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Review

Biheteroaromatic diphosphines and their transition metal complexes: synthesis, characterisation and applications in asymmetric catalysis

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Contents

Abstract

Chelating diphosphines supported by biheteroaromatic compounds find increasing application in metal-catalyzed homogeneous catalysis. This review describes recent development in the synthesis and characterisation of atropisomeric biheteroaromatic diphosphines and some of their metal complexes by spectroscopic methods. The applications of the diphosphines in the asymmetric hydrogenation of α-, β-amino acid precursors and ketones, 1,4-arylation of enones, bis-alkoxycarbonylation, Heck reaction and Diels–Alder reaction are also discussed.
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Keywords: Biheteroaromatic diphosphines; Axial chirality; Asymmetric hydrogenation; Asymmetric 1,4-addition; Bis-alkoxycarbonylation; Asymmetric Heck reaction; Asymmetric Diels–Alder reaction

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1. Introduction

The development of stereoselective organic transformations mediated by the catalytic use of chiral transition-metal complexes has been fuelled by both academic interests and practical needs in recent decades [1–3]. Most chiral catalysts are a combination of optically pure ligands and transition metals in different oxidation states. Often, the activity of a specific metal species can be adjusted by varying the electronic properties of the ligand. With regard to stereochemical control, a multitude of structurally diverse phosphine ligands are effective. Among which, the superiority of C_2-atropisomeric diphosphines, such as BINAP and BIPHEMP, especially in the hydrogenation of prochiral ketones [1,4], is commendable. Despite this, modifications of the electronic properties for these carbocyclic systems, and therefore the activity of the catalyst, are less flexible because regioselective introduction of other functional groups is not straightforward. Besides, the robustness of many of these ligands or their transition metal complexes, both well-defined and in situ generated, has not been sufficiently verified in solution under ambient conditions.

Over the past few years, a new design concept has emerged whereby biheteroaryls are utilized as supporting scaffolds for the phosphine groups. The reasons for using heteroaromatics are that: (i) some sites on a given heteroarene are inherently more reactive than other positions, thus leading to more predictable regiospecificity, (ii) heteroaromatic cycles can range from very electron-rich to very electron-poor, thereby flexibly adjusting the electron availability on the phosphorus atom and with the possibility of inducing extra stability on the resulting transition metal complex, and (iii) heteroarenes possessing basic sites may be amenable to recycling via a simple acidic extraction process.

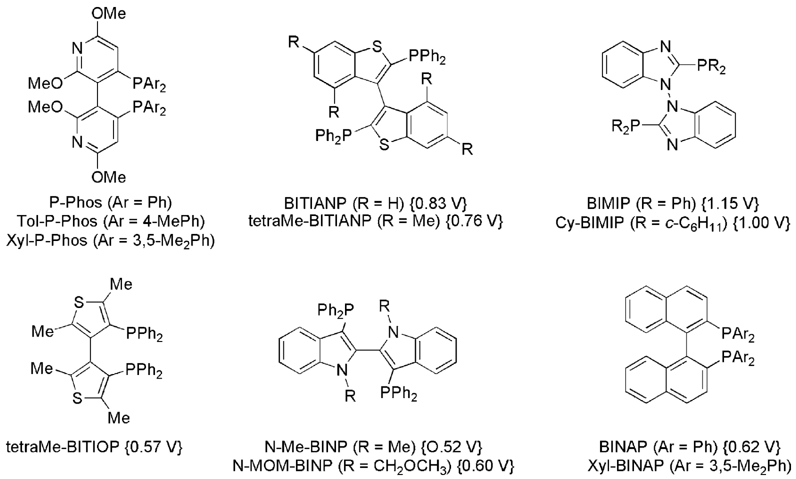
This article is a summary of the synthetic approach to biheteroaromatic diphosphines and their transition metal complexes, followed by their applications in asymmetric catalysis, with particular emphasis on the work from our laboratory. We are aware that Benincori et al. [5] has recently published a short review on the five-membered biheteroaromatic diphosphines, but for completeness, some of their material will be included here. The ligands to be discussed in this article are listed in Fig. 1.

2. Synthesis of biheteroaromatic diphosphine ligands

2.1. Synthesis of racemic biheteroaromatic diphosphine dioxides

Earlier studies showed that rhodium and ruthenium homogenous catalysts containing pyridylphosphine were ineffective in the hydrogenation of alkenes [6]. It was considered that the competitive coordination of the unprotected pyridyl group to the metal center had rendered the complex coordinately saturated. Our quest in this area began with the realization that phosphines containing 2,6-dimethoxypyridyl groups, a moiety in which the nitrogen atom was flanked by two methoxy groups to prevent complication arising from N-ligation to the metal center, are effective in the Rh-catalyzed hydrogenation of aldehydes, imines, C=C bond of enones and arylacrylic acids [7–9]. The catalyst could be separated from the product by phase extraction into a concentrated aqueous solution of HCl, and the acidified catalyst could be re-extracted from the aqueous solution with a water-immiscible organic solvent after the neutralization of the HCl with an inorganic base. The activity of the recovered rhodium–phosphine complex was proven to be intact as indicative in the ensuing hydrogenation reaction [7].

Emboldened by the above observations, we set out to design a family of atropisomeric diphosphine, P-Phos, whose synthesis represents one of the two broad synthetic strategies adopted for biheteroaromatic diphosphines. This approach involves the introduction of the phosphinoyl group onto the heterocyclic ring before a Cu-mediated homocoupling process to afford the C_2-symmetric diphosphine



P-Phos (Ar = Ph)
Tol-P-Phos (Ar = 4-MePh)
Xyl-P-Phos (Ar = 3,5-Me_2Ph)

BITIANP (R = H) {0.83 V}
tetraMe-BITIANP (R = Me) {0.76 V}

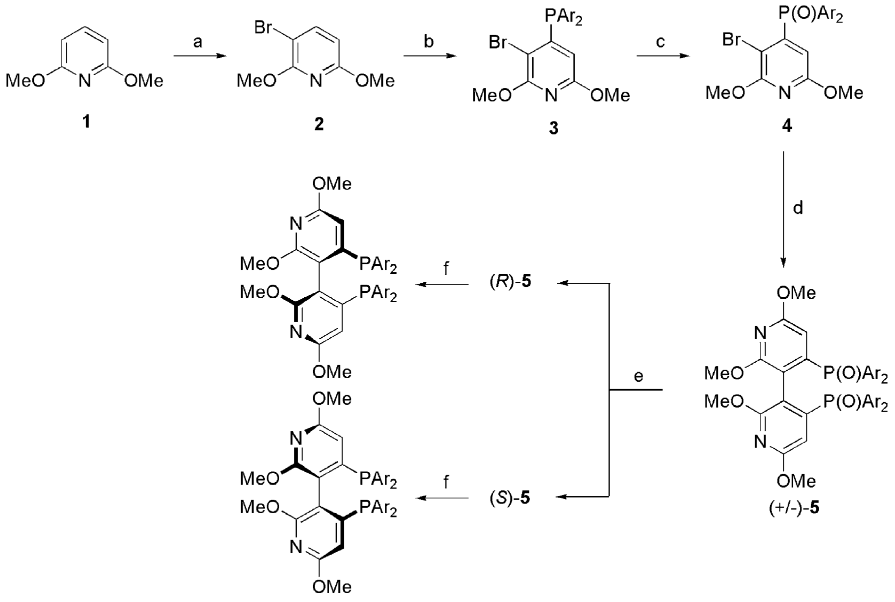
BIMIP (R = Ph) {1.15 V}
Cy-BIMIP (R = c-C_6H_{11}) {1.00 V}

tetraMe-BITIOP {0.57 V}

N-Me-BINP (R = Me) {O.52 V}
N-MOM-BINP (R = CH_2OCH_3) {0.60 V}

BINAP (Ar = Ph) {0.62 V}
Xyl-BINAP (Ar = 3,5-Me_2Ph)

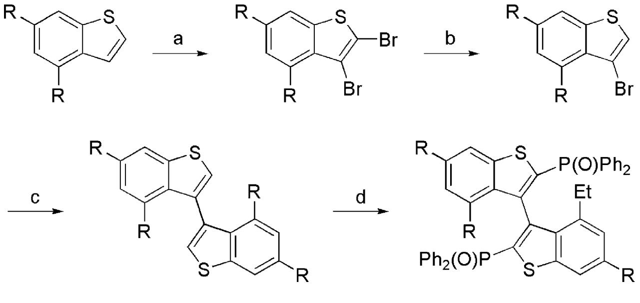
Fig. 1. Various C_2-atropisomeric diphosphines.



Scheme 1. Synthesis and resolution of the P-Phos family. (a) Br_2, CCl_4, −30 to −40 °C, 76%. (b) LDA, THF, −78 °C, then Ph_2PCl, −78 °C, 55–95%. (c) H_2O_2, acetone, 0 °C, 96–99%. (d) Cu, DMF, 140 °C, 80–85%. (e) (i) (+)-DBT or (−)-DBT; (ii) fractional crystallization (iii) 10% aqueous NaOH. (f) Cl_3SiH, Et_3N, toluene, 140 °C, 90–99%.

dioxide. The corresponding diphosphine was obtained by reduction with trichlorosilane. Thus, the commercially available 2,6-dimethoxypyridine **1** was brominated between −30 and −40 °C in CCl_4 using bromine. Regioselective lithiation of **2** at the 4-position with LDA at −78 °C in THF followed by treatment with chlorodiarylphosphine gave **3**, the oxidation of which with H_2O_2 led to the formation of the monophosphine oxide **4**. The racemic diphosphine dioxide **4** was obtained via Ullmann coupling of **4** (Scheme 1) [10-12].

The second approach is exemplified in the synthesis of BITIANP (Scheme 2) in which the Cu-mediated homocoupling of the heteroaromatic cycle takes place preceding the attachment of the phosphinoyl groups or phosphinyl groups [13]. For the BITIANP type ligand, methyl groups (R = Me) were originally introduced at the indicated positions to ensure hindered rotation about the interannular bond. Later, it was found that the substitution is, in fact, not necessary as the parent compound (R = H) is configurationally stable even at 140 °C in DMF solution.

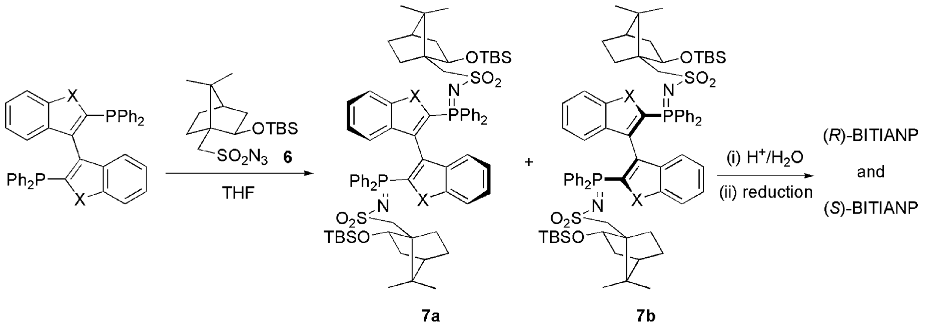


Scheme 2. Synthesis of (±)-BITIANP dioxides. (a) Br_2, $CHCl_3$. (b) (i) *n*-BuLi, THF, (ii) H_2O. (c) (i) *n*-BuLi, THF, (ii) $CuCl_2$. (d) (i) *n*-BuLi, THF (ii) Ph_2PCl, (iii) H_2O_2. (e) Cl_3SiH, Et_3N.

2.2. *Resolution of (±)-biheteroaromatic diphosphines or their dioxides*

No general optical resolution method is available to all racemic biheteroaromatic diphosphines. For reasonably electron-rich diphosphine dioxides, resolution could be readily achieved by fractional crystallization of the diastereomeric adducts formed from the racemic diphosphine dioxide with an enantiopure dibenzoyltartaric acid (DBT). The use of (−)-DBT furnished the (*R*)-isomer whereas the use of (+)-DBT provided the (*S*)-isomer for the non-benzocondensed diphosphines, such as the P-Phos series (Scheme 1) and tetraMe-BITIOP series, as the absolute configuration of their enantiomers have been experimentally corroborated by X-ray crystallography or by inference from their CD spectra. The opposite, however, applies to the condensed benzenoid-based diphosphines, such as BITIANP. The resolved, optically pure diphosphine dioxide was freed via a base extraction process. Subsequent reduction of the resolved diphosphine dioxides using trichlorosilane in toluene in the presence of triethylamine afforded the optically pure diphosphine.

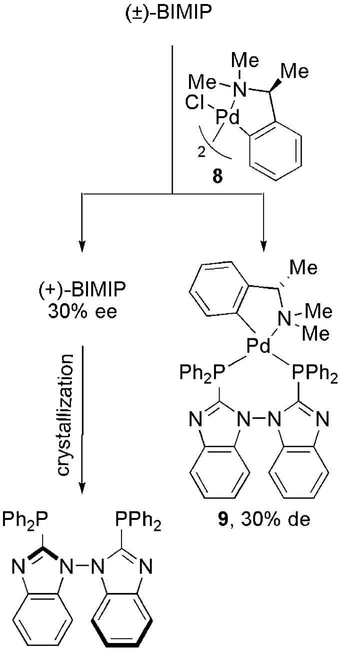
An alternative procedure for the resolution of BITIANP has been reported by Andersen et al. [14], who found that the diastereomeric phosphinimines derived from the Staudinger reaction of a racemic mixture of *P*-chirogenic monophosphines with sulfonyl azide **6** were stable toward flash chromatography on silica gel and prolonged storage under an ambient atmosphere. When the same method was applied to the BITIANP racemate, the respective enantiomers were successfully resolved after chromatographic separation of **7a** and **7b** followed by subsequent hydrolysis and then reduction (Scheme 3).



Scheme 3. Resolution of (±)-BITIANP via separation of diastereomeric phosphinimines.

Electron-poor diphosphines, such as BIMIPs, are not amenable to the above resolution [15]. A technique combining kinetic resolution and fractional crystallization was called for instead [16]. A quarter of a mole of chiral aminopalladacycle **8**, the resolving agent, was reacted with a racemic mixture of the diphosphine to give a diastereomeric palladium complex **9** with 30% de and the unreacted diphosphine with the same percentage ee (Scheme 4). Careful crystallization of the latter from ethyl acetate led to the isolation of the enantiopure (*R*)-(+)-BIMIP.

In order to study the electronic properties of the five-membered biheteroaromatic diphosphines, Sannicolò and coworkers measured the electrochemical oxidation potentials of the ligands using cyclic voltammetry. The measured value reflects the ease of removing an electron from the phosphorus atom. It is, therefore, obvious that more energy would be required to dislodge an electron off an electron-poor ligand, as reflected by a higher value in E° (V), and vice versa. Some of these values associated with the appropriate ligands pertinent to the following discussion are shown in Fig. 1. It is evident that the data follow an anticipated trend as the data should also relate to the rate of electrophilic substitution (ES) of the supporting heterocycle at the position bearing the phosphinyl group [17]. Thus, BINP is the most electron-rich system (ca. indole displays a very fast rate of ES especially at the 3-position), followed by BITIOP and BITIANP, while BIMIP is the most electron-poor ligand. The presence of the electron-releasing methyl groups also enhances the electron density on the heterocycle, and hence the connected diarylphosphinyl group.



Scheme 4. Resolution of (±)-BIMIP.

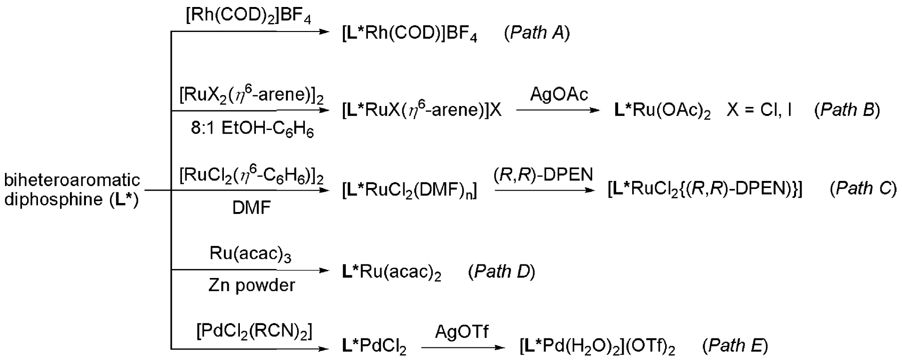
3. Synthesis and characterisation of transition metal complexes containing a biheteroaromatic disphosphine

3.1. Rhodium complexes

The rhodium complexes [**L***Rh(COD)]BF_4 **10–13** were synthesized by simply stirring a solution of $[Rh(COD)_2]BF_4$ with the biheteroaromatic diphosphine in methanol or dichloromethane at room temperature (Scheme 5, Path A). Diphosphine complexes of this type have been extensively investigated and the in situ generated complexes were already effective in the asymmetric hydrogenation reactions, therefore characterization was limited only to ^{31}P NMR spectroscopy (Table 1). Chemical shifts fall within a narrow range of 19.7–21.2 ppm. The P-Rh coupling constants of about 145 Hz are quite consistent for all the related complexes with a Rh(I) atom in a square planar environment.

3.2. Ruthenium complexes

Coordination complexes of the type [RuCl(biaryl diphosphine)(η^6-arene)]Cl are well known for their effectiveness in the asymmetric hydrogenation of functionalized ketones. The complexes could be conveniently prepared by mixing $[RuCl_2(\eta^6\text{-arene})]_2$ with the biheteroaryl diphopshine in a 8:1 mixture of ethanol-hexane at 50–60 °C for 1–2 h according to the method of Mashima et al. [18] (Scheme 5, Path B). Because of the magnetic non-equivalence of the phosphorus atoms, two signals were displayed with a coupling



Scheme 5. Synthetic methods for the transition metal complexes of biheteroaryl diphosphines.

constant of ~62–63 Hz in the ^{31}P NMR spectrum for each of the complexes at around δ 22.5–33.5 ppm for one signal and δ 38.3–40.0 ppm for the other. The analogous [RuI(biaryl diphosphine)(η^6-arene)]I were also prepared by adopting the same procedure. Further treatment of the cationic ruthenium halide complex with silver acetate afforded the neutral **L***Ru(OAc)$_2$ compound **15**–**16**.

Using the same starting materials as above but performing the reaction at 100 °C in DMF, complexes containing a variable number of coordinated solvent molecules were obtained as multiple phosphorus signals ranging from 17.7 to 69.4 ppm, all appearing as doublets (37–63 Hz), were observed. These compounds can be further transformed, using a Noyori procedure [19], into the six-coordinate diphosphine/diamino-Ru-complex {(*R*)-P-Phos member}RuCl$_2$-{(*R*,*R*)-DPEN} **30**–**32** [20] by treating them in the presence of *trans*-(*R*,*R*)-1,2-diphenylethylene-diamine {(*R*,*R*)DPEN}. ^{31}P NMR spectroscopic analysis shows a singlet at a chemical shift of δ 46.0 ppm for **30**, δ 45.1 ppm for **31** and δ 44.4 ppm for **32**. The near C$_2$-molecular structure of **31** (Fig. 2) was unambiguously determined by single-crystal X-ray diffractometry. The ruthenium center was ligated by two neutral phosphorus atoms and two neutral nitrogen atoms on the equatorial plane, and the chloride ligands in the axial positions. A dihedral angle of 3.2° between the P–Ru–P and N–Ru–N planes, a severely deviated N–Ru–N angle of 77.8° (cf. 90° for a perfect octahedral complex), and an angle of 166.1° formed by the two *trans* chlorides with the Ru-center reveal that the octahedral geometry around the ruthenium center is significantly distorted. Both Tol–P–Phos and DPEN chelate ligands coordinated to Ru adopt a distorted skew boat conformation of λ-helicity. A torsion angle of 109.9° between the least-squares planes of the two pyridyl planes and a natural bite angle of 94.4° for P–Ru–P were observed.

Another Ru-complex of P-Phos was synthesized via a different route (Scheme 5, Path D). In the presence of a reducing agent (e.g., zinc powder), ruthenium(III) complex Ru(acac)$_3$, which already contains the required anionic ligand, reacted with (*R*)-P-Phos in a non-diastereoselective fashion to yield compound **14** as a mixture of two isomers with Δ- or Λ-metal chirality in approximate 1:1 ratio [21]. The corresponding {(*R*)-BINAP}Ru(acac)$_2$ synthesized by the same method also behaves in a similar way [22]. This is to compare with the analogous [Ru{(*R*)-BINAP}(OCOCH$_3$)$_2$] com-

Table 1
The ^{31}P NMR data of biheteroaromatic diphosphines in various transition metal complexes

Metal complex	^{31}P NMR δ (*J* in Hz)	Metal complex	^{31}P NMR δ (*J* in Hz)
[{(*R*)-P-Phos}Rh(COD)]BF$_4$ **10**	21.1 (145)	[{(*R*)-P-Phos}RuCl(η^6-benzene)]Cl **26**	32.4 (63), 39.5 (63)
[{(*R*)-Tol-P-Phos}Rh(COD)]BF$_4$ **11**	19.7 (145)	[{(*R*)-Tol-P-Phos}RuCl(η^6-benzene)]Cl **27**	31.2 (63), 38.3 (63)
[{(*R*)-Xyl-P-Phos}Rh(COD)]BF$_4$ **12**	21.2 (145)	[{(*R*)-Xyl-P-Phos}RuCl(η^6-benzene)]Cl **28**	33.5 (63), 40.0 (63)
[{(*S*)-tetraMe-BITIOP}Rh(COD)]BF$_4$ **13**	20.5 (146)	[{(*S*)-tetraMe-BITIOP}RuCl(η^6-benzene)]Cl **29**	22.5 (62), 38.7 (62)
{(*R*)-P-Phos}Ru(acac)$_2$ **14**	56.6, 57.1	{(*R*)-P-Phos}RuCl$_2${(*R*,*R*)-DPEN)} **30**	46.0
{(*S*)-tetraMe-BITIANP}Ru(OAc)$_2$ **15**	60.7	{(*R*)-Tol-P-Phos}RuCl$_2${(*R*,*R*)-DPEN)} **31**	45.1
{(*R*)-BITIANP}Ru(OAc)$_2$ **16**	59.6	{(*R*)-Xyl-P-Phos}RuCl$_2${(*R*,*R*)-DPEN)} 32	44.4
{(*S*)-tetraMe-BITIOP}RuCl$_2$(dmf)$_n$ **17**	53.9–69.4 (38–53)	{(*S*)-tetraMe-BITIOP}PdCl$_2$ **33**	25.7
{(*S*)-tetraMe-BITIANP}RuCl$_2$(dmf)$_n$ **18**	48.0–54.0	{(*S*)-tetraMe-BITIANP}PdCl$_2$ **34**	21.2
{(*R*)-BITIANP}RuCl$_2$(dmf)$_n$ **19**	26.5–56.5 (37–63)	{(*R*)-BITIANP}PdCl$_2$ **35**	19.3
{(*S*)-*N*-Me-BINP}RuCl$_2$(dmf)$_n$ **20**	17.7–53.4 (37–44)	{(*S*)-*N*-Me-BINP}PdCl$_2$ **36**	20.5
{(*R*)-*N*-MOM-BINP}RuCl$_2$(dmf)$_n$ **21**	46.0–48.0	{(*R*)-BIMIP}PdCl$_2$ **37**	13
[{(*S*)-tetraMe-BITIOP}RuI(η^6-*p*-cymene)]I **22**	15.3 (63), 38.0 (63)	{(*R*)-Cy-BIMIP}PdCl$_2$ **38**	33.1, 29.8
[{(*S*)-tetraMe-BITIANP}RuI(η^6-*p*-cymene)]I **23**	19.0 (58), 37.0 (58)	[{(*R*)-P-Phos}Pd(H$_2$O)$_2$](OTf)$_2$ **39**	30.6
[{(*S*)-*N*-Me-BINP}RuI(η^6-*p*-cymene)]I **24**	27.6 (40), 36.8 (40)	[{(*R*)-Tol-P-Phos}Pd(H$_2$O)$_2$](OTf)$_2$ **40**	30.6
{(*S*)-tetraMe-BITIOP}Ru(2-Me-η^3-C$_3$H$_5$)$_2$ **25**	36.3	[{(*R*)-Xyl-P-Phos}Pd(H$_2$O)$_2$](OTf)$_2$ **41**	32.2

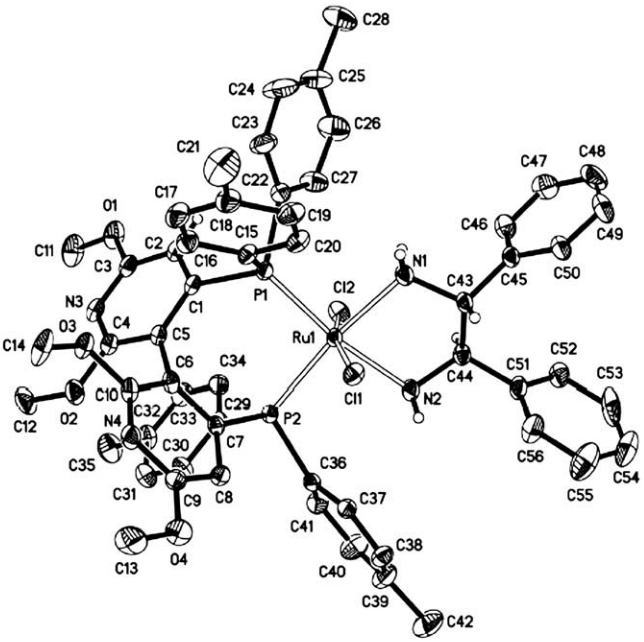


Fig. 2. X-ray structure of 31.

plex, prepared first by introducing the chiral ligand and later the acetate anion, where the Δ-configured was exclusively isolated [23]. The molecular structure of the Δ-isomer of **14** is shown in Fig. 3 [10]. The complex approaches closer to a true octahedral geometry with a P(1)–Ru(1)–P(2) angle of 93.4°, an O(1)–Ru(1)–O(2) angle of 91.4°, and an O(3)–Ru–O(4) angle of 90.6°. Furthermore, the two pseudo-axial phenyl groups are edge-exposed and one of the two pseudo-equatorial phenyl groups is face-exposed with respect to the P(1)–Ru(2)–P(2) plane.

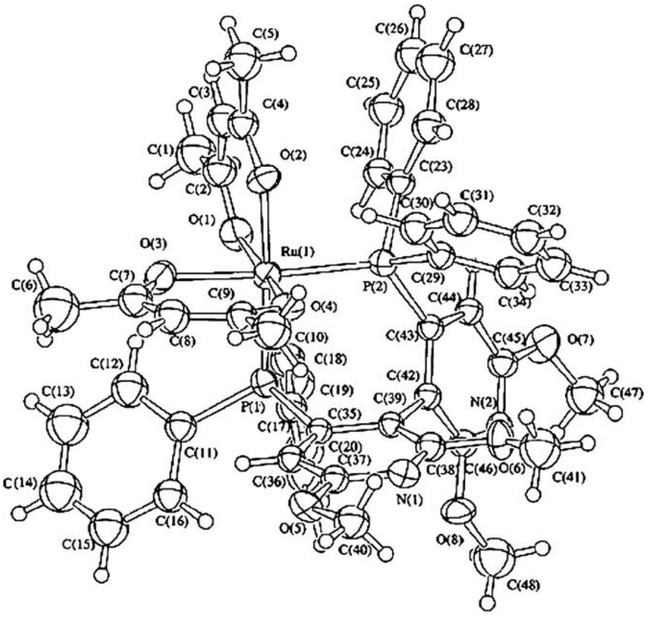


Fig. 3. X-ray structure of 14.

3.3. Palladium complexes

The palladium dichlorides of the five-membered biheteroaromatic diphosphines were prepared by reacting a bis(nitrile)palladium dichloride with the appropriate diphosphine in dichloromethane (Scheme 5, Path E). They could be used as catalyst precursors without purification; but suitable single crystals could be obtained by slow diffusion of diethyl ether into the chlorinated organic solvent. This had led to the determination of the X-ray structure of (BITIANP)$PdCl_2$ **35** (Fig. 4) [13]. In this structure, two of the diagonal P-phenyl groups are oriented almost parallel to their respective proximate benzothiophene moiety exhibiting a “quasi-graphitic” interaction, a phenomenon commonly observed with the triphenylphosphine ligand [24]. The biheteroaryl torsion angle is 110.4° for this complex.

The microcrystalline hydrated (*R*)-P-Phos-palladium triflate complexes **39**–**41** were synthesized by first reacting $[PdCl_2(PhCN)_2]$ with the corresponding P-Phos ligand in toluene at 70 °C for 2.5 h to give the chelates (P-Phos member)$PdCl_2$ (Scheme 5, Path E) [25]. The latter complexes, without further purification, were next treated with 2 equivalents of silver triflate in THF in the exclusion of light at room temperature for 2 h to afford the desired **39**–**41**. The chemical shifts for these compounds fall within the range of δ 30.6–32.2 ppm in the ^{31}P NMR spectra. The X-ray crystal structure of [{(*R*)-P-Phos}$Pd(H_2O)_2](OTf)_2$ **39** was shown in Fig. 5. The Pd atom is located on the two-fold rotation axes and there are two independent half molecules in the crystal. The square planar Pd complex is ligated by the (*R*)-P-Phos ligand in a bidentate fashion and the other two vacancies are occupied by two water molecules in a *cis* manner. The torsion angle of the pyridine rings of the bipyridine system in the ligand is 111.7°(6) and the natural P-Pd-P bite angle is 91.7°. The seven-membered heterometallacyclic ring involving the

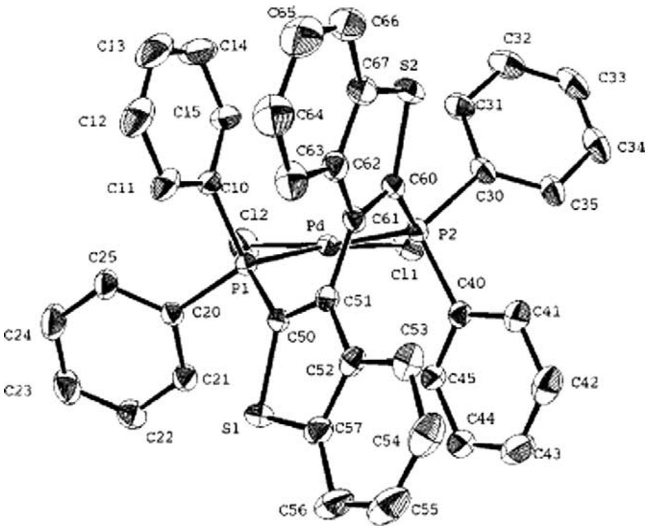


Fig. 4. X-ray structure of 35.

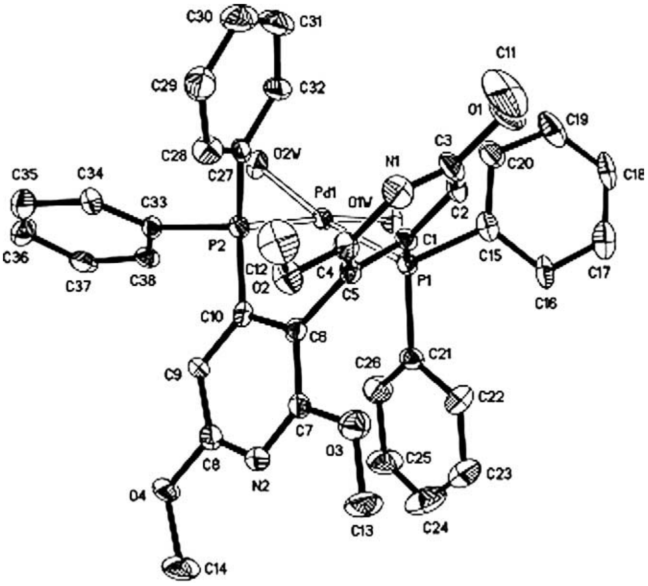


Fig. 5. X-ray structure of 39.

(*R*)-P-Phos ligand adopts a skewed boat conformation with a λ absolute configuration.

4. Applications in asymmetric catalysis

4.1. Hydrogenation of prochiral substrates containing C=C bonds

4.1.1. Hydrogenation of α-substituted acrylic acids

Complex {(*R*)-P-Phos}Ru(acac)$_2$ **14** was employed in the synthesis of the nonsteroidal anti-inflammatory drug naproxen via the hydrogenation of 2-(6′-methoxy-2′-naphthyl)propenoic acid derivative [11] (Fig. 6). An ee value of 95.3% for **42** was obtained at 0 °C under a 1000 psi H$_2$ pressure in methanol after 13–18 h. A marginal improvement (1–2%) was seen when an 0.6 equivalent of phosphoric acid was further added to the reaction mixture. The results compared favorably with the corresponding (*R*)-BINAP complex.

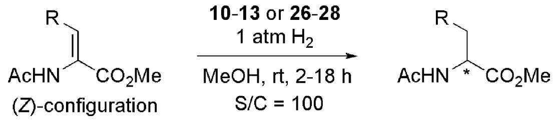


Fig. 7. Hydrogenation of β-substituted α-(acylamino)acrylate.

In the hydrogenation of tiglic acid precursor (Fig. 7), the ruthenium diacetate complex of BITIANP or tetraMe-BITIANP at *S*/*C* = 500 under 10 atm H$_2$ [13] was less enantioselective than the corresponding BINAP complex at *S*/*C* = 160 under 4 atm H$_2$ [26] while the ruthenium bis(allyl) complex of tetraMe-BITIOP gave slightly better enantioselection at a much lower catalyst loading (*S*/*C* = 3000) and under 10 atm H$_2$ [27]. The same trend was noted in the hydrogenation of atropic acid precursor.

4.1.2. Hydrogenation of β-substituted α-(acylamino)acrylates

The Rh-catalyzed asymmetric hydrogenation of (*Z*)-2-amido-3-substituted acrylic esters and acids has become an indispensable way for access to many natural and unnatural amino acids, including bioconjugates and building blocks for drugs and natural products. Various classes of phosphorus ligands are suitable for this reaction [28]; but that of biaryl diphosphines are relatively less investigated. The reaction involving the cationic Rh(I) complexes of P-Phos **10–12** could be carried out in a variety of common organic solvents, although methanol was found to be the best solvent. Thus, the reaction proceeded smoothly in methanol at ambient temperature with 1 atm initial H$_2$ pressure for 2 h to give a quantitative yield of the product with up to 94% ee for *para*-substituted methyl (*Z*)-2-acetamidocinnamate (Fig. 8, Table 2) [29].

[{(*R*)-Xyl-P-Phos}Rh(COD)]BF$_4$ **12** was found to be better than [{(*R*)-Tol-P-Phos}Rh(COD)]BF$_4$ **11** and the parent analogue [{(*R*)-P-Phos}Rh(COD)]BF$_4$ **10** in all the reactions investigated. This is in good agreement with some of our previous observations for BINAPO- [30] and BDPAB-related [31] bidentate ligands in Rh-catalyzed reactions—that ligands bearing 3,5-xylyl groups on the phosphorus outper-

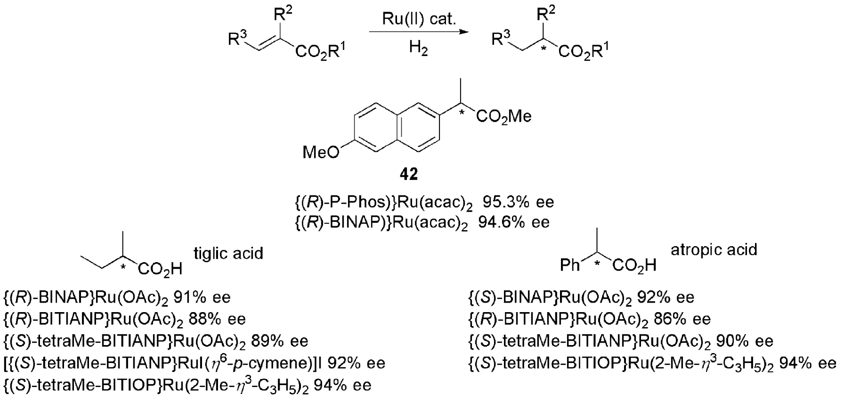


Fig. 6. Hydrogenation of α-substituted acrylic acids.

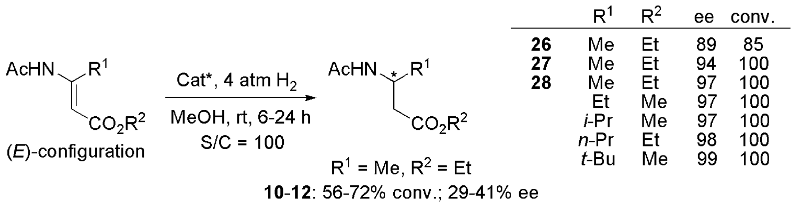


Fig. 8. Hydrogenation of β-substituted β-(acylamino)acrylate.

formed those bearing parent phenyl groups by a substantial margin.

On the contrary, the ruthenium complex **26** containing the parent P-Phos was the best catalyst for the same hydrogenation reaction under identical conditions to those described above. The *ortho*-substituted methyl (*Z*)-2-acetamidocinnamate gave a maximum 97% ee (Fig. 7). Miyaashita et al. [32,33] reported that the hydrogenation of dehydroamino acid derivatives catalyzed by (*R*)-BINAP-Ru(II) system led to the production of the hydrogenated product in 79–92% ee with an (*R*)-configuration whereas [{(*R*)-BINAP}Rh(CH_3OH)$_2$]ClO_4 exhibited an opposite sense of stereoinduction. Thus, it is intriguing that the use of the same (*R*)-configured P-Phos in either the Rh(I)- or the Ru(II)-system gave products of the same absolute configuration. However, the origin of this incongruity with the BINAP case is not understood.

4.1.3. *Hydrogenation of* β*-substituted* β*-(acylamino)acrylate*

Lately, the development of various methods to synthesize chiral β-amino acids have received considerable interest from researchers due to their special structural properties, pharmacological activities, and usefulness as building blocks for the synthesis of numerous biologically active compounds such as β-lactams and β-peptides [34]. As such, the [**L***RuCl(η^6-C_6H_6)]Cl catalyst system of the P-Phos series was found to be effective in the asymmetric hydrogenation of (*E*)-ethyl-3-acetamido-2-butenoate [35]. The presence of the methyl group(s) in **27** and **28** was apparently conducive to the enhancement of reaction rate and enantioselectivity as they promoted faster reactions and optically purer products. Other β-amino acid derivatives could also be obtained via enantioselective hydrogenation of the corresponding (*E*)-β-alkyl-β-(acylamino)acrylates with **28**. The resulting enantioselectivities were in the range of 89–99% ee with ee increasing as the steric bulk of the β-position increased (Fig. 8). However, the [**L***Rh(COD)]BF_4 catalyst system **10**–**12** of the P-Phos series worked much less efficiently. Interestingly though, the hydrogenation products catalyzed by the Rh- and Ru-complexes with the same chiral ligand were found to be of opposite configuration, in agreement with the observation by Lubell et al. [36].

For a comparison, the (*Z*)-isomer was also hydrogenated with the Rh- and Ru-catalysts. The catalytic activity was strongly affected by the reaction solvent. For instance, the hydrogenation of the (*Z*)-isomer using **28** was not at all active in aprotic solvents such as THF and CH_2Cl_2, but quantitative conversion was observed in MeOH albeit with low ee. In contrast, the Rh catalyst **12** was much more active in THF coverting (*Z*)-β-alkyl-β-(acylamino)acrylates to the corresponding β-amino acid derivatives under 8 atm hydrogen pressure and at ambient temperature. Nevertheless, the enantioselectivity was only moderate (68–82% ee).

Table 2
Enantioselective hydrogenation of β-substituted α-(acylamino)acrylate

Catalyst	R, ee (%)						
	Ph	2-ClPh	3-ClPh	4-ClPh	4-MePh	4-OMePh	1-Naphthyl
10	38	–	–	–	–	–	
11	46[a]	–	–	–	–	–	
12	90	92	93	93	94	94	
26	90	97	91	94	91	90	
27	85	95	86	84	83	81	
28	73[b]	92	82	81	74	76	
13	94[c]						94[d]

[a] 70% conversion.

[b] 64% conversion.

[c] Hydrogenation of the acid in EtOH (*S*/*C* = 90, 3 atm H_2) instead of the methyl ester.

[d] Reaction in THF/MeOH, *S*/*C* = 80, 20 atm H_2.

4.2. *Hydrogenation of simple and functionalized ketones*

4.2.1. *Hydrogenation of β-ketoesters*

Optically pure β-hydroxy carboxylic esters are an important class of intermediates for the synthesis of many bioactive or natural compounds. The first efficient asymmetric catalytic transformation of the β-ketoesters to the β-hydroxy esters via transition metal complexes in homogeneous hydrogenation reaction was demonstrated by Noyori et al. [37] utilizing the BINAP/Ru(II) system. Following this success, various ruthenium(II) complexes of the five-membered biheteroaromatic diphosphine series and the P-Phos family were found to be well-suited also for this transformation, achieving enantioselectivity of up to 99% ee with the use of Tol–P–Phos [11] and the BITIANP family [13] (Fig. 9). The useful pharmaceutical intermediate, (*S*)-3-hydroxy-3-phenyl propionate **43** [38], was synthesized previously via hydrogenation with the BINAP/Ru(II) system with unsatisfactory enantiopurity (ca. 85% ee) [37]. With a switch to the use of the P-Phos members, the compound was obtained in far better ee's.

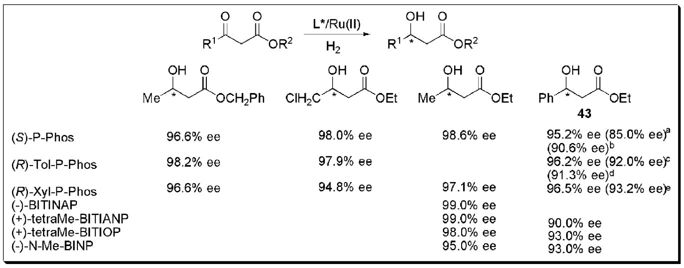
While enantioselectivity is a major concern in asymmetric synthesis, the demonstration of high substrate-to-catalyst ratio with consistently high enantioselectivity is an important measure of the commercial feasibility of a reaction. Using [(P-Phos member)RuCl(η^6-C_6H_6)]Cl and at a catalyst loading of 7500:1, **43** was obtained after 15 h with only slight reduction in enantioselectivity on a 30 g scale [12]. However, under these conditions, marked differences in the reactivity of the catalyst were observed, with Xyl–P–Phos imparting the best activity (98% conversion) when compared with Tol–P–Phos and P-Phos (90 and 84% conversion, respectively). This observation is in good agreement with that of the Sannicolò group where electron-rich biaryl diphosphine enhances catalyst activity [39].

Another critical issue is the stability of the metal phosphine catalyst under a normal atmosphere since many of the existing systems are sensitive to air in solution, and exposure to only trace amounts of air may seriously hamper its activity and enantioselectivity. The rigorous degassing of reaction systems using nitrogen gas is essential to keep the activities of many catalysts alive, which makes industrial applications more difficult. We are therefore delighted to learn that when [{(*R*)-Tol-P-Phos}RuCl(η^6-C_6H_6)]Cl **27** or [{(*R*)-Xyl-P-Phos}RuCl(η^6-C_6H_6)]Cl **28** in a 1:1 EtOH:CH_2Cl_2 solution, without prior degassing and pre-drying, was exposed to air for 10 h before charging hydrogen into the system, both the activity (100% conversion) and enantioselectivity (~96% ee for both catalysts) were essentially unchanged in the hydrogenation of the prescursor ketoester of **43**. Although little change in activity was noted for [{(*R*)-BINAP}RuCl(η^6-C_6H_6)]Cl under the same conditions, a sharp decrease in ee from 92 to 66% was observed.

We also attempted to recycle the catalyst by passing the reaction mixture through a silica gel-based cation exchange column. Both [{(*R*)-P-Phos}RuCl(η^6-C_6H_6)]Cl and [{(*R*)-BINAP}RuCl (η^6-C_6H_6)]Cl could be recovered by this method. In the hydrogenation of methyl acetoacetate, the P-Phos catalyst gave 99% ee in the initial run and BINAP gave 98% ee. While the recovered catalysts were equally active after three recycling processes, the enantioselectivity of the BINAP system dropped much more rapidly than the P-Phos counterpart [40] (Fig. 10). These experiments serve to highlight the merits, namely recyclizability and air-stability, of P-Phos from an industrial perspective.

4.2.2. *Hydrogenation of simple ketones*

Among the most sought after chiral intermediates are simple chiral secondary alcohols. A number of methods employing organometallic reagents have been developed for this purpose [41,42], but none live up to the expectations of industrial requirements because sub-stoichiometric amount of ligands are often used. In another development, frustrations were frequently met in attempts to achieve high enantioselectivities in the hydrogenation of simple ketones due to the lack of a contiguous ancillary chelating group in the substrate. An important breakthrough had appeared in recent years when the Noyori group unveiled complexes of the type $RuCl_2$(diphosphine)(diamine) **44** [43], coupled with a catalytic amount of a strong base, can efficiently hydrogenate a diverse array of unfunctionalized simple ketones with a substrate-to-catalyst ratio of over two million, and yet, retaining high stereoselectivity. The best catalyst was found to be *trans*-$RuCl_2$\{(*S*)-Xyl-BINAP)\}\{(*S*)-DAIPEN)\}. While the optimal P-Ar substituent (complex **32**) was still the 3,5-xylyl group in our P-Phos case [19,44], a much cheaper diamine (*trans*-1,2-diphenylethylenediamine, DPEN) was sufficient to attain extremely high enantioinduction, thereby obviating the use of the exotic DAIPEN diamine. Excellent



				43
(*S*)-P-Phos	96.6% ee	98.0% ee	98.6% ee	95.2% ee (85.0% ee)[a] (90.6% ee)[b]
(*R*)-Tol-P-Phos	98.2% ee	97.9% ee		96.2% ee (92.0% ee)[c] (91.3% ee)[d]
(*R*)-Xyl-P-Phos	96.6% ee	94.8% ee	97.1% ee	96.5% ee (93.2% ee)[e]
(-)-BITINAP			99.0% ee	
(+)-tetraMe-BITIANP			99.0% ee	90.0% ee
(+)-tetraMe-BITIOP			98.0% ee	93.0% ee
(-)-N-Me-BINP			95.0% ee	93.0% ee

[a] Result obtained with (BINAP)$RuBr_2(dmf)_n$. [b] At S/C = 7500 with 84% conv. [c] Result obtained from the analogous BINAP/Ru(II) complex under the same conditions. [d] At S/C = 7500 with 90% conv. [e] At S/C = 7500 with 90% conv.

Fig. 9. Hydrogenation of β-ketoesters.

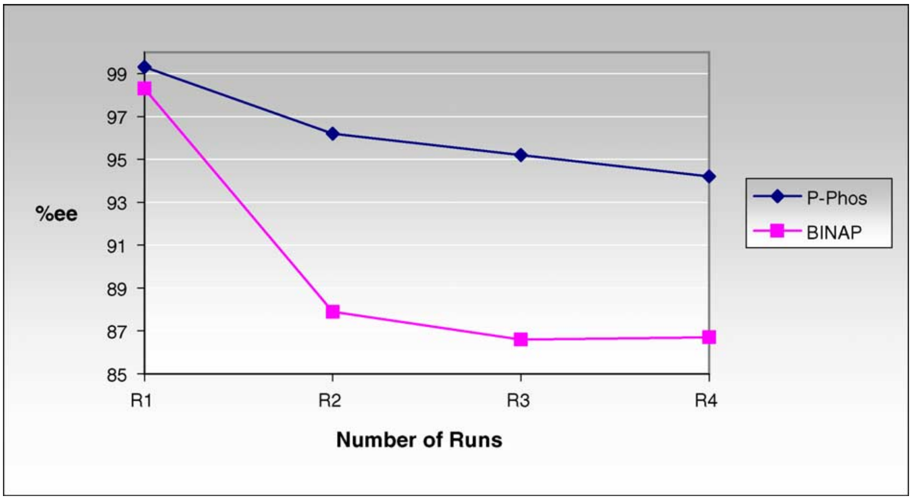


Fig. 10. Recycling experiments using (*R*)-P-Phos and (*R*)-BINAP in the Ru-catalyzed hydrogention of methyl acetoacetate.

ee's have been obtained for the hydrogenation of a variety of Ar-substituted acetophenones **45**, heteroaryl methyl ketones **46** and aryl cyclopropyl ketones **47** with up to >99.0% ee at *S*/*C* = 100,000 (Fig. 11). As for unsymmetrical benzophenones **48**–**50**, the position of the substituent has an enormous effect on enantioselectivity. *Ortho*-substituent on the benzene ring usually provides enough steric bias for excellent stereocontrol. However, *meta*- or *para*-groups are too distant to exert significant stereodiscrimination, resulting in extremely low to moderate ee. In addition, a profound electronic effect was observed for **50**. When R in **50** was a normal methyl group, ee of just 3.9% was resulted; whereas when this methyl group was fully fluorinated, the ee rose up to 77.2%.

4.3. *C–C bond-forming reactions*

4.3.1. *1,4-Addition of arylboronic acids to α,β-unsaturated ketones*

Enantioselective Rh-catalyzed β-arylation of α,β-unsaturated compounds, particularly with BINAP, has enjoyed great success within the last several years [45]. We found that (*S*)-P-Phos is an alternative outstanding chiral ligand for the Rh(I)-catalyzed 1,4-addition of arylboronic acids to an assortment of cyclic and acyclic enones (Fig. 12) [46]. Thus, at 100 °C in a 20:1–10:1 mixture of dioxane/water and in the presence of 3 mol% of the P-Phos/Rh(I) catalyst and 1.4–5.0 equivalents of the organoboron reagent, *o*-, *m*- and *p*-substituted aryl groups were successfully introduced at the β-position of an enone in remarkable yields and ee's up to 99% (Fig. 13). Apart from obtaining comparable results, the P-Phos/Rh(I) catalyst system had overcome some of the problems that were encountered by the analogous BINAP/Rh(I) system. For example, while either no or low yields were obtained for **52**, **55**, **57** and **59** using the BINAP system, the P-Phos system remained highly active providing the addition products in excellent yields and enantioselectivities.

4.3.2. *Bis-alkoxycarbonylation of styrene*

Pd-catalyzed bis-alkoxycarbonylation of olefins was reported by Heck back in the early 1970s [47]. To achieve an asymmetric version of this type of multiple carbonylation of

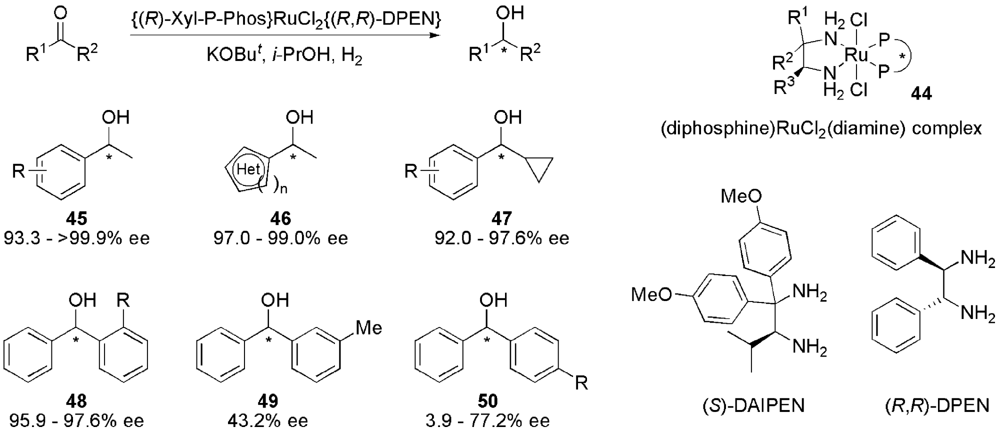


Fig. 11. Hydrogenation of simple ketones.

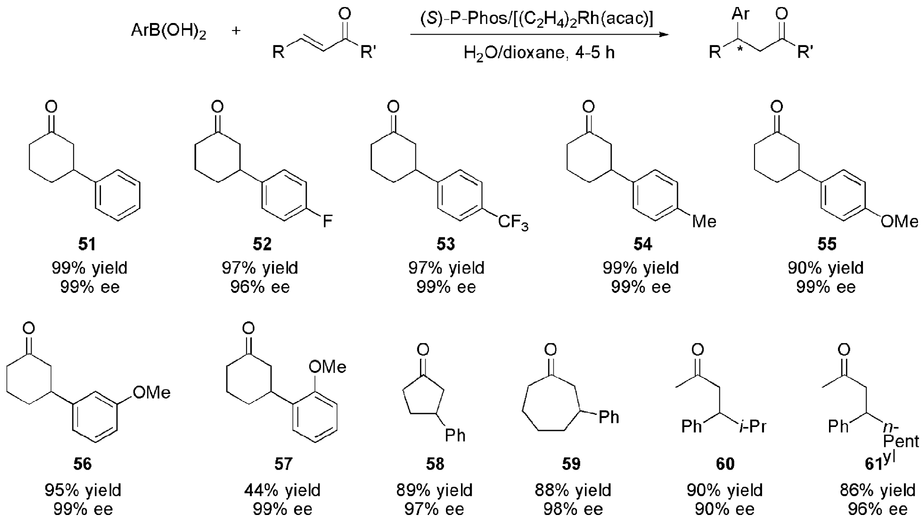


Fig. 12. Eanantioselective 1,4-addition of arylboronic acids to α,β-unsaturated ketones.

olefins remains a formidable challenge, the successful development of which may open up an excellent opportunity for the synthesis of optically active butanedioic acid derivatives. These are important intermediates for certain pharmaceuticals [48], building blocks for renin inhibitors [49] and chiral polyketones [50,51]. In this regard, we used 0.8 mol% of the Pd-complexes **39**–**41** to catalyze the bis-alkoxycarbonylation of styrene in methanol in the presence of 2 equivalents of an oxidant (benzoquinone) at an initial CO pressure of 125 bar (Scheme 6) [25]. Apart from the desired product dimethyl-2-phenylsuccinate (DMPS), the reaction also produced by-products methyl cinnamate (MC), methyl phenylpropionates (MP) and some unidentified oligomeric compounds. It was found that complete conversion was difficult to achieve, ranging only between 56 and 67%. It was interesting to note that all three ligands showed the same level of stereoinduction. The best chemoselectivity being 76% was attained by using **39**.

4.3.3. Heck reaction

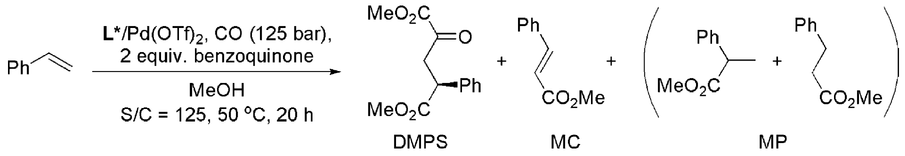
In the intermolecular asymmetric Heck reaction between dihydrofuran and aryltriflate or alkenyltriflate (Scheme 7) [52], Tietze found that the reaction proceeded at a rate depending upon the electronic property of the diphosphine. The relatively electron-deficient BITIANP promoted the reaction with a rate comparable to that of BINAP and a rate almost four times higher than that of the most electron-rich BITIOP among the tested ligands. In addition, BITIANP produced **62a** as the exclusive product, but BINAP and BITIOP showed a somehow less effective regiocontrol, giving **62b** as a side product with low ee value. Exhibiting good enantioselectivity in the preliminary study, the use of the kinetically efficient BITIANP further led to a variety of chiral Heck products with up to 96% ee and 93% yield.

With a view to synthesize non-racemic benzazepines via an intramolecular Heck reaction, BITIANP and BITIOP were again employed along with the standard ligands MeO-BIPHEP and BINAP [53] (Scheme 8). Contrary to the foregoing Heck case, BITIOP displayed a much better stereoselectivity (92%) and chemoselectivity giving **63b** as the sole product, whereas the rest of the other ligands tested gave **63a** in variably low yields and **63b** with poor ee's.

Although the relatively electron-poor (*R*)-BITIANP gave rise to the most active catalysts in the above cases, there is no clear relationship between enantioselectivity and kinetic efficiency.

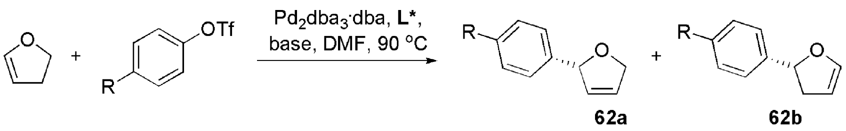
4.3.4. Diels–Alder reaction

Early reservation for the use of C_2-diphosphines in combination with a transition metal is probably a repercussion of an early report in which DIOP and CHIRAPHOS showed only poor to mediocre enantioinduction in the Ru(II)-



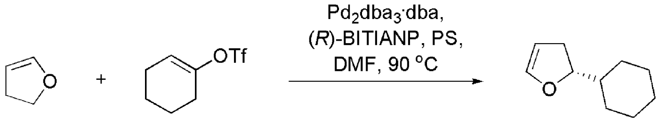
	DMPS	MC	MP
L* = (*R*)-P-Phos	47.6% (83% ee)	13.4%	1.8%
L* = (*R*)-Tol-P-Phos	30.1% (82% ee)	13.9%	2.6%
L* = (*R*)-Xyl-P-Phos	23.5% (82% ee)	15.7%	1.0%

Scheme 6. Asymmetric bis-alkoxycarbonylation of styrene.



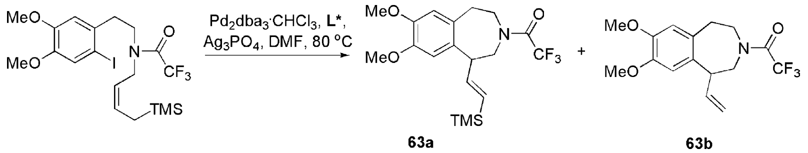
L*	R	*t* (h)	Yield (%) 62a	Yield (%) 62b	ee (%) 62a	ee (%) 62b
(*R*)-BINAP	H	18	58	20	42	33
(*S*)-tetraMe-BITIOP[a]	H	72	73	12	4	0
(*R*)-BITIANP	- H	18	84	--	91	--
(*R*)-BITIANP	Cl, OMe, CN, COMe	18-24	84-93[b]		90-96[c]	

[a] Reaction in benzene at 70 °C. [b] Only **62a** was detected. [c] Ee for **62a**.



76% yield, 86% ee

Scheme 7. Asymmetric intermolecular Heck reaction.

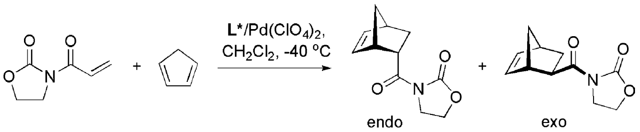


L*	*t* (h)	Yield (%) 63a	Yield (%) 63b	ee (%) 63a	ee (%) 63b
PPh_3[a]	6	4	70		
(*R*)-BINAP	40	7	72	18	64
(*R*)-MeO-BIPHEP	65	15	42	5	25
(*R*)-BITIANP	19	2	42	--	20
(*S*)-tetraMe-BITIOP	58	--	71	--	92

[a] $Pd(OAc)_2$, KOAc and Pr_4NBr were used instead of $Pd_2dba_3.CHCl_3$ and Ag_3PO_4.

Scheme 8. Enantioselective synthesis of benzazepines via intramolecular Heck reaction.

catalyzed hetero-Diels–Alder reaction [54]. Apparently, the choice of the transition metal and ligand is critical. Following recent successful work on the catalytic BINAP/Pd(II)- and Pt(II)-promoted Diels–Alder reaction [55], the Sannicolò group utilized the palladium(II) (perchlorate) complexes of their biheteroaromatic diphosphine complexes in the cycloaddition of *N*-acryloyl-1,3-oxazolidin-2-one with cyclopentadiene, obtained by thermal retro-Diels–Alder reaction, in dichloromethane (Scheme 9) [56]. Carrying out the reaction at low temperatures was essential in order to slow down the competitive, non-stereoselective background reaction. Thus, high endo-to-exo selectivity and enantioselectivity were achieved at −40 °C with further improvement at −60 °C but at the sacrifice of rate (Table 3). It was discovered that the electron-poor phosphorus ligands, such as



Scheme 9. Pd-catalyzed asymmetric Diels–Alder reaction.

Table 3
Asymmetric Diels–Alder reaction catalyzed by biheteroaryl diphosphine-palladium complexes

L*	$E°$ (V)	Time (h)	Conv. (%)	de (%)[a]	ee (%)[b]
(−)-*R*-BIMIP	1.15	40	60	59	48
(+)-Cy-BIMIP	1.00	110	50	85	20
(−)-*S*-BITIANP	0.83	15	100	82	72
(+)-*R*-BINAP	0.63	15	100	86 (90)[c]	89 (99.7)[c]
(+)-*S*-tetraMe-BITIOP	0.57	15	100	81 (84)[c]	90 (94)[c]
(−)-*S*-*N*-Me-2-BINP	0.52	15	100	87 (92)[c]	91 (96)[c]

[a] The endo-isomer was the major product.

[b] Enantiomeric excesses were determined by chiral HPLC (chiralcel OD; eluant: hexane-*iso*-propanol, 85:15.

[c] Reaction at −60 °C.

the BIMIP series, generated less active catalysts as conversions were still moderate even after prolonged reaction times. Remarkably, the kinetically less efficient catalysts were also the least stereoselective catalysts as it was contended that the uncatalyzed reaction was still significant at $-40\,^{\circ}$C.

5. Conclusion

By utilizing the unique chemistry of heteroaromatic chemistry, two general synthetic routes for C_2-biheteroaromatic diphosphines have been developed in recent years. These ligands, when complexed with a transition metal precatalyst, have been successfully applied in enantioselective hydrogenation of prochiral ketones and acrylic acid derivatives, 1,4-addition of arylboronic acids to enones, bis-alkoxycarbonylation, Heck reaction and Diels–Alder reaction. Because of the wide range of electronic properties exhibited by the biheteroaromatic diphosphines, they sometimes show better activity or enantioselectivity in comparison with the analogous carbocyclic atropisomeric diphosphines, such as the benchmark ligands BINAP and MeO-BIPHEMP. The potential use of these ligands under industrial settings have also been realized, as in the case of P-Phos, whose ruthenium(II) complexes have been demonstrated to be air stable and can be used with a low catalyst loading. We believe that with the inherently special characteristics of heteroarenes, their related phosphines, not necessarily confined to C_2-symmetric ligands, will be able to adapt to the various nature of asymmetric transition metal-catalyzed reactions.

Acknowledgements

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