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Review

Recent advances in developing new axially chiral phosphine ligands for asymmetric catalysis

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Contents

Abstract

This review article illustrates the concept and approach for designing new C_2-symmetric chelating atropisomeric chiral phosphines containing heterocyclic scaffolds. The versatility in structural modification is highlighted, and that it offers an effective avenue to access chiral ligands of diverse electronic and steric properties for optimization in various catalytic asymmetric transformations. In this article, the uses of atropisomeric

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chiral phosphines in some asymmetric transformations such as hydrogenation and alkyl-/arylation reactions will be discussed with reference to updated literature findings as well as the author's original research.

Keywords: Asymmetric catalysis; Chiral ligands; Phosphines

1. Introduction

Significant achievements have been made in chiral transition metal complex-catalyzed stereoselective organic transformations [1]. Thus far, most of these chiral catalysts are a combination of optically pure ligands and transition metal ions 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) are proved to be highly effective for a myriad of asymmetric transformations.

Over the past two decades, enormous success has been achieved in the use of the C_2-symmetric atropisomeric diphosphine ligands for Rh- or Ru-catalyzed asymmetric hydrogenation reactions. Notwithstanding, 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 procedures for structural modification of the ligand scaffold. Moreover, due to the sensitivity toward oxidation, the robustness of many of these chiral transition metal-ligand systems, both well-defined and *in situ* generated, has hardly been meticulously verified in solution under ambient conditions.

The catalytic property of transition metal complexes with chiral phosphine ligands bearing heterocyclic moieties such as pyridyl rings has been relatively unexplored. Here we present some recent development in the preparation of new classes of axially chiral phosphine ligands with heterocyclic scaffolds. Their uses for transition metal catalyzed asymmetric catalysis will also be discussed [2]. The ligands described in this section are depicted in Fig. 1.

2. Development of new chiral diphosphine ligands

2.1. Preparation of bipyridyl diphosphine ligands

Earlier studies showed that rhodium and ruthenium complexes containing pyridylphosphines were ineffective catalysts for homogenous hydrogenation of alkenes [3]. The poor catalytic activities are attributed to competitive coordination of the unprotected pyridyl group to the metal center. With this point in mind, we embarked in our research in the design and synthesis of a series of bipyridyl phosphine 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 [4]. Indeed, the Rh-P-Phos complexes were found to be effective for a variety of asymmetric hydrogenation reactions [5].

Apparently, the P-substituents can be systematically varied to produce some chiral phosphine ligands of diverse electronic and steric properties for reaction optimization. In this context, several P-Phos analogues: Tol-P-Phos, Xyl-P-Phos and Cy-P-Phos have been prepared by attaching different P-substituents onto the dipyridyl skeleton instead of 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 (Scheme 1), the commercially available 2,6-dimethoxypyridine **7** was brominated at −40 to −30 °C in CCl_4 to give compound **8**. Regioselective lithiation of **8** at the 4-position with LDA at −78 °C in THF followed by treatment with chlorodiarylphosphine gave **9**. Oxidation of **9** with H_2O_2 led to the formation of the monophosphine oxide **10**. The racemic diphosphine dioxide **11** was obtained by copper promoted Ullmann coupling of **10** (Scheme 1).

Racemic P-Phos dioxide was resolved by fractional crystallization using enantiopure dibenzoyltartaric acid (DBT) as resolving agent. The use of (−)-DBT furnished the (*R*)-isomer, and (+)-DBT provided the (*S*)-isomer of the diphosphine oxide. The absolute configurations of their enantiopure diphosphine oxides were experimentally established by X-ray crystallography.

The axially chiral bis(aryldicyclohexylphosphine) dioxide [(*S*)-Cy-P-Phos oxide, (*S*)-**13**] can be prepared by PtO_2-catalyzed hydrogenation of the enantiopure P-Phos oxide (*S*)-**12** [6]. Similarly, (*R*)-**13** was readily prepared from (*R*)-**12** (Scheme 2).

Initially, attempts to effect catalytic hydrogenation of (±)-**12** to the corresponding (±)-**13** using Pd/C as catalyst and an ethanol–acetic acid mixture as solvent under 500 psi of hydrogen at 50 °C after 36 h were unsuccessful. However, when PtO_2 was employed as catalyst, the reaction proceeded smoothly in acetic acid, and a mixture of the desired (±)-**13** along with some partially hydrogenated (±)-**14** (molar ratio = 5:1 according to ^{1}H and ^{31}P NMR analyses) was obtained after 72 h at room temperature. The ratio of (±)-**13** and (±)-**14** was further improved to 10:1 when the reaction temperature increased to 50 °C within the same reaction time frame. Eventually, (±)-**13** was obtained exclusively by simply prolonging the reaction time to 120 h at 50 °C. Thus, under the same conditions, optically pure **13** was obtained from the hydrogenation of the corresponding enantiomer of **12**.

2.2. Development of BisbenzodioxanPhos ligand

Built upon the success of P-Phos and other related chiral heteroaromatic phosphine ligands, we turned to development of a new type of chiral ligand, BisbenzodioxanPhos ligand. [7] BisbenzodioxanPhos bears a bis-benzodioxane structure, a structural feature similar to that H_8-BINAP. This ligand is

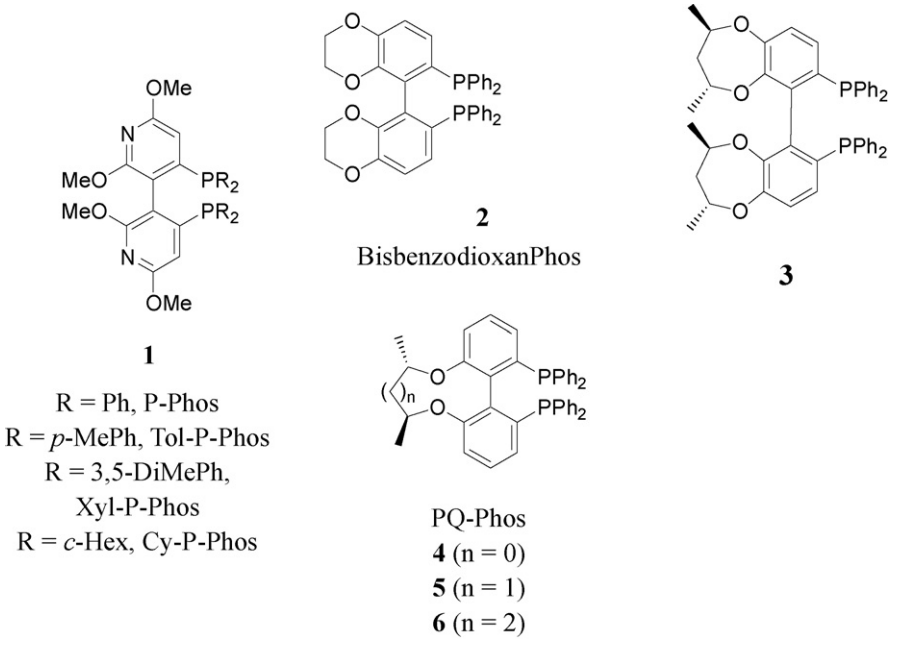
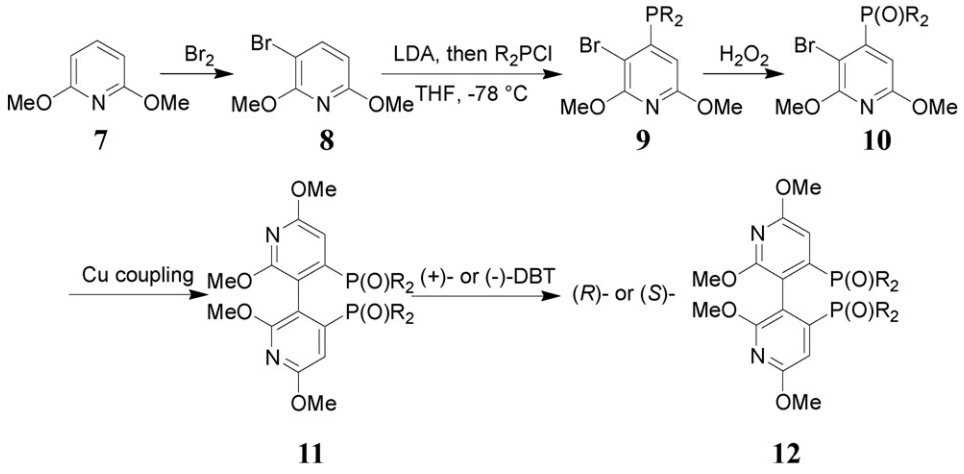
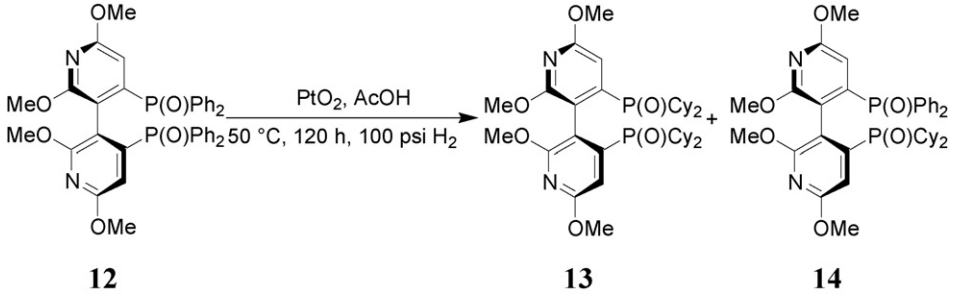


Fig. 1. Structures of axially chiral diphosphine ligands.

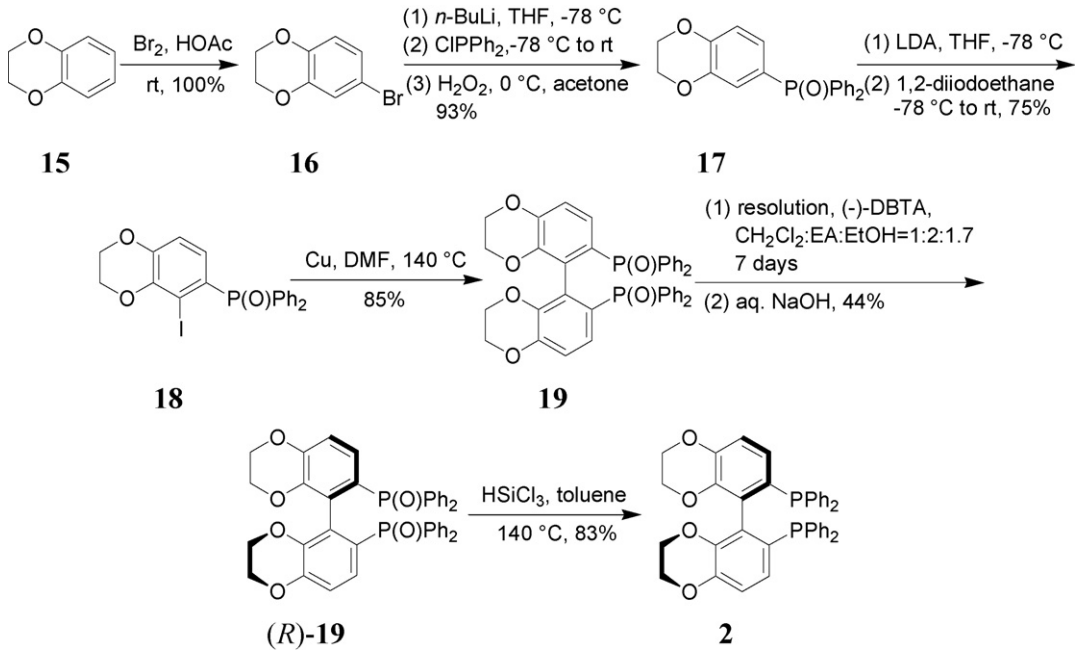


Scheme 1. Preparation of P-Phos dioxide.

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 ligands. Bromination of a commercially available **15** gave the corresponding bromide **16** in almost quantitative yield. Lithiation of **16** with *n*-butyllithium in THF at −78 °C, followed by the addition of chlorodiphenylphosphine and subsequent oxidation with hydrogen peroxide, produced phosphine oxide **17**. A sequence of *ortho*-lithiation/iodination with LDA *via* a thermodynamic-



Scheme 2. Preparation of Cy-Phos oxide **14**.



Scheme 3.

controlled process instead of the generally used iodination with diiodoethane gave product **18** in 75% isolated yield. The racemic bis(diphenylphosphine oxide) **19** was obtained in good yield (85%) *via* Ullmann coupling of the iodophosphine oxide **18**. The enantiomeric products **19** were resolved using either (−)- or (+)-DBTA as resolving agent; the (*R*)-phosphine oxide was obtained with (−)-DBTA as resolving agent. The structure and the absolute configuration of (−)-DBTA·(*R*)-**19** were determined by X-ray crystallography. The chiral ligand BisbenzodioxanPhos (**2**) was obtained in over 99% optical purity after trichlorosilane reduction of **19** at 140 °C.

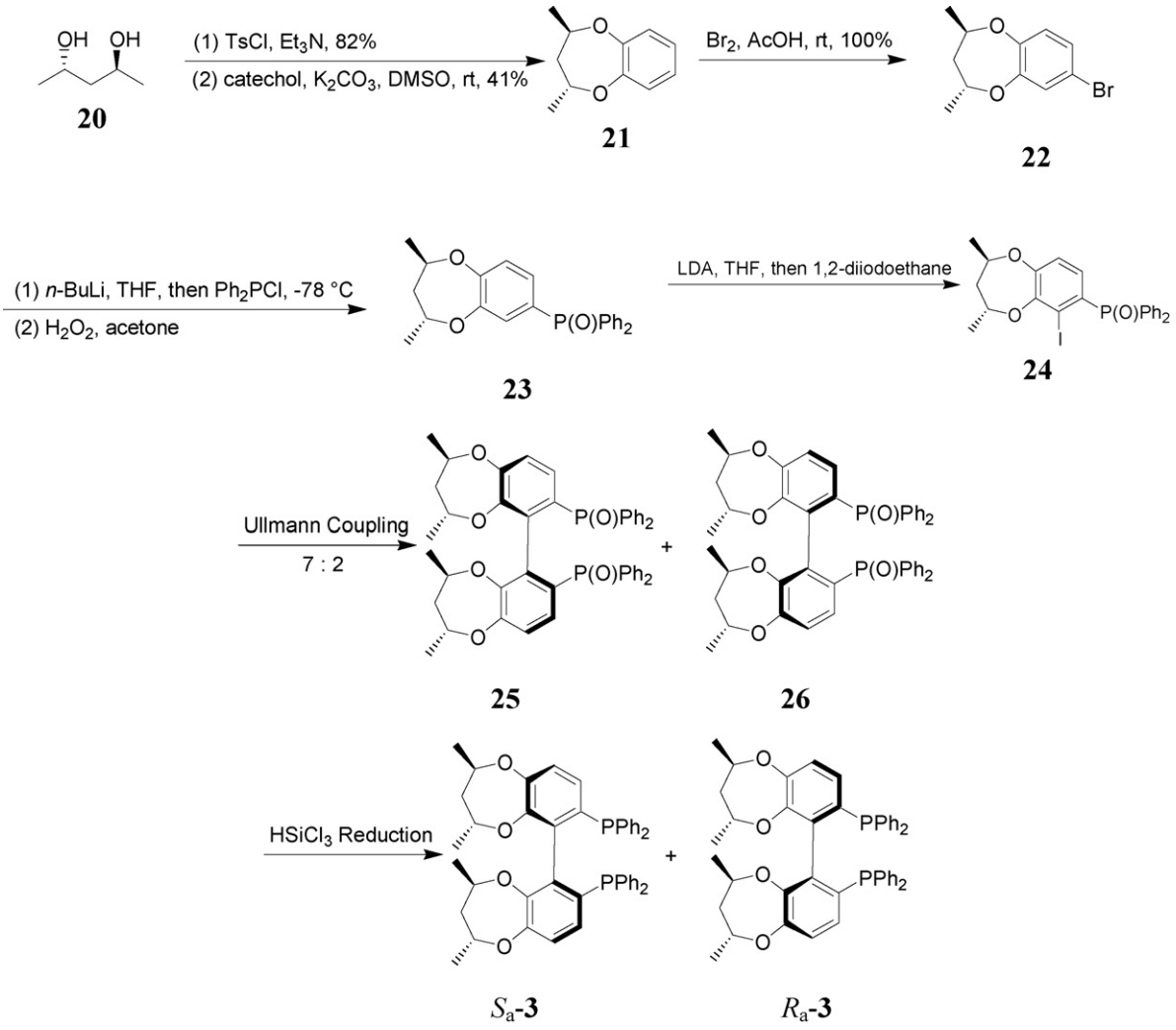
2.3. Diastereoselective synthesis of chiral phosphine ligands without resolution

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 good-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 [8], kinetic resolution of racemic substrates [9], asymmetric catalytic coupling [10], and chirality transfer from central, axial, and planar asymmetry have been reported [11].

Compared to the classical approaches involving chiral resolution, diastereoselective syntheses of atropisomeric biaryl diphosphine oxides – the precursors of the chiral diphosphine ligands – was unexplored with respect to chiral phosphine synthesis. In this regard, we pursued earlier a stereoselective intermolecular Ullmann coupling of two chiral phosphine oxide for synthesis of chiral atropisomeric diphosphine ligands [12]. As shown in Scheme 4, reaction of catechol with (2*S*,4*S*)-pentanediol di-*p*-tosylate derived from **20** gave (2*R*,4*R*)-2,4-dimethyl-3,4-dihydro-2*H*-1,5-benzodioxepine **21**. Subsequent bromination gave compound **22**, which was converted to **23** after phosphinylation and subsequent oxidation. Iodination of compound **23** gave **24**, and the copper-mediated Ullmann coupling produced a pair of diastereomers **25** and **26** (**25**:**26** = 7:2). With special care, both diastereomers of the chiral phosphine oxides **23**–**24** can be separated by column chromatography, and subsequent trichlorosilane reduction should readily produce the target chiral ligands **3**.

To further improve the diastereoselectivity of the Ullmann coupling reaction and to study the effects of the 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) [13].

Differing from chiral ligands **3** in which each aryl ring contains one chiral inducing element, the two aryl rings in **4**–**6** 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 diols, and such design was expected to promote 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 **27** produced the corresponding di(*m*-bromophenyl)ether **28**. Lithiation of compounds **28a**–**28c** followed by phosphylation and oxidation gave the corresponding phosphine oxides **29a**–**29c**. At this point, one can either prepare the axially chiral diphosphine oxides **31a**–**31c** *via* direct oxidative coupling, or *via* Ullman type coupling reaction of the corresponding diiodides **30a**–**30c** which were prepared *via* lithiation of **29** and subsequent addition of iodine. Ullman type reaction of the **30a**–**30c** were found to be



Scheme 4.

more effective, and compounds **31a**–**31c** were obtained in satisfactory yields and over 99% distereoselectivity (**31a**: 91% yield, de > 99%; **31c**: 71% yield, de > 99%; **31c**: 61% yield, de = 98%). The desired chiral ligands **4**–**6** were finally obtained after reduction of compounds **31a**–**31c** (Scheme 5). This route obviates the tedious and time-consuming resolution step. This method, in combination of the preparation of chiral ligands **3** would offer a general and practical tool for the development of previously un-investigated atropdiastereomeric biaryl diphosphine ligands.

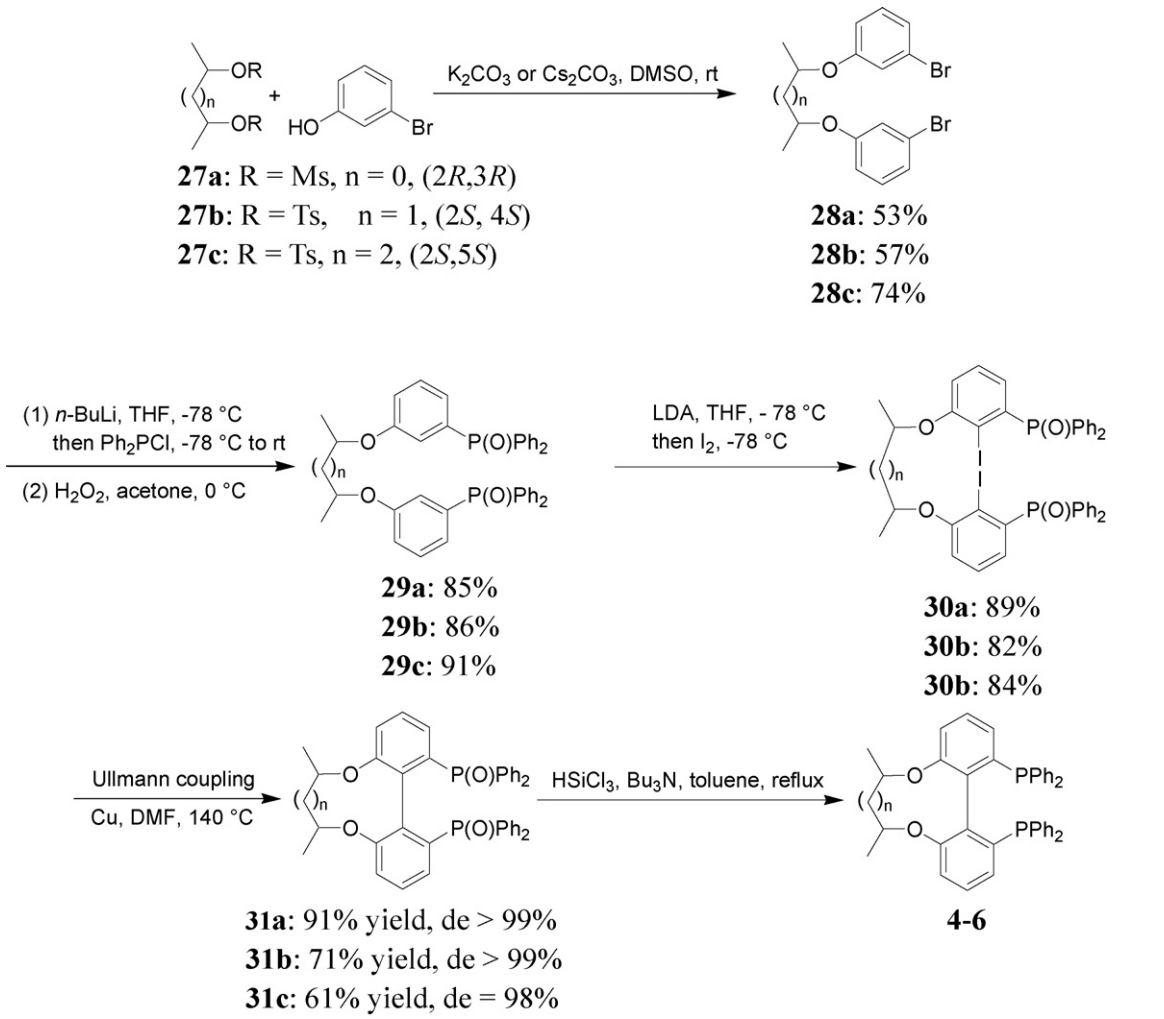
2.4. Axially chiral ligands with phosphorus and heterocyclic nitrogen donors

Mixed donor P,N-type ligands belong to a class of hemilabile ligands. Possessing with a combination of hard and soft donor atoms, the P,N-mixed donor ligands exhibit unsymmetrical coordination to transition metals resulting in unique reactivity to their metal complexes (Fig. 1) [14,15]. As such, the hard ends weakly coordinate to soft metal centers and easily dissociate to afford a vacant site for substrate coordination [16,17].

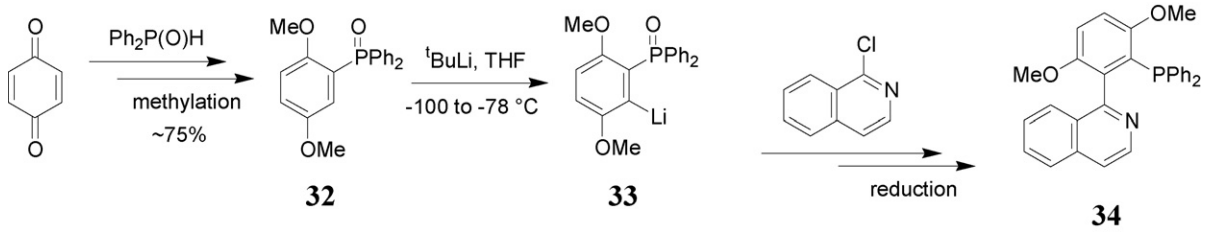
Brown and co-workers pioneered in the preparation of axially chiral phosphineamine ligand, 1-(2′-diphenylphosphino-3′-6′-dimethoxyphenyl)isoquinoline **34** (Scheme 6). [18] Initially, Michael addition of the commercially available diphenylphosphine oxide to benzoquinone followed by the methylation of phenol group afforded compound **32**. Liathiation of the substituted phosphine oxide **32** by *tert*-buyllithium at −100 °C produced the thermodynamically preferred 6-lithio compound **33**. Cross-coupling reaction of **33** with substituted 1-chloroisoquinoline, followed by reduction of the product phosphine oxide yielded the desired atropisomeric P,N ligand **34**.

However, this ligand was found to racemize (half-life ∼ 1 h) at ambient temperature (Scheme 7), and that this precluded its application in asymmetric catalysis [19].

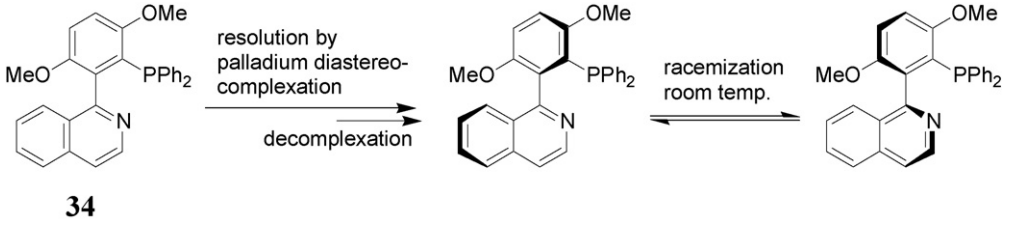
To provide a more conformationally stable analogue, Brown et al. reported the synthesis of 1,1′-(2-diphenylphosphino-1-naphthyl)isoquinoline (QUINAP) **41** in 1993 (Scheme 8) [20]. Treatment of 2-naphthol with bromine and later methylation of the hydroxyl group afforded 1-methoxy-2-bromonaphthlene (**35**). Compound **35** was converted to arylboronic acid **36** by lithiation with *n*-BuLi and subsequently quenched with triisopropylborate and acid hydrolysis. Suzuki cross-coupling reaction of **36** with chloroisoquinoline gave **37** in good yield.



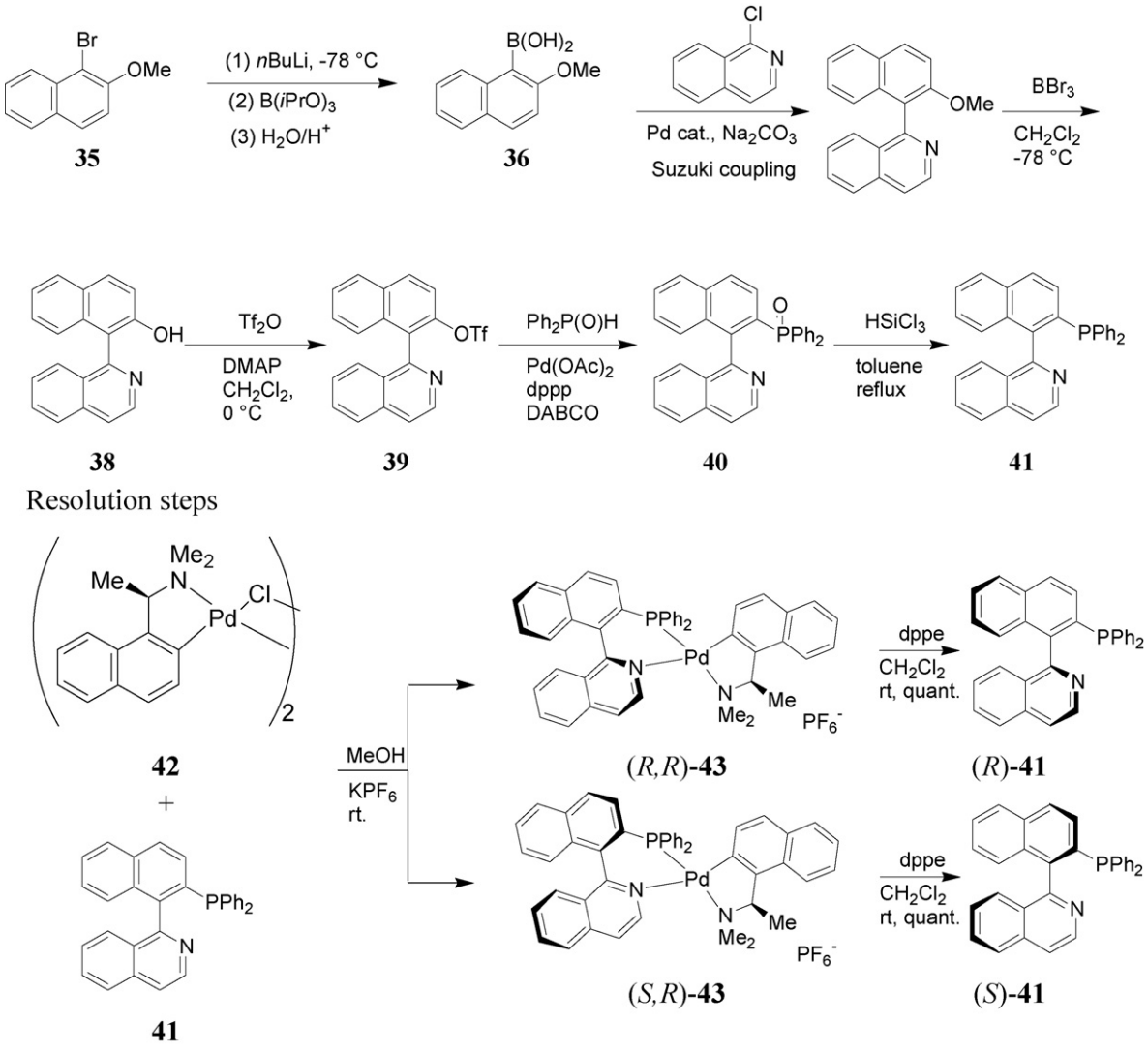
Scheme 5. Preparation of PQ-Phos **4**–**6**.



Scheme 6.



Scheme 7.



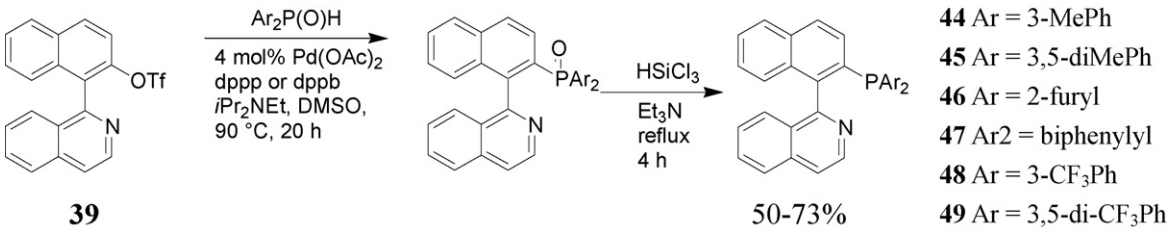
Scheme 8.

The compound **37** was transformed to its aryl triflate **39**, which was then transformed to phosphine oxide **40** by the palladium-catalyzed cross-coupling reaction with diphenylphosphine oxide. Reduction of **40** with trichlorosilane produced the racemic QUINAP **41**, which was then subjected to diastereomeric resolution by treatment with chiral (*R*)-palladium-amine-napthyl complex **42**. Fractional crystallization of these diastereomeric complexes with different solvents afforded pure diastereomers. Brown and co-workers found that the diastereomers were inseparable when palladium-amine-phenyl complex was used. Decomplexation of the pure diastereomer (*R*,*R*)-**43** or (*S*,*R*)-**43** by 1,2-bis(diphenylphosphino)ethane (dppe) yielded optically active QUINAP (*R*)-**41** or (*S*)-**41**, respectively [20]. The axially chiral QUINAP was found to be configurationally stable at room temperature.

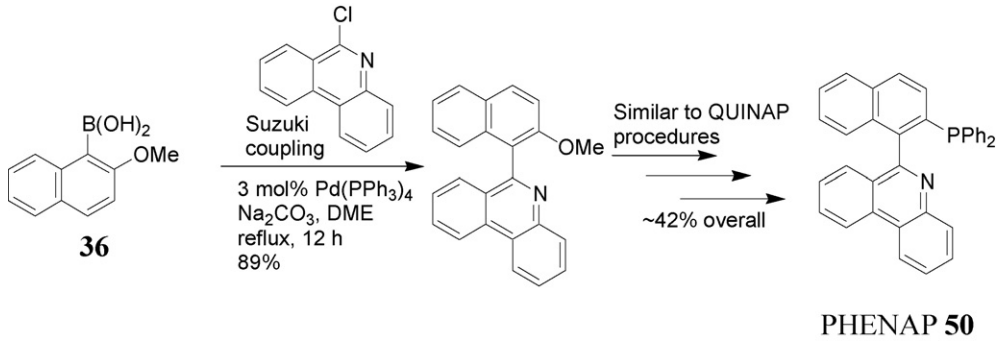
Brown and co-workers also reported the preparation of various QUINAP analogs with different aryl substituents at the phosphorus center (Scheme 9). [21] These analogs were prepared by reacting **39** with different diarylphosphine oxides [$Ar_2P(O)H$] by palladium-catalyzed C–P bond formation. Regardless of the similar synthetic procedures, the resolution steps would require individual optimization. Different substituted QUINAP **44**–**49** required different counter anions in the diastereomeric complexation as well as different solvent mixtures for the effective fractional crystallization step.

Analogous atropisomeric ligands PHENAP **50** and 1-methyl-2-diphenylphosphino-3-(1′-isoquinolyl)indole **(56)** were also reported recently by the same research group. PHENAP **50** was synthesized by a procedure similar to that of QUINAP, while substituting 1-chloroisoquinoline with 6-chlorophenanthridine [22] instead for the Suzuki cross-coupling reaction (Scheme 10) [23].

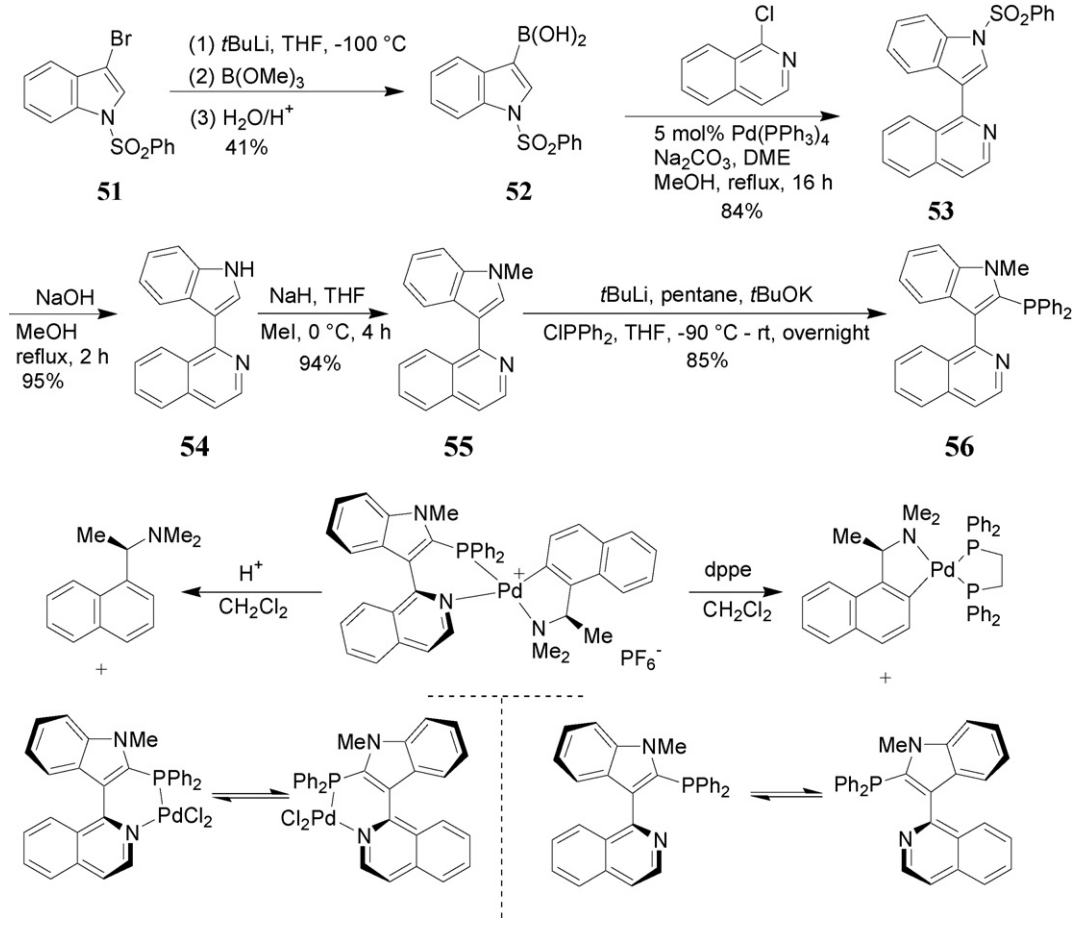
Exhibiting a different bite angle, indolyl P,N ligand **28** containing a 2-diphenylphosphinoinodole group instead of a naphthyldiphenylphosphinine group, was prepared according to Scheme 6 [24]. The bromoindole [25] **51** underwent lithium-halide exchange with *tert*-BuLi and the intermediate was trapped at −100 °C by trimethylborate, followed by acid hydrolysis to obtain the indolylboronic acid **52**. The Suzuki cross-coupling of



Scheme 9.

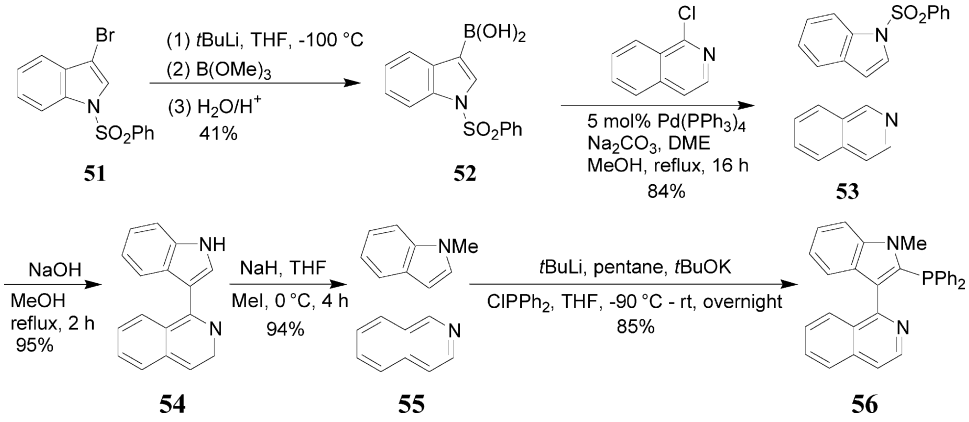


Scheme 10.



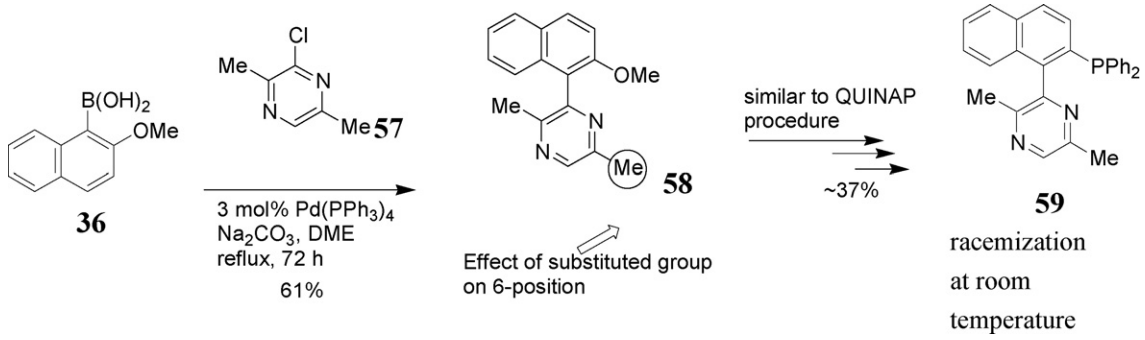
Scheme 11.

boronic acid **52** with 1-chloroisoquinoline gave **53** as product. Removal of the $-SO_2Ph$ group afforded a free −NH indole **54**, which was protected with methyl group under basic conditions to yield compound **55**. The introduction of diphenylphoshine group to the ligand precursor was accomplished by *ortho*-metalation with *tert*-BuLi to abstract the 2-H proton of the indole group and subsequent quenching with chlorodiphenylphosphine to yield P,N ligand **56**. Unfortunately, indolyl P,N ligand **56** was found to be stereochemically labile at ambient temperature, either in the form of dichloropalladium-PN complex or as a free ligand (Scheme 11). Therefore, attempt to resolve ligand **56** by diastereocomplexation with chiral palladium-amine-naphthyl complex was unsuccessful.



Recently, Guiry synthesized ligand **59** by cross-coupling of **36** with pyrazine **57** (Scheme 12) [26]. Of interest was to determine the effect of the 6-methyl group on the enantioselection and the enantiomeric stability of the ligand provided by the locking interaction of the naphthyl group (8-H) and the 3-methyl group. Moreover, the authors also aimed to examine the effect of basicity of the nitrogen donor atom in the new ligand compared to that of QUINAP **11**. A similar cross-coupling synthetic procedure was adapted for the preparation of ligand **59** (Scheme 12). However, the half-life of the racemization of the ligand **59** was found to be 24 h at 25 °C. This suggested that the 3-methyl group in pyrazine scaffold in ligand **59** and the methoxy group in ligand **34** are not bulky enough (with naphthalene 8-H, and isoquinoline 8-H, respectively) to prevent racemization at room temperature (Fig. 2).

Guiry and Quéguiner disclosed a new type of P,N ligand **63** containing 2-phenylquinazoline moiety independently in 1999 (Scheme 13) [27,28]. Commercially available



Scheme 12.

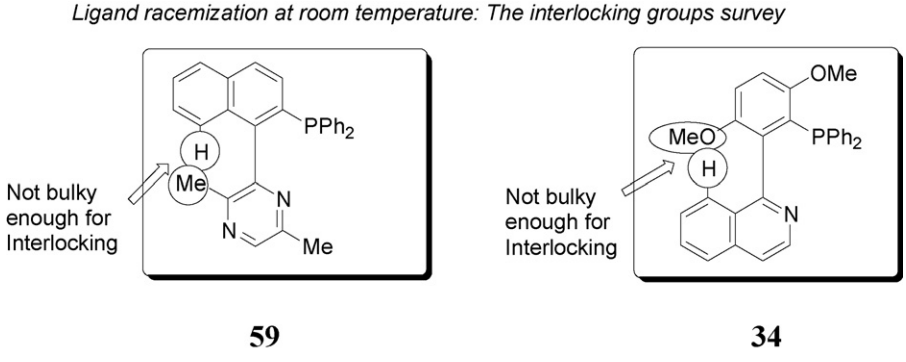
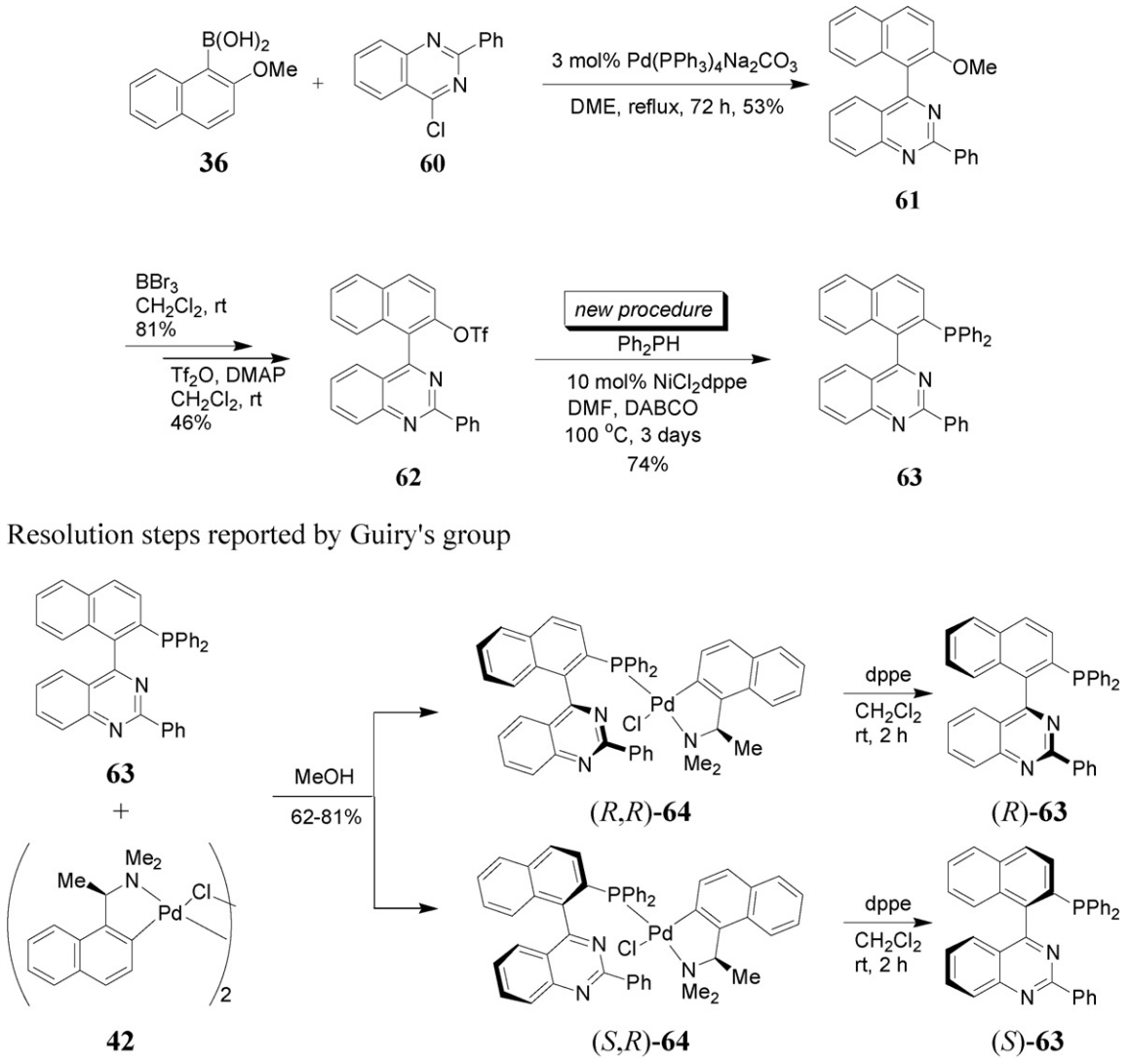


Fig. 2. Ligand racemization at room temperature. The interlocking groups survey.

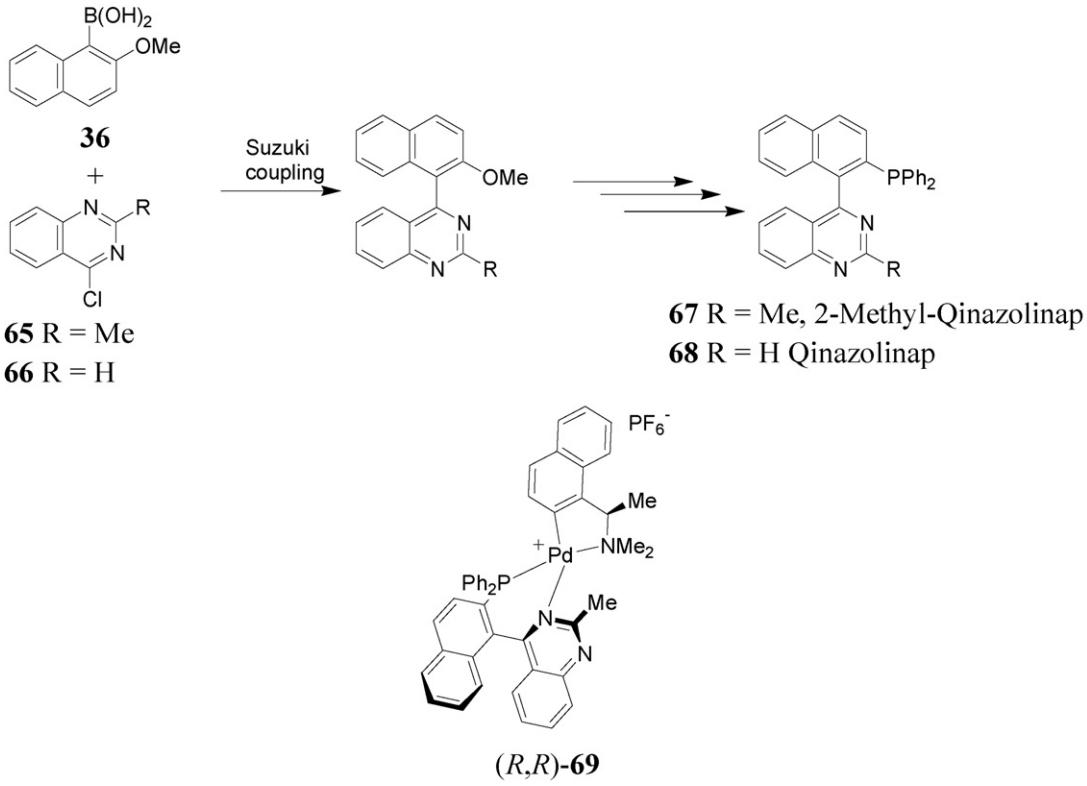


Scheme 13.

4-chloro-2-phenylquinazoline (**60**) was reacted with 2-methoxy-1-naphthylboronic acid **36** using the Suzuki cross-coupling protocol to afford **61** which was transformed to the corresponding triflate **62** by demethylation and trifluoromethanesulfonation [29]. Both Guiry and Quéguiner group adopted a direct carbon–phosphorus bond formation for the introduction of diphenylphoshine group to P,N ligand [30], which bypassed the phosphine oxide/reduction of phosphine oxide steps [31] (Scheme 13). Guiry's group also reported the resolution of the new ligand, named 2-phenyl-Quinazolinap **63** and the resolution approach is similar to that of **41**, while the nitrogen donor atom in P,N ligand **63** does not coordinate to palladium center in the diastereomeric complex (*R*,*R*)-**64** and (*S*,*R*)-**64** (Scheme 13), the fractional crystallization of the diastereomeric complexes was successful.

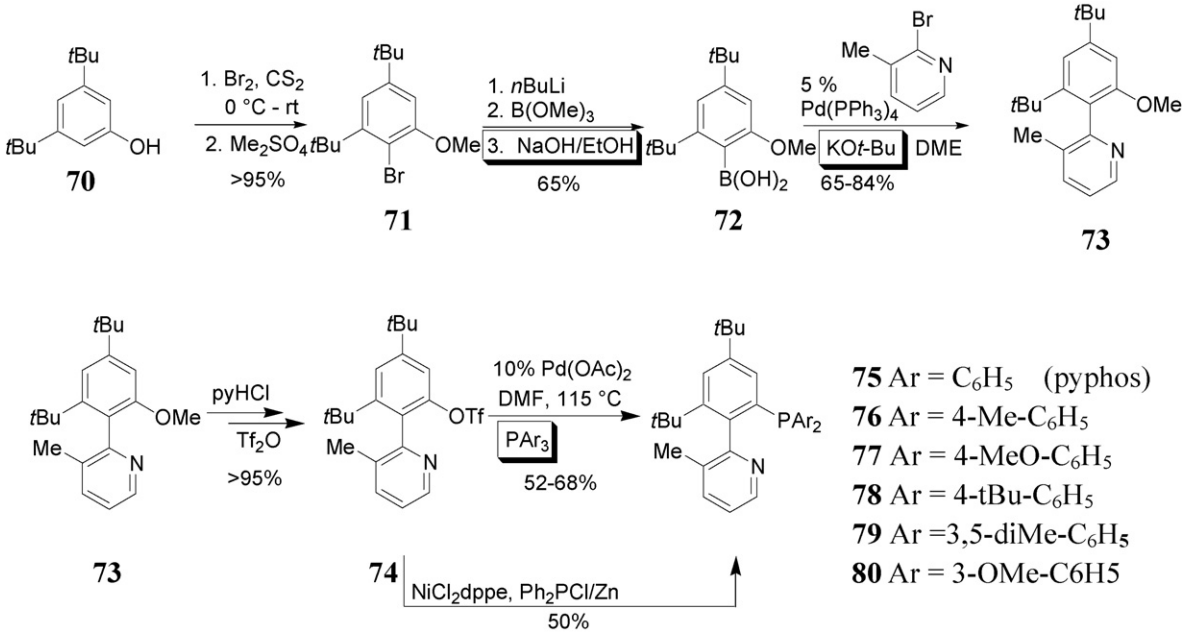
Guiry's group also reported the synthesis of other Quinazolinap derivatives, 2-methyl-Quinazolinap **67** and Qinazolinap **68** for direct comparison of steric effect in 2-substituted group in asymmetric catalysis [32]. The authors employed the same synthetic approach of 2-phenyl-Qinazolinap to synthesize the target derivatives (Scheme 14). The electrophilic component of the Suzuki coupling, 4-chloro-2-methylquinazoline **65**, was prepared from 2-methyl-4(*3H*)-quinazolinone and phosphorus oxychloride [33]. The new ligand **67** was resolved using diastereomeric complexation (Scheme 14), and the X-ray crystallographic studies of (*R*,*R*)-**69** revealed that both the phosphorus and the nitrogen donor atoms are coordinated to the palladium center. Unlike **69**, only the phosphorus donor atom is coordinated for complex (*R*,*R*)-**64** (Scheme 14).

Kwong and Chan recently reported some atropisomeric P,N "pyphos" ligands that exhibit a large dihedral angle [34]. These new ligands possess a *tert*-butyl group at the phenyl ring and a methyl group at the pyridine ring; it provides a bulky interlocking environment **75**–**80**. The synthesis of pyphos ligand and its derivatives involves three major steps: (1) hydrolysis of aryldimethylborate compound to arylboronic acid [35], (2) Suzuki cross-coupling using KO*t*-Bu as strong base [35], and (3) catalytic and user-friendly phosphination of aryltriflate with air-stable triarylphosphines [36,37] (Scheme 15).



Scheme 14.

Commercially available 3,5-di-*tert*-butylphenol (**70**) was converted to bromoanisole **71** by sequential bromination with Br_2 and methylation with dimethylsulfate (Scheme 15). Treatment of **71** with *n*BuLi and subsequent quenching with trimethylborate afforded the aryldimethylborate intermediate. Alkaline hydrolysis of the aryldimethylborate yielded the boronic acid **72**. Usual acid hydrolysis protocol was found to be unsuccessful. Suzuki cross-coupling of boronic acid **72** with bromopicoline afforded the pyridylanisole **73**. It was found that the use of strong base such as KO*t*-Bu (as well as the cation in the base) was important for the coupling reaction of bulky arylboronic acid **72** with 2-bromopicoline [35]. Other bases, such as Na_2CO_3, Cs_2CO_3 were found to give far inferior results. Demethylation of pyridylanisole **73**



Scheme 15.

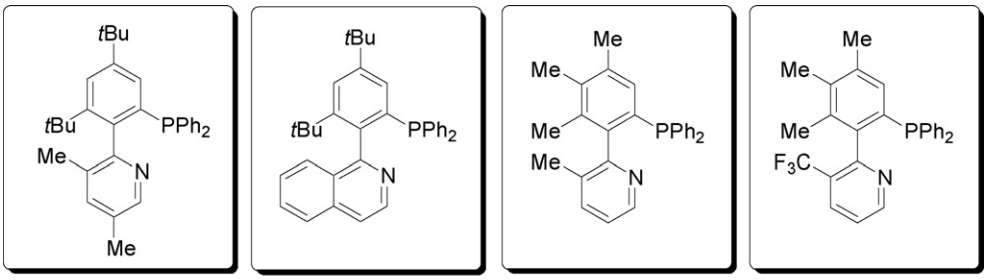


Fig. 3.

with dry pyridinium hydrochloride gave the pyridylphenol compound, which was subsequently transformed to aryltriflate **74** by trifluoromethanesulfonic anhydride (Scheme 15). The phosphination of triflate **74** was found to be critical. Several methodologies such as Pd/$Ph_2P(O)H$ [31], Ni/Ph_2PH were unsuccessful [30]. Chan et al. demonstrated the pyridine retardation effect for Ni/Ph_2PCl/Zn protocol in the synthesis of pyphos **75** [38]. Recently, Kwong and Chan disclosed a novel palladium-catalyzed phosphination of aryltriflates/nonaflate using triphenylphosphine [39]. This new methodology was applied to the synthesis of other P,N ligand (Scheme 15). Air-stable triarylphosphines were used as the phosphinating agent, instead of air- and/or moisture-sensitive $Ph_2P(O)H$, Ph_2PH, Ph_2PCl. Other P,N ligands **81**–**83** were also successfully prepared by the same method (Fig. 3) [37].

The resolution of pyphos **75** was accomplished by diastereomeric complexation (Scheme 16). The PN-palladium-amine-phenyl complexes (*R*,*S*)-**84** and (*R*,*R*)-**84** were found to be inseparable by fractional crystallization. However, the naphthyl analogues (*R*,*S*)-**85** and (*R*,*R*)-**85** were separated by crystallization in dichloromethane (Scheme 16) [34]. Decomplexation of (*R*,*R*)-**85** in the presence of 1,2-bis(diphenylphosphino)ethane afforded (*R*)-pyphos (*R*)-**75** in quantitative yield.

An alternative resolution pathway for P,N ligand pyphos **75** was also described by Chan et al. (Scheme 17).

A new type of axially P,N ligand **94** was reported by Altenbach and co-workers in 2002 [40]. This new ligand possesses a substituted benzoimidazole ring, and the synthetic pathway is described in Scheme 18. The diamine **89** was prepared from 2-nitroaniline **87** by reductive amination with acetone and $BH_3{\cdot}SMe_2$ to give **88** [41], followed by reduction of the nitro group with H_2 over Pd/C in ethanol [42]. Heating **89** with aldehyde **90** gave *N*,*N*-acetal **91**, which was transformed to imine **92** by dehydration with MnO_2 in benzene. Trifluoromethansulfonation of **92** gave triflate **93**, which was transformed to P,N ligand **94** BIMNAP by nickel-catalyzed phosphination. Resolution of the racemate by diastereomeric complexation of chiral palladium-amine complex yielded the optically active ligand (*S*)-**94**.

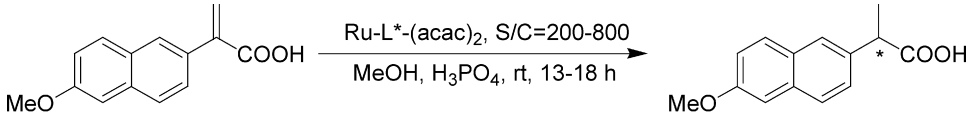
3. Application of diphosphine ligands in asymmetric catalytic hydrogenations

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 ee's, which clearly shows the versatility of this new class of ligands.

3.1. Hydrogenation of C=C double bonds

3.1.1. Asymmetric hydrogenation of 2-substituted propenoic acid

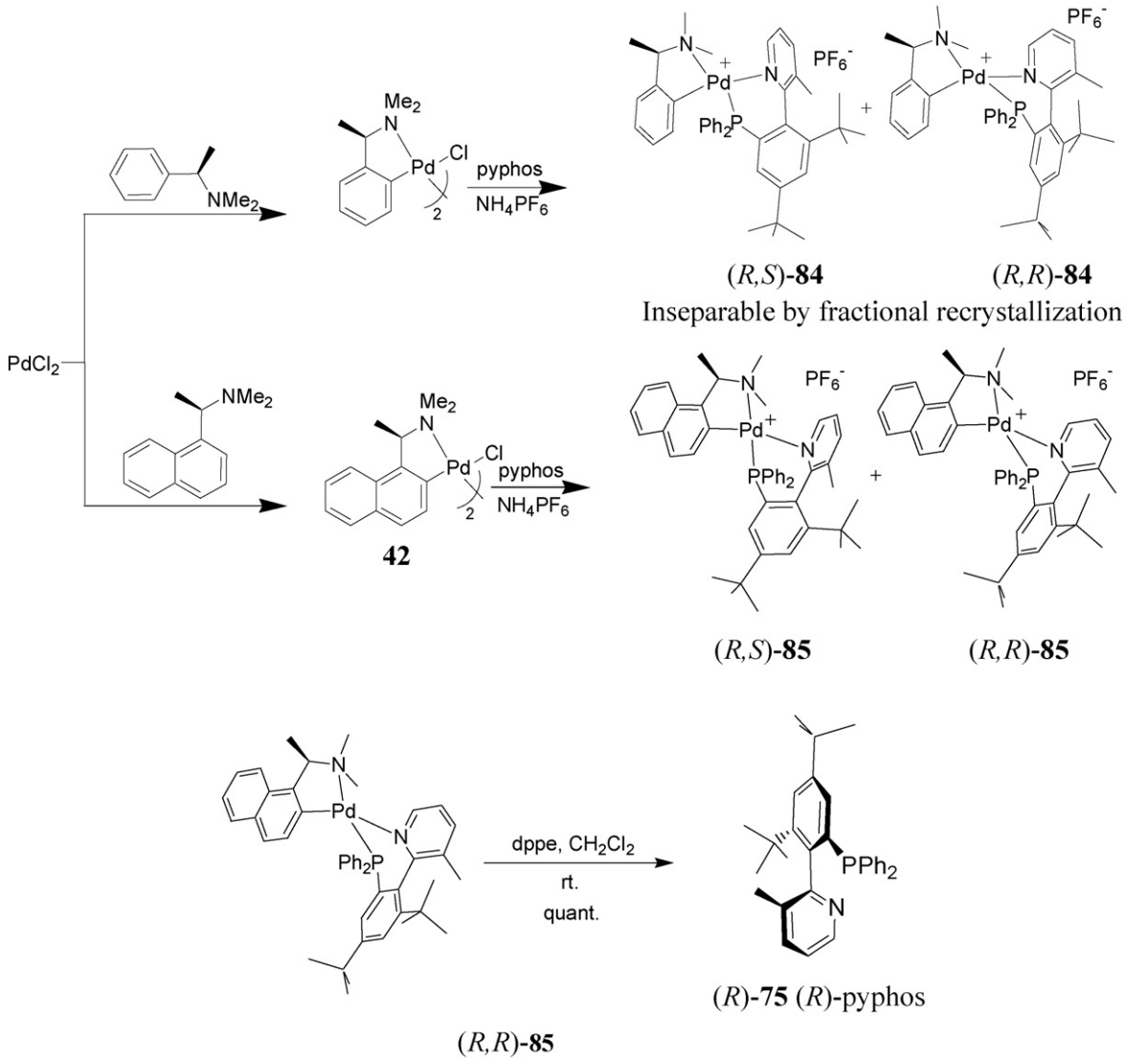
Complex {(*R*)-P-Phos}Ru(acac)$_2$ was employed for the synthesis of the nonsteroidal anti-inflammatory drug naproxen (**96**) by hydrogenation of 2-(6′-methoxy-2′-naphthyl)propenoic acid derivative **95** [5]. An ee value of 95% was obtained at 0 °C under a 1000 psi H_2 pressure in methanol after 13–18 h. A minor 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% ee).



95 **96** 95% ee

When Ru[(*R*-**2**)Cl(*p*-cymene)]Cl was used as catalyst for 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%, 1000 psi H_2 pressure and ambient temperature) [7].

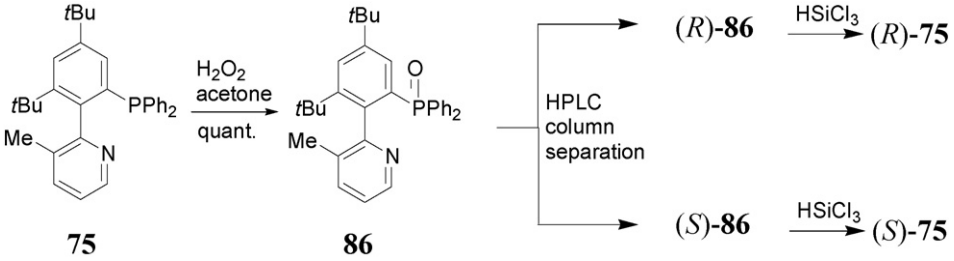
Ruthenium complexes of the chiral ligands S_a-**3** and R_a-**3** were also tested for asymmetric hydrogenation of 2-(6′-methoxy-2′-naphthyl)propenoic acid. Results showed that [RuCl(*p*-cymene)-R_a-**3**]Cl gave better ee than [RuCl(*p*-



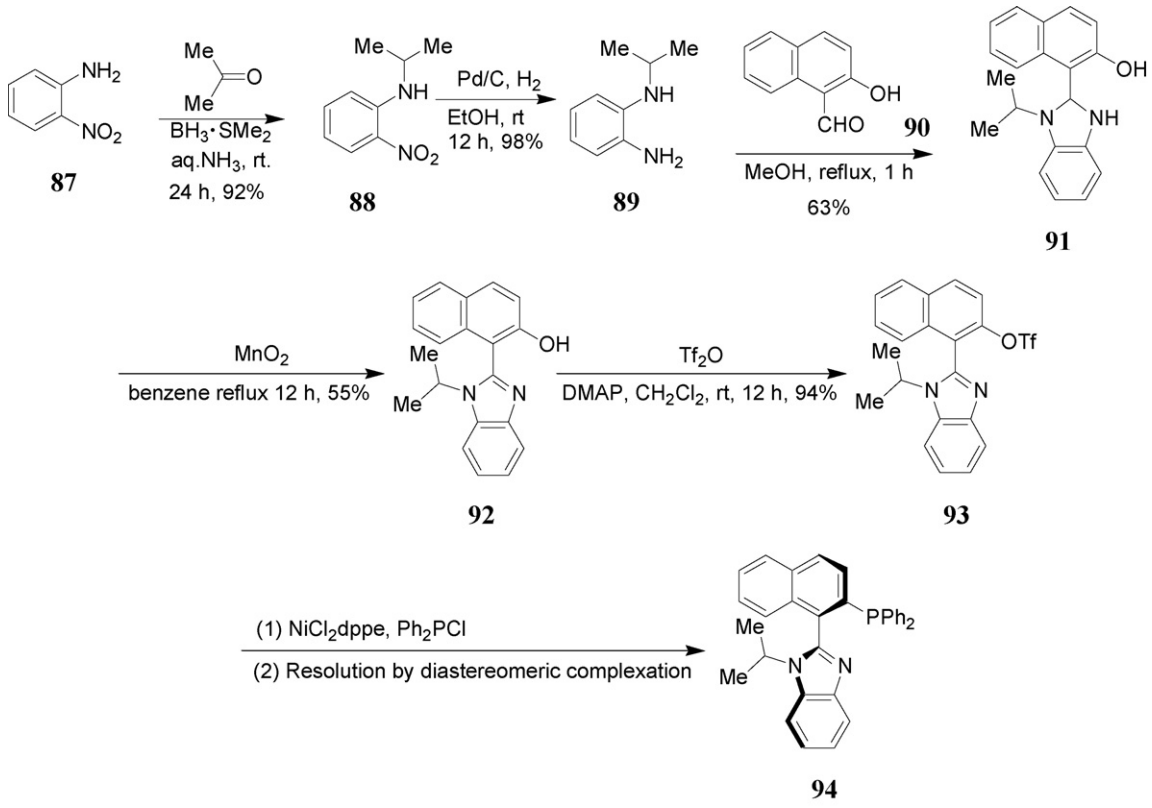
Scheme 16.

cymene)(S-BINAP)]Cl did, and the latter in turn produced better results than [RuCl(*p*-cymene)-S_a-**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 could be attained when the chirality of the chiral auxiliary matched the chirality of the biaryl moiety (in the case of R_a-**3**). Thus, when carried out at 0 °C under 1750 psi of H_2, asymmetric hydrogenation 2-(6′-methoxy-2′-naphthyl)propenoic acid proceeded smoothly to afford naproxen in up to 97% ee [12].

Similarly, asymmetric hydrogenation of 2-(6′-methoxy-2′-naphthyl)propenoic acid with the PQ-Phos-based Ru-S_a-**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



Scheme 17.



Scheme 18.

of the chiral catalyst when the chirality of the chiral diol matched the chirality of the biaryl. Furthermore, comparing the results produced by ligands having different chiral auxiliaries, 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 β-aryl-substituted α-(acylamino)acrylates

In the past three decades, Rh-catalyzed asymmetric hydrogenation of α-(acylamino)acrylic acids and esters has become a standard procedure for the synthesis of optically active α-amino acids, a variety of chiral ligands are known to be suitable ligands for this purpose [1]. However, the analogous reaction mediated by ruthenium catalysts is relatively unexplored, despite the fact that ruthenium catalysts are widely employed in the enantioselective hydrogenation of other substrates [43].

The parent ligand P-Phos was proved to be more effective ligand than its Xyl- and Cy-analogues in the Ru-catalyzed low-pressure hydrogenation of (*Z*)-β-aryl-substituted α-(acylamino)acrylates in methanol. The α-amino acid derivatives were obtained in 90–97% ee (Scheme 19) [44].

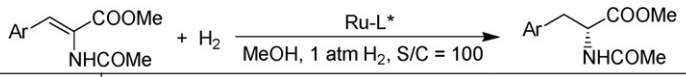
For the analogous hydrogenation reactions catalyzed by Rh(I) complexes of P-Phos-type ligands, sterically more encumbered ligands favor high enantioselectivities. Quantitative yield of the products could be easily realized in a range of common organic solvents, and methanol was found to be the most suitable solvent. Several 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 H_2 pressure.

With Cy-P-Phos as ligand, the Rh-catalyzed asymmetric hydrogenation of (Z)-β-aryl-α-(acylamino)acrylates [6] exhibited similar enantioselectivity but substantially higher activity as compared to Xyl-P-Phos under the optimized conditions. In addition, acetone appeared to be the solvent of choice, although the reactions could proceed smoothly in several aprotic/protic organic solvents.

3.1.3. Asymmetric hydrogenation of (Z)-β-alkyl-β-(acylamino)acrylates

Chiral β-amino acids have received considerable interest from researchers because of 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 [45]. Employing chiral rhodium diphosphine complexes (such as BICP, DuPhos, MiniPhos, BDPMI, and TangPhos) as catalysts, enantioselective hydrogenation of β-alkyl-substituted β-(acylamino)acrylates afforded good-to-excellent ee's [1e]. 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 employing the $Ru(O_2CCH_3)_2$-(BINAP) catalyst system [46], and the highest ee of 96% was attained for the (*E*)-isomers of substrates.

The Ru complexes of the P-Phos ligands exhibit better activity and enantioselectivity in the asymmetric hydrogenation of (*E*)-β-alkyl-β-(acylamino)acrylates than the corresponding Rh



Entry	Ar	ee (%)		
		Ru-(S)-P-Phos	Rh-(S)-Xyl-P-Phos	Rh-(S)-Cy-P-Phos
1	*o*-ClPh	97% ee	92% ee	90% ee
2	*m*-ClPh	91% ee	93% ee	92% ee
3	*p*-ClPh	94% ee	93% ee	91% ee
4	*p*-MePh	91% ee	94% ee	93% ee
5	*p*-MeOPh	90% ee	94% ee	95% ee

Scheme 19. Asymmetric hydrogenation of (*Z*)-β-aryl-α-(acylamino)acrylates by P-Phos-type catalysts.

complexes (Scheme 20) [47]. Interestingly, opposite enantioselection by the Ru and Rh complexes of an identical chiral ligand were observed, which is in agreement with the findings by Lubell et al. [46].

When ruthenium complexes were used as the catalysts, the sterically hindered P-Phos ligands provided higher ee's and faster reaction rates. The reaction was strongly solvent-dependent, and methanol was found to be the best solvent. Thus, using Ru-Xyl-P-Phos catalyst under the preferred conditions, the β-amino acids were obtained in 97–99% enantiopurities. Yet, hydrogenation of the (*Z*)-isomers using the Ru-Xyl-Phos catalyst in methanol produced the markedly inferior enantioselectivity under otherwise identical conditions to that of the (*E*)-isomers.

For instance, hydrogenation of (*Z*)-β-dehydroamino acids using [{(*R*)-Xyl-P-Phos}RuCl(η^6-benzene)]Cl as catalyst was not at all effective in aprotic solvents such as THF and CH_2Cl_2, 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 H_2 pressure 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 enantiofacial selection.

The PQ-Phos type ligand S_a-**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 H_2 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 substrate with a bulky alkyl substituent gave the best ee (up to 99%) [13a].

Other ligands such as **5** or **6** also gave high ee's 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 [13b].

3.2. Hydrogenation of C=O double bonds

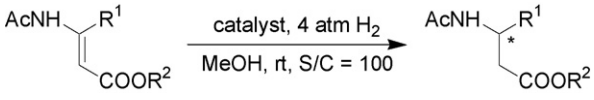
3.2.1. Hydrogenation of α-ketoesters

Enantioselective hydrogenation of α-ketoesters provides a direct approach to optically pure α-hydroxyesters, which are important building blocks for organic syntheses. In contrast to the success of the asymmetric hydrogenation of β-ketoesters, the homogeneous asymmetric hydrogenation of α-ketoesters has been undeveloped [48,49]. 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 [49b].

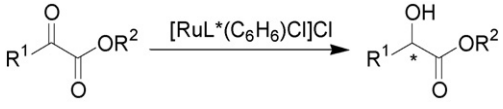
In the catalytic asymmetric hydrogenation of methyl benzoylformate, the Ru catalyst with R_a-**4** afforded better enantioselectivity (97% ee) than that when using BINAP (79% ee) as ligand [13]. Other chiral ligands such as S_a-**5** or S_a-**6** also gave products with excellent enantiomeric excess. As expected, good results (91–92% ee) were obtained for the asymmetric hydrogenation of pyruvate. These ligands are also effective for the asymmetric hydrogenation of α-ketoesters with a bulky functional group R^1 (Scheme 21).

3.2.2. Hydrogenation of β-ketoesters

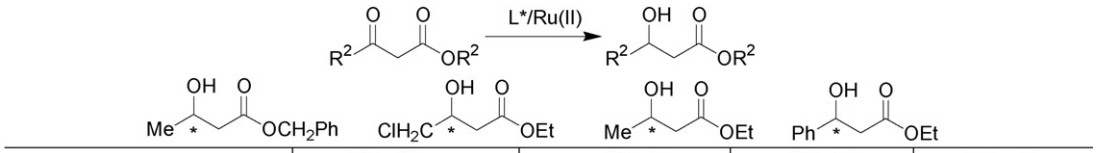
Optically pure β-hydroxy carboxylic esters are an important class of intermediates for the synthesis of many bioactive or natural compounds [50,51]. The first efficient asymmetric catalytic transformation of the β-ketoesters to β-hydroxy esters *via* transition metal complexes catalyzed homogeneous hydrogenation was demonstrated by Noyori and co-workers utilizing the BINAP/Ru(II) system [52]. 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 trans-



Scheme 20. Asymmetric hydrogenation of (*E*)-β-alkyl-β-(acylamino)acrylates.



Scheme 21.



	Me OCH2Ph	ClH2C OEt	Me OEt	Ph OEt
(*S*)-P-Phos	96%	98%	98%	95% (85%)[a] (90%)[b]
(*R*)-Tol-P-Phos	98%	97%		96% (92%)[a] (91%)[c]
(*R*)-Xyl-P-Phos	96%	94%	97%	96% (93%)[c]

Scheme 22. Asymmetric hydrogenation of β-ketoesters.

formation, achieving enantioselectivity of up to 99% ee with Tol-P-Phos as ligand [53]. For example, asymmetric hydrogenation of 3-oxo-3-phenyl propionate employing the BINAP/Ru(II) system gave products with only 85% ee [52]. Notably, far better ee's were obtained when P-Phos ligands were used for the same reactions (Scheme 22) [5,53,54].

In the hydrogenation of substrates bearing a chlorine atom nearby the carbonyl group, the Ru-BINAP catalysts failed to give the desired products in satisfactory enantiopurities at room temperature, probably due to the competitive coordination of the ester group and the halogen atom. Elevated temperature (100 °C) led to excellent chiral efficiency (97% ee) under 100 atm H_2 pressure [55]. Interestingly, the employment of the Ru-P-Phos [5b] or Tol-P-Phos [53] complexes furnished higher enantioselectivity (98% ee) under relatively milder conditions (80 °C, 4–20 atm H_2).

Asymmetric hydrogenations of β-keto esters catalyzed by the ruthenium complexes of BisbenzodioxanPhos (e.g. Ru-**2**) were carried out in 50 psi of H_2 pressure at 80–90 °C. The results revealed that the catalytic reactions are highly effective in producing alcohols of up to 99% optical purities [7b].

When catalysts Ru-**3**-$Cl_2(DMF)_n$ 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]$Cl_2(DMF)_n$ system [12]. In the asymmetric hydrogenation of methyl acetoacetate, 99% ee was obtained when the reaction was catalyzed by the Ru-S_a-**4** ($n = 0$) complex [13].

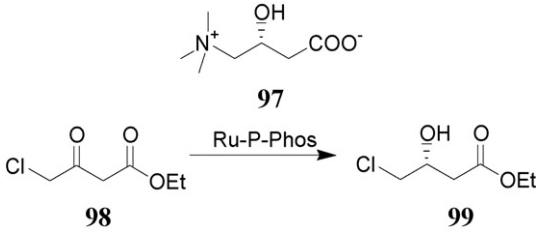
Carnitine (**97**), also known as L-carnitine (levocarnitine), is a quaternary ammonium compound derived from the amino acid lysine and is responsible for the transport of fatty acids from the cytosol into the mitochondria. This compound is often sold as a nutritional supplement. Traditionally, chemical synthesis of optically pure L-carnitine was carried out through resolution, and asymmetric hydrogenation of β-ketoester would be one of the most efficient routes to this important compound. We found that asymmetric hydrogenation of 4-chloro-3-oxo-butanoic acid (**98**) proceeded readily in the presence of Ru-P-Phos complex, leading to the corresponding 3-hydroxyl product **99** in high yield and high ee (Scheme 23). Compound **99** is the key intermediate for L-carnitine and can be easily converted to the final product *via* routine chemistry [56].

3.2.3. Asymmetric hydrogenation of simple ketones

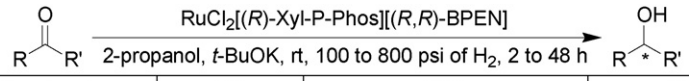
Chiral secondary alcohols are important intermediates of organic synthesis, and a number of methods have been developed for production of this type of compounds [57]. However none of these methods live up to the expectations of industrial requirements because of high catalyst/ligand loading required 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.

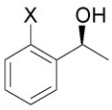
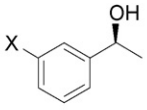
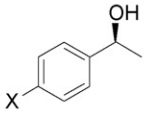
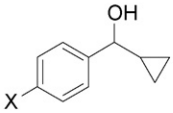
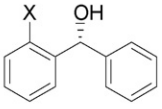
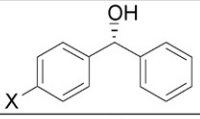
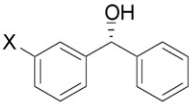
An important breakthrough was made when Noyori's group developed the BINAP-DIAPEN catalyst system [58]. Coupled with a catalytic amount of a strong base, a diverse array of unfunctionalized simple ketones were hydrogenated with a substrate-to-catalyst ratio of over two million, and yet, retaining high stereoselectivity.

When Xyl-P-Phos was used, a much cheaper diamine (trans-1,2-diphenylethylenediamine, DPEN) was sufficient to attain high degree of enantio-induction without using the exotic DAIPEN diamine. Excellent ee's have been obtained for the hydrogenation of a variety of Ar-substituted acetophenones, heteroaryl methyl ketones and aryl cyclopropyl ketones with up to >99% ee at S/C = 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 stere-



Scheme 23.



Product	X	S/C	ee (%)
	H	100,000	99
	Me	4,000	97
	OMe	4,000	93
	Br	10,000	>99
	Me	12,000	97
	OMe	4,000	98
	Br	4,000	99
	Me	20,000	98
	OMe	20,000	98
	Br	50,000	>99
	CF_3	12,000	97
	H	5,000	97
	OMe	1,000	96
	F	2,000	92
	Cl	5,000	92
	Me	2,000	95
	F	2,000	97
	Cl	10,000	97
	Me	2,000	3
	Cl	2,000	47
	CF_3	2,000	77
	Me	2,000	43

Scheme 24. Asymmetric hydrogenation of simple ketones.

odiscrimination, and the products with only low to moderate ee's were obtained. In addition, a profound electronic effect was observed for the hydrogenation of *p*-R-C_6H_4-COPh. When R was a methyl group, product with 3% ee was obtained; when this methyl group was fully fluorinated (R = CF_3), the ee value rose to 77% (Scheme 24) [59].

3.2.4. Asymmetric hydrogenation of enol acetate

Asymmetric hydrogenation of enol acetate 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 sparse in the literature [60]. In our study of the asymmetric hydrogenation of enol acetates, it was found that asymmetric hydrogenation using R_a-**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 [60b]. Yet, the Ru-**3** catalyzed reaction still brought about effective formation of the desired products in up to 94% ee.

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 (50–500) rendered previous hydrosilylation work not competitive with hydrogenation [61].

By using the Buchwald's protocol for conjugate reduction [62], Lipshutz and co-workers disclosed a highly active $Cu^{I}Cl$/\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

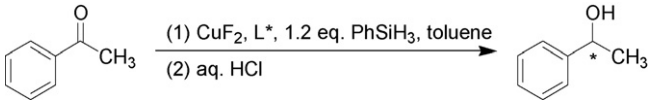
over 100,000 [63]. Very recently, they also described a robust $Cu(OAc)_2{\cdot}H_2O$/DTBM-SEGPHOS/PMHS hydrosilylation system (CuH in a bottle) [64], which offered a new opportunity for asymmetric hydrosilylation in conjunction to practical applications.

At the time that we initiated our investigation in this area, we noted an air-accelerated and base-free CuF_2/BINAP/$PhSiH_3$ system demonstrated by Riant et al. which catalyzed the hydrosilylation of some aryl alkyl ketones in moderate to good ee's at lower S/L ratios of 100–200 under ambient conditions [65]. Although the mechanism of this air-accelerated system remained elusive at this 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.

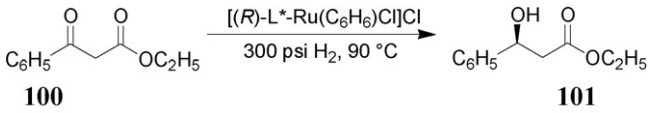
Indeed, the dipyridylphosphine/CuF_2/$PhSiH_3$ system served as an effective system rendering competitive levels of enantioselectivities of up to 97% ee for the hydrosilylation of *meta*- and *para*-substituted acetophenones (Scheme 25) [66]. Moreover, the excellent practical viability of this catalyst 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 environmentally benign reducing reagent since it is inexpensive, nontoxic, and stable to air and moisture [67]. In light of this, the efficiency of the present catalyst system using PMHS as the hydride source have 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% ee, whereas, in the case of PMHS, 76% conversion was achieved within 25 min with 75% ee under otherwise identical conditions.

In addition, the enantioselective hydrosilylation of unsymmetrical diaryl ketones to benzhydrol remained a formidable challenge, and the highest enantioselectivity reported in the literature prior to our study was around 20% ee [68]. In this regard, the P-Phos catalyst system was found to be surprisingly effective in the stereoselective hydrosilylation of ortho-substitued benzophenones with good to excellent ee's (up to 98%, Scheme 11). As expected, because of the lack of steric bias, *meta*- and *para*-substituted benzophenones were converted to the corresponding alcohols in low to moderate ee's.



Scheme 25. Asymmetric hydrosilylation of acetophenone.



Scheme 26.

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 [69]. In the presence of Ru(*R*-Xyl-P-Phos)$(C_6H_6)Cl_2$, 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% ee [54]. Even with a substrate-to-catalyst ratio as high as 7500, 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% ee).

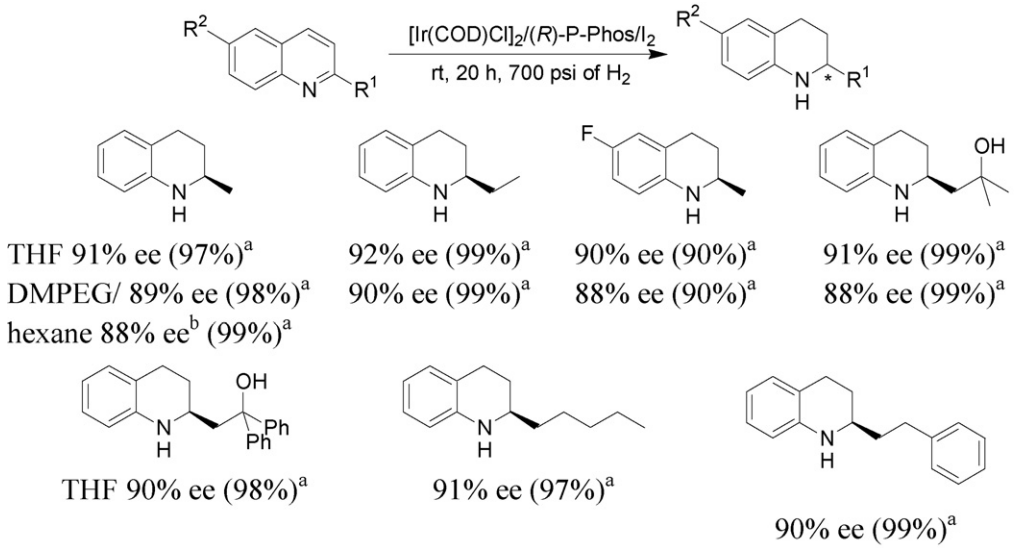
Further, the Ru complexes of the P-Phos family of ligands have been found to be highly air stable. When experimental procedures prior to the charging of hydrogen were performed in air and solvents without pre-degassing and drying, or even when the catalyst solution was exposed to air for 10 h before its application, both the catalyst activity and enantioselectivity for the hydrogenation of **100** remained unchanged (Scheme 26, >94% conversion, 94–96% ee for product **101**) from the air-proved system (96% ee) [54], while the ee obtained from Ru(R-BINAP)-$(C_6H_6)Cl_2$ catalyst precursor, in a side by side comparison study, sharply dropped from 92% to 66%.

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, which are easily available, provides enantiomerically pure tetrahydroquinoxalines and heterocycloalkanes of great biological interest [70].

The catalytic asymmetric hydrogenation of easily accessible and less expensive quinoline derivatives is a direct and convenient access toward enantiomerically enriched tetrahydroquinoline derivatives, which are synthetic intermediates for biologically active compounds [71]. 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 [72].

Iridium complex generated *in situ* from $[Ir(COD)Cl]_2$ and P-Phos in combination with 0.1 equiv. of I_2 in THF served as a highly efficient catalyst system for the hydrogenation of this class of challenging substrates at room temperature (Scheme 27) [73], furnishing hydrogenation products in 90–92% ee. Meanwhile, we found that the Ir-(P-Phos) catalyst was particularly robust and air stable. No variation was detected in the ^{31}P NMR spectrum of the catalyst solution even after 2 weeks in air. The reactivity and enantioselectivity for the hydrogenation of



a: isolated yield. B; catalyst recycled 8 times. Reaction conditions: solvent: THF or DMPEG/hexane(1:1); Substrate : Ir : L : I_2= 100 : 0.5 : 1.1 : 10

Scheme 27. Asymmetric hydrogenation of quinolines.

2-methylquinoline were virtually retained even though the catalyst solution had been exposed to air for 24 h. 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, the recyclability of this catalyst has been examined using 2-methylquinoline as 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 27).

Iridium complexes containing PQ-Phos type ligands **4**–**6** were also effective in the asymmetric hydrogenation of *N*-hetereoaromatic 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 more suitable than the others.

The enantioselectivities of these reactions were highly sensitive to the dihedral angles of the chiral ligands used. For example, with R_a-**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 S_a-**6** as ligand (dihedral angle = 88.8°). The best results (89% ee) were attained with ligand S_a-**5** with dihedral angle = 80.0°, which was 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 [13b].

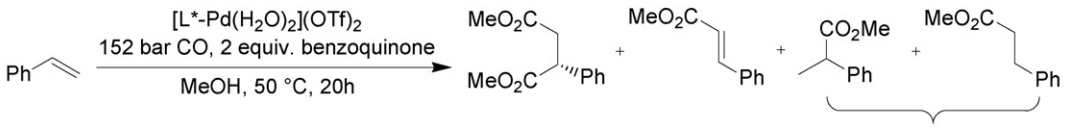
4. Asymmetric catalytic C–C bond formation

4.1. Bis-alkoxycarbonylation of styrene

The Pd(II)-catalyzed asymmetric bis-alkoxycarbonylation of styrene for the synthesis of optically active butanedioic acid derivatives with high chemoselective, enantioselective control, or both represents a significant challenge [74]. 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 initial 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 chiral P-Phos with a catalyst loading of 1.6% mol (Scheme 28) [75].

4.2. 1,4-Conjugate addition to α,β-unsaturated ketones

Enantioselective construction of quaternary carbon stereocenters is an important objective in organic chemistry [76], and asymmetric 1,4-conjugate addition of carbon nucleophiles to α,β-unsaturated compounds is a very useful method to the preparation of this type of compounds. This could be realized by copper-catalyzed asymmetric 1,4-conjugate addition of dialkylzinc reagents [77] and trialkylaluminum reagents [78], or by rhodium complex-catalyzed 1,4-addition of alkenylboronic acids to α,β-unsaturated pyridyl sulfones [79].



	S/C	DMPS	MC	MP
(*R*)-P-Phos	125	67% conv. 71% (83% ee)	20%	2%
(*R*)-P-Phos	63	67% conv. 79% (84% ee)	18%	1%
(*R*)-Tol-P-Phos	125	58% conv. 52% (82% ee)	24%	4%
(*R*)-Xyl-P-Phos	125	56% conv. 42% (82% ee)	28%	1%

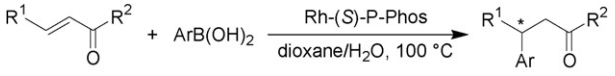
Scheme 28. Palladium-catalyzed asymmetric bis-alkoxycarbonylation of styrene.

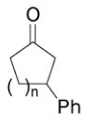
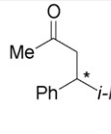
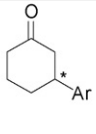
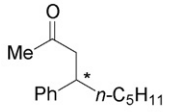
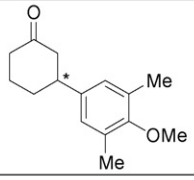
Since Hayashi et al. reported the asymmetric 1,4-addition of organoboronic acids to α,β-unsaturated ketones mediated by rhodium(I)-BINAP catalyst [80], impressive progress has been made in reactions involving a variety of other electron-deficient olefins [81]. [Rh(acac)((*S*)-P-Phos)] complex, generated *in situ* from an equimolar amount of Rh(acac)–(CH_2=CH_2)$_2$ and (*S*)-P-Phos in dioxane/H_2O (10/1) at 100 °C, has also been found to be well-suited for this transformation [82]. 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 ee's (up to 99%) in most cases, which are either comparable to or better than the relevant Rh-BINAP system (Scheme 29).

4.3. Asymmetric Pauson–Khand-type reaction

Asymmetric transition-metal-catalyzed/mediated [2 + 2 + 1] carbonylative cycloaddition of an alkene and an alkyne, or asymmetric Pauson–Khand-type reaction, offers an excellent opportunity for the preparation of various optically active cyclopentenones [83]. Nevertheless, no catalytic asymmetric aqueous PKR systems had been developed prior to our study. Recently, we found that P-Phos was 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 [84].

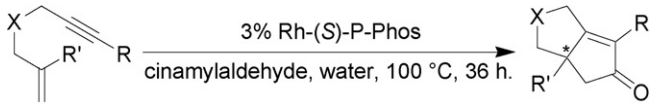
The higher concentration of reactants in conventional organic solvents proved to offer higher rates in the reaction. This finding prompted us to use water as the sole solvent, which was expected to increase the effective concentration of the reactants based on the aqueous micellar concept [85] and thereby to accelerate the reaction. In effect, water turned out to be much more conducive than organic solvents to higher reactivity and ee's (Scheme 30, R = Ph, R′ = H), and P-Phos displayed far superior efficacy to the other screened chiral ligands. 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



			
n = 1 n = 2 n = 3	97 % (89%)[a] 99% (99%) 98% (88%)	90% ee (90%)	*o*-MeC_6H_4, 90% ee (99%)[b] *o*-$MeOC_6H_4$, 99% ee, (99%)[b] *m*-$MeOC_6H_4$, 95% ee (99%) *m*-ClC_6H_4, 97% ee (99%) *p*-MeC_6H_4, 99% ee (99%) *p*-$MeOC_6H_4$, 99% ee (99%)[b] *p*-FC_6H_4, 96% ee (97%) *p*-$CF_3C_6H_4$, 99% ee (97%)
			
96% ee (86%)		99% ee (94%)	

a: isolated yields. b: dioxane/H_2O = 20:1.

Scheme 29. Enantioselective addition of arylboronic acids to α,β-unsaturated ketones.



Scheme 30. Rh-P-Phos-catalyzed asymmetric Pauson–Khand reactions.

collection of oxygen-, nitrogen-, and carbon-tethered enynes providing excellent isolated yields in most cases and 74–95% ee (Scheme 30).

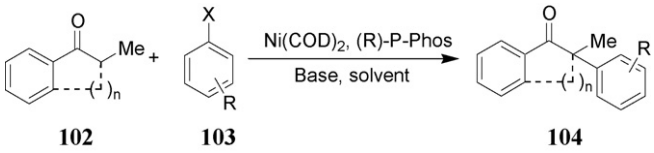
Diphosphane ligand (*S*)-**2** (BisbenzodioxanPhos) was also highly effective in the co-operative processes of aldehyde decarbonylation and cascade enantioselective Pauson–Khand-type reactions. Various 1,6-enynes were transformed to the corresponding bicyclic cyclopentenones in good yields and enantiomeric 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 [86].

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, pharmaceutically attractive molecules, synthetically useful intermediates and precursors to emissive polymers [87]. 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 [88] or dialkylphosphinobinaphthyl ligands [89]. Studies revealed that the atropisomeric dipyridyldiphosphine P-Phos serves as effective ligand for the asymmetric α-arylation of ketone enolates, and the corresponding all-carbon quaternary stereogenic center was generated in high enantioselectivity (Scheme 31) [90].

In a prototypical reaction, 2-methyl-1-tetralone (**102**, $n = 2$) was treated with bromobenzene (**103**, X = Br) in the presence of 2 mol% $Ni(COD)_2$ and 2.4 mol% (*R*)-P-Phos. The α-phenylated product **104** was obtained in 88% isolated yield and 90% ee with NaHMDS as base. Further study indicated that toluene in combination with sodium *tert*-butoxide were 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 would increase slightly the product yield, albeit with a compromised ee value.

Various aryl bromides **103** were examined under these preliminary optimized conditions using **102** as substrate. The



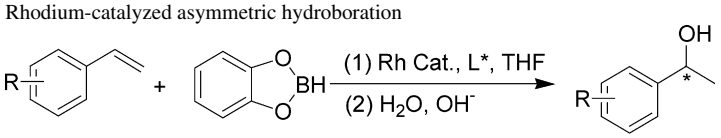
Scheme 31. Nickel-catalyzed asymmetric α-arylation of ketone enolates.

meta- and *para*-substituted aryl bromides showed 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 is 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 **102** in Ni-catalyzed reaction conditions to yield the coupling product in 91%.

4.5. Asymmetric hydroboration

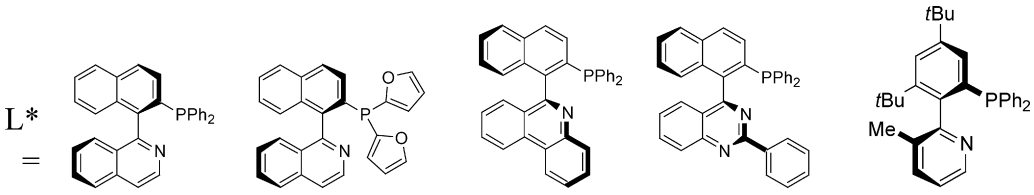
The discovery of the oxidative addition of Wilkinson's catalyst $Rh(PPh_3)Cl$ with boron hydrides such as catecholborane has led to the development of metal-catalyzed hydroboration [91]. The asymmetric version of this reaction was developed by Burgess using chiral Rh-DIOP catalyst and norbornene with 55% ee being achieved [92]. A highly enantioselective hydroboration was then reported by Hayashi to obtain 96% ee using styrene as the prototypical substrate [93]. Recently, some other catalysts that contain P,N ligands with axially chirality were found to be effective in asymmetric hydroboration (Table 1), and Brown was one of the pioneers in asymmetric hydroboration to obtain high enantioselectivity [94]. The optically active (*S*)-QUINAP (*S*)-**41** was applied in asymmetric hydroboration of styrene and gave 88% enantiomeric excess (Table 1, entry 1) [95]. Better ee value was observed when electron-rich 4-methoxystyrene was used (Table 1, entry 2). However, the electron-deficient 4-chlorostyrene only gave moderate yield and enantioselectivity of the product (Table 1, entry 3). Excellent ee value, 96% was observed when 6-membered cyclic vinylarene was used (Table 1, entry 5). The difurylphosphino analogue of QUINAP, (*S*)-**46**, showed significant improvement on the yield of the reaction and slightly better ee value, when electron-deficient 4-chlorostyrene was used (Table 1, entries 6–9). PHENAP ligand (*R*)-**50** generally gave lower enantioselectivity in asymmetric hydroboration, when compared to its parent QUINAP ligand (Table 1, entries 10–12 vs. 1 and 4–5). [96] Guriy recently reported a biaryl P,N ligand, which used qinazoline as the nitrogen donor moiety. They showed that 2-phenyl-Qinazolinap ligand (*R*)-**63** gave a better ee value (compared to QUINAP) when indene was used as substrate (Table 1, entry 15 vs. 4). However, both acyclic electron-neutral and -deficient styrenes gave poorer yield (Table 1, entries 13–14). The authors explained these results by inferring that the increased steric bulkiness of the ligand in the 2-position, and hence ruined the asymmetric induction in the transition state. A direct comparison of QUINAP and 2-H-Qinazolinap is now in progress as mentioned by the authors. Recently, Chan and co-workers demonstrated the use of pyphos (*R*)-**75** in rhodium-catalyzed asymmetric hydroboration [34]. They showed this ligand, which gave good-to-excellent enantioselectivity for both electron-rich and -deficient styrenes (Table 1, entries 17–20). Two independent groups, Brown and Chan found that the enantioselectivities in this catalyzed hydroboration of *para*-substituted styrenes depends on the electronic

Table 1
Rhodium-catalyzed asymmetric hydroboration



105

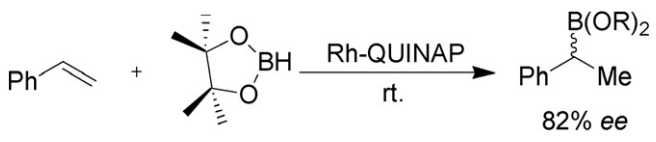
Entry	Ligands	Vinylarene	Yield (%)	ee% (configuration)
1	(*S*)-**41**	R = H	69	88 (*S*)
2	(*S*)-**41**	R = 4-MeO	57	94 (*S*)
3	(*S*)-**41**	R = 4-Cl	56	78 (*S*)
4	(*S*)-**41**	Indene	75	76 (*S*)
5	(*S*)-**41**	Dihydronaphthalene	78	96 (*S*)
6	(*S*)-**46**	R = 4-Me	79	88 (*S*)
7	(*S*)-**46**	R = 4-Cl	78	82 (*S*)
8	(*S*)-**46**	Indene	80	78 (*S*)
9	(*S*)-**46**	Dihydronaphthalene	81	82 (*S*)
10	(*R*)-**50**	R = H	70	67 (*R*)
11	(*R*)-**50**	Indene	59	64 (*R*)
12	(*R*)-**50**	Dihydronaphthalene	69	84 (*R*)
13	(*R*)-**63**	R = H	98	63 (*R*)
14	(*R*)-**63**	R = 4-Cl	95	46 (*R*)
15	(*R*)-**63**	Indene	98	84 (*R*)
16	(*R*)-**63**	Dihydronaphthalene	99	89 (*R*)
17	(*R*)-**75**	R = 4-MeO	70	94 (*R*)
18	(*R*)-**75**	R = 4-Me	70	93 (*R*)
19	(*R*)-**75**	R = H	72	90 (*R*)
20	(*R*)-**75**	R = 4-Cl	72	79 (*R*)



(*S*)-**41** (*S*)-QUINAP | (*S*)-**46** | (*R*)-**50** PHENAP | (*R*)-**63** 2-Phenyl-Quinazolinap | (*R*)-**75** PyPhos

effect of styrene. The plots of log(*R*/*S*) of the hydroboration product **105** versus Hammett constant σ_p yielded a straight line ($R^2 > 0.98$), indicative of the linear free energy relationship being obeyed.

Recently, the application of less moisture sensitive pinacol borane instead of catecholborane in regio- and enantiocontrolled hydroboration of vinyl arenes was reported [97]. The authors showed that the hydroboration could be performed at room temperature with good enantioselectivity (Scheme 32). It is interesting to note that reversal in enantioselectivity was observed with chiral diphosphine-ligated catalysts when pinacol borane was employed in place of catecholborane [97].

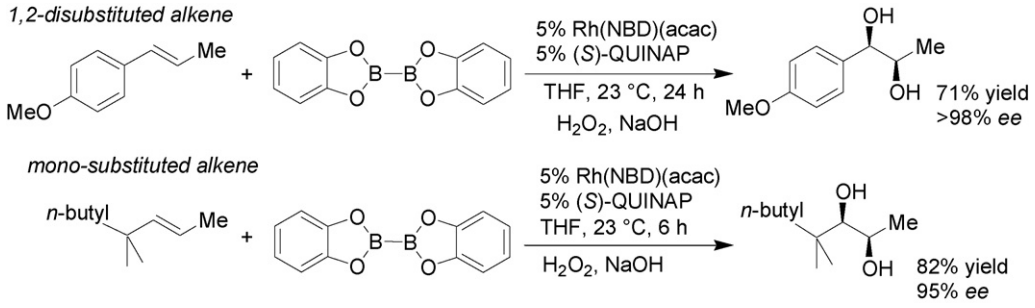


Scheme 32.

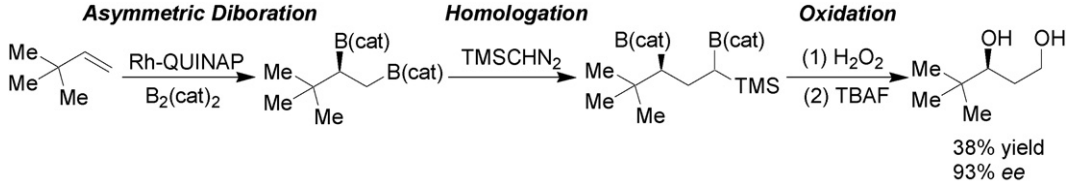
An in-depth study on the factors that control the enantioselective Markovnikov hydroboration/oxidation of vinylarenes was reported [98]. A comparison of experimental data provided by (*R*)-QUINAP modified system with computational data evidenced by DFT calculations and QM/MM strategies was described.

The Rh-catalyzed reaction between bis(catecholato)diboron and simple alkene results in the syn addition of the diboron across the alkene. These diboration products are subsequently oxidized to provide the 1,2-diol. In the presence of chiral QIUNAP ligand, high enantioselection in the diboration can be achieved [99]. The reaction is highly selective for *trans*- and trisubstituted alkenes and can be selective for some mono-substituted alkenes as well (Scheme 33) [100].

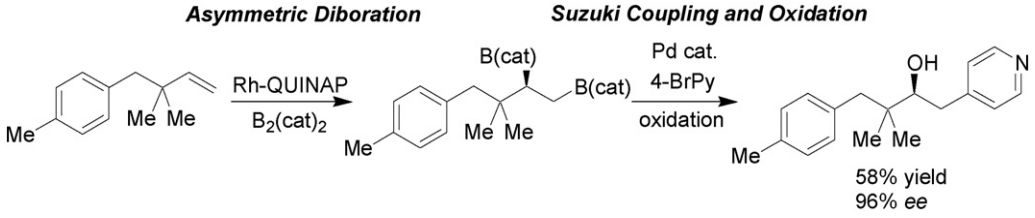
Recently, Fernández and co-workers reported the nature of the catalytic system and the electronic effectes of the substrate that affected the asymmetric diboration and dihydroboration [101]. They determined the nature of the side reactions and by-products generated during the catalytic asymmetric diboration of vinylarenes.



Scheme 33.



Scheme 34.

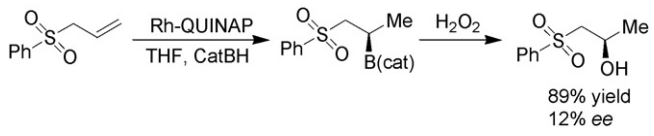


Scheme 35.

In addition to the highly applicable Rh-QUINAP-catalyzed enantioselective diboration, other tandem processes have also been reported recently. An operationally simple diboration–homologation–oxidation procedure is reported where alkene diboration and the subsequent homologation reaction (by treatment of $TMSCHN_2$) are accomplished in one-pot (Scheme 34) [102].

The cascade asymmetric diboration–Suzuki coupling–oxidation reaction was also reported by the same research group in 2004 [103]. This simple protocol offers single-pot carbohydroxylation of olefin substrates (Scheme 35).

In 2006, Fernández and co-workers reported the first asymmetric hydroboration of allylic system (other then vinyl arenes, Scheme 36) [104]. Aryl allylic sulfones are reacted with catecholborane in the presence of cationic Rh complexes with chiral ligands to generate the branched heteroorganoboronate ester. This is the first example of direct access to enantiomerically enriched mixtures of 1-phenylsulfonyl-2-propanol although relatively low enantiomeric excess is observed.



Scheme 36.

5. Summary

This review article portrays the versatility of axially chiral phosphine ligands containing heterocyclic rings in catalytic asymmetric transformations. Transition metal complexes of these ligands have been successfully applied 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. These catalysts sometimes showed better reactivity or stereoselectivity comparing to that of BINAP and MeO-BIPHEMP, probably due to the wide range of electronic properties exhibited by these diphosphine ligands. Especially worth mentioning is that the ruthenium(II) complexes of the P-Phos series are air stable compounds that can be handled in air, and be used with a low catalyst loading. Further, with the inherently special characteristics of the additional chiral auxiliary, axially chiral birayl 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 diphosphine ligands in large scale.

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