary interactions proposed for the palladium-catalyzed asymmetric allylation of unsymmetrically substituted 1,3-diketones with ligands bearing a chirotopic functional group (**1** and **2**) (a), with ferrocenylphosphine ligand bearing a hydroxyl group **5a** (b), and with crown ether-modified ligand **6d** (c).

Similar ligand modification was performed on chiral ferrocenylphosphine ligand **5** and used in the same palladium-catalyzed allylation.[9] Results of asymmetric allylation of **3** are summarized in Table 2. The palladium catalyst bearing ferrocenylphosphine **5a**, which contains one hydroxyl group on the terminal position of pendant chain, is the most catalytically active and stereoselective, giving the allylation product in 73% ee at −50 °C and in 81% ee at −60 °C. The ligand possessing two terminal hydroxyl groups, **5b**, shows less stereoselectivity (49% ee), although this ligand is better than **5a** in the allylic alkylation where new stereogenic center is created at allylic substrates (vide infra, II-B). The dependency of the stereoselectivity on the linker chain length (ligand **5d** and **5e**) is herein observed.

It should be noted that the catalysts with higher stereoselectivity are more catalytically active in general. Hayashi et al. have proposed that a secondary interaction between the chiral ligands and the nucleophile accelerates the allylation by drawing the nucleophile up to the π-allyl and that a hydrogen bonding between the hydroxyl group and enolate anion is more probable

Table 2. Asymmetric Allylation of Sodium Enolate of 2-Acetylcyclohexanone (3) (Scheme 1) Catalyzed by Palladium Complexes of Chiral Ferrocenylphosphine Ligands 5a–h[a]



(*R*)-(*S*)-BPPF-X, **5**

chiral ligand X of (*R*)-(*S*)-**5**		*T* (°C)	% ee
$NMeCH_2CH_2OH$	**(5a)**	−50	73 (*S*)
	(5a)	−60	81 (*S*)
$NMeCH(CH_2OH)_2$	**(5b)**	−50	49 (*S*)
$NHCH_2CH_2OH$	**(5c)**	−50	62 (*S*)
$NH(CH_2)_3OH$	**(5d)**	−50	46 (*S*)
OH	**(5e)**	−30	30 (*S*)
$NHCH_2CH_2NHMe$	**(5f)**	−30	20 (*R*)
$NHCH_2CH_2OMe$	**(5g)**	−30	6 (*R*)
NMe_2	**(5h)**	−30	22 (*R*)

[a] 1/allyl acetate/[(π-allyl)PdCl]$_2$/chiral ligand = 1/1.25/0.005/0.011.

Figure 2. X-ray structure of π-allylpalladium(II) complex bearing ferrocenylphosphine ligand **5a**.

for the secondary interaction than coordination to sodium of enolate (Figure 2) because the replacement of the terminal hydroxyl group with amino or methoxy group resulted in the formation of **4** with opposite configuration in low optical yield (ligand **5f** and **5g**). Recently, the X-ray crystal structure of the π-allylpalladium complex bearing hydroxylated ligand **5a** was reported,[10] in which the pendant hydroxyl group reaches over the π-allyl group and is located in close proximity to one of the π-allyl carbon atoms (Figure 2). Hayashi et al. proposed a hypothetical transition-state model (Figure 3a), where hydrogen bonding between the hydroxyl group and enolate anion causes preferential attack of the enolate on π-allyl carbon atom C1, arranging larger substituent L and smaller one S to outside (left side in Figure 3a) and inside (right side), respectively.[9,10]

Although the palladium catalyst bearing **5a** is also effective for other cyclic diketones, near-racemic product is formed in the reaction of 2-acetylcyclopentanone. Moderate stereoselectivities are obtainable, however, in the reaction of acyclic active methine compounds (Figure 4).

Ito, Sawamura, Hayashi, and co-workers reported the palladium-catalyzed asymmetric allylation of α-isocyanocarboxylates using hydroxylated ferrocenylphosphine ligand **5a**.[11] Enantioselectivities are very low under usual reaction conditions, but improved significantly by an addition of 1 equiv of zinc halides, which may be coordinated to an isocyano group. The highest

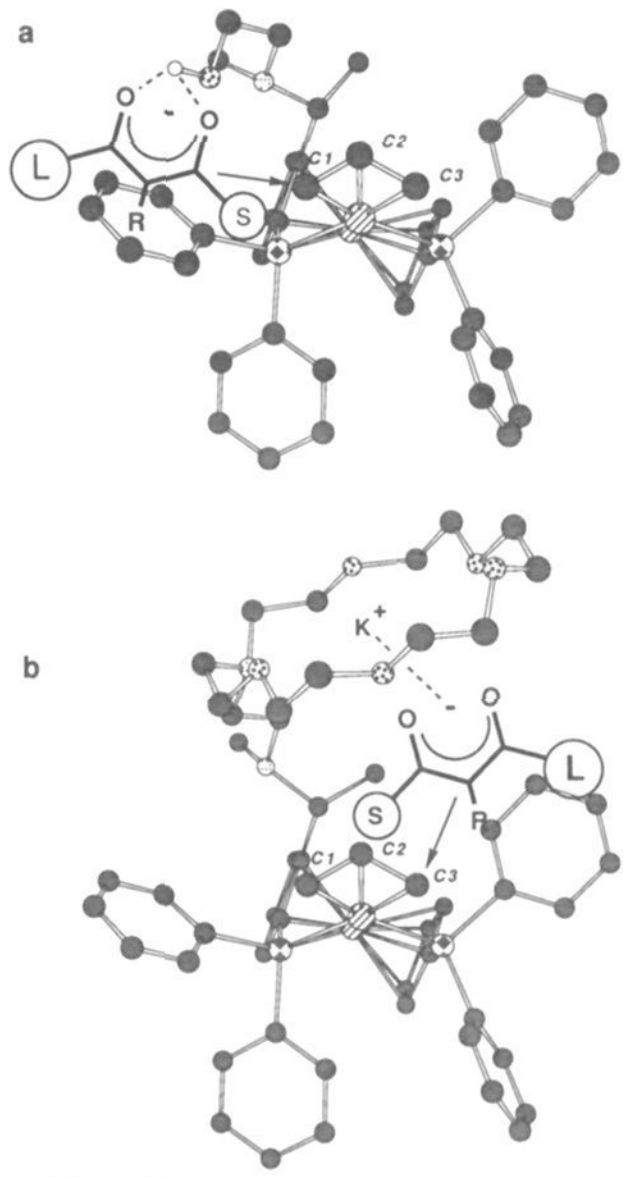


Figure 3. Transition-state model proposed for the palladium-catalyzed asymmetric allylation of unsymmetrically substituted 1,3-diketones with ferrocenylphosphine ligand **5a** (a) and with crown ether-modified ligand **6b** (b).

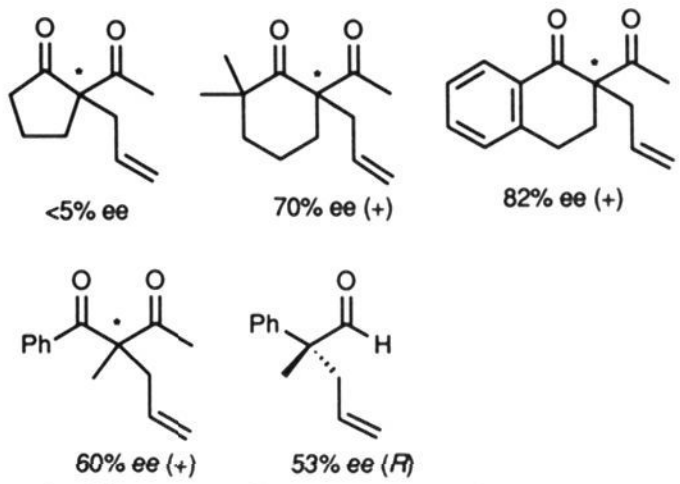
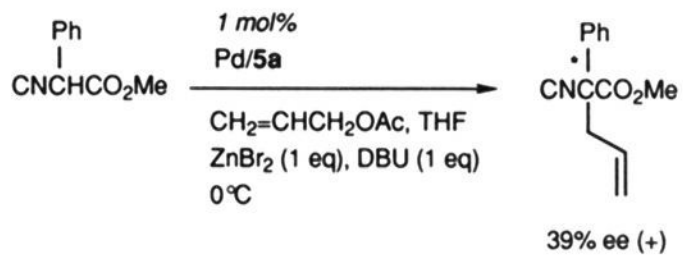


Figure 4. List of products resulting from the palladium-catalyzed asymmetric allylation with ferrocenylphosphine **5a**. Values of enantiomeric excess are accompanied with the structural formulas.

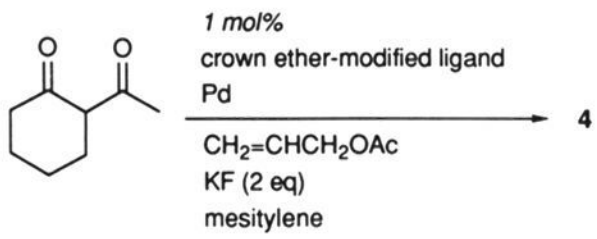
Scheme 2



optical yield (39%) is obtained in the allylation of methyl α-isocyanophenylacetate in the presence of DBU as a base and $ZnBr_2$ additive (Scheme 2).

Recently, Sawamura, Ito, and co-workers have synthesized a series of chiral ferrocenylphosphine ligands modified by monoaza or diaza crown ethers of varying

Table 3. Palladium-Catalyzed Asymmetric Allylation of 2-Acetylcyclohexanone under the Two-Phase Reaction Conditions[a]



L*	T (°C)	t (h)	conv (%)	% ee
6a	−25	40	30	49 (*R*)
6b	−25	40	100	60 (*R*)
	−40	150	100	68 (*R*)
6c	−25	40	59	49 (*R*)
6d	−25	40	97	72 (*R*)
	−40	150	100	75 (*R*)
6e	−25	40	40	53 (*R*)
7	−25	40	16	9 (*R*)
8a	−25	40	65	22 (*R*)
5h	−25	40	78	32 (*R*)

[a] Diketone/allyl acetate/KF/$Pd_2(dba)_3$/chiral ligand = 1/1.5/2/0.005/0.011.

ring sizes and linker chain lengths (**6a–e** and **7**) and applied them to the palladium-catalyzed asymmetric allylation of β-diketones.[12] These ligands were designed to interact with the nucleophile through the formation of inclusion complex with the crown ether (Figure 1c).

The crown ether-modified ligands were examined for the enantioselectivity and catalytic activity in the asymmetric allylation of **3** in the solid–liquid, two-phase reaction condition using potassium fluoride as a base in mesitylene solvent (Table 3). Ligands **6a–c** have monoaza crown ethers of varying ring sizes tethered with the same length of linker chain. As expected from the complementarity between hole size of crown ether and ionic radius of a guest cation, ligand **6c** with monoaza-18-crown-6 moiety significantly accelerates the allylation with increased enantioselectivity (60%) compared with **5h** (32% ee) and **8a** (22% ee), which are the ferrocenylphosphine ligand lacking the crown ether moiety, while monoaza-15-crown-5 and monoaza-21-crown-7 of **6a** and **6c** retard the reaction, giving the allylation product in low yield with 49% ee. The highest enantioselectivity of 75% is obtained in the allylation at −40 °C with the ligand bearing 1,10-diaza-18-crown-6 moiety (**6d**). Length of linker chain is also important for both stereoselectivity and catalytic activity as shown by the reaction with ligand **6e** and **7**. Ligand **6d** is also effective for the allylation of 2-acetylcyclopentanone [65% ee (−)] and acyclic β-diketone, 2-methyl-1-phenyl-1,3-butanedione [72% ee (−)].

Interestingly, the chiral sense of enantioselection by the use of crown-modified ligands is always opposite to that of Hayashi's hydroxylated ligand **5a**. It was proposed that the opposite sense may originate from the regiochemical alternation at the π-allyl carbon atoms in nucleophilic attack of enolate and that the sterically bulky crown ether moiety blocks the approach of the enolate to π-allyl carbon C1, providing a chiral pocket around π-allyl carbon C3 for the nucleophilic attack, as shown in Figure 3b.

The NOE study of the π-allylpalladium(II) complex of **6b** suggests that the aza crown ether moiety of **6b** is in a proper orientation to interact with the incoming nucleophile (Figure 5).

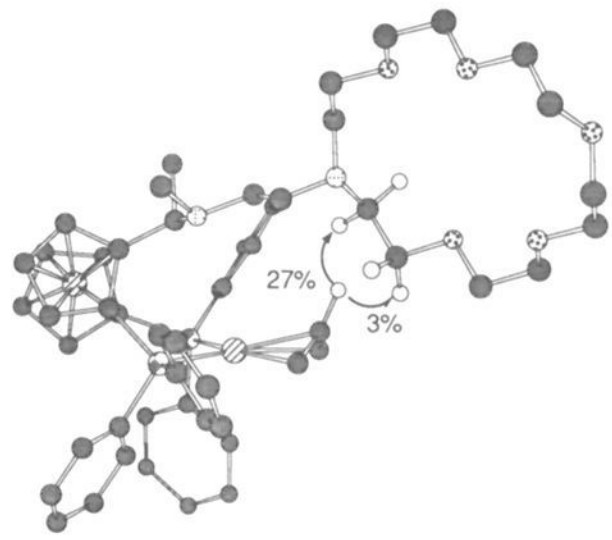
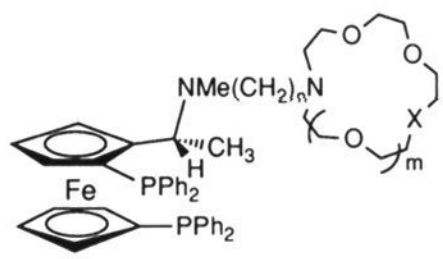
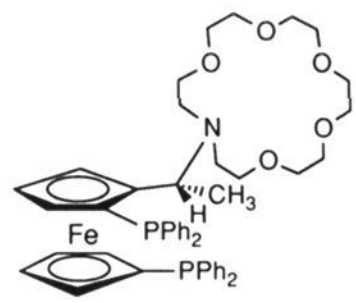


Figure 5. Molecular model of the π-allylpalladium(II) complex bearing crown ether-modified ligand **6b**. Arrows show $^1H\{^1H\}$ NOE's observed.



6a: n = 2, m = 1, X = O
6b: n = 2, m = 2, X = O
6c: n = 2, m = 3, X = O
6d: n = 2, m = 2, X = NMe
6e: n = 3, m = 2, X = O



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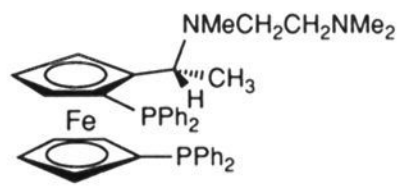


8a

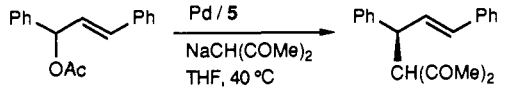
B. Asymmetric Induction at Allylic Substrates

Hayashi, Ito, and co-workers applied the hydroxylated ferrocenylphosphine ligands to the palladium-catalyzed asymmetric allylic alkylation of 1,3-disubstituted allylic acetates with sodium acetylacetonate and related stabilized carbon nucleophiles.[13] As shown in Table 4, the enantioselectivity in the reaction of (*E*)-1,3-diphenyl-3-acetoxy-1-propene (**9**) with acetylacetonate increases as the number of hydroxyl group on the pendant side chain of chiral ligand increases. Extremely high enantioselectivity (96%) is attained with trihydroxylated ligand **5i**.

Palladium-catalyzed asymmetric allylic amination with benzylamine or its derivatives takes place more stereoselectively than the allylic alkylations (Scheme 3).[10,14] The reaction of 1,3-diphenyl-2-propenyl ethyl carbonate with benzylamine gives an amination product in 97% ee with dihydroxylated ligand **5b**. Ligand **5b** is also effective for the amination of 2-propenyl carbonates or phosphinates substituted with alkyl groups.

^{31}P NMR of π-allylpalladium(II) acetate bearing 1,3-diphenyl π-allyl group and chiral ligand **5b** indicated that the complex exists as an equilibrium mixture of two isomeric forms in a ratio of 20:1, which are tentatively assigned to W form and M form, respectively, as shown in Figure 6. An addition of an excess of benzylamine to the equilibrium mixture gave the allylic amination product in 96% ee. On the other hand, a 2:1 equilibrating mixture of (1,3-diphenyl-π-allyl)-

Table 4. Asymmetric Allylic Alkylation of (*E*)-1,3-Diphenyl-3-acetoxy-1-propene (9) with Sodium Acetylacetonate Catalyzed by Palladium Complexes Containing Ferrocenyl Ligands 5[a]



9

chiral ligand X of (*R*)-(*S*)-5		% ee
$NMeCH_2CH_2OH$	(**5a**)	71 (*S*)
$NMeCH(CH_2OH)_2$	(**5b**)	90 (*S*)
$NMeC(CH_2OH)_3$	(**5i**)	96 (*S*)
NMe_2	(**5h**)	62 (*S*)

[a] $9/NaCH(COMe)_2/[(\pi\text{-allyl})PdCl]_2/L^* = 1/1.2/0.005/0.01$.

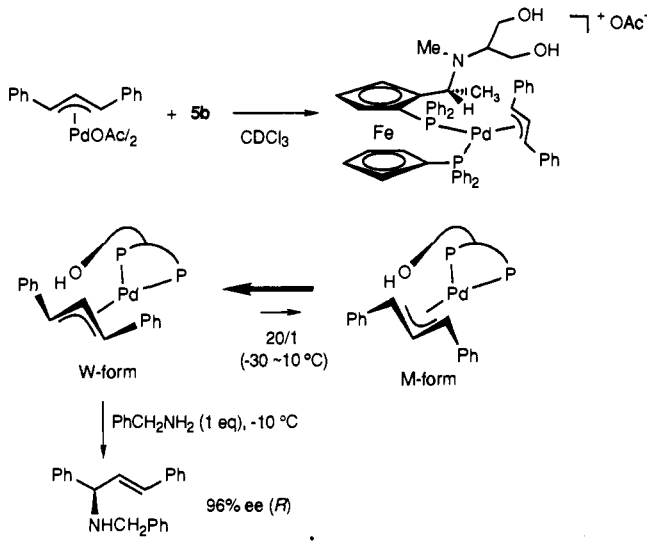
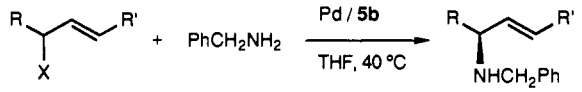


Figure 6. Preparation of (1,3-diphenyl-π-allyl)palladium-(II) complex bearing ferrocenylphosphine ligand **5b** and stoichiometric reaction of the π-allylpalladium(II) complex with benzylamine.

Scheme 3



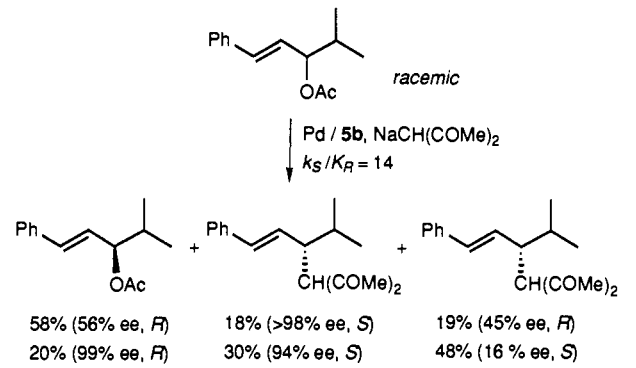
R = R' = Ph, X = OCO_2Et, 97% ee (*R*)
R = R' = Me, X = $OPOPh_2$, 73% ee (*S*)
R = R' = *i*-Pr, X = OCO_2Et, 97% ee (*S*)
R = Me, R' = H, X = OAc, 84% ee (*S*)

palladium complex bearing chiral ligand **5h**, which lacks the hydroxyl pendant, gave the amination product of low enantiomeric purity (62% ee) on treatment with an excess of benzylamine.

Chiral ligand **5b** is also effective for asymmetric allylic alkylation of allyl acetates which have two different substituents at 1 and 3 positions, resulting in kinetic optical resolution of racemic 1-[(*E*)-styryl]-2-methylpropyl acetate (Scheme 4),[15] and for intramolecular asymmetric cyclization of carbamate **10** to give 4-vinyloxazolidones (up to 77% ee) (Scheme 5).[16]

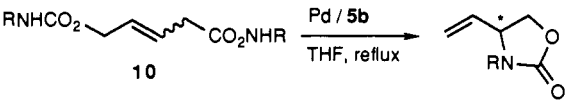
Minami and co-workers have synthesized a series of chiral monodentate phosphine ligands, which have a carboxylic acid functionality and a cyclobutane or cyclopentane backbone (**11** and **12**), and applied them to the asymmetric allylic alkylation of 3-acetoxy-1,3-diphenyl-1-propene with triethyl sodiophosphonoacetate (**14a**) and dimethyl malonate (**14b**) (Table 5).[17]

Scheme 4



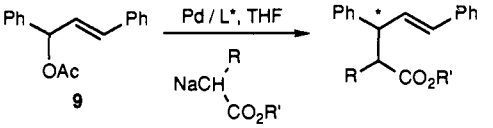
58% (56% ee, *R*) 18% (>98% ee, *S*) 19% (45% ee, *R*)
20% (99% ee, *R*) 30% (94% ee, *S*) 48% (16 % ee, *S*)

Scheme 5



R = Ph (*E*): 73% ee (*S*) R = 1-Np (*E*): 70% ee (+)
R = Ph (*Z*): 77% ee (*S*) R = (*E*)-PhCH=CH (*E*): 70% ee (*S*)

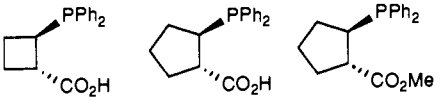
Table 5. Asymmetric Allylic Alkylation of 9 Catalyzed by Palladium Complexes Containing Chiral Ligands 11–13[a]



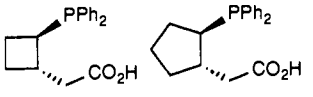
14a: R = P(O)(OEt)2, R' = Et
14b: R = CO_2Me, R' = Me

nucleophile	L*	% ee	nucleophile	L*	% ee
14a	(+)-**11a**	79 (+)	**14b**	(+)-**11b**	85 (*R*)
14a	(+)-**11b**	83 (+)	**14b**	(+)-**12a**	2 (*R*)
14a	(+)-**12a**	2 (+)	**14b**	(+)-**12b**	7 (*R*)
14a	(+)-**12b**	48 (+)	**14b**	(+)-**13**	37 (*R*)
14b	(+)-**11a**	77 (*R*)			

[a] $9/14/Pd(OAc)_2/L^* = 1/1.5/0.01/0.02$.



11a **11b** **13**



12a **12b**

Although high enantioselectivity of around 80% ee is obtained in the reaction with both nucleophiles in the presence of chiral ligands 2-(diphenylphosphino)-cyclopentanecarboxylic acid (**11b**) and its cyclobutane analogue **11a**, a drastic decrease of the stereoselectivity is caused by the use of the chiral ligands whose carboxyl group is connected with a cycloalkane backbone via a methylene group (**12a,b**), indicating that the position of the carboxyl substituent is important for the stereoselective allylic alkylation. The importance of the carboxyl group is further supported by the low enantioselectivity observed for the reaction using ligand **13**, which is the ester analogue of **8b**. It has been proposed that the high stereoselectivity with **11a,b** is

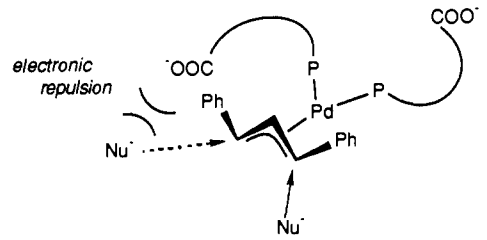
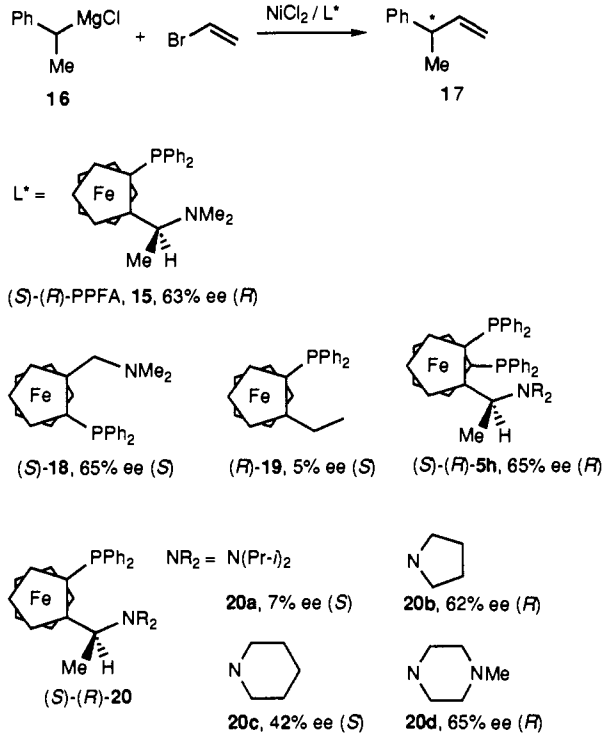


Figure 7. Repulsive secondary interaction proposed for the palladium-catalyzed asymmetric allylic alkylation with chiral ligand bearing carboxyl group 11.

Scheme 6



caused by an electronic repulsion between the carboxylate anion on the ligands and the negative charge of the incoming nucleophiles, which directs the nucleophilic attack on one of the π-allyl carbons, as shown in Figure 7.

III. Asymmetric Grignard Cross-Coupling

In 1976, Kumada, Hayashi, and co-workers reported the nickel-catalyzed asymmetric Grignard cross-coupling using chiral [(aminoalkyl)ferrocenyl]phosphine ligand PPFA, **15**.[18] The cross-coupling of 1-phenylethyl Grignard reagent **16** with vinyl bromide is catalyzed enantioselectively by nickel–PPFA complex (0.5 mol %), giving coupling product **17** in 63% ee at 0 °C (Scheme 6). Various chiral ferrocenylphosphine ligands (**5h** and **18–20**) were examined for the asymmetric Grignard cross-coupling.

Chiral ligand **18**, which contains an amino group on the ferrocene side chain but lacks the central chirality, shows almost the same degree of enantioselectivity, while chiral ligand **19**, which lacks both the central chirality and amino group, gives almost racemic product, indicating that the planar chirality is more important for the stereoselection than the central chirality and that the amino group on the side chain is crucial. Dramatic change of stereoselectivity is observed by

Scheme 7

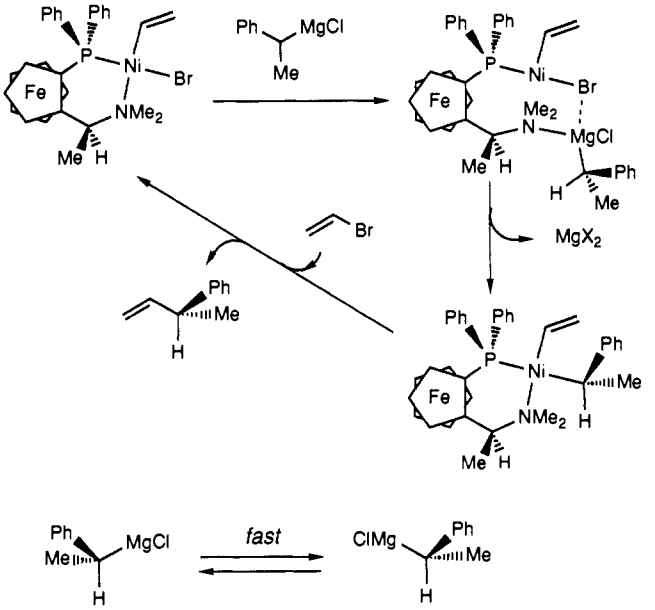
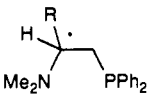


Table 6. Nickel-Catalyzed Asymmetric Grignard Cross-Coupling of 16 with Vinyl Bromide Using Various Chiral (β-Aminoalkyl)phosphines 21 (Scheme 6)



21

	R	% ee of 17
(S)-Alaphos (**21a**)	Me	38 (S)
(S)-Phephos (**21b**)	$PhCH_2$	71 (S)
(R)-PhGlyphos (**21c**)	Ph	70 (R)
(S)-Valphos (**21d**)	*i*-Pr	81 (S)
(R)-*t*-Leuphos (**21e**)	*t*-Bu	83 (R) (94)[a]

[a] Value corrected for the optical purity of ligand **21e**.

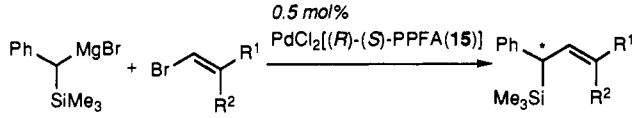
changing alkyl substituents on amino group [for **20a–d**, 7% ee (S) to 65% ee (R)]. BPPFA (**5h**), which is a diphosphine ligand bearing a dimethylamino group on the side chain, is also an effective chiral ligand.

Kumada, Hayashi, and co-workers have proposed a mechanism of asymmetric induction by PPFA as shown in Scheme 7, where the amino group of PPFA coordinates to the magnesium atom of the in-coming Grignard reagent. This coordination occurs selectively with one of the enantiomers of the racemic Grignard reagent (kinetic optical resolution), whose racemization is much faster than the cross-coupling, and permits it to readily undergo subsequent transmetalation.

Chiral (β-aminoalkyl)phosphines **21**, which are prepared from optically active amino acids, are also effective chiral ligands for the asymmetric Grignard cross-coupling of **16** with vinyl bromide (Table 6).[19] When *t*-Leuphos (**21e**) is used as the chiral ligand the highest optical yield of 83% ee is obtained. The optical yield is corrected to 94% ee for the optical purity of the ligand. The chiral ligand with larger substituent at the chiral carbon atom induces higher stereoselectivity, that is, the order of efficiency for asymmetric induction is **21e** (R = *t*-Bu) > **21d** (R = *i*-Pr) > **21b** (R = $PhCH_2$) ≅ **21c** (R = Ph) > **23a** (R = Me).

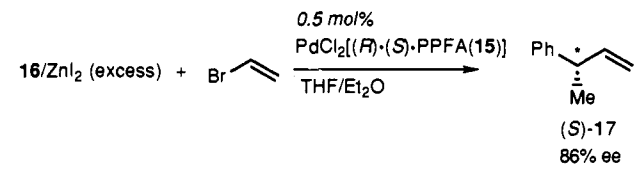
The cross-coupling of phenyl(trimethylsilyl)methylmagnesium bromide with vinyl bromide proceeds with

Scheme 8



R_1	R_2	% ee
H	H	95
Me	H	85
H	Me	24
Ph	H	95
H	Ph	13

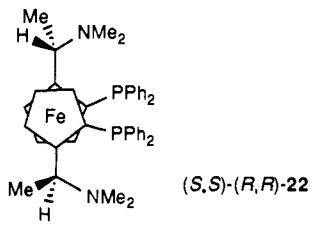
Scheme 9



(*S*)-17
86% ee

extremely high stereoselectivity in the presence of PPFA-Pd catalyst, giving an optically active allylsilane (Scheme 8).[20] Although the reaction of both (*E*)-1-propenyl bromide and (*E*)-cinnamyl bromide is highly stereoselective, the corresponding (*Z*) isomers give coupling products in very low optical yield.

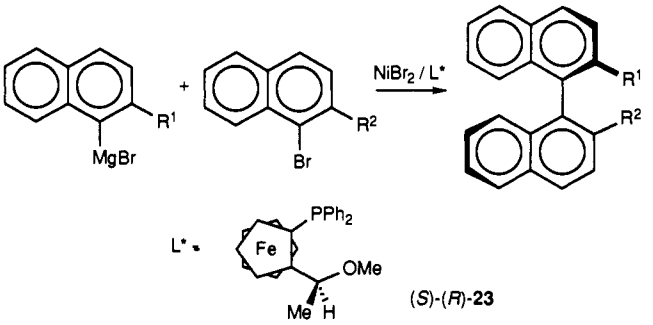
The cross-coupling of organozinc reagents, which are prepared in situ from Grignard reagent **16** and zinc halides, proceeds in the presence of PPFA-Pd catalyst more stereoselectively than that of the Grignard reagent (Scheme 9).[21] C_2-Symmetric ferrocenyldiphosphine **22** is an excellent ligand in this reaction, giving the coupling product **17** in 93% ee.[22]



(*S,S*)-(*R,R*)-**22**

The asymmetric cross-coupling has been successfully applied to the synthesis of optically active binaphthyls (up to 95% ee, Table 7).[23] Ferrocenylphosphine ligand **23**, which has a methoxy group on the ferrocene side chain, is the chiral ligand of choice. The nickel complex of PPFA (**15**), which has a dimethylamino group instead of methoxy group, is catalytically inactive in this case. Although 2-methyl-1,1′-binaphthyl is obtained in 83% ee by the cross-coupling of (2-methyl-1-naphthyl)magnesium bromide with 1-naphthyl bromide, the same product with a much lower enantiomeric excess is produced in another cross-coupling of 1-naphthylmagnesium bromide with 2-methyl-1-naphthyl bromide. This result suggests that the stereochemistry of binaphthyl is determined kinetically in the formation of diastereomeric diorganonickel(II) species, which has a chiral propeller structure and hardly undergoes epimerization due to a steric hindrance preventing rotation of nickel–carbon bonds. It has been proposed that coordination of the methoxy group of ligand **23** with the magnesium atom in the Grignard reagent favors the stereoselective transmetalation forming the diorganonickel species.

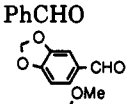
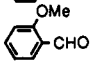
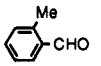
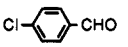
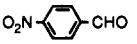
Table 7. Asymmetric Grignard Cross-Coupling Producing Optically Active Binaphthyls in the Presence of $NiBr_2$/(*S*)-(*R*)-PPFOMe Catalyst



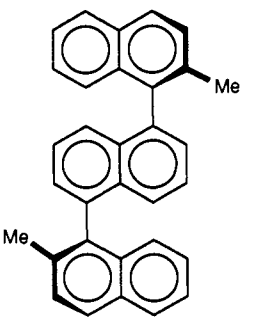
(*S*)-(*R*)-**23**

R_1	R_2	cat. mol %	*T* (°C)	% ee
Me	Me	5	−15	95 (*R*)
Me	H	2	−30	83 (*R*)
H	Me	2	−10	16 (*R*)
Et	H	5	−20	77 (*R*)

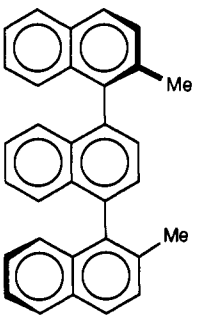
Table 8. Gold-Catalyzed Asymmetric Aldol Reaction of Isocyanoacetate 29a with Aldehydes (Scheme 14)

entry	aldehyde	L*	ratio of trans/cis	% ee of *trans*-**30**
1	PhCHO	**8a**	90/10	91
2	PhCHO	**8b**	89/11	93
3	PhCHO	**8c**	94/6	95
4	PhCHO	**8d**	95/5	95
5		**8d**	95/5	96
6		**8d**	92/8	92
7		**8d**	96/4	95
8		**8d**	94/6	94
9		**8d**	83/17	86
10	MeCHO	**8a**	78/22	37
11	MeCHO	**8b**	84/16	72
12	MeCHO	**8d**	89/11	89
13	*i*-BuCHO	**8d**	96/4	87
14	*i*-PrCHO	**8a**	99/1	94
15	*t*-BuCHO	**8d**	100/0	97
16	(*E*)-*n*-PrCH=CHCHO	**8d**	87/13	92

The cross-coupling of 2-methyl-1-naphthylmagnesium bromide with 1,5- and 1,4-dibromonaphthanenes



(*R,R*)-**24**
98.7% ee



(*R,R*)-**25**
95.3% ee

gives optically active ternaphthalenes **24** and **25**, respectively, in the presence of the same catalyst.[23b]

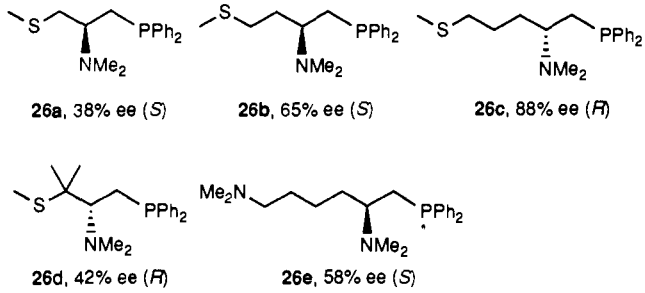
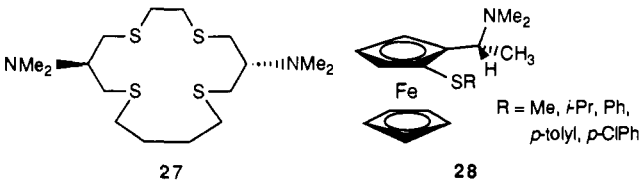


Figure 8. Chiral (β-aminoalkyl)phosphine bearing a functionalized side chain **26** and results of nickel-catalyzed asymmetric cross-coupling of Grignard reagent **16** with vinyl bromide. Compound numbers are accompanied with the values of enantiomeric excess of coupling product **17**.

Kellogg et al. have synthesized a series of chiral (β-aminoalkyl)phosphine ligands **26**, which have a side chain containing a functional group such as sulfide or amine and applied them to the nickel-catalyzed cross-coupling of Grignard reagent **16** with vinyl bromide (Figure 8).[24] Chiral ligand **26c**, derived from homomethionine, gives **17** of the highest optical purity (88%). Kellogg et al. have proposed two possibilities for the role of the sulfur atom on the side chain, i.e., coordination of the sulfur atom to the nickel in the reductive elimination process or to magnesium atom of Grignard reagent in the transmetalation process. They also prepared various chiral macrocyclic amino sulfide ligands and examined them for the cross-coupling.[25] The highest enantioselectivity is, however, only 46% with macrocyclic tetrasulfide ligands **27**.

Brubaker et al. have synthesized new chiral ferrocenyl sulfide ligands **28** and have tested them for the asymmetric cross-coupling of allylmagnesium chloride with 1-phenylethyl chloride (<25% ee).[26]



27 28

IV. Asymmetric Aldol Reaction of α-Isocyanocarboxylates

A. Gold-Catalyzed Asymmetric Aldol Reaction

In 1986, Ito, Sawamura, and Hayashi reported that the aldol-type reaction of isocyanoacetate **29** with aldehydes is catalyzed by gold complexes containing chiral ferrocenylphosphine ligands **8** bearing a tertiary amino group at the terminal position of the pendant chain, giving optically active 5-alkyl-2-oxazoline-4-carboxylates **30** with high enantio- and diastereoselectivity (Scheme 10, Table 8).[27,28] The *trans*-oxazolines thus obtained can be readily hydrolyzed to the corresponding *threo*-β-hydroxy α-amino acids.

For instance, the reaction of methyl isocyanoacetate (**8a**) with benzaldehyde in methylene dichloride at 25 °C in the presence of 1 mol % of cationic gold(I) catalyst prepared in situ by mixing bis(cyclohexyl isocyanide)-gold(I) tetrafluoroborate (**31**) and chiral ligand **8a**, which has a terminal dimethylamino group, gives almost quantitative yield of the oxazoline with 91% ee in 90/10 trans/cis ratio (Table 8, entry 1). Both enantio- and diastereoselectivity are remarkably dependant on the structure of the terminal amino group of the ligand (entries 1–4 and 10–12), indicating that the amino group is playing a key role in the stereoselection. In general, six-membered ring amino groups such as piperidino and morpholino groups are effective as the terminal amino group. Various substituents on the aromatic aldehyde are acceptable for the highly stereoselective aldol reaction with isocyanoacetate (entries 5–9). Secondary and tertiary alkyl aldehydes give the corresponding *trans*-oxazolines almost exclusively with high enantioselectivity (entries 14 and 15).

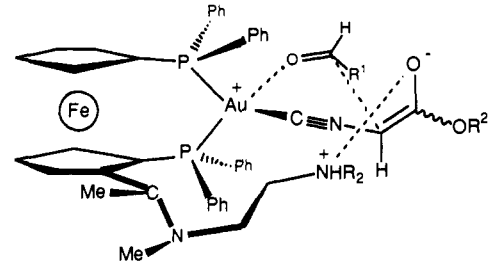
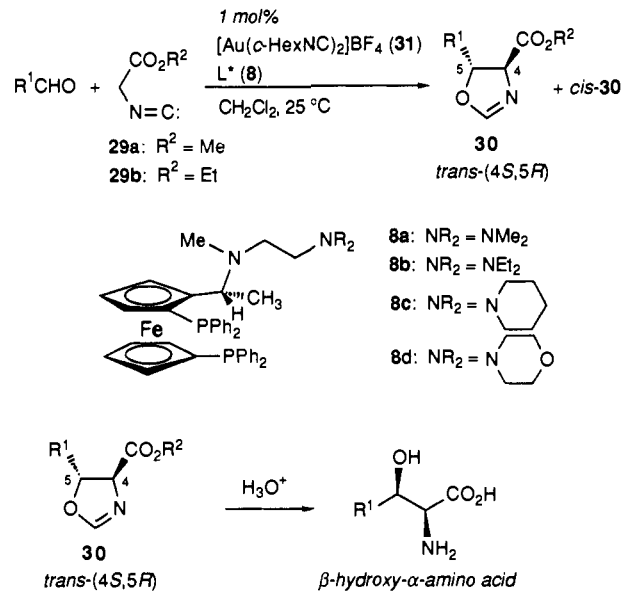


Figure 9. Hypothetical transition-state model proposed for the gold-catalyzed asymmetric aldol reaction of **29**.

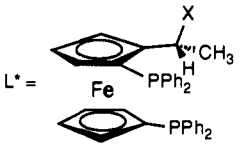
Scheme 10



Ito, Sawamura, and Hayashi have proposed a hypothetical transition-state model as shown in Figure 9, where the chiral ligand chelates to gold with the two phosphorus atoms, leaving the two nitrogen atoms in the pendant chain free, and the terminal amino group abstracts one of α-methylene protons of gold-coordinated isocyanoacetate, forming an ion pair between enolate anion and ammonium cation. The attractive interaction permits a favorable arrangement of the enolate and aldehyde on the gold at the stereodifferentiating transition state. Later, the possibility of coordination of the aldehyde to the gold at the transition state was suggested by the results of silver(I)-catalyzed asymmetric aldol reaction (vide infra, IV-B).

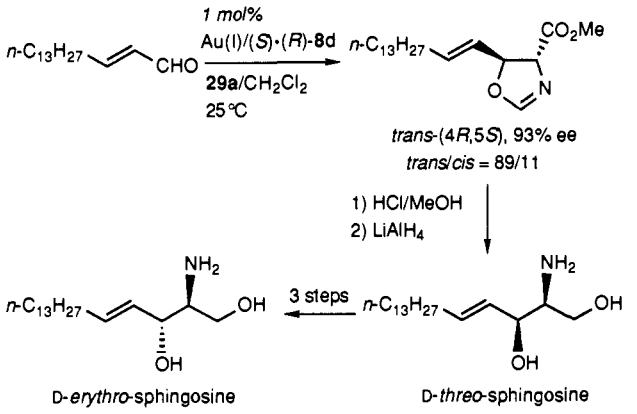
Use of ligands **32a,b**, which are analogous to **8a,b** but with a longer tether between the terminal amino groups and the ferrocene moiety, or ligand **5a**, which has a

Table 9. Gold-Catalyzed Asymmetric Aldol Reaction of Isocyanoacetate 29a with PhCHO Using Various Ferrocenyl Ligands (Scheme 10)



L*	X in L*	ratio of trans/cis	% ee of *trans*-30
32a	$NMe(CH_2)_3NMe_2$	89/11	23
32b	$NMe(CH_2)_3NEt_2$	86/14	26
5a	$NMeCH_2CH_2OH$	69/31	37
5h	NMe_2	68/32	racemic
5j	OMe	86/14	racemic

Scheme 11



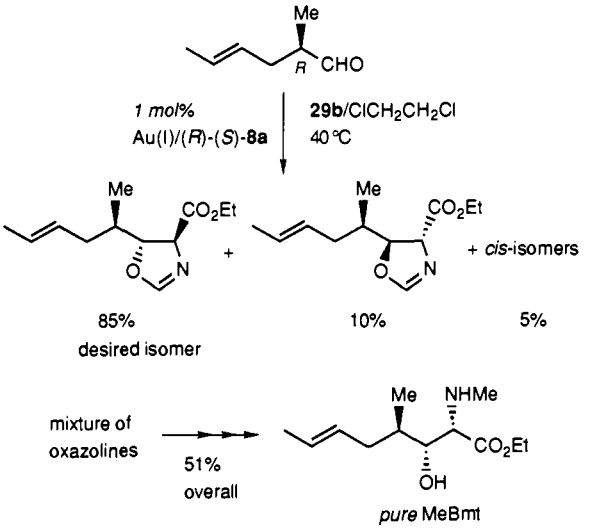
hydroxyl group instead of the terminal amino group, causes a drastic decrease in stereoselectivity. The gold catalysts containing ferrocenyl phosphine BPPFA (**5h**) and **5j**, which lack the terminal amino group, as well as chiraphos, DIOP, and *p*-TolBINAP, are catalytically much less active and give almost racemic oxazolines (Table 9).

The usefulness of the gold-catalyzed aldol reaction was demonstrated by the application to asymmetric synthesis of D-*erythro*- and D-*threo*-sphingosine, an important membrane component and its stereoisomer (Scheme 11),[29] and MeBmt, an unusual amino acid in the immunosuppressive undecapeptide cyclosporine (Scheme 12).[30]

Togni and Pastor have pointed out that enantioselectivity in the gold-catalyzed aldol reaction of aldehyde containing α-heteroatom is significantly different from that of simple aldehydes (Table 10).[31] Low enantioselectivities for the corresponding *trans*-oxazoline are observed in the aldol reaction of 2-thiophene-, 2-furan-, and 2-pyridinecarboxaldehyde (entries 2, 4, and 7). Worthy of note is the fact that the *cis*-oxazolines are formed as minor product in rather low trans/cis ratio with fairly high enantioselectivities in the reaction of the 2-furan- and 2-pyridinecarboxaldehyde. A similar α-heteroatom effect is also observed in the aldol reaction of 2,3-*O*-isopropylidene-D-glyceraldehyde.[31a]

The gold-catalyzed aldol reaction of α-isocyanocarboxylates (**29a** and **33–36**) with paraformaldehyde produces optically active 4-alkyl-2-oxazoline-4-carboxylates (**37**) in moderate to good enantioselectivity.[32] These products can be easily converted to biologically interesting α-alkylserines and their derivatives (Scheme 13).

Scheme 12



Scheme 13

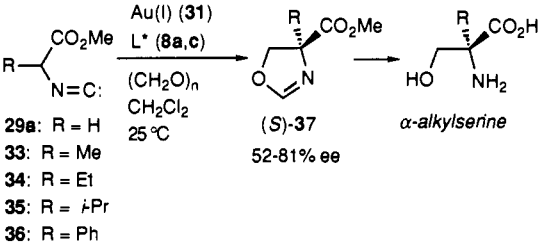


Table 10. Asymmetric Aldol Reaction of Isocyanoacetate 29b with Functionalized Aldehydes in the Presence of Gold(I) Catalyst Containing Ligand 8a (Scheme 14)[a]

aldehyde, R^1	ratio of trans/cis	% ee of *trans*-30	% ee of *cis*-30
3-thienyl	90/10	78	1
2-thienyl	95/5	33	17
3-furyl	86/14	87	7
2-furyl	68/32	32	83
4-pyridyl	88/12	75	78
3-pyridyl	88/12	79	62
2-pyridyl	75/25	6	84

[a] Reaction at 50 °C in dichloromethane.

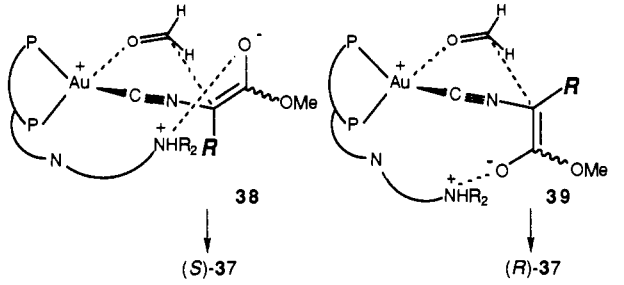


Figure 10. Hypothetical transition-state model of the gold-catalyzed asymmetric aldol reaction of isocyanocarboxylates (**29a** and **33–36**) with paraformaldehyde.

A proposed transition state **38** and **39** (Figure 10) in the aldol reaction with formaldehyde is relatively simple, in which the stereoselection is concerned only with the enantioface differentiation of the enolate. The absolute configuration (*S*) of the products **37** indicates that the hydroxymethylation occurs preferentially from the *si* face of the donor center of the enolate in **38**. Noteworthy is the fact that the enolates of all the iso-

Scheme 14

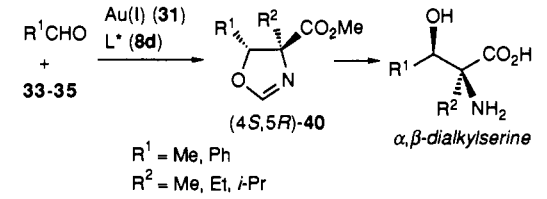
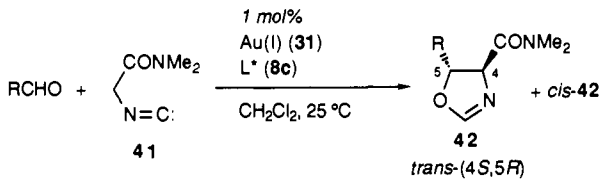
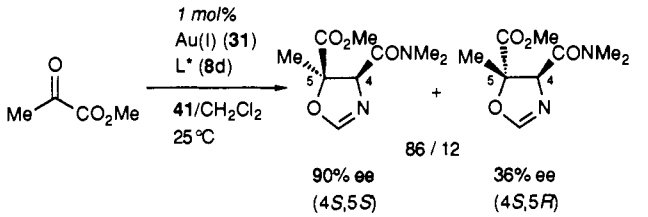


Table 11. Gold-Catalyzed Asymmetric Aldol Reaction of Isocyanoacetamide 41 with Aldehydes



aldehyde	ratio of trans/cis	% ee of *trans*-**42**
MeCHO	91/9	98.6
EtCHO	95/5	96.3
i-BuCHO	94/6	97.3
p-BnOC$_6$H$_4$CH$_2$CHO	>95/5	94.5
PhCHO	94/6	94.1

Scheme 15



cyanocarboxylates (**29** and **33–35**) react on the *si* face irrespective of the steric bulkiness of the α-alkyl substituent. From these results, it is likely that the reaction face of the enantiotopic enolate is determined mainly by the attractive interaction rather than by steric repulsions between the substituents on the enolate and the chiral ligand.

The aldol reaction of α-alkyl-α-isocyanoacetates **33–35** with benzaldehyde or acetaldehyde gives optically active 4,5-dialkyl-2-oxazoline-4-carboxylates **40** with high enantioselectivities (Scheme 14).[33] The oxazolines can be converted into α,β-dialkylserine derivatives.

Extremely high enantioselectivity has been achieved in the aldol reaction of acetaldehyde (98.6% ee) or primary alkyl aldehydes such as propionaldehyde (96.3% ee) or isovaleraldehyde (97.3% ee) with *N,N*-dimethyl-α-isocyanoacetamide (**41**) rather than with isocyanoacetate (Table 11).[34] Conversion of the oxazolinecarboxamides (**42**) to β-hydroxy-α-amino acid can be similarly accomplished by acidic hydrolysis.

The aldol reaction of α-keto esters with isocyanoacetamide **41** proceeds with moderate to high enantioselectivity, giving the corresponding oxazolines of up to 90% ee (Scheme 15).[35]

The methodology of the gold-catalyzed asymmetric aldol reaction has been further extended to the aldol-type condensation of (isocyanomethyl)phosphonates (**43**) with aldehydes, which provides a useful method for the synthesis of (1-aminoalkyl)phosphonic acids, phosphonic analogs of α-amino acids (Scheme 16).[36,37] Higher enantioselectivity and reactivity are obtained

Scheme 16

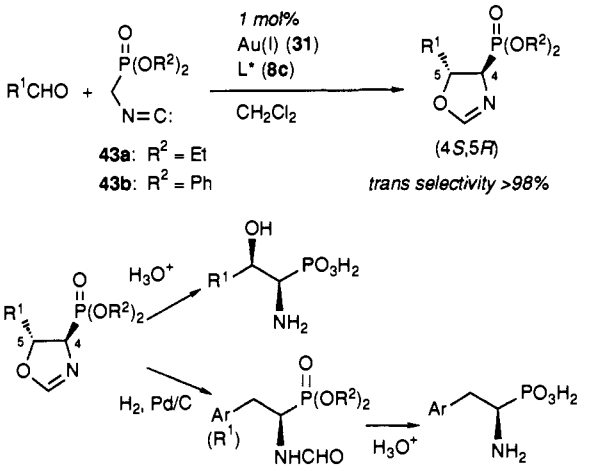


Table 12. Gold-Catalyzed Aldol-Type Condensation of (Isocyanomethyl)phosphonate 43 with Aldehydes (Scheme 21)

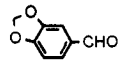
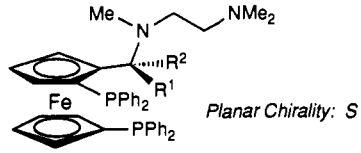
isocyanide, R^2	aldehyde	*T*(°C)	% ee
43a, Et	PhCHO	40	92
43a, Et	*i*-PrCHO	60	88
43b, Ph	PhCHO	25	96
43b, Ph		40	95
43b, *i*-Pr	*i*-PrCHO	40	95

Table 13. Gold-Catalyzed Aldol Reaction of Isocyanoacetate 29a with PhCHO by the Use of Ferrocenyl Ligands (*R*)-(*S*)-8a or (*S*)-(*S*)-8a (Scheme 10)



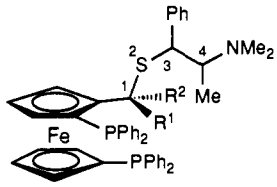
(*R*)-(*S*)-**8a**: R^1 = H, R^2 = Me
(*S*)-(*S*)-**8a**: R^1 = Me, R^2 = H

L*	trans/cis	*trans*-**30** % ee	*cis*-**30** % ee
(*R*)-(*S*)-**8a**	90/10	91 (4*S*,5*R*)	7 (4*S*,5*S*)
(*S*)-(*S*)-**8a**	84/16	41 (4*R*,5*S*)	20 (4*S*,5*S*)

with diphenyl ester **43b** rather than with diethyl ester **43a** (Table 12).

The ferrocenyl ligands **8** possess both central and planar chiralities which are cooperative for the stereoselection (concept of *internal cooperativity of* chirality) as pointed out by Pastor and Togni.[31b,38] Table 13 reveals that not only does the change of the central chirality of the stereogenic carbon atom from *R* to *S* result in both a reduction of trans/cis ratio and enantiomeric excess of the trans isomer but also the opposite *trans*-oxazoline enantiomer is formed in moderate enantiomeric excess. Analysis of the NMR spectral data of (*R*)-(*S*)-**8a** and (*S*)-(*S*)-**8a** suggests that their preferred time-averaged conformations in solution are different from each other. Togni and a co-worker prepared sulfur-containing ferrocenylphosphine ligands **44**, which possess an additional two stereogenic centers on their β-(aminoalkyl)thio side chain (Table 14). Enantioselectivities in the gold-catalyzed aldol reaction with **44** are dramatically changed by varying the configuration of the two stereogenic centers on the side chain.[28b] Long-

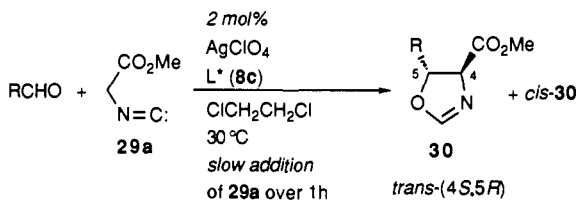
Table 14. Gold-Catalyzed Aldol Reaction of Isocyanoacetate 29a with PhCHO by the Use of Sulfur-Containing Ferrocenylphosphine Ligands 44 (Scheme 10)



44a (3*R*,4*S*)
44b (3*S*,4*R*)
44c (3*S*,4*S*)
44d (3*R*,4*R*)

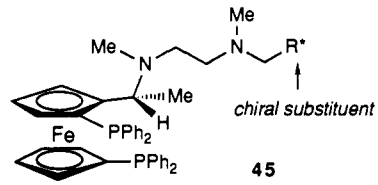
L*	trans/cis	*trans*-30 % ee	*cis*-30 % ee
44a	72/28	13 (4*S*,5*R*)	22 (4*S*,5*S*)
44b	83/17	84 (4*S*,5*R*)	71 (4*R*,5*R*)
44c	88/12	89 (4*S*,5*R*)	12 (4*R*,5*R*)
44d	74/26	17 (4*S*,5*R*)	18 (4*S*,5*S*)

Table 15. Silver-Catalyzed Asymmetric Aldol Reaction of Isocyanoacetate 29a with Aldehydes



aldehyde	trans/cis	% ee of *trans*-30
PhCHO	96/4	80
i-PrCHO	99/1	90
t-BuCHO	>99/1	88
CH_2=CMeCHO	97/3	87

range chiral cooperativity in chiral ferrocenyl ligands as presented by the general structure **45**, which contains both planar chirality and multiple stereogenic carbon atoms, has been further demonstrated.[39]



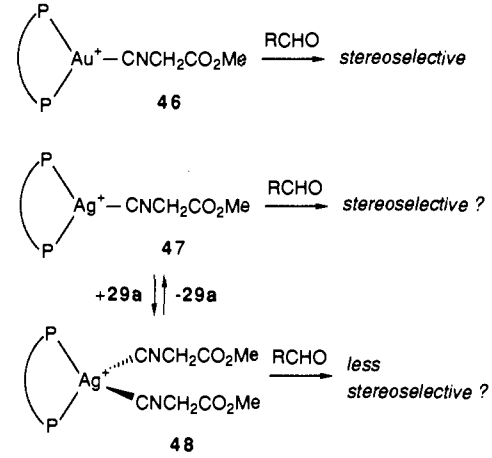
45

B. Silver-Catalyzed Asymmetric Aldol Reaction

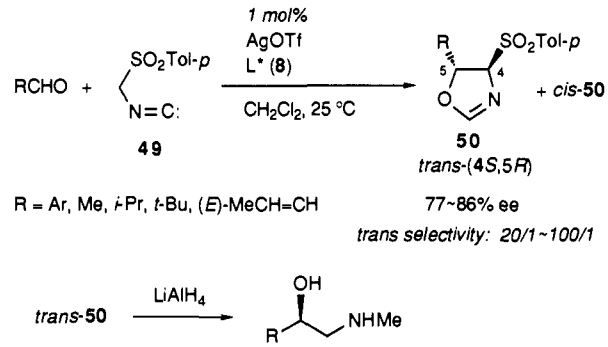
Recently, it has been found that high stereoselectivity in the asymmetric aldol reaction of isocyanoacetate is also obtainable with silver(I) catalyst containing ferrocenyl ligands **8** by controlling isocyanoacetate in low concentration throughout the reaction (Table 15).[40] *trans*-Oxazolines **30** of over 80% ee can be obtained in the silver-catalyzed aldol reaction of several aldehydes by the slow addition of **29a** over a period of 1 h.

IR studies on the structure of gold(I) and silver(I) complexes coordinated with ferrocenyl ligand **8a** in the presence of isocyanoacetate revealed that the most significant difference between those metal catalysts is in the coordination number of the isocyanide to metal (Scheme 17). Thus, the gold complex adopts tricoordinated structure **46** even in the presence of a large excess of isocyanide, while the silver complex is in equilibrium between tricoordinated complex **47** and tetracoordinated complex **48**. In the presence of 20 equiv of **29a**, only **48** was observed.

Scheme 17



Scheme 18



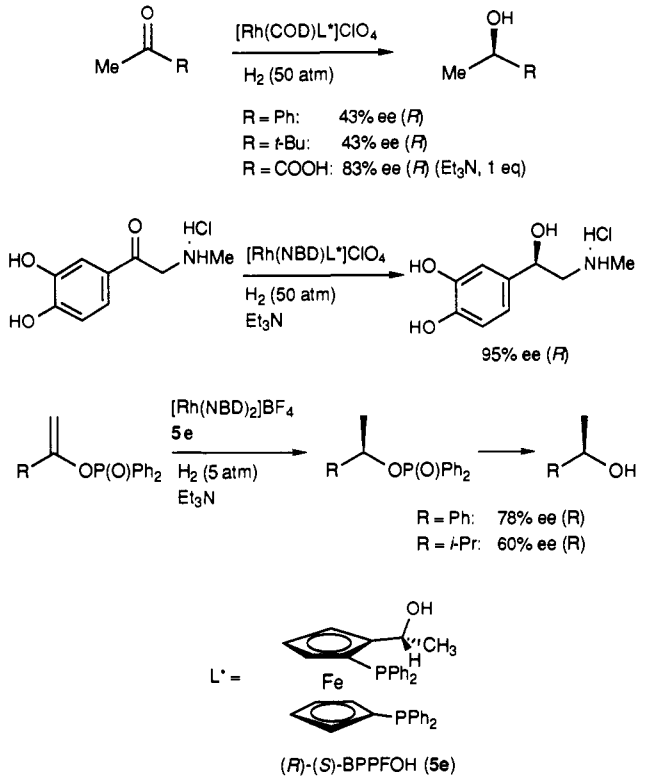
The slow addition method in the silver-catalyzed aldol reaction should keep the isocyanide in a low enough concentration in the reaction system to diminish the unfavorable tetracoordinate species. The high stereoselectivity of the tricoordinated catalyst may result from the presence of one vacant coordination site on the metal which is in the chiral surroundings of the ligand. The aldol reaction of the aldehyde in the chiral coordination site (transition state shown in Figure 9) may be more stereoselective than that of aldehyde without coordination on the metal catalyst. Therefore, a coordinative interaction between aldehyde and gold at the transition state of the gold-catalyzed aldol reaction is also conceivable, although there exists indirect experimental evidence against such an interaction at a ground state.[31b]

Interestingly, aldol-type condensation of tosylmethyl isocyanide (**49**) with aldehyde is catalyzed by the silver catalyst more stereoselectively than by the gold catalyst *under the usual reaction conditions* (Scheme 18).[41] The elucidation of the mechanistic differences between gold and silver catalyst in the asymmetric aldol reaction of **49** needs to be further studied. Oxazoline **50** can be converted to optically active α-alkyl-β-(*N*-methylamino)ethanols.

V. Asymmetric Hydrogenation

Although there has been many reports on highly stereoselective asymmetric hydrogenation of olefins and ketones by the use of chiral phosphine–rhodium or ruthenium catalysts, the unsaturated substrates have been restricted to those containing a functional group at a proper position. For example, enantioselective

Scheme 19

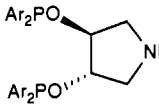


hydrogenation of a simple prochiral ketone is a difficult task. Hayashi, Kumada, et al. have reported that rhodium catalysts containing chiral ferrocenylphosphine ligand **5e** (BPPFOH), which has a hydroxyl group α to ferrocenyl moiety, showed high catalytic activity with good enantioselectivity in the asymmetric hydrogenations of the simple ketones such as acetophenone (43% ee) or pinacolone (43% ee) (Scheme 19).[42] The hydrogenated product of lower enantiomeric excess with reversed configuration was obtained with BPPFA (**5h**), which has a dimethylamino group instead of the hydroxyl group of BPPFOH. The ability of BPPFOH ligand to cause higher asymmetric induction may possibly be ascribed to hydrogen bonding between the carbonyl group on a substrate and the hydroxyl group on BPPFOH. Functionalized ketones such as pyruvic acid and aminomethyl aryl ketone hydrochlorides can be hydrogenated by the Rh–BPPFOH catalyst with higher enantioselectivity than the simple ketones.[43]

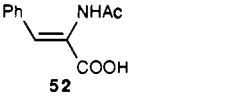
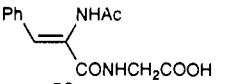
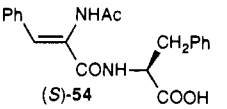
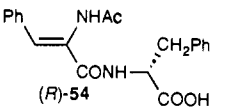
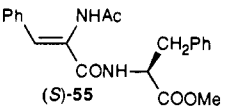
The BPPFOH–Rh complex is also good catalyst for hydrogenation of enol phosphinates to give optically active secondary alcohols with up to 78% ee (Scheme 19).[44] The hydrogenation with (−)-DIOP or BPPM as chiral ligands results in low conversion and formation of ethylbenzene as a byproduct, although the enantioselectivities are comparable. The role of the hydroxyl group on the ligand in this hydrogenation remains to be clarified.

Yamagishi and co-workers have synthesized chiral diphosphinite ligands, which have a pyrrolidine moiety (**51a–e**), some of them (**51b–d**) having a (dimethylamino)alkyl pendant chain, and applied them to the rhodium-catalyzed asymmetric hydrogenation of a dehydroamino acid and dehydrodipeptides (Table 16).[45] Although the diphosphinite ligand with the amino group (**51b,c**) gives lower enantioselectivity in the hydrogenation of achiral Ac-ΔPhe-OH (**52**) and Ac-ΔPhe-Gly-OH (**53**) than the diphosphinite without the amino group (**51a**), the former ligands (**51b,c**) significantly improve the diastereoselectivity in the hydrogenation of some chiral dehydrodipeptides compared with **51a**.

Table 16. Asymmetric Hydrogenation of a Dehydroamino Acid and Dehydrodipeptides Catalyzed by Rhodium(I) Complexes with Diphosphinite Ligand 51[a]



51a: R = $CH_2CH_2CH(CH_3)_2$, R = Ph
51b: R = $CH_2CH_2NMe_2$, R = Ph
51c: R = $CH_2CH_2CH_2NMe_2$, R = Ph
51d: R = $CH_2CH_2NMe_2$, R = Ph-OMe-*p*
51e: R = $CH_2CH_2CH(CH_3)_2$, R = Ph-OMe-*p*

olefinic substrate	ligand	ee or de, %
 **52**	**51a**	29 (*S*)
	51b	16 (*S*)
	51c	13 (*S*)
 **53**	**51a**	48 (*S*)
	51b	34 (*S*)
	51c	16 (*S*)
 (*S*)-**54**	**51a**	58 (*S,S*)
	51b	90 (*S,S*)
	51c	86 (*S,S*)
	51d	>98 (*S,S*)
 (*R*)-**54**	**51d**	86 (*R,R*)
	51e	82 (*R,R*)
 (*S*)-**55**	**51a**	2 (*S,S*)
	51b	no reaction
	51c	low yield
	51d	no reaction
	51e	10 (*S,S*)

[a] Substrate/$[Rh(COD)_2]BF_4$/51 = 50/1/1.5. P_{H_2} = 1 atm. Solvent: EtOH.

For Ac-ΔPhe-(*S*)-Phe-OH [(*S*)-**53**], diphosphinites **51b** and **51c** give (*S,S*)-product with high diastereoselectivity (90% and 86%, respectively), whereas **51a** gives much lower selectivity (58%). Ligand **51d** with 4-methoxyphenyl groups on phosphorus atom gives extremely high selectivity, more than 98% de. On the other hand, ligand **51d** gives (*R,R*)-product in 86% de, in the hydrogenation of Ac-ΔPhe-(*R*)-Phe-OH [(*R*)-**53**], and the selectivity is almost the same as that with ligand **51e**, which is an analogue of **51d** but lacks the terminal amino group. The phosphinite ligands bearing the terminal amino group (**51b–d**) are catalytically inactive in the hydrogenation of methyl ester of (*S*)-**54** [(*S*)-**55**].

As a possible explanation for the stereoselectivity, Yamagishi et al. have proposed that the electrostatic interaction between the terminal amino group in ligand and the carboxyl group in substrate is more effectively operative with (*S*) substrate than with (*R*) substrate and that the steric effect is more important for (*R*) substrate than the electrostatic interaction. Figure 11 shows the proposed mechanism of asymmetric induction in the (*S*) substrates. Thus, coordination of the substrate onto rhodium by the ($C_\alpha si$, $C_\beta re$) face of the double bond is unfavorable because of the steric repulsion between the substituent on the chiral carbon of the substrate and the phenyl group of the ligand (Figure 11a). So the coordination by the ($C_\alpha re$, $C\beta si$) face becomes favorable, resulting in the predominant (*S,S*) product formation (Figure 11b).

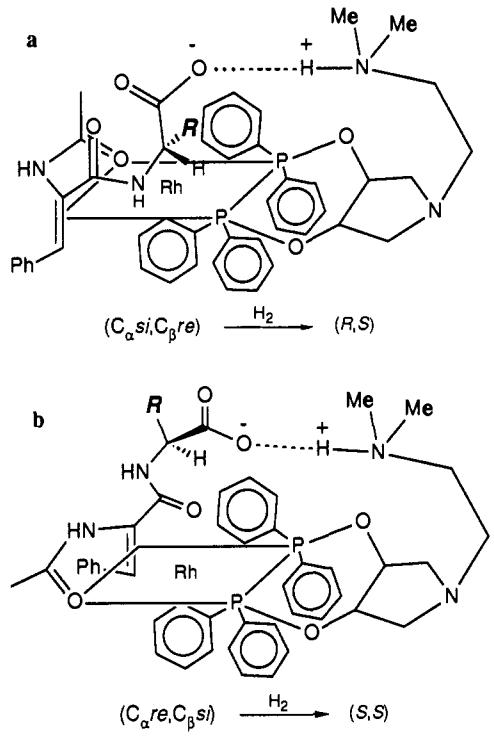
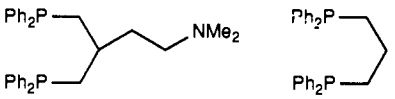


Figure 11. Secondary interactions proposed for the asymmetric hydrogenation of optically active dehydropeptides with a diphosphinite ligand bearing aminoalkyl side chain **51b**.

Table 17. 1,4-Asymmetric Induction in the Hydrogenation of Dehydrodipeptide Catalyzed by Rhodium(I) Complexes with Achiral Phosphine Ligands[a]



56

57

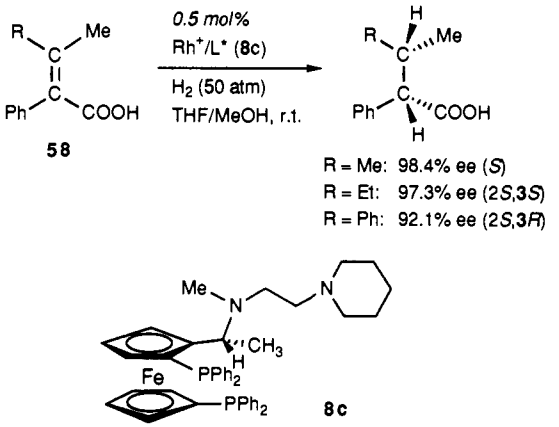
ligand	substrate	de, %	ligand	substrate	de, %
56	(*S*)-**54**	94 (*S*,*S*)	**57**	(*S*)-**55**	68 (*S*,*S*)
56	(*S*)-**55**	47 (*S*,*S*)	**57** + Et_3N[b]	(*S*)-**54**	66 (*S*,*S*)
56·HCl	(*S*)-**54**	63 (*S*,*S*)	**57** + Et_3N	(*S*)-**54**	64 (*S*,*S*)
57	(*S*)-**54**	34 (*S*,*S*)			

[a] Substrate/$[Rh(COD)_2]BF_4$/ligand = 50/1/1.1. Solvent: MeOH. [b] Et_3N/Rh = 10/1.

Achiral diphosphine ligand **56** bearing a (dimethylamino)ethyl pendant can induce (*S*,*S*) or (*R*,*R*) selectivity comparable to that of the chiral phosphinite ligand **51b–d** in the hydrogenation of **54**.[46] The important role of the dimethylamino group in **56** has been well documented in the hydrogenation of (*S*)-**54** by comparing **56** with 1,3-bis(diphenylphosphino)propane (**57**) (Table 17). Entry 2 shows that the free carboxyl group in the substrate is indispensable for high stereoselectivity. Conversion of the amino group in **56** to an ammonium group, or use of diphosphine **57** without an amino group, lower the diastereoselectivity (entries 3 and 4). Although the addition of a catalytic amount of triethylamine to the Rh–**57** system raised the selectivity, the diastereoselectivity can not reach the level observed with **56** (entry 7). The addition of triethylamine to the Rh–**56** system lowers the selectivity (entry 6).

This 1,4-asymmetric induction methodology by the use of achiral aminoalkylated phosphine **56** has been applied to the diastereoselective synthesis of dipeptides with a polycondensed aromatic ring.[47]

Scheme 20

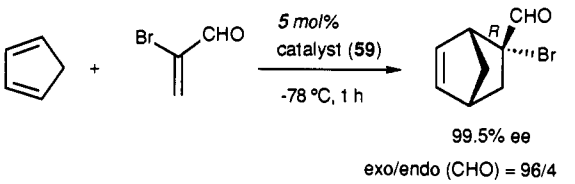


58

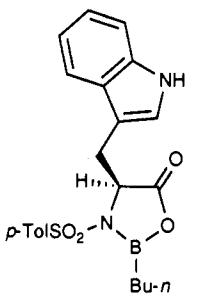
R = Me: 98.4% ee (*S*)
R = Et: 97.3% ee (2*S*,3*S*)
R = Ph: 92.1% ee (2*S*,3*R*)

8c

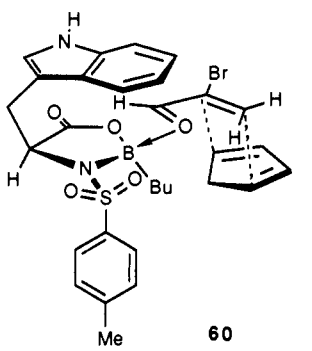
Scheme 21



99.5% ee
exo/endo (CHO) = 96/4



59



60

Hayashi, Ito, and a co-worker have applied [(aminoalkyl)ferrocenyl]phosphine ligands **8**, which have been employed successfully in the gold-catalyzed asymmetric aldol reaction, to the rhodium-catalyzed asymmetric hydrogenation of fully substituted acrylic acids **58** (Scheme 20).[48] The rhodium complexes with chiraphos, pyrphos, and ferrocenylphosphines without the aminoalkyl pendant, such as BPPFA (**5h**), are catalytically much less active for the hydrogenation, acrylic acids **58**, giving low enantiomeric excess (<25% ee) with low conversion even at higher reaction temperature. It has been proposed that the terminal amino group on ligand **8** forms an ammonium carboxylate with the olefinic substrate and consequently attracts the substrate to the coordination sphere of the catalyst to promote the hydrogenation. The attractive interaction is also expected to permit the selective enantioface differentiation of the olefin.

VI. Lewis Acid-Catalyzed Asymmetric Diels–Alder Reaction

Corey and a co-worker reported a highly enantioselective Diels–Alder reaction promoted by (*S*)-tryptophan-derived oxazaborolidine catalyst **59** (Scheme 21).[49] It has been proposed that an attractive donor–acceptor π–π interaction favors coordination of the dienophile at the coordination site of boron which is cis to the 3-indolylmethyl substituent (transition-state model **60**). The existence of the π–π interaction is

Scheme 22

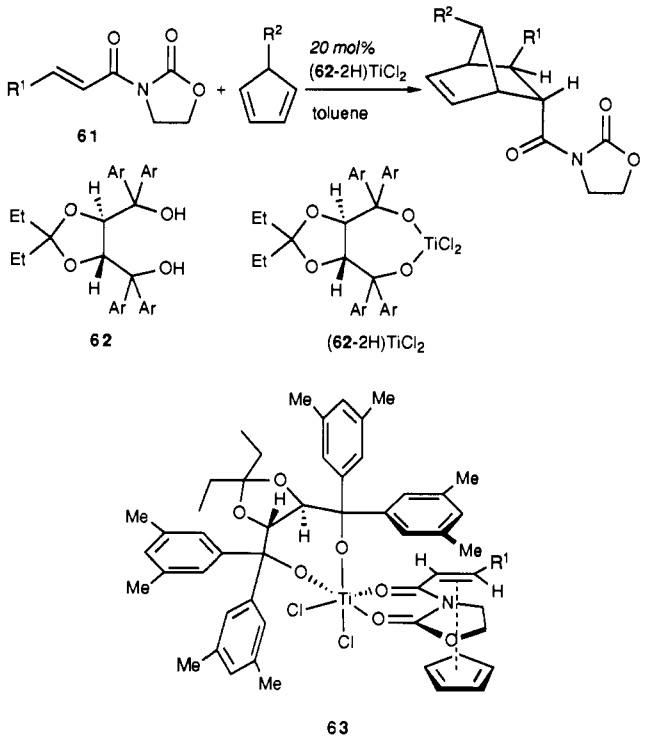


Table 18. Effect of Aromatic Substituent of Chiral Diol Ligands 62 on the Asymmetric Diels–Alder Reaction of 61, R^1 = H, with Cyclopentadiene (Scheme 22)

62, Ar	endo/exo	% ee (endo)
62a, Ph	93/7	73
62b, β-Naphth	93/7	68
62c, 6-MeO-β-Naphth	90/10	82
62d, 3,5-Me_2Ph	95/5	94
62e, 3,5-$(CF_3)_2$Ph	92/8	68
62f, 3,5-Cl_2Ph	93/7	44

suggested from the result that the Diels–Alder reaction under catalysis of the oxazaborolidines corresponding to **59** from *N*-tosyl derivatives of (*S*)-valine or (*S*)-hexahydrophenylalanine gave the opposite enantiomer of the Diels–Alder product with ca. 70% enantiomeric excess.

Corey has proposed that the π–π interaction is also important in the titanium(IV)-catalyzed asymmetric Diels–Alder reaction of α,β-unsaturated *N*-acyloxazolidinones (**61**),[50] which has originally been reported by Narasaka et al[51] (Scheme 22). Various chiral diol ligands bearing aromatic substituents with varying π-basisities, **62**, were synthesized and compared with each other in the Diels–Alder reaction of *N*-acryloyloxazolidinone with cyclopentadiene. The results summarized in Table 18 suggest that π-basisity of the aromatic substituent favors enantioselectivity. The chiral ligand with 3,5-dimethylphenyl substituents (**62d**) is the best ligand. A beneficial effect of meta substituents on the aromatic ring was explained to be steric effect. The high enantioselectivity and the absolute stereocourse of the reaction with chiral ligand **62d** was explained with the transition-state model represented by structure **63**.

VII. Conclusion

This review article has emphasized the importance of the design of chiral ligands in enantioselective catalytic asymmetric reactions, highlighting the secondary ligand–substrate interaction, which uses coordinative, hydrogen bonding, electrostatic, or π–π stacking interactions. It is conceivable that a properly functionalized chiral ligand makes higher enantioselective reactions possible through the highly well-organized transition state rather than the conventional chiral ligands. Most of the functionalized chiral ligands developed so far have been phosphine ligands, whose complexes with late transition metals are utilized for asymmetric synthesis. Other chiral ligands such as cyclopentadienyl ligands, amino ligands, alkoxo ligands, etc. might be potentially useful chiral ligands in asymmetric synthesis with the proper modification in the future.

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