

Chiral Phosphorus Ligands with Interesting Properties and Practical Applications

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Abstract Asymmetric transformations using a catalytic approach remain significantly important in organic synthesis, especially in the preparation of pharmaceutically interesting molecules. Indeed, chiral phosphorus ligands play an important role in this area. In this chapter, the recent development and advancement of chiral phosphines, phosphites, phosphoramides, etc. are reviewed. The potentially practical organic transformations are also described.

Keywords Asymmetric hydrogenation • Bisphosphine ligands • Enantioselectively catalytic bond-formation • Mixed-donor ligands • Transition-metal catalysts

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1 Introduction

Significant achievements have been made in chiral transition-metal complexes-catalyzed stereoselective organic transformations [1–3]. So far, most of these chiral catalysts are a combination of optically pure ligands and transition metals in various oxidation states. Often, the activity of the metal complexes can be modulated by varying the electronic properties of the ligands. With regard to stereochemical control, many structurally diverse phosphine ligands, especially the chelating C_2 -symmetric atropisomeric diphosphines (e.g., BINAP, BIPHEMP and MeO-BIPHEP) prove to be highly effective for a myriad of asymmetric transformations.

Over the past two decades, enormous success has been achieved in the use of C_2 -symmetric atropisomeric diphosphine ligands in Rh- or Ru-catalyzed asymmetric hydrogenation reactions. Irrespective to this, modification of the electronic/steric properties of these ligand systems in attempt to adjust the catalyst activity are far from trivial because of the difficulty and cumbersome procedure for structural modification of the ligand scaffold. Besides, due to the sensitivity of these chiral ligands/catalysts towards oxidation, the robustness of many of these transition metal-ligand systems, both well defined and in situ generated, has hardly been meticulously verified in solution under ambient conditions.

The catalytic properties of transition-metal complexes with chiral phosphine ligands embodying heterocyclic moieties such as pyridyl ring has been relatively unexplored even though the expansion of the scope of metal phosphine chemistry coupled with the rich chemistry of heterocycles is obvious. Here we present some recent development in the preparation of axially chiral biaryl diphosphine ligands based on heterocyclic scaffolds. Their uses in transition metal-catalyzed asymmetric synthesis will also be discussed [4]. The ligands described in this section are depicted in Fig. 1.

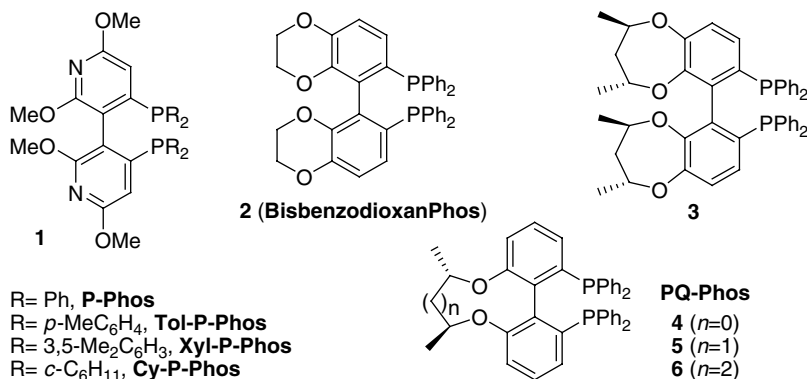


Fig. 1 Structures of diphosphine ligands containing heteroatoms

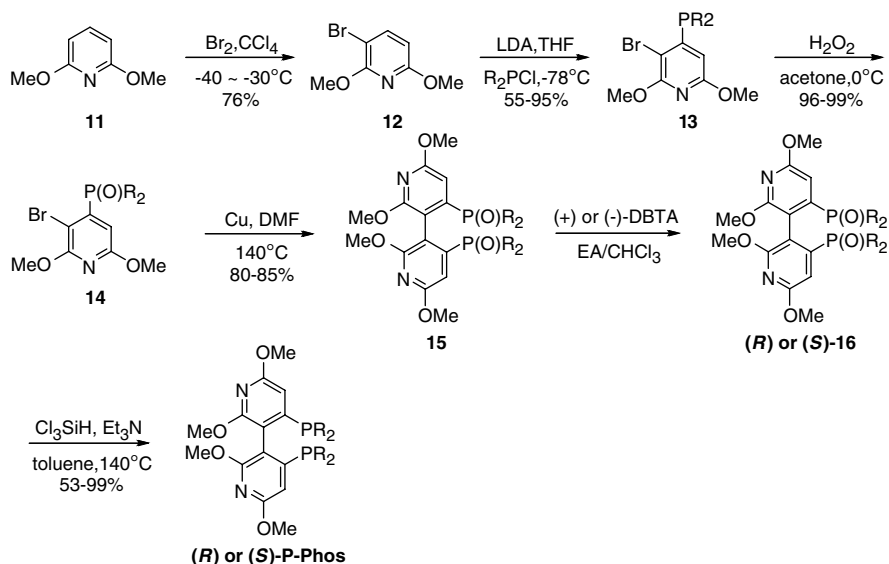
2 Development of New Chiral Diphosphine Ligands

2.1 Preparation of Bipyridyl Diphosphine Ligands

Earlier studies showed that rhodium and ruthenium complexes containing pyridylphosphine were ineffective catalysts for homogeneous hydrogenation of alkenes [5]. Competitive coordination of the unprotected pyridyl group to the metal center was thought to be the main reason for the poor catalytic activities. Having envisaged this, we embarked our research in the design and synthesis of a series of bipyridyl phosphine ligands bearing 2,2',6,6'-tetramethoxyl groups, namely the P-Phos series, in which more hindered substituents were introduced to the *ortho* positions of the nitrogen atom. As such, steric effect should hinder access of the metal center to the pyridyl ring [6, 7]. Indeed, the Rh-P-Phos complexes were found to be effective for a variety of asymmetric hydrogenation reactions [8].

For the optimization of non-racemic diphosphines, the P-substituents represent an important structural or electronic module that can be systematically varied, and that a diverse range of chiral diphosphine ligands can be created for further examination. In this context, several P-Phos analogues: Tol-P-Phos [9], Xyl-P-Phos [10] and Cy-P-Phos [11] had been prepared by attaching different P-substituents onto the dipyrindyl skeleton rather than changing the backbone itself. This modification approach is simple and straightforward for obtaining structurally distinct P-Phos analogues.

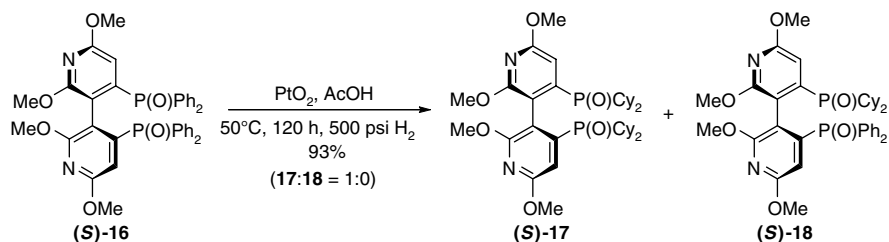
For preparation of the P-Phos ligands, the commercially available 2,6-dimethoxypyridine **11** was brominated at -40 to -30°C in CCl₄ to give compound **12**. Regioselective lithiation of **12** at *para*-position with LDA at -78°C in THF followed by treatment with chlorodiarylphosphine gave **13**. Oxidation of **13** with H₂O₂ led to the formation of the monophosphine oxide **14**. The racemic diphosphine dioxide **15** was obtained by copper-mediated Ullmann coupling of **14**, and followed by chiral resolution and subsequent reduction with trichlorosilane in the presence of triethylamine led to the target chiral ligands P-Phos (Scheme 1).



Scheme 1 Preparation of P-Phos dioxide

Racemic P-Phos dioxide **15** was resolved by fractional crystallization using enantiopure dibenzoyltartaric acid (DBTA) as resolving agent. The use of (–)-DBTA furnished the (*R*)-isomer, and (+)-DBTA provided the (*S*)-isomer of the diphosphine oxide. The absolute configuration of the corresponding enantiomer was established by single crystal X-ray diffraction studies.

With the enantiopure P-Phos oxide (*S*)-**16** in hand, the axially chiral bis(aryldicyclohexyl phosphine) dioxide [(*S*)-Cy-P-Phos oxide, (*S*)-**17**] was prepared via PtO_2 -catalyzed hydrogenation [8]. Similarly, (*R*)-**17** was readily prepared from (*R*)-**16** (Scheme 2).

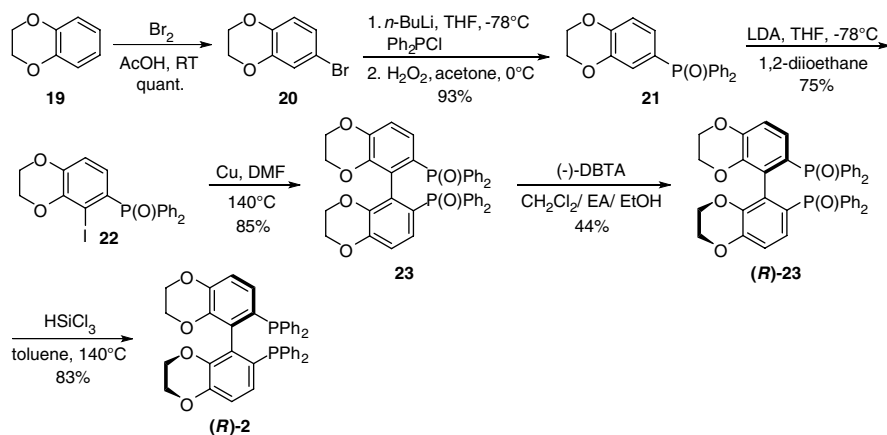


Scheme 2 Preparation of Cy-P-Phos oxide

In our initial attempt, the Pd/C system failed to catalyze the hydrogenation of (\pm)-**16** to the corresponding (\pm)-**17** using an ethanol–acetic acid mixture as solvent under 500 psi H₂ pressure at 50°C after 36 h. However, when PtO₂ was employed as catalyst, the reaction proceeded smoothly in acetic acid, and a mixture of the desired (\pm)-**17** along with some partially hydrogenated (\pm)-**18** (molar ratio as 5:1 based on ¹H and ³¹P-NMR analyses) was obtained after 72 h at room temperature. The ratio of (\pm)-**17** and (\pm)-**18** was further improved to 10:1 when the reaction temperature was increased to 50°C within the same reaction time frame. Eventually, (\pm)-**17** was obtained exclusively by simply prolonging the reaction time to 120 h at 50°C. Thus, under identical conditions, optically pure **17** was obtained from the hydrogenation of the corresponding enantiomer of **16** [11].

2.2 Development of BisbenzodioxanPhos Ligand

Built upon the success of P-Phos and other related heteroaromatic phosphine ligands, we turned to the development of a new type of chiral ligand, BisbenzodioxanPhos [12], which was independently synthesized by Genêt et al. and was named SynPhos by these authors [13]. BisbenzodioxanPhos bears a bis-benzodioxane scaffold, a structural feature similar to that H₈-BINAP. This ligand is expected to exhibit good reactivity and selectivity in asymmetric catalytic reactions in which BINAP is uniquely useful. The dioxane moieties offer good opportunities for easy modification and tuning. Scheme 3 depicts the preparation of the chiral ligand. Bromination of a commercially available compound **19** gave the corresponding bromide **20** in almost quantitative yield. Lithiation of **20** with *n*-butyllithium in THF at –78°C, followed by the addition of chlorodiphenylphosphine and subsequent oxidation with hydrogen peroxide, produced phosphine oxide **21**. A sequence of *ortho*-lithiation/iodination with LDA via a thermodynamic-controlled process instead of the generally used iodination with diiodoethane gave product **22** in 75% isolated yield. The racemic bis(diphenylphosphine oxide) **23** was obtained in good yield (85%) via Ullmann coupling of the iodophosphine oxide **22**. The enantiomeric products **23** were resolved using either (–) or (+)-DBTA as the resolving agent. (*R*)-Phosphine oxide was obtained with (–)-DBTA as the resolving agent. The structure and the absolute configuration of (–)-DBTA.(*R*)-**23** was determined by X-ray crystallography. The chiral ligand BisbenzodioxanPhos (**2**) was obtained in over 99.9% optical purity after trichlorosilane reduction of **23** at 140°C.

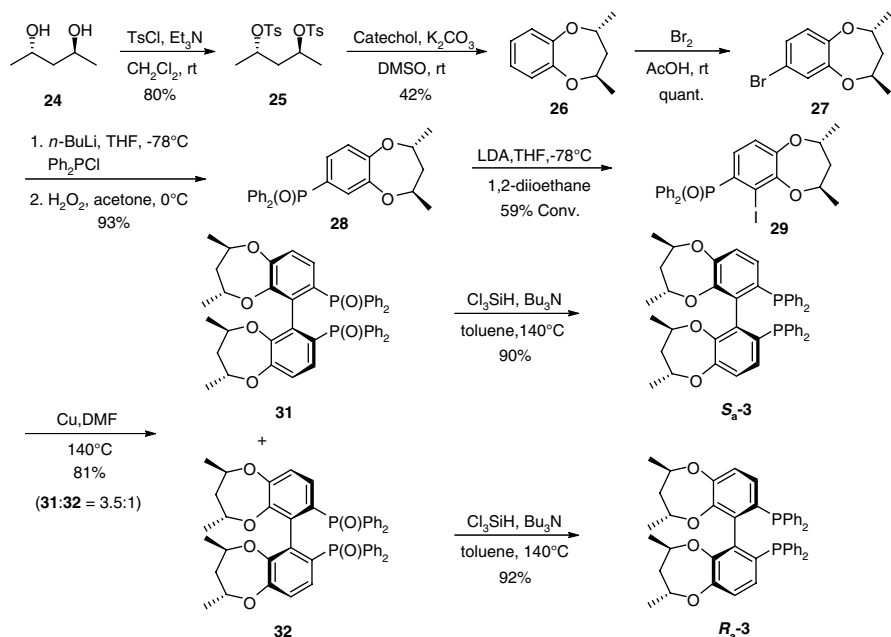


Scheme 3 Synthesis of BisbenzodioxanPhos

2.3 Diastereoselective Synthesis of Chiral Phosphine Ligands Without Resolution

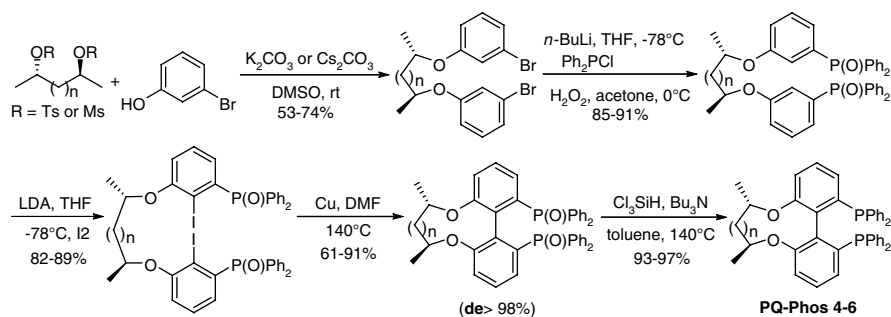
A classical method for preparing enantiomerically pure biaryl ligands involves aryl–aryl coupling followed by a resolution of the racemic atropisomers. The apparent disadvantage of the classical approach is that the maximum yield of the desired atropisomer cannot exceed 50%, and the enantiomeric purities of the ligands vary from high-to-moderate, not to mention that resolution procedures are frequently tedious. From a practical standpoint, it is desirable to develop efficient methodologies for the enantioselective synthesis of atropisomeric biaryl ligands. Various approaches, including desymmetrization of prochiral biaryls, [14] kinetic resolution of racemic substrate, [15] asymmetric catalytic coupling, [16–21] and chirality transfer from central, axial, and planar asymmetry have been reported [22–36].

Previously, most of the research focused on the syntheses of biphenols and binaphthols; however, diastereoselective syntheses of atropisomeric biaryl diphosphine oxides – the precursors of the chiral diphosphine ligands received less attention. In this regard, we pursued earlier a stereoselective intermolecular Ullmann coupling of two chiral phosphine oxides for synthesis of chiral atropisomeric diphosphine ligands. [37] As shown in Scheme 4, the reaction of catechol with (2*S*,4*S*)-pentanediol di-*p*-tosylate **25** derived from **24** gave (2*R*,4*R*)-2,4-dimethyl-3,4-dihydro-2*H*-1,5-benzodioxepine **26**. Subsequently, tandem functionalization furnished iodophosphine oxide **29**; copper-mediated Ullmann coupling gave a pair of diastereomers **31** and **32** (in a ratio of 3.5:1). With special care, both diastereomers of the chiral phosphine oxides **31/32** can be separated by column chromatography, and subsequent trichlorosilane reduction readily produced the target chiral ligands **3**.



Scheme 4 Diastereoselective synthesis of chiral ligand 3

To further improve the diastereoselectivity of the Ullmann coupling reaction, and to study the effects of the presence of additional chirality element as well as dihedral angle on the performance of the chiral ligands, we designed PQ-Phos type chiral ligands **4–6** ($n=0, 1, 2$) (Scheme 5) [38, 39].



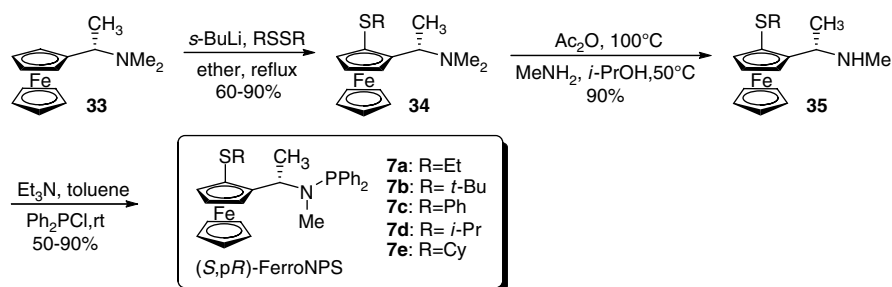
Scheme 5 Diastereoselective synthesis of PQ-Phos

Differing from chiral ligands **3** in which each aryl ring contains one chiral-inducing element, the two aryl rings in **4** were tethered by one chiral auxiliary derived from a chiral diol. The dihedral angle of the two aryl rings would be varied

by using different chiral diol, and such design was expected to have some positive effect on the stereoselectivity and reactivity of the chiral ligands. Similar to the preparation of **3**, preparation of the PQ-Phos series also started from sulfonate of optically pure chiral diols. Reaction of excess *m*-bromophenol with the chiral sulfonate produced the di(*m*-bromophenyl)ether. Subsequent conversion of the bromide to phosphine oxide, followed by Ullmann-type coupling, gave the desired chiral ligand **4–6** in almost complete diastereoselectivity ($\geq 98\%$). Apparently, this route obviates the tedious and time-consuming resolution step. This method, in combination with the preparation of chiral ligands **4–6** would offer a general and practical tool for the development of previously unexplored atropdiastereomeric biaryl diphosphine ligands.

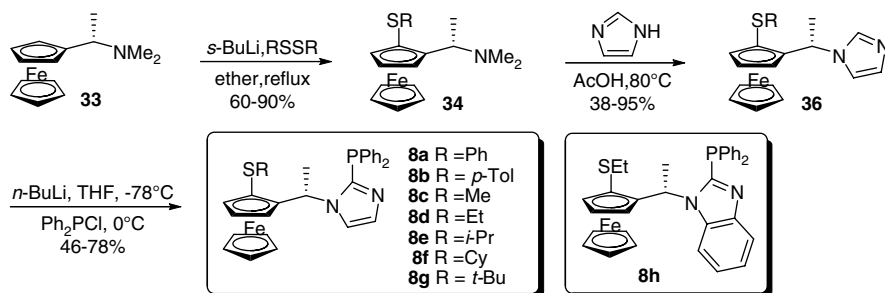
2.4 Development of Chiral Ferrocenyl Phosphine-Sulfur Mixed-Donor Ligands

We recently developed a convenient synthesis of Ugi amine (**33**) in an enantiomerically pure form by using Ru-(P-Phos)-catalyzed asymmetric hydrogenation of ferrocenyl methyl ketones [40] (For a large scale of production of chiral Ugi amine by asymmetric hydrogenation, see: [41]). This enantiopure Ugi amine is an important and versatile building block for further chiral ligand synthesis. In particular, a new family of P,S-type chiral ligands bearing a ferrocene scaffold with modular thioether moieties, namely (*S,pR*)-FerroNPS, were made (Scheme 6) [42]. The chiral intermediate aminothioether **34** was synthesized by diastereoselective *ortho*-lithiation of **33** using *s*-BuLi in Et₂O followed by quenching with disulfides (Scheme 6). Further treatment of **34** in hot acetic anhydride and aqueous methylamine solution gave ferrocenyl methylamine **35**. Phosphination of **35** using Ph₂PCl under basic conditions afforded enantiopure P,S-type ligands **7**. This route offered an easy pathway to an array of ligands with modular steric and electronic properties at both the thioether and phosphino moieties [43]. The thioether group of FerroNPS ligands in fact provided a tool for the structural modification of the ligands to achieve better results either on rate of reaction or enantioselectivity [44].



Scheme 6 Synthetic route of (*S,pR*)-FerroNPS chiral ligands

In 2007, we further developed a class of ferrocenyl P,S ligands **8** with imidazole or benzimidazole moiety (Scheme 7) [45]. Parts of their synthetic route are the same as FerroNPS, and aminothioether **34** which was obtained by diastereoselective *ortho*-lithiation of (*S*)-Ugi amine and tandem quenching with various disulfides. Reacting **34** with imidazole or benzimidazole in hot AcOH afforded compound **36** with retention of configuration at the central chirality. After a typical procedure of phosphination, ligands **8** were isolated in 46–78% yields.



Scheme 7 Synthetic protocol of chiral ferrocenyl ligands **8**

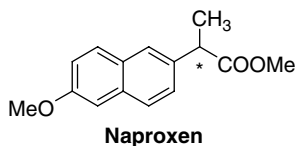
3 Application of Diphosphine Ligands in Asymmetric Catalytic Hydrogenations

Catalytic asymmetric hydrogenation is probably the simplest and yet the most powerful and economically attractive method for the production of amino acid derivatives, chiral amines, chiral alcohols, etc., which comprise a large proportion of enantiomerically pure pharmaceuticals. By utilization of various catalyst systems based on the P-Phos family of ligands, a broad scope of unsaturated substrates can be hydrogenated with high ees, which clearly shows the versatility of this new class of ligands.

3.1 Hydrogenation of C=C Bonds

3.1.1 Asymmetric Hydrogenation of Two-Substituted Propenoic Acids

Complex {(*R*)-P-Phos}Ru(acac)₂ was employed in the synthesis of the non-steroidal anti-inflammatory drug naproxen via the hydrogenation of 2-(6'-methoxy-2'-naphthyl) propenoic acid derivatives [8, 46]. An ee value of 95.3% was obtained at 0°C under a 1,000 psi H₂ pressure in methanol after 13–18 h. A marginal improvement (1–2%) was seen when 0.6 equiv of phosphoric acid was further added to the reaction mixture. The results compared favorably with the corresponding (*R*)-BINAP complex (94.8% ee).



When Ru[(*R*-2)Cl(*p*-cymene)]Cl was used as catalyst for the asymmetric hydrogenation of 2-(6'-methoxy-2'-naphthyl)propenoic acid, the product naproxen was obtained in 91% ee. The stereoselectivity of the reaction compared favorably with that using BINAP as the chiral ligand under similar reaction conditions (89%, 1,000 psi H₂ pressure and ambient temperature) [13].

Ruthenium complexes of chiral ligand *Sa*-3 and *Ra*-3 were also tested for the asymmetric hydrogenation of 2-(6'-methoxy-2'-naphthyl)propenoic acid. Results with respect to the observed enantioselectivities showed that [RuCl(*p*-cymene)-*Ra*-3]Cl is a better catalyst than [RuCl(*p*-cymene)(*S*)-BINAP]Cl, which in turn produced better results than [RuCl(*p*-cymene)-*Sa*-3]Cl. These findings indicated that the enantioselectivity of the hydrogenation reaction was mainly governed by the axial chirality, and the additional chiral auxiliary would influence the performance of the axially chiral ligand: better enantioselectivity was attained when the chirality of the chiral auxiliary matched the chirality of the biaryl moiety (in the case of *Ra*-3).

Similarly, asymmetric hydrogenation of 2-(6'-methoxy-2'-naphthyl)propenoic acid with the PQ-Phos-based Ru-*Sa*-4 complex as catalyst afforded naproxen with up to 97% ee. The results indicated that introduction of an additional chiral auxiliary such as 2,3-butanediol would improve the stereoselectivity of the chiral catalyst when the chirality of the diol matched the chirality of the biaryl. Further, comparison of the results produced by ligands having different chiral auxiliaries indicated that the rigidity of the ether ring would influence the dihedral angle of the biaryl ligands, and therefore affect the stereoselectivity of the corresponding chiral catalysts.

3.1.2 Asymmetric Hydrogenation of (*Z*)-β-Aryl-Substituted α-(Acylamino)Acrylates

In the past three decades, Rh-catalyzed asymmetric hydrogenation of α-(acylamino) acrylic acids and their esters has been developed to be a standard procedure for the synthesis of optically active α-amino acids including bio-conjugates and building blocks for drugs and natural products, a variety of chiral ligands are suitable for this purpose. [1, 47–49] However, the corresponding chemistry mediated by ruthenium catalysts has been relatively less investigated, although ruthenium catalysts were widely applied in the enantioselective hydrogenation of other types of substrates [50].

The parent ligand P-Phos proved to be more effective than its analogues in the Ru-catalyzed low-pressure hydrogenation of (*Z*)-β-aryl-substituted α-(acylamino) acrylates in methanol, and the α-amino acid derivatives were obtained in 90–97% ee (Fig. 2) [51].

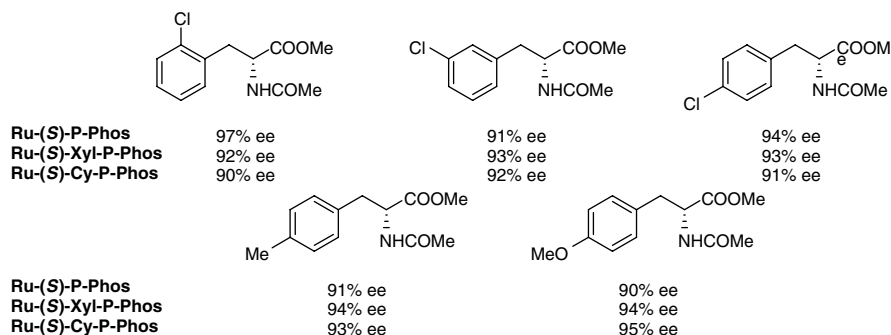


Fig. 2 Asymmetric hydrogenation of (Z)-β-aryl-α-(acylamino)acrylates by P-Phos

For the analogous hydrogenation reactions catalyzed by Rh(I) complexes of cationic P-Phos-type ligands, a sterically more encumbered catalyst was required for higher enantioselectivities. Quantitative yield of the products could be easily realized in a range of common organic solvents, while methanol was found to be the most suitable solvent. Therefore, a number of methyl (Z)-2-acetamidocinnamate derivatives were hydrogenated quantitatively with consistently high enantioselectivities (92–94% ee) in methanol for 18 h by using Rh-[(R)Xyl-P-Phos] as catalyst at 0°C under 1 atm hydrogen pressure.

To evaluate the catalytic activities of Cy-P-Phos, this ligand was used in the Rh-catalyzed asymmetric hydrogenation of (Z)-β-aryl-α-(acylamino)acrylates [11]. Under the optimized conditions for the P-Phos ligand series, Cy-Phos exhibited similar enantioselectivity but substantially higher activity as compared to Xyl-P-Phos. In addition, acetone appeared to be the best solvent of choice, although the reactions could proceed smoothly in several other organic solvents.

3.1.3 Asymmetric Hydrogenation of (Z)-β-Alkyl-β-(Acylamino)Acrylates

Chiral β-amino acids have received considerable interest from researchers due to their unique structural properties, pharmacological activities, and usefulness as building blocks for the synthesis of numerous biologically active compounds such as β-lactams and β-peptides [52]. Employing chiral diphosphine-rhodium complexes (such as Rh complexes of BICP, DuPhos, MiniPhos, BDPMI, and TangPhos) as catalysts, the enantioselective hydrogenation of β-alkyl-substituted β-(acylamino)acrylates afforded good to excellent ees [48]. However, studies on the analogous ruthenium-catalyzed hydrogenation of similar substrates are comparatively limited. A few such substrates have been examined by Noyori and co-workers based on the Ru(OCOCH₃)₂-(BINAP) catalyst system [53] and the highest ee for the (E)-isomers of substrates was 96%.

In terms of both activity and enantioselectivity, Ru complexes of the P-Phos series displayed remarkably better utility in the enantioselective hydrogenation of

Table 1 Asymmetric hydrogenation of (*E*)- β -alkyl- β -(acylamino)acrylates

$ \begin{array}{ccc} \text{R}^2\text{OOC} & & \text{R}^2\text{OOC} \\ & \diagdown & \\ & \text{C} = \text{C} & \text{C} - \text{C} \\ & / \quad \backslash & \quad \\ \text{R}^1 & & \text{NHAc} \end{array} $ $ \xrightarrow[8 \text{ atm H}_2, \text{MeOH}, 0^\circ\text{C}, 30 \text{ h}]{\text{Ru}-[(R)\text{-Xyl-P-Phos}](\text{C}_6\text{H}_6)\text{Cl}_2} $ $ \text{S/C} = 100 $				
Entry	R1	R2	Conv. (%)	Ee (%)
1	Me	Et	>99	93 (<i>R</i>)
2	Me	Me	>99	92 (<i>R</i>)
3	<i>i</i> -Pr	Et	>99	98 (<i>R</i>)
4	Ph	Me	>99	98 (<i>R</i>)
5	Ph	Et	>99	98 (<i>R</i>)
6	Ph(CH ₂) ₂	Et	>99	98 (<i>R</i>)

(*E*)- β -alkyl- β -(acylamino)acrylates than the corresponding Rh complexes, irrespective of the ligand incorporated (Table 1) [54]. Interestingly, opposite enantioselection of hydrogenation by the Ru and Rh complexes of an identical chiral ligand was observed, which is in agreement with the findings by Lubell et al. [53].

When ruthenium complexes were used as the catalysts, the sterically hindered auxiliary ligand provided higher ees and faster reaction rates. The reaction was strongly solvent-dependent, and methanol was found to be the best solvent. Thus, using Ru-[(*R*)-Xyl-P-Phos] catalyst under the preferred conditions, a variety of β -amino acid derivatives were obtained in 97.9–99.7% enantiopurities. Yet, hydrogenation of the (*Z*)-isomers using the Ru-Xyl-P-Phos catalyst in methanol produced the markedly inferior enantioselectivity under otherwise identical conditions to that of the (*E*)-isomers.

The hydrogenation of (*Z*)- β -dehydroamino acids using [(*R*)-Xyl-P-Phos]RuCl (η^6 -benzene)]Cl as catalyst was not effective at all in aprotic solvents such as THF and CH₂Cl₂, and quantitative conversion was observed in MeOH with low ee. In contrast, the Rh catalyst exhibited much higher catalytic activities in THF, converting (*Z*)- β -alkyl- β -(acylamino)acrylates to the corresponding β -amino acid derivatives under 8 atm of hydrogen pressures and at ambient temperature. Nevertheless, the enantioselectivity remained moderate (68–82% ee). Again, the Rh- and Ru-complexes of the same ligands exhibited an opposite sense of asymmetric control.

The PQ-Phos type ligand **Sa-4** in combination with a cationic Ru(II) complex was found to effect highly enantioselective hydrogenation of β -alkyl-substituted β -(acylamino)acrylates. Optimization studies revealed that methanol was the best solvent for this system. The hydrogen pressure had little influence on the enantioselectivity. Lower reaction temperature afforded higher enantioselectivity albeit with slower reaction rate. Excellent enantioselectivities were achieved in the hydrogenation of (*E*)- β -alkylsubstituted β -(acylamino)acrylates, and substrates with a bulky alkyl-substituent gave the best ee (up to 99.8%) [38].

Other ligands such as **5** or **6** also gave high ees in most of the asymmetric hydrogenation of (*E*)- β -alkylsubstituted β -(acylamino)acrylates, and no characteristic dependence of the enantioselectivity on the dihedral angles of the ligands was observed [39].

3.2 Hydrogenation of C=O Bonds

3.2.1 Asymmetric Hydrogenation of α -Ketoesters

Enantioselective hydrogenation of α -ketoesters provides a direct approach to optically pure α -hydroxyesters, which are important building blocks for organic syntheses. Notwithstanding the success in the asymmetric hydrogenation of β -ketoesters, the homogeneous asymmetric hydrogenation of α -ketoesters has been substantially less developed [13, 55–64]. α -Ketoesters are known to be difficult substrates for asymmetric hydrogenation and often require delicate optimization of reaction conditions. Occasionally, acid additives may be necessary to increase both the activity and selectivity of the ruthenium catalysts for the hydrogenation of the keto group [59].

In the catalytic asymmetric hydrogenation of methyl benzoylformate, the Ru catalyst with **Ra-4** afforded better enantioselectivity (97% ee) than that using BINAP (79% ee) as ligand [38, 39]. Other chiral ligands such as **Sa-5** or **Sa-6** also gave products with excellent enantiomeric excess. As expected, good results (91–92% ee) were obtained in the asymmetric hydrogenation of pyruvate. These ligands are also effective for the asymmetric hydrogenation of α -ketoesters with a bulky functional group R^1 such as *i*-Pr, Ph and $\text{Ph}(\text{CH}_2)_2$ etc. (Table 2).

3.2.2 Hydrogenation of β -Ketoesters

Optically pure β -hydroxy carboxylic esters are an important class of intermediates for the synthesis of bioactive or natural compounds [65, 66]. The first efficient asymmetric catalytic transformation of the β -ketoesters to β -hydroxyesters via transition metal complexes-catalyzed homogeneous hydrogenation was demonstrated by Noyori et al. utilizing BINAP/Ru(II) system [67]. Various ruthenium(II) complexes of the five-membered biheteroaromatic diphosphine series and the P-Phos family were also found to be well-suited for this transformation, providing

Table 2 Asymmetric hydrogenation of α -ketoesters catalyzed by **Ra-4** complex

$ \begin{array}{c} \text{O} \\ \parallel \\ \text{R}^1-\text{C}-\text{C}-\text{OR}^2 \\ \parallel \\ \text{O} \end{array} \xrightarrow[\text{S/C} = 600]{\begin{array}{c} [\text{Ru}-(\text{Ra-4})(\text{C}_6\text{H}_5)\text{Cl}]\text{Cl} \\ 500 \text{ psi H}_2, \text{ MeOH, rt} \end{array}} \begin{array}{c} \text{OH} \\ \\ \text{R}^1-\text{C}^*-\text{C}-\text{OR}^2 \\ \parallel \\ \text{O} \end{array} $				
Entry	R1	R2	Conv. (%)	Ee (%)
1	Me	Et	>99	93 (R)
2	Me	Me	>99	92 (R)
3	<i>i</i> -Pr	Et	>99	98 (R)
4	Ph	Me	>99	98 (R)
5	Ph	Et	>99	98 (R)
6	$\text{Ph}(\text{CH}_2)_2$	Et	>99	98 (R)

Table 3 Asymmetric hydrogenation of β -ketoesters

$\text{R}-\overset{\text{O}}{\parallel}\text{C}-\text{CH}_2-\overset{\text{O}}{\parallel}\text{C}-\text{OR}'$	$\xrightarrow{\text{Ru(II)/L}^*}$				
	(<i>R</i>)-BINAP	(<i>S</i>)-P-Phos	(<i>R</i>)-Xyl-P-Phos	(<i>R</i>)-Tol-P-Phos	(<i>R</i>)-2
$\text{Me}-\overset{\text{OH}}{\underset{*}{\text{CH}}}-\text{CH}_2-\overset{\text{O}}{\parallel}\text{C}-\text{OBn}$		96.6% ee	98.2% ee	96.6% ee	96.9% ee
$\text{Cl}-\text{CH}_2-\overset{\text{OH}}{\underset{*}{\text{CH}}}-\text{CH}_2-\overset{\text{O}}{\parallel}\text{C}-\text{OEt}$		98.0% ee	97.9% ee	94.8% ee	97.0% ee
$\text{Me}-\overset{\text{OH}}{\underset{*}{\text{CH}}}-\text{CH}_2-\overset{\text{O}}{\parallel}\text{C}-\text{OEt}$	99% ee	98.6% ee		97.1% ee	99.5% ee
$\text{Ph}-\overset{\text{OH}}{\underset{*}{\text{CH}}}-\text{CH}_2-\overset{\text{O}}{\parallel}\text{C}-\text{OEt}$	85% ee	95.2% ee	96.2% ee	96.2% ee	

enantioselectivities of up to 98% ee with the use of Tol-P-Phos [9]. In comparison, the asymmetric hydrogenation of 3-oxo-3-phenylpropionate employing the BINAP/Ru(II) system gave products with only 85% ee [67]. A comparison of the performance of several relevant ligands is shown in Table 3 [8–10].

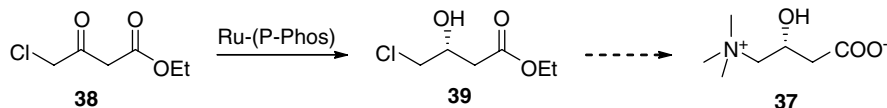
In the hydrogenation of substrates bearing a chlorine atom nearby the carbonyl group, the Ru-[(*S*)-BINAP] catalysts failed to give the desired products in satisfactory enantiopurities at room temperature. Elevated temperature (100°C) led to excellent chiral efficiency (97% ee) under 100 atm H₂ pressure [68]. Interestingly, the employment of Ru-P-Phos [8] or Tol-P-Phos [9] complexes furnished higher enantioselectivity (98% ee) under relatively milder conditions (80°C, 4–20 atm H₂).

Asymmetric hydrogenations of β -ketoesters catalyzed by the ruthenium complexes of BisbenzodioxanPhos such Ru[(*R*-2)Cl₂(DMF)_{*n*}] were carried out under 50 psi H₂ pressure at 80–90°C. The results revealed that the catalytic reactions are highly effective in producing alcohols of up to 99.5% ee [12].

When catalysts Ru-3-Cl₂(DMF)_{*n*} were applied to the asymmetric hydrogenation of β -ketoesters, the enantioselectivities for the corresponding products were also very high and compared favorably with the Ru[(*S*)-BINAP]Cl₂(DMF)_{*n*} system [37]. In the asymmetric hydrogenation of methyl acetoacetate, 99.8% ee was obtained when the reaction was catalyzed by the Ru-(Sa-4) complex [38, 39].

Carnitine (37), also known as L-carnitine (*levo*-carnitine), is a quaternary ammonium compound derived from the amino acid lysine and is responsible for the transport of fatty acids from the cytosol into the mitochondria. This compound is often sold as a nutritional supplement. Traditionally, chemical synthesis of optically pure L-carnitine was carried out through resolution, and asymmetric hydrogenation of β -ketoesters would be one of the most efficient routes to this important compound. We found that asymmetric hydrogenation of 4-chloro-3-oxo-butanoate (38) proceeded readily in the presence of Ru-(P-Phos) complex, leading to the

corresponding 3-hydroxyl product **39** in high yield and high ee (Scheme 8). Compound **39** is the key intermediate for L-carnitine and can be easily converted to the final product via routine chemistry [69].



Scheme 8 Synthesis of optically pure carnitine

3.2.3 Asymmetric Hydrogenation of Simple Ketones

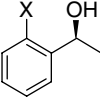
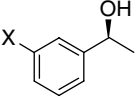
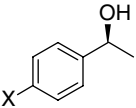
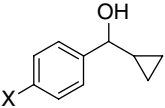
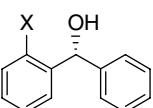
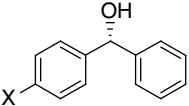
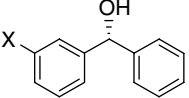
Simple secondary alcohols are important chiral intermediates, and a number of methods have been developed for the production of this type of compounds (For a review, see: [70]). However none of these methods live up to the expectations of industrial requirements because of high catalyst loading required to ensure a reasonable conversion as well as enantioselectivity of the reaction. Moreover, asymmetric hydrogenation of simple ketones was also problematic due to the lack of a contiguous ancillary coordinating group in the substrate.

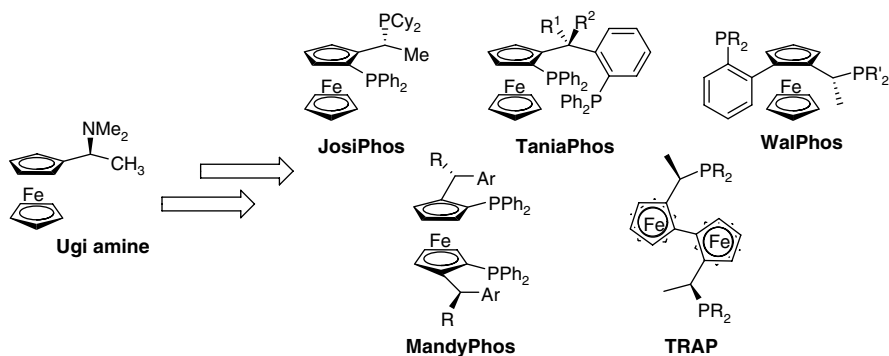
An important breakthrough was made when Noyori's group developed the BINAP-DIAPEN catalyst system [71]. Coupled with a catalytic amount of a strong base, a diverse array of unfunctionalized simple ketones were hydrogenated with a substrate-to-catalyst ratio of over two million, and yet, retaining high stereoselectivity.

When Xyl-P-Phos was used, a much cheaper diamine (*trans*-1,2-diphenylethylene diamine, DPEN) was sufficient to attain high degree of enantio-induction without using the exotic DIAPEN diamine. Excellent ees have been obtained for the hydrogenation of a variety of aryl-substituted acetophenones, heteroaryl methyl ketones and aryl cyclopropyl ketones with up to >99% ee at *S/C* ratio of 100,000. As for unsymmetrical benzophenones, the position of the substituent has an enormous effect on enantioselectivity. *Ortho*-substituent on the benzene ring usually provides steric bias for excellent stereocontrol. However, *meta*- or *para*-groups are too distant to exert significant stereodiscrimination, and the products with only low to moderate ees were obtained. In addition, a profound electronic effect was observed for the hydrogenation of *para*-R-C₆H₄-COPh. When R was a methyl group, product with 3.9% ee was obtained while this methyl group was fully fluorinated (R=CF₃), the ee value rose up to 77.2% (Table 4) [40].

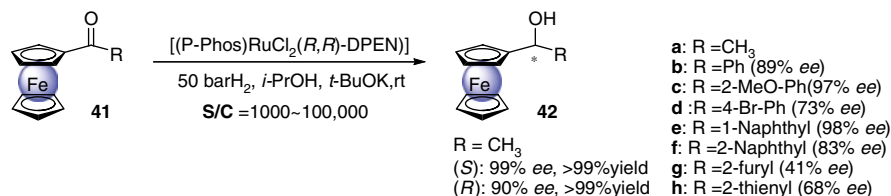
Most of the well-known chiral ferrocenyl ligands with 1,2-disubstituted functionalities are originally derived from chiral Ugi amine (Fig. 3). However, the laborious procedure for accessing an optically pure Ugi amine by resolution is expensive. In this regard, our group developed a convenient method for the synthesis of the versatile Ugi amine and its derivatives via the asymmetric hydrogenation of ferrocenyl ketones [41] in which up to 150 g-scaled prochiral ketones were successfully transformed to the corresponding enantio-enriched ferrocenyl

Table 4 Ru-catalyzed asymmetric hydrogenation of ketones

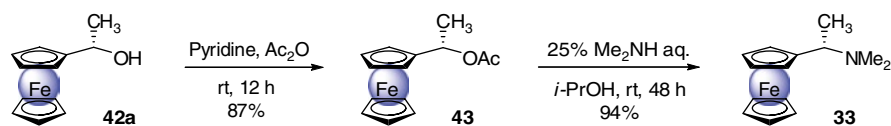
$\text{R}-\overset{\text{O}}{\parallel}{\text{C}}-\text{R}' \xrightarrow[\text{t-BuOK, rt, 100-800 psi H}_2, \text{2-48 h}]{\{\text{RuCl}_2[(R)\text{-Xyl-P-Phos}]\{(R,R)\text{-DPEN}\}} \text{ i-PrOH, } \text{R}-\underset{\text{R}'}{\underset{*}{\text{C}}}-\text{OH}$			
	X	S/C	Ee (%)
	H	100,000	99.1
	Me	4,000	97.7
	OMe	4,000	93.3
	Br	10,000	>99.9
	Me	12,000	97.7
	OMe	4,000	98.8
	Br	4,000	99.5
	Me	20,000	98.8
	OMe	20,000	98.7
	Br	50,000	>99.9
	CF ₃	12,000	97.7
	H	5,000	97.6
	OMe	1,000	96.1
	F	2,000	92.0
	Cl	5,000	92.3
	Me	2,000	95.9
	F	2,000	97.6
	Cl	10,000	97.4
	Me	2,000	3.9
	Cl	2,000	47.3
	CF ₃	2,000	77.2
	Me	2,000	43.2

**Fig. 3** Various ferrocenyl chiral ligands derived from the chiral Ugi amine

precursors in an enantioselective catalytic manner (Scheme 9). The precursors can be further converted into the optically pure Ugi amine in (*S*)- or (*R*)-configuration by a simple transformation (Scheme 10) [72, 73].



Scheme 9 Asymmetric hydrogenation of prochiral ferrocenyl ketones



Scheme 10 Transformation of ferrocenylethanol to Ugi amine

3.2.4 Asymmetric Hydrogenation of Enol Acetates

Asymmetric hydrogenation of enol acetates is an attractive alternative to the direct hydrogenation of unfunctionalized ketones. In addition to a π -donating olefin group, this type of substrate supplies a secondary donor group for chelation, which is helpful for obtaining high enantioselectivities in hydrogenation. Most of the studies on this reaction focused on using Rh-phosphines as catalysts. The use of the Ru-phosphine system in this reaction is limited in the literature [74, 75]. In our study of the asymmetric hydrogenation of enol acetates, it was found that asymmetric hydrogenation using **Ra-3** as chiral ligand produced the corresponding product with enantioselectivity similar to those obtained using the Ru-TunaPhos system. In the hydrogenation of relatively electron-rich substrates such as 1-(4-methoxyphenyl)-1-(acetyloxy)ethylene and 1-phenyl-1-(acetyloxy)ethylene, no reaction was observed with Ru-TunaPhos as catalyst [75]. Yet, the Ru-**3** catalyzed reaction still brought about effective formation of the desired products in high ees (up to 94.9%).

3.2.5 Asymmetric Catalytic Hydrosilylation of Simple Ketones

The development of asymmetric hydrosilylation of prochiral ketones as a desirable alternative to asymmetric hydrogenation could be highly rewarding due to the mild reaction conditions employed and the technical simplicity. However, the high cost of the catalysts and the rather low substrate-to-catalyst ratio ($S/C = 50\text{--}500$) rendered previous hydrosilylation work not competitive with hydrogenation [76, 77].

By using the Buchwald's protocol for conjugate reduction [78, 79], Lipshutz and co-workers disclosed a highly active $\text{Cu}^{\text{I}}\text{Cl}/\text{diphosphine}$ (e.g., 3,5-xyl-MeO-BIPHEP or DTBM-SegPhos)/*t*-BuONa/polymethylhydrosiloxane (PMHS) system for the enantioselective hydrosilylations of both aryl alkyl and heteroaromatic ketones even at a substrate-to-ligand ratio (*S/L*) of over 100,000 [80–82]. Recently, they also described a robust $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}/\text{DTBM-SegPhos}/\text{PMHS}$ hydrosilylation system (CuH in a bottle) [83, 84], which offered a new opportunity for asymmetric hydrosilylation in conjunction to practical applications.

At the time that we initiated our investigation in this area, we noted an air-accelerated and base-free $\text{CuF}_2/\text{BINAP}/\text{PhSiH}_3$ system demonstrated by Riant et al. which catalyzed the hydrosilylation of some aryl alkyl ketones in moderate to good ees at lower *S/L* ratios of 100–200 under ambient conditions [85]. Although the mechanism of this air-accelerated system remained elusive at that stage, it appeared that air played a key role in the formation of the active catalyst precursor in the catalytic cycle, and the much less air-sensitive diphosphine ligands would therefore be very crucial to the generation of the active catalyst systems. We then conjectured that our P-Phos-type ligands embracing unique air stability might be especially suited for this important reaction.

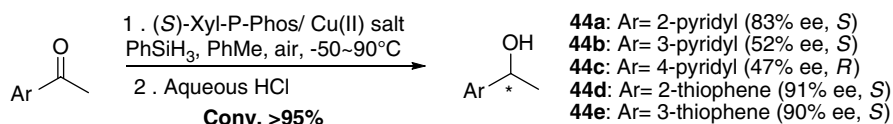
Indeed, the dipyriddyphosphine/ $\text{CuF}_2/\text{PhSiH}_3$ system served as an effective system rendering competitive levels of enantioselectivities of up to 97% ee for the hydrosilylation of *para*-substituted acetophenones [86]. Moreover, the excellent practical viability of this catalyst system was evident by its remarkably high activities (*S/L* ratio up to 100,000) and very mild reaction conditions such as normal atmosphere, moderately low temperatures (ambient temperature to -20°C) and compatibility with traces of moisture.

Polymethylhydrosiloxane (PMHS) is an attractive reducing reagent for environmentally benign reductive processes since it is inexpensive, nontoxic, and stable to air and moisture [87]. In light of this, the efficiency of the present catalyst system using PMHS as the hydride source has been examined. The sense of enantioselective induction appeared to be independent of silane regardless of using either P-Phos or Xyl-P-Phos, but PMHS was less reactive than PhSiH_3 . For instance, when the hydrosilylation of acetophenone was carried out with 1 mol% CuF_2 and 0.05 mol% (*S*)-Xyl-P-Phos with 1.2 equiv of PhSiH_3 at room temperature under air atmosphere, complete conversion was observed in 10 min with 76.7% ee, whereas, in the case of PMHS, 76.8% conversion was achieved within 25 min with 75.3% ee under otherwise identical conditions.

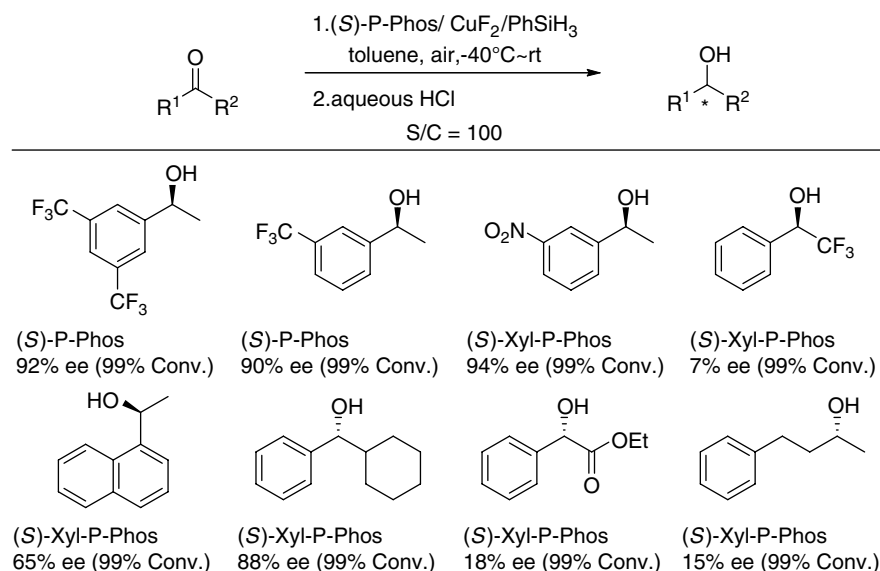
In addition, the enantioselective hydrosilylation of unsymmetrical diaryl ketones to benzhydrol had remained a formidable challenge, and the highest enantioselectivity reported in the literature prior to our study was around 20% ee [88]. In this regard, the P-Phos catalyst system was found to be surprisingly effective in the stereoselective hydrosilylation of *ortho*-substituted benzophenones with good to excellent ees (up to 98%) [86]. As expected, because of the lack of steric bias, *meta*- and *para*-substituted benzophenones were converted to the corresponding alcohols in low to moderate ees.

Optically active alcoholic compounds with heterocyclic moieties serve as useful building blocks for a vast array of physiologically active target products [89, 90]. The

asymmetric hydrosilylation of heteroaromatic ketones to these alcohols represents a harsh challenge for chemists [91]. Lipshutz et. al. found that the heteroaromatic ketones were converted to the corresponding alcohols in good-to-excellent enantiopurities by using a SegPhos-ligated CuH catalytic system [82]. Recently, we have successfully established an asymmetric hydrosilylation system, (*S*)-P-Phos/Cu(II)salt/PhSiH₃, in the effective reduction of heteroaromatic and several other type of ketonic substrates [92]. In this study, hydrosilylation of three pyridyl ketones (**44a-c**) was performed by (*S*)-P-Phos/ or (*S*)-Xyl-P-Phos/CuF₂ in air at various temperatures, and remarkable temperature effects on the asymmetric induction of the pyridyl ketones were observed. The combination of (*S*)-Xyl-P-Phos/ Cu(OAc)₂·H₂O, an air- and moisture-stable catalyst system, quantitatively provided the desirable product in 91% ee (**44d**) and 90% ee (**44e**), respectively (Scheme 11). To the best of our knowledge, this is the first highly effective copper-catalyzed enantioselective hydrosilylation of acetyl thiophene-type substrates. The catalyst system of CuF₂/(*S*)-P-Phos/PhSiH₃ was employed to transform several ketonic substrates to crucial chiral intermediates of physiologically active targets depicted in Scheme 12. This catalytic system features widespread substrate scope, high air stability, fast rate of reaction, good-to-excellent enantioselectivity, and mild reaction conditions and thus affords a practical protocol to access optically enriched alcohols.



Scheme 11 Cu-catalyzed asymmetric hydrosilylation of acetyl pyridines and thiophenes

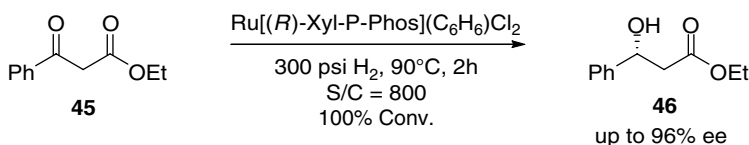


Scheme 12 Cu-catalyzed asymmetric hydrosilylation of several ketonic substrates

3.2.6 Activity and Air Stability of the Ru-(P-Phos) Catalyst System

The hydrogenation of 3-oxo-3-phenyl propionate leads to a useful pharmaceutical intermediate, (*S*)-3-hydroxy-3-phenyl propionate [93]. In the presence of Ru[(*R*)-Xyl-P-Phos]-(C₆H₆)Cl₂, the reaction with a substrate-to-catalyst molar ratio (*S/C*) of 800 was completed in 2 h, giving the desired product in up to 96.2% ee [10]. Even with a substrate-to-catalyst ratio as high as 7,500, the hydrogenation can be conveniently conducted on a 30 g substrate scale leading to 98% conversion within 15 h with the retention of high enantioselectivity (93.2% ee).

Further, the Ru complexes of the P-Phos family of ligands have been found to be highly air stable. When experimental procedures prior to the charging of hydrogen were performed in air and solvents without pre-degassing and drying, or even when the catalyst solution was exposed to air for 10 h before its application, both the catalyst activity and enantioselectivity for the hydrogenation of **45** remained unchanged (Scheme 13, 100% conversion, 95.5–96.1% ee for product **46**) from the air-purged system (96.2% ee) [10], while the ee obtained from using Ru[(*R*)-BINAP](C₆H₆)Cl₂ as catalyst precursor, in a side-by-side comparison study, sharply dropped from 92.0 to 66.6%.



Scheme 13 Ru-catalyzed asymmetric hydrogenation of β -ketoester

3.3 Asymmetric Hydrogenation of C=N Bonds

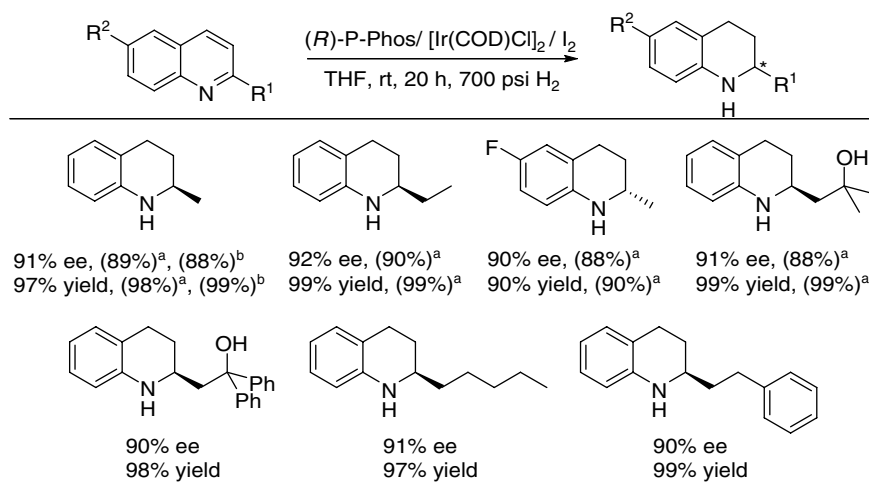
The asymmetric hydrogenation of C=N bonds is an appealing protocol for the synthesis of chiral amines. The enantioselective hydrogenation of quinolines, and other *N*-heteroaromatic compounds can provide enantiomerically pure tetrahydroquinoxalines and heterocycloalkanes of great biological interest [94, 95].

The catalytic asymmetric hydrogenation of easily accessible and less expensive quinoline derivatives is doubtlessly the most direct and convenient access toward enantiomerically enriched tetrahydroquinoline derivatives, which are significant synthetic intermediates for biologically active compounds [96]. Reports on this methodology are rather scarce. Zhou and co-workers recently discovered that iridium complexes bearing MeO-BIPHEP or ferrocenyloxazoline-derived P/*N*-ligand performed effectively for this conversion into optically active tetrahydroquinolines containing a chiral carbon at the 2-position [97–99].

Iridium complex generated in situ from [Ir(COD)Cl]₂ and P-Phos in combination with 0.1 equiv of I₂ in THF served as a highly efficient catalyst system for the hydrogenation of this class of challenging substrates at room temperature (Scheme 14) [100], furnishing hydrogenation products in 90–92% ee. Meanwhile,

we found that the Ir-(P-Phos) catalyst was particularly robust and air-stable. No deterioration was detected according to the ^{31}P NMR spectrum of the catalyst solution even after two weeks in air. The reactivity and enantioselectivity for the hydrogenation of 2-methylquinoline were virtually retained even though the catalyst solution had been exposed to air for 24 h before use. In contrast, sharp diminutions both in conversion (from 99 to 21%) and in ee (from 94 to 28%) occurred if Ir-(MeO-BIPHEP) was used under the same conditions.

Given the high efficiency and the air stability of the Ir-(P-Phos) catalyst system, we further explored the recyclability of this catalyst using 2-methylquinoline as a model substrate. By using a two-phase reaction medium involving a 1:1 mixture of hexane and poly(ethylene glycol)dimethyl ether (DMPEG), complete conversion and high enantioselectivity were essentially maintained (89% ee vs. 91% ee in THF). Most importantly, the product was conveniently separated by simple decantation of the hexane layer. Upon extraction of the product residue with hexane, the DMPEG phase encompassing the Ir-(P-Phos) catalyst could be reused. In a catalyst reusability study, we observed essentially no loss of the ee after eight times of recycle (Scheme 14).



Molar ratio of substrate: Ir: L^* : I_2 =100: 0.5: 1.1: 10. ^aThe mixture of DMPEG/hexane mixture was used as solvent instead of THF. ^bThe catalyst was recycled 8 times.

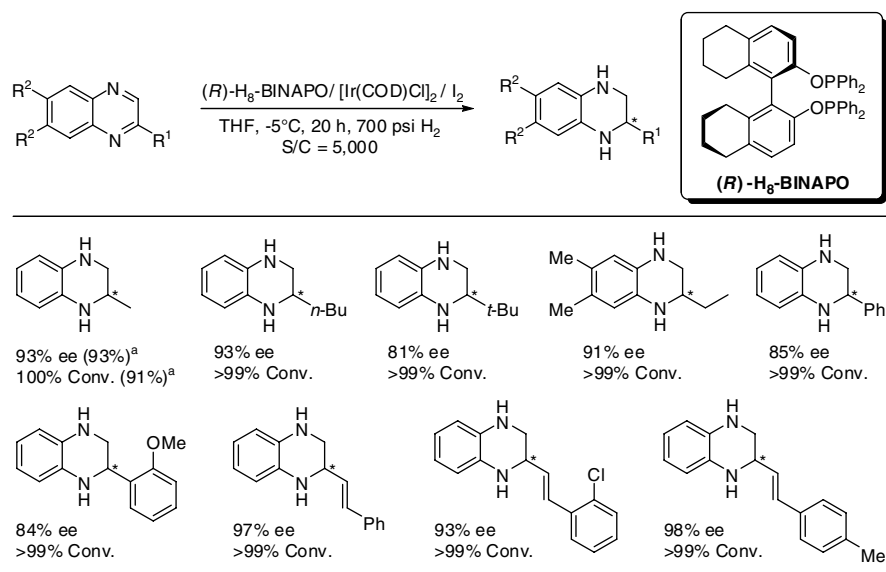
Scheme 14 Asymmetric hydrogenation of quinolines

Iridium complexes containing PQ-Phos type ligands **4–6** are also effective in the asymmetric hydrogenation of *N*-heteroaromatic compounds. The reaction was strongly solvent dependent. Toluene was found to be the solvent of choice for the reaction of quinoline. For example, the best enantioselectivity (92% ee) was

obtained for the hydrogenation of 2,6-dimethylquinoline in toluene. Nevertheless, for the hydrogenation of 2-methylquinoxaline and 2,3,3-trimethylindolenine, THF and CH_2Cl_2 appeared to be the better choices of solvents.

The enantioselectivities of these reactions are highly sensitive to the dihedral angles of the chiral ligands used. For example, with *Ra*-**4** ligand (dihedral angle = -66.5°), the catalytic hydrogenation of 6-methoxy-2-methylquinoline gave 6-methoxy-2-methyl-1,2,3,4-tetrahydro-quinoline in 93% yield and 77% ee. Likewise, 91% yield and 84% ee were obtained for the analogous reaction with *Sa*-**6** as ligand (dihedral angle = 88.8°). The best result (89% ee) was attained with ligand *Sa*-**5** [with dihedral angle = 80.0° , which is close to that of MeO-BIPHEP (83.2°)]. A more pronounced dihedral angle effect was observed for the hydrogenation of 2-methylquinoxaline and 2,3,3-trimethylindolenine [39].

The 1,2,3,4-tetrahydroquinoxaline ring is an important structural unit in many bioactive compounds [101–106], and the most convenient and straightforward protocol to its enantio-enriched form is achieved by asymmetric hydrogenation of quinoxalines. However, the enantioselective hydrogenation of substituted quinoxalines derivatives has been less extensively studied and successful cases are limited [39, 107–111]. Recently, we have developed a highly efficient Ir-(H_8 -BINAPO)-catalyzed asymmetric hydrogenation of quinoxalines with high *S/C* ratio (up to 20,000) to access the optically pure tetrahydroquinoxalines derivatives in excellent ee (up to 98%) depicted in Scheme 15 [112]. Initially, Ir/(*R*)- H_8 -BINAPO (*S/C*=100) enantiomerically hydrogenated 2-methylquinoxalines to give the desired product in 89% ee with complete conversion at ambient temperature; while



^aThe *S/C* ratio was set to 20,000.

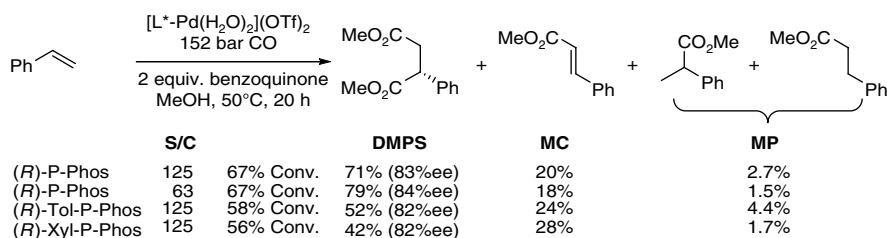
Scheme 15 Asymmetric hydrogenation of quinoxalines catalyzed by H_8 -BINAPO

under identical reaction conditions, Ir/BINAP and Ir/MeO-BIPHEP only provided the hydrogenation product in 18 and 59% ee, respectively. With optimization of reaction parameters, the enantioselectivity of the Ir/(*R*)-H₈-BINAPO system was improved to 93% ee at -5°C . This ee value represented the highest enantioselectivity attained so far in the catalytic asymmetric hydrogenation of 2-methylquinoxaline. Remarkably, when the *S/C* ratio was increased to 20,000, 2-methylquinoxaline was hydrogenated in 1 h to give the desired product without any loss of enantioselectivity. The 28% conversion indicated a TON of 18,140 and a TOF 5,620 h⁻¹. Notably, this TOF value was the highest reported so far in the asymmetric hydrogenation of heteroaromatic compounds. Under the same reaction conditions, various two-substituted quinoxalines were tested and generally afforded the corresponding desired products in high ees (up to 98%).

4 Asymmetric Catalytic C–C Bond Formation

4.1 Bis-Alkoxy carbonylation of Styrene

Pd(II)-catalyzed asymmetric bis-alkoxy carbonylation of styrene for the synthesis of optically active butanedioic acid derivatives with high chemoselective and/or enantioselective control represents a significant challenge [113]. With the use of 0.8 mol% of catalyst and 2 equiv of benzoquinone as oxidant, the reaction was carried out in methanol under 152 bar CO pressure with 56–67% conversion. The best chemoselectivity of 79% and enantioselectivity of 84% for the desired product dimethyl-2-phenylsuccinate (DMPS) were achieved in the presence of P-Phos with a catalyst loading of 1.6 mol% (Scheme 16) [114].



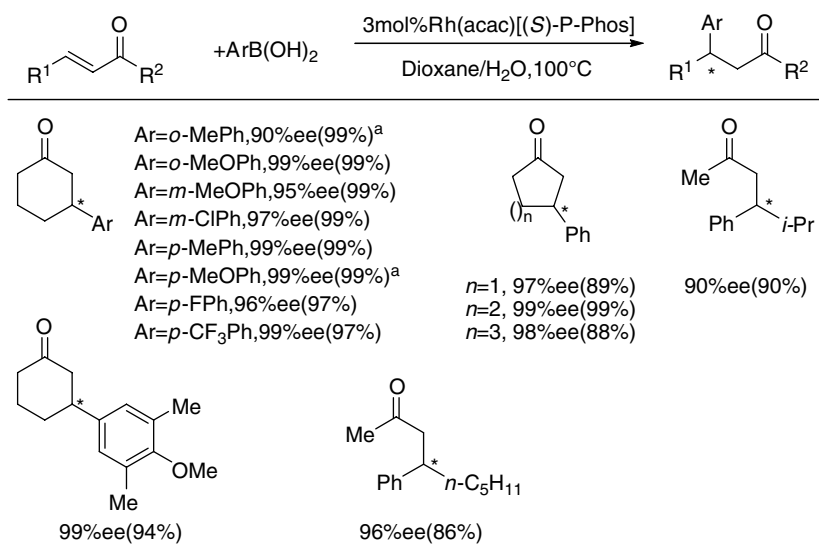
Scheme 16 Pd(P-Phos) complex-catalyzed asymmetric bis-alkoxy carbonylation of styrene

4.2 1,4-Conjugate Addition to α , β -Unsaturated Ketones

Enantioselective construction of quaternary carbon stereocenters is an important objective in organic chemistry (For reviews, see: [115], [116–118], and asymmetric

1,4-conjugate addition of carbon nucleophiles to α,β -unsaturated compounds is a useful method for it. Successful examples include copper-catalyzed asymmetric 1,4-conjugate addition of dialkylzinc reagents [119–121] and trialkylaluminum reagents [122, 123], and rhodium complex-catalyzed 1,4-addition of alkenylboronic acids to α,β -unsaturated pyridyl sulfones [124].

Since Hayashi et al. reported the asymmetric 1,4-addition of organoboronic acids to α,β -unsaturated ketones mediated by Rh(I)-BINAP catalyst [125], impressive progress has been made in reactions involving a variety of other electron-deficient olefins [126]. [Rh(acac)(P-Phos)] complex, generated in situ from equimolar amounts of Rh(acac)(CH₂=CH₂)₂ and P-Phos in dioxane/H₂O (10/1) at 100°C, has also been found to be well suited for this transformation [127]. In the presence of excess of arylboronic acids (1.4–5.0 equiv), a vast selection of aryl groups with either electron-donating or electron-withdrawing substituents on the *ortho*-, *meta*- or *para*-position have been readily incorporated onto the β -position of several kinds of cyclic and acyclic enones with exceptionally good yields and ees (up to 99%) in most cases, which are either comparable to or better than the relevant Rh-BINAP system (Scheme 17).



Note: The yield was given in brackets. ^aRatio of dioxane/water was changed to 20:1

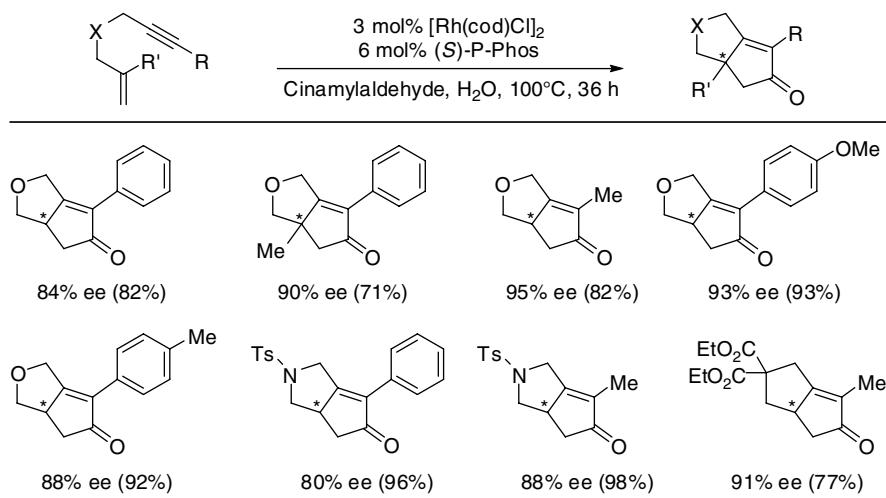
Scheme 17 Enantioselective addition of arylboronic acids to α,β -unsaturated ketones

4.3 Asymmetric Pauson–Khand-Type Reaction (PKR)

Asymmetric transition metal-catalyzed/mediated [2+2+1] carbonylative cycloaddition of an alkene and an alkyne (asymmetric Pauson–Khand-type reaction) offers

an excellent opportunity for the preparation of various optically active cyclopentenones [128]. No catalytic asymmetric aqueous PKR systems had been developed prior to our study. Recently, we found that P-Phos is highly effective in a rhodium-catalyzed PKR using aldehydes as nontoxic “carbon monoxide” source and water as the only solvent without a surfactant. This protocol allowed the handling of both the catalyst and the reactants under air without special precautions [129].

The higher concentration of reactants in conventional organic solvents proved to offer higher rates in the reaction. This finding prompted us to use water as the sole solvent, which was expected to increase the effective concentration of the reactants based on the aqueous micellar concept [130] and thereby to accelerate the reaction. Indeed, water turned out to be much more conducive than organic solvents to higher reactivity and ees (Scheme 18, R=Ph, R'=H), and P-Phos displayed far superior efficacy to the other screened chiral ligands we screened. Aldehydes as CO surrogates also appeared influential in determining both optical and chemical outcomes, and cinnamylaldehyde gave the best results among the aldehydes examined. Additionally, these attractive aqueous conditions were also well-adapted to a broad collection of oxygen-, nitrogen-, and carbon-tethered enynes providing excellent isolated yields in most cases and an ee range of 74–95% (Scheme 18).



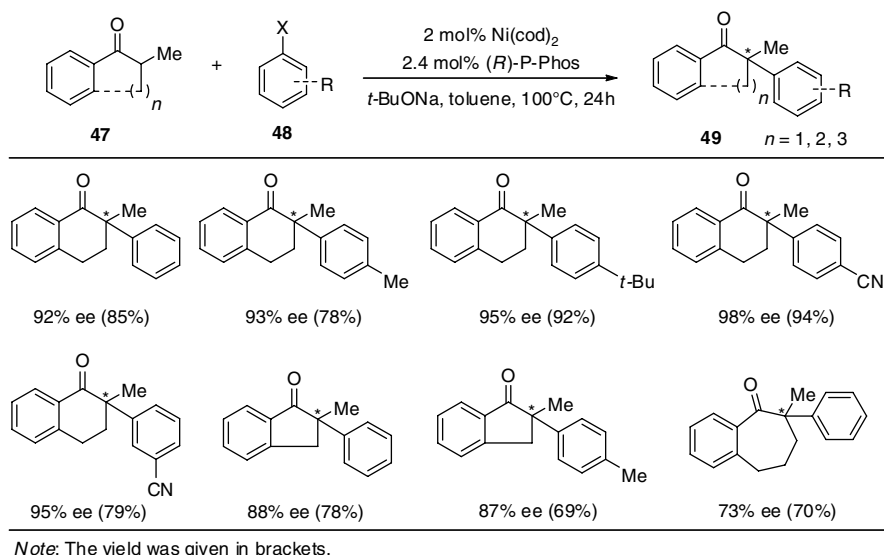
Note: The isolated yield was given in brackets.

Scheme 18 Rh(P-Phos)-catalyzed asymmetric Pauson–Khand reaction

Diphosphane ligand (*S*)-**2** (BisbenzodioxanPhos) was also highly effective in the co-operative processes of aldehyde decarbonylation and cascade enantioselective Pauson–Khand-type reactions. Various 1,6-enynes were transformed to the corresponding bicyclic cyclopentenones in good yields and enantiomeric excesses (up to 96% ee). The attractive feature of this new Rh-catalyzed homogeneous dual catalysis system is that the reaction can be performed in alcoholic solution [131].

4.4 Nickel-Catalyzed Asymmetric α -Arylation of Ketone Enolates

Optically active α -aryl carbonyl moieties are important structural features of many naturally occurring products, pharmaceuticals, synthetically useful intermediates and precursors to emissive polymers [132–134]. The asymmetric arylation of enolates is an attractive means to prepare optically active carbonyl compounds. Buchwald et al. achieved the asymmetric α -arylation of ketone enolates in good yield and enantioselectivity by using Pd complex of BINAP [135] or dialkylphosphinobinaphthyl ligands [136]. Studies revealed that the atropisomeric dipyrindyl-diphosphine P-Phos served as an effective ligand for the asymmetric α -arylation of ketone enolates, and the corresponding all-carbon quaternary stereogenic center was generated in high enantioselectivity (Scheme 19) [137].



Scheme 19 Ni-catalyzed asymmetric α -arylation of ketone enolates

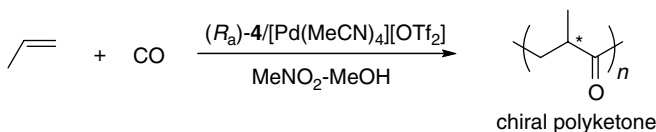
In a prototypical reaction, 2-methyl-1-tetralone (**47**, $n=2$) was treated with bromobenzene (**48**, X=Br) in the presence of 2 mol% $\text{Ni}(\text{COD})_2$ and 2.4 mol% (*R*)-P-Phos. The α -phenylated product **49** was obtained in 88% isolated yield and 90% ee with NaHMDS as base. Further study indicated that toluene in combination with sodium *tert*-butoxide formed a superior reaction system. Weaker inorganic bases such as K_3PO_4 resulted in lower productivity even with prolonged reaction time. The yield and enantioselectivity decreased in THF at 60°C. Addition of ZnBr_2 led to poor reactivity and enantioselectivity. Adding LiOAc increased the product yield slightly, albeit with a compromised ee value.

Various aryl bromides **48** were examined under these preliminarily optimized conditions using **47** as substrate. The *meta*- and *para*-substituted aryl bromides

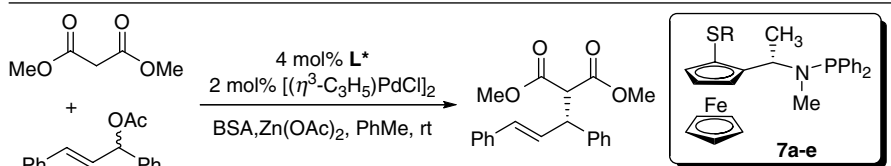
gave good yields and moderate-to-excellent enantioselectivities. However, poor reactivity was observed with 2-bromoanisole. Excellent enantioselectivity (98% ee) was attained for the reaction with 4-bromobenzonitrile. Iodobenzene was also an effective reactant under these reaction conditions at 70°C, furnishing the coupling product in 97% yield and 92% ee. Notably, unactivated aryl chloride was found, for the first time, to react with **47** in Ni-catalyzed reaction conditions to give the coupling product in 91% yield.

4.5 Asymmetric Alternating Co-Polymerization of Propene and Carbon Monoxide

The alternating copolymerization of propene with carbon monoxide catalyzed by chiral diphosphine ligand modified cationic palladium(II) complexes is a useful tool to generate a variety of polyketones with main-chain chirality. It is known that chiral polyketones exhibit unique chemical and physical properties. Their beneficial features include biodegradable nature which makes them attractive and environmentally friendly materials. Additionally, they are valuable as piezo-, pyro-, and ferroelectric, nonlinear optical materials, chromatographic supports and excellent starting materials for further functionalization [138–148]. Though cationic palladium(II) complexes bearing chiral C_2 -symmetric bidentate ligands were successfully employed for this type of copolymerization, only a few examples of highly regio- and stereo-selective propene/CO copolymerization were documented [149–151]. Recently, we have reported a highly efficient chiral-bridged biphenyl diphosphine ligand (*Ra*-**4**) modified cationic Pd(II) catalyst system for the synthesis of optically active polyketone via stereoselective alternating copolymerization of propene and carbon monoxide (Scheme 20) [152]. The screening results showed that $[Pd(MeCN)_4][OTf]_2$ was an excellent catalyst precursor in a mixed solvent of $MeNO_2$ –MeOH for the copolymerization, and the catalytic activity was found to be up to 221 g polymer/(g Pd·h). In addition, a chiral polyketone with high molecular weight ($M_n = 2.9 \times 10^4$), narrow polydispersity ($M_w/M_n = 1.4$), and high stereoregularity (which was supported by molar optical rotation = $+37^\circ$) was afforded under optimized reaction conditions. To the best of our knowledge, the catalytic activity and this molecular weight were the highest among Pd-catalyzed propene/CO alternating copolymerization using atropisomeric biphenyl diphosphine as ligands, including chiral BINAP and BIPHEP.



Scheme 20 Asymmetric alternating copolymerization of propene and CO catalyzed by Pd/(*Ra*-4) catalyst

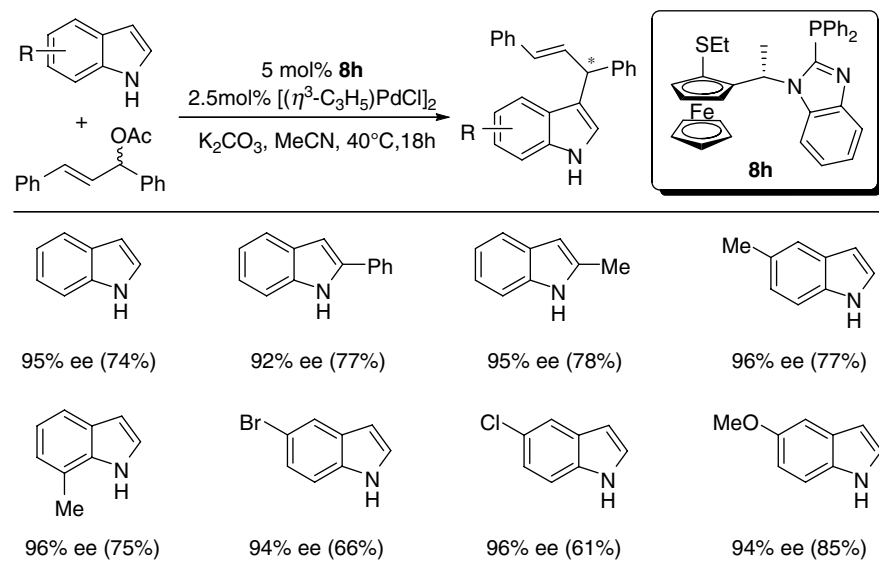
Table 5 Effect of thioether moiety on catalyst activity and enantioselectivity


L*	R	<i>t</i> (min)	Yield (%)	ee (%)
7a	Et	45	97	91.8 (<i>R</i>)
7b	<i>t</i> -Bu	90	94	92.7 (<i>R</i>)
7c	Ph	120	94	93.5 (<i>R</i>)
7d	<i>i</i> -Pr	45	94	96.6 (<i>R</i>)
7e	Cy	45	96	95.7 (<i>R</i>)

5 Application of FerroNPS Catalysts in Asymmetric Allylic Substitutions

5.1 Asymmetric Catalytic C–C Bond Formation

The effectiveness of the FerroNPS family was examined under the optimized reaction conditions for allylic alkylation. The results from Table 5 showed that all of the N-P/S ligands were effective with high to excellent enantioselectivity.



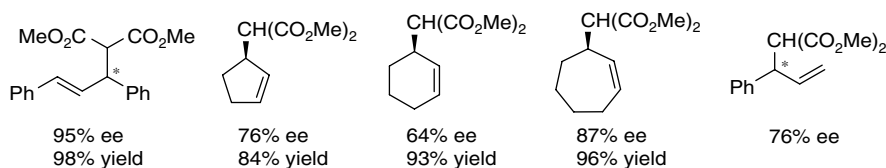
Note: The yield was given in brackets.

Scheme 21 Pd-catalyzed indole allylation using P,S-type ligands 8h

Although the effect on the size of the thioether group was found to be not dominant for the stereochemical outcome, relatively sluggish catalyst activity was found in using ligands containing sterically hindered R groups such as *tert*-butyl and phenyl group. For both enantioselectivity and reactivity, **7d** was found to be the best ligand.

This class of ferrocene-based P/S-type ligands was initially adopted in Pd-catalyzed asymmetric allylic alkylation of 1,3-diphenyl-2-propenyl acetate with indoles (Scheme 21). Through systematic evaluation of the ligand library and optimization studies, **8h** was found to be the best ligand for the Pd-catalyzed asymmetric indole alkylation with up to 96% *ee* [45].

In addition, ligand **8h** was further applied in the Pd-catalyzed asymmetric allylic alkylation of various allylic acetates with different nucleophiles and produced the alkylated products in modest to high enantioselectivities with high yields (Scheme 22) [153].



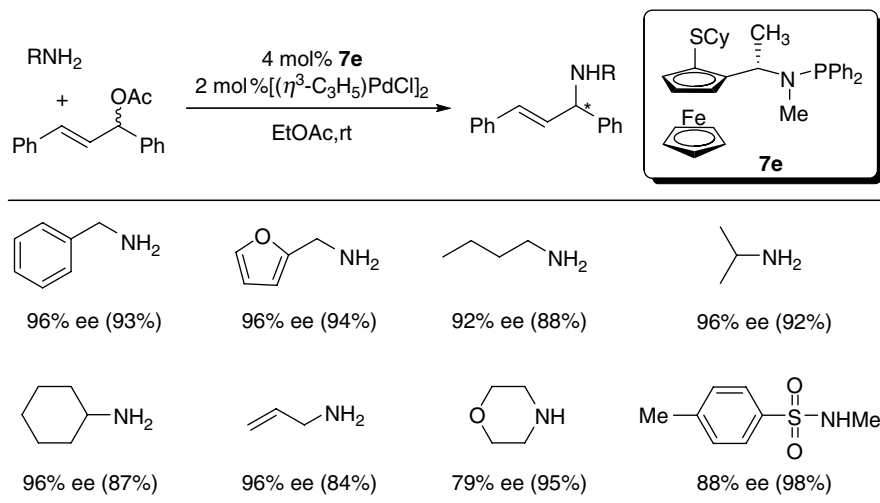
Scheme 22 Various alkylated products afforded from their corresponding substrates

5.2 Asymmetric Catalytic C–N Bond Formation

FerroNPS ligands were also applied to allylic amination and were found to exhibit excellent enantioselectivity (Scheme 23). Ligand **7e** which possessed a cyclohexylthioether group was found to be the ligand of choice. Under the optimized reaction conditions, heteroaromatic, primary and secondary amines were compatible in the palladium-catalyzed allylic amination system. In general, the corresponding amine products were obtained in excellent enantiopurities and high yields, except in the cases of morpholine, pyrrolidine, piperidine, and *para*-toluenesulfonamide. Interestingly, by adding BSA as an additional base, the case of sulfonamide gave the desired product in high enantioselectivity and excellent chemical yield.

5.3 Asymmetric Catalytic C–O Bond Formation

The enantioselective transition-metal-catalyzed allylic substitution [1–3, 154, 155] has been one of the most powerful tools for the generation of carbon–carbon and carbon–heteroatom bonds with various nucleophiles. The development of the synthesis of chiral compounds containing carbon–carbon or carbon–nitrogen bonds



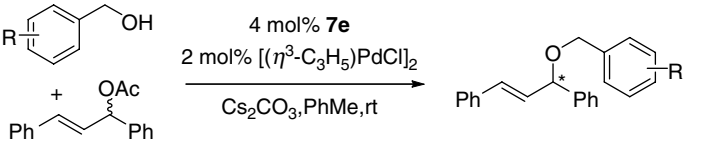
Note: The yield was given in brackets.

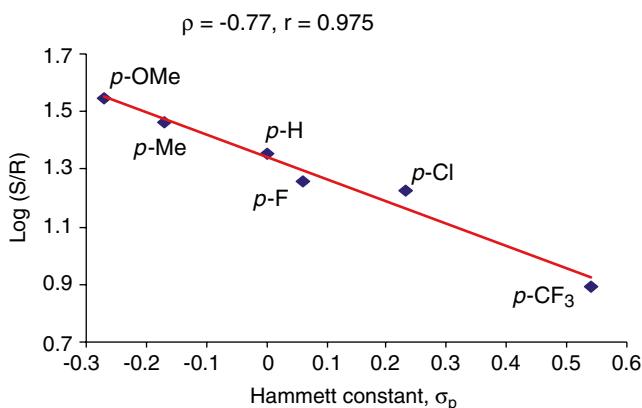
Scheme 23 Pd-catalyzed asymmetric allylic amination

from racemic allylic electrophiles has been well documented. However, the enantioselective allylic substitution of oxygen nucleophiles has only been sporadically studied. Enantioselective iridium-catalyzed allylic substitutions with a broad range of phenols (relatively soft nucleophiles) have been reported previously [156–160]. The reaction furnished good enantioselectivity by using monodentate phosphoramidites ligands. Apart from the iridium system, asymmetric palladium-catalyzed C–O bond formation between phenols and various allylic substrates to give ethereal products has also been studied [161, 162] (For Pd-catalyzed enantioselective etherification with limited scope of O-nucleophiles, see: [163]), [164–169]. In 2002, Kim and Lee [170] demonstrated that palladium-catalyzed etherification of allylic acetates with aliphatic alcohols afforded achiral ethers by using zinc alkoxides generated from diethyl zinc and an alcohol. These investigators claimed that zinc alkoxide-based nucleophile was critical for promoting the etherification and that might have resulted from a “softening” of the alkoxide anion by Zn(II) center [171, 172]. We explored the etherification under mild reaction conditions with good stereocontrol [173]. The fine-tunable ferrocenyl phosphinamidite-thioether ligands, (*S,pR*)-FerroNPS was used for this investigation. The ligand efficiency, which was studied by using ligand **7** with a thioether containing ethyl, *tert*-butyl, phenyl, and isopropyl group, showed somewhat lower enantioselectivities compared to the cyclohexyl analogue **7e** which afforded 91.6% *ee* and 98% isolated yield.

We further tested the effectiveness of the Pd-**7e** catalyst system. A diverse array of substituted benzyl alcohols were examined (Table 6). It was notable that an intriguing relationship between the enantioselectivity of the product and the electronic property of the substituted benzyl alcohols was found. A higher value of *ee* was observed when the benzyl alcohol containing an electron-rich *para*-substituent

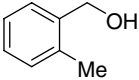
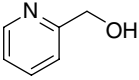
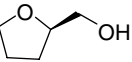
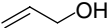

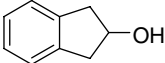
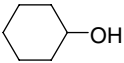

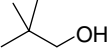
Table 6 The non-conjugate electronic effect on product enantioselectivities

			
R	Hammett constant (σ_p)	Yield (%)	ee (%)
H	0	98	91.6 (S)
<i>p</i> -OCH ₃	-0.27	94	94.5
<i>p</i> -CH ₃	-0.17	94	93.4
<i>p</i> -F	0.06	95	89.6
<i>p</i> -Cl	0.23	92	88.8
<i>p</i> -CF ₃	0.54	93	77.4

**Fig. 4** Hammett Plot for the Pd-catalyzed asymmetric allylic etherification with **7e** (ee range: 77–95%)

(such as OMe, Me etc.), while the selectivity gradually diminished as the substituent became more electron-deficient. The aromatic electronic effect was represented by a Hammett relationship (For a review of Hammett study, see: [174], [175], which showed a linear-free energy relationship between enantioselectivity and the electronic character of the substituent (Fig. 4) [129] (For recent references on aromatic electronic effects in asymmetric catalysis, see: [176]), [177–181]). This electronic effect on enantioselectivity was reported to be significant in this non-conjugated system, which has not been reported before.

The substrate scope of this etherification was further extended (up to 21 examples). Various substrates, such as primary, secondary, tertiary, and aromatic alcohols were compatible in the Pd-**7e**-catalyzed system (Scheme 24). The Pd-**7e** catalyst system was found to be also compatible with heterocycles. The reaction of the problematic substrate 2-pyridinemethanol, whereas the nitrogen atom of which might coordinate competitively to the metal center of the catalyst, proceeded smoothly to give the corresponding ether, although the reaction time had to be extended to 21 hours.

				
95% ee 87% yield	83% ee 71% yield	93% de 78% yield	93% ee 98% yield	94% ee 98% yield
				
93% ee 94% yield	96% ee 58% yield (73%)	ee (not determined) yield (trace)	ee (not determined) 80% yield (90%)	

Note: The conversion was given in brackets.

Scheme 24 Examples of alcohol substrates examined in the asymmetric allylic etherification

Primary aliphatic alcohols, such as allyl alcohol and *n*-butanol underwent the reaction to provide the desired etheral product in excellent yield with high enantioselectivity. The use of the secondary alcohol 2-indanol led to the desired product in good yield with 93% *ee*, whereas only moderate conversion was observed with the less strained cyclohexanol under the same reaction conditions albeit it gave a better *ee* value of 96%. *tert*-Butanol was found to be an inferior substrate in this transformation and such a result may be obtained from a highly steric congestion from the *tert*-butyl functional group. So as for an acquisition of proof, *neo*-pentyl alcohol was used under the identical conditions and the reaction provided the desired product with almost complete conversion (90% conversion attained).

6 Summary

The modular ligands with phosphorus donor atom have an extraordinary broad performance profile, are useful for a variety of synthetic applications, and have been successfully proven in enantioselective hydrogenation of prochiral ketones and acrylic acid derivatives, 1,4-addition of arylboronic acids to enones, bisalkoxycarbonylation, and other C–C bond formation reactions. The newly developed catalysts sometimes showed better reactivity or stereoselectivity comparing to the state-of-the-art BINAP and MeO-BIPHEP, probably due to the wide range of electronic properties exhibited by these diphosphine ligands. Particularly noteworthy is that the ruthenium(II) complexes of the P-Phos series are air-stable compounds that can be handled in air and can be used with a low catalyst loading. Further, with the inherently beneficial feature of the additional chiral auxiliary, axially chiral biaryl diphosphine ligands could be easily prepared without carrying out the tedious and time-consuming resolution. This strategy significantly simplified the preparation of chiral ligands and would make it possible to produce chiral ligands on a large scale.

Acknowledgment We thank the Research Grants Council of Hong Kong (CERG: PolyU5001/07P) and the University Grants Committee Areas of Excellence Scheme (AoE/P-10/01) for financial support. Fuk Loi Lam is grateful to the PolyU Postdoctoral Fellowship (G-YX1L).

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Asymmetric Catalysis from a Chinese Perspective

Ma, S. (Ed.)

2011, XII, 364 p., Hardcover

ISBN: 978-3-642-19471-9