Research Article

Development of P-Chirogenic Phosphine Ligands Based on Chemistry of Phosphine–Boranes: Searching for Novelty and Utility in Synthetic Organic Chemistry

Tsuneo Imamoto

Chiba University
Yayoi-cho, Inage-ku, Chiba 263-8522, Japan
E-Mail: imamoto@faculty.chiba-u.jp

This paper is dedicated to Professor Teruaki Mukaiyama on the occasion of his 90th birthday.

Abstract: This paper describes the synthesis and utilization of P-chirogenic phosphine ligands, mainly by reviewing our study on this research area. Various optically pure P-chirogenic phosphine ligands have been synthesized by the use of phosphine–boranes as the intermediates more conveniently than the previously existing methods using phosphine oxides. Conformationally rigid P-chirogenic phosphine ligands bearing a bulky alkyl group such as the *tert*-butyl group and a small group like the methyl group at the phosphorus atoms exhibit excellent enantioselectivity and catalytic efficiency in transition-metal-catalyzed asymmetric reactions. 2,3-Bis(*tert*-butylmethylphosphino)quinoxaline (QuinoxP*) has been widely used as an efficient ligand in both academia and industry by virtue of its air-stability and high enantioinduction ability. Electron-rich P-chirogenic bisphosphine ligands have been used for the elucidation of the mechanism of rhodium-catalyzed asymmetric hydrogenations of enamides and related substrates, and it has been revealed that the hydrogenations proceed via Rh-dihydride intermediates and the enantioselection is determined at the step of formation of hexacoordinated Rh(III) complexes involving the bisphosphine ligand, dihydride, and the substrate.

Keywords: P-Chirogenic phosphine ligands, Phosphine–borane, Design of chiral ligands, Catalytic asymmetric synthesis, Asymmetric hydrogenation, Enantioselection mechanism

1. Introduction

Chiral phosphine ligands play pivotal roles in transition-metal-catalyzed asymmetric reactions. Chiral ligands coordinate to metal centers to create an asymmetric environment around the reaction centers, which eventually affects enantioselectivity and reaction rate. Asymmetric catalytic performance is determined not only by the metal center but also by the chiral ligand selected. The design and synthesis of chiral phosphine ligands has been an important actively investigated research subject. Many chiral phosphine ligands have been produced and utilized for the synthesis of useful optically active compounds.[1)] However, no all-purpose ligands, which can be used in a wide range of reactions and substrates, have been created.

Chiral phosphine ligands are categorized into two general classes: backbone chirality ligands and P-chirogenic ligands. Figure 1 shows representative asymmetric bidentate phosphine ligands. Typical examples of backbone chirality ligands include DIOP, CHIRAPHOS, BINAP, DuPHOS, JosiPhos, and SEGPHOS. The most well-known example of P-chirogenic phosphine ligands is DIPAMP, which was developed by Knowles and co-workers at Monsanto in 1975 and used for rhodium-catalyzed asymmetric hydrogenation of dehydroamino acid derivatives with high enantioselectivities (up to 96%), the greatest enantioselectivity achieved at that time. Use of the DIPAMP-Rh catalyst system allowed the industrial production of (*S*)-3,4-dihydroxyphenylalanine (L-DOPA), used to treat Parkinson's disease.[2)] However, despite this important application, P-chirogenic phosphine ligands, including DIPAMP, have not been widely used for more than 20 years, mainly due to the difficulty of their synthesis using phosphine oxides as the intermediates. In addition, many backbone chirality phosphine ligands, such as BINAP and DuPhos, were synthesized and successfully used in various catalytic asymmetric syntheses.

On the other hand, investigations into the synthesis and reactions of phosphine–boranes revealed a new method for synthesis of P-chirogenic phosphine ligands through the use of phosphine–boranes as intermediates. This discovery led to the design and synthesis of new P-chirogenic phosphine ligands and their application in catalytic asymmetric reactions, including for mechanistic studies of Rh-catalyzed asymmetric hydrogenation. This paper describes the outline of our studies on phosphine–boranes and P-chirogenic phosphine ligands.

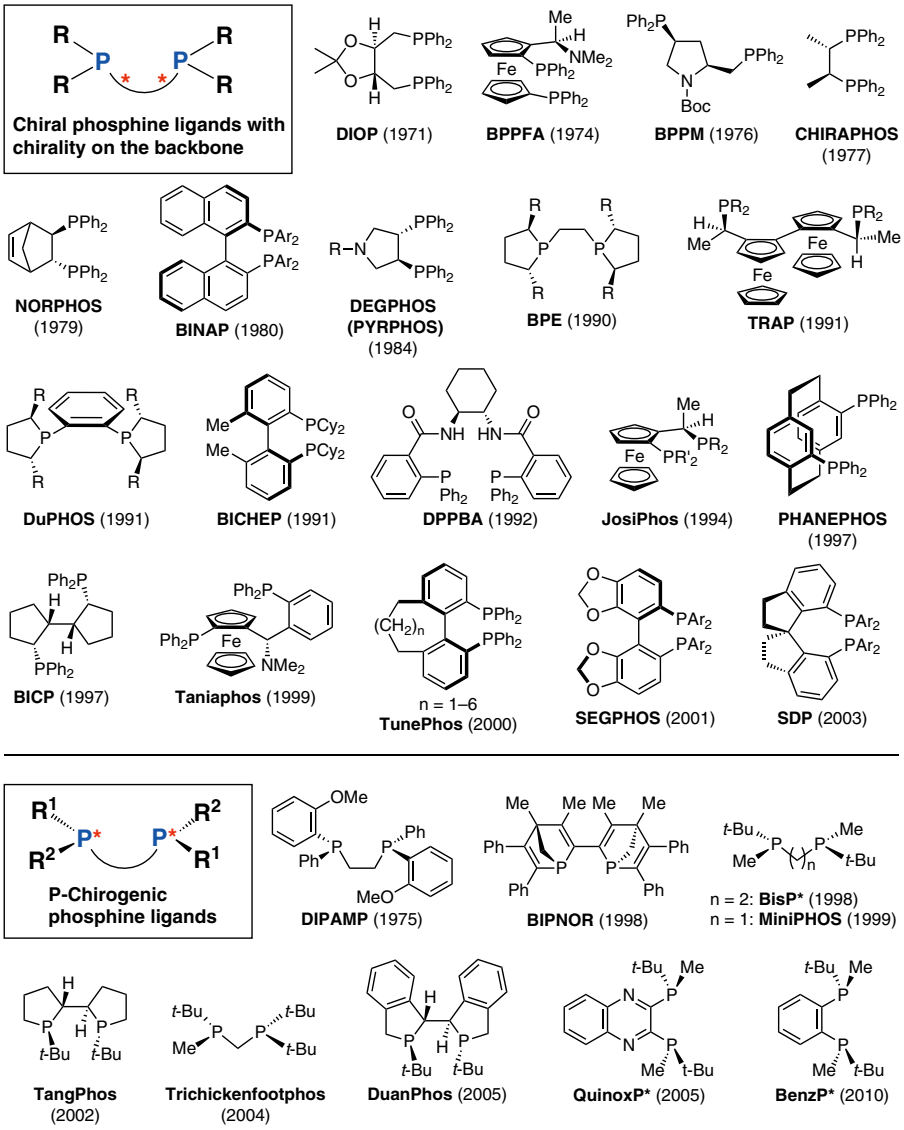


Figure 1. Representative chiral bidentate phosphine ligands

2. Prologue to the Study on P-Chiral Phosphine Ligands

2-1. Studies in America and Research at the University of Tokyo

Before joining the faculty of Chiba University, some circumstances greatly affected my research, including the relationships between Tokyo Chemical Industry and myself.

In August 1975, I resigned as an assistant professor at Osaka University, and traveled to America with my wife and two small daughters. Three months before my departure, I asked my supervising professor to describe the work I would be doing next, saying "I wish to work not only on industrial-focused research but also on more academic research." However, this attitude led to me being asked to leave the laboratory. For many years, I had hoped to study abroad under the guidance of an outstanding researcher, and my departure from the Osaka University laboratory opened the possibility for me to study abroad. In America, I joined the laboratory of Professor Carl R. Johnson at Wayne State University in Detroit, Michigan. In those days, Professor Johnson published many reports on asymmetric synthesis using optically active sulfoximines. At Osaka University, I had studied β-lactam antibiotics, such as penicillin and cephalosporin derivatives, and so was interested in chiral compounds and their chemical transformations. However, asymmetric synthesis, particularly catalytic asymmetric synthesis, was not yet recognized as a valuable area of scientific study, even though I believed that it would develop into an important area of research. Because Professor Johnson was an outstanding researcher in the field of asymmetric synthesis, I decided his laboratory was a useful place for me. The resulting course of events confirmed that I made the correct decision. Actually I worked on asymmetric synthesis for more than 40 years.

Even while working as a postdoctoral fellow in Johnson's laboratory, I was investigating possibilities for my next position. However, finding a suitable position was difficult even with the help of my connections. When my visa was nearly expired, I was offered a lecturer position at a certain university and returned to Japan in August, 1978. However, the position was eliminated shortly afterward for other unrelated reasons. I

considered working as a lecturer for a private school that helps students pass exams ("cram school") until I could find a more suitable academic position. After interviewing at a cram school and informally offered a position, I mentioned the offer to Professor Teruaki Mukaiyama, who had been my supervisor at the Tokyo Institute of Technology, and I visited his office at the University of Tokyo. He recommended that I join his laboratory as a research student, instead of accepting the position at the cram school. He also asked Mr. Koji Asakawa, the president of Tokyo Chemical Industry at the time, to help find a suitable apartment for my family. Mr. Asakawa contacted me and offered a 2-story annex, rent-free, in the residence where his mother lived. My family and I lived in the annex for 1.5 years. To express my appreciation for the annex, I offered to help in the Fukaya factory of Tokyo Chemical Industry for one week. However, I was learning more than helping, especially about industrial processes that produce chemicals with high quality.

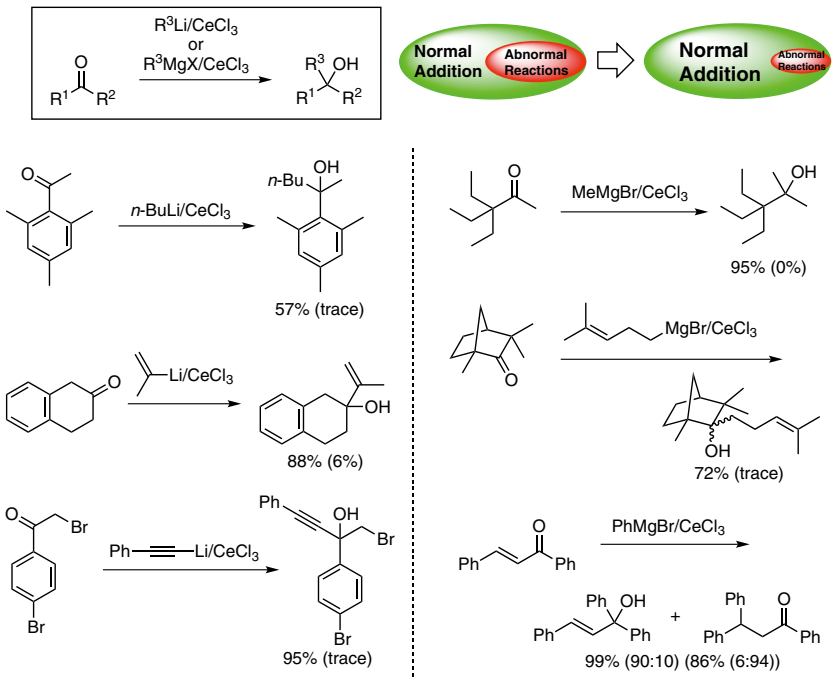
Thus, I could continue to perform research, but the situation, of a 36 year old research student having a family, was quite difficult mentally and economically. After studying abroad in America, I had to start from the beginning to build my career. This situation affected my ability to concentrate on the work and to obtain the results expected for researchers in Professor Mukaiyama's laboratory. These hardships continued until I was offered employment as an assistant professor of the Faculty of Science at Chiba University.

2-2. Work with Phosphine–Boranes

At Chiba University, I devoted my time to research and education. I worked in the laboratory on Sundays and national holidays, and on New Year's Day I wished for the success of my research from my own bench.

My initial studies involved the use of lanthanide elements in organic synthesis. Despite the pioneering research of Professors Kagan and Luche, I believed that this area was largely unexplored and held the possibility of discovering new useful synthetic methods. After many trials, we were able to develop organocerium reagents. Reactions of Grignard reagents or organolithium reagents with carbonyl compounds are important methods for the synthesis of alcohols and related compounds, but they often accompany enolization, 1,4-addition, and reduction to decrease the yields of desired 1,2-addition products. In such cases, the use of organocerium reagents suppresses these unwanted reactions to afford the products in good to high yields.[3] Several representative reaction examples are shown in Scheme 1. This method, together with Knochel's improved method,[4] is now widely used in organic synthesis.

The reduction of phosphine oxides with $LiAlH_4$ was attempted in the presence of cerium chloride utilizing the moderately strong Lewis acidity of cerium chloride. Results showed that reduction proceeded rapidly under mild conditions to produce the corresponding phosphines in high yields.[5] This



Scheme 1. Representative examples of reactions of organocerium reagents with carbonyl compounds (value in parentheses represent yield when reaction was conducted without cerium chloride).

reduction is interesting because when the reaction is conducted in the absence of cerium chloride, it proceeds sluggishly to afford the phosphines in low yields due to the carbon–phosphorus bond cleavage. In contrast, the use of $NaBH_4$ in place of $LiAlH_4$ resulted in quite low yields. Next, a three-component reagent, $LiAlH_4$–$NaBH_4$–$CeCl_3$, was used. Instead of the expected formation of phosphines, phosphine–boranes were produced in good yields (Scheme 2).[6)]

With the phosphine–boranes in hand, we were surprised to find that these compounds, including secondary ones, were virtually inert to air and moisture and barely decomposed, even on contact with strong acids or bases, such as hydrochloric acid and sodium hydroxide. These characteristic properties led us to study phosphine–boranes from the view point of organic synthesis.

3. Studies Based on Mukaiyama's Methodology: Catch the Interesting while Running

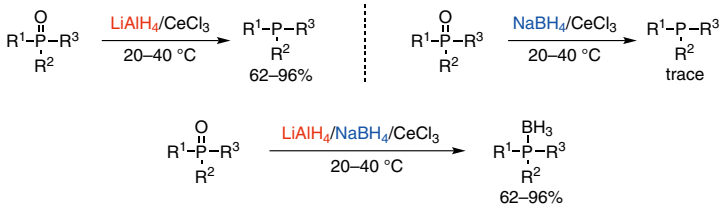
Professor Mukaiyama had many memorable witty remarks, such as "Obedience, Brightness, and Passion," which I keep in mind because I want to be a person with these characteristics. Another saying that became my motto was "Catch the Interesting While Running." He admonishes us, saying "Run whole heartedly, and new seeds shall be found. Practice first! Otherwise, only empty theories are left." [7)]

Chemistry researchers, especially organic chemists, can be classified into experiment-precedence types or thought-precedence types. Professor Mukaiyama is a typical experiment-precedence (practice-precedence) type researcher. In contrast, Professor Yasuhide Yukawa, who was my supervisor when I learned as a graduate student at Osaka University, was an outstanding researcher in the field of organic reaction mechanisms and preferred active research discussion. Because I had trained in the Yukawa lab that encouraged discussion, I was surprised to experience Mukaiyama's experiment-precedence approach when I became a postdoctoral fellow at the Tokyo Institute of Technology. My first impression was that the researchers performed too many "useless" experiments. However, I gradually began to appreciate the importance of Professor Mukaiyama's methods, particularly in the development of new synthetic methods. The probability of success for practice-precedence research is lower than that for well-planned research based on thorough literature searches, deep insight, and discussion; but big discoveries and truly new methods can be discovered through much experimentation, sharp observation, and deep consideration.

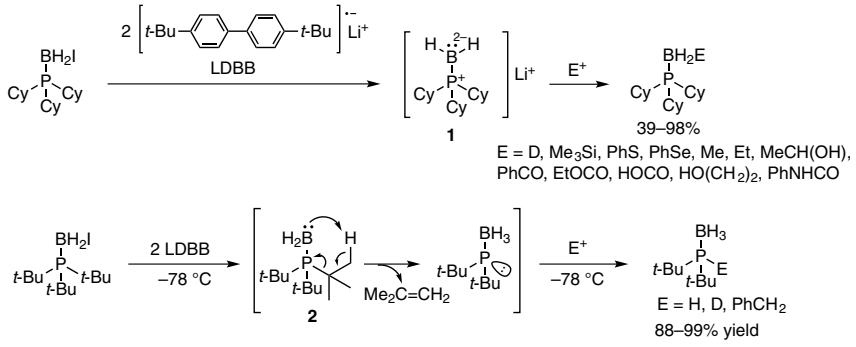
The research on phosphine–boranes was conducted according to Mukaiyama's methodology. The significance of the research was emphasized to my collaborator students by mentioning that two Nobel Prize winners, G. Wittig and H. C. Brown, were involved in phosphine–borane research. The following three studies were conducted in parallel with the synthesis of P-chirogenic phosphine ligands. The goal of these studies was to create interesting and fundamentally important chemical species and to find unprecedented reactions by utilizing the characteristic properties of phosphine–boranes.

3-1. Generation of and Reactions with Boron Dianions Isoelectronic with Carbanions

Carbanions are the most important chemical species in organic chemistry because they react with various electrophiles to afford a variety of organic compounds. Numerous investigations have been conducted on tetracoordinated boron-ate complexes, but few studies have been done on boron anions (formally boron dianions) that are isoelectronic with carbanions. We envisioned that the corresponding boron anions could be generated by taking advantage of the characteristic properties of phosphine–boranes. After various trials, the desired anions could be generated, and their nucleophilic properties and strong basicity, similar to those of carbanions, were confirmed (Scheme 3).[8)] Thus, boron anion **1**, which was generated by reduction of tricyclohexylphosphine–monoiodoborane with



Scheme 2. Reactions of phosphine oxides with $LiAlH_4$ and/or $NaBH_4$ in the presence of $CeCl_3$



Scheme 3. Generation of tricoordinate boron anions and their reactions with electrophiles

LDBB, reacted with electrophiles such as aldehydes, esters, carbon disulfide, isocyanates, epoxides, and disulfides to give *B*-functionalized phosphine-borane derivatives. Another boron anion **2**, generated from tri-*tert*-butylphosphine–monoiodoborane, underwent electrocyclic reaction at –78 °C. This reaction was compared with the corresponding carbanion (phosphorus ylide), which undergoes the same type of electrocyclic reaction at 20 °C. The results clearly demonstrate that the basicity of this boron anion was greater than that of the carbanion.

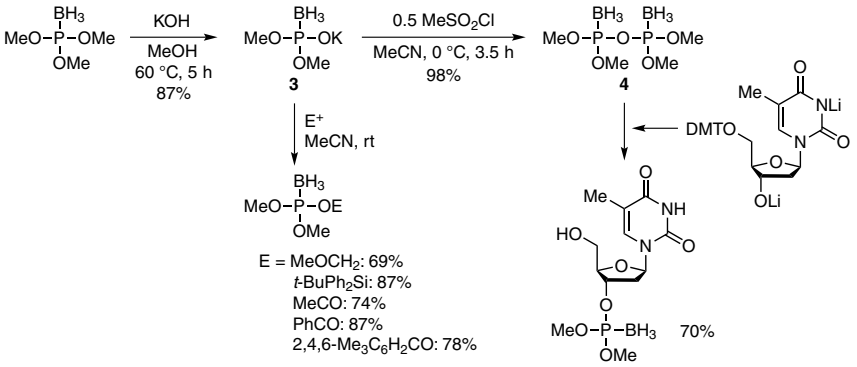
3-2. Preparation of Boranophosphorylation Reagents and Their Reactions

Boranophosphates, which have an isoelectronic relationship with phosphates, are useful in biochemical investigations. They also have potential utility as carriers of ^{10}B in boron neutron capture therapy (BNCT) for the treatment of cancer. We attempted to develop new reagents for the synthesis of similar compounds. As shown in Scheme 4, dimethyl boranophosphate monopotassium salt **3** and tetramethyl boranopyrophosphate **4** were prepared from the borane adduct of trimethylphosphite. The former compound underwent substitution reactions with various electrophilic reagents, while the latter reacted with metal alkoxides to give the corresponding boranophosphate derivatives.[9] These results provide simple synthetic routes to various boranophosphate derivatives, including borano analogues of naturally occurring phosphates.

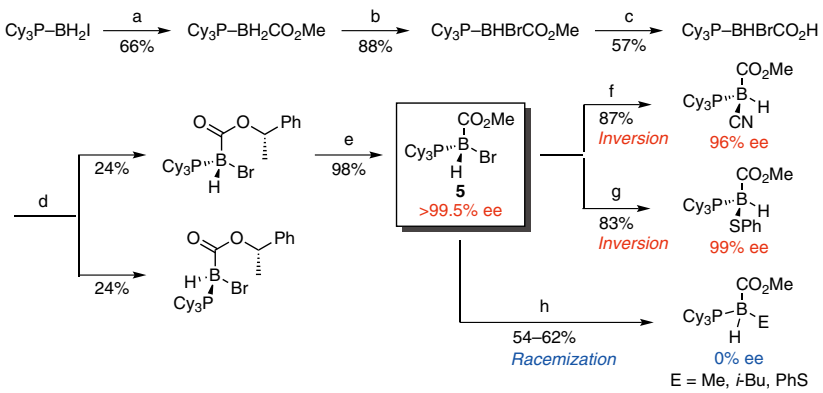
3-3. Synthesis of Optically Pure Tetracoordinated Boron Compounds and Stereochemistry of the Substitution Reactions at the Chirogenic Boron Atom

Although reports have indicated that nucleophilic substitution reactions occur at the tetracoordinated boron atom, little attention has been paid to the stereochemistry of the reactions. In 1999, Gall and Mioskowski synthesized tetracoordinated boron compounds bearing chirogenic centers at the boron atom, and demonstrated that nucleophilic substitution reactions proceeded with Walden inversion of configuration.[10] However, the compounds they used were diastereomers possessing an isopinocampheyl group; therefore, the results cannot completely rule out the possibility that the other chiral center influenced the stereochemistry of the substitution reaction.

We synthesized enantiopure B-chirogenic tetracoordinated boron compounds and examined the substitution reactions at the boron atom (Scheme 5). The model substrates containing a bromine atom as the leaving group were synthesized in five steps from tricyclohexylphosphine–monobromoborane. This compound reacted with lithium cyanide or lithium phenylsulfide to give the corresponding inversion products in high yields.



Scheme 4. Preparation and reactions of boranophosphorylation agents



Conditions: (a) (i) LDBB (2.5 equiv)–TMEDA, THF, –78 °C, (ii) $(MeO)_2CO$, (b) Br_2, MeOH, 0 °C to rt. (c) aq 48% HBr, THF, rt, 12 h; recrystallization from AcOEt. (d) (*S*)-(–)-1-phenylethanol, 120 °C, 10 min; fractional crystallization from hexane. (e) H_2SO_4 (cat.), MeOH–THF, rt, 4 h. (f) LiCN, DMF–THF, 50 °C, 4 h. (g) LiSPh, THF, 0 °C, 2 h. (h) (i) LDBB –TMEDA, –78 °C, 5 min, (ii) MeI, *i*-BuBr, or PhSSPh, –78 °C to rt.

Scheme 5. Substitution reactions of optically active tetracoordinated boron compounds at the chirogenic boron atom

These results unequivocally demonstrate that the S_N2 reaction at the sp^3 boron atom proceeded with Walden inversion of configuration, like that in the S_N2 reaction at the sp^3 carbon atom.[11]

In contrast, compound **5** was subjected to reduction with LDBB, followed by reaction with electrophiles, to afford completely racemized products. These results indicate that the intermediate boron anion was extremely stereochemically unstable and underwent rapid racemization, even at –78 °C.

4. Synthesis of P-Chirogenic Phosphine Ligands

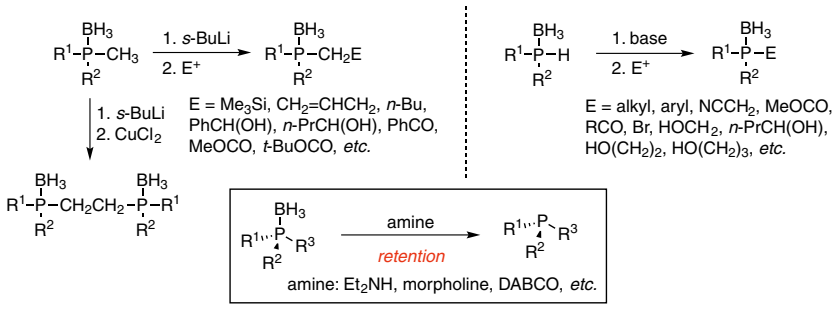
4-1. Synthesis of Phosphine–Borane Derivatives and Deboranation Reactions

Along with examination of reactions at the borane moiety of phosphine–boranes, functionalization of the phosphine moiety was attempted, which led to the observation of valuable experimental facts. Tertiary phosphine–boranes containing a methyl group readily underwent deprotonation and subsequent reaction with alkyl halides or carbonyl compounds to give various phosphine–borane derivatives. Oxidative dimerization occurred while retaining the boranato group. Secondary phosphine–boranes reacted in the presence of base, similar to the reactions of secondary phosphine oxides, with a variety of electrophiles to give the corresponding phosphine–borane derivatives (Scheme 6).[6,12]

The phosphine–borane derivatives obtained were reacted with various reagents to convert them to useful compounds. Treatment with amines, such as diethylamine or morpholine, removed the boranato group (BH_3) to produce parent tertiary phosphines in almost quantitative yield. Additional trials using optically active phosphine–boranes indicated that this deboranation occurred with complete retention of configuration (Scheme 6). We were excited with these results and convinced that a variety of phosphines, including optically active ones, could be synthesized *via* this deboranation process. In addition, the results indicated that the BH_3 group can act as a protecting group of phosphines susceptible to air oxidation or alkylation with alkyl halides or sulfonates. Various P-chirogenic phosphine ligands could be synthesized by utilizing the boranato group as a protecting group of phosphines. This method was also applicable to the preparation of various achiral phosphine ligands.[13]

4-2. Synthesis of P-Chirogenic Bidentate Phosphine Ligands Containing Aryl Groups at the Phosphorus

Based on the results mentioned above, the utility of this method was confirmed by preparation of DIPAMP in satisfactory yield. New P-chirogenic phosphine ligands **6**–**8** were synthesized and their enantioinduction ability was evaluated in the Rh-catalyzed asymmetric hydrogenation of enamides such as methyl α-*N*-acetamidocinnamate (Figure 2). While ligands **6** and **7** were not effective, providing only moderate enantioselectivity, **8a** and **8b** led to 92% and 97% enantioselectivity, respectively; greater than 99% enantioselectivity was observed by the use of **8c** and **8d**. The first achievement of selectivities greater than that of DIPAMP (96%) after 20 years was very satisfying. The main purpose of this study was to clarify whether the high enantioselectivity of DIPAMP was responsible for coordinative interaction between the methoxy oxygen atom and rhodium atom. The results clearly indicated that the coordinate interaction was not the main stereo-regulating factor and that enantioselection was determined by the spatial properties of the ligands. The excellent enantioselectivity suggested that P-chirogenic phosphine ligands were potentially useful in catalytic asymmetric reactions.



Scheme 6. Synthesis of phosphine–borane derivatives and stereospecific deboranation reaction

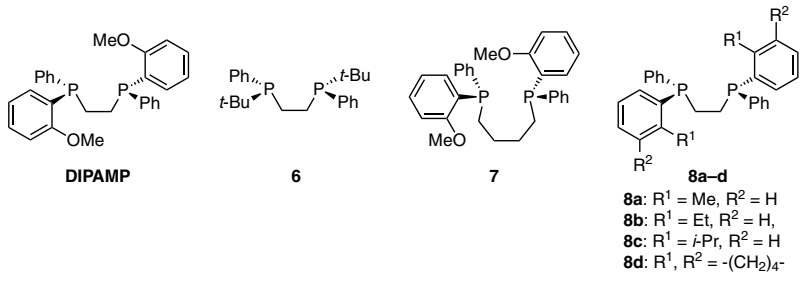


Figure 2. P-Chirogenic bidentate phosphine ligands containing aryl groups at the phosphorus atom, prepared using phosphine–boranes

4-3. Synthesis of Electron-rich P-Chirogenic Phosphine Ligands and Their Enantioinduction Ability

Although ligands **8c** and **8d** exhibited greater enantioselectivity than DIPAMP, their structures resembled DIPAMP and, thus, lacked originality. Could more original ligands be developed? One characteristic of P-chirogenic phosphine ligands is that the phosphorus atom becomes the chiral center, allowing an ideal chiral reaction environment by the correct selection of two substituents at the phosphorus atom. Very high enantioselectivity was considered possible through the use of C_2 symmetric phosphine ligands containing a sterically bulky alkyl group and a small group at the phosphorus atoms. This idea was based on the quadrant diagram proposed by Knowles, and we envisioned that it would be most effectively realized by utilizing this intrinsic property of P-chirogenic phosphine ligands (Figure 3).

This idea was immediately tested through experimentation. A *t*-butyl group or 1-adamantyl group was selected as the bulky alkyl group and a methyl group was selected as the small functionality. The number of substitution patterns was limited, but we hoped that one of them would lead to a good result. Scheme 7 shows the synthesis of (*S*,*S*)-1,2-bis(alkylmethylphosphino)ethanes (BisP*) (**9a**–**g**) and their rhodium complexes (**10a**–**g**).

First, *t*-Bu-BisP* (**9a**) and its rhodium complex (**10a**) were prepared, and the enantioinduction ability for asymmetric hydrogenation of a model compound, methyl α-acetamidocinnamate, was examined. The substrate, Rh-complex, and solvent were added to the hydrogenation bottle, and hydrogenation pressure set to 2 atm, and the pressure gauge was observed for a decrease. However, the pressure did not decrease, even after 2 h, and work-up of the reaction mixture was done even though hydrogenation did not appear to have occurred. Surprisingly, the NMR spectrum of the reaction mixture clearly showed that the hydrogenation product was produced in nearly quantitative yield. We realized that the catalytic activity of the rhodium complex was so great that hydrogenation had already been completed during the operation to change the reaction system to hydrogen gas. The product ee was >99.5%.[15]

Based on these results, we synthesized structurally simpler (*R*,*R*)-bis(alkylmethylphosphino)methane (MiniPHOS) (**11a**–**d**) and their rhodium complexes (Scheme 8).[16,17] Figure 4 shows the ORTEP drawing of the Rh-complex **12** prepared by reaction of *t*-Bu-MiniPHOS (**11a**) with $[Rh(cod)_2]SbF_6$.[18] Note that the four-membered chelate is nearly flat and the bulky *tert*-butyl groups effectively shield the diagonal quadrants and the two methyl groups locate on the other diagonal quadrants, constructing the asymmetric environment just as designed. This C_2 symmetric complex is one of my favorite compounds because of the beauty arising from its simple structure.

The enantioinduction ability of BisP* and MiniPHOS

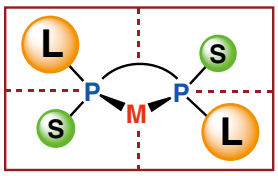
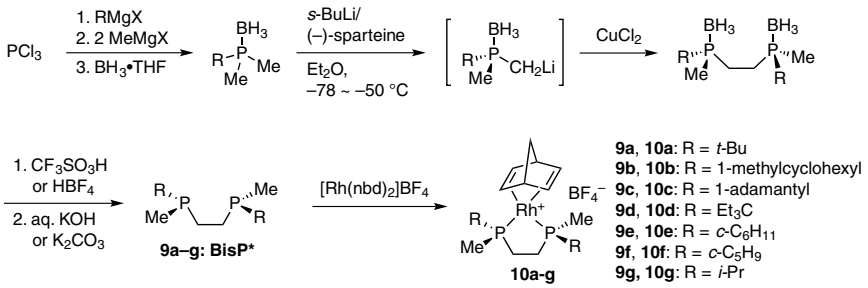
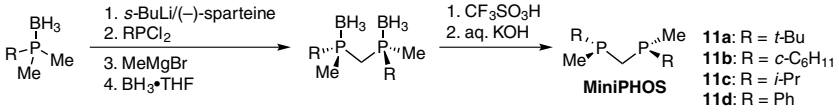


Figure 3. Quadrant diagram of metal complexes of C_2 symmetric P-chirogenic phosphine ligands



Scheme 7. Synthesis of BisP* and their rhodium complexes



Scheme 8. Synthesis of (*R*,*R*)-bis(alkylmethylphosphino)methanes (MiniPHOS) (**11a**–**d**)

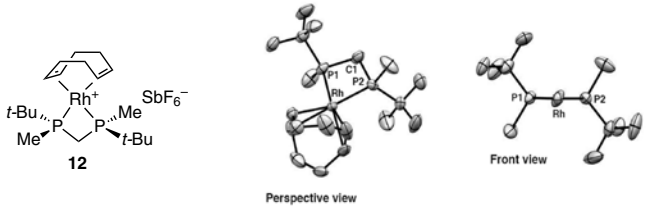
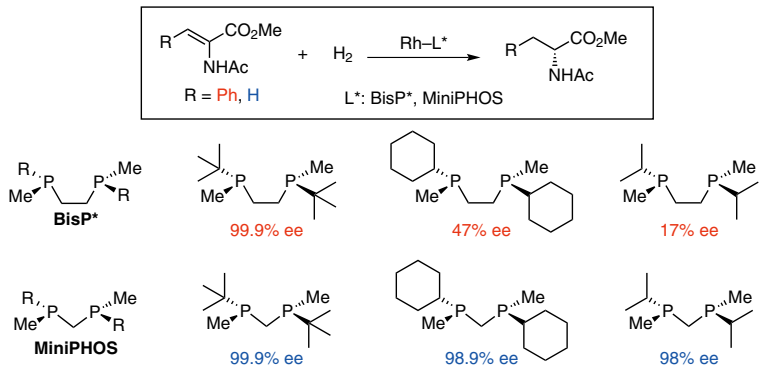


Figure 4. ORTEP drawing of complex **12**

were largely affected by the substituents at the phosphorus atom. Scheme 9 shows typical examples. While both BisP* and MiniPHOS exhibited 99.9% selectivity in the case of a *t*-butyl group, very different selectivities were observed using a cyclohexyl or isopropyl group. Selectivity was significantly decreased to 47% and 17% for BisP* containing a cyclohexyl or isopropyl group, respectively. In contrast, very high selectivity (98%) was still observed for MiniPHOS, even with an isopropyl group, due to the rigid molecular structure of MiniPHOS as well as its asymmetric environment that fit the reaction. This *i*-Pr-MiniPHOS is the smallest among the reported chiral bisphosphine ligands and we were surprised to find that very high enantioselectivity was present even in this extremely small chiral ligand, depending on the reaction and substrate.

The next research target was the development of more efficient chiral bisphosphine ligands. Day after day, we concentrated on the design of new ligands using molecular models and decided that ligand **13** containing two phospholane rings would be rigid and produce an ideal asymmetric environment due to the three fused five-membered rings (Figure 5).

First, we assumed that this ligand could be synthesized readily from 1-*tert*-butylphospholane–borane **15**. However, the first step in oxidative dimerization proceeded sluggishly to form meso-isomer **17** in 10% yield, rather than the desired C_2 symmetric dimer **16** (Scheme 10).[19] Next, we examined the reaction under different conditions and through different synthetic routes, but did not obtain the desired results. Meanwhile, we were surprised to read the paper by Tang and Zhang describing the synthesis and excellent enantioinduction ability of ligand **13** (Scheme 11).[20] Their synthetic method used phosphine sulfide **18** to afford the C_2 symmetric dimer **19** as the major product. We had attempted the dimerization using the same sulfide **18**, but our reaction conditions did not afford **18**. Therefore, we were disappointed by the publication of Tang's and Zhang's report.



Scheme 9. Comparison of enantioinduction ability of BisP* and MiniPHOS in Rh-catalyzed asymmetric hydrogenations

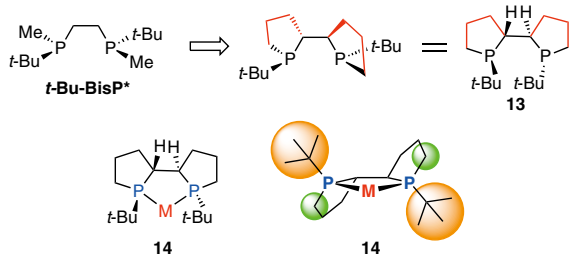
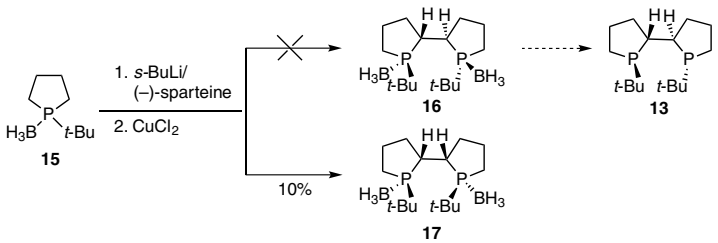
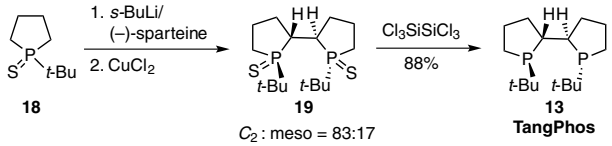


Figure 5. Design of P-chirogenic phosphine ligand **13** and its metal complex **14**



Scheme 10. Attempts to synthesize ligand **13**



Scheme 11. Synthesis of **13** by Tang and Zhang

The outstanding efficiency of TangPhos, not only in Rh-catalyzed asymmetric hydrogenation, but also in other catalytic asymmetric reactions, was demonstrated by their extensive investigations.[21,22] Thereafter, analogous P-chirogenic phosphine ligands **20**–**25** possessing *t*-butyl groups at the phosphorus atom were reported (Figure 6).[23–28] We prepared ligands **21** and **22** containing more rigid four-membered phosphines, expecting that they would provide higher enantioselectivity.[23,24] Among these ligands, Binaphine, DuanPhos, BIPOP, and WingPhos are now used for the production of optically active compounds. Reading about the excellent results of these reactions published in reputable journals causes vexation. At the same time, I feel happy recognizing that this area has been developed based on our original work.

4-4. Synthesis of Air-stable P-Chirogenic Phosphine Ligands

4-4-1. 2,3-Bis(*tert*-butylmethylphosphino)quinoxaline (QuinoxP*)

P-Chirogenic bis(trialkylphosphine) ligands, such as BisP* and MiniPHOS, exhibit high enantioinduction ability, but readily undergo oxidation upon contact with air. This air sensitivity has prevented their widespread utility, despite their high enantioinduction activity. We designed a new ligand that overcame the limitation of air sensitivity and was applicable to a wide range of catalytic asymmetric reactions. The newly designed ligand **27** (QuinoxP*) was prepared from *tert*-butyl(dimethyl)phosphine–borane (Scheme 12).

The most important intermediate, optically active secondary phosphine–borane (*S*)-**29**, was synthesized *via* oxidative, stereospecific one-carbon degradation of compound **28** through the use of a ruthenium catalyst.[29] Subsequent aromatic substitution reaction and deboranation proceeded smoothly to give the desired (*R*,*R*)-QuinoxP* ((*R*,*R*)-**27**) as an orange crystalline solid. Confirmation that this ligand was not readily oxidized in air or epimerized at room temperature, and was applicable to a few representative catalytic reactions indicated that it may be an ideal chiral phosphine ligand.[30]

4-4-2. 1,2-Bis(*tert*-butylmethylphosphino)benzene (BenzP*)

After synthesis of *t*-Bu-BisP*, the synthesis of 1,2-bis(*tert*-butylmethylphosphino)benzene, which is structurally fundamental and more rigid than *t*-Bu-BisP* owing the *ortho*-phenylene backbone, was pursued.[31] Many synthetic attempts, including Pd-catalyzed cross-coupling reactions of (*S*)-**29** with *o*-halobenzenes, were unsuccessful. However, in 2010, synthesis of the ligand on a 10-g scale was accomplished successfully. The synthetic route is shown in Scheme 13.

Discovery of this method can be attributed to Professor Sylvain Jugé at the University of Bourgogne. Reaction of lithiated secondary phosphine–boranes with *o*-dibromobenzene to produce *o*-bromophenylphosphine–boranes was developed by Jugé and co-workers,[32] and I learned about this reaction when I visited his laboratory in 2008. After returning to Japan, I confirmed that the reaction using (*S*)-**29** proceeded with complete retention of configuration to give compound **31** in

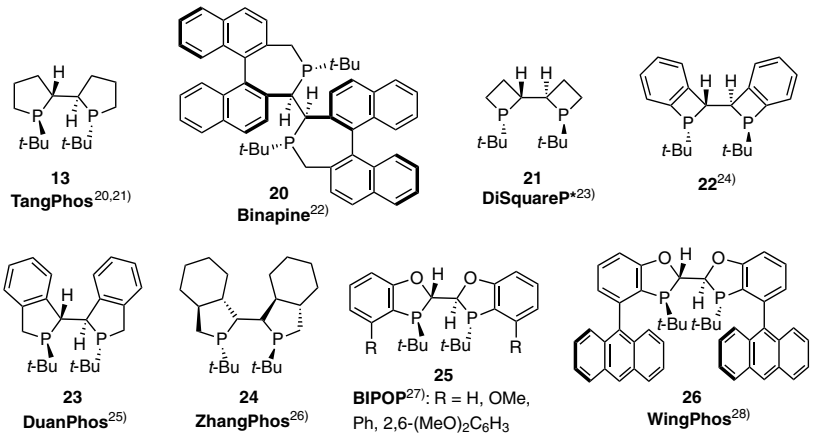
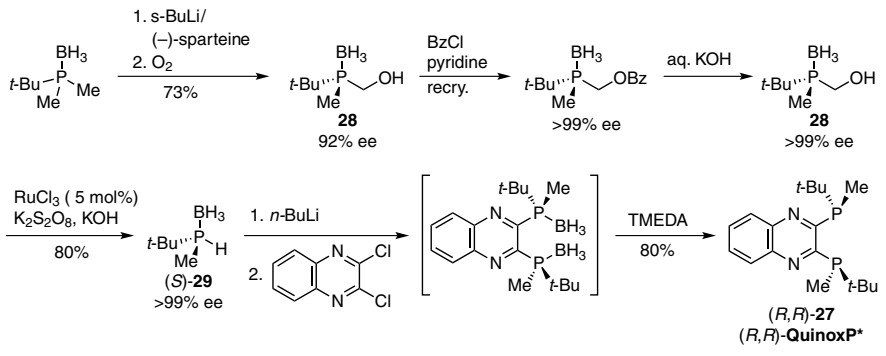


Figure 6. P-Chirogenic bisphosphine ligands possessing *tert*-butyl groups at the phosphorus atoms



Scheme 12. Synthesis of (*R*,*R*)-QuinoxP*

good yield. Conversion of **31** to (*R*,*R*)-**30** in four steps was achieved in one pot. During this reaction sequence, introduction of the *t*-butylmethylphosphino group did not proceed stereoselectively, resulting in the production of a large amount of undesired meso-isomer. However, the desired (*R*,*R*)-BenzP* could be obtained by crystallization from methanol.

BenzP* is not readily oxidized upon exposure to air. This property in conjunction with its high enantioinduction ability makes it potentially useful for catalytic asymmetric syntheses. However, the present synthetic method is not applicable to large-scale production of this ligand, and we are searching for a more efficient and practically useful method.

4-5. Synthesis of Chiral Bisphosphines via Optically Active *tert*-Butylmethylphosphine–Borane

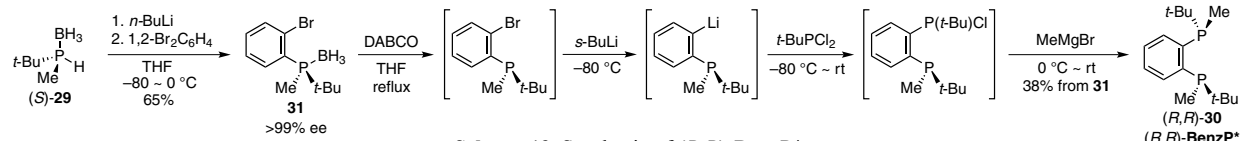
Optically active *tert*-butylmethylphosphine–borane played a key role in the synthesis of QuinoxP* and BenzP*. This secondary phosphine–borane looks very attractive to me, because of the chirogenic phosphorus atom, boranato group, hydrogen atom, methyl group, and *t*-butyl group, which all participate directly in ligand synthesis or asymmetric induction. The most attractive and reliable is the powerful nucleophilicity of the generated phosphide anion toward electrophiles, which can be utilized for the preparation of various P-chirogenic bisphosphines (Figure 7). Both enantiomers of *tert*-butylmethylphosphine–borane are presently produced on a large scale at Nippon Chemical Industrial Co. Therefore, some bisphosphines can be prepared more conveniently than methods used previously. For example, both enantiomers of *t*-Bu-BisP* can be obtained via substitution of the phosphide anion with 1,2-dichloroethane.[18]

5. Enantioselection Ability of QuinoxP* and BenzP* in Transition-Metal-Catalyzed Asymmetric Reactions

5-1. Rhodium-Catalyzed Asymmetric Hydrogenation

The enantioselectivity of air-stable P-chirogenic phosphine ligands QuinoxP* and BenzP* was examined in several representative catalytic asymmetric reactions. Figure 8 shows the enantioselectivities obtained from Rh-catalyzed asymmetric hydrogenation of functionalized olefins such as dehydroamino acids and enamides.[33] The resulting ee values were comparable to or greater than those obtained using other chiral phosphine ligands. These results indicate that the ligands, particularly QuinoxP*, are applicable to the production of chiral ingredients containing an amino acid or amine moiety.

High enantioselectivities have also been observed in asymmetric hydrogenations of ketones using QuinoxP* and BenzP*. While the Ru-catalyzed asymmetric hydrogenation of β-keto esters was investigated extensively by Noyori and other researchers, comparable or higher enantioselectivities in comparison with previously reported values were observed (depending on substrates).[34] In addition, asymmetric hydrogenation of β-secondary-amino ketones by a Rh-BenzP* catalyst was significantly promoted by $ZnCl_2$ to afford the corresponding hydrogenation products with excellent enantiomeric excesses in high yields.[35] This procedure is potentially useful for the production of synthetic intermediates for (*S*)-duloxetine, (*R*)-fluoxetine, and (*R*)-atomoxetine, compounds used as antidepressant drugs.



Scheme 13. Synthesis of (*R*,*R*)-BenzP*

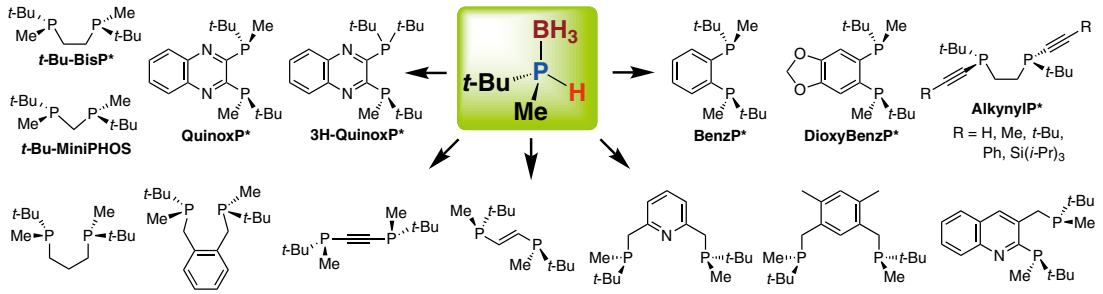


Figure 7. Chiral bisphosphines prepared from optically active *tert*-butylmethylphosphine–borane

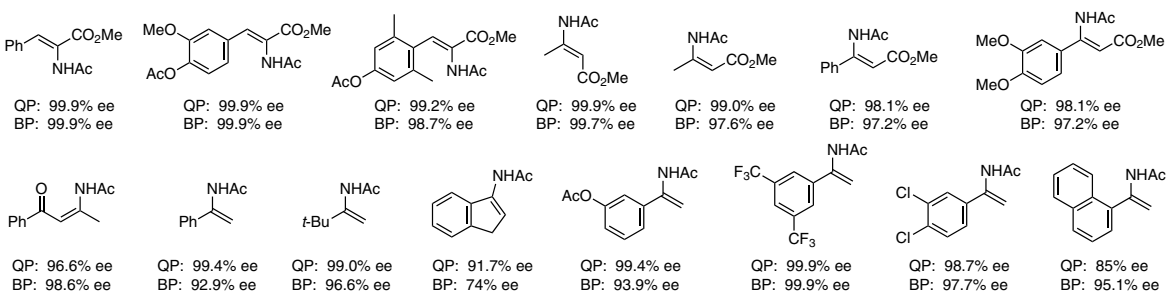
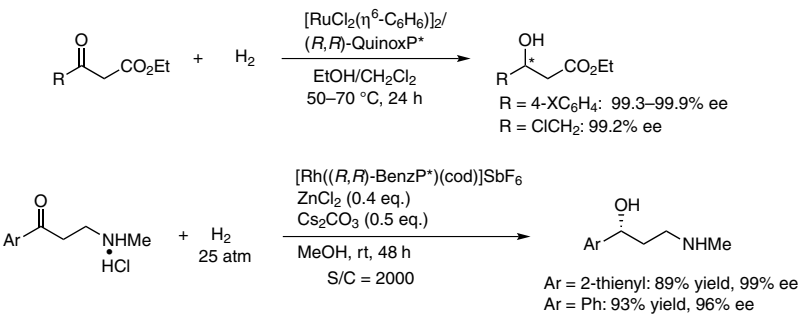


Figure 8. Examples of asymmetric hydrogenation using Rh-complexes of QuinoxP* (QP) and BenzP* (BP)



Scheme 14. Ru/Rh-catalyzed asymmetric hydrogenations of ketones using QuinoxP* or BenzP* as the chiral phosphine ligand

5-2. Carbon–Carbon and Carbon–Heteroatom Bond-forming Reactions

QuinoxP* and BenzP* have also been used for metal-catalyzed asymmetric carbon–carbon and carbon–heteroatom bond-forming reactions. These ligands provide very high enantioselectivity when reactions and substrates match. Representative examples are shown in Figure 9.[30,36–60] In most cases, the enantioselectivities observed were greater than previously reported values obtained using other chiral phosphine ligands. The enantioselective reactions shown result from leading studies in the field of asymmetric catalysis. In addition, the QuinoxP* ligand, because of its availability in large quantities, is being used for industrial production of chiral therapeutic agents for hepatitis C.[57,60]

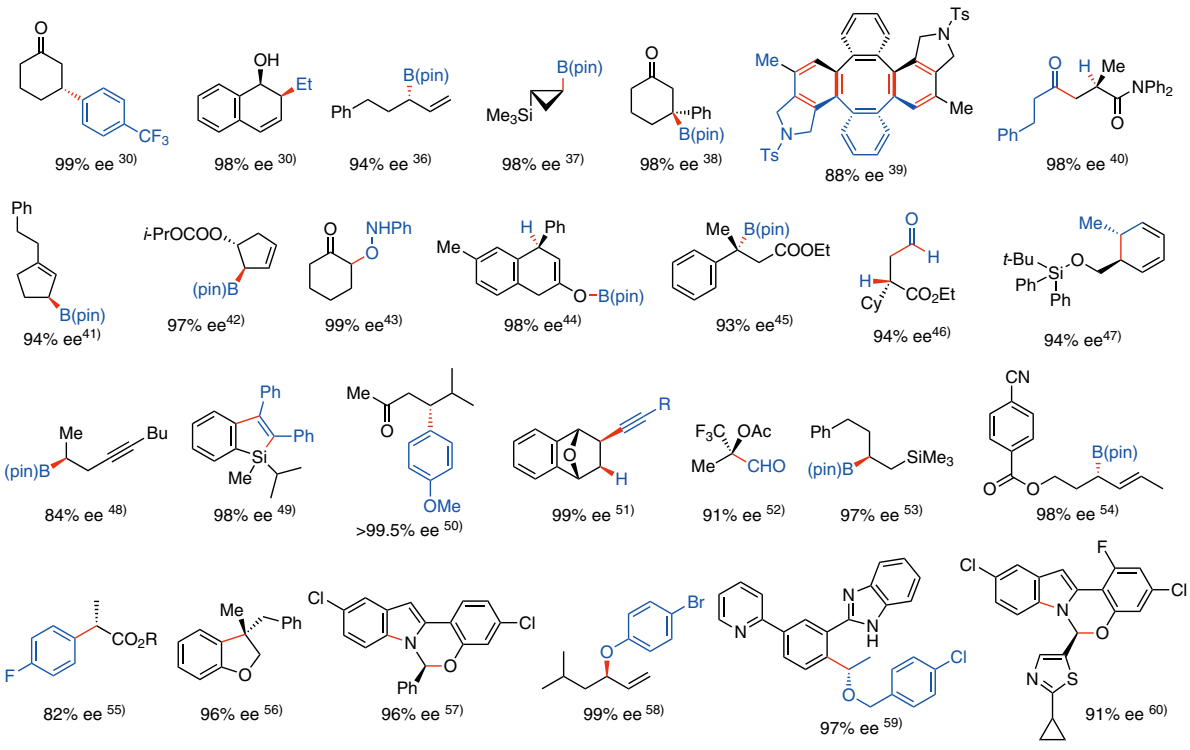


Figure 9. Asymmetric carbon–carbon and carbon–heteroatom bond-forming reactions catalyzed by metal complexes of QuinoxP* or BenzP*

6. Mechanistic Study on Rhodium-Catalyzed Asymmetric Hydrogenation

Rhodium-catalyzed asymmetric hydrogenation of enamides and related substrates is representative of transition-metal-catalyzed asymmetric reactions, and its reaction mechanism (including the catalytic cycle and origin of enantioselectivity) has been investigated extensively. Early studies using C_2 symmetric phosphine ligands DIPAMP and CHIRAPHOS containing two aryl groups at each phosphorus atom led to the so-called "alkene mechanism (alkene-first mechanism)" appearing in textbooks and presented in lectures on organometallic chemistry.[61,62] This mechanism, proposed by Halpern, is based on the following experimental facts and considerations (Scheme 15).

1. The rhodium(I) solvated complex generated from the catalyst precursor by hydrogenation reacts with a prochiral substrate to form two diastereomer alkene complexes (rhodium complexes coordinated with the alkene moiety and amide oxygen atom) in a high diastereomer ratio. For example, Rh-(*S*,*S*)-DIPAMP solvated complex reacts with methyl α-acetamidocinnamate (MAC) to give the corresponding alkene complexes in *ca*. 10:1 ratio.
2. In reactions of these alkene complexes with H_2, the coordination stereochemistry of the alkene complex at relatively greater concentration does not correspond to the chirality of the hydrogenation product. Thus, the chirality of the product does not correspond to the structure of the major alkene complex, but to that of the minor alkene complex, if it is assumed that the oxidative addition of H_2 in an endo-manner and the stereochemical integrity is maintained through to the migratory insertion and final reductive elimination step.
3. The minor alkene complex is much more reactive toward H_2 than is the major complex. For example, for the Rh-DIPAMP-MAC alkene complex, the minor diastereomer reacts 570 times faster than that of the major diastereomer to give the hydrogenation product in *R*:*S* = 98:2 (96% ee).
4. Interconversion between major and minor complexes occurrs very rapidly at room temperature, and the more reactive alkene complex reacts more rapidly with H_2 to yield the product.
5. Oxidative addition of H_2 to the Rh-alkene complex is the rate-determining step of hydrogenation and the enantioselection step.
6. When using the DIPAMP-Rh complex, enantioselectivity decreases significantly at lower temperatures. This temperature effect is considered to be due to the slower interconversion between both alkene complexes. The enantioselectivity is decreased remarkably at higher H_2 pressure as well. This effect can be understood by considering that the increase in H_2 concentration enhances oxidative addition of the major diastereomer to increase the amount of the corresponding hydrogenation product.

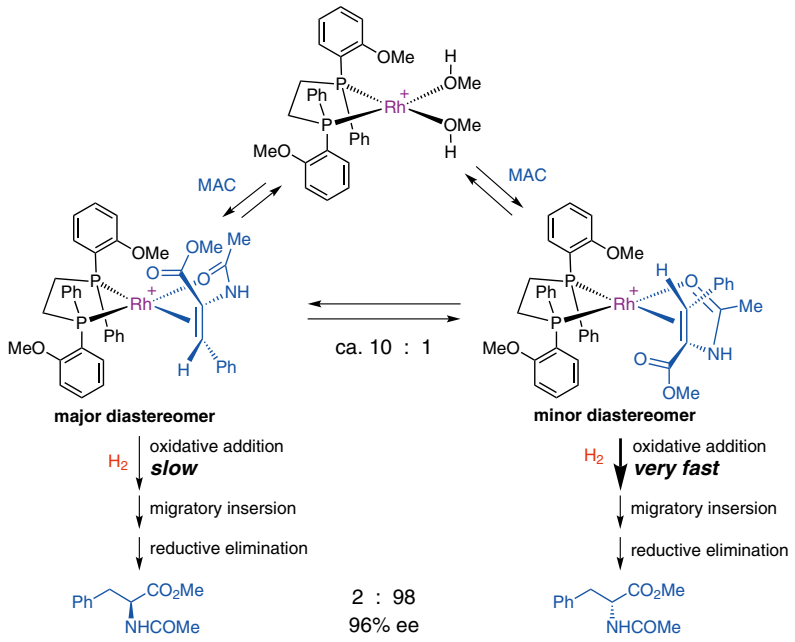
The mechanism proposed by Halpern is entirely different from the "lock-and-key" mechanism often used to explain the high stereoselectivity in enzyme reactions. The mechanism is due mainly to the relative instability and so greater reactivity of the minor diastereomer compared to that of the major diastereomer. While this explanation has been described previously and can be intuitively understood, the major/minor explanation does not appear to explain the phenomenon. Thus, it can be understood that the undetectable intermediate exhibits very high reactivity, but its stereochemistry does not always correspond to the product chirality. By chance, the stereochemistry of the minor diastereomer can match the product chirality, or can have the opposite relation depending on the ligand and substrate used, and the reaction conditions. Several studies in which the stereochemistry of the major diastereomer corresponded to the product chirality have been reported.

We synthesized P-chirogenic bis(trialkylphosphine) ligands and found a surprisingly high degree of enantioinduction ability, and also were interested in the mechanism, especially the origin of the enantioselectivity. However, our attempts to explain the results using known empirical rules and mechanisms were unsuccessful.

Then, Dr. Ilya Gridnev, an enthusiastic researcher with both experiment-precedence and thought-precedence experience, joined our research group. He was very strong in physical chemistry and developed this research using NMR analysis and DFT calculations.

We conducted a mechanistic study using rhodium cation complexes of *t*-Bu-BisP*, *t*-Bu-MiniPHOS, Trichickenfootphos (TCFP), and BenzP*. α- And β-dehydroamino acid esters, enamides, and α,β-unsaturated phosphonic acid esters were used as prochiral alkene substrates. New experimental data were obtained through these studies, which led to a new proposed mechanism.[63–65]

The initial study was conducted with NMR experiments using [Rh((*S*,*S*)-*t*-Bu-BisP*)(nbd)]BF_4 (**32**) and MAC. The results are shown in Scheme 16. The precatalyst **32** reacted



Scheme 15. Alkene mechanism (Alkene-first mechanism) of Rh-catalyzed asymmetric hydrogenation

with H_2 to give solvated complex **33** that reacted with H_2 at low temperatures to generate equilibrium amounts (*ca*. 20% at –95 °C) of **34a** and **34b**, the first observable dihydrides of Rh(I) with a bisphosphine ligand. Compound **33** was a cationic complex, but the electron density at the rhodium metal was increased by the electron-rich ligand and underwent oxidative addition of H_2 to generate the dihydride species. The dihydrides **34a** and **34b** reacted immediately with the substrate MAC, even at –90 °C to give monohydride complex **38**. This reaction was suspected to proceed *via* **35**, **36**, and **37**. Thus, the amide oxygen atom coordinated to the Rh metal at the position *trans* to the hydrogen atom to form non-chelated complex **35**; subsequently, the alkene coordinates to generate **36**. This hexacoordinated Rh(III) dihydride complex was extremely unstable and immediately underwent migratory insertion of the C=C double bond to the Rh–H bond to form monohydride complex **37**, which then isomerized to **38**. At –50 °C, the monohydride complex **38** underwent reductive elimination leading to **33** and hydrogenation product **39*R*** (99% ee).

In contrast, solvated complex **33** reacted with MAC to afford Rh-alkene complexes **40** and **40'** in a ratio of *ca*. 10:1. These alkene complexes reacted with H_2 (2 atm) at –80 °C for 1 h to give **38**, which was converted into **39*R*** (97% ee) at –50 °C. The absolute configuration of product **39** was *R*, corresponding to the structure of the minor diastereomer **40'**. It appeared that stereoselection followed the Halpern mechanism. However, this transformation proceeded at higher temperatures and for longer reaction times compared with reaction of the dihydride complexes **34a** and **34b** with MAC. Therefore, it is rather reasonable to consider that the alkene complexes **40** and **40'** are not directly subjected to hydrogenation, but dissociate to **33** and then are converted to **38** *via* the dihydride pathway.

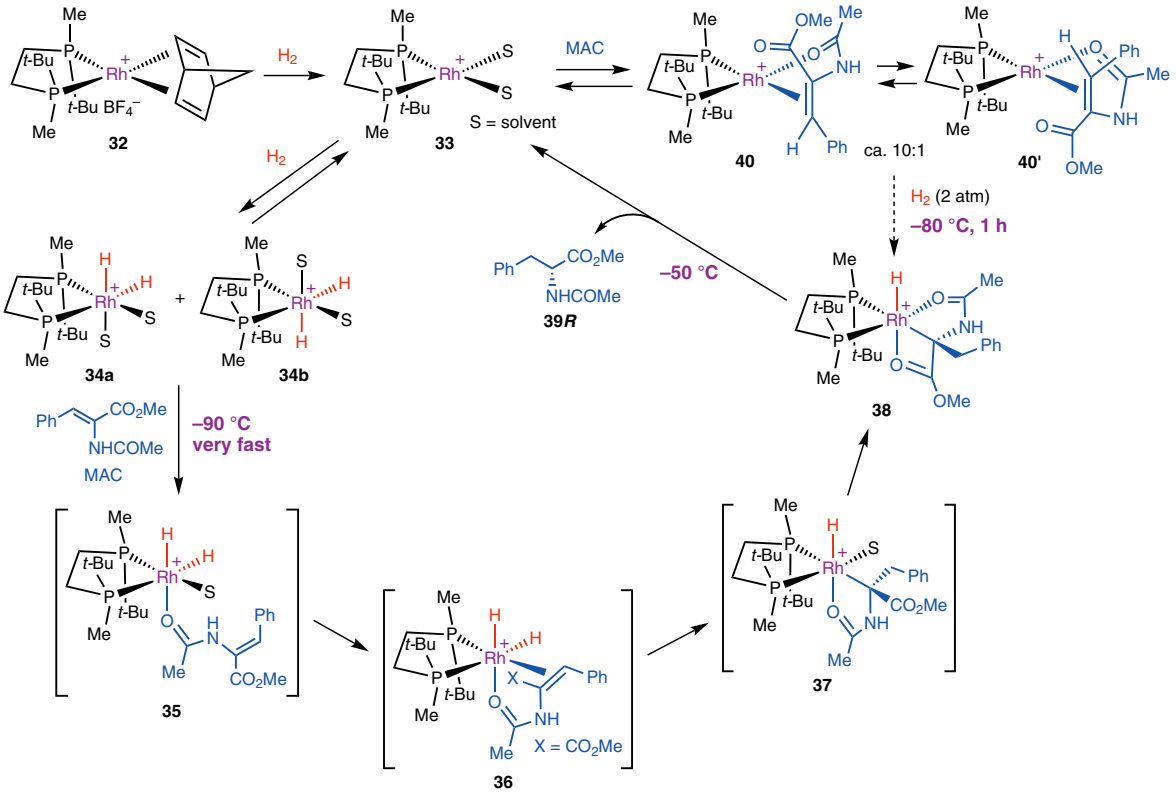
The enantioselection may be determined upon formation of hexacoordinated Rh(III) dihydride complex **36**. Among total eight possible isomers of **36**, only **36** satisfies the following conditions:

1. A chelate ring is formed, avoiding steric repulsion with the bulky *t*-butyl group of the ligand.
2. The C=C double bond undergoes migratory insertion to the Rh–H bond trans to the Rh–P bond.
3. The α-carbon of the ester binds to the Rh atom during the migratory insertion.

Scheme 17 shows the pathways from **34a** and **34b** to **39*R*** and **39*S***, respectively. Associated complex **36** satisfies all three above-mentioned conditions. In contrast, complex **36'** satisfies 2 and 3, but not 1. Therefore, the reaction must proceed through **36**, resulting in formation of **39*R***.

The origin of the greater than 99.5% enantioselectivity can be explained by cooperative interaction of multiple factors for lowering the transition state energy. The enantioselection mechanism is similar to that of enzyme reactions, despite the small size of the catalyst molecule (rhodium complexes of *t*-Bu-BisP* and *t*-Bu-MiniPHOS are not macromolecules, but asymmetric molecular catalysts). In addition, the relationship between the structure of the catalyst and product chirality can be reasonably explained by considering the transition state structure that forms the associated complex **36**.

Studies on the alkene complexes produced from Rh-solvated complexes and enamide substrates with various combinations of phosphine ligands and substrates showed no distinct relationships between the concentration ratio (major/minor ratio) of the alkene complexes and the chirality of the product. The ratios ranged from very large to almost 1:1, and in some cases no alkene complexes were detected. Very high enantioselectivity (greater than 99%) was observed depending on the substrate and ligand. For example, methyl

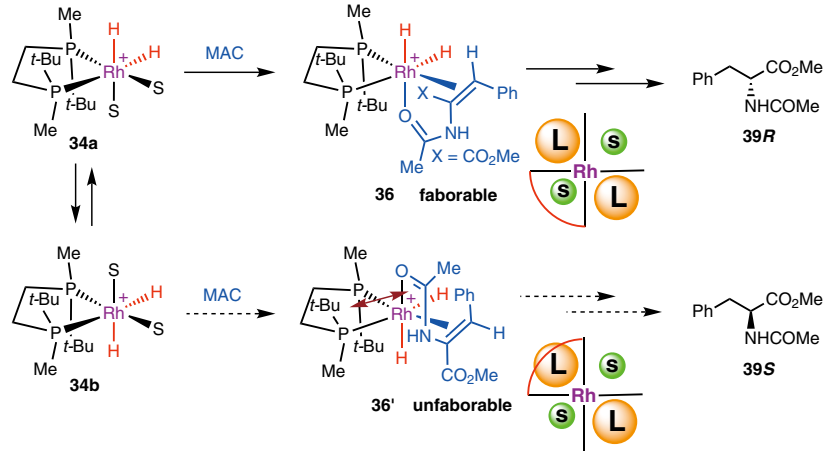


Scheme 16. Plausible reaction mechanism of asymmetric hydrogenation of MAC with [Rh((*S*,*S*)-*t*-Bu-BisP*)(nbd)]BF_4

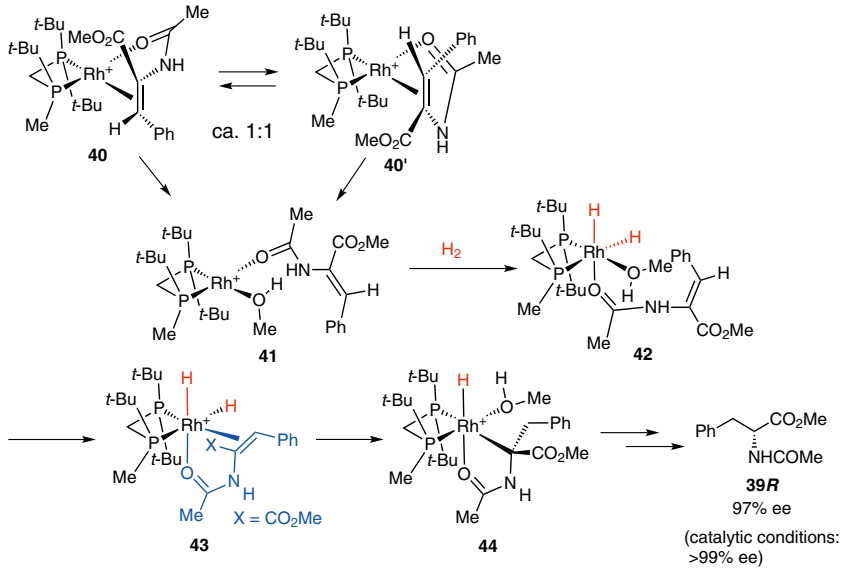
(*E*)-3-acetamido-2-butenoate did not bind to the Rh-solvated complex of Trichickenfootphos (TCFP) or BenzP* ligand, but hydrogenation of this substrate proceeded in >99% enantioselectivity.[63l] We also found that the reaction of the major diastereomer was more reactive than that of the minor one, but the product chirality was directly related to the structure of the minor one.[63m]

Scheme 18 shows reactions of Rh-alkene complexes at a ratio of about 1:1 with H_2. The TCFP ligand is C_1 symmetric and hence four diastereomers of its Rh-alkene complexes are possible. The Rh-TCFP solvated complex reacted with MAC to generate four diastereomers, but two were unstable and were converted into the thermodynamically stable isomers **40** and **40'** in a ratio of approximately 1:1. After reaction of these diastereomers with H_2 at −78 °C, both diastereomers led to the same *R* configuration product. Further studies involving detection of the intermediates by NMR and DFT calculations indicated that the reaction proceeded *via* the pathway shown in Scheme 18. Thus, **40** and **40'** did not react with H_2 directly, but were converted to the same intermediate **41** *via* dissociation of the alkene moiety. This intermediate **41** underwent oxidative addition with H_2 to give dihydride complex **42**, which then formed hexacoordinated dihydride complex **43** by intramolecular coordination of the C=C double bond to the rhodium atom. This complex is very unstable and underwent migratory insertion, leading to **44** followed by formation of **39*R***. Enantioselection is considered to be determined at the step to form **43**. Thus, like complex **36**, complex **43** is in the lowest energy state compared with other possible diastereomers and reaction proceeds *via* **43** to provide excellent enantioselectivity.[63j]

In addition to the examples mentioned, the mechanism of Rh-catalyzed asymmetric hydrogenation of many prochiral substrates bearing a coordinative functional group were also examined. The resulting high enantioselectivity and stereochemical outcome (*R* or *S*) were reasonably explained by considering the dihydride pathway. In addition, chirality of the product can be predicted by considering the mechanism. Furthermore, the mechanism proposed is useful for the design of more efficient chiral ligands and catalysts. More details have been described in original papers,[63] accounts,[64] and a book.[65]



Scheme 17. Enantioselection-determining step of Rh-catalyzed asymmetric hydrogenation of MAC



Scheme 18. Reaction of [Rh((*R*)-TCFP)]–MAC complexes with H_2

7. Closing Remarks

While nine years have passed since my retirement from Chiba University, I continue to study organic synthesis at Nippon Chemical Industrial Company. Thus, I understand the importance of direct observation in synthetic organic chemistry and am happy to have had the opportunity to devote my time to organic chemistry research for many years. I owe a great debt to Professor Mukaiyama, who directly mentored me and taught his methodology and philosophy.

Tokyo Chemical Industry generously gave me the opportunity to write this paper. I have described not only the synthesis and application of P-chirogenic phosphine ligands but also related research subjects. I have emphasized my approach to finding useful research subjects, performing the research, and obtaining informative results. I also have described situations that caused doubt about my ability to move forward and my tactics for overcoming obstacles. I hope this paper will be helpful for readers, especially young researchers and students.

Acknowlegments

The work described in this paper has been carried out at Chiba University and Nippon Chemical Industrial Co., Ltd., where many coworkers engaged in these studies. I deeply thank all enthusiastic collaborators, whose names are listed in the literatures cited below. My wife, Sachie, has strongly supported and encouraged me for long years, and I wish to express my sincere appreciation to her.

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Intoduction of the author:

Tsuneo Imamoto
Professor Emeritus, Chiba University, Ph.D.

Tsuneo Imamoto was born in 1942 in Shizuoka Prefecture, Japan. He received his Bachelor degree in chemistry from Shizuoka University. Curiosity and a scholarship brought him to Osaka University, where he studied physical organic chemistry under the direction of Professor Yasuhide Yukawa, obtaining his Ph.D. in 1972. After one year postdoctoral work with Professor Teruaki Mukaiyama at Tokyo Institute of Technology, he was appointed an assistant professor of Osaka University. In 1975 he moved to Wayne State University, Detroit, where he studied organophosphorus chemistry as a postdoctoral fellow under Professor Carl R. Johnson. In 1978 he joined the research group of Professor Mukaiyama at the University of Tokyo as a research student and in 1980 he moved to Chiba University as an assistant professor. He was promoted to Associate Professor in 1987 and Professor in 1993, and in 2008 he retired from Chiba University. Currently, he is a Professor Emeritus and a Grand Fellow of Chiba University, a Research Consultant of Nippon Chemical Industrial Co., Ltd., and a Visiting Professor of Shanghai Jiao Tong University. His research interests are in the areas of synthetic methodology, organoelement chemistry, asymmetric catalysis, organic reaction mechanism, and process chemistry. He received the Synthetic Organic Chemistry Award (Academic Division), Japan (1997), the Rare Earth Society Award, Japan (2001), the Prize for Science and Technology by the Ministry of Education, Culture, Sports, Science and Technology (2008), and the Synthetic Organic Chemistry Award (Technology Division), Japan (2013).
[E-mail] imamoto@faculty.chiba-u.jp

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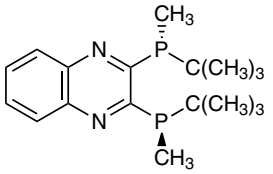

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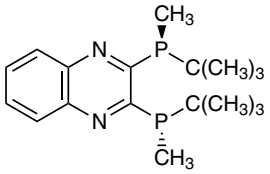

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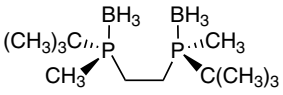

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B5301	(*R*,*R*)-QuinoxP*			100mg
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B2089	(*S*,*S*)-1,2-Bis[(*tert*-butyl)methylphosphino]ethane Bis(borane)			100mg
B3035	(*R*,*R*)-DIPAMP			100mg
B3036	(*S*,*S*)-DIPAMP		100mg	1g
B1112	(+)-DIOP			1g
B1113	(-)-DIOP			1g
D2537	(*R*)-(*S*)-BPPFA			100mg
D2538	(*S*)-(*R*)-BPPFA			100mg
B3449	(2*R*,3*R*)-(-)-Norphos			100mg
B3450	(2*S*,3*S*)-(+)-Norphos			100mg
B1406	(*R*)-(+)-BINAP	1g	5g	25g
B1405	(*S*)-(-)-BINAP		1g	5g
T3152	(*R*)-(+)-TolBINAP		1g	5g
T3153	(*S*)-(-)-TolBINAP		1g	5g
X0070	(*R*)-(+)-XylBINAP		200mg	1g
X0071	(*S*)-(-)-XylBINAP		200mg	1g
S0930	(*R*)-(+)-SEGPHOS®		200mg	1g
S0929	(*S*)-(-)-SEGPHOS®		200mg	1g
D4499	(*R*)-(+)-DM-SEGPHOS®		200mg	1g
D4498	(*S*)-(-)-DM-SEGPHOS®		200mg	1g
D4501	(*R*)-(-)-DTBM-SEGPHOS®		200mg	1g
D4500	(*S*)-(+)-DTBM-SEGPHOS®		200mg	1g
B2091	$[Rh(nbd)_2]BF_4$ (= Bis[η-(2,5-norbornadiene)]rhodium(I) Tetrafluoroborate)		100mg	1g
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S0461	(-)-Sparteine		1g	5g