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SYNTHETIC COMMUNICATIONS REVIEWS

Chiral phosphine-phosphoramidite ligands in asymmetric catalysis

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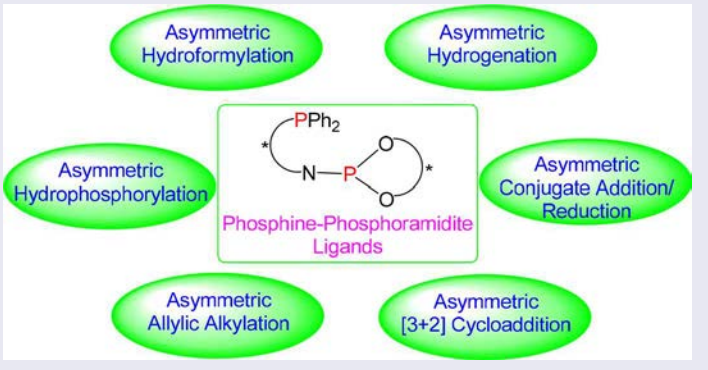
ABSTRACT

Chiral phosphine-phosphoramidite ligands, featuring ready availability, easy modification, and stability towards air and moisture, have recently emerged as a new kind of robust ligands for asymmetric catalysis. They have been found to display wide utilities in various catalytic asymmetric reactions, giving excellent enantioselectivities in the Rh-, Ru-, and Ir-catalyzed asymmetric hydrogenation of C=C, C=O, and C=N double bonds; Rh-catalyzed asymmetric hydroformylation; Pd-catalyzed asymmetric hydrophosphorylation; Pd-catalyzed asymmetric allylic alkylation; Ag-catalyzed asymmetric [3 + 2] cycloaddition; and Cu-catalyzed conjugate addition and reduction. In this review, the progress on the development of chiral phosphine-phosphoramidite ligands in asymmetric catalysis has been summarized.

GRAPHICAL ABSTRACT



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Introduction

Asymmetric catalysis has been one of the most active research areas in modern chemistry. The development of chiral catalysts, in particular those transition-metal complexes modified with various chiral ligands, is at the central of research in asymmetric catalysis, thus leading to thousands of chiral ligands developed in the past decades.[1,2] Since the pioneering work from Kagan in the development of 2,3-O-Isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane (DIOP),[3] followed by the success of

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1,2-bis((2-methoxyphenyl)(phenyl)phosphanyl)ethane (DIPAMP)[4] and 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP)[5] in the catalytic asymmetric hydrogenation, the principle of C_2 symmetry has strongly influenced the design of chiral ligands for asymmetric catalysis.[6] It is believed that C_2-symmetric ligands would reduce the number of possible catalyst–substrate arrangements and transition states, which would have a beneficial effect on enantioselectivity because the competing less-selective pathways are possibly eliminated. However, as Pfaltz indicated,[7] there is no fundamental reason why a C_2-symmetric ligand should necessarily be superior to a nonsymmetric counterpart. In fact, ligands with two different coordinating groups should allow for a better stereocontrol in many situations. In the past two decades, there has been increasing interest in the design and application of unsymmetrical ligands in asymmetric catalysis.[8]

Phosphine-phosphoramidite ligand[9–12] represents an important class of unsymmetrical hybrid bidentate phosphorus ligands, which shows excellent results in various asymmetric transformations. In this review, we will summarize and discuss recent advances on the synthesis and application of chiral phosphine-phosphoramidite ligands in asymmetric catalysis according to the reaction type.

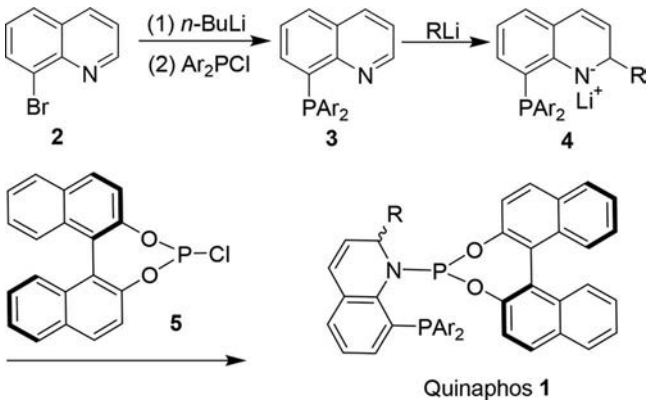
Asymmetric hydrogenation

Rh-catalyzed asymmetric hydrogenation of C = C double bonds

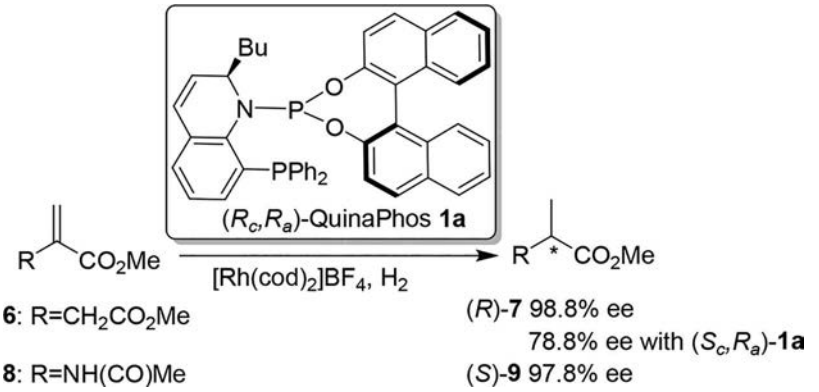
Quinaphos, Me-anilaphos, and matphos

In 2000, Leitner et al.[13] reported a new class of phosphine-phosphoramidite ligands, quinaphos **1**, which could be obtained from readily available 8-bisarylphosphanylquinolines **3** by nucleophilic addition of an organometallic reagent and direct quenching of the resulting 1,2-dihydroquinoline salt **4** with chlorophosphites **5** (Scheme 1). During the reaction, a new chiral center was generated at 2-position of the quinolone skeleton, therefore leading to a 1:1 mixture of diastereomers for ligands containing enantiomerically pure (R_a)-binaphthol, which could be separated by column chromatography.

Quinaphos **1a** showed high enantioselectivities in the Rh-catalyzed asymmetric hydrogenation of dimethyl itaconate **6** and methyl 2-acetamidoacylate **8** (Scheme 2). A remarkable matched/mismatched effect was observed for this hydrogenation with the



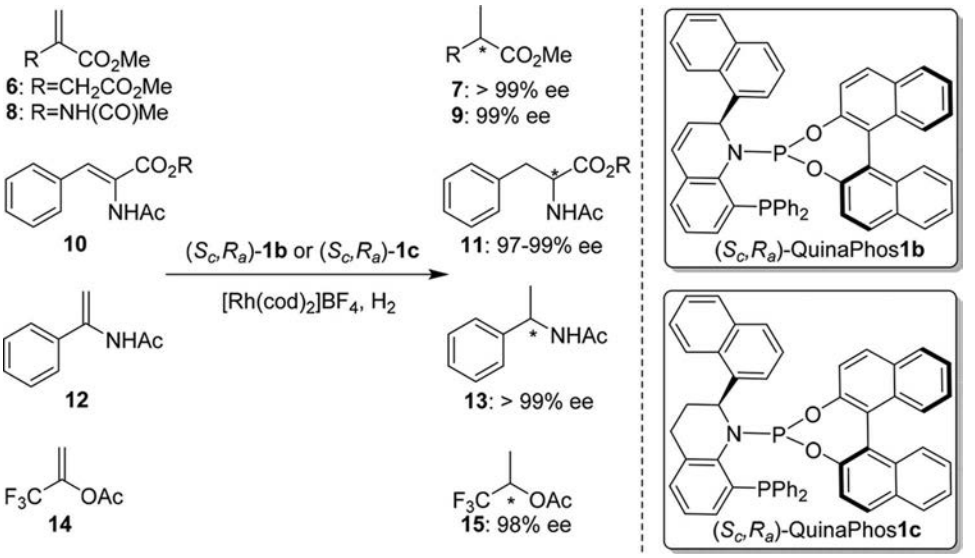
Scheme 1. Procedure for the synthesis of quinaphos **1**.



Scheme 2. Asymmetric hydrogenation of **6** and **8** with (R_c,R_a)-quinaphos **1a**.

two diastereomeric ligands, and (R_c,R_a)-quinaphos proved to be the more effective diastereomer. Quinaphos represents the first successful chiral phosphine-phosphoramidite ligands for asymmetric catalysis.

Following this work, Leitner et al.[14] in 2010 developed a modular synthetic approach to the new quinaphos family, and a 1-naphthyl substituent was introduced at C-2, which significantly affected the solubility profile of the diastereomers and enabled a gram-scale isolation of the (S_c,R_a) and (R_c,R_a)-diastereomers. The new quinaphos-type ligands (S_c,R_a)-**1b** showed remarkably high enantioselectivities and activities in the Rh-catalyzed asymmetric hydrogenation of functionalized olefins, including dehydroamino acid derivatives and enamides. In most cases, ≥99% *ee* values were obtained, combined with TOF values of up to 20,000 h^{-1} (Scheme 3). The same excellent level of enantioselectivity were also observed when using dihydroquinaphos **1c** with the more flexible 1,2,3,4-tetrahydroquinoline backbone.



Scheme 3. Asymmetric hydrogenation of **6, 8, 10, 12,** and **14** with (S_c,R_a)-quinaophos **1b** and **1c.**

More recently, Leitner et al.[15] demonstrated a highly efficient continuous-flow process for the asymmetric hydrogenation by using a chiral transition-metal catalyst in supported ionic liquid phase (SILP) with $ScCO_2$ flow. Excellent enantioselectivity of $>99\%$ *ee* and quantitative conversion were achieved in the Rh-catalyzed asymmetric hydrogenation of dimethyl itaconate **6** with ligand (R_c,S_a)-quinaphos **1b** (Scheme 4). This method demonstrated that the use of organic solvents or additional purification steps is unnecessary in some asymmetric synthesis.

A more flexible *N*-methylaniline derived phosphine-phosphoramidite ligand Me-anilaphos **16** was reported by Kostas et al. in 2006,[16] which was considered as the acyclic analog of quinaphos **1**. Indeed, the Rh-complex of Me-anilaphos **16** was proved to be highly efficient for the hydrogenation of dimethyl itaconate **6** and methyl (*Z*)-α-acetamidocinnamate **10**, giving enantioselectivities of 96% and 98% *ee*, respectively (Scheme 5).

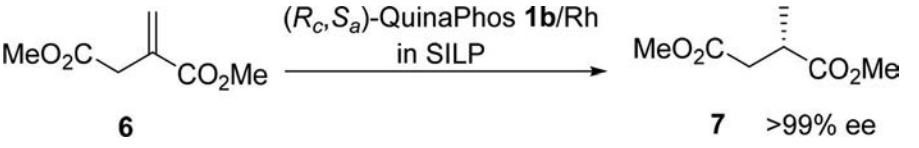
Leitner et al. reported the derivatives of Me-anilaphos containing additional chiral substituents on the amine moiety, named matphos **17**, which proved to be efficient for the asymmetric hydrogenation of different classes of functionalized olefins with *ee*s of $\geq$99%.[17] More importantly, (S_c,S_a)-matphos **17a** was also successfully applied in the asymmetric hydrogenation of vinyl enol esters **18,**[18] opening a general access to chiral secondary alcohols including for the first time simple alkan-2-ols in synthetically useful enantiopurity with excellent enantioselectivities (Scheme 6).

Indolphos

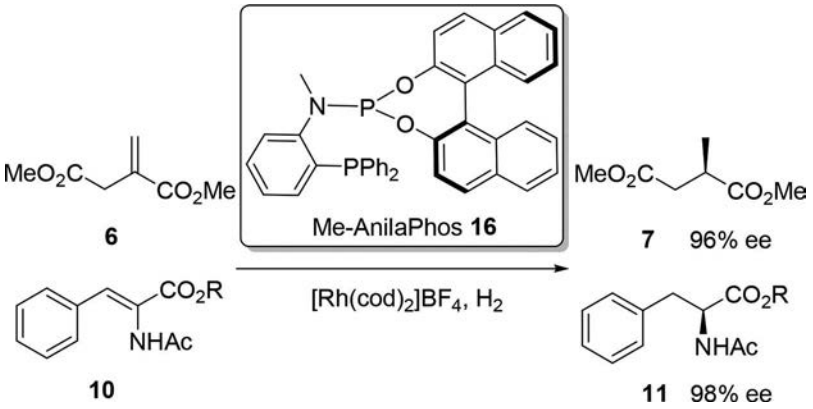
In 2007, Reek et al. reported the synthesis of Indolphos **20** in two steps from 3-methylindole **21** (Scheme 7).[19] Selective lithiation in the 2-position of 3-methylindole **21** was achieved by in situ protection of nitrogen with CO_2, which also acted as a directing group. Subsequent addition of R_2PCl gave the corresponding indolylphosphine **22**, which reacted with chlorophosphites **5** to give the desired indolphos **20**.

Indolphos **20** displayed high efficiency in the Rh-catalyzed asymmetric hydrogenation of dimethyl itaconate **6**, α-dehydroamino acid esters **10**, enamides **12**, β-dehydroamino acid esters **23**, α-enol, and enamido phosphonates **25** (Scheme 8).[20] High reactivities and good to excellent enantioselectivities of up to 99% *ee* were obtained for a broad range of structurally diverse substrates, giving important chiral products such as α, β^2, β^3 amino acid derivatives, arylamines, and hydroxy phsophonates. The mechanism of the indolphos-Rh catalyzed asymmetric hydrogenation of prochiral olefins has been investigated by Reek et al.[21] The mechanism study indicated that the reaction follows an unsaturated/dihydride mechanism. Such a mechanism was in accordance with previous studies on the mechanism of asymmetric hydrogenation with C_1-symmetric P/S ligands and monodentate ligands.

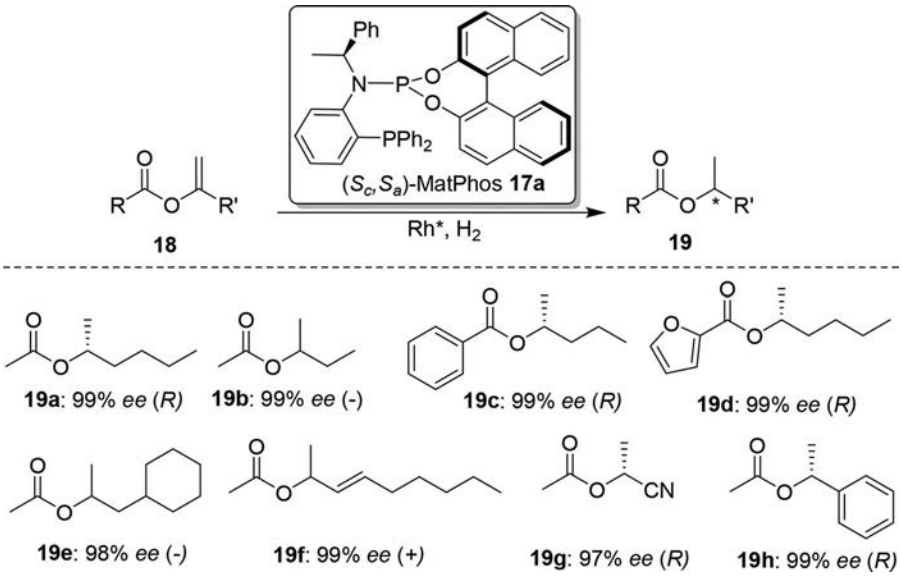
The indolphos **20** was also subjected to Rh-catalyzed hydrogenation of methyl 2-hydroxymethylacrylate derivatives **27**, which provided a direct way to asymmetric



Scheme 4. Asymmetric hydrogenation of dimethyl itaconate **6** with (R_c,S_a)-quinaphos **1b** in SILP under $ScCO_2$ flow.

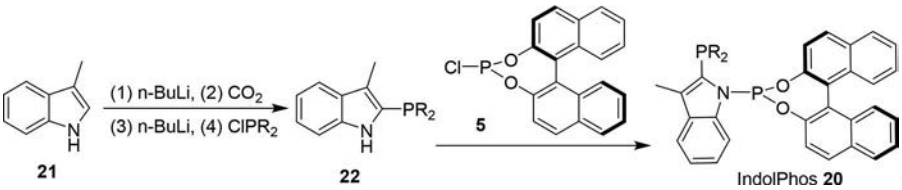


Scheme 5. Asymmetric hydrogenation of **6** and **10** with Me-anilaphos **16**.

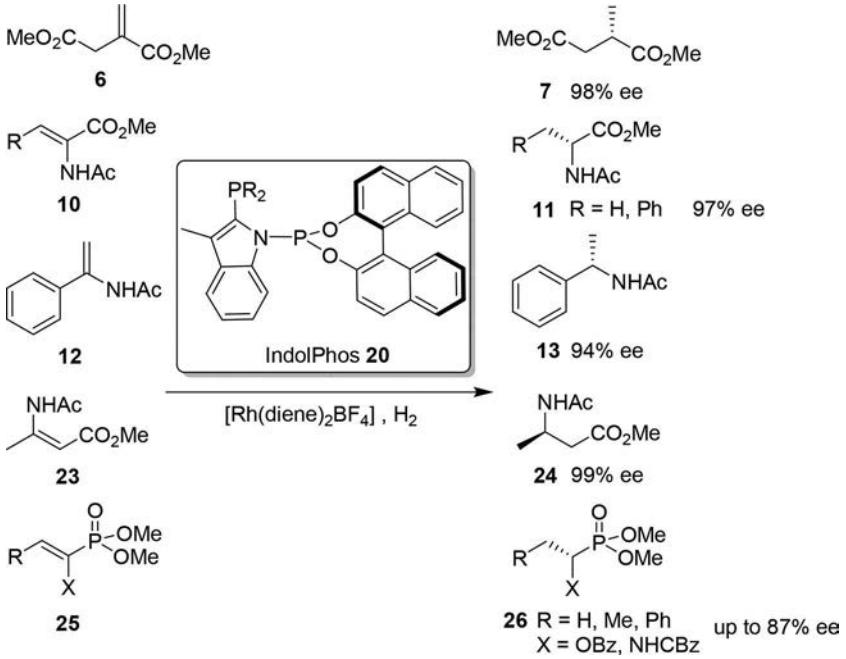


Scheme 6. Asymmetric hydrogenation of vinyl enol esters **18** with (S_c,S_a)-matphos **17a**.

synthesis of Roche ester **28**, an important building block for the enantioselective synthesis of many natural products and pharmaceutical compounds (Scheme 9).[22] The primary alcohol had an important function as the acyl-protected substrate **27c** was hydrogenated



Scheme 7. Procedure for the synthesis of indolphos **20**.

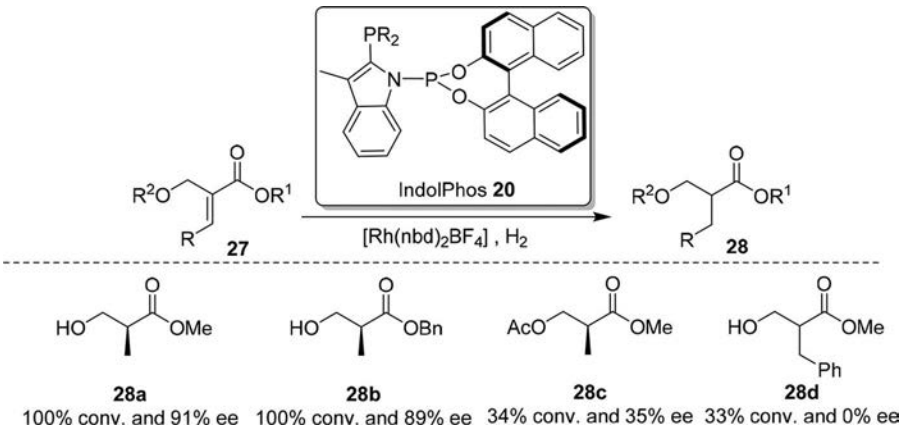


Scheme 8. Asymmetric hydrogenation of **6**, **10**, **12**, **23**, and **25** with indolphos **20**.

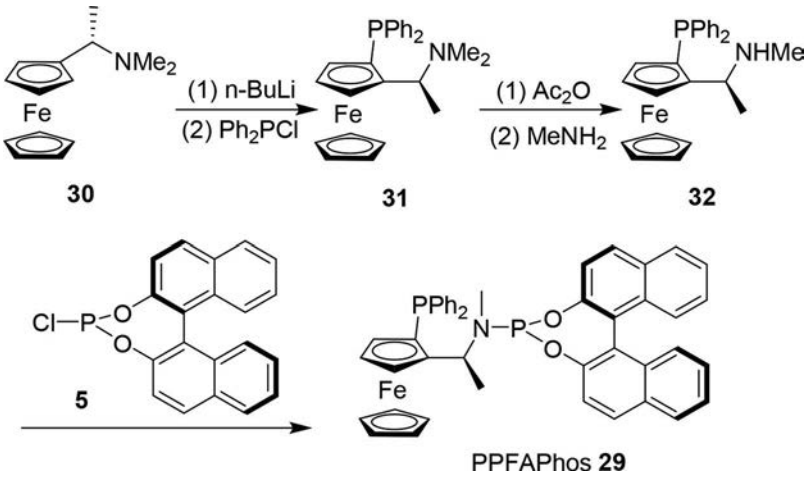
in very low conversion and enantioselectivity. The trisubstituted substrate **27d** also was less reactive and gave poor yield of the product in a racemeric form.

PPFAphos

In 2004, Chan et al.[23] and Zheng et al.[24] independently reported a planar-chiral ferrocene backbone phosphine-phosphoramidite ligand PPFAphos **29** (Scheme 10). It was prepared from commercially available Ugi's amine **30** in a four-step procedure as outlined in Scheme 10. Ugi's amine **30** was treated successively with *n*-BuLi and Ph_2PCl to give the amino-phosphine **31**. The substitution of the dimethyl amino group by a secondary amine



Scheme 9. Asymmetric hydrogenation of **27** with indolphos **20**.

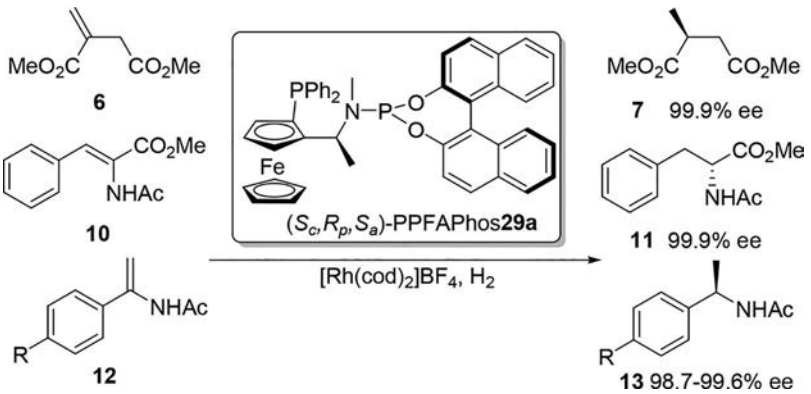


Scheme 10. Procedure for the synthesis of PPFAphos **29**.

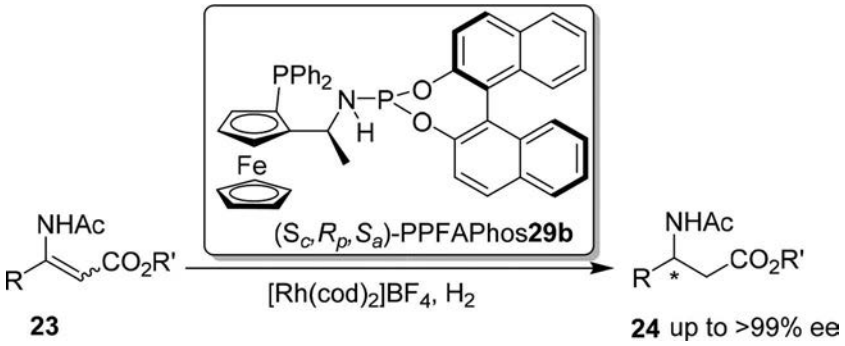
was performed by sequential treatment of **31** with Ac_2O and methylamine. The resulting compound **32** reacted with chlorophosphites **5** to give the expected PPFAphos **29**.

The ligand (S_c,R_p,S_a)-PPFAphos **29a** was demonstrated to be highly efficient in the Rh-catalyzed asymmetric hydrogenation of various functionalized olefins including dimethyl itaconate **6**, α-dehydroamino acid esters **10**, and enamides **12**, normally giving over 99% *ee* (Scheme 11). The hydrogenation can be performed even under a catalyst loading as low as 0.01 mol%, without loss of the reactivity and enantioselectivity. Similar results were obtained using the H_8-BINOL-derived ferrocenyl phosphine-phosphoramidite ligands.[25] The stereogenic elements in the ligand structure had important effect in the enantioselectivity: (1) the axial chirality in binaphthyl moiety played a crucial role in the enantioselectivity and controlled the chirality of the hydrogenation products; and (2) *S*-central, *R*-planar and *S*-axial chiralities were the matched configuration.

However, the (S_c,R_p,S_a)-PPFAphos **29a** exhibited a very poor enantioselectivy in the hydrogenation of β-dehydroamino acid esters **23**. Further research disclosed that an N-H proton on the amino moiety of the ligands had a crucial role in achieving high



Scheme 11. Asymmetric hydrogenation of **6**, **10**, and **12** with (S_c,R_p,S_a)-PPFAphos **29a**.



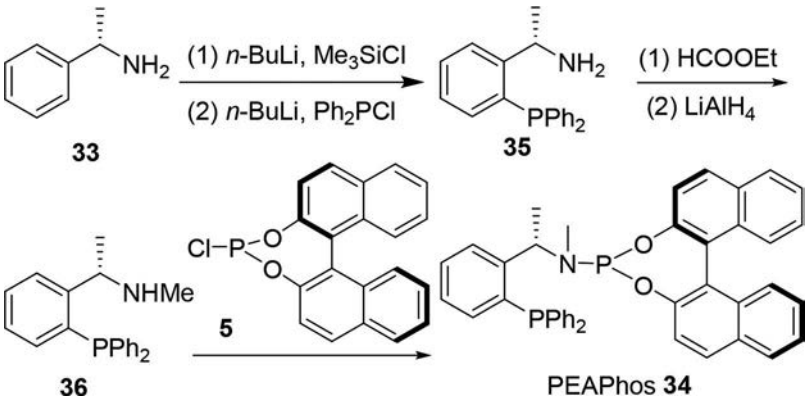
Scheme 12. Asymmetric hydrogenation of **23** with N-H based (S_c,R_p,S_a)-PPFAphos **29b**.

stereocontrol in the hydrogenation of β-dehydroamino acid esters **23**, presumably due to a potential second interaction between the N-H proton in the ligand and the substrate. Thus, ligand (S_c,R_p,S_a)-PPFAphos **29b** with an N-H proton on the amine moiety was found to be highly efficient for the Rh-catalyzed asymmetric hydrogenation of a variety of β-dehydroamino acid esters **23**, in particular (*Z*)-β-dehydroamino acid esters, which remains a challenging task in catalytic asymmetric hydrogenation (Scheme 12).[26]

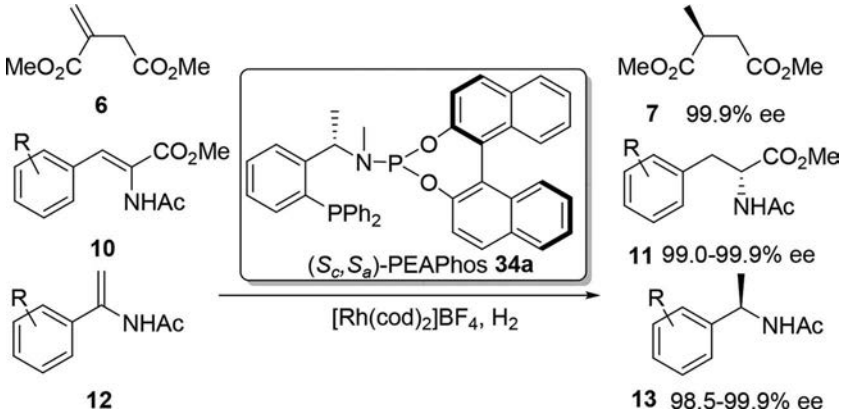
PEAphos, THNAphos, and HY-phos

Considering the structure similarity between 1-ferrocenylethylamine **30** and 1-phenylethylamine **33**, Hu and Zheng et al. prepared a 1-phenylethylamine-derived phosphine-phosphoramidite ligand PEAphos **34** though a three-step transformation as outlined in Scheme 13.[27] Thus (*S*)-1-phenylethylamine **33** was sequentially treated by *n*-BuLi and TMSCl to give an intermediate, which was dilithiated by further addition of *n*-BuLi. Subsequent *ortho*-phosphination with Ph_2PCl gave the amine-phosphine **35**. The resulting compound **35** was monomethylated to give the corresponding **36**, which could be easily converted into the desired phosphine-phosphoramidite ligand PEAphos **34**.

The ligand (S_c,S_a)-PEAphos **34a** was evaluated in the Rh-catalyzed asymmetric hydrogenation of a variety of functionalized olefins including dimethyl itaconate **6**, α-dehydroamino acid esters **10**, and enamides **12**, in which up to 99.9% *ee* was obtained



Scheme 13. Procedure for the synthesis of PEAphos **34**.

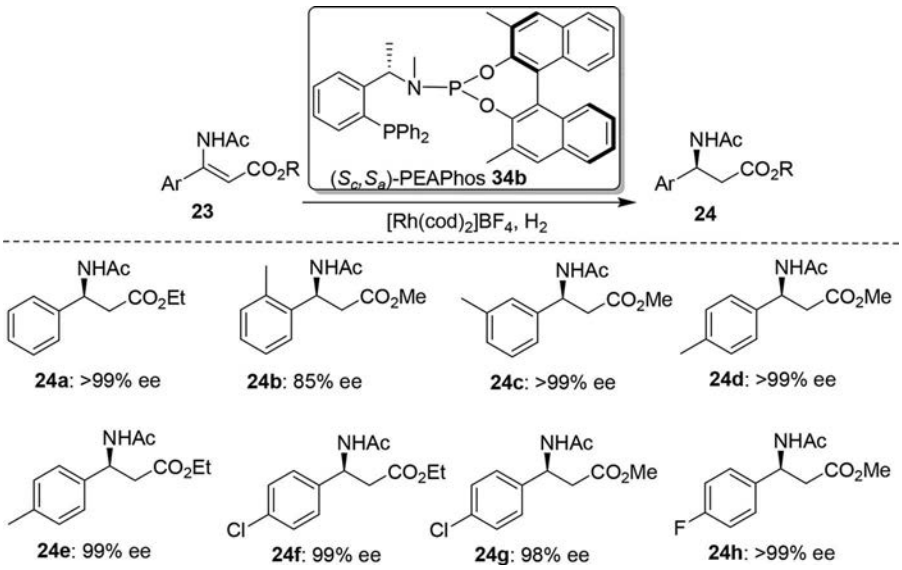


Scheme 14. Asymmetric hydrogenation of **6**, **10**, and **12** with (S_c,S_a)-PEAphos **34a**.

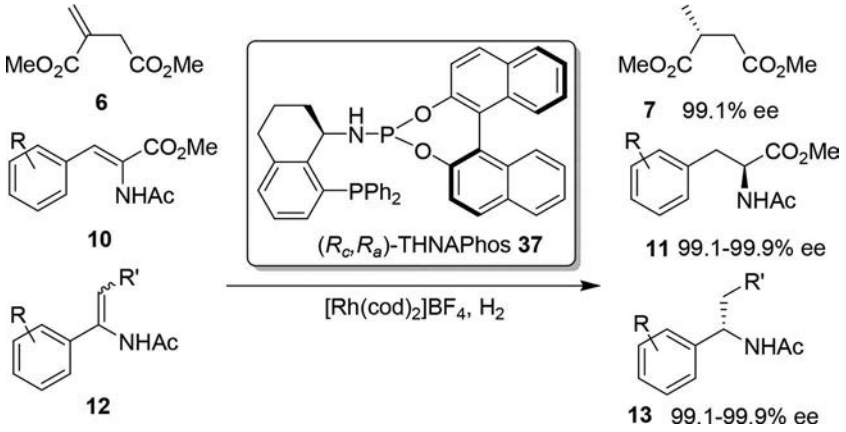
for all of these kinds of substrates (Scheme 14).[27] Most interestingly, the central chirality in 1-phenylethylamine backbone decided the absolute configuration of the hydrogenation products, contrary to the result obtained with PPFAphos **29** in which the binaphthyl moiety controlled the chirality of the hydrogenation products.

Further results disclosed that for the asymmetric hydrogenation of β-dehydroamino acid esters **23**, the presence of substituents on the 3,3′-positions of the binaphthyl moiety significantly improved the enantioselectivity.[28] Thus, the ligand (S_c,S_a)-PEAphos **34b** displayed excellent enantioselectivity in the Rh-catalyzed asymmetric hydrogenation of challenging (*Z*)-β-dehydroamino acid esters **23**, giving up to > 99% *ee* (Scheme 15).

As the rigidity of a ligand structure had significant influence on the enantioselectivity, Hu and Zheng et al. then prepared a more rigid 1,2,3,4-tetrahedro-1-naphthylamine



Scheme 15. Asymmetric hydrogenation of **23** with (S_c,S_a)-PEAphos **34b**.

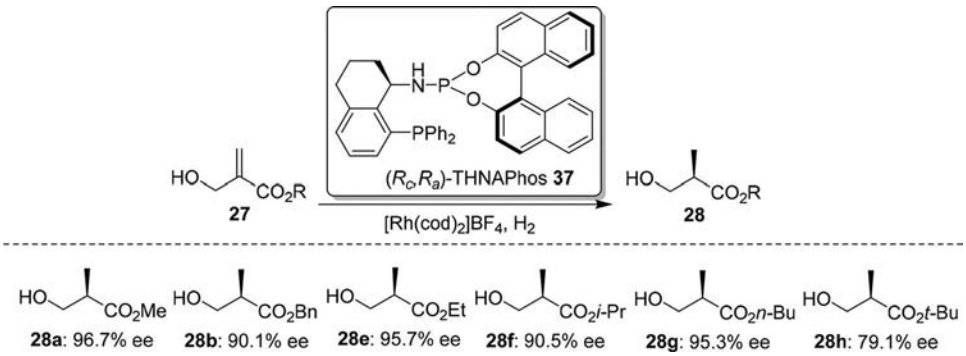


Scheme 16. Asymmetric hydrogenation of **6**, **10**, and **12** with (R_c,R_a)-THNAphos **37**.

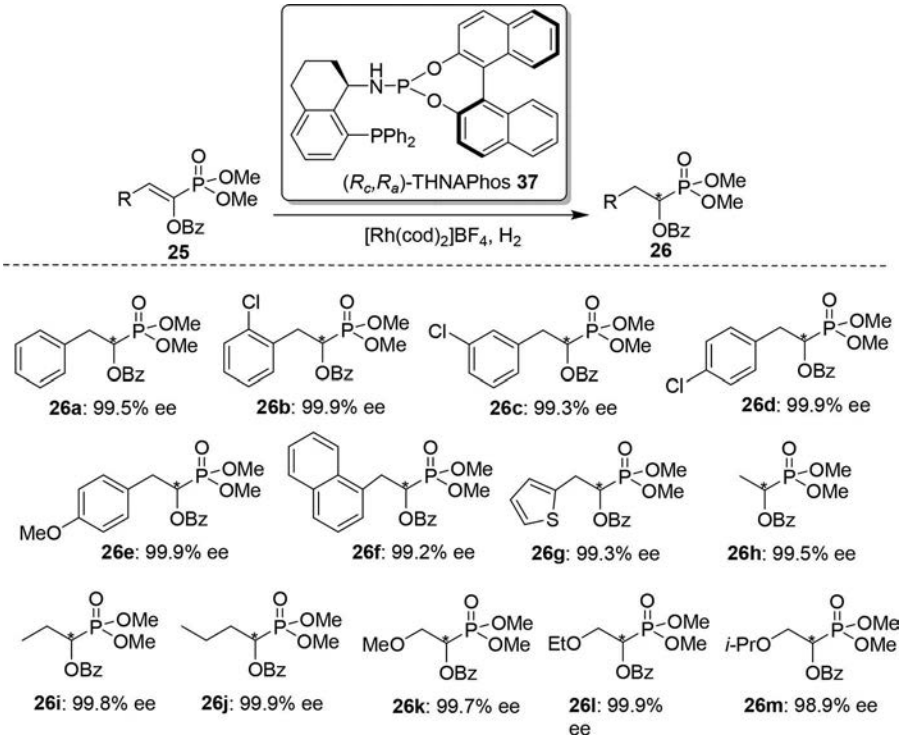
derived phosphine-phosphoramidite ligand THNAphos **37**.[29] The ligand (R_c,R_a)-THNAphos **37** demonstrated high efficiency in the Rh-catalyzed asymmetric hydrogenation of dimethyl itaconate **6**, α-dehydroamino acid esters **10**, and enamides **12**, affording the corresponding hydrogenation products in excellent enantioselectivities (normally over 99% *ee*) (Scheme 16).

Despite the high efficiency of PEAphos **34** in the Rh-catalyzed asymmetric hydrogenation of some traditional functionalized olefin substrates, it showed insufficient selectivity in some challenging hydrogenation such as 2-hydroxymethylacrylate **27**, presumably due to its flexible backbone. Delightedly, the ligand (R_c,R_a)-THNAphos **37** provided improved enantioselectivity in the Rh-catalyzed asymmetric hydrogenation of **27**, giving the corresponding Roche ester in up to 96.7% *ee* (Scheme 17).[30]

The most important application of (R_c,R_a)-THNAphos **37** was in the catalytic asymmetric hydrogenation of α-enol phosphonates **25**. Hu and Zheng found that the (R_c,R_a)-THNAphos **37** was highly efficient for the Rh-catalyzed asymmetric hydrogenation of various of enol ester phosphonates including β-aryl-, β-alkoxy-, and β-alkyl-substitutedsubstrates providing unprecedented enantioselectivities (up to 99.9% *ee*) (Scheme 18).[31]



Scheme 17. Asymmetric hydrogenation of **27** with (R_c,R_a)-THNAphos **37**.



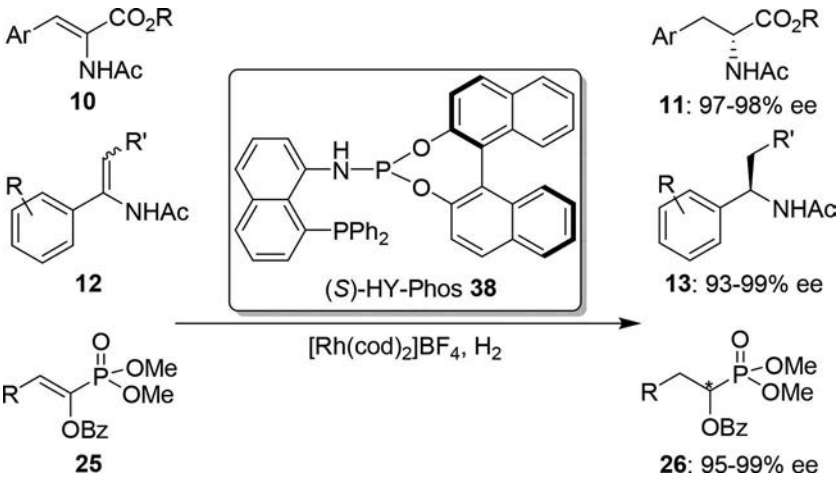
Scheme 18. Asymmetric hydrogenation of **25** with (R_c,R_a)-THNAphos **37**.

Because of the high cost of chiral 1,2,3,4-tetrahydro-1-naphthylamine, the search for an inexpensive alternative for the synthesis of phosphine-phosphoramidite ligands was carried out by Hu and Zheng. Thus, new chiral phosphine-phosphoramidite ligand HY-phos **38** was developed from inexpensive 1-naphthylamine.[32] Despite the absence of the central chirality in comparison with (R_c,R_a)-THNAphos **37**, (*S*)-HY-phos **38** displayed excellent enantioselectivites in the Rh-catalyzed asymmetric hydrogenation of various functionalized olefins including α-dehydroamino acid esters **10**, enamides **12**, and α-enol ester phosphonates **25**, in which up to 98%, 99%, and 99% *ee* were achieved respectively (Scheme 19).

UPphos

Replacing the aminoaryl phosphine with an aminoalkyl phosphine backbone, Bakos et al. reported a new phosphine-phosphoramidite ligand UPphos **39** by a three-step procedure as outlined in Scheme 20.[33,34] Treatment of enantiomerically pure (4*R*,6*R*)-4,6-dimethyl-1,3,2-dioxathiane-2,2-dioxide **40** with *i*-$PrNH_2$ gave the amino sulfate compound **41**. The addition of Ph_2PLi to compound **42** provided the aminoalkylphosphine **42**, which can be easily converted into the desired phosphine-phosphoramidite ligand UPphos **39**.

(*S*)-(2*S*,4*S*)-UPphos **39** was subjected to the Rh-catalyzed asymmetric hydrogenation of dimethyl itaconate **6** and α-dehydroamino acid derivatives **10** in green solvents such as ethylene carbonate and propylene carbonate, giving the corresponding hydrogenation products in 96.7–99.9% *ee* (Scheme 21). More importantly, the dimethyl itaconate **6** could be hydrogenated under solvent-free conditions at 50 °C with 98.7% *ee*. Further research



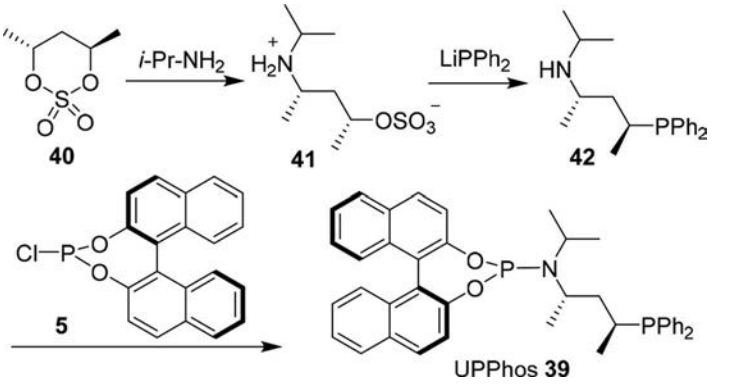
Scheme 19. Asymmetric hydrogenation of **10**, **12**, and **25** with (*S*)-HY-phos **37**.

disclosed that the central chirality in the bridge determined the configuration of the hydrogenation products with a cooperative effect from the terminal groups.[35]

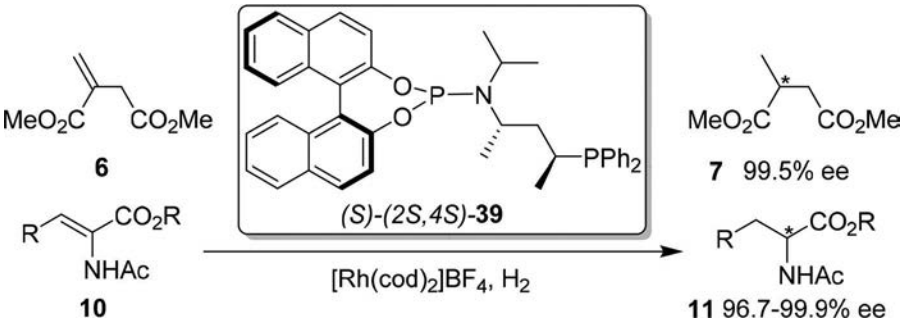
Zhang's triphosphorous bidentate phosphine-phosphoramidite ligands

In 2006, Zhang et al.[36] reported the synthesis of triphosphorous bidentate phosphine-phosphoramidite ligands **43** by a four-step procedure (Scheme 22). Protection of the hydroxy group of BINOL **44** with CH_3OCH_2Cl, followed by lithiation and subsequent treatment with Ph_2PCl, gave the *ortho*-substituted diphenylphosphino BINOL **46**. Removal of the methoxy methyl (MOM) groups gave the diphosphine **47**. The desired phosphine-phosphoramidite ligands **43** was then prepared by heating **47** with hexamethylphosphorous tramide (HMPT) or hexaethylphosphorous triamide (HEPT).

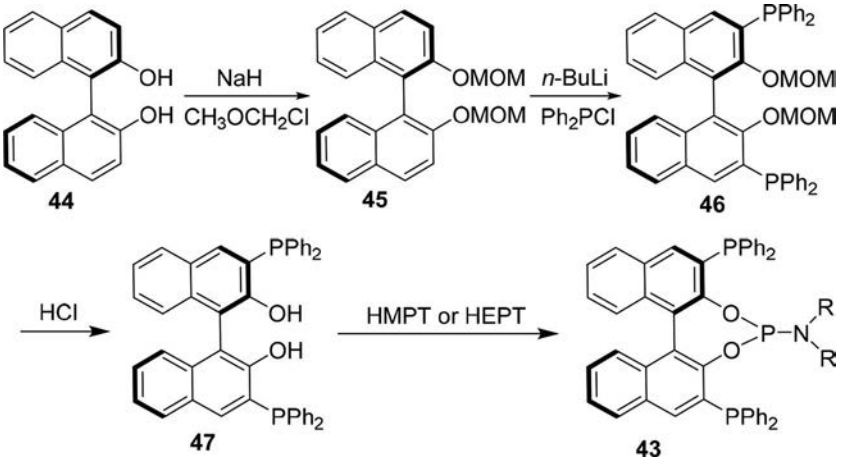
The Zhang's triphosphorous bidentate ligands **43** showed excellent enantioselectivities (up to 99.6% *ee*) in the Rh-catalyzed asymmetric hydrogenation of itaconate derivatives **6**, α-dehydroamino acid esters **10**, and enamides **12** in particular some challenging *ortho*-subsituted aryl enamides and 1-naphtylenamide (Scheme 23).[37] Interestingly, a dramatic solvent effect was observed in the hydrogenation of itaconates, which induced



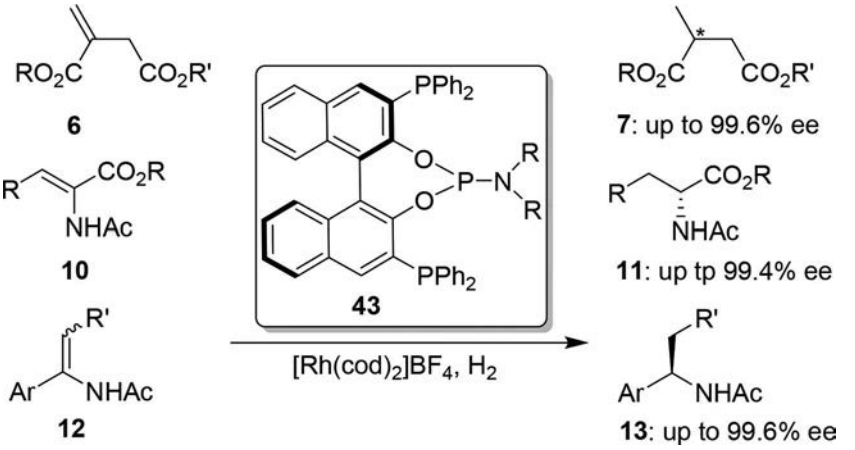
Scheme 20. Procedure for the synthesis of UPphos **39**.



Scheme 21. Asymmetric hydrogenation of **6** and **10** with UPphos **39**.



Scheme 22. Procedure for the synthesis of Zhang's triphosphorous bidentate ligands **43**.



Scheme 23. Asymmetric hydrogenation of **6**, **10**, and **12** with Zhang's ligands **43**.

opposite chiralities of the product with the same catalytic system by use of different solvents (e.g., 99.6% *ee* (*R*) in TFE vs 71.2% *ee* (*S*) in methyl ethyl ketone). An x-ray diffraction experiment revealed a highly preferential chelating of metal with only two phosphorous donors, leaving a third uncoordinated phosphine.

Ru- and Rh-catalyzed asymmetric hydrogenation of C = O double bonds

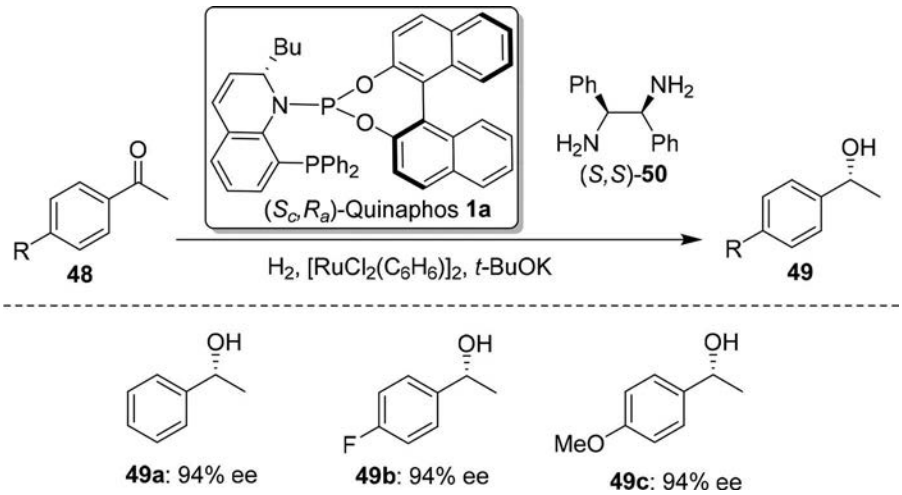
Leitner et al.[38] had demonstrated the efficiency of (S_c,R_a)-quinaphos **1a** in the Ru-catalyzed asymmetric hydrogenation of ketones **48** (Scheme 24). The two diastereomers showed significantly different activity towards C=C and C=O double bonds. Thus, (R_c, R_a)-quinaphos **1a** was the diastereomer of choice for the Rh-catalyzed asymmetric hydrogenation of C=C double bonds, whereas (S_c,R_a)-quinaphos **1a** proved to be superior for the Ru-catalyzed asymmetric hydrogenation of C=O double bonds. It was noteworthy that the enantioselectivity could be further improved with a chiral diamine (*S*,*S*)-**50** as cocatalyst.

Using the ligand (S_c,S_a)-matphos **17a**, high enantioselectivity had also been achieved in the Ru-catalyzed asymmetric hydrogenation of β-ketoesters **51**, giving the corresponding β-hydroxy esters **52** in up to 96% ee (Scheme 25).[17] Different from the Ru-catalyzed asymmetric hydrogenation of ketones **48**, (S_c,S_a)-configuration of the ligand proved to be matched in the Ru-catalyzed hydrogenation of β-ketoesters **51**.

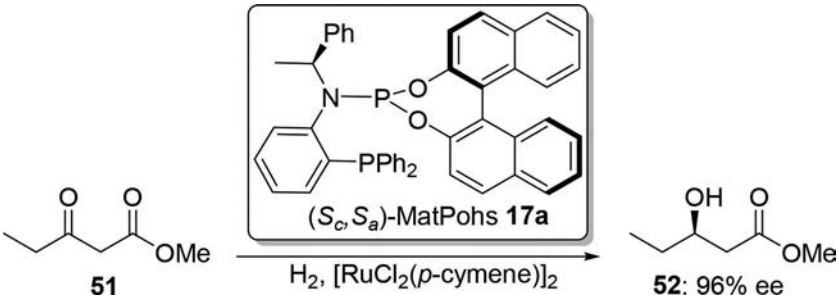
Recently, Hou and Hu[39] reported the first Rh-catalyzed asymmetric hydrogenation of α-keto phosphonates **53** (Scheme 26). With a *N*-substituted PEAphos-typed phosphine-phosphoramidite ligand (R_c,R_a)-**34c**, a wide range of challenging α-keto phosphonates **53** were hydrogenated in moderate to good enantioselectivities (up to 87% *ee*). It provided a new access to chiral α-hydroxy phosphonates **54**.

Ir-catalyzed asymmetric hydrogenation of C = N double bonds

In 2012, Hu et al.[40] developed an Ir-catalyzed asymmetric hydrogenation of challenging sterically hindered N-aryl imines **55** with a H_8-BINOL derived PEAphos-typed



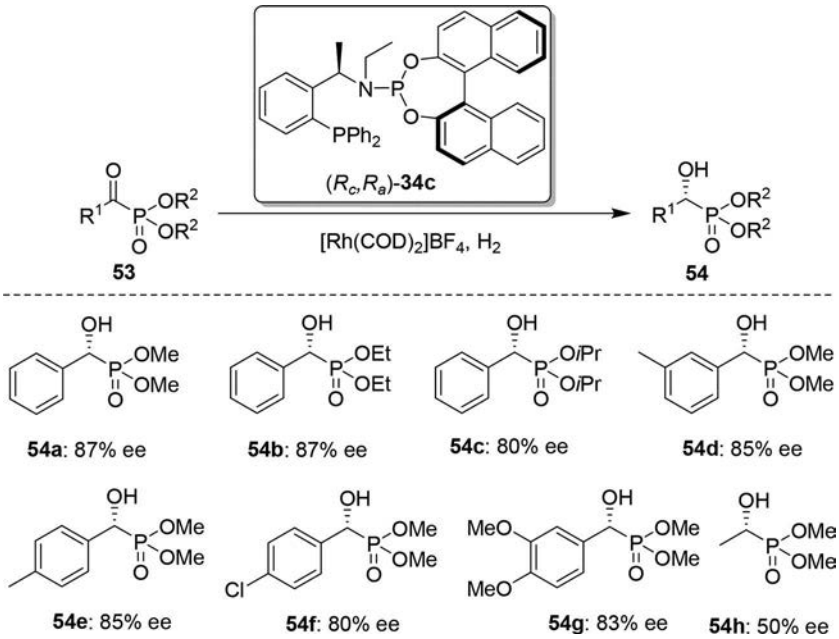
Scheme 24. Asymmetric hydrogenation of **48** with (S_c,R_a)-quinaphos **1a**.



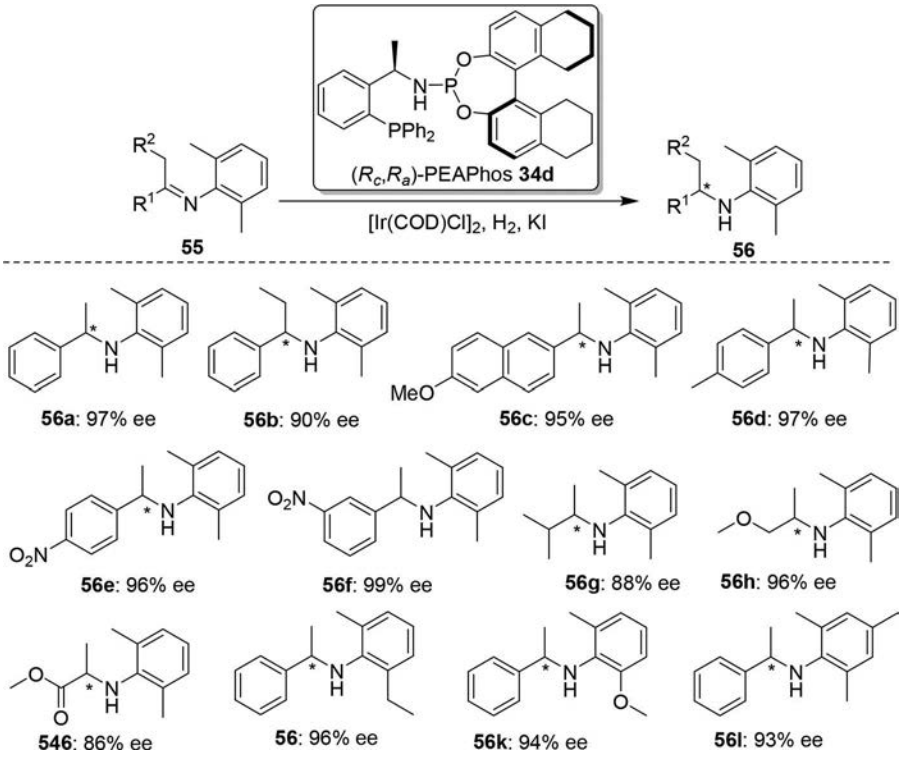
Scheme 25. Asymmetric hydrogenation of **51** with (S_c,S_a)-matphos **17a**.

phosphine-phosphoramidite ligand (R_c,R_a)-**34d** (Scheme 27). The results suggested that the presence of an N-H proton and a H_8-BINOL moiety on the ligand backbone was crucial for this hydrogenation to obtain high catalytic activity and enantioselectivity. The catalytic system featured high turnover numbers (up to 100,000) and good to perfect enantioselectivities (up to 99% *ee*) for the hydrogenation of a variety of sterically hindered N-aryl imines, representing the most versatile catalyst in the hydrogenation of sterically hindered imines.

Very recently, Hou and Hu[41] have reported the asymmetric hydrogenation of N-arylimines **55** and **57** with (S_c,S_a)-PEAphos **34b**, in which high turnover numbers (up to 50,000) and excellent enantioselectivity (up to 98% *ee*) were achieved (Scheme 28). The results revealed that the presence of the substituents on the 3,3′-positions of the binaphthyl backbone significantly improved the enantioselectivity. The utility of this methodology has been demonstrated by the synthesis of chiral fungicide (*R*)-metalaxyl at a catalyst loading of 0.002 mol%. It should be noted that the asymmetric hydrogenation



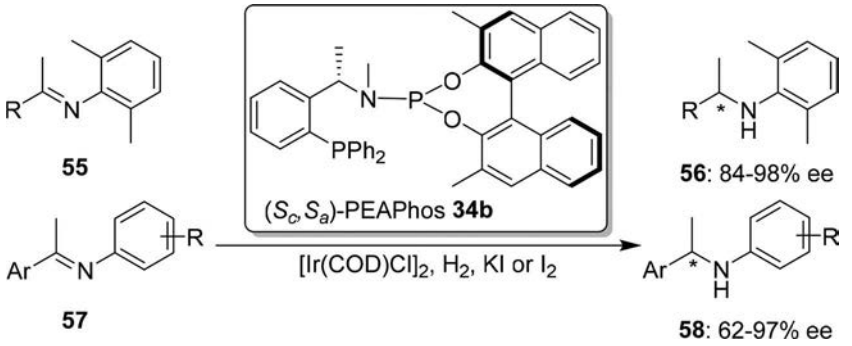
Scheme 26. Asymmetric hydrogenation of **53** with (R_c,R_a)-PEAphos **34c**.



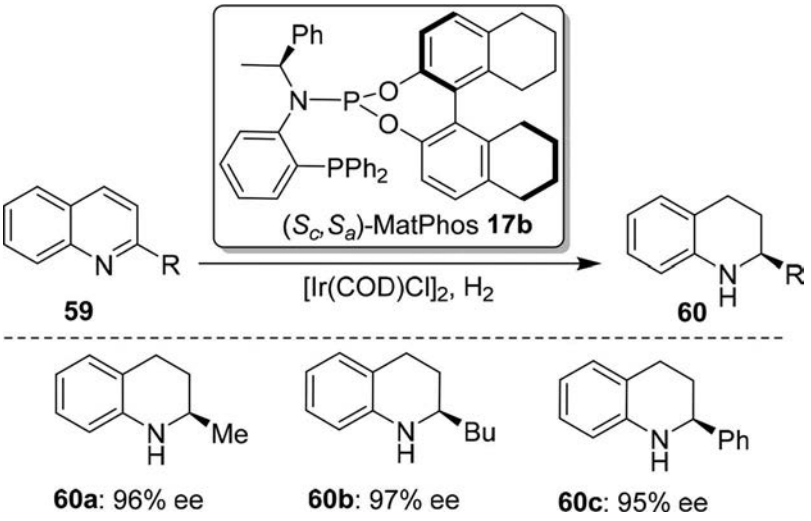
Scheme 27. Asymmetric hydrogenation of **55** with (R_c,R_a)-PEAphos **34d**.

can be carried out on a gram scale and operated in air without loss of the enantioselectivity and activity.

Besides its successful application in the Rh-catalyzed asymmetric hydrogenation of C=C double bonds and Ru-catalyzed asymmetric hydrogenation of C=O double bonds, the ligand matphos **17** also showed good performance in the Ir-catalyzed asymmetric hydrogenation of C=N double bonds (Scheme 29).[17] With H_8-BINOL-derived (S_c,S_a)-matphos **17b**, 2-substituted quinolines **59** could be hydrogenated in excellent enantioselectivities up to 97% *ee*, providing an efficient access to chiral 1,2,3,4-tetrahydroquinolines derivatives **60**, an important class of biologically active compounds.



Scheme 28. Asymmetric hydrogenation of **55** and **57** with (S_c,S_a)-PEAphos **34b**.



Scheme 29. Asymmetric hydrogenation of **59** with (S_c,S_a)-matphos **17b**.

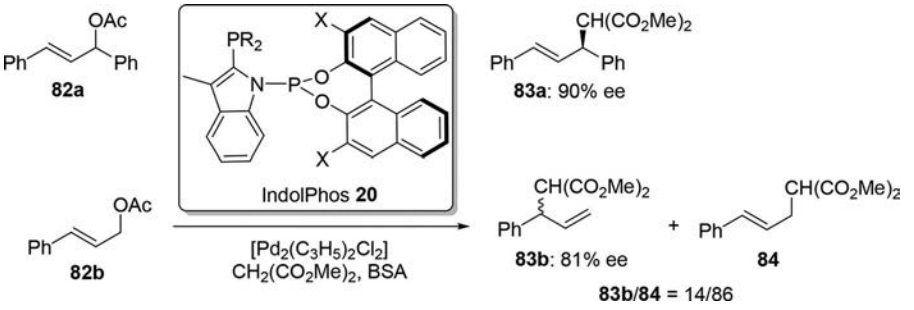
Asymmetric hydroformylation

Quinaphos

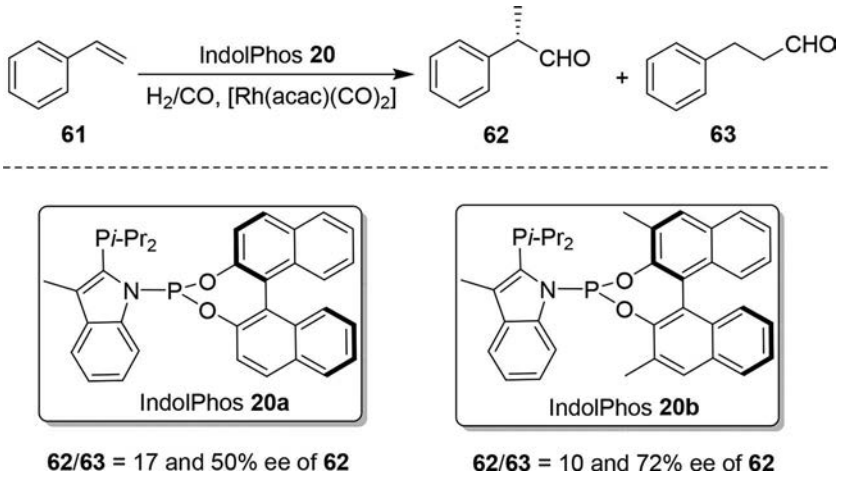
Leithner et al.[13] applied (S_c,R_a)-quinaphos **1a** in the Rh-catalyzed asymmetric hydroformylation of styrene **61** (Scheme 30). The reaction gave a mixture of the branched aldehyde **62** and the linear aldehyde **63** in favor of the former in high regioselectivity ($b/l = 96.7/3.3$) and moderate enantioselectivity (74% *ee*). However, ligand (R_c,R_a)-quinaphos **1a,** which proved to be matched in the Rh-catalyzed asymmetric hydrogenation of olefins, gave the aldehyde **62** with very poor enantioselectivity (4.8% *ee*).

Indolphos

Reek et al.[19] showed the application of indolphos **20** in the Rh-catalyzed asymmetric hydroformylation of styrene **61** (Scheme 31). A high regioselectivity ($b/l = 17$) in favor of the branched aldehyde **62** was obtained with ligand **20a**, but the enantioselectivity was moderate (50% *ee*) and the reaction cannot be completed even at a prolonged time.



Scheme 30. Asymmetric hydroformylation of **61** with (S_c,R_a)-quinaphos **1a**.

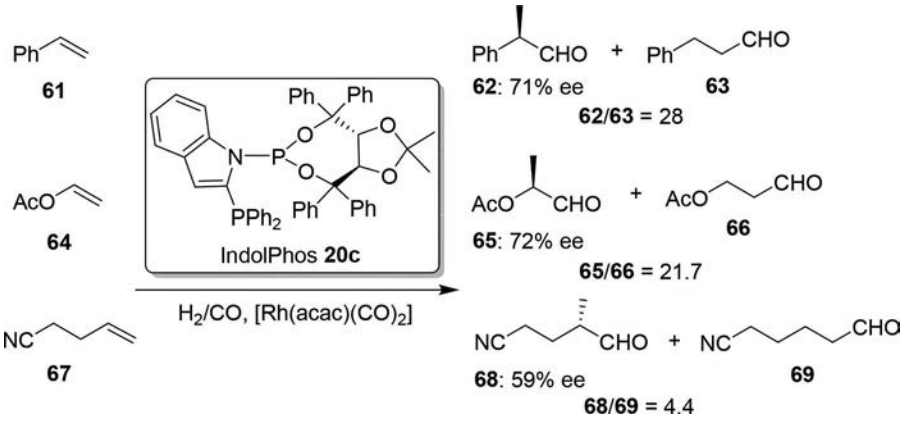


Scheme 31. Asymmetric hydroformylation of **61** with indolphos **20a** and **20b**.

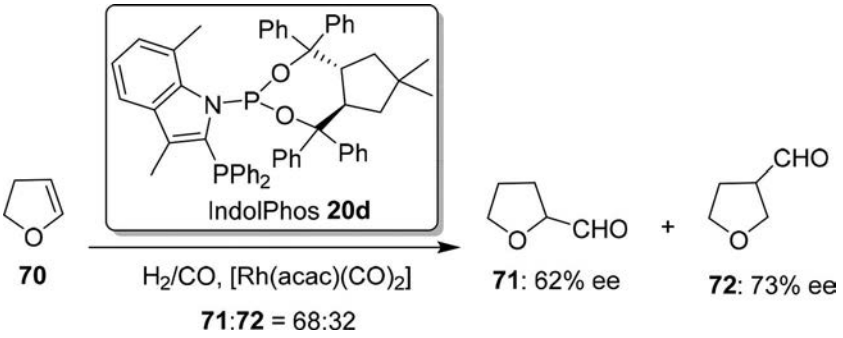
On the other hand, a nearly full conversion was observed with a more sterically hindered ligand **20b**, and the product **62** was obtained with an improved *ee* value (72% *ee*).

A (2,2-dimethyl-1,3-dioxolane-4,5-diyl)bis(diphenylmethanol) (TADDOL)-based indolphos **20c** had been developed by Reek et al.[42] and applied in the Rh-catalzyed asymmetric hydroformylation reactions (Scheme 32). High *b*/*l* ratios, as well as moderate to good enantioselectivities of up to 71%, 72%, and 59% *ee,* were obtained for styrene **61**, vinyl acetate **64**, and allyl cyanide **67**, respectively, therefore resulting in a high yield of the desired chiral aldehydes. Interestingly, an unprecedented temperature-dependent reversal of enantioselectivity was observed.

Another TADDOL-based indolphos **20d** has been successfully applied in the Rh-catalzyed asymmetric hydroformylation of the more challenging substrate 2,3-dihydrofuran **70,** yielding the 2-carbaldehyde **71** as the major regioisomer in up to 68% yield along with good *ee* value of up to 62% (Scheme 33).[43] This is the first example in which the asymmetric hydroformylation of **70** is both regio- and enantioselective for the isomer



Scheme 32. Asymmetric hydroformylation of **61**, **64**, and **67** with TADDOL-based indolphos **20c**.



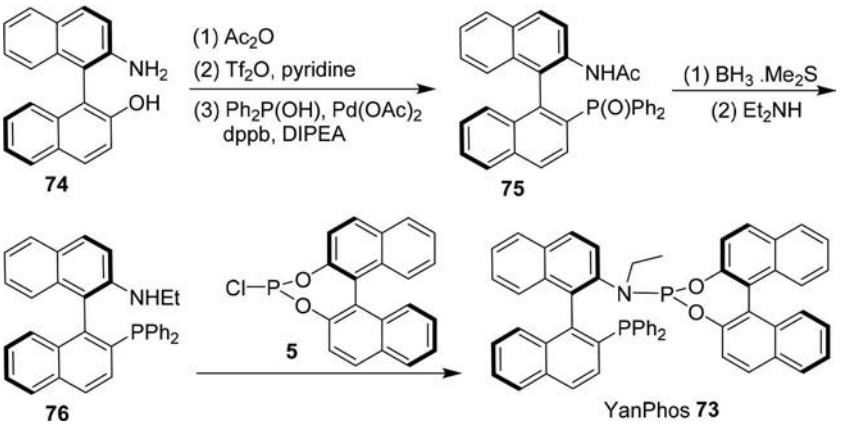
Scheme 33. Asymmetric hydroformylation of **70** with TADDOL-based indolphos **20d**.

71. A remarkably high regioselectivity (>99% yield) and enantioselectivity (91% *ee*) to 3-carbaldehyde **72** was achieved with a phosphine-phosphonite ligand.

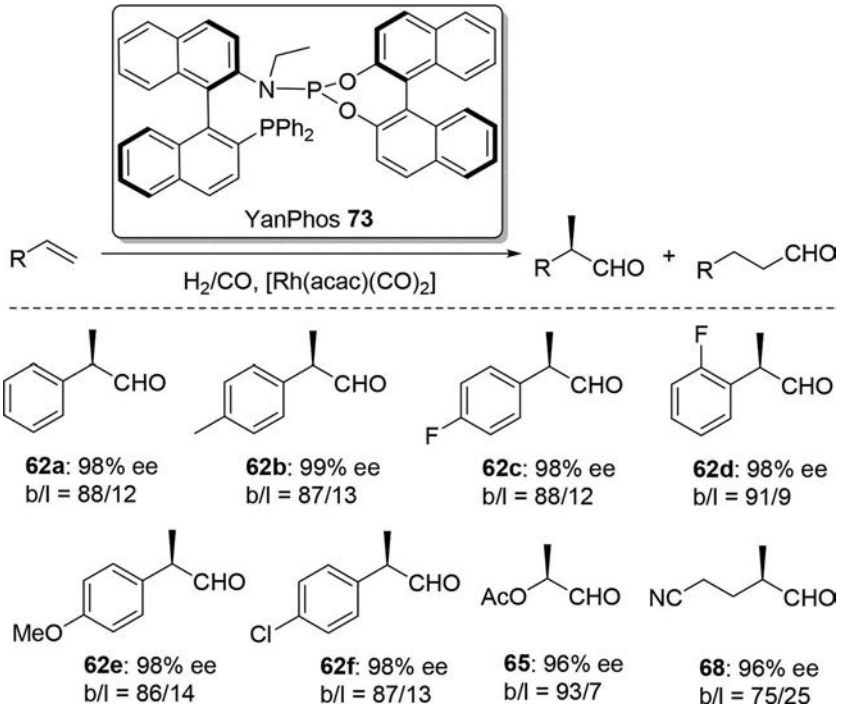
Yanphos

In 2006, Zhang et al.[44] replaced the oxygen linker in phosphine-phosphite ligand binaphos[45] with an ethylamino group to obtain its phosphine-phosphoramidtie analog yanphos **73**, which could be readily prepared from chiral NOBIN (2-amino-2′-hydroxy-1,1′-binaphthyl) **74** (Scheme 34). Thus, NOBIN **74** was successively *N*-acetylated and *O*-triflated to give a product that was submitted to the Pd-catalyzed phosphonoylation to afford the phosphine oxide amide **75**. Reduction of both phosphine oxide and amide group in **75** with BH_3, followed by the treatment with diethylamine, gave the compound **76**, which was deprotonated and quenched with clorophosphites **5** to give the desired phosphine-phosphoramidite yanphos **73**.

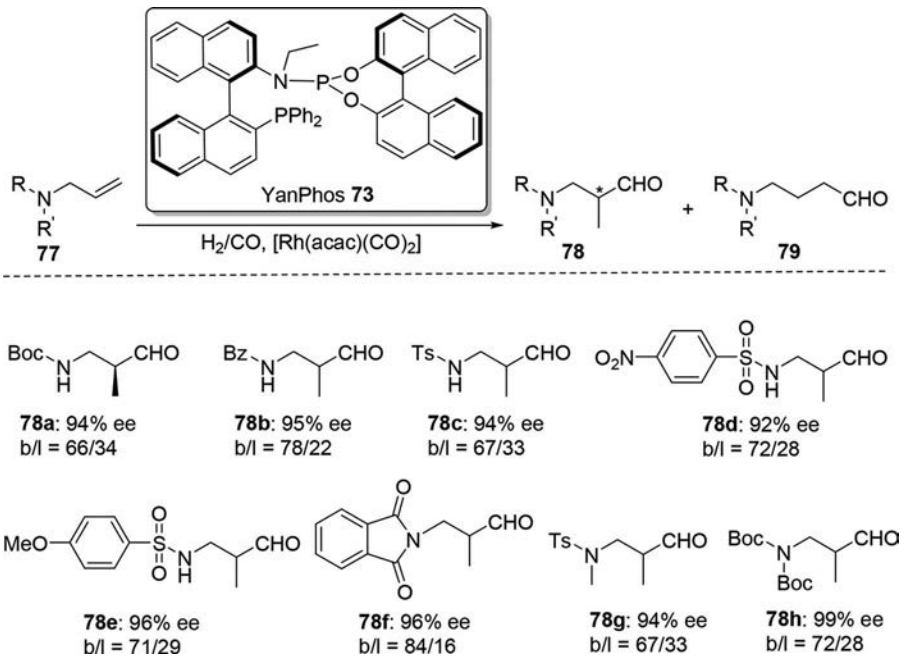
Yanphos **73** was evaluated in the Rh-catalyzed asymmetric hydroformylation of a wide range of styrene derivatives **61** (Scheme 35). Unprecedentedly high enantioselectivities (98–99% *ee*) had been achieved for the branched aldehyde **62**. The reaction could be performed at a lowered catalyst loading of 0.01 mol% without any loss of reigo- and enantioselectivity. It must be noted that the dramatic decrease of enantiomeric excess after full conversion



Scheme 34. Procedure for the synthesis of yanphos **73**.



Scheme 35. Asymmetric hydroformylation of **61** with yanphos **73**.



Scheme 36. Asymmetric hydroformylation of **77** with yanphos **73**.

obtained in binaphos was not observed with yanphos. High enantioselectivities (96% *ee*) were also achieved when vinyl acetate **64** and allyl cyanide **67** were engaged in this reaction.[46]

Following the success of yanphos **73** in the asymmetric hydroformylation of styrene derivatives, Zhang et al.[47] next examined the efficiency of yanphos in the Rh-catalyzed asymmetric hydroformylation of *N*-allylamides and *N*-allylsulfonamides **77** (Scheme 36). Excellent enantioselectivities (92–99% *ee*) and a turnover number (TON) of up to 9700 were achieved for the hydroformylation products. This represents the first example of asymmetric hydroformylation using *N*-allyamides and *N*-allysulfonamides as substrates, providing an alternative route to β^2-amino aldehydes, acids, and alcohols.

Asymmetric hydrophosphorylation

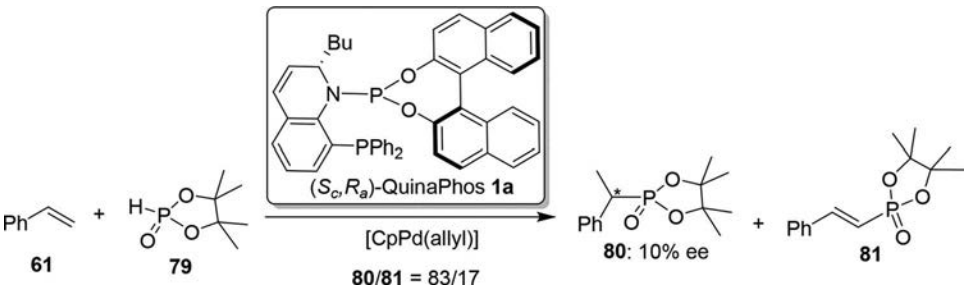
Leitner et al.[48] had developed a metal-catalyzed hydrophosphorylation of styrene **61** with **79**, controllably providing either the branched product **80** or the linear (*anti*-Markovnikov) product **81** (Scheme 37). The results disclosed that the Pd catalysts led preferentially to the branched product, whereas Rh-catalytic systems generally gave the linear product. A Pd catalyst formed in situ from (S_c,R_a)-quinaphos **1a** led to more than 83% regioselectivity for branched product **80**; however, very low enantioselectivity (10% *ee*) was obtained. Moderate enantioselectivity of 56% *ee* could be obtained when phosphine-phosphite ligand binaphos was used. This was the first example of the catalytic enantioselective hydrophosphorylation, adding a new possibility to the still very limited number of enantioselective P-H bond additions across double bonds.

Asymmetric allylic alkylation

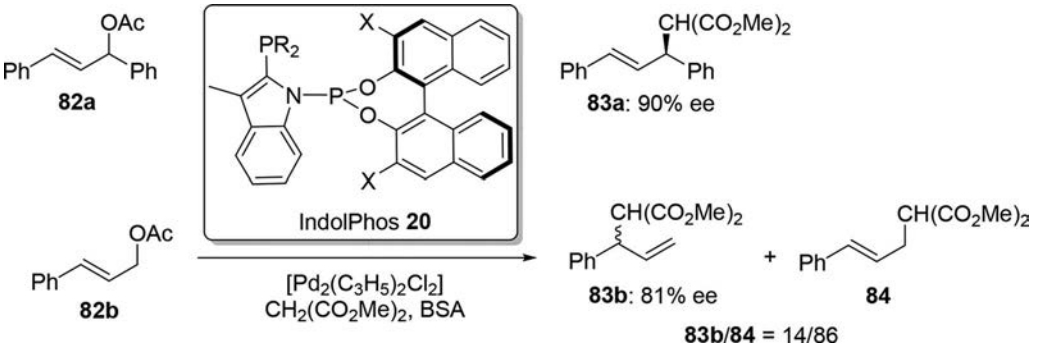
Reek et al.[49,50] had demonstrated the Pd-catalyzed asymmetric allylic alkylation of allylic acetates **82** with indolphos **20** (Scheme 38). For the 1,3-disubstituted propenyl acetate **82a**, high activity was found along with excellent enantioselectivity of up to 90% *ee*. For the more challenging monosubstituted cinnamyl acetate **82b**, good enantioselectivity of 81% *ee* but low *b*/*l* of 14/86 was obtained. These results showed that the phosphine-phosphoramidite ligands were able to induce good to excellent enantioselectivity for a range of substrates in the asymmetric allylic alkylation.

Asymmetric [3 + 2] cycloaddition

In 2009, Hu and Zheng[51] developed an Ag-catalyzed asymmetric [3 + 2] cycloaddition of azomethine ylides **85** with dimethyl maleate **86** with ferrocene-based

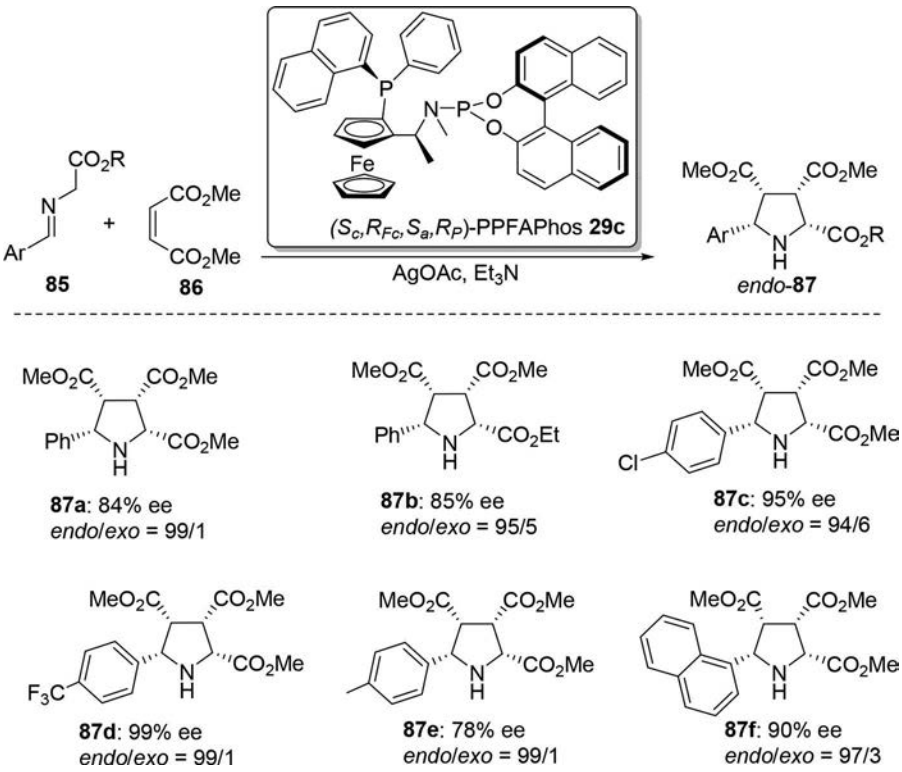


Scheme 37. Asymmetric hydrophosphorylation of **61** with (S_c,R_a)-quinaphos **1a**.

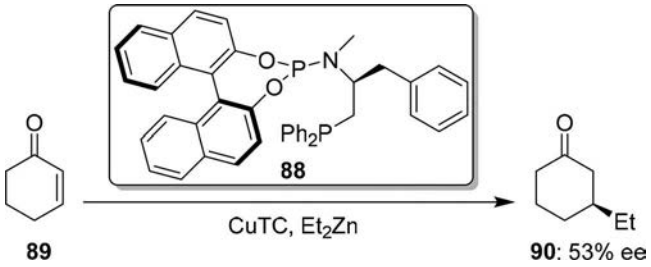


Scheme 38. Asymmetric allylic alkylation of **82** with indolphos **20**.

phosphine-phosphoramidite ligand PPFAphos **29** (Scheme 39). The results showed that ligand (S_c,R_{Fc},S_a,R_p)-PPFAphos **29c** with a stereogenic *P* center in the phosphine moiety displayed the best diastereo- and enantioselectivities, in which up to 99% *ee* and 99/1 of *endo*/*exo*-selectivities had been achieved. However, the catalyst system was less efficient for the asymmetric 1,3-dipolar cycloaddition of azomethine ylides with other dipolarophiles such as N-phenylmaleimide and *tert*-butyl acrylate, in which low enantioselectivities were obtained.



Scheme 39. Asymmetric [3 + 2] cycloaddition of **85** and **86** with (S_c,R_{Fc},S_a,R_p)-PPFAphos **29c**.

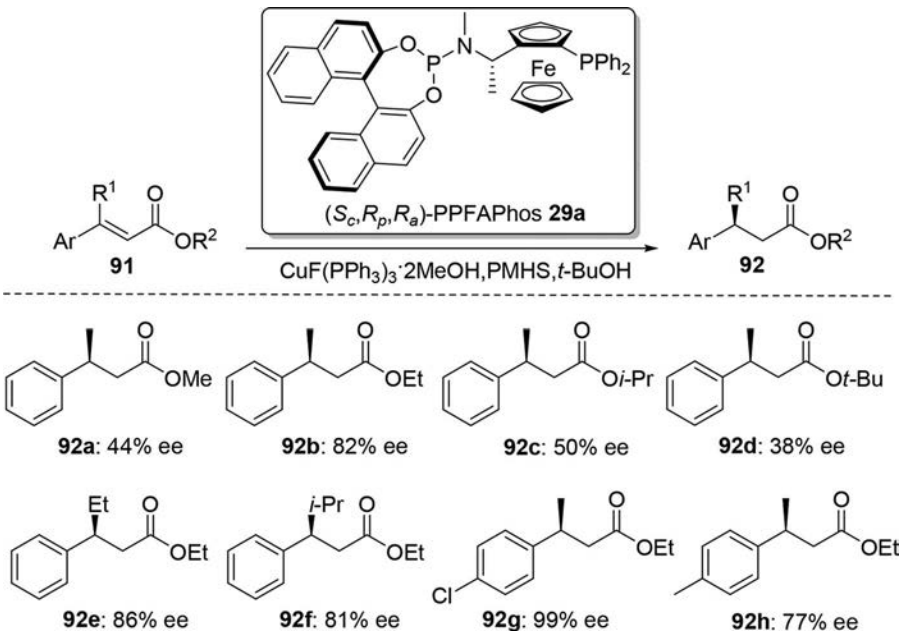


Scheme 40. Asymmetric conjugate addition of diethylzinc to cyclic enones **89** with ligand **88**.

Asymmetric conjugate addition and reduction

In 2006, Crévisy et al.[52] reported the synthesis of phosphine-phosphoramidite ligand **88** and its application in the Cu-catalyzed conjugate addition of diethylzinc to cyclic enones **89** (Scheme 40). Although only moderate enantioselectivity of 53% *ee* was obtained, it was the first example of the application of phosphine-phosphoramidite ligand in the asymmetric conjugate addition.

Recently, Hu and Zheng[53] had applied for the first time the ferrocenyl phosphine-phosphoramidite ligands PPFAphos **29** in the Cu-catalyzed asymmetric conjugate reduction of β-aryl α,β-unsaturated esters **91** (Scheme 41). The research revealed that ligand (S_c,R_a,R_p)-PPFAphos **29a** bearing (S_c)-central, (R_p)-planar, and (R_a)-axial chiralities showed the best performance. With the $CuF(PPh_3)_3$·2MeOH/(S_c,R_a,R_p)-PPFAphos **29a** catalytic system, a wide range of β-aryl-α,β-unsaturated esters **91** were reduced in moderate to excellent enantioselectivities (up to 99% *ee*) in the presence of polymethylhydrosiloxane (PMHS) and *t*-BuOH.



Scheme 41. Asymmetric conjugate reduction of α,β-unsaturated esters **91** with (S_c,R_a,R_p)-PPFAphos **29a**.

Conclusion

This review summarized the synthesis and application of chiral phosphine-phosphoramidite ligands in asymmetric catalysis. In past decades, numerous chiral phosphine-phosphoramidite ligands such as quinaphos, indolphos, PPFAphos, PEAphos, and yanphos have been developed. These ligands have the advantages of easy accessibility, modularity, and stability towards the air and moisture, which make them highly appealing for asymmetric catalysis. Gratifyingly, high enantioselectivities have been achieved in the Rh-catalyzed asymmetric hydrogenation of C=C double bonds, Ru-and Rh-catalyzed asymmetric hydrogenation of C=O double bonds, and Ir-catalyzed asymmetric hydrogenation of C=N double bonds. High enantioselectivities along with moderate to excellent regioselectivities are also achieved in the Rh-catalyzed asymmetric hydroformylation with chiral phosphine-phosphoramidite ligands. In addition, these ligands also demonstrate excellent performance in a wide range of reactions such as the Pd-catalyzed asymmetric hydrophosphorylation, Pd-catalyzed asymmetric allylic alkylation, Ag-catalyzed [3 + 2] cycloaddition, and Cu-catalyzed asymmetric conjugate addition and reduction.

Despite significant progress having been made, there are still many challenges in asymmetric catalysis with chiral phosphine-phosphoramidite ligands. Asymmetric hydrogenation and hydroformylation are undoubtedly the best-studied asymmetric transformations, in which excellent reactivities and enantioselectivities have been obtained. In contrast, studies on other asymmetric reactions are still unsatisfactory. Either low to moderate enantioselectivities are obtained, or there is narrow substrate scope encountered in these reactions. Therefore, more effort in searching for new, efficient chiral phosphine-phosphoramidite ligands as well as new asymmetric reactions with broad substrate scope and high enantioselectivities is necessary.

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