Recent Advances of BINAP Chemistry in the Industrial Aspects

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Abstract: New efficient synthetic methods of optically active BINAP [BINAP = 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl] and its variants are described. Application of these BINAP variants in asymmetric catalytic hydrogenation of prochiral ketones and olefins to various industrially important compounds is discussed.

Key words: BINAP ligands, ruthenium and iridium catalysts, asymmetric hydrogenation, ketones, unsaturated carboxylic acids

Introduction

Enantioselective syntheses have been gaining more and more importance in a wide range of fields such as pharmaceuticals, agrochemicals, food additives, aromachemicals and functional materials because the biological activities of these materials are often associated with their absolute configuration.

Known methods to obtain enantiomerically pure compounds are classified as follows: 1) optical resolution, 2) modification of naturally occurring materials, 3) biological transformation, and 4) asymmetric catalysis using a prochiral compound as the starting material. Among these methods, asymmetric catalysis is emerging as one of the most efficient and versatile methods for the preparation of a wide range of chiral target molecules. In recent years, numerous catalytic asymmetric reaction processes that transform prochiral substrates into chiral products with high enantioselectivity have been developed.[1] Asymmetric hydrogenation is one of the most powerful tools for the synthesis of enantiomerically pure compounds. For this purpose, several kinds of metal–optically active phosphine complexes have been synthesized so far. In general, a chiral transition metal catalyst precursor L_nM can be regarded as composed of two key parts, the chiral ligand L and the central metal M. Thus, the proper combination of well-designed chiral ligands and selected metals is the most important requirement for high catalytic efficiency. Over the past twenty-five years, various kinds of chiral phosphines have been developed by researchers in academic, pharmaceutical and fine chemical companies. Among them, 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl[2] (BINAP) has been found to have remarkable chiral recognition ability and broad applicability in various transition metal-catalyzed asymmetric reactions such as hydrogenation,[3] hydrosilylation,[4] 1,3-hydrogen migration,[5] etc. For example, BINAP–ruthenium catalysts are well recognized to be highly efficient catalysts for asymmetric hydrogenations of various functionalized olefins and ketones such as α-(acylamino)acrylic acids,[6] enamides,[7] α,β-unsaturated carboxylic acids,[8] allylic and homoallylic alcohols,[9] alkylidene lactones,[10] alkenyl ethers,[10] β-keto esters,[11] β-hydroxyketones,[12] and β-aminoketones.[12]

Starting with the development of *l*-menthol process using BINAP–Rh catalyzed asymmetric isomerization of allylamines,[5a] we have been investigating catalytic asymmetric synthesis mainly based on BINAP chemistry for two decades and have developed various asymmetric synthetic processes. All of these results are based on the success of the marvelous abilities of the BINAP ligands. Recently the targets of asymmetric synthesis have become varied and complicated, while BINAP sometimes shows its limitation. It becomes necessary to develop new ligands to compensate for the limitations of BINAP. In this paper we described recent developments of BINAP chemistry, especially about syntheses and applications of new BINAP ligands from the industrial point of view.

New Synthetic Methods of BINAP and Its Variants

Since the practical methods for synthesis of 2,2'-bis(diarylphosphino)-1,1'-binaphthyls (BINAPs) were reported in 1986,[13] a series of BINAP analogues have been prepared. However, this route requires harsh conditions for the conversion of binaphthol to the corresponding dibromide and tedious optical resolution of BINAP derivatives (Scheme 1).

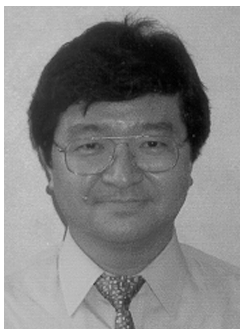
Recently, Cai et al. of Merck developed a new method for direct asymmetric synthesis of BINAP by use of nickel-catalyzed coupling reaction of easily accessible chiral 2,2'-bis((trifluoromethanesulfonyl)oxy)-1,1'-binaphthyl (**1**) with diphenylphosphine in the presence of DABCO (Scheme 2).[14] Similarly, Laneman et al. of Monsanto reported the nickel-catalyzed cross-coupling of **1** with chlorodiphenylphosphine in the presence of zinc.[15] These methods, however, have some drawbacks in industrialization, such as use of pyrophoric diphenylphosphine or moisture-sensitive chlorodiphenylphosphine.

On the other hand, we have explored two unique procedures for the synthesis of chiral BINAPs by using the metal-catalyzed coupling reaction of **1** with diarylphosphine oxides, which are readily prepared by the reaction of arylmagnesium halide with diethyl phosphite and easy to handle in large quantity.[16] The first one is well illustrated by coupling of (*R*)-**1** with diphenylphosphine oxide, which

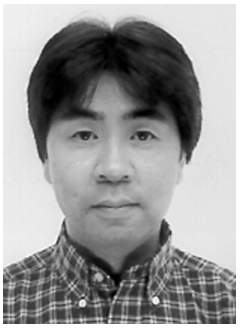
Biographical Sketches

Hidenori Kumobayashi was born in Niigata, Japan. In 1967 he obtained a B.S. degree from Shinsyu University and joined Takasago International Corporation. In 1986 he earned his Ph. D. from Osaka University under the direction of Prof. Sei Otsuka where he worked on development of industrial synthetic process of *l*-menthol with enantioselective isomerization of allylamines catalyzed by BINAP—Rh(I) complexes as the key reaction. This was followed by studies on efficient synthesis of key intermediates of carbapenem antibiotics by using BINAP—Ru(II)-catalyzed asymmetric hydrogenation of ketone compounds. In 1997 he received the Chemical Society of Japan Award for Technical Development. He is now a vice president at Takasago International Corporation and the general manager of Fine Chemical Devision. His main research interests include asymmetric synthesis using transition metal catalysts.

Takashi Miura obtained a Ph.D. from Tokyo Metropolitan University in 1979 under the guidance of Prof. Michio Kobayashi. He pursued postdoctoral research on the 2,3-sigmatropic rearrangement of sulfonium salts and selenonium salts with Prof. Paul G. Gassman at University of Minnesota from 1979 to 1981. In 1982 he joined Takasago International Corporation and is now general manager at Fine & Aroma Chemical Laboratory in Central Research Laboratory of Takasago International Corporation. Like his collaborator, he is convinced that asymmetric catalysis offers many attractive options for organic chemist and industry.

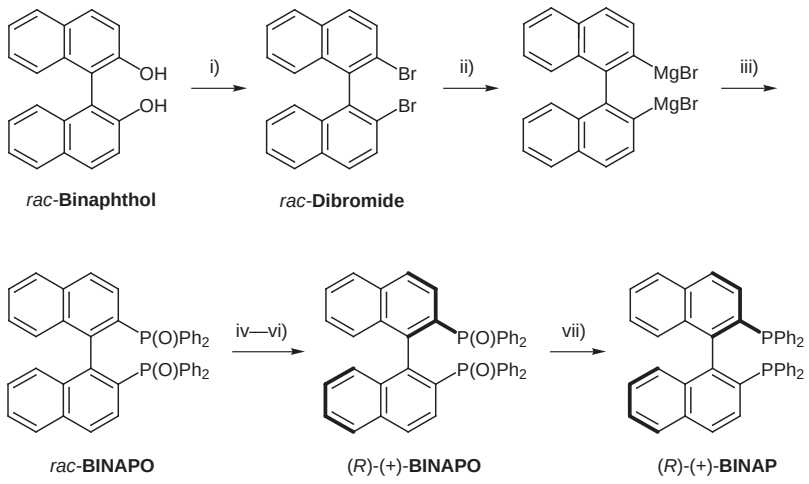


Noboru Sayo, born in Hyogo, Japan, in 1954, studied applied chemistry at Shinsyu University, and obtained his M. S. degree in applied chemistry from Okayama University in 1979. He moved to Tokyo Institute of Technology to join the Professor Nakai's research group and worked in the field of carbanion chemistry. After obtaining his Ph.D. in 1984, he entered Takasago International Corporation. Now he is assistant director at Fine & Aroma Chemical Laboratory in Central Research Laboratory of Takasago International Corporation. His main research interests have been associated with the development of catalytic asymmetric synthesis.

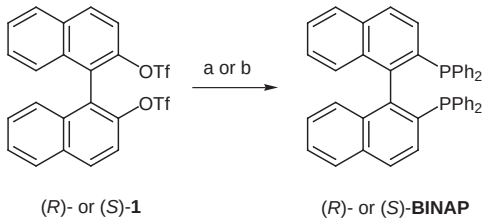


Takao Saito was born in Ibaraki (Japan) in 1960. He obtained his M.S. degree from Meiji College of Pharmacy in 1985 and then joined Takasago International Corporation. He received his Ph. D. from Osaka University under supervision of Prof. Shun-ichi Murahashi in 1996 and is now research associate at Fine & Aroma Chemical Laboratory in Central Research Laboratory of Takasago International Corporation. His current area of research includes the development of new molecular catalysts.

Xiaoyong Zhang was born in Zhejiang, China and received his M.S. degree in organic chemistry at Institute of Chemistry, Chinese Academy of Sciences in 1987. He earned his Ph.D. from Kyoto University under supervision of the late Prof. Hidemasa Takaya in 1994 and then joined Takasago International Corporation where he is now a senior chemist at Fine & Aroma Chemical Laboratory in Central Research Laboratory. He is pursuing exploration of new efficient synthetic methods of chiral ligands and their application to asymmetric catalysis.



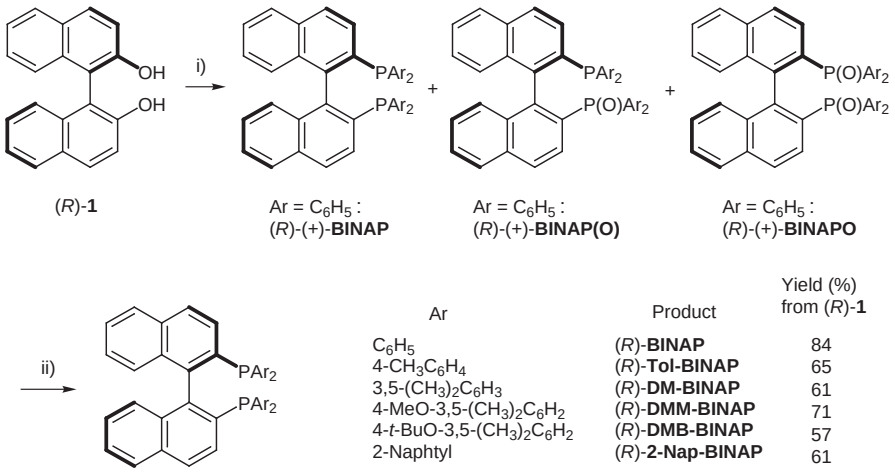
Scheme 1 i) Br_2, PPh_3, 230 °C; ii) Mg; iii) $Ph_2P(O)Cl$; iv) (2*R*,3*R*)-(−)-di-*O*-benzoyltartaric acid; v) fractional crystallization; vi) NaOH; vii) Cl_3SiH, $PhNMe_2$.



Scheme 2 a) Ph_2PH, $NiCl_2$(dppe) / 75% yield (Merck); b) Ph_2PCl, $NiCl_2$(dppe), Zn / 52% yield (Monsanto).

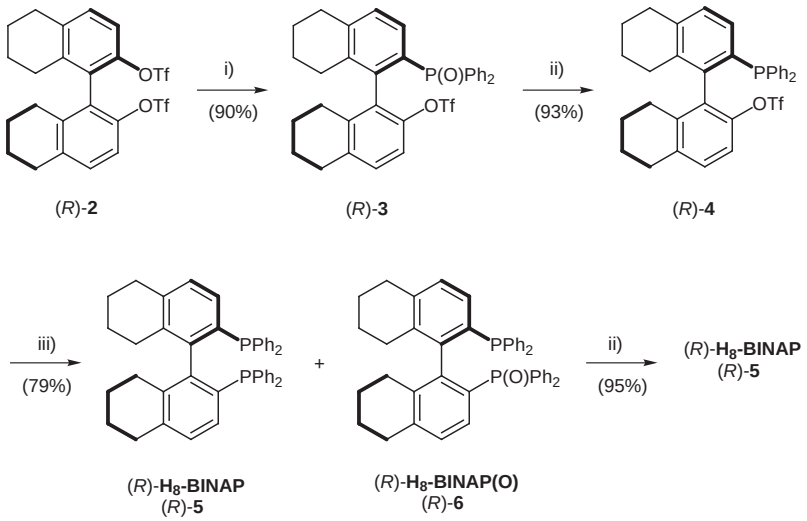
proceeded smoothly in the presence of 1,2-bis(diphenylphosphino)ethane (dppe) and nickel (II) chloride to give a mixture of (*R*)-BINAP, (*R*)-BINAP(O) and (*R*)-BINAPO in a ratio of 35.4: 60.8: 3.7 in 87% combined yield (Scheme 3). This mixture was then reduced by a mixture of trichlorosilane and *N*,*N*-dimethylaniline in refluxing toluene, giving (*R*)-BINAP in 96% yield. This procedure has been successfully applied to the synthesis of a series of known or new chiral BINAP ligands in reasonable to good yields. It is noteworthy that most of these new BINAPs had been difficult to obtain through the optical resolution route shown in Scheme 1.

However, when (*R*)-2,2'-bis((trifluoromethanesulfonyl)oxy)-5,5',6,6',7,7',8,8'-octahydro-1,1'-binaphthyl [(*R*)-**2**] was subjected to the phosphinylation with diphenylphoshine oxide in the presence of nickel catalyst, no coupling reaction occured. Hayashi et al. reported that monophosphinylation of (*S*)-**1** with diphenylphosphine oxide in the presence of catalytic amount of palladium diacetate and 1,2-bis(diphenylphosphino)butane (dppb) in DMSO at 100 °C gave 2-(diphenylphosphino)-2'-((trifluoromethanesulfonyl)oxy)-1,1'-binaphthyl.[17] As presented in Scheme 4, monophosphinylation of (*R*)-**2** with diphenylphosphine oxide under Hayashi's conditions proceeded smoothly to afford (*R*)-2-(diphenylphosphinyl)-2-



Ar	Product	Yield (%) from (*R*)-**1**
C_6H_5	(*R*)-**BINAP**	84
4-$CH_3C_6H_4$	(*R*)-**Tol-BINAP**	65
3,5-$(CH_3)_2C_6H_3$	(*R*)-**DM-BINAP**	61
4-MeO-3,5-$(CH_3)_2C_6H_2$	(*R*)-**DMM-BINAP**	71
4-*t*-BuO-3,5-$(CH_3)_2C_6H_2$	(*R*)-**DMB-BINAP**	57
2-Naphtyl	(*R*)-**2-Nap-BINAP**	61

Scheme 3 i) $Ar_2P(O)H$, $NiCl_2$(dppe); ii) Cl_3SiH, $PhNMe_2$.



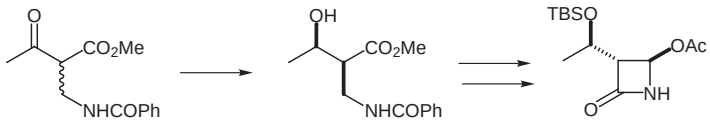
Scheme 4 i) $Ph_2P(O)H$, $Pd(OAc)_2$–dppp, i-Pr_2NEt/DMSO; ii) Cl_3SiH, $PhNMe_2$; iii) $Ph_2P(O)H$, $NiCl_2$(dppe), DABCO.

[(trifluoromethanesulfonyl)oxy]-5,5',6,6',7,7',8,8'-octahydro-1,1'-binaphthyl [*R*-**3**] in 90% yield. As (*R*)-**3** did not react with diphenylphosphine oxide in the presence of nickel catalyst, it was reduced with trichlorosilane-*N*,*N*-dimethylaniline to 2-(diphenylphosphino)-2-[(trifluoromethanesulfonyl)oxy]-5,5',6,6',7,7',8,8'-octahydro-1,1'-binaphthyl [(*R*)-**4**] in 93% yield. Subsequent nickel-catalyzed coupling reaction of (*R*)-**4** with diphenylphosphine oxide gave a mixture of 2,2'-bis(diphenylphosphino)-5,5',6,6',7,7',8,8'-octahydro-1,1'-binaphthyl [(*R*)-H_8-BINAP, (*R*)-**5**][18] and its monooxide H_8-BINAP(O) [(*R*)-**6**] in 79% yield. Reduction of (*R*)-**6** with trichlorosilane–*N*,*N*-dimethylaniline afforded (*R*)-**5** in 95% yield (Scheme 4).

Among the above easily prepared BINAP variants, 2,2'-bis(di(3,5-dimethylphenyl)phosphino)-1,1'-binaphthyl (DM-BINAP) acts as a very efficient ligand for enantio- and diastereoselective hydrogenation of 2-substituted cyclic ketones and enantioselective hydrogenation of unfunctionalized ketones with BINAP–Ru(II)–chiral diamine–base catalytic system. On the other hand, H_8-BINAP shows excellent enantioselectivities in Ru(II)-catalyzed asymmetric hydrogenation of olefinic compounds such as α,β-unsaturated carboxylic acids and allyl alcohols.

DM-BINAP

Enantioselective hydrogenation of functionalized ketones with BINAP–Ru(II) complex catalysts into optically active secondary alcohols have been extensively studied and industrial processes for the synthesis of key intermediates of antibiotic carbapenems and antibacterial Levofloxacin have been established. On the other hand, though it has been reported that asymmetric hydrogenation of 2-chloroacetophenone with BINAP–Ru(II) catalysts gives the corresponding secondary alcohol in high enantioselectivity,[19] simple ketones that lack heteroatoms anchoring the Ru atom have not been hydrogenated with BINAP–Ru(II) catalysts. Recently, Noyori and co-workers reported that a BINAP–Ru–chiral diamine–inorganic base combined catalyst system acts as a very efficient catalyst for asymmetric hydrogenation of unfunctionalized simple ketones such as acetophenones, benzophenones, hetero-aromatic ketones, and alkenyl and cyclopropyl ketones.[20] In asymmetric hydrogenation of unfunctionalized ketones catalyzed by this BINAP–Ru(II)–chiral diamine–inorganic base system, the use of DM-BINAP as a chiral phosphine not only increases the enantioselectivity but also expands the scope of the substrates hydrogenated with high enantioselectivity. For instance, the hydrogenation of acetophenone in 2-propanol containing *trans*-$RuCl_2$[(*S*)-tol-binap][(*S*,*S*)-dpen] (DPEN = 1,2-diphenylethylenediamine) and *t*-BuOK with S/C = 2,400,000 afforded (*R*)-1-phenylethanol in 80% ee and in 100% yield.[20d] In contrast, hydrogenation of acetophenone in 2-propanol containing *trans*-$RuCl_2$[(*S*)-dm-binap][(*S*,*S*)-dpen] with S/C = 2000 or *trans*-$RuCl_2$[(*S*)-dm-binap][*(S)*-daipen] (DAIPEN = 1,1-di(4-anisyl)-2-isopropyl-1,2-ethylene-diamine) with S/C = 100,000 gave (*R*)-1-phenylethanol in 99% ee and almost quantitative yield.[18e] The acetate of (*R*)-1-phenylethanol thus obtained is now produced as a fragrance material which has clean floral, fresh green note like Gardenia. On the other hand, the acetate of (*S*)-1-phenylethanol has metallic green note and is not favorable as a fragrance material. Hydrogenation of benzophenones using the BINAP–Ru(II)–chiral diamine–inorganic base system also proceeds smoothly to afford the corresponding chiral benzhydrols with high enantioselectivities. In this case, it was found that the enantioselectivity is markedly influenced by the structure of chiral phosphine ligands. For instance, hydrogenation of 2-methoxybenzophenone (**7**) using Ru_2Cl_4[*(S)*-binap]$_2$•NEt_3–(*S*,*S*)-DPEN or Ru_2Cl_4[(*S*)-tol-binap]$_2$•NEt_3–



(±)-**9** *syn*-(2*S*,3*R*)-**10** **11**

Scheme 5

(*S*,*S*)-DPEN in 2-propanol/THF (3/1) containing *t*-BuOK afforded (*S*)-2-methoxybenzhydrol [(*S*)-**8**] in 23.7% ee and 25.7% ee, respectively. By contrast, the use of Ru_2Cl_4[(*S*)-dm-binap]$_2$•NEt_3 resulted in (*S*)-**8** in 72.8% ee, and even higher ee (89%) was achieved by use of the {RuI(*p*-cymene)[(*S*)-dm-binap]}I–(*S*,*S*)-DPEN system (Table 1). In the year 2000, Noyori and co-workers reported selective hydrogenation of benzophenones to benzhydrols using a BINAP–Ru(II)−chiral diamine complex. In their report, 2-methoxybenzophenone was successfully hydrogenated with *trans*-$RuCl_2$[(*S*)-dm-binap][(*S*)-daipen] in the presence of $KOC(CH_3)_3$ to give (*S*)-**8** in 99% ee and quantitative yield.[20f] Asymmetric hydrogenation of a variety of benzophenone derivatives, heteroaromatic[20g] and alkenyl ketones[20e] with a DM-BINAP–Ru(II)–chiral diamine complex proceeds smoothly with a substrate to catalyst ratio of 1,000−40,000 to chiral alcohols with high ee and high yield.

7 (*S*)-**8**

Table 1 Asymmetric Hydrogenation of 2-Methoxybenzophenone (**7**)[a]

Ru-cat.	diamine	% ee
Ru_2Cl_4[(*S*)-binap]$_2$•NEt_3	(*S*,*S*)-DPEN	23.7
Ru_2Cl_4[(*S*)-tol-binap]$_2$•NEt_3	(*S*,*S*)-DPEN	25.7
Ru_2Cl_4[(*S*)-dm-binap]$_2$•NEt_3	(*S*,*S*)-DPEN	72.8
[RuI(*p*-cymene)((*S*)-dm-binap)] I	(*S*,*S*)-DPEN	89.0
trans-$RuCl_2$[(*S*)-dm-binap][(*S*)-daipen][b]		99.0

[a] Hydrogenation was carried out under an hydrogen pressure of 50 atm at 50 °C (substrate/catalyst = 500 mol/mol). Ru/(*S*,*S*)-DPEN/*t*-BuOK = 1/4/35. [b] Ref. 20f.

Diastereo- and enantioselective hydrogenation of ketones to secondary alcohols is very powerful tool for the synthesis of chiral alcohols having contiguous stereogenic centers. Diastereo- and enantioselective hydrogenation of 2-substituted 3-oxo carboxylic esters was reported in 1989.[21] In the course of our research on asymmetric hydrogenation of various functionalized ketones, we found that DM-BINAP is superior to BINAP in diastereoselective asymmetric hydrogenation of methyl (±)-2-(benzamidomethyl)-3-oxobutanoate [(±)-**9**], giving *syn*-(2*S*,3*R*)-**10** in 91% de (98% ee) and 84% de (97% ee), respectively.[22] This procedure has been successfully applied to the industrial production of a carbapenem key intermediate **11** (Scheme 5) on a scale of 100 tons per year.

However, diastereo- and enantioselective hydrogenation of simple ketones such as 2-substituted cyclohexanones has remained difficult. In 1996, Noyori and co-workers reported that a BINAP–Ru–chiral diamine system acts as very efficient catalyst for diastereo- and enantioselective hydrogenation of cyclic ketones. Hydrogenation of (±)-2-isopropylcyclo-hexanone using $RuCl_2$[(*S*)-binap](dmf)$_n$–(*R*,*R*)-DPEN–KOH ternary system in 2-propanol afforded (1*R*,2*R*)-2-isopropylcyclohexanol in 99.6% de and 93% ee.[20c] The effectiveness of a DM-BINAP–Ru(II) complex as a catalyst in diastereo- and enantioselective hydrogenation of 2-substituted cyclohexanone is well demonstrated in hydrogenation of (±)-2-methoxycyclohexanone [(±)-**12**] to (1*R*,2*S*)-2-methoxycyclohexanol [(1*R*,2*S*)-**13**] (Table 2). [23]

(±)-**12** (1*R*,2*S*)-**13**

Table 2 Asymmetric Hydrogenation of Racemic 2-Methoxycyclohexanone [(±)-**12**][a]

Ru-cat.	% de	% ee
$RuCl_2$[(*S*)-binap] (dmf)$_n$	93	87
Ru_2Cl_4[(*S*)-binap]$_2$•NEt_3	97	92
Ru_2Cl_4[(*S*)-tol-binap]$_2$•NEt_3	95	88
Ru_2Cl_4[(*S*)-dm-binap]$_2$•NEt_3	96	96
Ru_2Cl_4[(*S*)-dm-binap]$_2$•NEt_3[b]	99	99

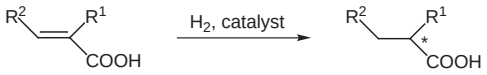
[a] Ru-cat (0.1 mol%), (*S*,*S*)-DPEN (0.2 mol%), and KOH (3.0%) were used. Unless otherwise stated, reactions were carried out at 50 atm of H_2 and 50 °C. [b] Reaction temperature was 5 °C.

As shown in Table 2, asymmetric hydrogenation of (±)-**12** using Ru_2Cl_4[(*S*)-dm-binap]$_2$•NEt_3– (*S*,*S*)-DPEN–KOH ternary system at 50 °C provided (1*R*,2*S*)-**13** in 96% de and 96% ee, while the use of $RuCl_2$[(*S*)-binap](dmf)$_n$ or Ru_2Cl_4[(*S*)-binap]$_2$•NEt_3 afforded (1*R*,2*S*)-**13** in 93% de

(87% ee) and 97% de (92% ee), respectively. In addition, hydrogenation of (±)-**12** with Ru_2Cl_4[*(S)*-dm-binap]$_2$•NEt_3–(*S*,*S*)-DPEN–KOH at lower reaction temperature (5 °C) gave (1*R*,2*S*)-**13** in 99% de and 99% ee, which is an important chiral building block for the synthesis of a tricyclic β-lactam antibiotic, sanfetrinem.[24]

H_8-BINAP

As one of the most prominent asymmetric catalytic reactions, hydrogenation of unsaturated carboxylic acids provides a convenient way to obtain optically active carboxylic acids, which are very important building blocks for the synthesis of new materials such as non-steriodal anti-inflammatory (NSAI)[24] agents and ferroelectric liquid crystals (FLCs).[25] BINAP–Ru(II) complexes, such as the chiral dicarboxylate complex Ru(binap)$(OCOCH_3)_2$ (**14**) and halide complex [RuI(binap)(*p*-cymene)]I (**15**), have been found to catalyze the enantioselective hydrogenation of various α,β-unsaturated carboxylic acids in very high ee's.[8a,22]



18 **19**

	R^1	R^2
a:	CH_3	CH_3
b:	CH_3	C_2H_5
c:	CH_3	n-C_3H_7
d:	C_2H_5	n-C_3H_7
e:	CH_3	C_6H_5

Table 3 Asymmetric Catalytic Hydrogenation of α,β-Disubstituted (*E*)-Acrylic Acids[a,26]

entry	substrate	catalyst	H_2, atm	time, h	% conv	% ee
1	**18a**	(*S*)-**16**	1.5	20	100	97 (*S*)
2	**18a**	(*S*)-**16**	4	15	100	96 (*S*)
3	**18a**	(*R*)-**17**	4	15	94	96 (*R*)
4[8a]	**18a**	(*R*)-**14**	4	12	100	91 (*R*)
5	**18b**	(*S*)-**16**	1.5	24	100	96 (*S*)
6	**18b**	(*R*)-**14**	1.5	24	75	84 (*R*)
7[b]	**18c**	(*S*)-**16**	4	4	59	93 (*S*)
8[b]	**18c**	(*R*)-**14**	4	4	27	79 (*R*)
9	**18d**	(*S*)-**16**	1.5	20	100	95 (*S*)
10	**18d**	(*R*)-**14**	1.5	37	100	88 (*R*)
11	**18e**	(*S*)-**16**	1.5	48	95	89 (*S*)
12	**18e**	(*R*)-**14**	1.5	48	30	30 (*R*)

[a] Hydrogenation was carried out in an autoclave at 10–30 °C in methanol (substrate/catalyst = 197–220 mol/mol, solvent/substrate = 5–50 mL/g) unless otherwise stated, and the chemoselectivity was 100% as given by ^{1}H NMR analysis. [b] At 50 °C in MeOH–H_2O (10:1). Substrate/catalyst = 1016–1074 mol/mol.

Recently Takaya et al. reported that the chiral H_8-BINAP–Ru(II) complexes, Ru(H_8-binap)$(OCOCH_3)_2$ (**16**) and [RuI(H_8-binap)(*p*-cymene)]I (**17**), serve as even more effective catalysts for the asymmetric hydrogenation of α,β- and β,γ-unsaturated carboxylic acids than the BINAP–Ru(II) ones.[26] As shown in Table 3, in the presence of 0.5 mol% of (*S*)-**16** or (*R*)-**17** hydrogenation of tiglic acid (**18a**) proceeded smoothly under mild conditions, affording (*S*)- or (*R*)-2-methylbutanoic acid [(*S*)- or (*R*)-**19a**] in as high as 97% ee (entries 1–3). (*S*)-2-Methylbutanoic acid and its esters are very important in creating fruit flavors (e.g. apple, strawberry, grape). Similarly high ee's (93–96%) have been achieved in hydrogenation of other (*E*)-2-alkyl-2-alkenoic acids **18b**–**d** catalyzed by (*S*)-**16** (entries 5, 7, and 9). On the other hand, use of the BINAP complex (*R*)-**14** as catalyst for **18a**–**d** caused decreases both in ee's by 5–14% and in catalytic activities (entries 4, 6, 8, and 10).[8a] The difference between the Ru(II) complexes of H_8-BINAP and those of BINAP in catalytic efficiency becomes dramatic in the case of a β-aryl-(*E*)-acrylic acid, 2-methylcinnamic acid (**18e**), which was hydrogenated to (*S*)-**19e** by use of *(S)*-**16** in 95% conversion at 48 h and in 89% ee (entry 11), significantly surpassing those (merely 30% conversion and 30% ee) achieved by (*R*)-**14** (entry 12).

The superiority of H_8-BINAP over BINAP in enantioselectivity was also observed in hydrogenation of other types of unsaturated carboxylic acids, including β-disubstituted acrylic acids **20a** (93% ee vs 75% ee, Table 4, entries 1 and 2) and **20b** (70% ee vs 27% ee, entries 3 and 4), trisubstituted acrylic acid **22** (entries 5 and 6), as well as β,γ-unsaturated substrate **24** (entries 7 and 8).

20 **21**

	R^1	R^2
a:	CF_3	CH_3
b:	C_6H_5	CH_3

22 **23**

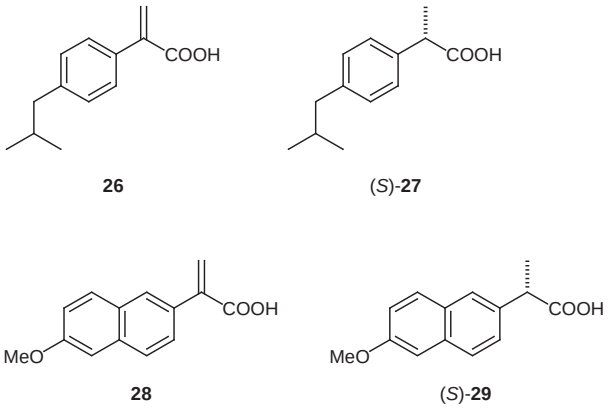
24 **25**

The synthetic significance of this asymmetric catalysis is well demonstrated in the hydrogenation of 2-(4-isobutylphenyl)propenoic acid (**26**) catalyzed by (*S*)-**16**, which provided directly and quantitatively the important antiinflammatory agent (*S*)-ibuprofen [(*S*)-**27**] in 97% ee (Table 5, entry 1) as compared to 96% ee obtained with (*R*)-**14**

Table 4 Asymmetric Catalytic Hydrogenation of α,β- and β,γ-Unsaturated Carboxylic Acids[a,26]

entry	substrate	catalyst	time, h	% conv	% ee
1	**20a**	(*S*)-**16**	8	100	93 (+)
2	**20a**	(*R*)-**14**	8	100	75 (–)
3	**20b**	(*S*)-**16**	7	100	70 (*S*)
4	**20b**	(*R*)-**14**	7	89	27 (*R*)
5[b]	**22**	(*S*)-**16**	3	100	88 (*S*)
6[b]	**22**	(*R*)-**14**	44	100	82 (*R*)
7[c]	**24**	(*S*)-**16**	2	100	83 (*R*)
8[c]	**24**	(*R*)-**14**	2	39	74 (*S*)

[a] Hydrogenation was carried out in an autoclave under an hydrogen pressure of 100 atm at 10–25 °C in methanol (substrate/catalyst = 200 mol/mol, solvent/substrate = 10–33 mL/g) unless otherwise stated, and the chemoselectivity was 100% as given by ^{1}H NMR analysis. [b] In THF. Substrate/catalyst = 600 mol/mol. [c] Hydrogen pressure was 1.5 atm.



26 (*S*)-**27** **28** (*S*)-**29**

(entry 2). Similarly, hydrogenation of 2-(6-methoxy-2-naphthyl)propenoic acid (**28**) using (*S*)-**15** as the catalyst gave another useful antiinflammatory agent *(S)*-naproxen [(*S*)-**29**] in 96% ee (entry 3).[22] In this case, a large excess of solvent methanol was used to dissolve **28**. Further investigation from the industrial viewpoint showed that addition of diethylamine (3 equivalences to **28**) greatly increased both the solubility of **28** and the catalytic activity of (*S*)-**15** (entry 4). Again, use of the analogous H_8-BINAP-containing complex (*S*)-**17** led to an increase in ee by 2% (entry 5). Even higher enantioselectivity (92% ee) and substrate to catalyst ratio (5000 mol/mol) have been realized by use of Ru[(*S*)-H_8-binap](OCOCF$_3$)$_2$ (**30**) (entry 6), illustrating the industrial applicability of this catalysis.

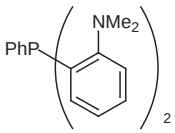
As was observed with DM-BINAP (vide supra), H_8-BINAP also showed excellent chiral induction ability in the diastereo- and enantioselective hydrogenation of methyl (±)-2-(benzamidomethyl)-3-oxobutanoate [(±)-**9**] in CH_2Cl_2–MeOH (7: 1) with (*S*)-**17** as the catalyst, yielding *syn*-(2*R*,3*S*)-**10** in 92% de and 99% ee[18b] as compared to those (84% de and 99% ee) obtained with (*R*)-**15**[22] (Scheme 5).

In addition to the above asymmetric catalytic reactions by use of ruthenium complexes, H_8-BINAP also showed good chiral induction ability in Ir(I)-catalyzed asymmetric hydrogenation of certain prochiral ketones. Although achiral iridium complexes were known to act as homogeneous catalysts in a wide variety of reactions,[27] there have been very limited applications of chiral iridium complexes to asymmetric catalysis, mainly to hydrogenation[28] and transfer hydrogenation[29] of functionalized ketones as well as hydrogenation of imines and enamides.[29b,30] In 1993, Takaya et al. reported that the new catalytic systems consisting of [Ir(binap)(cod)]BF_4 (**31**)[31] or [Ir(H_8-binap)(cod)]BF_4 (**32**)[31] and bis(*o*-dimethylaminophenyl)phenylphosphine (**33**) showed outstanding enantioselectivities in the asymmetric hydrogenation of a series of relatively simple prochiral ketones such as 1,2-benzocycloalkanones and β-thiacycloalkanones,[32] which had remained unsuccessful with conventional chiral phosphine—metal catalysts. Again, matching between the catalyst and substrate is important. The catalytic system **31–33** showed higher conversions and ee's for hydrogenation of 1,2-benzocycloalkanones. On the other hand, the system **32–33** was more suitable for that of β-thiacycloalkanones **34**, giving–β-thiacyclopentanol (*R*)-**35a**, an important building block in the synthesis of β-lactam antibacterials,[33] and β-thiacyclohexanol (*R*)-**35b** in 75–82% and 70% ee, respectively, as compared to those obtained with the **31–33** system (60 and 40% ee, respectively).[34]

Table 5 Asymmetric Catalytic Hydrogenation of α-Substituted Acrylic Acids[a,26]

entry	substrate	catalyst	S/C[b]	S/S[c]	H_2, atm	temp, °C	time, h	% conv	% ee
1	**26**	(*S*)-**16**	200	25	100	r.t.	8	100	97 (*S*)
2	**26**	(*R*)-**14**	200	25	100	r.t.	8	100	96 (*R*)
3[23]	**28**	(*S*)-**15**	200	263	116	-20	17	94	96 (*S*)
4[d]	**28**	(*S*)-**15**	1000	6	50	15	18	100	88 (*S*)
5[d]	**28**	(*S*)-**17**	1000	6	50	15	18	100	90 (*S*)
6[d]	**28**	(*S*)-**30**	5000	6	50	15	8	100	92 (*S*)

[a] Hydrogenation was carried out in an autoclave in methanol. The chemoselectivity was 100% as given by ^{1}H NMR analysis. [b] Substrate/catalyst ratio (mol/mol). [c] Solvent/substrate ratio (mL/g). [d] Diethylamine (3 equivalences to the substrate) was added.



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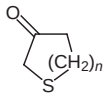

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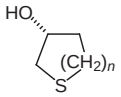


(*R*)-**35**

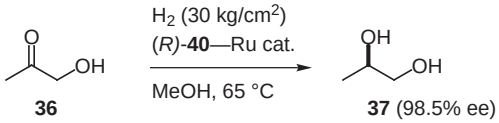
a: $n = 1$
b: $n = 2$

Although the mechanism of the above catalyses are not yet clear, the differences in the sense and efficiency of chiral induction between BINAP and H_8-BINAP seem to be ascribable to their structural difference. X-ray crystallographic studies of the Ir(I) complex (*S*)-**32** and its Rh(I) analog, {Rh[(*S*)-H_8-binap](cod)}ClO_4, revealed that they both show a significantly large dihedral angle (θ) [80.0(0)° and 80.3(4)°, respectively,][18b,34] between the two phenyl rings of the bitetralin moiety as compared to that [74.4(2)°] between the two naphthalene rings in {Rh[(*R*)-binap](nbd)}ClO_4.[35] This is considered to be a reflection of the larger steric hindrance of the hydrogen atoms attached to the sp^3 carbon atoms in the bitetralin moiety of H_8-BINAP than the hydrogen atoms on the sp^2 carbon atoms in the naphthalene rings of BINAP and is believed to exert influence on the arrangements of four phenyls on the phosphorous atoms, making the equatorial coordination sites of the H_8-BINAP–metal complex more crowded and the apical ones wider than those of the BINAP analogs. Consequently, the H_8-BINAP–metal complexes shows different enantioselectivity on the coordination of substrate to metal because of the crowded equatorial sites and different hydrogenolysis rate of the metal–C bond by H_2 due to a wider apical one as compared to those in the BINAP–metal complexes.[26b]

SEGPHOS[36]

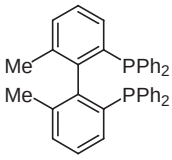
Atropisomeric biaryl systems have often been used as bridges to produce an asymmetric environment, which can be applied to many chiral diphosphine ligands for the transition-metal complex catalyzed asymmetric reactions. The landmark ligand is the BINAP, in which the two phenyl groups of the phosphine are oriented in an axial-equatorial relationship by the axially chiral binaphthyl backbone. Despite the insufficient information in the literature concerning the mechanism of the asymmetric control, in the biaryl-type ligands, one of the predominant factors could be the dihedral angle in the chiral backbone.[37]

The dihedral angle of the binaphthyl system is expected to exert influence on the effect of the steric bulk of the diphenylphosphino groups. The narrower dihedral angles should increase the steric repulsion between the substrate and the phenyl group on phosphine. The following experimental results support our working hypothesis. The enantioselectivities in the hydrogenation of 2-oxo-1-propanol (**36**) to (2*R*)-1,2-propanediol (**37**) are influenced remarkably by the ligand choice, and increase in the following order: BINAP (89.0% ee), BIPHEMP (**38**) (92.5% ee),[38] and MeO-BIPHEP (**39**) (96.0% ee).[39] As dihedral angles become narrower from BINAP (73.49°) to BIPHEMP (72.02°) and MeO-BIPHEP (68.56°), higher% ee's are obtained. In the previous X-ray crystallographic studies, it is reported that the dihedral angle between the two phenyl rings in {Rh[(*S*)-biphemp](nbd)}ClO_4 is narrower than that between the two naphthalene rings in {Rh[(*R*)-binap](nbd)}ClO_4.[35] In order to introduce the narrower dihedral angle into the biaryl backbone, we could employ the 4,4'-bi-1,3-benzodioxole system, which is thought to have the least rotational barrier among the atropisomeric biaryl systems. The dihedral angle of the bi-1,3-benzodioxole system in the ruthenium complex was estimated to be 65° by using CAChe MM2 calculations. Compared with naphthyl, Me or MeO group, its steric hindrance at these position is decreased by fixing to the cyclic system. Thus, we have synthesized the novel chiral diphosphine ligand, (4,4'-bi-1,3-benzodioxole)-5,5'-diylbis(diphenylphosphine), which is called SEGPHOS (**40**).

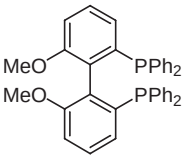


36 **37** (98.5% ee)

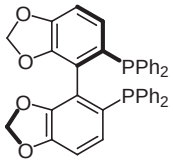
Application of these ligands to ruthenium-catalyzed hydrogenations has given us an exceptionally active and highly enantioselective catalytic system. The excellent chiral recognition ability of (*R*)-SEGPHOS–Ru(II) complex catalysts can be demonstrated by the hydrogenation of **36** to afford (2*R*)-**37**, which is a chiral building block of new quinolone antibacterial agents, in 98.5% ee (*cf*., BINAP, 89% ee) and with substrate-to-catalyst ratio up to 10,000.[12]



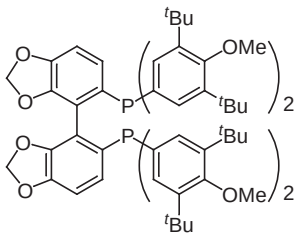
BIPHEMP 38



MeO-BIPHEP 39



(*R*)-**SEGPHOS 40**



DTBM-SEGPHOS 41

Also, the (*R*)-SEGPHOS–Ru(II) complex was shown to be the efficient catalyst for the hydrogenation of the carbonyl compounds. However, the diastereoselectivity in the hydrogenation of methyl (±)-2-(benzamidomethyl)-3-oxobutanoate [(±)-**9**] was disappointingly low giving *syn*-(2*S*,3*R*)-**10** with 79.6% de (Scheme 5). Aiming to attain the highest diastereoselectivity, we investigated to incorporate the substituents on the phenyl rings of SEGPHOS. Then we found that a diastereoselectivity was dramatically increased in the hydrogenation of **9** along with a high enantioselectivity by employing a (−)-DTBM-SEGPHOS[40]–Ru(II) complex catalyst. Thus, the hydrogenation of **9** catalyzed by a (−)-**41**–Ru(II) complex gave (2*S*,3*R*)-**10** in 98.6% de and 99.4% ee (*cf*., BINAP, 86% de).[21]

The SEGPHOS ligands based on our working hypothesis has been shown the high efficiency in the asymmetric catalytic hydrogenations of a wide variety of carbonyl compounds. Other potentialities and the theoretical studies of the SEGPHOS ligands in asymmetric reactions are now in progress.

References and Notes

(1) Reviews: (a) *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press, New York, 1985; Vol. 5. (b) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; John Wiley & Sons: New York, 1994. (c) *Catalytic Asymmetric Synthesis*, Ojima, I., Ed.; VCH Publishers: New York, 1993. (d) Takaya, H.; Noyori, R. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 8, p 443. (e) Noyori, R.; Kitamura, M. In *Modern Synthetic Methods* 1989; Scheffold, R., Ed.; Springer-Verlag, Berlin, 1989; p 115. (f) Blystone, S. L. *Chem. Rev.* **1989**, *89*, 1663. (g) *Comprehensive Asymmetric Catalysis*, Jacobson, E. N., Pfaltz, A., Yamamoto, H.,Eds.; Springer-Verlag, Berlin, 2000. (h) *Catalytic Asymmetric Synthesis*, Ojima, I., Ed.; John Wiley & Son: New York, 2000.

(2) Miyashita, A.; Yasuda, A.; Takaya, H.; Toriumi, K.; Ito, T.; Souchi, T.; Noyori, R. *J. Am. Chem. Soc.* **1980**, *102*, 7932.

(3) Reviews: (a) Noyori, R. In ref 1b; Chapter 1. (b) Takaya, H.; Ohta, T.; Noyori, R. In ref 1c; Chapter 1. (c) Takaya, H.; Ohta, T.; Mashima, K. In *Homogeneous Transition Metal Catalyzed Reactions*; Moser, W. R.; Slocum, D. W. Eds.; Advances in Chemistry Series 230; American Chemical Society: Washington, DC **1992**, p 124. (d) Noyori, R.; Takaya, H.; *Acc. Chem. Res.* **1990**, *23*, 345. (e) Noyori, R.; Takaya, H. *Chem. Scr.* **1985**, *25*, 83.

(4) Bergens, S. H.; Nohada, P.; Whelan, J.; Bosnich, B. *J. Am. Chem. Soc.* **1992**, *114*, 2121 and 2128.

(5) (a) Tani, K.; Yamagata, T.; Akutagawa, S.; Kumobayashi, H.; Taketomi, T.; Takaya, H.; Miyashita, A.; Noyori, R.; Otsuka, S. *J. Am. Chem. Soc.* **1984**, *106*, 5208. (b) Inoue, S.; Takaya, H.; Tani, K.; Otsuka, S.; Sato, T.; Noyori, R. *J. Am. Chem. Soc*. **1990**, *112*, 4897.

(6) Lubel, W. D.; Kitamura, M.; Noyori, R. *Tetrahedron: Asymmetry* **1991**, *2*, 543.

(7) (a) Noyori, R.; Ohta, M.; Hsiao, Y.; Kitamura, M.; Ohta, T.; Takaya, H. *J. Am. Chem. Soc*. **1986**, *108*, 7117. (b) Kitamura, M.; Hsiao, Y.; Noyori, R.; Takaya, H. *Tetrahedron Lett.* **1987**, *28*, 4829. (c) Kitamura, M.; Hsiao, Y.; Ohta, M.; Tsukamoto, M.; Ohta, T.; Takaya, H.; Noyori, R. *J. Org. Chem.* **1994**, *59*, 297.

(8) (a) Ohta, T.; Takaya, H.; Kitamura, M.; Nagai, K.; Noyori, R. *J. Org. Chem.* **1987**, *52*, 3174. (b) Ohta, T.; Takaya, H.; Noyori, R. *Tetrahedron Lett.* **1990**, *31*, 7189.

(9) Takaya, H.; Ohta, T.; Sayo, N.; Kumobayashi, H.; Akutagawa, S.; Inoue, S.-I.; Kasahara, I.; Noyori, R. *J. Am. Chem. Soc.* **1987**, *109*, 1596, 4129.

(10) Ohta, T.; Miyake, T.; Seido, N.; Kumobayashi, H.; Takaya, H. *J. Org. Chem.* **1995**, *60*, 357.

(11) Noyori, R.; Ohkuma, T.; Kitamura, M.; Takaya, H.; Sayo, N.; Kumobayashi, H.; Akutagawa, S. *J. Am. Chem. Soc.* **1987**, *109*, 5856.

(12) Kitamura, M.; Ohkuma, T.; Sayo, N.; Kumobayashi, H.; Akutagawa, S.; Ohta, T.; Takaya, H.; Noyori, R. *J. Am. Chem. Soc*. **1988**, *110*, 629.

(13) Takaya, H.; Mashima, K.; Koyano, K.; Yagi, M.; Kumobayashi, H.; Taketomi, T.; Akutagawa, S.; Noyori, R. *J. Org. Chem.* **1986**, *51*, 629.

(14) Cai, D.; Payack, J. F.; Bender, D. R.; Hughes, D. L.; Verhoeven, T. R.; Reider, P. J. *J. Org. Chem.* **1994**, *59*, 7180.

(15) Ager, D. J.; East, M. B.; Eisenstadt, A.; Laneman, S. A. *Chem. Commun*. **1997**, 2359.

(16) (a) Sayo, N.; Zhang, X.; Ohmoto, T.; Yoshida, A.; Yokozawa, T. *United States Patent* 5,693,868; December, 2, 1997. (b) Zhang, X.; Sayo, N. *United States Patent* 5,922,918; July, 13, 1999. (c) Zhang, X.; Kumobayashi, H.; Miura, T.; Sayo, N.; Tada, K.; Yoshida, A. To be published.

(17) Uozumi, Y.; Tanahashi, A.; Lee, S.; Hayashi, T. *J. Org. Chem.* **1993**, *58*, 1945.

(18) (a) Zhang, X.; Mashima, K.; Koyano, K.; Sayo, N.; Kumobayashi, H.; Akutagawa, S.; Takaya, H. *Tetrahedron Lett.* **1991**, *32*, 7283. (b) Zhang, X.; Mashima, K.; Koyano, K.; Sayo, N.; Kumobayashi, H.; Akutagawa, S.; Takaya, H. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2309.

(19) Doucet, H.; Gendre, P. L.; Bruneau, C.; Dixneuf, P. H.; Souvie, J.-C. *Tetrahedron: Asymmetry* **1996**, *7*, 525.

(20) (a) Ohkuma, T.; Ooka, H.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc*. **1995**, *117*, 2675. (b) Ohkuma, T.; Ooka, H.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 10417. (c) Ohkuma, T.; Ooka, H.; Yamakawa, M.; Ikariya, T.; Noyori, R. *J. Org. Chem*. **1996**, *61*, 4872. (d) Doucet, H.; Ohkuma, T.; Murata, K.; Yokozawa, T.; Kozawa, M.; Katayama, E.; England, A. F.; Ikariya, T.; Noyori, R. *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 1703. (e) Ohkuma, T.; Koizumi, M.; Doucet, H.; Pham, T.; Kozawa, M.; Murata, K.; Katayama, E.; Yokozawa, T.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1998**, *120*, 13529. (f) Ohkuma, T.; Koizumi, M.; Ikehara, H.; Yokozawa, T.; Noyori, R. *Org. Lett.* **2000**, *2*, 659. (g) Ohkuma, T.; Koizumi, M.; Yoshida, M.; Noyori, R. *Org. Lett*. **2000**, *2*, 1749. (h) Ohkuma, T.; Ishii, D.; Takeno, H.; Noyori, R. *J. Am. Chem. Soc*. **2000**, *122*, 6510.

(21) Noyori, R.; Ikeda, T.; Ohkuma, T.; Widhalm, M.; Kitamura, M.; Takaya, H.; Akutagawa, S.; Sayo, N.; Saito, T.; Taketomi, T.; Kumobayashi, H. *J. Am. Chem. Soc*. **1989**, *111*, 9134.

(22) Mashima, K.; Kusano, K.; Sato, N.; Matsumura, Y.; Nozaki, K.; Kumobayashi, H.; Sayo, N.; Hori, Y.; Ishizaki, T.; Akutagawa, S.; Takaya, H. *J. Org. Chem.* **1994**, *59*, 3064.

(23) Matsumoto, T.; Murayama, T.; Mitsuhashi, S.; Miura, T. *Tetrahedron Lett.* **1999**, *40*, 5043.

(24) (a) Shen, T. Y. *Angew. Chem., Int. Ed. Engl.* **1972**, 11, 460. (b) Lednicer, D.; Mitscher, L. A. *The Organic Chemistry of Drug Synthesis*; Wiley, New York, 1977 and 1980; Vols. 1 and 2. (c) Rieu, J.-P.; Boucherle, A.; Cousse, H.; Mouzin, G. *Tetrahedron* **1986**, *42*, 4095. (d) Botteghi, C.; Paganelli, S.; Schinato, A.; Marchetti, M. *Chirality* **1991**, *3*, 355.

(25) (a) Nohira, H.; Nakamura, S.; Kamei, M. *Mol. Cryst. Liq. Cryst.* **1990**, *180B*, 379. (b) Nakamura, S.; Nohira, H. *Mol. Cryst. Liq. Cryst.* **1990**, *185*, 199.
(26) (a) Zhang, X.; Uemura, T.; Matsumura, K.; Sayo, N.; Kumobayashi, H.; Takaya, H. *Synlett* **1994**, 501. (b) Uemura, T.; Zhang, X.; Matsumura, K.; Sayo, N.; Kumobayashi, H.; Ohta, T.; Nozaki, K.; Takaya, H. *J. Org. Chem.* **1996**, *61*, 5510.
(27) Serpone, N.; Jamieson, M. A. In *Comprehensive Coordination Chemistry;* Wilkinson, G., Gillard, R. D., McCleverty, J. A., Eds.; Pergamon Press: Oxford, 1987; Vol. 4, p 1097.
(28) (a) Spogliarich, R.; Vidotto, S.; Farnetti, E.; Graziani, M.; Gulati, N. V. *Tetrahedron: Asymmetry* **1992**, *3*, 1001. (b) Spogliarich, R.; Farnetti, E.; Kaspar, J.; Graziani, M.; Cesarotti, E. *J. Mol. Catal.* **1989**, *50*, 19. (c) Cesarotti, E.; Prati, L.; Pallavicini, M.; Villa, L.; Spogliarich, R.; Farnetti, E.; Graziani, M. *Ibid.* **1990**, *62*, L29.
(29) (a) Zassinovich, G.; Mestroni, G.; Gladiali, S. *Chem. Rev.* **1992**, *92*, 1051. (b) Palmer, M. J.; Wills, M. *Tetrahedron: Asymmetry* **1999**, *10*, 2045
(30) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069.
(31) Mashima, K.; Akutagawa, T.; Zhang, X.; Takaya, H.; Taketomi, T.; Kumobayashi, H.; Akutagawa, S. *J. Organomet. Chem.* **1992**, *428*, 213.
(32) Zhang, X.; Taketomi, T.; Yoshizumi, T.; Kumobayashi, H.; Akutagawa, S.; Mashima, K.; Takaya, H. *J. Am. Chem. Soc.* **1993**, *115*, 3318.
(33) Volkmann, R. A., Pfizer Inc. PCT Int. Appl. WO 88 08,845, 1988; *Chem. Abstr*. **1989**, *110*, 231330p.
(34) Zhang, X. In Ph. D. Dissertation, Kyoto University, Japan, 1994.
(35) Toriumi, K.; Ito, T.; Takaya, H.; Souchi, T.; Noyori, R. *Acta Crystallogr., Sect. B* **1982**, *38*, 807.
(36) Saito, T.; Yokozawa, T.; Ishizaki, T.; Moroi, T.; Sayo, N.; Miura, T.; Kumobayashi, H. "New Chiral Diphosphine Ligands Designed to have a Narrow Dihedral Angle in the Biaryl Backbone" is submitted for publication to Advanced Synthesis & Catalysis.
(37) Lustenberger, P.; Martinborough, E.; Denti, T. M.; Diederich, F. *J. Chem. Soc., Perkin Trans. 2* **1998**, 747. Harada, T.; Takeuchi, M.; Hatsuda, M.; Ueda, S.; Oku, A. *Tetrahedron: Asymmetry* **1996**, *7*, 2479.
(38) Schmid, R.; Cereghetti, M.; Heiser, B.; Schonholzer, P.; Hansen, H.-J. *Helv. Chim. Acta* **1988**, *71*, 897.
(39) (a) Schmid, R.; Foricher, J.; Cereghetti, M.; Heiser, B.; Schonholzer, P. *Helv. Chim. Acta* **1991**, *74*, 370. (b) Schmid, R.; Borger, E. A.; Cereghetti, M.; Crameri, Y.; Foricher, J.; Lalonde, M.; Muller, R. K.; Scalone, M.; Schottel, G.; Zutter, U. *Pure Appl. Chem.* **1996**, *68*, 131.
(40) The absolute configuration of (−)-DTBM-SEGPHOS was not determined.

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