trichothecenes with respect to *Baccharis*? What are the details of the biosynthetic conversions of trichoverrins to roridins and verrucarins, and could this knowledge help us devise synthetically useful pathways in constructing macrocyclic trichothecenes from the simple trichothecenes? What are the details, at the molecular level, for biological activity of the trichothecenes, and could this information be useful in devising new anticancer derivatives? These are but a few of the questions that we hope to address in future research.

We are grateful to our collaborators, whose names appear in the references cited. B.B.J. also acknowledges support from the National Cancer Institute, Grant CA 25967.

Asymmetric Synthesis Catalyzed by Transition-Metal Complexes with Functionalized Chiral Ferrocenylphosphine Ligands

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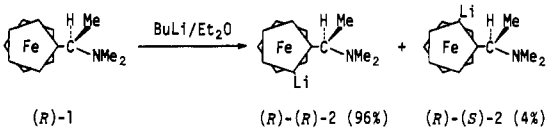
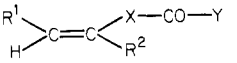
Among various types of asymmetric reactions, reaction with a chiral catalyst is obviously the best choice since catalytic asymmetric reactions can proceed with high stereoselectivity, producing the desired enantiomeric isomer in high yield.[1] Catalytic asymmetric synthesis requires ideally only one molecule of a chiral catalyst in order to produce a large quantity of an optically active substance. Catalytic reactions by homogeneous transition-metal complexes have been rapidly developed recently, and now a wide variety of reactins can be effected by transition-metal catalysts. Since many of the transition-metal complexes used for catalytic reactions have tertiary phosphines as ligands, it is convenient to use optically active phosphine ligands to make the metal complexes function as chiral catalysts. Thus, the most significant point for obtaining high stereoselectivity in catalytic asymmetric reactions is the design and preparation of a ligand that will fit in with a given reaction as efficiently in stereoselectivity as possible.

In 1968, the first asymmetric reaction by homogeneous transition-metal catalysts was reported by Knowles and Horner and their co-workers.[2] They used methylphenylpropylphosphine as a chiral ligand with a rhodium catalyst and got 4–15% optical yields in asymmetric hydrogenation of prochiral olefins. Since that time, over 100 various kinds of ligands have been developed in order to obtain higher optical yield, mostly

Scheme I



in rhodium-catalyzed asymmetric hydrogenations, and some of the phosphine ligands have been found very effective for the hydrogenation of α-(acylamino)acrylic acids, producing α-amino acids of over 90% ee.[1e,g] Recently, it has been shown that the high stereoselectivity attained is due to a characteristic structure of the olefinic substrates as well as chiral phosphine ligands. α-(Acylamino)acrylic acids and analogous functionalized olefins that can be hydrogenated with high stereoselectivity have the structural features shown below,



X = NH, O, CH_2
Y = R, OR

containing the carbonyl oxygen three atoms away from the carbon–carbon double bond, and the carbonyl group can coordinate with the rhodium, forming a chelate in the diastereomeric transition states.[1,3] Thus, attractive

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(1) For reviews: (a) Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1978**, *10*, 175–285. (b) Scott, J. W.; Valentine, Jr., D. *Science (Washington, D.C)* **1974**, *184*, 943. (c) Valentine, Jr., D.; Scott, J. W. *Synthesis* **1978**, 329. (d) Pearce, R. *Catalysis* **1978**, *2*, 176. (e) Caplar, V.; Comisso, G.; Sunjic, V. *Synthesis* **1981**, 85. (f) Bosnich, B.; Fryzuk, M. D. *Top. Stereochem.* **1981**, *12*, 119–154. (g) Merrill, R. E. "Asymmetric Synthesis Using Chiral Phosphine Ligands"; Design Corporation, Inc.: Hillside, NJ, 1979.

(2) (a) Knowles, W. S.; Sabacky, M. J. *Chem. Commun.* **1968**, 1445. (b) Horner, L.; Siegel, H.; Buthe, H. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 942.

(3) (a) Brown, J. M.; Chaloner, P. A. *J. Chem. Soc., Chem. Commun.* **1980**, 344 and their previous papers cited therein. (b) Chan, A. S. C.; Pluth, J. J.; Halpern, J. *J. Am. Chem. Soc.* **1980**, *102*, 5952 and their previous papers cited therein.

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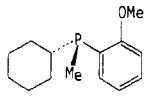
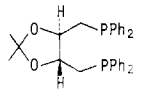
interactions (in hydrogenation, rhodium–carbonyl coordination) can enhance stereoselectivity by making the diastereomeric transition states rigid. We expected that introduction of functional groups onto the chiral phosphine ligands might affect stereoselectivity favorably by attractive interactions between the functional groups on a substrate and on the chiral ligand coordinated to a transition-metal catalyst.

When we started to prepare new chiral phosphine ligands in 1974, there had been only a few chiral phosphines reported, some of them containing the chiral center at the phosphorus atom and others chiral carbons in groups bonded to phosphorus. Representatives are Knowles' CAMP[4] and Kagan's DIOP,[5] both of



(*R*)-CAMP



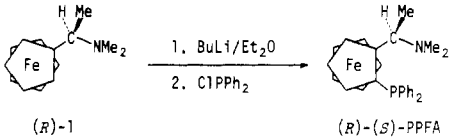
(-)-DIOP

which had been found effective for rhodium-catalyzed asymmetric hydrogenation. At that time, the correlations between the structural features of chiral ligands and the extent of asymmetric induction were not well understood, and the choice of a chiral phosphine ligand for a given reaction seemed to be quite empirical. We planned to design and synthesize new phosphine ligands that fulfill the following necessary conditions: (1) a highly efficient chiral structure to bring about high stereoselectivity; (2) a functional group that can be substituted by other appropriate groups as occasion demands; (3) easy preparation in large quantities. We chose, as a chiral source, planar chirality due to 1,2-unsymmetrically substituted ferrocene structures. One of the important factors that drove us to phosphines with ferrocene planar chirality was Ugi's paper published in 1970,[6] where he reported that optical resolution of (1-ferrocenylethyl)dimethylamine (1) was particularly easy, both antipodes were obtained in high yield, and lithiation of the amine 1 proceeded with high stereoselectivity as shown in Scheme I.

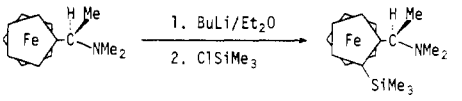
By use of the stereoselective lithiation of **1**, various kinds of chiral ferrocenylphosphines could be prepared. The ferrocenylphosphines are a new type of chiral phosphine ligands and have several advantages over other chiral phosphine ligands (vide infra). In this Account, we describe the asymmetric reactions by chiral ferrocenylphosphine-transition-metal catalysts, focusing attention upon the role played by functional groups on the phosphine ligands.

Chiral Ferrocenylphosphines

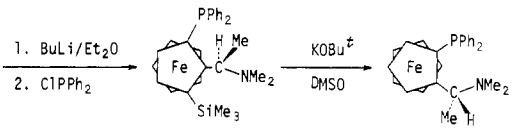
(*R*)-*N*,*N*-Dimethyl-1-[(*S*)-2-(diphenylphosphino)-ferrocenyl]ethylamine[7,8] [(*R*)-(*S*)-PPFA] was obtained in 55% isolated yield by diphenylphosphination of the lithiated ferrocene **2**, generated by the reaction of (*R*)-**1** with butyllithium according to Ugi's procedure (eq 1).



(*R*)-**1** (*R*)-(*S*)-PPFA (1)



(*R*)-**1** (*R*)-(*S*)-**3**

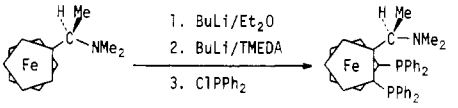


(2)

(*R*)-(*R*)-PPFA

The absolute configuration of the PPFA has been confirmed by an X-ray crystallographic study.[9] A small amount of diastereomeric byproduct (*R*)-(*R*)-PPFA, formed via (*R*)-(*S*)-**2**, was removed by simple recrystallization. When the isomer (*R*)-(*R*)-PPFA is required, it can be prepared in quantity via silylated ferrocene (*R*)-(*S*)-**3** (eq 2), the trimethylsilyl group protecting the ring hydrogen liable to the stereoselective lithiation.

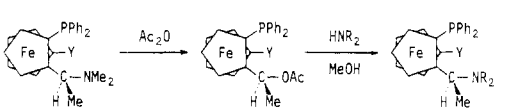
The stepwise lithiation of (*R*)-**1** with butyllithium in ether and then with butyllithium in TMEDA followed by treatment with chlorodiphenylphosphine led to the introduction of two diphenylphosphino groups, one onto each of the cyclopentadienyl rings, to give (*R*)-(*S*)-BPPFA in 58% yield[7] (eq 3). The bisphosphine



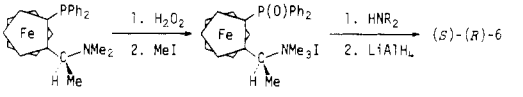
(*R*)-**1** (*R*)-(*S*)-BPPFA (3)

BPPFA will coordinate with a transition metal through two diphenylphosphino groups while the monophosphine PPFA will coordinate as a monodentate ligand or may possibly be a new type of chiral ligand coordinating through both the phosphorus and nitrogen atoms.

The dimethylamino group in PPFA or BPPFA was found to be substituted by other amino groups via the acetate **4** or **5**, respectively[7] (eq 4). The substitution



Y = H: (*S*)-(*R*)-PPFA Y = H: **4** Y = H: **6**
Y = PPh2: (*S*)-(*R*)-BPPFA Y = PPh2: **5** Y = PPh2: **7** (4)



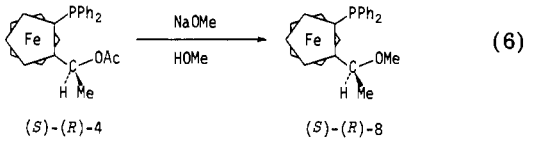
(*S*)-(*R*)-PPFA (*S*)-(*R*)-**6** (5)

reactions proceeded with complete retention of configuration, as have been usually observed in nucleophilic substitution at the α position of ferrocenylethane de-

(4) Knowles, W. S.; Sabacky, M. J.; Vineyard, B. D. *J. Chem. Soc., Chem. Commun.* **1972**, 10.
(5) (a) Dang, T. P.; Kagan, H. B. *J. Chem. Soc., Chem. Commun.* **1971**, 481. (b) Kagan, H. B.; Dang, T. P. *J. Am. Chem. Soc.* **1972**, *94*, 6429.
(6) Marquarding, D.; Klusacek, H.; Gokel, G.; Hoffmann, P.; Ugi, I. *J. Am. Chem. Soc.* **1970**, *92*, 5389.
(7) Hayashi, T.; Mise, T.; Fukushima, M.; Kagotani, M.; Nagashima, N.; Hamada, Y.; Matsumoto, A.; Kawakami, S.; Konishi, M.; Yamamoto, K.; Kumada, M. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1138.
(8) Cullen, W. R.; Einstein, F. W. B.; Huang, C.-H.; Willis, A. C.; Yeh, E.-S. *J. Am. Chem. Soc.* **1980**, *102*, 988.
(9) Einstein, F. W. B.; Willis, A. C. *Acta Crystallogr., Sect. B* **1980**, *B36*, 39.

rivatives. The conversion of the dimethylamino group into other amino groups was also effected by way of the trimethylammonium salt, though it was less convenient because the diphenylphosphino group had to be protected against quaternization (eq 5).

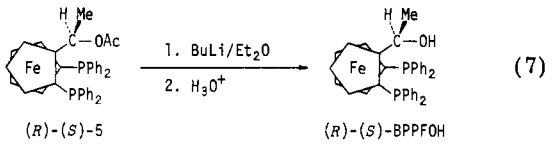
A methoxyl group could also be introduced into the side chain by treating the acetate **4** with sodium methoxide in refluxing methanol[7] (eq 6).



(6)

(*S*)-(*R*)-4 (*S*)-(*R*)-8

A ferrocenylphosphine with a hydroxyl group, (*R*)-1-[(*S*)-1′,2-bis(diphenylphosphino)ferrocenyl]ethanol (BPPFOH), was obtained in quantitative yield by treatment of **5** with an excess of butyllithium in ether followed by hydrolysis[7] (eq 7). Direct acid or base

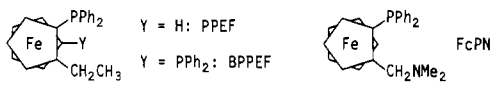


(7)

(*R*)-(*S*)-5 (*R*)-(*S*)-BPPFOH

hydrolysis of the acetate **5** in the usual way gave lower yields.

The ferrocenylphosphines mentioned above all contain both planar and central elements of chirality and also a functional group such as amino, methoxyl, or hydroxyl. We also prepared such ferrocenylphosphines as 1-diphenylphosphino-2-ethylferrocene (PPEF) and its diphosphine analogue BPPEF, starting with PPFA

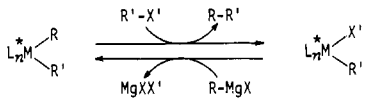


and BPPFA, respectively.[7] Those ligands have only a planar element of chirality, bearing no functional group on the carbon side chain. In addition, optically active 1-((dimethylamino)methyl)-2-(diphenylphosphino)-ferrocene (FcPN),[7,10] which is analogous to PPFA but lacks the carbon central chirality, was prepared by optical resolution of its phosphine sulfide dibenzoyltartaric acid salt.

In summary, the ferrocenylphosphines have the following unique and significant features: (1) Various kinds of functional groups such as amino, alkoxyl, or hydroxyl can be introduced into the side chain. (2) They all contain a planar element of chirality that does not racemize or epimerize under usual reaction conditions. (3) Phosphines having either of the two configurations of the carbon central chirality on the side chain of ferrocene and also those lacking this central chirality can be prepared; examples are (*S*)-(*R*)-PPFA, (*R*)-(*R*)-PPFA, and (*R*)-FcPN. (4) Both mono- and bisphosphines can be prepared from the same chiral source, simply by changing the lithiation procedure. (5) They can be isolated and purified very readily because of their stability in air, their good crystallizability, and orange color, making chromatographic separation easy. (6) They are triarylphosphines, which are often more favorable ligands for transition metal catalyzed reactions than alkylphosphines. A disadvantage of the ferrocenylphosphines is that their preparation requires optical resolution of the starting racemic 1-ferrocenylethyldimethylamine (**1**), whereas some of other chiral phosphine ligands have been derived from optically active natural products.

(10) Sokolov, V. I.; Troitskaya, L. L.; Reutov, O. A. *J. Organomet. Chem.* **1980**, *202*, C58.

Scheme II



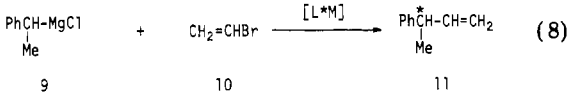
Grignard Cross-Coupling

First, we describe the asymmetric cross-coupling of secondary alkyl Grignard reagents with organic halides catalyzed by nickel or palladium complexes, where the functional groups on the phosphine ligands exert a remarkable influence on the stereoselectivity.

The Grignard cross-coupling is a useful carbon–carbon bond forming reaction found by Corriu and by us in 1972, and the catalytic cycle is proposed to consist of a sequence of steps involving a diorganometal complex as a key intermediate (Scheme II).[11] Use of an optically active ligand L* for the reaction of a racemic Grignard reagent must bring about kinetic resolution of the Grignard reagent to form an optically active cross-coupling product.

The first reports on the asymmetric Grignard cross-coupling appeared in 1973–1974, where DIOP was used as a chiral ligand of the nickel catalyst and 7–16% ee of the products were obtained in the reaction of (1-phenylethyl)magnesium chloride or 2-butylmagnesium chloride with bromobenzene or vinyl chloride.[12]

We have examined various types of chiral ferrocenylphosphine ligands for the nickel- or palladium-catalyzed reaction of (1-phenylethyl)magnesium chloride (**9**) with vinyl bromide (**10**) (eq 8).[13] The reaction gave



(8)

9 10 11

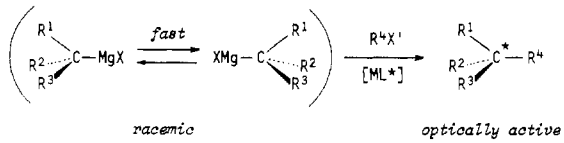
the coupling product **11** quantitatively, in most cases, at 0 °C in 24 h in the presence of 0.5 mol % of catalyst, a preformed phosphine–palladium complex, or an in situ nickel catalyst prepared from nickel chloride and a phosphine ligand. The optical purity of the coupling product **11** turned out not to be affected appreciably by the degree of conversion of the Grignard reagent **9**, indicating that the inversion of the Grignard reagent is relatively fast compared with the coupling reaction. Although the present asymmetric reaction may be

(11) (a) For a pertinent review, see: Tamao, K.; Kumada, M. In "Organometallic Reactions and Syntheses"; Becker, E. I., Tsutsui, M., Eds.; Plenum: New York, in press. (b) Tamao, K.; Sumitani, K.; Kiso, Y.; Zembayashi, M.; Fujioka, A.; Kodama, S.; Nakajima, I.; Minato, A.; Kumada, M. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 1958 and references cited therein. (c) Morrell, D. G.; Kochi, J. K. *J. Am. Chem. Soc.* **1975**, *97*, 7262. (d) Corriu, R. J. P.; Massé, J. P. *J. Chem. Soc., Chem. Commun.* **1972**, 144. (e) Hayashi, T.; Konishi, M.; Kumada, M. *Tetrahedron Lett.* **1979**, 1871 and references cited therein.

(12) (a) Consiglio, G.; Botteghi, C. *Helv. Chim. Acta* **1973**, *56*, 460. (b) Kiso, Y.; Tamao, K.; Miyake, N.; Yamamoto, K.; Kumada, M. *Tetrahedron Lett.* **1974**, 3.

(13) (a) Hayashi, T.; Tajika, M.; Tamao, K.; Kumada, M. *J. Am. Chem. Soc.* **1976**, *98*, 3718. (b) Hayashi, T.; Konishi, M.; Fukushima, M.; Mise, T.; Kagotani, M.; Tajika, M.; Kumada, M. *J. Am. Chem. Soc.* **1982**, *104*, 180.

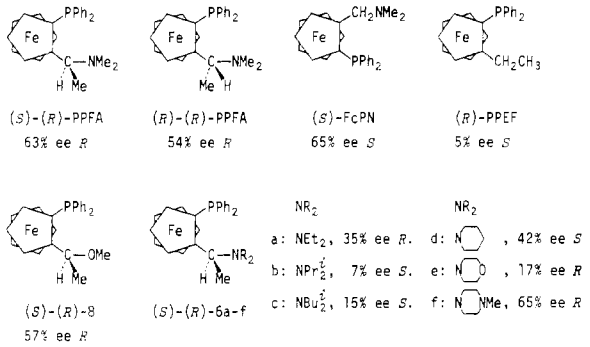
Scheme III



racemic *optically active*

classified as kinetic resolution of the racemic reagent, the present reaction can produce optically active product even if all the Grignard reagent is consumed (Scheme III).

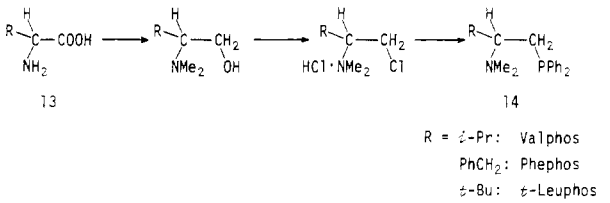
Some of the results obtained for the asymmetric Grignard cross-coupling are summarized below, the enantiomeric purity and configuration of the product **11** being shown beside the phosphine ligand employed.



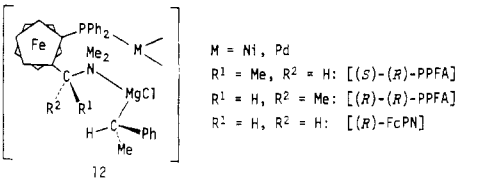
These data contain several significant features: (1) The stereoselectivity obtained here (~65% ee) with PPFA, FcPN, and one of the ligands, **6**, is much higher than that reported before. (2) On comparison of the data obtained with (*S*)-(*R*)-PPFA, (*R*)-(*R*)-PPFA, and (*S*)-FcPN, it turns out that the ferrocene planar chirality plays an important role rather than the carbon central chirality on the side chain of the ferrocene. Both FcPN, which is analogous to PPFA but has planar chirality only, and (*R*)-(*R*)-PPFA, which has *R* configuration of carbon central chirality as opposed to its epimer (*S*)-(*R*)-PPFA having *S* configuration, exhibit a comparable efficiency to the (*S*)-(*R*)-PPFA ligand. (3) A dramatic decrease in asymmetric induction is observed with (*R*)-PPEF as a ligand, indicating that the presence of an amino group is of primary importance for the high stereoselectivity. The methoxyl group in the phosphine (*S*)-(*R*)-**8**, which gave the product **11** of high enantiomeric purity (57%), has nearly the same efficiency as the dimethylamino group. (4) The steric bulkiness of the amino substituent has a powerful effect on the stereoselection. Thus, the ferrocenylphosphines with dimethylamino (PPFA) and diethylamino (**6a**) afforded the *R* product **11**, while the use of phosphines with diisopropylamino (**6b**), diisobutylamino (**6c**), and piperidino (**6d**) resulted in the formation of (*S*)-**11**. Morpholino and *N*-methylpiperazino groups are considered to have almost the same steric bulkiness as the piperidino group, but the phosphines **6d**, **6e**, and **6f** gave very different stereochemical results.

According to the mechanism proposed for the Grignard cross-coupling,[11] it is most probable that the optical purity and configuration of the coupling product are mainly determined by transmetallation of alkyl group from the Grignard reagent to the transition-metal catalyst. When the Grignard reagent **9** approaches the catalyst, the amino group in the ferrocenylphosphine ligand may coordinate with the magnesium atom in the

Scheme IV



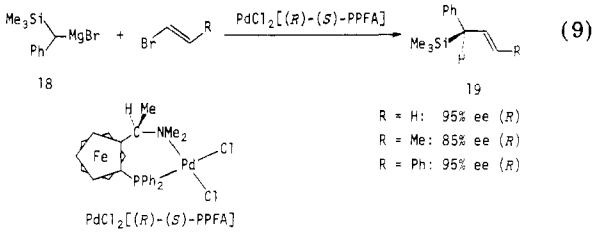
Grignard reagent to form the diastereomeric transition state (or intermediate), as exemplified by **12**. The



coordination is considered to occur selectively with one of the enantiomers of the racemic Grignard reagent and allow it to readily undergo subsequent transmetallation. Stereoselection by this coordination must be much more effective than that by simple steric repulsion, since the coordination brings about enhanced steric interactions.

On the basis of the data that the amino group on the phosphine ligand is the first requisite for high stereoselectivity and that the surroundings around the nitrogen atom exert a strong effect on the stereoselectivity, a new type of phosphine ligands was designed for asymmetric Grignard cross-coupling. They are (β-(dimethylamino)alkyl)phosphines (**14**) derived from amino acids (**13**) (Scheme IV).[14] The phosphine ligands were indeed effective for the cross-coupling. The coupling product **11** with 81% ee (*S*), 71% ee (*S*), and 94% ee (*R*) was obtained in the reaction of eq 8 with ligand, (*S*)-Valphos, (*S*)-Phephos, and (*R*)-*t*-Leuphos, respectively, and the presence of the dimethylamino group on the ligands was observed to be responsible for the high optical yields again.

(*S*)-Valphos was used for the reaction of (1-arylethyl)magnesium chlorides **15** with vinyl bromide to give the olefins **16** with over 80% ee; these were converted into optically active 2-arylpropionic acids **17** (antiinflammatory drugs) by oxidative cleavage of the olefinic bond (eq 9).[15]

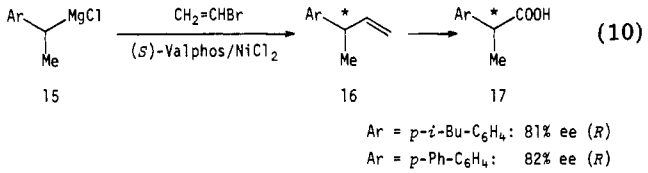


(9)

To return to the ferrocenylphosphine ligands: PPFA was found also effective for the asymmetric cross-coupling of α-(trimethylsilyl)benzyl Grignard reagent **18** forming optically active allylsilanes **19** of about 90% ee (eq 10).[16] Allylsilanes are useful intermediates in or-

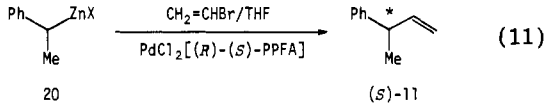
(14) (a) Hayashi, T.; Fukushima, M.; Konishi, M.; Kumada, M. *Tetrahedron Lett.* **1980**, *21*, 79. (b) Hayashi, T.; Nagashima, N.; Kumada, M. *Tetrahedron Lett.* **1980**, *21*, 4623. (c) Hayashi, T.; Kanehira, K.; Hioki, T.; Kumada, M. *Tetrahedron Lett.* **1981**, *22*, 137.

(15) Hayashi, T.; Konishi, M.; Kumada, M., unpublished results.

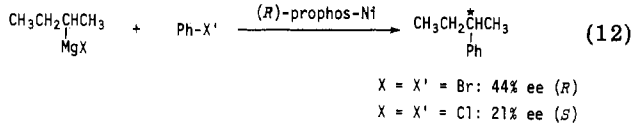


ganic synthesis, reacting with a wide range of electrophiles in a regiospecific manner.[17] Use of the optically active allylsilanes **19** for the S_E' reactions produced various kinds of optically active compounds by an asymmetric induction and provided significant information regarding the mechanism of the S_E' reaction.[16]

Reactions of organozinc reagent **20** catalyzed by the PPFA–Pd complex gave the coupling product **11** with higher optical purity (~85% ee) than that of the Grignard reagent (eq 11).[18]



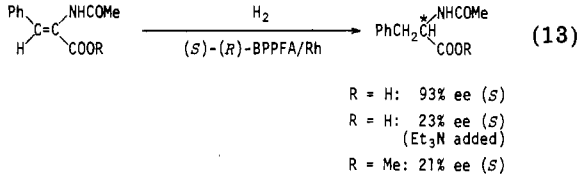
Dichloro[(*R*)-1,2-bis(diphenylphosphino)propane]-nickel(II) [(*R*)-prophos-Ni] has been reported to be an effective catalyst for the reaction of *sec*-butyl Grignard reagents with phenyl halides, where the optical purity and configuration of the product, 2-phenylbutane, were dependent on the halogen atoms (Cl, Br, I) in both the Grignard reagents and the halides (eq 12).[19]



Hydrogenation

Extensive studies on asymmetric hydrogenation of olefins have been made by use of chiral phosphine–rhodium complexes as catalysts, and optical yields of over 90% have often been achieved in the hydrogenation of α-(acylamino)acrylic acids, producing acylamino acids.[1,20]

Among the ferrocenylphosphine ligands, (*S*)-(*R*)-BPPFA, which is a bisphosphine with the dimethylamino group, was found most effective for rhodium-catalyzed asymmetric hydrogenation.[21] A high optical yield (93%) was obtained in the hydrogenation of (*Z*)-α-acetaminocinnamic acid, but relatively low optical yields were observed in the reaction of its ammonium salt or methyl ester (eq 13).



These data may indicate that attractive interactions forming an ammonium carboxylate between the amino group in (*S*)-(*R*)-BPPFA and the carboxyl group in the olefinic substrate control the stereoselectivity. Thus, the BPPFA ligand might be different from other chiral phosphine ligands in a way of stereocontrol, the latter controlling stereoselectivity mainly by steric repulsion between phenyl groups on phosphorus atom(s) and the olefinic substrate forming the chelate with the rhodium.

Cullen and co-workers have reported[8] that asymmetric hydrogenation was effectively catalyzed by the PPFA–rhodium complex, where the PPFA was coordinated with the rhodium through both phosphorus and nitrogen atoms. The PPFA–rhodium catalyst produced acylamino acids with different configuration than did the BPPFA–rhodium catalyst. Thus, (*S*)-(*R*)-PPFA led to (*R*)-acylamino acids while (*S*)-(*R*)-BPPFA led to *S* isomers.

While the rhodium-catalyzed asymmetric hydrogenation of olefins has resulted in great success, little has been achieved in the reaction of prochiral carbonyl compounds due either to low catalytic activity or to low stereoselectivity of a homogeneous rhodium catalyst. Attempted hydrogenation of acetophenone by use of cationic rhodium complexes with (*R*)-($PhCH_2$)MePhP, (*R*)-EtMePhP, and (–)-DIOP showed less than 10% stereoselectivity.[22] Recently Marko and co-workers have found that the neutral rhodium complex with DIOP in benzene solution brings about high optical yield (80%) for the reaction of acetophenone though the catalytic activity does not seem high.[23] Activated carbonyl compounds such as α-diketones or α-keto esters, in contrast to simple ketones such as acetophenone, have often been reported to undergo the asymmetric hydrogenation with high stereoselectivity.[24]

We have found that a chiral ferrocenylphosphine with a hydroxyl group (BPPFOH) is a very effective ligand for the rhodium-catalyzed asymmetric hydrogenation of several carbonyl compounds.[25] A rhodium catalyst, either a cationic complex [Rh(1,5-cyclooctadiene)-{(*R*)-(*S*)-BPPFOH}]$^+ClO_4^-$ or an in situ catalyst formed from [Rh(1,5-hexadiene)Cl]$_2$ and BPPFOH, catalyzed the hydrogenation of acetophenone (**21a**), pinacolone (**21b**), and pyruvic acid (**21c**) rapidly and quantitatively in methanol (2% H_2O) solvent at 0–30 °C and 50-atm initial hydrogen pressure to give the corresponding secondary alcohols **22** with *R* configuration of 43%, 43%, and 83% ee, respectively (eq 14).

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(23) Toros, S.; Heil, B.; Kollar, L.; Marko, L. *J. Organomet. Chem.* **1980**, *197*, 85.
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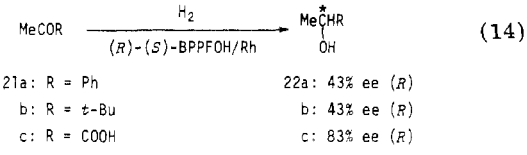
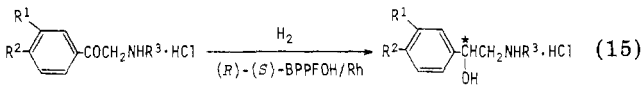


(14)

21a: R = Ph — 22a: 43% ee (*R*)
b: R = *t*-Bu — b: 43% ee (*R*)
c: R = COOH — c: 83% ee (*R*)

The ability of BPPFOH ligand to cause high asymmetric induction can probably be ascribed to hydrogen bonding possible between the carbonyl group on a substrate and the hydroxyl group on the BPPFOH ligand, which may activate the carbonyl group toward hydrogenation and increase conformational rigidity in the diastereomeric transition states or intermediates. The hydrogenated products **22** with much lower optical purity and reversed configuration *S* were obtained with (*R*)-(*S*)-BPPFA and (*S*)-BPPEF, which are both analogous to (*R*)-(*S*)-BPPFOH but lack the hydroxyl group. This fact may well support the above-mentioned participation of the hydroxyl group in the asymmetric hydrogenation of carbonyl compounds.

The rhodium complex with the BPPFOH ligand was also found effective for hydrogenation of aminomethyl aryl ketone hydrochlorides **23** (eq 15).[26] Optically ac-

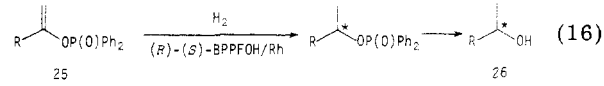


(15)

23a: $R^1 = R^2 = OH$, $R^3 = Me$ — 24a: 95% ee (*R*)
b: $R^1 = R^2 = OH$, $R^3 = i$-Pr — b: 77% ee (*R*)
c: $R^1 = H$, $R^2 = OH$, $R^3 = H$ — c: 69% ee (*R*)
d: $R^1 = R^2 = OMe$, $R^3 = H$ — d: 92% ee (*R*)

tive 2-amino-1-arylethanol hydrochlorides **24** of up to 95% ee were obtained in quantitative yield. Here again, the BPPFA- and DIOP–rhodium catalysts were much less effective, giving the products in low yield with low stereoselectivity (12–26% ee). The high enantioselectivity of the BPPFOH ligand shown here may be associated not only with the hydrogen bonding by the hydroxyl group on BPPFOH, as mentioned above, but also with an interaction between the hydroxyl group and the ammonium group on the ketone. The 2-amino-1-arylethanols are useful as adrenergic or cardiac stimulants. Their preparation by asymmetric hydrogenation provides a novel and efficient route to asymmetric synthesis of these optically active compounds, which are obtainable with difficulty by a conventional method for asymmetric reduction of prochiral carbonyl compounds using chiral hydride reagents because of the presence of active hydrogens on the starting ketones and their instability under basic conditions.

The BPPFOH–rhodium complex has been found to be the best catalyst for hydrogenation of enol phosphinates **25** to give optically active secondary alkyl alcohols **26** with up to 78% ee;[27] the role of the hydroxyl group on BPPFOH in this hydrogenation remains to be clarified (eq 16).



25 — 26

(16)

R = Ph: 78% ee (*R*)
R = *i*-Pr: 60% ee (*R*)

(26) Hayashi, T.; Katsumura, A.; Konishi, M.; Kumada, M. *Tetrahedron Lett.* **1979**, 425.
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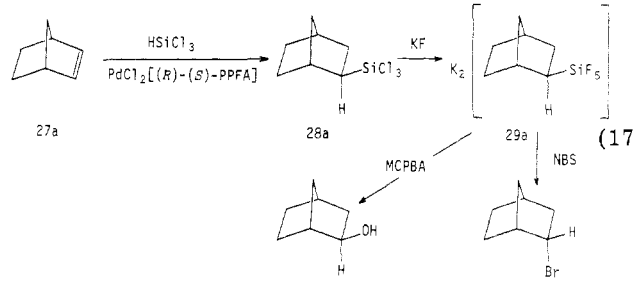
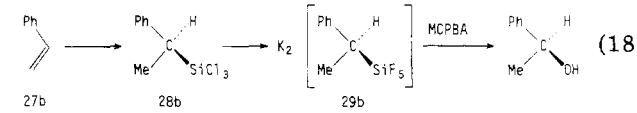
Hydrosilylation

A palladium complex with (*R*)-(*S*)-PPFA catalyzed the hydrosilylation of prochiral olefins **27** with trichlorosilane with higher enantioselectivity[28] than other chiral phosphine–transition-metal complexes (eq 17 and 18).[29] The optically active alkyltrichlorosilanes **28**



27a — 28a — 29a

(17)

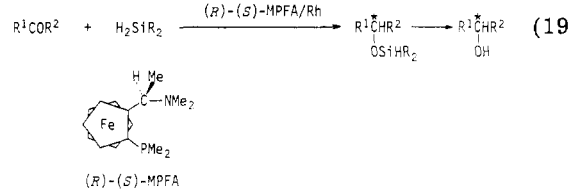


27b — 28b — 29b

(18)

obtained were converted into optically active alcohols and bromides (~50% ee) via potassium pentafluorosilicates **29**. In this hydrosilylation, the structure of the catalytically active species is not clear, but the ligand PPFA is imagined to coordinate with palladium through the phosphorus atom only as a monodentate ligand rather than through both phosphorus and nitrogen atoms as a bidentate ligand, because palladium complexes with bidentate bis(phosphine) ligands were catalytically inactive for hydrosilylation under the usual reaction conditions.[30]

For asymmetric hydrosilylation of ketones, a rhodium complex with the dimethylferrocenylphosphine (MPFA) ligand was found effective to give optically active alcohols (up to 52% ee) after hydrolysis (eq 19).[31]



(19)

(*R*)-(*S*)-MPFA

Concluding Remarks

We have emphasized the importance of the design of chiral phosphine ligands for asymmetric synthesis catalyzed by chiral transition-metal complexes and shown that high stereoselectivity can be achieved by use of appropriately functionalized chiral ferrocenylphosphines in several catalytic asymmetric reactions. The high efficiency of ferrocenylphosphine ligands is ascribed mainly to attractive interactions between functional groups on a substrate and on the chiral lig-

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(29) (a) Yamamoto, K.; Hayashi, T.; Zembayashi, M.; Kumada, M. *J. Organomet. Chem.* **1976**, *118*, 161. (b) Yamamoto, K.; Hayashi, T.; Uramoto, Y.; Ito, R.; Kumada, M. *J. Organomet. Chem.* **1976**, *118*, 331.
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ands coordinated to the transition-metal catalyst, e.g., hydrogen bonding between the hydroxyl group on the phosphine ligand and the carbonyl group of a prochiral carbonyl compound in the hydrogenation or coordination of an amino group on the ligand with the magnesium atom on a Grignard reagent in the cross-coupling reaction. Thus, chiral ferrocenylphosphines are superior to others in that structural modification can be readily made by introduction of a desired functional group on to the side chain according to the demand of the reaction type. In the field of asymmetric synthesis by stoichiometric chiral reagents, high stereoselectivity has been sometimes attained by the stereocontrol based on the attractive interactions, e.g., chelation in the asymmetric alkylation by Meyers.[32] This type of stereocontrol should be more extensively applied to asymmetric synthesis with homogeneous transition-metal catalysts, which will certainly bring about much higher stereoselectivity. Our current interest is in development of new catalyst systems efficient for catalytic asymmetric reactions other than those described here.

This work was supported in part by a Grant-in-Aid for Scientific Research of the Ministry of Education and the Asahi Glass Foundation for the Contribution to Industrial Technology. We wish to thank all our co-workers, whose names are listed in the references, for their invaluable contributions.

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Temperature Dependence of the Primary Kinetic Hydrogen Isotope Effect as a Mechanistic Criterion

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Organic chemists have traditionally applied the primary isotope effect as a mechanistic criterion by measuring k_H/k_D at a single, convenient temperature. This single value is then invested with significance, being related to whether it is large, small, or intermediate; it also suffices to establish whether H transfer is occurring in the rate-determining step of the mechanism.

Various efforts have been made to correlate the size of this single value of k_H/k_D with the occurrence of hydride, proton, or hydrogen atom transfer with no outstanding success. The failure to take advantage of existing theoretical treatments[1] that teach a broader significance of the temperature dependence of k_H/k_D is probably related to experimental difficulties in obtaining, over a sufficient temperature range, k_H/k_D data of the accuracy and precision demanded.

Several categories of transition states (hereafter abbreviated TS) of H-transfer reactions may be discerned through application of the "full" criterion, meaning the temperature dependence of the kinetic isotope effect (TDKIE). The development of techniques[2,3] that afford the required precision in measurements of k_H/k_D over extensive ranges of temperature has created a position from which the transition states of common H-transfer processes may be characterized by means of the "full" criterion. It is useful to review the origins of the temperature-dependence of k_H/k_D based on a simple two-dimensional TS model of a three-center process[4] (where X and Y may be atoms or molecules):

$$X\text{–}H + Y \rightarrow X + HY$$

Background

The TDKIE criterion is ultimately based on the Arrhenius relation:

$$k_H/k_D = A_H/A_D \exp(-[\Delta E_a]_D^H/RT) \qquad (1)$$

Two categories of transition states can be defined in

Harold Kwart did his undergraduate work at Brooklyn College and had started graduate work with Harold C. Urey at Columbia University when World War II interfered. During the war, he was involved in isotope studies on the Manhattan Project. In 1945, he commenced graduate work to the Ph.D. at Harvard University, where Paul D. Bartlett was his mentor. After 2 years of postdoctoral work at Harvard, he joined the faculty of Bryn Mawr College. In 1951 he moved to the University of Delaware, where he is now H. Fletcher Brown Professor of Organic Chemistry.

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(2) H. Kwart and J. J. Stanulonis, *J. Am. Chem. Soc.*, **98**, 4009 (1976). The high-precision method of measuring isotope effects developed here depends on the use of a (nonmagnetic) quadrupole mass spectrometer that is characterized by a very short time of flight of the isotopic masses of interest. This assures that two such masses can be compared under virtually identical conditions of ionization and collection. This instrument is coupled to a computer programmed to look at two discrete mass peaks in rapid succession and deduce the ratio of their intensities. If a relatively constant pressure of substrate flowing into the ionization chamber for several minutes is maintained, thousands of mass ratio data are gathered by the computer, which is also programmed to perform several statistical operations on these data before expressing the average isotopic mass ratio of a block. A number of blocks consisting of several thousand mass ratio measurements are taken, spaced at intervals of time to detect the occurrence of such vagaries as memory effects and drifts in tuning and calibration factors.

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